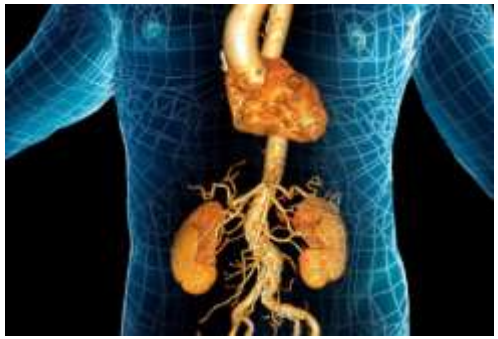
Σακχαρώδης διαβήτης
ΧΝΝ



Αθανάσιος Ε. Ράπτης
Καθηγητής
Παθολογίας – Σακχαρώδη Διαβήτη

Β΄ Προπαιδευτική Παθολογική Κλινική, Μονάδα Έρευνας και Διαβητολογικό Κέντρο Πανεπιστημίου Αθηνών, Πανεπιστημιακό Γ.Ν. ΄΄ Αττικόν΄΄

5-3-2024

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, Menarini, MSD, Novo Nordisk, Sanofi, Vianex

CKD is a major global public health issue

CKD affects approximately **1 in 10 adults** or an estimated **850 million people** and has recently been **acknowledged as the 'hidden epidemic'**[1–3]

The 10-year **excess mortality risk can exceed 47%** and an estimated **5–10 million people die** each year from CKD[4,5]

CKD leads to **increased hospitalizations, healthcare resource utilisation** and development of kidney failure, **further straining** donor and dialysis infrastructure[6]

In high- and middle-income countries, CKD is **most commonly caused by diabetes or hypertension**[7]

CKD, chronic kidney disease

1. Kidney Disease: Improving Global Outcomes (KDIGO) CKD Work Group. Kidney Int Suppl 2013;3:1; 2. ASN. The hidden epidemic: worldwide, over 850 million people suffer from kidney diseases. 2018. https://www.era-online.org/press/180626_Prevalence_Data_Project.pdf (accessed Oct 2022); 3. Jager KJ *et al. Nephrol Dial Transplant* 2019;34:1803; 4. Afkarian M *et al. J Am Soc Nephrol* 2013;24:302. 5. Luyckx VA *et al. Bull World Health Organ* 2018;96:414; 6. United States Renal Data System. 2021 USRDS Annual Data Report. 2021. https://adr.usrds.org/2021 (accessed Oct 2022); 7. Webster AC *et al. Lancet* 2017;389:1238

What is Chronic Kidney Disease?

KDIGO definition criteria

Definition

The National Kidney Foundation KDIGO define CKD as:[1]
Duration of >3 months of either:

1. Kidney damage, as defined by structural or functional abnormalities of the kidney, with or without decreased GFR manifest by either:
   a. Pathological abnormalities; or
   b. Markers of kidney damage, including albuminuria ≥30 mg/g (≥3 mg/mmol) or other abnormalities in the composition of urine, or abnormalities in histology or imaging tests, or history of kidney transplantation
2. GFR <60 mL/min/1.73 m^2 with or without kidney damage

ESRD

ESRD* is the final stage of kidney disease, when the kidneys no longer function well enough to meet the needs of everyday life[2]

Chronic kidney disease – Global statistics[3]

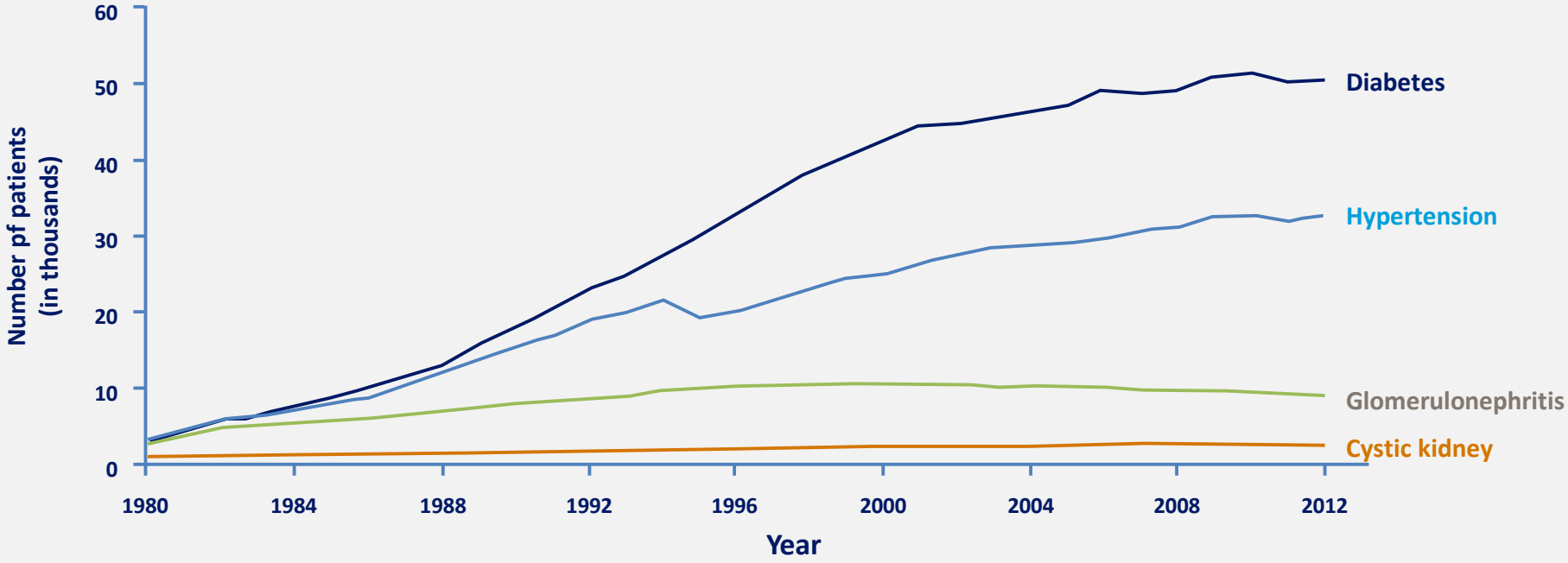
- CKD has a global prevalence of 9.1%; prevalence is higher in women than in men

- CKD has a major effect on global health, both as a direct cause of global morbidity and mortality
- It is the 12th leading cause of death worldwide resulting in 1.2 million deaths and 35.8 million DALYs in 2017

*End-stage renal disease - defined by maintenance dialysis that is sustained for at least 30 days, renal transplantation, or eGFR <15 mL/min per 1.73 m^2 sustained for at least 30 days[1,4,5]
CKD, chronic kidney disease; DALY, disability-adjusted life year; GFR, glomerular filtration rate; KDIGO, Kidney Disease Improving Global Outcome
1. KDIGO 2020 Clinical Practice Guideline for Diabetes Management in Chronic Kidney Disease. Kidney Int. 2020;98(45):S1–S115 2. Rodger RSC et al. Clin Med 2012;12:472–475; 3. Carney EF. Nat Rev Nephrol 2020;16:251; 4. Perkovic V et al. Lancet Diabetes Endocrinol 2018;6:691–704; 5. Mann JFE et al. N Engl J Med 2017;377:839–848

Diabetes is the leading cause of kidney failure

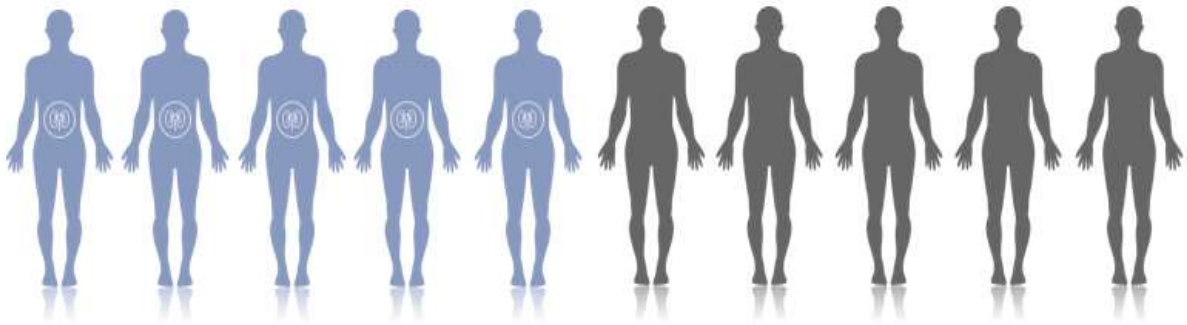
US DATA



United States Renal Data System. 2018 USRDS annual data report: Epidemiology of kidney disease in the United States. National Institutes of Health, National Institute of Diabetes and Digestive and Kidney Diseases, Bethesda, MD, 2018

Χρόνια
Νεφρική
Νόσος

Οι ασθενείς με διαβήτη διατρέχουν υψηλό κίνδυνο νεφρικής νόσου



Η ΧΝΝ εκτιμάται ότι επηρεάζει το ~ 50% των ασθενών με ΣΔτ2 παγκοσμίως…[1]

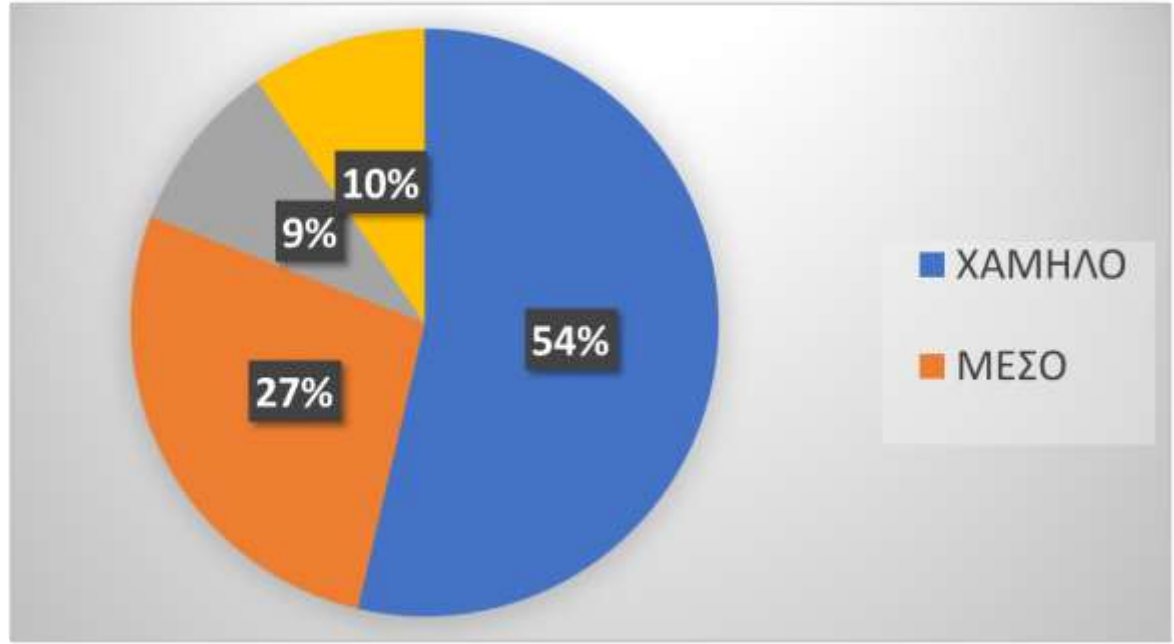
…& είναι ο πιο συνηθισμένος λόγος για εξέλιξη σε νεφρική νόσο τελικού σταδίου σε πολλά μέρη του κόσμου[1–3]

ΧΝΝ: Χρόνια Νεφρική Νόσος

1. Thomas M *et al. Nat Rev Nephrol* 2016;12:73; 2. Toth-Manikowski S & Atta MG. *J Diabetes Res* 2015;2015:697010; 3. Stewart JH *et al. Nephrology* 2007;12:520

The prevalence of diabetic chronic kidney disease in adult Greek subjects with type 2 diabetes mellitus: A series from hospital-based diabetes clinics

Ilias N Migdalis [1], Nikolaos Papanas [2], Athanasios E Raptis [3], Ioannis M Ioannidis [4], Alexios E Sotiropoulos [5], George D Dimitriadis [3], Hellenic Diabetic Nephropathy Study (HDNS) Group

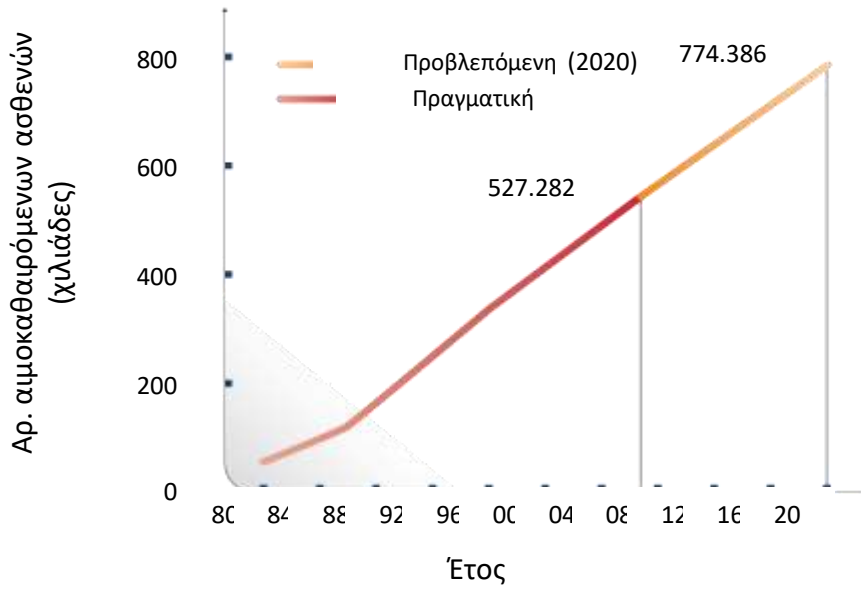


Αν εξαιρεθούν οι ελλιπείς τιμές (71 ασθενείς), τότε το ποσοστό των συμμετεχόντων πάσχει από μέτρια / σοβαρή / πολύ σοβαρή ΧΝΝ τροποποιείται από 46% σε 44.55%

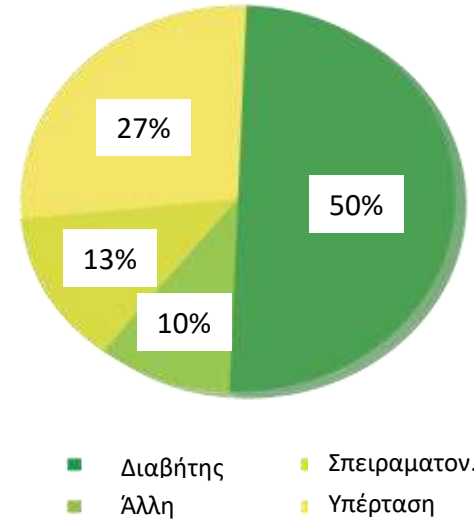
Diabetes Res Clin Pract . 2020 Aug;166:108243

Ο διαβήτης είναι το κύριο αίτιο νεφρικής ανεπάρκειας τελικού σταδίου[1]

- **Η επίπτωση αυξάνεται δραματικά**



- **Αρχική διάγνωση για ασθενείς που ξεκινούν αιμοδιύλιση**

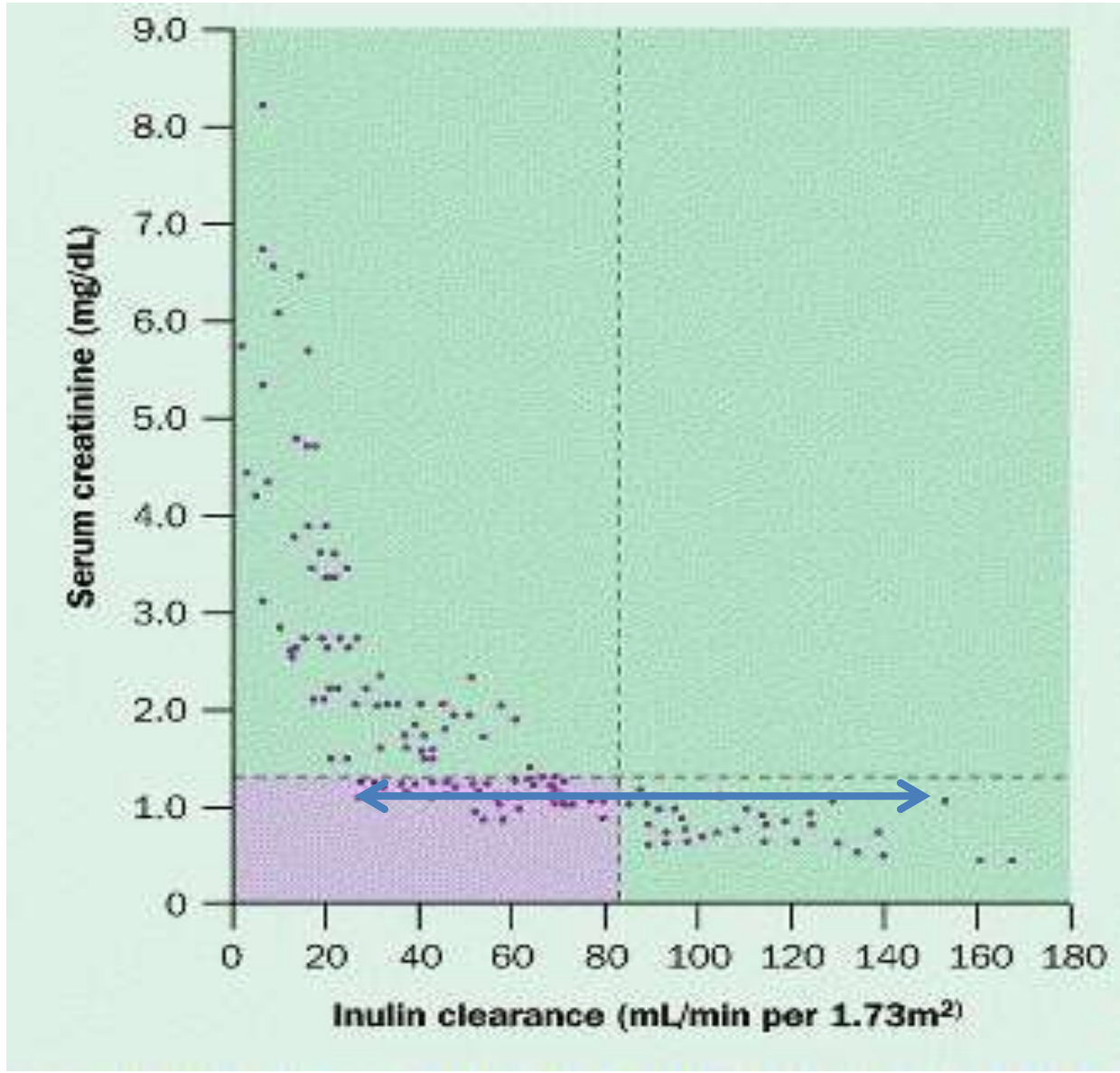


1. United States Renal Data System. Annual data report. 2000, 2007. http://www.usrds.org/atlas.htm , http://www.usrds.org/adr_2000.htm. Accessed 10 January 2011.

Εκτίμηση Χρόνιας Νεφρικής Νόσου

ΝΕΦΡΟΛΟΓΙΚΗ ΕΚΤΙΜΗΣΗ (1)

- Ρυθμός σπειραματικής διήθησης
  Glomerular Filtration Rate


9.0
8.0
7.0
6.0
5.0
4.0
3.0
2.0
1.0
0
Serum creatinine (mg/dL)
0
20
40
60
80
100
120
140
160
180
Inulin clearance (mL/min per 1.73m2)

Υπολογισμός σπειραματικής διήθησης (ml/min)

MDRD
CKD-EPI

CKD-EPI Equations for Glomerular Filtration Rate (GFR)

Estimates GFR based on serum creatinine, serum cystatin C, or both.

IMPORTANT

The 2021 CKD-EPI equation is now the recommended standard. This version does not include race, as do the 2009 and 2012 CKD-EPI creatinine and creatinine-cystatin C equations. See here (https://www.mdcalc.com/race) for more on our approach to addressing race and bias on MDCalc.

With the 2021 equation, for the same creatinine value, the 2021 equation will estimate a lower GFR for Black patients and a higher GFR for non-Black patients.

INSTRUCTIONS

For use in patients with stable kidney function. While the combined creatinine and cystatin C equation can add accuracy, cystatin c is not available in all laboratories and the creatinine-based equation is adequate for many clinical purposes.

2021 CKD-EPI creatinine is currently recommended by the ASN and NKF for GFR reporting in the United States.

When to Use | Pearls/Pitfalls | Why Use

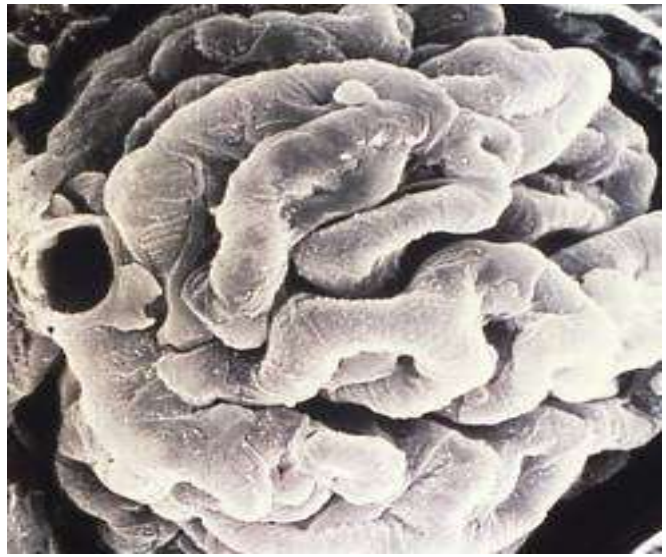
Equation	2021 CKD-EPI Creatinine	
	2021 CKD-EPI Creatinine-Cystatin C	
	2009 CKD-EPI Creatinine	
	2012 CKD-EPI Cystatin C	
	2012 CKD-EPI Creatinine-Cystatin C	
Sex	Female	
	Male	
Age	48	years
Serum creatinine	1.3	mg/dL

51 ml/min/1.73 m²

Estimated GFR by 2021 CKD-EPI Creatinine

ΝΕΦΡΟΛΟΓΙΚΗ ΕΚΤΙΜΗΣΗ (2)

- Απώλεια αλβουμίνης* και λευκωμάτων στα ούρα



Στοιχεία Παραπεμπτικού

Τύπος Παραπεμπτικού: ΤΥΠΙΚΟ

Κατηγορία Εξετάσεων: Εξετάσεις Βιολογικών Υλικών 1 (Βιοπαθολογίας) (Α

* Αιτιολογία Παραπεμπτικού: ELEGXOS

Σημειώσεις:

Περιπτώσεις Μηδενικής Συμμετοχής:

Προσθήκη Διάγνωσης ICD-10

Κωδικός ICD-10	Διάγνωση
Z10.8	Γενικός προσυμπτωματικός έλεγχος ρουτίνας άλλων καθορισμένων υποπληθυσμών

Εξετάσεις | Ιατρικές Εξετάσεις | Αγαπημένες Εξετάσεις | Καθαρισ

Εξέταση	Διάγνωση
ΜΙΚΡΟΑΛΕΥΚΩΜΑΤΙΝΗ ΟΥΡΩΝ	Z10.8
Κρεατινίνη ούρων (CREAT)	Z10.8

☑	ΒΙΟΧΗΜΙΚΕΣ	77	ΜΙΚΡΟΑΛΕΥΚΩΜΑΤΙΝΗ ΟΥΡΩΝ	5
☐	ΒΙΟΧΗΜΙΚΕΣ	88	Καμπύλη καλοσακχάρου	4.75
☐	ΒΙΟΧΗΜΙΚΕΣ	92	Ολική Χολερυθρίνη (TBIL)	2.88
☐	ΒΙΟΧΗΜΙΚΕΣ	94	Κρεατινίνη αίματος (CREAT)	4.05
☑	ΒΙΟΧΗΜΙΚΕΣ	95	Κρεατινίνη ούρων (CREAT)	4.05
☐	ΗΛΕΚΤΡΟΦΟΡΗΣΕΙΣ	97	Ηλεκτροφόρηση λευκωμάτων ορού - Ηλεκτροφόρηση ορού επί οξικής κυτ...	10.8

GFR and albuminuria are used to assess kidney function and damage

For a healthy person eGFR is ≥90 mL/min/1.73 m^2 and UACR is <30 mg/g

GFR/eGFR[1-5]

- GFR is accepted as the best overall index of kidney function
- Serum creatinine and urea (both endogenous filtration markers) are used as measures of renal function, and these vary inversely with GFR
- Measuring GFR is cumbersome and time consuming
- Kidney function or kidney disease and its severity is assessed using estimated GFR (eGFR) which is based on calculations using a patient's serum creatinine level, age, gender and race
- Commonly used formulas to calculate eGFR include the CKD-EPI equation and MDRD study equation

Albuminuria[6,7]

Albuminuria is the increased urinary albumin excretion and is commonly used as an indirect measure of kidney damage and marker of risk for kidney disease progression

Assessment:

- In a spot urine measured by dipstick method or by laboratory assessment of the ratio of urinary albumin and creatinine (UACR). UACR is used to correct for variation in urinary albumin concentrations related to hydration and is widely used in clinical trials
- In urine collected over a 24-hour period as the albumin excretion rate (AER; mg/24 hours); AER is considered to be the gold standard method for assessing albuminuria

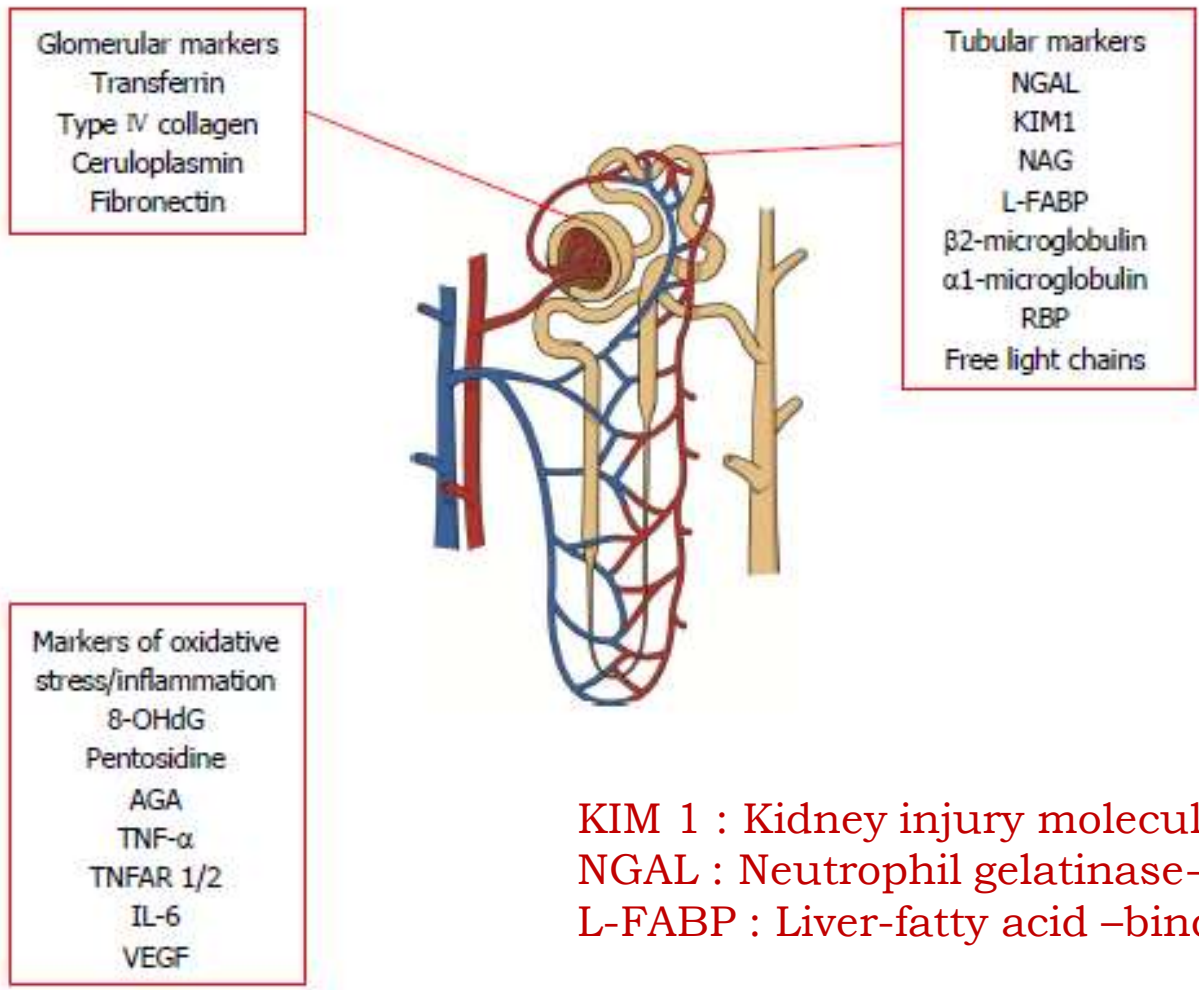
Category	AER (mg/day)	ACR (approximate equivalent)		Terms
		mg/mmol	mg/g	
A1	<30	<3	<30	Normal
A2	30–300	3–30	30–300	Microalbuminuria†
A3	>300	>30	>300	Macroalbuminuria‡

†Moderately increased; ‡Severely increased; AER, albumin excretion rate; CKD, chronic kidney disease; CKD-EPI, Chronic Kidney Disease Epidemiology Collaboration; eGFR, estimated glomerular filtration rate, GI, gastrointestinal; MDRD, Modification of Diet in Renal Disease; UACR, urinary albumin-to-creatinine ratio

1. National Kidney Foundation. Frequently asked questions about GFR estimates. 2014. Available at: http://www.kidney.org/sites/default/files/12-10-4004_FAQ-ABE.pdf. Accessed June 2020; 2. National Kidney Foundation. Kidney Int Suppl 2013;3:1–150; 3. Traynor J et al. BMJ 2006;333:733–737; 4. Gowda S et al. N Am J Med Sci. 2010 Apr; 2(4): 170–173. 5. Mula-Abed WS et al. Oman Med J. 2012 Mar; 27(2):108–113; 6 National Kidney Foundation. Kidney Int Suppl 2013;3:1-150; 7. Johnson DW et al. Med J Aus 2012;197:224–225

Biomarkers in diabetic nephropathy: Present and future

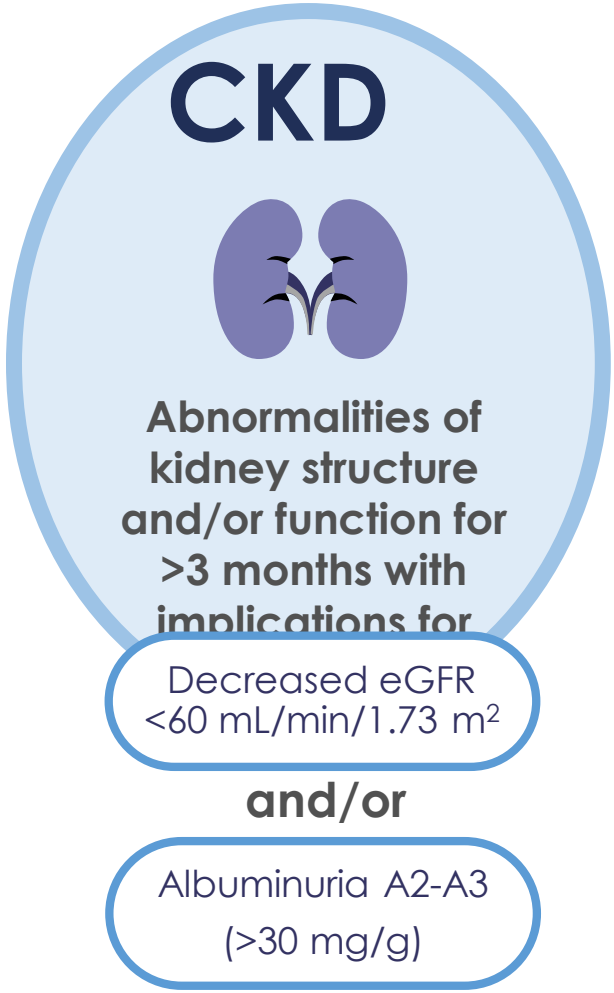
Gemma Currie, Gerard McKay, Christian Delles



KIM 1 : Kidney injury molecule 1
NGAL : Neutrophil gelatinase-associated lipocalin
L-FABP : Liver-fatty acid –binding protein

World J Diabetes 2014 December 15; 5(6): 763-776

Criteria for diagnosis and risk stratification of CKD require both eGFR and UACR



KDIGO: Classification and prognosis of CKD

eGFR categories (mL/min/1.73 m²) Description and range				Persistent albuminuria categories Description and range		
				A1	A2	A3
				Normal to mildly increased	Moderately increased	Severely increased
				<30 mg/g <3 mg/mmol	30-300 mg/g 3-30 mg/mmol	>300 mg/g >30 mg/mmol
	G1	Normal or high	≥90	**Low***	**Moderately increased**	**High**
	G2	Mildly decreased	60-89	**Low***	**Moderately increased**	**High**
	G3a	Mildly to moderately decreased	45-59	**Moderately increased**	**High**	**Very high**
	G3b	Moderately to severely decreased	30-44	**High**	**Very high**	**Very high**
	G4	Severely decreased	15-29	**Very high**	**Very high**	**Very high**
	G5	Kidney failure	<15	**Very high**	**Very high**	**Very high**

Risk of progression

Risk of progression

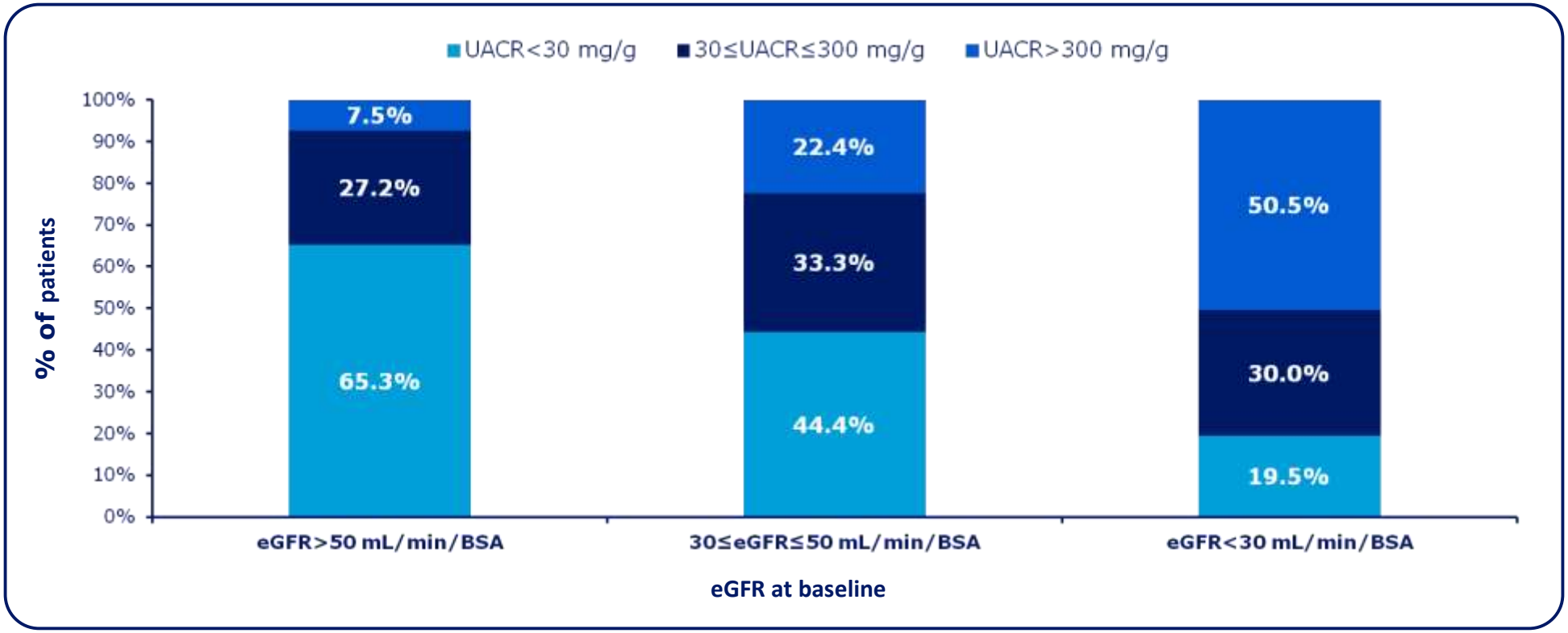
*If no other markers of kidney disease, no CKD.

CKD, chronic kidney disease; eGFR, estimated glomerular filtration rate. KDIGO, Kidney Disease: Improving Global Outcomes.

Kidney Disease: Improving Global Outcomes (KDIGO) Diabetes Work Group. *Kidney Int.* 2020;98(suppl):S1-S115.

eGFR and UACR do not always correlate

SAVOR TIMI-53 study (n=16,492)



BSA, body surface area; eGFR, estimated glomerular filtration rate; UACR, urinary albumin-to-creatinine ratio
Mosenzon O, et al. Diabetes Care 2017;40:69–76

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

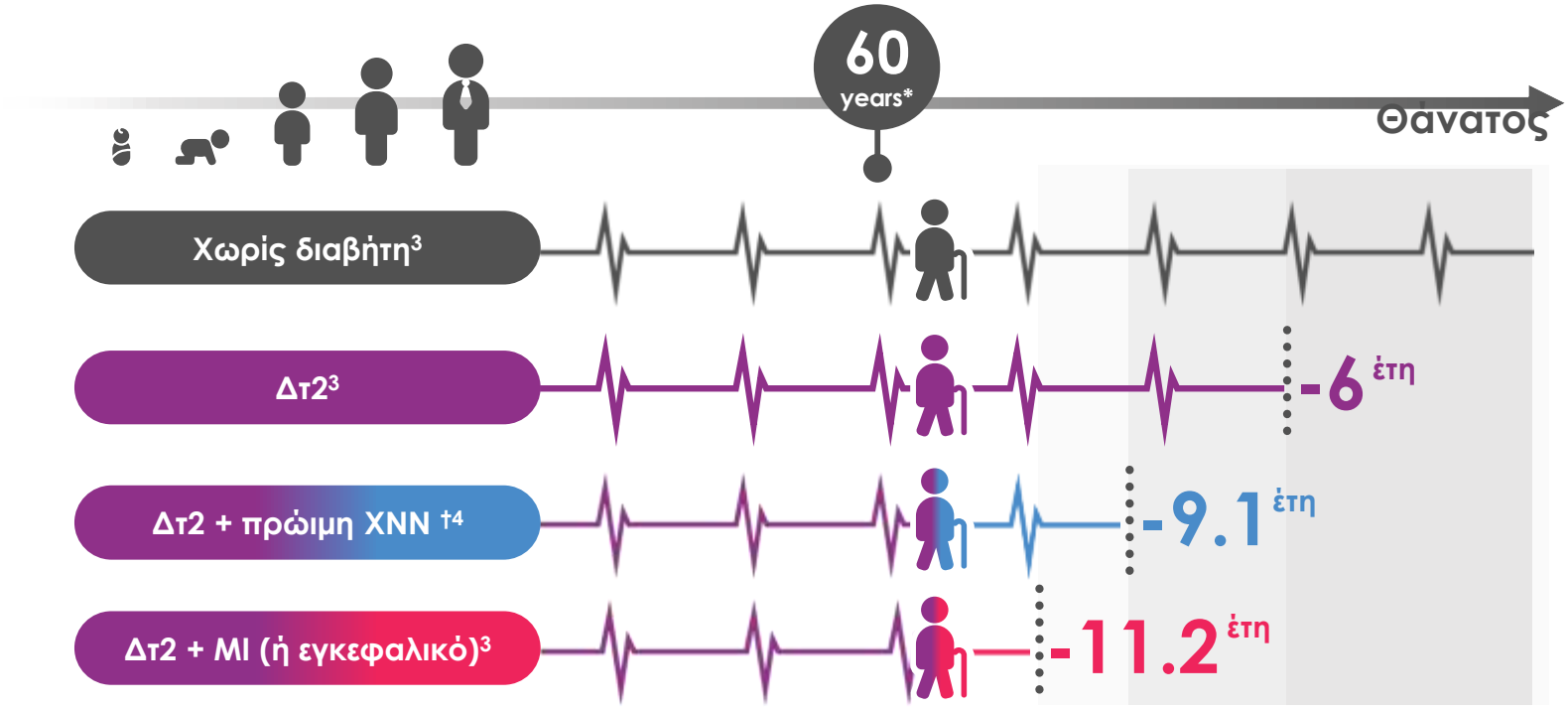
Νεφρική βλάβη

Νεφρική νόσος

Χωρίς σημεία νεφρικής βλάβης
** Λευκωματινουρία – νεφρική βλάβη

- National Kidney Foundation.
- Am J Kidney Disease 2007.

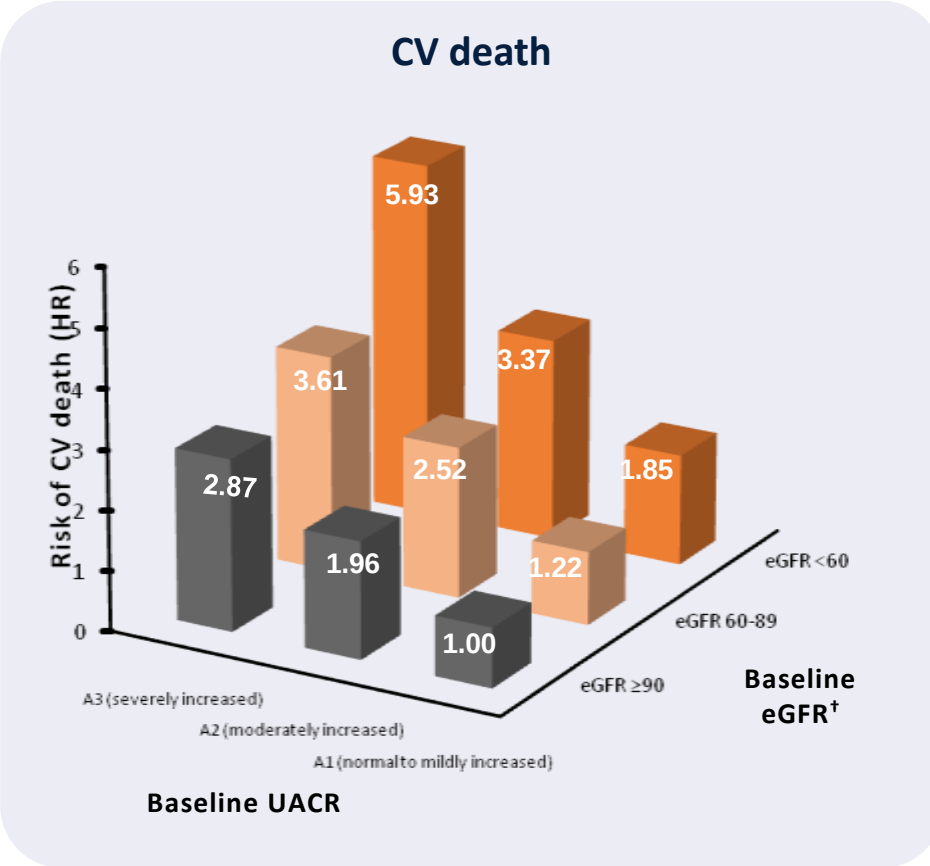
Οι παθήσεις των Καρδιο-Νεφρο-Μεταβολικών συστημάτων είναι μεταξύ των κυριότερων αιτιών πρόωρου θανάτου

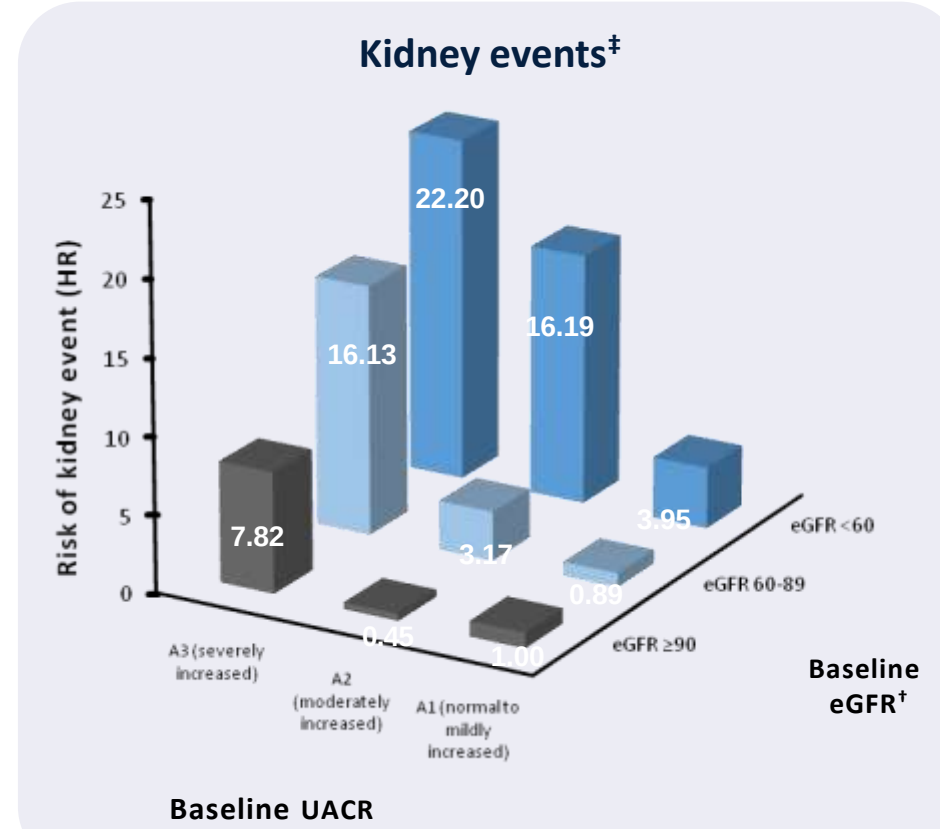


* Άνδρας 60 ετών με διαβήτη και ΚΑ νόσο ή ΧΝΝ πεθαίνει, κατά μέσο όρο, 9-12 έτη νωρίτερα σε σχέση με κάποιον με ΚΑ νόσο ή ΧΝΝ χωρίς διαβήτη[3,4]; † στάδια ΧΝΝ 1-3
ΧΝΝ, χρόνια νεφρική νόσος. CRM, καρδιο-νεφρο-μεταβολικό. CVD, καρδιαγγειακή νόσος. MI, έμφραγμα του μυοκαρδίου. Δτ2: Διαβήτης τύπου 2

1. GBD 2017 Disease and Injury Incidence and Prevalence Collaborators. *Lancet* 2018;392:1789; 2. GBD 2015 Mortality and Causes of Death Collaborators. *Lancet* 2016;388:1459;
3. The Emerging Risk Factors Collaboration. *JAMA* 2015;314:52; 4. Wen C *et al. Kidney Int* 2017;92:388

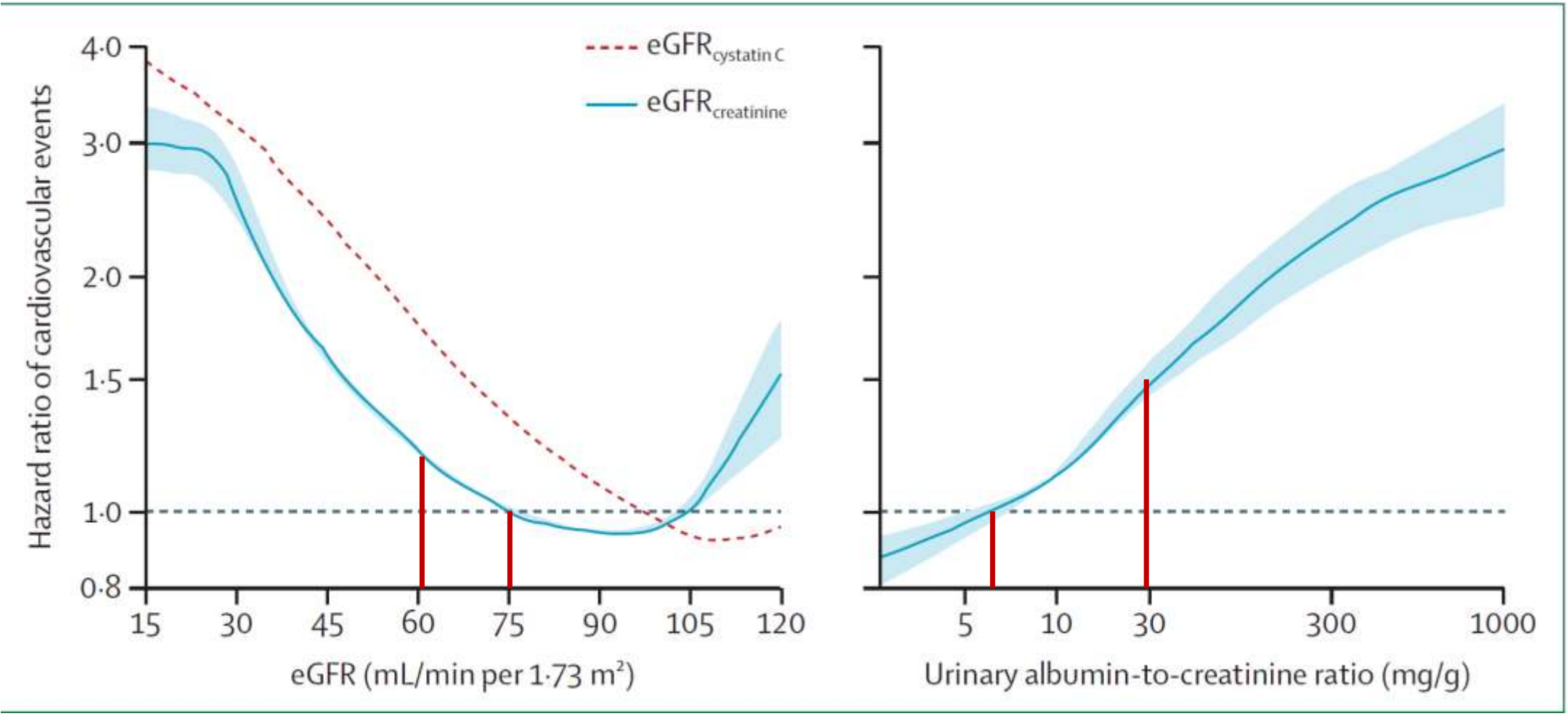
Reduced eGFR and increased albuminuria are independently associated with increased risk of CV death and kidney events*





*Average time to follow-up for risk assessment was 4.3 years; †eGFR in mL/min/1.73 m^2; ‡A kidney event was defined as death as a result of kidney disease, requirement for dialysis or transplantation, or doubling of serum creatinine to >2.26 mg/dL. HR, hazard ratio. Figure used with permission of The American Society of Nephrology, from "Albuminuria and Kidney Function Independently Predict Cardiovascular and Renal Outcomes in Diabetes", Ninomiya T, et al, on behalf of the ADVANCE Collaborative Group, Journal of the American Society of Nephrology, vol 20, pages 1813-1821, copyright 2009; permission conveyed through Copyright Clearance Center, Inc.
Ninomiya T *et al. J Am Soc Nephrol* 2009;20:1813

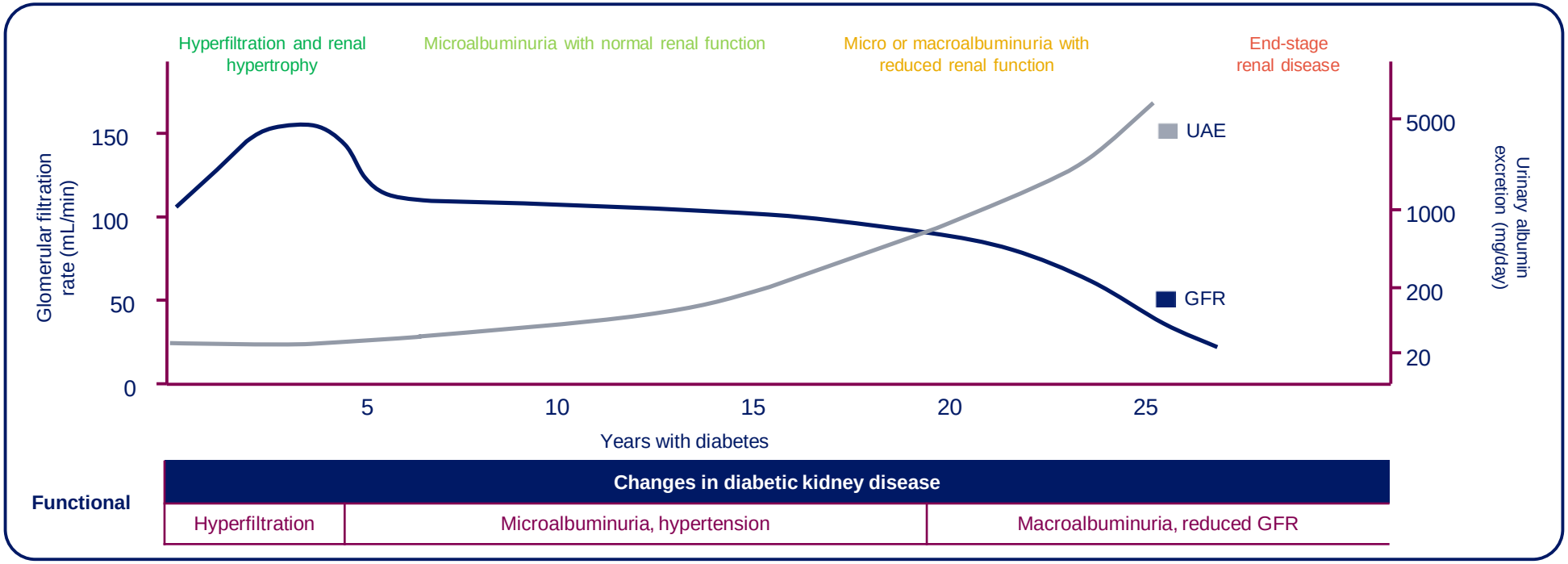
Association of eGFR and albuminuria with hazard ratio of cardiovascular events



Shlipak MG, Matsushita K, Ärnlöv J, et al. Cystatin C versus creatinine in determining risk based on kidney function. *N Engl J Med* 2013; 369: 932–43.

Progression of CKD in diabetes

An initial hyperfiltration is followed by progressive decline in GFR accompanied by microalbuminuria progressing to macroalbuminuria



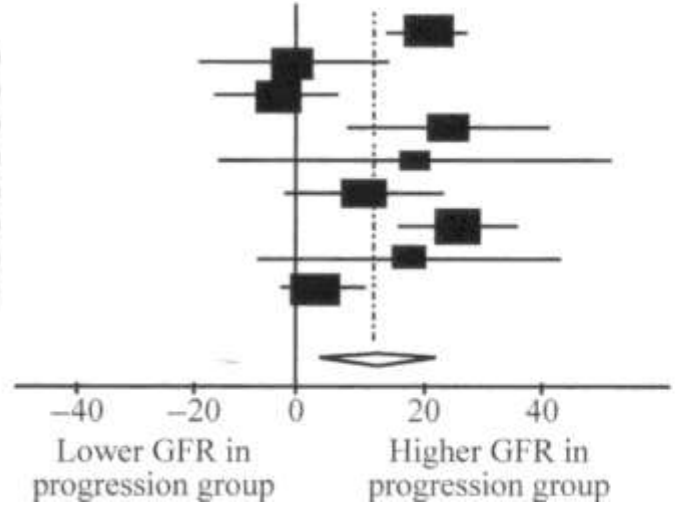
CKD stage; GFR, glomerular filtration rate; UAE, urinary albumin excretion

Modified, based on: Leoncini G et al. J Nephrol 2020; https://doi.org/10.1007/s40620-020-00803-3 and Bailey CJ et al. Br J Diabetes Vasc Dis 2012;12:167–171

Υπερδιήθηση και εξέλιξη νεφρικής νόσου
Μετανάλυση

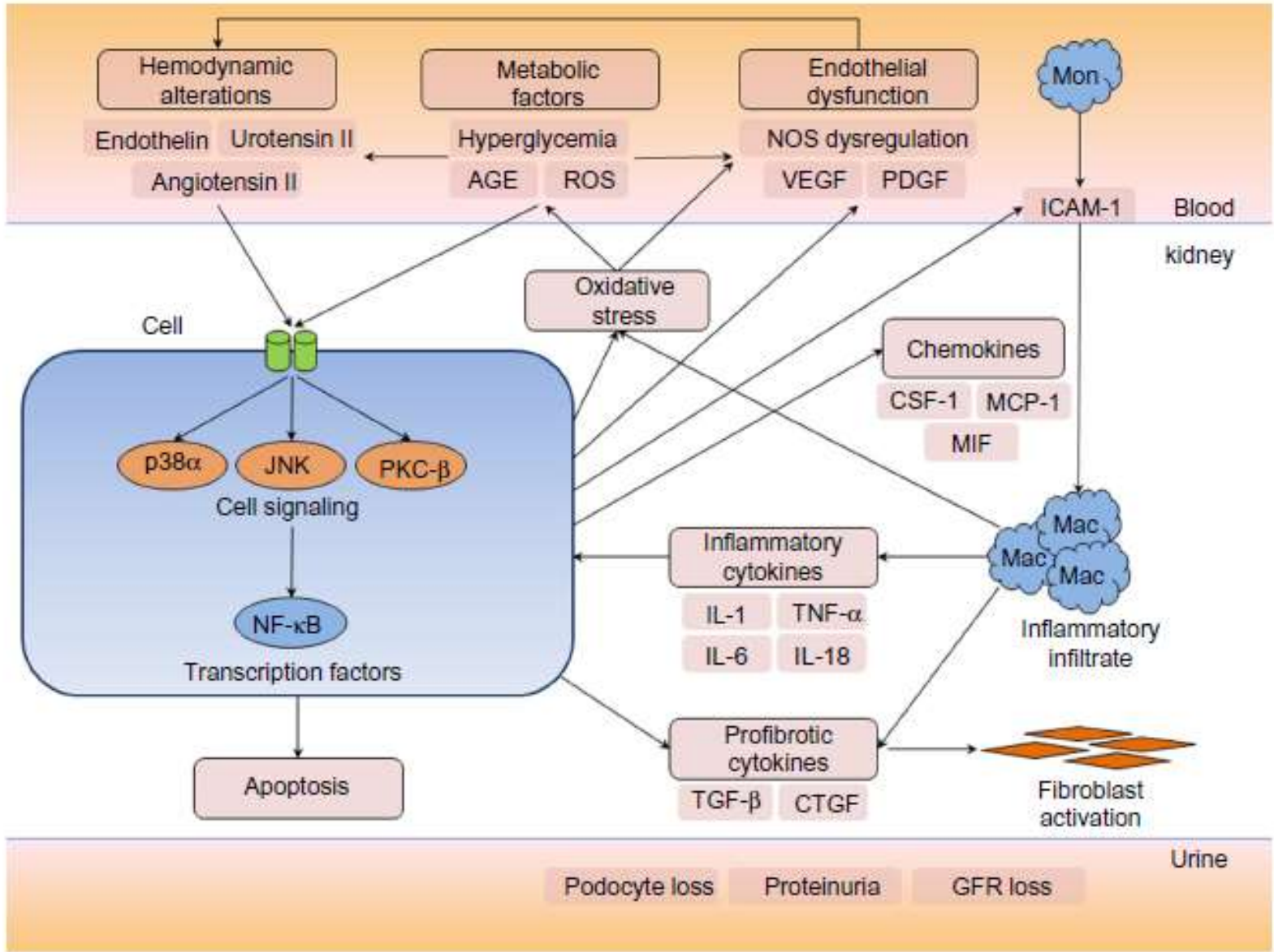
First author [reference no.]	Progression *n*	Progression Mean (SD)	No progression *n*	No progression Mean (SD)	Difference in mean (95% CI)	Relative weight (%
Mogensen [22]	6	157.0 (7.0)	17	134.0 (9.0)	23.3 (16.0–30.1)	15
Lervang [23]	8	144.1 (20.6)	21	144.3 (19.1)	0 (–16.7–16.3)	10
Lervang [24]	17	134.0 (17.5)	17	137.0 (14.0)	–3.0 (–13.7–7.7)	13
Chiarelli [25]	8	168.8 (21.7)	38	142.2 (27.7)	26.6 (9.2–44.0)	10
Caramori [27]	3	156.5 (28.8)	30	135.7 (28.0)	20.8 (–13.3–55.0)	5
Dahlquist [28]	19	141.0 (25.3)	24	129.0 (20.0)	12.0 (–1.9–25.9)	12
Amin [29]	30	166.8 (26.2)	243	138.6 (30.6)	28.2 (18.1–38.3)	14
Steinke [30]	8	163.0 (37.0)	99	143.0 (28.0)	20.0 (–6.2–46.2)	7
Zerbini [31]	27	121.7 (18.3)	119	117.6 (19.0)	4.1 (–3.6–11.8)	15
Total	126		608			
Overall[a]					13.8 (5.0–22.7)	

Difference in mean = (progression group – non progression group)

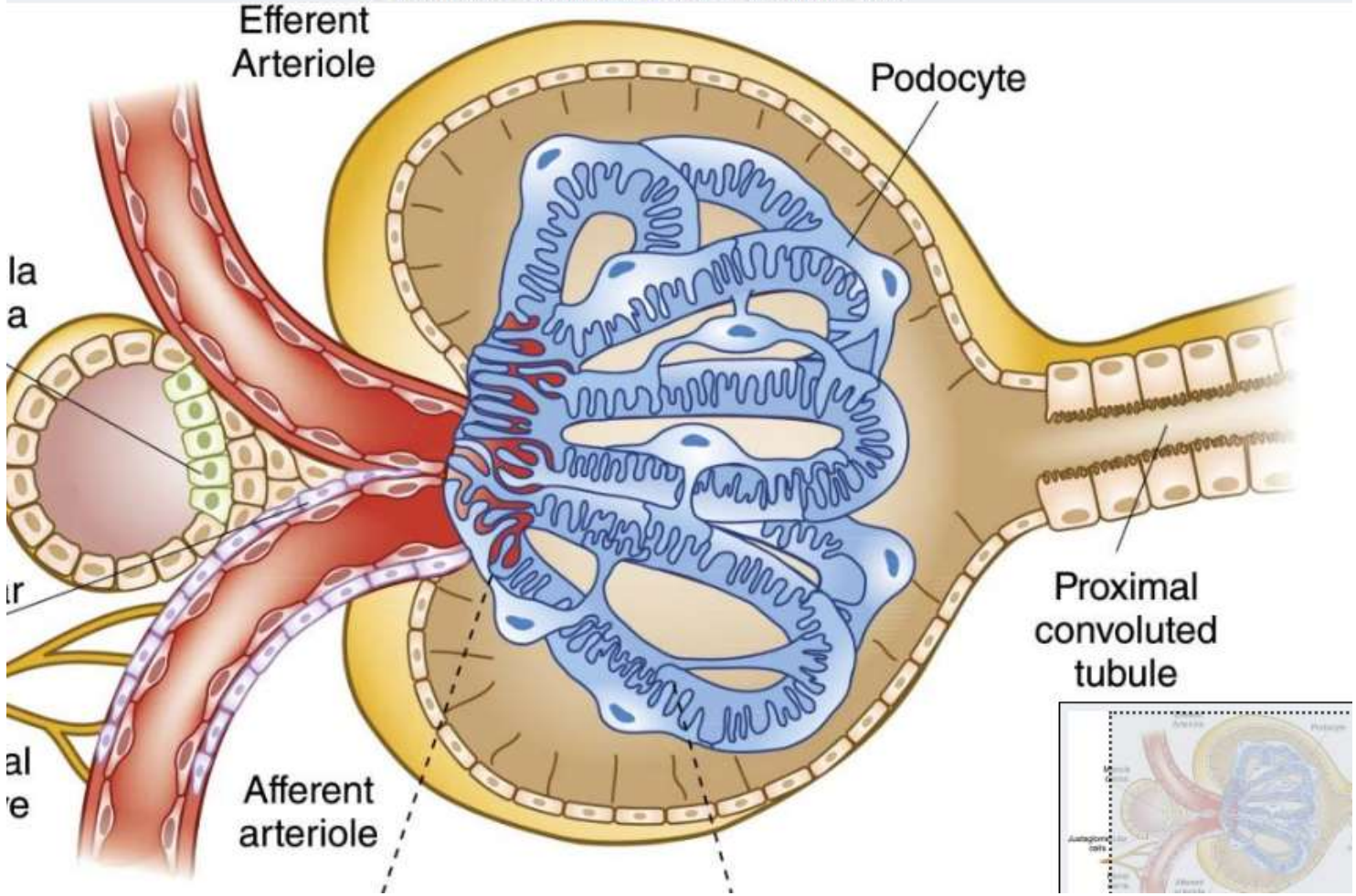


Οι πιθανότητες ανάπτυξης ΜΑ σε ασθενείς με υπερδιήθηση ήταν **2,71** φορές περισσότερες σε σχέση με αυτούς με φυσιολογική διήθηση

Magee et. al., Diabetologia,52,April, 2009


Hemodynamic alterations
Metabolic factors
Endothelial dysfunction
Mon
Endothelin
Urotensin II
Angiotensin II
Hyperglycemia
AGE
ROS
NOS dysregulation
VEGF
PDGF
ICAM-1
Blood
kidney
Oxidative stress
Cell
Chemokines
CSF-1
MCP-1
MIF
p38α
JNK
PKC-β
Cell signaling
Mac
Mac
Mac
Inflammatory cytokines
IL-1
TNF-α
IL-6
IL-18
Inflammatory infiltrate
NF-κB
Transcription factors
Profibrotic cytokines
TGF-β
CTGF
Fibroblast activation
Apoptosis
Urine
Podocyte loss
Proteinuria
GFR loss

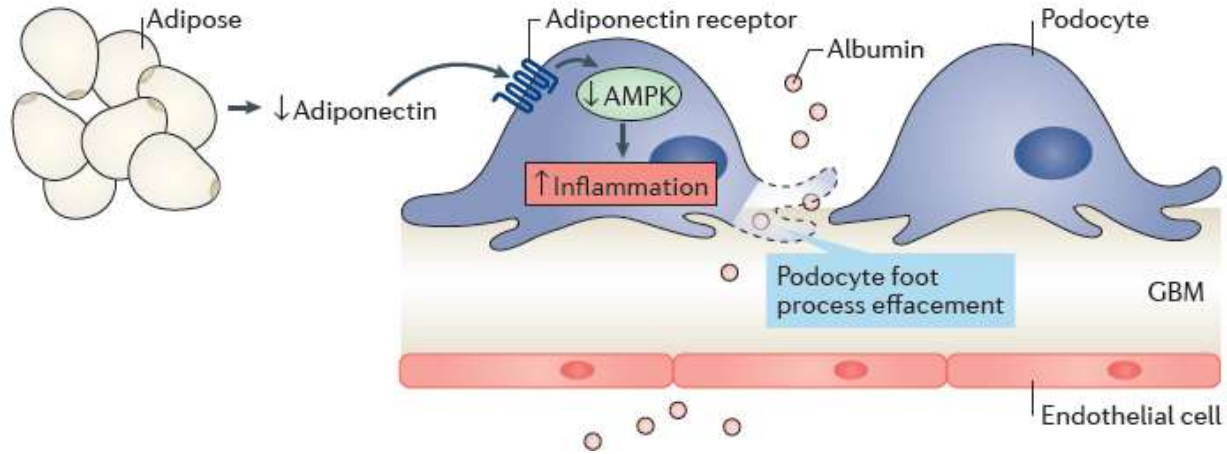
Drag image to reposition. Double click to magnify further.



Kidney disease and obesity: epidemiology, mechanisms and treatment

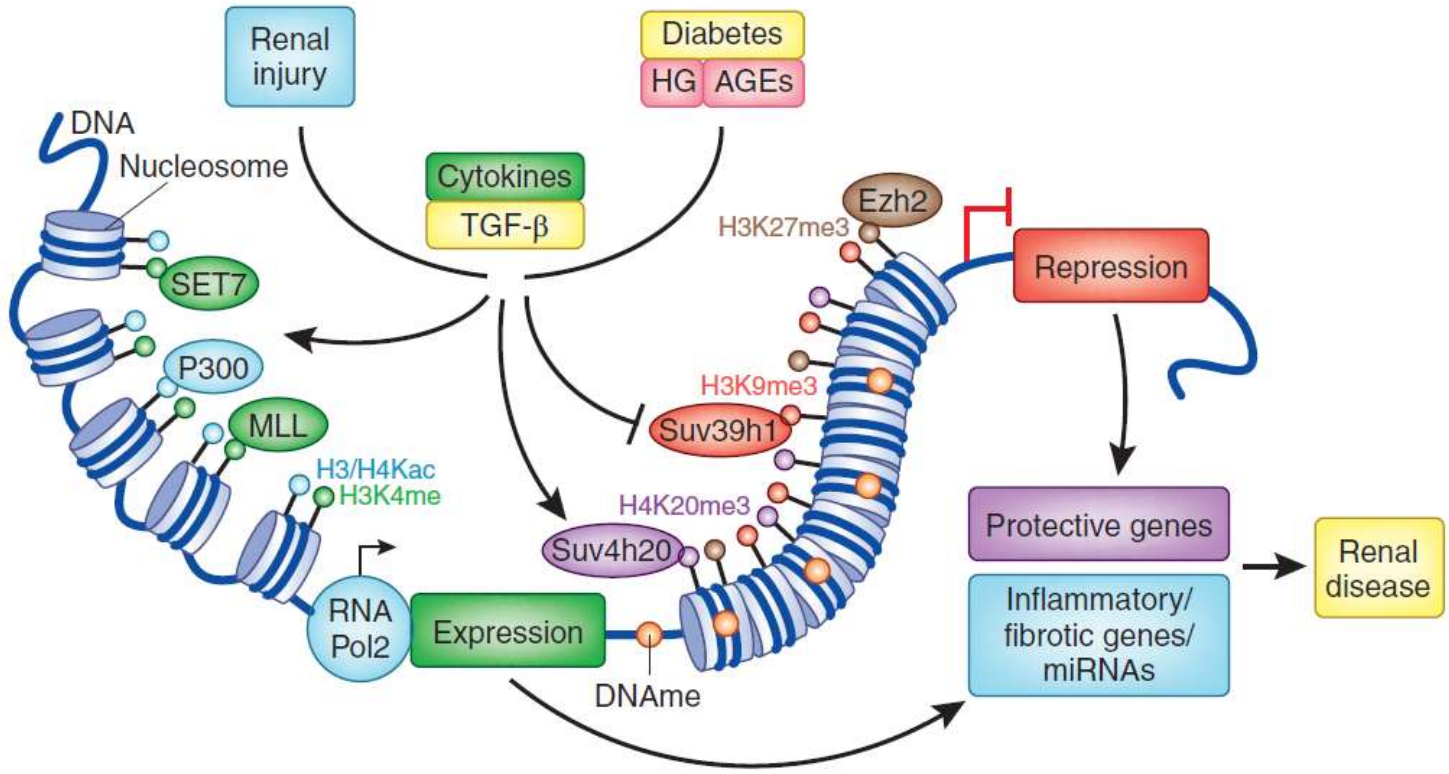
Niels Olsen Saraiva Câmara, Kunitoshi Iseki, Holly Kramer, Zhi-Hong Liu and Kumar Sharma

Effects of adiponectin on podocyte function. |



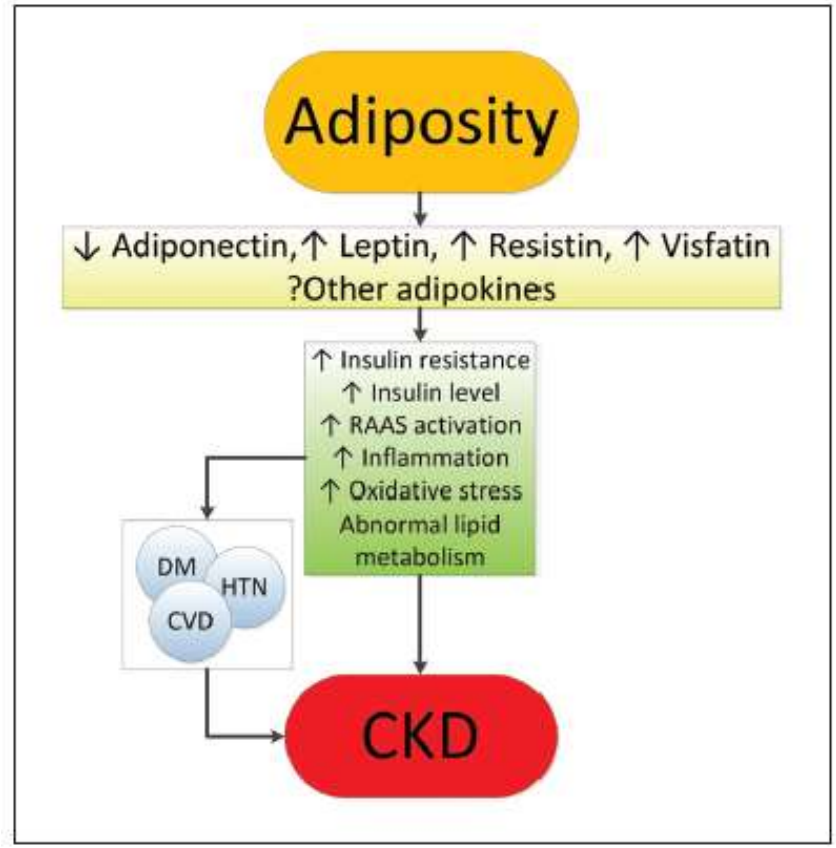
Epigenetics in Diabetic Kidney Disease

Marpadga A. Reddy and Rama Natarajan



J Am Soc Nephrol 22: 2182–2185, 2011

Obesity and Kidney Disease: Hidden Consequences of the Epidemic



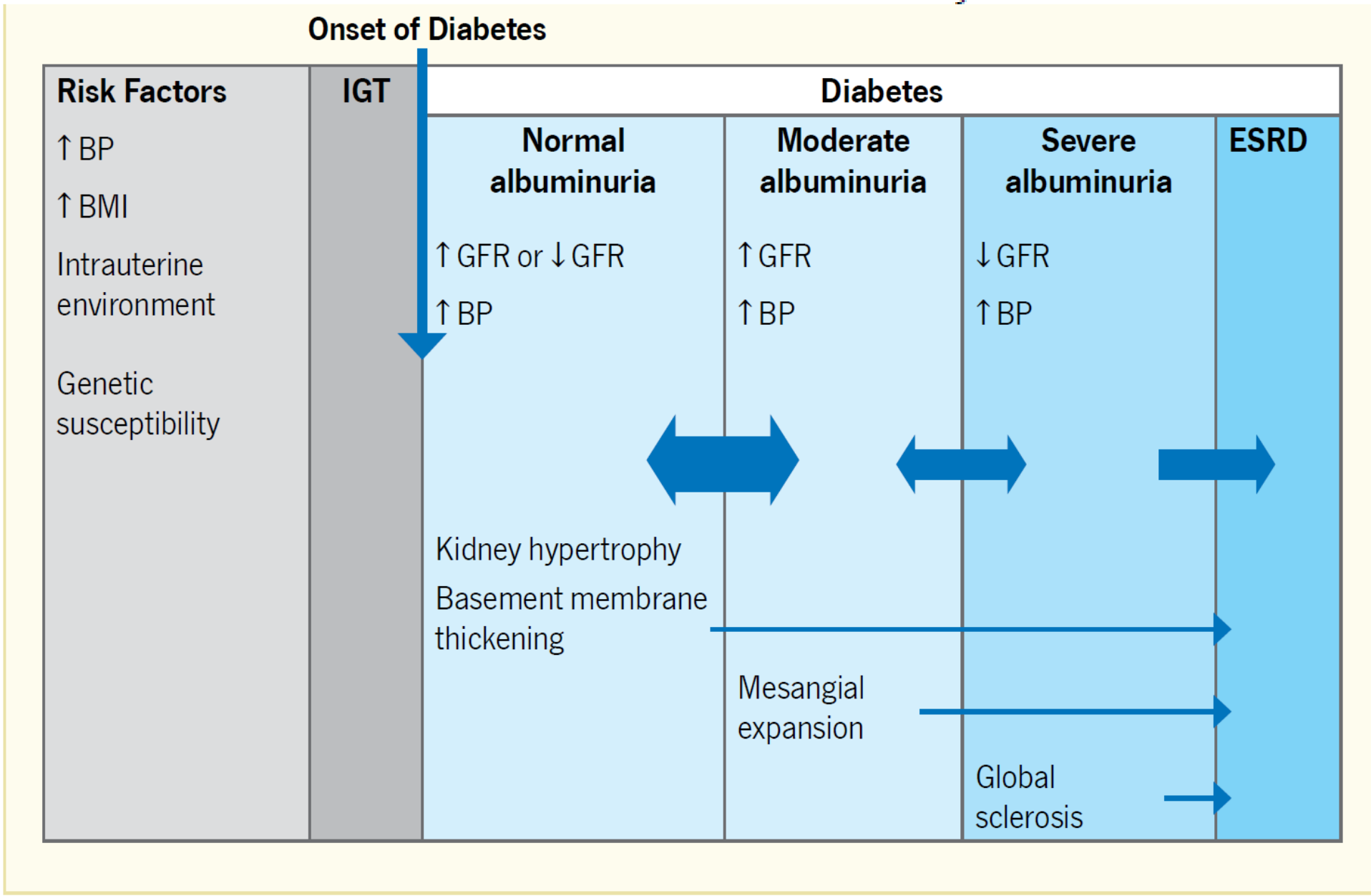
Csaba P. Kovesdy[1]

Canadian Journal of Kidney Health and Disease
Volume 4: 1–10

ΔΙΑΦΟΡΙΚΗ ΔΙΑΓΝΩΣΗ ΧΝΝ

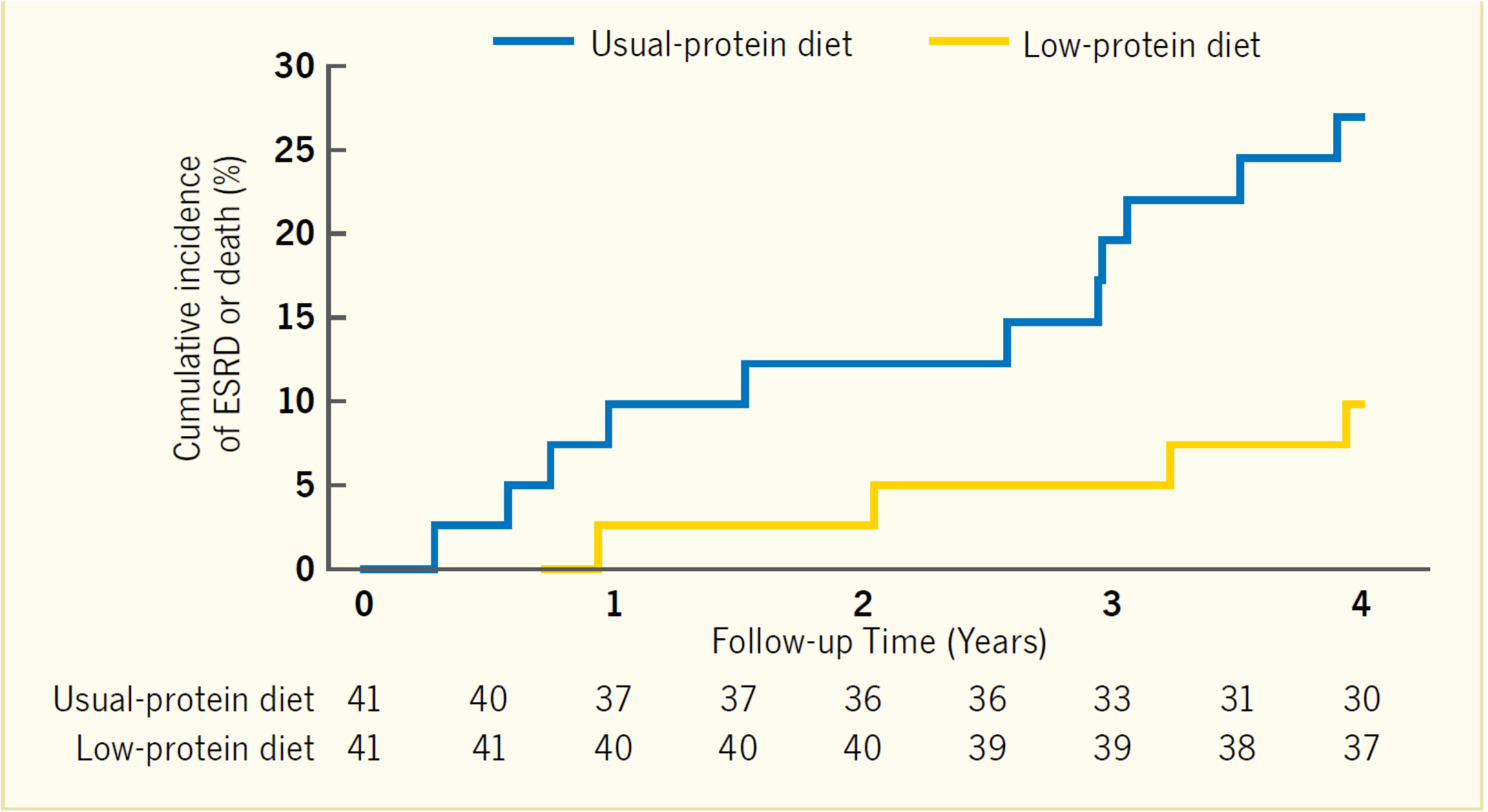
- Μέγεθος νεφρών
- Ίζημα ούρων - κύλινδροι
- Ρυθμός απώλειας GFR
- Ρυθμός αύξησης λευκωματινουρίας

FIGURE 22.3. Risk Factors For and Clinical Course of Kidney Disease in Diabetes



ΘΕΡΑΠΕΥΤΙΚΕΣ ΠΑΡΕΜΒΑΣΕΙΣ

FIGURE 22.53. Cumulative Incidence of End-Stage Renal Disease or Death in Persons With Type 1 Diabetes, by Protein Intake

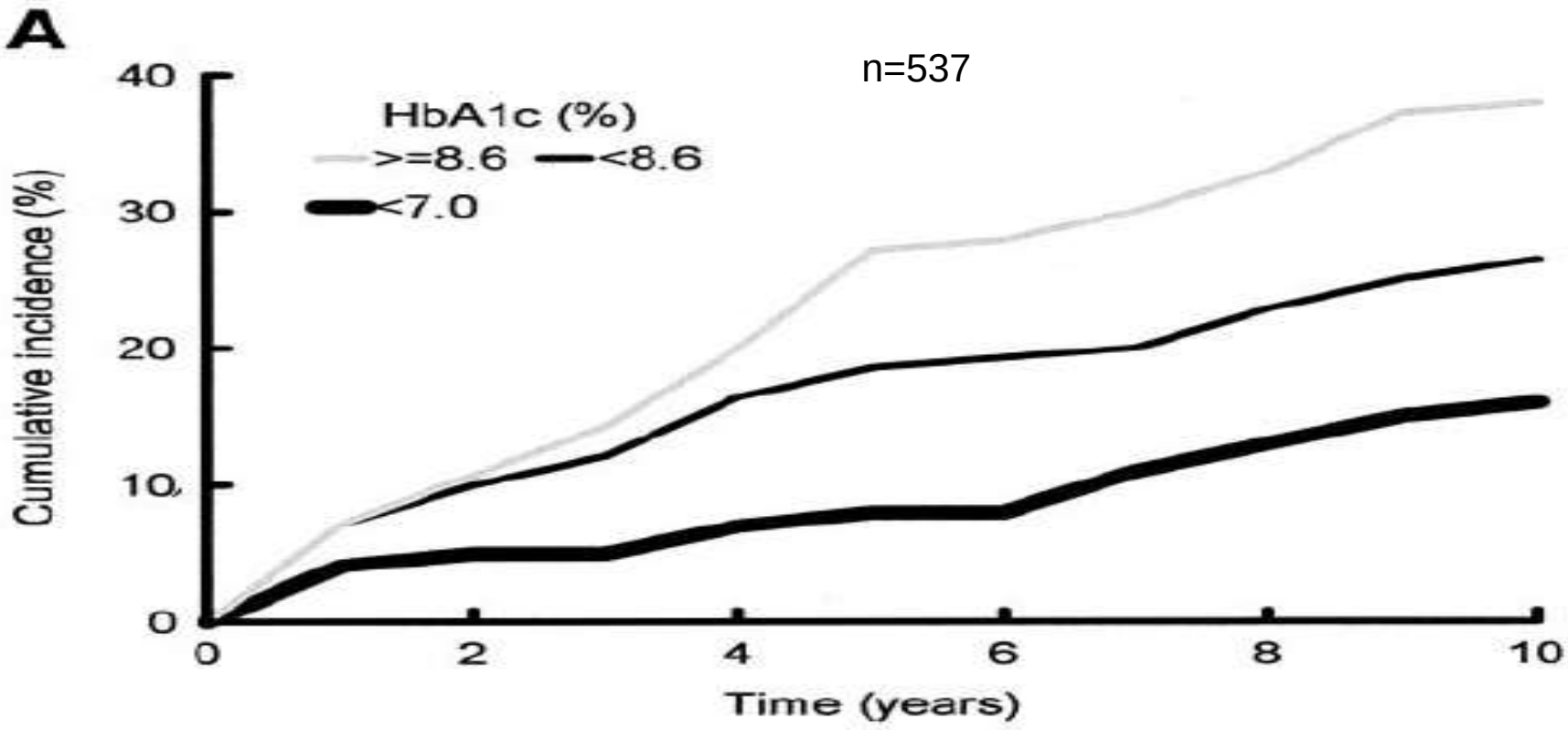


Usual-protein diet	41	40	37	37	36	36	33	31	30
Low-protein diet	41	41	40	40	40	39	39	38	37

Hansen HP et.al., Kidney Int. 62:220,2002

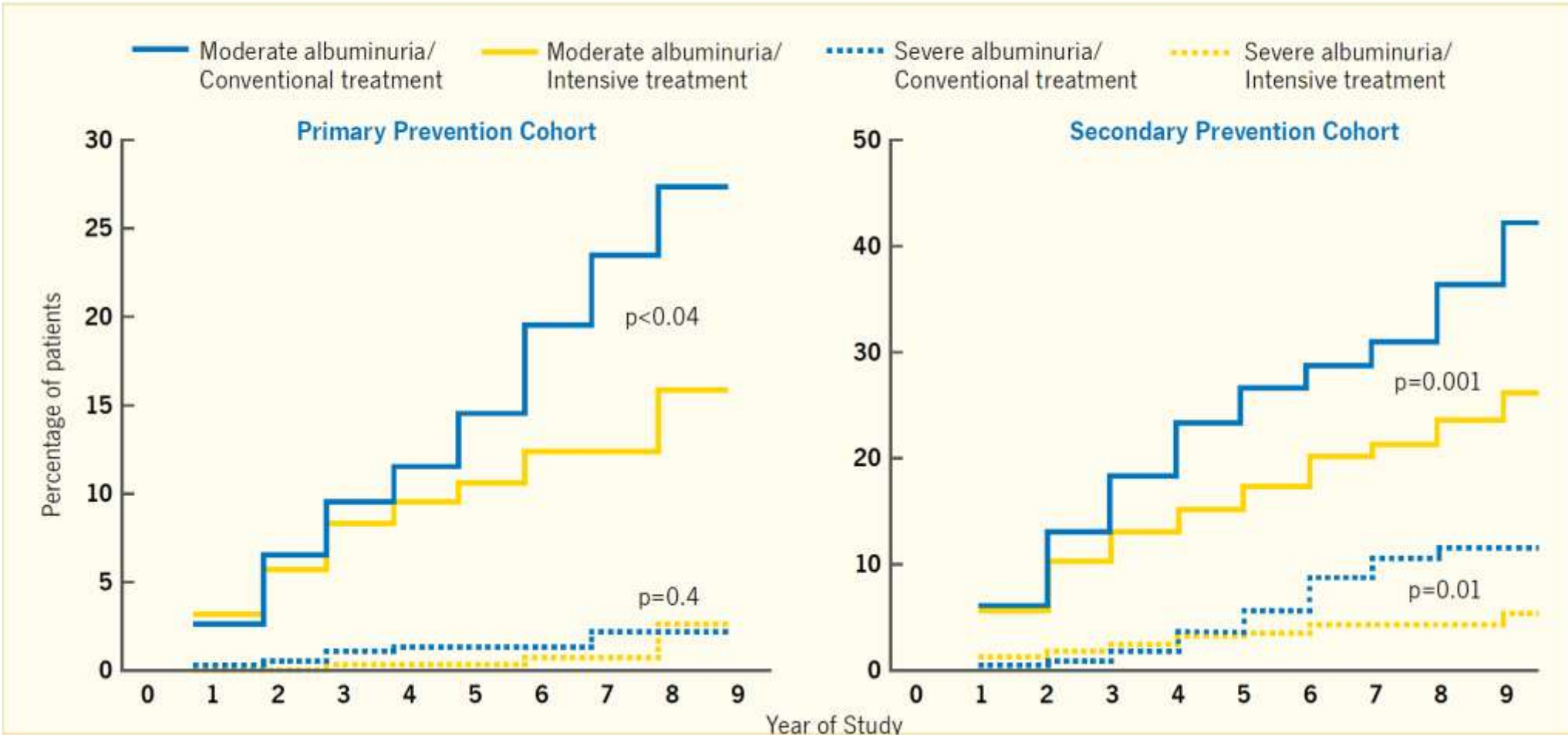
Risk Factors for Development of Incipient and Overt Diabetic Nephropathy in Type 1 Diabetic Patients

A 10-year prospective observational study



Rossing et al, Diabetes Care, 25,5,2003

FIGURE 22.49. Cumulative Incidence of Moderately Elevated Albuminuria and Severe Albuminuria in Participants With Type 1 Diabetes, Diabetes Control and Complications Trial



- 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%). . The Diabetes Control and Complications Trial Research Group. N Engl J Med. 1993;329:977-86.

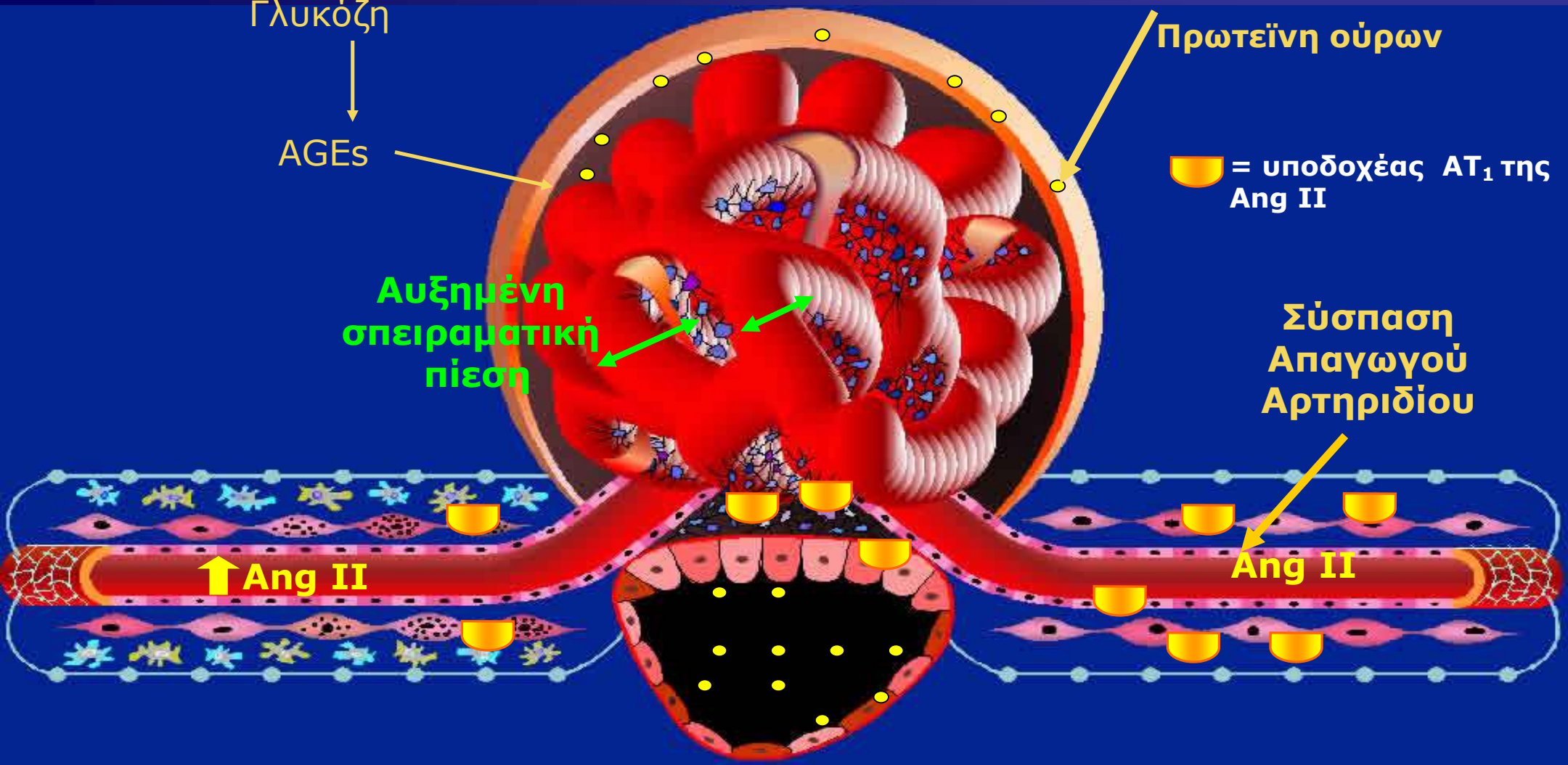
UKPDS: Αποτελέσματα γλυκαιμικού ελέγχου

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

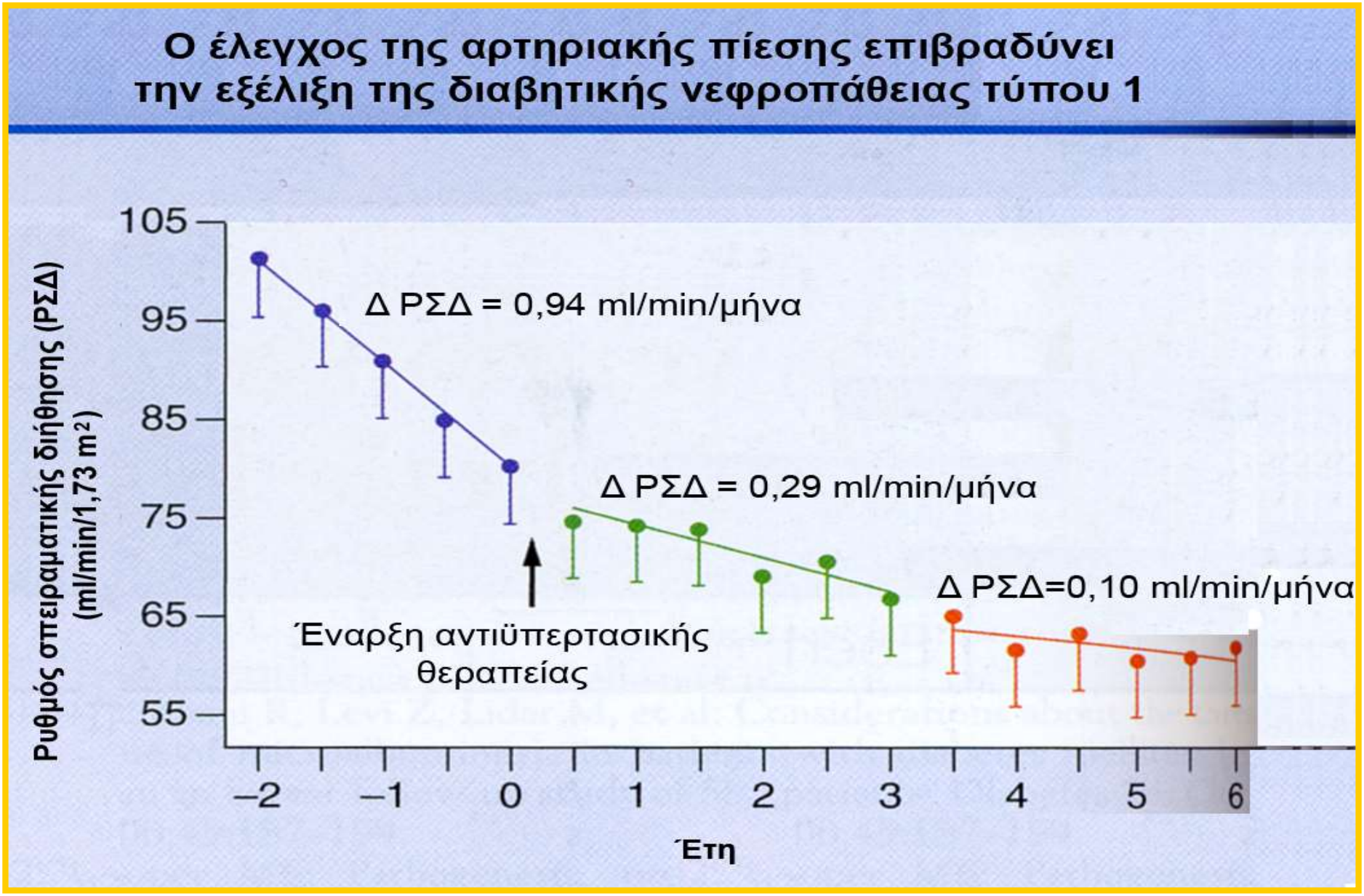
	Μεταβολές στον κίνδυνο*	*P* value
Μικρολευκωματινουρία στα 12 έτη	33% ↓	<0.001

UKPDS Group. *Lancet*. 1998;352:837-853.

Παθογενετικοί μηχανισμοί που οδηγούν σε βλάβη του σπειράματος και πρωτεϊνουρία

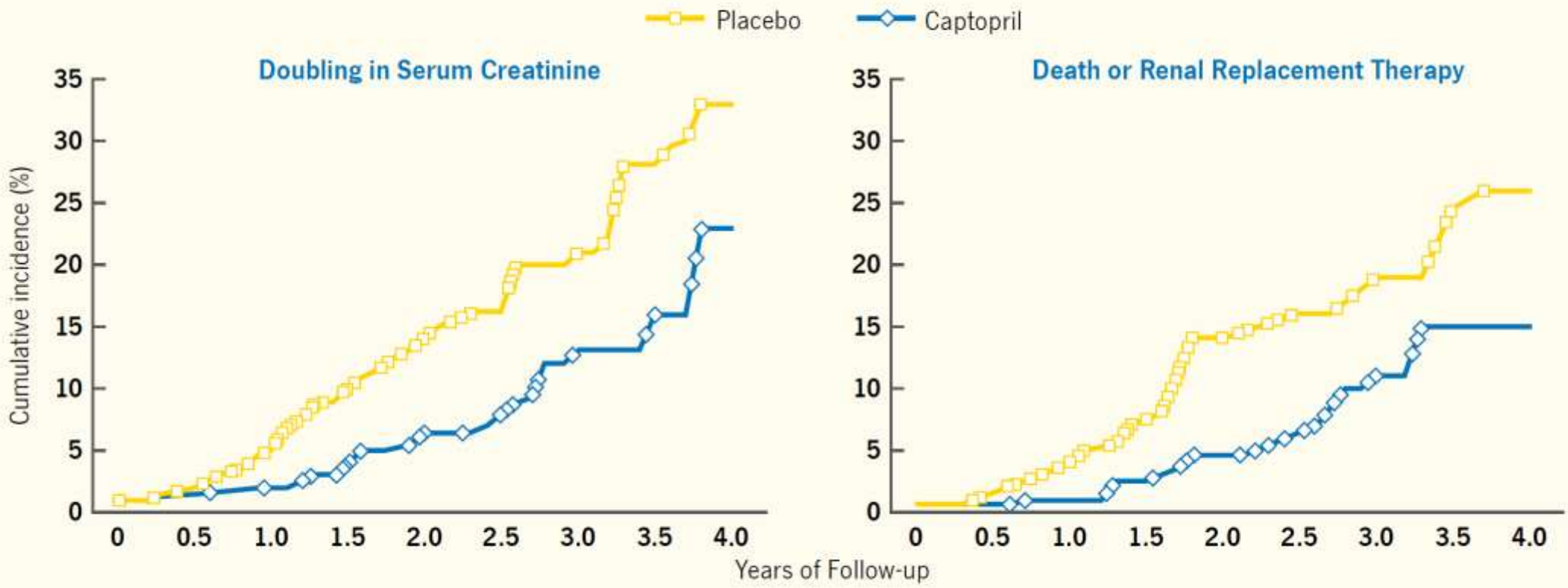


Ο έλεγχος της αρτηριακής πίεσης επιβραδύνει την εξέλιξη της διαβητικής νεφροπάθειας τύπου 1



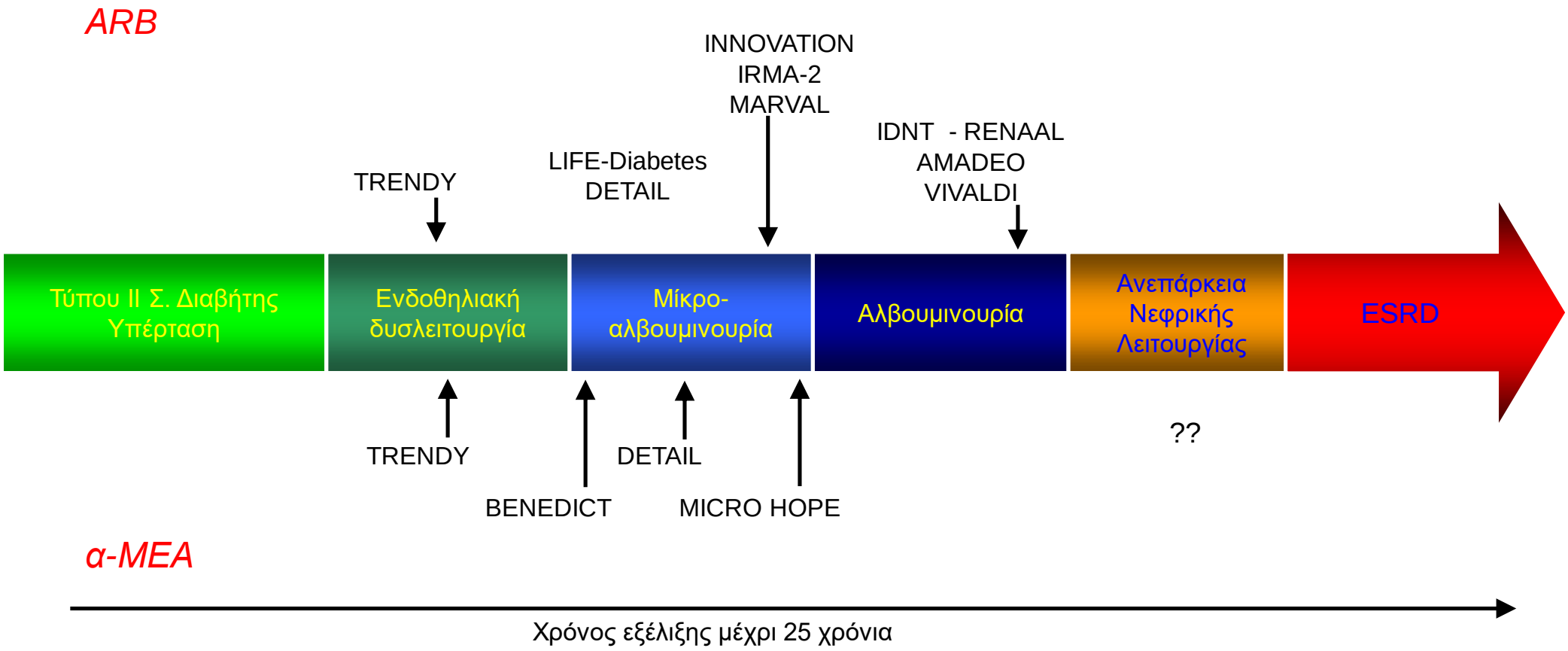
Parving et al, Lancet 1983

FIGURE 22.51. Effect of Captopril on Incidence of Kidney Disease in Persons With Type 1 Diabetes and Proteinuria, 1987–1992



Lewis et.al., N.E.J.M. 329:1456, 1993

Αναστολή της εξέλιξης της διαβητικής νεφροπάθειας μέσω του αποκλεισμού του RAS



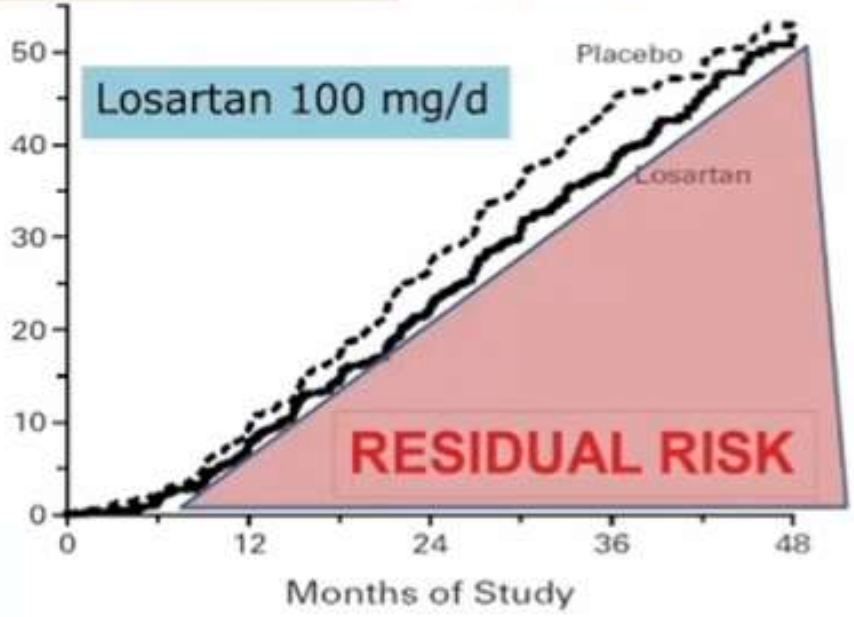
Schmieder RE. J Hypertens.Suppl 2006;24:S31–S35

The Only Proven Treatment for Renoprotection in T2DM-RAS BLOCKERS: RENAAL & IDNT

Doubling of serum creatinine, ESKD, or death

Risk reduction, 16%
P = 0.02

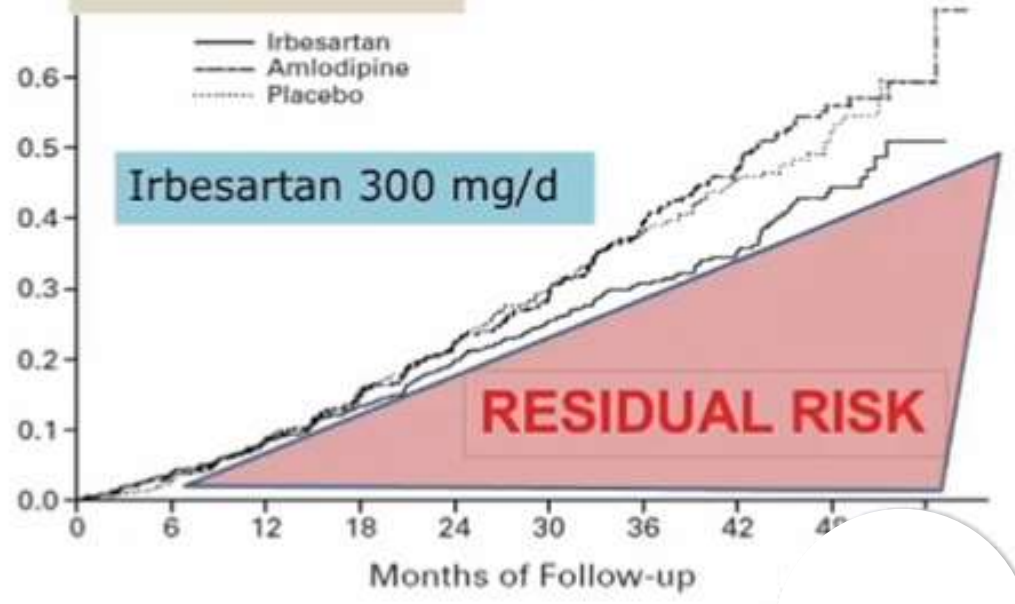
RENAAL



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

Risk reduction, 20%
P = 0.02

IDNT

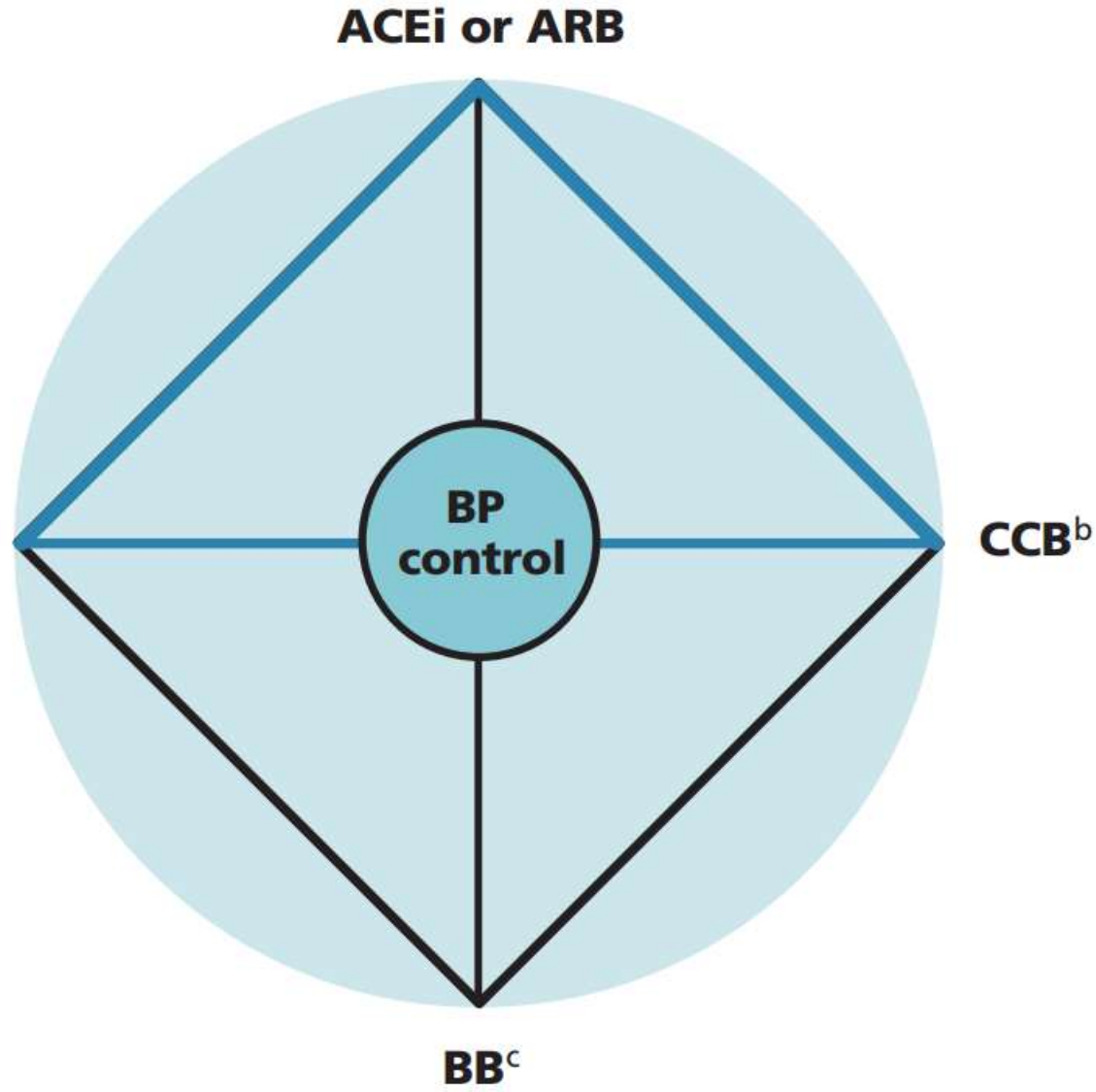


Lewis EJ, et al. *N Eng J Med*. 2001;345(12):851-860.

2023 ESH Guidelines

Prescribing patterns:

- Start with dual combination therapy in most patients
- Uptitrate to maximum well tolerated doses and to triple therapy if needed
- **Once daily (preferred in the morning)**
- **Add further drugs if needed**
- **Preferred use of SPCs at any step**



Additional drug classes

General antihypertensive therapy:

- Steroidal MRA
- Loop Diuretic
- Alpha-1 Blocker
- Centrally acting agent
- Vasodilator

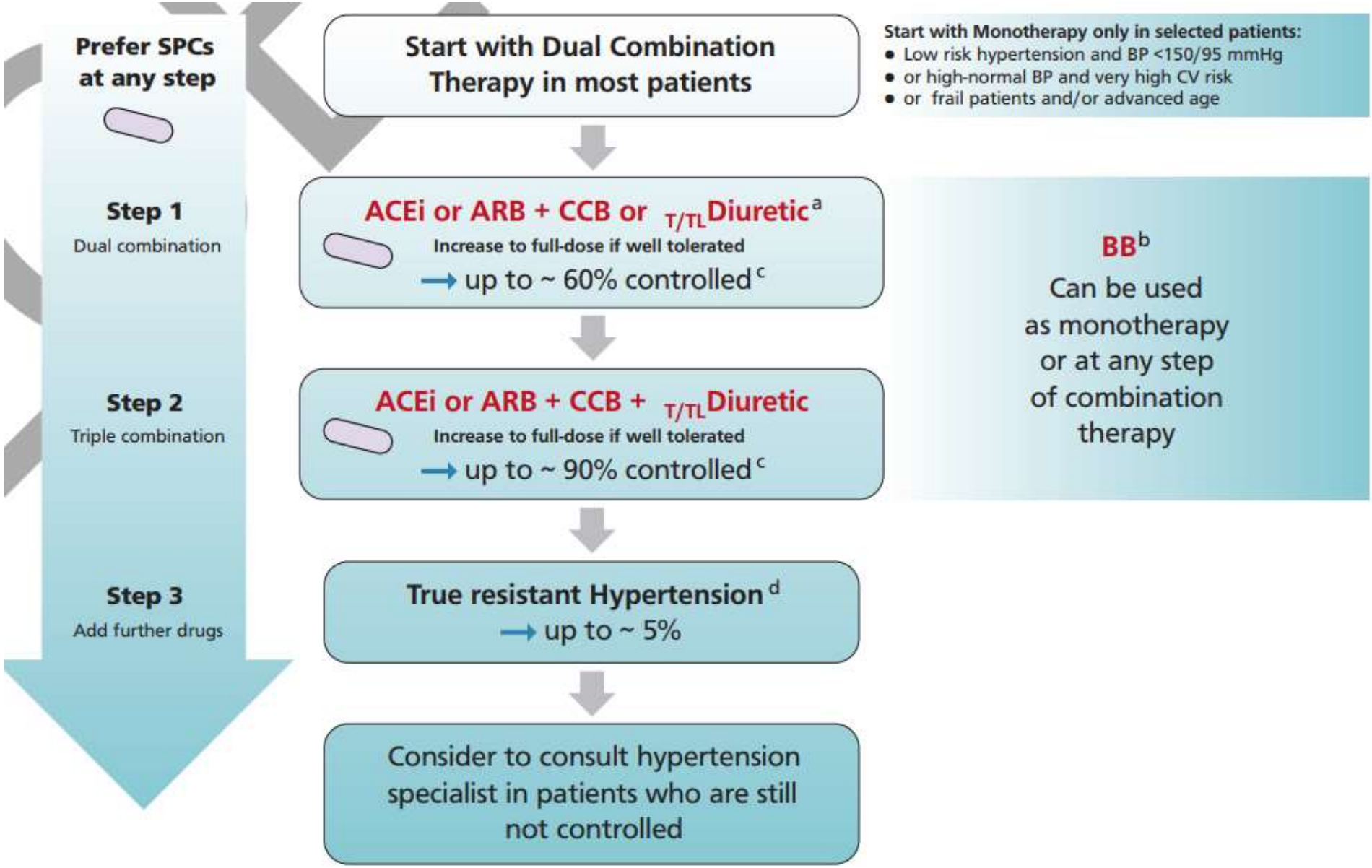
Special comorbidities:

- ARNi
- SGLT2i
- Non-Steroidal MRA

Mancia et al., Journal of Hypertension Volume 41 Number 1 , 2023

2023 ESH Guidelines

Mancia et al., Journal of Hypertension Volume 41 Number 1 , 2023



USE OF GLUCOSE-LOWERING MEDICATIONS IN THE MANAGEMENT OF TYPE 2 DIABETES

HEALTHY LIFESTYLE BEHAVIORS; DIABETES SELF-MANAGEMENT EDUCATION AND SUPPORT (DSMES); SOCIAL DETERMINANTS OF HEALTH (SDOH)

TO AVOID THERAPEUTIC INERTIA REASSESS AND MODIFY TREATMENT REGULARLY (3–6 MONTHS)

Goal: Cardiorenal Risk Reduction in High-Risk Individuals with Type 2 Diabetes (in addition to comprehensive CV risk management)*

+ASCVD†

Defined differently across CVOTs but all included individuals with established CVD (e.g., MI, stroke, any revascularization procedure). Variably included: conditions such as transient ischemic attack, unstable angina, amputation, symptomatic or asymptomatic coronary artery disease.

+Indicators of high risk

While definitions vary, most comprise ≥55 years of age with two or more additional risk factors (including obesity, hypertension, smoking, dyslipidemia, or albuminuria)

+ASCVD/Indicators of High Risk

GLP-1 RA# with proven CVD benefit — EITHER/OR — SGLT2i§ with proven CVD benefit

If A1C above target

- For patients on a GLP-1 RA, consider adding SGLT2i with proven CVD benefit or vice versa
- TZD^

+HF

Current or prior symptoms of HF with documented HFrEF or HFpEF

+HF

SGLT2i§ with proven HF benefit in this population

+CKD

eGFR <60 mL/min per 1.73 m² OR albuminuria (ACR ≥3.0 mg/mmol [30 mg/g]). These measurements may vary over time; thus, a repeat measure is required to document CKD.

+CKD (on maximally tolerated dose of ACEI/ARB)

PREFERABLY

SGLT2i§ with primary evidence of reducing CKD progression

Use SGLT2i in people with an eGFR ≥20 mL/min per 1.73 m²; once initiated should be continued until initiation of dialysis or transplantation

OR

GLP-1 RA with proven CVD benefit if SGLT2i not tolerated or contraindicated

If A1C above target, for patients on SGLT2i, consider incorporating a GLP-1 RA or vice versa

If additional cardiorenal risk reduction or glycemic lowering needed

Goal: Achievement and Maintenance of Glycemic and Weight Management Goals

Glycemic Management: Choose approaches that provide the efficacy to achieve goals:

Metformin OR Agent(s) including COMBINATION therapy that provide adequate EFFICACY to achieve and maintain treatment goals

Prioritize avoidance of hypoglycemia in high-risk individuals

In general, higher efficacy approaches have greater likelihood of achieving glycemic goals

Efficacy for glucose lowering

Very High:
Dulaglutide (high dose), Semaglutide, Tirzepatide
Insulin
Combination Oral, Combination Injectable (GLP-1 RA/Insulin)

High:
GLP-1 RA (not listed above), Metformin, SGLT2i, Sulfonylurea, TZD

Intermediate:
DPP-4i

Achievement and Maintenance of Weight Management Goals:

Set individualized weight management goals

General lifestyle advice: medical nutrition therapy/eating patterns/physical activity

Intensive evidence-based structured weight management program

Consider medication for weight loss

Consider metabolic surgery

When choosing glucose-lowering therapies:

Consider regimen with high-to-very-high dual glucose and weight efficacy

Efficacy for weight loss

Very High:
Semaglutide, Tirzepatide

High:
Dulaglutide, Liraglutide

Intermediate:
GLP-1 RA (not listed above), SGLT2i

Neutral:
DPP-4i, Metformin

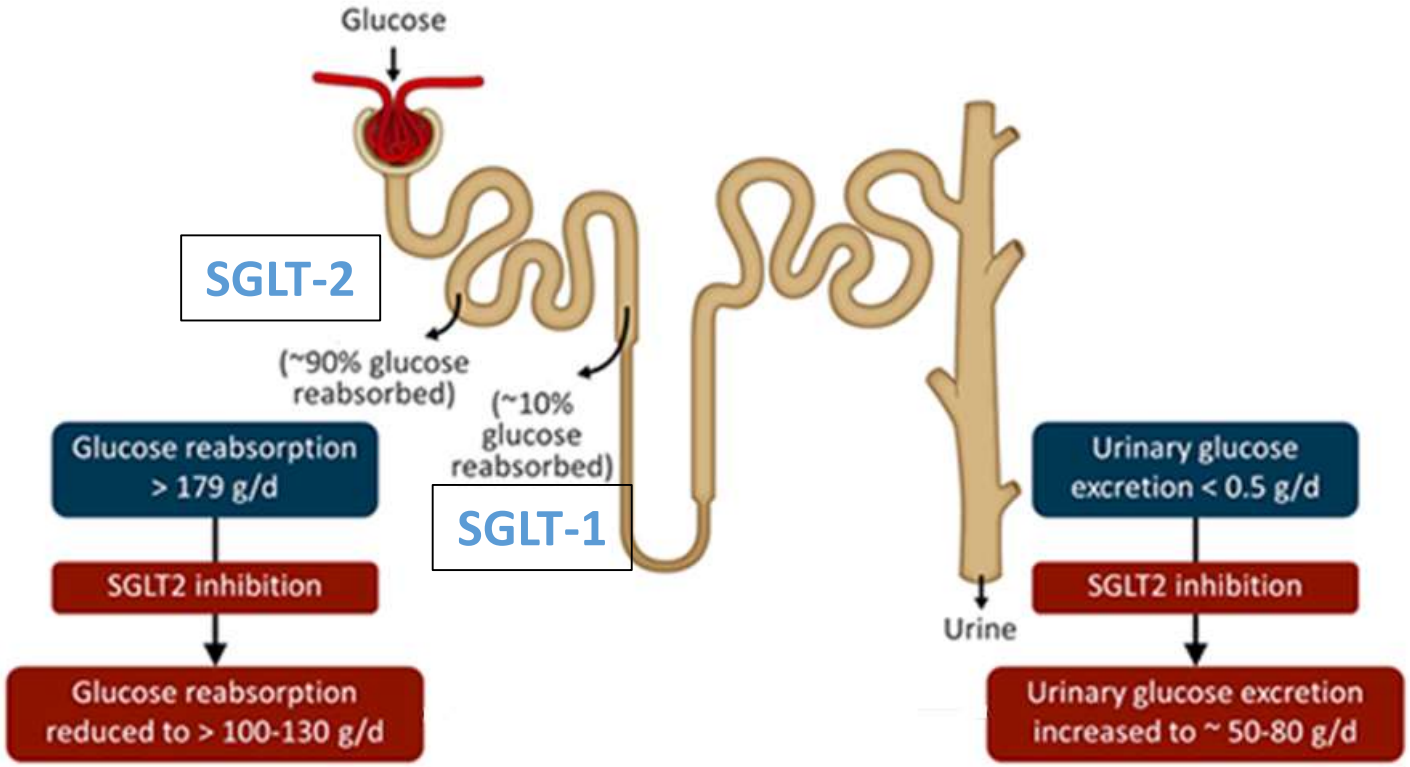
If A1C above target

Identify barriers to goals:

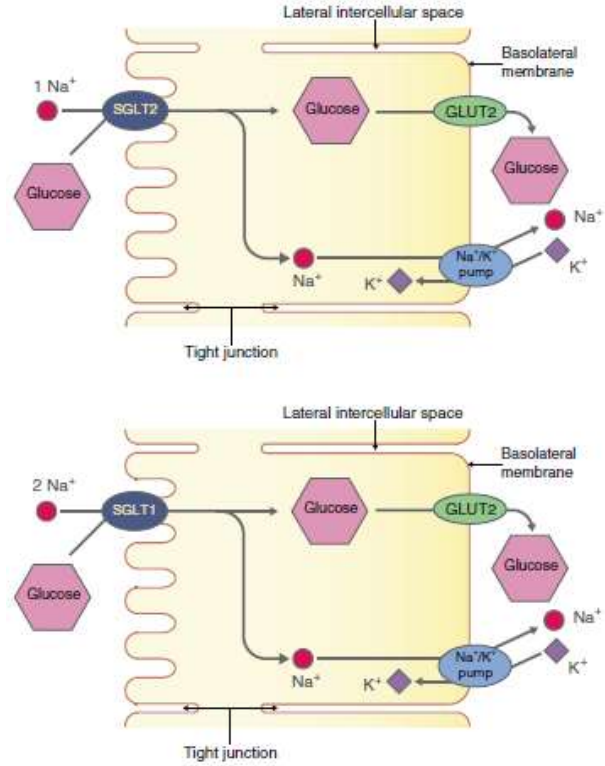
- Consider DSMES referral to support self-efficacy in achievement of goals
- Consider technology (e.g., diagnostic CGM) to identify therapeutic gaps and tailor therapy
- Identify and address SDOH that impact achievement of goals

* In people with HF, CKD, established CVD, or multiple risk factors for CVD, the decision to use a GLP-1 RA or SGLT2i with proven benefit should be independent of background use of metformin; † A strong recommendation is warranted for people with CVD and a weaker recommendation for those with indicators of high CV risk. Moreover, a higher absolute risk reduction and thus lower numbers needed to treat are seen at higher levels of baseline risk and should be factored into the shared decision-making process. See text for details; ^ Low-dose TZD may be better tolerated and similarly effective; § For SGLT2i, CV/renal outcomes trials demonstrate their efficacy in reducing the risk of composite MACE, CV death, all-cause mortality, MI, HHF, and renal outcomes in individuals with T2D with established/high risk of CVD; # For GLP-1 RA, CVOTs demonstrate their efficacy in reducing composite MACE, CV death, all-cause mortality, MI, stroke, and renal endpoints in individuals with T2D with established/high risk of CVD.

Αναστολείς SGLT



Nauck Drug Design, Development and Therapy. 2014;8:1335



Ghezzi Diabetologia (2018) 61:2087

Αναστολείς SGLT-2

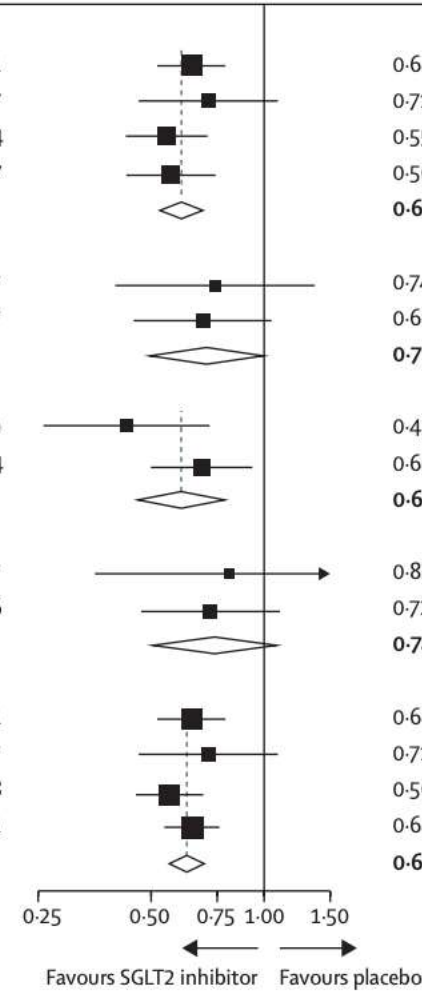
	Αναστολή SGLT	Δοσολογία (pos)	Συχνότητα χορήγησης	Μεταβολισμός	Ηπατική λειτουργία	Νεφρική λειτουργία
Dapafliflozin	2	5mg, 10mg	1 φορά ημερησίως	ήπαρ, νεφροί	Child-Pugh class C 5mg→10mg	έναρξη >25 $mL \cdot min^{-1} \cdot 1.73\ m^{-2}$
Empagliflozin	2	10mg, 25mg	1 φορά ημερησίως	Glucuronosyl transferases UG2B7, UGT1A3, UGT1A8, UGT1A9	Child-Pugh class C δεν συνιστάται	έναρξη >30 $mL \cdot min^{-1} \cdot 1.73\ m^{-2}$
Canagliflozin	1 και 2	100mg, 300mg	1 φορά ημερησίως	ήπαρ	Child-Pugh class C δεν συνιστάται	έναρξη >30 $mL \cdot min^{-1} \cdot 1.73\ m^{-2}$

Effects of SGLT2 on kidney disease progression

Collaborative meta-analysis of large placebo-controlled trials

	Mean baseline eGFR, mL/min per 1·73m²	Events/participants		Event rate per 1000 patient-years		RR (95% CI)
		SGLT2 inhibitor	Placebo	SGLT2inhibitor	Placebo	
Diabetic kidney disease or nephropathy*						
CREDENCE	56	153/2202	230/2199	27	41	0·64 (0·52–0·79)
SCORED	44	37/5292	52/5292	5	7	0·71 (0·46–1·08)
DAPA–CKD	43	93/1271	157/1239	36	64	0·55 (0·43–0·71)
EMPA–KIDNEY	36	85/1032	133/1025	42	67	0·56 (0·43–0·74)
Subtotal	**46**	**368/9797**	**572/9755**	..	..	**0·60 (0·53–0·69)**
Ischaemic and hypertensive kidney disease						
DAPA–CKD	43	18/324	26/363	28	37	0·74 (0·40–1·36)
EMPA–KIDNEY	35	37/706	52/739	27	37	0·69 (0·45–1·05)
Subtotal	**38**	**55/1030**	**78/1102**	..	..	**0·70 (0·50–1·00)**
Glomerular disease						
DAPA–CKD	43	21/343	46/352	33	70	0·43 (0·26–0·72)
EMPA–KIDNEY	42	69/853	95/816	44	64	0·68 (0·50–0·93)
Subtotal	**42**	**90/1196**	**141/1168**	..	..	**0·60 (0·46–0·78)**
Other kidney disease or unknown						
DAPA–CKD	43	10/214	14/198	25	37	0·81 (0·35–1·83)
EMPA–KIDNEY	36	36/713	52/725	26	36	0·72 (0·47–1·10)
Subtotal	**38**	**46/927**	**66/923**	..	..	**0·74 (0·51–1·08)**
Any diagnosis						
CREDENCE	56	153/2202	230/2199	27	41	0·64 (0·52–0·79)
SCORED	44	37/5292	52/5292	5	7	0·71 (0·46–1·08)
DAPA–CKD	43	142/2152	243/2152	33	58	0·56 (0·45–0·68)
EMPA–KIDNEY	37	227/3304	332/3305	36	52	0·64 (0·54–0·76)
Total	**44**	**559/12 950**	**857/12 948**	..	..	**0·62 (0·56–0·69)**

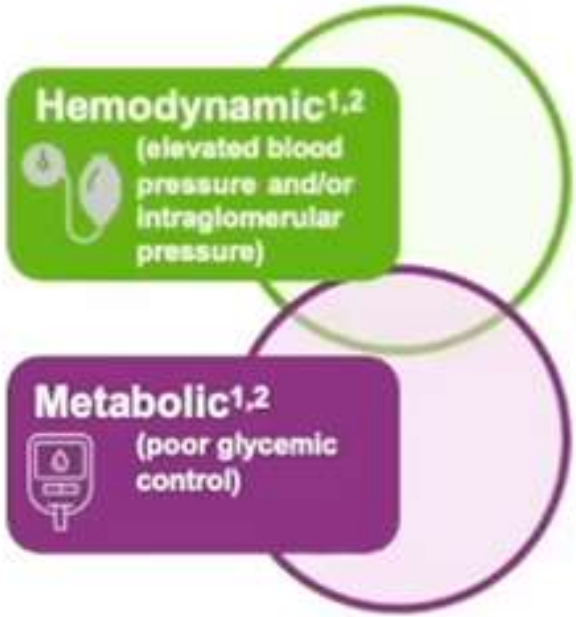
Heterogeneity across groups of primary kidney disease: p=0·67
Trend across trials sorted by eGFR for any diagnosis: p=0·88



Lancet 2022; 400: 1788–801

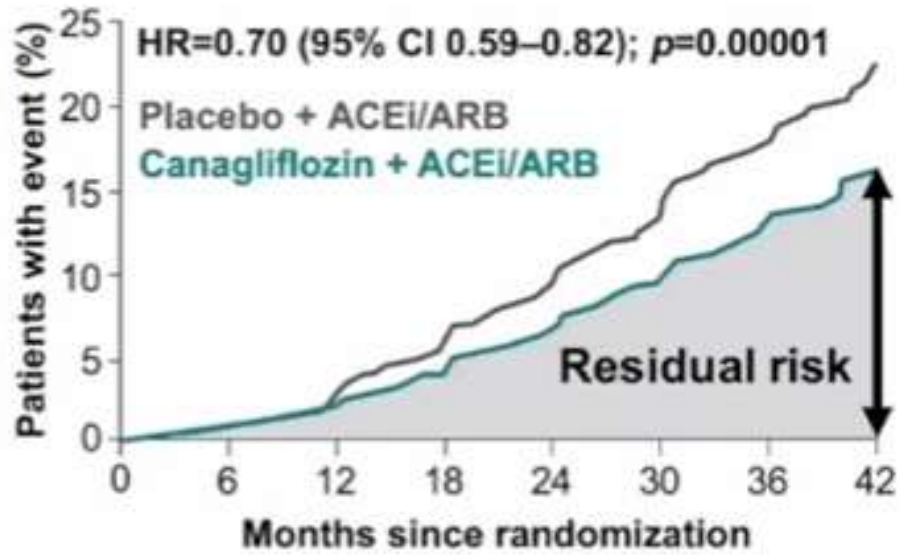
Adding NS-MRA rationale

High residual risk of CKD progression with current therapies



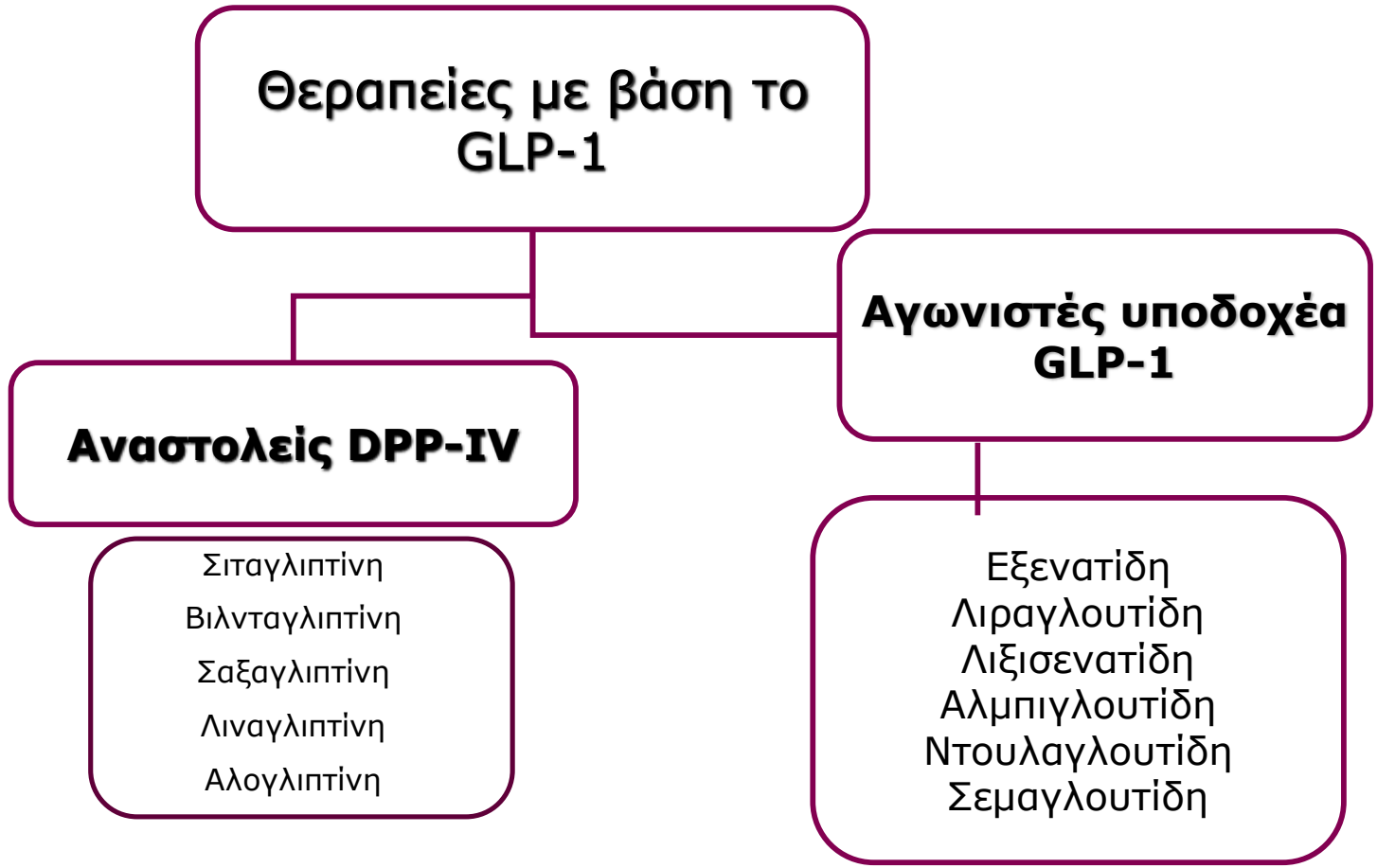
CREDENCE[3]

Cardiorenal composite endpoint*



1. Alicic RZ, *et al. Clin J Am Soc Nephrol* 2017;12:2032; 2. Mora-Fernández C, *et al. J Physiol* 2014;18:3997;
3. Perkovic V, *et al. N Engl J Med* 2019;380:2295

Ταξινόμηση θεραπειών που βασίζονται στο GLP-1

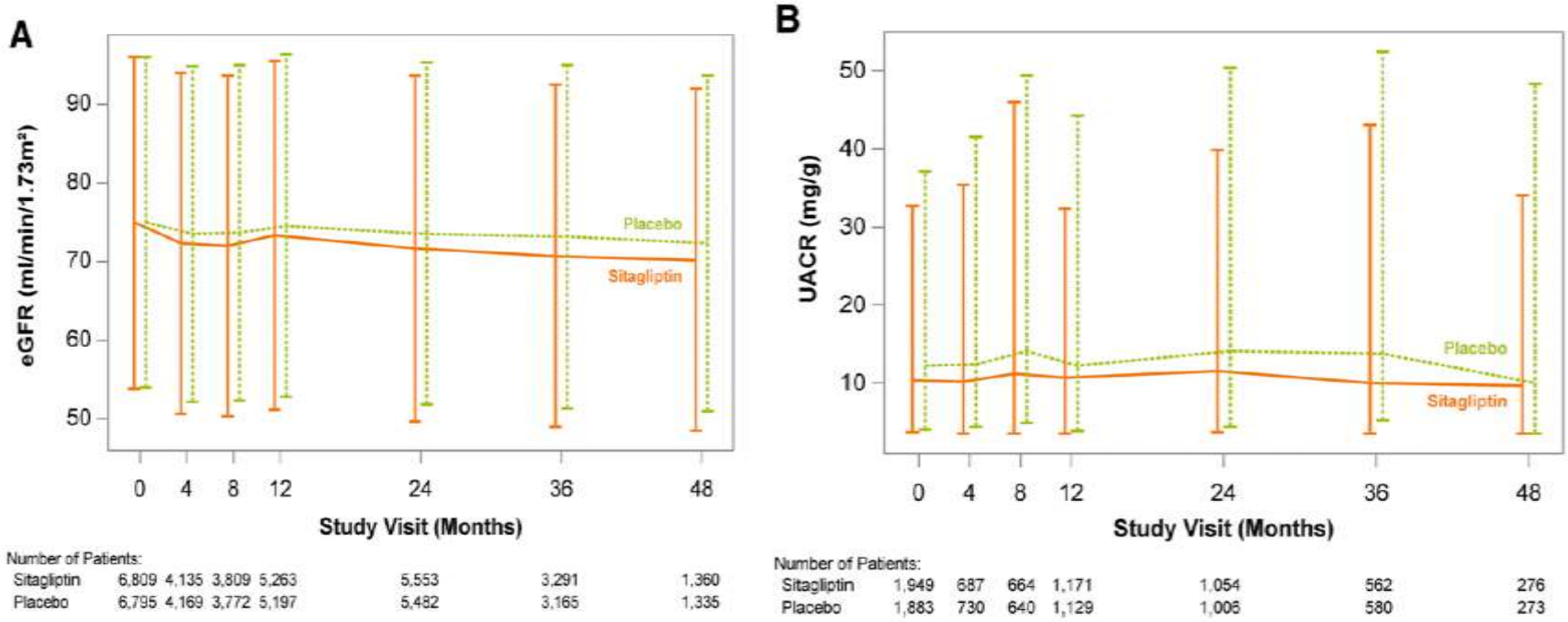


Diabetes Care

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,[5] Lee-Ming Chuang,[6] Samuel S. Engel,[8] Renato D. Lopes,[7] Darren K. McGuire,[7] Axel Riefflin,[9] Helena Wachtlicht Rodbard,[10] Isaac Shaw,[11] Tiwtakina Tankova,[12] Julie Wennstein,[13] Eric D. Peterson,[7] and Rury R. Holman,[14] on behalf of the TECOS Study Group



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

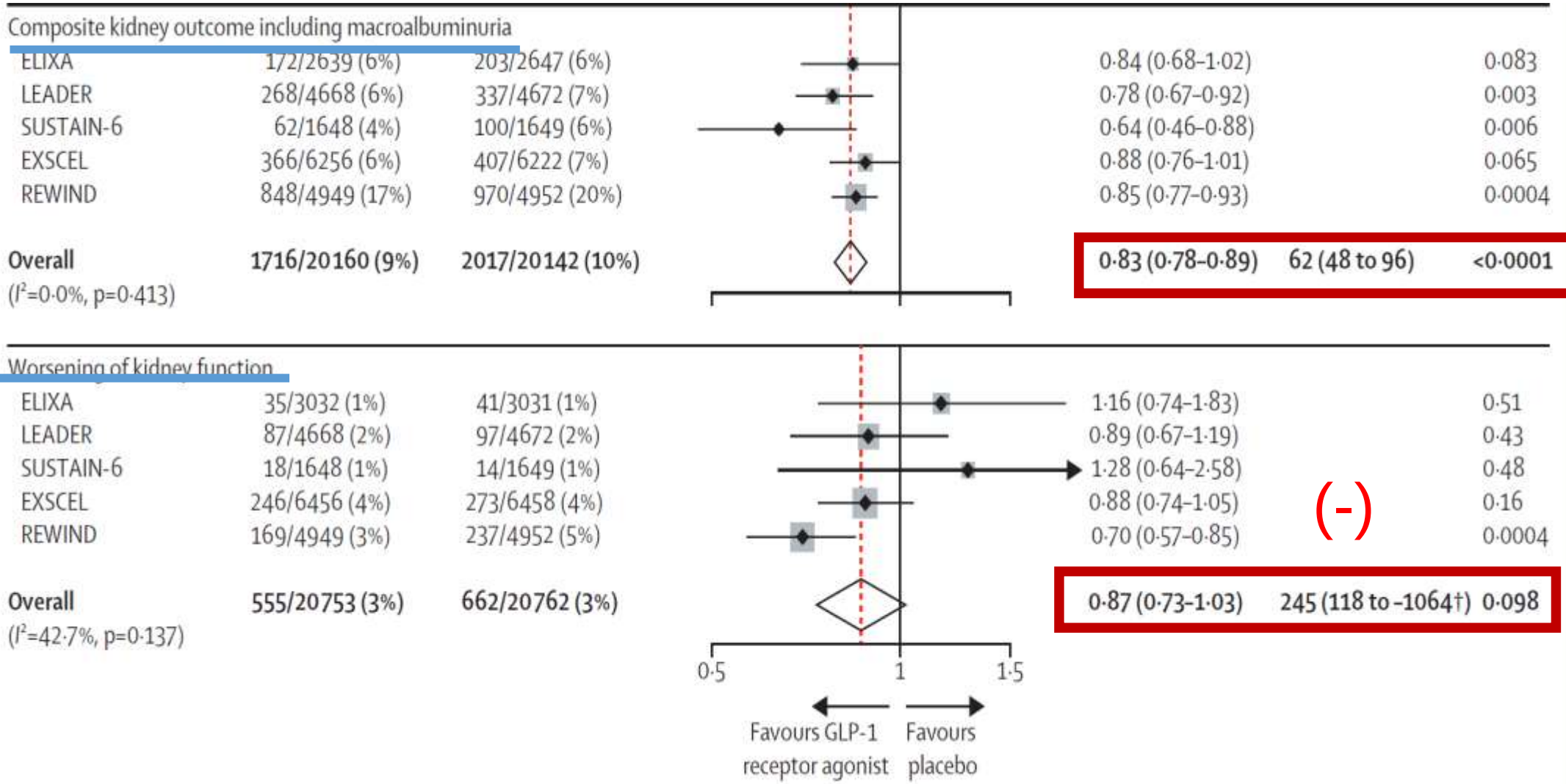
Cornel JH et al, Diabetes Care. 2016 Oct 14. pii: dc161415. [Epub ahead of print]

GLP-1 ανάλογα

		Δοσολογία (sc)	Συχνότητα χορήγησης	Χορήγηση πριν το γεύμα	Μεταβολισμός	Ηπατική λειτουργία	Νεφρική λειτουργία
Βραχείας δράσης	Exenatide standard release	5μg → 10μg	2 φορές ημερησίως	Ναι	νεφροί	Ίδια δόση	>30 mL·min^{-1}·1.73 m^{-2} 30-50: 5μg → 10μg <30 όχι
	Lixisenatide	10μg → 20μg	1 φορά ημερησίως	Ναι	νεφροί	Ίδια δόση	>30 mL·min^{-1}·1.73 m^{-2} <30 όχι
Μακράς δράσης	Liraglutide	0,6mg →1,2mg → 1,8mg	1 φορά ημερησίως	Όχι	μεταβολισμός πεπτιδίων	Ίδια δόση	>15 mL·min^{-1}·1.73 m^{-2} <15 περιορισμένα δεδομένα
	Exenatide modified release	2 mg	1 φορά εβδομαδιαία	Όχι	νεφροί	Ίδια δόση	>50 mL·min^{-1}·1.73 m^{-2} 30-50: περιορισμένα δεδομένα <30 όχι
	Albiglutide	30 mg → 50mg	1 φορά εβδομαδιαία	Όχι	μεταβολισμός πεπτιδίων	Ίδια δόση	>30 mL·min^{-1}·1.73 m^{-2} <30 περιορισμένα δεδομένα
	Dulaglutide	0,75mg → 1,5mg	1 φορά εβδομαδιαία	Όχι	μεταβολισμός πεπτιδίων	Ίδια δόση	>15 mL·min^{-1}·1.73 m^{-2} <15 περιορισμένα δεδομένα
	Semaglutide*	0,25mg → 0,5mg – 1mg	1 φορά εβδομαδιαία	Όχι	μεταβολισμός πεπτιδίων	Ίδια δόση	>15 mL·min^{-1}·1.73 m^{-2} <15 περιορισμένα δεδομένα

*υπό ανάπτυξη χορήγηση semaglutide από το στόμα

GLP-1RA vs placebo στις CVOT μελέτες :
Η επίδραση στις νεφρικές εκβάσεις



Kristensen et *Lancet Diabetes Endocrinol* 2019

11/10/2023at 10:02PHARMA & BIOTECH

Novo Nordisk stops trials in kidney patients early after efficacy results

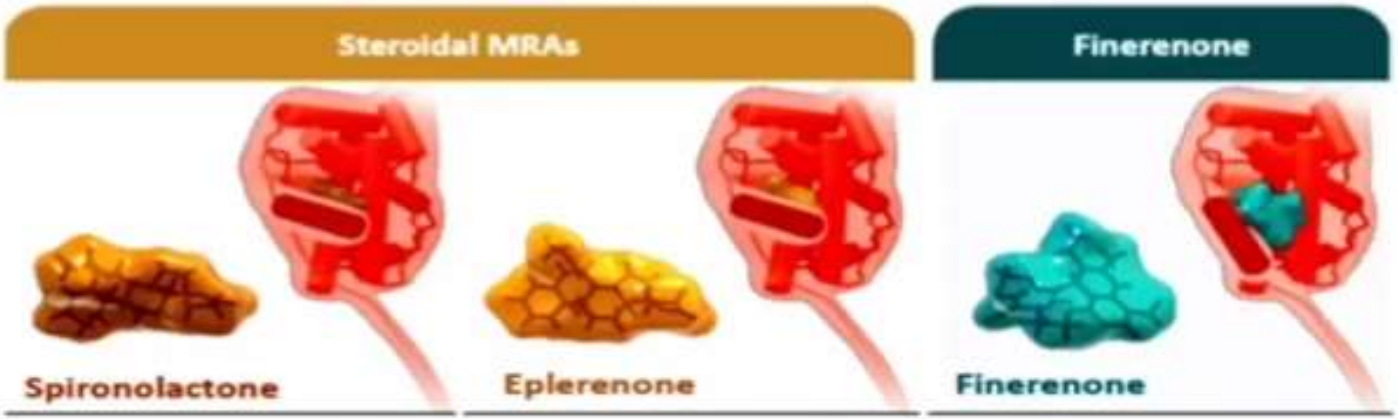
The group expects results from the Flow study to be presented in the first half of 2024.

BY MARKETWIRE

"The decision to stop the trial is based on a recommendation from the independent data monitoring committee which concluded that the results from an interim analysis met certain predetermined criteria for stopping the trial early due to efficacy," the announcement states. Novo Nordisk will close the study on this basis, but the results will be blinded to Novo Nordisk for the continued "integrity" of the trial.

The Danish pharmaceutical group expects results from the Flow study to be presented in the first half of 2024.

Comparison of MRA inhibitors: Steroidal and Non-steriodal

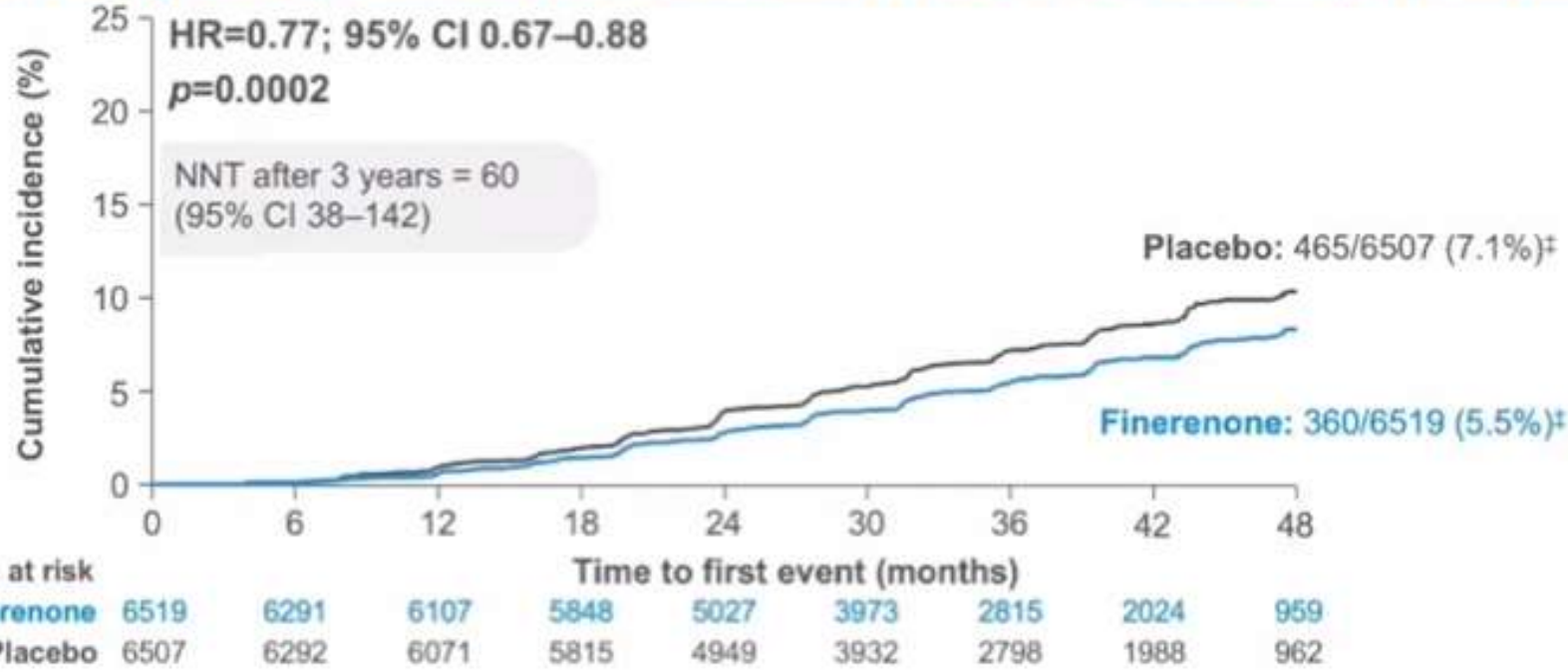


	Spironolactone	Eplerenone	Finerenone
Structural properties	Flat (steroidal)	Flat (steroidal)	Bulky (nonsteroidal)
Potency to MR	+++	+	+++
Selectivity to MR	+	++	+++
CNS penetration	+	+	-
Sexual side effects	++	(+)	-
Half-life	> 20 hours	4-6 hours	2-3 hours
Active metabolites	++	-	-
Effect on BP	+++	++	+

Kintscher U, Bakris GL, and Kolkhof P. Br J Pharmacol 2022;179:3220-3234

FIDELITY pooled analysis: Effect of finerenone on the ≥57% eGFR kidney composite outcome

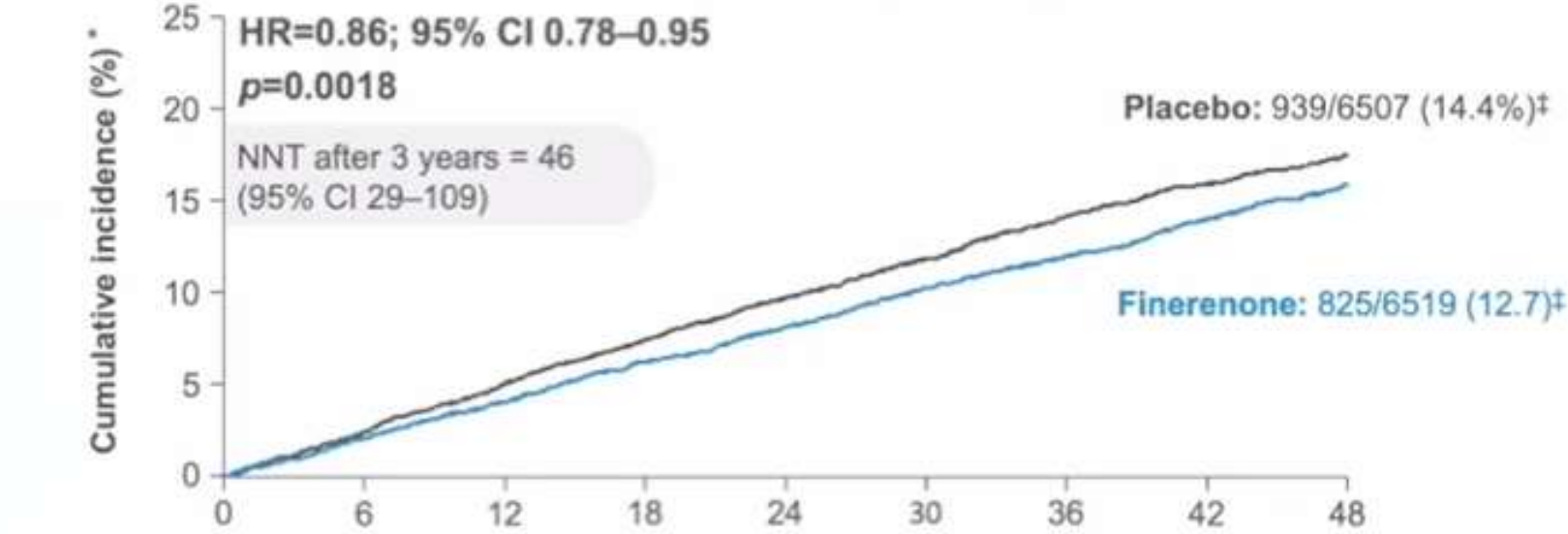
Time to kidney failure,* sustained ≥57% decrease in eGFR from baseline, or renal death#



Agarwal R, Filipattos G, et.al….and Bakris GL, Eur Heart J 2022 ;43:474-484

FIDELITY pooled analysis: Finerenone significantly reduced the risk of the CV composite outcome by 14%

Time to CV death, non-fatal MI, non-fatal stroke, or hospitalisation for HF

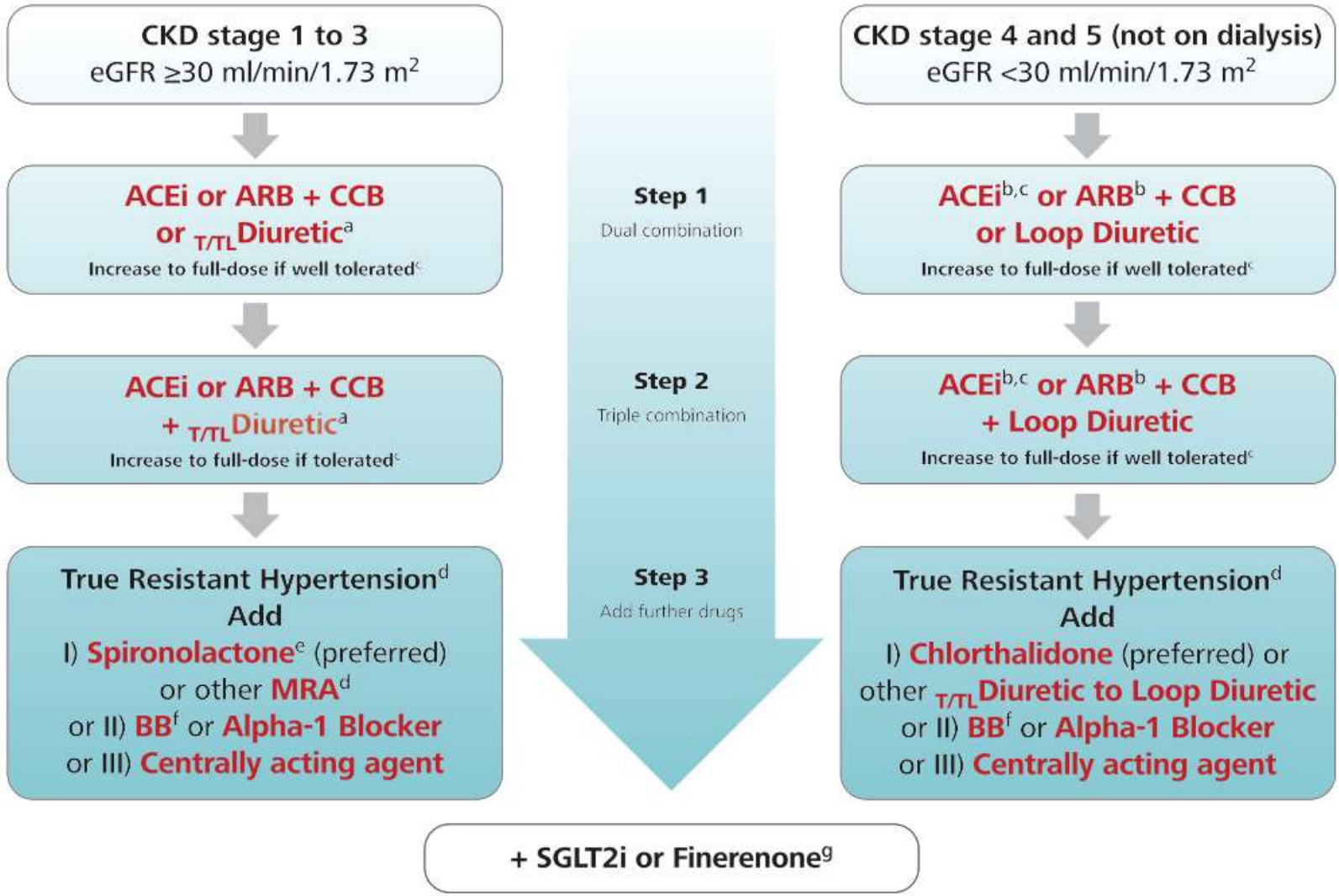


No. at risk#									
Finerenone	6519	6360	6202	6009	5273	4207	3065	2187	1087
Placebo	6507	6330	6125	5938	5184	4147	2969	2135	1082

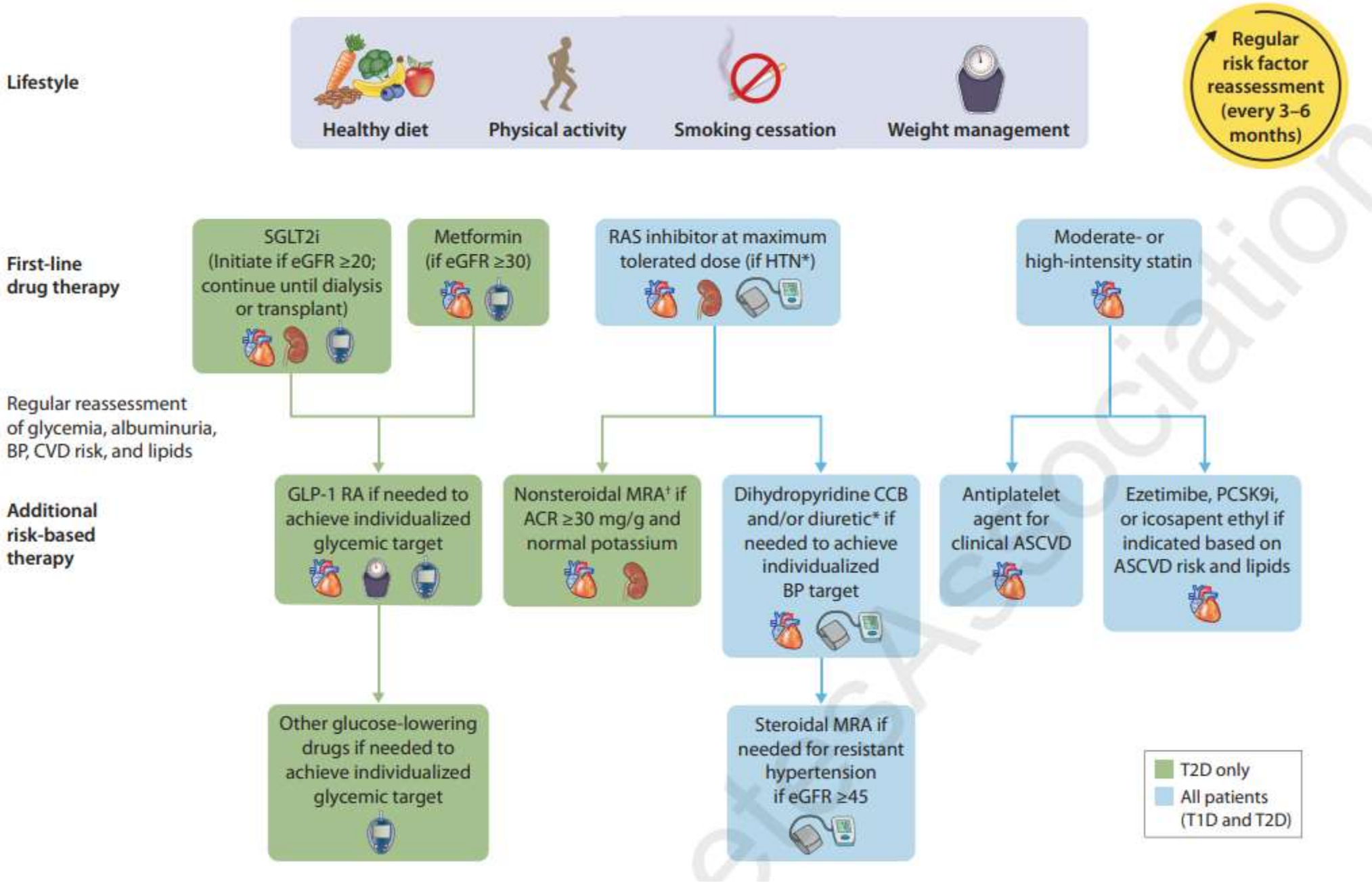
Agarwal R , Filipattos G, et.al....and Bakris GL, Eur Heart J 2022 ;43:474-484

2023 ESH Guidelines

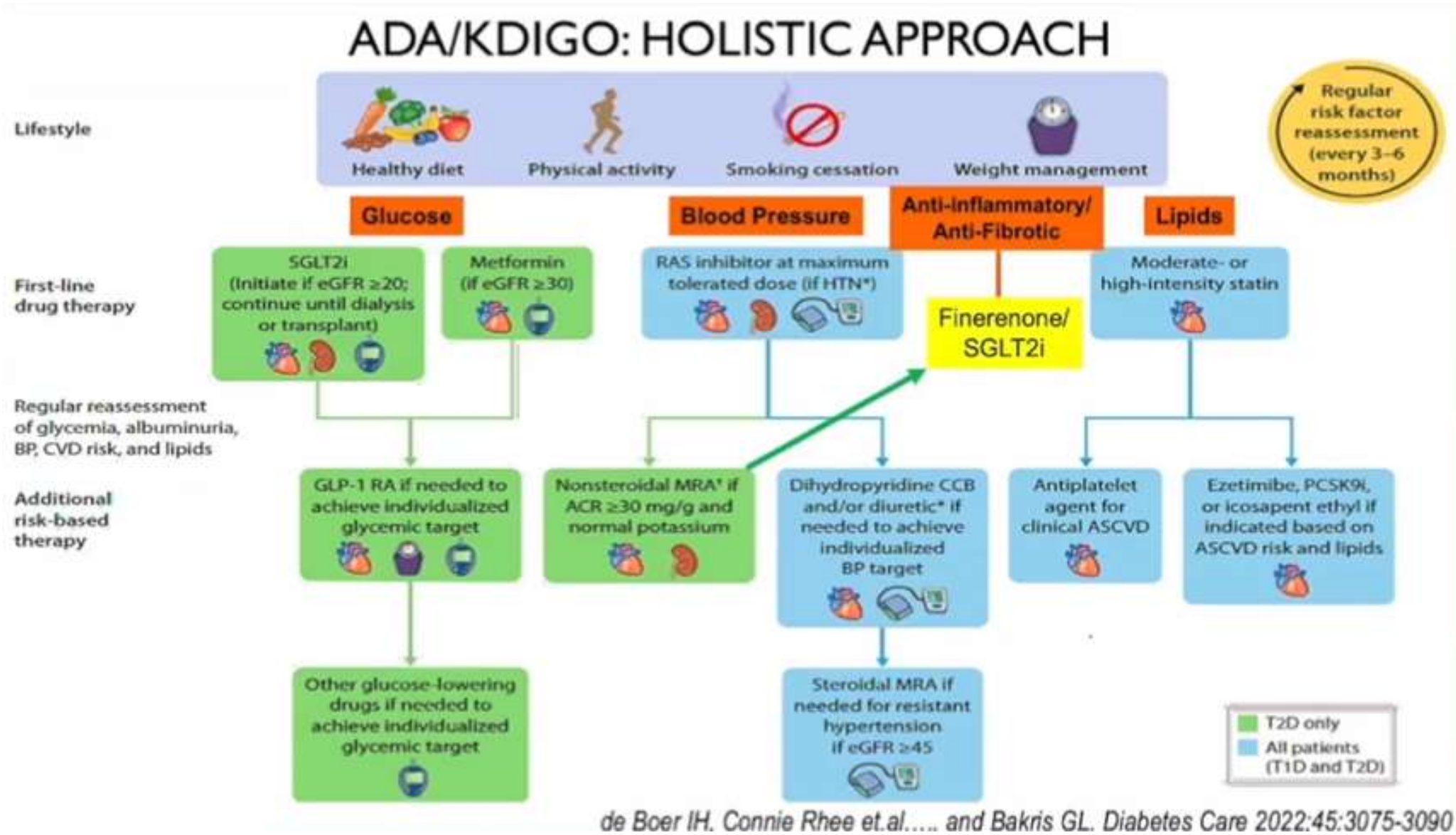
HYPERTENSION AND THE KIDNEY



Mancia et al., Journal of Hypertension Volume 41 Number 1 , 2023

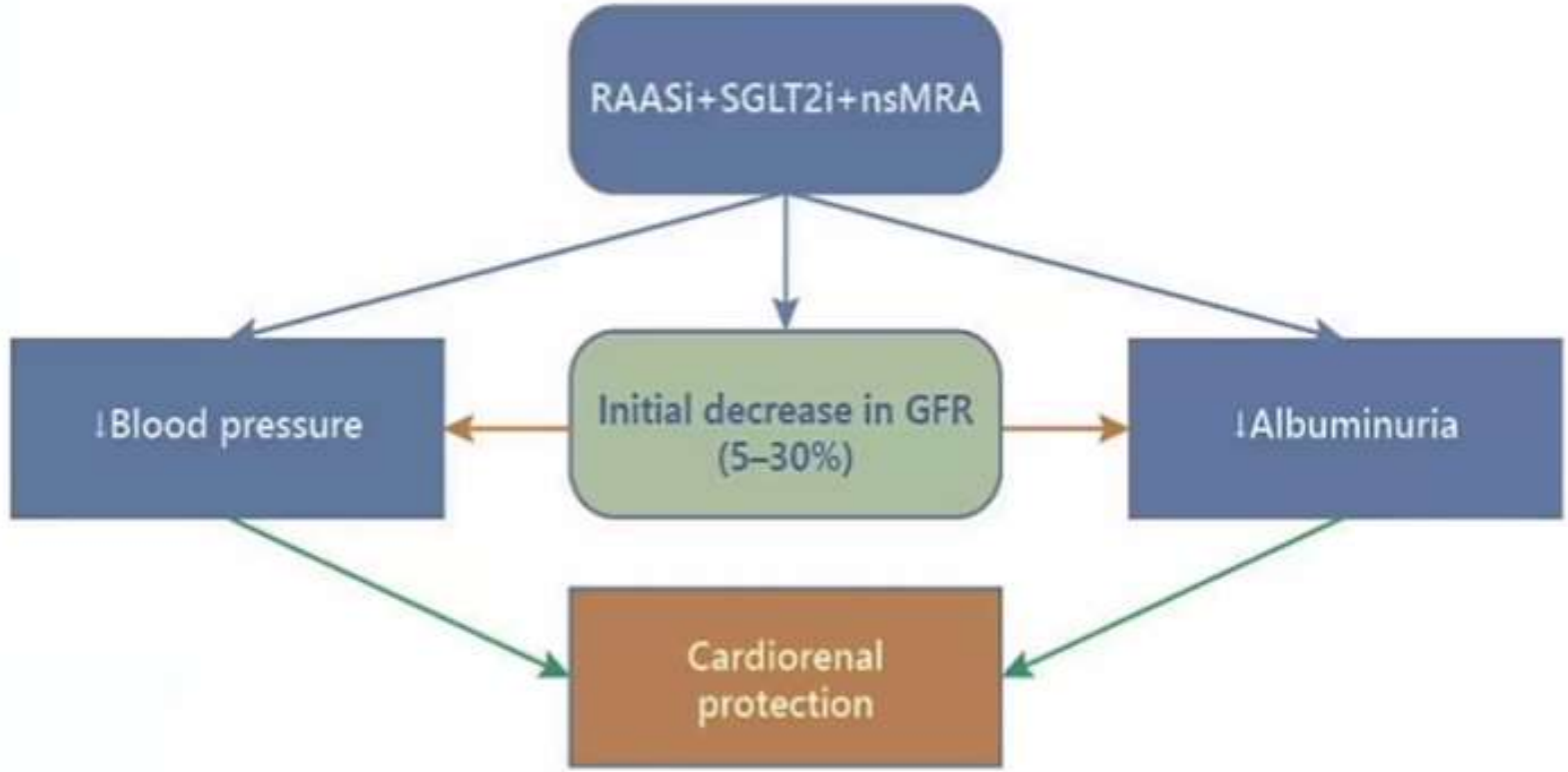

Lifestyle
Healthy diet
Physical activity
Smoking cessation
Weight management
Regular risk factor reassessment (every 3–6 months)
First-line drug therapy
SGLT2i (Initiate if eGFR ≥20; continue until dialysis or transplant)
Metformin (if eGFR ≥30)
RAS inhibitor at maximum tolerated dose (if HTN*)
Moderate- or high-intensity statin
Regular reassessment of glycemia, albuminuria, BP, CVD risk, and lipids
Additional risk-based therapy
GLP-1 RA if needed to achieve individualized glycemic target
Nonsteroidal MRA† if ACR ≥30 mg/g and normal potassium
Dihydropyridine CCB and/or diuretic* if needed to achieve individualized BP target
Antiplatelet agent for clinical ASCVD
Ezetimibe, PCSK9i, or icosapent ethyl if indicated based on ASCVD risk and lipids
Other glucose-lowering drugs if needed to achieve individualized glycemic target
Steroidal MRA if needed for resistant hypertension if eGFR ≥45
T2D only
All patients (T1D and T2D)

ADA/KDIGO: HOLISTIC APPROACH



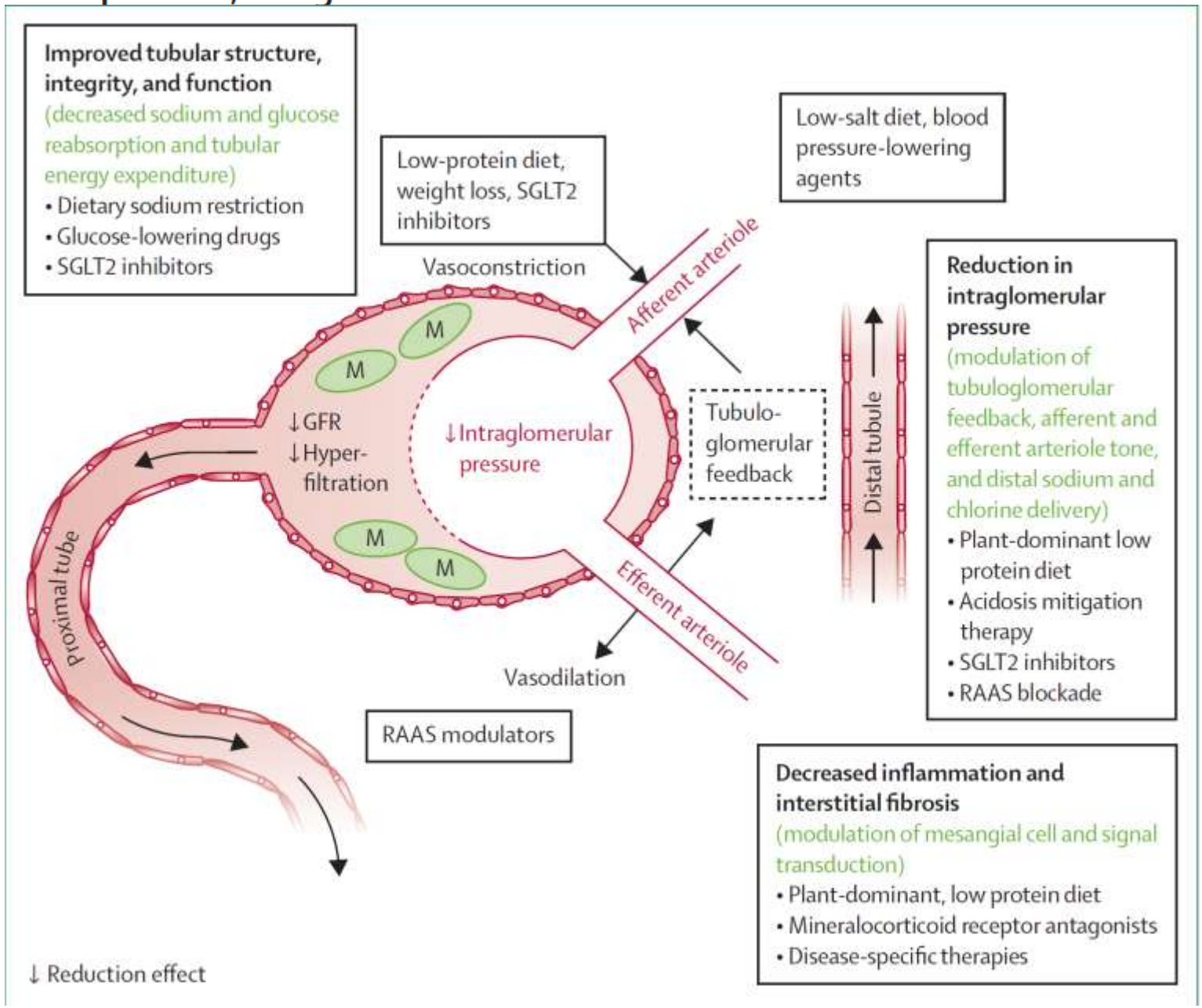
de Boer IH, Connie Rhee et.al..... and Bakris GL. Diabetes Care 2022;45:3075-3090

Initial Drops in Glomerular Filtration Rate with Certain Drug Classes Retard Kidney Disease Progression



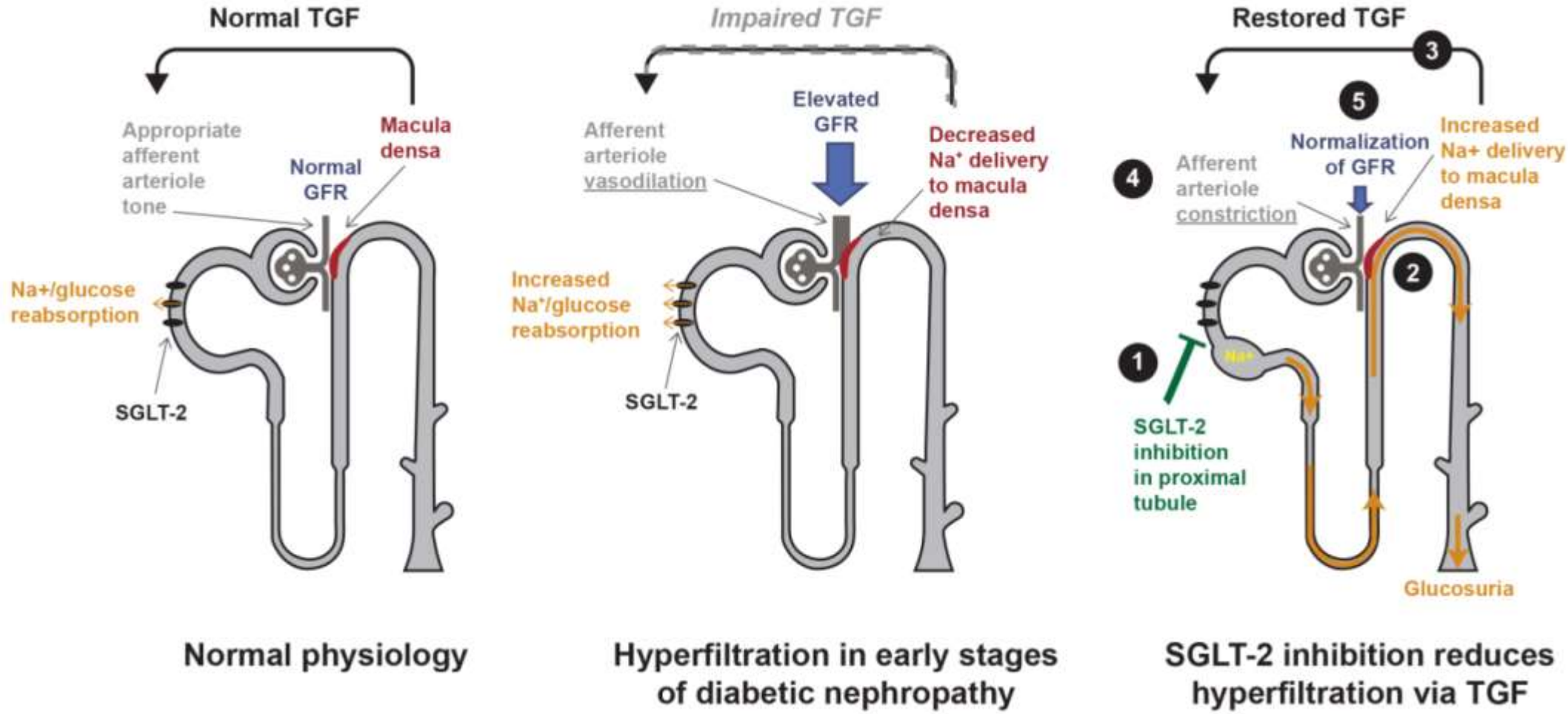
Bakris G and Weir M Am J Nephrol. 2022;53(7):513-515

Figure 2: **Effects of dietary protein and sodium intake and pharmacological therapies on afferent and efferen arteriolar tone, intraglomerular pressure, and glomerular structures and functions**



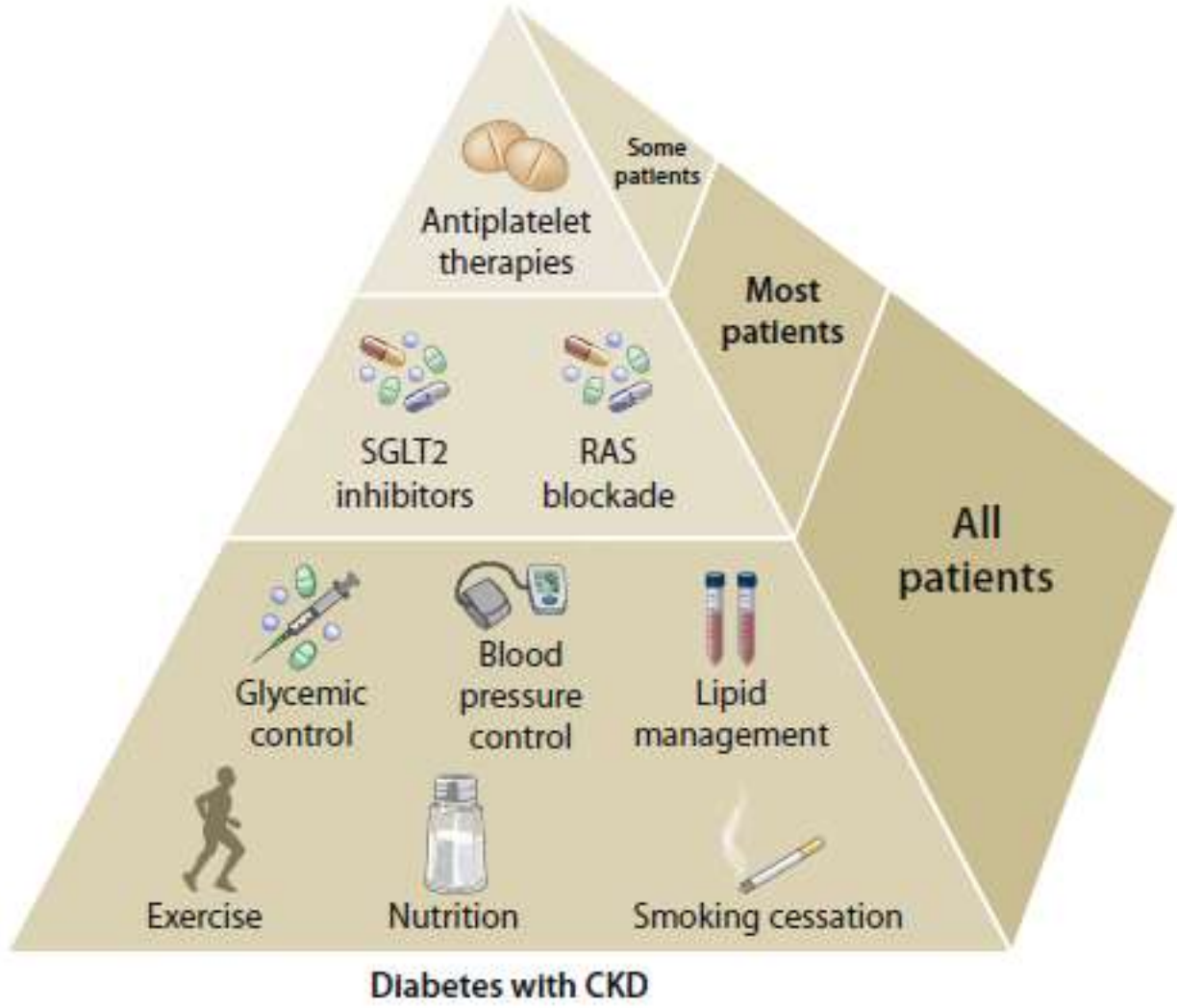
Kalantaz-Zadeh K., et.al.,398:28,2021

ΑΙΜΟΔΥΝΑΜΙΚΕΣ ΑΛΛΑΓΕΣ ΣΤΟ ΣΠΕΙΡΑΜΑ



ΟΧΙ ΤΑΥΤΟΧΡΟΝΗ ΕΝΑΡΞΗ SGLT2i ΚΑΙ ΦΑΡΜΑΚΟ ΤΟΥ ΑΞΟΝΑ

KDIGO 2020


Some patients
Antiplatelet therapies
Most patients
SGLT2 inhibitors
RAS blockade
All patients
Glycemic control
Blood pressure control
Lipid management
Exercise
Nutrition
Smoking cessation
Diabetes with CKD

Αντιμετώπιση της ΧΝΝ στο ΣΔ

Ευχαριστώ για την προσοχή σας