Il Paziente Diabetico Anziano:
Strategie del Trattamento del Diabete e Protezione Renale

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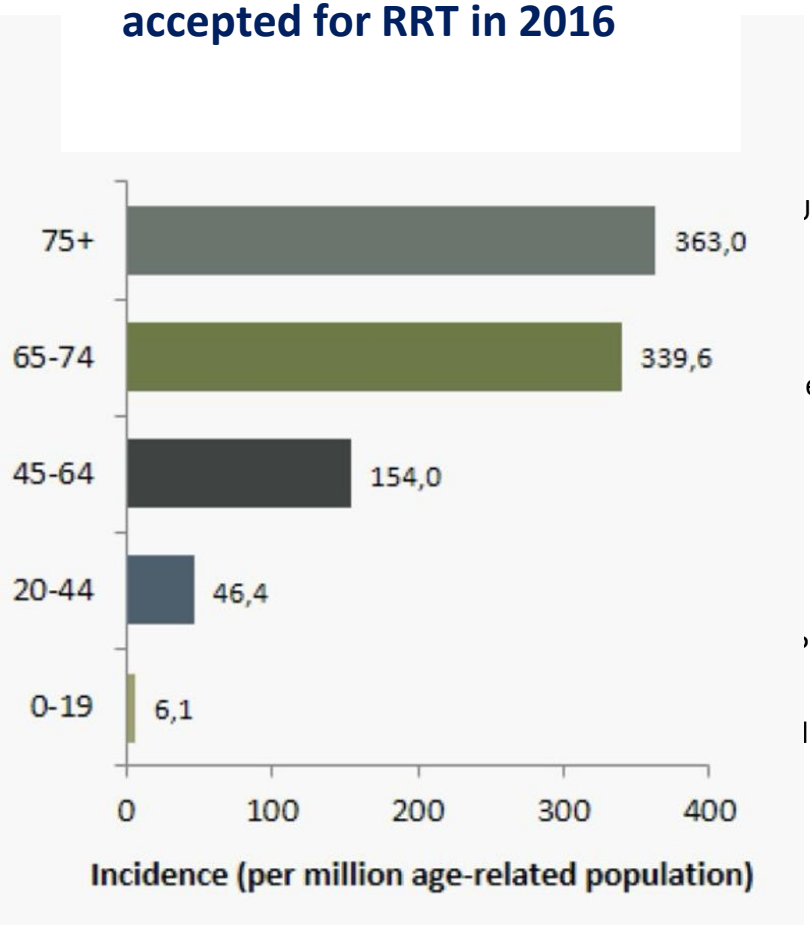
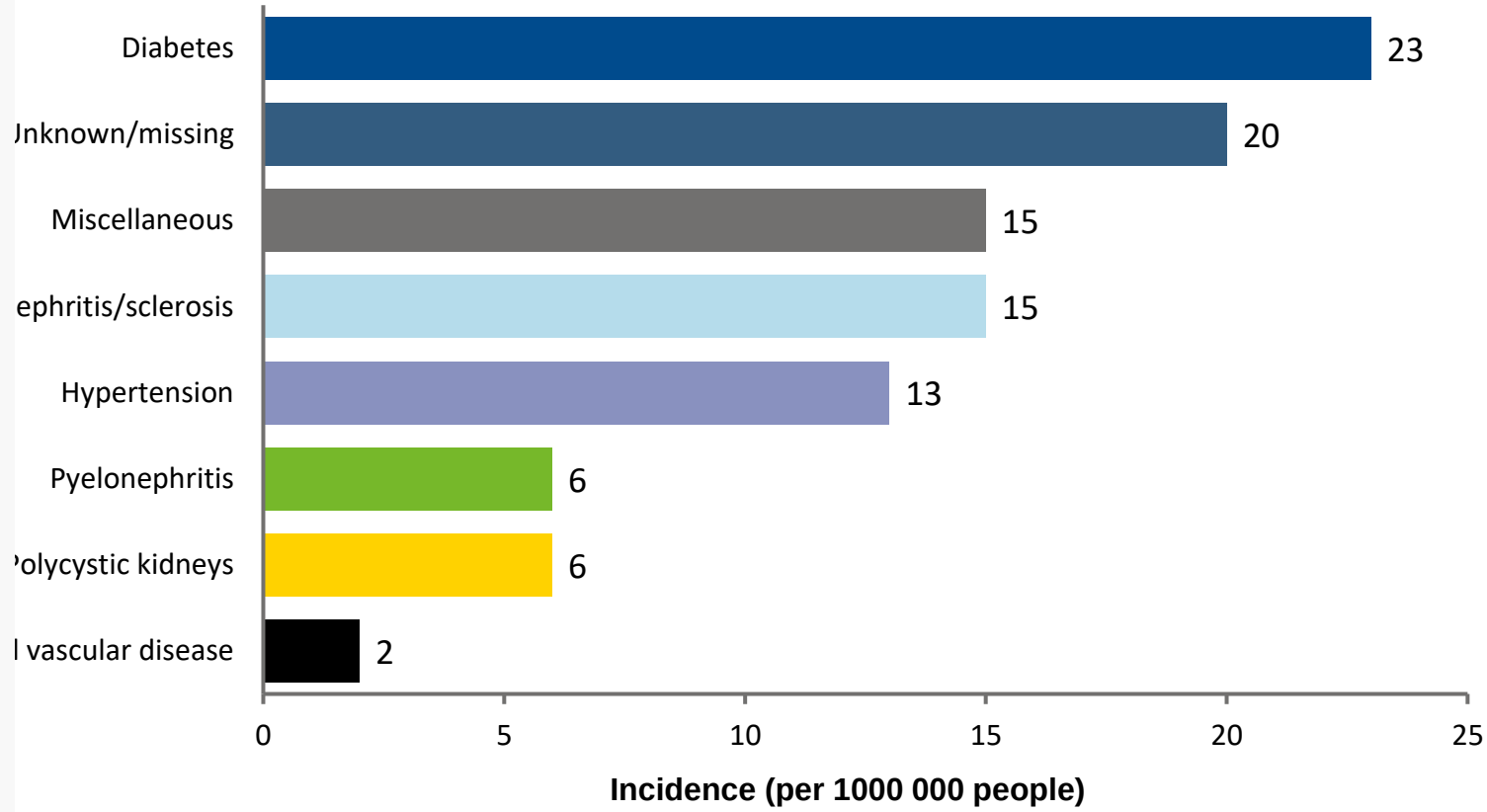
Older age and diabetes are the two main features of patients starting dialysis

Age in patients accepted for RRT in 2016



Primary renal disease in patients accepted for RRT in 2016



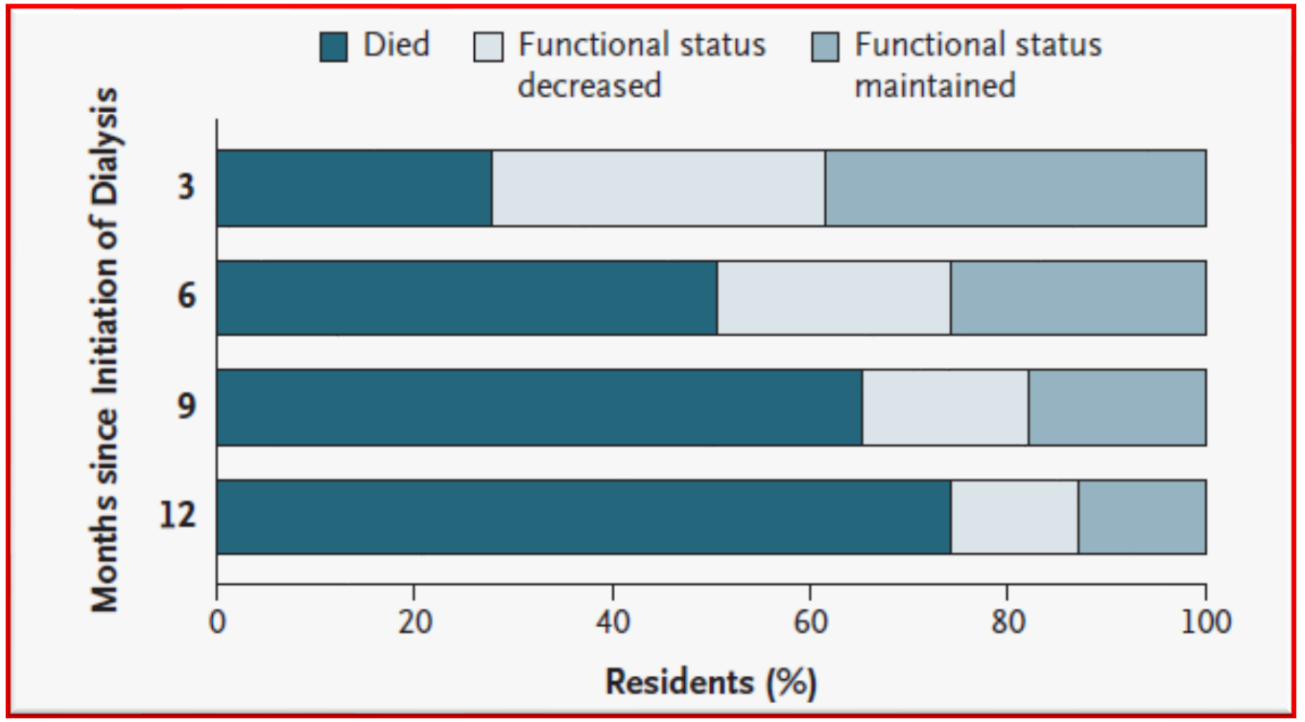
Data from the ERA–EDTA registry 52 national and regional registries (N = 6.87 million)
Kramer , Clinical Kidney J , 2019

Functional Status of Elderly Adults before and after Initiation of Dialysis

Table 1. Characteristics of the Subjects at the Initiation of Dialysis.*

Characteristic	Subjects†
Age (yr)	73.4±10.9
Estimated glomerular filtration rate (ml/min/1.73 m^2 of body-surface area)	10.7±4.9
Albumin (g/dl)	2.9±0.6
Female sex (%)	60
Race (%)‡	
White	64
Black	32
Other	4
Coexisting condition (%)	
Diabetes	68
Congestive heart failure	66
Coronary artery disease	44
Peripheral vascular disease	37
Cerebrovascular disease	39
Chronic obstructive pulmonary disease	24
Cancer	12
Dementia	22
Depression	35
Hemodialysis (vs. peritoneal dialysis) (%)	95
Hospitalized at initiation of dialysis (%)	69

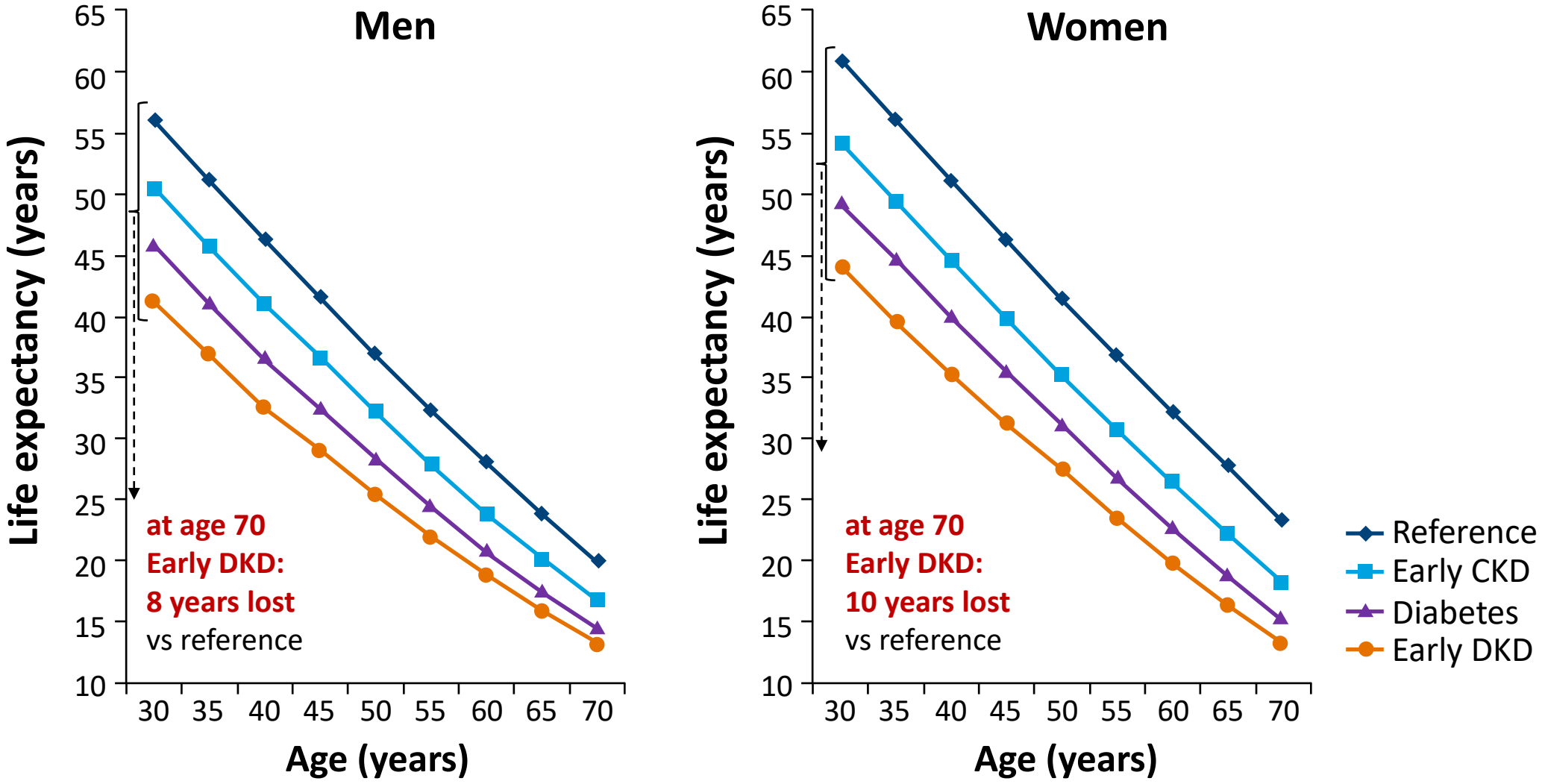
3702 nursing home residents in US who started HD between 6/1998 and 10/2000 and with at least one measurement of functional status available before dialysis



Kurella Tamura, NEJM 2009

Diabetic Kidney Disease (DKD) shortens life span…

…well before dialysis and at all ages



Wen CP, Kidney Int 2017

Paradigm Shift

In the treatment of CKD

ASN
American Society of Nephrology

Preserving Kidney Function Instead of Replacing It

*Alan S. Kliger,[1] and Frank C. Brosius,[2] on behalf of the Diabetic Kidney Disease Task Force of the American Society of Nephrology**

It is time for nephrology to embrace a change in paradigm: returning to our traditional focus on pathophysiology and kidney preservation.

CJASN 15: 129–131, 2020.

The Aging Kidney (I)…

Age and the course of glomerular filtration rate in persons aged 70 and above

CJASN Clinical Journal of the American Society of Nephrology

Berlin Initiative Study (BIS)

Longitudinal population-based cohort

Objectives

To describe the course of eGFR in individuals aged ≥70, and to define reference values for both sexes

To compare the patterns of eGFR decline in old age calculated by five eGFR equations

Materials and Methods

Nov 2009 – Jun 2011
Recruitment

80.4y
Mean age

6.1y
Median follow-up

n = 2,069

Biennial eGFR assessment

5,239
Follow-up visits

Results

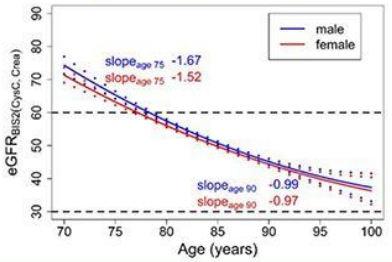
eGFR >60 ml/min/1.73m²

70-74y o–o–o–o→ 75%

80-84y o–o–o–o→ 25%

90-94y o–o–o–o→ 5%

Course of eGFR



Elke S. Schaeffner et al. CJASN 2022;17:1119-1128

Results

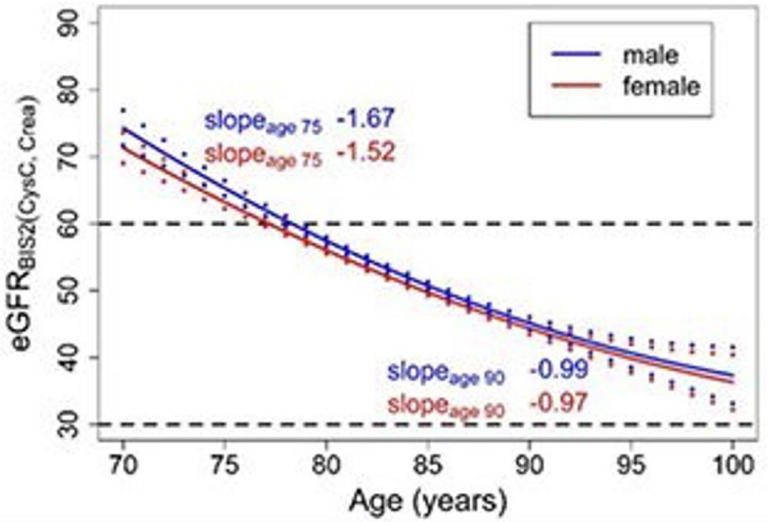
eGFR >60 ml/min/1.73m²

70-74y o–o–o–o→ 75%

80-84y o–o–o–o→ 25%

90-94y o–o–o–o→ 5%

Course of eGFR



The Aging Kidney (II)…

Age as a determinant of renal sodium conservation in normal man

MURRAY EPSTEIN,* and NORMAN K. HOLLENBERG *Miami, Fla. and Boston, Mass.*

Age modifies a number of factors which determine renal sodium handling including the rate of glomerular filtration, renal hemodynamics, and the responsiveness of the renin-angiotensin-aldosterone system. This study was carried out, therefore, to examine the effects of age on the capacity of the normal human kidney to respond to restriction of sodium intake. Renal conservation of sodium and response to dietary sodium restriction was assessed in 89 healthy subjects who were free of cardiovascular, renal, or adrenal disease. The daily reduction in urine sodium which followed restriction of intake to 10 mEq. of sodium and 100 mEq. of potassium per day conformed well to an exponential function, defined by an unweighted least-squares fit. The half-time for the reduction in renal sodium excretion in subjects under 30 years was −17.6 ± 0.7 hours, significantly faster than for subjects aged 30 to 59, who had a relatively constant half-time (23.4 ± 1.1 hours). In subjects over 60 years of age the half-time was prolonged to 30.9 ± 2.8 hours, significantly greater than that of the younger age group. These observations indicate that age significantly influences the kidney's capacity to conserve sodium. Age-related change must be considered in the assessment of this function in human disease.

J Lab Clin Med 1976

The Aging Kidney (III)…

Community-based incidence of acute renal failure

C-y Hsu[1], CE McCulloch[2], D Fan[3], JD Ordoñez[4], GM Chertow[1,2] and AS Go[1,2,3]

- **Health care delivery system –Kaiser Permanente of Northern California**
- **15 953 549 person-years of observation in the 1996-2003 period**
- **ARF definition (Hou) increase in sCreat of:**
  - **0.5 mg/dl if basal <1.9 mg/dl**
  - **1.0 mg/dl if basal 2.0-4.9 mg/dl**
  - **1.5 mg/dl if basal ≥5.0 mg/dl.**

Nephroprotective agents in older versus younger DKD patients

Target, Efficacy, Safety ???

Kidney International (2007)

The Aging Kidney (III)…

Community-based incidence of acute renal failure

C-y Hsu[1], CE McCulloch[2], D Fan[3], JD Ordoñez[4], GM Chertow[1,2] and AS Go[1,2,3]

	Overall rate (95% CI)	By age group
1996–2003	384.1 (381.1–387.2)	Age < 50: 78.0 (76.3–79.7) Age 50–59: 320.0 (313.2–326.9) Age 60–69: 814.8 (801.3–828.3) Age 70–79: 1809.1 (1783.5–1834.7) Age ⩾ 80: 3545.4 (3481.4–3609.5)
1996–1997	322.7 (316.7–328.5)	Age < 50: 64.7 (61.4–68.0) Age 50–59: 224.5 (212.6–236.3) Age 60–69: 597.8 (574.4–621.3) Age 70–79: 1362.1 (1318.3–1405.9) Age ⩾ 80: 2867.5 (2760.9–2974.2)
1998–1999	388.3 (382.1–394.5)	Age < 50: 72.9 (69.5–76.2) Age 50–59: 303.8 (290.4–317.3) Age 60–69: 796.6 (770.0–823.3) Age 70–79: 1813.2 (1762.2–1864.2) Age ⩾ 80: 3796.3 (3665.5–3927.1)
2000–2001	453.6 (447.1–460.1)	Age < 50: 90.7 (87.1–94.3) Age 50–59: 393.7 (378.6–408.9) Age 60–69: 985.9 (956.4–1015.4) Age 70–79: 2220.7 (2164.1–2277.4) Age ⩾ 80: 4388.0 (4293.9–4590.4)
2002–2003	522.4 (515.5–529.3)	Age < 50: 106.4 (102.6–110.2) Age 50–59: 483.8 (467.2–500.3) Age 60–69: 1238.2 (1205.2–1271.3) Age 70–79: 2741.3 (2677.1–2805.4) Age ⩾ 80: 4884.3 (4722.8–5045.7)

Incidence rates
(per 100 000 person-years)
non-dialysis requiring AKI

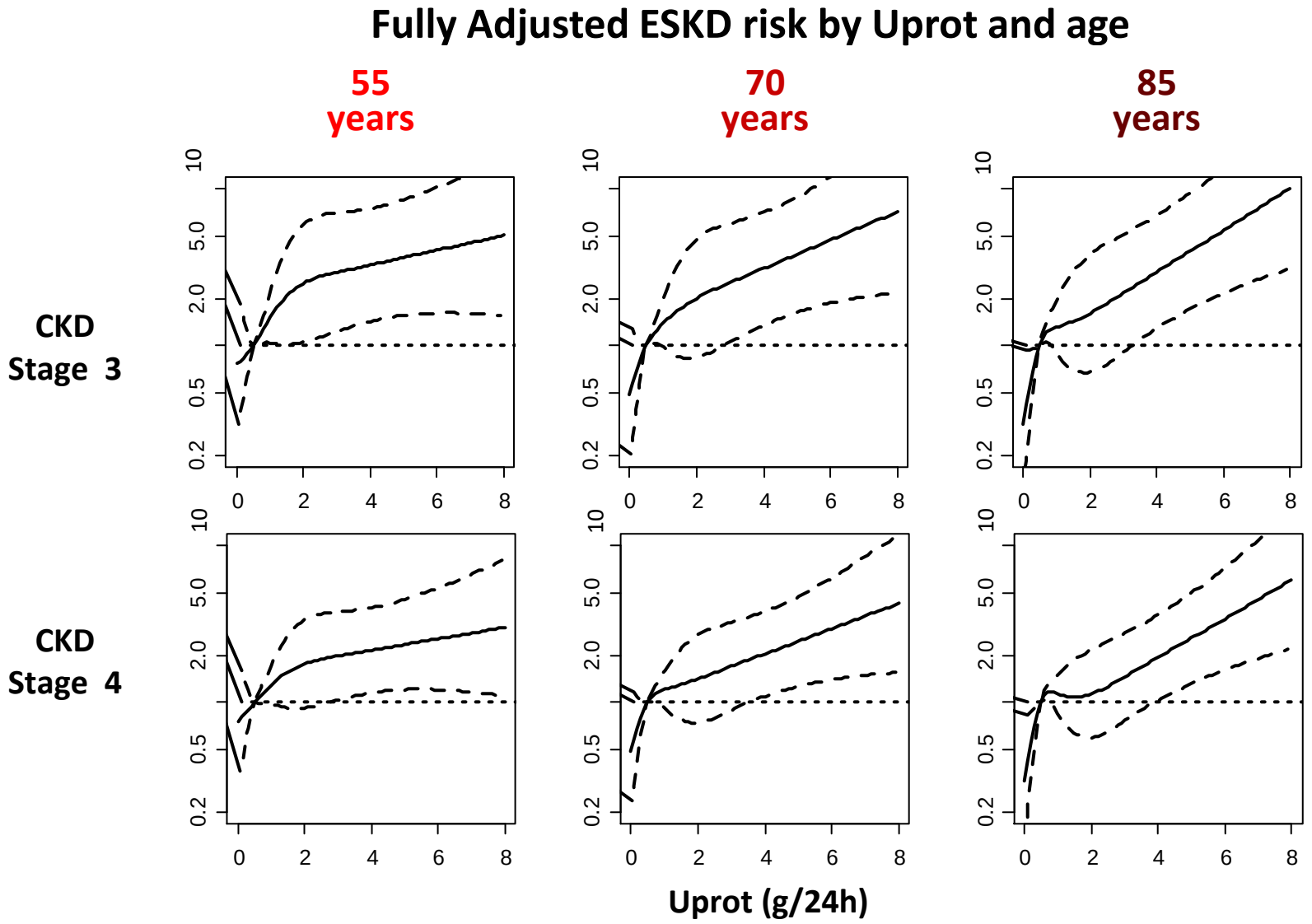
Kidney International (2007)

Proteinuria as target of nephroprotective therapies…

…at older age the prognostic role of proteinuria on ESKD is higher !!!

Interaction Age*Uprot
P=0.012

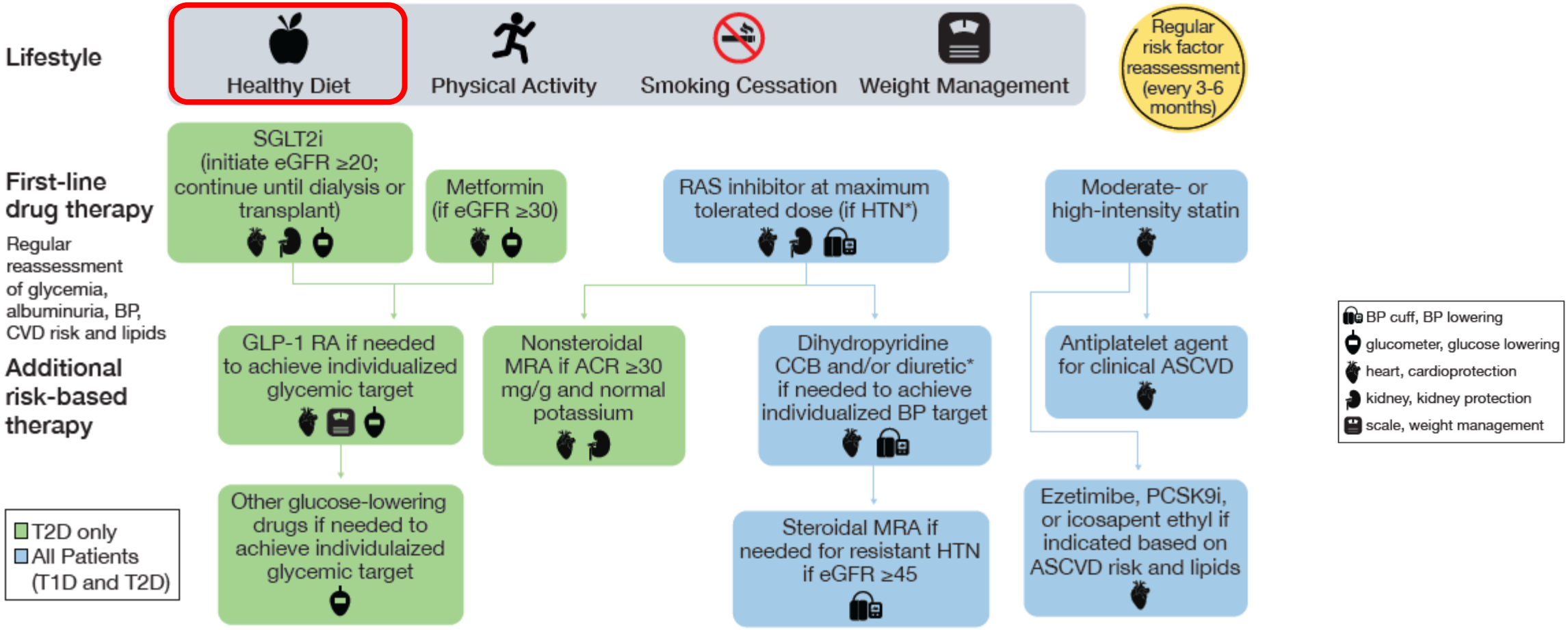
ESKD risk associated with Uprot increases more at older age



De Nicola L et al.., KI 2012

Diabetes management in chronic kidney disease: a consensus report by the American Diabetes Association (ADA) and Kidney Disease: Improving Global Outcomes (KDIGO)

Novel holistic approach



Kidney Int, 2022

Low Salt Diet: Yes but...caution in older !!!

Predictive effect of salt intake on patient and kidney survival in non-dialysis CKD: competing risk analysis in older versus younger patients under nephrology care

- **769 younger vs 1016 older CKD pts from 40 Italian renal clinics (30% DM2)**
- **eGFR: 41±25 in younger and 34±16 in older**
- **Median salt intake on ≥ 2 measurements of 24h UNaV:**
  - **8.6 g/24h in younger**
  - **8.2 g/24h in older**

	<6 g/day	6-8 g/day	>8 g/day
	HR (95% CI)	HR (95% CI)	HR (95% CI)
ESKD risk			
Age ≤65	Reference	1.189 (0.788-1.795)	1.096 (0.763-1.574)
Age >65	1.024 (0.656-1.599)	**0.577 (0.361-0.924)**	**0.564 (0.382-0.833)**
Death risk			
Age ≤65	Reference	0.791 (0.318-1.966)	0.620 (0.275-1.397)
Age >65	**3.810 (1.829-7.936)**	**3.695 (1.808-7.550)**	**2.938 (1.457-5.926)**

Adjusted for gender, BMI, DM, primary renal disease, history of CVD, SBP, eGFR, Uprot, Hb, sP, albumin, RAASI, diuretics

Garofalo...De Nicola NDT 2021

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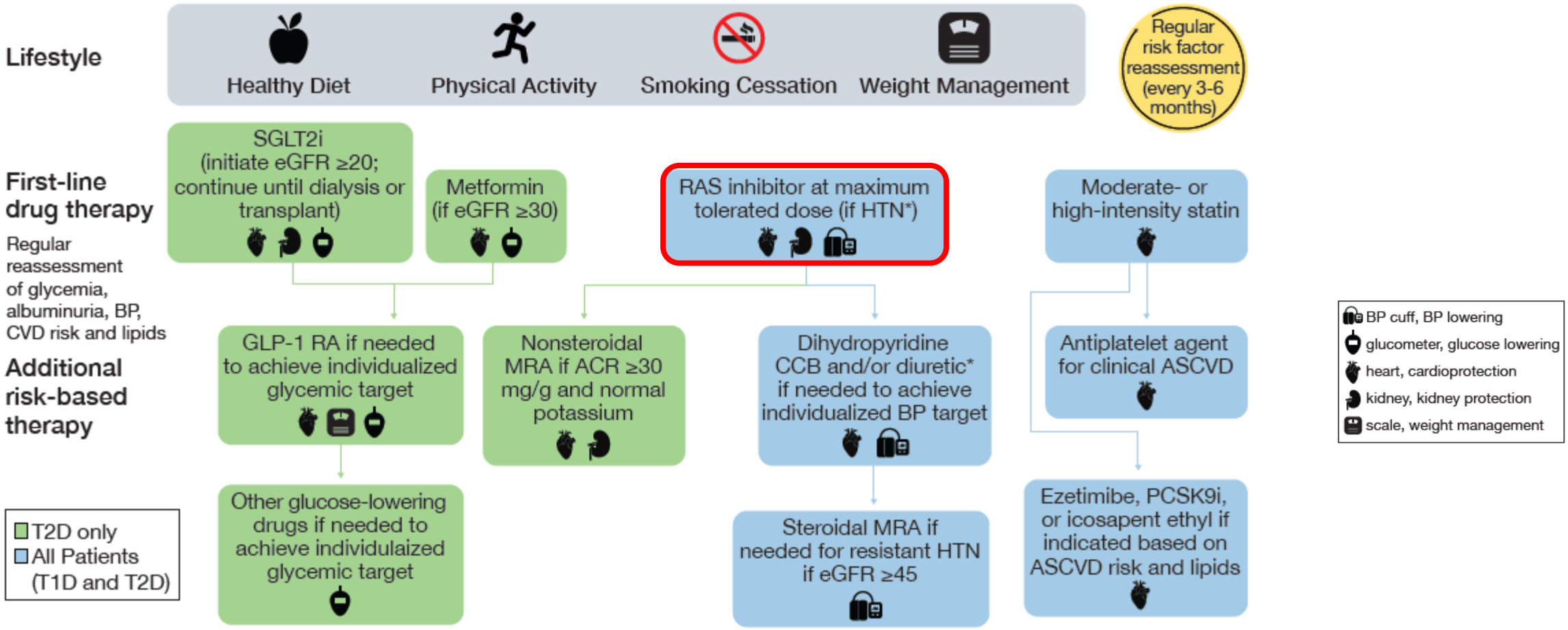

Kidney Int, 2022

Key trials on nephroprotective effects of RAS inhibition in CKD

Studio	Popolazione	Tipo di intervento	Endpoint	Riduzione del rischio renale connesso all'albuminuria
RENAAL[7]	Nefropatia in DMT2	Losartan vs placebo	Raddoppio creatinina, ESRD o morte	Nei primi 6 mesi per ogni dimezzamento dell'albuminuria si aveva una riduzione del 50% del rischio di ESRD
IDNT[8]	Nefropatia in DMT2	Irbesartan vs amlodipina vs placebo	Raddoppio creatinina, ESRD	Nei primi 12 mesi per ogni dimezzamento dell'albuminuria si aveva una riduzione del 56% del rischio di endpoint
AASK[9]	Nefrosclerosi i	mipril vs elo	ESRD	Nei primi 6 mesi per ogni dimezzamento dell'albuminuria si aveva una riduzione significativa del 53% del rischio di ESRD
ROAD[10]	Nefropatia - IgA	Los benazepri	nio creatinina,	Il rischio era 80% minore fra i soggetti che avevano avuto una riduzione della proteinuria >50% vs riduzione <25%
REIN[11]	Nefropatia non diabetica	Ramipril vs placebo	Declino	dell'eGFR minore nei pazienti con proteinuria al terzo mese ml/min/1.73 m²)
IRMA-2[12]	Microalbuminuria in DMT2	Irbesartan vs placebo	Declino dell'eGFR	Declino de eGFR (ml/min/1.73 m²) di 1.1 per riduzione >50% dell'albuminuria vs 2.6 per aumento dell'albuminuria >34%
ONTARGET[13]	Alto rischio cardiovascolare	Ramipril vs telmisartan vs ramipril e telmisartan	Raddoppio creatinina, ESRD	Diminuzione di 2 volte dell'albuminuria associata a una riduzione relativa del rischio renale del 27% vs nessun cambiamento nell'albuminuria

middle-age patients !!!

De Nicola, G Ital Cardiol 2019

Interpreting Treatment Effects From Clinical Trials in the Context of Real-World Risk Information

End-Stage Renal Disease Prevention in Older Adults

- Retrospective CKD cohort of VA hospitals
- 371,470 older pts (mean age 78 y), DM2 47%, all treated with anti-RAS
- Comparing number needed to treat (NNT) to prevent 1 case of ESKD over 3 yrs in real-world cohort vs key trials

	Entry Criteria			Mortality, %			ESRD, %			ESRD Outcomes[a]		
Percentage of Patients Who Developed ESRD Within 3 Years of Cohort Entry and Corresponding ARR and NNT												
	Level of eGFR, mL/min/1.73 m^2											
	≥60 (n = 17 089)			45-59 (n = 223 119)			30-44 (n = 103 671)			15-29 (n = 27 591)		
Dipstick Proteinuria Measurement	ESRD, %	ARR, %	NNT	ESRD, %	ARR, %	NNT	ESRD, %	ARR, %	NNT	ESRD, %	ARR, %	NNT
Negative or trace (n = 137 175)	NA	NA	NA	0.13	0.04	2500	0.49	0.15	667	4.43	1.33	75
1+ (n = 26 655)	0.13	0.04	2500	0.31	0.09	1111	0.86	0.26	385	9.55	2.87	35
≥2+ (n = 22 536)	0.25	0.08	1250	0.98	0.29	345	3.58	1.07	94	21.17	6.35	16
Unmeasured (n = 185 104)	NA	NA	NA	0.19	0.06	1667	0.83	0.25	400	8.47	2.54	39
et al,[21] 2001	amlodipine besylate				mL/min/ 1.73 m^2		of protein to creatinine levels, ≤2.5 mg/mg					

Extent of anti-RAS related nephroprotection seen in real-world older patients is markedly reduced vs the key RCTs...

...especially if patients are low-proteinuric !!!

O'Hare, JAMA Internal Med , March 2014

RASi can increase risk of Normotensive AKI in older CKD patients

- ✓ Mild salt restriction (6-8 g/day) in older
- ✓ Strict monitoring of kidney function
- ✓ Prompt intervention in ECV depletion

Ischemic Acute Kidney Injury
despite SBP 90-100 mmHg
impaired autoregulation

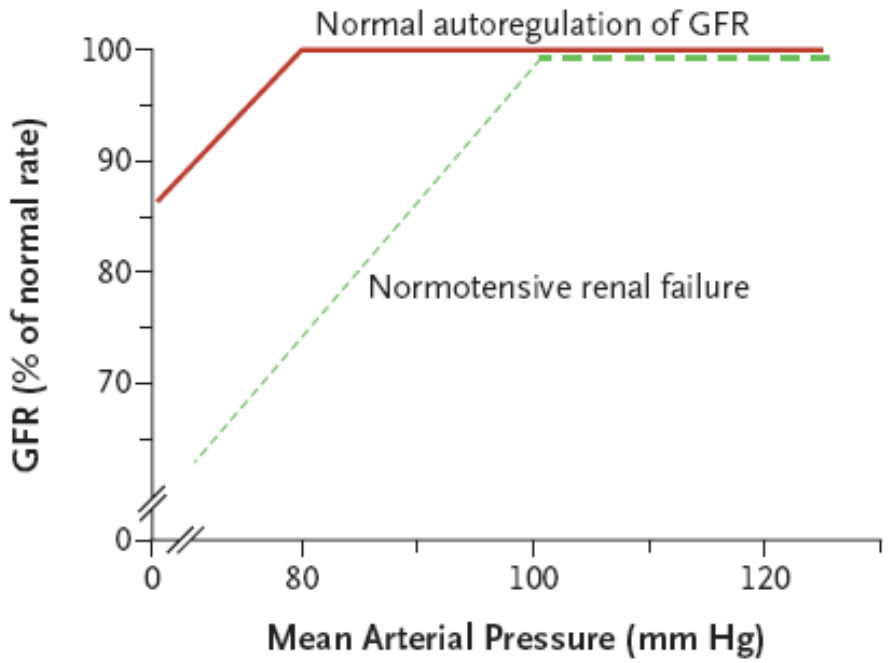

Table 1. Factors Increasing Susceptibility to Renal Hypoperfusion.

Failure to decrease arteriolar resistance
Structural changes in renal arterioles and small arteries
Old age
Atherosclerosis
Chronic hypertension
Chronic kidney disease
Malignant or accelerated hypertension
Reduction in vasodilatory prostaglandins
Nonsteroidal antiinflammatory drugs
Cyclooxygenase-2 inhibitors
Afferent glomerular arteriolar vasoconstriction
Sepsis
Hypercalcemia
Hepatorenal syndrome
Cyclosporine or tacrolimus
Radiocontrast agents
Failure to increase efferent arteriolar resistance
Angiotensin-converting–enzyme inhibitors
Angiotensin-receptor blockers
Renal-artery stenosis

Abuelo J, NEJM 2007

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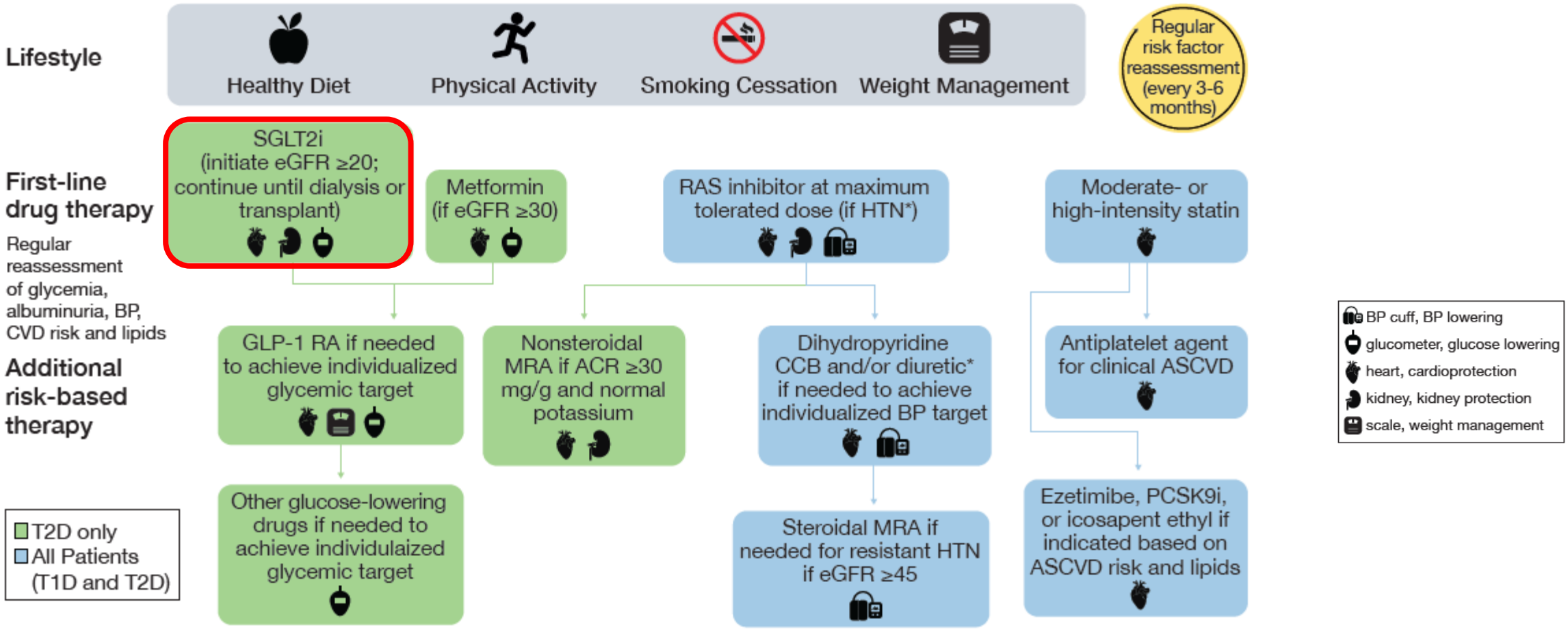
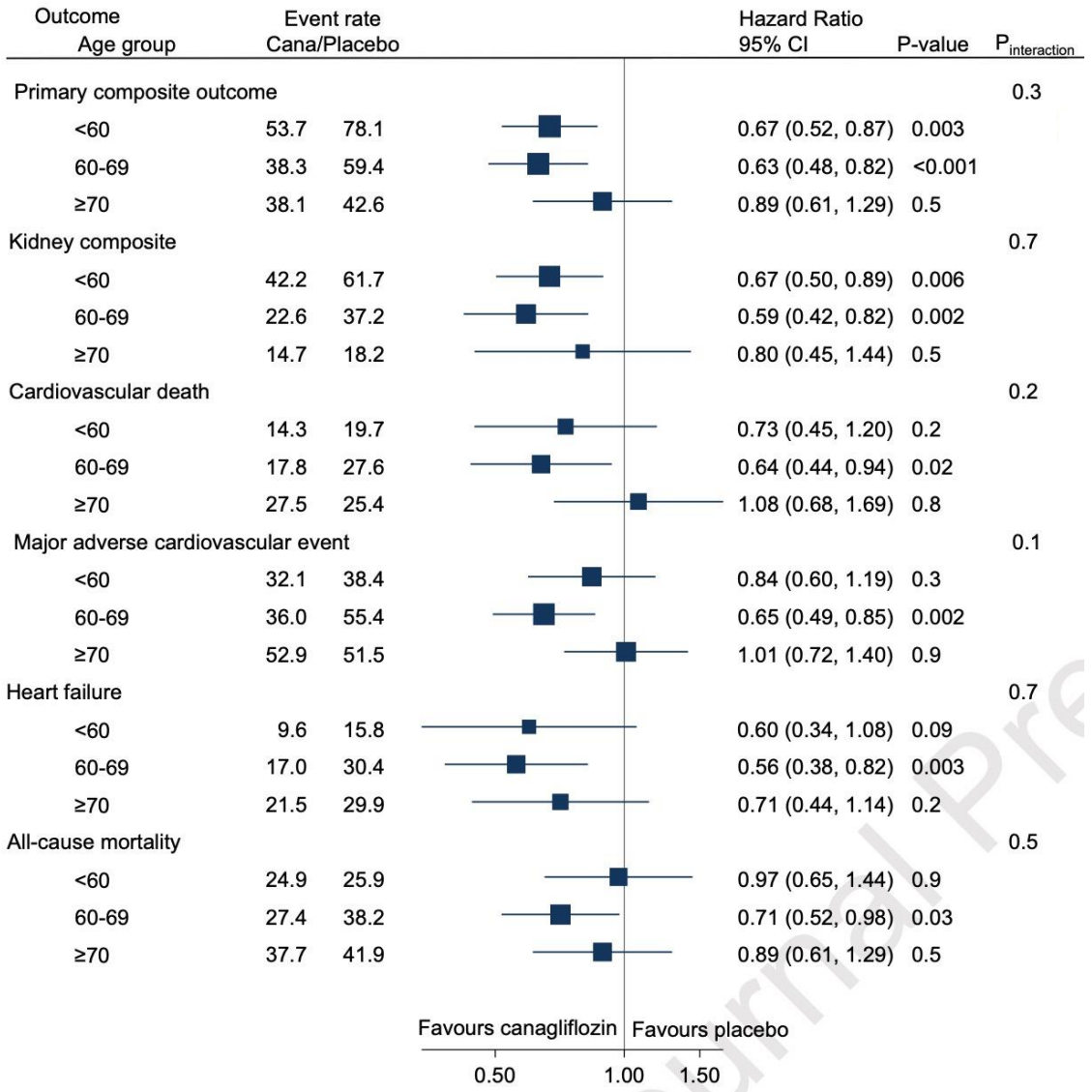
Novel holistic approach



Kidney Int, 2022

Nephroprotection according to Age and Sex:
Post Hoc Analysis of the CREDENCE trial



Tae Won Yi, et al., Am J Kidney Dis 2023

Dapagliflozin in Patients with Chronic Kidney Disease

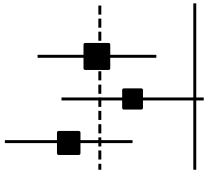
DAPA-CKD Trial Committees and Investigators

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)

Empagliflozin in Patients with Chronic Kidney Disease

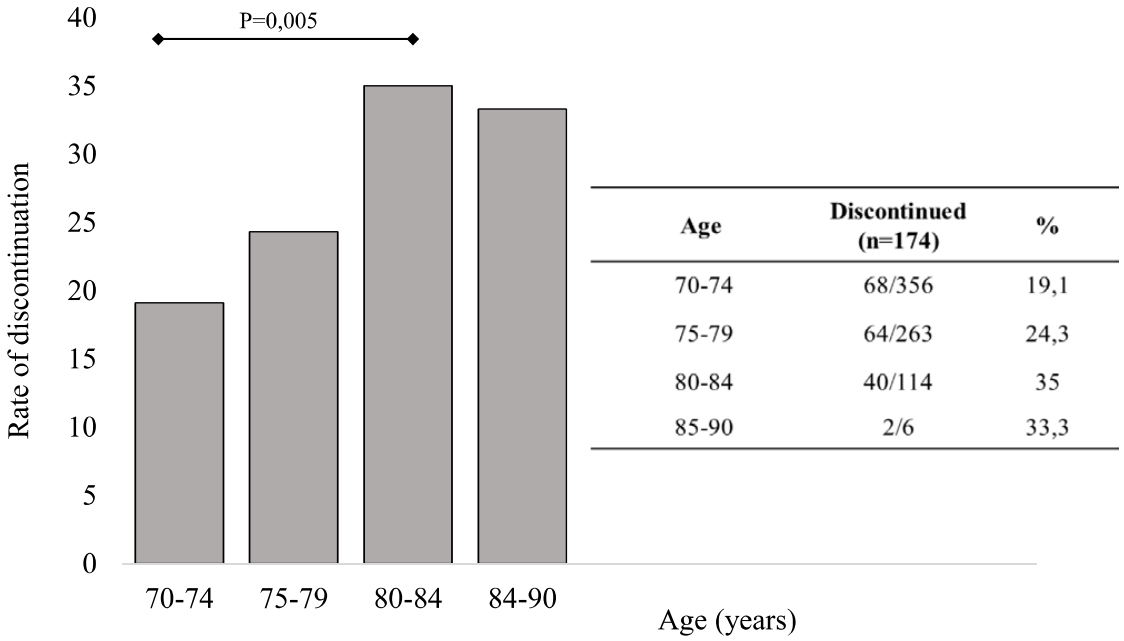
The EMPA-KIDNEY Collaborative Group*

Subgroup	Empagliflozin	Placebo	Hazard ratio (95% CI)
	no. of participants/total no.		
Age (years)			
<60	176/1136	222/1116	0.72 (0.59–0.88)
[illegible]	120/853	142/867	0.81 (0.64–1.04)
[illegible]	136/1315	194/1322	0.65 (0.52–0.81)



SGLT2-I in elderly are efficacious on HbA1c…but higher discontinuation !

- **739 adults (mean age 75.4 ±3.9 years, eGFR 73 ±19) with T2D**
- **SGLT2i started after the age of 70 with at least one year of FU**
- **Data collected at baseline, at 6 and 12 months of follow-up**
- **174 (23.5%) interrupted SGLT2i after 6 or 12 months.**



Age	Discontinued (n=174)	%
70-74	68/356	19,1
75-79	64/263	24,3
80-84	40/114	35
85-90	2/6	33,3

Discontinuation rate for SGLT2i treatment according to age.

Baseline characteristics of subjects that discontinued or maintained the SGLT2i treatment.

	Discontinued (n = 174)	Ongoing (n = 565)	P value
Age (yrs)	75.8 ± 4.2	74.7 ± 3.8	0.002
Sex (M/F)	101/73	319/246	0.390
BMI (Kg/m^2)	27.9 ± 3.3	29.2 ± 4.7	0.001
Weight (Kg)	78.0 ± 11.3	79.3 ± 14.6	0.067
FPG (mg/dL)	184.6 ± 55.9	184.8 ± 43.3	0.954
HbA1c (%, mmol/mol)	8.1 ± 1.03, 65.0 ± 8.2	7.8 ± 1.1, 62.0 ± 8.7	0.001
S-Creatinine (mg/dL)	0.98 ± 0.16	0.91 ± 0.19	0.000
eGFR (mL/min/1,73 m^2)	67.2 ± 12.4	75.4 ± 20.1	0.000
U-Albumin (mg/L)	32.8 ± 37.7	35.0 ± 74.0	0.722
Total cholesterol (mg/dL)	183.5 ± 35.3	174.0 ± 36.0	0.000
HDL (mg/dL)	41.4 ± 10.6	45.3 ± 12.6	0.000
LDL (mg/dL)	117.3 ± 35.3	103.3 ± 35.4	0.000
Tryglicerides (mg/dL)	130.8 ± 40.2	141.8 ± 69.0	0.055
Ejection Fraction (%)	45.9 ± 7.6	52.3 ± 7.8	0.000

Lunati ME et al. (SOLD study), Pharmacological Research 2022

High unmet treatment needs in patients with chronic kidney disease and type 2 diabetes: real-world evidence from a US claims database

Background

We evaluated treatment initiation and discontinuation in patients with type 2 diabetes (T2DM) who had incident CKD (incident cohort), and rates of clinical/economic outcomes in patients with T2D who had any CKD (prevalent cohort).

Methods

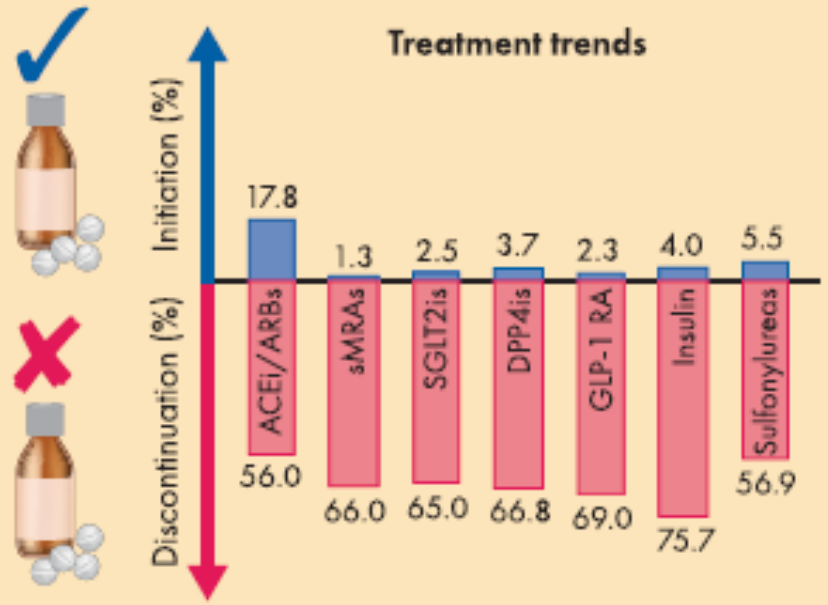
Retrospective study of administrative claims

1 January 2007 – 31 March 2019

Incident CKD: n = 63 271
Prevalent CKD: n = 326 763

Age 72y, 50% eGFR 60-45, 28% ACR 30-300

Results



Hospitalization rates per 1000 person years

All-cause	Kidney-related
283.1	36.6

Clinical outcome rates per 1000 person years

Mortality	ESKD
35.1	104.2

Conclusion

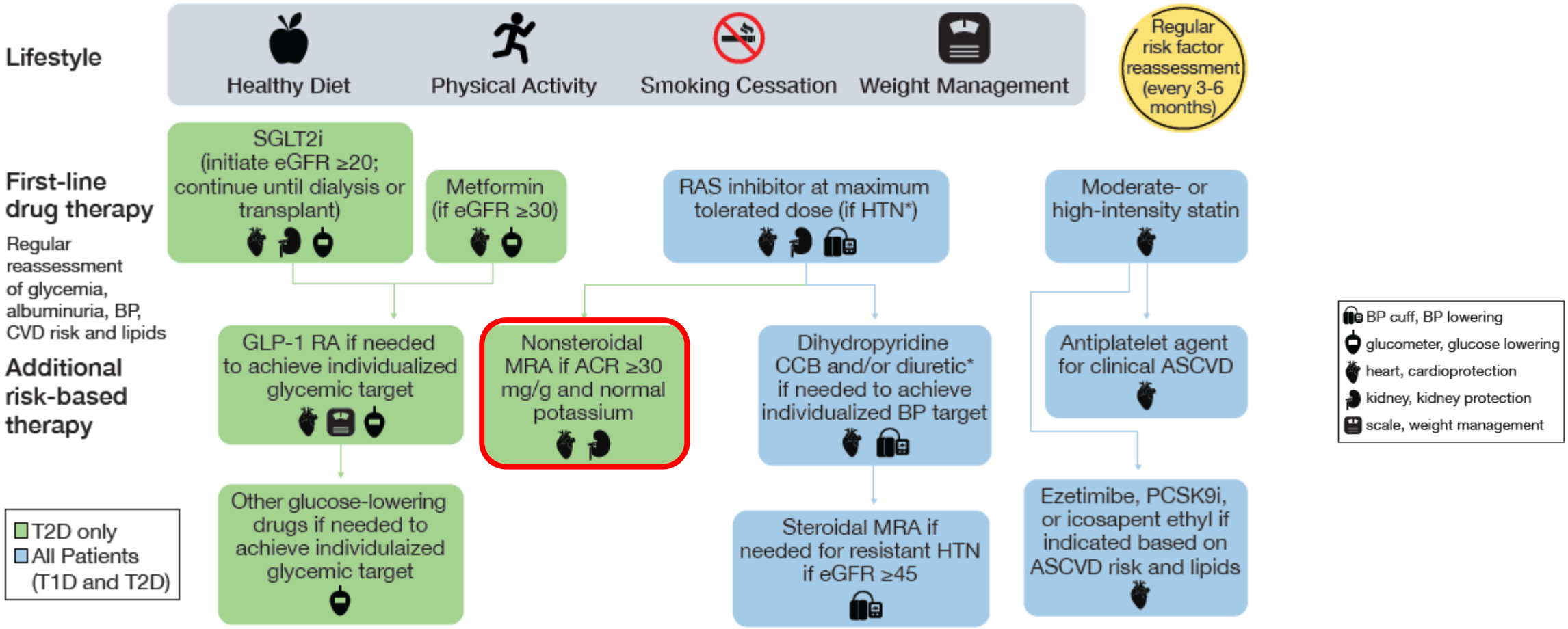
Our results highlight high unmet needs of CKD and T2D. Low initiation and high discontinuation of recommended treatments suggest that adherence to guidelines for halting CKD progression is suboptimal. These high-risk patients may benefit from further treatment options to improve morbidity and mortality and reduce the economic burden.

NEPHROLOGY DIALYSIS TRANSPLANTATION

Fried, L., et al. NDT (2022)
@NDTSocial

Diabetes management in chronic kidney disease: a consensus report by the American Diabetes Association (ADA) and Kidney Disease: Improving Global Outcomes (KDIGO)

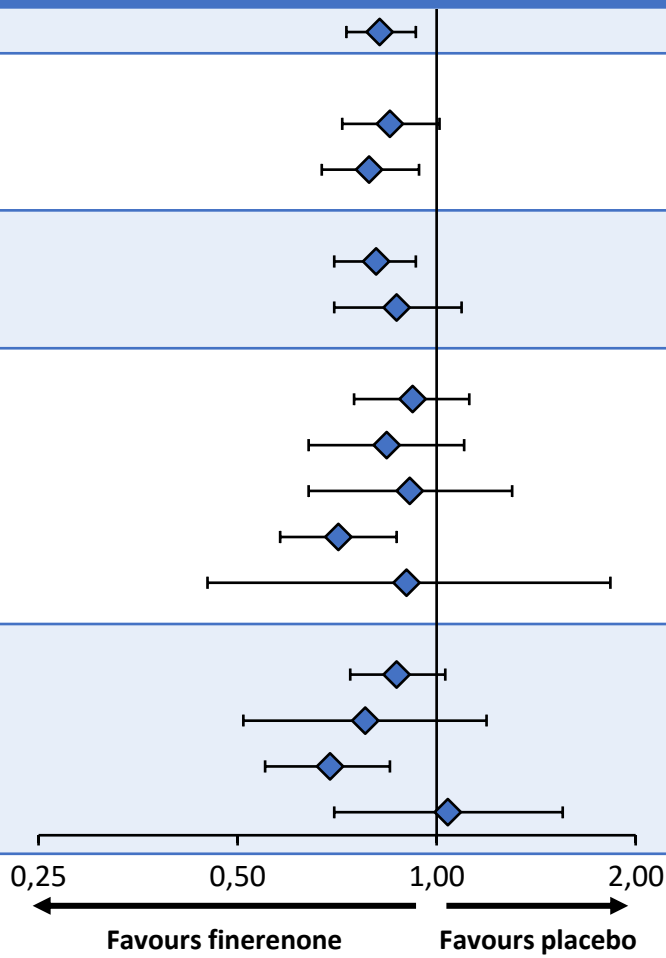
Novel holistic approach



Kidney Int, 2022

Finerenone had consistent effects on the primary kidney endpoint irrespective of age

Subgroup	Finerenone	Placebo	Finerenone	Placebo	Hazard ratio (95% CI)
	n/N		n per 100 PY		
All patients	**504/2833**	**600/2841**	**7.59**	**9.08**	**0.82 (0.73–0.93)**
Age at run-in visit					
<65 years	267/1205	302/1174	9.70	11.29	0.85 (0.72–1.01)
≥65 years	237/1628	298/1667	6.09	7.58	0.79 (0.67–0.94)
Sex					
Male	351/1953	432/2030	7.60	9.14	0.81 (0.70–0.93)
Female	153/880	168/811	7.57	8.93	0.87 (0.70–1.09)
Region					
Europe	177/1182	196/1176	6.17	6.82	0.92 (0.75–1.12)
North America	95/467	110/477	8.76	10.14	0.84 (0.64–1.10)
Latin America	58/295	64/298	10.01	11.17	0.91 (0.64–1.30)
Asia	160/790	213/789	8.50	11.61	0.71 (0.58–0.87)
Other	14/99	17/101	6.24	7.12	0.90 (0.45–1.83)
Race					
White	265/1777	309/1815	6.26	7.15	0.87 (0.74–1.03)
Black/African American	43/140	42/124	13.85	17.24	0.78 (0.51–1.19)
Asian	145/717	201/723	8.54	12.04	0.69 (0.55–0.85)
Other	51/199	48/179	12.73	12.98	1.04 (0.70–1.55)



Bakris GL et al.(FIDELIO-DKD), N Engl J Med 2020

Nephroprotective Agents in Older Patients with Diabetes

Treat as youngers to prevent ESKD as "the major goal"

…BUT…stricter follow up and personalized therapy !!!