Quelle place pour la finerenone?

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MÉDECINE SORBONNE UNIVERSITÉ

Conflits d’intérêt

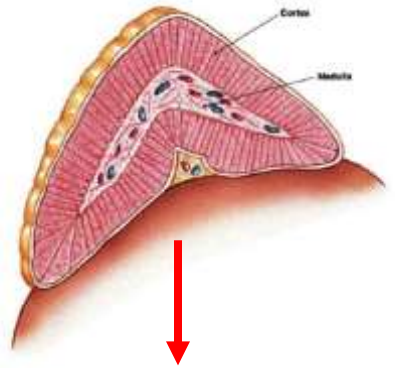
- Astrazeneca: Board, congrès, investigateur d’essais
- Boehringer-Ingelheim: Board, formation – conseil
- GSK: board, séminaire, formation
- Roche: congrès, investigateur d’essai
- Viforpharma: board, investigateur, congrès
- Novartis: board, congrès, investigateur essais
- Otsuka: board, congrès, investigateur essais
- **Bayer**: board, symposium
- Amicus: board, séminaire

PLAN

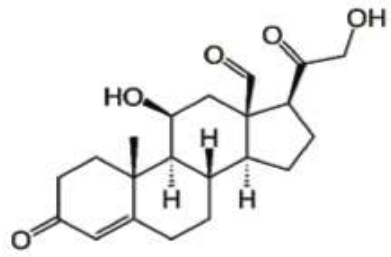
1. Les MRA et la finerenone
2. Finerenone : résultats des essais
3. Questions en suspend pour son positionnement
4. Conclusion

Action de l'aldostérone

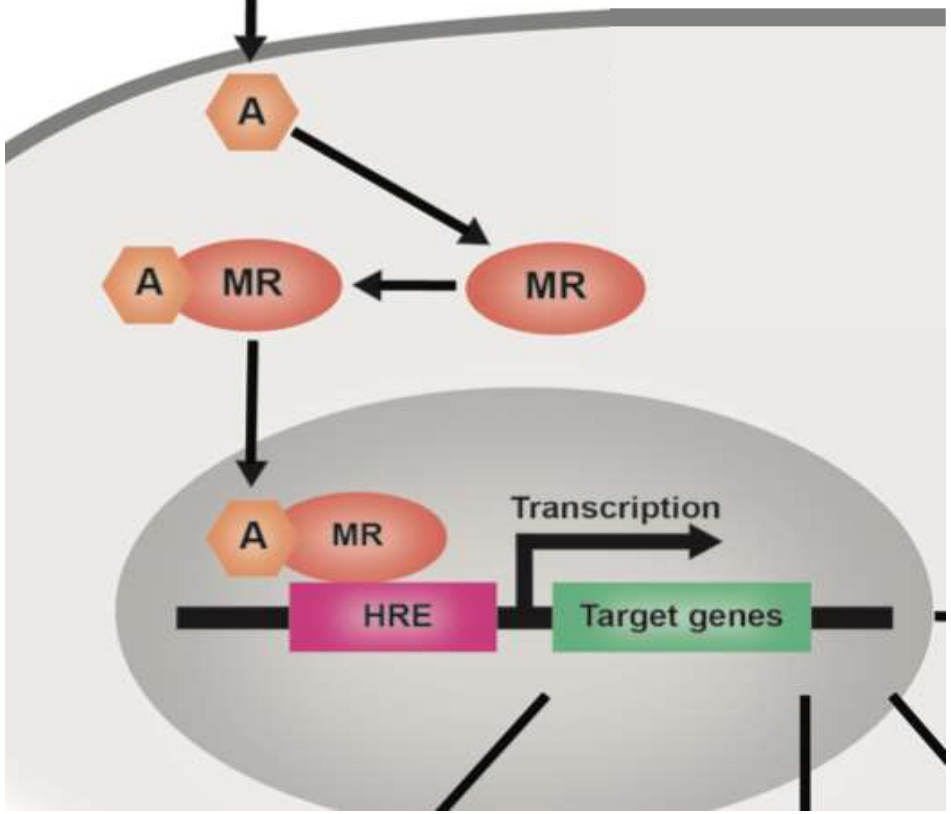
Angiotensine II



Aldostérone → **Réabsorption tubulaire de Na+ (CC)**

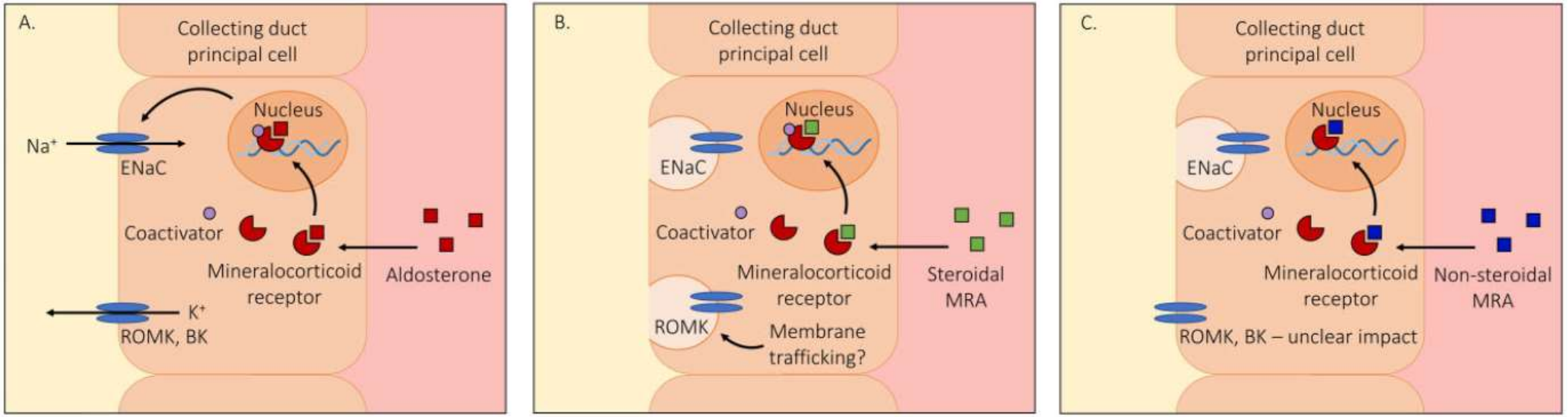


Aldosterone



Buonafine et al. Am J of Hypertension 2018

L’aldostérone induit la réabsorption de Na dans le tube collecteur cortical

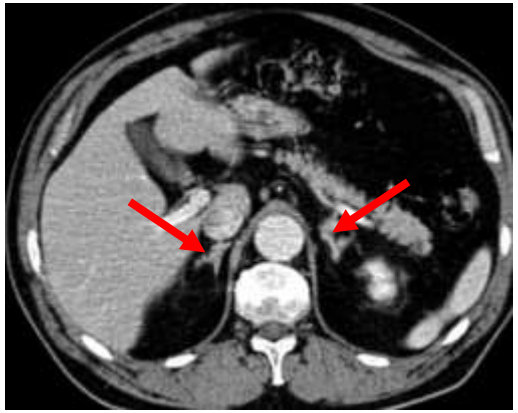


- Liaison Aldostérone sur son récepteur
- **Fixation de co-activateurs**
- Inhibe ubiquination et endocytose d’ENaC,
- Stimule réabsorption de Na, qui génère électronégativité luminale, entrée de K par la Na/K-ATPase
- Sortie de K par ROMK et BK.

- La Finerenone (MRA non-steroidien)
- **Se fixe le site de liaison ligand-MR et empêche la liaison des co-activateurs**
- Effets anti-inflammatoire et anti-fibrosant plus importants que MRA stéroïdien.

Hyperaldostéronisme primaire vs HTA : atteinte des organes ?

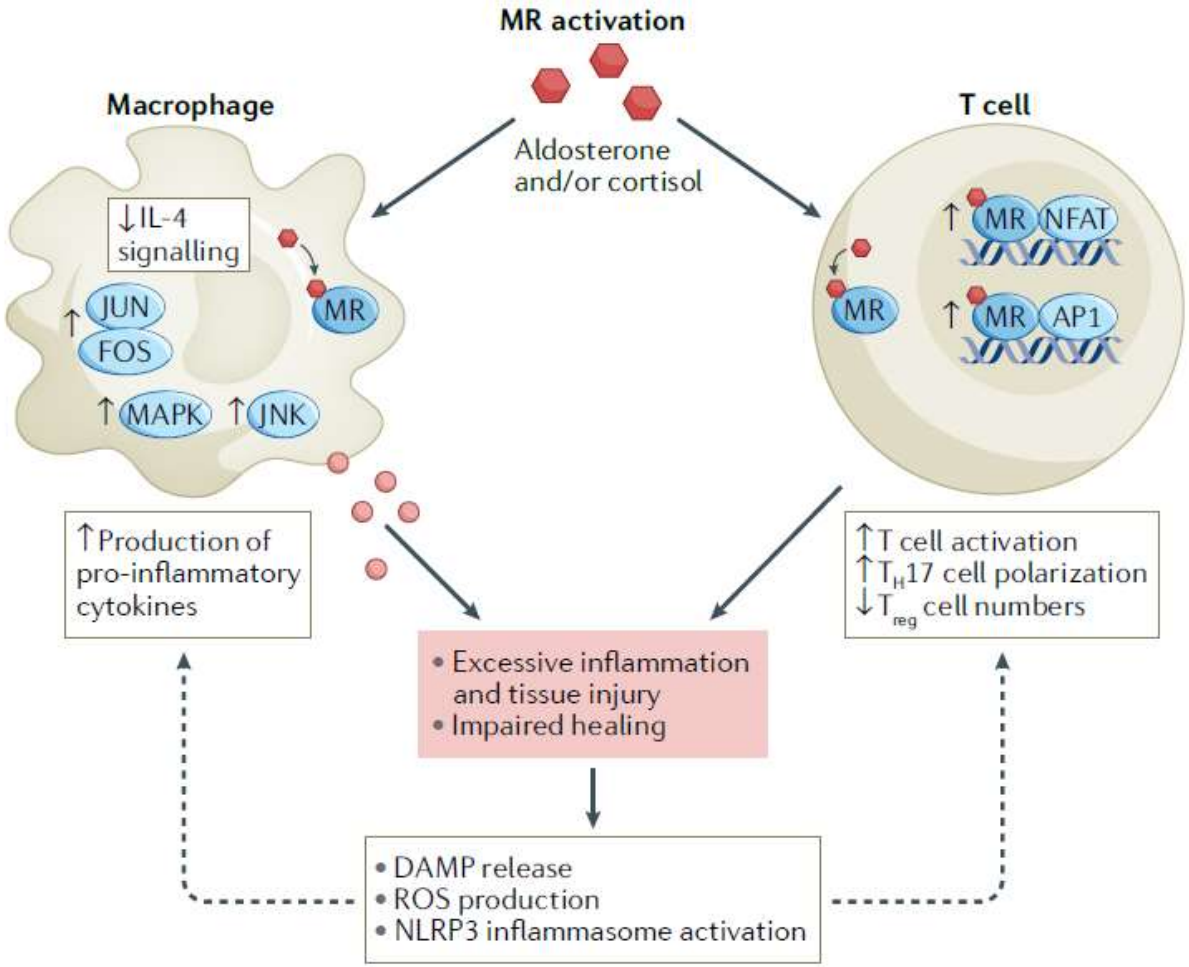
- HTA + hypokaliémie
- Rénine basse, aldostérone augmentée
- Imagerie
- Traitement
  - Spironolactone/Eplérenone
  - Surrénalectomie si latéralisé au KTVS



	HAP	HTA essentielle	OR (IC 95%)
Insuffisance cardiaque	1344	4395	2,05 (1,11-3,78)
AVC	1063	3893	2,58 (1,93-2,45)
Fibrillation atriale	1478	5120	3,52 (2,06-5,99)
Infarctus du myocarde	1803	5464	1,77 (1,10-2,83)

Monticone S. The Lancet Diab & Endoc 2018

L'action du RM ne se limite pas au sodium



L'activation du MR n'induit pas qu'une réabsorption sodée

→ **Molécules pro fibrosantes** : ET1, TGF béta, PAI 1, collagène

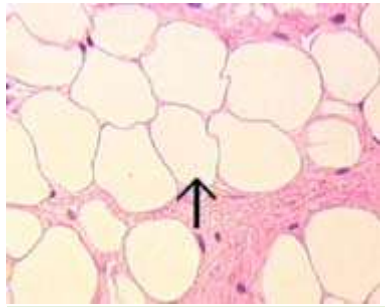
→ **Activation de cytokines pro inflammatoires** : ROS, NFKB, IL6, TNF, IFN

→ **Activations cellulaires** (lymphocytes, macrophages)

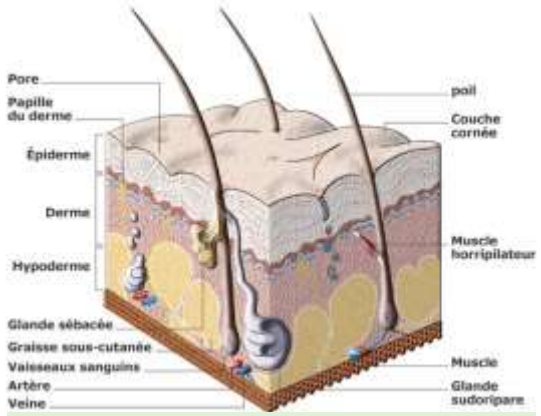
FIBROSE + INFLAMMATION

Buonafine et al. Am J of Hypertension 2018

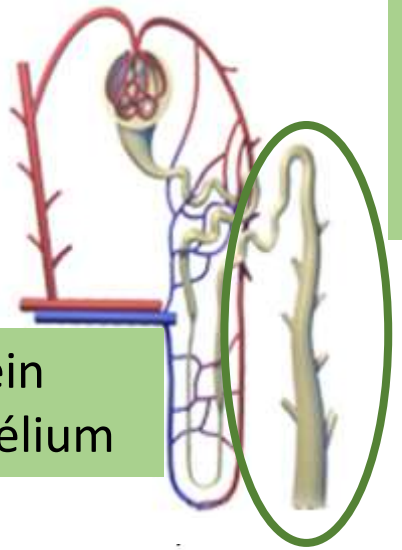
L’expression du RM est diffuse



Adipocytes

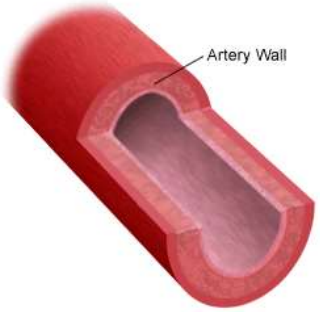


Peau

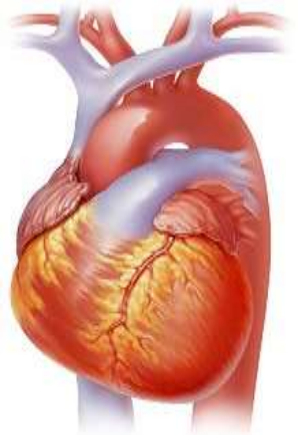


Rein
épithélium

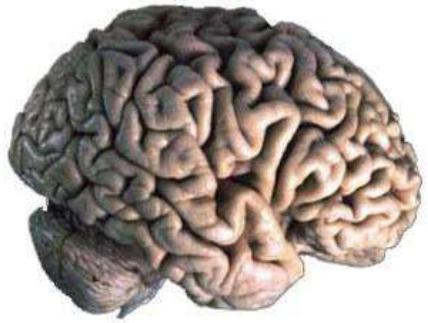
Rein
podocytes,
endothelium,
fibroblastes



Cellules endothéliales
CMLV



Coeur



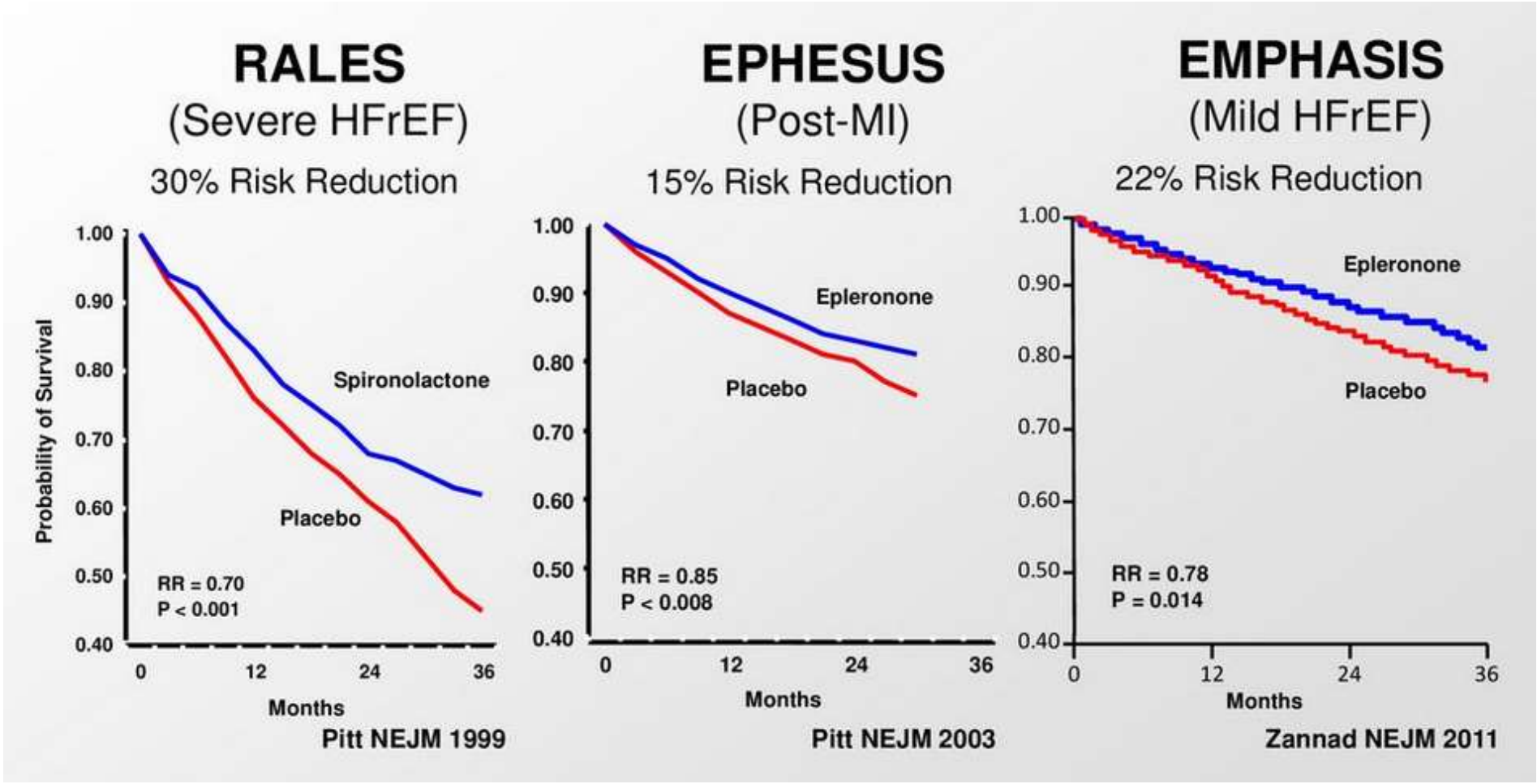
Système nerveux
central

Epstein et al. AJKD 2022

Les antagonistes des récepteurs minéralocorticoïdes (MRA)

	ARM stéroïdiens		Finérénone
			
Propriétés de structure	Plat (stéroïdien)	Plat (stéroïdien)	Volumineux (non stéroïdien)
Affinité aux RM	Élevée	Modérée	Elevée
Sélectivité aux RM	Faible	Modérée	Elevée
EI sexuels	Oui (gynecomastie)	Rares	Aucun signal
Distribution Tissulaire	>6 1	~3 1	1 1
$T^{1/2}$, Métabolites	1-4h / métabolites actifs 12-35h	2-6h / Pas de metabolites actifs	2-3h /Pas de metabolites actifs
Hyperkaliémie	Oui	Oui	Augmentation modérée

Bénéfice des MRA sur le cœur (mortalité)

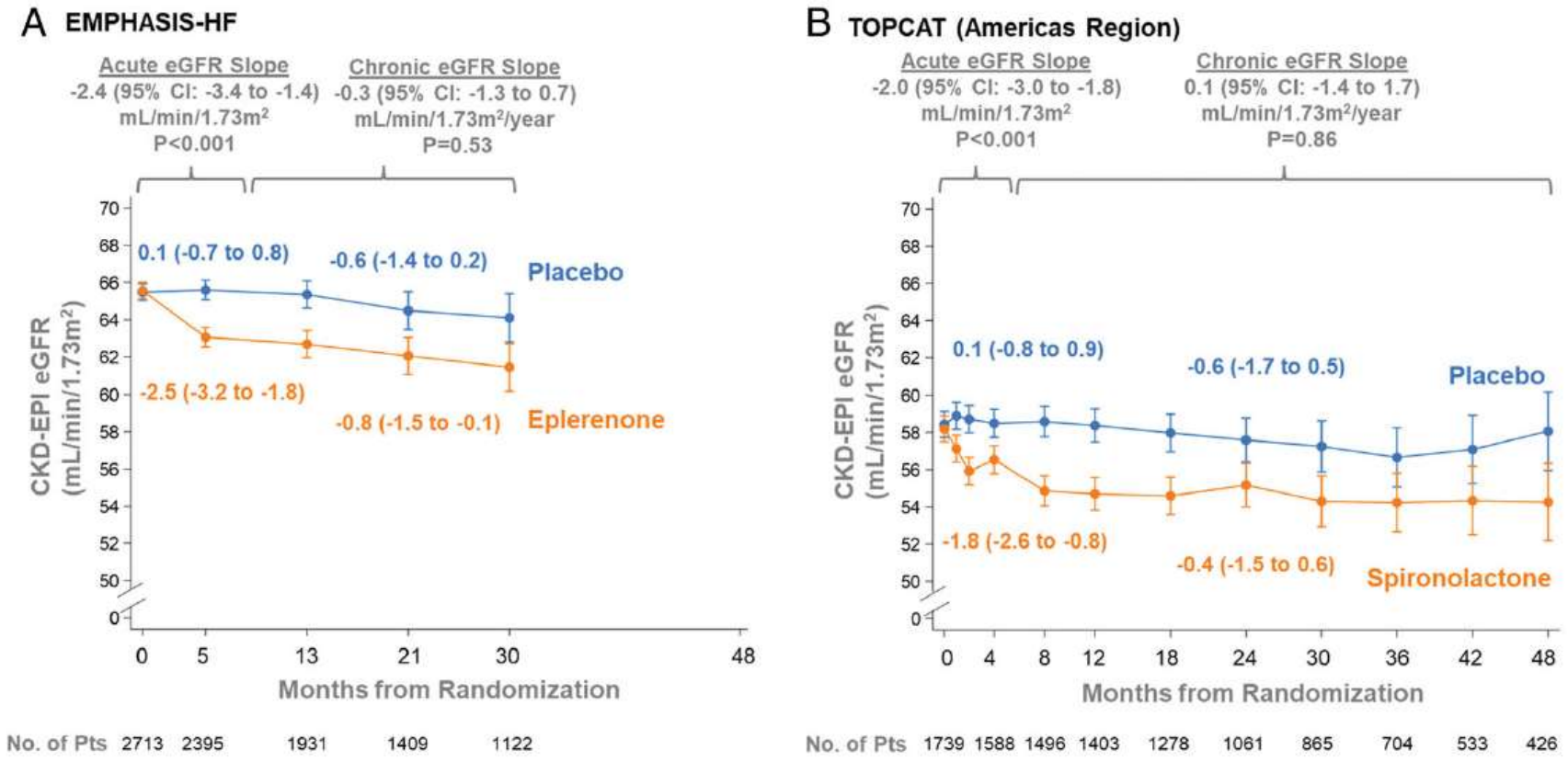


Bénéfice des MRA sur le rein ? protéinurie?

Authors	Design	Subjects	No. of patients	Daily dosage	Duration	Proteinuria
SPL						
Rossing et al.[28]	Crossover	Type 2 DM with macroalbuminuria	20	25 mg	16 weeks	↓ 33%
van den Meiracker et al.[29]	RCT	Type 2 DM with macroalbuminuria	59	25–50 mg	1 year	↓ 40%
Schjoedt et al.[30]	Crossover	Type 1 DM with macroalbuminuria	20	25 mg	4 weeks	↓ 30%
Schjoedt et al.[31]	Crossover	Type 1 or 2 DM, albuminuria > 2.5 g/day	20	25 mg	4 weeks	↓ 32%
Chrysostomou et al.[32]	RCT	Proteinuria > 1.5 g/day; serum creatinine < 200 μmol/L	41	25 mg	3 months	↓ 42%
Furumatsu et al.[33]	RCT	Nondiabetic CKD, proteinuria > 0.5 g/day	32	25 mg	1 year	↓ 58%
Tylicki et al.[34]	Crossover	Nondiabetic CKD, proteinuria > 0.3 g/day	18	25 mg	24 weeks	↓ 55%
Bianchi et al.[35]	RCT	Idiopathic GN, proteinuria > 1 g/g Cr	165	25 mg	1 year	↓ 57%
EPL						
Epstein et al.[36]	RCT	Type 2 DM, albuminuria > 50 mg:g Cr	268	50–100 mg	12 weeks	↓ 45%
Boesby et al.[37]	Crossover	Nondiabetic CKD, proteinuria > 0.3 g/day	40	25–50 mg	16 weeks	↓ 22%

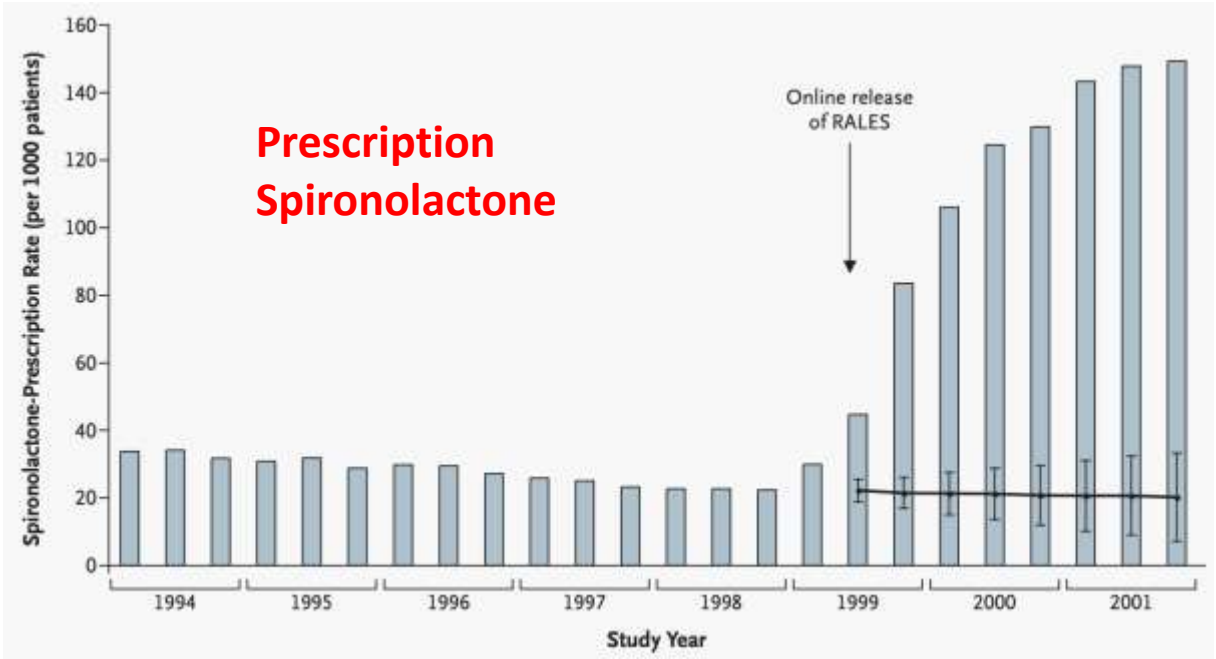
Ma and Szeto. Renal Failure 2012.

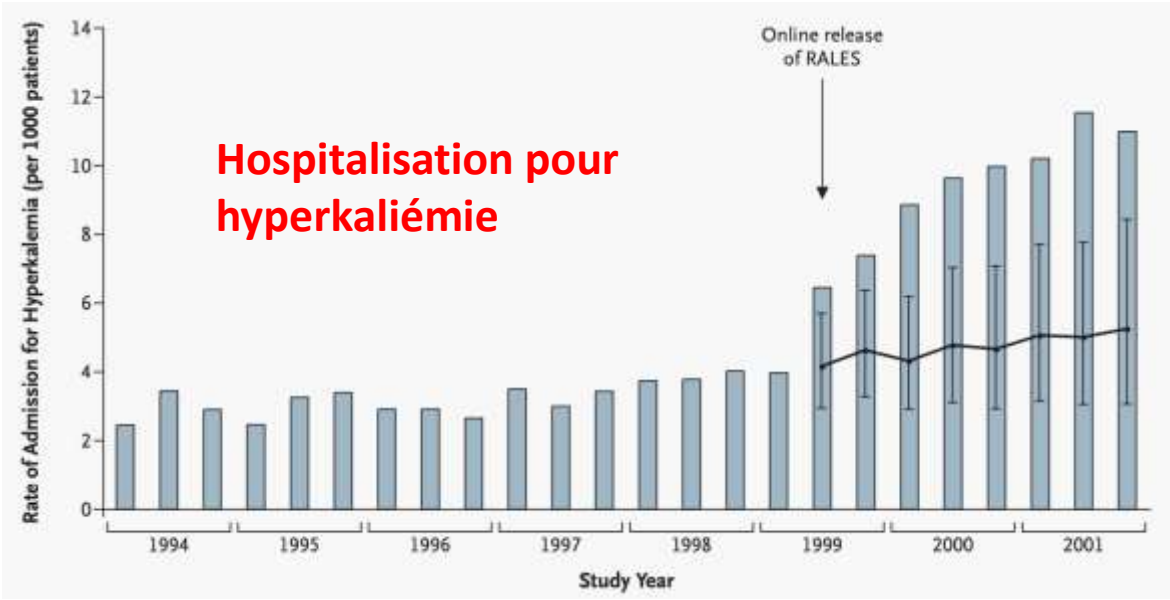
Bénéfice des MRA sur le rein: sur la pente de DFG?

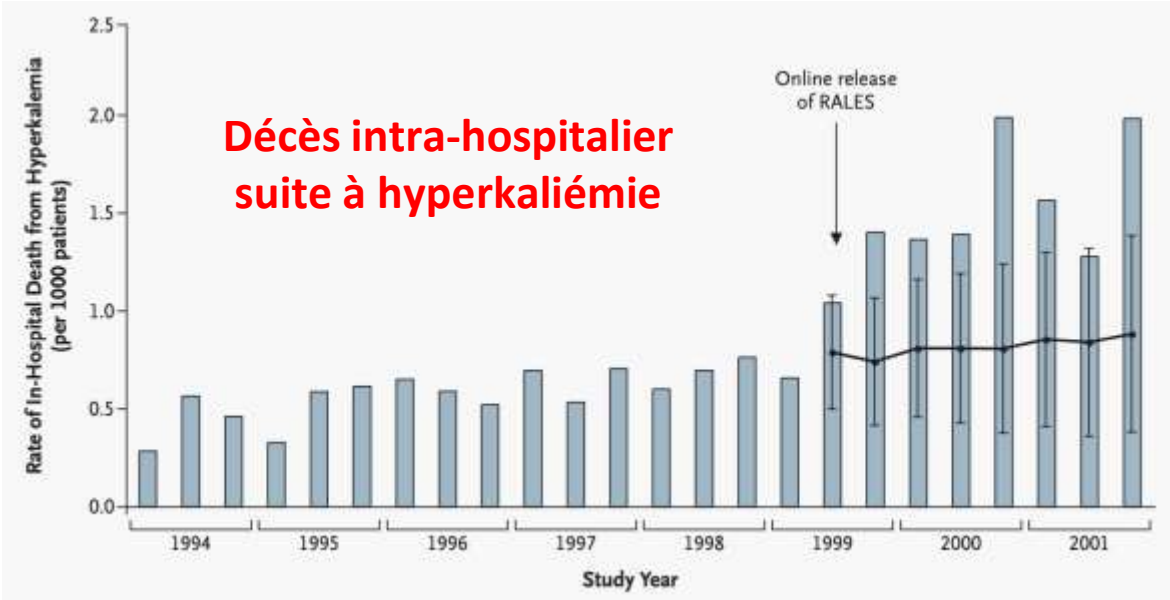


- **Baisse initiale du DFG** à l'introduction des MRA: -2,5 et -1,8 ml/min/1.73m2 pour eplerenone 50 mg et spironolactone 45 mg/j.
- **Pas de différence de pente** après la phase initiale avec les groupes MRA vs placebo.

Post RALES







Juurlink et al. N Engl J Med 2004;351:543-51.

Etudes de phase 2 : ARTS

- Patients avec IC avec FE réduite et MRC

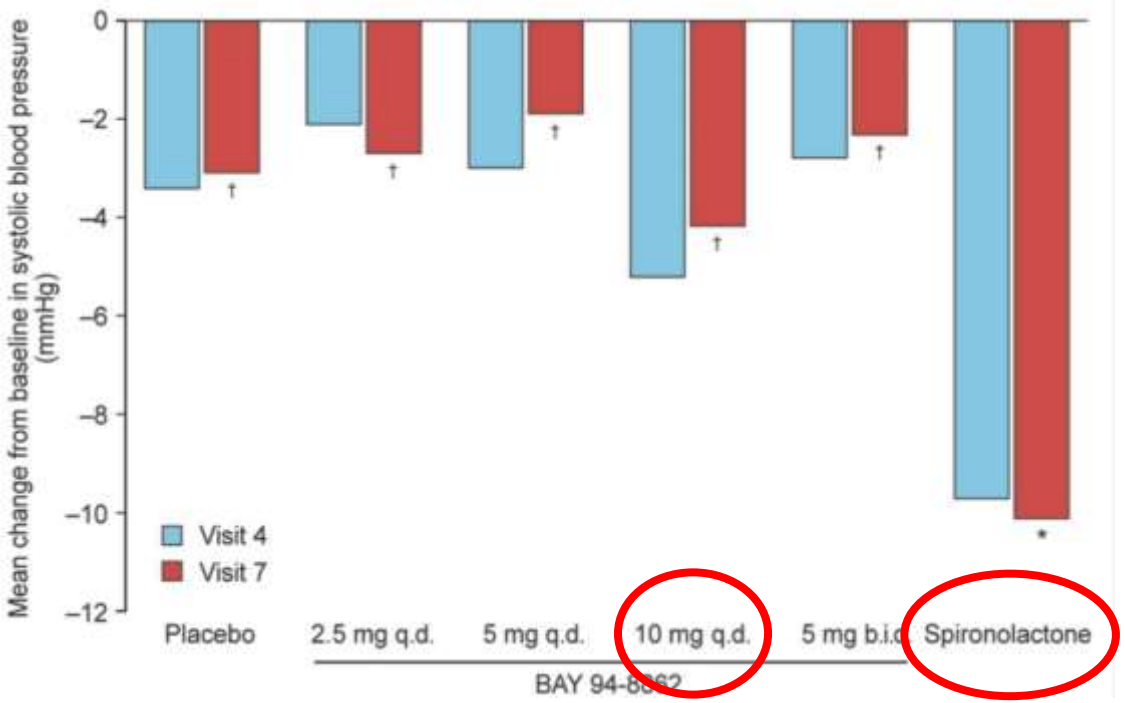
- PART A = DFG 60-90 et K+ $\leq$ 4,8 mmol/L (65 patients)
  - Evaluer efficacité et sécurité de Finerenone vs placebo
  - Dosages : 2,5, 5, 10 mg

- **PART B = DFG 30-60 et K+ $\leq$ 4,8 mmol/L (392 patients)**
  - **Evaluer K+**
  - **Finérénone (dosages 2.5, 5 et 10 mg) vs placebo vs spironolactone (25 mg, augmenté à J15 à 50 mg (V4) si K+ $\leq$ 4,8 mmol/L)**

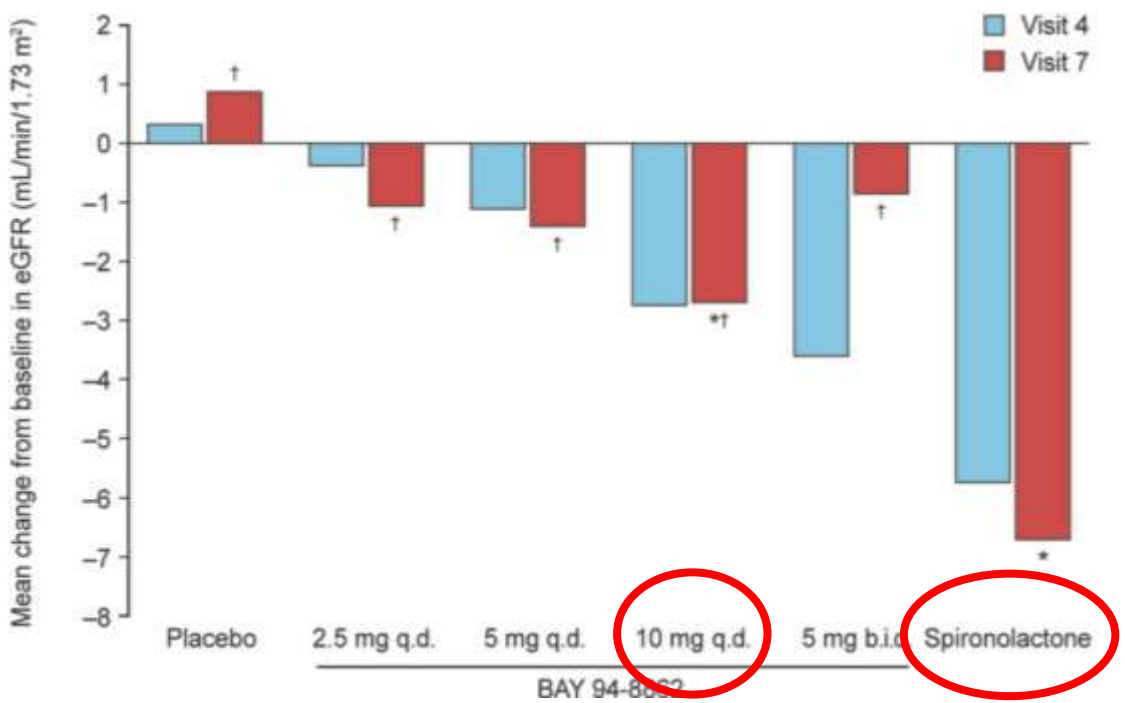
Pitt et al. European Heart Journal 2013

ARTS-B : Spironolactone (37mg) versus finérénone (10mg)

Baisse de la PA systolique



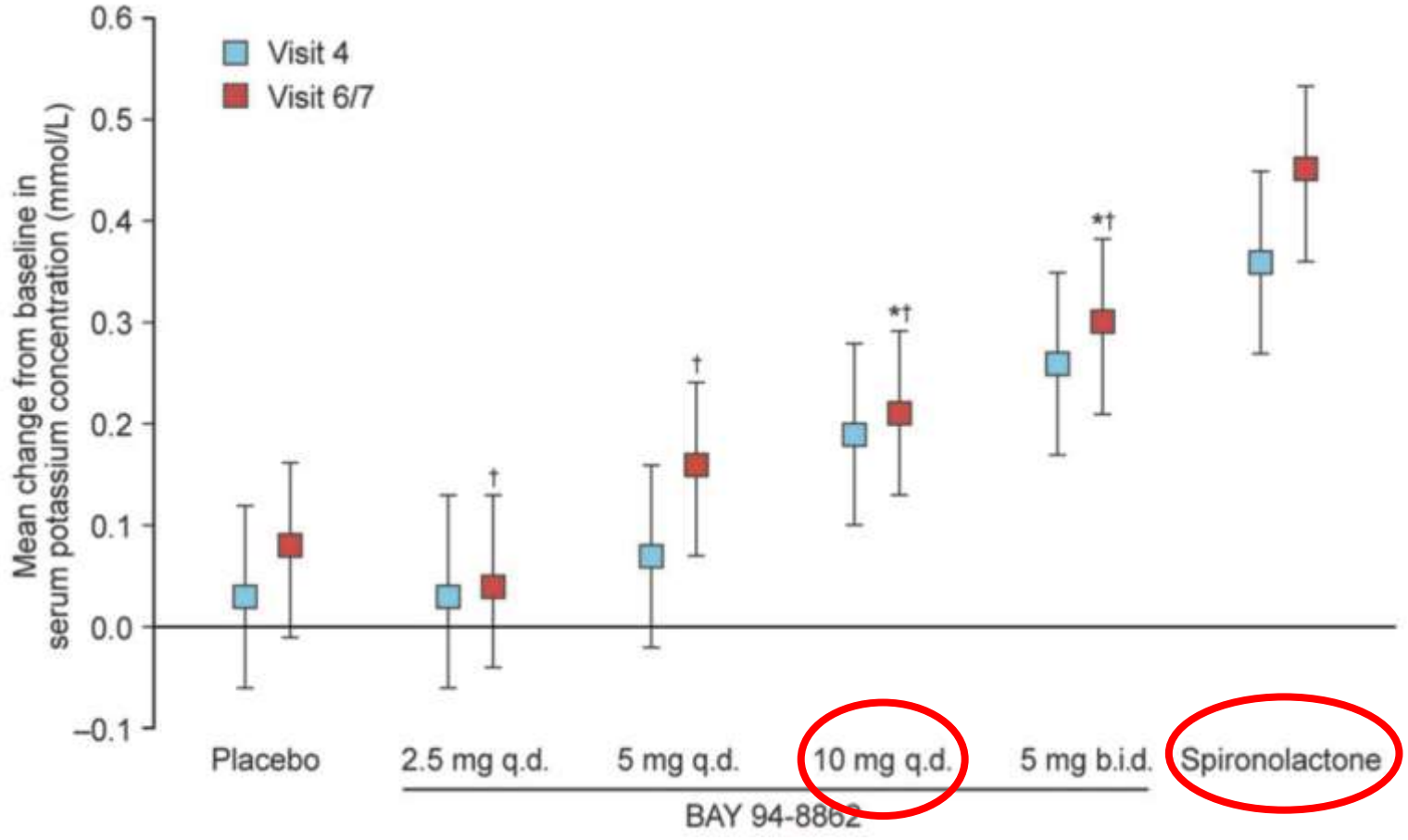
Baisse du DFG



La Finérénone 10 mg fait moins baisser la PA et le DFG que la Spironolactone 37 mg (mean dose)

Pitt et al. European Heart Journal 2013

ARTS-B : Spironolactone (37mg) versus finérénone (10mg)

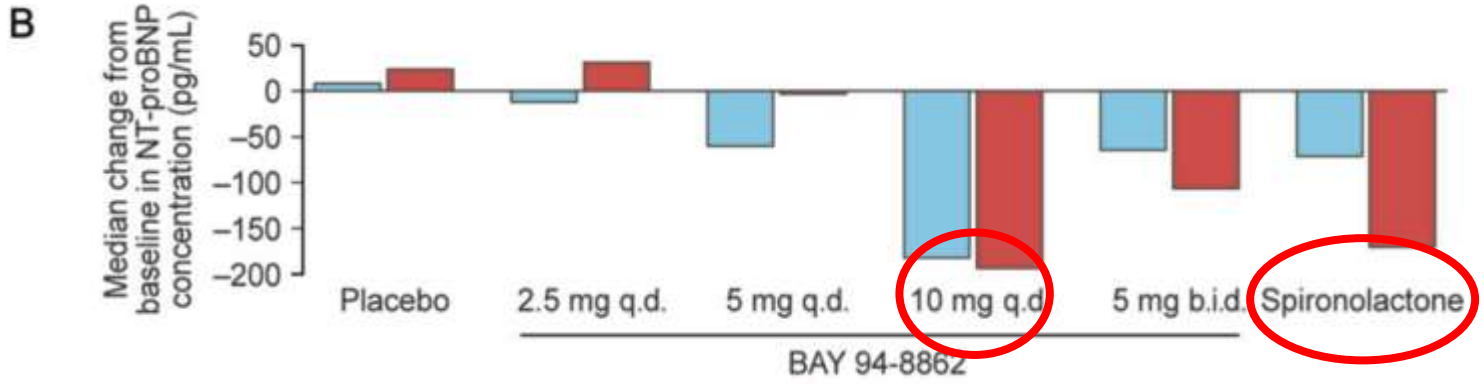


Moindre augmentation de la kaliémie avec la finerenone vs Spironolactone

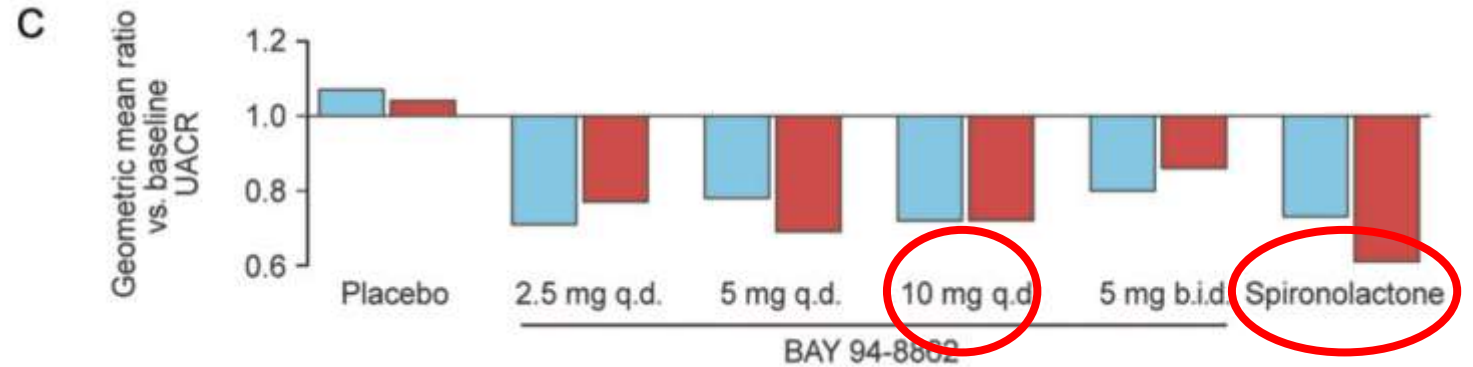
Pitt et al. European Heart Journal 2013

ARTS-B : Spironolactone (37mg) versus finérénone (10mg)

NT-ProBNP



RAC



Malgré une baisse de PA moins importante, efficacité identique sur RAC et BNP

Pitt et al. European Heart Journal 2013

Bénéfice des MRA non stéroïdien dans la MRC ?

ORIGINAL ARTICLE

Effect of Finerenone on Chronic Kidney Disease Outcomes in Type 2 Diabetes

George L. Bakris, M.D., Rajiv Agarwal, M.D., Stefan D. Anker, M.D., Ph.D., Bertram Pitt, M.D., Luis M. Ruilope, M.D., Peter Rossing, M.D., Peter Kolkhof, Ph.D., Christina Nowack, M.D., Patrick Schloemer, Ph.D., Amer Joseph, M.B., B.S., and Gerasimos Filippatos, M.D., for the FIDELIO-DKD Investigators*

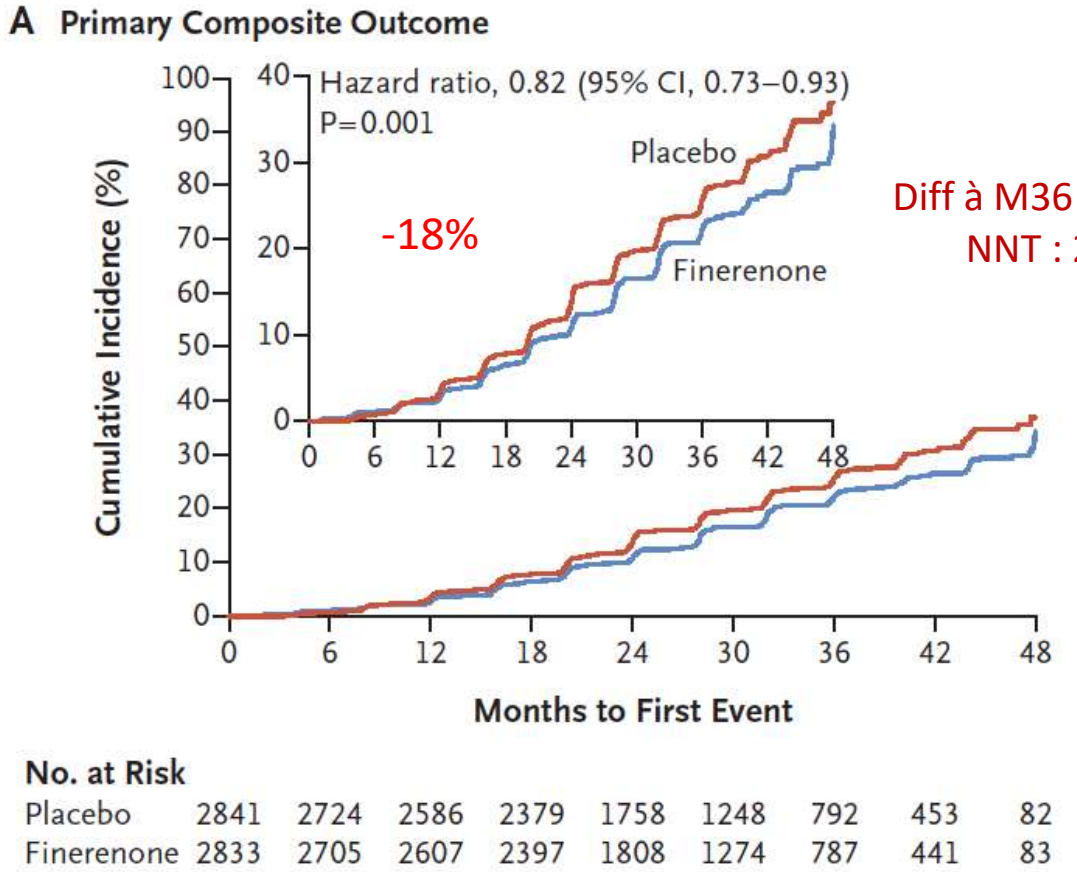
Bakris G. NEJM 2020; 383: 2219

n=5734 patients, 48 pays
DT2 et MRC, K ≤4,8; Randomisation finerenone vs placebo

RAC 30-300 mg/g et DFG 25-60 + FO+
RAC 300-5000 mg/g et DFG 25-75
(DFGm 44, RACm 852)

IEC/ARA2 : 100%
Diurétique : 56%
iSGLT2: 4,6%

Critère rénal composite :
Diminution DFG >40% ou
DFG <15 ml/min ou
Dialyse/transplantation ou
Décès de cause rénale

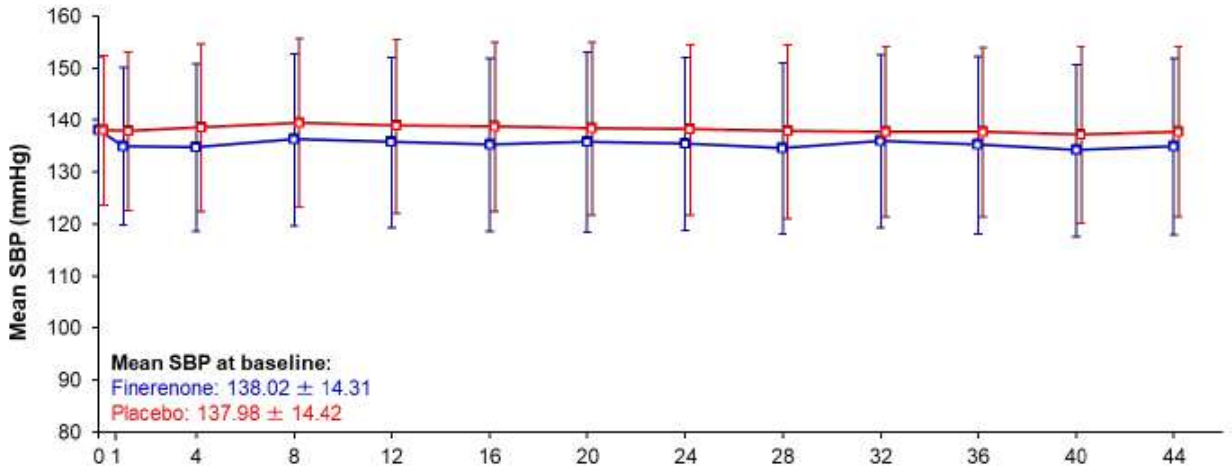


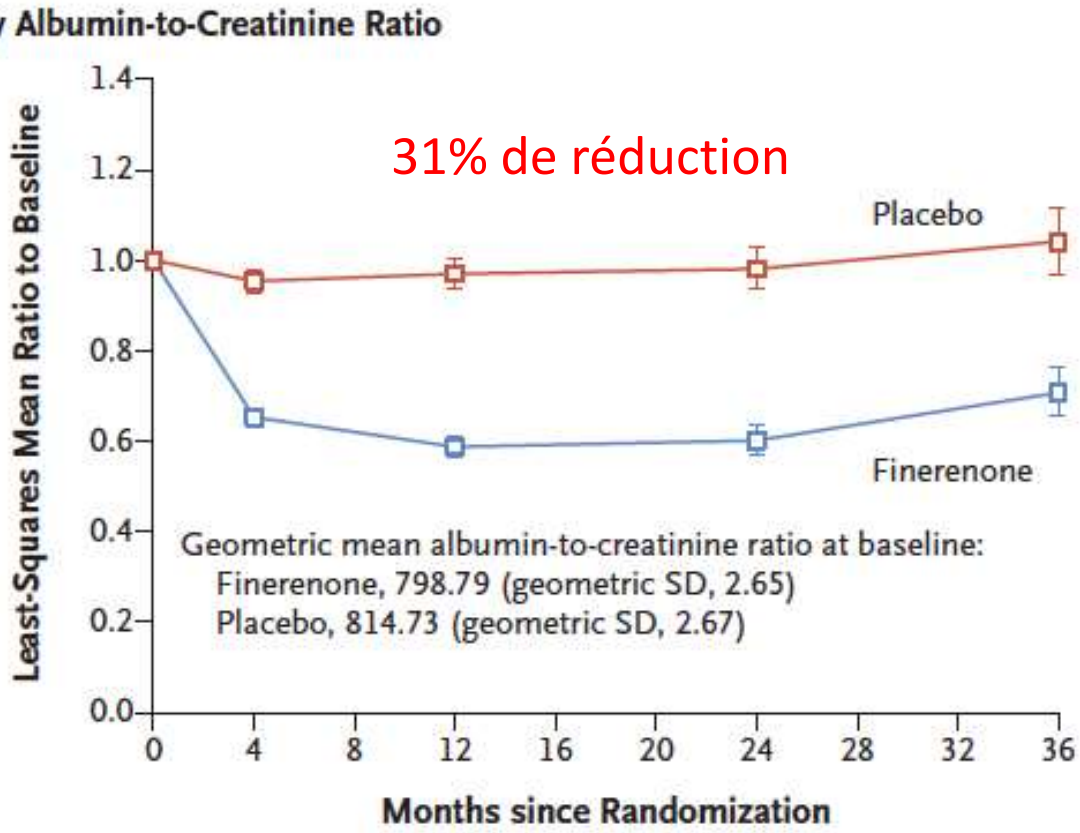
Diff à M36 : 3.4%
NNT : 29

Bénéfice des MRA non stéroïdien dans la MRC ?

- Critère composite CV (Décès, IDM, AVC, HIC)
  - HR: 0,86 [0,75-0,99], p=0,03
- Mortalité globale, NS
- ΔDFG > 57% + décès rénal
  - HR: 0,76 [0,65-0,9]
- PA; RAC

Bakris G. NEJM 2020; 383: 2219





Bénéfice des MRA non stéroïdien sur les événements CV ?

ORIGINAL ARTICLE

Cardiovascular Events with Finerenone in Kidney Disease and Type 2 Diabetes

B. Pitt, G. Filippatos, R. Agarwal, S.D. Anker, G.L. Bakris, P. Rossing, A. Joseph, P. Kolkhof, C. Nowack, P. Schloemer, and L.M. Ruilope, for the FIGARO-DKD Investigators*

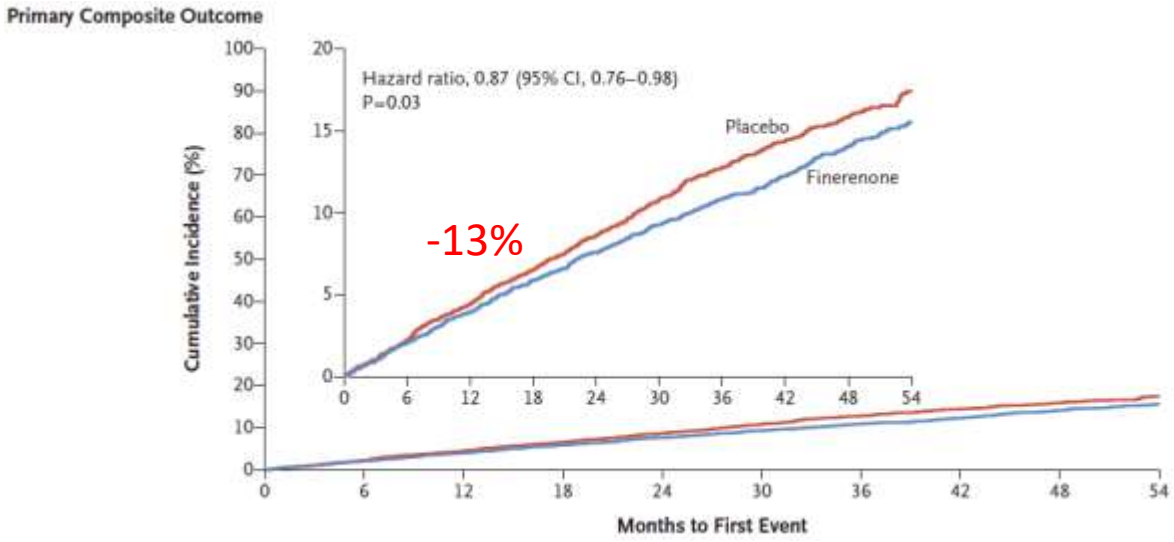
n=7437 patients, 48 pays
DT2 et MRC, K ≤4,8; Randomisation finerenone vs placebo

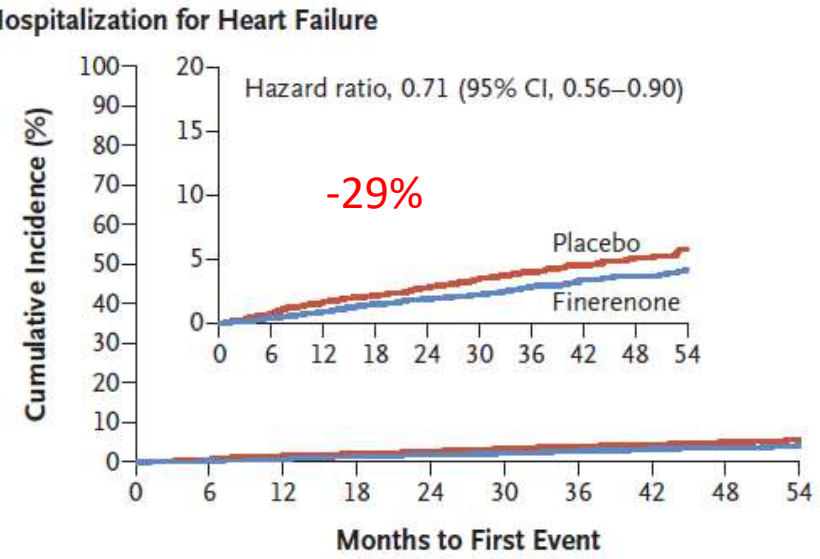
DFG 25-90 et RAC 30-300 mg/g
DGF >60 et RAC 300-5000 mg/g

(DFGm 68, RACm 308)

IEC/ARA2 : 100%
Diurétique : 47%
iSGLT2: 8,4%

Critère CV composite :
1/Décès, IDM, AVC, HIC
2/Diminution DFG >40% ou DFG <15 ml/min ou Dialyse/transplantation ou Décès de cause rénale





Bénéfice et tolérance des MRA non stéroïdien sur les événements CV ?

- Défaillance rénale, ΔDFG >40%

+ décès rénal:

  - HR 0,87 [CI 0,76-1,01], NS

- IRT:
  - HR 0,64 [CI 0,41-0,995]
- RAC:
  - 0,68 [CI 0,65-0,7]
- ΔDFG >57% + décès rénal:
  - HR 0,77 [CI 0,6-0,99]

- PAS -3,5 et PAD -2,6 mm Hg

- Tolérance

Table 2. Safety Outcomes.*

Event	Finerenone (N=3683)	Placebo (N=3658)
Investigator-reported adverse events — no. (%)		
Any adverse event	3134 (85.1)	3129 (85.5)
Adverse event related to finerenone or placebo	560 (15.2)	413 (11.3)
Hyperkalemia†	396 (10.8)	193 (5.3)
Hyperkalemia related to finerenone or placebo	240 (6.5)	114 (3.1)
Serious hyperkalemia	25 (0.7)	4 (0.1)
Hospitalization due to hyperkalemia	21 (0.6)	2 (0.1)
Permanent discontinuation of trial regimen due to hyperkalemia	46 (1.2)	13 (0.4)

Cardiovascular finerenone in pa chronic kidney analysis

Rajiv Agarwal [1*†], Gerasi
Peter Rossing [5,6], Amer J
Martin Gebel [10], Luis M.
of the FIDELIO-DKD and F

Eur Heart J, Vol

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

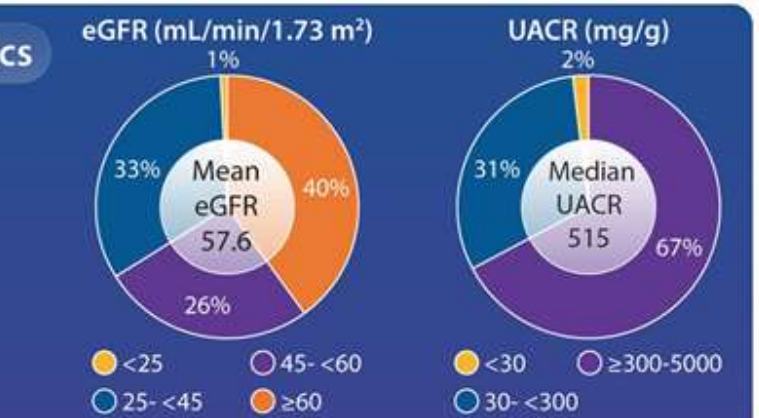
Outcomes

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

Hyperkalemia Risk with Finerenone: Results from the FIDELIO-DKD Trial

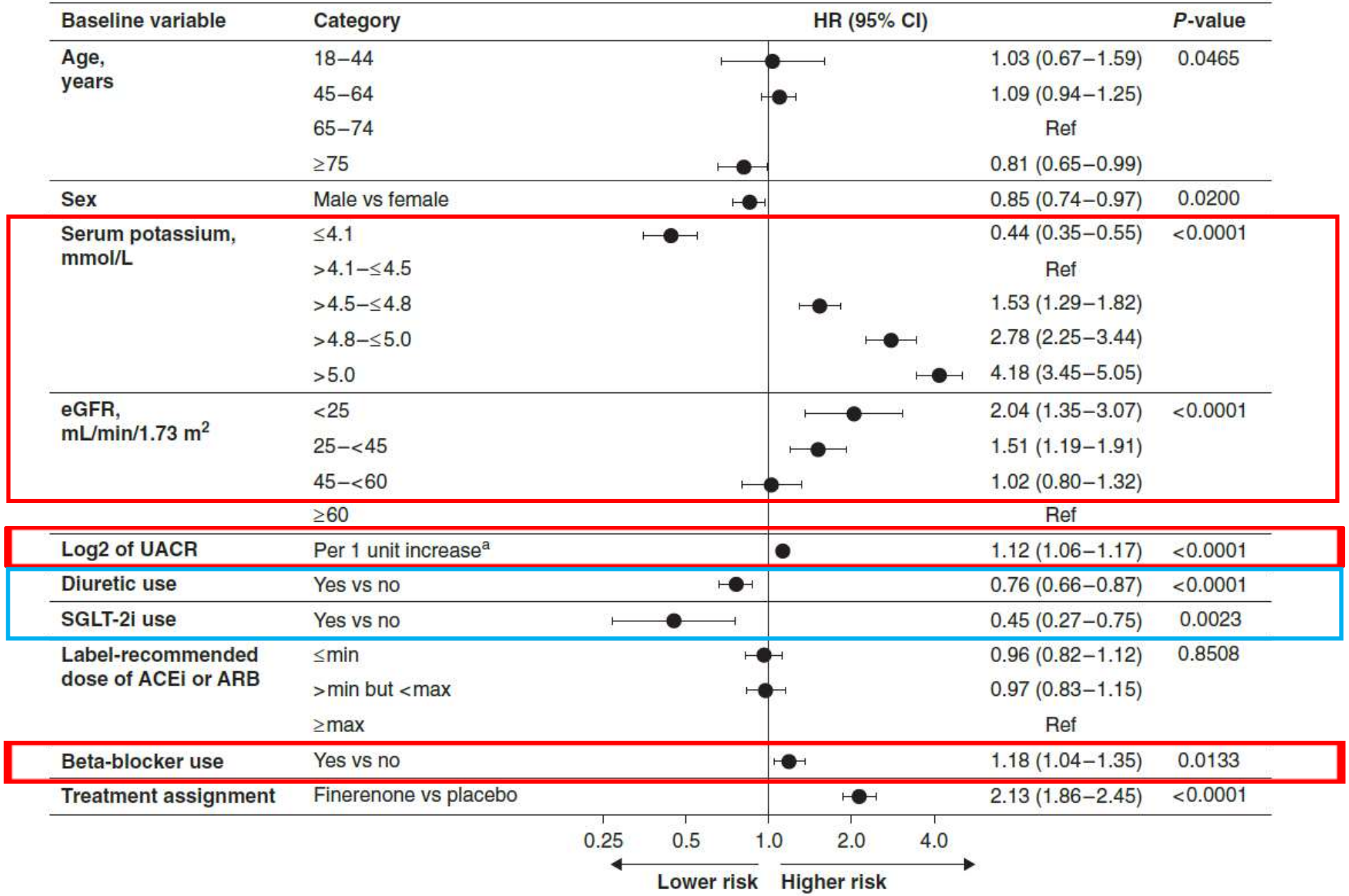
Rajiv Agarwal,[1] Amer Joseph,[2] Stefan D. Anker,[3] Gerasimos Filippatos,[4] Peter Rossing,[5,6] Luis M. Ruilope,[7,8,9] Bertram Pitt,[10] Peter Kolkhof,[11] Charlie Scott,[12] Robert Lawatscheck,[13] Daniel J. Wilson,[14] and George L. Bakris,[15] on behalf of the FIDELIO-DKD Investigators*

Agarwal R. JASN 2023

- Méthodes: Incidence et facteurs de risque d'HyperK avec finerenone et placebo chez FIDELIO-DKD?
  - HyperK > 5,5 (modérée) et > 6 mmol/l (moyenne) ?

- Résultats:
  - Survenue d'une **hyperK modérée chez 21,4% et 9,2%**
  - Survenue d'une HyperK moyenne dans 4,5% et 1,4%

  - Facteurs associés à la survenue d'une hyperK:


Baseline variable
Category
HR (95% CI)
P-value
Age, years
18–44
1.03 (0.67–1.59)
0.0465
45–64
1.09 (0.94–1.25)
65–74
Ref
≥75
0.81 (0.65–0.99)
Sex
Male vs female
0.85 (0.74–0.97)
0.0200
Serum potassium, mmol/L
≤4.1
0.44 (0.35–0.55)
<0.0001
>4.1–≤4.5
Ref
>4.5–≤4.8
1.53 (1.29–1.82)
>4.8–≤5.0
2.78 (2.25–3.44)
>5.0
4.18 (3.45–5.05)
eGFR, mL/min/1.73 m2
<25
2.04 (1.35–3.07)
<0.0001
25–<45
1.51 (1.19–1.91)
45–<60
1.02 (0.80–1.32)
≥60
Ref
Log2 of UACR
Per 1 unit increase[a]
1.12 (1.06–1.17)
<0.0001
Diuretic use
Yes vs no
0.76 (0.66–0.87)
<0.0001
SGLT-2i use
Yes vs no
0.45 (0.27–0.75)
0.0023
Label-recommended dose of ACEi or ARB
≤min
0.96 (0.82–1.12)
0.8508
>min but <max
0.97 (0.83–1.15)
≥max
Ref
Beta-blocker use
Yes vs no
1.18 (1.04–1.35)
0.0133
Treatment assignment
Finerenone vs placebo
2.13 (1.86–2.45)
<0.0001
0.25
0.5
1.0
2.0
4.0
Lower risk
Higher risk

Données de vrai vie: Essai FINE-REAL

FINE-REAL objective: To evaluate the **characteristics and treatment patterns** of participants with CKD associated with T2D who were **treated with finerenone** in routine clinical practice

Recruitment	~2 years*
Study sites	~21 countries
Patients	Adult patients with a diagnosis of **CKD associated with T2D** who are prescribed finerenone (10 or 20 mg) under routine clinical treatment conditions
Design	International, prospective, observational, multicentre, single-arm study

Patients prescribed finerenone according to local label (N ~5500)

Baseline | 1 month | 3 months | 6 months | 12 months

Suggested follow-up (maximum: 12 months)

Key dates

- **First patient first visit**: 2022
- **Last patient last visit**: 2027

Desai N. J of Diab & its complications 2023

The FINE-REAL interim analysis included 504 patients

Characteristic*	All participants (N=504)
Age, years, mean ± SD	66.1 (11.0)
Sex, n (%)	
Male	306 (60.7)
Female	198 (39.3)
Race or ethnic group, n (%)	
White	269 (53.4)
Asian	112 (22.2)
Black/African American	65 (12.9)
Other/not reported#	58 (11.5)
Duration of T2D, years, median (Q1–Q3)	14.0 (8.0–22.0)
History of heart failure, n (%)	67 (13.3)
UACR,‡ mg/g, median (Q1–Q3)	295.0 (85.9–897.0)
UACR category, n (%)	
<30	40 (8.0)
30–<300	143 (28.6)
≥300	176 (35.2)

Characteristic*	All participants (N=504)
eGFR,§ ml/min/1.73 m^2, mean ± SD	**52**.0 (24.3)
eGFR category, n (%)	
<15	3 (0.6)
15–29	72 (14.7)
30–44	154 (31.4)
45–59	119 (24.3)
60–89	93 (19.0)
≥90	49 (10.0)
Serum [K^+], mmol/l, mean ± SD	4.4 (0.4)
HbA1c, %, mean ± SD	7.5 (1.5)
Systolic blood pressure, mmHg, mean ± SD	138.0 (18.7)
Prior/concomitant medication, n (%)	
Statins	387 (76.8)
ACEi/ARB	362 (71.8)
Insulin	241 (47.8)
SGLT-2i	235 **(46.6)**
GLP-1RA	168 (**33**.3)

Pas d’hyperkaliémie menaçante

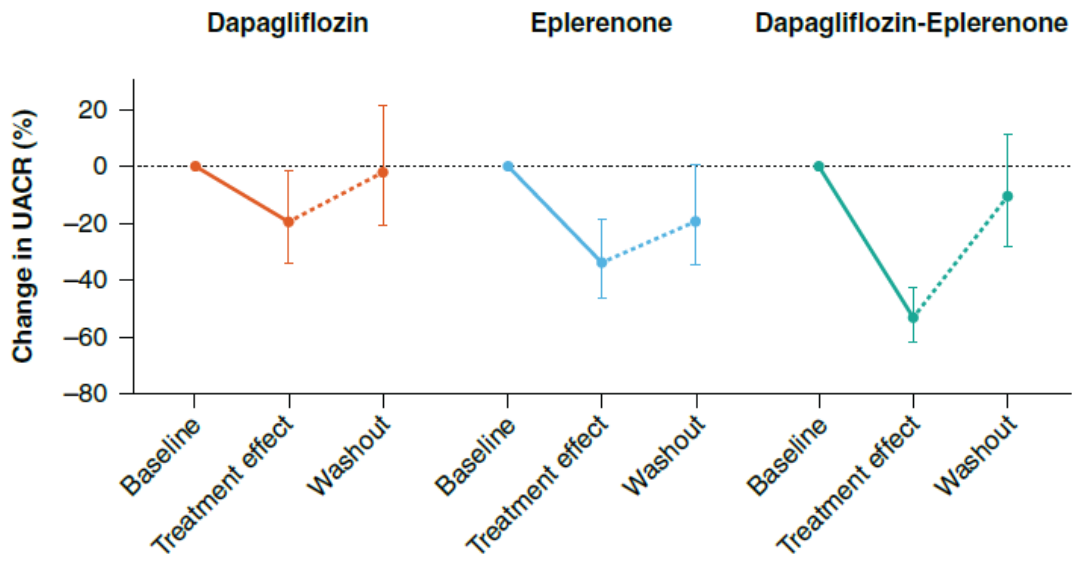
Outcome, n (%)	All participants (N=504)
Any event	**25** (5.0)
Symptomatic event	1 (0.2)
Clinical signs/symptoms (multiple answers possible)	
Paraesthesia	1 (0.2)
Leading to dialysis	0
Leading to hospitalisation	0
Serum potassium >5.5 mmol/l	**21** (4.2)
Serum potassium >6.0 mmol/l	2 (0.4)

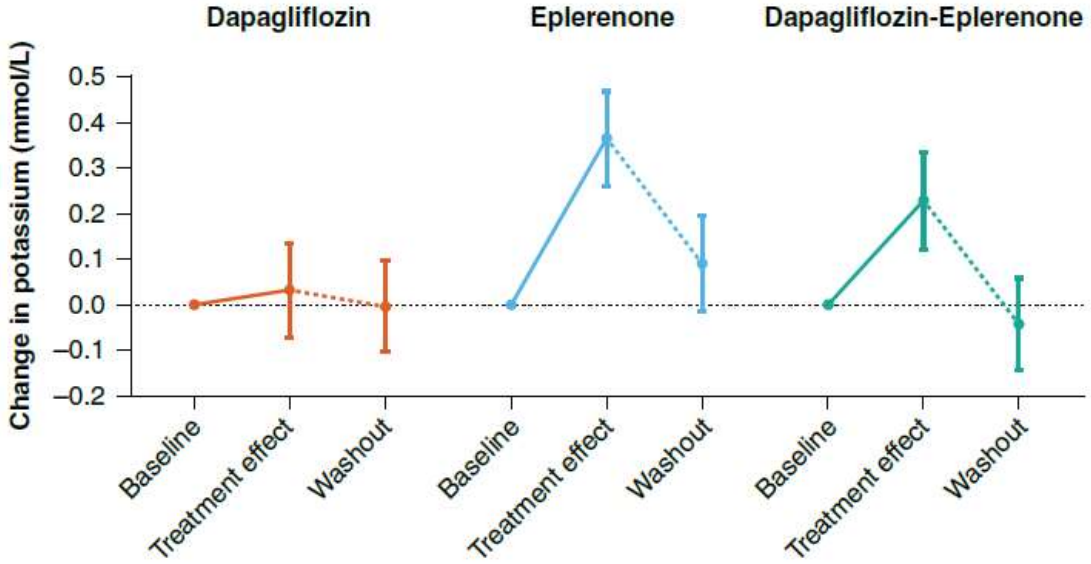
Bénéfice de l'association MRA et iSGLT2?

Provenzano M. JASN 2022

- Méthodes:
  - **Efficacité et tolérance iSGLT2 (Dapa) + MRA (Eplerenone) chez l'IRC**?
  - Etude randomisée, ouverte, crossover chez DFG 30-90, RAC > 100mg/j
  - Dapa 10 mg, Eplerenone 50 mg et association.

- Résultats:
  - Baisse du RAC de -20%, -33%, -53%. Augmentation de la kaliémie de 0,03; 0,36 et 0,23 mmol/l

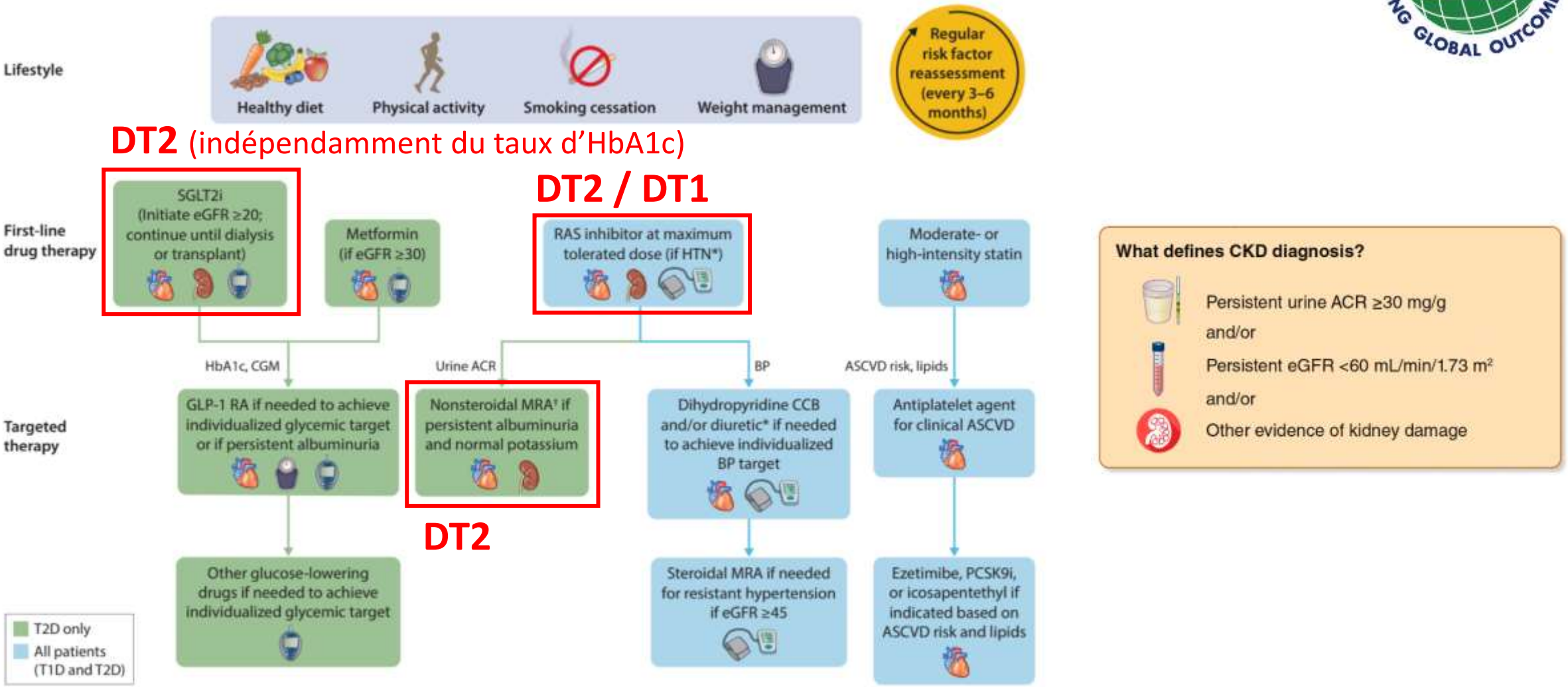




- L'association d'un MRA avec un iSGLT2 permet d'avoir une moindre augmentation de la kaliémie et une baisse du RAC

KDIGO guidelines 2022

Clinical practice guideline for diabetes management in chronic kidney disease



KDIGO **2022** Clinical Practice Guideline for Diabetes Management in Chronic **Kidney** Disease. **Kidney Int**.2022 Nov;102(5S):S1-S127

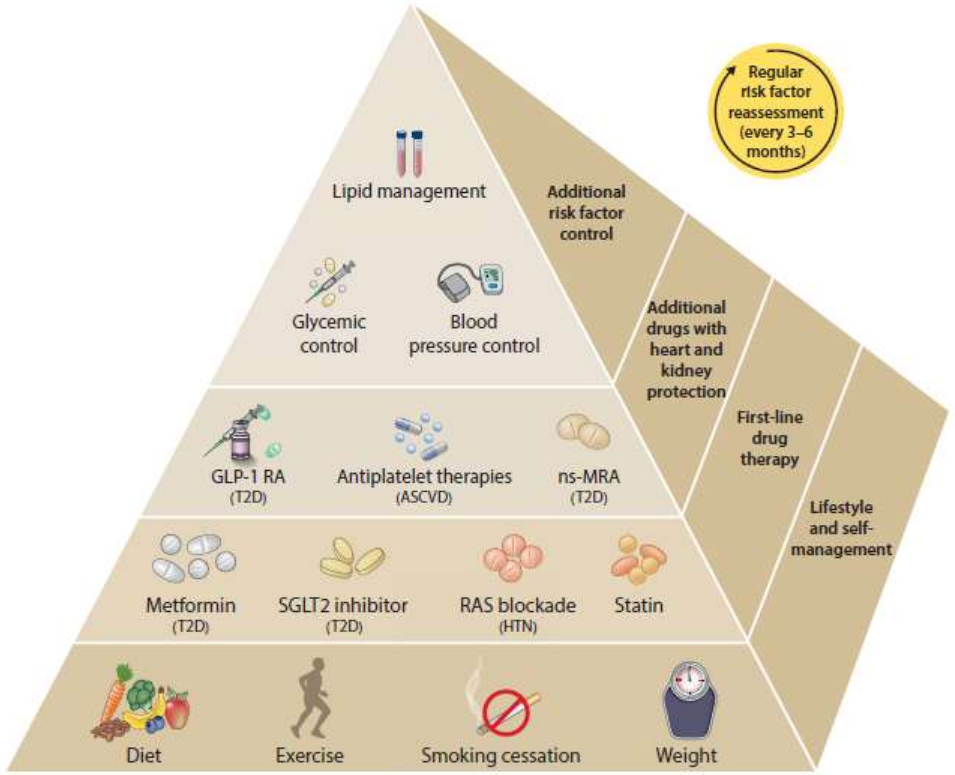
De Boer IH et al. Diabetes Care 2022 Oct 3;dci220027; De Boer IH et al. Kidney Int. 2022 Nov;102(5):974-989

The KDIGO 2022 guidelines include a class 2A recommendation for finerenone

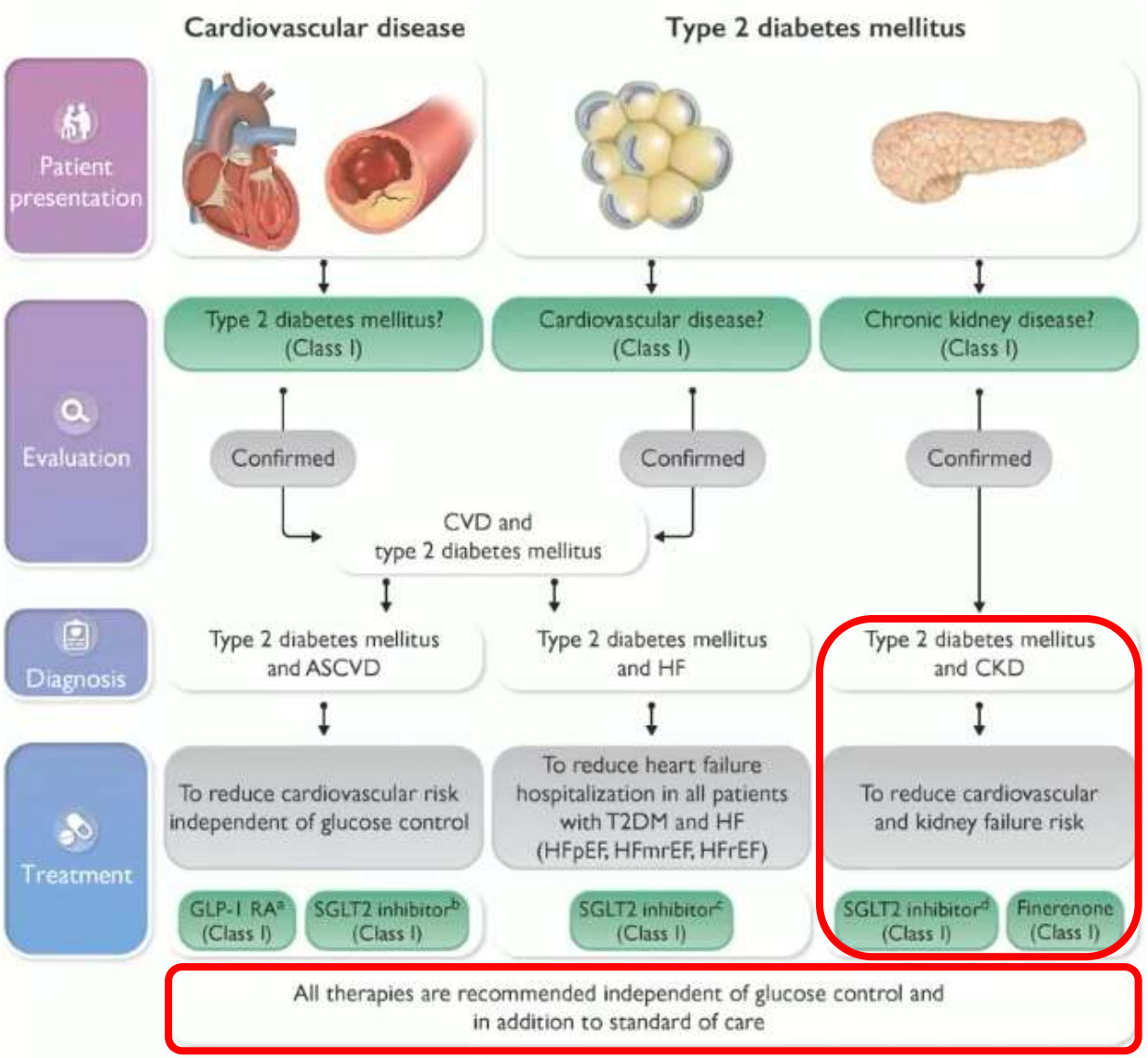
Recommendations (2022)

Recommendation	Level/grade
Comprehensive diabetes and CKD management	
An ACEi or an ARB is recommended in patients with diabetes, hypertension and albuminuria, titrated to the highest approved dose that is tolerated	1B
An SGLT-2i is recommended in patients with T2D, CKD and **an eGFR ≥20 ml/min**/1.73 m^2	1A
A nonsteroidal MRA with proven kidney and CV benefit is suggested in patients with T2D, eGFR ≥25 ml/min/1.73 m^2, normal serum [K^+] and albuminuria (≥30 mg/g) despite maximum tolerated RASi	2A
Antihyperglycaemic therapies in patients with T2D and CKD	
Metformin is recommended in patients with T2D, CKD and an eGFR ≥30 ml/min/1.73 m^2	1B
A long-acting GLP-1RA is recommended in patients with T2D and CKD who have not achieved individualised HbA1c targets despite metformin and SGLT-2i (or are unable to use them)	1B

Kidney–heart risk factor management



Recommandations de l'ESC 2023 - Prise en charge des maladies cardiovasculaires chez les patients atteints de diabète de type 2



Chronic kidney disease and diabetes—*Section 9*		
Intensive LDL-C lowering with statins or a statin/ezetimibe combination is recommended.	I	A
A SGLT2 inhibitor (canagliflozin, empagliflozin, or dapagliflozin) is recommended in patients with T2DM and CKD with an eGFR ≥20 mL/min/1.73 m^2 to reduce the risk of CVD and kidney failure.	I	A
Finerenone is recommended in addition to an ACE-I or ARB in patients with T2DM and eGFR >60 mL/min/1.73 m^2 with a UACR ≥30 mg/mmol (≥300 mg/g), or eGFR 25–60 mL/min/1.73 m^2 and UACR ≥3 mg/mmol (≥30 mg/g) to reduce CV events and kidney failure.	I	A
Low-dose ASA (75–100 mg o.d.) is recommended in patients with CKD and ASCVD.	I	A
Treatment with intensive medical or an initial invasive strategy is recommended in people with CKD, diabetes, and stable moderate or severe CAD, due to similar outcomes.	I	B
Kidney specialist advice may be considered for managing a raised serum phosphate, other evidence of CKD-MBD, and renal anaemia.	IIb	C
Combined use of an ARB with an ACE-I is not recommended.	III	B

Marx N et al. European Heart Journal (2023) 00, 1–98

Recommandations ESC 2023 pour le traitement des patients DT2 atteints de maladie rénale chronique

Pour réduire le risque CV

Régime à base de statines — IA

Une réduction intensive du LDL-C avec des statines ou une combinaison statine/ézétimibe est recommandée

Pour réduire le risque d'insuffisance rénale

IEC/ARA2 — IA

La dose maximale tolérée d'un ACEi ou ARB est recommandée

Pour réduire le risque cardiovasculaire et rénal

SGLT-2i — IA

Recommandé chez les patients atteints de DT2 et d'IRC avec un DFGe ≥20 ml / min / 1,73 m2 pour réduire le risque de MCV et de MRC

Contrôle de la PA — IA

Une PA cible de 130/80 mmHg est recommandée pour réduire le risque de MCV et d'albuminurie

Finerenone — IA

La finérénone est recommandée en plus d'un IEC ou d'un ARA2 chez les patients atteints de DT2 avec un DFGe >60 mL/min/1,73 m2 et un RAC ≥30 mg/mmol (≥300 mg/g) ou un DFGe de 25 à 60 mL/min/1,73 m2 et RAC ≥3 mg / mmol (≥30 mg / g) pour réduire les événements cardiovasculaires et rénaux

Marx N, *et al. Eur Heart J* 2023;00:1–98

2023 ESH Guidelines for the management of arterial hypertension

The Task Force for the management of arterial hypertension of the European Society of Hypertension

Endorsed by the International Society of Hypertension (ISH) and the European Renal Association (ERA)

J. Hypertension 2023; 41: 1874

Dual combination of an ACEi with an ARB is not recommended.	III	A
SGLT2is inhibitors are recommended for patients with diabetic and non-diabetic nephropathies CKD if eGFR is at least 20 ml/min/1.73².[a]	I	A
The non-steroidal MRA finerenone is recomended in patients with CKD and albuminuria associated with type 2 diabetes mellitus if eGFR is at least 25 ml/min/1.73² and serum potassium <5.0 mmo/L.	I	A
In CKD patients with hyperkalemia a potassium binder can be used to maintain normal or near normal serum potassium levels (<5.5 mmol/L) in order to allow optimal treatment with a RAS-blocker or a MRA to continue.	II	B

FINERENONE : AMM EUROPEENNE

COMMISSION EUROPÉENNE

Finérénone, antagoniste sélectif non stéroïdien des récepteurs aux minéralocorticoïdes (RM), est indiqué chez l'adulte pour le traitement de la maladie rénale chronique (avec albuminurie) associée au diabète de type 2 :

- ✓ Au vu de l'absence de données comparatives versus un inhibiteur du SGLT2 (ou gliflozine) et du faible effectif (moins de 5 %) de patients inclus dans l'étude de phase III traités par un inhibiteur du SGLT2**, la Finérénone ne peut être positionnée par rapport aux inhibiteurs du SGLT2 dans la maladie rénale chronique** (stades 3 et 4 avec albuminurie) du patient diabétique de type 2.

- ✓ Le bénéfice clinique de l'association finérénone + traitement standard optimisé par IEC ou sartan + gliflozine n'étant pas établi, l'instauration d'une trithérapie dans la maladie rénale chronique n'est pas recommandée.

(1) Avis HAS KERENDIA, du 19 octobre 2022 KERENDIA 10 mg et 20 mg- (2) Avis HAS KERENDIA, du 20 septembre 2023 KERENDIA 10 mg et 20 mg

Questions en suspend pour le positionnement de la finérénone ?

1. Intérêt de l’association avec un iSGLT2 chez MRC diabétique?
2. Positionnement vis-à-vis d’autres traitements du diabète (GLP1A)?
3. Bénéfice chez MRC non diabétique?
4. Positionnement vis-à-vis d’autres MRC (anti-ET1...)

Bénéfice de la trithérapie, iSRA + iSGLT2 + nsMRA chez le patient MRC diabétique?

Finérénone in combination with empagliflozin for the treatment of chronic kidney disease in type 2 diabetes

- CONFIDENCE – A randomised controlled trial

Green J. NDT 2023; 38: 894

Design of the COmbinatioN effect of FInerenone anD EmpaglifloziN in participants with chronic kidney disease and type 2 diabetes using a UACR Endpoint study (CONFIDENCE)

Background

Both finerenone (nonsteroidal MRA) and empagliflozin (SGLT2i) can reduce kidney and cardiovascular events in people with CKD and T2D.

CONFIDENCE (NCT05254002) investigates whether dual therapy with finerenone and empagliflozin is superior to either agent alone in reducing albuminuria.

Participants

- 807 participants
- 125 centres
- 13 countries

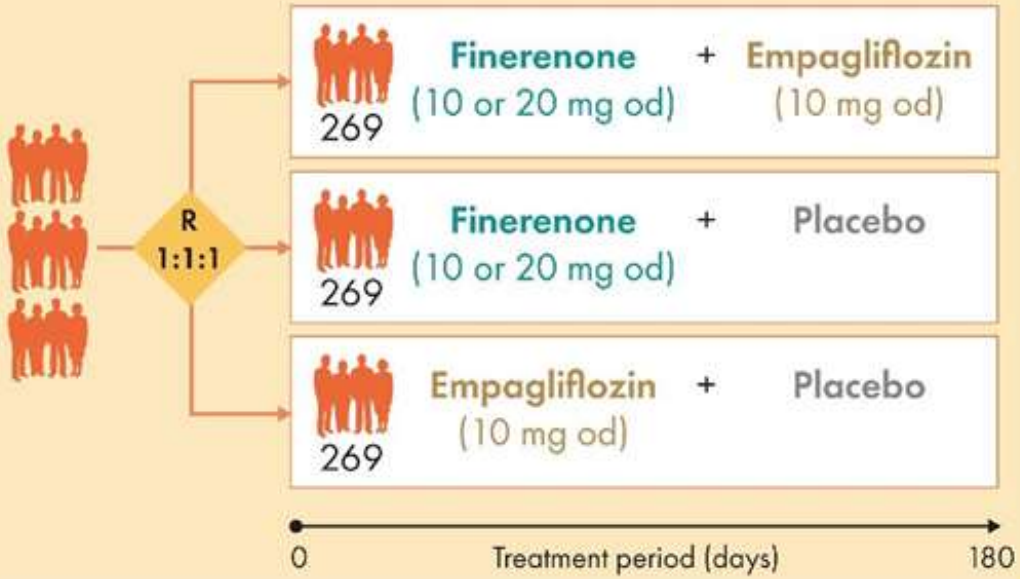
✓

- ≥ 18 years
- T2D, CKD stage 2–3
- UACR ≥ 300 to < 5000 mg/g

✗

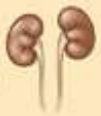
- T1D
- Serum K^+ > 4.8 mmol/L
- Treatment with SGLT1/2i or MRA

Treatment arms



Primary outcomes

Relative change in UACR from baseline to 180 days in:



Dual therapy vs. Finerenone

Dual therapy vs. Empagliflozin

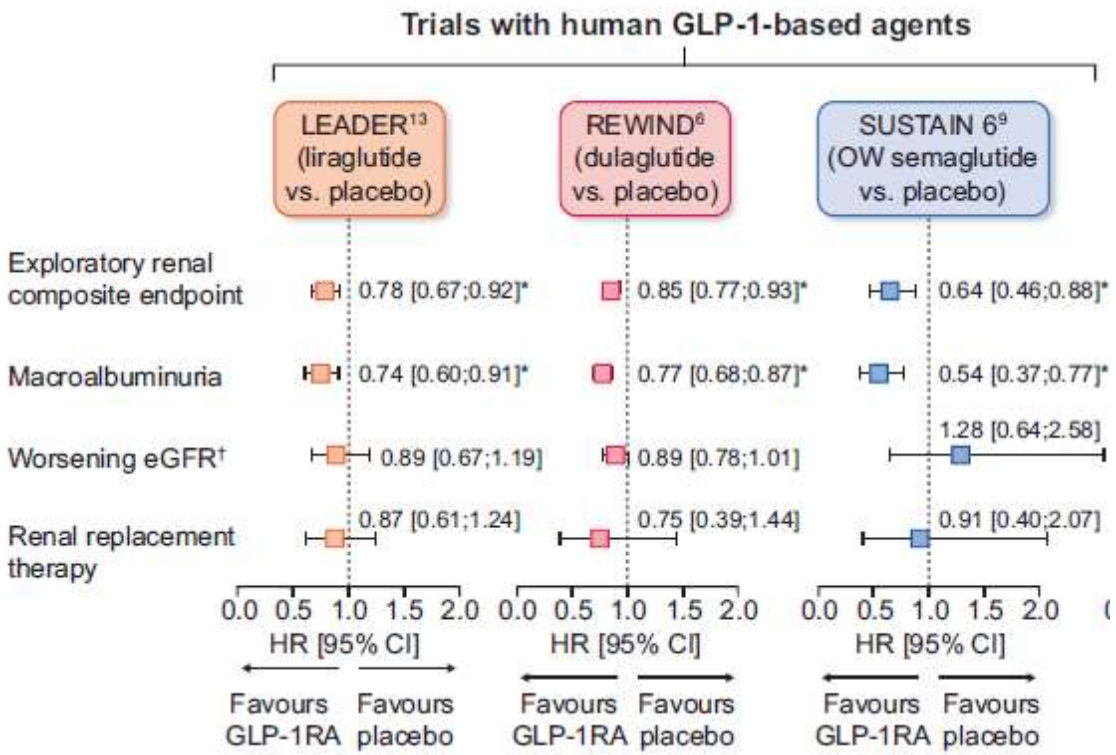
Conclusion

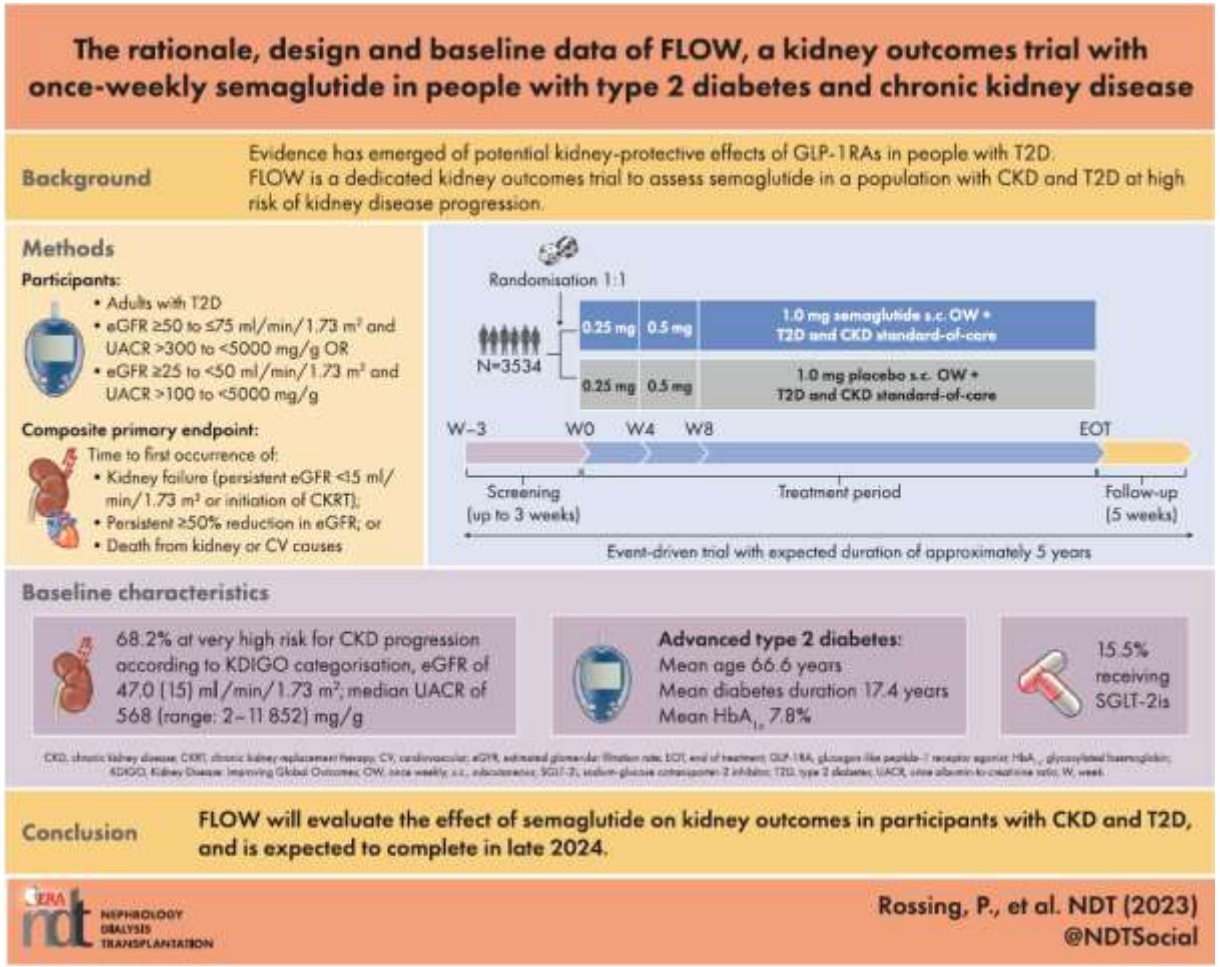
Should an additive effect be shown, early and efficient intervention with dual finerenone and SGLT2i therapy could slow disease progression and provide long-term benefits for people with CKD and T2D.

ERA NDT NEPHROLOGY DIALYSIS TRANSPLANTATION

Green, J. et al. NDT (2022)
@NDTSocial

Bénéfice rénal d'autres traitements chez le patient MRC diabétique? Les agonistes du GLP1 ?



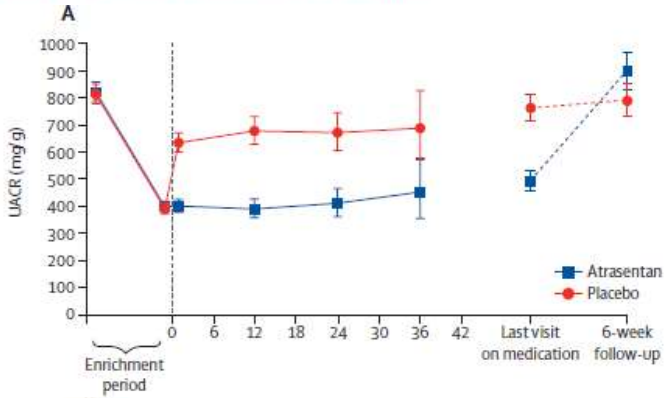


Bénéfice rénal d'autres traitements chez patient MRC & diabètique? Les bloqueurs de l'ET-1?

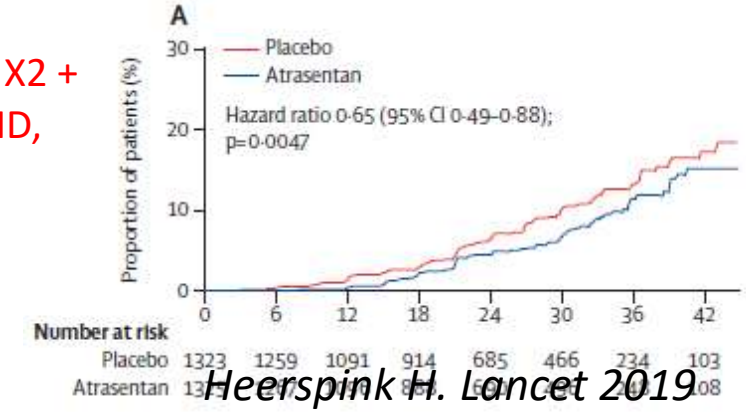
Atrasentan and renal events in patients with type 2 diabetes and chronic kidney disease (SONAR): a double-blind, randomised, placebo-controlled trial

*Hiddo J L Heerspink, Hans-Henrik Parving, Dennis L Andress, George Bakris, Ricardo Correa-Rotter, Fan-Fan Hou, Dalane W Kitzman, Donald Kohan, Hirofumi Makino, John J V McMurray, Joel Z Melnick, Michael G Miller, Pablo E Pergola, Vlado Perkovic, Sheldon Tobe, Tingting Yi, Melissa Wigderson, Dick de Zeeuw, on behalf of the SONAR Committees and Investigators**

RAC: -33%



CJP: Creat X2 + DFG<15, HD, Transpl

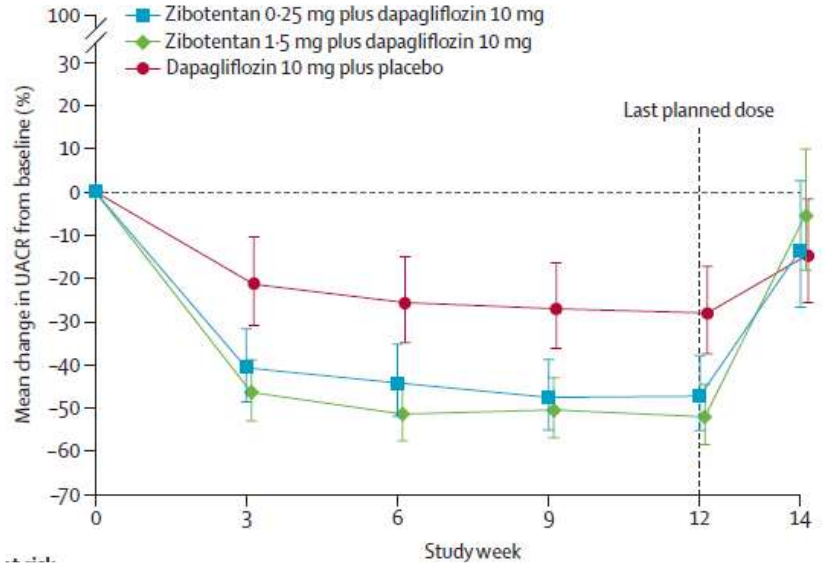


Heerspink H. Lancet 2019

Zibotentan in combination with dapagliflozin compared with dapagliflozin in patients with chronic kidney disease (ZENITH-CKD): a multicentre, randomised, active-controlled, phase 2b, clinical trial

Hiddo J L Heerspink, Arihiro Kiyosue, David C Wheeler, Min Lin, Emma Wijkmark, Glenn Carlson, Anne-Kristina Mercier, Magnus Åstrand, Sebastian Ueckert, Peter J Greasley, Phil Ambery

RAC: -52%, -47%; -27%



Heerspink H. Lancet 2023

Perspectives:

Bénéfice de la finérénone au cours de la MRC non diabétique ?

Design and Baseline Characteristics of the FIND-CKD Trial: Efficacy of Finerenone on Kidney Disease Progression in People with Non-Diabetic Chronic Kidney Disease (CKD)

Hiddo J.L. Heerspink,[1] Rajiv Agarwal,[2] George L. Bakris,[3] David Z.I. Cherney,[4] Carolyn S.P. Lam,[5,6] Brendon L. Neuen,[7] Katherine R. Tuttle,[8] Christoph Wanner,[9] Meike D. Brinker,[10] Sara Dizayee,[11] Peter Kolkhof,[12] Patrick Schloemer,[13] Paula H. Vesterinen,[14] Vlado Perkovic[7]

[1]University Medical Center Groningen, Groningen, Netherlands; [2]Indiana University School of Medicine, Indianapolis, Indiana, United States; [3]The University of Chicago Medicine, Chicago, Illinois, United States; [4]University Health Network, Toronto, Ontario, Canada; [5]National Heart Centre Singapore, Singapore, Singapore; [6]Duke-National University of Singapore, Singapore, Singapore; [7]The George Institute for Global Health, Sydney, New South Wales, Australia; [8]Providence Washington, Seattle, Washington, United States; [9]Universitatsklinikum Wurzburg, Wurzburg, Germany; [10]Cardiology and Nephrology Clinical Development, Bayer AG, Wuppertal, Germany; [11]Regulatory Strategy Cardiology and Nephrology, Bayer AG, Wuppertal, Germany; [12]Preclinical Research Cardiovascular, Research and Development, Bayer AG, Wuppertal, Germany; [13]Research and Development, Statistics and Data Insights, Bayer AG, Berlin, Germany; [14]Cardiology and Nephrology Clinical Development, Bayer AG, Espoo, Finland

Presented at the American Society of Nephrology Kidney Week, Philadelphia, Pennsylvania, November 2-5, 2023

Contact details: Name: Hiddo J.L. Heerspink; Email: h.j.lambers.heerspink@umcg.nl

Eligible Patients are Those With Non-Diabetic CKD on Optimized SoC Therapy With an ACEi or ARB

Key inclusion criteria

Age ≥18 years

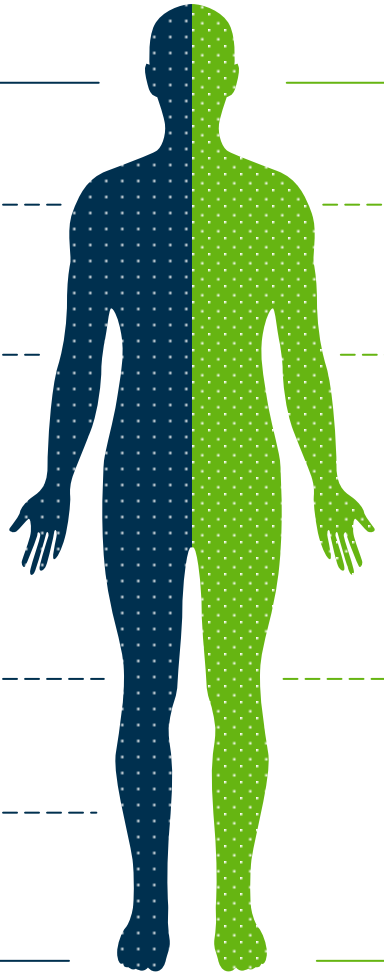
eGFR of ≥25 to <60 mL/min/1.73 m^2 and UACR of ≥200 to <500 mg/g†

OR

eGFR ≥25 to <90 mL/min/1.73 m^2 and UACR of ≥500 to ≤3500 mg/g

Serum potassium ≤4.8 mmol/L

On stable maximal tolerated labelled dose of ACEi or ARB



Key exclusion criteria

T1D, T2D, or HbA1c ≥6.5%

SBP ≥160 or DBP ≥100 mmHg

Symptomatic HF with reduced ejection fraction with class 1A indication for MRAs

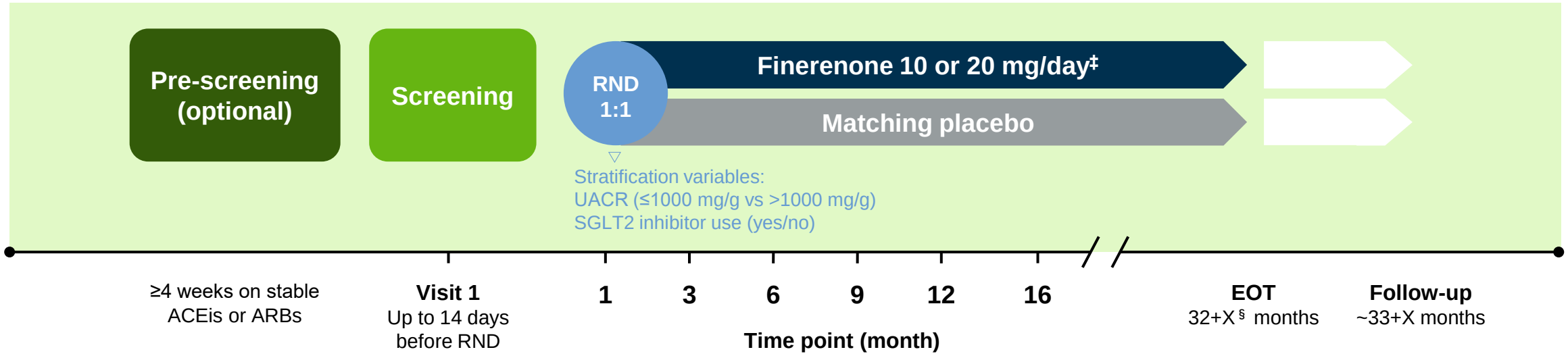
Autosomal dominant or autosomal recessive polycystic kidney disease

Lupus nephritis or ANCA-associated vasculitis or any other kidney disease requiring immunosuppressive therapy within 6 months prior to screening

†To ensure a pre-specified ratio for a population at risk of progressive renal function decline, the number of participants with eGFR of ≥25 to 60 mL/min/1.73 m^2 and UACR ≥200 to <500 mg/g is planned to be capped at approximately 10% of the total population.

ACEi, angiotensin-converting enzyme inhibitor; ARB, angiotensin receptor blocker; ANCA, anti-neutrophilic cytoplasmic autoantibody; CKD, chronic kidney disease; DBP, diastolic blood pressure; eGFR, estimated glomerular filtration rate; HbA1c, glycated hemoglobin; HF, heart failure; K^+, potassium; MRA, mineralocorticoid receptor antagonist; SBP, systolic blood pressure; SoC, standard of care; T1D, type 1 diabetes; T2D, type 2 diabetes; UACR, urinary albumin:creatinine ratio. Presented at the American Society of Nephrology Kidney Week, Philadelphia, Pennsylvania, November 2-5, 2023.

FIND-CKD is a Multicenter, Randomized, Double-Blind, Placebo-Controlled, Parallel-Group, Phase 3 Study†



Primary endpoint

Total eGFR slope (defined as the mean annual rate of change in eGFR from baseline to Month 32)

Secondary endpoints

Composite of kidney failure, sustained eGFR decline of ≥57% from baseline, HHF, or CV death.
Composite of kidney failure or sustained eGFR decline of ≥57% from baseline.
Composite of HHF or CV death

Safety outcomes

Occurrence of treatment-emergent AEs, treatment-emergent serious AEs, and hyperkalemia AEs

†Study duration and the number of study visits will depend on the time of enrollment of the patient. ‡Starting dose of finerenone: 10 mg once daily if eGFR is ≥25 mL/min/1.73 m^2 to <60 mL/min/1.73 m^2 or 20 mg once daily if eGFR is ≥60 mL/min/1.73 m^2 at screening visit. Finerenone will be up- or downtitrated based on potassium and eGFR levels. § All participants will stay in the study until the last randomized participant has reached 32 months of treatment.

ACEi, angiotensin-converting enzyme inhibitor; AE, adverse event; ARB, angiotensin receptor blocker; CV, cardiovascular; eGFR, estimated glomerular filtration rate; FIND-CKD, **FI**nerenone, in addition to standard of care, on the progression of kidney disease in patients with **N**on-**D**iabetic **C**hronic **K**idney **D**isease; HHF, hospitalization for heart failure; EOT, end of treatment; RND, randomization; SGLT2, sodium–glucose cotransporter 2; UACR, urinary albumin:creatinine ratio. Presented at the American Society of Nephrology Kidney Week, Philadelphia, Pennsylvania, November 2-5, 2023.

Finérénone en pratique en France


HAS
HAUTE AUTORITÉ DE SANTÉ

ÉVALUER LES TECHNOLOGIES DE SANTÉ

AVIS SUR LES MÉDICAMENTS

finérénone

KERENDIA 10 mg et 20 mg,

comprimé pelliculé

Première évaluation

Adopté par la Commission de la transparence le 19 octobre 2022

- Pas disponible en France
- HAS oct 2022 (Fidelio)
  - MRC 3-4 diabète + albuminurie
  - Remboursement
  - ASMR IV
- HAS Nov 2023 (Figaro)
  - MRC 1-2 diabète + albuminurie
  - Remboursement
  - ASMR V

- Indications supposées
  - MRC (DFG ≥ 25, K≤5), diabète, albuminurie
  - IEC/ARA2
  - Poso: 10 ou 20 mg selon DFG
- Les contre-indications
  - Hypersensibilité
  - Insuffisance surrénalienne
  - Administration concomitante d'inhibiteur CYP3A4 (Ketoconazole, Clarythromycine...)

Conclusion

- La finérénone réduit le risque cardiovasculaire et rénal chez le patient diabétique de type 2 et ayant une MRC, une albuminurie et une kaliémie normale.
- Déjà traité par une pleine dose d'inhibiteur du SRA
- Ce traitement est recommandé par nos sociétés savantes avec un niveau de preuve élevé (IA ou 2A).
- Il reste à préciser sa place et son effet en association avec les iSGLT2 chez le patient diabétique et patient MRC non diabétique.

Merci de votre attention