

SGLT2-inhibitors in chronic kidney disease

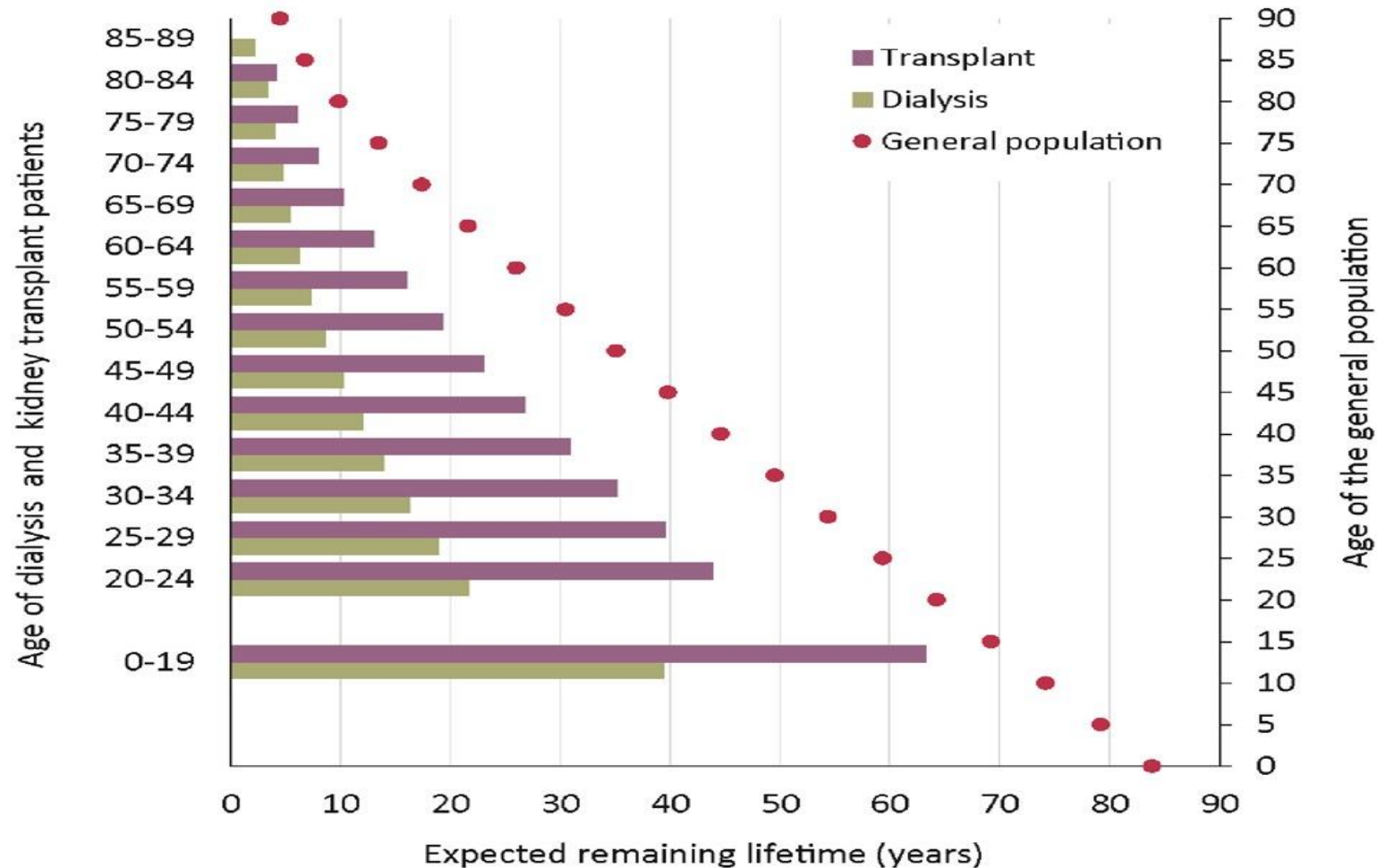
Ágnes Haris MD PhD

Péterfy Hospital, Department of Internal Medicine and Nephrology

Budapest

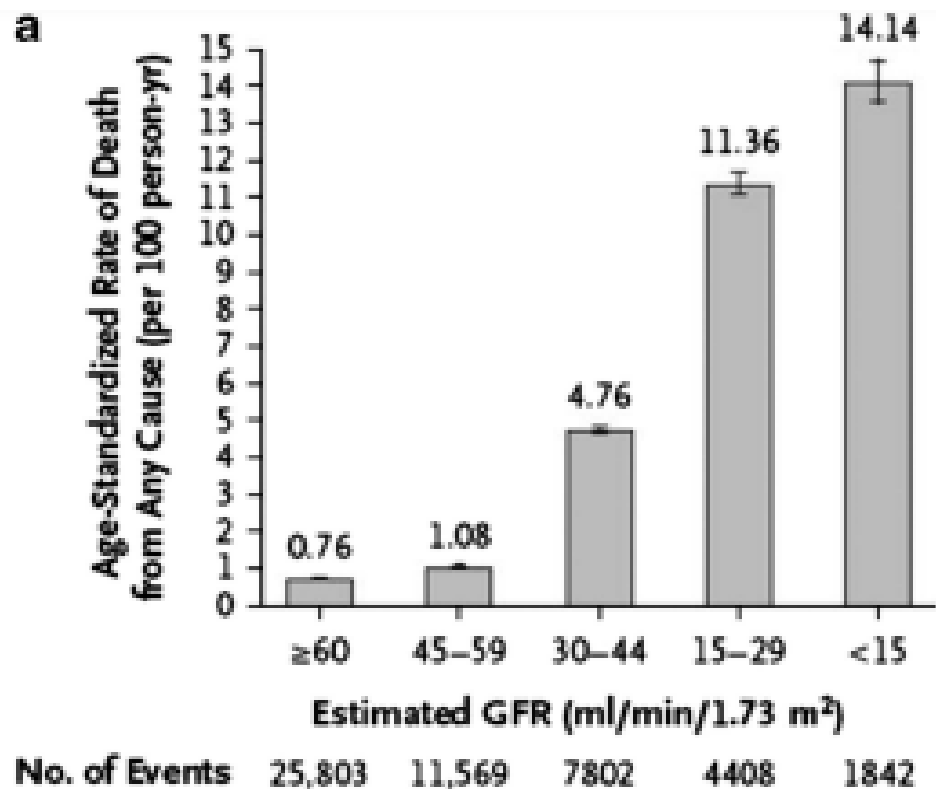
Budapest Nephrology School, 2023.

Expected remaining lifetime: general population, transplanted patients, dialysed patients

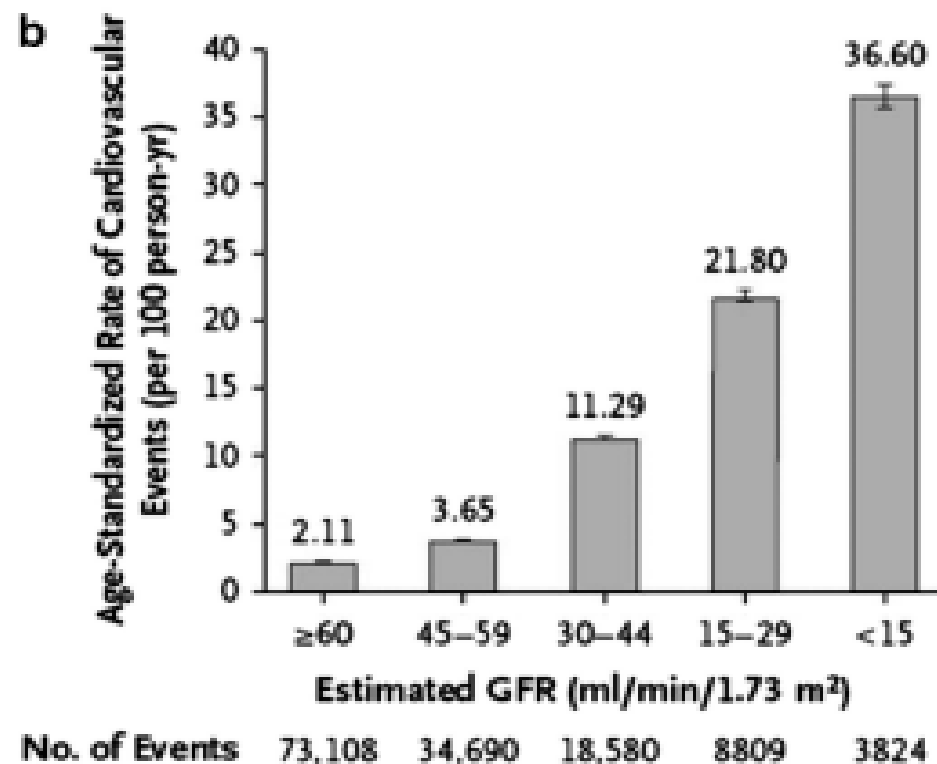


Rate of death according to eGFR

All cause mortality

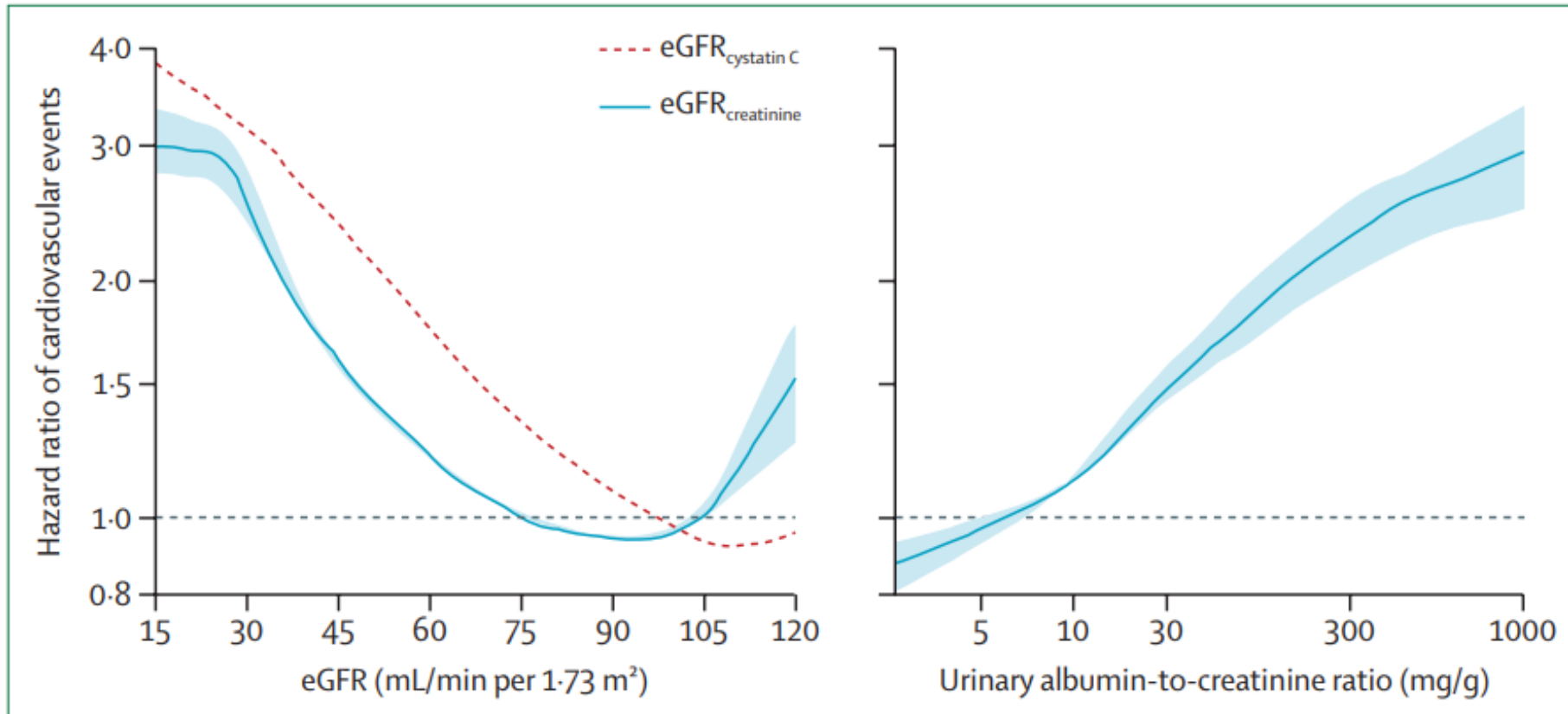


Cardiovascular mortality

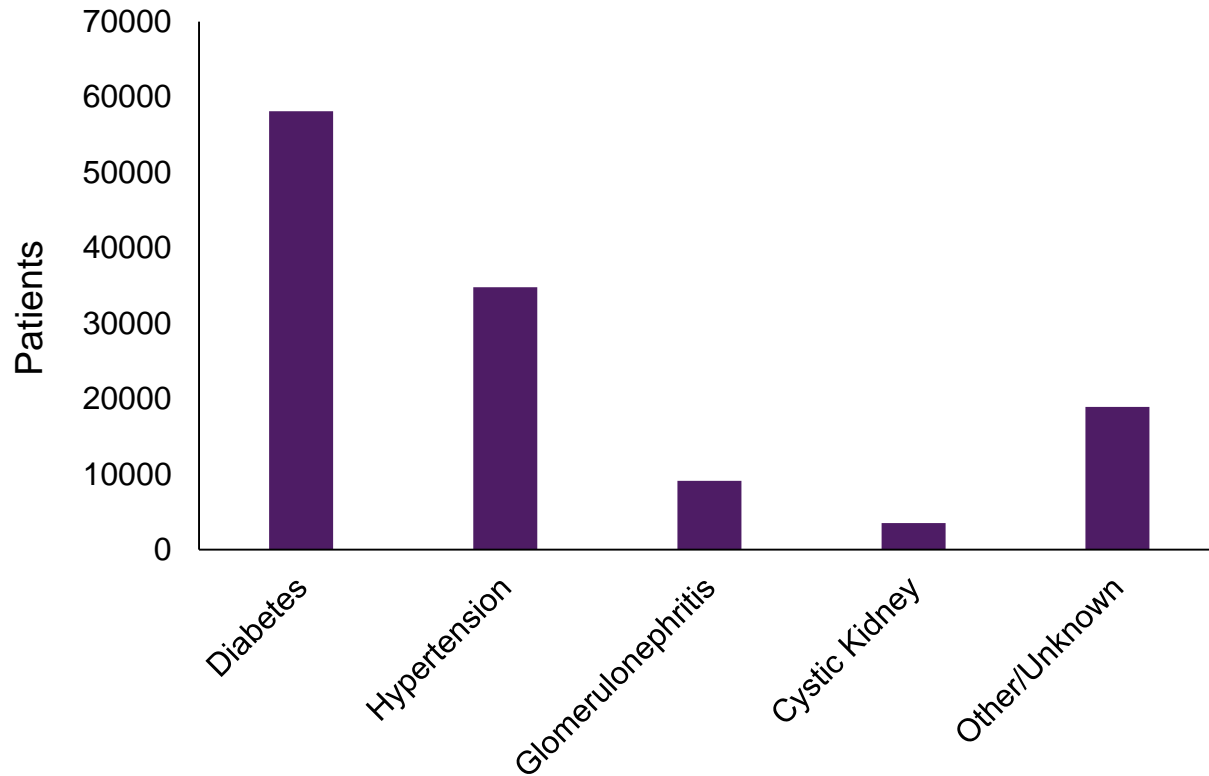


Association of eGFR and albuminuria with hazard ratio of cardiovascular events

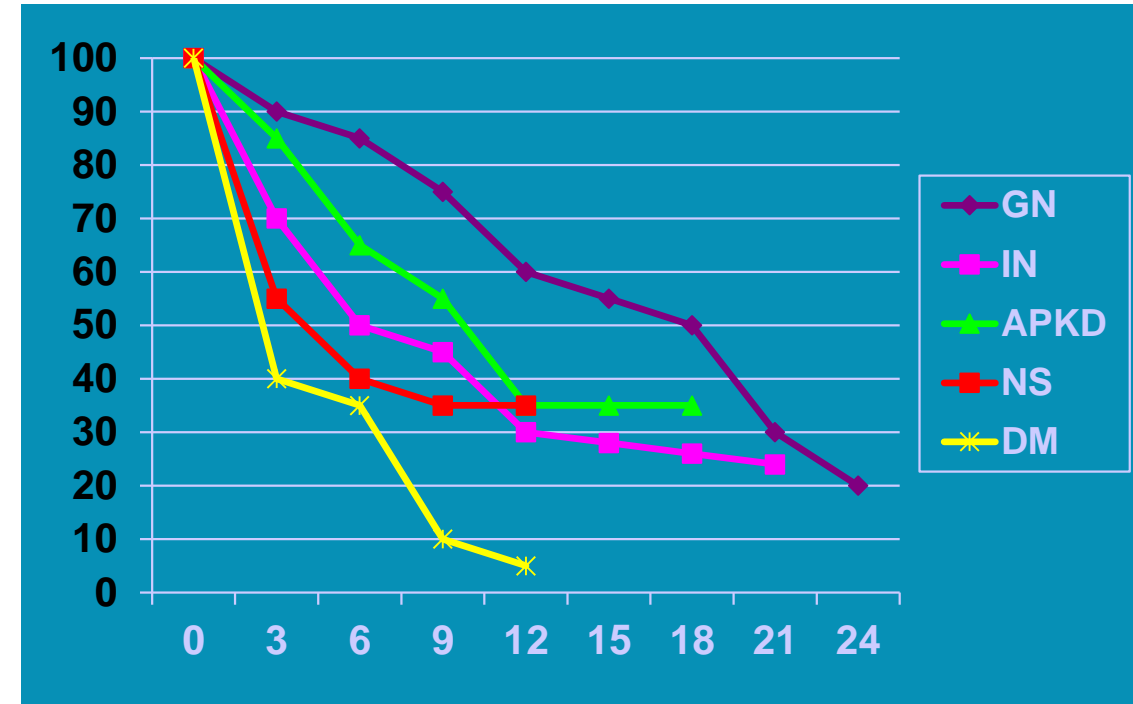
Kalantar-Zadeh et al. Lancet 2021; 398: 786–802



Etiology of CKD



Progression without intervention



HEART FAILURE AND DIABETES IN CHRONIC KIDNEY DISEASE

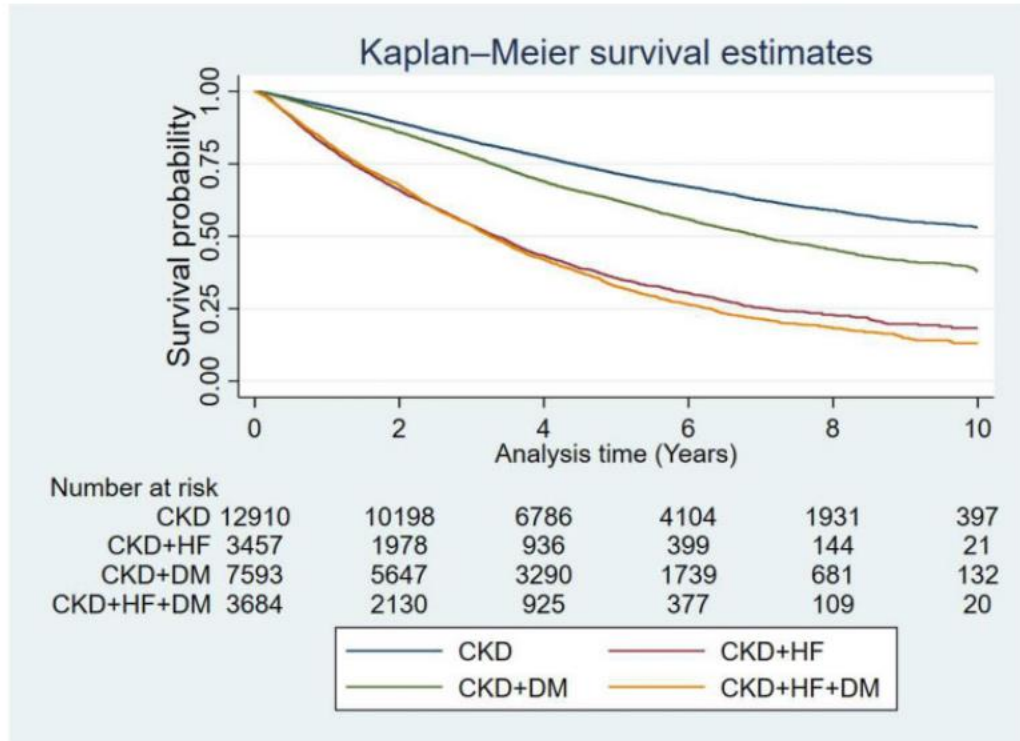
Österman J et al. ERA Congress 2023, abstract

HR

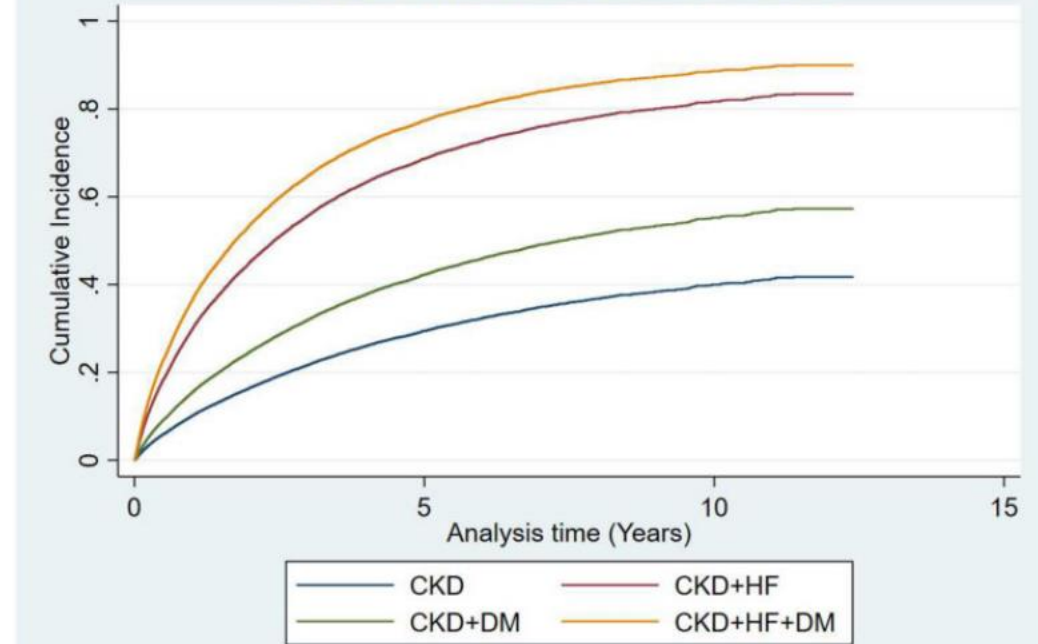
3,22

2,54

1,53



Cumulative incidence curve MACE



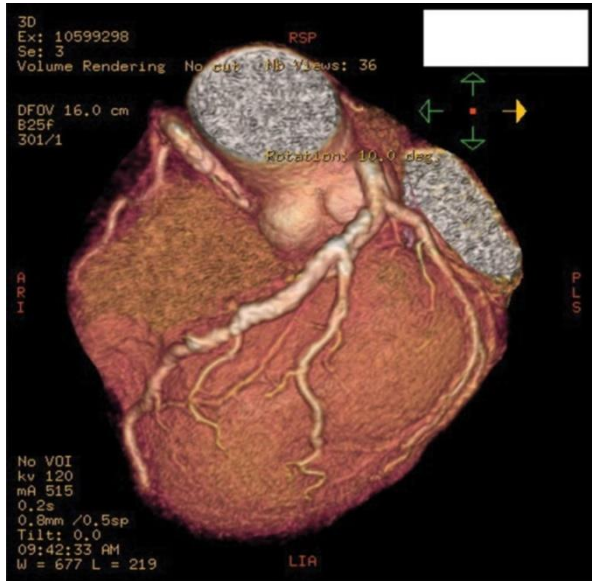
HR

4,82

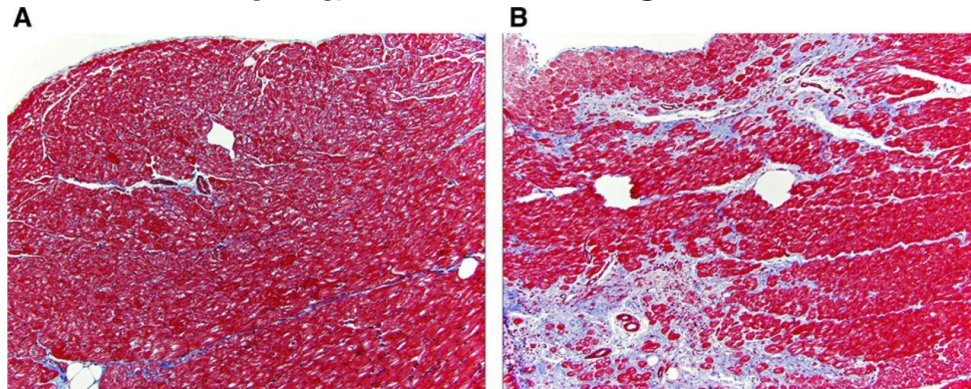
3,82

1,63

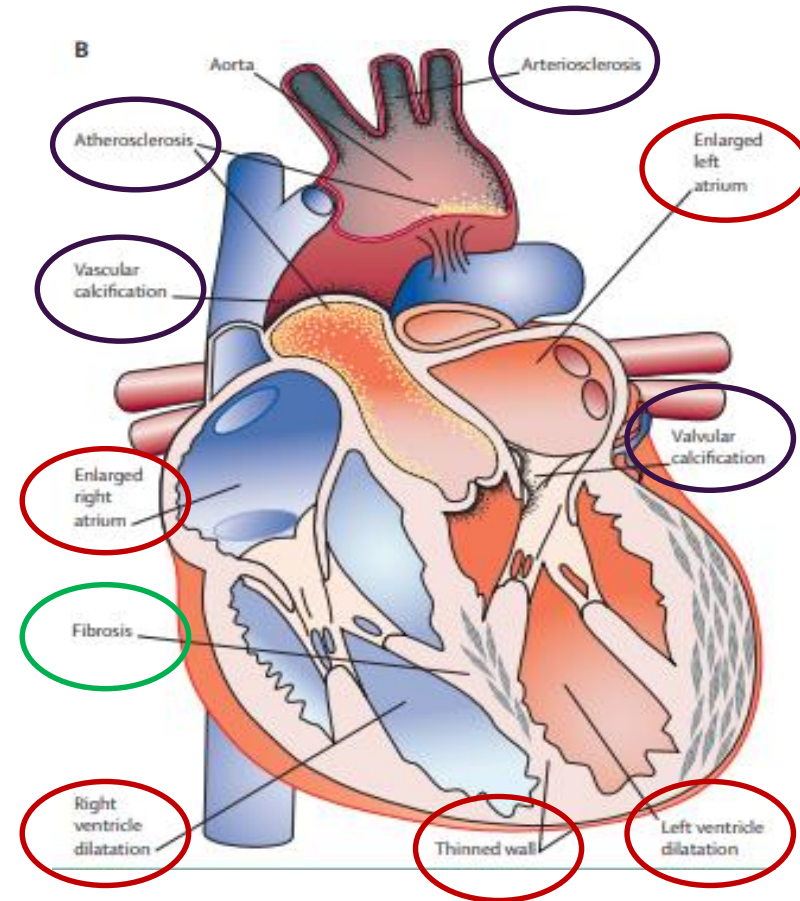
CKD: severe micro- and macrovascular lesions in the heart



Myocardial histology:
Normal in CKD



Tonelli M et al. Circulation. 2016;133:518



Wanner C et al. Lancet 2016. 388:276

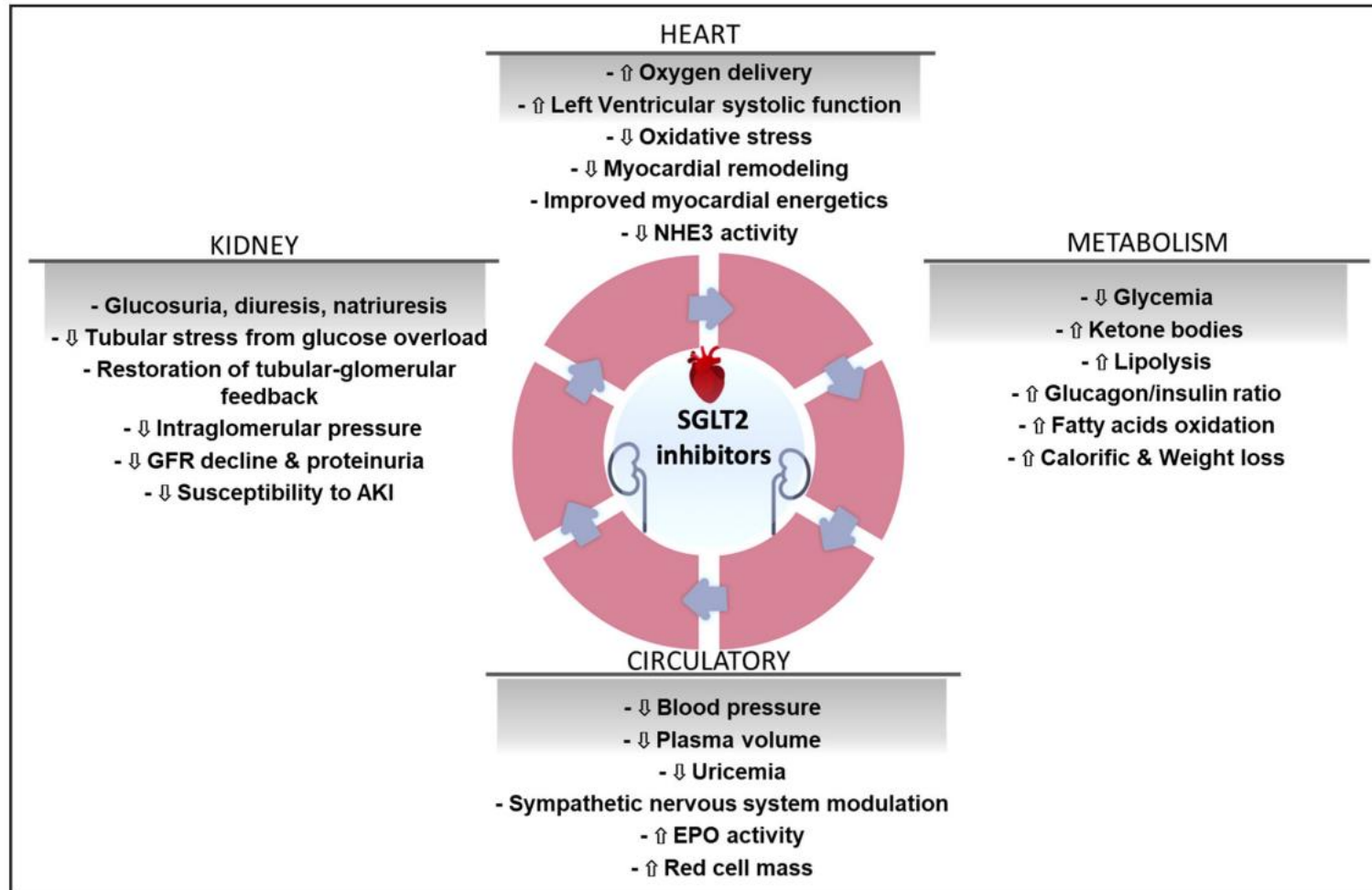
SGLT2i – The Sodium-glucose cotransporter 2 inhibitors

Beginning of the story of SGLT2 inhibitors

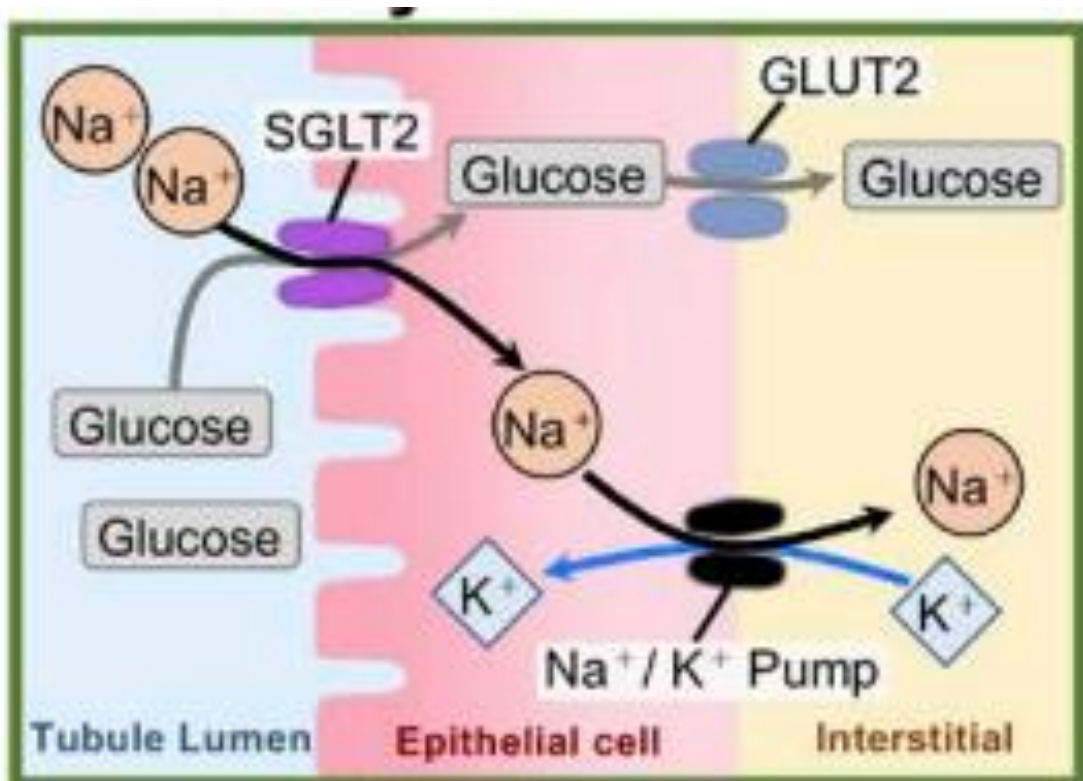
- Phlorizin was extracted from the bark of apple tree in 1835 as the first „SGLT inhibitor” with glucosuric properties
- In 2008 rosiglitazone, an antidiabetic agent was found to increase CV disease.
- FDA requested all new antidiabetics to be tested for CV effects and demonstrate that the therapy will not result in an unacceptable increase in cardiovascular risk.
- In 2012, three SGLT2i were approved by FDA and EMA:
dapagliflozin, canagliflozin and empagliflozin
- Later ertugliflozin and sotagliflozin

Mechanisms of action of the SGLT2 inhibitors

Protective effects of SGLT2 inhibitors on the metabolism, cardiovascular and renal function



Glucose and sodium reabsorption in the proximal tubular epithelial cells



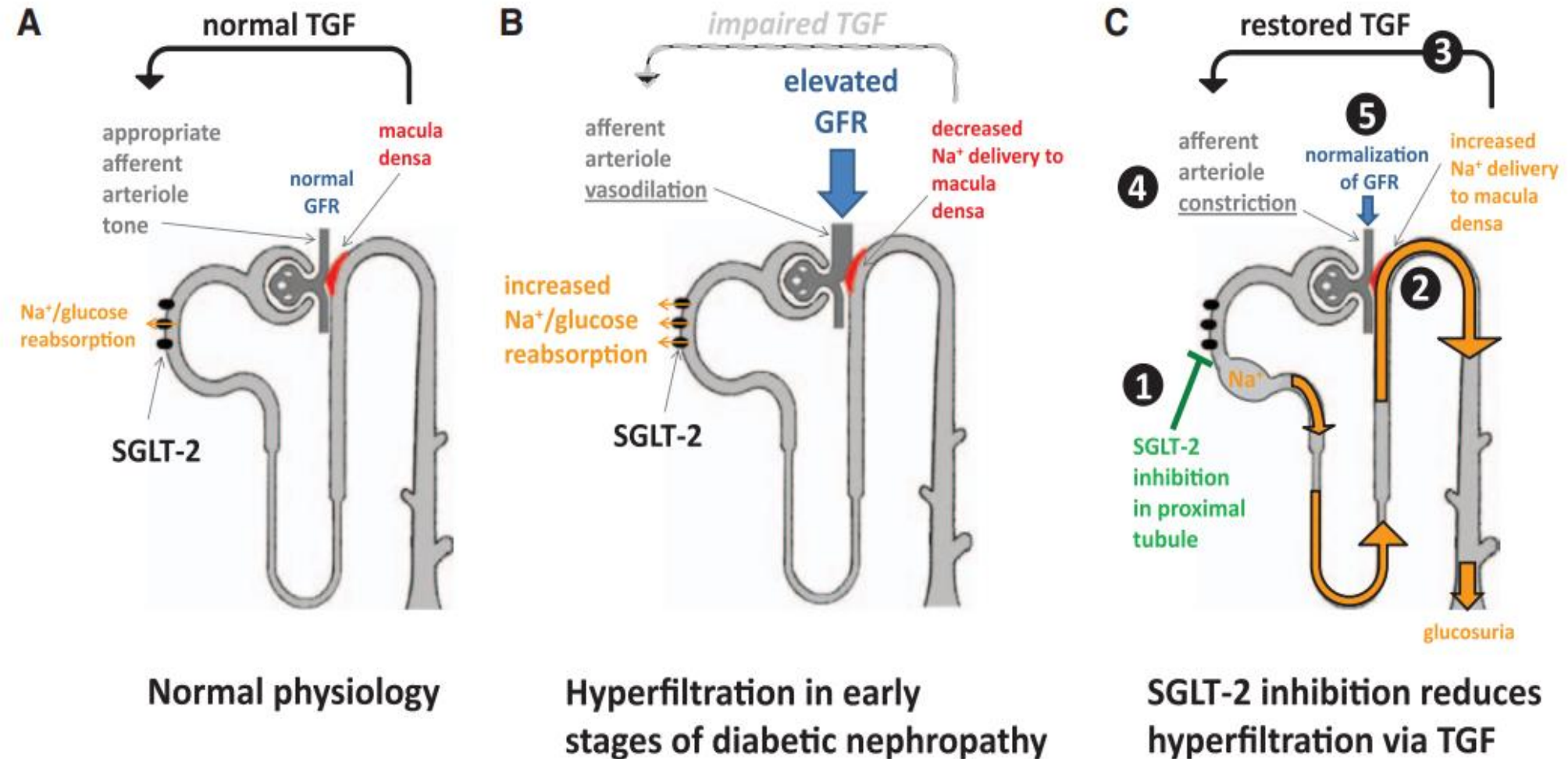
In S1 segment of proximal tubule SGLT2 reabsorbs 90% of filtered glucose (T_{max} ~10 mmol/l) and 65% of sodium

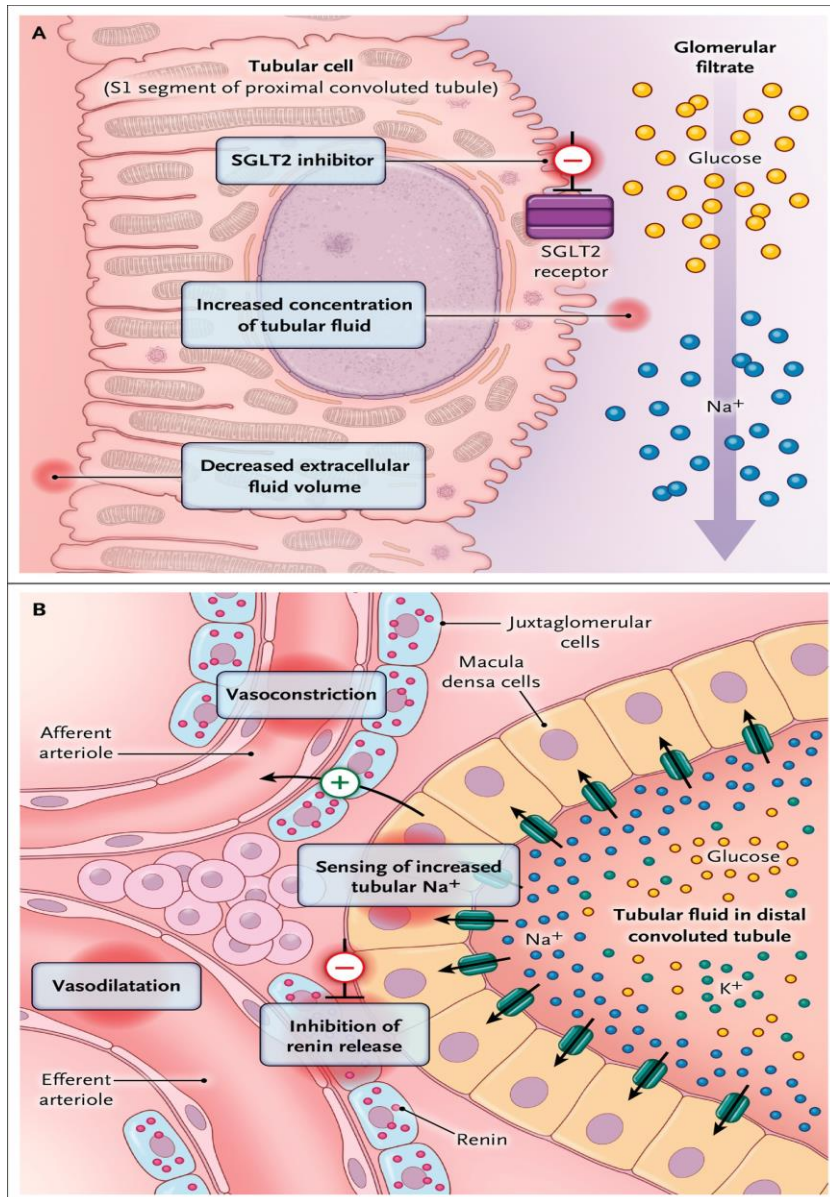
In S2-3 segment SGLT1 reabsorbs the remaining glucose

In diabetes, SGLT overexpression, higher tubular glucose reabsorption + higher Na reabsorption – fluid retention
High oxygen demand in the cortex – less O₂ supply for the medulla

Renal Hemodynamic Effect of Sodium-Glucose Cotransporter 2 Inhibition in Patients With Type 1 Diabetes Mellitus

Cherney et al. Circulation 2014





Effect of SGLT2 inhibition in the glomeruli

Increased tubular Na concentration

→ **Activation of the tubuloglomerular feedback:**
macula densa (adenosine-mediated signal cascades)

→ vasoconstriction of the afferent arteriole

→ **Inhibition of renin release** by macula densa
from the juxtaglomerular cells

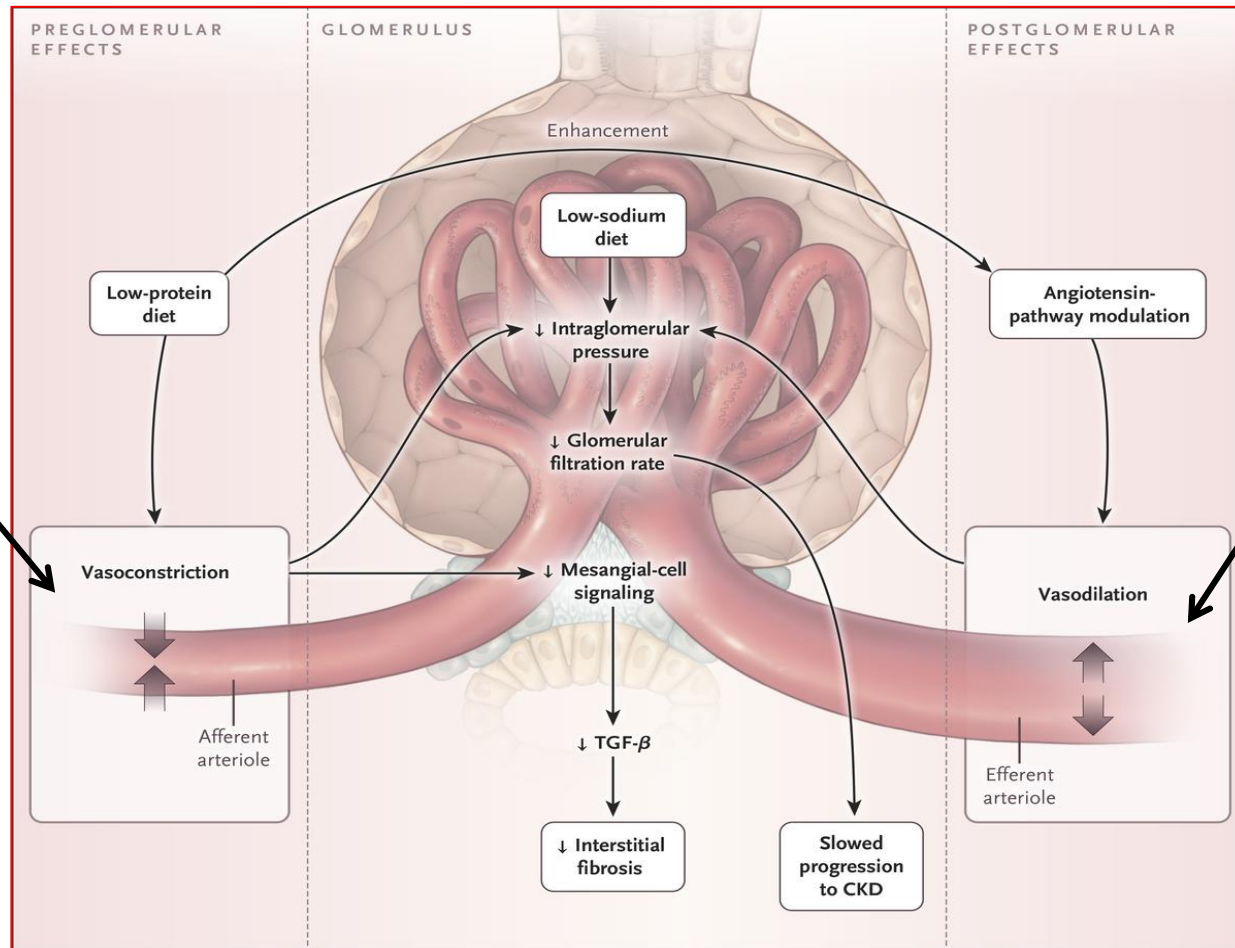
→ dilatation of the efferent arteriole

→ → **Reduced glomerular filtration rate**

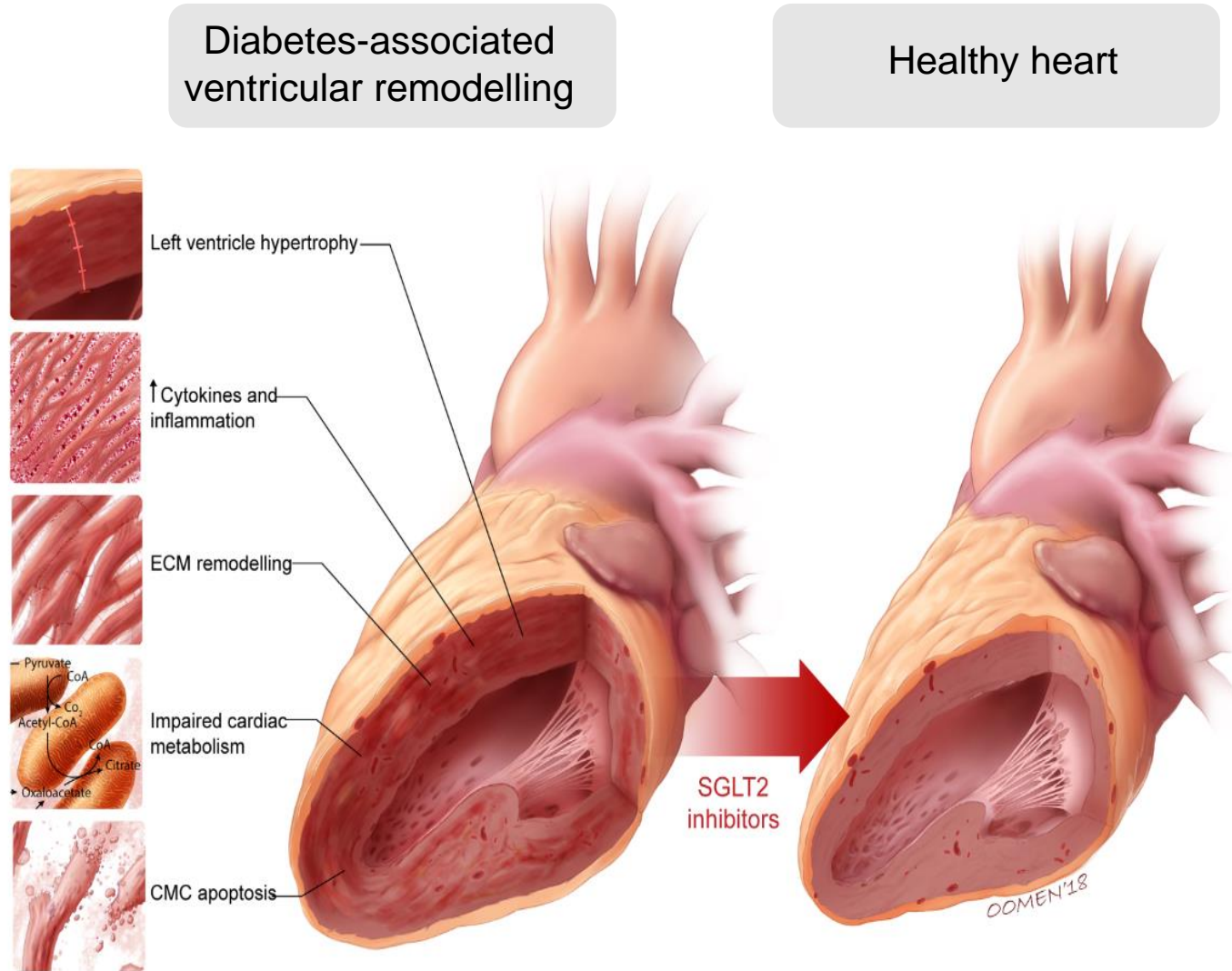
Protective mechanisms in the glomeruli

SGLT2-inhibitors

RAAS-inhibitors

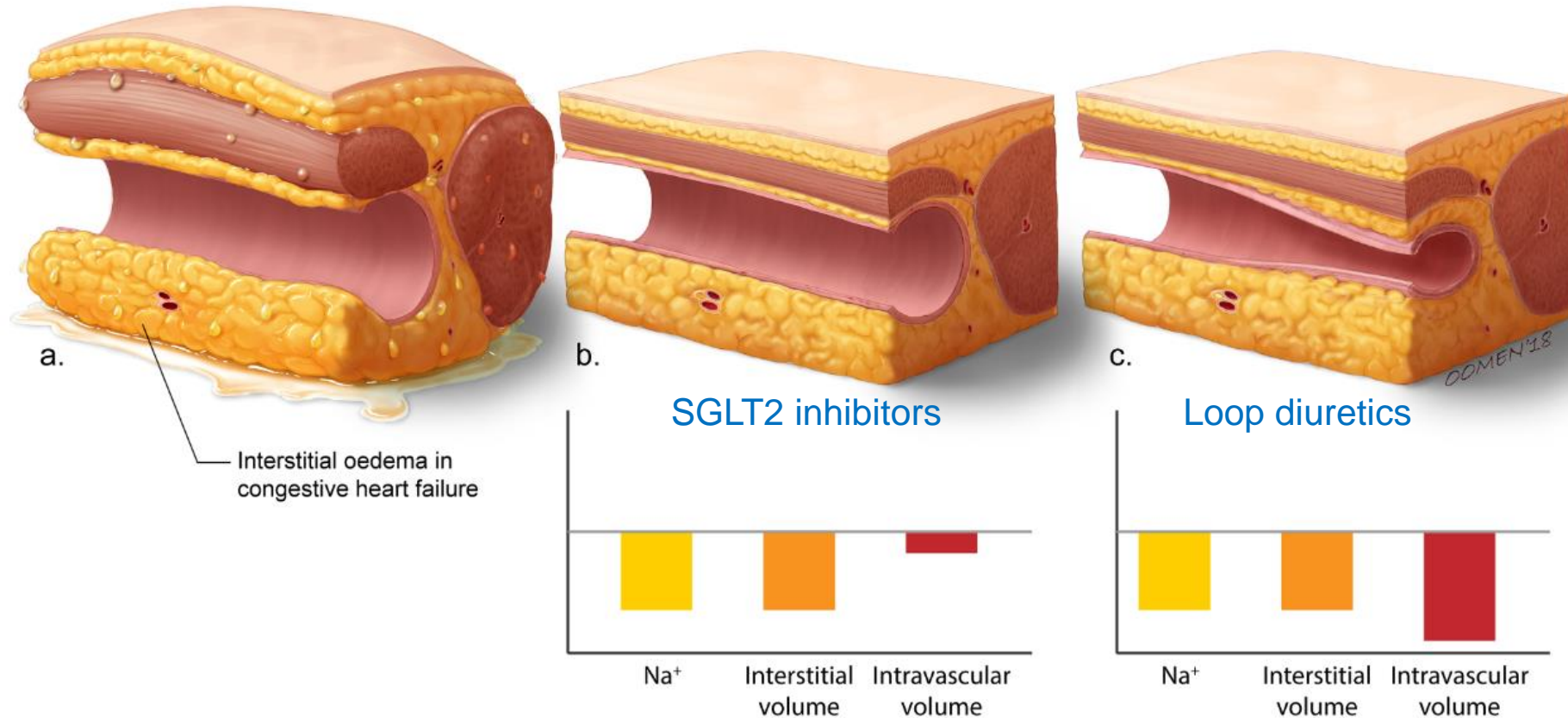


Diabetes associated ventricular remodelling and the SGLT2 inhibitors



- Improved myocardial metabolism – ketogenesis efficient energy source
- Restoring mitochondrial function
- Improving microcirc. abnormalities, endothelial function
- Reducing oxidative stress
- Reducing fibrosis

SGLT2 inhibitors may differentially regulate the interstitial vs intravascular compartment when compared with loop diuretics



SGLT2i selectively decrease interstitial edema and do not decrease intravascular volume. No neurohormonal stimulation

SGLT-2-inhibition with dapagliflozin reduces tissue sodium content: a randomised controlled trial

M.V. Karg, A. Bosch, D. Kannenkeril, K. Striepe, C. Ott, M.P. Schneider, F. Boemke-Zelch, P. Linz, A.M. Nagel, J. Titze, M. Uder, R.E. Schmieder. Cardiovasc Diabetol (2018) 17:5

- Aim: measure tissue Na content after 6 weeks of treatment with dapagliflozin in T2D patients (^{23}Na -MRI, compared to baseline)
- Results: significantly decreased Na content in the skin, but not in the muscles
- Bigger change in younger patients
- No significant change in tissue water content
- Decreased systolic BP, decreased body weight, improved glucose control

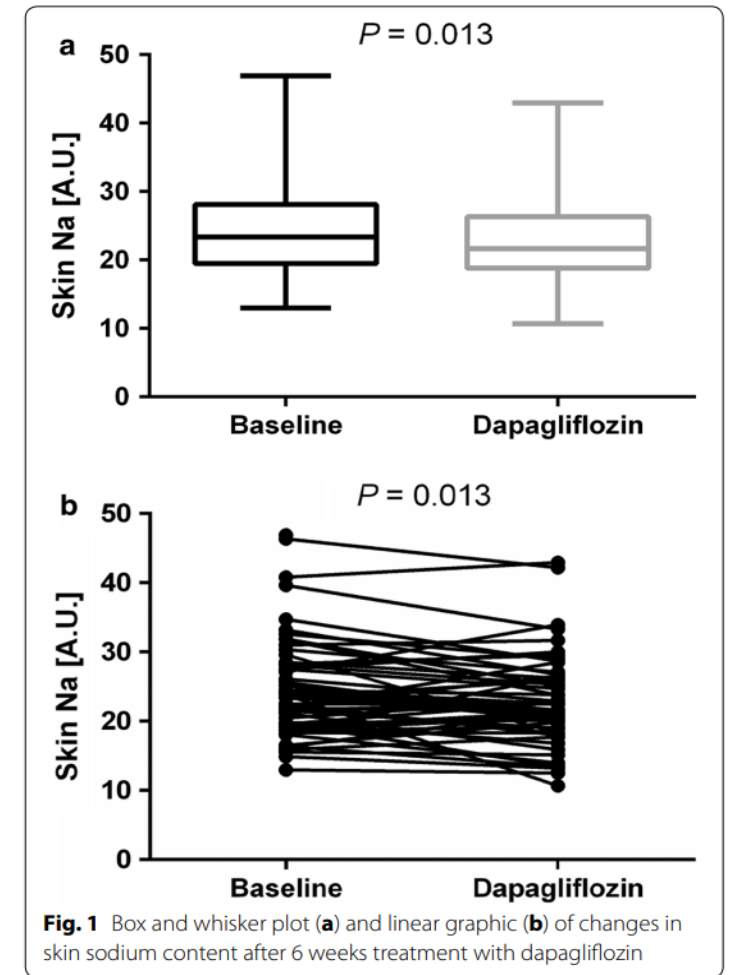


Fig. 1 Box and whisker plot (a) and linear graphic (b) of changes in skin sodium content after 6 weeks treatment with dapagliflozin

Mechanism of the hematocrit elevation

Sano M, Goto S. Circulation 2019

SGLT2 inhibitors increase Ht by 2-4%, and increase the EPO level

- Hypothesis
- High O₂ demand due to increased glucose reabsorption in T2D causes local hypoxia and cytokine release
- EPO secreting fibroblasts transform to myofibroblasts
- Reduction of metabolic stress of the proximal tubular and adjacent cells increases EPO production

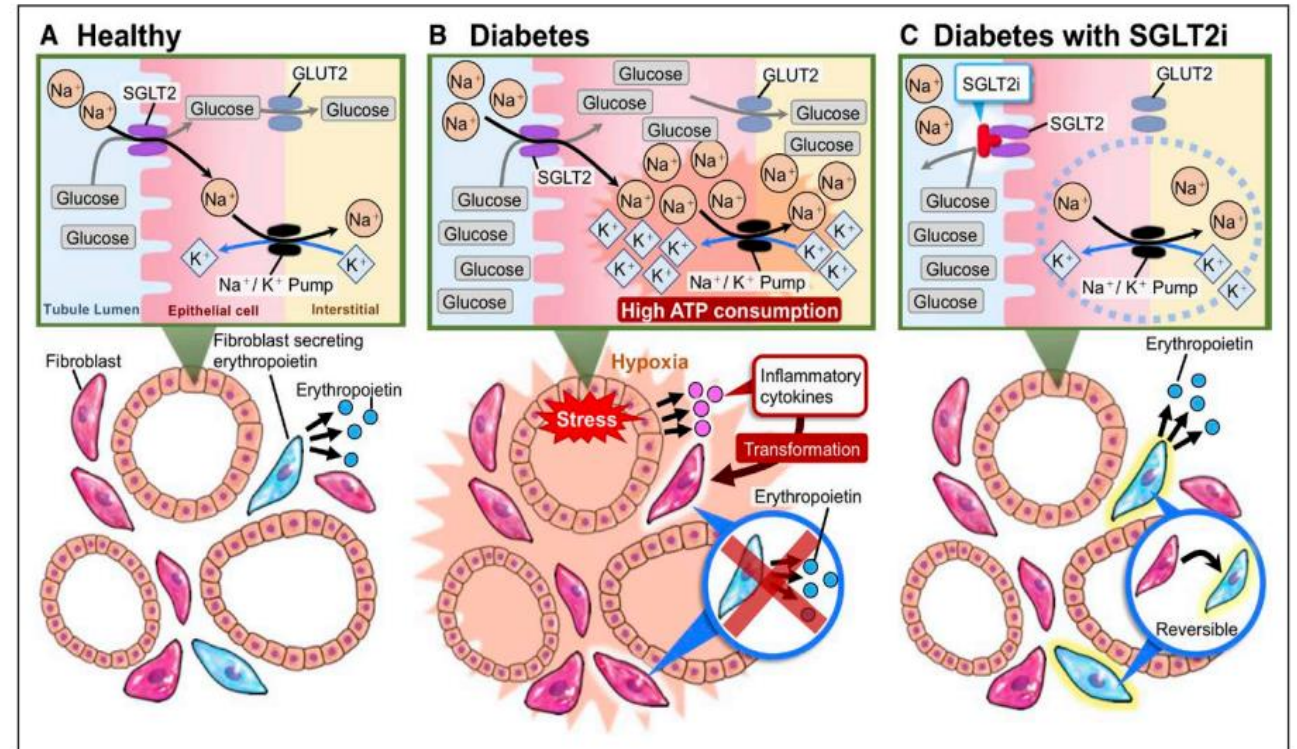
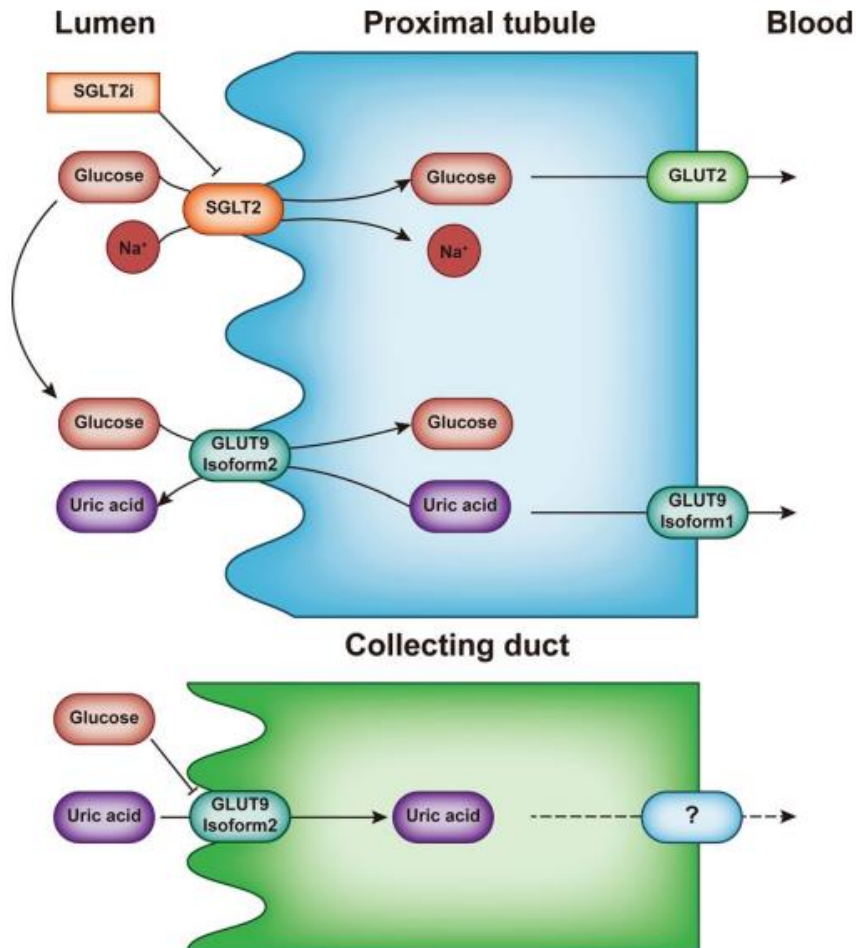


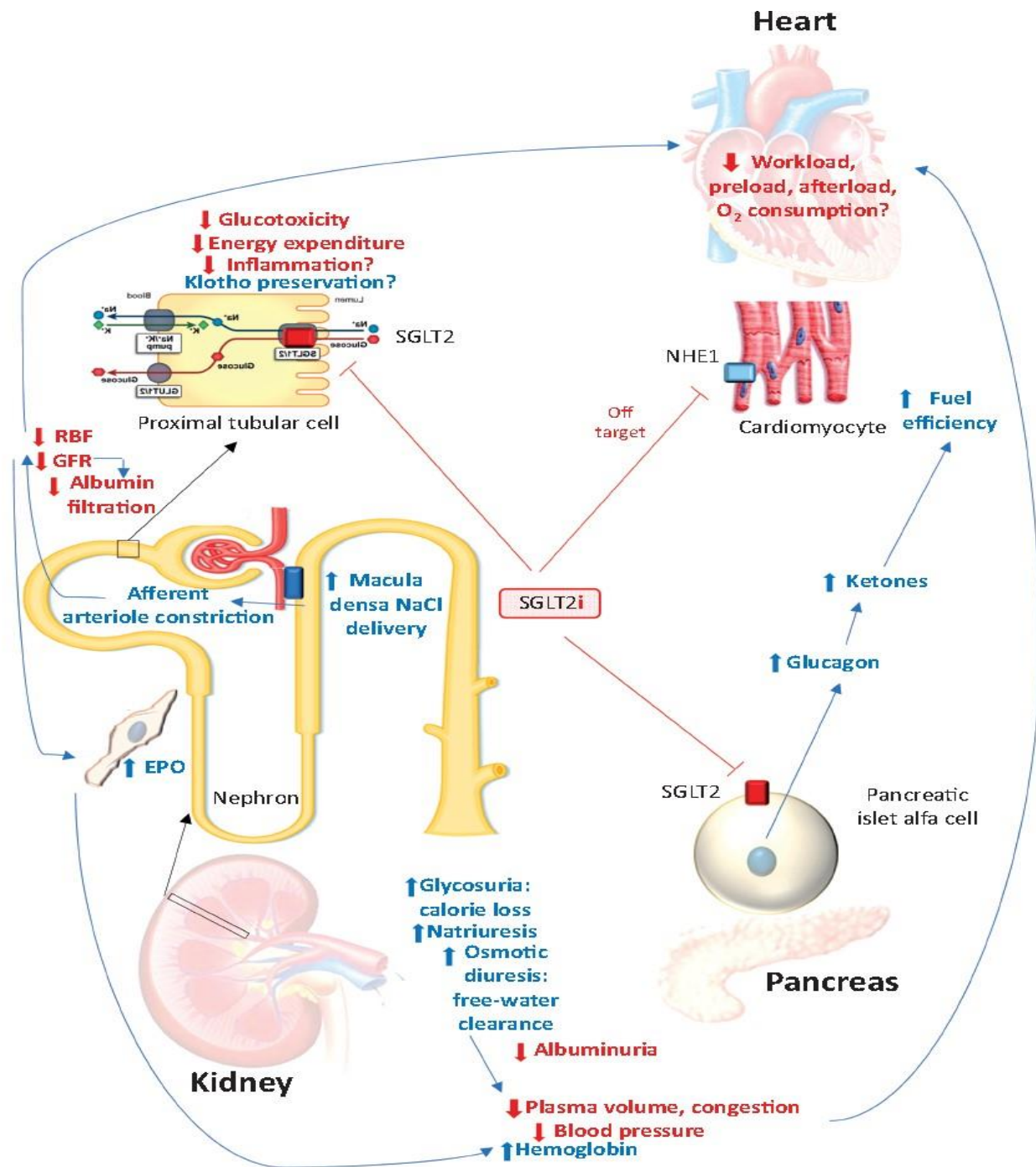
Figure. Possible mechanism by which sodium glucose cotransporter 2 (SGLT2) inhibitors (SGLT2is) increase erythropoietin production. Diagram of the proximal renal tubular environment in a healthy adult (A), a patient with diabetes mellitus (B), and a patient with diabetes mellitus receiving SGLT2i therapy (C). SGLT2 is coupled with the Na⁺/K⁺ pump, which consumes ATP. In the healthy adult, fibroblasts around the proximal tubules produce erythropoietin (blue cells). In the patient with diabetes mellitus, glucose uptake via SGLT2 is increased, resulting in high ATP consumption by the Na⁺/K⁺ pump. To meet the high demand for ATP, oxygen consumption increases in the proximal tubular epithelial cells. This leads to local hypoxia and release of inflammatory cytokines by the stressed proximal tubular epithelial cells. Inflammatory cytokines stimulate the transformation of erythropoietin-secreting fibroblasts to myofibroblasts that lack the capacity to secrete erythropoietin, leading to decreased erythropoietin secretion despite local hypoxia. SGLT2is reduce ATP consumption by the Na⁺/K⁺ pump and alleviate metabolic stress in the proximal tubular epithelial cells, thus improving hypoxia and inflammation in the microenvironment around the proximal tubules and allowing myofibroblasts to revert to erythropoietin-producing fibroblasts. GLUT2 indicates glucose transporter 2.

SGLT2i increases uric acid excretion and decreases inflammation in blood vessels

Huang et al. Cardiovascular Diabetology (2023) 22:86



- **High urate concentration** reduces NO activity and induces NF- κ B, \rightarrow induction of monocyte chemoattractant protein 1 and cyclooxygenase 2 (COX-2), \rightarrow **inflammation and atherosclerosis**.
- **SGLT2i** increases glucose concentrations in the lumen, which is exchanged with uric acid by GLUT9 isoform 2.
- In the collecting duct, high levels of glucose reduce the absorption of uric acid.
- **Lowering the concentration of uric acid** in the blood helps reduce inflammation in the blood vessels.



Renoprotective and cardioprotective actions of SGLT-2 inhibitors

Dedicated kidney outcome trials

The dedicated kidney outcome trial: DAPA-CKD

Dapagliflozin in Patients With Chronic Kidney Disease^{1,2}



Objective

To assess whether treatment with dapagliflozin, compared with placebo, reduced the risk of renal and CV events in patients with CKD with or without T2D, and who were receiving standard of care including a maximum tolerated dose of an ACEi or ARB

Key Inclusion Criteria

- ≥18 years of age
- eGFR ≥25 to ≤75 mL/min/1.73m²
- UACR ≥200 to ≤5000 mg/g
- Stable max tolerated dose of ACEi/ARB for ≥4 weeks
- With and without T2D

Key Exclusion Criteria

- T1D
- Polycystic kidney disease, lupus nephritis, ANCA-associated vasculitis
- Immunosuppressive therapy ≤6 months prior to enrollment

1:1
Double-blind

Dapagliflozin 10 mg
+ standard of care

Placebo
+ standard of care

4304 Randomized
Median follow-up 2.4 years

End Points

Primary Outcome

Composite of sustained ≥50% eGFR decline, ESKD^a, renal or CV death

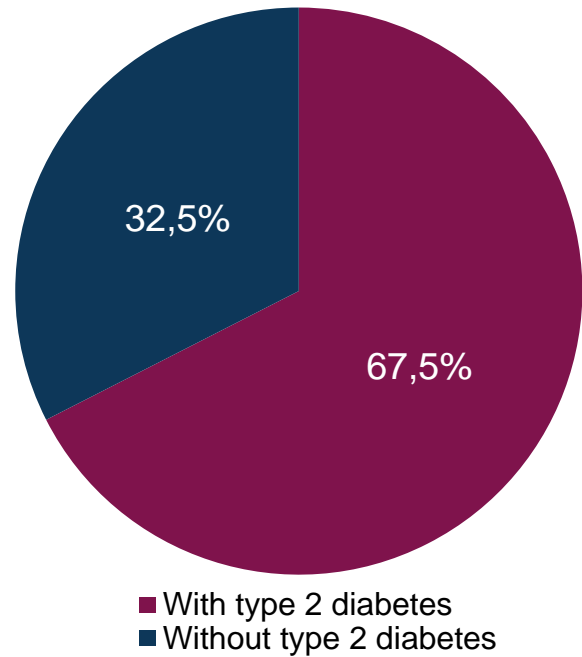
Secondary Outcomes

- Composite of sustained ≥50% eGFR decline, ESKD, or renal death
- Composite of CV death or hHF
- All-cause mortality

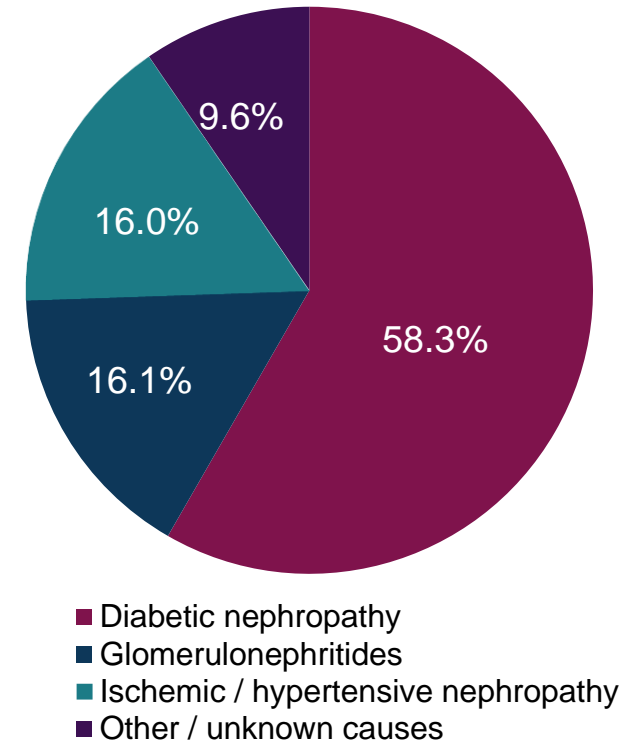
1. Heerspink HJL et al. *Nephrol Dial Transplant*. 2020;35:274–282; 2. Heerspink HJL et al. *N Engl J Med*. 2020; 383:1436-1446.

Diabetes status and cause of kidney disease

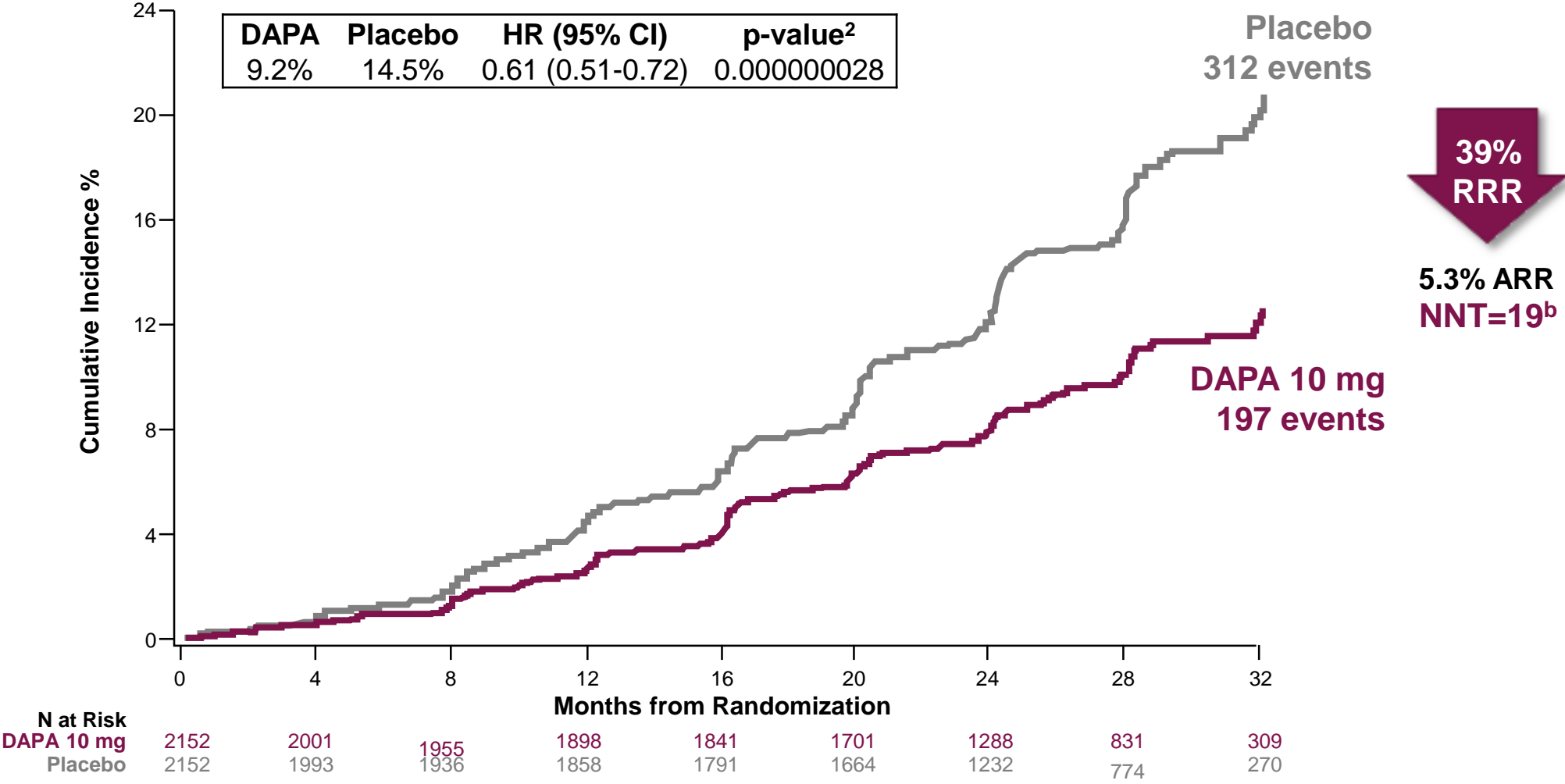
Diabetes Status



Investigator-reported Cause of Kidney Disease

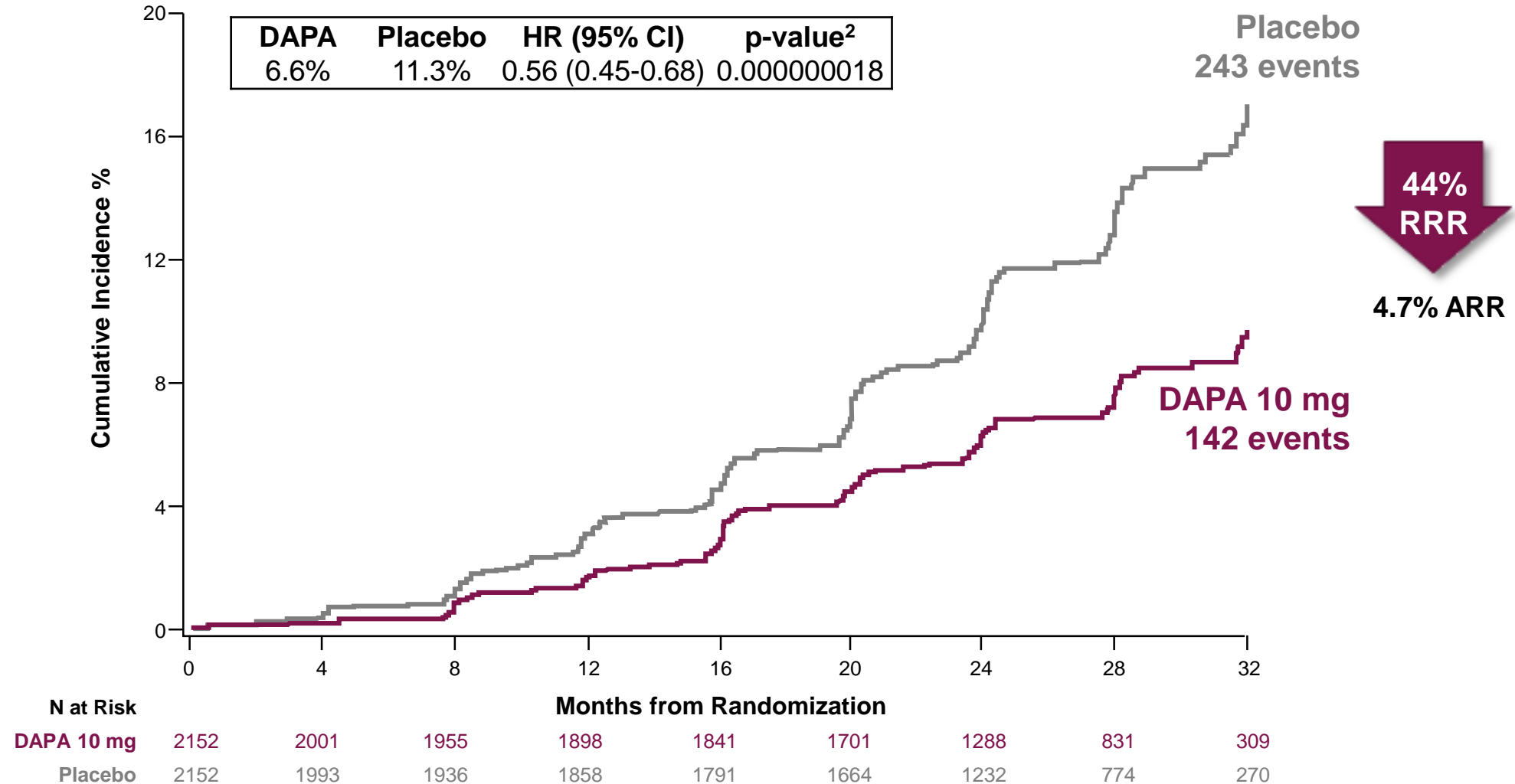


Primary composite outcome: eGFR decline $\geq 50\%$, ESKD, renal or CV death

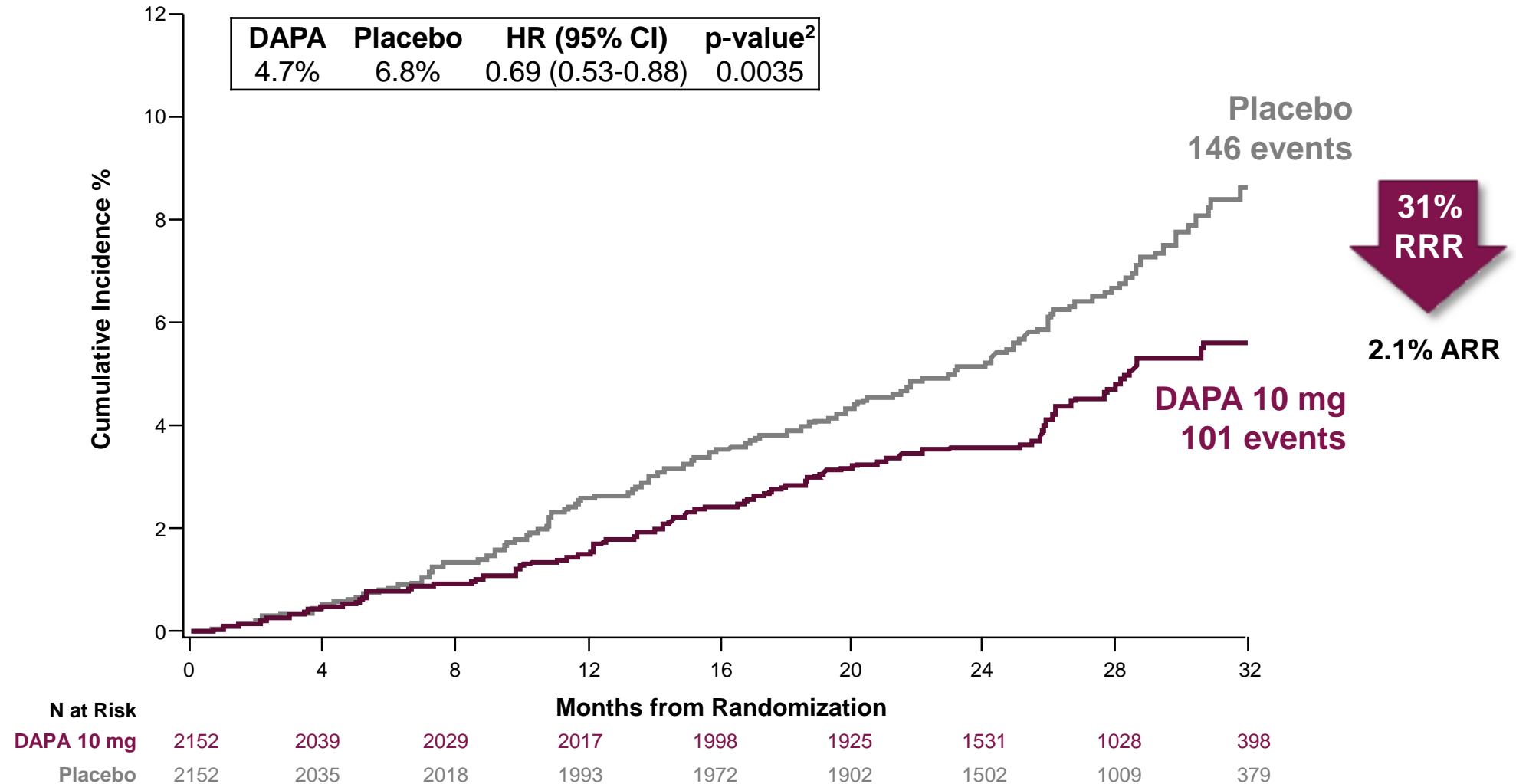


1. Heerspink HJL et al. *N Engl J Med.* 2020; 383:1436-1446; 2. Heerspink HJL. Presented at: ESC Congress – The Digital Experience; August 29 – September 1, 2020; 3. Heerspink HJL et al. *Nephrol Dial Transplant.* 2020;35:274–282.

Composite kidney outcome: eGFR decline $\geq 50\%$, ESKD, renal death



Secondary outcome: Death from any cause

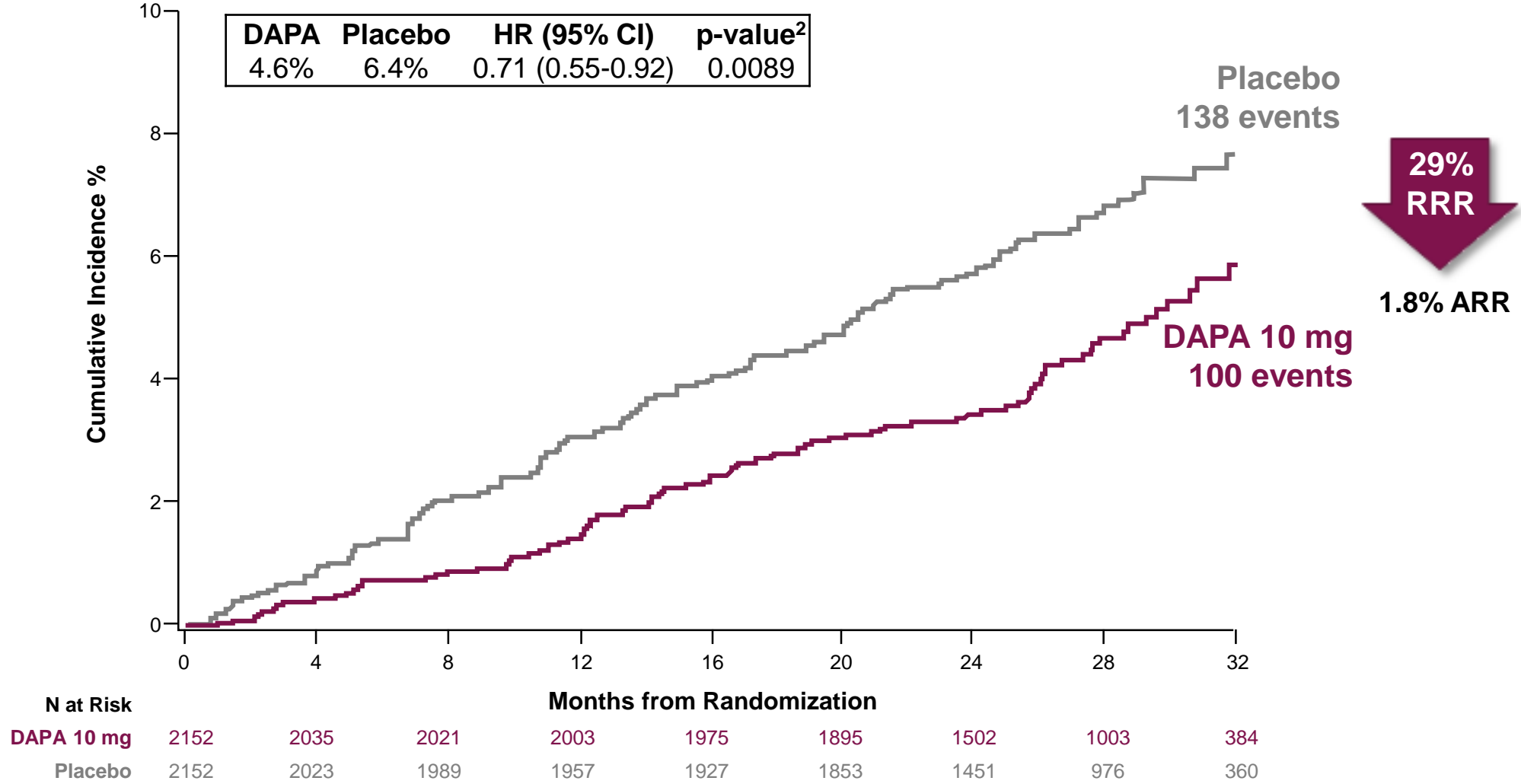


ARR = absolute risk reduction; DAPA = dapagliflozin; HR = hazard ratio; RRR = relative risk reduction.

1. Heerspink HJL et al. *N Engl J Med.* 2020; 383:1436-1446; 2. Heerspink HJL. Presented at: ESC Congress – The Digital Experience; August 29 – September 1, 2020.

© AstraZeneca 2021

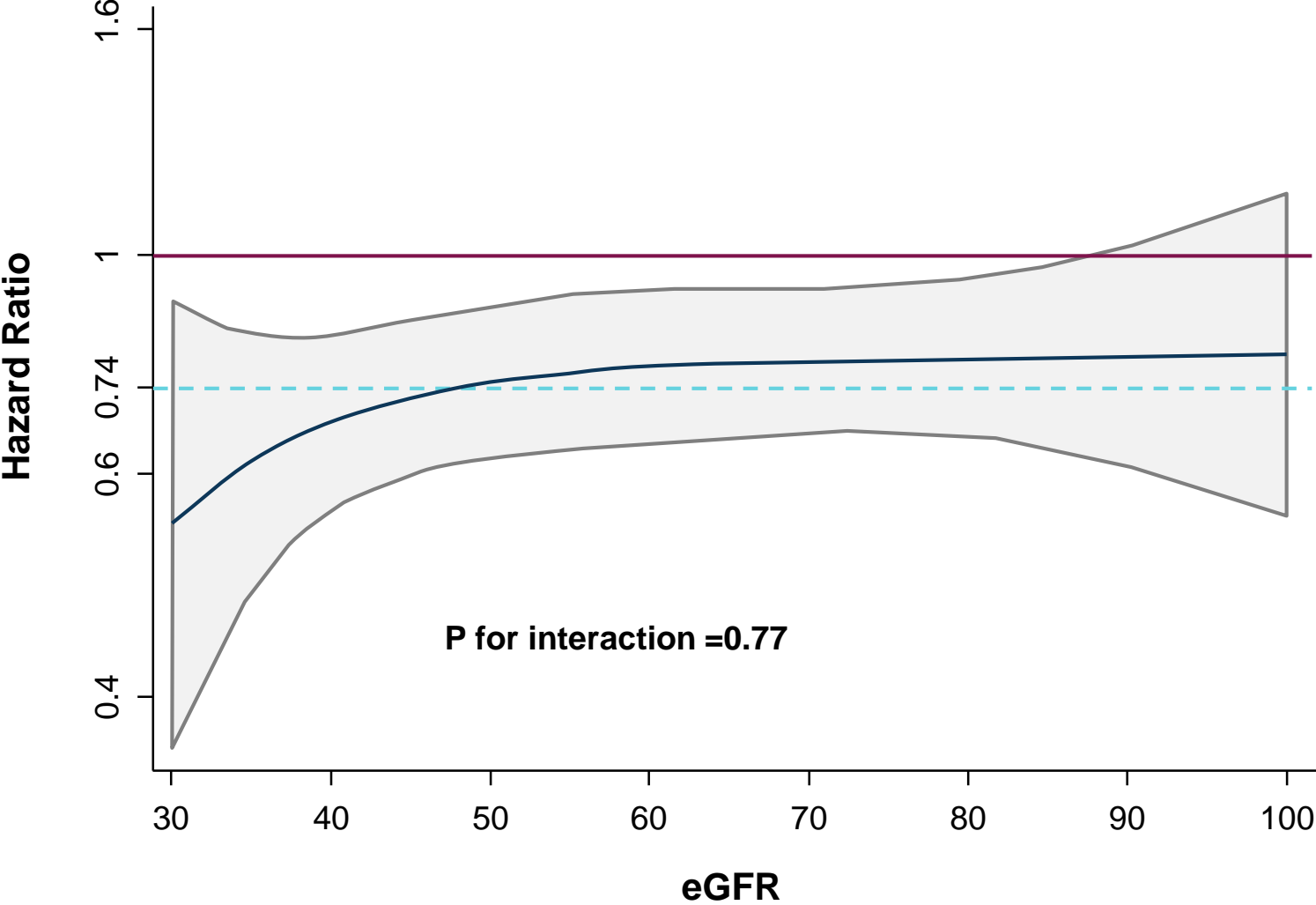
Composite cardiovascular outcome: CV mortality or hospitalization for HF



ARR = absolute risk reduction; CV = cardiovascular; DAPA = dapagliflozin; HR = hazard ratio; RRR = relative risk reduction.

1. Heerspink HJL et al. *N Engl J Med.* 2020; 383:1436-1446; 2. Heerspink HJL. Presented at: ESC Congress – The Digital Experience; August 29 – September 1, 2020.

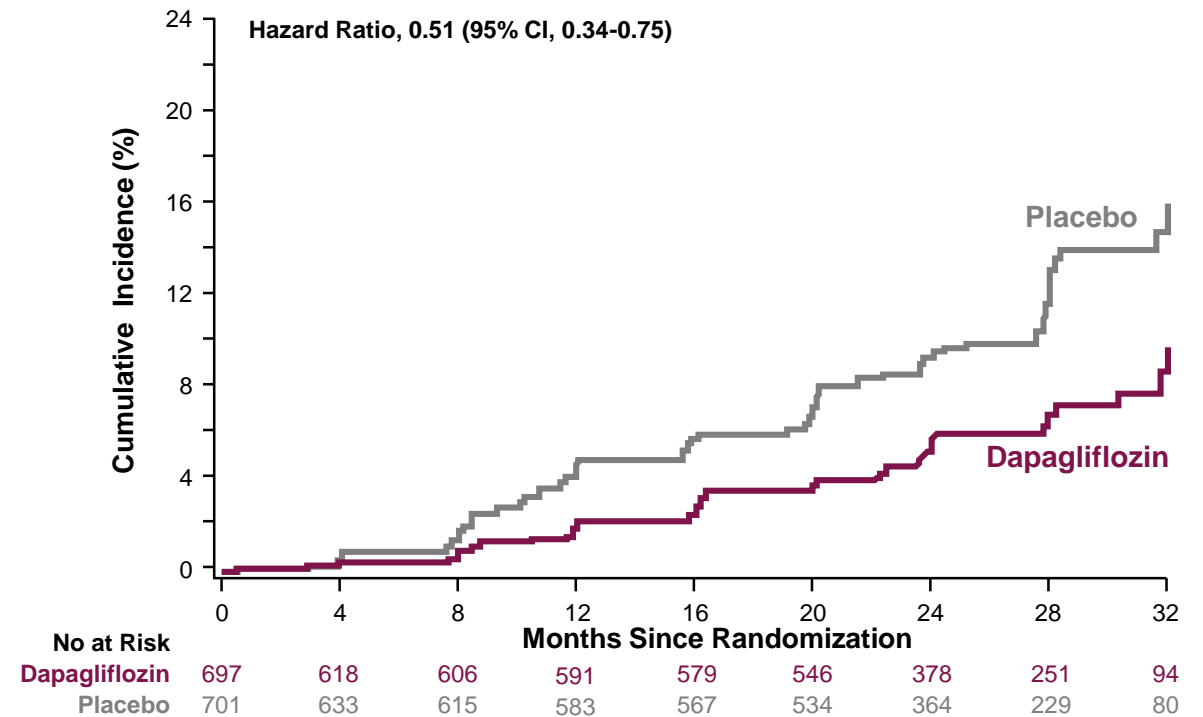
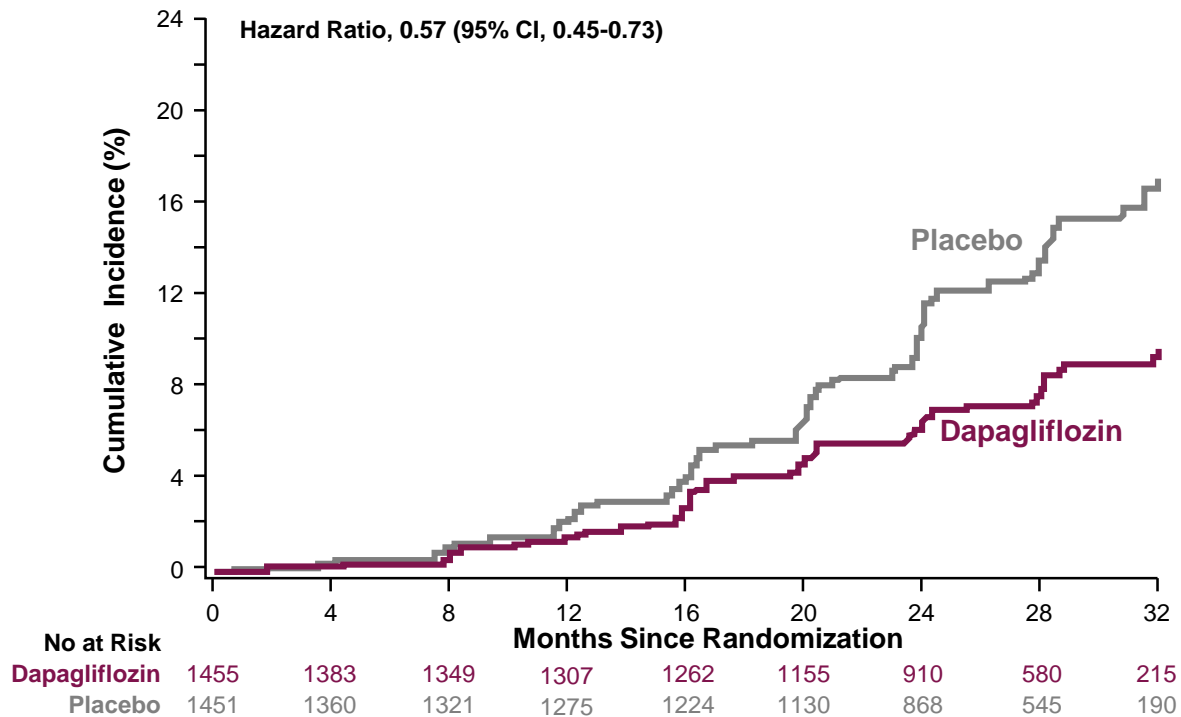
Dapagliflozin reduced the incidence of primary endpoint across the range of baseline eGFR (>30 mL/min/1.73 m²)



Composite kidney outcome according to diabetes status ($\geq 50\%$ \downarrow of eGFR, ESKD, renal death)

Patients With T2D

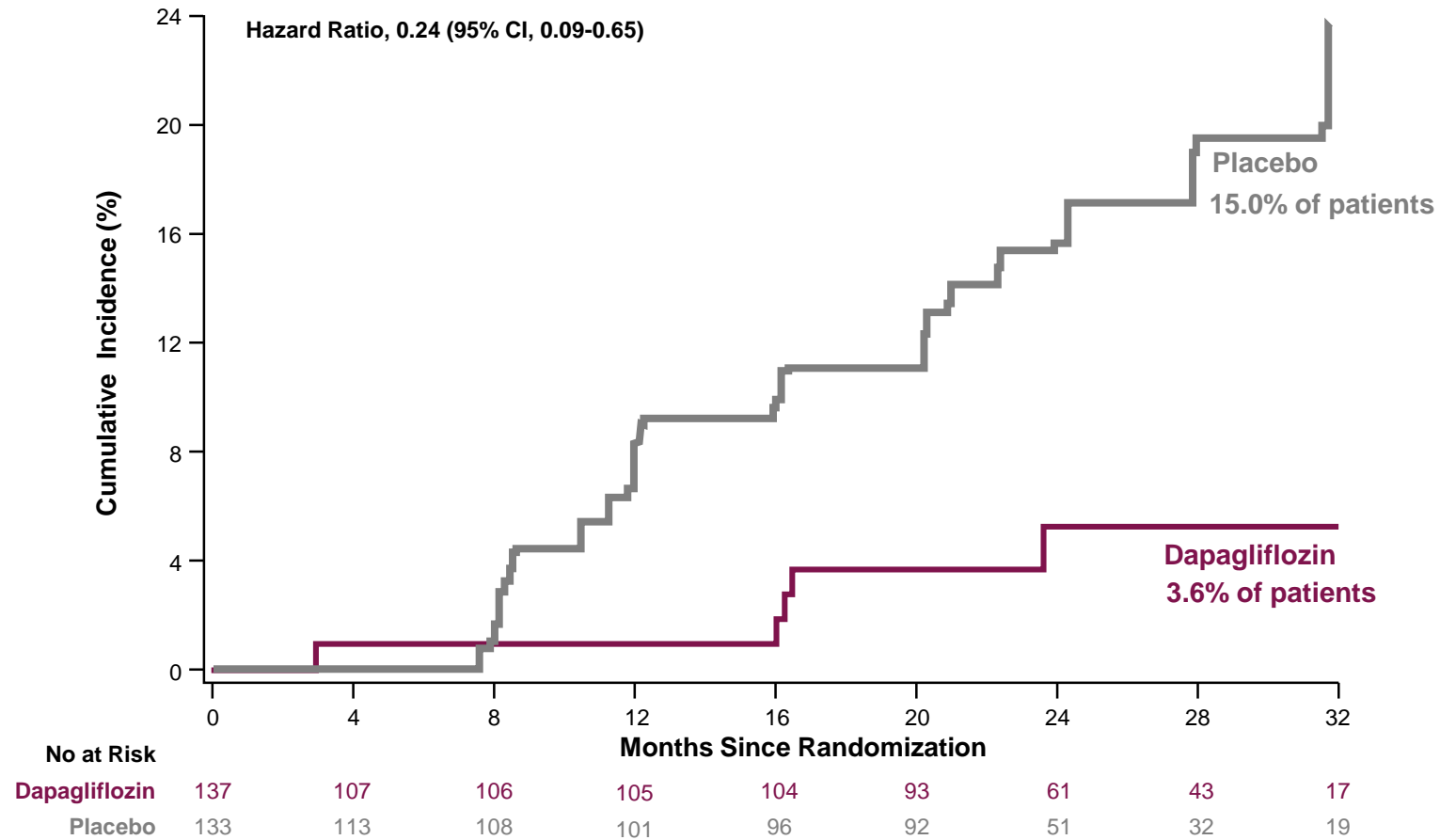
Patients Without T2D



p-interaction=0.57

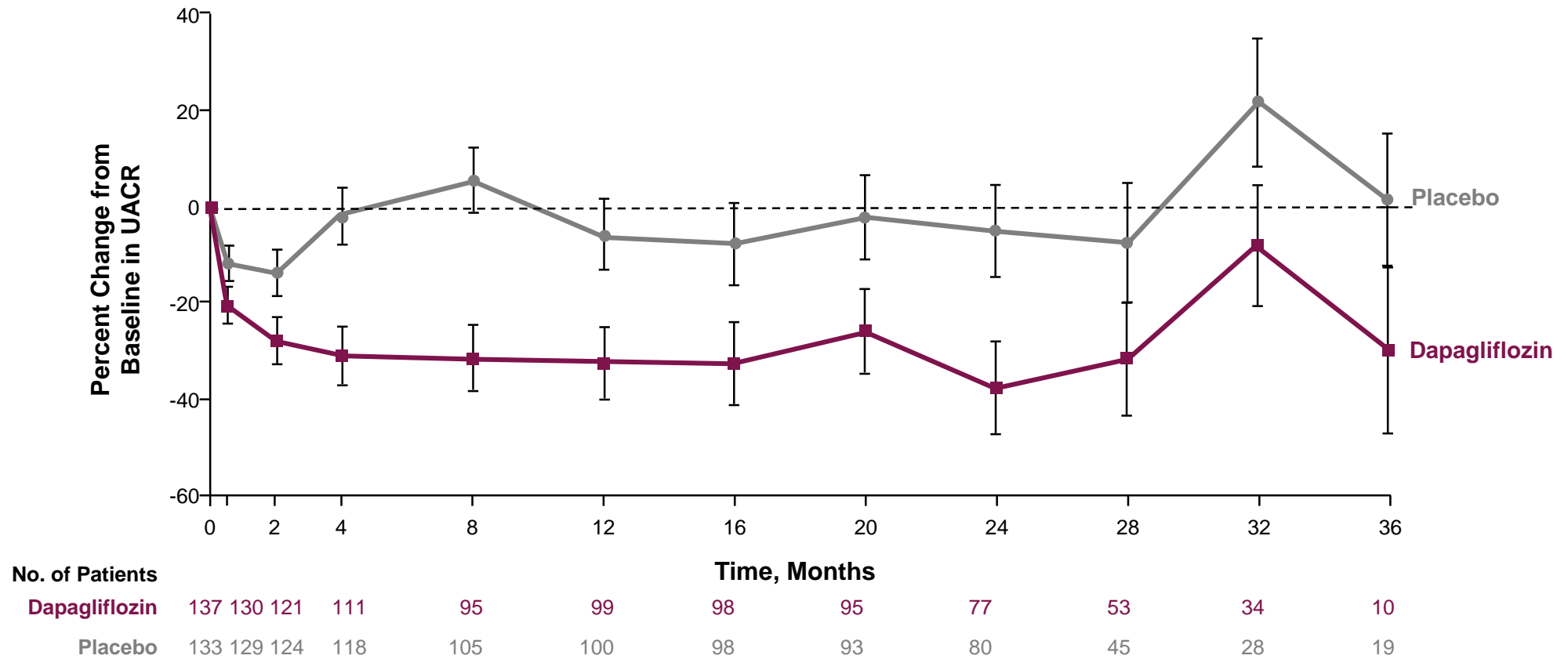
1. Wheeler DC et al. *Lancet Diabetes Endocrinol.* 2021;9:22–31; 2. Heerspink HJL et al. *Nephrol Dial Transplant.* 2020;35:274–282.

Composite kidney outcome according in IgA nephropathy ($\geq 50\%$ \downarrow of eGFR, ESKD, renal death)



1. Wheeler DC et al. *Kidney Int.* 2021;100:215-224; 2. Heerspink HJL et al. *Nephrol Dial Transplant.* 2020;35:274–282.

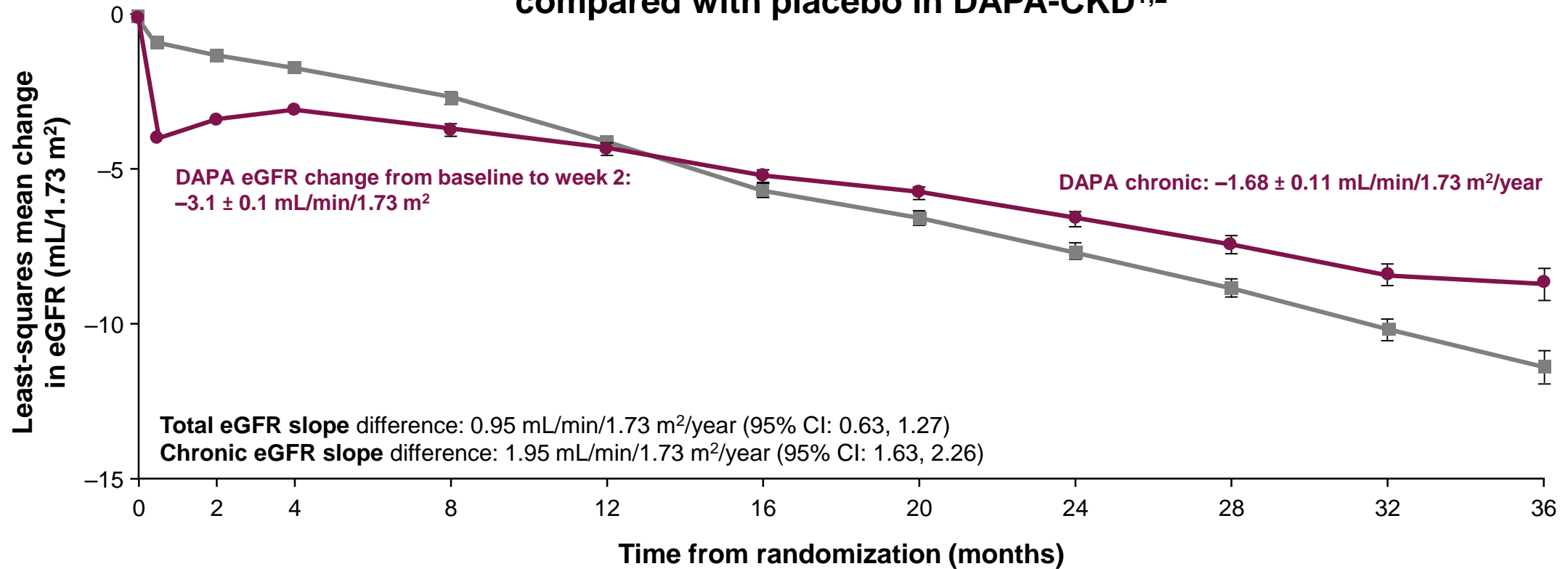
Urinary albumin/creatinine ratio (UACR) in IgA nephropathy



Mean difference^b: -26 (95% CI, -37 to -14; p<0.001)

Change from baseline in eGFR – initial hemodynamic effect

Change in eGFR in patients with CKD treated with dapagliflozin compared with placebo in DAPA-CKD^{1,2}



No. of patients

Dapagliflozin	2152	2031	2001	1896	1832	1785	1705	1482	978	496	157
Placebo	2152	2029	1981	1866	1795	1753	1672	1443	935	447	157

1. Heerspink HJL, et al. *N Engl J Med* 2020;383:1436–1446; 2. Heerspink HJL, et al. *Lancet Diabetes Endocrinol* 2021;9:743–75

RESEARCH SUMMARY

Empagliflozin in Patients with Chronic Kidney Disease

The EMPA-KIDNEY Collaborative Group DOI: 10.1056/NEJMoa2204233

Key Inclusion Criteria

- eGFR 20-45 mL/min/1.73m² regardless of albuminuria or
- eGFR 45-90 mL/min/1.73m² and UACR > 200 mg/g
- On ACEi/ARB
- With and without diabetes (46/54%)

Key Exclusion Criteria

- Polycystic kidney disease
- Patients with kidney transplantation

EMPA-KIDNEY trial

Empagliflozin 10 mg
or placebo
+ standard of care

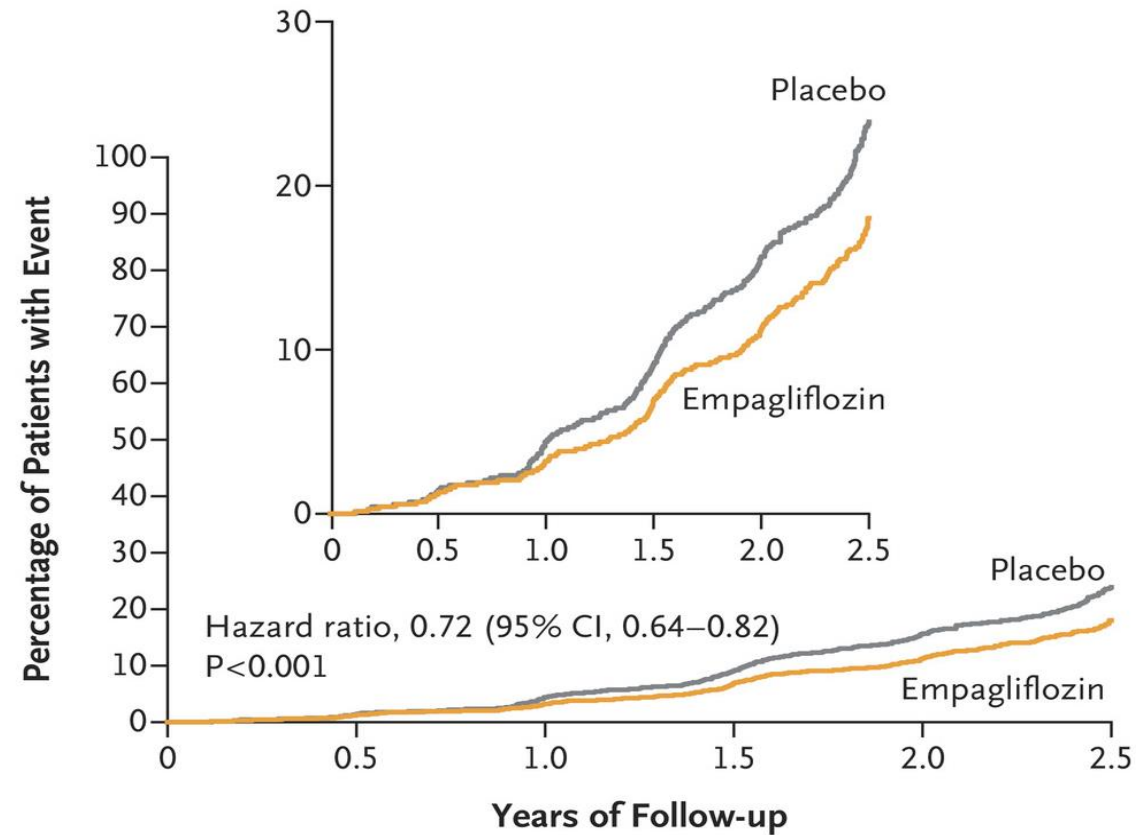
Primary outcome

Composite of sustained $\geq 40\%$ eGFR decline, 10 ml/min eGFR decline, ESKD^a, renal or CV death

Secondary outcome

- Hospitalization for heart failure or death from CV causes
- Death from any cause

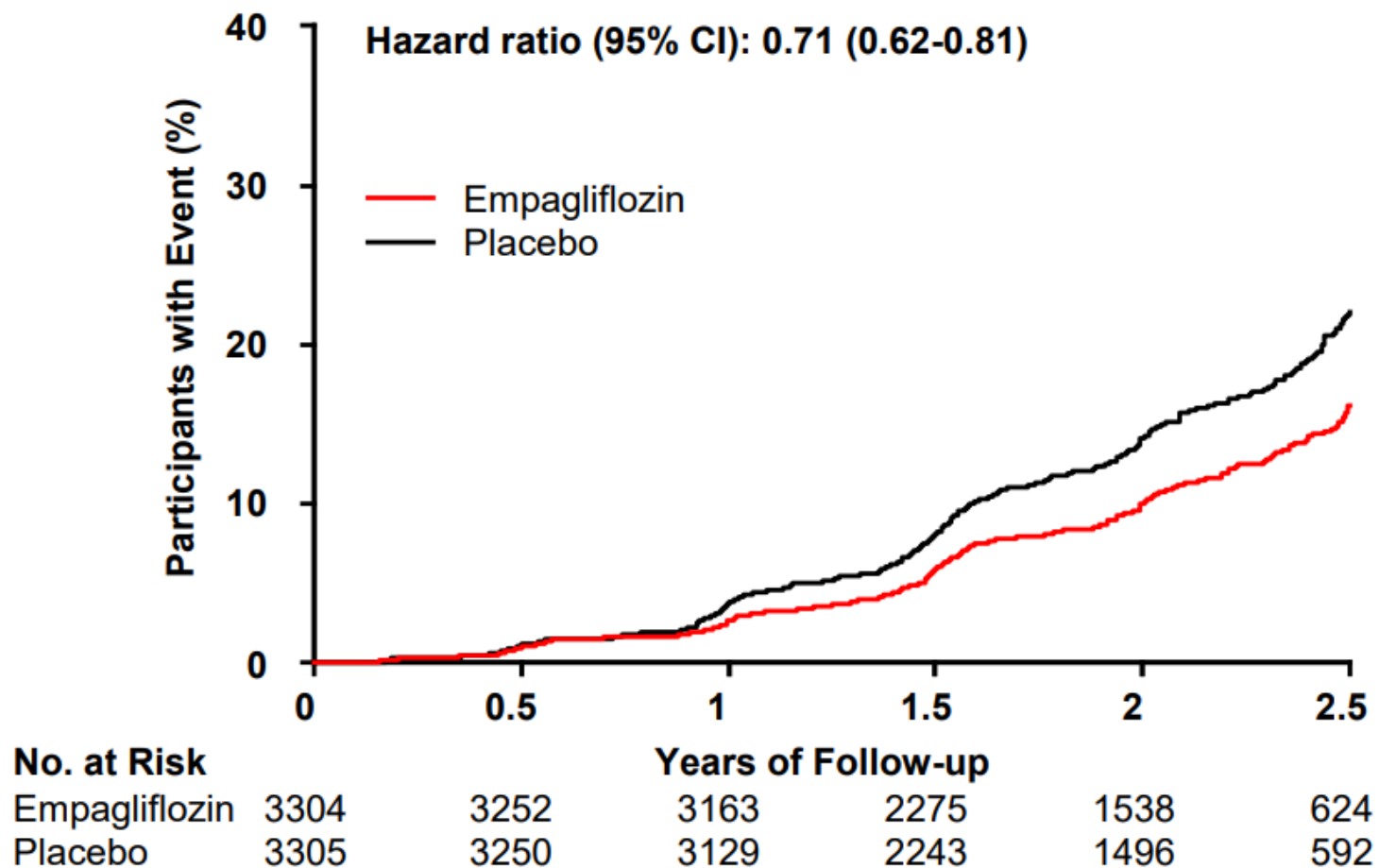
Progression of Kidney Disease or Death from Cardiovascular Causes



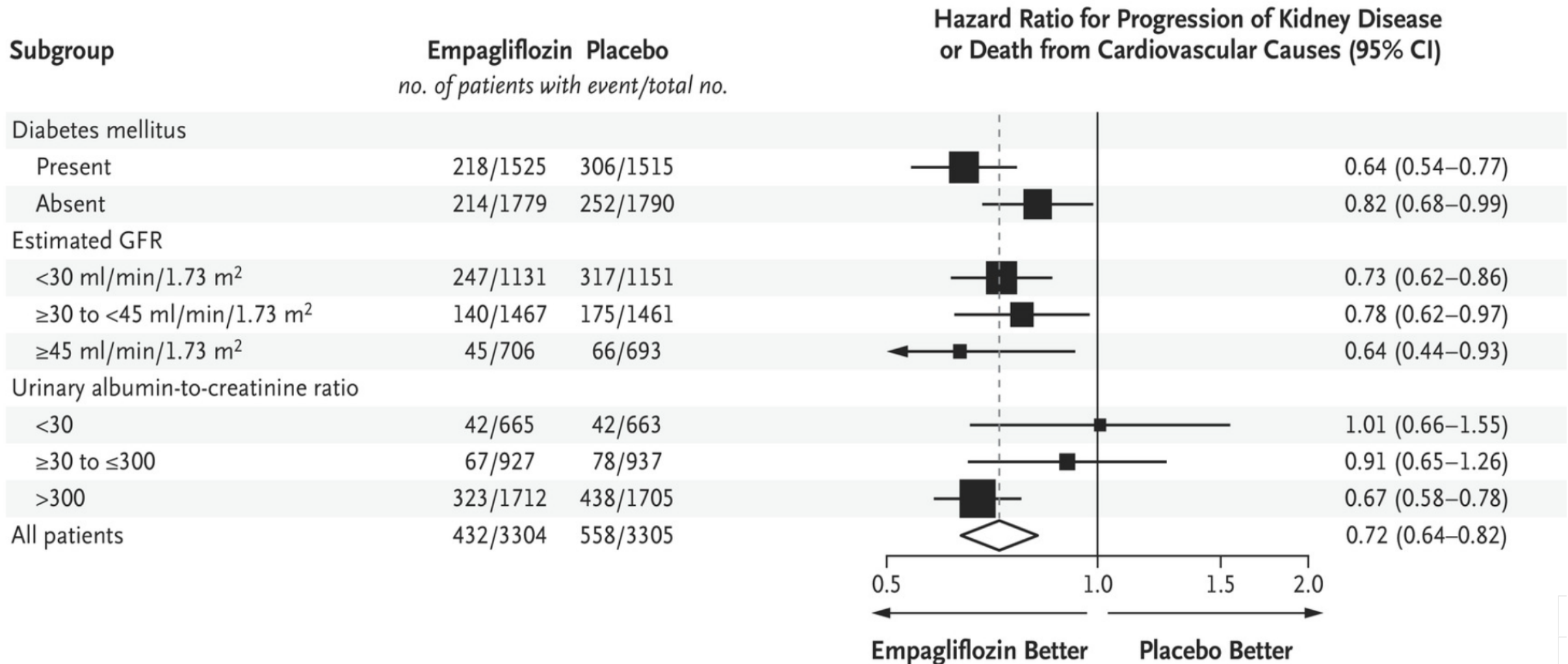
No. at Risk

Placebo	3305	3250	3129	2243	1496	592
Empagliflozin	3304	3252	3163	2275	1538	624

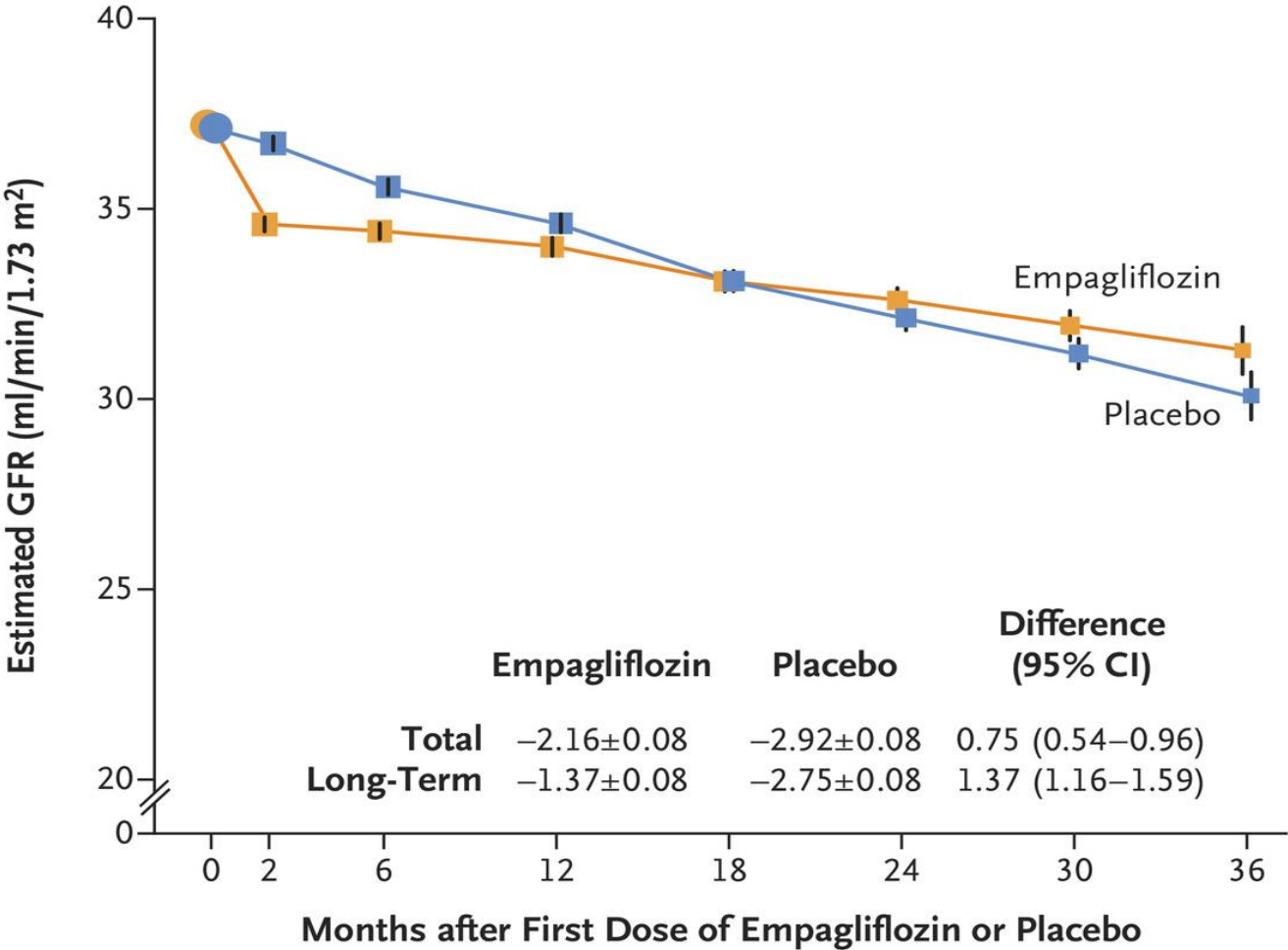
Progression of Kidney Disease



Primary Outcome in Key Prespecified Subgroups



Change from Baseline in the Estimated GFR



The most recent data – Collaborative meta-analysis

Nuffield Department of Population Health Renal Studies Group and the SGLT2 inhibitor Meta-Analysis Cardio-Renal Trialists' Consortium
Lancet 2022. 400:1788

13 RCTs with >90 000 patients

- T2D at high risk of atherosclerotic CV disease (>42 000 patients)
- heart failure (~22 000 patients) and
- CKD (eGFR 20-90 ml/min) with and without DM (~26 000 patients)

Aims: kidney disease progression, acute kidney injury, cardiovascular death, hospitalization for heart failure, safety outcomes

Kidney disease progression

Acute kidney injury

	Mean baseline eGFR, mL/min per 1.73m ²	Events/participants		Event rate per 1000 patient-years		RR (95% CI)	Events/participants		Event rate per 1000 patient-years		RR (95% CI)
		SGLT2 inhibitor	Placebo	SGLT2 inhibitor	Placebo		SGLT2 inhibitor	Placebo			

		Events/participants		Event rate per 1000 patient-years		RR (95% CI)	Events/participants		Event rate per 1000 patient-years		RR (95% CI)
	Mean baseline eGFR, mL/min per 1.73m ²	SGLT2 inhibitor	Placebo	SGLT2 inhibitor	Placebo		SGLT2 inhibitor	Placebo	SGLT2 inhibitor	Placebo	
Diabetes											
DECLARE-TIMI 58	85	56/8582	102/8578	1.6	3.0	0.55 (0.39-0.76)	125/8574	175/8569	3.5	4.9	0.69 (0.55-0.87)
CANVAS Program	77	80/5795	81/4347	3.6	5.8	0.61 (0.45-0.83)	30/5790	28/4344	1.6	2.5	0.66 (0.39-1.11)
VERTIS CV	76	49/5499	32/2747	2.6	3.4	0.76 (0.49-1.19)	42/5493	22/2745	2.5	2.7	0.95 (0.57-1.59)
EMPA-REG OUTCOME	74	51/4645	47/2323	4.0	7.6	0.51 (0.35-0.76)	45/4687	37/2333	2.5	6.2	0.41 (0.27-0.63)
DAPA-HF	63	18/1075	24/1064	12	16	0.73 (0.39-1.34)	31/1073	39/1063	19	24	0.79 (0.50-1.25)
EMPEROR-REDUCED	61	13/927	23/929	13	24	0.52 (0.26-1.03)	26/927	33/929	21	27	0.77 (0.46-1.28)
EMPEROR-PRESERVED	60	38/1466	44/1472	15	18	0.82 (0.53-1.27)	60/1466	84/1472	20	28	0.69 (0.50-0.97)
DELIVER	60	33/1578	37/1572	9.5	11	0.87 (0.54-1.39)	59/1578	52/1572	17	15	1.13 (0.78-1.63)
CREDENCE	56	153/2202	230/2199	27	41	0.64 (0.52-0.79)	86/2200	98/2197	17	20	0.85 (0.64-1.13)
SOLOIST-WHF	51	NA/NA	NA/NA	25/605	27/611	55	59	0.94 (0.55-1.59)
SCORED	44	37/5292	52/5292	5.0	7.0	0.71 (0.46-1.08)	116/5291	111/5286	16	16	1.04 (0.81-1.35)
DAPA-CKD	44	103/1455	173/1451	35	60	0.57 (0.45-0.73)	48/1455	69/1451	15	22	0.66 (0.46-0.96)
EMPA-KIDNEY	36	108/1525	175/1515	36	59	0.55 (0.44-0.71)	73/1525	81/1515	24	27	0.88 (0.64-1.20)
Subtotal: diabetes	67	739/40041	1020/33489	0.62 (0.56-0.68)	566/40664	856/34087	0.79 (0.72-0.88)
No diabetes											
DAPA-HF	68	10/1298	15/1307	5.0	8.0	0.67 (0.30-1.49)	18/1295	30/1305	9.9	16	0.60 (0.34-1.08)
EMPEROR-REDUCED	63	5/936	10/938	5.2	10	0.50 (0.17-1.48)	20/936	34/938	16	28	0.56 (0.32-0.98)
DELIVER*	63	17/1551	17/1557	5.0	4.9	1.01 (0.51-1.97)	30/1551	47/1558	8.8	14	0.64 (0.41-1.02)
EMPEROR-PRESERVED	62	12/1531	18/1519	4.5	6.9	0.68 (0.33-1.40)	37/1531	47/1519	12	15	0.80 (0.52-1.23)
DAPA-CKD	42	39/697	70/701	29	53	0.51 (0.34-0.75)	16/697	21/701	11	15	0.75 (0.39-1.43)
EMPA-KIDNEY	39	119/1779	157/1790	35	47	0.74 (0.59-0.95)	34/1779	54/1790	10	16	0.63 (0.41-0.97)
Subtotal: no diabetes	56	202/7792	287/7812	0.69 (0.57-0.82)	55/7789	233/7811	0.66 (0.54-0.81)
Total: overall	65	941/47833	1307/41301	0.63 (0.58-0.69)	621/48453	1089/41898	0.77 (0.70-0.84)

Trend across trials sorted by eGFR:
 Diabetes p=0.87;
 No diabetes p=0.86;
 Heterogeneity by diabetes status: p=0.31

0.25 0.50 0.75 1.00 1.50
 Favours SGLT2 inhibitor Favours placebo

Trend across trials sorted by eGFR:
 Diabetes p=0.02;
 No diabetes p=0.66;
 Heterogeneity by diabetes status: p=0.12

0.25 0.50 0.75 1.00 1.50
 Favours SGLT2 inhibitor Favours placebo

Figure 1: Effect of sodium glucose co-transporter-2 inhibition on kidney disease outcomes by diabetes status

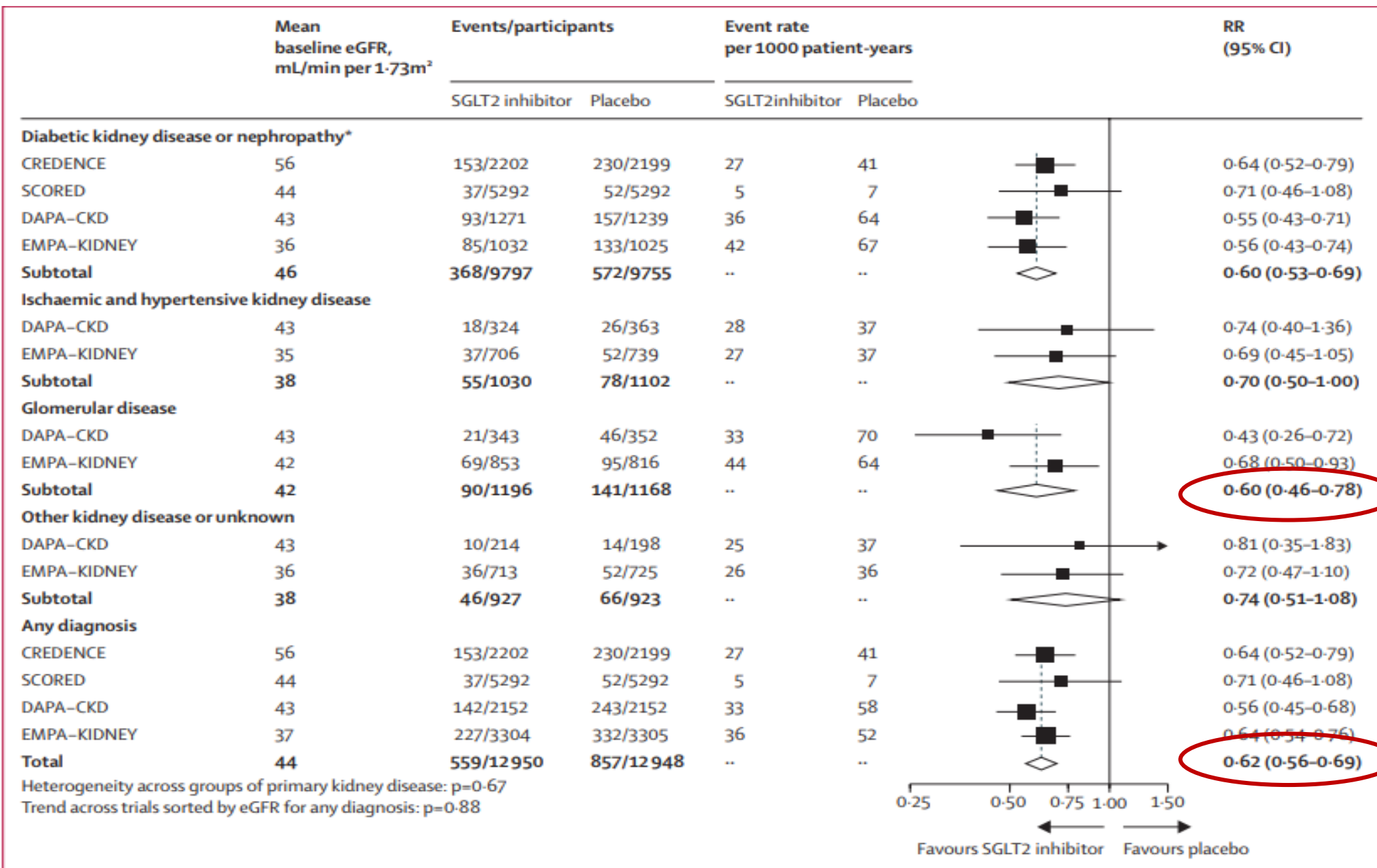


Figure 2: Effect of sodium glucose co-transporter-2 inhibition on kidney disease progression by presumed primary kidney disease (chronic kidney disease trials only)

Cardiovascular outcome trials

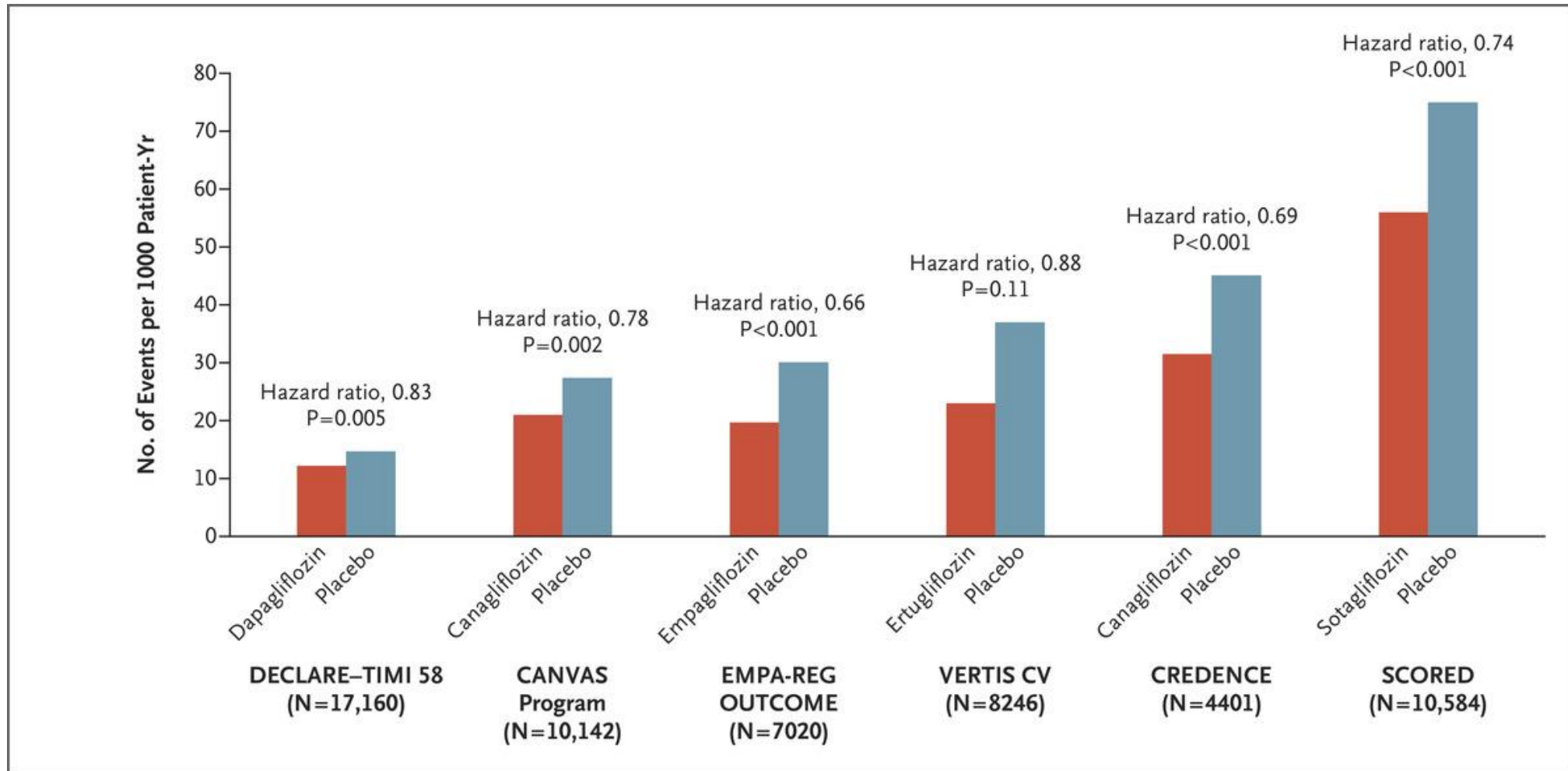
Table 1. Cardiovascular Outcome Trials Involving Patients with Type 2 Diabetes.*

Variable	EMPA-REG OUTCOME	CANVAS Program	CREDENCE	DECLARE-TIMI 58	VERTIS CV	SCORED	All
Drug	Empagliflozin	Canagliflozin	Canagliflozin	Dapagliflozin	Ertugliflozin	Sotagliflozin	
No. of patients	7020	10,142	4401	17,160	8246	10,584	57,553
Atherosclerotic cardiovascular disease — % of patients	100	65.6	50.4	40.6	100	48.6	63.0
History of heart failure — % of patients	10.1	14.4	14.8	10.0	23.7	31.0	17.0
Outcomes — hazard ratio (95% CI)†							
Major adverse cardiovascular events	0.86 (0.74–0.99)	0.86 (0.75–0.97)	0.80 (0.67–0.95)	0.93 (0.84–1.03)	0.99 (0.88–1.12)	0.77 (0.65–0.91)	0.89 (0.84–0.94)
Cardiovascular death	0.62 (0.49–0.77)	0.87 (0.72–1.06)	0.78 (0.61–1.00)	0.98 (0.82–1.12)	0.92 (0.77–1.10)	0.90 (0.73–1.12)	0.86 (0.79–0.93)
Hospitalization for heart failure	0.65 (0.50–0.85)	0.67 (0.52–0.87)	0.61 (0.47–0.80)	0.73 (0.61–0.88)	0.70 (0.54–0.90)	0.67 (0.55–0.82)	0.68 (0.62–0.75)

* Data sources for the individual trials are as follows: EMPA-REG OUTCOME, Zinman et al.¹⁴; CANVAS Program, Neal et al.¹⁵; CREDENCE, Perkovic et al.¹⁶; DECLARE-TIMI 58, Wiviott et al.¹⁷; VERTIS CV, Cannon et al.¹⁸; and SCORED, Bhatt et al.¹⁹ Data are also based on a meta-analysis by McGuire et al.²⁰

† Hazard ratios are based on a time-to-first event analysis, except for SCORED, which estimated hazard ratios for major adverse cardiovascular events and hospitalization for heart failure on the basis of a total-event analysis. CI denotes confidence interval.

Cardiovascular Death or Hospitalization for Heart Failure among Patients with Type 2 Diabetes Enrolled in Six Treatment Trials.



Side effects and sick day counselling

Potential side effects – pooled data from 13 studies, >90 000 patients

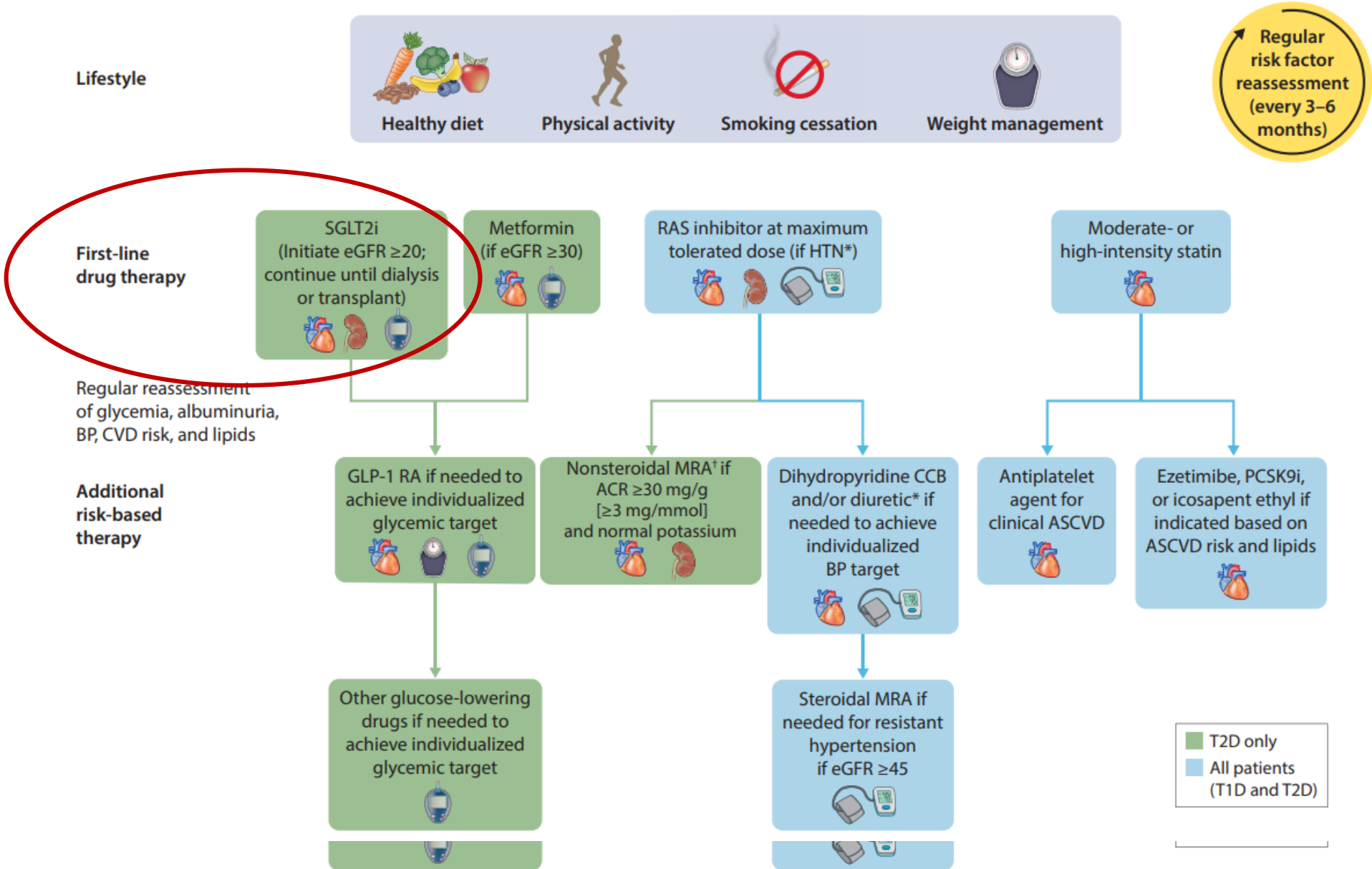
- Mycotic genital infections (6%), RR 3,57
- Urinary tract infections, pyelonephritis
- Fournier's gangrene (necrotizing fasciitis in the perineum)
- Normoglycemic ketoacidosis 0-2% (T1D 4-6%!) HR 2.1
- Volume depletion – diuretic treatment may have to be decreased
- (increased risk of lower limb amputations - CANVAS trial only)
- (Increased risk of bone fractures in some studies but not in others)

Sick day counselling

- In cases of acute disease, fasting, surgery, etc – withhold SGLT2 inhibitors!
- Increased hygiene – keep dry the genital region
- Immediate treatment of infections

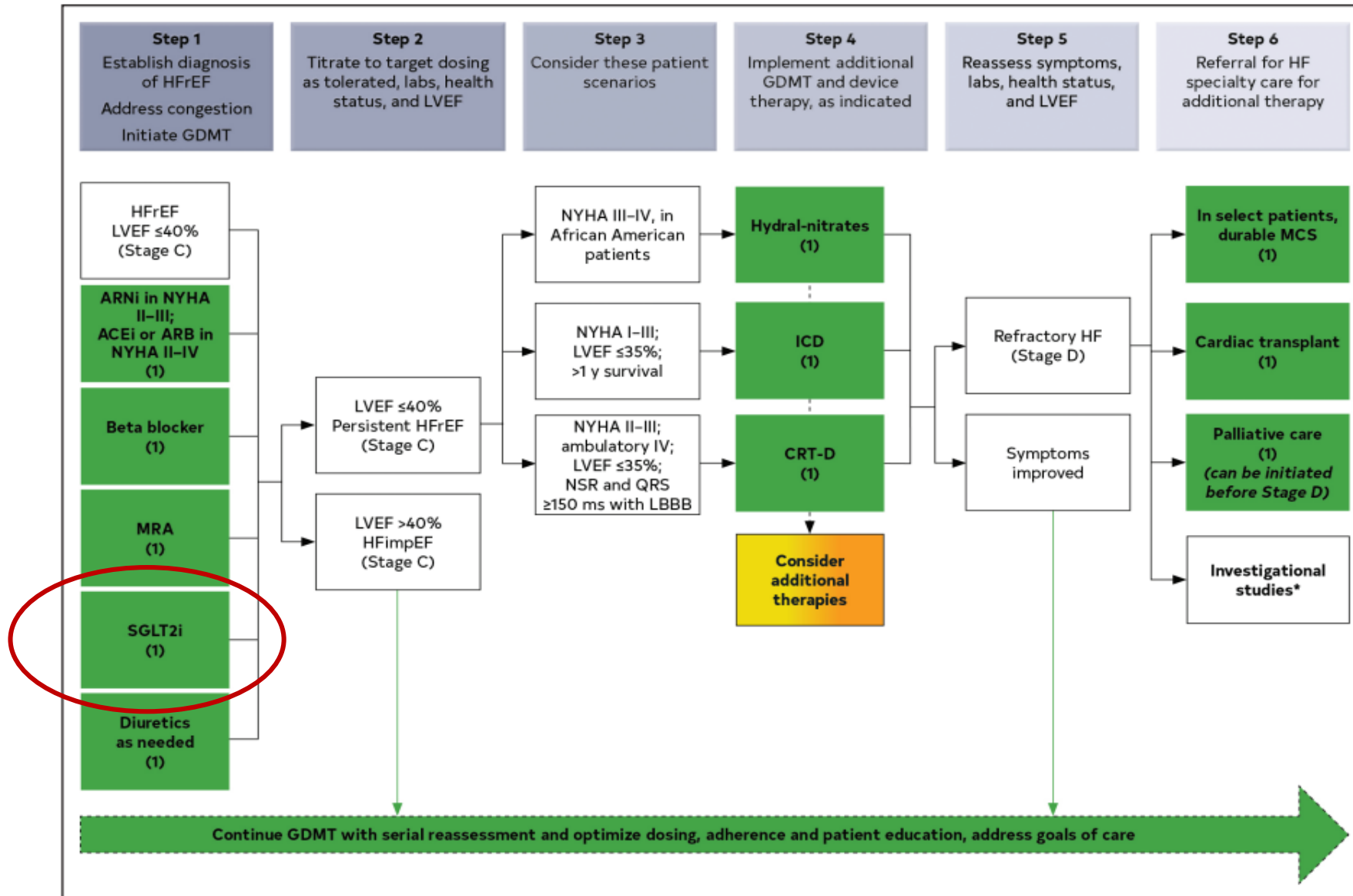
Treatment recommendations

ADA/KDIGO consensus statement 2022



2022 AHA/ACC/HFSA Guideline for the Management of Heart Failure

Heidenreich et al. Circulation 2022



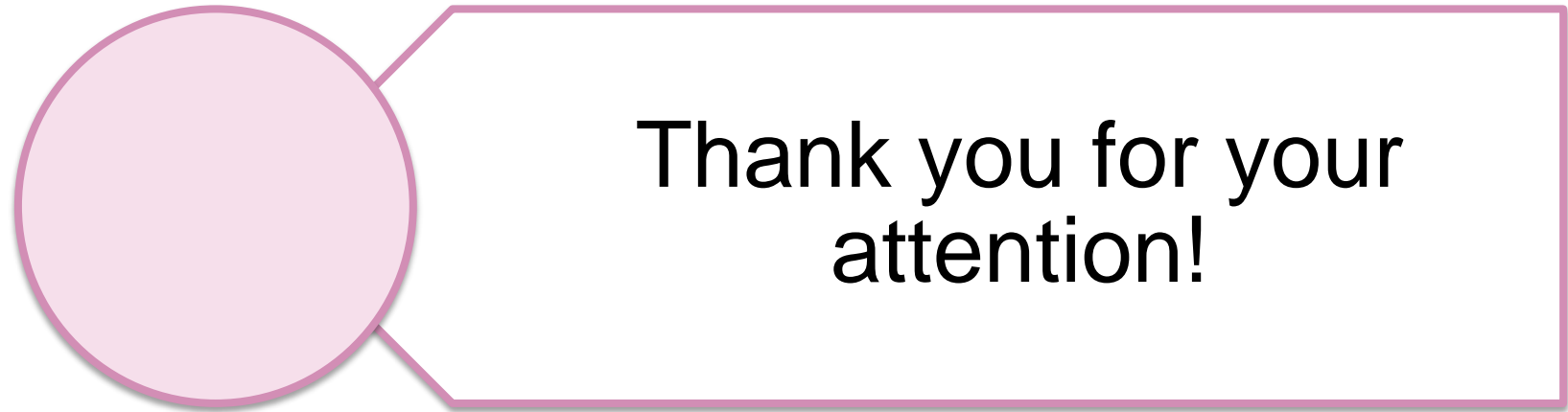
KDIGO 2022 CLINICAL PRACTICE GUIDELINE FOR DIABETES MANAGEMENT IN CKD

We recommend treating patients with **type 2 diabetes** (T2D), CKD, and an **eGFR 20 ml/min per 1.73 m²** with an SGLT2i (1A)

The recommendation for SGLT2i is for **kidney and cardiovascular protection** and SGLT2i have been shown to have safety and benefit in CKD patients, **even for those without T2D.**

Once an SGLT2i is initiated, **it is reasonable to continue** an SGLT2i even if the eGFR falls **below 20 ml/min per 1.73 m²**, **unless** it is not tolerated or **kidney replacement** therapy is initiated

SGLT2i have not been adequately studied in kidney transplant recipients, who may benefit from SGLT2i treatment, but are immunosuppressed and potentially at increased risk for infections; therefore, the recommendation to use SGLT2i **does not apply to kidney transplant recipients**



Thank you for your
attention!

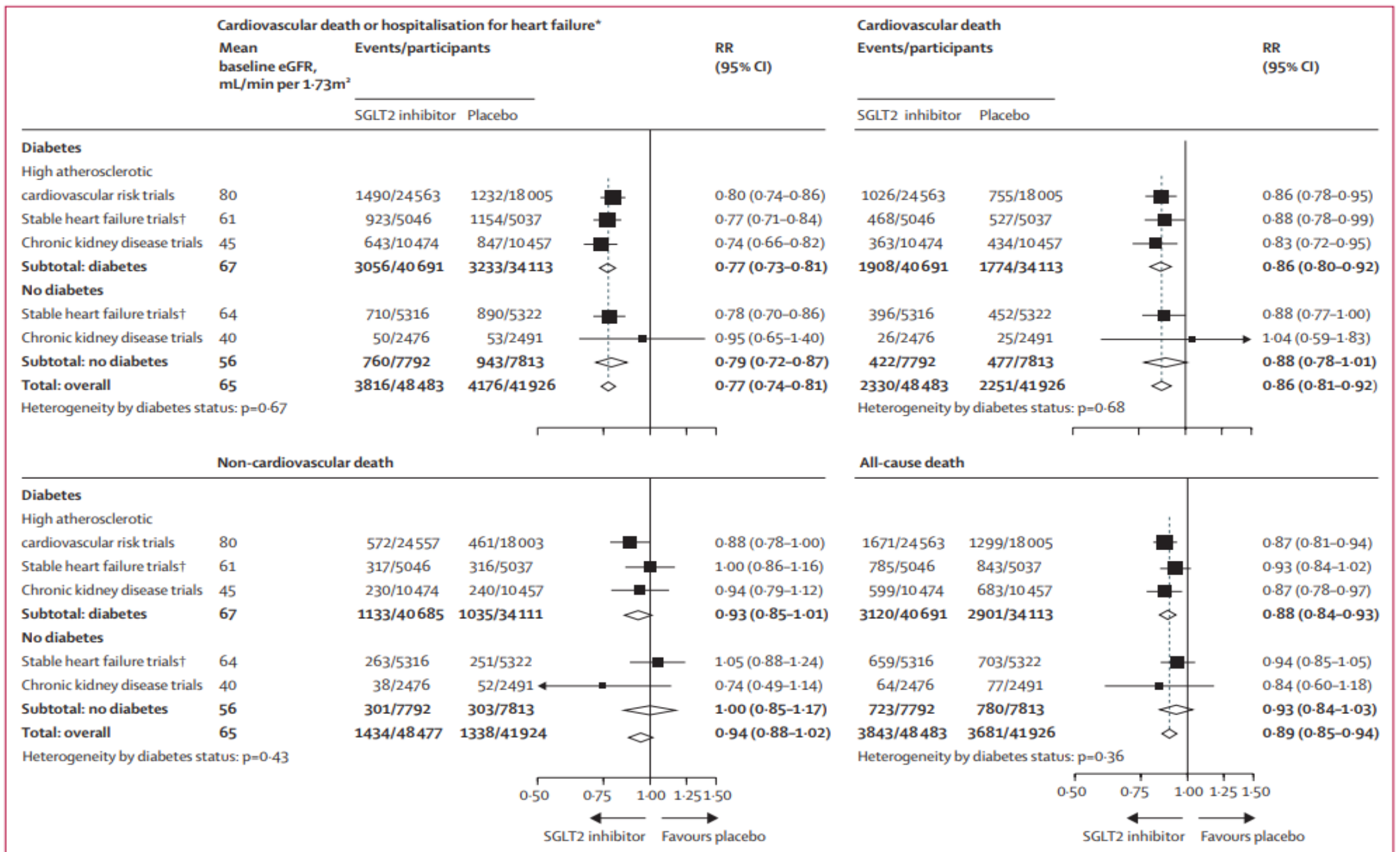


Figure 3: Effect of sodium glucose co-transporter-2 inhibition on heart failure and mortality outcomes by diabetes status

The Nuffield Department of Population Health Renal Studies Group* and the SGLT2 inhibitor Meta-Analysis Cardio-Renal Trialists' Consortium

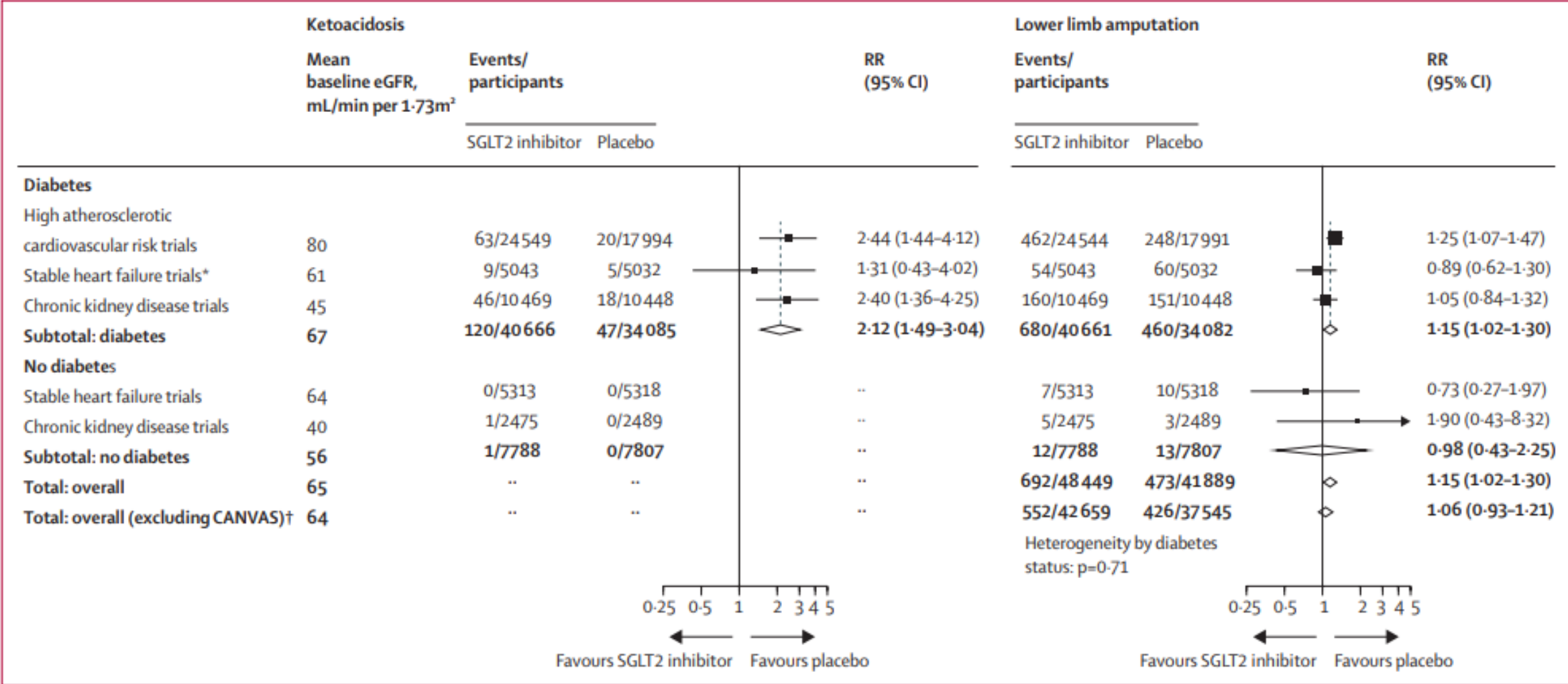


Figure 4: Effect of sodium glucose co-transporter-2 inhibition on ketoacidosis and lower limb amputation by diabetes status