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SGLT2 inhibitors in CKD
Another pillar

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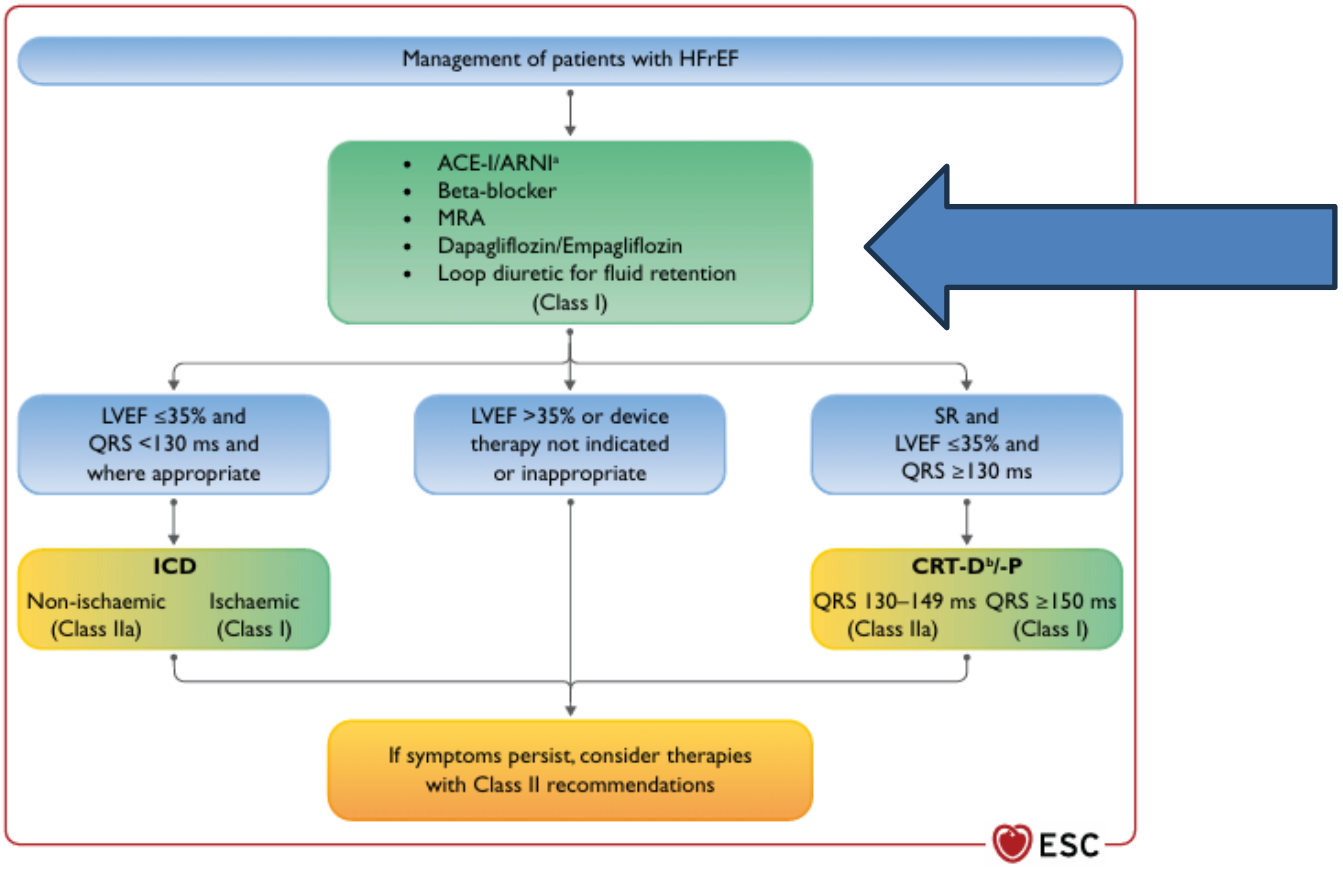
University of BRISTOL

Disclosures

Honoraria from AstraZeneca, Astellas, Bayer, Boehringer Ingelheim, CSL Vifor, GSK, Otsuka, Pharmacosmos.

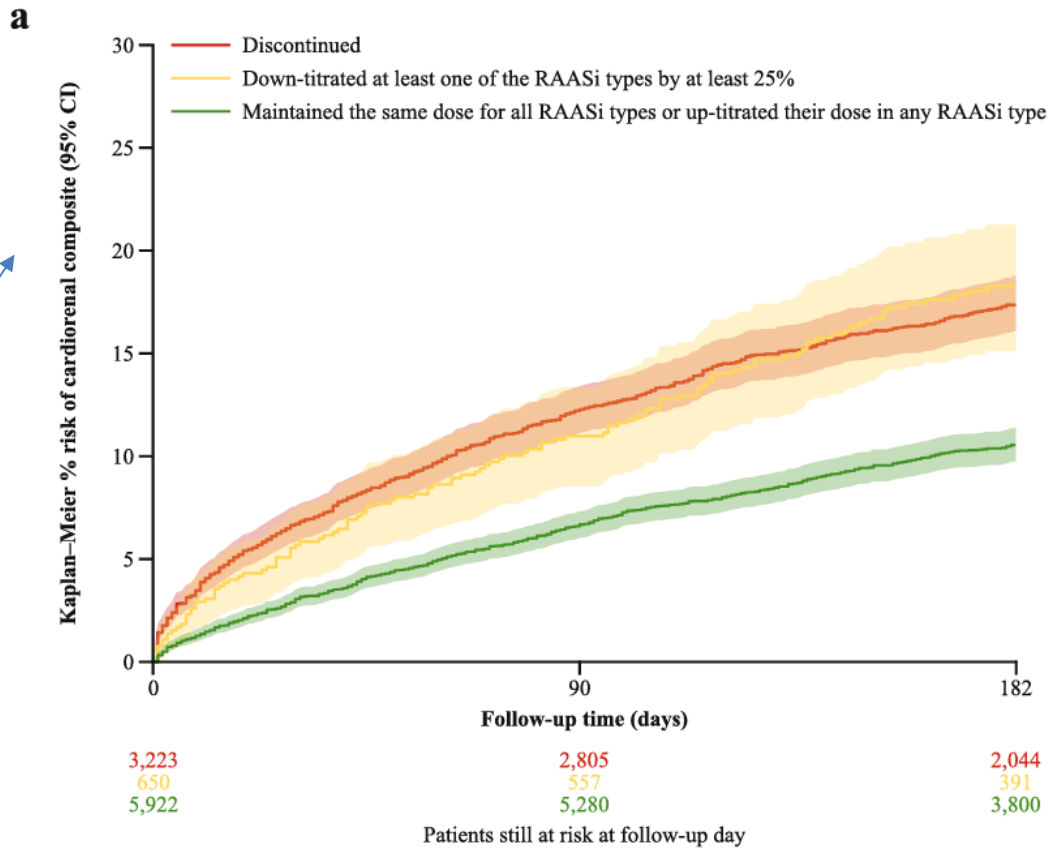
Pillars of therapy – we know them for HF



Established role for RAASi

US EHR data (2019-2021)
N=15,488
CKD Stage 3-4 ± HF
With hyper-K event

ESRD or HF hospitalisation



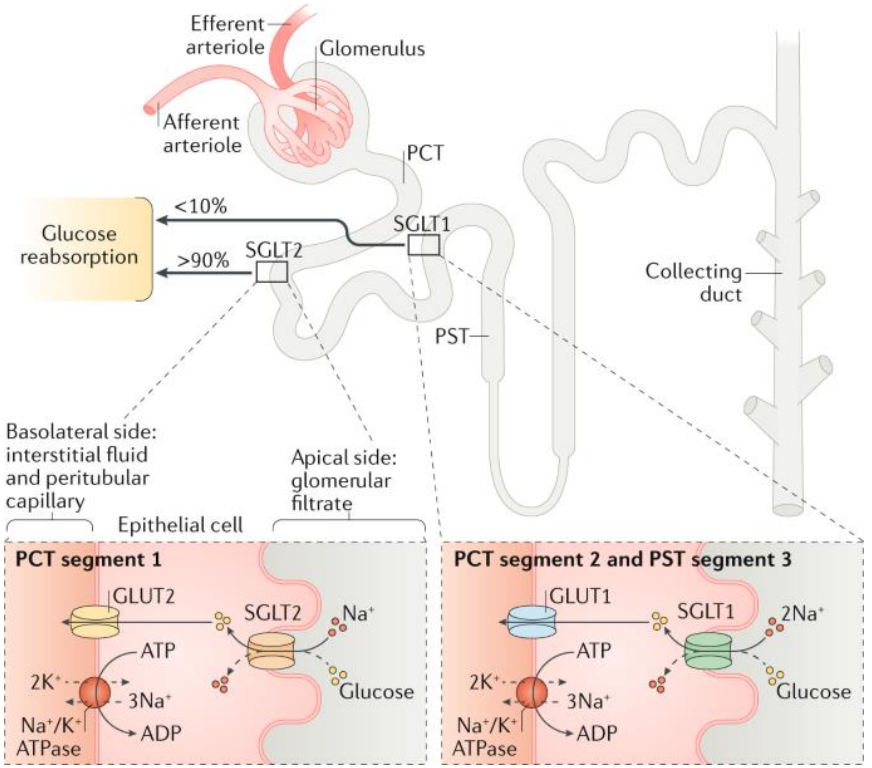
Kanda et al. BMC Nephrol (2023);24: 18.

SGLT2

Sodium-glucose co-transporter
Proximal tubule

>90% reabsorption all filtered glucose

Along with sodium



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SGLT2

Sodium-glucose co-transporter
Proximal tubule

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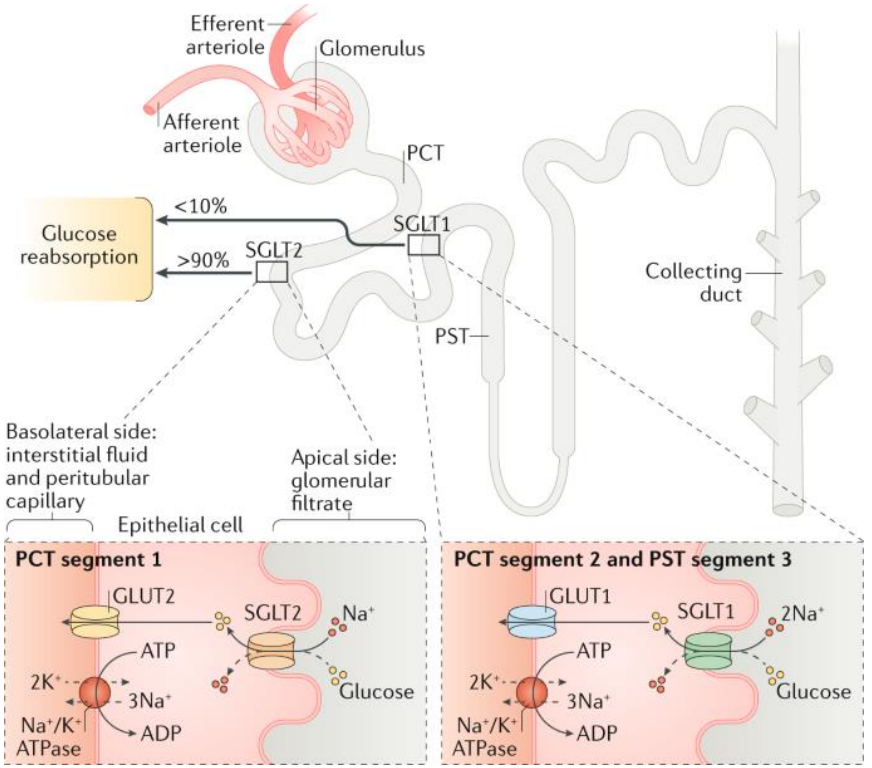
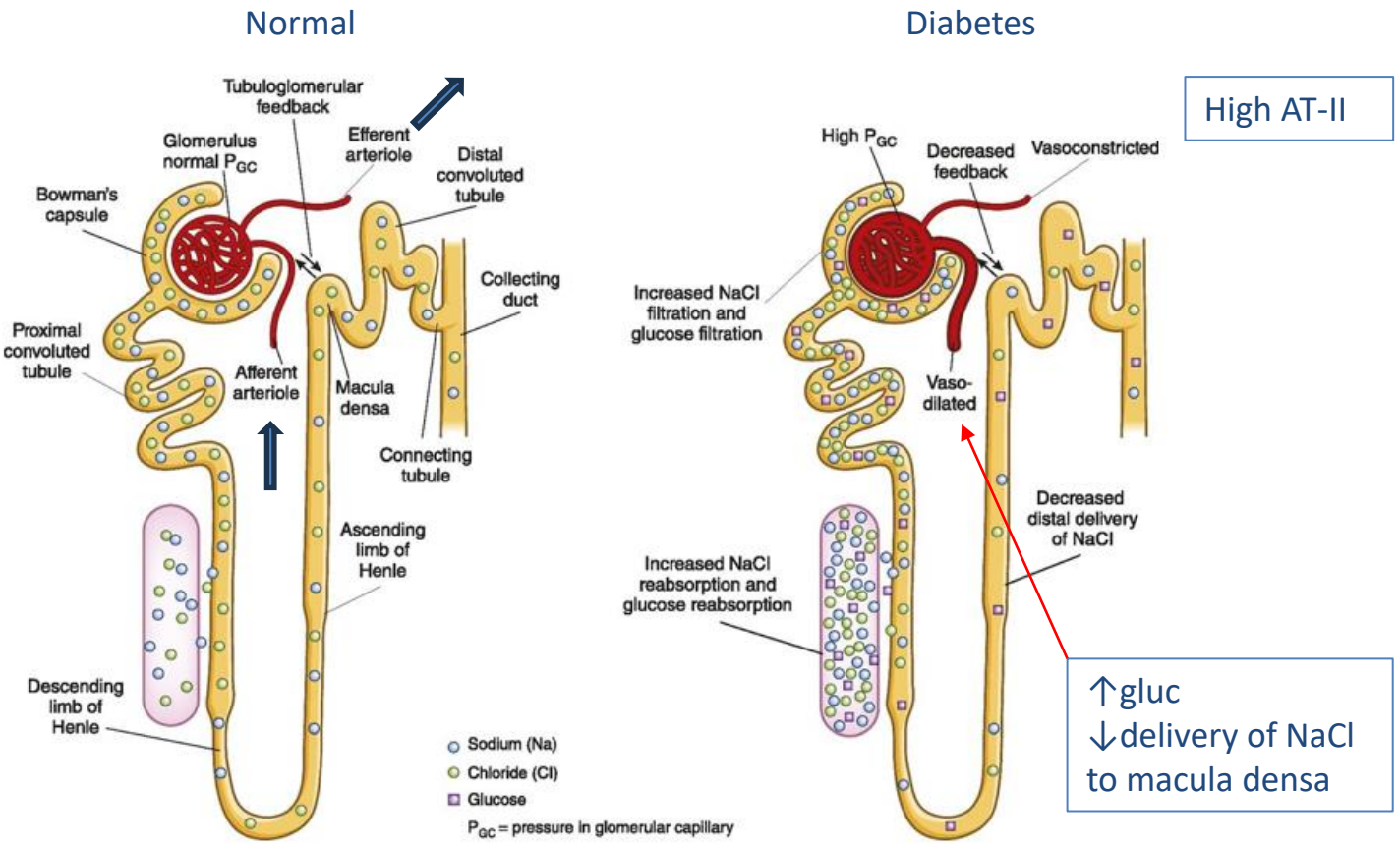
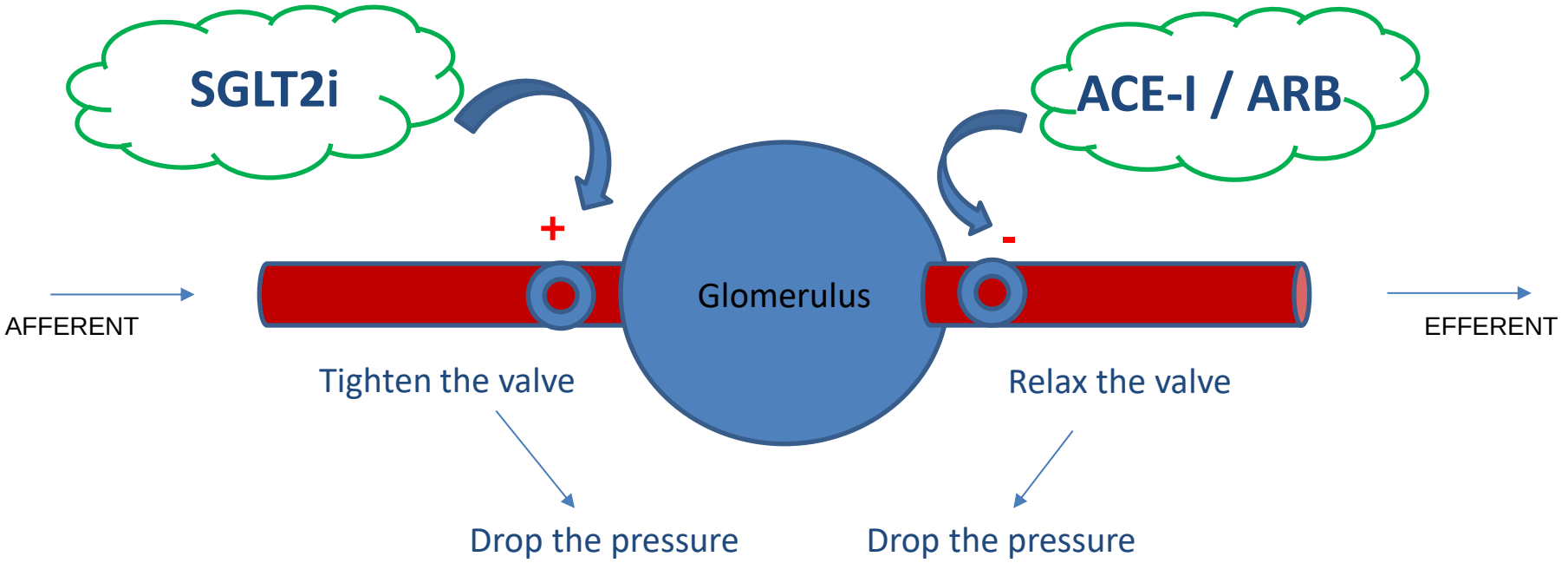
Along with sodium

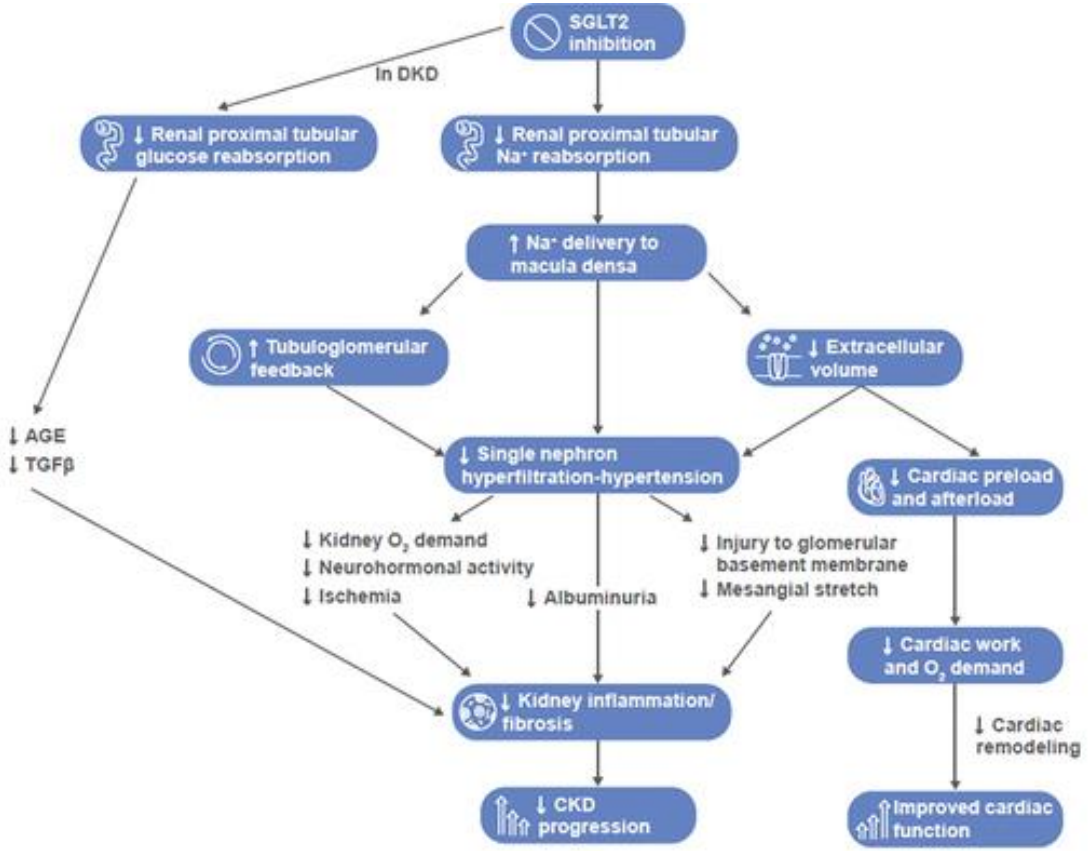


TGF


Normal
Diabetes
Tubuloglomerular feedback
Glomerulus normal P_{GC}
Efferent arteriole
Distal convoluted tubule
Bowman's capsule
Collecting duct
Proximal convoluted tubule
Afferent arteriole
Macula densa
Connecting tubule
Ascending limb of Henle
Descending limb of Henle
Sodium (Na)
Chloride (Cl)
Glucose
P_{GC} = pressure in glomerular capillary
High P_{GC}
Decreased feedback
Vasoconstricted
Increased NaCl filtration and glucose filtration
Vaso-dilated
Decreased distal delivery of NaCl
Increased NaCl reabsorption and glucose reabsorption
High AT-II
↑gluc
↓delivery of NaCl to macula densa


SGLT2i
ACE-I / ARB
+
-
AFFERENT
Glomerulus
EFFERENT
Tighten the valve
Relax the valve
Drop the pressure
Drop the pressure

Renoprotection



Sloan. Postgrad Med (2024) 136(8), 801–809.

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Kidney benefits seen in all the CVOTs

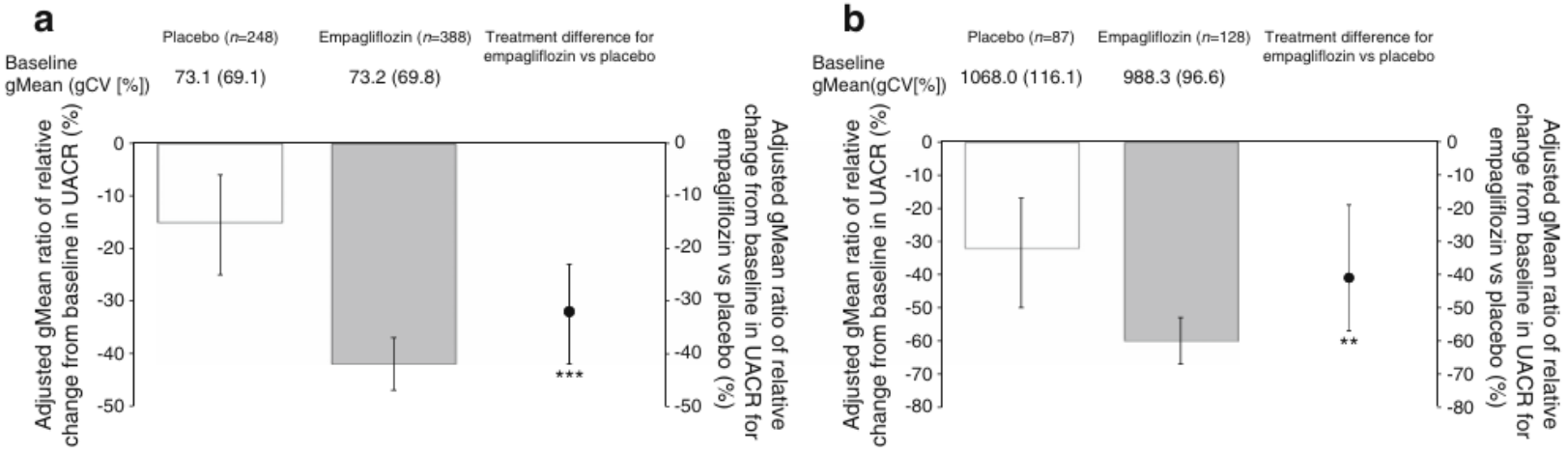
Empagliflozin / Dapagliflozin / Canagliflozin
All patients had T2DM
eGFR >60 ml/min
Standard of care
"=" placebo

Good BP control
High prevalence of ACEi/ARB

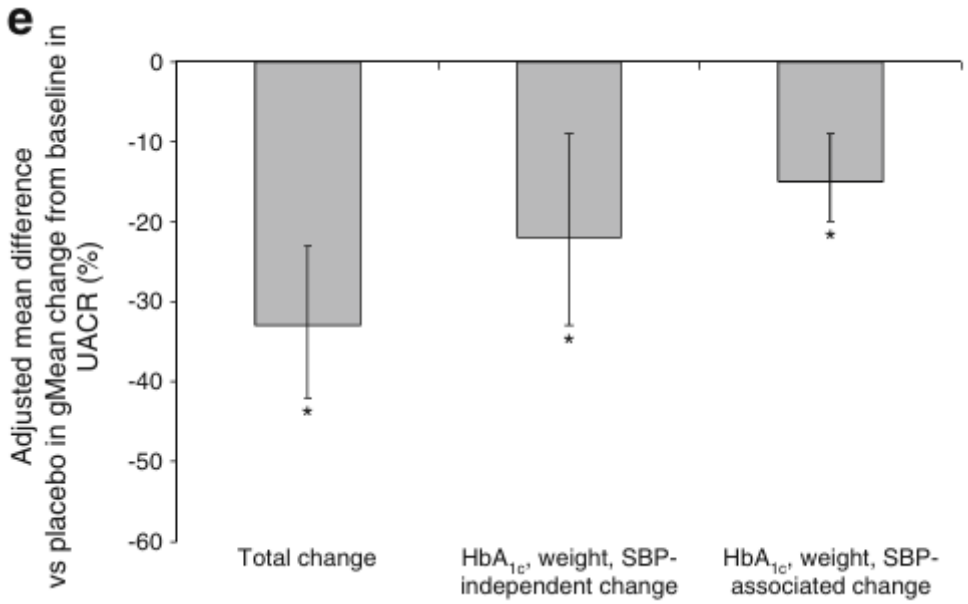
	EMPA-REG OUTCOME	CANVAS	DECLARE-TIMI 58
Drug	Empagliflozin	Canagliflozin	Dapagliflozin
n	7020	10 142	17 160
Study dose, mg	25, 10	300, 100	10
Duration of T2D, mean±SD or median (IQR), y	≥10 (4011 [57% had T2D >10 y])	13.5±7.8	11 (6–16)
Median follow-up, y	3.1	2.4	4.2
Statin use (baseline), n (%)	5403 (77)	7599 (75)	12 868 (75)
ACE inhibitor/ARB, n (%)	5666 (81)	8116 (80)	13 950 (81)
MRA, n (%)	441 (6)	…	…

Heerspink et al. Circulation (2016);134 :752-772.

SGLT2i reduce proteinuria

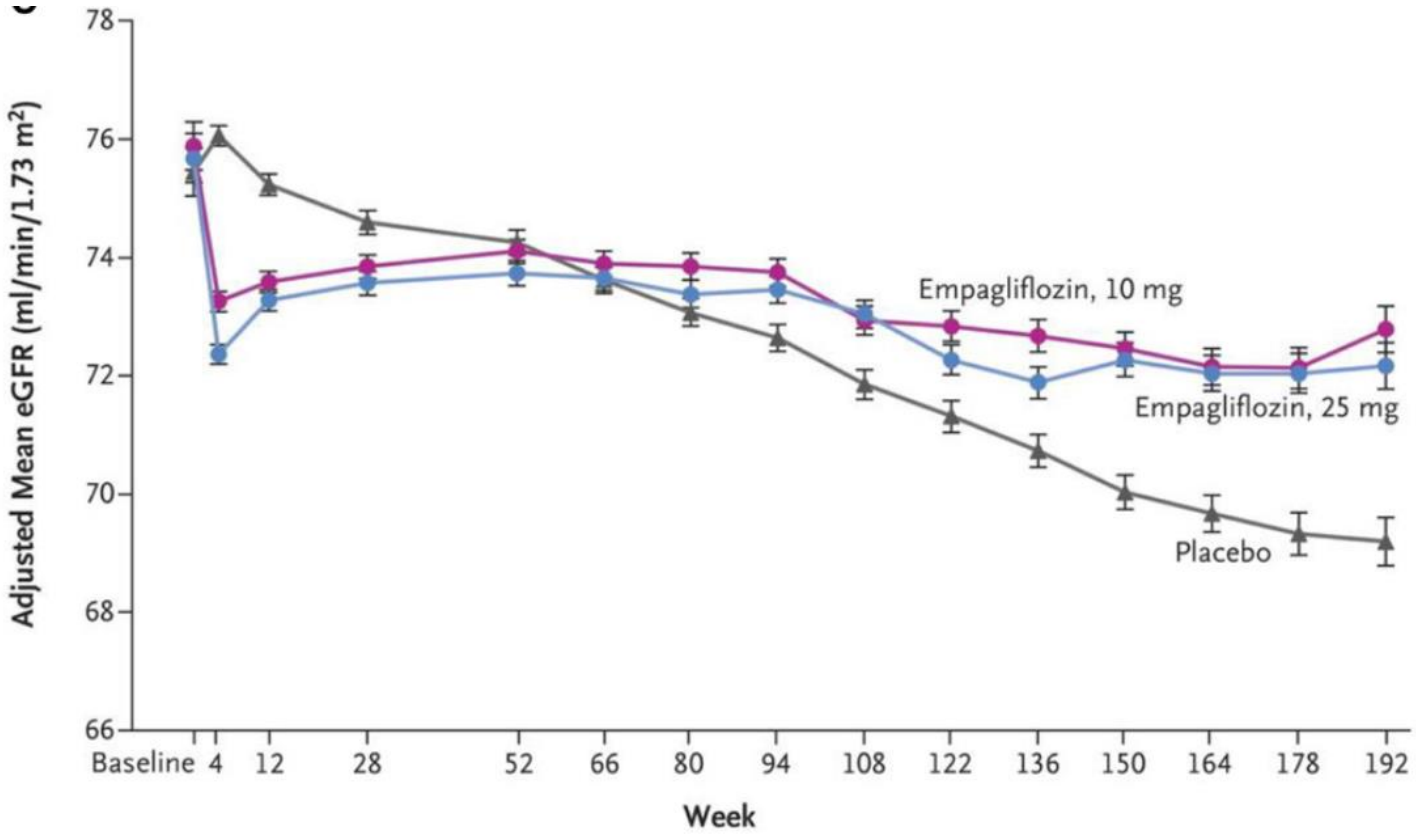


SGLT2i reduce proteinuria



Cherney et al. Diabetologia (2016); 59: 1860-1870.

Kidney benefits from EMPA-REG



Wanner et al. NEJM (2016);375: 323-334.

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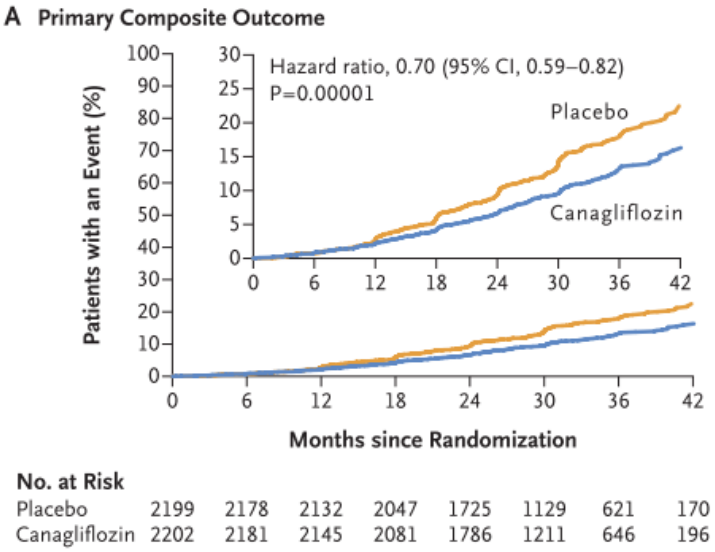
SGLT2i used in CKD

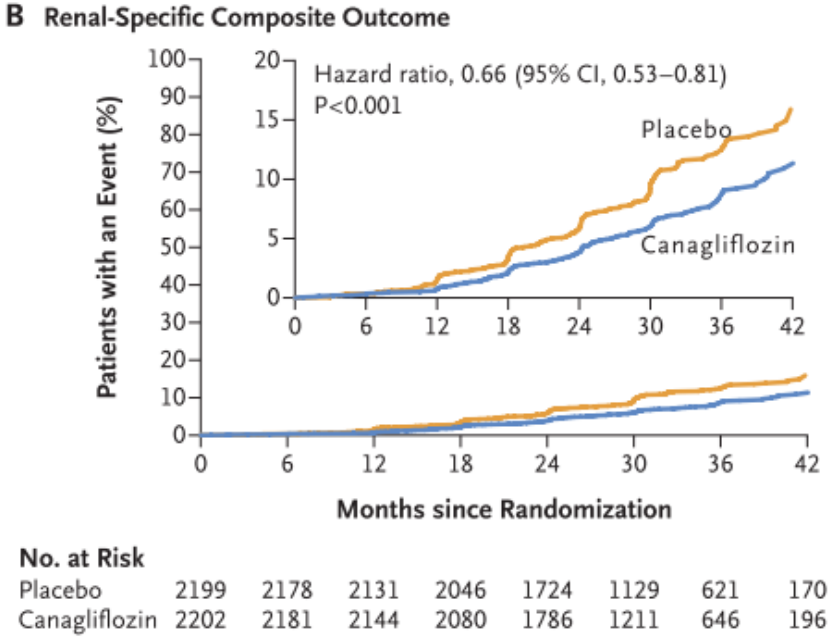
CREDENCE

N=4401
eGFR 30-90 ml/min [mean 56 ml/min]
100 % diabetic
99.9 % treated with ACE/ARB
UrACR ≥22.6 mg/mmol
Mean BP 140/78 mmHg

SGLT2i used in CKD

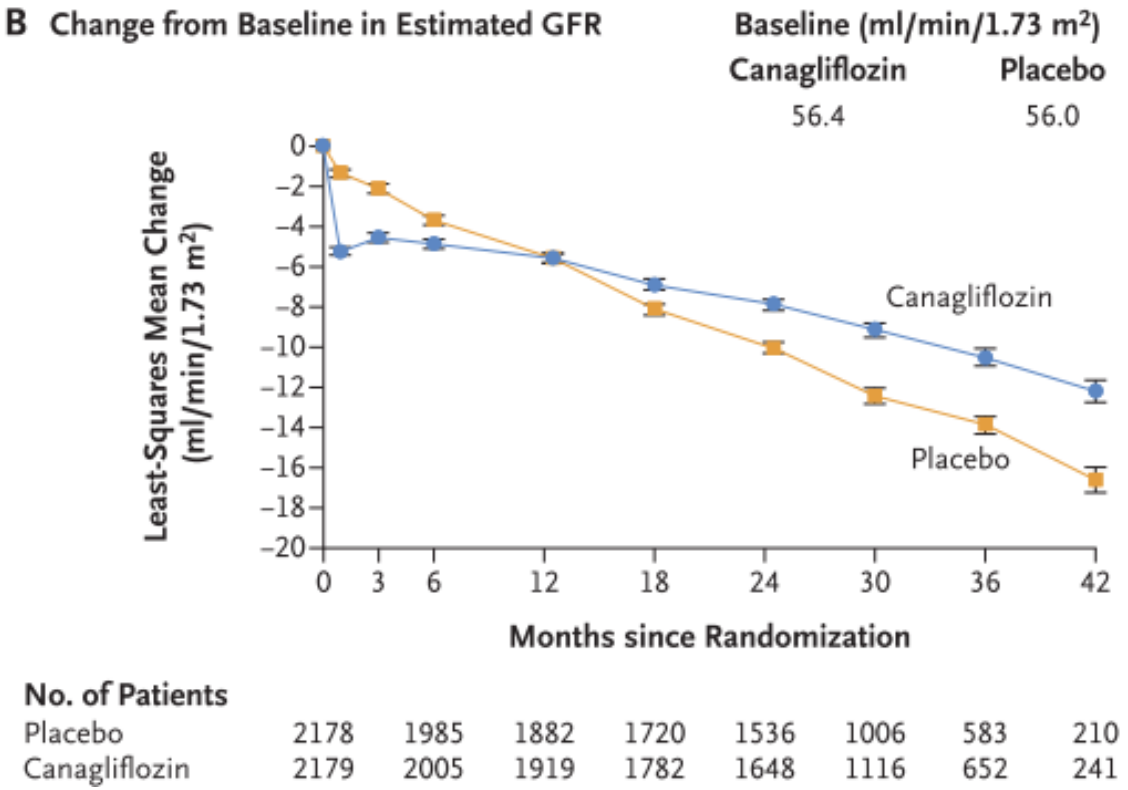
CREDENCE





SGLT2i used in CKD

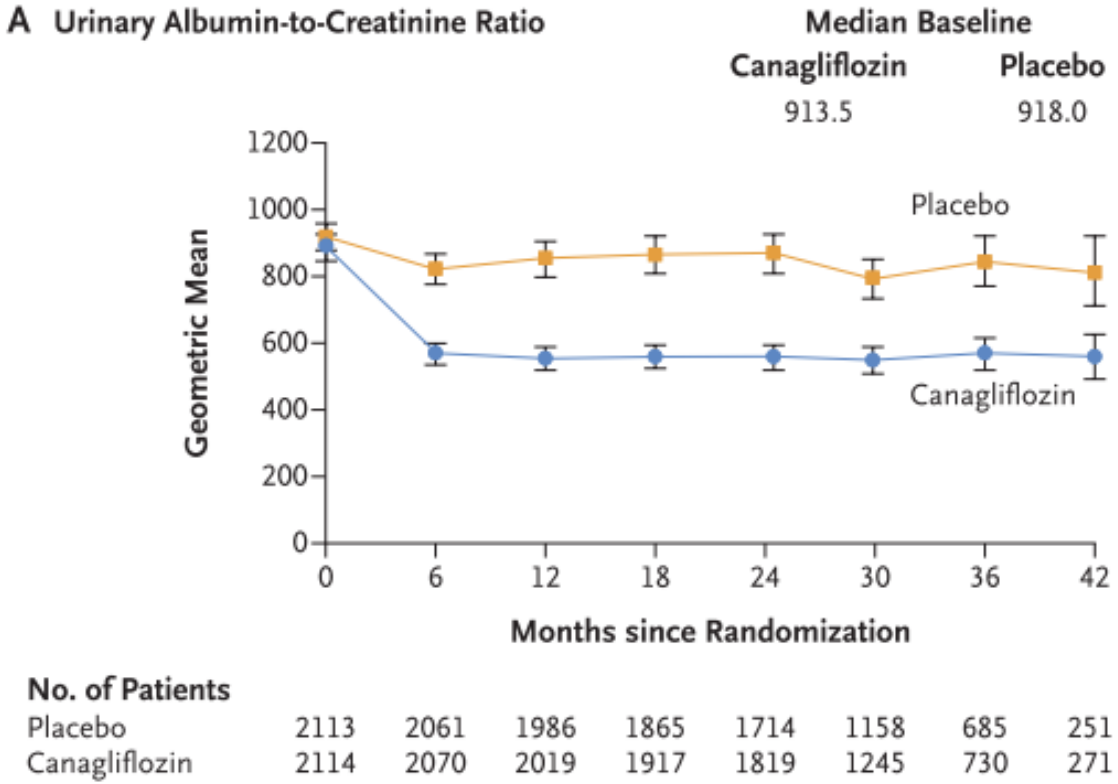
CREDENCE



Percovic et al. NEJM (2019); 380: 2295-2306.

SGLT2i used in CKD

CREDENCE



Percovic et al. NEJM (2019); 380: 2295-2306.

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SGLT2i used in CKD

DAPA-CKD

N=4304
eGFR 25-75 ml/min
67 % diabetic
c. 90 % treated with ACE/ARB
UrACR ≥22.6 mg/mmol
Mean BP 137/78 mmHg

Heerspink et al. NEJM (2020); 383: 1436-1446.

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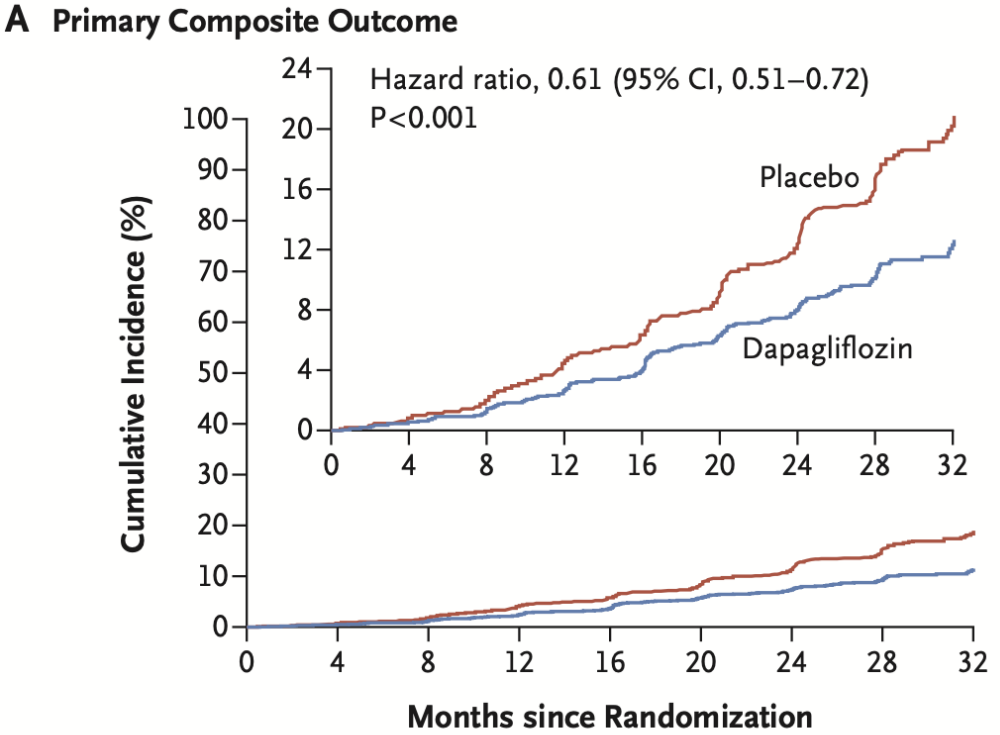
SGLT2i used in CKD



No. at Risk

Placebo	2152	1993	1936	1858	1791	1664	1232	774	270
Dapagliflozin	2152	2001	1955	1898	1841	1701	1288	831	309

Heerspink et al. NEJM (2020); 383: 1436-1446.

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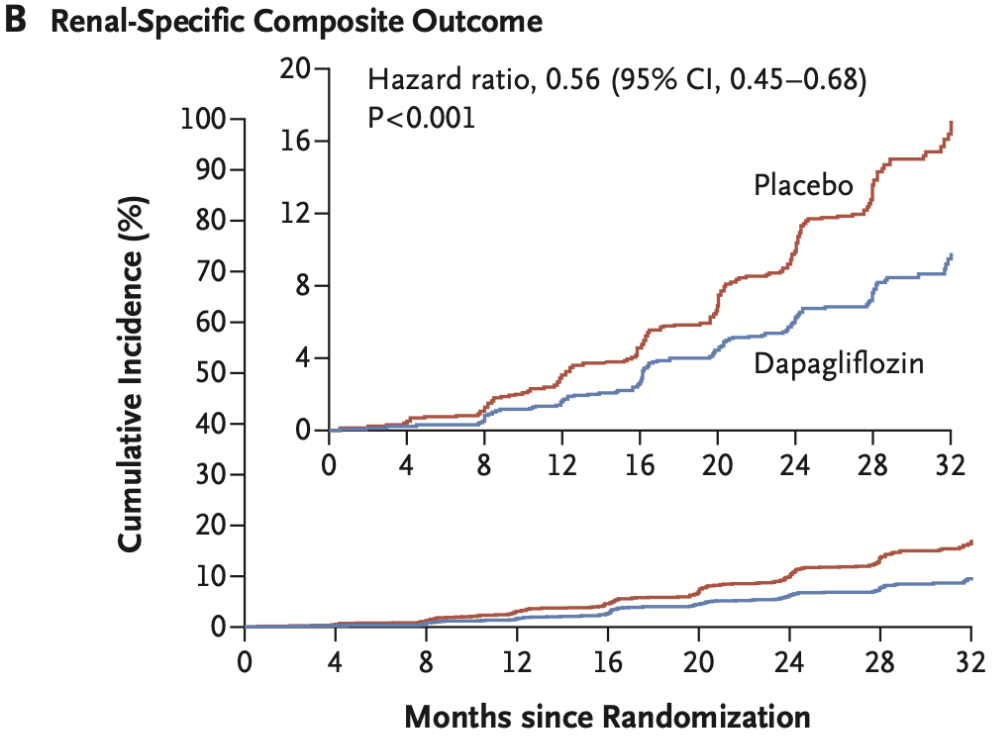
SGLT2i used in CKD



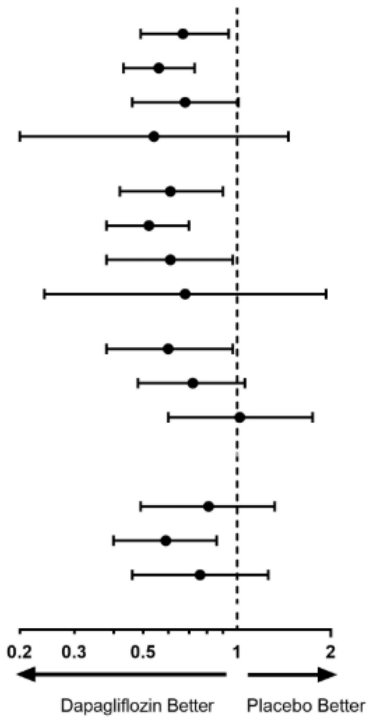
Heerspink et al. NEJM (2020); 383: 1436-1446.

SGLT2i in CKD – Give them

DAPA-CKD

Consistent benefit

	Dapagliflozin	Placebo	Hazard Ratio (95% CI)	P Value for Interaction
	Events/100 patient-years			
Primary outcome: eGFR decline ≥50%, ESKD, or kidney or CV death				
Target dose	4.9	7.1	0.67 (0.49, 0.94)	0.76
≥50 to <100% target dose	4.6	8.1	0.56 (0.43, 0.73)	
>0 to <50% target dose	4.2	6.0	0.68 (0.46, 1.01)	
None	6.0	13.2	0.54 (0.20, 1.46)	
Secondary outcome: eGFR decline ≥50%, ESKD or kidney death				
Target dose	3.6	5.6	0.61 (0.42, 0.90)	0.86
≥50 to <100% target dose	3.3	6.3	0.52 (0.38, 0.70)	
>0 to <50% target dose	2.8	4.3	0.61 (0.38, 0.97)	
None	6.0	11.6	0.68 (0.24, 1.93)	
Secondary outcome: Hospitalization for heart failure or CV death				
Target dose	2.1	3.4	0.60 (0.38, 0.97)	0.38
≥50 to <100% target dose	2.1	3.0	0.72 (0.48, 1.06)	
>0 to <50% target dose	2.5	2.5	1.02 (0.60, 1.75)	
None	0.9	4.5	NC	
Secondary outcome: All-cause mortality				
Target dose	2.1	2.5	0.81 (0.49, 1.32)	0.77
≥50 to <100% target dose	2.0	3.5	0.59 (0.40, 0.86)	
>0 to <50% target dose	2.4	3.3	0.76 (0.46, 1.26)	
None	2.7	3.6	NC	



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SGLT2i used in CKD

EMPA-KIDNEY

N=6609	*larger*
eGFR 20-90 ml/min	*wider eGFR ranges*
46 % diabetic	*fewer diabetics*
c. 86 % treated with ACE/ARB	*similar*
Mean BP 136/78 mmHg	*same*

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SGLT2i used in CKD

EMPA-KIDNEY

Stratified entry based on eGFR & proteinuria
Wanted to see if benefits those with lower/no proteinuria

eGFR 20 – 44	No UrACR criterion
eGFR ≥45	UrACR ≥22.6 mg/mmol

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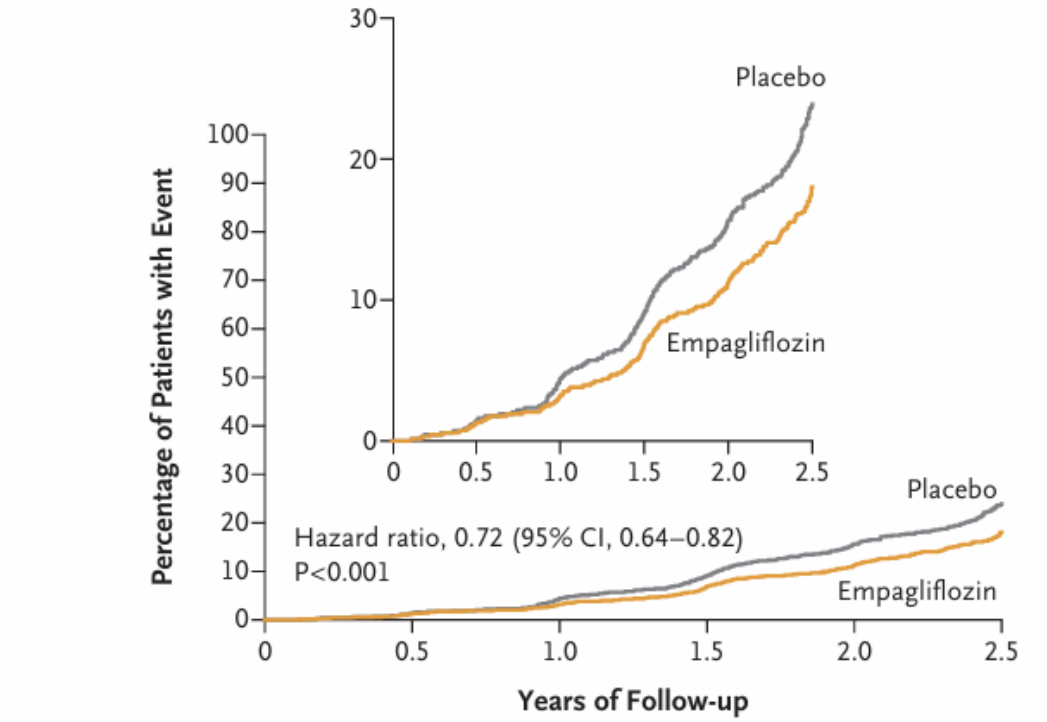
SGLT2i used in CKD

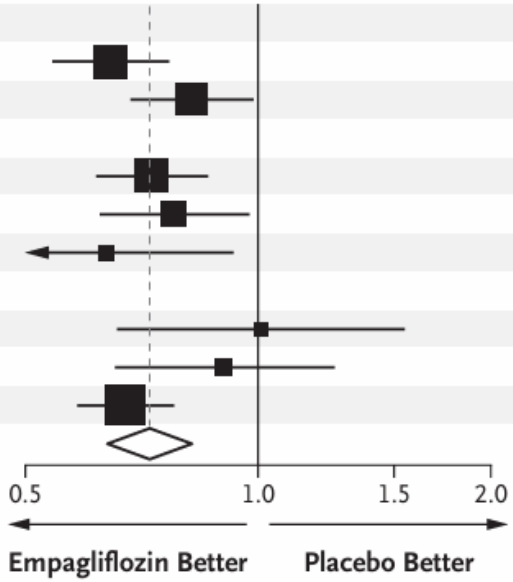


No. at Risk						
Placebo	3305	3250	3129	2243	1496	592
Empagliflozin	3304	3252	3163	2275	1538	624

EMPA-KIDNEY. NEJM (2023); 388: 117-127

SGLT2i used in CKD

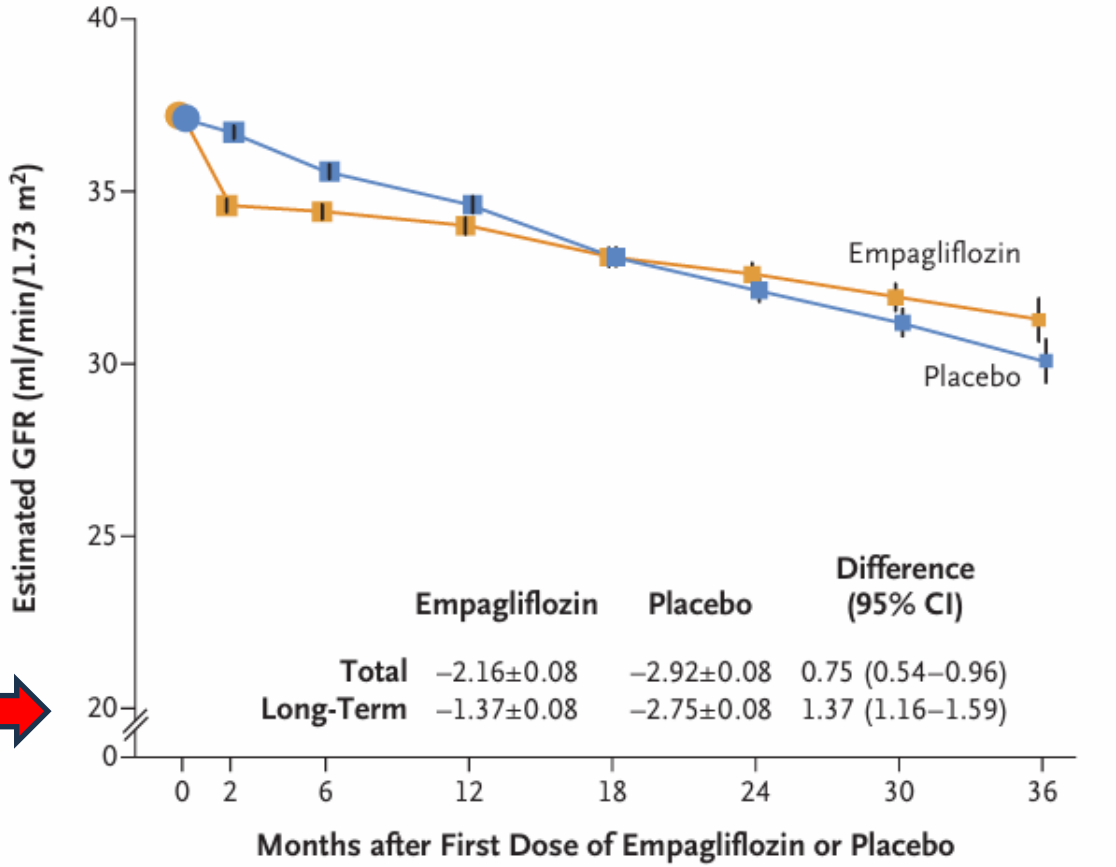
Subgroup	Empagliflozin (no. of patients with event/total no.)	Placebo (no. of patients with event/total no.)	Hazard Ratio for Progression of Kidney Disease or Death from Cardiovascular Causes (95% CI)
Diabetes mellitus			
Present	218/1525	306/1515	0.64 (0.54–0.77)
Absent	214/1779	252/1790	0.82 (0.68–0.99)
Estimated GFR			
<30 ml/min/1.73 m^2	247/1131	317/1151	0.73 (0.62–0.86)
≥30 to <45 ml/min/1.73 m^2	140/1467	175/1461	0.78 (0.62–0.97)
≥45 ml/min/1.73 m^2	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)



EMPA-KIDNEY. NEJM (2023); 388: 117-127

SGLT2i used in CKD

Impact on GFR slope

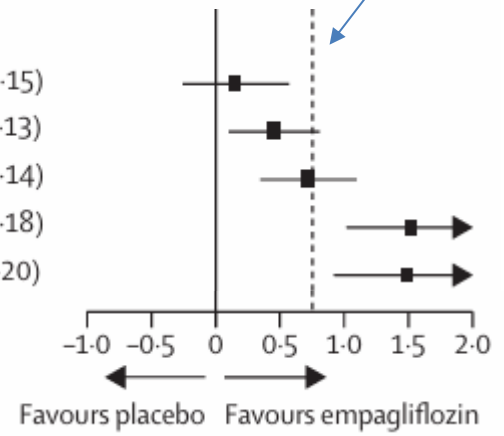


EMPA-KIDNEY. NEJM (2023); 388: 117-127

SGLT2i used in CKD

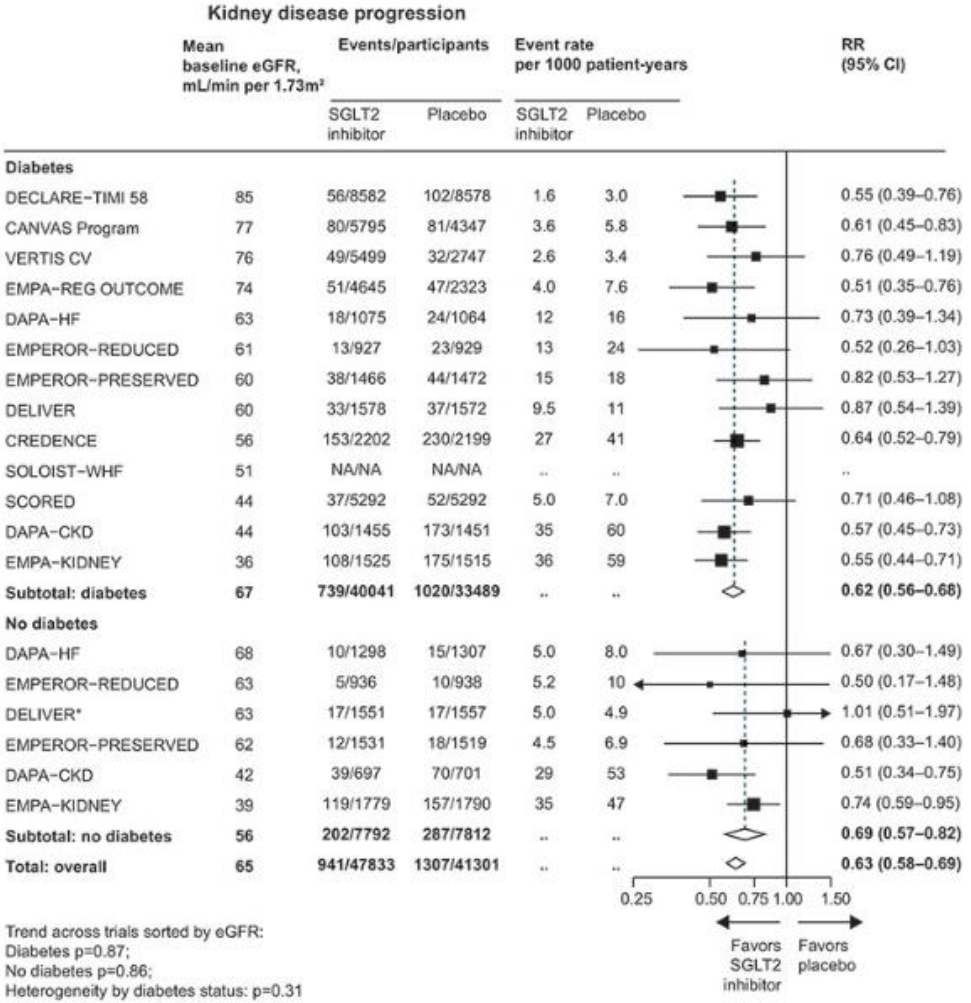
	Study average reduction in uACR, %	Mean (SE) slope, mL/min per 1·73 m² per year	
		Empagliflozin	Placebo
uACR (mg/g); χ^2_1=0·45; p_{trend}=0·50			
<30	−5%	−0·72 (0·15)	−0·88 (0·15)
30 to 300	−17%	−1·19 (0·13)	−1·64 (0·13)
>300 to <1000	−32%	−2·17 (0·13)	−2·89 (0·14)
1000 to <2000	−18%	−3·31 (0·17)	−4·82 (0·18)
≥2000	−19%	−5·60 (0·21)	−7·10 (0·20)

Benefits seen with lower/no proteinuria



EMPA-KIDNEY. NEJM (2023); 388: 117-127

SGLT2i


Kidney disease progression
Mean baseline eGFR, mL/min per 1.73m²
Events/participants
SGLT2 inhibitor
Placebo
Event rate per 1000 patient-years
SGLT2 inhibitor
Placebo
RR (95% CI)
Diabetes
DECLARE-TIMI 58 85 56/8582 102/8578 1.6 3.0 0.55 (0.39–0.76)
CANVAS Program 77 80/5795 81/4347 3.6 5.8 0.61 (0.45–0.83)
VERTIS CV 76 49/5499 32/2747 2.6 3.4 0.76 (0.49–1.19)
EMPA-REG OUTCOME 74 51/4645 47/2323 4.0 7.6 0.51 (0.35–0.76)
DAPA-HF 63 18/1075 24/1064 12 16 0.73 (0.39–1.34)
EMPEROR-REDUCED 61 13/927 23/929 13 24 0.52 (0.26–1.03)
EMPEROR-PRESERVED 60 38/1466 44/1472 15 18 0.82 (0.53–1.27)
DELIVER 60 33/1578 37/1572 9.5 11 0.87 (0.54–1.39)
CREDENCE 56 153/2202 230/2199 27 41 0.64 (0.52–0.79)
SOLOIST-WHF 51 NA/NA NA/NA .. .. ..
SCORED 44 37/5292 52/5292 5.0 7.0 0.71 (0.46–1.08)
DAPA-CKD 44 103/1455 173/1451 35 60 0.57 (0.45–0.73)
EMPA-KIDNEY 36 108/1525 175/1515 36 59 0.55 (0.44–0.71)
Subtotal: diabetes 67 739/40041 1020/33489 .. .. 0.62 (0.56–0.68)
No diabetes
DAPA-HF 68 10/1298 15/1307 5.0 8.0 0.67 (0.30–1.49)
EMPEROR-REDUCED 63 5/936 10/938 5.2 10 0.50 (0.17–1.48)
DELIVER* 63 17/1551 17/1557 5.0 4.9 1.01 (0.51–1.97)
EMPEROR-PRESERVED 62 12/1531 18/1519 4.5 6.9 0.68 (0.33–1.40)
DAPA-CKD 42 39/697 70/701 29 53 0.51 (0.34–0.75)
EMPA-KIDNEY 39 119/1779 157/1790 35 47 0.74 (0.59–0.95)
Subtotal: no diabetes 56 202/7792 287/7812 .. .. 0.69 (0.57–0.82)
Total: overall 65 941/47833 1307/41301 .. .. 0.63 (0.58–0.69)
0.25 0.50 0.75 1.00 1.50
Favors SGLT2 inhibitor
Favors placebo
Trend across trials sorted by eGFR:
Diabetes p=0.87;
No diabetes p=0.86;
Heterogeneity by diabetes status: p=0.31

SGLT2i

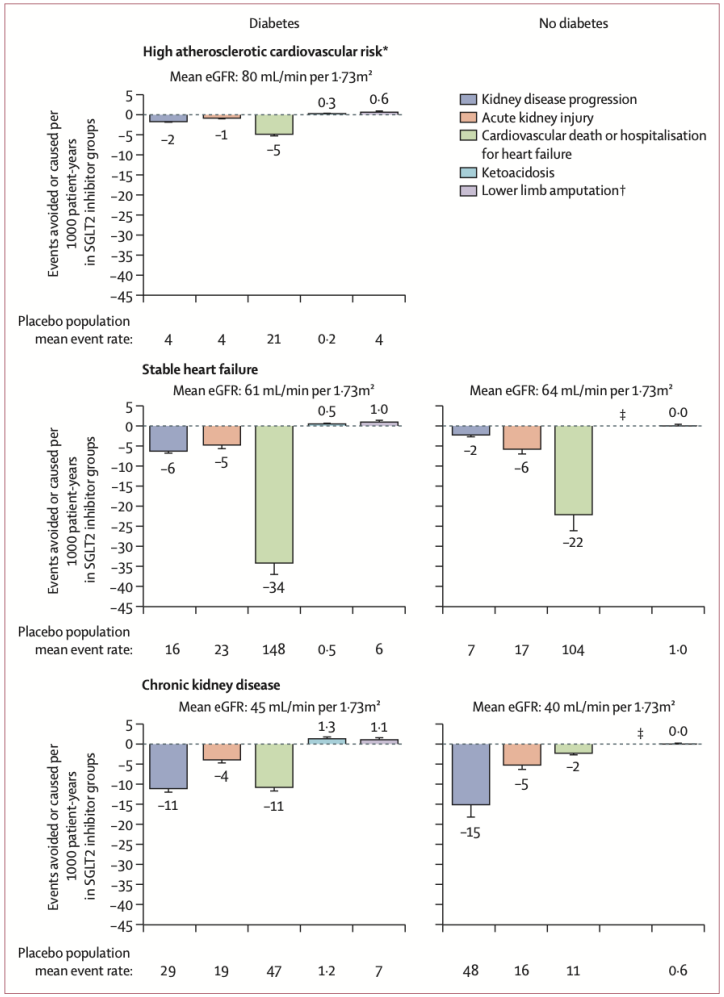


Figure 5: **Absolute benefits and harms of SGLT2 inhibition per 1000 patient-years by diabetes status and patient group**

Baigent et al. Lancet (2022); 400:1788-1801.

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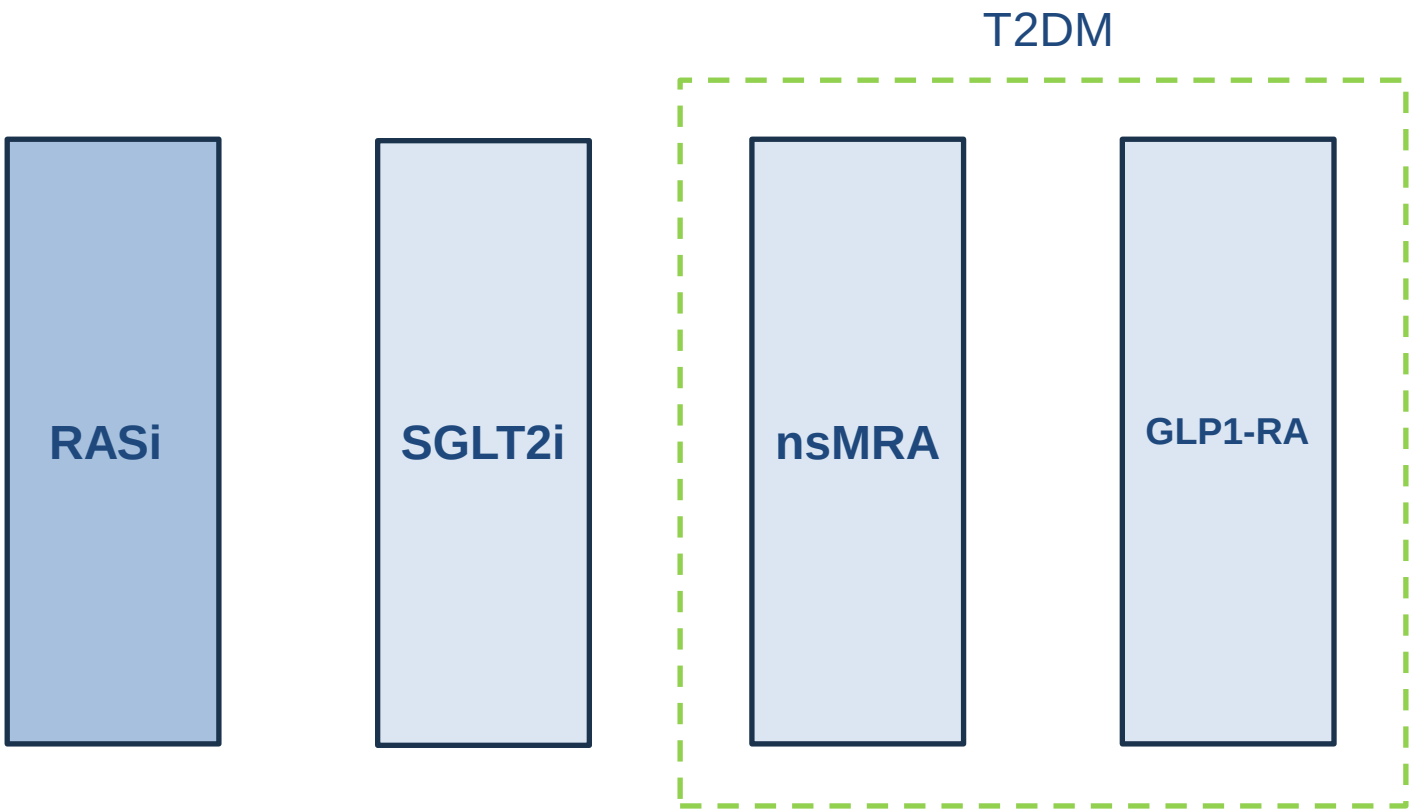
Pillars of Therapy



Baigent et al. Lancet (2022); 400:1788-1801.

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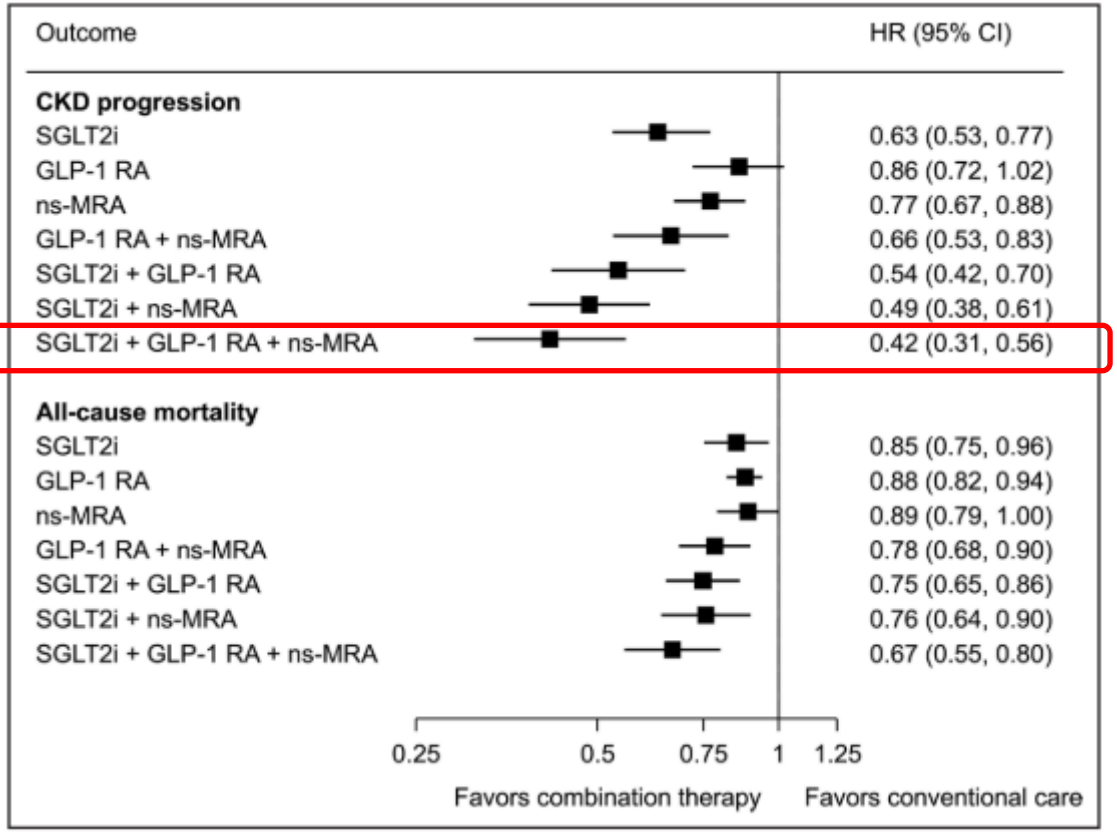
CKD Pillars and CVRM

Estimated Lifetime Cardiovascular, Kidney, and Mortality Benefits of Combination Treatment With SGLT2 Inhibitors, GLP-1 Receptor Agonists, and Nonsteroidal MRA Compared With Conventional Care in Patients With Type 2 Diabetes and Albuminuria



Neuen et al. Circulation (2024);149: 450-462.

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CKD Pillars and CVRM

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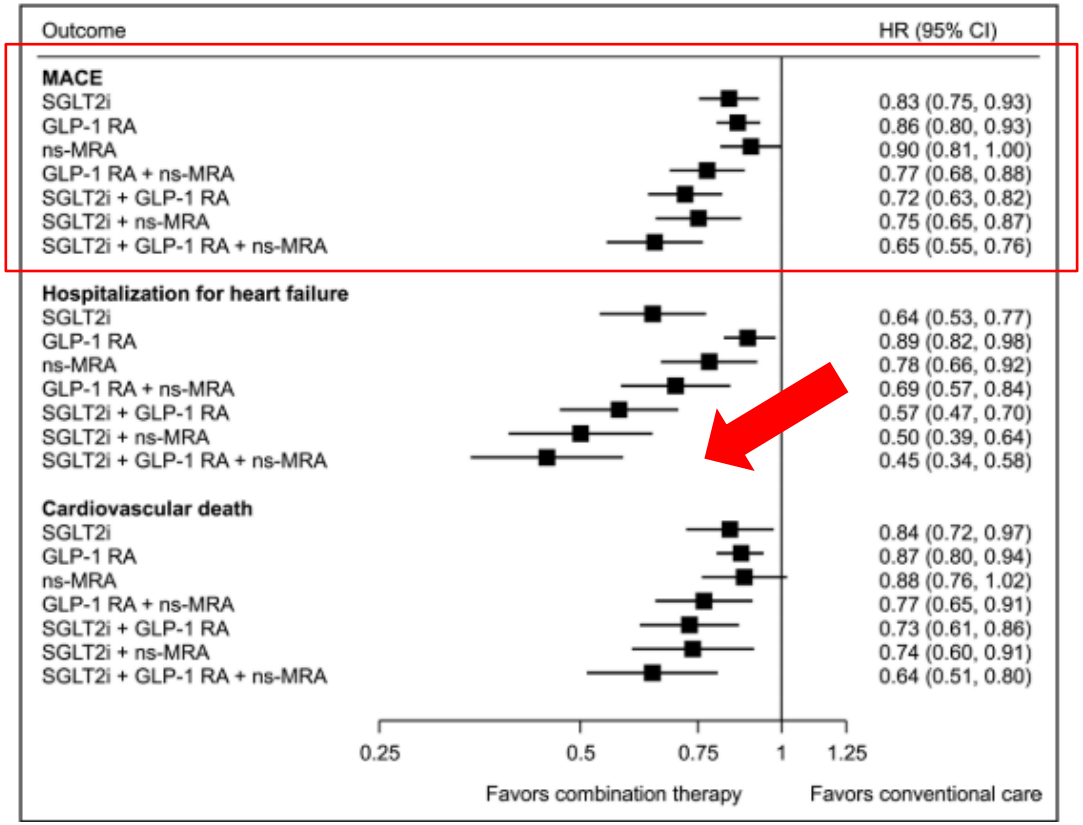
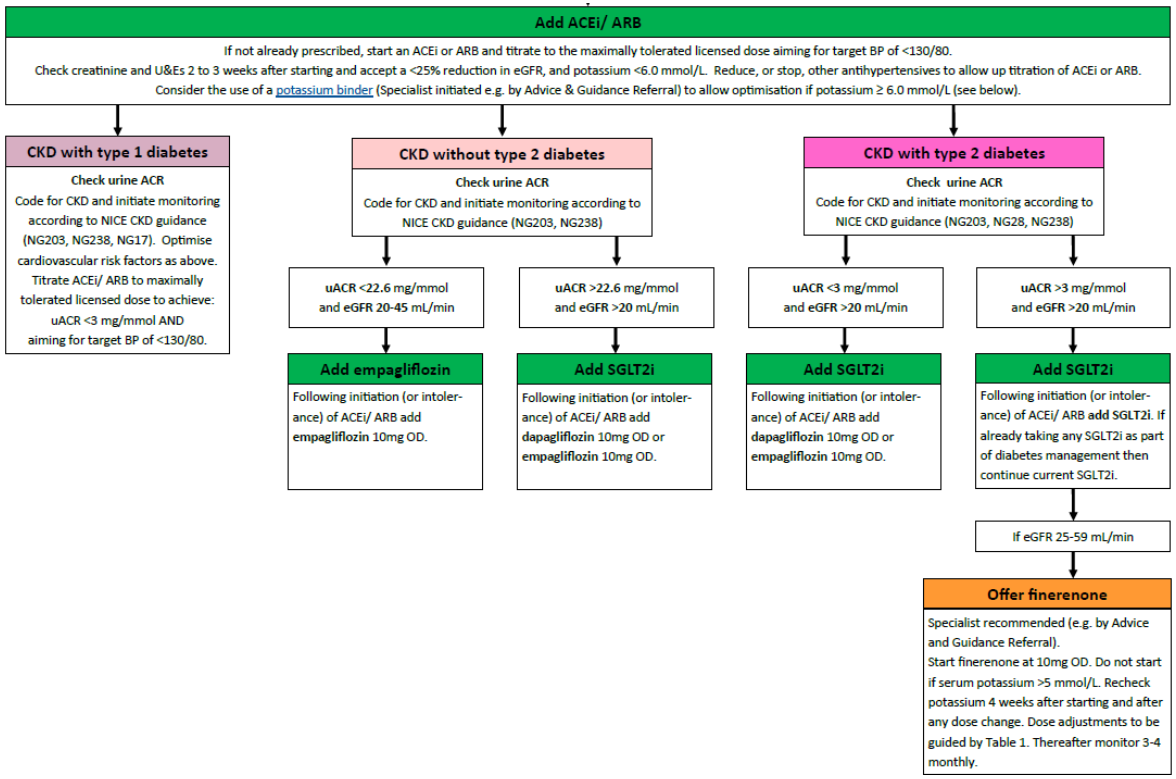


Neuen et al. Circulation (2024);149: 450-462.

CKD Pillars - Bristol



ACE/ARB

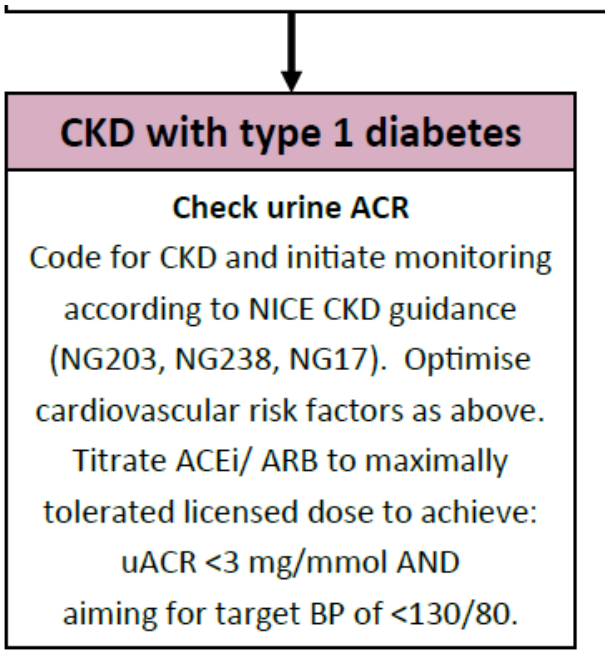
SGLT2i

nsMRA

GLP1-RA [?]

CKD Pillars

No additional licensed options for people with Type 1 diabetes



FINE-ONE clinical study

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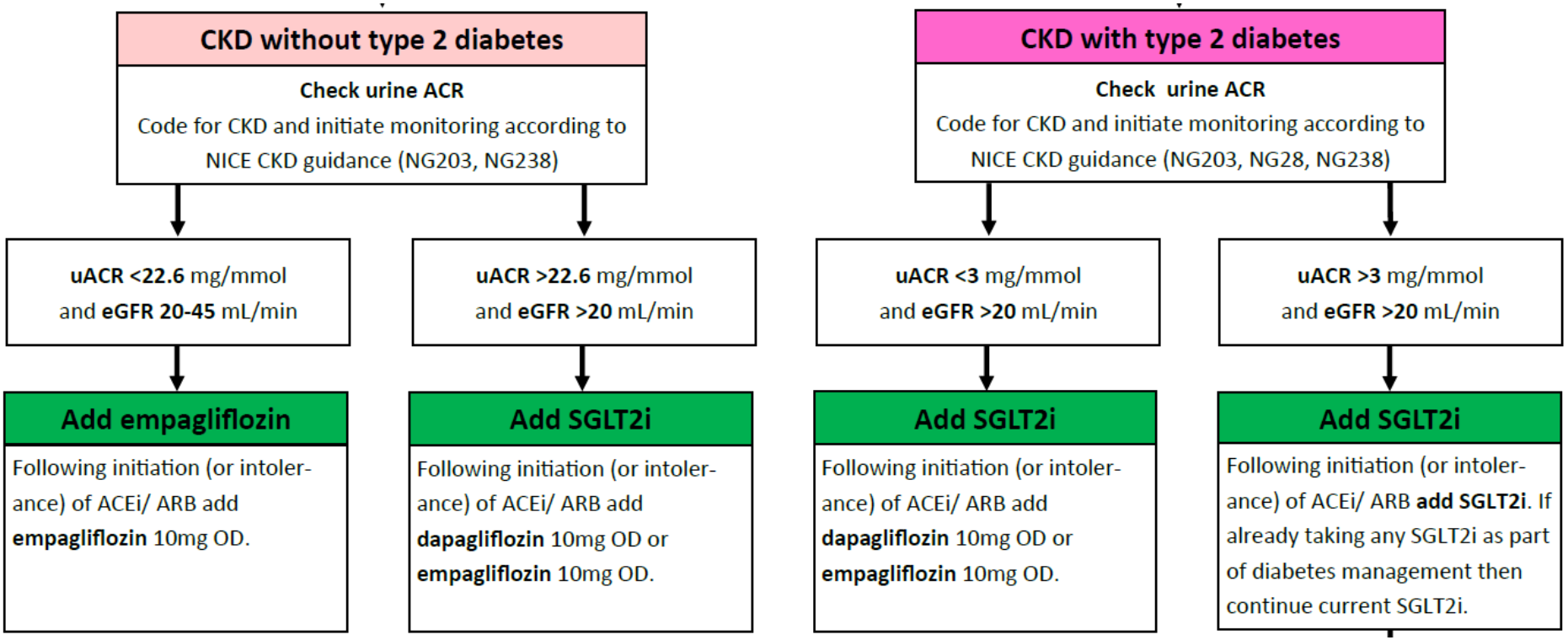
Thank you

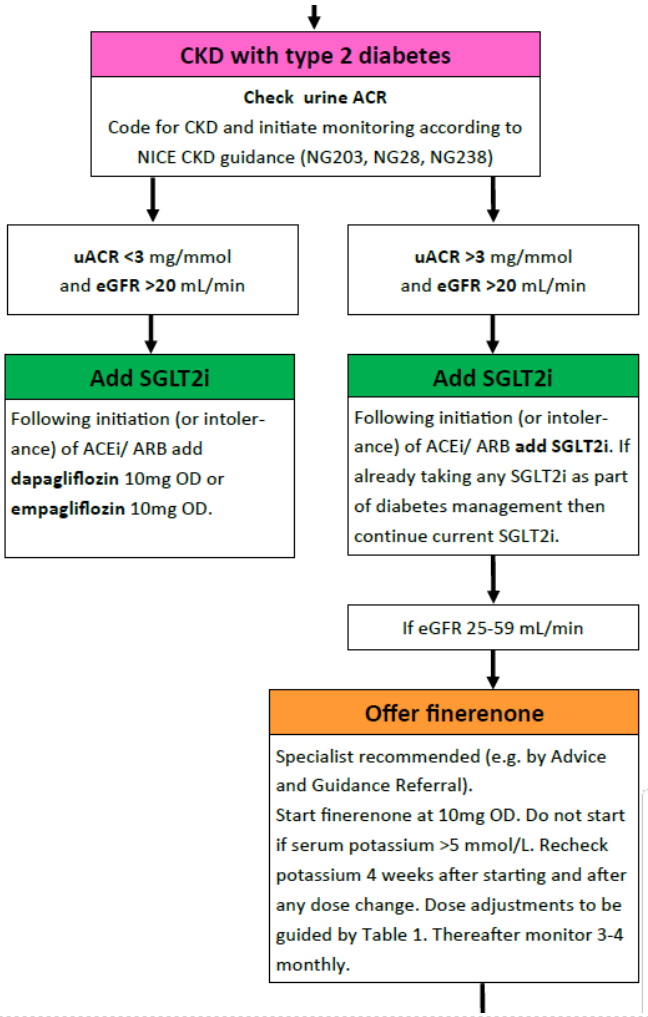
SGLT2i in CKD



CKD management in T2DM

Serum potassium (mmol/L)	Current finerenone dose	
	10 mg OD	20mg OD
<4.8	Increase to 20mg OD	Maintain 20mg OD
4.8 - 5.5	Maintain 10 mg OD	Maintain 20mg OD
>5.5	Withhold finerenone. Consider restarting when serum potassium < 5 mmol/L. Consider use of a potassium binder.	Withhold finerenone. Consider restarting when serum potassium < 5 mmol/L. Consider use of a potassium binder.

Table 1: Continuation of finerenone and dose adjustment



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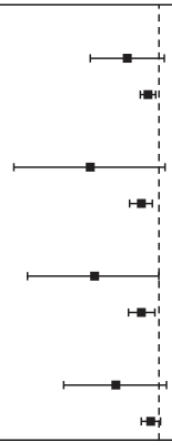
Finerenone – NICE TAG

Finerenone in Patients With Chronic Kidney Disease and Type 2 Diabetes by Sodium–Glucose Cotransporter 2 Inhibitor Treatment: The FIDELITY Analysis

Diabetes Care 2022;45:2991–2998 | https://doi.org/10.2337/dc22-0294

	Finerenone	Placebo	Finerenone	Placebo	HR (95% CI)	$P_{interaction}$
	n/N (%)		*n* per 100 PY			
Analysis for outcomes in patients receiving/not receiving an SGLT2i at baseline						
Cardiovascular composite						
SGLT2i at baseline	39/438 (8.9)	52/439 (11.8)	2.95	4.08	0.67 (0.42–1.07)*	0.46†
No SGLT2i at baseline	786/6,081 (12.9)	887/6,068 (14.6)	4.44	5.08	0.87 (0.79–0.96)*	
Kidney composite						
SGLT2i at baseline	9/438 (2.1)	17/439 (3.9)	0.70	1.37	0.42 (0.16–1.08)*	0.29†
No SGLT2i at baseline	351/6,081 (5.8)	448/6,068 (7.4)	2.06	2.64	0.80 (0.69–0.92)*	
Hospitalization for heart failure						
SGLT2i at baseline	10/438 (2.3)	22/439 (5.0)	0.74	1.68	0.44 (0.19–0.99)*	0.18†
No SGLT2i at baseline	246/6,081 (4.0)	303/6,068 (5.0)	1.35	1.68	0.80 (0.68–0.95)*	
All-cause death						
SGLT2i at baseline	20/438 (4.6)	30/439 (6.8)	1.46	2.23	0.58 (0.30–1.10)*	0.24†
No SGLT2i at baseline	532/6,081 (8.7)	584/6,068 (9.6)	2.86	3.16	0.90 (0.80–1.02)*	



Rossing et al. Diabetes Care (2022); 45: 2991

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Finerenone – NICE TAG

Finerenone for treating chronic kidney disease in type 2 diabetes

Technology appraisal guidance [TA877] Published: 23 March 2023

1.1 Finerenone is recommended as an option for treating stage 3 and 4 chronic kidney disease (with albuminuria) associated with type 2 diabetes in adults. It is recommended only if:

- it is an add-on to optimised standard care; this should include, unless they are unsuitable, the highest tolerated licensed doses of:
  - angiotensin-converting enzyme (ACE) inhibitors or angiotensin-receptor blockers (ARBs) and
  - sodium–glucose cotransporter-2 (SGLT2) inhibitors and
- the person has an estimated glomerular filtration rate (eGFR) of 25 ml/min/1.73 m^2 or more.

https://www.nice.org.uk/guidance/ta877

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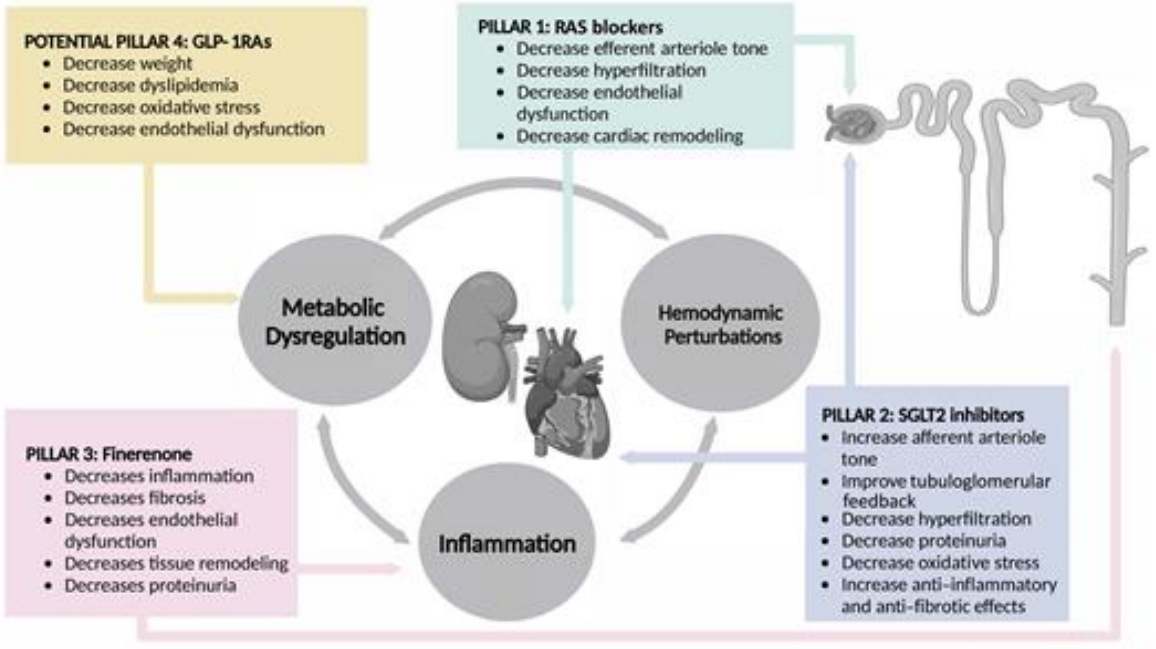
CKD management – More pillars ?



Naaman & Bakris. Diab Care (2023);46:1574-1586