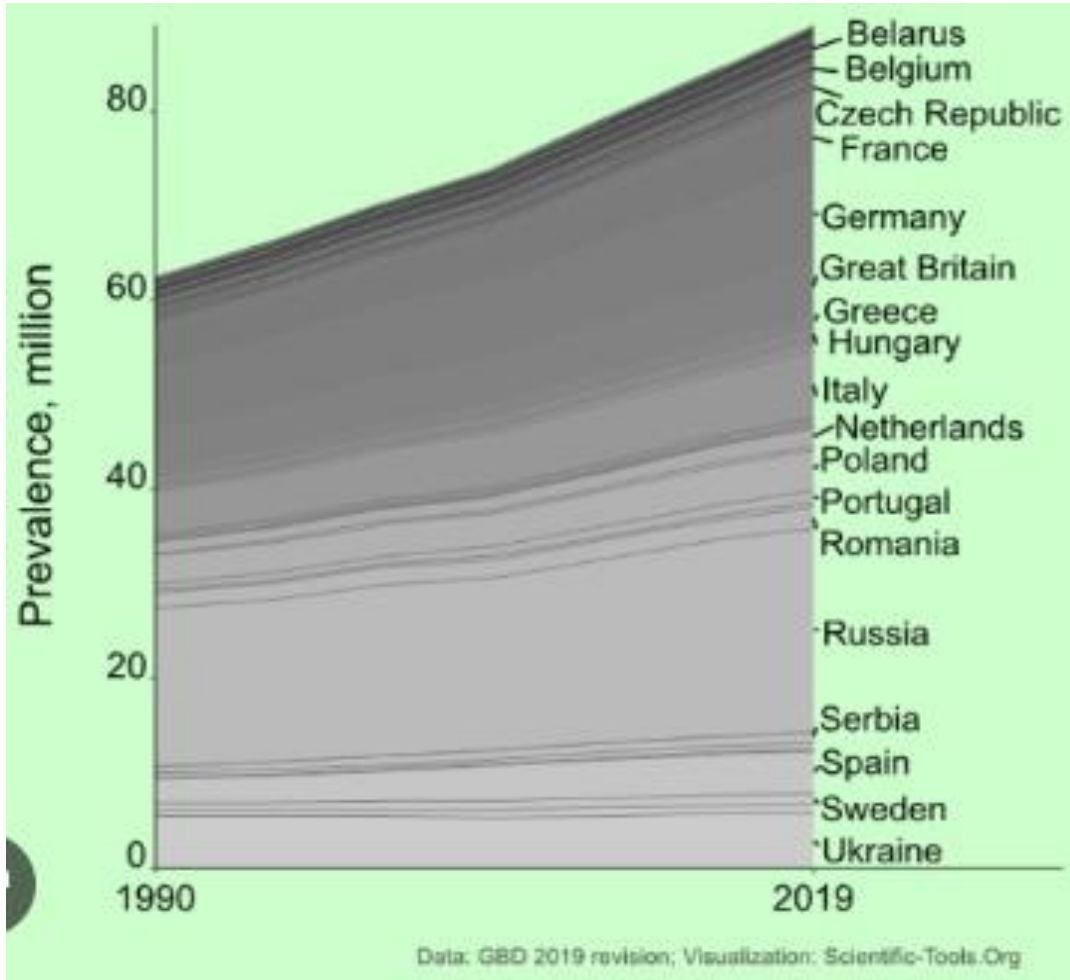
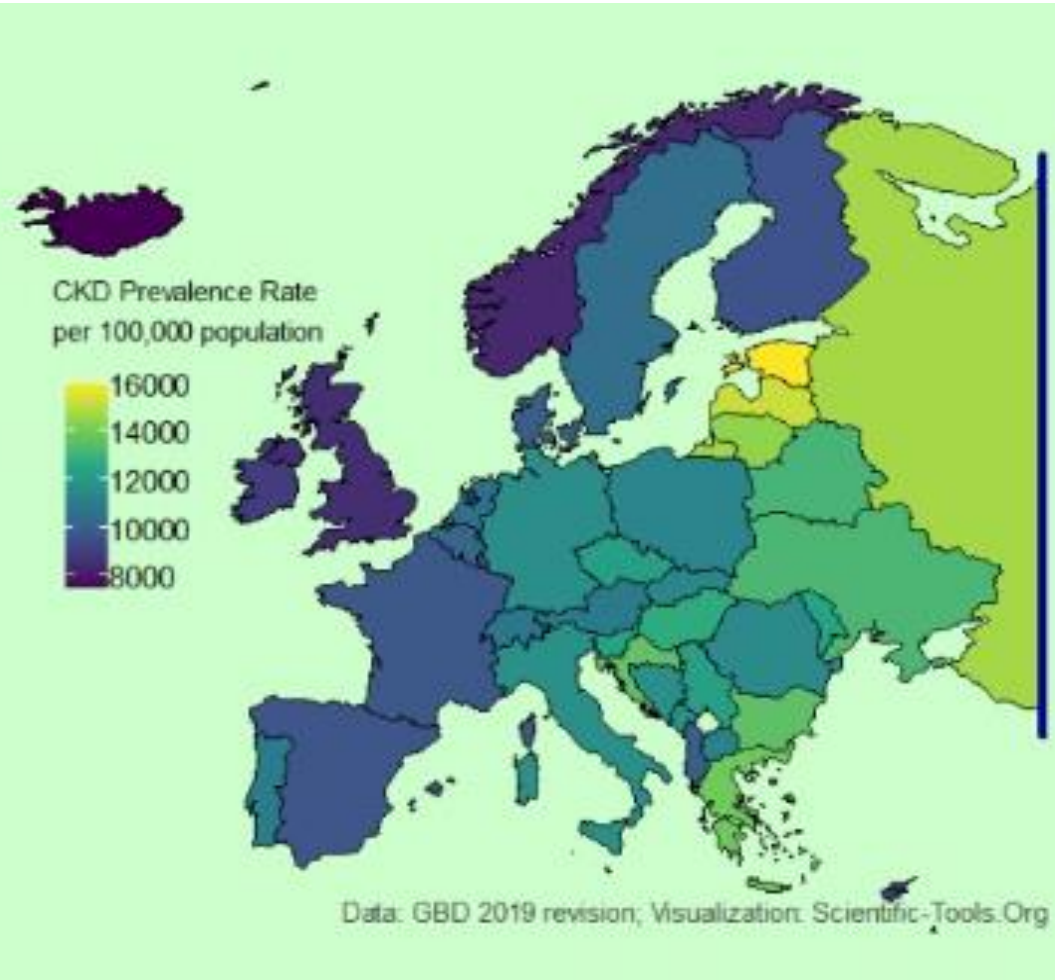
# Addressing CardioRenal Risk in Diabetes It's More Than the Sugar Control

**Myftar Barbullushi**

**FERA of Nephrology**

# Global, regional, and national burden of diabetes from 1990 to 2021, with projections of prevalence to 2050



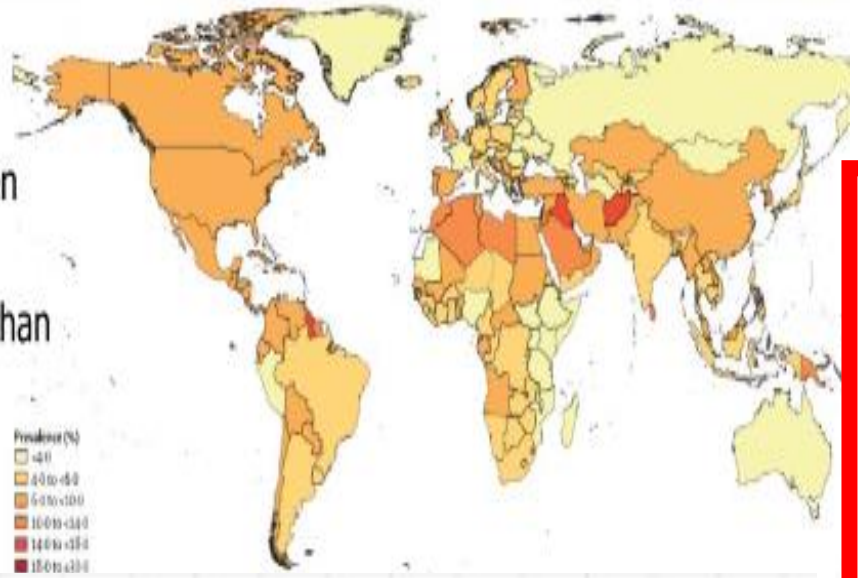



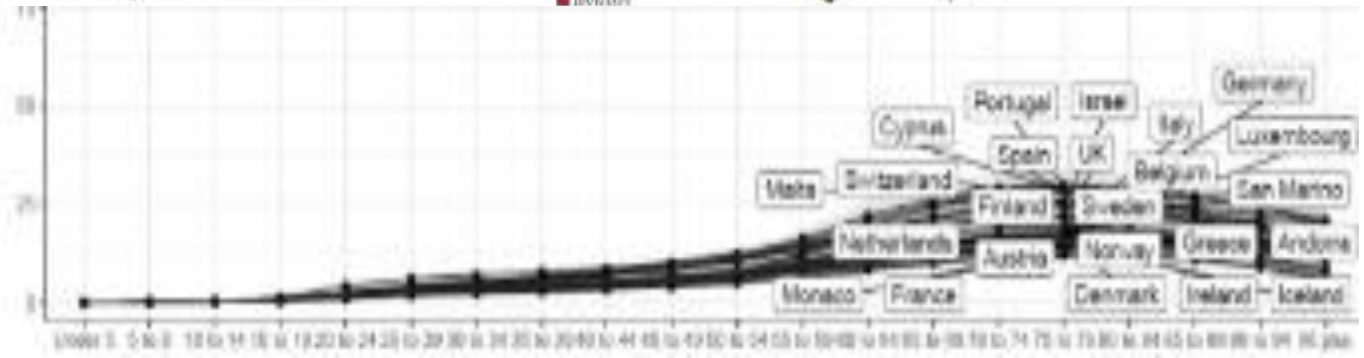
# Global, regional, and national burden of diabetes from 1990 to 2021, with projections of prevalence to 2050

THE LANCET
Volume 402, ISSUE 10397,
p. 203-234, July 15, 2023

Global, regional, and national burden of diabetes from 1990 to 2021, with projections of prevalence to 2050: a systematic analysis for the Global Burden of Disease Study 2021

"More than half a billion people are living with diabetes worldwide, affecting men, women, and children of all ages in every country, and that number is projected to more than double to 1.3 billion people in the next 30 years, with every country seeing an increase."






**CVD and CKD remain the leading cause of morbidity and mortality among persons with diabetes.**

**Coronary heart disease**

Prevalence: 14–21%[5,16]

Most frequently reported form of CVD and most lethal one.[5]
Risk of death from CHD is higher in women then in men (HR, 95% CI: 1.81 [1.27–2.59] versus 1.48[1.10–1.99]).[5]

**Heart failure**

Prevalence: 19–26%[23]

Second most common initial manifestation of CVD in T2DM.[16]
Risk of HF is up to 2-fold in men and 5-fold in women.[22]

**Peripheral artery disease**

Prevalence: 16–29%[15,16]

Most common initial manifestation of CVD in T2DM.[16]
Prevalence is 1.8-fold higher in women compared to men.[16]

**Stroke**

Prevalence: 8–12%[2,10]

Second more frequent cause of death in patients with T2DM after CHD[10]
Prevalence is similar in men and women.[21]

**Retinopathy**

Prevalence: 34%[29]
Most common microvascular complication of diabetes;[29] responsible of 2.6% of all cases of blindness worldwide.[30]
Prevalence rates are higher in TIDM compared to T2DM (77.3 vs. 25.2%).[31]

**Neuropathy**

Cardiac autonomic neuropathy

Prevalence: 31–73% in people with T2DM[32]
No difference in prevalence between men and women.[32]

**Nephropathy**

Prevalence: 29–61%[28]
Leading cause of end stage renal disease in the adult population worldwide.[2]
Female sex is a risk factor for nephropathy in T2DM.[28]

# 30 to 40%

**of these patients will develop CKD**

**850 MILLION**
PEOPLE
**WORLDWIDE**
are now estimated to have some form of kidney disease[3].



***Centers for Disease Control and Prevention Accessed September 2022***

## Attempt to Better Define Why Diabetics Die Younger

**they examined 10-year mortality by diabetes and kidney-disease status for 15046 partecipiant.**

JASN Journal of the American Society of Nephrology

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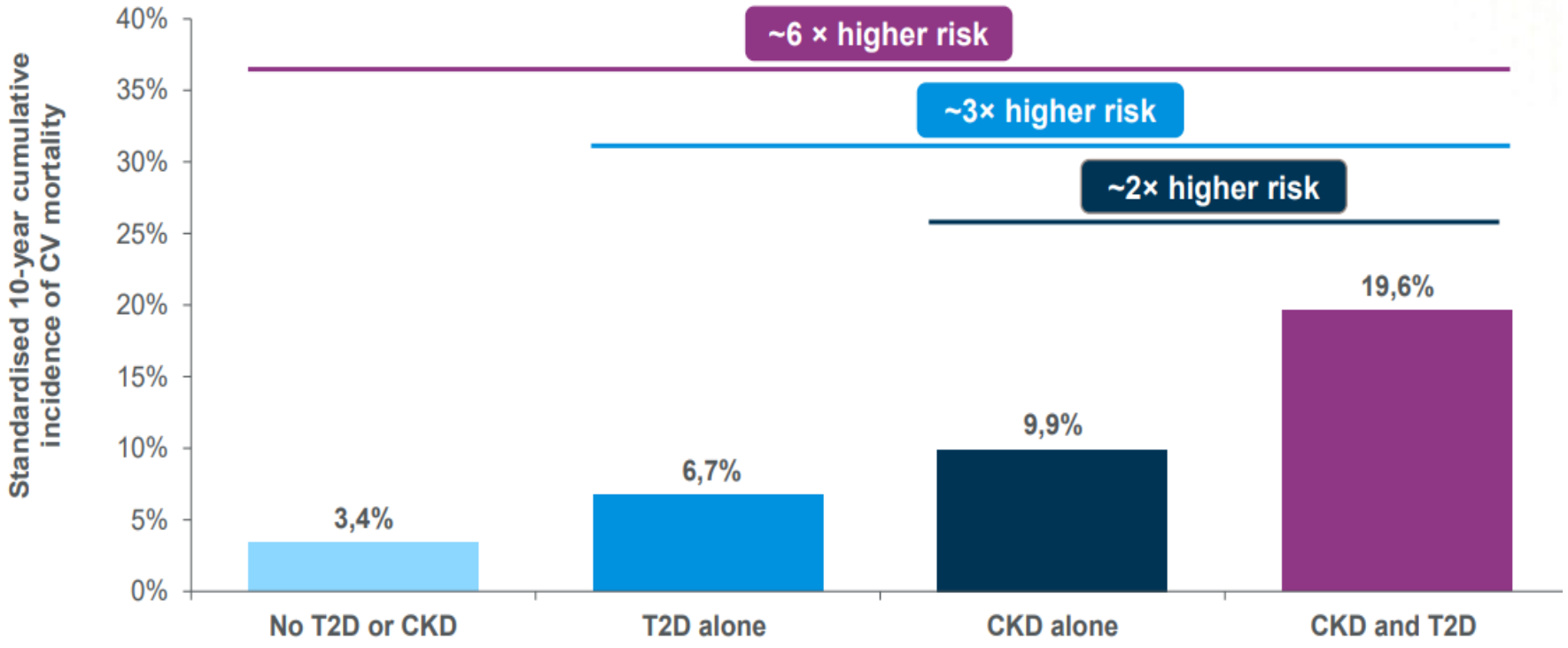
### Kidney Disease and Increased Mortality Risk in Type 2 Diabetes

Maryam Afkarian, Michael C. Sachs, Bryan Kestenbaum, Irl B. Hirsch, Katherine R. Tuttle, Jonathan Himmelfarb and Ian H. de Boer

JASN February 2013, 24 (2) 302-308; DOI: https://doi.org/10.1681/ASN.2012070718

## Compared with T2D alone, comorbid CKD significantly increases CV mortality

### Standardised 10-year cumulative incidence of CV mortality by diabetes and kidney disease status




- Presence of **Kidney Disease in Diabetes,** increase **CV Mortality** by more than **6 times confirming that** Diabetes with **CKD is a CVD Risk accelerator**

## Attempt to Better Define Why Diabetics Die Younger

**they examined 10-year mortality by diabetes and kidney-disease status for 15046 partecipiant.**

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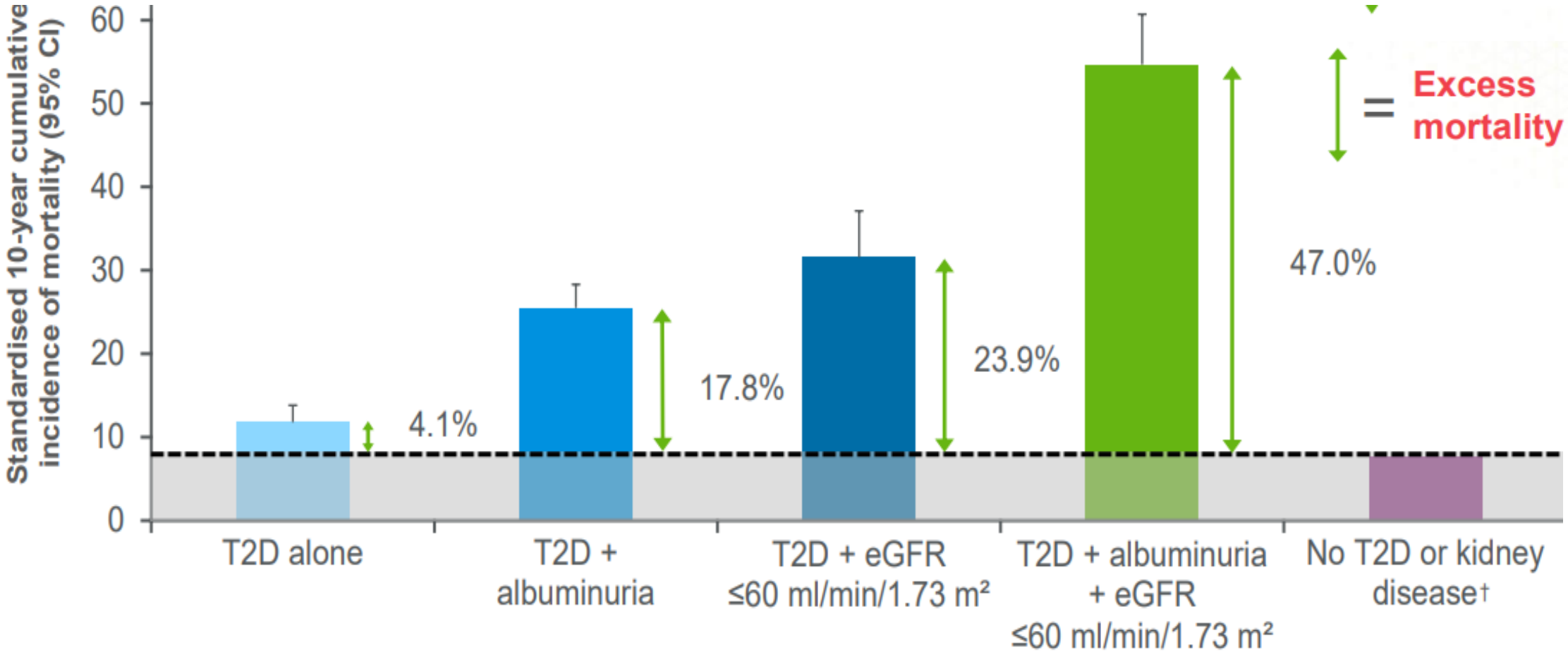


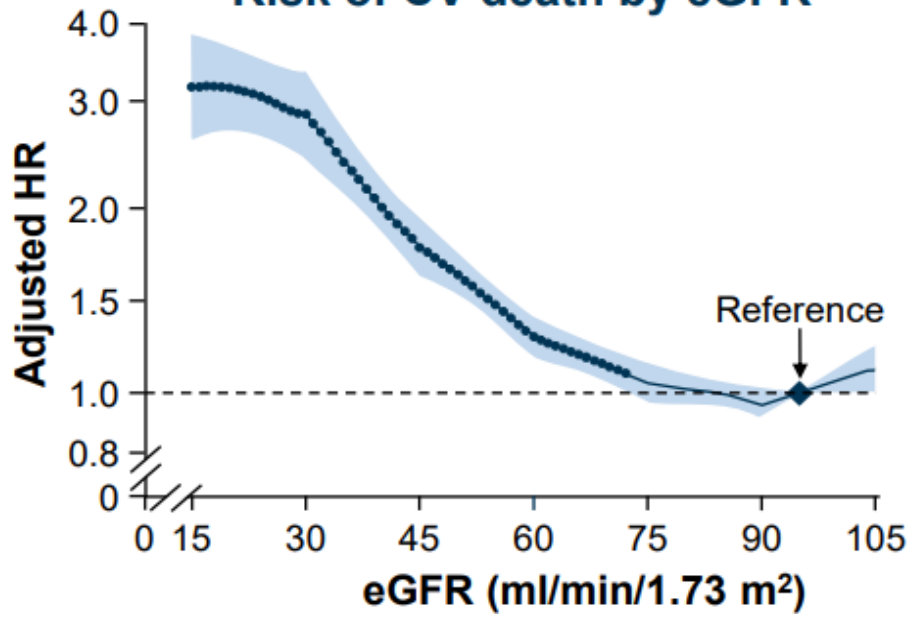
# CV risk in patients with CKD and T2D increases as eGFR falls and as UACR rises

**CKD = eGFR <60 ml/min/1.73 m²** for >3 months[1]

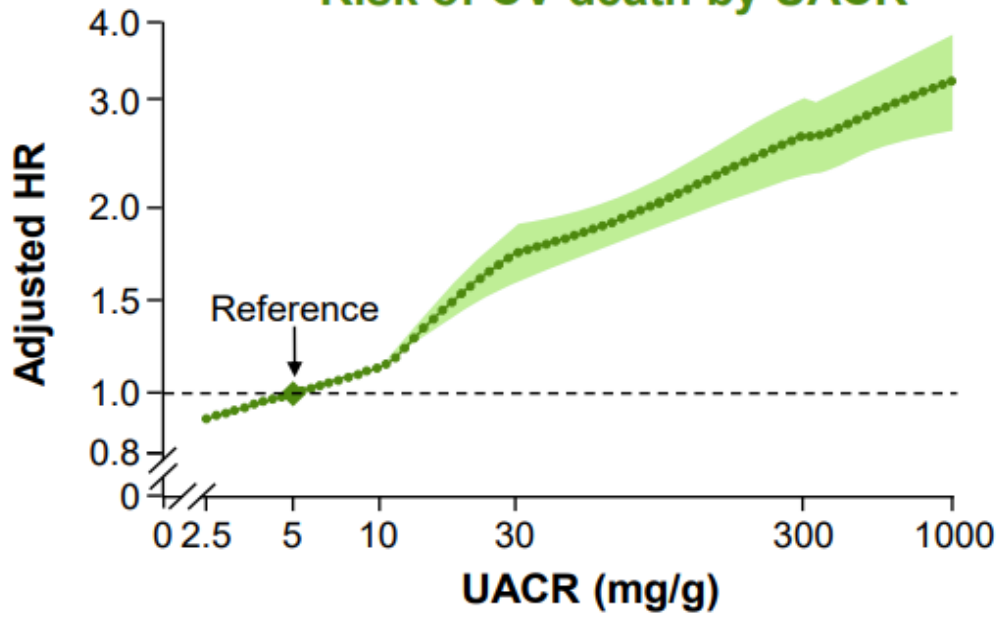
and
OR

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

## Risk of CV death by eGFR[2]




## Risk of CV death by UACR[2]

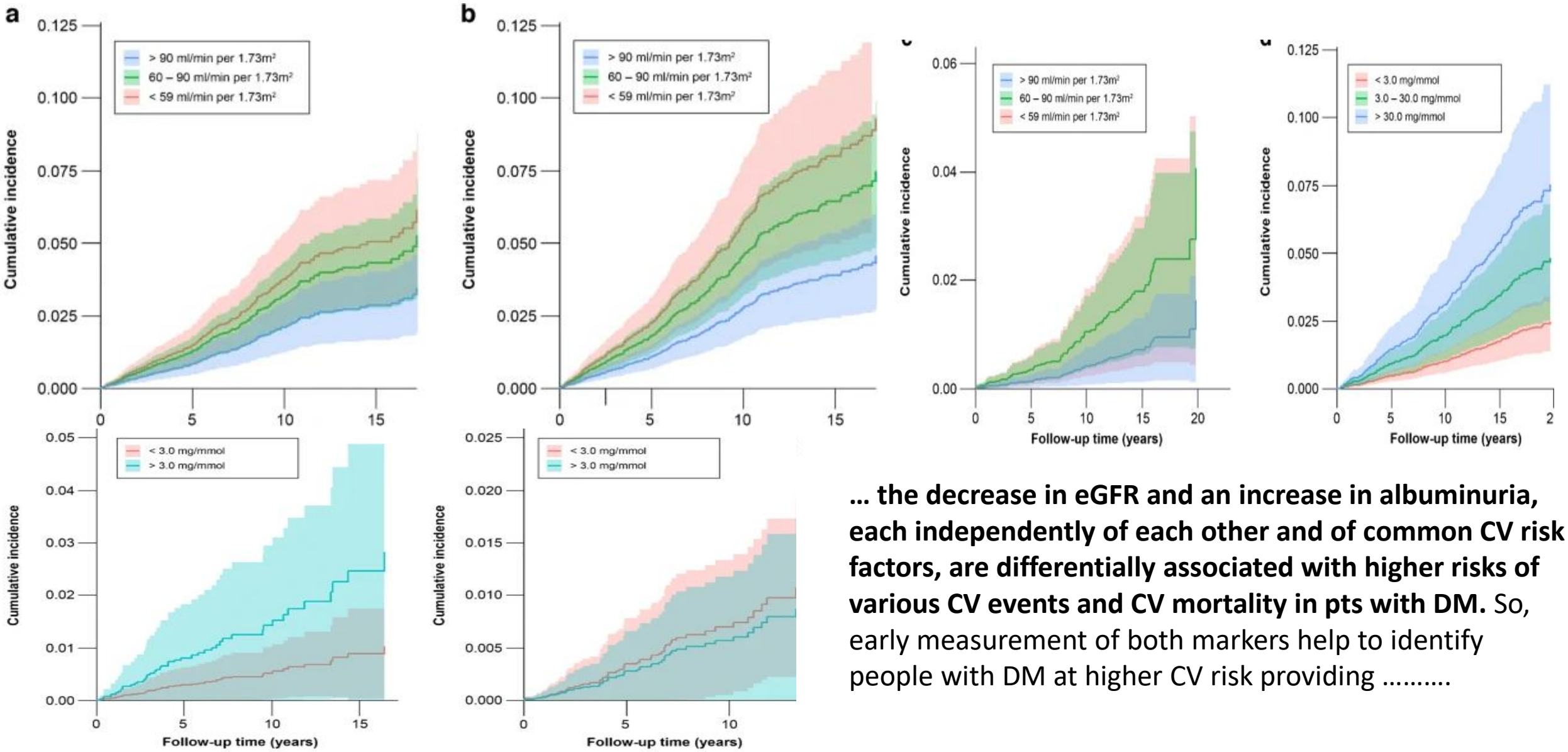



CKD, Chronic kidney disease; CV, Cardiovascular; eGFR, estimated glomerular filtration rate; HR, Hazard ratio; T2D, Type 2 diabetes; UACR, Urine albumin-to-creatinine ratio

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

# Kidney Function and CV Outcome in People With DM: The Hoorn Diabetes Care System Cohort *Diabetology 2022*

**13.657 adults with DM; Annually repeated kidney function measures. eGFR + Albuminuria**



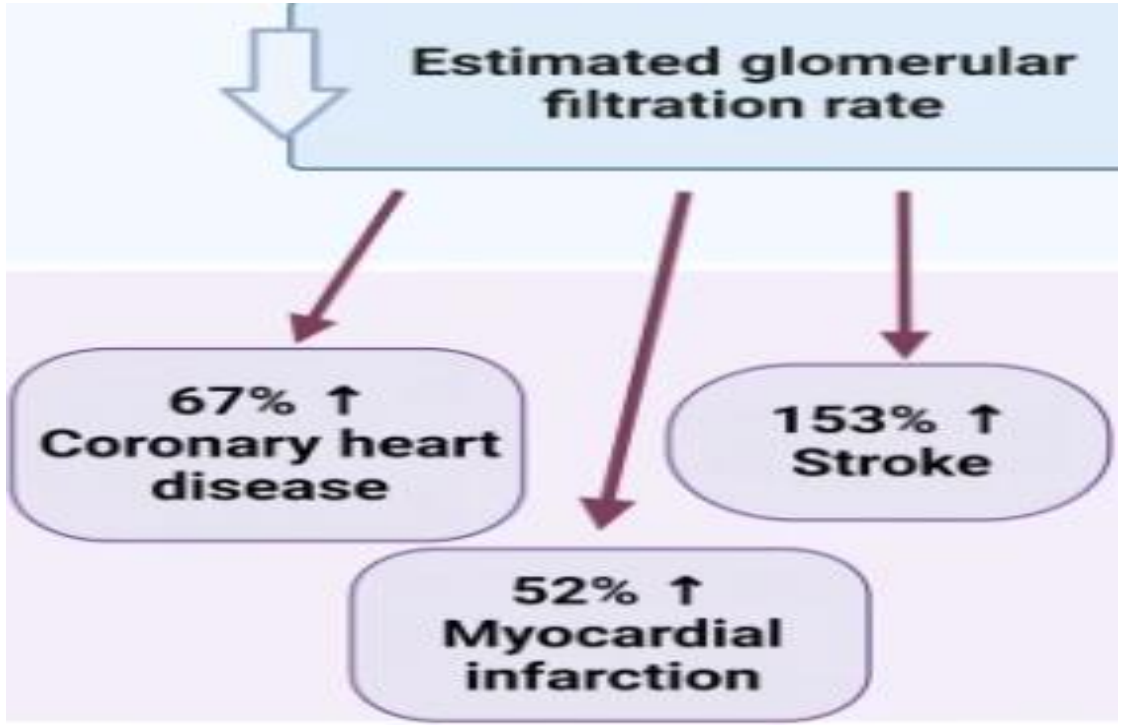

**… the decrease in eGFR and an increase in albuminuria, each independently of each other and of common CV risk factors, are differentially associated with higher risks of various CV events and CV mortality in pts with DM.** So, early measurement of both markers help to identify people with DM at higher CV risk providing …….

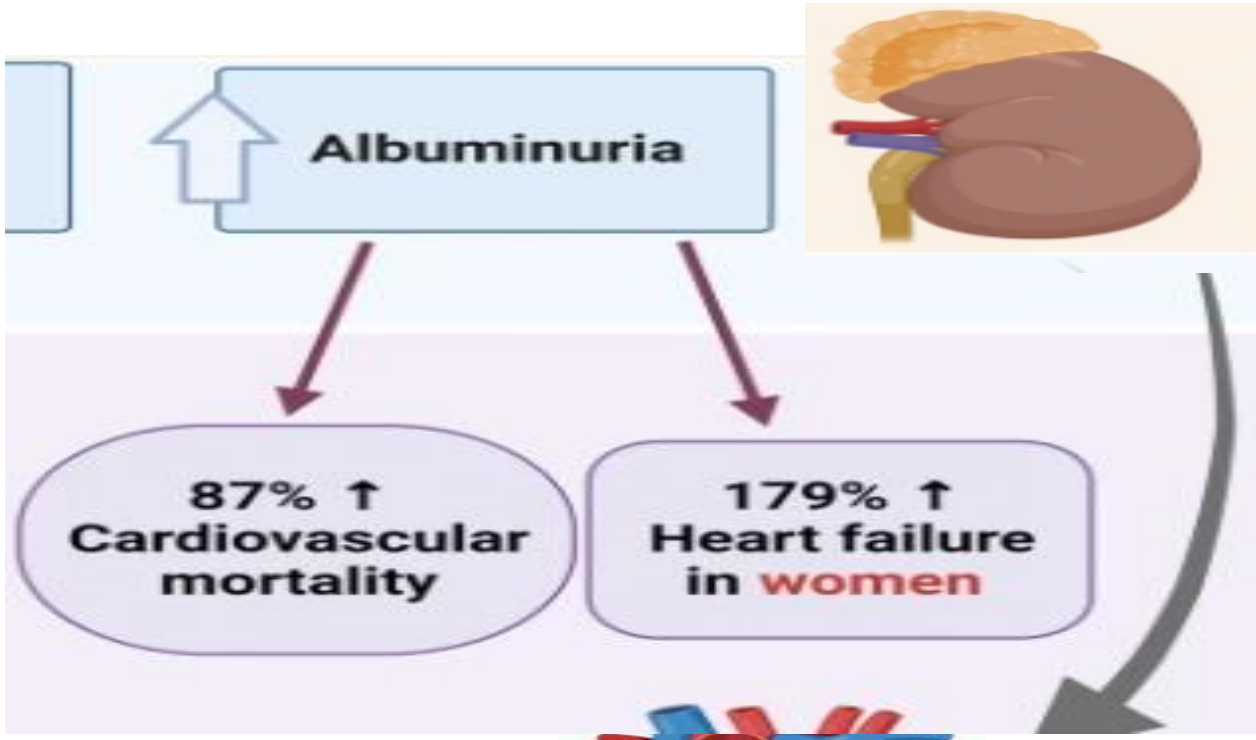
# Kidney Function and CV Outcome in People With DM: The Hoorn Diabetes Care System Cohort *Diabetology 2022*

***… providing additional information on specific CVD subtypes.***

**13.657 adults with DM**

**Annually repeated kidney function measures**



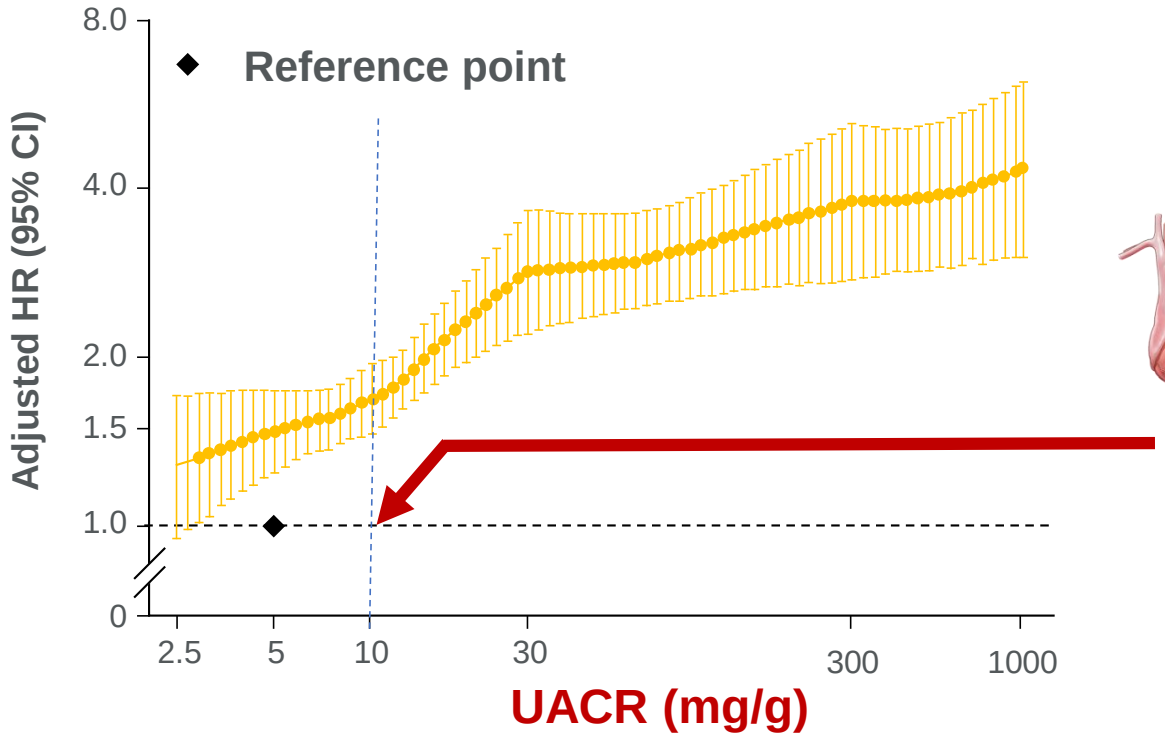



# It’s really, really important  to measure albuminuria

**.. And moreover…..**

## CV mortality according to UACR

**Risk of CV mortality is significantly increased as UACR rises above  10 mg/g**




**Albuminuria is a predictor of CV mortality in pts with DM**

**Meta-analysis including data from 128,505 patients with diabetes**

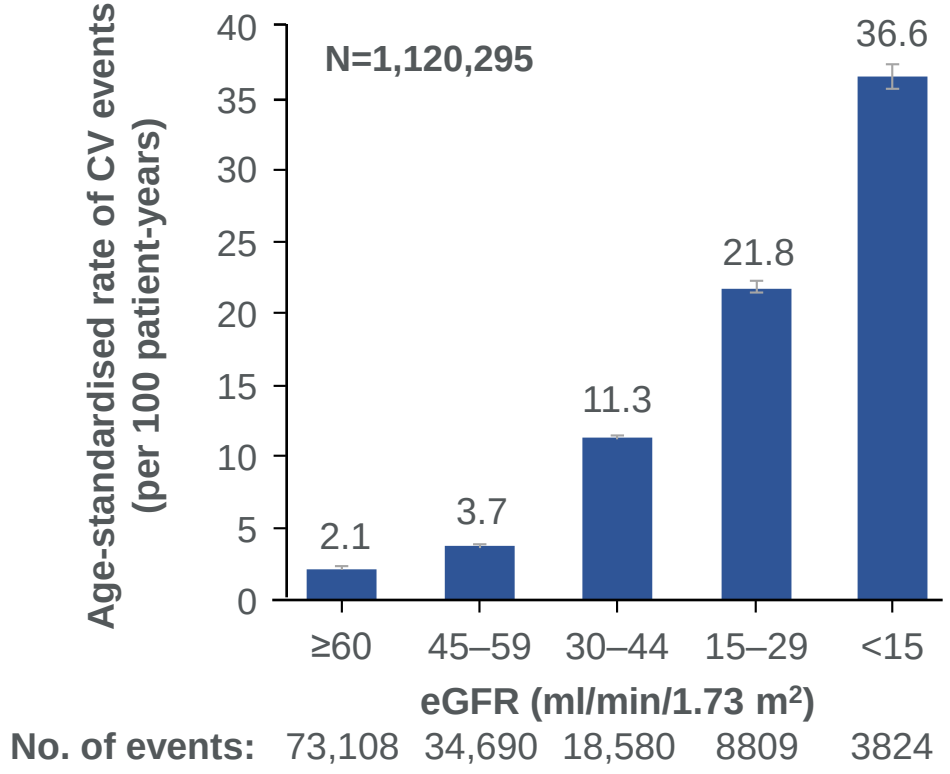
presents point of reference in patients without diabetes to which other comparisons were made (UACR 5 mg/g)

*Adjusted for age, sex, race, smoking, history of CV disease, serum total cholesterol concentration, BMI and albuminuria

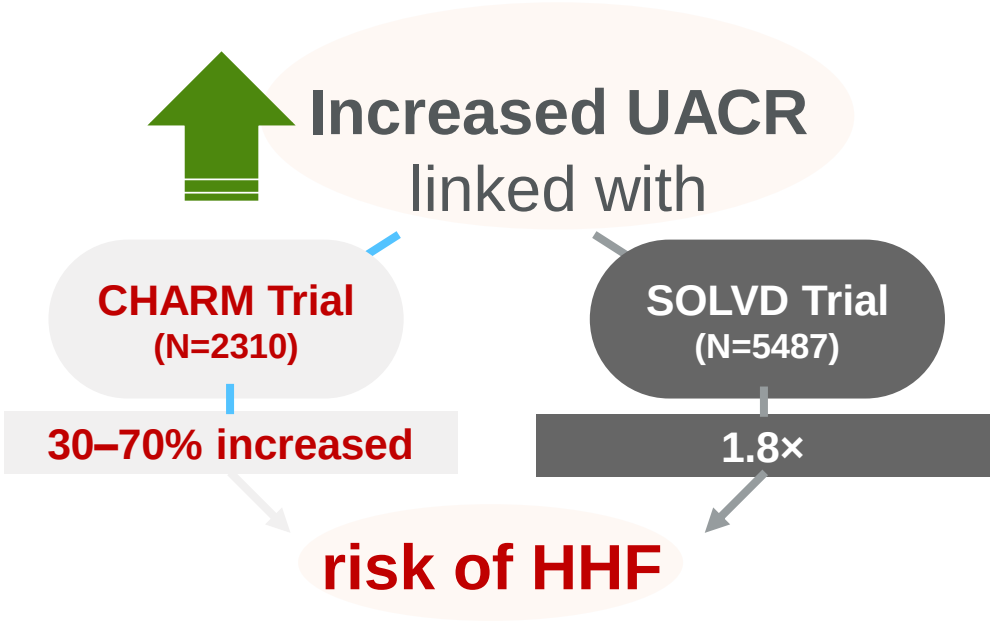
Fox CS, *et al. Lancet* 2012;380:1662–1673

# Lower eGFR and albuminuria are associated with an increased risk of CV events and HHF; *therefore, preserving kidney function in patients with CKD is important*

## Lower eGFR linked to CV events[1]




## Albuminuria in progression of HF*,[2]

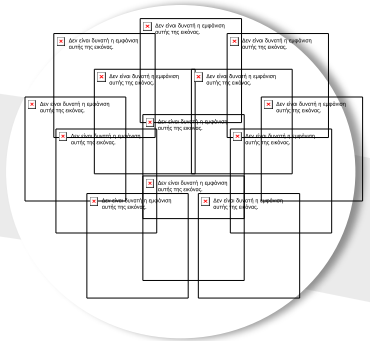



**UACR was a strong independent predictor of adverse prognosis in HF irrespective of HTN or T2D**

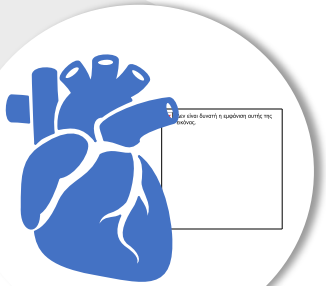
1. Go AS, *et al. N Engl J Med* 2004, 2. Khan MS, *et al. JACC Rev* 2023

# Early diagnosis based on UACR can lead to prevention of CV events

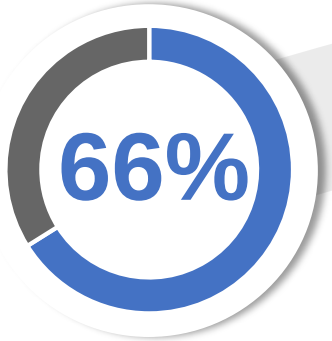
Estimated
**6.4 million**
individuals with T2D and albuminuric CKD eligible for finerenone



**67** first CV events prevented per 10,000 PY with finerenone in FIDELITY



**38,359**
CV events prevented per year with finerenone in the US




of these CV events could be prevented in individuals diagnosed with CKD based on UACR

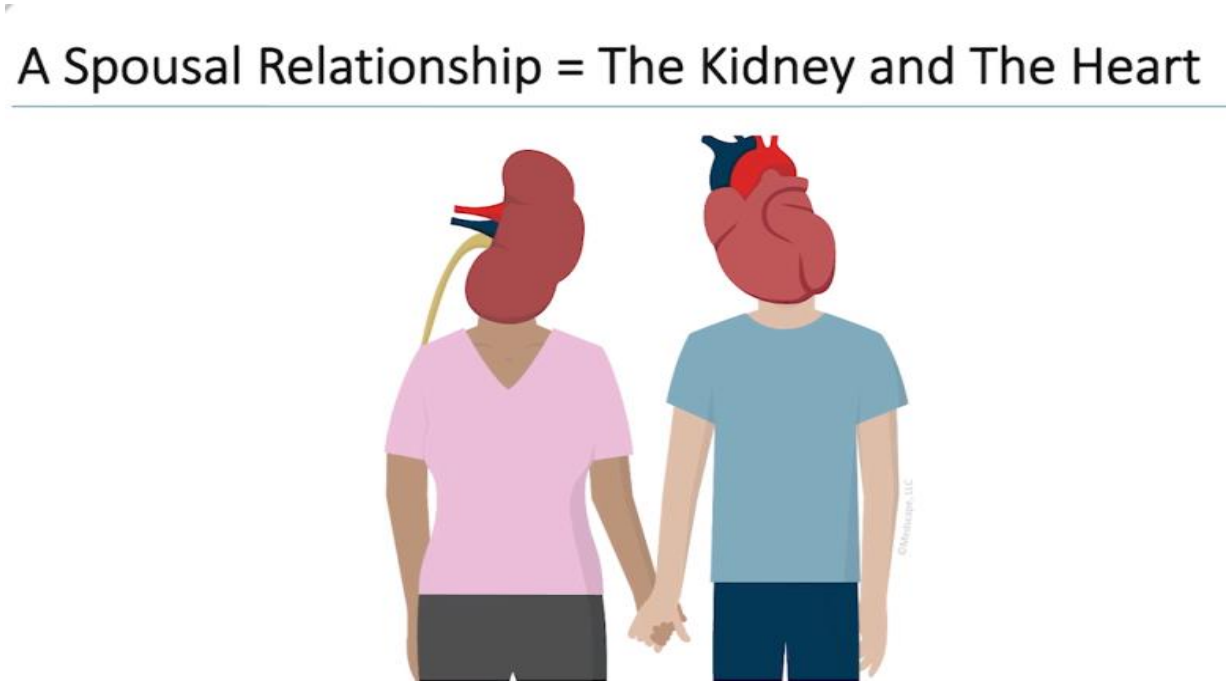


Agarwal R, *et al. JAMA Cardiol* 2023; 2023;

FIDELITY

# *But, How does renal impairment lead to CV morbidity and mortality ?*

**George L. Bakris**




***If you think of the kidney and the heart as a spousal relationship, then you can really understand what's going on.***

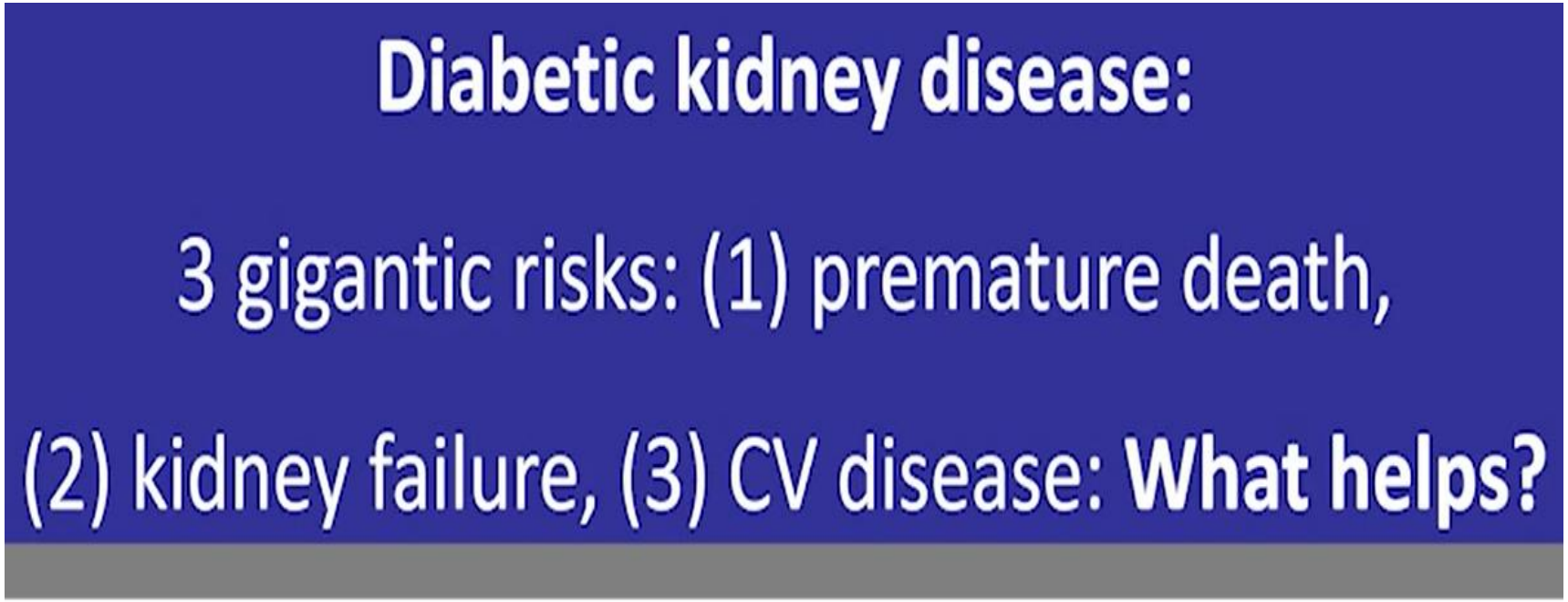
***In a marriage situation, if one spouse isn't doing well – their health isn't good – then the other spouse is also suffering.***

**If the heart is failing, the kidney will try to be supportive through compensatory mechanisms; but it's not going to be functioning as well as it could.**

**Likewise, if the kidney is failing, the heart will try to be as supportive as it can; but it's going to be under influences that make it more difficult to perform well.**

# How can we collaborate to achieve holistic heart and kidney management of patients with CKD and T2D ?

**1. Diabetologists should change the glucocentric approach of DM medication** to a deeper drive into the treatment of T2D, with a strong focus on the role of **newer medications** in the prevention and management of **co-morbid CV and Renal Disease …. opening a new era of management for DKD.**




- Insulin (ORIGIN)
- SUs (CAROLINA)
- DPP-4i (CARMELINA)
- SGLT-2i (CREDENCE, DAPA_CKD)
- GLP-1 RA (FLOW)

**MRAs (FIGARO, FIDELIO)**

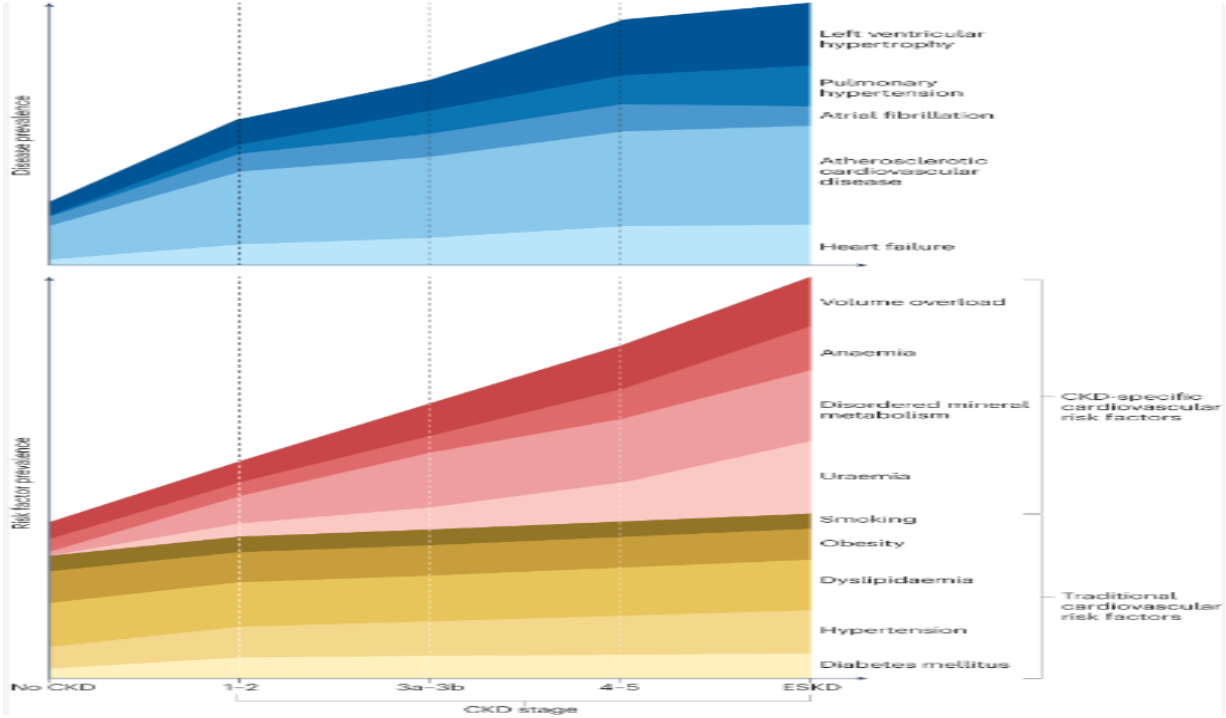
# How can we collaborate to achieve holistic heart and kidney management of patients with CKD and T2D ?

## 2. Cardiologists must be convinced that the kidney disease is an important risk factor of CVD

Circulation

**Kidney Disease as a Risk Factor for Development of Cardiovascular Disease**

A Statement From the American Heart Association Councils on Kidney in Cardiovascular Disease, High Blood Pressure Research, Clinical Cardiology, and Epidemiology and Preventio




**Therefore; *preserving kidney function in patients with CKD is important***

**"To Protect the Heart, You Need to Protect the Kidney" -**

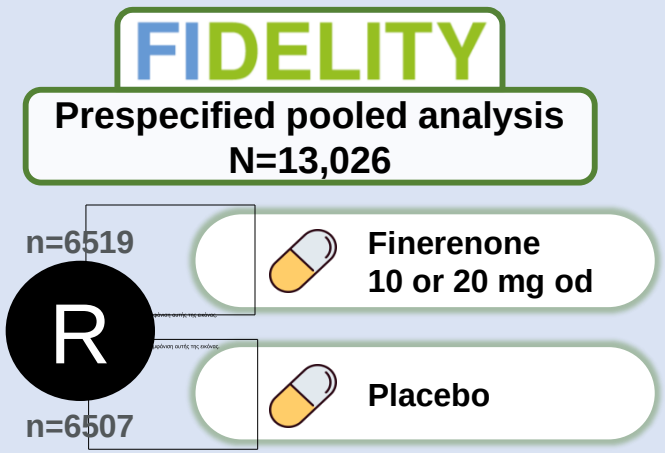
**Valerie Luyckx ESC Congress 2023**

# How can we collaborate to achieve holistic heart and kidney management of patients with CKD and T2D ?

## 3….. and what is more important is that CKD, as jointly defined by UACR and eGFR, is a modifiable CV risk factor

**FIDELITY presented an opportunity to investigate whether CKD, as jointly defined by UACR and eGFR, is a modifiable CV risk factor**

### Study design

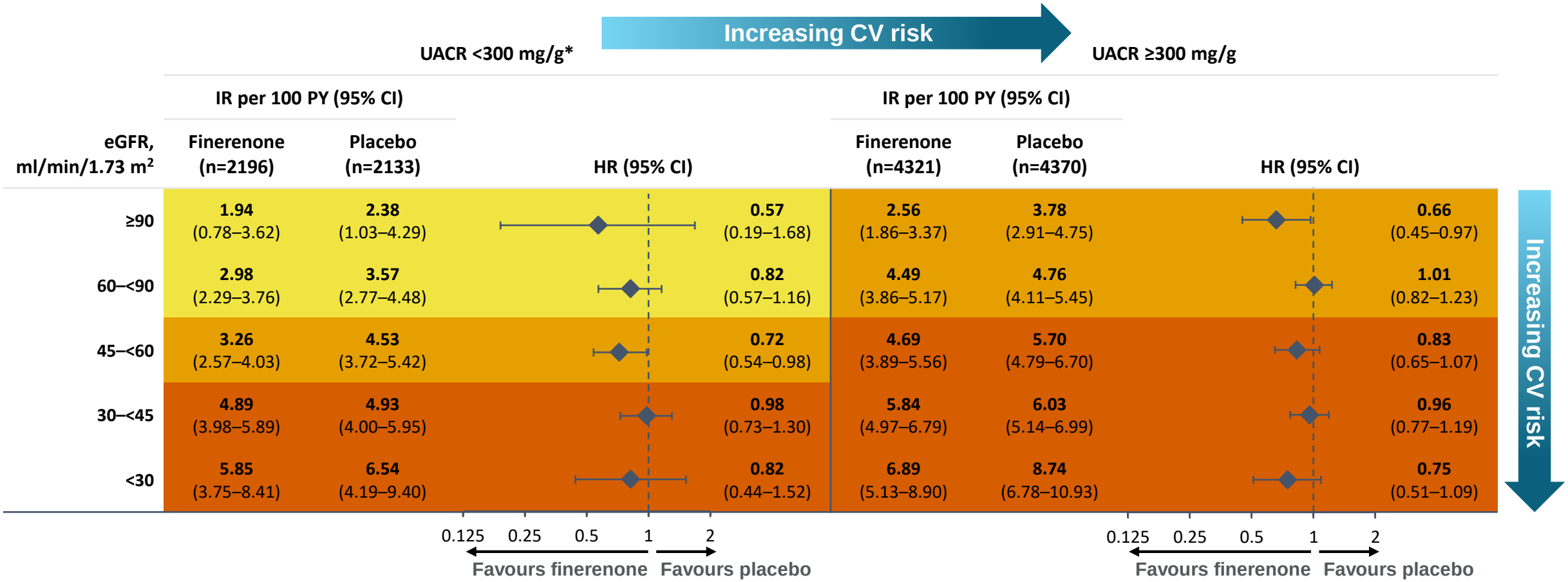



### Outcome

- **Incidence rates of CV events** (composite of CV death, nonfatal MI, nonfatal stroke or HHF)
  - Evaluated across **eGFR and albuminuria categories**

FIDELITY

# .....the fact that CV risk was reduced with finerenone across all ranges of UACR and eGFR, suggesting CKD is a modifiable CV risk factor in patients with T2D



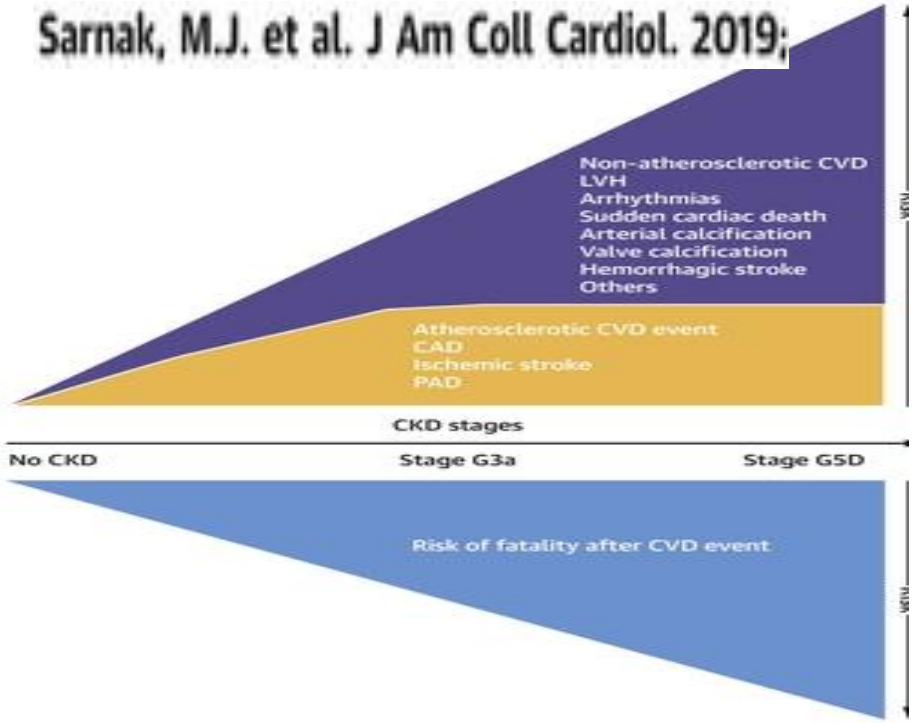

**Finerenone reduced CV risk across all UACR and eGFR ranges**



FIDELITY

# How can we collaborate to achieve holistic heart and kidney management of patients with CKD and T2D ?

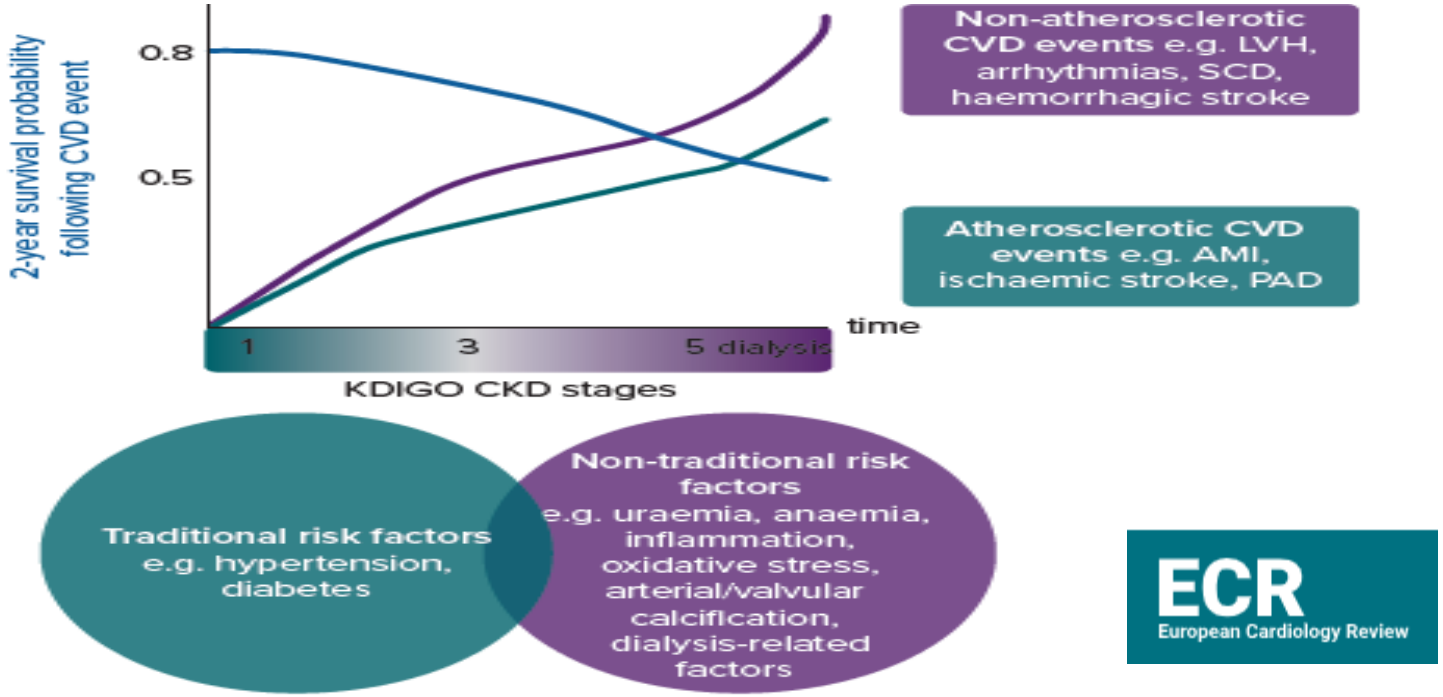
**4. Cardiologists must be convinced that to achieve this management, they must understand that, as CKD progresses, traditional risk factors, contribute less to CVD events than non-traditional risk factors.**




## CV Complications of CKD; An Introduction

*Hilary Warrens 2022*

## Changing CVD Risk Progressing CKD




ECR European Cardiology Review

**Non – atherosclerotic causes contribute more than atherosclerotic causes as CKD progress.**

# Cardiovascular-Kidney-Metabolic Syndrome; Advisory From the American Heart Association

Circulation October 9, 2023

**A Synopsis of the Evidence for the Science and Clinical Management of Cardiovascular-Kidney-Metabolic (CKM) Syndrome: A Scientific Statement From the American Heart Association**

Chiadi E. Ndumele, Ian J. Neeland, Katherine R. Tuttle, Sheryl L. Chow, Roy O. Mathew, Sadiya S. Khan, Josef Coresh,

**…….** Citing the strong overlap between heart disease, kidney disease, T2DM, and obesity, the AHA has for the first time formally defined what they are calling **CV-kidney-metabolic syndrome**.

Cardiovascular-kidney-metabolic (CKM) syndrome is a systemic disorder with connections among heart disease, kidney disease, diabetes, and obesity.

•CKM syndrome leads to premature morbidity and mortality, primarily because of a higher burden of CVD.

**•In addition, there are unique management considerations for individuals with established CVD and coexisting metabolic risk factors, CKD, or both.**

# Recent clinical guidelines for the management of CKD in T2D recommend a combination of drug therapies to optimally reduce risks (pillar therapy)

**5. ….. To accept the evolution of "pillars therapy" to reduce HF risk and slow DKD progression.**

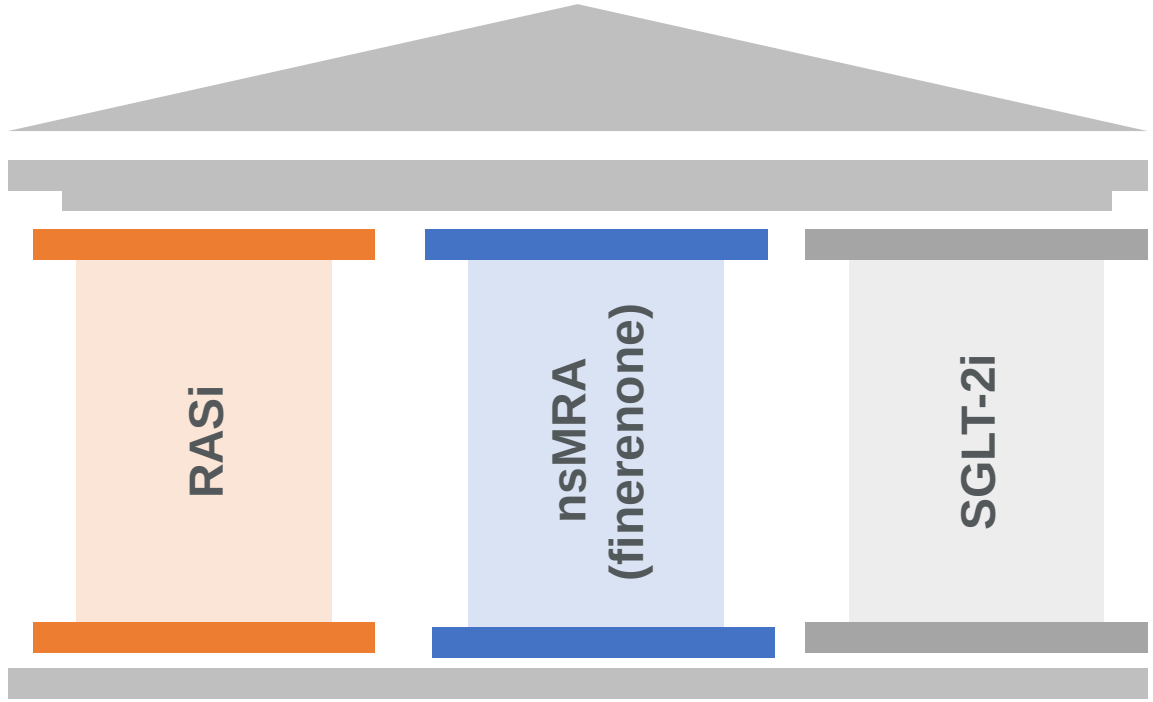
ERBP European Renal Best Practice

KDIGO Kidney Disease Improving Global Outcomes

ESC European Society of Cardiology

American Diabetes Association®

ADA KDIGO Consensus 2022



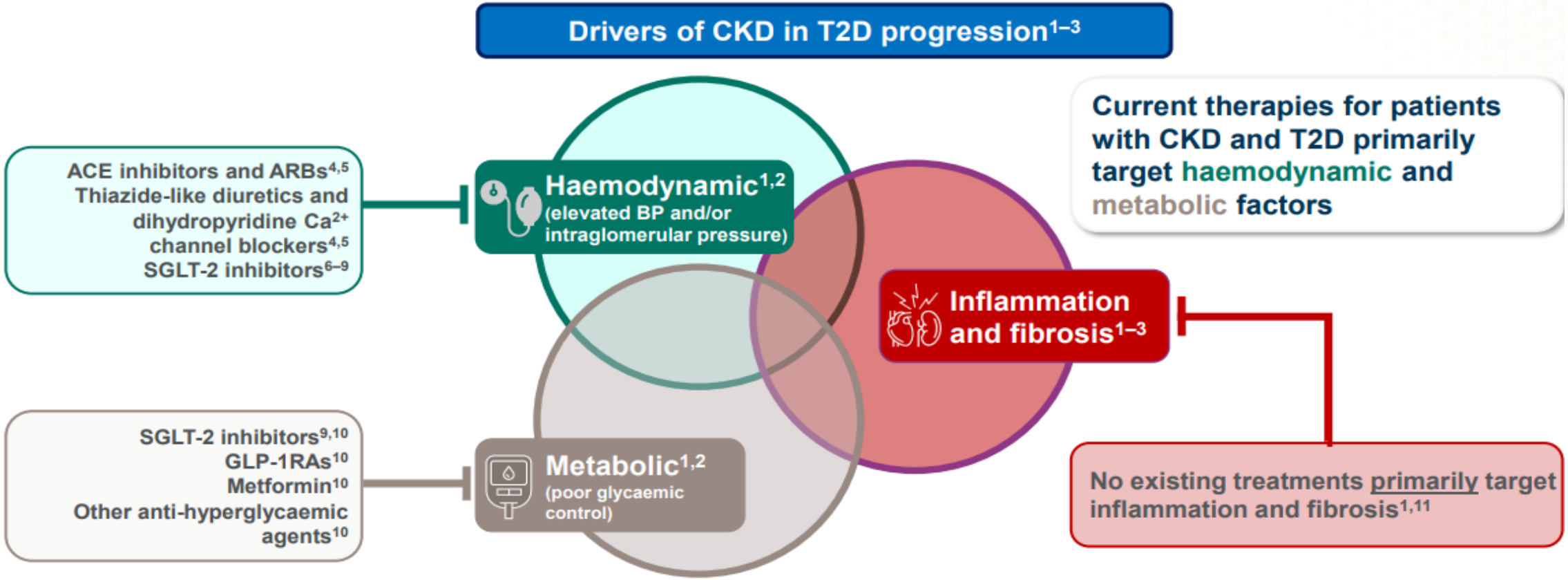

"Pillared Approach" to Therapy in Patients with Diabetic Kidney Disease for Cardiorenal Risk Reduction

ADA, American Diabetes Association; SGLT-2i, sodium-glucose co-transporter-2 inhibitor

1. Kidney Disease: Improving Global Outcomes (KDIGO). *Kidney Int* 2022;102:S1–S128;
2. 2. American Diabetes Association. *Diabetes Care* 2023;46(Suppl 1):S191–S202;
3. de Boer IH, *et al. Diabetes Care* 2022;45:3075–3090; 4. Blazek O, *et al. Am Heart J Plus* 2022;19:100187;
5. Marx N, Federici M, Schutt K, *et al*. 2023 ESC Guidelines for the management of CVD in patients with diabetes. *EHJ* 2023

…. Sepse….

# Progression of CKD in T2D is driven by the combined effects of hemodynamic, metabolic, inflammatory and fibrotic factors



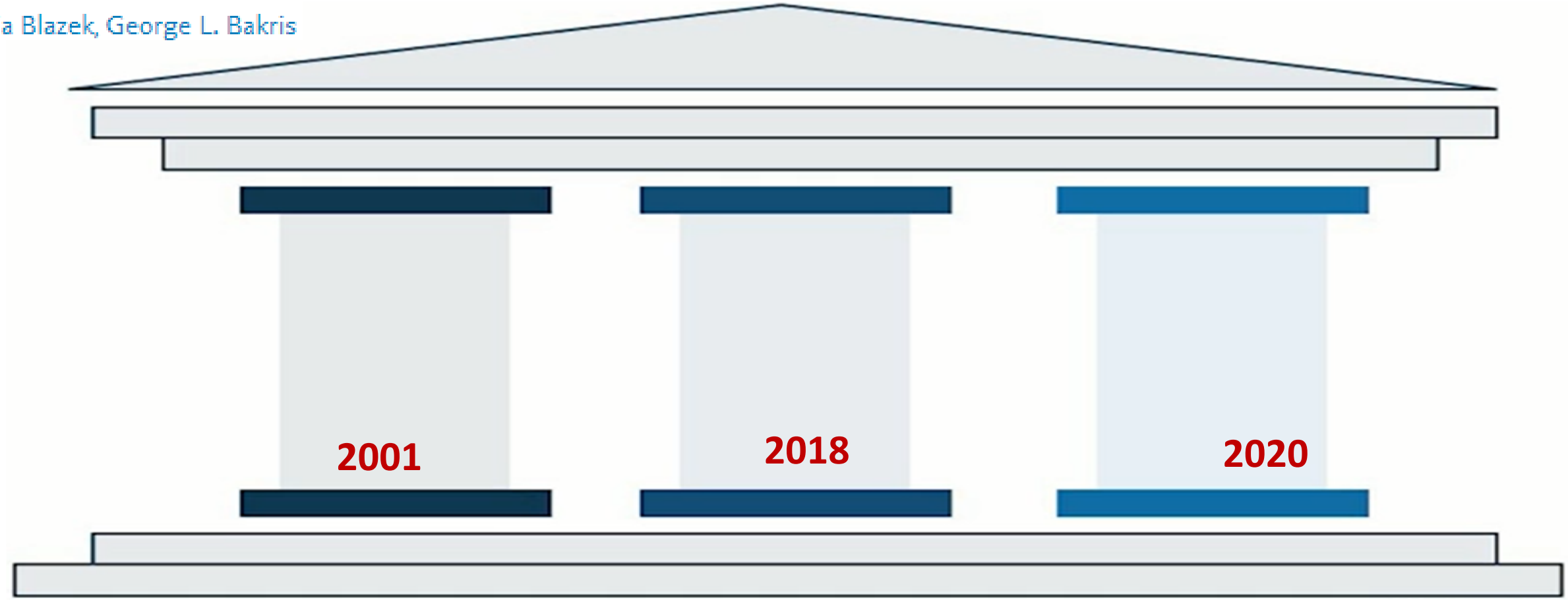

CKD, Chronic kidney disease; T2D, Type 2 diabetes; ACE, Angiotensin-converting enzyme; ARB, Angiotensin receptor blocker; SGLT-2, Sodium-glucose cotransporter-2; GLP-1RA, Glucagon-like peptide-1 receptor a

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:S175–184; 5. American Diabetes Association. *Diabetes Care* 2022;45:S144–174; 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.

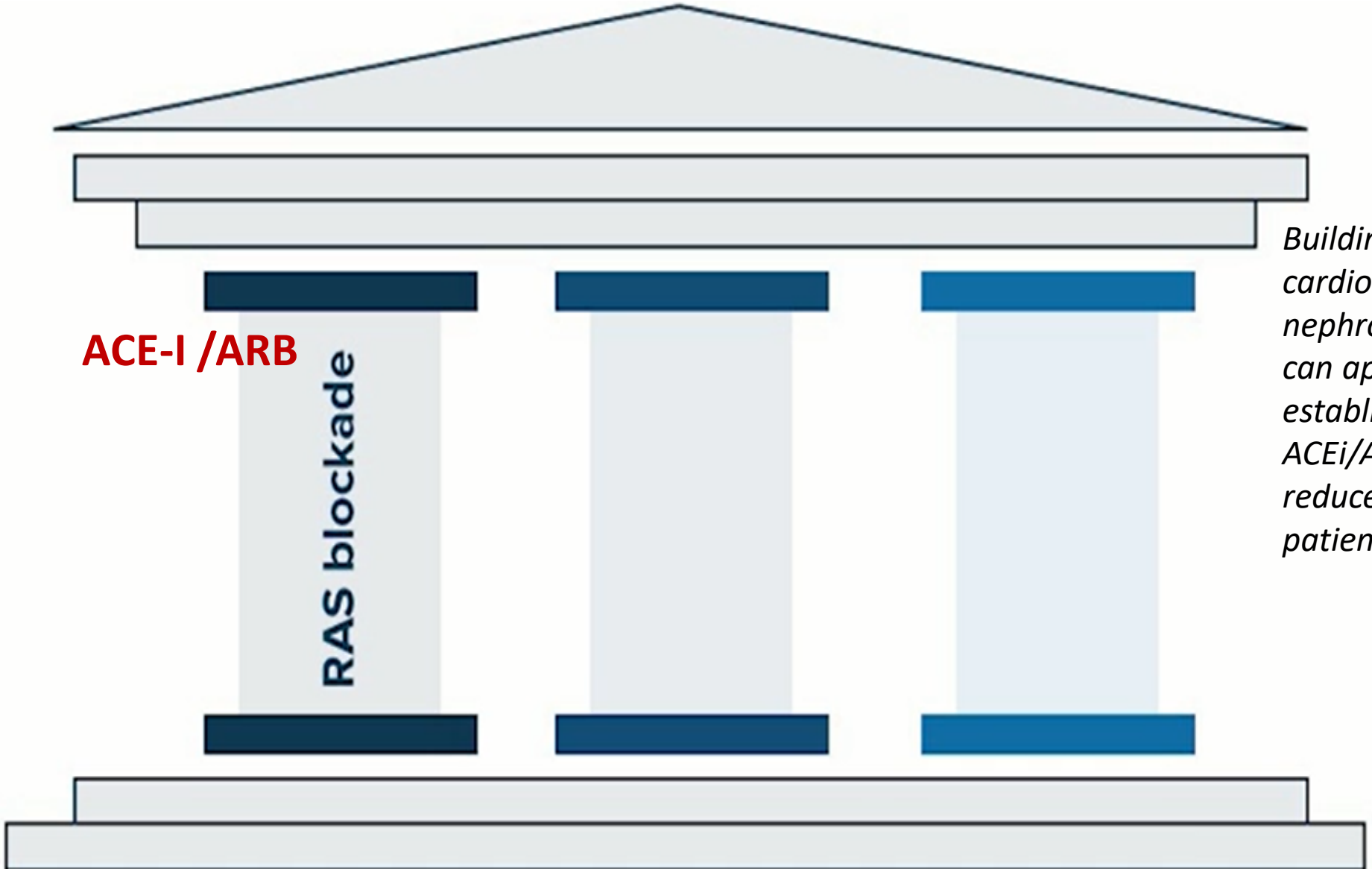
American Heart Journal Plus: Cardiology Research and Practice
Volume 19, July 2022, 100187

# The evolution of “pillars therapy” to reduce heart failure risk and slow diabetic kidney disease progression.

Olivia Blazek, George L. Bakris



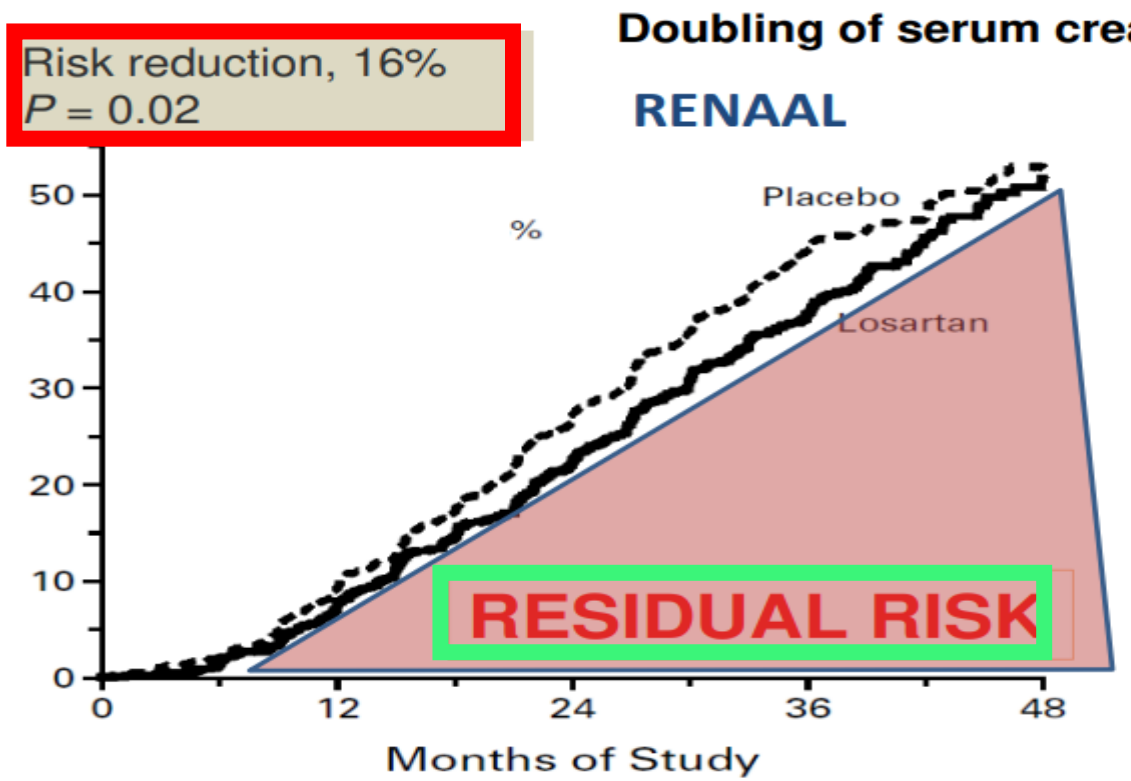
# 3 Pillars of Therapy to Reduce CardioRenal Risk

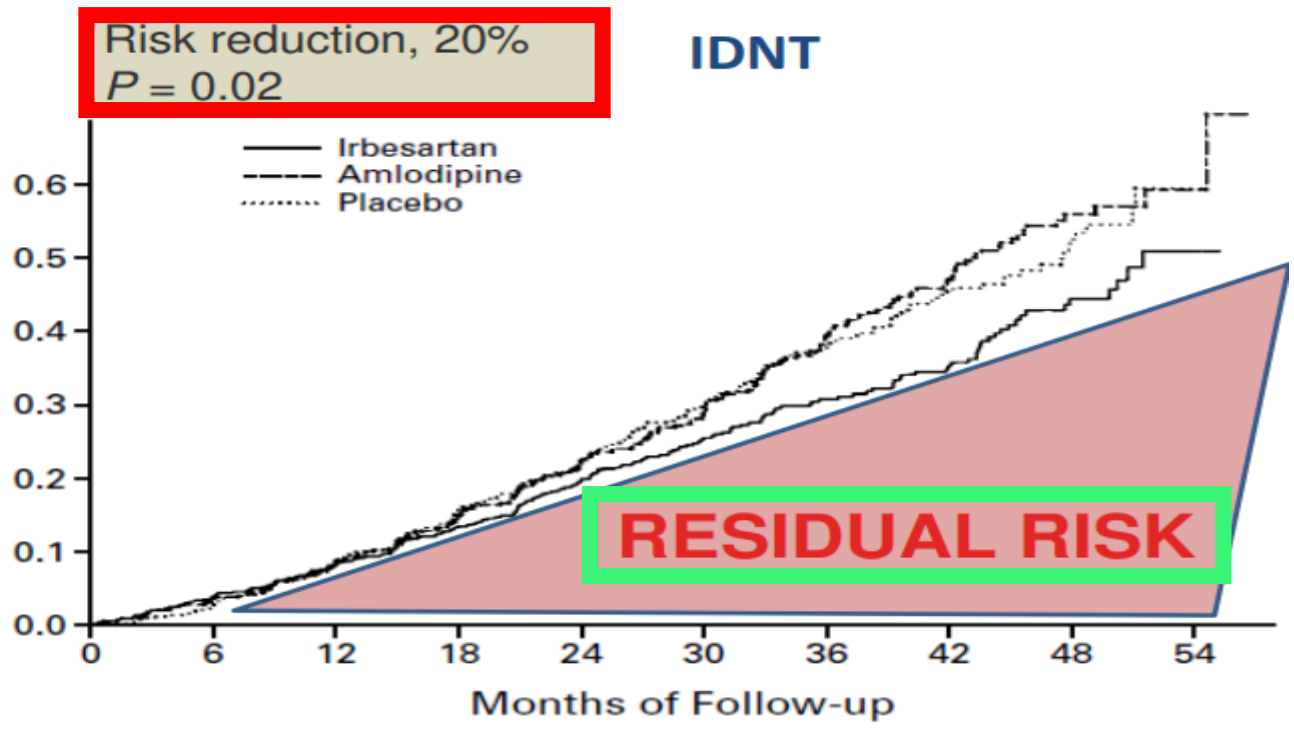



*Building upon the concept used by cardiologists in HF, for the first time, nephrologists and endocrinologists can apply the principles of three established "pillars of therapy"—ACEi/ARB, SGLT2i, and Finerenone to reduce CardioRenal Risk in DM patients.*

# ARBs Are Effective for Slowing Progression of Diabetic Nephropathy

## The Only Proven Treatment for Renoprotection in T2DM – RAS Blockers; RENAAL and IDNT




Brenner B, et al. *N Engl J Med*. 2001;345(12):861-869.

Lewis EJ, et al. *N Eng J Med*. 2001;345(12):851-860.

# What's new in nephrology

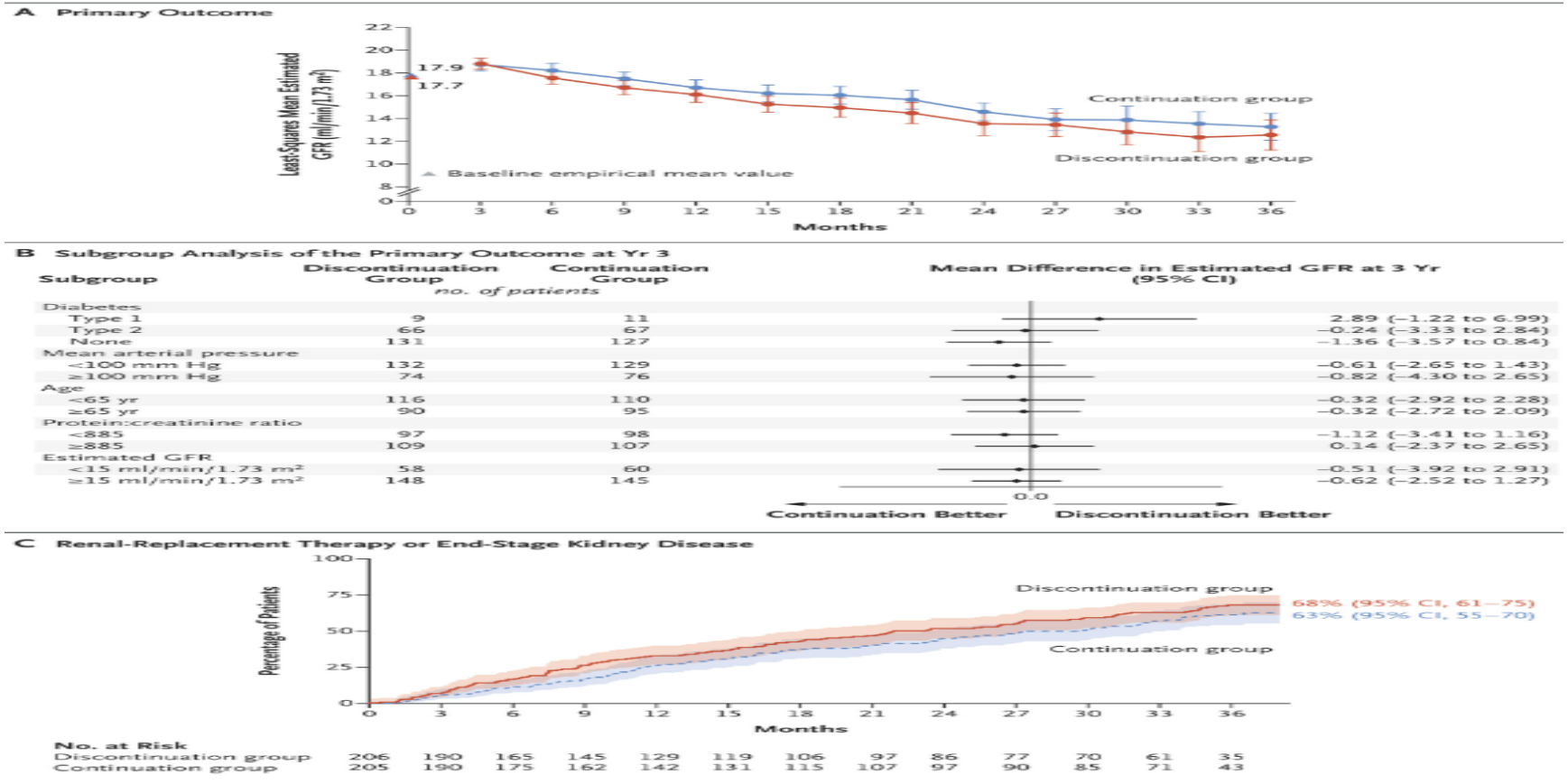
The NEW ENGLAND JOURNAL of MEDICINE

Renin–Angiotensin System Inhibition in Advanced Chronic Kidney Disease

STOP ACEi Trial

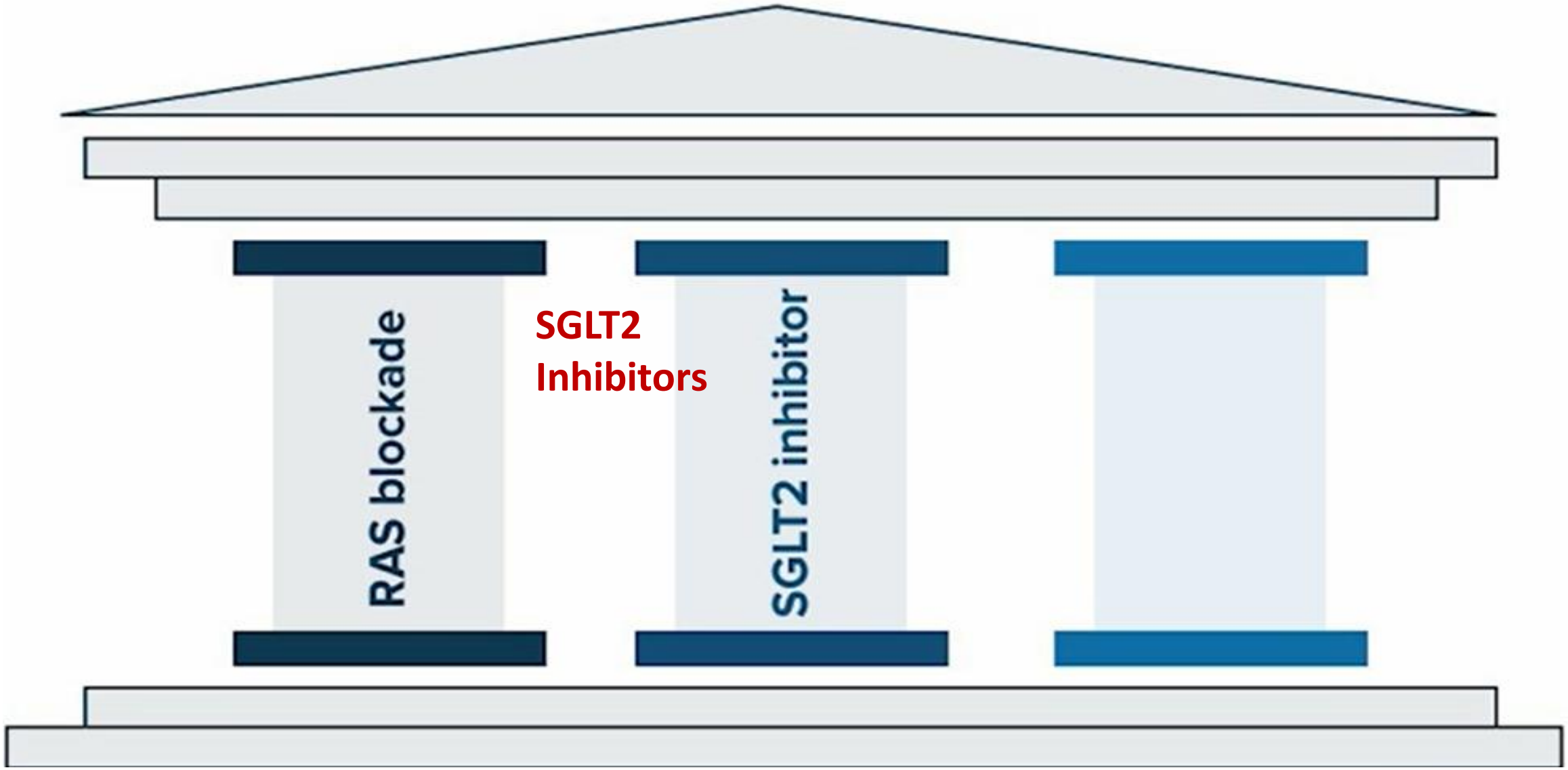
## STOP-ACEi: Or rather, Don’t Stop ACEi in CKD!

- In pts with CKD who take ACE I or ARBs chronically, the question of whether **to discontinue these agents when pts progress to advanced CKD is debated.**
- In a trial whith 400 pts with advanced CKD (GFR-18 ml/min) on therapy with an ACE I or ARB were randomly assigned to continue or discontinue these drugs ?




**In conclusion,** The STOP-ACEi trial did not find any benefit by stopping ACEi (or ARBs) in advanced and progressive CKD.

# 3 Pillars of Therapy to Reduce CardioRenal Risk



# The way of dreams

**Apple the forbidden fruit; forbidden fruit, is a symbol that has conditioned the belief of humanity for centuries.**

***Think Different***

Front. Nephrol., 29 April 2022 | https://doi.org/10.3389/fneph.2022.867075

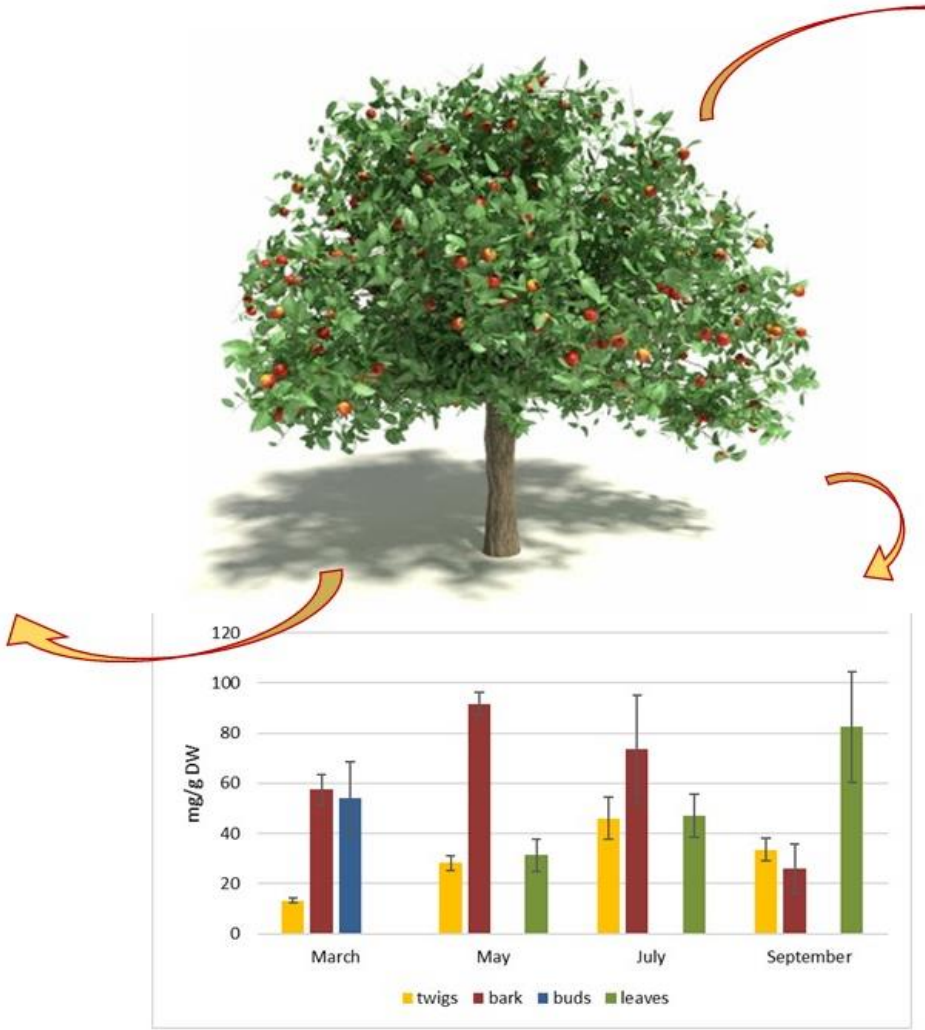
# SGLT2 Inhibitors: A Broad Impact Therapeutic Option for the Nephrologist

***Isolated from the bark of the apple tree by Petersen in 1835***

**SGLT2i; CardioRenal Protection in T2 DM**

HISTORY

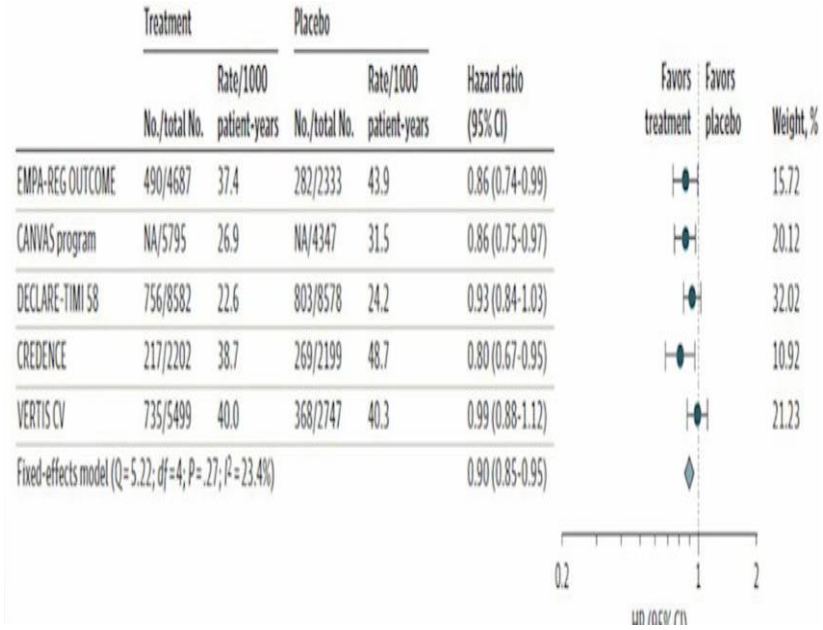
Phlorizin, a bitter white glycoside isolated from apple tree bark by French chemists in 1835, is a naturally occurring inhibitor of both SGLT1 and SGLT2 and was used for the treatment of diabetes in the pre-insulin era.



# Slowing the Progression of Diabetic Kidney Disease

- Olivia Blazek and George Bakris Cell 2023

## SGLT2 i Reduce Risk of Major Adverse CV Events



| | Treatment | | Placebo | | |
|---|---|---|---|---|---|
| | No./total No. | Rate/1000 patient-years | No./total No. | Rate/1000 patient-years | Hazard ratio (95% CI) |
| EMPA-REG OUTCOME | 490/4687 | 37.4 | 282/2333 | 43.9 | 0.86 (0.74-0.99) |
| CANVAS program | NA/5795 | 26.9 | NA/4347 | 31.5 | 0.86 (0.75-0.97) |
| DECLARE-TIMI 58 | 756/8582 | 22.6 | 803/8578 | 24.2 | 0.93 (0.84-1.03) |
| CREDENCE | 217/2202 | 38.7 | 269/2199 | 48.7 | 0.80 (0.67-0.95) |
| VERTIS CV | 735/5499 | 40.0 | 368/2747 | 40.3 | 0.99 (0.88-1.12) |
| Fixed-effects model (Q=5.22; df=4; P=.27; I²=23.4%) | | | | | 0.90 (0.85-0.95) |

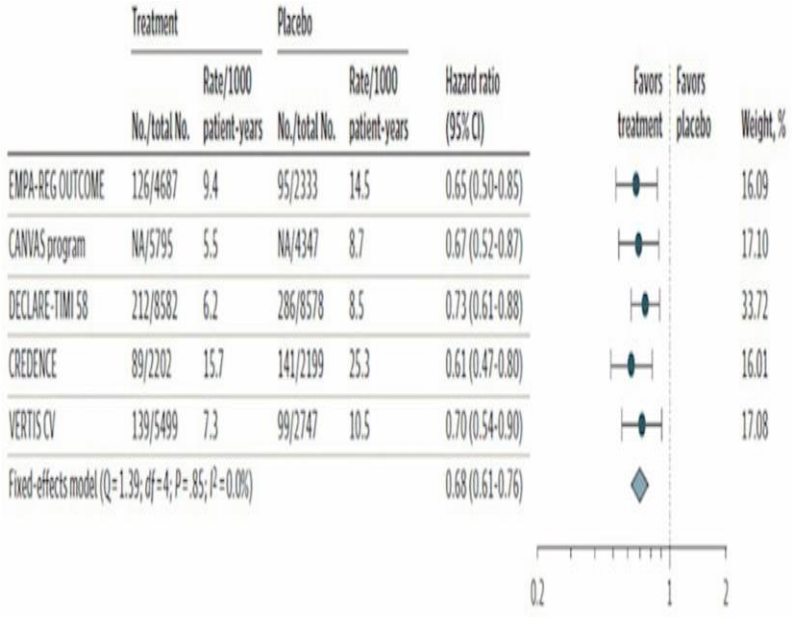
Favors treatment | Favors placebo | Weight, %

15.72
20.12
32.02
10.92
21.23

0.2 1 2

HR (95% CI)

## SGLT2 i Reduce Risk of HHF



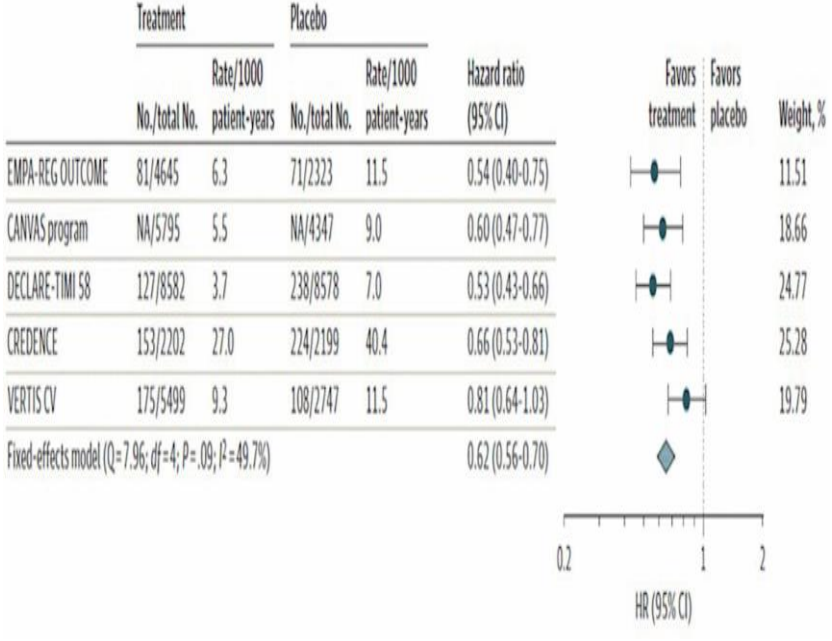
| | Treatment | | Placebo | | |
|---|---|---|---|---|---|
| | No./total No. | Rate/1000 patient-years | No./total No. | Rate/1000 patient-years | Hazard ratio (95% CI) |
| EMPA-REG OUTCOME | 126/4687 | 9.4 | 95/2333 | 14.5 | 0.65 (0.50-0.85) |
| CANVAS program | NA/5795 | 5.5 | NA/4347 | 8.7 | 0.67 (0.52-0.87) |
| DECLARE-TIMI 58 | 212/8582 | 6.2 | 286/8578 | 8.5 | 0.73 (0.61-0.88) |
| CREDENCE | 89/2202 | 15.7 | 141/2199 | 25.3 | 0.61 (0.47-0.80) |
| VERTIS CV | 139/5499 | 7.3 | 99/2747 | 10.5 | 0.70 (0.54-0.90) |
| Fixed-effects model (Q=1.39; df=4; P=.85; I²=0.0%) | | | | | 0.68 (0.61-0.76) |

Favors treatment | Favors placebo | Weight, %

16.09
17.10
33.72
16.01
17.08

0.2 1 2

## SGLT2 i Reduce Risk of Kidney Outcomes



| | Treatment | | Placebo | | |
|---|---|---|---|---|---|
| | No./total No. | Rate/1000 patient-years | No./total No. | Rate/1000 patient-years | Hazard ratio (95% CI) |
| EMPA-REG OUTCOME | 81/4645 | 6.3 | 71/2323 | 11.5 | 0.54 (0.40-0.75) |
| CANVAS program | NA/5795 | 5.5 | NA/4347 | 9.0 | 0.60 (0.47-0.77) |
| DECLARE-TIMI 58 | 127/8582 | 3.7 | 238/8578 | 7.0 | 0.53 (0.43-0.66) |
| CREDENCE | 153/2202 | 27.0 | 224/2199 | 40.4 | 0.66 (0.53-0.81) |
| VERTIS CV | 175/5499 | 9.3 | 108/2747 | 11.5 | 0.81 (0.64-1.03) |
| Fixed-effects model (Q=7.96; df=4; P=.09; I²=49.7%) | | | | | 0.62 (0.56-0.70) |

Favors treatment | Favors placebo | Weight, %

11.51
18.66
24.77
25.28
19.79

0.2 1 2

HR (95% CI)

## SGLT2 Trials have recruited pts with CKD with DM

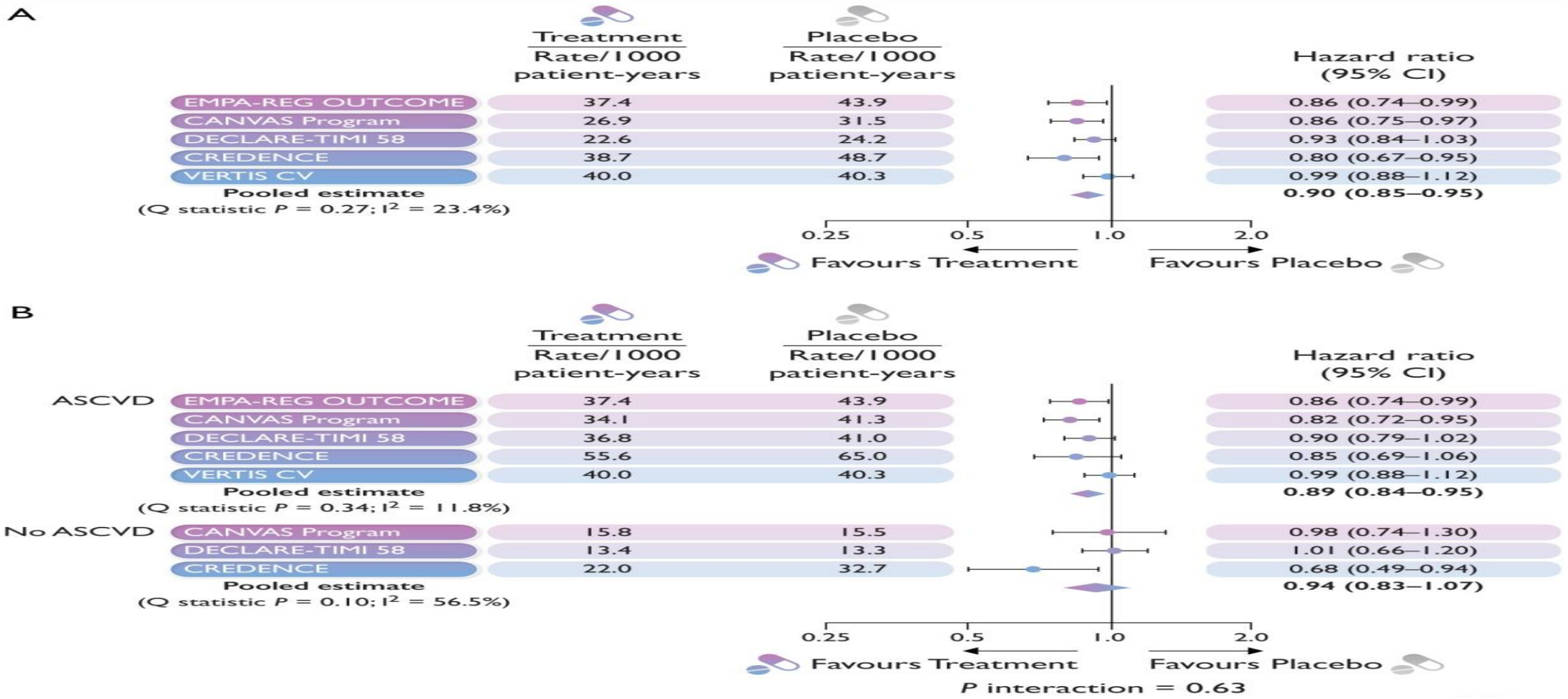
SGLT2i reduce all cause and cardiovascular death by 15%

SGLT2i reduce major cardiovascular events by 10% and heart failure events by 30%

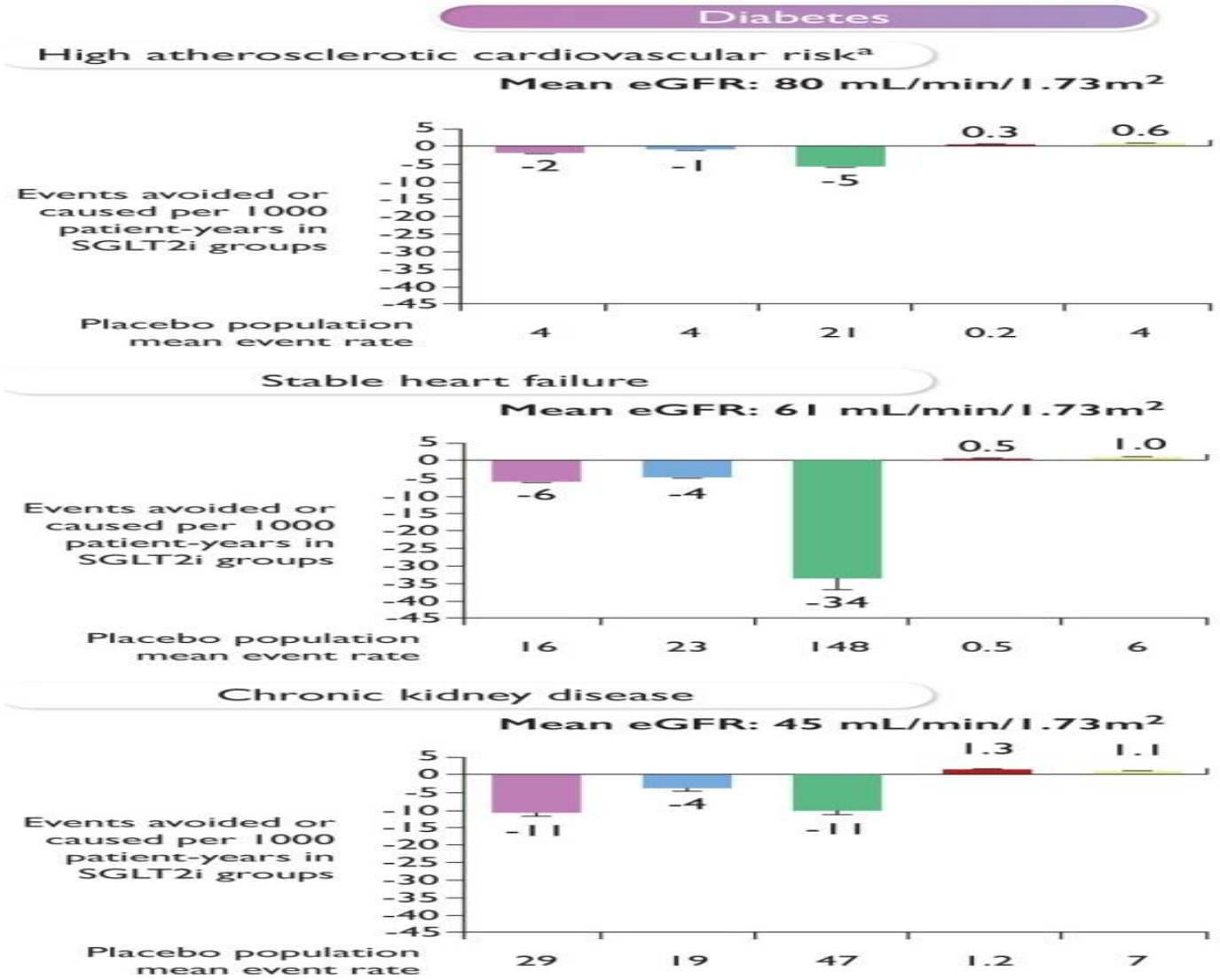
SGLT2i reduced rates of ESKD by 37% and the composite kidney outcome of worsening kidney function/ ESKD by 39%

# Meta-analysis of CV outcomes trial results of SGLT-2 I among pts with T2DM with or at high risk for atherosclerotic CVD.

ESC European Society of Cardiology



# Absolute benefits of SGLT-2 i in pts with and without DM ...




## Conclusion

- SGLT2 I are cardiorenal risk reduction drugs with glucose lowering as a beneficial side effects.
- *And with DAPA-CKD and DAPA-HF results-can say;*
- SGLT2 I are cardiorenal risk reduction drugs irrespective of glucose level.

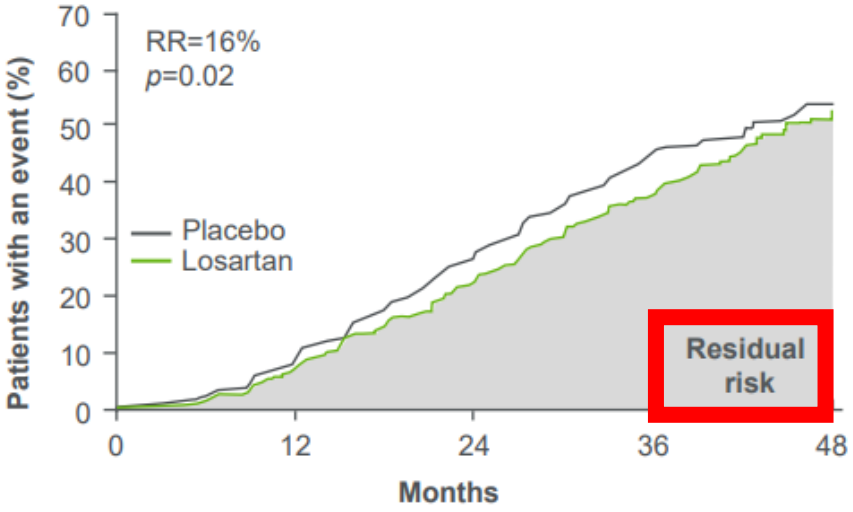
*Eur Heart J*, 2023

ESC European Society of Cardiology

# but…RAS blockers and SLT2i are NOT going to be the end of (D) CKD

## Patients with T2D and CKD are at risk of CKD progression when treated with RAS and SGLT-2 inhibition

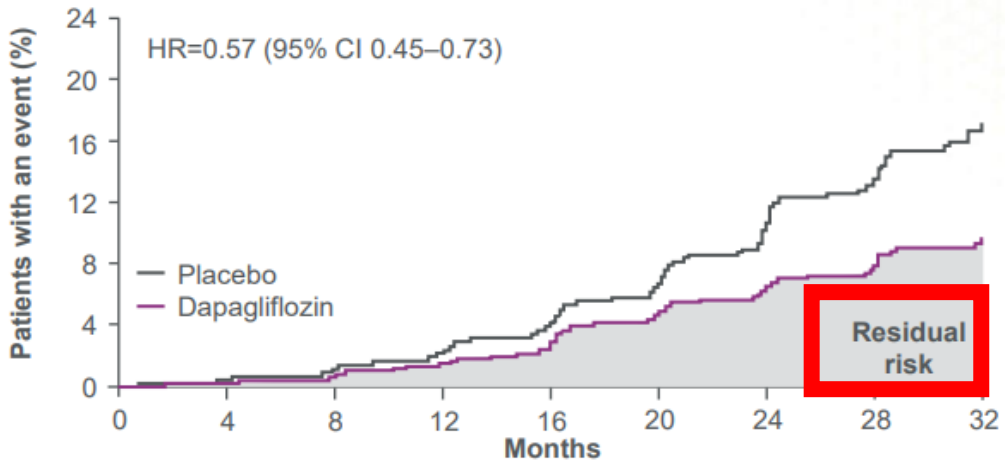
### RENAAL: Losartan *vs.* placebo[1]




**Patients with severely increased albuminuria:** 100%
**Median UACR:** 1249 mg/g

**Primary composite endpoint:**
Doubling of SCr, kidney failure or death

### DAPA-CKD: Dapagliflozin (+ACEi/ARB) vs placebo (T2D subgroup)[2]




**Patients with severely increased albuminuria:** 89.7%
**Median UACR:** 949 mg/g

**Primary composite endpoint:**
Sustained ≥50% eGFR decline, ESKD or renal death

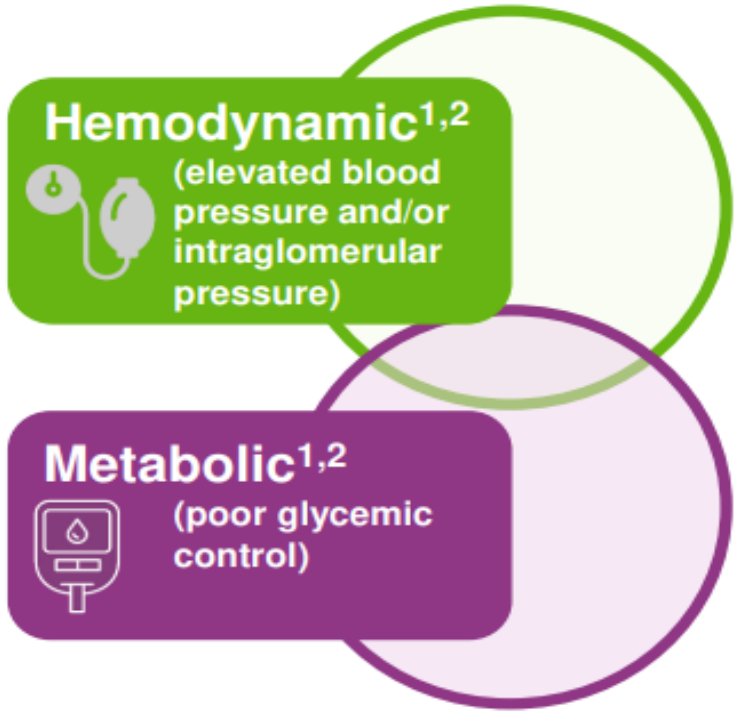
**Inflammation and Fibrosis are a potential treatment target to adress the Risk in CKD and T2DM**

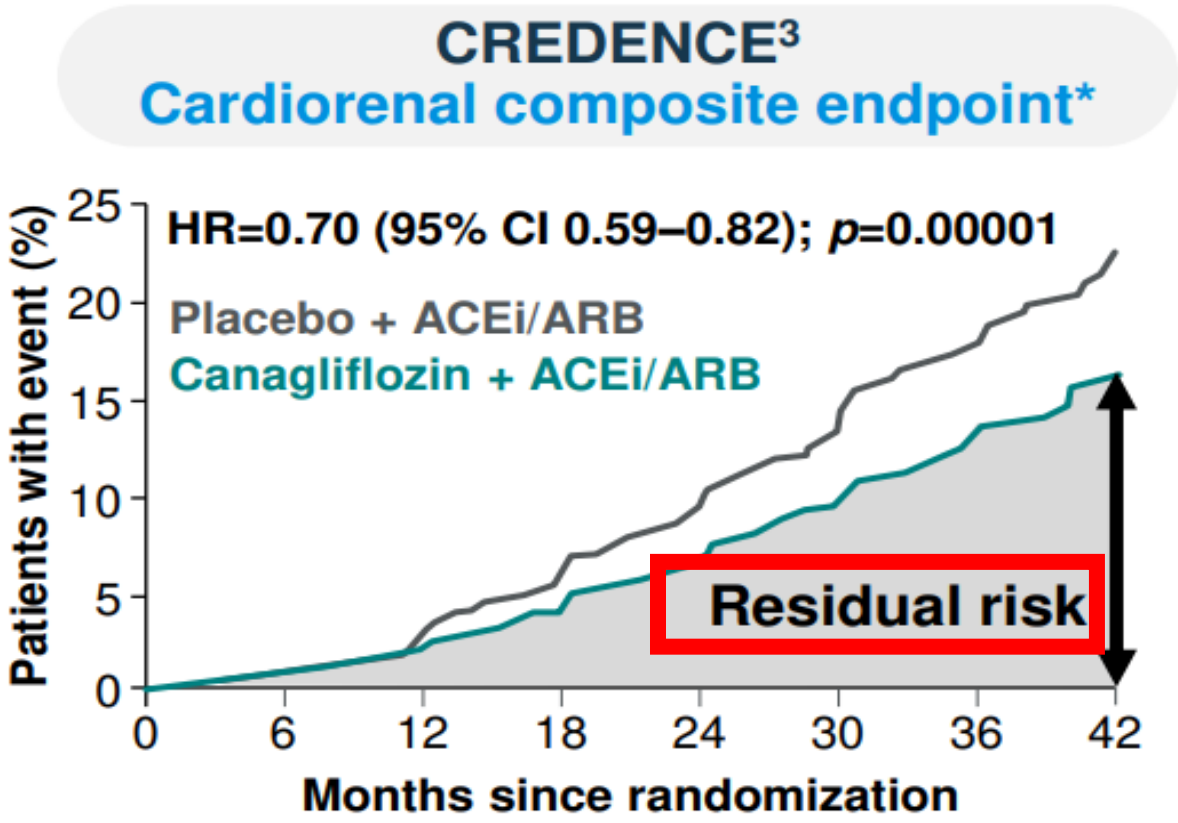
RAS, Renin-angiotensin system; SGLT-2, Sodium glucose cotransporter 2; T2D, Type 2 diabetes; CKD, Chronic kidney disease; DAPA, Dapagliflozin; RR, Relative risk; HR, Hazard ratio; CI, Confidence interval; UACR, Urine albumin-to-creatinine ratio; eGFR, estimated glomerular filtration rate; ESKD, End-stage kidney disease

1. Brenner BM, *et al. N Engl J Med* 2001; 345: 861–869; 2. Wheeler DC, et al. Lancet Diabetes Endocrinol 2021; 9: 22–31

# FIDELIO-DKD rationale

## High residual risk of CKD progression with current therapie

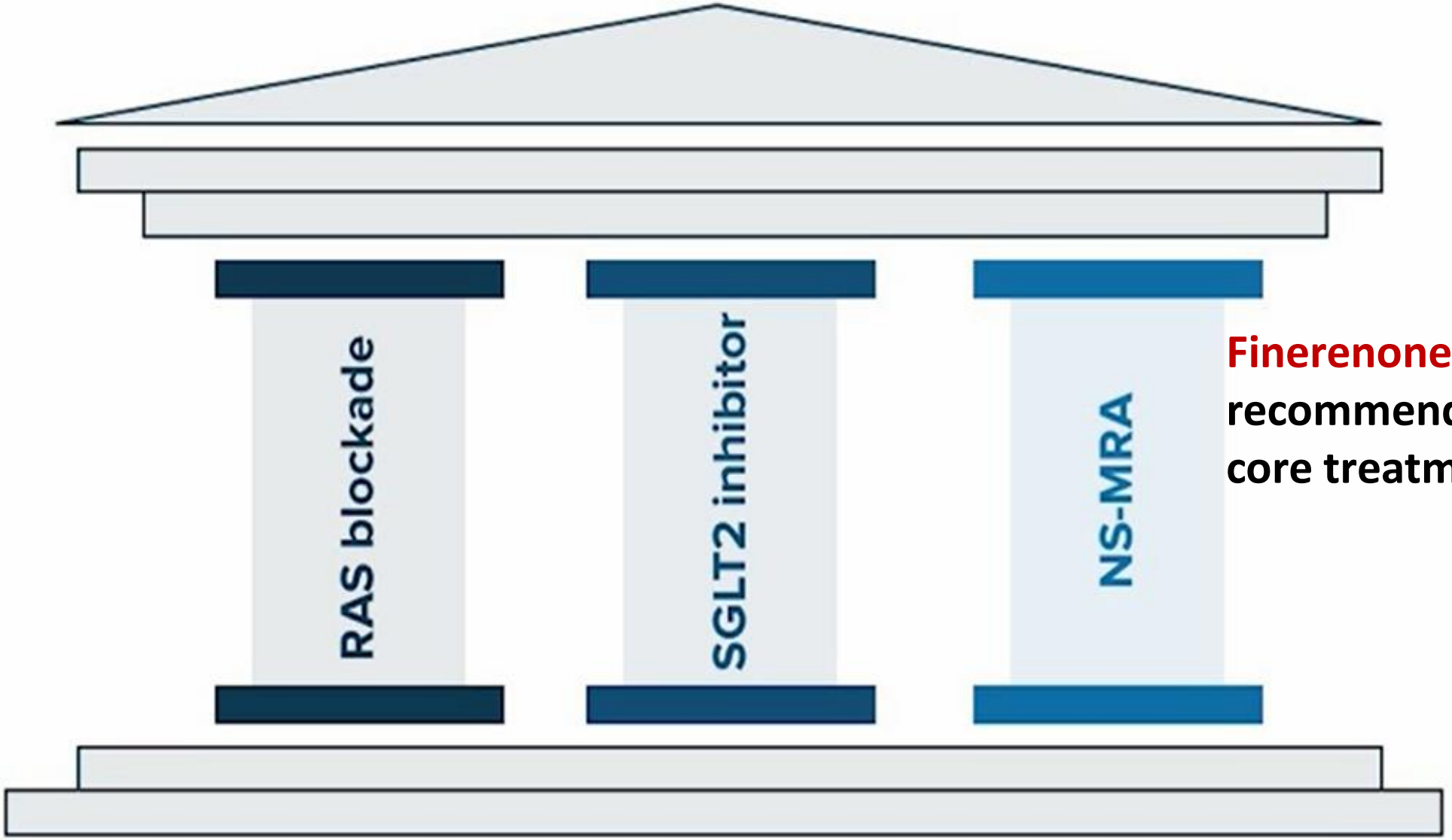



**Inflammation and Fibrosis are a potential treatment target to adress the Risk in CKD and T2DM**

1. Alicic RZ, *et al. Clin J Am Soc Nephrol* 2017;12:2032; 2. Mora-Fernández C, *et al. J Physiol* 2014;18:3997;
3. Perkovic V, *et al. N Engl J Med* 2019;380:2295

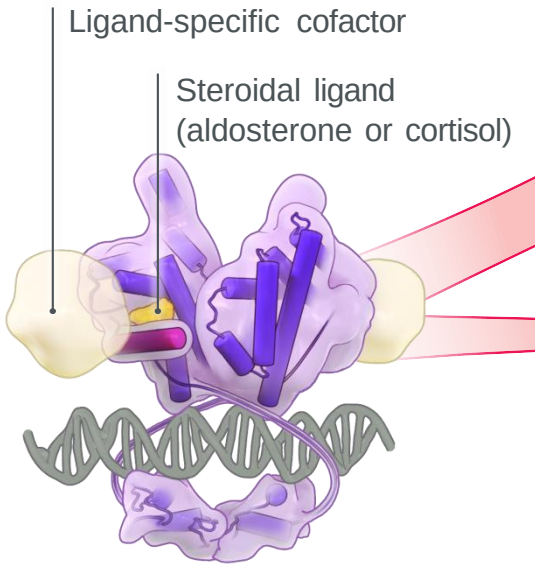
# 3 Pillars of Therapy to Reduce CardioRenal Risk




**Finerenone**
**recommended as a core treatment pillar.**

# MR overactivation is a key driver of heart and kidney diseases, including HF

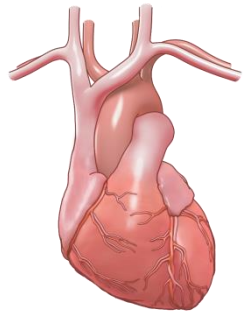
- Hyperglycaemia[2]
- High salt load[1–3]
- Oxidative stress[1,3]



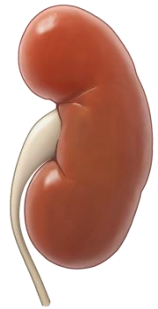

**MR overactivation**

**Drivers**

- Inflammation and fibrosis[1,3]
- Haemodynamic factors[3]
- Metabolic factors[2]



**Worsening of CVD/HF and CKD[1–3]**

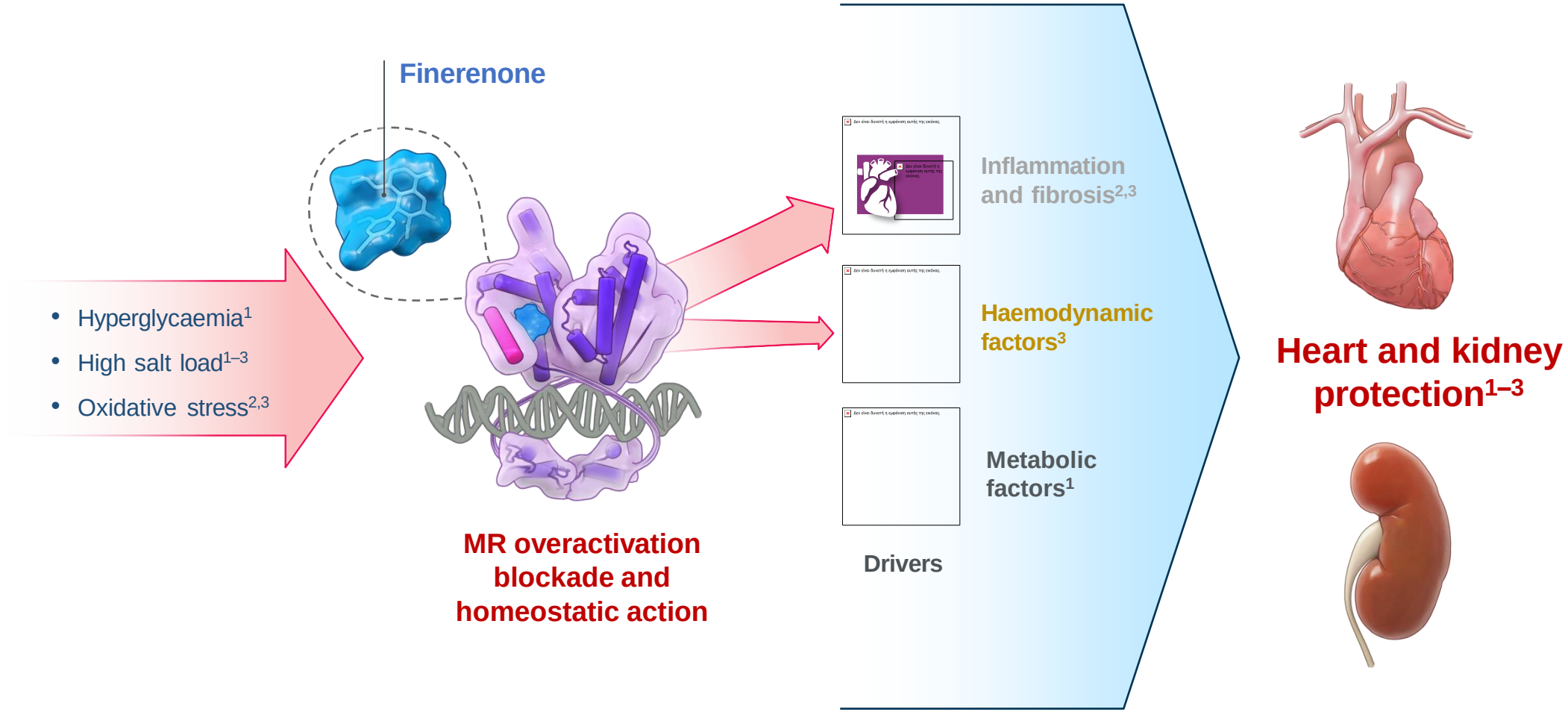


*The current understanding of the role of MR overactivation in CKD in T2D is largely based on preclinical evidence

CVD, cardiovascular disease; CKD, chronic kidney disease; HF, heart failure; MR, mineralocorticoid receptor; T2D, type 2 diabetes.

1. Bauersachs J, *et al.* Hypertension 2015;65:257–263; 2. Fujita T. *Hypertension* 2010:55:813–818: 3. Barrera-Chimal J, *et al. Kidney Int*

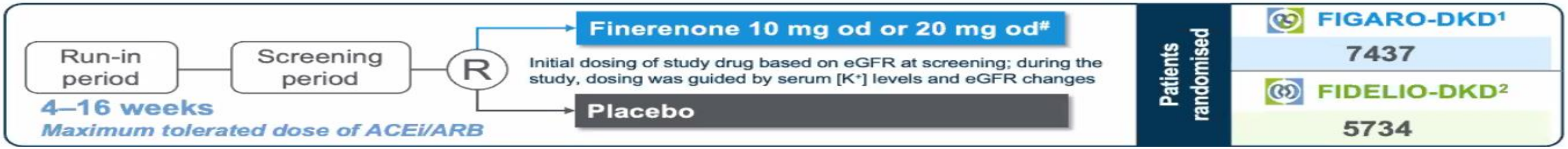
# Finerenone, a nonsteroidal, highly selectively MRA blocks MR overactivation, which slows kidney and CVD progression in pts with T2D




CV, cardiovascular; MR, mineralocorticoid receptor; MRA, mineralocorticoid receptor antagonist; T2D, type 2 diabetes

1. Fujita T. *Hypertension* 2010;55:813–818; 2. Bauersachs J, *et al. Hypertension* 2015;65:257–263; 3. Barrera-Chimal J, *et al. Kidney Int* 2019:96:302–319

# FIGARO-DKD and FIDELIO-DKD investigated the effects of finerenone on kidney and CV outcomes in over 13,000 patients with CKD and T2D[1,2]




## FIGARO-DKD[1]

**Clinical efficacy primary endpoint**

**Composite endpoint:**
Time to CV death, non-fatal MI, non-fatal stroke, or hospitalisation for HF

**Key secondary endpoint**

Same as primary endpoint in **FIDELIO-DKD**

## FIDELIO-DKD[2]

**Composite endpoint:**
Time to kidney failure,* sustained ≥40% eGFR decline, or renal death

Same as primary endpoint in **FIGARO-DKD**

## FIDELITY[3]

**Pooled analysis**

**Key outcomes**

**CV composite:**
Time to CV death, non-fatal MI, non-fatal stroke, or hospitalisation for HF

**57% kidney composite:**
Time to kidney failure,* sustained ≥57% eGFR decline, or renal death

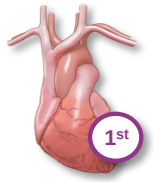
*Kidney failure defined as initiation of chronic dialysis for ≥90 days or kidney transplantation or sustained eGFR <15 ml/min/1.73 m$^2$[2,3]; #patients received an initial dose of finerenone of 10 mg od or 20 od based on an eGFR at the screening visit of 25–<60 or ≥60 ml/min/1.73 m$^2$, respectively.[1,2] 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]

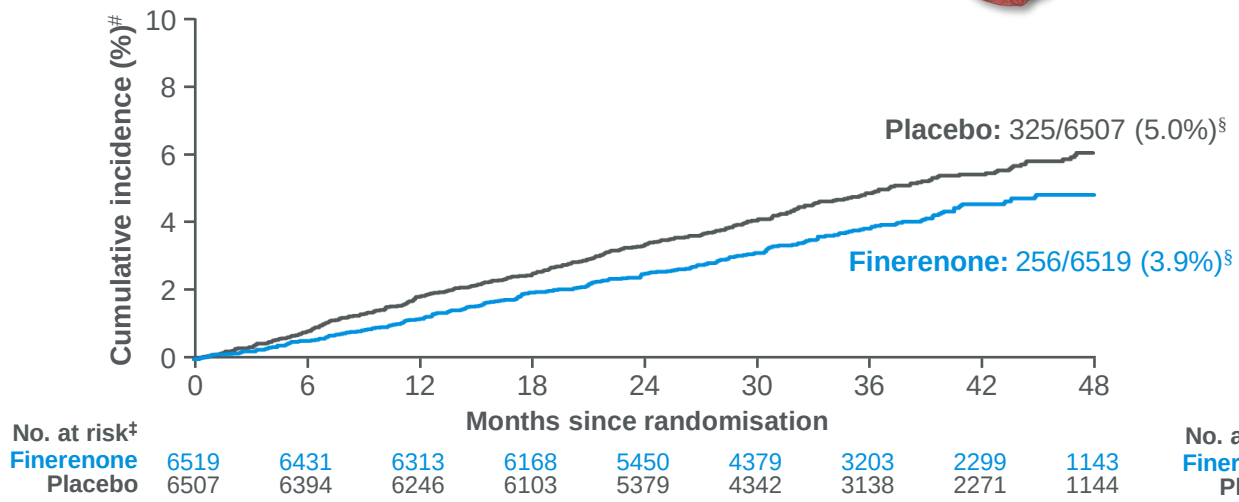
CKD, chronic kidney disease; CV, cardiovascular; eGFR, estimated glomerular filtration rate; HF, heart failure; MI, myocardial infarction; od, once daily; T2D, type 2 diabetes

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. Filippatos G, *et al. Circulation 2022*

# In pooled analysis FIDELITY, finerenone significantly reduced the risk of CV death and first HHF versus placebo

## Time to first HHF*



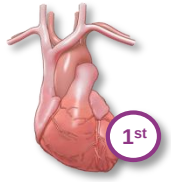



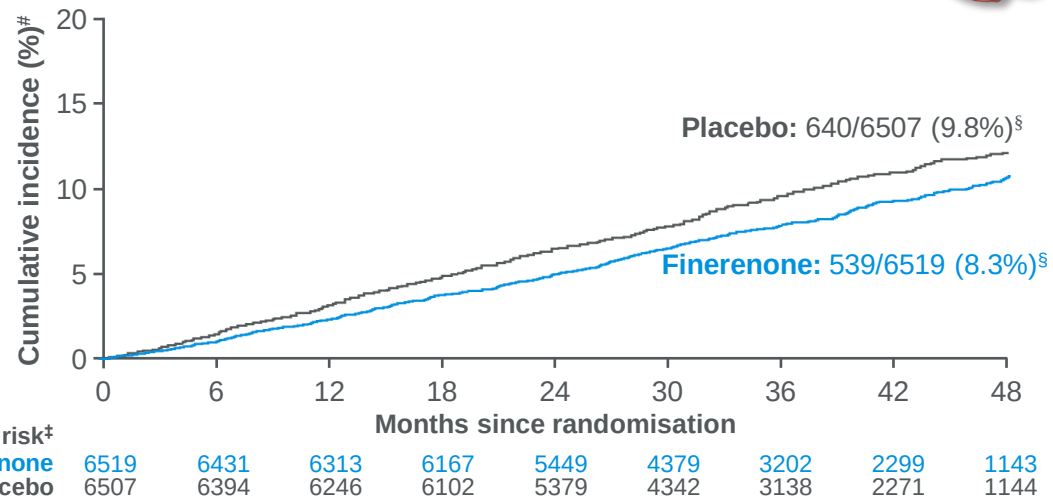

No. at risk‡

| | | | | | | | | | |
|---|---|---|---|---|---|---|---|---|---|
| Finerenone | 6519 | 6431 | 6313 | 6168 | 5450 | 4379 | 3203 | 2299 | 1143 |
| Placebo | 6507 | 6394 | 6246 | 6103 | 5379 | 4342 | 3138 | 2271 | 1144 |

**22%** reduced **risk of first HHF*** versus placebo
(HR=0.78; 95% CI 0.66–0.92)
*p*=0.0030

## Time to CV death and first HHF*




No. at risk‡

| | | | | | | | | | |
|---|---|---|---|---|---|---|---|---|---|
| Finerenone | 6519 | 6431 | 6313 | 6167 | 5449 | 4379 | 3202 | 2299 | 1143 |
| Placebo | 6507 | 6394 | 6246 | 6102 | 5379 | 4342 | 3138 | 2271 | 1144 |

**17%** reduced **risk of CV death and first HHF*** versus placebo
(HR=0.83; 95% CI 0.74–0.93)
*p*=0.0018

***First hospitalisation for HF.** Hospitalisation for heart failure; HR,

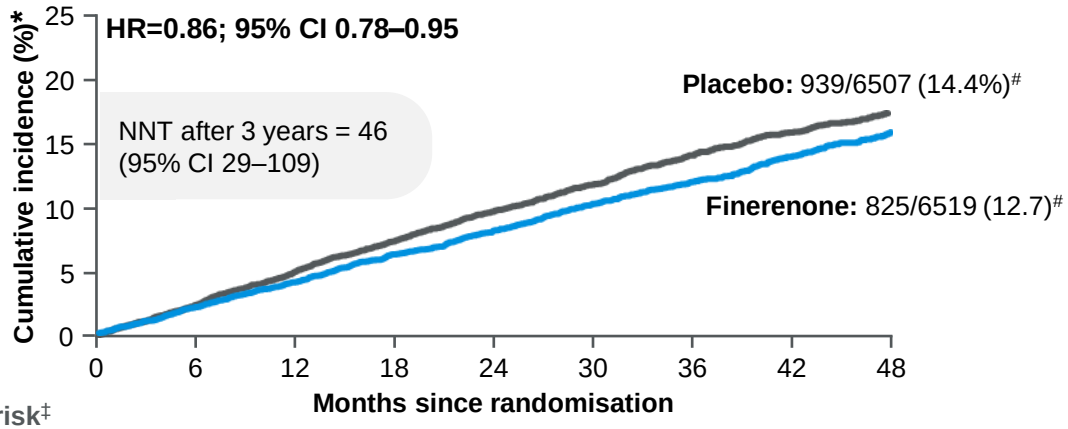
Filippatos G, *et al. JACC HF* 2022;10:860–870

FIDELITY

# In FIDELITY, on top of optimised RASi, finerenone significantly reduced the risk of the composite CV and kidney outcomes

## CV composite

**Time to CV death, nonfatal MI, nonfatal stroke or HHF**

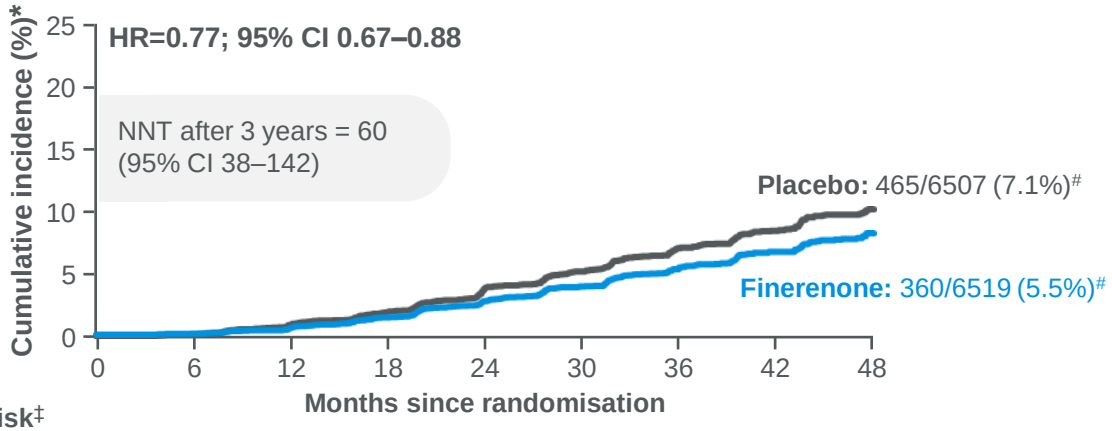



| No. at risk‡ | | | | | | | | | |
|---|---|---|---|---|---|---|---|---|---|
| Finerenone | 6519 | 6360 | 6202 | 6009 | 5273 | 4207 | 3065 | 2187 | 1087 |
| Placebo | 6507 | 6330 | 6125 | 5938 | 5184 | 4147 | 2969 | 2135 | 1082 |

**14%** reduced **risk of CV morbidity and mortality** versus placebo (HR=0.86; 95% CI 0.78–0.95); *p*=0.0018

## Kidney composite

**Time to kidney failure,§ sustained ≥57% decrease in eGFR from baseline, or kidney-related death**




| No. at risk‡ | | | | | | | | | |
|---|---|---|---|---|---|---|---|---|---|
| Finerenone | 6519 | 6291 | 6107 | 5848 | 5027 | 3973 | 2815 | 2024 | 959 |
| Placebo | 6507 | 6292 | 6071 | 5815 | 4949 | 3932 | 2798 | 1988 | 962 |

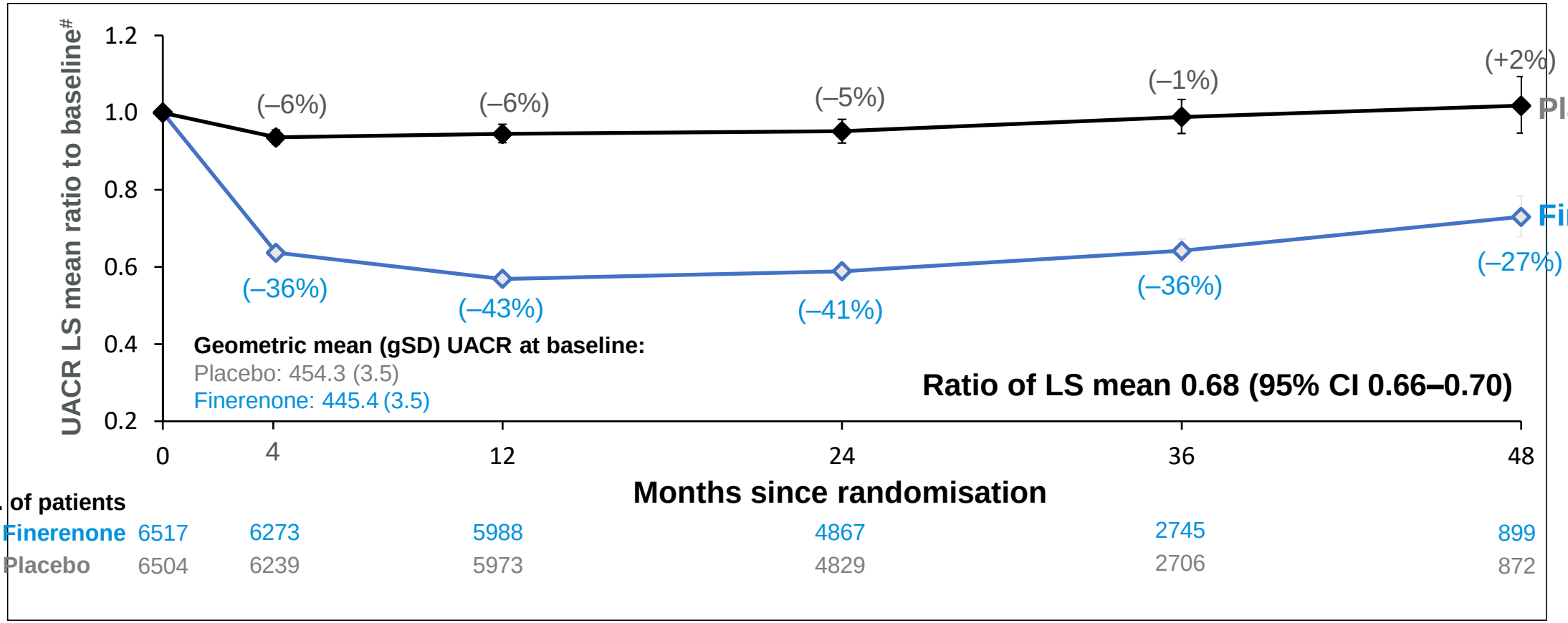
**23%** reduced **risk of CKD progression*** versus placebo (HR=0.77; 95% CI 0.67–0.88); *p*=0.0002

*Cumulative incidence calculated by Aalen–Johansen estimator using deaths due to other causes as competing risk; #number of patients with an event over a median of 3.0 years of follow-up; ‡at-risk subjects were calculated at start of time point; § ESKD or an eGFR <15 ml/min/1.73 $m^2$
CI, confidence interval; CKD, chronic kidney disease; CV, cardiovascular; eGFR, estimated glomerular filtration rate; ESKD, end-stage kidney disease HHF, hospitalisation for heart failure; HR hazard ratio; MI, myocardial infarction; NNT, number needed to treat; RASi, renin–angiotensin system inhibitor. Agarwal R, *et al. Eur Heart J* 2022;43:474–484

FIDELITY

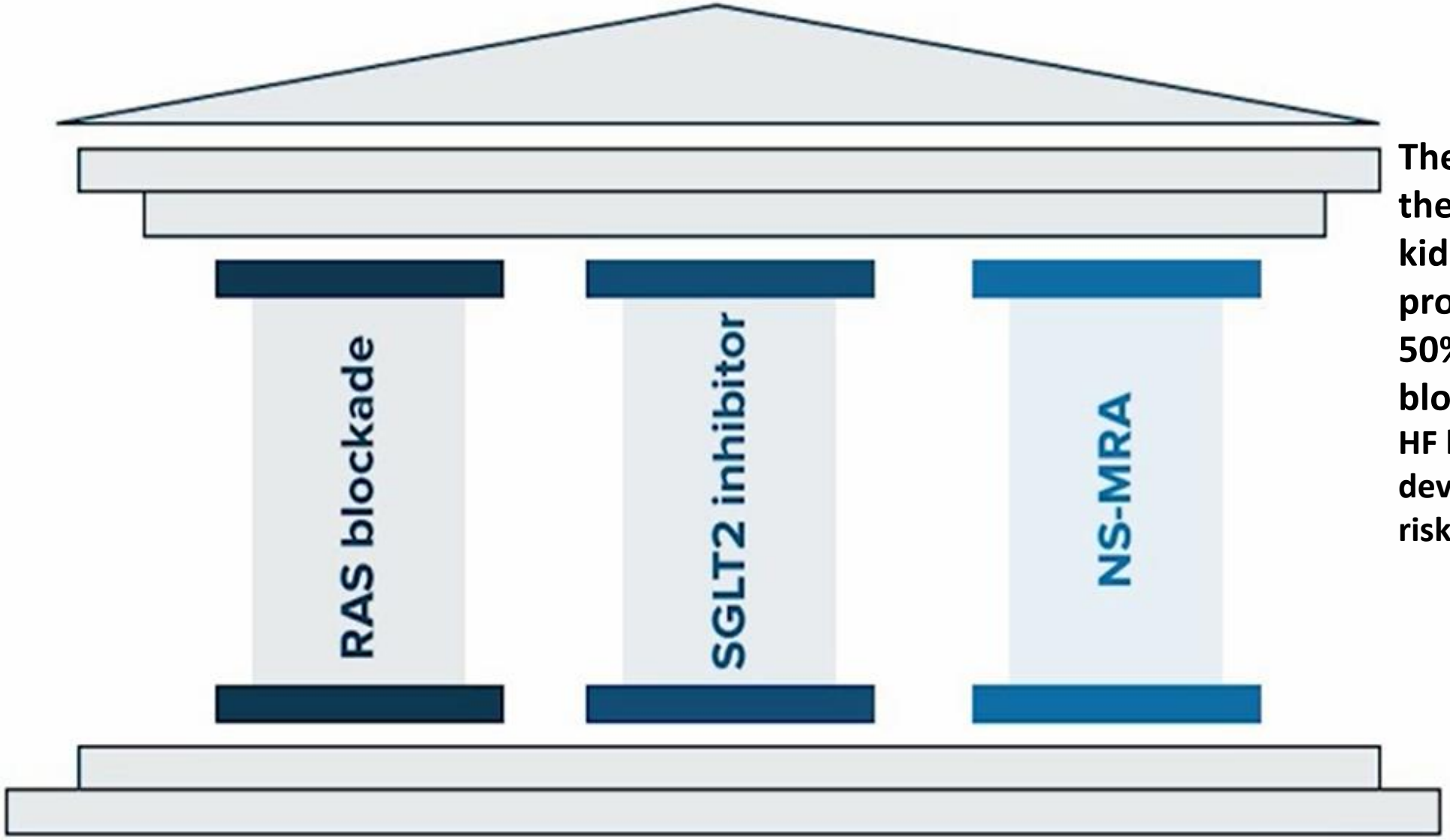
# In FIDELITY, finerenone reduced UACR by 32% between baseline and month 4 versus placebo*

## A lower mean UACR with finerenone versus placebo was maintained throughout the study




FIDELITY

# 3 Pillars of Therapy to Reduce CardioRenal Risk

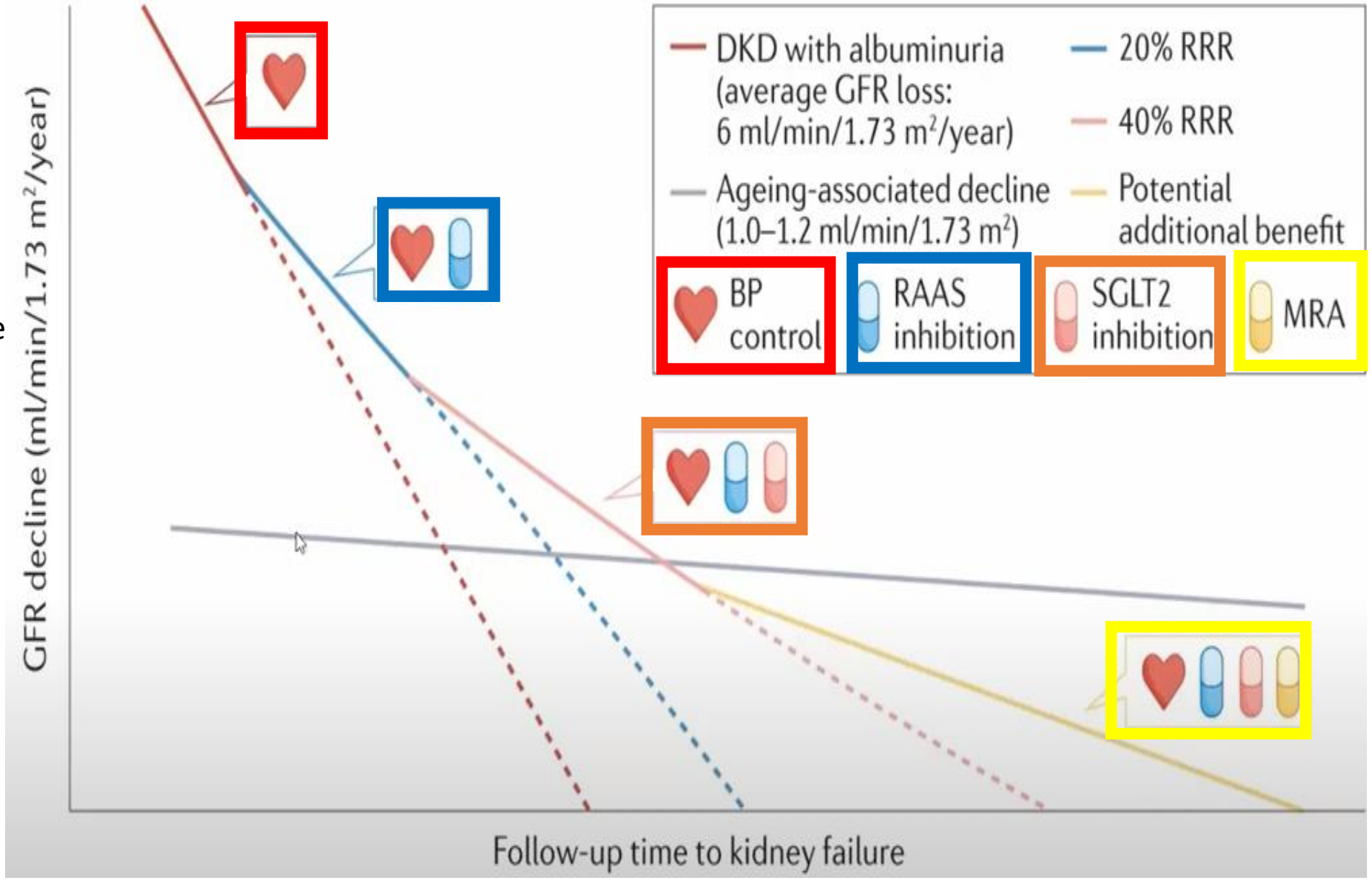



**These three "pillars of therapy" have slowed kidney disease progression by more than 50% compared to RAS blockers alone, reducing HF hospitalizations, the development of HF and the risk of CV death.**

# *Prevent/Delay CKD*

These 3 'pillars of therapy' are able to slow renal functional decline from approximately **10–12 ml/min per year** loss in the early 1980s to now about **2–3 ml/min/year.**

The average loss of kidney function in people without kidney disease or diabetes is about **0.7–0.9 ml/year .**



# Pillars of Therapy to Reduce CardioRenal Risk



FLOW trial focusing on slowing DKD progression in 3508 pts ongoing comparing semaglutide to placebo on renal outcomes.
Novo Nordisk Stops Ozempic Kidney Trial After Early Signs of Success October 11, 2023.
Novo Nordisk stops a trial studing Ozempic to treat kidney failure in DM pts because it was clear that the treatment would succeed.

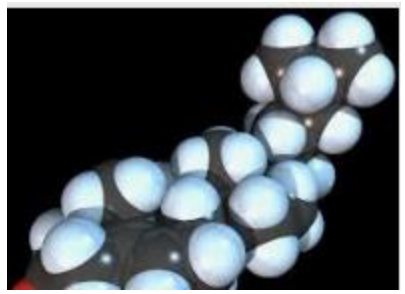
# 4 Pillars of Therapy to Reduce CardioRenal Risk

# Key Takeaways

A B C D E

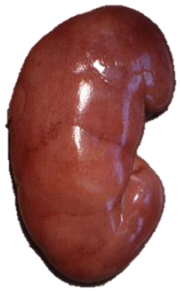
**A**lbuminuria

**B**pressure



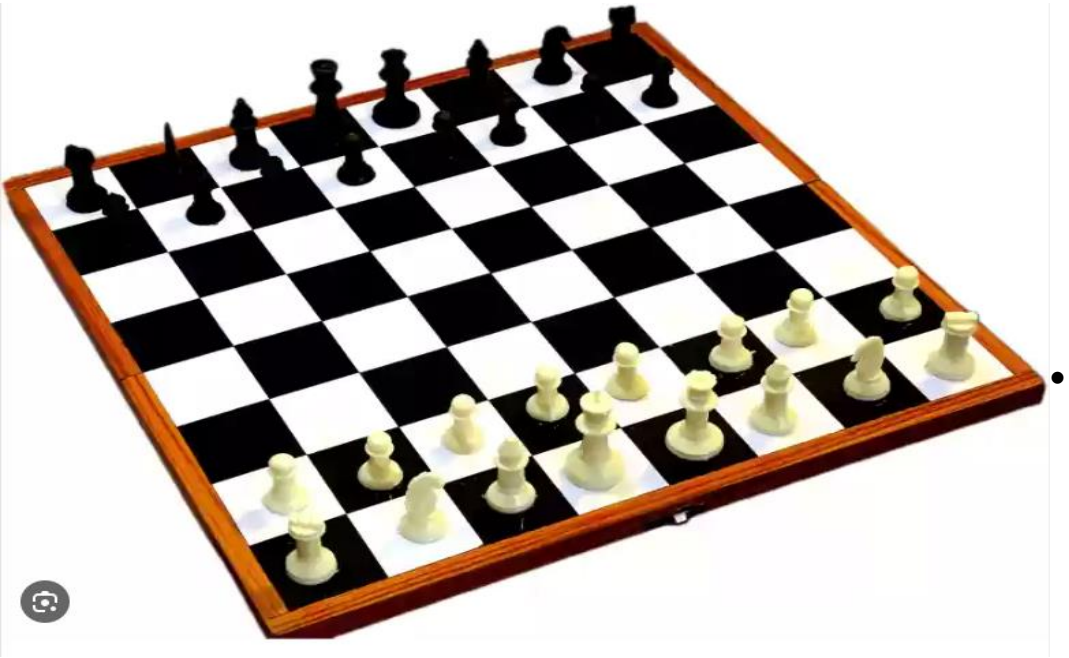
**C**holesterol

**D**iabetes



**E**-GFR (ml/min/1.73 $m^2$)

## *Instead of closing……*



- **Treating a patient with diabetic nephropathy, especially when the eGFR is below 30 ml/min, is like playing a chess game to the death, where you, with three white pieces, RAAS-i, SGLT2-I and our Queen Kerendia, are challenged by her, who plays with the black pieces: clinical conditions, high blood pressure, levels of creatinine, potassium, uricemia, and diuresis. It is a match you must win.**
- **•The insistence to win, up to the level of the search for beauty, means that not only will you save lives but, crucially, you will understand why you chose to become a doctor, why this profession means dealing more with life than death. However, this requires passion. Without it, nothing is acquired (achieved). Without it you will never find the beauty and you will never be reborn, risking a double checkmate: the death of the patient and your own professional death.**