Inhibiteurs du SGLT2 dans la MRC, Données chez les transplantés et les dialysés

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Actualités Néphrologiques Jean Hamburger

13 mai 2025

Liens d’intérêt

- https://www.transparence.sante.gouv.fr
- AstraZeneca: lectures, consulting, financement GREAT-ASTRE

Recommandation iSGLT2 et MRC

Recommendation 3.7.1: We recommend treating patients with type 2 diabetes (T2D), CKD, and an eGFR ≥20 ml/min per 1.73 m^2 with an SGLT2i *(1A)*.

Practice Point 3.7.1: Once an SGLT2i is initiated, it is reasonable to continue an SGLT2i even if the eGFR falls below 20 ml/min per 1.73 m^2, unless it is not tolerated or KRT is initiated.

Practice Point 3.7.2: It is reasonable to withhold SGLT2i during times of prolonged fasting, surgery, or critical medical illness (when people may be at greater risk for ketosis).

Recommendation 3.7.2: We recommend treating adults with CKD with an SGLT2i for the following *(1A)*:

- **eGFR ≥20 ml/min per 1.73 m^2 with urine ACR ≥200 mg/g (≥20 mg/mmol), or**
- **heart failure, irrespective of level of albuminuria.**

Practice Point 3.7.3: SGLT2i initiation or use does not necessitate alteration of frequency of CKD monitoring and the reversible decrease in eGFR on initiation is generally not an indication to discontinue therapy.

Recommendation 3.7.3: We suggest treating adults with eGFR 20 to 45 ml/min per 1.73 m^2 with urine ACR <200 mg/g (<20 mg/mmol) with an SGLT2i *(2B)*.

Kidney International (2024) **105** (Suppl 4S), S117–S314

Les patients exclus des études / stade MRC

ORIGINAL ARTICLE

Empagliflozin in Patients with Chronic Kidney Disease

The EMPA-KIDNEY Collaborative Group*

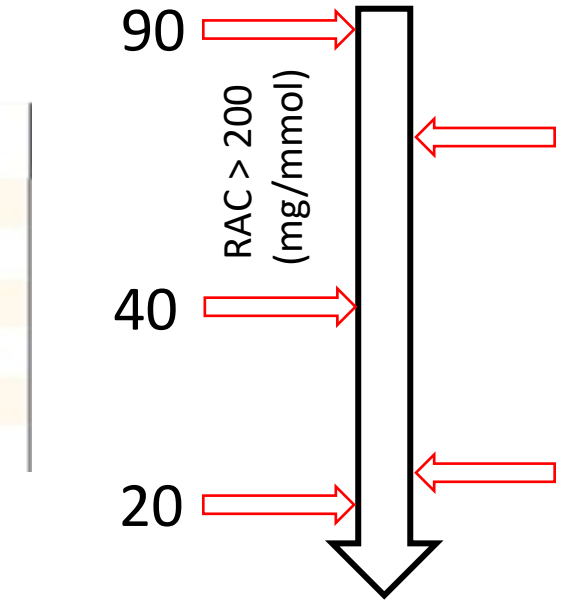
	Empagliflozin (N=3304)	Placebo (N=3305)
Estimated GFR		
Mean — ml/min/1.73 m²	37.4±14.5	37.3±14.4
Distribution — no. (%)		
≥45 ml/min/1.73 m²	706 (21.4)	693 (21.0)
≥30 to <45 ml/min/1.73 m²	1467 (44.4)	1461 (44.2)
<30 ml/min/1.73 m²	1131 (34.2)	1151 (34.8)

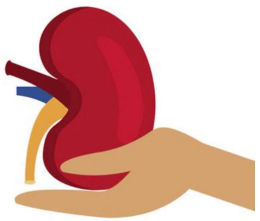
ORIGINAL ARTICLE

Dapagliflozin in Patients with Chronic Kidney Disease

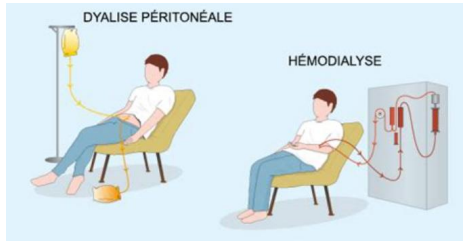
for the DAPA-CKD Trial Committees and Investigators*

	Dapagliflozin (N=2152)	Placebo (N=2152)
Estimated GFR		
Mean — ml/min/1.73 m²	43.2±12.3	43.0±12.4
Distribution — no. (%)		
≥60 ml/min/1.73 m²	234 (10.9)	220 (10.2)
45 to <60 ml/min/1.73 m	646 (30.0)	682 (31.7)
30 to <45 ml/min/1.73 m	979 (45.5)	919 (42.7)
<30 ml/min/1.73 m²	293 (13.6)	331 (15.4)

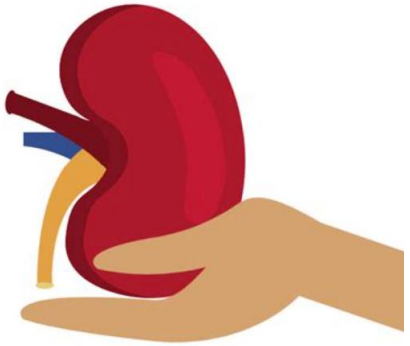




IRCT



Exclusion des patients transplantés



Risque accru d'effets indésirables
Immunosuppression
Risque accru d'infection urinaire (reflux, matériel)

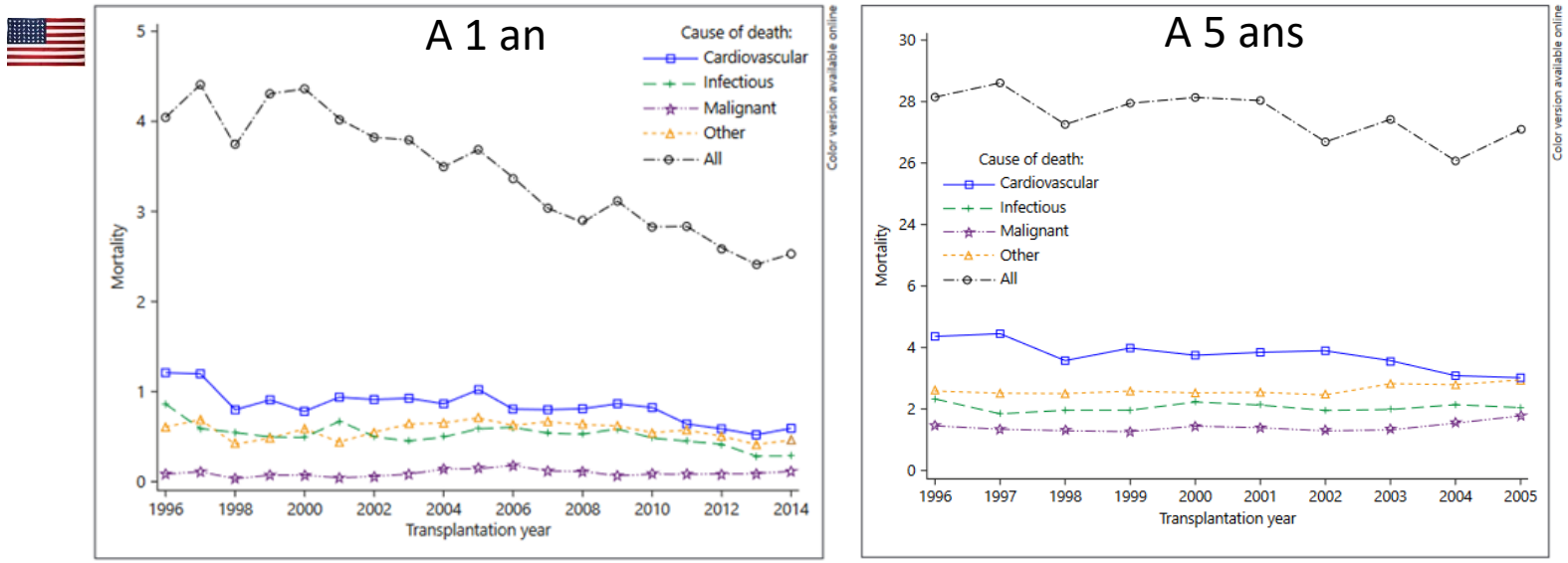
Mécanismes d'action des iSGLT2
Dénervation rénale (tonus vasculaire, réabsorption du sodium)
Altération rétrocontrôle tubulo-glomérulaire

Hétérogénéité des mécanismes de dégradation de la fonction rénale
Risque d'échec / end point « rénaux »
Difficulté d'interpréter les résultats

Autres
Pas de données préliminaires
Population moins fréquente / MRC
Les interactions médicamenteuses

Des risques mais aussi des bénéfices potentiels

CV = première cause de mortalité



Awan, Am J Nephrol 2018

Period	Causes of Death (*n*)				
	Cardiovascular	Cancer	Infection Related	Other	Total
1980–1984	50	7	27	27	111
1985–1989	135	36	58	45	274
1990–1994	181	89	66	77	413
1995–1999	224	143	91	71	529
2000–2004	252	214	126	112	704
2005–2009	299	238	129	95	761
2010–2014	310	318	172	208	1008
2015–2018	280	263	136	286	965
Total	1731	1308	805	921	4765

Ying, JASN 2020

Des risques mais aussi des bénéfices potentiels

CV = première cause de mortalité

Albuminurie

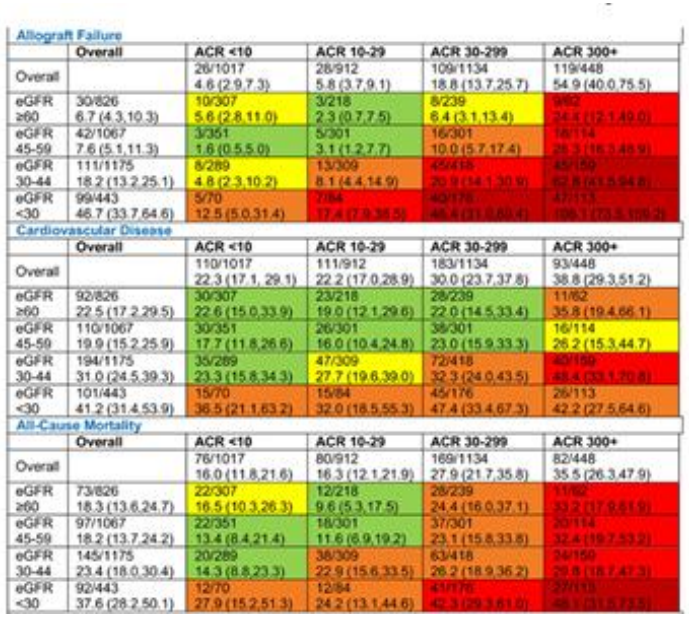
IRCT

	OR*	95% CI	p-value
Crude risk	14.25	3.88–52.29	<0.0001
Model 1	11.29	3.03–42.09	0.0003
Model 2	10.66	1.81–37.46	0.0005
Model 3	10.83	2.89–40.55	0.0004
Model 4	10.92	2.89–41.24	0.0004
Model 5	10.19	2.67–38.86	0.0007

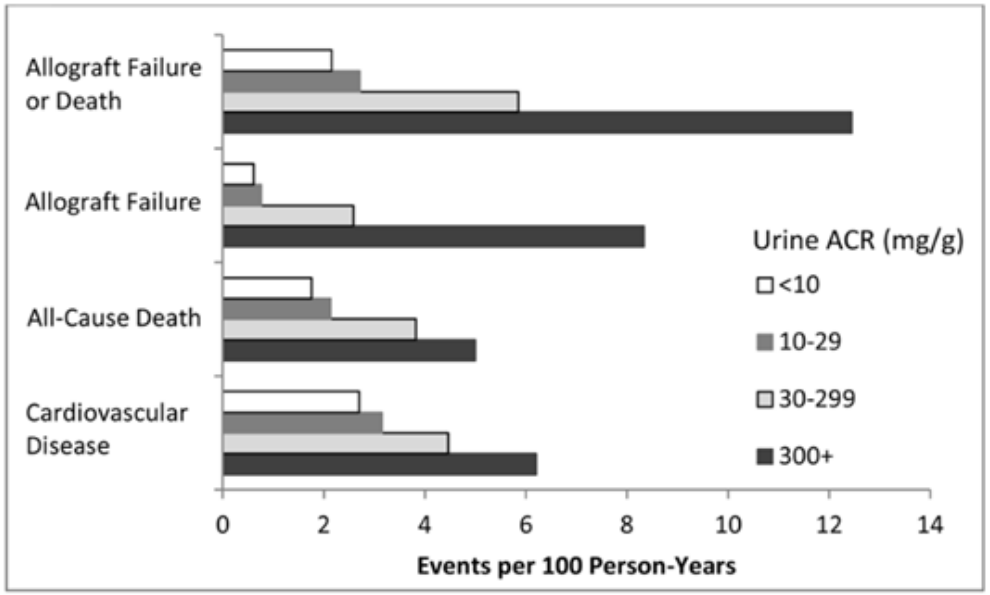
Décès

	OR*	95% CI	p-value
Crude risk	16.41	7.49–36.0	<0.000
Model 1	14.94	6.73–33.2	<0.000
Model 2	14.82	6.73–33.7	<0.000
Model 3	16.97	7.47–32.7	<0.000
Model 4	15.89	6.90–36.6	<0.000
Model 5	14.81	6.35–34.5	<0.000

Halimi, AJT 2007



		Overall	ACR <10	ACR 10-29	ACR 30-299	ACR 300+
Allograft Failure						
Overall			26/1017 4.6 (2.9,7.3)	28/912 5.8 (3.7,9.1)	109/1134 18.8 (13.7,25.7)	119/448 54.9 (40.0,75.5)
eGFR ≥60	30/826 6.7 (4.3,10.3)		10/307 5.6 (2.8,11.0)	3/218 2.3 (0.7,7.5)	8/239 6.4 (3.1,13.4)	9/62 24.4 (12.1,49.0)
eGFR 45-59	42/1067 7.6 (5.1,11.3)		3/351 1.6 (0.5,5.0)	5/301 3.1 (1.2,7.7)	16/301 10.0 (5.7,17.4)	18/114 28.3 (16.3,48.9)
eGFR 30-44	111/1175 18.2 (13.2,25.1)		8/289 4.8 (2.3,10.2)	13/309 8.1 (4.4,14.9)	45/418 20.9 (14.1,30.9)	45/159 62.8 (43.5,94.8)
eGFR <30	99/443 46.7 (33.7,64.6)		5/70 12.5 (5.0,31.4)	7/84 17.4 (7.9,36.5)	40/176 46.8 (31.0,69.4)	47/113 109.1 (73.5,159.2)
Cardiovascular Disease						
Overall			110/1017 22.3 (17.1, 29.1)	111/912 22.2 (17.0,28.9)	183/1134 30.0 (23.7,37.8)	93/448 38.8 (29.3,51.2)
eGFR ≥60	92/826 22.5 (17.2,29.5)		30/307 22.6 (15.0,33.9)	23/218 19.0 (12.1,29.6)	28/239 22.0 (14.5,33.4)	11/62 35.8 (19.4,66.1)
eGFR 45-59	110/1067 19.9 (15.2,25.9)		30/351 17.7 (11.8,26.6)	26/301 16.0 (10.4,24.8)	38/301 23.0 (15.9,33.3)	16/114 26.2 (15.3,44.7)
eGFR 30-44	194/1175 31.0 (24.5,39.3)		35/289 23.3 (15.8,34.3)	47/309 27.7 (19.6,39.0)	72/418 32.3 (24.0,43.5)	40/159 48.4 (33.1,70.8)
eGFR <30	101/443 41.2 (31.4,53.9)		15/70 36.5 (21.1,63.2)	15/84 32.0 (18.5,55.3)	45/176 47.4 (33.4,67.3)	26/113 42.2 (27.5,64.6)
All-Cause Mortality						
Overall			76/1017 16.0 (11.8,21.6)	80/912 16.3 (12.1,21.9)	169/1134 27.9 (21.7,35.8)	82/448 35.5 (26.3,47.9)
eGFR ≥60	73/826 18.3 (13.6,24.7)		22/307 16.5 (10.3,26.3)	12/218 9.6 (5.3,17.5)	28/239 24.4 (16.0,37.1)	11/62 33.2 (17.9,61.9)
eGFR 45-59	97/1067 18.2 (13.7,24.2)		22/351 13.4 (8.4,21.4)	16/301 11.6 (6.9,19.2)	37/301 23.1 (15.8,33.8)	20/114 32.4 (19.7,53.2)
eGFR 30-44	145/1175 23.4 (18.0,30.4)		20/289 14.3 (8.8,23.3)	38/309 22.9 (15.6,33.5)	63/418 26.2 (18.9,36.2)	24/159 29.8 (18.7,47.3)
eGFR <30	92/443 37.6 (28.2,50.1)		12/70 27.9 (15.2,51.3)	12/84 24.2 (13.1,44.6)	41/176 42.3 (29.3,61.0)	27/113 48.5 (31.5,73.5)



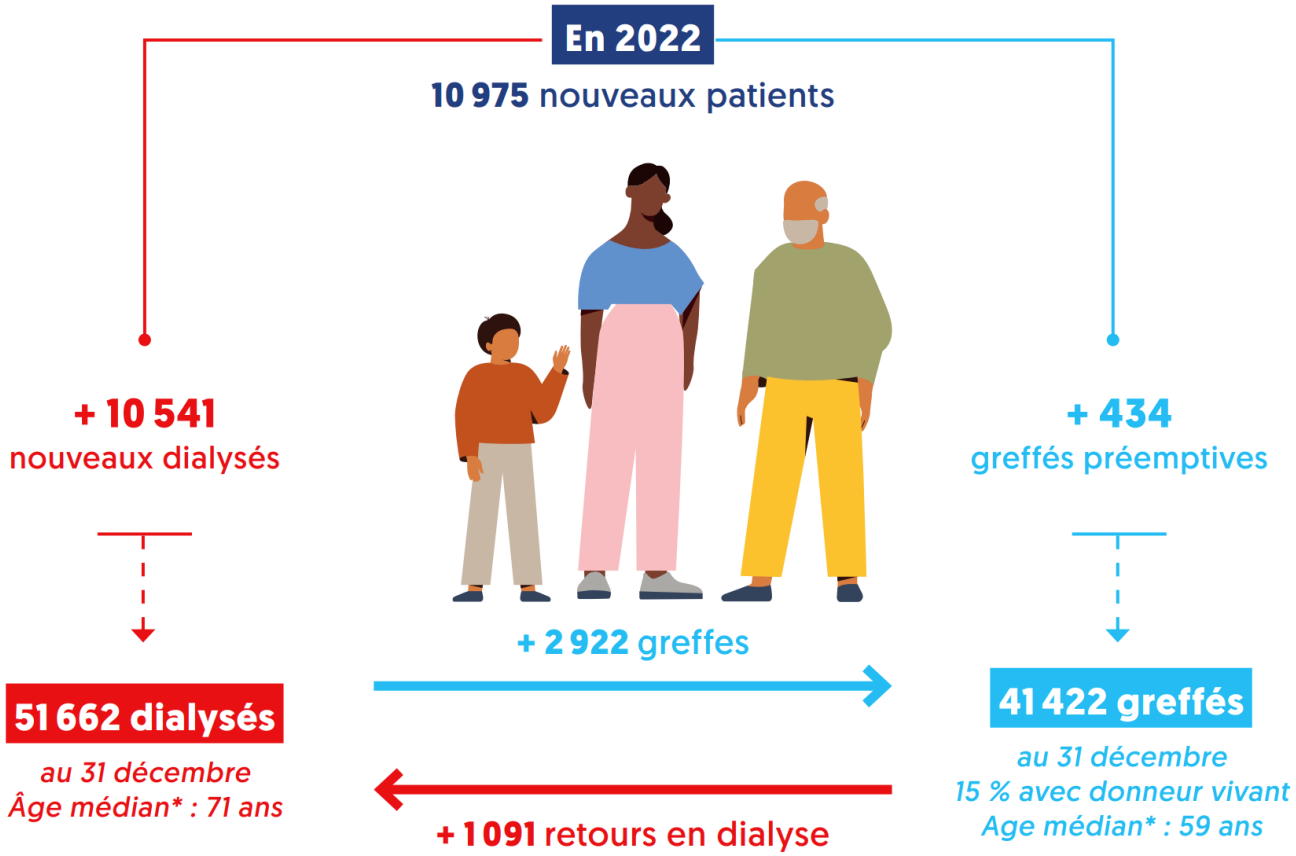
Weiner, AJKD 2019

Des risques mais aussi un enjeu épidémiologique

CV = première cause de mortalité

Albuminurie

3/4ème cause d'IRCT



Rapport REIN, 2022 (www.agence-biomedecine.fr)

Quelques expériences

Reference number[a]	Study design	Treatment arm(s)	n[b]	Patient population	Study length	Considerations	Effects on A1C, kidney function, AEs
SGLT2 inhibitors							
73	Retrospective, single-center, case series	Canagliflozin with prior antidiabetics	10	• Inclusion: N/A • Exclusion: N/A	80.5 Months	T2DM and PTDM (80%) population • PTDM diagnosis: N/A • Posttransplant: pancreas-kidney (3.5 years) and kidney (4.4 years)	• ↔ • ↔ • NR
70	Prospective, single-center, interventional, noninferiority trial	Empagliflozin 10 mg with prior antidiabetics	14	• Inclusion: >6 months posttransplant, eGFR > 30 mL/min/1.73 m^2, treated PTDM for >6 months, receiving exogenous insulin • Exclusion: insulin therapy > 40 units daily, A1C > 8.5%	4 Weeks	PTDM population • PTDM diagnosis: 68.1 months • Posttransplant: 69.4 months	• ↔ • ↓ • UTI, mild hyponatremia
71	Retrospective, single-center, case series	Empagliflozin with prior antidiabetics	8	• Inclusion: N/A • N/A	12 Months	T2DM and PTDM (50%) population • PTDM diagnosis: 16.8 months • Posttransplant: 21 months	• ↓ (No *P* value) • ↓ (No *P* value) • Nausea, UTI
72	Prospective, single-center, observational, case series	Empagliflozin with prior antidiabetics	10	• Inclusion: eGFR > 45 mL/min/1.73 m^2 • Exclusion: T1DM, history of recurrent UTIs	12 Months	T2DM and PTDM (40%) population • DM diagnosis: 18 years • Posttransplant: 5.9 years	• ↔ (No *P* value) • ↔ (No *P* value) • UTI, AKI stage I, diabetic ulcer
74	Retrospective, single-center, observational study	Canagliflozin 100 mg with prior antidiabetics	24	• Inclusion: creatinine clearance > 60 mL/min, A1C > 6.5% • Exclusion: N/A	6 Months	T2DM and NODAT (20.8%) population • DM diagnosis: 14 years • Posttransplant: 2.7 years	• ↓ • ↔ • Fatigue
75	Prospective, single-center, double-blind, randomized controlled trial	Empagliflozin 10 mg; placebo with prior antidiabetics	22; 22	• Inclusion: > 1 year posttransplant, <20% deviation in SCr within past 2 months, stable immunosuppression >3 months, FPG > 126 mg/dL, or OGTT > 200 mg/dL, or A1C > 6.5% • Exclusion: eGFR < 30 mL/min/1.73 m^2	24 Weeks	PTDM population • PTDM diagnosis: N/A • Posttransplant: 3 years	Compared with placebo • ↓ • ↔ • Urosepsis, genital yeast infection

Petites séries monocentriques, 1 seule prospective
2/6 rapportent une diminution DFG
4/6 rapportent infections urinaires

1 étude en cours avec empagliflozin
(70 patients, NCT03642184)

Anderson et al. Annals of Pharmacotherapy, 2021

Utilisation des iSGLT2i chez transplantés diabétiques en EU

Methods

DESCaRTES
Developing Education Science and Care for Renal Transplantation in European States

A survey was distributed to transplant centers across Europe to gather more information on current clinical practice

Responses were collected from 121/241 transplant centers across Europe
(23/4 → 23/9)

4. 'Do you use antidiabetic drugs other than insulin in hyperglycaemic patients during the early post-transplant period (≤45 days)?'
Yes $n = 85/121$ (70%)
4.1. 'Which antidiabetic drugs other than insulin do you consider in the early post-transplant period (≤45 days)?' (more than one answer possible)

• DPP-4 inhibitors	52/85 (61%)
• Metformin	42/85 (49%)
• Sulfonylurea or glinides	38/85 (45%)
• SGLT2-inhibitors	21/85 (25%)
• GLP-1 analogues	17/85 (20%)

9. 'Which antidiabetic drugs other than insulin do you consider in patients who have developed PTDM (after 45 days post-transplant)?' (more than one answer possible)

• Metformin	52/70 (74%)
• DPP-4 inhibitors	49/70 (70%)
• SGLT2-inhibitors	48/70 (69%)
• GLP-1 analogues	45/70 (64%)
• Sulfonylurea or glinides	28/70 (40%)

⇨ Utilisation préférentielle des SGLT2i au-delà de 45 jours post greffe

Laghrib CKJ 2025

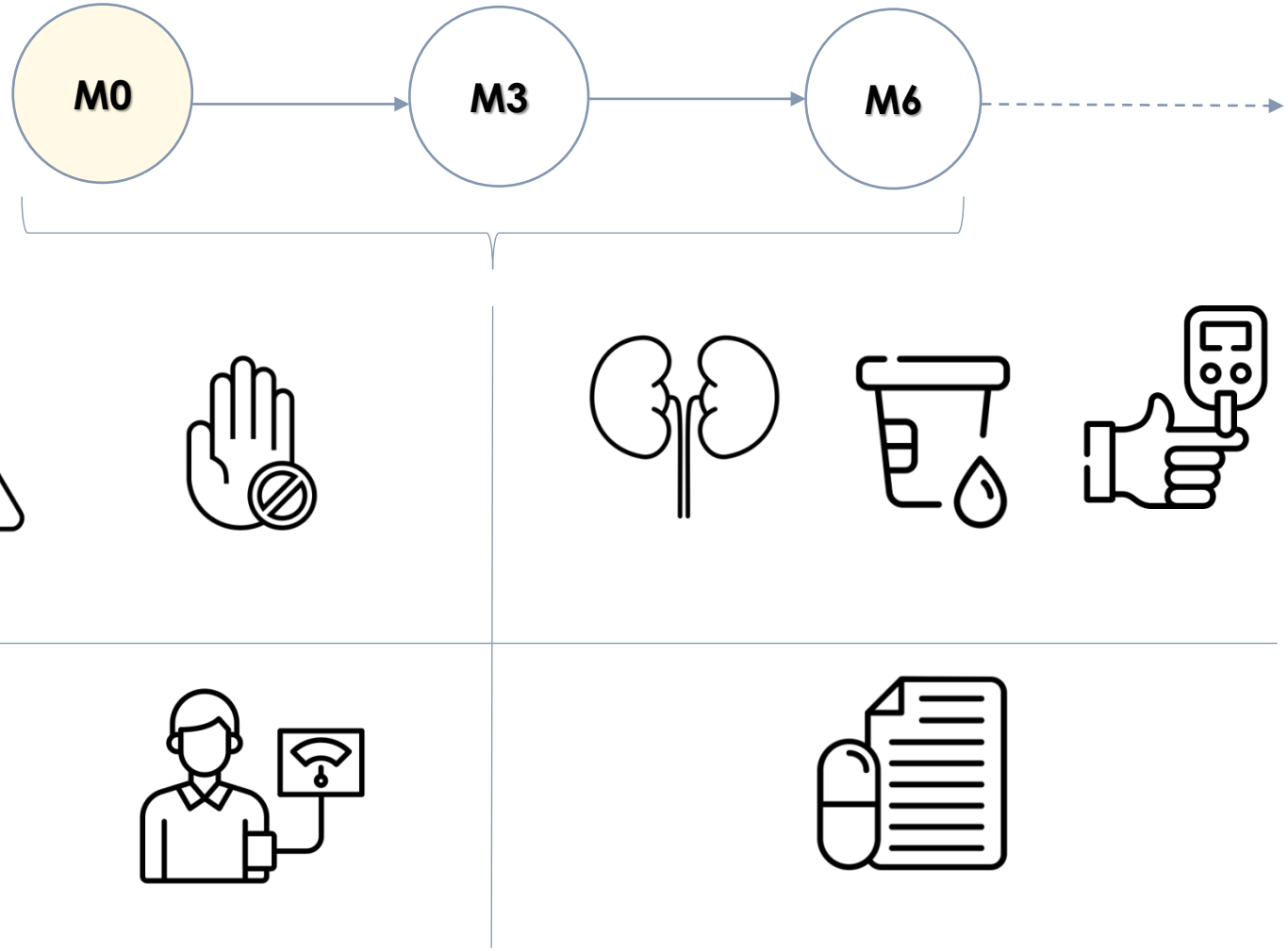
KI REPORTS
KIReports.org
CLINICAL RESEARCH

Sodium-Glucose Cotransporter-2 Inhibitor in Diabetic and Nondiabetic Renal Transplant Recipients

Lucie Maigret[1], Lucile Basle[2], Valérie Chatelet[3], Laure Ecotiere[4], Peggy Perrin[5], Léonard Golbin[6], Dominique Bertrand[7], Dany Anglicheau[8], Coralie Poulain[9], Cyril Garrouste[10], Clément Danthu[11], Charlotte Boud'hors[12], Yannick Le Meur[13], Manon Dekeyser[14], Fabien Duthe[4], Bénédicte Sautenet[1], Pierre-Guillaume Deliège[2] and Philippe Gatault[1,15]

Design

Observationnelle
Tous patients traités par iSGLT2
13 centres (Groupe Spiesser)
Recueil prospectif (Base ASTRE)



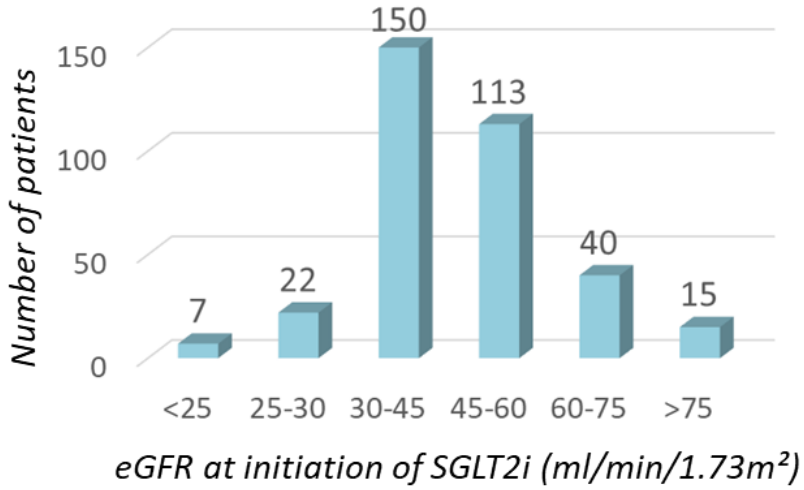
Caractéristiques des patients

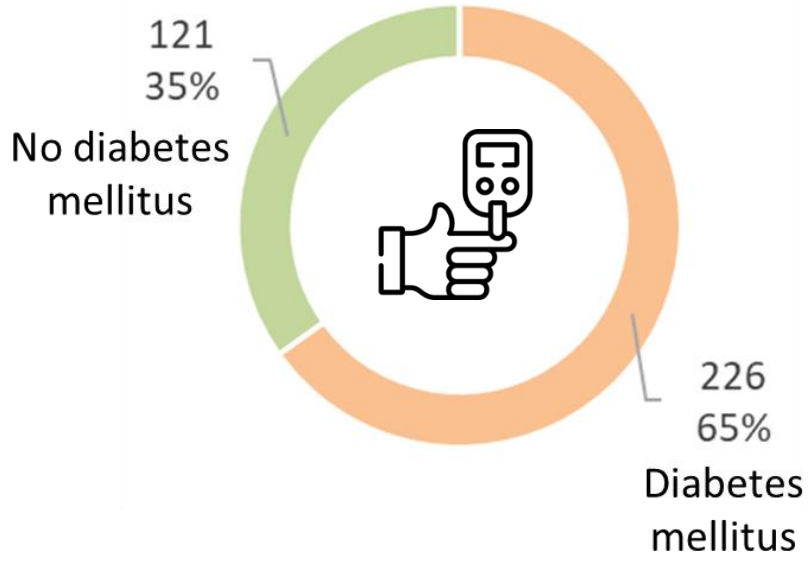
347 | 62,6 ans, H 76,4%

97% | Dapagliflozine

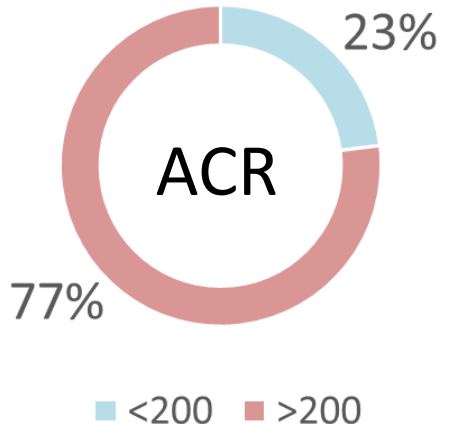
87% | Introduction > 1 an

DFG
44 ml/min
(25-75: 94%)



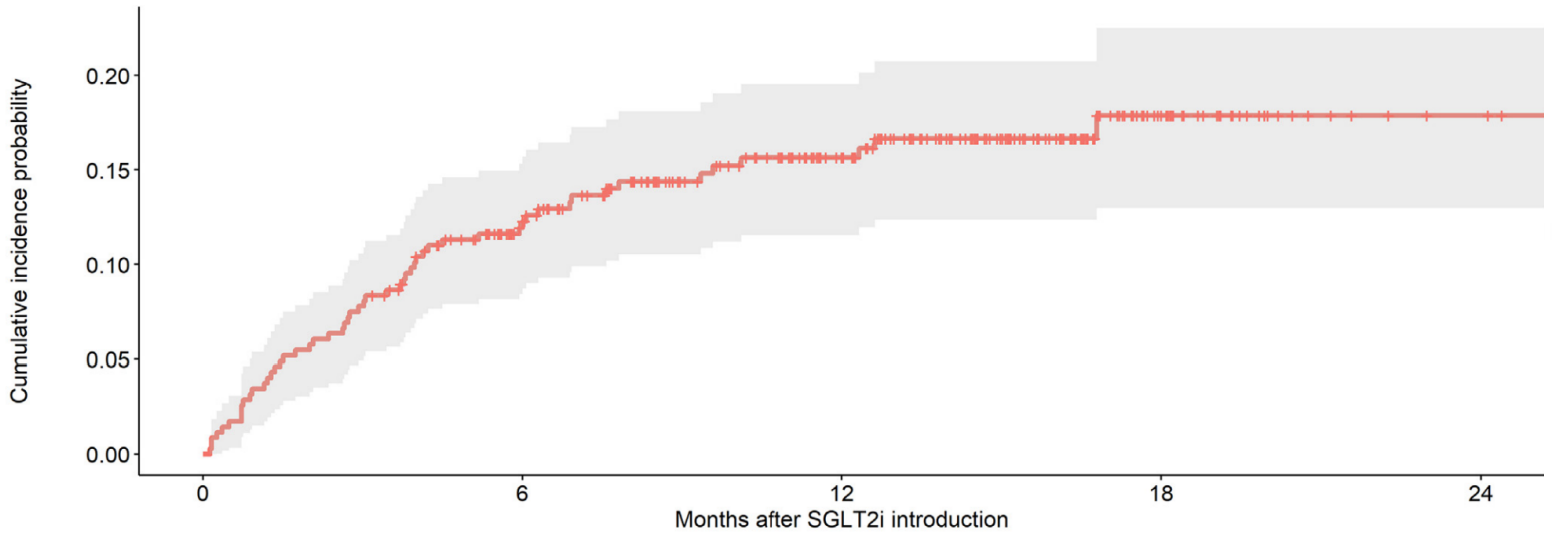


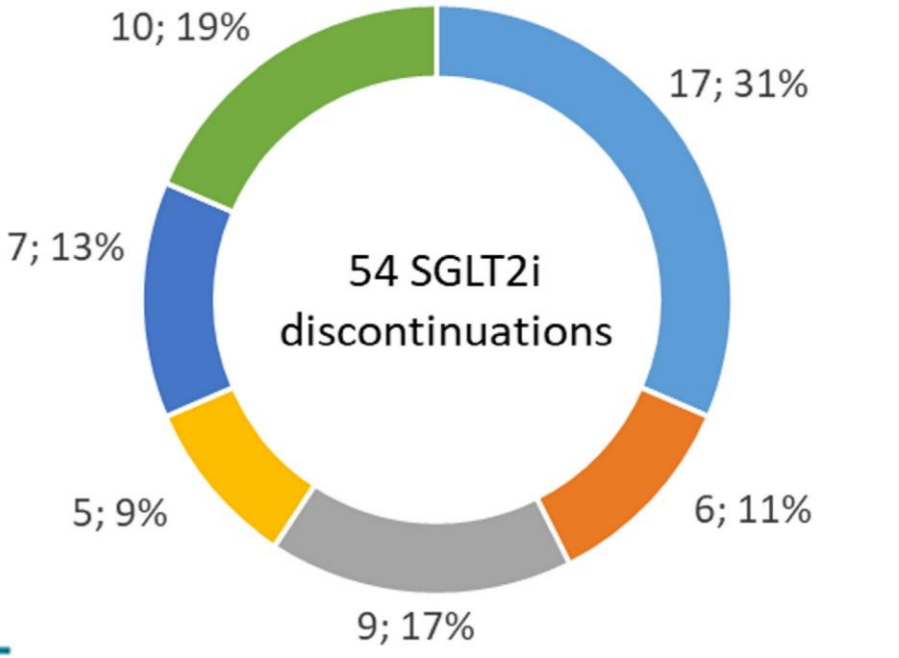
PU 506 mg/g
(ou/24h)



Maigret KI Reports 2025

Les arrêts de traitements





	Multivariate analysis		
	HR	95% CI	*P*-value
eGFR (per ml/min per 1.73 m^2)	0.979	0.956–1.003	0.086
BMI (per kg/m^2)	0.934	0.881–0.990	0.022

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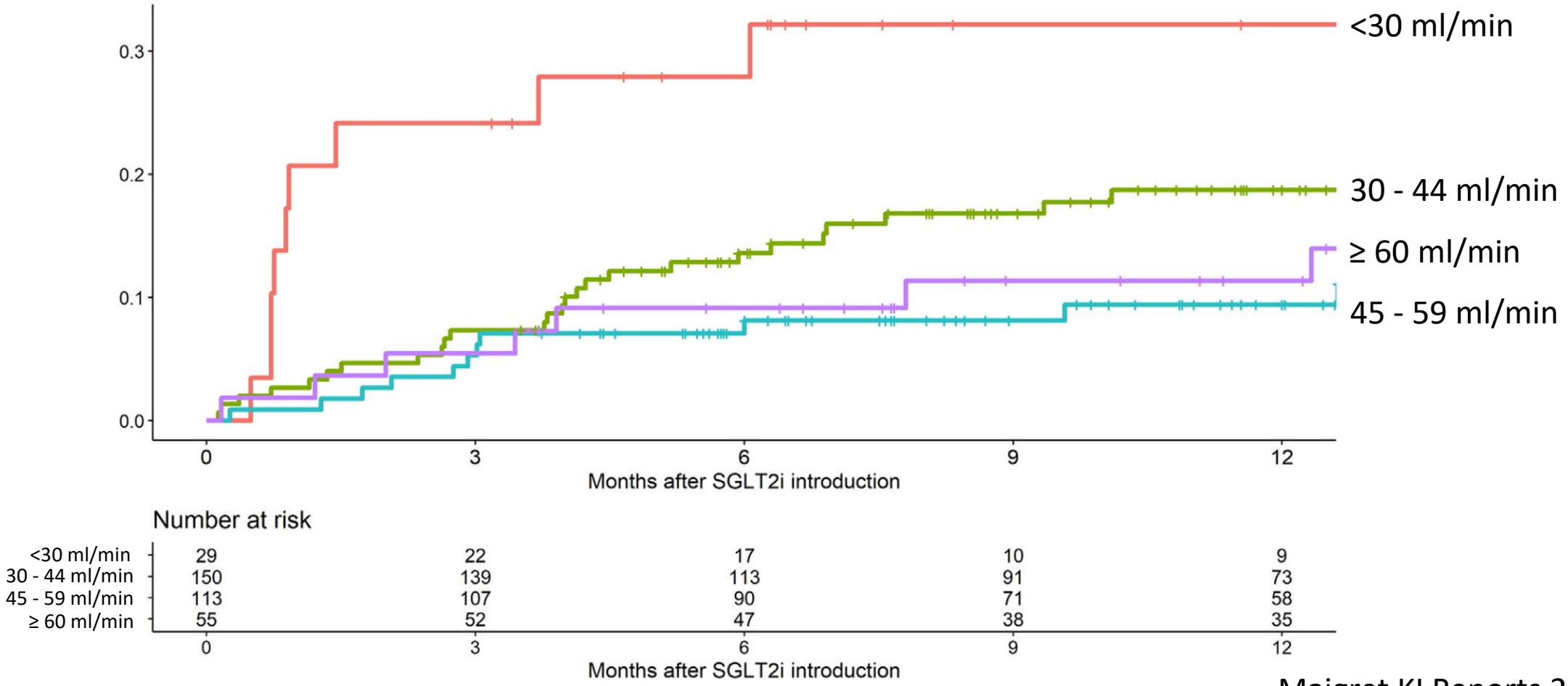
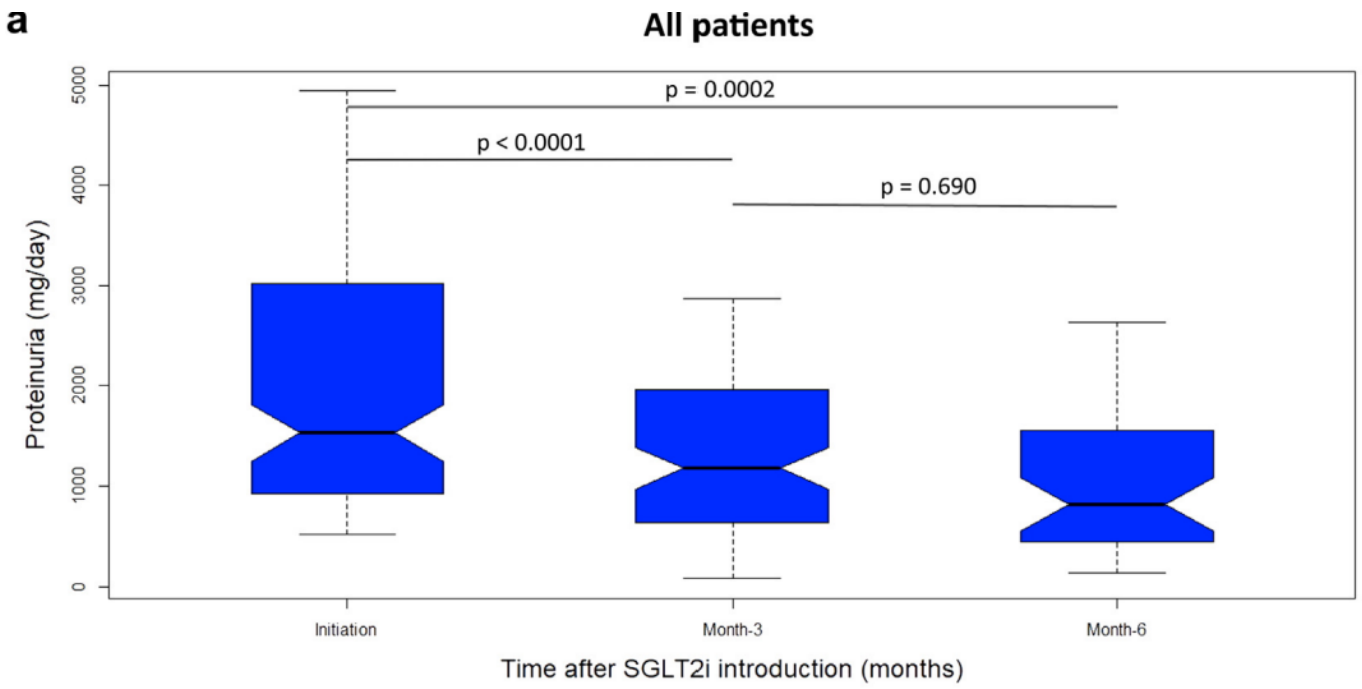
Plus d’arrêt chez patients avec IRC stade III



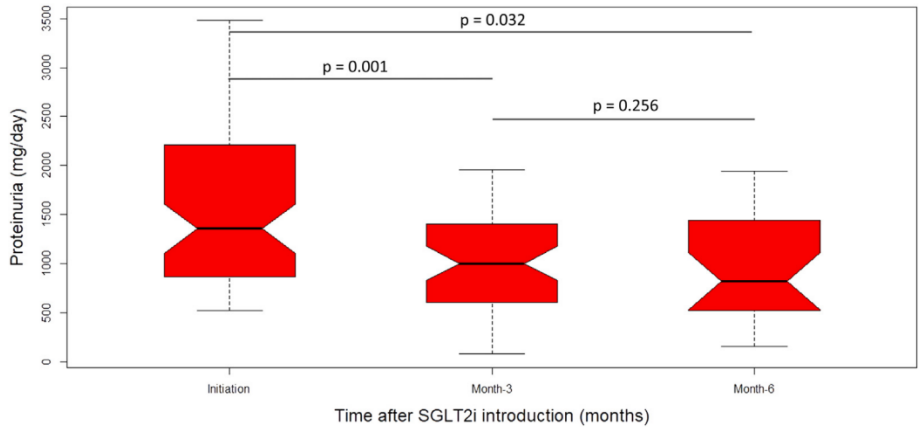
Maigret KI Reports 2025

La dapagliflozine réduit la protéinurie

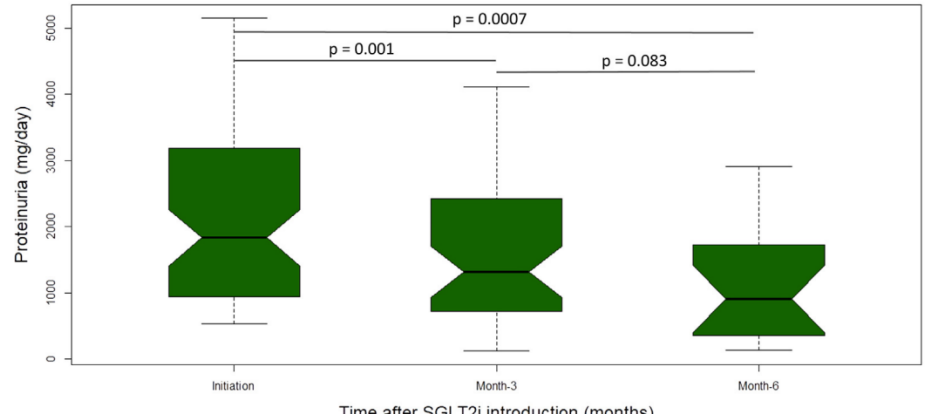
138 patients with proteinuria > 500 mg/d:
↘ 36% at 6 months



Diabétiques



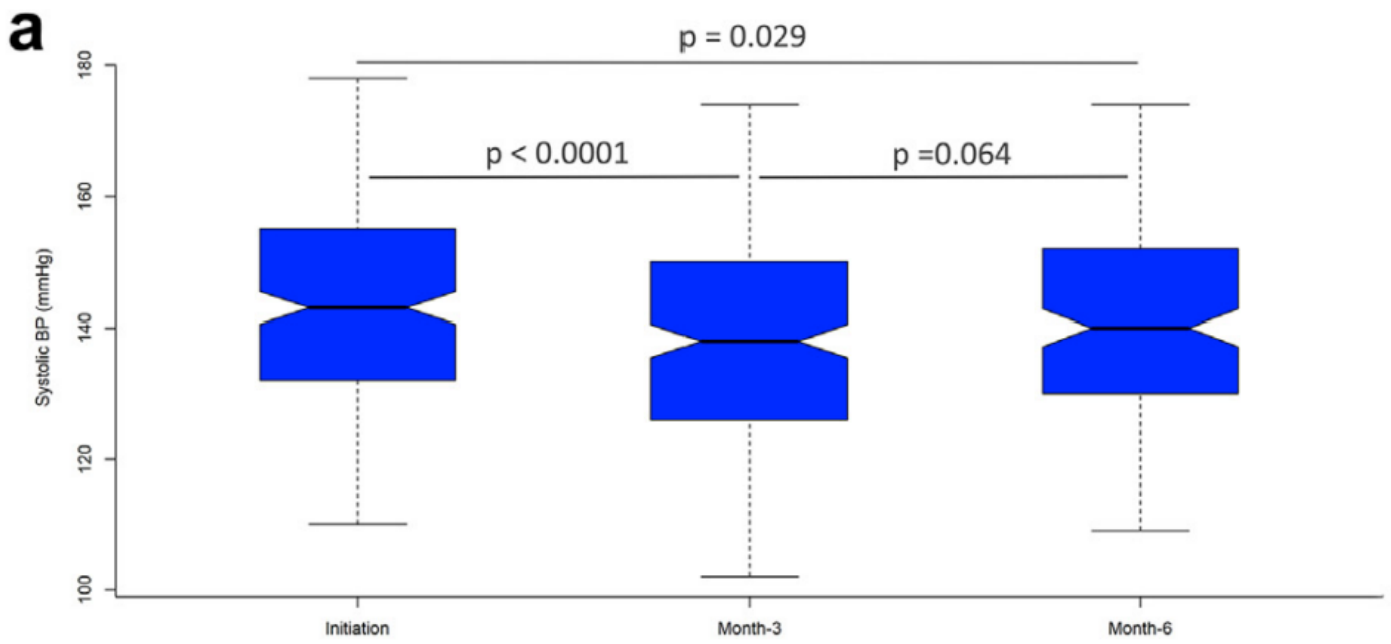
Non diabétiques



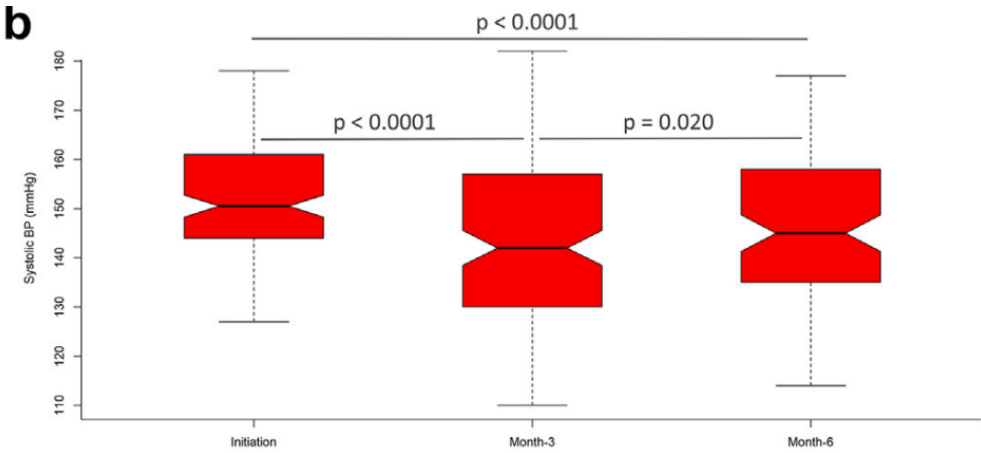
Maigret KI Reports 2025

La dapagliflozine réduit la PA, seulement chez les hypertendus

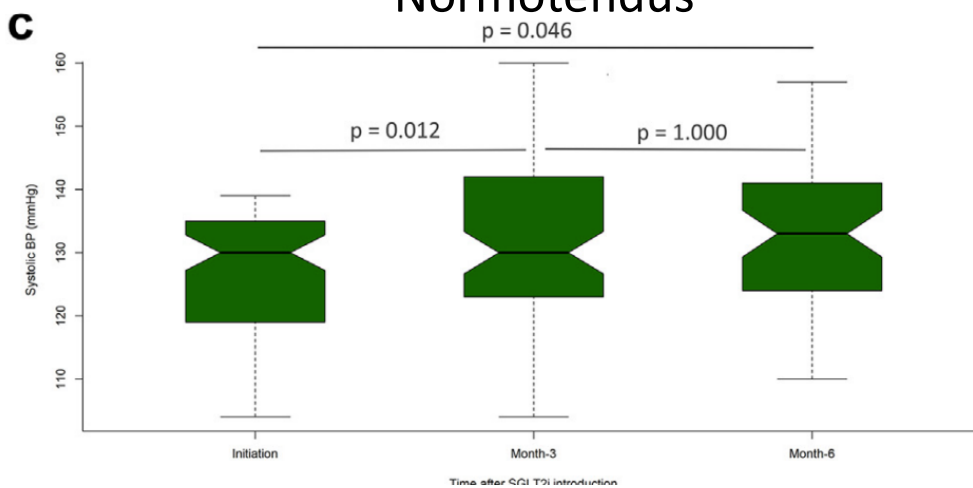
↘ PAS 5 mmHg et PAD 3 mmHg



Hypertendus : ↘ PAS 10 mmHg



Normotendus



Maigret KI Reports 2025

Comparaisons aux autres études

	GREAT ASTRE	Sanchez Fructuoso *et al.*	Lim *et al.*	DAPA-CKD
Transplantés rénaux	Oui	Oui	Oui	Non
Diabète	65,1%	100%	100%	67,6%
Effectif sous iSGLT2	347	339	226	2149
Durée médiane de suivi	1 an	1 an	?	2,4 ans
Dapagliflozine	96,5%	24%	33,6%	100%
Age médian initial	61 ans	62 ans	51 ans	62 ans
PAS / PAD initiales (mmHg)	143/81	137/76	-	137/78
DFG médian initial (ml/min/1,73m²)	44	58,4	69,8	43
Protéinurie initiale (mg/g ou /24h) (>200)	1028	760	-	965
IEC ou ARA2	71%	60%	49%	98%

Sanchez Fructuose *et al. CKJ* 2023
Lim *et al. Transplantation* 2022
Heerspink *et al. NEJM* 2020

Clinical Kidney Journal

Sodium-glucose cotransporter-2 inhibitor therapy in kidney transplant patients with type 2 or post-transplant diabetes: an observational multicenter study

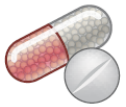
Sodium-glucose cotransporter-2 inhibitors (SGLT2i) have cardioprotective and renoprotective effects. However, experience with SGLT2i in diabetic kidney transplant recipients (DKT) is limited.

Methods

Observational study

n = 339 DKT

Demographic, clinical and laboratory data



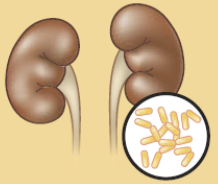
6 months' treatment

↓

Adverse effects (AE)

Results

AE – 26% ⟶ 14%



Risk factors for developing UTI

- Prior episode [OR 7.9 (CI 3.6–17.21)]
- Female sex [OR 2.5 (CI 1.2–5.0)]

6 months' efficacy

↓ Body weight	↓ Uric acid
↓ Blood pressure	↓ Urinary protein/creatinine ratio
↓ Fasting-glycemia	↑ Mg
↓ HbA1c	↑ Hemoglobin

Conclusion: SGLT2i offers benefits controlling weight, blood pressure, uric acid, Mg, glycemia and proteinuria. UTI was the most frequent AE and caution should be taken in female DKT and those with a history of UTI.

Sánchez Fructuoso A., et al.
Clinical Kidney Journal (2023)
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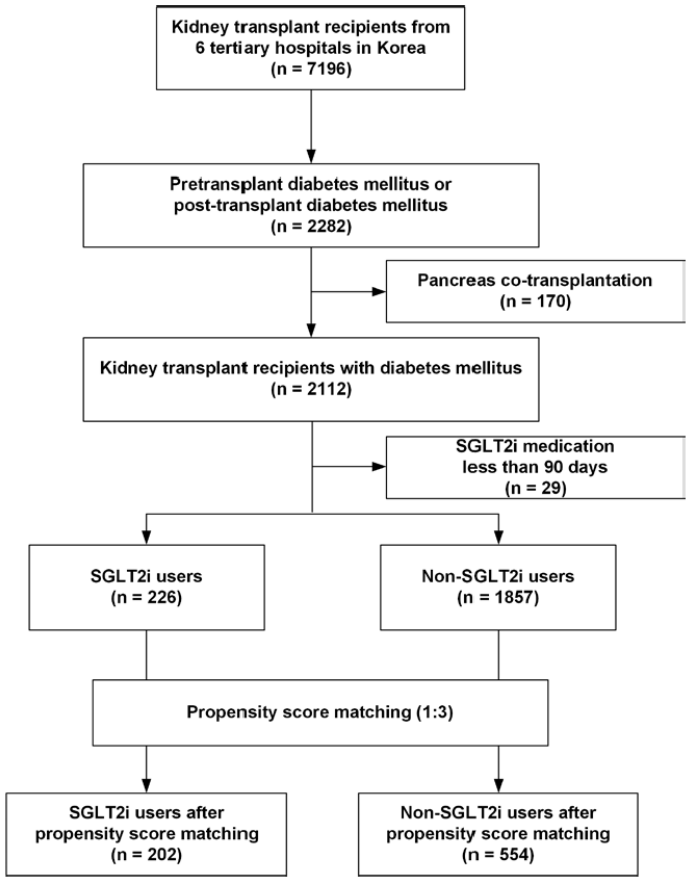
Essai thérapeutique coréen

The Efficacy and Safety of SGLT2 Inhibitor in Diabetic Kidney Transplant Recipients

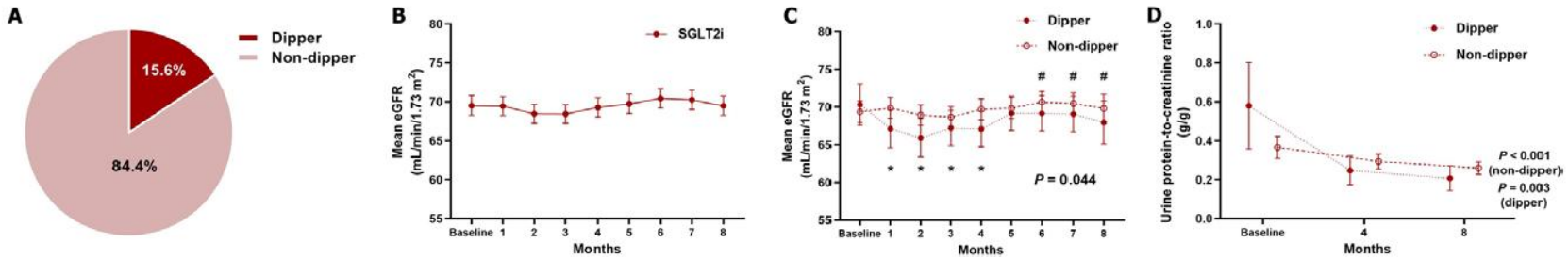
Jeong-Hoon Lim, MD, PhD,[1] Sole Kwon, MD, MS,[2] Yena Jeon, MS,[3] Young Hoon Kim, MD, PhD,[4] Hyunwook Kwon, MD, PhD,[4] Yon Su Kim, MD, PhD,[2] Hajeong Lee, MD, PhD,[2] Yong-Lim Kim, MD, PhD,[1] Chan-Duck Kim, MD, PhD,[1] Sun-Hee Park, MD, PhD,[1] Jong Soo Lee, MD, PhD,[3] Kyung Don Yoo, MD, PhD,[3] Hyung Eun Son, MD, MS,[8] Jong Cheol Jeong, MD, PhD,[6] Jeonghwan Lee, MD, PhD,[7] Jung Pyo Lee, MD, PhD,[7] and Jang-Hee Cho, MD, PhD[1]

Primary outcome: all-cause mortality, death-censored graft failure [DCGF] or serum creatinine doubling



	Primary composite outcome		All-cause mortality		Death-censored graft failure		Serum creatinine doubling	
Model	**HR (95% CI)**	***P***	**HR (95% CI)**	***P***	**HR (95% CI)**	***P***	**HR (95% CI)**	***P***
Model 1[a]	0.45 (0.27-0.75)	0.002	0.17 (0.04-0.70)	0.014	0.27 (0.10-0.72)	0.009	0.49 (0.29-0.85)	0.010
Model 2[b]	0.37 (0.22-0.62)	<0.001	0.22 (0.05-0.90)	0.034	0.22 (0.08-0.59)	0.003	0.37 (0.54-0.90)	<0.001
Model 3[c]	0.38 (0.22-0.64)	<0.001	0.24 (0.06-0.99)	0.049	0.22 (0.08-0.61)	0.004	0.38 (0.22-0.66)	<0.001
Model 4[d]	0.43 (0.24-0.78)	0.006	0.35 (0.08-1.45)	0.147	0.34 (0.12-0.95)	0.040	0.41 (0.22-0.77)	0.005
Model 5[e]	0.45 (0.24-0.85)	0.013	0.31 (0.07-1.32)	0.112	0.30 (0.09-0.98)	0.046	0.45 (0.23-0.88)	0.019

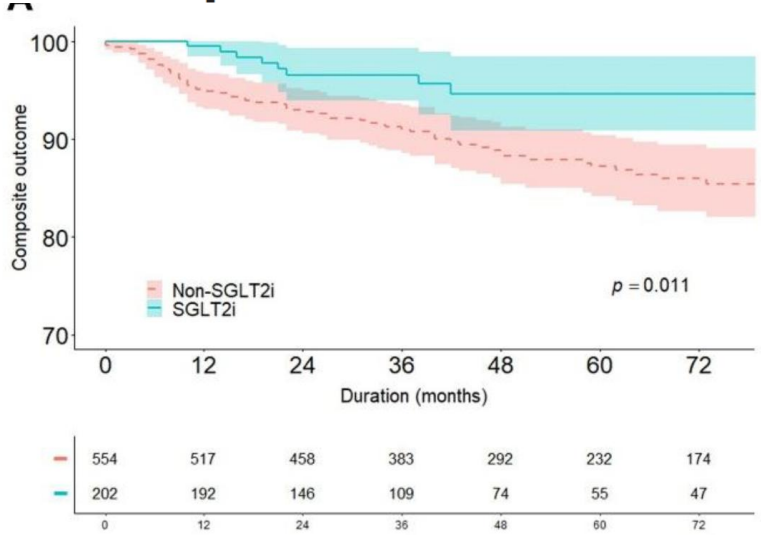
[a]Unadjusted.
[b]Adjusted for age, sex, body mass index, donor type (deceased or living), ABO incompatibility, and acute rejection.
[c]Adjusted for age, sex, body mass index, donor type (deceased or living), ABO incompatibility, underlying comorbidities (diabetes, hypertension, and dyslipidemia), diabetic end-stage kidney disease, ACEi or ARB usage, and eGFR at 3 mo after transplant.
[d]Adjusted for age, sex, body mass index, donor type (deceased or living), ABO incompatibility, underlying comorbidities (diabetes, hypertension, and dyslipidemia), diabetic end-stage kidney disease, posttransplantation 1-y mean HbA1c (%) calculated by area under the curve, and metformin usage.
[e]Propensity score-matched covariates: age, sex, donor type (deceased or living), ABO incompatibility, underlying comorbidities (diabetes, hypertension, and dyslipidemia), diabetic end-stage kidney disease, posttransplantation 1-y mean HbA1c (%) calculated by area under the curve, metformin usage, acute rejection, ACEi or ARB usage, and eGFR at 3 mo after transplant.
ACEi, angiotensin-converting enzyme inhibitor; ARB, angiotensin receptor blocker; CI, confidence interval; eGFR, estimated glomerular filtration rate; HbA1c, hemoglobin A1c; HR, hazard ratio.



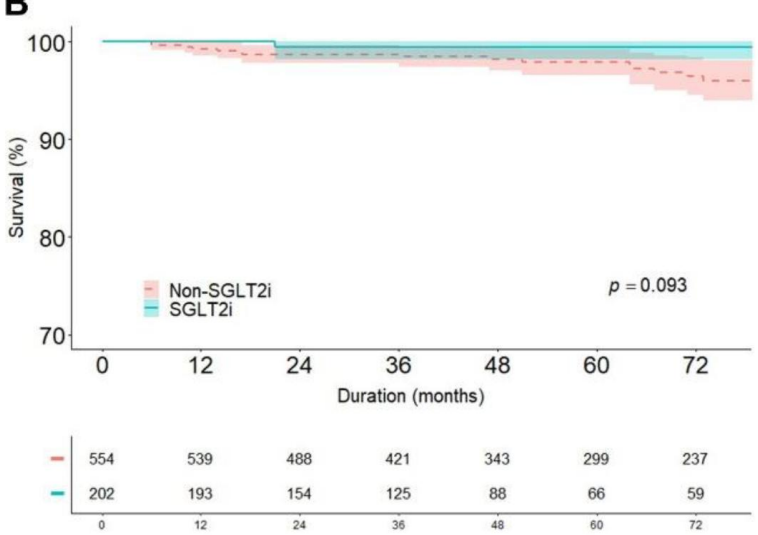
Lim Transplantation 2022

The Efficacy and Safety of SGLT2 Inhibitor in Diabetic Kidney Transplant Recipients

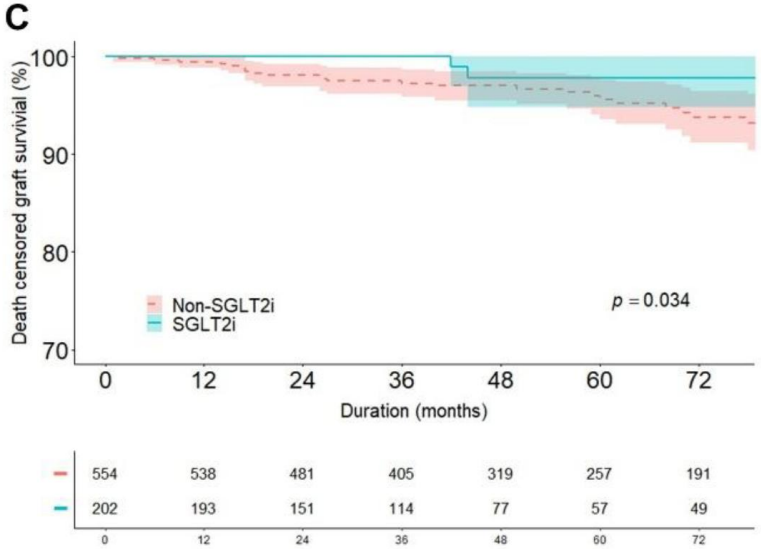
Composite end-point



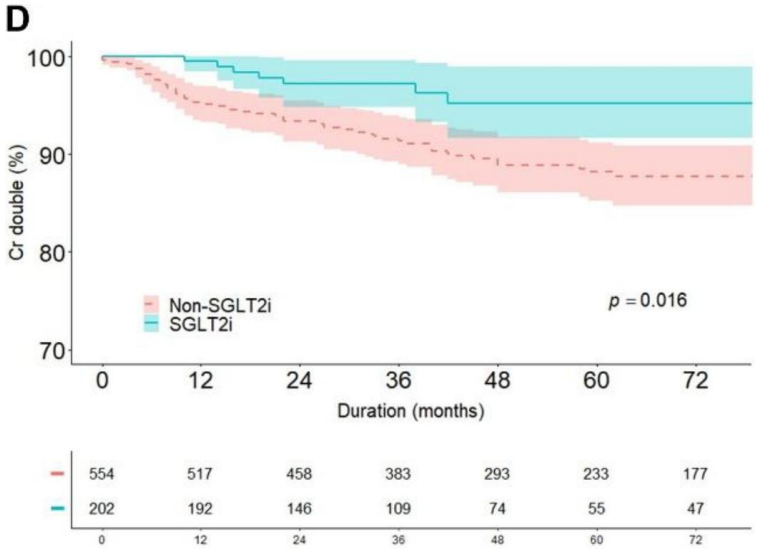
All-cause mortality



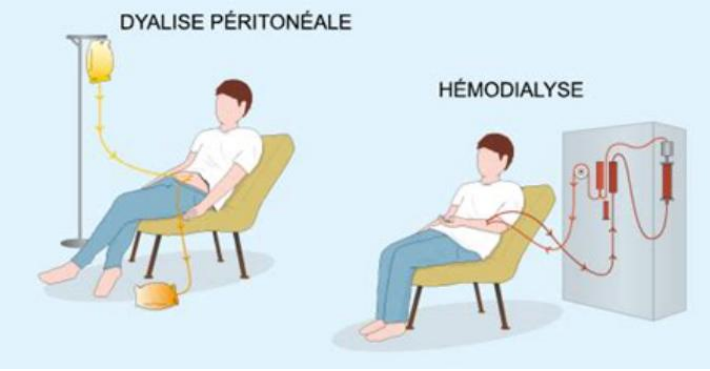
Death-censored graft failure



Serum creatinine doubling



Exclusion des patients dialysés



Mortalité cardiovasculaire très élevée mais FDR spécifiques
Médiacalcose, perturbations du métabolisme phosphocalcique
Inflammation chronique
Anémie
Variations ioniques per dialytiques
Effets spécifiques de certaines toxines urémiques

Raisons pharmacologiques
Accès limité voire nul à la cible avec la chute du DFG
Molécule non dialysable: risques liés à l'accumulation?

Risques spécifiques?
Hypotension per dialytique
AOMI

Autres
Pas de données préliminaires
Population moins fréquente / MRC

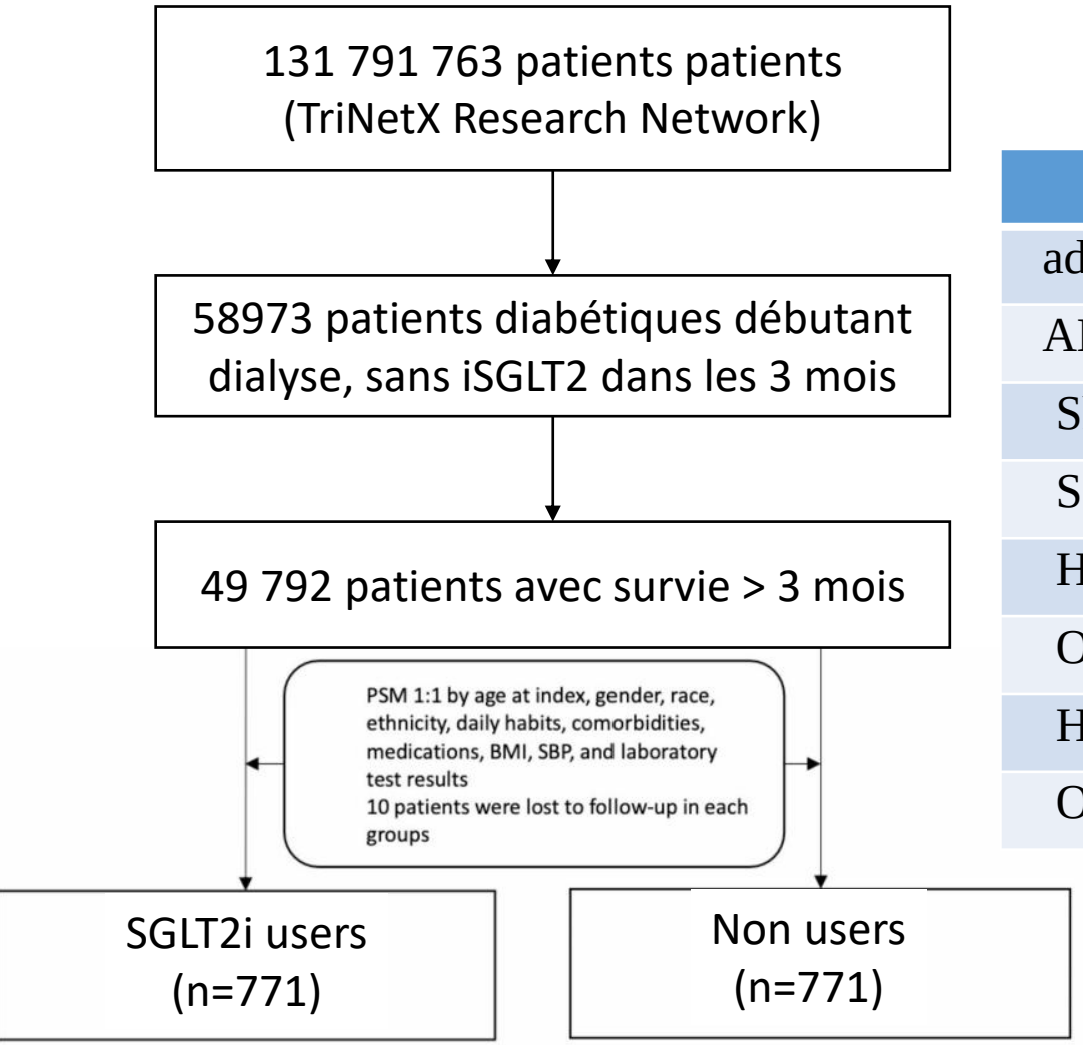
Wang et al. Cardiovascular Diabetology (2024) 23:327
https://doi.org/10.1186/s12933-024-02424-7

Cardiovascular Diabetology

RESEARCH Open Access

Exploring the mortality and cardiovascular outcomes with SGLT-2 inhibitors in patients with T2DM at dialysis commencement: a health global federated network analysis

Population

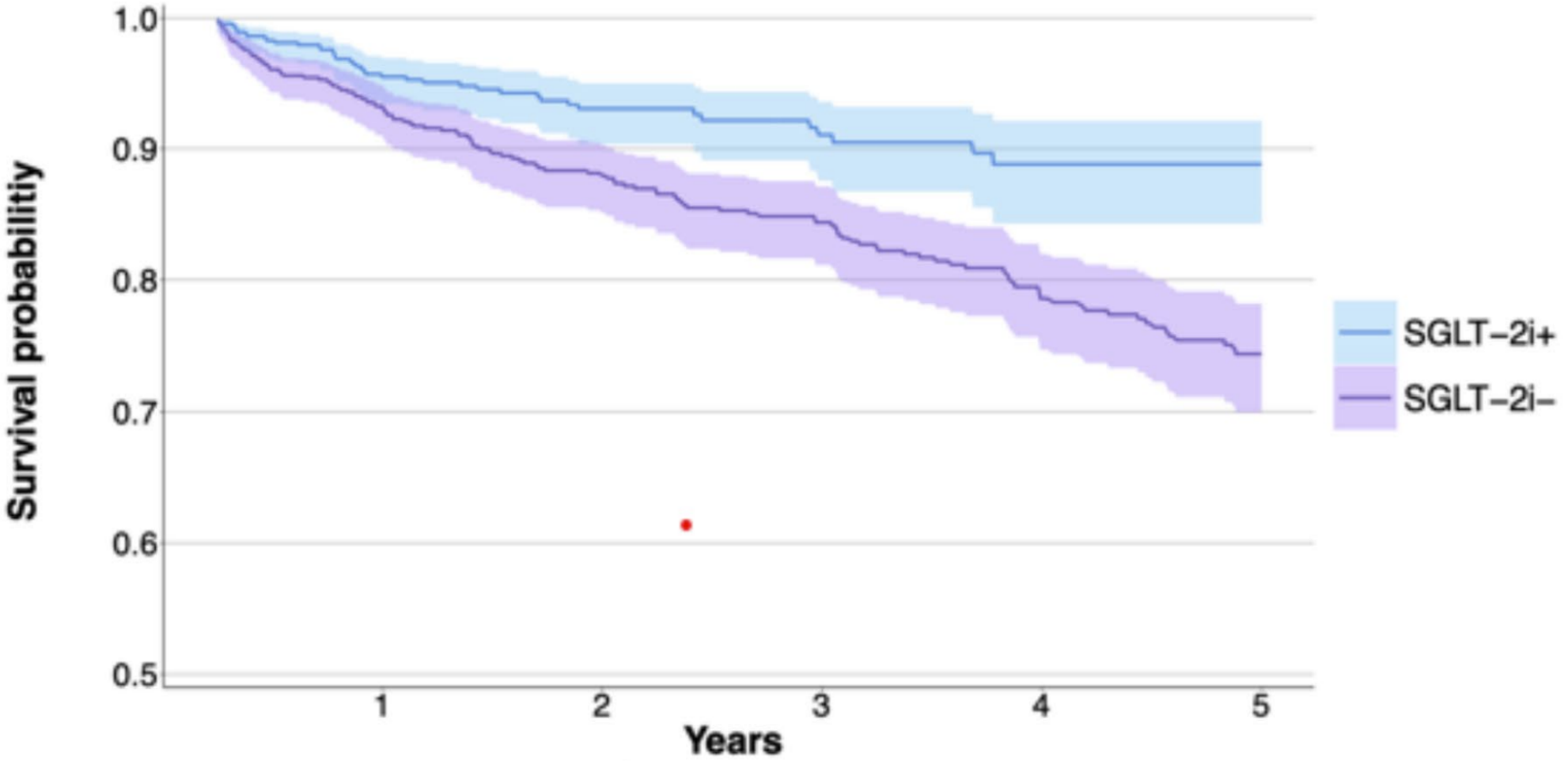


After PSM	SGLT-2i users	Non-users	P-value
advanced CKD	184 (23.9%)	187 (24.3%)	0.9051
AKI	587 (76.1%)	584 (75.7%)	0.9051
Shock	61 (7.9%)	62 (8.0%)	0.9999
Sepsis	180 (23.3%)	177 (23.0%)	0.9038
Hepatorenal sd	21 (2.7%)	18 (2.3%)	0.7456
Obstructive	15 (2.0%)	16 (2.1%)	0.9999
Heart failure	285 (37.0%)	286 (37.1%)	0.9999
Others	25 (3.2%)	26 (3.3%)	0.9999

Suivi médian: 2.0 (IQR, 0.3–3.9) years

Wang Card. Diab 2024

Mortalité toute cause

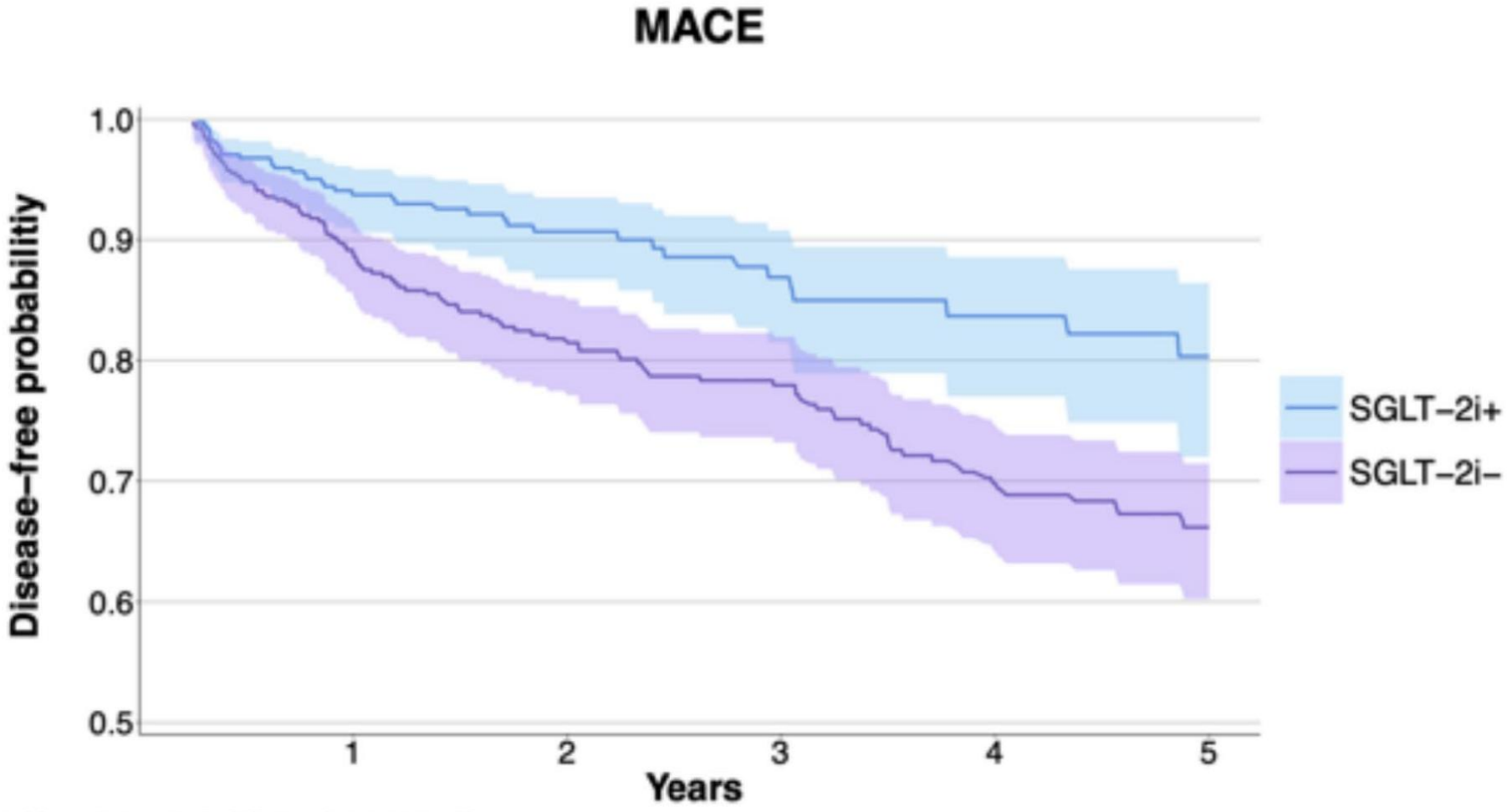


All-cause mortality : Number at risk(number event)

SGLT-2i+	3.6% (28)	7.8% (37)	5.2% (40)	5.3% (41)	5.4% (42)
SGLT-2i-	6.0% (46)	11.4% (88)	12.0% (93)	14.9% (115)	16.5% (127)

Wang Card. Diab 2024

Evènements cardio-vasculaires



MACE : Number at risk(number event)

SGLT-2i+	4.9% (22)	6.4% (29)	7.5% (35)	8.1% (37)	8.6% (39)
SGLT-2i-	7.1% (34)	12.1% (57)	17.2% (81)	18.6% (88)	22.5% (106)

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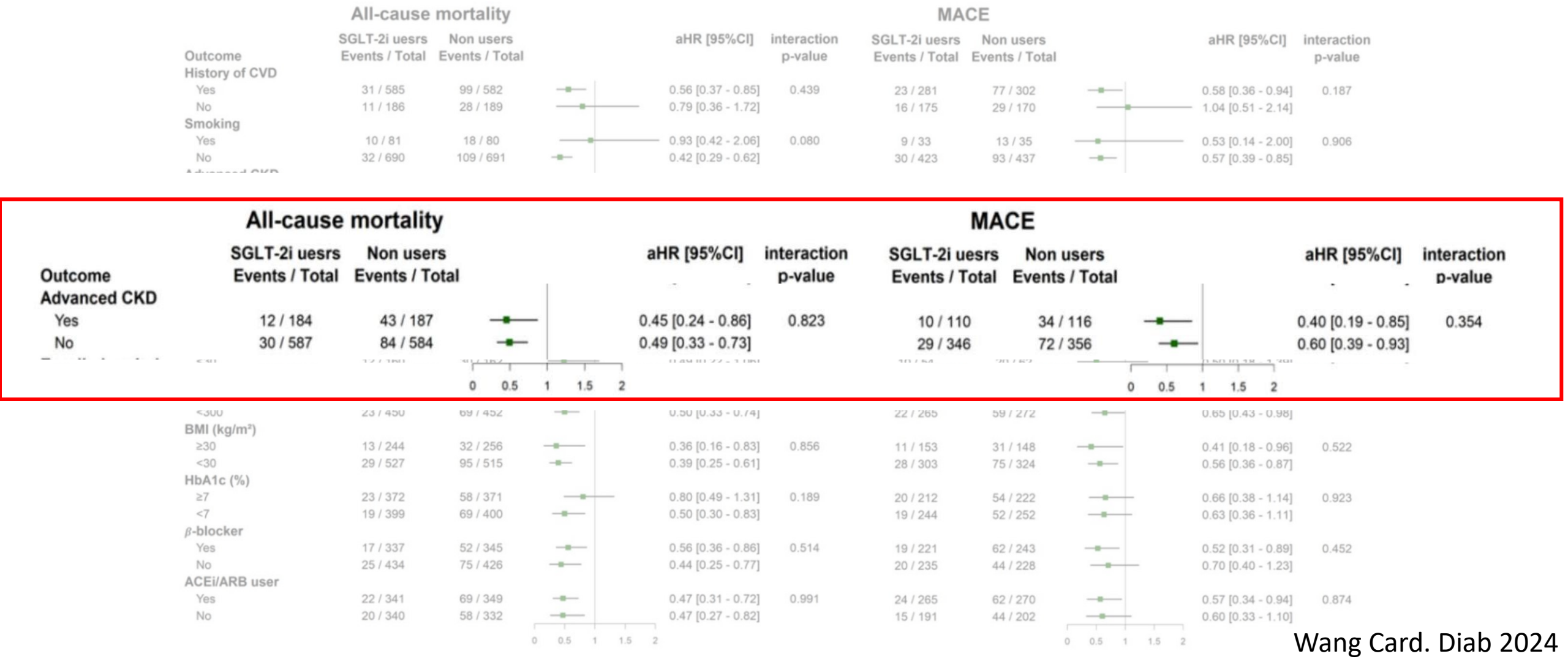
Effet bénéfique observé dans HD aiguë et chronique



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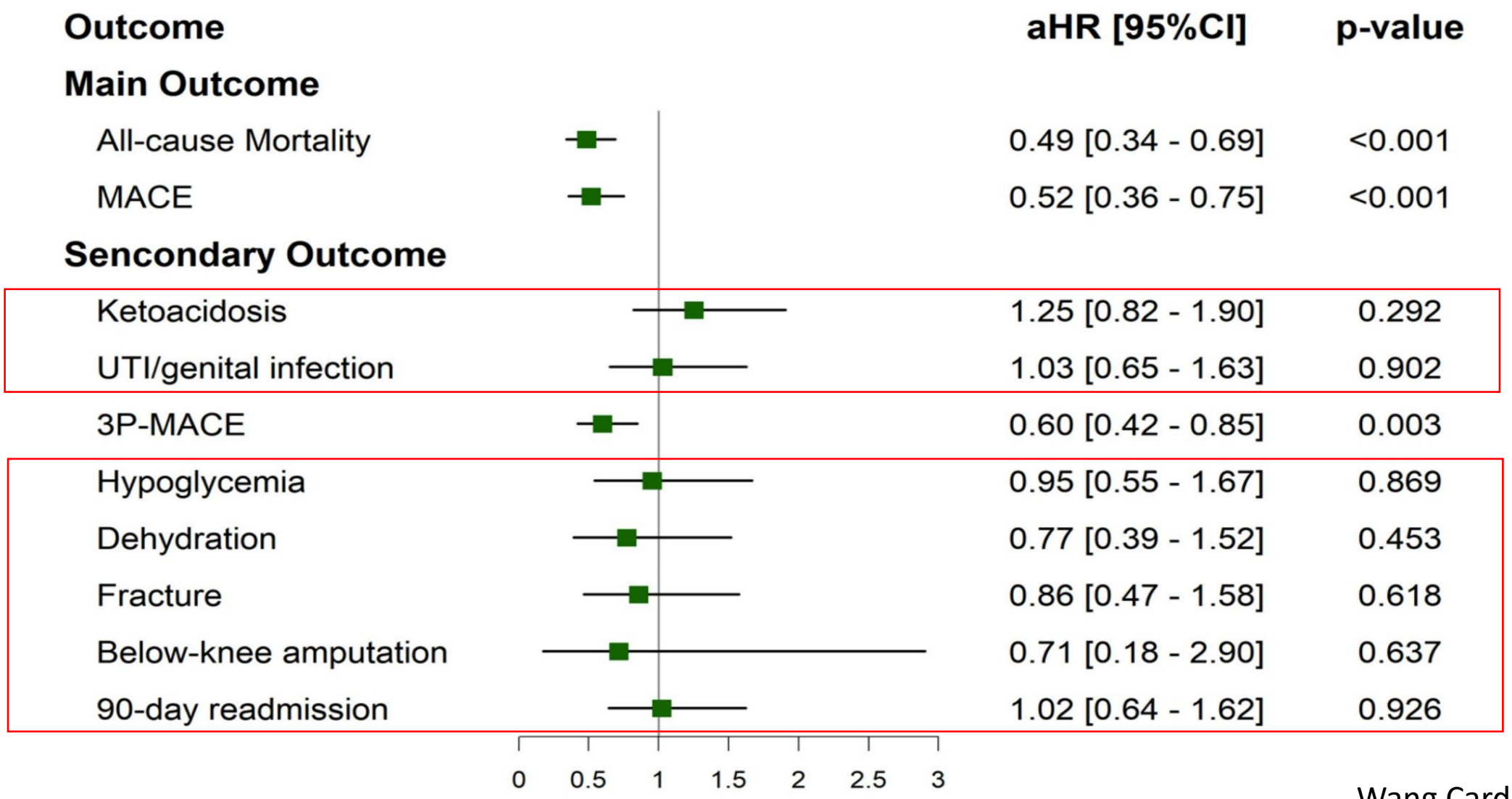
Safety



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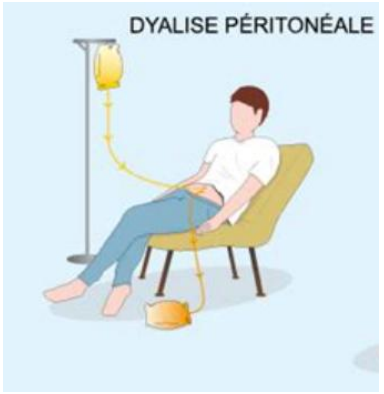
Intérêt des iSGLT2 en dialyse péritonéale ?



Expression SGLT2 par les cellules mésothéliales de la membrane péritonéales
Non modifiée par CKD ou DP
Mais augmentée dans péritonite sclérosante (cause? Conséquence?)

Inhibition SGLT2 voire SGLT2/1
Augmentation UF
Réduction inflammation péritonéal (modèles murins)

Canadian Society of Nephrology/ Société canadienne de néphrologie
CANADIAN JOURNAL OF KIDNEY HEALTH AND DISEASE

Narrative Review

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Role of SGLT-2 Inhibitors in Ultrafiltration Failure in Peritoneal Dialysis: A Narrative Review

Magdalena Riedl Khursigara[1], Ping Liu[2], Reetinder Kaur[3], and Thomas A. Mavrakanas[4]

Lai *et al. BMC Nephrology* (2023) 24:106
https://doi.org/10.1186/s12882-023-03164-8

BMC Nephrology

CASE REPORT Open Access

SGLT-2 inhibitors may increase ultrafiltration in incident peritoneal dialysis patients: a case report

Jia-Wen Lai[1], Hsuan-Jen Lin[1,2] and Che-Yi Chou[1,2,3*]

Study	Design	Participants	Intervention	Primary outcome
Hamdan et al[23]	Prospective interventional cohort study (pre-post)	Prevalent PD patients (N = 20)	Dapagliflozin 10 mg daily for 30 days	Changes in PET parameters
PRESERVE (NCT05250752)	Prospective interventional cohort study (pre-post)	PD patients (N = 10)	Dapagliflozin 10 mg daily for 3 days	D4/D0 ratio
EMPA-PD (NCT05671991)	Crossover randomized study[a]	PD patients with residual urine output ≥400 mL/24 h (N = 30)	Empagliflozin 25 mg (single dose) or placebo	Total glucose absorption
EMPOWERED[24] (jRCTs051230081)	Crossover randomized study	PD patients with heart failure (N = 36)	Empagliflozin 10 mg or placebo for 8 weeks	Change in daily UF volume from baseline
CANARY (NCT05715814)	Single-arm, open-label study	PD patients with residual renal function[b]	Empagliflozin 25 mg daily for 2 weeks	Change in measured GFR from baseline
RENAL LIFECYCLE (NCT05374291)	Randomized controlled trial	PD patients with residual urine output >500 mL/24 h (N = 100)[c]	Dapagliflozin 10 mg daily or placebo	Mortality or heart failure hospitalization

Efficacy and Safety of Dapagliflozin in Patients With CKD Stage 4-5

Study Design

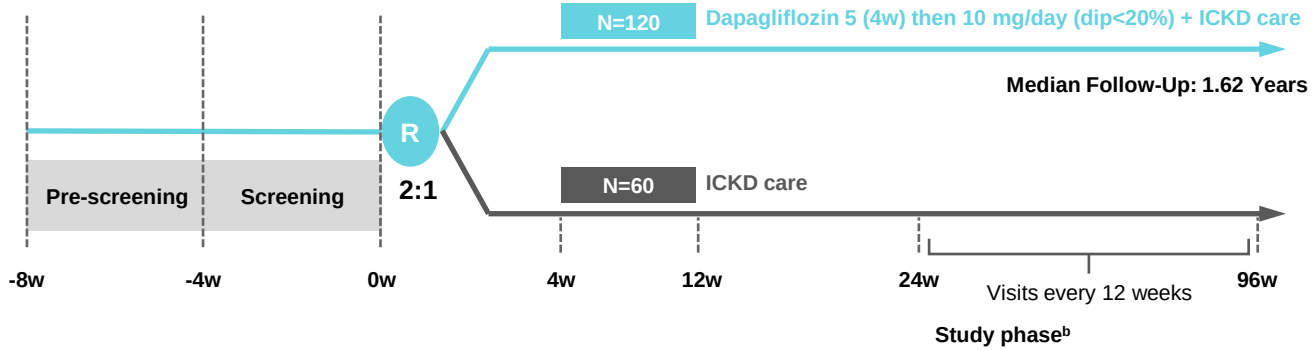
To assess the **efficacy and safety** of dapagliflozin in patients with CKD stage 4-5 under the ICKD care.

Key inclusion criteria:

- ≥20 years of age
- eGFR 10 to 30 mL/min/1.73 m^2
- eGFR decline ≥2.5 mL/min/1.73 m^2/year
- Pre-ESKD program ≥1 month before randomization

Key exclusion criteria:

- Lupus nephritis, ANCA-associated vasculitis
- Urinary tract obstruction, frequent urosepsis



Primary outcome
Difference of total eGFR slope after randomization

Secondary outcomes

- **Renal composite:** Sustained ≥50% eGFR decline, ESRD[c], and renal or CV death
- **Renal and HF composite:** Renal composite + hospitalization for HF and hospitalization for AKI
- **Renal and CV composite:** Renal and HF composite + 5p-MACEs[d]

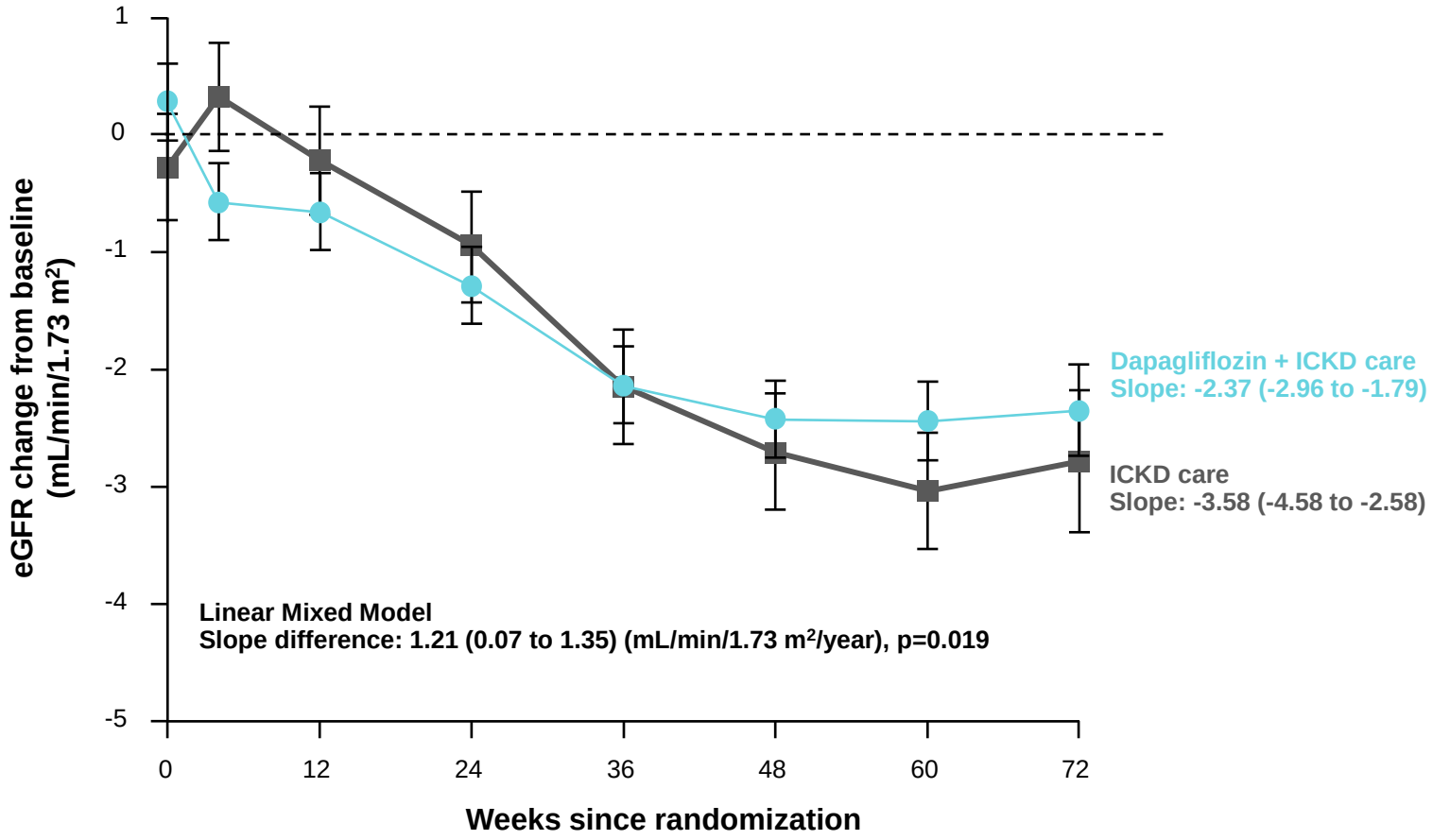
Safety
Serious AEs, discontinuation due to AEs, and CKD complications

Baseline Characteristics

Characteristics	Dapagliflozin + ICKD care (N=120)	ICKD care (N=60)
Age, years, mean (SD)	67.5 (11.7)	71.4 (8.3)
Female sex, no. (%)	41 (34.2)	27 (45.0)
Body mass index, kg/m^2, mean (SD)	26.1 (4.7)	25.8 (4.0)
T2D, no. (%)	63 (52.5)	32 (53.3)
Systolic blood pressure, mm Hg, mean (SD)	135.1 (13.2)	133.3 (18.4)
eGFR, mL/min/1.73 m^2, mean (SD)	18.9 (5.5)	19.7 (5.8)
eGFR <20 mL/min/1.73 m^2, no. (%)	69 (57.5)	32 (53.3)
eGFR slope, mL/min/1.73 m^2/year, median (IQR)	-5.4 (-9.1 to -3.4)	-5.5 (-9.9 to -4.0)
UPCR, mg/g, median (IQR)	1388 (554 to 2483)	963 (322 to 2046)
UACR, mg/g, median (IQR)	765 (320 to 1587)	609 (144 to 1221)
RAS inhibitors, no. (%)	72 (60.0)	33 (55.0)

Presented at: ASN Kidney Week; October 24-27, 2024; San Diego, CA.

Primary Outcome: Difference of eGFR Slope



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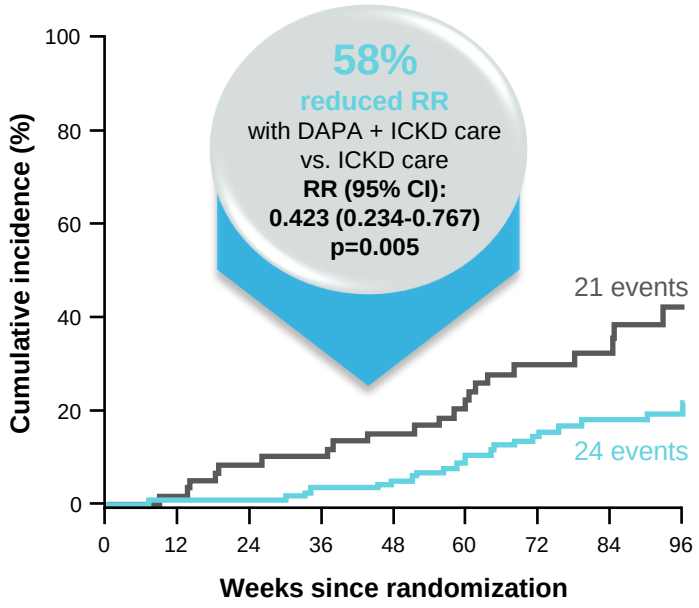
Kaplan–Meier Curve of Secondary Outcomes

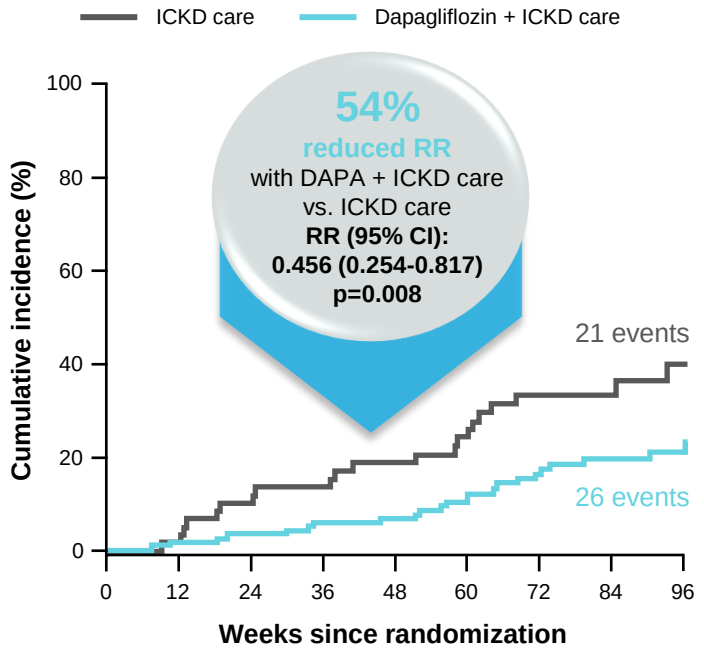
Renal composite outcome



No. at Risk									
ICKD care	60	59	54	53	50	43	30	24	13
Dapagliflozin + ICKD care	120	118	118	114	111	96	82	62	36

- Sustained ≥50% eGFR decline,
- ESRD
- Renal Death
- CV death

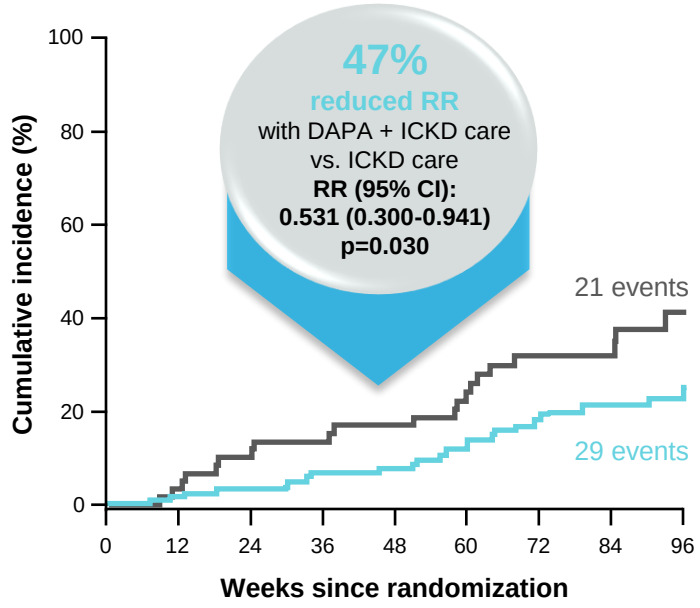
Renal and heart failure composite outcome



	60	59	53	51	48	41	29	24	14
	120	117	115	111	109	94	81	61	35

- Renal composite
- Hospitalization for HF
- Hospitalization for AKI

Renal and cardiovascular composite outcome[a]



	60	58	53	51	49	42	30	25	14
	120	117	115	110	108	92	80	60	36

- Renal and HF composite
- MACEs

Presented at: ASN Kidney Week; October 24-27, 2024; San Diego, CA.

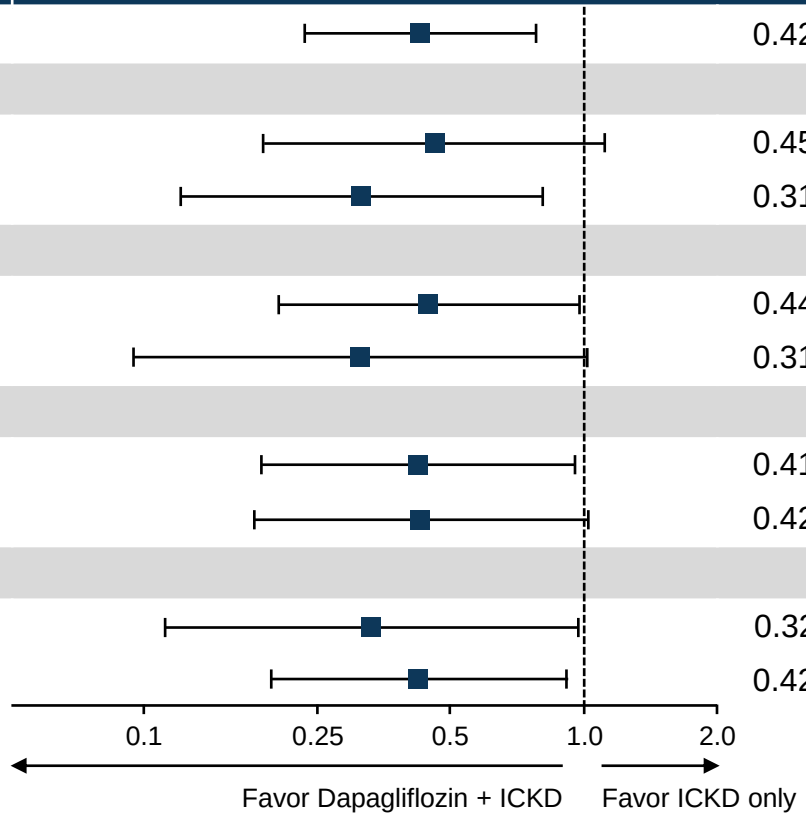
Safety Outcomes (Contd.)

Safety outcomes, no. (%)	Dapagliflozin + ICKD care with hard outcome (N=17)	ICKD care with hard outcome (N=17)	p-value
Non-fatal SAE led to hard outcome[a]			
AKI hospitalization	**1 (5.9)**	**7 (41.2)**	**0.039**
HF hospitalization	1 (5.9)	3 (17.6)	0.601
CKD fluid overload hospitalization	2 (11.8)	2 (11.8)	1.000
5p-MACE[b]	2 (11.8)	2 (11.8)	1.000

Presented at: ASN Kidney Week; October 24-27, 2024; San Diego, CA.

Subgroup Analysis of Renal Composite Outcome

Subgroup	Dapagliflozin + ICKD care	ICKD care	Hazard ratio[a] (95% CI)
	no. of events/no. of participants		
All participants	24/120	21/60	0.423 (0.234-0.767)
Age			
<70 yr	16/60	9/23	0.459 (0.187-1.120)
≥70 yr	8/60	12/37	0.313 (0.121-0.808)
Sex			
Male	19/79	13/33	0.447 (0.206-0.971)
Female	5/41	8/27	0.312 (0.096-1.010)
Type 2 diabetes			
Yes	13/63	11/32	0.419 (0.185-0.948)
No	11/57	10/28	0.428 (0.180-1.017)
Systolic blood pressure			
≤130 mm Hg	7/50	9/34	0.329 (0.112-0.968)
>130 mm Hg	17/70	12/26	0.422 (0.196-0.908)



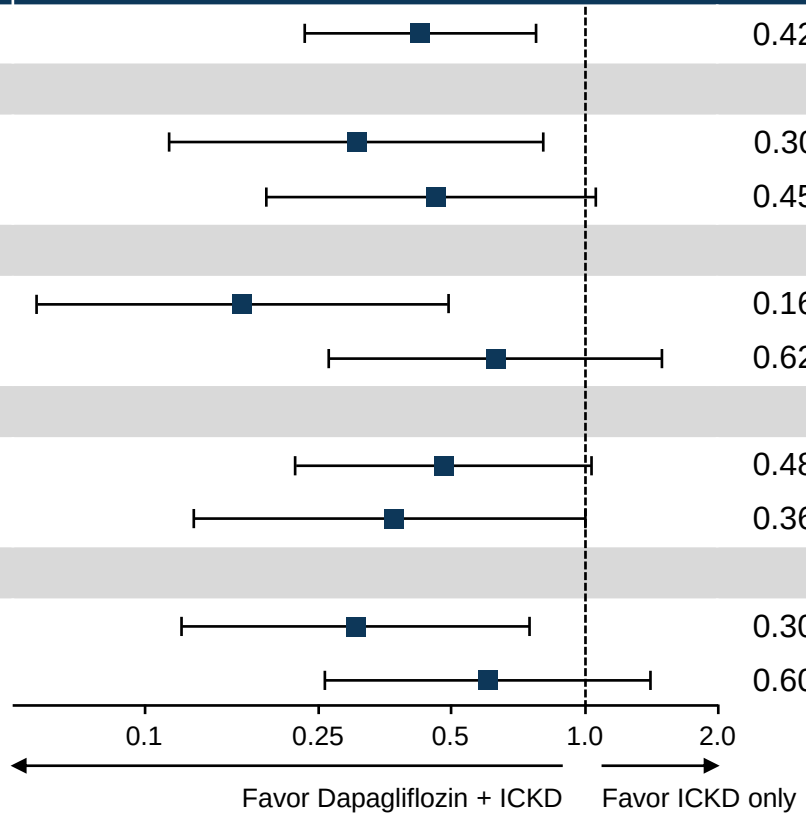
[a]Cox proportional hazard model stratified by diabetes, eGFR and baseline eGFR slope.

CI = confidence interval; eGFR = estimated glomerular filtration rate; ICKD = integrated chronic kidney disease.

Hung CC et al. Presented at: ASN Kidney Week ; October 24-27, 2024; San Diego, CA.

Subgroup Analysis of Renal Composite Outcome

Subgroup	Dapagliflozin + ICKD care	ICKD care	Hazard ratio[a] (95%CI)
	no. of events/no. of participants		
All participants	24/120	21/60	0.423 (0.234-0.767)
CKD stage			
Stage 4	7/82	11/42	0.303 (0.114-0.805)
Stage 5	17/38	10/18	0.456 (0.192-1.086)
UACR			
<1000 mg/g	8/67	12/39	0.167 (0.057-0.488)
≥1000 mg/g	16/53	9/21	0.629 (0.264-1.490)
Over-hydration (OH)			
Yes (OH ≥1 L)	16/59	12/29	0.481 (0.220-1.048)
No (OH <1 L)	8/61	9/31	0.365 (0.133-1.001)
RAS inhibitor			
Yes	9/72	11/33	0.302 (0.122-0.746)
No	15/48	10/27	0.609 (0.260-1.421)



[a]Cox proportional hazard model stratified by diabetes, baseline eGFR and baseline eGFR slope.

CI = confidence interval; CKD = chronic kidney disease; eGFR = estimated glomerular filtration rate; ICKD = integrated chronic kidney disease; OH = over-hydration; RAS = renin angiotensin aldosterone system; UACR = urine albumin-to-creatinine ratio.

Hung CC et al. Presented at: ASN Kidney Week ; October 24-27, 2024; San Diego, CA.

Safety Outcomes

Safety outcomes, no. (%)	Dapagliflozin + ICKD care (N=120)	ICKD care (N=60)	p-value
Serious adverse events	41 (31.2)	24 (40.0)	0.466
Discontinuation due to adverse events	3 (2.5)	-	-
Adverse events of interest			
Acute eGFR dip >30%	2 (2.5)	0 (0.0)	0.217
Volume depletion	1 (0.8)	1 (1.7)	0.615
Major hypoglycemia	1 (0.8)	1 (1.7)	0.615
Urinary tract infection with hospitalization	6 (5.0)	3 (5.0)	1.000
Diabetic ketoacidosis	0 (0.0)	0 (0.0)	-
CKD complications of interest			
Anemia and iron insufficiency			
Hemoglobin <9 g/dL	19 (15.8)	11 (18.3)	0.671
Iron saturation <20%	15 (12.5)	13 (21.7)	0.129
Ferritin >500 ng/mL	12 (10.0)	9 (15.0)	0.334
Electrolyte imbalance of interest			
Serum potassium >5.5 mEq/L	20 (16.7)	10 (16.7)	1.000
Uric acid >9 mg/dL	22 (18.3)	8 (13.3)	0.396

CKD = chronic kidney disease; eGFR = estimated glomerular filtration rate; ICKD = integrated chronic kidney disease.

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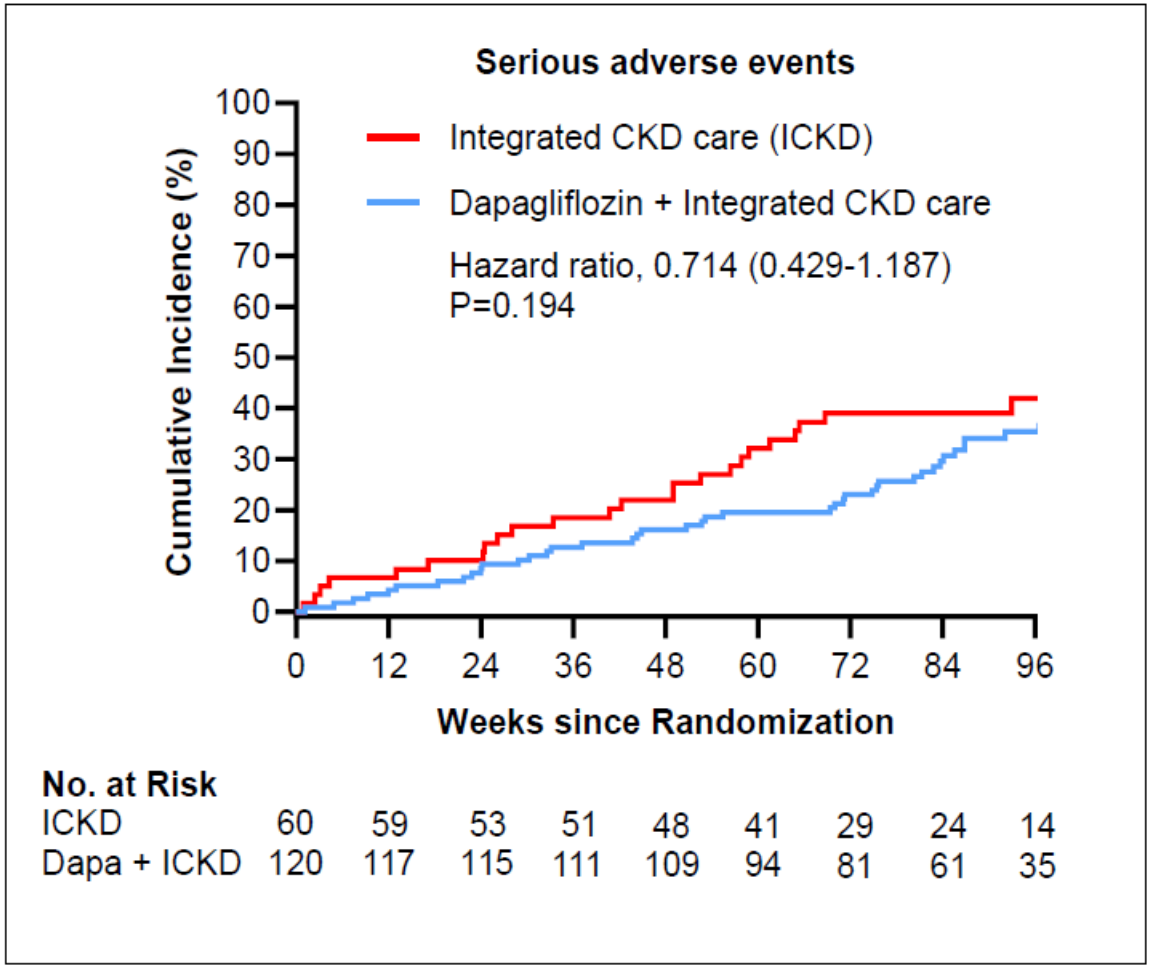
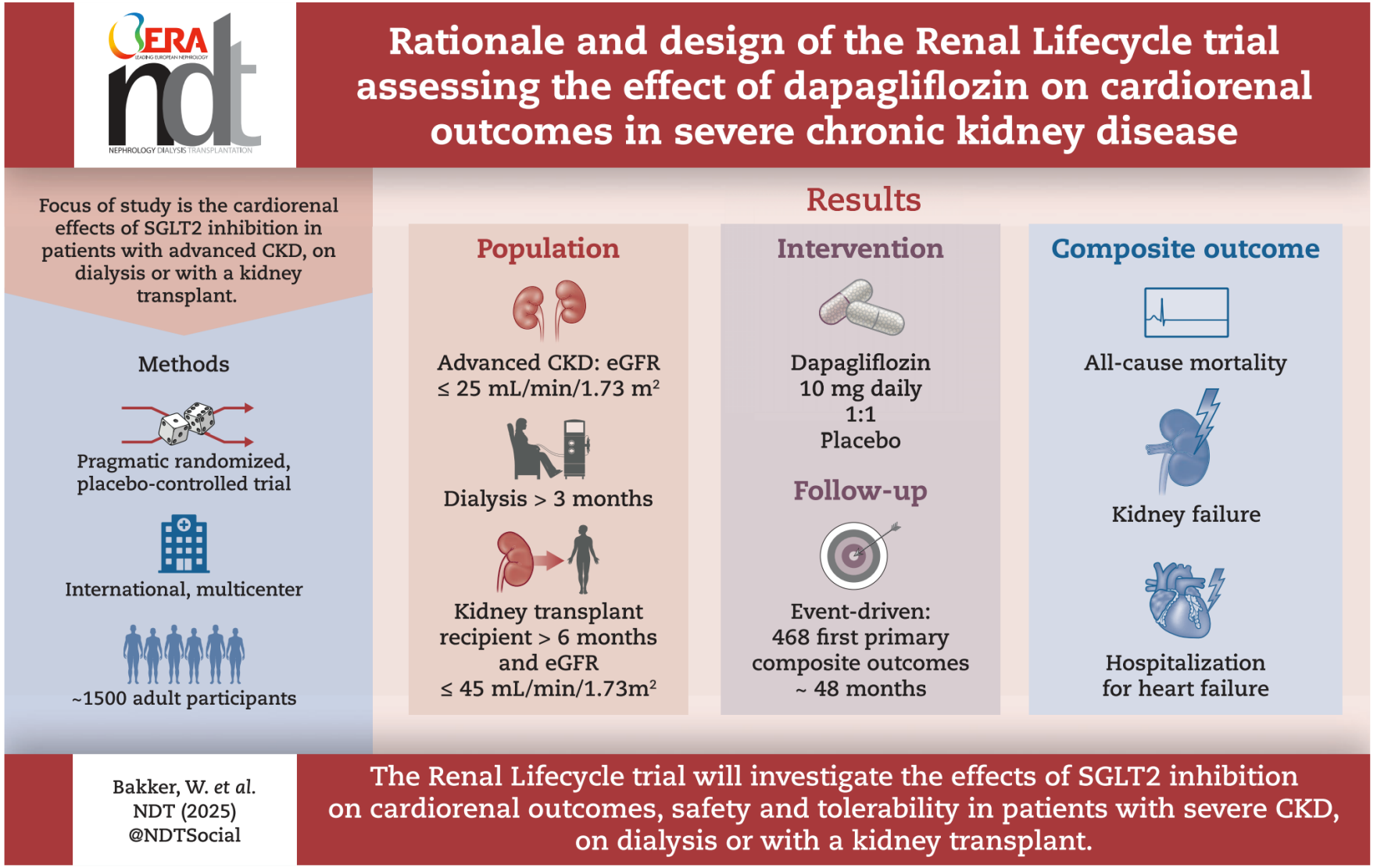
Kaplan–Meier curve of safety outcome

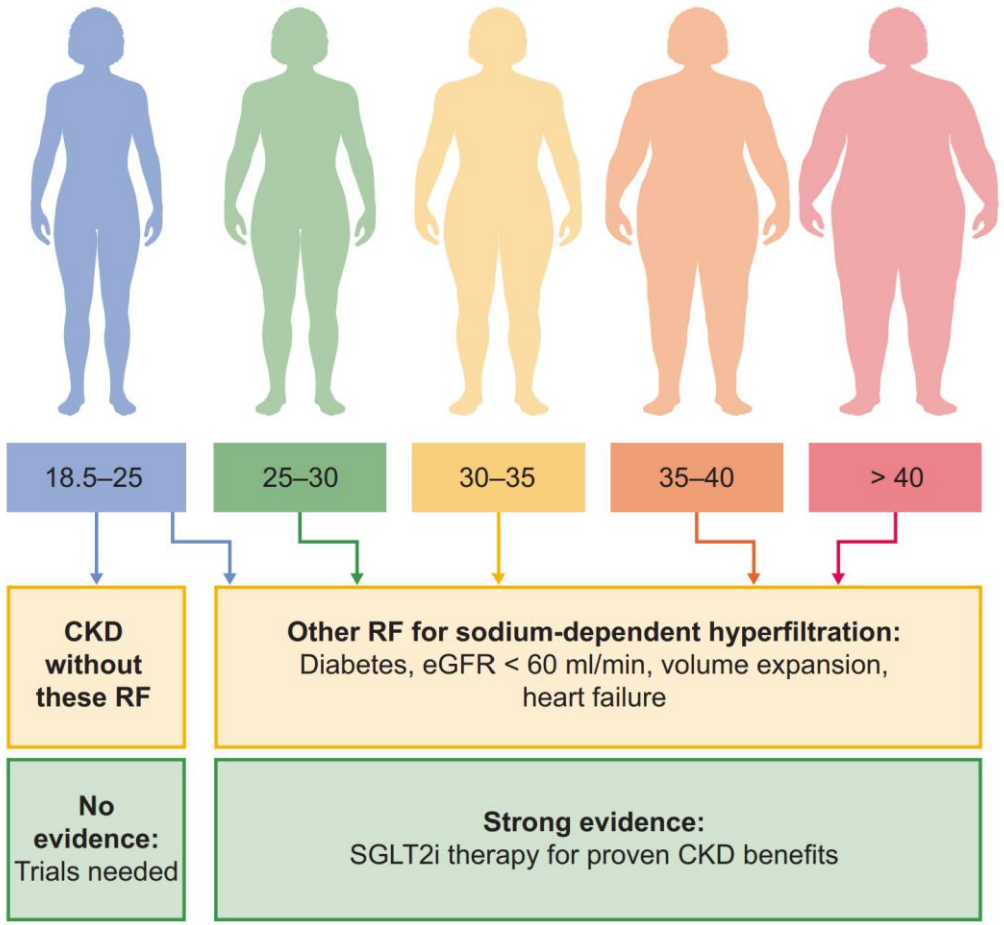


CKD, chronic kidney disease; Dapa, dapagliflozin; eGFR, estimated glomerular filtration rate; ICKD, integrated CKD care

Next step : essai clinique chez les patients en IRCT



Une autre population spécifique = la MRC du sujet sans surpoids non diabétique



Populations avec hyperfiltration
et hypervolémie sur représentée dans les essais cliniques dont DAPA CKD et EMPA-KIDNEY

Autres mécanismes de progression
Génétique (PKR, Alport)
Inflammation
Toxiques

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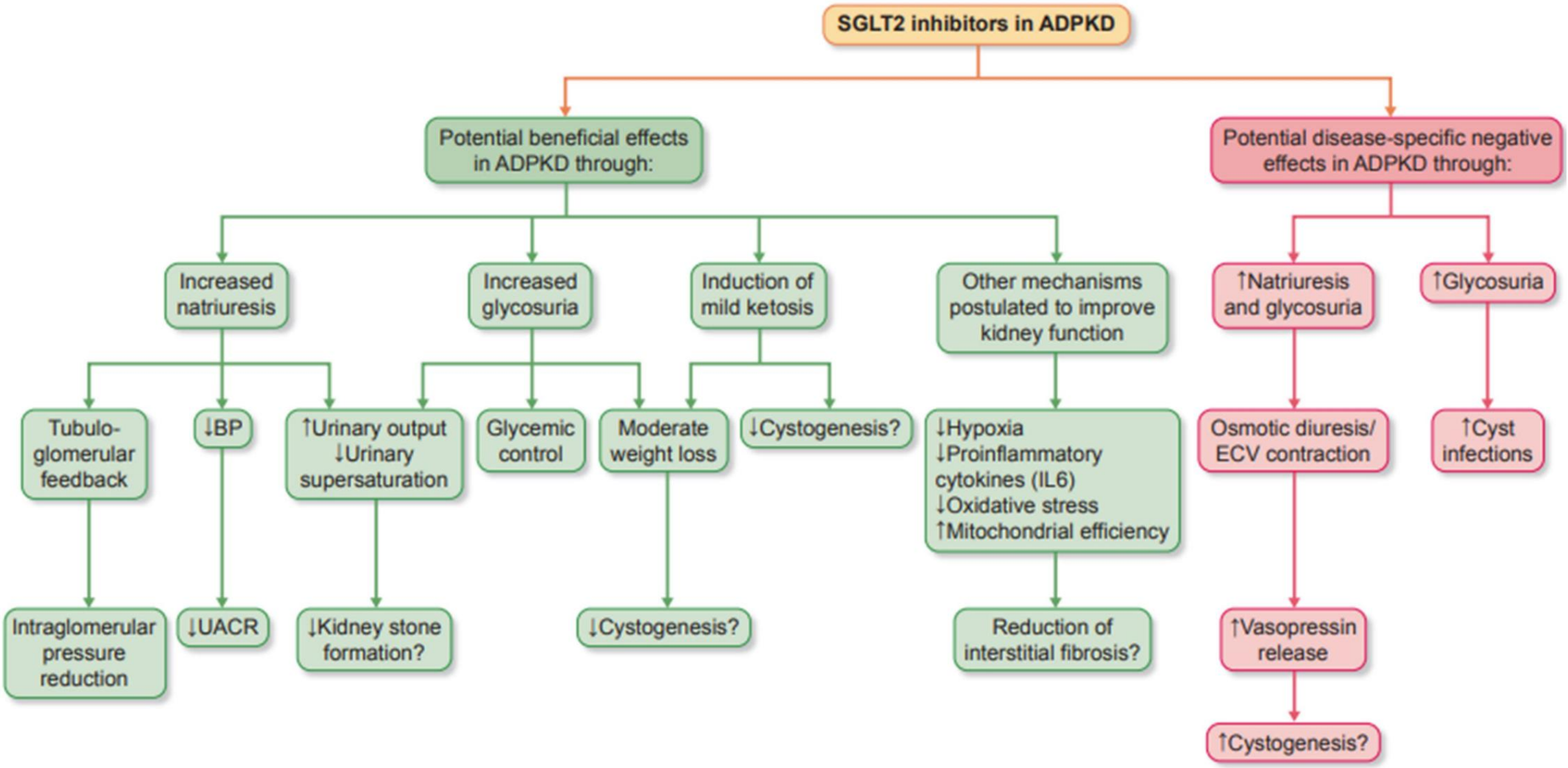
Une autre population spécifique = les polykystiques



Muller NDT 2025

Conclusion

La réduction de la mortalité et le ralentissement de la dégradation de la fonction rénale des patients MRC traités par iSGLT2 justifient leur évaluation dans les populations spécifiques non inclues dans les RCTs

- Spécificité = maladie
- Spécificité = stade d'Insuffisance rénale
- Spécificité = âge

} Quel objectif, quel critère de jugement?