# *Therapeutic Transformation of Chronic Kidney Disease*

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In the spirit of honoring the composition of place, I acknowledge that I live and work on the homelands of the Spokane, Palouse, Nez Perce, Coeur d'Alene, and Kootenai Tribal People.

I am grateful to be on this land and ask for its support as we work to create an equitable, diverse, and inclusive community.

DIABETIC KIDNEY DISEASE COLLABORATIVE

# Disclosures

Therapeutics for diabetes and kidney disease:

- Eli Lilly and Company
- Boehringer Ingelheim
- Bayer
- Novo Nordisk
- Travere
- ProKidney

# Goals

- Describe the scale, risks, and mechanisms of chronic kidney disease (CKD).
- Define guideline directed medical therapies (GDMT) to reduce kidney and cardiovascular risks of CKD.
- Discuss strategies to implement GDMT in persons with CKD.

# CKD is a major public health concern

## Worldwide[1]

**Extremely common**

**844 MILLION**

in 2017

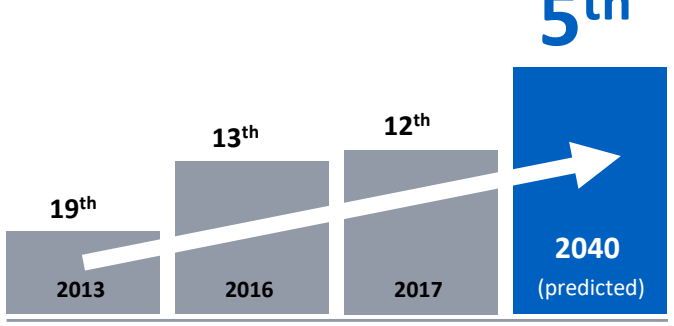
**1 in 10**

people in the general population have CKD

**Increasing death rate**

**41.5%**

from 1990 to 2017




Rank in cause of death

## USA[2]

**~39 MILLION**

in 2017

and caused almost

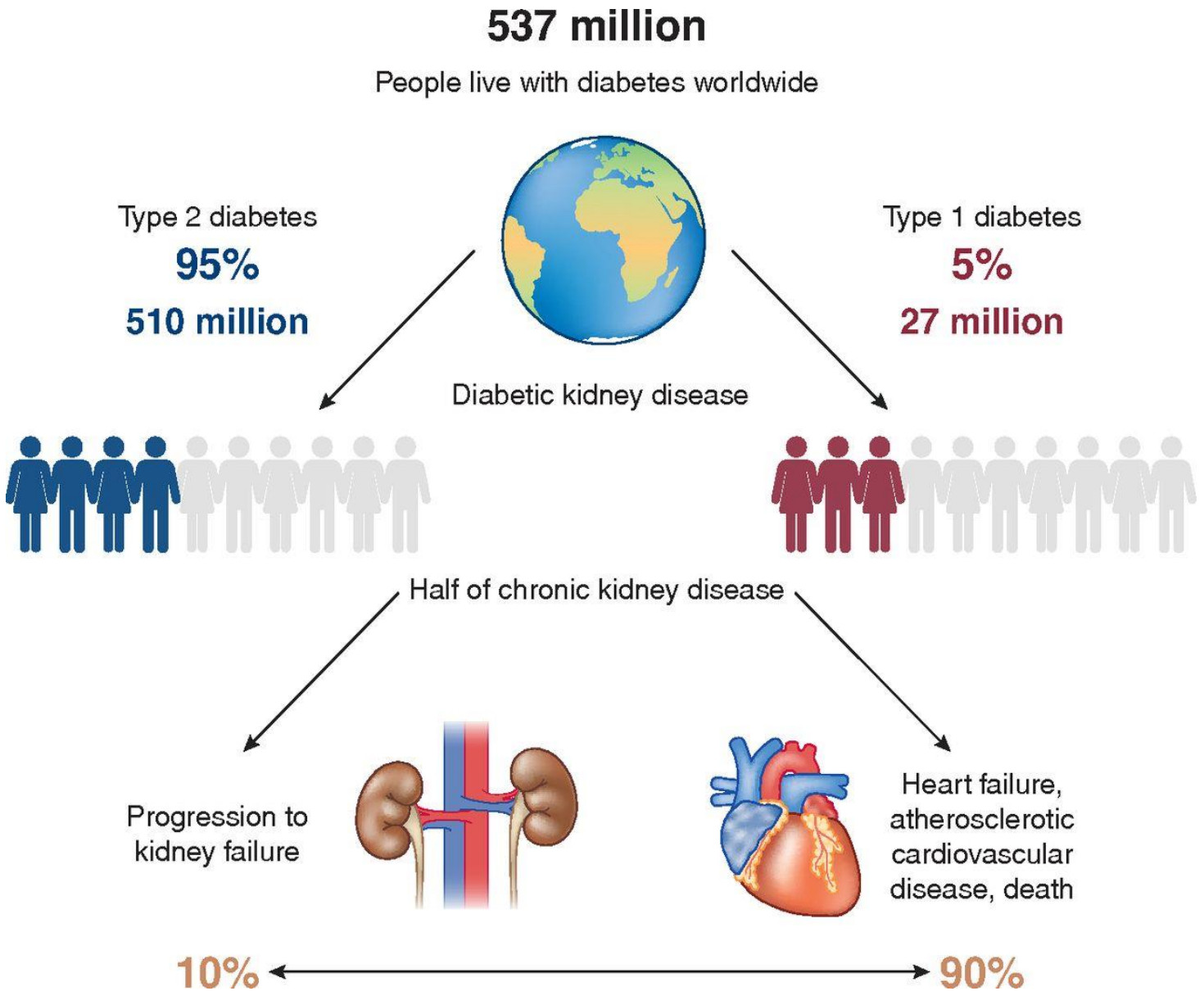
**85,000 deaths**

in 2017

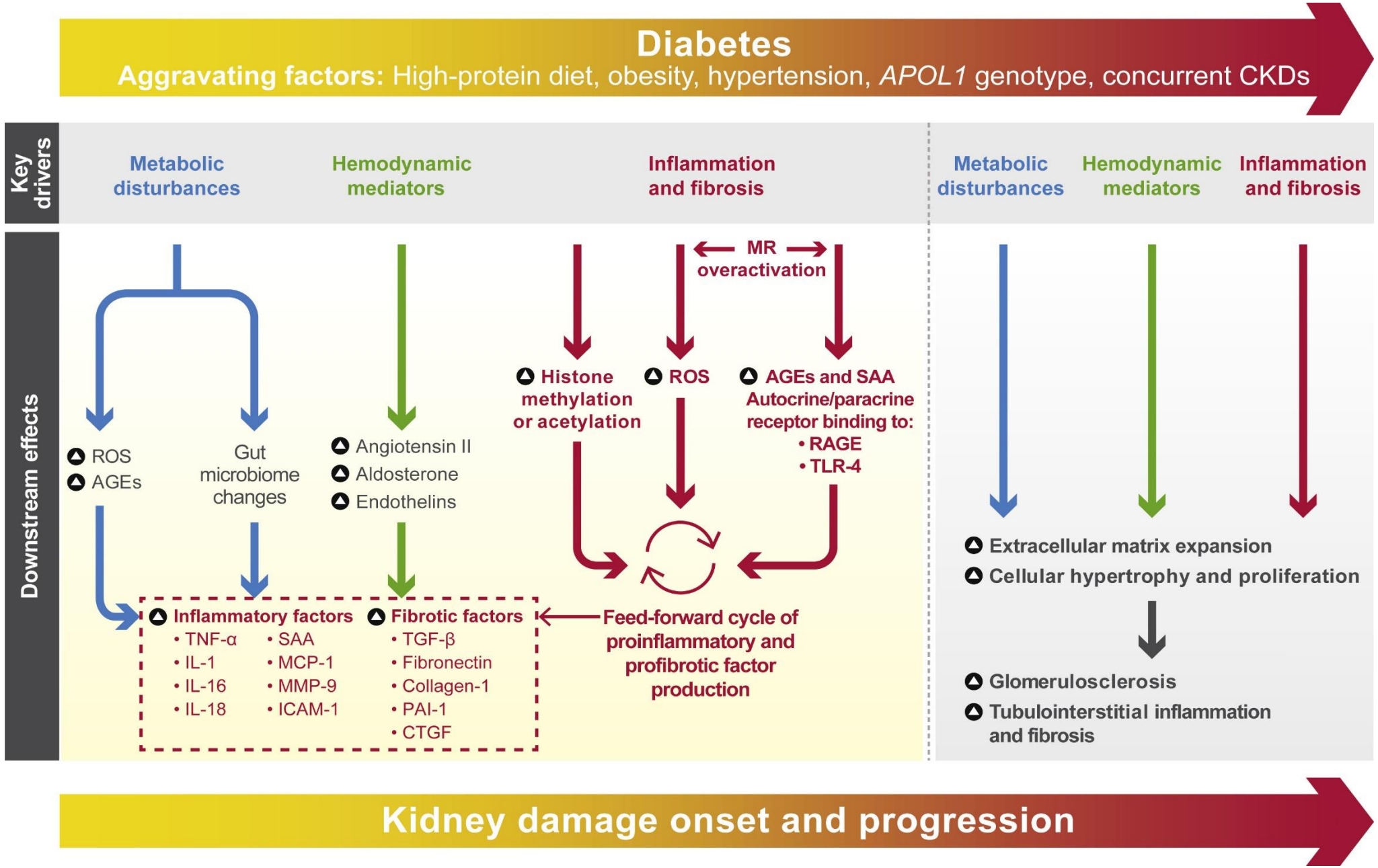
CKD, chronic kidney disease.

1. Kovesdy CP. *Kidney Int Suppl (2011)* 2022;12:7–11; 2. GBD Chronic Kidney Disease Collaboration. *Lancet* 2020;395:709–733.

# What Problem are We Trying to Solve?

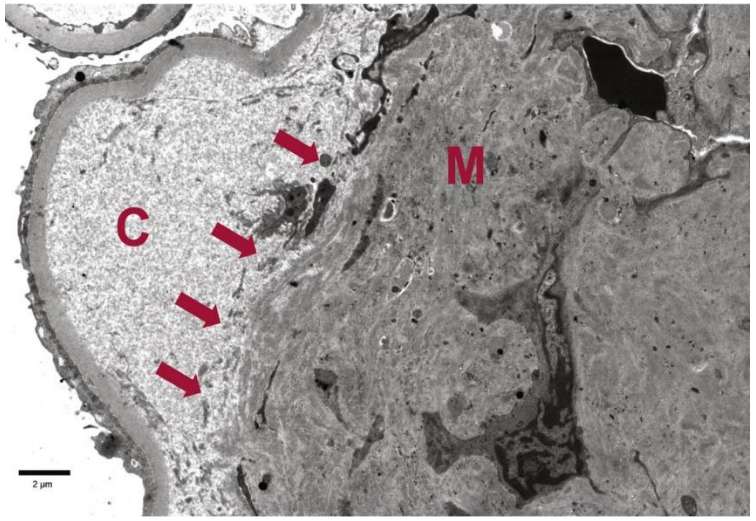


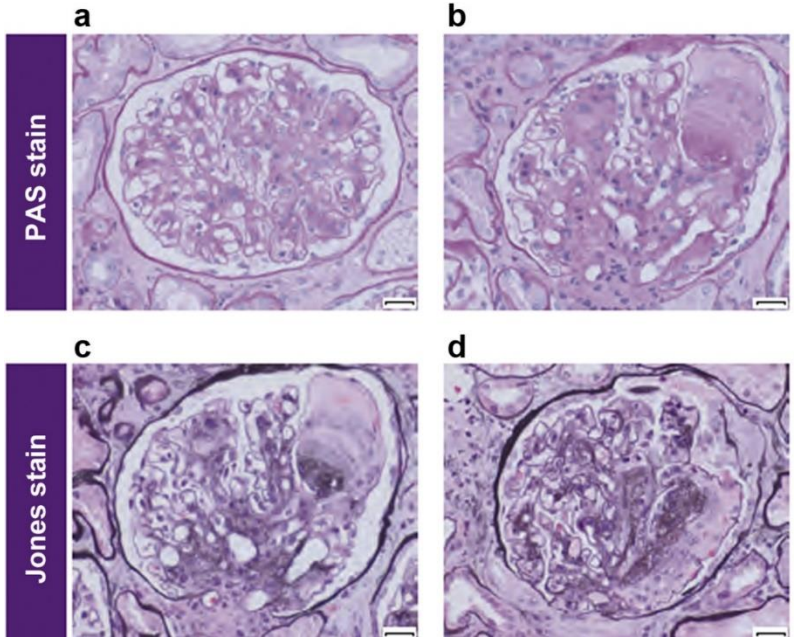

Tuttle KR *et al. CJASN* 2022;17:1092-1103

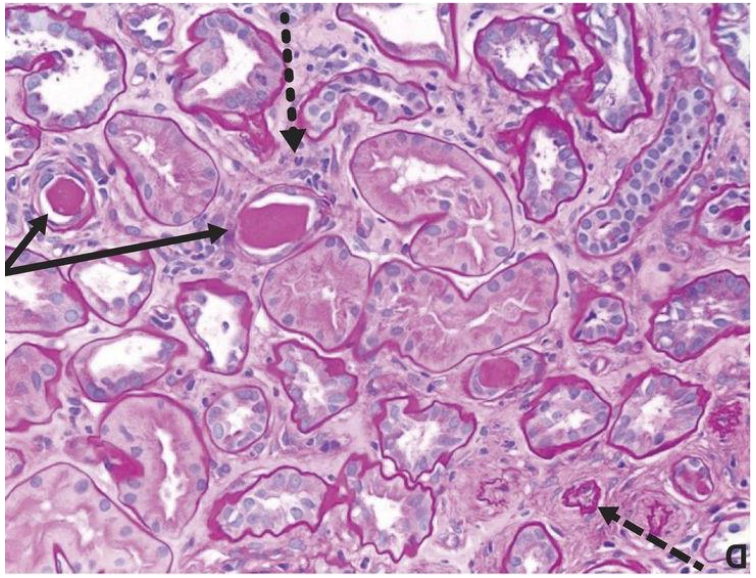


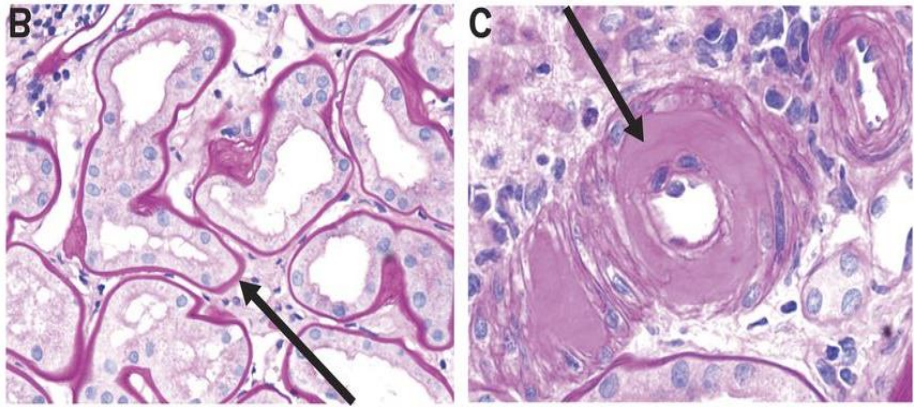

Tuttle KR *et al. Kidney Int* 2022;102:248-260

# Diabetic Kidney Disease: Glomerular, Tubulointerstitial, and Arteriolar Pathology



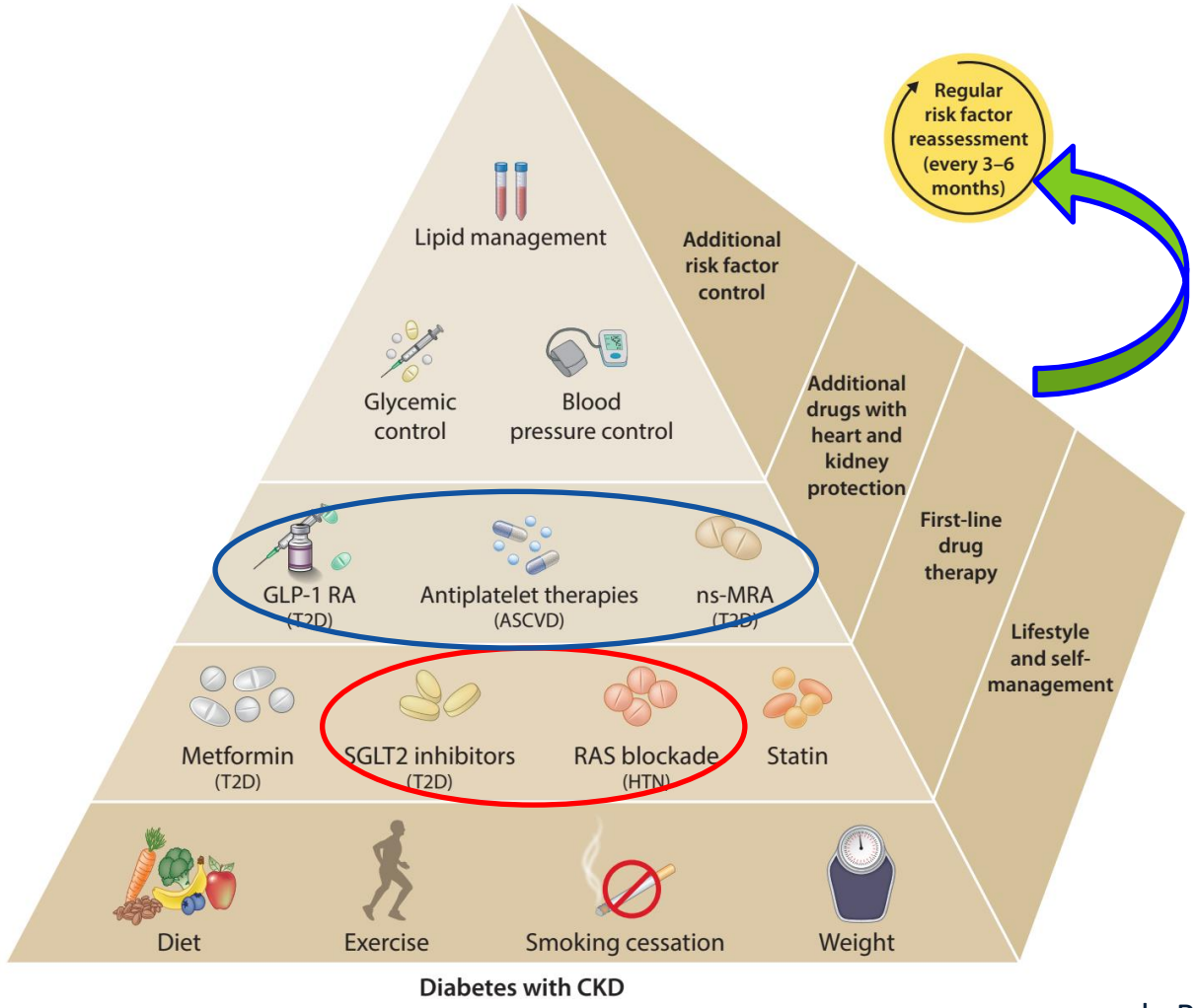






Tuttle KR, Alpers CE *et al. Kidney Int* 2022;102:248-260
Alicic RZ, Tuttle KR *et al*. *CJASN* 2017;12:2032-2045

# KDIGO 2022 Clinical Practice Guideline for Management of Diabetes in CKD

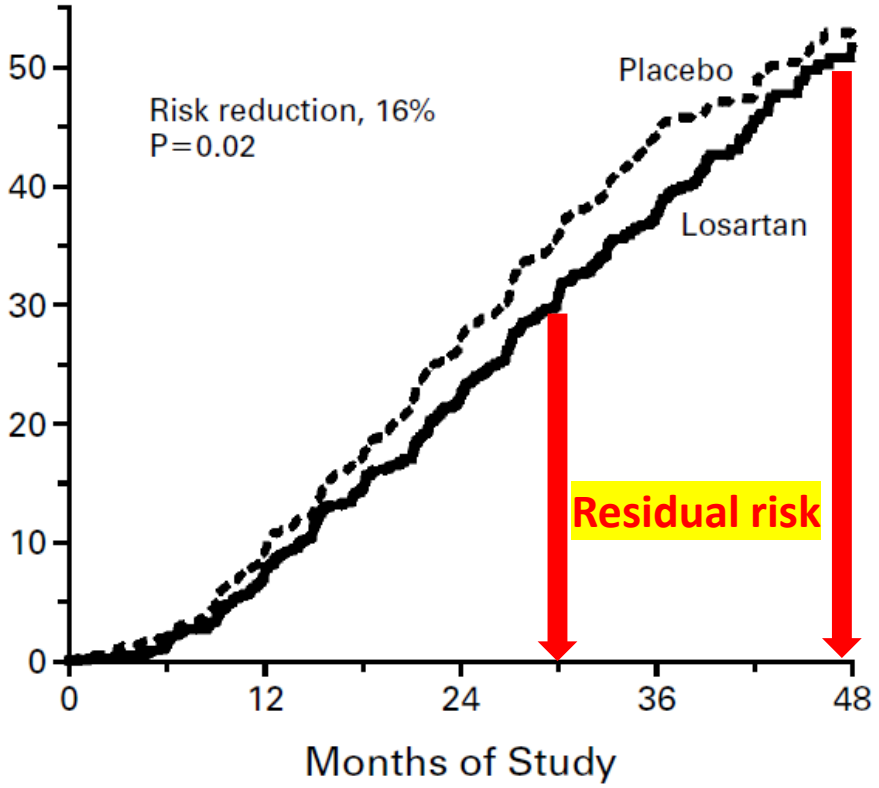



de Boer IH *et al. Diabetes Care* 2022;45:3075-3090

# Angiotensin Receptor Blockade in Type 2 Diabetes and CKD

**Doubling of serum creatinine, ESKD, or death**

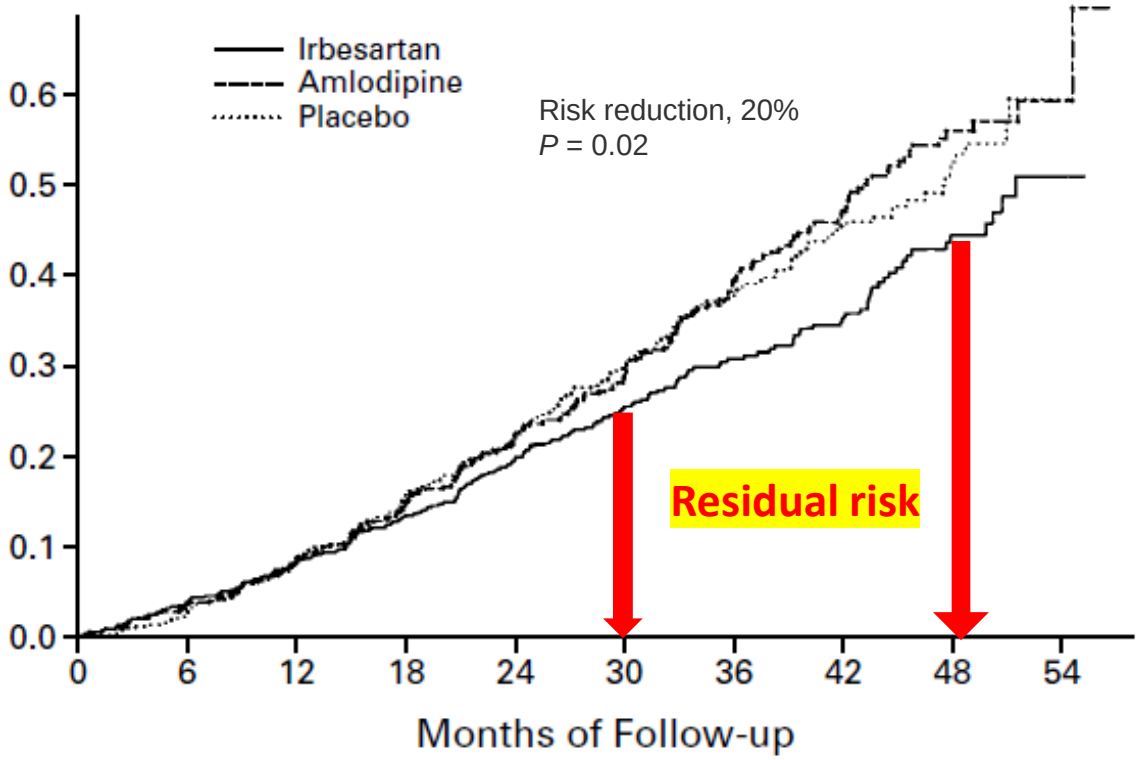
**RENAAL**




**2.5 and 4-year absolute residual risks:**
~30% and ~45%

Brenner B *et al. N Engl J Med* **2001**;345:861–869

**IDNT**




**2.5 and 4-year absolute residual risks:**
~25% and ~40%

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

# SGLT2 Inhibition
# Cardiovascular Trials in Type 2 Diabetes

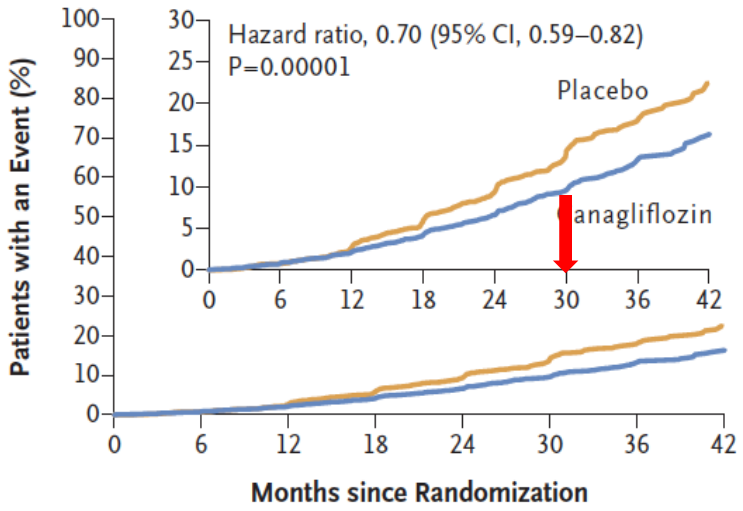
- Reduce risk of major adverse CVD Events.
  - Heart failure (empagliflozin, canagliflozin, dapagliflozin)
  - Atherosclerotic CVD (3-point MACE: myocardial infarction, stroke, CVD death)
  - CVD death (empagliflozin, dapagliflozin)
- Decrease macroalbuminuria, eGFR decline, and kidney failure.
- CVD and CKD benefits are present in patients with CKD.

# The Trilogy of SGLT2 Inhibitors for CKD

***All SGLT2 inhibitor trials in CKD were stopped early based on clear evidence of benefit – A first in Nephrology***

Primary outcomes: Substantial eGFR decline (40%, 50%, 57%), kidney failure, or death due to kidney or cardiovascular causes

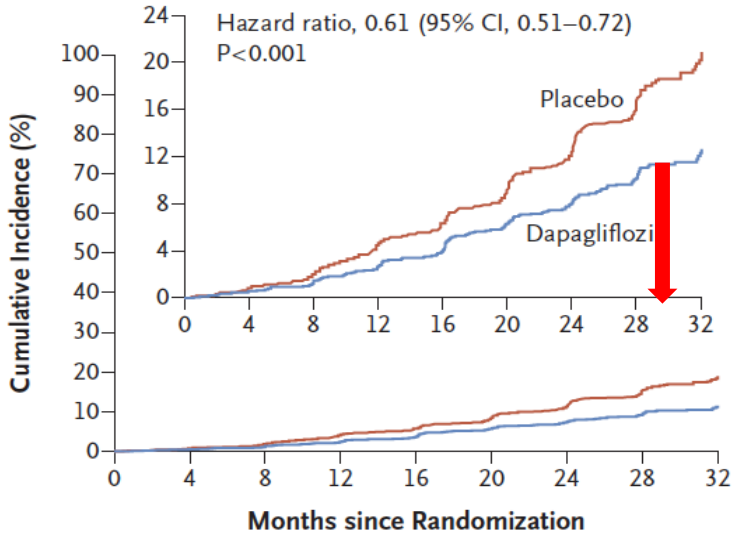
**Residual risk**




**CREDENCE**

Adults with type 2 diabetes, eGFR ≥30 mL/min/1.73 m2, UACR >300 mg/g (N=4401)

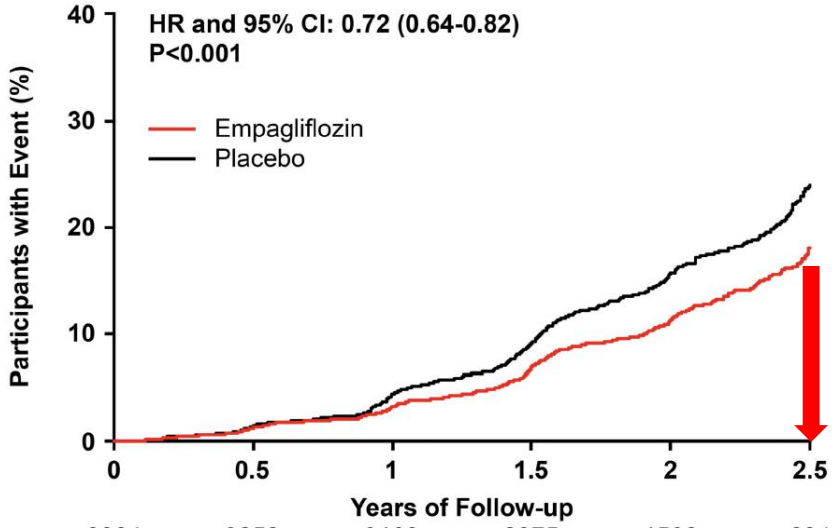
Perkovic V *et al. N Engl J Med*. 2019;380:2295-2306




**DAPA-CKD**

Adults with or without type 2 diabetes, eGFR ≥25 mL/min/1.73 m2, UACR >200 mg/g (n=2906).

Heerspink HJL et *al. N Engl J Med.* 2020;383(15):1436-1446




**EMPA-KIDNEY**

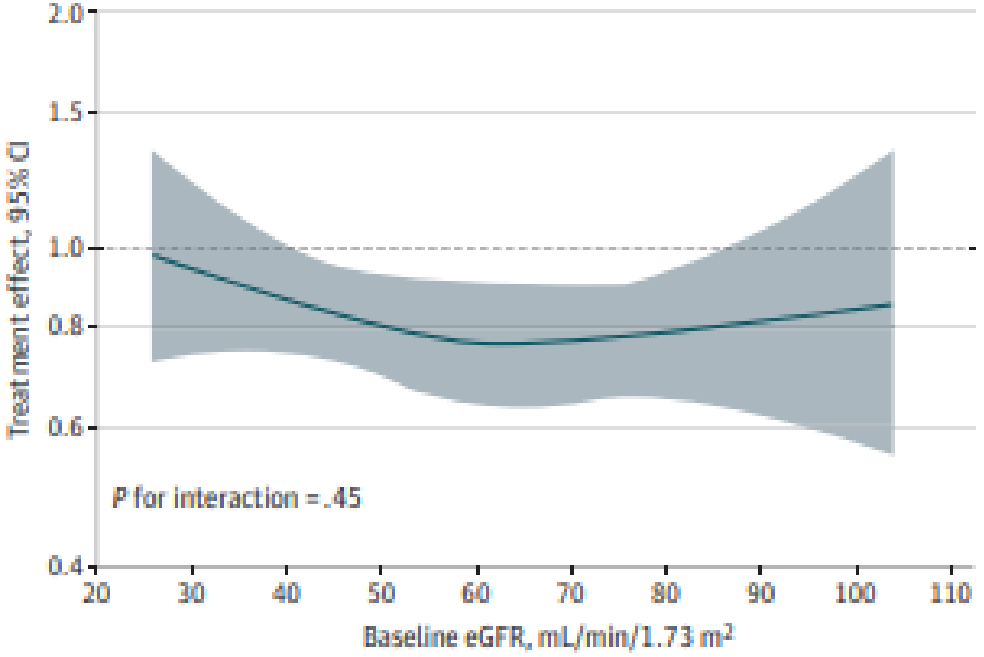
Adults with or without type 2 diabetes, eGFR ≥45 to <90 mL/min/1.73 $m^2$ and UACR ≥200 mg/g or ≥20 to <45 mL/min/1.73 $m^2$ irrespective of albuminuria (N=6609).

Herrington W *et al.* for the EMPA-KIDNEY Collaborative Group. *N Engl J Med.* 2023;388:117-127

# Dapagliflozin Effects on Heart Failure Events and Cardiovascular Death by Kidney Function

## DELIVER

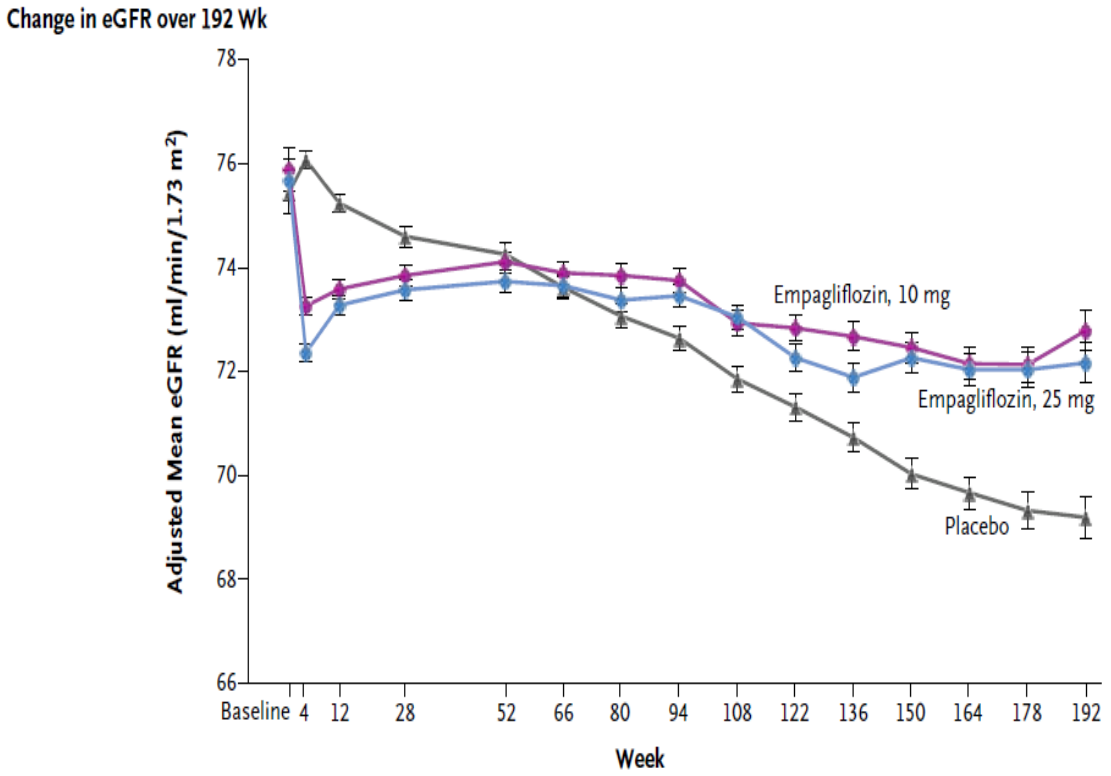
## HFpEF and HFmrEF



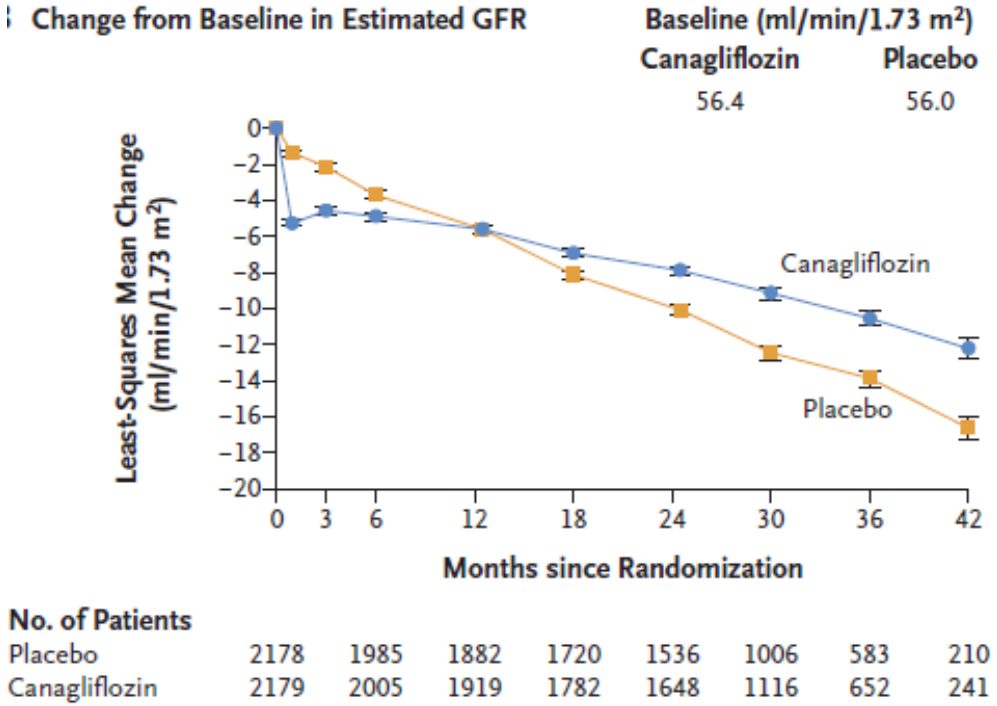

| Characteristic | eGFR ≥60 mL/min/1.73 m² | | eGFR 45 to <60 mL /min/1.73 m² | |
|---|---|---|---|---|
| | Placebo (n = 1577) | Dapagliflozin (n = 1615) | Placebo (n = 831) | Dapagliflozin (n = 826) |
| CV death, heart failure hospitalization or urgent heart failure visit | | | | |
| Events, No. (%) | 255 (16) | 223 (14) | 159 (19) | 113 (14) |
| Rate/100 patient-years, (95% CI) | 7.7 (6.8-8.7) | 6.4 (5.6-7.3) | 9.5 (8.1-11.1) | 6.5 (5.4-7.8) |
| HR (95% CI) | 0.84 (0.70-1.00) | | 0.68 (0.54-0.87) | |
| NNT[a] | 33 | | 18 | |

McCausland FR *et al. JAMA Cardiol* 2023;8:56-65

# EMPA-REG and CREDENCE
# Preventing eGFR Decline in Type 2 Diabetes

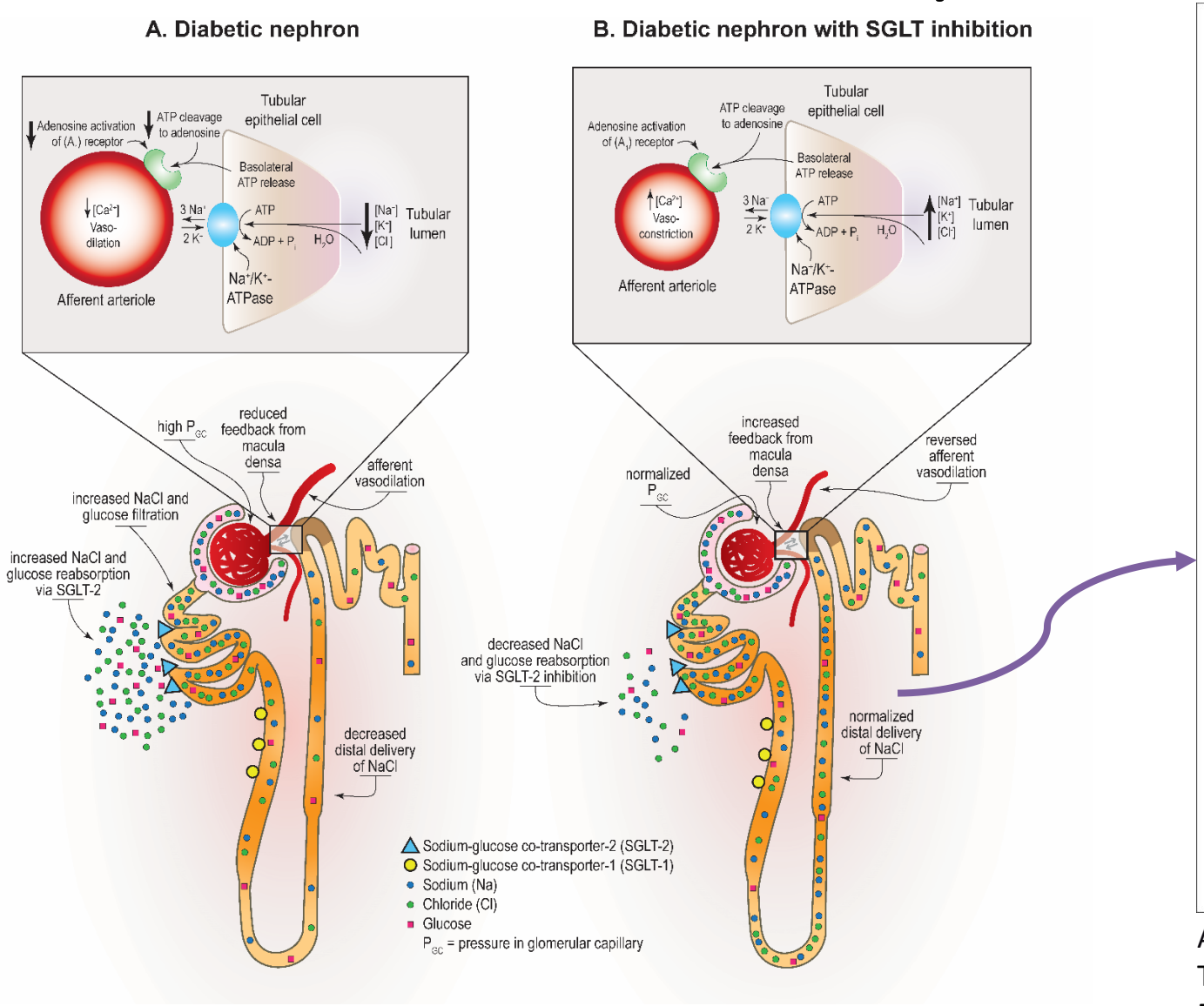


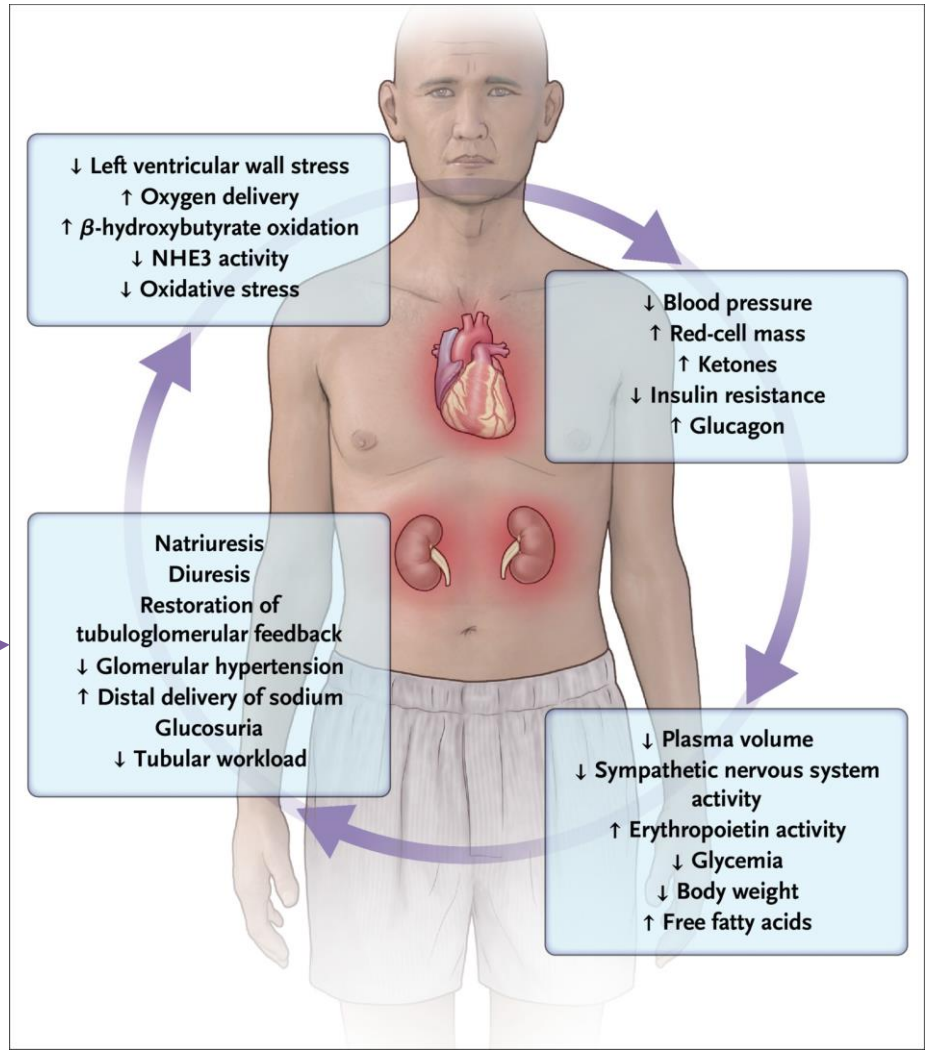

Wanner C *et al. N Engl J Med* 2016;375:323-334




Perkovic V *et al. N Eng J Med* 2019;380:2295-2306

# The Kidney–Heart Connection for Organ Protection by SGLT2 Inhibitors

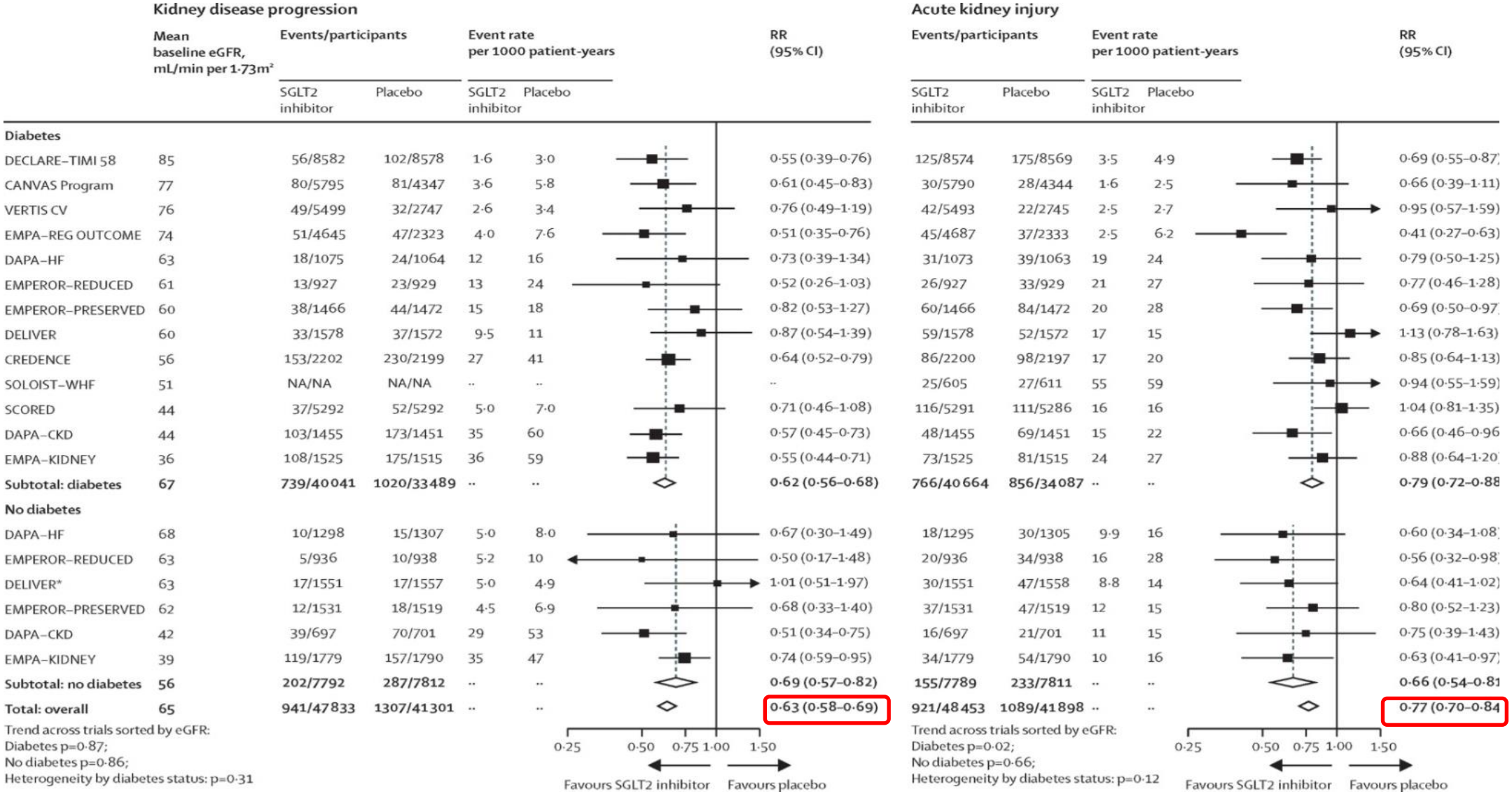




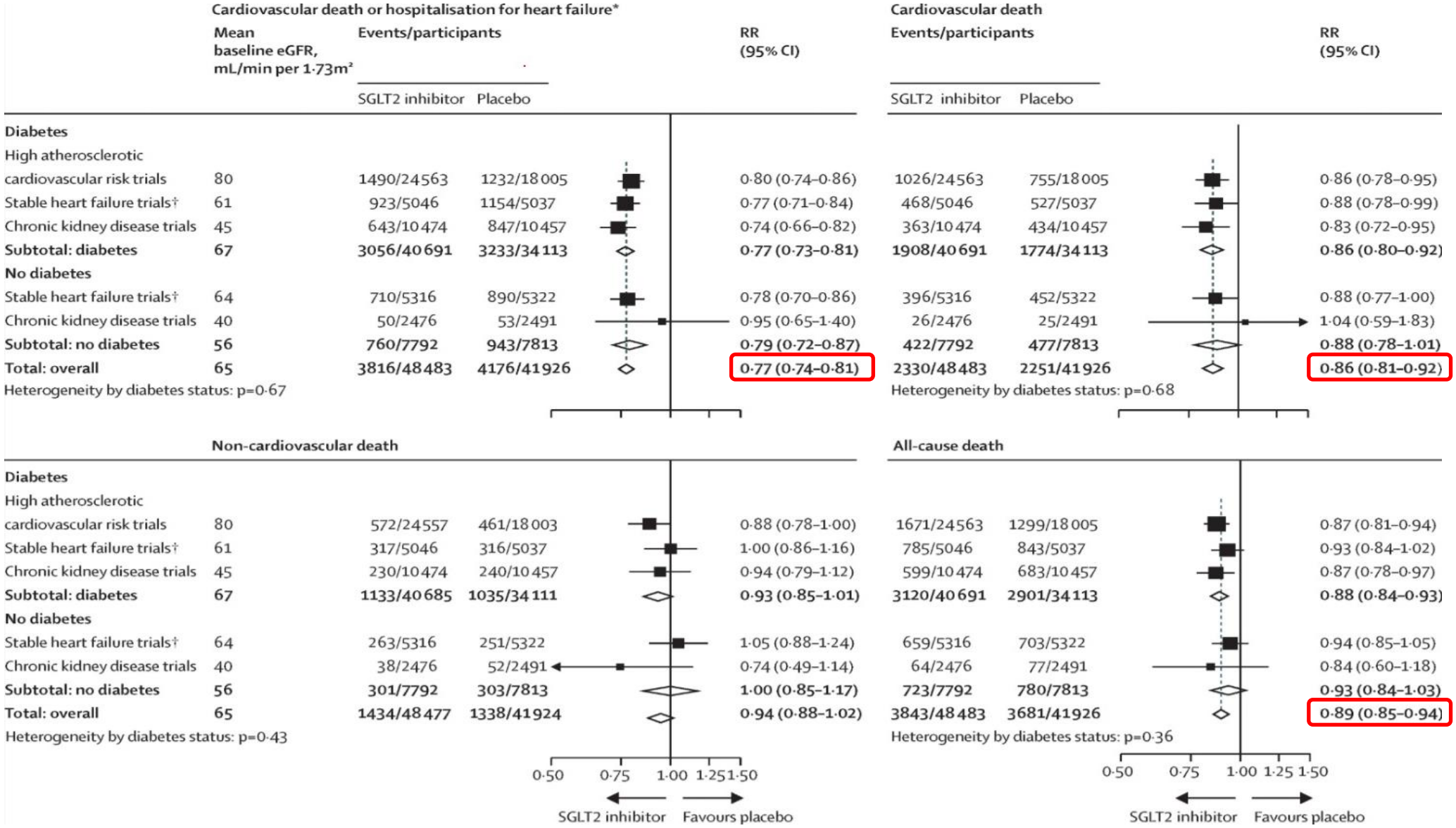
Alicic RZ, Johnson EJ, Tuttle KR. *Am J Kidney Dis* 2018;72:267-277
Tuttle KR *et al. Am J Kidney Dis* 2021;77:94-109
Braunwald E. *N Engl J Med* 2022;386:2024-2034

# CKD Risks are Reduced in Clinical Trials of Patients with and without CKD or Diabetes



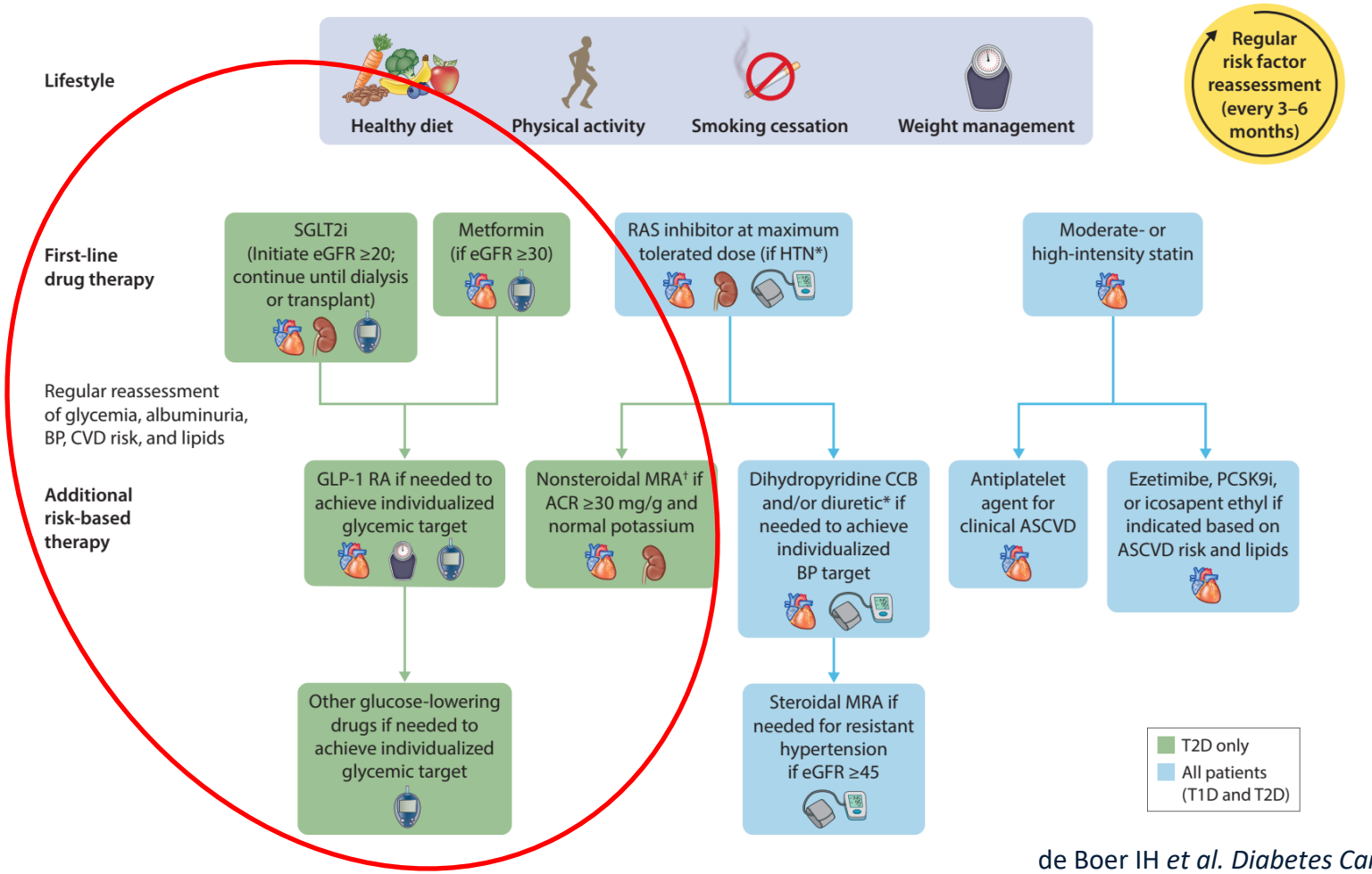

Herrington W, Nuffield Population Health and SMART Consortium. *Lancet* 2022;400:1788-1801

# Benefits of SGLT2 inhibitors on Heart Failure and Death with and without CKD or Diabetes




Herrington W, Nuffield Population Health and SMART Consortium. *Lancet* 2022;400:1788-1801

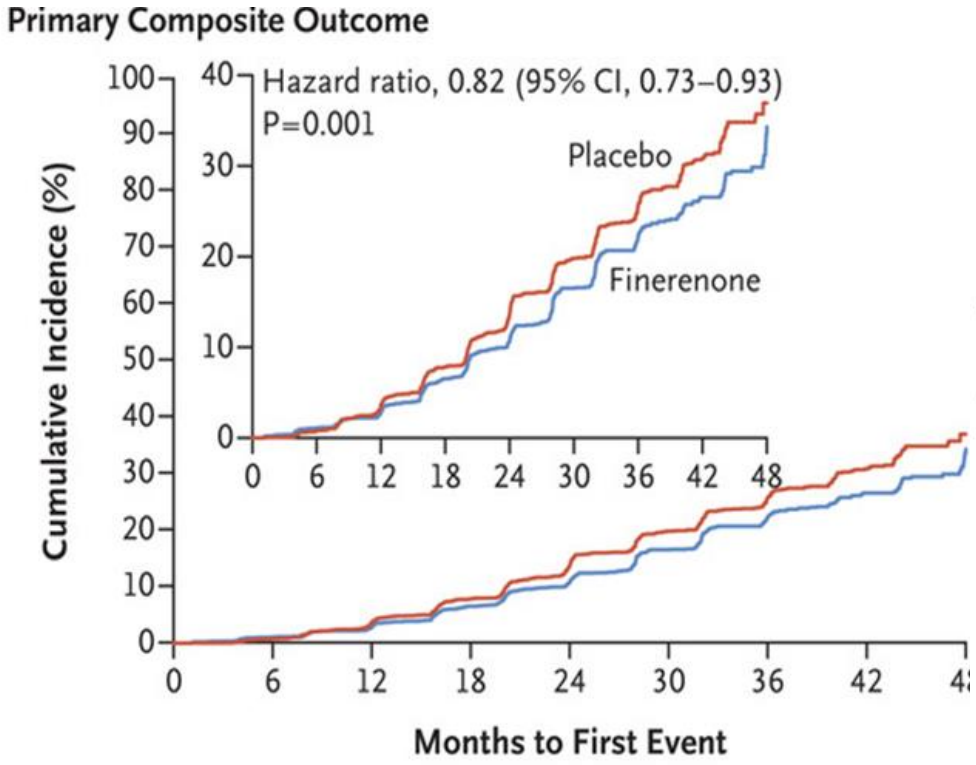
# Holistic Approach for Patients with Diabetes and CKD




de Boer IH *et al. Diabetes Care* 2022;45:3075-3090
KDIGO Diabetes Work Group. *Kidney Int* 2022;102(5S):S1-S127

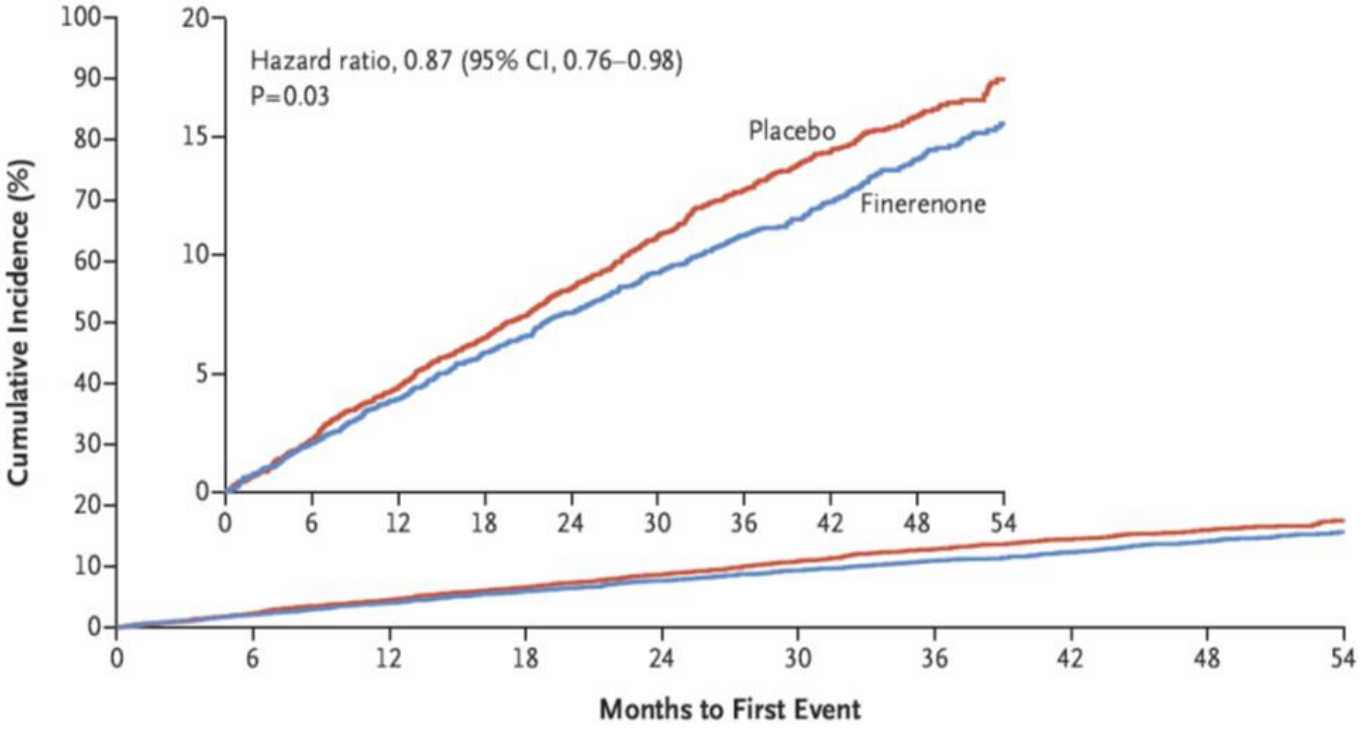
# FIDELIO and FIGARO
# Finerenone in CKD and Type 2 Diabetes

Finerenone 10/20 mg daily versus placebo
Standard-of-care with ACE inhibitor or ARB use




**FIDELIO**
eGFR decline 40%, kidney failure, kidney disease death

Bakris GL *et al. N Engl J Med* 2020;383:2219-2229



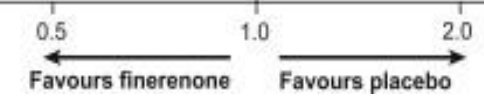

**FIGARO**
MI, stroke, heart failure hospitalization, CVD death

Pitt B *et al. N Engl J Med* 2021;385:2252-2263

# FIDELITY Meta-Analysis: Kidney and Cardiovascular Events with Finerenone versus Placebo

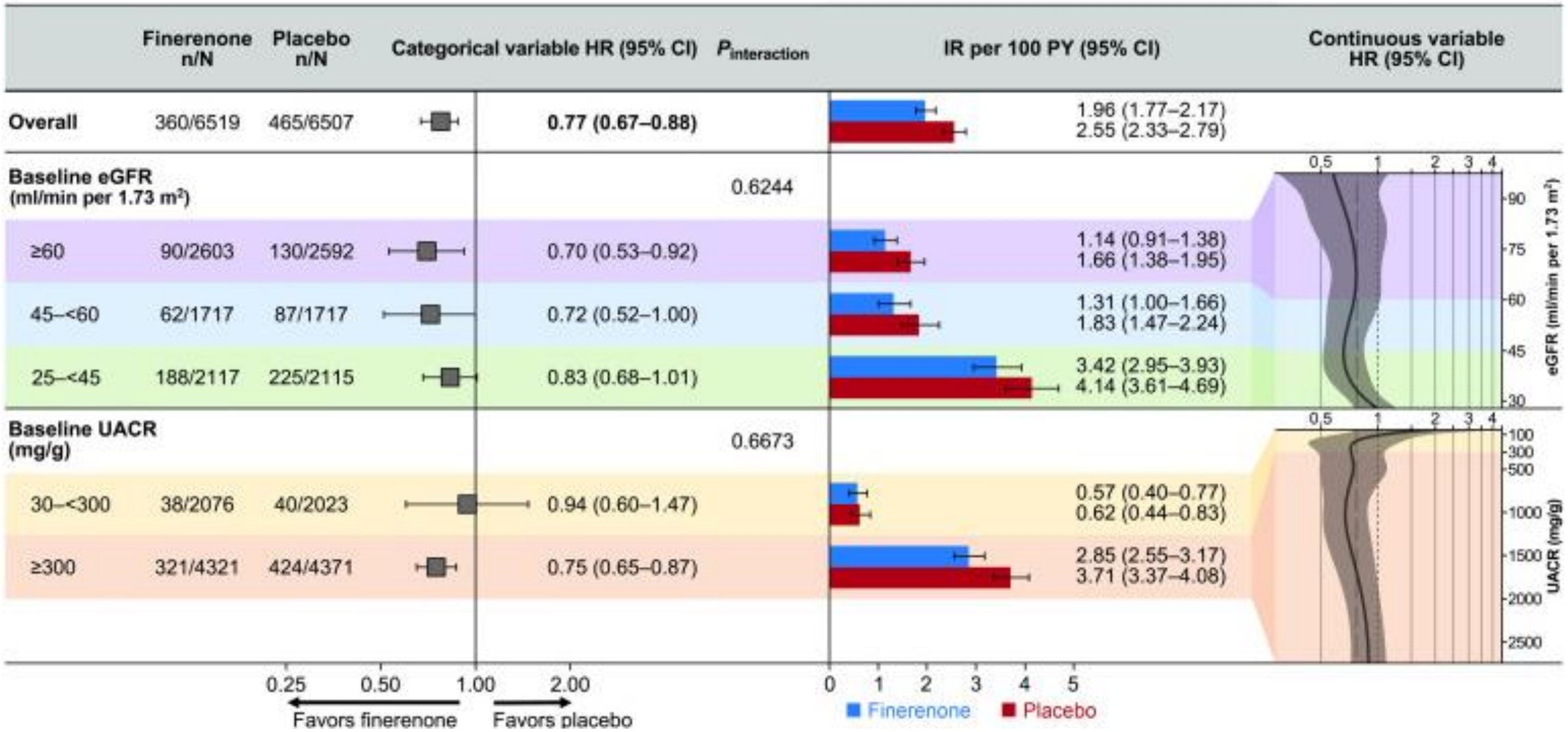
- 13,026 patients followed for median of 3.0 years
- CVD outcome HR 0.86; 95% CI 0.78–0.95
- Kidney disease outcome HR 0.77; 95% CI 0.67–0.88
- Similar risk reductions in SGLT2 inhibitor users (5-10%)

| Outcome | Finerenone (n = 6519) | | Placebo (n = 6507) | | Hazard ratio (95% CI) | *P*-value[a] |
|---|---|---|---|---|---|---|
| | Number of patients with event (%) | Number of patients with event per 100 patient-years | Number of patients with event (%) | Number of patients with event per 100 patient-years | | |
| **Composite cardiovascular outcome**[b] | 825 (12.7) | 4.34 | 939 (14.4) | 5.01 | 0.86 (0.78–0.95) | 0.0018 |
| Death from cardiovascular causes | 322 (4.9) | 1.61 | 364 (5.6) | 1.84 | 0.88 (0.76–1.02) | 0.092 |
| Non-fatal myocardial infarction | 173 (2.7) | 0.88 | 189 (2.9) | 0.97 | 0.91 (0.74–1.12) | 0.36 |
| Non-fatal stroke | 198 (3.0) | 1.01 | 198 (3.0) | 1.02 | 0.99 (0.82–1.21) | 0.95 |
| Hospitalization for heart failure | 256 (3.9) | 1.31 | 325 (5.0) | 1.68 | 0.78 (0.66–0.92) | 0.0030 |
| **eGFR ≥57% composite kidney outcome**[c] | 360 (5.5) | 1.96 | 465 (7.1) | 2.55 | 0.77 (0.67–0.88) | 0.0002 |
| Kidney failure | 254 (3.9) | 1.38 | 297 (4.6) | 1.62 | 0.84 (0.71–0.99) | 0.039 |
| End-stage kidney disease[d] | 151 (2.3) | 0.76 | 188 (2.9) | 0.96 | 0.80 (0.64–0.99) | 0.040[e] |
| Sustained decrease in eGFR to <15 mL/min/1.73 m$^2$ | 195 (3.0) | 1.06 | 237 (3.6) | 1.29 | 0.81 (0.67–0.98) | 0.026[e] |
| Sustained ≥57% decrease in eGFR from baseline | 257 (3.9) | 1.40 | 361 (5.5) | 4.03 | 0.70 (0.60–0.83) | < 0.0001 |
| Renal death | 2 (<0.1) | 0.01 | 4 (<0.1) | 0.02 | 0.53 (0.10–2.91) | 0.46[e] |
| **eGFR ≥40% composite kidney outcome**[f] | 854 (13.1) | 4.81 | 995 (15.3) | 5.64 | 0.85 (0.77–0.93) | 0.0004 |
| Sustained ≥40% decrease in eGFR from baseline | 817 (12.5) | 4.60 | 962 (14.8) | 5.45 | 0.84 (0.76–0.92) | 0.0002 |
| **Death from any cause** | 552 (8.5) | 2.76 | 614 (9.4) | 3.10 | 0.89 (0.79–>1.00[g]) | 0.051[e] |
| **Hospitalization for any cause** | 2836 (43.5) | 19.04 | 2926 (45.0) | 19.91 | 0.96 (0.91–1.01) | 0.087[e] |




Agarwal R, et al. *Eur Heart J* 2022;43:474-484

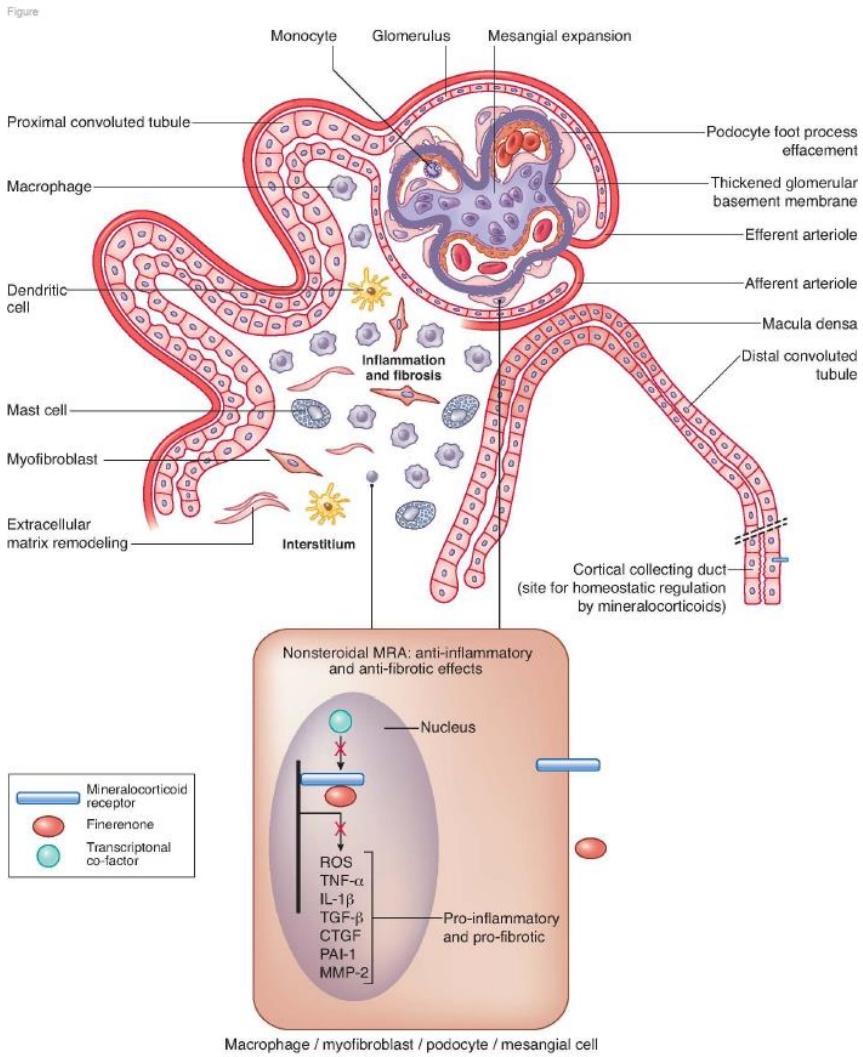
# FIDELITY: Finerenone Use and Kidney Disease Outcomes by eGFR and Albuminuria Strata




Bakris GL *et al. Kidney International* 2023;103:196-206

# Mineralocorticoid Receptors in CKD

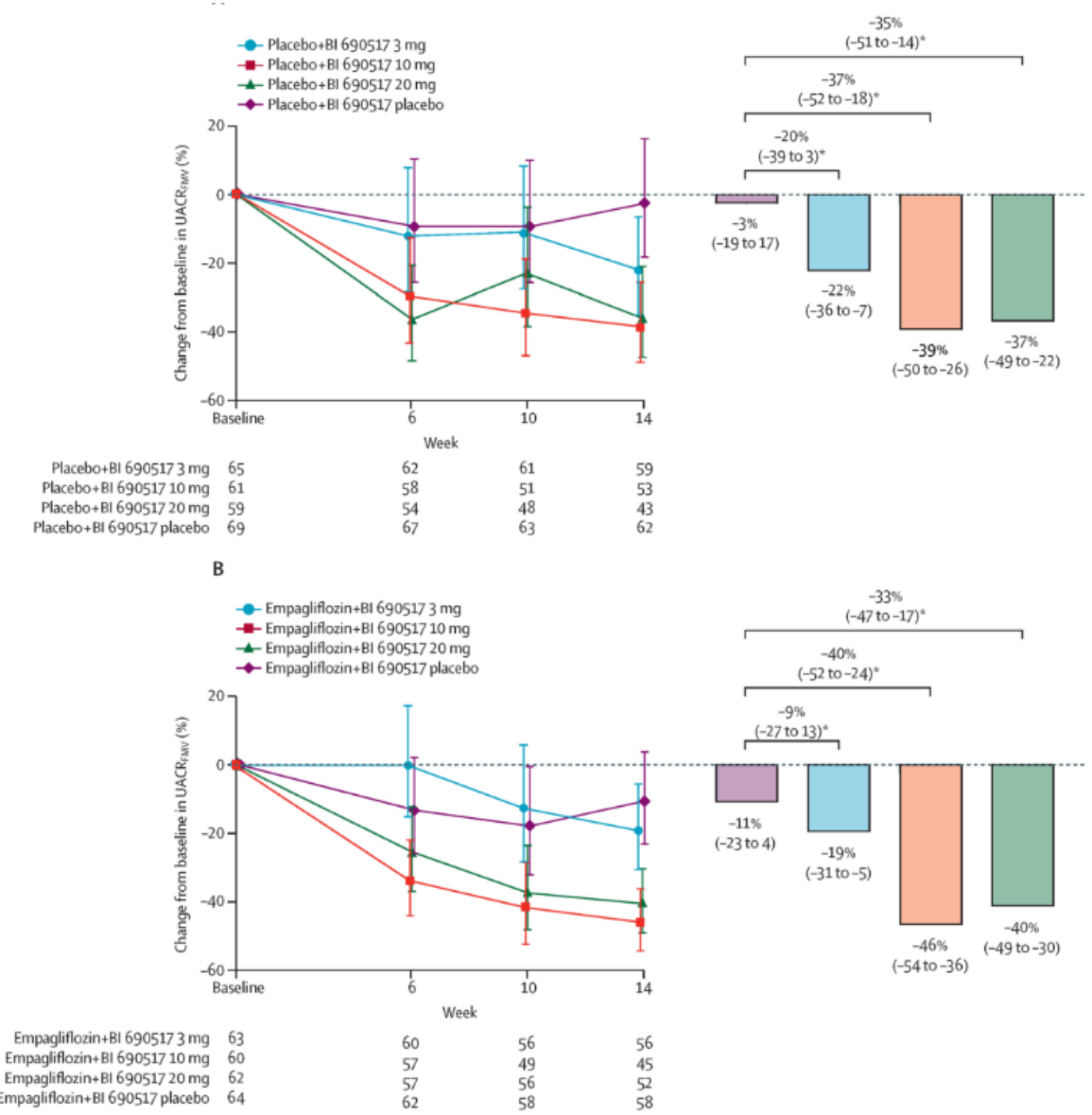
- Homeostatic regulation of electrolyte transport occurs in the cortical collecting duct
- Mineralocorticoid receptors upregulate inflammatory and fibrotic pathways in non-epithelial cells



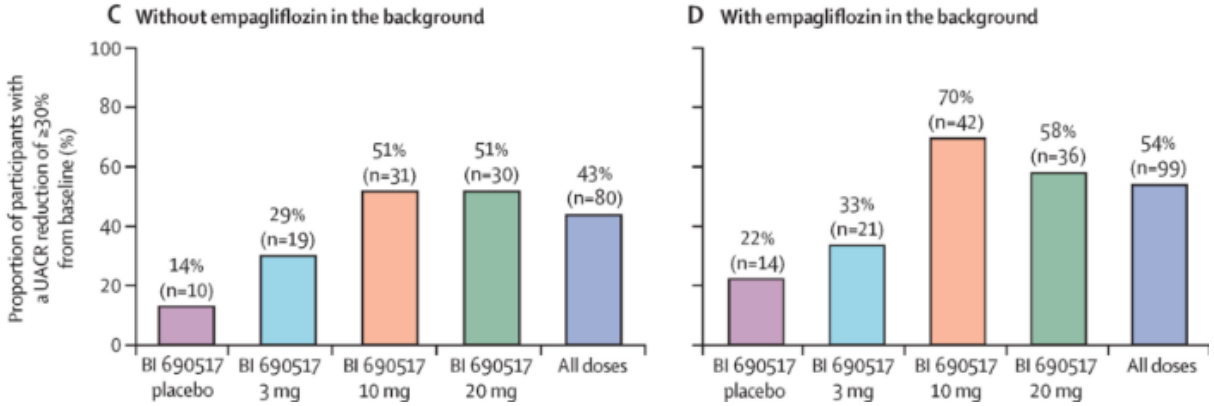

**Rationale for Non-Steroidal Mineralocorticoid Antagonist (MRA)**

Ghuman J, Tuttle K. *Kidney 360* 2022;3:744-748

# Aldosterone Synthase Inhibition with or without SGLT2 inhibition in CKD




## Responder Analysis




Tuttle KR *et al. Lancet* 2024;403:379-390

# EASi-KIDNEY™: phase III trial for BI 690517 in CKD

Oxford Population Health and Boehringer Ingelheim plan a phase III international trial called EASi-KIDNEY™

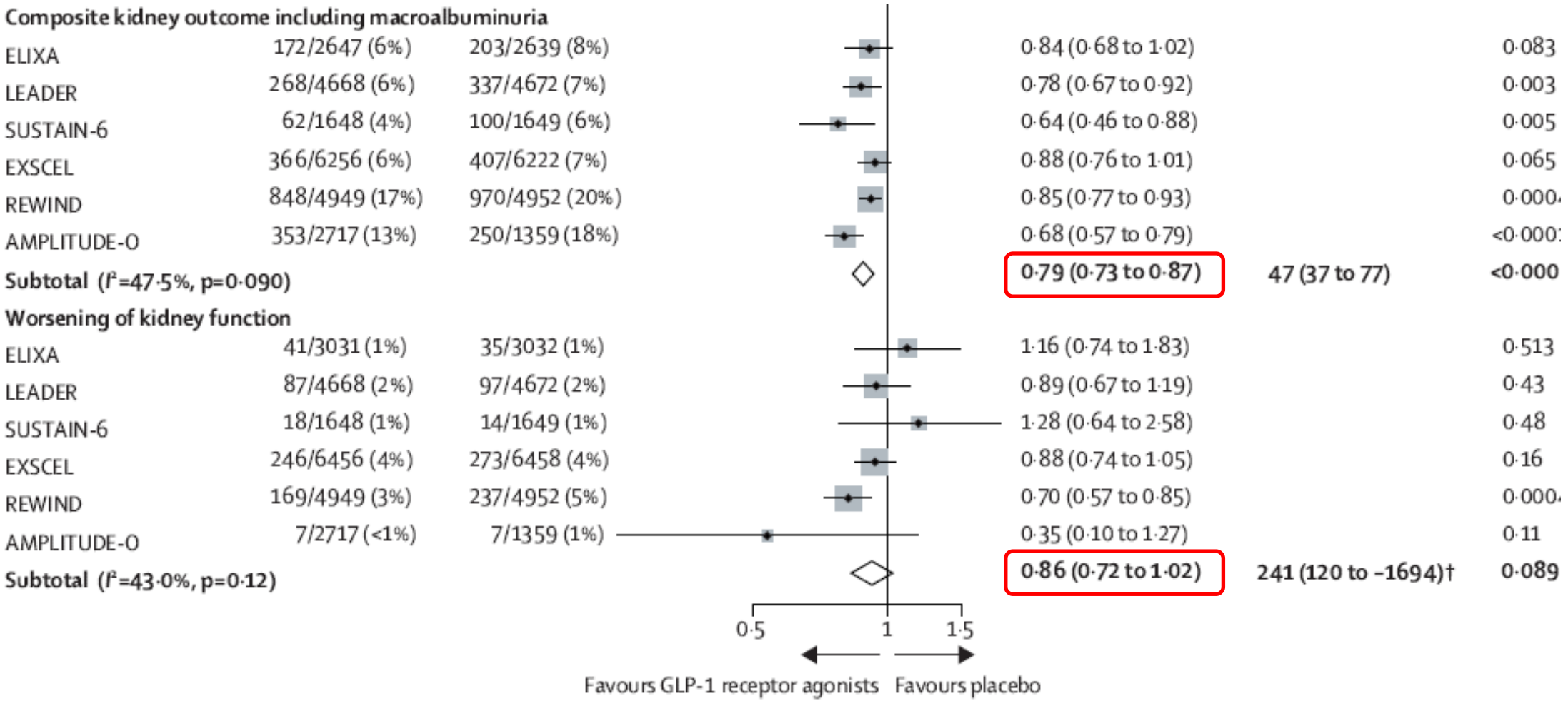
In 2024, EASi-KIDNEY will begin recruitment to test the efficacy and safety of the aldosterone synthase inhibitor BI 690517 versus matching placebo, given on top of standard-of-care including both a RAS inhibitor and an SGLT2 inhibitor.

EASi-KIDNEY™ will recruit and follow >11,000 participants with CKD

# GLP-1 Receptor Agonism Cardiovascular Trials in Type 2 Diabetes

- Reduce risk of major adverse CVD events.
  - Atherosclerotic CVD (3-point MACE: myocardial infarction, stroke, CVD death)
  - CVD death (liraglutide, semaglutide)
- Decrease macroalbuminuria and eGFR decline from early- to late-stage CKD (liraglutide, dulaglutide, semaglutide)
- CVD and CKD benefits are present in patients with CKD.

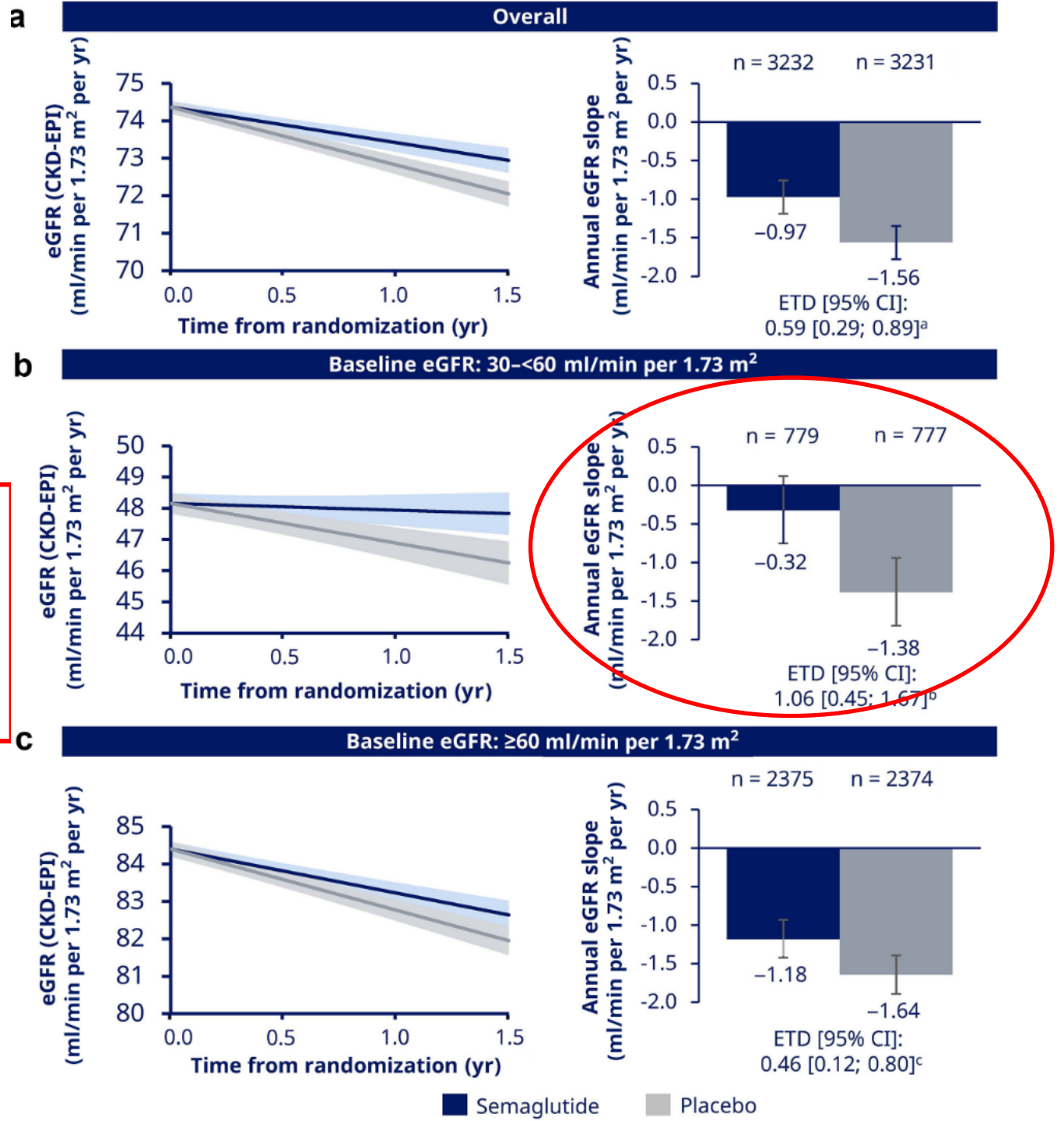
# GLP-1 Receptor Agonists for Prevention of Kidney Disease Outcomes




Sattar N *et al. Lancet Diabet Endo* 2021;9:653-652

# SUSTAIN-6 and PIONEER-6: Kidney Function Stabilized by Semaglutide

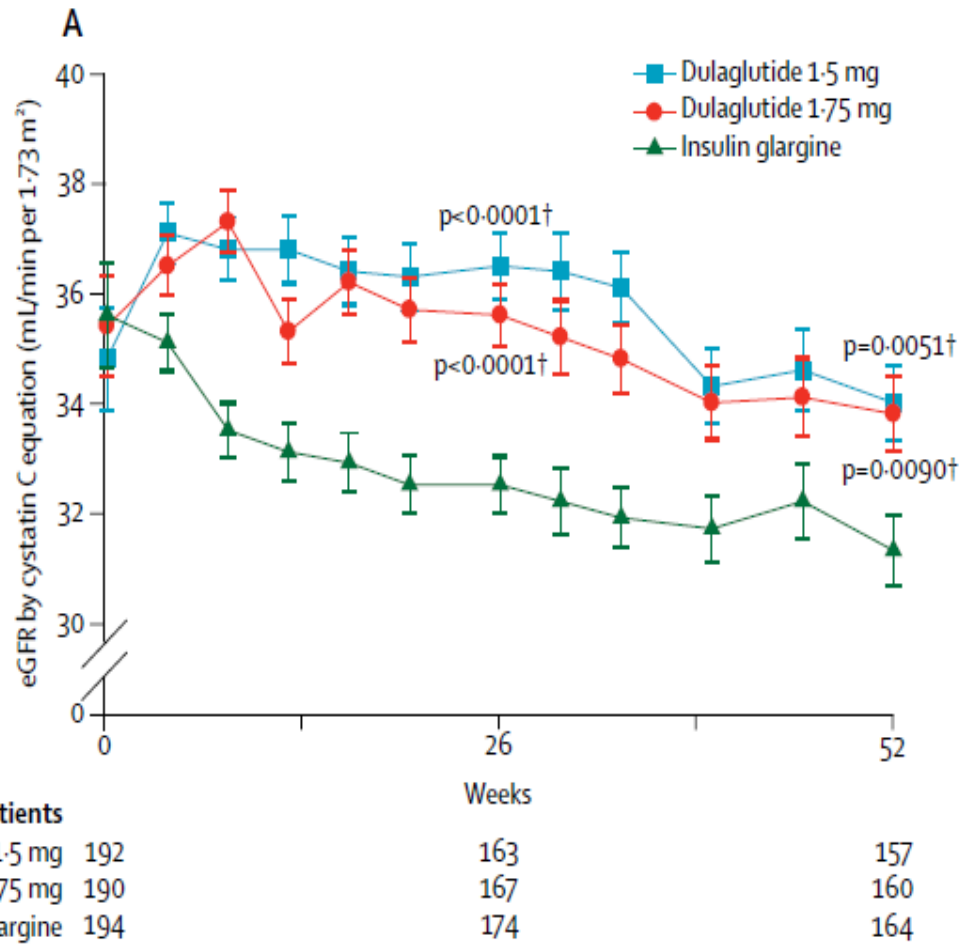
eGFR slope with estimated treatment difference (ETD) >0.75 mL/min/1.73m$^2$ per year predicts significantly lower risk of kidney failure versus placebo

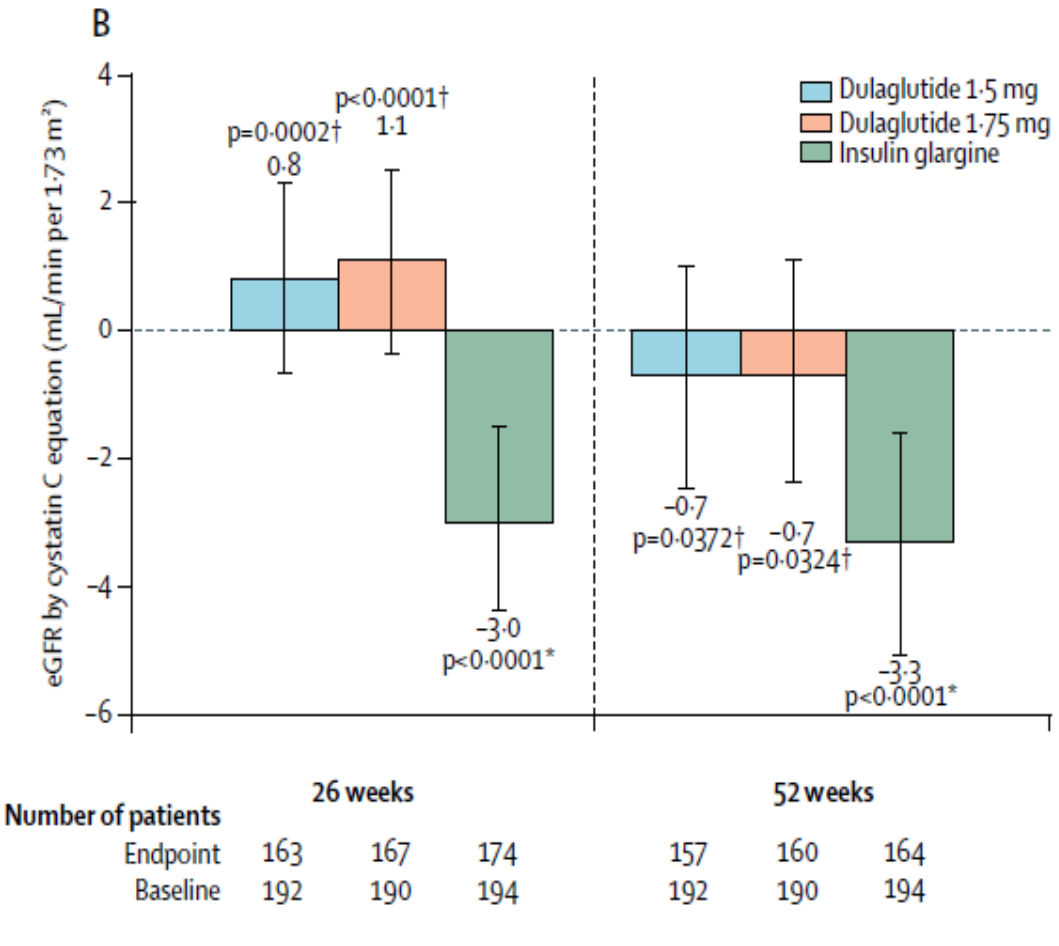




Tuttle KR *et al. Kidney Int* 2023;103:772-781
Inker LA *et al. J Am Soc Nephrol* 2019;30:1735-1745

# AWARD-7: Dulaglutide versus Insulin Glargine in Type 2 Diabetes and Moderate-to-Severe CKD




Tuttle KR *et al. Lancet Diabetes Endocrinol* 2018;6:605-617

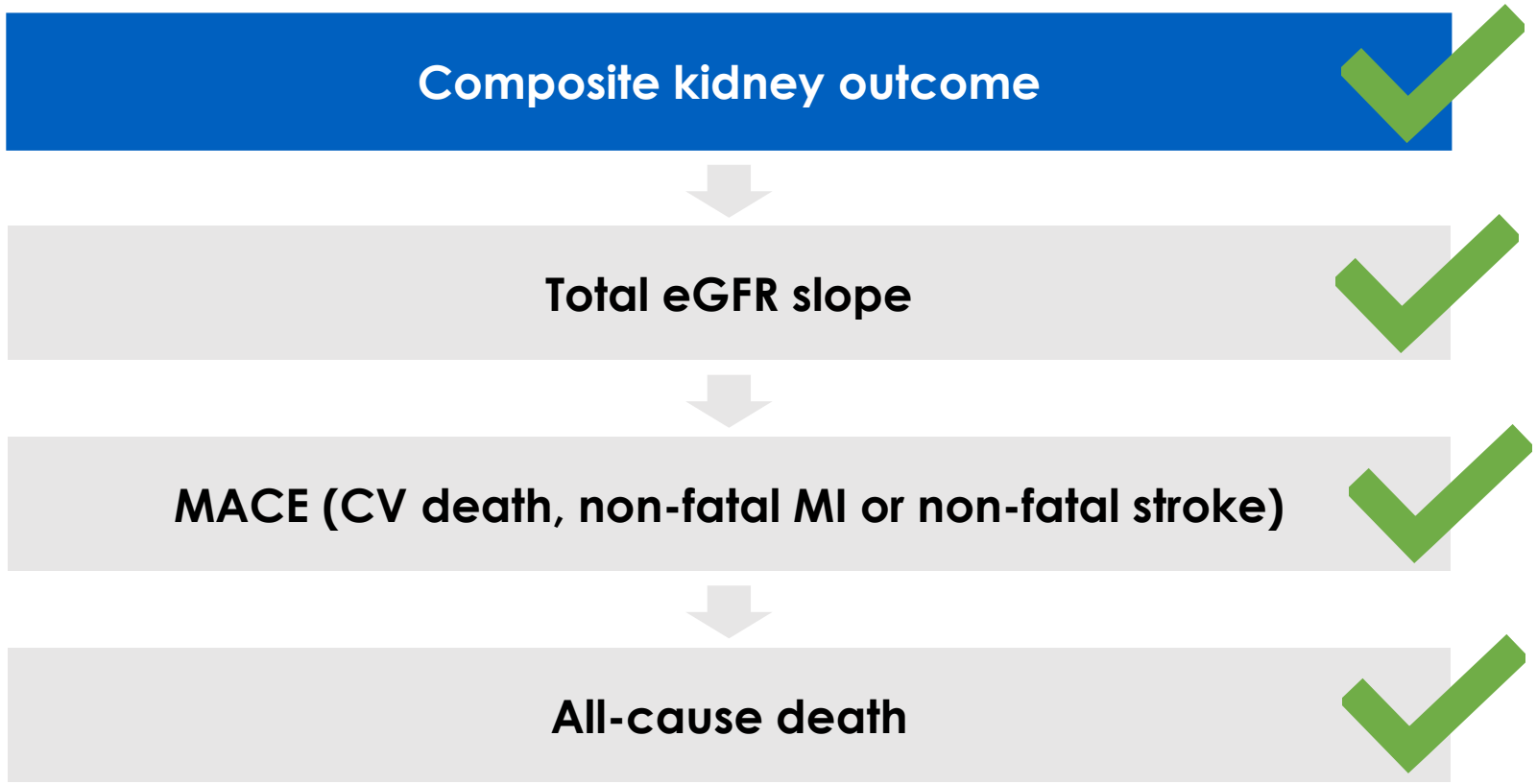
# FLOW Trial Design:
# Kidney Disease Outcomes Trial in Type 2 Diabetes

**Stopped early for clear positive efficacy**



Perkovic V, Tuttle KR, *et al. N Engl J Med* 2024;391:109-121
Rossing P, Pratley R *et al. Nephrol Dial Transplant* 2023;38:2041–2051

# Hierarchical Testing Strategy




Perkovic V, Tuttle KR, *et al. N Engl J Med* 2024;391:109-121

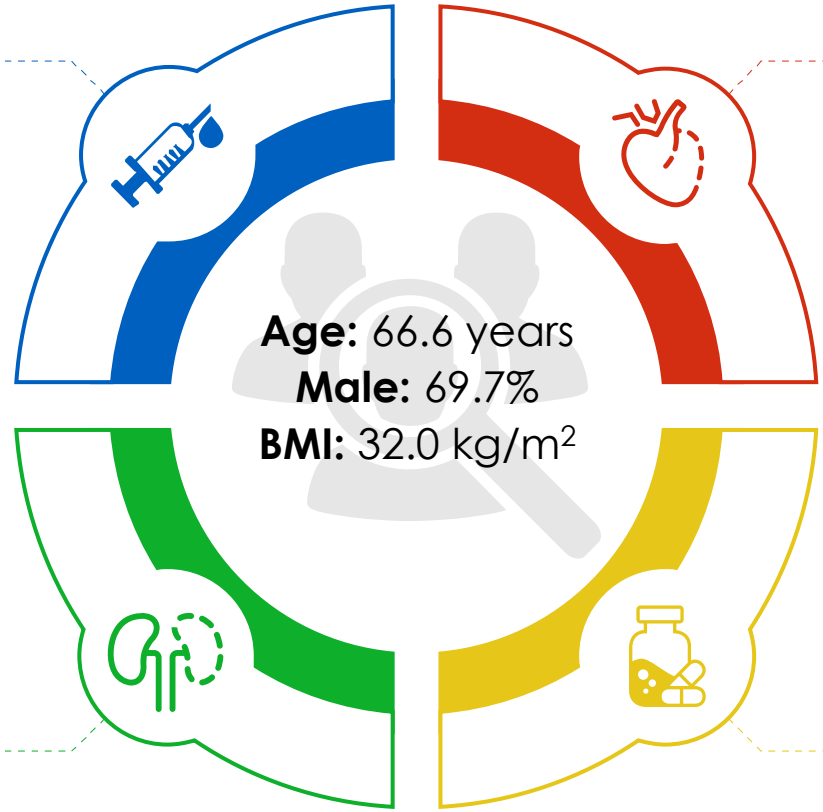
# FLOW Included Participants with Type 2 Diabetes and High- and Very-High-Risk CKD

## T2D

- $HbA_{1c}$: 7.8%
- T2D duration ≥15 years: 56.8%

## CVD

- BP: 138.6/76.4 mmHg
- Prior MI or stroke: 22.9%
- Chronic heart failure: 19.2%




## CKD

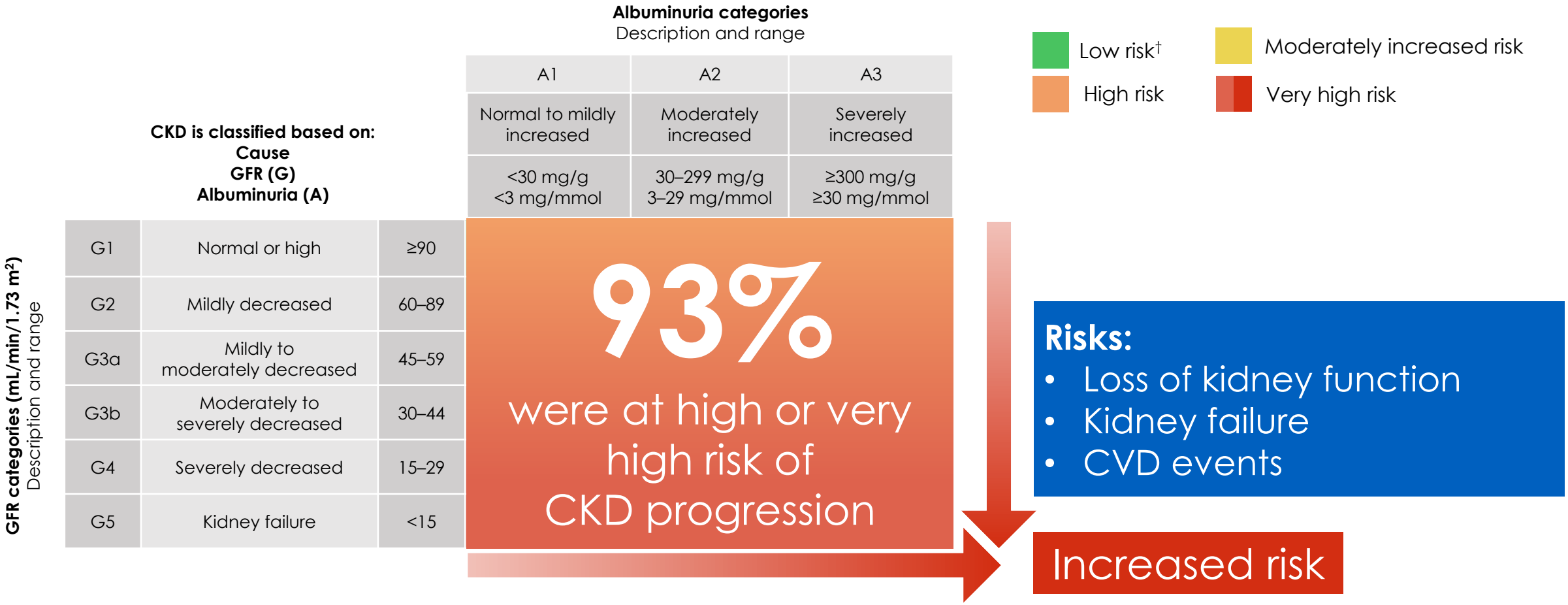
- eGFR: 47.0 mL/min/1.73 m²
- Median UACR: 567.6 mg/g

## Medication use

- RAAS blocker: 95.3%
- SGLT2 inhibitor: 15.6%

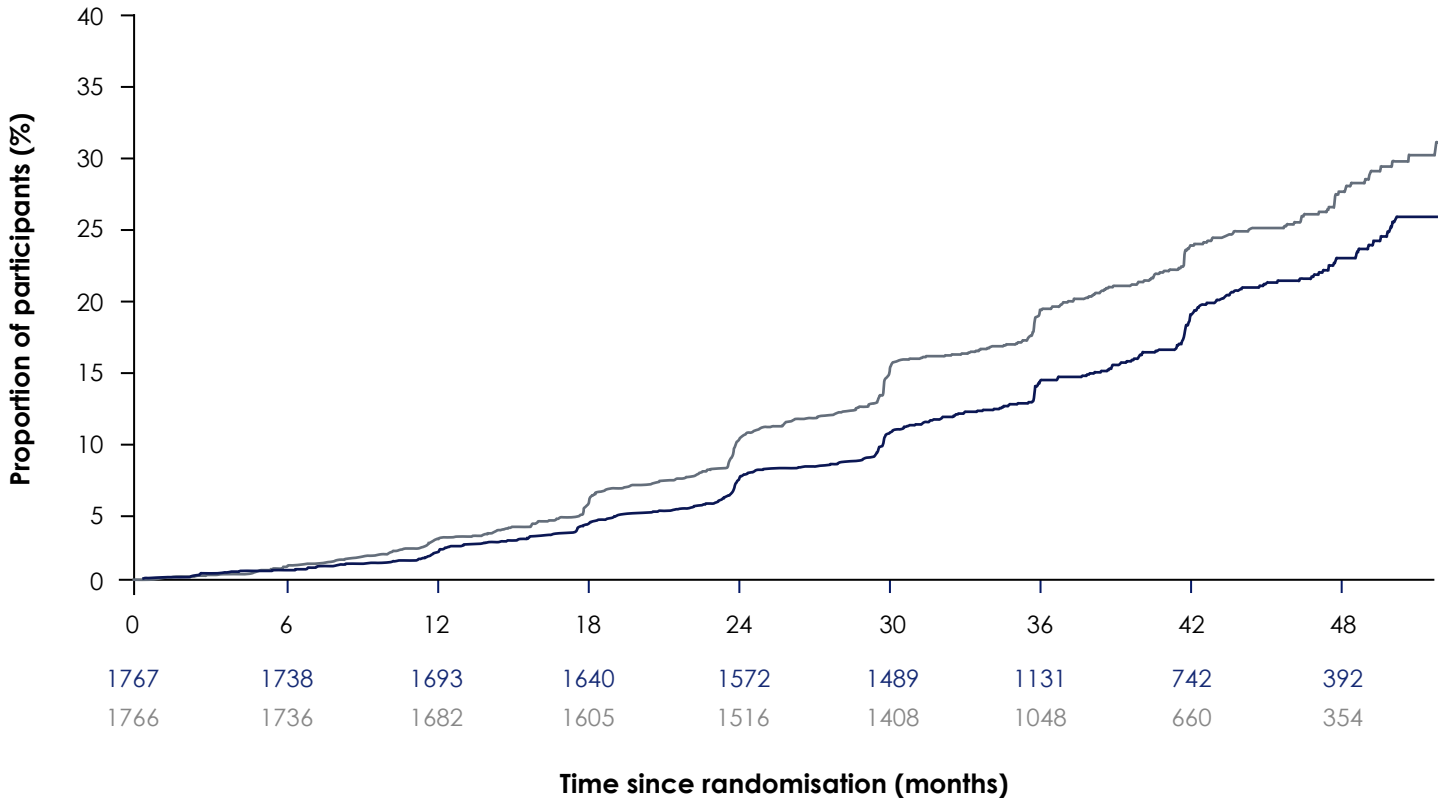
Perkovic V, Tuttle KR *et al. N Engl J Med* 2024;391:109-121

# CKD Risk Categories Guide Management




Perkovic V, Tuttle KR *et al. N Engl J Med* 2024;391:109-121
de Boer IH et al. *Diabetes Care* 2022;45:3075–3090; Kidney Disease: Improving Global Outcomes (KDIGO) Diabetes Work Group. *Kidney Int* 2022;102:S1–S127.

# Composite Primary Kidney Disease Outcome




**Placebo 23.2%**
(410/1766)

**Semaglutide 18.7%**
(331/1767)

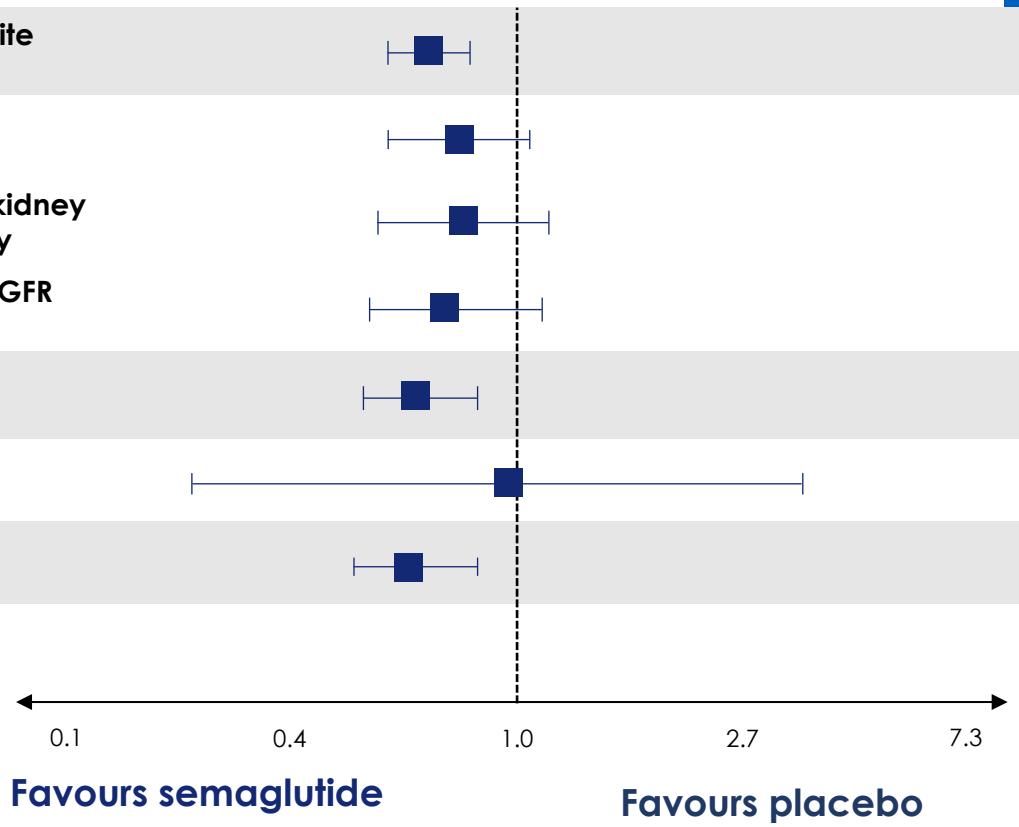
**HR 0.76** (95% CI 0.66, 0.88)
**p=0.0001**

Perkovic V, Tuttle KR *et al. N Engl J Med* 2024;391:109-121

Superiority if one-sided
p value <0.01612

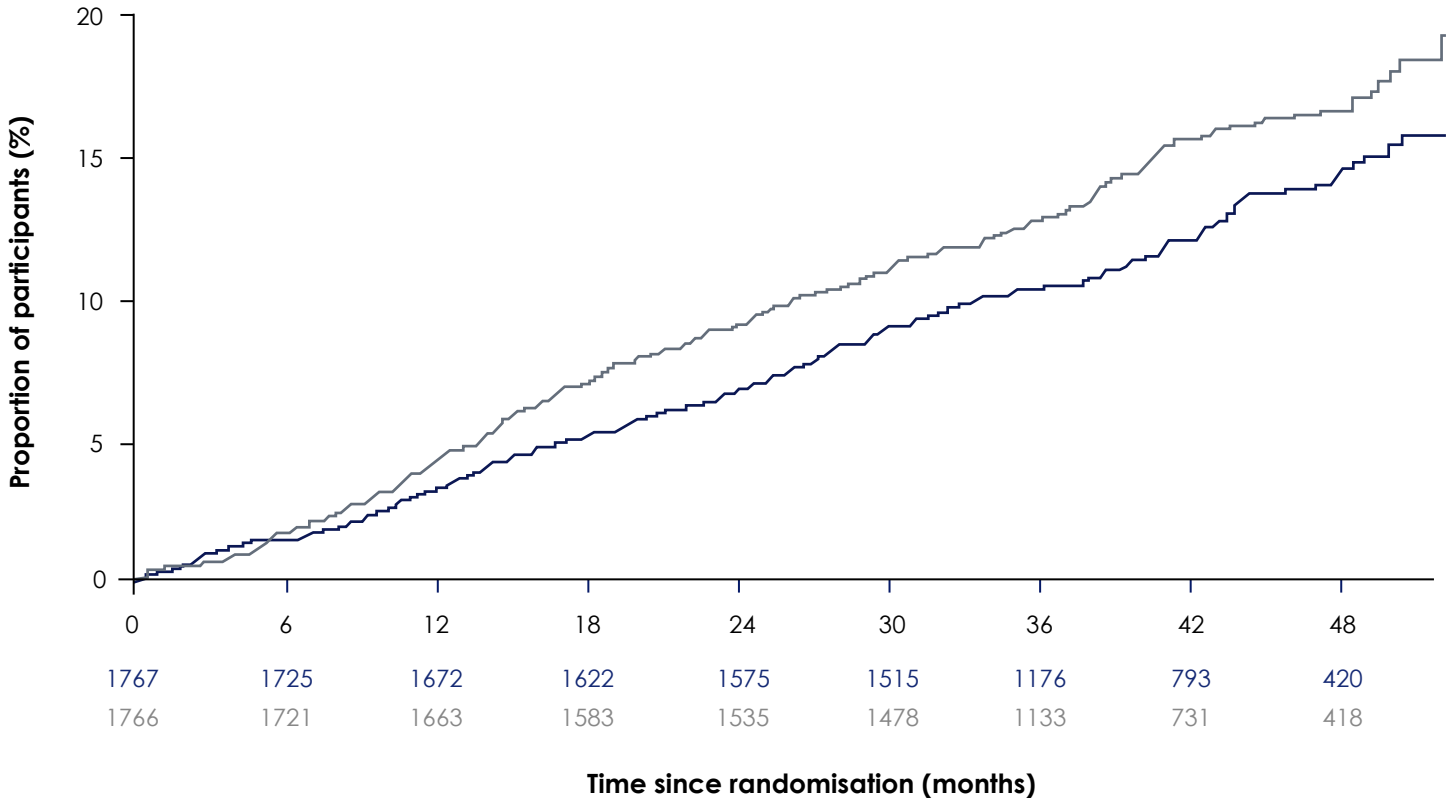
# Composite Kidney Disease Outcome by Components

| | HR (95% CI) | Semaglutide (n/N) | Placebo (n/N) |
|---|---|---|---|
| **Primary outcome:** Composite kidney outcome | **0.76** (0.66, 0.88) | 331/1767 | 410/1766 |
| Kidney failure | **0.83** (0.66, 1.03) | 142/1767 | 165/1766 |
| Initiation of chronic kidney replacement therapy | **0.84** (0.63, 1.12) | 87/1767 | 100/1766 |
| Onset of persistent eGFR <15 mL/min/1.73 $m^2$ | **0.80** (0.61, 1.06) | 92/1767 | 110/1766 |
| Onset of persistent ≥50% reduction in eGFR | **0.73** (0.59, 0.89) | 165/1767 | 213/1766 |
| Kidney death | **0.97** (0.27, 3.49) | 5/1767 | 5/1766 |
| CV death | **0.71** (0.56, 0.89) | 123/1767 | 169/1766 |




Perkovic V, Tuttle KR *et al. N Engl J Med* 2024;391:109-121

# Cardiovascular Death, Non-Fatal MI or Non-Fatal Stroke




**Placebo 14.4%**

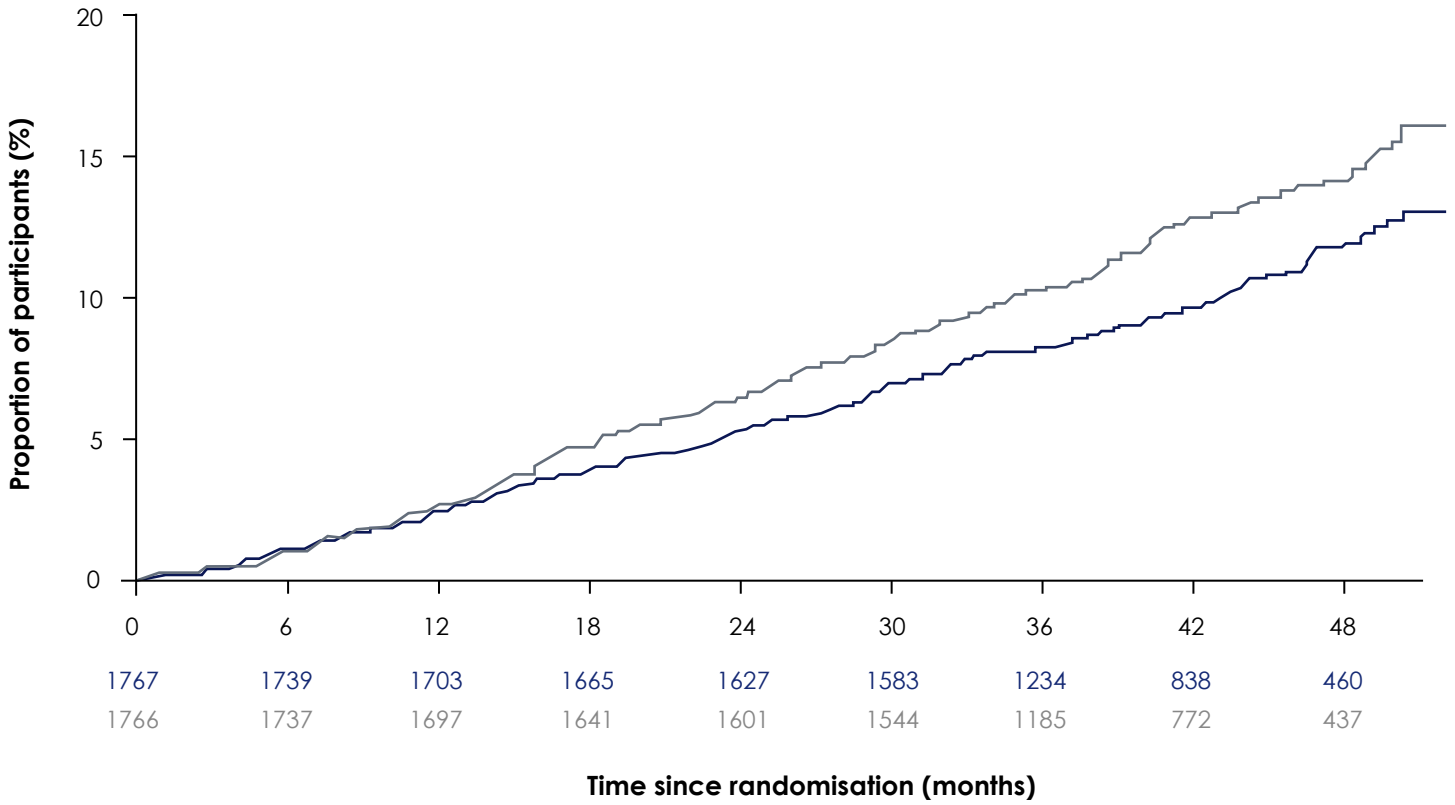
**Semaglutide 12.0%**

**HR 0.82** (95% CI 0.68, 0.98)
**p=0.0145**

Superiority if one-sided
p value <0.01612

Perkovic V, Tuttle KR *et al. N Engl J Med* 2024;391:109-121

# All-Cause Death




**Placebo 15.8%**

**Semaglutide 12.8%**

**HR 0.80** (95% CI 0.67, 0.95)
**p=0.0052**

Superiority if one-sided
p value <0.01612

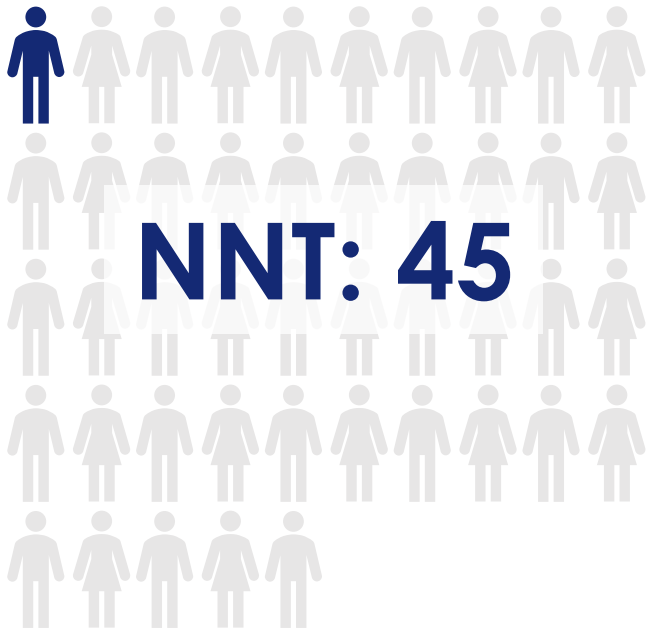
Perkovic V, Tuttle KR *et al. N Engl J Med* 2024;391:109-121

# Clinical Benefits of Semaglutide over 3 Years

**To prevent one primary outcome:**

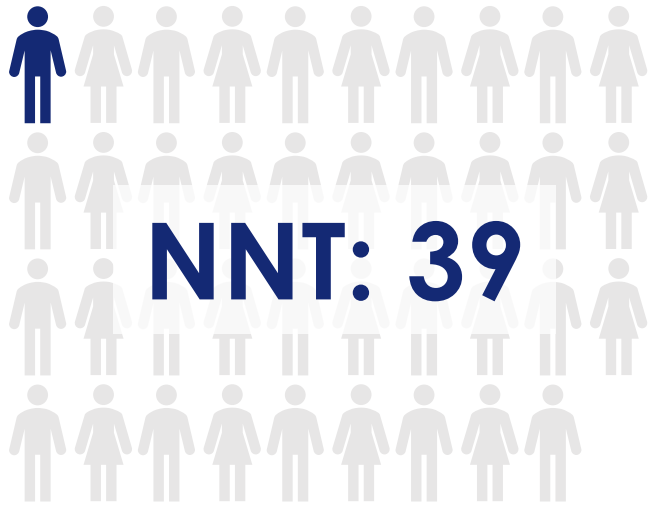
**NNT: 20**

**To prevent one MACE:**



**NNT: 45**

**To prevent one death due to any cause:**



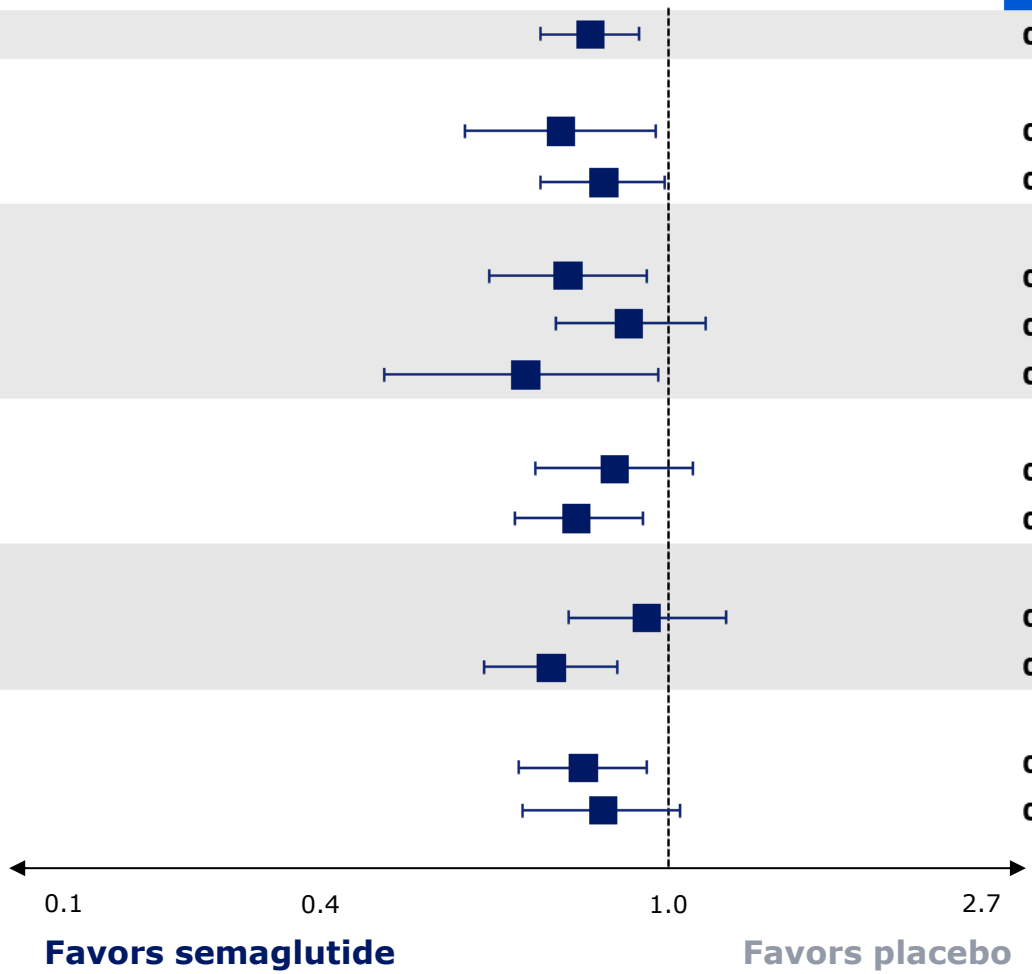
**NNT: 39**

Perkovic V, Tuttle KR *et al. N Engl J Med* 2024;391:109-121

# Primary Kidney Disease Outcome Subgroup Analyses

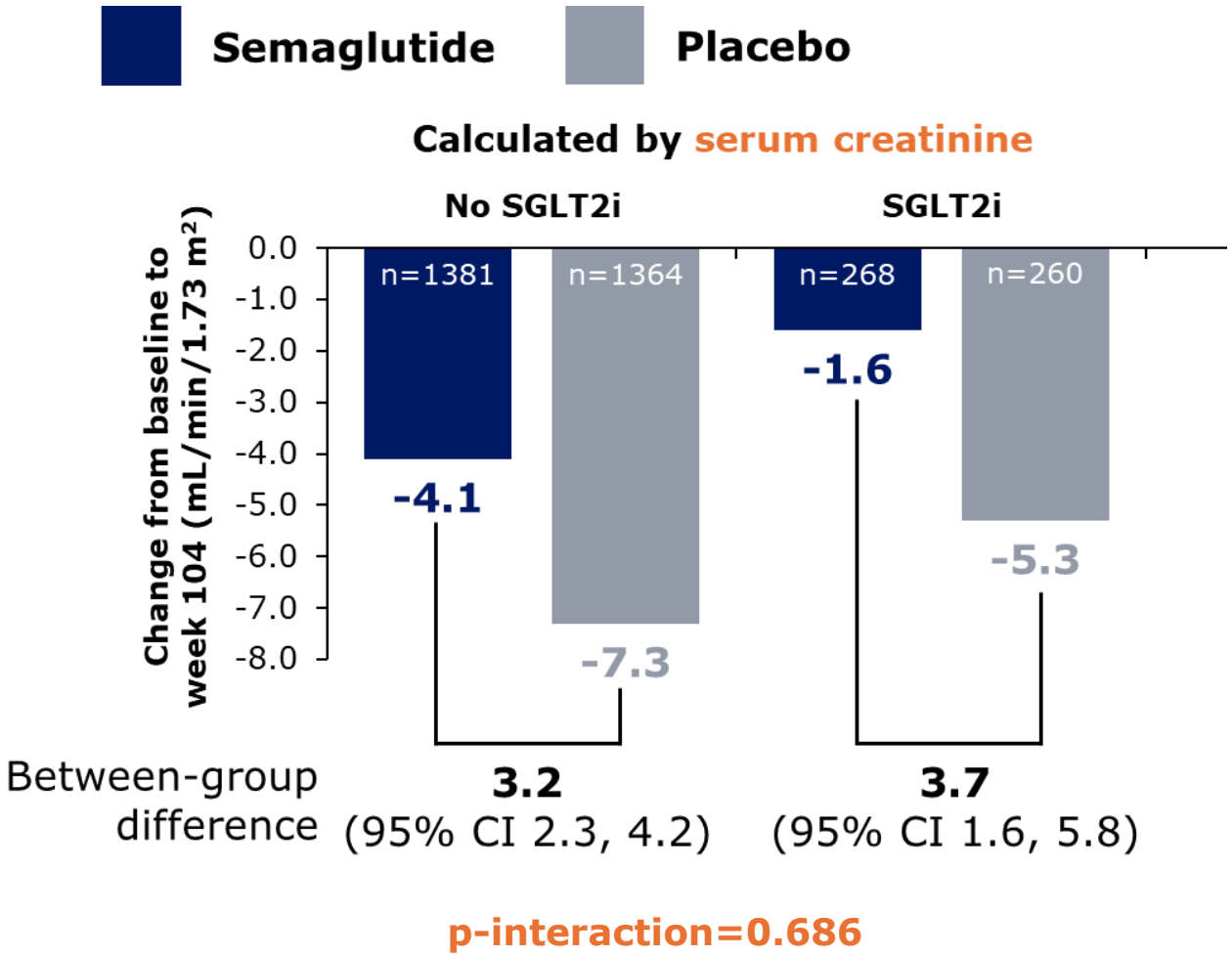
FLOW
semaglutide | renal outcomes trial

| | HR (95% CI) | p heterogeneity | Semaglutide, n/N | Placebo, n/N |
|---|---|---|---|---|
| **Primary analysis** | **0.76** (0.66, 0.88) | | 331/1767 | 410/1766 |
| **Sex** | | | | |
| Female | **0.70** (0.53, 0.92) | 0.46 | 88/519 | 127/550 |
| Male | **0.79** (0.66, 0.94) | | 243/1248 | 283/1216 |
| **Age, years** | | | | |
| <65 | **0.71** (0.57, 0.90) | 0.33 | 131/633 | 175/652 |
| ≥65–<75 | **0.85** (0.69, 1.06) | | 160/816 | 170/773 |
| ≥75 | **0.63** (0.42, 0.93) | | 40/318 | 65/341 |
| **BMI, kg/m²** | | | | |
| ≤30 | **0.82** (0.65, 1.03) | 0.46 | 142/734 | 164/733 |
| >30 | **0.73** (0.61, 0.89) | | 189/1031 | 244/1029 |
| **Diabetes duration, years** | | | | |
| <15 | **0.90** (0.72, 1.13) | 0.06 | 148/774 | 153/733 |
| ≥15 | **0.68** (0.56, 0.82) | | 183/992 | 257/1013 |
| **$HbA_{1c}$, %** | | | | |
| ≤8.0 | **0.75** (0.62, 0.90) | 0.68 | 200/1106 | 251/1093 |
| >8.0 | **0.79** (0.63, 1.00) | | 131/659 | 159/672 |




Full analysis set. Data from the in-trial period.
BMI, body mass index; CI, confidence interval; $HbA_{1c}$, glycated hemoglobin; HR, hazard ratio.
Perkovic V, Tuttle KR *et al. N Engl J Med* 2024;391:109-121

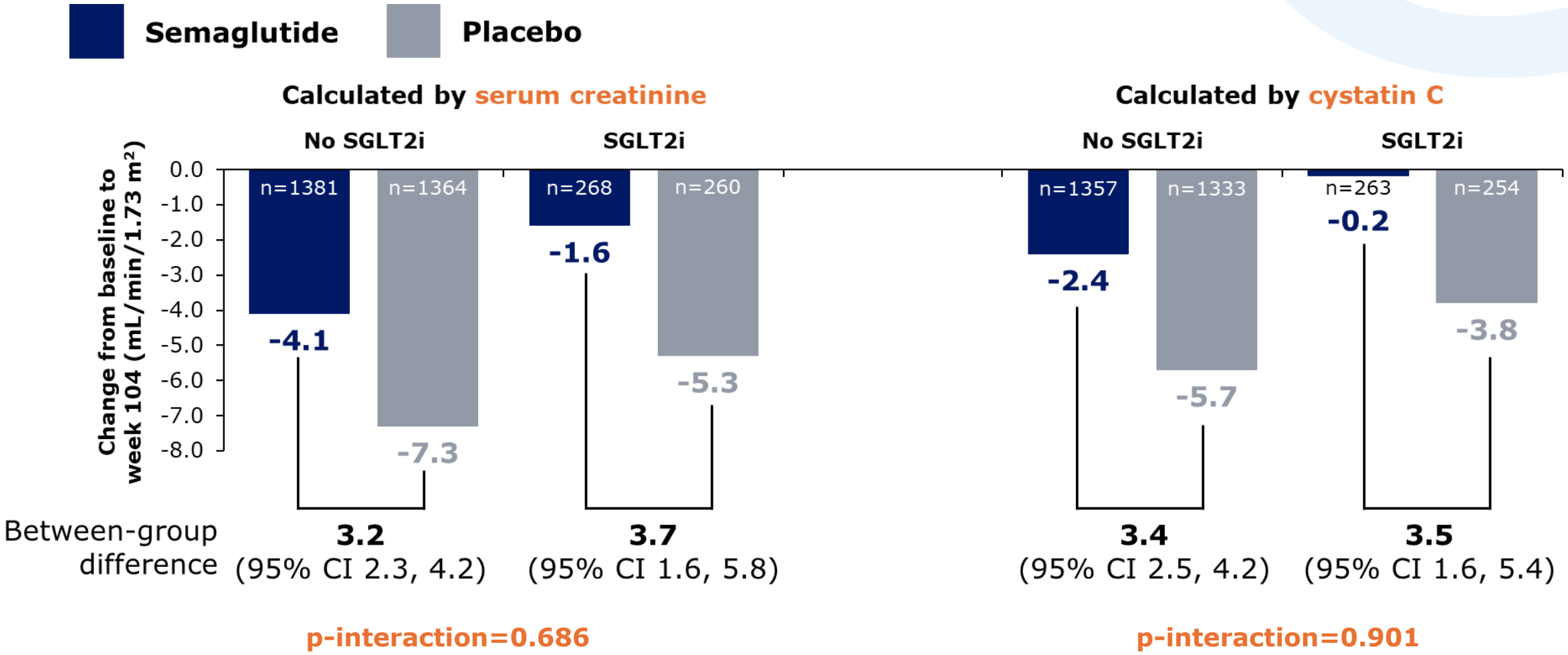
# Change in eGFR at Week 104 by Baseline SGLT2i Use




Full analysis set. Data from the in-trial period. Data shown are mean estimates (SE) (95% CI).
CI, confidence interval; eGFR, estimated glomerular filtration rate; SE, standard error; SGLT2i, sodium–glucose cotransporter-2 inhibitor.
Mann JFE et al. *Nat Med* 2024; doi: 10.1038/s41591-024-03133-0.

# Change in eGFR at Week 104 by Baseline SGLT2i Use

FLOW semaglutide | renal outcomes trial



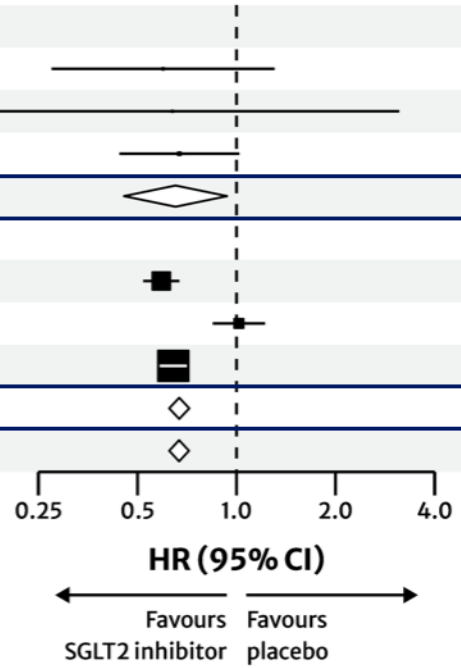

Full analysis set. Data from the in-trial period. Data shown are mean estimates (SE) (95% CI).
CI, confidence interval; eGFR, estimated glomerular filtration rate; SE, standard error; SGLT2i, sodium–glucose cotransporter-2 inhibitor.
Mann JFE et al. *Nat Med* 2024; doi: 10.1038/s41591-024-03133-0.

# Consistent Benefit of SGLT2i on Kidney Outcomes by Baseline GLP-1RA use

(40% decline in eGFR, kidney failure or death due or kidney failure)

FLOW semaglutide | kidney outcomes trial

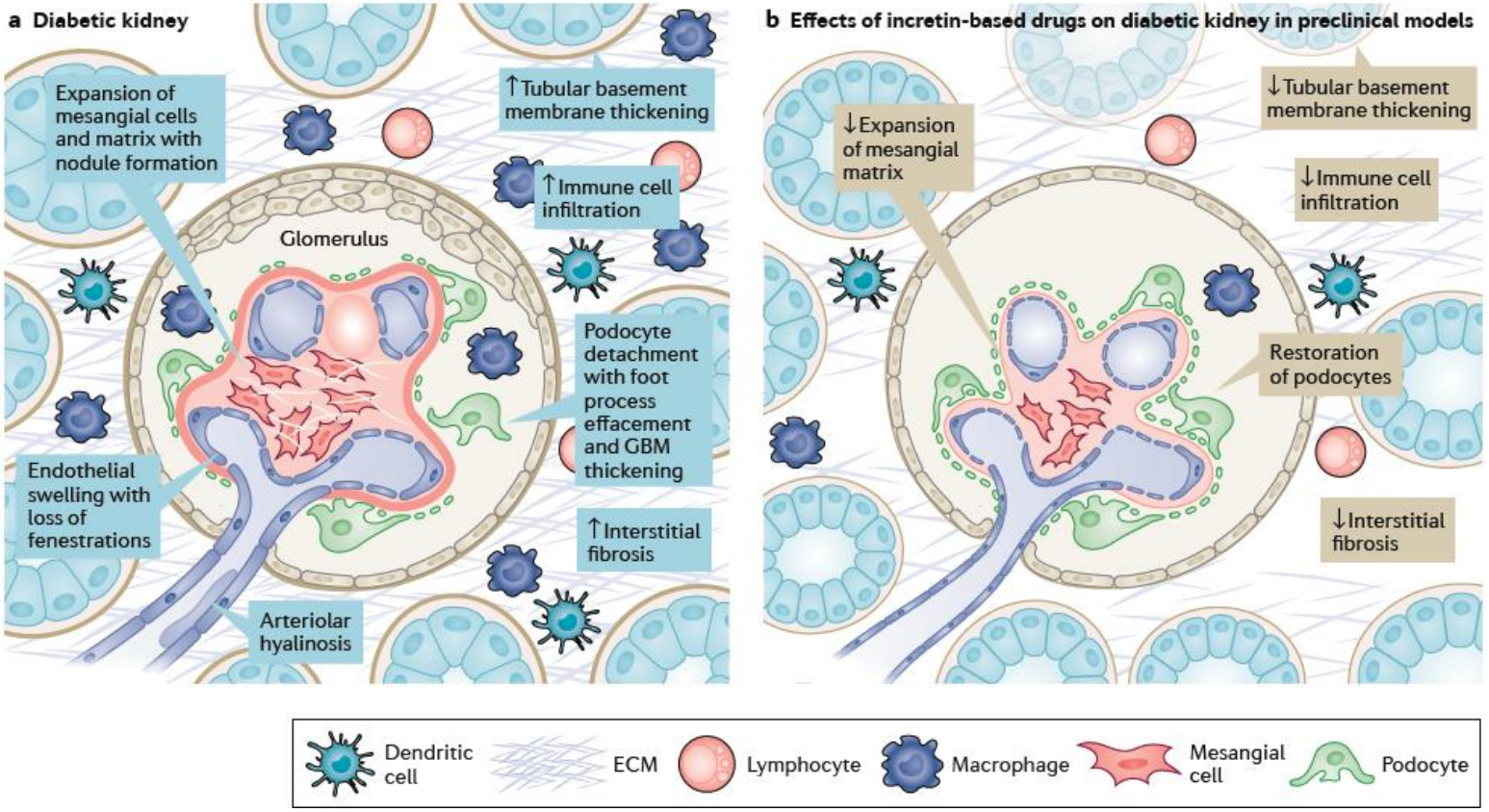
| | Events/patients (%) | | Event rate per 100 patient years | | HR (95% CI) |
|---|---|---|---|---|---|
| | SGLT2 inhibitor | Placebo | SGLT2 inhibitor | Placebo | |
| **Baseline use of GLP-1 RA** **2,984** | | | | | |
| High atherosclerotic cardiovascular risk trials | 14/936 (1·5) | 17/693 (2·5) | 0·4 | 1·0 | 0·60 (0·27 to 1·31) |
| Stable heart failure trials | 3/47 (6·4) | 3/33 (9·1) | 2·2 | 4·7 | 0·64 (0·13 to 3·12) |
| Chronic kidney disease trials | 40/635 (6·3) | 53/640 (8·3) | 3·2 | 4·5 | 0·67 (0·44 to 1·02) |
| Subtotal (I-squared = 0·0%, p = 0·64) | 57/1618 (3·5) | 73/1366 (5·3) | 1·6 | 2·9 | 0·65 (0·46 to 0·94) |
| **No baseline use of GLP-1 RA** **70,122** | | | | | |
| High atherosclerotic cardiovascular risk trials | 469/23585 (2·0) | 526/17302 (3·0) | 0·6 | 1·3 | 0·59 (0·52 to 0·67) |
| Stable heart failure trials | 235/4781 (4·9) | 231/4798 (4·8) | 2·9 | 3·1 | 1·02 (0·85 to 1·22) |
| Chronic kidney disease trials | 688/9839 (7·0) | 1015/9817 (10·3) | 3·7 | 5·6 | 0·64 (0·58 to 0·71) |
| Subtotal (I-squared = 70·4%, p<0.001) | 1392/38205 (3·6) | 1772/31917 (5·6) | 1·7 | 2·9 | 0·67 (0·62 to 0·72) |
| Total **73,106** | 1449/39823 (3·6) | 1845/33283 (5·5) | 1·7 | 2·9 | 0·67 (0·62 to 0·72) |
| **Heterogeneity by use of GLP-1 RA: p = 0·81** | | | | | |

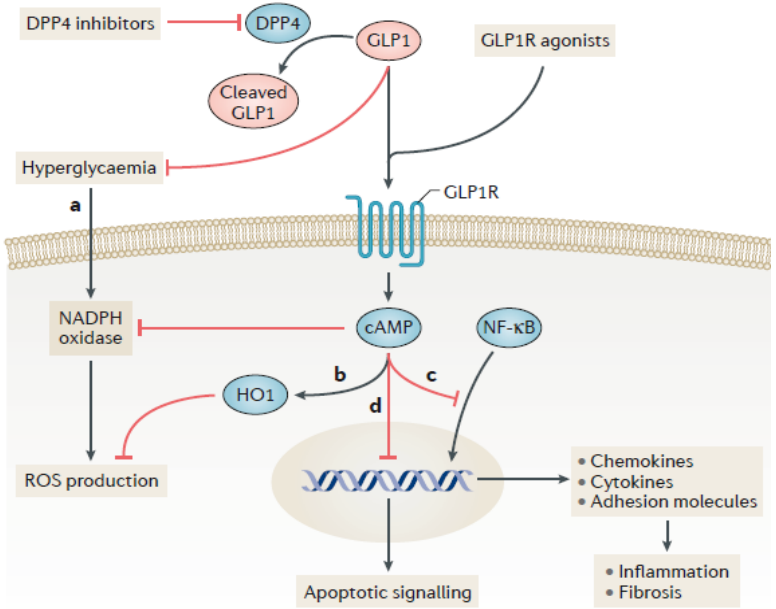



Apperloo EM *et al. Lancet Diabetes Endocrinol* 2024;12:545-557

SMART-C

# GLP-1 Receptor Agonists in Discovery and Pre-Clinical Science




**Kidney GLP-1 receptors**

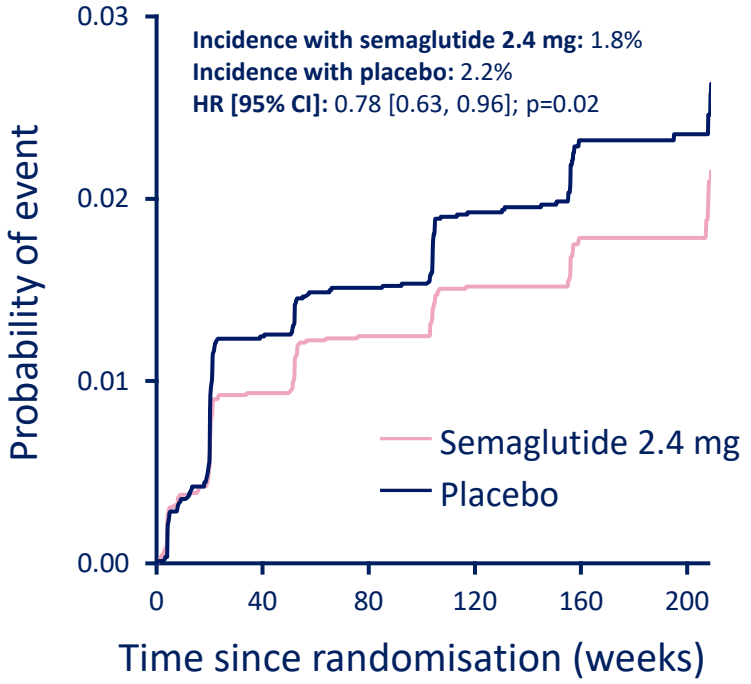
- Intrinsic cells
  - Endothelial
  - Proximal tubular cells?
- Infiltrating cells
  - Macrophages
  - T lymphocytes


Tanaka T *et al. Kidney Int* 2014; 86:701–711

Alicic RZ, Cox EJ, Neumiller JJ, Tuttle KR. *Nature Reviews Nephrology* 2021;17:227-244

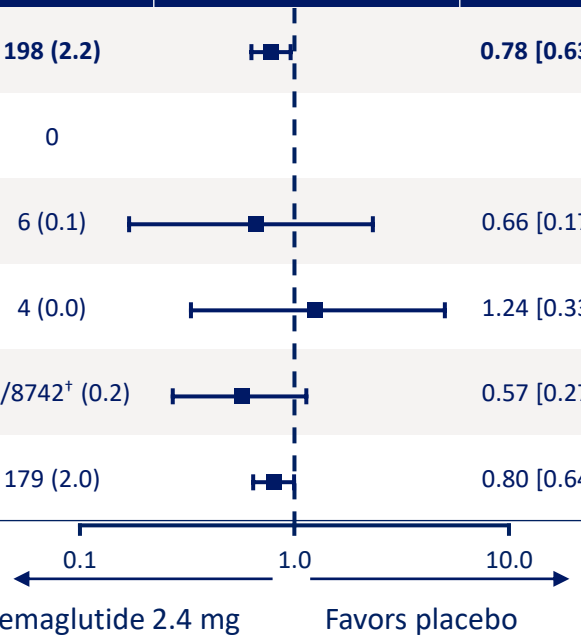
# Semaglutide 2.4 mg in Overweight or Obesity and CVD Reduced the Secondary Kidney Outcome by 22%

## Time to first occurrence of the main 5-component kidney composite outcome




## 5-component kidney composite outcome

| | Semaglutide 2.4 mg (N=8803), n (%) | Placebo (N=8801), n (%) | HR [95% CI]; p value |
|---|---|---|---|
| **5-component kidney composite outcome** | **155 (1.8)** | **198 (2.2)** | **0.78 [0.63, 0.96]; 0.02** |
| Death due to kidney disease | 0 | 0 | N/A |
| Initiation of chronic kidney replacement therapy* | 4 (0.0) | 6 (0.1) | 0.66 [0.17, 2.32]; 0.52 |
| Onset of persistent eGFR <15 mL/min/1.73m$^2$ | 5 (0.1) | 4 (0.0) | 1.24 [0.33, 5.02]; 0.74 |
| Onset of persistent ≥50% reduction in eGFR | 12/8724† (0.1) | 21/8742† (0.2) | 0.57 [0.27, 1.14]; 0.11 |
| Onset of persistent macroalbuminuria | 144 (1.6) | 179 (2.0) | 0.80 [0.64, 1.00]; 0.05 |

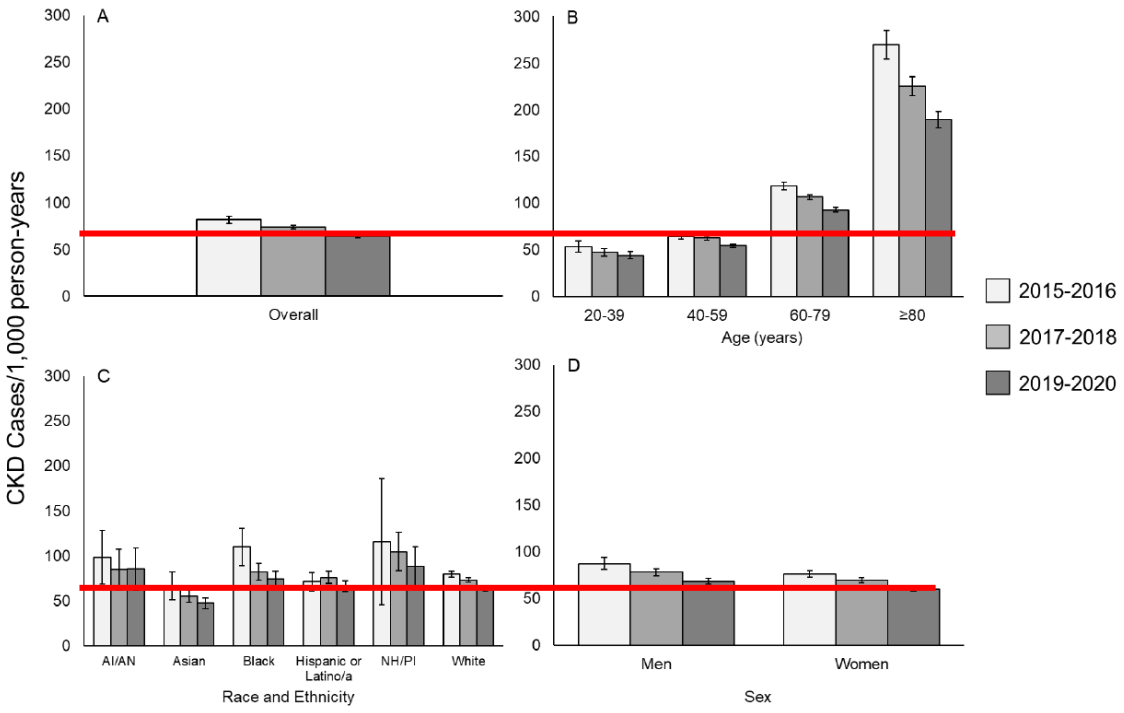


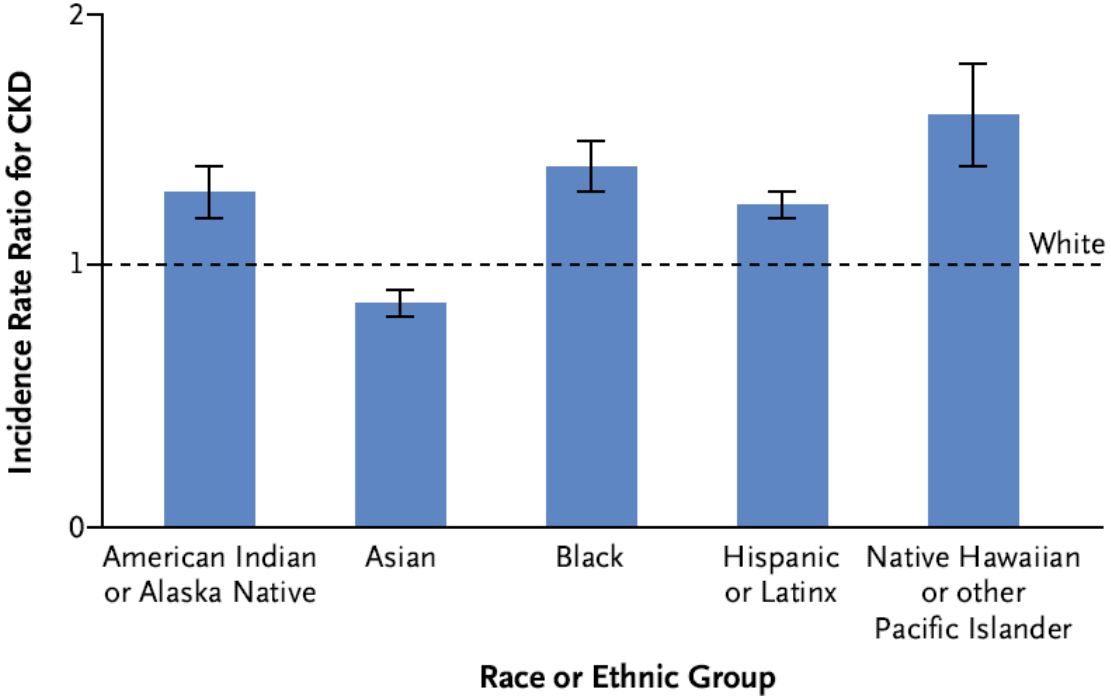

**eGFR <60 mL/min/1.73 m$^2$ or UACR ≥30 mg/g in 21.3%**

Colhoun HM, *et al. Nat Med* 2024;30:2058-2066

# CKD Onset in Diabetes: Who and When? CURE-CKD 2015-2020 (N=654,459)

## CKD Incidence in Diabetes by Demography




Tuttle KR *et al. N Engl J Med* 2022;387:1430-1431

# CKD Identification, Monitoring, and Actions by Risk Categories

| 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

**CKD Risks:**

- **Lose kidney function**
  **Kidney failure**
- **CVD events**

**Moving DOWN increases risk**

**Moving RIGHT increases risk**

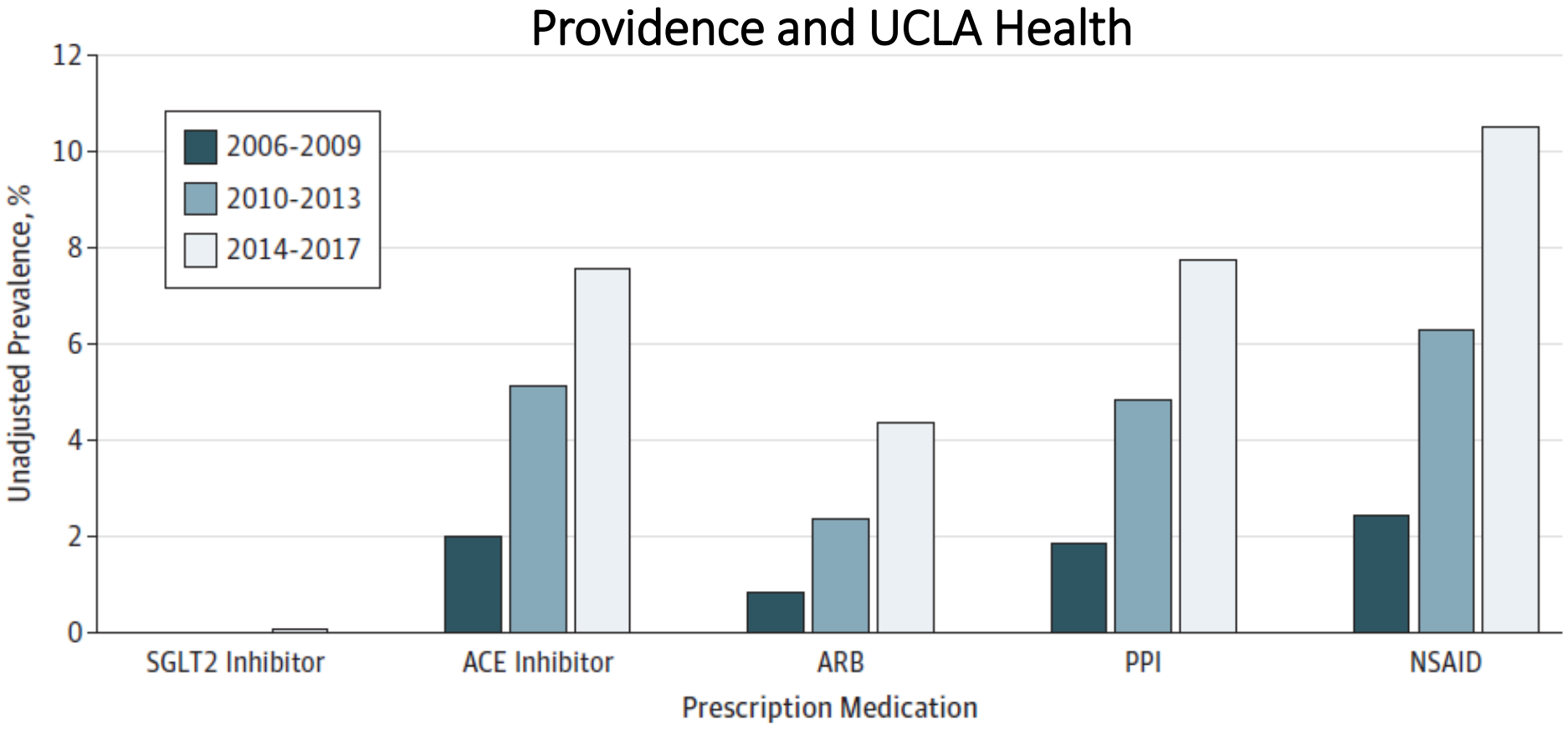
de Boer IH *et al. Diabetes Care* 2022;45:3075-3090
KDIGO Diabetes Work Group. *Kidney Int* 2022;102(5S):S1-S127

# Albuminuria/Proteinuria Monitoring is Low in CKD CURE-CKD 2006-2017 (N=606,064)

| | All CKD | CKD/DM/PDM/HTN | CKD/HTN | CKD/DM/PDM | CKD Alone |
|---|---|---|---|---|---|
| UACR, mg/g | | | | | |
| ≤30 | 17 651 (2.9) | 12 703 (4.2) | 1776 (1.3) | 2224 (2.7) | 948 (1.1) |
| >30 to ≤300 | 27 227 (4.5) | 21 435 (7.1) | 1089 (0.8) | 4066 (5.0) | 637 (0.7) |
| >300 | 7673 (1.3) | 5860 (2.0) | 509 (0.4) | 995 (1.2) | 309 (0.3) |
| Not measured | 553 513 (91.3) | 260 159 (86.7) | 131 126 (97.5) | 73 981 (91.0) | 88 247 (97.9) |
| UPCR, mg/g | | | | | |
| ≤150 | 14 467 (2.4) | 7823 (2.6) | 2723 (2.0) | 2076 (2.6) | 1845 (2.0) |
| >150 to ≤500 | 5688 (0.9) | 3087 (1.0) | 1163 (0.9) | 763 (0.9) | 675 (0.7) |
| >500 | 4880 (0.8) | 2978 (1.0) | 785 (0.6) | 696 (0.9) | 421 (0.5) |
| Not measured | 581 029 (95.9) | 286 269 (95.4) | 129 829 (96.5) | 77 731 (95.7) | 87 200 (96.7) |
| Age, median (IQR) [No.], y | 70 (59-81) [606 064] | 70 (60-79) [300 157] | 72 (60-83) [134 500] | 73 (63-83) [81 266] | 64 (42-81) [90 141] |
| eGFR, median (IQR) [No.], mL/min/1.73 $m^2$ | 53 (41-61) [524 169] | 54 (43-63) [266 838] | 53 (44-59) [115 061] | 49 (35-59) [74 366] | 53 (41-66) [67 904] |
| SBP, mean (SD) [No.], mm Hg | 129 (18) [365 561] | 131 (18) [202 951] | 132 (18) [92 051] | 119 (17) [25 533] | 119 (16) [45 026] |
| DBP, mean (SD) [No.], mm Hg | 72 (11) [365 561] | 72 (10) [202 951] | 74 (11) [92 051] | 67 (10) [25 533] | 70 (10) [45 026] |

Tuttle KR *et al. JAMA Netw Open* 2019;2:e1918169

# Medication Use in CKD Stages 3-5 ND CURE-CKD 2006-2017 (N=606,064)



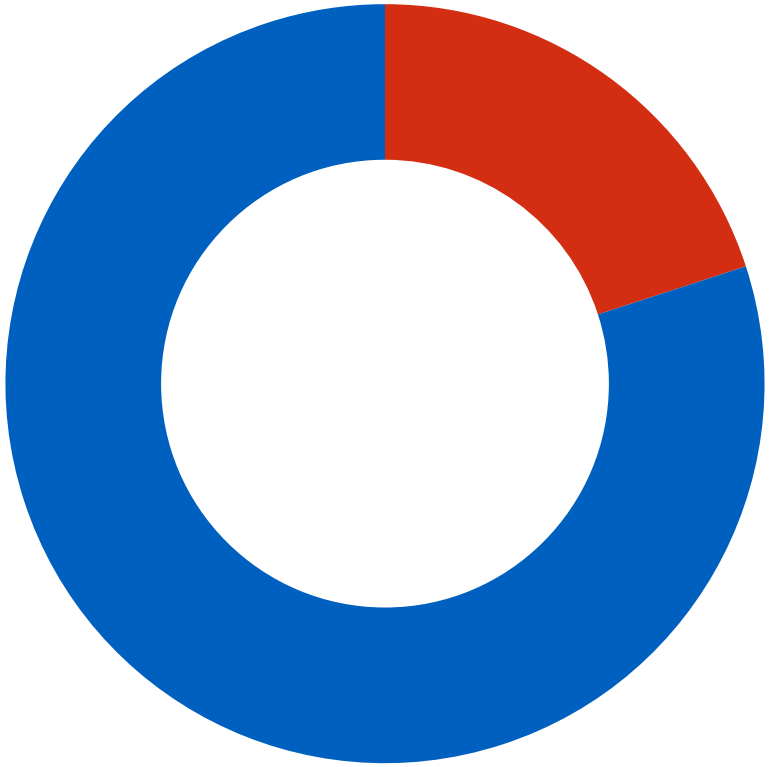

**Diabetes with CKD and hypertension: ACE Inhibitor or ARB use 25%**

Tuttle KR *et al. JAMA Netw Open* 2019;2:e1918169

# The Majority of People with CKD are Unaware of Their Condition

**80–93%**

**Unaware of CKD**

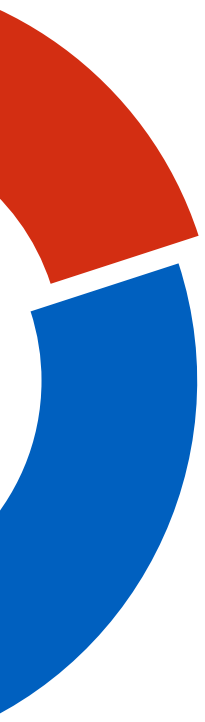


**7–20%**

**Aware of CKD**

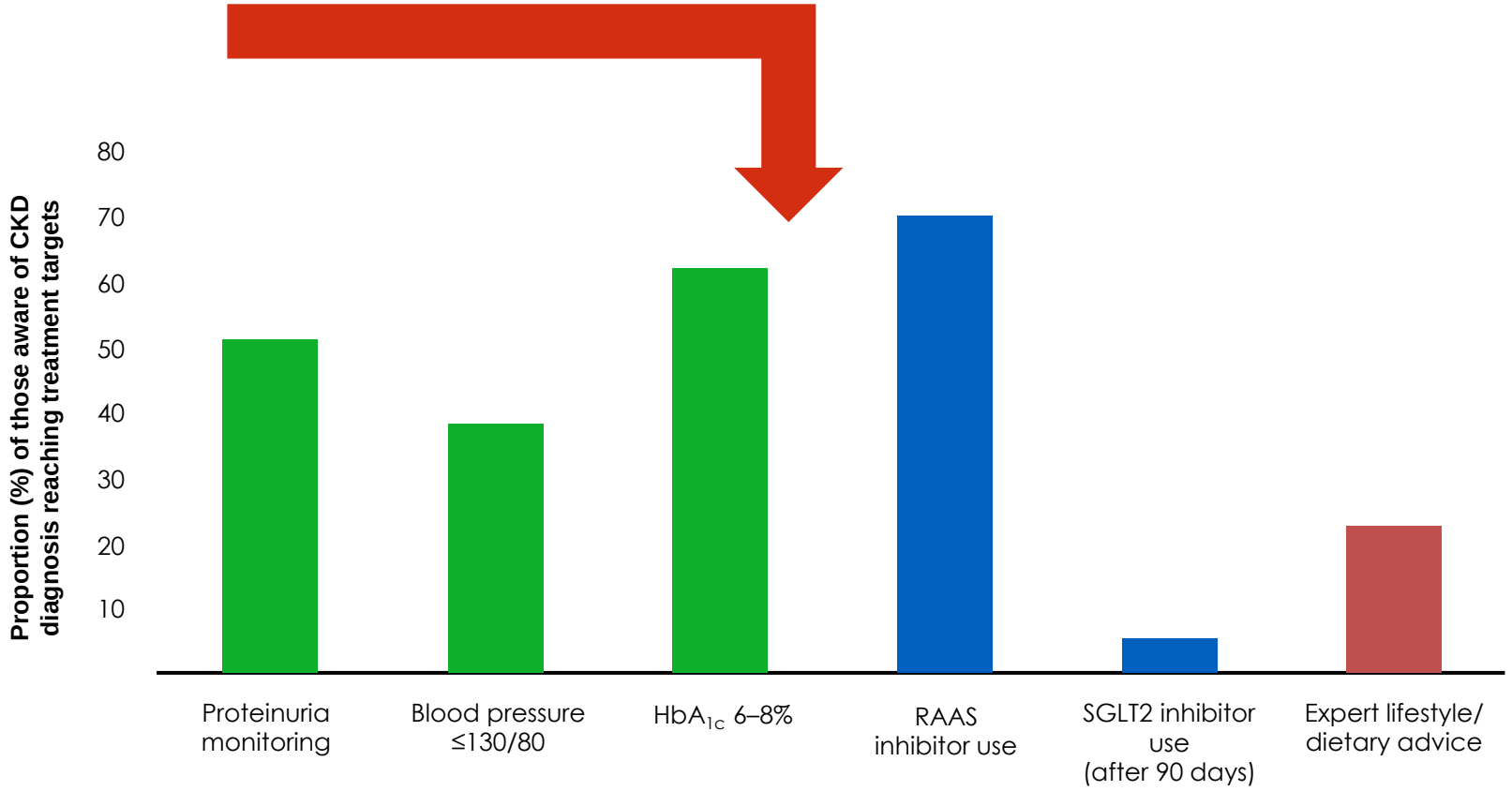
Luyckx VA, Tuttle KR *et al. Kidney Int* 2024;105:406–417

# The Majority of People with CKD are Unaware of Their Condition



**7–20%**

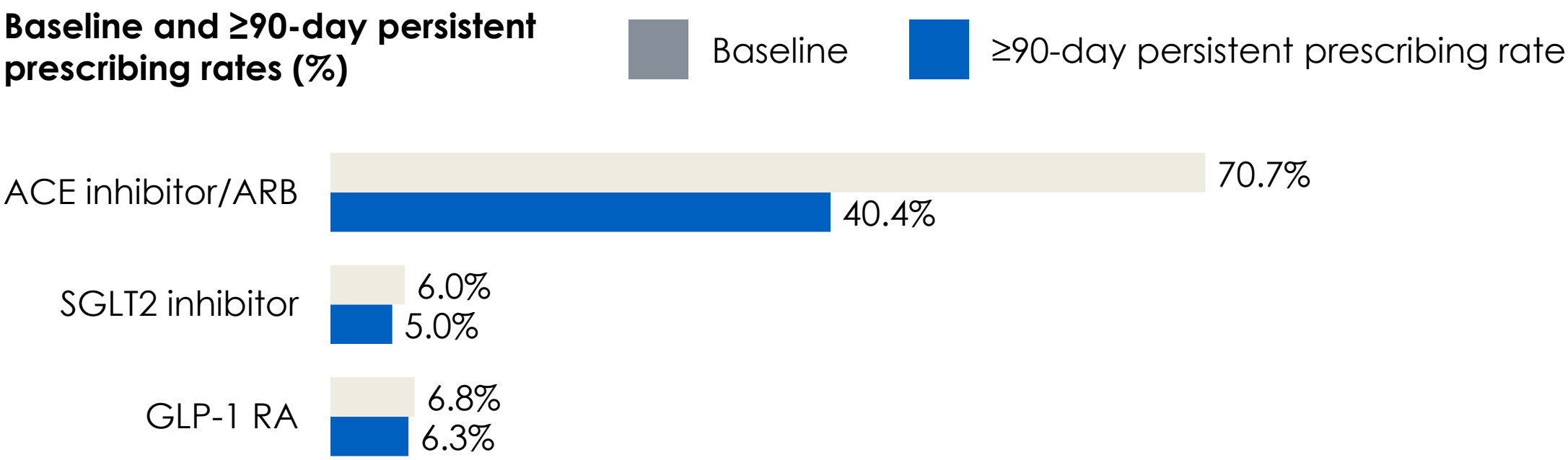
**Aware of CKD**




Luyckx VA, Tuttle KR *et al. Kidney Int* 2024;105:406–417

# Prescription of Guideline-Directed Medical Therapy Is Suboptimal in Diabetes and CKD

US CURE-CKD Registry study, an electronic health records database from Providence and UCLA Health system (2019–2020)




Nicholas SB *et al. Diabetes Obes Metab* 2023;25:2970–2979

# High unmet treatment needs in patients with chronic kidney disease and type 2 diabetes: real-world evidence from a US claims database

**Background**

We evaluated treatment initiation and discontinuation in patients with type 2 diabetes (T2DM) who had incident CKD (incident cohort), and rates of clinical/economic outcomes in patients with T2D who had any CKD (prevalent cohort).

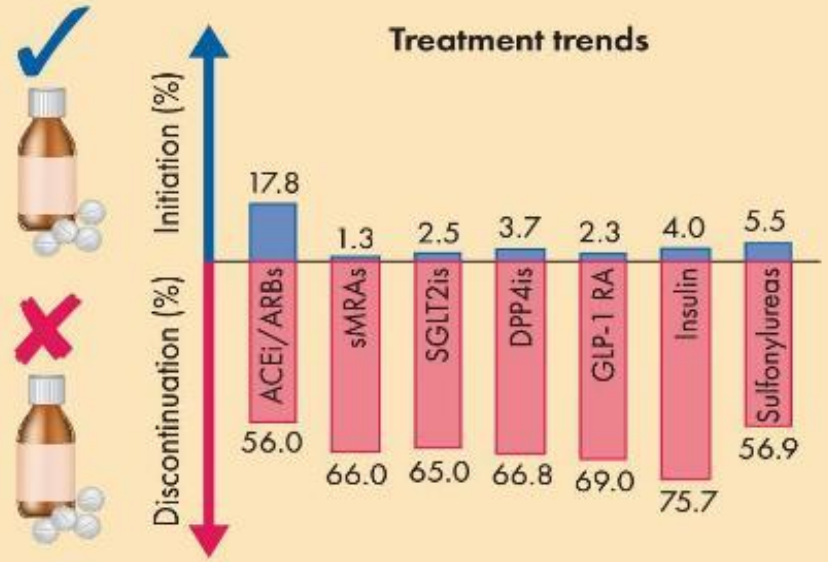
**Methods**

Retrospective study of administrative claims

1 January 2007 – 31 March 2019

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

**Results**




**Hospitalization rates per 1000 person years**

| All-cause | Kidney-related |
|---|---|
| 283.1 | 36.6 |

**Clinical outcome rates per 1000 person years**

| Mortality | ESKD |
|---|---|
| 35.1 | 104.2 |

**Conclusion**

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


ERA ndt NEPHROLOGY DIALYSIS TRANSPLANTATION

Fried, L., et al. NDT (2022)
@NDTSocial



Fried L *et al. Nephrol Dial Transplant* 2023;38:630–643

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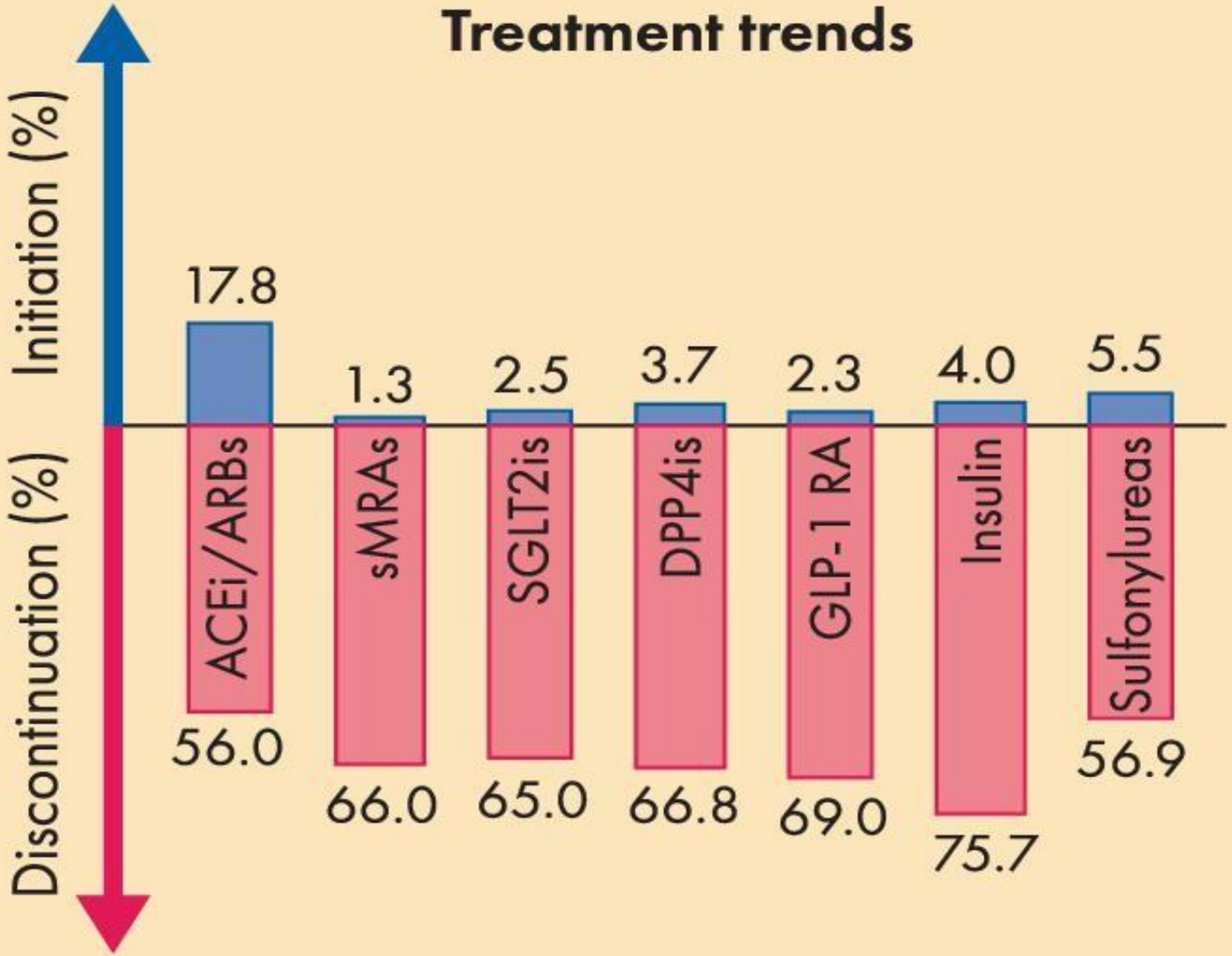
## Results

### Treatment trends

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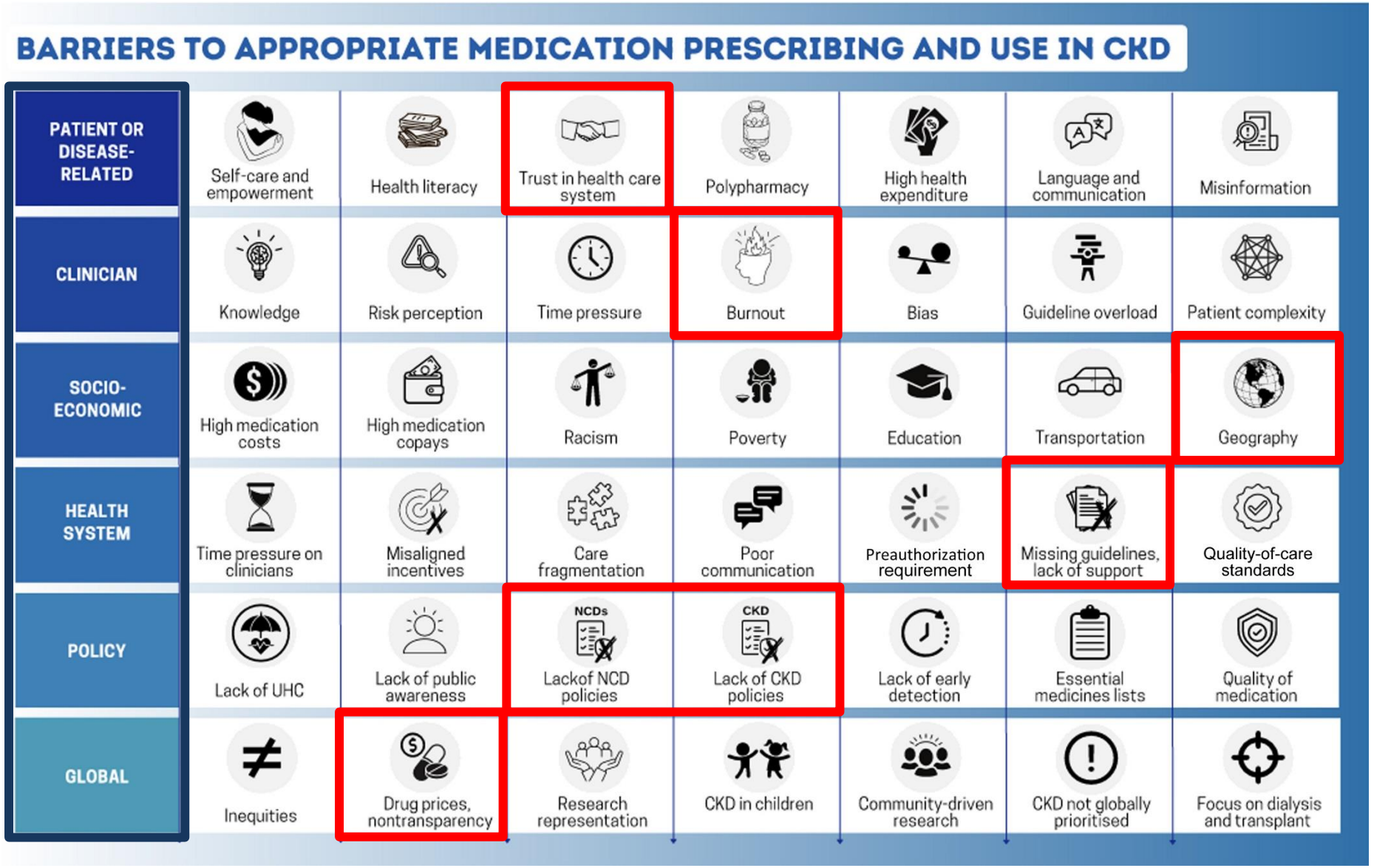



Luyckx VA, Tuttle KR *et al. Kidney Int* 2024;105:406–417

# International Retail Drug Prices for a 30-Day Supply GDMT for Diabetes and CKD

| Drug Classes | Retail Price for a 1-mo Supply, US$ | | | | | |
|---|---|---|---|---|---|---|
| | United States | Canada | United Kingdom | India | Australia and New Zealand | Turkey |
| **SGLT2 inhibitors** | | | | | | |
| Empagliflozin | 550–660 | 40–90 | 90 | 30–150 | 80–90 | 30–50 |
| Dapagliflozin | 530–650 | 40–180 | 90–120 | 40–80 | 100–150 | 40–80 |
| Canagliflozin | 560–650 | 70–170 | 100–140 | 60–140 | ND | ND |
| Finerenone | 580–690 | ND | ND | ND | ND | ND |
| **GLP-1 receptor agonists** | | | | | | |
| Dulaglutide | 770–1050 | ND | ND | ND | ND | ND |
| Semaglutide | 880–1300 | 320–340 | 200 | ND | ND | ND |
| Liraglutide | 1000–1220 | ND | ND | ND | ND | ND |

The sources were the PharmacyChecker (46) and GoodRx (43) websites (accessed April 11, 2022) (41,44). Prices are rounded to nearest $10. Semaglutide prices are for subcutaneous and oral formulations. SGLT2, sodium-glucose cotransporter 2; ND, no data; GLP-1, glucagon-like peptide 1.

Tuttle KR *et al. CJASN* 2022;17:1092-1103

# Accelerated Risk-Based GDMT for CKD in Type 2 Diabetes

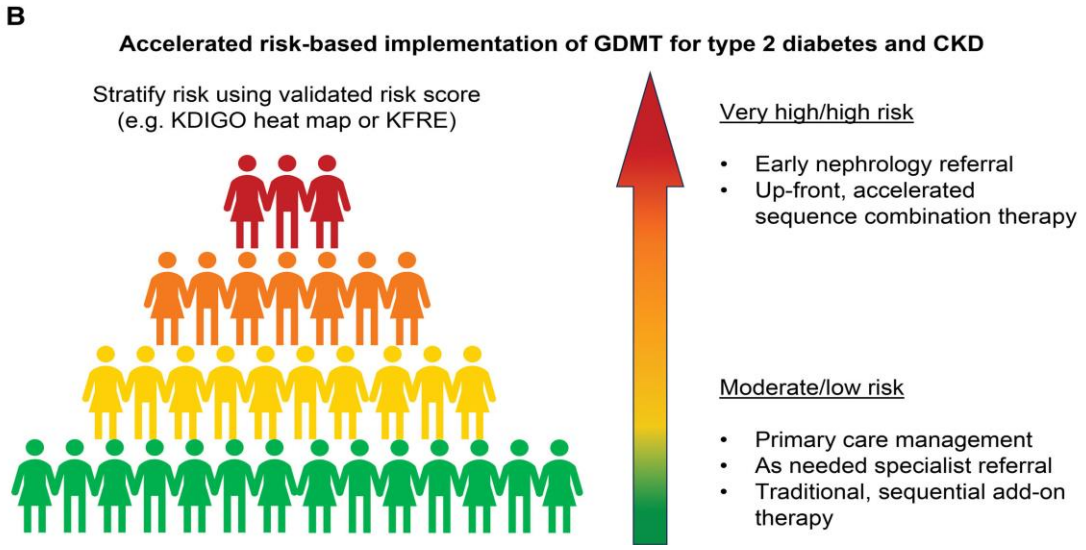
**A**

**TRADITIONAL APPROACH**
Maximise RAS blockade, add SGLT2i, re-assess in 3-6 months, add ns-MRA, consider GLP-1 RA
Limitations: Ignores excess early cardiovascular risk, very high risk of therapeutic inertia

**RAPID SEQUENCE APPROACH**
Simultaneous or rapid implementation of GDMT for type 2 diabetes and CKD
Considerations: Assumes all patients with CKD are at equally high risk, cost-effectiveness and early safety uncertain

**ACCELERATED RISK-BASED APPROACH**
Identify patients at highest risk using validated risk score, prioritise accelerated implementation of GDMT for type 2 diabetes and CKD
Appeal: Match intensity of treatment to risk, prioritise patients likely to obtain greatest absolute benefits

**B**




Neuen BL, Tuttle KR, Vaduganathan M. *Circulation* 2024:149:1238-1240

# Take Home Points

- An SGLT2 inhibitor, and an ACE inhibitor or an ARB, are first-line GDMT for persons with CKD with or without diabetes.
- A GLP-1 receptor agonist and a non-steroidal MRA are currently considered risk-based GDMT for albuminuria, glycemia, weight, and CVD for CKD with type 2 diabetes.
- Semaglutide is the first GLP-1 receptor agonist proven to improve kidney, CVD, and survival outcomes in patients with CKD and type 2 diabetes.
- CKD detection, awareness, access to care, and implementation strategies are needed to realize the benefits of kidney-heart-lifesaving therapies.

***Save kidneys, hearts, and lives!***