Het gebruik van SGLT2-remmers bij ernstig nierfalen en hypertensie

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Disclosures

|	
Voor presentatie mogelijk relevante relaties	
Sponsoring of onderzoeksgeld:	Abbvie, Astra-Zeneca, Bayer, Galapagos, GSK, Healthy.io, Mironid, Otsuka, Roche (alle geld betaald aan de werkgever).
Honorarium of andere (financiële) vergoeding:	Bayer, Mironid, Otsuka (alle geld betaald aan de werkgever).
Aandeelhouder:	Niet van toepassing
Andere relatie, namelijk …	Niet van toepassing

SGLT-2-inhibitors

Mode of Action
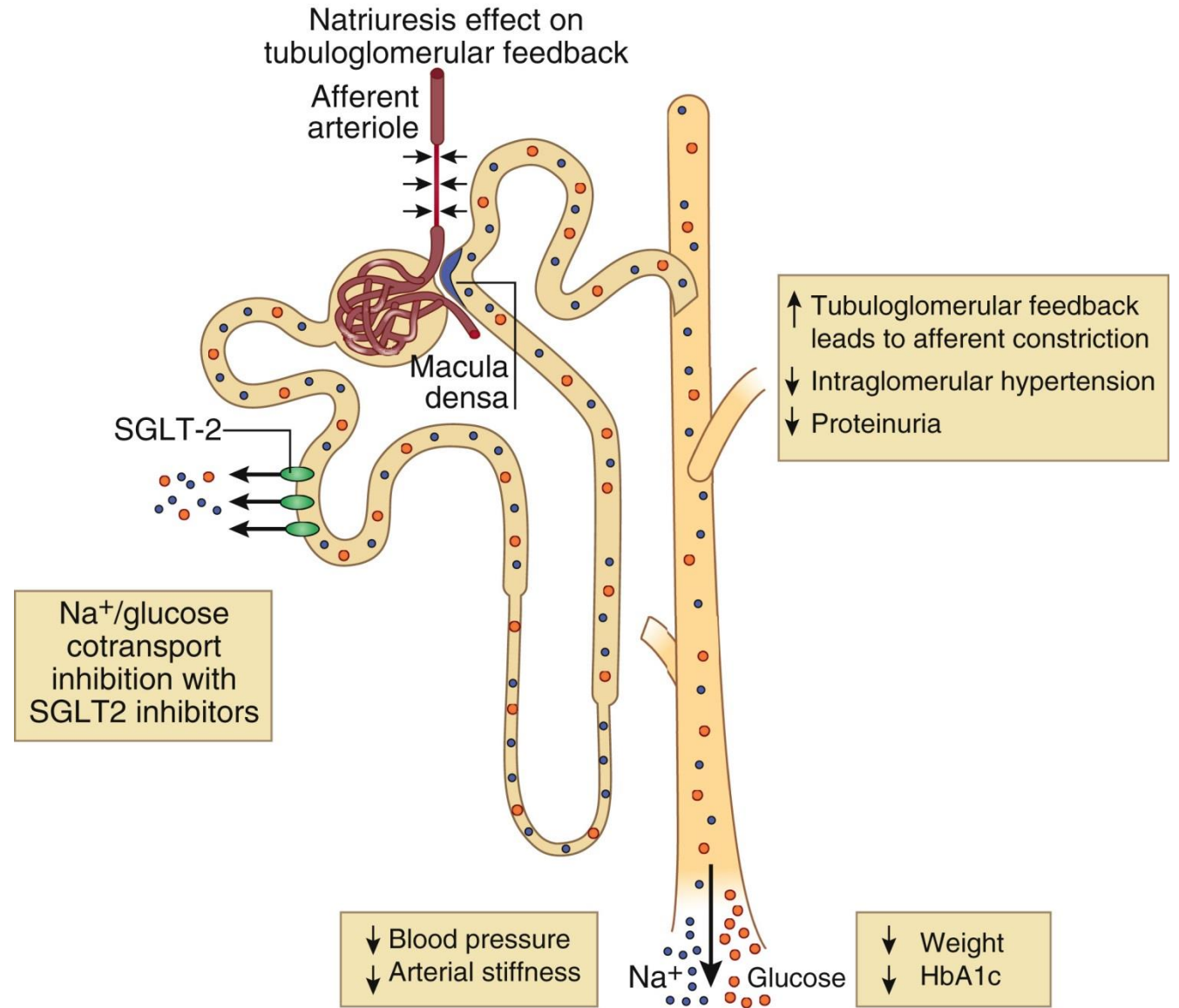
SGLT2i effect on bodyweight
Maximal after 12 − 28 weeks

Least square means body weight with 95% confidence interval:
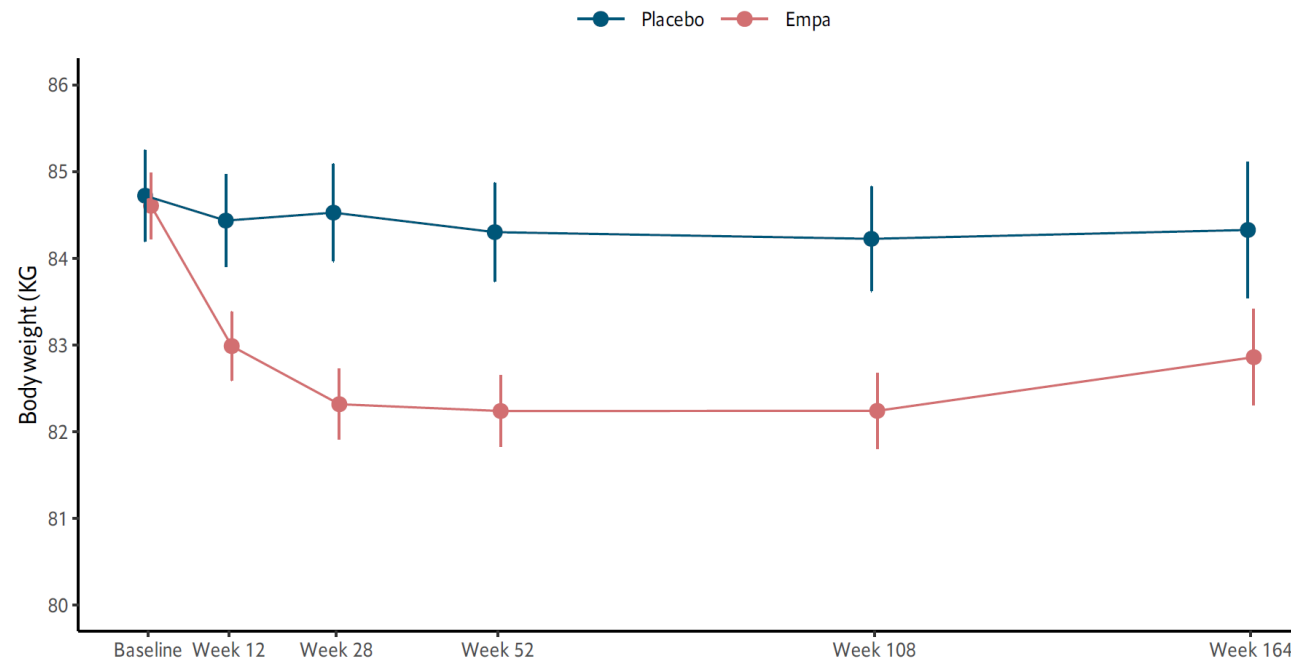
		Baseline	Week 12	Week 28	Week 52	Week 108	Week 164
Placebo	n=	706	745	731	749	729	138
Empagliflozine	n=	1417	1499	1441	1464	1534	281

BP lowering with SGLT2i
Comparison to placebo

Systolic Blood Pressure (mmHg)
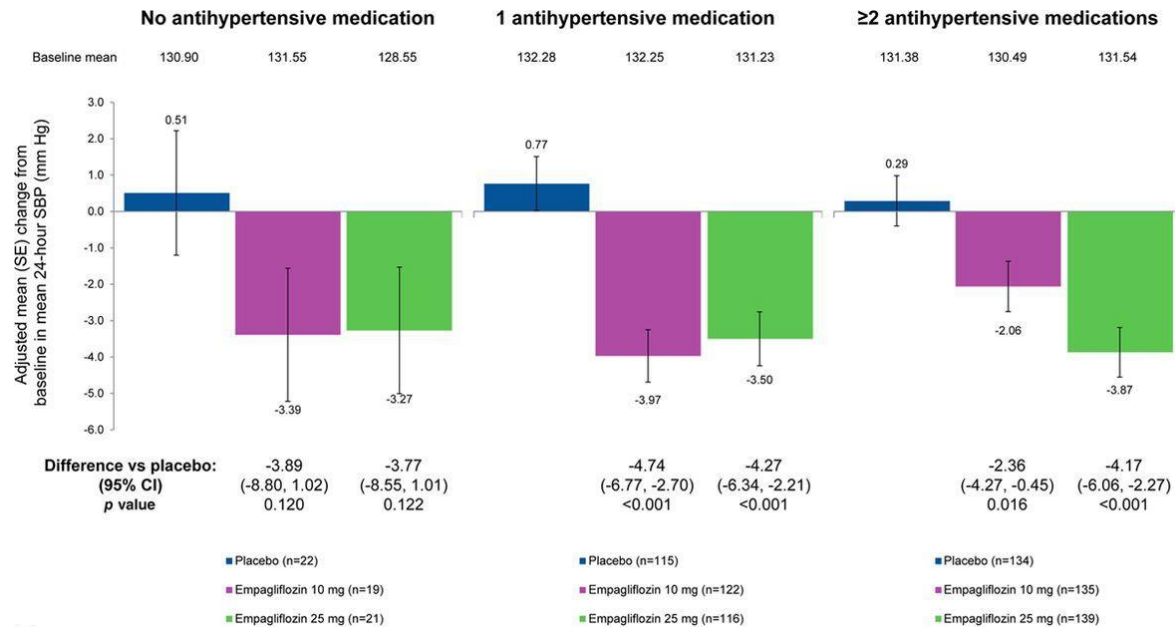
Diastolic Blood Pressure (mmHg)
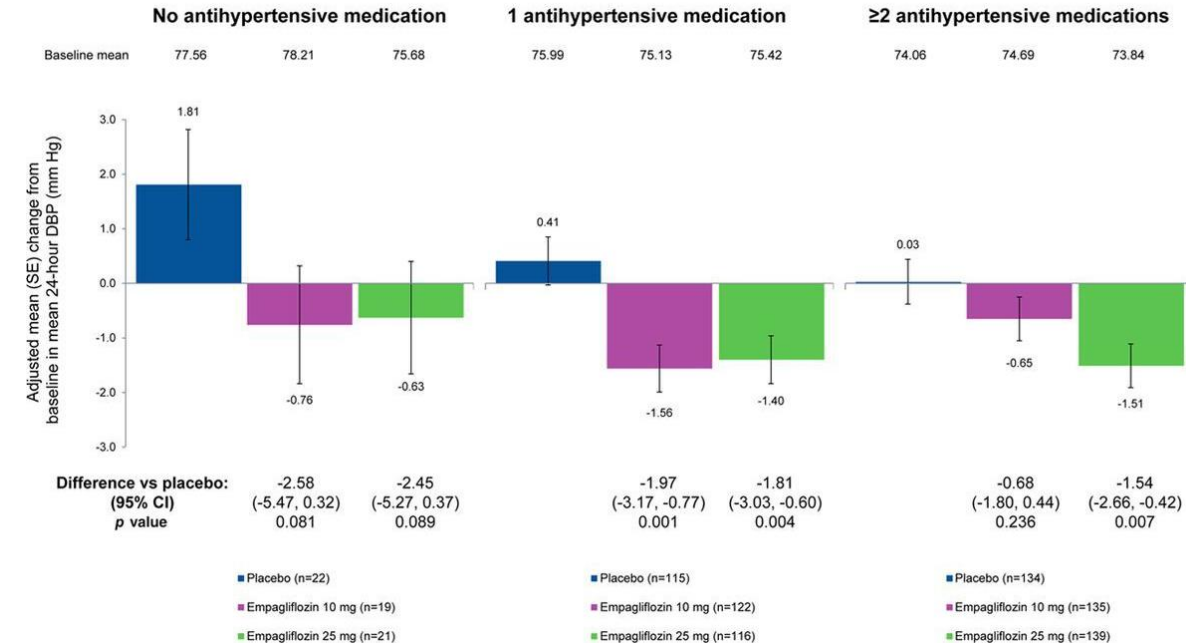
Cardioprotective effects of SGLT2i
Similar with/without a diuretic

End point	Placebo No./total No.	Events/100 py	Empagliflozin No./total No.	Events/100 py	Adjusted HR (95% CI)	P trend (by dose)	P interaction (no diuretics vs any dose)
CV death or first HHF							
All patients	551/2991	8.7	415/2997	6.9	0.79 (0.69-0.90)		
No diuretics	60/589	5.0	42/590	3.5	0.72 (0.48-1.06)	.91	.58
<40 mg	104/865	5.8	87/860	4.9	0.81 (0.61-1.08)		
40 mg	179/889	10.5	152/883	8.6	0.82 (0.66-1.02)		
>40 mg	151/563	14.7	127/576	11.8	0.77 (0.61-0.98)		
Any dose	434/2317	9.6	366/2319	7.9	0.81 (0.70-0.93)		
Total (first and recurrent) HHF							
All patients	541	NA	407	NA	0.73 (0.61-0.88)		
No diuretics	41	NA	28	NA	0.73 (0.42-1.29)	.68	.94
<40 mg	106	NA	76	NA	0.72 (0.50-1.05)		
40 mg	189	NA	136	NA	0.71 (0.52-0.98)		
>40 mg	184	NA	163	NA	0.81 (0.58-1.15)		
Any dose	479	NA	375	NA	0.75 (0.62-0.92)		
Composite kidney end point							
All patients	62/2991	1.2	50/2997	1.0	0.78 (0.54-1.13)		
No diuretics	9/589	0.9	3/590	0.3	NA	.40	NA
<40 mg	11/865	0.7	11/860	0.7	0.90 (0.39-2.08)		
40 mg	21/889	1.4	15/883	1.0	0.74 (0.38-1.45)		
>40 mg	19/563	2.0	19/576	2.0	0.87 (0.46-1.65)		
Any dose	51/2317	1.3	45/2319	1.1	NA		

Favors empagliflozin | Favors placebo

0.25 0.50 1 2
Adjusted HR (95% CI)

Post-hoc analysis of the EMPEROR trial (n=5,815) , subgroups according to diuretic use
Loop diuretic (n=3,346), thiazide (n=755), both (535), no diuretic (n=589)

Butler, Packer et al, *JAMA Cardiol* 2023;8:640-9
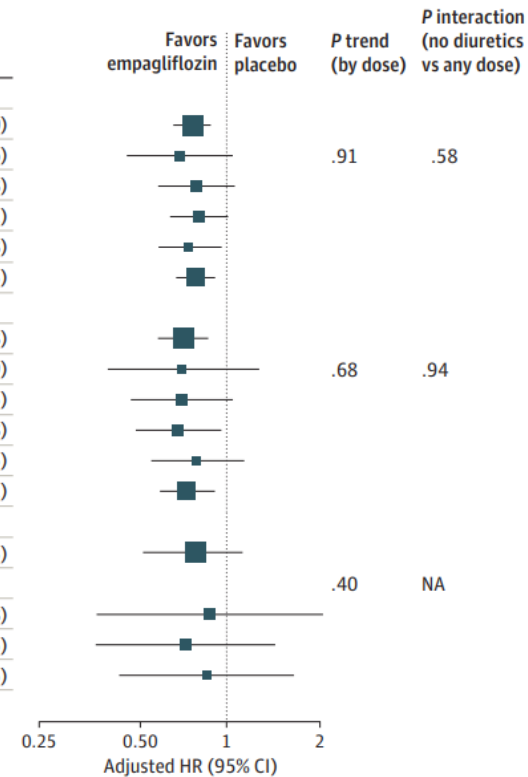
Improving Renoprotective Therapy by Targeting the Body Sodium Balance

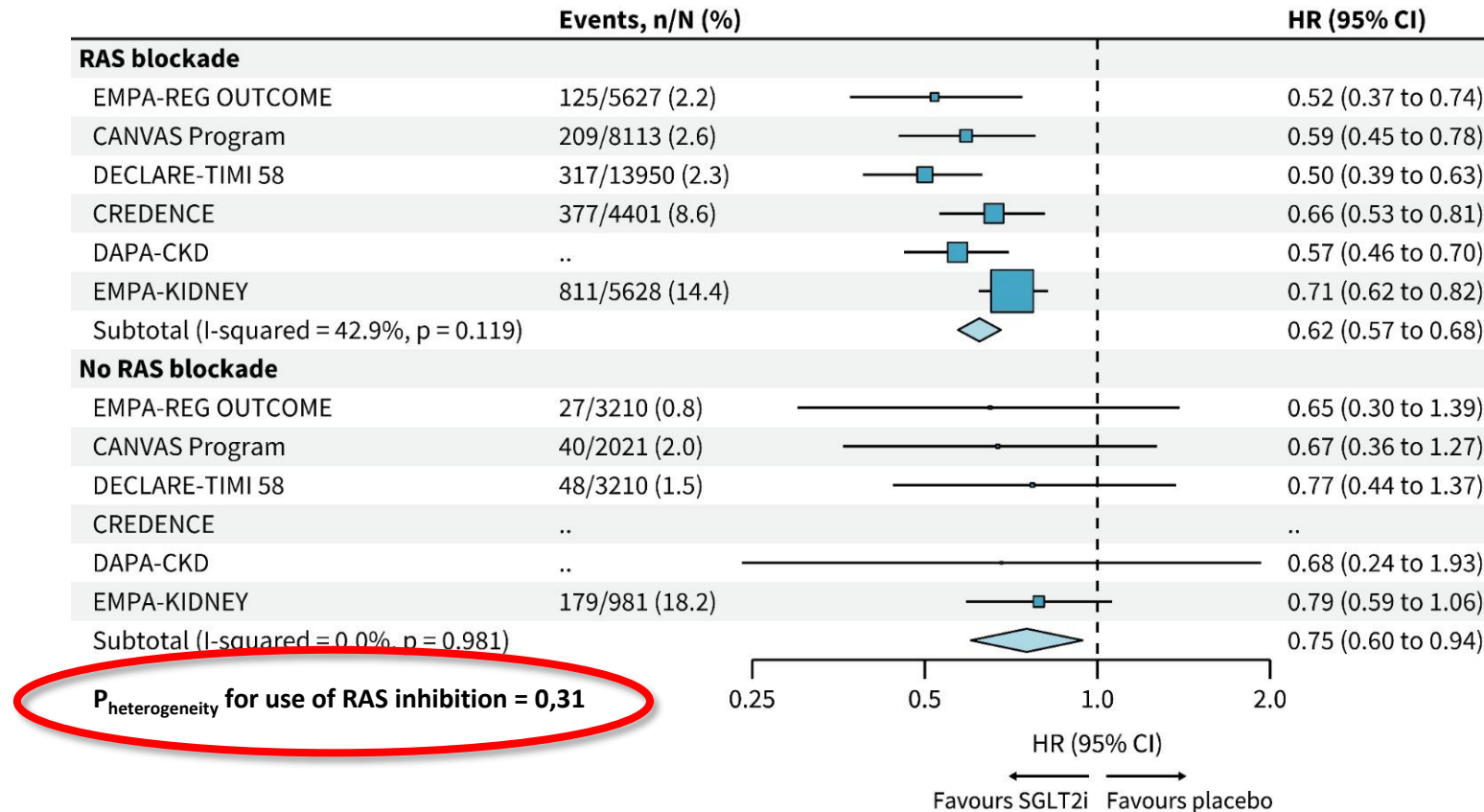Liffert Vogt[a]   Ron T. Gansevoort[b]

[a]Department of Internal Medicine, Section Nephrology, Amsterdam Cardiovascular Sciences, Amsterdam UMC, University of Amsterdam, Amsterdam, The Netherlands; [b]Division of Nephrology, University Medical Center Groningen, University of Groningen, Groningen, The Netherlands

BP + albuminuria lowering with SGLT2i
Combining with RASi
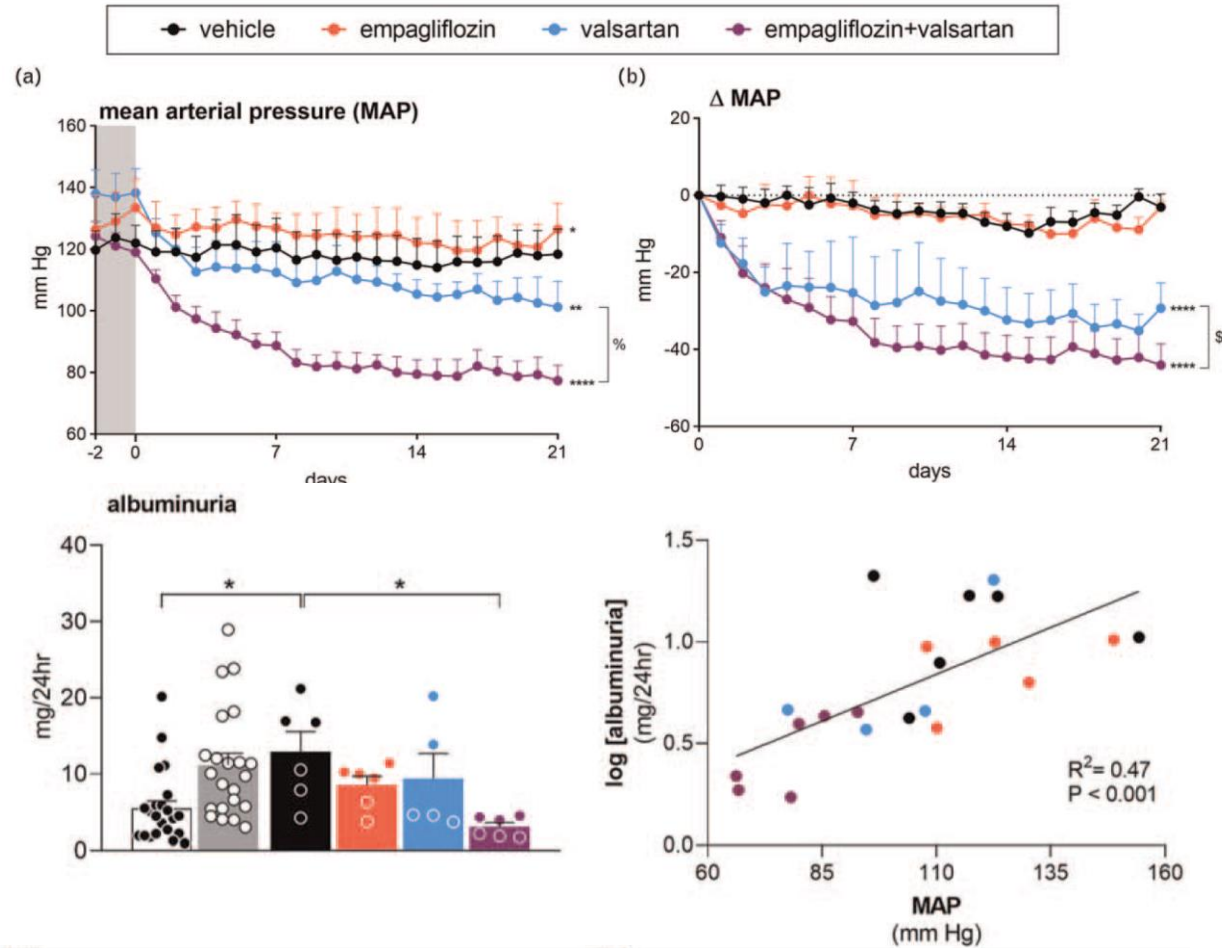
SGLT2i effects with/without RAAS inhibition
Incidence of the combined kidney outcome (ESKD, 57% eGFR, death)

	Events, n/N (%)		HR (95% CI)
RAS blockade			
EMPA-REG OUTCOME	125/5627 (2.2)		0.52 (0.37 to 0.74)
CANVAS Program	209/8113 (2.6)		0.59 (0.45 to 0.78)
DECLARE-TIMI 58	317/13950 (2.3)		0.50 (0.39 to 0.63)
CREDENCE	377/4401 (8.6)		0.66 (0.53 to 0.81)
DAPA-CKD	..		0.57 (0.46 to 0.70)
EMPA-KIDNEY	811/5628 (14.4)		0.71 (0.62 to 0.82)
Subtotal (I-squared = 42.9%, p = 0.119)			0.62 (0.57 to 0.68)
No RAS blockade			
EMPA-REG OUTCOME	27/3210 (0.8)		0.65 (0.30 to 1.39)
CANVAS Program	40/2021 (2.0)		0.67 (0.36 to 1.27)
DECLARE-TIMI 58	48/3210 (1.5)		0.77 (0.44 to 1.37)
CREDENCE	..		..
DAPA-CKD	..		0.68 (0.24 to 1.93)
EMPA-KIDNEY	179/981 (18.2)		0.79 (0.59 to 1.06)
Subtotal (I-squared = 0.0%, p = 0.981)			0.75 (0.60 to 0.94)

$P_{heterogeneity}$ for use of RAS inhibition = 0,31

HR (95% CI) 0.25 0.5 1.0 2.0

Favours SGLT2i ← → Favours placebo

Positioning the SGLT2 inhibitor trials
Lowering the threshold?

			Albuminuria stages, description and range		
			A1	A2	A3
			Normoalbuminuria	Microalbuminuria	Macroalbuminuria
			<30 mg/g	30–300 mg/g	>300 mg/g
GFR categories (mL/min/1.73 m²)	Stage 1	≥90			
	Stage 2	60–89	E C D		
	Stage 3a	45–59			
	Stage 3b	30–44			
	Stage 4	15–29			
	ESKD 5	<15			

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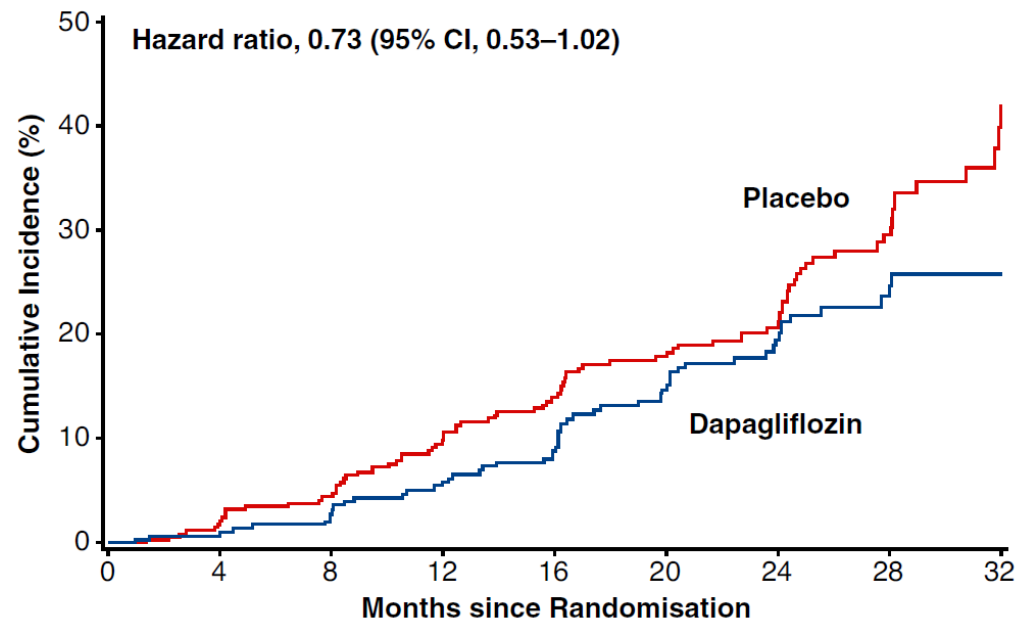and UACR ≥300 mg/g

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

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

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

The DAPA-CKD trial
Severely impaired eGFR, does it matter ?

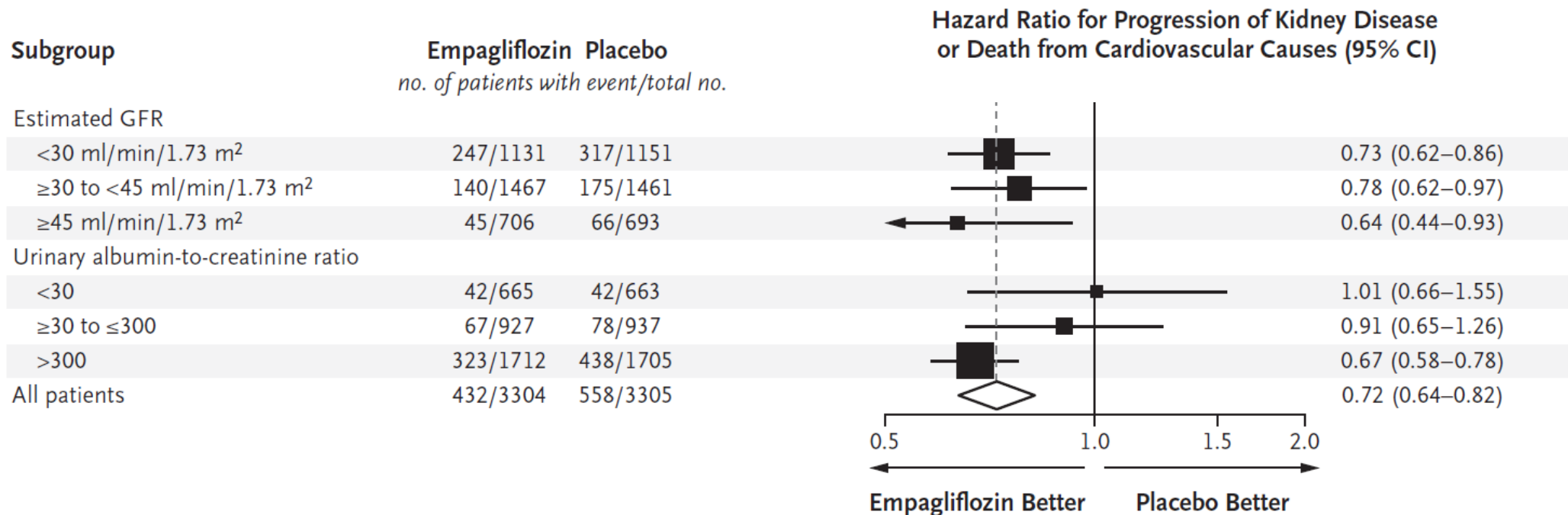Hazard ratio, 0.73 (95% CI, 0.53–1.02)

Participants:

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

Primary outcome:

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

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

Subgroup	Empagliflozin	Placebo	Hazard Ratio for Progression of Kidney Disease or Death from Cardiovascular Causes (95% CI)
	no. of patients with event/total no.		
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)

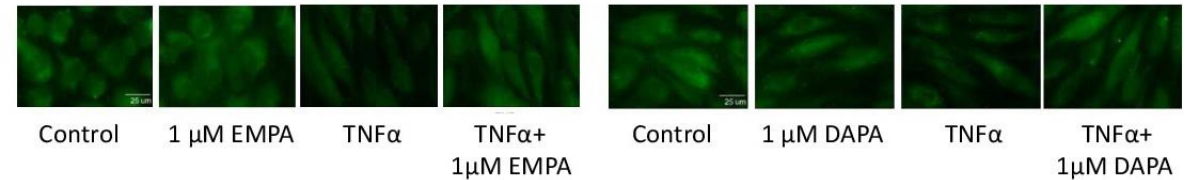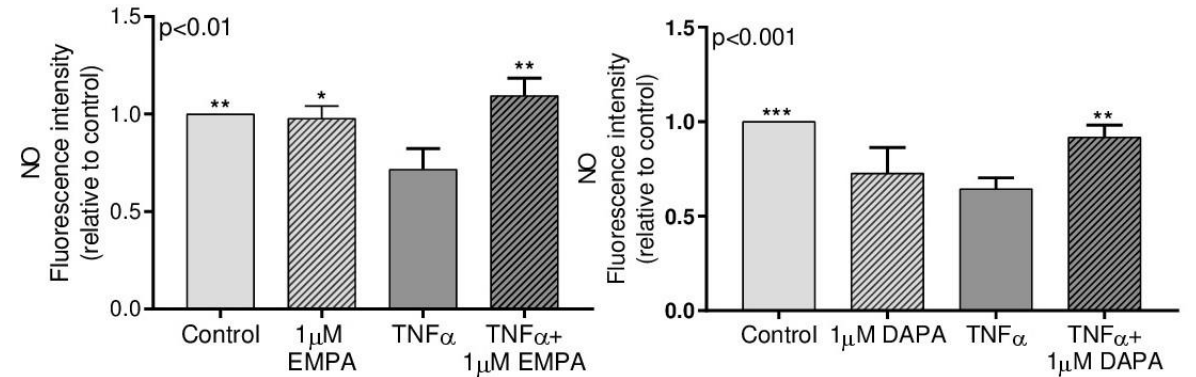Empagliflozin Better   Placebo Better

SGLT2 inhibition
Effects independent of tubular SGLT2 ?
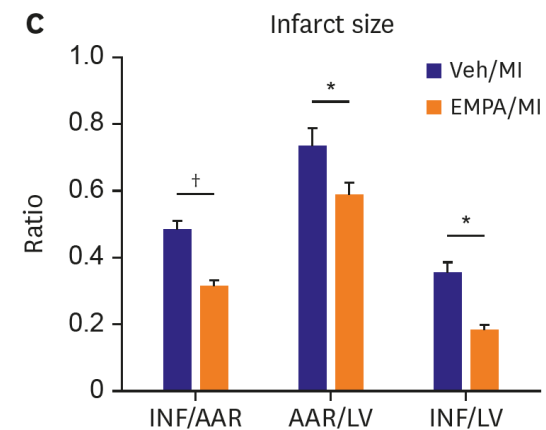

Reactive Oxygen Species (ROS) levels
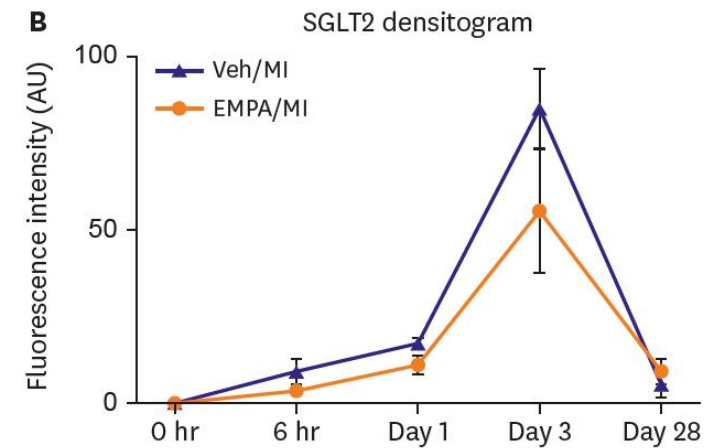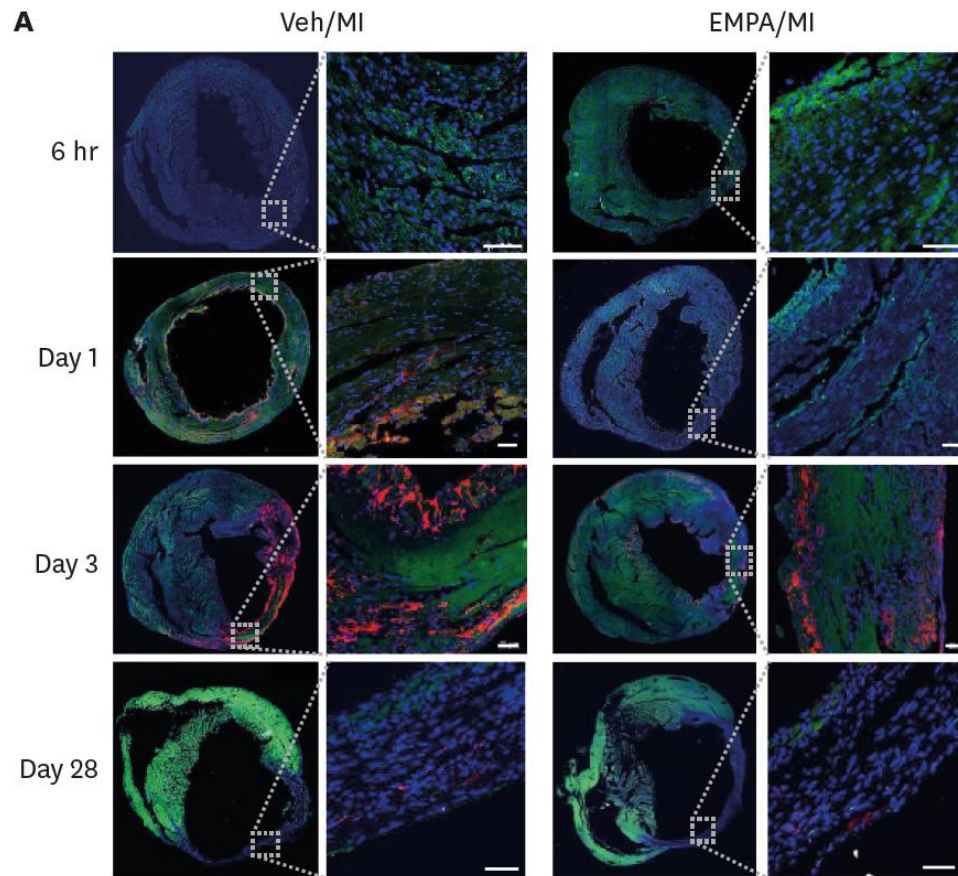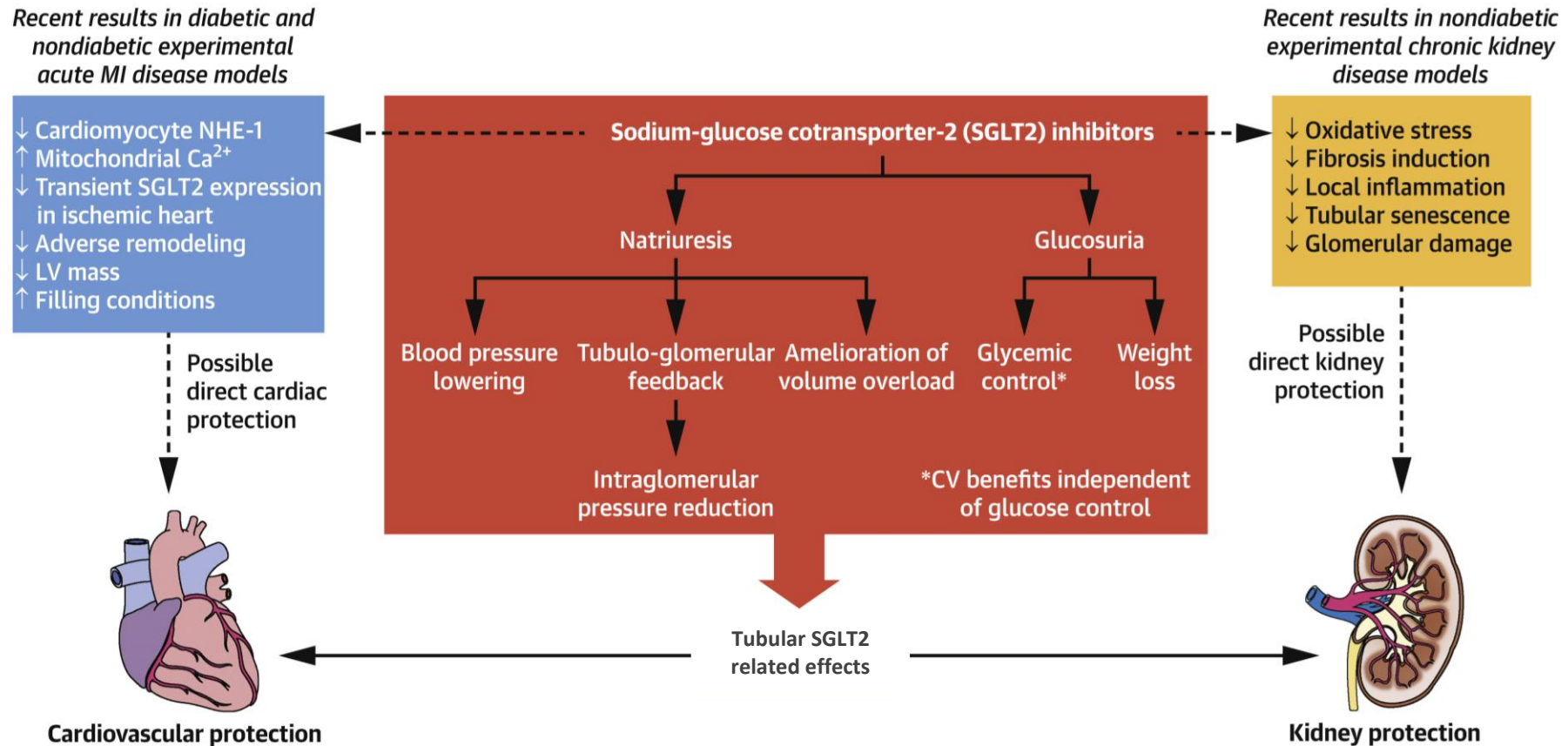Vasoconstricting
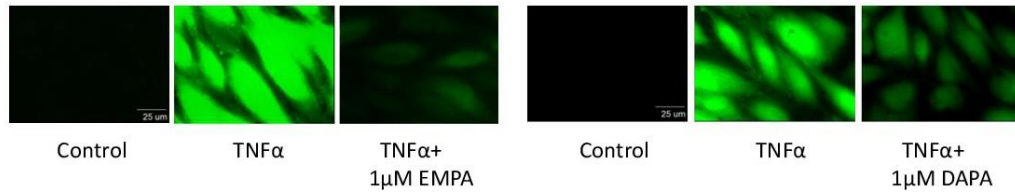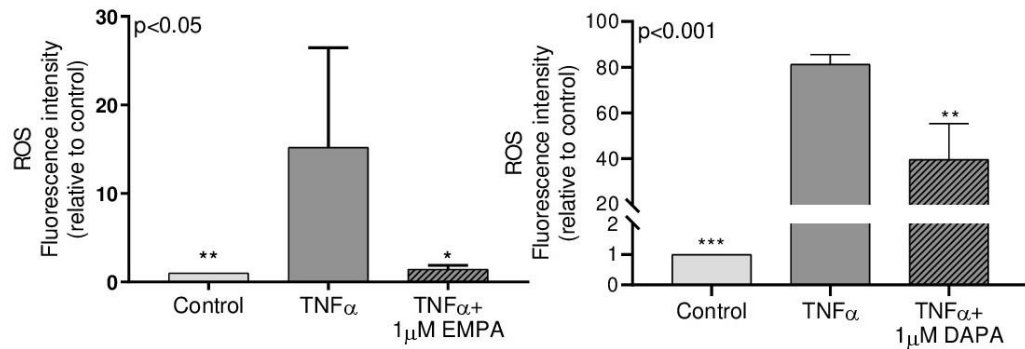
Nitric oxide (NO) levels
Vasodilating

SGLT2 inhibition
SGLT2 is expressed in the heart

SGLT2 inhibition
Pleiotropic, direct effects on the kidney and the heart?

Recent results in diabetic and nondiabetic experimental acute MI disease models

↓ Cardiomyocyte NHE-1
↑ Mitochondrial Ca^{2+}
↓ Transient SGLT2 expression in ischemic heart
↓ Adverse remodeling
↓ LV mass
↑ Filling conditions

Possible direct cardiac protection

Sodium-glucose cotransporter-2 (SGLT2) inhibitors

Natriuresis

Glucosuria

Blood pressure lowering

Tubulo-glomerular feedback

Amelioration of volume overload

Glycemic control*

Weight loss

Intraglomerular pressure reduction

*CV benefits independent of glucose control

Recent results in nondiabetic experimental chronic kidney disease models

↓ Oxidative stress
↓ Fibrosis induction
↓ Local inflammation
↓ Tubular senescence
↓ Glomerular damage

Possible direct kidney protection

Tubular SGLT2 related effects

Cardiovascular protection

Kidney protection

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

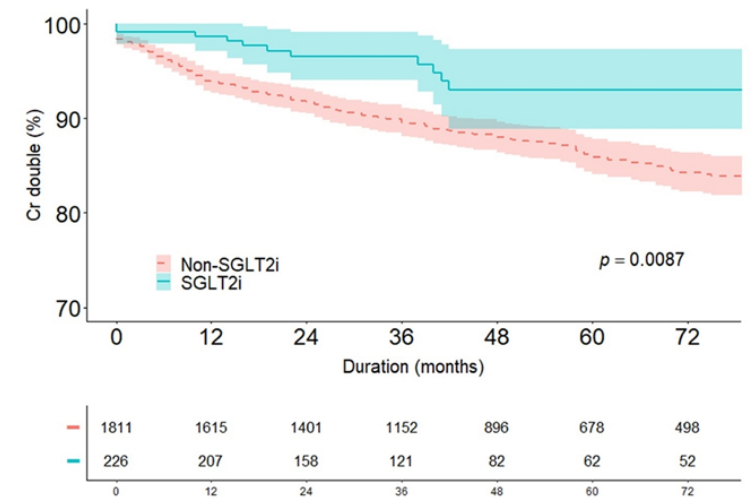# SGLT2 inhibition in kidney transplant recipients
Limited experience

All cause mortality
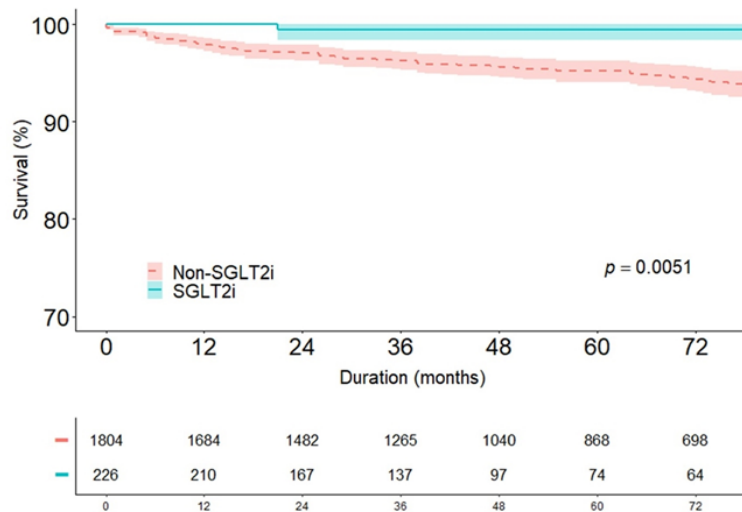
Death censored graft failure
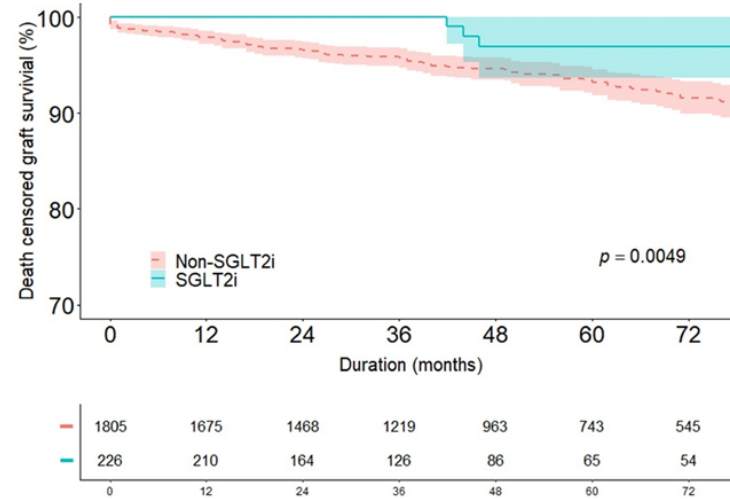
Doubling sCreat

SGLT2 inhibition in kidney transplant recipients
Limited experience

Cox regression analysis of primary composite outcome and individual components

Model	Primary composite outcome HR (95% CI)	P	All-cause mortality HR (95% CI)	P	Death-censored graft failure HR (95% CI)	P	Serum creatinine doubling 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.

Interim

Convincing results in kidney patients with or without T2D.
But all trials performed in patients with relatively preserved kidney function.

GP guidelines: prescribe ONLY to patients with eGFR > 30 (or 25 or 20)*[1-3] mL/min/1.73m^2

Patients can continue SGLT2i use when kidney function decreases to below this level[1-3]

The advice is to stop SGLT-2i when starting dialysis or when receiving a kidney transplant[1-3]

The problem

Efficacy unknown in CKD G4/5, dialysis or living with a kidney transplant, whereas these are the high risk patients.

Pharma not able to single sponsor new large-scale FDA approved RCTs (patent runs off)

Such large scale RCTs are expensive

How to address this knowledge gap ?

The solution

The Renal Lifecycle trial
Design
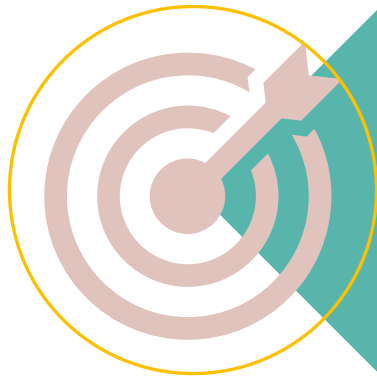
A pragmatic approach

1) Research procedures with a minimal burden for patients and researchers as often as possible as part of routine clinical care

2) Central support and monitoring by the UMC Groningen

3) Support by regional representatives and local research nurses
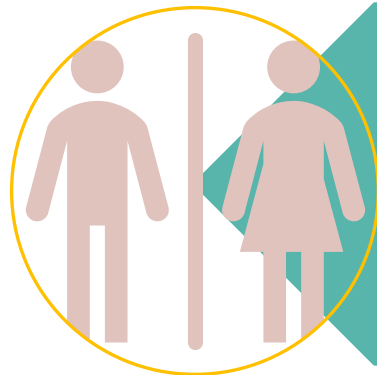
In total 1500 – 2000 patients (endpoint driven)

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

or 2) patients on dialysis with a residual diuresis ≥500 ml/24hr

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

End points

A combined primary endpoint

- Mortality
- Kidney failure (incidence of start of dialysis or a kidney transplant)
- Hospitalization for heart failure

Secondary endpoints

- Each component of the primary endpoint for the overall study population
- The combined primary endpoint in each of the 3 subgroups of patients
- Safety and tolerability (SAEs, AESI hypoglycemia, UTI, ketoacidosis)
- Quality of life
- Cost-effectiveness

A joint project

The Netherlands
In total 67 centers
- 59 centers participate
- Only 8 declined (limited local feasibility)

Belgium
- Leuven (prof. Dirk Kuypers) + 9 sites

Germany
- Wurzburg (prof. Christoph Wanner) + 15 sites

Australia
- Sydney (dr. Sunil Badve) + 13 sites
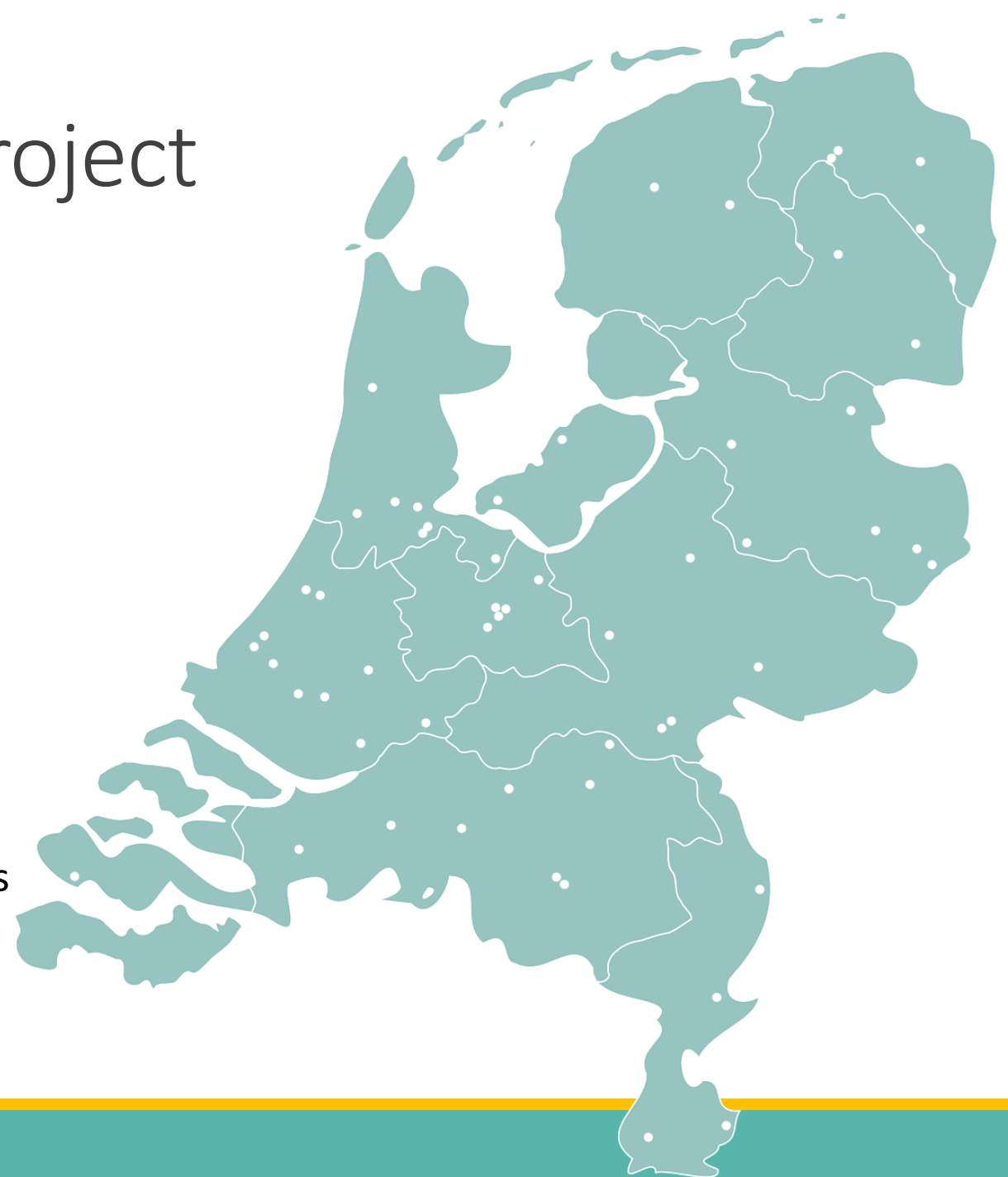
Conclusies

SGLT2-remmers beperkt diuretisch effect met weinig consequenties voor bloeddruk

Vooralsnog moeten SGLT2-remmers i.g.v. ernstig nierfalen vermeden worden

- Theoretisch minder effectief igv verminderde nierfunctie

- Slechts zeer beperkt klinische data (verrassend genoeg effectifiteit suggererend)

- Dierexperimentele studies suggereren directe, nierfunctie onafhankelijke effecten

- Mogelijk veiligheids aspect, mn in niertranplantatie patienten (rUWIs/genitale infecties)

De Renal Lifecycle trial zal duidelijk moeten maken of de balans effectiviteit / veiligheid voldoende is in deze groep patiënten

BP lowering with SGLT2i
Comparison to other glucose lowering agents

Systolic Blood Pressure (mmHg)

WMD (95% CI)

Canagliflozin	−3.38 (−4.27 to −2.49)
Empagliflozin	−3.29 (−4.16 to −2.41)
Semaglutide PO	−3.06 (−4.21 to −1.91)
Semaglutide SC	−2.93 (−3.97 to −1.90)
Exenatide	−2.68 (−4.03 to −1.34)
Ertugliflozin	−2.66 (−3.86 to −1.47)
Liraglutide	−2.48 (−3.24 to −1.73)
Dapagliflozin	−2.34 (−3.08 to −1.59)
Exenatide ER	−1.76 (−2.82 to −0.70)
Dulaglutide	−1.34 (−2.36 to −0.31)
Metformin	−1.07 (−2.09 to −0.05)
DPP-4 inhibitors	−0.73 (−1.29 to −0.16)
Pioglitazone	−0.70 (−1.77 to 0.36)
Lixisenatide	−0.40 (−2.32 to 1.52)
Meglitinides	−0.11 (−2.88 to 2.66)
Basal insulin	0.30 (−0.77 to 1.37)
Premixed insulin	0.42 (−2.28 to 3.12)
α-glucosidase inhibitors	0.44 (−1.19 to 2.08)
Sulphonylureas	0.77 (−0.11 to 1.65)
Prandial insulin	0.85 (−1.38 to 3.07)

−4 −2 0 2 4
Favours treatment   Favours placebo

Diastolic Blood Pressure (mmHg)

WMD (95% CI)

Empagliflozin	−1.68 (−2.09 to −1.27)
Dapagliflozin	−1.45 (−1.87 to −1.03)
Canagliflozin	−1.42 (−1.78 to −1.05)
Exenatide	−1.03 (−1.73 to −0.33)
Pioglitazone	−1.02 (−1.55 to −0.49)
Lixisenatide	−0.96 (−2.23 to 0.31)
Ertugliflozin	−0.85 (−1.47 to −0.23)
Semaglutide SC	−0.68 (−1.17 to −0.20)
Semaglutide PO	−0.53 (−1.06 to 0.00)
Metformin	−0.26 (−0.76 to 0.23)
Basal insulin	−0.23 (−0.78 to 0.32)
DPP-4 inhibitors	−0.18 (−0.46 to 0.10)
Liraglutide	−0.17 (−0.55 to 0.21)
Exenatide ER	−0.13 (−0.64 to 0.39)
Premixed insulin	−0.03 (−1.59 to 1.53)
Prandial insulin	−0.00 (−1.09 to 1.09)
α-glucosidase inhibitors	0.15 (−0.73 to 1.04)
Meglitinides	0.17 (−1.45 to 1.80)
Dulaglutide	0.24 (−0.20 to 0.68)
Sulphonylureas	0.50 (0.05 to 0.95)

−2 −1 0 1 2
Favours treatment   Favours placebo

Safety of SGLT2 inhibition
Meta-analysis

Number Needed to Treat

Fracture	NNT 522, not significant
Amputation	NNT 418 not significant
Urinary tract infection	NNT 319, not significant
Diabetic keto-acidosis	NNTH 1014
Genital infection	NNTH 41
Acute kidney injury	NNTB 157
Severe hypoglycemia	NNTB 561
ESKD	NNTB 102
CV death or HF admission	NNTB 134
All Cause mortality	NNTB 299

100 NNTB   **30 NNTH**