

# Maestro Yoda



“Siempre en movimiento  
el futuro está”



#SGAN2019

## Nuevas oportunidades terapéuticas en la Enfermedad Renal Diabética

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Grupo Español de  
Estudio de la  
Nefropatía Diabética



# DiABETES



## NEFROPROTECCIÓN

# Nefroprotección en la Diabetes Mellitus

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## RENAAL

### EFFECTS OF LOSARTAN ON RENAL AND CARDIOVASCULAR OUTCOMES IN PATIENTS WITH TYPE 2 DIABETES AND NEPHROPATHY

BARRY M. BRENNER, M.D., MARK E. COOPER, M.D., PH.D., DICK DE ZEEUW, M.D., PH.D., WILLIAM F. KEANE, M.D.,  
WILLIAM E. MITCH, M.D., HANS-HENRIK PARVING, M.D., GIUSEPPE REMUZZI, M.D., STEVEN M. SNAPINN, PH.D.,  
ZHONXIN ZHANG, PH.D., AND SHAHNNAZ SHAHINFAR, M.D., FOR THE RENAAL STUDY INVESTIGATORS\*

## IDNT

### RENOPROTECTIVE EFFECT OF THE ANGIOTENSIN-RECEPTOR ANTAGONIST IRBESARTAN IN PATIENTS WITH NEPHROPATHY DUE TO TYPE 2 DIABETES

EDMUND J. LEWIS, M.D., LAWRENCE G. HUNSICKER, M.D., WILLIAM R. CLARKE, PH.D., TOMAS BERL, M.D.,  
MARC A. POHL, M.D., JULIA B. LEWIS, M.D., EBERHARD RITZ, M.D., ROBERT C. ATKINS, M.D., RICHARD ROHDE, B.S.,  
AND ITAMAR RAZ, M.D., FOR THE COLLABORATIVE STUDY GROUP\*

## IRMA-2

### THE EFFECT OF IRBESARTAN ON THE DEVELOPMENT OF DIABETIC NEPHROPATHY IN PATIENTS WITH TYPE 2 DIABETES

HANS-HENRIK PARVING, M.D., D.M.Sc., HENDRIK LEHNERT, M.D., JENS BRÖCHNER-MORTENSEN, M.D., D.M.Sc.,  
RAMON GOMIS, M.D., STEEN ANDERSEN, M.D., AND PETER ARNER, M.D., D.M.Sc.,  
FOR THE IRBESARTAN IN PATIENTS WITH TYPE 2 DIABETES AND MICROALBUMINURIA STUDY GROUP\*

- 2002: El euro entra en España



- 2003: Se completa el PGH



- 2010: España gana mundial fútbol



- 2014: Cuba 🤝 EEUU



**Bardoxolona**

**Sulodexide**

**Aliskiren**

**Piridorina**

**Pirfenidona**

## **Nefroprotección en la DM → Una travesía en el desierto**



**Steven Nissen, M.D.**  
Cardiologist, Cleveland Clinic, OH (USA)



# *The* NEW ENGLAND JOURNAL *of* MEDICINE

ESTABLISHED IN 1812

JUNE 14, 2007

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## Effect of Rosiglitazone on the Risk of Myocardial Infarction and Death from Cardiovascular Causes

Our data show that, as compared with placebo or with other antidiabetic regimens, treatment with rosiglitazone was associated with a significant increase in the risk of myocardial infarction and with an increase in the risk of death from cardiovascular causes that was of borderline significance.



U.S. Department of Health and Human Services

Food and Drug Administration



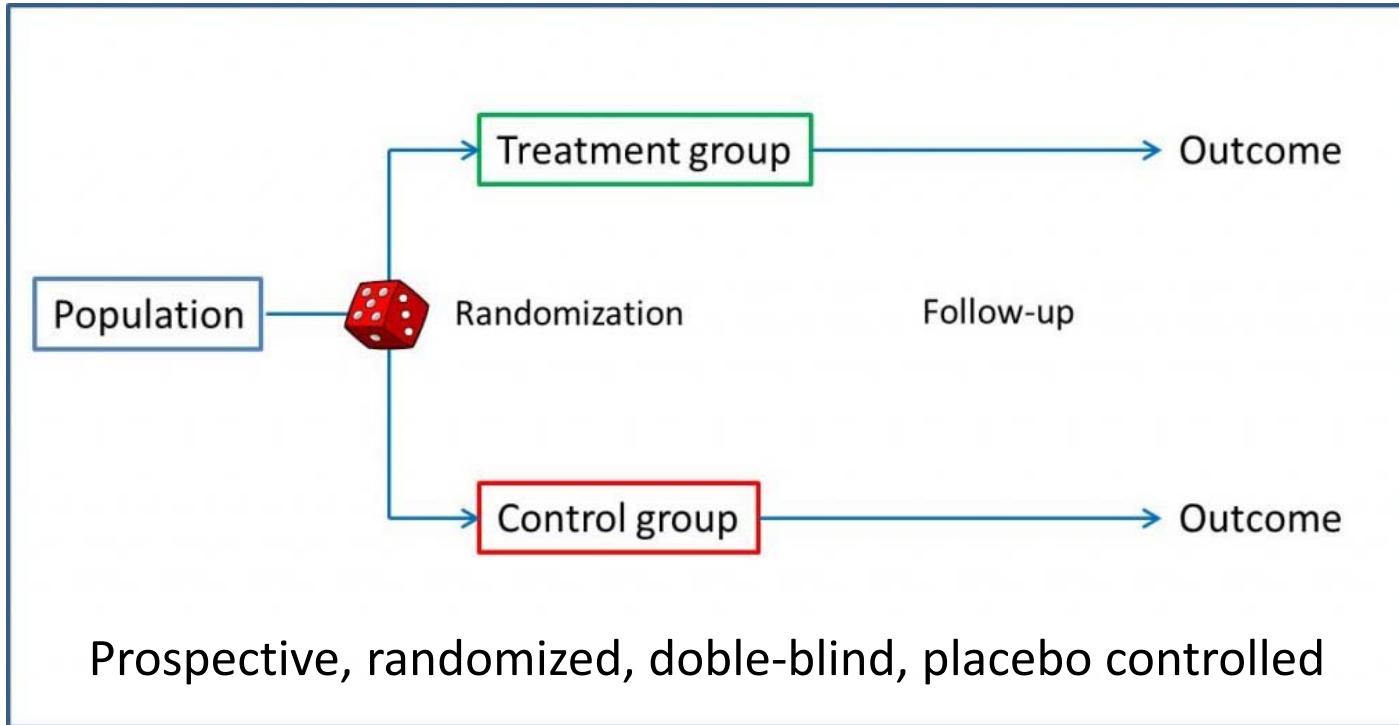
EUROPEAN MEDICINES AGENCY  
SCIENCE MEDICINES HEALTH

# Guidance for Industry

## Diabetes Mellitus — Evaluating Cardiovascular Risk in New Antidiabetic Therapies to Treat Type 2 Diabetes

'Demonstrate that a new anti-diabetic therapy is not associated with **unacceptable increase** in cardiovascular risk'

# Cardiovascular outcomes trials for new antidiabetic agents



## PRIMARY OUTCOME

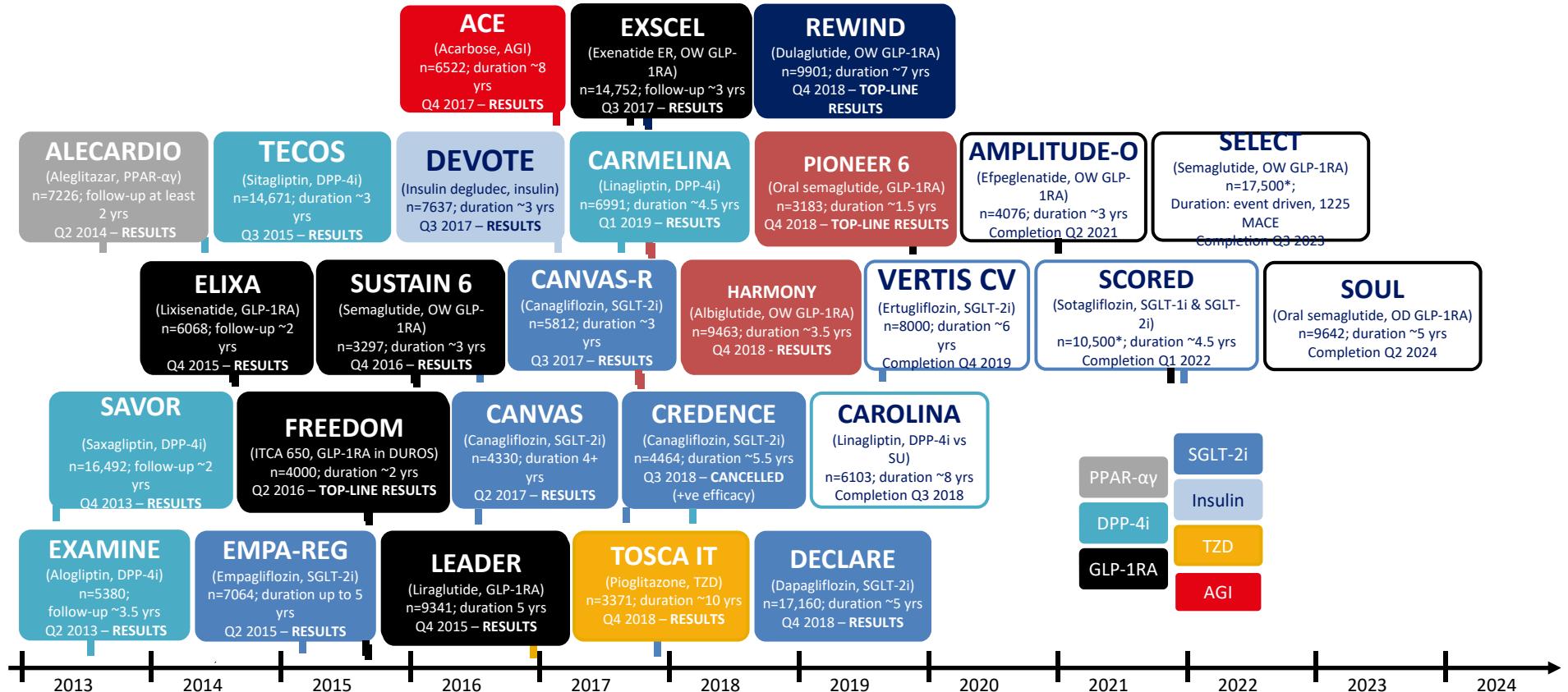
**3P-MACE:** Cardiovascular death, non-fatal myocardial infarction, non-fatal stroke

**4P-MACE:** 3P-MACE + hospitalization for unstable angina

## SECONDARY OUTCOMES

Microvascular endpoints → Renal events

# CVOTs en DM2



**LEADER®**  
Liraglutide Effect and Action in Diabetes:  
Evaluation of cardiovascular outcome Results

**FREEDOM**

**SUSTAIN™**  
SEMAGLUTIDE UNABATED SUSTAINABILITY  
IN TREATMENT OF TYPE 2 DIABETES

**EXSCEL**  
Exenatide Study of Cardiovascular Event Lowering

**HARMONY**

**REWIND Trial**

**TECOS**

**CARMELINA**  
H2 and renin-angiotensin study with Degludec

**savor**  
MEASURE TIMI 53

**EXAMINE**

**DEVOTE**  
Degludec Cardiovascular Outcomes Trial

**VERTIS**

**EMPA-REG OUTCOME®**

**CANVAS Program**

**CREDENCE**

**DECLARE**  
TIMI-58 TIM Study Group/Physicians Medical, Inc.

## Agonistas receptor GLP1 / Inhibidores SGLT2

# **Heloderma Suspectum (Monstruo de Gila)**



**EXENDINA-**

H-G-E-G-T-F-T-S-D-L-S-K-Q-M-E-E-E-A-V-R-L-F-I-E-W-L-K-N-G-G-P-S-S-G-A-P-P-P-S

**GLP-1**

H-A-E-G-T-F-T-S-D-V-S-S-Y-L-E-G-O-A-A-K-E-F-I-A-W-L-V-K-G-R-G

## Semaglutide and Cardiovascular Outcomes in Patients with Type 2 Diabetes

N = 4346 / Randomized = 3297  
Mediana de seguimiento: 2.1 años

### Perfil de riesgo cardiovascular

- 83% ECV establecida, incluyendo ERC estadio 3 o superior
- 58.5% ECV establecida sin ERC

≈ 28% eGFR < 60 ml/min

### PRIMARY OUTCOME

3P-MACE: Cardiovascular death, non-fatal myocardial infarction, non-fatal stroke

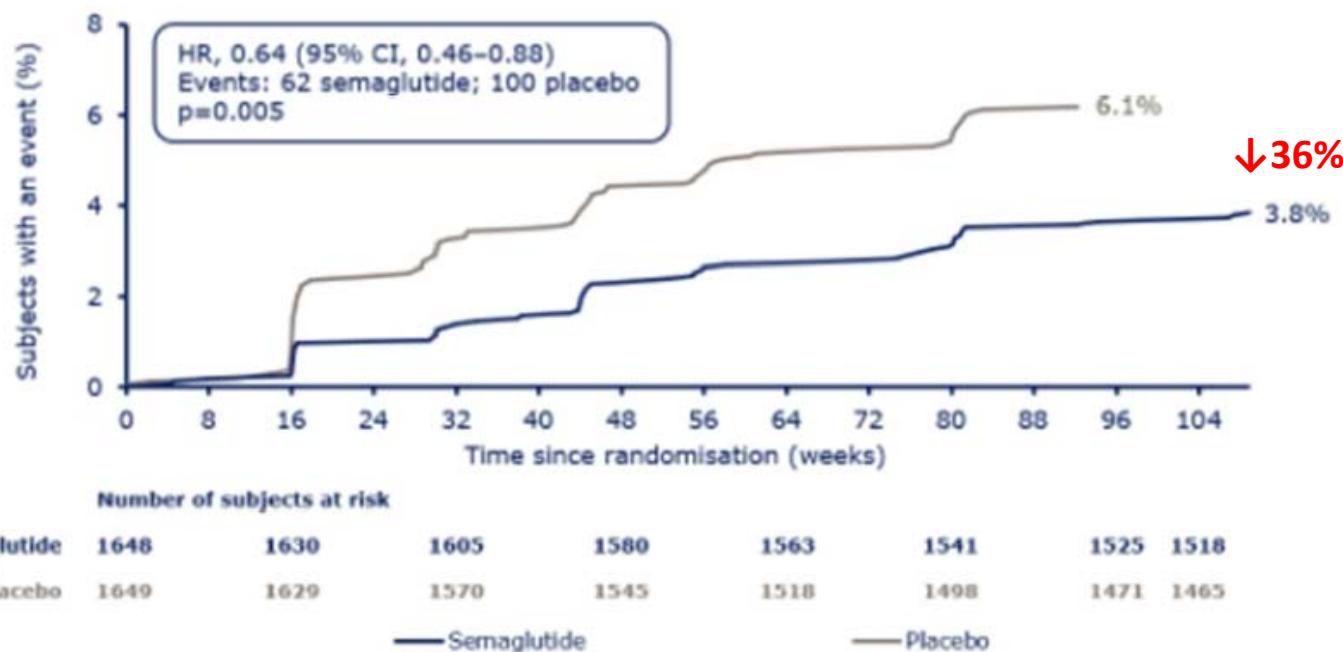
## Semaglutide and Cardiovascular Outcomes in Patients with Type 2 Diabetes

### Microvascular outcomes

- **Diabetic retinopathy complications**
  - Need for retinal photocoagulation
  - Treatment with intravitreal agents
  - Vitreous haemorrhage
  - Diabetes-related blindness
    - Snellen visual acuity of <20/200 [6/60]
    - Visual field of <20° in the better eye with best correction possible
- **New or worsening nephropathy**
  - New onset of persistent macroalbuminuria ( $>300 \text{ mg/g}/24 \text{ hrs}$ )
  - Persistent doubling of serum creatinine level and creatinine clearance
    - Per MDRD  $\leq 45 \text{ mL/min}/1.73 \text{ m}^2$
  - Continuous renal-replacement therapy
  - Death due to renal disease

## Semaglutide and Cardiovascular Outcomes in Patients with Type 2 Diabetes

### New or worsening nephropathy



Macroalbuminuria persistente duplicación de Cr sérica con FGe < 45 ml/min o necesidad de TSR

HR 0.54 (0.37-0.77) P<0.001 ↓46%

## Liraglutide and Cardiovascular Outcomes in Type 2 Diabetes

N = 12076 / Randomized = 9340  
Mediana de seguimiento: 3.8 años

### Baseline characteristics.

|                                  | Liraglutide<br>(N=4,668) | Placebo<br>(N=4,672) |
|----------------------------------|--------------------------|----------------------|
| Normal (eGFR $\geq$ 90)          | 1620 (34.7)              | 1655 (35.4)          |
| Mild impairment (eGFR 60–89)     | 1932 (41.4)              | 1975 (42.3)          |
| Moderate impairment (eGFR 30–59) | 999 (21.4)               | 935 (20.0)           |
| Severe impairment (eGFR <30)     | 117 (2.5)                | 107 (2.3)            |
| Microalbuminuria or proteinuria  | 501 (10.7)               | 558 (11.9)           |

$\approx$  23% eGFR < 60 ml/min

$\approx$  11.5% micro/macroalbuminuria

### PRIMARY OUTCOME

3P-MACE: Cardiovascular death, non-fatal myocardial infarction, non-fatal stroke

ORIGINAL ARTICLE

## Liraglutide and Renal Outcomes in Type 2 Diabetes

**Objetivo 2º microvascular pre-especificado → Combinado renal y ocular**

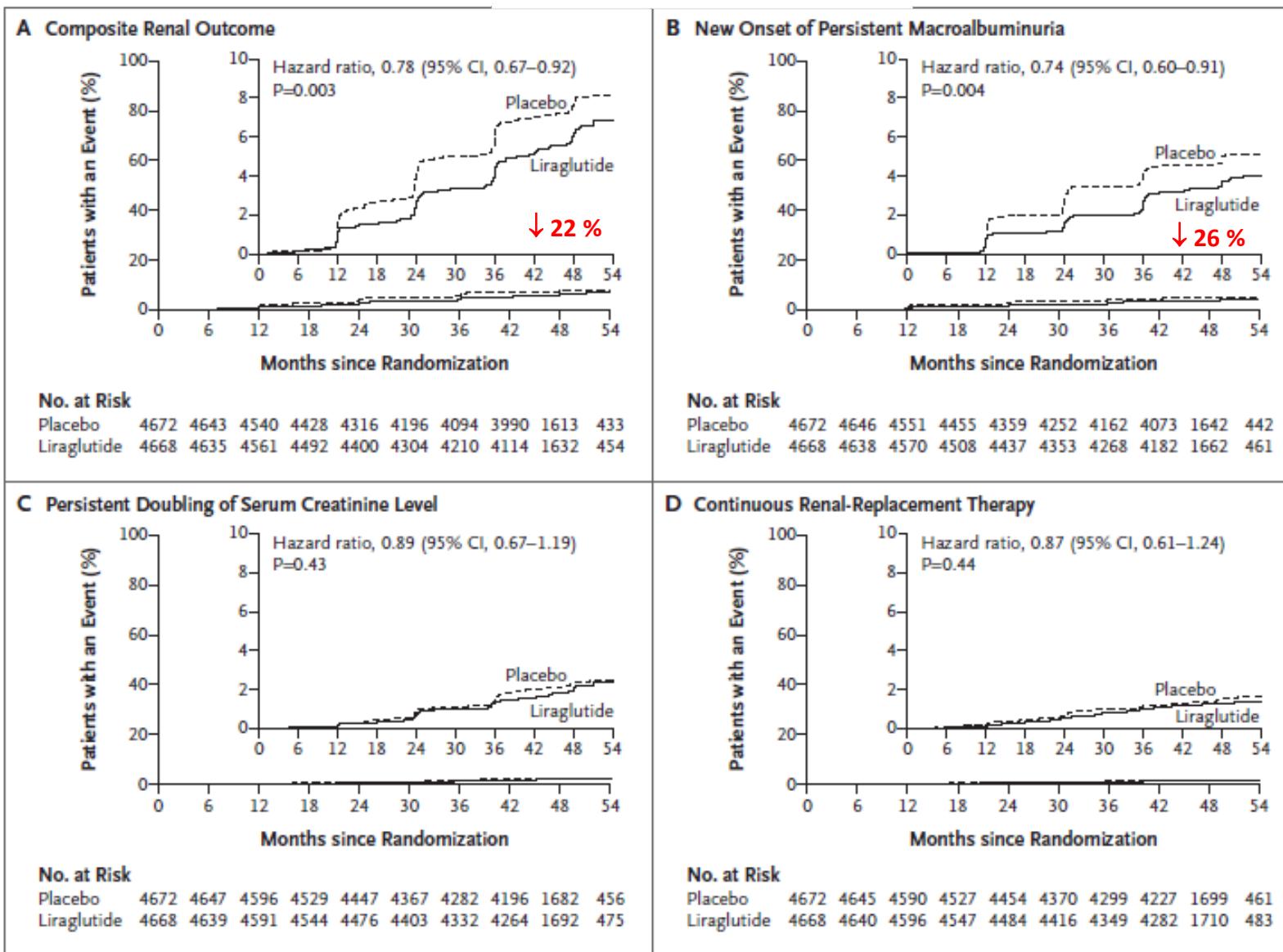
|                     | Liraglutide<br>(N=4668)    | Incidence<br>Rate                        | Placebo<br>(N=4672)        | Incidence<br>Rate                        | Hazard Ratio<br>(95% CI) | P Value |
|---------------------|----------------------------|--|----------------------------|--|--------------------------|---------|
|                     | <i>no. of patients (%)</i> | <i>no. of events/<br/>100 patient-yr</i> | <i>no. of patients (%)</i> | <i>no. of events/<br/>100 patient-yr</i> |                          |         |
| Microvascular event | 355 (7.6)                  | 2.0                                      | 416 (8.9)                  | 2.3                                      | 0.84 (0.73–0.97) ↓ 16 %  | 0.02    |

Objetivo 2º renal →

- Nuevo comienzo de macroalbuminuria persistente
- Duplicar creatinina sérica con FGe ≤ 45 ml/min
- Necesidad de tratamiento sustitutivo renal
- Muerte de causa renal

# LEADER®

Liraglutide Effect and Action in Diabetes:  
Evaluation of cardiovascular outcome Results



# Dulaglutide and cardiovascular outcomes in type 2 diabetes (REWIND): a double-blind, randomised placebo-controlled trial

N = 12133 / Randomized = 9901  
Mediana de seguimiento: 5.4 años

Perfil de riesgo cardiovascular  
• 31.5% ECV establecida

≈ 22% eGFR < 60 ml/min

≈ 35% Albuminuria

## PRIMARY OUTCOME

3P-MACE: Cardiovascular death, non-fatal myocardial infarction, non-fatal stroke

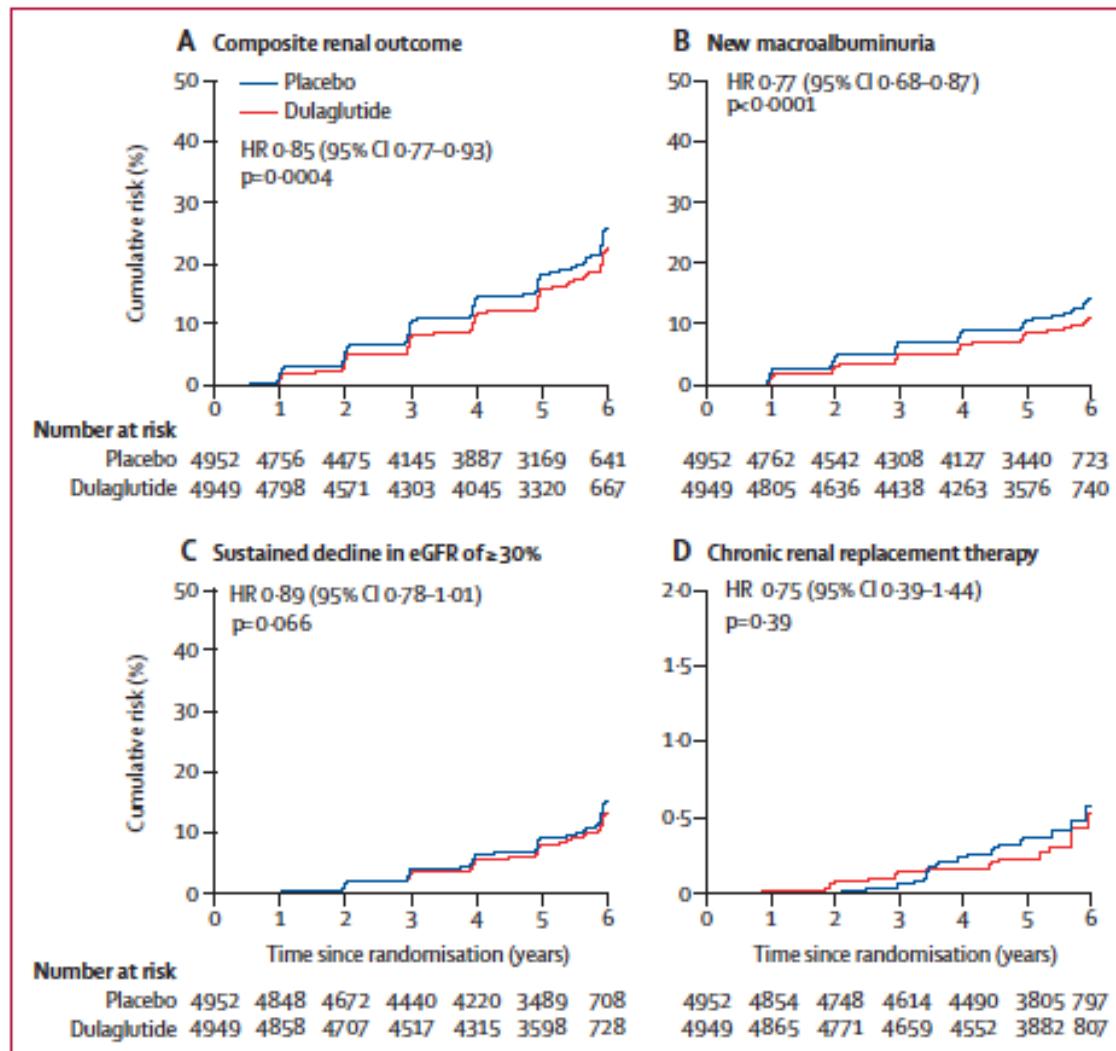
## COMPOSITE MICROVASCULAR OUTCOME

|  |             |      |              |      |                         |        |
|--|-------------|------|--------------|------|-------------------------|--------|
| Composite microvascular outcome (eye or renal outcome) | 910 (18.4%) | 3.76 | 1019 (20.6%) | 4.31 | 0.87 (0.79–0.95)        | 0.0020 |
| Eye outcome‡   | 95 (1.9%)   | 0.37 | 76 (1.5%)    | 0.30 | 1.24 (0.92–1.68)        | 0.16   |
| Renal outcome§   | 848 (17.1%) | 3.47 | 970 (19.6%)  | 4.07 | ↓ 15 % 0.85 (0.77–0.93) | 0.0004 |

## RENAL OUTCOME

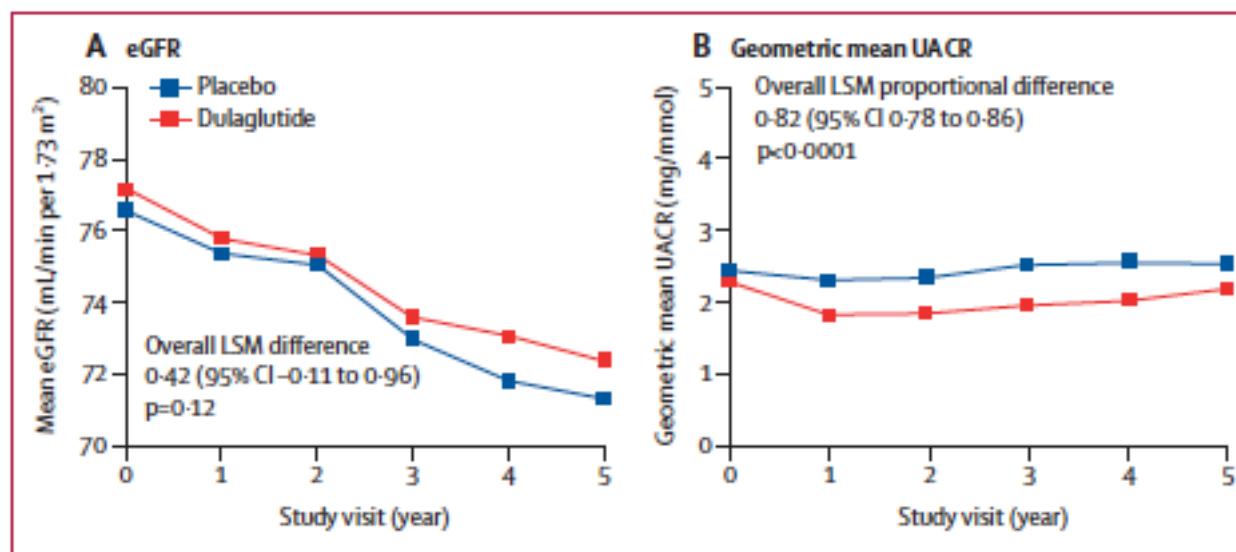
New development macroalbuminuria, sustained decline ≥ 30% eGFR, new RRT (dialysis/Tx)

# Dulaglutide and renal outcomes in type 2 diabetes: an exploratory analysis of the REWIND randomised, placebo-controlled trial



# Dulaglutide and renal outcomes in type 2 diabetes: an exploratory analysis of the REWIND randomised, placebo-controlled trial

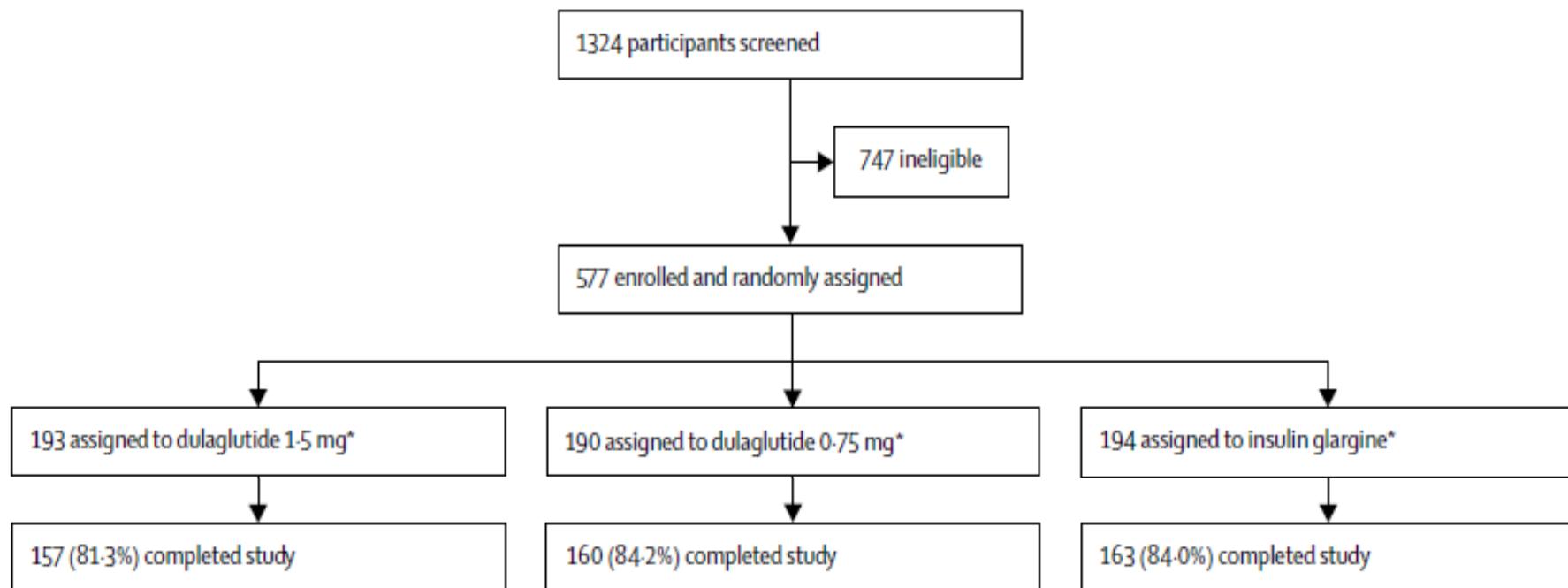
|  | Composite renal outcome |                     |                     |                             | Sustained decline in eGFR of $\geq 30\%$ |                     |                     |                             | New macroalbuminuria* |                     |                     |                             |
|--|-------------------------|---------------------|---------------------|-----------------------------|--|---------------------|---------------------|-----------------------------|-----------------------|---------------------|---------------------|-----------------------------|
|  | Dulaglutide             | Placebo             | HR (95% CI)         | $P_{interaction}^{\dagger}$ | Dulaglutide                              | Placebo             | HR (95% CI)         | $P_{interaction}^{\dagger}$ | Dulaglutide           | Placebo             | HR (95% CI)         | $P_{interaction}^{\dagger}$ |
| Overall effect                         | 848/4949<br>(17.1%)     | 970/4952<br>(19.6%) | 0.85<br>(0.78-0.93) | --                          | 453/4949<br>(9.2%)                       | 500/4952<br>(10.1%) | 0.89<br>(0.78-1.01) | --                          | 441/4949<br>(8.9%)    | 561/4952<br>(11.3%) | 0.77<br>(0.68-0.87) | --                          |
| eGFR (mL/min per 1.73 m <sup>2</sup> ) | --                      | --                  | --                  | 0.65                        | --                                       | --                  | --                  | 0.47                        | --                    | --                  | --                  | 0.046                       |
| <60                                    | 219/1081<br>(20.3%)     | 251/1118<br>(22.5%) | 0.88<br>(0.73-1.05) | --                          | 81/1081<br>(7.5%)                        | 102/1118<br>(9.1%)  | 0.81<br>(0.60-1.08) | --                          | 154/1081<br>(14.2%)   | 171/1118<br>(15.3%) | 0.91<br>(0.73-1.13) | --                          |
| $\geq 60$                              | 610/3734<br>(16.3%)     | 701/3707<br>(18.9%) | 0.83<br>(0.75-0.93) | --                          | 372/3734<br>(10.0%)                      | 398/3707<br>(10.7%) | 0.91<br>(0.79-1.04) | --                          | 268/3734<br>(7.2%)    | 372/3707<br>(10.0%) | 0.70<br>(0.59-0.81) | ←                           |
| Baseline albuminuria status            | --                      | --                  | --                  | 0.66                        | --                                       | --                  | --                  | 0.64                        | --                    | --                  | --                  | 0.84                        |
| Normoalbuminuria                       | 330/2917<br>(11.3%)     | 365/2863<br>(12.7%) | 0.87<br>(0.75-1.01) | --                          | 214/2917<br>(7.3%)                       | 237/2863<br>(8.3%)  | 0.87<br>(0.73-1.05) | --                          | 123/2917<br>(4.2%)    | 154/2863<br>(5.4%)  | 0.78<br>(0.61-0.99) | --                          |
| Microalbuminuria or macroalbuminuria   | 468/1707<br>(27.4%)     | 543/1760<br>(30.9%) | 0.84<br>(0.74-0.95) | --                          | 224/1707<br>(13.1%)                      | 240/1760<br>(13.6%) | 0.93<br>(0.78-1.12) | --                          | 279/1707<br>(16.3%)   | 360/1760<br>(20.5%) | 0.76<br>(0.65-0.89) | --                          |



# Dulaglutide versus insulin glargine in patients with type 2 diabetes and moderate-to-severe chronic kidney disease (AWARD-7): a multicentre, open-label, randomised trial

Non-inferiority study

Primary efficacy outcome: Change in HbA1c from baseline to week 26  
Secondary efficacy outcome: Change in HbA1c at week 52

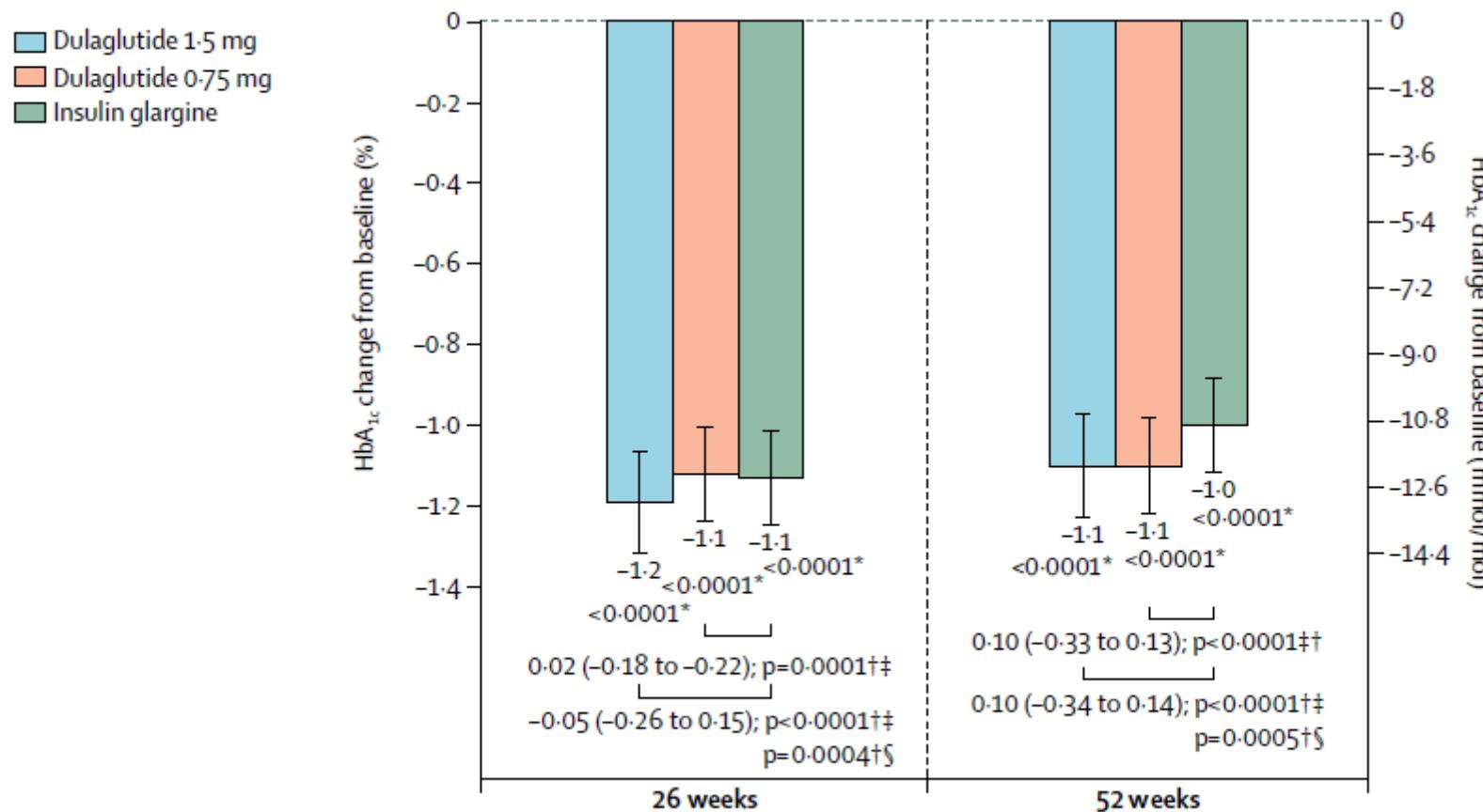


# Dulaglutide versus insulin glargine in patients with type 2 diabetes and moderate-to-severe chronic kidney disease (AWARD-7): a multicentre, open-label, randomised trial

|   | Dulaglutide 1·5 mg (n=192) | Dulaglutide 0·75 mg (n=190) | Insulin glargine (n=194) |
|---|----------------------------|-----------------------------|--------------------------|
| Sex (women, men)  | 88 (46%), 104 (54%)        | 86 (45%), 104 (55%)         | 101 (52%), 93 (48%)      |
| Age (years)   | 64·7 (8·8)                 | 64·7 (8·6)                  | 64·3 (8·4)               |
| Duration of diabetes (years)  | 17·6 (8·7)                 | 18·0 (8·8)                  | 18·7 (8·7)               |
| eGFR by creatinine (mL/min per 1·73 m <sup>2</sup> )                      | 38·1 (13·2)                | 38·3 (12·3)                 | 38·5 (13·0)              |
| eGFR by creatinine (mL/min per 1·73 m <sup>2</sup> , geometric mean [SE]) | 35·7 (1·0)                 | 36·2 (0·9)                  | 36·1 (0·9)               |
| Baseline eGFR ≥60 to <90  | 9 (5%)                     | 7 (4%)                      | 14 (7%)                  |
| Baseline eGFR ≥45 to <60  | 53 (28%)                   | 53 (28%)                    | 51 (26%)                 |
| Baseline eGFR ≥30 to <45  | 73 (38%)                   | 75 (39%)                    | 67 (35%)                 |
| Baseline eGFR ≥15 to <30  | 55 (29%)                   | 55 (29%)                    | 61 (31%)                 |
| Baseline eGFR <15   | 2 (1%)                     | 0 (0%)                      | 1 (1%)                   |
| eGFR by cystatin C (mL/min per 1·73m <sup>2</sup> , mean [SE])            | 37·3 (14·2)                | 37·7 (13·7)                 | 38·3 (14·8)              |
| eGFR by cystatin C (mL/min per 1·73m <sup>2</sup> , geometric mean [SE])  | 34·8 (1·0)                 | 35·4 (0·9)                  | 35·6 (1·0)               |
| UACR (mg/g, median [IQR])   | 213·7 (45·8–868·0)         | 233·6 (36·7–946·5)          | 195·6 (30·1–1015·1)      |
| Normal albuminuria (UACR <30)   | 34 (18%)                   | 44 (23%)                    | 48 (25%)                 |
| Microalbuminuria (UACR 30–300)  | 74 (39%)                   | 61 (32%)                    | 56 (29%)                 |
| Macroalbuminuria (UACR >300)  | 84 (44%)                   | 84 (44%)                    | 90 (46%)                 |

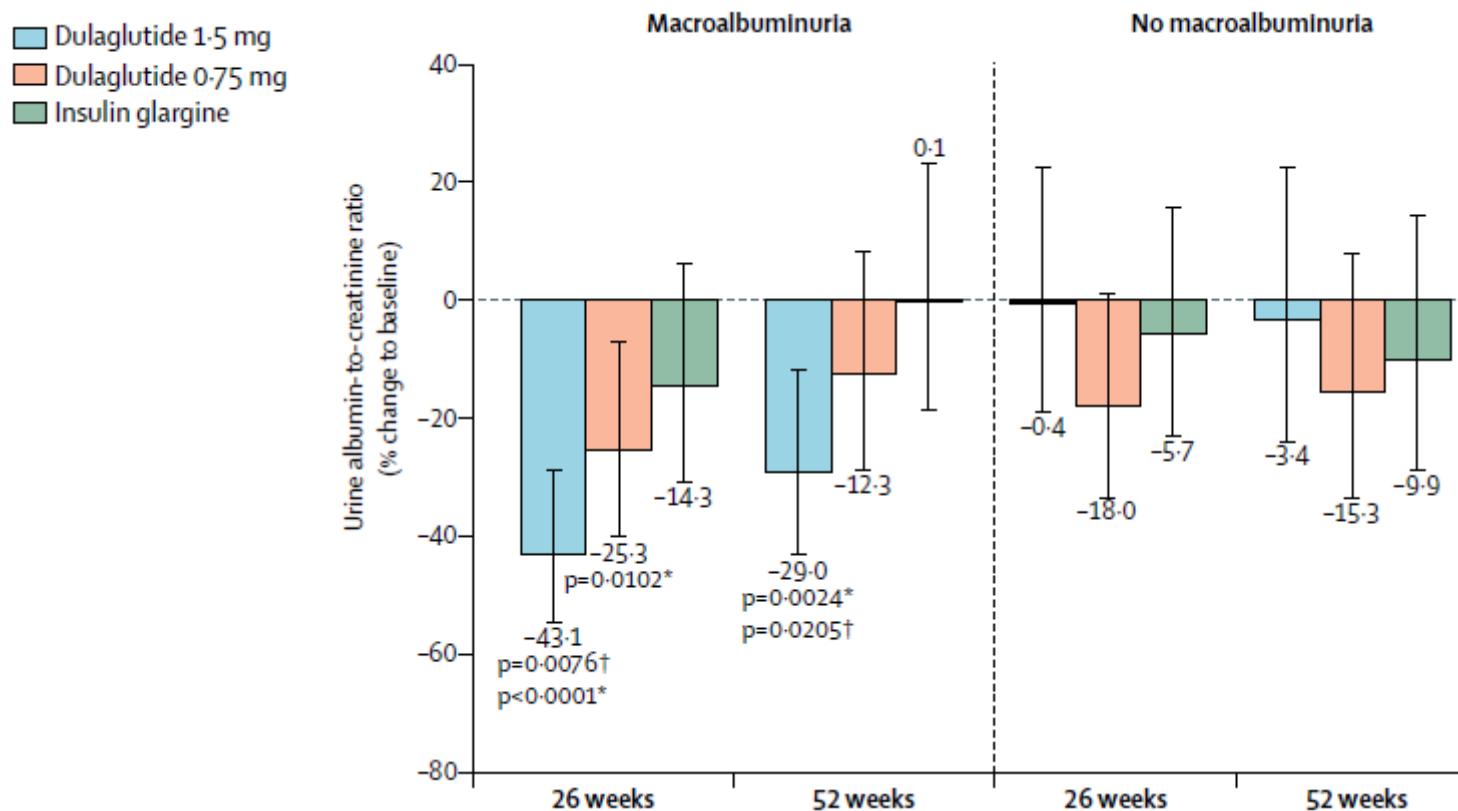
**97% de los pacientes con ERC estadios 3-4 (ERC moderada-severa)  
Filtrado glomerular estimado entre 15 y 60 ml/min**

# Dulaglutide versus insulin glargin in patients with type 2 diabetes and moderate-to-severe chronic kidney disease (AWARD-7): a multicentre, open-label, randomised trial



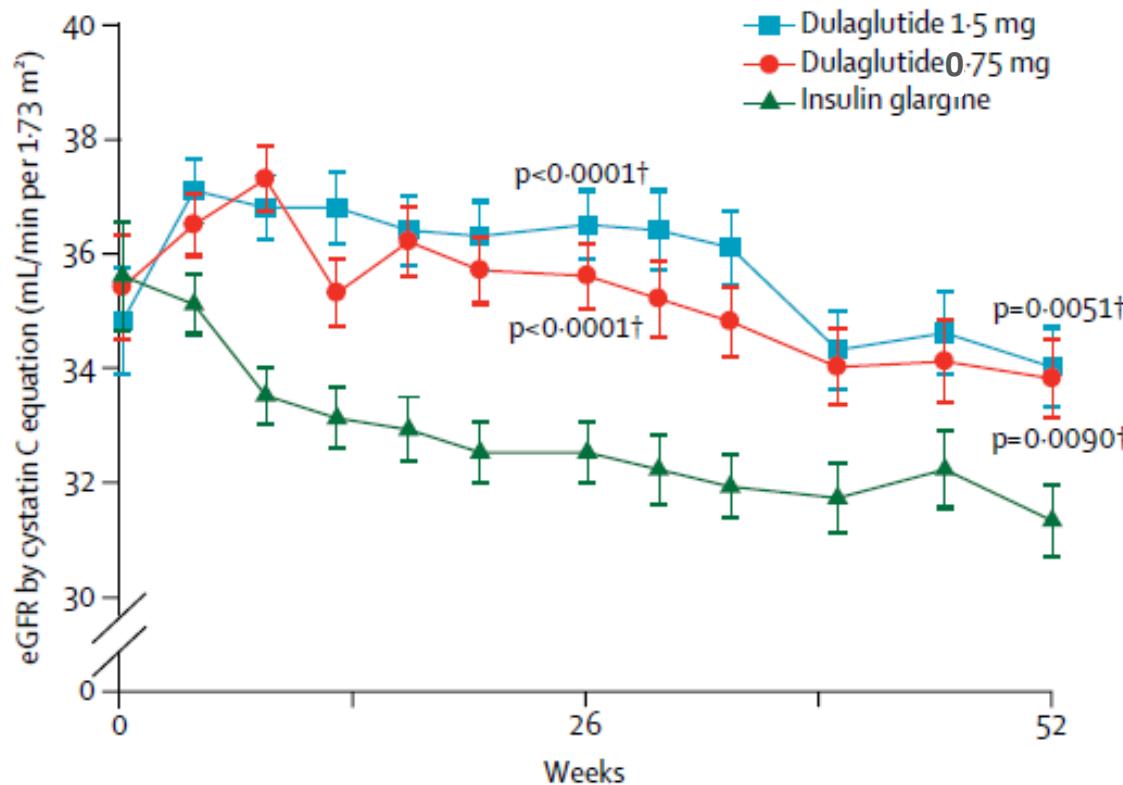
Dulaglutida semanal produjo una mejoría significativa del control glucémico con una eficacia similar a insulina glargina diaria en términos de descenso de HbA1c

# Dulaglutide versus insulin glargine in patients with type 2 diabetes and moderate-to-severe chronic kidney disease (AWARD-7): a multicentre, open-label, randomised trial



**Dulaglutida semanal produjo una mayor reducción en el cociente albúmina/creatinina que insulina glargina diaria en pacientes con macroalbuminuria, con un efecto dosis-dependiente**

## Dulaglutide versus insulin glargine in patients with type 2 diabetes and moderate-to-severe chronic kidney disease (AWARD-7): a multicentre, open-label, randomised trial



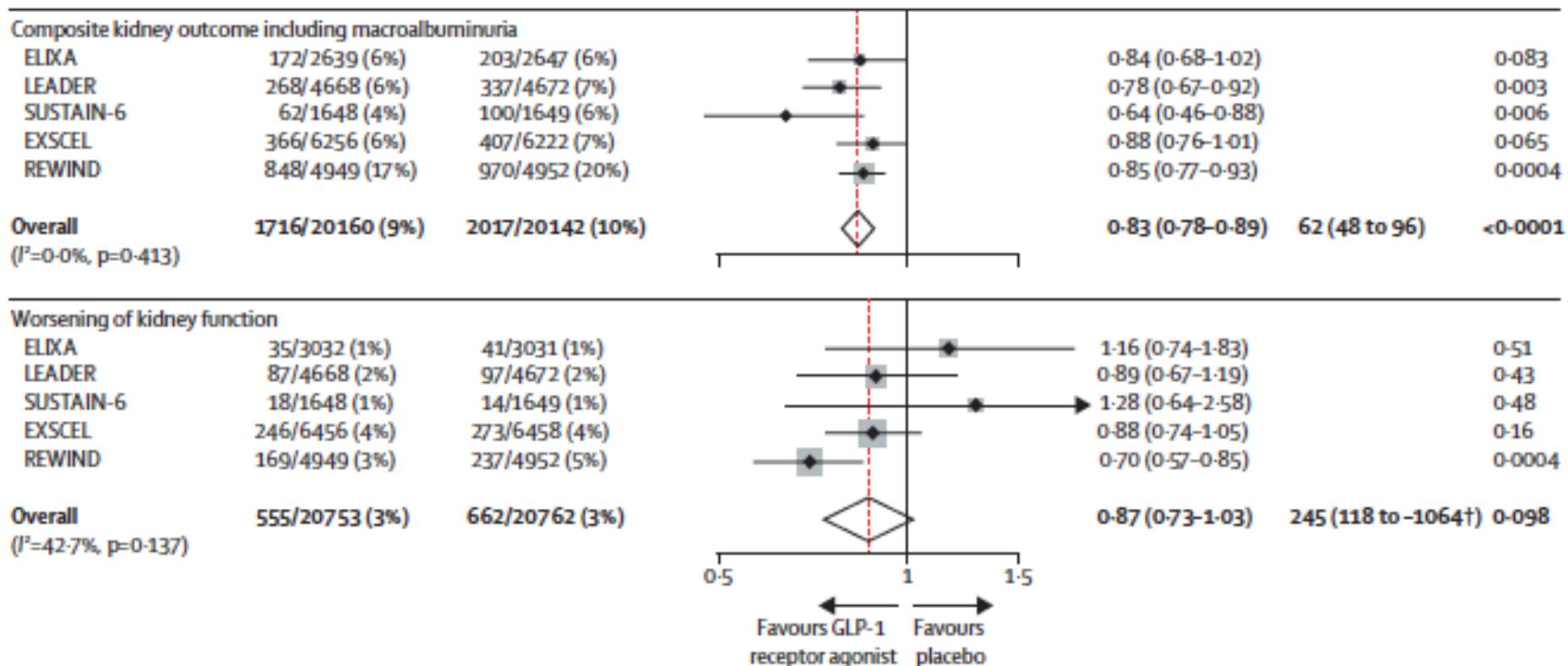
El tratamiento con dulaglutida semanal se asoció con una menor reducción en el filtrado glomerular estimado que insulina glargina diaria

# Cardiovascular, mortality, and kidney outcomes with GLP-1 receptor agonists in patients with type 2 diabetes: a systematic review and meta-analysis of cardiovascular outcome trials

|   | ELIXA<br>(n=6068) <sup>7</sup> | LEADER<br>(n=9340) <sup>8,14</sup> | SUSTAIN-6<br>(n=3297) <sup>9</sup> | EXSCEL<br>(n=14752) <sup>11</sup> | Harmony Outcomes<br>(n=9463) <sup>10</sup> | REWIND<br>(n=9901) <sup>12,13</sup> | PIONEER 6<br>(n=3183) <sup>14</sup> |
|---|--------------------------------|------------------------------------|------------------------------------|-----------------------------------|--|-------------------------------------|-------------------------------------|
| Drug                                    | Lixisenatide                   | Liraglutide                        | Semaglutide                        | Exenatide                         | Albiglutide                                | Dulaglutide                         | Semaglutide (oral)                  |
| Structural basis                        | Exendin-4                      | Human GLP-1                        | Human GLP-1                        | Exendin-4                         | Human GLP-1                                | Human GLP-1                         | Human GLP-1                         |
| Administration route                    | Subcutaneous                   | Subcutaneous                       | Subcutaneous                       | Subcutaneous                      | Subcutaneous                               | Subcutaneous                        | Oral                                |
| Dose                                    | 20 µg per day                  | 1.8 mg per day                     | 0.5 or 1 mg per week               | 2 mg per week                     | 30 or 50 mg per week                       | 1.5 mg per week                     | 14 mg per day                       |
| Age (years)                             | 60 (10)                        | 64 (7)                             | 65 (7)                             | 62 (9)                            | 64 (7)                                     | 66 (7)                              | 66 (7)                              |
| Sex                                     |                                |                                    |                                    |                                   |  |                                     |                                     |
| Men                                     | 4207 (69%)                     | 6003 (64%)                         | 2002 (61%)                         | 9149 (62%)                        | 6569 (69%)                                 | 5312 (54%)                          | 2176 (68%)                          |
| Women                                   | 1861 (31%)                     | 3337 (36%)                         | 1295 (39%)                         | 5603 (38%)                        | 2894 (31%)                                 | 4589 (46%)                          | 1007 (32%)                          |
| Ethnic origin                           |                                |                                    |                                    |                                   |  |                                     |                                     |
| White                                   | 4576 (75%)                     | 7238 (77%)                         | 2736 (83%)                         | 11175 (76%)                       | 6583 (70%)                                 | 7498 (76%)                          | 2300 (72%)                          |
| Other                                   | 1492 (25%)                     | 2102 (23%)                         | 561 (17%)                          | 3577 (24%)                        | 2880 (30%)                                 | 2403 (24%)                          | 883 (28%)                           |
| BMI (kg/m <sup>2</sup> )                | 30.1 (5.6)                     | 32.5 (6.3)                         | 32.8 (6.2)                         | 32.7 (6.4)                        | 32.3 (5.9)                                 | 32.3 (5.7)                          | 32.3 (6.5)                          |
| Diabetes duration (years)               | 9.2 (8.2)                      | 12.8 (8.0)                         | 13.9 (8.1)                         | 13.1 (8.3)                        | 14.2 (8.8)                                 | 10.6 (7.2)                          | 14.9 (8.5)                          |
| HbA <sub>1c</sub> (%)                   | 7.7 (1.3)                      | 8.7 (1.6)                          | 8.7 (1.5)                          | 8.1 (1.0)                         | 8.7 (1.5)                                  | 7.3 (1.1)                           | 8.2 (1.6)                           |
| Established cardiovascular disease      | 6068 (100%)                    | 7598 (81%)                         | 2735 (83%)                         | 10782 (73%)                       | 9463 (100%)                                | 3114 (31%)                          | 2695 (85%)                          |
| History of heart failure                | 1358 (22%)                     | 1667 (18%)                         | 777 (24%)                          | 2389 (16%)                        | 1922 (20%)                                 | 853 (9%)                            | 388 (12%)                           |
| Systolic blood pressure (mm Hg)         | 129 (17)                       | 136 (18)                           | 136 (17)                           | 135 (17)                          | 135 (17)                                   | 137 (17)                            | 136 (18)                            |
| eGFR (mL/min per 1.73 m <sup>2</sup> )* | 78 (21)                        | 80 (NR)                            | 80 (61-92)                         | 77 (61-92)                        | 79 (25)                                    | 75 (24)                             | 74 (21)                             |

No incluido el estudio AWARD

# Cardiovascular, mortality, and kidney outcomes with GLP-1 receptor agonists in patients with type 2 diabetes: a systematic review and meta-analysis of cardiovascular outcome trials



# Reabsorción renal de glucosa

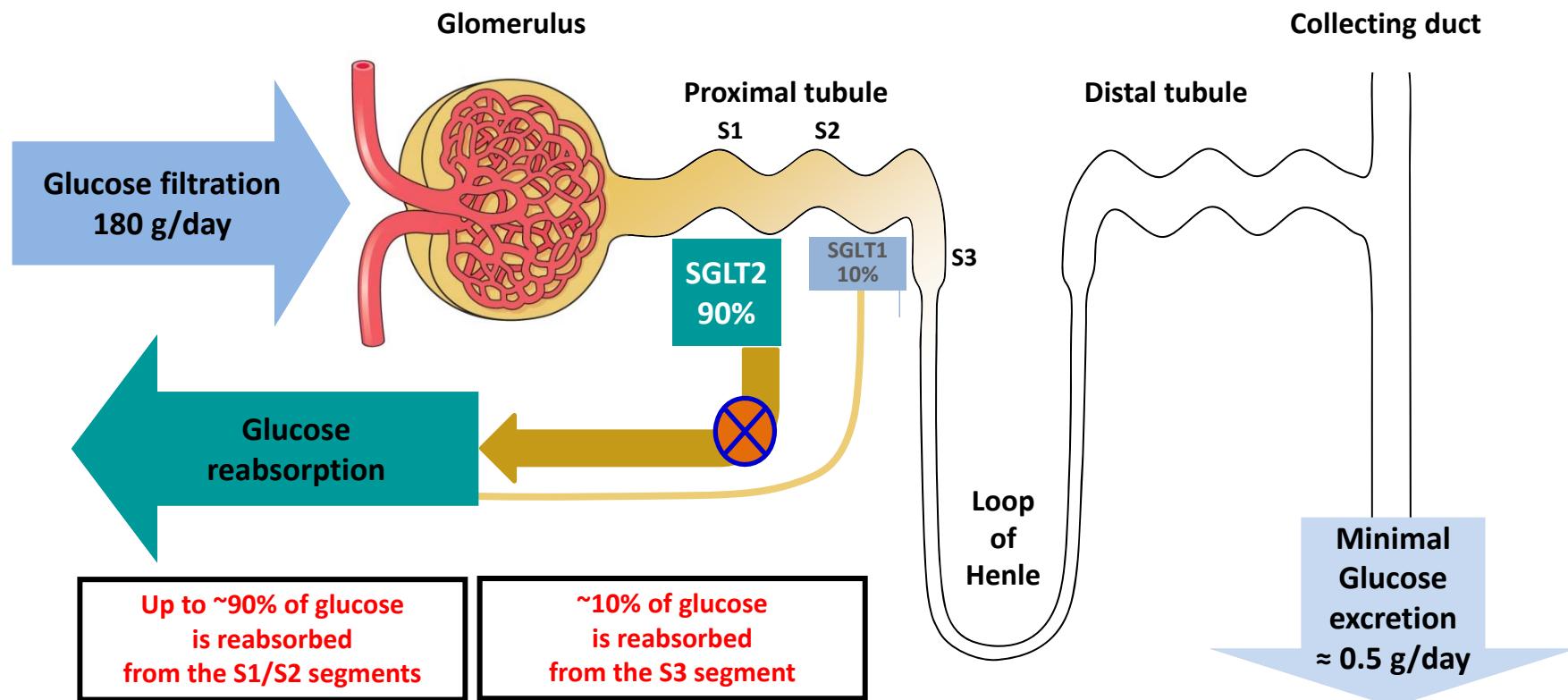
Dapagliflozina  
Empagliflozina

Canagliflozina  
Ertugliflozina

Tofogliflozina

Ipragliflozina

Luesogliflozina





ORIGINAL ARTICLE

## Empagliflozin and Progression of Kidney Disease in Type 2 Diabetes

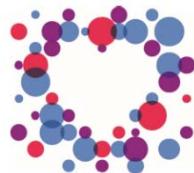
### Prespecified secondary outcome

#### Incident or Worsening Nephropathy

- Progression to macroalbuminuria
- Doubling of serum Cr accompanied by eGFR  $\leq 45$  ml/min
- Initiation of renal replacement therapy
- Death due to renal disease

#### Renal Composite Outcome

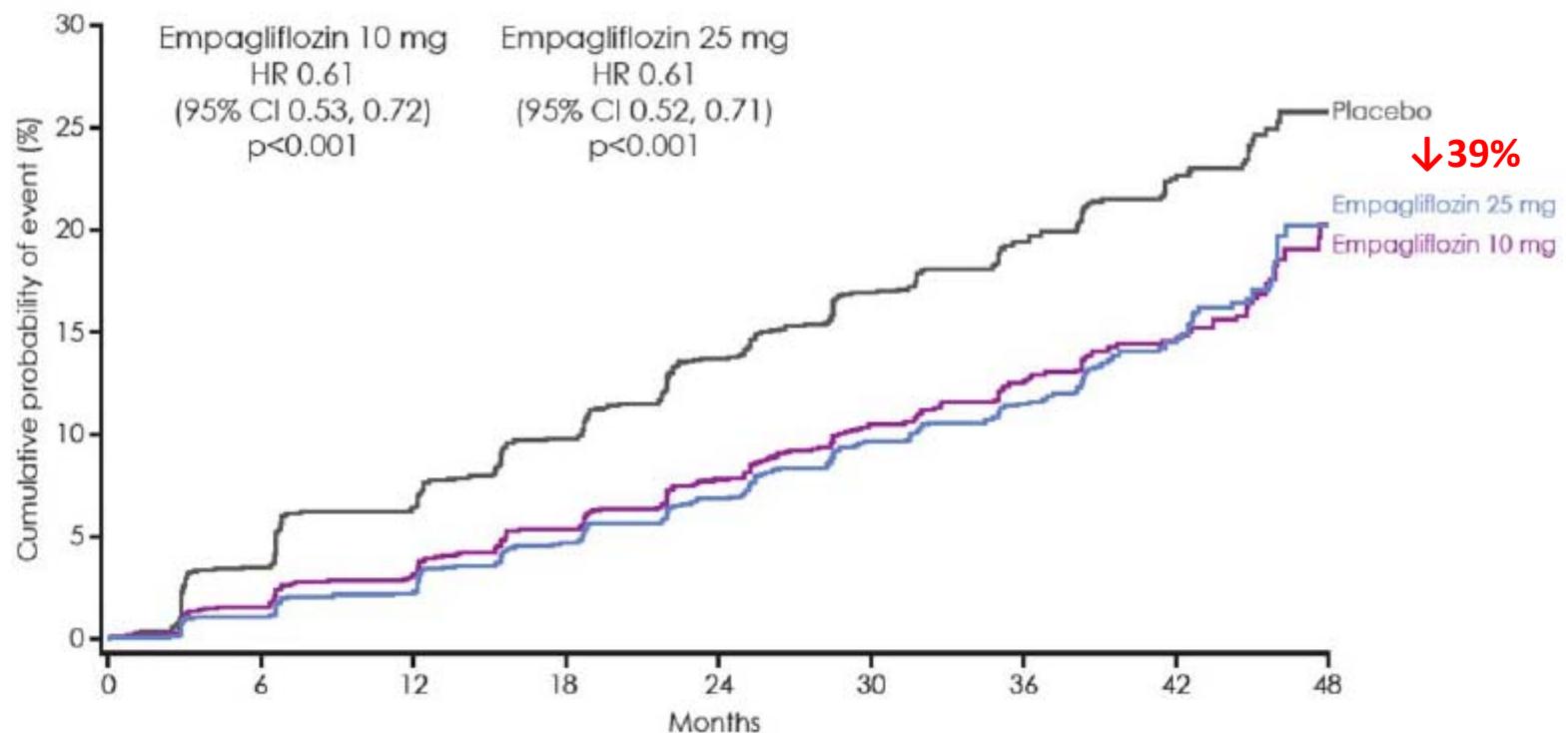
- Doubling of serum creatinine
- Initiation of renal replacement therapy
- Death due to renal disease



ORIGINAL ARTICLE

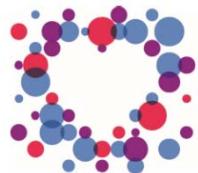
## Empagliflozin and Progression of Kidney Disease in Type 2 Diabetes

### Incident or Worsening Nephropathy



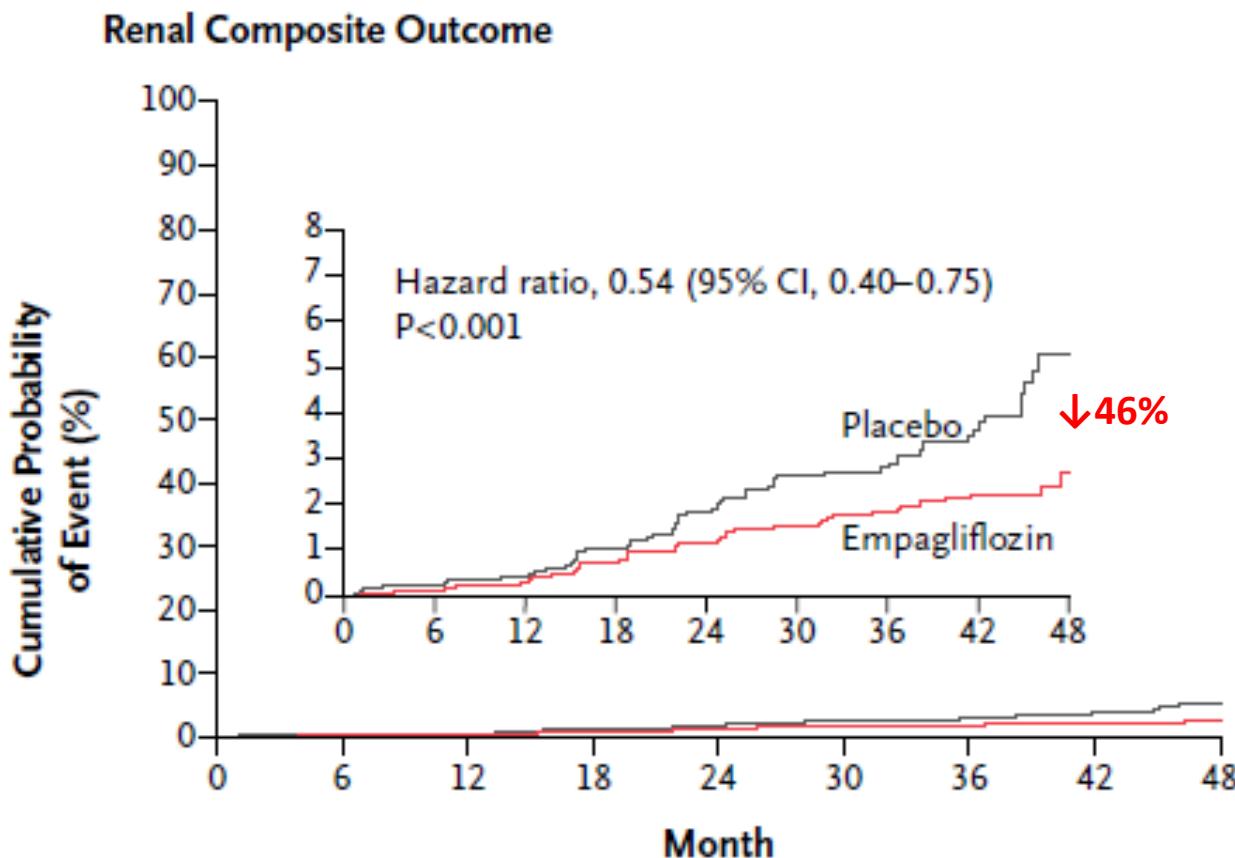
No. of patients

|                     | Empagliflozin 10 mg | Empagliflozin 25 mg | Placebo |
|---------------------|---------------------|---------------------|---------|
| Empagliflozin 10 mg | 2055                | 1991                | 1946    |
| Empagliflozin 25 mg | 2069                | 2003                | 1836    |
| Placebo             | 2061                | 1844                | 1703    |



## ORIGINAL ARTICLE

## Empagliflozin and Progression of Kidney Disease in Type 2 Diabetes

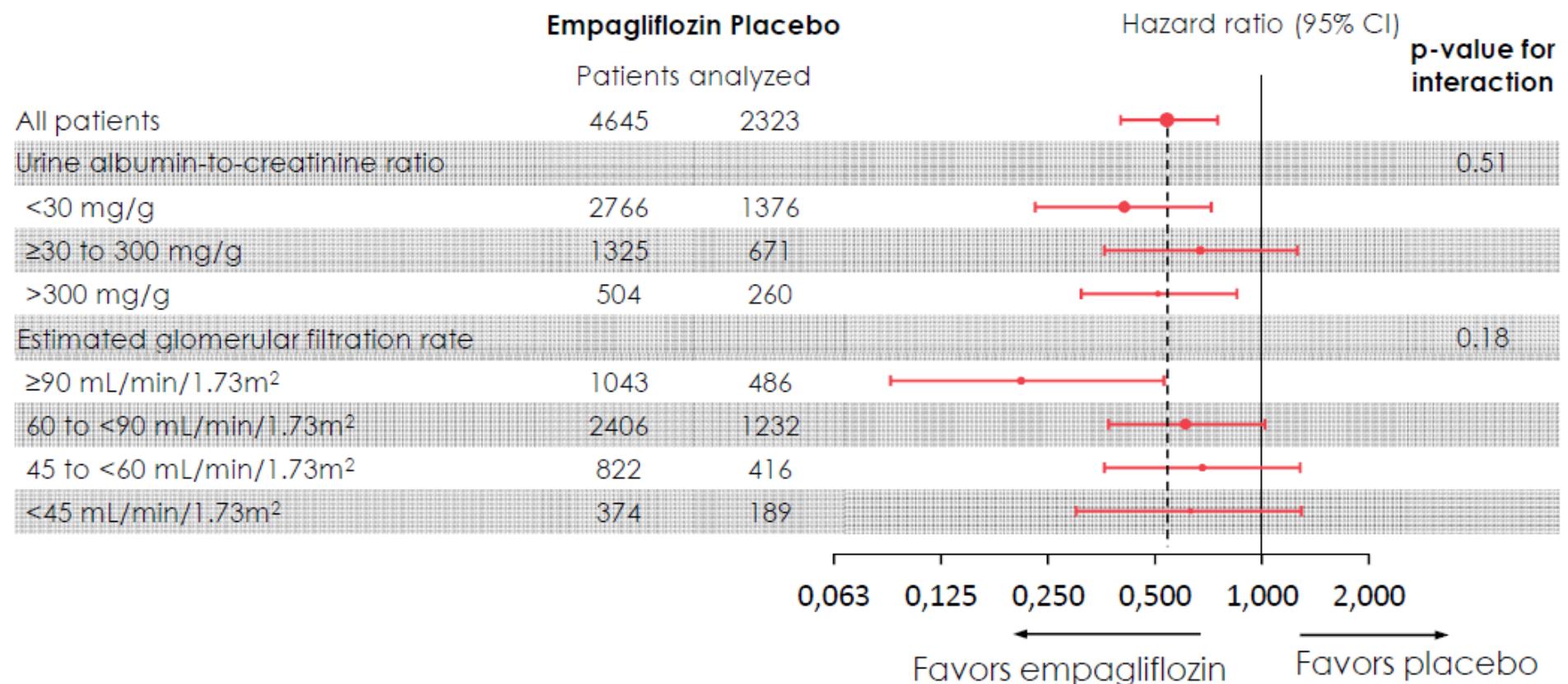
**No. at Risk**

|               |      |      |      |      |      |      |      |      |     |
|---------------|------|------|------|------|------|------|------|------|-----|
| Empagliflozin | 4645 | 4500 | 4377 | 4241 | 3729 | 2715 | 2280 | 1496 | 360 |
| Placebo       | 2323 | 2229 | 2146 | 2047 | 1771 | 1289 | 1079 | 680  | 144 |

## ORIGINAL ARTICLE

# Empagliflozin and Progression of Kidney Disease in Type 2 Diabetes

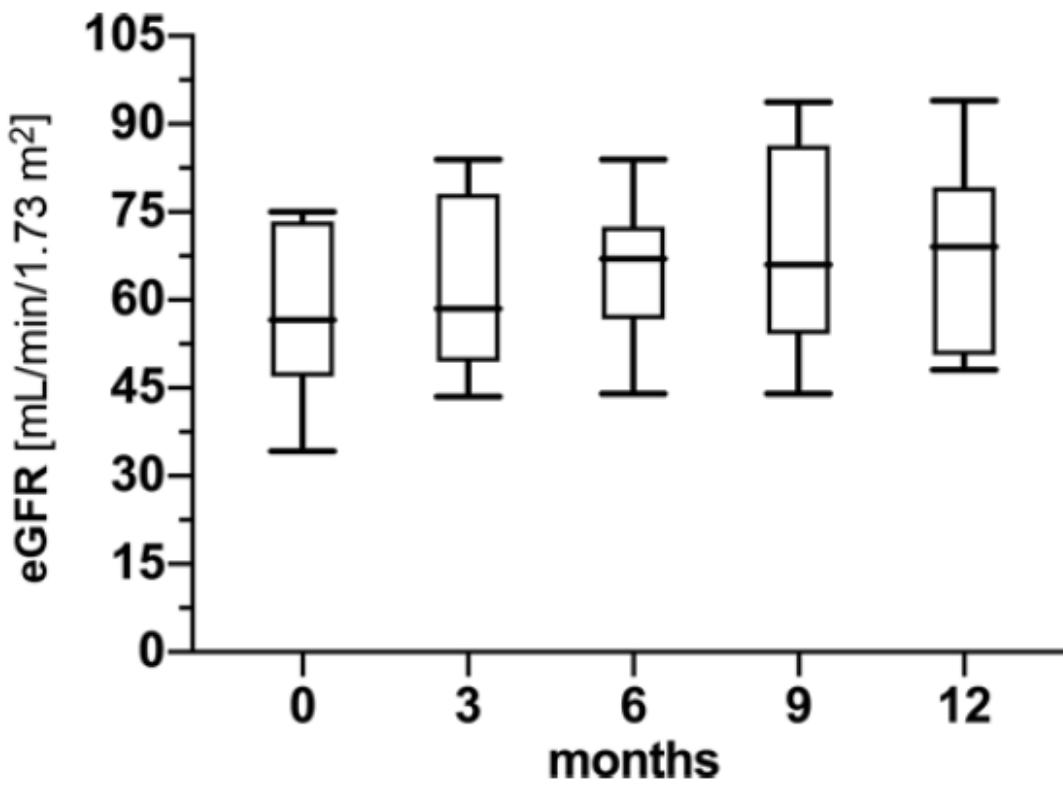
## Renal Composite Outcome



# Sodium-Glucose Cotransporter 2 (SGLT2) Inhibition in Kidney Transplant Recipients with Diabetes Mellitus

**Table 1.** Baseline characteristics of study participants

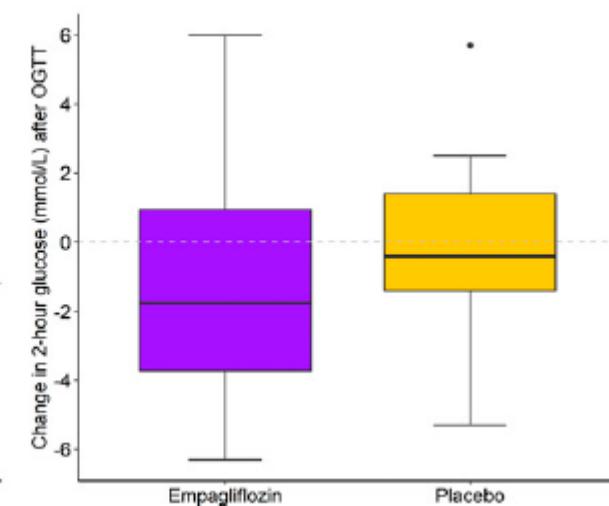
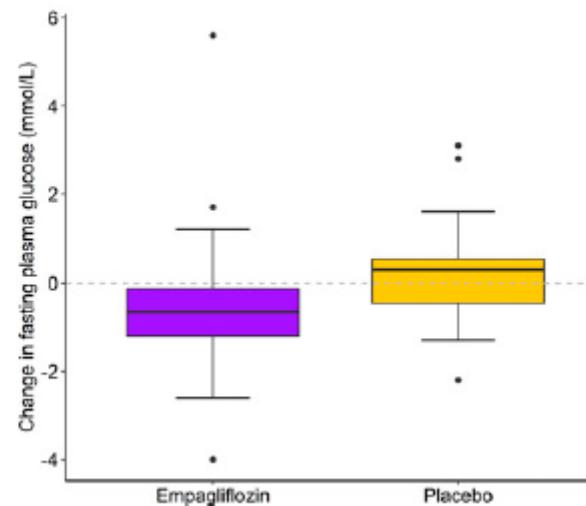
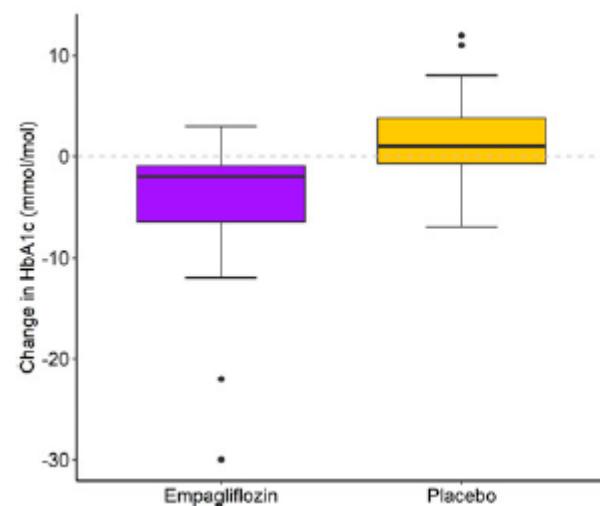
|  |               |
|--|---------------|
| Total, n                                 | 10            |
| Age, years                               | 66 (56–73)    |
| Gender, female/male, %                   | 20/80         |
| Living kidney donation, %                | 80            |
| Time since transplantation, years        | 5.9 (4.4–8.8) |
| Time since diabetes was diagnosed, years | 18 (6–33)     |
| Posttransplant diabetes mellitus, %      | 40            |
| Underlying chronic kidney disease, %     |               |
| Diabetic/hypertensive nephropathy        | 30            |
| IgA nephropathy                          | 20            |
| Unspecified glomerulonephritis           | 20            |
| Polycystic kidney disease                | 10            |
| Other                                    | 20            |



| Outcome                           | Median value<br>at start of<br>observation | Individual<br>absolute change, % | Individual<br>relative change, % |
|-----------------------------------|--|----------------------------------|----------------------------------|
| Body weight, kg                   | 75   | -1.9 (-1.9 to 0.1)               | -0.9 (-2.8 to 0.2)               |
| Waist circumference, cm           | 110  | -2.0 (-6.0 to 0.0)               | -1.8 (-6.2 to 0.0)               |
| Blood pressure (systolic), mm Hg  | 135  | -2.5 (-36.3 to 0.8)              | -1.4 (-19.8 to 0.6)              |
| Blood pressure (diastolic), mm Hg | 80   | -0.5 (-9.5 to 7.5)               | -0.6 (-11.1 to 9.4)              |
| Hematocrit                        | 38   | +2.5 (0.8 to 4.1)                | +6.5 (2.3 to 9.3)                |
| Uric acid, mg/dL                  | 5.2  | -0.2 (-0.8 to 0.5)               | -3.4 (-16.5 to 7.4)              |

# Efficacy and Safety of Empagliflozin in Renal Transplant Recipients With Posttransplant Diabetes Mellitus

|                                    | Empagliflozin, n = 22 | Placebo, n = 22   |
|------------------------------------|-----------------------|-------------------|
| Sex (male/female), n               | 17/5                  | 17/5              |
| Age (years)                        | 63 (31, 72)           | 59 (21, 75)       |
| Time since transplantation (years) | 3 (1, 16)             | 3 (1, 15)         |
| BMI ( $\text{kg}/\text{m}^2$ )     | 28.8 (24.7, 39.3)     | 27.5 (22.4, 45.8) |
| WHR (cm)                           | 1.01 (0.82, 1.25)     | 0.98 (0.80, 1.11) |
| Systolic blood pressure (mmHg)     | 143 (111, 176)        | 140 (100, 163)    |
| Diastolic blood pressure (mmHg)    | 79 (63, 94)           | 82 (55, 94)       |
| $\text{HbA}_{1\text{c}}$ (%)       | 6.9 (6.5, 8.2)        | 6.8 (6.1, 7.2)    |



# Renal Outcomes

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## Biomarker outcome

- Change in albuminuria

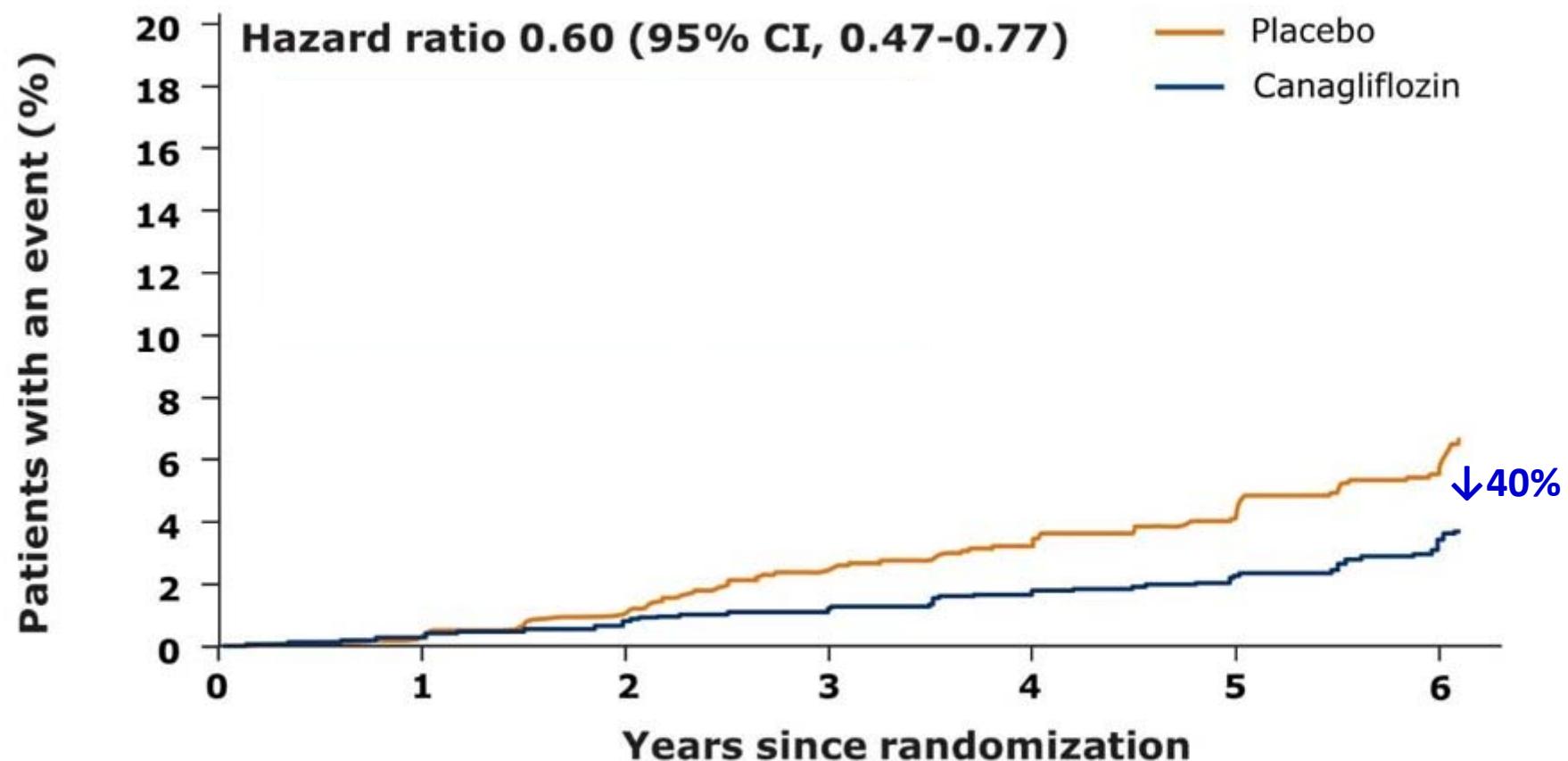
## Renal intermediate outcomes

- Progression of albuminuria
- Regression of albuminuria

## Composite renal outcome [confirmed and adjudicated]

- 40% decrease in glomerular filtration rate (GFR)
- End-stage renal disease
- Renal death

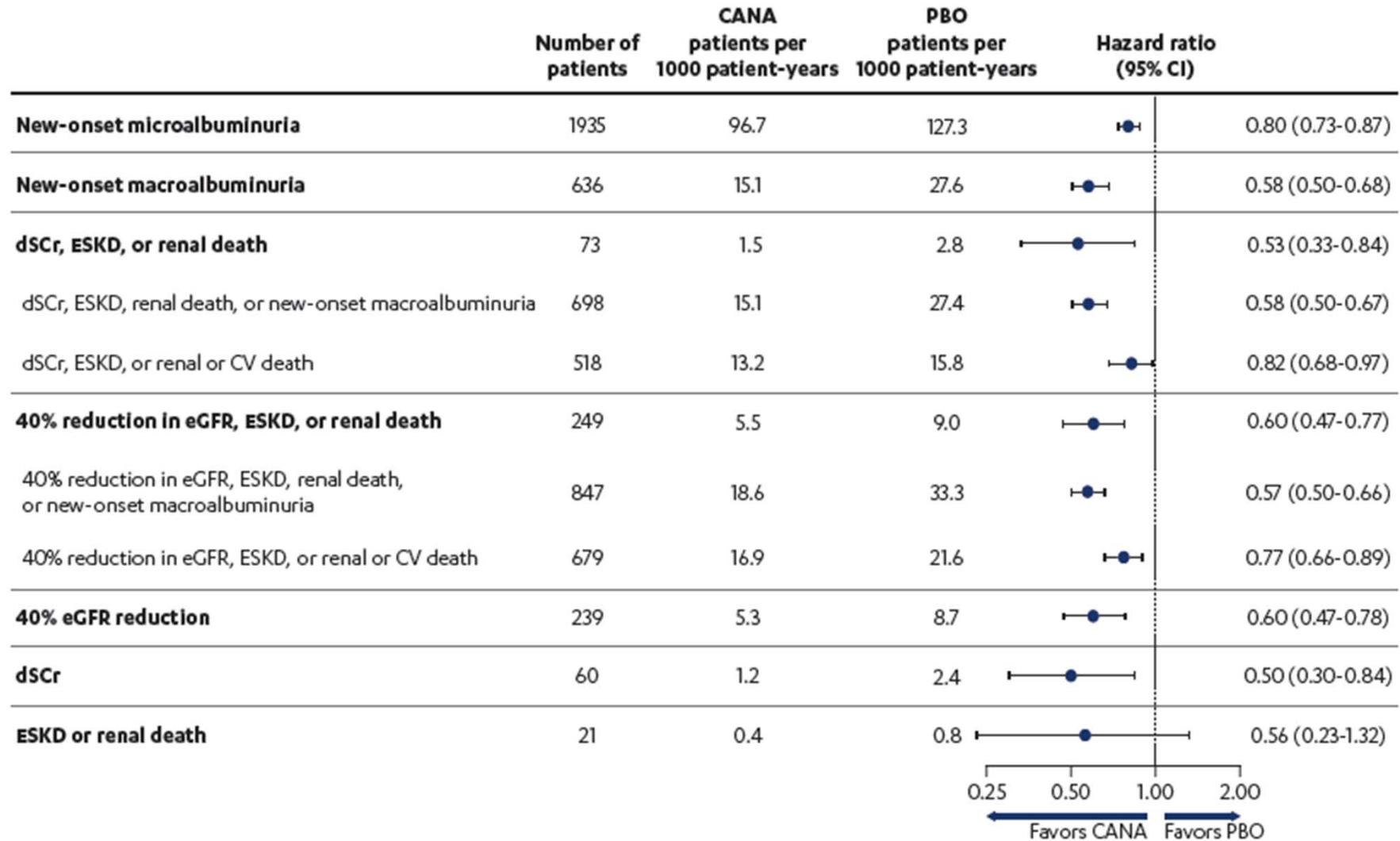
# Composite of 40% Reduction in eGFR, End-stage Renal Disease, or Renal Death



No. of patients

|               |      |      |      |      |      |      |      |
|---------------|------|------|------|------|------|------|------|
| Placebo       | 4347 | 4227 | 3029 | 1274 | 1229 | 1173 | 819  |
| Canagliflozin | 5795 | 5664 | 4454 | 2654 | 2576 | 2495 | 1781 |

# Canagliflozin and “renal outcomes”



## Effects of dapagliflozin on development and progression of kidney disease in patients with type 2 diabetes: an analysis from the DECLARE-TIMI 58 randomised trial

Ofri Mosenzon, Stephen D Wiviott, Avivit Cahn, Aliza Rozenberg, Ilan Yanuv, Erica L Goodrich, Sabina A Murphy, Hiddo JL Heerspink, Thomas A Zelniker, Jamie P Dwyer, Deepak L Bhatt, Lawrence A Leiter, Darren K McGuire, John P H Wilding, Eri T Kato, Ingrid A M Gause-Nilsson, Martin Fredriksson, Peter A Johansson, Anna Maria Langkilde, Marc S Sabatine, Itamar Raz

*Lancet Diabetes Endocrinol*  
2019; 7: 606-17

### Variable compuesta Reno-Vascular

- ↓ sostenida del FGe ≥ 40% por debajo de 60 ml/min
- Enfermedad renal terminal: FGe < 15 ml/min, Diálisis > 90 días, Tx renal
- Muerte de causa renal o cardiovascular

### Variable compuesta específica renal

- ↓ sostenida del FGe ≥ 40% por debajo de 60 ml/min
- Enfermedad renal terminal: FGe < 15 ml/min, Diálisis > 90 días, Tx renal
- Muerte de causa renal

N = 25698 / Randomized = 17160  
Mediana de seguimiento: 4.2 años



**93.2% patients with eGFR > 60 ml/min  
(47.5% eGFR > 90)**



**> 90% PACIENTES CON FUNCIÓN RENAL NORMAL**

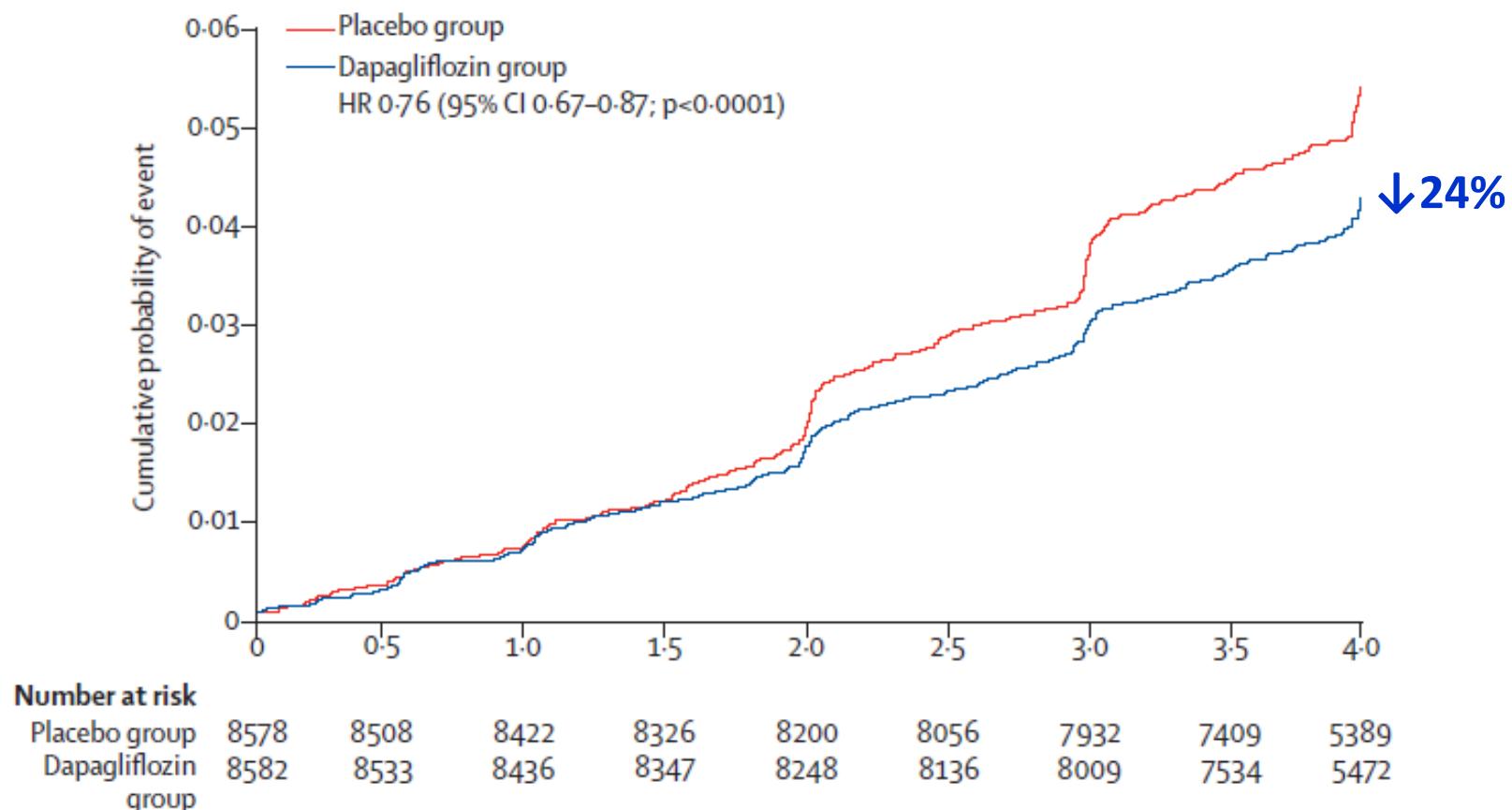
**67.9% pacientes con Normoalbuminuria  
19.4% pacientes con Microalbuminuria**



**87.3% PACIENTES SIN LESIÓN RENAL  
o CON LESIÓN RENAL INCIPIENTE**

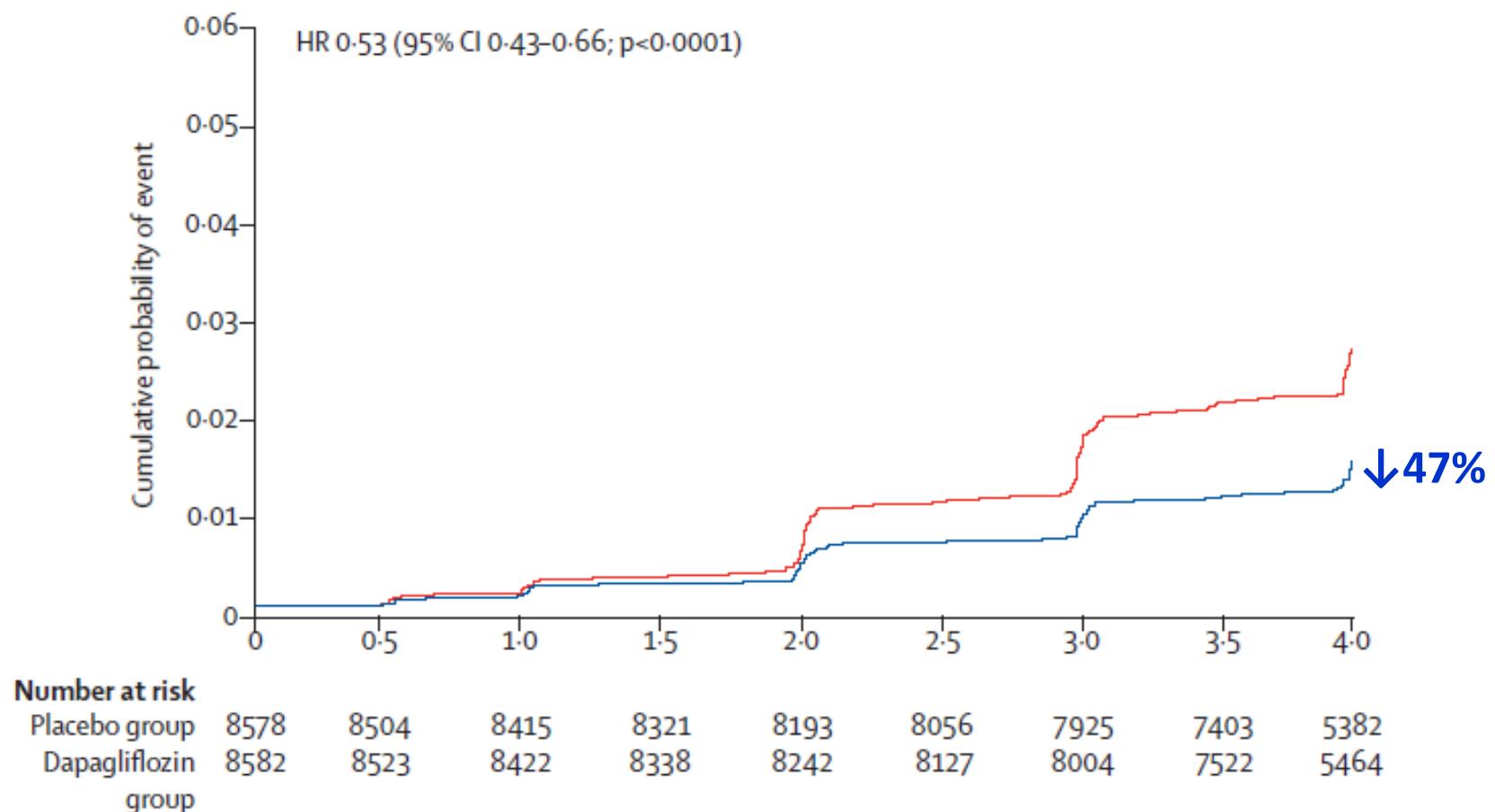
## Variable compuesta Reno-Vascular

- ↓ sostenida del FGe ≥ 40% por debajo de 60 ml/min
- Enfermedad renal terminal: FGe < 15 mil/min, Diálisis > 90 días, Tx renal
- Muerte de causa renal o cardiovascular

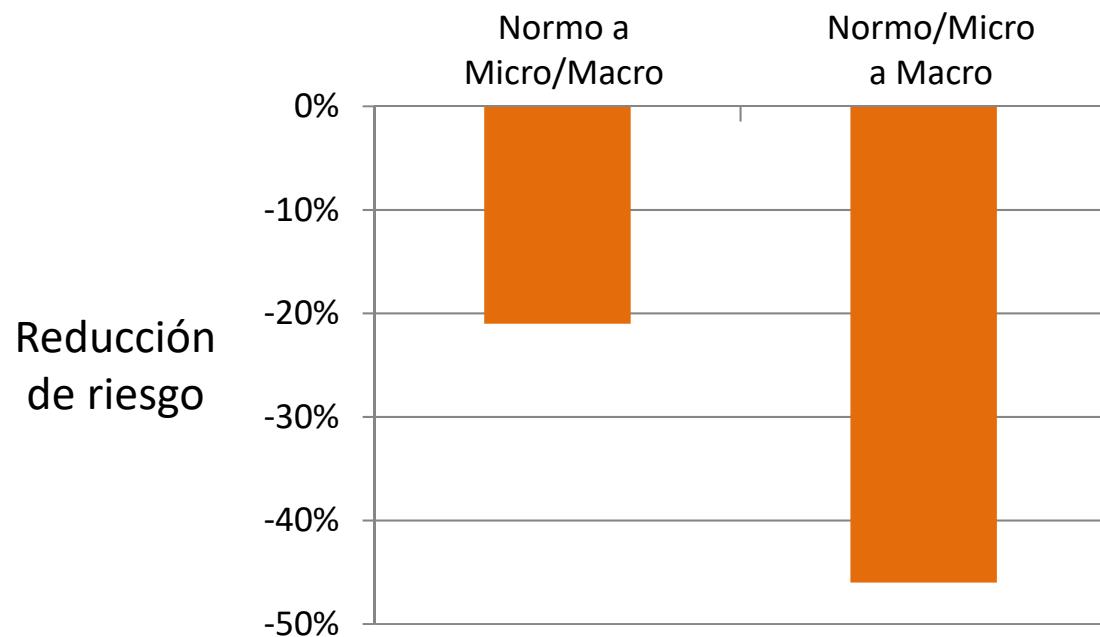
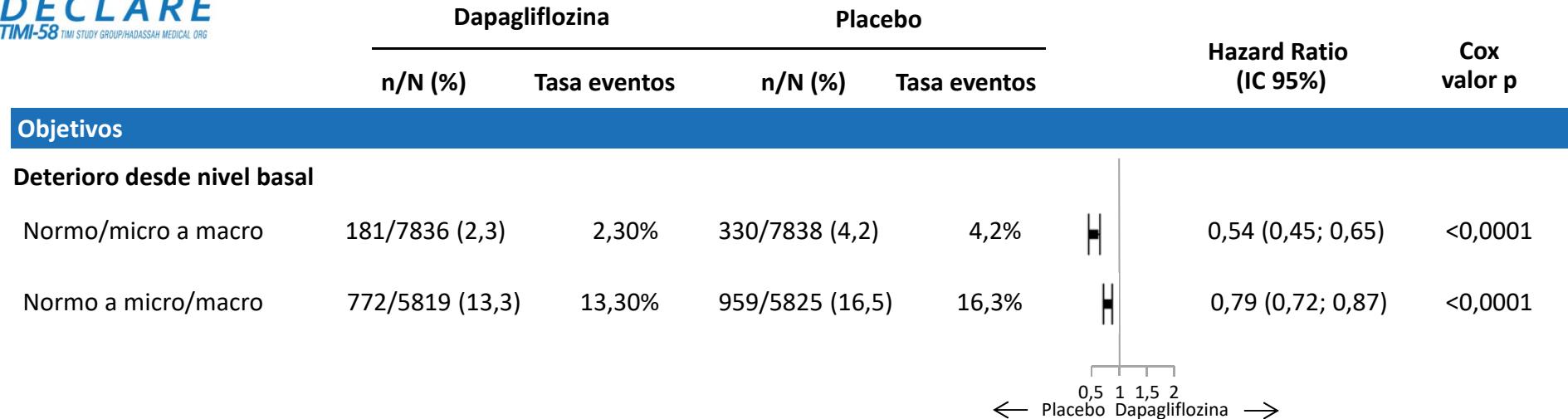


## Variable compuesta específica renal

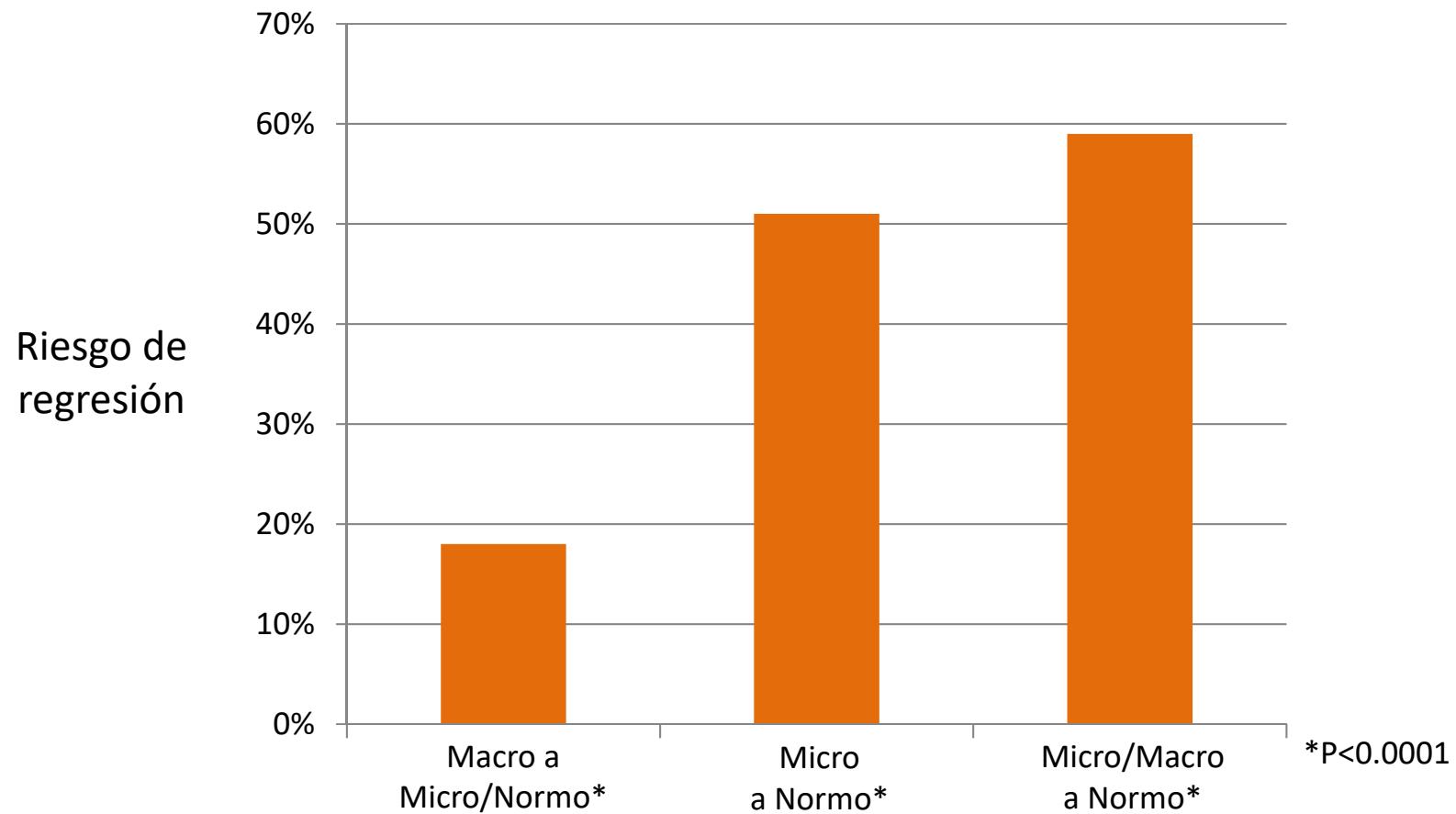
- ↓ sostenida del FGe ≥ 40% por debajo de 60 ml/min
- Enfermedad renal terminal: FGe < 15 mil/min, Diálisis > 90 días, Tx renal
- Muerte de causa renal



# Riesgo de progresión de ERD



# “Riesgo” de regresión de ERD



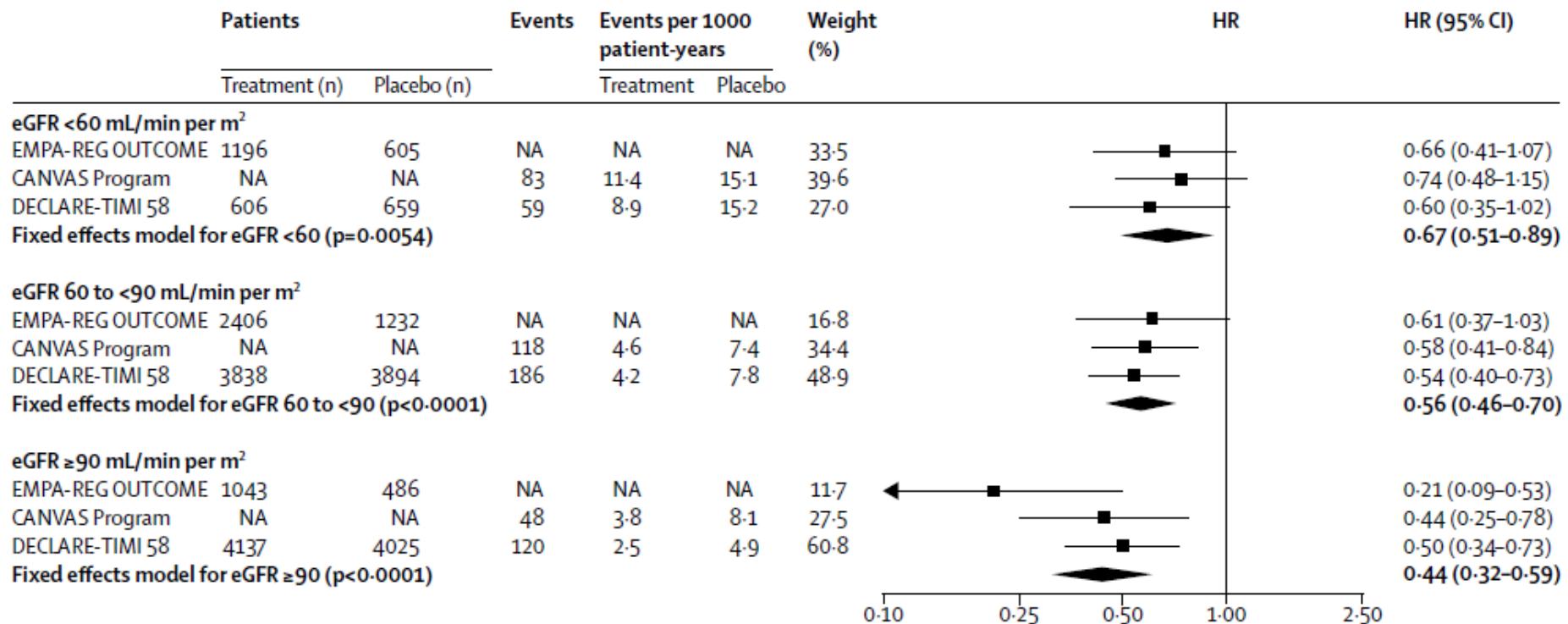


The NEW ENGLAND JOURNAL of MEDICINE

ORIGINAL ARTICLE

## Canagliflozin and Renal Outcomes in Type 2 Diabetes and Nephropathy

# Why is CREDENCE Important?





# Objectives

People with T2DM, **eGFR 30 to 90 ml/min/1.73 m<sup>2</sup>**, and **UACR 300 to 5000 mg/g** who are receiving standard of care including a **maximum tolerated dose of an ACEi or ARB**, to assess whether canagliflozin compared with placebo reduces

## Primary:

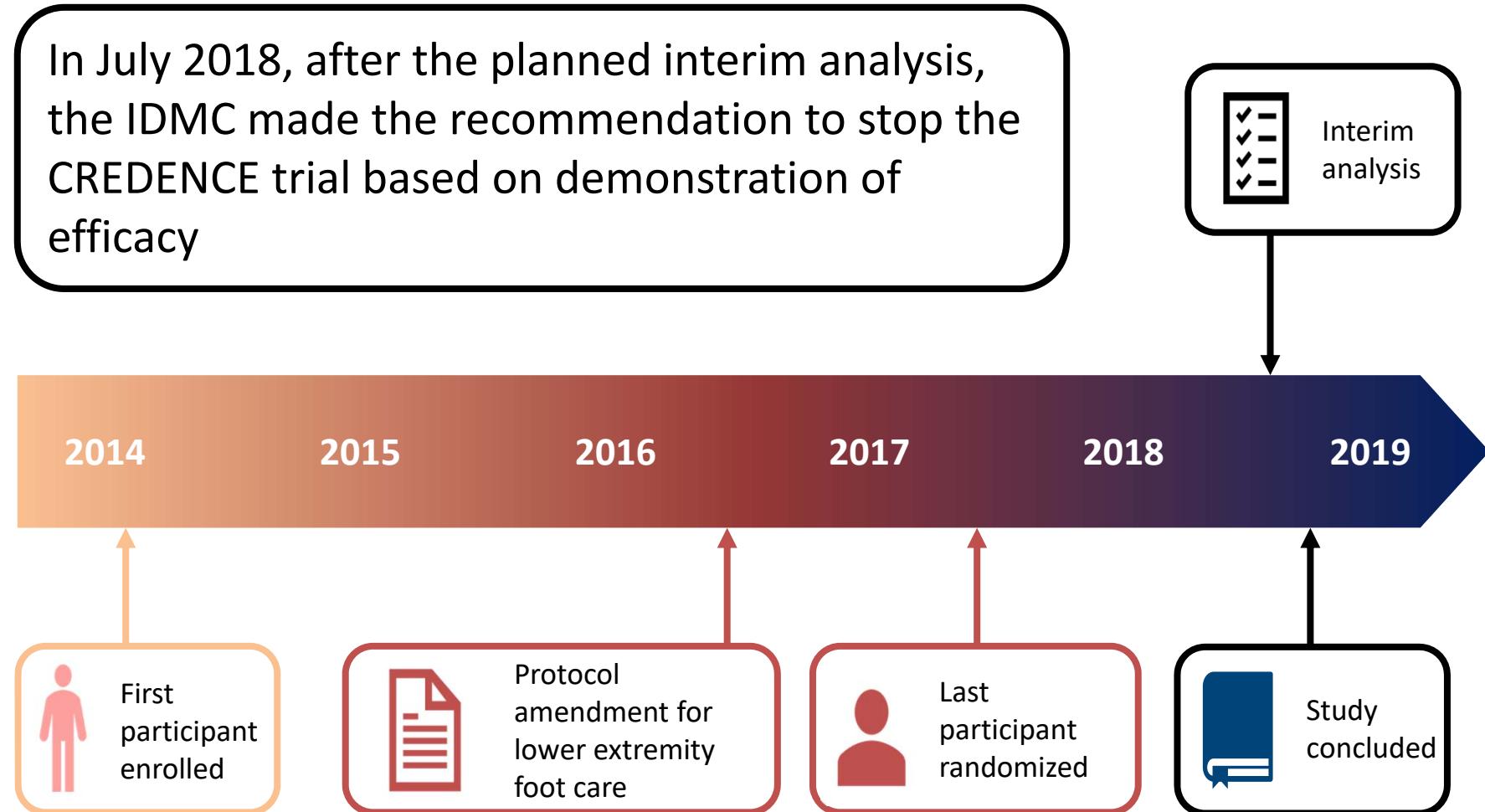
- **Composite outcome of ESKD, doubling of serum creatinine, or renal or CV death**

## Secondary:

- CV death or hospitalization for heart failure
- Major cardiovascular events (3-point MACE: CV death, MI, or stroke)
- Hospitalization for heart failure
- ESKD, doubling of serum creatinine, or renal death
- CV death
- All-cause mortality
- CV death, MI, stroke, hospitalization for heart failure, or hospitalization for unstable angina



# Study Timeline





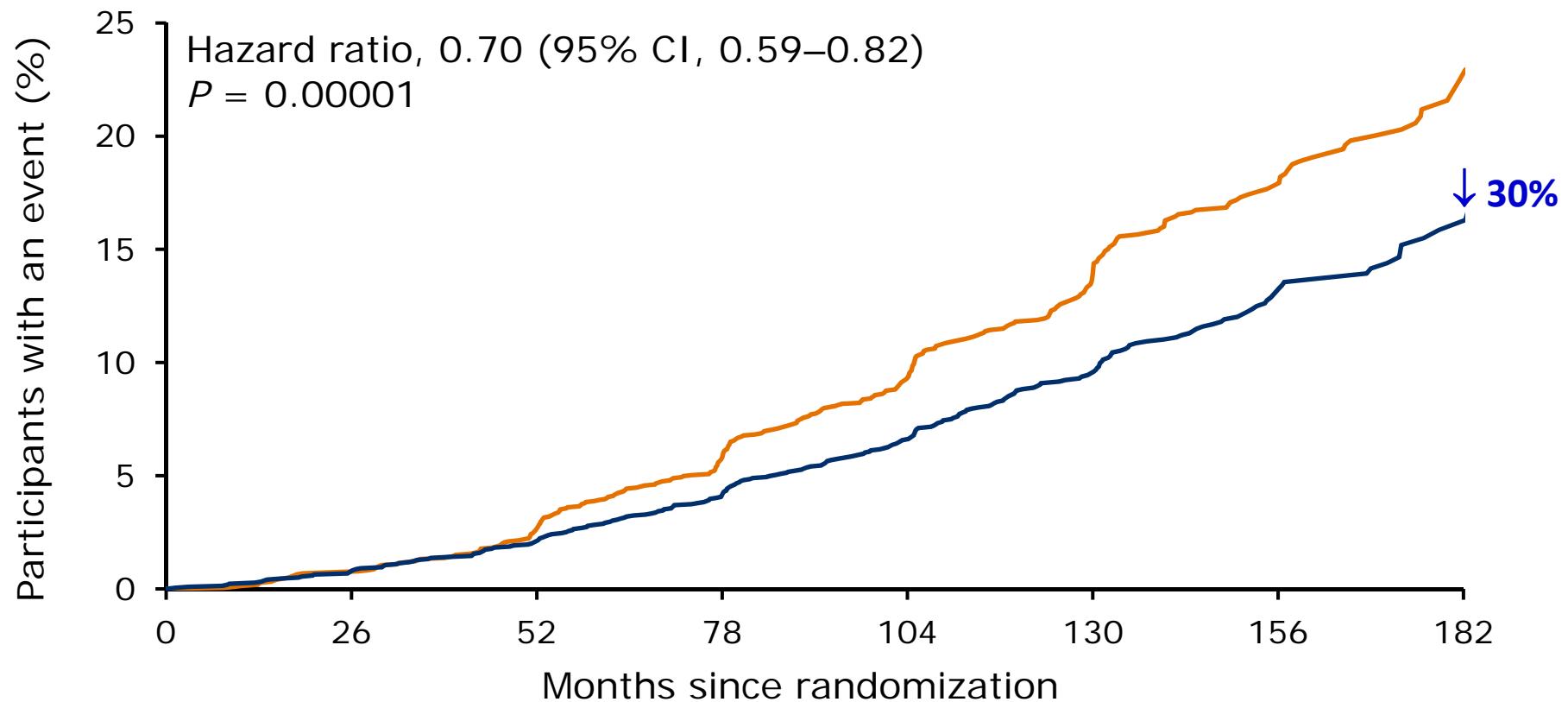
# Baseline Renal Characteristics

|   | Canagliflozin<br>(n = 2202) | Placebo<br>(n = 2199)    | Total<br>(N = 4401)      |
|---|-----------------------------|--------------------------|--------------------------|
| <b>Mean eGFR, mL/min/1.73 m<sup>2</sup></b> | <b>56</b>                   | <b>56</b>                | <b>56</b>                |
| eGFR ≥90, %                                 | 5                           | 5                        | 5                        |
| eGFR ≥60 to <90, %                          | 36                          | 35                       | 35                       |
| eGFR ≥45 to <60, %                          | 29                          | 29                       | 29                       |
| eGFR ≥30 to <45, %                          | 27                          | 27                       | 27                       |
| eGFR <30, %                                 | 4                           | 4                        | 4                        |
| <b>Median UACR (IQR), mg/g</b>              | <b>923</b><br>(459-1794)    | <b>931</b><br>(473-1868) | <b>927</b><br>(463-1833) |
| UACR <30, %                                 | <1                          | <1                       | <1                       |
| UACR 30-300, %                              | 11                          | 11                       | 11                       |
| UACR >300-≤3000, %                          | 77                          | 76                       | 77                       |
| UACR >3000, %                               | 11                          | 12                       | 11                       |



# Primary Outcome

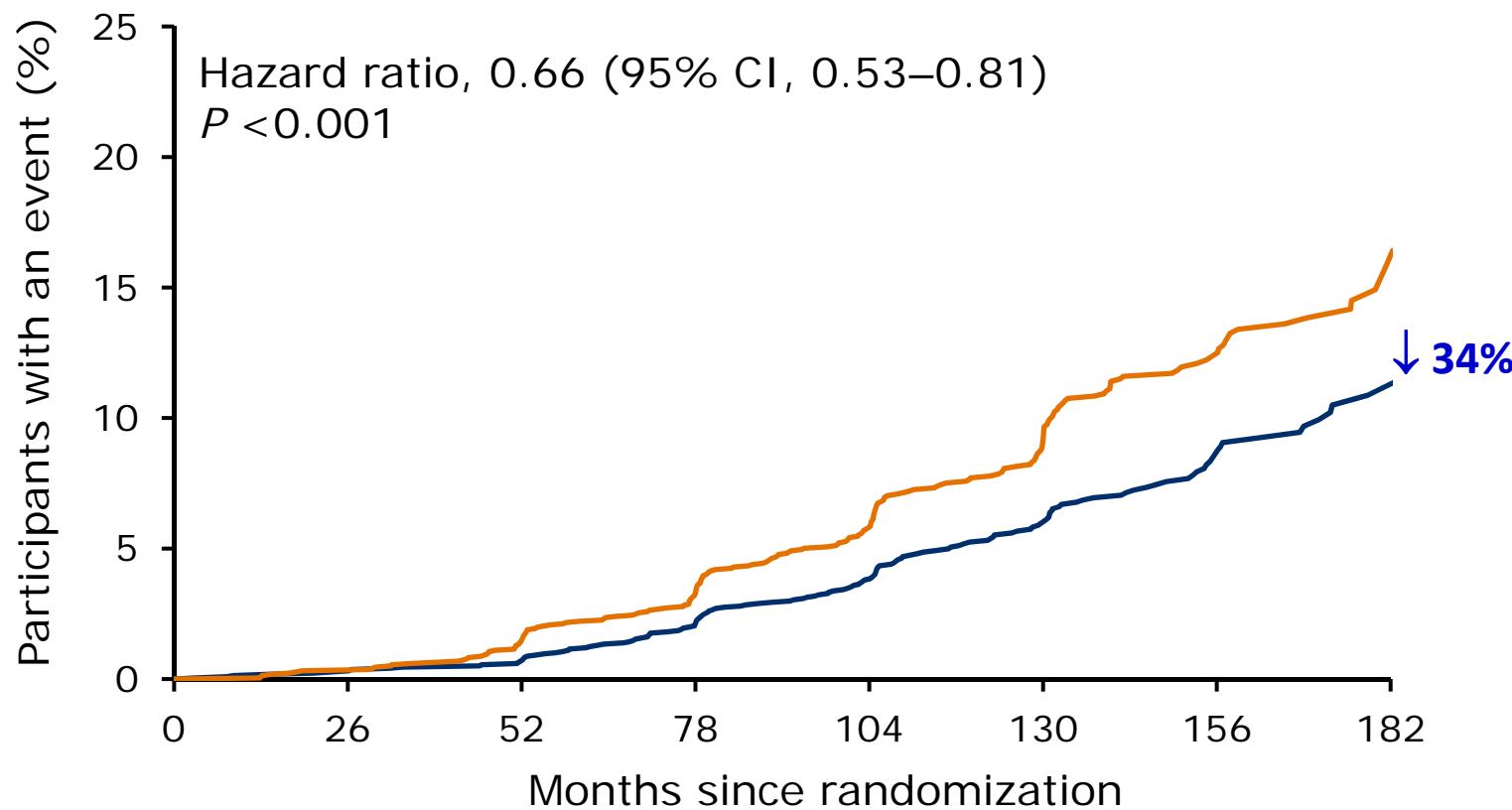
## ESKD, Doubling of Serum Cr, or Renal or CV Death





# Primary Outcome

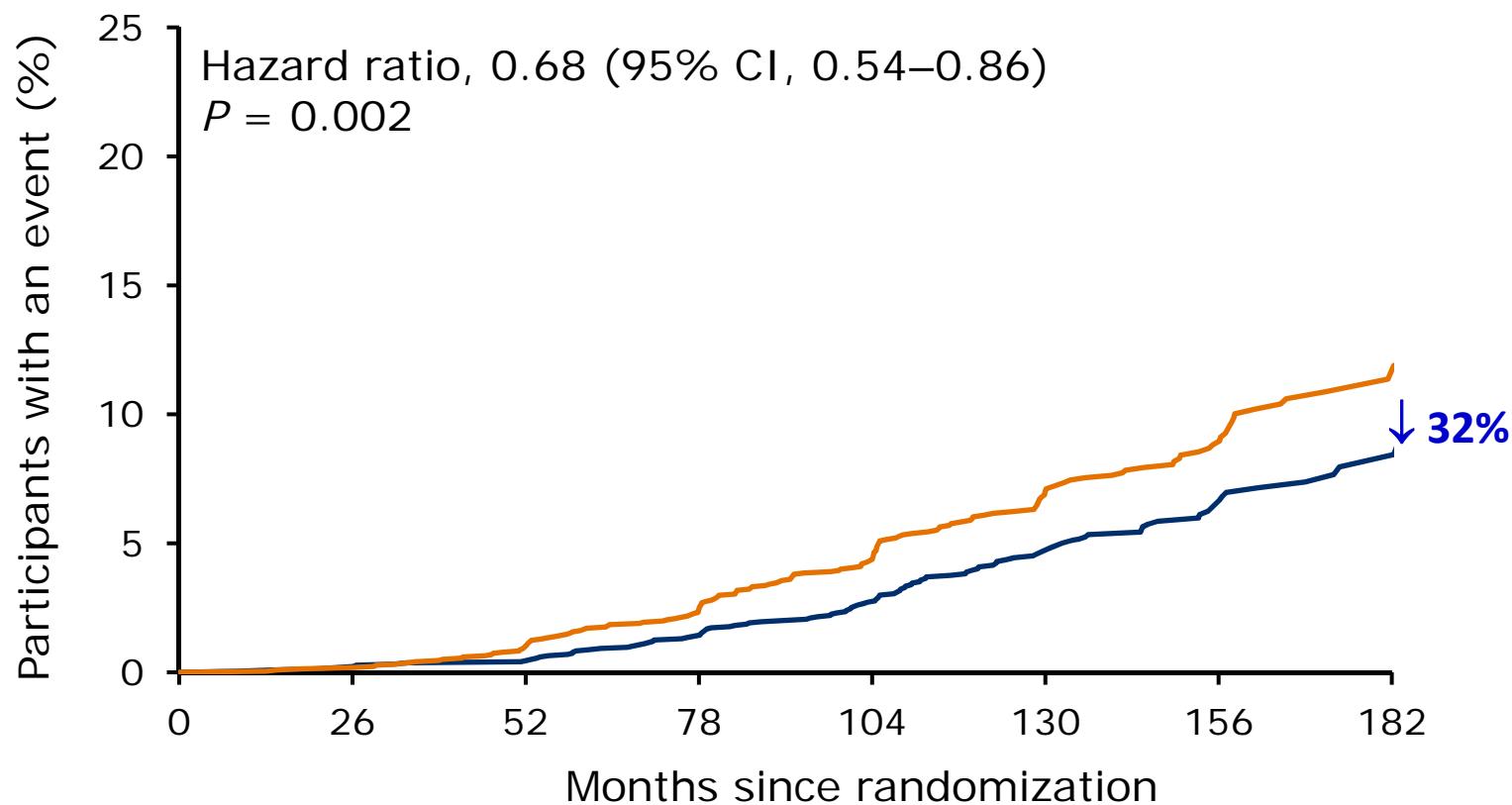
## ESKD, Doubling of Serum Cr or Renal Death





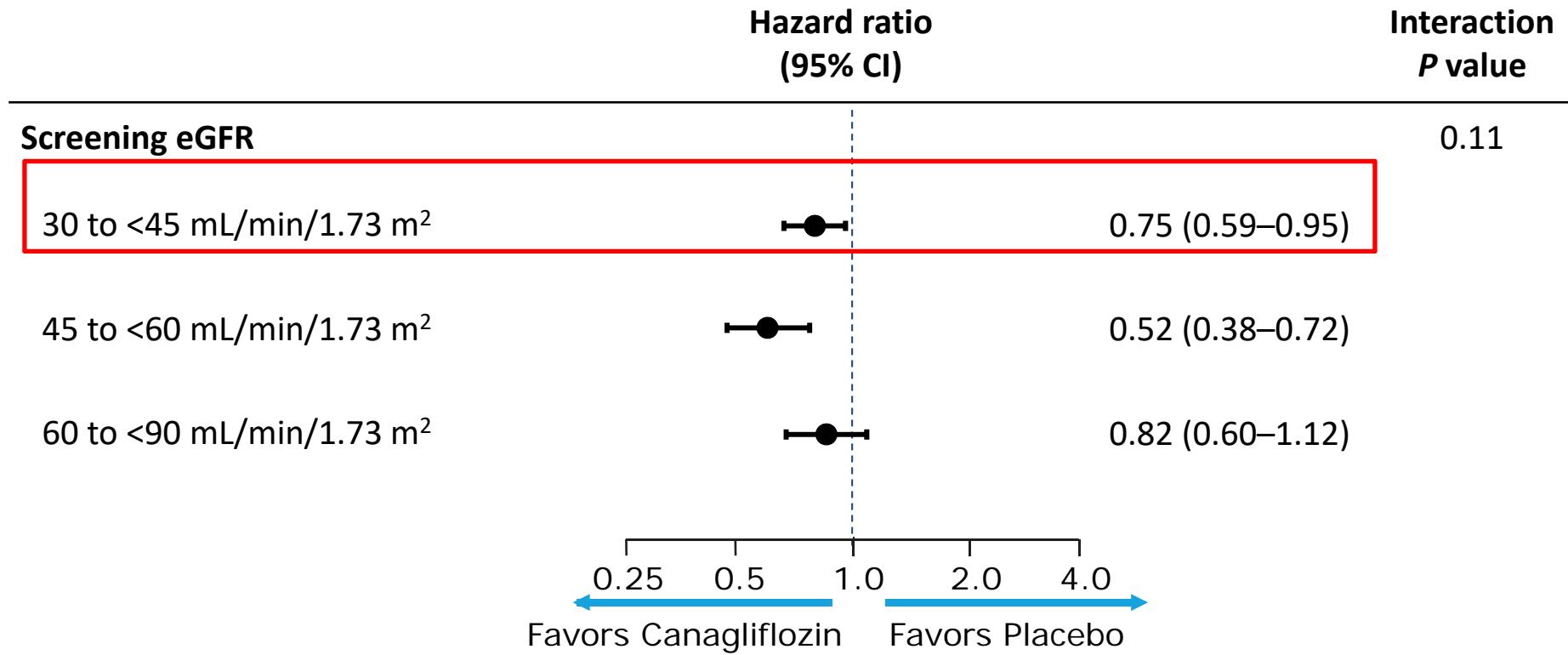
# Primary Outcome

## End-stage Kidney Disease

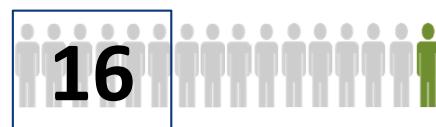




# Primary Outcome Benefits in eGFR 30 to <45 Subgroup

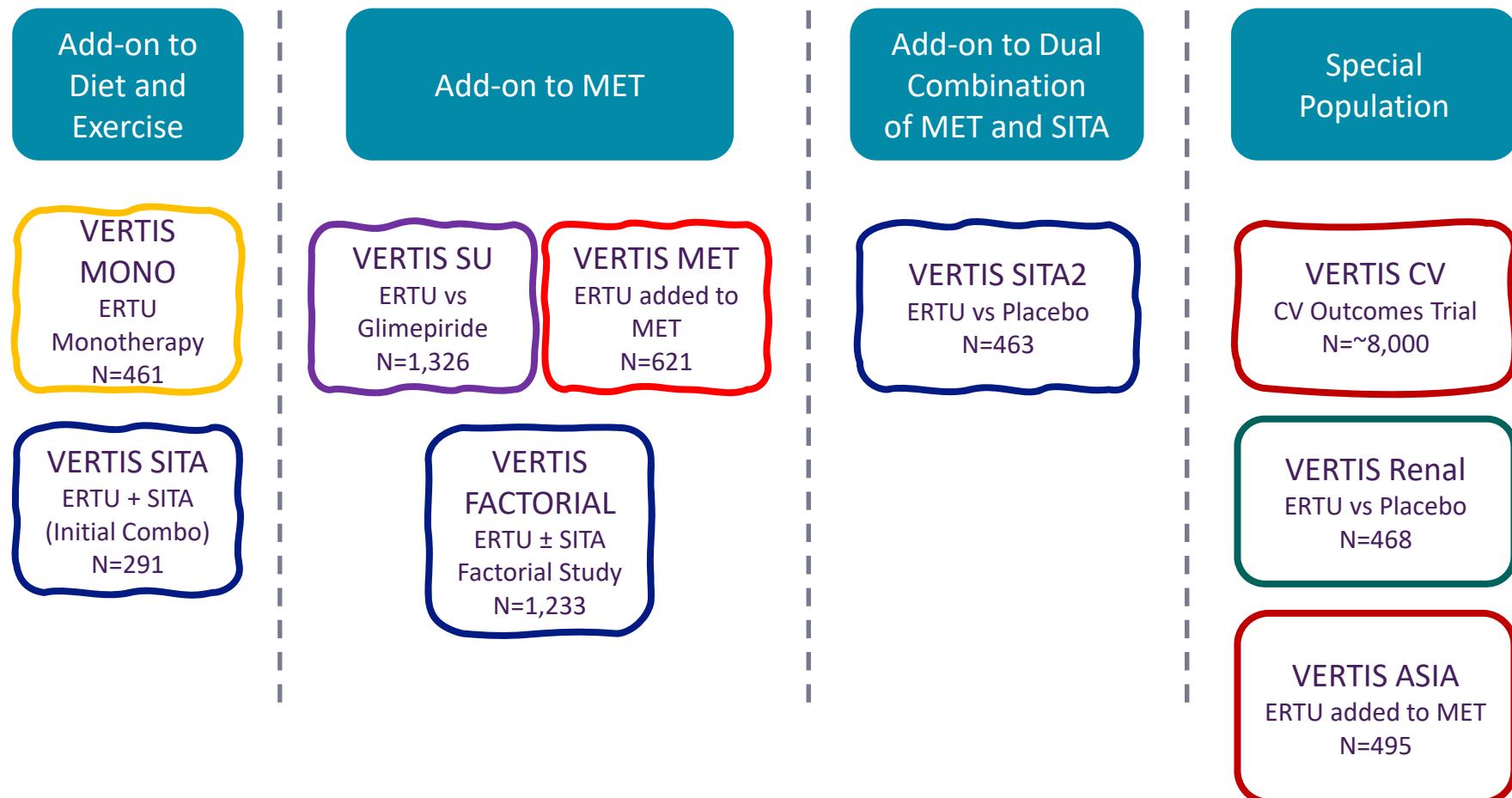


NNT in patients with eGFR 30 to <45 mL/min/1.73 m<sup>2</sup>

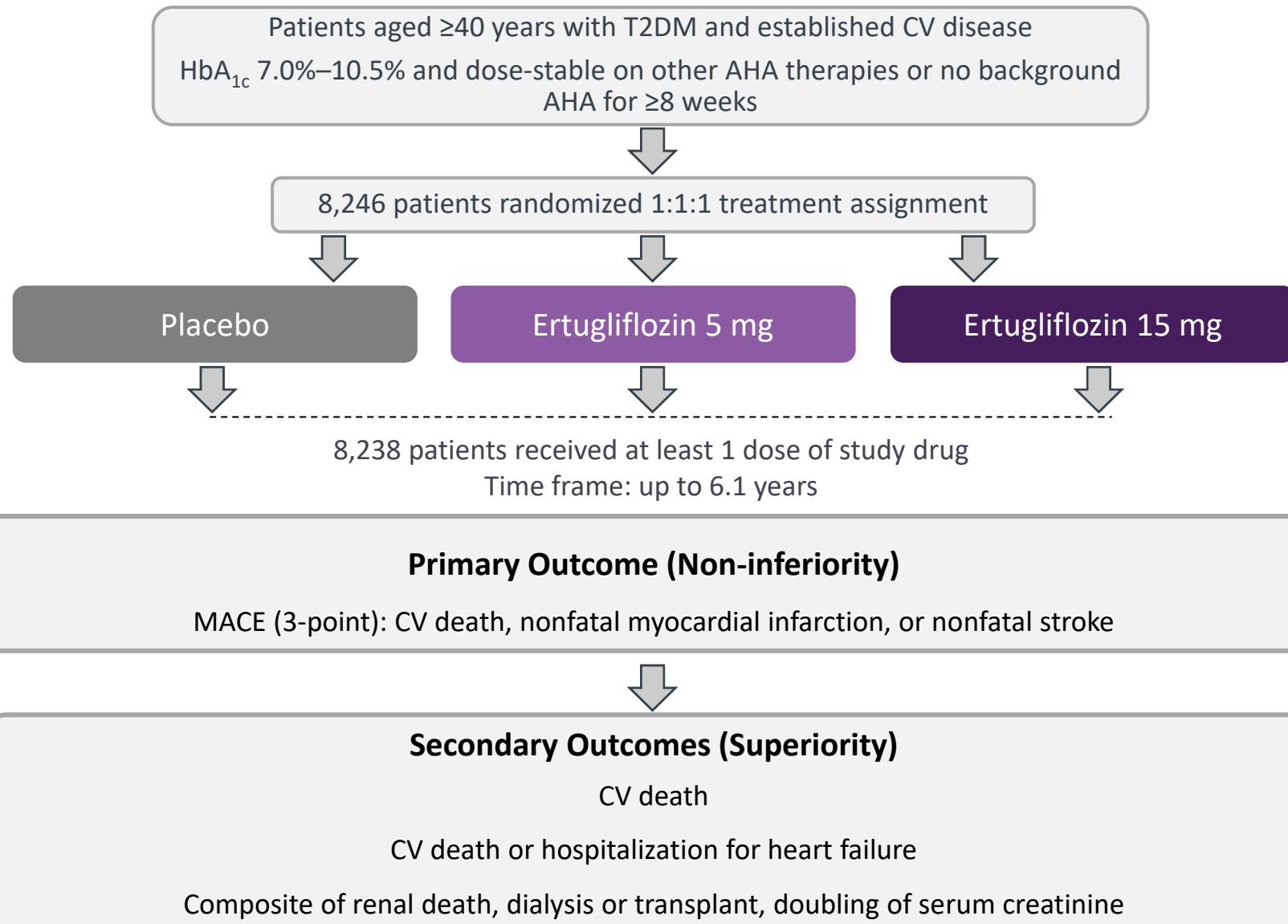


# VERTIS

## Ertugliflozin Phase 3 Clinical Trial Program

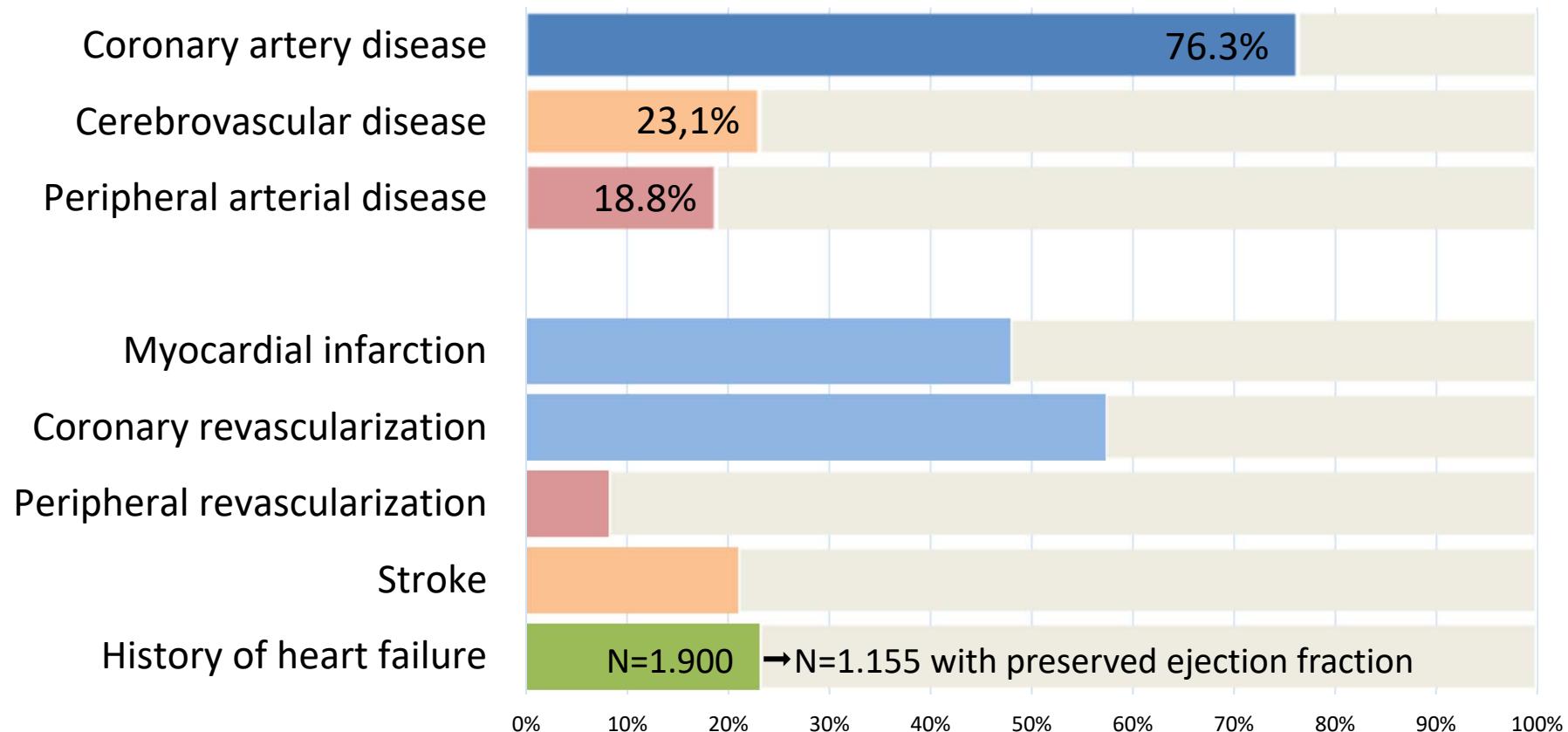


# **VERTIS CV** Adults With T2DM and established CVD

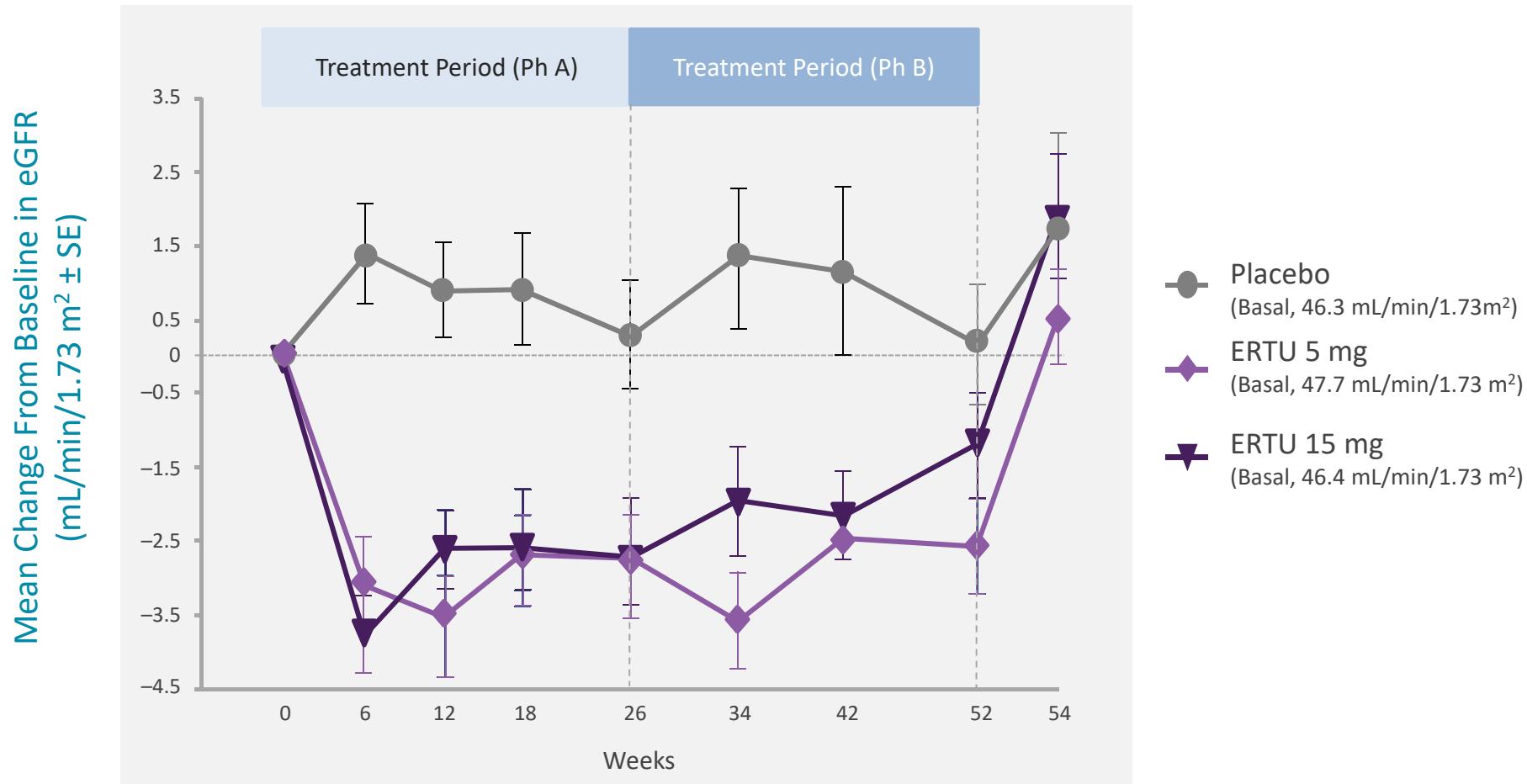


# VERTIS CV Adults With T2DM and established CVD

## History of Cardiovascular Disease



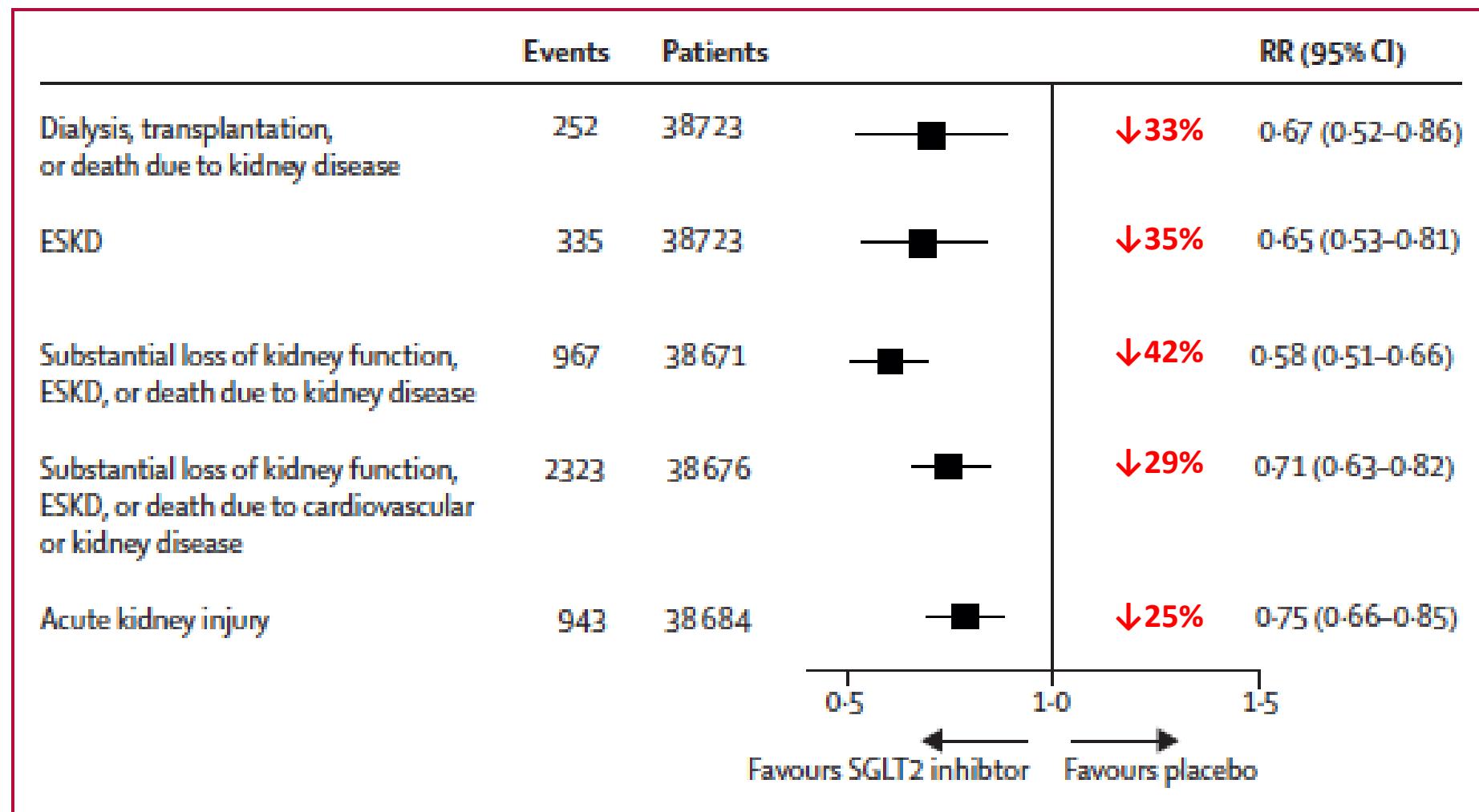
# VERTIS RENAL Adults With T2DM and Stage 3 CKD

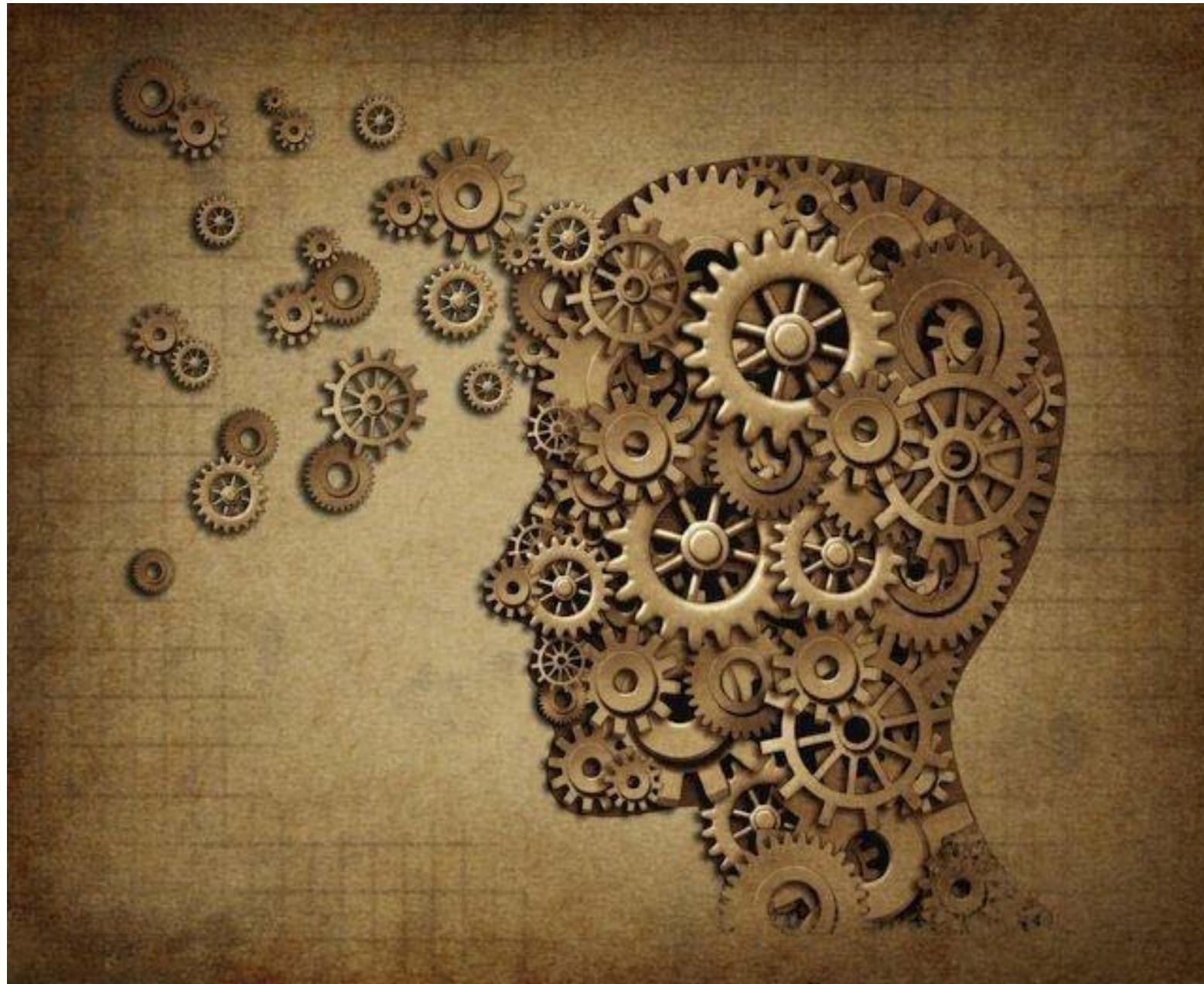


# SGLT2 inhibitors for the prevention of kidney failure in patients with type 2 diabetes: a systematic review and meta-analysis

|   | EMPA-REG<br>OUTCOME | CANVAS<br>Program | DECLARE-TIMI 58   | CREDENCE                  |
|---|---------------------|-------------------|---|---------------------------|
| Drug  | Empagliflozin       | Canagliflozin     | Dapagliflozin   | Canagliflozin             |
| Dose (mg)   | 10 and 25           | 100 and 300       | 10  | 100                       |
| Number of participants                                    | 7020                | 10 142            | 17 160  | 4401                      |
| Mean age (years)  | 63.1                | 63.3              | 63.9  | 63.0                      |
| Sex   |                     |                   |   |                           |
| Men   | 5016 (71.5%)        | 6509 (64.2%)      | 10738 (62.6%)   | 2907 (66.1%)              |
| Women   | 2004 (28.5%)        | 3633 (35.8%)      | 6422 (37.4%)  | 1494 (33.9%)              |
| Median follow-up (years)                                  | 3.1                 | 2.4               | 4.2   | 2.6*                      |
| eGFR inclusion criteria                                   | $\geq 30$ (MDRD)    | $\geq 30$ (MDRD)  | $\text{CrCl} \geq 60 \text{ mL/min}$<br>(Cockcroft-Gault) | 30 to $< 90$<br>(CKD-EPI) |
| Baseline eGFR subgroup (mL/min per $1.73 \text{ m}^2$ )†‡ |                     |                   |   |                           |
| $\geq 90$   | 1538 (21.9%)        | 2476 (24.4%)      | 8162 (47.6%)  | 0                         |
| 60 to $< 90$  | 3661 (52.2%)        | 5625 (55.5%)      | 7732 (45.1%)  | 1809 (41.1%)              |
| 45 to $< 60$  | 1249 (17.8%)        | 1485 (14.6%)      | 1265 (7.4%)§  | 1279 (29.1%)              |
| $< 45$  | 570 (8.1%)          | 554 (5.5%)        | NA  | 1313 (29.8%)              |
| Missing baseline eGFR                                     | 2 (<0.1%)           | 2 (<0.1%)         | 1 (<0.1%)   | 0                         |
| UACR criteria (mg/g)                                      | None                | None              | None  | >300 to 5000              |
| Baseline UACR subgroup (mg/g)‡                            |                     |                   |   |                           |
| <30   | 4171 (59.4%)        | 7007 (69.1%)      | 11 644 (67.9%)  | 0                         |
| 30–300  | 2013 (28.7%)        | 2266 (22.3%)      | 4030 (23.5%)  | 0                         |
| >300  | 769 (11.0%)         | 760 (7.5%)        | 1169 (6.8%)   | 4401 (100.0%)             |
| Missing baseline UACR                                     | 67 (1.0%)           | 109 (1.1%)        | 317 (1.8%)  | 0                         |
| Baseline use of RAS blockade                              | 5666 (80.7%)        | 8116 (80.0%)      | 13 950 (81.3%)  | 4395 (99.9%)              |

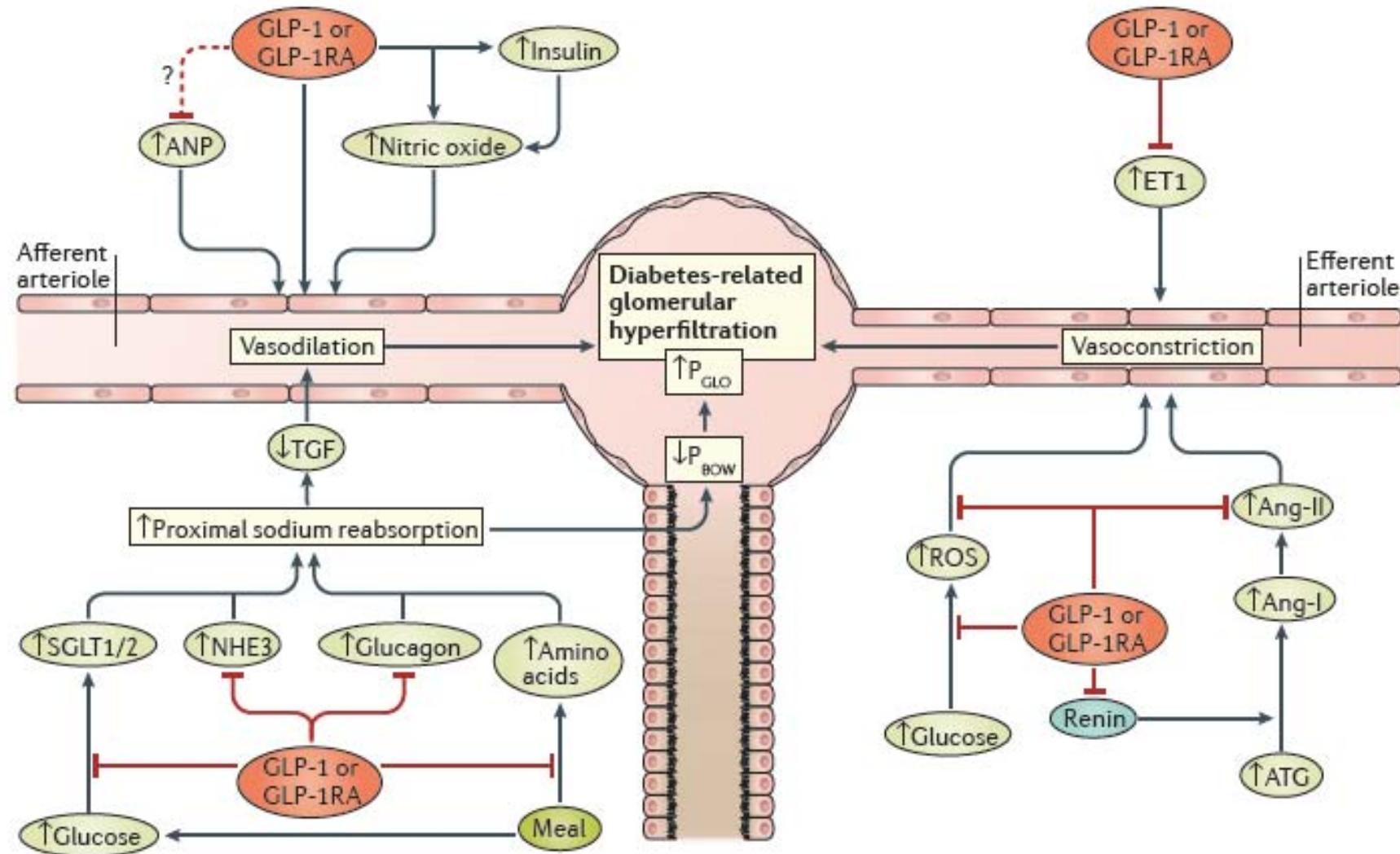
# SGLT2 inhibitors for the prevention of kidney failure in patients with type 2 diabetes: a systematic review and meta-analysis



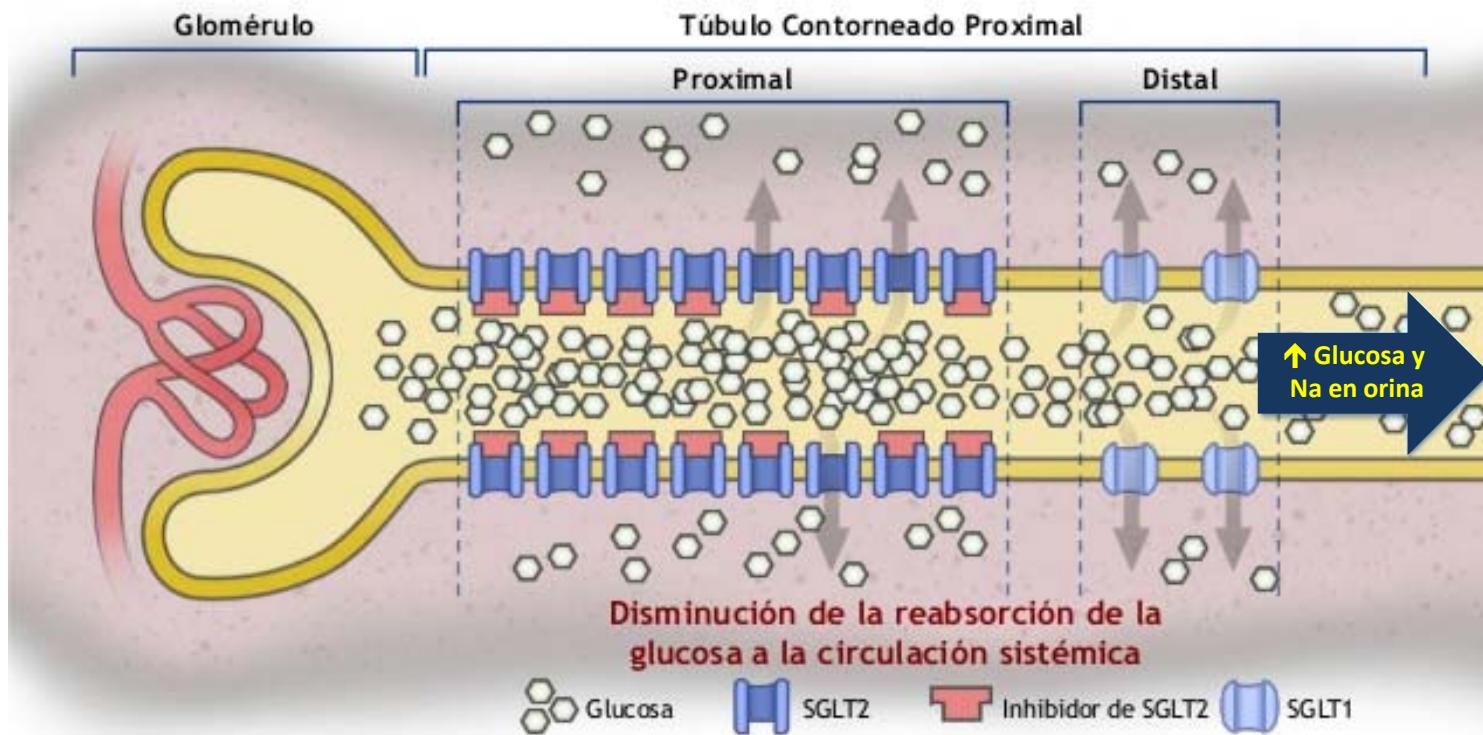


# Mecanismos nefro-protectores de los arGLP1

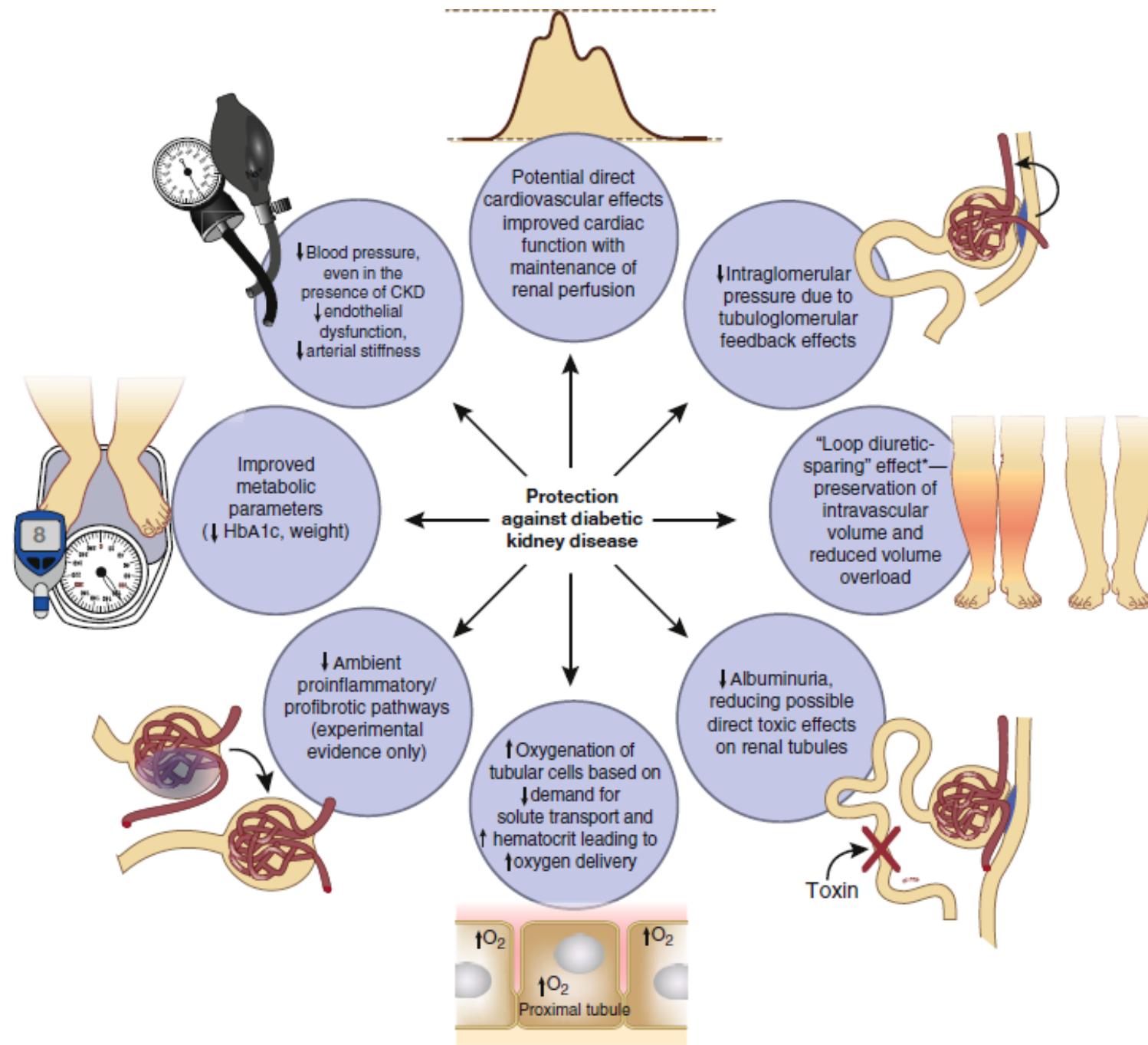
## Disminución hipertensión Intraglomerular



## Mecanismo de acción de SGLT2



**Clinical findings**  
↓ Plasma glucose  
↓ Body weight  
↓ Blood pressure  
↓ Plasma uric acid

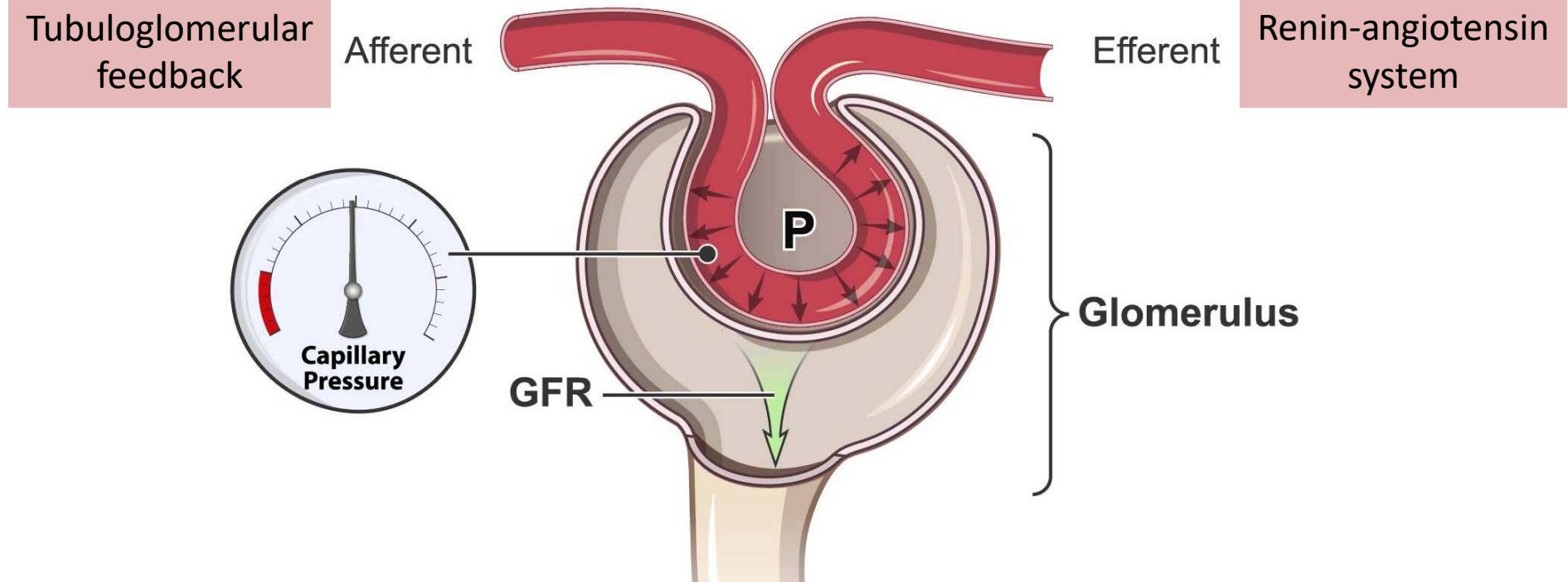


# Renoprotective effects of SGLT2i

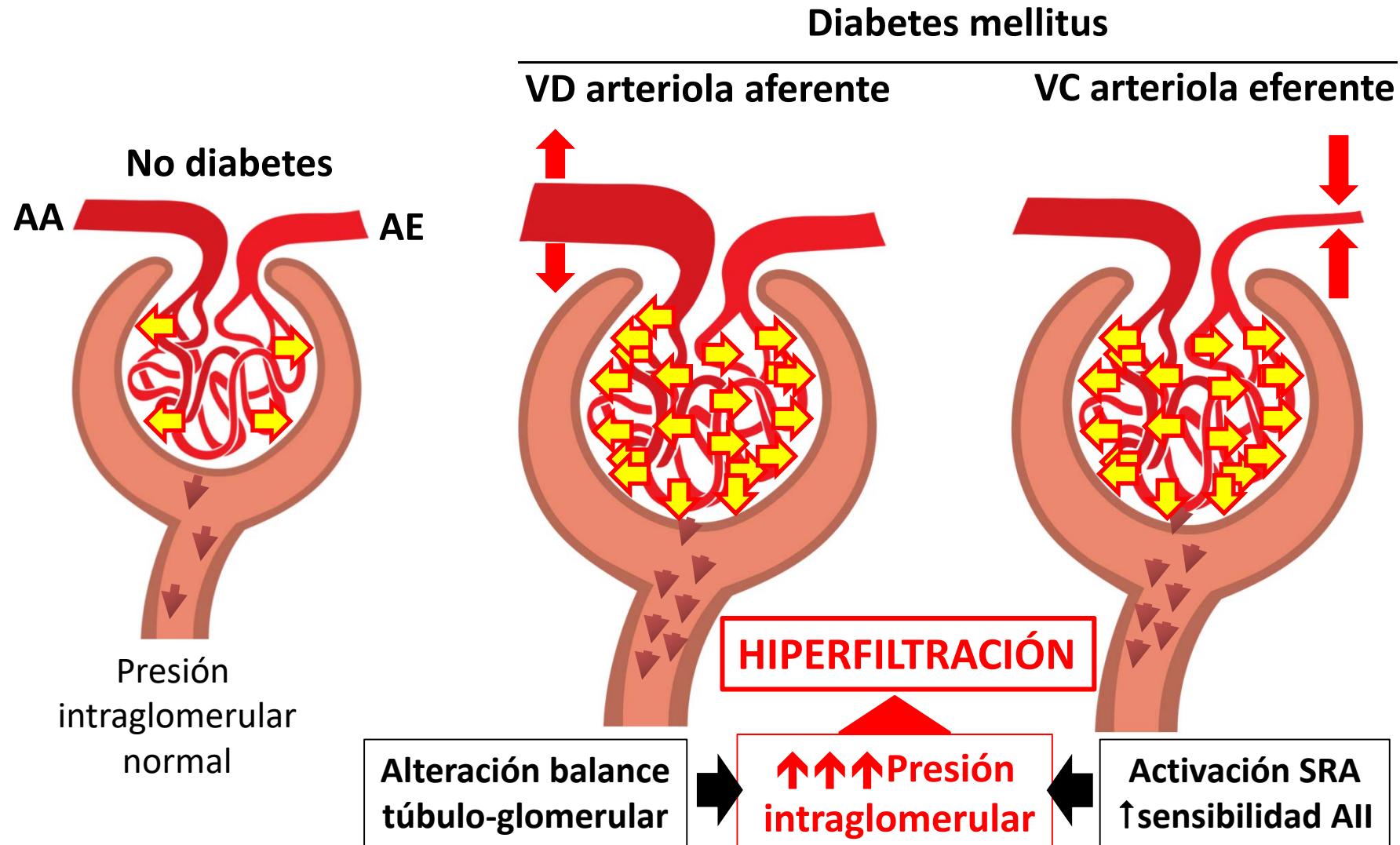
## Intraglomerular hemodynamics



Vasodilation / Vasoconstriction  
of glomerular arterioles

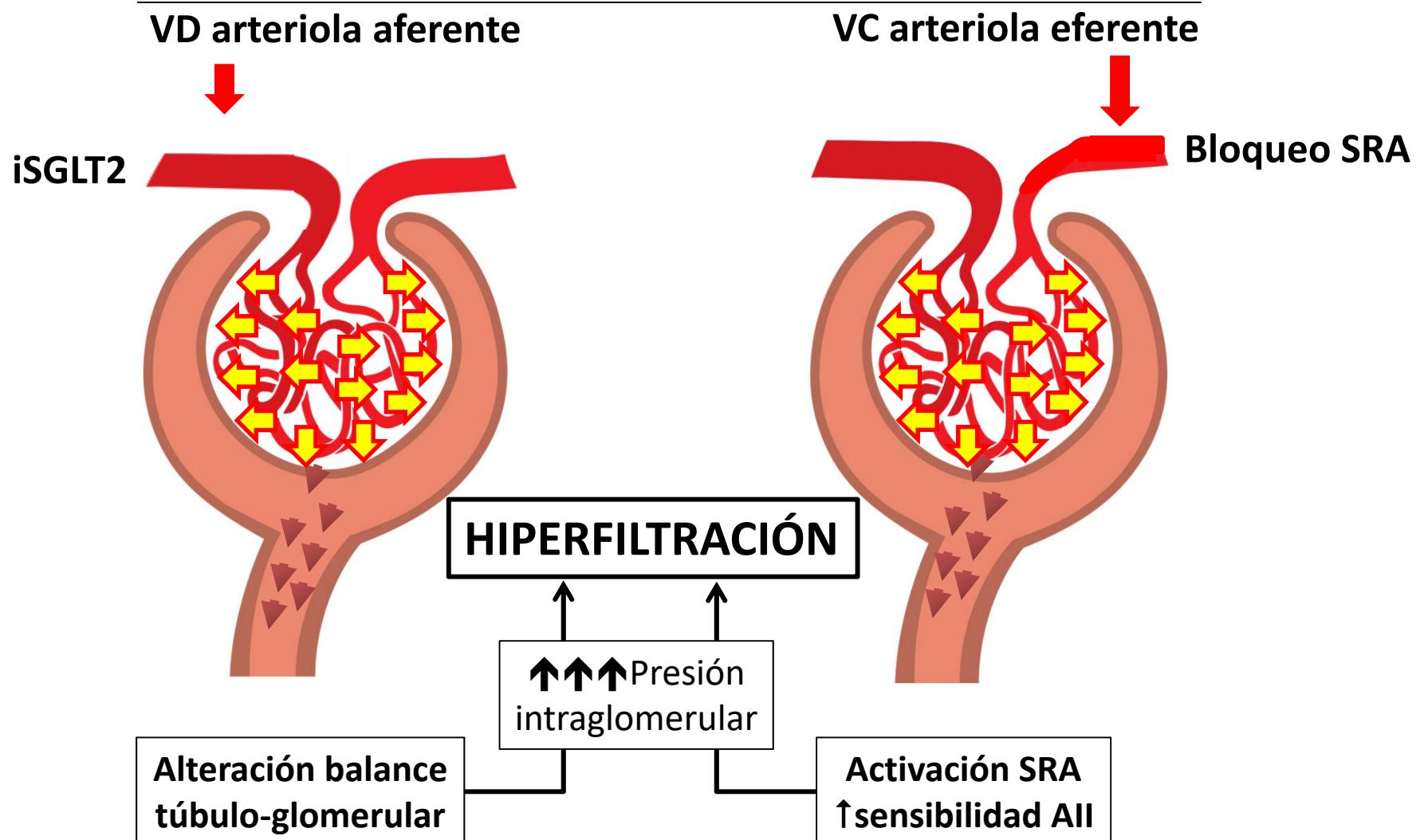


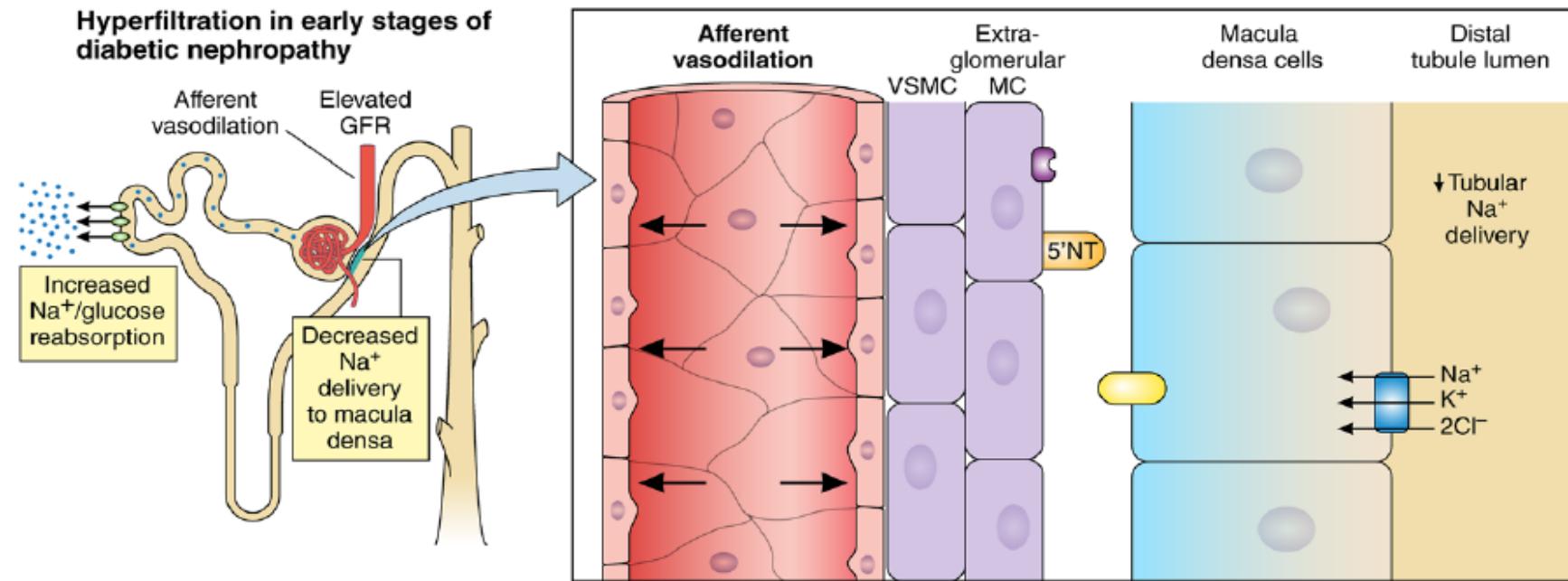
# Hemodinámica intraglomerular



# Hemodinámica intraglomerular en la DM

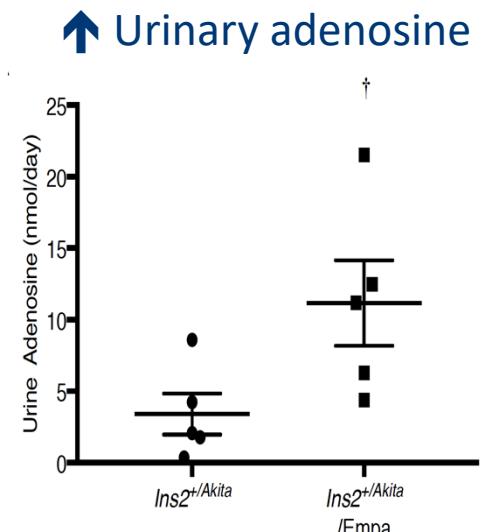
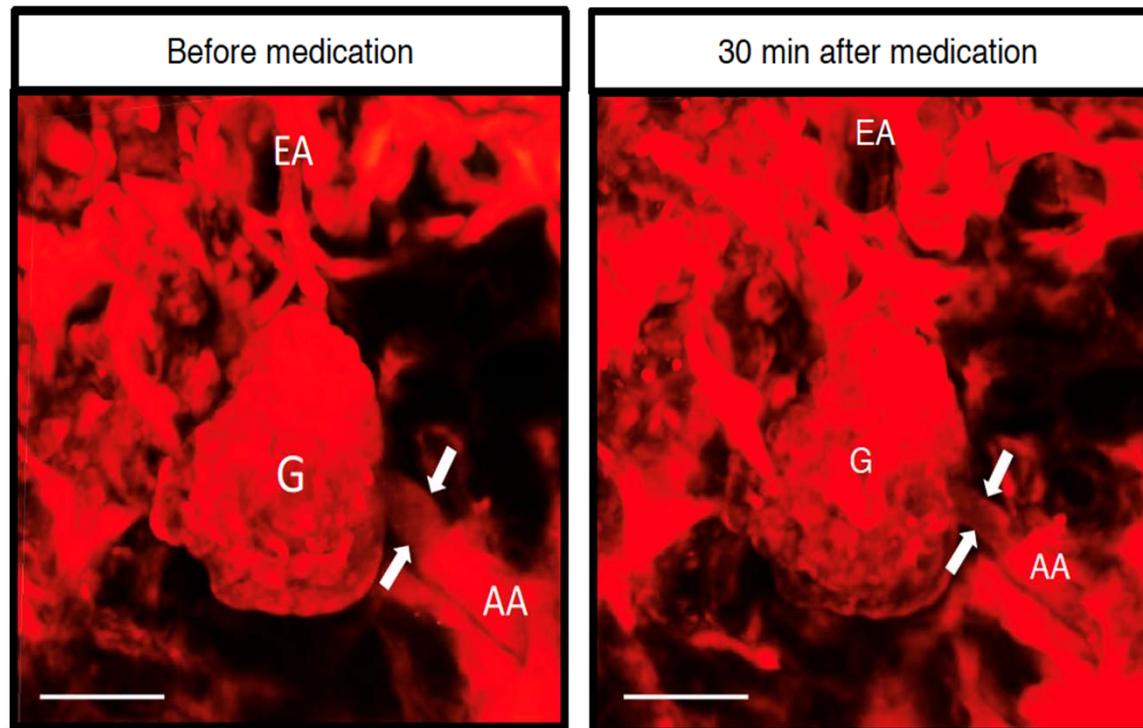
## Abordaje terapéutico



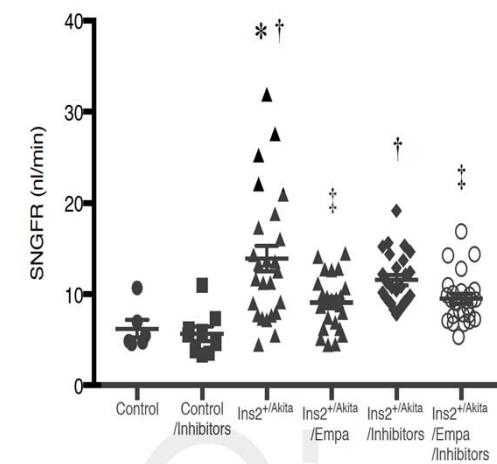


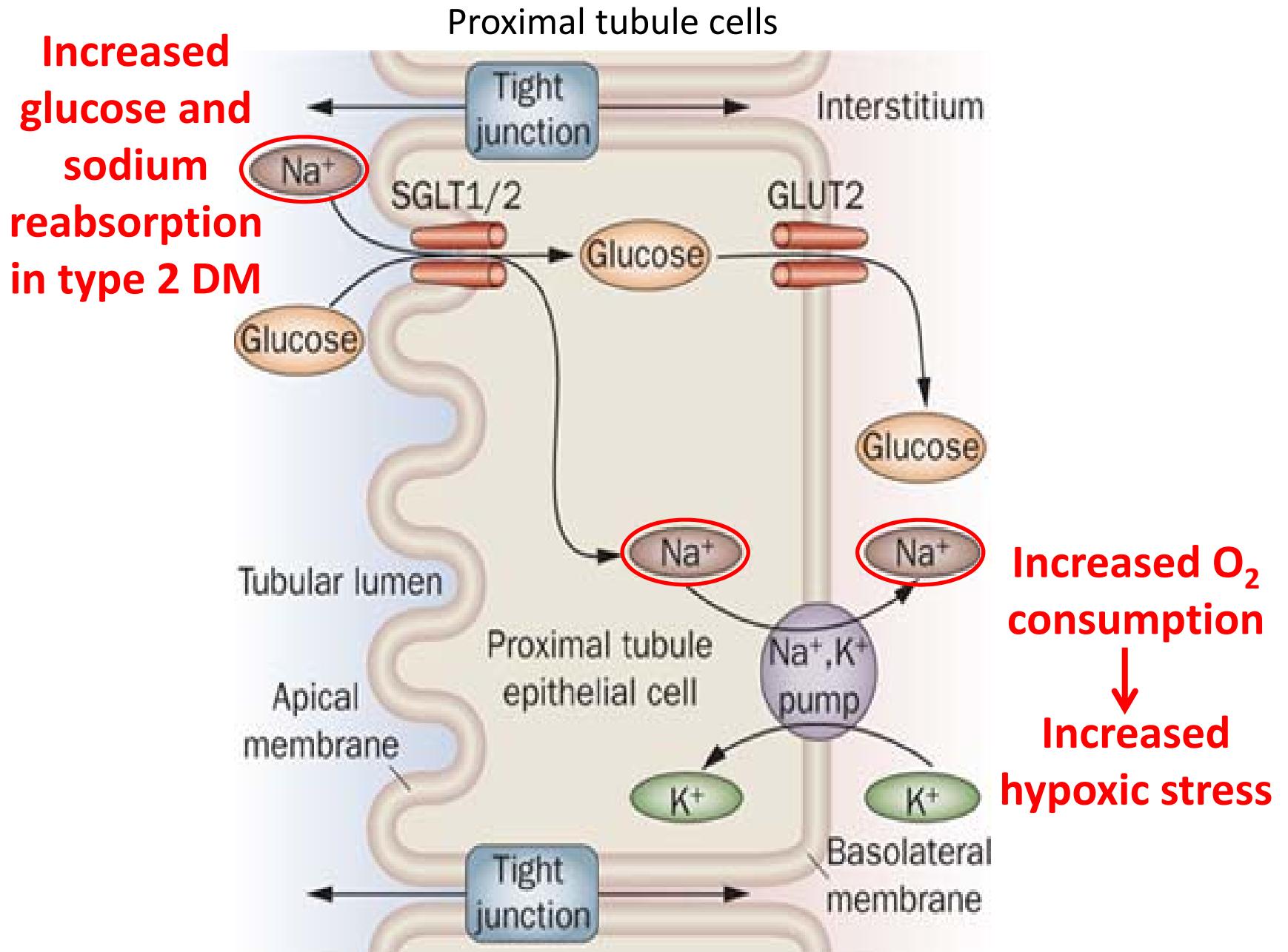
# SGLT2i constricts afferent arteriole mediated by adenosine

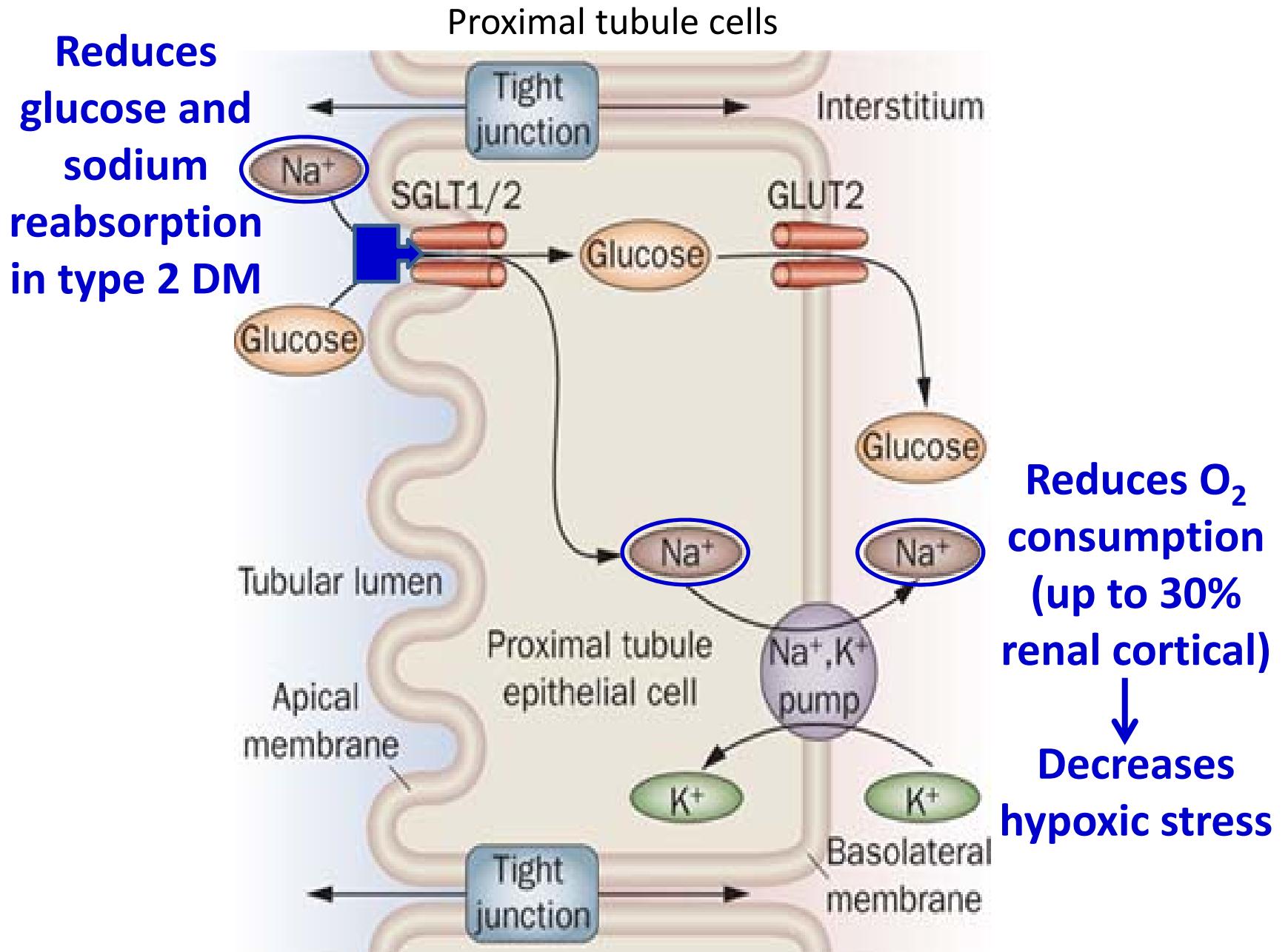
*In vivo* imaging of AA change before and after empagliflozin



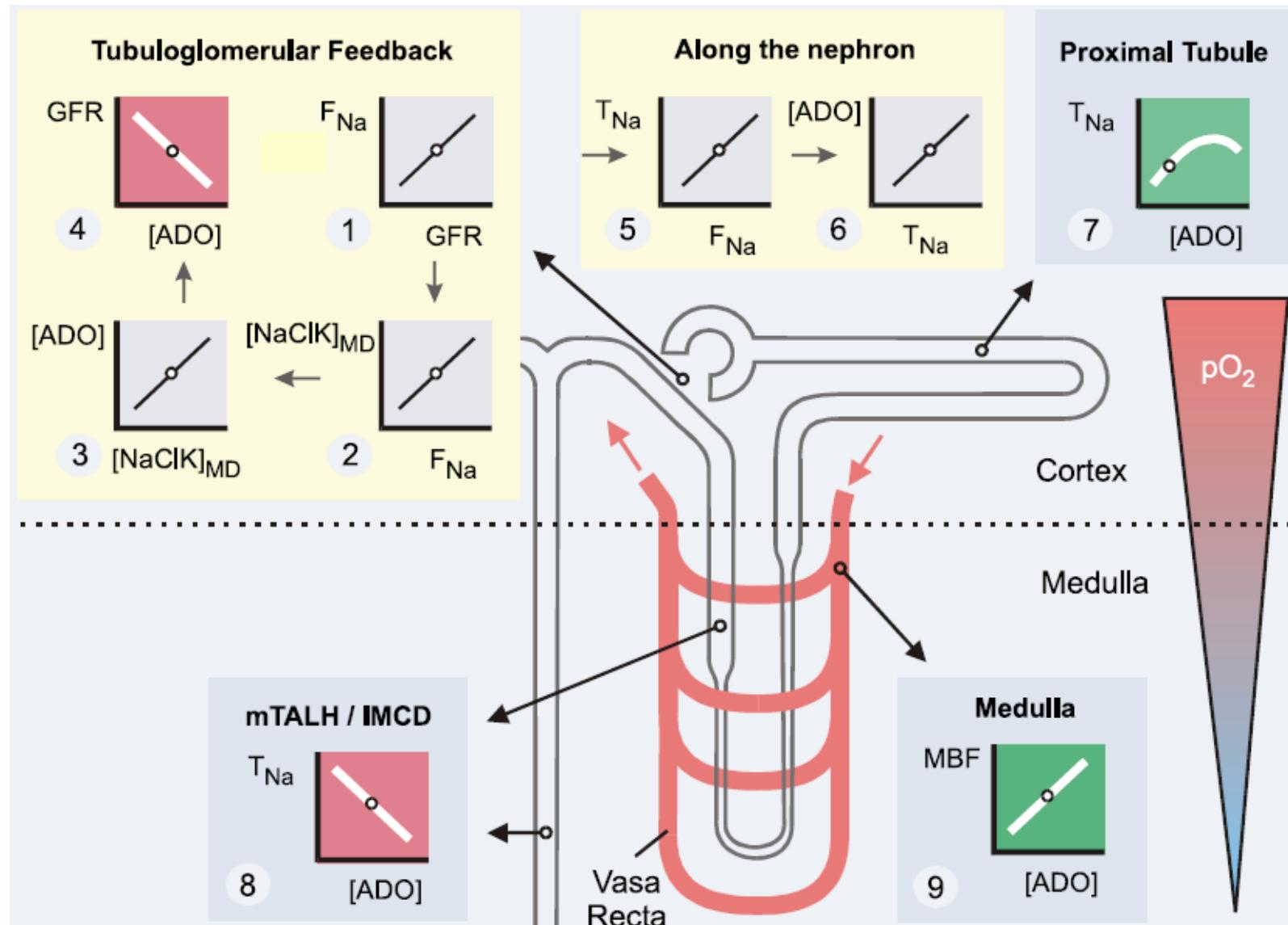
Adenosine antagonist



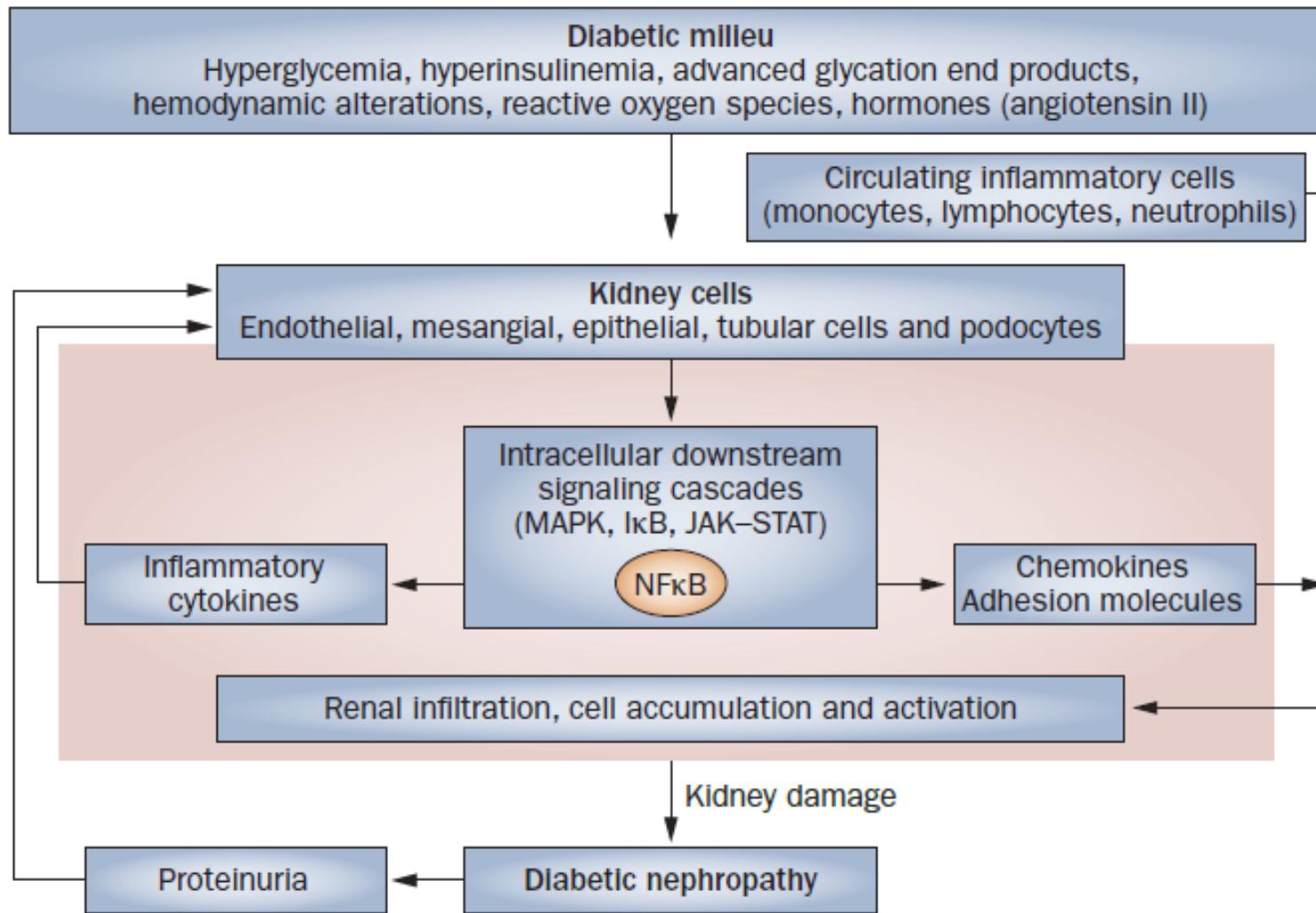


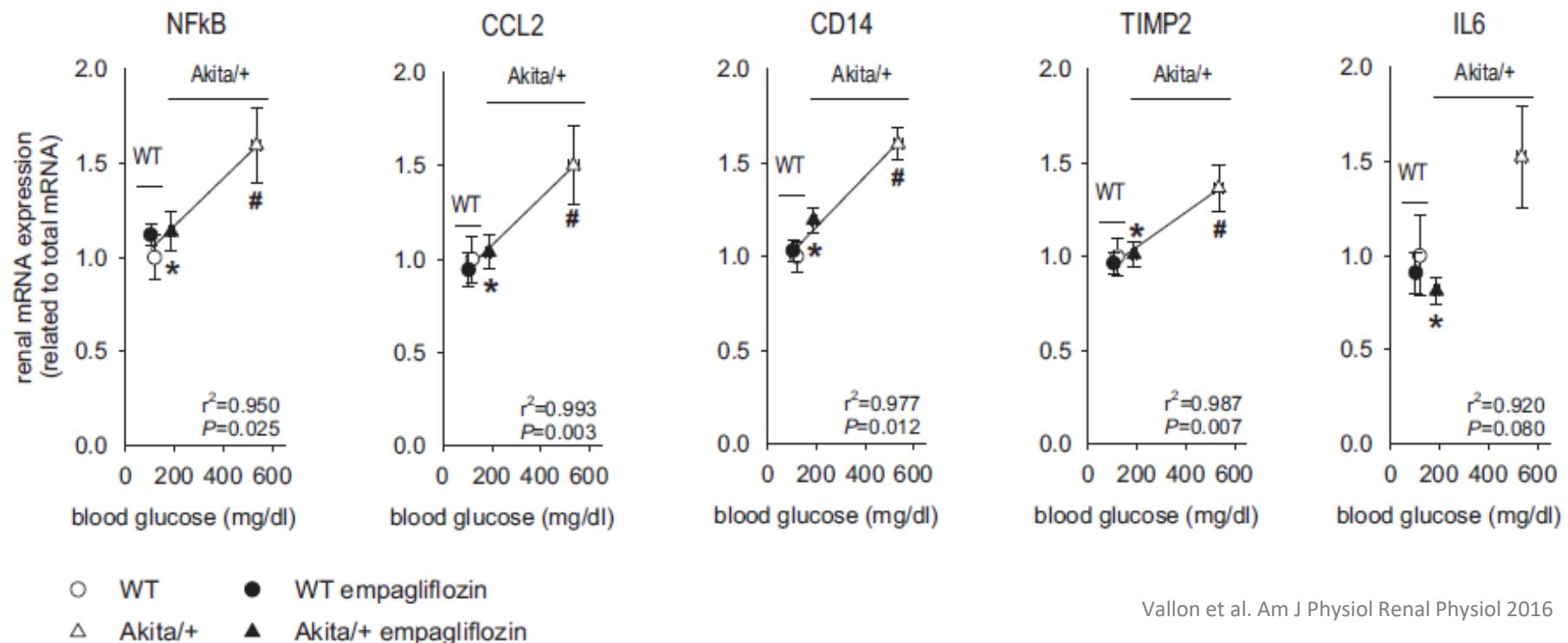


# Adenosin and hypoxic stress in the kidney

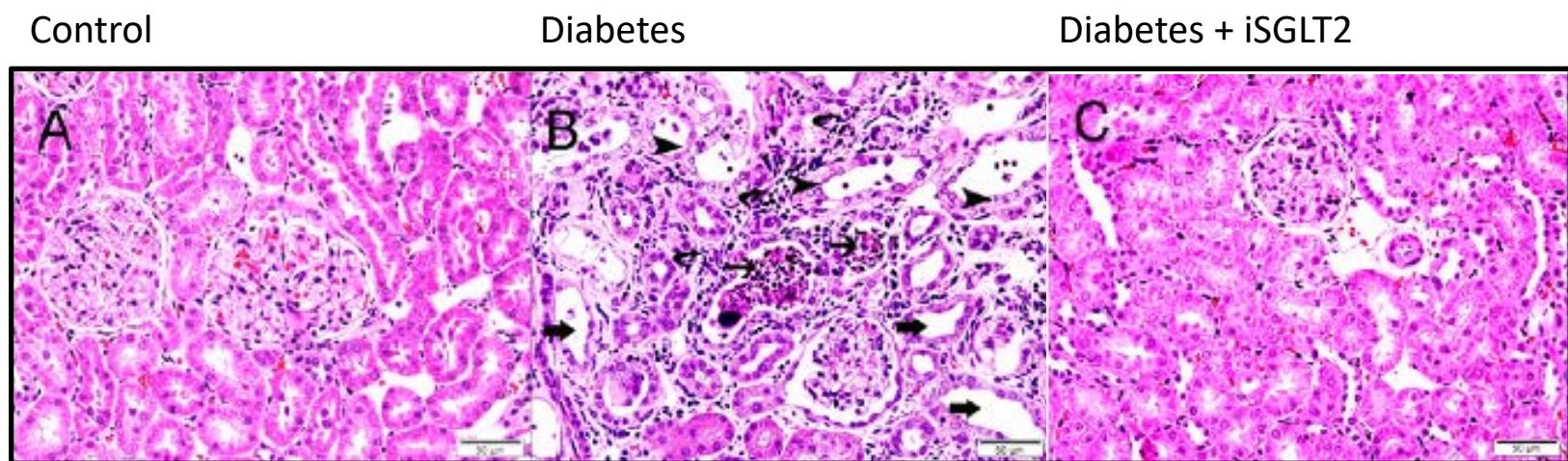


# Inflammation in Diabetic Kidney Disease





Vallon et al. Am J Physiol Renal Physiol 2016



Ali BH et al. Cell Physiol Chem 2019

Received: 21 January 2018 | Revised: 9 March 2018 | Accepted: 20 March 2018

DOI: 10.1111/dom.13301

WILEY

**BRIEF REPORT**

## Effects of the SGLT-2 inhibitor dapagliflozin on glomerular and tubular injury markers

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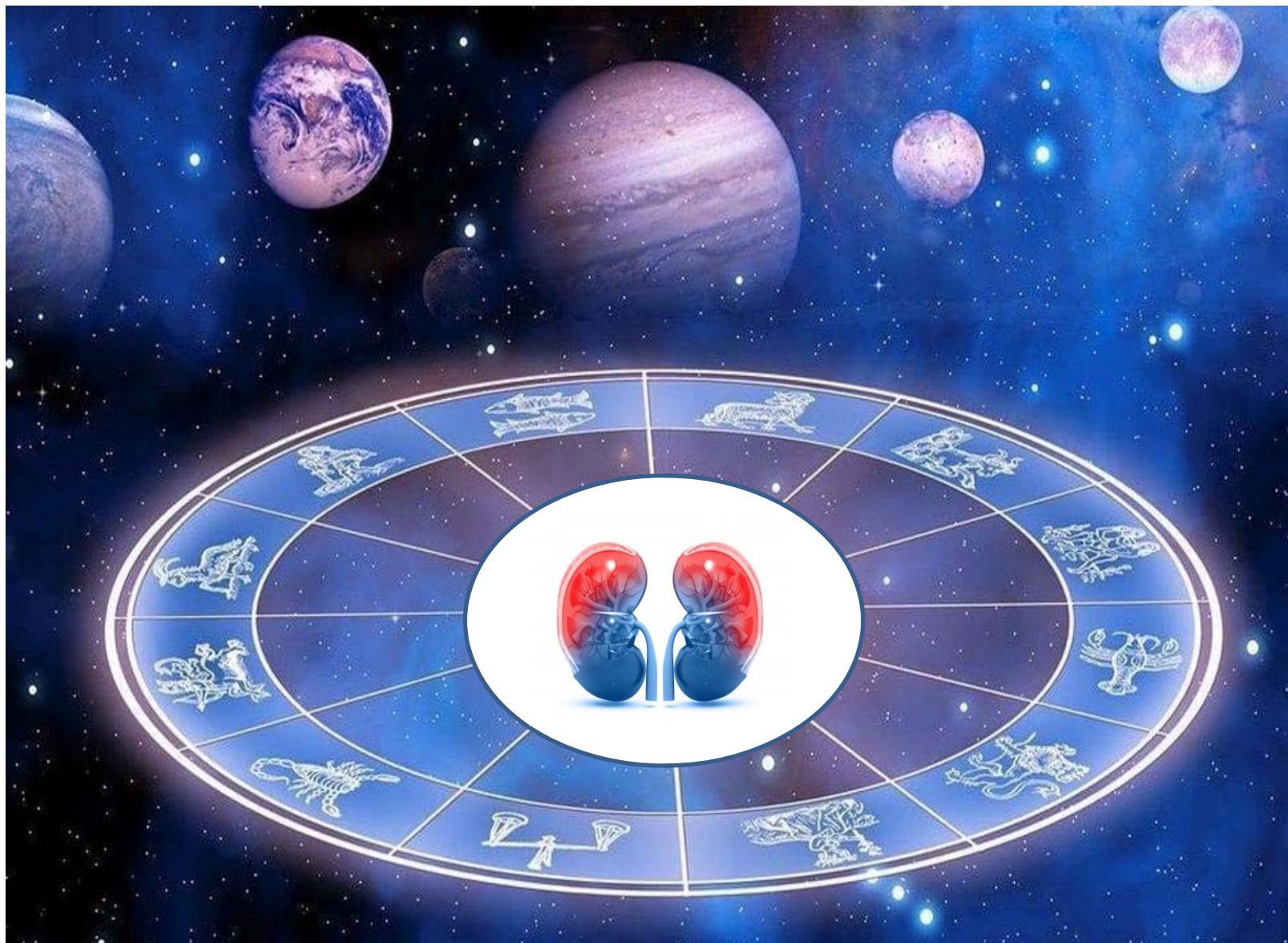
## Effects of sodium-glucose cotransporter 2 inhibitor, tofogliflozin, on the indices of renal tubular function in patients with type 2 diabetes

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**“NADA SUCEDE HASTA  
QUE ALGO SE MUEVE”**

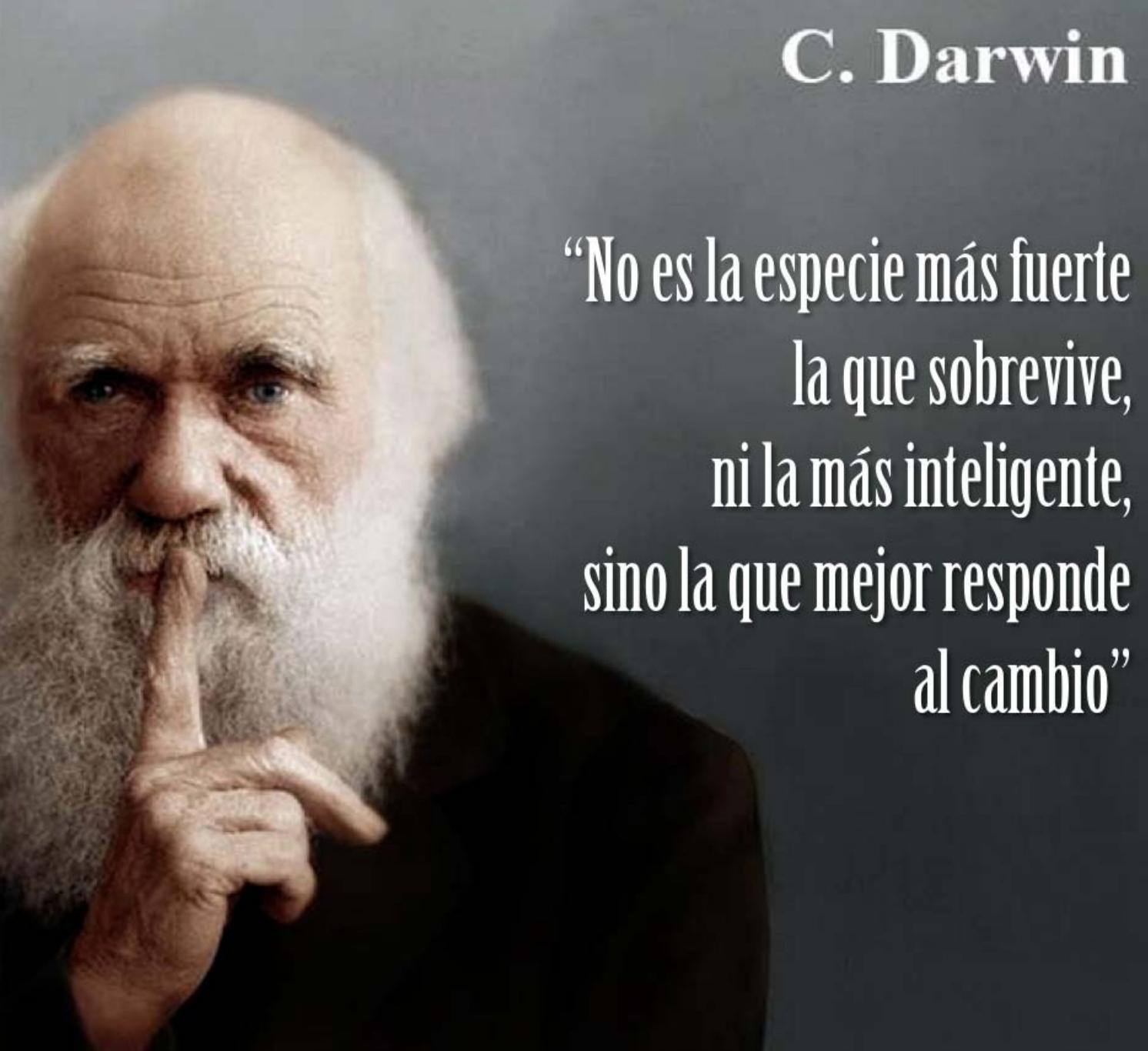
ALBERT EINSTEIN



# **SGLT2i and GLP1ra**

## **A new avenue to renal protection in type 2 diabetes**



A portrait of Charles Darwin, an elderly man with a full white beard and receding hairline, looking slightly to the side with a thoughtful expression. He is holding his index finger to his lips, suggesting silence or contemplation. The background is a soft, out-of-focus grey.

C. Darwin

“No es la especie más fuerte  
la que sobrevive,  
ni la más inteligente,  
sino la que mejor responde  
al cambio”

The future  
is always beginning



Marc Strand



*Deberíamos tratar de ser  
los padres de nuestro  
futuro en lugar de los  
descendientes de nuestro  
pasado.*

*Miguel de Unamuno*