

Early screening and risk identification of CKD in patients with diabetes: Why is it so important?

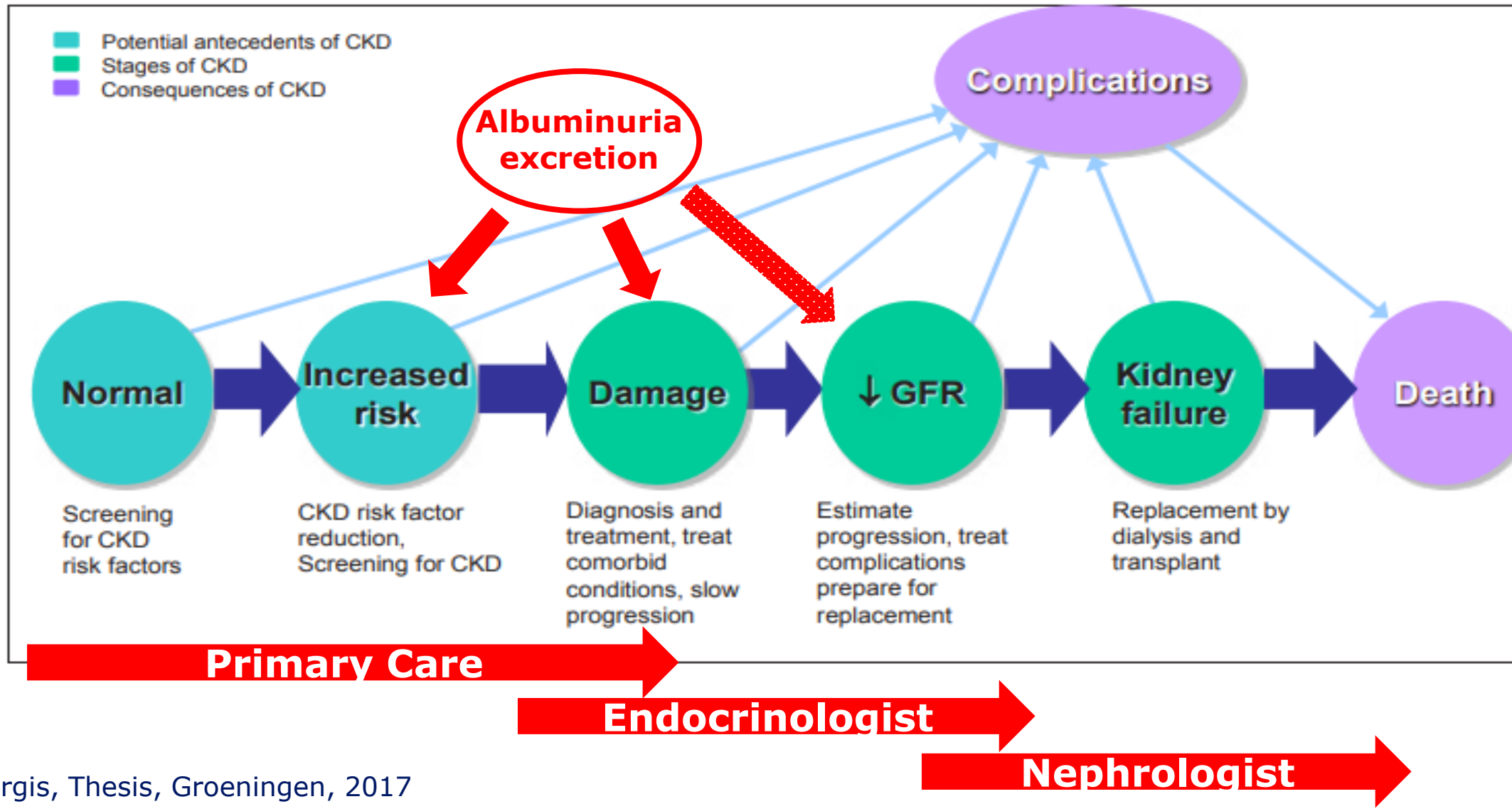
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Roskilde, Denmark

Rethinking the role of nephrologists in prevention of CKD – The opportunity of early risk identification



Kidney Disease – a continuum

development, progression, consequences



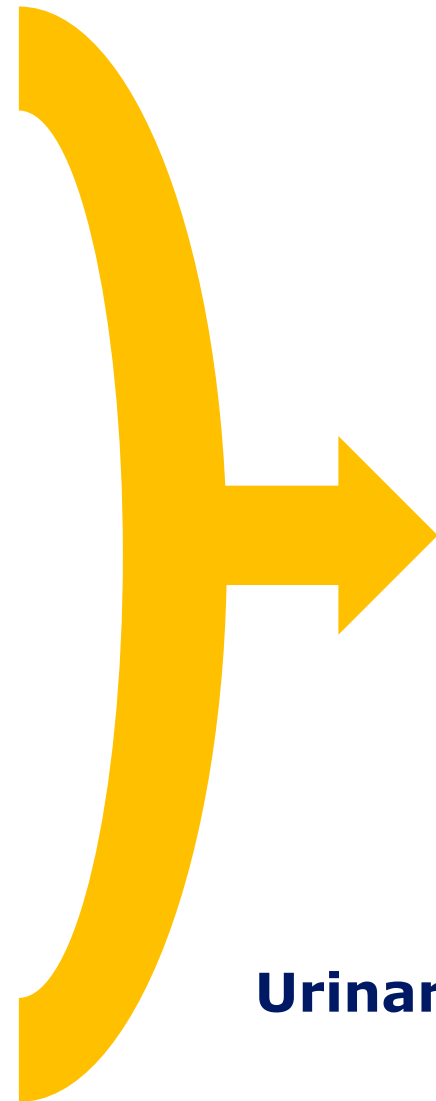
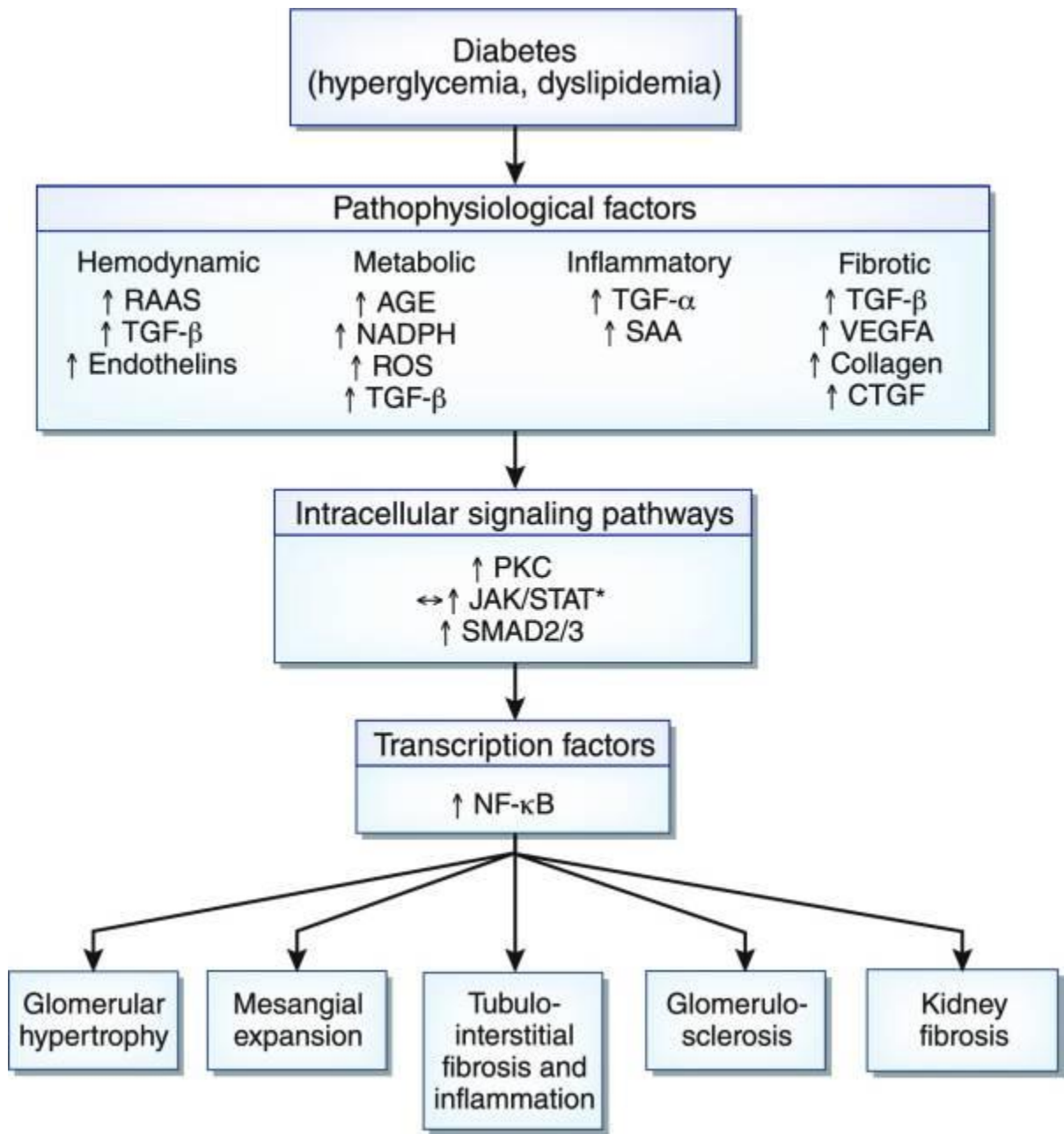
Microalbuminuria or moderately increased

uACR 30 – 300 mg/g

Predicts

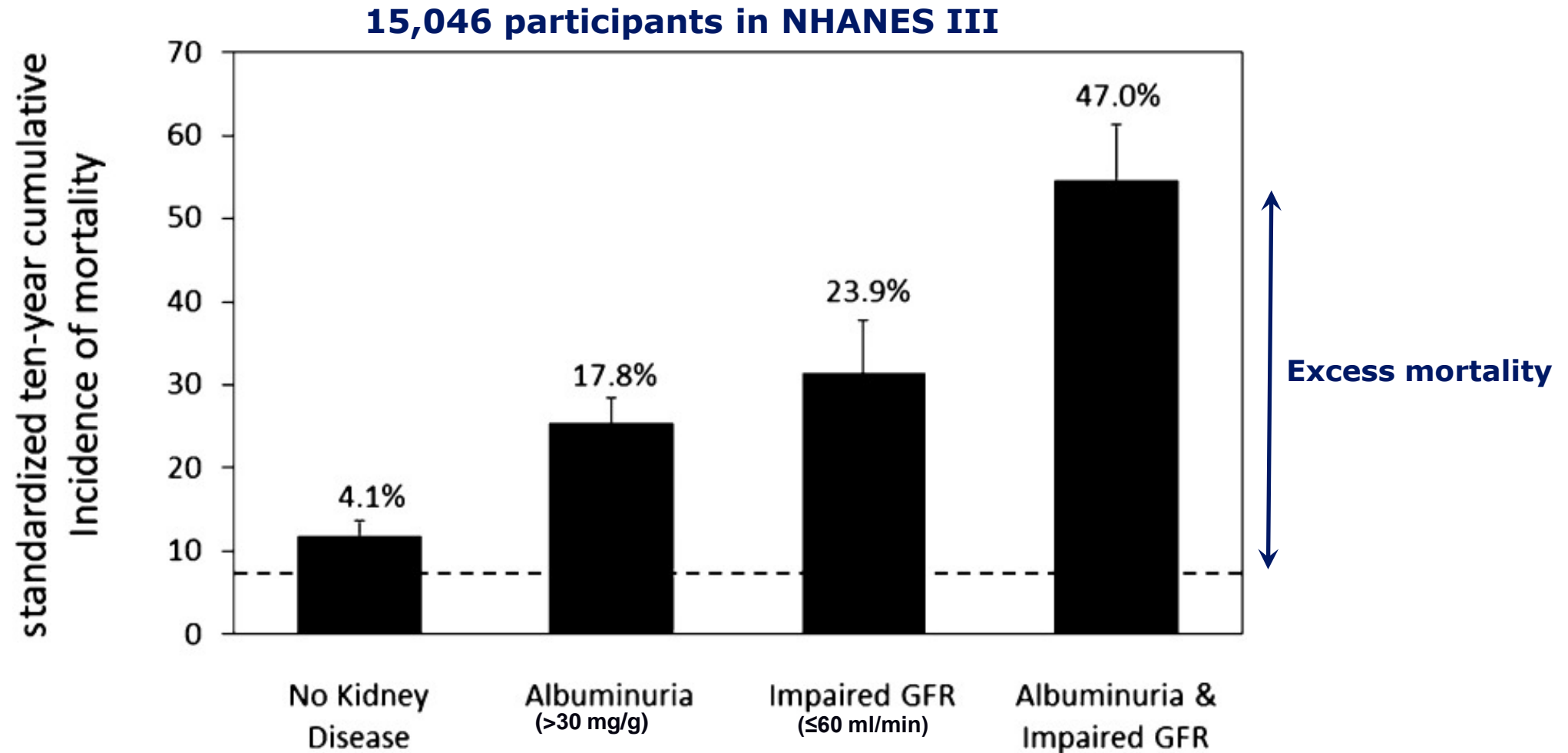
- development of diabetic nephropathy
- higher prevalence of retinopathy, neuropathy and foot ulcers
- cardiovascular morbidity
- mortality – all-cause and especially cardiovascular mortality
- significant correlation to blood pressure

- A marker of widespread endothelial dysfunction

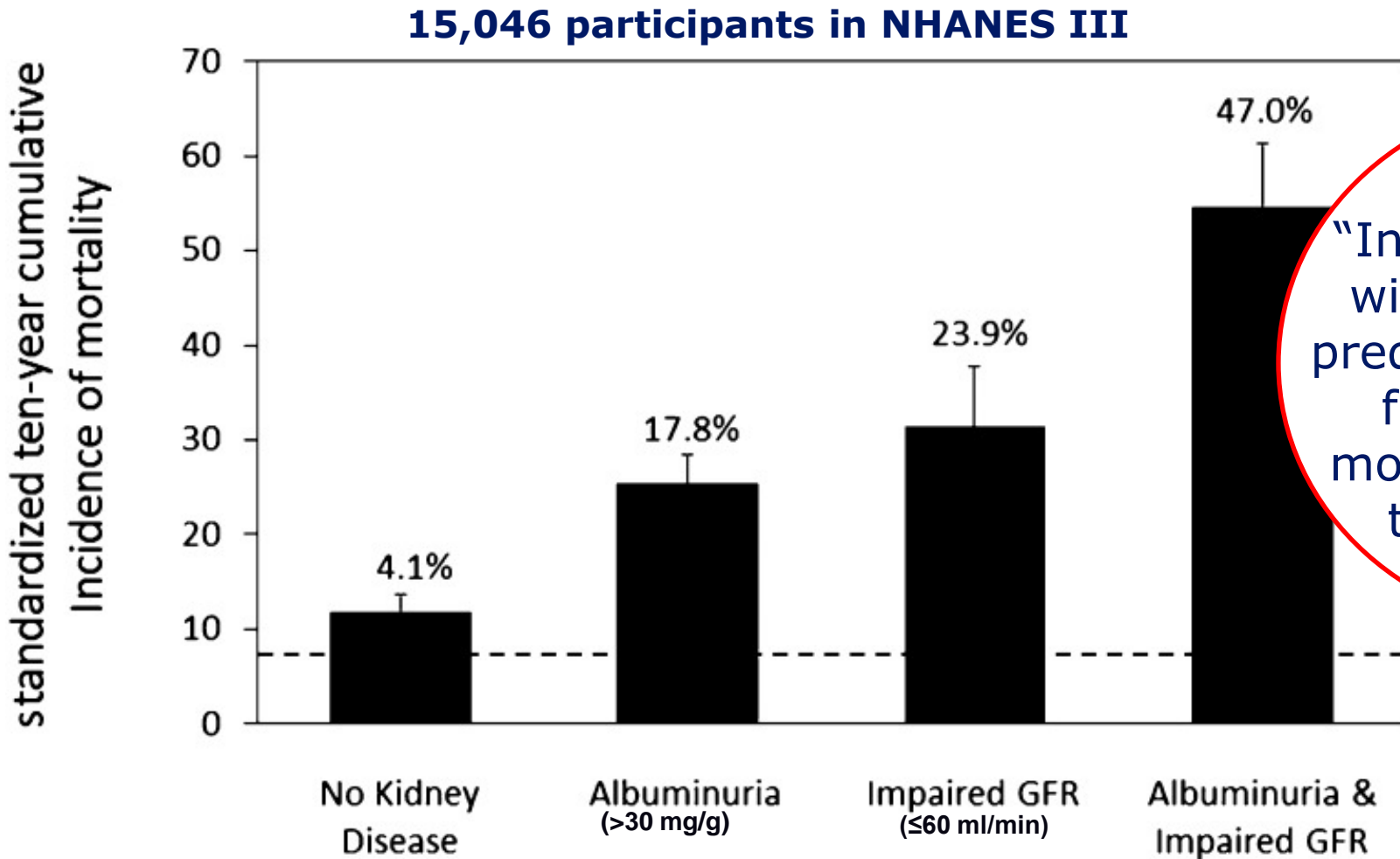


**Strongest marker:
Urinary albumin/creatinine ratio**

10-year mortality in T2DM by kidney disease status

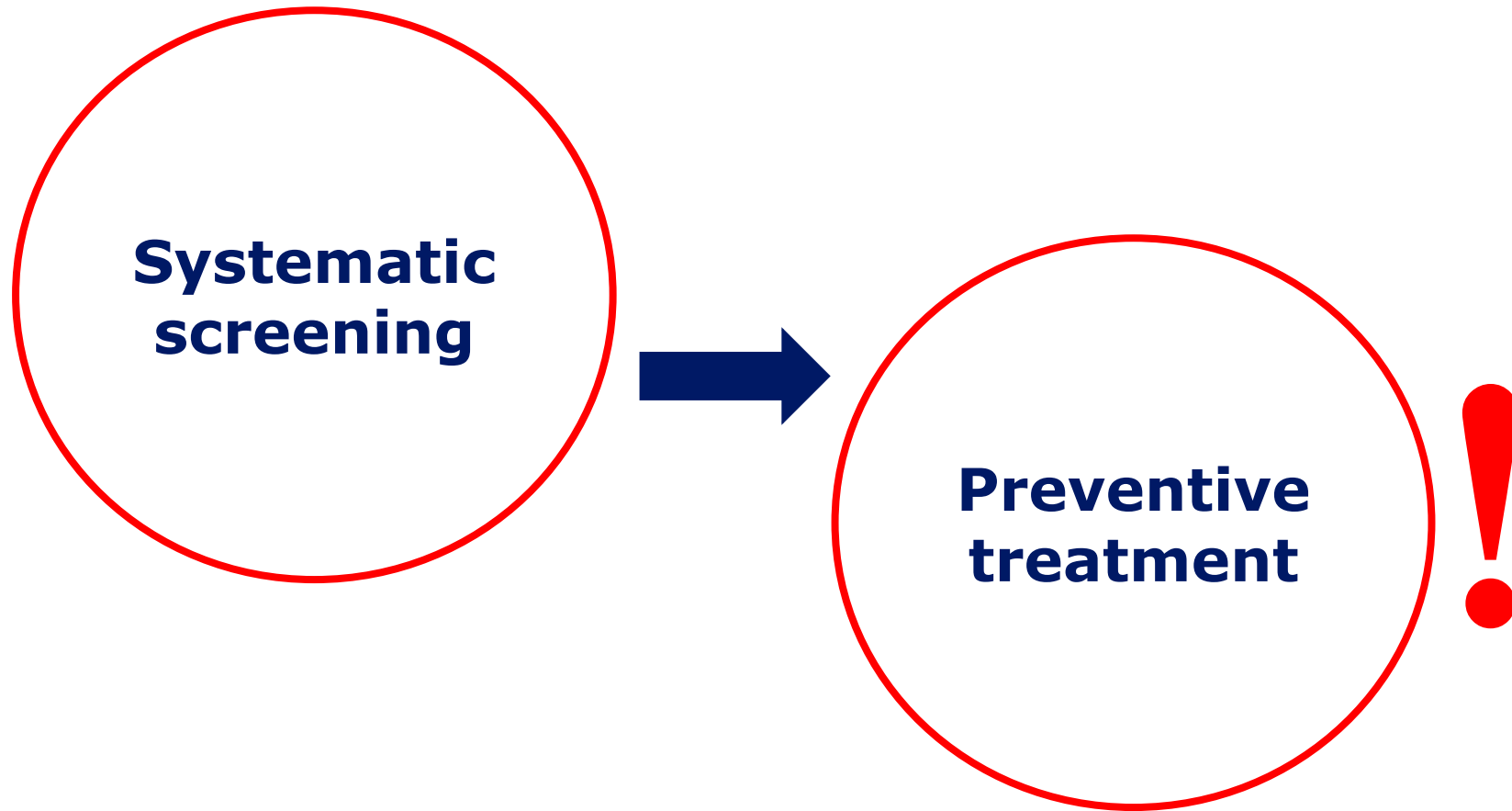


10-year mortality in T2DM by kidney disease status



“In conclusion, those with kidney disease predominantly account for the increased mortality observed in type 2 diabetes”

Changing diabetic nephropathy



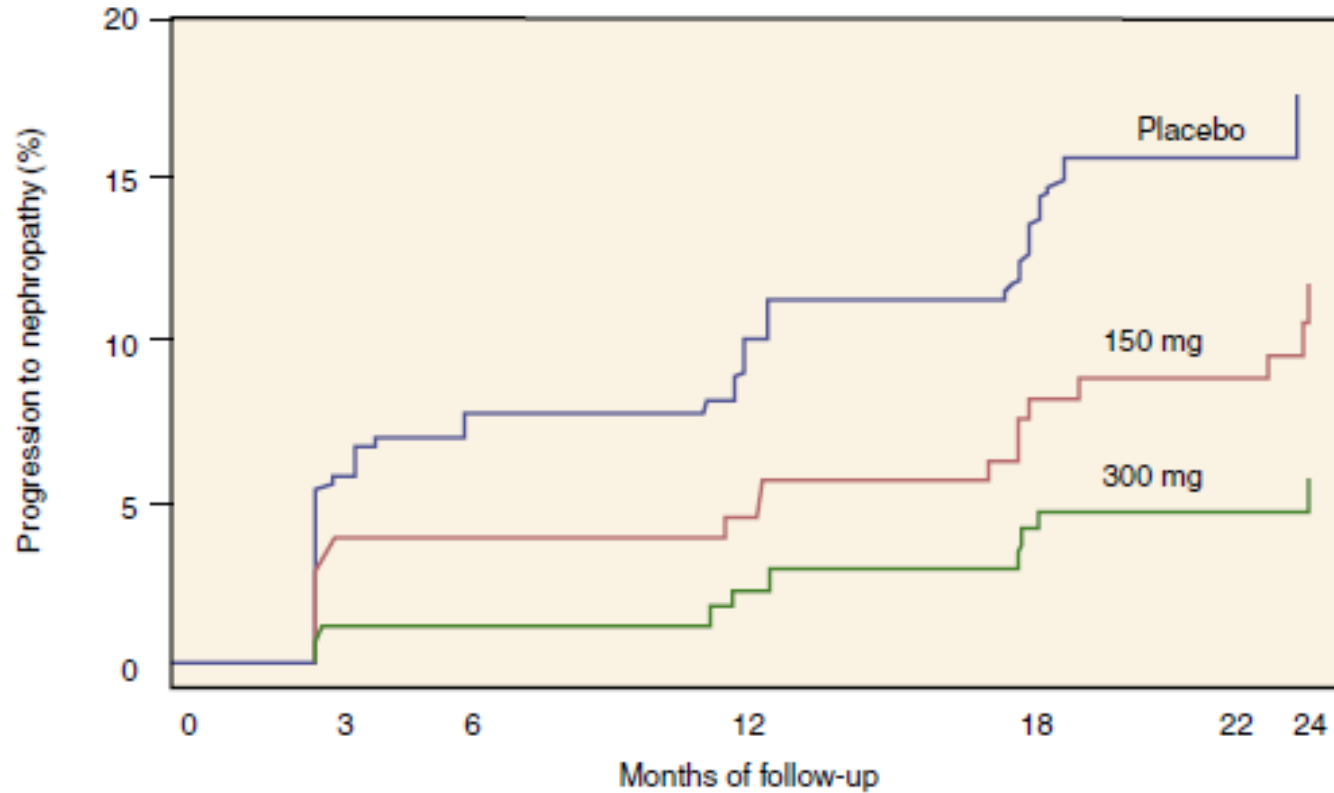
Changing diabetic nephropathy

Renin-Angiotensin System (RAS) inhibition

IRMA 2; irbesartan; type 2 diabetes with microalbuminuria

Progression to Nephropathy

N=590



Placebo	201	201	164	154	139	129	36
150 mg	195	195	167	161	148	142	45
300 mg	194	194	180	172	159	150	49

Changing diabetic nephropathy

Multifactorial treatment; The Steno2 Study

- 160 patients
- Type 2 diabetes and microalbuminuria
 - Mean age 55 yrs, BMI 30 kg/m²; HbA_{1c} 8.4 %
- Randomized to
 - conventional therapy assigned to their GPs
 - or intensive care at Steno Diabetes Center

Ambitious goals
Aggressive drug treatment
(RAAS inhibition, statin, aspirin, blood pressure)
Proactive behaviour modelling
Continued patient education/motivation

21 year data

combined ESRD/death significantly reduced
hazard ratio of 0.53

Years life gained
7,9 years

Systematic screening in diabetes

Established guidelines



Ophthalmoscopy/
fundusphotography



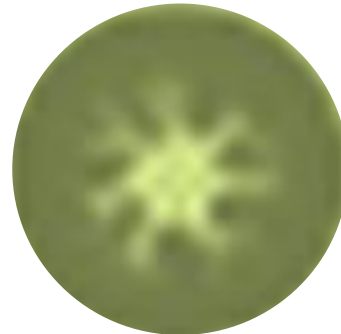
Urinary albumin excretion
s-creatinine/eGFR



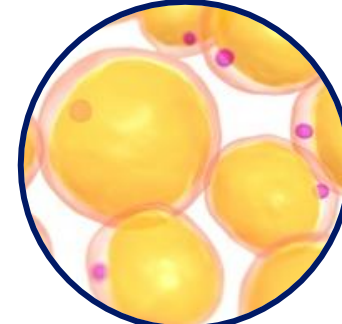
Blood pressure



Foot inspection, pulse
and vibration
sensation threshold



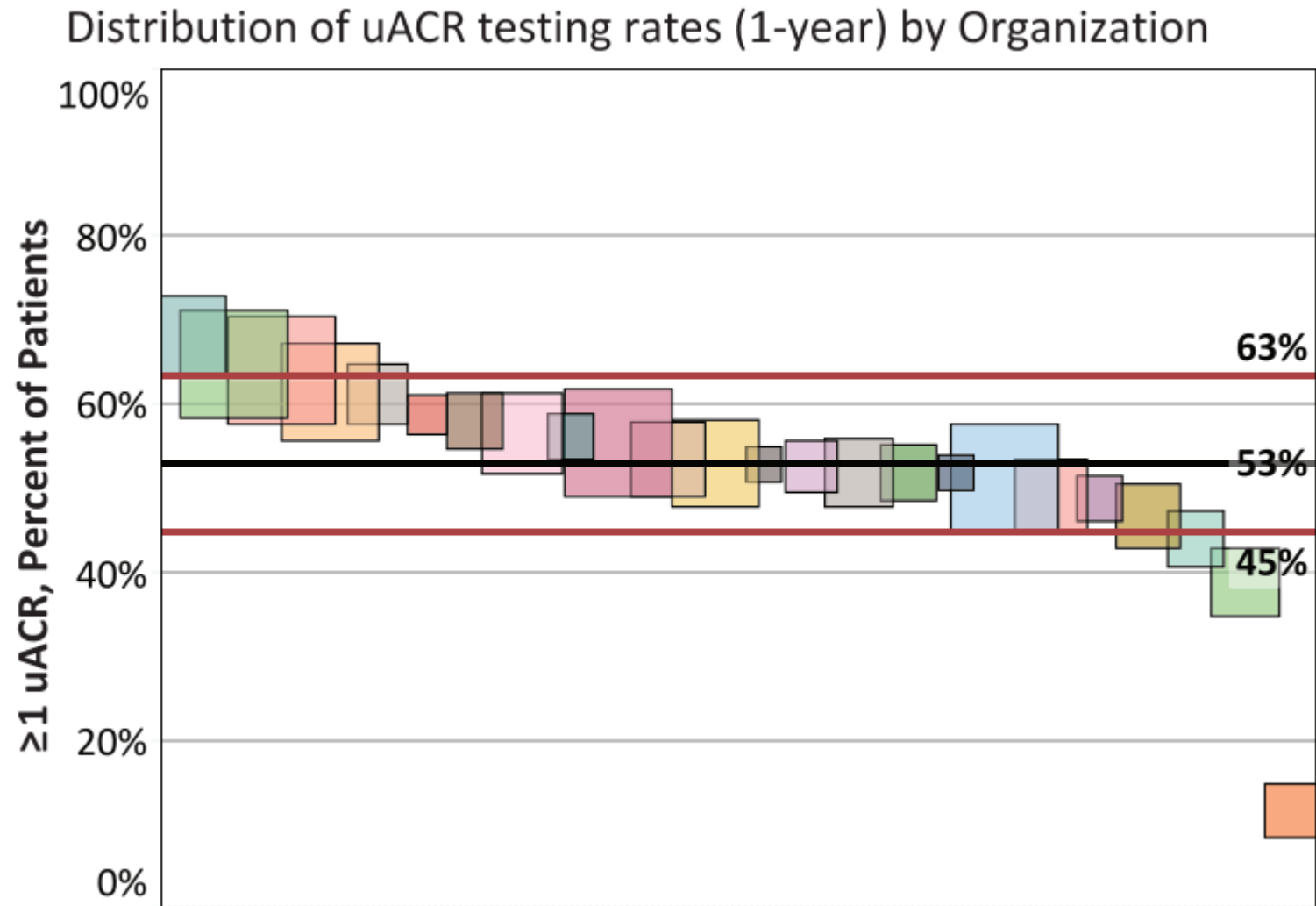
Autonomic
neuropathy



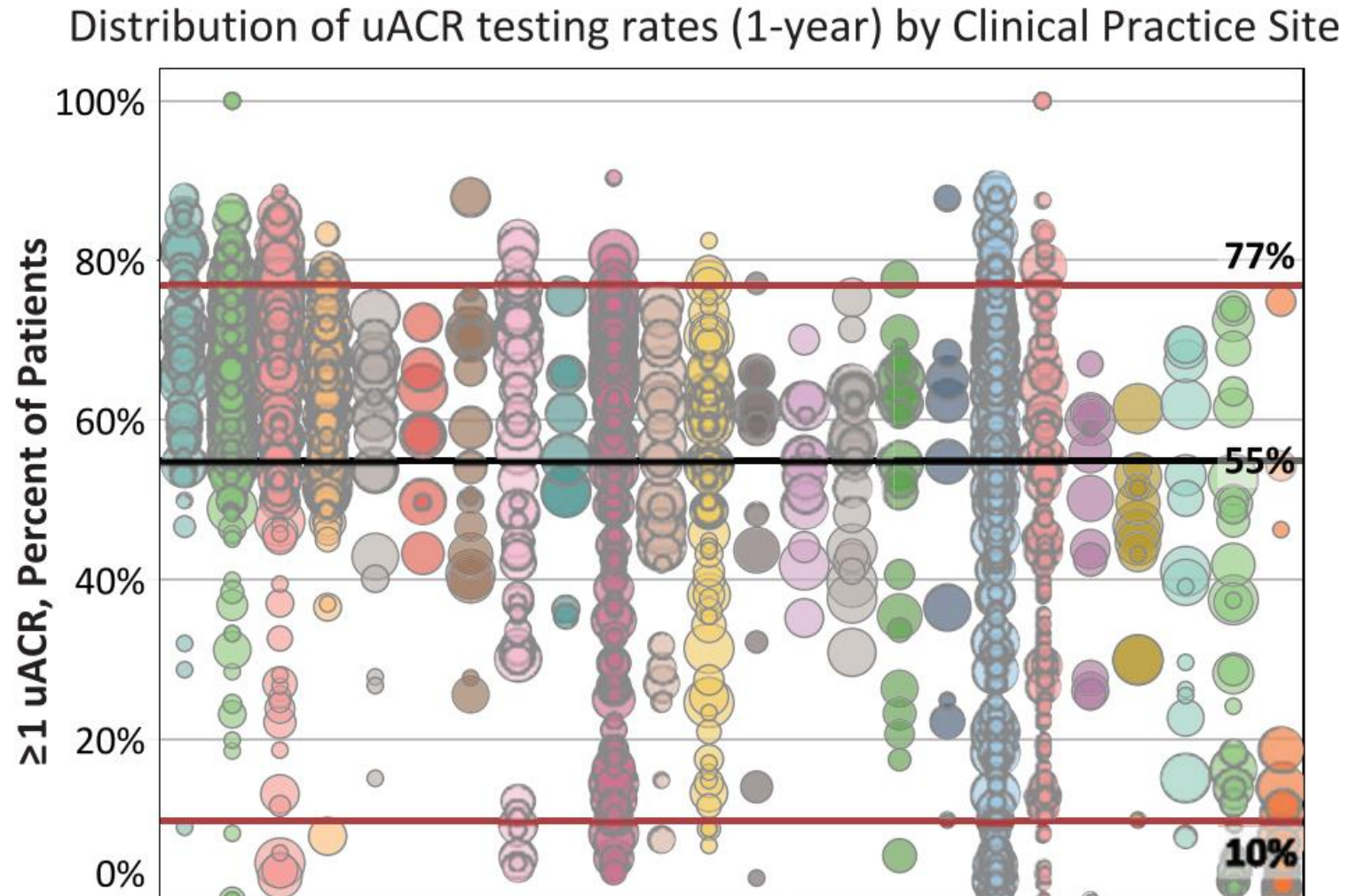
Lipids

Annual uACR testing

across 24 U.S. primary care organizations

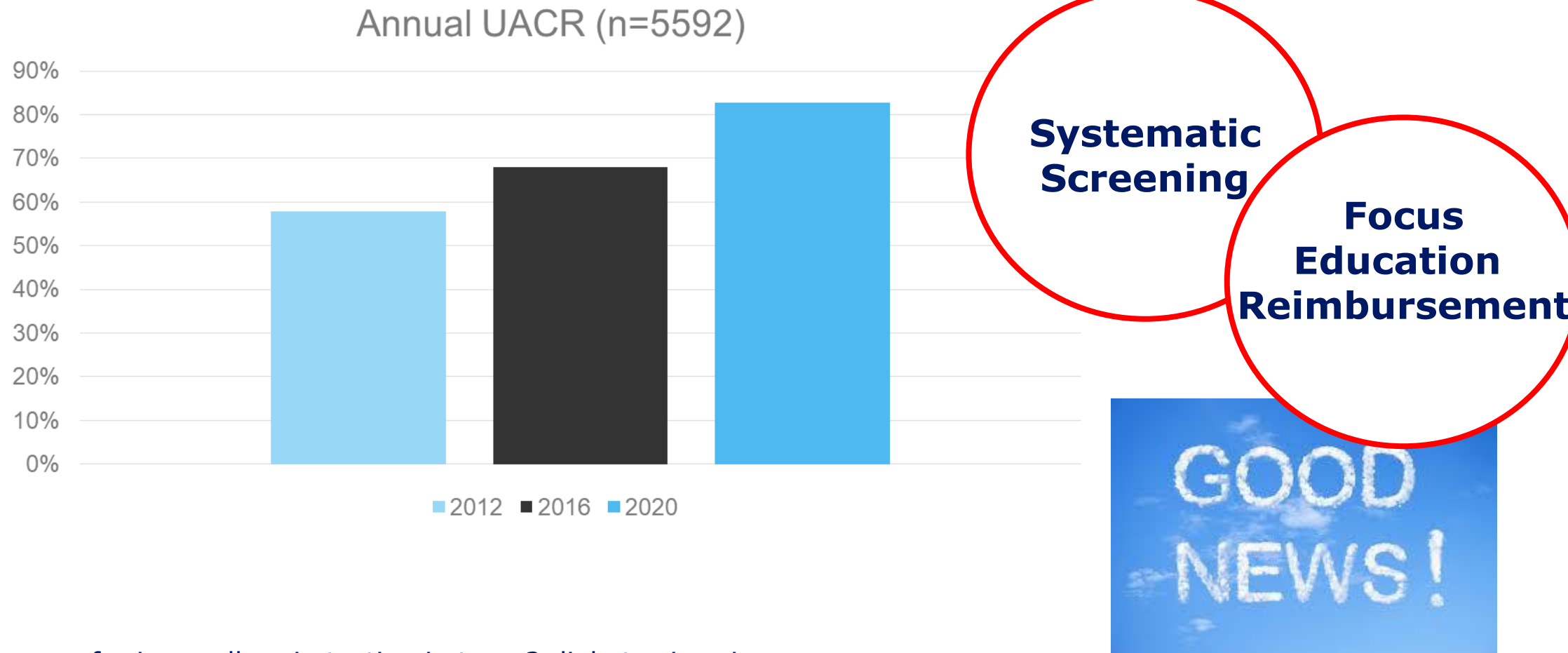


Annual uACR testing across 24 U.S. primary care organizations



Improved albuminuria measurement in primary care

cross-sectional studies in general practices in Denmark (2012-2020)



Improving frequency of urinary albumin testing in type 2 diabetes in primary care
Persson et al. Primary Care Diabetes 2021

Approaches to Glycemic Treatment in T2D

FIRST-LINE Therapy is Metformin and Comprehensive Lifestyle (including weight management and physical activity)

INDICATORS OF HIGH-RISK OR ESTABLISHED ASCVD, CKD, OR HF

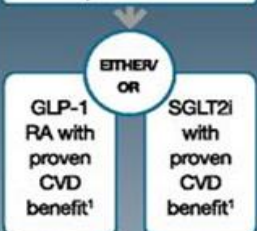
CONSIDER INDEPENDENTLY OF BASELINE A1C, INDIVIDUALIZED A1C TARGET, OR METFORMIN USE*

NO

IF A1C ABOVE INDIVIDUALIZED TARGET PROCEED AS BELOW

+ASCVD/Indicators of High Risk

- Established ASCVD
- Indicators of high ASCVD risk (age ≥ 55 years with coronary, carotid, or lower-extremity artery stenosis $>50\%$, or LVH)



If A1C above target

If further intensification is required or patient is unable to tolerate GLP-1 RA and/or SGLT2i, choose agents demonstrating CV benefit and/or safety:

- For patients on a GLP-1 RA, consider adding SGLT2i with

+HF

Particularly HFrEF (LVEF $<45\%$)

SGLT2i with proven benefit in this population^{5,6,7}

+CKD

DKD and Albuminuria⁸

NO

PREFERABLY

SGLT2i with primary evidence of reducing CKD progression

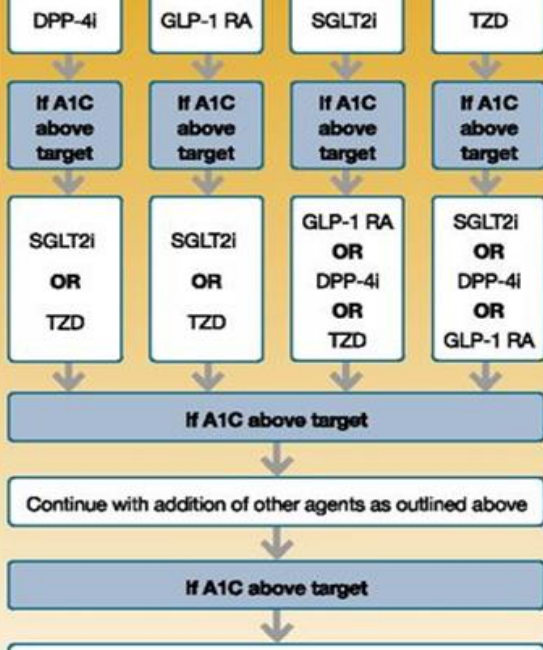
OR

SGLT2i with evidence of reducing CKD progression in CVOTs^{5,8,9}

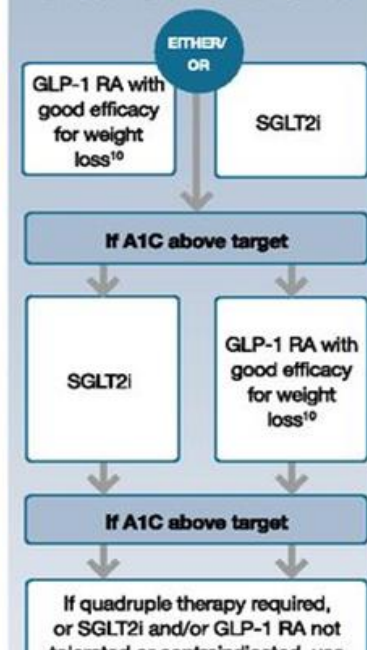
OR

GLP-1 RA with proven CVD benefit¹ if SGLT2i not tolerated or contraindicated

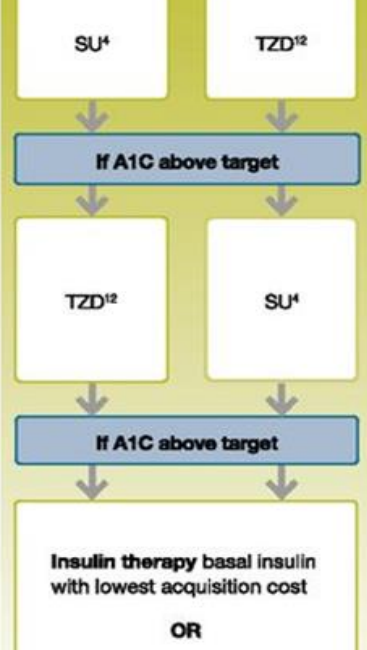
COMPELLING NEED TO MINIMIZE HYPOGLYCEMIA



COMPELLING NEED TO MINIMIZE WEIGHT GAIN OR PROMOTE WEIGHT LOSS



COST IS A MAJOR ISSUE^{11,12}



ADA Guideline: Glucose-Lowering Medication in T2D

INDICATORS OF HIGH-RISK OR ESTABLISHED ASCVD, CKD, OR HF[†]

**CONSIDER INDEPENDENTLY OF BASELINE A1C,
INDIVIDUALIZED A1C TARGET, OR METFORMIN USE***

Organ Protection

ADA Guideline: ~~Glucose-Lowering~~ Medication in T2D

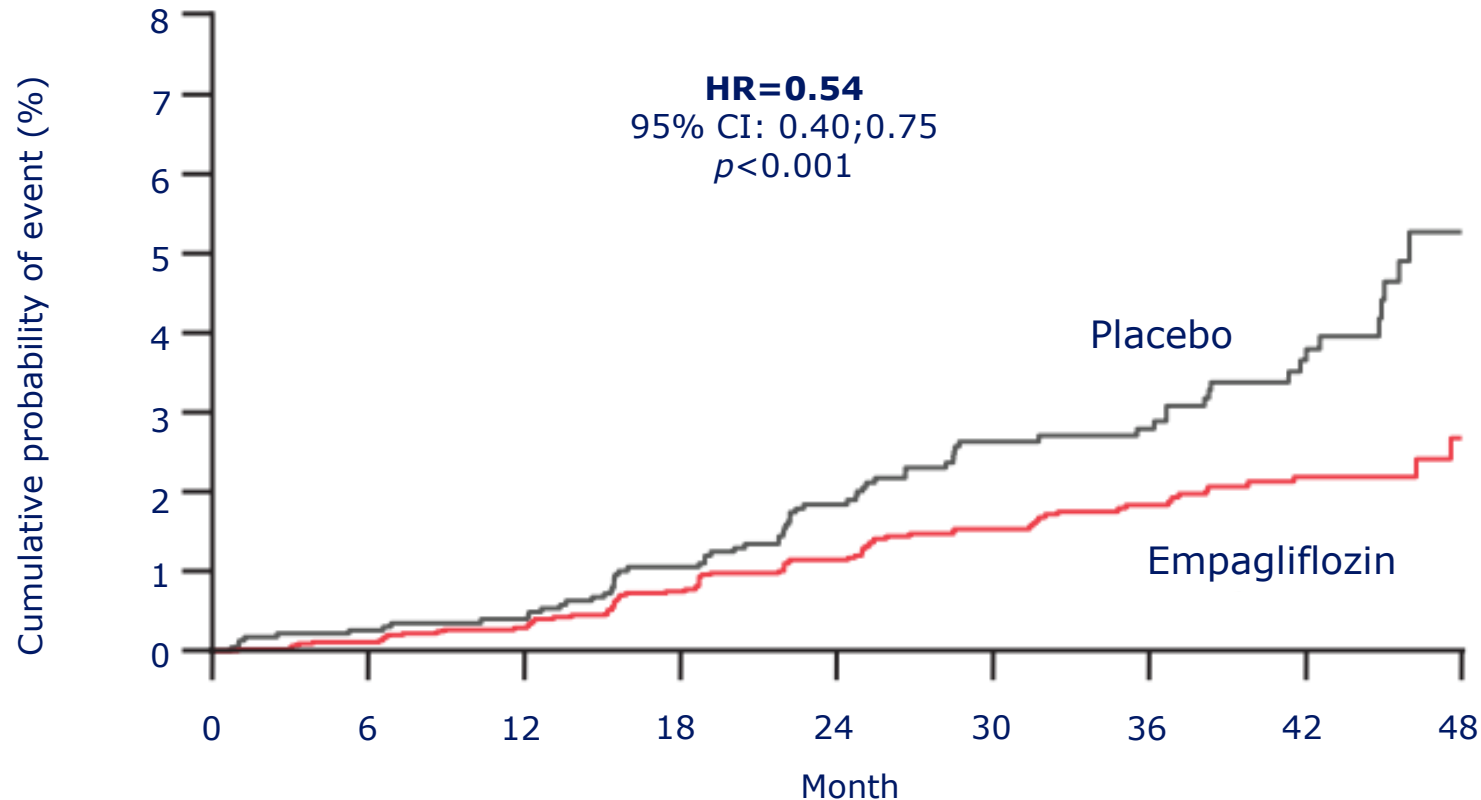
INDICATORS OF HIGH-RISK OR ESTABLISHED ASCVD, CKD, OR HF[†]

**CONSIDER INDEPENDENTLY OF BASELINE A1C,
INDIVIDUALIZED A1C TARGET, OR METFORMIN USE***

EMPA-REG: Time to first renal event

SGLT2 inhibitor; empagliflozin, T2DM + CVD/high risk

doubling of the serum creatinine, initiation of renal-replacement therapy, or renal death

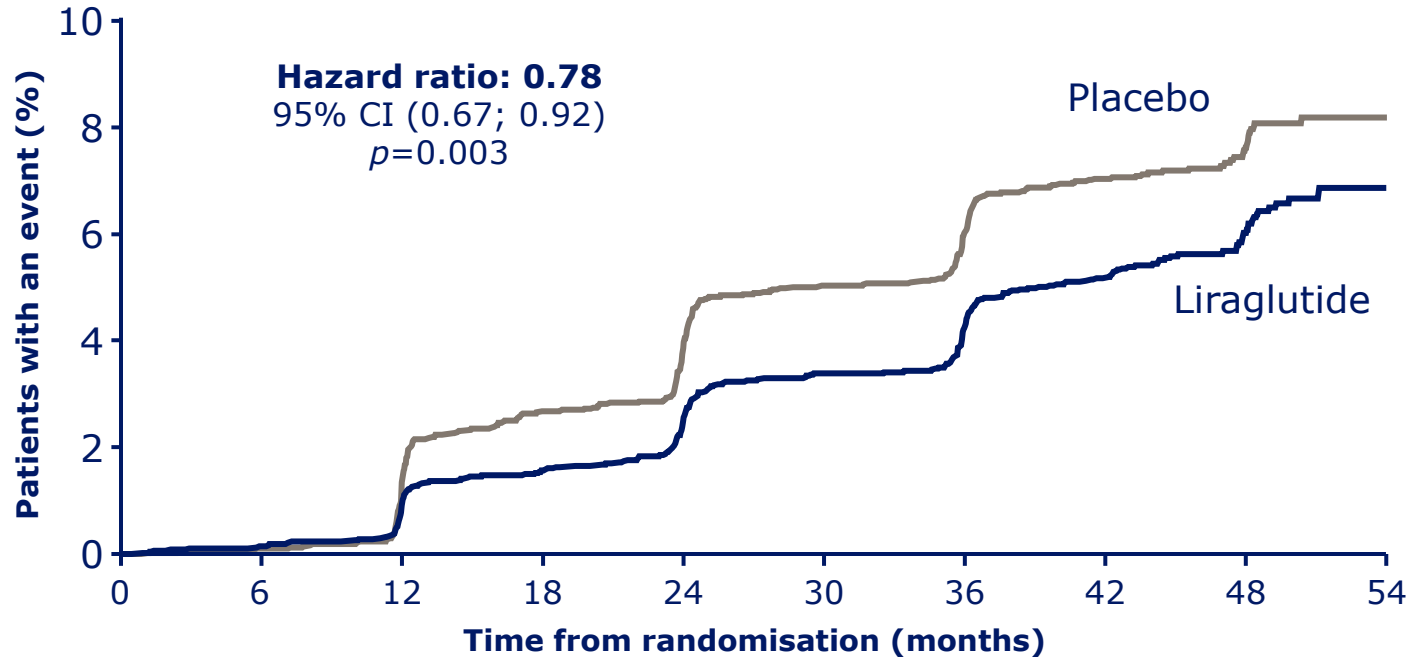


CI, confidence interval; HR, hazard ratio

LEADER: Time to first renal event

GLP1 receptor agonist; liraglutide in T2DM

†Macroalbuminuria, doubling of serum creatinine/eGFR ≤ 45 mL/min/1.73 m², ESRD, renal death



Patients at risk

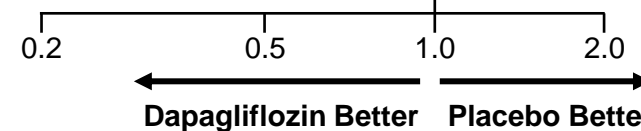
Liraglutide	4668	4635	4561	4492	4400	4304	4210	4114	1632	454
Placebo	4672	4643	4540	4428	4316	4196	4094	3990	1613	433

The cumulative incidences were estimated with the use of the Kaplan–Meier method, and the HRs with the use of the Cox proportional-hazard regression model. The data analyses are truncated at 54 months because less than 10% of the patients had an observation time beyond 54 months. CI, confidence interval; ESRD, end-stage renal disease; eGFR, estimated glomerular filtration rate; HR, hazard ratio

DAPA CKD

Primary and Secondary Outcomes by Diabetes Status

	Dapagliflozin 10 mg No. of patients with event/total no. patients	Placebo No. of patients with event/total no. patients	Hazard Ratio (95% CI)	P-value for Interaction
Primary outcome				0.24
Overall	197/2152	312/2152	0.61 (0.51, 0.72)	
With type 2 diabetes	152/1455	229/1451	0.64 (0.52, 0.79)	
Without type 2 diabetes	45/697	83/701	0.50 (0.35, 0.72)	
Renal-specific outcome				0.57
Overall	142/2152	243/2152	0.56 (0.45, 0.68)	
With type 2 diabetes	103/1455	173/1451	0.57 (0.45, 0.73)	
Without type 2 diabetes	39/697	70/701	0.51 (0.34, 0.75)	
CV death or hHF				0.78
Overall	100/2152	138/2152	0.71 (0.55, 0.92)	
With type 2 diabetes	85/1455	119/1451	0.70 (0.53, 0.92)	
Without type 2 diabetes	15/697	19/701	0.79 (0.40, 1.55)	
All-cause mortality				0.25
Overall	101/2152	146/2152	0.69 (0.53, 0.88)	
With type 2 diabetes	84/1455	113/1451	0.74 (0.56, 0.98)	
Without type 2 diabetes	17/697	33/701	0.52 (0.29, 0.93)	



Diabetic Kidney Disease

Kussman et al., JAMA, 1976

- Diabetic nephropathy is irreversible in humans
- No cases of recovery or cure have been reported in the literature
- Once the clinical signs of nephropathy have become manifest, the natural course is inexorable progressive to death
- The rate of progression is accelerated in the later stages

Diabetic Kidney Disease

Yearly eGFR decline – change in slope!

- **Untreated, hypertensive diabetic kidney disease:** >12 mL/min/1.73 m²/year
- **Antihypertensive treatment and RAS-inhibition:** 3-5 mL/min/1.73 m²/year

- **CREDESCENCE (T2DM + CKD)**
Placebo group 4.6 mL/min/1.73 m²/year

- **EMPEROR-Reduced (Heart Failure, +/- T2DM)**
Placebo group 2.3 mL/min/1.73 m²/year

- **DAPA CKD (CKD, +/- T2DM)**
Placebo group 3.6 mL/min/1.73 m²/year



We have come
a long way

Take Home Messages

- Changes happen early
 - In primary care: use your tools for systematic approach
 - Discuss in your local setting who is responsible
- Focus on guideline recommended yearly uACR measurement
 - A reliable marker
 - Can predict high risk individuals – in need of organ protection/ “modern diabetes treatment”
 - Can guide treatment effect
- We might have to consider similar approach in non-diabetic CKD

Le Penseur - the Thinker

a bronze sculpture by Auguste Rodin (1904)
exhibited at Musée Rodin in Paris

“a pose of deep thought and contemplation”

**Rethinking the role
of nephrologists
in prevention
of CKD**

