CMHC
Cardiometabolic Health Congress

WEBCAST

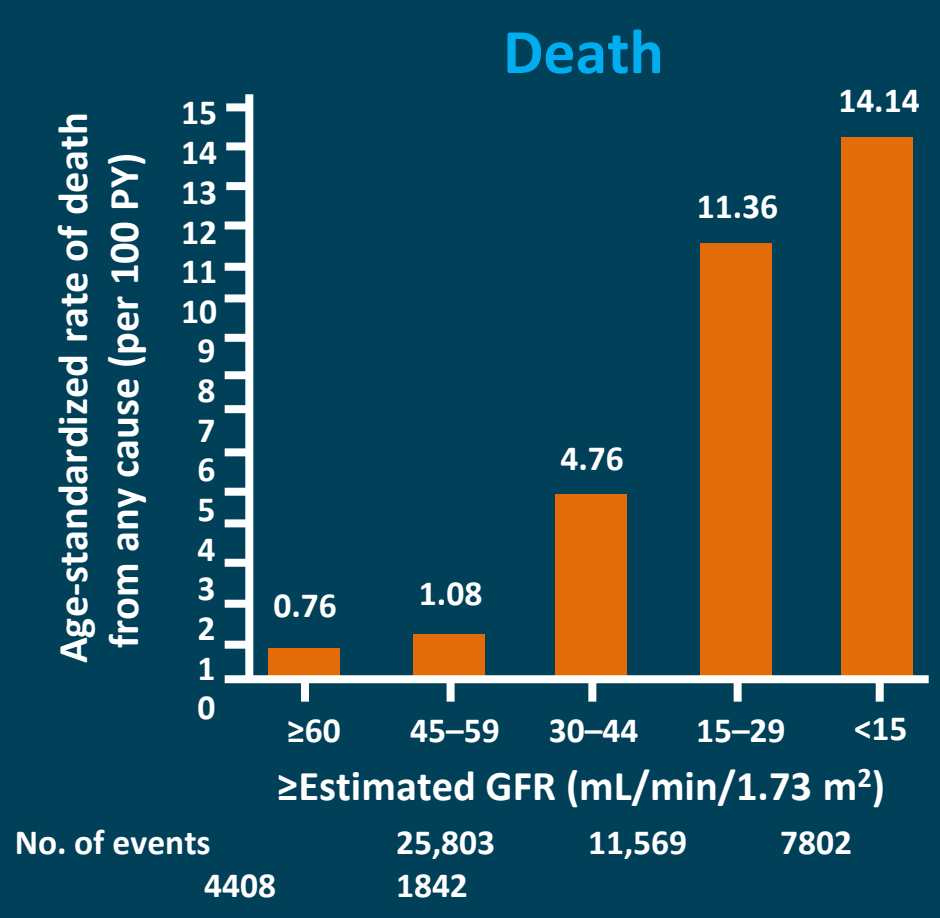
Optimizing the Recognition and Treatment of Chronic Kidney Disease in Patients with Type 2 Diabetes:

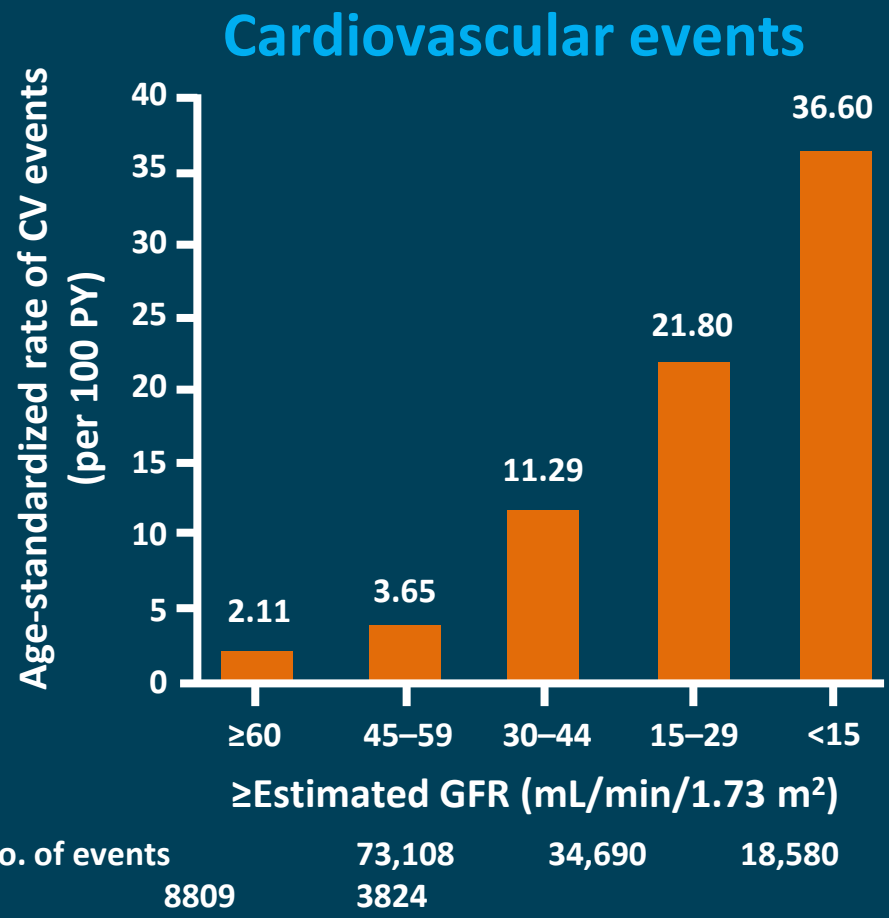
What Primary Care Clinicians Need to Know

Module 1: The Detection of CKD in Patients with T2DM

George L. Bakris, MD
Professor of Medicine
University of Chicago Medicine

Lower eGFR Is Associated With Cardiovascular Events and Death





Large integrated health system including 1,120,295 patients who had serum creatinine measured between 1996 and 2000 and median follow-up of 2.84 years

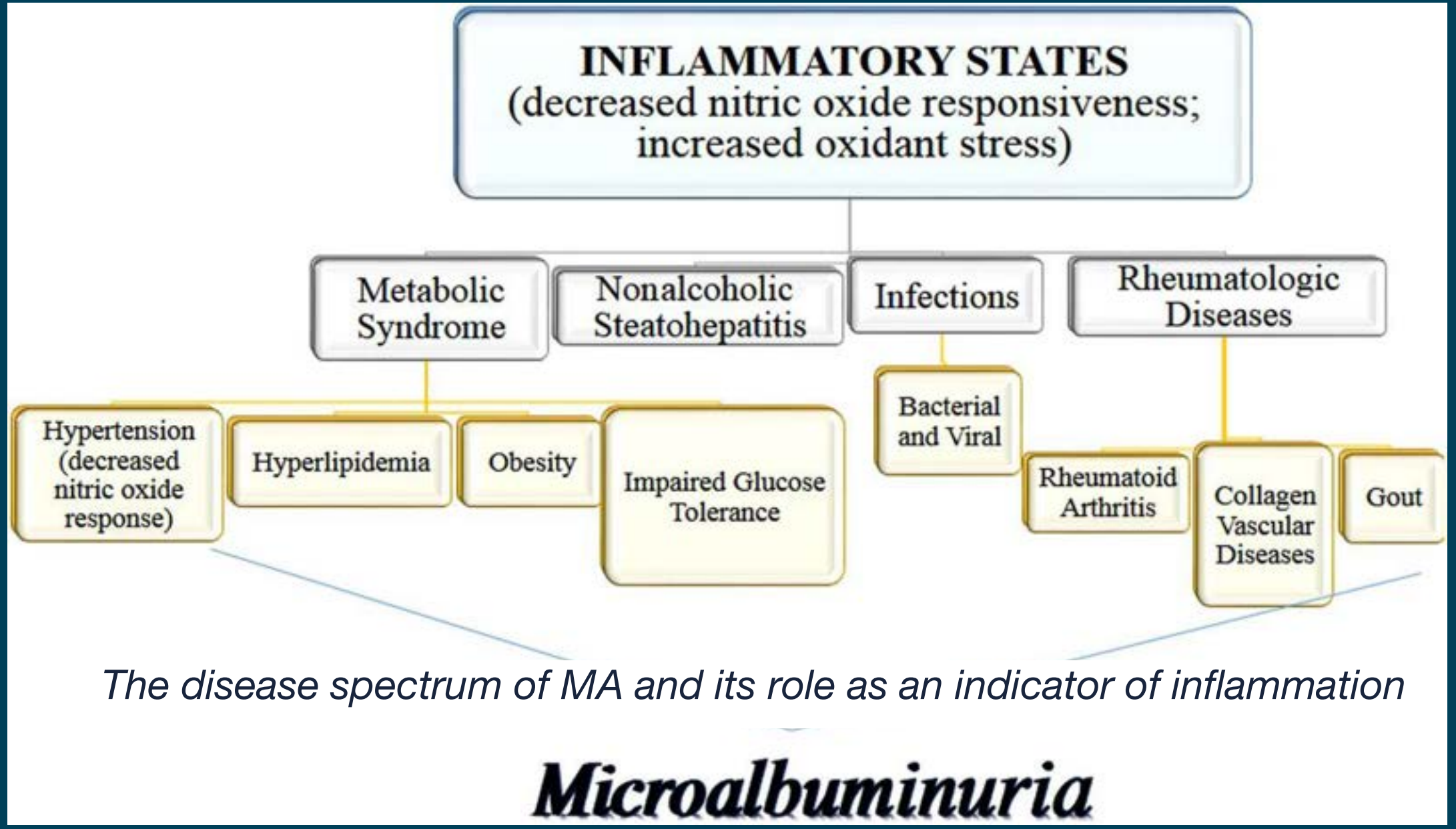
GFR = glomerular filtration rate; eGFR = estimated GFR; PY = person/patient years; CV = cardiovascular.

Go AS, et al. *N Engl J Med*. 2004;351:1296-1305.

Composite Ranking for Relative Risks by Glomerular Filtration Rate (GFR) and Albuminuria (Kidney Disease: Improving Global Outcomes (KDIGO) 2020

CKD is classified based on: • Cause (C) • GFR (G) • Albuminuria (A)				Albuminuria categories Description and range		
				A1	A2	A3
				Normal to mildly increased	Moderately increased	Severely increased
				< 30 mg/g < 3 mg/mmol	30–299 mg/g 3–29 mg/mmol	≥ 300 mg/g ≥ 30 mg/mmol
GFR categories (ml/min/1.73 m²) Description and range	G1	Normal or high	≥ 90	Screen 1	Treat 1	Treat and refer 3
	G2	Mildly decreased	60–89	Screen 1	Treat 1	Treat and refer 3
	G3a	Mildly to moderately decreased	45–59	Treat 1	Treat 2	Treat and refer 3
	G3b	Moderately to severely decreased	30–44	Treat 2	Treat and refer 3	Treat and refer 3
	G4	Severely decreased	15–29	Treat and refer* 3	Treat and refer* 3	Treat and refer 4+
	G5	Kidney failure	< 15	Treat and refer 4+	Treat and refer 4+	Treat and refer 4+

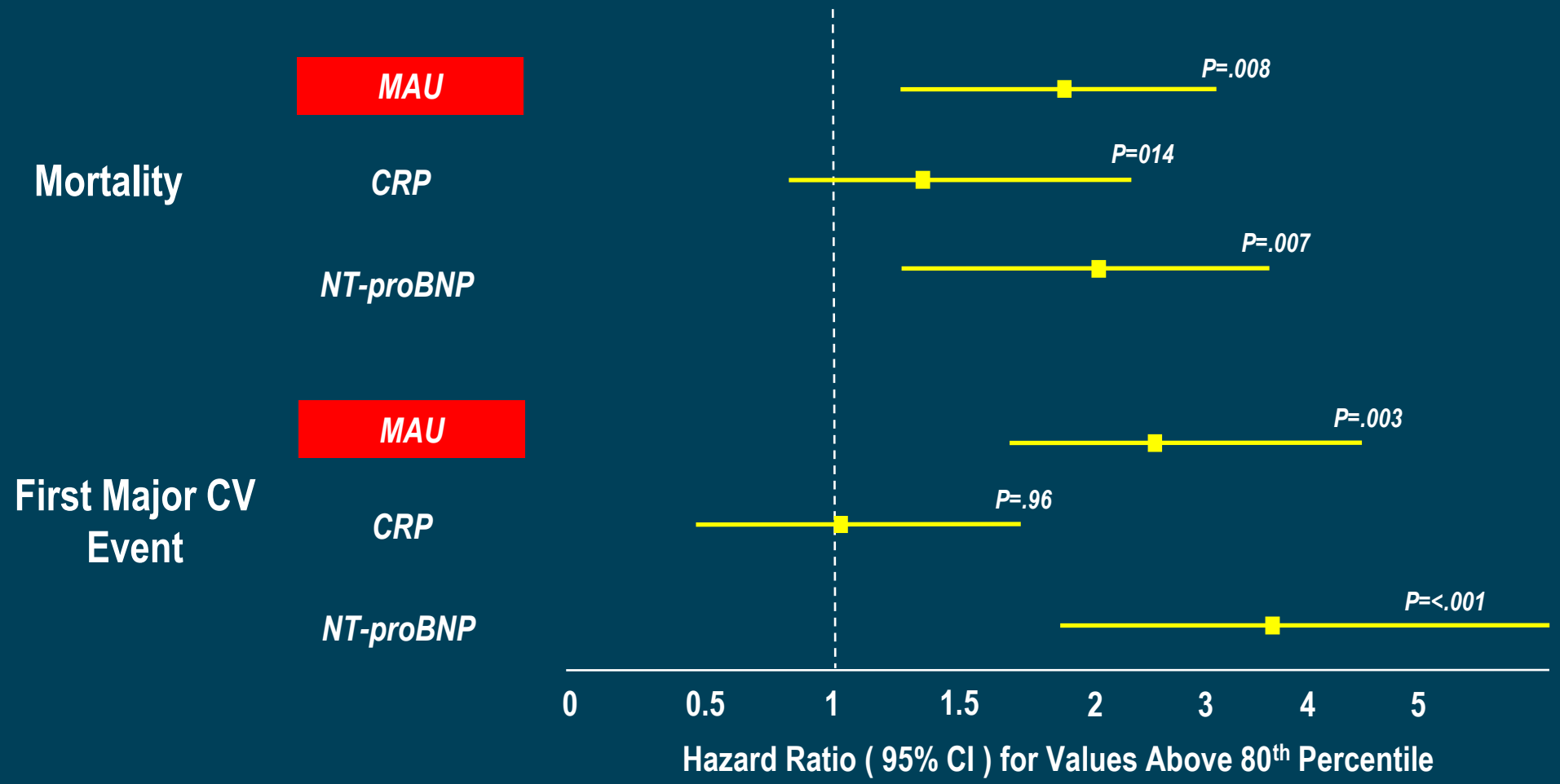
Low risk (if no other markers of kidney disease, no CKD)
Moderately increased risk
High risk
Very high risk



The disease spectrum of MA and its role as an indicator of inflammation

Bakris GL and Molitch M *Diabetes Care* 2014;37:867–875

Use of MAU, CRP, and BNP as Predictors of Mortality and CV Events



Adjusted for age, sex, smoking, DM, HTN, Afib, LVEF<50%, LVH, total cholesterol, serum creatinine. Mortality analysis based on 91 deaths, and CV event data based on 63 events due to missing covariates. The 80th percentile corresponds to values more than 5.85 pg/mL for NT-proBNP, 5.76 mg/L for CRP, and 18.4 mg/g for MAU.

Kistorp K, et al. *JAMA*. 2005;293:1609-1616.

Albuminuria as a Risk Marker for Heart Failure

Albuminuria as a Risk Marker for HF

- Progressive continuous relationship with HF
- Prediction power outperforms creatinine based eGFR in HF
- Regression of albuminuria associated with reduced risk of HF
- Marker of early kidney damage
- Enhances HF risk prediction models
- Cost-effective metric to denote CV risk profile

Albuminuria in Progression of HF

- **SOLVD Trial**
  - ↑Albuminuria→↑1.8 x risk of HHF
- **CHARM Trial**
  - ↑Albuminuria→↑30-70% risk of HHF
- **GISSI-HF and CHARM Trials**
  - Strong independent predictor of adverse prognosis in HF irrespective of HTN or T2DM

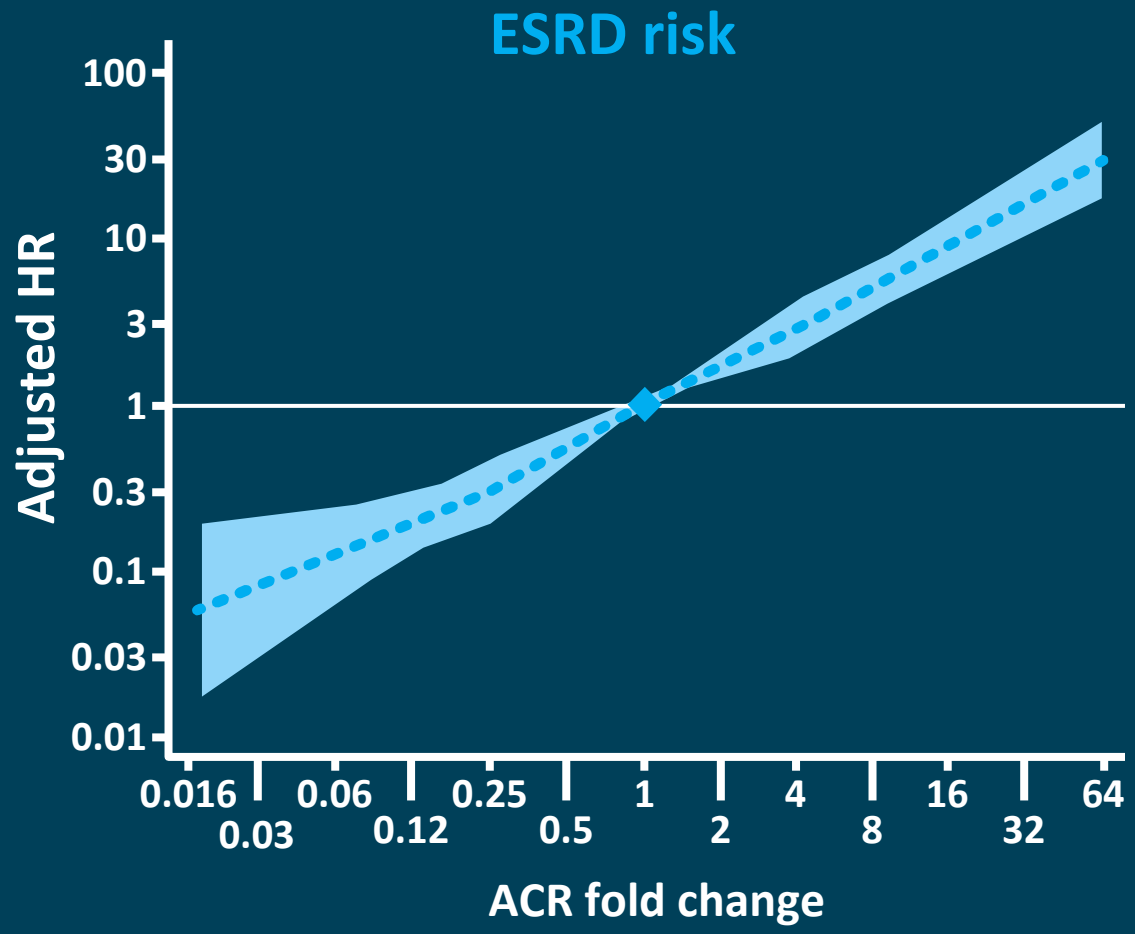
Albuminuria in HF

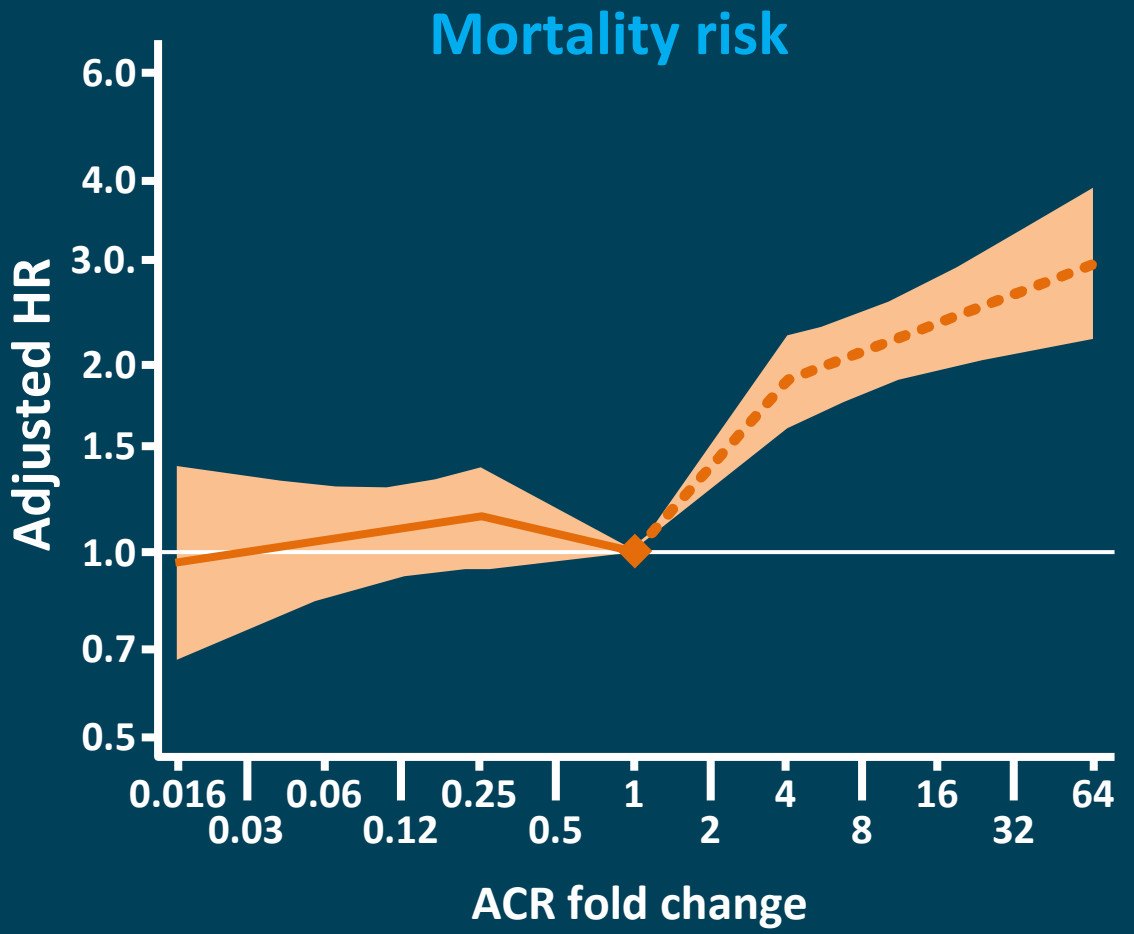
Albuminuria Predicts Risk of Incident HF

- **RENAAL Trial**
  - ↑Albuminuria→↑2.7 x risk of incident HF
- **FHS Study**
  - ↑Albuminuria→↑1.7 x risk of incident HF
- **MESA Study**
  - ↑Albuminuria→↑2.7 x risk of incident HF
- **ARIC Study**
  - ↑Albuminuria→↑2.5 x risk of incident HF

Khan MS, et al. *J Am Coll Cardiol*. 2023;81(3):270-282.

Distribution of 2-Year Albumin-To-Creatinine Ratio (ACR)-Fold Changes





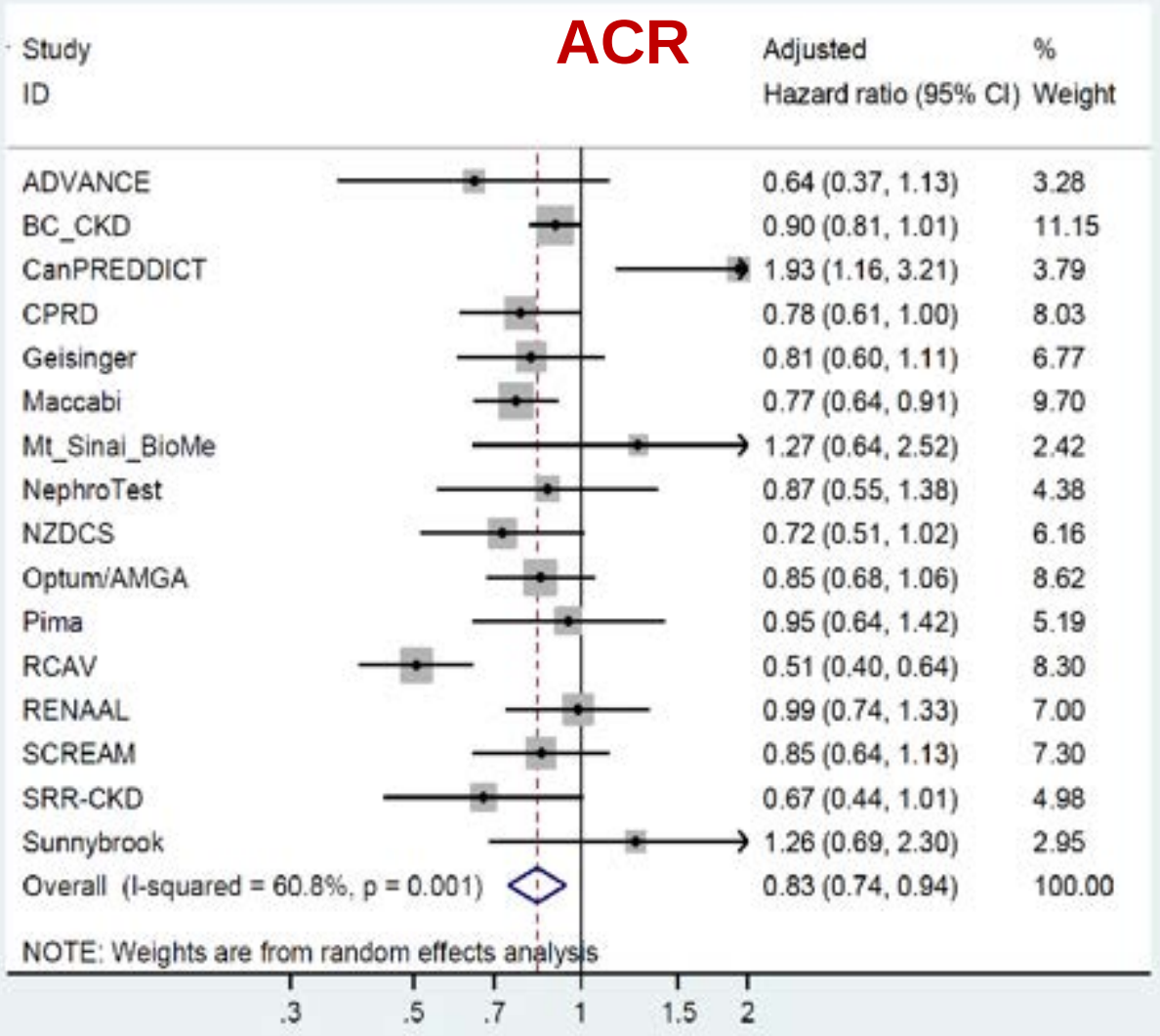
ACR (1-fold change), N = 19,897—shaded area represents 95% confidence intervals

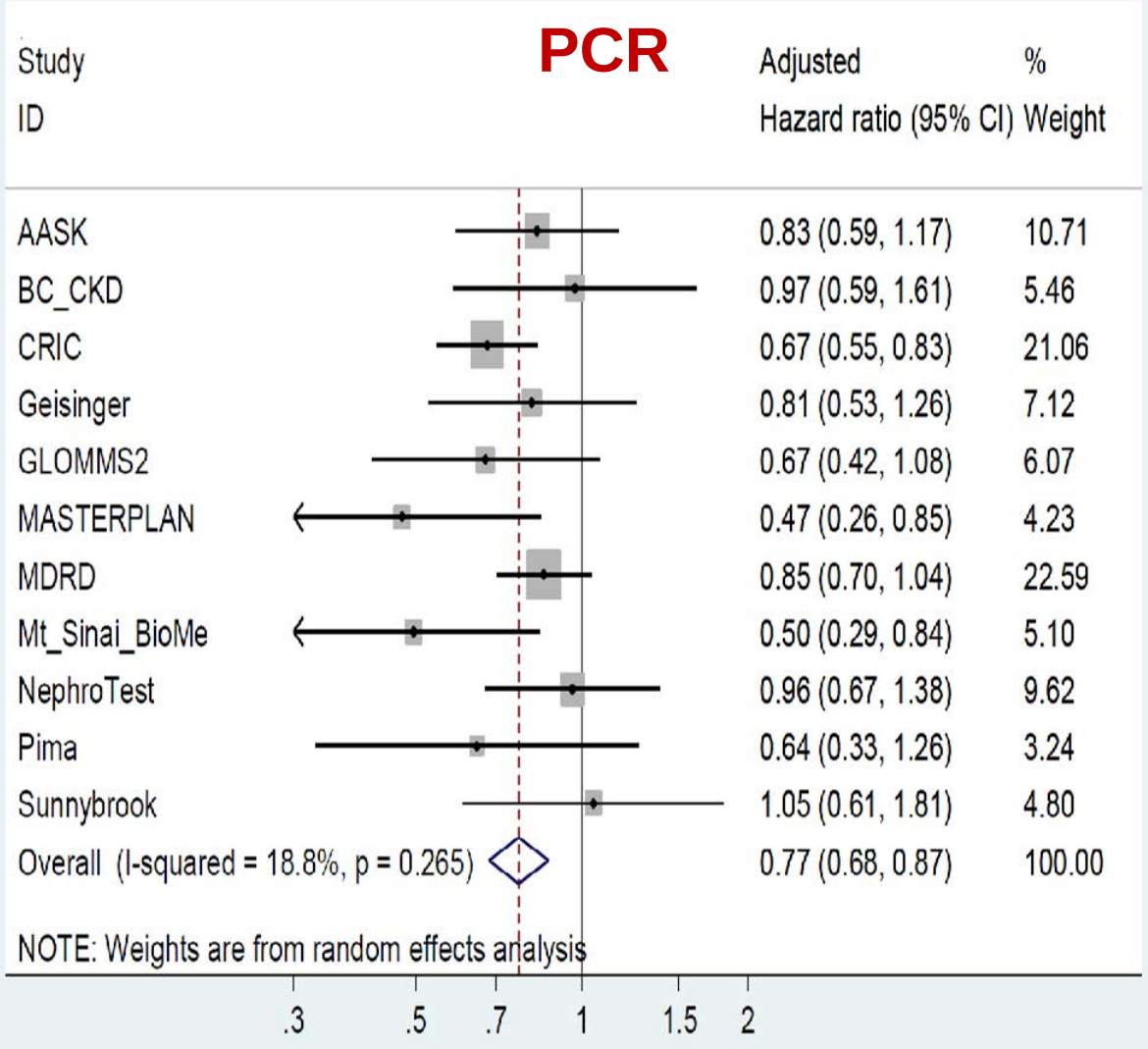
ESRD = end-stage renal disease; HR = hazard ratio.

Carrero JJ, et.al. *Kidney Int.* 2017;91:244-251.

Forest Plot of Individual Studies and Meta-analyzed Estimate of Adjusted Hazard Ratio of ESKD at 2-year ACR

>30% Decrease

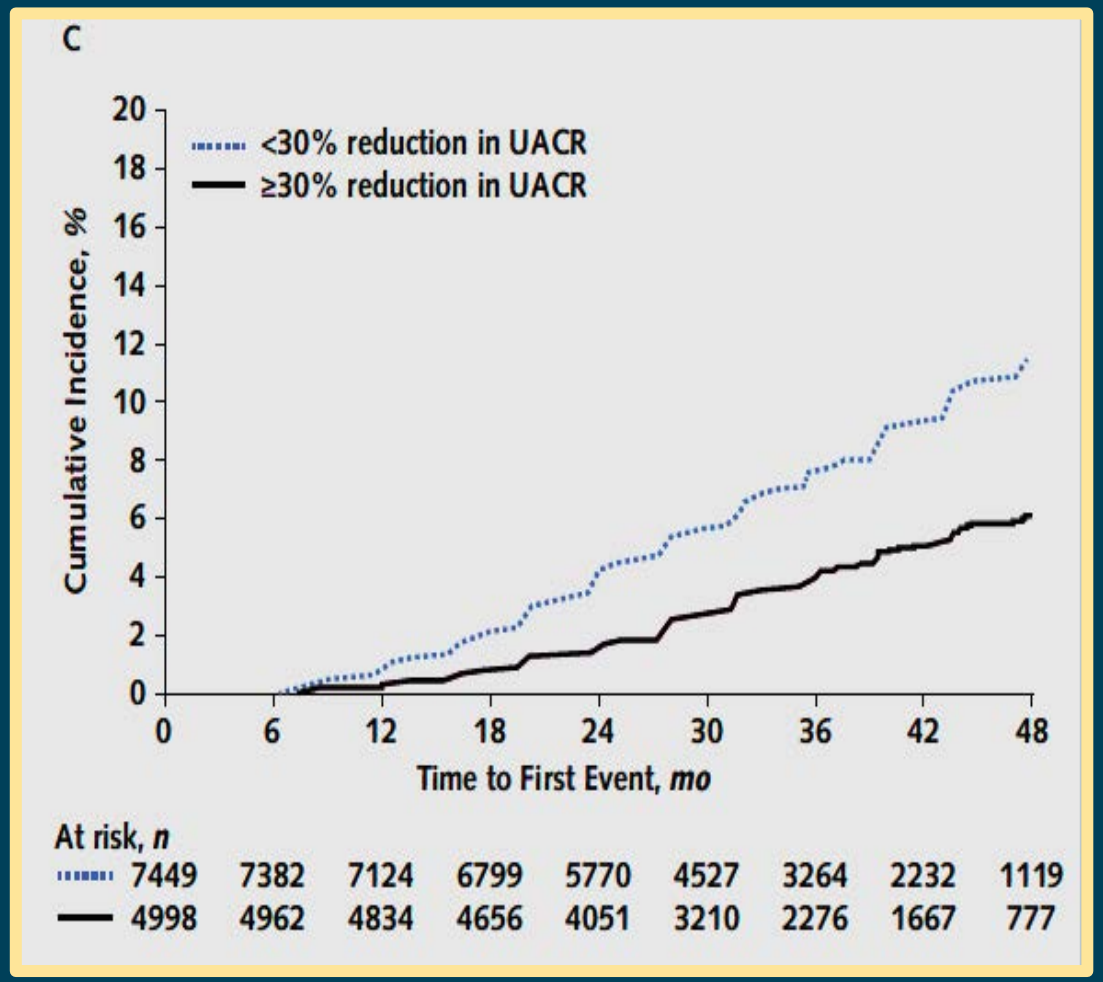




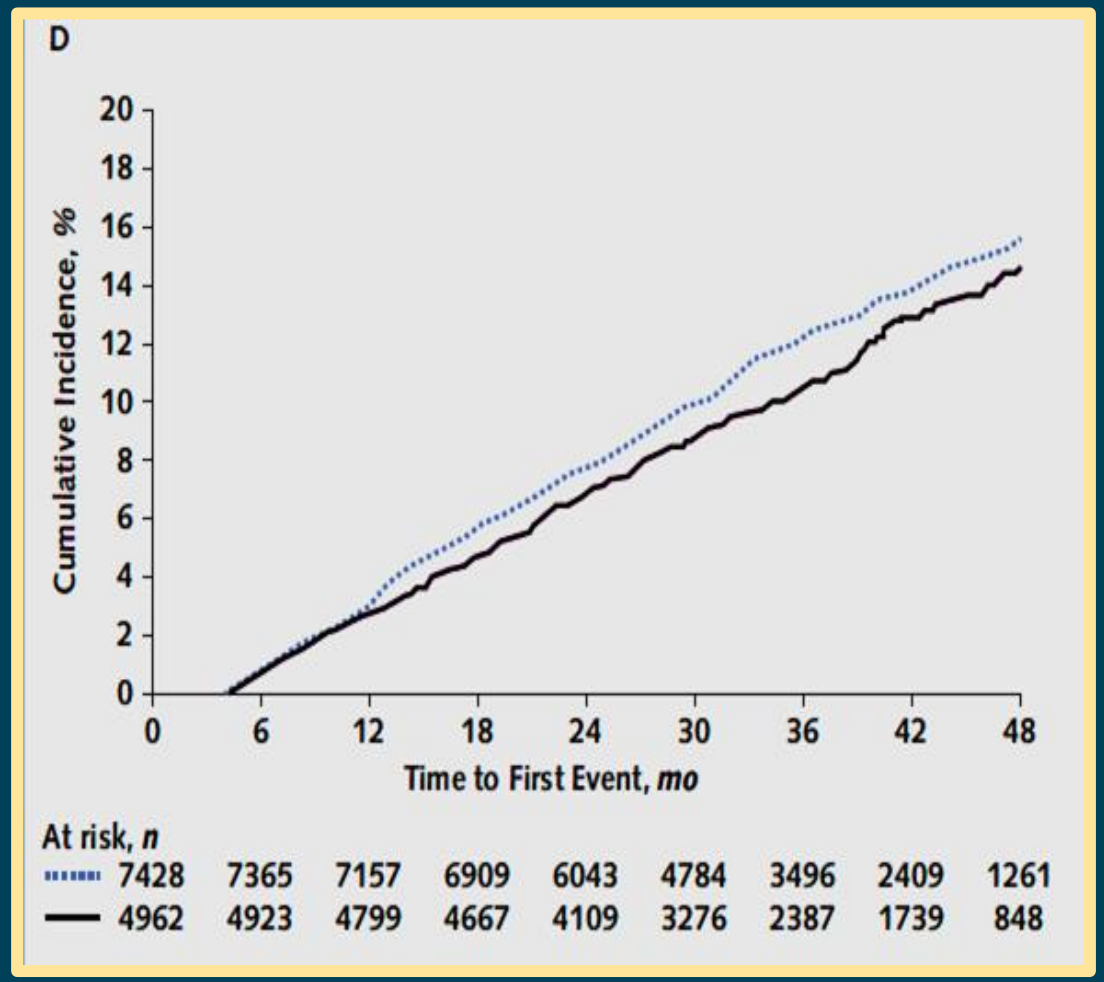
Coresh J et.al. *Lancet Diabetes Endocrinol* 2019;7:115-127

Relative Change in UACR From Baseline to Month 4 on CKD and CV Outcomes

Cumulative incidences for kidney composite outcome



Cumulative incidences for cardiovascular composite outcome



Agarwal R, Tu W, Farjat AE, et.al…and Bakris GL. *Ann Intern Med*. 2023;176(12):1606-1616.

ADA – Standards of Care in Diabetes UPDATE
Section 11: Chronic Kidney Disease and Risk Management

2023

- **11.5c** In people with type 2 diabetes and diabetic kidney disease, consider use of sodium–glucose cotransporter 2 inhibitors (if estimated glomerular filtration rate is ≥20 mL/min/1.73 m2), a glucagon-like peptide 1 agonist, **or a nonsteroidal mineralocorticoid receptor antagonist (if estimated glomerular filtration rate is ≥25 mL/min/1.73 m2) additionally for cardiovascular risk reduction. A**

- **11.5d** In people with chronic kidney disease and albuminuria who are at increased risk for cardiovascular events or chronic kidney disease progression, a nonsteroidal mineralocorticoid receptor antagonist shown to be effective in clinical trials is recommended to reduce chronic kidney disease progression and cardiovascular events. **A**

- ***11.6*** *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*

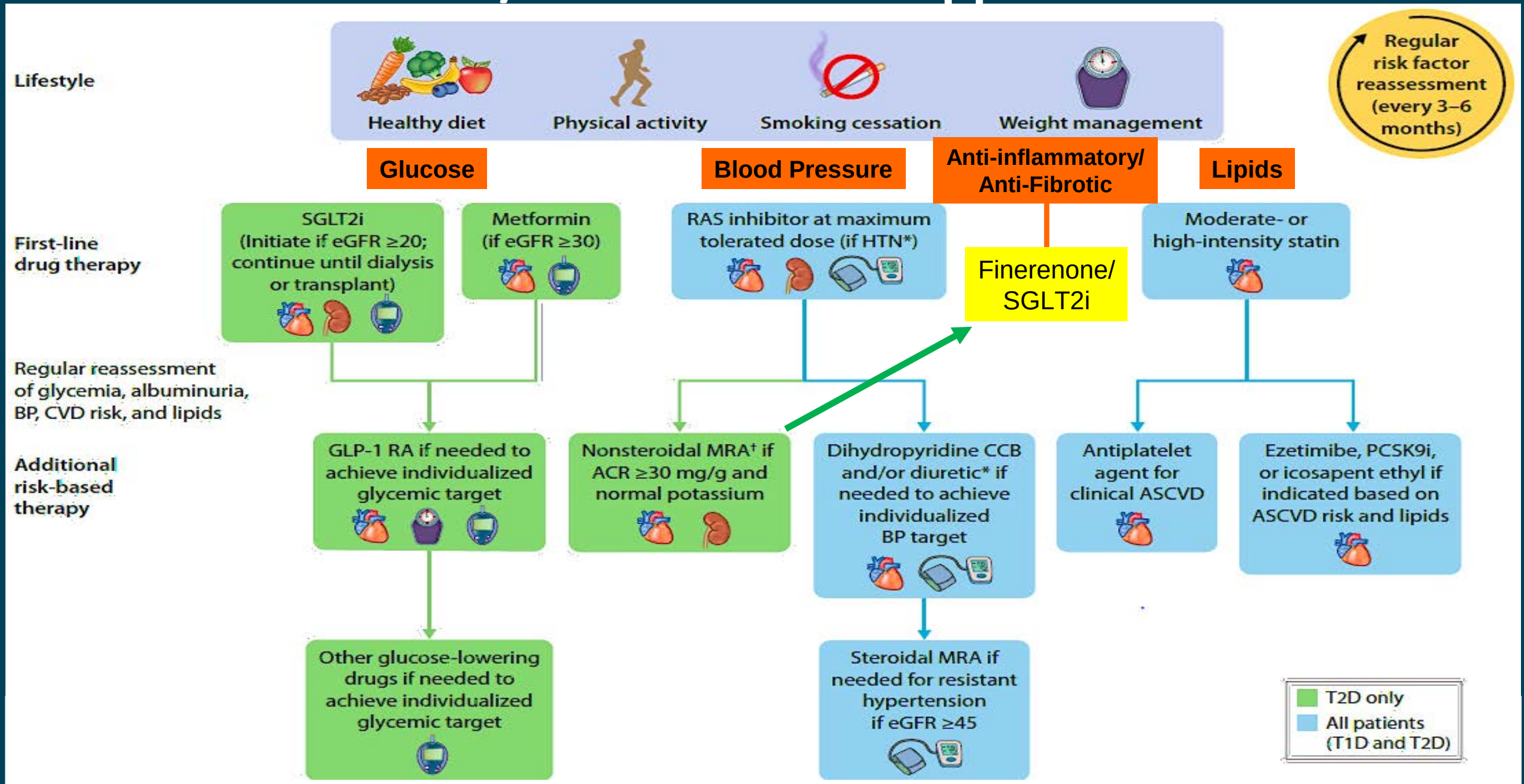
2024

- **11.5c** For cardiovascular risk reduction in people with type 2 diabetes and CKD, consider use of an SGLT2 inhibitor (if eGFR is ≥20 mL/min/ 1.73 m2), a glucagon-like peptide 1 agonist, **or a nonsteroidal mineralocorticoid receptor antagonist (if eGFR is ≥25 mL/min/1.73 m2). A**

- **11.5d** As people with CKD and albuminuria are at increased risk for cardiovascular events and CKD progression, a nonsteroidal mineralocorticoid receptor antagonist that has been shown to be effective in clinical trials is recommended to reduce cardiovascular events and CKD progression (if eGFR is ≥25 mL/min/1.73 m2). Potassium levels should be monitored. **A**

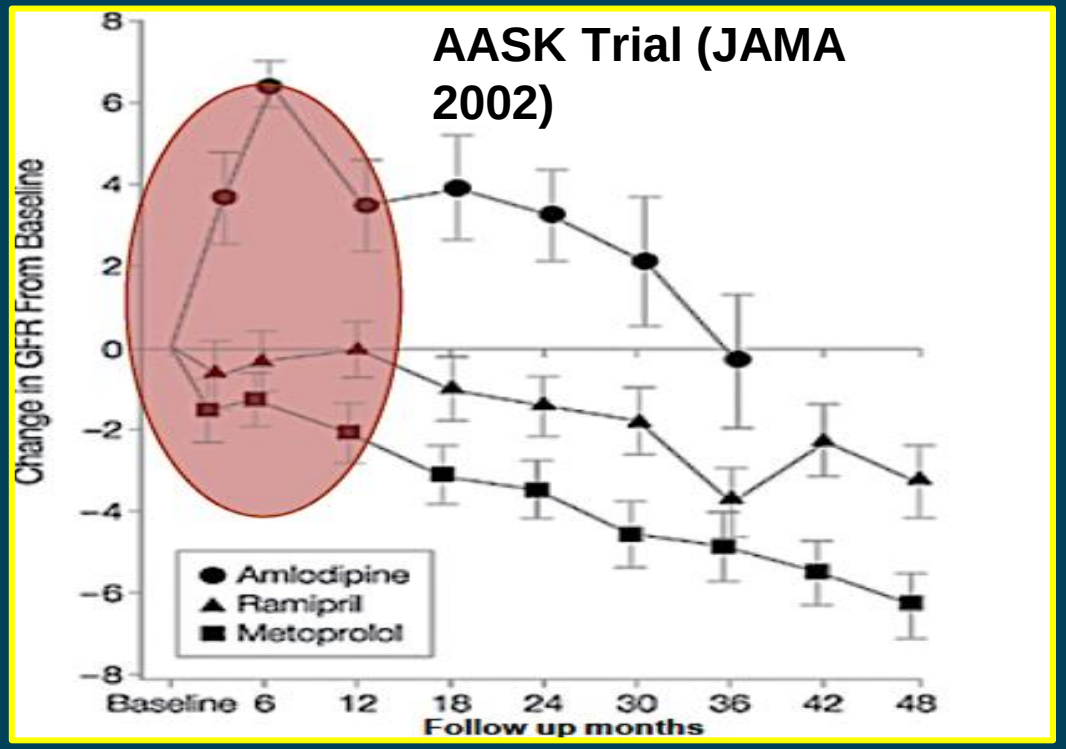
- **11.6** In people with CKD who have ≥300 mg/g urinary albumin, a reduction of 30% or greater in mg/g urinary albumin is recommended to slow CKD progression. **C**

ADA/KDIGO: Holistic Approach

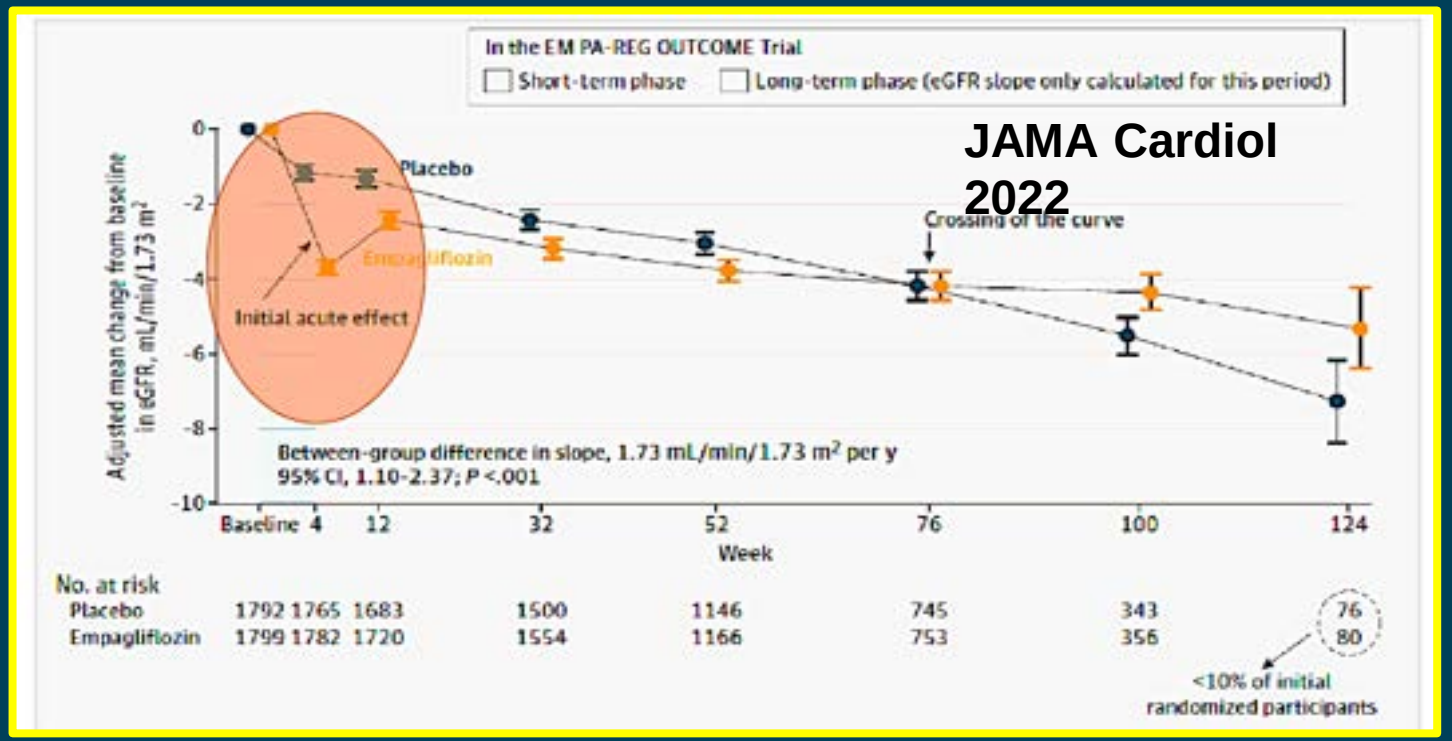


de Boer IH, Connie Rhee et.al..... and Bakris GL. *Diabetes Care* 2022;45:3075-3090.

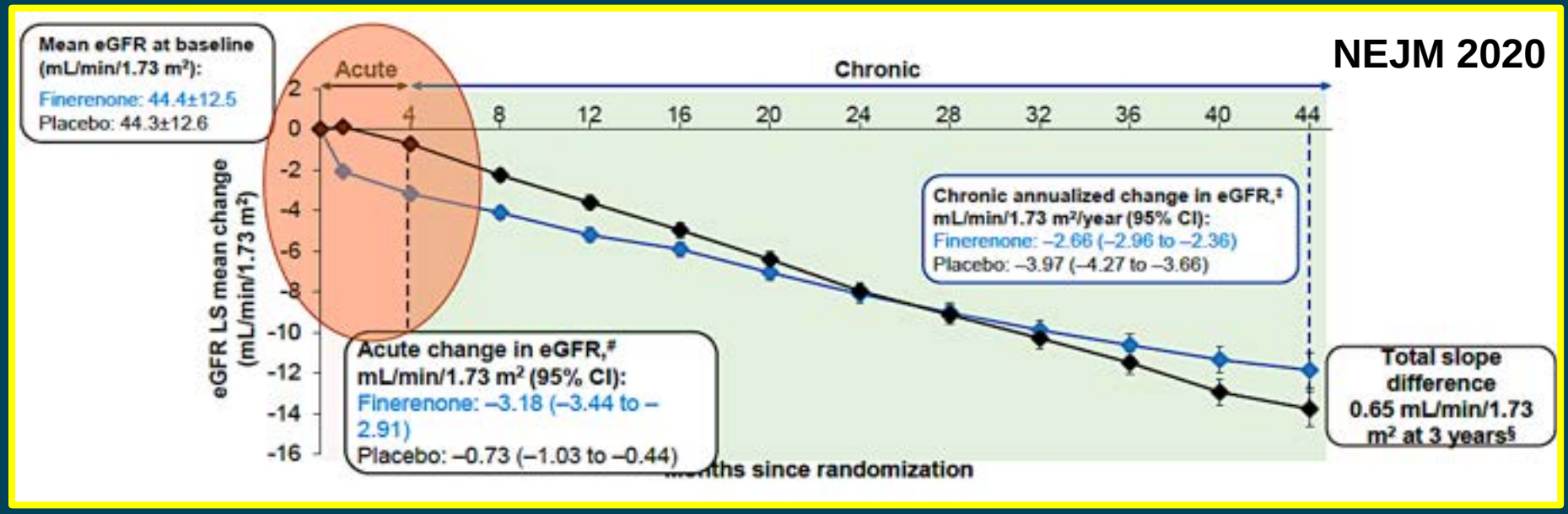
AASK Trial (JAMA 2002)



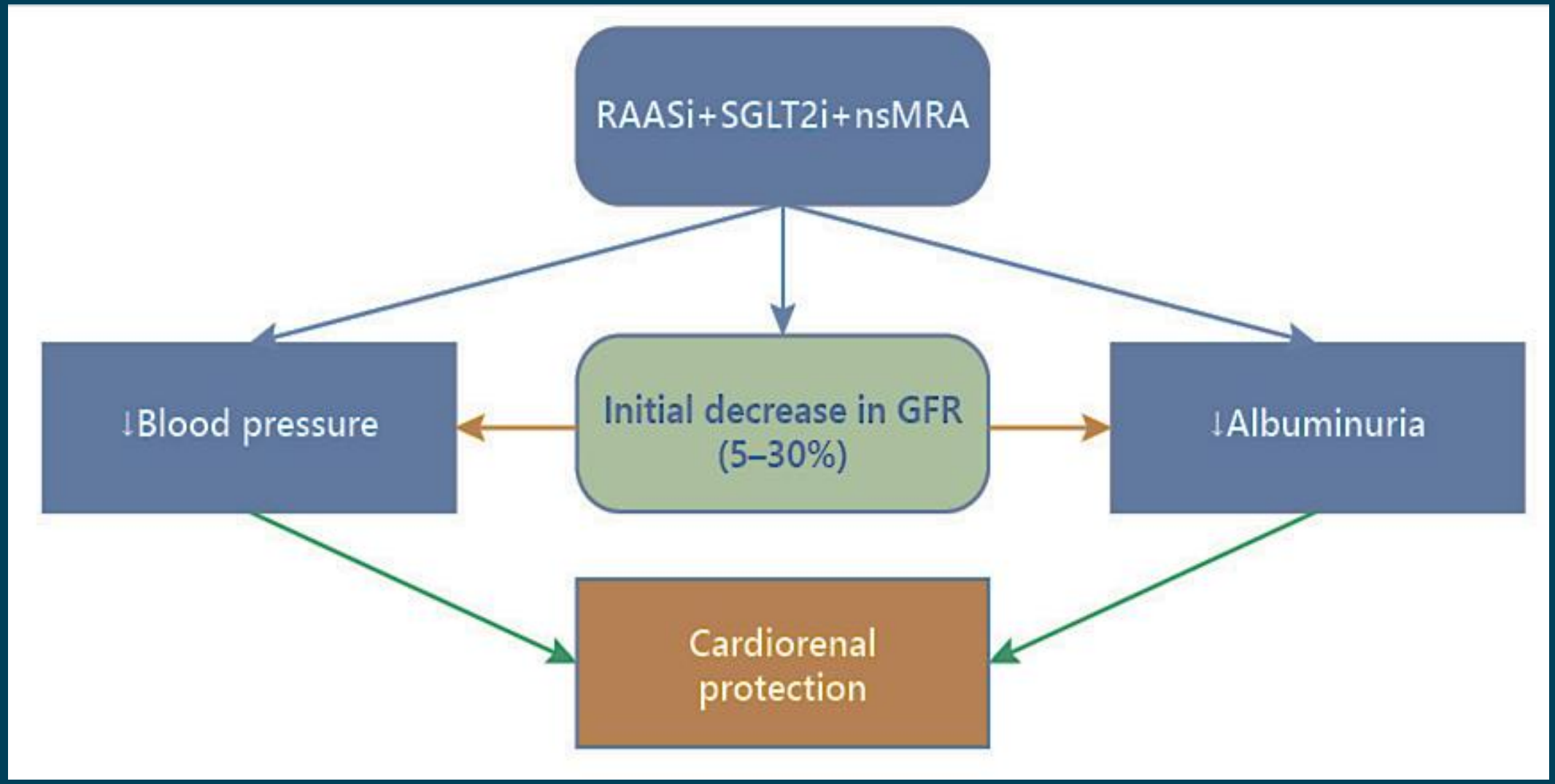
JAMA Cardiol 2022



NEJM 2020



Initial Drops in Glomerular Filtration Rate with Certain Drug Classes Retard Kidney Disease Progression



Bakris G and Weir M *Am J Nephrol*. 2022;53(7):513-515

Module II. Risk Factor Control in Patients with CKD and T2DM

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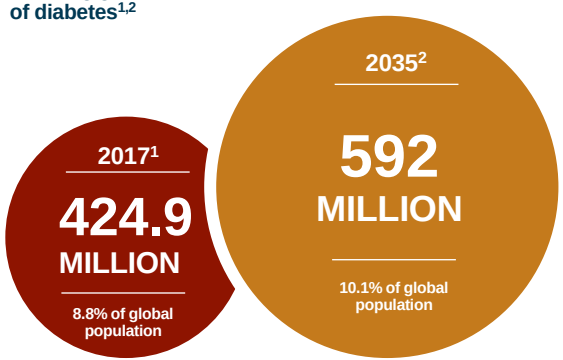
Emeritus Professor of Medicine
Indiana University School of Medicine and VA Medical Center
Indianapolis, Indiana

Diabetes Mellitus is a Major Global Threat:

A growing medical problem associated with high mortality

Deaths due to diabetes (20-79 years)[1] in 2017 (millions)

Growing global incidence of diabetes[1,2]



Diabetes accounted for ~4.0 million deaths and cost ~$727 billion (USD) in health spending in 2017[1]

AFR = Africa; EUR = Europe; MENA = Middle East and North Africa; NAC = North America and Carribean; SACA = South and Central America; SEA = Southeast Asia; WP = Western Pacific.
1. International Diabetes Foundation. *IDF Diabetes Atlas*, 8th ed. Brussels, Belgium; 2017.2. International Diabetes Foundation. *IDF Diabetes Atlas*, 6th ed. Brussels, Belgium; 2013.
Deaths due to diabetes illustration used with permission of the International Diabetes Foundation from the *IDF Diabetes Atlas*, 8th ed. Brussels, Belgium; 2017.

Lifestyle measures

- ❑ Healthy Diet
- ❑ Physical activity
- ❑ Weight
- ❑ Cessation of tobacco use

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American Diabetes Association recommendations

Fruits, non-starchy vegetables, legumes

Whole grain, low fat dairy

Avoidance of saturated and Trans fats

Minimize added sugars and refined grains

Limiting caloric intake in overweight or obese

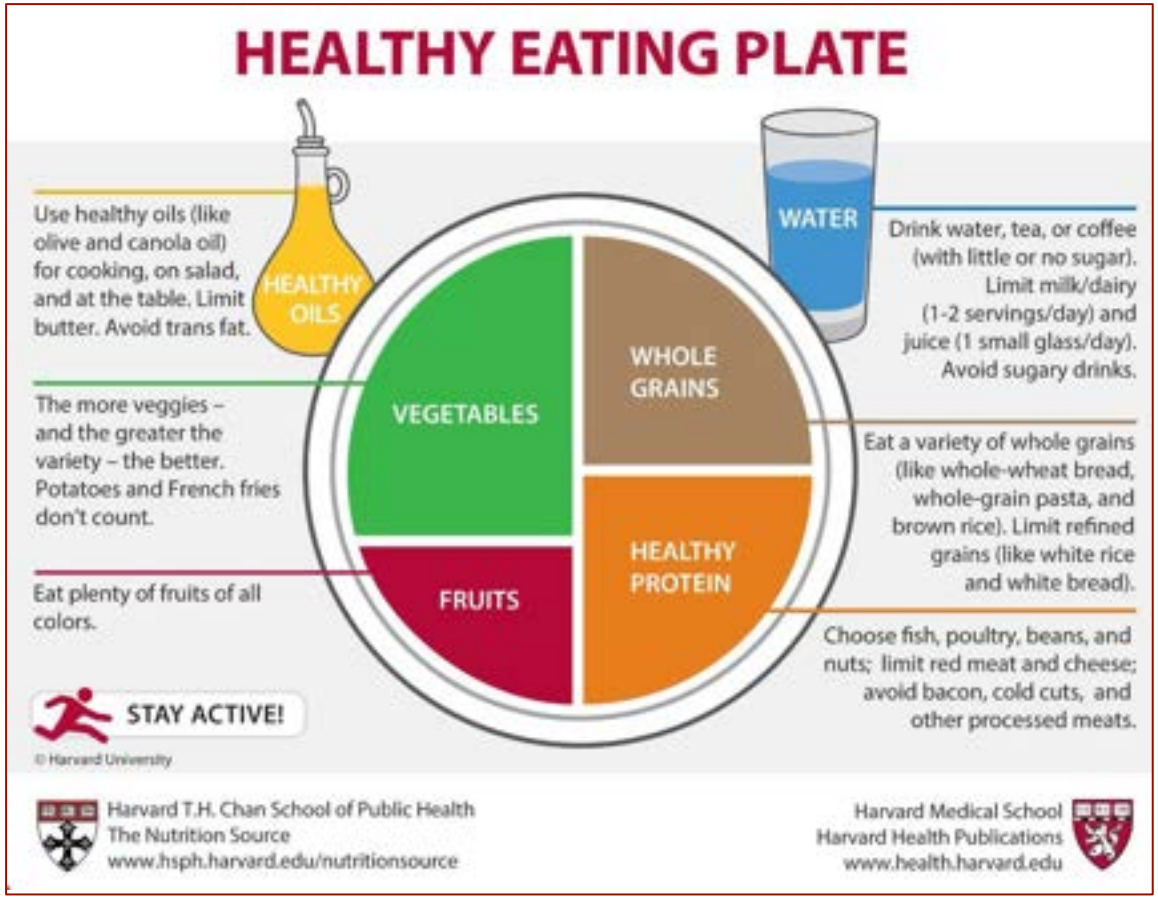
Dietary Na <2300 mg/d (ADA), <1500 mg (ACC/AHA)

Nutrition Therapy for Adults With Diabetes or Prediabetes: A Consensus Report

Diabetes Care 2019;42:731–754 | https://doi.org/10.2337/dci19-0014

Alison B. Evert,[1] Michelle Dennison,[2] Christopher D. Gardner,[3] W. Timothy Garvey,[4,5] Ka Hei Karen Lau,[6] Janice MacLeod,[7] Joanna Mitri,[8] Raquel F. Pereira,[9] Kelly Rawlings,[10] Shemera Robinson,[11] Laura Saslow,[12] Sacha Uelmen,[13] Patricia B. Urbanski,[14] and William S. Yancy Jr.[15,16]

A simple tool to implement the diet



Lifestyle measures

- ❑ Healthy Diet
- ❑ Physical activity
- ❑ Weight
- ❑ Cessation of tobacco use

The Six S's of physical behaviors over 24-hours

1. Sitting
2. Stepping
3. Sweating
4. Strengthening
5. Sarcopenia
6. Sleep

Management of Hyperglycemia in Type 2 Diabetes, 2022. A Consensus Report by the American Diabetes Association (ADA) and the European Association for the Study of Diabetes (EASD)

Diabetes Care. 2022;45(11):2753-2786. doi:10.2337/dci22-0034

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Lifestyle measures

- ❑ Healthy Diet
- ❑ Physical activity
- ❑ Weight
- ❑ Cessation of tobacco use

U.S. Preventive Services Task Force

Interventions for Tobacco Smoking Cessation in Adults, Including Pregnant Persons: Recommendation Statement

- ❑ Treat smoking as a vital sign
- ❑ Ask, advise, refer
- ❑ Behavioral counseling
- ❑ Pharmacotherapy
  - nicotine replacement therapy
  - bupropion sustained-release
  - varenicline

https://www.aafp.org/dam/brand/aafp/pubs/afp/issues/2021/0615/od1.pdf

Multifactorial intervention reduces CV risk in patients with T2D and moderately increased albuminuria

STENO-2 trial[1]: 160 patients with T2D and moderately increased albuminuria were randomised to receive either conventional or intensive multifactorial therapy*

Intensive multifactorial therapy

- **Behavioral modification**: Diet, exercise, smoking cessation
- **Pharmacological modification**: Including ACEis/ARBs, metformin/insulin, thiazides and β-blockers

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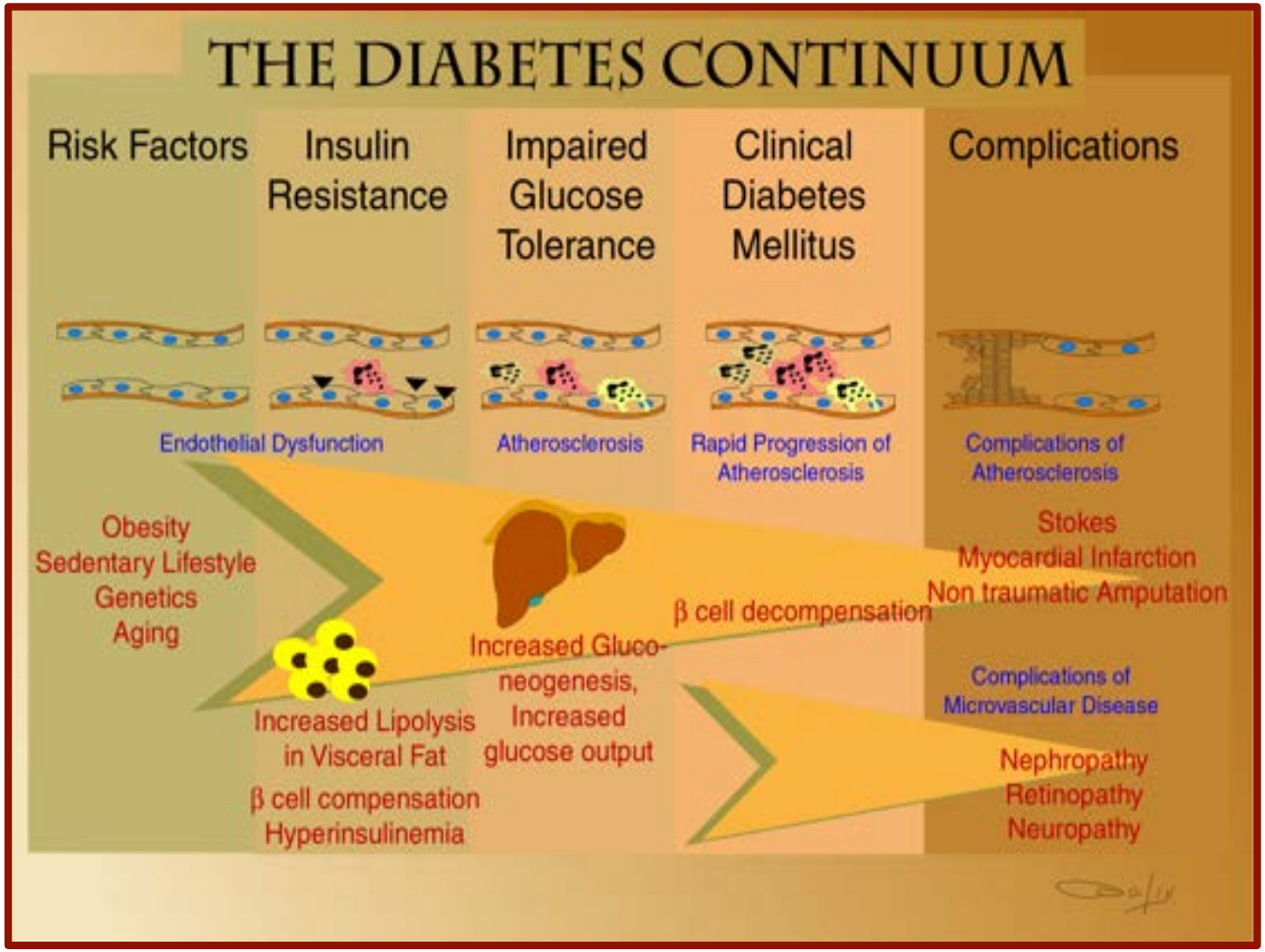
Steno-2: Benefits of multifactorial intervention over time

1984	...	1999	2003	2008	2016
Discovery of albuminuria		Reduced microvascular complications after 4 years[1]	CV benefit after 7.8 years[3]	Mortality benefit after 13 years[4]	Benefits maintained after 21 years[5]
First study (N=6) to show antihypertensive treatment can slow kidney disease in patients with CKD and T2D[2]		Slowed progression of: Nephropathy, Retinopathy	~50% reduction in risk of CV and microvascular events	20% reduction in risk of mortality	The initial 8 years of intervention give a median gain of life of 7.9 years

*The mean treatment period was 7.8 years and the primary endpoint at 13.3 years of follow-up was the time to death from any cause; conventional therapy was defined as treatment by their general practitioner according to the 1988 recommendations of the Danish Medical Association

ACEi, angiotensin-converting enzyme inhibitor; ARB, angiotensin receptor blocker; T2D, type 2 diabetes

1. Gæde P, *et al. Lancet* 1999;353:617–611; 2. Mogensen CE. *N Engl J Med* 1984;310:356–360; 3. Gæde P, *et al. N Engl J Med* 2003;348:383–393; 4. Gæde P, *et al*. *N Engl J Med* 2008;358:580–591; 5. Gæde P, *et al*. *Diabetologia* 2016;59:2298–2307


THE DIABETES CONTINUUM
Risk Factors
Insulin Resistance
Impaired Glucose Tolerance
Clinical Diabetes Mellitus
Complications
Endothelial Dysfunction
Atherosclerosis
Rapid Progression of Atherosclerosis
Complications of Atherosclerosis
Obesity
Sedentary Lifestyle
Genetics
Aging
Increased Lipolysis in Visceral Fat
β cell compensation
Hyperinsulinemia
Increased Gluco-neogenesis, Increased glucose output
β cell decompensation
Stokes
Myocardial Infarction
Non traumatic Amputation
Complications of Microvascular Disease
Nephropathy
Retinopathy
Neuropathy

Question

Does intensive glycemic control reduce cardiovascular outcomes in type 2 diabetes?

ORIGINAL ARTICLE

Intensive Blood Glucose Control and Vascular Outcomes in Patients with Type 2 Diabetes

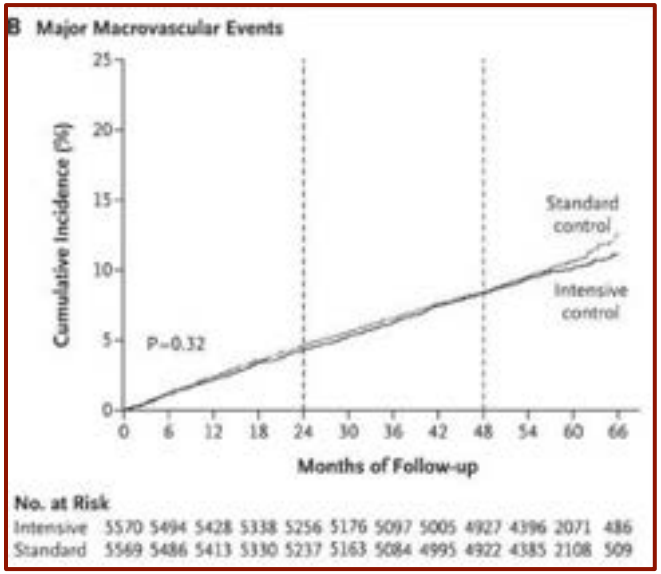
The ADVANCE Collaborative Group*

11,140 patients with type 2 diabetes randomized to either standard glucose control or intensive glucose control (HbA1c<6.5%)

Macrovascular outcome: MI, stroke, CV death

Severe hypoglycemia more common in intensive (2.7%), than standard group.

No significant effect on major macrovascular events.



ADVANCE Collaborative Group. "Intensive blood glucose control and vascular outcomes in patients with type 2 diabetes." New England journal of medicine 358.24 (2008): 2560-2572.

ORIGINAL ARTICLE

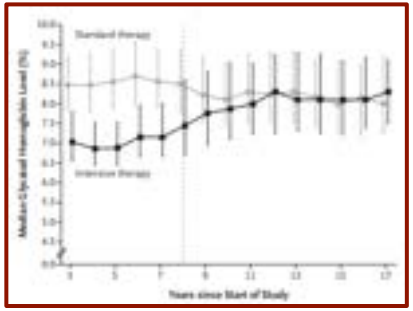
Intensive Glucose Control in Patients with Type 2 Diabetes — 15-Year Follow-up

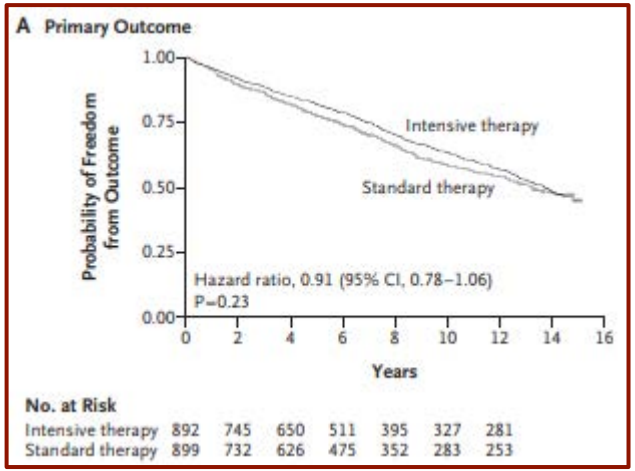
Peter D. Reaven, M.D., Nicholas V. Emanuele, M.D., Wyndy L. Wiitala, Ph.D., Gideon D. Bahn, Ph.D., Domenic J. Reda, Ph.D., Madeline McCarren, Ph.D., William C. Duckworth, M.D., and Rodney A. Hayward, M.D., for the VADT Investigators*

1665 patients with type 2 diabetes randomized to either standard glucose control or intensive glucose control followed long-term. Primary results were negative

Macrovascular outcome: MI, stroke, CV death, amputation from ischemic gangrene, new or worsening heart failure

No significant effect on major macrovascular events.





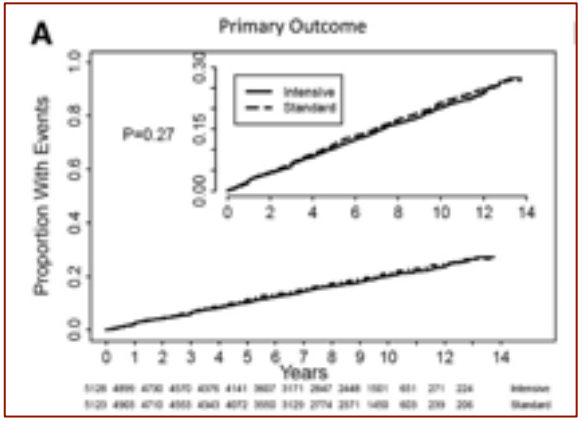
Reaven, Peter D., et al. "New England Journal of Medicine 380.23 (2019): 2215-2224.

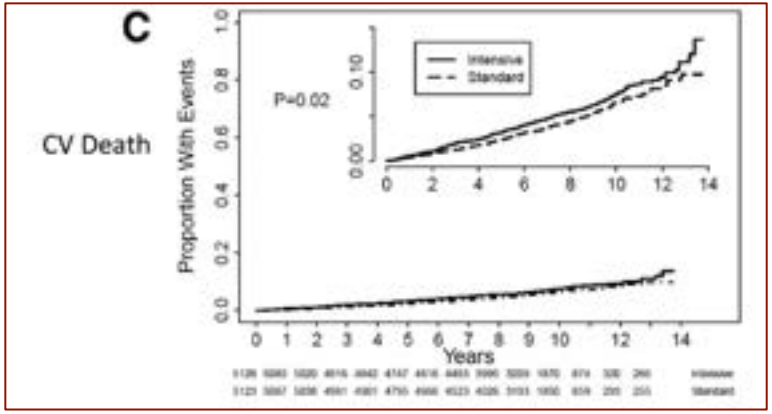
Nine-Year Effects of 3.7 Years of Intensive Glycemic Control on Cardiovascular Outcomes

Diabetes Care 2016;39:701–708 | DOI: 10.2337/dc15-2283

8601 patients with type 2 diabetes survivors of ACCORD trial randomized to either standard glucose control or intensive glucose control were followed long-term. Macrovascular outcome: MI, stroke, CV death

No significant effect on major macrovascular events but cv death increased

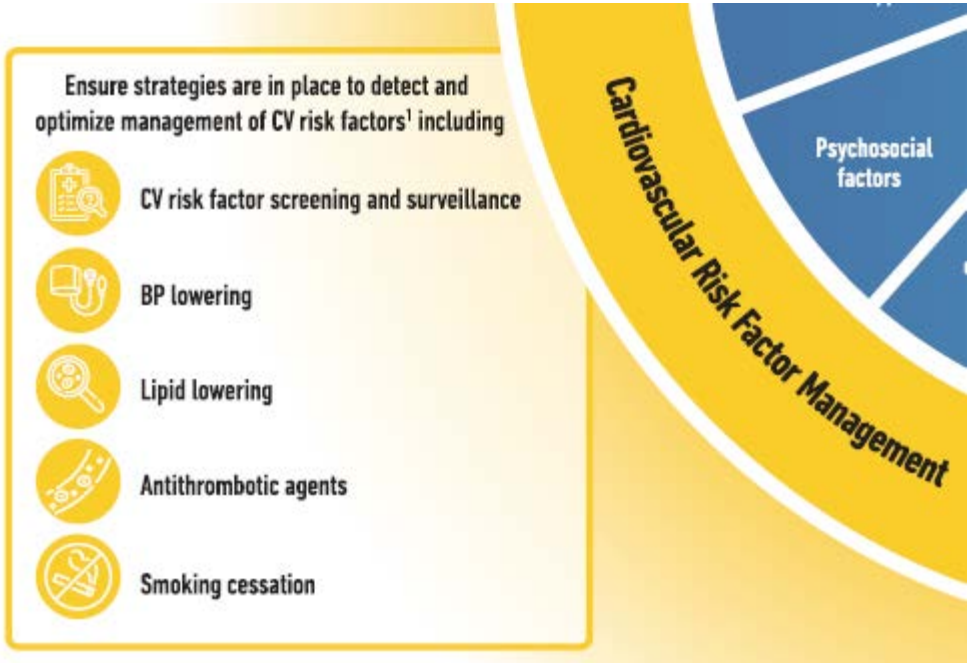




Diabetes Care

American Diabetes Association.

Management of Hyperglycemia in Type 2 Diabetes, 2022. A Consensus Report by the American Diabetes Association (ADA) and the European Association for the Study of Diabetes (EASD)



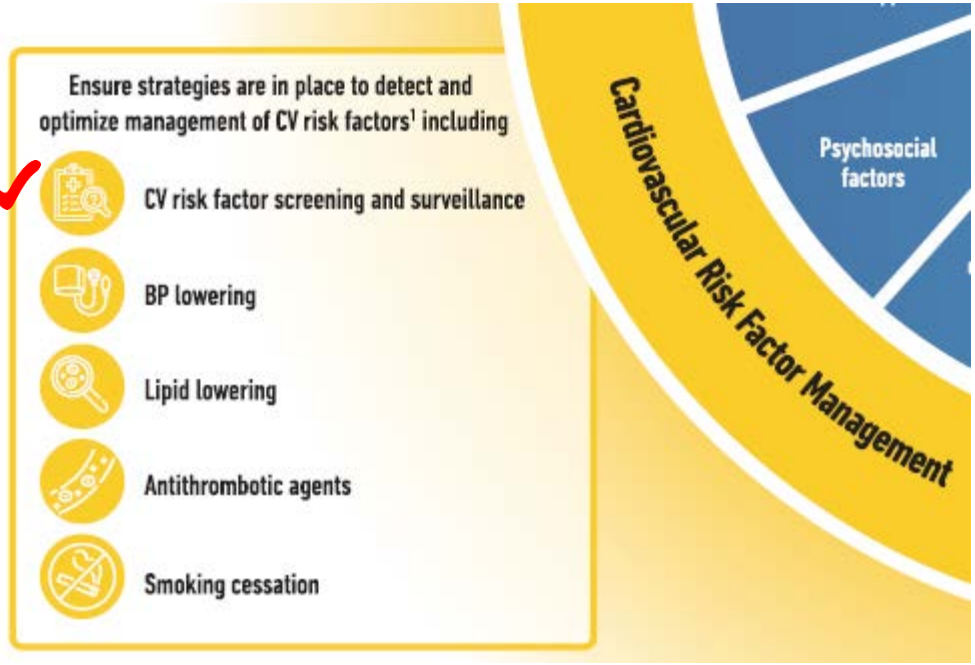
Blood Pressure Control

- Essential first step in management
- Goal BP <130/80 mmHg
- ACE inhibitors or Angiotensin Receptor Blockers first line in patients with albuminuria
- Combination therapy needed by most e.g. ARB plus diuretic

Diabetes Care

American Diabetes Association.

Management of Hyperglycemia in Type 2 Diabetes, 2022. A Consensus Report by the American Diabetes Association (ADA) and the European Association for the Study of Diabetes (EASD)



Hemoglobin A1C is modifiable risk factor but does NOT modify CV risk

- ✗ A_1C
- ✓ Blood pressure
- ✓ Cholesterol

Albuminuria is as important as BP or Cholesterol for identifying CV risk

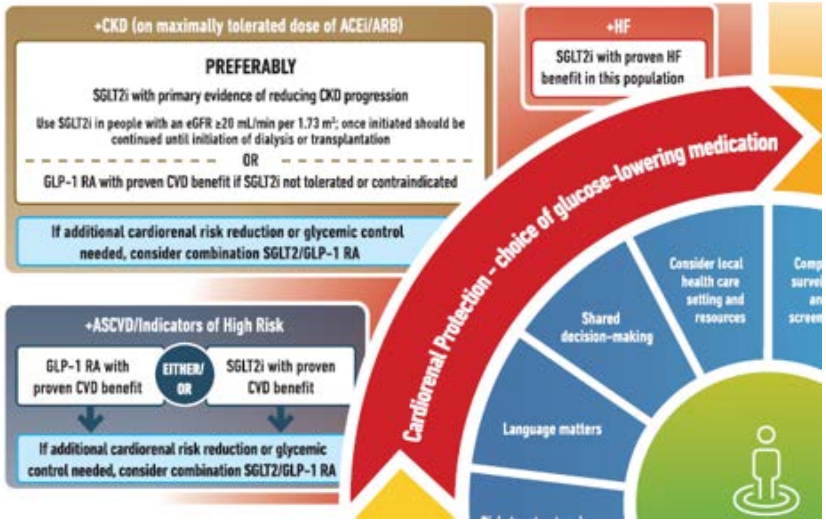
- ✔ Albuminuria
- ✔ Blood pressure
- ✔ Cholesterol

Lifestyle Measures

- ❑ Healthy Diet
- ❑ Physical activity
- ❑ Weight
- ❑ Cessation of tobacco use

1. Sitting
2. Stepping
3. Sweating
4. Strengthening
5. Sarcopenia
6. Sleep

- ✔ Albuminuria
- ✔ Blood pressure
- ✔ Cholesterol



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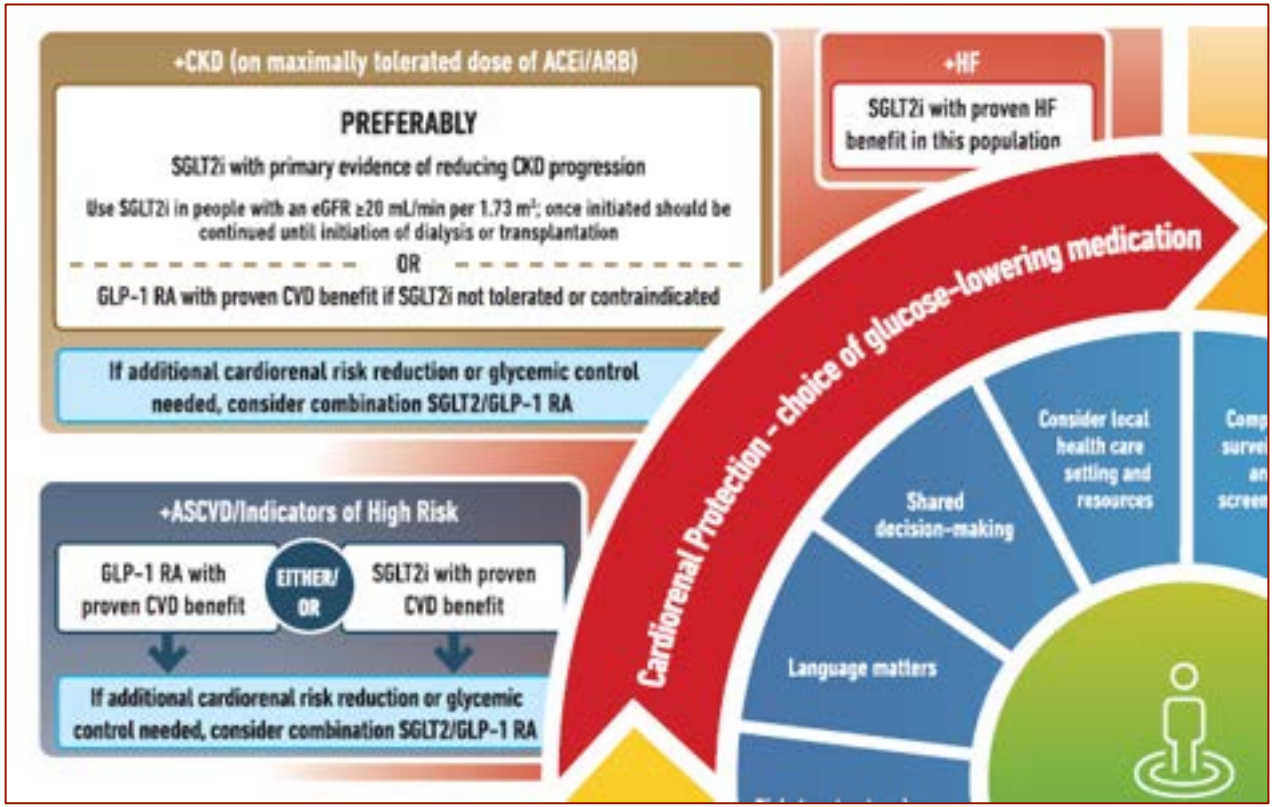
Management of Hyperglycemia in Type 2 Diabetes, 2022. A Consensus Report by the American Diabetes Association (ADA) and the European Association for the Study of Diabetes (EASD)



Comorbidity	ACE/ARB	SGLT2i	GLP1RA	Finerenone
ASCVD	Yes	Yes	Yes	No data
Heart failure	HFrEF	HFrEF + HFpEF	No benefit	Unknown, HFpEF study ongoing
CKD with UACR >200 mg/g	Yes (1g in RENAAL, IDNT)	Cardiorenal protection	ASCVD less, Kidney protection (FLOW)	ASCVD, HF, Kidney protection (FIDELITY)
CKD with UACR 30 mg/g-300 mg/g	Yes (IRMA2, INNOVATION, MICRO-HOPE)	No sig protection EMPA-KIDNEY	Unknown	ASCVD and HF protection > kidney protection

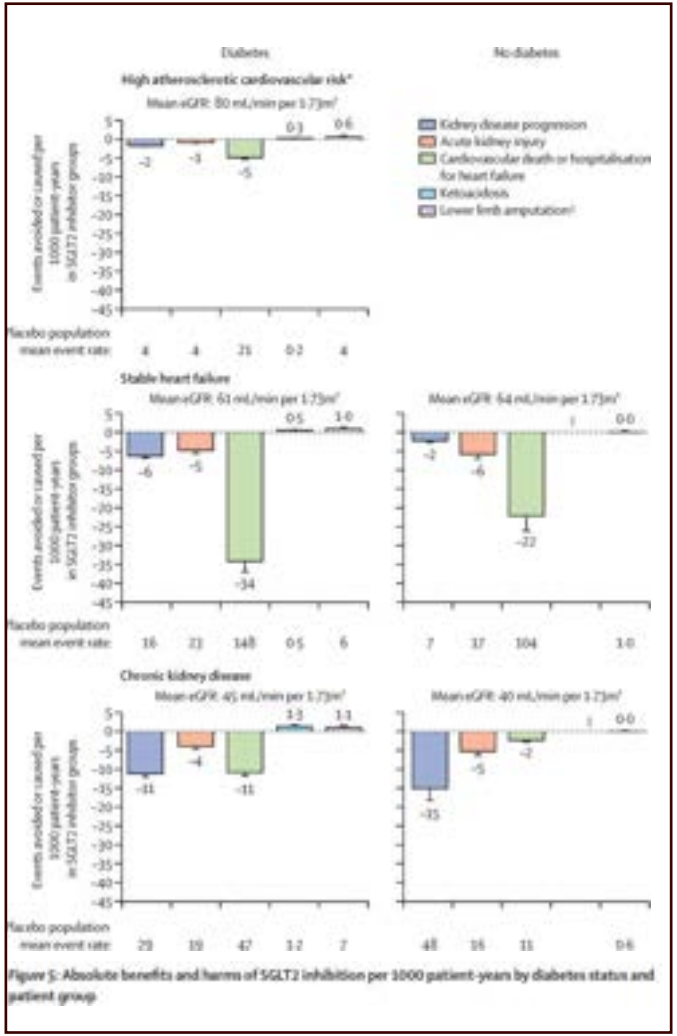


Figure 5: Absolute benefits and harms of SGLT2 inhibition per 1000 patient-years by diabetes status and patient group

Meta-analyses support the protective effect of SGLT2 inhibitors

1. Indicated for any patient with type 2 diabetes with albuminuria (>200 mg/g creatinine) and eGFR >20 if patient is on optimal dose of RASi.
2. Indicated for any patient with heart failure (with preserved or reduced ejection fraction) if eGFR >20
3. Any patient with type 2 diabetes and ASCVD

Impact of diabetes on the effects of sodium glucose co-transporter-2 inhibitors on kidney outcomes: collaborative meta-analysis of large placebo-controlled trials

Lancet. 2022 Nov 19; 400(10365): 1788–1801. doi: 10.1016/S0140-6736(22)02074-8 Writing Committee, and Smart-C Steering Committee *Lancet (London, England)*.

Comorbidity	ACE/ARB	SGLT2i	GLP1RA	Finerenone
ASCVD	Yes	Yes	Yes	No data
Heart failure	HFrEF	HFrEF + HFpEF	No benefit	Unknown, HFpEF study ongoing
CKD with UACR >200 mg/g	Yes (1g in RENAAL, IDNT)	Cardiorenal protection	ASCVD less, Kidney protection ±	ASCVD, HF, Kidney protection (FIDELITY)
CKD with UACR 30 mg/g-300 mg/g	Yes (IRMA2, INNOVATION, MICRO-HOPE)	No sig protection EMPA-KIDNEY	Uncertain	ASCVD and HF protection > kidney protection

Module III. Monitoring Treatment Response in CKD Patients with T2DM

Rajiv Agarwal, MD, MS
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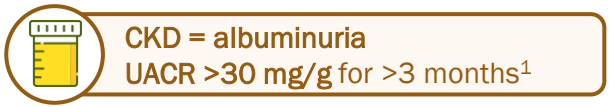
Indiana University School of Medicine and VA Medical Center
Indianapolis, Indiana

CV risk in patients with CKD and T2D increases as eGFR falls and as UACR rises

CKD = eGFR <60 ml/min/1.73 m^2
for >3 months[1]

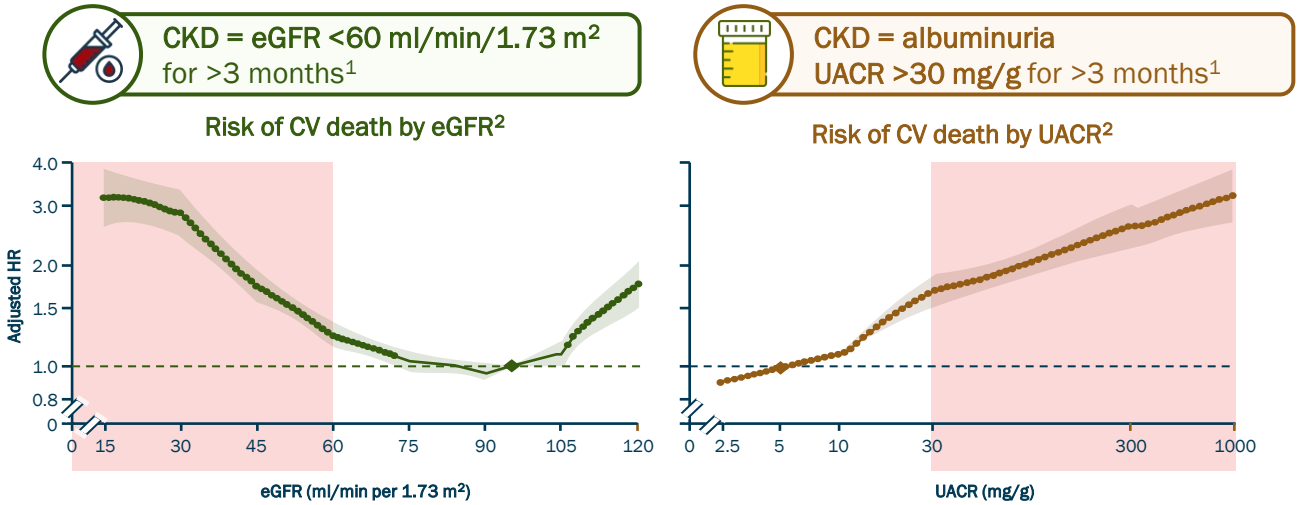


CKD = albuminuria
UACR >30 mg/g for >3 months[1]

CKD, chronic kidney disease; CV, cardiovascular; eGFR, estimated glomerular filtration rate; HR, hazard ratio; T2D, type 2 diabetes; UACR, urine albumin-to-creatinine ratio

1. Kidney Disease Improving Global Outcomes. *Kidney Int* 2013;3:1–150; 2. Matsushita K, *et al. Lancet Diabetes Endocrinol* 2015;3:514–525

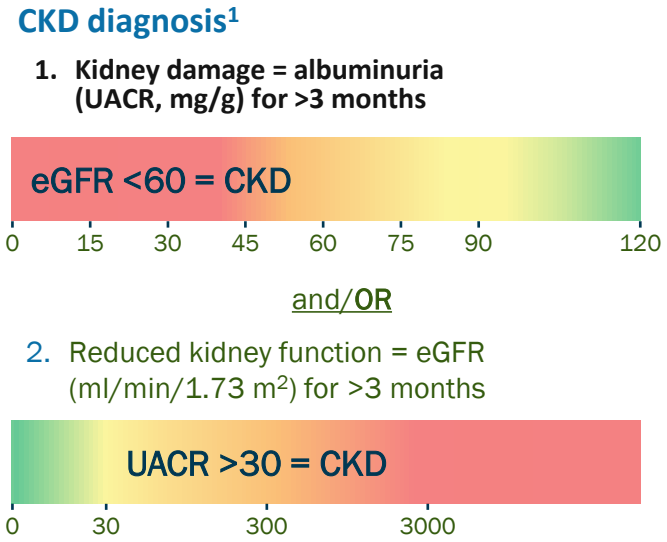
CV risk in patients with CKD and T2D increases as eGFR falls and as UACR rises



CKD, chronic kidney disease; CV, cardiovascular; eGFR, estimated glomerular filtration rate; HR, hazard ratio; T2D, type 2 diabetes; UACR, urine albumin-to-creatinine ratio

1. Kidney Disease Improving Global Outcomes. Kidney Int 2013;3:1–150; 2. Matsushita K, et al. Lancet Diabetes Endocrinol 2015;3:514–525

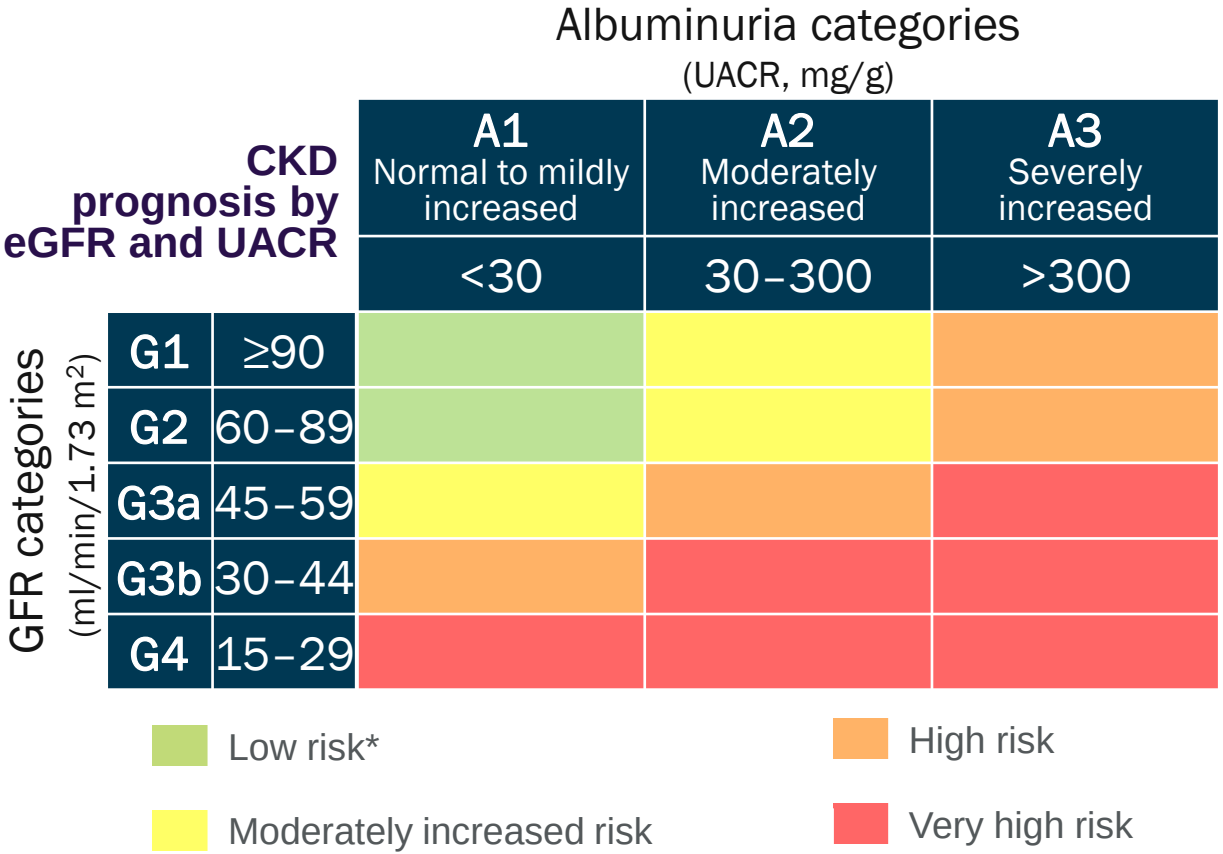
CV risk increases with declining eGFR and increasing UACR



CKD, chronic kidney disease; CV, cardiovascular; eGFR, estimated glomerular filtration rate; HR, hazard ratio; T2D, type 2 diabetes; UACR, urine albumin-to-creatinine ratio

1. Kidney Disease Improving Global Outcomes. Kidney Int 2013;3:1–150; 2. Levey et al. Kidney Int 2011;40:17–28

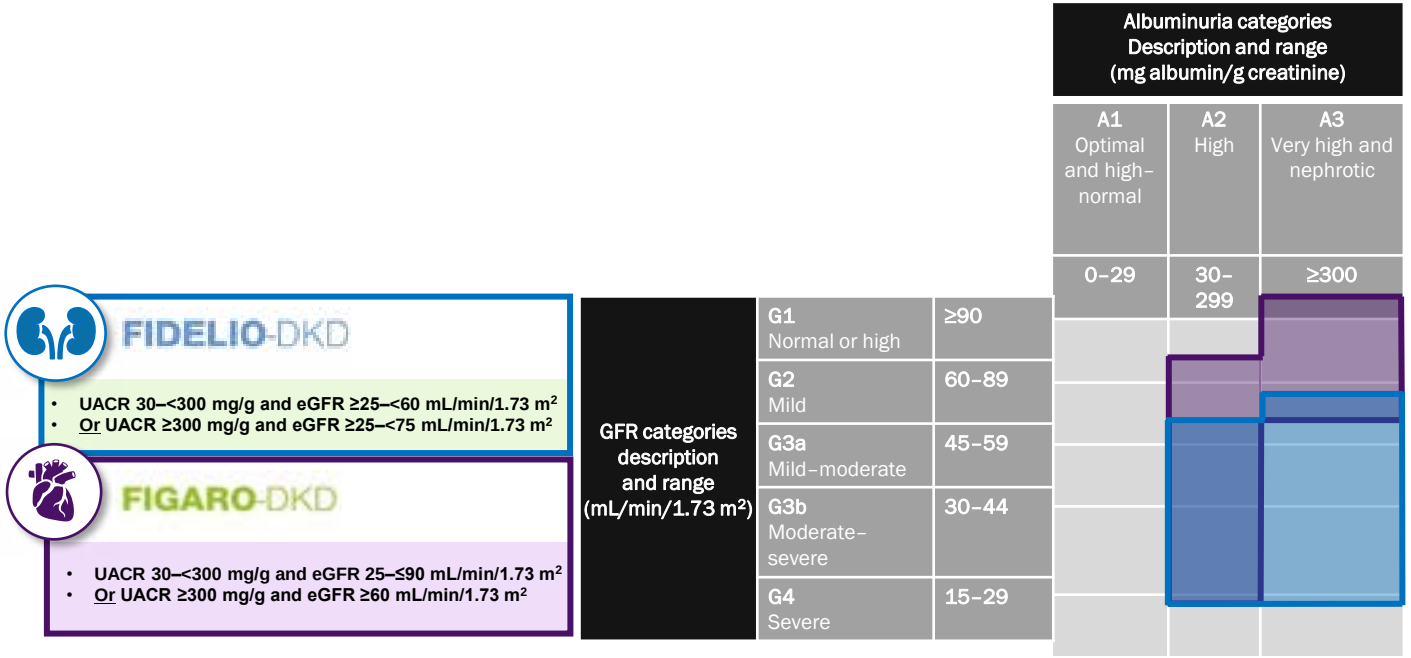
KDIGO risk assessment



CKD is a modifiable CV risk factor in type 2 diabetes—

Albuminuria as important as BP or cholesterol

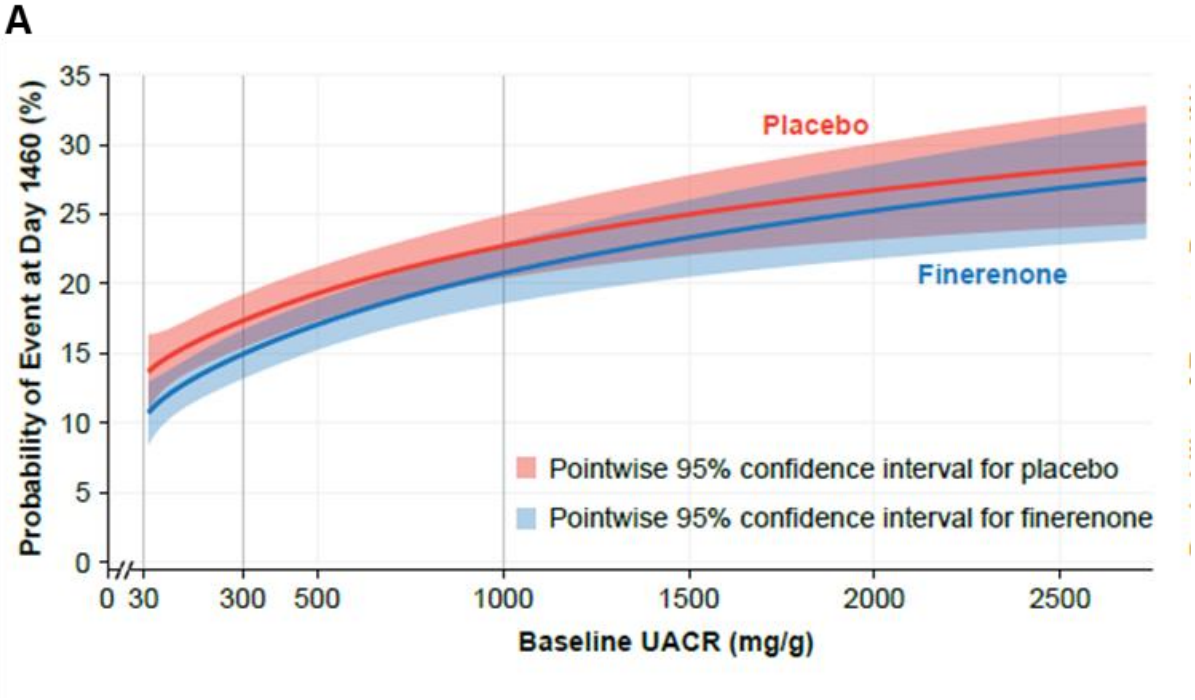
Albuminuria and eGFR distribution



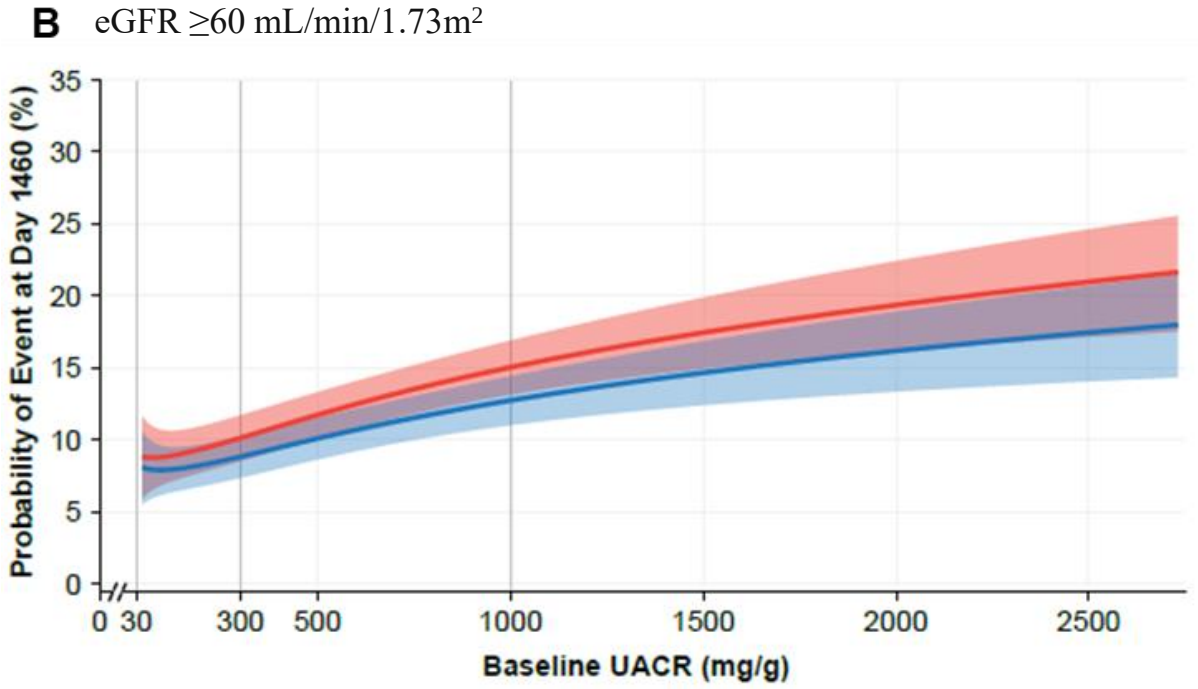
Bakris GL, et al. Am J Nephrol 2019; 50:333–344; 2. Ruilope LM, et al. Am J Nephrol 2019; 50:345–356

Predicted Probability of Cardiovascular Events at 4 Years in those with eGFR <60 mL/min/1.73m2

eGFR <60 mL/min/1.73m^2



Predicted Probability of Cardiovascular Events at 4 Years in those with eGFR ≥60 mL/min/1.73m2



Number of People with T2D eligible for treatment in USA			
eGFR	UACR <300 mg/g	UACR ≥300 mg/g	Total by eGFR
>60	62%	13%	75%
≤60	15%	10%	25%
Total by UACR	77%	23%	6,423,000

Number of Excess first CV events prevented by Finerenone			
eGFR	UACR <300 mg/g	UACR ≥300 mg/g	Total by eGFR
>60	53%	13%	66%
≤60	22%	11%	34%
Total by UACR	75%	25%	38,322

Albuminuria is as important as BP or Cholesterol for identifying CV risk

- ✔ Albuminuria
- ✔ Blood pressure
- ✔ Cholesterol

Annals of Internal Medicine ORIGINAL RESEARCH

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

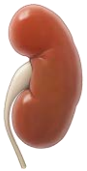
A Mediation Analysis

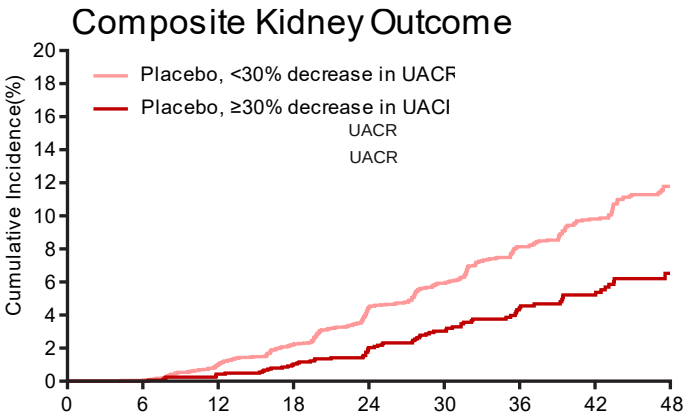
Rajiv Agarwal, MD, MS; Wanzhu Tu, PhD; Alfredo E. Farjat, PhD; Youssef M.K. Farag, MD, PhD, MPH; Robert Toto, MD; Sanjay Kaul, MD; Robert Lawatscheck, MD; Katja Rohwedder, MD; Luis M. Ruilope, MD; Peter Rossing, MD; Bertram Pitt, MD; Gerasimos Filippatos, MD; Stefan D. Anker, MD, PhD; and George L. Bakris, MD; on behalf of the FIDELIO-DKD and FIGARO-DKD Investigators*

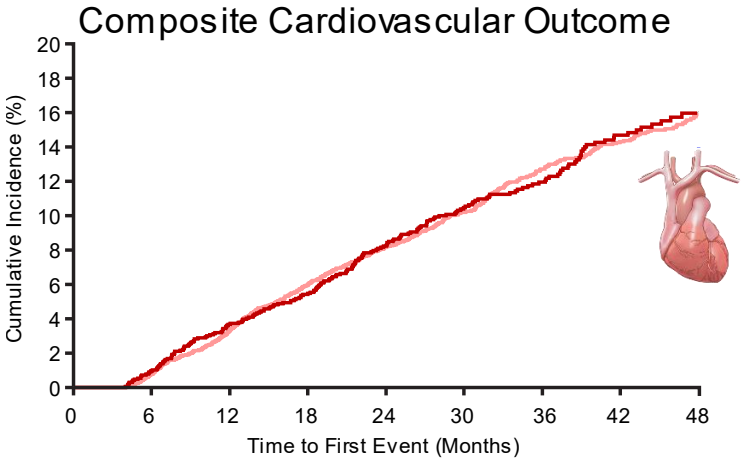
Ann Intern Med. doi:10.7326/M23-1023 Annals.org
For author, article, and disclosure information, see end of text.
This article was published at Annals.org on 5 December 2023.* For a full list of the FIDELIO-DKD and FIGARO-DKD Investigators, see the Supplement (available at Annals.org).

* For a full list of the FIDELIO-DKD and FIGARO-DKD Investigators, see the Supplement (available at Annals.org).

Size of mediation effect of UACR between composite kidney and CV outcomes was different: larger for the kidney than CV

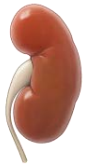


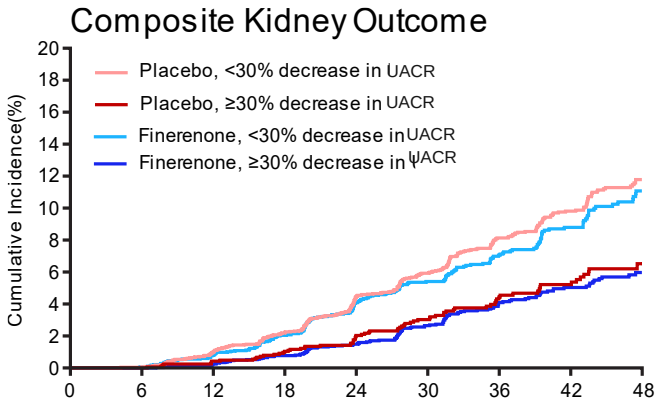


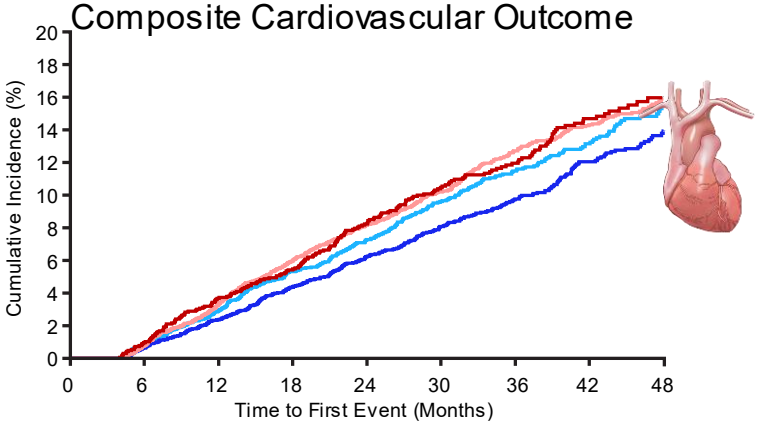


Agarwal, Rajiv, et al. *Annals of internal medicine* 176.12 (2023): 1606-1616.

However, UACR mediated both kidney and cardiovascular outcomes







Agarwal, Rajiv, et al. *Annals of internal medicine* 176.12 (2023): 1606-1616.

Outcomes mediated by an early UACR reduction

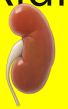
Percent of outcomes mediated by an early UACR reduction (baseline to 4 months)

	Kidney 	CV 
UACR continuous	84%	37%

Agarwal, Rajiv, et al. *Annals of internal medicine* 176.12 (2023): 1606-1616.

Outcomes mediated by an early UACR reduction

Percent of outcomes mediated by an early UACR reduction (baseline to 4 months)

	Kidney 	CV 
UACR continuous	84%	37%
UACR binary (<30% vs ≥30%)	64%	26%

Agarwal, Rajiv, et al. *Annals of internal medicine* 176.12 (2023): 1606-1616.

UACR change mediates kidney and CV outcomes of finerenone

Early albuminuria reduction with finerenone in CKD and T2D mediates a large proportion of the treatment effect against **CKD progression** and a modest proportion of the effect against CV outcomes.

The current findings are not readily extendable to other drugs.

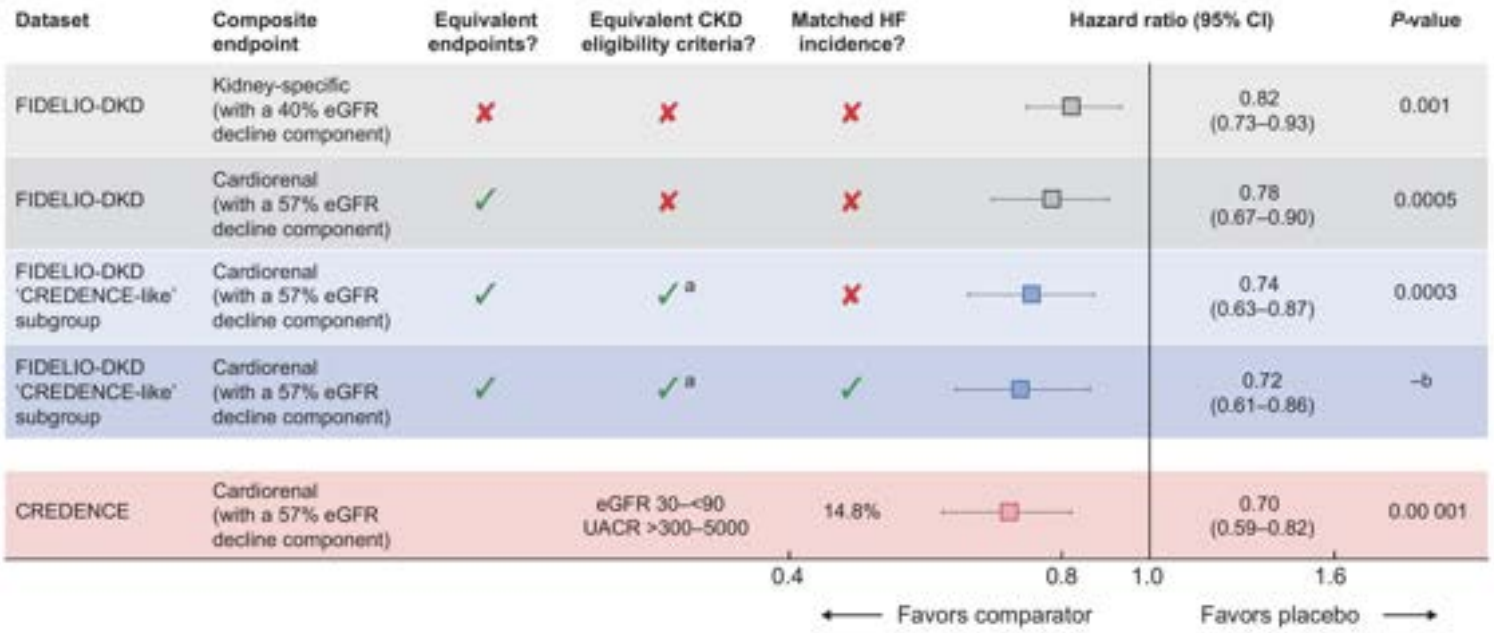
Agarwal, Rajiv, et al. *Annals of internal medicine* 176.12 (2023): 1606-1616.

Finerenone

1. Indicated for any patient with type 2 diabetes with albuminuria and eGFR >25 and serum K ≤5.0 if patient is on optimal dose of RASi.
2. Monitor K, BP, and serum Na on an ongoing basis. Stop RAASi if K >5. 5 mEq/L
3. Reduced risk for heart failure hospitalizations by ~1/5
4. Reduced risk for dialysis by ~1/5

Agarwal, Rajiv, et al. *Annals of internal medicine* 176.12 (2023): 1606-1616.

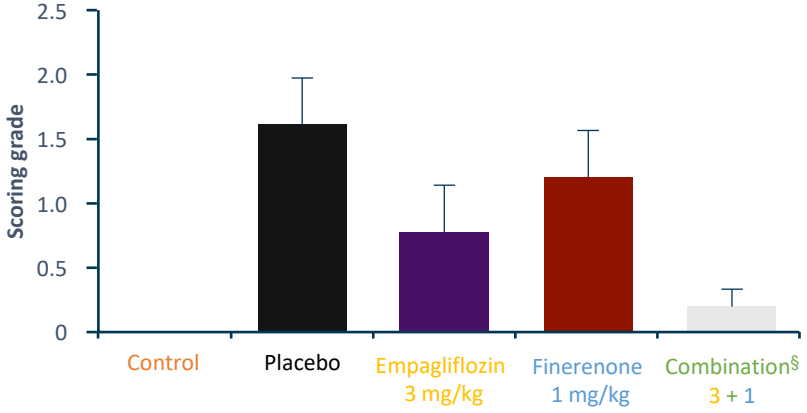
Trial design



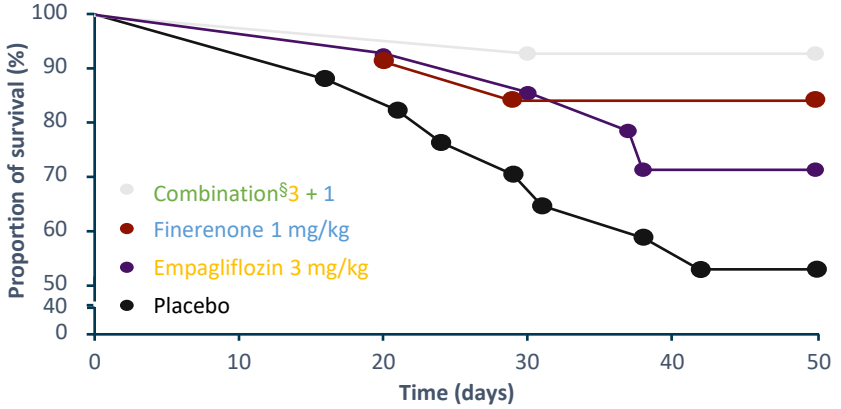
Agarwal R, NDT 2022

Preclinical data show that combination therapy with finerenone and an SGLT-2i has benefits over monotherapy*

Cardiac fibrosis#



Survival‡



Low-dose combination tended to have more anti-fibrotic effects than each low-dose monotherapy

Greatest survival benefit observed with combined treatment with finerenone and empagliflozin

Red/Fast Green staining; ‡proportion of survival defined as the absence of mortality and severe morbidity per group over the course of the study; §combination therapy of finerenone (1 mg/kg) and empagliflozin (3 mg/kg); Data are mean ± SEM.

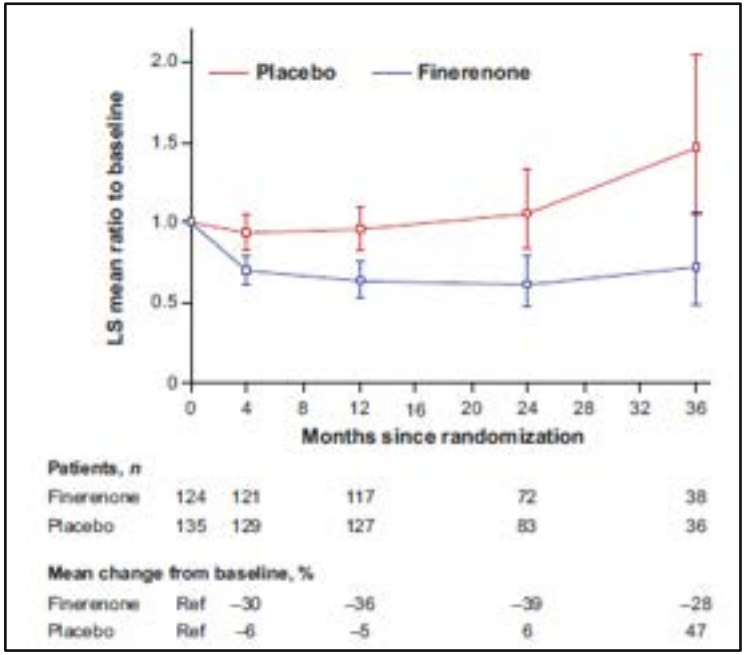
SEM, standard error of the mean

Kolkhof P *et al. Am J Nephrol* 2021; doi: 10.1159/000516213

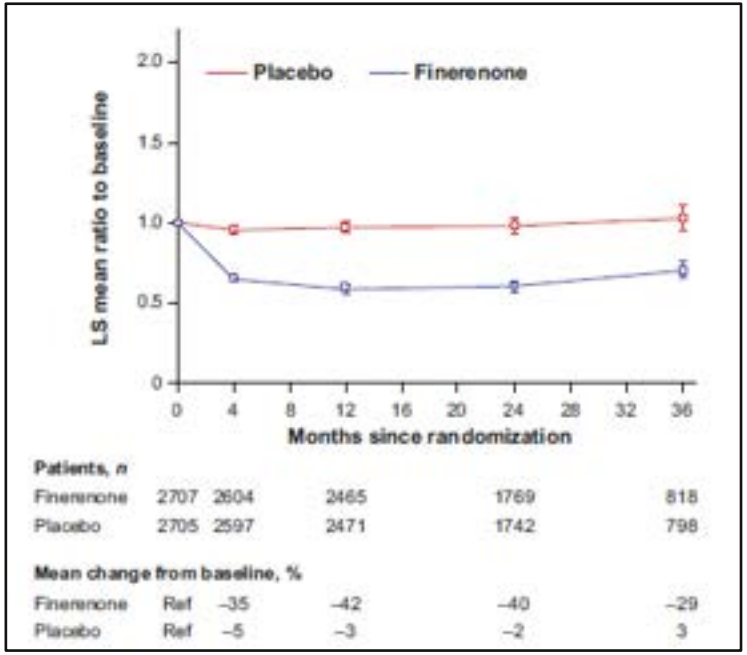
FIDELITY

Effect on albuminuria over time by baseline SGLT-2i use

SGLT2 inh

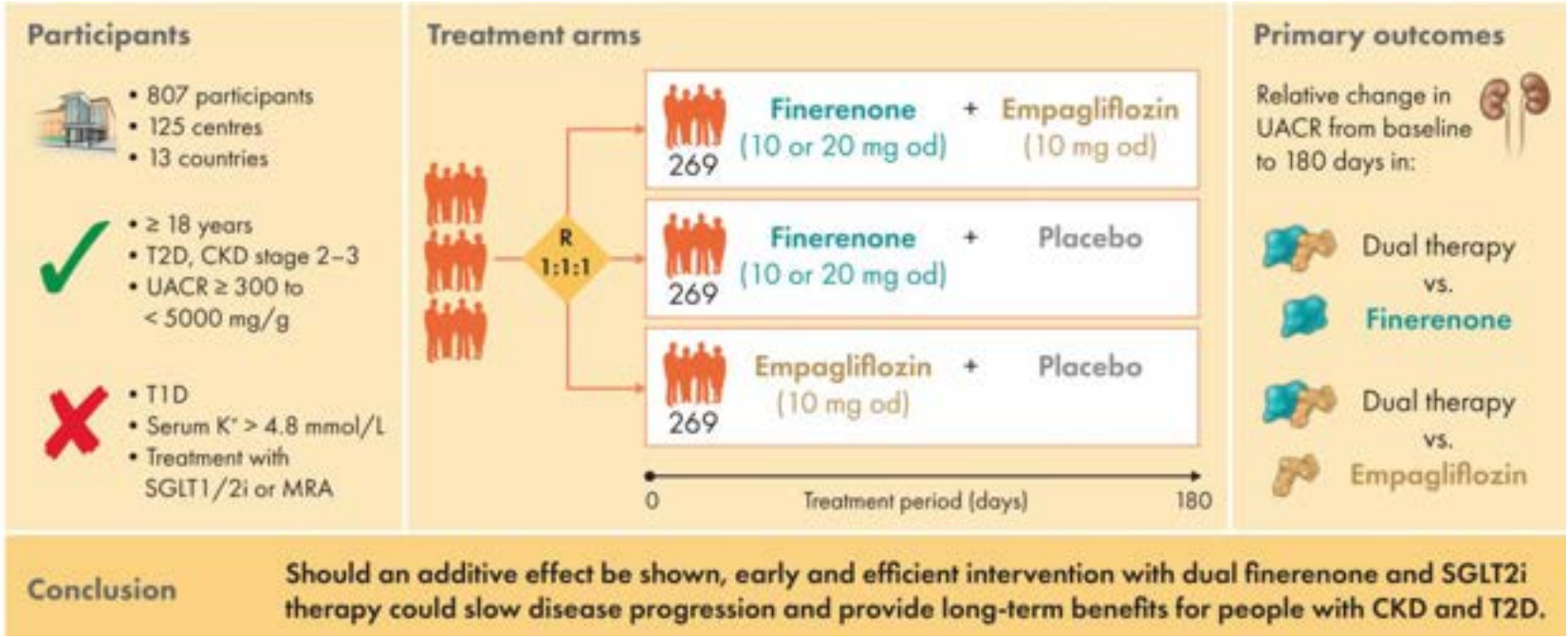


No SGLT2 inh



Rossing, Peter, et alKidney international 102.5 (2022): S1-S127.

COmbinatioN effect of FInerenone anD EmpaglifloziN in participants with chronic kidney disease and type 2 diabetes using a UACR Endpoint study (CONFIDENCE)



Green, Jennifer B., et al. Nephrology Dialysis Transplantation 38.4 (2023): 894-903.

Module 4: Patients Case #1

George L. Bakris, MD
Professor of Medicine
University of Chicago Medicine

Case

- 63 y/o African American male presents with BP 168/88 mmHg, heart rate-84 bpm and new onset dyspnea on excretion. Also says he has gained 15lbs in last month.
- PMH-Hypertension at least 15 years, Type 2 diabetes-10 years, hyperlipidemia for at least 10 yrs.
- FH-+ MI, CAD, HTN and DM
- SH-denies smoking has occas. alcohol, denies detailed sodium education
- PE- pertinent positives-S4, bibasilar crackles in lungs and 1+ pedal edema
- Labs-all normal except K 4.9 mEq/L , eGFR-48 ml/min HbA1c-7.2%, FBS-155mg/dl and LDL-109, urine albumin-524 mg/d, ECHO-2yrs. earlier showed EF of 56% and had neg. stress test 3 yrs. Earlier
- Meds. Losartan 100mg/d, HCTZ 25 mg/d, amlodipine 10mg/day, atorvastatin 40mg/d, metformin 1 gr BID, sitagliptin 100mg/d, canagliflozin 100 mg/d

Case

- Risk Factors to correct and follow:
- BP 168/88 mmHg, <130/80 mmHg, including volume management. Better lipid and glycemic control <7%, albuminuria >30% reduction, and LDL <70 mg/dl.
- How to ACHIEVE: Meds. Losartan 100mg/d-change to olmesartan or azilsartan 40 or 80 mg/d respectively. Change diuretic Chlorthalidone 25 mg, increase to atorvastatin 80mg/d +ezetimibe, metformin 1 gr BID, sitagliptin 100mg/d, canagliflozin 100 mg/d

Amlodipine was continued and carvedilol 12.5 mg bid and spironolactone 25 mg was added as well as education of <2000 mg/d sodium diet.

- Patient returned in one month-BP 132/78 mmHg UACR dropped >42% and stated his DOE was gone and that he felt better. Repeat labs however show K 5.2mEq/L and GFR now 40 ml/min.

Case – Interactivity Question

Given these findings and assuming you controlled his cholesterol and glucose better, what would be the next steps in managing this patient's risk factors

A. Stop the ARB and spiro and start hydralazine and nitrates
B. Stop the spiro, give a loop diuretic and educate about low K diet
C. Continue treatment but change chlorthalidone to torsemide and educate about low K diet
D. Continue treatment and add a potassium binding agent and educate about low K diet
E. Refer to a nephrologist due to fall in GFR

Case – Interactivity Question

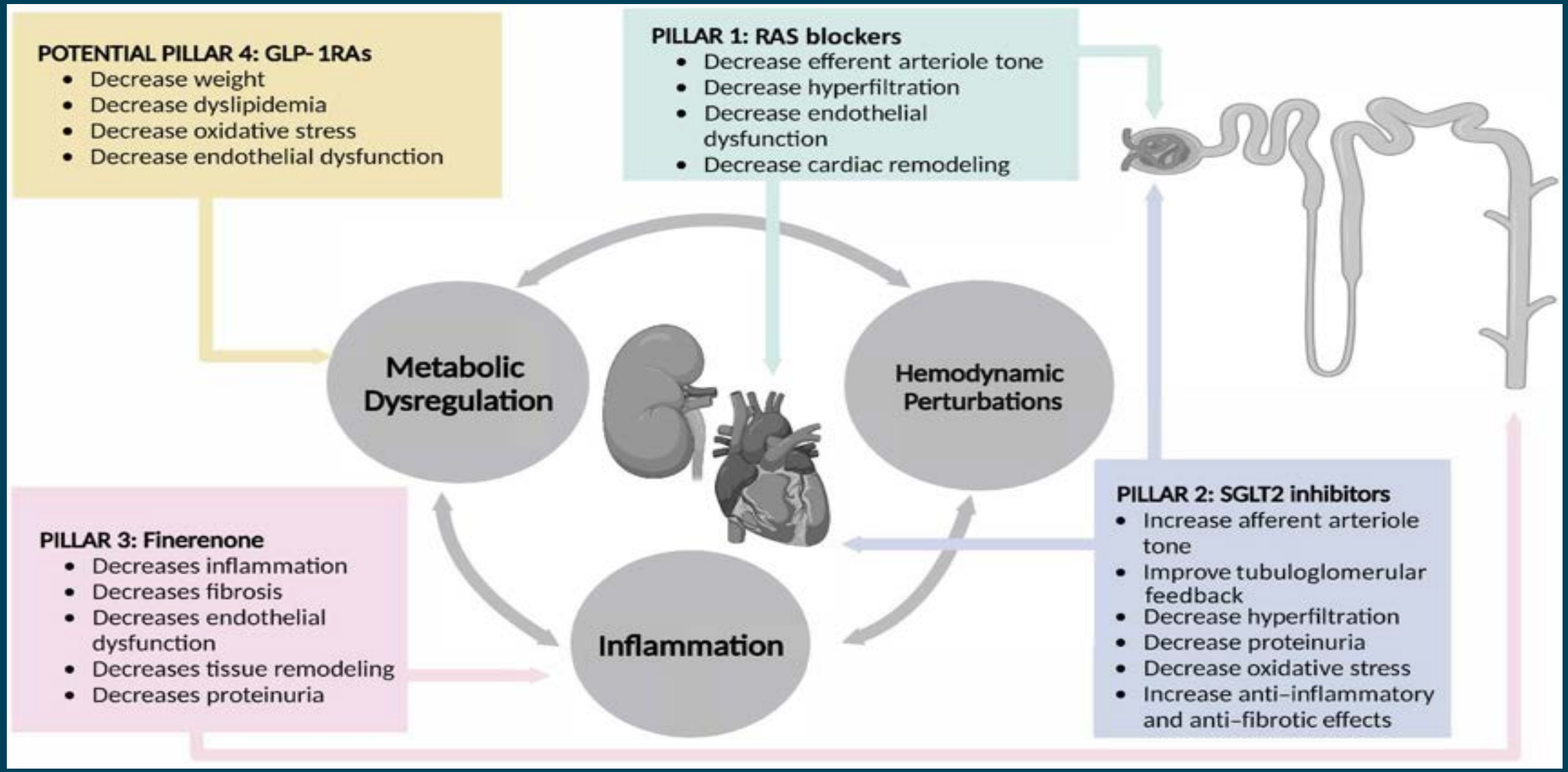
Given these findings and assuming you controlled his cholesterol and glucose better, what would be the next steps in managing this patient's risk factors

A. Stop the ARB and spiro and start hydralazine and nitrates
B. Stop the spiro, give a loop diuretic and educate about low K diet
C. Continue treatment but change chlorthalidone to torsemide and educate about low K diet

   Repeat labs in one week K-4.9mEq/L and BP was 130/76 mmHg.

D. Continue treatment and add a potassium binding agent and educate about low K diet
E. Refer to a nephrologist due to fall in GFR

PILLARS OF THERAPY TO REDUCE NEPHROPATHY PROGRESSION AND REDUCE CV RISK



Naaman S and Bakris GL. *Diabetes Care* 2023;46:1574-1586.

Module 4: Patients Case #2

Rajiv Agarwal, MD, MS
Emeritus Professor of Medicine
Indiana University School of Medicine and VA Medical Center
Indianapolis, Indiana

Key questions to be addressed today:

How do we identify patients with CKD and T2D?

How has the treatment landscape for CKD in T2D changed over recent years?

What are the latest guidelines for the treatment of CKD in T2D?

What is the finerenone phase III clinical trial programme?

What is the clinical impact of finerenone for patients with CKD and T2D?

How do we identify patients with CKD and T2D?

How has the treatment landscape for CKD in T2D changed over recent years?

What are the latest guidelines for the treatment of CKD in T2D?

What is the finerenone phase III clinical trial programme?

What is the clinical impact of finerenone for patients with CKD and T2D?

Meet Ann* – a 63-year-old woman with T2D

Ann's **HbA1c and blood pressure are relatively well controlled** but her physician is **concerned about her kidney health**

"Aside from the usual ailments, I feel good and I hope to stay like this for many years to come"

- 63 years old
- Diagnosed with T2D 8 years ago

- HbA1c 7.4%
  - Metformin
  - DPP-4 inhibitor

- Office blood pressure 137/88 mmHg
  - Calcium channel blocker
  - Hydrochlorothiazide

*Fictitious case study

DPP-4, dipeptidyl peptidase-4; HbA1c, glycated haemoglobin

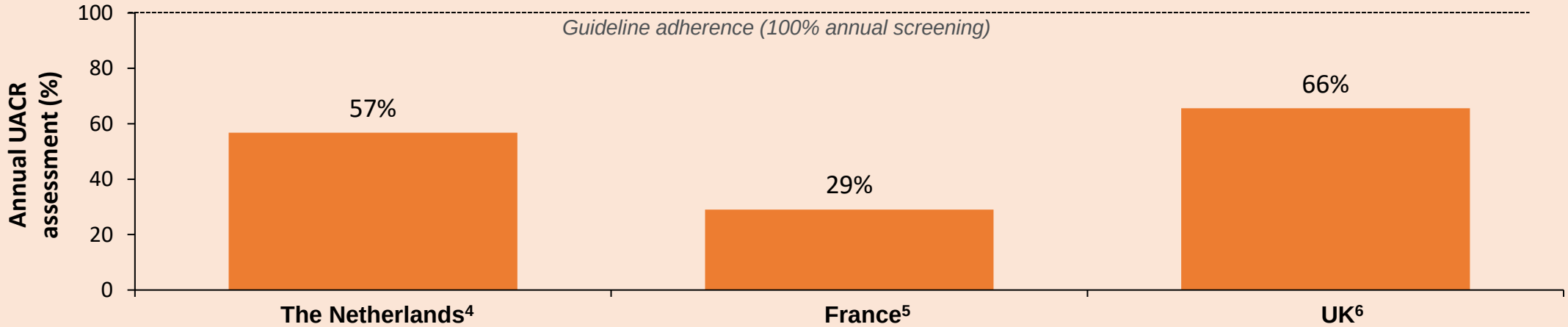
Early CKD in T2D is asymptomatic; therefore, annual UACR and eGFR screening are recommended

CKD screening guidelines

International guidelines (including the ADA 2022 updated guidelines) recommend screening in patients with CKD and/or T2D[1–3]

It is recommended that **both UACR and eGFR** is assessed **at least once a year** in all patients with T2D[1,2] and/or CKD[3]

Global UACR screening rates are suboptimal



ADA, American Diabetes Association; eGFR, estimated glomerular filtration rate; KDIGO, Kidney Disease: Improving Global Outcomes; UACR, urine albumin-to-creatinine ratio

1. American Diabetes Association. *Diabetes Care* 2022;45(Suppl 1):S175–S184; 2. Cosentino F, *et al*. *Eur Heart J* 2020;41:255–323; 3. Kidney Disease: Improving Global Outcomes (KDIGO) *Kidney Int* 2013;3:1–150; 4. Hellemons ME, *et al. Nephrol Dial Transplant* 2013;28:706–715; 5. Assogba GF, *et al. Diabetes Metab* 2012;38:558–566; 6. NHS Diabetes Audit. 2017–2018 Full Report 1: [Link]. Accessed 3 March 2022

Animated

Ann is screened for decreased eGFR and elevated UACR, and is diagnosed with CKD associated with T2D

CKD is classified based on eGFR and UACR levels. Risk of CKD progression increases with decreasing eGFR and increasing UACR

GFR stages description and range (ml/min/1.73 m²)			Albuminuria categories Description and range (UACR)		
			A1 Normal–mildly increased	**A2** Moderately increased	**A3** Severely increased
			<30 mg/g (<3 mg/mmol)	**30–300 mg/g** (3–30 mg/mmol)	**>300 mg/g** (>30 mg/mmol)
	G1 Normal or high	**≥90**			
	G2 Mild	**60–89**			
	G3a Mild–moderate	**45–59**			
	G3b Moderate–severe	**30–44**			
	G4 Severe	**15–29**			
	G5 Kidney failure	**<15**			

Ann's latest laboratory results show she has decreased eGFR and elevated UACR levels

eGFR: 65 ml/min/1.73 m²

UACR: 310 mg/g

Ann is at high risk of CKD progression and very high risk of CV death

CV, cardiovascular; GFR, glomerular filtration rate

How do we identify patients with CKD and T2D?

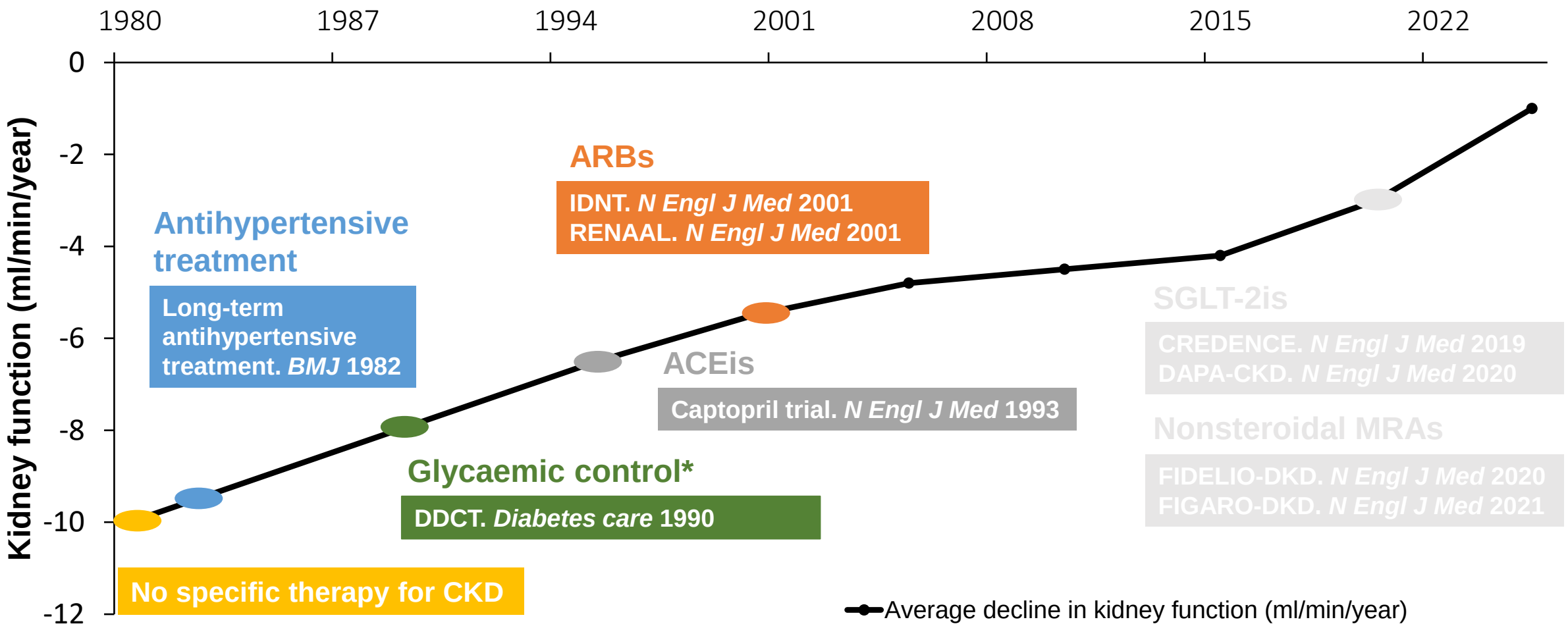
How has the treatment landscape for CKD in T2D changed over recent years?

What are the latest guidelines for the treatment of CKD in T2D?

What is the finerenone phase III clinical trial programme?

What is the clinical impact of finerenone for patients with CKD and T2D?

Therapies to slow CKD progression associated with T2D have evolved over the past 40 years



*Microvascular complications

ACEi, angiotensin-converting enzyme inhibitor; ARB, angiotensin receptor blocker; MRA, mineralocorticoid receptor antagonist; SGLT-2i, sodium-glucose co-transporter-2 inhibitor

Adapted from Naaman SC & Bakris GL. *American Diabetes Association* 2021;28–32

Animated

Over recent years, kidney outcome trials have expanded to include patients across the spectrum of CKD severity

GFR categories description and range (ml/min/1.73 m²)			Albuminuria categories Description and range (mg albumin/g creatinine)[1]			
			A1 Optimal and high–normal	A2 High	A3 Very high and nephrotic	
			0–29	30–299	300–3499	≥3500
	G1	>90				
	G2	60–89				
	G3a	45–59				
	G3b	30–44				
	G4	15–29				
	G5	<15				

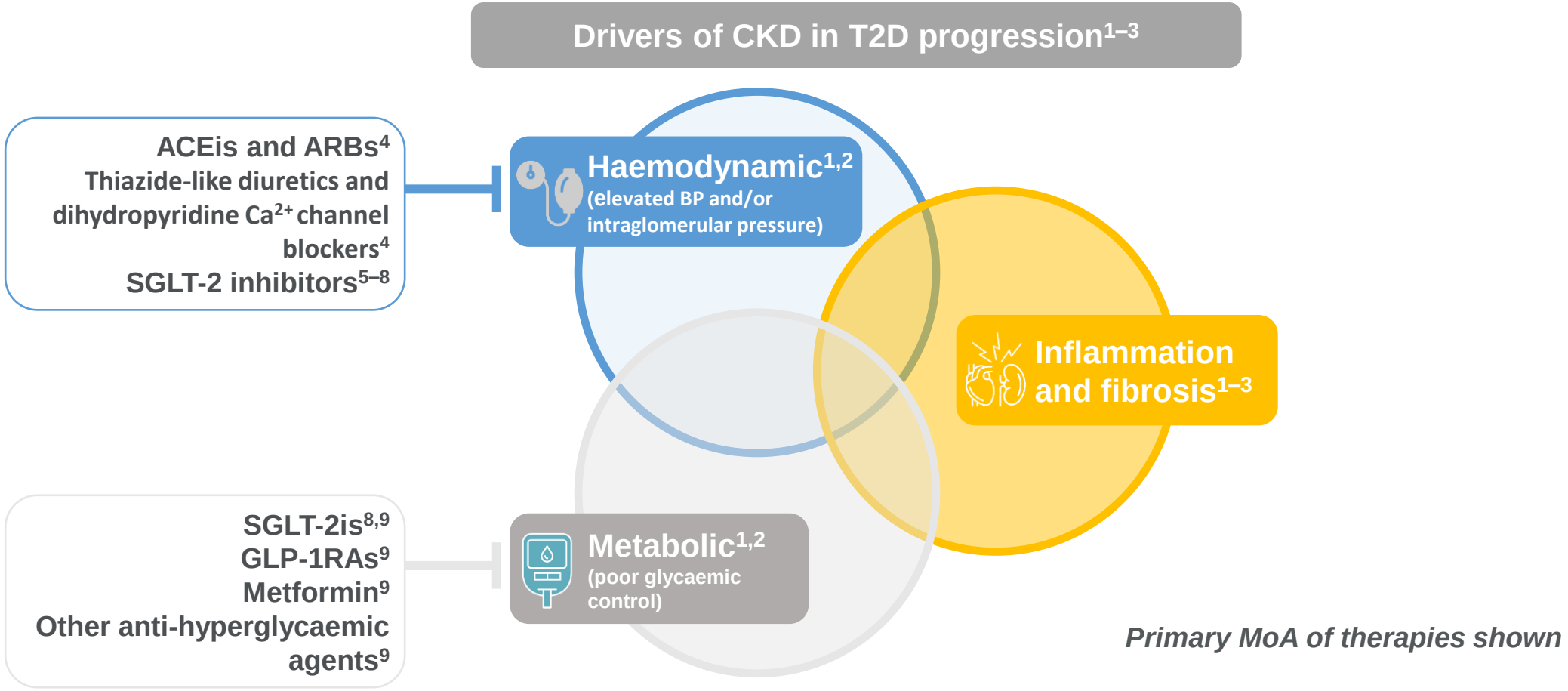
CREDENCE[2]
Canagliflozin (2019)

DAPA-CKD[3–5]
Dapagliflozin (2020)

FIDELITY[6]
Finerenone (2021)

1. Kidney Disease: Improving Global Outcomes. Clinical practice guideline on diabetes management in chronic kidney disease. October 2020. https://kdigo.org/guidelines/diabetes-ckd/ [accessed 2 Feb 2022]; 2. Perkovic V, *et al*. *N Engl J Med* 2019;380:2295–2306; 3. Wheeler DC, *et al*. *Nephrol Dial Transplant* 2020;35:1700–1711; 4. Heerspink HJL, *et al*. *Nephrol Dial Transplant* 2020;35:274–282; 5. Heerspink HJL, *et al*. *N Engl J Med* 2020;383:1436–1446; 6. Agarwal R, *et al*. *Eur Heart J* 2021; doi:10.1093/eurheartj/ehab777

Current therapies for patients with CKD and T2D primarily target haemodynamic and metabolic drivers of CKD



BP, blood pressure; GLP-1RA, glucagon-like peptide-1 receptor agonist; HbA1c, glycated haemoglobin; MoA, mechanism of action

1. Alicic RZ, *et al*. *Clin J Am Soc Nephrol* 2017;12:2032–2045; 2. Mora-Fernández C, *et al*. *J Physiol* 2014;18:3997; 3. Bauersachs J, *et al*. *Hypertension* 2015;65:257–263; 4. American Diabetes Association. *Diabetes Care* 2022;45(Suppl 1):S175–S184; 5. Kidokoro K, *et al*. *Circulation* 2019:140;303–315; 6. Zelniker TA & Braunwald E. *J Am Coll Cardiol* 2018;72:1845–1855; 7. Heerspink HJ, *et al. Circulation* 2016;134:752–772; 8. Zelniker TA & Braunwald E. *J Am Coll Cardiol* 2020;75:422–4349. American Diabetes Association. *Diabetes Care* 2020;43:S98–S110

How do we identify patients with CKD and T2D?

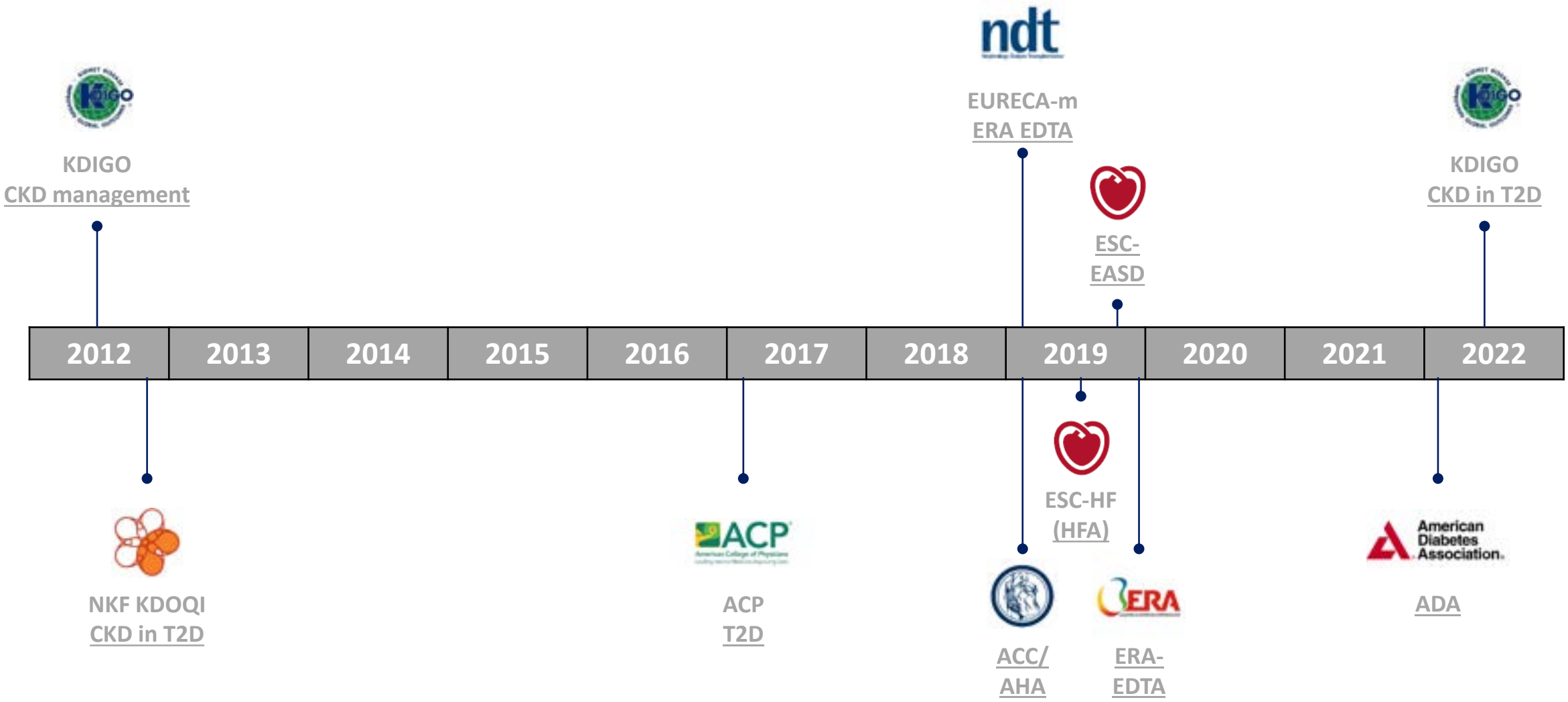
How has the treatment landscape for CKD in T2D changed over recent years?

What are the latest guidelines for the treatment of CKD in T2D?

What is the finerenone phase III clinical trial programme?

What is the clinical impact of finerenone for patients with CKD and T2D?

Treatment guidelines for CKD in T2D have evolved over the past 10 years



ACC, American College of Cardiology; ACP, American College of Physicians; ADA, American Diabetes Association; AHA, American Heart Association; EASD, European Association for the Study of Diabetes; EDTA, European Dialysis and Transplant Association; ERA, European Renal Association; ESC, European Society of Cardiology; EURECA-m, European Renal and Cardiovascular Medicine; HFA, Heart Failure Association; KDIGO, Kidney Disease: Improving Global Outcomes; NKF, KDOQI, Kidney Disease Outcomes Quality Initiative; National Kidney Foundation

Finerenone is recommended to reduce CKD progression and CV events in patients with CKD and T2D

	ESC/EASD 2019[1]	KDIGO 2020[2]	ADA 2022[3]
ACEi/ ARB	Strongly recommended for the treatment of hypertension in patients with T2D and CKD, particularly in the presence of proteinuria, microalbuminuria or LVH	Recommended in patients with diabetes, hypertension and albuminuria and these medications should be titrated to the highest approved dose that is tolerated	Strongly recommended in patients with hypertension and UACR ≥300 mg/g and/or eGFR <60 ml/min/1.73 m^2 Recommended in patients with hypertension and UACR 30–299 mg/g
SGLT-2i	Recommended in patients with T2D, CKD and eGFR 30–<90 ml/min/1.73 m^2	Recommended in combination with metformin in patients with T2D, CKD and an eGFR ≥30 ml/min/1.73 m^2	Recommended for patients with an eGFR ≥25 ml/min/1.73 m^2 and UACR ≥300 mg/g to reduce risk of CKD progression and CV events
GLP-1RA	Should be considered for treatment of T2D and CKD if eGFR is >30 ml/min/1.73 m^2	A long-acting GLP-1RA is recommended in patients with T2D and CKD who have not achieved individual glycaemic targets despite use of metformin/SGLT-2i or are unable to use those therapies	May reduce risk of progression of albuminuria, CV events or both in patients with **CKD and increased CV risk**
nsMRA	–	–	Recommended for patients with CKD who are at **increased risk for CV events or CKD progression OR are unable to tolerate use of an SGLT-2i**

LVH, left ventricular hypertrophy; nsMRA, nonsteroidal mineralocorticoid receptor antagonist

1. Cosentino F, *et al*. *Eur Heart J* 2020;41:255–323; 2. Kidney Disease: Improving Global Outcomes (KDIGO). *Kidney Int* 2020;98(4S):S1–S115;
3. American Diabetes Association. *Diabetes Care* 2022;45(Suppl 1):S175–S184

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Animated

Two years after her diagnosis of CKD and T2D, Ann's laboratory results show worsening eGFR and UACR levels

Ann is now at very high risk of CKD progression and CV death

eGFR: 53 ml/min/1.73 m^2

UACR: 590 mg/g

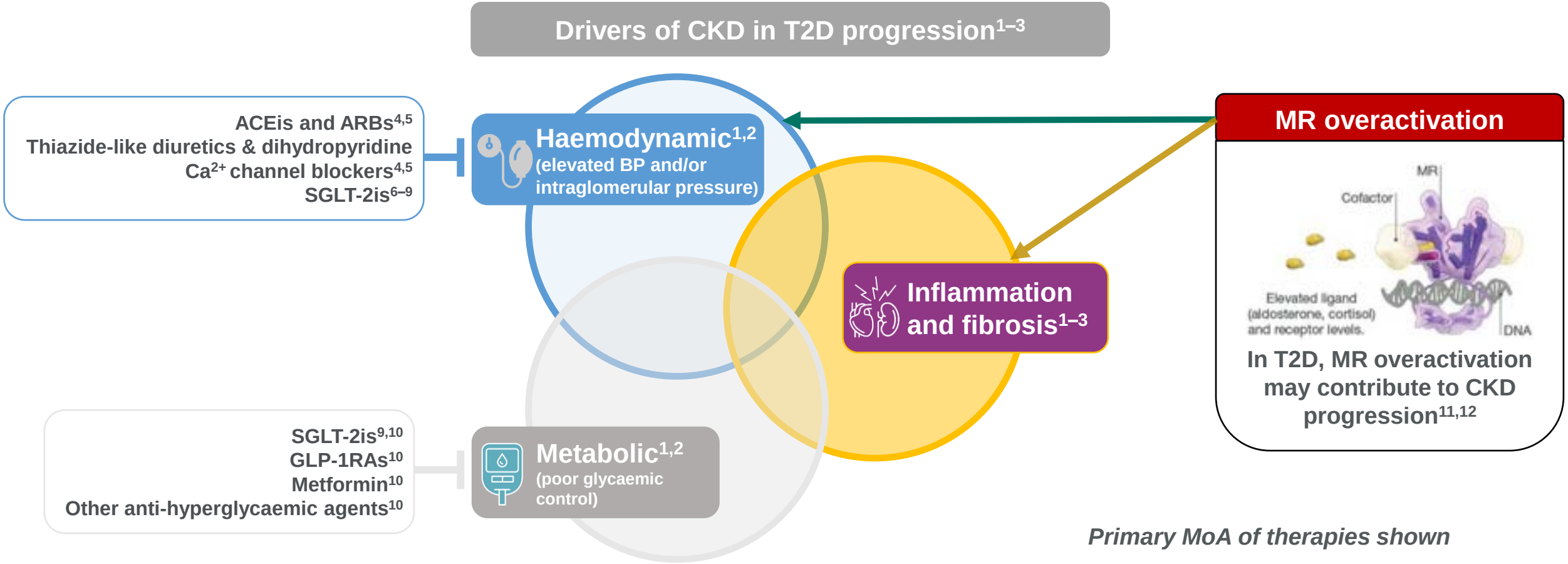
Patients with CKD and T2D have a **6×** higher risk of dying from CV complications*

GFR stages description and range (ml/min/1.73 m^2)			Albuminuria categories Description and range (urine albumin-to-creatinine ratio)		
			A1 Normal–mildly increased	**A2** Moderately increased	**A3** Severely increased
			<30 mg/g **(<3 mg/mmol)**	**30–300 mg/g** **(3–30 mg/mmol)**	**>300 mg/g** **(>30 mg/mmol)**
	G1 Normal or high	**≥90**			
	G2 Mild	**60–89**			
	G3a Mild–moderate	**45–59**			
	G3b Moderate–severe	**30–44**			
	G4 Severe	**15–29**			
	G5 Kidney failure	**<15**			

*Compared with people without CKD or T2D (based on 19.6% vs 3.4% standardised 10-year cumulative incidence of CV mortality, respectively)
Afkarian M, *et al. J Am Soc Nephrol* 2013;24:302–308

What are the treatment targets for this patient?

Current therapies for patients with CKD and T2D primarily target haemodynamic and metabolic drivers of CKD



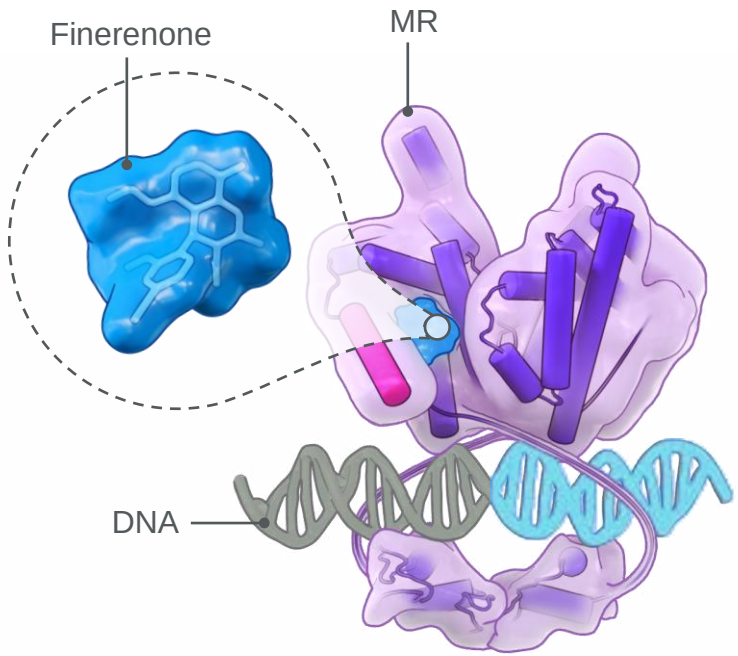
Primary MoA of therapies shown

MoA, mechanism of action; MR, mineralocorticoid receptor

1. Alicic RZ, *et al*. *Clin J Am Soc Nephrol* 2017;12:2032–2045; 2. Mora-Fernández C, *et al*. *J Physiol* 2014;18:3997; 3. Bauersachs J, *et al*. *Hypertension* 2015;65:257–263;
4. American Diabetes Association. *Diabetes Care* 2020;43:S135–S151; 5. American Diabetes Association. *Diabetes Care* 2020;43:S111–S1340; 6. Kidokoro K, *et al*. *Circulation* 2019:140;303–315;
7. Zelniker TA & Braunwald E. *J Am Coll Cardiol* 2018;72:1845–1855; 8. Heerspink HJ, *et al. Circulation* 2016;134:752–772; 9. Zelniker TA & Braunwald E. *J Am Coll Cardiol* 2020;75:422–434;
10. American Diabetes Association. *Diabetes Care* 2020;43:S98–S110. 11. Agarwal R, *et al. Eur Heart J* 2021;42:152–162; 12. Agarwal R, *et al. Nephrol Dial Transplant* 2020; doi: 10.1093/ndt/gfaa294

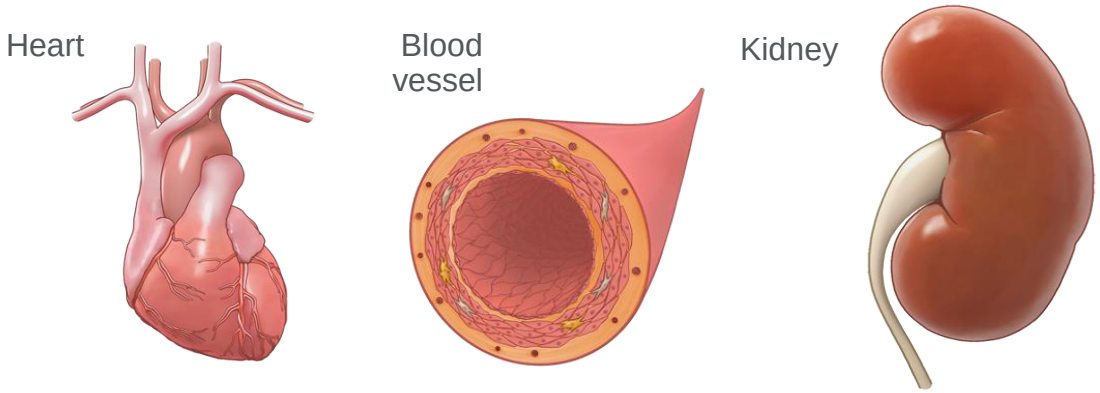
Finerenone primarily targets and blocks MR overactivation, which may slow CKD progression in patients with T2D

Finerenone is a novel, selective, **nonsteroidal MRA** that is different from available steroidal MRAs[1–3]



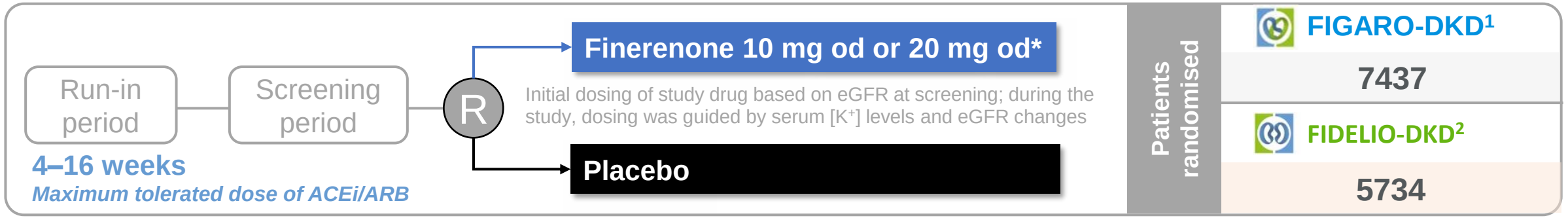
Finerenone **blocks MR overactivation and its downstream effects[4,5] to provide**

Kidney and heart protection in people with CKD and T2D[6,7]



1. Bärfacker L, *et al. ChemMedChem* 2012;7:1385–1403; 2. Pitt B, *et al. Eur J Heart Fail* 2012;14:668–675; 3. Kolkhof P, *et al. J Cardiovasc Pharmacol* 2014;64:69–78;
4. Agarwal R, *et al. Eur Heart J* 2021;42:152–162; 5. Agarwal R, *et al. Nephrol Dial Transplant* 2020; doi: 10.1093/ndt/gfaa294;
6. Bakris GL, *et al. Am J Nephrol* 2019;50:333–344; 7. Pitt B, *et al. N Engl J Med* 2021; 385:2252–2263

FIGARO-DKD and FIDELIO-DKD investigated finerenone in over 13,000 patients with CKD and T2D[1,2]



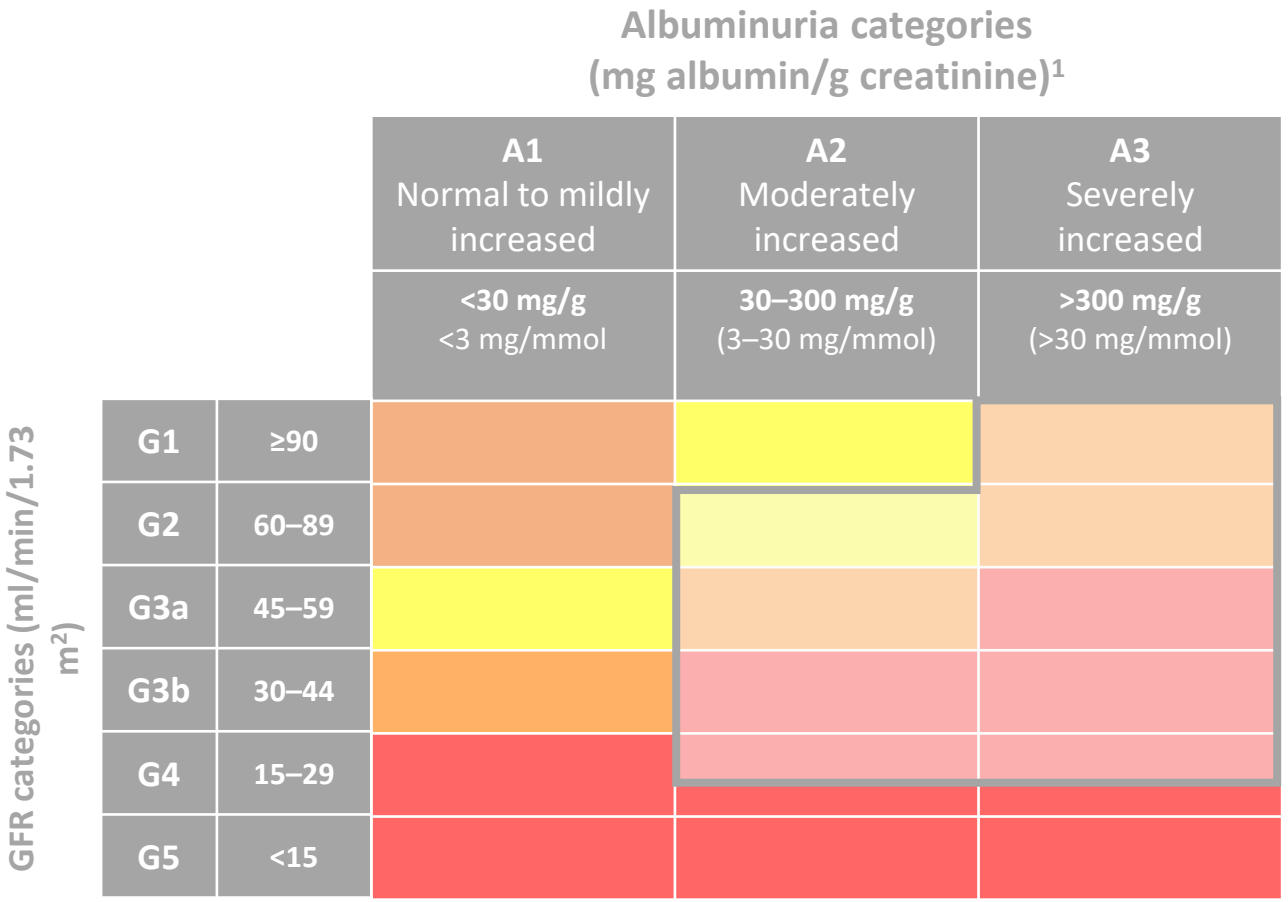
	FIGARO-DKD[1]	FIDELIO-DKD[2]	FIDELITY[3] Prespecified pooled analysis
Clinical efficacy primary endpoint	**Composite endpoint:** Time to CV death, non-fatal MI, non-fatal stroke, or hospitalisation for HF	**Composite endpoint:** Time to kidney failure,# sustained ≥40% eGFR decline, or renal death	**Key outcomes** **CV composite:** Time to CV death, non-fatal MI, non-fatal stroke, or hospitalisation for HF
Key secondary endpoint	Same as primary endpoint in **FIDELIO-DKD**	Same as primary endpoint in **FIGARO-DKD**	**57% kidney composite:** Time to kidney failure,# sustained ≥57% eGFR decline, or renal death

*Patients received an initial dose of finerenone of 10 mg od or 20 od based on an eGFR at the screening visit of 25–<60 or ≥60 ml/min/1.73 m^2, respectively.[1,2] Up-titration to finerenone 20 mg od was permitted at any time after visit 2 (month 1); down-titration to finerenone 10 mg od was permitted at any time after start of treatment. Dose titrations were initiated in response to changes in potassium and eGFR[1,2; #]kidney failure defined as initiation of chronic dialysis for ≥90 days or kidney transplantation or sustained eGFR <15 ml/min/1.73 m^2.[2,3]

[K+], potassium concentration; MI, myocardial infarction; od, once daily

1. Ruilope LM, *et al. Am J Nephrol* 2019;50:345–356; 2. Bakris GL, *et al. Am J Nephrol* 2019;50:333–344; 3. Agarwal R, et al. *Eur Heart J* 2022;43:474–484

The finerenone phase III programme included patients across the spectrum of CKD severity



Ann is representative of the population included in the finerenone phase III programme

FIDELITY (N=13,171)[2]
Prespecified pooled analysis

1. Kidney Disease: Improving Global Outcomes (KDIGO). *Kidney Int* 2020;98:S1–S115; 2. Agarwal R, *et al. Eur Heart J* 2021; doi: 10.1093/eurheartj/ehab777

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Impact of Finerenone—five facts, in T2D

- Start if K<5
- Keep going till K at most 5.5
- Use if eGFR >25 (5 x 5)
- Expect a 5th reduction in dialysis
- and more than a 5th reduction in HHF