Warum SGLT2-inhibitoren auch bei GFR unter 20 getest werden

Why SGLT2 inhibitors are also tested in patients with GFR <20

Ron Gansevoort, MD PhD, FERA

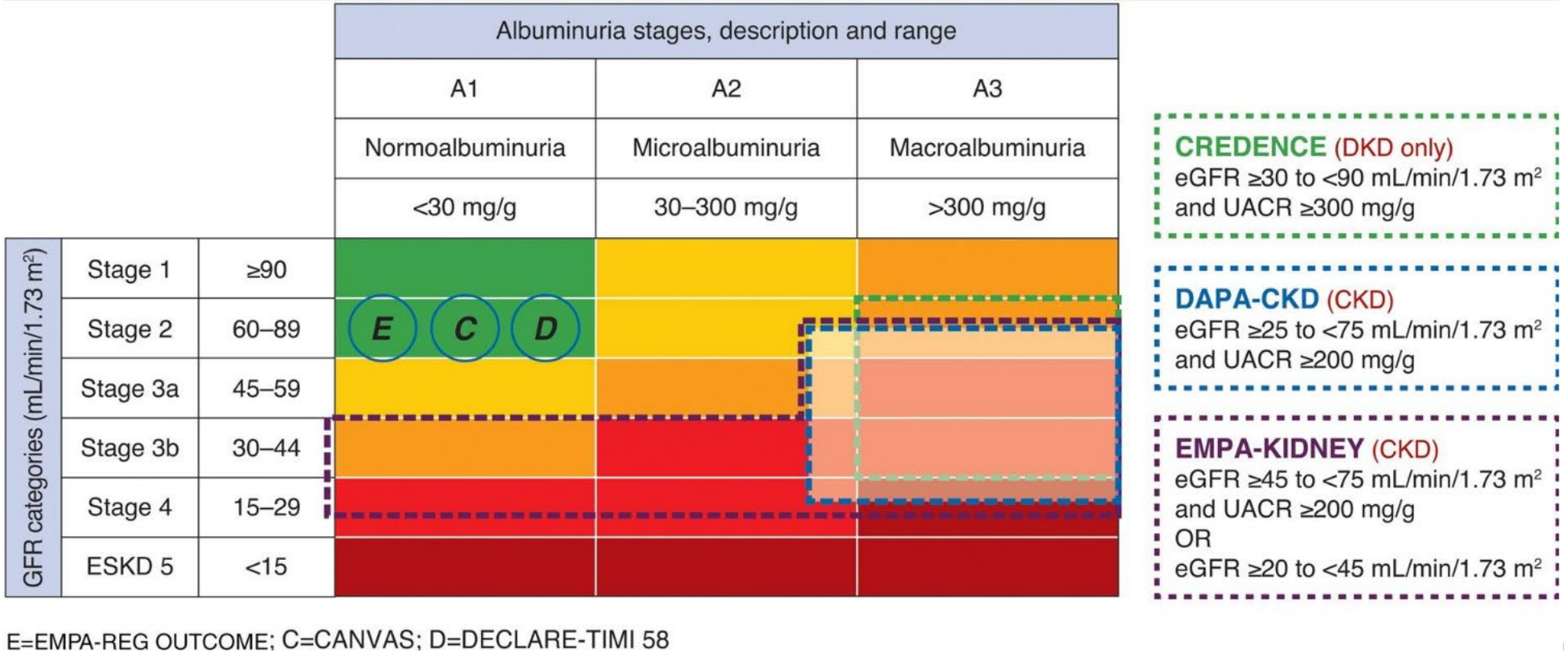
Prof. Medicine
Dept. Nephrology
UMC Groningen, the Netherlands

NL-11279 prod 3/23

Conflicts of interest

- Fees for concultancy and/or grants for research from Abbvie, Astra-Zeneca, Baxter, Bayer, Dutch Kidney Foundation, Dutch Heart Foundation, Galapagos, Happitech, Healthy.io, Health Holland, Ipsen, Mironid, Roche, Sanofi-Genzyme, Sandoz, Otsuka and ZonMw
- All money is paid to the employing institution (the UMC Groningen)
- No stock nor patents

Positioning the SGLT2 inhibitor trials

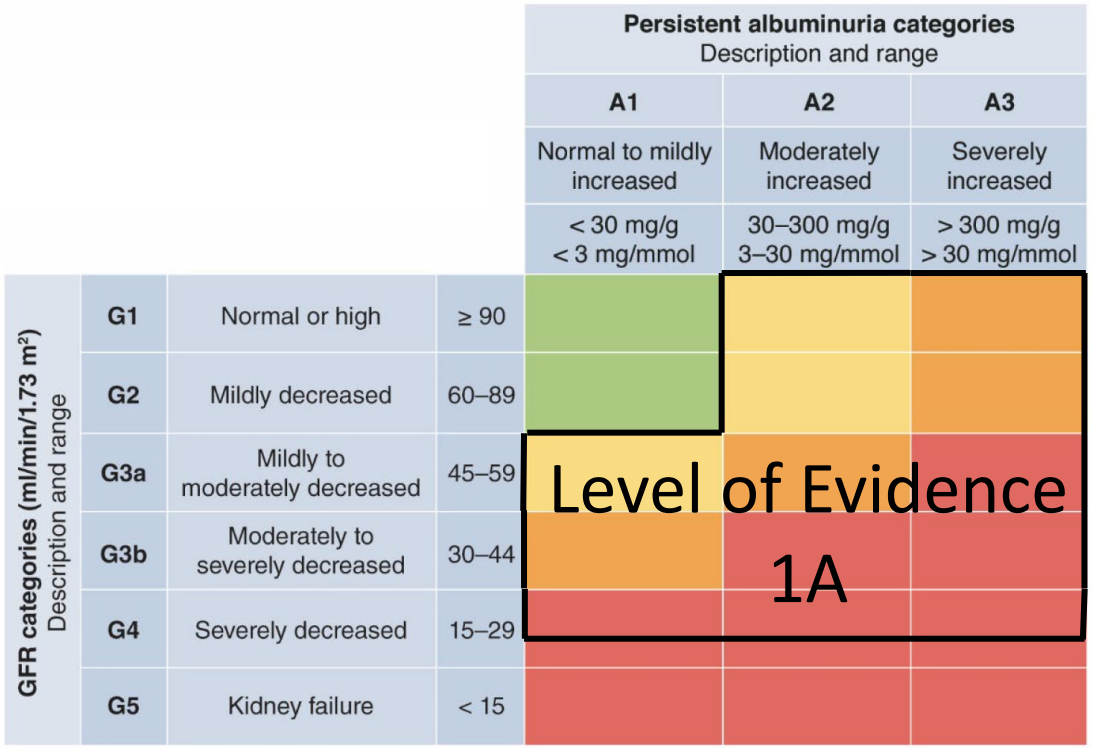


E=EMPA-REG OUTCOME; C=CANVAS; D=DECLARE-TIMI 58

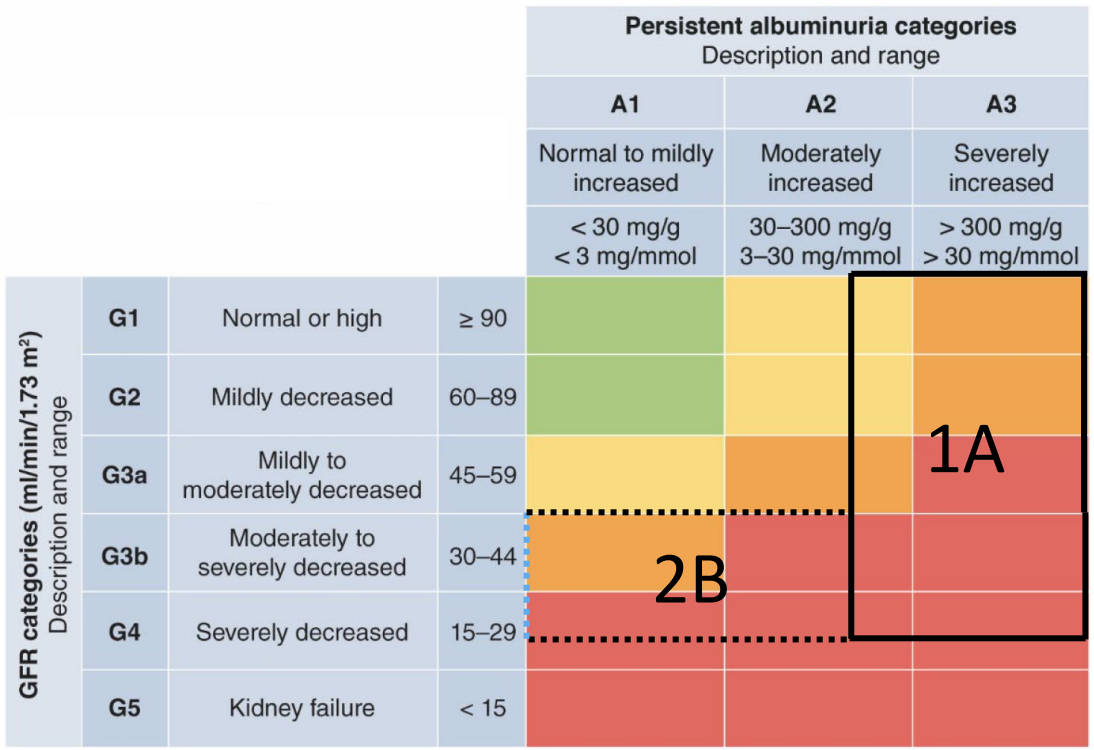
Lambers Heerspink et al, Nephrol Dial Transplant 2020;35:274-82

The 2024 KDIGO guideline
Evaluation and Management of CKD

CKD with T2DM



Non-diabetic CKD

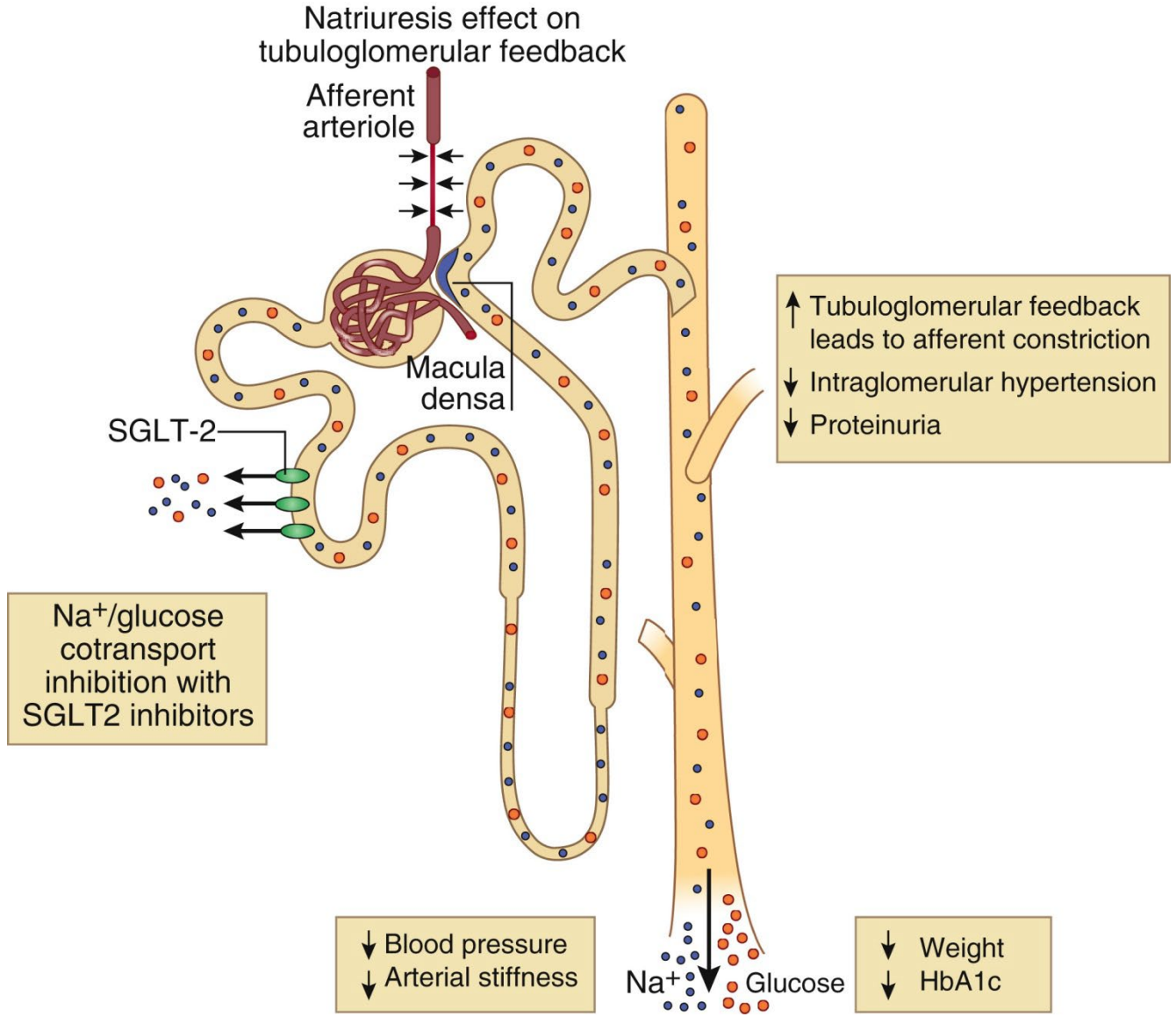


In press

KDIGO Guideline for the Evaluation and Management, of CKD. Kidney Int 2024

SGLT-2-inhibitors

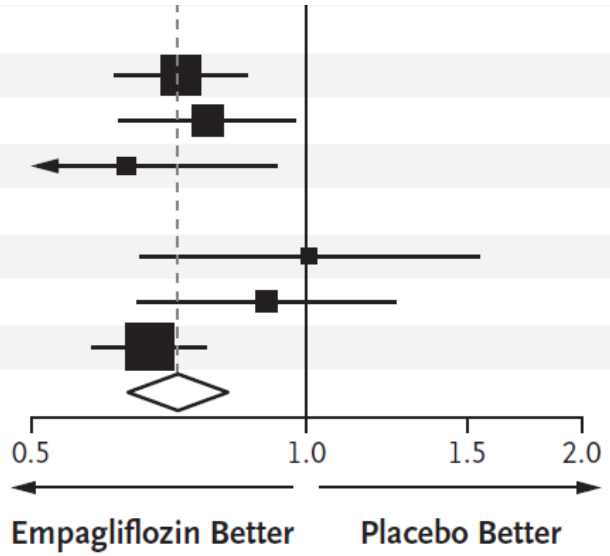
Mode of Action



Lambers Heerspink et al, *Kidney Int* 2018;94:26-39

The EMPA-KIDNEY trial
Severely impaired eGFR, does it matter?

Subgroup	Empagliflozin (no. of patients with event/total no.)	Placebo (no. of patients with event/total no.)	Hazard Ratio for Progression of Kidney Disease or Death from Cardiovascular Causes (95% CI)
Estimated GFR			
<30 ml/min/1.73 m²	247/1131	317/1151	0.73 (0.62–0.86)
≥30 to <45 ml/min/1.73 m²	140/1467	175/1461	0.78 (0.62–0.97)
≥45 ml/min/1.73 m²	45/706	66/693	0.64 (0.44–0.93)
Urinary albumin-to-creatinine ratio			
<30	42/665	42/663	1.01 (0.66–1.55)
≥30 to ≤300	67/927	78/937	0.91 (0.65–1.26)
>300	323/1712	438/1705	0.67 (0.58–0.78)
All patients	432/3304	558/3305	0.72 (0.64–0.82)

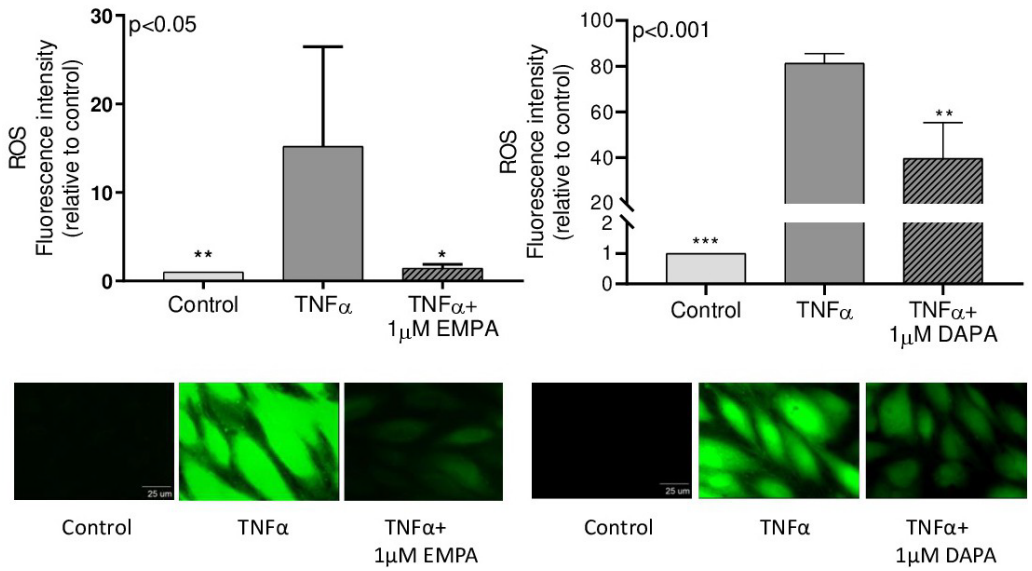


Inclusion: eGFR 20-45 OR eGFR 45-75 mL/min/1.73m2 and ACR >200 mg/g

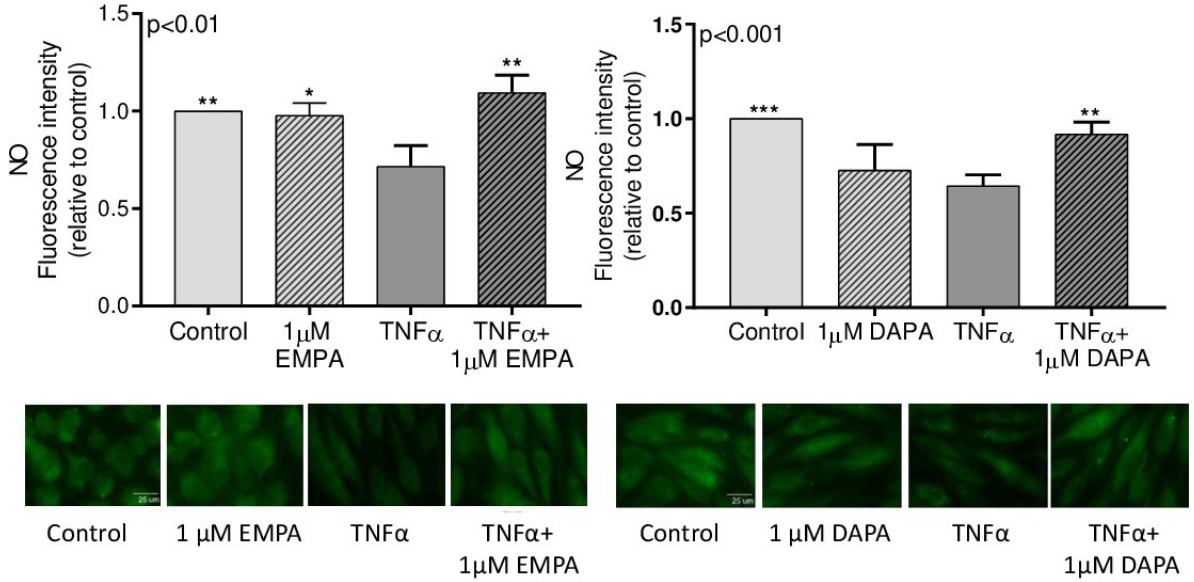
Herrington et al, *N Eng J Med* 2023;388:117-27

SGLT2 inhibition
Effects independent of tubular SGLT2 ?

Reactive Oxygen Species (ROS) levels
Vasoconstricting



Nitric oxide (NO) levels
Vasodilating

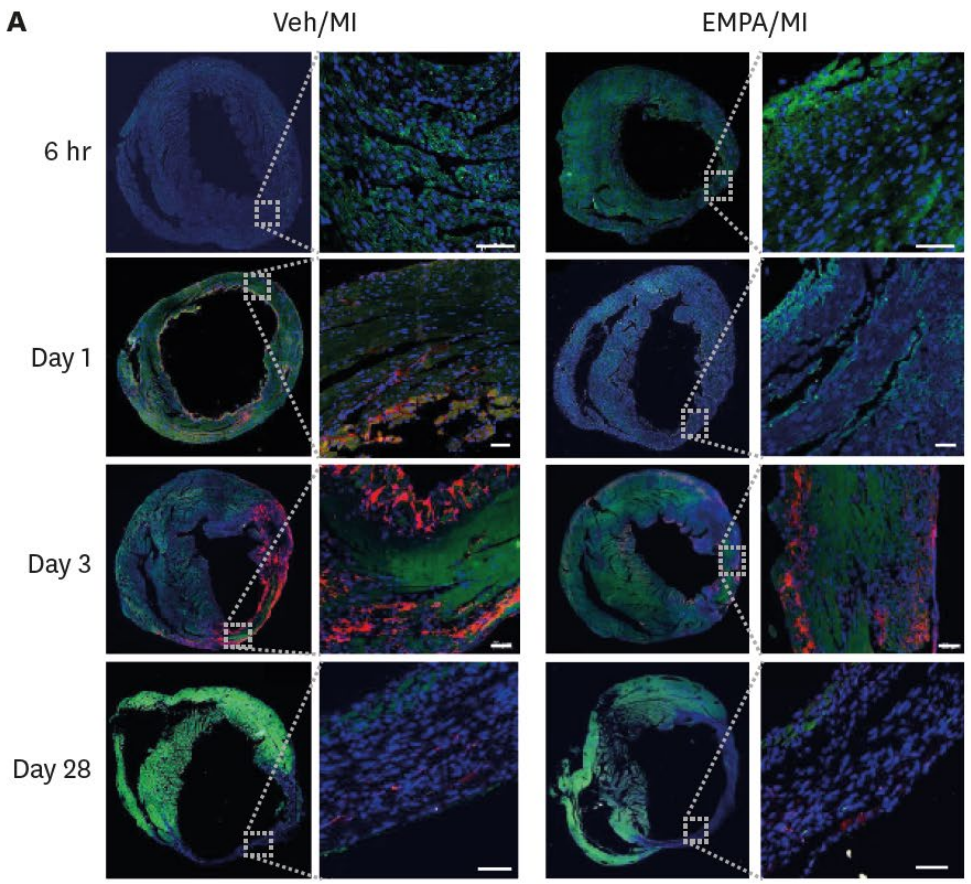


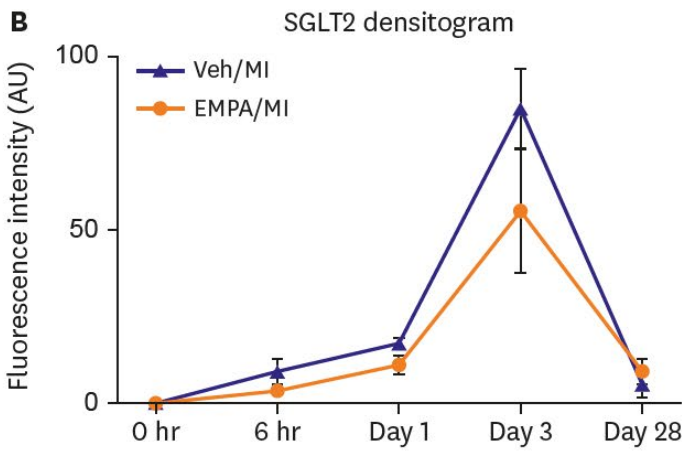
In vitro stimulating growth of human coronary artery endothelial cells with TNFα / SGLT2i

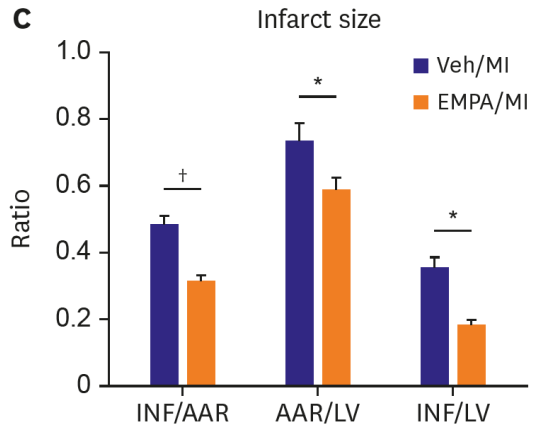
Uthman et al, *Cell Physiol Biochem* 2019;53:865-886

SGLT2 inhibition

SGLT2 is expressed in the heart





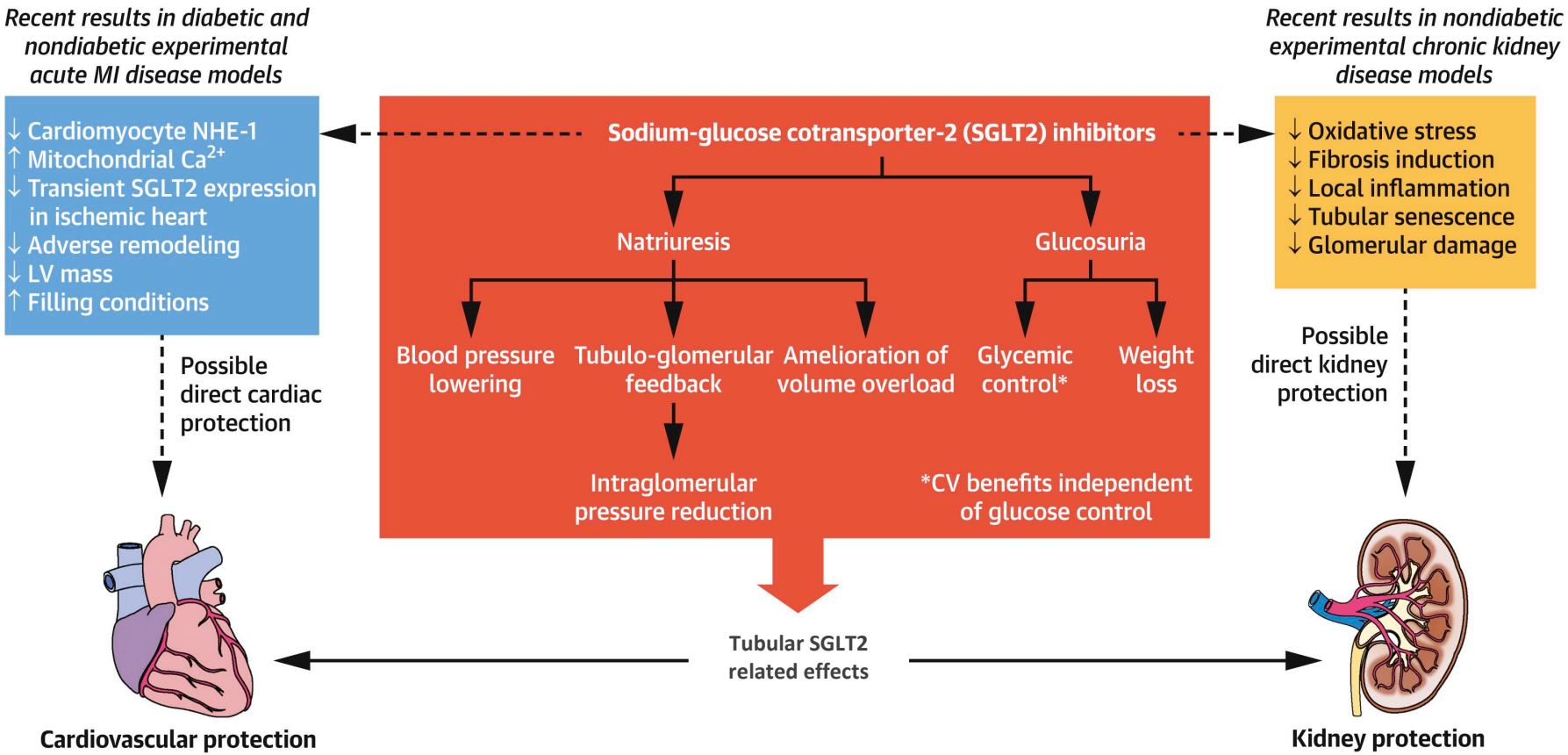


Mice myocardial infarction model, pretreated with vehicle or empagliflozin, staining DNA (blue), TnT (green), SGLT2 (red)

Lee et al, *Kor Cir J* 2021;51:251-62

SGLT2 inhibition

Pleiotropic, direct effects on the kidney and the heart?



Udell et al, *J Am Col Cardiol* 2022;79:2058-2068

SGLT2 inhibition in dialysis
Limited experience

	Dapagliflozin		Placebo		Total	
	n (%)	Event rate (100 patient-years)	*n* (%)	Event rate (100 patient-years)	*n* (%)	Event rate (100 patient-years)
Overall mortality	101/2152 (4.7)	2.2	146/2152 (6.8)	3.1	247/4304 (5.7)	2.6
Without chronic dialysis, *n*	2084		2053		4137	
All-cause mortality	89 (4.3)	1.9	121 (5.9)	2.6	210 (5.1)	2.2
Cardiovascular death	35 (1.7)	0.7	44 (2.1)	0.9	79 (1.9)	0.8
Non-cardiovascular death	31 (1.5)	0.7	48 (2.3)	1.0	79 (1.9)	0.8
Undetermined cause of death	23 (1.1)	0.5	29 (1.4)	0.6	52 (1.3)	0.5
With chronic dialysis, *n*	68		99		167	
All-cause mortality	12 (17.6)	8.6	25 (25.3)	13.4	37 (22.2)	11.4
Cardiovascular death	6 (8.8)	3.9	6 (6.1)	2.6	12 (7.2)	3.1
Non-cardiovascular death	5 (7.4)	3.2	18 (18.2)	9.0	23 (13.8)	6.5
Undetermined cause of death	1 (1.5)	0.6	1 (1.0)	0.4	2 (1.2)	0.5

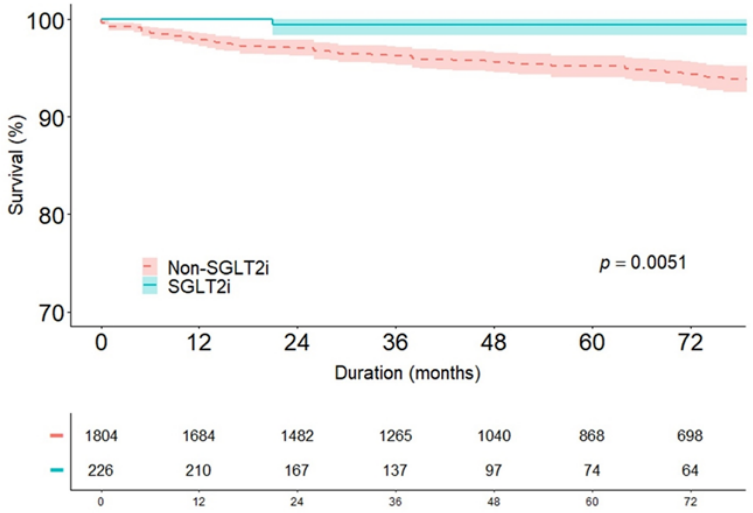
HR 0.64
P<0.01

Post-hoc analysis of the DAPA-CKD trial

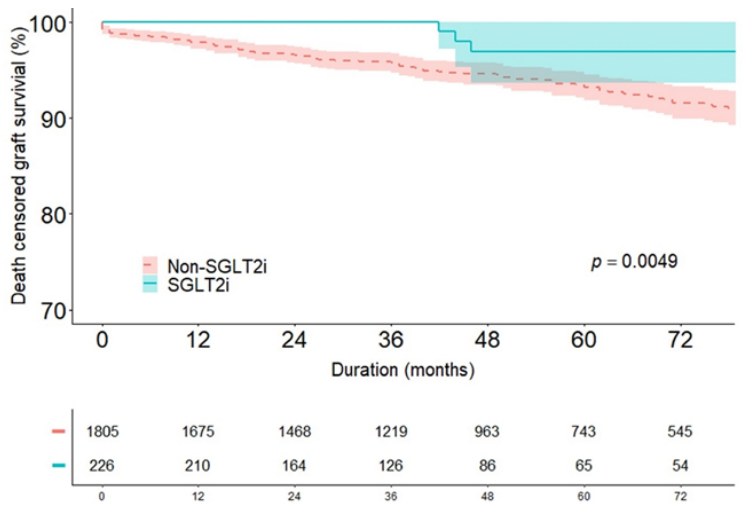
Lambers Heerspink et al, *Eur Heart J* 2021; 42:1216-27

SGLT2 inhibition in kidney transplant recipients
Limited experience

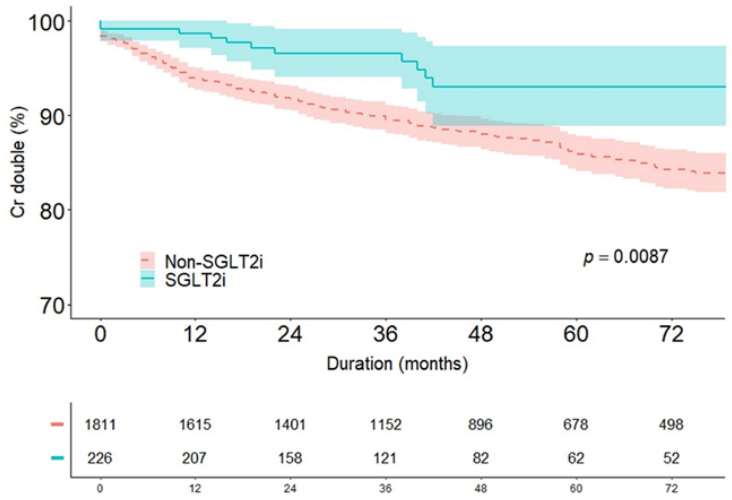
All cause mortality



Death censored graft failure



Doubling sCreat



Retrospective cohort study, 226 SGLT2i users and 1857 controls, all KTR with diabetes

Lim et al, *Transplantation* 2022; 106:e404-12

SGLT2 inhibition in kidney transplant recipients
Limited experience

Cox regression analysis of primary composite outcome and individual components

	Primary composite outcome		All-cause mortality		Death-censored graft failure		Serum creatinine doubling	
Model	**HR (95% CI)**	***P***	**HR (95% CI)**	***P***	**HR (95% CI)**	***P***	**HR (95% CI)**	***P***
Model 1[a]	0.45 (0.27-0.75)	0.002	0.17 (0.04-0.70)	0.014	0.27 (0.10-0.72)	0.009	0.49 (0.29-0.85)	0.010
Model 2[b]	0.37 (0.22-0.62)	<0.001	0.22 (0.05-0.90)	0.034	0.22 (0.08-0.59)	0.003	0.37 (0.54-0.90)	<0.001
Model 3[c]	0.38 (0.22-0.64)	<0.001	0.24 (0.06-0.99)	0.049	0.22 (0.08-0.61)	0.004	0.38 (0.22-0.66)	<0.001
Model 4[d]	0.43 (0.24-0.78)	0.006	0.35 (0.08-1.45)	0.147	0.34 (0.12-0.95)	0.040	0.41 (0.22-0.77)	0.005
Model 5[e]	0.45 (0.24-0.85)	0.013	0.31 (0.07-1.32)	0.112	0.30 (0.09-0.98)	0.046	0.45 (0.23-0.88)	0.019

[a]Unadjusted.
[b]Adjusted for age, sex, body mass index, donor type (deceased or living), ABO incompatibility, and acute rejection.
[c]Adjusted for age, sex, body mass index, donor type (deceased or living), ABO incompatibility, underlying comorbidities (diabetes, hypertension, and dyslipidemia), diabetic end-stage kidney disease, ACEi or ARB usage, and eGFR at 3 mo after transplant.
[d]Adjusted for age, sex, body mass index, donor type (deceased or living), ABO incompatibility, underlying comorbidities (diabetes, hypertension, and dyslipidemia), diabetic end-stage kidney disease, posttransplantation 1-y mean HbA1c (%) calculated by area under the curve, and metformin usage.
[e]Propensity score-matched covariates: age, sex, donor type (deceased or living), ABO incompatibility, underlying comorbidities (diabetes, hypertension, and dyslipidemia), diabetic end-stage kidney disease, posttransplantation 1-y mean HbA1c (%) calculated by area under the curve, metformin usage, acute rejection, ACEi or ARB usage, and eGFR at 3 mo after transplant.
ACEi, angiotensin-converting enzyme inhibitor; ARB, angiotensin receptor blocker; CI, confidence interval; eGFR, estimated glomerular filtration rate; HbA1c, hemoglobin A1c; HR, hazard ratio.

Retrospective cohort study, 226 SGLT2i users and 1857 controls, all KTR with diabetes

Lim et al, *Transplantation* 2022; 106:e404-12

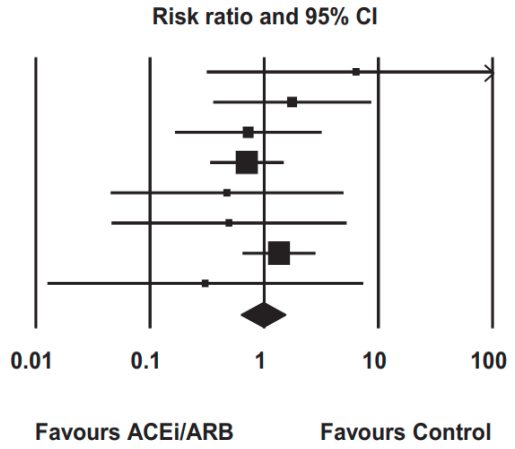
ACE inhibition in kidney transplant recipients

Limited experience

All cause mortality

Trial	Year	Risk ratio	95% CI		p	Dead / Total: RAS blockade	Control
Midtvedt	2001	6.36	0.31	129.85	0.2	2 / 54	0 / 69
Amara	2010	1.76	0.36	8.70	0.5	4 / 25	2 / 22
Philipp	2010	0.73	0.16	3.21	0.7	3 / 255	4 / 247
Ibrahim	2013	0.71	0.33	1.49	0.4	10 / 77	14 / 76
Paoletti	2013	0.47	0.04	4.97	0.5	1 / 36	2 / 34
Salzberg	2014	0.49	0.05	5.30	0.6	1 / 66	2 / 65
Knoll	2015	1.35	0.64	2.83	0.4	14 / 103	11 / 109
Mandelbrot	2015	0.30	0.01	7.41	0.5	0 / 138	1 / 126
Summary RR		**0.96**	**0.62**	**1.51**	**0.9**		

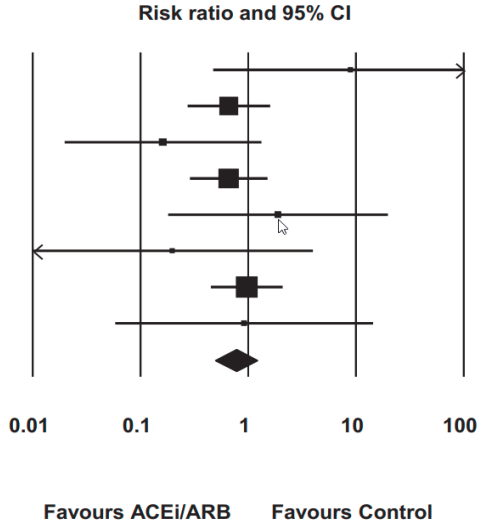
Q 4.8; p 0.87; $I^2 = 0\%$



Graft failure

Trial	Year	Risk ratio	95% CI		p	Graft failure / Total: RAS blockade	Control
Midtvedt	2001	8.91	0.47	168.87	0.2	3 / 54	0 / 69
Amara	2010	0.66	0.27	1.61	0.4	6 / 25	8 / 22
Philipp	2010	0.16	0.02	1.33	0.09	1 / 255	6 / 247
Ibrahim	2013	0.66	0.29	1.52	0.3	8 / 77	12 / 76
Paoletti	2013	1.89	0.18	19.89	0.6	2 / 36	1 / 34
Salzberg	2014	0.20	0.01	4.03	0.3	0 / 66	2 / 65
Knoll	2015	0.97	0.45	2.10	0.9	11 / 103	12 / 109
Mandelbrot	2015	0.91	0.06	14.44	0.9	1 / 138	1 / 126
Summary RR		**0.76**	**0.49**	**1.18**	**0.2**		

Q 6.7; p 0.46 $I^2 = 0\%$



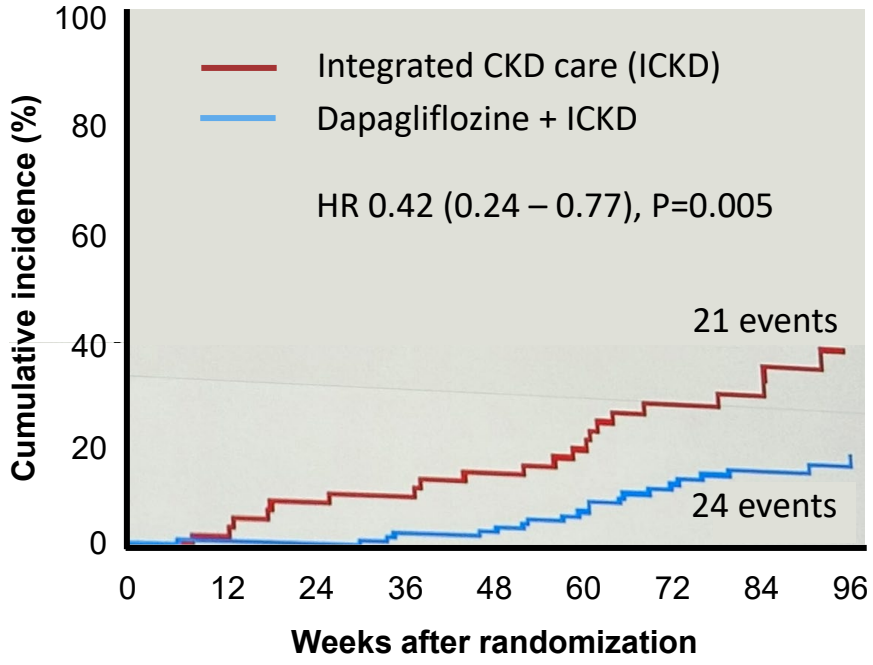
Meta-analysis of RCTs with RAASi in KTR >1 yr FU

LHiremath et al, *Am J Kidney Dis* 2016; 69:78-86

SGLT2 inhibition in CKD stages G4-5
Limited experience

Renal composite outcome

≥50% eGFR decline, eGFR<5 or start of KRT



ICKD	60	59	54	53	50	43	30	24	13
Dapa + ICKD	120	118	118	114	111	96	82	62	36

Renal and HF outcome

Renal outcome + incidence HF hospitalization

HR 0.46 (0.25 – 0.82), p=0.008

Renal and CV outcome

Renal outcome + incidence AP, PTCA/CABG, MI, CVA and HF hospitalization

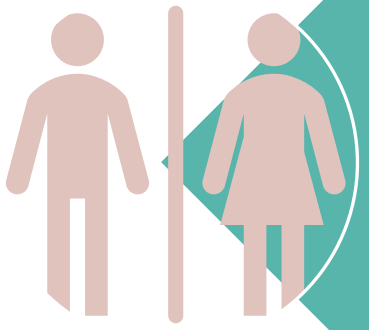
HR 0.53 (0.30 – 0.94), p=0.03

Open label (i.e. no placebo)
Single center
Limited number of patients (n=180)
Powered for n=225, aborted early

Open label RCT, 180 patients CKD stages G4-5 randomized 1:2 to SC (standard care) or SC + dapagliflozin 5-10 mg OD

Chiu Y et al, ASN LBCT session 2024

The Renal Lifecycle trial
An Investigator Initiated Study

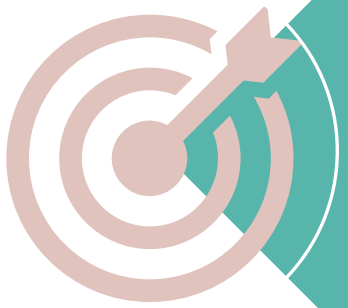


In total n=1750 (endpoint driven)

or 1) severely impaired kidney function; eGFR <25 ml/min/1.73m^2

or 2) patients on dialysis

or 3) kidney transplant recipients with an eGFR <45 ml/min/1.73m^2

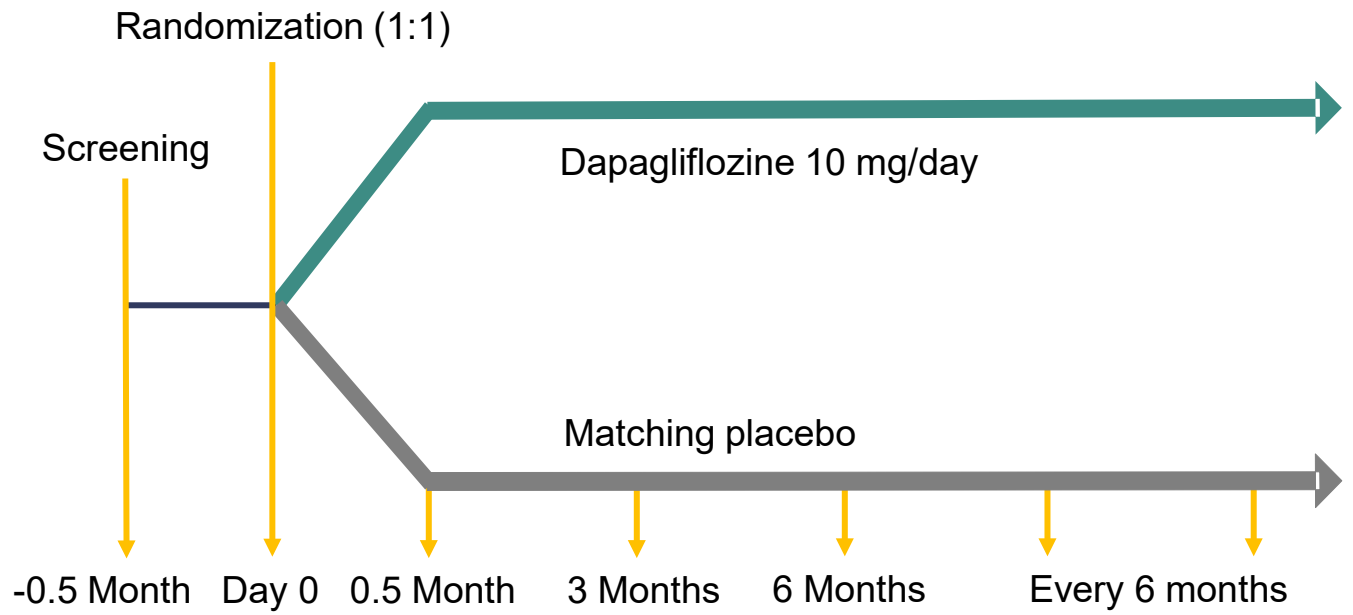


Endpoints

1) Composite of incidence kidney failure, HF hospitalization, mortality
2) Incidence of each compontent in the overall population
3) Incidence of compostie in each subgroup
4) Safety & tolerability

Trial design

- Pragmatic: visits as part of routine clinical



- Trial will last ± 4 yr, dependent on incidence “primary end points”

A joint project

The Netherlands

- Groningen + 59 centers

Germany

- Wurzburg (prof. Christoph Wanner) + 15 sites

Belgium

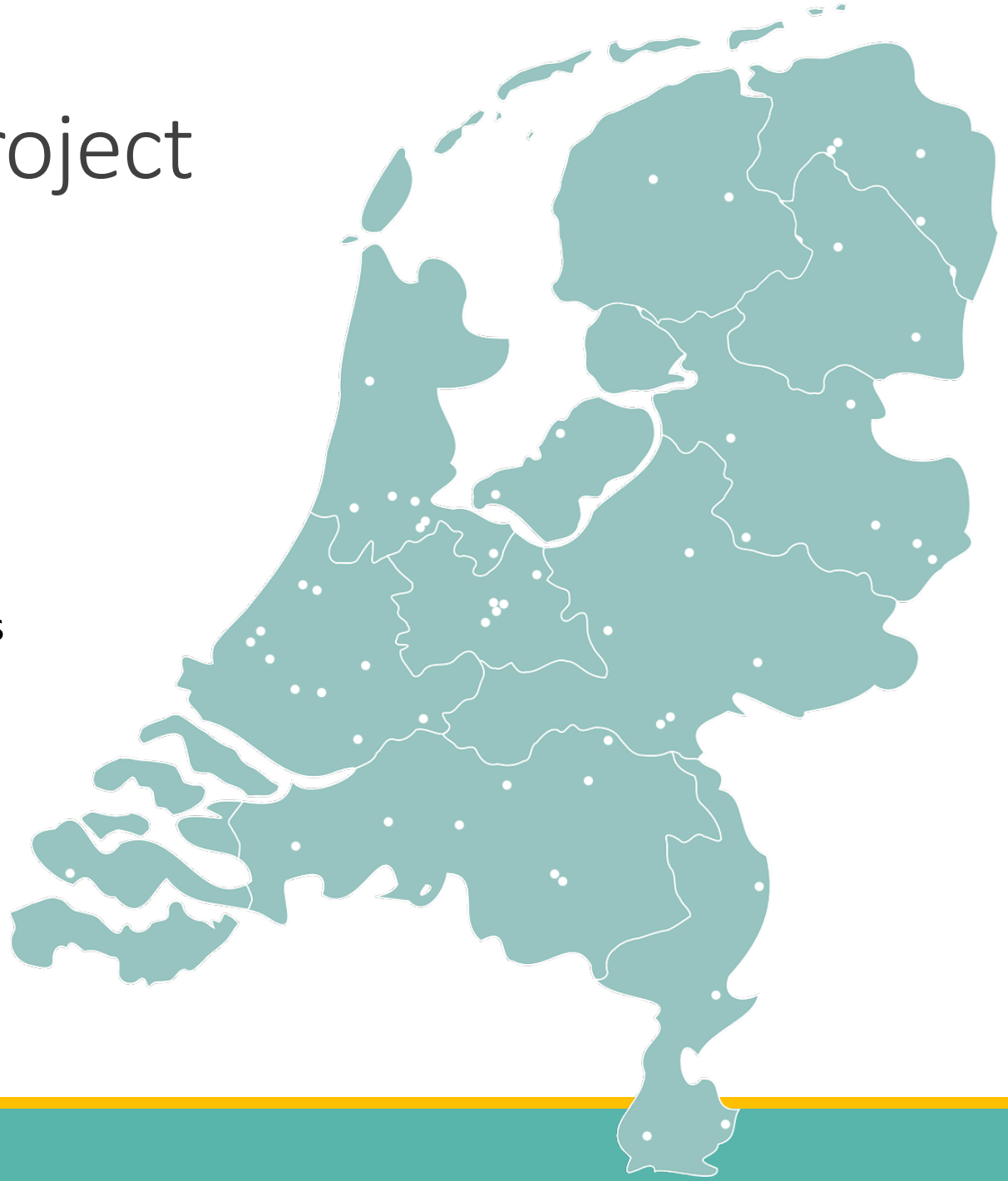
- Leuven (prof. Dirk Kuypers) + 9 sites

Australia

- Sydney (dr. Sunil Badve) + 13 sites

Spain

- Valencia (dr. Jose Gorriz) + 19 sites



Conclusions

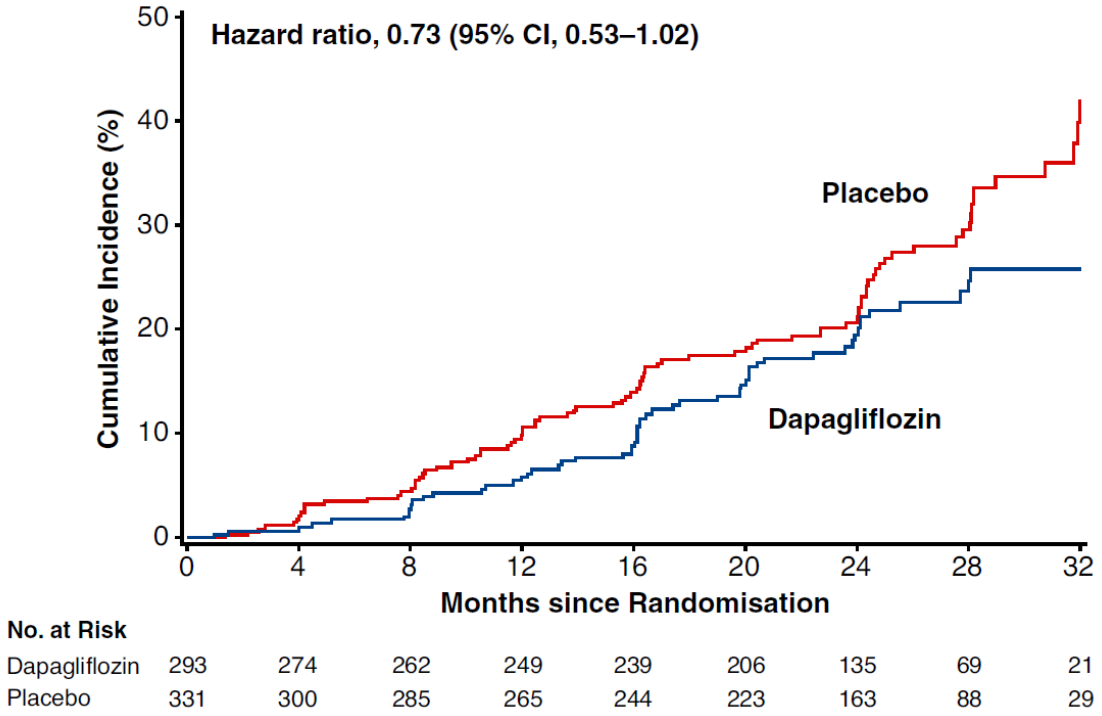
As yet starting SGLT2 inhibitors in case of severe CKD should be avoided

- Theoretically, this class of drugs should be less / not effective at low kidney function
- Very few clinical data (but surprisingly these preliminary findings do suggest efficacy)
- Experimental data suggest direct effects, independent of SGLT2 in the proximal tubules
- Safety concern, especially in immune suppressed kidney transplant recipients (UT/genital infections)

The Renal Lifecycle trial has been designed to specifically test the efficacy of SGLT2 inhibition in case of severe CKD. This study will have to provide the answer whether the efficacy / safety balance is sufficient in this vulnerable patient group

The DAPA-CKD trial

Severely impaired eGFR, does it matter ?



Participants:

CKD with or without T2D, *eGFR 25-30 ml/min,* n = 624

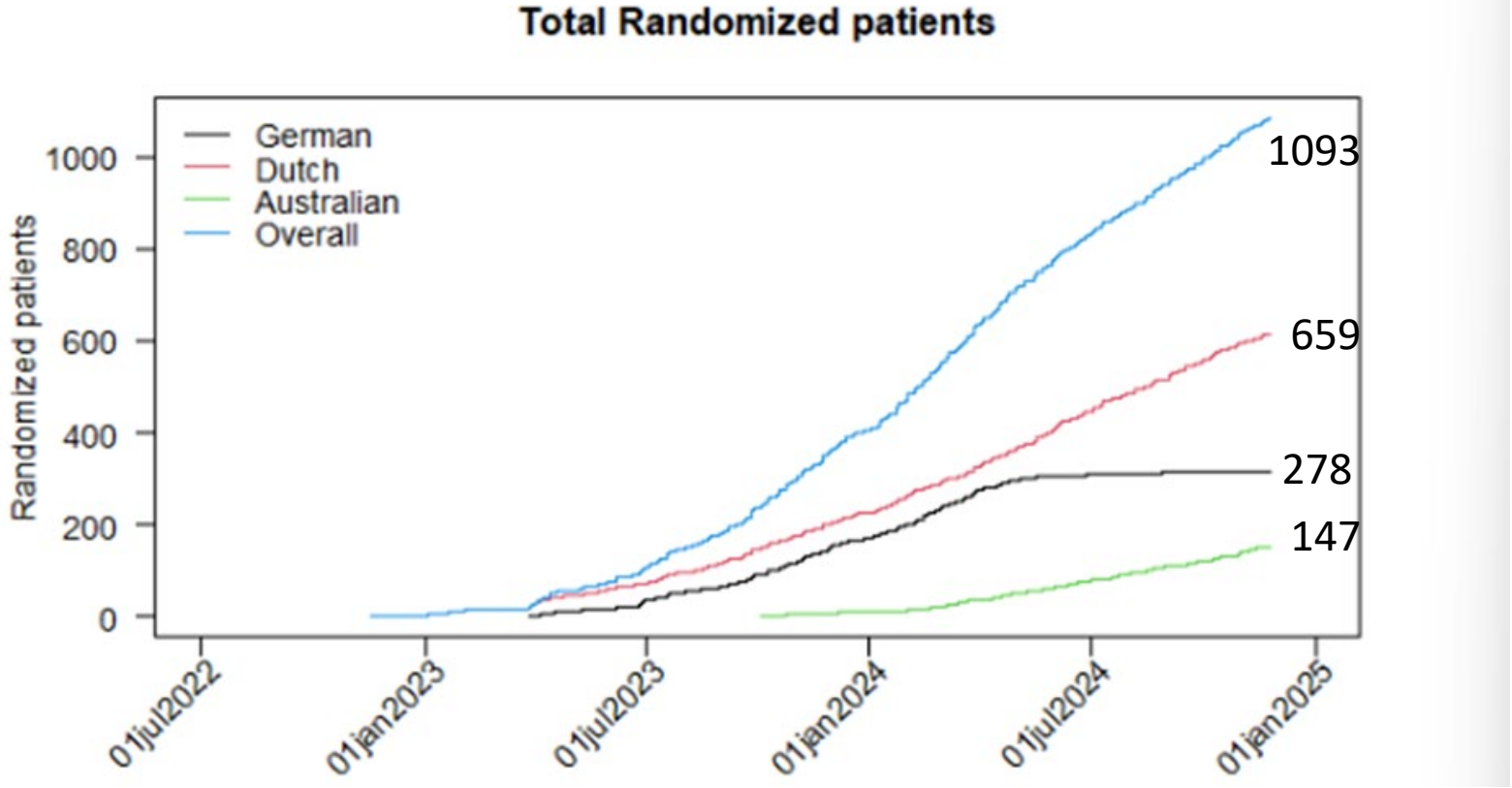
Primary outcome:

Incidence of 50% decrease in eGFR, kidney failure, or renal and cardiovascular mortality

Inclusion: eGFR 25-75 mL/min/1.73m2 and ACR >200 mg/g

Chertow et al, *JASN* 2021;32:2352-2361

Inclusion overall and per country
Progress 28 Nov 2024



RCT, double-blind, placebo vs dapagliflozin 10 mg, in 1500-2000 patients with severe CKD