Prise en charge de la lithiase rénale, quoi de neuf en 2025 ?

Dr Thomas Ernandez
Néphrologie FMH
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Colloque de formation continue
Société médicale de Neuchâtel
27 mars 2025

Plan

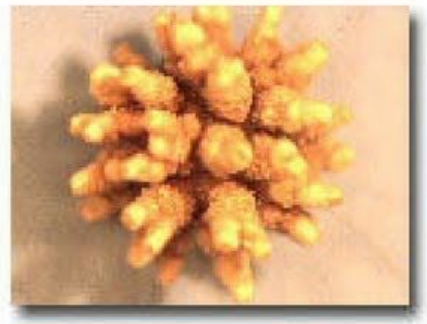
- Introduction : incidence, principes physiopathologiques
- Quel bilan métabolique pour quels patients
- Nouveautés dans les mesures préventives non-médicamenteuses ?
- Nouveautés dans les mesures préventives médicamenteuses ?

Introduction

- Colique néphrétique, un problème fréquent :
  - Env. 10% des gens au cours de leur vie
  - F << H, incidence en augm. chez les F
  - Récurrent : 10-20% l'année suivante,
    25-40% à 5 ans
  - 700'000 – 1 million consultations urgentes aux USA en 2009
  - 985 consultations urgentes aux HUG en 2010
  - 10'000 hospitalisations/an en CH (25'000/an en UK)

- Coûts importants :
  - Directs et indirects
  - 3 milliards USD en 2009 aux USA (coûts directs)
    + 3 millions de jours de travail manqués
  - Coût très élevé des PEC uro (URS > 10'000chf)

TYPES OF KIDNEY STONE



Agony

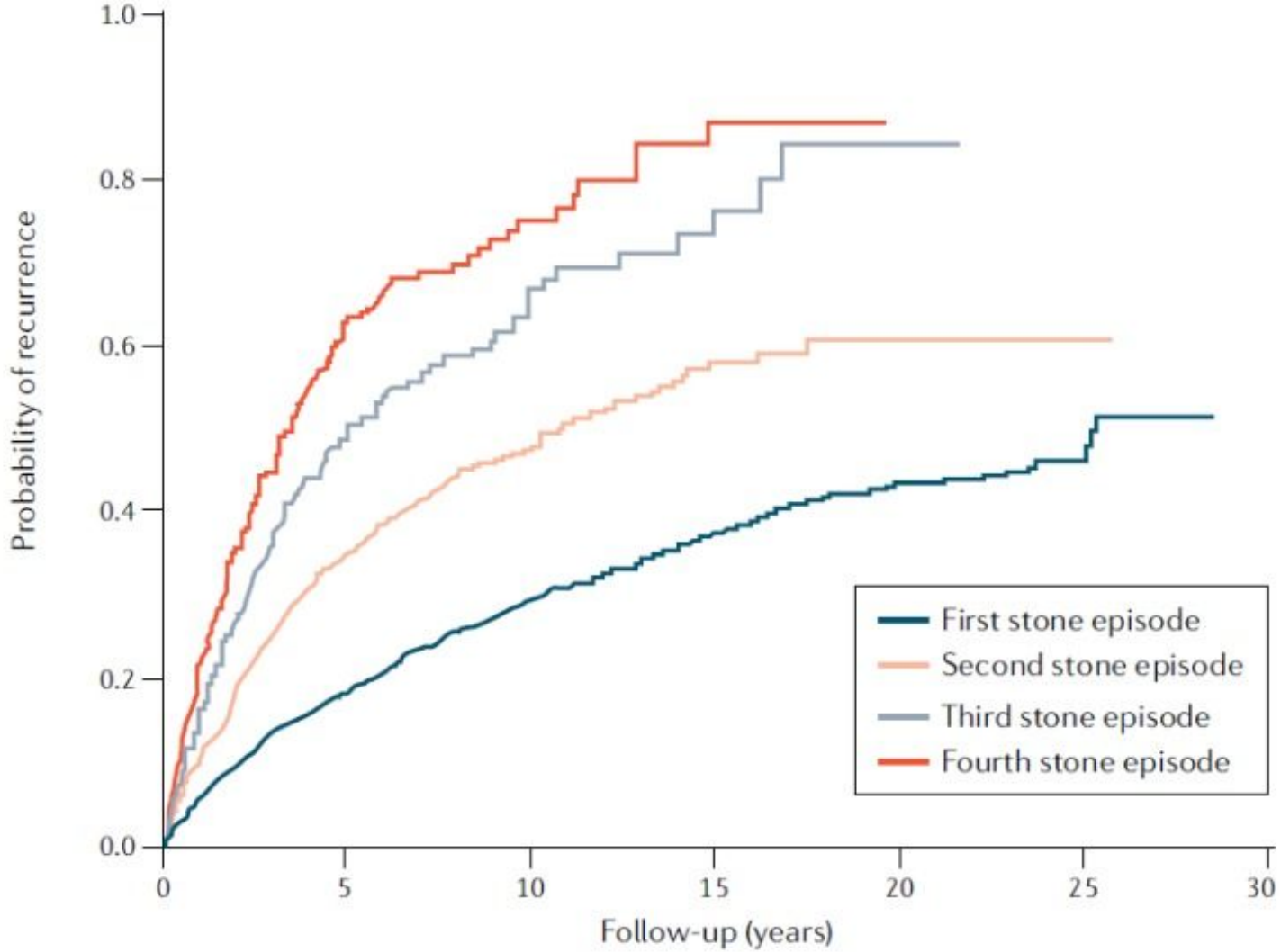
Pain

Misery

Moe. Lancet 2006
Ernandez et al. RMS. 2013
Pickard et al. Lancet. 2015
Bony et al. (SKSC) Kidney Blood Press Res 2023

Introduction

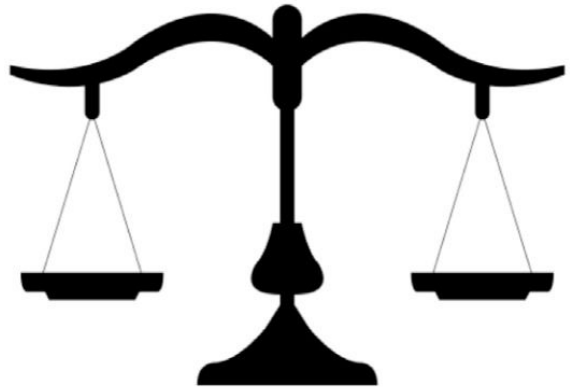
Traitement médical = PREVENTION DE LA RECIDIVE



Thongprayoon et al. Nature Review Nephrol. 2020

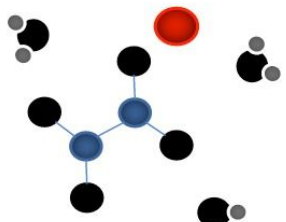
Physiopathologie de l'urolithiase

Stone Inhibitors
Citrate
Uromodulin
Magnesium
Others
(pyrophosphate, osteopontin, etc.)



Stone Promotors
High substrate concentration
Slow urinary flow
"Salting out"
Randall's plaques/plugs
Bacterial products
Cell injury

↑pH↓

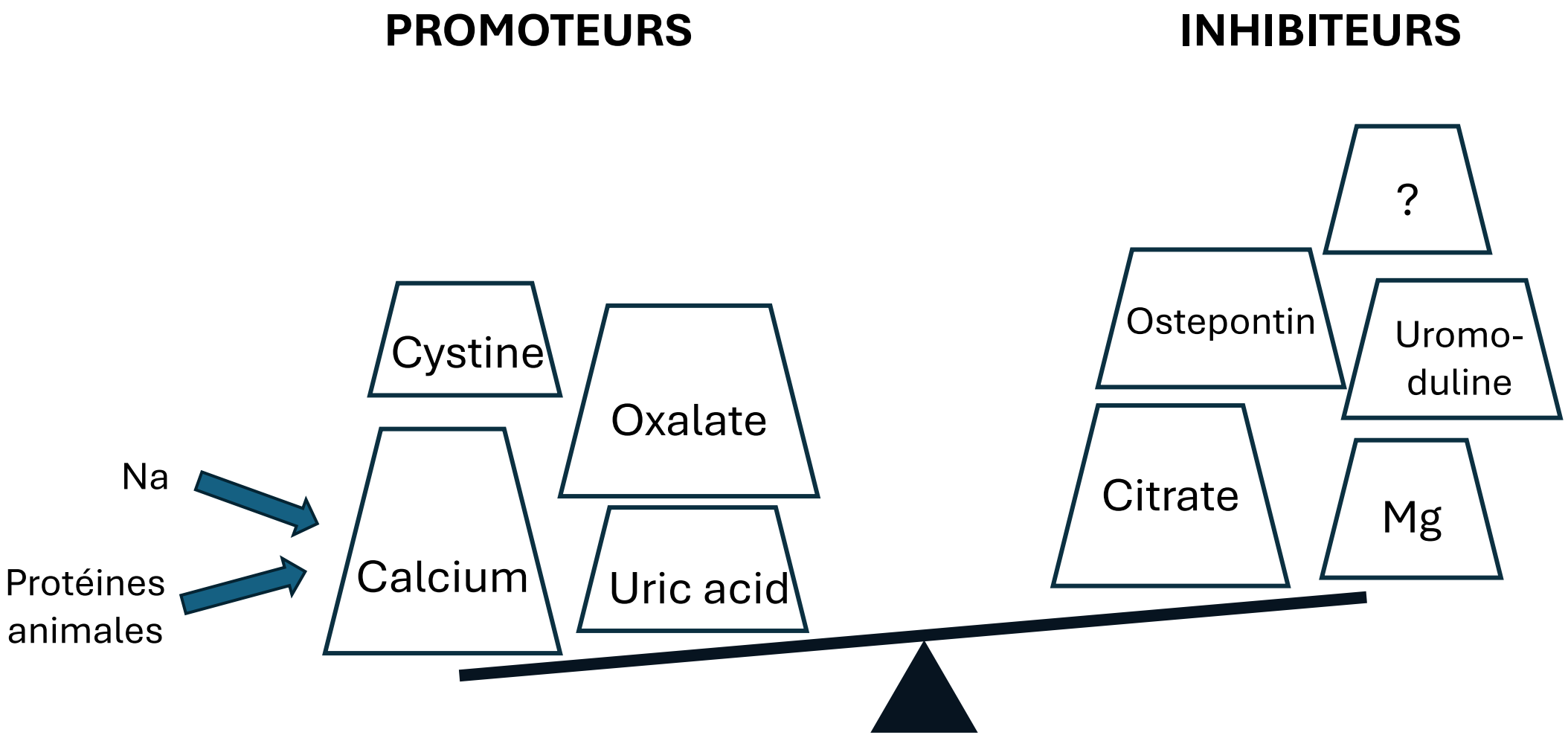


Supersaturation

Nucleation, Growth, Aggregation

Shastri et al. AJKD 2023

Physiopathologie de l'urolithiase



AUA Guidelines

Medical Management of Kidney Stones: AUA Guideline

Margaret S. Pearle, David S. Goldfarb, Dean G. Assimos, Gary Curhan, Cynthia J. Denu-Ciocca, Brian R. Matlaga, Manoj Monga, Kristina L. Penniston, Glenn M. Preminger, Thomas M. T. Turk and James R. White

J Urol 2014. Reviewed and validated in 2019

Evaluation

5. Clinicians should perform additional metabolic testing in high-risk or interested first-time stone formers and recurrent stone formers. (*Standard; Evidence Strength: Grade B*)

6. Metabolic testing should consist of one or two 24-hour urine collections obtained on a random diet and analyzed at minimum for total volume, pH, calcium, oxalate, uric acid, citrate, sodium, potassium and creatinine. (*Expert Opinion*)

Follow-up

22. Clinicians should obtain a single 24-hour urine specimen for stone risk factors within six months of the initiation of treatment to assess response to dietary and/or medical therapy. (*Expert Opinion*)

23. After the initial follow-up, clinicians should obtain a single 24-hour urine specimen annually or with greater frequency, depending on stone activity, to assess patient adherence and metabolic response. (*Expert Opinion*)

Bilan métabolique : pour quels patients ?

Bilan métabolique indiqué chez les patients « à risque » (pratique local + SKSC)

- > 1 épisode de calcul rénal
- 1 seul épisode avec au moins 1 facteur de risque additionnel :
  - Premier calcul < 25 ans
  - AF +
  - Calcul non composé d'oxalate de Ca
  - Maladies gastro-intestinales (y.c. s/p bypass)
  - Ostéoporose
  - Néphrocalcinose
  - Rein unique ou anomalie anatomique des voies urinaires
  - IRC (eGFR < 60ml/min/1.73m^2 ou protéinurie)
  - Grossesse
  - Goutte, syndrome métabolique ou DM
  - Calculs résiduels ou bilatéraux
  - Infection urinaire chronique ou récurrente
  - S/p transplantation rénale

Bonny et al (SKSC group). Kidney Blood Press Res 2020

Bilan métabolique : quels paramètres ?

Bilan sanguin :

- glucose, Na, K, urée, créatinine, CO2 total, acide urique,
  (bilan lipidique, Hb glyquée)
- Ca, phosphate, phosphatase alcaline osseuse, PTH, vitamine 25-D3 et 1,25-D3

Spot urinaire
(2ème urine du matin) :

- pH (électrode),
- cristallurie,
- leucocyturie
- (+/-culture d'urine)
- test qualitatif de la cystine

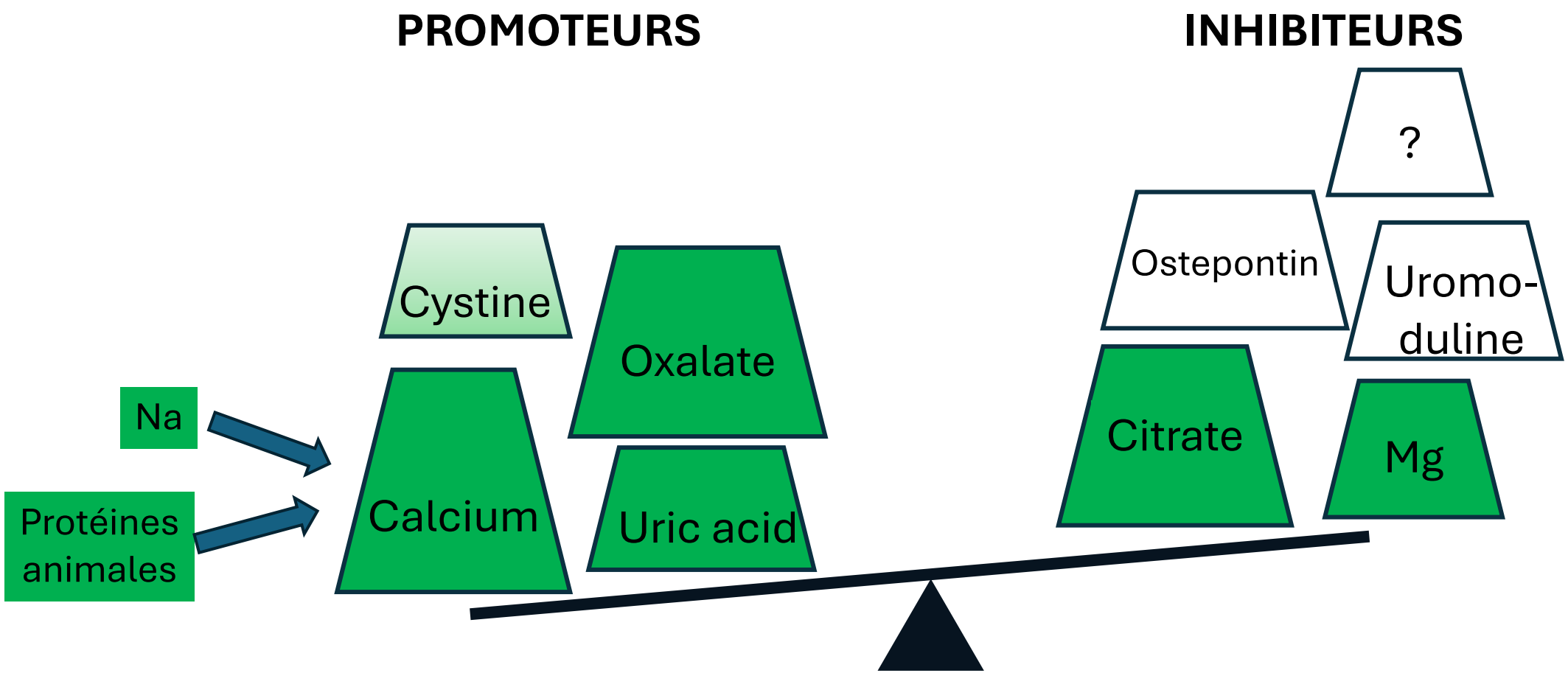
Récoltes d'urine de 24h (2x ?)
(si possible un jour de semaine et un jour de week-end) :

- Volume
- Créatinine
- Na, K
- Ca, phosphate
- urée, acide urique
- oxalate
- citrate, Mg
- (ammonium, sulfate)

Mesures préventives non médicamenteuses

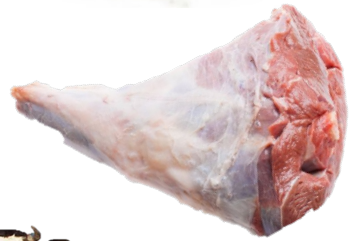
Mesures préventives non-médicamenteuses

Habitude de vie : hydratation et régime alimentaire



Mesures préventives non-médicamenteuses

- **Hyperhydratation** : > 2.5l/j, répartie au cours de la journée, y compris en soirée (dilution urinaire nocturne)
- **Augmentation des apports en fruits et légumes** = source de citrate, 5 portions par jour, > ½ de la portion alimentaire
- **Diminution du sel** < 6g/j (NaCl), soit Na-U < 100mmol/24h
  (effet sur la calciurie)
- **Diminution des protéines animales**, toutes sources confondues, < 1g/kg/j
  (effet sur la calciurie et sur la citraturie)
- Maintien **d'apports en calcium de l'ordre de 1000mg/j**, soit 3 portions de produits laitiers (3dl de lait, 30g de fromage pâte dure, 150g de yogourt). Diminution de l'absorption intestinale des oxalates (chélation digestive) et prévention du risque osseux associé à l'urolithiase
- **Diminution des sources alimentaires d'oxalate**.
  Eviter en particulier les « à-coups » alimentaires



Mesures préventives non-médicamenteuses

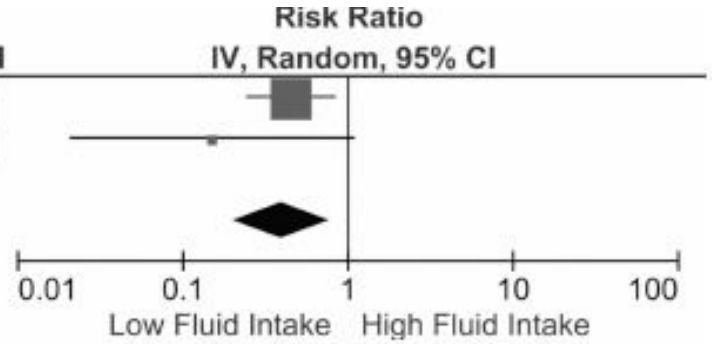
Effets de l'hyperhydratation

RCTs

Study or Subgroup	log[Risk Ratio]	SE	Weight	Risk Ratio IV, Random, 95% CI
Borghi et al.	-0.79851	0.319582	88.5%	0.45 [0.24, 0.84]
Sarica et al	-1.89712	1.015225	11.5%	0.15 [0.02, 1.10]
Total (95% CI)			**100.0%**	**0.40 [0.20, 0.79]**

Heterogeneity: $Tau^2 = 0.04$; $Chi^2 = 1.07$, df = 1 (P = 0.30); $I^2 = 6\%$

Test for overall effect: Z = 2.64 (P = 0.008)

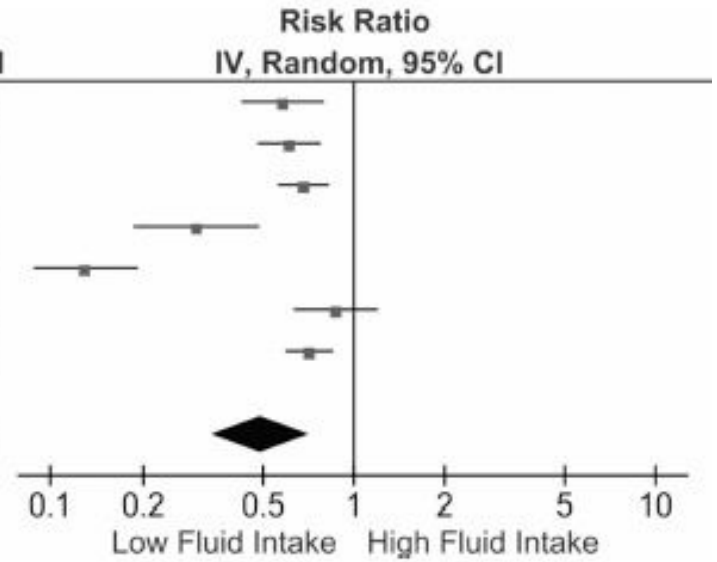


Observational

Study or Subgroup	log[Risk Ratio]	SE	Weight	Risk Ratio IV, Random, 95% CI
Curhan et al. (1)	-0.54473	0.161168	14.3%	0.58 [0.42, 0.80]
Curhan et al. (2)	-0.4943	0.123854	14.9%	0.61 [0.48, 0.78]
Curhan et al. (3)	-0.38566	0.10038	15.2%	0.68 [0.56, 0.83]
Daudon et al.	-1.20397	0.244841	12.6%	0.30 [0.19, 0.48]
Hosking et al.	-2.04022	0.19864	13.5%	0.13 [0.09, 0.19]
Linder et al.	-0.13926	0.164377	14.2%	0.87 [0.63, 1.20]
Taylor et al.	-0.34249	0.093141	15.3%	0.71 [0.59, 0.85]
Total (95% CI)			**100.0%**	**0.49 [0.34, 0.71]**

Heterogeneity: $Tau^2 = 0.22$; $Chi^2 = 77.22$, df = 6 (P < 0.00001); $I^2 = 92\%$

Test for overall effect: Z = 3.76 (P = 0.0002)



Cheungpasitporn. J Nephrol 2016

Diminution du risque relatif de >50% si hydratation > 2.5l/j ou diurèse > 2l/j

Mesures préventives non-médicamenteuses

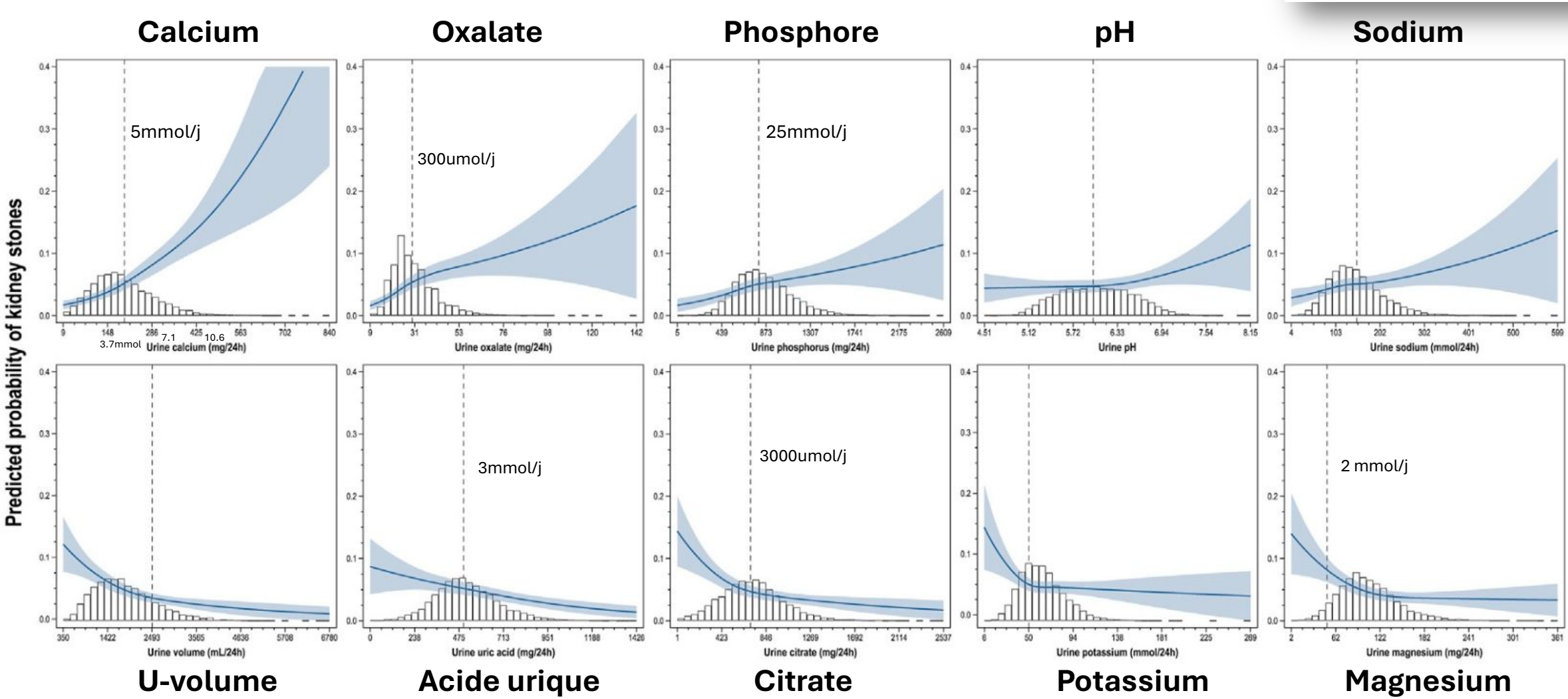
Table 1. Characteristics of the Study Population by Stone Status

	Overall	Stone Formers	Non-Stone-Formers
N	6,217	2,577	3,640
No. of collections			
1	3,680 (59%)	907 (35%)	2,773 (76%)
2	2,246 (36%)	1,380 (54%)	866 (24%)
3	291 (5%)	290 (11%)	1 (<1%)
Age, y	57 ± 9	59 ± 11	55 ± 7
BMI, kg/m^2	26 ± 5	27 ± 5	26 ± 5
Women	5,094 (82%)	1,864 (72%)	3,230 (89%)
Urine parameter			
Creatinine, mg/24 h	1,264 ± 325	1,281 ± 380	1,251 ± 278
Calcium, mg/24 h	200 ± 99	210 ± 107	194 ± 93
Oxalate, mg/24 h	32 ± 12	32 ± 12	31 ± 11
Uric acid, mg/24 h	533 ± 174	517 ± 193	545 ± 157
Citrate, mg/24 h	732 ± 305	668 ± 315	777 ± 289
Volume, mL/24 h	1,890 ± 780	1,660 ± 660	2,050 ± 820
Phosphorus, mg/24 h	860 ± 286	887 ± 313	841 ± 264
Potassium, mmol/24 h	64 ± 22	61 ± 23	66 ± 22
Magnesium, mg/24 h	107 ± 40	105 ± 42	109 ± 39
Sodium, mmol/24 h	149 ± 63	158 ± 66	143 ± 59
pH	6.06 ± 0.51	5.94 ± 0.50	6.14 ± 0.51

Variables are reported as mean ± SD or as count (%); for participants with more than 1 collection, values from the first collection are reported.

Ferraro et al. AJKD 2024

Mesures préventives non-médicamenteuses



Ferraro et al. AJKD 2024

Mesures préventives non-médicamenteuses

Table 3. Dominance Analysis of Urinary Parameters and Kidney Stones

Urinary Parameter	Standardized Dominance Statistic	Rank
Calcium	0.270	1
Volume	0.216	2
Citrate	0.137	3
Oxalate	0.099	4
Potassium	0.099	5
Magnesium	0.071	6
Uric acid	0.044	7
Phosphorus	0.037	8
Sodium	0.027	9

The standardized dominance statistic reflects the fraction of variance in the outcome explained by a given urinary parameter (eg, 27% of variance in the kidney stone outcome is explained by urinary calcium excretion).

Ferraro et al. AJKD 2024

Mesures préventives médicamenteuses

Mesures préventives médicamenteuses

- Peu de données et de qualité limitée démontrant l'utilité des interventions pharmacologiques dans la prévention du risque urolithiasique
- Thiazides pour les lithiases calciques, mais …
- Supplémentation en citrate de K pour les lithiases calciques, revue Cochrane
- Alcalinisation urinaire pour le traitement des lithiases d'acide urique et dans une certaine mesure la prévention de leur récidive
- Pas d'indication de l'allopurinol dans la prévention des lithiases d'acide urique

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J Urol 2014. Reviewed and validated in 2019

Pharmacologic Therapies

14. Clinicians should offer thiazide diuretics to patients with high or relatively high urine calcium and recurrent calcium stones. (*Standard; Evidence Strength: Grade B*)

17. Clinicians should offer thiazide diuretics and/or potassium citrate to patients with recurrent calcium stones in whom other metabolic abnormalities are absent or have been appropriately addressed and stone formation persists. (*Standard; Evidence Strength: Grade B*)

AUA Guidelines

Medical Management of Kidney Stones: AUA Guideline

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Pharmacologic Th

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17. Clinicians should offer thiazide diuretics and/or potassium citrate to patients with recurrent calcium stones in whom other metabolic abnormalities are absent or have been appropriately addressed and stone formation persists. (*Standard; Evidence Strength: Grade B*)

Mesures préventives médicamenteuses

Table 1. Randomized controlled trials of thiazides in the prevention of recurrent nephrolithiasis.

Author, Year	Treatment, Dose	Allocation Concealment	Blinding	Intention-to-treat Analysis	Withdrawals described	Selection for Hypercalciuria	Follow-Up (Years)	Treated/ Placebo, n/N	Events/Total, n/N Thiazide	Events/Total, n/N Placebo	RR [c]	Recurrence Outcome
Brocks, 1981 [52]	Bendroflumethiazide, 2.5 mg TID [a]	Unclear	Double-blind	No	No	No	1.6	33/29	5/33	5/29	NS	Composite
Scholz, 1982 [54]	HCTZ, 25 mg BID [b]	Unclear	Double-blind	No	No	No	1	25/26	6/25	6/26	NS	Symptomatic
Laerum, 1984 [46]	HCTZ, 25 mg BID	Unclear	Double-blind	Yes	Yes	No	3	23/25	5/23	12/25	0.45	Composite
Wilson, 1984 [49]	HCTZ, 100 mg daily	Unclear	Open-label	No	No	No	2.8	23/21	0.15 stones/year	0.32 stones/year	0.48	Symptomatic
Robertson, 1985 [50]	Bendroflumethazide, 2.5 mg TID	Unclear	Open-label	No	No	No	3 - 5	13/9	0.22 stones/year	0.58 stones/year	0.38	Symptomatic
Mortensen, 1986 [47]	Bendroflumethazide, 2.5 mg	Unclear	Double-blind	No	No	No	2	12/10	0/12	4/10	-	Composite
Ettinger, 1988 [45]	Chlorthalidone, 25 m /50 mg	Adequate	Double-blind	No	Yes	No	3	19/23/31 (25 mg /50 mg/placebo)	6/42	14/31	0.32	Composite
Ohkawa, 1992 [48]	Trichlormethiazide, 4 mg	Unclear	Open-label	No	No	Yes	2.14 - 2.21	82/93	24/82	57/93	0.42	Composite
Borghi, 1993 [44]	Indapamide, 2.5 mg daily	Unclear	Open-label	No	Yes	Yes	3	43/14	3/19	9/21	0.37	Composite
Ahlstrand, 1996 [53]	HCTZ, 25 mg BID	Unclear	Open-label	Yes	Yes	Yes	3.6 – 4.3	17/22	9/17	19/22	0.61	Composite
Fernandez-Rodriguez, 2006 [51]	HCTZ, 50 mg daily	Unclear	None stated	Yes	No withdrawals	No	3	50/50	16/50	28/50	0.57	Composite

[a] TID, three times daily
[b] BID, twice times daily
[c] RR, relative risk

Green color indicates trials included in the recent metaanalysis by Fink et al. [63]

Mesures préventives médicamenteuses

nostone

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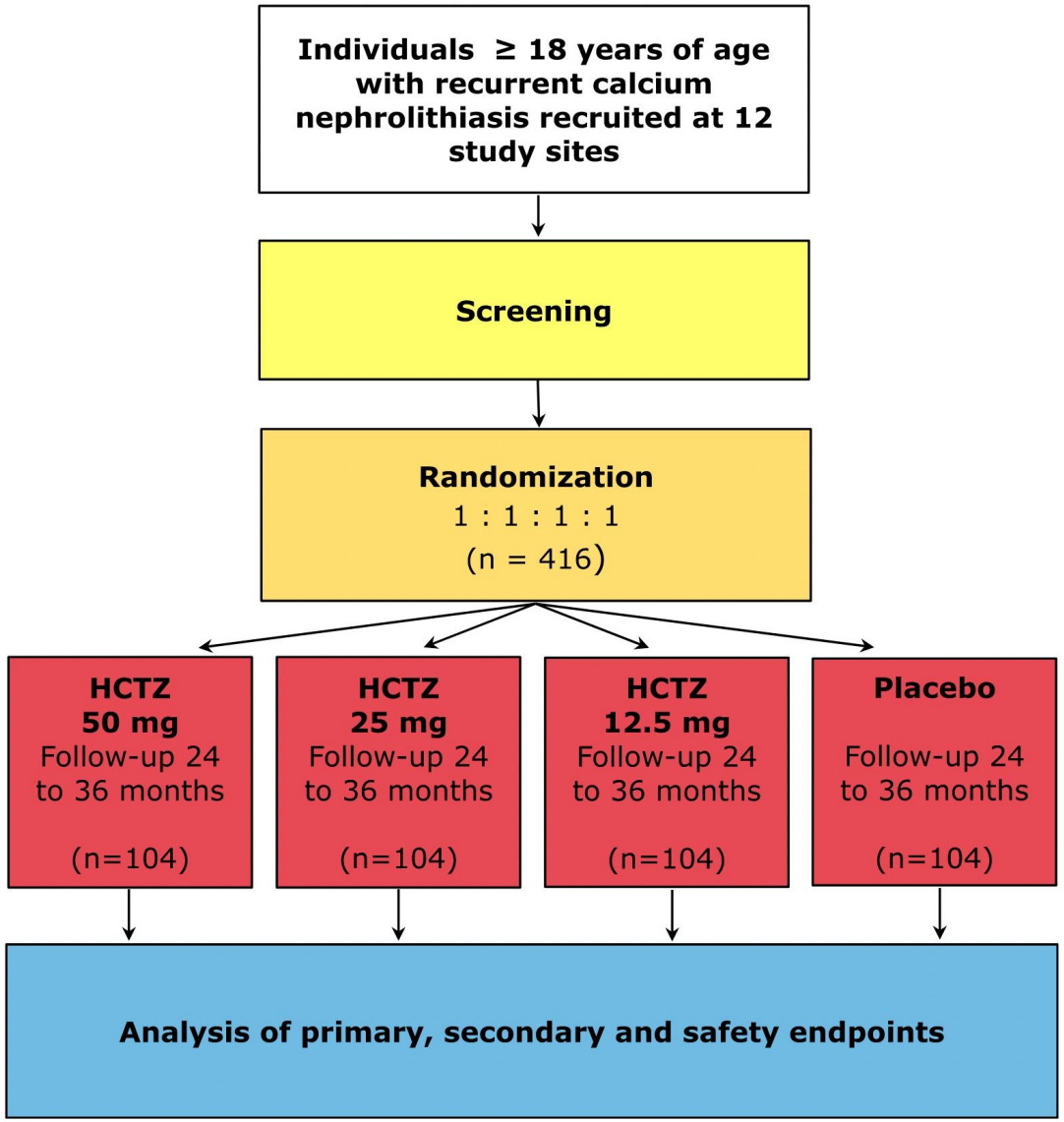
Hydrochlorothiazide and Prevention of Kidney-Stone Recurrence

Nasser A. Dhayat, M.D., Olivier Bonny, M.D., Ph.D., Beat Roth, M.D., Andreas Christe, M.D., Alexander Ritter, M.D., Nilufar Mohebbi, M.D., Nicolas Faller, M.D., Ph.D., Lisa Pellegrini, M.D., Giulia Bedino, M.D., Reto M. Venzin, M.D., Philipp Grosse, M.D., Carina Hüsler, M.D., Irene Koneth, M.D., Christian Bucher, M.D., Rosaria Del Giorno, M.D., Luca Gabutti, M.D., Michael Mayr, M.D., Urs Odermatt, M.D., Florian Buchkremer, M.D., Thomas Ernandez, M.D., Catherine Stoermann-Chopard, M.D., Daniel Teta, M.D., Bruno Vogt, M.D., Marie Roumet, Ph.D., Luca Tamò, Ph.D., Grazia M. Cereghetti, Ph.D., Sven Trelle, M.D., and Daniel G. Fuster, M.D.

Mesures préventives médicamenteuses



Primary outcome

- Composite of symptomatic or radiological stone recurences

Secondary outcome

- Individual components of primary
- Change in urinary biochemistery
- Impact of stone composition
- Impact of disease activity

Safety outcomes

- HypoK, hypoNa, hypoMg
- Gout, DM, allergy

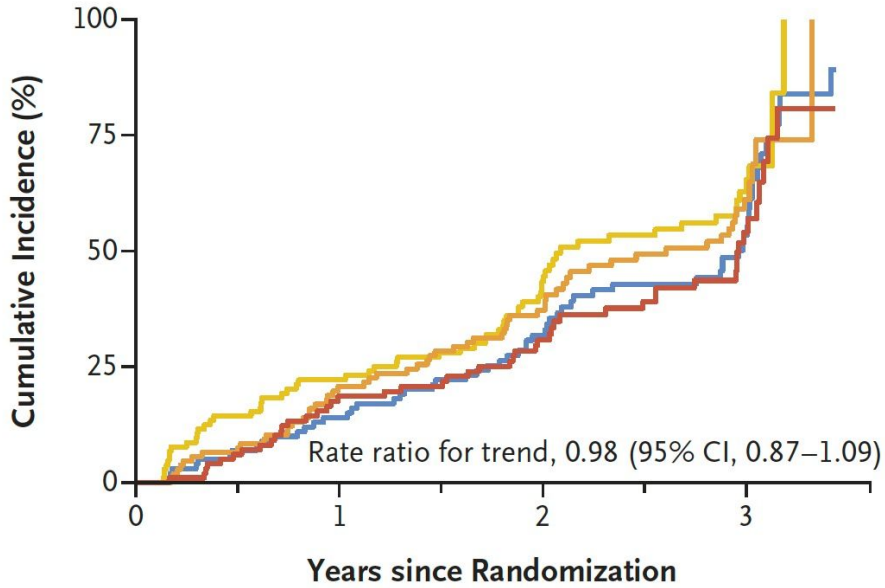
Mesures préventives médicamenteuses

Table 1. Demographic and Clinical Characteristics of the Patients at Baseline.*

Characteristic	Total (N=416)	Placebo (N=102)	12.5-mg Hydrochlorothiazide (N=105)	25-mg Hydrochlorothiazide (N=108)	50-mg Hydrochlorothiazide (N=101)
Median age (IQR) — yr	49 (39–55)	47 (35–55)	49 (40–57)	48 (39–56)	50 (42–55)
Female sex — no. (%)	85 (20)	26 (25)	16 (15)	22 (20)	21 (21)
Race — no. (%)†					
White	411 (99)	100 (98)	105 (100)	106 (98)	100 (99)
Black	2 (<1)	0	0	1 (1)	1 (1)
Asian	2 (<1)	1 (1)	0	1 (1)	0
Other	1 (<1)	1 (1)	0	0	0
No. of stone events in the past 10 yr — no. (%)‡					
2 or 3	277 (67)	70 (69)	68 (65)	73 (68)	66 (65)
≥4	139 (33)	32 (31)	37 (35)	35 (32)	35 (35)
Median urinary calcium excretion (IQR) — mg/24 hr§	244 (165–340)	257 (157–339)	239 (164–317)	256 (167–369)	238 (168–338)
Hypercalciuria — no. (%)¶ {q50}	258 (62)	60 (59)	63 (60)	69 (64)	66 (65)

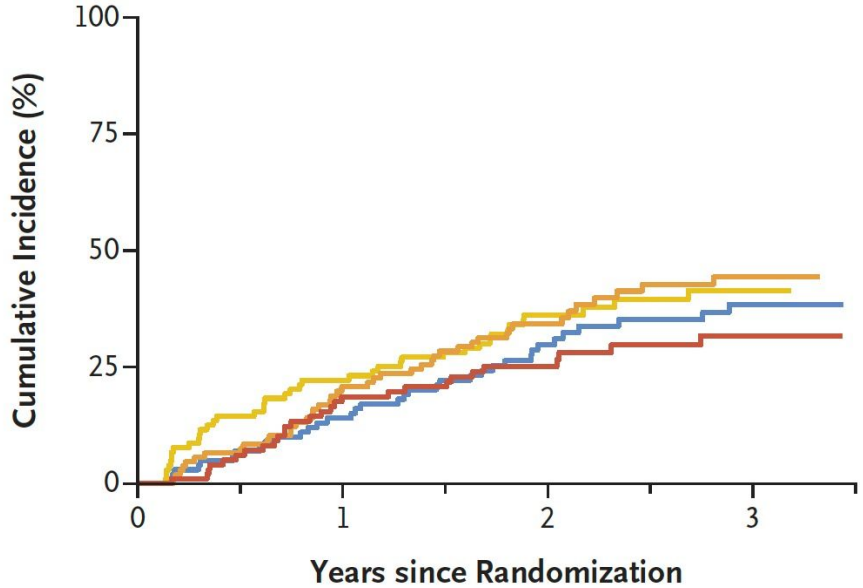
Mesures préventives médicamenteuses

A Symptomatic or Radiologic Recurrence of Kidney Stones



No. at Risk				
Placebo	102	85	59	25
12.5-mg HCT	105	79	50	14
25-mg HCT	108	83	57	15
50-mg HCT	101	77	56	17

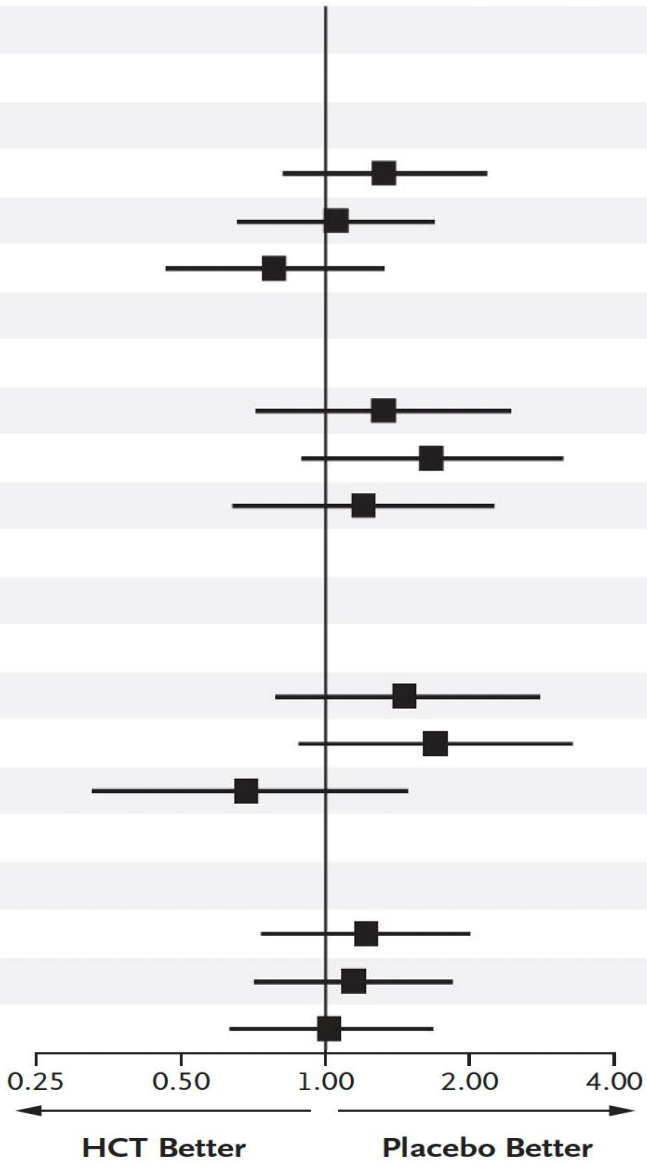
B Symptomatic Recurrence of Kidney Stones



No. at Risk				
Placebo	102	85	59	25
12.5-mg HCT	105	79	50	14
25-mg HCT	108	83	57	15
50-mg HCT	101	77	56	17

Mesures préventives médicamenteuses

Subgroup	No. of Events/Total No.	Rate Ratio (95% CI)	Rate Ratio for Trend
No. of stone events in the past 10 yr			
2 or 3			
Placebo	38/70		0.92 (0.80–1.07)
12.5-mg HCT	37/68	1.34 (0.84–2.14)	
25-mg HCT	37/73	1.05 (0.66–1.66)	
50-mg HCT	26/66	0.78 (0.47–1.30)	
≥4			
Placebo	22/32		1.05 (0.88–1.25)
12.5-mg HCT	25/37	1.33 (0.73–2.41)	
25-mg HCT	24/35	1.68 (0.91–3.09)	
50-mg HCT	23/35	1.18 (0.64–2.16)	
Hypercalciuria			
No			
Placebo	23/41		0.95 (0.78–1.14)
12.5-mg HCT	24/40	1.46 (0.79–2.71)	
25-mg HCT	21/35	1.68 (0.88–3.19)	
50-mg HCT	13/34	0.68 (0.32–1.43)	
Yes			
Placebo	37/60		0.99 (0.84–1.07)
12.5-mg HCT	36/63	1.19 (0.74–1.93)	
25-mg HCT	38/69	1.13 (0.71–1.79)	
50-mg HCT	35/66	1.01 (0.63–1.48)	



Mesures préventives médicamenteuses

Table 2. Laboratory Test Results in Urine at Baseline and during Follow-up.*

Variable	Baseline		Follow-up{q54}		Effect vs. Placebo (95% CI)
	No. of Patients	Mean	No. of Patients	Mean	
Total urine volume — liters/24 hr					
Placebo	101	1.74±0.80	252	2.06±0.74	Reference
12.5-mg Hydrochlorothiazide	103	1.90±0.74	267	2.12±0.75	–0.01 (–0.16 to 0.13)
25-mg Hydrochlorothiazide	104	1.93±0.82	277	2.15±0.80	0.07 (–0.09 to 0.22)
50-mg Hydrochlorothiazide	100	1.68±0.66	245	2.06±0.68	0.05 (–0.1 to 0.19)
Urinary sodium excretion — mmol/24 hr					
Placebo	101	170.82±76.95	252	183.16±81.91	Reference
12.5-mg Hydrochlorothiazide	103	179.65±85.04	267	181.89±79.69	–4.32 (–19.81 to 11.18)
25-mg Hydrochlorothiazide	104	197.06±85.65	277	191.80±83.87	–0.37 (–16.87 to 16.13)
50-mg Hydrochlorothiazide	100	168.93±71.63	245	198.58±81.34	15.67 (–0.72 to 32.07)
Urinary calcium excretion — mg/24 hr					
Placebo	101	256.90±124.66	252	277.46±137.07	Reference
12.5-mg Hydrochlorothiazide	103	256.15±132.02	267	231.96±119.53	–42.01 (–68.05 to 15.97)
25-mg Hydrochlorothiazide	104	280.69±159.96	277	232.52±156.80	–40.54 (–67.88 to 13.21)
50-mg Hydrochlorothiazide	100	274.39±154.14	245	236.82±139.19	–51.13 (–78.87 to 23.39)

Calcium

Mesures préventives médicamenteuses

Variable	Baseline		Follow-up{q54}		Effect vs. Placebo (95% CI)
	No. of Patients	Mean	No. of Patients	Mean	
Urinary citrate excretion — mg/24 hr					
Placebo	101	575.28±326.39	252	588.74±314.08	Reference
12.5-mg Hydrochlorothiazide	103	530.00±267.89	267	588.38±328.68	32.20 (–20.26 to 84.66)
25-mg Hydrochlorothiazide	104	522.16±246.10	276	520.57±292.50	–8.47 (–58.75 to 41.81)
50-mg Hydrochlorothiazide	100	554.09±288.86	245	536.51±309.71	–36.28 (–85.48 to 12.92)
Urinary oxalate excretion — mg/24 hr					
Placebo	101	30.02±18.41	252	34.98±20.60	Reference
12.5-mg Hydrochlorothiazide	103	29.92±17.33	267	37.24±19.63	2.62 (–1.47 to 6.71)
25-mg Hydrochlorothiazide	104	29.90±18.55	276	39.58±24.08	4.68 (0.25 to 9.11)
50-mg Hydrochlorothiazide	100	28.39±13.52	245	34.98±20.52	0.12 (–4.09 to 4.34)

Citrate ↓

Oxalate ↑ ?

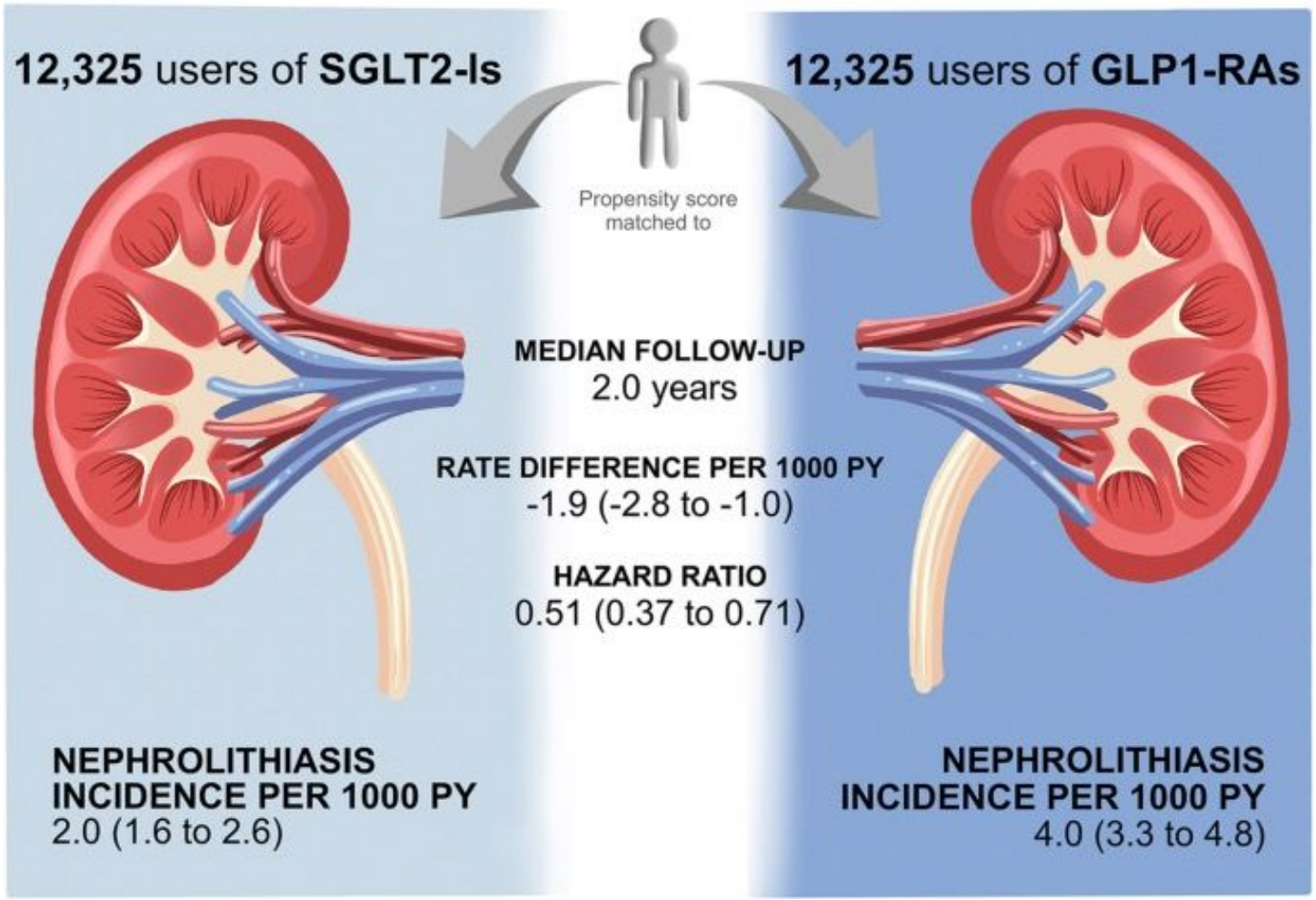
Mesures préventives médicamenteuses

Table 3. Adverse Events during the Treatment Period.

Event	Placebo (N=102)		12.5-mg Hydrochlorothiazide (N=105)		25-mg Hydrochlorothiazide (N=108)		50-mg Hydrochlorothiazide (N=101)	
	no. of patients (%)	*no. of events*	*no. of patients (%)*	*no. of events*	*no. of patients (%)*	*no. of events*	*no. of patients (%)*	*no. of events*
Adverse events of special interest{q55}*								
Total	8 (8)	8	11 (10)	12	18 (17)	21	16 (16)	20
Hypokalemia	1 (1)	1	1 (1)	1	3 (3)	3	6 (6)	8
Gout	0	0	1 (1)	1	1 (1)	2	0	0
New-onset diabetes mellitus	1 (1)	1	2 (2)	2	7 (6)	7	2 (2)	2
Serious adverse event	30 (29)	34	17 (16)	18	24 (22)	27	14 (14)	16

Mesures préventives médicamenteuses

Active comparator new user study of the association between SGLT2-Inhibitors or GLP-1 Receptor Analogues and the risk of nephrolithiasis



Kristensen et al. Diabetologia. 2021

Mesures préventives médicamenteuses

Empagliflozin Changes Urine Supersaturations by Decreasing pH and Increasing Citrate

JASN
JOURNAL OF THE AMERICAN SOCIETY OF NEPHROLOGY

METHODS

Healthy volunteers

placebo N=13 vs. empagliflozin N=27

10 mg/d
4 wks

- Day/night urine collections
- Calculation of relative supersaturation ratios

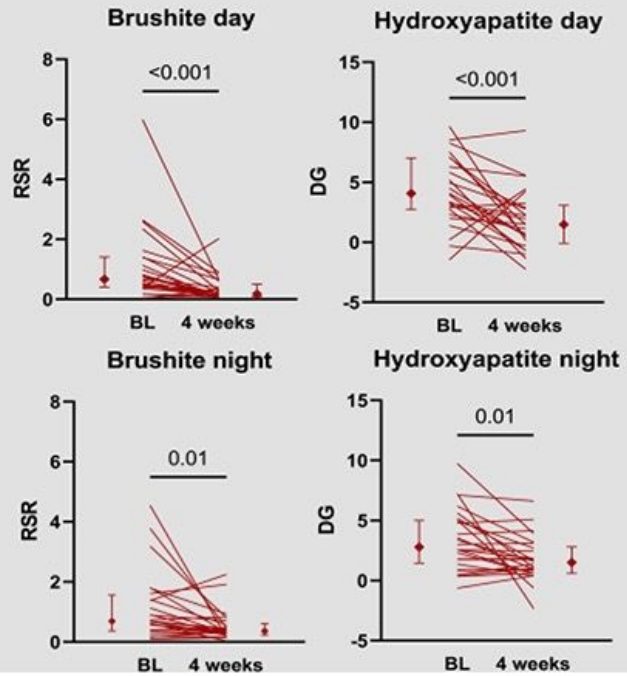
OUTCOME

Effect of empagliflozin

24h U-citrate +45% at 4 wks (p=0.01)

U-pH day 6.4±0.9 → 5.9±0.9 (p=0.004)

U-pH night 6.0±0.8 → 5.6±0.6 (p=0.02)



Conclusion
SGLT2i may reduce kidney calcium containing stone risk by decreasing the RSR of CaP minerals in healthy subjects. This effect seems to be mediated by increased urine citrate and reduced urine pH.

doi: 10.1681/ASN.2021111515

Pas de diminution du RSR CaOx et augmentation du RSR AU

Harmacek et al. JASN 2021

Mesures préventives médicamenteuses

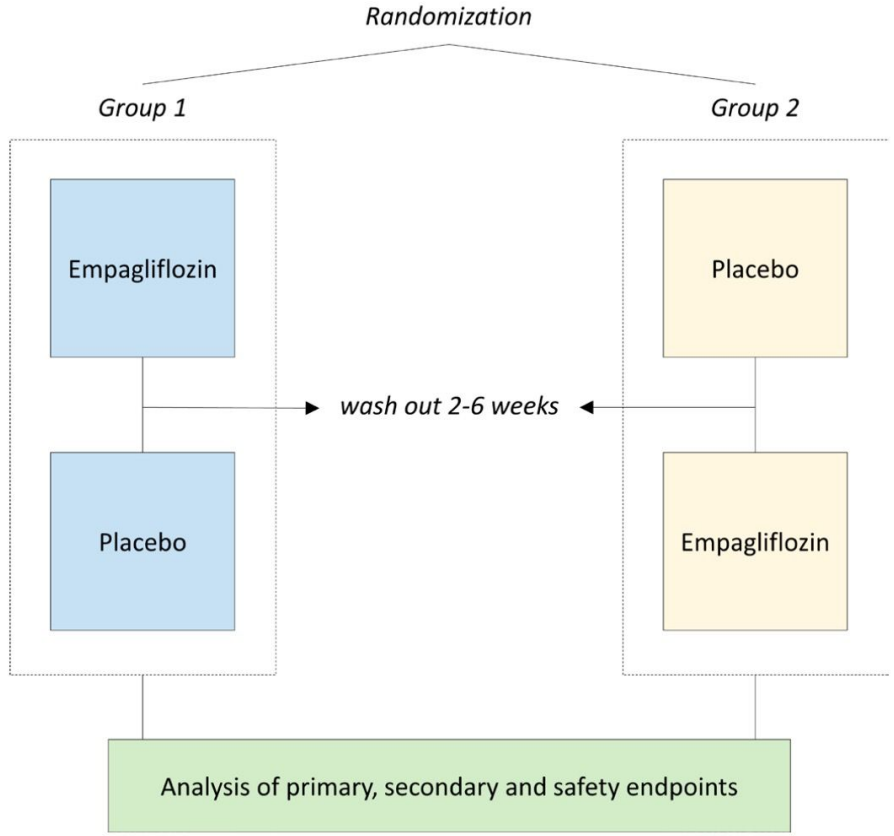
Impact of the SGLT2 inhibitor empagliflozin on urinary supersaturations in kidney stone formers (SWEETSTONE trial): protocol for a randomised, double-blind, placebo-controlled cross-over trial

Simeon Schietzel ,[1] Lia Bally ,[2] Grazia Cereghetti,[1,3] Nicolas Faller,[1] Matthias B Moor,[1] Bruno Vogt,[1] Felix Rintelen,[3] S Trelle,[3] Daniel Fuster[1]

BMJ open. 2022

Inclusion criteria

- Informed consent as documented by signature.
- Age between 18 and 74 years.
- One or more kidney stone event(s) in the past.
- Any past kidney stone containing ≥80% of calcium or ≥80% of uric acid.
- HbA1c <6.5%.



N = 46 (2x23)

Primary outcomes :

- SS Ca-Ox
- SS Ca-P
- SS AU

Secondary outcomes :

- Paramètres biochimiques sanguins
- Paramètres biochimiques U-24h

Safety outcomes

Mesures préventives médicamenteuses

nature medicine

Article

https://doi.org/10.1038/s41591-024-03330-x

Empagliflozin in nondiabetic individuals with calcium and uric acid kidney stones: a randomized phase 2 trial

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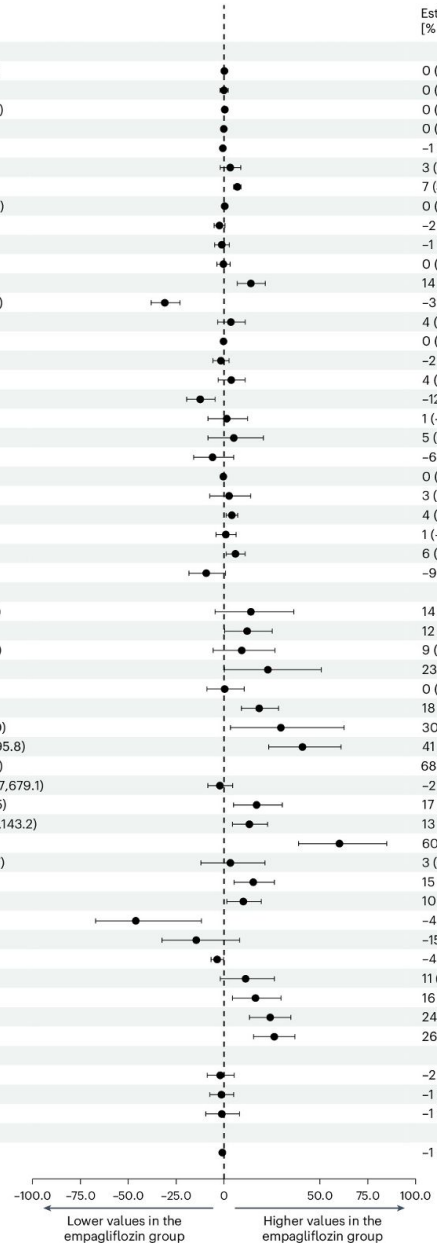
Manuel A. Anderegg[1,4,5], Simeon Schietzel[1,5], Matteo Bargagli[1], Lia Bally[2], Nicolas Faller[1], Matthias B. Moor[1], Grazia M. Cereghetti[1], Marie Roumet[3], Sven Trelle[3] & Daniel G. Fuster[1]

Anderegg et al. Nature Med. Jan 2025

Mesures préventives médicamenteuses

Outcome	N[a]	Placebo (median (IQR))	N[b]	Empagliflozin (median (IQR))	Estimated relative difference [% (95% CI)][c]
Secondary outcomes, blood					
Sodium (mmol l^{-1})	24	140.0 (139.0, 141.0)	25	140.0 (138.0, 141.0)	0 (−1 to 1)
Potassium (mmol l^{-1})	24	3.9 (3.7, 4.0)	25	3.8 (3.7, 4.0)	0 (−2 to 2)
Chloride (mmol l^{-1})	24	105.0 (104.0, 106.0)	25	105.0 (104.0, 106.0)	0 (−1 to 1)
Calcium total (mmol l^{-1})	24	2.4 (2.3, 2.4)	25	2.4 (2.3, 2.4)	0 (−1 to 1)
Calcium ionized (mmol l^{-1})	25	1.2 (1.2, 1.2)	25	1.2 (1.2, 1.2)	−1 (−1 to 0)
Phosphate (mmol l^{-1})	24	1.0 (0.9, 1.2)	25	1.0 (1.0, 1.2)	3 (−2 to 9)
Magnesium (mmol l^{-1})	24	0.8 (0.8, 0.8)	25	0.9 (0.9, 0.9)	7 (5 to 9)
Osmolality (mosm kg^{-1})	24	285.0 (282.8, 289.0)	24	286.5 (284.0, 289.2)	0 (0 to 1)
Glucose (mmol l^{-1})	23	5.0 (4.8, 5.4)	24	5.0 (4.8, 5.4)	−2 (−5 to 0)
Albumin (g l^{-1})	24	39.5 (38.0, 42.2)	25	39.0 (37.0, 42.0)	−1 (−5 to 3)
Creatinine (µmol l^{-1})	24	74.0 (67.2, 84.5)	25	74.0 (65.0, 81.0)	0 (−4 to 3)
Urea (mmol l^{-1})	24	4.4 (3.4, 5.7)	25	4.9 (4.7, 5.9)	14 (7 to 22)
UA (µmol l^{-1})	24	292.0 (250.5, 326.5)	25	196.0 (184.0, 226.0)	−31 (−38 to −23)
Venous pCO_2 (mmHg)	25	44.0 (40.0, 46.0)	25	43.0 (41.0, 47.0)	4 (−3 to 11)
pH	25	7.4 (7.4, 7.4)	25	7.4 (7.4, 7.4)	0 (−1 to 0)
Venous bicarbonate (mmol l^{-1})	25	25.6 (23.9, 26.2)	25	25.1 (23.4, 26.7)	−2 (−6 to 3)
25-OH Vitamin D (nmol l^{-1})	25	59.0 (34.0, 66.0)	25	50.0 (32.0, 67.0)	4 (-3 to 11)
1,25-OH Vitamin D (pmol l^{-1})	25	136.0 (113.0, 154.0)	25	121.0 (94.0, 144.0)	−12 (−20 to −5)
PTH (pg ml^{-1})	25	36.3 (26.5, 49.6)	25	35.2 (29.7, 50.6)	1 (−8 to 12)
FGF23 (pg ml^{-1})	25	41.9 (32.2, 50.2)	24	43.5 (37.0, 51.9)	5 (−8 to 21)
Triglycerides (mmol l^{-1})	23	1.1 (0.9, 1.6)	24	1.1 (0.9, 1.4)	−6 (−16 to 5)
HbA1c (%)	25	5.4 (5.2, 5.8)	25	5.4 (5.2, 5.7)	0 (−1 to 1)
Alkaline phosphatase (U l^{-1})	24	68.5 (63.5, 80.2)	25	75.0 (64.0, 79.0)	3 (−8 to 14)
Total cholesterol (mmol l^{-1})	24	4.8 (4.2, 5.3)	25	5.2 (4.3, 5.6)	4 (1 to 7)
HDL cholesterol (mmol l^{-1})	24	1.3 (1.2, 1.4)	25	1.3 (1.1, 1.5)	1 (−4 to 6)
LDL cholesterol (mmol l^{-1})	24	2.9 (2.1, 3.5)	25	2.9 (2.4, 3.7)	6 (1 to 11)
TSH (mU l^{-1})	25	1.7 (1.4, 2.5)	25	1.5 (1.1, 2.2)	−9 (−18 to 1)
Secondary outcomes, urine					
Sodium (mmol per 24 h)	25	164.4 (132.3, 205.5)	25	184.6 (120.9, 253.0)	14 (−5 to 36)
Potassium (mmol per 24 h)	25	56.8 (42.8, 65.2)	25	60.4 (50.6, 68.4)	12 (0 to 25)
Chloride (mmol per 24 h)	25	151.0 (122.0, 184.0)	25	159.4 (108.0, 234.3)	9 (−6 to 26)
Calcium (mmol per 24 h)	25	6.2 (4.8, 8.3)	25	8.1 (6.3, 9.1)	23 (0 to 51)
Magnesium (mmol per 24 h)	25	4.1 (3.6, 5.0)	25	4.3 (3.3, 5.0)	0 (−9 to 10)
Phosphate (mmol per 24 h)	25	30.5 (21.1, 38.4)	25	35.2 (29.5, 42.9)	18 (9 to 28)
Osmolality (mosm kg^{-1})	22	509.5 (376.5, 640.0)	23	670.0 (522.5, 859.0)	30 (3 to 63)
Osmole excretion (mosm per 24 h)	22	882.9 (697.3, 978.9)	23	1,209.0 (940.5, 1,595.8)	41 (23 to 61)
Glucose (mmol per 24 h)	25	0.5 (0.3, 0.6)	25	289.2 (190.8, 389.2)	68,356 (56,202 to 83,132)
Creatinine (µmol per 24 h)	25	15,129.9 (12,019.4, 16,537.2)	25	15,685.2 (11,418.2, 17,679.1)	−2 (−9 to 5)
Urea (mmol per 24 h)	25	361.8 (284.2, 462.9)	25	384.0 (339.3, 584.5)	17 (5 to 30)
Uric acid (µmol per 24 h)	25	3,186.6 (2,573.3, 3,776.2)	25	4,334.0 (3,072.4, 5,143.2)	13 (4 to 23)
Citrate (mmol per 24 h)	25	3.2 (2.1, 3.9)	25	4.9 (3.3, 7.1)	60 (39 to 85)
Oxalate (µmol per 24 h)	25	513.7 (382.8, 599.1)	25	470.3 (356.4, 626.7)	3 (−12 to 21)
Sulfate (mmol per 24 h)	25	19.4 (14.1, 26.8)	25	24.7 (15.6, 29.8)	15 (5 to 26)
Ammonium (mmol per 24 h)	24	39.7 (20.6, 45.5)	24	42.2 (24.0, 50.0)	10 (1 to 19)
Bicarbonate (mmol per 24 h)	25	1.3 (0.5, 2.6)	25	0.9 (0.4, 1.7)	−46 (−67 to −12)
pCO_2 (mmHg)	25	38.0 (33.9, 57.0)	25	38.6 (27.1, 50.0)	−15 (−32 to 8)
Venous pH	25	5.8 (5.6, 6.4)	25	5.6 (5.5, 6.1)	−4 (−7 to 0)
Total volume per 24 h[d] (l)	25	1.8 (1.2, 2.5)	25	2.3 (1.4, 2.9)	11 (−2 to 26)
Titratable acid[e] (mEq per 24 h)	25	24.3 (16.6, 36.8)	25	33.2 (24.9, 35.8)	16 (4 to 30)
NGIA[e] (mEq per 24 h)	25	38.1 (26.9, 57.7)	25	49.9 (34.6, 63.6)	24 (13 to 35)
NAE[e] (mEq per 24 h)	24	62.1 (34.1, 80.4)	24	70.7 (53.2, 83.0)	26 (15 to 37)
Secondary outcomes, vital signs					
Systolic blood pressure (mmHg)	25	124.7 (118.7, 136.7)	25	122.0 (113.7, 128.7)	−2 (−9 to 5)
Diastolic blood pressure (mmHg)	25	81.0 (72.3, 87.7)	25	78.3 (72.3, 84.3)	−1 (−7 to 5)
Heart rate (beats per min)	25	70.3 (61.7, 79.3)	25	70.0 (62.3, 78.0)	−1 (−10 to 8)
Explorative outcome					
Weight (kg)	25	81.0 (75.0, 99.0)	25	78.0 (74.0, 99.5)	−1 (−1 to 0)



Anderegg et al. Nature Med. Jan 2025

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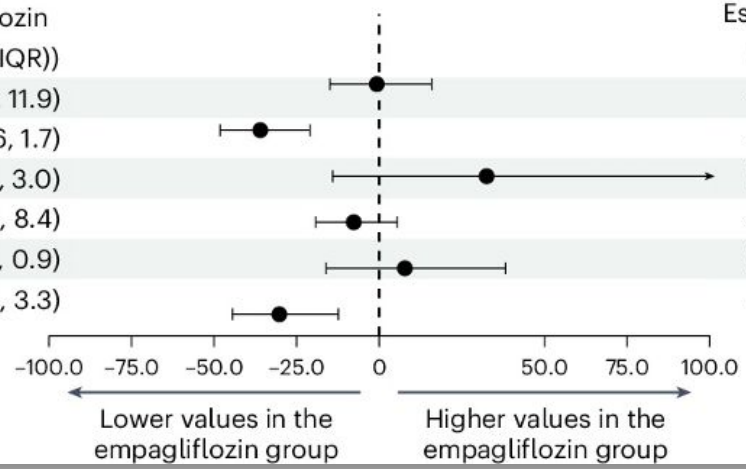
Calcium (mmol per 24 h)	25	6.2 (4.8, 8.3)	25	8.1 (6.3, 9.1)	23 (0 to 51)
Magnesium (mmol per 24 h)	25	4.1 (3.6, 5.0)	25	4.3 (3.3, 5.0)	0 (−9 to 10)
Phosphate (mmol per 24 h)	25	30.5 (21.1, 38.4)	25	35.2 (29.5, 42.9)	18 (9 to 28)
Osmolality (mosm kg^{-1})	22	509.5 (376.5, 640.0)	23	670.0 (522.5, 859.0)	30 (3 to 63)
Osmole excretion (mosm per 24 h)	22	882.9 (697.3, 978.9)	23	1,209.0 (940.5, 1,595.8)	41 (23 to 61)
Glucose (mmol per 24 h)	25	0.5 (0.3, 0.6)	25	289.2 (190.8, 389.2)	68,356 (56,202 to 83,132)
Creatinine (µmol per 24 h)	25	15,129.9 (12,019.4, 16,537.2)	25	15,685.2 (11,418.2, 17,679.1)	−2 (−9 to 5)
Urea (mmol per 24 h)	25	361.8 (284.2, 462.9)	25	384.0 (339.3, 584.5)	17 (5 to 30)
Uric acid (µmol per 24 h)	25	3,186.6 (2,573.3, 3,776.2)	25	4,334.0 (3,072.4, 5,143.2)	13 (4 to 23)
Citrate (mmol per 24 h)	25	3.2 (2.1, 3.9)	25	4.9 (3.3, 7.1)	60 (39 to 85)
Oxalate (µmol per 24 h)	25	513.7 (382.8, 599.1)	25	470.3 (356.4, 626.7)	3 (−12 to 21)
Sulfate (mmol per 24 h)	25	19.4 (14.1, 26.8)	25	24.7 (15.6, 29.8)	15 (5 to 26)
Ammonium (mmol per 24 h)	24	39.7 (20.6, 45.5)	24	42.2 (24.0, 50.0)	10 (1 to 19)
Bicarbonate (mmol per 24 h)	25	1.3 (0.5, 2.6)	25	0.9 (0.4, 1.7)	−46 (−67 to −12)
pCO_2 (mmHg)	25	38.0 (33.9, 57.0)	25	38.6 (27.1, 50.0)	−15 (−32 to 8)
Venous pH	25	5.8 (5.6, 6.4)	25	5.6 (5.5, 6.1)	−4 (−7 to 0)
Total volume per 24 h[d] (l)	25	1.8 (1.2, 2.5)	25	2.3 (1.4, 2.9)	11 (−2 to 26)

Anderegg et al. Nature Med. Jan 2025

Mesures préventives médicamenteuses

Type of SF	Primary outcomes	N[a]	Placebo (median (IQR))	N[b]	Empagliflozin (median (IQR))	Estimated relative difference (% (95% CI))[c]	P value[d]
Calcium	Calcium oxalate supersaturation	25	8.9 (7.7, 13.4)	25	9.1 (7.3, 11.9)	−1 (−15 to 16)	0.921
Calcium	Calcium phosphate supersaturation	25	1.9 (1.0, 2.7)	25	1.0 (0.6, 1.7)	−36 (−48 to −21)	<0.001*
Calcium	UA supersaturation	25	1.3 (0.9, 2.3)	25	2.2 (1.1, 3.0)	32 (−14 to 104)	0.204
UA	Calcium oxalate supersaturation	21	6.6 (4.4, 10.0)	21	5.8 (4.4, 8.4)	−8 (−19 to 5)	0.236
UA	Calcium phosphate supersaturation	21	0.5 (0.3, 0.8)	21	0.4 (0.3, 0.9)	8 (−16 to 38)	0.559
UA	UA supersaturation	21	3.3 (2.6, 5.4)	21	2.5 (1.8, 3.3)	−30 (−44 to −12)	0.002



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David S. Goldfarb

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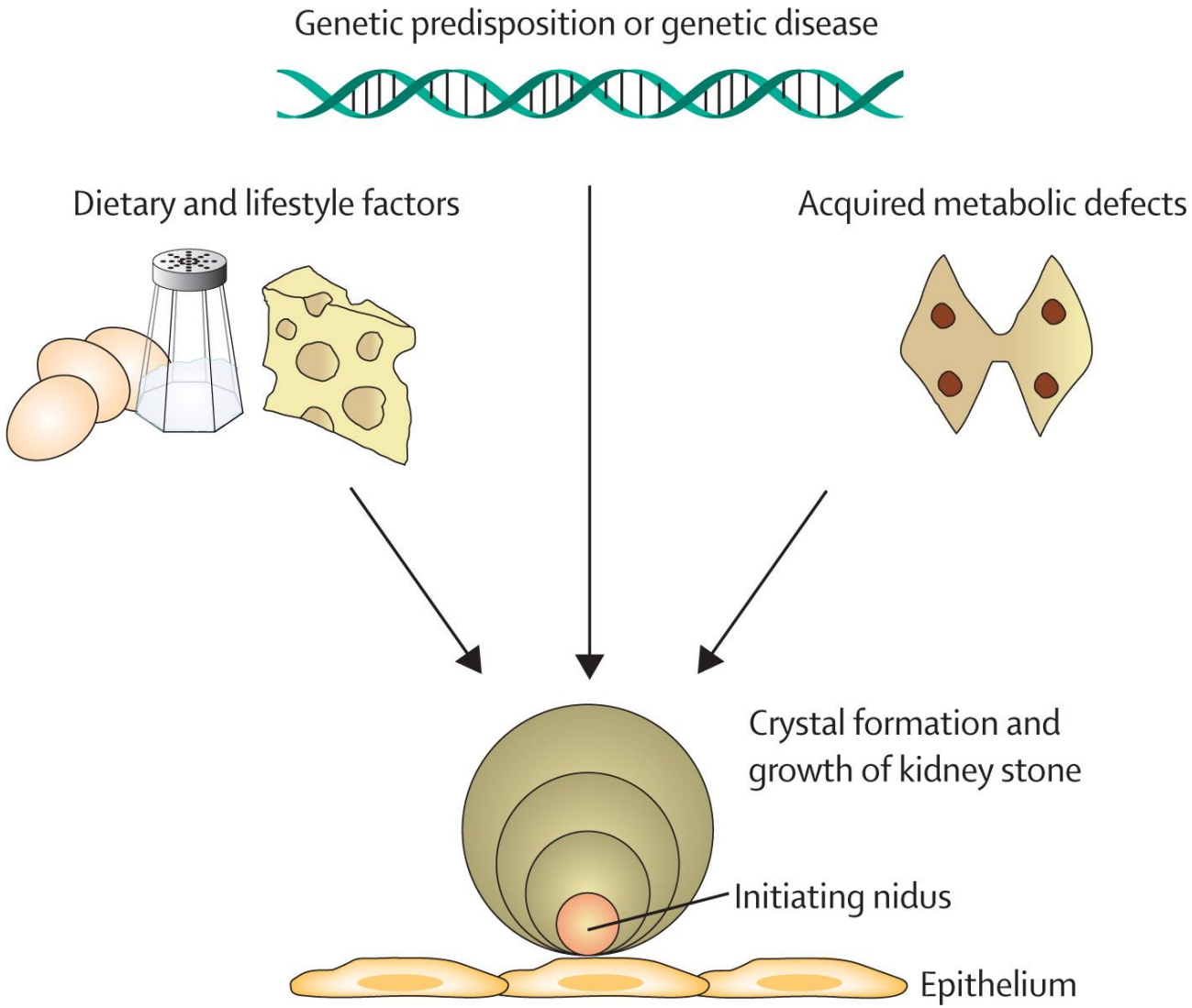
Physiopathologie de l'urolithiase



Orson Moe. Lancet 2006

Physiopathologie de l'urolithiase

Risque lithiasique =

rapport promoteurs / inhibiteurs cristallisation urinaire

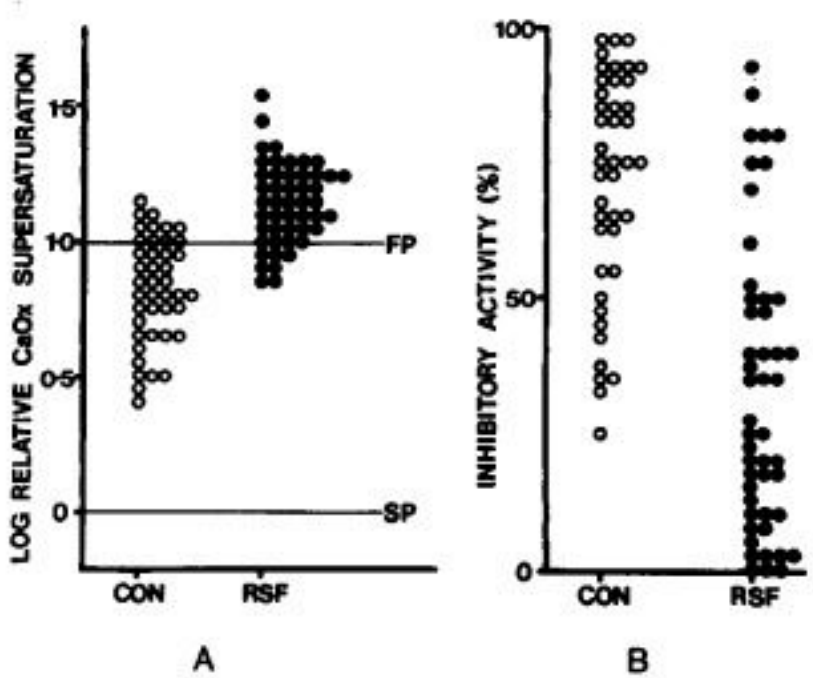


Figure 1. Log of Relative Calcium Oxalate (CaOx) Supersaturation Values (A) and Levels of Inhibitory Activity (B) in the Urine Samples of the Patients with Recurrent Stone Formation (RSF) and the Controls (CON).

The supersaturation values are plotted in relation to the formation (FP) and solubility (SP) products of calcium oxalate.

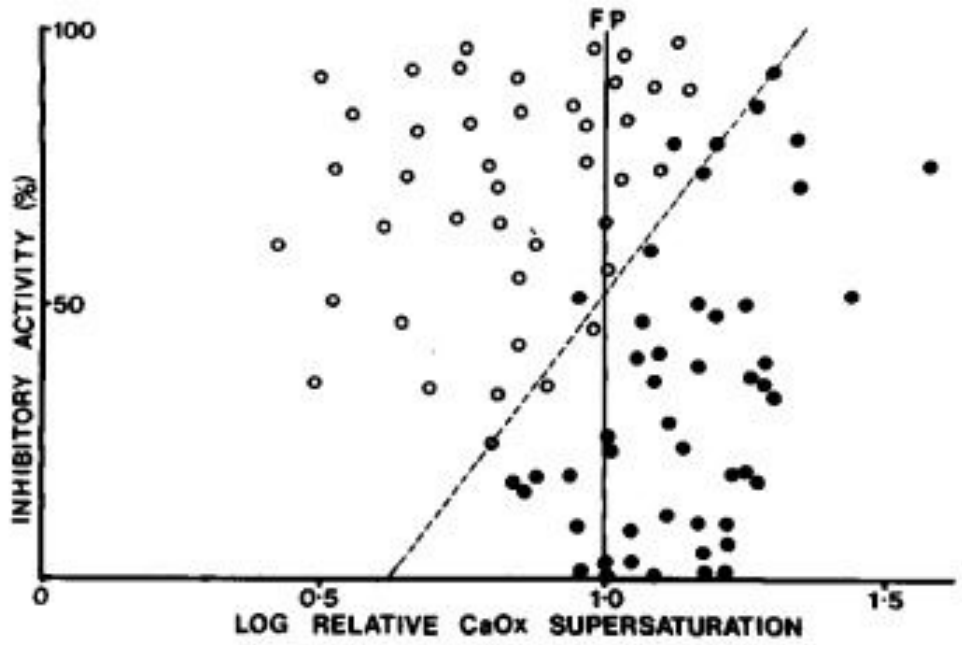
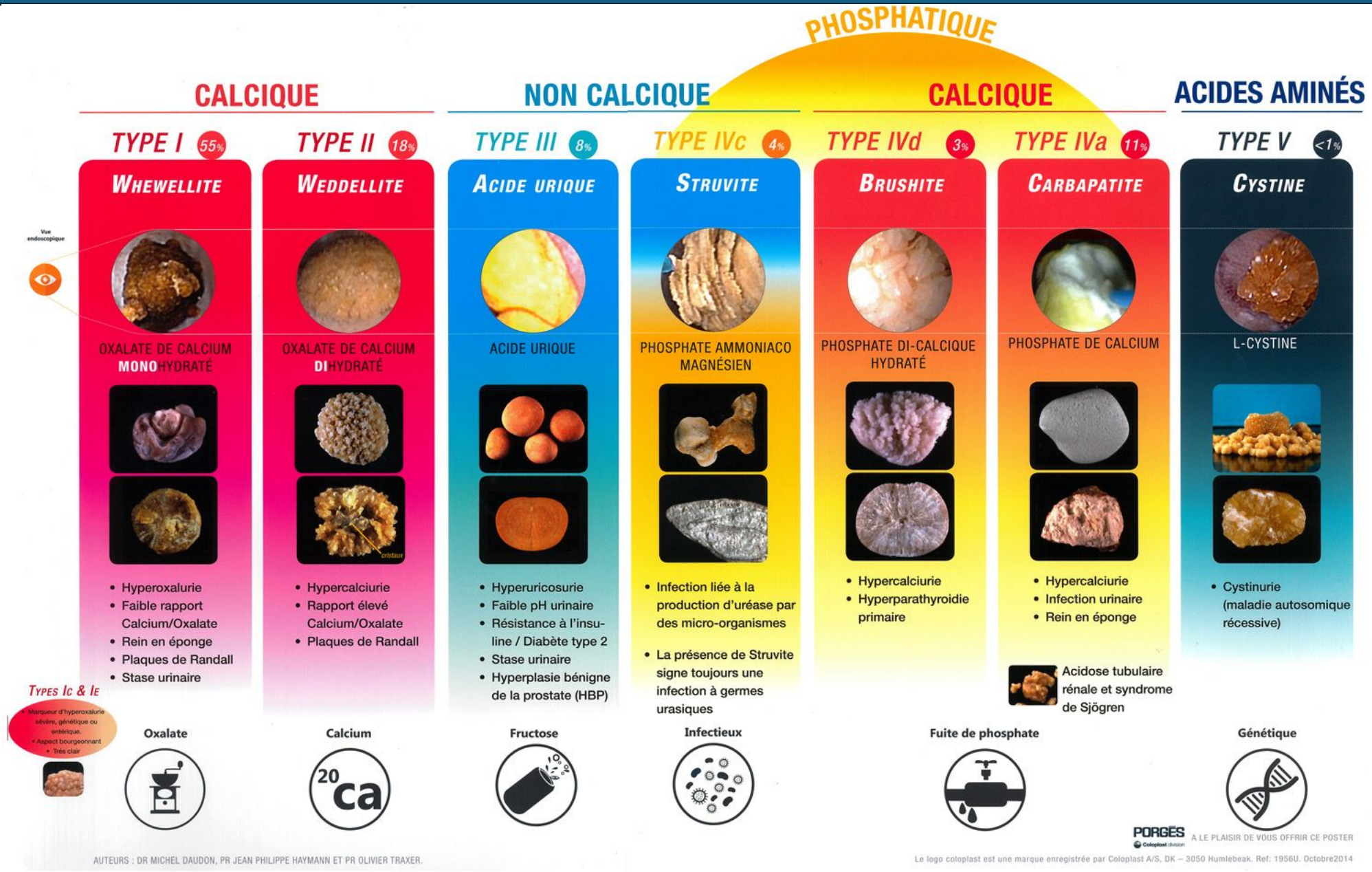


Figure 2. Scattergram of Inhibitory Activity Plotted against Log of Relative Calcium Oxalate (CaOx) Supersaturation in the Urine Samples of the Patients with Recurrent Stone Formation (●) and the Controls (○).

The full line represents the formation product (FP) of calcium oxalate, and the dotted line the calculated discriminant function.

W. Robertson et al. NEJM 1976

Physiopathologie de l'urolithiase



Bilan métabolique : rationnel

La composition urinaire à t0 prédit le risque de récidive lithiasique calcique

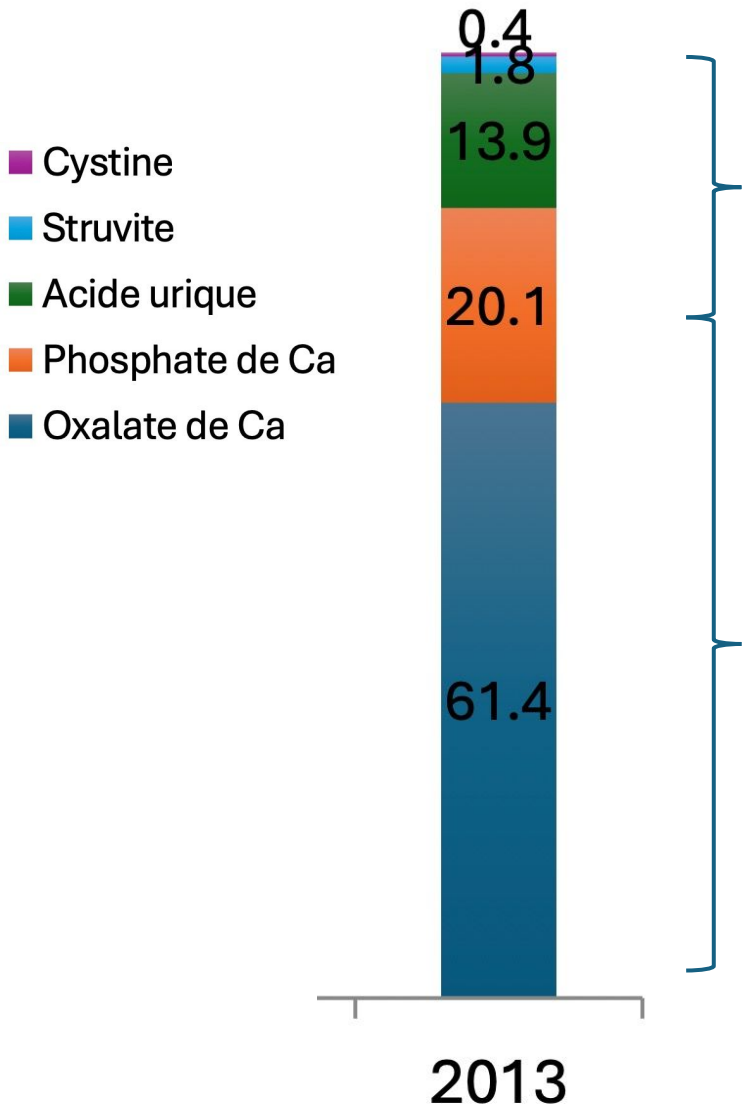
- Analyse post-hoc d'un essai clinique de 120 hommes lithiasiques hypercalciuriques soumis à des mesures diététiques standardisées. 5y FU
- Sursaturation relative (RSS) des sels lithogènes prédit le risque de récidive

Recurrence risk associated with relative supersaturation at baseline and changes at 1 week, and with 24-hour urine parameter changes at 1 week

	HR (95% CI)	p Value
Baseline relative supersaturation		
Calcium oxalate (1 U):		
EQUIL2[8]	1.08 (1.01—1.15)	0.03
JESS[9]	1.10 (1.04—1.16)	0.001
LithoRisk[10]	1.06 (1.01—1.10)	0.007
Calcium phosphate (1 U):		
EQUIL2	1.13 (0.91—1.40)	0.25
JESS	1.10 (0.96—1.25)	0.16
LithoRisk	1.05 (0.95—1.17)	0.33
Uric acid (1 U):		
EQUIL2	1.03 (0.87—1.22)	0.75
JESS	1.03 (0.81—1.30)	0.82
LithoRisk	1.08 (0.69—1.71)	0.73

Ferraro et al., J Urol 2018

Physiopathologie de l'urolithiase



Env. 20% : secondaire, métabolique (y.c. hyperinsulinisme du syndrome métabolique), hormonale (HPP), monogénique

Env. 80% : cause primaire « idiopathique » dont 25-30% d'hypercalciurie idiopathique

Deffert, Stoermann et Ernandez. SSN 2015

#1 : Mesures préventives diététiques et d'hydratation

Association Française d'Urologie
www.urofrance.org

https://www.urofrance.org/wp-content/uploads/2021/12/hygieno-dietetique-calculs-1.pdf

En résumé

Boissons : 2 litres par jour, répartis sur la journée et la nuit + 2 verres de jus d'orange
Calcium : 800 à 1000 mg par jour
Protéines : Pas plus de 150 g de viande ou poisson
Sel : Ne jamais ajouter de sel à table
Oxalate : Éviter les aliments riches en oxalate : chocolat, cacao et cacahuètes
Acide urique : Éviter la charcuterie, les abats et le gibier
Sucres : Éviter les sucreries, les bonbons, les pâtisseries et les sodas

- Maintenez une activité physique régulière
- Évitez l'excès de calories
- Variez l'alimentation et consommez des fibres (fruits et légumes)

Ces règles diététiques sont simples
Elles doivent être respectées à vie
Elles sont plus efficaces si vous buvez plus de 2 litres d'eau par jour
Elles réduisent fortement le risque de récidive

Suivre ces règles diététiques réduit également le risque d'hypertension artérielle, de diabète et d'obésité

BUVEZ, BUVEZ ENCORE, MANGEZ MOINS et MANGEZ MIEUX
cela diminue le risque de faire ou de refaire des calculs

#1 : Mesures préventives diététiques et d'hydratation

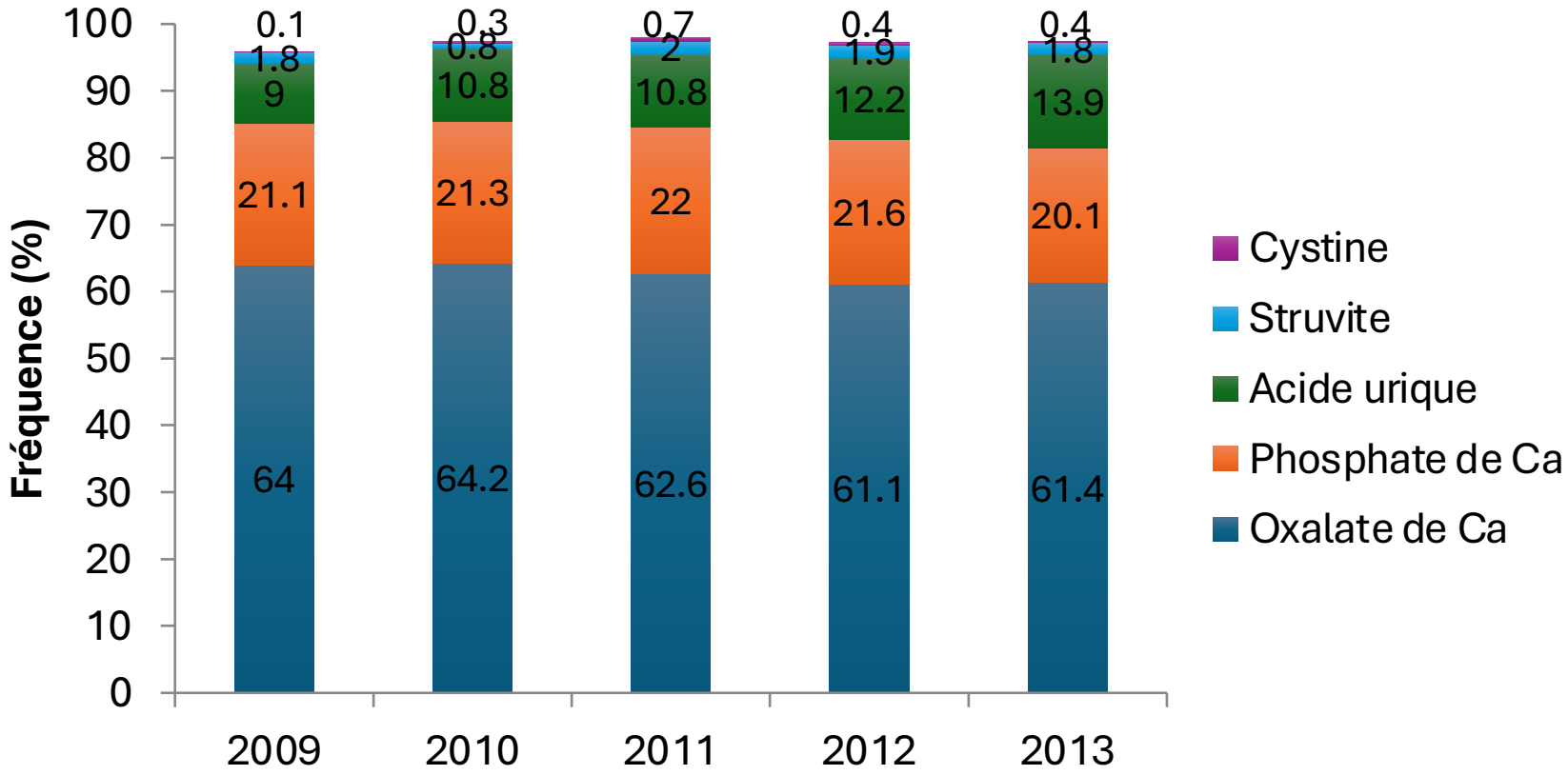
- Mesures diététiques et d'hyperhydratation doivent être systématiques. Toujours la première ligne du traitement préventif.
- Relativement bon marché, pas d'effets secondaires, efficaces.
- 8% des patients à « haut risque » de récidive d'urolithiase bénéficie d'une récolte urinaire de 24h et conseils spécifiques

  Milose et al. J Urol. 2014
  Goldfarb. Urolithiasis. 2019
- Incertitude si bénéfice supplémentaire de mesures spécifiques guidées par le bilan métabolique versus mesures « génériques ».

  Goldfarb. Urolithiasis. 2019
  Hsi et al. Urolithiasis. 2023

Physiopathologie de l'urolithiase

Composition des calculs analysés aux HUG



Deffert, Stoermann et Ernandez. SSN 2015

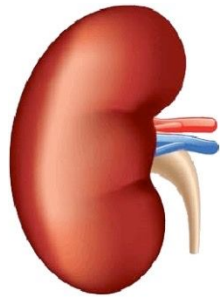
Bilan métabolique : quels paramètres ?

Interprétation du bilan métabolique urinaire selon des objectifs thérapeutiques

U-24h	Objectifs
Créatinine	♂ < 0.2mmol/kg/24h ♀ < 0.15mmol/24h +/- 20%
Volume	> 2000ml/24h
Densité urinaire matinale	< 1.015
Na	< 100mmol/24h (<135mmol/24h)
K	> 80mmol/24h
Ca	♂ < 7.5mmol/24h ♀ < 6.25mmol/24h (<0.1mmol/kg)
Ca concentration	< 3.8mmol/l

U-24h	Objectifs
Urée	/5/kg < 1.0g/kg/24h (<0.8g/kg/24h)
Sulfate	< 25mmol/24h (< 20mmol/24h)
Acide urique	*<4.5mmol24h* *(<4.0mmol/24h)*
Oxalate	♂ < 420umol/24h ♀ < 350umol/24h
Oxalate concentration	? < 250umol/l
Citrate	> 2500umol/24h (> 3000umol/24h)

Urolithiase : une maladie multisystémique

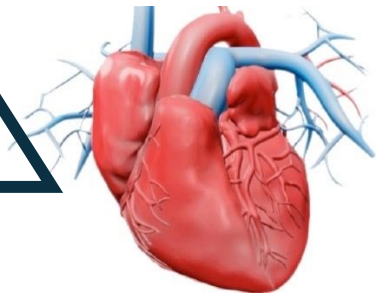


Calculs rénaux

Calcium

(Acide urique)

ostéoporose

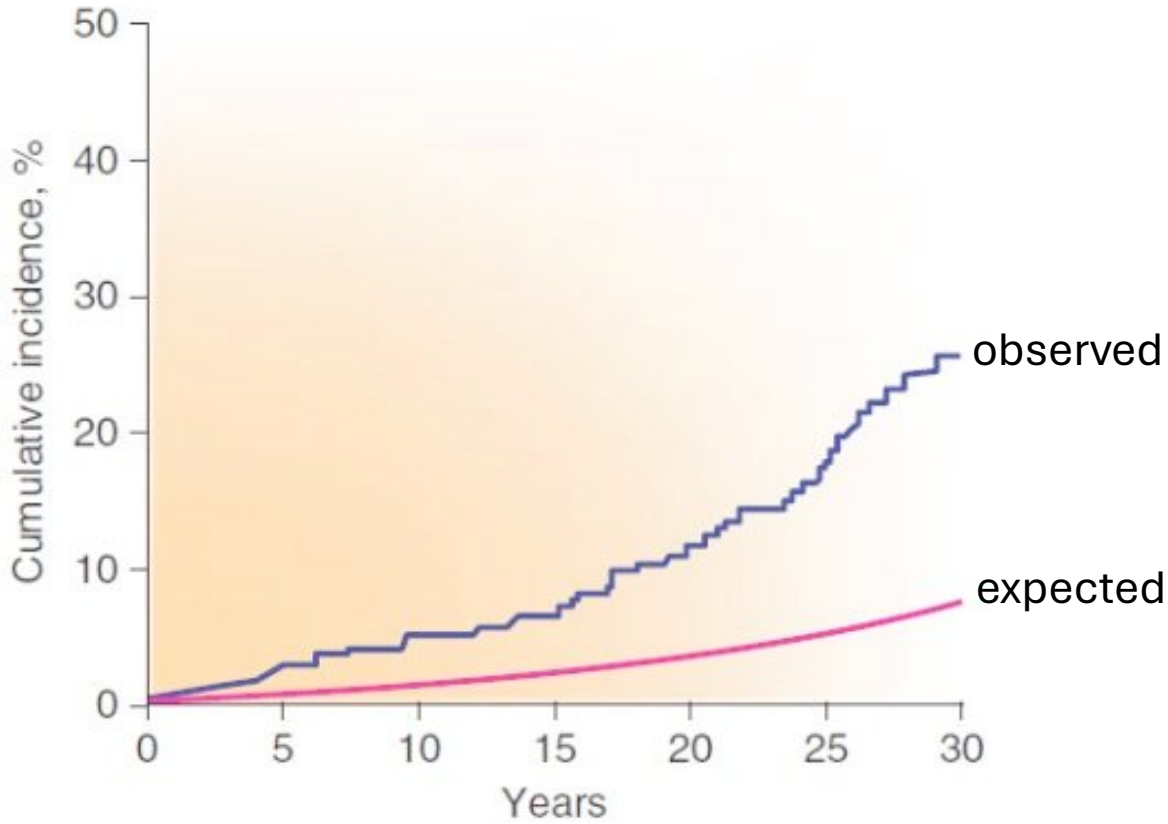


Evénements CV

Urolithiase et risque osseux

Calculs rénaux calciques associés à un risque osseux augmenté

Incidence cumulée de fractures vertébrales après un premier épisode de calcul rénal

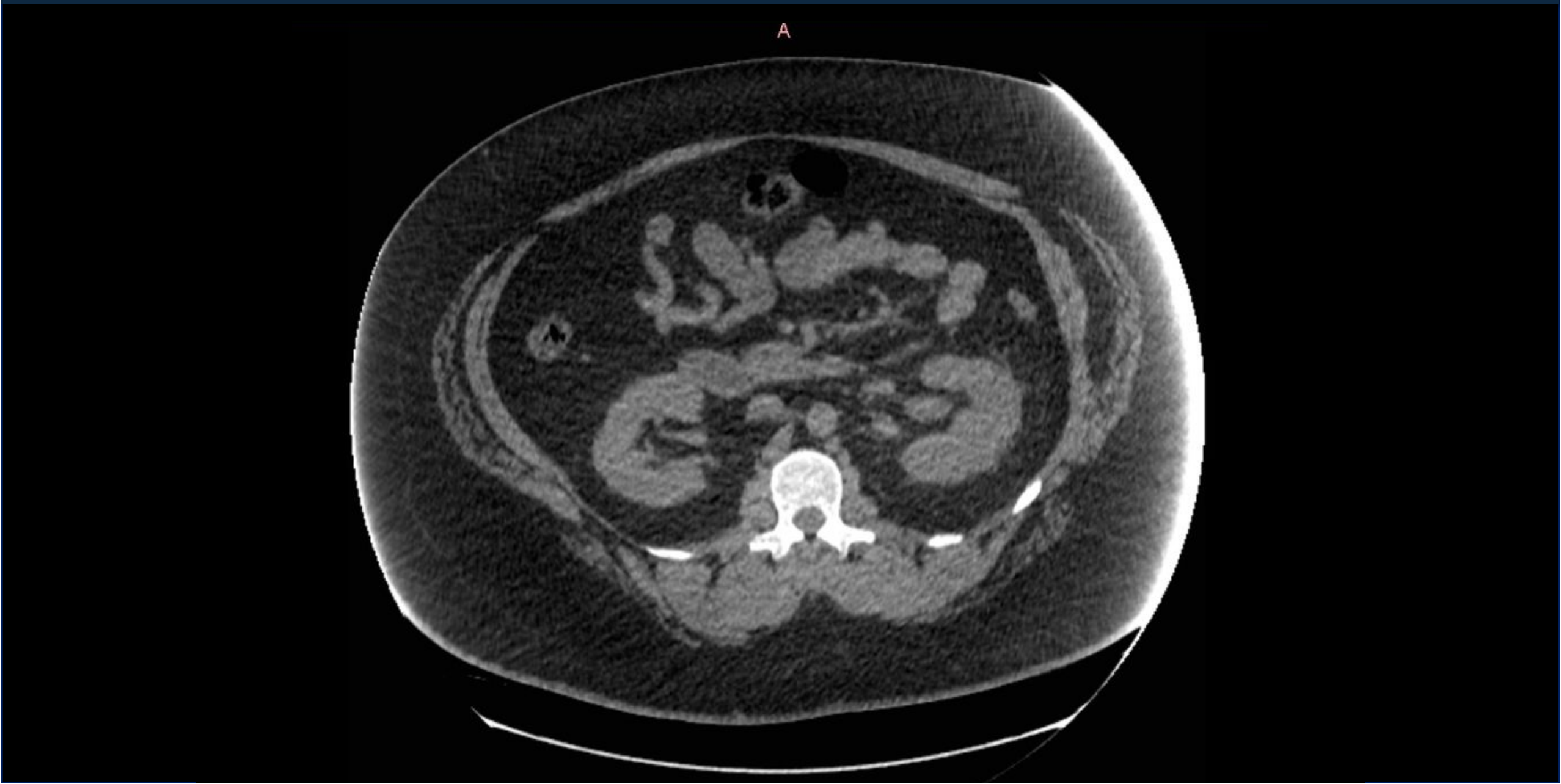


Sakhae et al. Kidney Int 2011
Melton et al. Kidney Int 1998

Hypothèses

- Excrétion urinaire de calcium augmentée génétiquement déterminée
  = Balance calcique négative
- «Western diet»
  charge acide
  >
  apports en alkali
  = augmentation de la résorption osseuse

Urolithiase et syndrome métabolique



Urolithiase et syndrome métabolique

Corrélation entre augmentation du poids et risque urolithiasique

Table 3. Association between BMI category and incident kidney stones in multivariate-adjusted analyses

BMI	aHR[a] (95% CI)	*P* Value
		<0.001
<18.5 kg/m^2 (underweight)	0.79 (0.47 to 1.32)	
18.5–24.9 kg/m^2 (normal weight)	Reference	
25–29.9 kg/m^2 (overweight)	1.30 (1.17 to 1.44)	
30–34.9 kg/m^2 (moderately obese)	1.62 (1.43 to 1.83)	
≥35 kg/m^2 (severely obese)	1.81 (1.57 to 2.10)	

This model does not include physical activity or calibrated dietary energy intake.

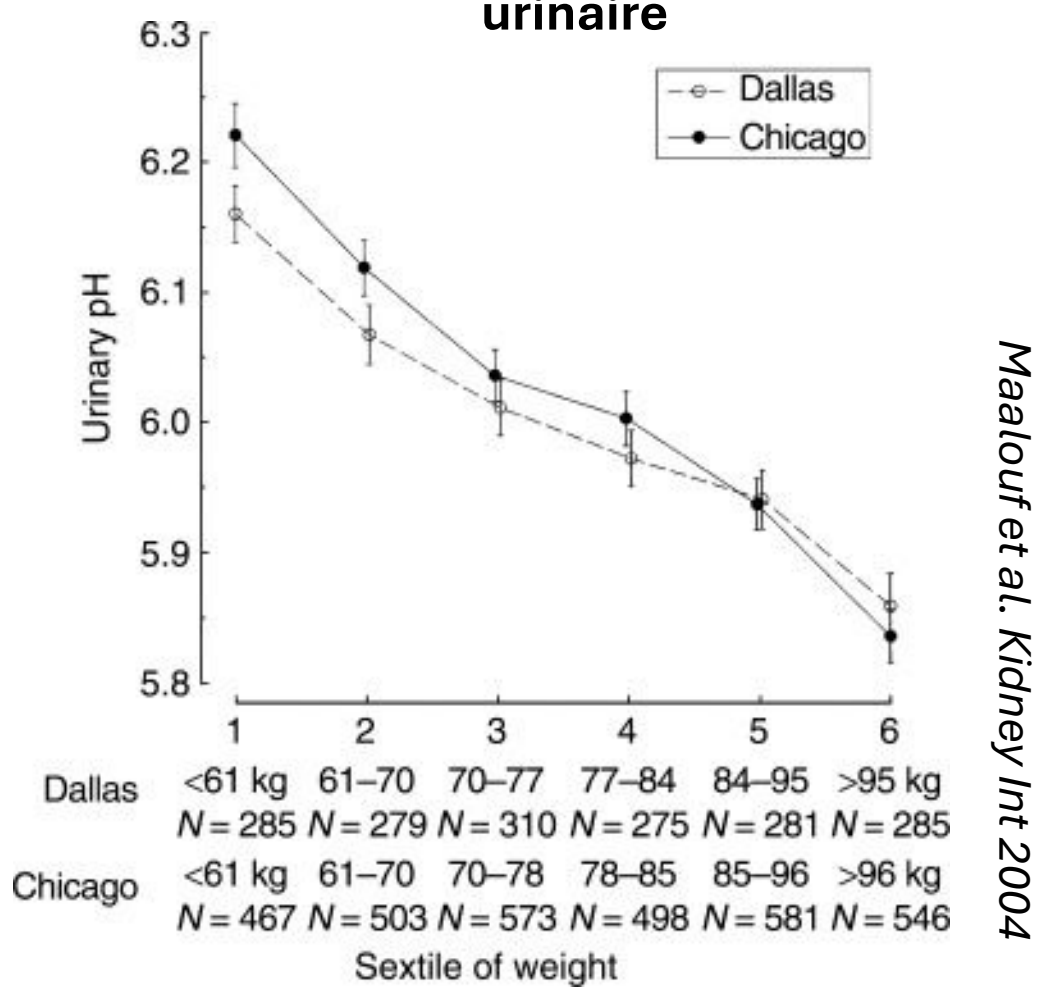
[a]Adjusted for age (continuous); race (category); history of diabetes; use of calcium supplement; hormone replacement therapy (category); income (dichotomized); region (category); and quintile intake of water, sodium, animal protein, and dietary calcium.

Sorensen et al. JASN 2014

Urolithiase et syndrome métabolique

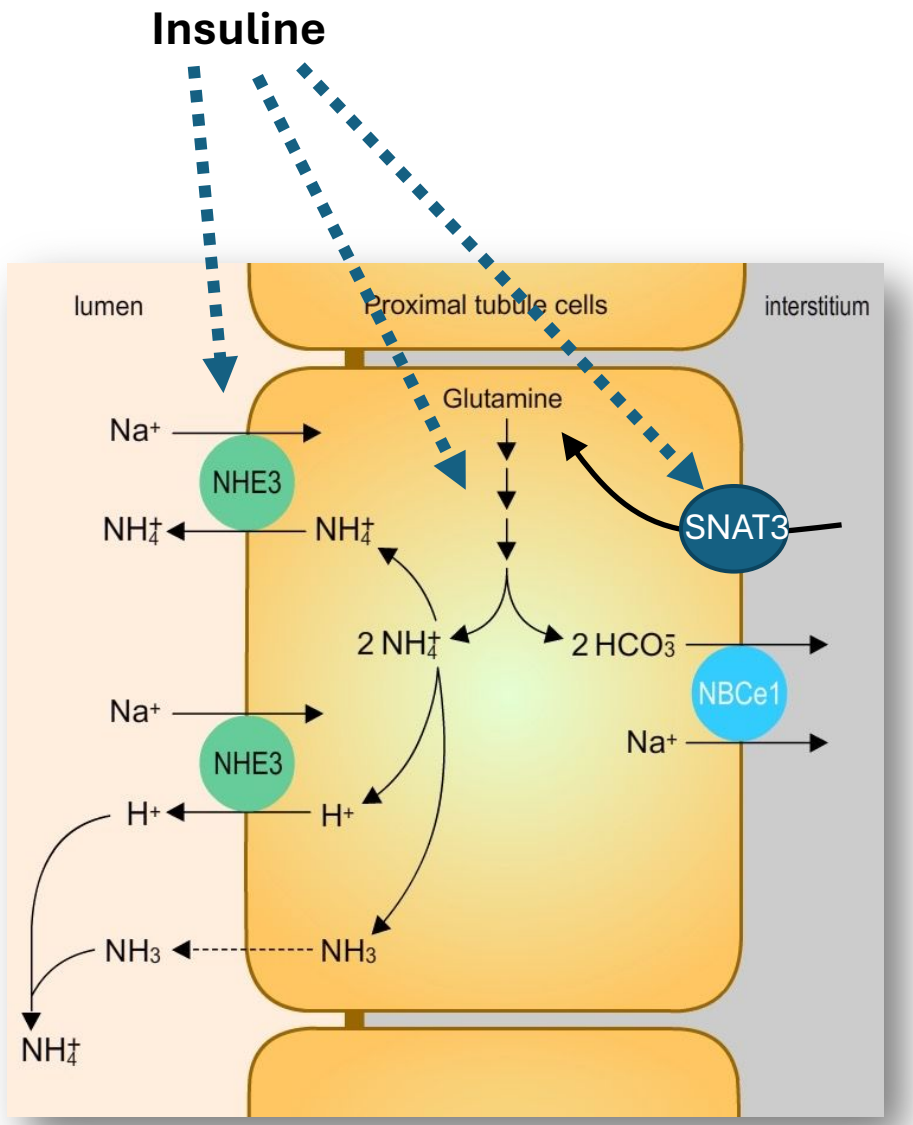
Augmentation forte de l'incidence de calculs d'acide urique en particulier

= corrélation entre augmentation du poids et diminution du pH urinaire



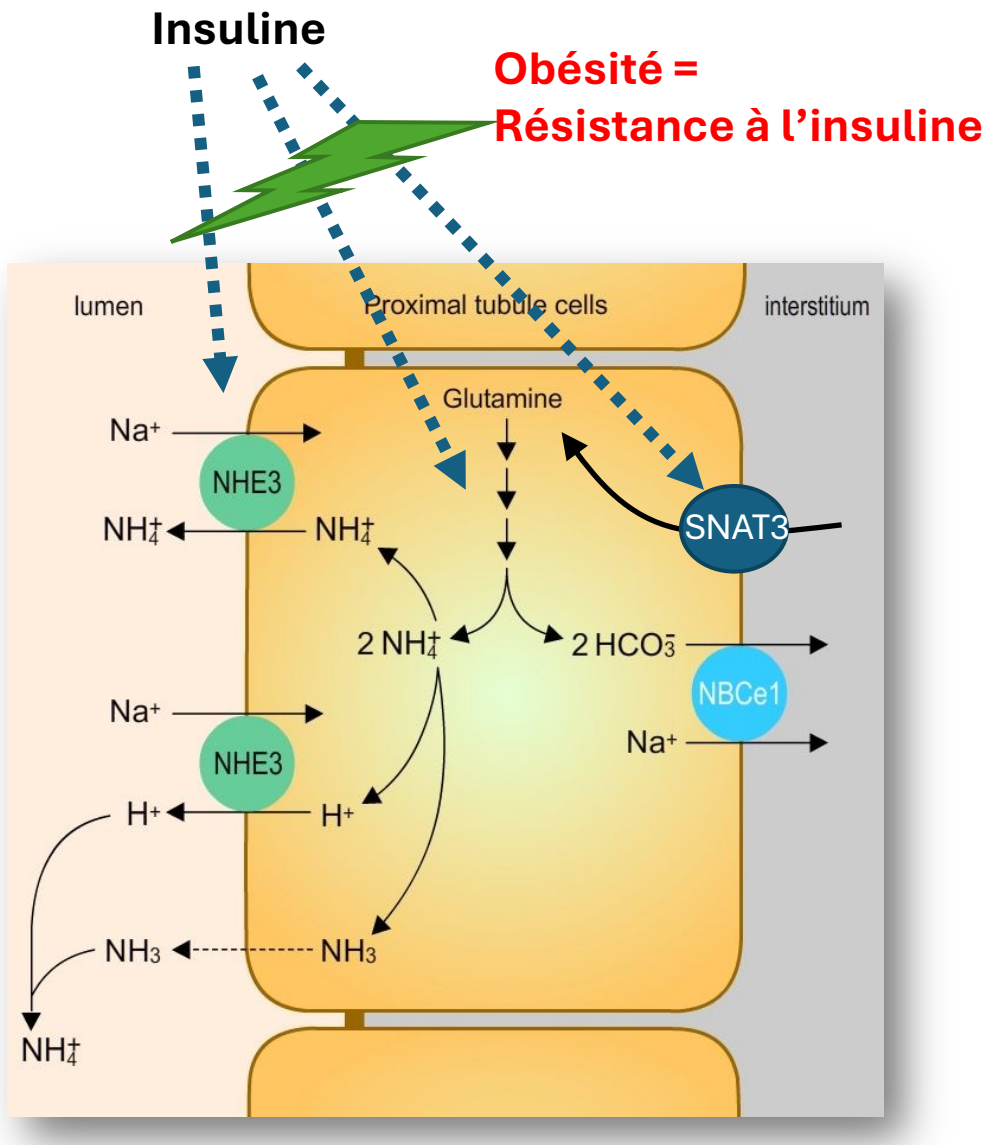
Maalouf et al. Kidney Int 2004

Urolithiase et syndrome métabolique



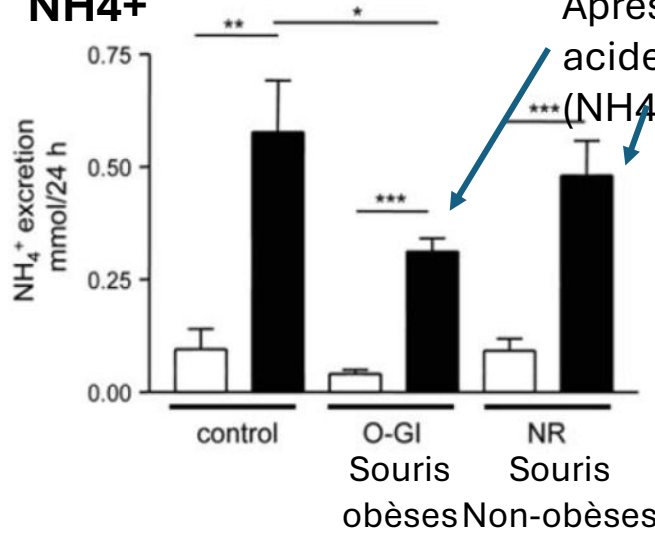
L'insuline pourrait jouer un rôle dans la régulation de l'ammoniogenèse dans le tube proximal

Urolithiase et syndrome métabolique

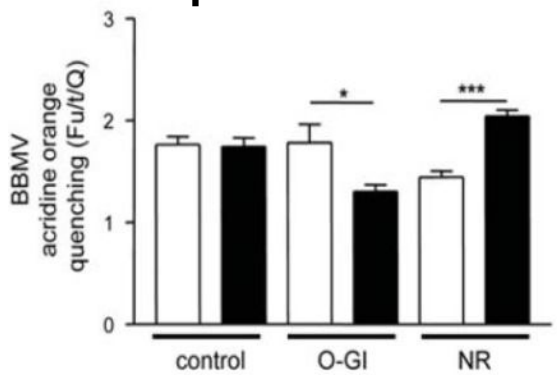


Diminution de l'excrétion U de NH4+

Après charge acide (NH_4Cl)



Dysfonction de la NHE3 du tube proximale



Carsten Wagner et al. Cell Physiol Biochem 2014

Urolithiase et syndrome métabolique

Obésité

↓

Résistance à l'insuline → **Diabète type 2**

↓

Défaut d'ammoniogenèse
Tube proximal

= «lipotoxicité tubulaire»

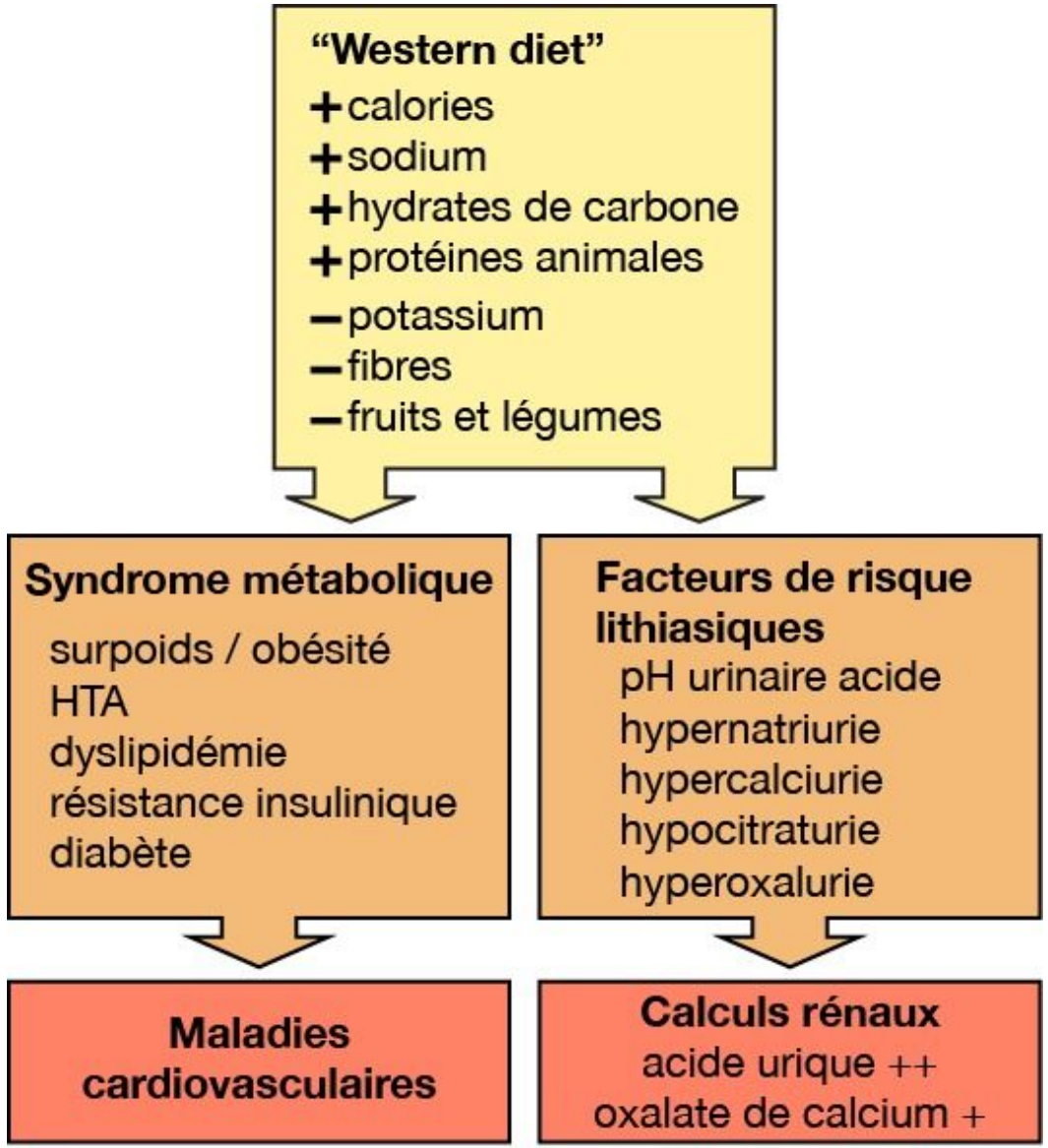
↓

pH urinaire acide

↓

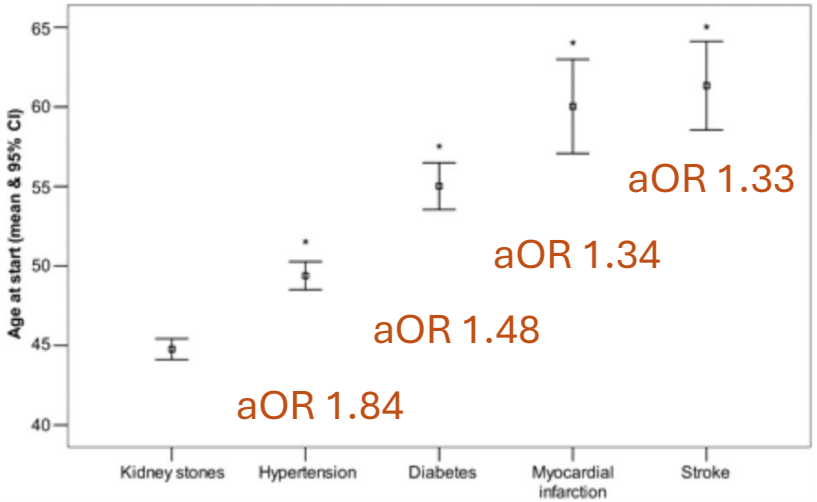
Lithiases d'acide urique
(pH dépendantes) → Lithiases calciques (pH indépendantes, hétéronucléation)

Urolithiase et syndrome métabolique



Ernandez et Bonny. RMS 2014

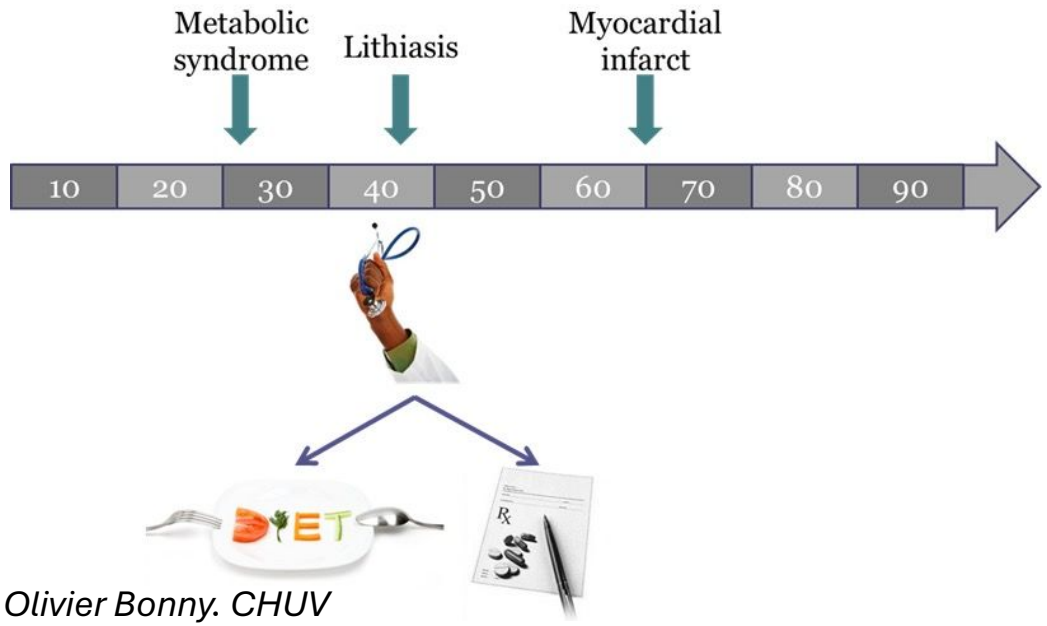
Urolithiase, syndrome métabolique et risque cardio-vasc.



Domingos et al. NDT 2011

Lithiase d'acide urique fortement associée au syndrome métabolique = **marqueur du risque cardiovasculaire**

Ernandez et Bonny. RMS 2014



Olivier Bonny. CHUV

Opportunité pour dépister FRCV et les prendre en charge précocement

Conclusions

- Le déséquilibre entre facteurs promoteurs et inhibiteurs de la cristallisation urinaire est le principal déterminant de la formation des lithiases urinaires.
- Le bilan métabolique, basé sur un échantillon ponctuel, permet de mesurer (en partie) ce déséquilibre et prédit le risque d'urolithiase et la nature des calculs
- Les mesures diététiques orientée par le bilan métabolique visent à restaurer cet équilibre.
- Les habitudes alimentaires prédisent le risque d'urolithiase
- L'amélioration des paramètres biochimiques par des mesures diététiques est associée à une diminution du risque de récidive.

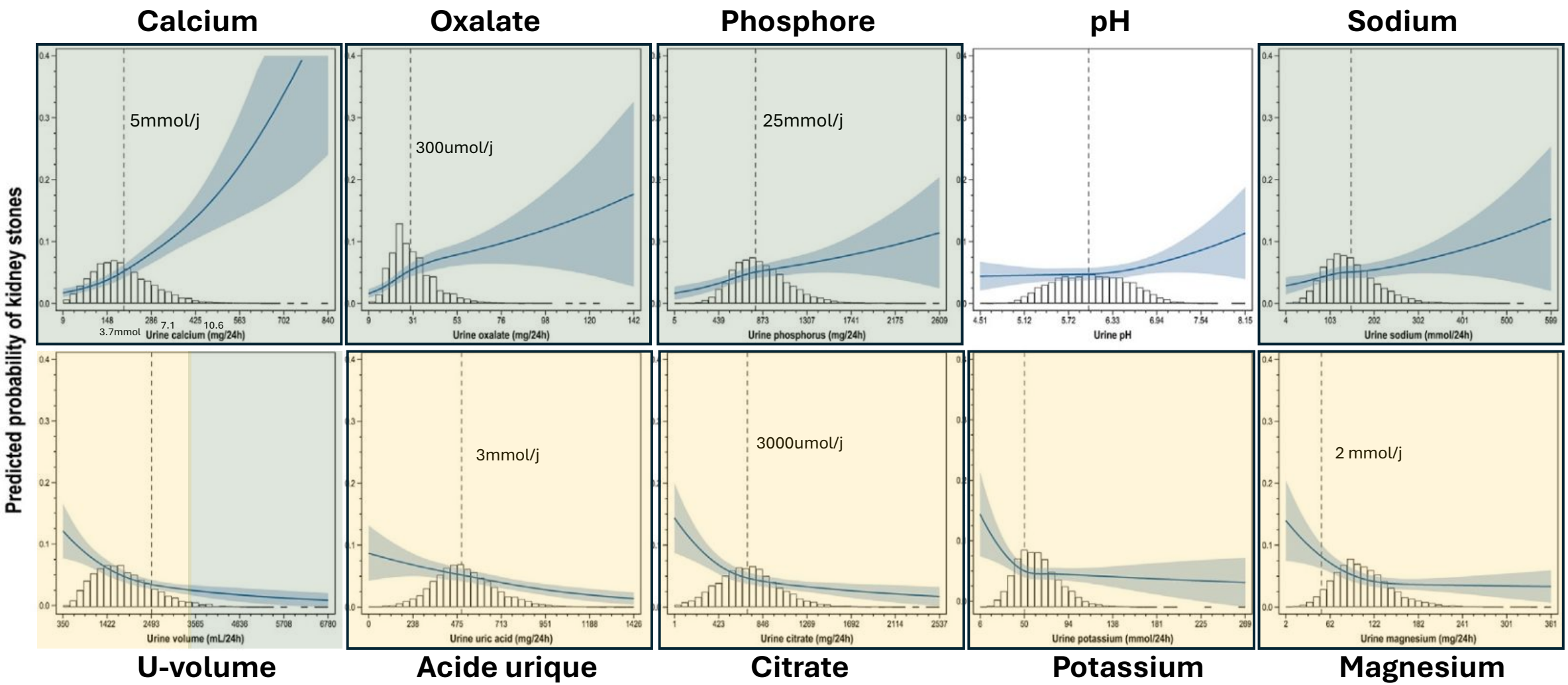
To be done …

- Meilleurs outils pour « éduquer » le patient lithiasique et motiver des changements durables de leur mode de vie / habitudes alimentaires
- Mieux définir la place des mesures médicamenteuses dans la lithiase oxalocalcique idiopathique

Conclusions

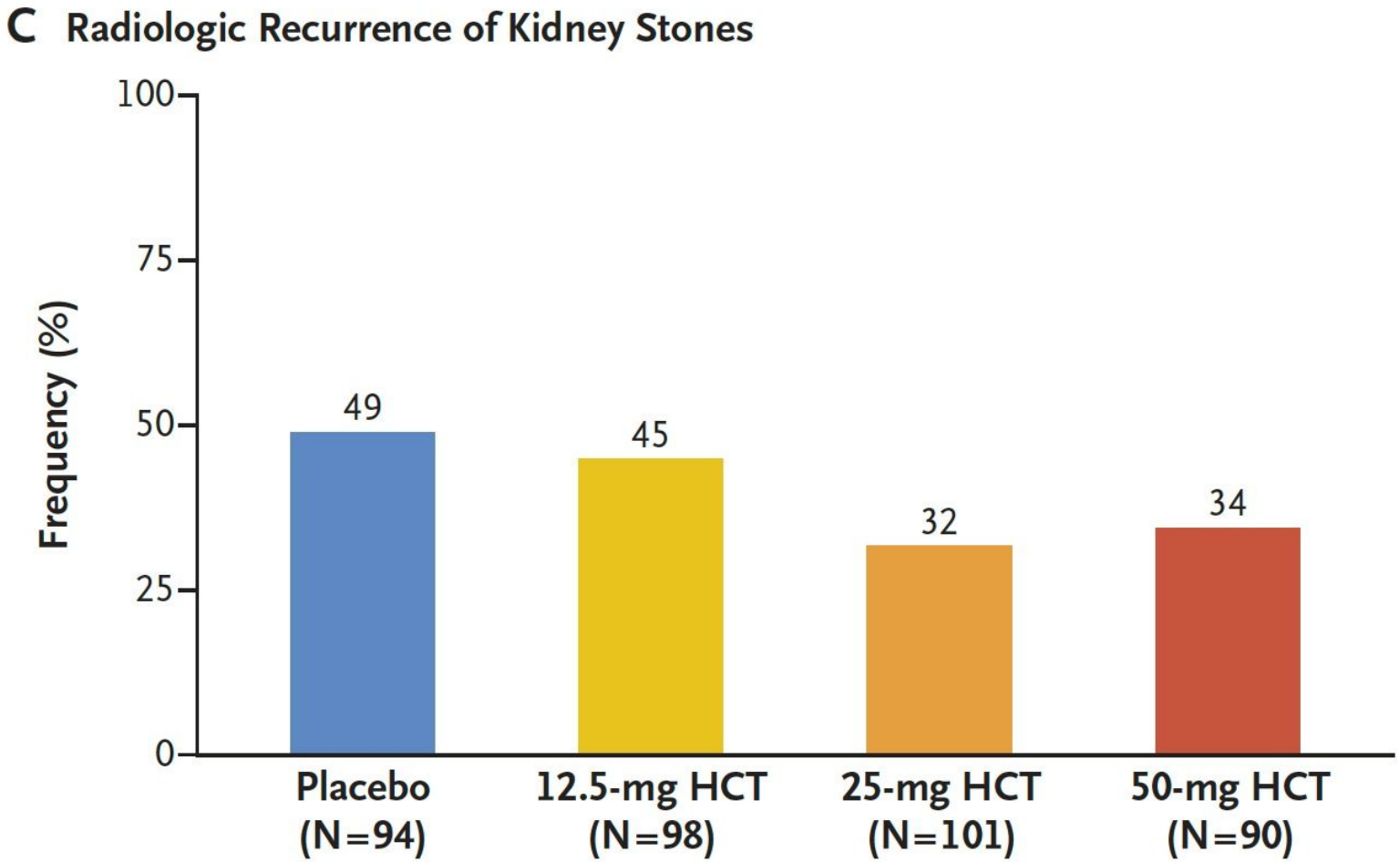
- Peu d'évidence en faveur de traitements pharmacologiques de la récidive d'urolithiase …
- Un fort rationnel physiopathologique liant la composition urinaire et le risque de récidive lithiasique
- Intervention non-pharmacologique restent centrales dans la prévention de la récidive :
  - Hyperhydratation
  - Diminution du sel et des protéines animales
  - Augmentation des apports en alcali (fruits et légumes)
  - Maintien d'apports réguliers en calcium (1g/j)
  - Diminution des apports alimentaires en oxalate (?)

Mesures préventives non-médicamenteuses



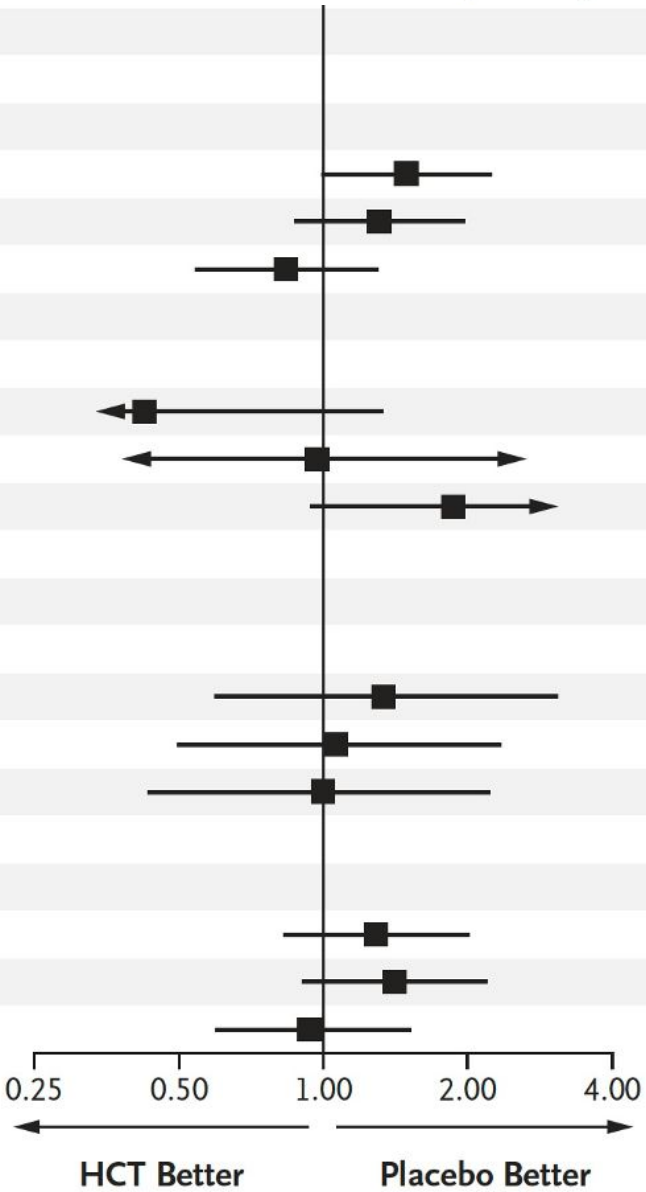
Ferraro et al. AJKD 2024

Mesures préventives médicamenteuses

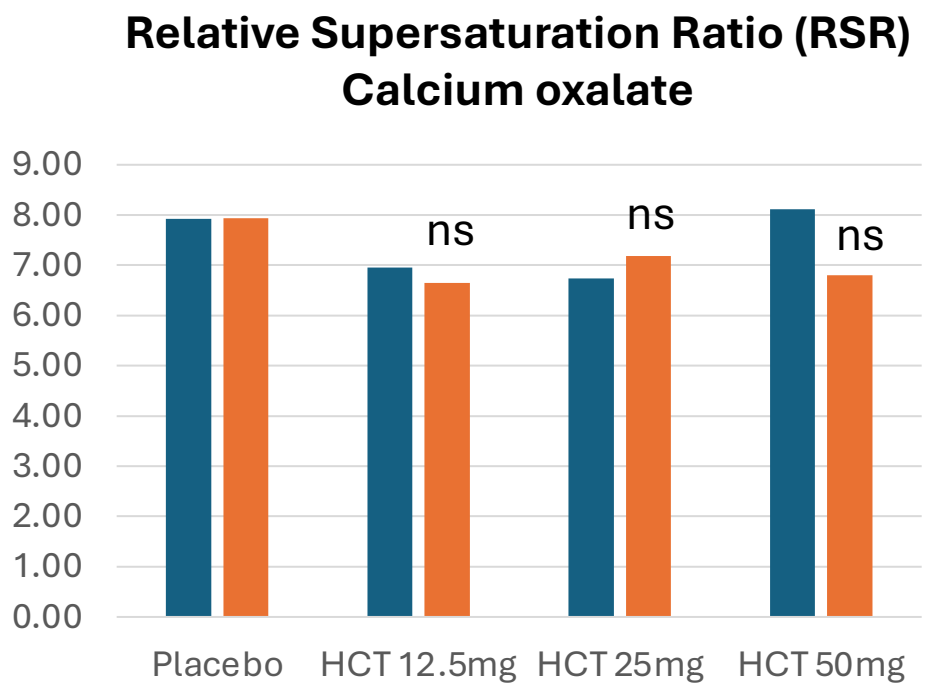


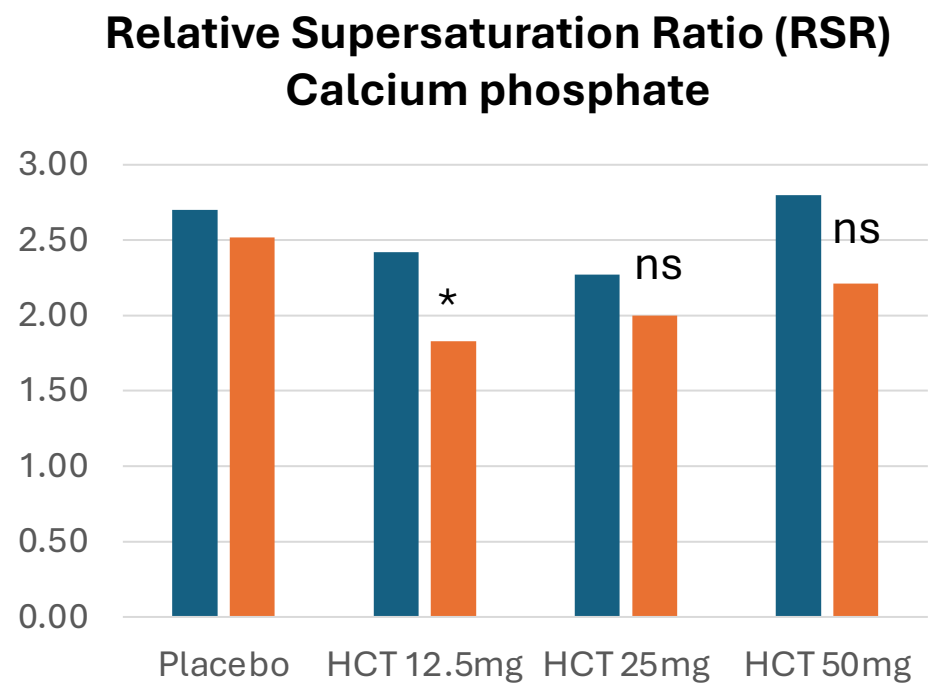
Mesures préventives médicamenteuses

Subgroup	No. of Events/Total No.	Rate Ratio (95% CI)	Rate Ratio for Trend
Stone composition			
>50% Calcium oxalate			
Placebo	53/89		0.95 (0.84–1.07)
12.5-mg HCT	56/94	1.47 (0.99–2.18)	
25-mg HCT	56/100	1.30 (0.88–1.93)	
50-mg HCT	38/87	0.84 (0.55–1.28)	
>50% Calcium phosphate			
Placebo	7/12		1.23 (0.83–1.82)
12.5-mg HCT	5/10	0.35 (0.07–1.75)	
25-mg HCT	3/5	0.95 (0.21–4.31)	
50-mg HCT	8/11	1.96 (0.73–5.52)	
Any stone at baseline			
No			
Placebo	13/26		0.99 (0.77–1.27)
12.5-mg HCT	14/29	1.33 (0.59–2.97)	
25-mg HCT	15/39	1.05 (0.49–2.25)	
50-mg HCT	13/33	1.00 (0.44–2.23)	
Yes			
Placebo	46/71		1.00 (0.87–1.14)
12.5-mg HCT	44/69	1.27 (0.83–1.96)	
25-mg HCT	44/64	1.40 (0.91–2.17)	
50-mg HCT	34/57	0.93 (0.59–1.47)	



HCT - NOSTONE





Baseline

After treatment

(Non-)adhérence aux traitements médicamenteux préventifs

Table 1. PPT Use by Study Population

Medication Class	Frequency	Percent
Thiazide Monotherapy	3,234	40.5
Citrate Monotherapy	2,484	31.1
Allopurinol Monotherapy	1,074	13.5
Thiazide and Allopurinol	225	2.8
Thiazide and Citrate	419	5.3
Citrate and Allopurinol	461	5.8
Thiazide, Citrate, and Allopurinol	83	1.0

Adhérence à 6 mois :

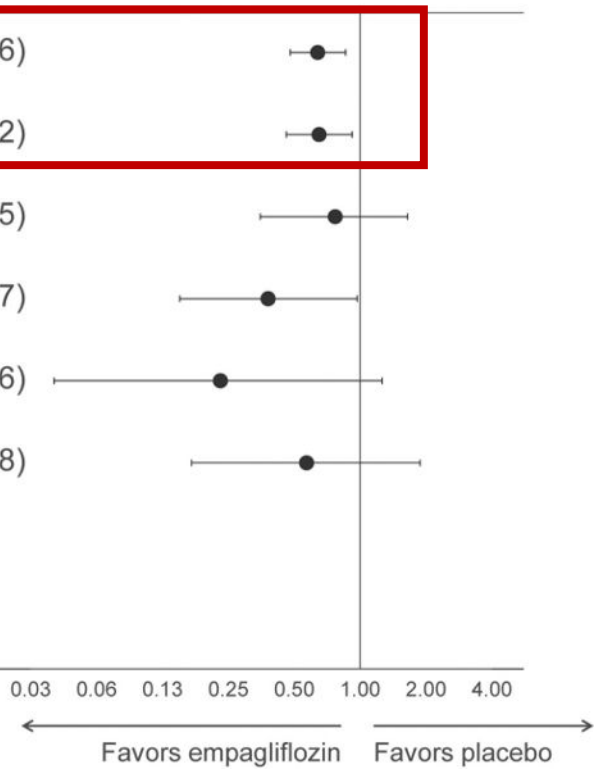
- Thiazide 42.5%
- Allopurinol 40.0%
- Citrate 13.4%

Dauw et al. Urology 2016

Mesures préventives médicamenteuses

Analyse post-hoc 20 RCTs empaglifozin vs placebo
(y.c. EMPA-REG Outcome study)
N = 15'081 pts DM2

	Empagliflozin		Placebo		Incidence rate ratio (95% CI)
	n with events/ N analyzed	Rate/ 100pt-yrs (95% CI)	n with events/ N analyzed	Rate/ 100pt-yrs (95% CI)	
Urinary tract lithiasis (all preferred terms)	104/10177	0.63 (0.51, 0.76)	79/4904	1.01 (0.80, 1.25)	0.64 (0.48, 0.86)
Nephrolithiasis	75/10177	0.45 (0.36, 0.57)	57/4904	0.72 (0.55, 0.94)	0.65 (0.46, 0.92)
Renal colic	16/10177	0.10 (0.05, 0.16)	10/4904	0.13 (0.06, 0.23)	0.77 (0.35, 1.65)
Ureterolithiasis	8/10177	0.05 (0.02, 0.09)	10/4904	0.13 (0.06, 0.23)	0.38 (0.15, 0.97)
Calculus bladder	2/10177	0.01 (0.00, 0.04)	4/4904	0.05 (0.01, 0.13)	0.23 (0.04, 1.26)
Calculus urinary	6/10177	0.04 (0.01, 0.08)	5/4904	0.06 (0.02, 0.15)	0.57 (0.17, 1.88)
Calculus urethral	1/10177	0.01 (0.00, 0.03)	0/4904		-
Nephrocalcinosis	2/10177	0.01 (0.00, 0.04)	0/4904		-



Balasubramanian et al. J Clin Endocrinol Metab. 2022