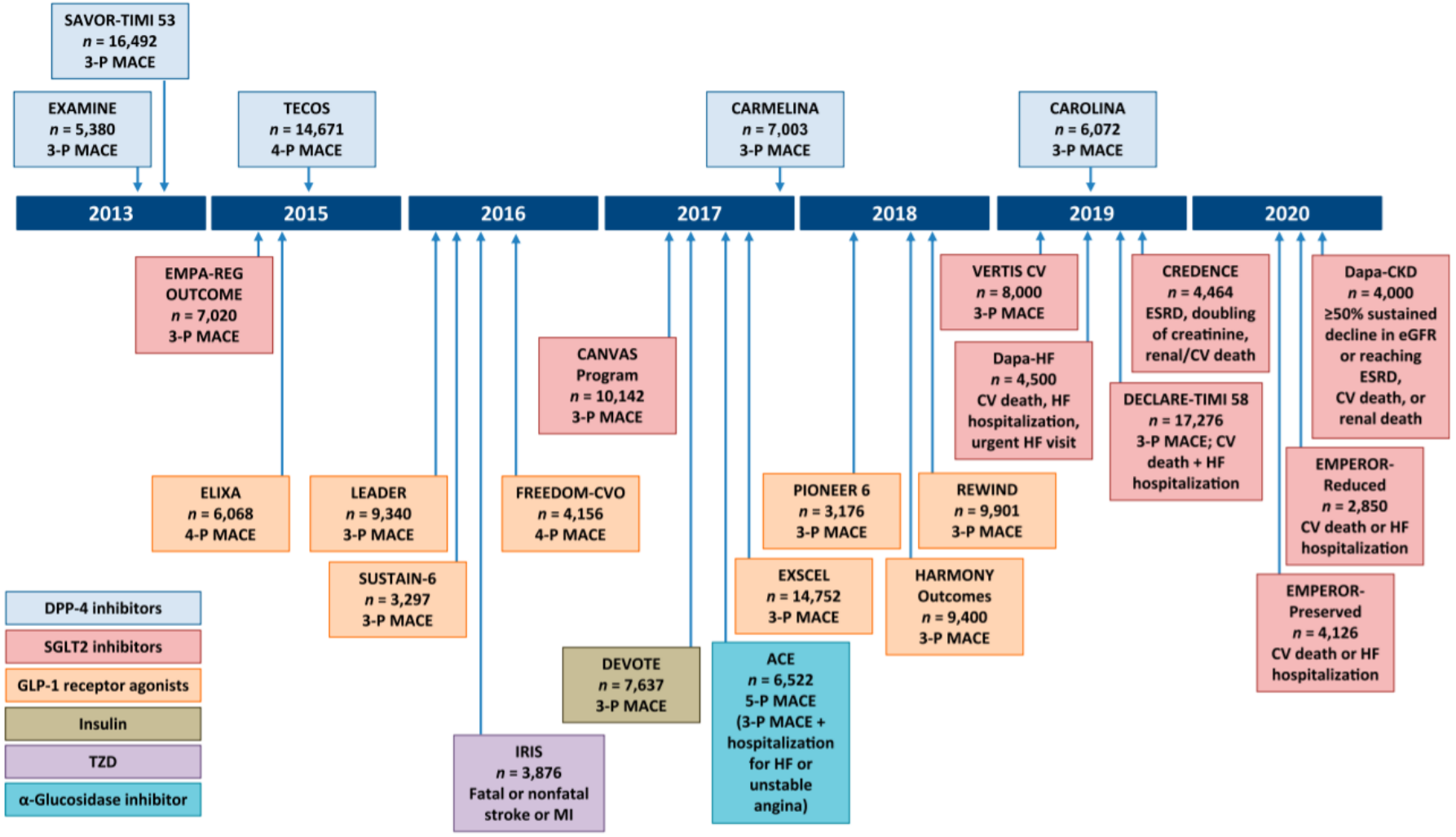
# Visie van de nefroloog

Prof. Dr. M. Speeckaert

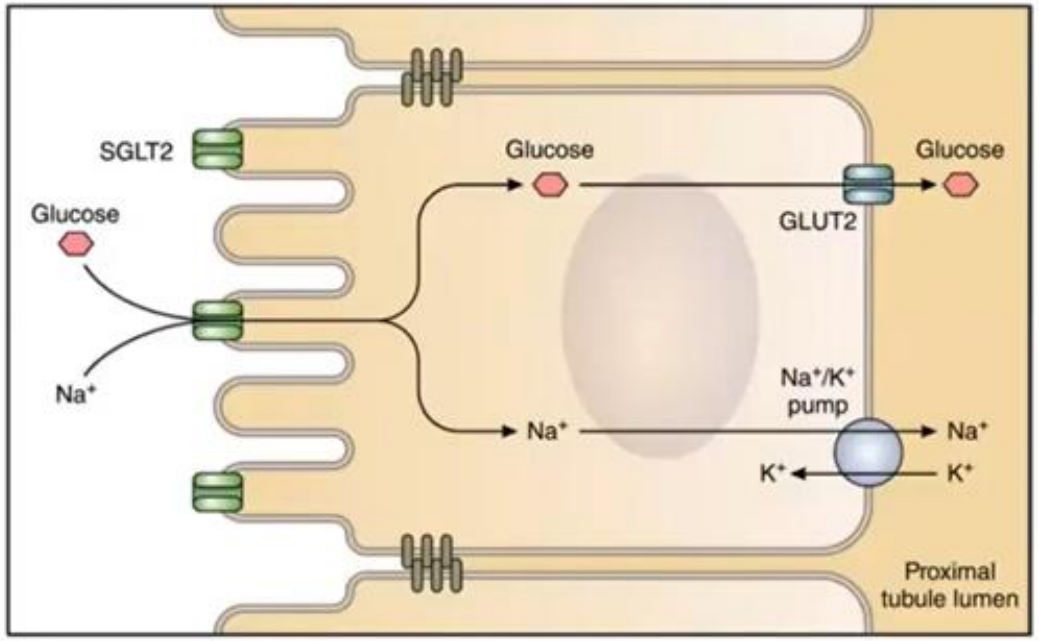
# CLINICAL TRIALS OF NEW DIABETIC DRUGS



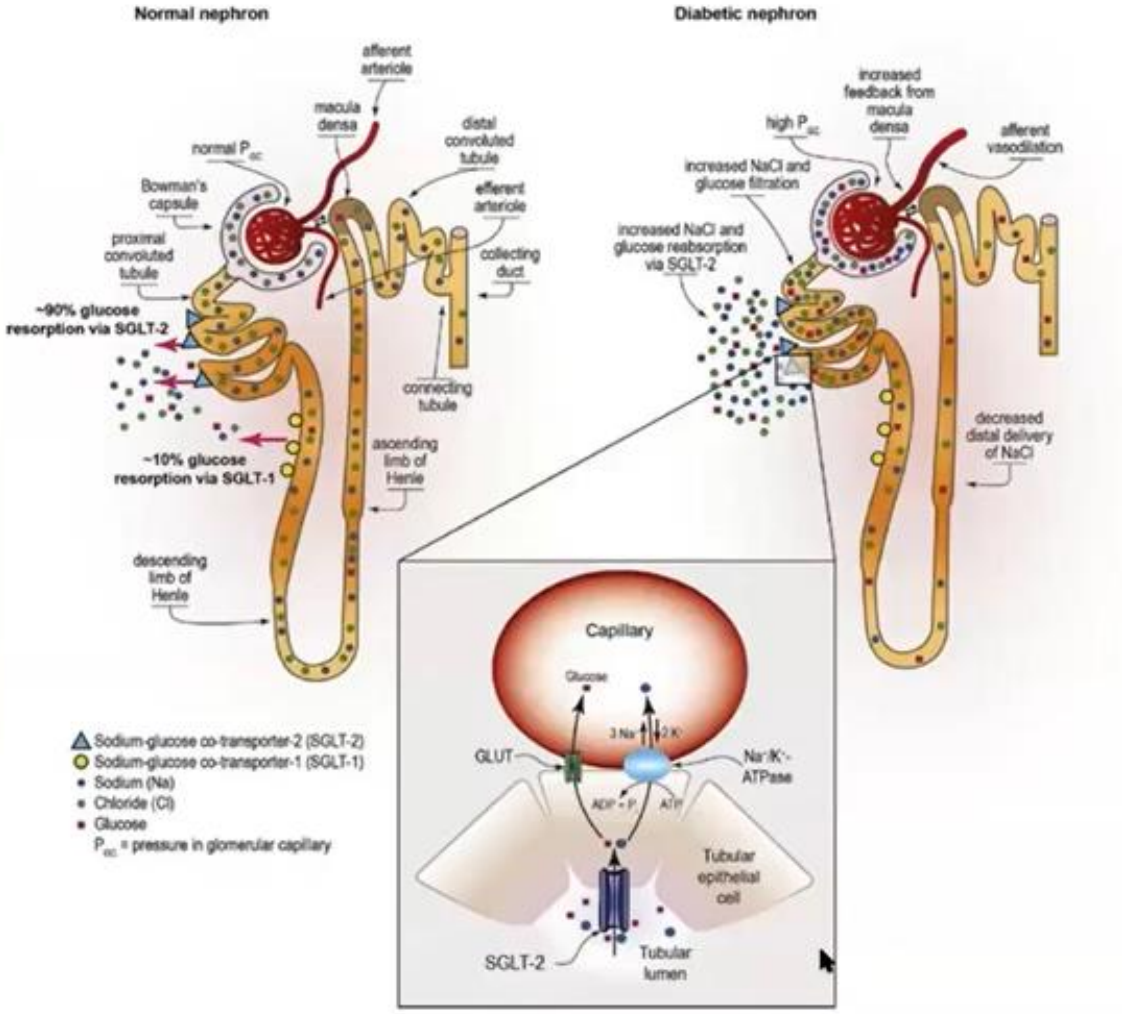
# SUMMARY OF THE MAIN EFFECTS OF THE NEW DIABETIC DRUGS

| | | Cardiovascular effects | | Kidney effects | | |
|---|---|---|---|---|---|---|
| **Drug** | **$HbA_{1c}$ lowering** | **Major atherosclerotic cardiovascular events** | **Heart failure** | **Albuminuria or albuminuria-containing composite outcome** | **GFR loss*** | **Notable adverse effects** |
| **SGLT2 inhibitors** | ↓ 0.6–0.9% (CKD G1–G2)<br>↓ 0.3–0.5% (CKD G3a)<br>↔<br>(CKD G3b–G4)<br>NA<br>(CKD G5) | ↓/– | ↓↓ | ↓↓ | ↓↓ | Genital mycotic infections, diabetic ketoacidosis, possibly amputations (canagliflozin) |
| **GLP-1 receptor agonists** | ↓ 1.0–1.2% (CKD G3a–4) | ↓/– | – | ↓ | ↓/– | Gastrointestinal, primarily nausea and vomiting |
| **DPP-4 inhibitors** | ↓ 0.5–0.7% (CKD G3a–4) | – | –/↑ | ↓ | – | Possibly heart failure (saxagliptin) |

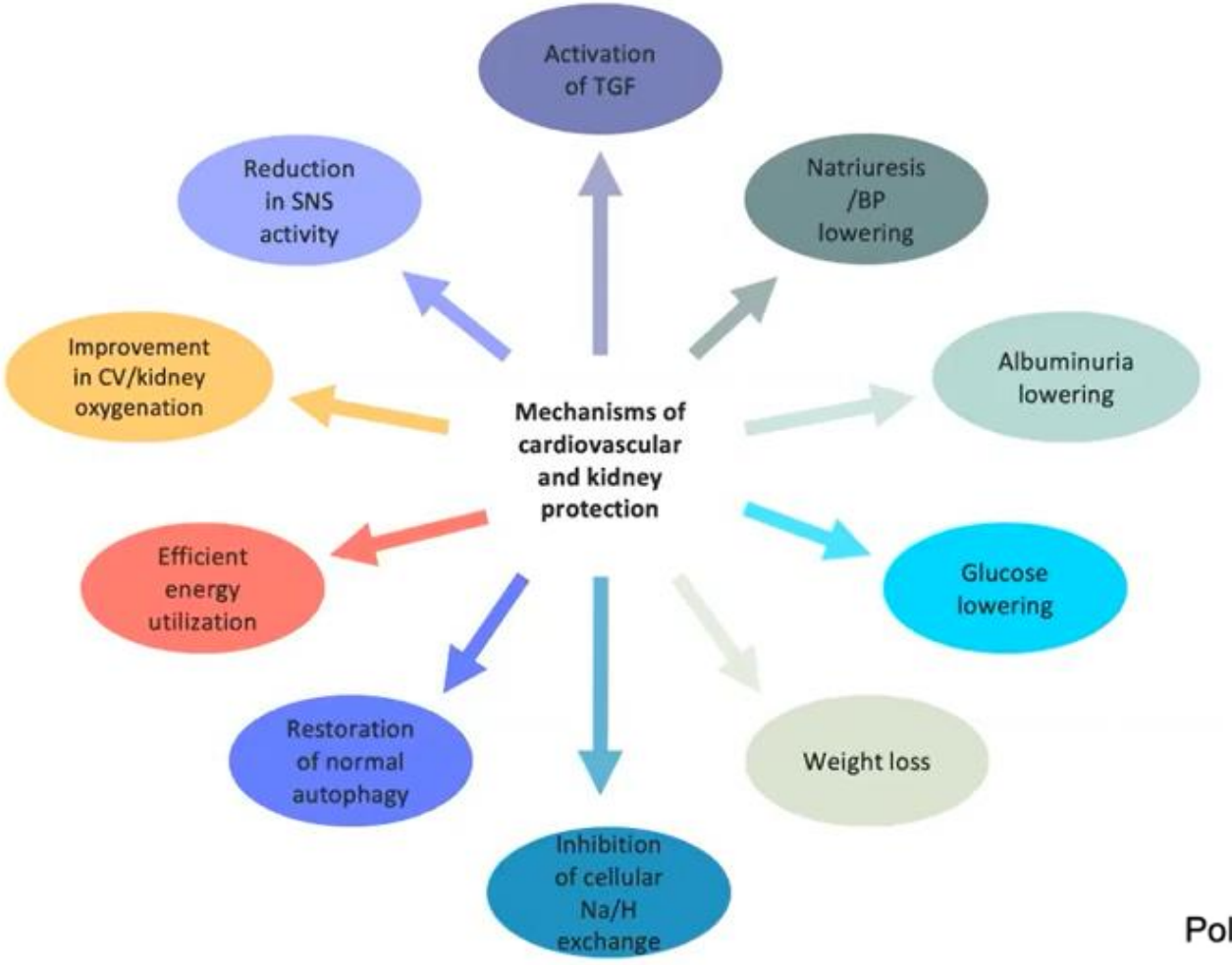
# SGLT2 INHIBITORS




Alicic et al. AJKD 2018
Heerspink et al. Circulation 2016

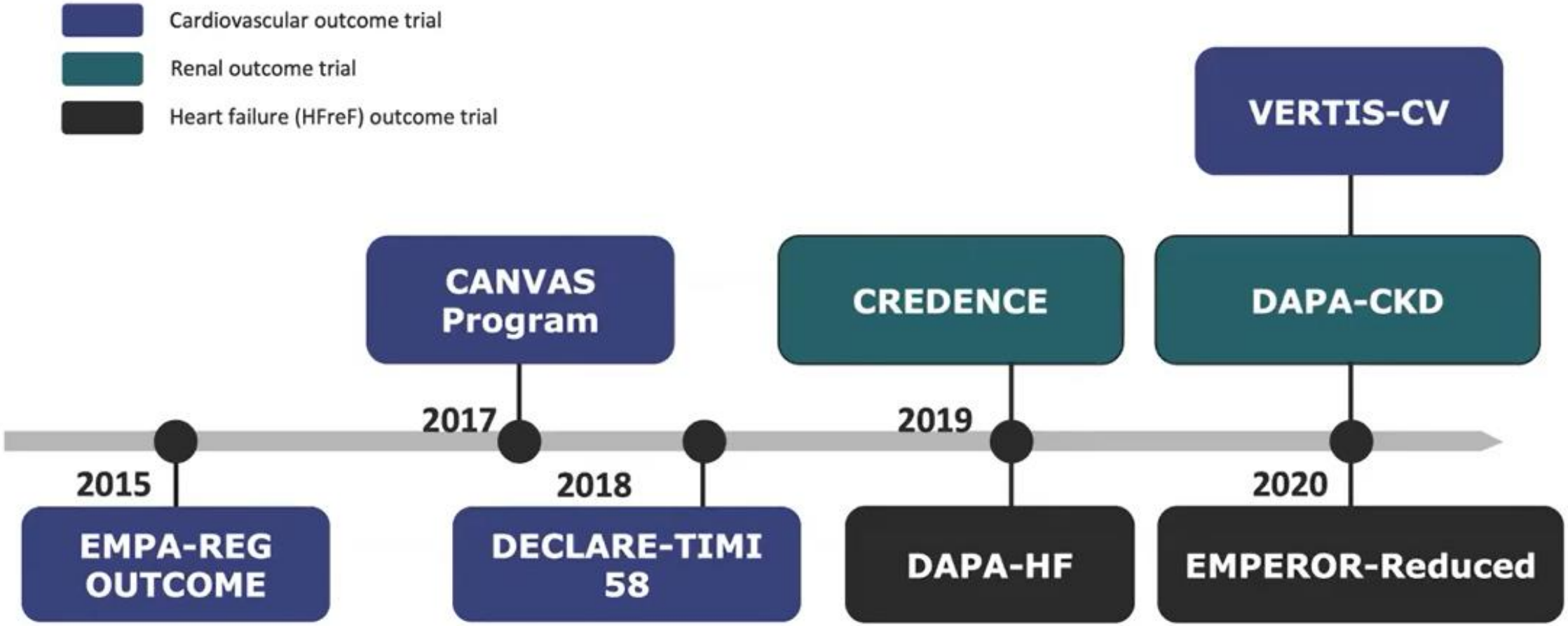


# MECHANISMS OF RENAL (AND CV) BENEFIT




Pollock Nov 2020. Not published

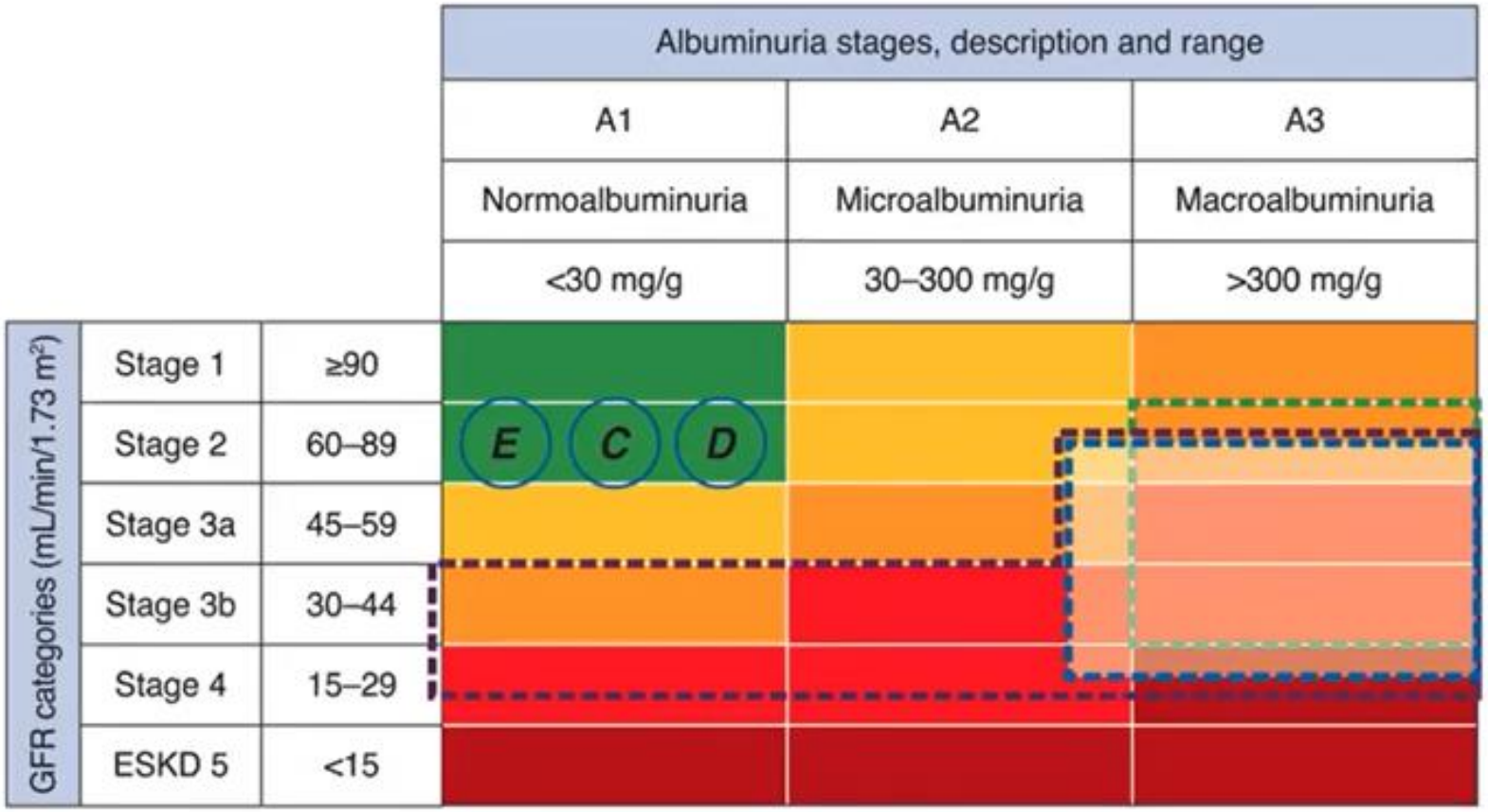
# KEY SGLT2 INHIBITOR TRIALS: 2015-2020



# PARTICIPANT CHARACTERISTICS IN THE KEY SGLT2 INHIBITOR TRIALS

| Study | EMPA-REG OUTCOME (n=7020) | CANVAS Program (n=10142) | DECLARE-TIMI 58 (n=17160) | CREDENCE (n=4401) | DAPA-CKD (n=4304) |
|---|---|---|---|---|---|
| Drug | Empagliflozin | Canagliflozin | Dapagliflozin | Canagliflozin | Dapagliflozin |
| Mean age (years) | 61 | 63 | 64 | 63 | 62 |
| Female, n (%) | 2004 (29) | 3633 (36) | 6422 (37) | 1494 (34) | 1425 (33) |
| Median follow-up (years) | 3.1 | 2.4 | 4.2 | 2.6 | 2.4 |
| Established atherosclerotic CV disease (%) | 7020 (100) | 6656 (66) | (6974 (41) | 2220 (50) | 1610 (37) |
| History of heart failure, n (%) | 706 (10) | 1461 (14) | 1724 (10) | 652 (15) | 468 (12) |
| Diabetes, n (%) | 7020 (100) | 10142 (100) | 17160 (100) | 4401 (100) | 2906 (68) |
| eGFR, mL/min/1·73m$^2$, (mean) | 74 | 76 | 85 | 56 | 43 |
| eGFR <60mL/min/1·73m$^2$, n (%) | 1819 (26) | 2039 (20) | 1265 (7) | 2592 (59) | 3850 (89) |
| UACR, mg/g, (median) | 18 | 12 | 13 | 927 | 949 |
| UACR >300 mg/g, n (%) | 764 (11) | 760 (7) | 1169 (7) | 4401 (100) | 3859 (90) |
| Baseline use of RAS blockade, n (%) | 5666 (81) | 8116 (80) | 13950 (81) | 4395 (>99) | 4174 (97) |

# BASELINE KIDNEY RISK IN THE KEY SGLT2 INHIBITOR TRIALS




**CREDENCE** (DKD only)
eGFR ≥30 to <90 mL/min/1.73 m²
and UACR ≥300 mg/g

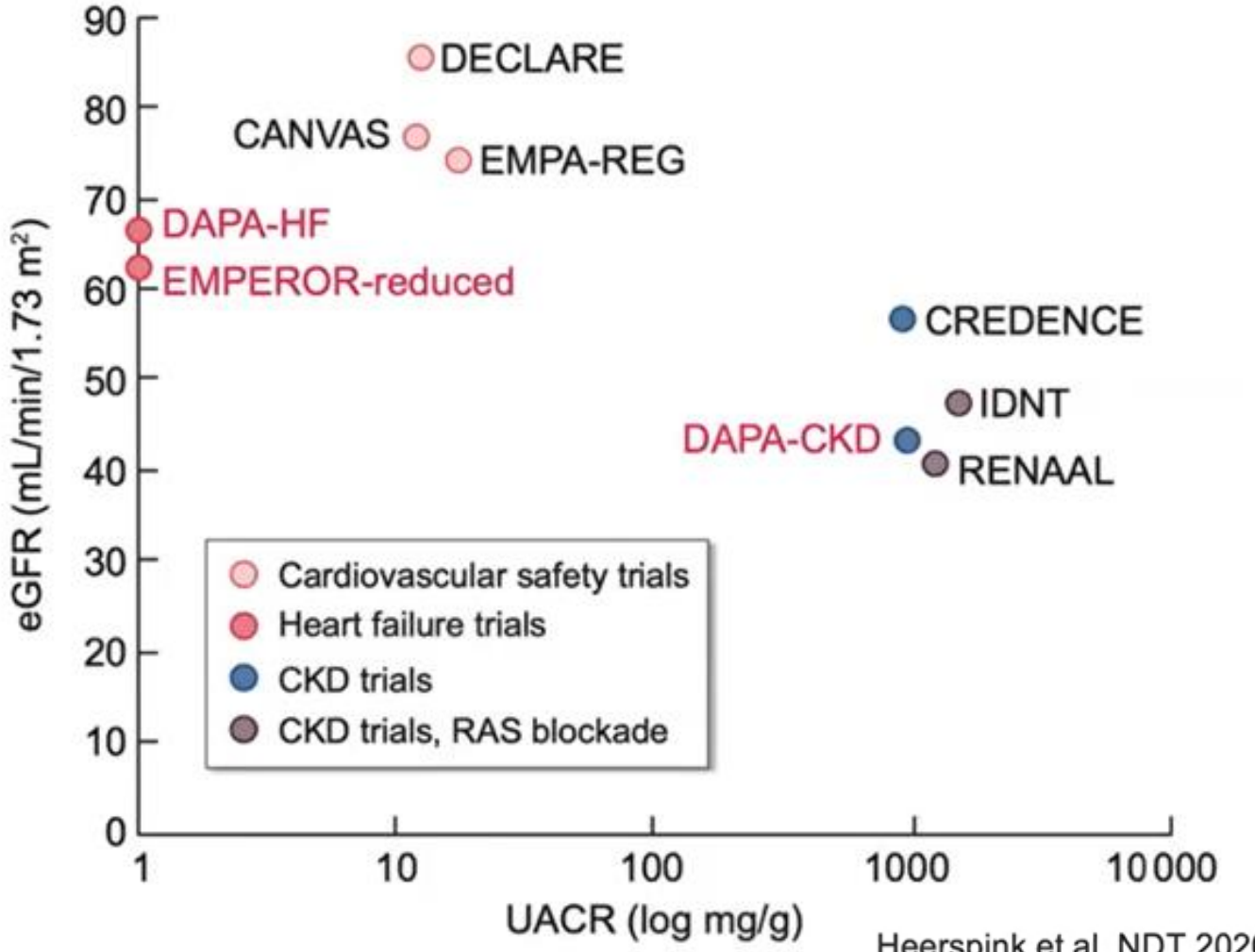
**DAPA-CKD** (CKD)
eGFR ≥25 to <75 mL/min/1.73 m²
and UACR ≥200 mg/g

**EMPA-KIDNEY** (CKD)
eGFR ≥45 to <75 mL/min/1.73 m²
and UACR ≥200 mg/g
OR
eGFR ≥20 to <45 mL/min/1.73 m²

E=EMPA-REG OUTCOME; C=CANVAS; D=DECLARE-TIMI 58

Heerspink et al. NDT 2020, Fernandez-Fernandez CKJ 2020

# BASELINE KIDNEY RISK IN THE KEY SGLT2 INHIBITOR TRIALS

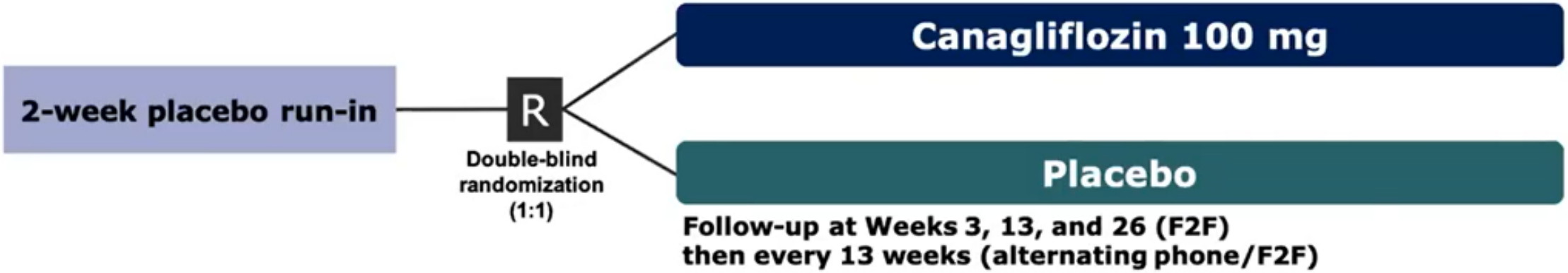



Heerspink et al. NDT 2020, Fernandez-Fernandez CKJ 2020

# CREDENCE DESIGN

**Key inclusion criteria**
- ≥30 years of age
- T2DM and HbA1c 6.5% to 12.0%
- eGFR 30 to 90 mL/min/1.73 $m^2$
- UACR 300 to 5000 mg/g
- Stable max tolerated labelled dose of ACEi or ARB for ≥4 weeks

**Key exclusion criteria**
- Other kidney diseases, dialysis, or kidney transplant
- Dual ACEi and ARB; direct renin inhibitor; MRA
- Serum $K^+$ >5.5 mmol/L
- CV events within 12 weeks of screening
- NYHA class IV heart failure
- Diabetic ketoacidosis or T1DM




**Participants continued treatment if eGFR was <30 mL/min/1.73 $m^2$ until chronic dialysis was initiated or kidney transplant occurred.**

# CREDENCE TRIAL

**Canagliflozin 100 mg**

## Inclusion/Baseline Criteria[1]

**≥30 years**
Canagliflozin n=2202
Placebo n=2199

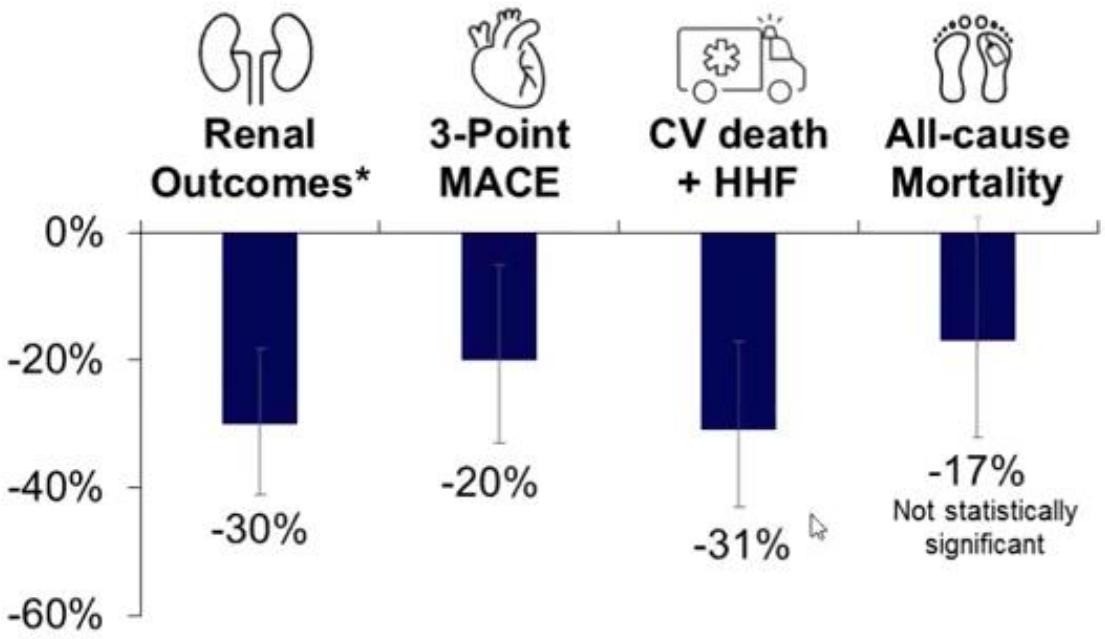
**≥30 to <90 mL/min/1.73 m²**
eGFR

**>33.9 to ≤565.6 mg/mmol**
UACR

**Confirmed T2D**
A1C ≥6.5% to ≤12.0%

ACEi/ARB use **99.9%**
Mean A1C **8.3%**
Mean sBP **140.0 mmHg**

## Key outcomes[2]

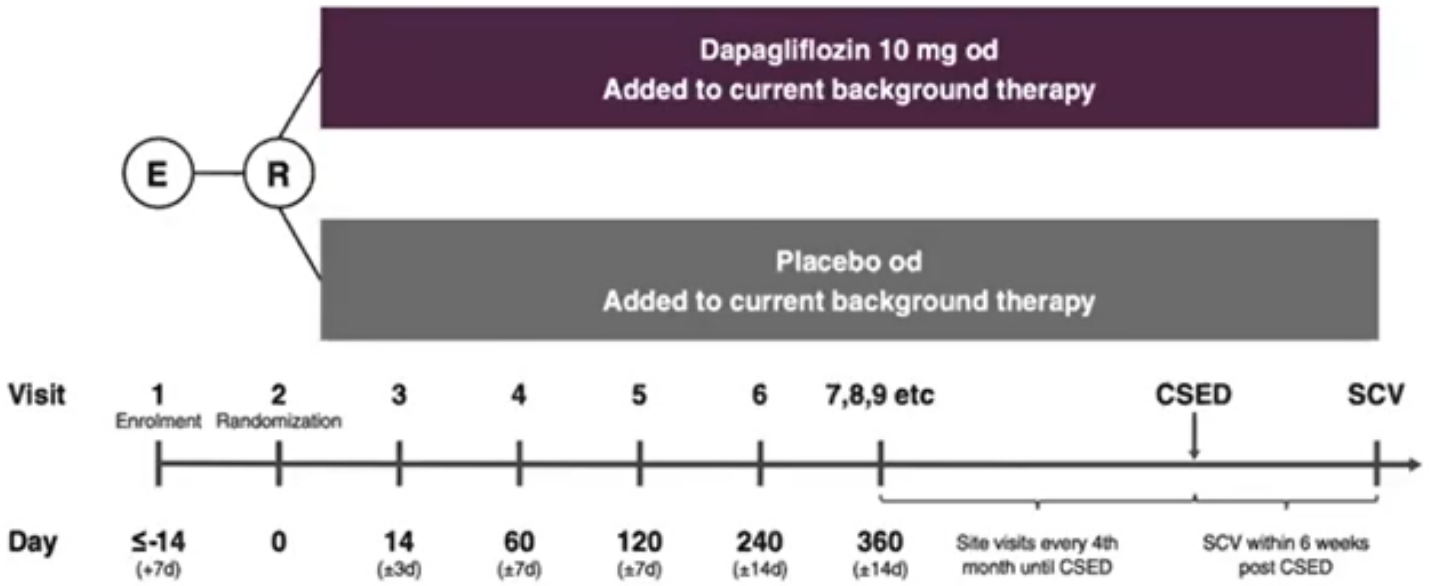



*Primary composite outcome: end-stage kidney disease, doubling of serum creatinine, or renal or cardiovascular death

# DAPA-CKD: STUDY DESIGN

**Key inclusion criteria**
- ≥18 years of age
- eGFR 25 to 75 mL/min/1.73m$^2$
- UACR 200 to 5000 mg/g
- Stable max tolerated dose of ACEi/ARB for ≥4 weeks

**Key exclusion criteria**
- T1DM
- Polycystic kidney disease, lupus nephritis, ANCA-vasculitis
- Immunosuppressive therapy 6 months prior to enrolment




**Primary outcome**
1. Sustained 50% decline in eGFR, ESKD, CV or renal death

**Secondary outcomes**
1. Sustained 50% decline in eGFR, ESKD, or renal death
2. HHF or CV death
3. All-cause death

# DAPA-CKD TRIAL

**Dapagliflozin 10 mg**

## Inclusion/Baseline Criteria[1]

**≥18 years**
Dapagliflozin n=2152
Placebo n= 2152

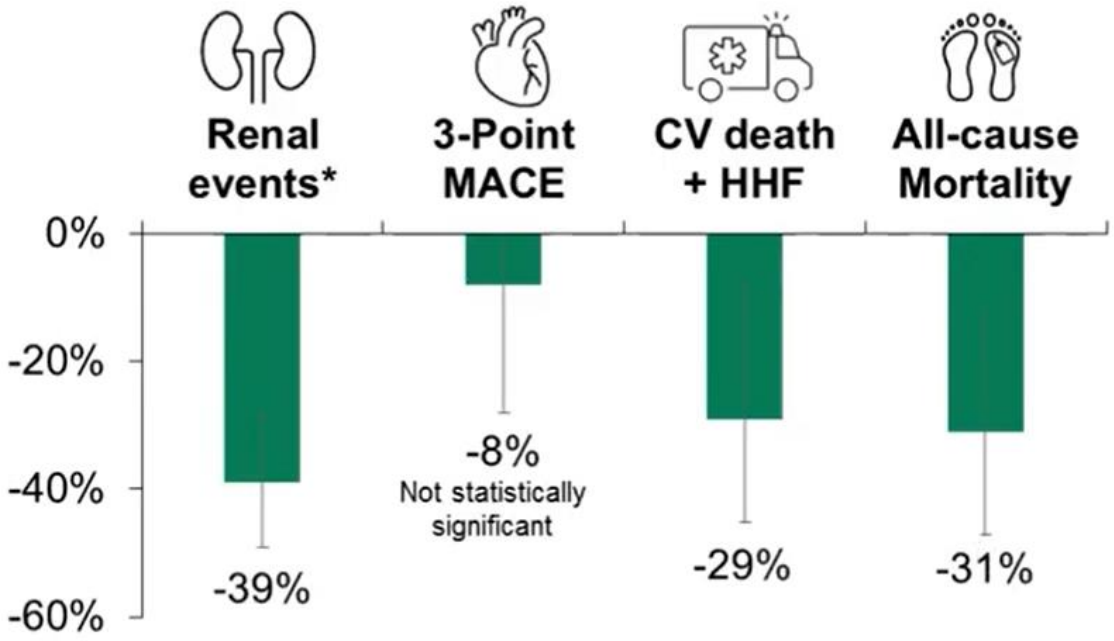
**≥25 to ≤75 mL/min/1.73 m²**
eGFR

**>22.6 to ≤565 mg/mmol**
UACR

**68% with T2D**

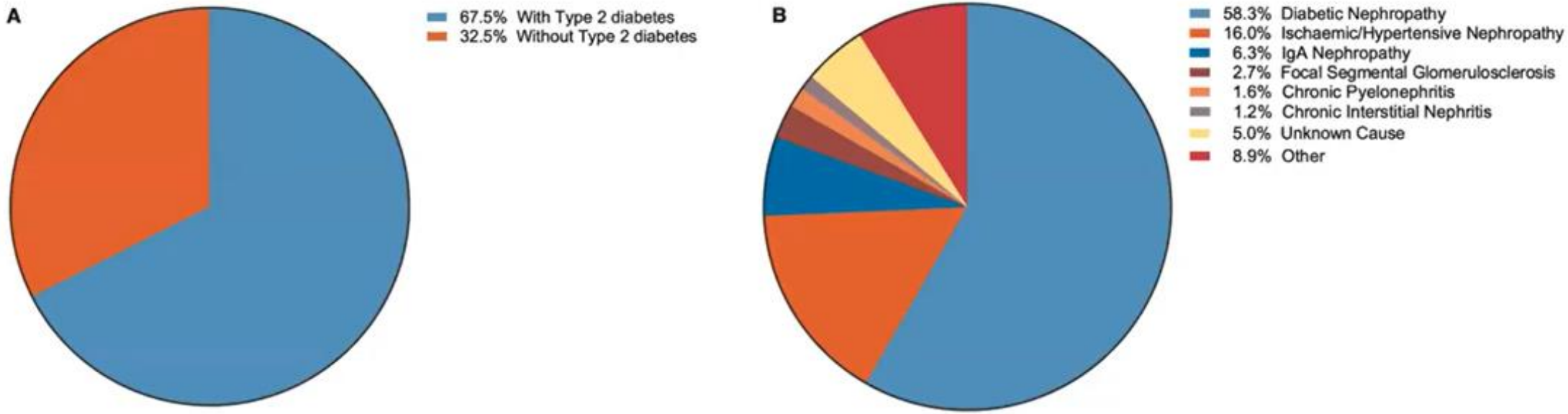
ACEi/ARB use **97%**
Mean sBP **137.4 mmHg**

## Key outcomes[2,3]



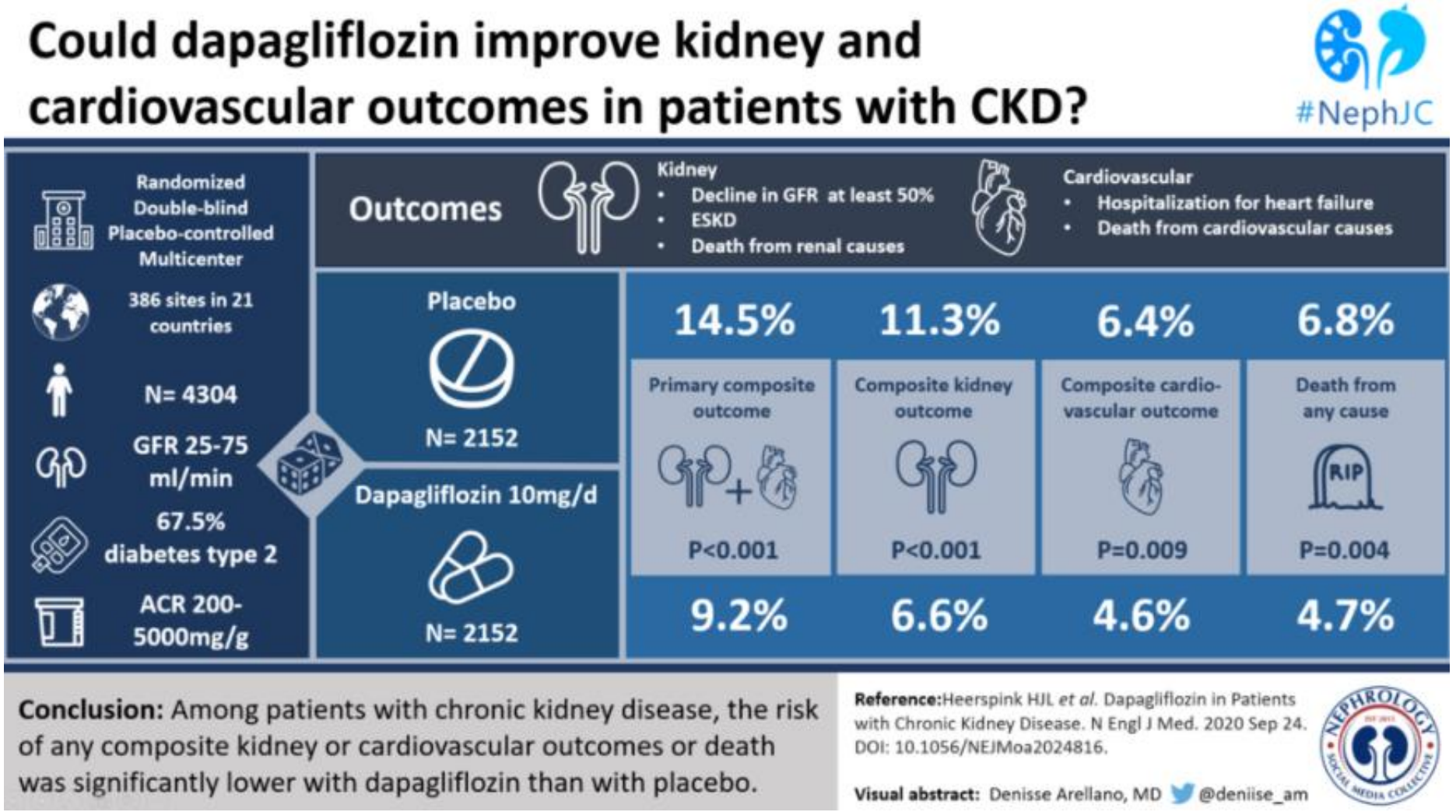

*Primary composite outcome: sustained decline in the estimated GFR of at least 50%, end-stage kidney disease, or death from renal or cardiovascular

# DAPA-CKD: ETIOLOGY OF CKD




Wheeler et al. NDT 2020

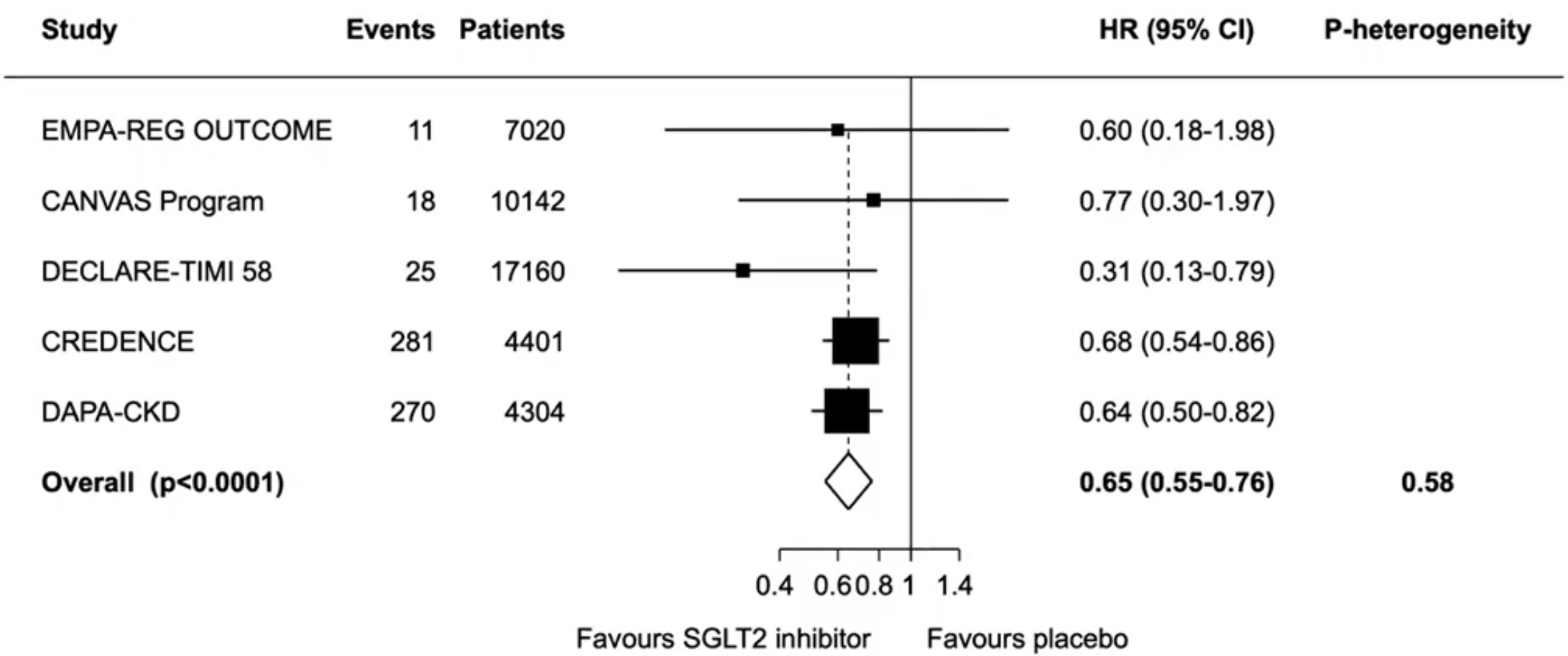
# DAPA-CKD: ETIOLOGY OF CKD



# DAPA-CKD: SAFETY RESULTS

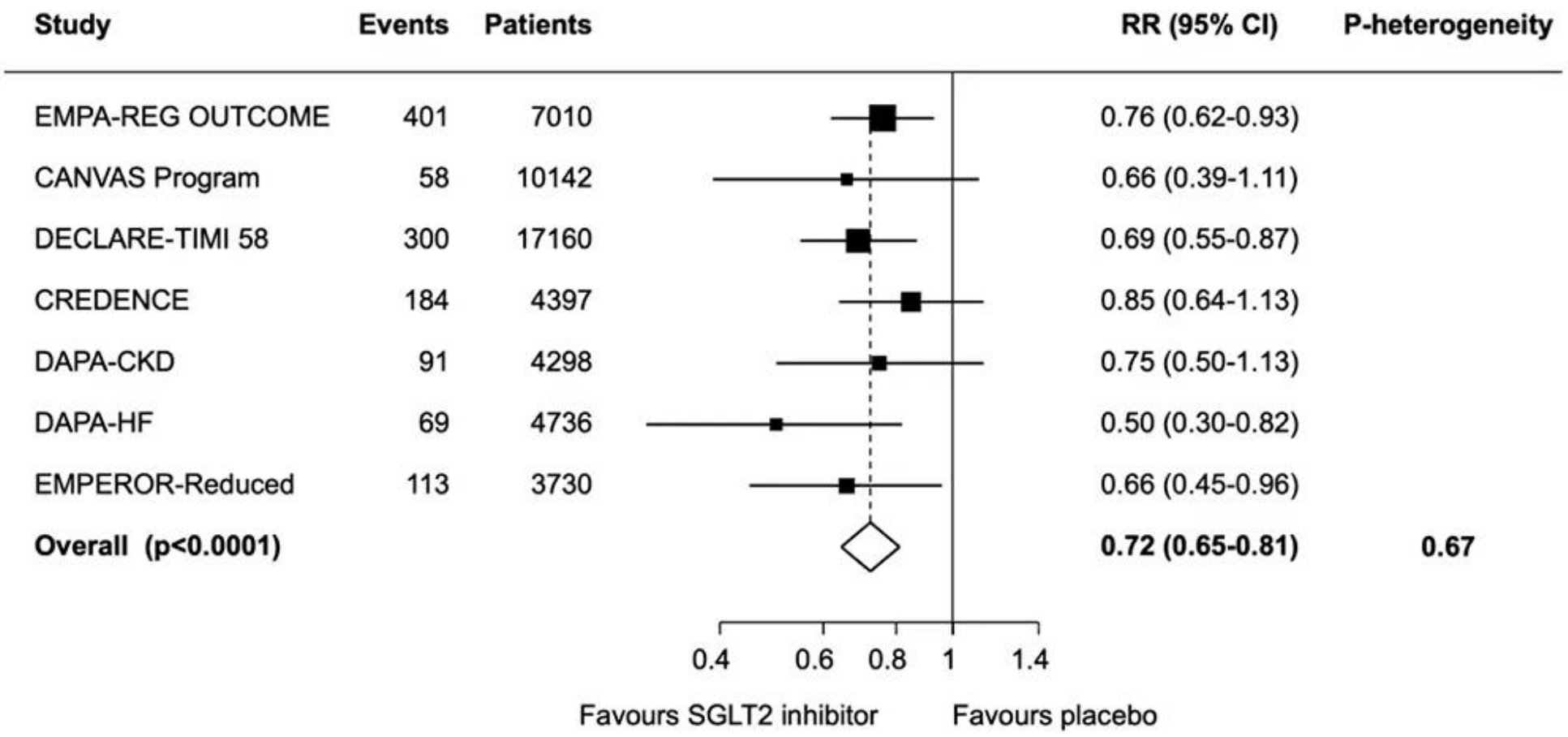
| Safety outcomes, n (%) | Dapagliflozin N=2149 | Placebo N=2149 |
|---|---|---|
| **Discontinuation of study drug** | 274 (12.8) | 309 (14.4) |
| **Discontinuation due to adverse event** | 118 (5.5) | 123 (5.7) |
| **Any serious adverse event** | 633 (29.5) | 729 (33.9) |
| **Adverse events of interest** | | |
| Amputation | 35 (1.6) | 39 (1.8) |
| DKA | 0 | 2 (0.1) |
| Fracture | 85 (4.0) | 69 (3.2) |
| Renal-related adverse event | 155 (7.2) | 188 (8.7) |
| Major hypoglycemia | 14 (0.7) | 28 (1.3) |
| Volume depletion | 127 (5.9) | 90 (4.2) |
| Serious adverse event of volume depletion | 22 (1.0) | 18 (0.8) |

# EFFECT OF SGLT2 INHIBITION OF KIDNEY FAILURE



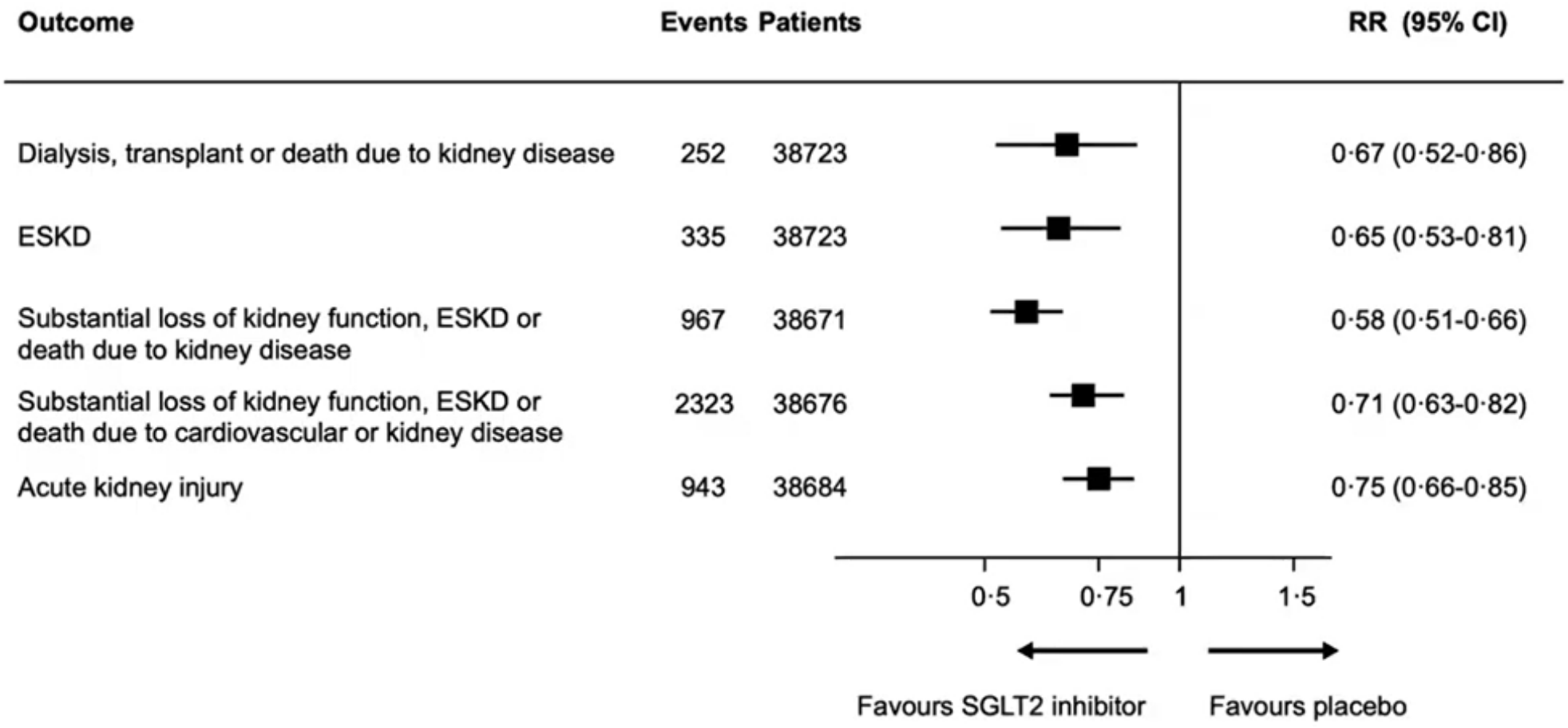

Adapted from Neuen et al. Lancet Diabetes Endocrinol 2019

# EFFECT OF SGLT2 INHIBITORS ON ACUTE KIDNEY INJURY




Adapted from Neuen et al. Lancet Diabetes Endocrinol 2019

# SGLT2 INHIBITORS AND MAJOR KIDNEY OUTCOMES IN T2DM

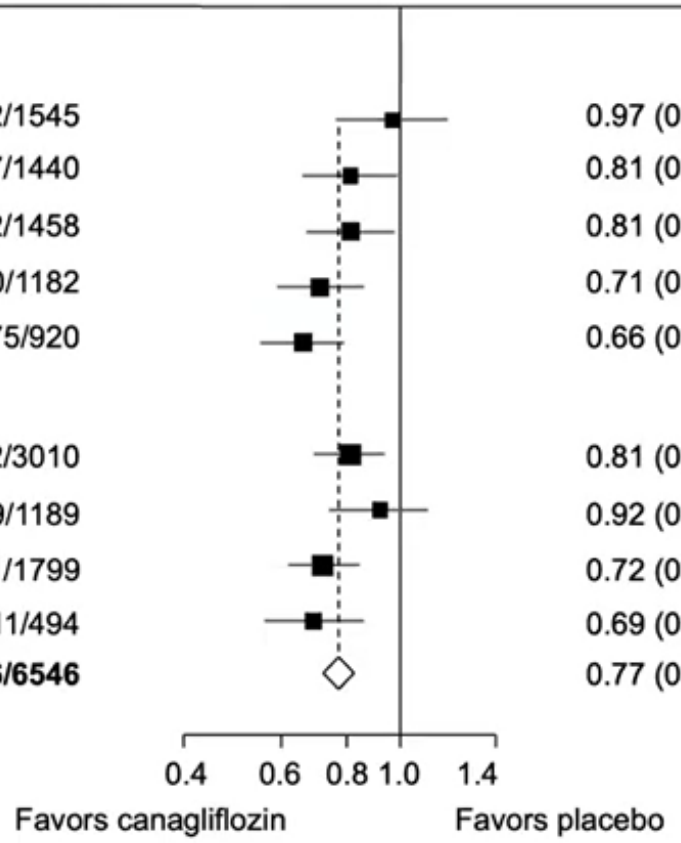



Adapted from Neuen et al. Lancet Diabetes Endocrinol 2019

# CARDIORENAL PROTECTION ACROSS THE FULL SPECTRUM OF EGFR/UACR: INTEGRATED DATA FROM CANVAS/CREDENCE

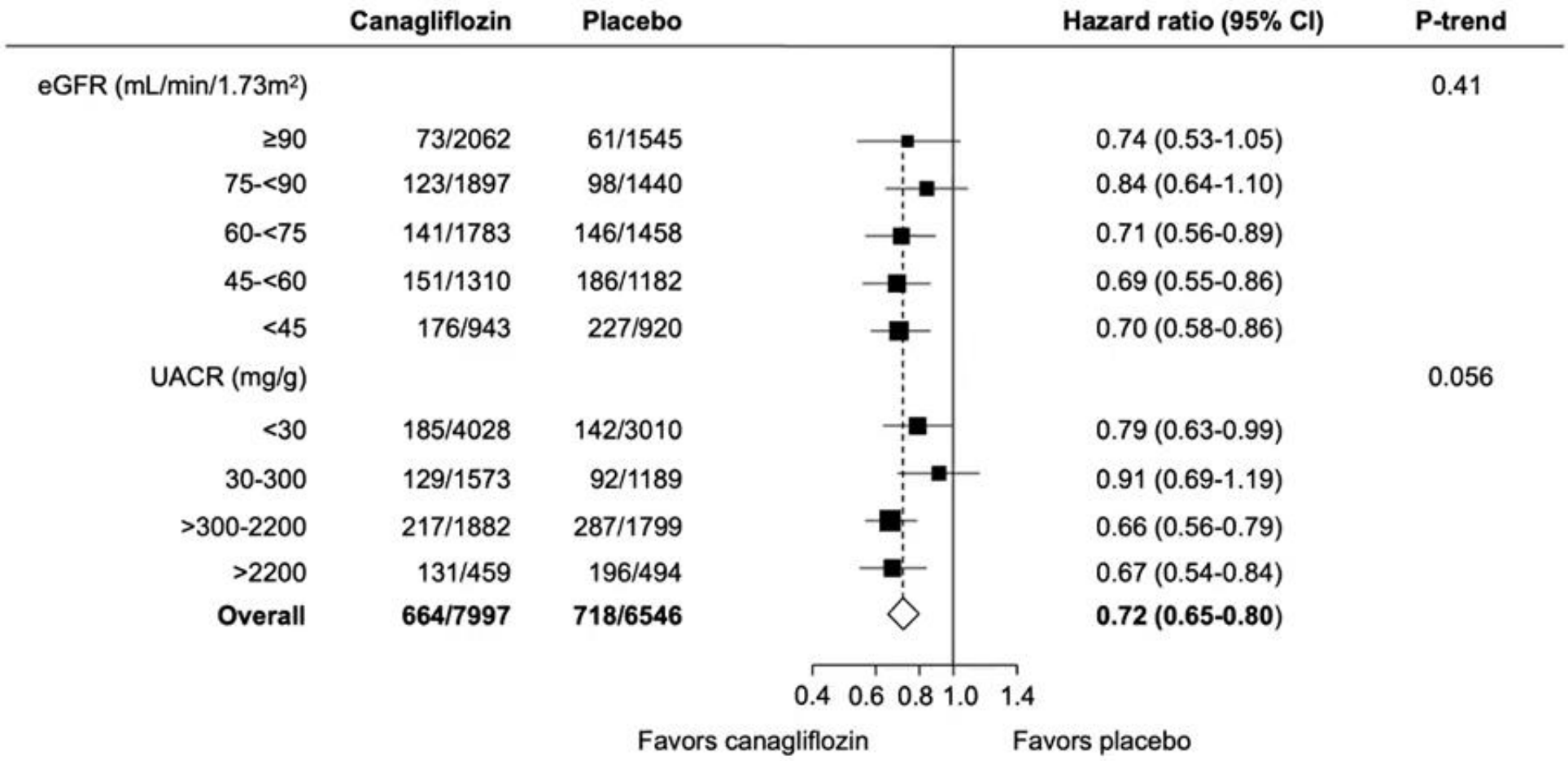
**Heart failure, nonfatal MI, nonfatal stroke, doubling of serum creatinine, kidney failure, CV or renal death**

| | Canagliflozin | Placebo | Hazard ratio (95% CI) | P-trend |
|---|---|---|---|---|
| eGFR (mL/min/1.73m$^2$) | | | | 0.0067 |
| ≥90 | 172/2062 | 112/1545 | 0.97 (0.76-1.23) | |
| 75-<90 | 217/1897 | 177/1440 | 0.81 (0.66-0.99) | |
| 60-<75 | 237/1783 | 212/1458 | 0.81 (0.67-0.98) | |
| 45-<60 | 204/1310 | 240/1182 | 0.71 (0.59-0.86) | |
| <45 | 205/943 | 275/920 | 0.66 (0.55-0.79) | |
| UACR (mg/g) | | | | 0.057 |
| <30 | 380/4028 | 292/3010 | 0.81 (0.69-0.94) | |
| 30-300 | 210/1573 | 149/1189 | 0.92 (0.74-1.13) | |
| >300-2200 | 294/1882 | 361/1799 | 0.72 (0.62-0.84) | |
| >2200 | 145/459 | 211/494 | 0.69 (0.56-0.86) | |
| **Overall** | **1035/7997** | **1016/6546** | 0.77 (0.70-0.84) | |



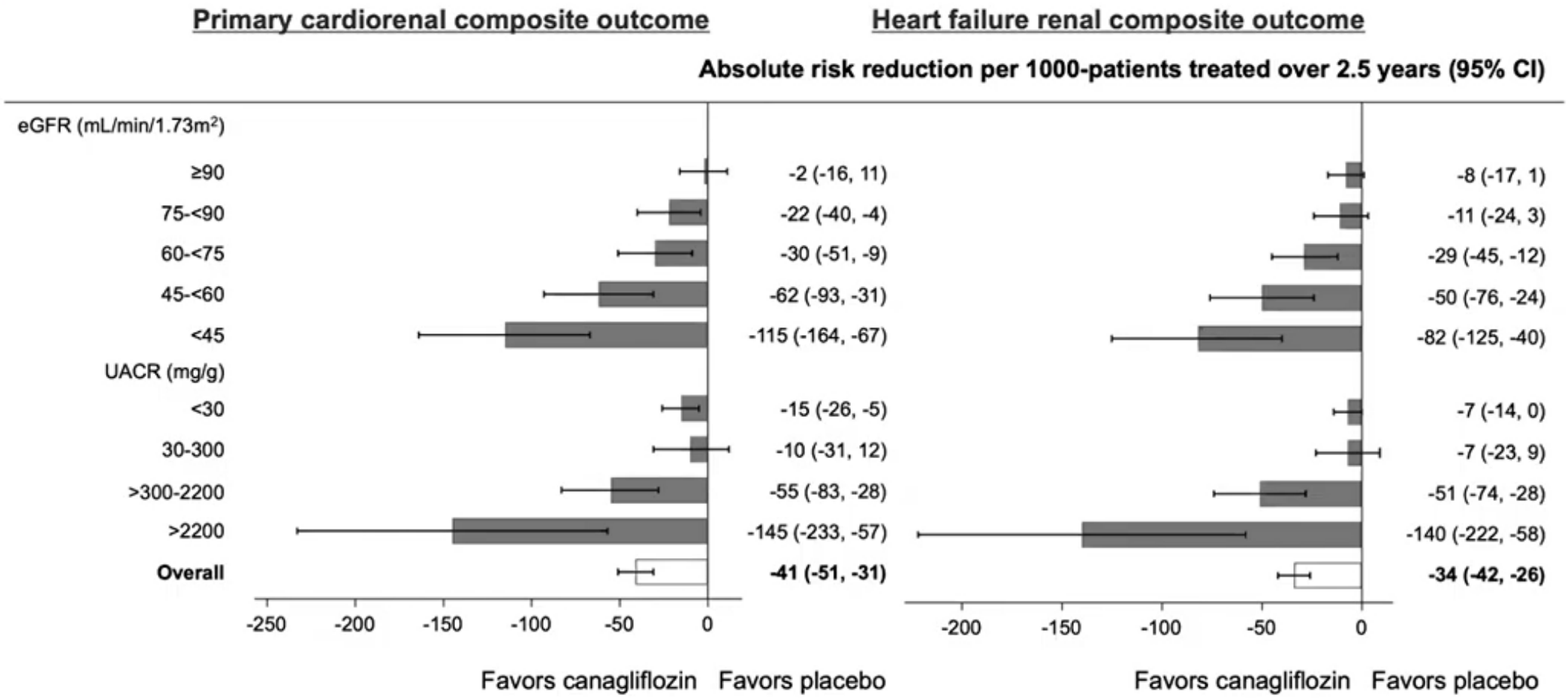

Neuen et al. ASN Kidney Week 2020

# HEART FAILURE RENAL COMPOSITE: INTEGRATED DATA FROM CANVAS/CREDENCE




Neuen et al. ASN Kidney Week 2020

# ABSOLUTE RISK REDUCTIONS ACROSS THE SPECTRUM OF eGFR/UACR: INTEGRATED DATA FROM CANVAS/CREDENCE

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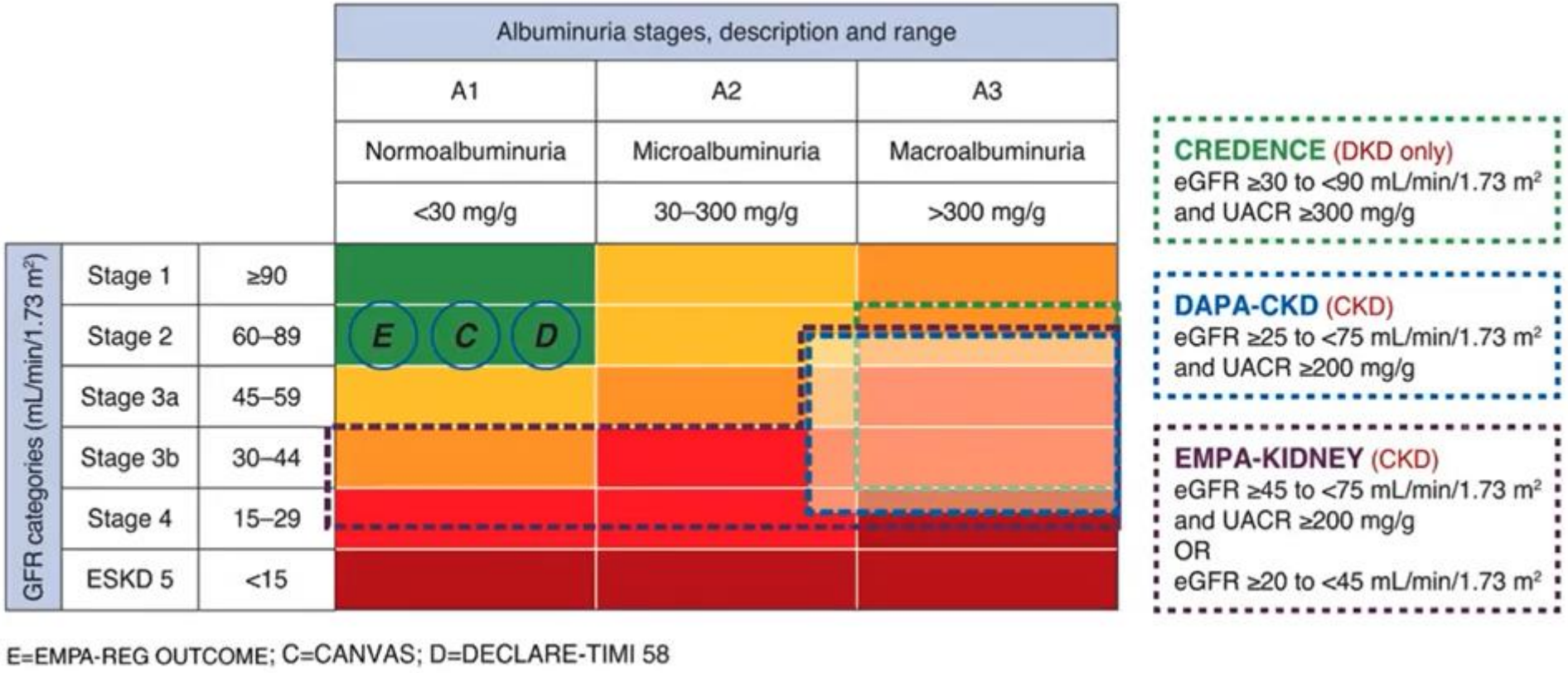
# SGLT2 INHIBITORS IN CKD: WHERE TO NEXT?




E=EMPA-REG OUTCOME; C=CANVAS; D=DECLARE-TIMI 58

Heerspink et al. NDT 2020, Fernandez-Fernandez CKJ 2020

# EMPA-KIDNEY

**Empagliflozin 10 mg**

## Inclusion Criteria[1]

**≥18 years +/- T2D**

Taking **ACEi/ARB**

Estimated enrollment: 6000 patients

**≥20 to <45 mL/min/1.73 m²** eGFR

**OR**

**≥45 to <90 mL/min/1.73 m²** eGFR

**≥22.6 mg/mmol** UACR

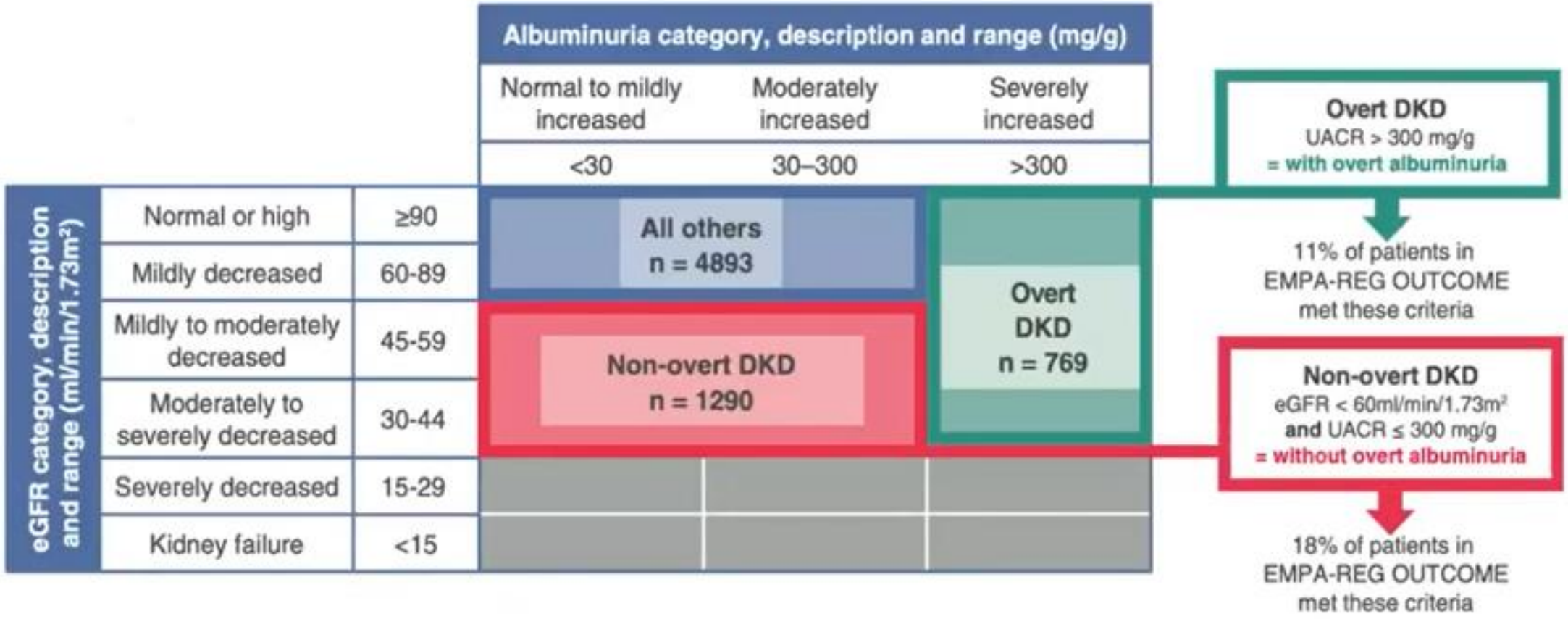
## Primary composite renal outcome*

**Key secondary endpoints:**

- Composite of CV death or HHF
- All-cause hospitalization
- All-cause mortality

*Time to first occurrence of (i) kidney disease progression (defined as ESKD, a sustained decline in eGFR to <10 mL/min/1.73 m², renal death, or a sustained decline of ≥40% in eGFR from randomization) or (ii) Cardiovascular death

# EMPAGLIFLOZIN ACROSS DIFFERENT DKD PHENOTYPES

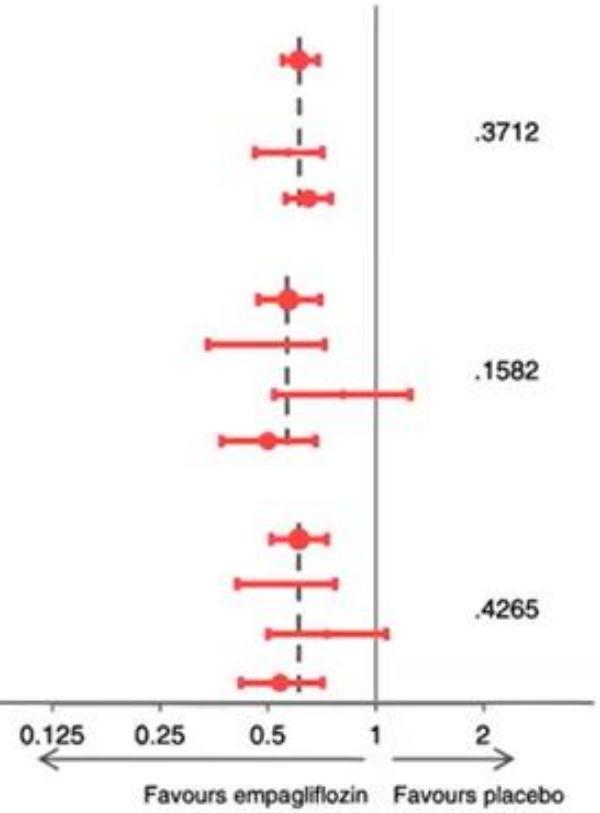



Wanner et al. Diabetes, Obesity and Metabolism 2020

# EMPAGLIFLOZIN ACROSS DIFFERENT DKD PHENOTYPES

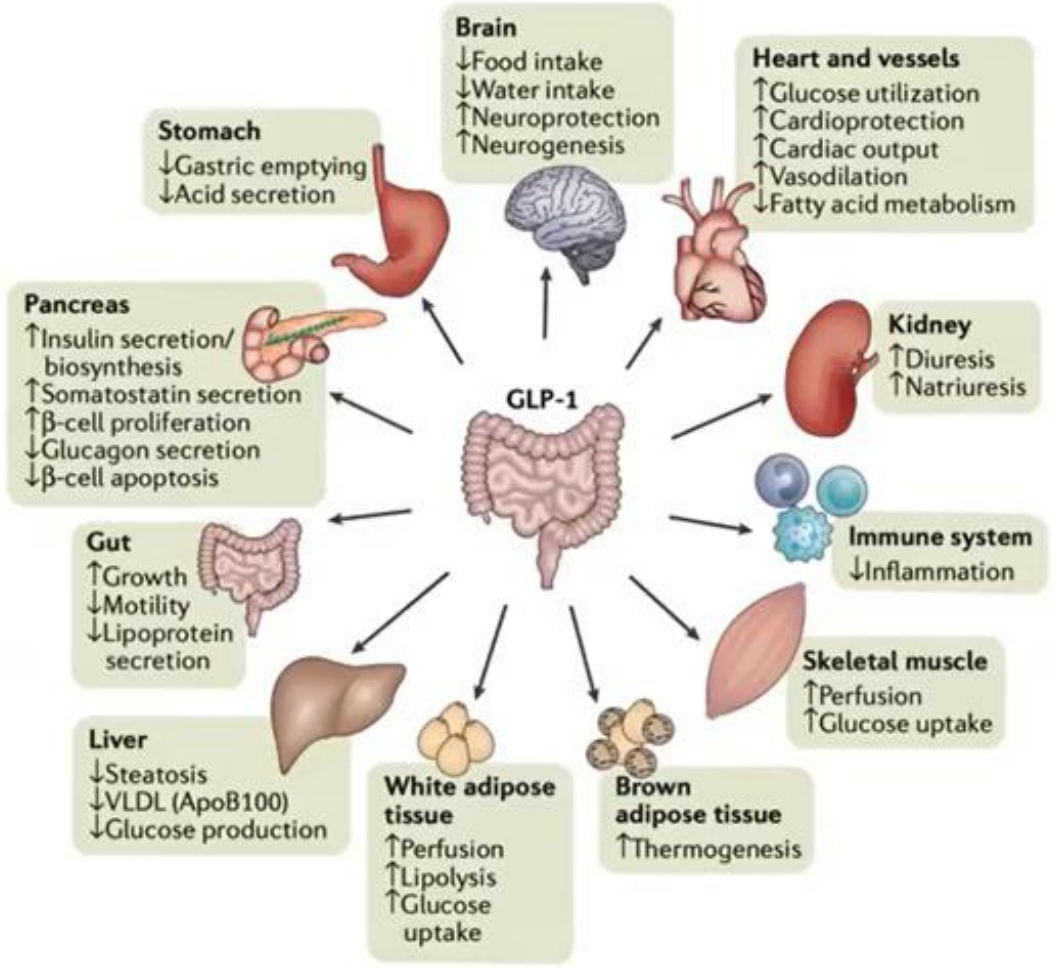
(C)

| | Empagliflozin | | Placebo | | Hazard ratio (95% CI) | Interaction *P*-value |
|---|---|---|---|---|---|---|
| | n event/N | % | n event/N | % | | |
| **Incident or worsening nephropathy** or CV death** | | | | | | |
| **All patients** | 675/4170 | 16.2 | 497/2102 | 23.6 | 0.61 (0.55, 0.69) | |
| Overt DKD | NA | NA | NA | NA | NC | .3712 |
| Non-overt DKD | 190/831 | 22.9 | 149/432 | 34.5 | 0.57 (0.46, 0.71) | |
| All others | 402/3223 | 12.5 | 285/1598 | 17.8 | 0.65 (0.56, 0.75) | |
| **Hard kidney endpoint† or CV death** | | | | | | |
| **All patients** | 201/4648 | 4.3 | 169/2325 | 7.3 | 0.57 (0.47, 0.70) | |
| Overt DKD | 58/506 | 11.5 | 51/260 | 19.6 | 0.49 (0.34, 0.72) | .1582 |
| Non-overt DKD | 52/839 | 6.2 | 33/439 | 7.5 | 0.81 (0.52, 1.25) | |
| All others | 89/3253 | 2.7 | 85/1610 | 5.3 | 0.50 (0.37, 0.68) | |
| **Alternative kidney endpoint‡ or CV death** | | | | | | |
| **All patients** | 275/4648 | 5.9 | 216/2325 | 9.3 | 0.61 (0.51, 0.73) | |
| Overt DKD | 90/506 | 17.8 | 68/260 | 26.2 | 0.56 (0.41, 0.77) | .4265 |
| Non-overt DKD | 66/839 | 7.9 | 45/439 | 10.3 | 0.73 (0.50, 1.07) | |
| All others | 116/3253 | 3.6 | 103/1610 | 6.4 | 0.54 (0.42, 0.71) | |




Wanner et al. Diabetes, Obesity and Metabolism 2020

# GLP-1 RECEPTOR AGONISTS




Muskiet et al. Nature Reviews Nephrology 2017

# GLP-1 RECEPTOR AGONISTS AND THE KIDNEY

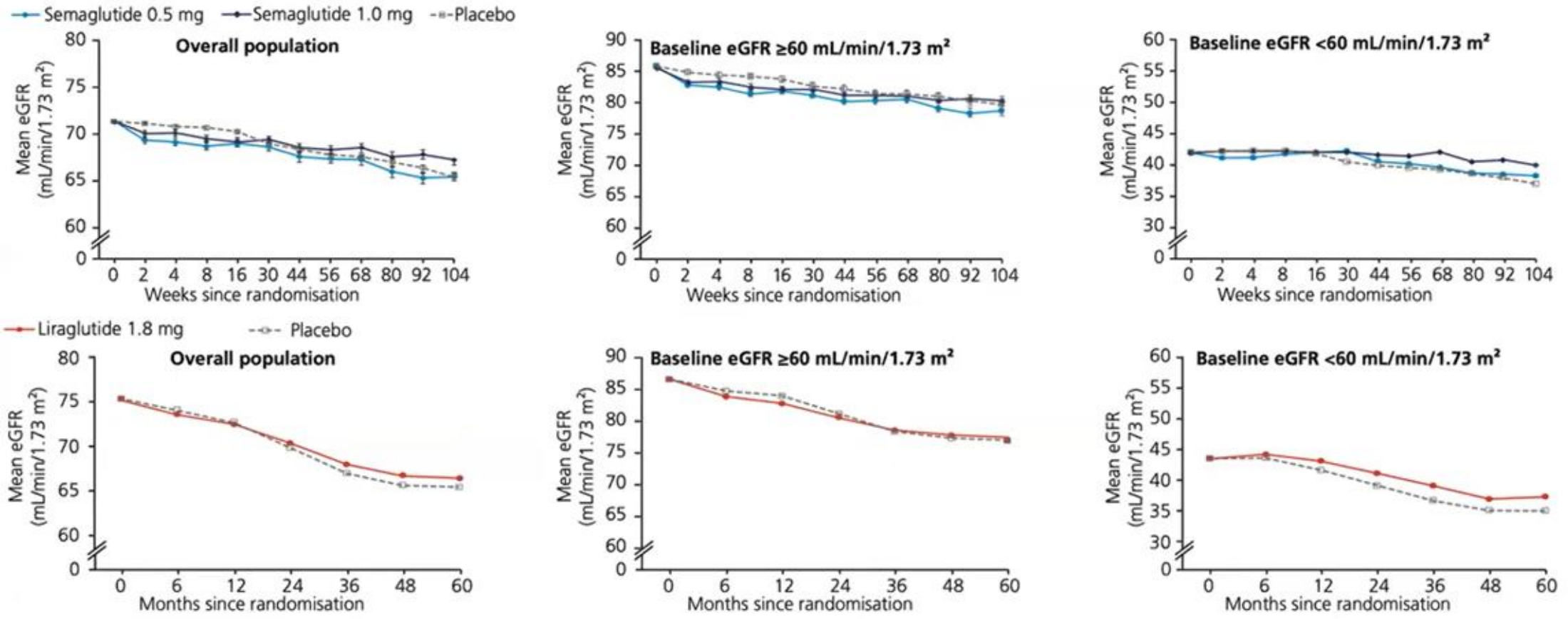
**Direct effects:**

- Anti-inflammatory effects
- Reduced oxidative stress
- Increased natriuresis
- Inhibition of RAAS

**Indirect effects**

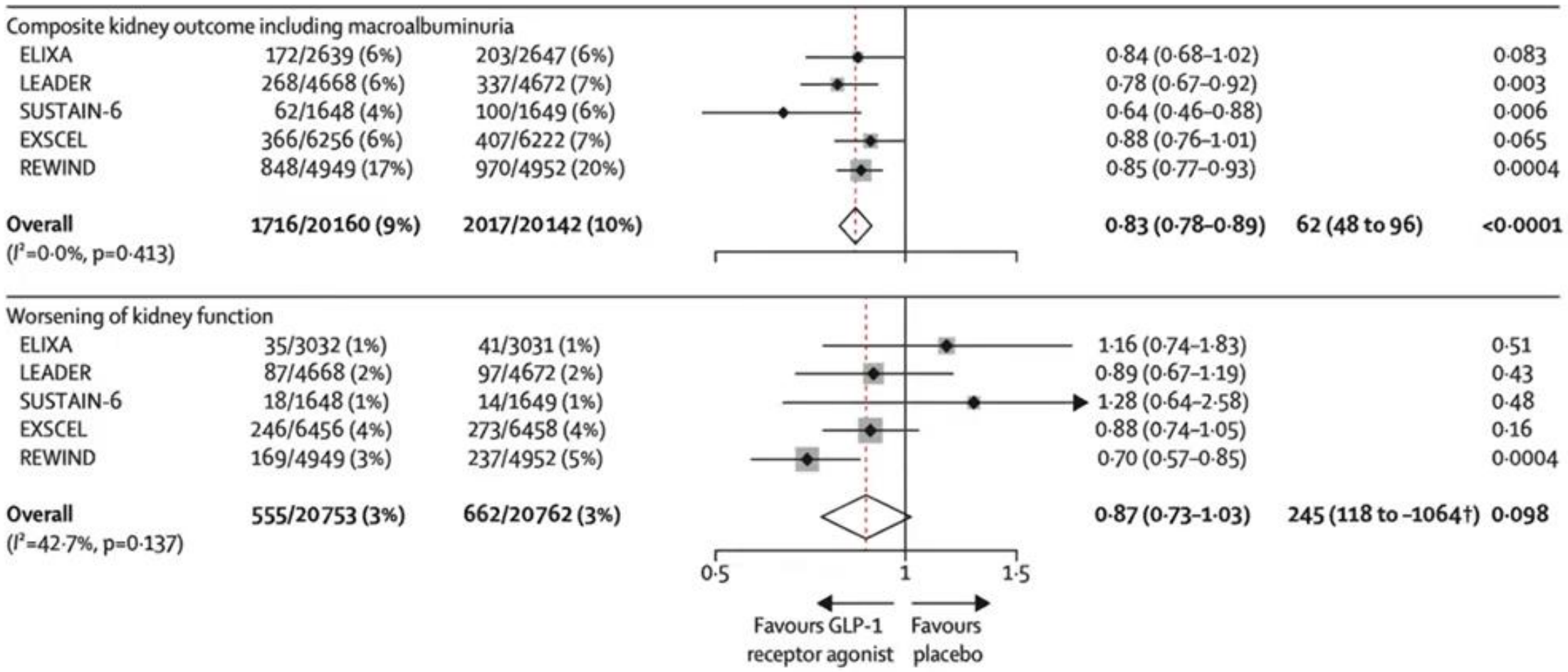
- Improved glucose control
- Reductions in blood pressure
- Weight loss

# GLP-1 RECEPTOR AGONISTS AND eGFR DECLINE OVER TIME



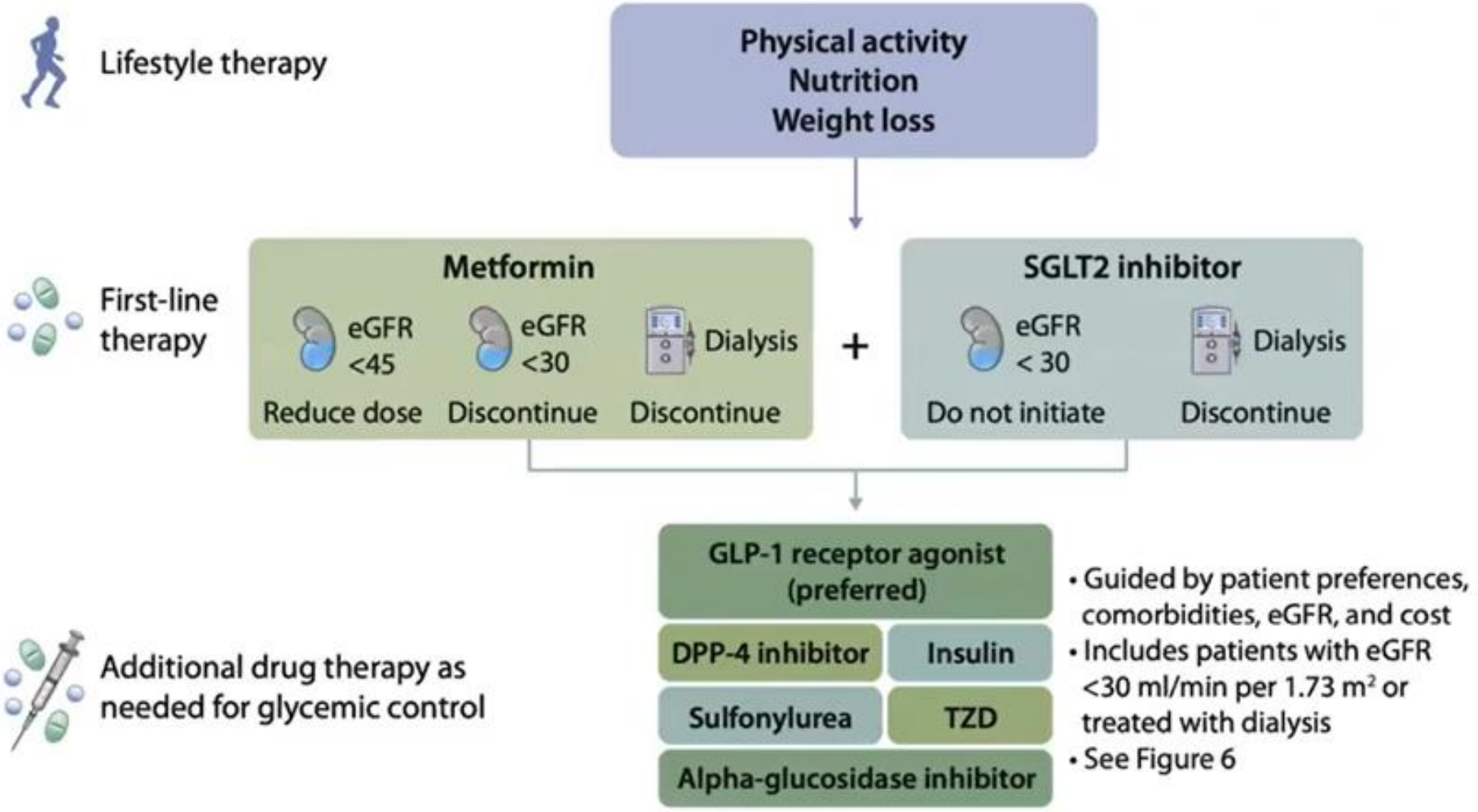

Perkovic et al. EASD 2019

# GLP-1 RECEPTOR AGONISTS AND KIDNEY OUTCOMES




Kristensen et al. Lancet Diabetes & Endocrinology 2019

# KDIGO GUIDELINES



# KDIGO GUIDELINES

**Recommendation 4.3.1. In patients with Type 2 diabetes and CKD who have not achieved individualized glycemic targets despite use of metformin SGLT2i, or who are unable to use those medications, we recommend a long acting glucagon-like peptide-1 receptor agonist (GLP-1 RA) *(1B)*.**

# FLOW TRIAL

- Estimated enrollment: 3508 participants
- T2DM and CKD
  - eGFR 50-75 and UACR >300
  - eGFR 25-50 and UACR >100
- S/C semaglutide vs. placebo
- Primary outcome: sustained 50% decrease in eGFR, kidney failure, CV or renal death
- Completion expected in 2024

# FUTURE DIRECTIONS IN DKD

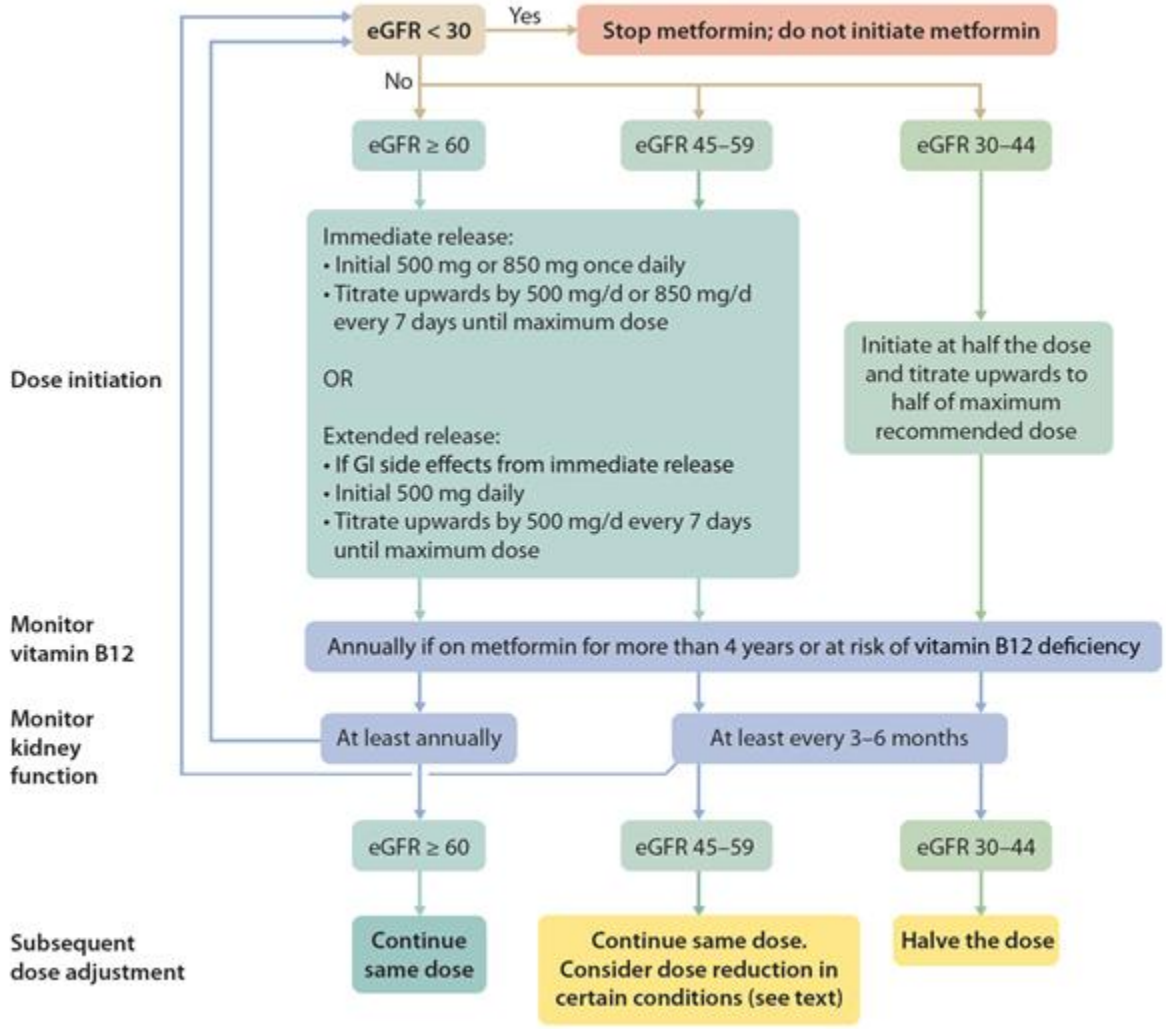
- Initiation of SGLT2i below starting eGFR 25 mL/min/1.73m$^2$
- Trials in normoalbuminuric CKD
- Kidney transplant recipients (and other understudied populations)
- Combination treatment strategies (i.e. with GLP-1 receptor agonists and finerenone)
- Challenges of access and implementation to new therapies

# SUMMARY

- SGLT2 inhibition safely reduce the risk of kidney failure in people with CKD, including in those without diabetes
  - These benefits are coupled with substantial risk reductions for CV outcomes
  - Patients with more advanced CKD (lower eGFR and higher UACR) stand to gain the greatest net clinical benefit from treatment with these agents
- GLP-1 receptor agonists have favorable effects on composite renal outcomes driven by reductions in albuminuria, but effects on hard renal outcomes are uncertain
- Combined RAS blockade plus SGLT2 inhibition should be routinely offered to people with or at high risk of CKD, including those without diabetes

# IN PRACTICE

# SUGGESTED APPROACH IN DOSING METFORMIN BASED ON THE LEVEL OF KIDNEY FUNCTION



# SGLT2 INHIBITORS

| SGLT2 inhibitor | Dose | Kidney function eligible for inclusion in pivotal randomized trials | Dosing approved by the US FDA |
|---|---|---|---|
| **Canagliflozin** **Invokana** | 100–300 mg once daily | CANVAS: eGFR ≥30 ml/min per 1.73 $m^2$<br>CREDENCE: eGFR 30–90 ml/min per 1.73 $m^2$ | No dose adjustment if eGFR >60 ml/min per 1.73 $m^2$<br>100 mg daily if eGFR 30–59 ml/min per 1.73 $m^2$<br>Avoid initiation with eGFR <30 ml/min per 1.73 $m^2$, discontinue when initiating dialysis |
| **Dapagliflozin** **Forxiga** | 5–10 mg once daily | DECLARE-TIMI 58: CrCl ≥60 ml/min<br>DAPA-HF: eGFR ≥30 ml/min per 1.73 $m^2$<br>DAPA-CKD: eGFR 25–75 ml/min per 1.73 $m^2$ | No dose adjustment if eGFR ≥45 ml/min per 1.73 $m^2$<br>Not recommended with eGFR <45 ml/min per 1.73 $m^2$<br>Contraindicated with eGFR <30 ml/min per 1.73 $m^2$ |
| **Empagliflozin** **Jardiance** | 10–25 mg once daily | EMPA-REG: eGFR ≥30 ml/min per 1.73 $m^2$<br>EMPA-KIDNEY: eGFR 20–90 ml/min per 1.73 $m^2$<br>EMPEROR-Reduced: eGFR ≥20 ml/min per 1.73 $m^2$ | No dose adjustment if eGFR ≥45 ml/min per 1.73 $m^2$<br>Avoid use, discontinue with eGFR persistently <45 ml/min per 1.73 $m^2$ |

# SITUATIE IN BELGIË

Albuminurie stadium: UACR (mg/g)

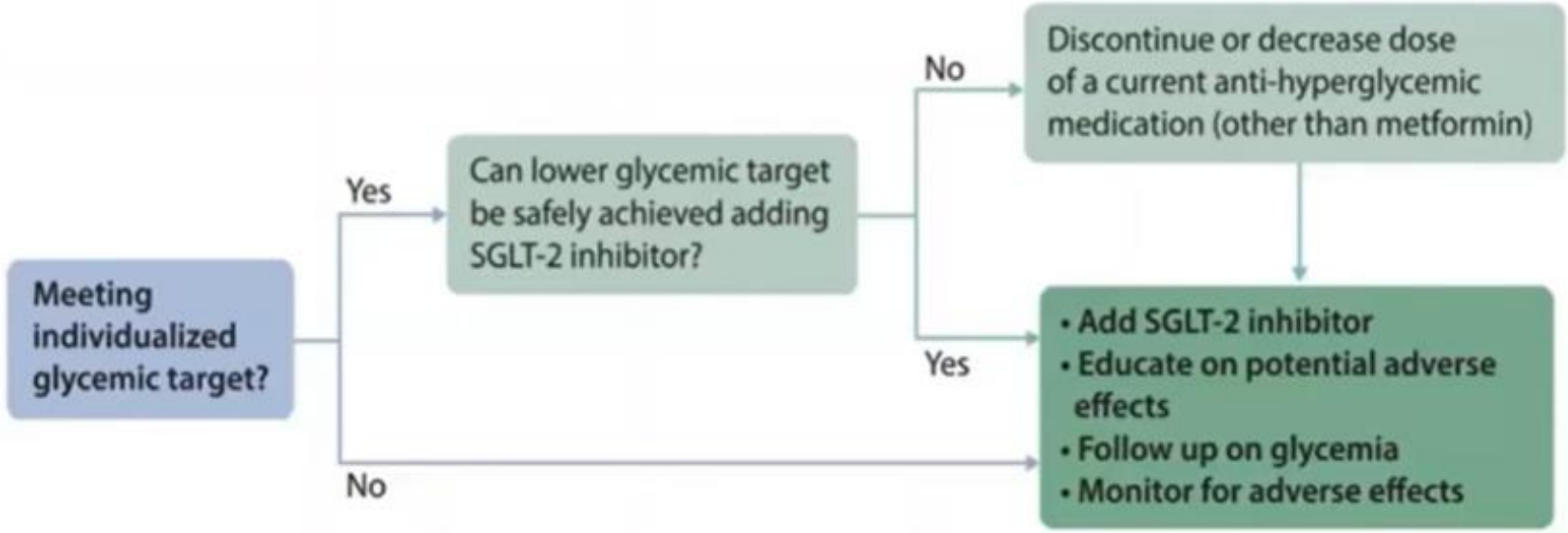
| | | A1: <30 | A2: 30-300 | A3 : >300 | |
|---|---|---|---|---|---|
| eGFR (ml/min/1.73 $m^2$) | ≥ 90 | | | | In label en reeds terugbetaald |
| | 60 tot < 90 | | | | |
| | 45 tot < 60 | | | | Ook in label sinds 1 juli 2020 (EMA approval)[1]; nog geen TB |
| | 30 tot < 45 | Off label | | | |
| | < 30 | | | | Ook in label sinds 1 juli 2020 (EMA approval)[1] voor verderzetting (NIET voor opstart); nog geen TB |

Invokana is geïndiceerd voor de behandeling van volwassenen met onvoldoende gereguleerde type 2-diabetes mellitus als aanvullend middel bij een dieet en lichaamsbeweging:
- als monotherapie wanneer metformine ongeschikt wordt geacht wegens intolerantie of contra-indicaties
- naast andere geneesmiddelen voor de behandeling van diabetes

Voor onderzoeksresultaten met betrekking tot combinatie van behandelingen, effecten op bloedglucoseregulatie, cardiovasculaire en **renale voorvallen** en voor de onderzochte populaties, zie rubriek 4 en 5.1 van de SmPC[1].

# MANAGING CONCOMITANT GLUCOSE LOWERING DRUGS

- Risk of hypoglycemia with SGLT2i is low
- In people achieving glycemic targets, reduction in insulin/discontinuation of other glucose lowering drugs is suggested to facilitate addition of an SGLT2i



# GLP-1 RECEPTOR AGONISTS

| GLP-1 RA | Dose | CKD adjustment |
|---|---|---|
| **Dulaglutide** Trulicity | 0.75 mg and 1.5 mg once weekly | No dosage adjustment<br>Use with eGFR >15 ml/min per 1.73 $m^2$ |
| **Exenatide** Byetta | 10 µg twice daily | Use with CrCl >30 ml/min |
| **Exenatide extended-release** | 2 mg once weekly | Use with CrCl >30 ml/min |
| **Liraglutide** Victoza | 0.6 mg, 1.2 mg, and 1.8 mg once daily | No dosage adjustment<br>Limited data for severe CKD |
| **Lixisenatide** Lyxumia | 10 µg and 20 µg once daily | No dosage adjustment<br>Limited data for severe CKD |
| **Semaglutide (injection)** Ozempic | 0.5 mg and 1 mg once weekly | No dosage adjustment<br>Limited data for severe CKD |
| **Semaglutide (oral)** Rybelsus | 3 mg, 7 mg, or 14 mg daily | No dosage adjustment<br>Limited data for severe CKD |