# iSGLT2 en vie réelle et combinaisons du futur

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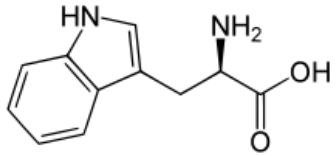
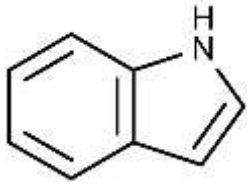
# Déclarations des liens d'intérêts

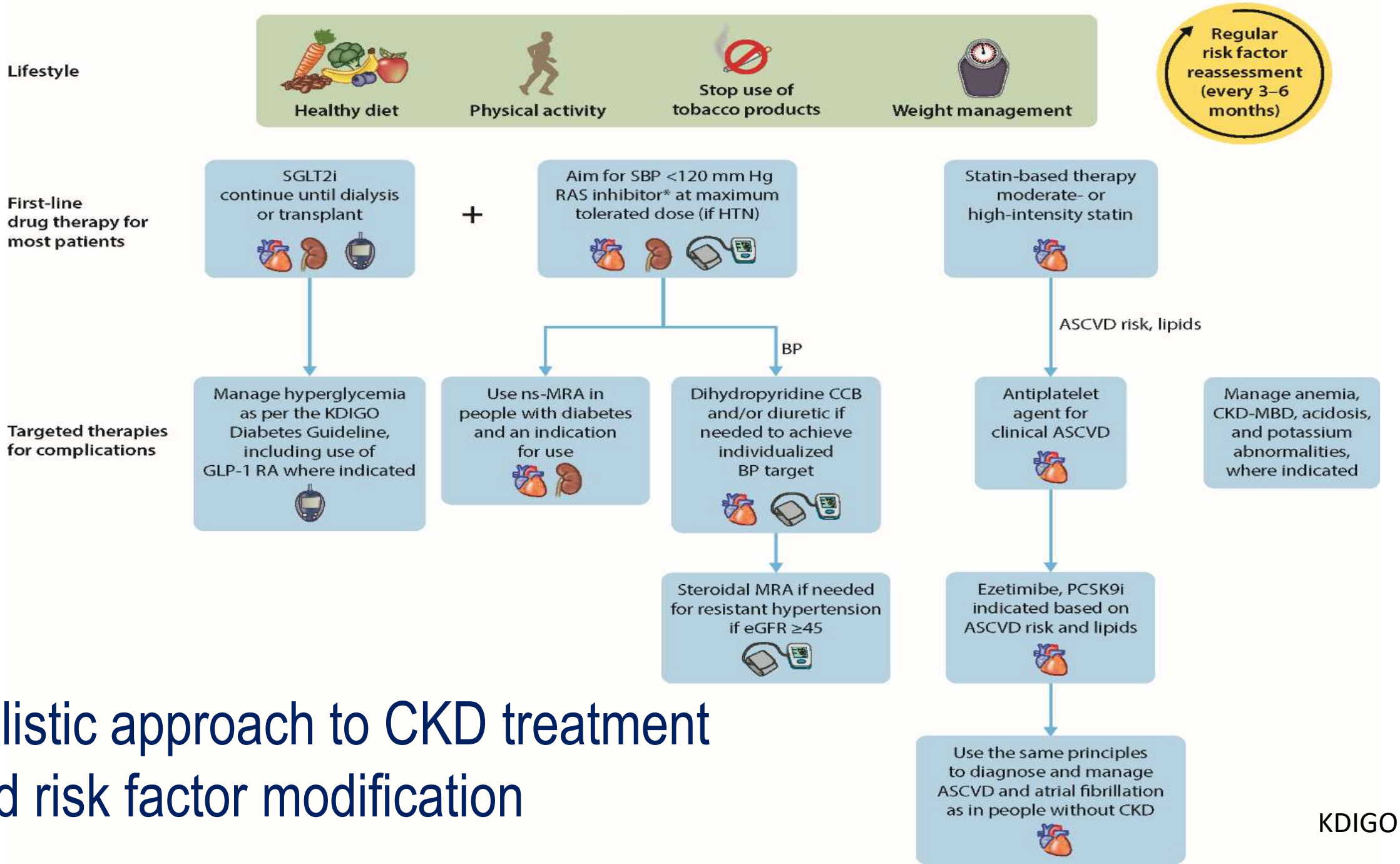
LE JEU DU SIÈCLE

- Je déclare les liens d'intérêts suivants pour cette présentation
  - Astra-Zeneca
  - Boerhinger-Ingelheim
  - Bayer
  - Amgen
  - Vifor-CSL
  - Alexion
- J'aime les pommes et les pommiers

- Je dirige une équipe qui travaille sur les toxines urémiques dérivées du tryptophane et Aryl Hydrocarbon Receptor



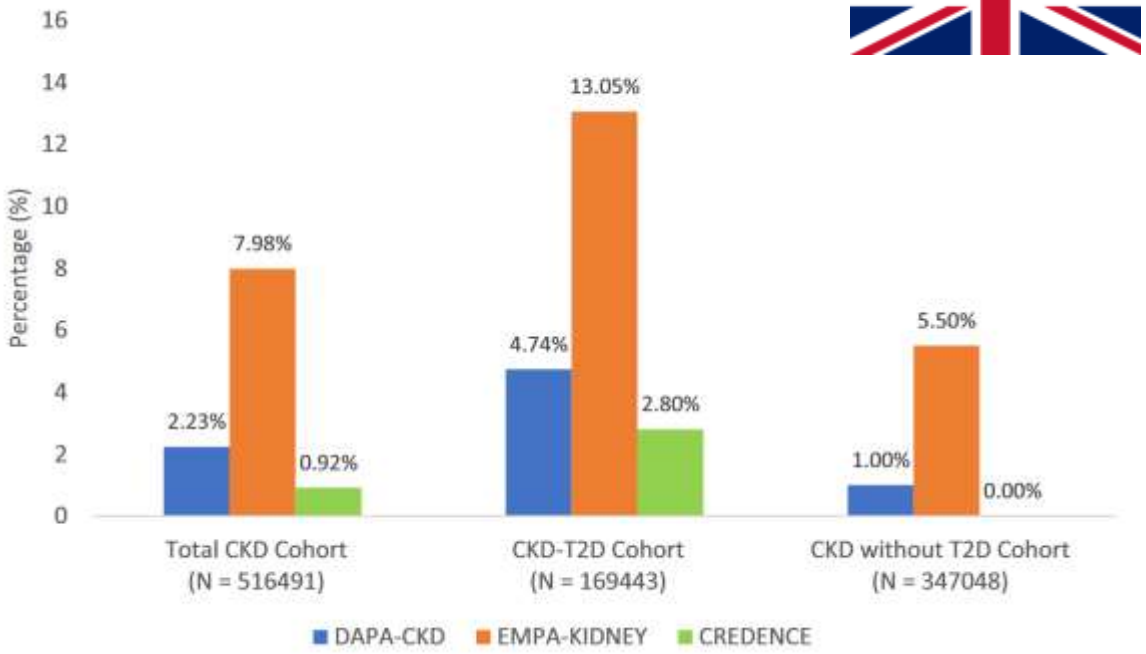



# Holistic approach to CKD treatment and risk factor modification

KDIGO 2024

# What is « in real life » compared to RCT?

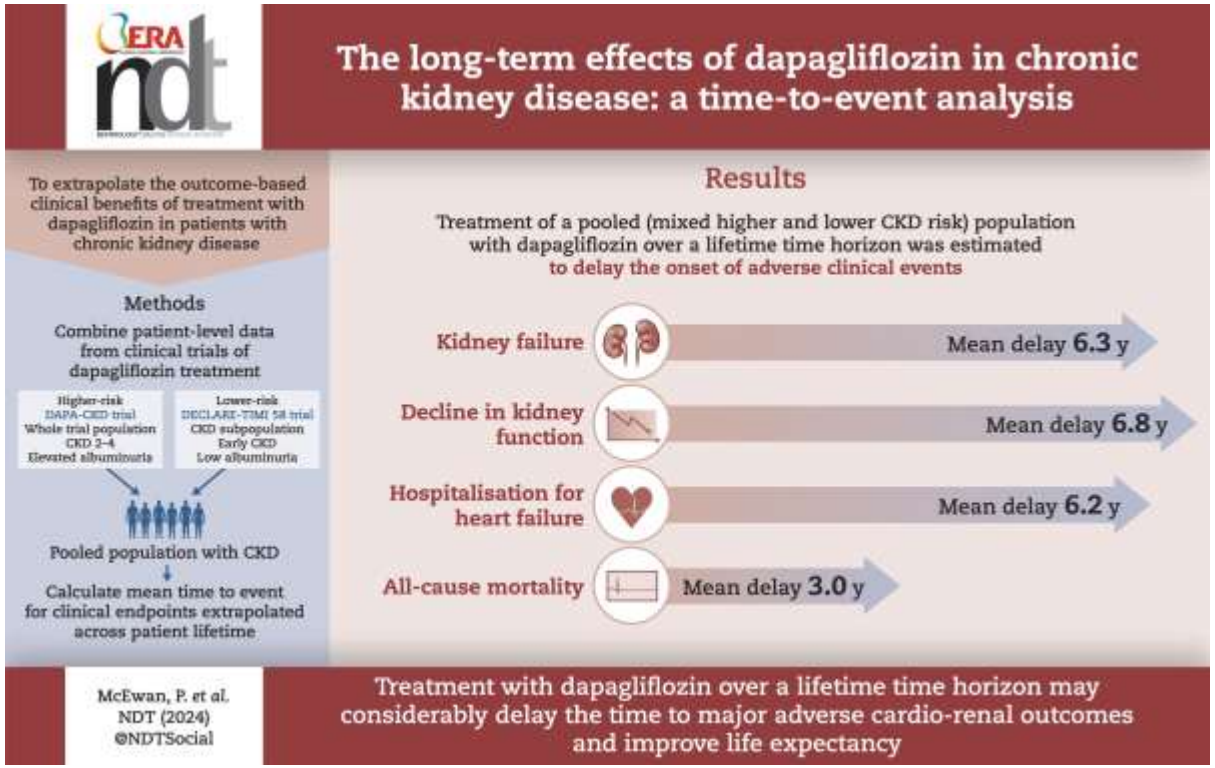
CKD patients, in real life cohort, test eligibility to SGLT2i RCT
516 491 patients




RCT patients more severe, more DT2 and more RASi

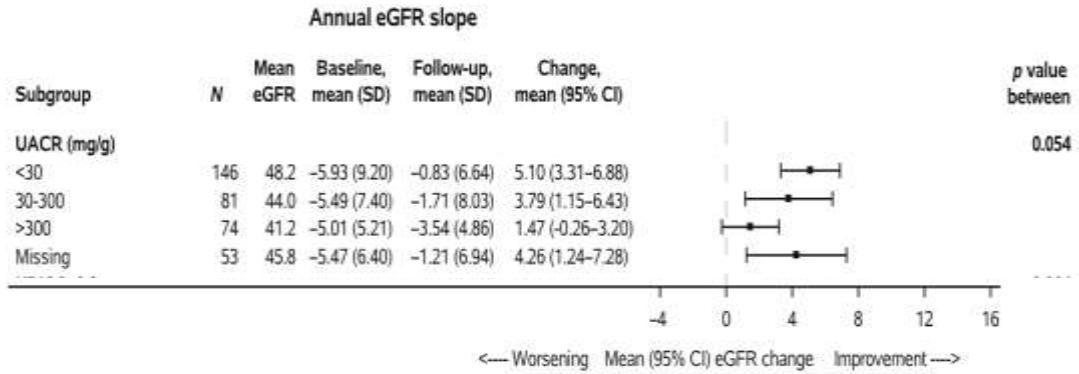
Forbes et al. NDT 2025

The answer of Trialists



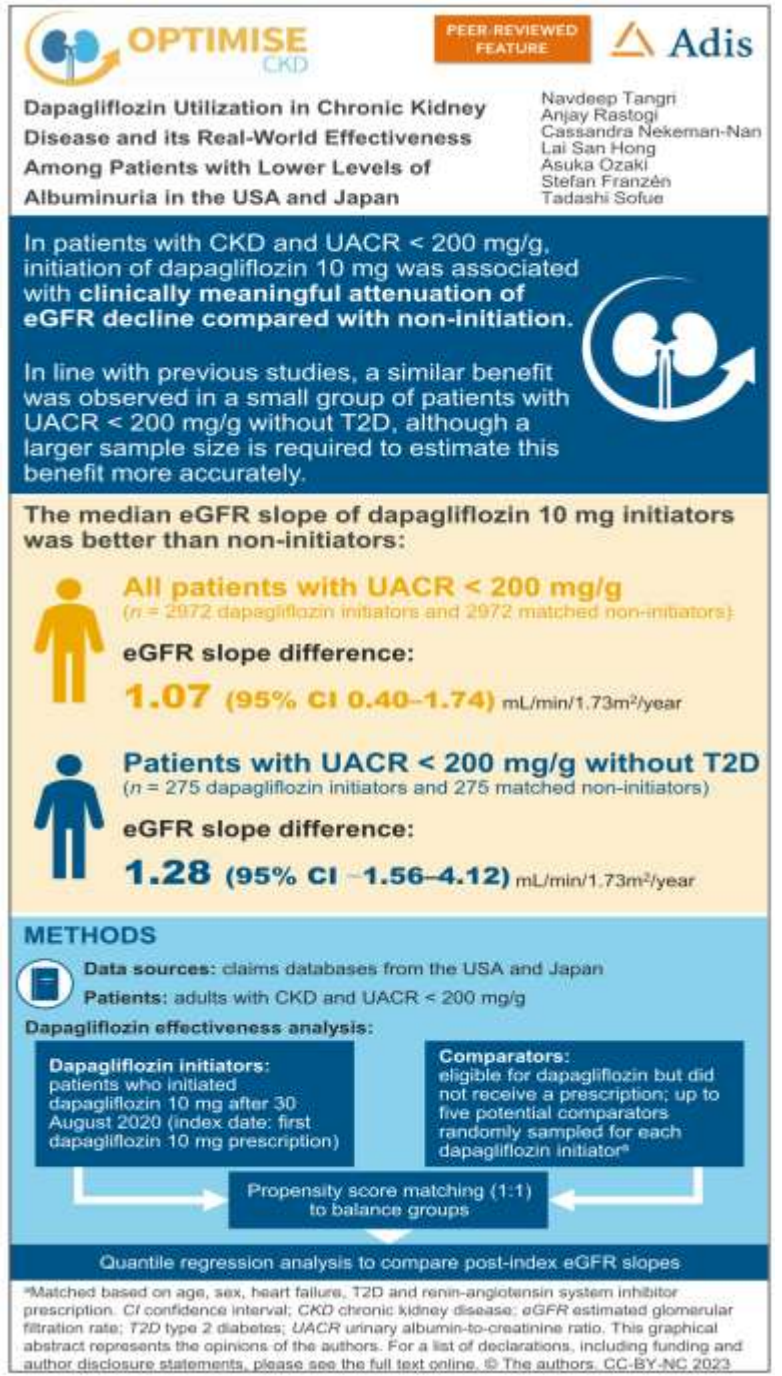
# SGLT2i in real life: Albuminuria

354 patients, age moyen 72 ans, 25% de femmes, DFG 45, 41% sans albU et 15% sans dosage



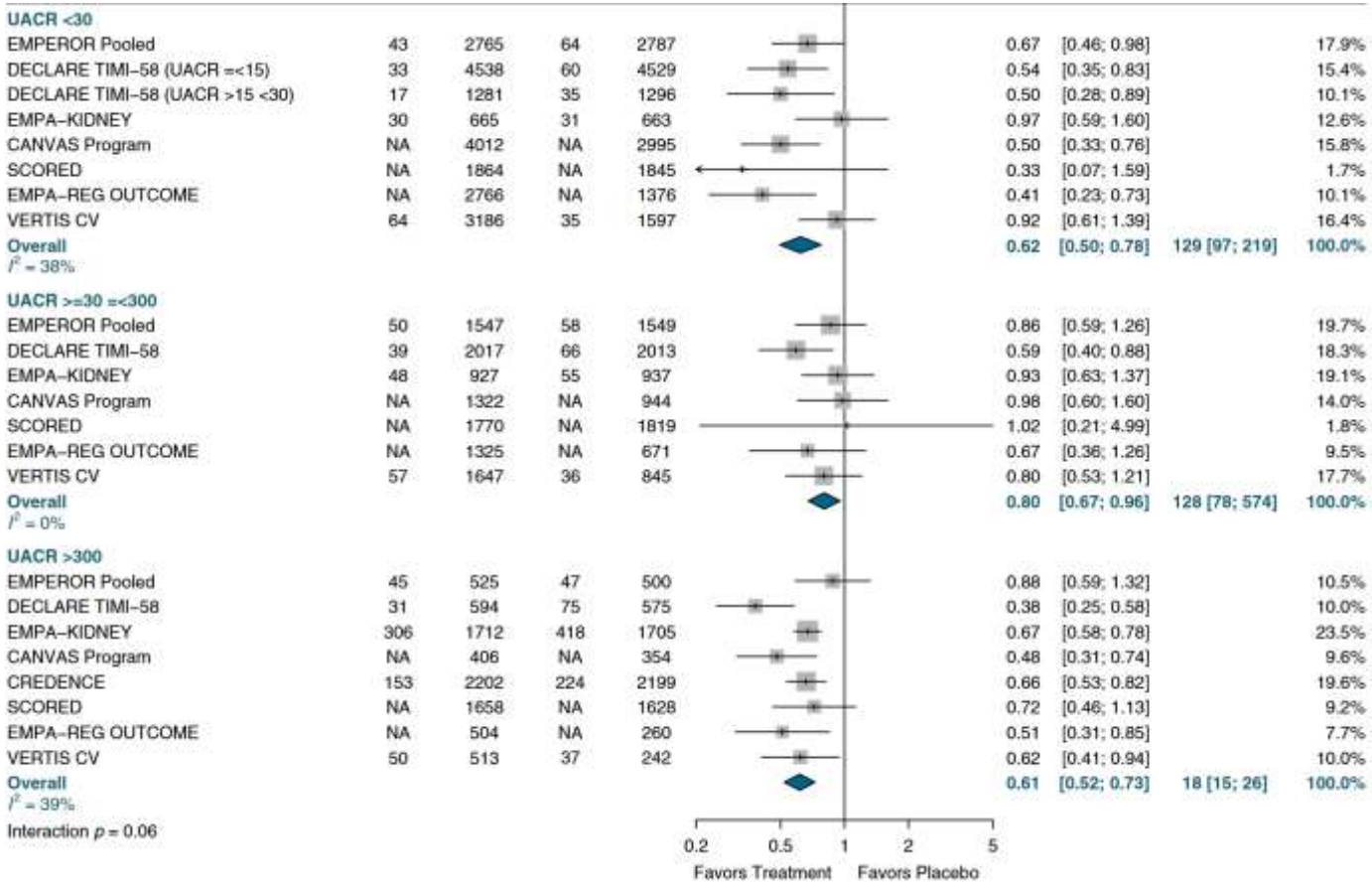

| | | Baseline UACR (mg/g) | | | | |
|---|---|---|---|---|---|---|
| Characteristic | | <30 | 30-300 | >300 | Missing | P-Value |
| Sex, n (%) | Males | 100 (68.5) | 65 (80.2) | 55 (74.3) | 42 (79.2) | 0.195 |
| Age, mean (SD), years | | 75.8 (7.9) | 74.4 (11.4) | 64.2 (13.8) | 74.2 (13.1) | <0.001 |
| Heart failure, n (%) | No | 63 (43.2) | 41 (50.6) | 63 (85.1) | 22 (41.5) | <0.001 |
| | Yes | 83 (56.8) | 40 (49.4) | 11 (14.9) | 31 (58.5) | |
| Loop diuretic, n (%) | No | 77 (52.7) | 41 (50.6) | 57 (77.0) | 26 (49.1) | 0.001 |
| | Yes | 69 (47.3) | 40 (49.4) | 17 (23.0) | 27 (50.9) | |
| Aldosterone antagonist, n (%) | No | 71 (48.6) | 51 (63.0) | 56 (75.7) | 24 (45.3) | <0.001 |
| | Yes | 75 (51.4) | 30 (37.0) | 18 (24.3) | 29 (54.7) | |

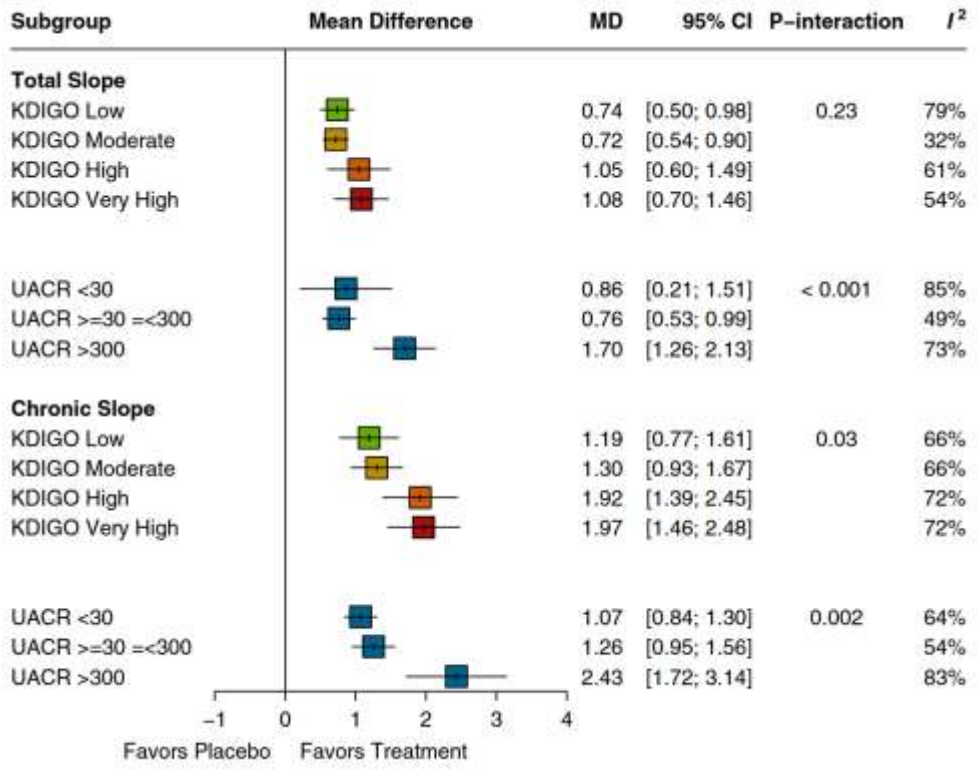
Nakhleh et al. Diabetes Obes Metab. 2024;26:3058–3067



# SGLT2i in real life: Albuminuria

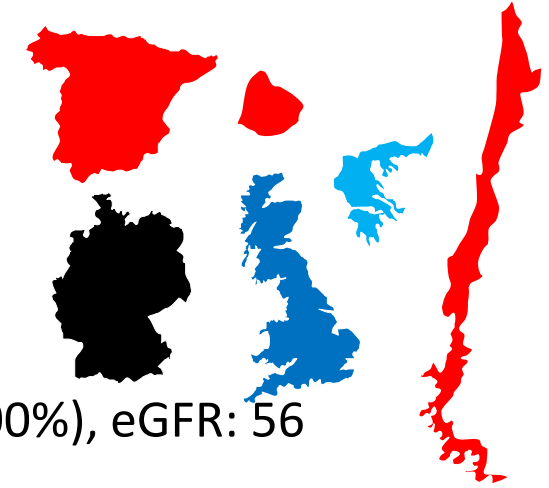
## Metaanalysis RCT, primary outcome: MAKE



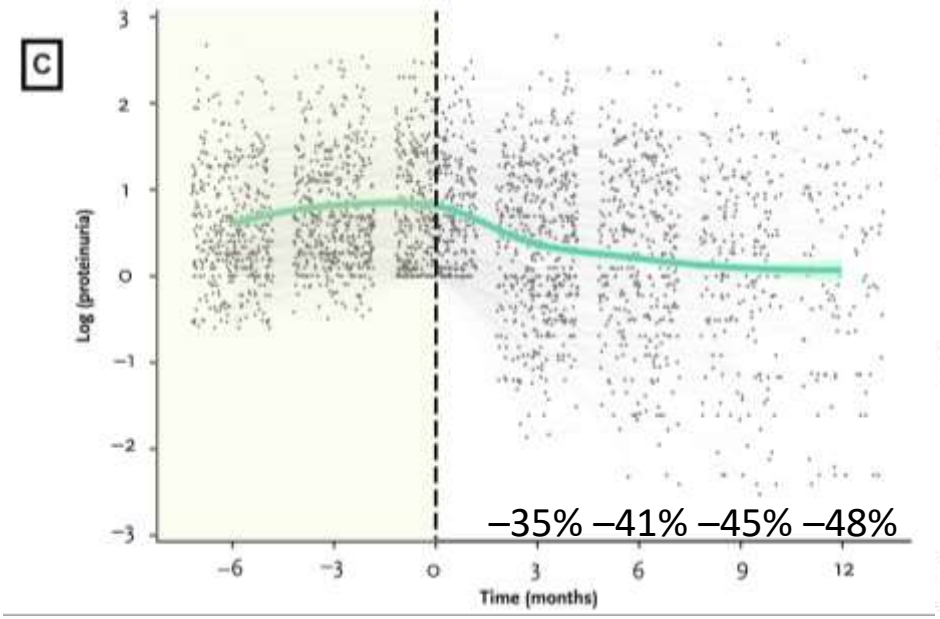




Spiazzi et al. CJASN 2025

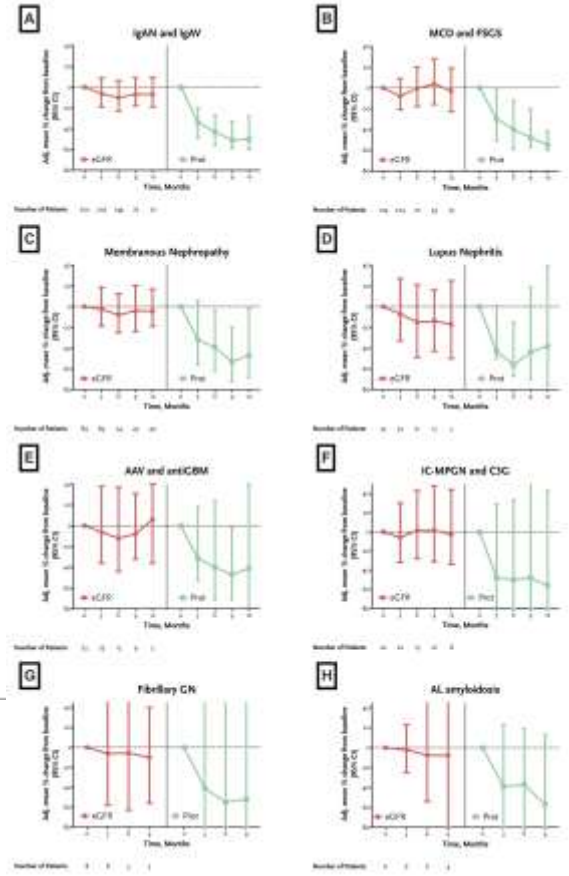
# SGLT2i in real life: Glomerulonephritis



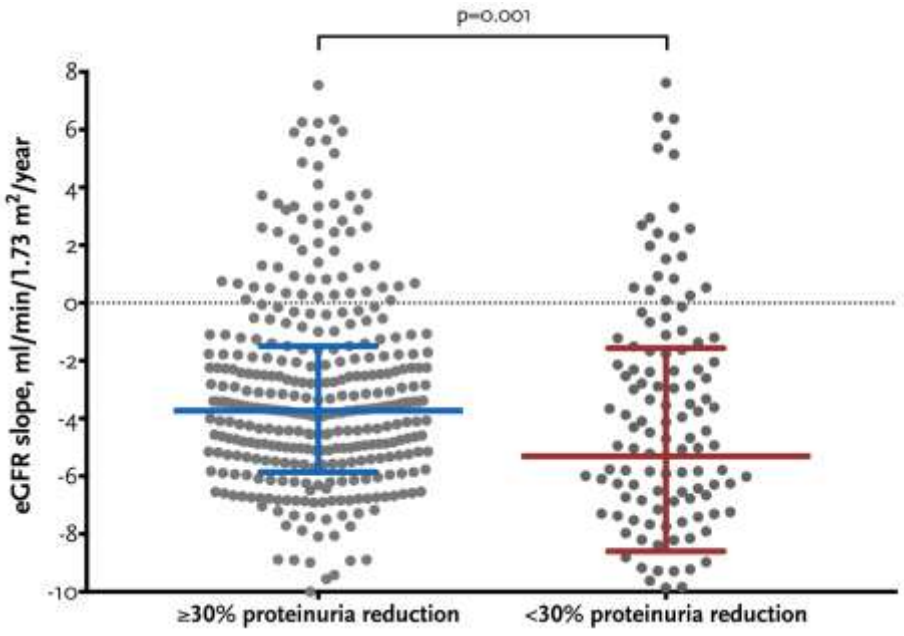
- Retrospective, 493 patients, IgA (41%), FSGS (18%), Membranous (18%), RASi(100%), eGFR: 56 ml/mn/1,73m2, 24h Pu: 2.1g.




Caravaca-Fontán, F. *et al. Nephrol Dial Transplant* 2024




Greater likelihood of reducing proteinuria:
Patients with BMI>30 and/or
Patients with albumin>35 g/l



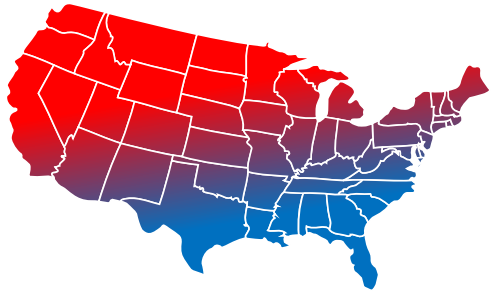
# SGLT2i in real life: Systemic lupus erythematous

- Emulated clinical trial, SLE and DT2, 2 ans de suivi moyen de 4330 patients SGLT2i vs DPP4, 58 ans, 90% de femmes, 12% de CKD

**Table 2.** Comparison of outcomes in patients with SLE with concomitant T2D prescribed SGLT2i versus DPP4i*

| Outcomes | Before propensity score matching | | | | | After propensity score matching | | | | |
|---|---|---|---|---|---|---|---|---|---|---|
| | SGLT2i (n = 2,464) Events | DPP4i (n = 4,761) Events | HR | 95% CI | *P* value (log-rank) | SGLT2i (n = 2,165) Events | DPP4i (n = 2,165) Events | HR | 95% CI | *P* value (log-rank) |
| All-cause mortality | 72 | 364 | 0.464 | (0.360–0.597) | <0.001 | 68 | 95 | 0.891 | (0.652–1.217) | 0.469 |
| Renal outcomes | | | | | | | | | | |
| Acute kidney failure | 105 | 493 | 0.425 | (0.345–0.525) | <0.001 | 94 | 222 | 0.493 | (0.387–0.627) | <0.001 |
| Chronic kidney disease | 138 | 481 | 0.513 | (0.424–0.619) | <0.001 | 126 | 239 | 0.614 | (0.495–0.762) | <0.001 |
| End-stage renal disease | 13 | 108 | 0.273 | (0.154–0.486) | <0.001 | 11 | 34 | 0.403 | (0.204–0.796) | 0.007 |
| Lupus nephritis | 24 | 82 | 0.657 | (0.417–1.035) | 0.068 | 20 | 36 | 0.665 | (0.384–1.149) | 0.141 |
| Cardiovascular outcomes | | | | | | | | | | |
| Myocardial infarction | 42 | 147 | 0.647 | (0.459–0.912) | 0.012 | 37 | 55 | 0.812 | (0.535–1.233) | 0.328 |
| Stroke | 69 | 188 | 0.824 | (0.625–1.087) | 0.170 | 63 | 76 | 1.032 | (0.738–1.442) | 0.854 |
| Heart failure | 113 | 389 | 0.602 | (0.488–0.743) | <0.001 | 102 | 170 | 0.717 | (0.560–0.916) | 0.008 |
| Safety outcomes | | | | | | | | | | |
| Emergency visits | 833 | 2,126 | 0.803 | (0.741–0.870) | <0.001 | 735 | 906 | 0.903 | (0.819–0.995) | 0.040 |
| Hospitalization | 50 | 139 | 0.813 | (0.588–1.124) | 0.209 | 41 | 65 | 0.758 | (0.513–1.122) | 0.165 |
| Genital infection | 240 | 315 | 1.740 | (1.471–2.059) | <0.001 | 193 | 175 | 1.308 | (1.066–1.606) | 0.010 |
| Urinary tract infection | 464 | 1,295 | 0.759 | (0.683–0.844) | <0.001 | 400 | 511 | 0.899 | (0.789–1.025) | 0.111 |
| Severe sepsis | 36 | 172 | 0.476 | (0.332–0.682) | <0.001 | 31 | 62 | 0.607 | (0.394–0.935) | 0.022 |
| Herpes zoster infection | 55 | 119 | 1.034 | (0.751–1.424) | 0.837 | 47 | 44 | 1.270 | (0.841–1.917) | 0.255 |
| Diabetic ketoacidosis | 19 | 53 | 0.831 | (0.492–1.404) | 0.488 | 15 | 17 | 1.065 | (0.531–2.135) | 0.860 |
| Fracture | 58 | 187 | 0.694 | (0.517–0.932) | 0.015 | 53 | 68 | 0.949 | (0.662–1.360) | 0.777 |
| New mycophenolate mofetil use | 33 | 87 | 0.826 | (0.553–1.233) | 0.348 | 30 | 36 | 1.000 | (0.615–1.625) | 0.999 |
| New rituximab use | 14 | 22 | 1.489 | (0.761–2.914) | 0.241 | 14 | 14 | 1.211 | (0.576–2.543) | 0.613 |

* The study population was limited to patients with at least two diagnostic records for SLE before the index date. CI, confidence interval; DPP4i, dipeptidyl peptidase-4 inhibitors; HR, hazard ratio; SGLT2i, sodium–glucose cotransporter 2 inhibitors; SLE, systemic lupus erythematosus; T2D, type 2 diabetes.



Ma et al. Arthritis & Rheumatology, 2025

# SGLT2i in real life: gliflozin vs gliflozin

***Kidney outcomes in patients with diabetes mellitus did not differ between individual sodium-glucose cotransporter-2 inhibitors.***

kidney INTERNATIONAL

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### *Cohort*

Retrospective study using the health check-up and claims database in Japan

12,100 individuals
- ✓ Diabetes mellitus
- ✓ Newly taking SGLT2 inhibitors

### *Methods*

Empagliflozin
vs.
Dapagliflozin
vs.
Canagliflozin
vs.
Other SGLT2-inhibitors

Mean follow-up of 773 days

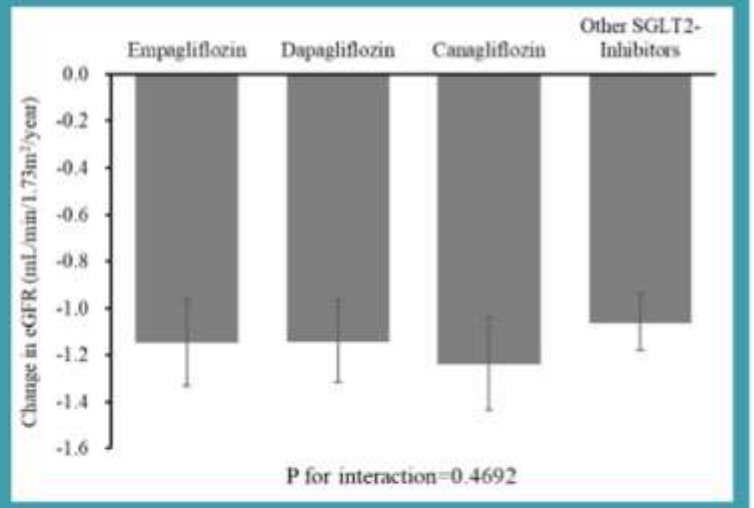
### *Outcomes*

**eGFR decline**

Annual eGFR slopes estimated using a linear mixed-effects model

### *Results*

Comparison of the change in eGFR among individual SGLT2 inhibitors



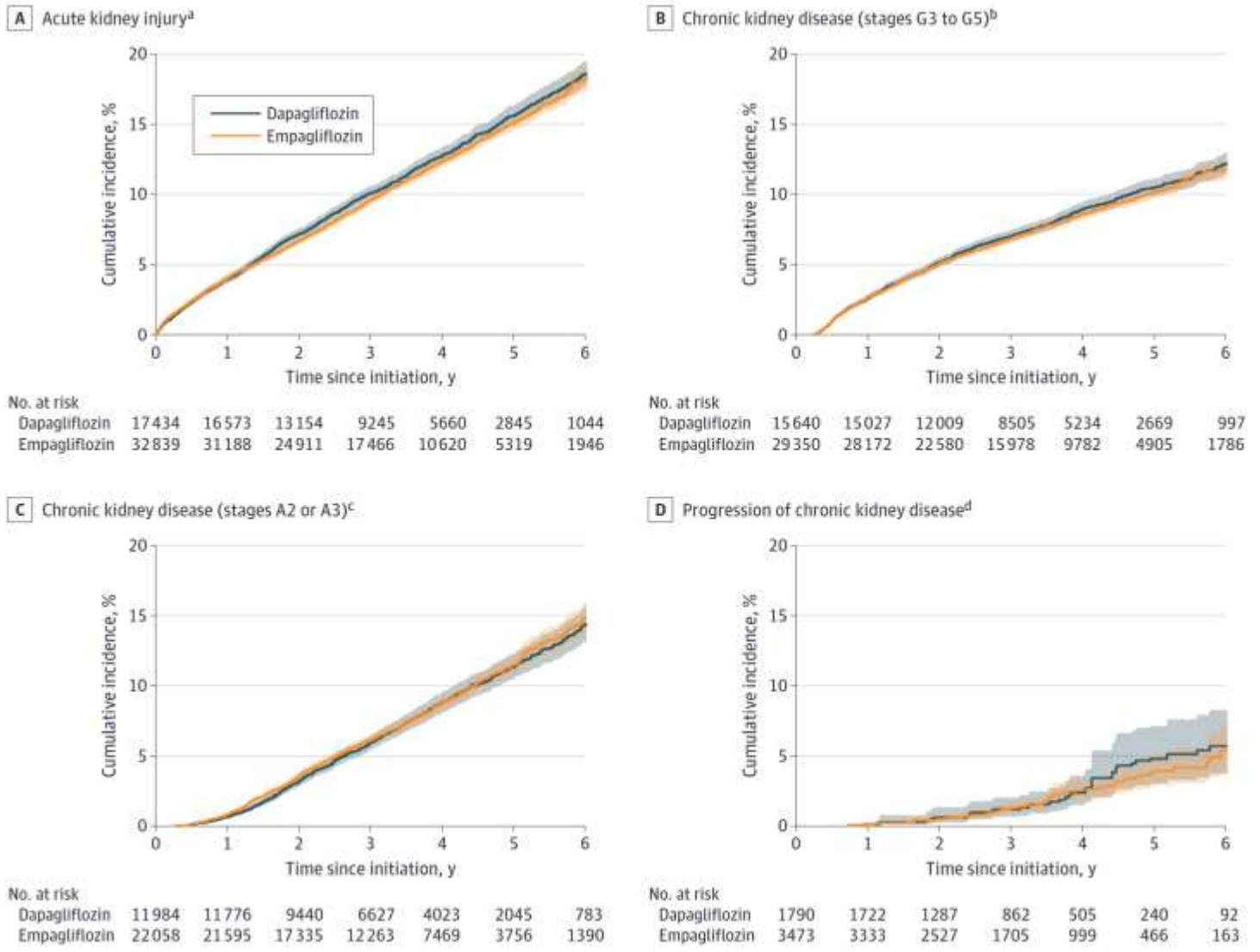

*Suzuki Y, et al. 2022*

**CONCLUSION:** Our analysis of a nationwide real-world dataset demonstrated that there was no significant difference in the annual eGFR changes between individual SGLT2 inhibitors.

# SGLT2i in real life: gliflozin vs gliflozin

Target trial emulation
Kidney outcomes in DT2
56 000 patients 62 ans
10% CKD 25% Albuminuria

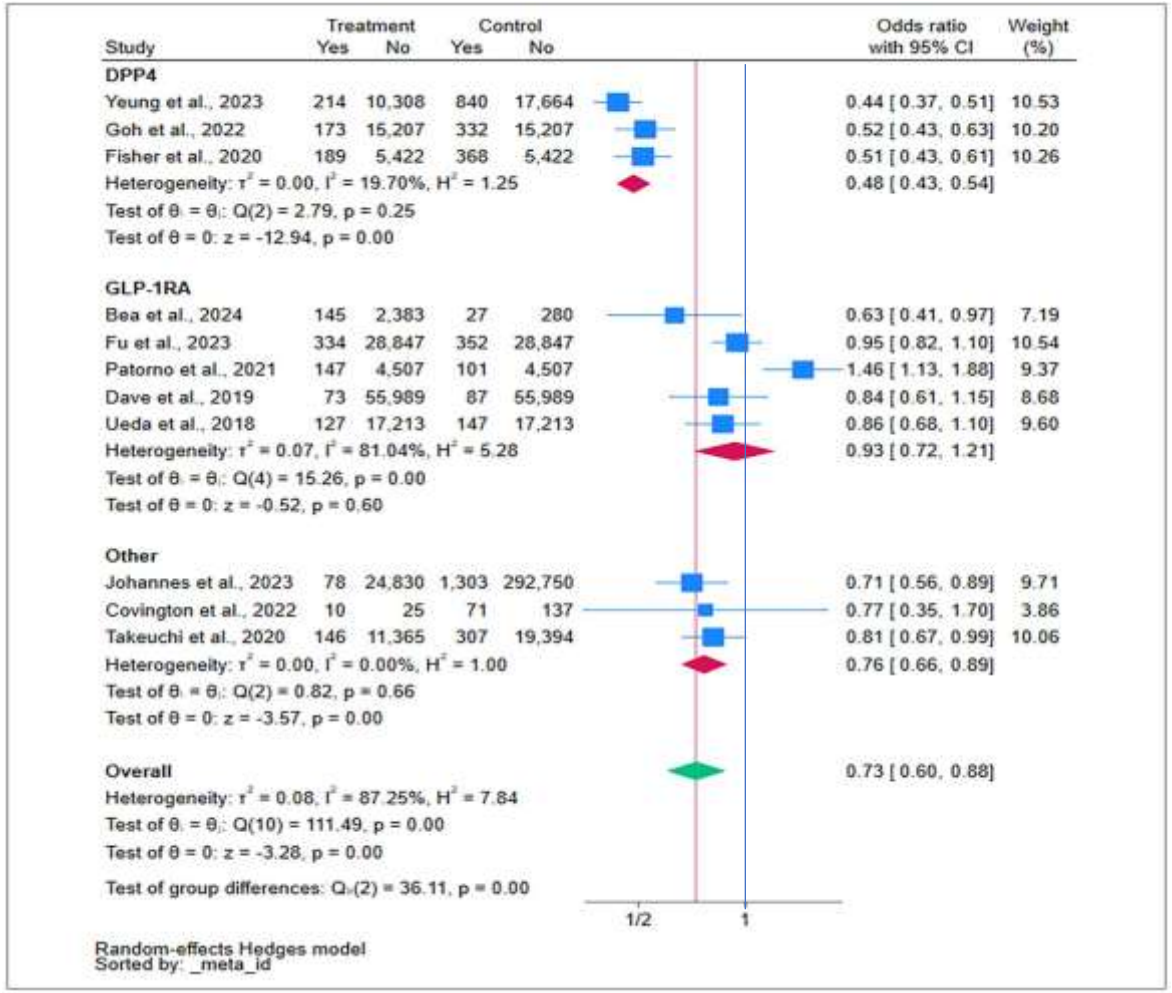
Bonnesen et al JAMA Intern Med 2025



# SGLT2i in real life: Urinary tract infection

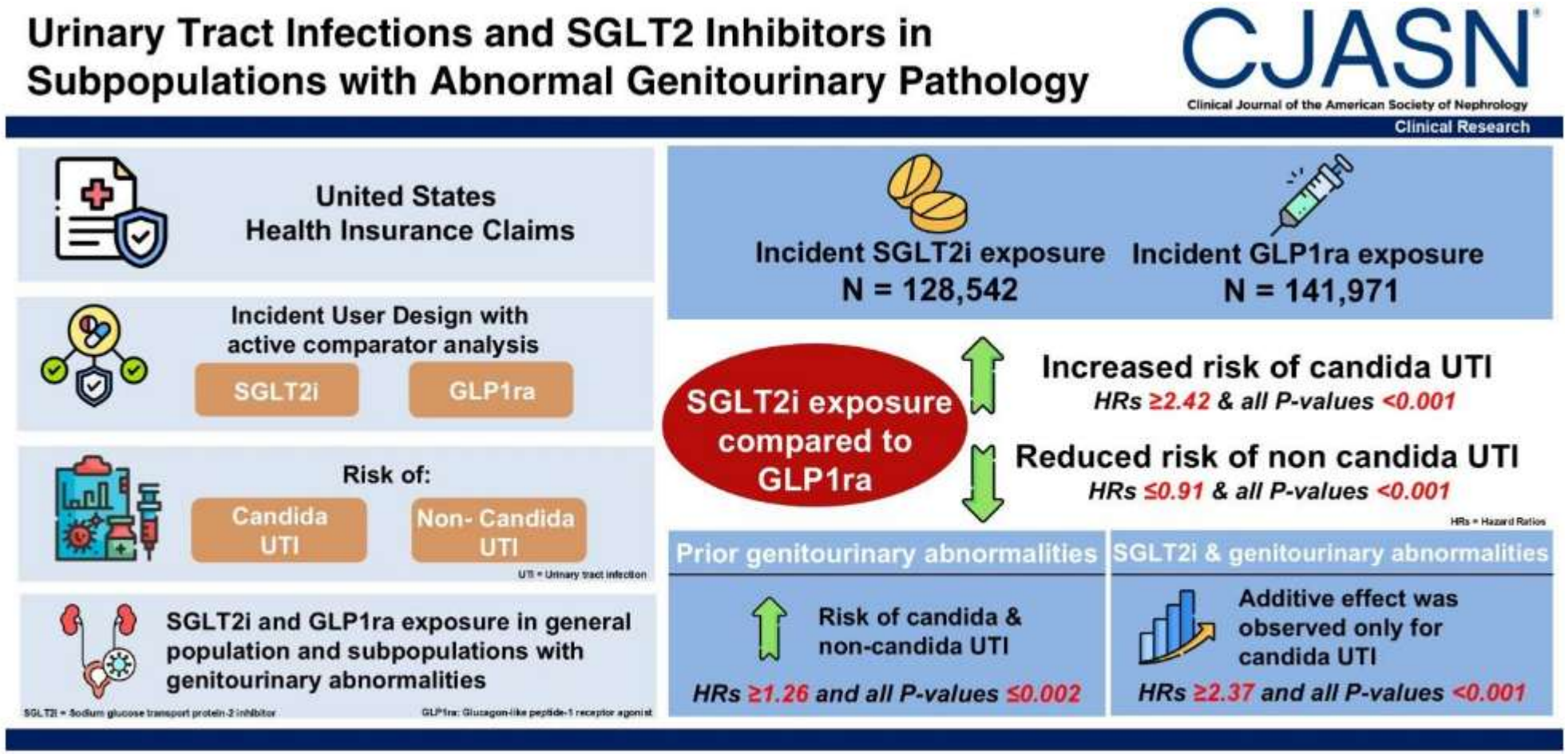
- Meta-Analysis of cohort studies, severe UTI (Hospitalisation, Pyelonephritis or urosepsis)


https://lectrr.be/nl/cartoon/urinary-infection/




Aboukaoud et Al. *Ann Pharmacother* (2025)

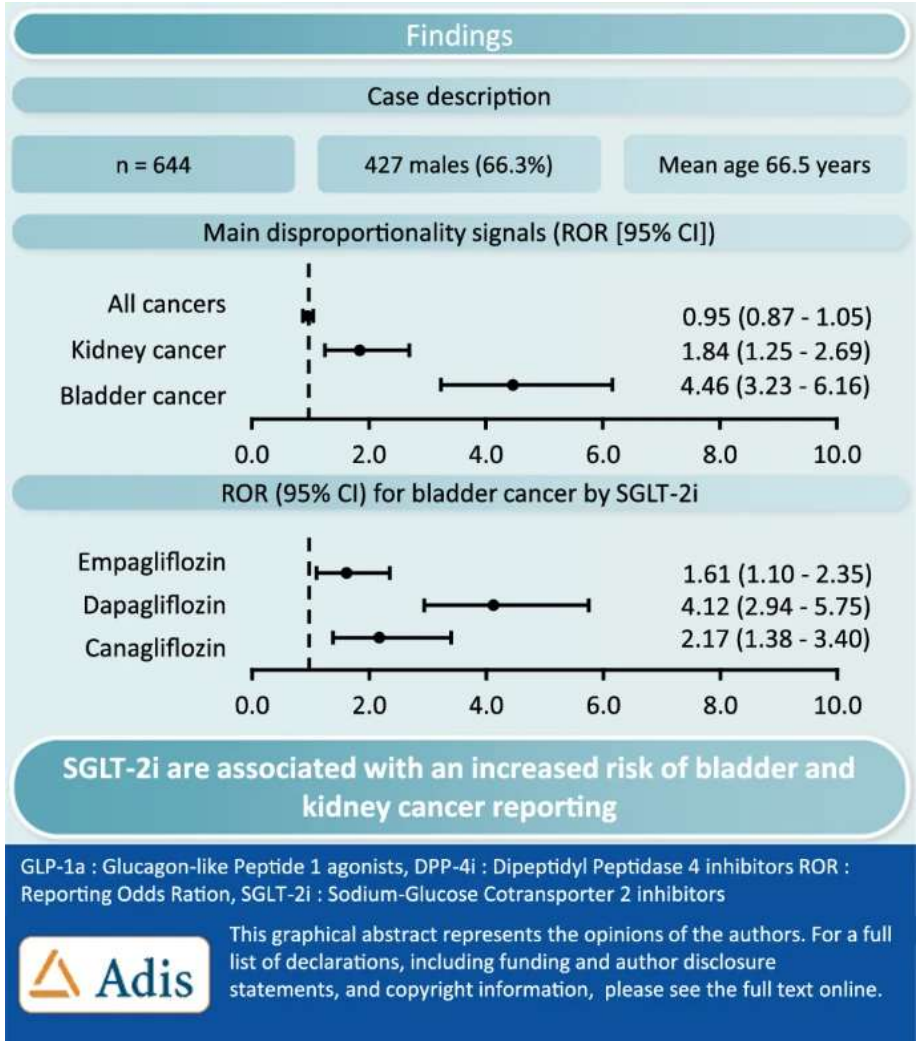
# SGLT2i in real life: Urinary tract infection




**Conclusions:** SGLT2i was associated with higher risk of candida UTI, but not non-candida UTI. Comparative risk of SGLT2i to GLP1ra of non-candida UTI was not higher with abnormal genitourinary abnormalities.

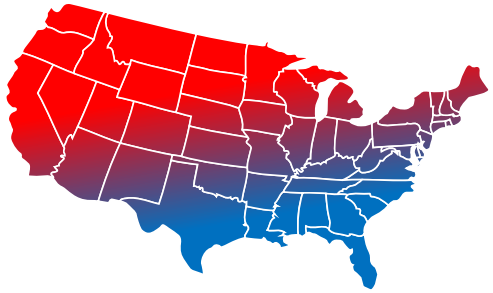
Jing Xu, Michael T. Eadon, Pengyue Zhang, et al. ***Risk of urinary tract infections with SGLT-2 inhibitors in subpopulations with abnormal genitourinary pathology***. CJASN DOI: 10.2215/CJN.0000000687.
**Visual abstract by Hector M. Madariaga, MD FASN**

# SGLT2i in real life: cancer risk

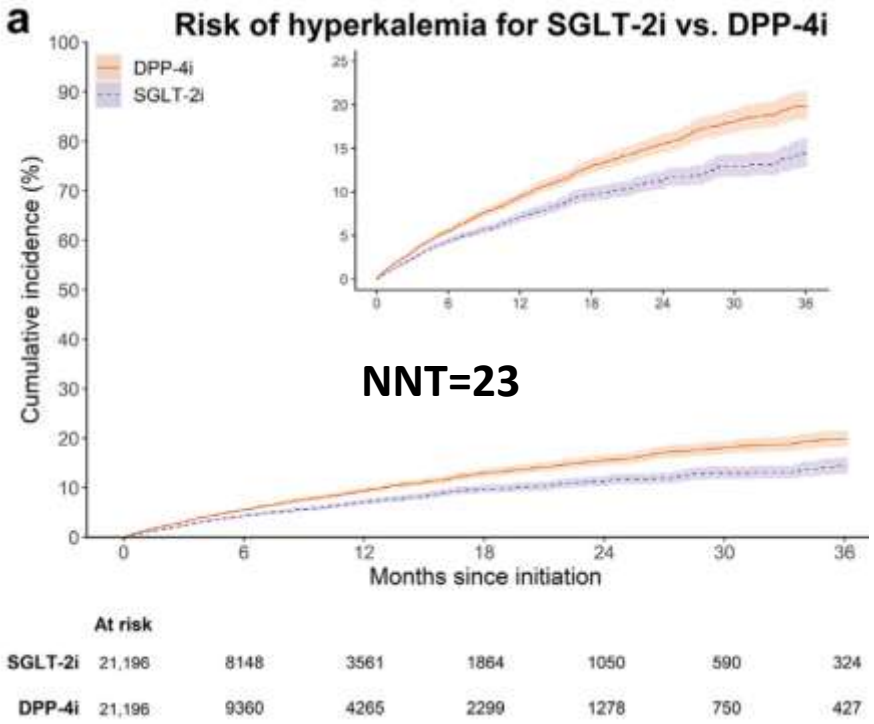

amU

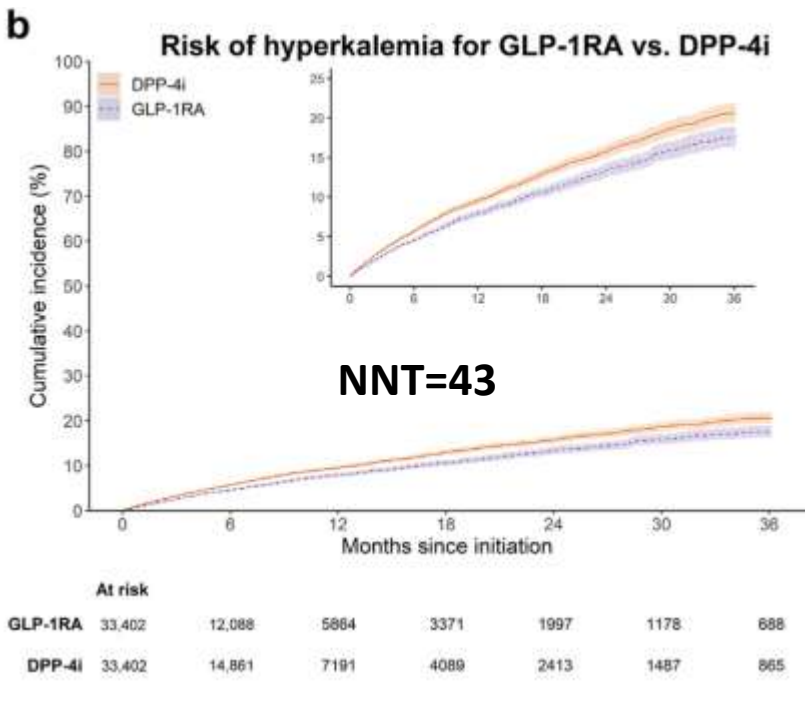
# SGLT2i in real life: hyperkalemia

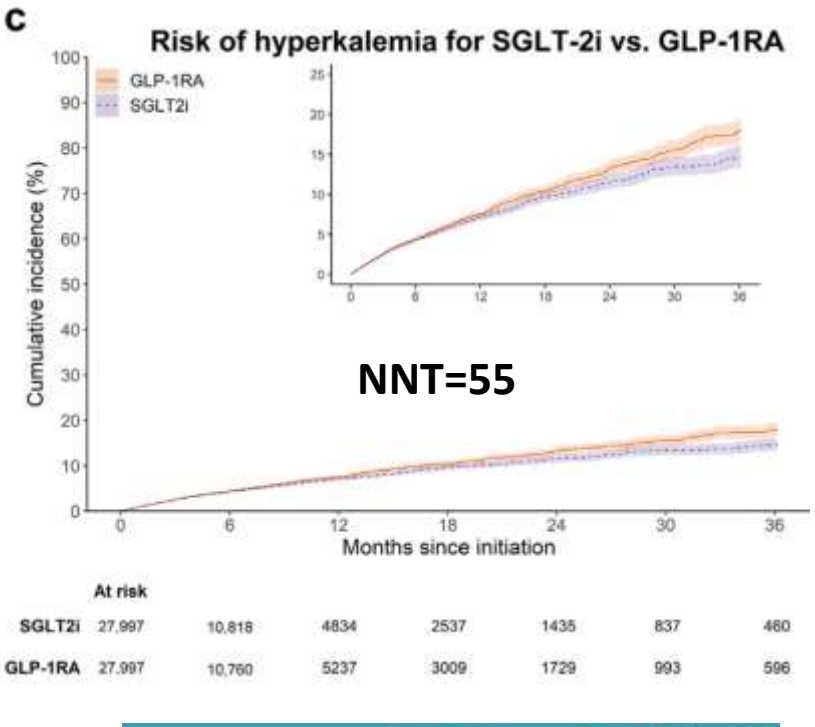


- CKD and Diabetes 2, Propensity score (140), HyperK diagnosis

Fu et al. Kidney International (2024) 105, 618–628



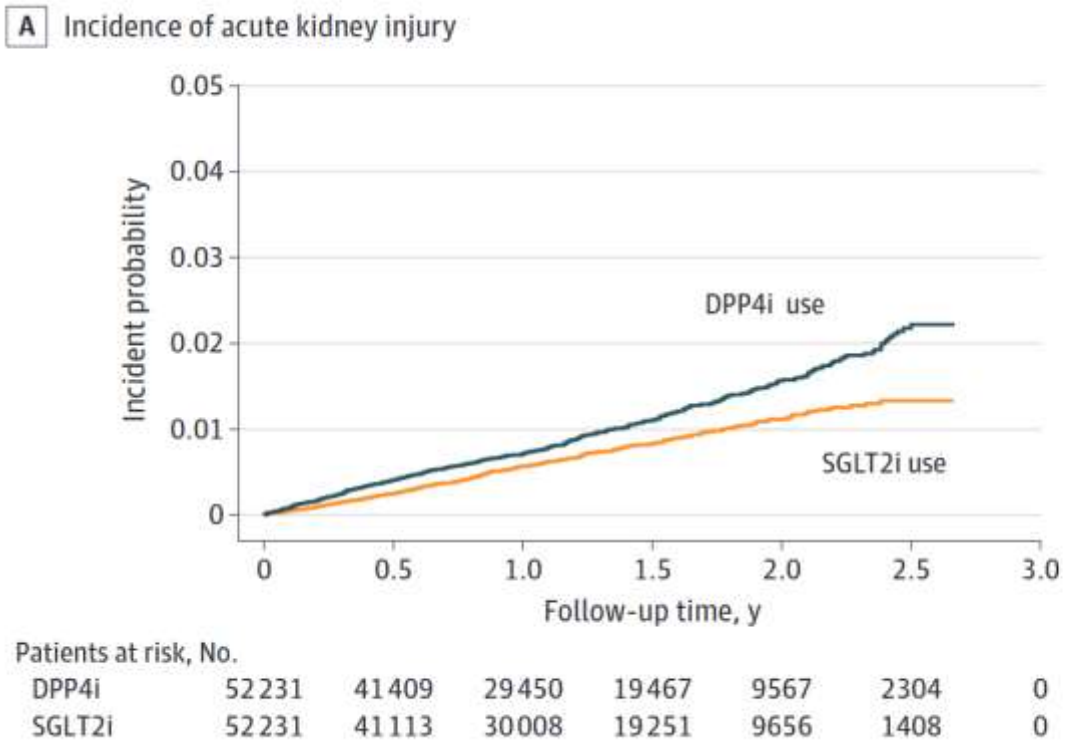

| | Hazard Ratio (95% CI) | 2-year absolute risk difference (95% CI) |
|---|---|---|
| SGLT-2i vs. DPP-4i (N = 42,392) | 0.74 (0.68-0.80) | -4.3% (-5.7% to -2.8%) |

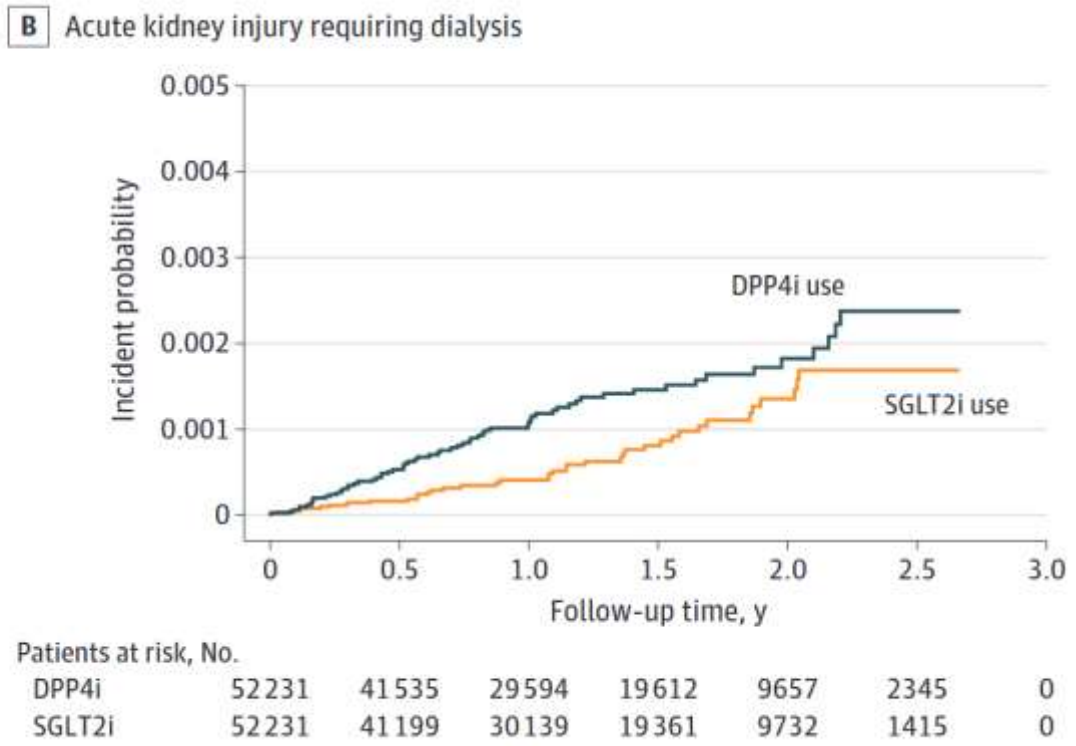
| | Hazard Ratio (95% CI) | 2-year absolute risk difference (95% CI) |
|---|---|---|
| GLP-1RA vs. DPP-4i (N = 66,804) | 0.80 (0.75-0.86) | -2.3% (-3.5% to -1.2%) |

| | Hazard Ratio (95% CI) | 2-year absolute risk difference (95% CI) |
|---|---|---|
| SGLT-2i vs. GLP-1RA (N = 55,994) | 0.92 (0.86-0.99) | -1.8% (-3.0% to -0.5%) |

# SGLT2i in real life: Before acute kidney injury

104 000 patients DT2, propensity score, 57 years-old, 9% CKD,
Primary outcome: AKI






Chung *et al. JAMA Netw Open* (2023).

# SGLT2i in real life: After acute kidney injury

**A cohort study of sodium-glucose cotransporter-2 inhibitors after acute kidney injury among Veterans with diabetic kidney disease.**

kidney INTERNATIONAL

ISN INTERNATIONAL SOCIETY OF NEPHROLOGY

***Cohort***

21,330 U.S. Veterans with baseline diabetes mellitus type 2 (DM2) and proteinuria and subsequent hospitalization with AKI after SGLT2i were introduced on Veterans Affairs formularies in 2016

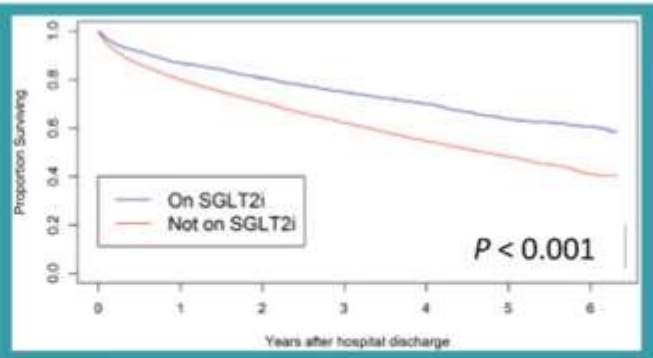
***Methods***

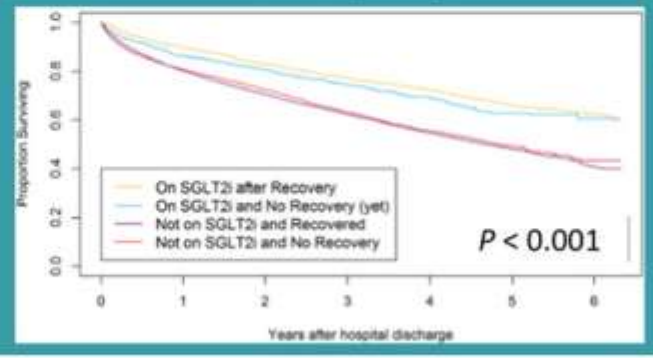
**Exposure**: time-varying initiation or resumption of SGLT2i after discharge from hospitalization with AKI

**Covariates**: time since hospital discharge and recovery from AKI

**Outcome**: all-cause mortality

***Outcomes***




Adjusted HR for post-AKI SGLT2i use vs. no use = 0.63 (95% CI: 0.58-0.68)

Adjusted HR for SGLT2i initiation after recovery* = 0.60 (95% CI: 0.54-0.67)

Adjusted HR for SGLT2i initiation before recovery* = 0.62 (95% CI: 0.55-0.71)

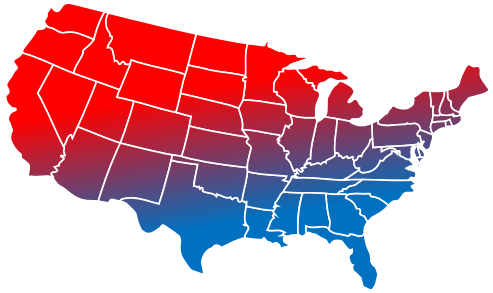
Multivariate model time-interaction $P = 0.19$

*** vs. neither SGLT2i nor recovery**

***Murphy, 2024***

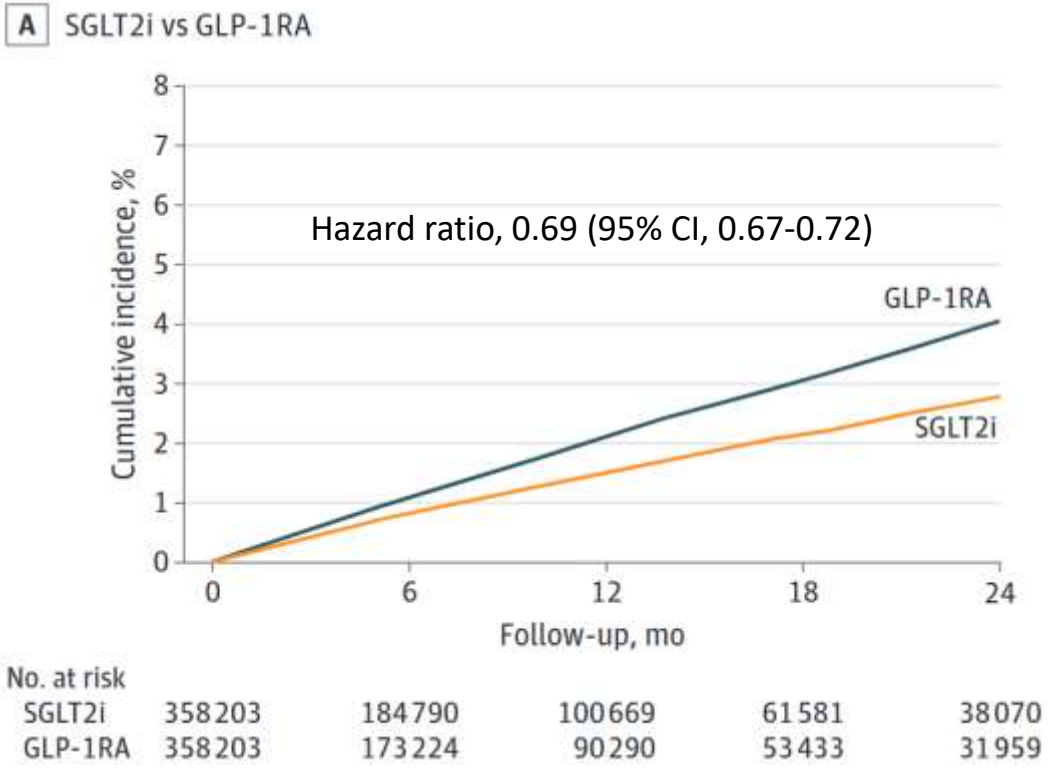
**CONCLUSION** ***We observed reduced mortality with SGLT2i use after AKI among Veterans with diabetic kidney disease whether started earlier or later or before or after recovery was observed.***

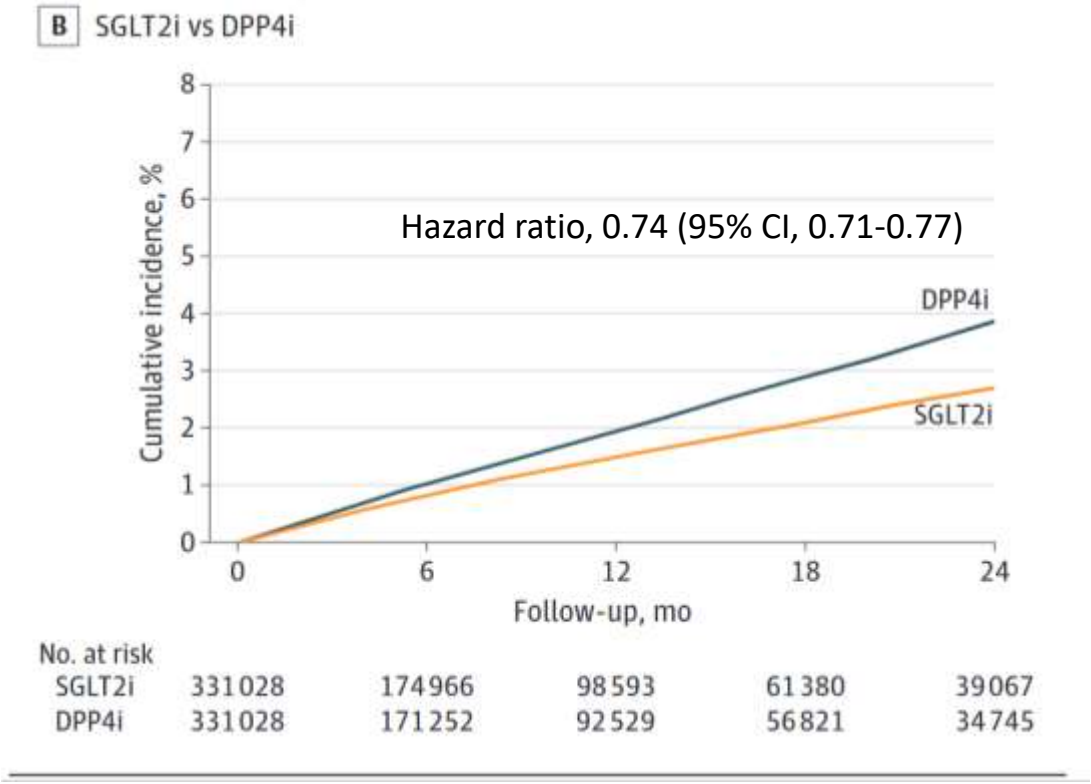
# SGLT2i in real life: nephrolithiasis



Diabetes 2, propension score, first event

Paik et al. JAMA Intern Med. 2024



# SGLT2i in real life: nephrolithiasis

## Nephrolithiasis, diabetes 2, Target trial emulation, prevention of recurrence

McCormick et al, BMJ, 2024

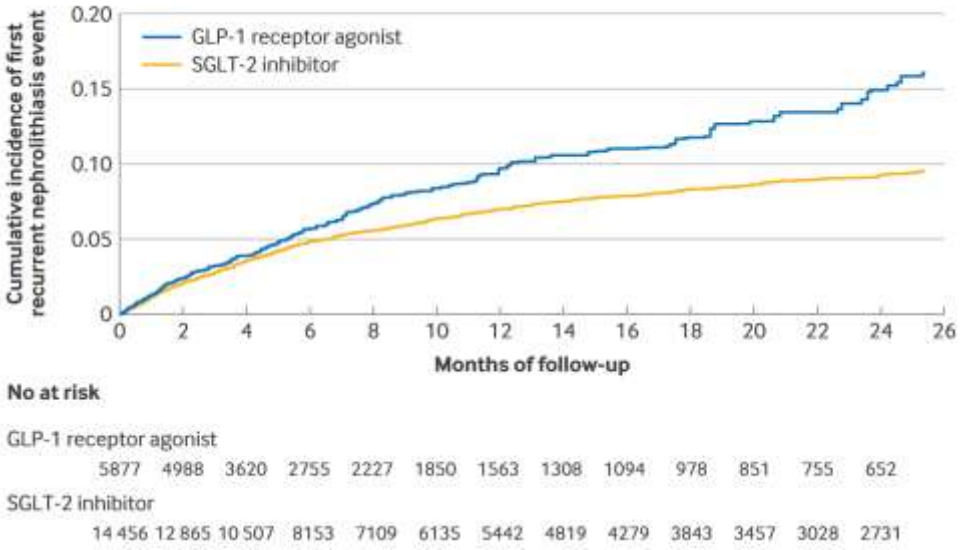



**Table 4 | Results for recurrent nephrolithiasis counts and recurrent gout flare-up counts among patients with nephrolithiasis, type 2 diabetes, and gout initiating an SGLT-2 inhibitor versus GLP-1 receptor agonist or DPP-4 inhibitor, after inverse probability weighting**

| | SGLT-2 inhibitor | GLP-1 receptor agonist | SGLT-2 inhibitor | DPP-4 inhibitor |
|---|---|---|---|---|
| **Recurrent nephrolithiasis** | | | | |
| No of patients | 3159 | 1272 | 2668 | 2028 |
| No of events | 479 | 218 | 418 | 439 |
| Mean follow-up (years) | 1.24 | 0.98 | 1.38 | 1.24 |
| Incidence rate per 1000 person years | 122.4 | 174.1 | 113.5 | 175.0 |
| Rate ratio (95% CI) | 0.67 (0.57 to 0.79) | 1.0 (reference) | 0.63 (0.55 to 0.72) | 1.0 (reference) |
| Rate difference (95% CI) | −53 (−78 to −27) | Reference | −62 (−81 to −42) | Reference |
| NNT (95% CI) | 19 (13 to 37) | Reference | 16 (12 to 24) | Reference |
| **Recurrent gout flare-up** | | | | |
| No of patients | 3159 | 1272 | 2668 | 2028 |
| No of events | 161 | 71 | 149 | 154 |
| Mean follow-up (years) | 1.24 | 0.98 | 1.38 | 1.24 |
| Incidence rate per 1000 person years | 41.0 | 57.1 | 40.5 | 61.5 |
| Rate ratio (95% CI) | 0.72 (0.54 to 0.95) | 1.0 (reference) | 0.65 (0.52 to 0.82) | 1.0 (reference) |
| Rate difference (95% CI) | −16 (−31 to −1) | Reference | −21 (−33 to −9) | Reference |
| NNT (95% CI) | 63 (32 to 1000) | Reference | 48 (30 to 111) | Reference |

CI=confidence interval; DPP-4=dipeptidyl peptidase-4; GLP-1=glucagon-like peptide-1; NNT=number needed to treat; SGLT-2=sodium-glucose cotransporter-2.

# SGLT2i in real life: nephrolithiasis

## Meta-analysis

Kanby et al. Nephrol Dial Transplant, 2025

| | SGLT2i | | Active control or placebo | | | Odds Ratio |
|---|---|---|---|---|---|---|
| Study or Subgroup | Events | Total | Events | Total | Weight | M-H, Random, 95% CI |
| Anan, 2023 | 155 | 16522 | 158866 | 10179104 | 27.1% | 0.60 [0.51, 0.70] |
| Balasubramanian, 2022 | 104 | 10177 | 79 | 4904 | 17.1% | 0.63 [0.47, 0.85] |
| Kristensen, 2021 | 58 | 12325 | 108 | 12325 | 15.6% | 0.53 [0.39, 0.74] |
| McMurray, 2019 | 1 | 2368 | 1 | 2368 | 0.4% | 1.00 [0.06, 16.00] |
| Paik, 2024 | 9108 | 689231 | 11903 | 689231 | 35.3% | 0.76 [0.74, 0.78] |
| Wiviott, 2019 | 12 | 8574 | 16 | 8569 | 4.5% | 0.75 [0.35, 1.58] |
| **Total (95% CI)** | | **739197** | | **10896501** | **100.0%** | **0.65 [0.55, 0.77]** |
| Total events | 9438 | | 170973 | | | |

Heterogeneity: $Tau^2 = 0.02$; $Chi^2 = 14.79$, df = 5 (P = 0.01); $I^2 = 66\%$

Test for overall effect: Z = 4.93 (P < 0.00001)

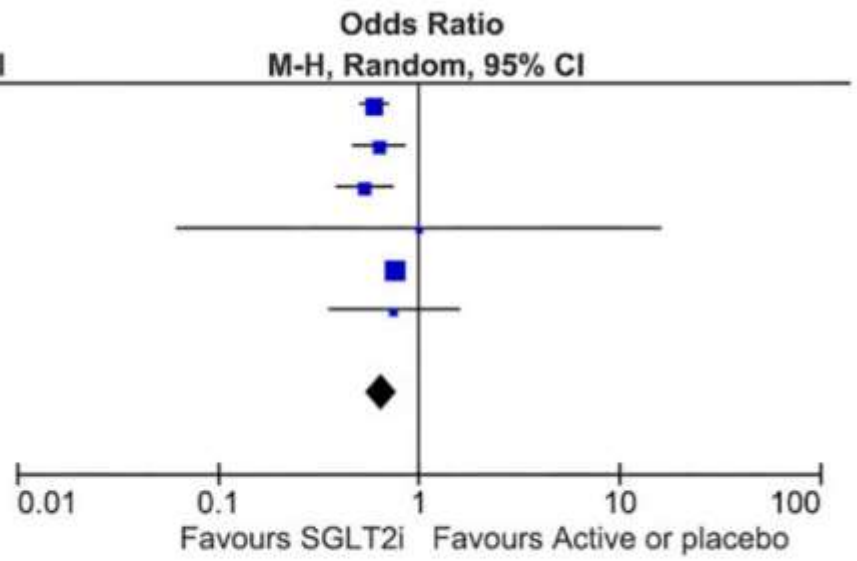
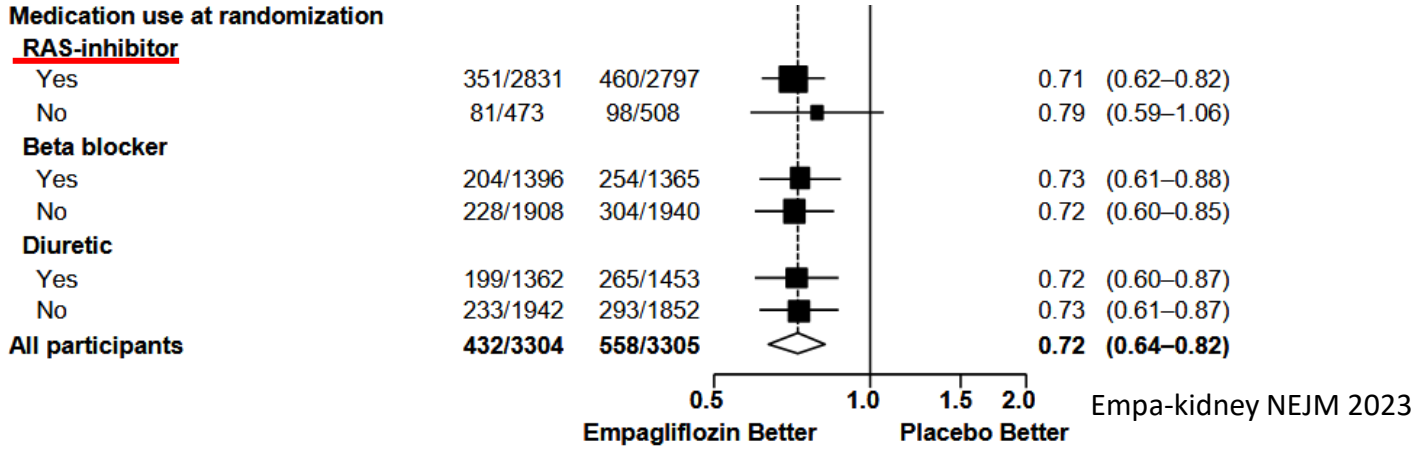



**Figure 1:** Risk of nephrolithiasis in the SGLT2i group compared with the control group (active control, placebo or no therapy).

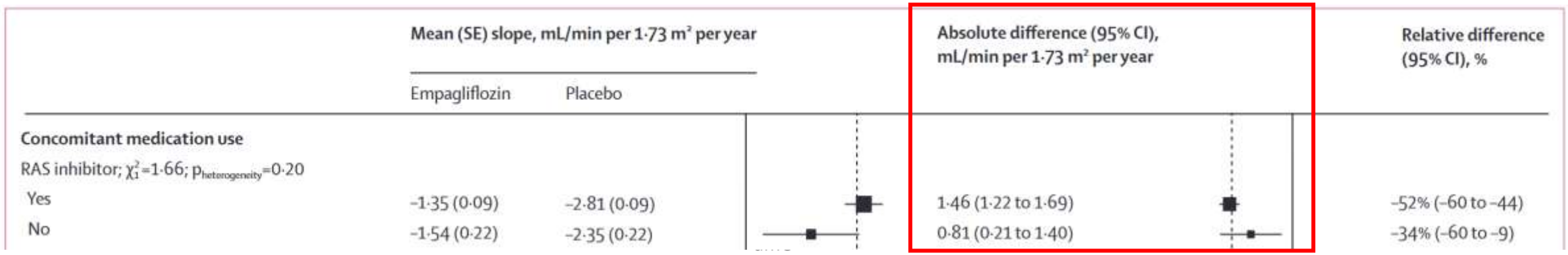
# SGLT2i combination: RASi

The evidence for the efficacy of iSGLT2 in CKD is based on RCT in which 85% to 99.9% of patients were using RASi.

Critère principal: diminution du DFGe >40%+IRCT+Mort cause rénale ou CV, suivi médian de 2 ans



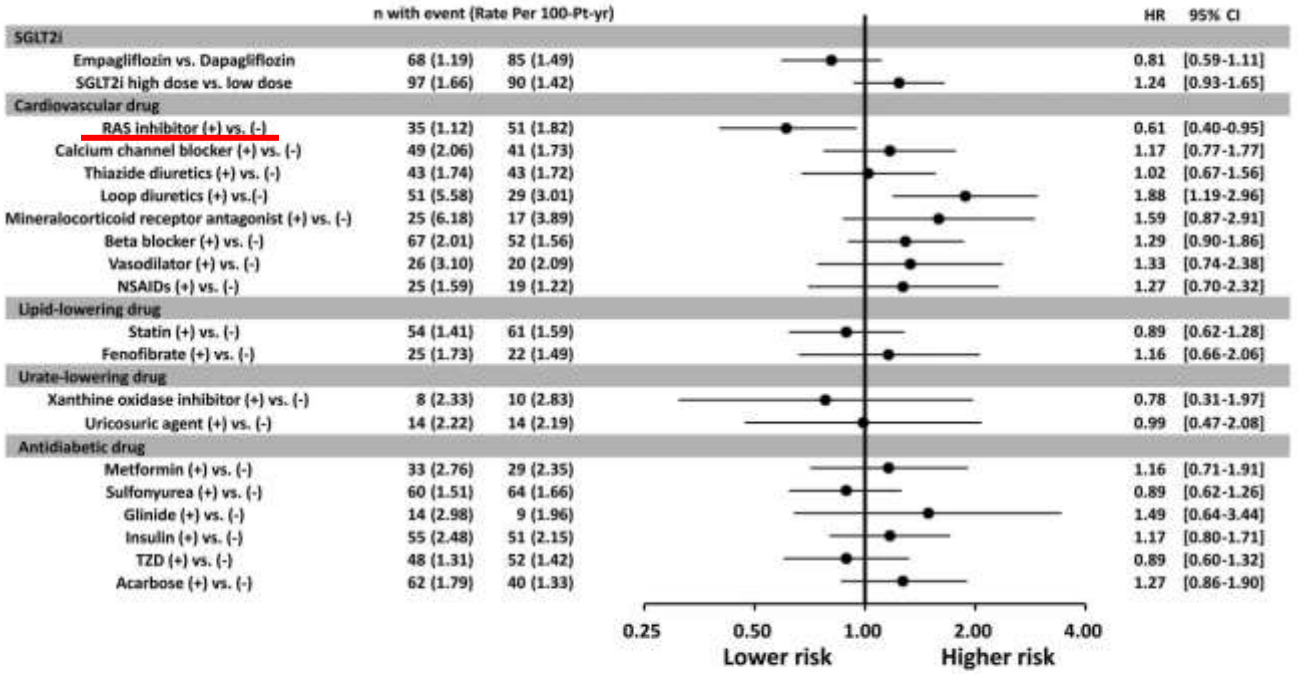

Empa-kidney NEJM 2023




Staplin, N. *et al.*. *The Lancet Diabetes & Endocrinology* 2024

# SGLT2i combination: RASi and cohorts

Cohort 10000 patients DT2, MAKE as primary outcome, eGFR: 92, Alb: 250mg/g



| | n with event (Rate Per 100-Pt-yr) | | HR | 95% CI |
|---|---|---|---|---|
| **SGLT2i** | | | | |
| Empagliflozin vs. Dapagliflozin | 68 (1.19) | 85 (1.49) | 0.81 | [0.59-1.11] |
| SGLT2i high dose vs. low dose | 97 (1.66) | 90 (1.42) | 1.24 | [0.93-1.65] |
| **Cardiovascular drug** | | | | |
| RAS inhibitor (+) vs. (-) | 35 (1.12) | 51 (1.82) | 0.61 | [0.40-0.95] |
| Calcium channel blocker (+) vs. (-) | 49 (2.06) | 41 (1.73) | 1.17 | [0.77-1.77] |
| Thiazide diuretics (+) vs. (-) | 43 (1.74) | 43 (1.72) | 1.02 | [0.67-1.56] |
| Loop diuretics (+) vs.(-) | 51 (5.58) | 29 (3.01) | 1.88 | [1.19-2.96] |
| Mineralocorticoid receptor antagonist (+) vs. (-) | 25 (6.18) | 17 (3.89) | 1.59 | [0.87-2.91] |
| Beta blocker (+) vs. (-) | 67 (2.01) | 52 (1.56) | 1.29 | [0.90-1.86] |
| Vasodilator (+) vs. (-) | 26 (3.10) | 20 (2.09) | 1.33 | [0.74-2.38] |
| NSAIDs (+) vs. (-) | 25 (1.59) | 19 (1.22) | 1.27 | [0.70-2.32] |
| **Lipid-lowering drug** | | | | |
| Statin (+) vs. (-) | 54 (1.41) | 61 (1.59) | 0.89 | [0.62-1.28] |
| Fenofibrate (+) vs. (-) | 25 (1.73) | 22 (1.49) | 1.16 | [0.66-2.06] |
| **Urate-lowering drug** | | | | |
| Xanthine oxidase inhibitor (+) vs. (-) | 8 (2.33) | 10 (2.83) | 0.78 | [0.31-1.97] |
| Uricosuric agent (+) vs. (-) | 14 (2.22) | 14 (2.19) | 0.99 | [0.47-2.08] |
| **Antidiabetic drug** | | | | |
| Metformin (+) vs. (-) | 33 (2.76) | 29 (2.35) | 1.16 | [0.71-1.91] |
| Sulfonyurea (+) vs. (-) | 60 (1.51) | 64 (1.66) | 0.89 | [0.62-1.26] |
| Glinide (+) vs. (-) | 14 (2.98) | 9 (1.96) | 1.49 | [0.64-3.44] |
| Insulin (+) vs. (-) | 55 (2.48) | 51 (2.15) | 1.17 | [0.80-1.71] |
| TZD (+) vs. (-) | 48 (1.31) | 52 (1.42) | 0.89 | [0.60-1.32] |
| Acarbose (+) vs. (-) | 62 (1.79) | 40 (1.33) | 1.27 | [0.86-1.90] |



**Figure 3. Risk of composite kidney outcomes (two-fold increase in the serum creatinine level or the development of end-stage kidney disease) among patients with type 2 diabetes after SGLT2i treatment receiving or not receiving a specific background medication.**

Chan et al. CJASN 2025

A propensity score analysis SGLT2i vs RASi, 7000 patients, MAKE as primary outcome, 70% CKD3, one major concern not albuminuria

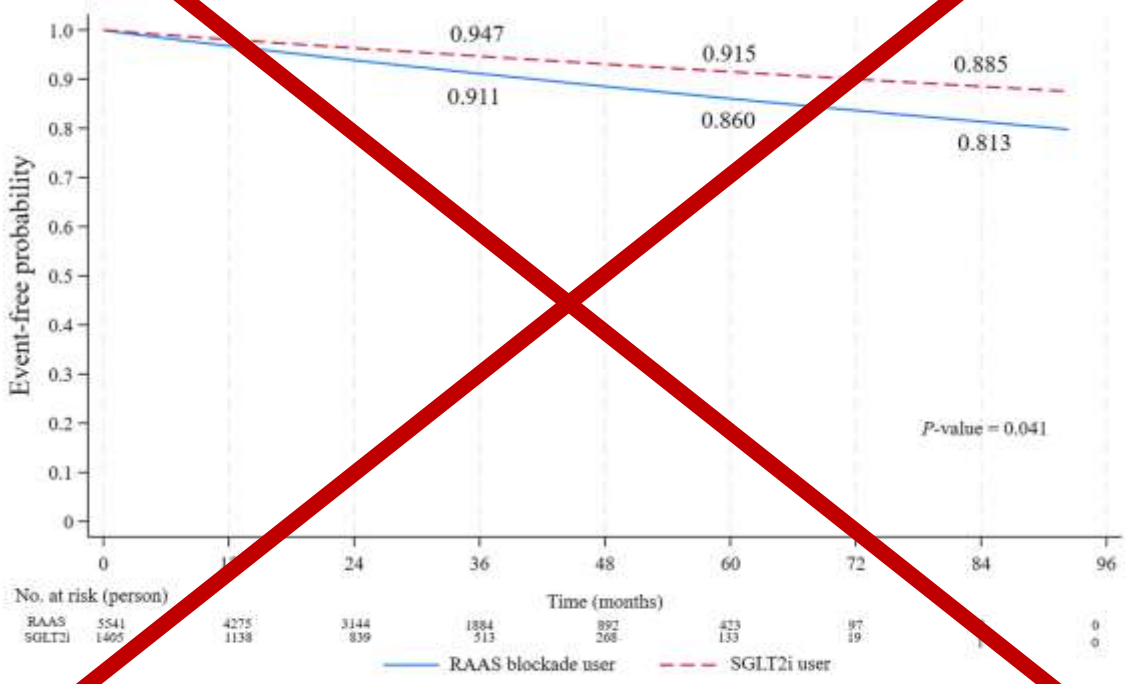
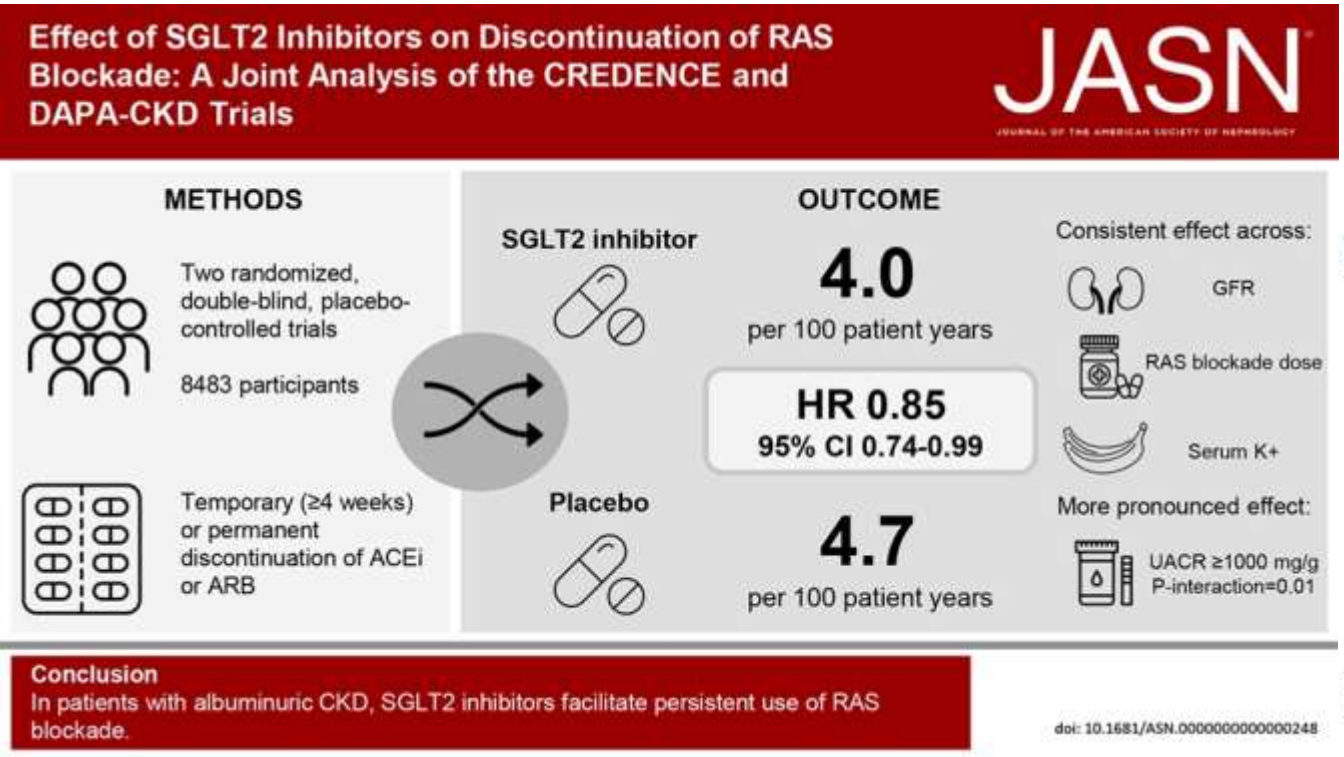



**Fig. 2.** Event-free probability curves for composite major adverse kidney events over time in SGLT2i and RAAS blockade users.

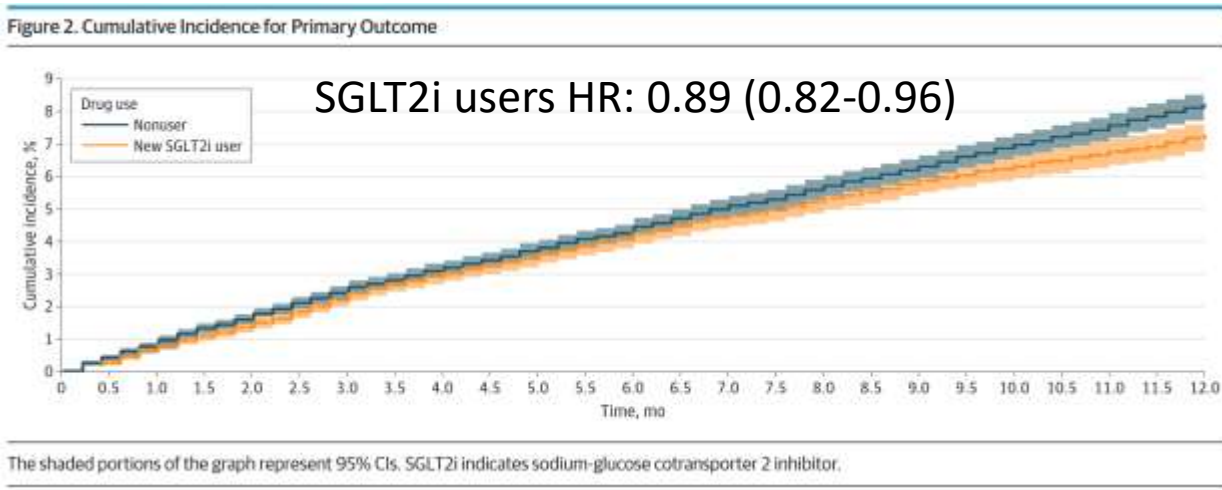
Hunsuwan et al. Scientific reports 2025

# SGLT2i combination: RASi discontinuation




Cohort ajustement IPTW, 40 000 patients with RASi, 30% eGFR<60 4 mesures de K et Creat.
Primary: HyperK>5.5 or code

Discontinuation RASi 36% in SGLT2i users vs 45% non users




SGLT2i users HR: 0.89 (0.82-0.96)

Wing et al. JAMA Intern Med 2025

# SGLT2i combination: GLP-1 RA+SGLT2i

meta-analysis of randomised controlled trials SGLT2i, with or without GLP-1 RA

| | Events/patients (%) | | Event rate per 100 patient years | | HR (95% CI) |
|---|---|---|---|---|---|
| | SGLT2 inhibitor | Placebo | SGLT2 inhibitor | Placebo | |
| **Baseline use of GLP-1 receptor agonist** | | | | | |
| High atherosclerotic cardiovascular risk trials | 14/936 (1·5%) | 17/693 (2·5%) | 0·4 | 1·0 | 0·60 (0·27–1·31) |
| Stable heart failure trials | 3/47 (6·4%) | 3/33 (9·1%) | 2·2 | 4·7 | 0·64 (0·13–3·12) |
| Chronic kidney disease trials | 40/635 (6·3%) | 53/640 (8·3%) | 3·2 | 4·5 | 0·67 (0·44–1·02) |
| Subtotal ($I^2$=0·0%, p=0·64) | 57/1618 (3·5%) | 73/1366 (5·3%) | 1·6 | 2·8 | 0·65 (0·46–0·94) |
| **No baseline use of GLP-1 receptor agonist** | | | | | |
| High atherosclerotic cardiovascular risk trials | 469/23585 (2·0%) | 526/17302 (3·0%) | 0·6 | 1·3 | 0·59 (0·52–0·67) |
| Stable heart failure trials | 235/4781 (4·9%) | 231/4798 (4·8%) | 2·9 | 3·1 | 1·02 (0·85–1·22) |
| Chronic kidney disease trials | 688/9839 (7·0%) | 1015/9817 (10·3%) | 3·7 | 5·6 | 0·64 (0·58–0·71) |
| Subtotal ($I^2$=70·4%, p<0·001) | 1392/38205 (3·6%) | 1772/31917 (5·6%) | 1·7 | 2·9 | 0·67 (0·62–0·72) |
| Total | 1449/39823 (3·6%) | 1845/33283 (5·5%) | 1·7 | 2·9 | 0·67 (0·62–0·72) |
| **Heterogeneity by use of GLP-1 receptor agonist: p=0·81** | | | | | |

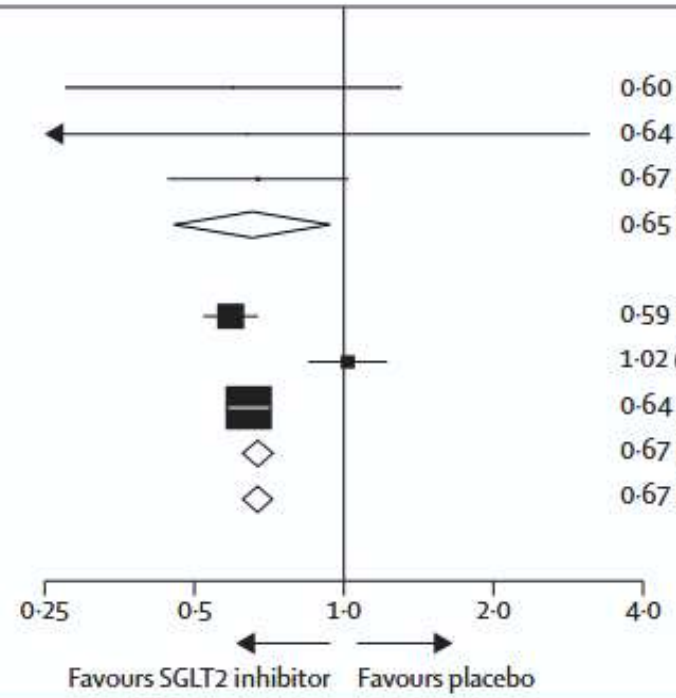


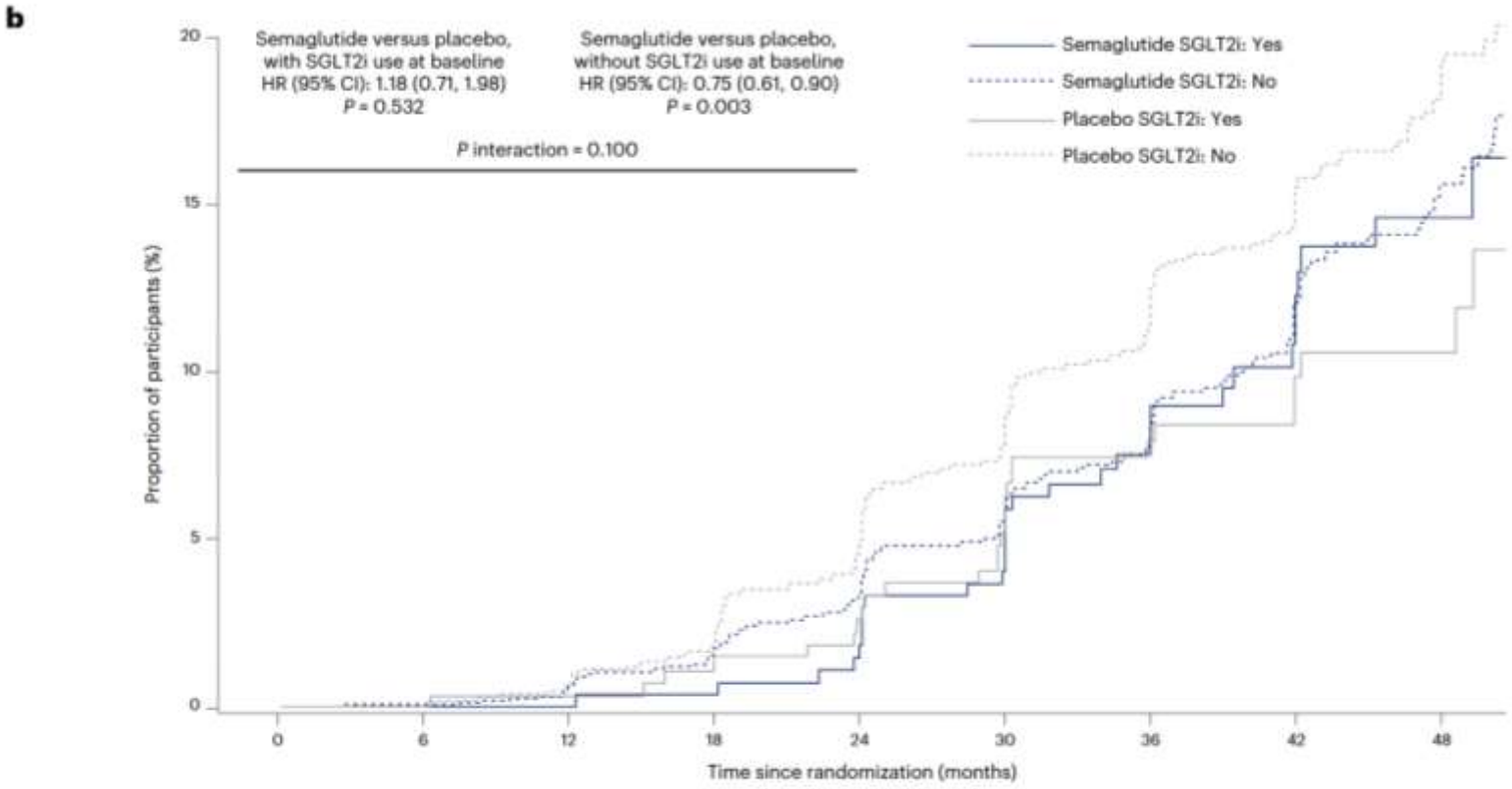

***Figure 3:*** **Effect of SGLT2 inhibitors on chronic kidney disease progression (≥40% decline in estimated glomerular filtration rate, kidney failure, or death due to kidney failure), with and without the use of GLP-1 receptor agonists at baseline**

HR=hazard ratio.

Apperloo et al. Lancet Diabetes Endocrinol 2024

# SGLT2i combination: SGLT2i+GLP-1 RA

Flow RCT analysis semaglutide vs placebo with or without SGLT2i.
Primary outcome kidney failure + ≥50% eGFR reduction +kidney death +CV death




Flow nature med 2024

# SGLT2i combination: GLP-1 RA

Analyse de cohorte, trial emulation DT2, Age: 57 years, CKD 10%, RASi 70%, serious renal events: AKI, CKD,, kidney failure, and renal complications of diabetes

**Table 2 | Hazard ratios for primary and secondary outcomes comparing GLP-1 receptor agonist-SGLT-2 inhibitor combination with GLP-1 receptor agonist use alone**

| Exposure | No of patients | Events | Person years | Incidence rate (95% CI)* | Hazard ratio (95% CI)† |
|---|---|---|---|---|---|
| **Primary outcomes** | | | | | |
| MACE: | | | | | |
| GLP-1 RAs | 6696 | 113 | 10971 | 10.3 (8.5 to 12.4) | 1.00 (reference) |
| GLP-1 RA-SGLT-2 inhibitor combination | 6696 | 45 | 6417 | 7.0 (5.1 to 9.4) | 0.70 (0.49 to 0.99) |
| Serious renal events: | | | | | |
| GLP-1 RAs | 6696 | 51 | 10992 | 4.6 (3.5 to 6.1) | 1.00 (reference) |
| GLP-1 RA-SGLT-2 inhibitor combination | 6696 | 13 | 6453 | 2.0 (1.1 to 3.4) | 0.43 (0.23 to 0.80) |

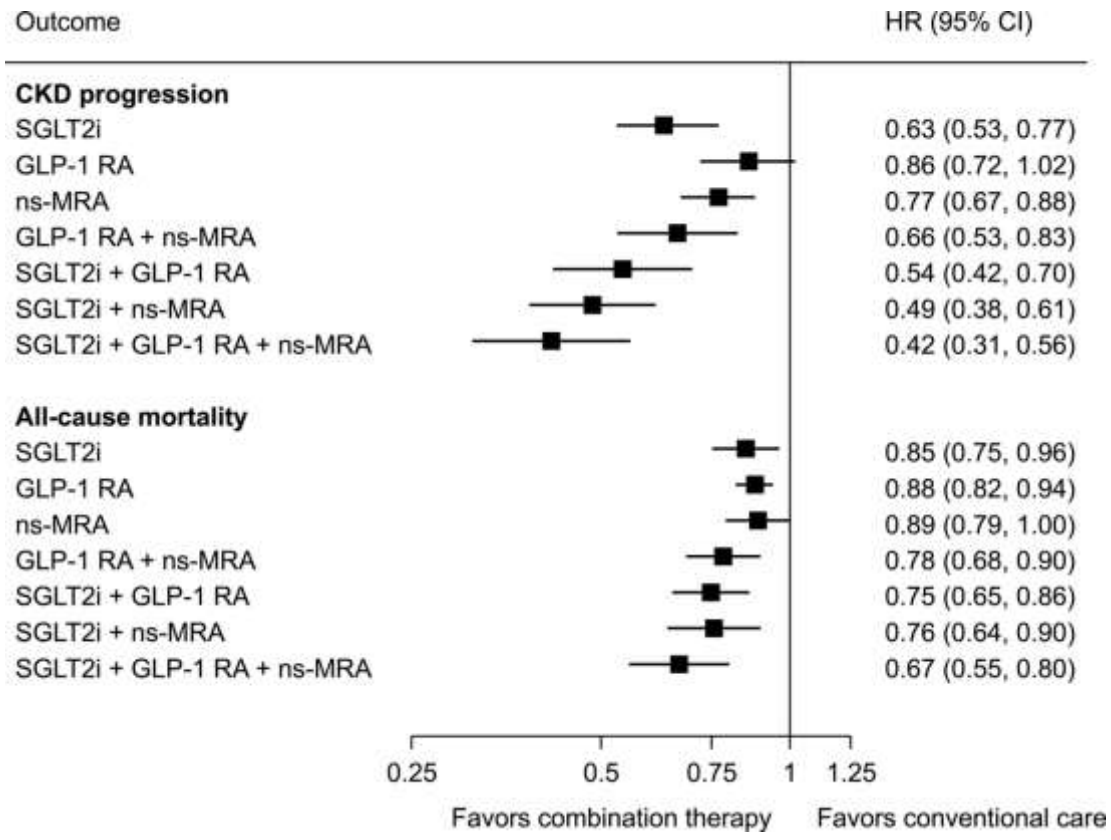
**Table 4 | Hazard ratios for primary and secondary outcomes comparing GLP-1 receptor agonist-SGLT-2 inhibitor combination with SGLT-2 inhibitor use alone**

| Exposure | No of patients | Events | Person years | Incidence rate (95% CI)* | Hazard ratio (95% CI)† |
|---|---|---|---|---|---|
| **Primary outcomes** | | | | | |
| MACE: | | | | | |
| SGLT-2 inhibitor | 8942 | 141 | 13160 | 10.7 (9.0 to 12.6) | 1.00 (reference) |
| SGLT-2 inhibitor-GLP-1 RA combination | 8942 | 55 | 7250 | 7.6 (5.7 to 9.9) | 0.71 (0.52 to 0.98) |
| Serious renal events: | | | | | |
| SGLT-2 inhibitor | 8942 | 26 | 13243 | 2.0 (1.3 to 2.9) | 1.00 (reference) |
| SGLT-2 inhibitor-GLP-1 RA combination | 8942 | 10 | 7278 | 1.4 (0.7 to 2.5) | 0.67 (0.32 to 1.41) |

Simms-Williams BMJ 2024

amU

Analyse d'essais randomisés

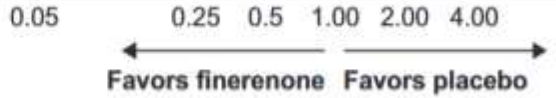



Neuen et al. Circulation 2024

# SGLT2i combination: ns-MRA

Fidelity posthoc analysis, DT2,  Kidney primary outcome: kidney failure + sustained ‡57% eGFR decline + renal death.
Better eGFR in SGLT2i group (9 ml/mn)

| | 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

# SGLT2i combination: ns-MRA

Cohort study analysing combination in CKD, DT2 89%, eGFR>45 75-80% Age : 66 ans ACR ?, Primary outcome MAKE: stage 5 CKD, ESRD

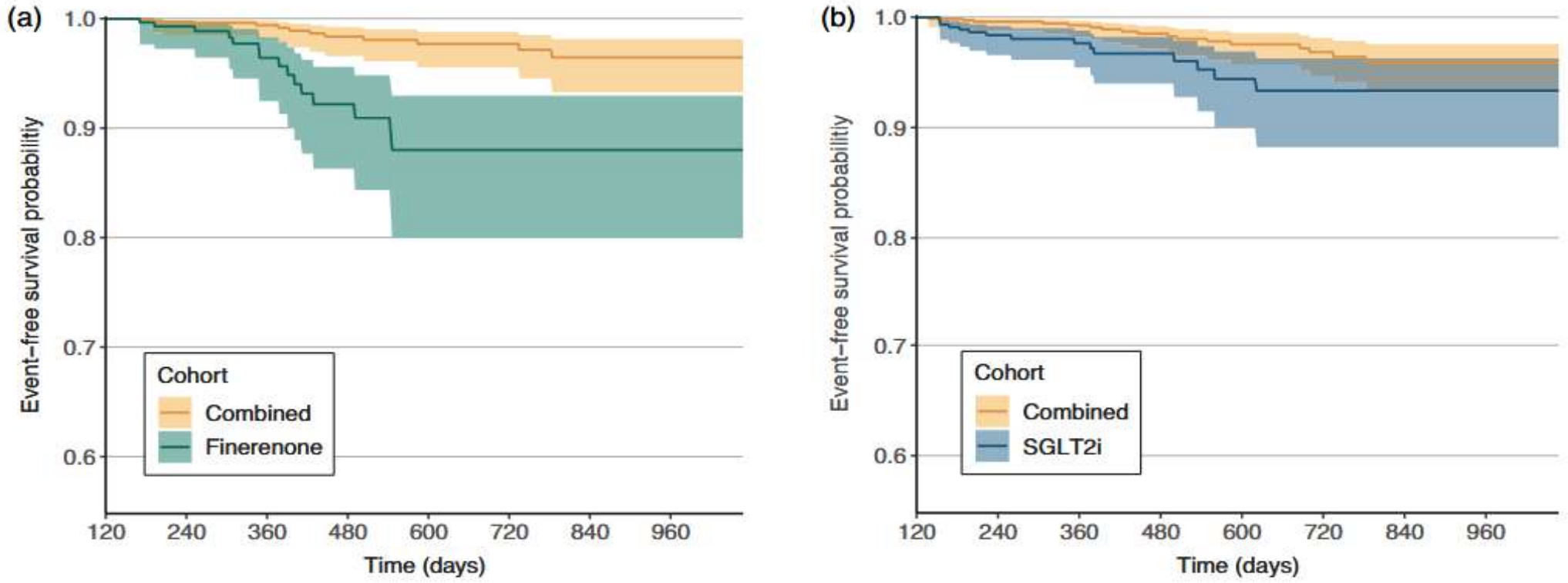
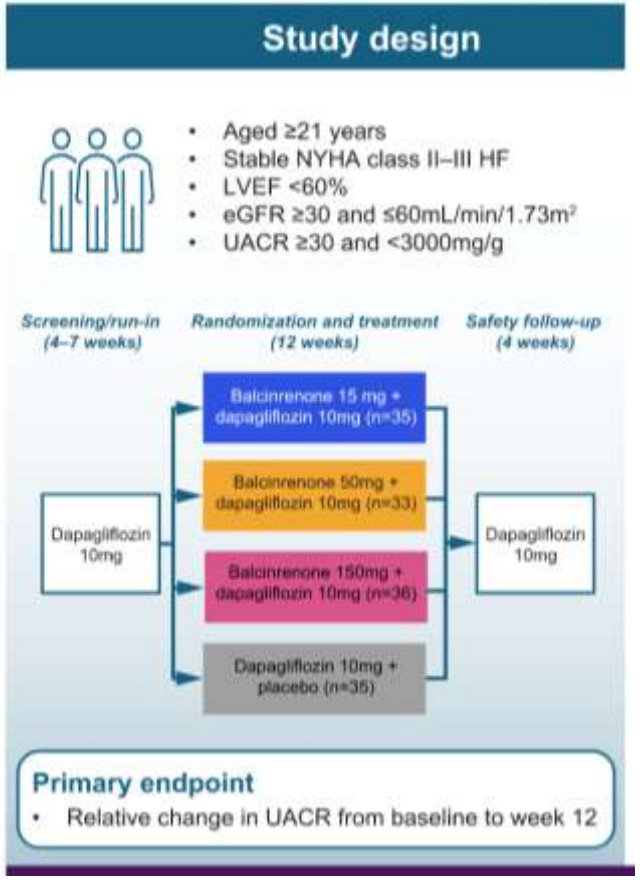


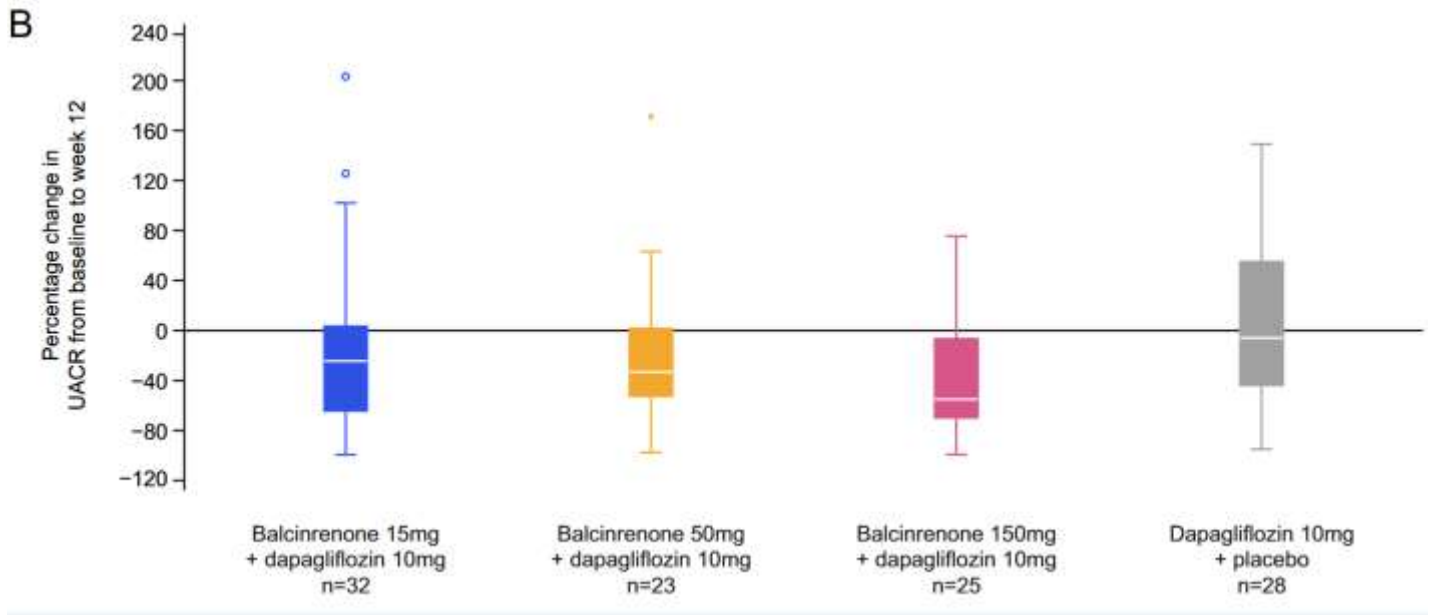

**Figure 3:** Kaplan–Meier curves of MAKE (**a**) between the combined and finerenone groups (log-rank test $P < .001$) and (**b**) between the combined and SGLT2i groups (log-rank test $P = .020$).

Chuang et al. NDT 2025

# SGLT2i combination: ns-MRA

Miracle 2b RCT, planed 125 patients/arm, balcinrenone+ dapagliflozin



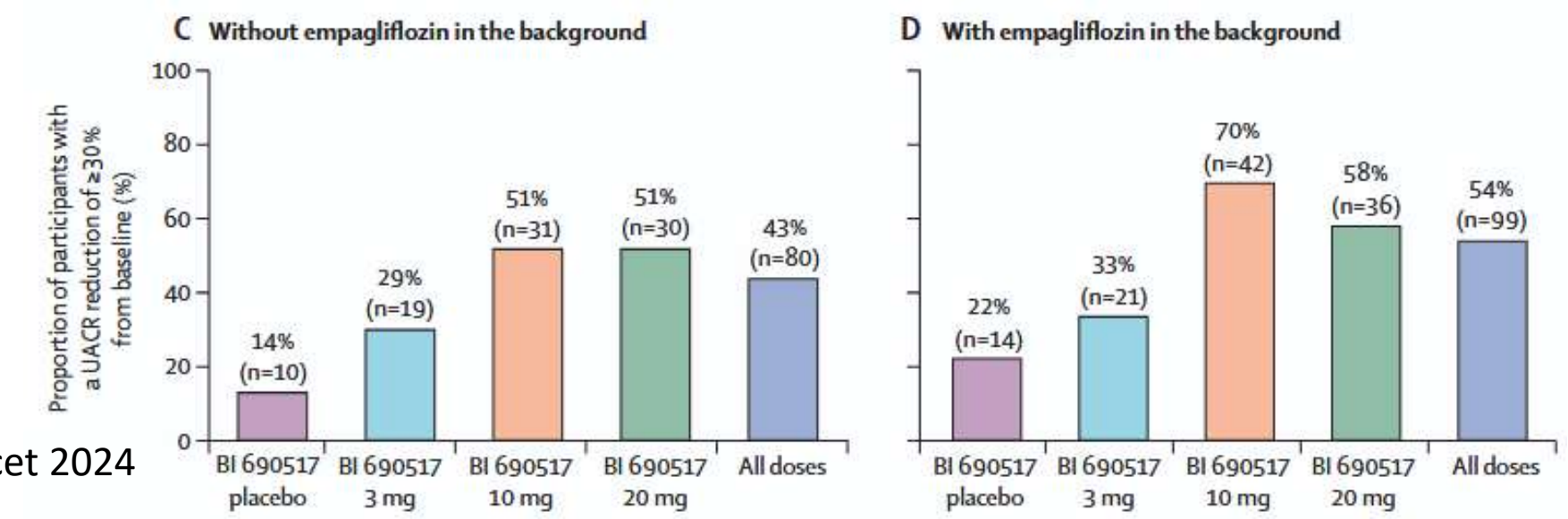

Lam et al, European Journal of Heart Failure 2024

# SGLT2i combination: MRA

- BARACK-D killed the use of s-MRA in CKD for cardio or nephroprotection.

Hobbs et al. Nature med 2024

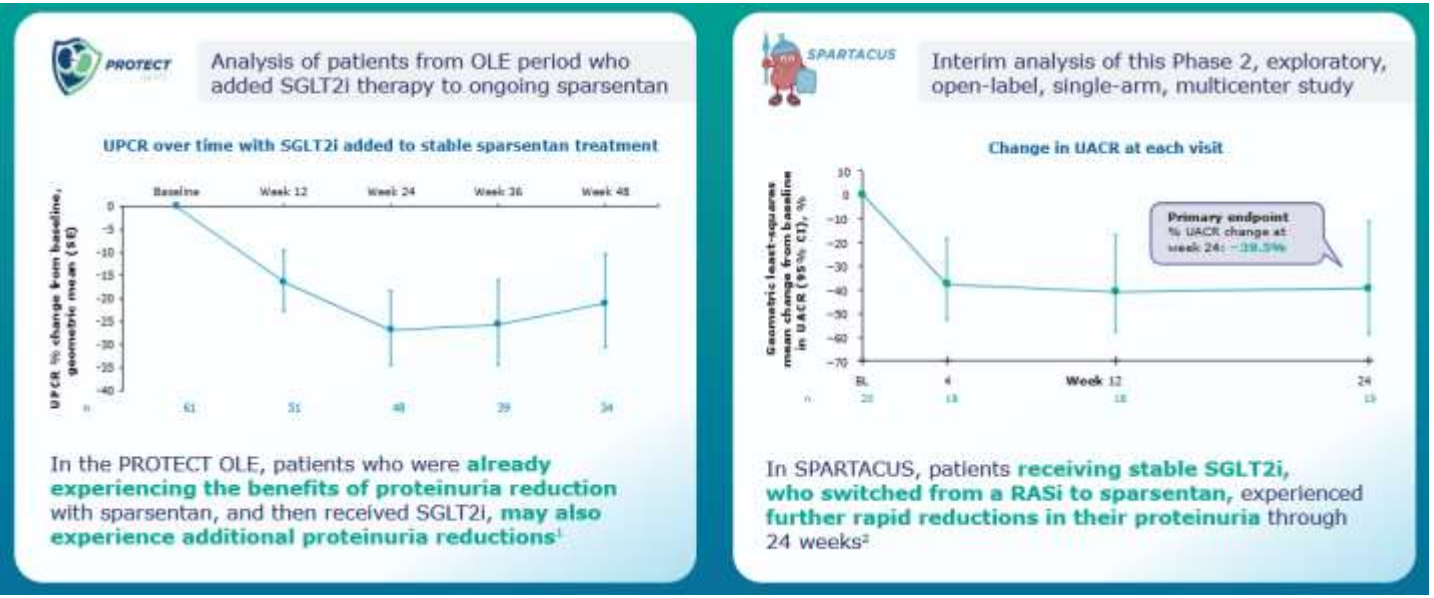
- Aldosterone synthase inhibitor
  - BI 690517+empagliflozin: Easi-Kidney
  - Baxdrostat+dapagliflozin: BaxDuo artic et pacific
  - En attendant: Phase 2, BI 690517+empagliflozin, CKD patients,primary outcome Albuminuria, kalemia<4,8 mmol/l.




Tuttle et al lancet 2024

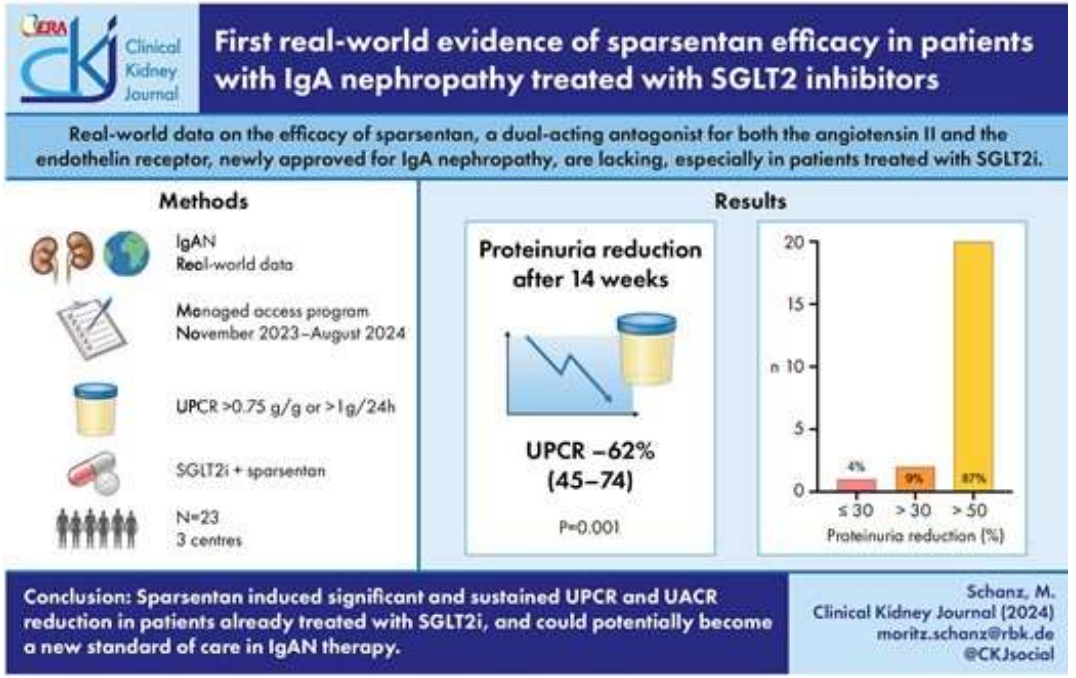
# SGLT2i combination: ERA, Sparsentan and IgAN

Travere study: Protect and Spartacus
Really additive




https://medicalaffairs.travere.com/posters/sparsentan-sglt2i-iga-nephropathy-spartacus-phase2/
ASN 2024

Real life cohort, 23 patients all with RASi and SGLT2i



# SGLT2i combination:ERA, Zibotentan

ZENITH-CKD: RCT zibotentan+SGLT2i vs SGLT2i, Primary outcome: albuminuria, Age: 62 ans, eGFR median 45, ACR median: 550 mg/g, DT2: 50%, 90% RASi, diuretic: 40% CCB: 50%

Heerspink et al, Lancet 2023

Main concern: fluid retention

# The Forgotten Antiproteinuric Properties of Diuretics

Hernando Trujillo[a] Fernando Caravaca-Fontán[b] Jara Caro[a, b]

Enrique Morales[a, b, c] Manuel Praga[a, b, c]

Am J Nephrol 2021

Figure 2: Mean change in UACR

# Conclusion


- SGLT2i with **RASi** are the key drugs for nephroprotection
- SGLT2i in monotherapy and low albuminuria could work
- The future in DT2 will be addition of GLP-1 AR and finerenone
- In CKD with proteinuria, addition of endothelin receptor antagonist are promissing
- Use of SGLT2i in nephrolithiasis could be a response to this frequent disease
- These must be validated in clinical trials
- SGLT2i reduce the risk of hyperkalemia and AKI, but these are not magic drugs that allow you to do anything you want.
- We did not finish to study the effects of SGLT2i.

Rebella

Granny smith

Chanteclerc

Gala

Spartan

Golden

# An apple per day keeps the cardiologist and nephrologist away

Braeburn

Boskoop

Gros hopital

Aport

Jazz

amU

Ariane

Reinette clochard