Troubles minéraux associés à la Maladie rénale Chronique

Dr Pierre Delanaye

Service de Dialyse, CHU Sart Tilman, Liège, Belgique

Troubles minéraux associés à la Maladie rénale Chronique **(terminale)**

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La triade infernale

Calcium

Phosphore

Parathormone

Un résultat d'un des membres de la triade ne peut s'interpréter qu'en fonction des deux autres en MRCT!!

La triade infernale

Calcium

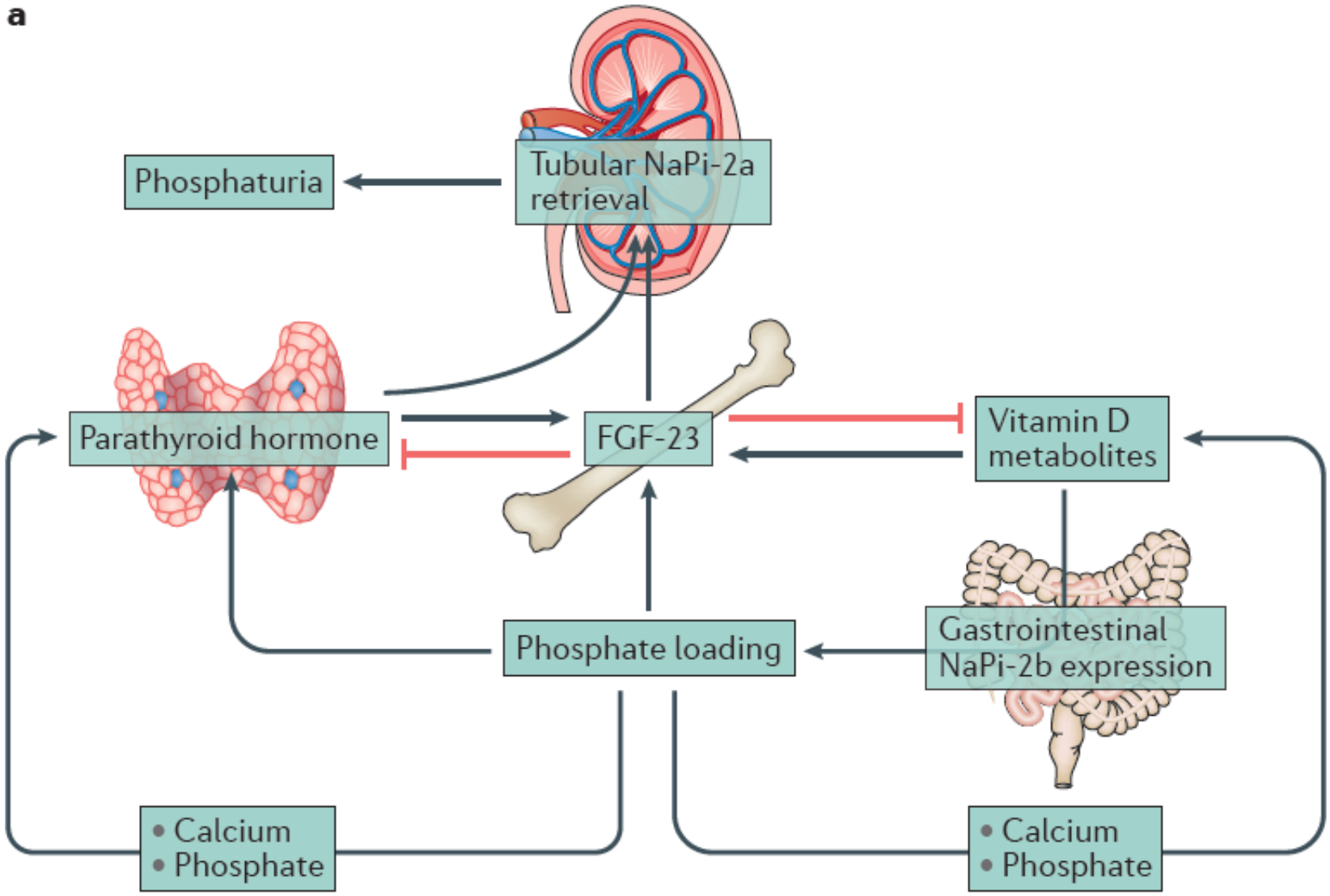
Phosphore

(Parathormone)

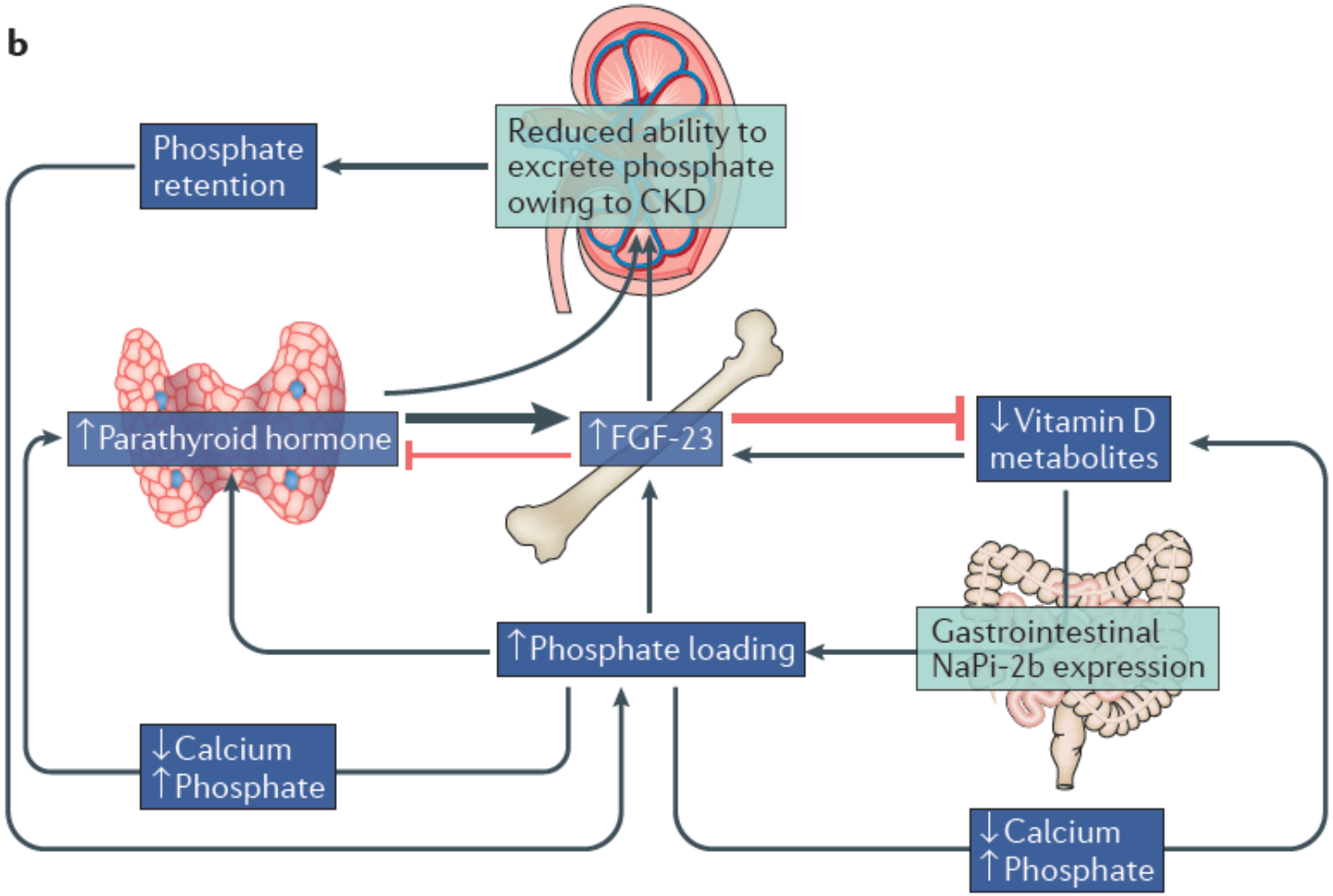
Un résultat d'un des membres de la triade ne peut s'interpréter qu'en fonction des deux autres en MRCT!!

Phosphore

- Ion indispensable à l'organisme (énergie cellulaire)
- Absorption intestinale très efficiente
- Excrétion rénale régulée (NaPi2a) par PTH et FGF-23 qui entrainent une phosphaturie
- Feedback négatif du FGF23 via vitamine D et PTH



Vervloet M, Nat Rev Nephrol, 2017



Vervloet M, Nat Rev Nephrol, 2017

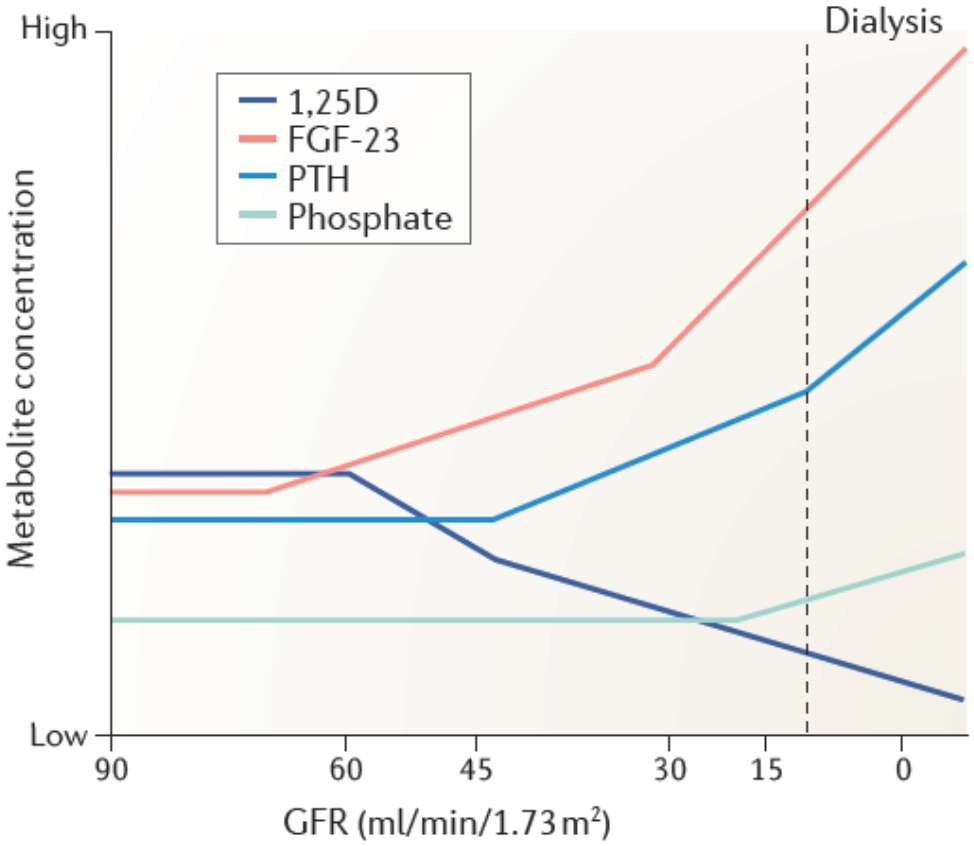
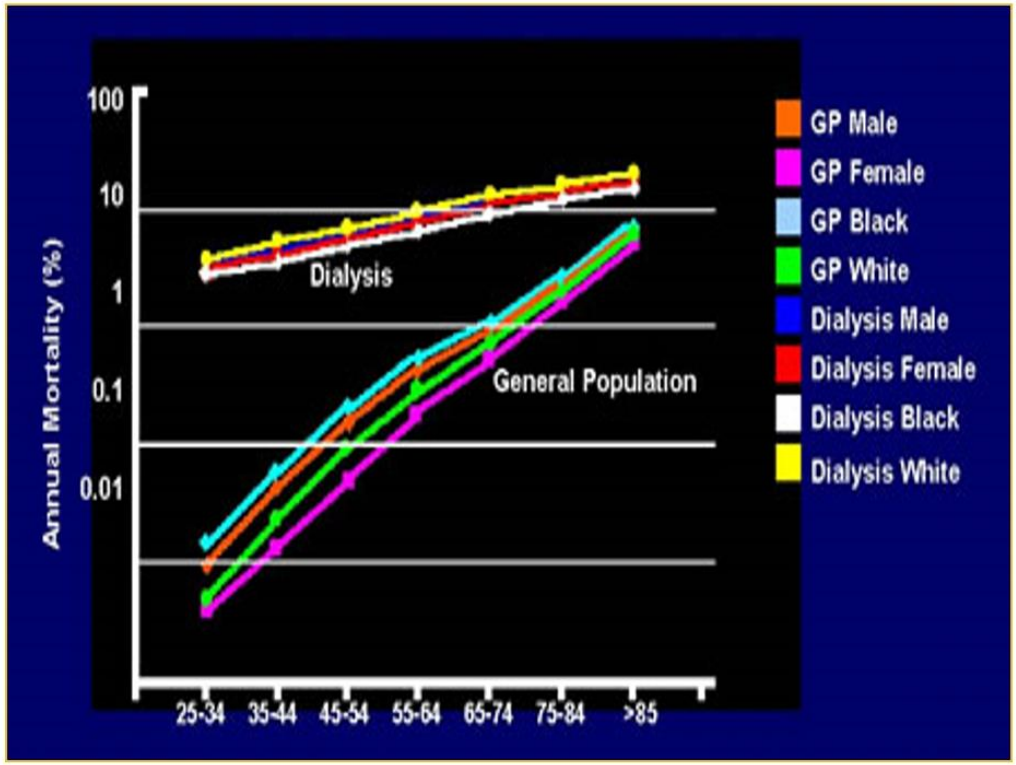


Figure 4 | **Model of changes in the serum levels of fibroblast growth factor 23 (FGF-23), 1,25 dihydroxyvitamin D (1,25D), parathyroid hormone (PTH) and phosphate during progression of chronic kidney disease.** As glomerular filtration rate (GFR) declines, the level of FGF-23 is the first to increase, followed by decreasing levels of 1,25D and increasing levels of PTH. The increase in phosphate levels occurs at a much lower level of kidney function than the changes in the other parameters.

Vervloet M, Nat Rev Nephrol, 2017

Dialysis phosphorus removal: 3 times per week

Diet	1000 mg/day 7 x 1000 (per week) =	7000 mg
Absorption	60% 7000 x 60% =	4200 mg
Dialysis	800 mg 3 x 800 (per week) =	2400 mg
Balance	4200 – 2400 =	1800 mg



Foley RN. Clinical epidemiology of cardiovascular disease in chronic renal disease. Am J Kidney Dis 1998 Nov;32(5 Suppl 3):S112-S119.

Mortalité (CV) et concentration de phosphore

Nephrol Dial Transplant (2013) 28: 360–367
doi: 10.1093/ndt/gfs404
Advance Access publication 6 November 2012

Control of mineral metabolism and bone disease in haemodialysis patients: which optimal targets?

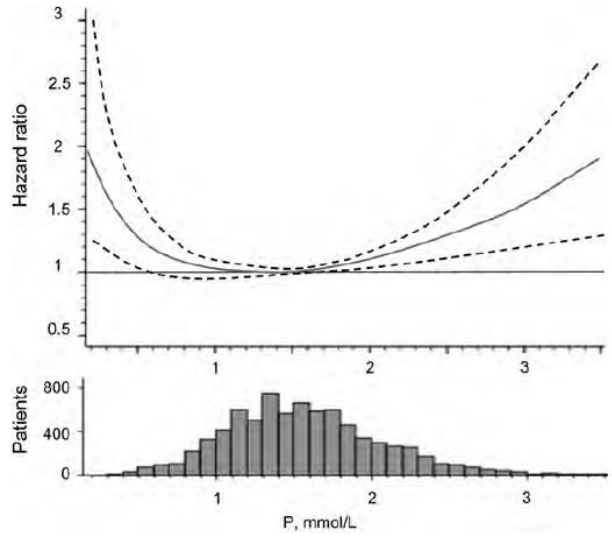
Denis Fouque[1], Hubert Roth[2], Solenne Pelletier[1], Gérard M. London[3], Thierry Hannedouche[4], Guillaume Jean[5], Jean-Louis Bouchet[6] and Tilman Drüeke[7]

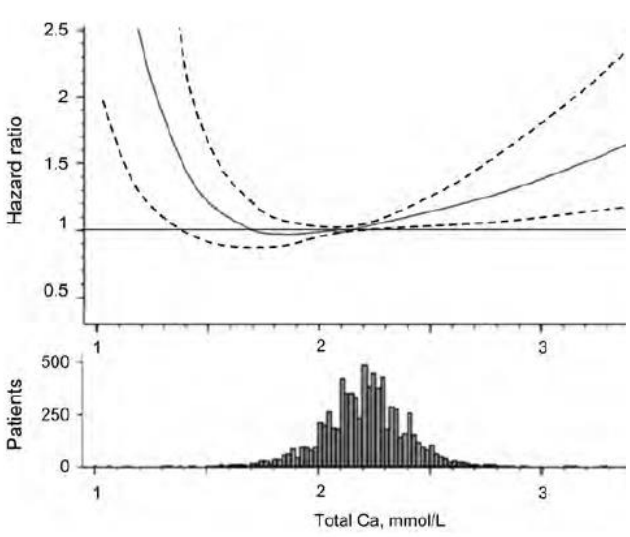
[1]Department of Nephrology, Hôpital Edouard Herriot, Université de Lyon, CENS, Lyon, France, [2]Centre de Recherche en Nutrition Humaine Rhône-Alpes, CHU-Grenoble, France, [3]Hôpital Manhes, Fleury-Mérogis, France, [4]Service de Néphrologie, Hôpitaux Universitaires de Strasbourg, & Faculté de Médecine, Strasbourg, France, [5]Centre de Rein Artificiel, Tassin-La-Demi-Lune, France, [6]Centre de Traitement des Maladies Rénales Saint-Augustin, Bordeaux, France and [7]Inserm Unit ERI-12, UFR de Médecine et Pharmacie, Université de Picardie Jules Verne, Amiens, France

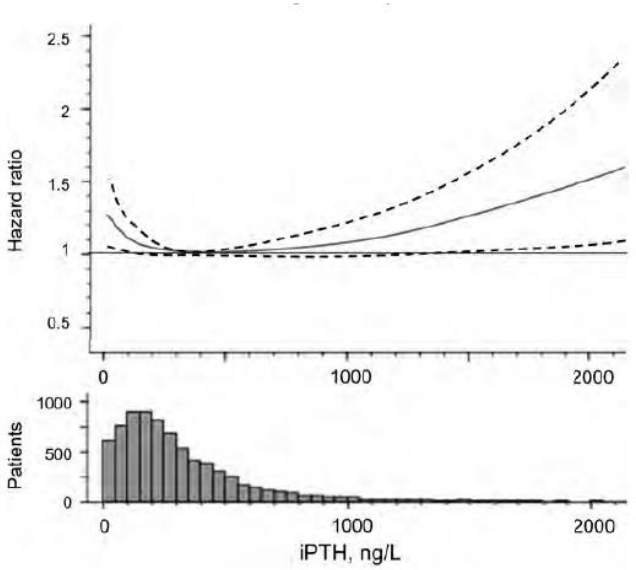
Correspondence and offprint requests to: Denis Fouque; E-mail: denis.fouque@chu-lyon.fr

Etude française, observationnelle,
Prospective (30 mois)
N=7,700

Mortalité (CV) et concentration de phosphore







Augmentation de la mortalité de 10%:

P: 0,72 – 1,98 mmol/L

Ca: 1,59 – 2,41 mmol/L

PTH: 100 – 1090 pg/mL

Mortalité et calcifications vasculaires

London GM. Nephrol Dial Transplant 2003 Sep;18(9):1731-40.
Blacher J. Hypertension 2001 Oct;38(4):938-42.
Matsuoka M. Clin Exp Nephrol 2004 Mar;8(1):54-8.
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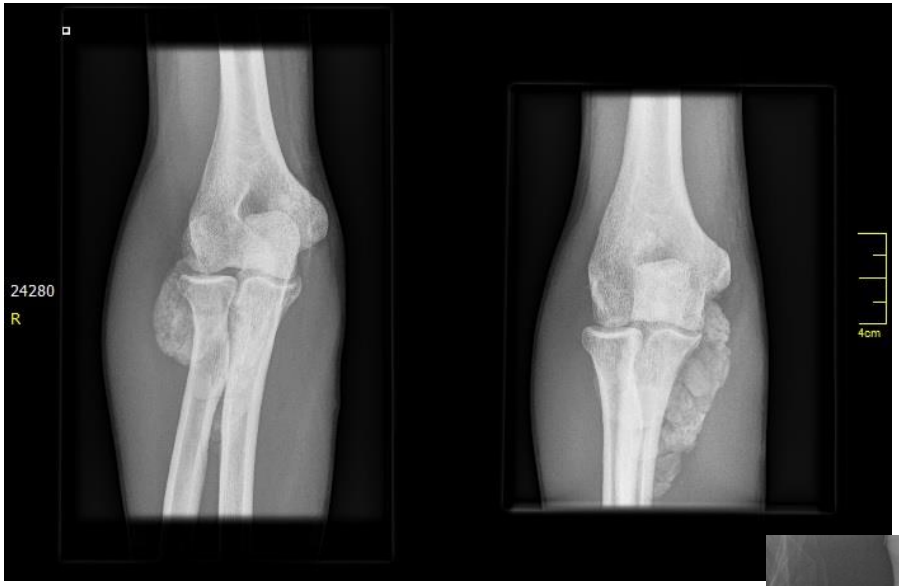
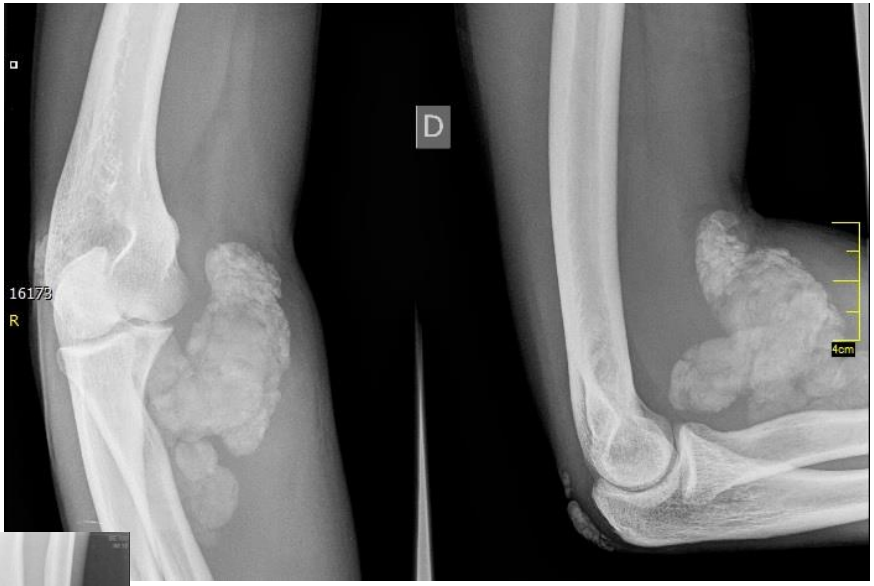
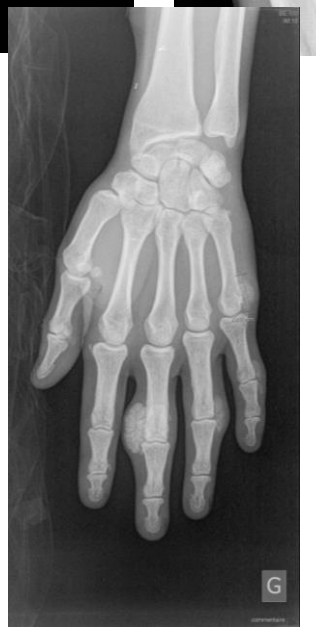
Schlieper G. Kidney Int 2008 Dec;74(12):1582-7.
Adragao T. Nephrol Dial Transplant 2004 Jun;19(6):1480-8.
Okuno S. Am J Kidney Dis 2007 Mar;49(3):417-25.
Jean G. Nephrol Dial Transplant 2009 Mar;24(3):948-55.
Adragao T. Nephrol Dial Transplant 2009 Mar;24(3):997-1002.

…et extra-vasculaires…







Phosphore et calcifications vasculaires

Goodman WG. N Engl J Med 2000 May 18;342(20):1478-83.
Hruska KA. Pediatr Nephrol 2010 Apr;25(4):769-78.
Mitsnefes MM. J Am Soc Nephrol 2005 Sep;16(9):2796-803.
Shroff RC. J Am Soc Nephrol 2007 Nov;18(11):2996-3003.
Braun J. Am J Kidney Dis 1996 Mar;27(3):394-401.
Goodman WG. Am J Kidney Dis 2004 Mar;43(3):572-9.
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Huting J. Chest 1994 Feb;105(2):383-8.
Oh J. Circulation 2002 Jul 2;106(1):100-5.
London GM. Nephrol Dial Transplant 2003 Sep;18(9):1731-40.

Donc…

- Sur-mortalité cardiovasculaire en dialyse…
- “Sur”-calcification vasculaire en dialyse
- Association entre calcification et mortalité
- Association entre P et mortalité
- Association entre P et calcification
- => logique de penser que traiter l’hyperphosphorémie est bénéfique
- Mais calcifications sont-elles réellement réversibles?
- Traiter l’hyperphosphorémie est-elle associée à un gain de mortalité?

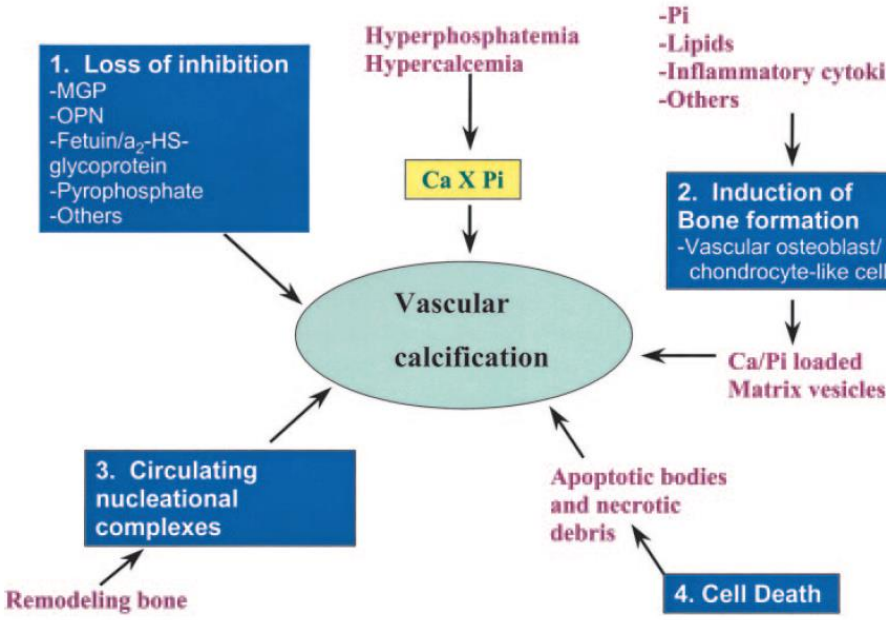
(pas de RCT versus placebo alors que marché à 1,5 milliards $ US)

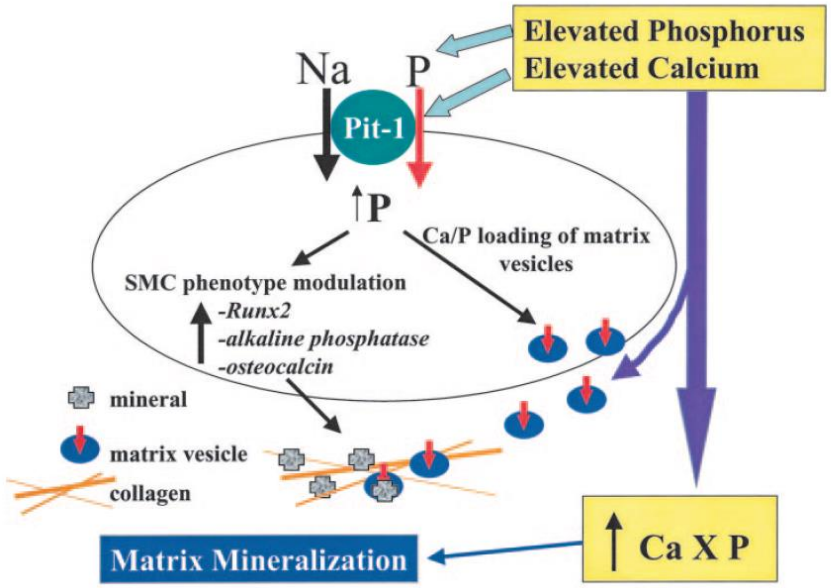
- La diminution des calcifications (ou la moindre évolution) est-elle associée à une meilleure survie?

J Am Soc Nephrol 15: 2959–2964, 2004

Vascular Calcification Mechanisms

CECILIA M. GIACHELLI
Bioengineering Department, University of Washington, Seattle, Washington.





Le phosphore dans l'alimentation

D'Alessandro *et al. BMC Nephrology* 2015, **16**:9
http://www.biomedcentral.com/1471-2369/16/9

BMC Nephrology

CORRESPONDENCE Open Access

The "phosphorus pyramid": a visual tool for dietary phosphate management in dialysis and CKD patients

Claudia D'Alessandro[1], Giorgina B Piccoli[2] and Adamasco Cupisti[1*]

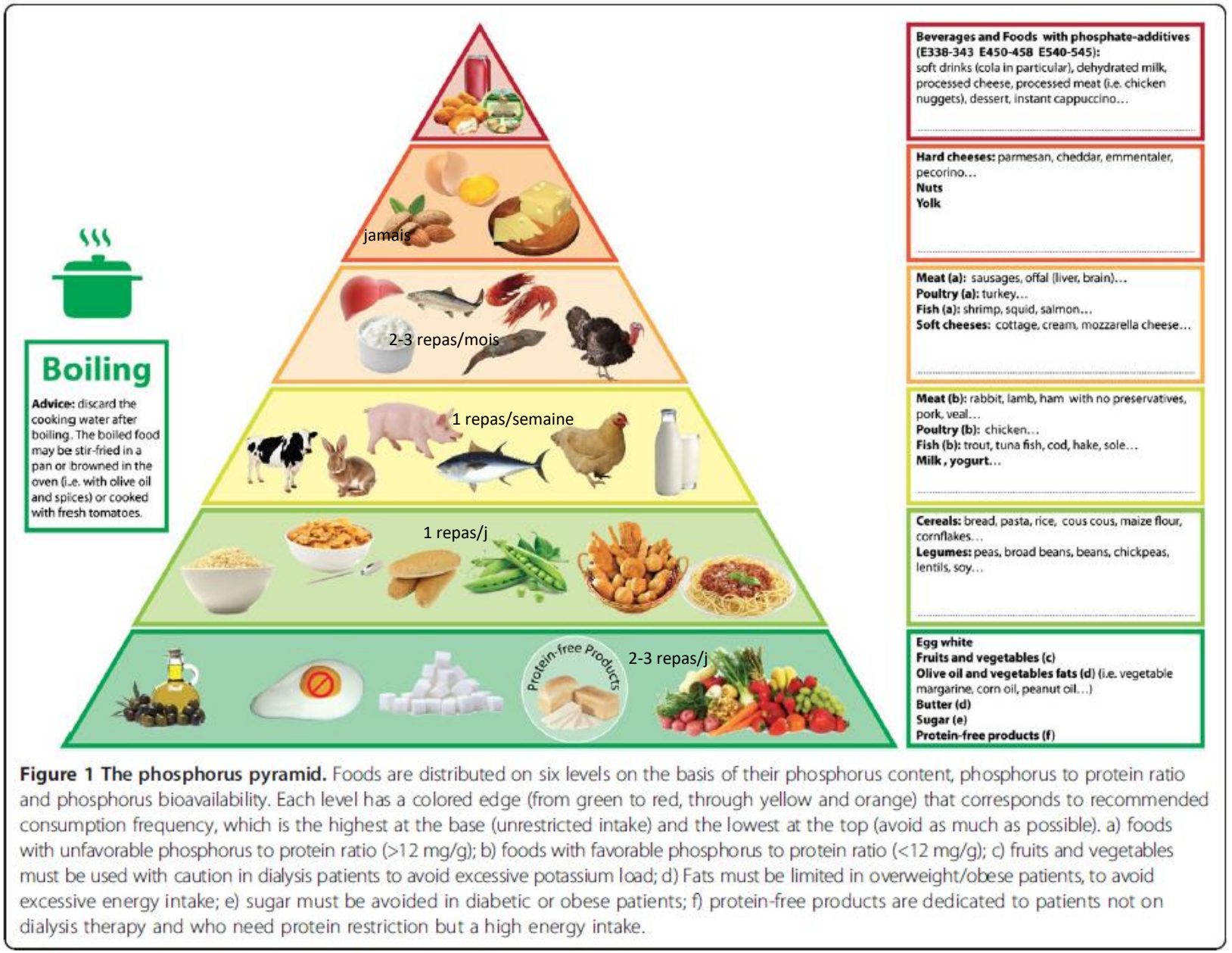


Figure 1 The phosphorus pyramid. Foods are distributed on six levels on the basis of their phosphorus content, phosphorus to protein ratio and phosphorus bioavailability. Each level has a colored edge (from green to red, through yellow and orange) that corresponds to recommended consumption frequency, which is the highest at the base (unrestricted intake) and the lowest at the top (avoid as much as possible). a) foods with unfavorable phosphorus to protein ratio (>12 mg/g); b) foods with favorable phosphorus to protein ratio (<12 mg/g); c) fruits and vegetables must be used with caution in dialysis patients to avoid excessive potassium load; d) Fats must be limited in overweight/obese patients, to avoid excessive energy intake; e) sugar must be avoided in diabetic or obese patients; f) protein-free products are dedicated to patients not on dialysis therapy and who need protein restriction but a high energy intake.

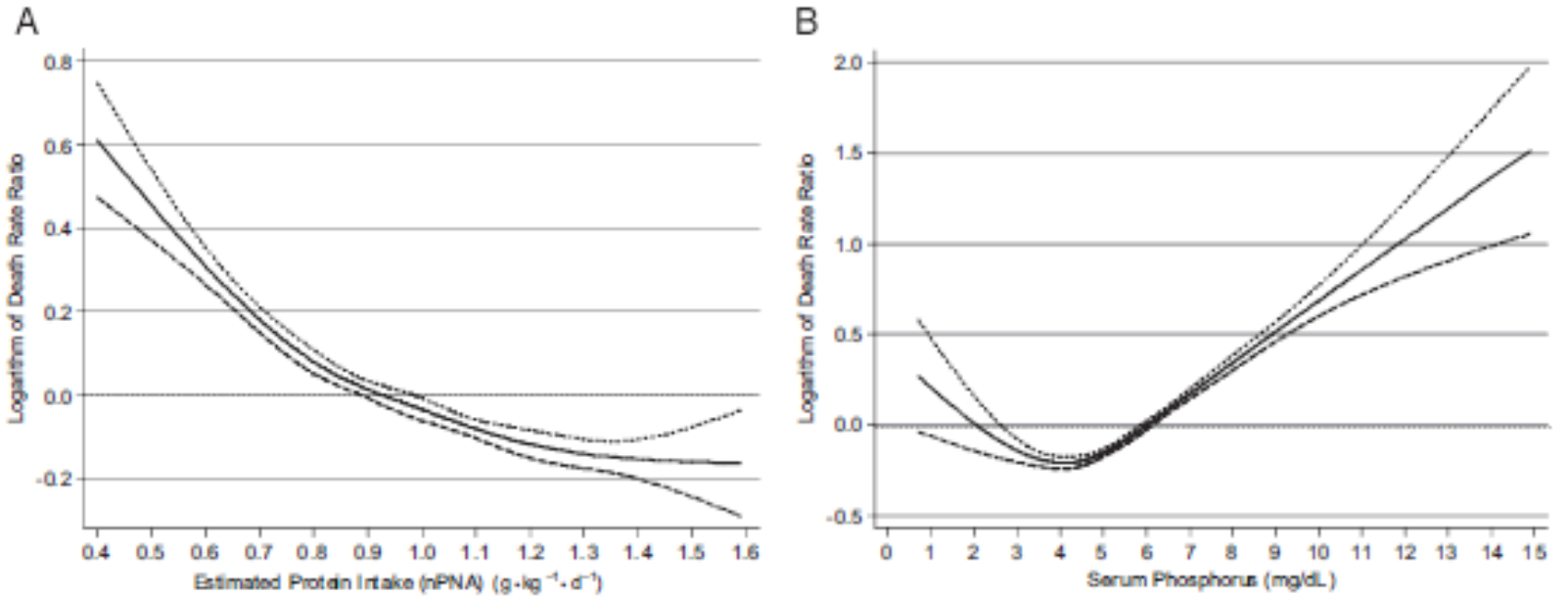
Pyramide « occidentale »

Is controlling phosphorus by decreasing dietary protein intake beneficial or harmful in persons with chronic kidney disease?[1–4]

Christian S Shinaberger, Sander Greenland, Joel D Kopple, David Van Wyck, Rajnish Mehrotra, Csaba P Kovesdy, and Kamyar Kalantar-Zadeh

Am J Clin Nutr 2008;88:1511–8.

- N=30,075 hémodialysés prévalent
- P et nPNA (normalized protein nitrogen appearence) associés à la mortalité



Is controlling phosphorus by decreasing dietary protein intake beneficial or harmful in persons with chronic kidney disease?[1–4]

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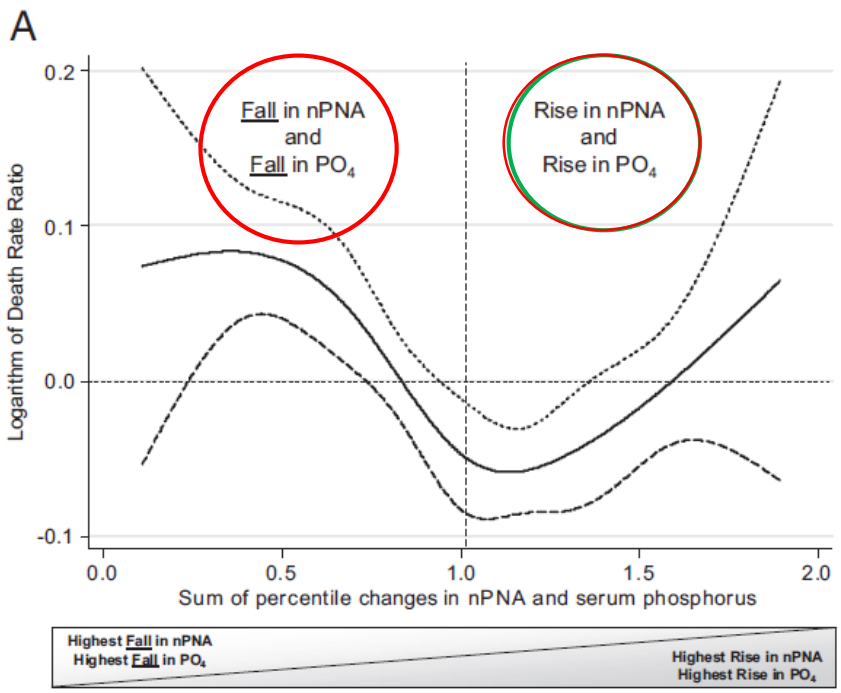
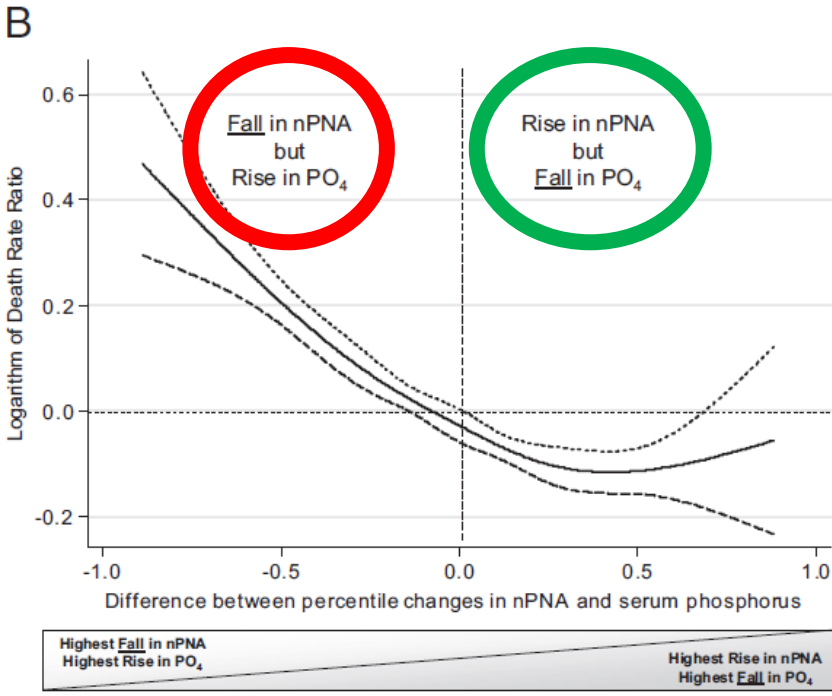
Am J Clin Nutr 2008;88:1511–8.

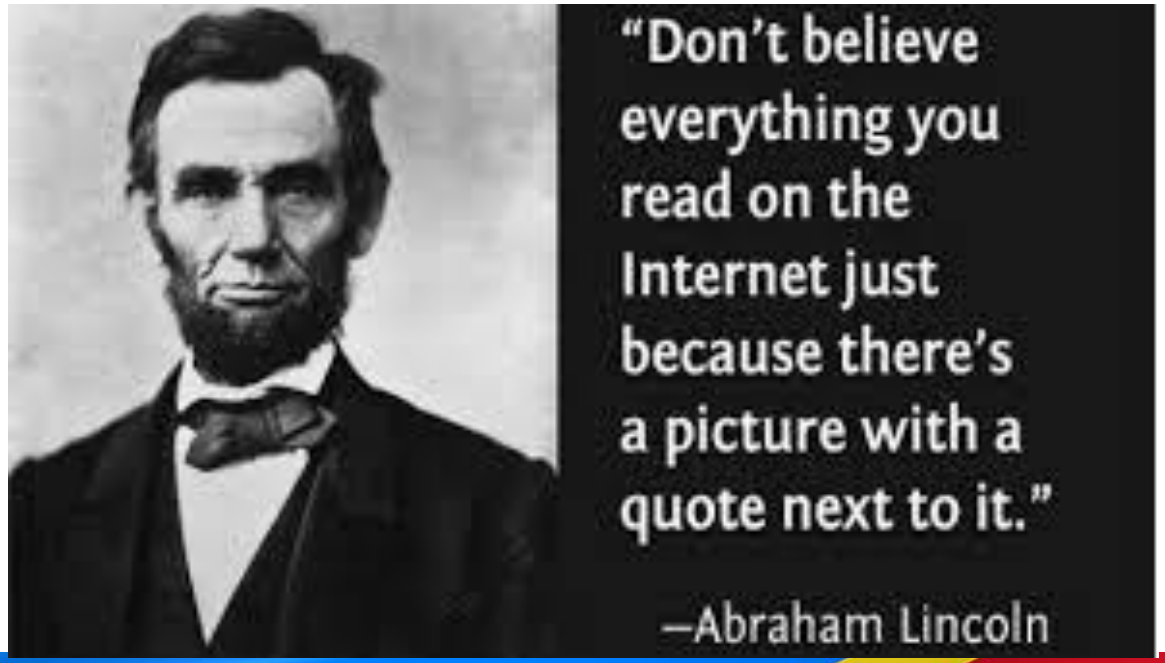
- N=30,075 hémodialysés prévalent
- ΔP et ΔnPNA (normalized protein nitrogen appearence) sur les 6 premiers mois et lien avec mortalité

Echelles!





Les chélateurs…



Calcium / Sevelamer / Lanthanum/Magnesium/Dérivés du fer

Calcium

- 1 g de carbonate calcique = 400 mg de calcium élément
- 1g d'acétate calcium = 250 mg de calcium élément
- Calcium recommandé dans l'alimentation est de 1000-1200 mg de calcium élément/j
- http://www.grio.org/espace-gp/calcul-apport-calcique-quotidien.php
- La calcémie n'est pas un reflet de la balance calcique !!
- Il y a une relation entre calcémie (peut-être quantité de calcium prise) et les CV
- Relation entre hypercalcémie et CV (et mortalité)

Spiegel DM, Kidney Int, 2012, p1116

Calcium

- Balance neutre: si régime contient 957 mg de Ca élément mg (=moyenne du régime américain)

….mais moyenne en CKD = 533 mg (et sans doute moins si dialysé et dénutri)

- Balance positive en CKD (stade 3 et 4) si 1500mg/2000 mg de calcium élément (+/- 4cp de carbonate et 6 cp d'acetate à 1g…sans compter le calcium du régime)
- Doses pour chelater le P dans les études: 1,2 à 2,3 g de calcium élément
- Idée de l'os tampon, integration de la PTH dans le concept
- Intégrer aussi la composition en Calcium dans le dialysat

Carbonate versus acetate

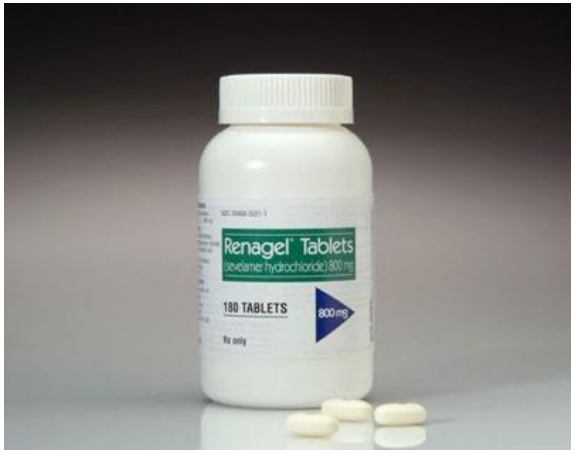
- Pas de différence en termes de tolérance
- Pas de différence en termes de calcémie
- Pas de différence en termes d'hypercalcémie
- Gain avec acétate pour le contrôle de la phosphatémie pour une méta-analyse (non pour l'autre)
- Etudes à court terme (max 24 semaines, le plus souvent 4 ou 8)
- Effet de l'acétate indépendant du pH alors que carbonate est plus efficace en milieu acide (IPP)

Navaneethan SD, Am J Kidney Dis, 2009, p619
Wang Y, PlosOne, 2015, e0121376

Est-on un assassin si on prescrit du calcium?

- Pas cher
- Efficace
- Apport en bicarbonate
- Patient dénutri
- Hypocalcémie et hyperparathyroïdie
- Moment de la prescription par apport aux repas
- Eviter l’hypercalcémie

Sevelamer (cp à 800 mg, poudre à 2,4 g)



Sevelamer (hydrochloride et carbonate)

- Même pouvoir de chélation que Calcium
- Moins d’hypercalcémie
- Calcémie moins haute et PTH plus haute

Kidney International, Vol. 62 (2002), pp. 245–252

Sevelamer attenuates the progression of coronary and aortic calcification in hemodialysis patients

GLENN M. CHERTOW, STEVEN K. BURKE, PAOLO RAGGI, for the TREAT TO GOAL WORKING GROUP[1]

- TREAT TO GOAL
- RCT, multicentrique
- 2 semaines de wash-out et si P>5,5 mg/dL => inclus
- Sevelamer (n=99) versus acetate (USA) ou carbonate (Europe) (n=101)
- 52 semaines: 12 semaines titration (/3sem)
- CAC par EBCT à 0, 26 et 52 semaines

Table 4. Absolute change from baseline calcification scores

		Sevelamer	Calcium	Between group *P* value	= 101) Final	*P* value
Phosphorus *mg/dL*	Coronary arteries at 26 weeks				5.1 ± 1.4	0.33
Calcium *mg/dL*	*N*	66	75		9.7 ± 0.7	0.002
Hypercalcemia %	Mean ± SD	−134 ± 697	110 ± 413	0.002	16%	0.04
Calcium-phosphorus product mg^2/dL^2	Median (interquartile range)	0 (−124; 53)	56 (0; 206)		49 ± 14	0.12
Intact PTH *pg/mL*	Within-group *P* value	0.51	0.0001		138	0.11
Total-C *mg/dL*	Coronary arteries at 52 weeks				182 ± 49	<0.0001
LDL-C *mg/dL*	*N*	62	70		103 ± 43	<0.0001
HDL-C *mg/dL*	Mean ± SD	−46 ± 692	151 ± 471	0.04	45 ± 12	0.16
Triglycerides *mg/dL*	Median (interquartile range)	0 (−33; 174)	37 (0; 330)		150	0.22
	Within-group *P* value	0.67	0.0002			
	Aorta at 26 weeks					
	N	66	75			
	Mean ± SD	−595 ± 1723	230 ± 1697	0.03		
	Median (interquartile range)	0 (−201; 90)	11 (−3; 201)			
	Within-group *P* value	0.27	0.02			
	Aorta at 52 weeks					
	N	62	70			
	Mean ± SD	−532 ± 1706	185 ± 3100	0.01		
	Median (interquartile range)	0 (−258; 158)	75 (0; 441)			
	Within-group *P* value	0.43	0.0007			

Hypercalcemia was defined as ca … ormone; LDL-C, low-density lipoprotein cholesterol; HDL-C, high-density lipo … evious phosphate binder. Values expressed as mean ± SD, except median for int … om baseline across treatment groups. Final values are last values carried forward

Sevelamer: 6,5 +/- 2,9g
(8 cp)
Calcium: 4,3 +/- 1,9 g
(7 phosplo et 8cp de carbonate à 500 mg)

17% des patients sous sevelamer ont au moins un épisode d'hypercalcémie versus 43% sous calcium

Effects of sevelamer and calcium-based phosphate binders on mortality in hemodialysis patients

WN Suki[1], R Zabaneh[2], JL Cangiano[3], J Reed[4], D Fischer[5], L Garrett[6], BN Ling[7,*], S Chasan-Taber[8], MA Dillon[8], AT Blair[8] and SK Burke[8]

[1]Renal Section, Department of Medicine, The Kidney Institute and Baylor College of Medicine, Houston, Texas, USA; [2]Northwest Louisiana Nephrology, Shreveport, Louisiana, USA; [3]Jose Cangiano Nephrology, San Juan, Puerto Rico, USA; [4]Nephrology Associates, Columbus, Mississippi, USA; [5]Kidney and Hypertension Center, Cincinnati, Ohio, USA; [6]Wake Nephrology, Raleigh, North Carolina, USA; [7]Mountain Kidney Associates, Asheville, North Carolina, USA and [8]Genzyme Corporation, Cambridge, Massachusetts, USA

Kidney International (2007) **72**, 1130–1137

- DCOR, multicentrique
- 2103 sujets randomisés (1053 sevelamer, 1068 calcium (acétate))
- Follow-up: 20 +/- 14 mois

Sevelamer: 6,9 g

Calcium: 5,3 g acetate et 4,9 g pour carbonate

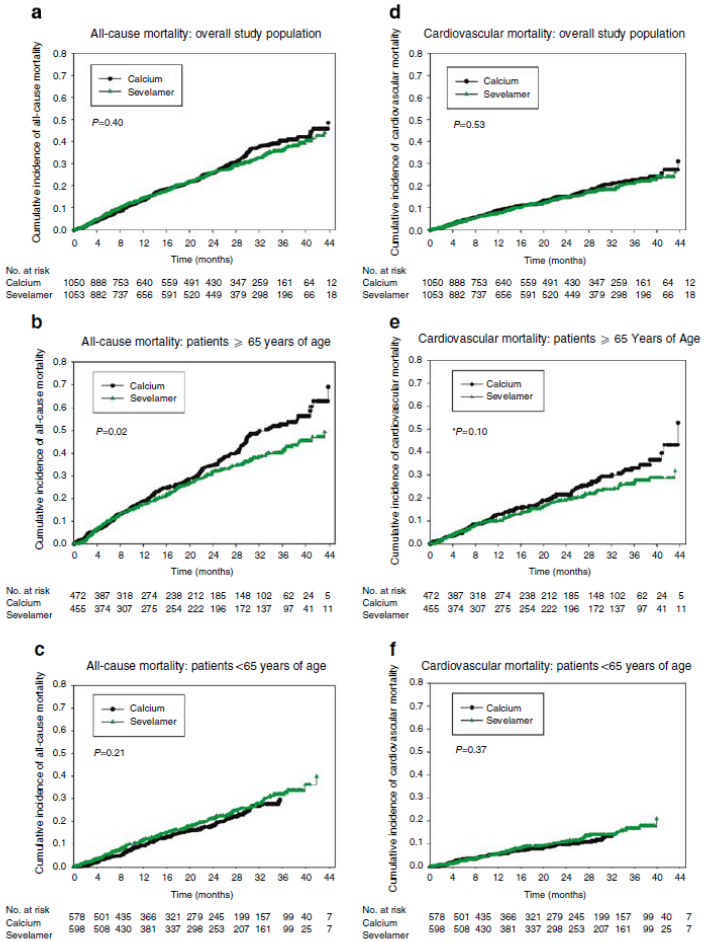


Figure 2 | Cumulative incidence of all-cause and cardiovascular mortality for the overall study population and in patients ⩾65 years of age and <65 years of age. (**a**) All-cause mortality in overall study population. (**b**) All-cause mortality in patients 65 years of age or order. (**c**) All-cause mortality in patients less than 65 years of age. (**d**) Cardiovascular mortality in overall study population. (**e**) Cardiovascular mortality in patients 65 years of age or order. (**f**) Cardiovascular mortality in patients less than 65 years of age. *This *P* value had incorrectly appeared online as *P*=0.02. This value is now corrected.

Table 3 | Time-weighted average of post-baseline assessments for serum phosphorus, calcium, calcium–phosphorus product, intact parathormone, total cholesterol , LDL-, HDL-cholesterol, and K_t/V

	Sevelamer		Calcium		
	N	Time weighted mean ± s.d.	*N*	Time weighted mean ± s.d.	*P*-value*
Phosphorus (mmol/l)	843	1.87 ± 0.42	843	1.84 ± 0.42	<0.01
Calcium (mmol/l)	835	2.30 ± 0.18	837	2.38 ± 0.18	<0.0001
Calcium × phosphorus product ($mmol^2/l^2$)	835	4.33 ± 0.98	833	4.33 ± 1.04	0.60
Intact parathormone[a] (pg/ml)	774	278 (200, 476)	768	226 (142, 387)	<0.0001
Total cholesterol (mmol/l)	526	3.77 ± 0.87	529	4.16 ± 0.90	<0.0001
LDL cholesterol (mmol/l)	197	1.78 ± 0.67	202	2.20 ± 0.80	<0.0001
HDL cholesterol (mmol/l)	247	1.17 ± 0.39	248	1.15 ± 0.41	0.62
K_t/V	823	1.6 ± 0.3	827	1.6 ± 0.3	0.11

HDL, high-density lipoprotein; LDL, low-density lipoprotein.

To convert values for phosphorus to mg/dl, divide by 0.3229. To convert values for calcium to mg/dl, divide by 0.25. To convert values for calcium × phosphorus product to mg^2/dl^2 divide by 0.0807. To convert values for cholesterol to mg/dl, divide by 0.02586.

[a]Presented as median (interquartile range).

*Wilcoxon rank sum test.

There was a suggestion that sevelamer was associated with lower overall, but not cardiovascular-linked, mortality in older patients. We suggest that further research is needed to confirm these findings.

Sevelamer Versus Calcium-Based Binders for Treatment of Hyperphosphatemia in CKD: A Meta-Analysis of Randomized Controlled Trials

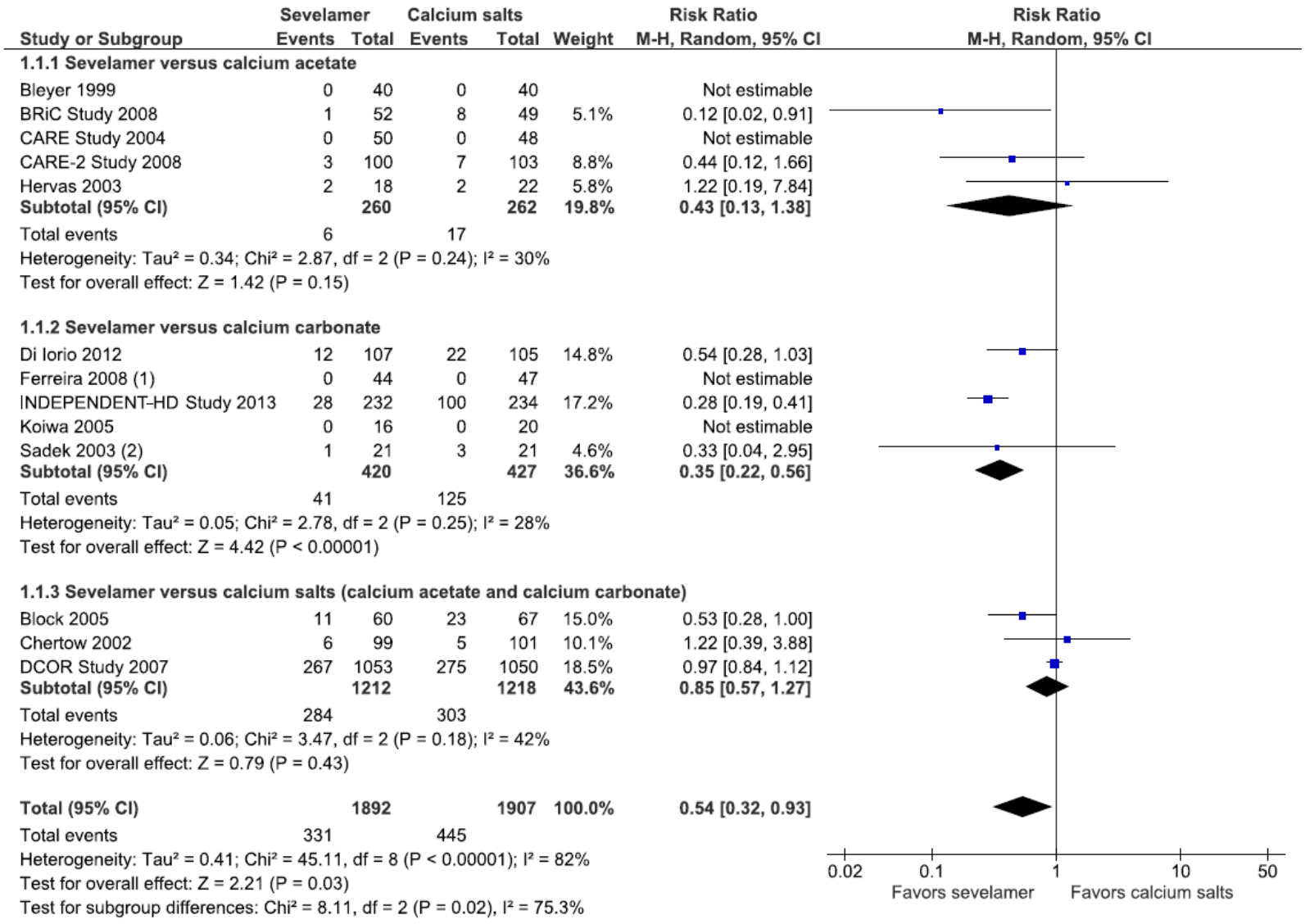
Leena Patel, Lisa M. Bernard,* and Grahame J. Elder†‡*

Clin J Am Soc Nephrol 11: 232–244, 2016

- Metanalyse
- Sevelamer car pas (peu) d'étude avec comparaison directe lanthanum/calcium ou sevelamer
- Critère de jugement principal: mortalité toute cause
- Critère de jugement secondaire: effets secondaires, CV, os, données biochimiques

Effect of sevelamer versus calcium-based binders on all-cause mortality in patients with CKD.

N=13
N=3799



Effect of sevelamer versus calcium-based binders on all-cause mortality in patients with CKD.

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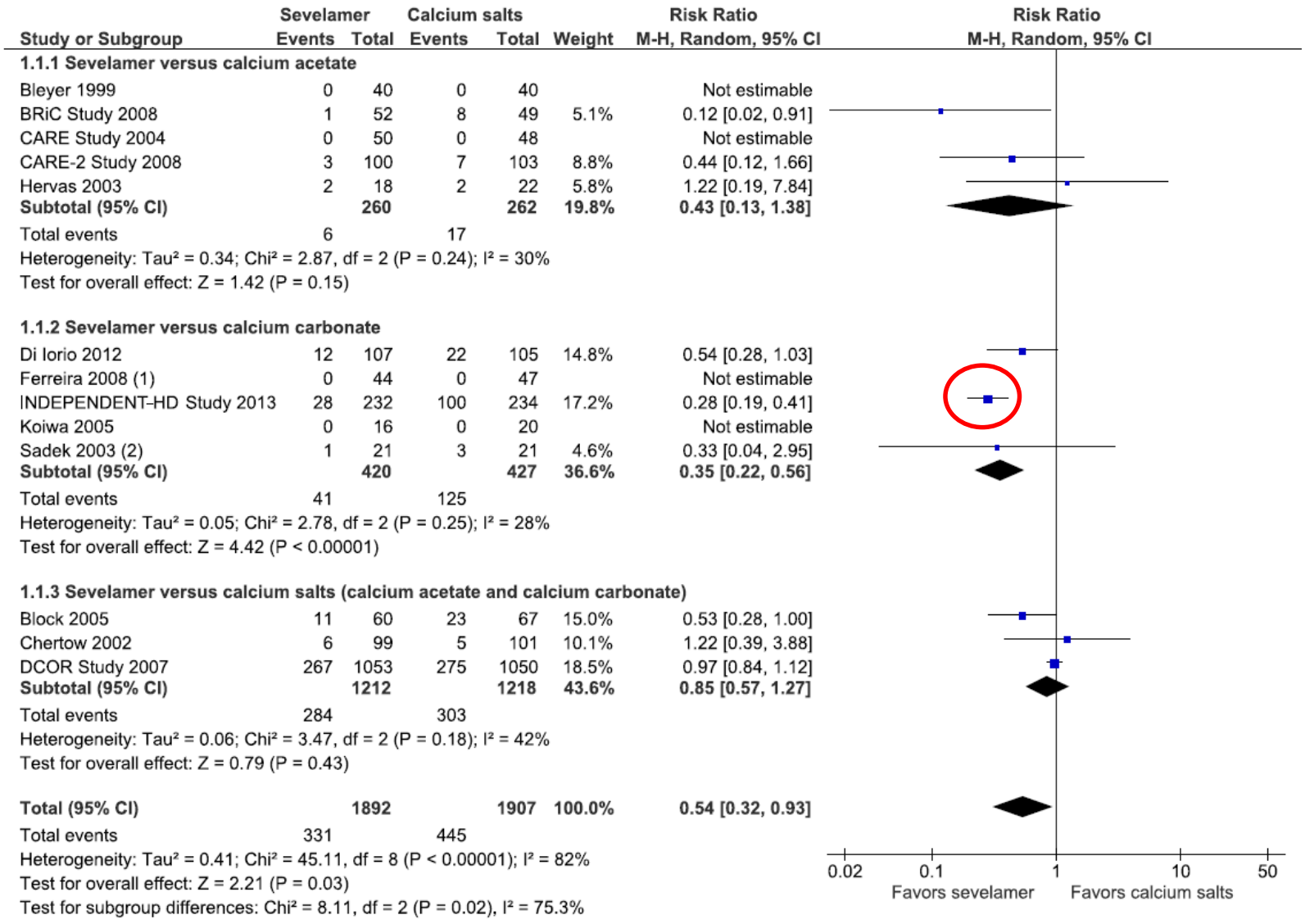

INDEPENDENT studies

AJKD

Original Investigation

Sevelamer Versus Calcium Carbonate in Incident Hemodialysis Patients: Results of an Open-Label 24-Month Randomized Clinical Trial

*Biagio Di Iorio, MD,[1] Donald Molony, MD,[2] Cynthia Bell, MS,[3] Emanuele Cucciniello, MD,[1†] Vincenzo Bellizzi, MD,[4] Domenico Russo, MD,[5] and Antonio Bellasi, MD,[6] on behalf of the INDEPENDENT Study Investigators**

Am J Kidney Dis. 62(4):771-778. © *2013*

- Sevelamer v carbonate calcique
- 18 centres en dialyse
- 28 +/- 10 mois de follow up
- Mesure tous les 6 mois
- Critère primaire = mortalité CV
- CAC

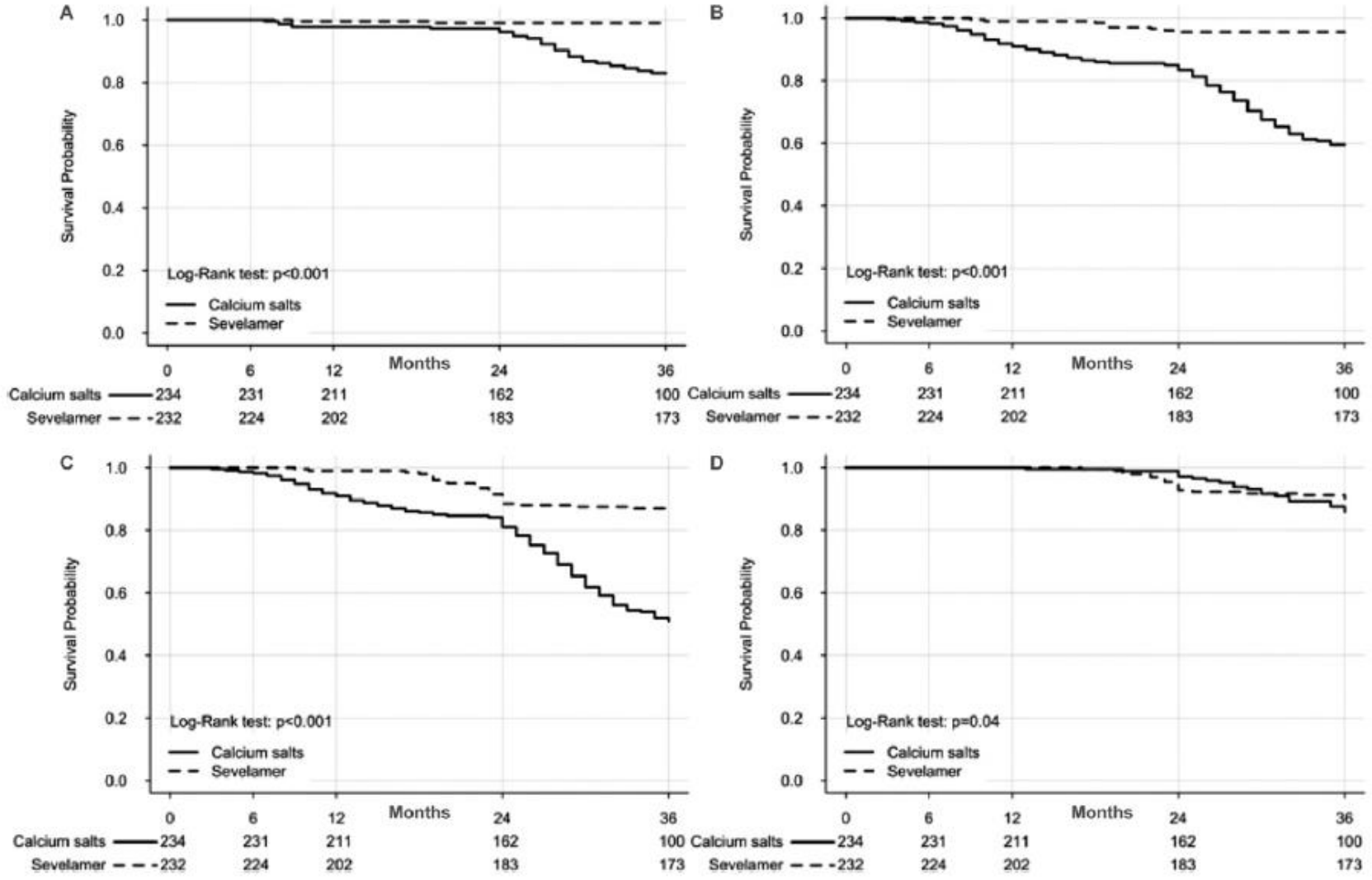

Figure 2. Kaplan-Meier (A) cardiovascular (CV) survival due to cardiac arrhythmias, (B) all-cause CV survival, (C) all-cause survival, and (D) non-CV survival according to phosphate-binder assignment.

Table 2. Mineral Metabolism Control at Study Entry and Completion Between Study Arms

	Sevelamer (n = 232)			Calcium Carbonate (n = 234)			Sevelamer vs Calcium Carbonate	
	Baseline	24 mo	Baseline vs 24 mo	Baseline	24 mo	Baseline vs 24 mo	Baseline	24 mo
Phosphorus (mg/dL)	5.6 ± 1.7	4.2 ± 1.2	−1.37 ± 1.93; $P < 0.001$	4.8 ± 1.4	4.8 ± 1.7	−0.10 ± 1.67; $P = 0.4$	0.75 ± 0.14	−0.65 ± 0.12; $P < 0.001$
Calcium (mg/dL)	8.9 ± 0.8	8.2 ± 0.5	−0.70 ± 0.91; $P < 0.001$	8.8 ± 0.7	9.6 ± 1.1	0.84 ± 1.21; $P < 0.001$	0.15 ± 0.07	−1.37 ± 0.09; $P < 0.001$
Intact PTH (pg/mL)	208 [135-265]	120 [78-137]	−153.7 ± 188.4; $P < 0.001$	218 [135-283]	240 [142-398]	2.1 ± 313.5; $P = 0.4$	17.5 ± 19.2	−173.7 ± 15.85; $P < 0.001$

Note: Values are given as mean ± standard deviation or median [interquartile range]. Conversion factors for units: phosphorus in mg/dL to mmol/L, ×0.3229; calcium in mg/dL to mmol/L, ×0.2495.
Abbreviation: PTH, parathyroid hormone.

CAC: plus bas dans le groupe sevelamer au départ…

Sevelamer: 4,3 +/- 1,4g

Calcium: 2,2 +/- 1,0 g
(7cp phosplo et 8cp de carbonate à 500 mg)

Sevelamer

- Efficace
- Moins d'hyperCa, moins d'os adynamique
- Gain en mortalité: oui, peut-être
- Ces études (mortalité, CAC…) ont le mérite d'exister…
- Nbr de comprimés élevé
- Effet sur cholestérol
- Cost-effectiveness par rapport au calcium: douteux

Fosrénol cp à (250), 500, 750 et 1000 mg, poudre à 750 et 1000 mg

- Globalement, mêmes résultats que sevelamer avec le calcium comme comparateur mais moins de cp de lanthanum
- 2 études de comparaison directe sevelamer - lanthanum

	Sprague	Kasai
n	181 (cross-over)	42 (cross-over)
Follow-up	4 sem	13 sem
Doses	Fixe: 4,8 à 6,4 g/2,25-3g	2,971g/945 mg
Contrôle P	idem	idem
ES	idem	idem

Sprague SM, Clin Nephrol, 2009, p252 and Kasai S, Ther Apher Dial, 2012, p341

Research

JAMA | Original Investigation

Effect of Treating Hyperphosphatemia With Lanthanum Carbonate vs Calcium Carbonate on Cardiovascular Events in Patients With Chronic Kidney Disease Undergoing Hemodialysis

The LANDMARK Randomized Clinical Trial

JAMA. 2021 May 18;325(19):1946-1954.

Hiroaki Ogata, MD; Masafumi Fukagawa, MD; Hideki Hirakata, MD; Tatsuo Kagimura, PhD; Masanori Fukushima, MD; Tadao Akizawa, MD; for the LANDMARK Investigators and Committees

1063 patients (prévalent) dans le groupe lanthanum vs 1072 dans le groupe calcium

1 facteur de risque de CV (+65 ans, ménopause, diabète) et PTH<240 pg/ml

Suivi moyen de 3,16 ans

Primaire: Composite CV

Research

JAMA | Original Investigation

Effect of Treating Hyperphosphatemia With Lanthanum Carbonate vs Calcium Carbonate on Cardiovascular Events in Patients With Chronic Kidney Disease Undergoing Hemodialysis

The LANDMARK Randomized Clinical Trial

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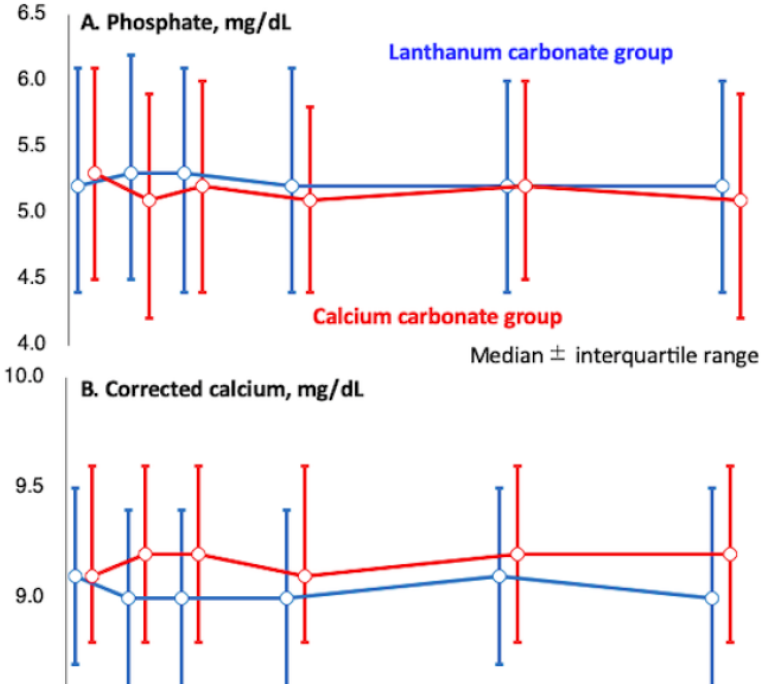
1063 patients (prévalent) dans le groupe lanthanum vs 1072 dans le groupe ca

1 e, diab

Su

Pr



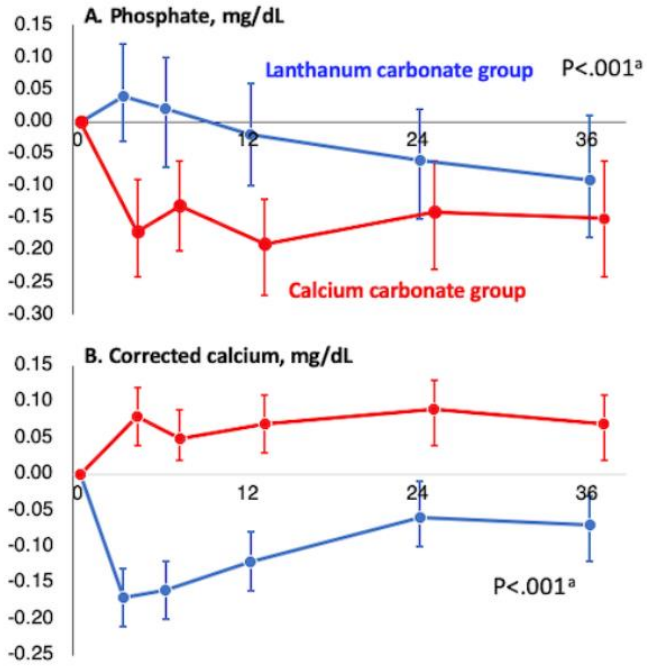


Figure 2. Primary Composite and All-Cause Mortality Outcomes

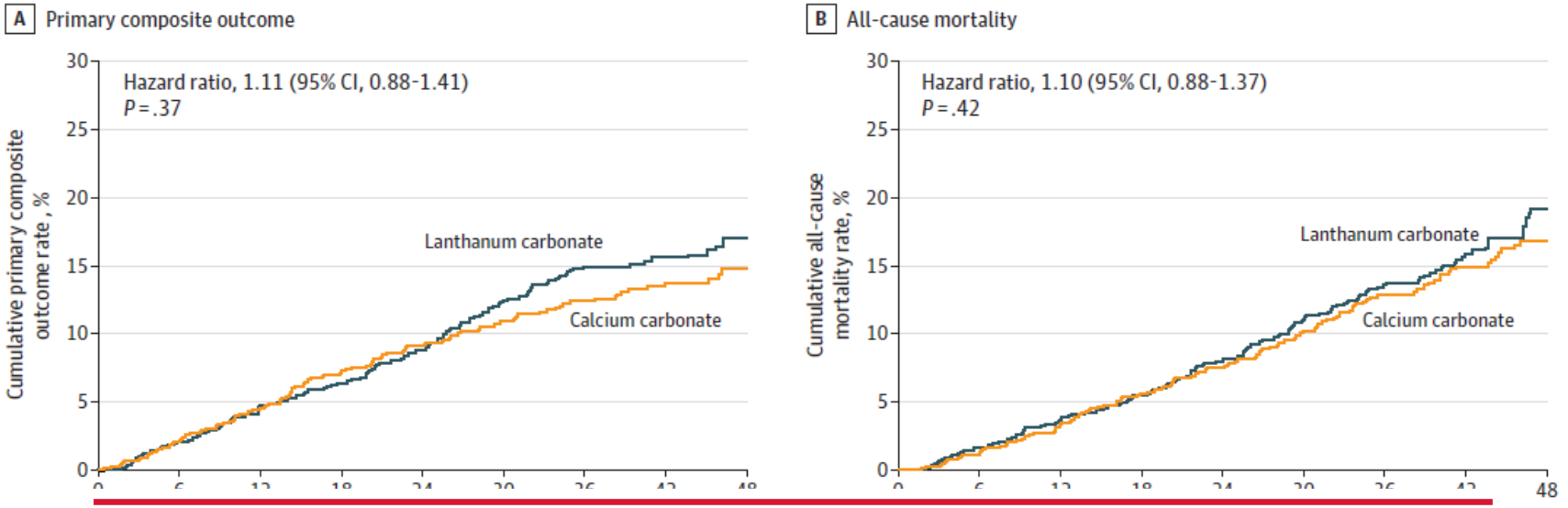


Table 2. Primary and Secondary Outcomes

Outcomes	Rate per 100 person-years (95% CI)		Absolute difference (95% CI)	Hazard ratio (95% CI)[a]	*P* value
	Lanthanum carbonate (n = 1063)	Calcium carbonate (n = 1072)			
Primary composite outcome[b]	4.80 (4.17 to 5.50)	4.30 (3.71 to 4.96)	0.50 (−0.57 to 1.56)	1.11 (0.88 to 1.41)	.37
Events, No.	147	134			
Secondary outcomes[c]					
All-cause death	4.96 (4.33 to 5.65)	4.53 (3.93 to 5.19)	0.43 (−0.63 to 1.49)	1.10 (0.88 to 1.37)	.42
No.	159	148			
Cardiovascular death	1.81 (1.44 to 2.25)	1.19 (0.90 to 1.56)	0.61 (0.02 to 1.21)	1.51 (1.01 to 2.27)	.045
No.	58	39			
Secondary hyperparathyroidism	3.51 (2.97 to 4.13)	2.17 (1.76 to 2.66)	1.34 (0.49 to 2.19)	1.62 (1.19 to 2.20)	.002
No.	105	68			
Hip fracture	0.60 (0.39 to 0.88)	0.49 (0.31 to 0.75)	0.10 (−0.26 to 0.47)	1.21 (0.62 to 2.35)	.58
No.	19	16			

[a] The adjusted hazard ratio was calculated using a proportional hazard model adjusted for age, presence or absence of diabetes, and sex.

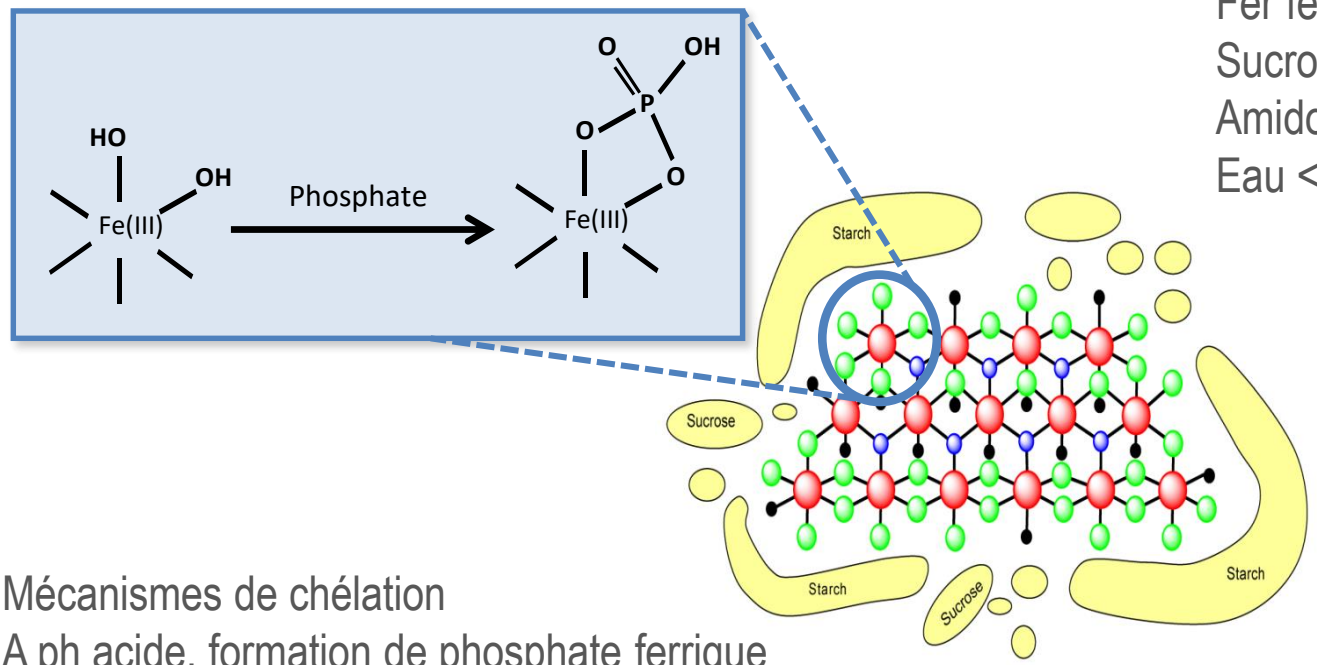
[b] The primary outcome was a composite of cardiovascular death, nonfatal myocardial infarction or stroke, unstable angina, and hospitalization for heart failure or ventricular arrhythmia.

[c] The CI values for the secondary end points were not adjusted for multiple comparisons.

Velphoro (cp à 500 mg)

Oxyhydroxide Sucroferrique

Fer ferrique 21%
Sucrose 30%
Amidon 30%
Eau < 10%



Mécanismes de chélation
A ph acide, formation de phosphate ferrique
A ph moins acide, adsorption de PO4-- sur
le complexe polynucléaire d'oxydroxide de fer

Randomized Clinical Trial of the Iron-Based Phosphate Binder PA21 in Hemodialysis Patients

Rudolf P. Wüthrich, Michel Chonchol,† Adrian Covic,‡ Sylvain Gaillard,§ Edward Chong,‖ and James A. Tumlin¶*

Clin J Am Soc Nephrol 8: 280–289, 2013.

- Oxyhydroxide sucroferrique
- Base de fer, cp (à 250 mg)et 500 mg (=quantité de Fer III)
- Chélation débute dans l'estomac
- La partie « ferrique » n'est (quasi) pas absorbable (0,3%)
- Interactions avec doxycycline and levo thyroxine
- Etude de phase II (6 semaines) chez 154 hémodialysés avec comme comparateur le sevelamer **4,8g/jour**: dose (cp à 250mg) soit 1cp, 4cp, 6cp 8cp ou 10cp/j
- 4 et 6 cp à 250 mg/j ont la même efficacité que 4,8g sevelamer

Table 2. Change in laboratory values from baseline to end of treatment according to treatment group (efficacy population)

	PA21					Sevelamer-HCl (*n*=24)
	1.25 g/d (*n*=26)	5.0 g/d (*n*=26)	7.5 g/d (*n*=25)	10.0 g/d (*n*=25)	12.5 g/d (*n*=24)	
Serum phosphorus (mg/dl)						
Baseline	6.82±1.64	6.61±1.08	6.85±1.15	6.77±1.75	6.47±1.19	6.94±1.61
End of treatment	6.69±2.05	5.53±1.94	5.60±1.18	4.77±1.92	4.78±1.67	5.88±1.47
Change	−0.13±2.01	−1.08±2.12	−1.25±1.21	−2.00±1.71	−1.69±1.81	−1.06±1.35

Table 4. Adverse events according to treatment group (safety population)

	PA21						Sevelamer-HCl (*n*=26)
	1.25 g/d (*n*=26)	5.0 g/d (*n*=26)	7.5 g/d (*n*=25)	10.0 g/d (*n*=27)	12.5 g/d (*n*=24)	All (*n*=128)	
Any adverse event	14 (53.8)	16 (61.5)	13 (52.0)	18 (66.7)	17 (70.8)	78 (60.9)	15 (57.7)
Any severe adverse event	2 (7.7)	1 (3.8)	0	1 (3.7)	0	4 (3.1)	1 (3.8)
Any serious adverse event	2 (7.7)	2 (7.7)	1 (4.0)	1 (3.7)	2 (8.3)	8 (6.3)	2 (7.7)
Discontinuation of study or treatment due to adverse event	5 (19.2)	5 (19.2)	4 (16.0)	8 (29.6)	5 (20.8)	27 (21.1)	6 (23.1)
Adverse events[a]							
Hypophosphatemia	2 (7.7)	4 (15.4)	2 (8.0)	8 (29.6)	7 (29.2)	23 (18.0)	3 (11.5)
Hyperphosphatemia	5 (19.2)	3 (11.5)	1 (4.0)	1 (3.7)	0	10 (7.8)	2 (7.7)
Hypercalcemia	2 (7.7)	2 (7.7)	1 (4.0)	1 (3.7)	1 (4.2)	7 (5.5)	2 (7.7)
Discolored feces	2 (7.7)	3 (11.5)	3 (12.0)	4 (14.8)	3 (12.5)	15 (11.7)	0
Diarrhea	1 (3.8)	2 (7.7)	2 (8.0)	1 (3.7)	1 (4.2)	7 (5.5)	3 (11.5)
Constipation	0	1 (3.8)	1 (4.0)	2 (7.4)	0	4 (3.1)	0
Vomiting	0	2 (7.7)	0	1 (3.7)	0	3 (2.3)	1 (3.8)
Muscle spasms	1 (3.8)	1 (3.8)	2 (8.0)	1 (3.7)	3 (12.5)	8 (6.3)	0
Pain in extremity	1 (3.8)	1 (3.8)	1 (4.0)	0	0	3 (2.3)	1 (3.8)
Hypertension	1 (3.8)	0	2 (8.0)	0	2 (8.3)	5 (3.9)	1 (3.8)
Hypotension	0	1 (3.8)	0	0	0	1 (0.8)	3 (11.5)
Anemia	0	0	3 (12.0)	0	0	3 (2.3)	0

Values are shown as *n* (%).
[a]Any adverse event reported by >1 participant in any treatment group or >2 participants in the pooled PA21 group.

Nephrol Dial Transplant (2015) 30: 1037–1046
doi: 10.1093/ndt/gfv006
Advance Access publication 16 February 2015

Long-term effects of the iron-based phosphate binder, sucroferric oxyhydroxide, in dialysis patients

Jürgen Floege[1], Adrian C. Covic[2], Markus Ketteler[3], Johannes F.E. Mann[4], Anjay Rastogi[5], Bruce Spinowitz[6], Edward M.F. Chong[7], Sylvain Gaillard[7], Laura J. Lisk[7] and Stuart M. Sprague[8], on behalf of the Sucroferric Oxyhydroxide Study Group

- 143 sites

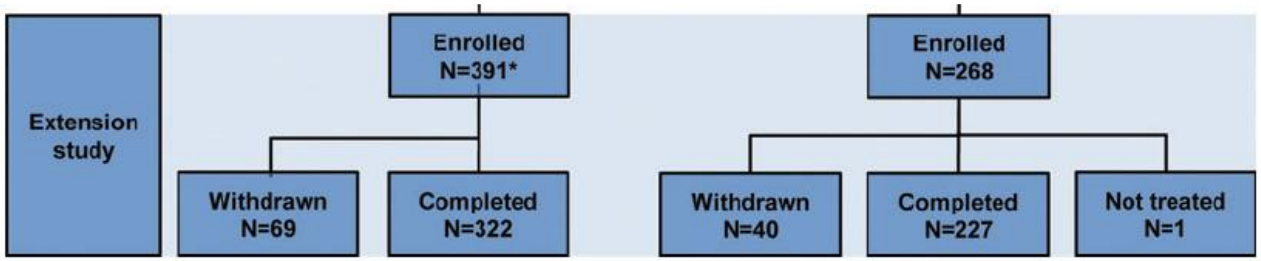
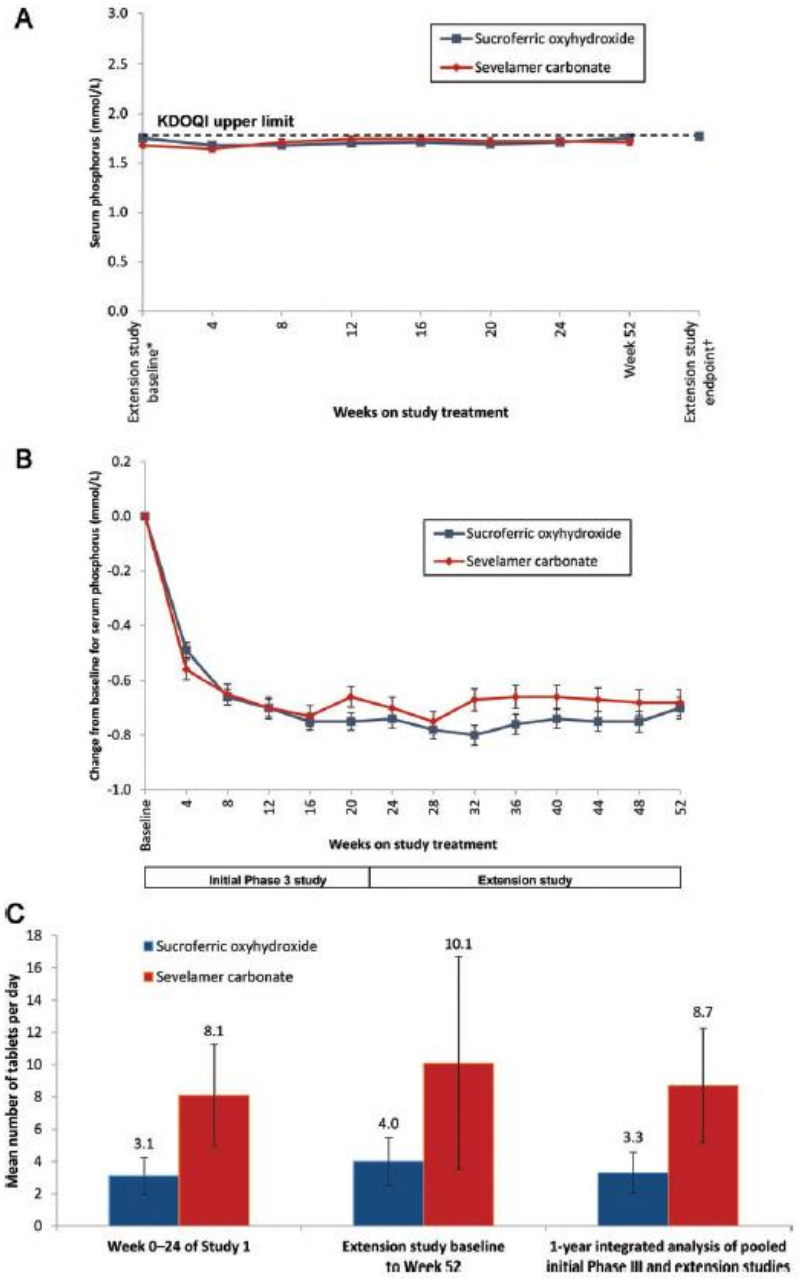


FIGURE 2: Patient disposition. *Comprises 344 patients who progressed directly to the extension study from Stage 1 of the initial Phase III study, 42 patients who completed Stage 2, as well as 5 patients who received extension study drug in error during Stage 2 and were subsequently transferred into the extension study. LD, low dose; MD, maintenance dose.

- Randomisation OK



idem

FIGURE 3: Serum phosphorus control and pill burden. (**A**) Mean (± standard error of the mean) serum phosphorus concentrations during the extension study (FAS-ext; $N = 644$). *Last available value prior to or on the date of the first extension study drug intake; †Last observation carried forward; KDOQI, Kidney Disease Outcomes Quality Initiative. (**B**) Mean change (± standard error of the mean) from baseline in serum phosphorus concentrations over 1 year (FAS-ext; $N = 644$). (**C**) Mean (± standard deviation) number of phosphate binder tablets per day (SS-ext; $N = 658$).

Table 4. Treatment-emergent adverse events (in order of frequency for sucroferric oxyhydroxide group) occurring in ≥5% of patients in either treatment arm during the extension study (SS-ext; *N* = 658)

Event, *n* (%)	Sucroferric oxyhydroxide (*n* = 391)	Sevelamer carbonate (*n* = 267)
Any TEAE	289 (73.9)	205 (76.8)
Any related TEAE	57 (14.6)	24 (9.0)
Any serious TEAE	78 (19.9)	52 (19.5)
Any severe TEAE	40 (10.2)	27 (10.1)
Withdrawals due to TEAEs	32 (8.2)	13 (4.9)
Death	7 (1.8)	7 (2.6)
Hyperphosphatemia	47 (12.0)	29 (10.9)
Hypertension	38 (9.7)	20 (7.5)
Diarrhea	32 (8.2)	15 (5.6)
Muscle spasms	26 (6.6)	16 (6.0)
Nausea	23 (5.9)	11 (4.1)
Hypophosphatemia	22 (5.6)	14 (5.2)
Headache	20 (5.1)	8 (3.0)
Hypotension	19 (4.9)	21 (7.9)
Hyperkalemia	17 (4.3)	16 (6.0)
Secondary hyperparathyroidism	15 (3.8)	23 (8.6)
Anemia	15 (3.8)	15 (5.6)

TEAE, treatment-emergent adverse event.

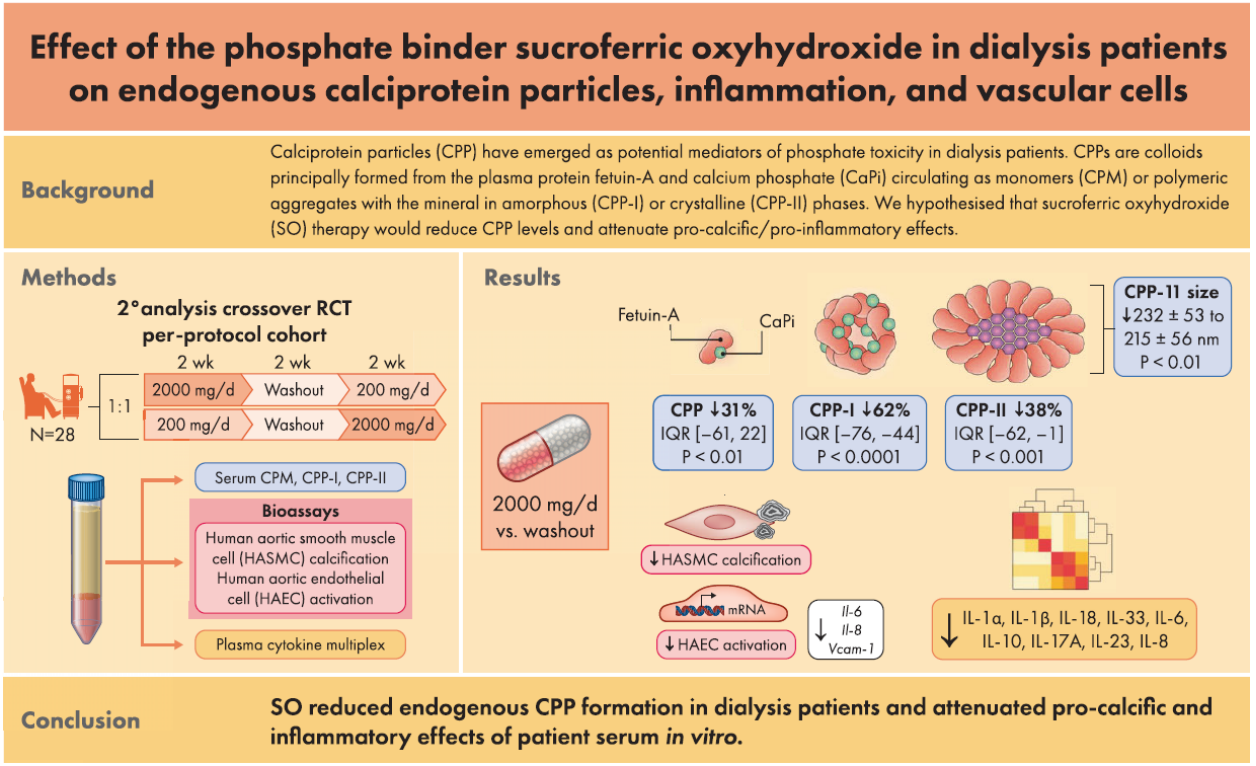
P=????

- Comparaison avec le sevelamer
- Même contrôle du P avec moins de comprimés (3cp de velphoro quand même)
- Meilleure compliance (cost-effectiveness): Gutzwiller FS, PharmacoEconomics 2015, p1311, Scottish NHS)
- Coloration des selles (gravité?)
- Diarrhées
- Comparaison lanthane, sevelamer poudre?
- Comparaison autres dérivés ferriques?
- Tolérance à long terme
- Critères de jugement « durs »: Cal Vasc (données animales+), mortalité – événements CV?

Nephrol Dial Transplant (2023) 38: 1282–1296
https://doi.org/10.1093/ndt/gfac271
Advance Access publication date 15 September 2022

Effect of the phosphate binder sucroferric oxyhydroxide in dialysis patients on endogenous calciprotein particles, inflammation and vascular cells

Ursula Thiem[1,2], Tim D. Hewitson[3,4], Nigel D. Toussaint[3,4], Stephen G. Holt[4], Maria C. Haller[1,5], Andreas Pasch[6,7,8], Daniel Cejka[1] and Edward R. Smith[3,4]



Magnésium

- Renepho: Acétate de calcium 435 mg équivalent à 110 mg de calcium élément et carbonate de magnésium, 235 mg correspondant à 60 mg de magnésium
- Tzanakis et al: 6 mois: MgCa (1552 mg) aussi efficace de Carbonate Ca (2,839g/j) avec bain en Mg à 0,6meq/L pour prévenir hyperMg
- Etude CALMAG: RCT, 24 semaines n =204 (dialysés), comparateur = sevelamer, Mg pas inférieur, même ES mais Magnésemie plus haute (1,3 v 1,0 mmol/L), nbr de cp un peu plus haut avec sevelamer (8,1 v 7,3)
- Effet à long terme =? (os adynamique? Ca = Mg)
- Effet sur CV (animal)

AJKD
Original Investigation

Phosphate-Binding Agents in Adults With CKD: A Network Meta-analysis of Randomized Trials

Suetonia C. Palmer, PhD,[1] Sharon Gardner, MA,[1] Marcello Tonelli, MD,[2] Dimitris Mavridis, PhD,[3,4] David W. Johnson, PhD,[5] Jonathan C. Craig, PhD,[6] Richard French, MBChB,[7] Marinella Ruospo, MScMed,[8,9] and Giovanni F.M. Strippoli, PhD[6,9,10]

Am J Kidney Dis. 68(5):691-702. © 2016

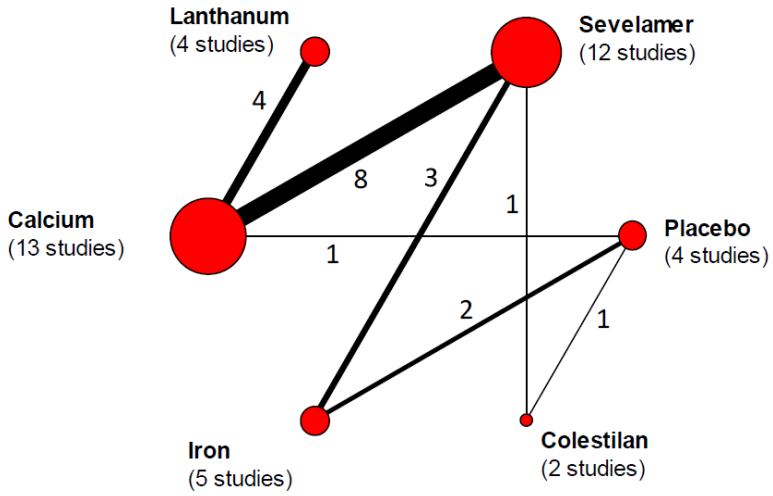
- Network meta-analysis
- Critère de jugement principal: mortalité tout cause
- Critère de jugement secondaire: mortalité CV, infar, stroke, nausée, constipation, diarrhée, contrôle du P, phosphorémie, hypercalcémie, CAC

- 77 RCT, n=12,562
- Risque de biais élevé, hétérogénéité élevée
- Sevelamer, lanthanum, calcium, dérivés fer, Mg, acide nicotinique, colestilan, bixalomer

Follow up (suivi médian)

- Placebo: 4 semaines à 3 mois
- Sevelamer v calcium: 15 mois
- Sevelamer v fer: 3 mois
- Lanthanum v calcium: 12 mois

Mortalité toute cause



N'est plus significatif quand l'étude INDEPEDENT (dialyse) est exclue…alors que exclure cette étude diminue l'hétérogénéité

Sevelamer					
0.50 (0.09, 2.65)	Lanthanum				
0.39 (0.21, 0.74)	0.78 (0.16, 3.72)	Calcium			
1.04 (0.27, 3.97)	2.08 (0.26, 16.5)	2.67 (0.63, 11.4)	Iron		
0.71 (0.09, 5.46)	1.42 (0.12, 17.4)	1.82 (0.23, 14.7)	0.68 (0.07, 6.40)	Colestilan	
0.47 (0.08, 2.59)	0.93 (0.11, 8.05)	1.20 (0.21, 6.77)	0.45 (0.08, 2.66)	0.66 (0.10, 4.29)	Placebo

- Pas assez de donnée pour analyser la mortalité CV, infar et AVC
- Nausées: plus avec le lanthanum comparé au calcium et fer
- Constipation: plus avec sevelamer que calcium, fer et lanthanum
- Diarrhée: plus avec fer que calcium
- CAC: diminue avec sevelamer plus que calcium
- Hypercalcémie et « target » de P

	Achieving serum phosphorus target								
Hypercalcemia	**Sevelamer**	1.43 (0.56, 3.61)	1.64 (0.70, 3.89)	**0.55 (0.30, 0.99)**	0.82 (0.28, 2.39)	1.57 (0.31, 7.86)	1.14 (0.13, 9.79)	0.97 (0.11, 8.69)	6.92 (0.00, 15.9)
	1.61 (0.46, 5.61)	**Lanthanum**	1.15 (0.56, 2.36)	**0.38 (0.16, 0.94)**	0.57 (0.15, 2.12)	1.09 (0.17, 7.02)	0.80 (0.10, 6.48)	0.67 (0.06, 7.30)	**4.82 (2.79, 8.34)**
	0.14 (0.07, 0.29)	**0.09 (0.03, 0.25)**	**Calcium**	**0.33 (0.14, 0.82)**	0.50 (0.14, 1.82)	0.96 (0.15, 5.93)	0.69 (0.10, 4.97)	0.59 (0.06, 6.22)	**4.20 (2.02, 8.74)**
	1.44 (0.12, 16.8)	0.90 (0.06, 14.1)	9.96 (0.77, 128)	**Iron**	1.48 (0.45, 4.85)	2.85 (0.51, 15.9)	2.08 (0.24, 18.1)	1.76 (0.18, 17.1)	**12.6 (5.79, 27.2)**
	--	--	--	--	**Bixalomer**	1.92 (0.28, 13.3)	1.39 (0.13, 14.8)	1.18 (0.10, 13.6)	**8.47 2.45, 29.2**
	--	--	--	--	–	**Nicotinic acid**	0.73 (0.05, 10.7)	0.62 (0.04, 9.38)	4.40 (0.72, 27.0)
	--	--	--	--	–	--	**Calcium + magnesium**	0.85 (0.04, 18.3)	6.05 (0.74, 49.4)
	0.52 (0.06, 4.33)	0.33 (0.03, 3.80)	3.62 (0.39, 33.6)	0.36 (0.01, 9.30)	–	--	--	**Sevelamer + calcium**	7.10 (0.68, 74.3)
	2.39 (0.20, 28.5)	1.48 (0.11, 19.7)	**16.4 (1.49, 181)**	1.66 (0.05, 54.5)	–	--	--	4.52 (0.18, 118)	**Placebo**

Conclusions: There is currently no evidence that phosphate-binder treatment reduces mortality compared to placebo in adults with CKD. It is not clear whether the higher mortality with calcium versus sevelamer reflects whether there is net harm associated with calcium, net benefit with sevelamer, both, or neither. Iron-based binders show evidence of greater phosphate lowering that warrants further examination in randomized trials.
Am J Kidney Dis. 68(5):691-702.

Divers, autres et/ou futur

- Cinacalcet (vitamine D native/active)
- Nicotinamide (Medice)
- Citrate ferrique (Keryxs Biopharma), Iron-Magnesium Hydroxycarbonate (OPKO)
- Polymère: Colestilan (Mitsubishi), Bixalomer (Amgen)
- Tenapanor: inhibition du récepteur de la réabsoption intestinale passive du P (NHE3)
- Autres inhibiteurs du NaPi2b Pit1 et Pit2 (EOS789, phase 1)

Modified-release nicotinamide for the treatment of hyperphosphataemia in haemodialysis patients: 52-week efficacy and safety results of the phase III randomised controlled NOPHOS trial

Background

Modified-release nicotinamide (NAMR) was superior to placebo in reducing serum phosphate concentrations over 12 weeks in a large cohort of haemodialysis patients with hyperphosphataemia in spite of treatment with one or two phosphate binders. Here, long-term follow-up outcomes after 52 weeks of treatment are presented.

Methods

96 sites
(Germany, Poland, Austria)

Haemodialysis patients
Intake of 1 or 2 phosphate binders
Serum phosphate > 4.5 mg/dl

3:1

NAMR
N = 539

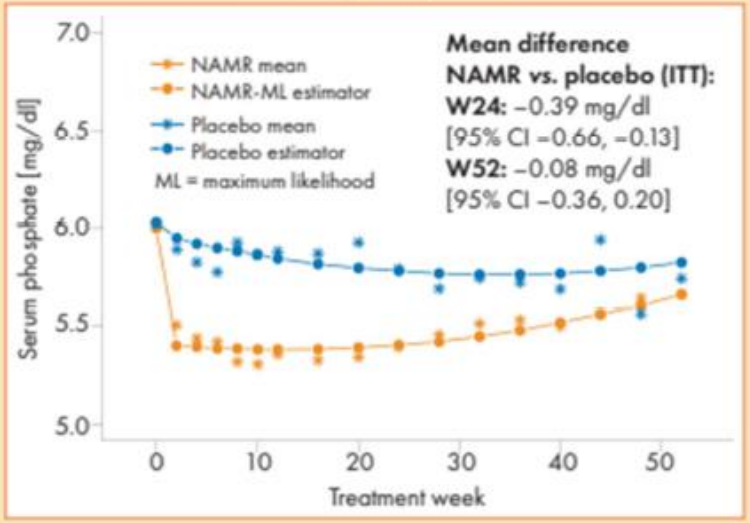
Add-on therapy

Placebo
N = 183

Follow-up: 52 weeks

Results

Serum phosphate



Adverse events

NAMR was associated with an increased risk of:

- Diarrhoea
- Anaemia
- Thrombocytopenia
- Pruritus
- Herpes zoster

Conclusion

NAMR combined with phosphate binders significantly reduced serum phosphate over the first 24 weeks of treatment, but the treatment effect was not maintained up to week 52.

ERA NDT NEPHROLOGY DIALYSIS TRANSPLANTATION

Ketteler, M., et al. NDT (2022)
@NDTSocial

Dose-Response of Tenapanor in Patients with Hyperphosphatemia Undergoing Hemodialysis in Japan- A Phase 2 Randomized Trial

ISN INTERNATIONAL SOCIETY OF NEPHROLOGY

Multicenter
Parallel group

Double blind

N = 207
Patients on hemodialysis

Phosphorus
6.1 – 9.9 mg/dL
Post phosphate binders washout

RANDOMIZATION

6-week treatment period

	Change in phosphorus	Diarrhea
Placebo	0.64 mg/dL	9.8%
5mg BID	-0.93 mg/dL *P<0.001*	50.0%
10mg BID	-1.36 mg/dL *P<0.001*	65.9%
30mg BID	-1.92 mg/dL *P<0.001*	76.2%
30mg BID Down titration	-1.99 mg/dL *P<0.001*	65.9%

KI REPORTS
Kidney International Reports

Inaba et al, 2022

Visual abstract by:
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Conclusion In Japanese hemodialysis patients, tenapanor showed a dose-responsive, serum phosphorus level-lowering effect. Diarrhea was the most frequent drug-related adverse effect; most cases were mild and generally tolerable.

Cibles??

KDIGO 2016 CLINICAL PRACTICE GUIDELINE UPDATE ON DIAGNOSIS, EVALUATION, PREVENTION AND TREATMENT OF CKD-MBD

2017 revised KDIGO CKD-MBD recommendations

4.1.6. In adult patients with CKD G3a–G5D receiving phosphate-lowering treatment, we suggest restricting the dose of calcium-based phosphate binder (*2B*).

4.1.4: In patients with CKD G5D, we suggest using a dialysate calcium concentration between 1.25 and 1.50 mmol/l (2.5 and 3.0 mEq/l) (*2C*).

4.1.7: In patients with CKD G3a-G5D, we recommend avoiding the long-term use of aluminum-containing phosphat binders and, in patients with CKD G5D, avoiding dialysate aluminum contamination to prevent aluminu intoxication (*1C*).

4.1.9: In patients with CKD G5D, we suggest increasing dialytic phosphate removal in the treatment of persiste hyperphosphatemia (*2C*).

2017 (?)

2009 (?)

4.1.2. In patients with CKD Stages 3a-5D, we suggest lowering elevated phosphorus levels towards the normal range. (*2C*)	4.1.1. In patients with CKD stages 3–5, we suggest maintaining serum phosphorus in the normal range (*2C*). In patients with CKD stage 5D, we suggest lowering elevated phosphorus levels toward the normal range (*2C*).	There is an absence of data that efforts to maintain phosphorus in the normal range are of benefit to CKD Stage 3a-4 patients, including some safety concerns. Treatment should aim at overt hyperphosphatemia.
4.1.1. In patients with CKD Stages 3a-5D, treatments of CKD-MBD should be based on serial assessments of phosphorus, calcium and PTH levels, considered together. (*Not Graded*)		This new recommendation was provided in order to emphasize the complexity and interaction of CKD-MBD laboratory parameters.

4.1.3: In adult patients with CKD G3a–G5D, we suggest avoiding hypercalcemia (*2C*).

CLINICAL RESEARCH www.jasn.org

Optimal Phosphate Control Related to Coronary Artery Calcification in Dialysis Patients

Yoshitaka Isaka,[1] Takayuki Hamano,[1,2] Hideki Fujii,[3] Yoshihiro Tsujimoto,[4] Fumihiko Koiwa,[5] Yusuke Sakaguchi,[1] Ryoichi Tanaka,[6,7] Noriyuki Tomiyama,[8] Fuminari Tatsugami,[9] and Satoshi Teramukai[10]

J Am Soc Nephrol. 2021 Mar;32(3):723-735.

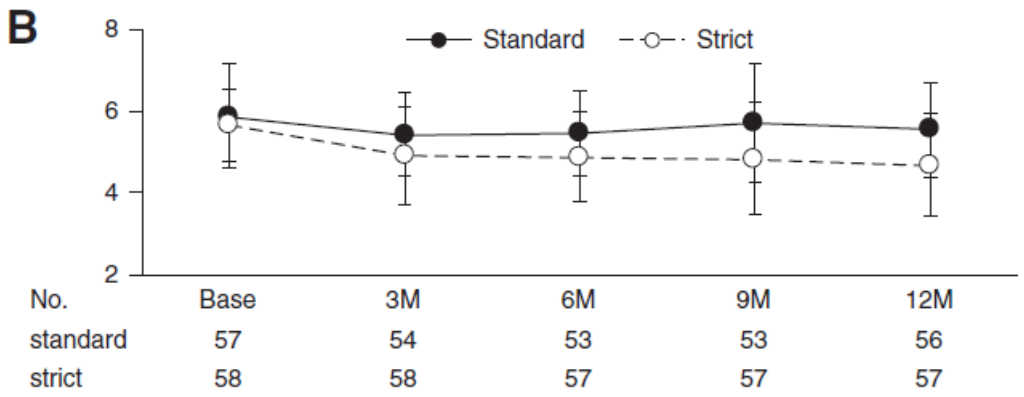
RCT, EPISODE
N=160 (=>115)
Soit Lanthanum, soit sucroferric avec deux cibles différentes de P:
3,5-4,5 mg/dL ou 5,06-6,0 mg/dL

Critère de jugement: CAC score à 12 mois

Table 1. Patients characteristics and baseline data (FAS) stratified by two factors

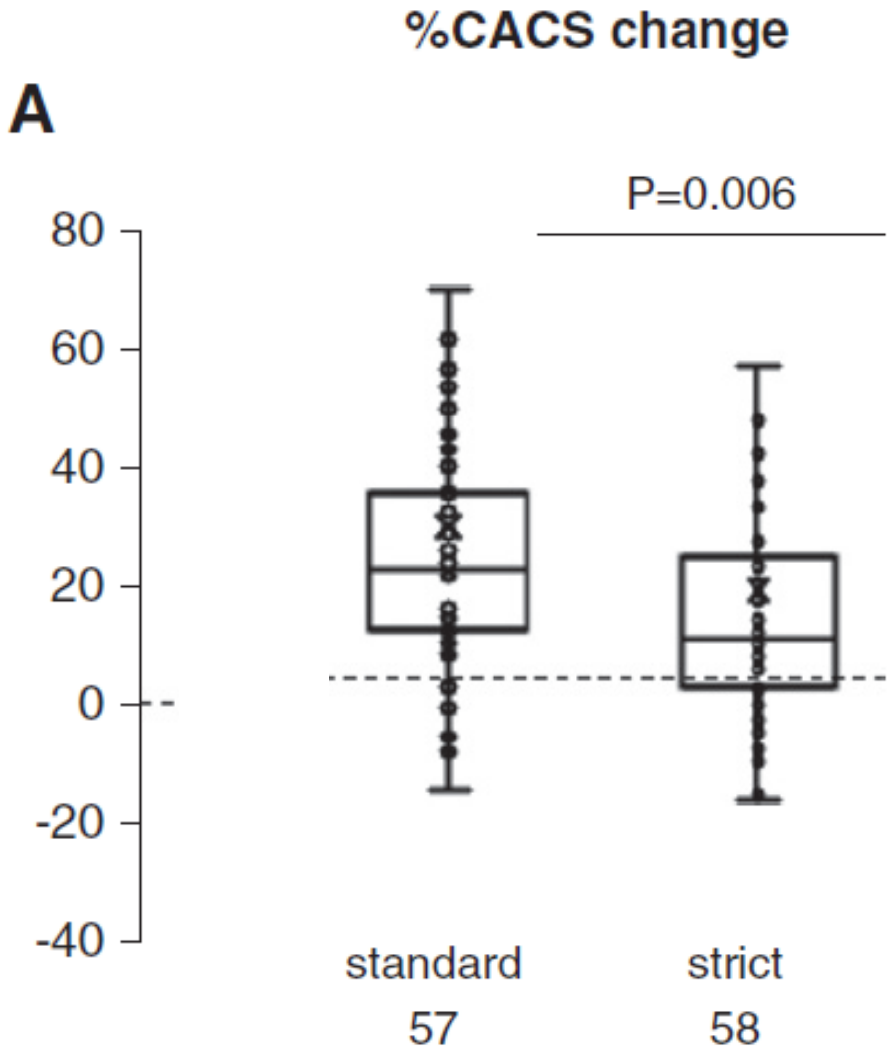
Characteristics	Factor 1		Factor 2	
	LC, *n*=62	SO, *n*=53	Standard Control, *n*=57	Strict Control, *n*=58
No. (women)	62 (21)	53 (17)	57 (20)	58 (18)
Age, yr	62.9±10.1	60.7±11.0	61.3±10.6	62.4±10.5
CACs	680 [340–2418]	824 [224–1513]	891 [257–1581]	711 [319–2270]
Phosphate, mg/dl	5.98±1.16	6.00±0.75	6.04±1.16	5.95±0.80
Calcium, mg/dl	8.74±0.70	8.91±0.69	8.90±0.67	8.73±0.71
Magnesium, mg/dl	2.56±0.35	2.64±0.37	2.59±0.39	2.61±0.33
TSAT, %	27.4±12.4	22.6±9.0	23.8±10.9	26.6±11.5
Ferritin, ng/ml	71 [39–126]	59 [29–135]	45 [30–114]	89 [35–146]
Intact PTH, pg/ml	137 [99–187]	124 [88–178]	132 [105–216]	130 [84–179]

[P]



[P] at 12 months:
Strict : 4.68±1.26 mg/dl
Standard: 5.5461.18 mg/dl

- Pas de différence entre les chélateurs



Nbre de Cp ???
supplem

Conclusions

- Traiter l'hyperphosphatémie est important en dialyse (même si…)
- Choix calcique – non calcique: trend, calcémie, PTH, calcifications (?)
- Limite supérieure en chélateur calcique: Dose maximale de calcium = sans hypercalcémie, celle qui permet un contrôle adéquat de la PTH avec 25OH normale et balance neutre
- Tendances
- Choix entre les non calciques: nombre de comprimés, galénique, tolérance (effets secondaires), goût, **individualisation**
- Compliance (le chélateur le plus efficace est celui que le patient prend)
- Régime, diététicien(ne), Phosphore caché
- Cibles mouvantes (basées sur l'épidémiologie… « remember » EPO)
- On fait ce qu'on peut…avec notre niveau de connaissance

MERCI

de

votre attention