Alcalinisation et MRC : quels niveaux de preuve ?

Antoine BRACONNIER

CHU REIMS

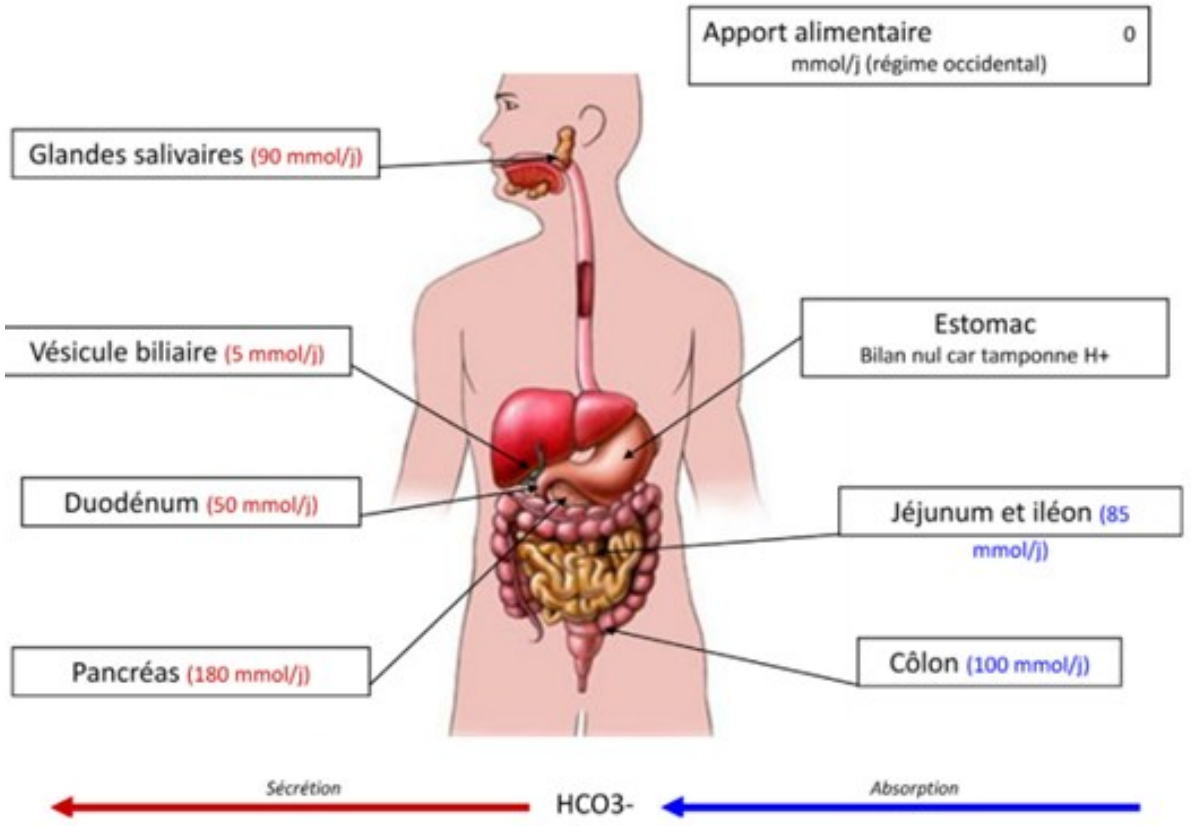
Liens d’Intérêt

- Vichy-Céléstins
  - via mon ex-activité au CJN
- Theradial :
  - via mon ex-activité au CJN
  - PEC congrès

PHYSIOLOGIE/PHYSIOPATHOLOGIE

Physiologie

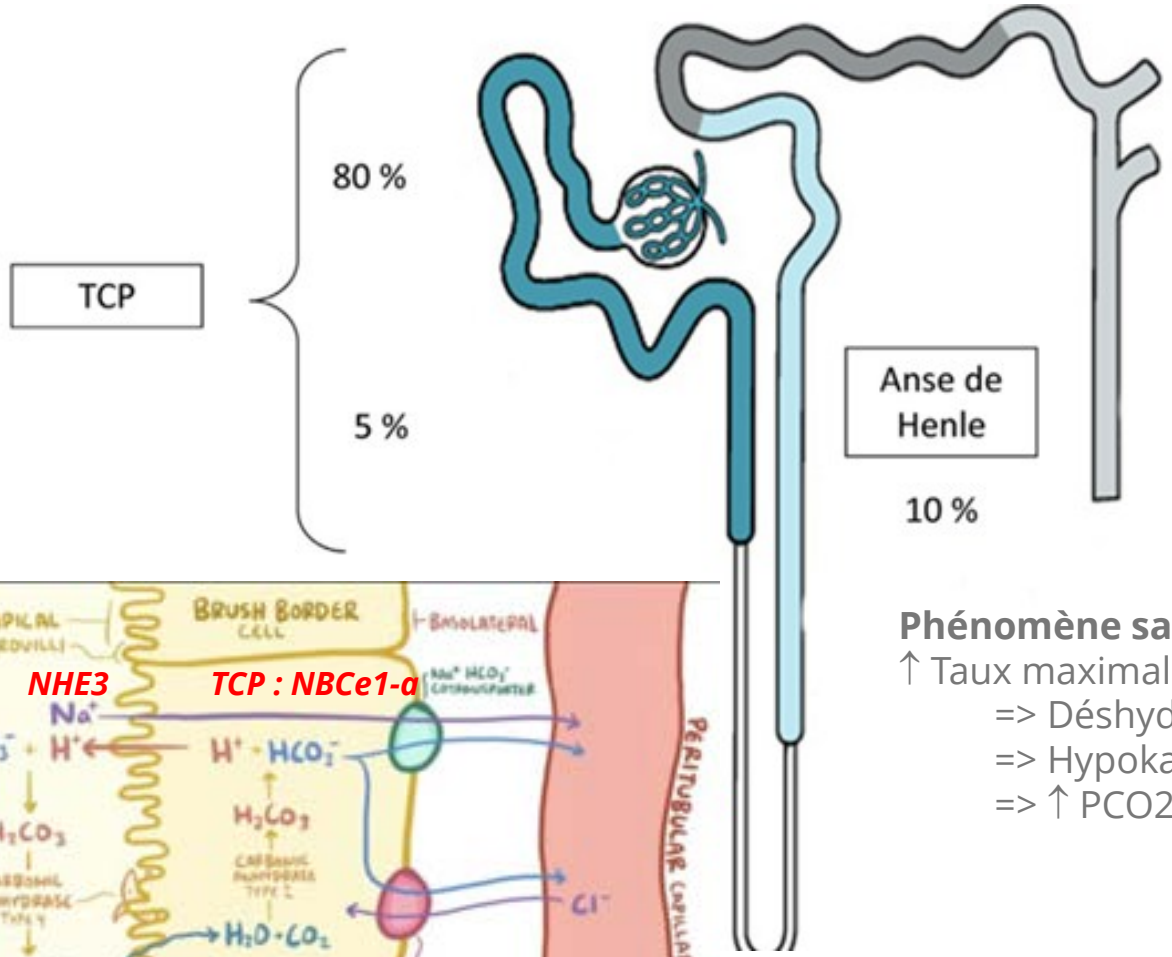
Cycle Digestif du Bicarbonate



Néphrologie & Thérapeutique 14 (2018) 13–23

Physiologie

Cycle rénal du Bicarbonate TCP et TCD



Phénomène saturable

↑ Taux maximal de réabsorption Tm/DFG

=> Déshydratation extra-cellulaire

=> Hypokaliémie

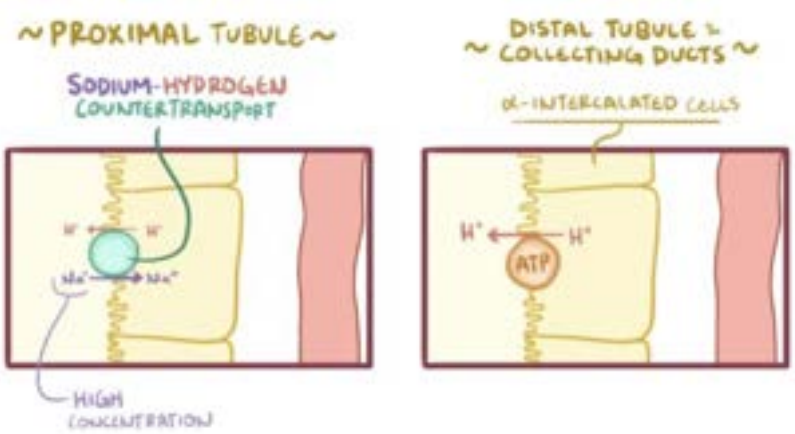
=> ↑ PCO2 (compensation métab. acidose respi)

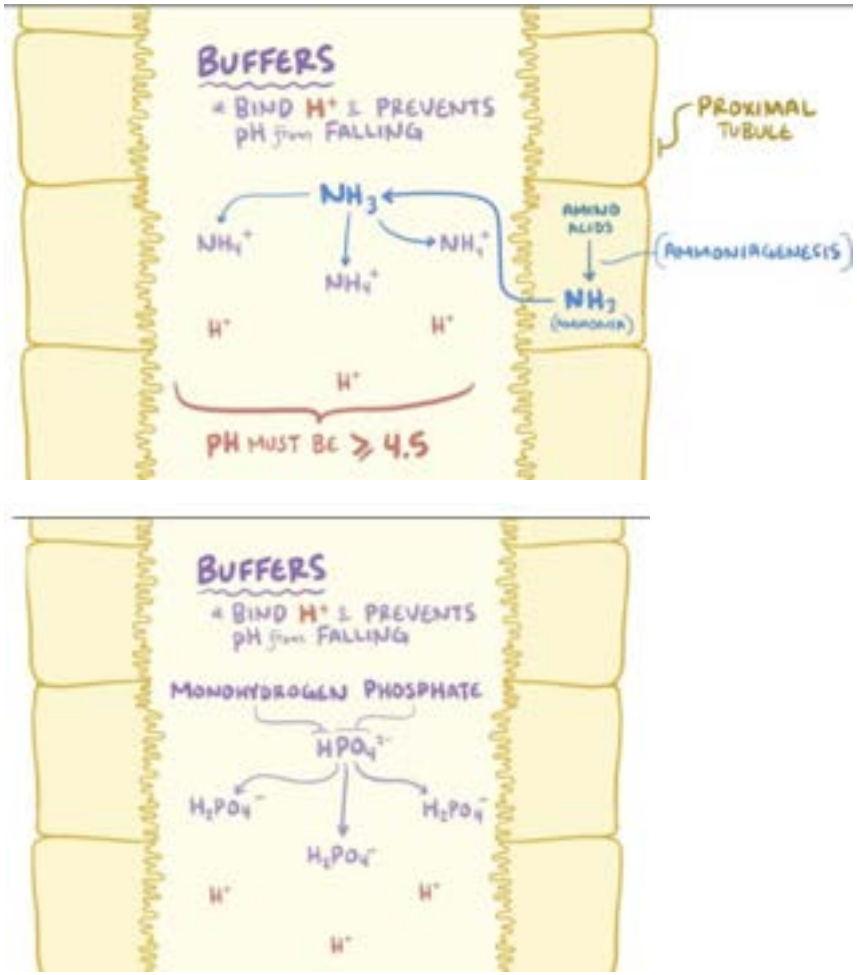
Néphrologie & Thérapeutique 14 (2018) 13–23

https://www.osmosis.org

Physiologie

Systèmes Tampon

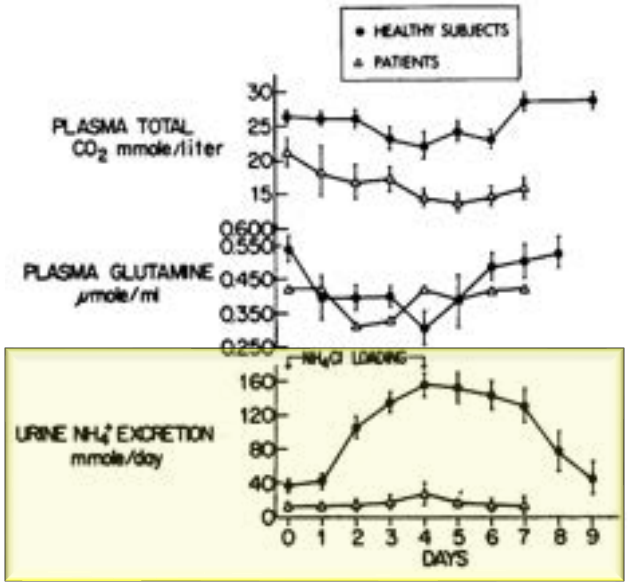


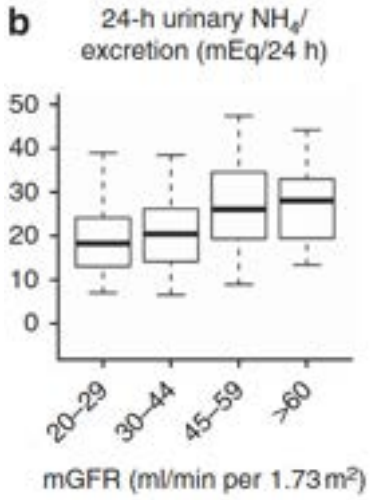


Néphrologie & Thérapeutique 14 (2018) 13–23

https://www.osmosis.org

Mécanisme de l'Acidose dans la MRC

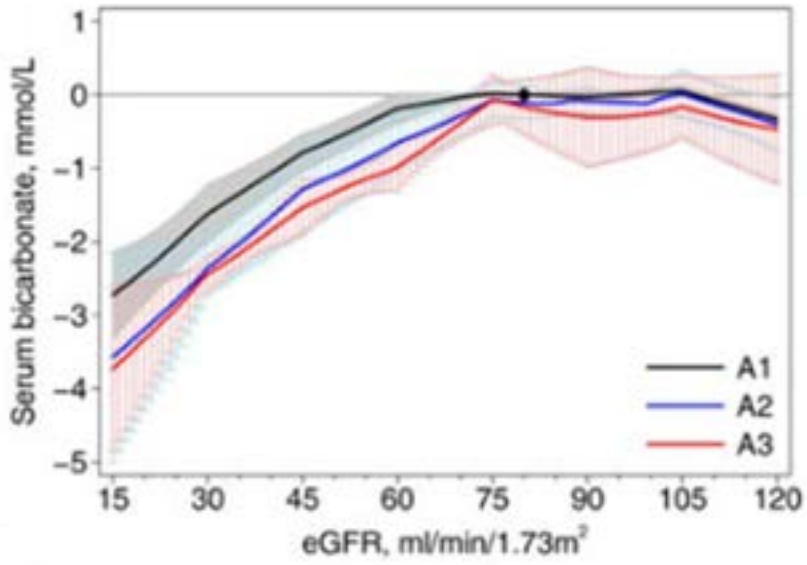


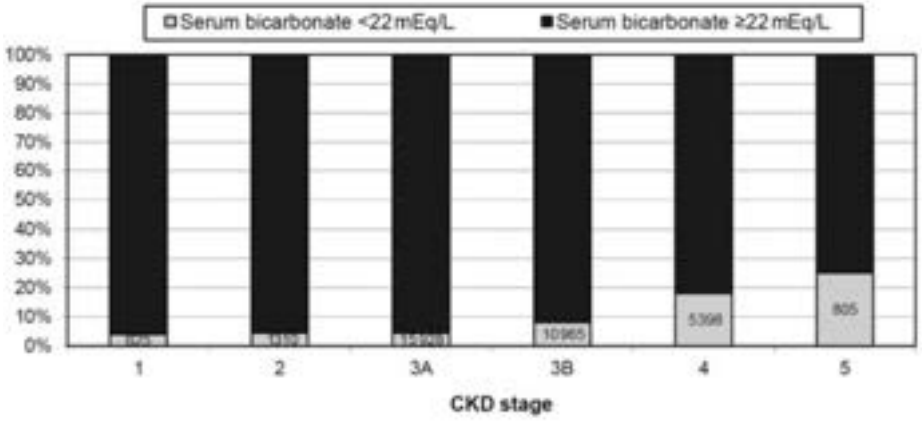


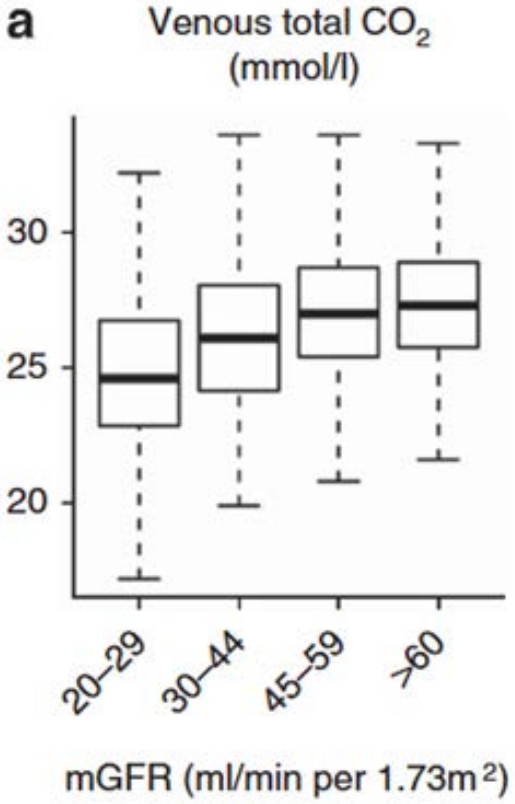
- Acidose métabolique à TAP normal
  - Défaut d'excrétion de la charge acide
    - DFG < 50ml/min
    - Trou anionique normal -> élevé (DFG < 15 ml/min)
  - Accumulation d'acide Organique
    - acides non-volatils à partir des AA soufrés
  - Perte de Bicarbonates
    - Compensation par OS, etc…

J Clin Invest. 1972;51(7):1852-1860
Kidney International (2015) 88, 137–145
Néphrologie & Thérapeutique 14 (2018) 13–23

Acidose et MRC







Nephrol Dial Transplant (2012) 27: 3056–3062
Kidney International (2015) 88, 137–145
Am J Kidney Dis. 2019 February ; 73(2): 206–217

Sous estimée, sous traitée

Metabolic acidosis is undertreated and underdiagnosed: a retrospective cohort study

Background

Guidelines recommend treatment of metabolic acidosis (MA) in patients with chronic kidney disease (CKD), but diagnosis and treatment rates in real-world settings are unknown. We investigated the frequency of MA treatment and diagnosis in patients with CKD using administrative health data.

Data sources and study population

Administrative health data from 3 North American databases:

- Optum® Integrated Claims + Clinical EHR, USA
- Symphony Health Solutions IDV®, USA (US Claims)
- Manitoba Centre for Health Policy Manitoba, Canada

Included all adults with at least:

- 2 eGFR tests < 60 mL/min/1.73 m² **AND**
- 2 serum bicarbonate tests 12 to < 22 mEq/L

Results

MA treatment and diagnosis patterns in people with lab-confirmed CKD and MA

	US EHR n = 6179	US Claims n = 86 782	Manitoba n = 3223
% receiving sodium bicarbonate treatment	17.6%	15.3%	8.7%
% with a MA diagnosis claim	44.7%	20.9%	20.9%

Conclusion

This analysis of 96 184 patients with laboratory-confirmed MA from 3 independent cohorts of patients with CKD and MA over a 3 year period, highlights an important diagnosis and treatment gap for this disease-modifying complication.

Whitlock, R.H., et al. NDT (2022)
@NDTSocial

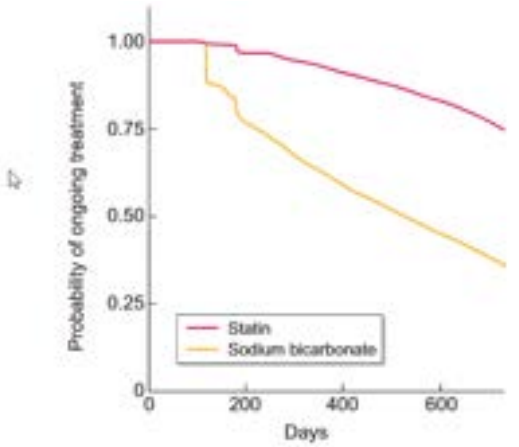
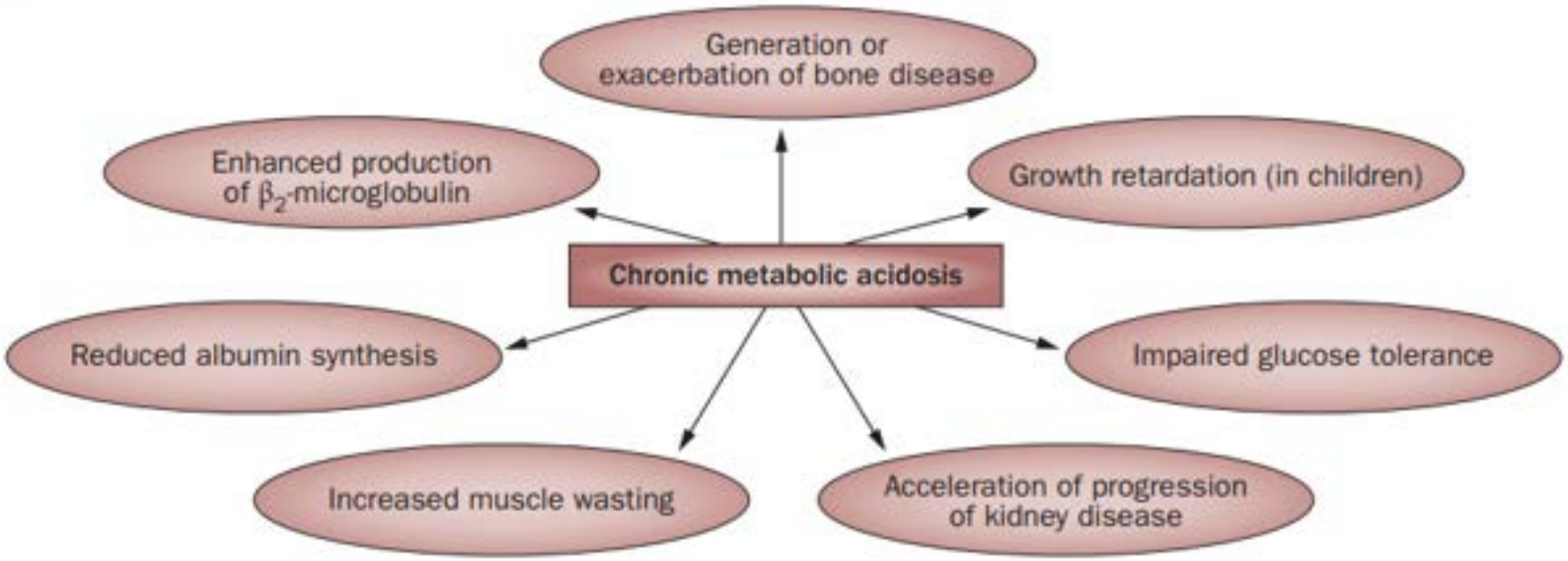


Figure 2: Adherence to oral sodium bicarbonate compared with statins in US Claims cohort.

Nephrology Dialysis Transplantation (2023) 38: 1477–1486

CONSÉQUENCE DE L'ACIDOSE

Conséquences de l'acidose métabolique

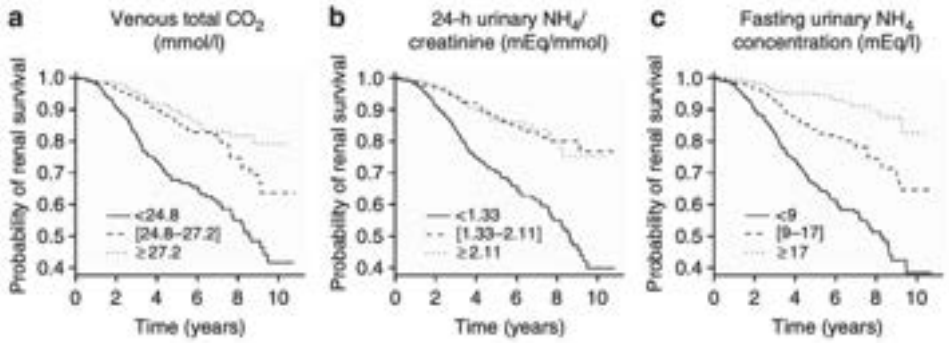


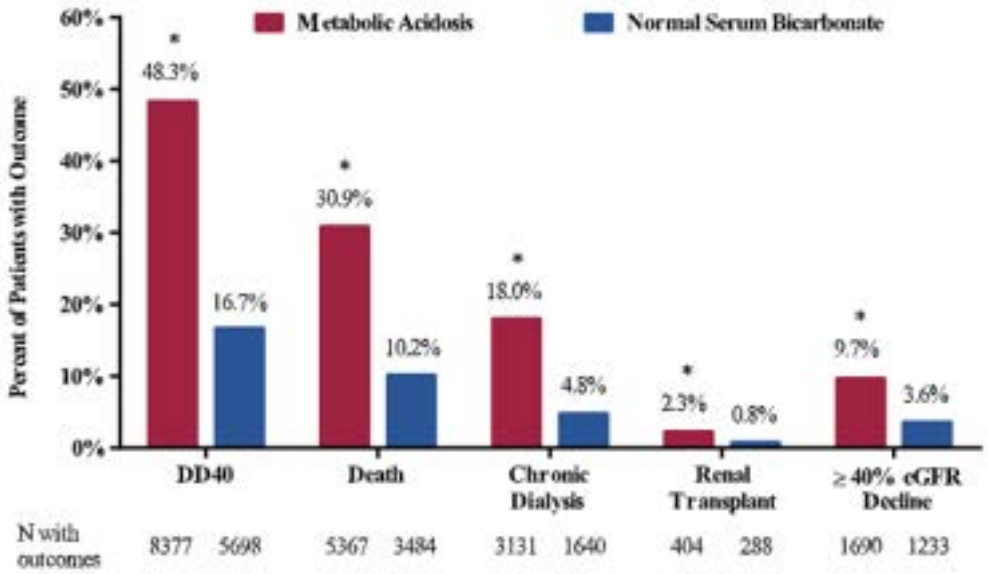
Kraut, J. A. & Madias, N. E., Nat. Rev. Nephrol. 6, 274–285 (2010)

Acidose et Progression de la MRC

Les faits

Cohorte NEPHROTEST





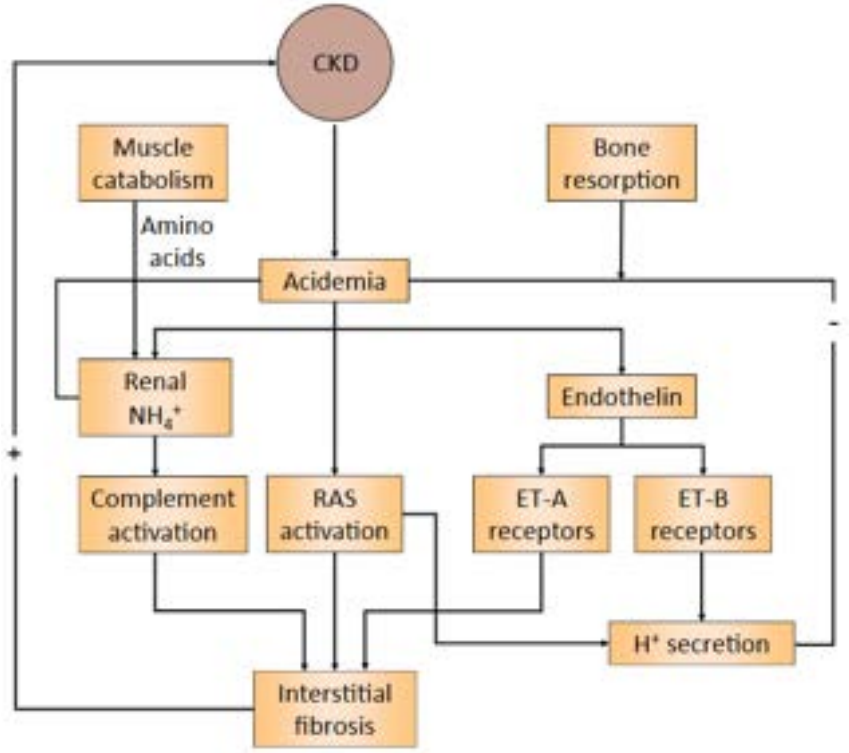
Base USA: 81 Millions

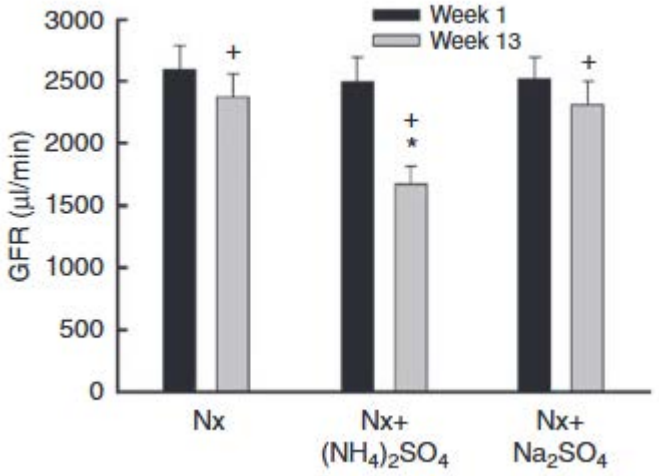
- CKD stade 3-5: 320 000
- > 3 mesures consécutives DFG/Bicar
- Devenir : 1 an avant , 2ans après
- HCO3 < 22: 17350 vs 22-29:34200
- DD40 = critère composite
  - décès, dialyse, perte de DFG >40%

Kidney International (2015) 88, 137–145
Tangri et al. BMC Nephrology (2021) 22:185

Acidose et Progression de la MRC

Pourquoi?





Kidney International (2010) 77, 567 – 569
Kidney International (2009) 75, 929–935
AJKD Vol 74 | Iss 2 | August 2019

Correction de l'Acidose et conséquence rénale

Table 1 | General demographic characteristics, SBP, Pcr, and eGFR at study entry in subjects before they were not treated (No-NaCit) or treated (NaCit) with Na^+ citrate

	No-NaCit (n=29)	NaCit (n=30)	P-value
Males (%)	48	47	0.891
Black/white/Hispanic (%)	55/14/31	53/23/23	0.591
	Mean ± s.d.	Mean ± s.d.	
Age (years)	53.9 ± 5.0	54.1 ± 6.4	0.928
SBP (mm Hg)	160.5 ± 8.9	161.8 ± 10.8	0.611
$VTCO_2$ (mM)	20.6 ± 0.8	20.8 ± 1.2	0.375
Pcr (mg/dl)	3.20 ± 0.89	3.27 ± 0.70	0.733
eGFRcr (ml/min)	33.4 ± 8.4	33.0 ± 8.5	0.871
Pcys (mg/l)	3.86 ± 1.09	3.88 ± 0.79	0.936
eGFRcys (ml/min)	32.3 ± 8.1	31.7 ± 8.3	0.767

Abbreviations: eGFR, estimated glomerular filtration rate; N, number of subjects per group; Pcr, plasma creatinine; Pcys, plasma cystatin C; SBP, systolic blood pressure; $VTCO_2$, venous serum total CO_2.

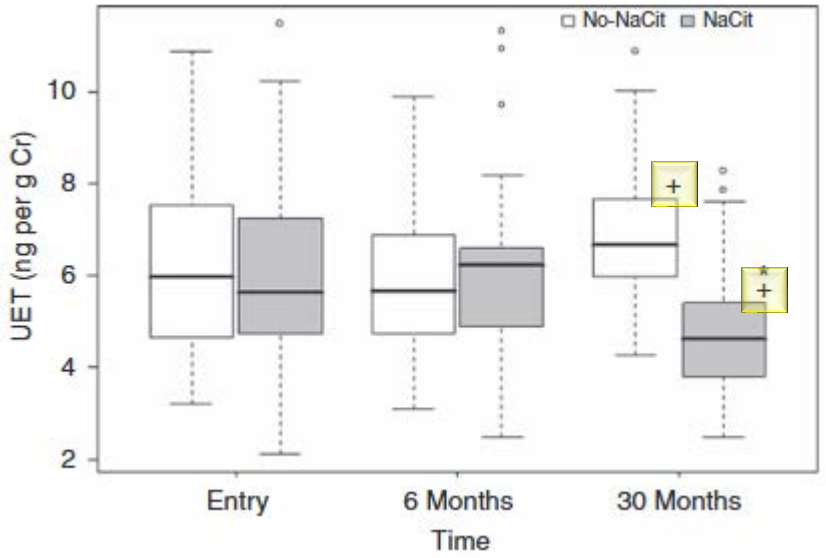
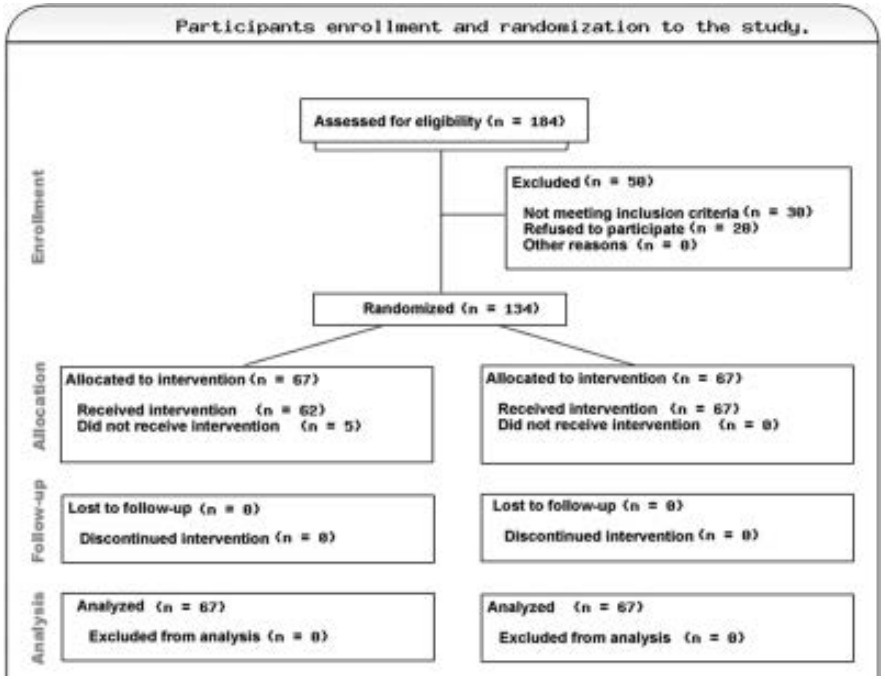


Table 2 | SBP, Pcr, and eGFR before (0 months) and after 24 months of No-NaCit vs NaCit

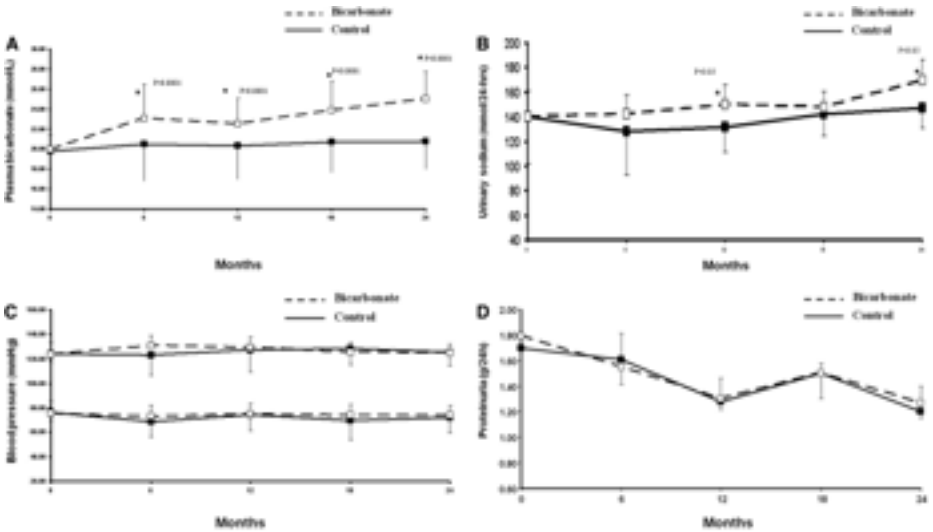
	No-NaCit (n=29)			NaCit (n=30)			P-value, NaCit vs No-NaCit	
	Month 6	Month 30	P-value, 30 vs 6 months	Month 6	Month 30	P-value, 30 vs 6 months	Month 6	Month 30
SBP	132.1 ± 6.3	131.9 ± 3.8	0.870	132.4 ± 6.2	132.7 ± 5.7	0.761	0.839	0.490
Pcr (mg/dl)	3.30 ± 0.91	4.24 ± 1.55	<0.0001	3.31 ± 0.69	3.61 ± 0.78	<0.0001	0.954	0.057
eGFRcr (ml/min)	32.5 ± 8.3	24.9 ± 9.7	<0.0001	32.7 ± 8.2	29.5 ± 8.8	<0.0001	0.945	0.066
Pcys (mg/l)	3.94 ± 1.10	5.24 ± 1.41	<0.0001	3.93 ± 0.80	4.33 ± 0.89	<0.0001	0.952	0.005
eGFRcys (ml/min)	31.7 ± 7.9	23.0 ± 6.05	<0.0001	31.4 ± 8.2	27.8 ± 7.4	<0.0001	0.885	0.008

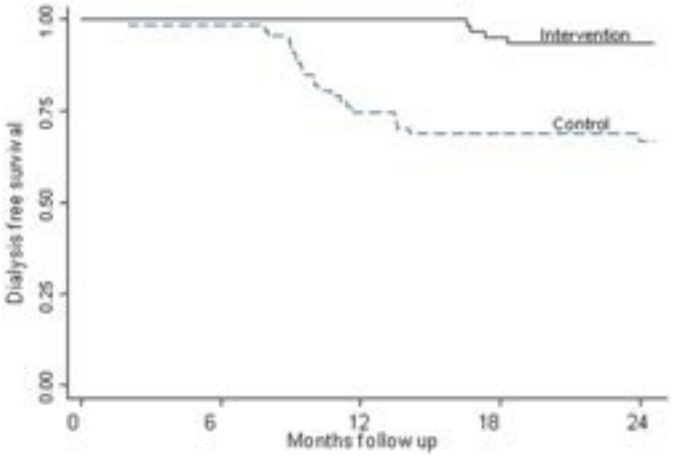
Abbreviations: eGFR, estimated glomerular filtration rate; Pcr, plasma creatinine; Pcys, plasma cystatin; SBP, systolic blood pressure.

Kidney Int. 2010 Apr 1;77(7):617–23

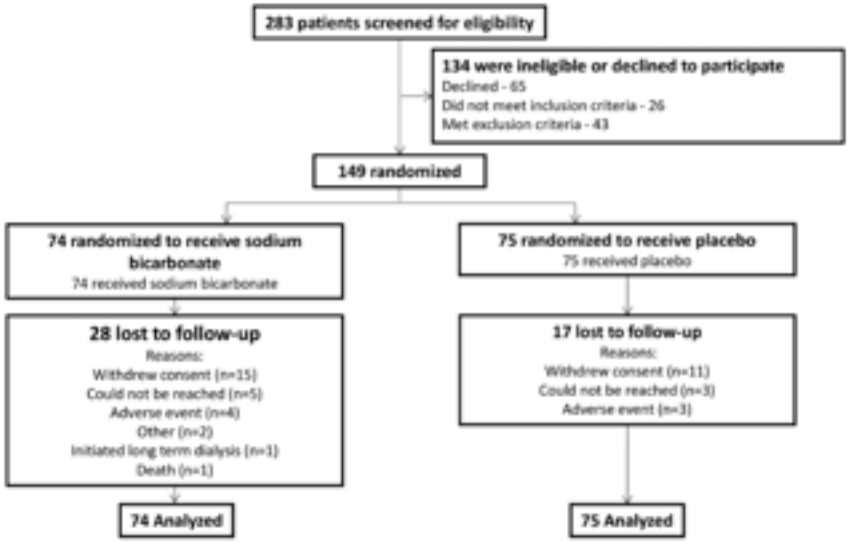


Variable	Control	Bicarbonate	*P*
Weight (kg)	74.9 ± 11.5	76.6 ± 21.1	0.84
Systolic BP (mmHg)	123.7 ± 1.2	124.0 ± 1.3	0.84
Diastolic BP (mmHg)	75.4 ± 1.9	76.1 ± 1.5	0.91
MAMC (cm)	24.8 ± 2.4	24.6 ± 2.9	0.81
Albumin (g/L)	35.1 ± 0.8	34.7 ± 0.5	0.76
Bicarbonate (mmol/L)	19.9 ± 1.5	19.8 ± 2.2	0.66
CrCl (ml/min per 1.73 m^2)	20.70 ± 5.55	20.12 ± 6.47	0.60
Urinary Na (mmol/L)	140.1 ± 4.4	140.0 ± 7.9	0.96
Urinary protein (g/24 h)	1.8 ± 0.2	1.7 ± 0.8	0.84

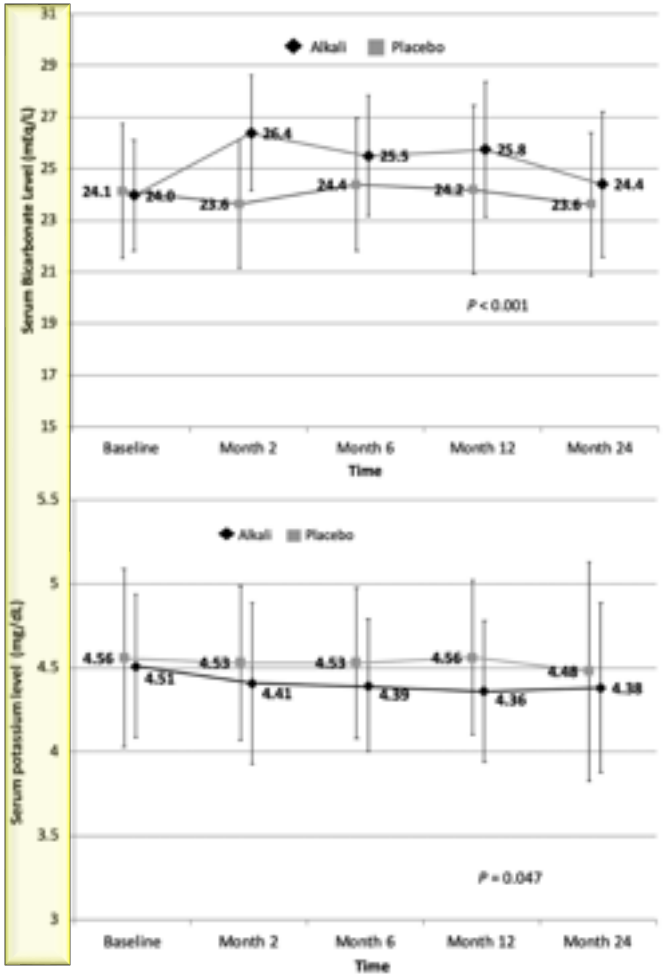




J Am Soc Nephrol. 2009 Sep;20(9):2075–2084.

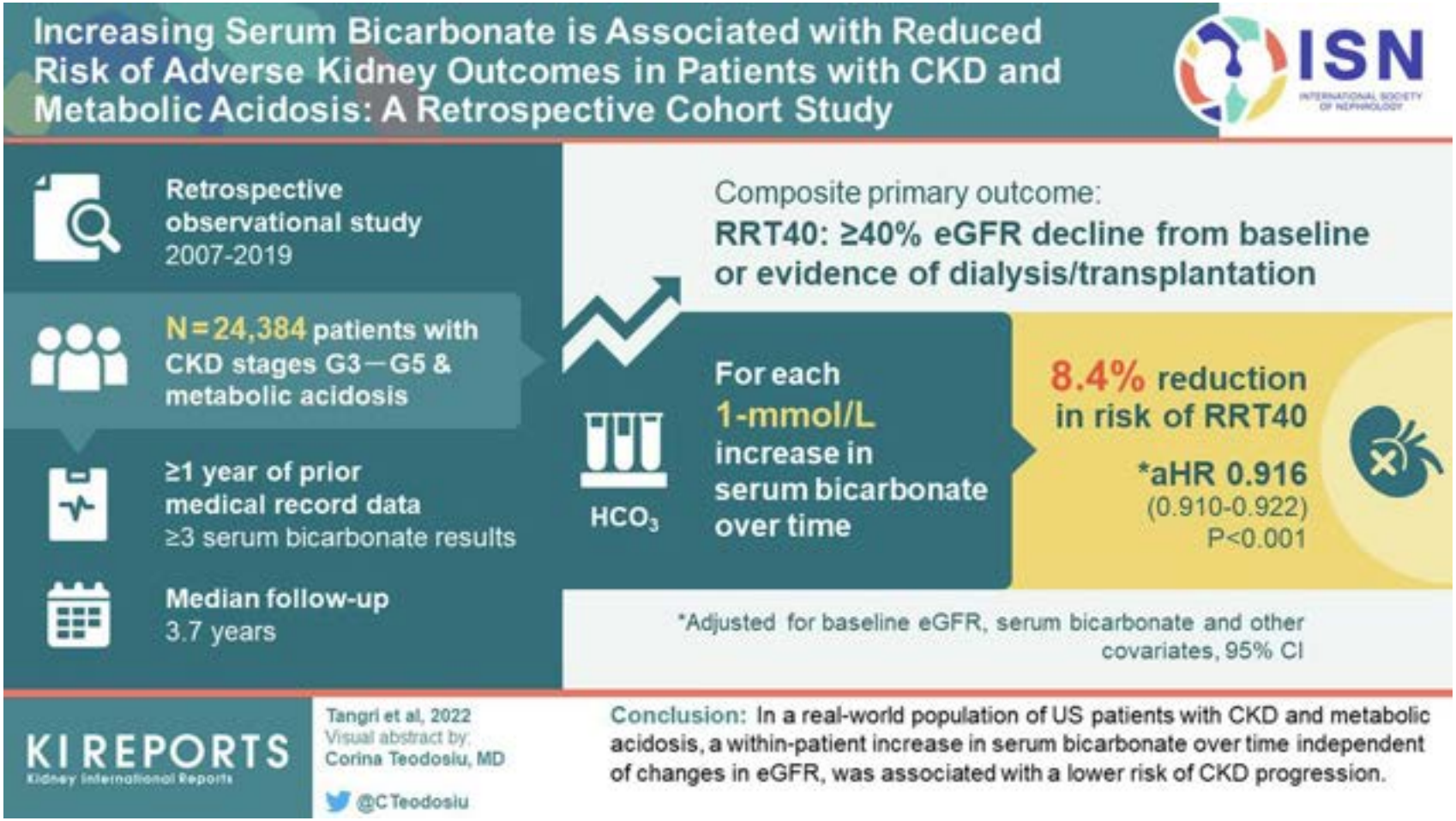


	Placebo					Sodium bicarbonate					p
	BL	Mo 2	Mo 6	Mo 12	Mo 24	BL	Mo 2	Mo 6	Mo 12	Mo 24	
Sit to stand time (sec)											
5 repetitions	11.7 (1.4)	11.3 (1.4)	10.9 (1.4)	11.1 (1.4)	10.3 (1.3)	12.6 (1.3)	11.9 (1.3)	11.8 (1.3)	11.6 (1.3)	10.8 (1.3)	0.1
10 repetitions	25.9 (9.8)	24.9 (9.9)	24.0 (7.7)	24.7 (7.8)	22.9 (6.5)	27.4 (8.0)	26.2 (7.6)	25.6 (7.6)	25.0 (6.9)	23.8 (5.8)	0.07
Handgrip Strength (kg)*	26.9 (9.9)	26.5 (10)	26.2 (10)	24.5 (9.5)	24.9 (10.2)	26.6 (10.6)	26.9 (9.6)	27.0 (9.3)	26.2 (8.7)	27.3 (9.8)	0.9
BMD (g/cm^2)	0.74 (0.16)	NA	0.74 (0.18)	0.74 (0.16)	0.73 (0.17)	0.76 (0.20)	NA	0.79 (0.22)	0.76 (0.20)	0.75 (0.23)	0.3
Weight (kg)	92.9 (26.1)	92.8 (26.3)	93.1 (26.4)	91.3 (27.3)	89.4 (28.5)	93.4 (22.7)	94.1 (23.6)	94.4 (22.7)	93.5 (22.9)	91.9 (23.0)	0.8
SBP (mmHg)	132 (17)	132 (21)	133 (19)	131 (19)	131 (17)	134 (21)	138 (20)	135 (19)	135 (24)	131 (17)	0.1
DBP (mmHg)	75 (12)	76 (13)	74 (13)	72 (11)	71 (10)	73 (11)	76 (11)	74 (13)	74 (12)	72 (10)	0.9
Quality of Life (SF-36)											
Physical function	43 (10)	42 (11)	42 (11)	41 (11)	43 (11)	42 (12)	41 (12)	41 (12)	41 (11)	40 (12)	0.7
Role physical	24 (3.6)	24 (4.1)	24 (3.5)	24 (3.9)	24 (4.0)	23 (4.3)	24 (4.0)	23 (4.0)	23 (4.2)	23 (4.1)	0.2
Body pain	48 (12)	48 (10)	48 (11)	48 (12)	49 (11)	48 (12)	47 (11)	45 (11)	46 (12)	46 (11)	0.3
Vitality	55 (13)	53 (12)	55 (12)	54 (12)	56 (13)	54 (13)	56 (12)	55 (12)	53 (11)	52 (12)	0.9
General health	43 (10)	44 (9)	44 (10)	42 (10)	43 (11)	41 (10)	42 (11)	43 (10)	43 (10)	45 (9)	0.5
PCS	39 (8.3)	40 (8.6)	40 (8.9)	39 (9.0)	40 (8.3)	39 (8.9)	38 (8.7)	38 (8.2)	38 (8.5)	38 (8.7)	0.2
MCS	48 (9.1)	46 (9.1)	46 (9.7)	46 (9.8)	47 (9.1)	46 (9.4)	47 (8.1)	47 (9.2)	46 (9.8)	47 (9.4)	0.7
eGFR (ml/min/1.73m^2)	37.1 (12.2)	37.3 (12.6)	37.2 (12.5)	35.4 (13.7)	36.3 (12.9)	39.2 (14.5)	38.2 (15.0)	37.2 (15.8)	36.1 (13.5)	38.5 (17.7)	0.7

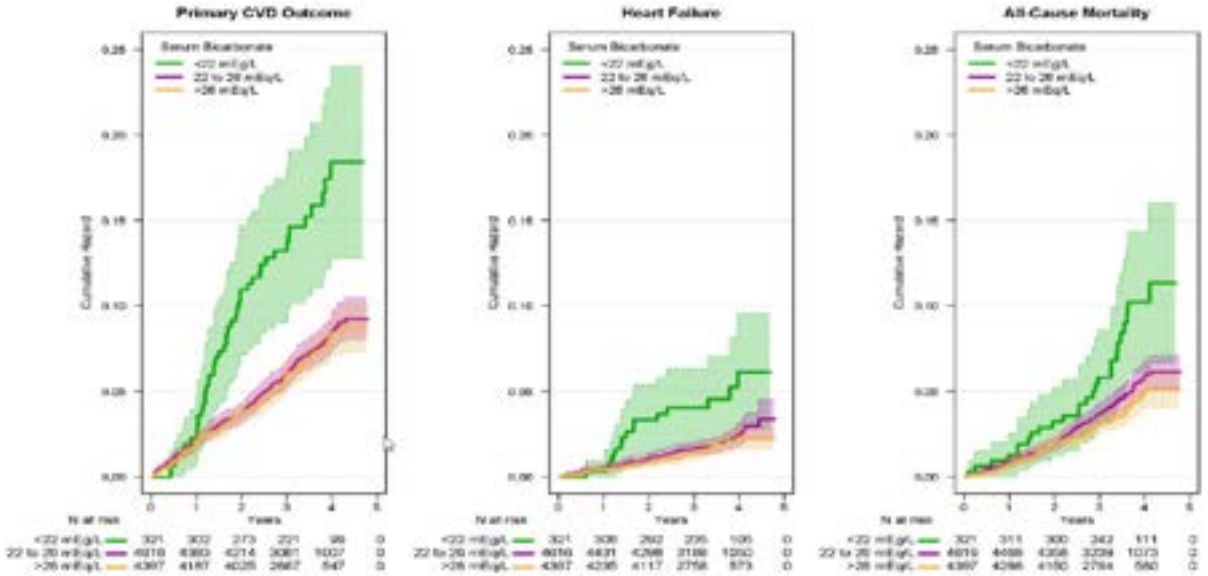


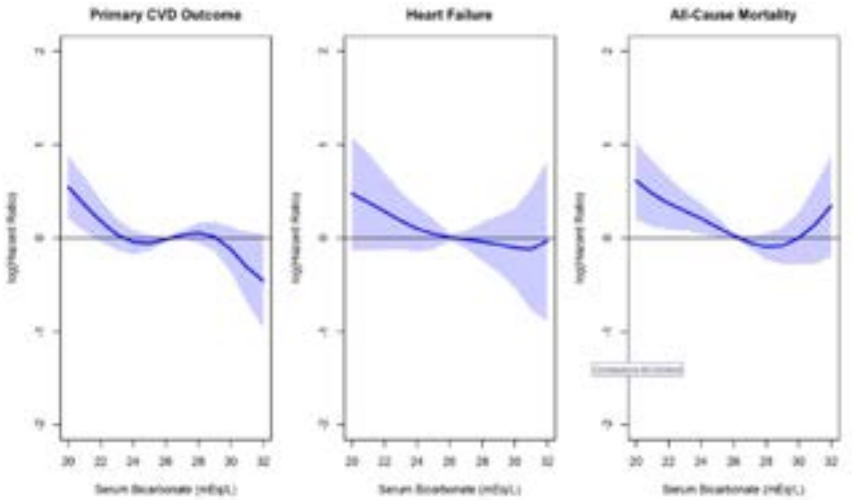
Am J Kidney Dis. 2020 February ; 75(2): 225–234

Observationnel



Acidose et Risque de décès CV



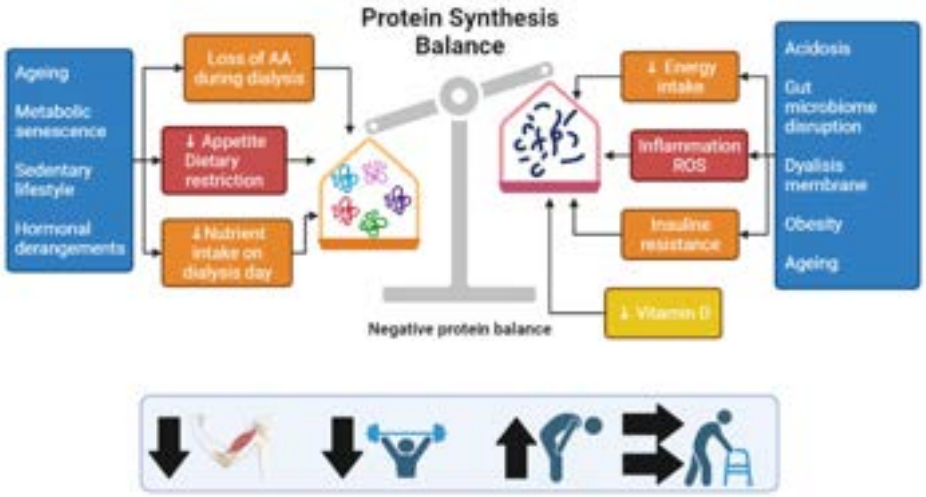


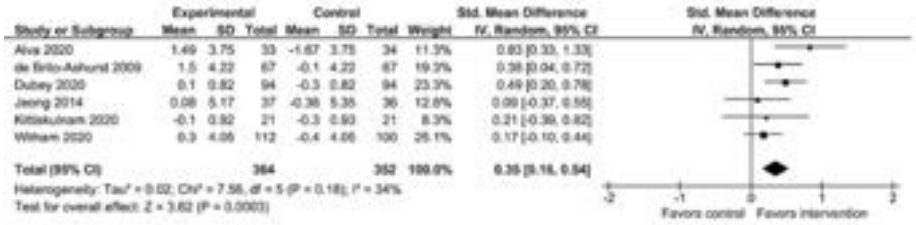
SPRINT Trial. 9334 sujets.

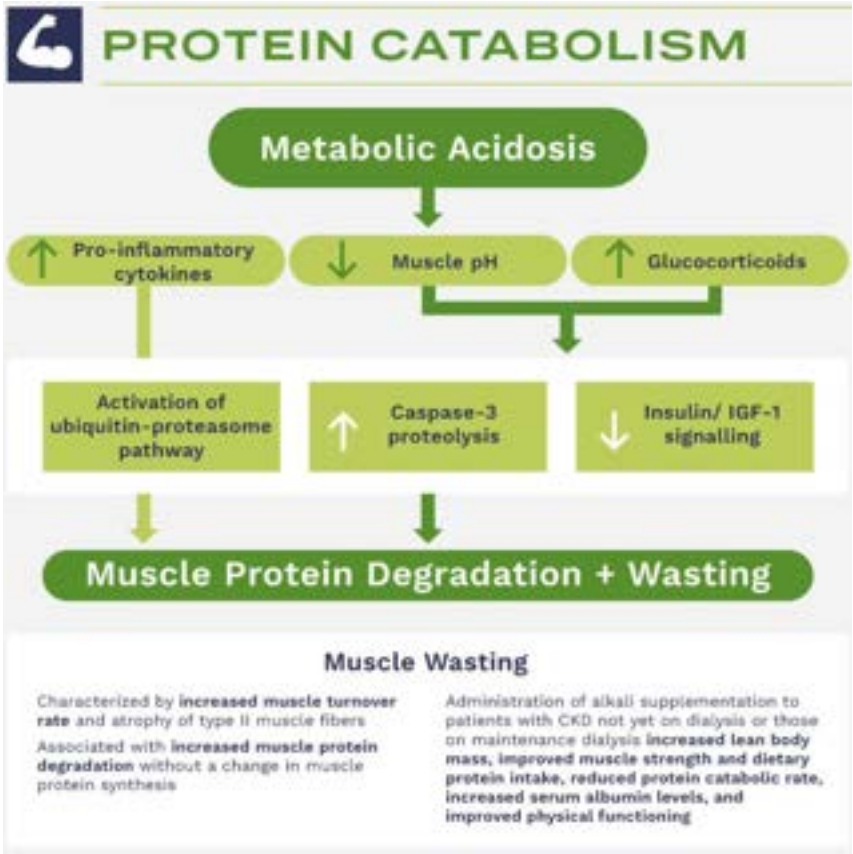
- Age 68 ans
- DFG moyen 72 ml/min.
  - 27% DFG < 60 ml/min.
- Bicar moyen: 26±2,6 mmol/L,
  - 3,4% Bicar < 22 ml/min.
- Suivi moyen : 3,3 ans.

Nephrol Dial Transplant (2020) 35: 1377–1384

Muscles

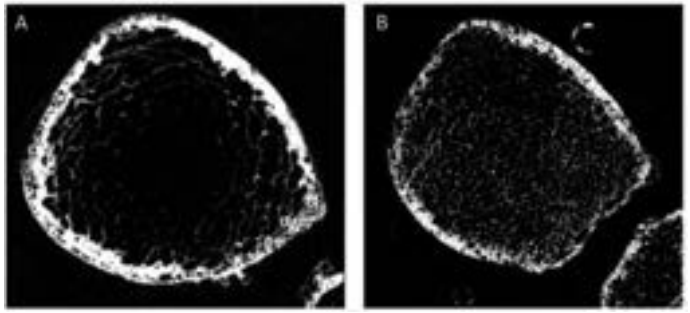


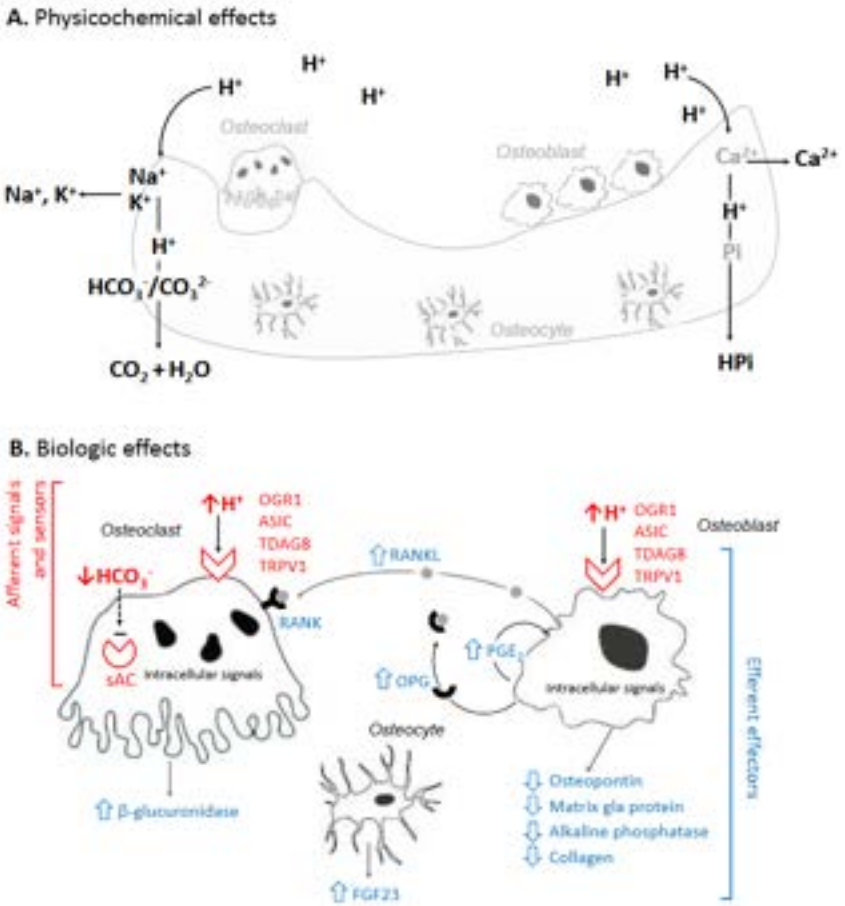


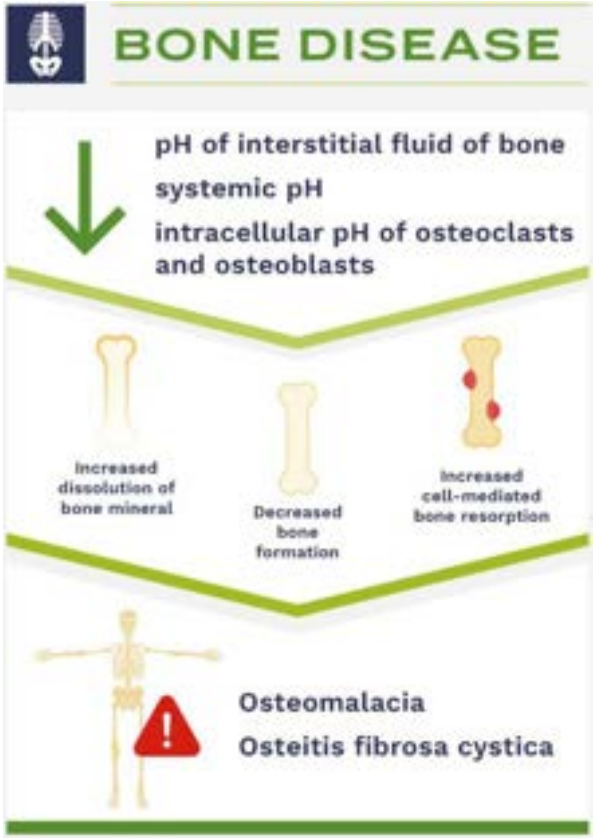


AJKD Vol 74 | Iss 2 | August 2019
Adv Chronic Kidney D 29, 329–336 (2022)
Journal of Cachexia, Sarcopenia and Muscle 2023; 14: 2498–2508
Nutrients. 2023 Jul 11;15(14):3107

Os



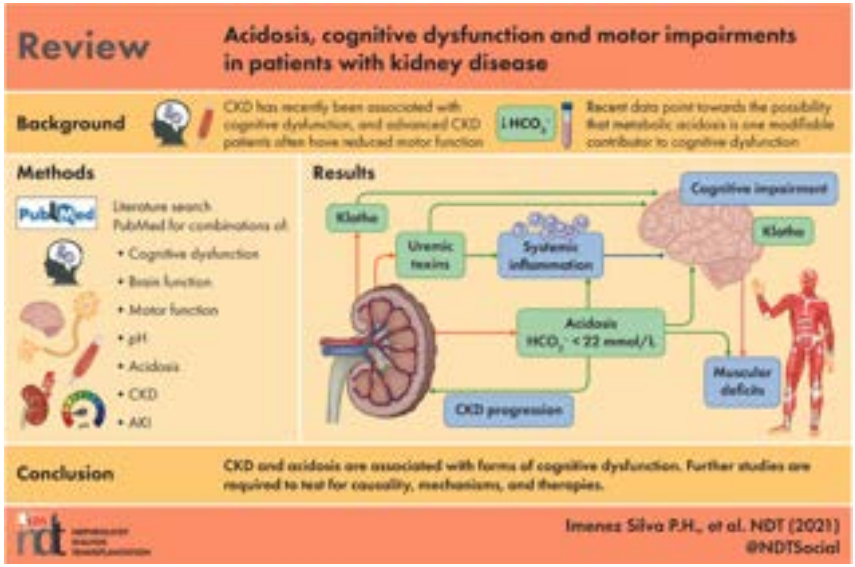




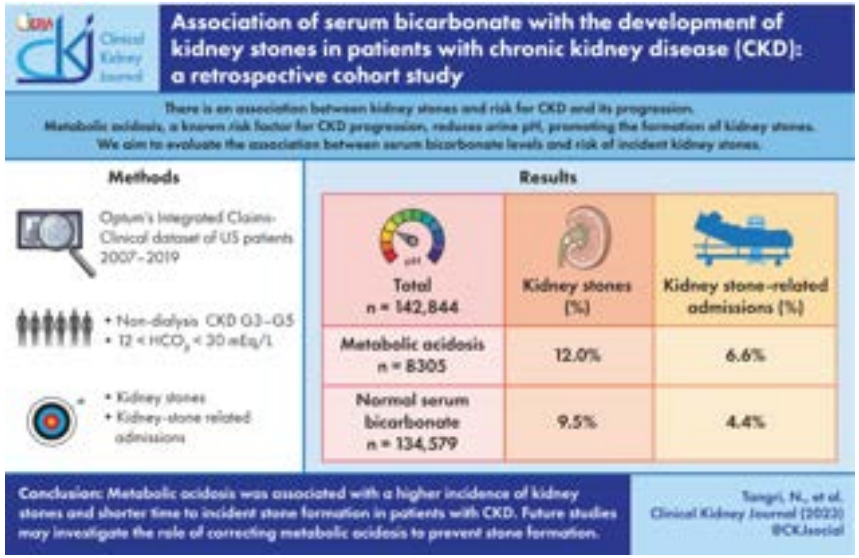
Osteoporos Int. 2015 Feb;26(2):563-70
Clinical Kidney Journal, 2022, vol. 15, no. 7, 1379–1386
J Am Soc Nephrol, . 2023 Apr 1;34(4):668-681.
Adv Chronic Kidney Dis . 2022 Jul;29(4):381-394

Autres

Trouble Cognitif

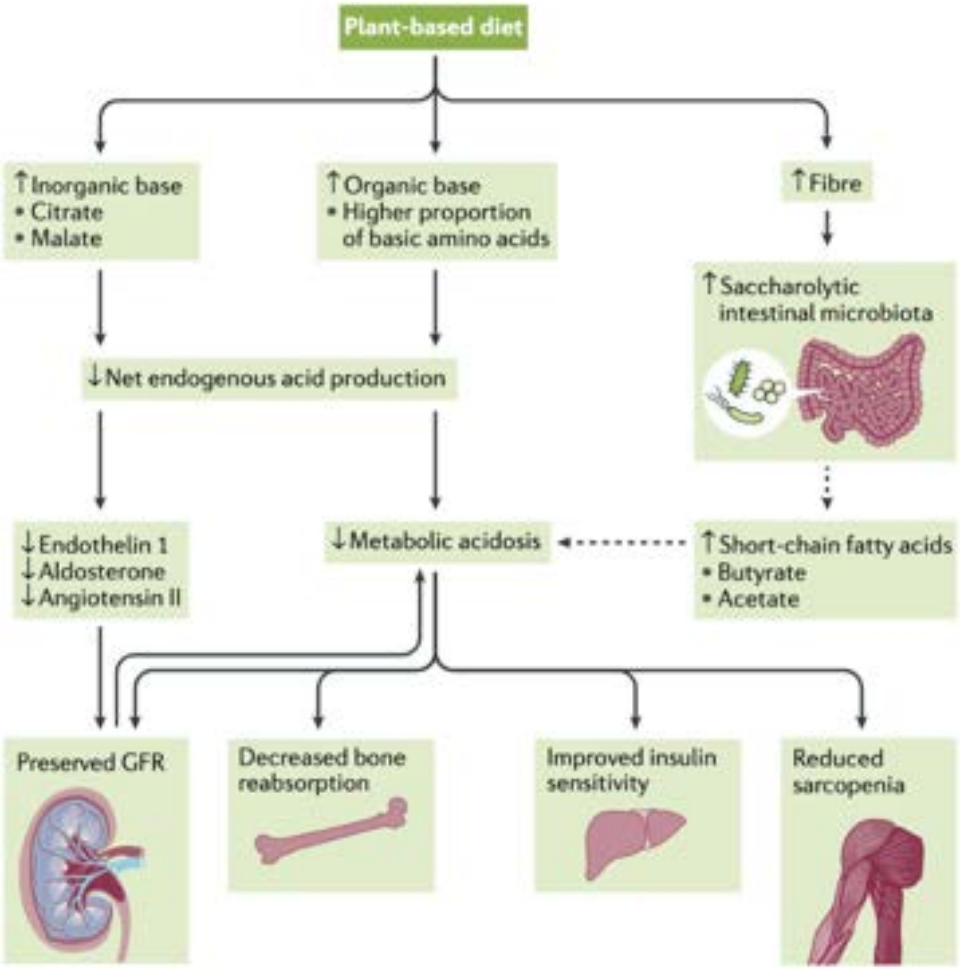


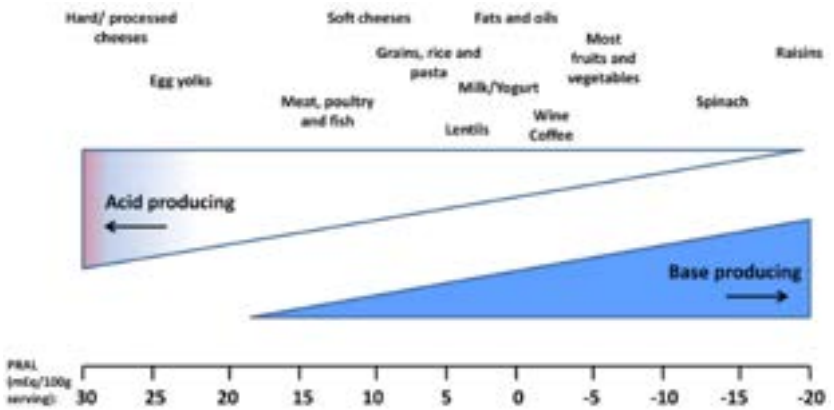
Lithiases



Quels Agents Alcalinisant?

Fruits et Légumes : + efficace?, moins cher





Adv Chronic Kidney Dis. 2013 March ; 20(2): 141–149
Nat Rev Nephrol., 2020 Sep;16(9):525-542
J Renal Nutr. 2021;31(3):239–47

Quels Agents Alcalinisants?

HCO3- > 22 mmol/L

Citrate (de K+ ou Na+)

- Préparation Magistrale

  - Eau de source
    - 3L par jour à répartir sur la journée
    - 3g de Citrate de potassium tripotassique officinal à diluer dans chaque litre d'eau de source (soit 9g au total)
      - Sachet en préparation magistrale à usage thérapeutique en l'absence de spécialité déjà existante

NaHCO3-

- Comprimés
  - BICAFRES® gélules de 1g
    - 2 à 8g/j
  - ~~Préparation magistrale~~
- Eaux bicarbonatées

Tableau II. Liste des principales eaux minérales gazeuses disponibles en France. La teneur en bicarbonate est exprimée en mg/L ou en mmoles/L.

	Teneur en bicarbonates en mg/L	Teneur en bicarbonates en mmoles/L
Saint-Yorre	4368	52
Vichy Celestin	2989	36
Arvie	2195	26
Rozana	1837	22
Badoit	1300	15
Quézac	1000	12
Salvetat	820	10
Perrier	420	5
San Pelligrino	242	3

Recommandations

KDOQI :
- Réduire les apports en acide
- Traitement oral si besoin

KDIGO:
- Réduire les apports protéines animales
- Proposer un régime « plant based diet »
- Ne propose pas < 0,8 g/kg en protéines
  - ↑ les protéines végétales
  - ↓ les aliments ultra-transformés

KDIGO 2023

3.9. Metabolic acidosis

Practice Point 3.9.1: In people with CKD, consider using dietary and/or pharmacological treatment to prevent severe acidosis (e.g., bicarbonate <16 mmol/l).

Practice Point 3.9.2: Monitor people with CKD to ensure correction of serum bicarbonate does not result in concentrations exceeding the upper limit of normal and does not adversely affect BP control, serum potassium, or fluid status.

3.3. Diet

Practice Point 3.3.1: Advise people with CKD to adopt healthy and diverse diets with a higher consumption of plant-based foods compared to animal-based foods and a lower consumption of ultra-processed foods.

Practice Point 3.3.2: Use registered dieticians or accredited nutrition providers to provide information for people with CKD about dietary adaptations regarding sodium, phosphorus, potassium, and protein intake, tailored to their individual needs, and severity of CKD and other comorbid conditions, where available.

KDOQI 2020

6.1 Statements on Acid Load

Dietary Management of Net Acid Production (NEAP)

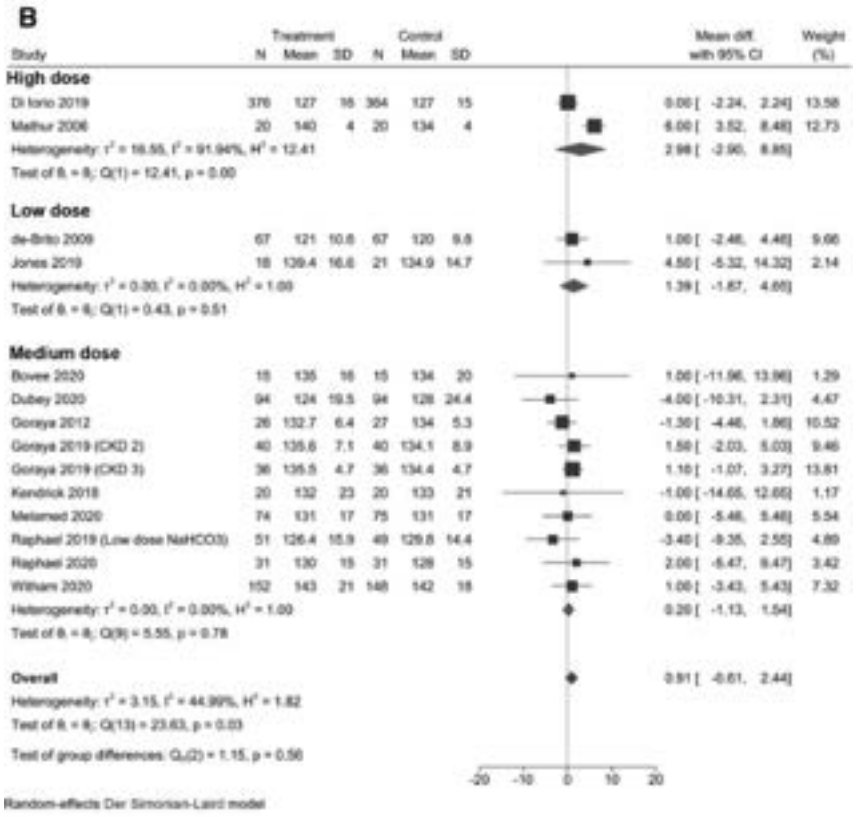
6.1.1 In adults with CKD 1-4, we suggest reducing net acid production (NEAP) through increased dietary intake of fruits and vegetables (*2C*) in order to reduce the rate of decline of residual kidney function.

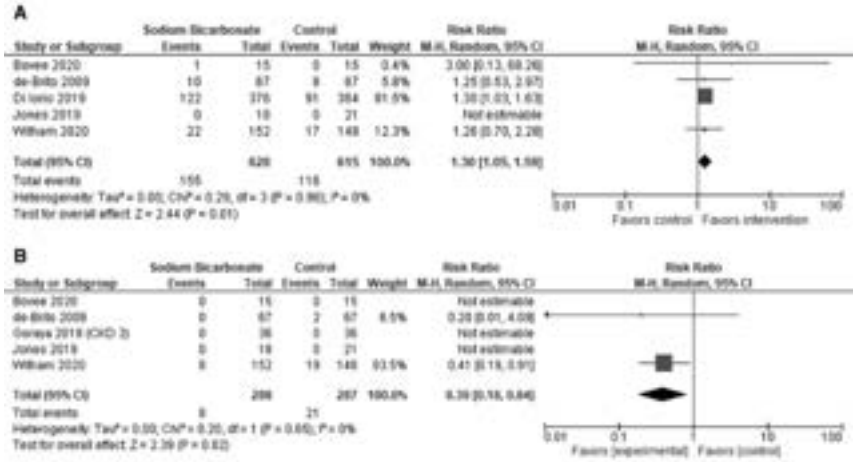
Bicarbonate Maintenance

6.1.2 In adults with CKD 3-5D, we recommend reducing net acid production (NEAP) through increased bicarbonate or a citric acid/sodium citrate solution supplementation (*1C*) in order to reduce the rate of decline of residual kidney function.

6.1.3 In adults with CKD 3-5D, it is reasonable to maintain serum bicarbonate levels at 24-26 mmol/L (*OPINION*).

Tolérance d’un Traitement Alcalinisant





(A) Decrease in antihypertensive medications.
(B) Increase in b-blockers.

Clin J Am Soc Nephrol. 2023 Apr 1;18(4):435-445

Veverimer

polymère qui capte les ions H+ dans l'estomac, non absorbable

VALOR-CKD: A Multicenter, Randomized, Double-Blind Placebo-Controlled Trial Evaluating Veverimer in Slowing Progression of Chronic Kidney Disease in Patients with Metabolic Acidosis

JASN

JOURNAL OF THE AMERICAN SOCIETY OF NEPHROLOGY

METHODS

randomized, double-blind, placebo controlled, multicenter clinical trial

Age ≥ 18, N = 1480
741 Ververimer, 6-9 g
739 placebo

eGFR 20-40 ml/min/1.73m^2

Serum HCO_3- 12-20 mmol/L

OUTCOMES

Progression of Kidney Disease
≥40% reduction in eGFR, end-stage kidney disease (ESKD), or death due to kidney failure

Ververimer	Placebo
n = 149	n = 148
9.9%	9.6%

hazard ratio, 0.99; 95 % CI, 0.8 to 1.2; P=0.90

KDQOL-PFD
Median difference in change from baseline between veverimer and placebo was 0; P=0.87

5-times Repeated Sit-Stand Test
Median difference in change from baseline between veverimer and placebo was -0.1; P=0.20

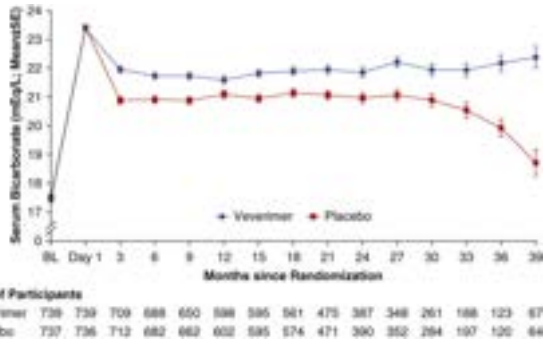
Time to ≥ 40% decline in eGFR
hazard ratio, 1.01; 95 % CI, 0.8 to 1.3; P=0.92

Time to ESKD or renal death
hazard ratio, 0.96; 95 % CI, 0.7 to 1.4; P=0.83

Time to all cause death
hazard ratio, 1.02; 95 % CI, 0.8 to 1.4; P=0.87

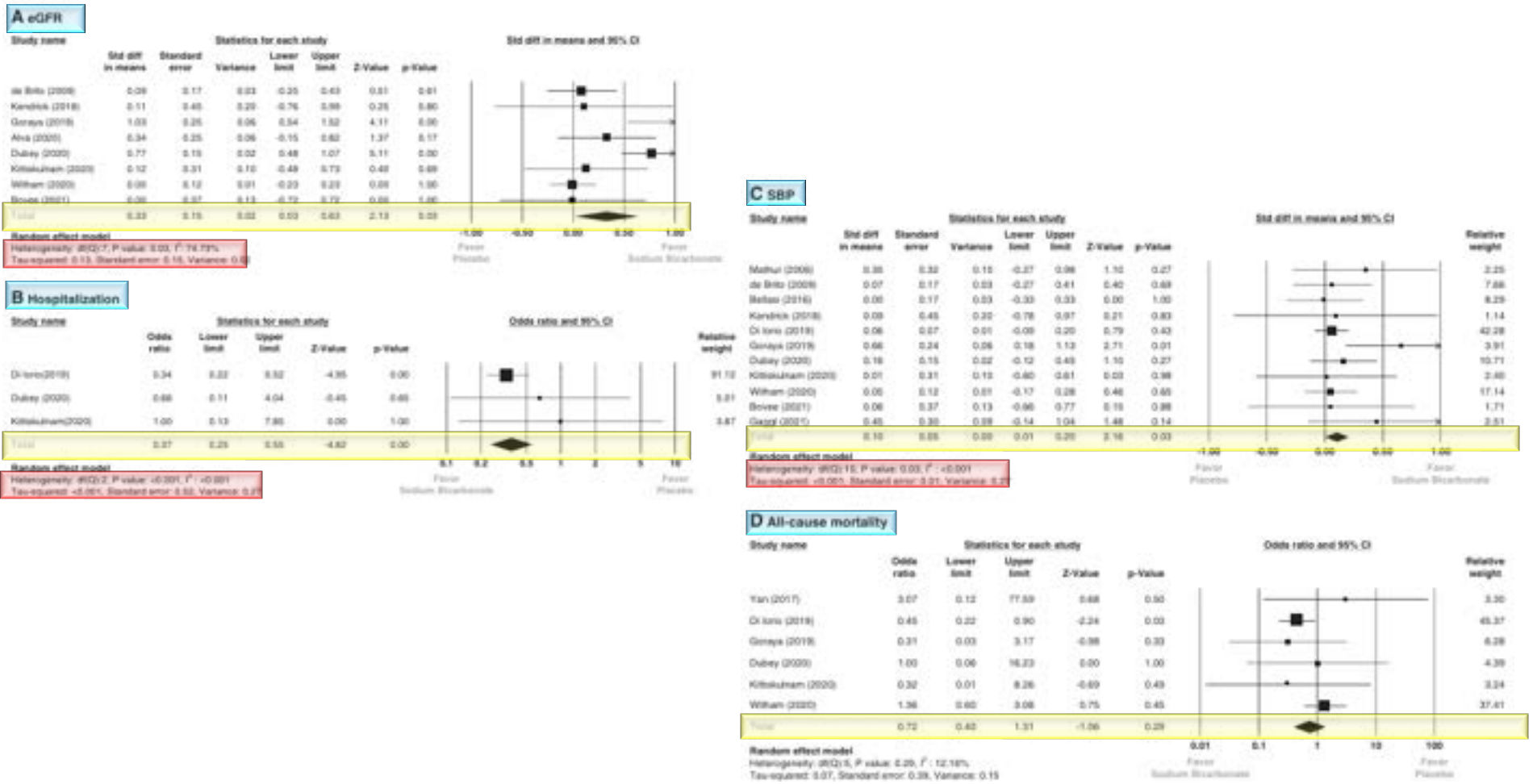
Conclusion
In patients with CKD and metabolic acidosis, treatment with ververimer did not reduce the risk of CKD progression. The effect of ververimer on serum bicarbonate levels, compared to placebo, was less than expected

doi: 10.1681/ASN.0000000000000292



J Am Soc Nephrol. 2024 Jan 23;35(3):311–320

Conclusion



CJASN 19: 959–969, 2024.