Nephrologist's take on the effect and impact of SGLT-2 inhibitors and GLP-1 RAs on Kidney Disease in people with diabetes

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Disclosures

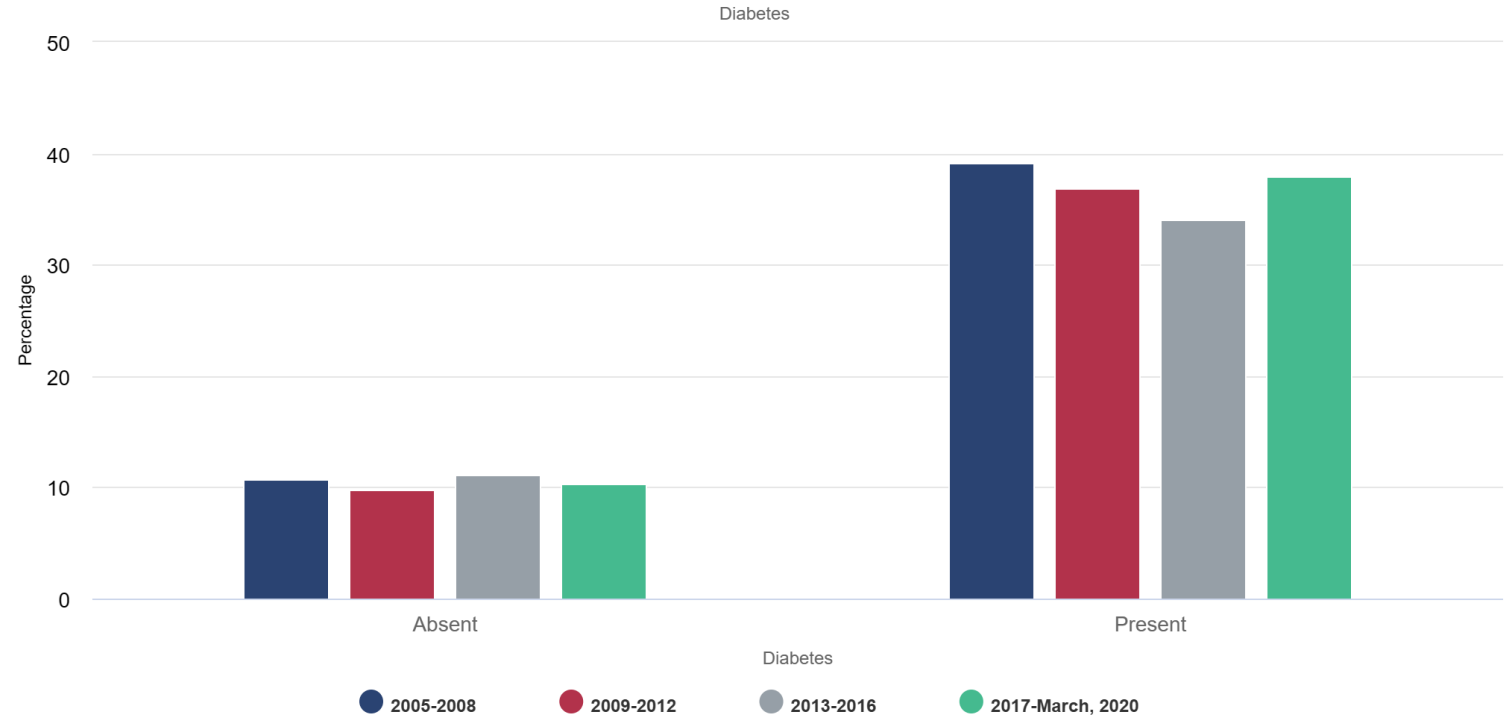
- Quanta

Objectives

1. Review strategies for monitoring disease, selection of new therapies and referrals to nephrology
2. Review the clinical data supporting the current pharmacological paradigm for treating Diabetes in CKD
3. Discuss the risk management of new therapies
4. Summarize considerations for special populations (elderly, kidney transplant recipients)

Diabetic Kidney Disease is still a problem in the 21st century

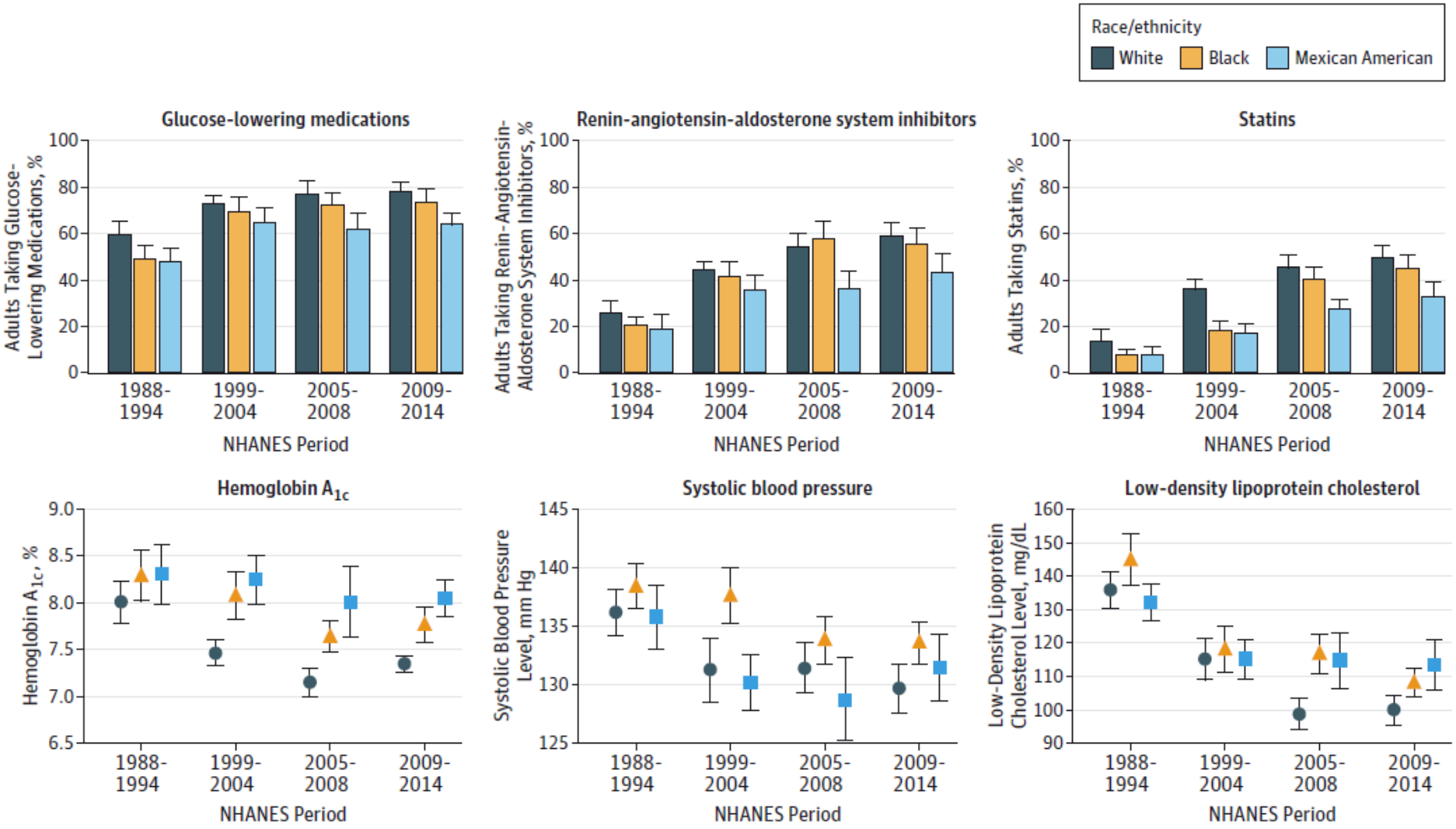
Figure 1.1 Prevalence of CKD in U.S. adults



Data Source: 2023 United States Renal Data System Annual Data Report

https://usrds-adr.niddk.nih.gov/2023/chronic-kidney-disease/

… despite improvements in care and



JAMA. 2016;316(6):602-610

Can you help me out?

You are scheduled to see a 58 year old patient with long standing (>15 years) history of somewhat controlled diabetes type 2 (A1c between 7.5 – 8.0) during the last 8 years. The patient has had a stroke 6 years ago but no retinopathy and their blood pressure is controlled at a level of 135/80 mmHg on 100mg of Losartan and 1.25 mg of Indapamide. The patient's estimated glomerular filtration rate is 45 ml/min/1.73m2 and the last urine albumin to creatinine ratio (UACR) is 18 mg/g of creatinine. What can you say about the patient's cause of CKD?

A. It cannot be due to diabetes because the UACR is low

B. It cannot be due to diabetes because the patient has no retinopathy

C. It is likely due to diabetes because the A1c is not < 6.5

D. Cannot rule out a diabetic or a non-diabetic cause based on the information provided

High overlap between DKD and CVD leading to high health care utilization => must address more than the lab value

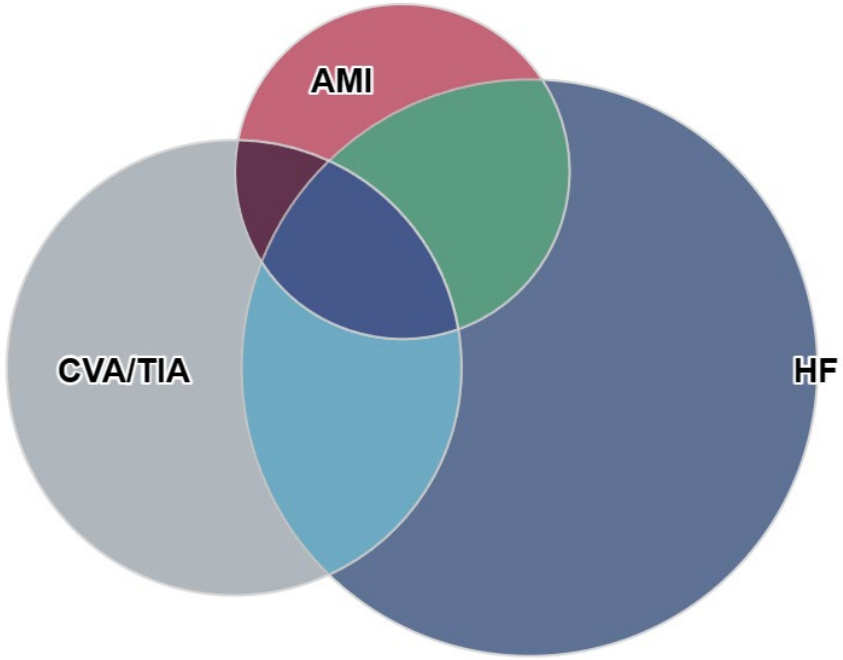
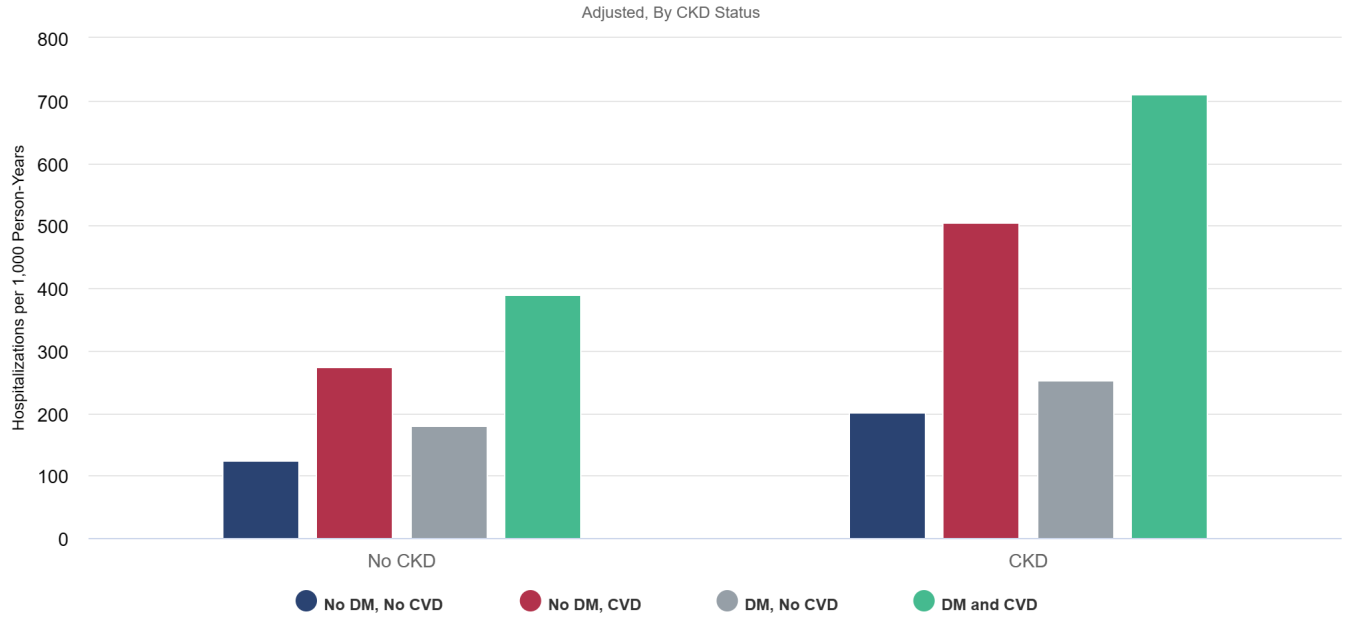
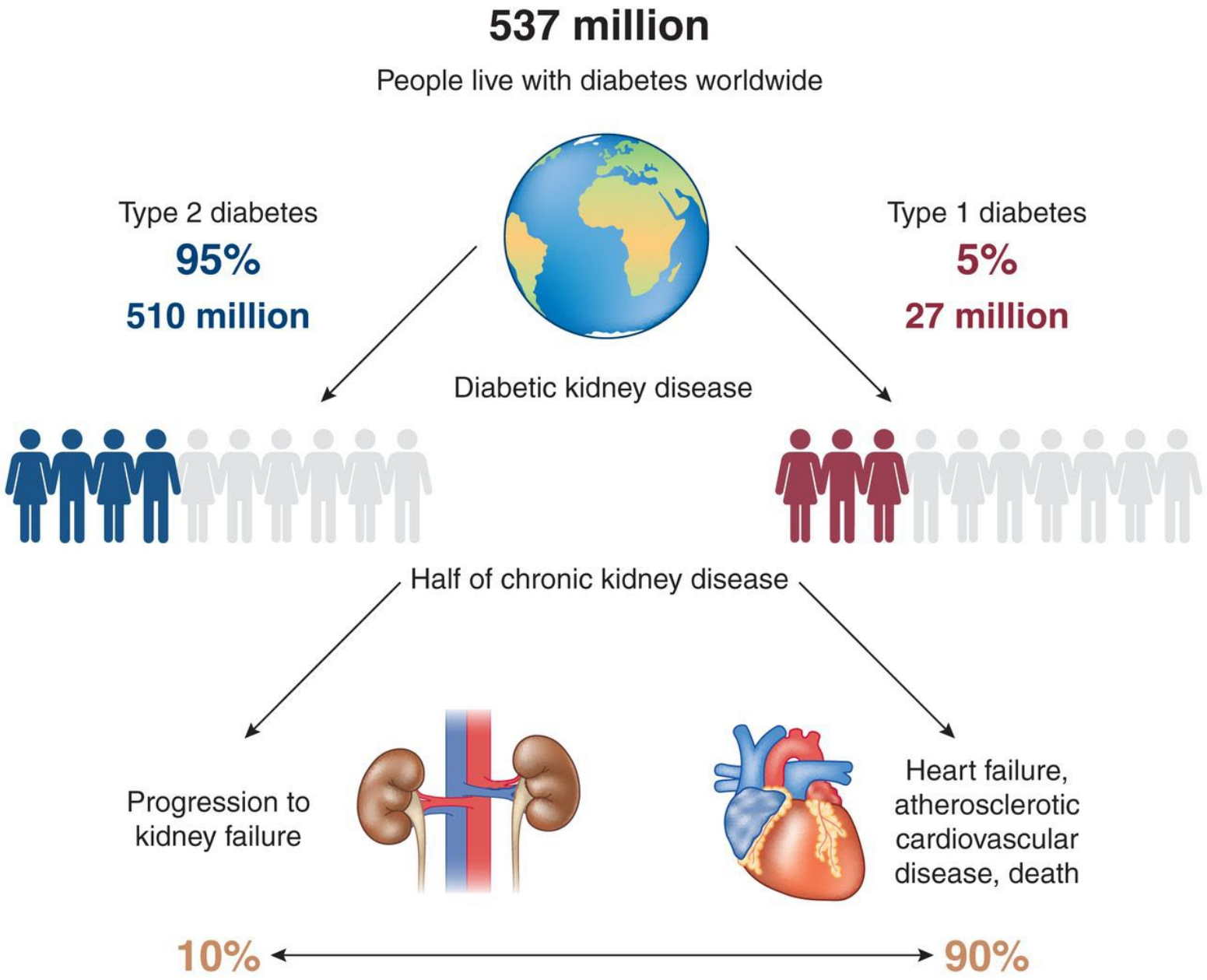


Figure 3.6 All-cause hospitalization rates in older adults, by presence of diabetes mellitus and cardiovascular disease, Medicare FFS, 2021



Data Source: 2023 United States Renal Data System Annual Data Report

What is the prob we are trying to solve?



https://cjasn.asnjournals.org/content/clinjasn/17/7/1092.full.pdf

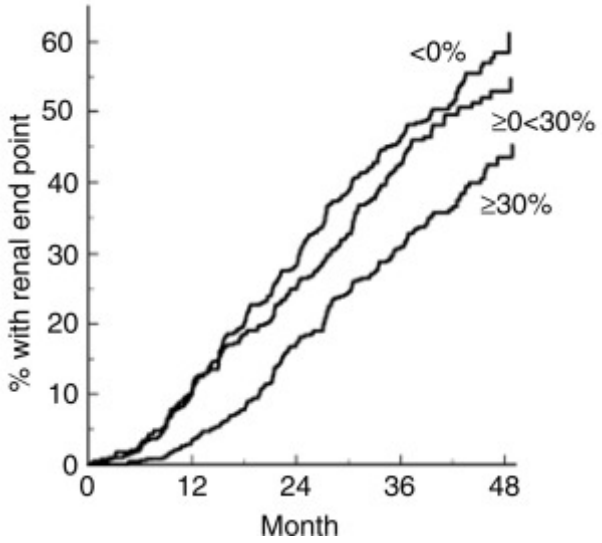
Residual albuminuria, Albuminuria Delta after ARB predict kidney outcomes

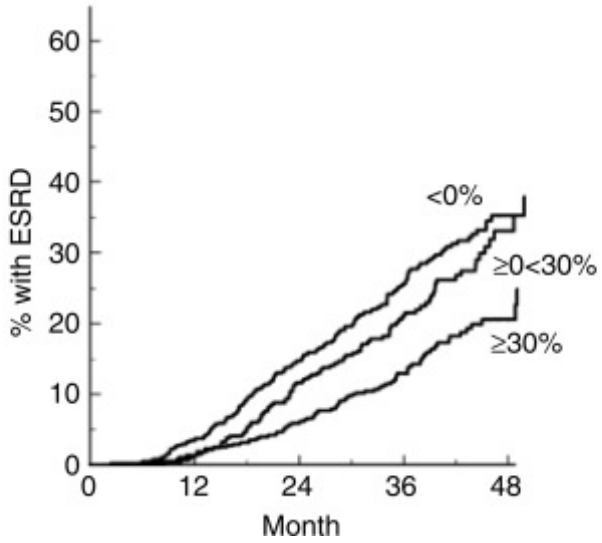
Renal end point

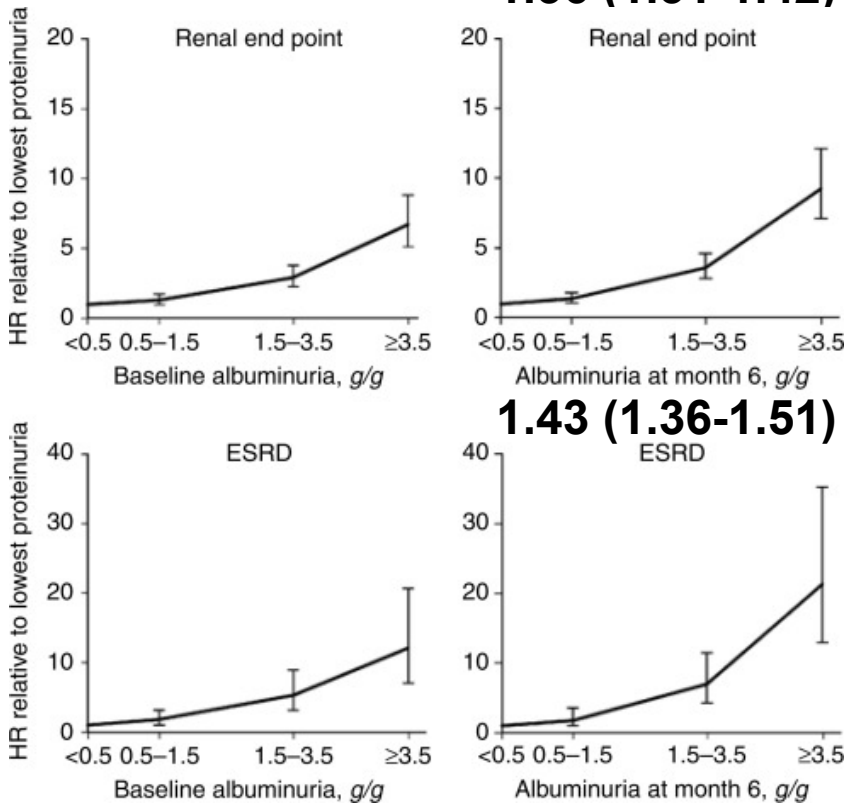
	Unadjusted		Adjusted	
	HR	*P* values	HR	*P* values
Δ Alb: ≥0<30 vs. <0%	0.88	0.1570	0.76	0.0028
Δ Alb: ≥30 vs. <0%	0.60	<.0001	0.46	<.0001
Δ Alb: ≥30 vs. ≥0<30%	0.68	0.0003	0.61	<.0001

ESRD

	Unadjusted		Adjusted	
	HR	*P* values	HR	*P* values
Δ Alb: ≥0<30 vs. <0%	0.82	0.1242	0.62	<.0003
Δ Alb: ≥30 vs. <0%	0.51	<.0001	0.37	<.0001
Δ Alb: ≥30 vs. ≥0<30%	0.62	0.0019	0.60	0.0010







https://doi.org/10.1111/j.1523-1755.2004.00653.x

Does this patient need saving?

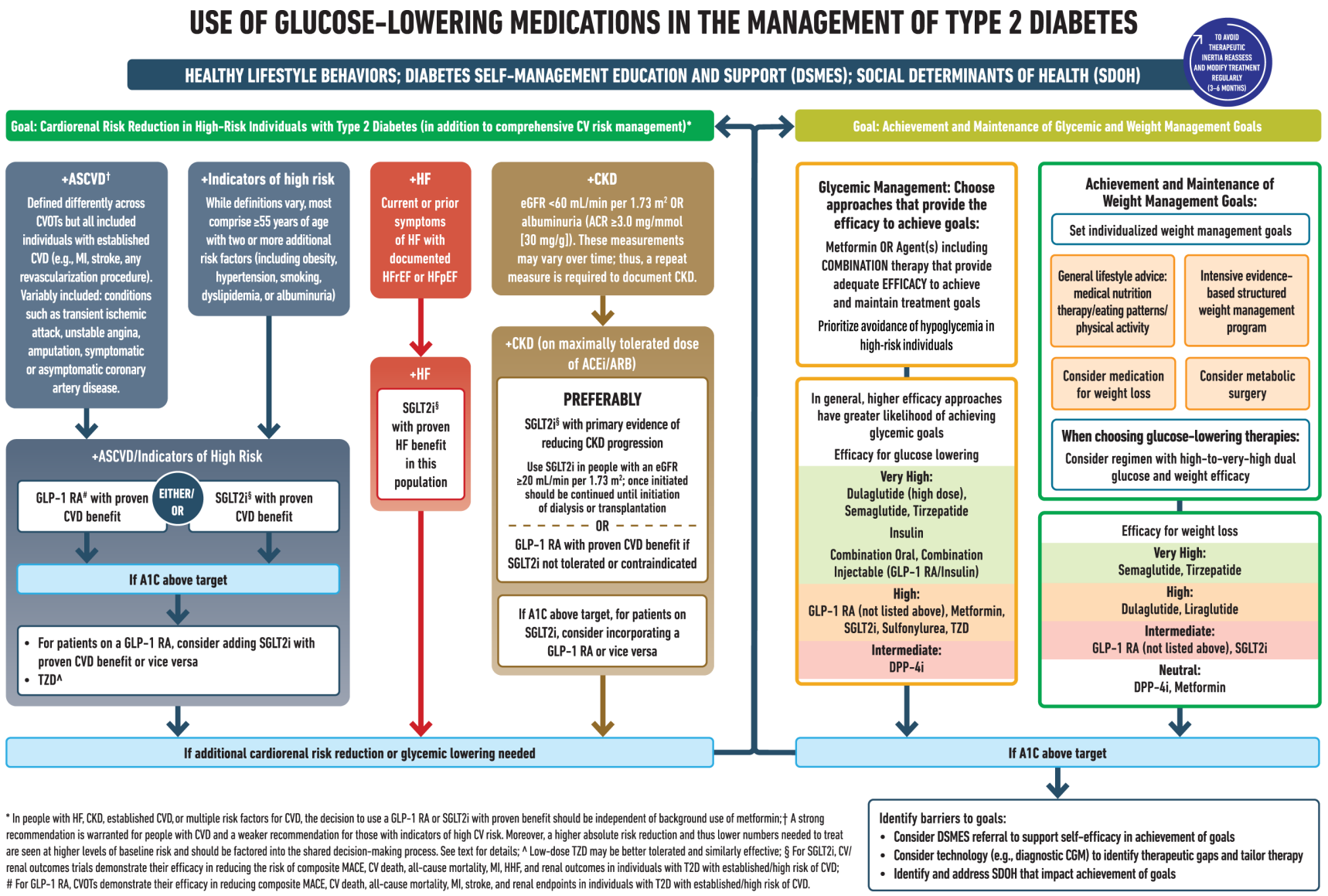
67-year-old patient with T2D for the last 18 years. Had an AMI with a stent to the LAD 10 years ago and their EF was 48% last year. The A1c is 6.8, the urine albumin to creatinine ratio is 55mg/g and the eGFR is 48 ml/min/1.73m2. They are currently receiving Metformin 1000mg bid, pioglitazone 30mg po daily and Sitagliptin 100mg po daily. What is the appropriate next step?

A. CYA in 4 months

B. Add Dapagliflozin

C. Add Dulaglutide

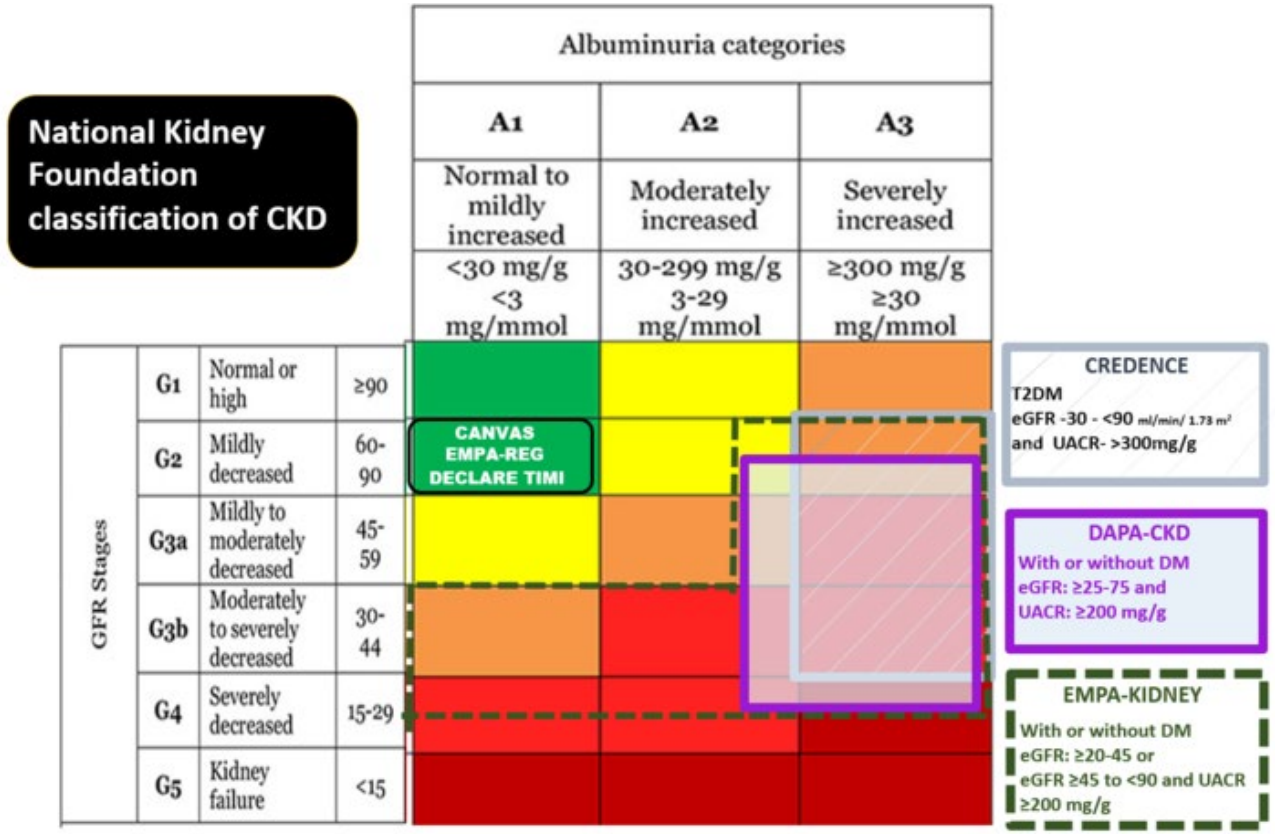
D. Make a plan to flip the regimen to Metformin+Dapa+Dula over the next 6 months



Glucose-lowering medication in DM2: 2024 version

DIABETES CARE. 2023;47(SUPPLEMENT_1):S158-S178. DOI:10.2337/DC24-S009

A snapshot of (D)CKD and CVOT SGLT2i trials

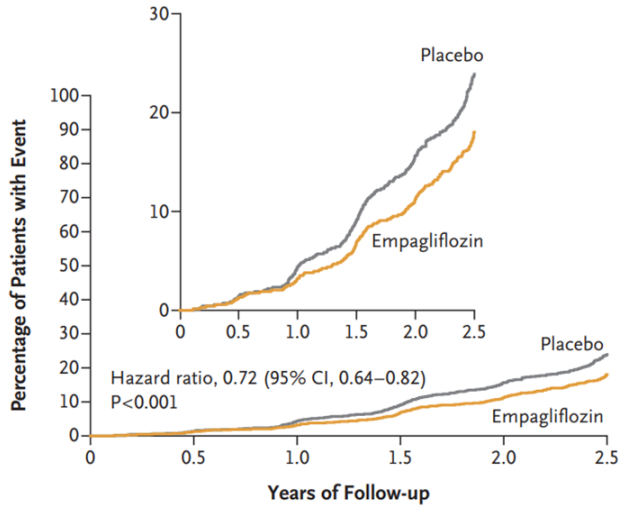


Heerspink et al 2020 https://www.ncbi.nlm.nih.gov/pmc/articles/PMC7005525/

Dr Priti Meena MD,FASN @priti899 http://www.nephjc.com/news/dapa-ckd

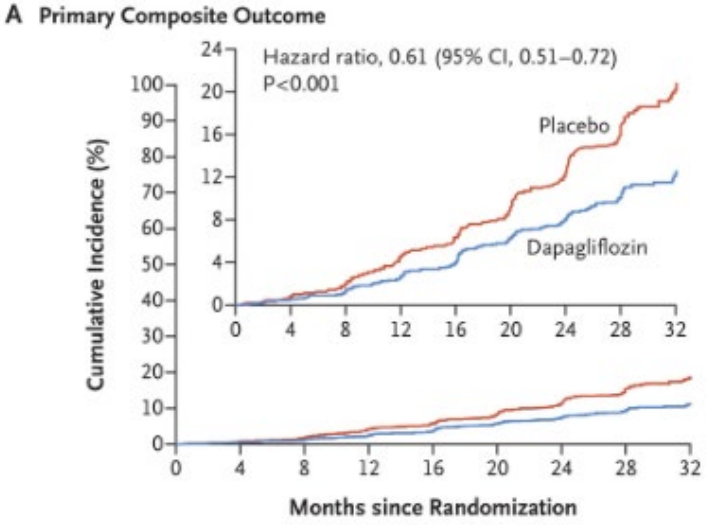
SGLT2i reduced the risk of kidney disease progression by 30-40%

EMPA-KIDNEY



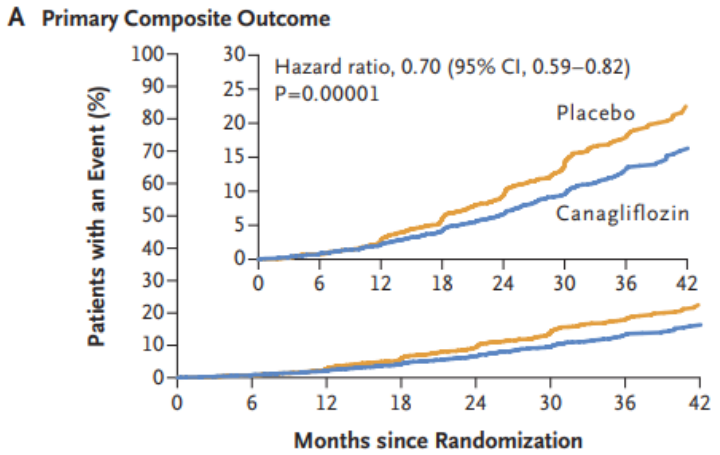
No. at Risk						
Placebo	3305	3250	3129	2243	1496	592
Empagliflozin	3304	3252	3163	2275	1538	624

DAPA-CKD



No. at Risk									
Placebo	2152	1993	1936	1858	1791	1664	1232	774	270
Dapagliflozin	2152	2001	1955	1898	1841	1701	1288	831	309

CREDENCE

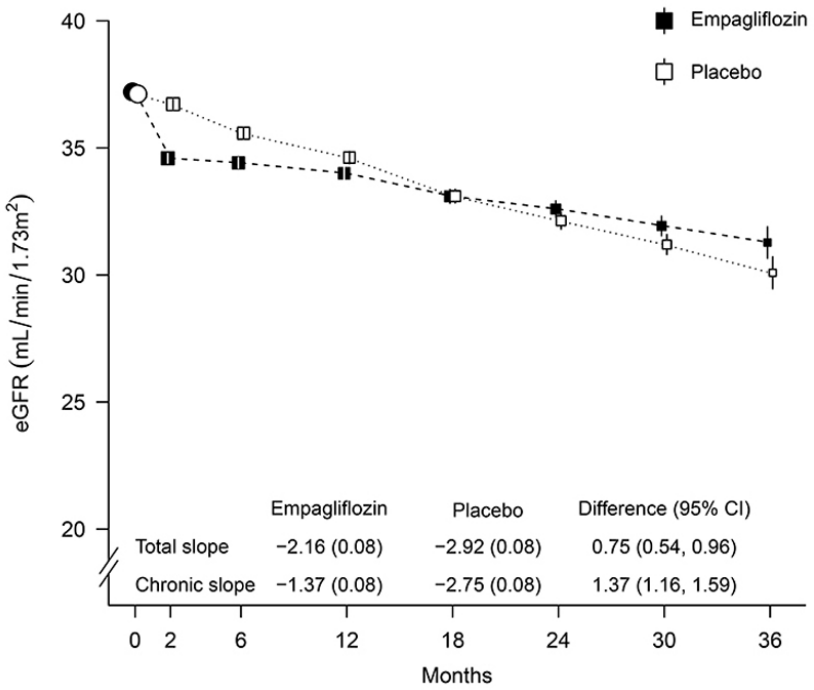


No. at Risk								
Placebo	2199	2178	2132	2047	1725	1129	621	170
Canagliflozin	2202	2181	2145	2081	1786	1211	646	196

https://www.ncbi.nlm.nih.gov/pmc/articles/PMC7614055/ https://www.nejm.org/doi/10.1056/NEJMoa2024816? https://spiral.imperial.ac.uk/handle/10044/1/69122

SGLT2i reduce the rate of loss of eGFR & proteinuria

EMPA-KIDNEY

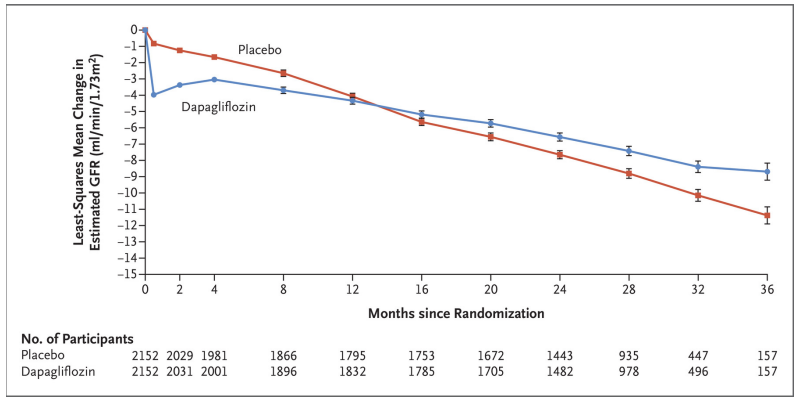


↓ UACR 19%
(95% CI 15% - 23%)

https://www.ncbi.nlm.nih.gov/pmc/articles/PMC7614055/

DAPA-CKD

~98% on RAS

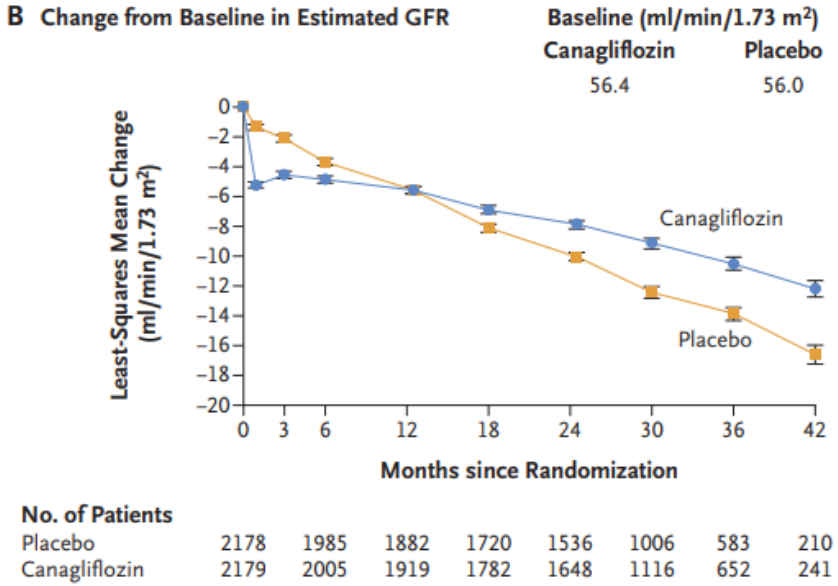


↓ UACR 35.1% **DM (+)**
(95% CI 39.4% - 30.6%)
↓ UACR 14.8% **DM (-)**
(95% CI 22.9% - 5.9%)

https://www.nejm.org/doi/10.1056/NEJMoa2024816?
https://pubmed.ncbi.nlm.nih.gov/34619106/

CREDENCE

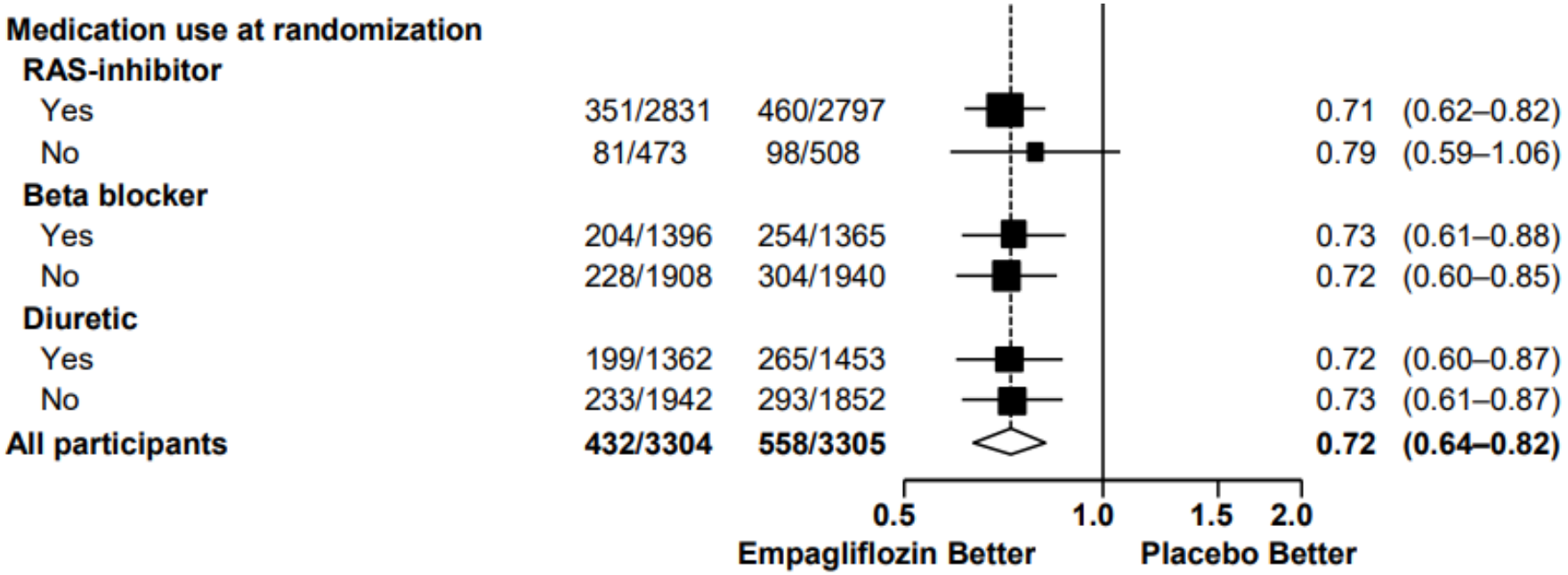
> 99% on RAS



↓ UACR 31%
(95% CI 26% - 35%)

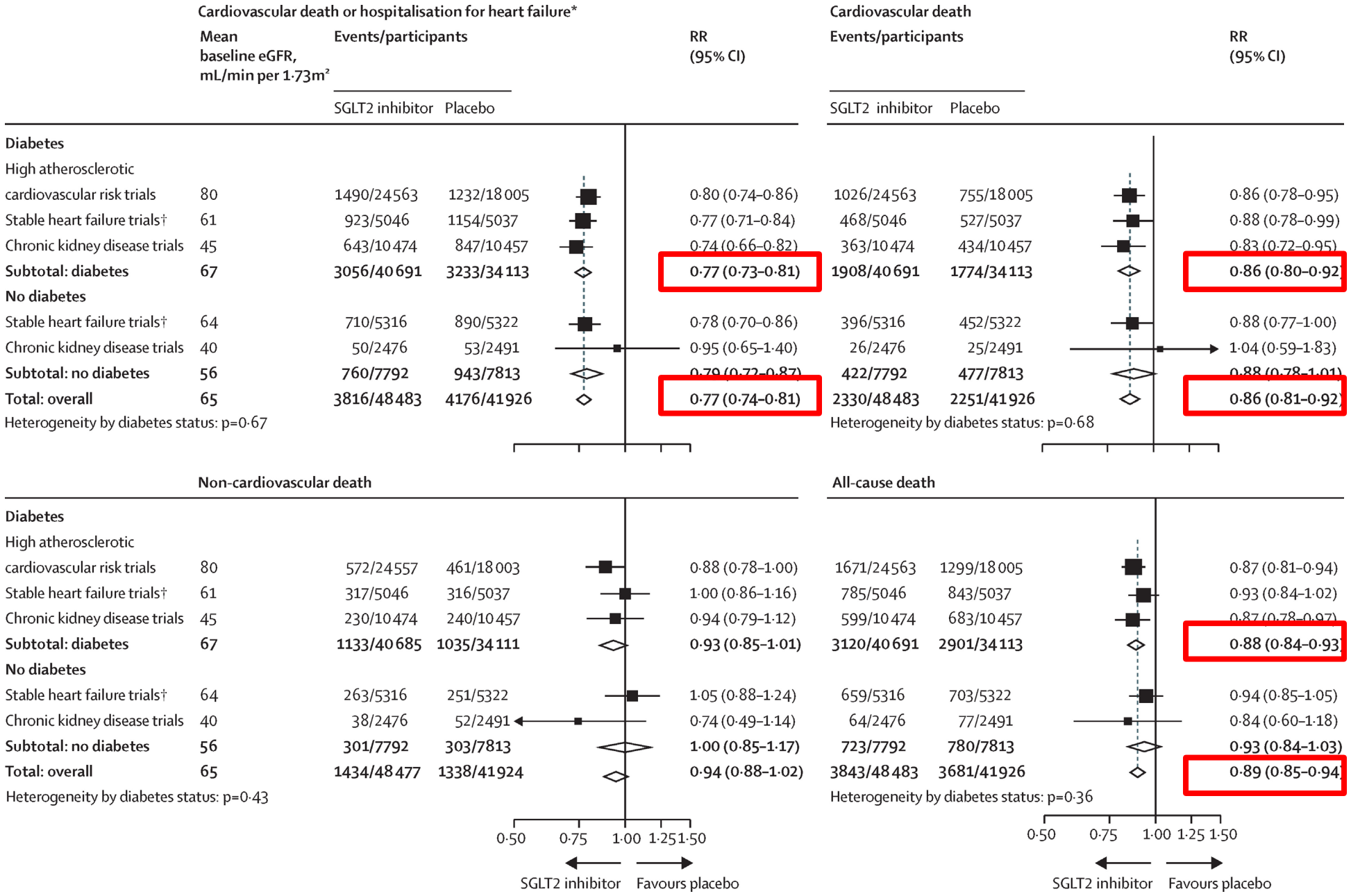
https://spiral.imperial.ac.uk/handle/10044/1/69122

EMPA-KIDNEY suggests that SGLT2i may work irrespective of whether the patient can tolerate an ACEi/ARB or not



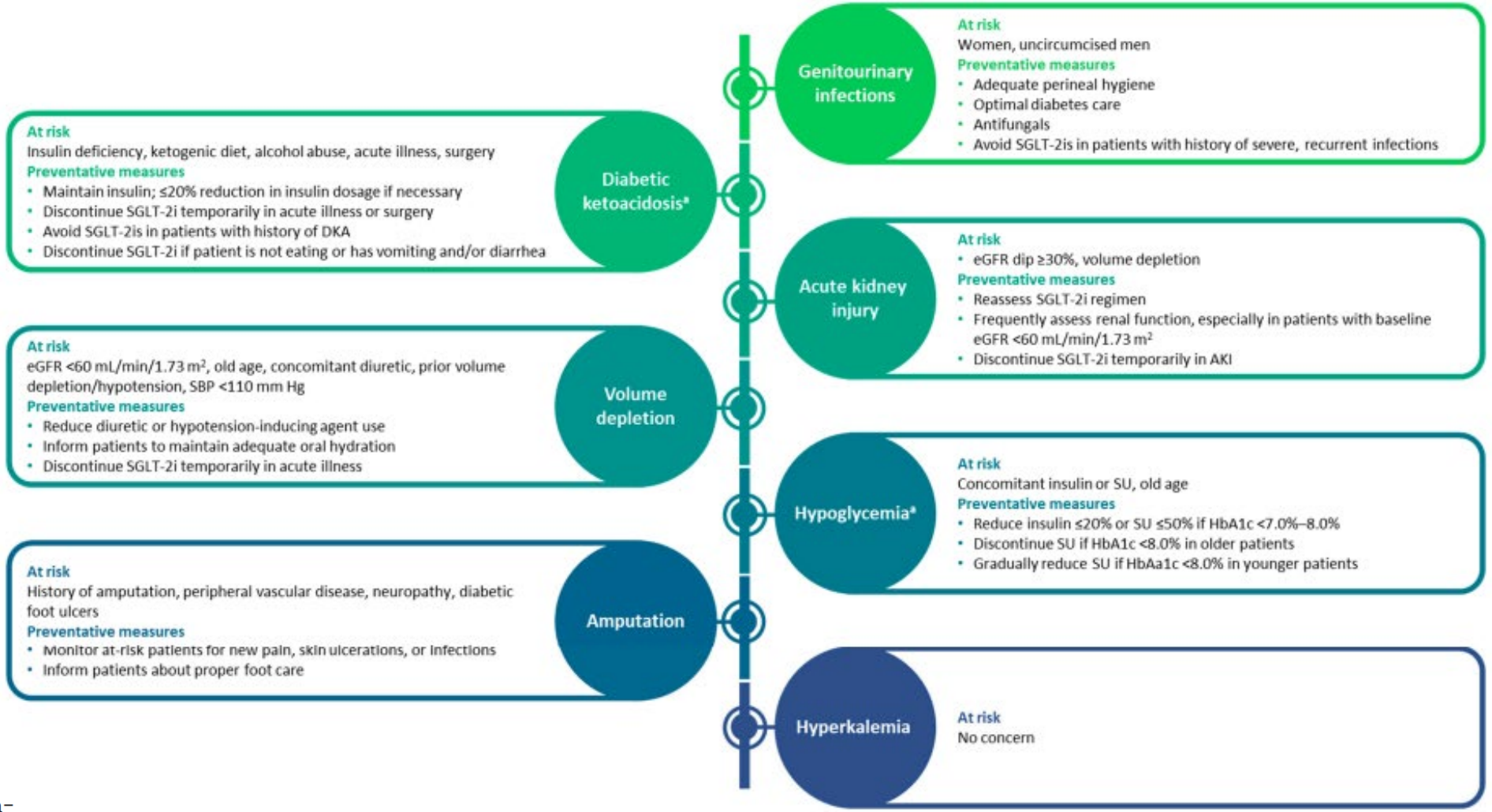
https://www.ncbi.nlm.nih.gov/pmc/articles/PMC7614055/

SGLT2i reduce CV deaths, heart failure and mortality regardless of diabetes



The Lancet 2022 400, 1788-1801
DOI: (10.1016/S0140-6736(22)02074-8)

“Derisking” SGLT2i therapy



Review › J Clin Med. 2022 Oct 13;11(20):6051. doi: 10.3390/jcm11206051.

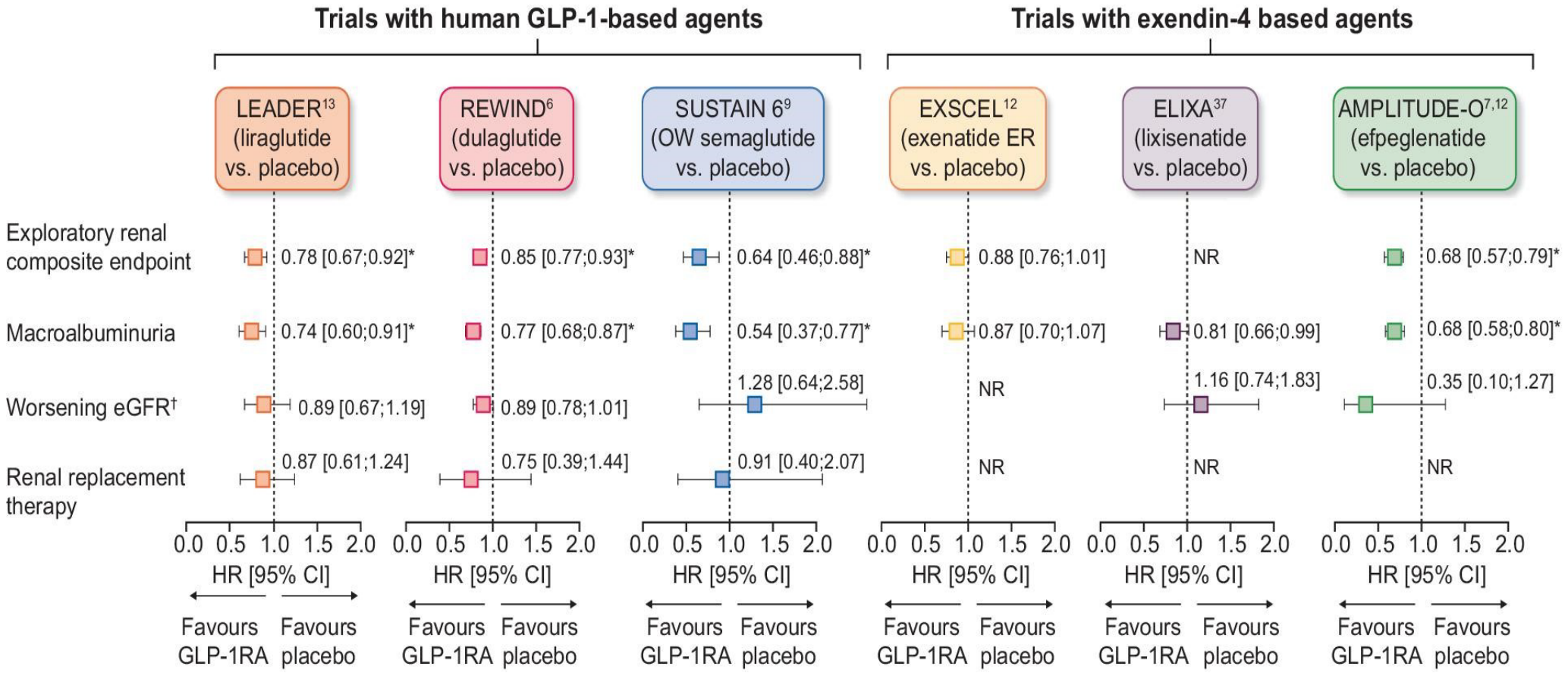
Physicians' Considerations and Practice Recommendations Regarding the Use of Sodium–Glucose Cotransporter–2 Inhibitors

Serge A Jabbour [1], Nasrien E Ibrahim [2], Christos P Argyropoulos [3]

Affiliations + expand

PMID: 36294370 PMCID: PMC9604628 DOI: 10.3390/jcm11206051

GLP1RA in diabetic Kidney Disease



https://academic.oup.com/ndt/article/38/9/2041/6991221

Go with the FLOW

Exclusion Criteria

@brian_rifkin

- Congenital or hereditary kidney disease
- Current NYHA Class IV heart failure
- History of malignancy within 5 years
- Pregnancy or breastfeeding
- MI, stroke, hospitalization for unstable angina or TIA within 60 days
- Use of any GLP1-RA (within 30 days) or combination RASi
- Planned coronary, carotid or peripheral artery revascularization
- Current dialysis (within 90 days)
- Uncontrolled proliferative diabetic retinopathy
- Transplant or awaiting transplant

HEALTH SCIENCES

https://www.nephjc.com/news/flow

FLOW trial – Kidney outcomes with semaglutide in T2DM and CKD

RANDOMIZED, DOUBLE-BLIND, PARALLEL-GROUP, MULTINATIONAL, PHASE 3B TRIAL

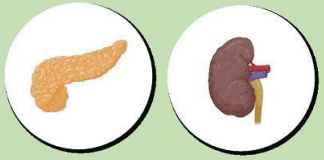
Background: GLP-1RAs improve glycaemic control and reduce body weight in patients with T2DM, and reduce the risk of CV events in patients at high CV risk. GLP-1RAs may also have kidney-protective effects, but their benefits on CKD progression remains to be confirmed.

Objectives: FLOW is a randomized kidney outcomes trial designed to assess the treatment effect of semaglutide OW in a population of patients with CKD and T2DM at high risk of kidney disease progression (based on KDIGO classification).

Clinical implications: The FLOW trial will provide evidence on the treatment effect of semaglutide on renal outcomes, potentially expanding treatment options for patients with T2DM to slow the progression of CKD and reduce renal failure.

Study population

N=3534

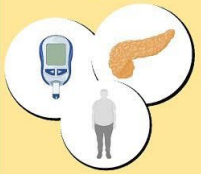


- Adult patients with T2DM
- eGFR ≥50 to ≤75 ml/min/1.73 m^2 and UACR >300 to <5000 mg/g OR eGFR ≥25 to <50 ml/min/1.73 m^2 and UACR >100 to <5000 mg/g

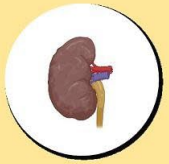
418 study sites in 28 countries

Baseline characteristics

Mean age: 66.6 years
Male: 69.7%
Caucasians: 65.7%



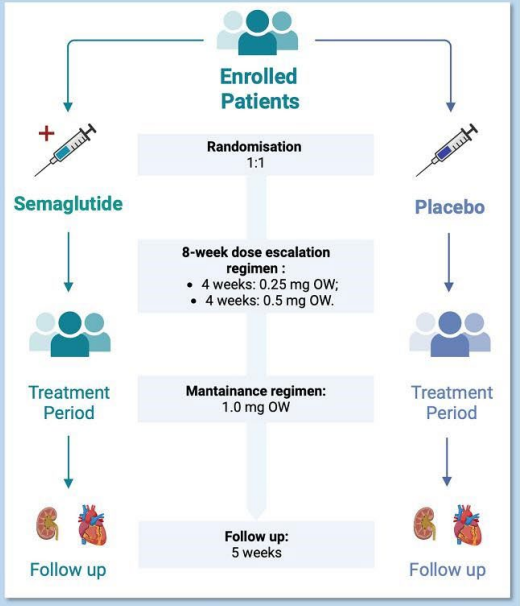
Diabetes
Mean baseline HbA_{1c}: 7.8%
Mean T2DM duration: 17.4 y
Mean BMI: 32.0 kg/m^2



Chronic kidney disease
Mean baseline eGFR: 47.0 ml/min/1.73 m^2
Median UACR: 568 mg/g
68.2% of patients at very high risk for CKD progression (according to KDIGO).

Medications
15.5% on SGLT2-I
95.3% on RAAS inhibitors

Study flow



Event-driven trial with an expected duration of ≈5 y. Randomization stratified by SGLT2-I use.

Primary composite endpoint

Time to first occurrence of:
- Kidney failure [persistent eGFR <15 ml/min/1.73 m^2 for at least 4 weeks or initiation of CKRT (dyalisis or kidney transplantation)]
- Persistent ≥50% reduction in eGFR versus baseline
- Death from kidney failure
- CV death

Experimental arm
Semaglutide
(1.0 mg s.c. OW)
+ T2DM and CKD standard of care

vs

Control arm
Placebo
(1.0 mg s.c. OW)
+ T2DM and CKD standard of care

https://doi.org/10.1093/ehjcvp/pvad080

Semaglutide for CKD in Patients with Type 2 Diabetes: "FLOW"ing with the Semaglu"TIDE"

#NephJC

METHODS

International, double-blind, placebo-controlled
28 countries

Type 2 DM and CKD:
GFR 50-75 ml/min +
ACR 300-5000 mg/g
or
GFR 25-<50 ml/min +
ACR 100-5000 mg/g

Median follow-up,
3.4 years

	Major kidney disease events	Death from any causes	Adverse event leading to discontinuation
Major kidney disease events- kidney failure, ≥50% reduction in GFR, death from CV or kidney-related causes			
Placebo n = 1766	7.5 events per 100 patient-years	279(15.8%)	211(11.9%)
	HR 0.76 (95% CI, 0.66-0.88)	HR 0.80 (95% CI, 0.67-0.95)	
Semaglutide n = 1767	5.8 events per 100 patient-years	227(12.8%)	233(13.2%)

HR= Hazard ratio

Reference: Perkovic,V et al. Effects of Semaglutide on Chronic Kidney Disease in Patients with Type 2 Diabetes. NEJM, May 2024.

VA by Anjana Gopal @anjanagopal9

Conclusion: Semaglutide reduced the risk of clinically important kidney outcomes and death from cardiovascular causes in patients with type 2 diabetes and chronic kidney disease.

Heart and Kidney Protection in FLOW

Table 2. Efficacy and Safety Outcomes.*

Outcome	Semaglutide (N=1767)	Placebo (N=1766)	Hazard Ratio (95% CI)	Estimated Difference (95% CI)	P Value
Primary outcome: major kidney disease events — no. (%)†	331 (18.7)	410 (23.2)	0.76 (0.66 to 0.88)	—	0.0003
Components of primary outcome — no. (%)					
Persistent ≥50% reduction from baseline in eGFR	165 (9.3)	213 (12.1)	0.73 (0.59 to 0.89)	—	—
Persistent eGFR <15 ml/min/1.73 m²	92 (5.2)	110 (6.2)	0.80 (0.61 to 1.06)	—	—
Initiation of kidney-replacement therapy	87 (4.9)	100 (5.7)	0.84 (0.63 to 1.12)	—	—
Death from kidney-related causes	5 (0.3)	5 (0.3)	0.97 (0.27 to 3.49)	—	—
Death from cardiovascular causes	123 (7.0)	169 (9.6)	0.71 (0.56 to 0.89)	—	—
Composite of kidney-specific components of the primary outcome	218 (12.3)	260 (14.7)	0.79 (0.66 to 0.94)	—	—
Confirmatory secondary outcomes					
Mean annual rate of change in eGFR — ml/min/1.73 m²	−2.19	−3.36	—	1.16 (0.86 to 1.47)	<0.001
Major cardiovascular events — no. (%)	212 (12.0)	254 (14.4)	0.82 (0.68 to 0.98)	—	0.029
Death from cardiovascular causes	123 (7.0)	169 (9.6)	0.71 (0.56 to 0.89)	—	—
Nonfatal myocardial infarction	52 (2.9)	64 (3.6)	0.80 (0.55 to 1.15)	—	—
Nonfatal stroke	63 (3.6)	51 (2.9)	1.22 (0.84 to 1.77)	—	—
Death from any cause — no. (%)	227 (12.8)	279 (15.8)	0.80 (0.67 to 0.95)	—	0.01

https://www.nejm.org/doi/full/10.1056/NEJMoa2403347

Some additional benefits of GLP1RA

Decrease in body weight by 4.1 kgr

Decrease in A1c by 0.81%

Decrease in SBP by 2.23 mmHg

44% reduction in major adverse limb events

No increase in hypoglycemic episodes

Safety events

4.5% v.s. 1.1% developed gastrointestinal side effects leading to drug discontinuation

Eye disorders (including cataracts) were reported in 3% v.s. 1.7%

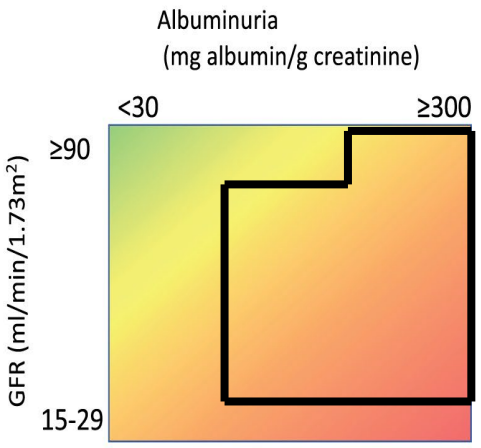
No change in diabetic retinopathy rates

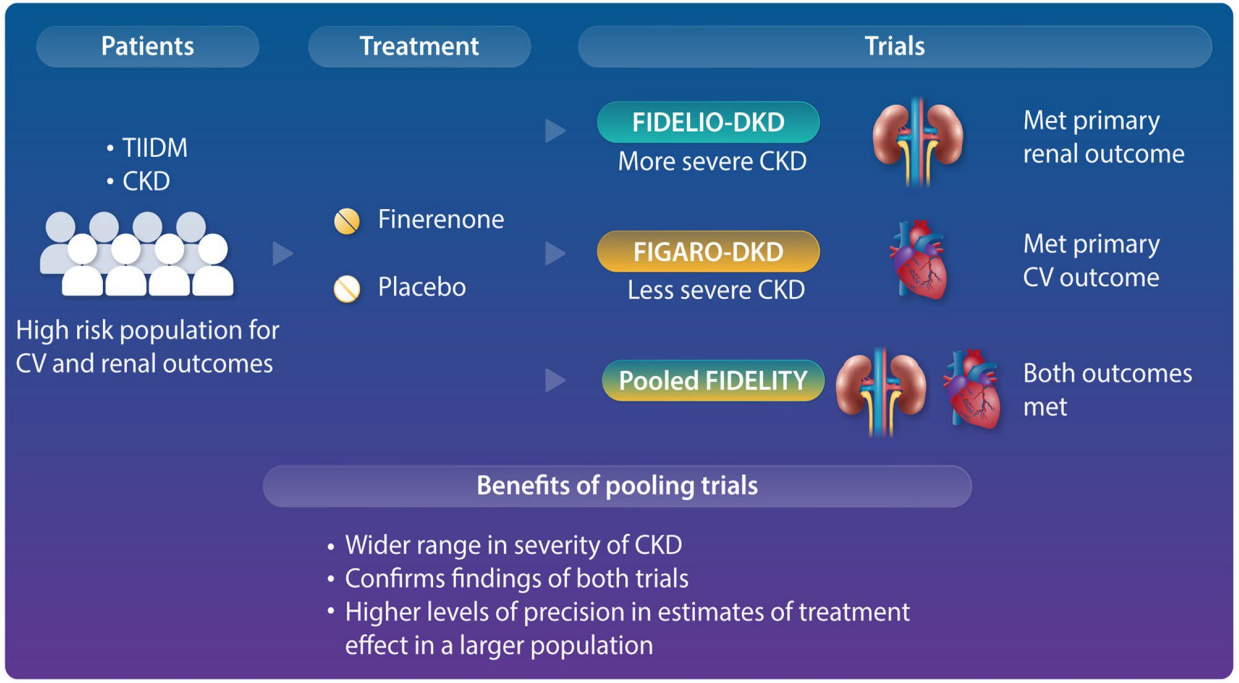
Aldosteronism Antagonism (MRA) for the reduction of cardiorenal risk across the spectrum of DKD

Risk defined in guidelines and trials

KDIGO risk			Albuminuria categories and range (mg albumin/g creatinine)		
Low risk			A1 Normal to mildly increased	A2 Moderately increased	A3 Severely increased
Moderate risk			<30	30 to <300	≥300
High risk					
Very high risk					
eGFR stages and range (mL/min/1.73 m²)					
G1	High and optimal	≥ 90			
G2	Mild	60-89			
G3a	Mild-moderate	45-59			
G3b	Moderate-severe	30-44			
G4	Severe	15-29			

Risk in patients





https://doi.org/10.1093/eurheartj/ehab827

Cardiovascular and kidney outcomes with finerenone in patients with type 2 diabetes and chronic kidney disease: the FIDELITY pooled analysis

Inclusion/exclusion

- ✓ T2D + CKD
- ✓ eGFR ≥25 mL/min/1.73m²
- ✓ Serum [K⁺] ≤ 4.8 mmol/L
- ✓ Maximum tolerated labeled dose of RAS
- ✗ HFrEF (NYHA class II-IV)

Protocol

6519 → Finerenone 10 mg or 20 mg od

R → Median follow-up 3 years

6507 → Placebo

Outcomes

CV composite:
Time to CV death, non- fatal MI, non-fatal stroke, or HHF

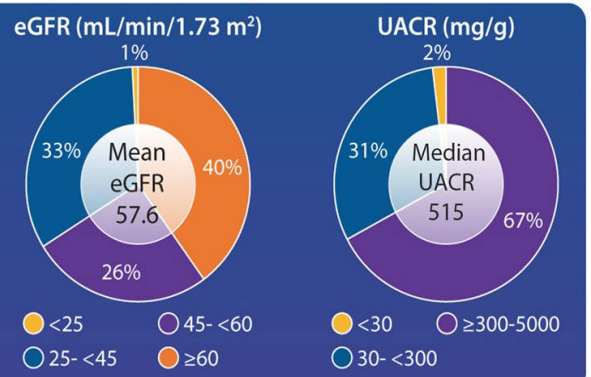
≥57% kidney composite:
Time to kidney failure, sustained ≥57% decrease in eGFR, or renal death

Baseline characteristics

Median age: 65 years
♂ 70% ♀ 30%

RAS inhibitors: 99.8%
Statins: 72.2%

HbA1c: 7.7%
BP: 137/76 mmHg
Prior HF: 7.7%



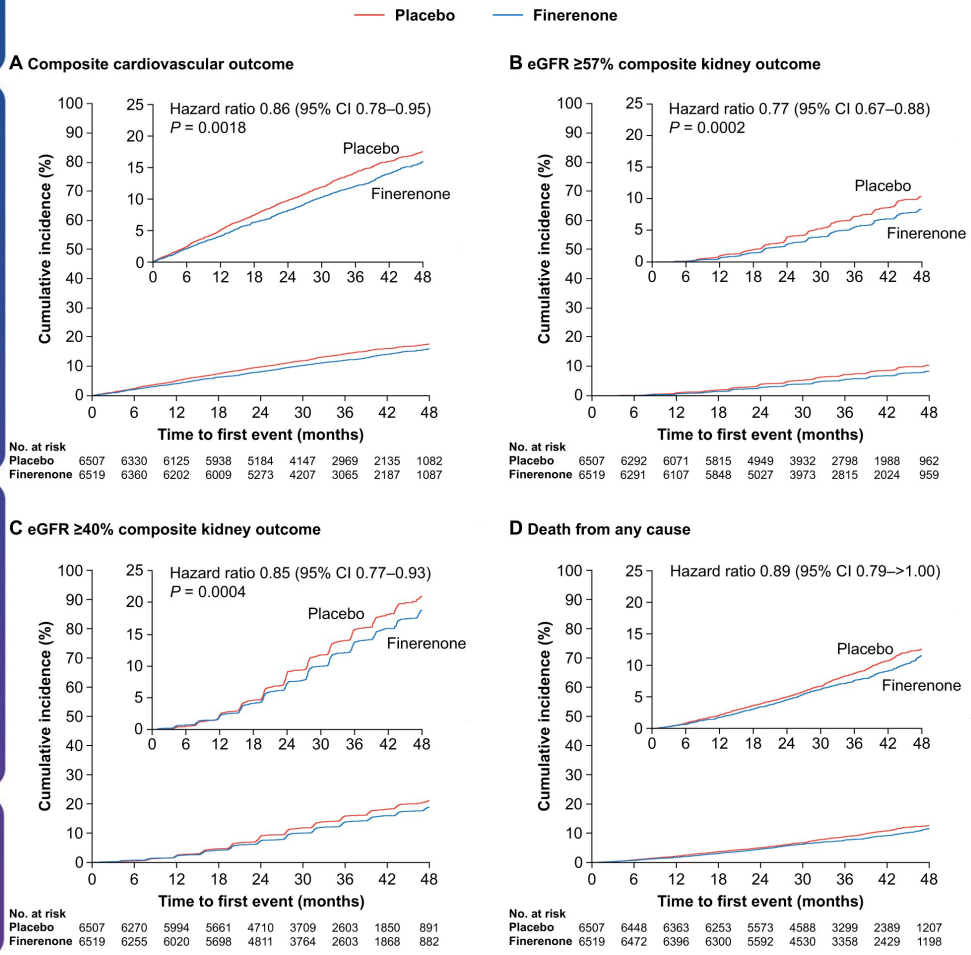
Few hyperkalemia-related discontinuations occurred

Results

	HR (95% CI)	p-value	Risk ↓
Endpoint CV composite	0.86 (0.78 – 0.95)	0.0018	14%
HHF	0.78 (0.66 – 0.92)	0.0030	22%
Kidney composite	0.77 (0.67 – 0.88)	0.0002	23%
Dialysis	0.80 (0.64 – 0.99)	0.040	20%

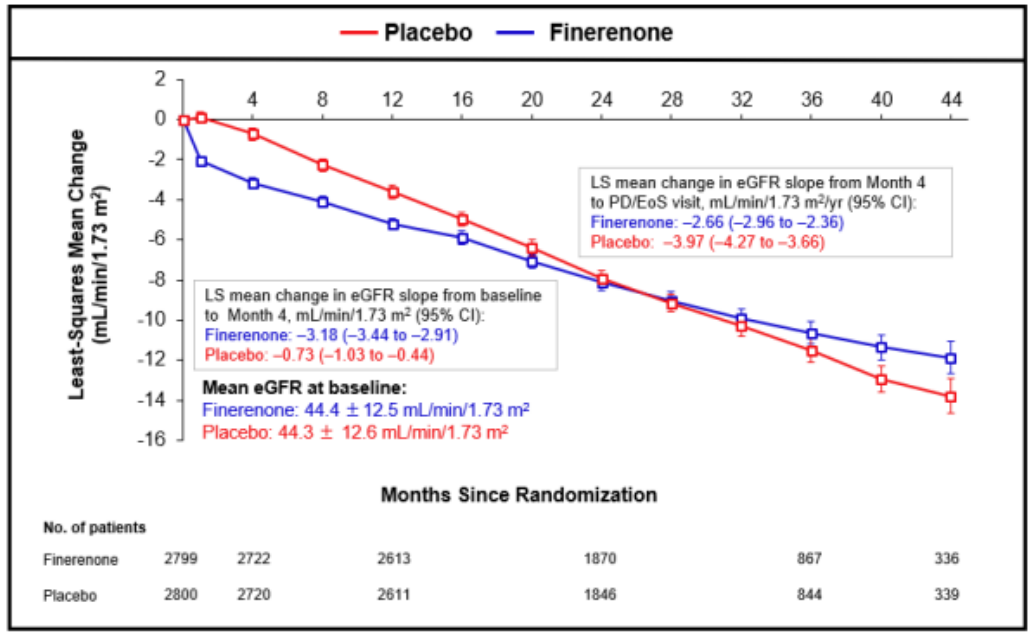
Conclusion

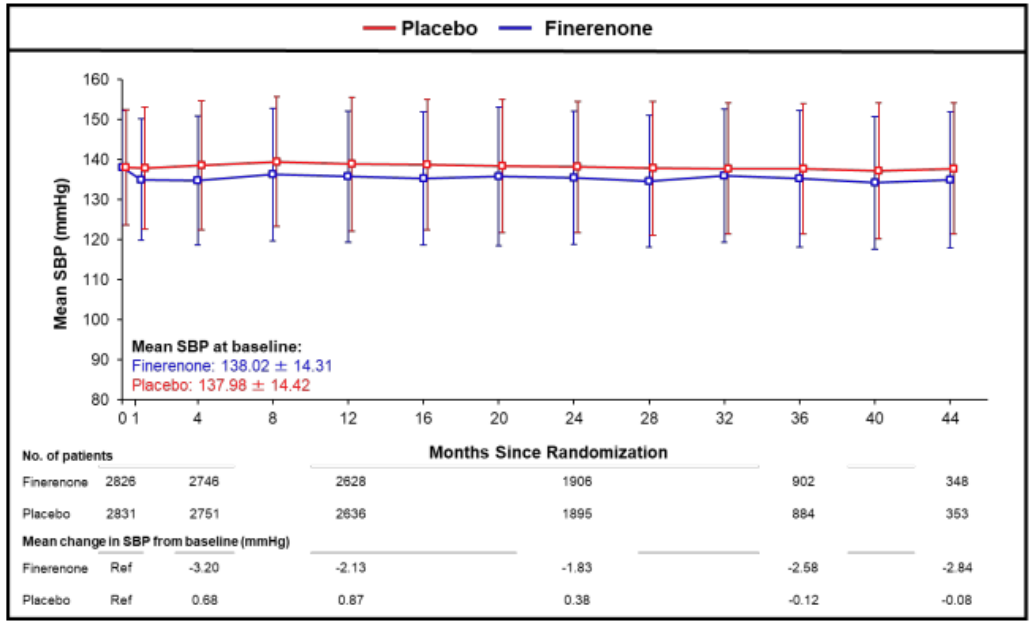
Finerenone on top of standard of care reduces the risk of clinically meaningful cardiovascular and kidney outcomes in patients with type 2 diabetes over a broad spectrum of chronic kidney disease



https://doi.org/10.1093/eurheartj/ehab777

Effects of Finerenone reduced loss of eGFR and had modest effects on BP





Change in SBP < 3 mmHg throughout FIDELIO-CKD

https://www.nejm.org/doi/10.1056/NEJMoa2025845

Management of hyperkalemia during aldosterone antagonism for diabetic and non-diabetic CKD under combined RASi + MRA

Hypekalemia will occur with MRA (can't escape ENAC!)

Hyperkalemia will occur with MRAs irrespective of the MRA and the diabetic (or not) nature of CKD

Management of hyperkalemia will allow the safe use of MRAs

Continued use of MRAs is required to deliver their cardiovascular and kidney benefits

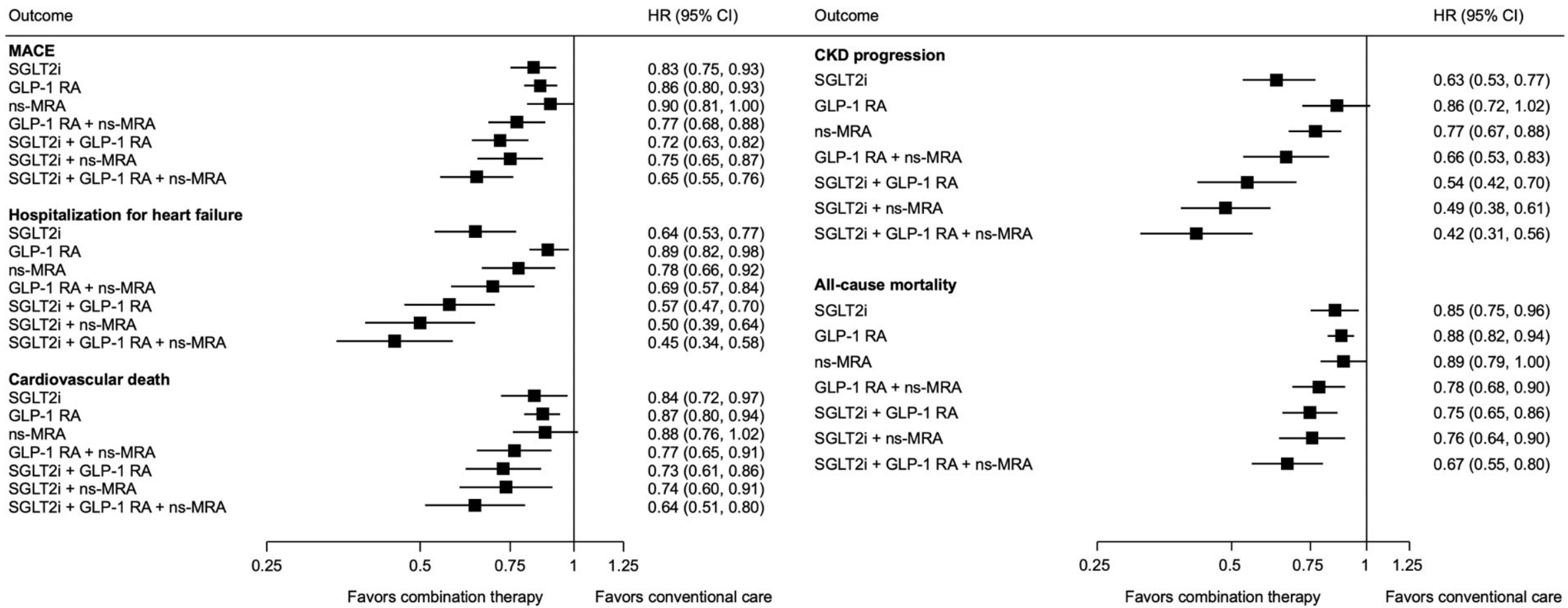
Potential strategies to manage the hyperkalemia risk by *any* MRA are:

- Measure the potassium (it never makes sense to "stop the count")
- Stop the MRA or reduce the dose
- "Convince" the kidneys to get rid of potassium (diuretics/SGLT2 inhibitors)
- Use a potassium binder

Protocol of the Finerenone trials gives guidance on how to manage potassium during MRA therapy safely

Circulation

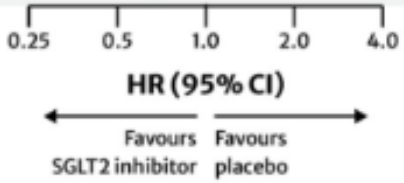
ESTIMATED LIFETIME BENEFITS OF COMBINATION TREATMENT WITH SGLT2 INHIBITORS, GLP-1 RECEPTOR AGONISTS AND NON-STEROIDAL MRA COMPARED WITH CONVENTION CARE IN PATIENTS WITH TYPE 2 DIABETES AND ALBUMINURIA



NEUEN BL ET AL. CIRCULATION 2023 [PUBLISHED ONLINE AHEAD OF PRINT]
HTTPS://WWW.AHAJOURNALS.ORG/DOI/10.1161/CIRCULATIONAHA.123.067584

SGLT2i have a consistent effect irrespective of baseline use of GLP1-RA

	Events/patients (%)		Event rate per 100 patient years		
	SGLT2 inhibitor	Placebo	SGLT2 inhibitor	Placebo	HR (95% CI)
Baseline use of GLP-1 RA					
High atherosclerotic cardiovascular risk trials	14/936 (1·5)	17/693 (2·5)	0·4	1·0	0·60 (0·27 to 1·31)
Stable heart failure trials	3/47 (6·4)	3/33 (9·1)	2·2	4·7	0·64 (0·13 to 3·12)
Chronic kidney disease trials	40/635 (6·3)	53/640 (8·3)	3·2	4·5	0·67 (0·44 to 1·02)
Subtotal (I-squared = 0·0%, p = 0·64)	57/1618 (3·5)	73/1366 (5·3)	1·6	2·9	0·65 (0·46 to 0·94)
No baseline use of GLP-1 RA					
High atherosclerotic cardiovascular risk trials	469/23585 (2·0)	526/17302 (3·0)	0·6	1·3	0·59 (0·52 to 0·67)
Stable heart failure trials	235/4781 (4·9)	231/4798 (4·8)	2·9	3·1	1·02 (0·85 to 1·22)
Chronic kidney disease trials	688/9839 (7·0)	1015/9817 (10·3)	3·7	5·6	0·64 (0·58 to 0·71)
Subtotal (I-squared = 70·4%, p<0.001)	1392/38205 (3·6)	1772/31917 (5·6)	1·7	2·9	0·67 (0·62 to 0·72)
Total	1449/39823 (3·6)	1845/33283 (5·5)	1·7	2·9	0·67 (0·62 to 0·72)
Heterogeneity by use of GLP-1 RA: p = 0·81					

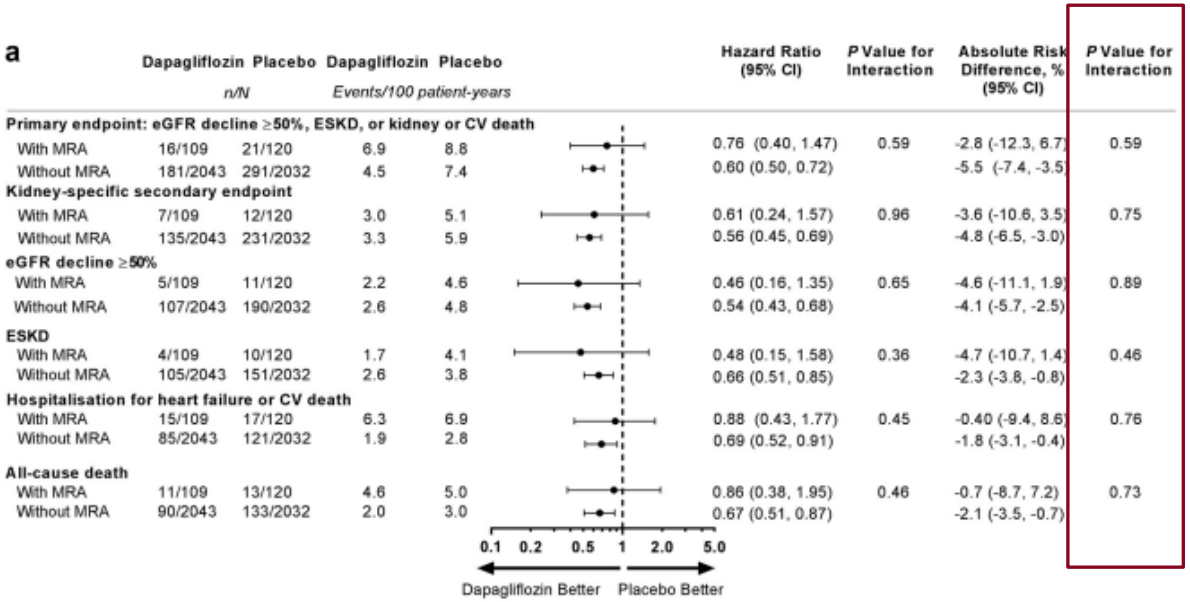


https://www.smart-c.net/resources/

https://www.sciencedirect.com/science/article/abs/pii/S2213858724001554

Do MRA/SGLT2i interfere with each other?

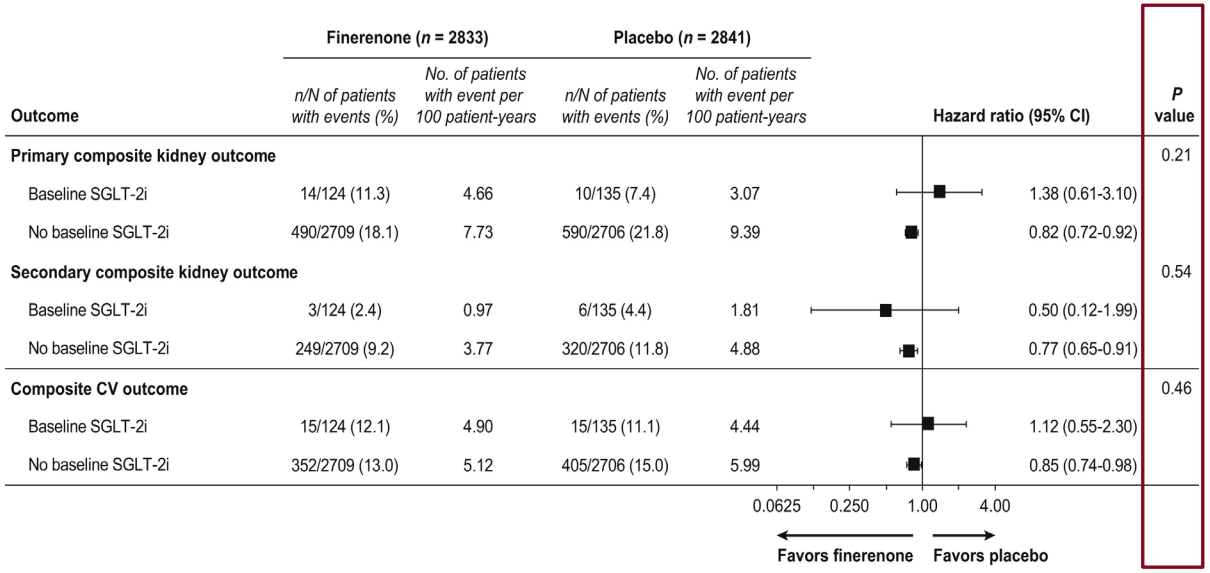
MRA IN DAPA-CKD



a

	Dapagliflozin n/N	Placebo n/N	Dapagliflozin Events/100 patient-years	Placebo Events/100 patient-years	Hazard Ratio (95% CI)	*P* Value for Interaction	Absolute Risk Difference, % (95% CI)	*P* Value for Interaction
Primary endpoint: eGFR decline ≥50%, ESKD, or kidney or CV death								
With MRA	16/109	21/120	6.9	8.8	0.76 (0.40, 1.47)	0.59	-2.8 (-12.3, 6.7)	0.59
Without MRA	181/2043	291/2032	4.5	7.4	0.60 (0.50, 0.72)		-5.5 (-7.4, -3.5)	
Kidney-specific secondary endpoint								
With MRA	7/109	12/120	3.0	5.1	0.61 (0.24, 1.57)	0.96	-3.6 (-10.6, 3.5)	0.75
Without MRA	135/2043	231/2032	3.3	5.9	0.56 (0.45, 0.69)		-4.8 (-6.5, -3.0)	
eGFR decline ≥50%								
With MRA	5/109	11/120	2.2	4.6	0.46 (0.16, 1.35)	0.65	-4.6 (-11.1, 1.9)	0.89
Without MRA	107/2043	190/2032	2.6	4.8	0.54 (0.43, 0.68)		-4.1 (-5.7, -2.5)	
ESKD								
With MRA	4/109	10/120	1.7	4.1	0.48 (0.15, 1.58)	0.36	-4.7 (-10.7, 1.4)	0.46
Without MRA	105/2043	151/2032	2.6	3.8	0.66 (0.51, 0.85)		-2.3 (-3.8, -0.8)	
Hospitalisation for heart failure or CV death								
With MRA	15/109	17/120	6.3	6.9	0.88 (0.43, 1.77)	0.45	-0.40 (-9.4, 8.6)	0.76
Without MRA	85/2043	121/2032	1.9	2.8	0.69 (0.52, 0.91)		-1.8 (-3.1, -0.4)	
All-cause death								
With MRA	11/109	13/120	4.6	5.0	0.86 (0.38, 1.95)	0.46	-0.7 (-8.7, 7.2)	0.73
Without MRA	90/2043	133/2032	2.0	3.0	0.67 (0.51, 0.87)		-2.1 (-3.5, -0.7)	

SGLT2I IN THE FIDELIO-DKD TRIAL



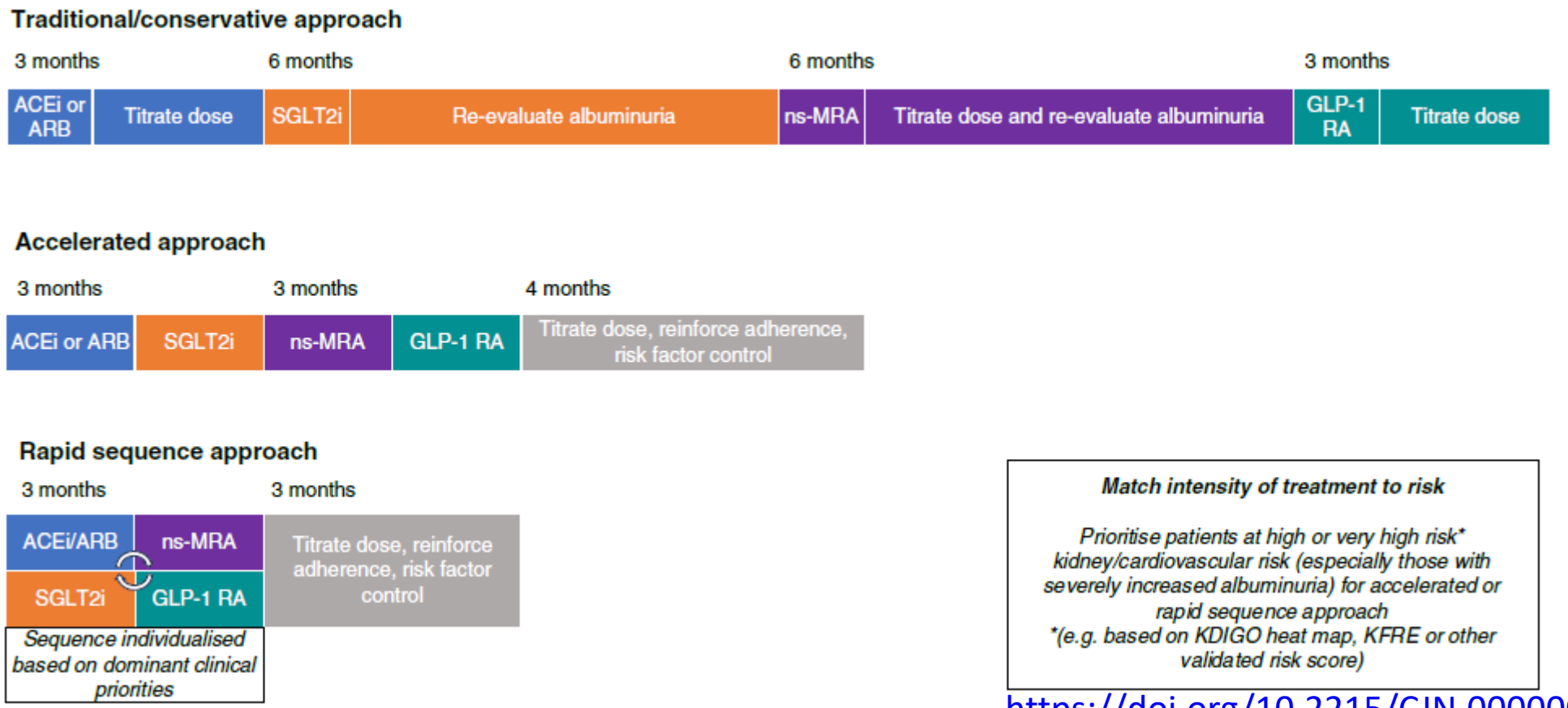
Outcome	Finerenone (*n* = 2833) *n/N* of patients with events (%)	Finerenone (*n* = 2833) *No.* of patients with event per 100 patient-years	Placebo (*n* = 2841) *n/N* of patients with events (%)	Placebo (*n* = 2841) *No.* of patients with event per 100 patient-years	Hazard ratio (95% CI)	*P* value
Primary composite kidney outcome						0.21
Baseline SGLT-2i	14/124 (11.3)	4.66	10/135 (7.4)	3.07	1.38 (0.61-3.10)	
No baseline SGLT-2i	490/2709 (18.1)	7.73	590/2706 (21.8)	9.39	0.82 (0.72-0.92)	
Secondary composite kidney outcome						0.54
Baseline SGLT-2i	3/124 (2.4)	0.97	6/135 (4.4)	1.81	0.50 (0.12-1.99)	
No baseline SGLT-2i	249/2709 (9.2)	3.77	320/2706 (11.8)	4.88	0.77 (0.65-0.91)	
Composite CV outcome						0.46
Baseline SGLT-2i	15/124 (12.1)	4.90	15/135 (11.1)	4.44	1.12 (0.55-2.30)	
No baseline SGLT-2i	352/2709 (13.0)	5.12	405/2706 (15.0)	5.99	0.85 (0.74-0.98)	

No evidence of effect modification based on limited and subject to selection effect post hoc subgroup data

https://doi.org/10.1016/j.ekir.2021.12.013

https://www.kireports.org/article/S2468-0249(21)01467-4/fulltext

Chronic Kidney Disease Means Urgent Kidney Disease



Match intensity of treatment to risk

Prioritise patients at high or very high risk kidney/cardiovascular risk (especially those with severely increased albuminuria) for accelerated or rapid sequence approach*
**(e.g. based on KDIGO heat map, KFRE or other validated risk score)*

https://doi.org/10.2215/CJN.0000000000000526

Some points from my personal practice

5 mg of Lisinopril does not qualify as maximum tolerated dose of ACEi/ARB

You can probe the max tolerated dose with dose escalation every 10 days

Prescribing a SGLT2i in a patient with prior intolerance (in my book only “real” AKI, not simply creatinine bumps) to ACEI or ARB is **not an issue** as we know from EMPA-KIDNEY but …

Strongly consider starting the SGLT2i to lower the K and then add ACEi/ARB + MRA (may need a K binder)

One may simultaneously start MRA and SGLT2i in those with eGFR > 45

For those with high cardiovascular risk and minimal proteinuria : ns-MRA on label, but SGLT2i off label: if you want to stay on label start with the ns-MRA (but your patient deserves both)

GLP1 can be started independently without even bothering to time it with respect to the other classes

You don’t need repeat office visits; you can get everyone on the four pillars using repeat lab slips and remote monitoring off labs (this is not the 1980s anymore)

Review > J Clin Med. 2024 Jan 8;13(2):348. doi: 10.3390/jcm13020348.

Chronic Kidney Disease in the Older Adult Patient with Diabetes

Raja Ravender [1], Maria-Eleni Roumelioti [1], Darren W Schmidt [1], Mark L Unruh [1], Christos Argyropoulos [1]

Affiliations + expand

PMID: 38256482 PMCID: PMC10816477 DOI: 10.3390/jcm13020348

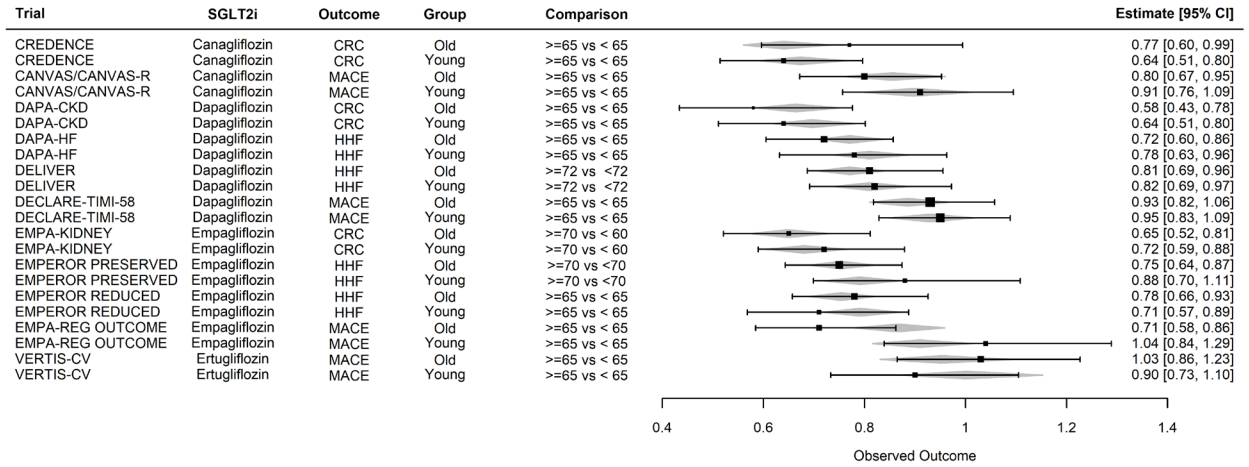


Table 5. Finerenone and clinical outcomes in older vs. younger individuals (hazard ratio and 95% confidence intervals).

Clinical Trial	Outcome	Effect in Younger Patients	Effect in Older Patients
FIGARO-DKD	MACE/HHF [2]	0.90 0.74–1.10	0.85 0.72–1.00
FIGARO-DKD [1]	CR [3]	0.72 0.52–0.99	0.92 0.61-1.38
FIDELIO-DKD	CR	0.85 0.72–1.01	0.79 0.67–0.94

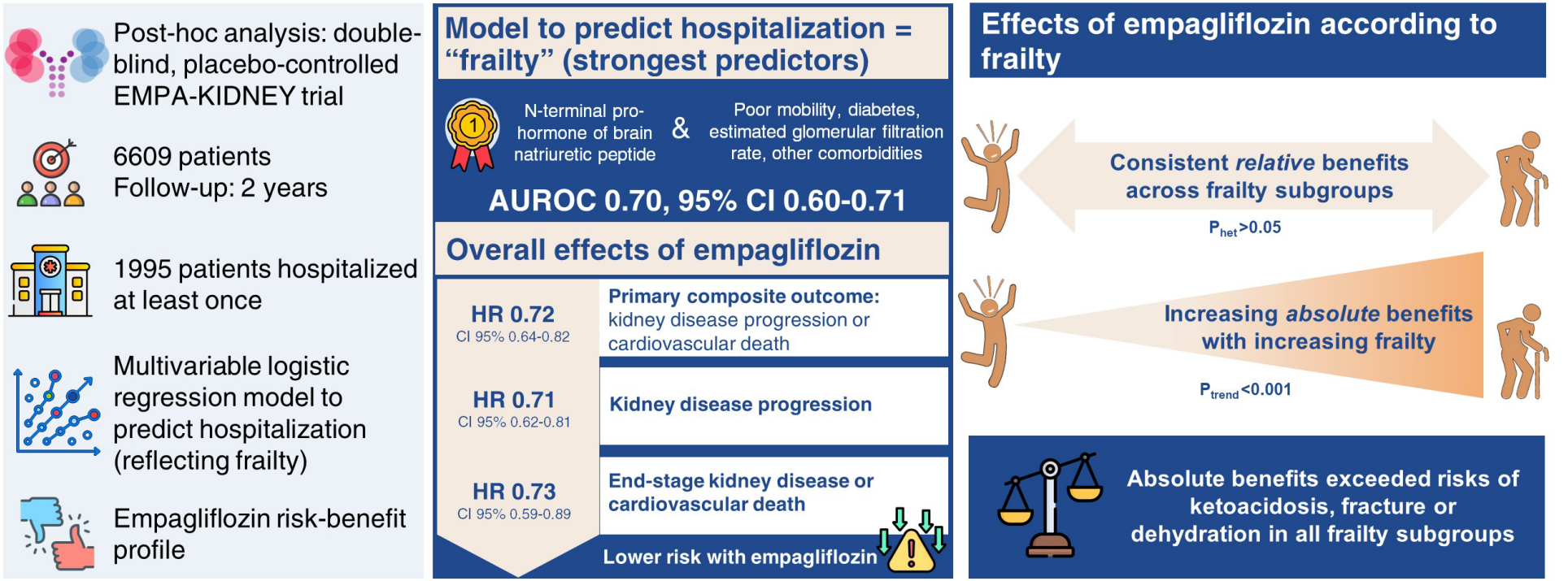
[1] The subgroup analysis was presented in a follow-up publication [136] and used a sustained reduction of eGFR > 57%, rather than the 40% used in the primary analysis of the FIGARO-DKD study. [2] HHF: hospitalization for heart failure, MACE: major adverse cardiovascular events (composite of cardiovascular death, non-fatal myocardial infarction, or stroke). [3] CR: composite renal outcome.

Don’t forget your elderly patients!

What about the frail patient on many drugs?

EMPA-KIDNEY: Does empagliflozin continue to show beneficial effects in frail patients with chronic kidney disease?

CJASN®
Clinical Journal of the American Society of Nephrology



AUROC- area under the receiver operating characteristic curve, HR- Hazard Ratio, CI- Confidence interval

Conclusions: The findings support the use of SGLT2 inhibitors in CKD, irrespective of frailty. Absolute benefits clearly exceeded any potential harm across the spectrum of frailty in EMPA-KIDNEY.

Kaitlin J. Mayne, Rebecca J. Sardell, Natalie Staplin, et al. **Frailty, multimorbidity, and polypharmacy: exploratory analyses of the effects of empagliflozin from the EMPA-KIDNEY trial**. 2024,CJASN DOI 10.2215/CJN.0000000000000498
Visual abstract by Cristina Popa, MD

http://bit.ly/CJASN0498

Highest frailty quartiles > 71 y/o

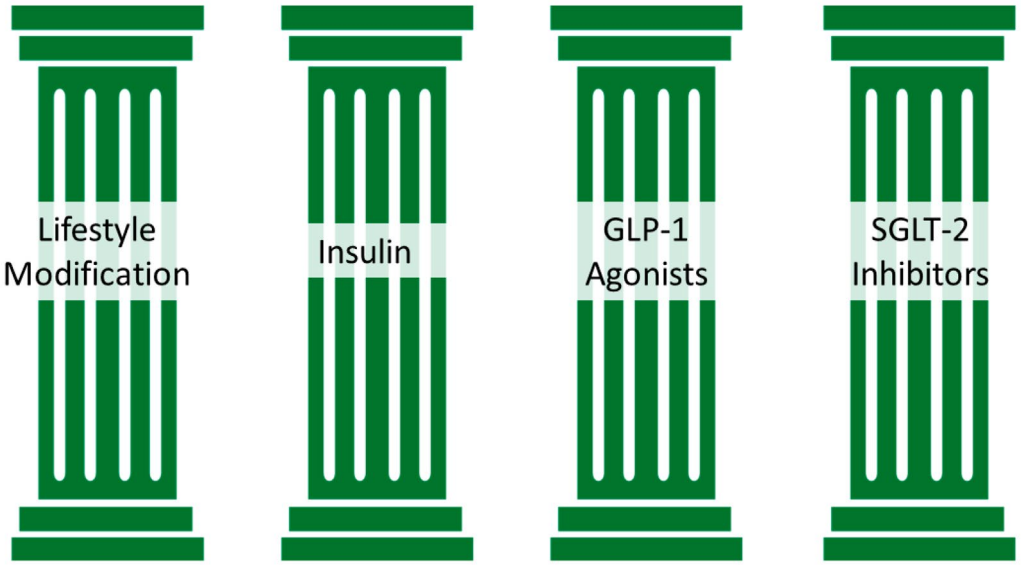
Kidney (and other solid organ) transplant recipients are at risk for NODAT & CKD

Drug Type	Pathophysiology
mTOR inhibitors	Increase in apoptosis Decrease in β-cell size Reduction in basal and insulin-stimulated glucose uptake and glycogen synthesis Reduction in basal and insulin-stimulated glucose uptake and glycogen synthesis Decrease in insulin-stimulated Akt phosphorylation
Calcineurin Inhibitors	Both tacrolimus and cyclosporin have diabetogenic effects Decrease in insulin secretion Increase in insulin resistance Toxicity on β-cells Tacrolimus has more diabetogenic effects than cyclosporin
Mycophenolate	No diabetogenic effect
Belatacept	Not independent diabetogenic effect Decreased risk compared to Tacrolimus
Glucocorticoids	Increased insulin resistance Increased gluconeogenesis Suppressed insulin secretion B-cell apoptosis

https://www.mdpi.com/2077-0383/13/3/793

Absence of Evidence ≠ Evidence of Absence

- Multiple (small) studies of SGLT2i and GLP1 or GIP-GLP1RA in transplant populations
- Underpowered for clinical outcomes
- Strong reductions in A1c and BW not different from the general population
- Strong insulin sparing effect (particularly with GLP1RA
- Increased incidence of UTI (not pyelonephritis) with SGLT2i
- No interactions with immunosuppressants
- Though not specifically studied in this population, CV risk drives decisions



https://www.mdpi.com/2077-0383/13/3/793

Which anti-glycemic/antifibrotic agents to recommend in 2024

1. Patient's cardiorenal risk
2. Cardiovascular and renal end-points
   - Medical literature
   - Regulatory submission documents
3. Safety profile
4. What the insurance will pay
5. The copay the patient can afford
6. Level of renal function : **is irrelevant. Start SGLT2i/GLP1RA/MRA up to eGFR of 20, continue until the patients are on dialysis**

Take home points for this section

1. Patients may be selected for further therapies based on UACR
2. SGLT2i have broad cardiovascular, renal and heart failure benefits
3. Cardiorenal benefits of SGLT2i are likely to be class, rather than agent specific
4. Effects of SGLT2i on CKD don't differ between diabetic and non-diabetic forms of CKD
5. Successful roll out of SGLT2i is likely to have the same population level effects that ACE/ARBs had
6. Selective, non-steroidal MRAs have the same effects on cardiorenal outcomes as SGLT2i
7. GLP1RA are part of the emerging SOC in DKD (sema will likely get FDA approval in 2024)
8. Don't ask who will prescribe the SGLT2i/MRA/GLP1RA for your patient, but when YOU will prescribe SGLT2i/MRA/GLP1RA and how you will do it like royalty

Resources

- ASN Diabetic Kidney Disease Collaborative - **online resource for patients and caregivers**
  https://epc.asn-online.org/learning_course/your-kidneys-and-your-health/
- ASN Diabetic Kidney Disease Collaborative - **online resource for healthcare professionals (PCPs/nephrologists/endocrinologists/cardiologists/pharmacists)**

https://epc.asn-online.org/learning_course/management-of-chronic-kidney-disease-in-people-with-diabetes/

- Special Issue Journal of Clinical Medicine (mostly reviews around pharmacotherapy, special populations and niche sglt2 and incretin therapy stuff)

  https://www.mdpi.com/journal/jcm/special_issues/5YPA16M6VN