SGLT-2 Inhibition in rheumatology?

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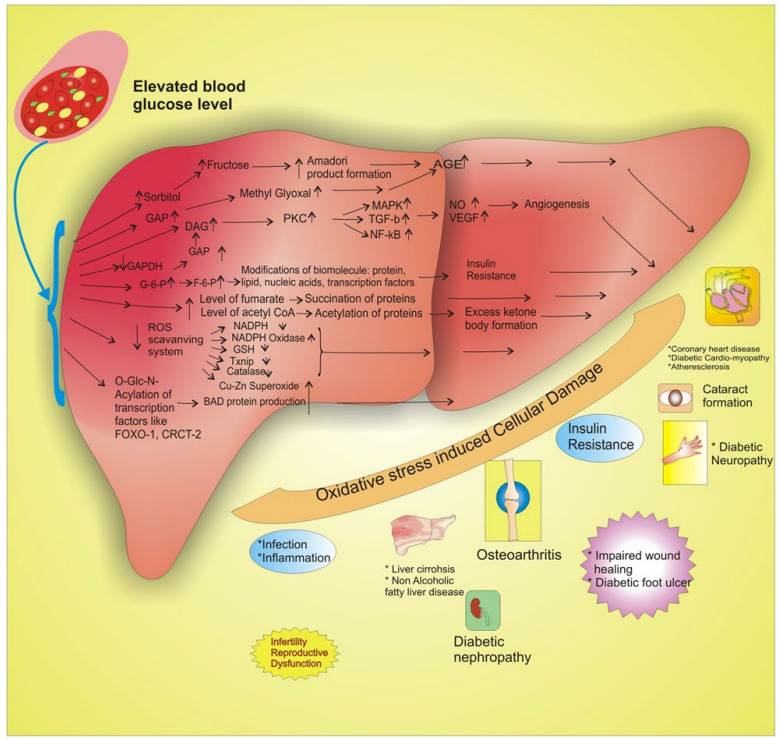
USB

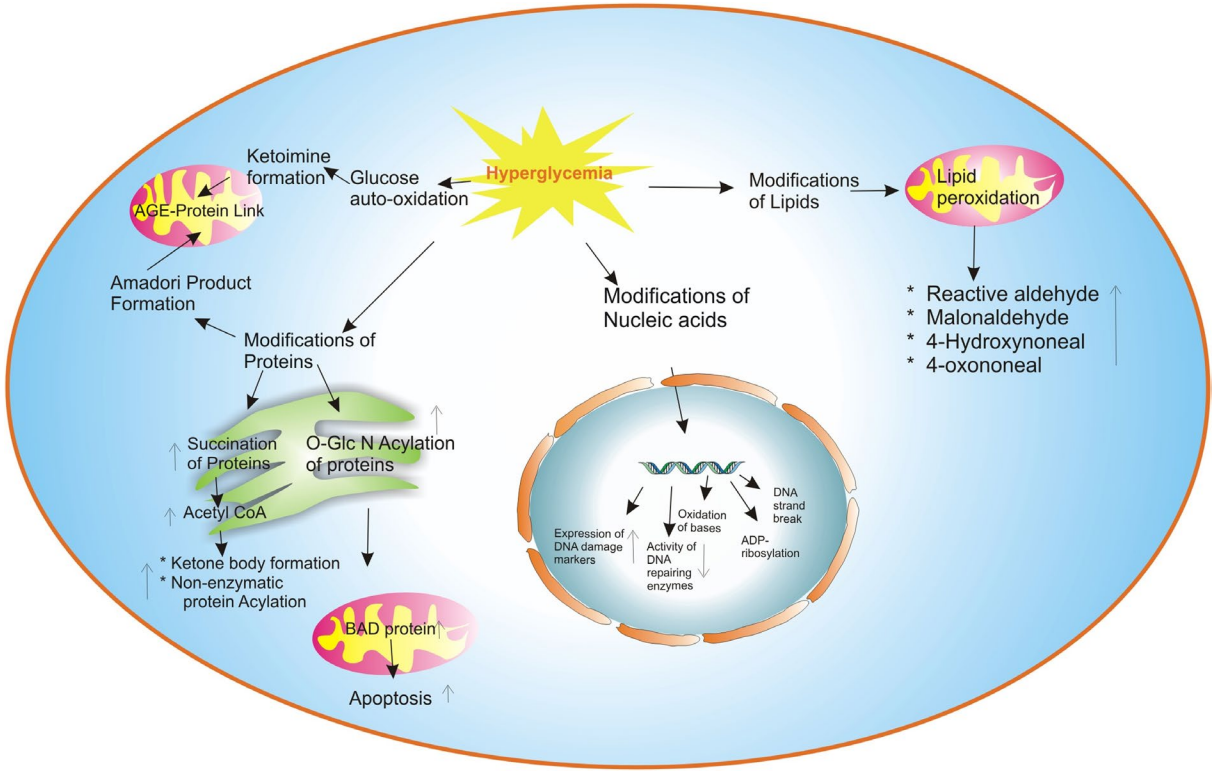
UNI
BASEL

Indication for SGLT-2 i

- Improvement of glycemic control in type **2 diabetes mellitus** (adjunct to diet and exercise)
- Reduction of major adverse **cardiovascular events** (nonfatal myocardial infarction and nonfatal stroke, cardiovascular death) in patients with **type 2 DM** and established **cardiovascular disease**.
- To decrease the risk of cardiovascular hospitalization and death for heart failure in patients with **HFrEF** (heart failure with reduced ejection fraction-NYHA class II-IV)
- Reduction of the risk of eGFR decline and hospitalization in patients with **chronic kidney disease** at risk of progression.
- Improvement of cardiovascular outcomes in patients with **HFpEF** (Heart failure with preserved ejection fraction)

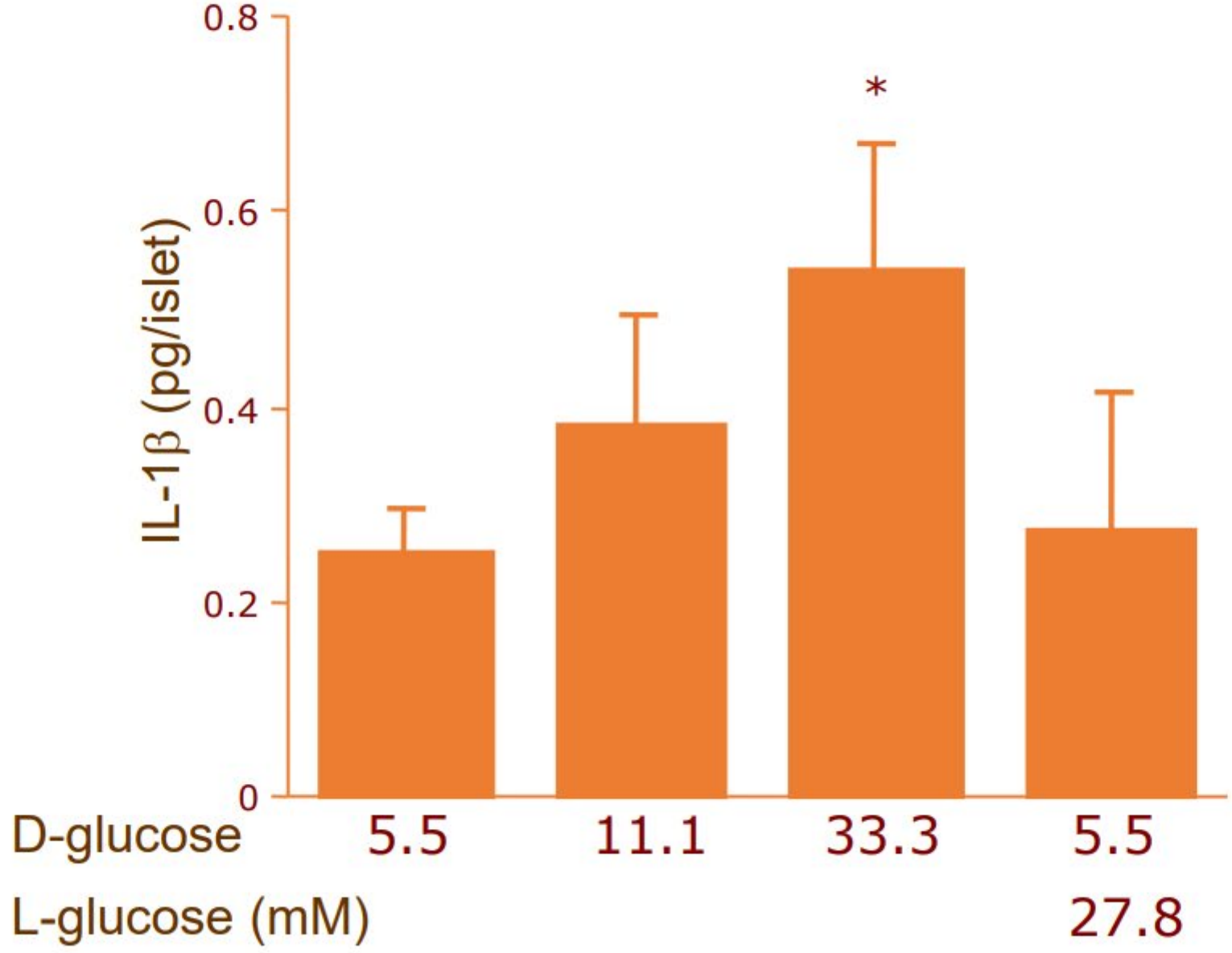
Hyperglycaemia promotes inflammation





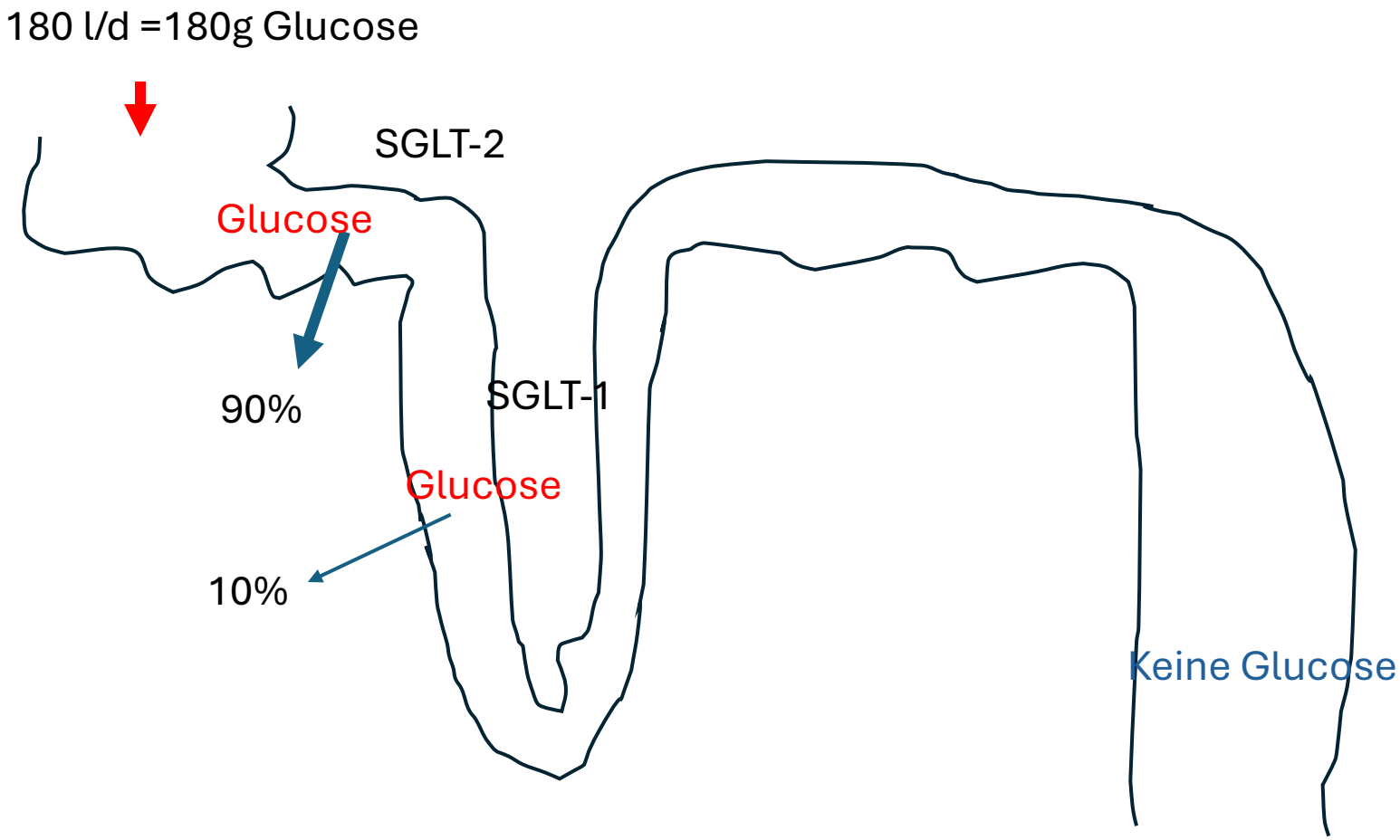
https://doi.org/10.1016/j.biopha.2018.07.157

Glucose induces IL-1β

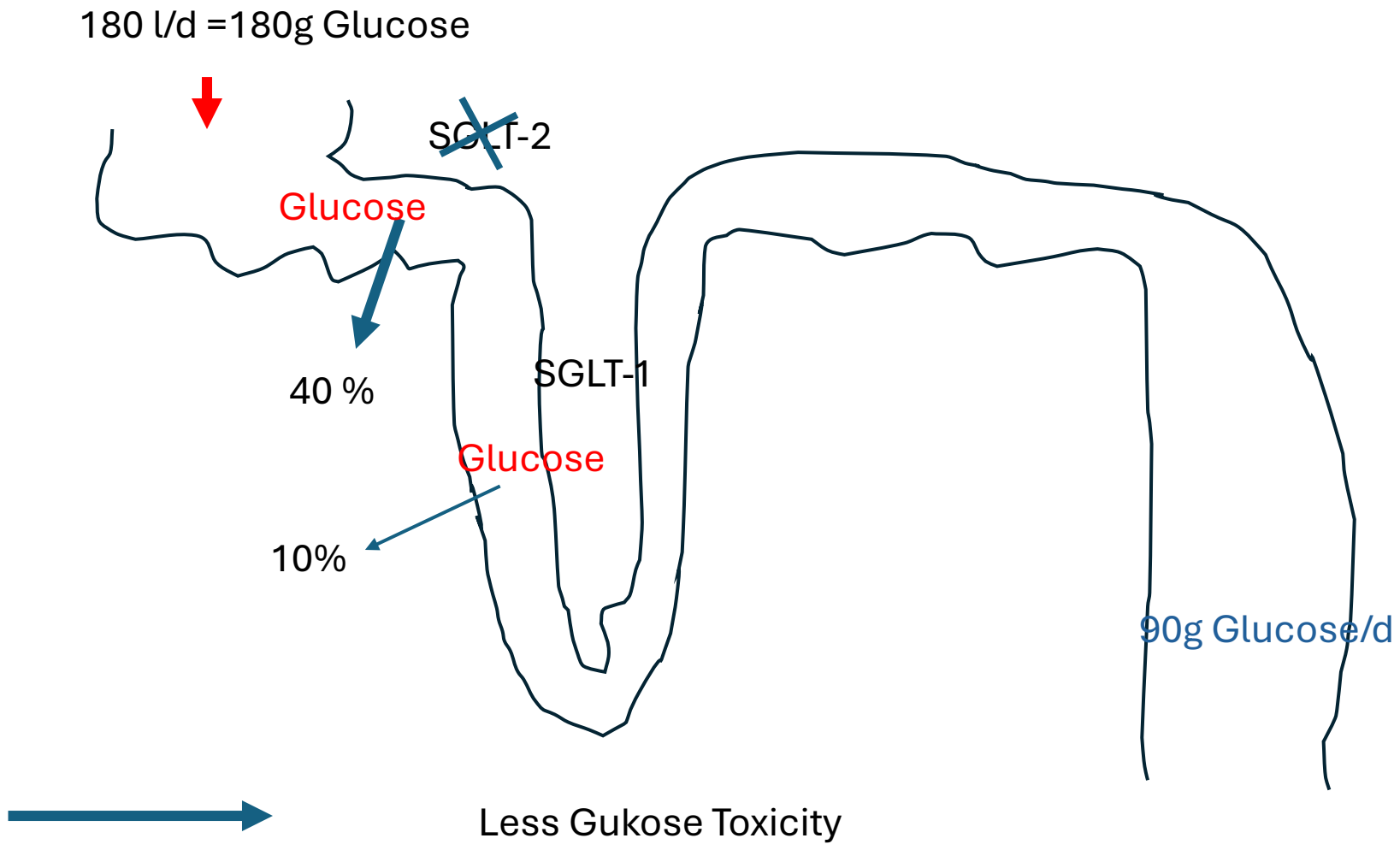


Maedler et al. *J Clin Invest* 2002;110:851–60

sodium-glucose linked transporter (SGLT)-2 Funktion

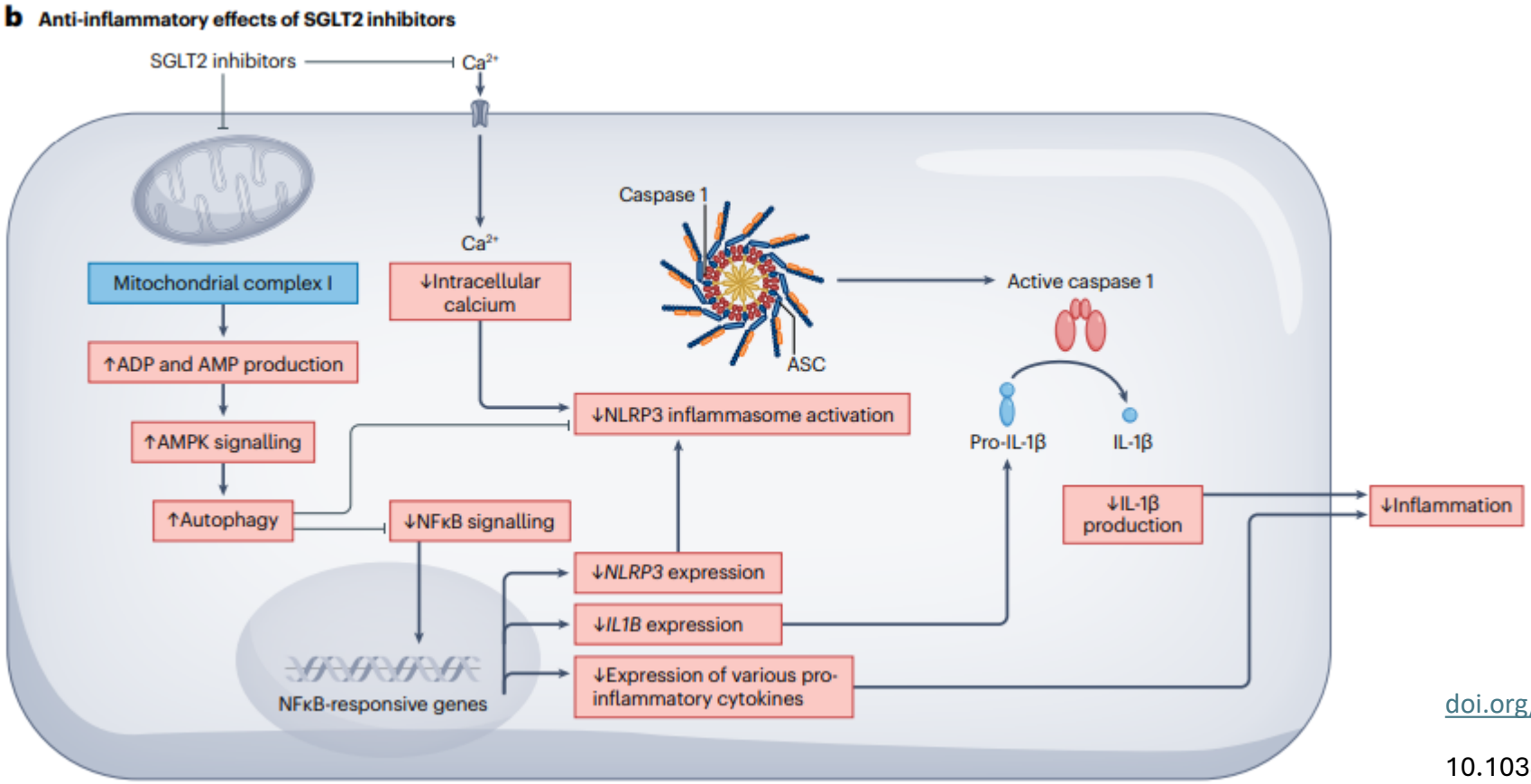


SGLT-2 Inhibition reduziert Blutglucose



Postulated anti-inflammatory mechanism of SGLT-2 i

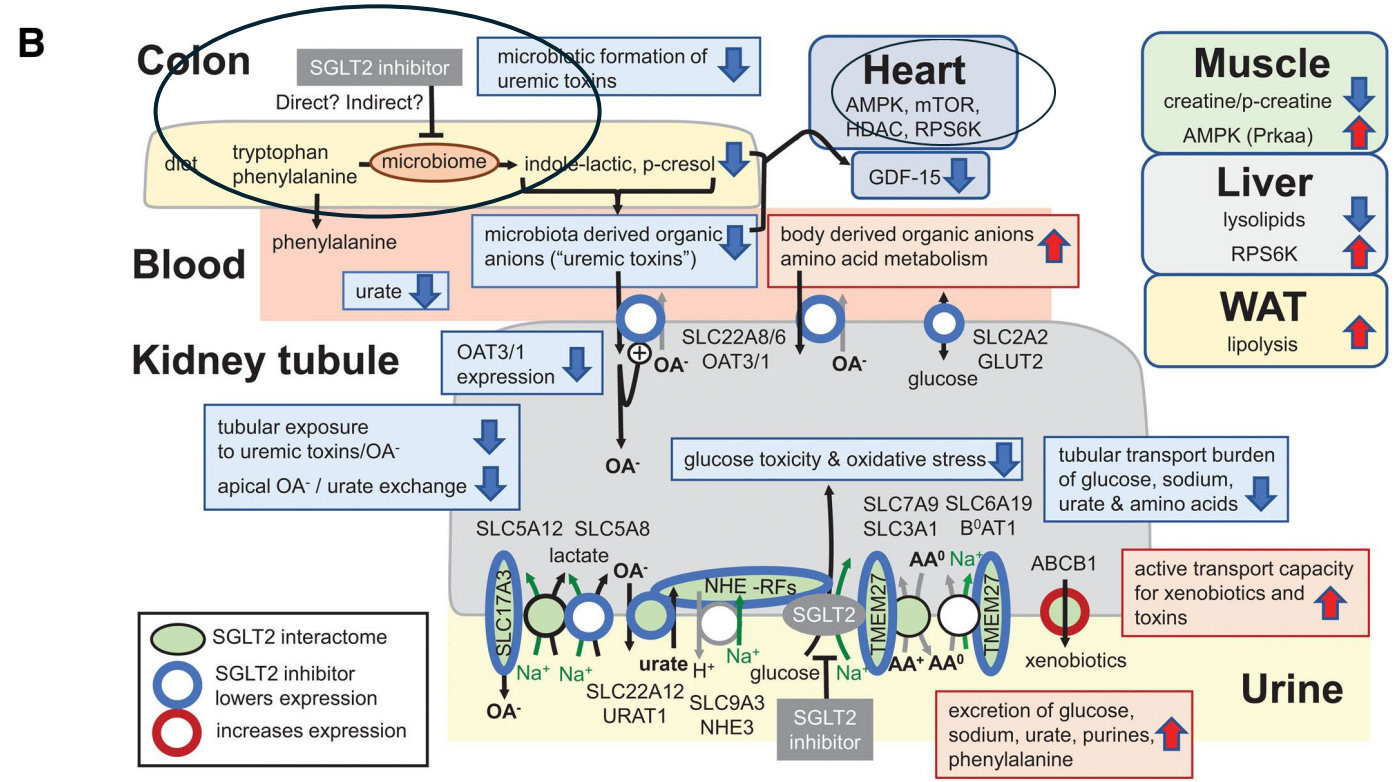
- Conflicting results modest decrease of IL-1, Il-6 and TNF inhibition



doi.org/10.3389/fphar.2022.1045235

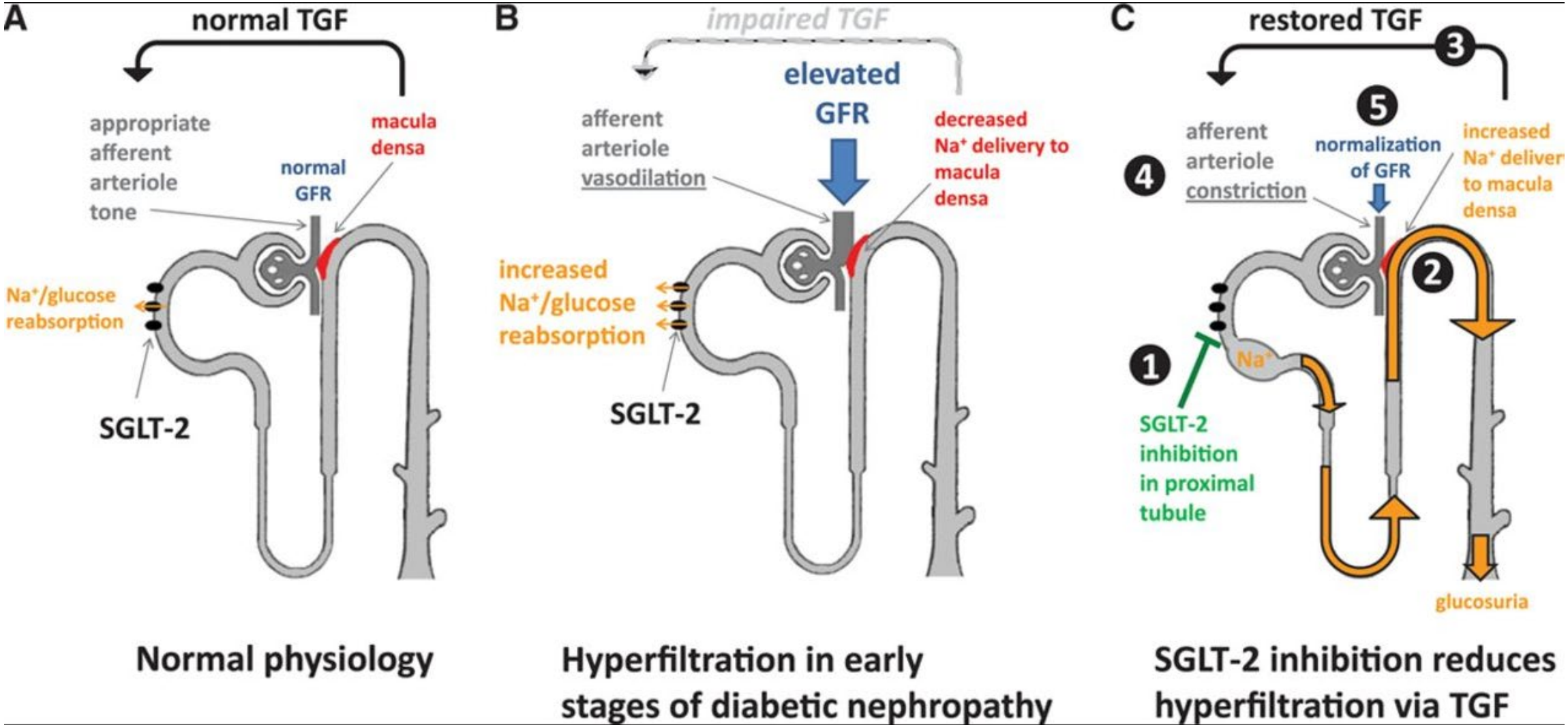
10.1038/s41584-024-01092-x

Universitätsspital Basel



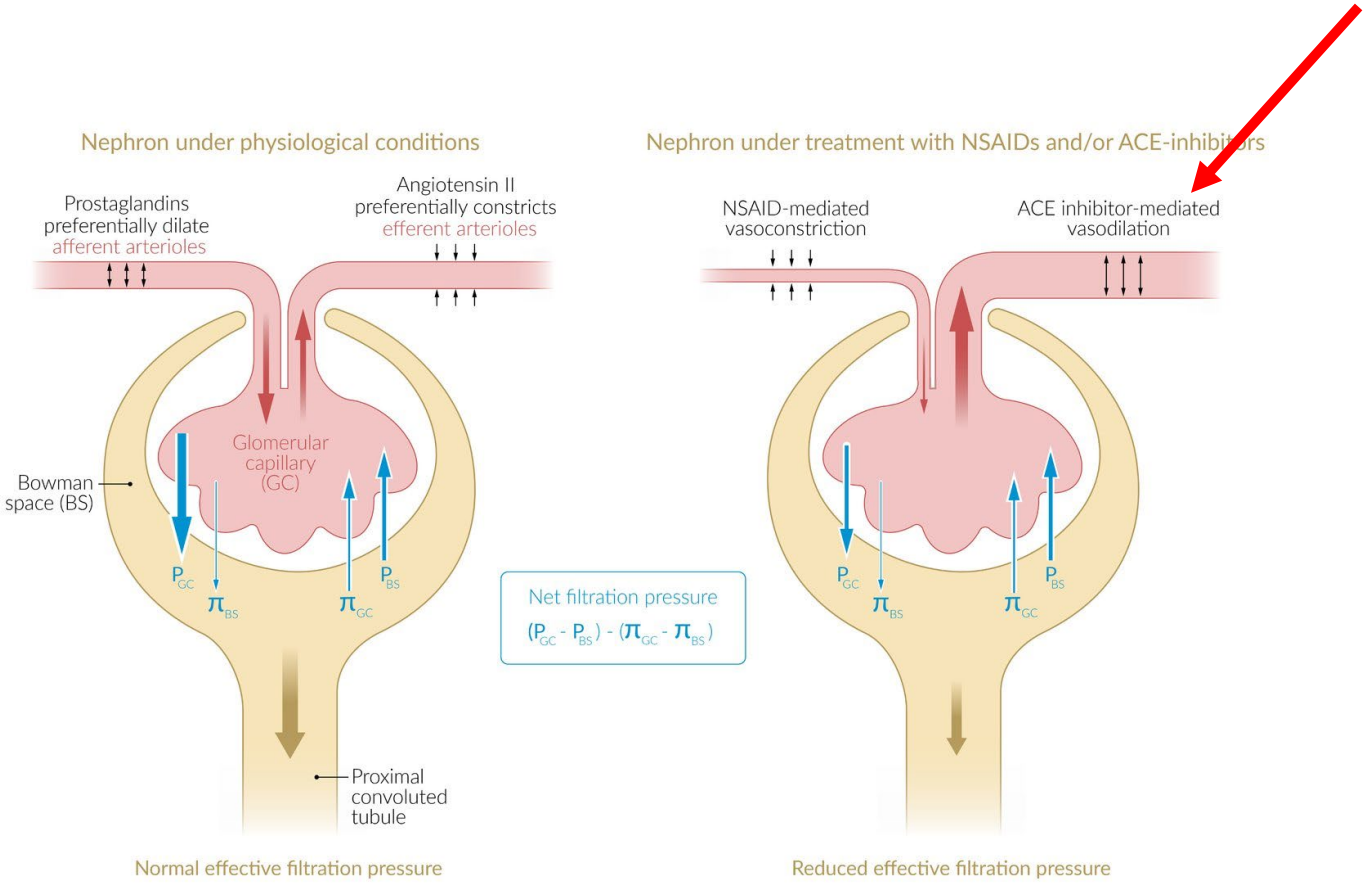
doi.org/10.1161/CIRCULATIONAHA.123.065517

SGLT-2 i Nephroprotektiv bei glomerulärer Hyperfiltration (Diabetes)

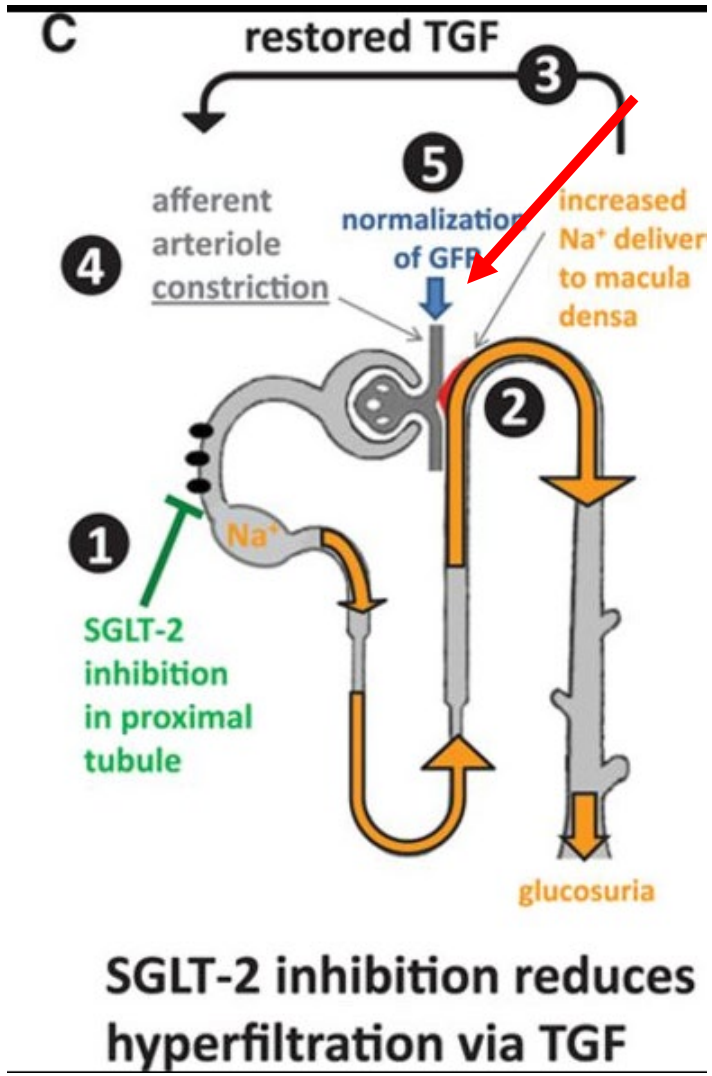


https://www.renalfellow.org/2014/05/14/sglt-2-and-genesis-of-hyperfiltration/

Additiver Effekt zu RAAS Blockade



Amboss



Effect of SGLT-2 i on proteinuria in pts. with glomerulonephritis

Table 1: Clinical characteristics at the time of kidney disease diagnosis.

Characteristic	Total (N = 493)
Baseline	
Age at diagnosis, years	47 (34–59)
Sex, female (%)	157 (32)
Hypertension, *N* (%)	357 (72)
Diabetes mellitus (type 2), *N* (%)	147 (30)
Current smoker, *N* (%)	125 (25)
Previous history of cardiovascular disease, *N* (%)	81 (16)
Glomerular/systemic disease	
Minimal change disease	14 (3)
Primary FSGS	32 (6)
Secondary FSGS	58 (12)
Membranous nephropathy	89 (18)
Immune-complex membranoproliferative glomerulonephritis	18 (4)
C3 glomerulopathy	4 (1)
Post-infectious glomerulonephritis	4 (1)
IgA nephropathy	192 (39)
IgA vasculitis	11 (2)
AL amyloidosis	6 (1)
Cryoglobulinemia	2 (0)
Fibrillary glomerulonephritis	8 (2)
ANCA-associated vasculitis	22 (4)
Anti-glomerular basement membrane disease	1 (0)
Lupus nephritis	32 (7)
Disease chronicity in kidney biopsy	
Glomerulosclerosis	
<10%	219 (44)
10%–25%	165 (34)
26%–50%	79 (16)
>50%	30 (6)
Interstitial fibrosis	
<10%	190 (39)
10%–25%	223 (45)
26%–50%	65 (13)
>50%	15 (3)
Tubular atrophy	
<10%	212 (43)
10%–25%	219 (44)
26%–50%	53 (11)
>50%	9 (2)
Arteriosclerosis	
No	352 (71)
Yes	141 (29)

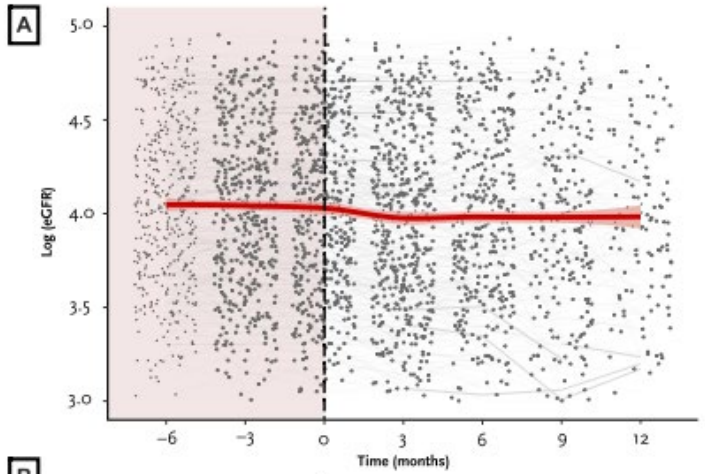
Data are presented as median (IQR) or *N* (%).

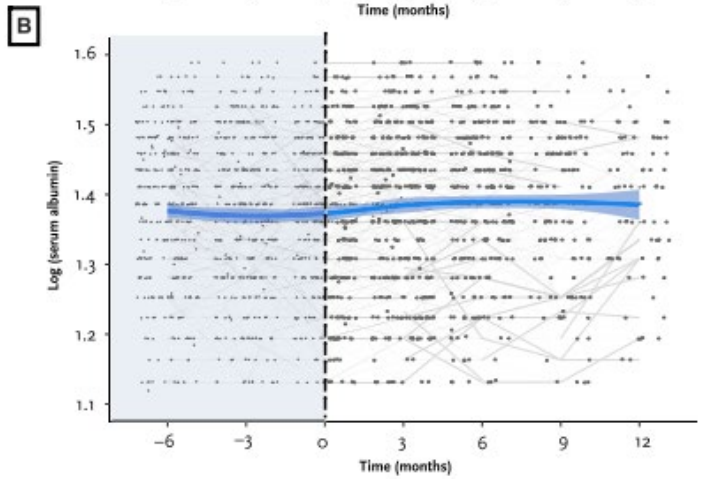
Table 2: Clinical characteristics at the time of SGLT2i initiation.

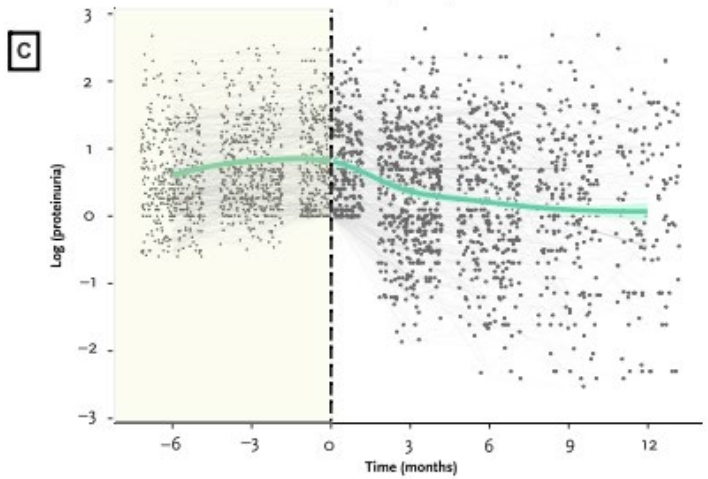
Characteristic	Total (N = 493)
Baseline	
Age at SGLT2i initiation, years	55 (42–65)
Weight, kg	84 (73–98)
BMI, kg/m^2	29 (26–33)
Weight classification, *N* (%)	
Underweight	5 (1)
Normal	108 (22)
Overweight	183 (37)
Obesity class I	122 (25)
Obesity class II	45 (9)
Obesity class III	30 (6)
RAS blockade, *N* (%)	
ACEi	225 (46)
ARB	253 (51)
Both	15 (3)
Diuretic, *N* (%)	
None	305 (62)
Thiazide-type/thiazide-like	56 (11)
Loop	69 (14)
Aldosterone antagonist	40 (8)
Combinations of diuretics[a]	23 (5)
Maintenance immunosuppression, *N* (%)	79 (16)
Prednisone	46 (9)
Mycophenolate mofetil	42 (8)
Calcineurin inhibitor	19 (4)
Other[b]	14 (3)
Onset of SGLT2i	
Type of SGLT2i, *N* (%)	
Dapagliflozin	386 (78)
Empagliflozin	70 (14)
Canagliflozin	37 (8)
Systolic blood pressure, mmHg	134 ± 17
Diastolic blood pressure, mmHg	78 ± 11
Serum creatinine, mg/dL	1.4 (1–1.9)
eGFR, mL/min/1.73m^2	56 (39–82)
Serum albumin, g/dL	3.9 (3.5–4.3)
UACR, mg/g[c]	1287 (729–2294)
24-h proteinuria, g/day	2.1 (1.2–3.6)
Patients with nephrotic-range proteinuria[d], *N* (%)	130 (26)

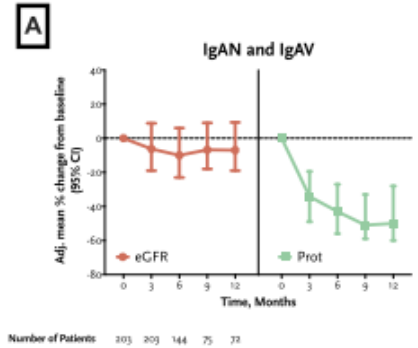
Data are presented as mean ± SD, median (IQR) or *N* (%).
[a]Including combination of loop plus thiazide diuretics (50%), thiazide plus aldosterone antagonist (32%) and loop plus aldosterone antagonist (18%).
[b]Including azathioprine in six patients (1%), belimumab in four (1%), maintenance rituximab in three (0.6%), leflunomide in one (0.2%).
[c]Only available in 378 (77%) patients.
[d]Defined as 24-h proteinuria ≥3.5 g/day.
UACR: urinary albumin-to-creatinine ratio.

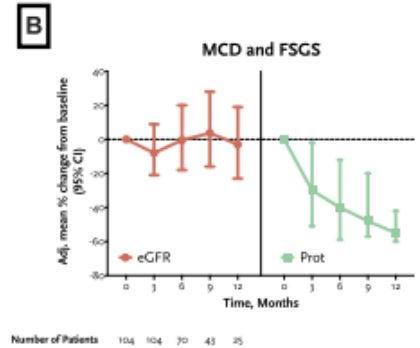
https://doi.org/10.1093/ndt/gfad175

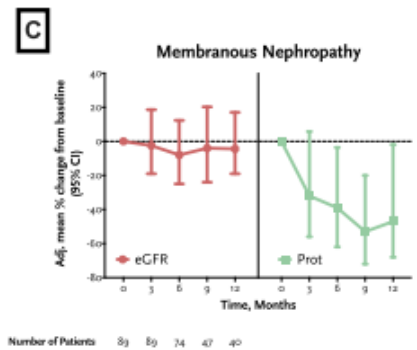

A
Log (eGFR)
Time (months)

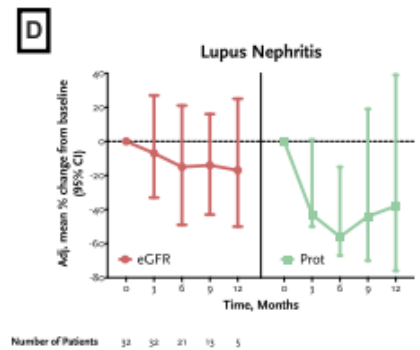

B
Log (serum albumin)
Time (months)

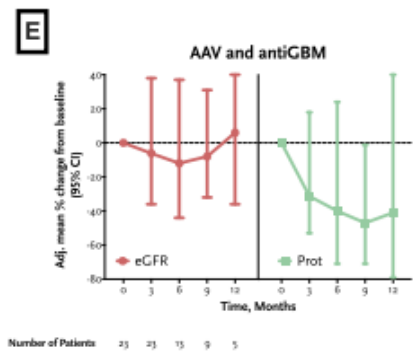

C
Log (proteinuria)
Time (months)

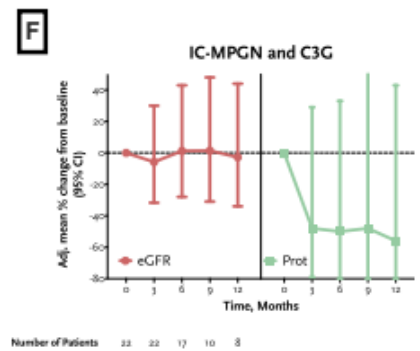

A
IgAN and IgAV
Adj. mean % change from baseline (95% CI)
eGFR
Prot
Time, Months
Number of Patients 203 203 144 75 72

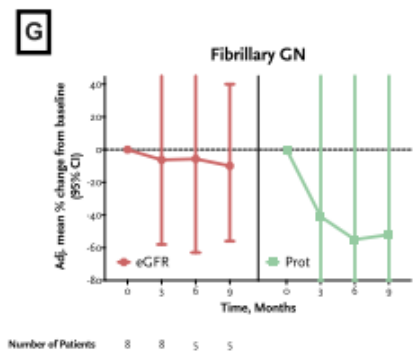

B
MCD and FSGS
Adj. mean % change from baseline (95% CI)
eGFR
Prot
Time, Months
Number of Patients 104 104 70 43 25

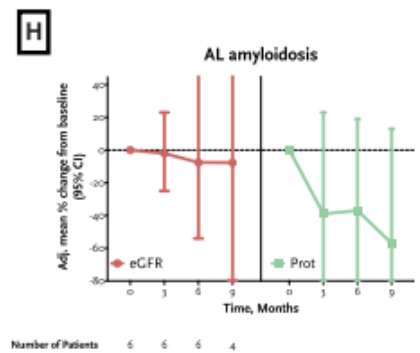

C
Membranous Nephropathy
Adj. mean % change from baseline (95% CI)
eGFR
Prot
Time, Months
Number of Patients 89 89 74 47 40


D
Lupus Nephritis
Adj. mean % change from baseline (95% CI)
eGFR
Prot
Time, Months
Number of Patients 32 32 21 13 5


E
AAV and antiGBM
Adj. mean % change from baseline (95% CI)
eGFR
Prot
Time, Months
Number of Patients 23 23 13 9 5


F
IC-MPGN and C3G
Adj. mean % change from baseline (95% CI)
eGFR
Prot
Time, Months
Number of Patients 22 22 17 10 8


G
Fibrillary GN
Adj. mean % change from baseline (95% CI)
eGFR
Prot
Time, Months
Number of Patients 8 8 5 5


H
AL amyloidosis
Adj. mean % change from baseline (95% CI)
eGFR
Prot
Time, Months
Number of Patients 6 6 6 4

Reduction of proteinuria

Independent of diabetes

Characteristic	≥30% proteinuria reduction (N = 340)	<30% proteinuria reduction (N = 153)	P
Previous comorbidities			
Hypertension, N (%)	239 (70)	118 (77)	.12
Diabetes mellitus (type 2), N (%)	104 (31)	43 (28)	.58
Current smoker, N (%)	90 (27)	35 (23)	.38
Cardiovascular disease, N (%)	57 (17)	24 (16)	.77
Glomerular/systemic disease			.42
Minimal change disease	13 (4)	1 (1)	
Primary FSGS	18 (5)	14 (9)	
Secondary FSGS	40 (12)	18 (12)	
Membranous nephropathy	60 (18)	29 (19)	
IC-MPGN	14 (4)	4 (2)	
C3 glomerulopathy	4 (1)	0 (0)	
Post-infectious glomerulonephritis	3 (1)	1 (1)	
IgA nephropathy	134 (39)	58 (38)	
IgA vasculitis	5 (2)	6 (4)	
AL amyloidosis	4 (1)	2 (1)	
Cryoglobulinemia	2 (1)	0 (0)	
Fibrillary glomerulonephritis	7 (2)	1 (1)	
ANCA-associated vasculitis	15 (4)	7 (4)	
Anti-GBM	1 (0)	0 (0)	
Lupus nephritis	20 (6)	12 (8)	
Disease chronicity in kidney biopsy			.71
Minimal	122 (36)	61 (40)	
Mild	150 (44)	59 (39)	
Moderate	57 (17)	28 (18)	
Severe	11 (3)	5 (3)	
Onset of SGLT2i			
Age, years	55 (42–65)	55 (41–64)	.93
Age < 55 years, N (%)	167 (49)	75 (49)	.98
Sex, female (%)	111 (33)	46 (30)	.57
Body mass index, kg/m^2	29 (26–33)	29 (26–34)	.91
Weight classification, N (%)			.86
Underweight	3 (0)	2 (1)	
Normal	77 (23)	31 (20)	
Overweight	124 (37)	59 (39)	
Obesity class I	87 (26)	35 (23)	
Obesity class II	28 (8)	17 (11)	
Obesity class III	21 (6)	9 (6)	
RAS blockade, N (%)			.88
ACEi	153 (45)	72 (47)	
ARB	177 (52)	76 (50)	
Both	10 (3)	5 (3)	
Diuretic, N (%)			.23
None	204 (60)	101 (66)	
Thiazide-type/thiazide-like	42 (12)	14 (9)	
Loop	49 (14)	20 (13)	
Aldosterone antagonist	32 (10)	8 (5)	
Combinations of diuretics	13 (4)	10 (7)	
Maintenance immunosuppression, N (%)	54 (16)	25 (16)	.89
Type of SGLT2i, N (%)			.96
Dapagliflozin	265 (78)	121 (79)	
Empagliflozin	49 (14)	21 (14)	
Canagliflozin	26 (8)	11 (7)	
Systolic blood pressure, mmHg	134 ± 17	133 ± 16	.88
Diastolic blood pressure, mmHg	79 ± 11	78 ± 10	.32
Serum creatinine, mg/dL	1.4 (1–1.9)	1.3 (1–1.9)	.66
eGFR, mL/min/1.73 m^2	56 (38–80)	57 (39–86)	.55
eGFR <60 mL/min/1.73 m^2, N (%)	192 (57)	81 (53)	.46
Serum albumin, g/dL	4 (3.5–4.3)	3.8 (3.4–4.2)	.04
Serum albumin <3.5 g/dL, N (%)	70 (21)	43 (28)	.04
24-h proteinuria, g/day	1.9 (1.2–3.5)	2 (1.2–3.7)	.80
24-h proteinuria <3.5 g/day, N (%)	251 (74)	112 (73)	.89
Nephrotic-range proteinuria, N (%)	89 (26)	41 (27)	.88

Effect of SGLT-2 i on kidney function

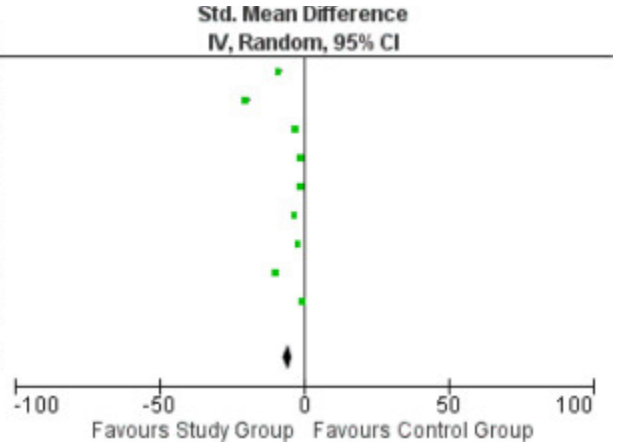
indications

Diabetes
CKD
HFrEF

Ca. 30000 patients

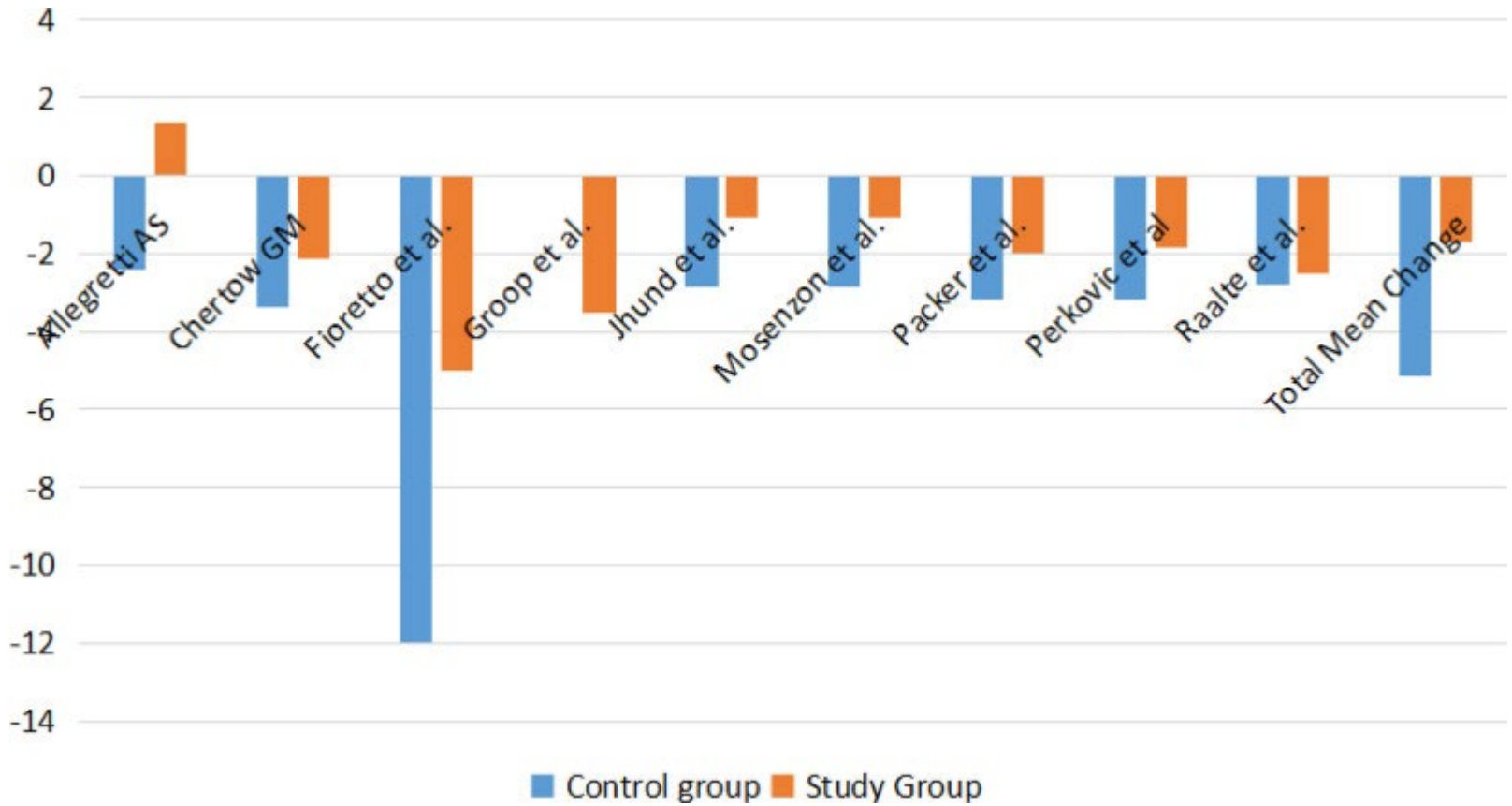
Study or Subgroup	Control Mean	Control SD	Control Total	Study Mean	Study SD	Study Total	Weight	Std. Mean Difference IV, Random, 95% CI
Allegretti AS et al. 2019	-3.38	0.15	155	-2.15	0.13	157	11.0%	-8.75 [-9.47, -8.02]
Chertow GM 2021	-4.59	0.14	331	-1.85	0.13	293	10.6%	-20.21 [-21.35, -19.08]
Fioretto et al. 2018	-12	2.36	161	-5	2.69	160	11.2%	-2.76 [-3.07, -2.45]
Groop et al. 2020	-4.7	1.2	87	-3.5	1.36	80	11.2%	-0.93 [-1.25, -0.61]
Jhund et al. 2021	-2.85	1.11	962	-1.09	2.25	960	11.2%	-0.99 [-1.09, -0.90]
Mosenzon et al. 2019	-2.85	0.59	2816	-1.09	0.44	1926	11.2%	-3.29 [-3.38, -3.21]
Packer et al. 2020	-2.85	0.95	1867	-1.09	0.78	1863	11.2%	-2.02 [-2.10, -1.95]
Perkovic et al., 2019	-3.19	0.15	2199	-1.85	0.13	2202	11.2%	-9.55 [-9.75, -9.34]
Raalte et al. 2019	-2.8	0.54	526	-2.5	0.58	524	11.2%	-0.54 [-0.66, -0.41]
Total (95% CI)			**9104**			**8165**	**100.0%**	**-5.34 [-6.86, -3.83]**

Heterogeneity: Tau² = 5.29; Chi² = 8052.79, df = 8 (P < 0.00001); I² = 100%
Test for overall effect: Z = 6.94 (P < 0.00001)



doi: 10.1097/MD.0000000000041422

Different FU



SGLT-2 Inhibitors are Associated with Lower Risk of End Stage Renal Disease (ESRD) and Lower Mortality in ANCA-associated Vasculitis With Kidney Involvement

ACR Convergence 2025 **ABSTRACT NUMBER: 1603**

- Retrospective cohort study used TriNetX (data of over 113 million patients)
- patients with GPA, EGPA, or microscopic polyangiitis and Type 2 diabetes, +- SLGT-2i for diabetes treatment.
- The participants were balanced based on age and sex
- Exclusion of a previous diagnosis/procedure of Chronic Kidney Disease (CKD), End Stage Renal Disease (ESRD), unclassified kidney disorders, dialysis, and kidney transplant.

Results

- 219 patients who used SGLT-2i at time of diagnosis of ANCA-associated vasculitis with kidney involvement age and sex matched controls?
- 33 patients who took SGLT-2i and were diagnosed with ESRD, compared to the 57 patients who did not take SGLT-2i ($p=0.003$).

TriNetX data

No data on SLE manifestations

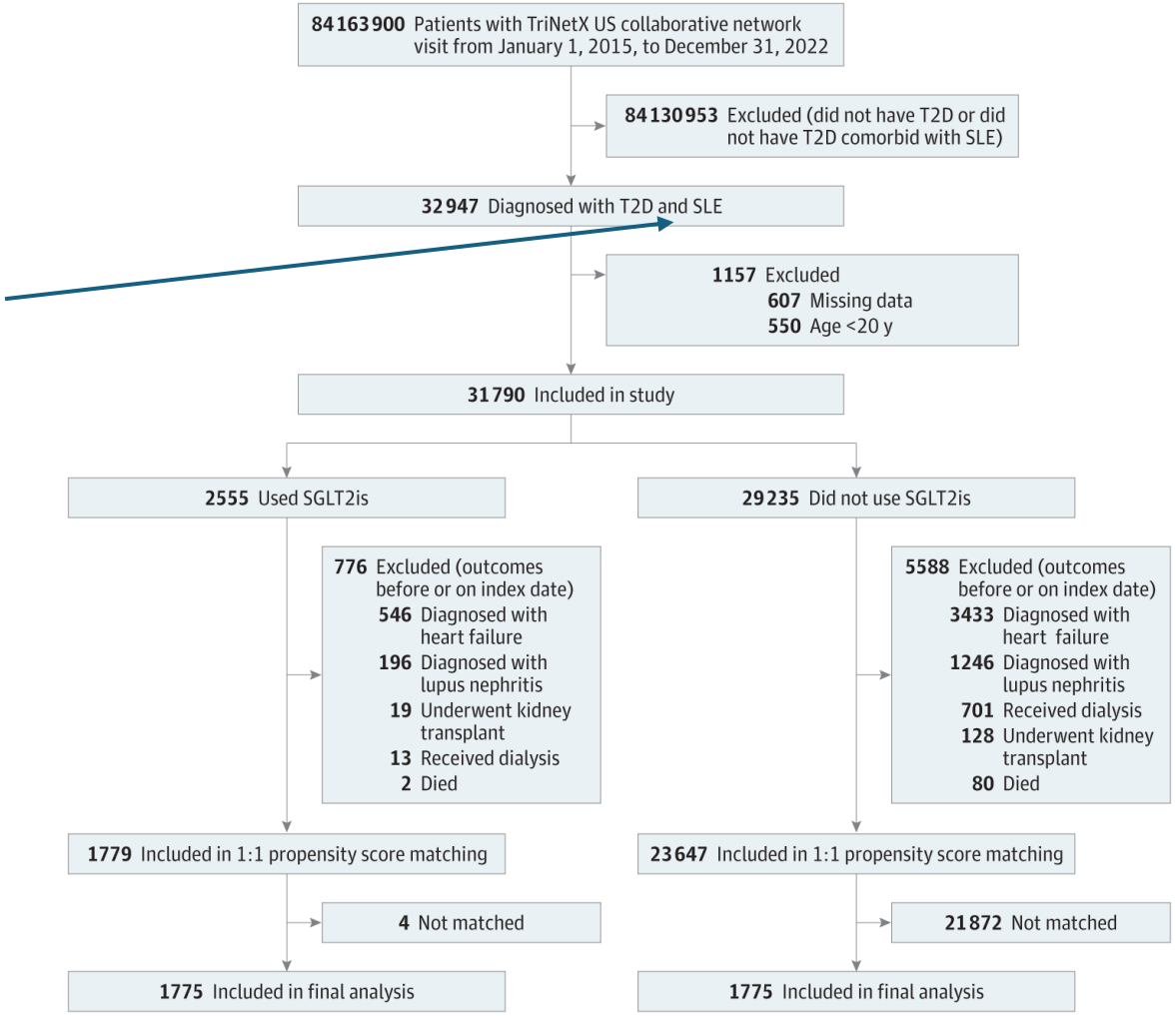


Table 2. Risk of Outcomes at 1 Day to 5 Years

Outcome	Patients, No. (%)[a]		Adjusted hazard ratio (95% CI)[b]
	SGLT2i users (n = 1775)	SGLT2i nonusers (n = 1775)	
Lupus nephritis	58 (3.27)	99 (5.58)	0.55 (0.40-0.77)
Dialysis	19 (1.07)	64 (3.60)	0.29 (0.17-0.48)
Kidney transplant	10 (0.56)	14 (0.79)	0.14 (0.03-0.62)
Heart failure	174 (9.80)	255 (14.37)	0.65 (0.53-0.78)
All-cause mortality	58 (3.27)	163 (9.18)	0.35 (0.26-0.47)

doi:10.1001/jamanetworkopen.2024.16578

Comparative Outcomes of GLP-1 Receptor Agonists Versus SGLT2 Inhibitors in Patients with Systemic Lupus Erythematosus and Diabetes: A Propensity-Matched Retrospective Cohort Study 0632 ACR 2025

- Retrospective cohort with TriNetX data
- Patients diagnosed with both SLE and diabetes
- Patients were grouped based on exposure to either GLP-1 receptor agonists or SGLT2 inhibitors.
- the primary outcome was all-cause mortality, while secondary outcomes included major adverse cardiovascular events (MACE) and lupus nephritis. Propensity score matching (1:1) was used to balance baseline characteristics between groups.

Results

- 885 patients were included in each group after matching
- The incidence of MACE was significantly lower in the GLP-1 group (3.2%) compared to the SGLT2 group (6.0%; RR, 0.53; 95% CI, 0.337–0.827; p = 0.0045)
- The incidence of lupus nephritis was significantly lower in the GLP-1 group (4.7%) compared to the SGLT2 group (9.8%; RR, 0.48; 95% CI, 0.338–0.689; p < 0.0001).

Comparing the Impact of GLP-1 Agonists and SGLT-2 Inhibitors on Outcomes in Lupus Nephritis: A Retrospective Cohort Study

EULAR 25 OP0078

- TriNetX data
- >1000 pts after propensity matching 694 patients remained in each group

Table 1: Baseline Characteristics of Both Cohorts Before and After Propensity Matching

Characteristics	SGLT-2	GLP-1	p-value	SGLT-2	GLP-1	p-value
Demographics						
Age at Index; mean ± SD	51.9 ± 16	48.2 ± 12.8	<0.0001	50.3 ± 15.8	49.6 ± 15.8	0.3863
Females	75.9%	85.5%	<0.0001	81.7%	82.4%	0.7265
Males	22.5%	11.2%	<0.0001	16.4%	15.1%	0.5075
Whites	30.8%	37.0%	0.0014	35.3%	35.1%	0.9552
Hispanic/Latino	12.7%	17.0%	0.0026	15.3%	17.0%	0.3813
Asians	13.0%	3.6%	<0.0001	5.0%	5.0%	1.0000
Other Races	6.3%	7.5%	0.2421	7.8%	7.6%	0.9198
Diagnoses						
Hypertension	85.0%	81.0%	0.0069	82.4%	82.9%	0.8317
Obesity	33.9%	70.2%	<0.0001	57.9%	56.9%	0.7040
Diabetes	37.2%	50.0%	<0.0001	46.4%	43.8%	0.3316
Tobacco Use	5.1%	3.6%	0.0745	4.2%	4.6%	0.6944
Medications						
Prednisone	61.7%	63.8%	0.2952	65.3%	64.3%	0.6941
HCQ	65.4%	56.0%	<0.001	59.8%	58.5%	0.6231
Azathioprine	12.9%	12.7%	0.8823	11.8%	12.0%	0.9339
Belimumab	11.2%	11.1%	0.9519	10.7%	11.8%	0.4966
Rituximab	6.3%	5.8%	0.5945	6.8%	5.9%	0.5087

Table 1: Complications and Outcomes in Patients with LN on SGLT2 inhibitors versus GLP-1 agonists

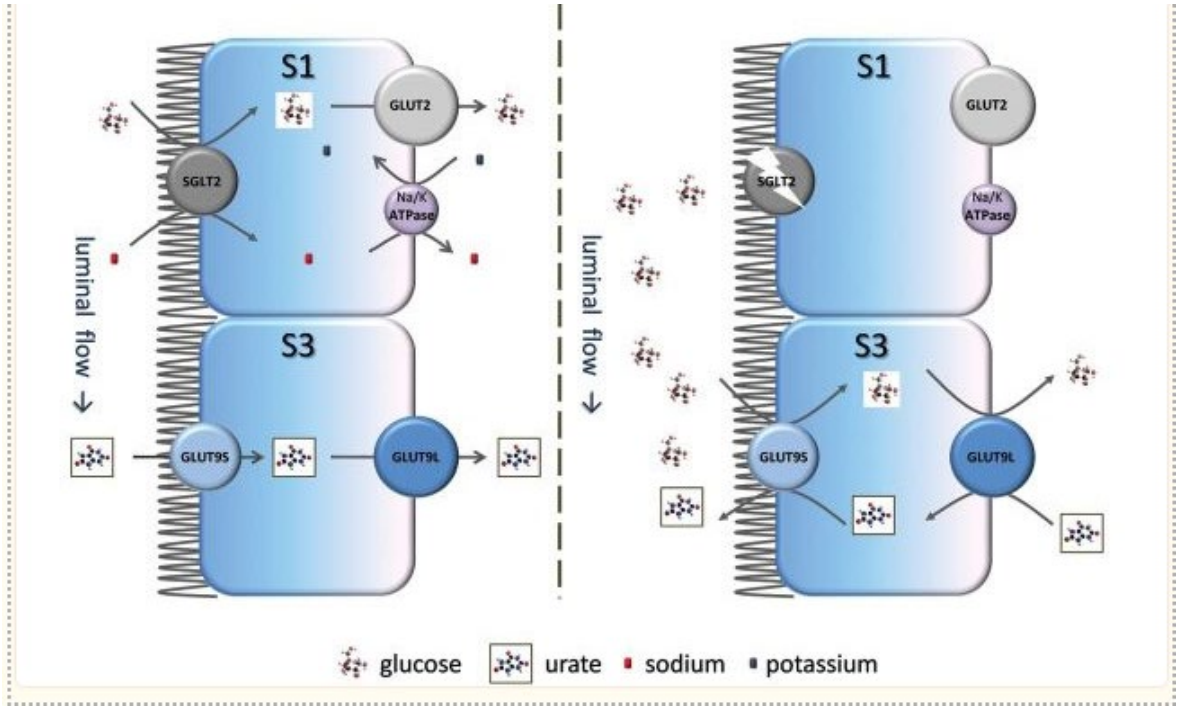
Outcomes[a,b]	LN on SGLT2	LN on GLP-1	RR (95% CI)	P-value
Dialysis (n,%)	36 (5.8%)	36 (6.26%)	0.926 (0.592-1.449)	0.7362
ESRD (n,%)	37 (6.38%)	31 (5.91%)	1.08 (0.68-1.715)	0.7431
CKD (n,%)	75 (43.35%)	73 (28.4%)	1.526 (1.179-1.976)	0.0014
Renal Transplant (n,%)	<10 (1.59%)	12 (2.1%)	0.759 (0.331-1.744)	0.5146
Mortality (n,%)	48 (6.96%)	24 (3.48%)	2 (1.239-3.227)	0.0037
Acute MI (n,%)	37 (6.3%)	18 (2.8%)	2.248 (1.294-3.904)	0.0030
Stroke (n,%)	21 (3.541%)	13 (2.0%)	1.754 (0.886-3.472)	0.1018
Heart Failure (n,%)	39 (10%)	40 (7.1%)	1.421 (0.932-2.166)	0.1013

Abbreviations: Acute MI: Acute Myocardial Infarction, CKD: Chronic Kidney Disease, ESRD: End-Stage Renal Disease, GLP-1: glucagon-like peptide-1agonists, LN: Lupus Nephritis, RR: Relative Risk, SGLT 2: sodium-glucose cotransporter-2 inhibitors, 95% CI: 95% Confidence Interval

[a] Propensity matched cohorts based on baseline demographics, comorbidities, and medication use.

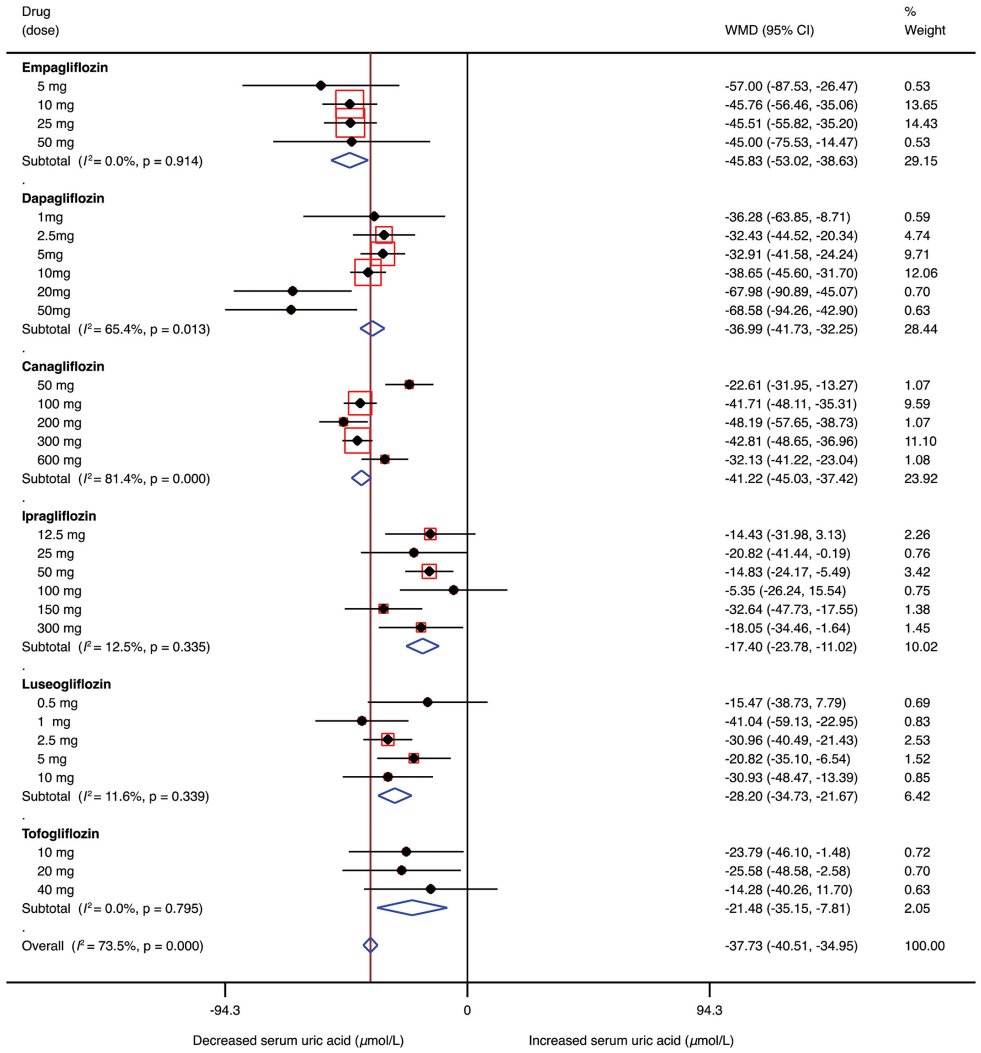
[b] All patients with outcomes that occurred prior to the time window were excluded from our cohorts.

SGLT-2 inhibition leads to an increase of urate excretion



doi: 10.1093/ckj/sft100

Effects of sodium-glucose co-transporter 2 (SGLT2) inhibitors on serum uric acid level: A meta-analysis of randomized controlled trials



- SUA levels decreased compared with control −37.73 μmol/L empagliflozin, −45.83 μmol/L canagliflozin, −41.22 μmol/L dapagliflozin, −36.99 μmol/L, luseogliflozin
- effect also in non DM patients
- did not occur in CKD patients (eGFR <60 mL/min/1.73 m2)
- Caveats trial not designed for evaluating pts with hyperuricaemia

https://doi.org/10.1111/dom.13101

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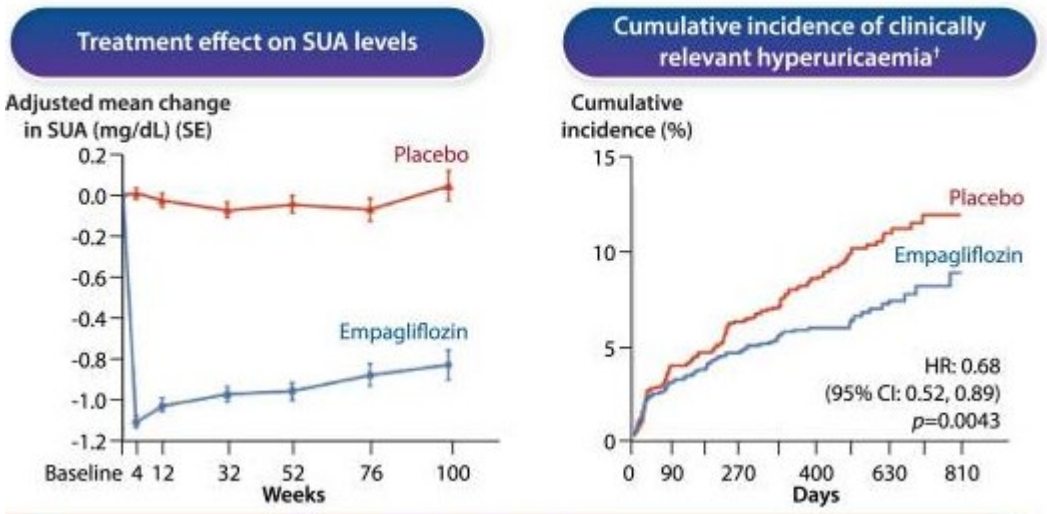
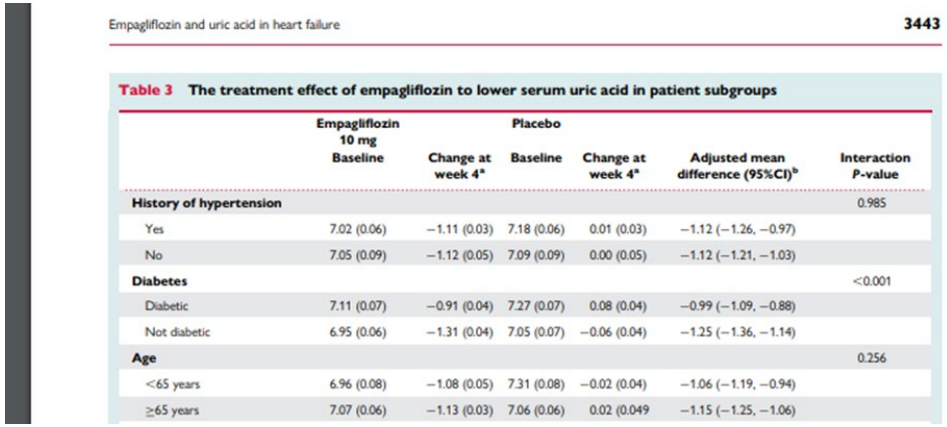
Uric acid and sodium-glucose cotransporter-2 inhibition with empagliflozin in heart failure with reduced ejection fraction: the EMPEROR-reduced trial





Empagliflozin and uric acid in heart failure 3443

Table 3 The treatment effect of empagliflozin to lower serum uric acid in patient subgroups

	Empagliflozin 10 mg		Placebo			
	Baseline	Change at week 4[a]	Baseline	Change at week 4[a]	Adjusted mean difference (95%CI)[b]	Interaction *P*-value
History of hypertension						0.985
Yes	7.02 (0.06)	−1.11 (0.03)	7.18 (0.06)	0.01 (0.03)	−1.12 (−1.26, −0.97)	
No	7.05 (0.09)	−1.12 (0.05)	7.09 (0.09)	0.00 (0.05)	−1.12 (−1.21, −1.03)	
Diabetes						<0.001
Diabetic	7.11 (0.07)	−0.91 (0.04)	7.27 (0.07)	0.08 (0.04)	−0.99 (−1.09, −0.88)	
Not diabetic	6.95 (0.06)	−1.31 (0.04)	7.05 (0.07)	−0.06 (0.04)	−1.25 (−1.36, −1.14)	
Age						0.256
<65 years	6.96 (0.08)	−1.08 (0.05)	7.31 (0.08)	−0.02 (0.04)	−1.06 (−1.19, −0.94)	
≥65 years	7.07 (0.06)	−1.13 (0.03)	7.06 (0.06)	0.02 (0.049	−1.15 (−1.25, −1.06)	

- the trial was a randomized, double-blind, parallel-group, placebo-controlled, and event driven study that evaluated the effects of the SGLT2 inhibitor empagliflozin on the morbidity and mortality of patients with HFrEF
- 3676 patients (98.6%) with a baseline assessment of SUA were included in this analysis

•10.1093/eurheartj/ehac320

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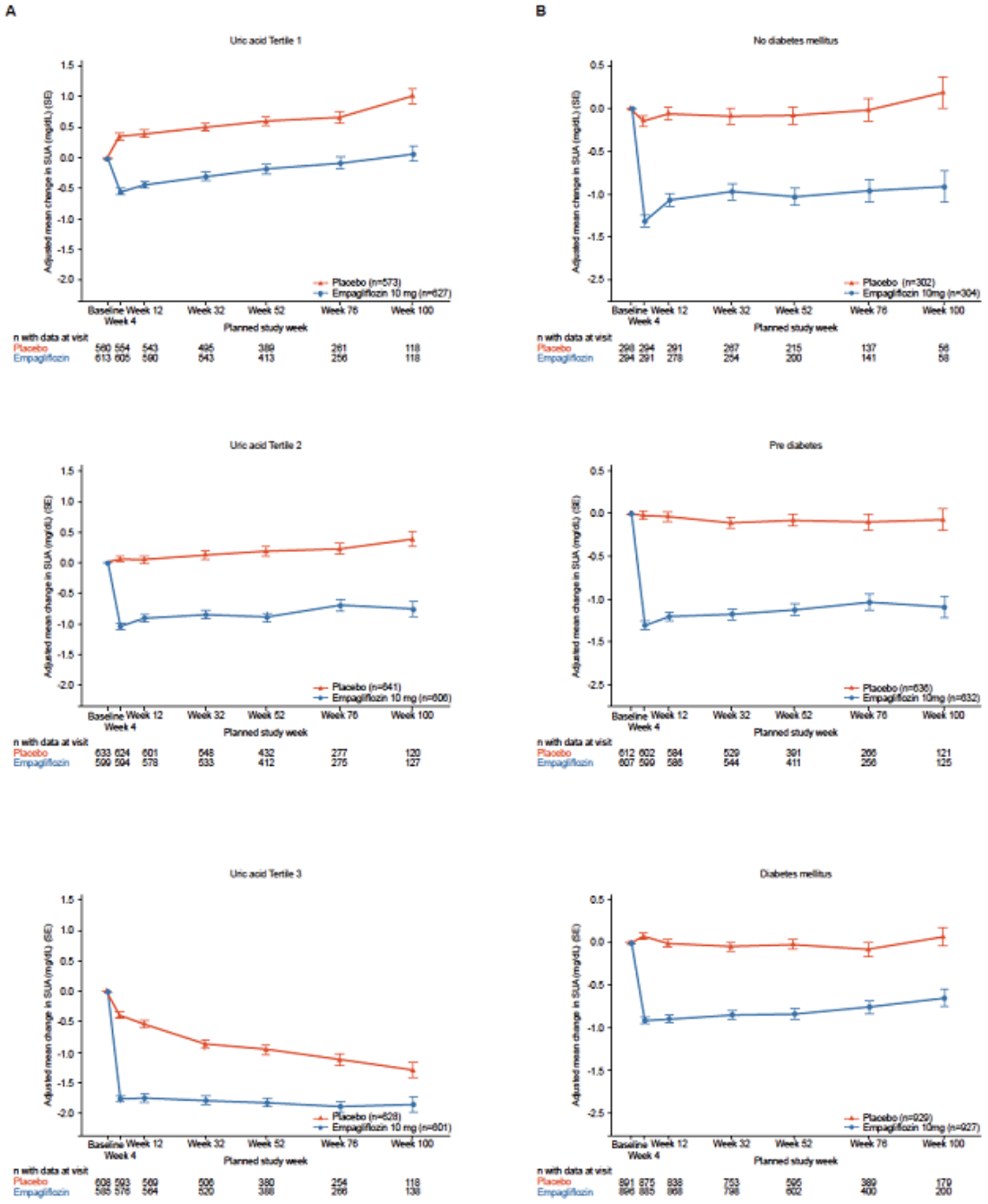
Effect independent

of the initial SUA value

and the presence of diabetes



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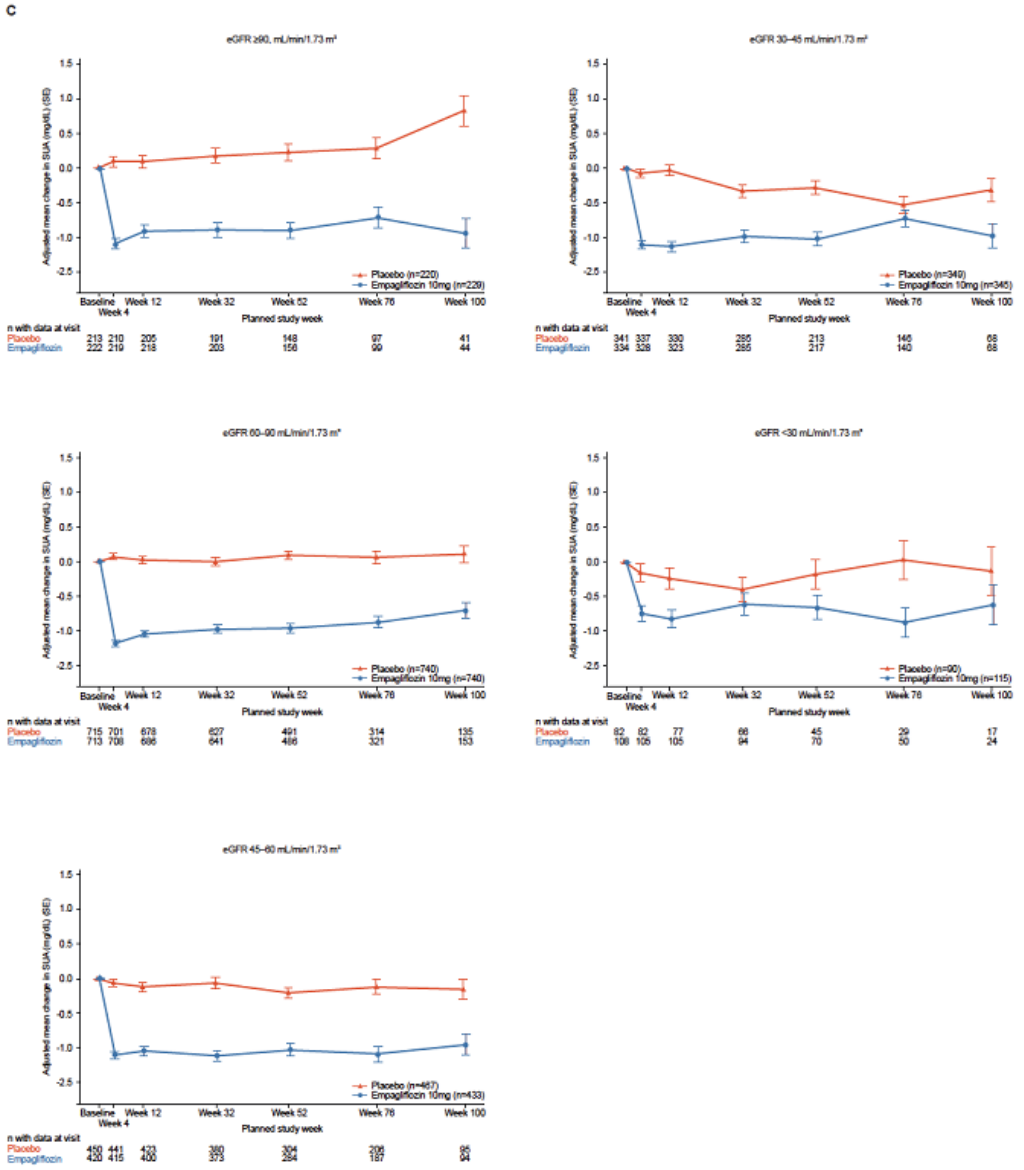
SGLT-2 i lower SUA only

in patients

with preserved renal function



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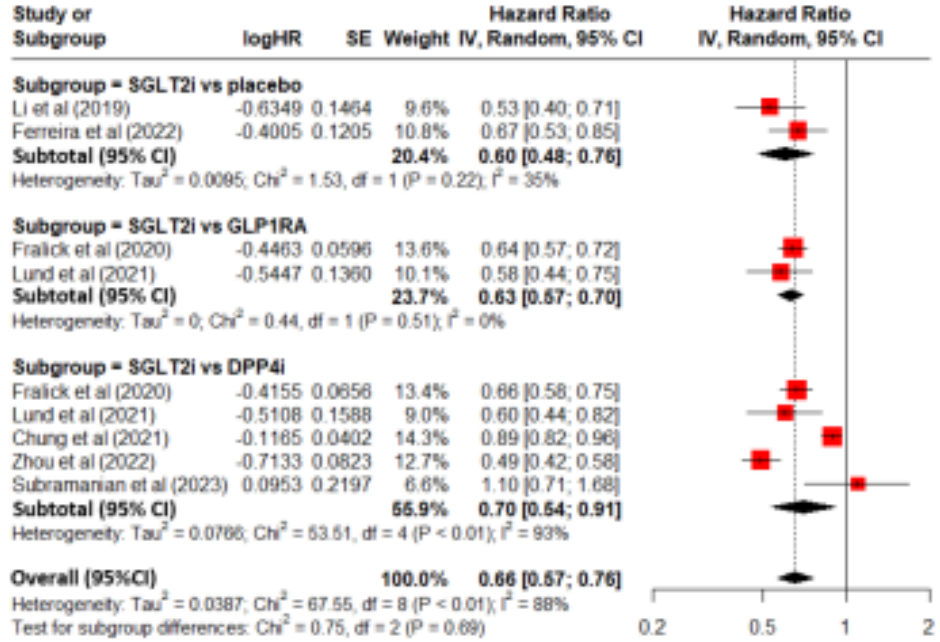
Can SGLT-2 inhibition prevent gout?



- Systematic review and meta-analysis
- 34% decreased risk of developing gout among patients with T2DM

https://doi.org/10.3389/fendo.2023.1158153

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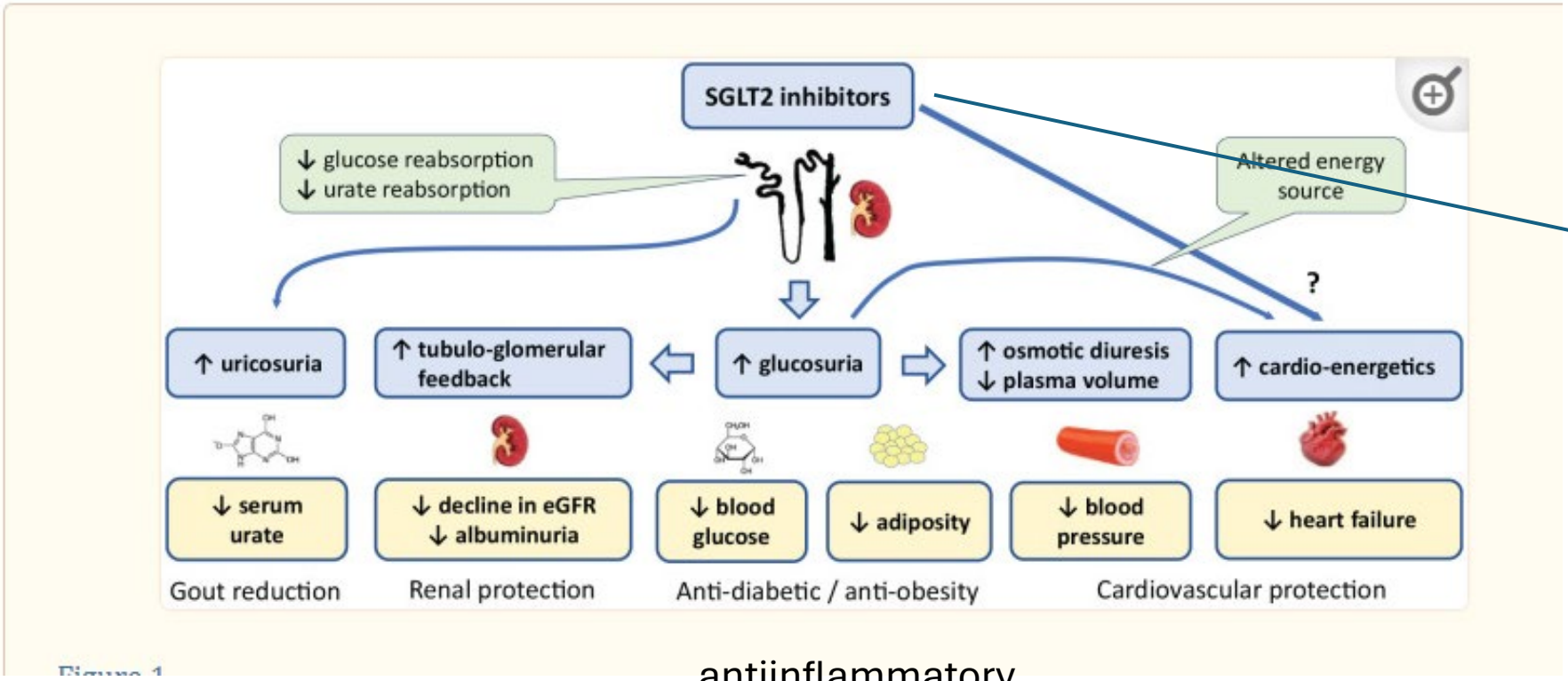
Sglt-2 Inhibition effects



doi: 10.1177/20420188241269178

Conclusion

- In addition to their cardioprotective effects
- SGLT-2 inhibitors
  - slow progression of CKD in patients with and without diabetes
  - Reduce significantly proteinuria in patients with inflammatory kidney disease
  - Reduce SUA in patients with preserved kidney function
  - Reduce the incidence of gout flares
- Role of other antidiabtic drugs unclear (e.g. GLP-1, metformin)
- More data needed.....