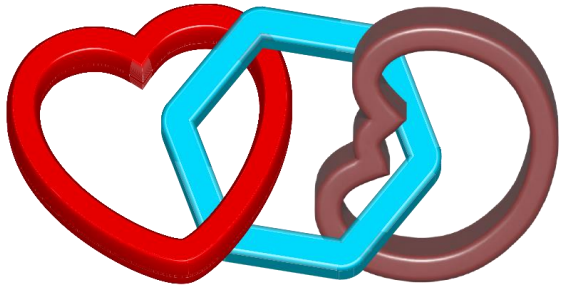


Vermindering van cardiovasculaire complicaties door nierbescherming

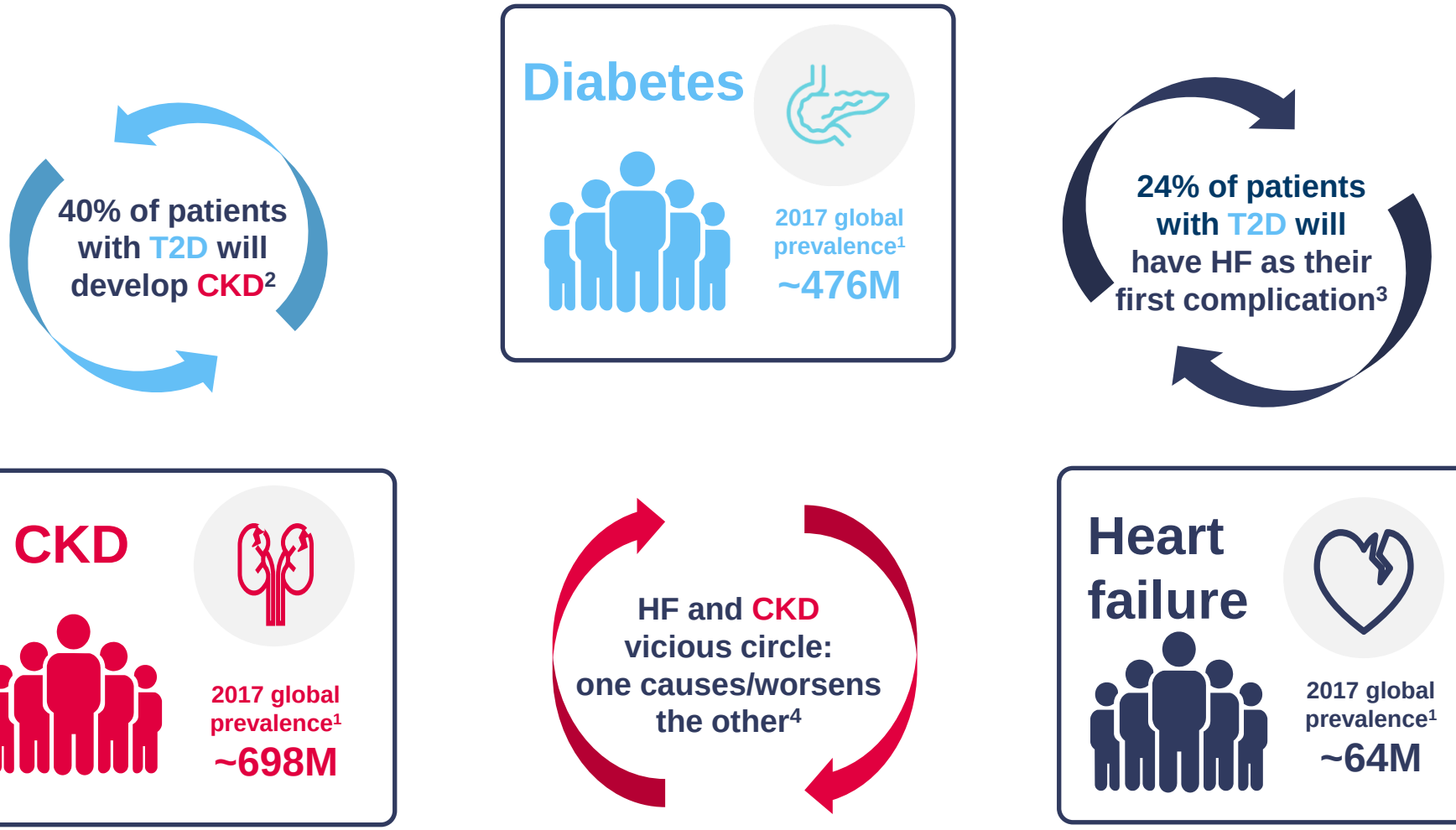
Prof. dr. Hiddo Lambers Heerspink

Klinisch farmacoloog, UMC Groningen

Disclosures

- HJLH is a consultant for AbbVie, AstraZeneca, Bayer, Boehringer Ingelheim, Chinook, CSL Behring, Dimerix, Eli-Lilly, Gilead, Janssen, Merck, NovoNordisk, and Travere Therapeutics
- He has received research support from AstraZeneca, Boehringer Ingelheim, Janssen and NovoNordisk

CKD, heart failure, and T2D are interrelated, leading to a vicious circle of cardiac, renal, and metabolic risk

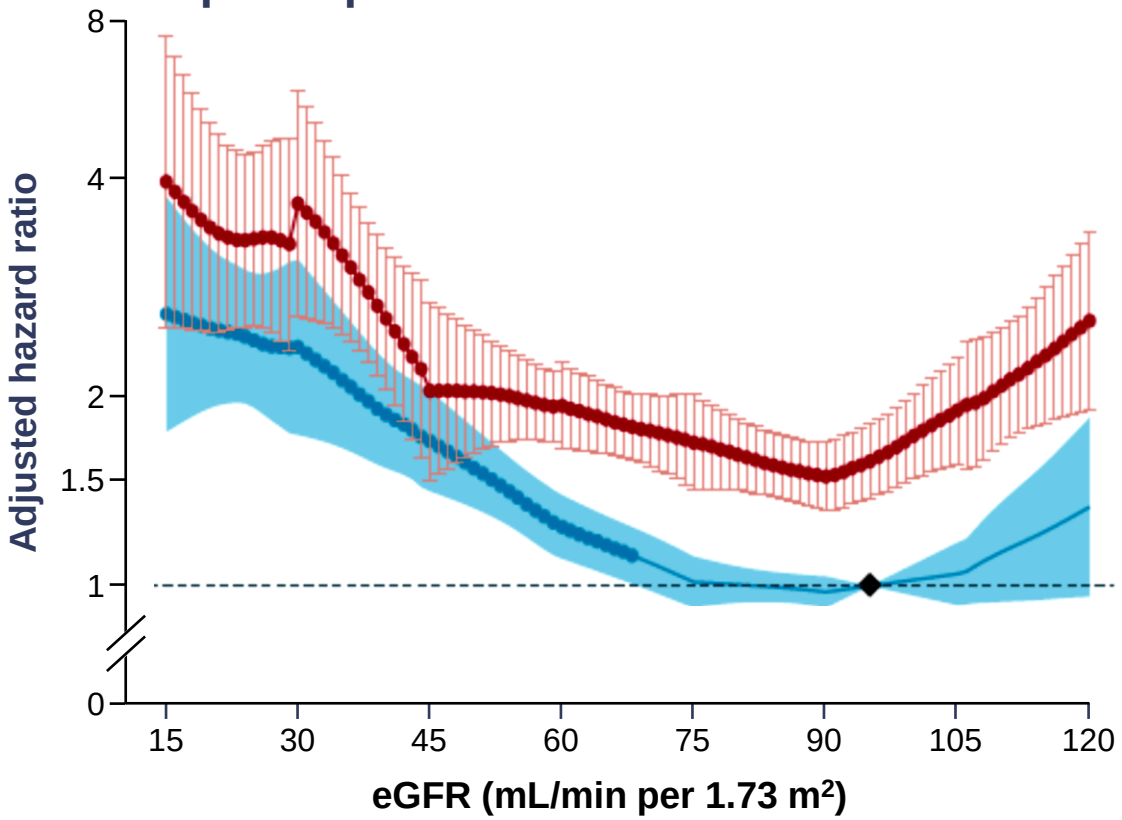


CKD, chronic kidney disease; HF, heart failure; T2D, type 2 diabetes

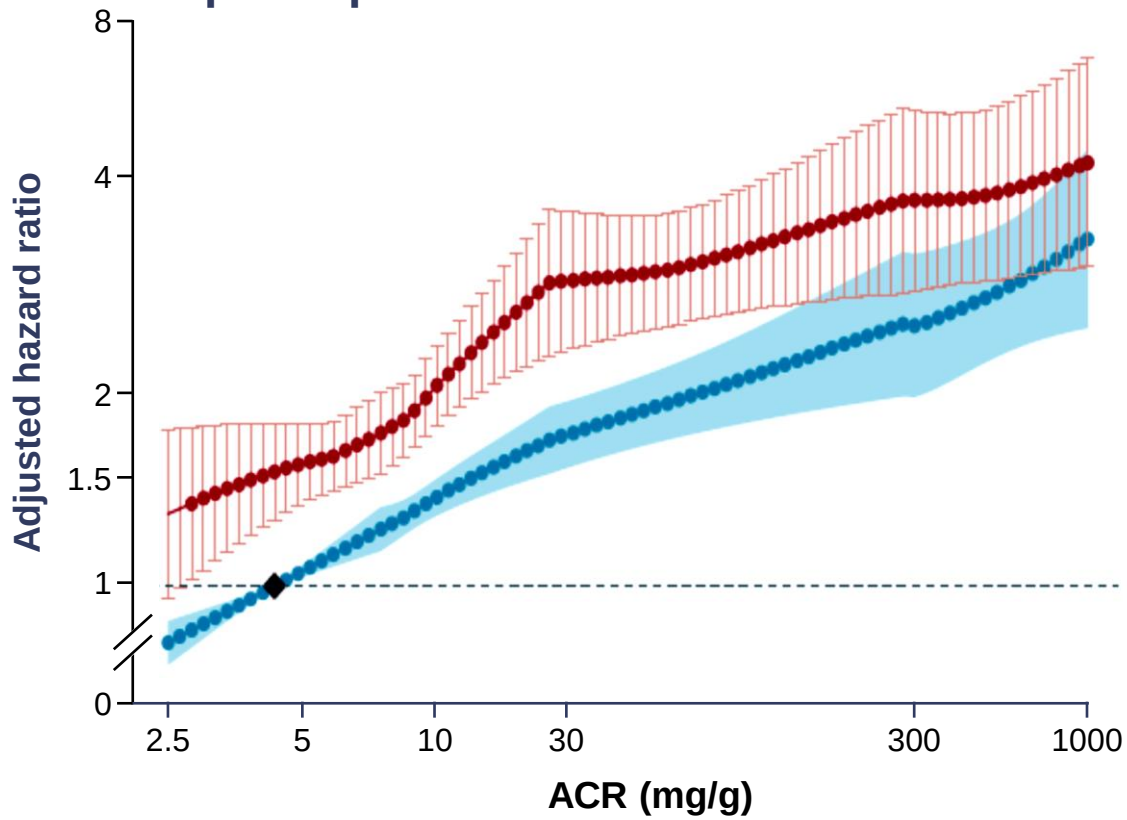
1. GBD 2017 Disease and Injury Incidence and Prevalence Collaborators. *Lancet* 2018;392:1789–1858; 2. Parving HH, et al. *Kidney Int* 2006;69:2057–2063;
3. Birkeland KI, et al. *Diabetes Obes Metab* 2020:22:1607–1618; 4. Ronco C, et al. *J Am Coll Cardiol* 2008;52:1527–1539

Both albuminuria and eGFR decline elevate the risk of CV death, which is increased further in T2D patients

CV mortality according to eGFR in participants with and without diabetes



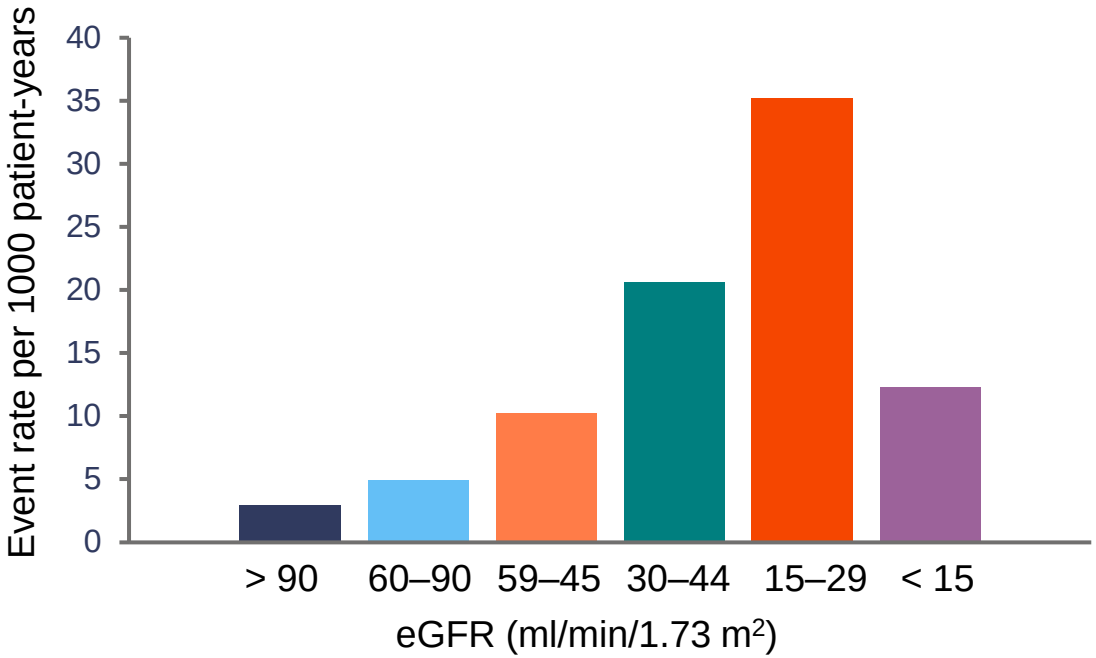
CV mortality according to ACR in participants with and without diabetes



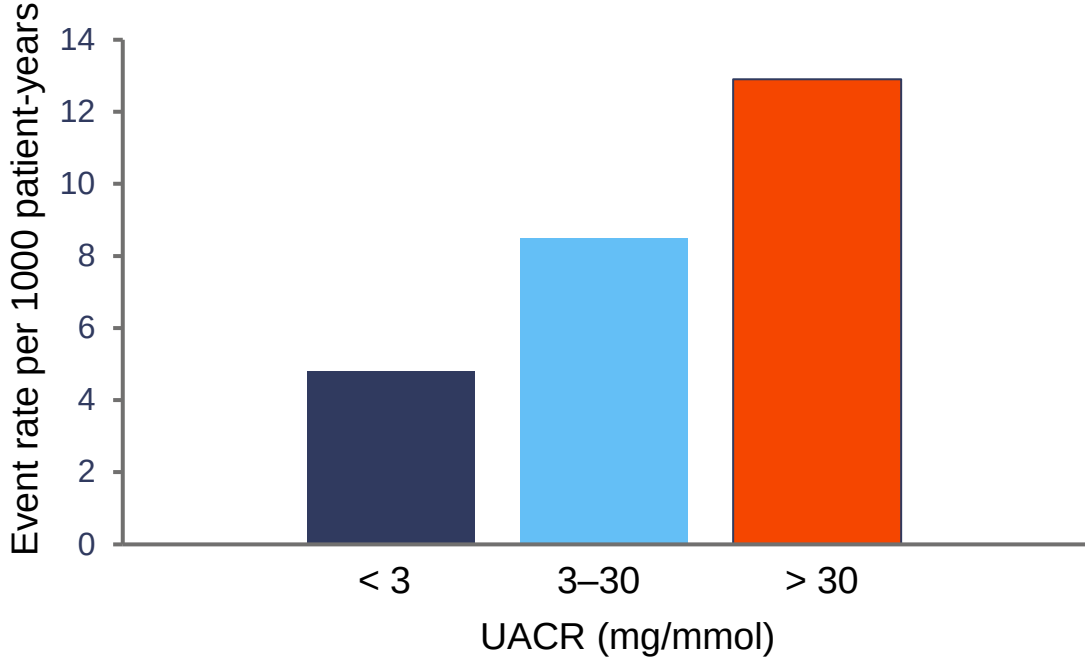
Fox et.al. Lancet 2012

Kidney impairment in patients with T2D increases the risk of hospitalisation for heart failure

eGFR and hospitalisation for HF



Albuminuria and hospitalisation for HF



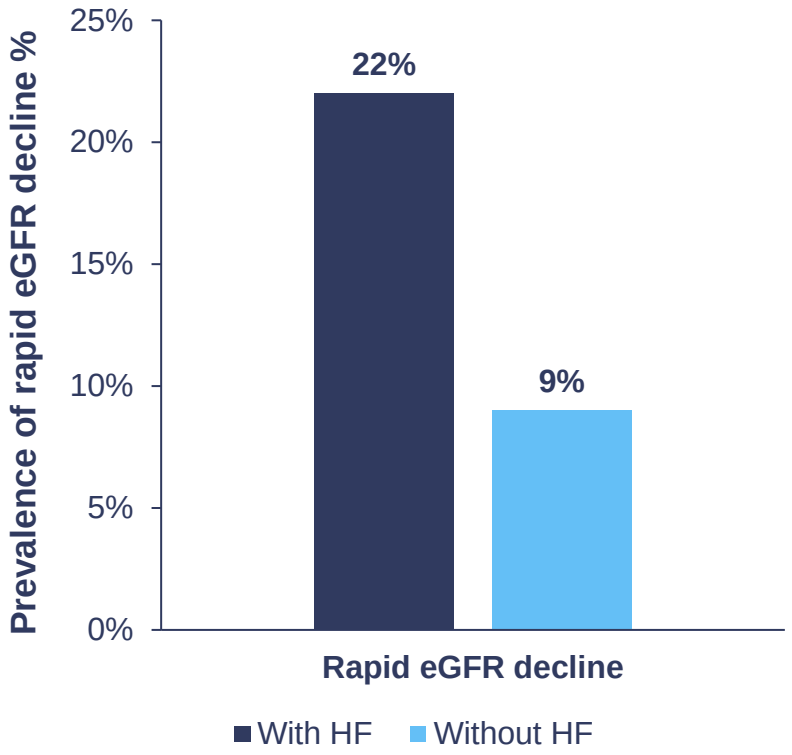
Population-matched Swedish database study; N = 266 305, median follow-up: 5.6 years

HF, heart failure

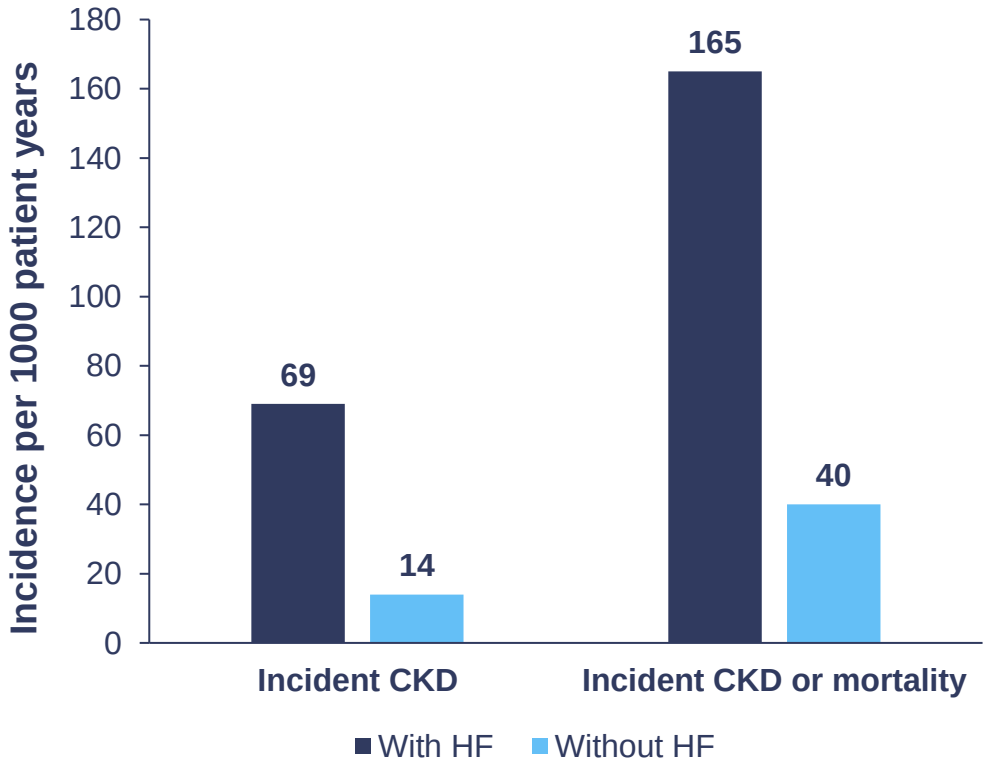
Rosengren A, *et al. Diabetologia* 2018;61:2300–2309

Conversely, heart failure increases the risk of kidney function decline and of adverse kidney outcomes

HF is associated with a more rapid decline in eGFR[a]

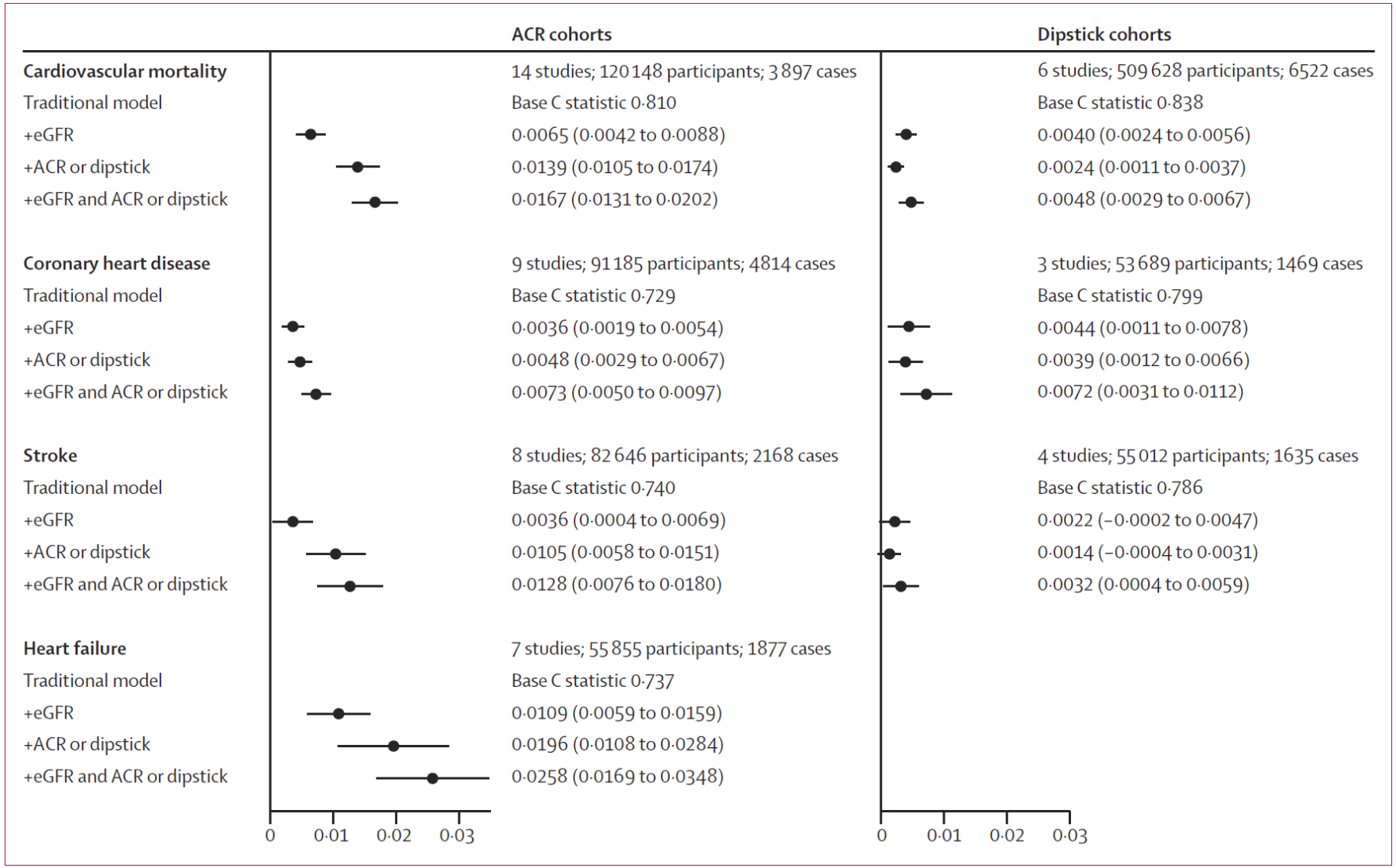


HF is associated with significantly higher risk of incident CKD[b] and incident CKD or mortality



[a]Rapid rate of eGFR decline was defined as slopes steeper than -5 mL/min/1.73 m^2/yr; [b]Incident CKD was defined as two eGFR values of <60 mL/min/1.73 m^2 occurring ≥3 months apart and a decrease from baseline eGFR of at least 25%.
CKD, chronic kidney disease; eGFR, estimated glomerular filtration rate; HF, heart failure
George LK, et al. *Circ Heart Fail* 2017;10:e003825

Adding Albuminuria (and eGFR) to CV risk models significantly improved discrimination and calibration



CKD-PC cohort
637315 participants
without CV disease
Median Follow-up 4.2 yrs

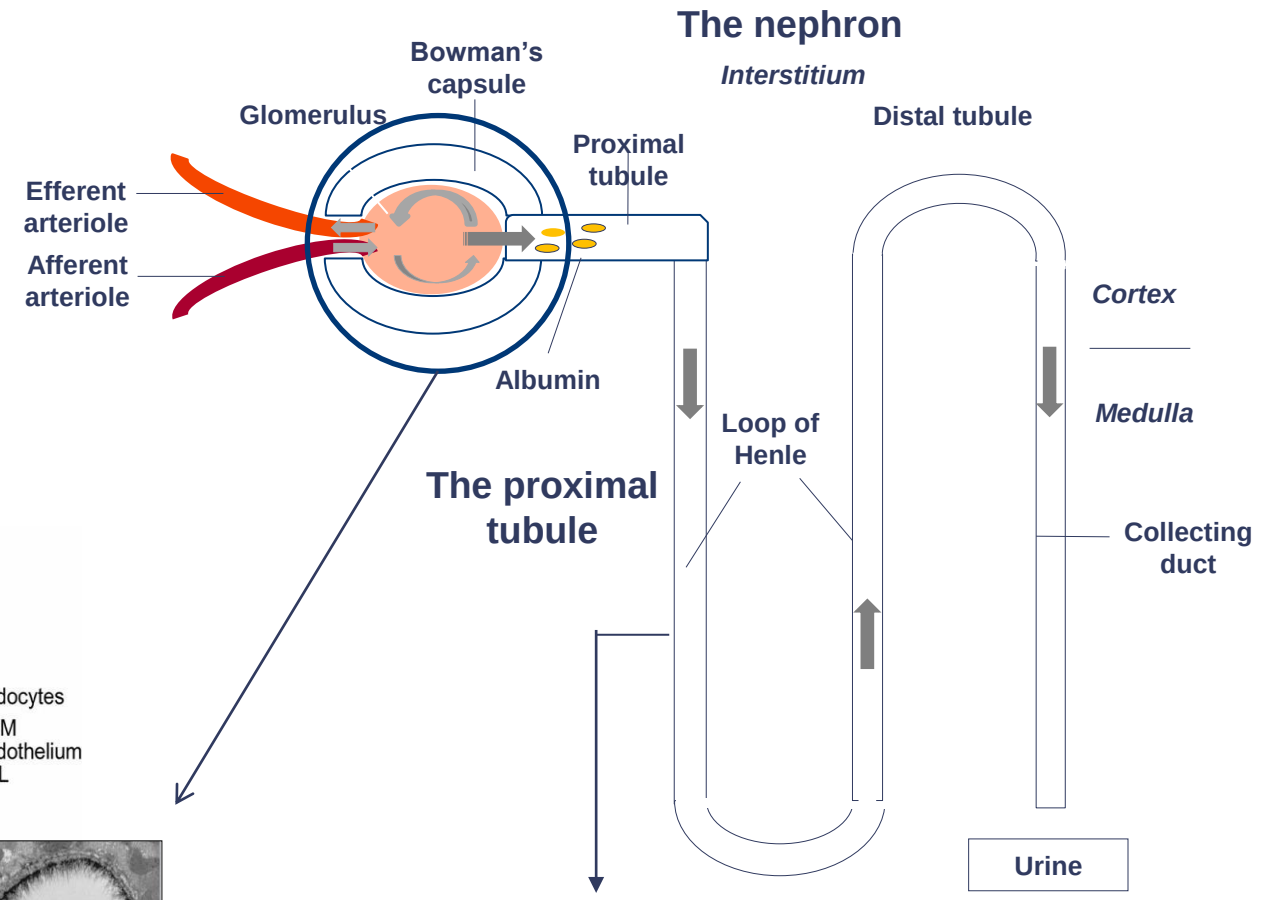
Matssuhita Lancet Diabetes & Endocrinology 2015:3:514-25

Risk marker or risk factor?

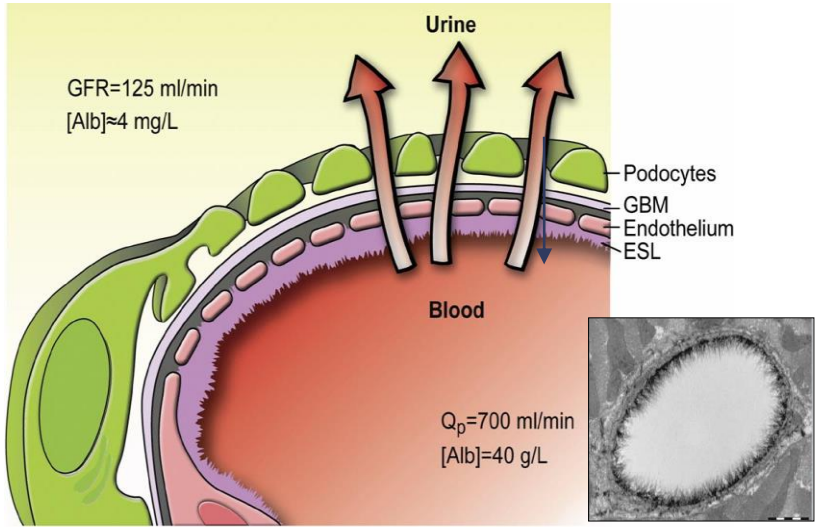
- eGFR and albuminuria are risk markers of disease progression
  - The lower the eGFR the more advanced CKD
  - Impairment to the glomerular basement membrane leads to increased leakage of albumin
- Albuminuria is also a risk factor for kidney and CV disease progression

What is the evidence that albuminuria is a risk factor for kidney and CV disease?

Glomerular albumin leakage reflects glycocalyx / endothelial dysfunction



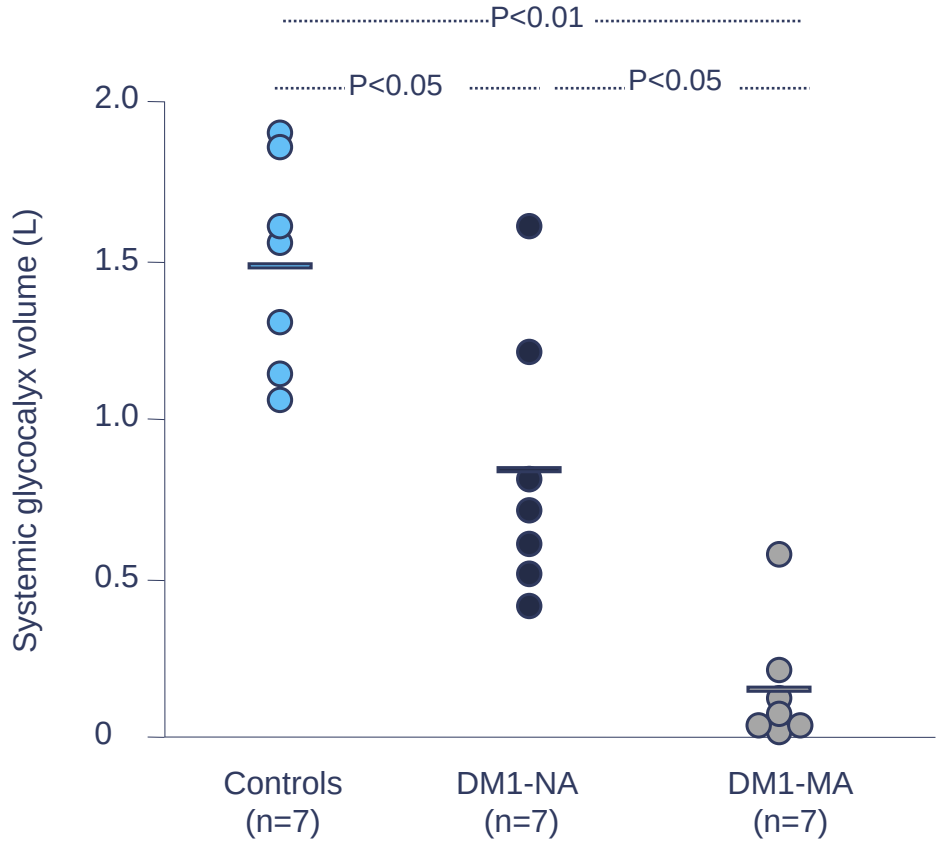
Endothelium dysfunction
Glycocalyx dysfunction

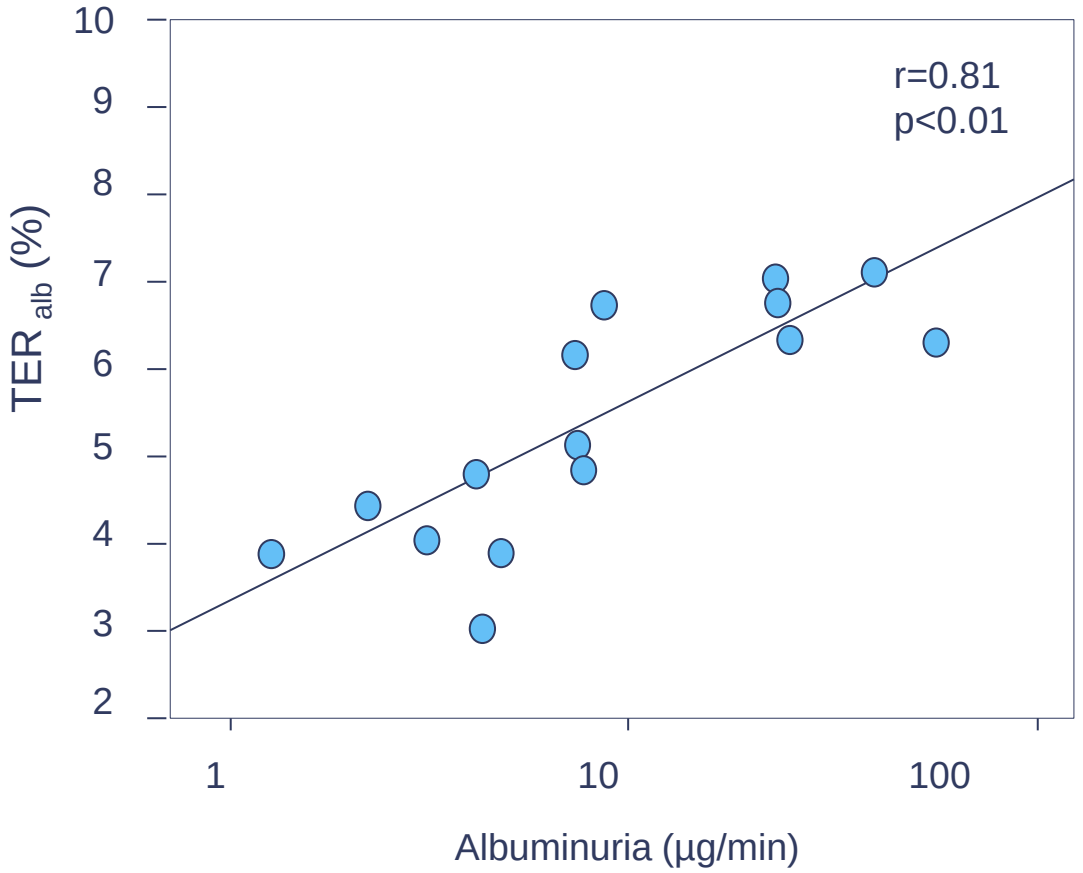


Podocyte injury/Inflammation/Mesangial expansion → **Progressive renal dysfunction**

Roscioni et.al. Kidney International 2013

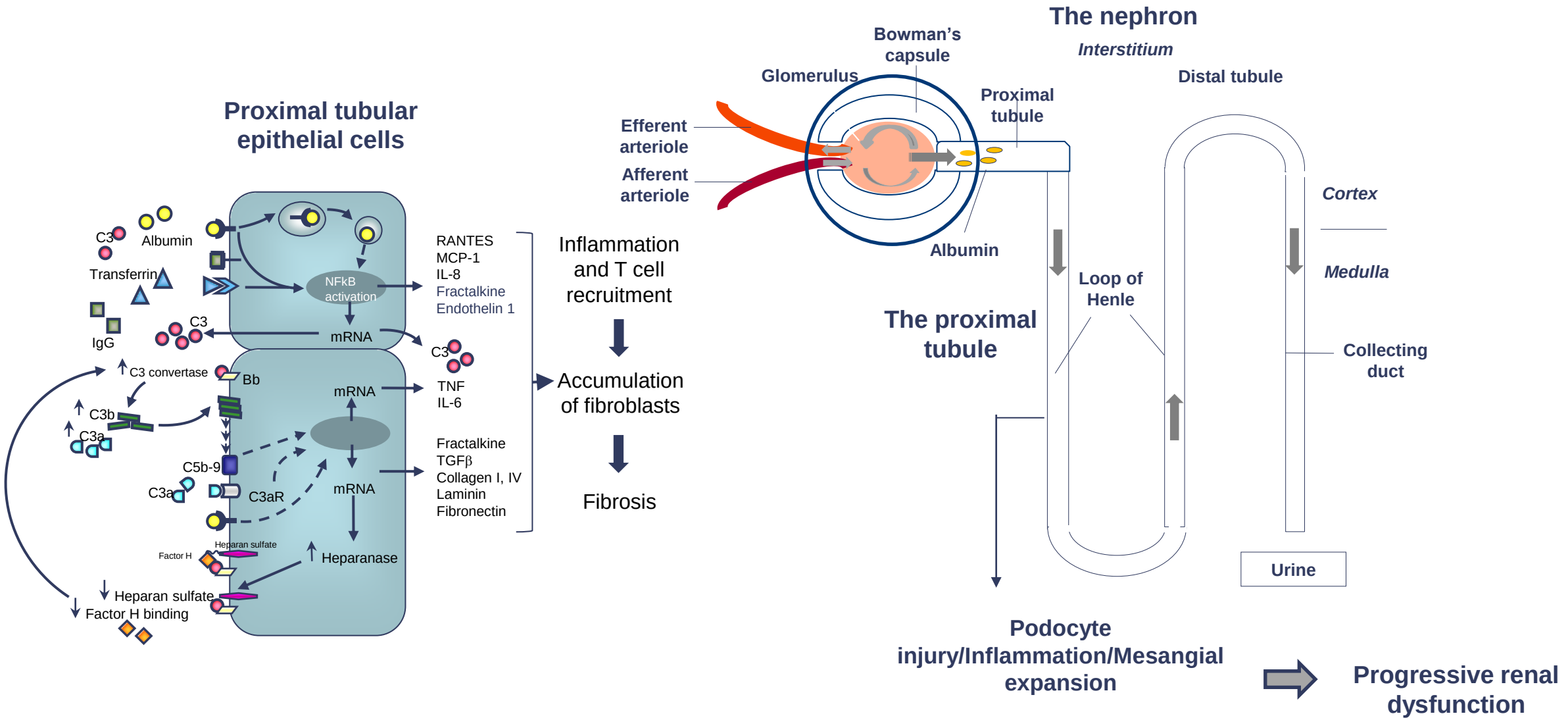
Glomerular albumin leakage associated with endothelial glycocalyx and vascular permeability





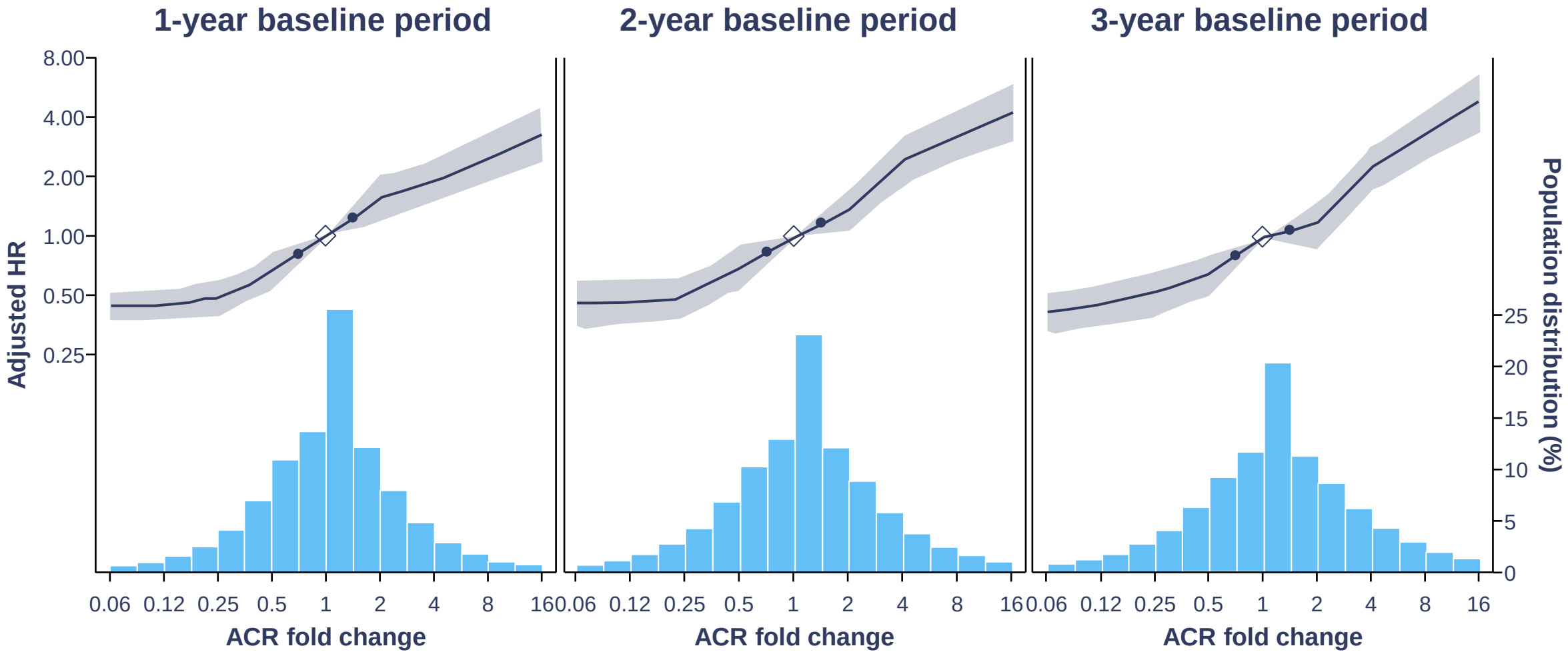
Nieuwdorp et al, Diabetes 2006
Knudsen ST. Diabetes Care, 2002, 25 (12):2328-2334

Increased albumin exposure to the tubules causes kidney injury



Zoja et al., Am J Kidney Dis, 1995; Eddy et al., Kidney Int, 1995; Zoja et al.. Kidney Int, 1998; Morigi et al., J Am Soc Nephrol, 2002
Abbate et al., Kidney Int, 2002; Tang et al., J Clin Invest, 2003; Donadelli et al., J Am Soc Nephrol, 2003; Perico et al., Nat Rev Drug Disc, 2008

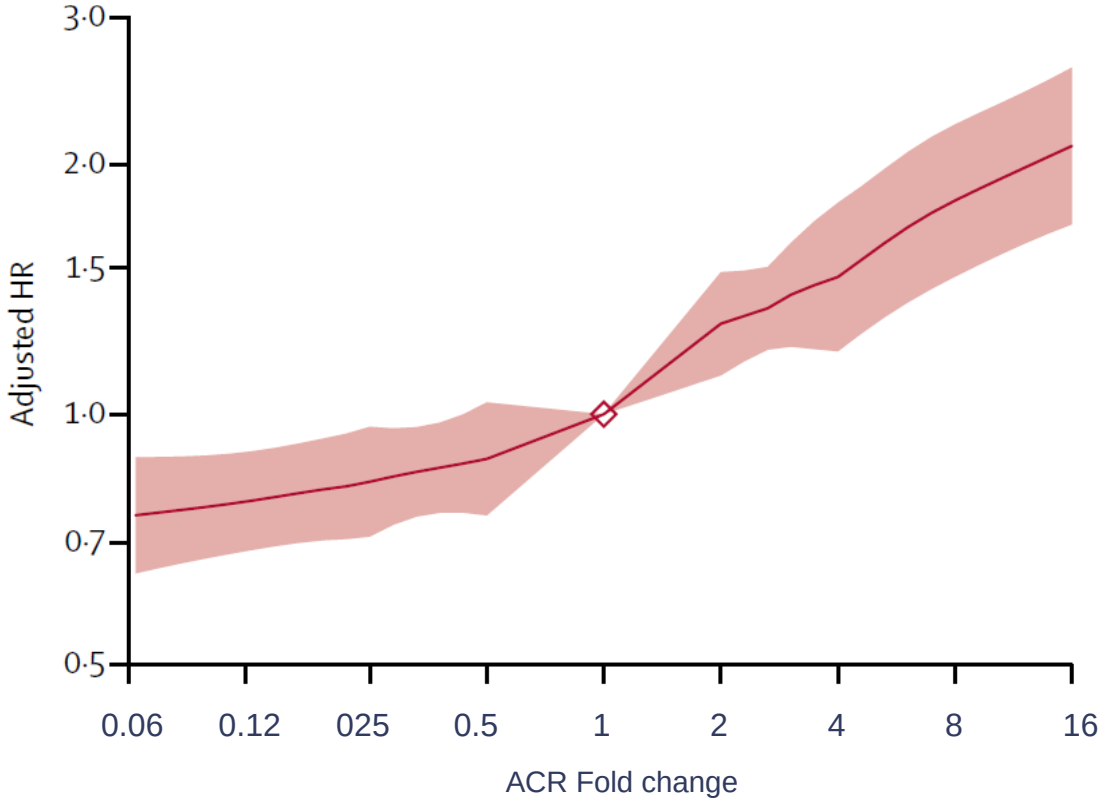
Changes in albuminuria are associated with kidney failure



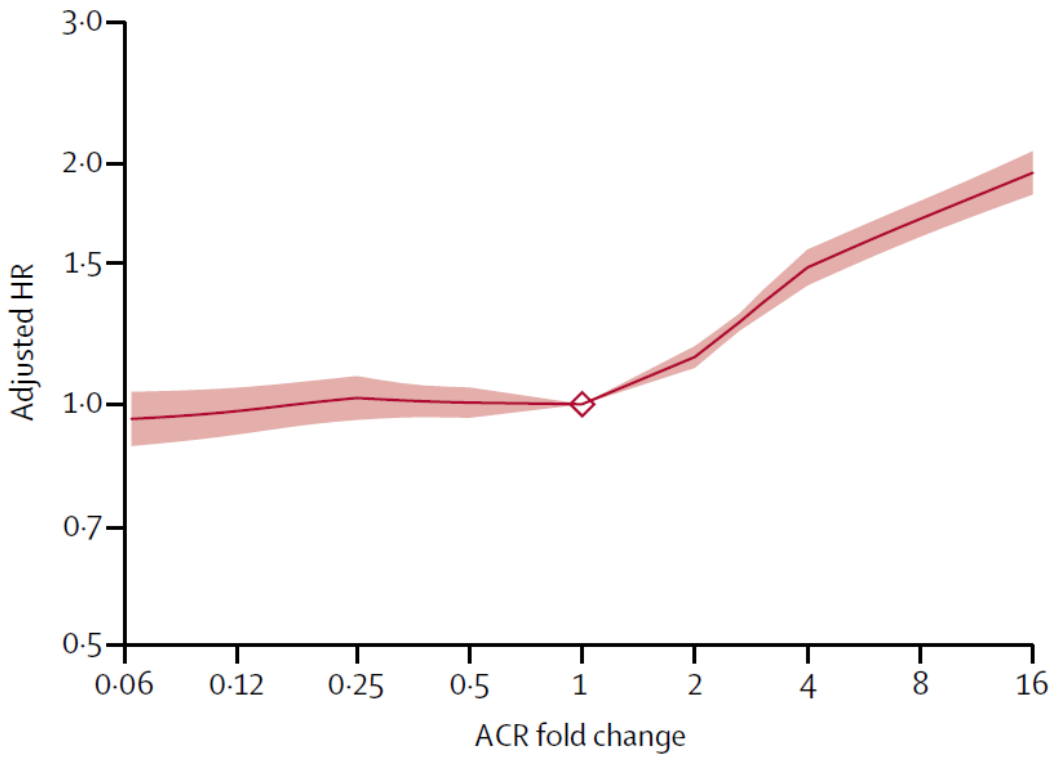
Meta-analysis of observational studies involving 675,904 participants and 7914 kidney failure events
ACR, albumin:creatinine ratio; HR, hazard ratio
Coresh J, et al. *Lancet Diabetes Endocrinol* 2019;7:115–127

Changes in albuminuria over 2 years are associated with CV mortality and all cause mortality

Cardiovascular mortality

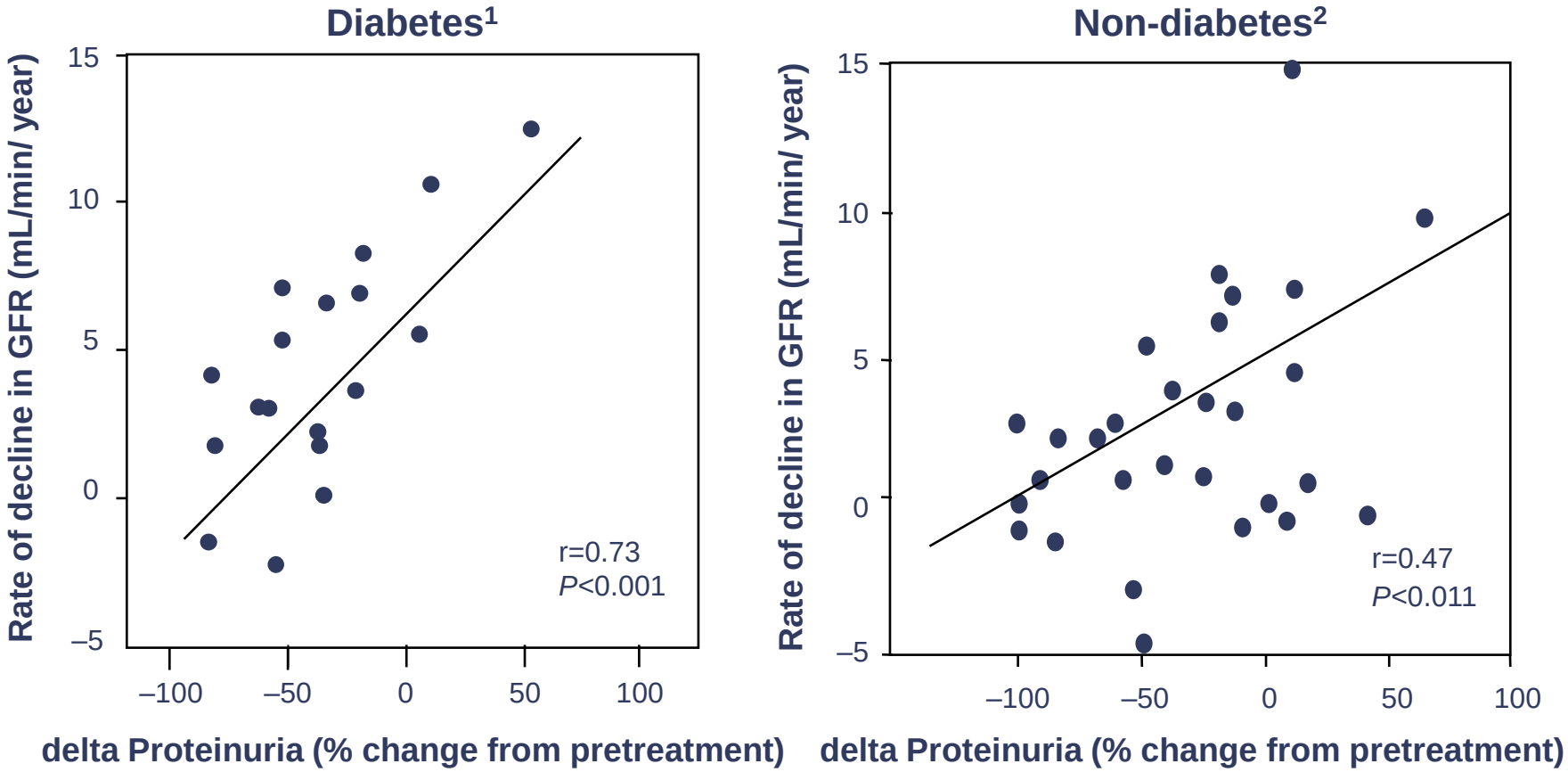


All-cause mortality



Coresh et.al. Lancet Diabetes & Endocrinology 2019

Initial albuminuria response to RAASi predicts long-term GFR decline



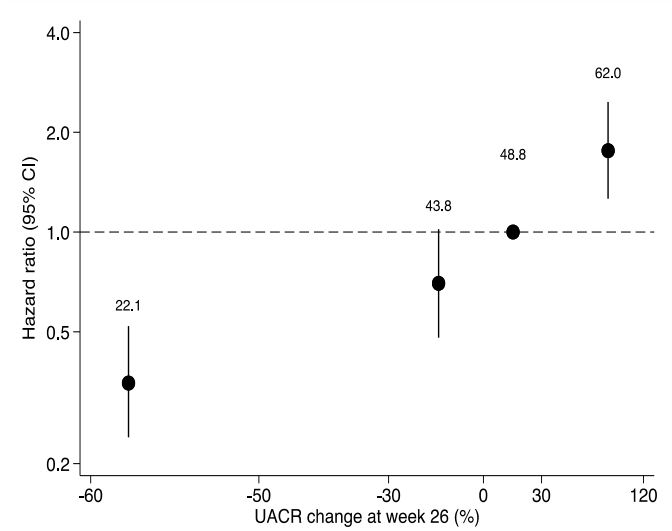
- Diabetes patients (n=18) treated in a non-randomised controlled trial with captopril alone, or in combination with furosemide/bendrofluazide
- Non-diabetes patients (N=29) treated in a randomised controlled trial with enalapril or atenolol

GFR, glomerular filtration rate; eGFR, estimated glomerular filtration rate; RAASi, renin–angiotensin–aldosterone system inhibitor

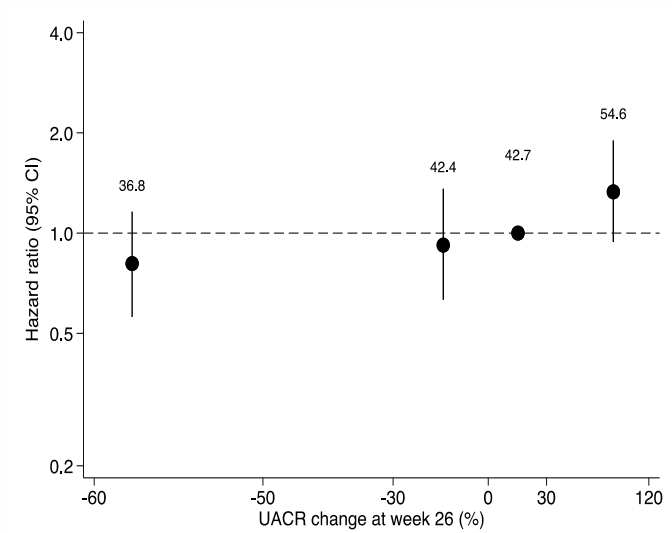
1. Rossing P, et al. *Diabetologia* 1994;37:511–516; 2. Apperloo AJ, et al. *Kidney Int* 1994;45:S174–178

CREDENCE: Early changes in UACR are associated with kidney and CV outcomes

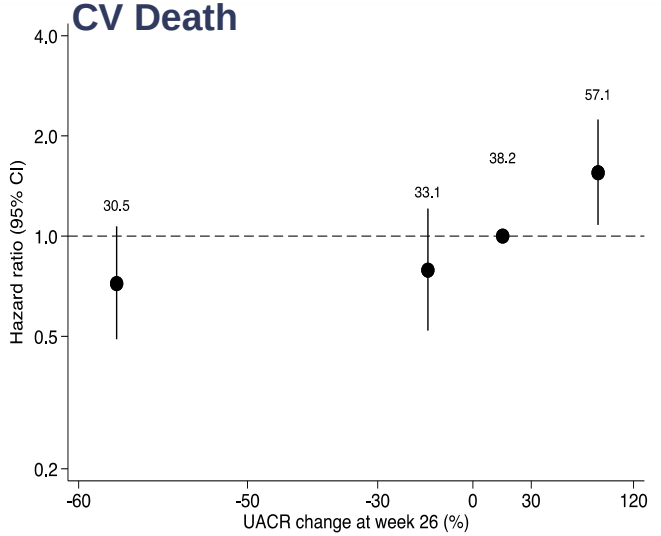
Kidney Outcome



CV Outcome



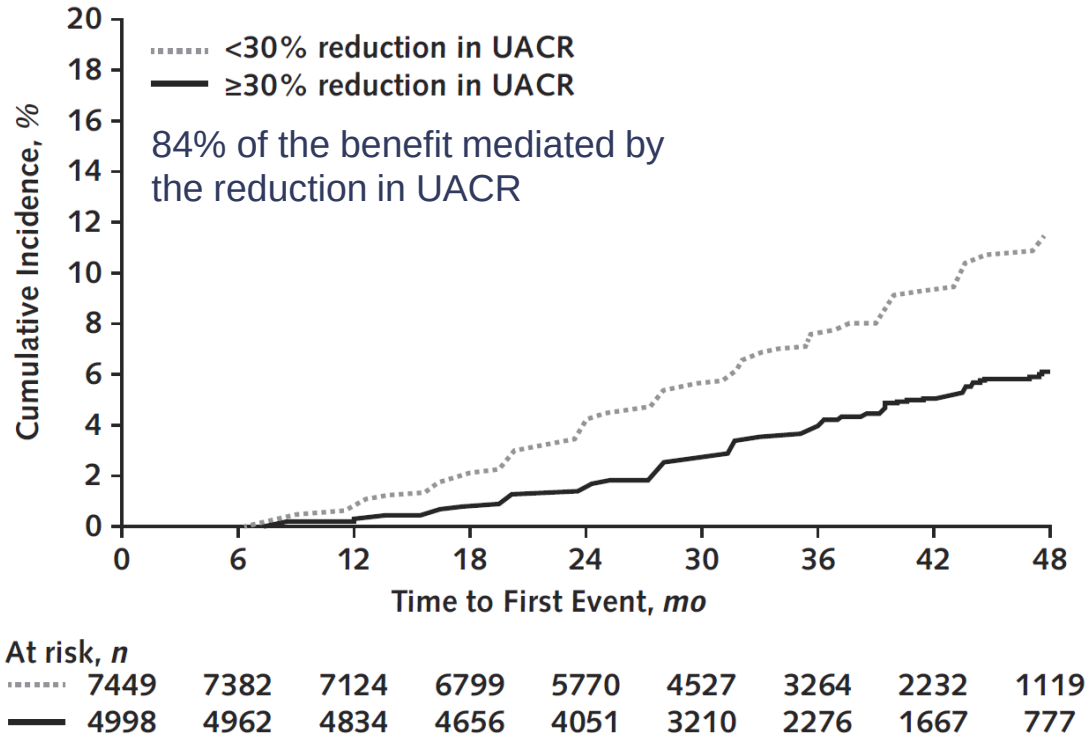
HF hospitalization or CV Death



Oshima et.al. J Am Soc Nephrol 2020

Impact of Finerenone Induced Decrease in UACR on CKD and CV Outcomes

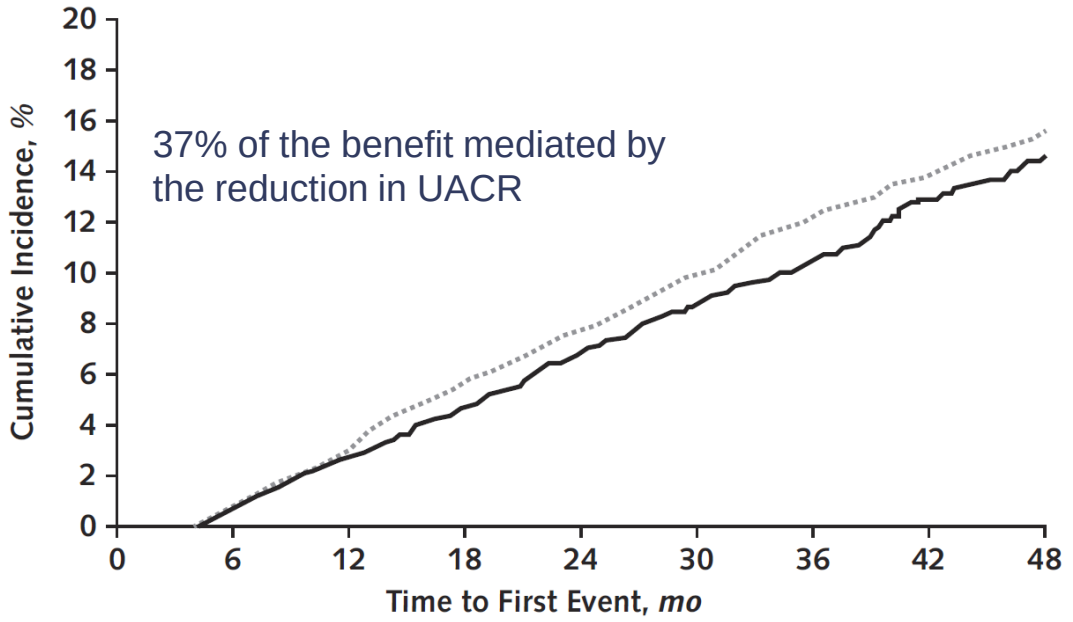
Kidney Outcome



At risk, *n*

<30% reduction in UACR	7449	7382	7124	6799	5770	4527	3264	2232	1119
≥30% reduction in UACR	4998	4962	4834	4656	4051	3210	2276	1667	777

CV Outcome

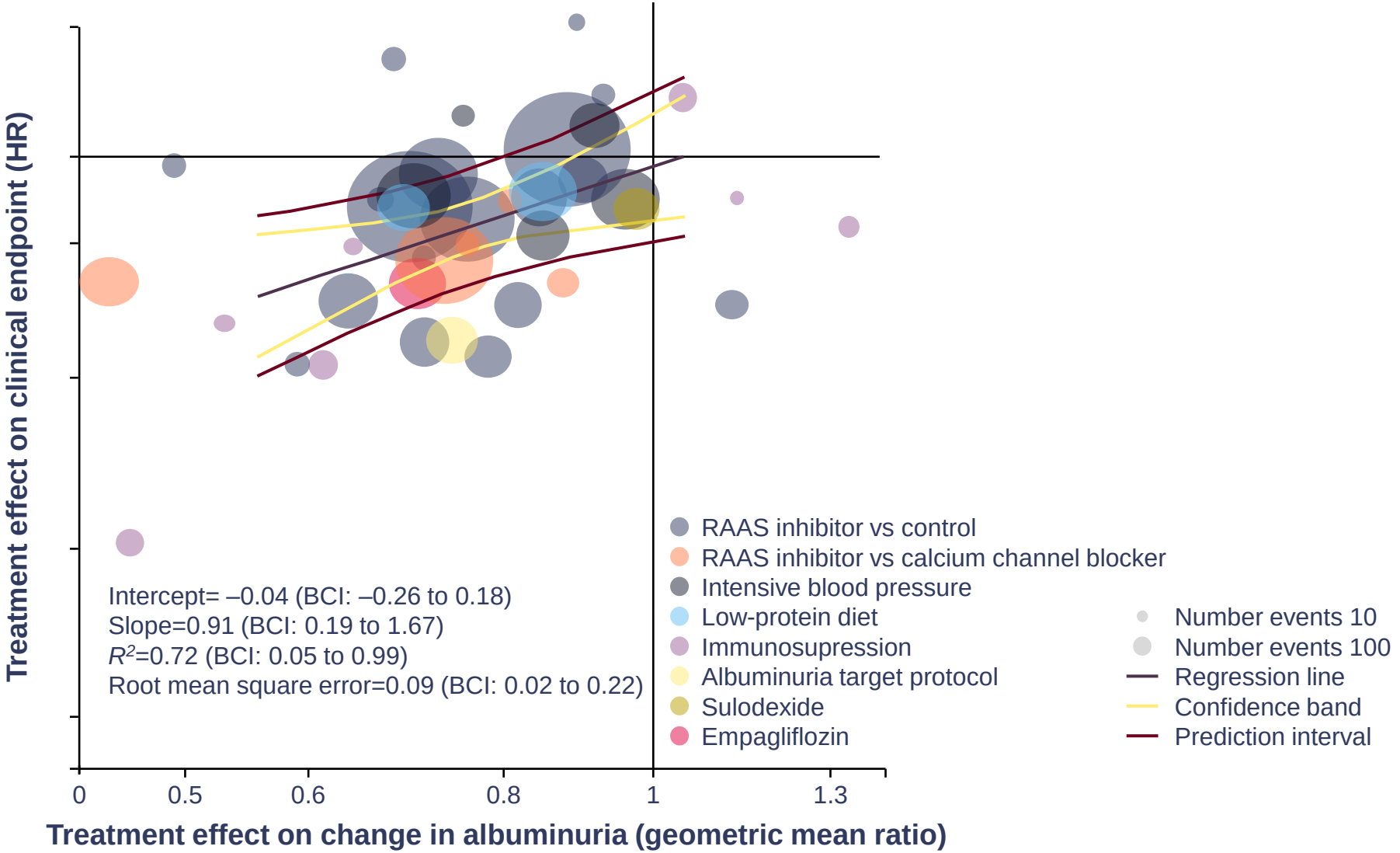


At risk, *n*

<30% reduction in UACR	7428	7365	7157	6909	6043	4784	3496	2409	1261
≥30% reduction in UACR	4962	4923	4799	4667	4109	3276	2387	1739	848

Agarwal et.al. Annals Intern Med 2023 epub ahead of print

Trial level analysis for the treatment effect on UACR and clinical kidney outcomes

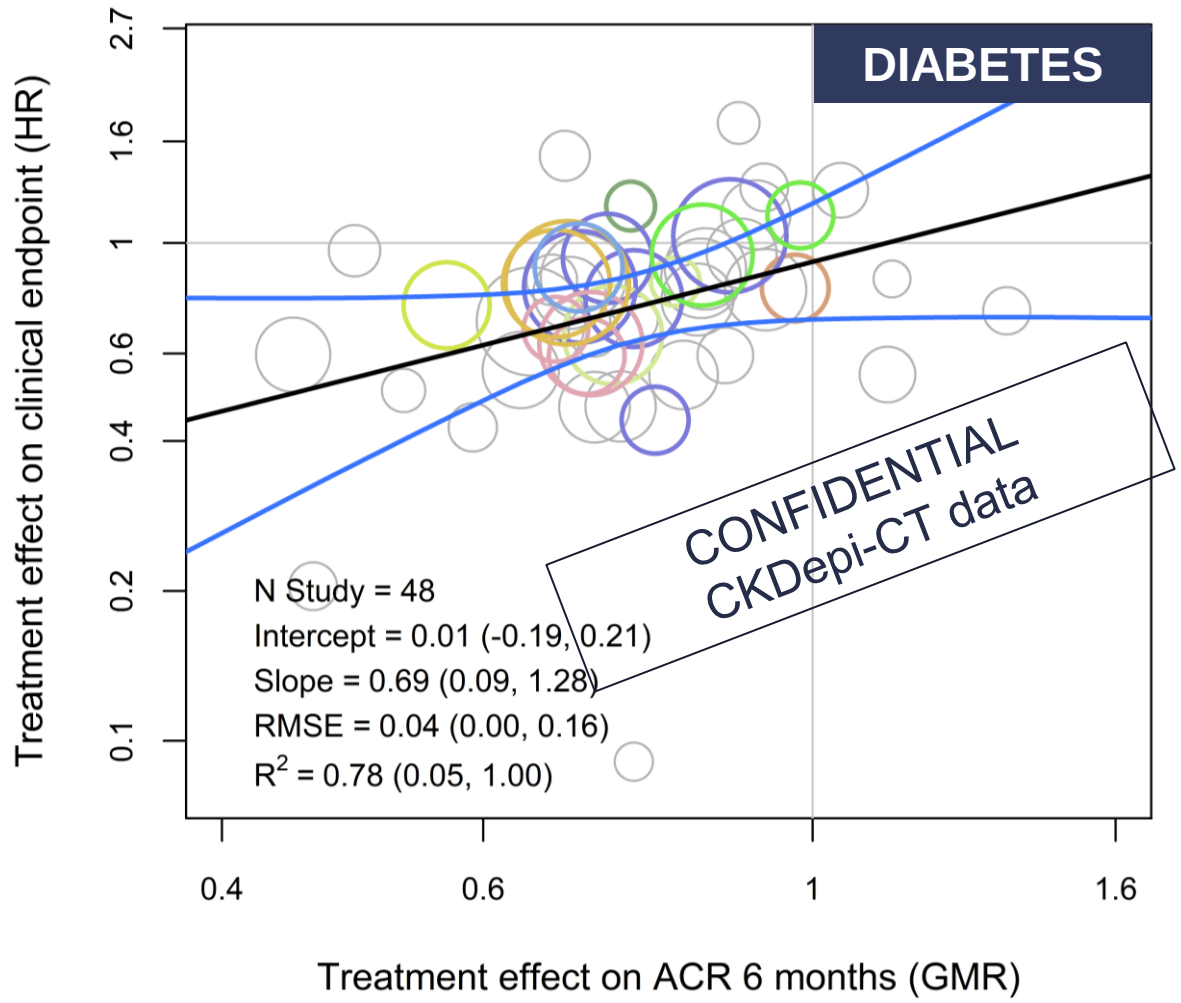


BCI , bootstrap standard confidence interval; HR, hazard ratio; RAAS, renin–angiotensin–aldosterone system; UACR, urine albumin:creatinine ratio

Heerspink HJL, et al. *Lancet Diabetes Endocrinol* 2019;7:128–139

CKD-EPI Chronic Kidney Disease Epidemiology Collaboration

Trial level analysis for the treatment effect on UACR and clinical kidney events in diabetes (at high CV risk) clinical trials

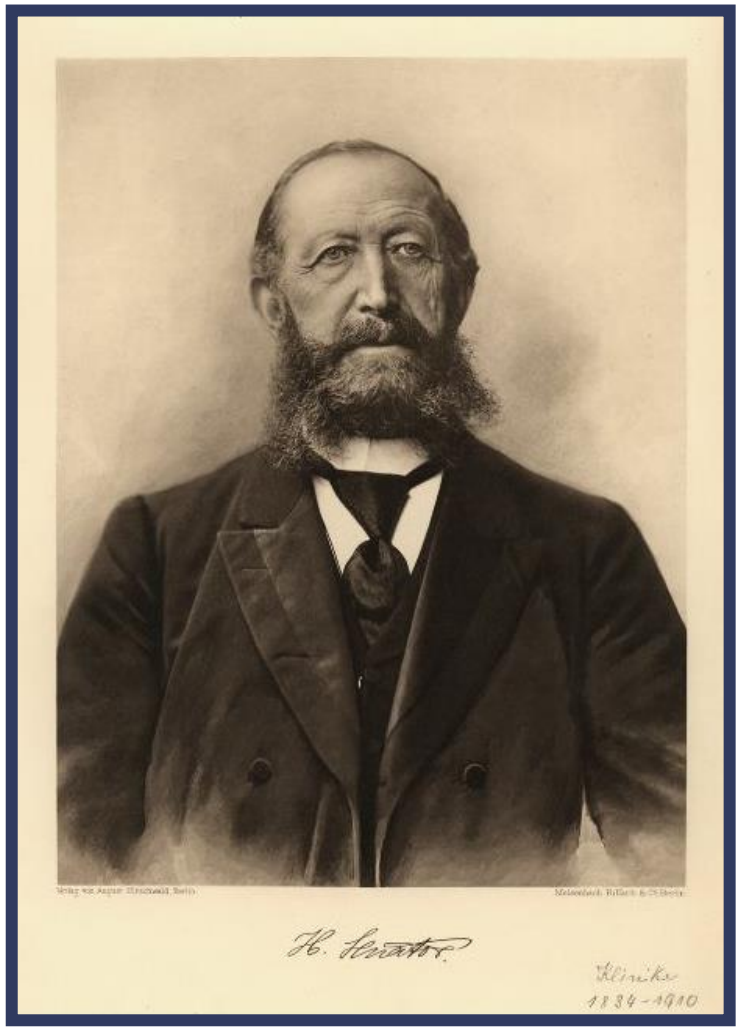


Type 2 diabetes	
CV disease	*Kidney disease*
ALTITUDE	CSG
ABCD	CREDENCE
CARMELINA	FIDELIO
CAROLINA	IDNT
CANVAS	ORIENT
EMPAREG	RENAAL
FIGARO	SUN-MACRO
LEADER	SONAR

Heerspink et.al. Confidential In Progress

CKD-EPI Chronic Kidney Disease Epidemiology Collaboration

A brief history of albuminuria



Hermann Senator (1834-1911)
Charité Hospital, Berlin

Questions addressed (1882)

"How is albumin handled by the kidneys?"

"How often is albuminuria found in "normal" individuals?"

"What is the variability of albuminuria?"

"Which factors influence intensity of albuminuria?"

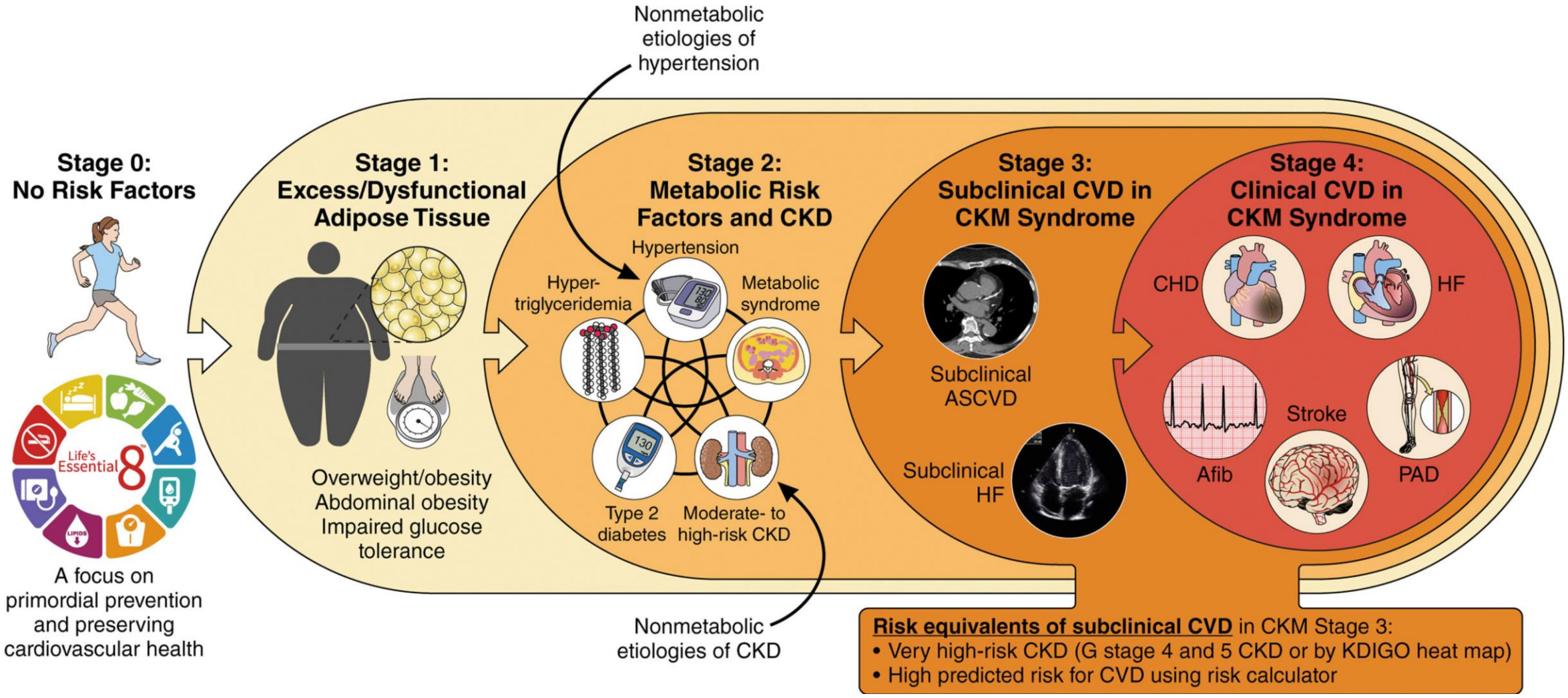
"Is some albumin not captured by the available techniques?"

"**What are the causes and risk associated with albuminuria?**"

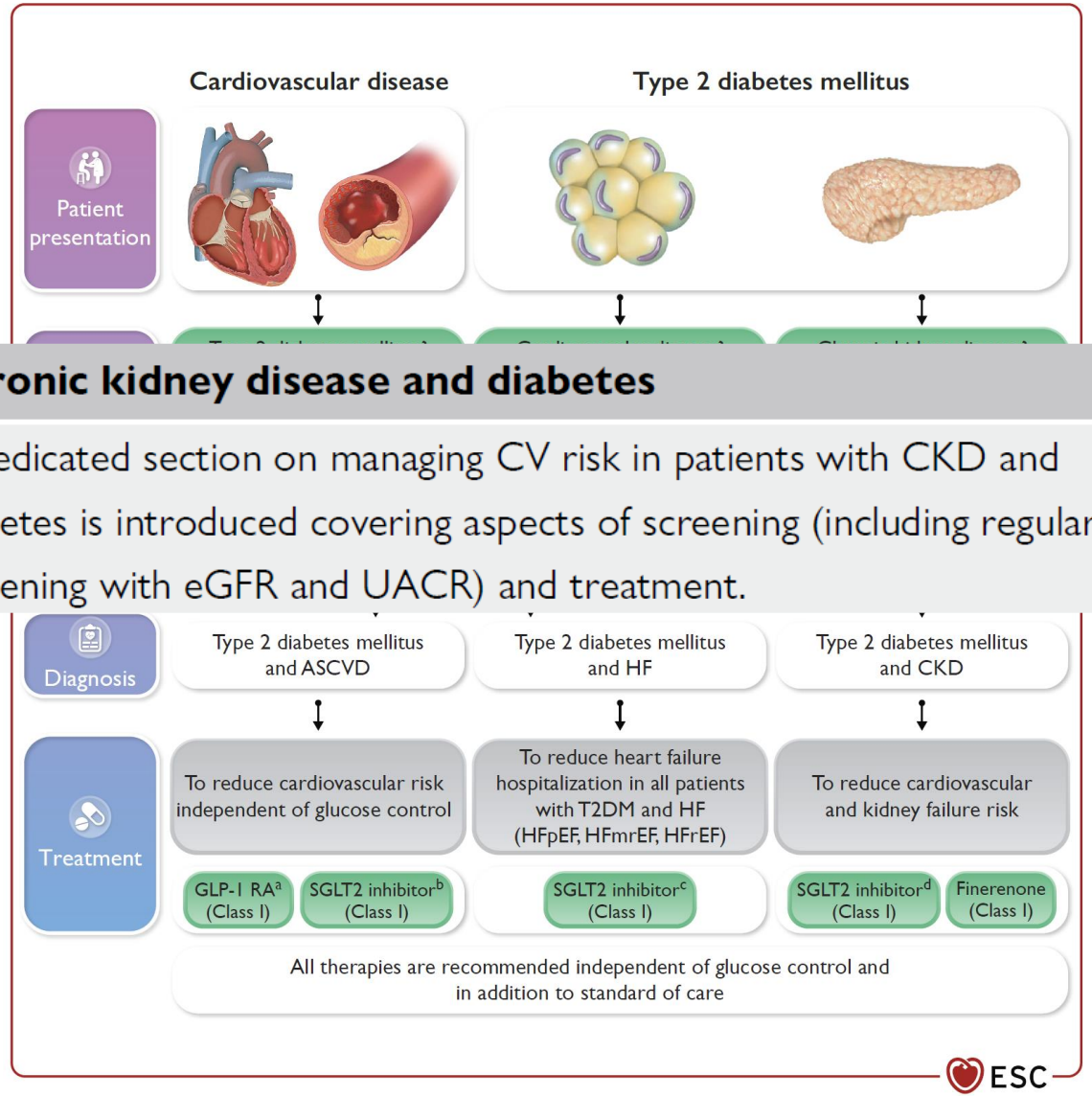
"**Can albuminuria and its risk be treated?**"

Gansevoort RT, Ritz E. *Nephrol Dial Transplant* 2009;24:1057–1062

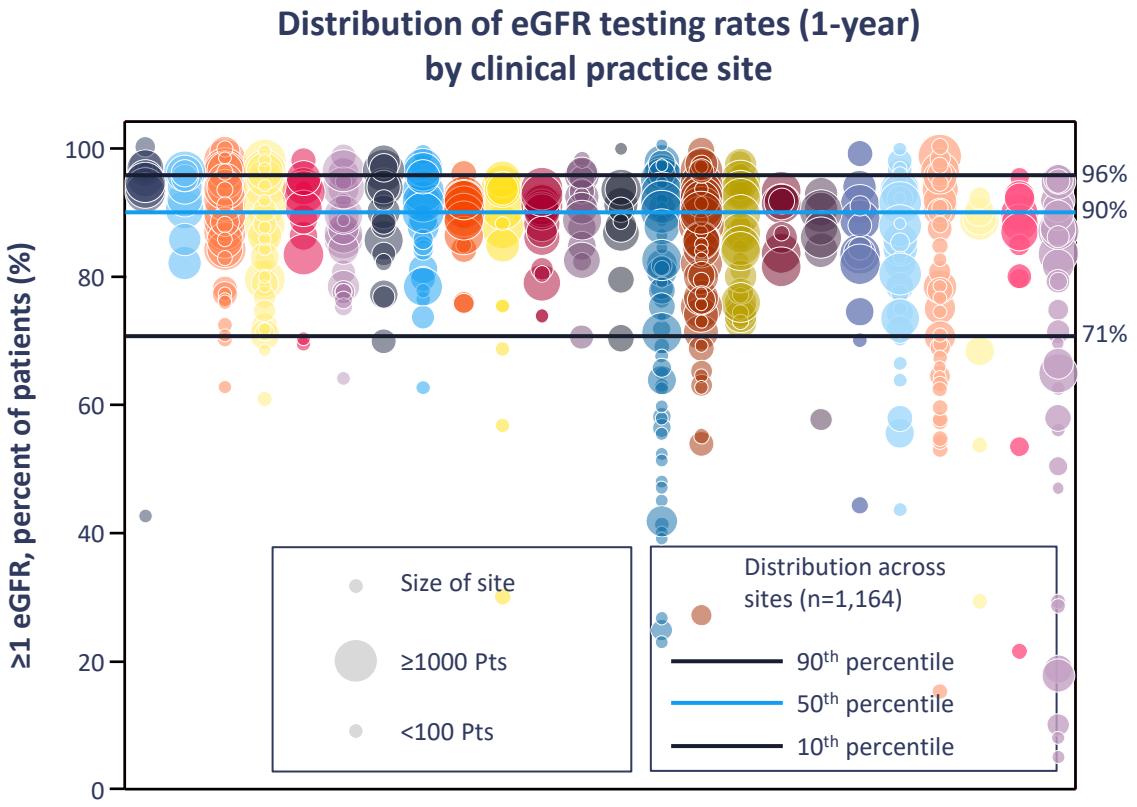
AHA consensus statement: Kidny Cardiovascular Metabolic

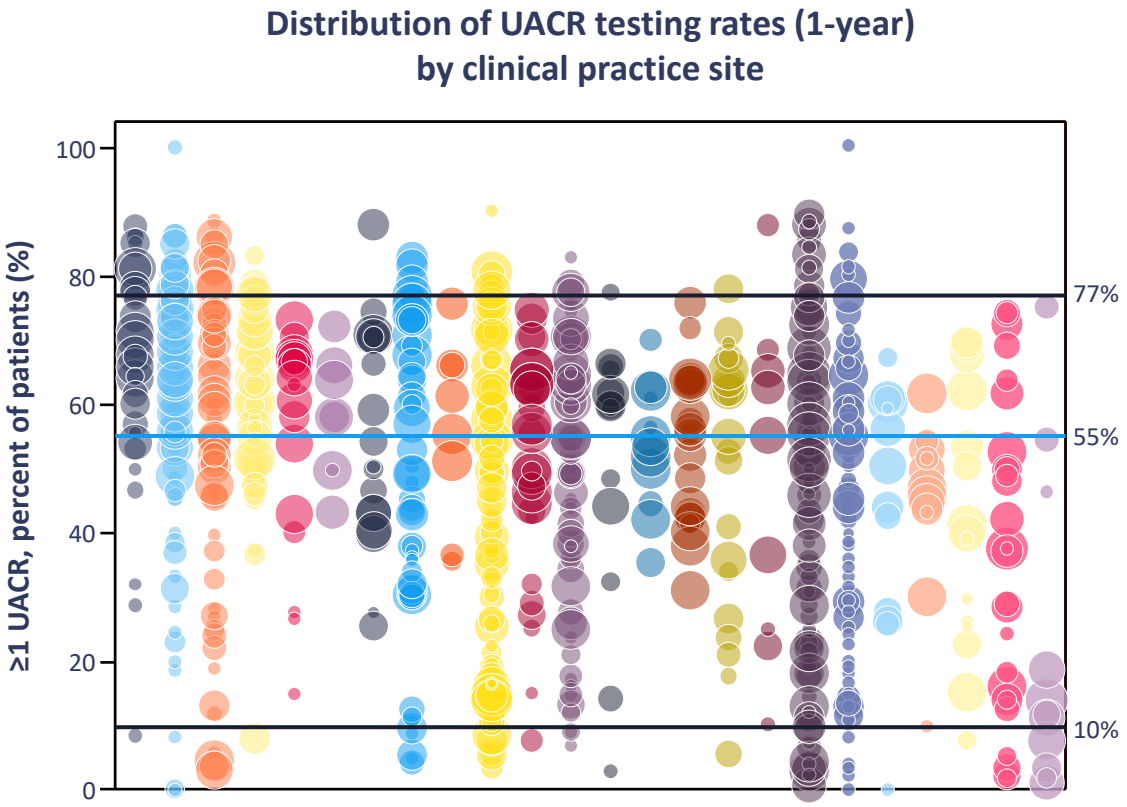


2023 ESC Guideline for the management of cardiovascular disease in patients with type 2 diabetes



In general, clinical practice monitoring of eGFR is appropriate but UACR monitoring is suboptimal in Type 2 diabetes





eGFR, estimated glomerular filtration rate; Pts, patients; UACR, urine albumin:creatinine ratio
Stempwienicz N, et al. *Diabetes Care* 2021;44:2000–2009

Summary

- eGFR and UACR are strong CV risk markers in people with or without diabetes
- Changes in albuminuria induced by different therapies are associated with risk of CV outcomes
- Early treatment effects on albuminuria are associated with treatment effects on kidney outcomes
  - Consistent association by different types of disease including diabetes (with high CV risk populations)
- More research required whether early treatment effects on albuminuria predict treatment effects on CV outcomes