HELLENIC SOCIETY OF NEPHROLOGY
MEETING & SEMINAR
Combined with:
18th BANTAO CONGRESS
October 19-22, 2023
Makedonia Palace Hotel THESSALONIKI, GREECE

ΔΙΑΒΗΤΙΚΗ ΝΕΦΡΟΠΑΘΕΙΑ

Ο ρόλος του Νεφρολόγου

Μάριος Θ. Θεοδωρίδης MD PhD

Νεφρολόγος , Διευθυντής ΕΣΥ

Νεφρολογική Κλινική - Π.Γ.Ν. Αλεξανδρούπολης

Diabetes Res Clin Pract. 2020 Aug;166:108243. doi: 10.1016/j.diabres.2020.108243. Epub 2020 Jun 2.

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

Affiliations + expand

PMID: 32502694 DOI: 10.1016/j.diabres.2020.108243

Abstract

Aims: To examine the prevalence of diabetic chronic kidney disease (DCKD) and its risk factors in adult Greek subjects with type 2 diabetes mellitus (T2DM) in a population from hospital-based diabetes clinics.

Methods: This is a cross-sectional multicentre study based on data collected from Greek hospital-based diabetes clinics from June 2015 to March 2016. DCKD severity was defined according to the Kidney Disease: Improving Global Outcomes (KDIGO) 2012 guidelines. Multivariate analyses assessed the associations between DCKD and its potential risk factors.

Results: Among the entire population (n = 1759), the overall prevalence of DCKD was 45% including mild, moderate and severe CKD. Older age, male gender, body-mass index, lack of exercise and diabetes duration were significantly associated with DCKD.

Conclusions: In Greece, DCKD in T2DM is highly prevalent. It is significantly associated with demographic and lifestyle parameters, as well as T2DM complications, suggesting that further efforts to prevent DCKD should be addressed to subjects with specific characteristics.

Data source: NHANES; Cohort: Participants aged ≥20 years with serum creatinine and urinary ACR measurements. Abbreviations: CKD, chronic kidney disease; ACR, albumin to creatinine ratio; NHANES, National Health and Nutrition Examination Survey.

Παράγοντες κινδύνου για την εμφάνιση και εξέλιξη της ΔΝΝ

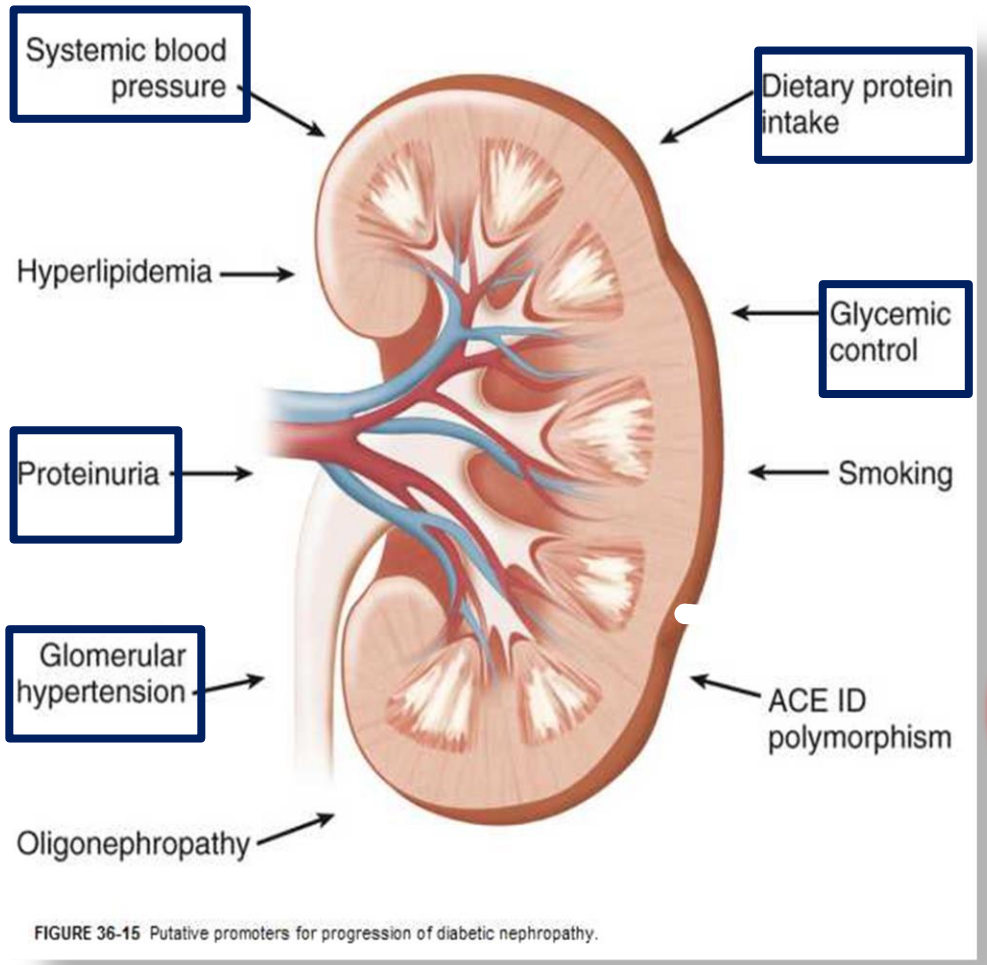
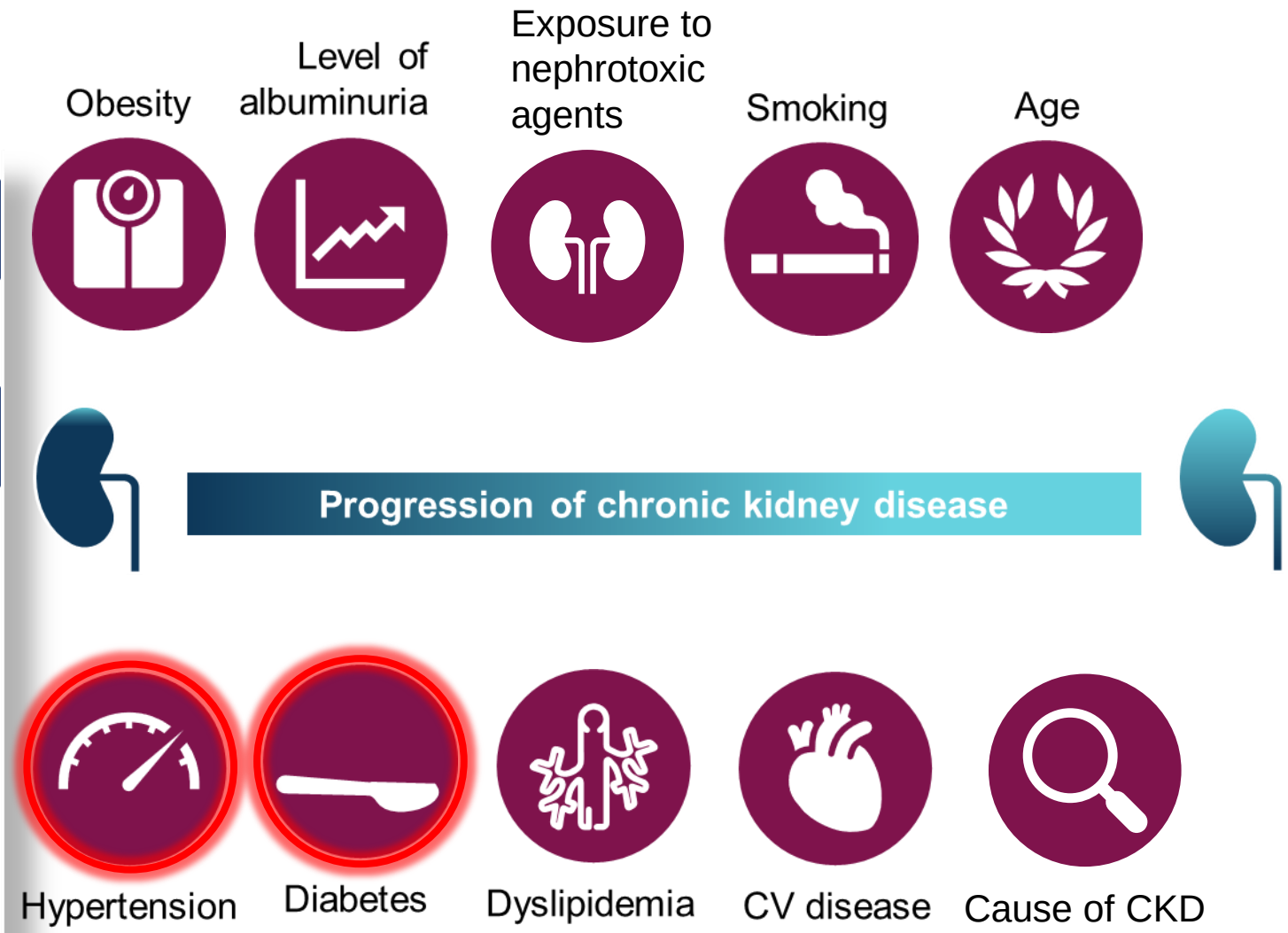


FIGURE 36-15 Putative promoters for progression of diabetic nephropathy.

Andrew S. MD AJKD, Vol 46, No 4 (October), 766 2005



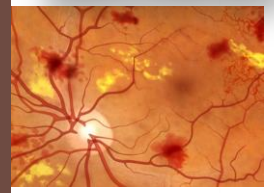
Shlipak MG et al. Kidney Int. 2021;99:34–47

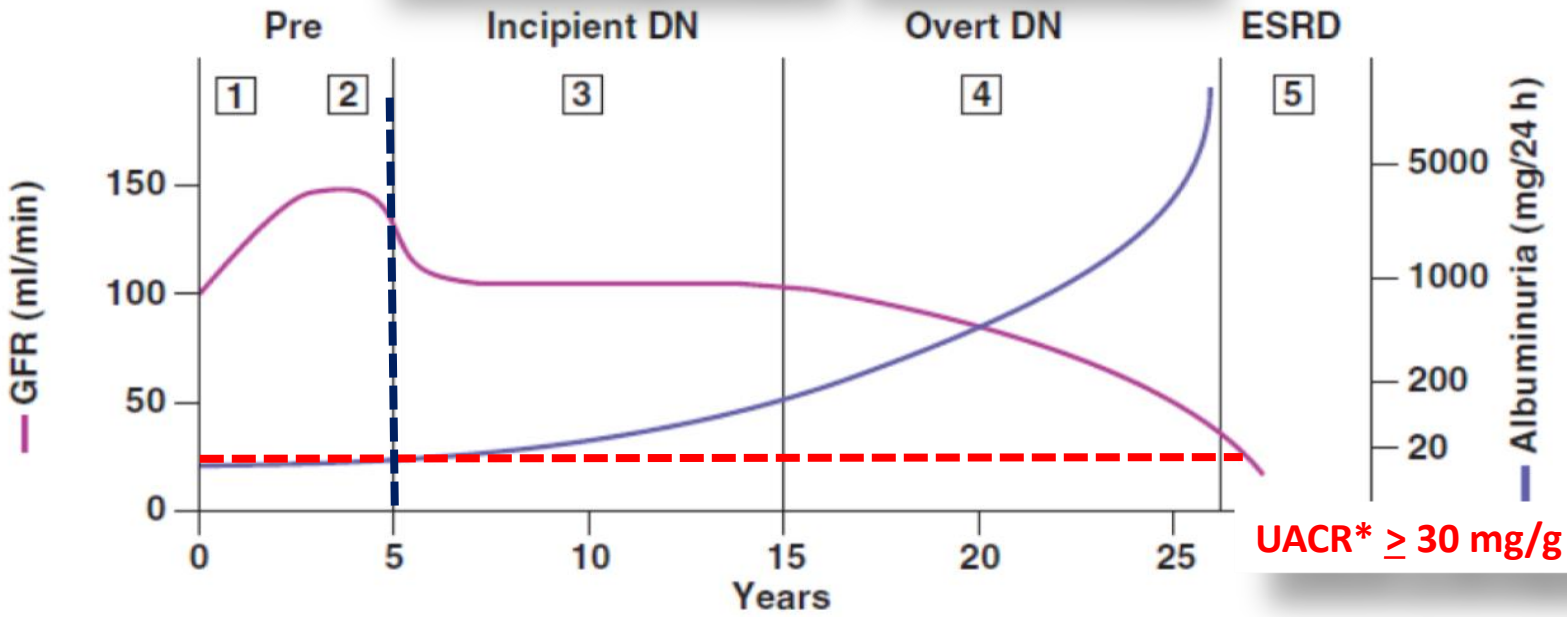
Στάδια Διαβητικής Νεφρικής Νόσου

Υποκλινική Νεφροπάθεια
Αλβουμινουρία 30 – 300 mg/24ωρο

Κλινική Νεφροπάθεια
Αλβουμινουρία >300 mg/24ωρο

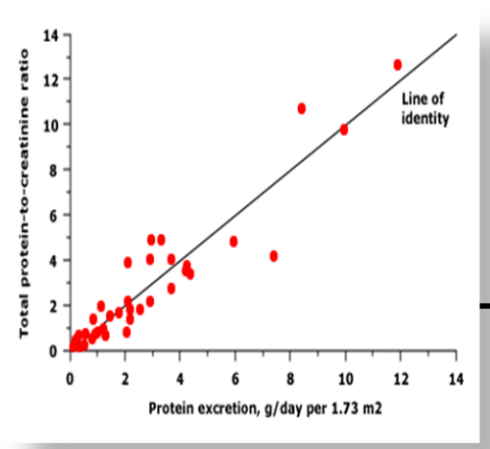
20 – 40 %





UACR* ≥ 30 mg/g Cr

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



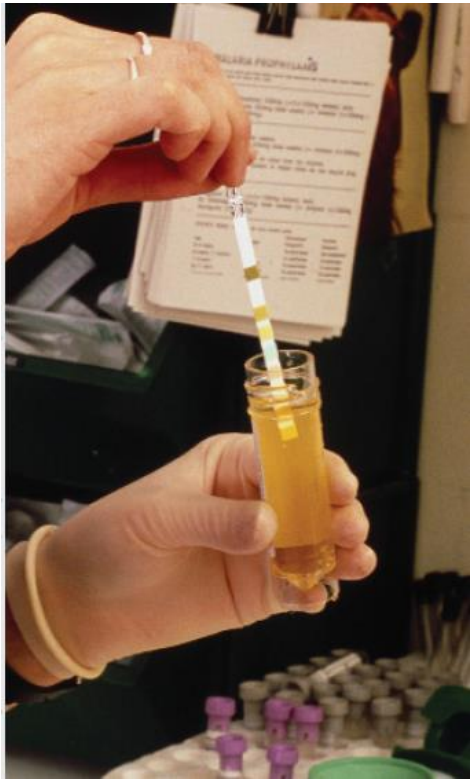
Εκτίμηση αλβουμινουρίας

	UAE mg / 24 h	UAER μg / min	ACR mg/g
ΦΥΣΙΟΛΟΓΙΚΑ	< 30	<20	<30
ΥΠΟΚΛΙΝΙΚΗ ΝΕΦΡΟΠΑΘΕΙΑ *"Ήπια Αλβουμινουρία "*	30-300	20-200	30-300
ΚΛΙΝΙΚΗ ΝΕΦΡΟΠΑΘΕΙΑ *" Σοβαρή Αλβουμινουρία "*	>300	>200	>300

σε πρώτο πρωινό δείγμα σε 2 από 3 δείγματα σε 3-6 μήνες

[1]. Mogensen CE, Chachati A, Christensen CK, et al: Microalbuminuria: An early marker of renal involvement in diabetes. Uremia Invest 9:85-95, 1985.

Έλεγχος για ύπαρξη Διαβητικής Νεφροπάθειας
Πότε & Πώς ???



11. Chronic Kidney Disease and Risk Management: *Standards of Medical Care in Diabetes—2022*

Diabetes Care 2022;45(Suppl. 1):S175–S184 | https://doi.org/10.2337/dc22-S011

Πότε ? → Ετήσια σε κάθε ασθενή με ΣΔΤ2 και σε κάθε ασθενή με ΣΔΤ1 με > 5 χρόνια διάρκειας διαβήτη

Πώς ? → Ποσοτικός έλεγχος αλβουμινουρίας με Albumin/Creatinine mg/gr [UACR] & υπολογισμός του eGFR

2 : 3 +ve σε διάστημα 3 – 6 μηνών

** Δεν προτείνεται η 24ωρη συλλογή γιατί δεν προσφέρει κάτι επιπλέον*

** Αποφυγή εκτίμησης μετά από άσκηση, σε πυρετό, σε υπεργλυκαιμία, σε λοιμώξεις & σε αρρύθμιστη Α.Π.*

Διαστρωμάτωση κινδύνου για ESRD

11. Chronic Kidney Disease and Risk Management: *Standards of Care in Diabetes—2023*

Diabetes Care 2023;46(Suppl. 1):S191–S202 | https://doi.org/10.2337/dc23-S011

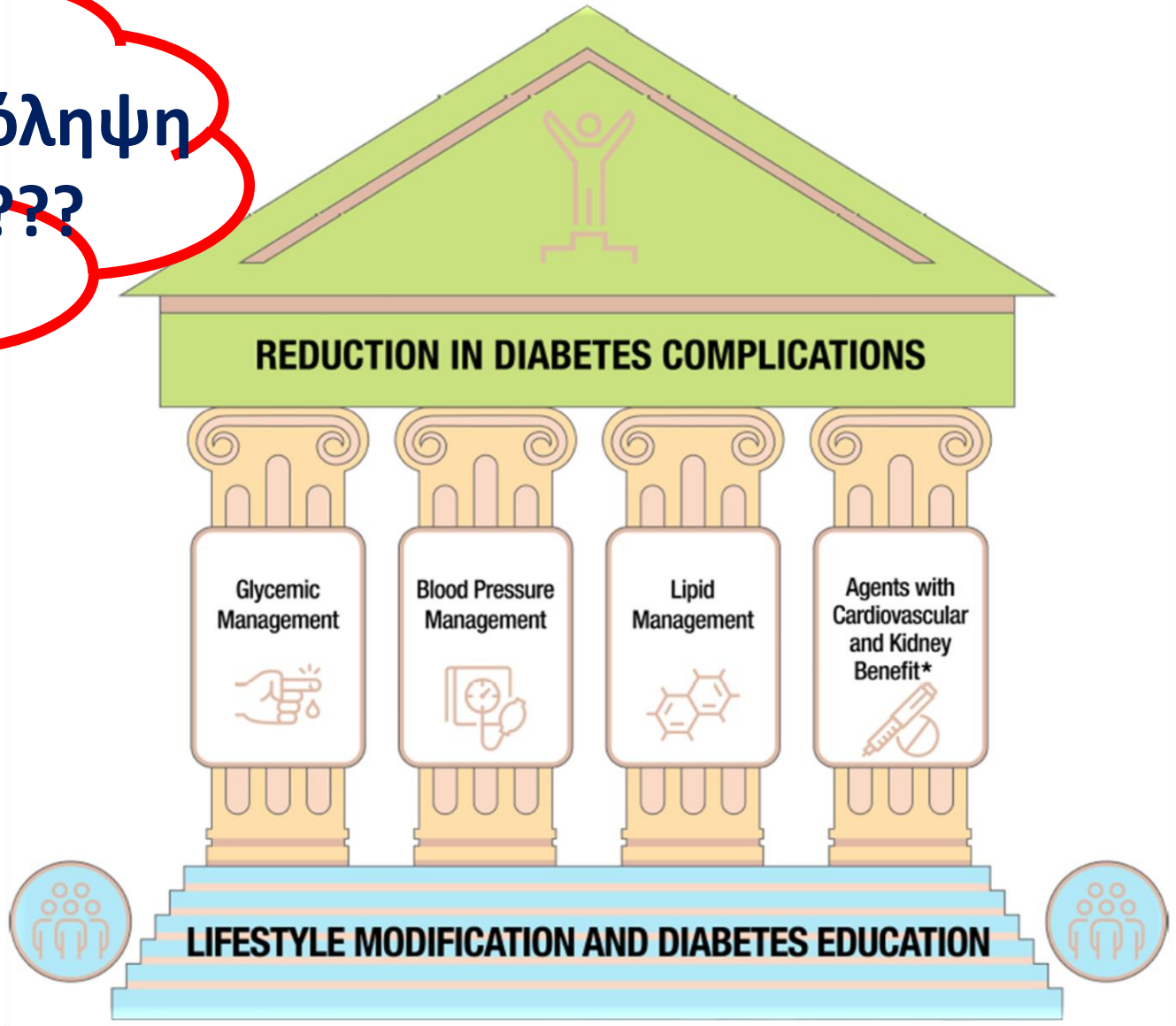
At least annually ACR & eGFR

Σε ΧΝΝ 1- 4 φορές / έτος ανάλογα eGFR

Σε νεφρολόγο ACR >300 ή/και eGFR <30

GFR categories (mL/min/1.73 m²) Description and range				Albuminuria categories Description and range		
				A1	A2	
				Normal to mildly increased	Moderately increased	ely increased
				<30 mg/g <3 mg/mmol	30-299 mg/g 3-29 mg/mmol	≥300 mg/g ≥30 mg/mmol
	G1	Normal to high	≥90	1 if CKD	Treat 1	Refer* 2
	2	Mildly decreased	60-89	1 if CKD	Treat 1	Refer* 2
	G3a	oderately	45-59	Treat 1	Treat 2	Refer 3
	G3b	Moderately to severely decreased	30-44	Treat 2	Treat 3	Refer 3
	G4	Severely decreased	15-29	Refer* 3	Refer* 3	Refer 4+
		Kidney failure	<15	Refer 4+	Refer 4+	Refer 4+

Ποια τα μέτρα για την πρόληψη & θεραπεία της ΔΝΝ ???



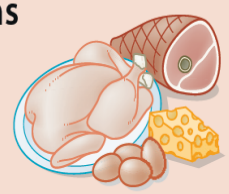
Lifestyle Interventions in Patients with Diabetes and CKD

1. **Recommendation 3.1.1: We suggest maintaining a protein intake of 0.8 g of protein/kg (weight)/d for those with diabetes and CKD not treated with dialysis *(2C)*.**

   Practice Point 3.1.2: Patients treated with hemodialysis, and particularly peritoneal dialysis should consume between 1.0 and 1.2 g protein/kg (weight)/d.

2. **Recommendation 3.1.2: We suggest that sodium intake be <2 g of sodium per day (or <90 mmol of sodium per day, or <5 g of sodium chloride per day) in patients with diabetes and CKD *(2C)*.**

Animal proteins



Meat, poultry, fish, seafood, eggs:
28 g (1 oz) = 6–8 g protein
1 egg = 6–8 g protein

Dairy, milk, yogurt, cheese:
250 ml (8 oz) = 8–10 g protein
28 g (1 oz) cheese = 6–8 g protein

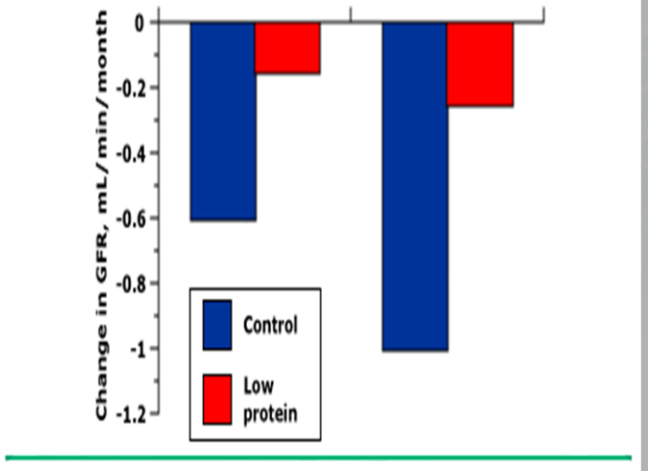
Plant proteins

Legumes, dried beans, nuts, seeds:
100 g (0.5 cup) cooked = 7–10 g protein

Whole grains, cereals:
100 g (0.5 cup) cooked = 3–6 g protein

Starchy vegetables, breads:
2–4 g protein

Graph showing effect of dietary protein restriction on progression of diabetic nephropathy



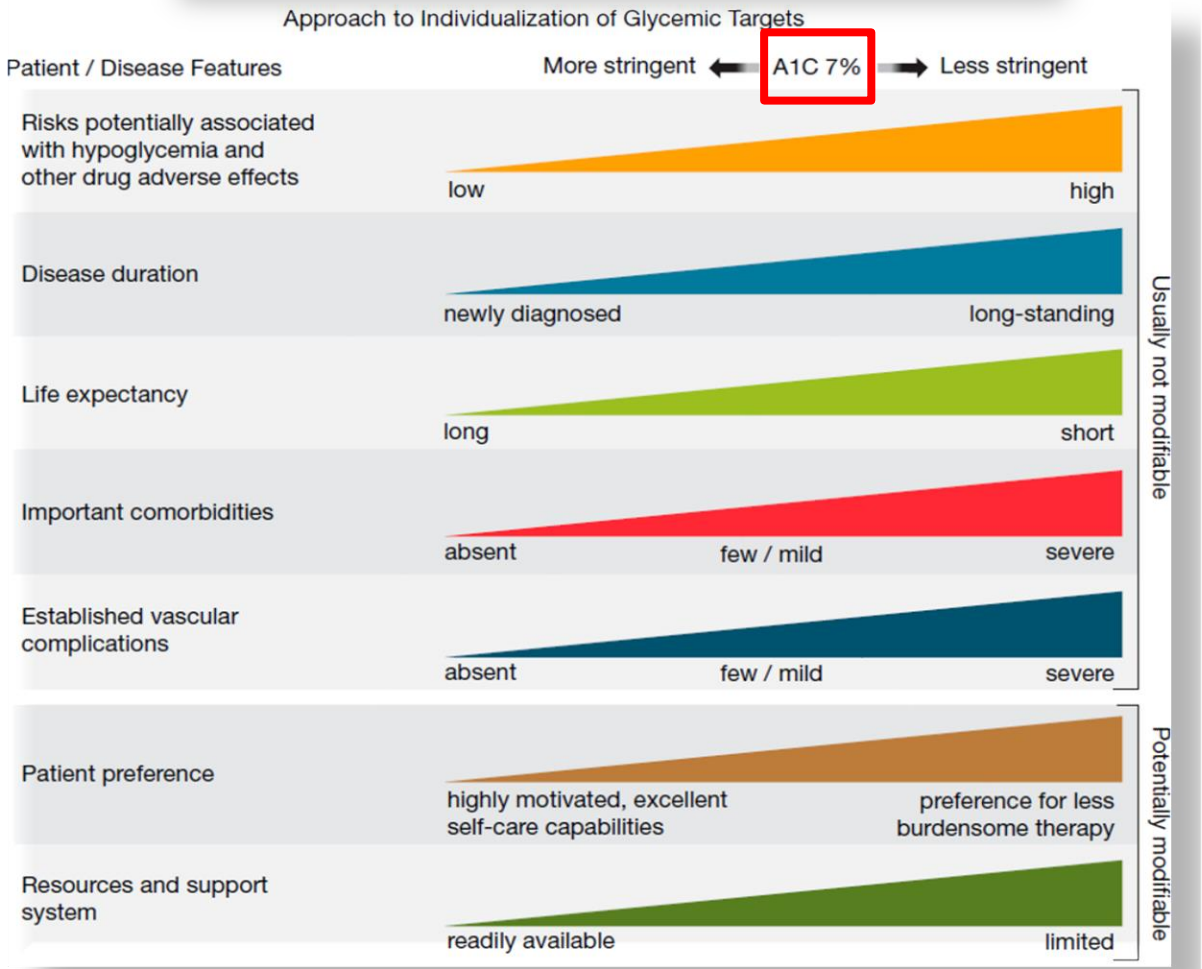
KDIGO 2020

Table 1. Summary of Key Glycemic Control Trials

Trial	Population	N	Achieved Intervention	Findings in Intensive Care Group	Comments
DCCT	T1DM	1,441	HbA_{1c} 7.3% vs 9.1%	Decreased microvascular complications (including microalbuminuria, proteinuria, retinopathy, and neuropathy)	
EDIC	T1DM	1,375 patients that completed DCCT	HbA_{1c} 7.8% vs 7.9%	Reduction in microalbuminuria and proteinuria	
UKPDS	Newly Diagnosed T2DM	3,867	HbA_{1c} 7% vs 7.9%	Reduction in any diabetes-related end point in aggregate	Reduction not seen in kidney-specific events (microalbuminuria, proteinuria, or doubling of Scr)
ACCORD	T2DM and CV event history or risk	10,251	HbA_{1c} 6.4% vs 7.5%	Increased CV and total mortality	No benefit on kidney end points
ADVANCE	T2DM and CV event history or risk	11,140	HbA_{1c} 6.3% vs 7.0%	No benefit on CV outcomes; reduction in microvascular events	Albuminuria reduced by 21%
VADT	T2DM and poor BP control	1,791	HbA_{1c} 6.9% vs 8.4%	No benefit	No benefit on kidney end points

6. Glycemic Targets: *Standards of Care in Diabetes—2023*

Diabetes Care 2023;46(Suppl. 1):S97–S110 | https://doi.org/10.2337/dc23-S006



Glycemic Monitoring and Targets in Patients with Diabetes and CKD

Recommendation 2.2.1. We recommend an individualized HbA1c target ranging from <6.5% to <8.0% in patients with diabetes and CKD not treated with dialysis (Figure 9) *(1C)*.

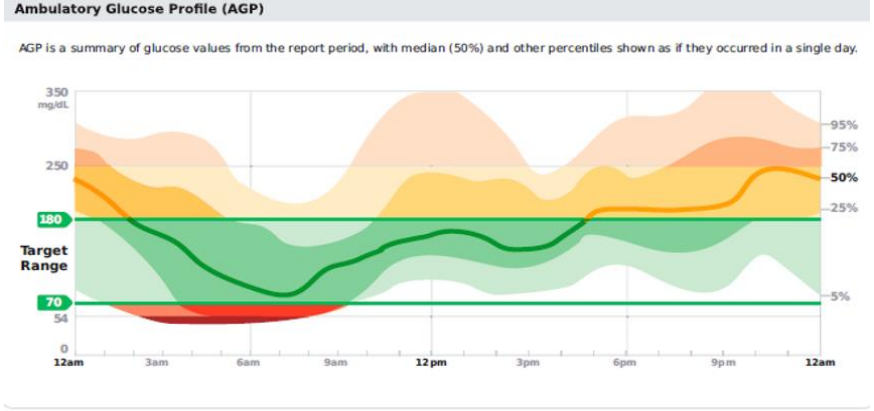
<6.5%	HbA1c	<8.0%
CKD G1	Severity of CKD	CKD G5
Absent/minor	Macrovascular complications	Present/severe
Few	Comorbidities	Many
Long	Life expectancy	Short
Present	Hypoglycemia awareness	Impaired
Available	Resources for hypoglycemia management	Scarce
Low	Propensity of treatment to cause hypoglycemia	High

KDIGO 2020

6. Glycemic Targets: *Standards of Care in Diabetes—2023*

Diabetes Care 2023;46(Suppl. 1):S97–S110 | https://doi.org/10.2337/dc23-S006

6.4 Time in range is associated with the risk of microvascular complications and can be used for

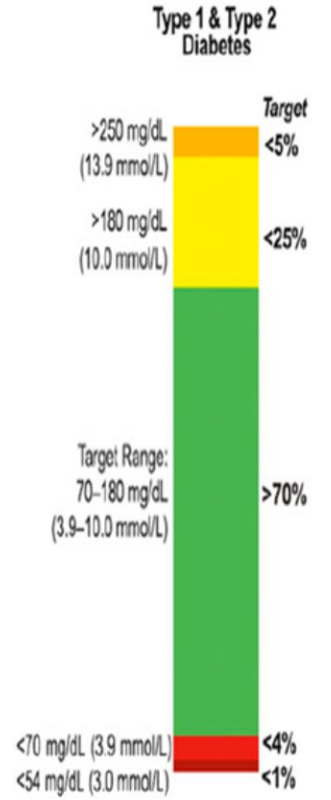


GLUCOSE STATISTICS AND TARGETS

Glucose Ranges	Targets [% of Readings (Time/Day)]
	14 days % Sensor Time
Target Range 70–180 mg/dL	Greater than 70% (16h 48min)
Below 70 mg/dL	Less than 4% (58min)
Below 54 mg/dL	Less than 1% (14min)
Above 180 mg/dL	Less than 25% (6h)
Above 250 mg/dL	Less than 5% (1h 12min)

Each 5% increase in time in range (70–180 mg/dL) is clinically beneficial.

TIME IN RANGES



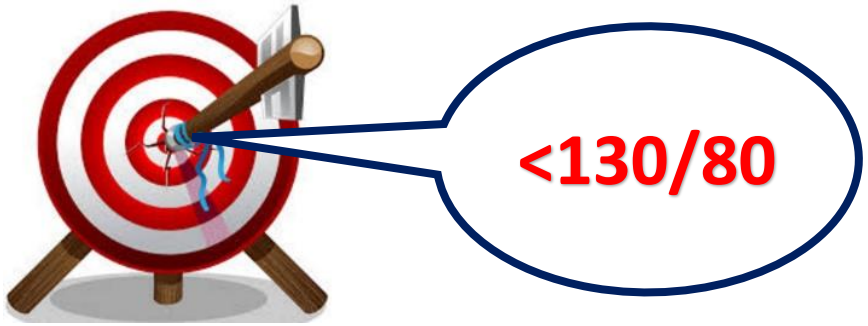
Time in range of >70%
with time below range <4%

Practice Point 2.1.2: Accuracy and precision of HbA1c measurement declines with advanced CKD (G4–G5), particularly among patients treated by dialysis, in whom HbA1c measurements have low reliability.

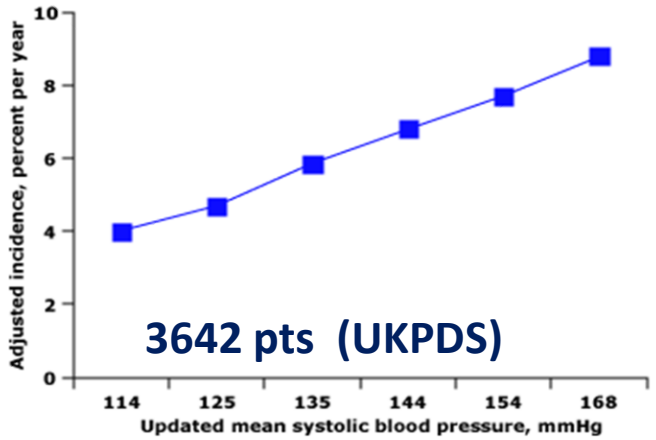
Practice Point 2.1.3: A glucose management indicator (GMI) derived from continuous glucose monitoring (CGM) data can be used to index glycemia for individuals in whom HbA1c is not concordant with directly measured blood glucose levels or clinical symptoms.

10. Cardiovascular Disease and Risk Management: *Standards of Care in Diabetes—2023*

Diabetes Care 2023;46(Suppl. 1):S158–S190 | https://doi.org/10.2337/dc23-S010

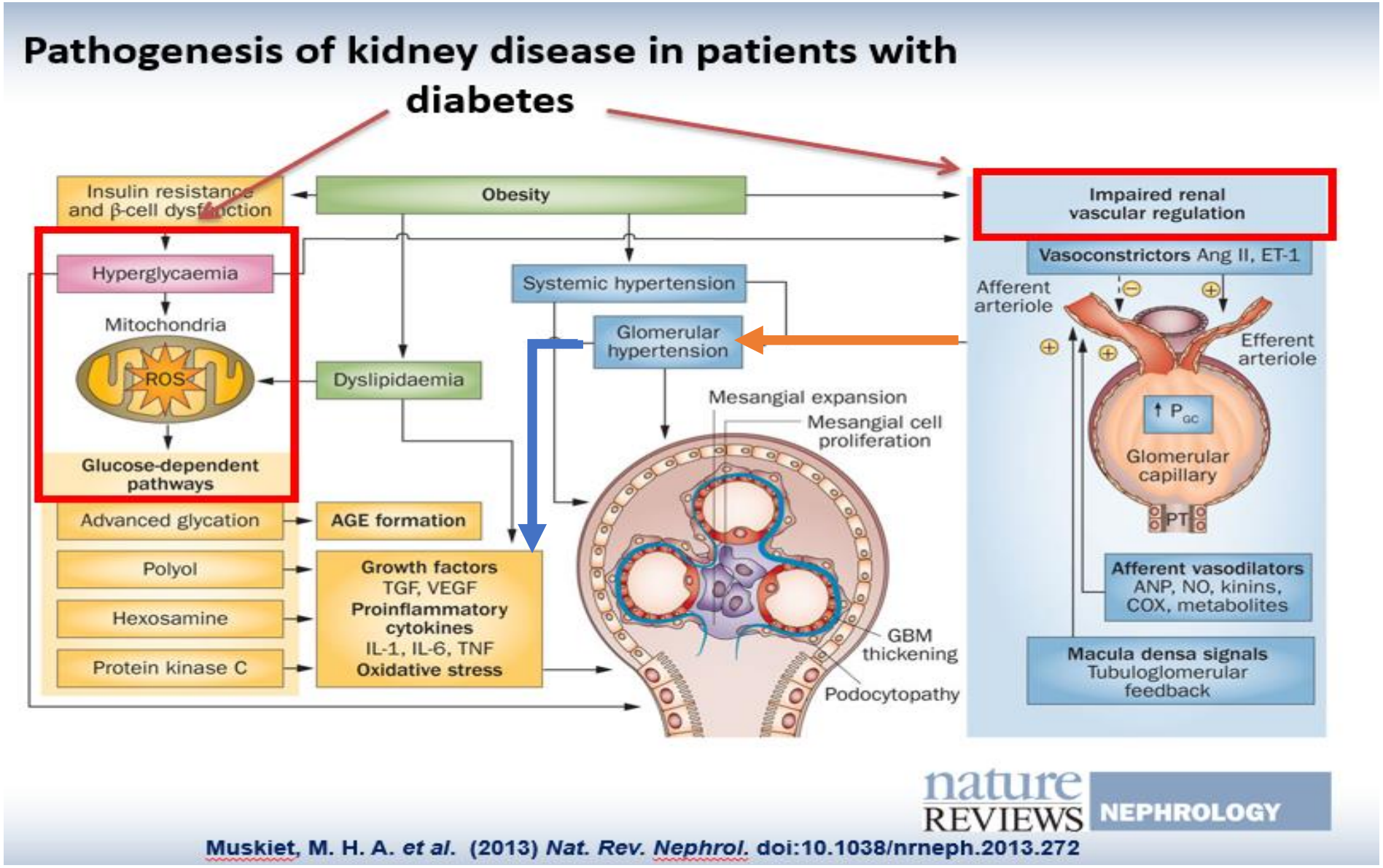


Lower systolic blood pressure (BP) is associated with fewer complications in patients with type 2 diabetes

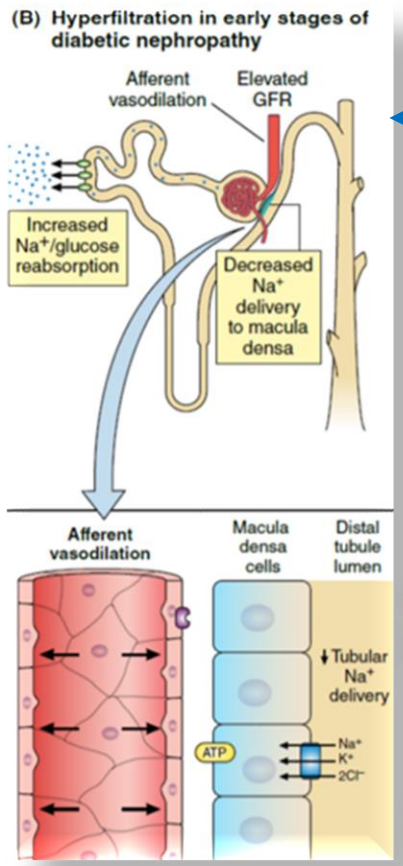


on a separate day, to diagnose hypertension. A Hypertension is defined as a systolic blood pressure ≥130 mmHg or a diastolic blood pressure ≥80 mmHg based on an average of ≥2 measurements obtained on ≥2 occasions. A

Παθογένεια της ΔΝΝ



Αιμοδυναμική απορρύθμιση του σπειράματος



Υπεργλυκαιμία

Υπερινσουλιναιμία

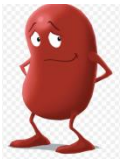
AII

ROS

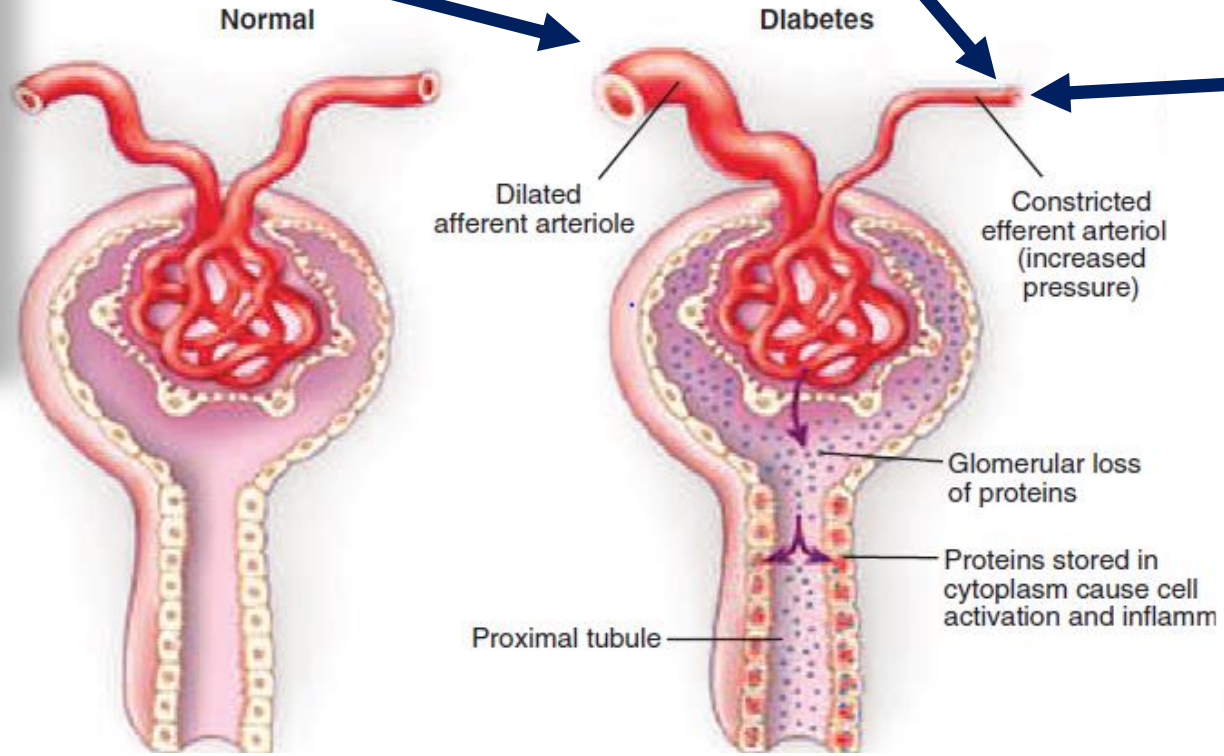
Ενδοθηλιακή βλάβη

ET1

ET-A receptors



Βλάβη ποδοκυττάρων
Οξειδωτικό Στρες
Φλεγμονή
Ίνωση



Y.-C. Lin et alJ Formos Med Assoc. 2018 Aug;117(8):662-675

ΔΝΝ : αΜΕΑ & ARB→Συστηματική/Ενδοσπειραματική Υπέρταση

Table 2. Summary of Key Renin-Angiotensin System Inhibition Trials

Trial	Population	N	Intervention	Conclusions	Comments
ROADMAP	T2DM without microalbuminuria	4,449	Olmesartan vs placebo	Olmesartan delayed the onset of microalbuminuria	Olmesartan group had lower BPs and more CV deaths
IRMA-2	T2DM and microalbuminuria	590	Irbesartan 150 mg vs irbesartan 300 mg vs placebo	Irbesartan reduced the development of overt proteinuria	Subgroup analysis suggested a dose-dependent effect
Captopril Trial	T1DM with proteinuria	409	Captopril 25 mg 3×/d vs placebo	Captopril reduced the risk for doubling of SCr as a primary outcome and death, dialysis therapy, or transplantation as a secondary outcome	
IDNT	T2DM with proteinuria and reduced kidney function	1,715	Irbesartan vs amlodipine vs placebo	Irbesartan reduced the risk for doubling of SCr, ESRD, or death	
RENAAL	T2DM with proteinuria and reduced kidney function	1,513	Losartan vs placebo	Losartan reduced the risk for doubling of SCr, ESRD, or death	
ONTARGET	Patients with CV risk	25,620	Ramipril vs telmisartan vs telmisartan and ramipril	No CV benefit among the 3 arms; proteinuria reduction in combination therapy arm	Increase in "DDT" events in combination therapy arm
VA NEPRON-D	T2DM and proteinuria	1,448	Losartan and lisinopril vs losartan and placebo	Trial terminated early due to AKI events and hyperkalemia in combination therapy arm	
ALTITUDE	T2DM, proteinuria, and CV risk	8,561	ACEi or ARB and aliskiren vs ACEi or ARB and placebo	Trial terminated early due to increase in adverse events and no apparent benefit in the dual-therapy arm	

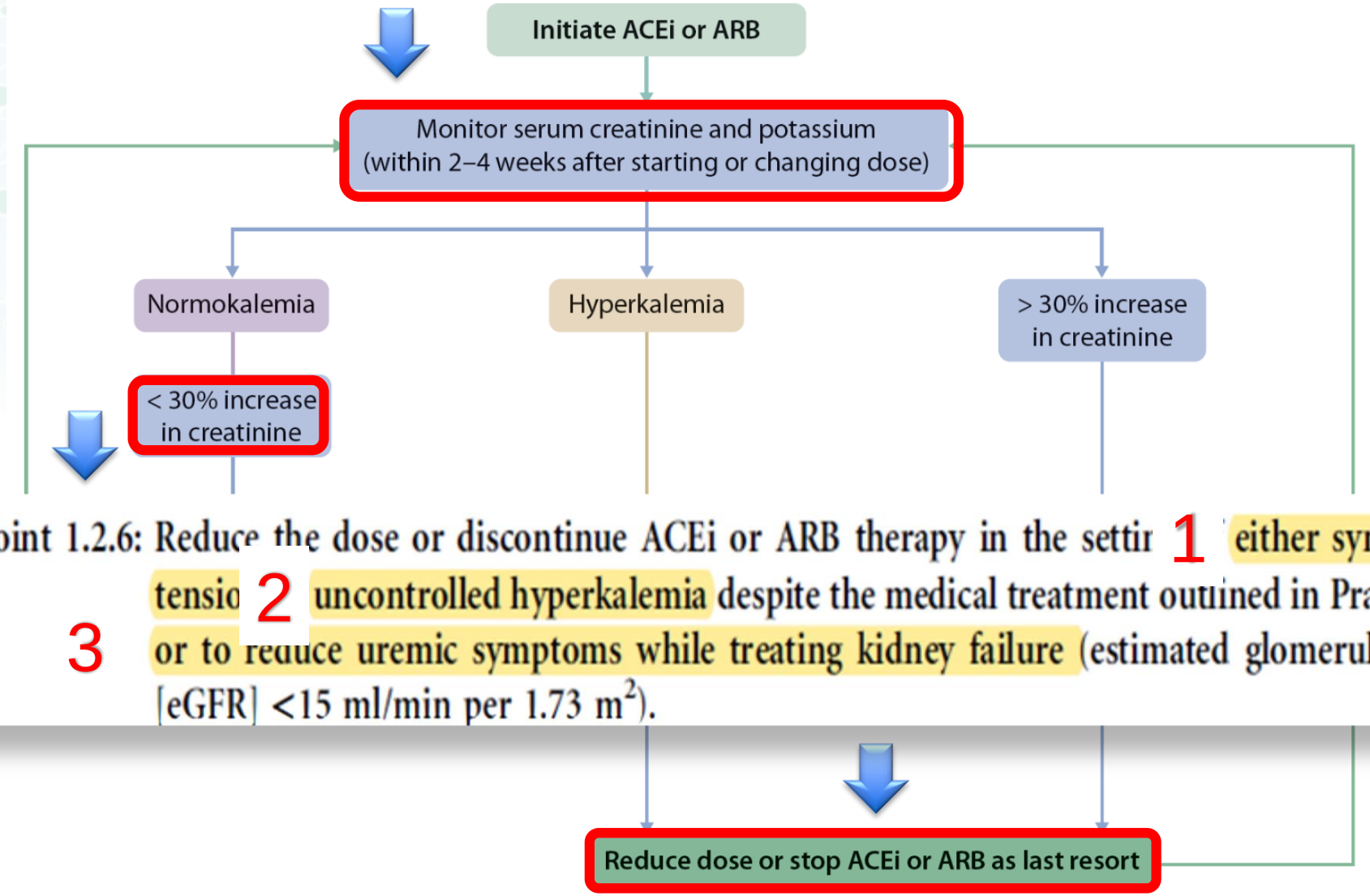
11. Chronic Kidney Disease and Risk Management: *Standards of Care in Diabetes—2023*

Diabetes Care 2023;46(Suppl. 1):S191–S202 | https://doi.org/10.2337/dc23-S011

- **ΔΕΝ προτείνεται η χορήγηση αΜΕΑ ή ARB σε ασθενείς με ΣΔ φυσιολογική ΑΠ και ACR < 30mg/gr**
- **Προτείνεται η χορήγηση αΜΕΑ ή ARB σε κάθε ασθενή με ΣΔ, ↑ΑΠ και ACR 30-299 mg/gr Cr (B)**
- **Προτείνεται ισχυρά σε κάθε ασθενή με ΣΔ, ↑ΑΠ & ACR ≥ 300mg/grCr και/ή eGFR <60ml/min (A)**

Monitor Cr , K^+ , eGFR , Αποφυγή συνδυασμού αΜΕΑ & ARB

FIGURE 4. MONITORING OF SERUM CREATININE AND POTASSIUM DURING ACEI OR ARB TREATMENT - DOSE ADJUSTMENT AND MONITORING OF SIDE EFFECTS



KDIGO 2020

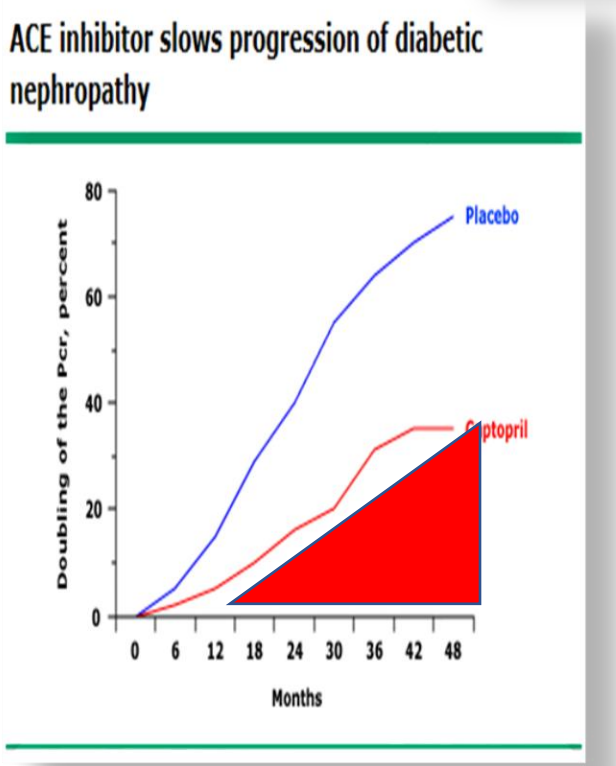
GFR ?

Table 1. Summaries of landmark trials with the RAAS blockade.

Trial	Publication Year	Treatment(s)	Primary Composite Kidney Outcome	Risk Reduction
CSG Captopril [11]	1993	Captopril vs. placebo	Doubling of the base-line serum creatinine concentration	48%
RENAAL [12]	2001	Losartan vs. placebo	Doubling of serum creatinine, ESKD or death	16%
IDNT [13]	2001	Irbesartan vs. amlodipine vs. placebo	Doubling of serum creatinine, ESKD or death	20% vs. placebo 23% vs. amlodipine

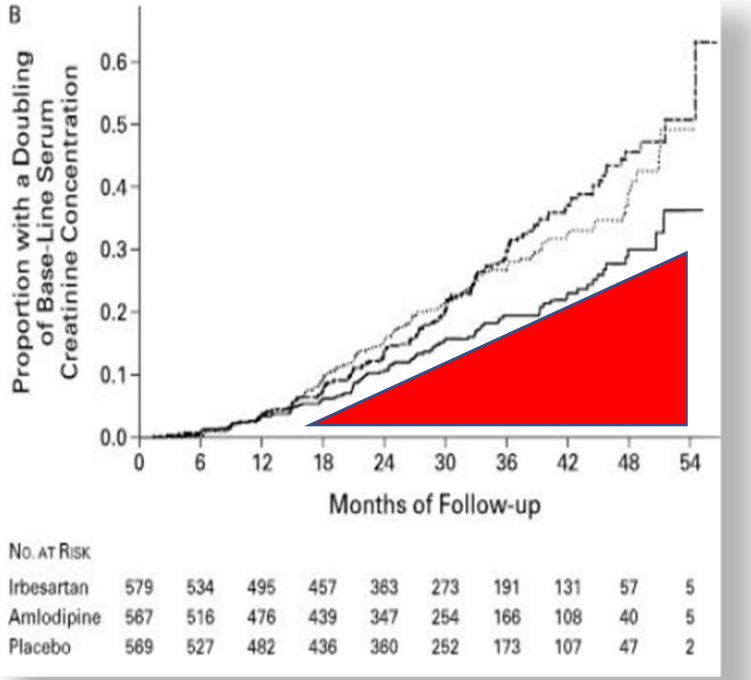
CSG Captopril = the collaborative study group; ESKD = end-stage kidney disease; IDNT = Irbesartan Diabetic Nephropathy Trial; RENAAL = reduction of end-points in non-insulin-dependent diabetes mellitus with the angiotensin II antagonist losartan.

K^+ ?



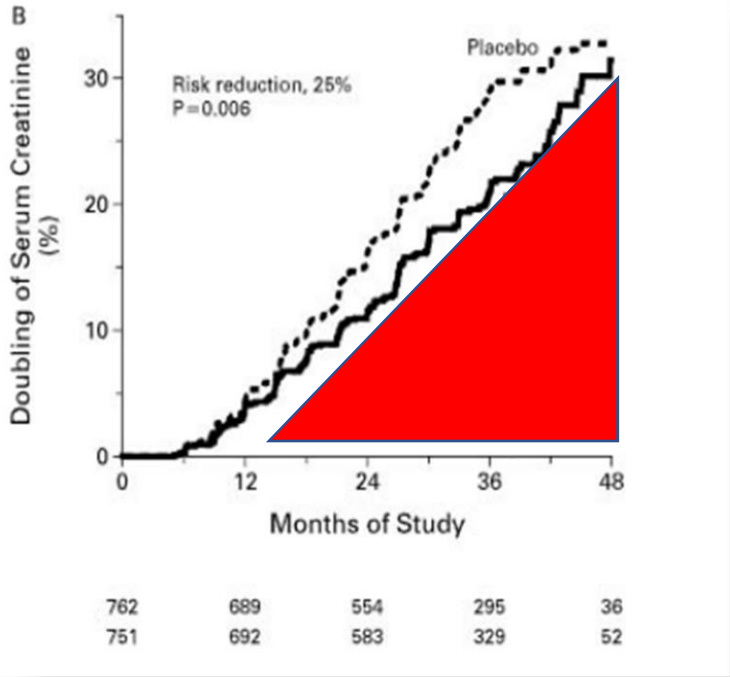
Lewis EJ N Engl J Med 1993; 329:1456

IDNT Study



EJ Lewis N Engl J Med, Vol. 345, No. 12 · 20/9/ 2001

RENAAL Study



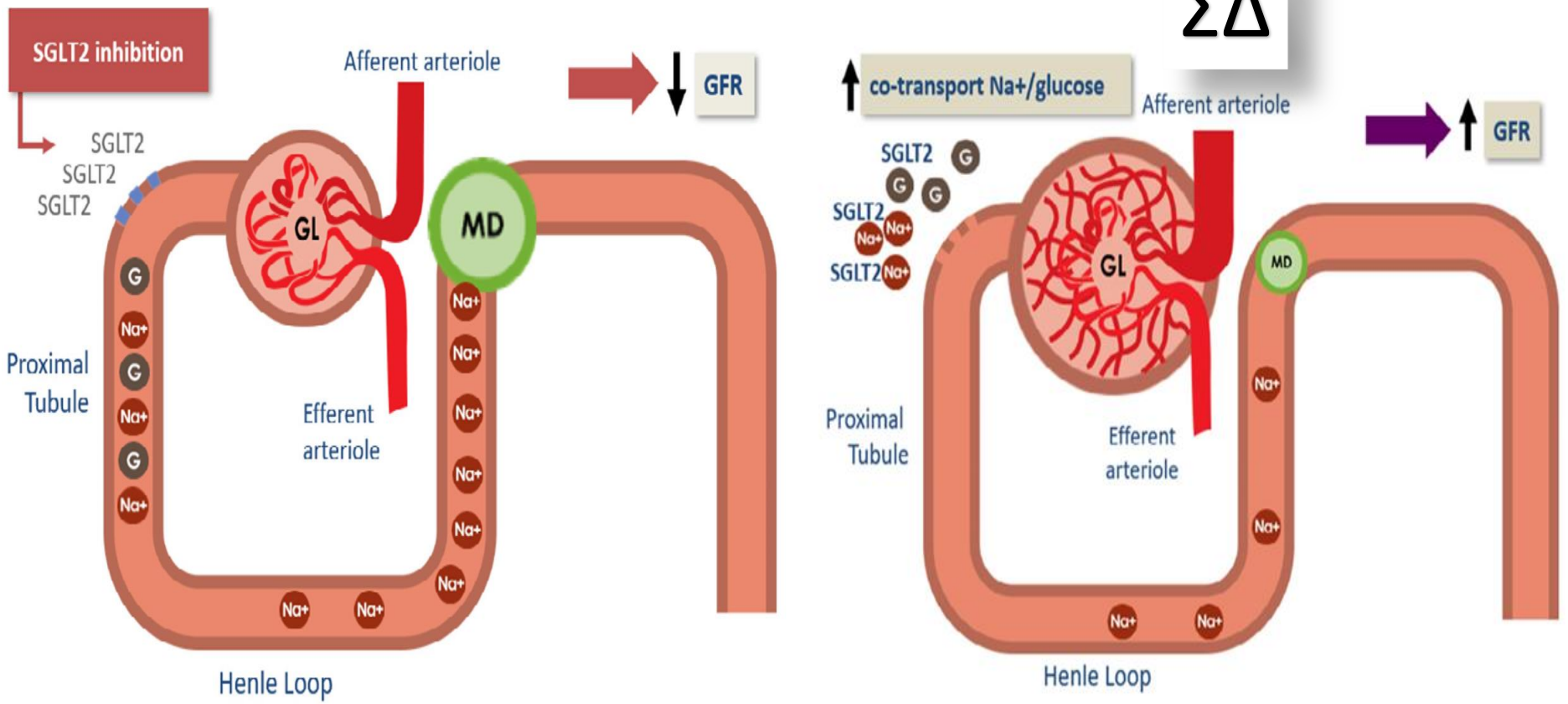
Barry M. Brenner N Engl J Med, Vol. 345, No. 12 · September 20, 2001

Παθογένεια – Θεραπεία ΔΝΝ

“Manage the disease from stage 1 not stage 3 of DKD…”

It takes 2 to Tango….

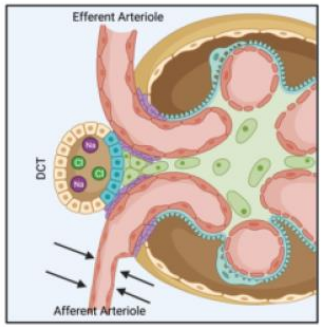
Ενδοσπειραματική Υπέρταση & ↑ SGLT2



SGLT2 Inhibitors → Γλυκοζουρία → **Ρύθμιση ΣΔ , ↓ ΣΒ**

→ Νατριούρηση → **↓ Ενδοσπειραματικής πίεσης & ↓ΑΠ**

→ **↓ Επαναρρόφηση γλυκόζης** → **↓ Περισωληναριακή φλεγμονή & ίνωση**



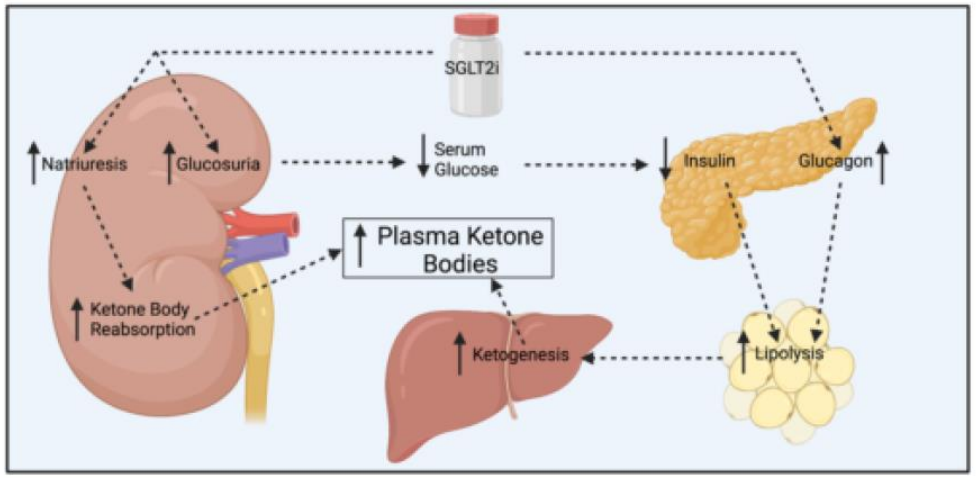
1. ↑ παραγωγή κετονών
2. ↓ έκκριση κετονών

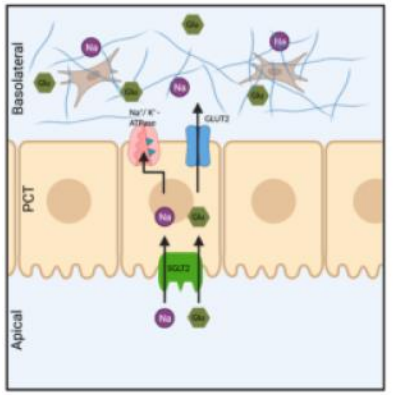
↓

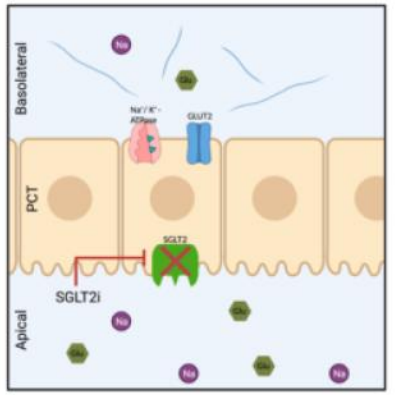
Προτεραιότητα στην οξείδωση σε σχέση με ΕΛΟ

↓

↓ Οξειδωτικού Στρες σε καρδιά και νεφρό







Hanny Sawaf et al J Clin Med 2022 Jan 13;11(2):378

Σύνοψη μελετών με SGLT2i : Πρωτεύων/Δευτερεύων Νεφρικό τελικό σημείο

Table 2. Summaries of landmark trials with SGLT2 inhibitors.

Trial	Year Published	Treatment (s)	Primary or Secondary End-Point	Composite Kidney Outcome	Hazard Ratio (95% CI)
EMPA-REG OUTCOME [24]	2015	Empagliflozin vs. placebo	Secondary	Doubling of serum creatinine, initiation of kidney replacement therapy or death from renal disease	0.54 (0.40–0.75)
CANVAS [25]	2017	Canagliflozin vs. placebo	Secondary	Sustained 40% reduction in eGFR, need for kidney replacement therapy, or death from renal cause	0.6 (0.47–0.77)
CREDENCE [26]	2019	Canagliflozin vs. placebo	Primary	End-stage kidney disease, doubling of the serum creatinine level, or death from renal or cardiovascular causes	0.70 (0.59– 0.82)
DECLARE-TIMI [27]	2019	Dapagliflozin vs. placebo	Secondary	Sustained ≥40% reduction in eGFR to <60 mL/min/1.73 m^2, new end-stage kidney disease or death from renal cause	0.53 (0.43–0.66)
DAPA-CKD [28]	2020	Dapagliflozin vs. placebo	Primary	Sustained ≥50% reduction in eGFR, end-stage kidney disease, or death from renal or cardiovascular cause	0.61 (0.51–0.72)
EMPEROR-Reduced [29]	2020	Empagliflozin vs. placebo	Secondary	Sustained ≥40% reduction in eGFR, chronic dialysis, renal transplant or sustained eGFR < 10–15 mL/min/1.73 m^2	0.50 (0.32–0.77)
EMPA-KIDNEY	2022	Empagliflozin vs. placebo	Primary	End-stage kidney disease, a sustained reduction in eGFR to <10 mL/min/1.73 m^2, renal death, or a sustained decline of ≥40% in eGFR	Ongoing

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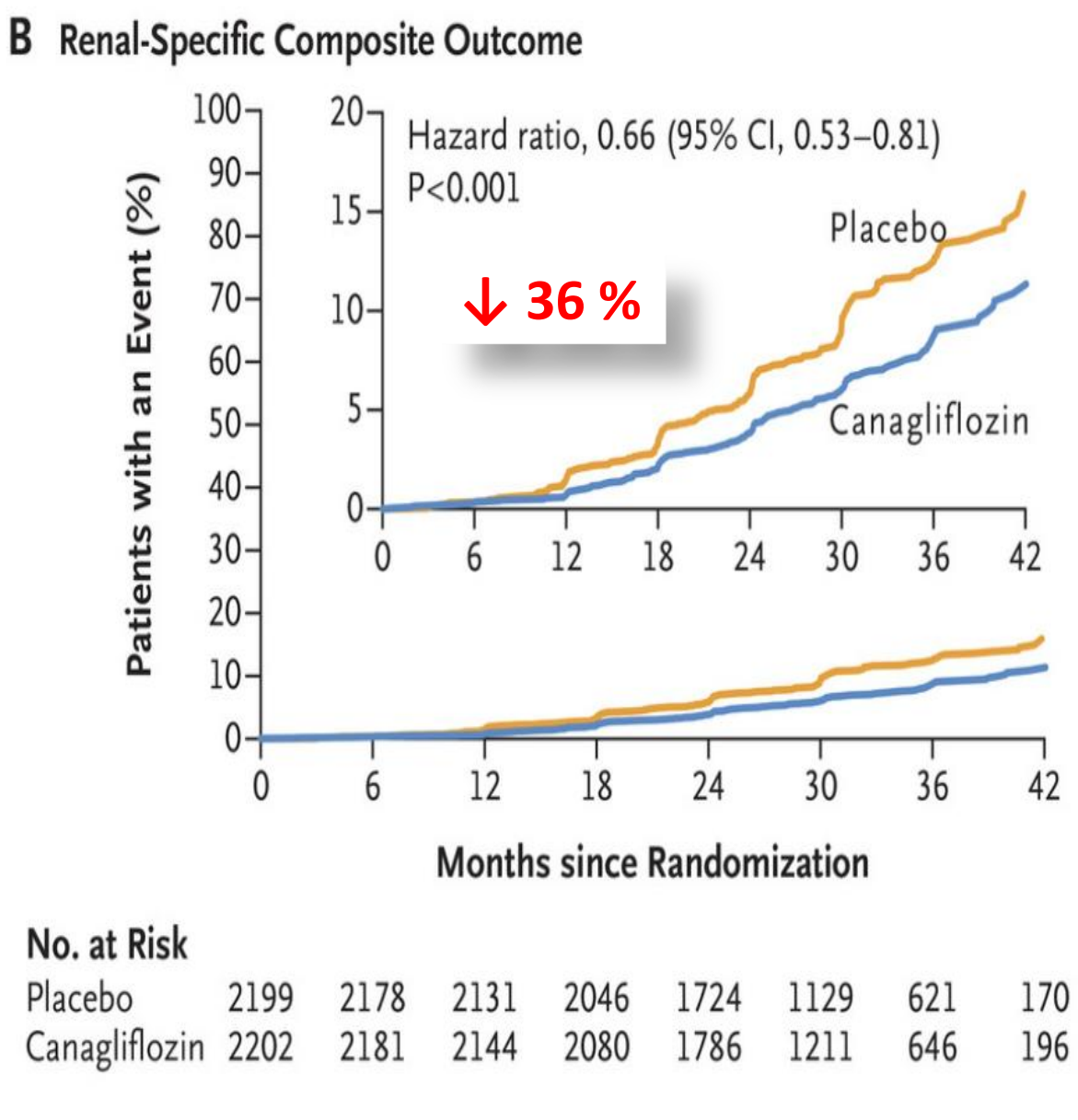
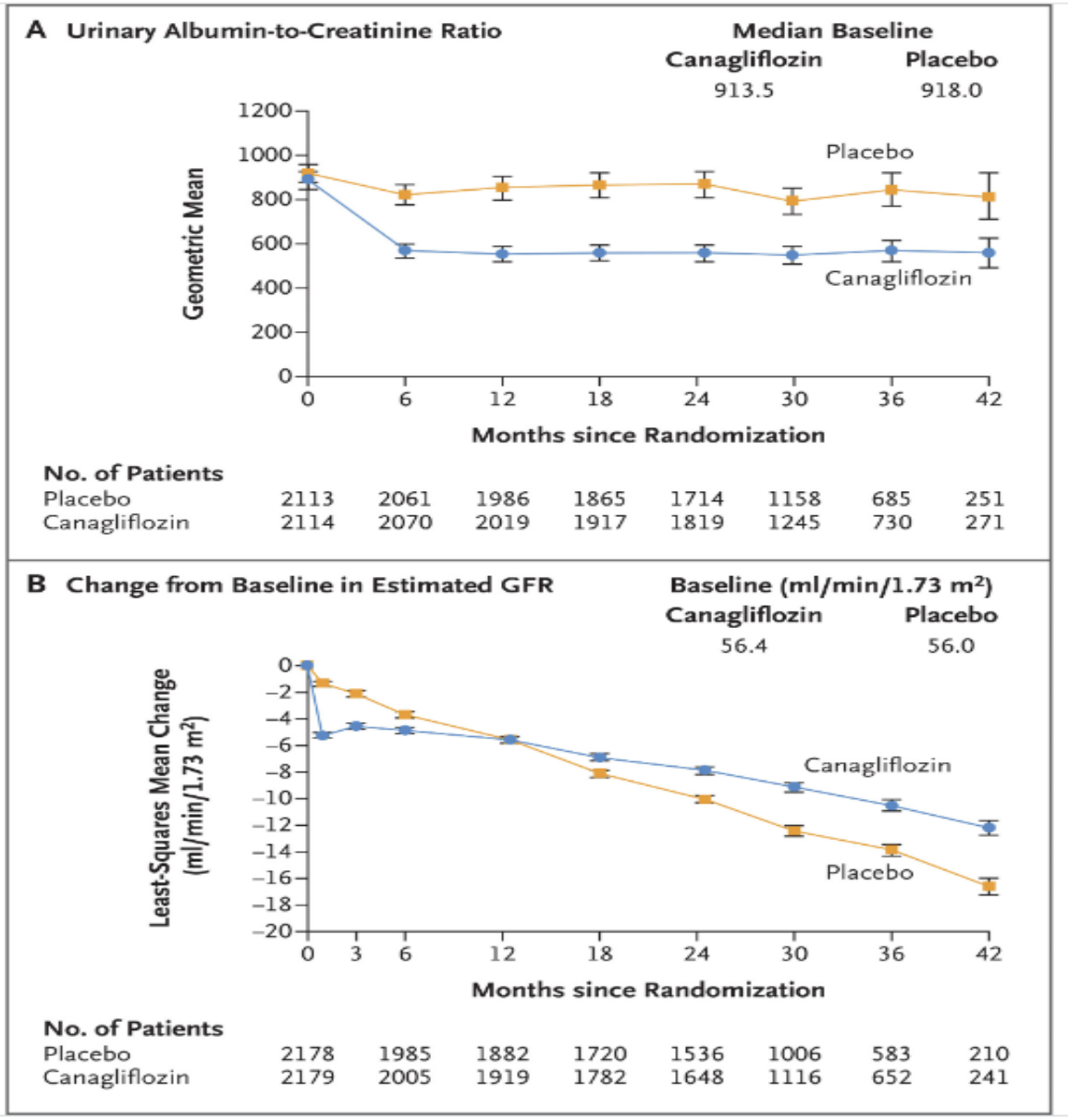
Canagliflozin and Renal Outcomes in Type 2 Diabetes and Nephropathy





Perkovic The New England Journal of Medicine April 14, 2019

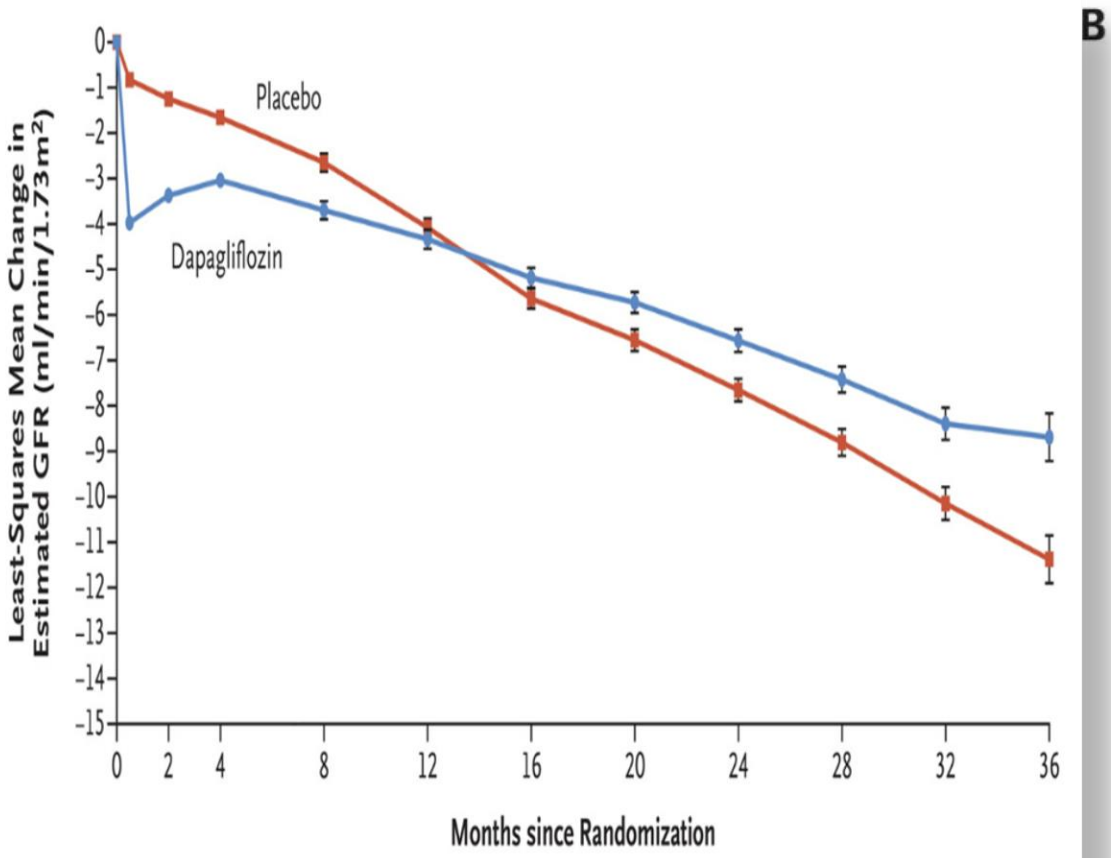
DAPA-CKD: Baseline characteristics

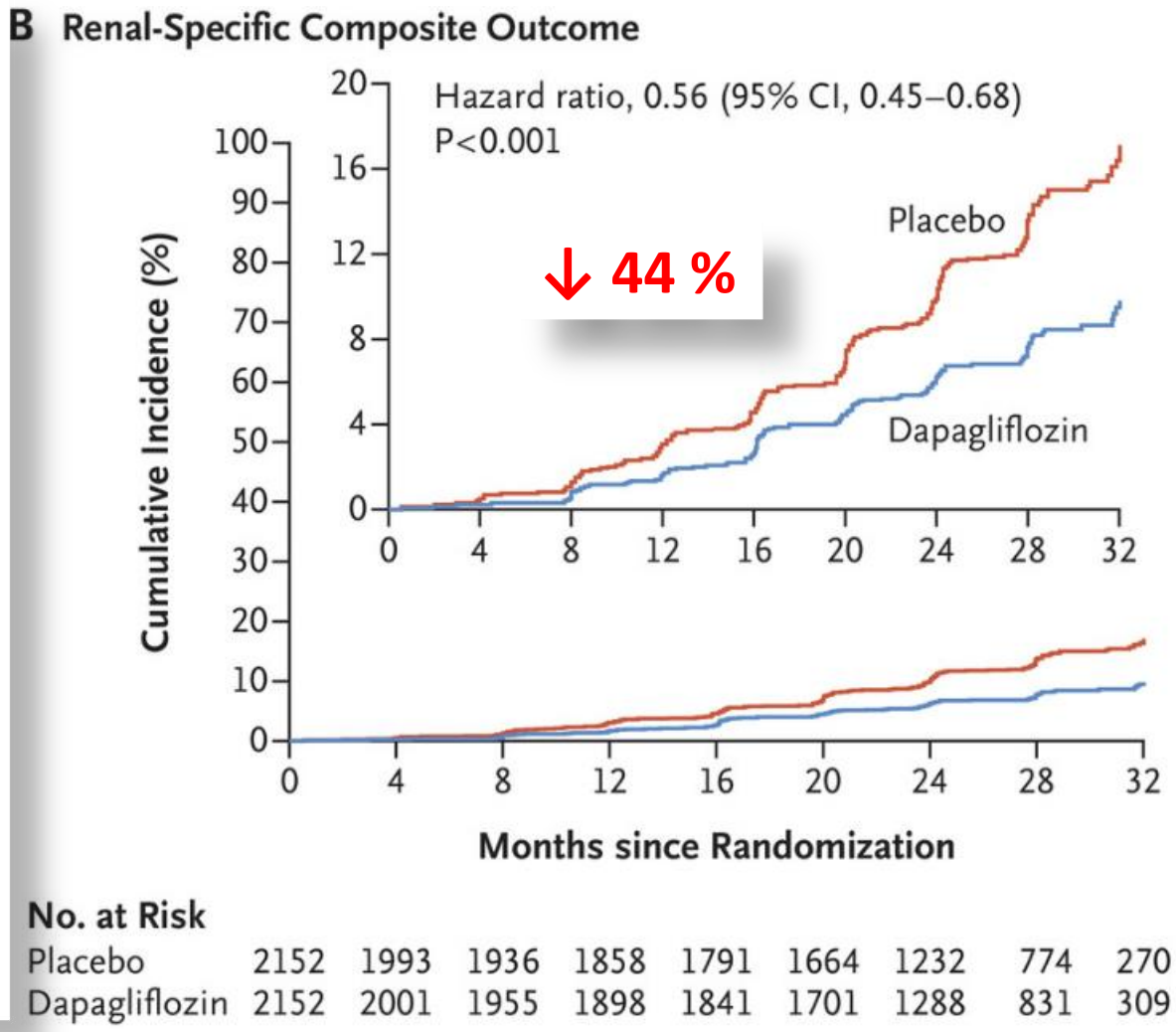
	Dapagliflozin (N=2152)	Placebo (N=2152)
Age, years, mean	62	62
Sex, female, %	33	33
Type 2 diabetes, %	68	67
Hypertension, %	96	96
Any cardiovascular disease, %	**38**	**37**
Myocardial infarction, %	8.6	9.6
Stroke, %	6.7	7.2
Atrial fibrillation/flutter, %	5.3	5.2
Heart failure, %	11	11
Systolic blood pressure, mmHg, mean	137	137
eGFR, mL/min/1.73m^2, mean	43	43
ACEi or ARB, %	97	97

Wheeler DC. et.al. Nephrol Dial Transplant. 2020 DOI 10.1093/ndt/gfaa234

Heerspink HJL et al. N Engl J Med. 2020; 383:1436-1446

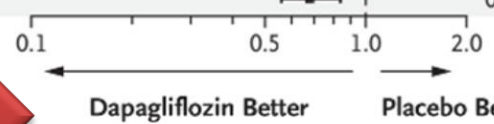
DAPA – CKD : πρωτεύοντα /δευτερεύοντα τελικά σημεία





Heerspink HJL et al. N Engl J Med. 2020; 383:1436-1446

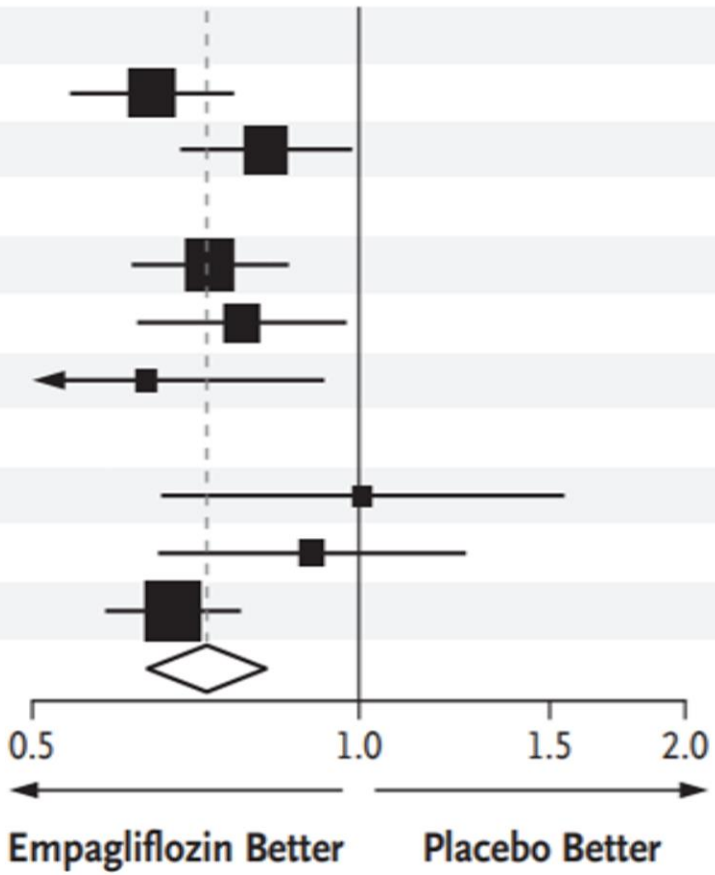
Subgroup	Dapagliflozin	Placebo	Hazard Ratio (95% CI)
	no. of participants/total no.		
All participants	197/2152	312/2152	0.61 (0.51–0.72)
Age			
≤65 yr	122/1247	191/1239	0.64 (0.51–0.80)
>65 yr	75/905	121/913	0.58 (0.43–0.77)
Sex			
Male	126/1443	209/1436	0.57 (0.46–0.72)
Female	71/709	103/716	0.65 (0.48–0.88)
Race			
White	110/1124	174/1166	0.62 (0.49–0.79)
Black	7/104	14/87	0.33 (0.13–0.81)
Asian	53/749	77/718	0.66 (0.46–0.93)
Other	27/175	47/181	0.54 (0.33–0.86)
Geographic region			
Asia	50/692	69/654	0.70 (0.48–1.00)
Europe	57/610	89/623	0.60 (0.43–0.85)
North America	35/401	69/412	0.51 (0.34–0.76)
Latin America	55/449	85/463	0.61 (0.43–0.86)
Type 2 diabetes			
Yes	152/1455	229/1451	0.64 (0.52–0.79)
No	45/697	83/701	0.50 (0.35–0.72)
Estimated GFR			
<45 ml/min/1.73 m^2	152/1272	217/1250	0.63 (0.51–0.78)
≥45 ml/min/1.73 m^2	45/880	95/902	0.49 (0.34–0.69)
Urinary albumin-to-creatinine ratio			
≤1000	44/1104	84/1121	0.54 (0.37–0.77)
>1000	153/1048	228/1031	0.62 (0.50–0.76)
Systolic blood pressure			
≤130 mm Hg	46/793	96/749	0.44 (0.31–0.63)
>130 mm Hg	151/1359	216/1403	0.68 (0.56–0.84)



Heerspink HJL et al. N Engl J Med. 2020; 383:1436-1446

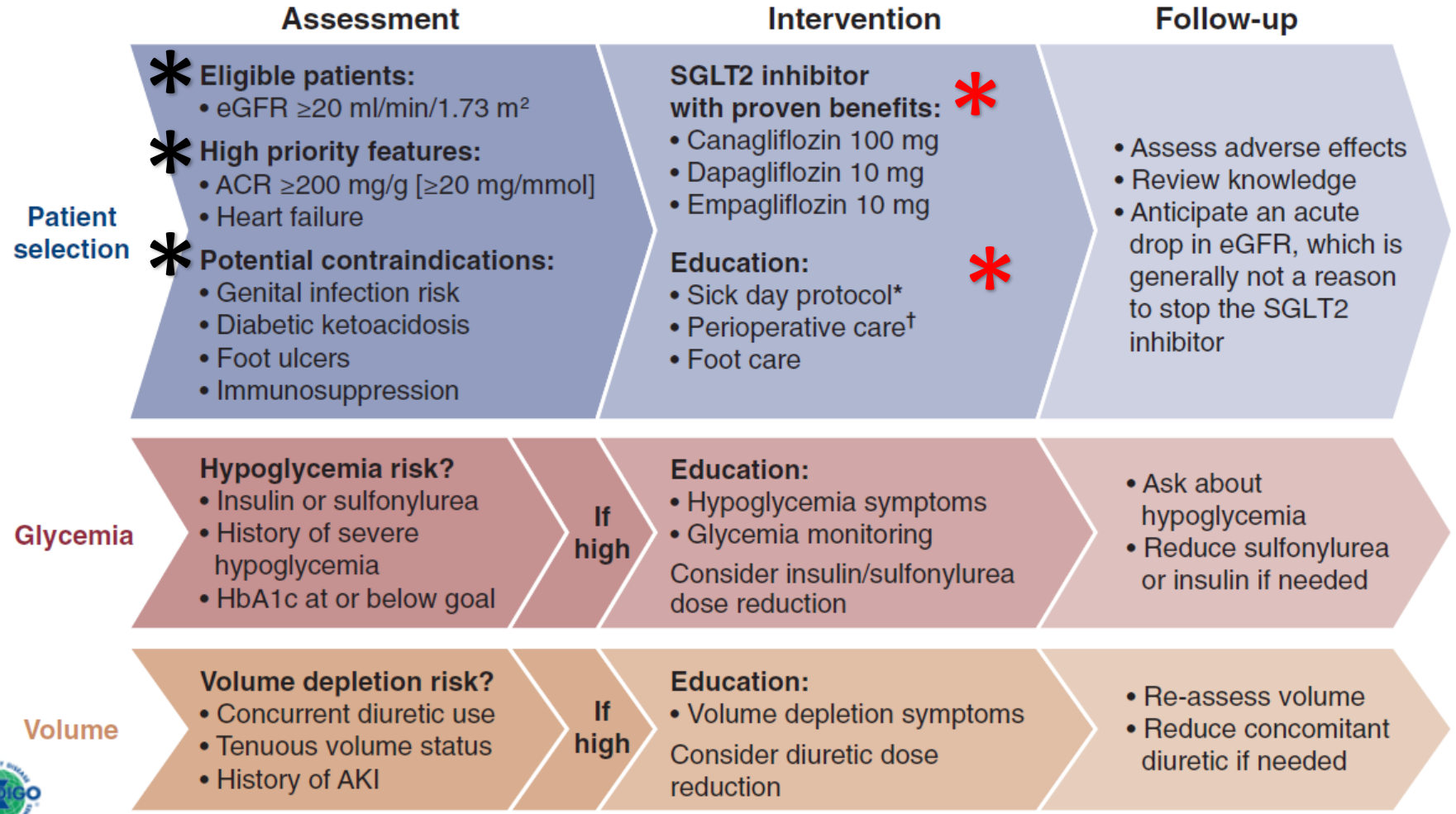
ORIGINAL ARTICLE

Subgroup	Empagliflozin	Placebo	Hazard Ratio for Progression of Kidney Disease or Death from Cardiovascular Causes (95% CI)
	no. of patients with event/total no.		
Diabetes mellitus			
Present	218/1525	306/1515	0.64 (0.54–0.77)
Absent	214/1779	252/1790	0.82 (0.68–0.99)
Estimated GFR			
<30 ml/min/1.73 m^2	247/1131	317/1151	0.73 (0.62–0.86)
≥30 to <45 ml/min/1.73 m^2	140/1467	175/1461	0.78 (0.62–0.97)
≥45 ml/min/1.73 m^2	45/706	66/693	0.64 (0.44–0.93)
Urinary albumin-to-creatinine ratio			
<30	42/665	42/663	1.01 (0.66–1.55)
≥30 to ≤300	67/927	78/937	0.91 (0.65–1.26)
>300	323/1712	438/1705	0.67 (0.58–0.78)
All patients	432/3304	558/3305	0.72 (0.64–0.82)



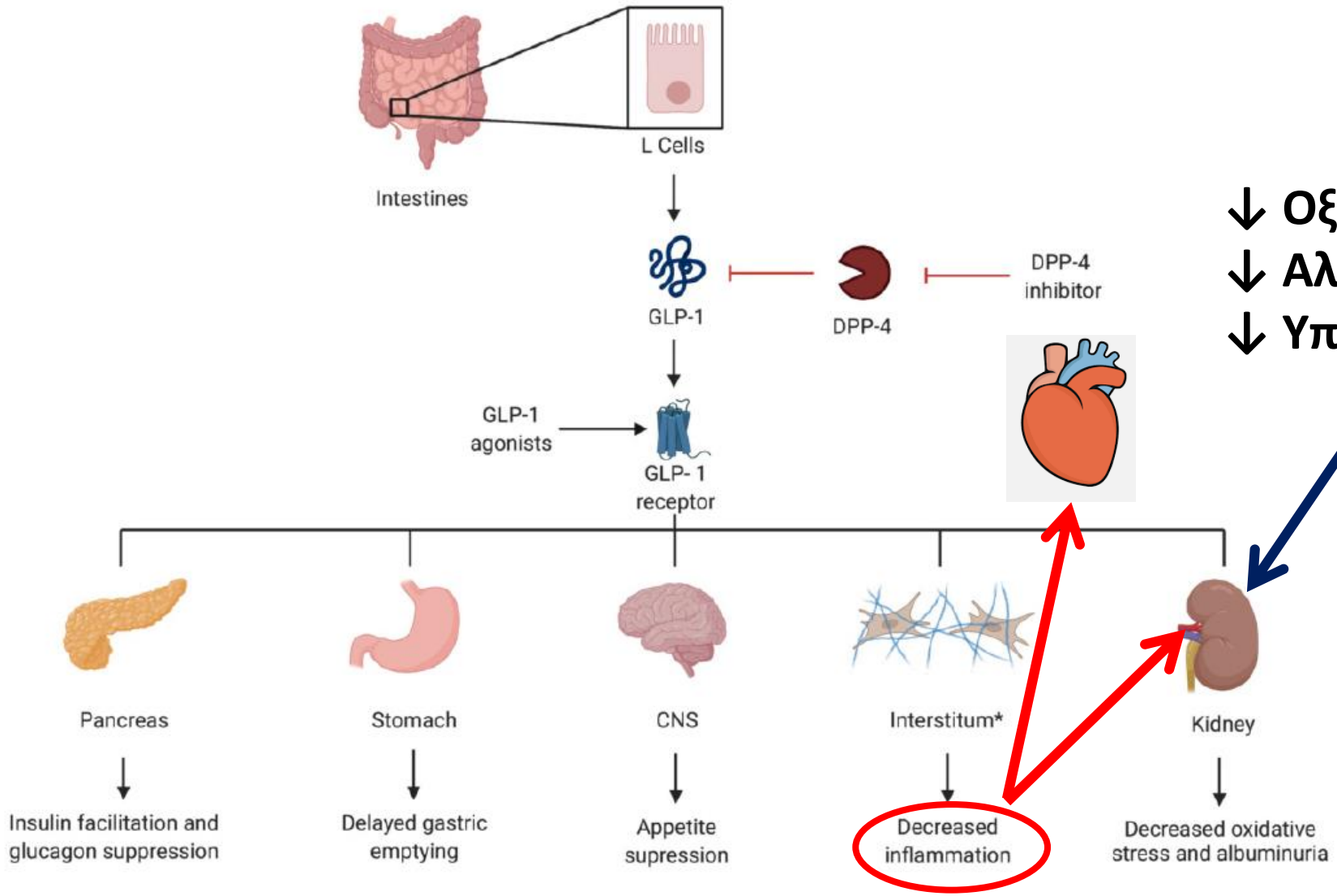
W.G. Herrington et al November 4, 2022, at NEJM.org.

Practical provider guide to initiating SGLT2 inhibitors in patients with type 2 diabetes and CKD



KDIGO 2020

GLP-1 Agonists



↓ Οξειδωτικού stress
↓ Αλβουμινουρία
↓ Υπερδιήθηση

Hanny Sawaf et al J Clin Med 2022 Jan 13;11(2):378

Σύνοψη μελετών με GLP-1 Agonists : Πρωτεύων/Δευτερεύων Νεφρικό τελικό σημείο

Table 3. Summaries of landmark trials with GLP-1 agonists.

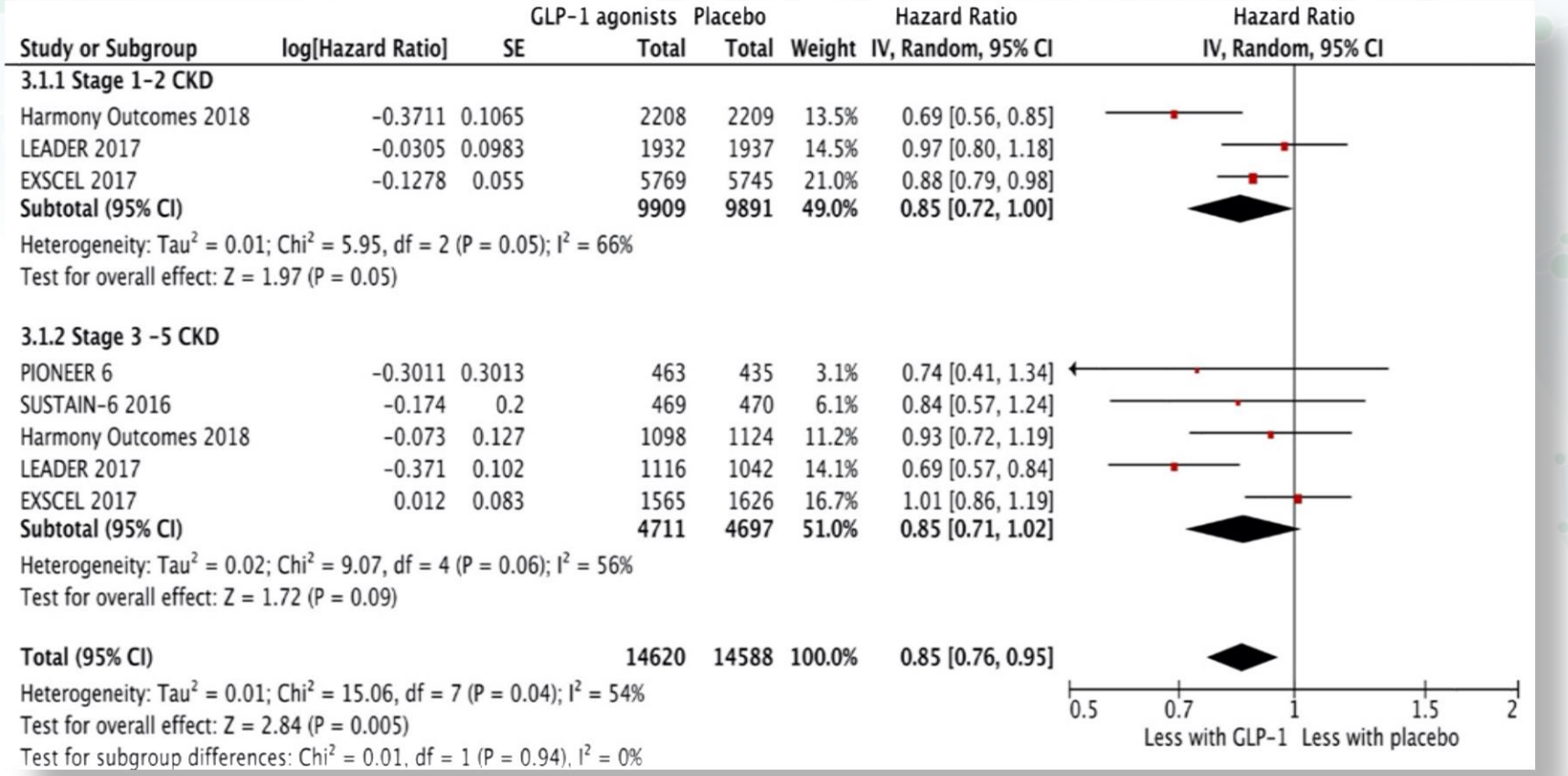
Trial	Year Published	Treatment (s)	Primary or Secondary	Kidney Outcome	Results
LEADER [39]	2016	Liraglutide vs. placebo	Secondary	Diabetic Nephropathy	HR 0.78 (95% CI 0.67–0.92)
SUSTAIN-6 [40]	2016	Semaglutide vs. placebo	Secondary	Macroalbuminuria, doubling of serum creatinine, Creatinine clearance $\leq$ 45 mL/min or KRT	HR 0.64 (95% CI 0.46–0.88)
AWARD-7 [41]	2018	Dulaglutide vs. insulin glargine	Secondary	eGFR and UACR	A decline in eGFR of the insulin arm but not in the higher-dose dulaglutide arm
REWIND [42]	2019	Dulaglutide vs. placebo	Secondary	300 mg/g > UACR in lower baseline concentration, sustained 30% > eGFR decline, KRT	HR 0.85 (95% CI 0.77–0.93)
Kristensen et. al. meta-analysis [43]	2019	GLP-1′s	—	New-onset macroalbuminuria, decline in eGFR, progression of kidney disease or death of kidney cause	HR 0.83 (95% CI 0.78–0.89)
AMPLITUDE-O [44]	2021	Efpeglenatide vs. placebo	Secondary	Incident microalbuminuria > 300mg/g, increase in UACR of at least 30% from baseline, sustained eGFR decrease > 40% for > 30 days, KRT for 90 days or more, eGFR < 15 for 30 days or more	HR 0.68 (95% CI 0.57–0.79)
FLOW	To be completed in 2024	Semaglutide vs. placebo	Primary	Persistent $\geq$ 50% reduction in eGFR, reaching ESKD, death from kidney disease or death from CV cause	Ongoing

Hanny Sawaf et al J Clin Med 2022 Jan 13;11(2):378

Anti-hyperglycemic Therapies in Patients with Diabetes and CKD

Recommendation 4.3.1: In patients with T2D and CKD who have not achieved individualized glycemic targets despite use of metformin and SGLT2i treatment, or who are unable to use those medications, we recommend a long-acting GLP-1 RA *(1B)*.

3-point Major Cardiovascular Events

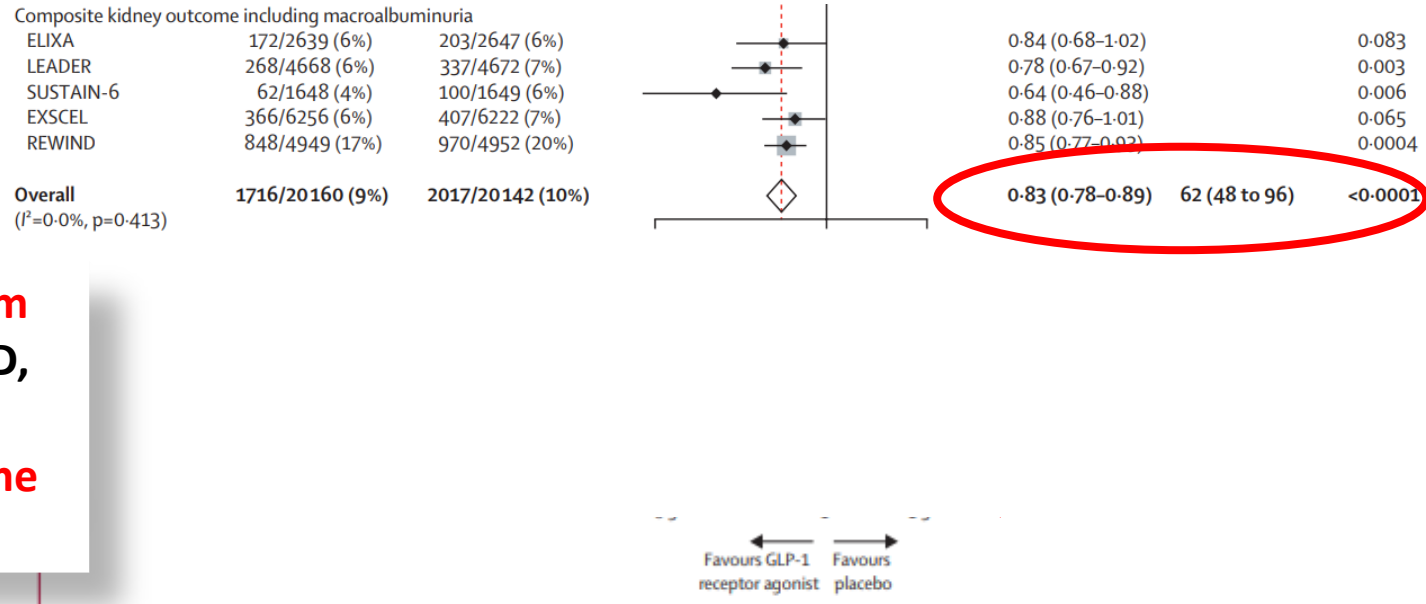


Meta-Analysis › Lancet Diabetes Endocrinol. 2019 Oct;7(10):776-785.
doi: 10.1016/S2213-8587(19)30249-9. Epub 2019 Aug 14.

Cardiovascular, mortality, and kidney outcomes with GLP-1 receptor agonists in patients with type 2 diabetes: a systematic review and meta-analysis of cardiovascular outcome trials

Søren L Kristensen [1], Rasmus Rørth [1], Pardeep S Jhund [2], Kieran F Docherty [2], Naveed Sattar [2], David Preiss [3], Lars Køber [4], Mark C Petrie [2], John J V McMurray [5]

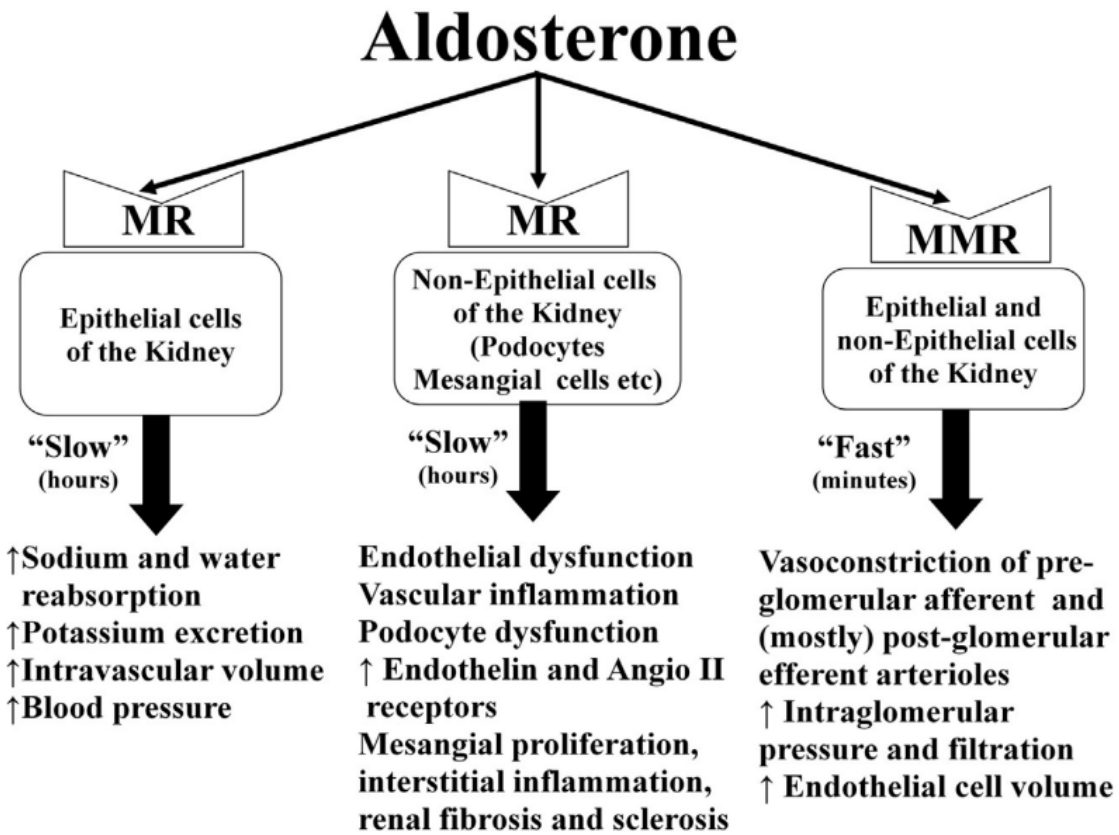
Νεφρο-Προστασία



A meta-analysis with a total of 56,004 participants from seven trials, including the LEADER, SUSTAIN-6, REWIND, ELIXA, EXSCEL, Harmony Outcomes, PIONEER 6 trials showed a 17% decrease in the composite renal outcome with GLP-1 agonists

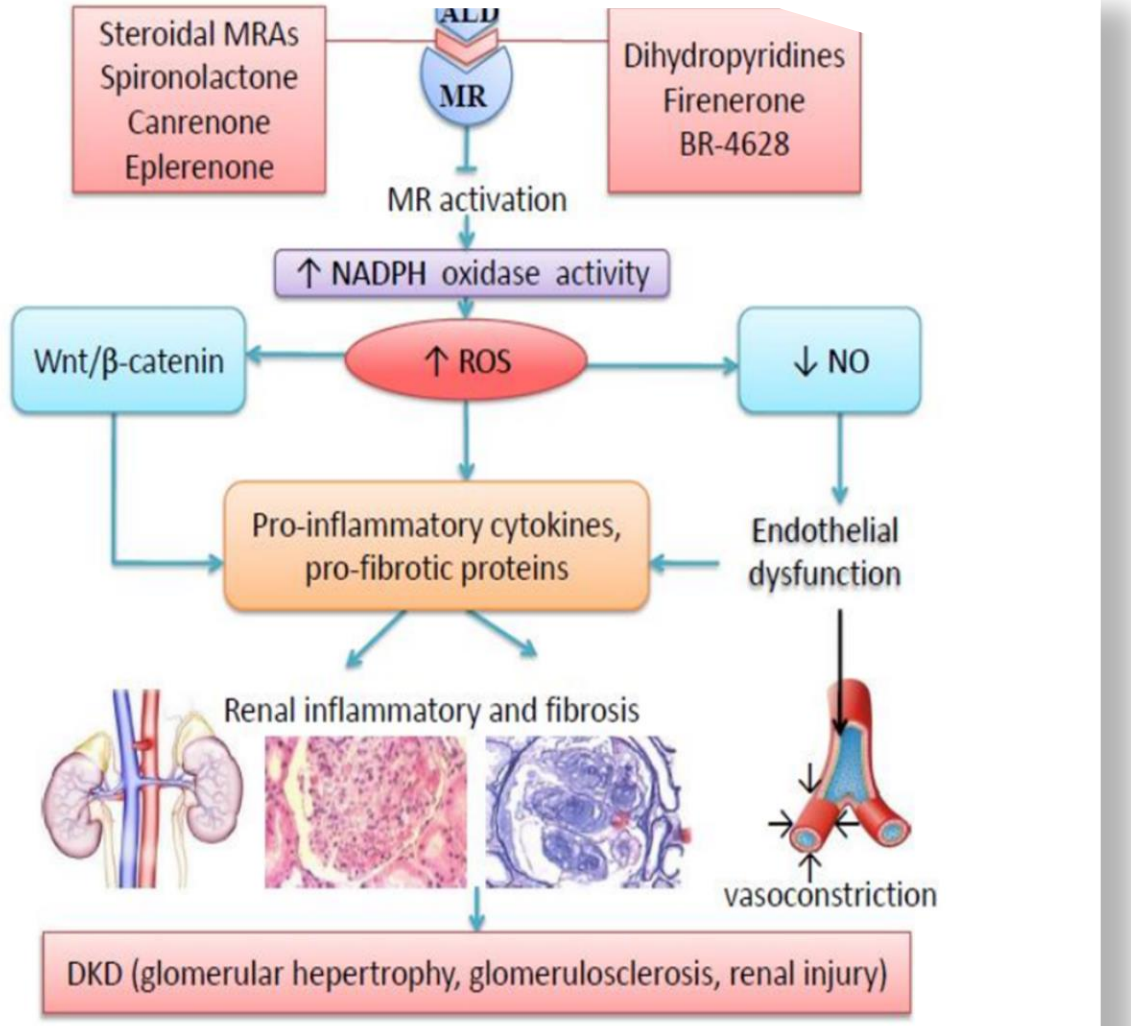
Kristensen, S.L et al Lancet Diabetes Endocrinol. 2019, 7, 776–785

Mineralocorticoid Receptor Antagonists



Pingping Yang et al Metabolism VOLUME 65, ISSUE 9, P1342-1349, SEPTEMBER 01, 2011

non-steroidal MRAs



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Μελέτες με non-steroidal MRAs : Πρωτεύων/Δευτερεύων Νεφρικό τελικό σημείο

Trial	Year Published	Composite Kidney Outcome	Primary or Secondary End-Point	Findings or Results
ARTS [62]	2013	Change in serum potassium	Primary	Significant increases in potassium concentrations at 10 mg/day or more
		Effect eGFR	Secondary	No change in renal impairment
ARTS-DN [63]	2015	Change in UACR	Primary	Dose dependent placebo-corrected mean UACR
		Potassium and eGFR safety points	Secondary	1.7–3.2% discontinuation for hyperkalemia in finerenone arm No finerenone discontinuation due to drop in eGFR
FIDELIO-DKD [64]	2020	Kidney failure, >40% decrease in eGFR, death from kidney cause	Primary	HR 0.82 (95% CI 0.73–0.93)
FIGARO-DKD [65]	2021	Kidney failure, >40% decrease in eGFR, death from kidney cause	Secondary	HR 0.87 (95% CI 0.76–1.01)

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A prespecified exploratory analysis from FIDELITY examined finerenone use and kidney outcomes in patients with chronic kidney disease and type 2 diabetes.

kidney INTERNATIONAL

ISN INTERNATIONAL SOCIETY OF NEPHROLOGY

K^+ ≤4.8 mmol/l

- Initiate finerenone
  - 10 mg daily if eGFR 25–59 ml/min per 1.73 m^2 *
  - 20 mg daily if eGFR ≥60 ml/min per 1.73 m^2
- Monitor K^+ at 1 month after initiation and then every 4 months
- Increase dose to 20 mg daily, if on 10 mg daily
- Restart 10 mg daily if previously held for hyperkalemia and K^+ now ≤5.0 mmol/l

K^+ 4.9–5.5 mmol/l

- Continue finerenone 10 mg or 20 mg
- Monitor K^+ every 4 months *

K^+ >5.5 mmol/l

- Hold finerenone *
- Consider adjustments to diet or concomitant medications to mitigate hyperkalemia
- Recheck K^+
- Consider reinitiation if/when K^+ ≤5.0 mmol/l

Bakris et al., 2022

*Time to first onset of kidney failure, sustained ≥57% decrease in eGFR from baseline over ≥4 weeks, or renal death; [b]*post hoc* analysis.

***Abbreviations**: AE, adverse event; CKD, chronic kidney disease; eGFR, estimated glomerular filtration rate; ESKD, end-stage kidney disease; HR, hazard ratio; RAS, renin-angiotensin system; RRR, relative risk reduction; T2D, type 2 diabetes; UACR, urine albumin-to-creatinine ratio.*

***Acknowledgments:** Funded by Bayer AG; ClinicalTrials.gov numbers NCT02540993 (FIDELIO-DKD) and NCT02545049 (FIGARO-DKD).*

CONCLUSION

Finerenone improves kidney outcomes, including reducing the risk of ESKD, and is well tolerated in patients with CKD and T2D

Αντιδιαβητικά δισκία ανάλογα με το στάδιο της ΧΝΝ

	Stage 3b (eGFR 30–44 mL/min/1.73 m²)	Stage 4 (eGFR 15–29 mL/min/1.73 m²)	Stage 5 (eGFR <15 mL/min/1.73 m²)
* Metformin	Reduce dose to 1000 mg/day	Contraindicated	
Insulin	Initiate and titrate conservatively to avoid hypoglycemia		
* **SGLT2 inhibitors***			
Canagliflozin	Maximum 100 mg daily	Initiation not recommended; may continue 100 mg daily if tolerated for kidney and CV benefit until dialysis	
Dapagliflozin	10 mg daily†	Initiation not recommended with eGFR <25 mL/min/1.73 m²; may continue if tolerated for kidney and CV benefit until dialysis	
Empagliflozin	10 mg daily‡	Initiation not recommended with eGFR <20 mL/min/1.73 m²; may continue if tolerated for kidney and CV benefit until dialysis	
Ertugliflozin	Use not recommended with eGFR <45 mL/min/1.73 m²		
GLP-1 receptor agonists§			
Exenatide	Caution initiating or increasing dose; avoid once-weekly formulation	Use not recommended	
* Dulaglutide	No dose adjustment required		
* Liraglutide	No dose adjustment required		
Lixisenatide	No dose adjustment required		Use not recommended
Semaglutide	No dose adjustment required		
DPP-4 inhibitors			
Alogliptin	Maximum 12.5 mg daily	Maximum 6.25 mg daily	
Linagliptin	No dose adjustment required		
Saxagliptin	Maximum 2.5 mg daily		
Sitagliptin	Maximum 50 mg daily	Maximum 25 mg once daily	
Sulfonylureas (2nd generation)			
Glimepiride	Initiate conservatively at 1 mg daily and titrate slowly to avoid hypoglycemia		
Glipizide	Initiate conservatively (e.g., 2.5 mg once daily) and titrate slowly to avoid hypoglycemia		
Glyburide	Use not recommended		
Thiazolidinediones			
Pioglitazone	No dose adjustment required		

HbA1C<7%

Pr: 0.8 gr/Kg
ΣB

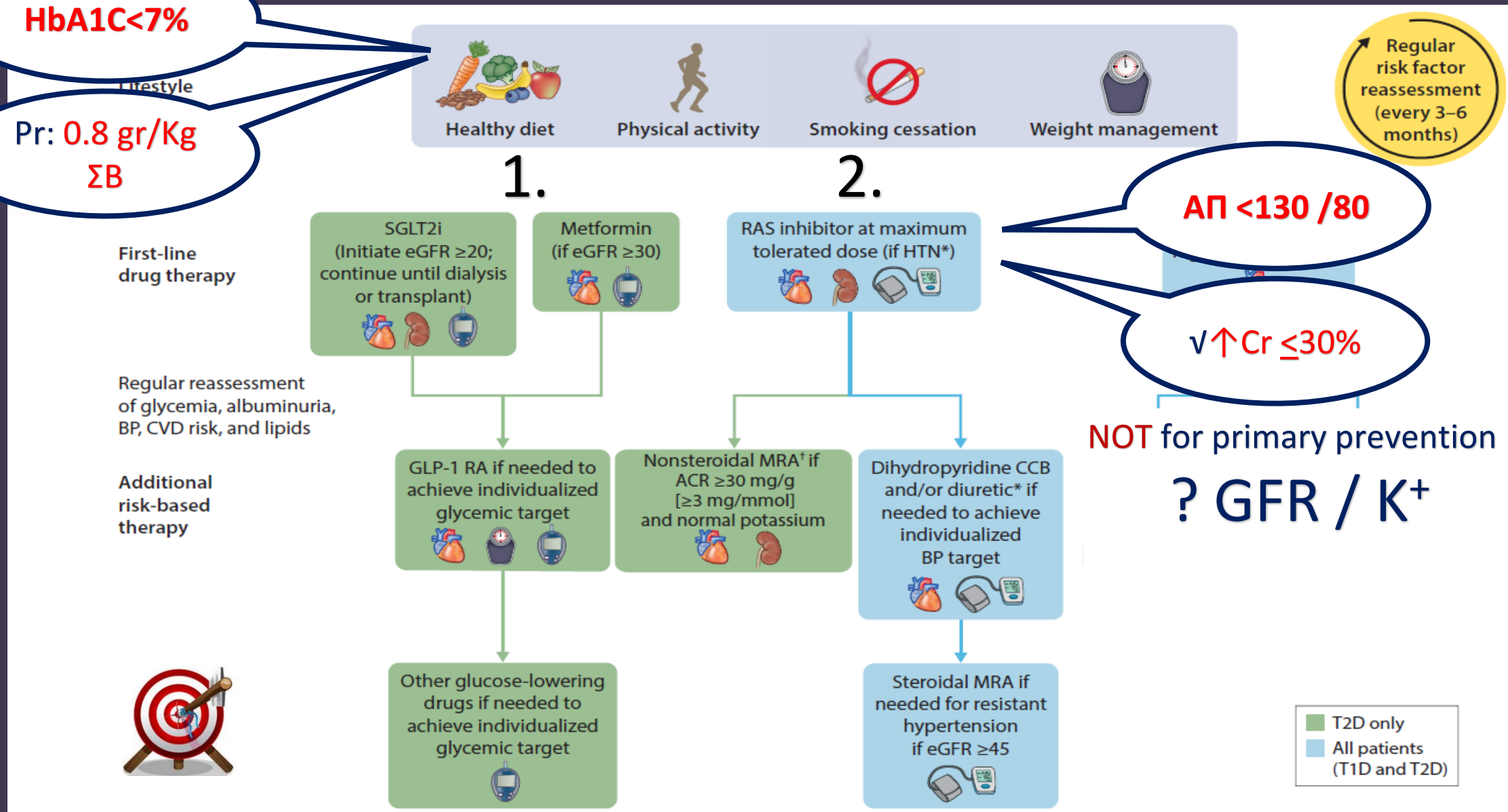


Figure 2| Holistic approach for improving outcomes in patients with diabetes and chronic kidney disease. *Angiotensin-converting

IH de Boer et al.: Diabetes management in CKD: consensus report by ADA and KDIGO Kidney International (2022)

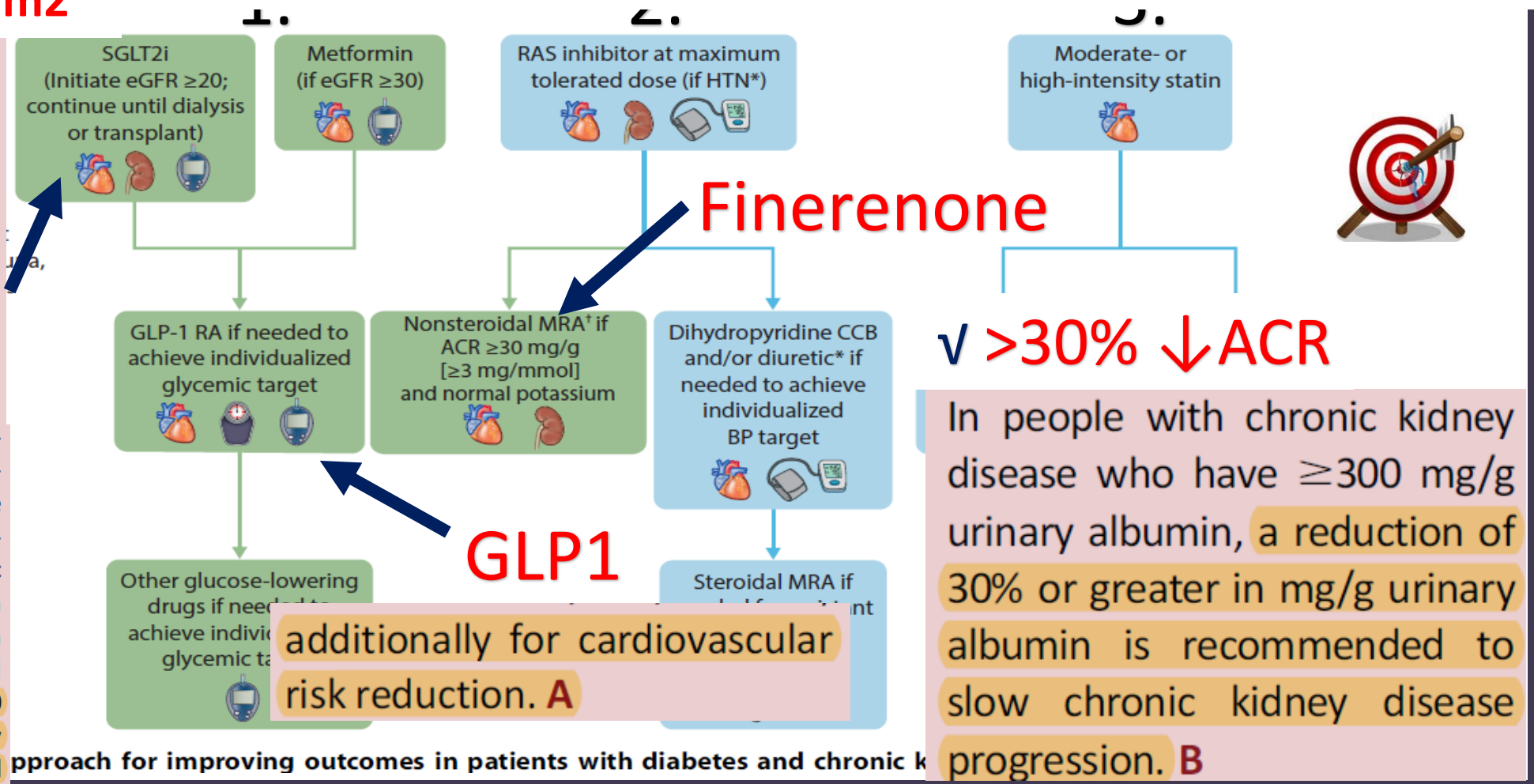
SGLT2i (ADA23)

≥20mL/min/1.73 m2

11.5a For people with type 2 diabetes and diabetic kidney disease, use of a sodium–glucose cotransporter 2 inhibitor is recommended to reduce chronic kidney disease progression and cardiovascular events in patients with an estimated glomerular filtration rate ≥20 mL/min/1.73 m^2 and urinary albumin ≥200 mg/g creatinine. **A**

11.5b For people with type 2 diabetes and diabetic kidney disease, use of a sodium–glucose cotransporter 2 inhibitor is recommended to reduce chronic kidney disease progression and cardiovascular events in patients with an estimated glomerular filtration rate ≥20 mL/min/1.73 m^2 and urinary albumin ranging from normal to 200 mg/g creatinine. **B**

Recommendation 1.4.1: We suggest a nonsteroidal mineralocorticoid receptor antagonist with proven kidney or cardiovascular benefit for patients with T2D, an eGFR ≥25 ml/min per 1.73 m^2, normal serum potassium concentration, and albuminuria (≥30 mg/g [≥3 mg/mmol]) despite maximum tolerated dose of RAS inhibitor (RASi) *(2A)*.



√ >30% ↓ACR

In people with chronic kidney disease who have ≥300 mg/g urinary albumin, a reduction of 30% or greater in mg/g urinary albumin is recommended to slow chronic kidney disease progression. **B**

IH de Boer et al.: Diabetes management in CKD: consensus report by ADA and KDIGO Kidney International (2022)

THANK YOU!