Basta con la DKD!

come "mettere in fila" le diverse opportunità (non dimenticando lifestyle e RASi)

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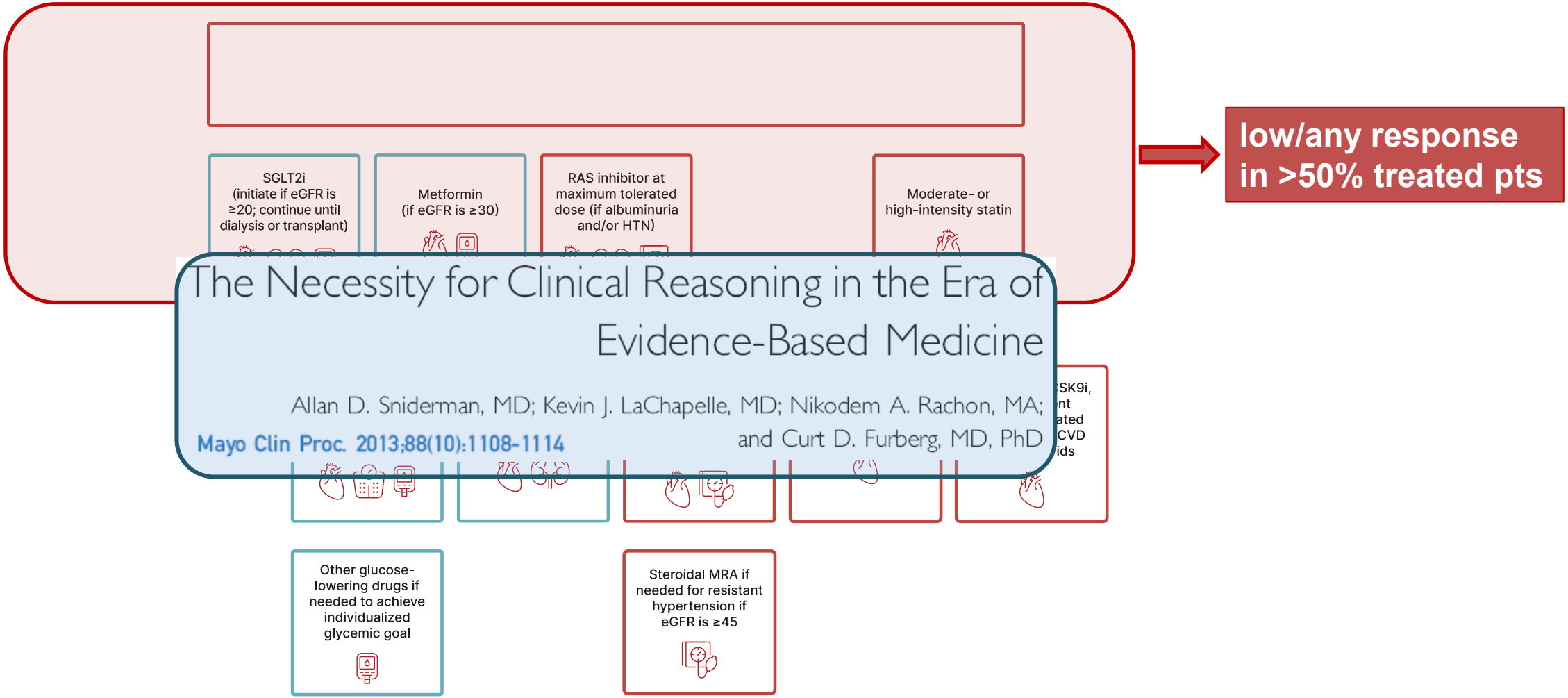
Il sottoscritto Prof. Luca De Nicola dichiara di aver ricevuto negli ultimi due anni compensi o finanziamenti dalle seguenti Aziende Farmaceutiche e/o Diagnostiche:

- Astellas
- Astrazeneca
- Bayer
- Novo Nordisk

Dichiara altresì il proprio impegno ad astenersi, nell'ambito dell'evento, dal nominare, in qualsivoglia modo o forma, aziende farmaceutiche e/o denominazione commerciale e di non fare pubblicità di qualsiasi tipo relativamente a specifici prodotti di interesse sanitario (farmaci, strumenti, dispositivi medico-chirurgici, ecc.).

Stepwise approach to DKD from RCTs

11. Chronic Kidney Disease and Risk Management: Standards of Care in Diabetes—2025



Diabetes Care Volume 48, Supplement 1, January 2025

Pragmatic Priorities in the Management of DKD

Lifestyle: what's most important?

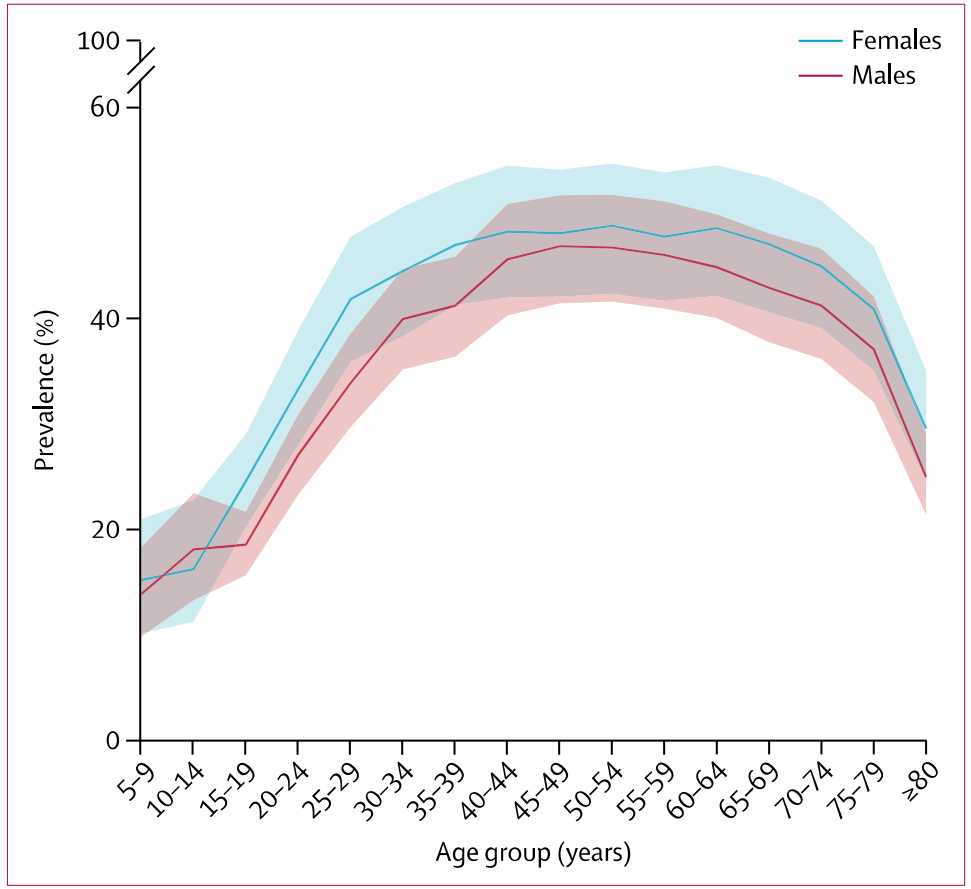
A. Exercise and calorie intake
B. Protein intake
C. Salt intake
D. A and C

Weight Control

National-level and state-level prevalence of overweight and obesity among children, adolescents, and adults in the USA, 1990–2021, and forecasts up to 2050

GBD 2021 US Obesity Forecasting Collaborators

Lancet 2024; 404: 2278–98



Sex-specific prevalence of obesity, by age group, in 2021 in the USA

In 2050, a projected 1/3 adolescents (aged 15–24 y) and 2/3 adults (≥25 y) will have obesity in US

↑↑ Burden

- DM2
- **CKD**
- CV disease
- Rethinopathy

Weight Control

8. Obesity and Weight Management for the Prevention and Treatment of Type 2 Diabetes: Standards of Care in Diabetes–2025

Diabetes Care Volume 48, Supplement 1, January 2025

In people with type 2 diabetes and overweight or obesity, weight management should represent a primary goal of treatment along with glycemic management **[A]**

Weight loss of 3–7% of baseline weight improves glycemia and other intermediate cardiovascular risk factors **[A]**

Sustained loss of >10% of body weight usually confers greater benefits, including disease-modifying effects and possible remission of type 2 diabetes, and may improve long-term cardiovascular outcomes and mortality **[B]**

Weight Control

8. Obesity and Weight Management for the Prevention and Treatment of Type 2 Diabetes: Standards of Care in Diabetes–2025

Diabetes Care Volume 48, Supplement 1, January 2025

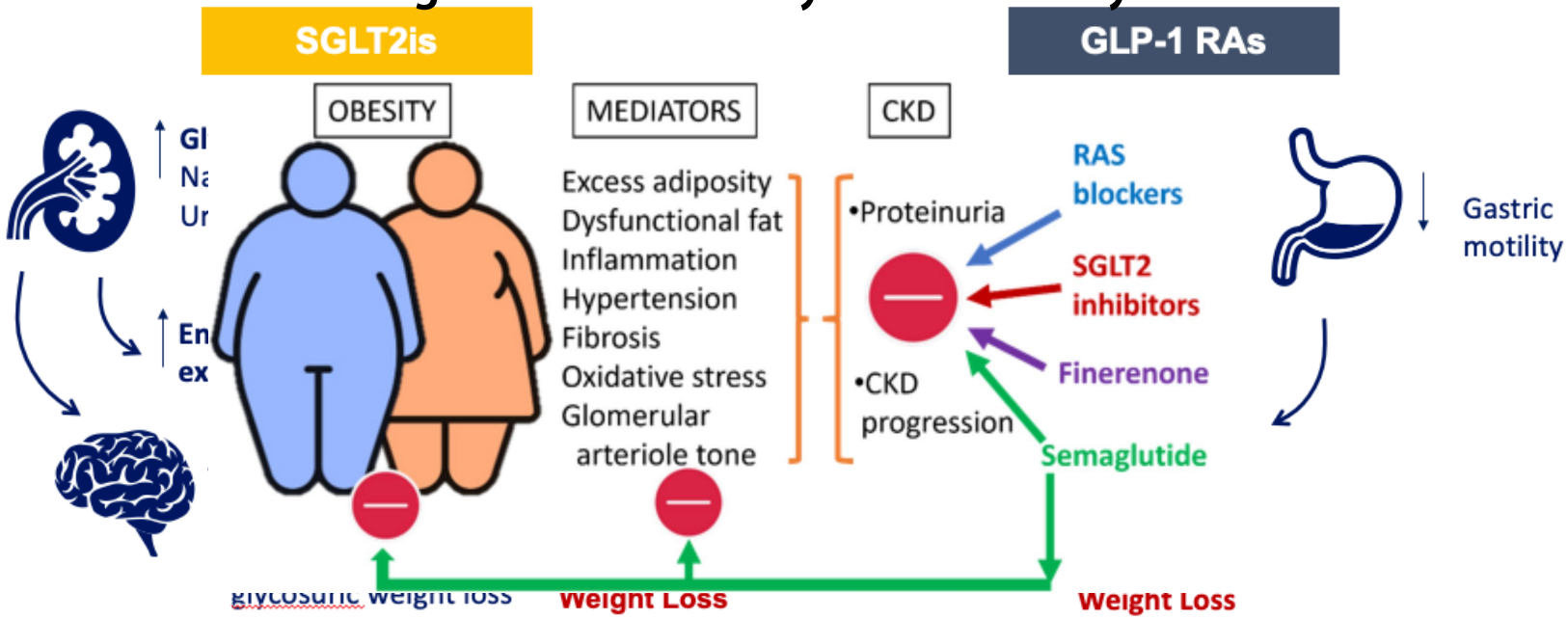
Pharmacotherapy should be considered for people with DM and overweight or obesity along with lifestyle changes **[A]**

The preferred therapy should be GLP1-RA or GLP1-RA+GIP with greater weight loss efficacy, especially considering their added weight-independent benefits (e.g., glycemic and cardiometabolic) **[A]**

Weight management therapy should be continued beyond reaching weight loss goals to maintain the health benefits **[A]**

GLP1-RAs >> SGLT2is

Semaglutide cuts kidney risk in obesity



Giugliano D, De Nicola L et al., J Endocrinol Invest, 4 Nov 2024
Ferrannini et al. Diabetes Care. 2015; Pereira M, Erisson J. Drugs. 2019

Salt Intake

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
- DM2 patients: 27%
- eGFR:
  - **41±25 in younger**
  - **34±16 in older**
- Median salt intake on ≥ 2 measurements of 24h UNa**:**
  - **8.6 g/24h in younger**
  - **8.2 g/24h in older**

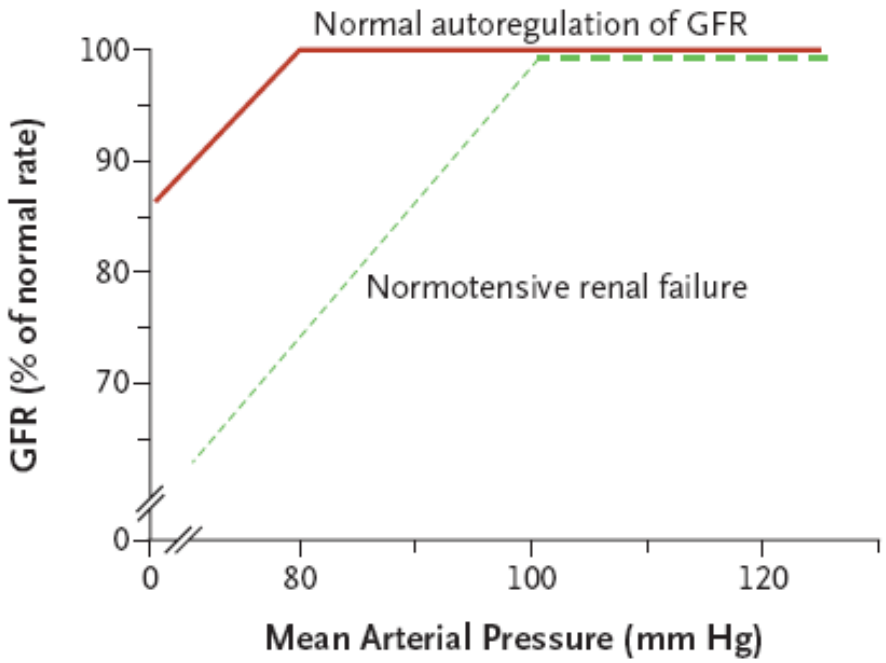
	<6 g/day	6-8 g/day	>8 g/day
	HR (95% CI)	HR (95% CI)	HR (95% CI)
ESKD risk			
Age ≤65	Reference	1.189 (0.788-1.795)	1.096 (0.763-1.574)
Age >65	1.024 (0.656-1.599)	**0.577 (0.361-0.924)**	**0.564 (0.382-0.833)**
Death risk			
Age ≤65	Reference	0.791 (0.318-1.966)	0.620 (0.275-1.397)
Age >65	**3.810 (1.829-7.936)**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

Older CKD patients are exposed to higher risk of normotensive AKI

Ischemic Acute Kidney Injury
despite SBP 100-110 mmHg
impaired autoregulation



Determimants of normotensive AKI in older DKD patients

- ✓ **Low salt intake, Diuretics**

(BP maintained by arteriosclerosis-induced peripheral vasoconstriction)

- ✓ **RASI**

(failure to increase efferent glom arteriole resistance)

- ✓ **SGLT2i and GLP1-RA**

(reduced salt intake/natriuresis, excessive afferent glom arteriole constriction)

In older patients...

- ✓ **Salt intake should be 6-8 g/day (UNa 100-140 mEq/24h)**
- ✓ **Strict monitoring of kidney function**
- ✓ **Prompt intervention (NaCl 0,9% ev) in ECV depletion**
- ✓ **SGLT2i + GLP1-RA+ Low Salt Diet/diuretics: risk of AKI !**

Abuelo J, NEJM 2007

Pragmatic Priorities in the Management of DKD

Drug Therapy: Follow albuminuria

1. True
2. False
3. Don’t know

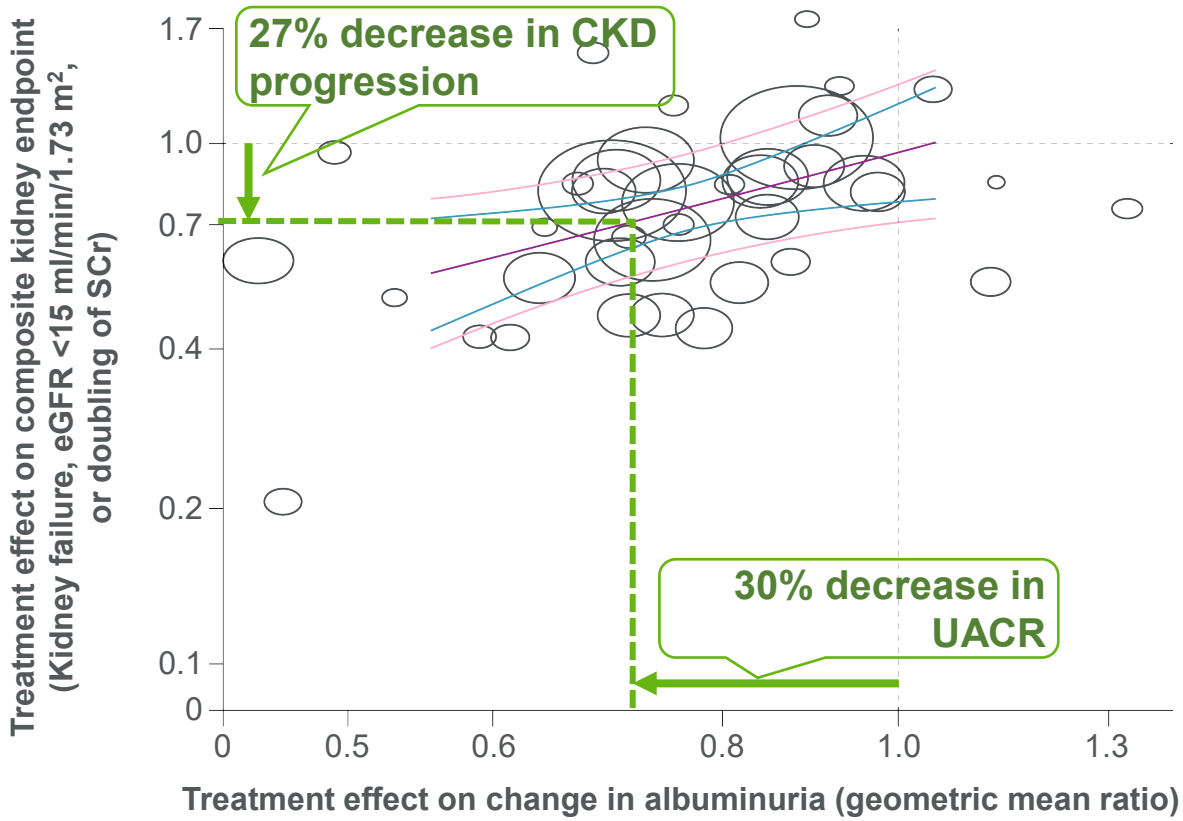
Albuminuria...*main therapeutic target*

Vestergaard A. et al. NDT, 1 July 2024

Albuminuria...*main therapeutic target*

6-month change in albuminuria and subsequent long-term renal prognosis:
metanalysis of 41 RCTs and 28 observational studies in CKD under various interventions (**DM2 in 70% patients**)

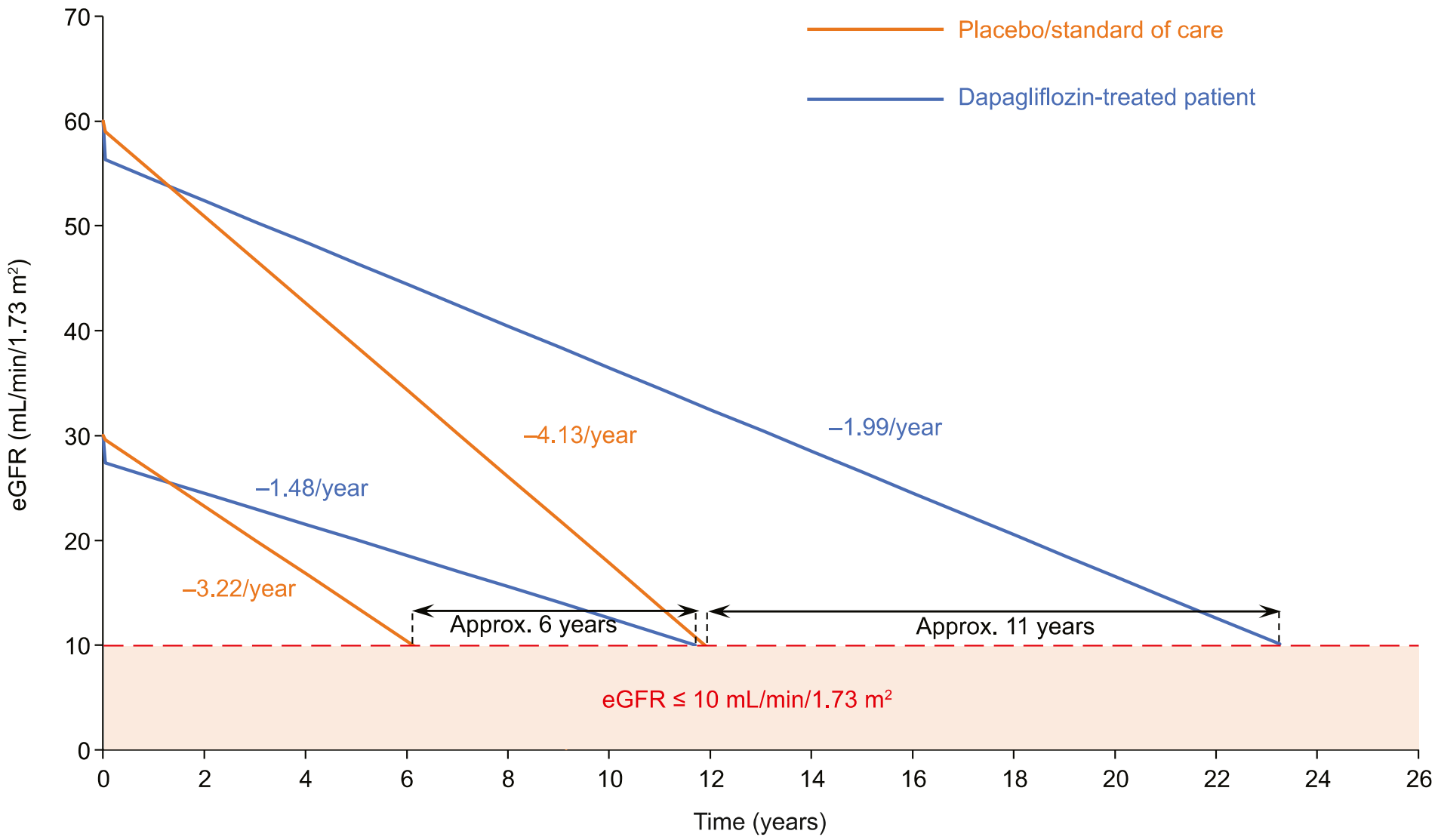
Patients with UACR ≥30 mg/g (N=22,544)



30% decrease in UACR associates with 27% reduction in the composite kidney endpoint (*kidney failure, eGFR <15, or doubling of SCr*)

adapted from: Levey AS, et al. Am J Kidney Dis 2019;
Heerspink HJL, et al. Lancet Diabetes Endocrinol 2019

Antialbuminuric Therapy...*the early the better*



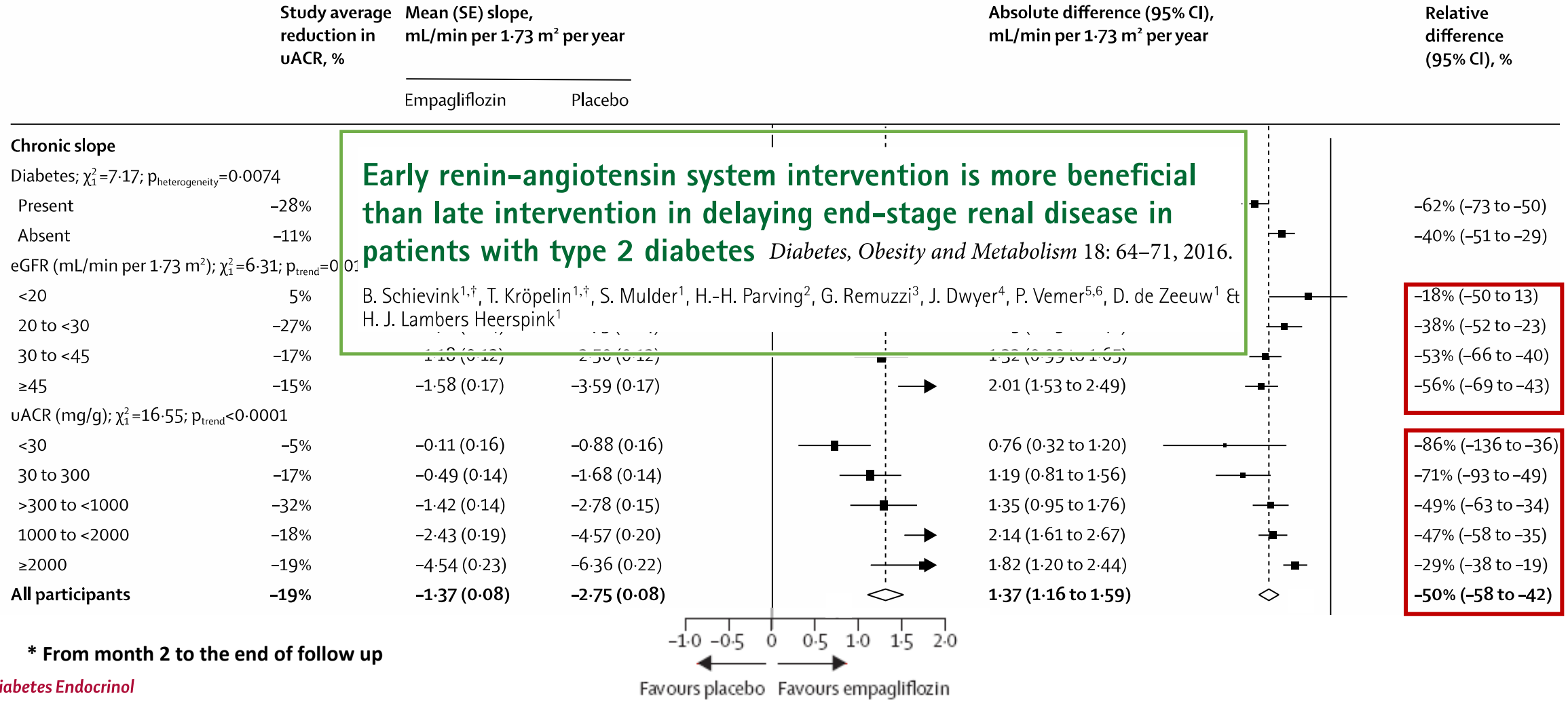
Data extrapolated from DAPA-CKD trial, Madero M et al., Kidney Med. 2024

Antialbuminuric Therapy...*the early the better*

Effects of empagliflozin on progression of chronic kidney disease: a prespecified secondary analysis from the EMPA-KIDNEY trial

- 6609 participants (46% DM, 27% CVD)
- eGFR ≥20 to <45
- ≥45 to <90 with ACR ≥200
- FU 2.0 years

✓ **Empa: ↓ 29% composite renal risk**



Early renin–angiotensin system intervention is more beneficial than late intervention in delaying end-stage renal disease in patients with type 2 diabetes *Diabetes, Obesity and Metabolism* 18: 64–71, 2016.

B. Schievink[1,†], T. Kröpelin[1,†], S. Mulder[1], H.-H. Parving[2], G. Remuzzi[3], J. Dwyer[4], P. Vemer[5,6], D. de Zeeuw[1] & H. J. Lambers Heerspink[1]

*** From month 2 to the end of follow up**

Lancet Diabetes Endocrinol
2024; 12: 39–50

Antialbuminuric Therapy...*nighttime BP*

- Multicentric prospective study in DKD under nephrology care in 83 DKD patients from 11 italian renal clinics
- Baseline and follow-up visit after 12±2 weeks of DAPA
- *AHA goals: daytime SBP <130 mmHg and nighttime SBP <110 mmHg, normal dipping status if nighttime to daytime SBP ratio was <0.9*
- **Aim: effects of dapa on nighttime BP**

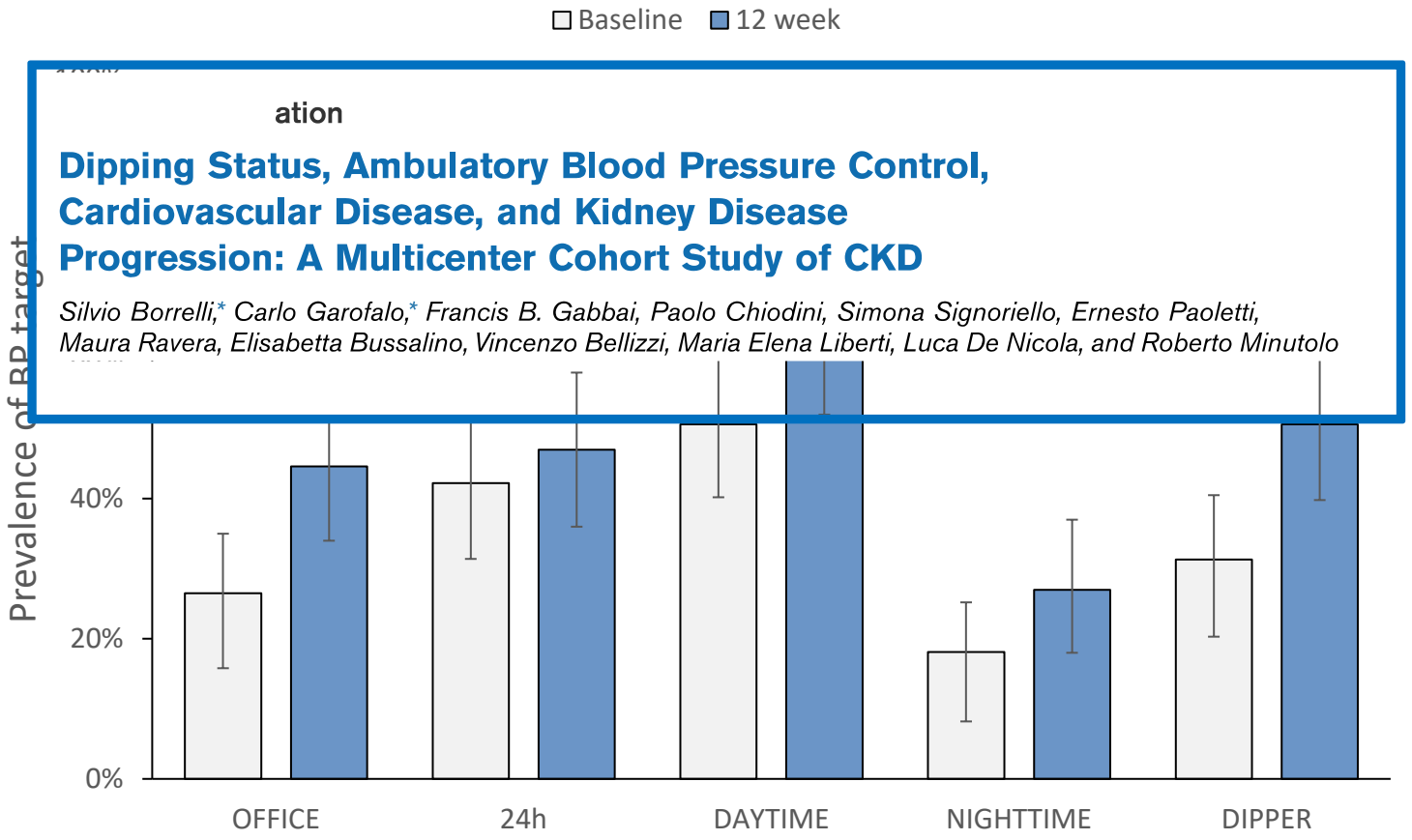
Changes in main clinical, lab and therapeutic features after 12 weeks of dapagliflozin

	Baseline	12-week	P
Body Weight (Kg)	82.8±17.3	80.6±16.9	**<0.001**
Body Mass Index (Kg/m2)	28.1(25.2-31.7)	27.4(24.6-31.0)	**<0.001**
eGFR (ml/min/1.73 m2)	49.1±16.5	50.1±19.6	0.297
Albuminuria (mg/die)	**0.18 (0.10-0.38)**	**0.12 (0.05-0.31)**	**<0.001**
Serum Total Cholesterol (mg/dL)	142(119-173)	141(116-160)	0.168
Serum LDL cholesterol (mg/dL)	72(53-97)	74(52-93)	0.708
Serum Triglycerides (mg/dL)	127(85-170)	107(90-153)	0.283
Serum hemoglobin (g/dL)	13.1±1.8	13.9±1.7	**<0.001**
Serum albumin (g/dL)	4.2±0.4	4.2±0.4	0.967

Borrelli...De Nicola, CKJ 2024

Antialbuminuric Therapy...*nighttime BP*

Albuminuria reduction associates with improved nighttime BP



Borrelli...De Nicola, CKJ 2024

Antialbuminuric Therapy...*Finerenone*

Impact of Finerenone-Induced Albuminuria Reduction on Chronic Kidney Disease Outcomes in Type 2 Diabetes

A Mediation Analysis

Objective: To quantify the proportion of kidney and cardiovascular risk reductions seen over a 4-year period mediated by a change in kidney injury, as measured by the change in log UACR between baseline and month 4.

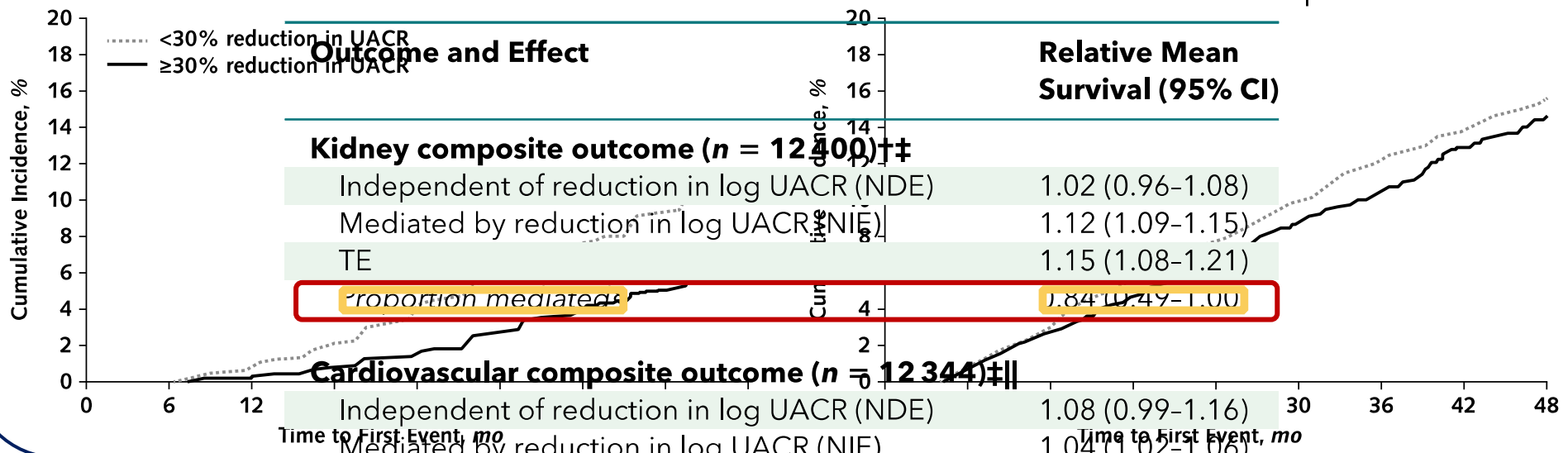
Patients: 12 512 patients with CKD and T2D.

Reduction ≥30% in UACR: 53% finerenone group vs 27% placebo group

Mediation Analysis: Change in Log UACR as a Continuous Variable*

kidney composite outcome

cardiovascular composite outcome



Outcome and Effect	Relative Mean Survival (95% CI)
Kidney composite outcome (n = 12 400)†‡	
Independent of reduction in log UACR (NDE)	1.02 (0.96–1.08)
Mediated by reduction in log UACR (NIE)	1.12 (1.09–1.15)
TE	1.15 (1.08–1.21)
Proportion mediated§	0.84 (0.49–1.00)
Cardiovascular composite outcome (n = 12 344)‡‖	
Independent of reduction in log UACR (NDE)	1.08 (0.99–1.16)
Mediated by reduction in log UACR (NIE)	1.04 (1.02–1.06)
TE	1.12 (1.04–1.21)
Proportion mediated§	0.37 (0.08–0.65)

Agarwal R for FIDELITY, Ann Int Med 2023

Discontinuation of therapy is as important as initiation !!!

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).

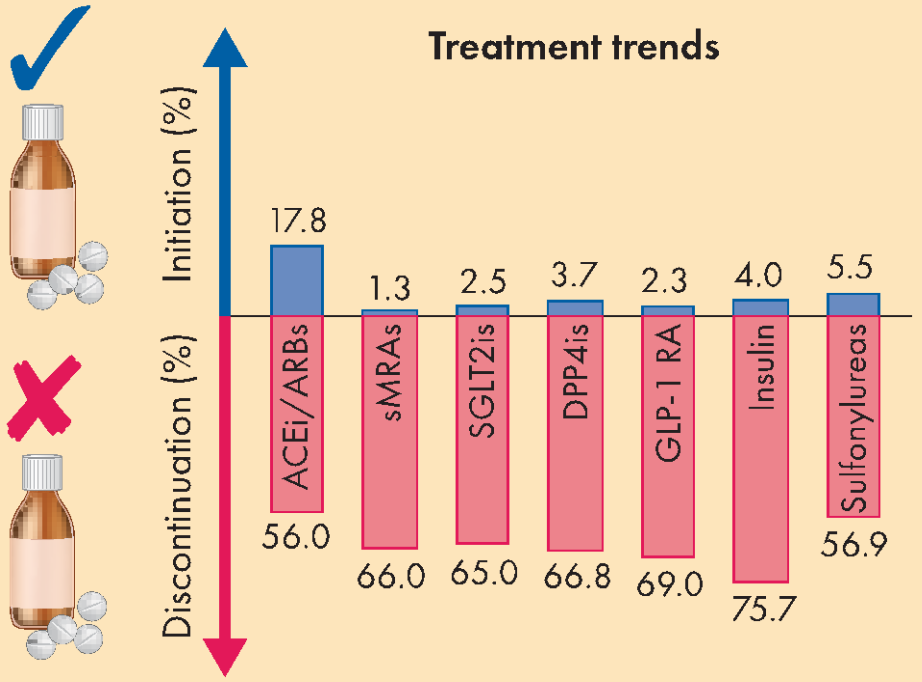
Methods

Retrospective study of administrative claims

1 January 2007 – 31 March 2019

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

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

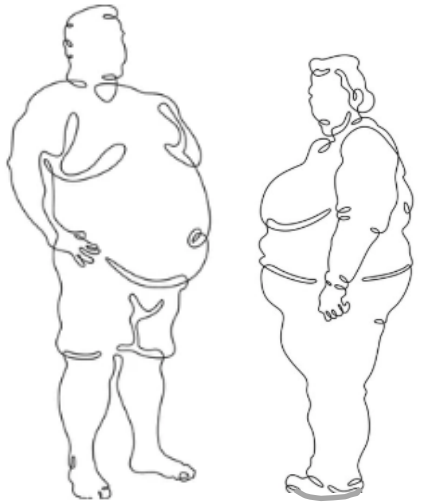
Conclusion

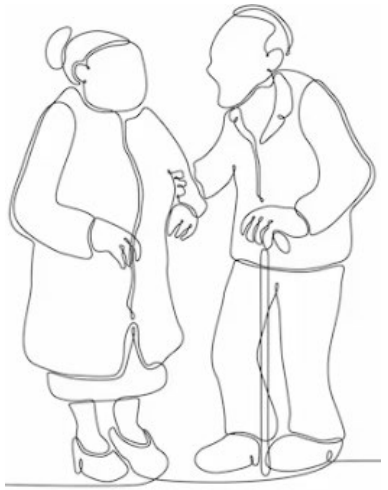
Our results highlight high unmet needs of CKD and T2D. Low initiation and high discontinuation of recommended treatments suggest that adherence to guidelines for halting CKD progression is suboptimal. These high-risk patients may benefit from further treatment options to improve morbidity and mortality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

Fried L et al, NDT 2023

CONCLUSION

Pragmatic Approach to Preserve Kidney Function in DKD





✓ **ACR 30-300**
✓ eGFR 60-30

1. **Salt intake ≤5 g/24h if office BP ≥130/80**
2. **RASI + SGLT2i**
3. **Finerenone if ACR ≥30 or SGLT2i i**
4. **GLP1-RA if high gly or atheroscler**

1. **Very low carb diet and exercise**

1. **Avoid malnutrition (GLP1-RA ???)**
2. **Salt intake 6-8 g/24h if office BP ≥130/80**
3. **RASI ⇨ SGLT2i (no in hypovolemia)**
4. **Finerenone if ACR ≥30**

Glycemic target

- ✓ less stringent in CKD
- ✓ HbA1c value limited when eGFR <30

✓ **ACR <30**
✓ eGFR 60-30

Same as above.

- **No Finerenor**
- **Avoid NSAIDs**

- **Avoid NSAIDs**

Same as above...but:

- **No Finerenone**
- **Avoid NSAIDs**

CONCLUSION
General Recommendations

irst !

- Abate clinical inertia:
  do not postpone the indicated therapeutic interventions:
  SGLT2i, Finerenone, GLP1-RA
- Check adherence to prescribed drugs at every control visit to avoid discontinuation
- Every 12 months check efficacy of antihypertensive treatment by 24h ABP (nighttime SBP goal 110 mmHg and/or dipping)
- Every 3-6 months (based on basal GFR), monitor kidney function to identify worsening of CKD or Acute Kidney Injury for prompt referral to nephrologist
- Careful management of older lean patients
  (avoid SGLT2i+GLP1-RA+low salt diet/diuretics)
- During sick days, stop transitorily RAASI, SGLT2i, Metformin, GLP1-RA±GIP and protect volemia