Optimalisation de la prise en charge du patient au stade V de la MRC

Pierre DELANAYE,
Université de Liège
BELGIQUE

- HTA (non stop)
- Anémie
- Acidose
- PTH-Ca-P
- HyperK

Timing of Onset of CKD-Related Metabolic Complications

Olivier Moranne,[*††] Marc Froissart,[‡§||] Jerome Rossert,[§] Cedric Gauci,[‡] Jean-Jacques Boffa,[¶**††] Jean Philippe Haymann,[**††‡‡] Mona Ben M'rad,[‡‡] Christian Jacquot,[§ §§] Pascal Houillier,[‡§||] Benedicte Stengel,[*†] Bruno Fouqueray,[**] and the NephroTest Study Group

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J Am Soc Nephrol 20: 164–171, 2009.

Table 1. Baseline characteristics of the 1038 cohort patients[a]

Characteristic	Value
Age (yr; mean ± SD)	59 ± 15
Men (%)	69
Black (%)	6
Renal disease (% biopsy-proven)[a]	
vascular nephropathy	34 (10)
glomerulonephritis	19 (55)
diabetic kidney disease	13 (10)
tubulointerstitial nephritis	11 (20)
polycystic kidney disease	5 (0)
undetermined	17 (5)
BMI (%; kg/m^2)	
<25	43
25 to 30	37
≥30	20
Diabetes (%)	26
BP ≥130/80 mmHg (%)	65
Any antihypertensive treatment (%)	92
ACEi or ARB treatment (%)	77
Albuminemia (g/L; mean ± SD)	39.5 ± 5.1
Proteinuria (%; g/g creatinine)	
<0.5	53
0.5 to 1.0	15
≥1.0	32
mGFR (ml/min per 1.73 m^2; mean ± SD)	37 ± 17
eGFRcl (ml/min per 1.73 m^2; mean ± SD)	38 ± 17
eGFRms (ml/min per 1.73 m^2; mean ± SD)	36 ± 16
CKD stages based on mGFR/eGFRcl/eGFRms (%)	
2 (60 to 89 ml/min per 1.73 m^2)	12/10/7
3 (30 to 59 ml/min per 1.73 m^2)	48/55/53
4 (15 to 29 ml/min per 1.73 m^2)	31/28/31
5 (<15 ml/min per 1.73 m^2, not on dialysis)	9/7/9

[a]Percentages in parentheses are those of biopsy-proven diagnoses among patients with each type of renal disease. mGFR, measured glomerular filtration rate; eGFRcl, estimated glomerular filtration rate, using the MDRD Study equation with serum creatinine values calibrated by the Cleveland Clinic Laboratory; eGFRms, eGFR using the MDRD equation with serum creatinine values standardized to mass spectrometry.

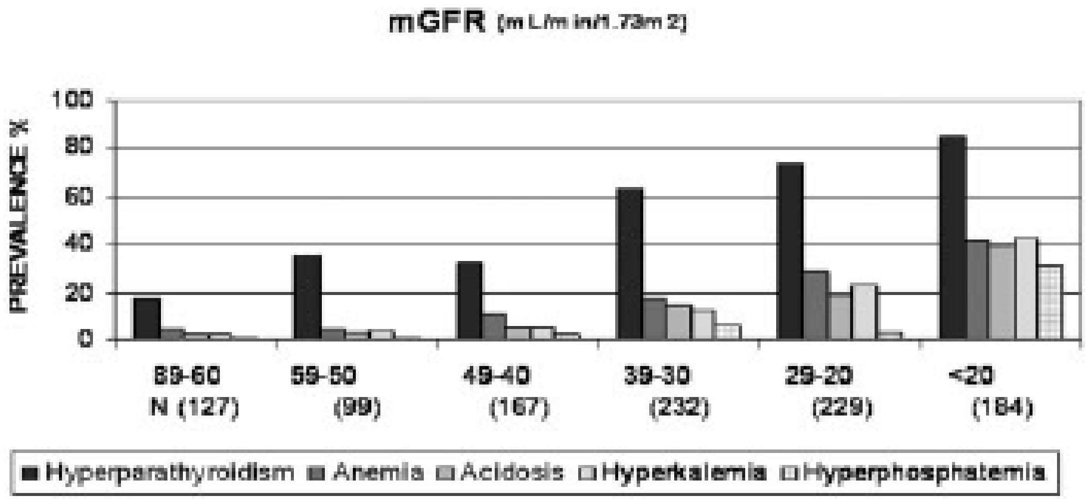


Table 2. Prevalence of metabolic complications[a] in the cohort

	Prevalence of Complications		Prevalence of Treatment among Patients with Complications	
	n	%	*n*	%
Hyperparathyroidism	610	59	87	14
Anemia	210	20	37	18
Acidosis	160	15	35	22
Hyperkalemia	176	17	87	49
Hyperphosphatemia	84	8	32	38

[a]Hyperparathyroidism was defined as a PTH >60 pg/ml or active vitamin D treatment; anemia was defined as Hb<110 g/L according to K/DOQI-based criteria or erythropoiesis-stimulating agent (ESA) treatment; acidosis was defined a tCO_2 <22 mmol/L) or bicarbonate treatment; hyperkalemia was defined as plasma potassium concentration >5 mmol/L or ion exchange resin treatment; hyperphosphatemia was defined as plasma phosphate concentration >4.3 mg/dl (1.38 mmol/L) or phosphate binder treatment.

STOP IEC ?

The NEW ENGLAND JOURNAL of MEDICINE

ESTABLISHED IN 1812 DECEMBER 1, 2022 VOL. 387 NO. 22

Renin–Angiotensin System Inhibition in Advanced Chronic Kidney Disease

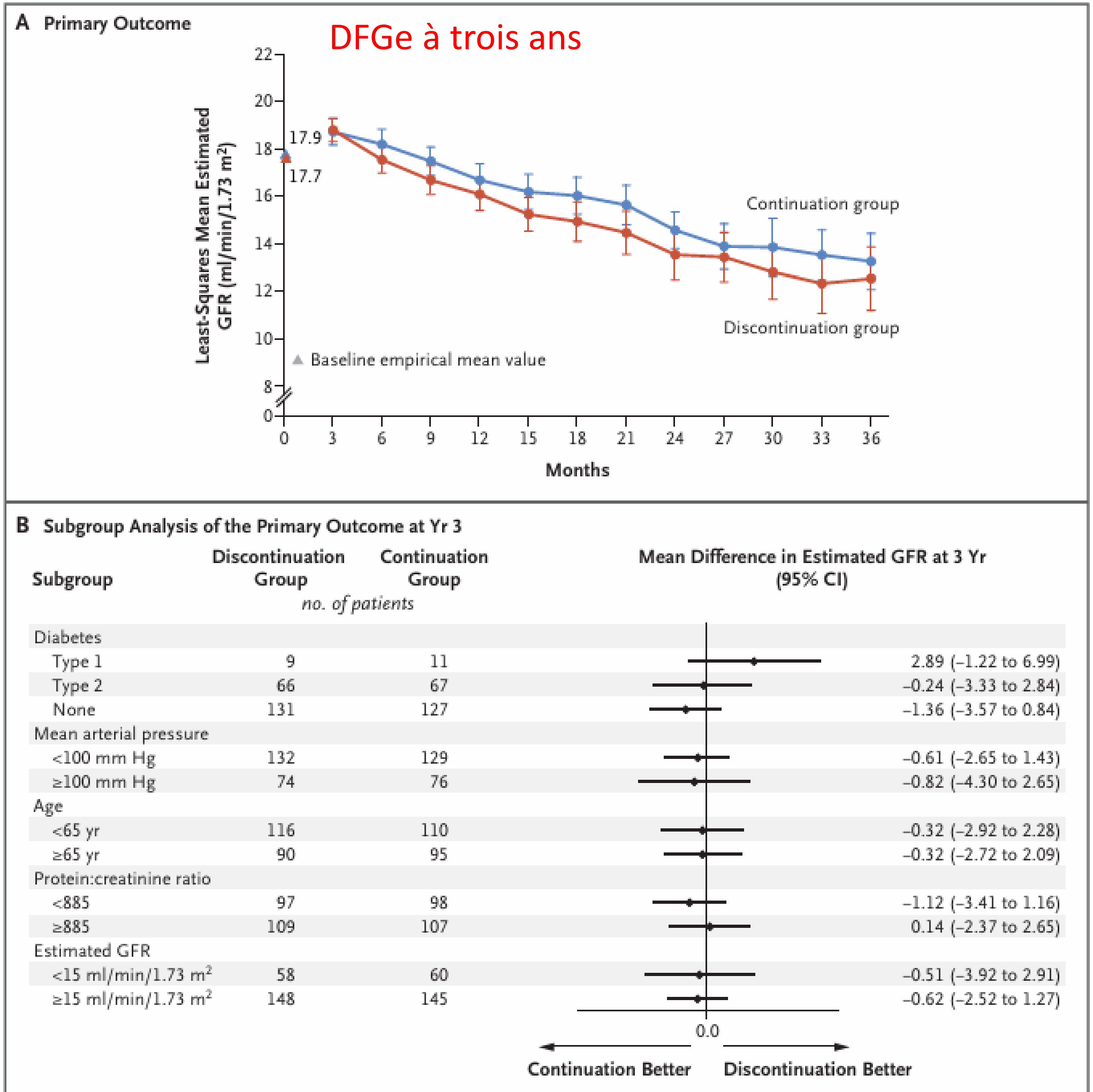
Sunil Bhandari, Ph.D., Samir Mehta, M.Sc., Arif Khwaja, Ph.D., John G.F. Cleland, M.D., Natalie Ives, M.Sc., Elizabeth Brettell, B.Sc., Marie Chadburn, Ph.D., and Paul Cockwell, Ph.D., for the STOP ACEi Trial Investigators*

Table 1. Characteristics of the Patients at Baseline.*

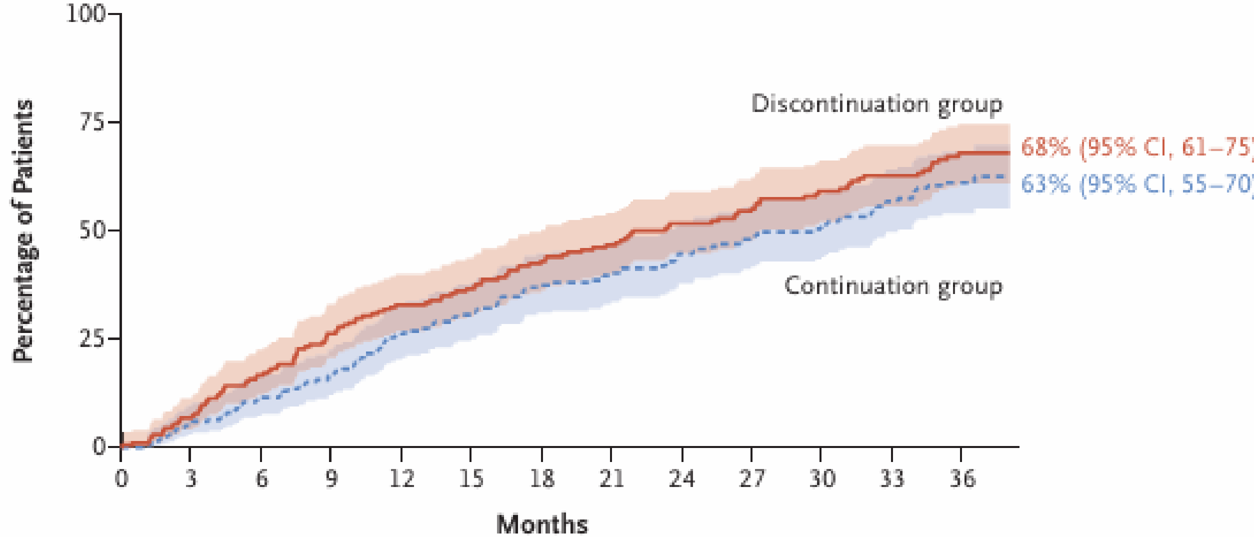
Characteristic	RAS Inhibitor Discontinuation Group (N=206)	RAS Inhibitor Continuation Group (N=205)
Demographic		
Age group		
<65 yr	116 (56)	110 (54)
≥65 yr	90 (44)	95 (46)
Male sex — no. (%)	140 (68)	141 (69)
Race — no. (%)†		
White	171 (83)	180 (88)
Black	16 (8)	7 (3)
Asian	14 (7)	16 (8)
Other	5 (2)	2 (1)
Medical history		
Smoking status — no. (%)		
Never smoked	86 (42)	100 (49)
Ex-smoker	97 (47)	80 (39)
Current smoker	23 (11)	23 (11)
Missing data	0	2 (1)
Diabetes — no. (%)		
Yes		
Type 1	9 (4)	11 (5)
Type 2	66 (32)	67 (33)
No	131 (64)	127 (62)

Estimated glomerular filtration rate		
Median (IQR) — ml/min/1.73 m²	18 (14 to 22)	18 (14 to 21)
Distribution — no. (%)		
<15 ml/min/1.73 m²	58 (28)	60 (29)
≥15 ml/min/1.73 m²	148 (72)	145 (71)
Median rate of decrease over 24 mo (IQR) — ml/min/yr	−4.8 (−7.6 to −3.3)	−4.7 (−7.3 to −3.5)
Median potassium (IQR) — mmol/liter	5 (4.6 to 5.4)	5 (4.6 to 5.4)
Protein:creatinine ratio§		
Median (IQR)	960 (230 to 2089)	1035 (265 to 2230)
Distribution — no. of patients(%)		
<885	97 (47)	98 (48)
≥885	109 (53)	107 (52)

DFGe à trois ans



C Renal-Replacement Therapy or End-Stage Kidney Disease



No. at Risk

Discontinuation group	206	190	165	145	129	119	106	97	86	77	70	61	35
Continuation group	205	190	175	162	142	131	115	107	97	90	85	71	43

Table 2. Primary Outcome with Sensitivity Analyses, Secondary Outcomes, and Adverse Events.*

Outcomes	Discontinuation Group	Continuation Group	Treatment Effect (95% CI)†
Primary outcome			
Estimated glomerular filtration rate at 3 yr — ml/min/1.73^2‡	12.6±0.7	13.3±0.6	−0.7 (−2.5 to 1.0)
Sensitivity analyses at 3 yr			
According to equation used§			
CKD-EPI creatinine	12.0±0.7	12.8±0.6	−0.8 (−2.5 to 1.0)
MDRD186	13.4±0.7	14.1±0.6	−0.8 (−2.6 to 1.1)
According to pattern-mixture models with use of MDRD175 equation¶			
Flat value 5 imputation for MNAR	9.4±0.4	9.9±0.4	−0.5 (−1.7 to 0.7)
Flat value 7 imputation for MNAR	10.6±0.4	11.0±0.4	−0.4 (−1.5 to 0.7)
LOCF imputation for MNAR	12.1±0.4	12.5±0.4	−0.4 (−1.5 to 0.6)
According to joint model with use of MDRD175	12.2±0.4	13.0±0.4	−0.8 (−2.0 to 0.4)
Secondary clinical outcomes			
ESKD or renal-replacement therapy — no./total no. (%)	128/206 (62)	115/205 (56)	1.28 (0.99 to 1.65)‖
Renal-replacement therapy (including patients with ESKD) or >50% decrease in estimated glomerular filtration rate — no./total no. (%)	140/206 (68)	127/202 (63)	1.07 (0.94 to 1.22)**
Death — no./total no. (%)	20/206 (10)	22/205 (11)	0.85 (0.46 to 1.57)‖
Hospitalization			
Patients — no./total no. (%)	135/206 (66)	147/205 (72)	—
No. of events	414	413	—
Blood pressure at 3 yr — mm Hg			
Systolic	140±2	140±2	0 (−4 to 5)
Diastolic	76±1	76±1	0 (−2 to 3)
Distance on 6-minute walk test at 3 yr — m	394±19	412±9	−18 (−57 to 22)
Adverse events			
Serious adverse events			
Patients — no./total no. (%)	107/206 (52)	101/205 (49)	—
No. of events	237	253	—
No. of cardiovascular events††	108	88	—
Secondary mechanistic outcomes			
Hemoglobin at 3 yr — g/dl	11.9±0.1	11.9±0.1	0 (−0.3 to 0.4)
Protein:creatinine ratio at 3 yr‡‡	1699±274	1708±195	−9 (−673 to 655)
Treatment with erythropoietin-stimulating agent — no./total no. (%)	114/206 (55)	112/202 (55)	0.96 (0.81 to 1.13)**

- LES KDIGO INSISTENT POUR NE PAS ARRÊTER LES IEC/ARAII et POUR GERER L’EVENTUELLE HYPERKALIEMIE
- On peut quand même arrêter si
- 1) on a pas le choix
- 2) on a besoin d’un peu de temps

Acidose

- Diminution excrétion des protons avec la diminution du DFG
- Définition: Bicarbonates < 22 mEq/L

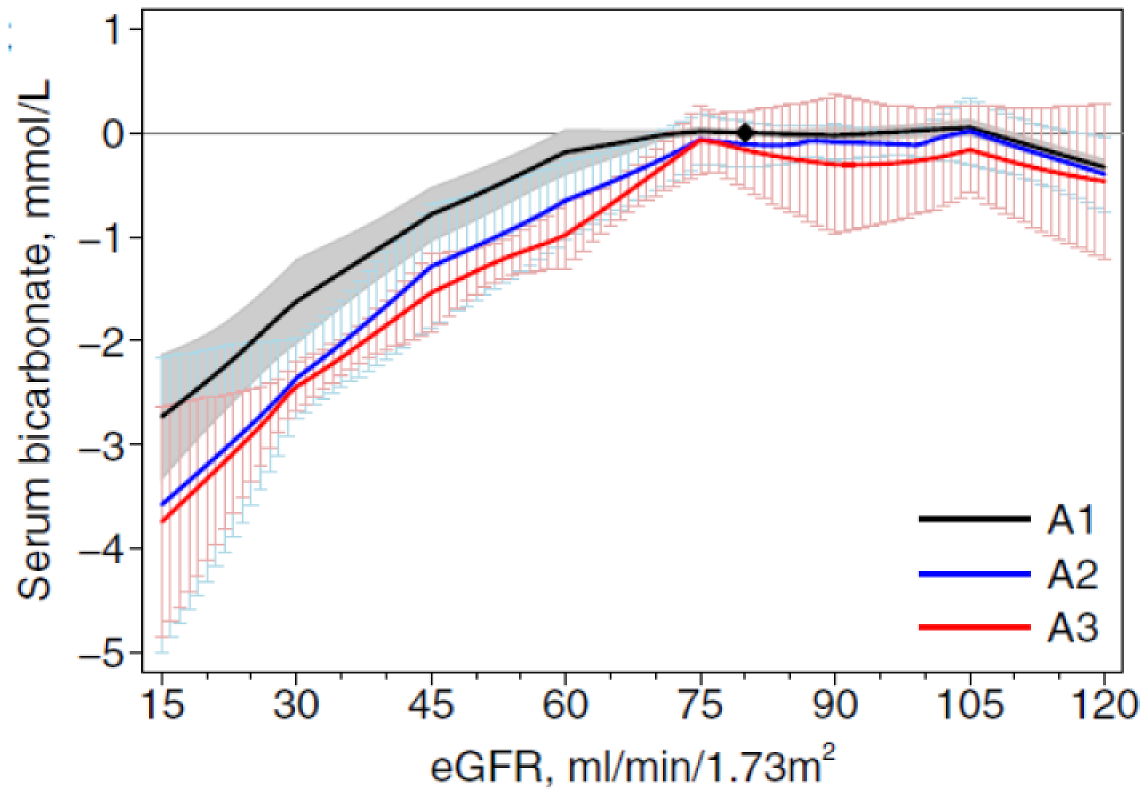
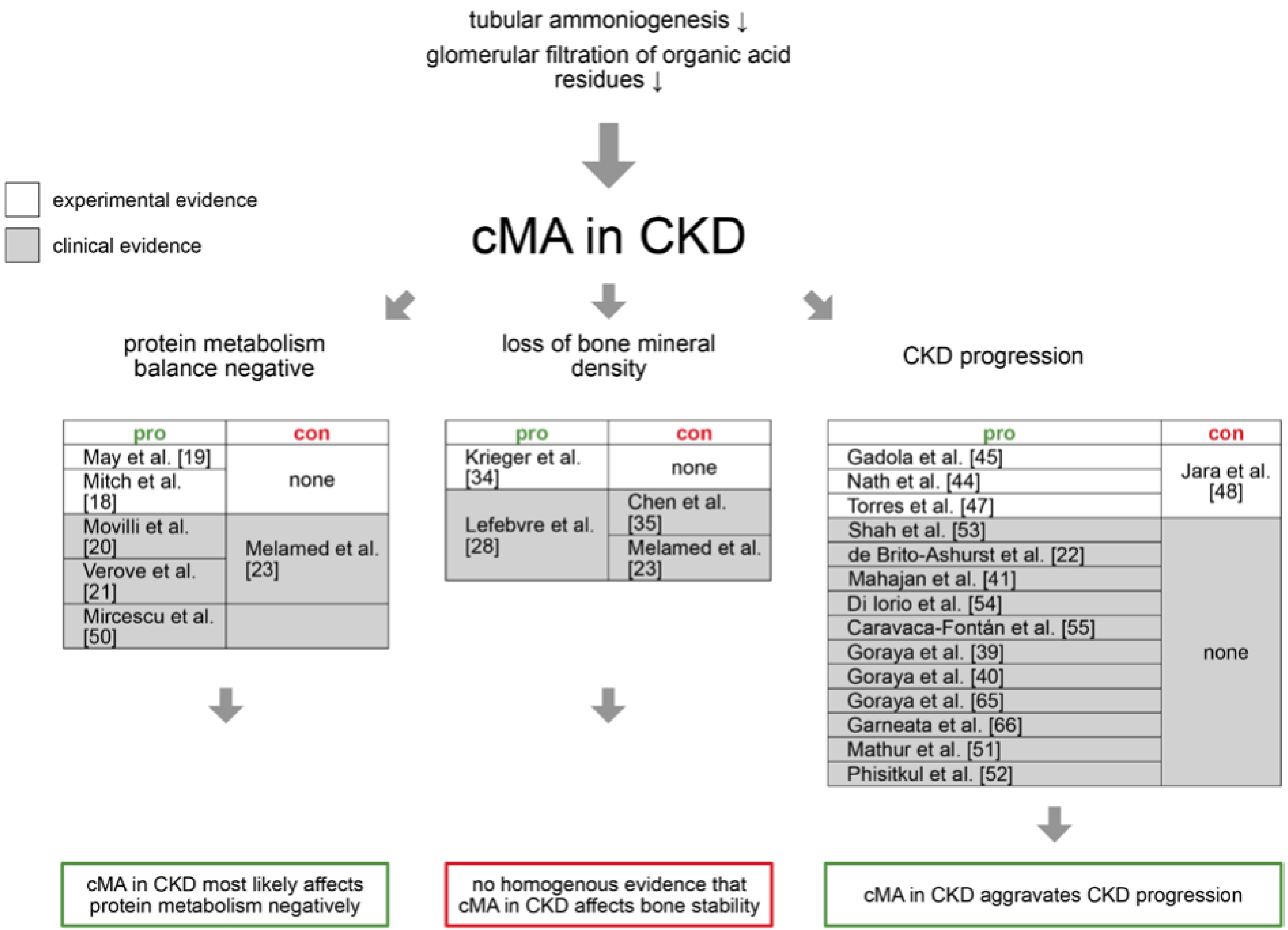


Figure 23. Association between estimated glomerular filtration rate (eGFR) with serum bicarbonate concentration in general population and high risk cohorts from the Chronic Kidney Disease (CKD) Prognosis Consortium, by level of albuminuria (A1–A3). The y axis represents the meta-analyzed absolute difference from the mean adjusted value at eGFR of 80 ml/min per 1.73 m^2 and albumin excretion <30 mg/g. Adapted from Inker *et al.* Relationship of Estimated GFR and Albuminuria to Concurrent Laboratory Abnormalities: An Individual Participant Data Meta-analysis in a Global Consortium. AJKD Figure 2.[431]


tubular ammoniogenesis ↓
glomerular filtration of organic acid residues ↓
experimental evidence
clinical evidence
cMA in CKD
protein metabolism balance negative
loss of bone mineral density
CKD progression
pro
con
May et al. [19]
Mitch et al. [18]
Movilli et al. [20]
Verove et al. [21]
Mircescu et al. [50]
none
Melamed et al. [23]
pro
con
Krieger et al. [34]
Lefebvre et al. [28]
none
Chen et al. [35]
Melamed et al. [23]
pro
con
Gadola et al. [45]
Nath et al. [44]
Torres et al. [47]
Shah et al. [53]
de Brito-Ashurst et al. [22]
Mahajan et al. [41]
Di Iorio et al. [54]
Caravaca-Fontán et al. [55]
Goraya et al. [39]
Goraya et al. [40]
Goraya et al. [65]
Garneata et al. [66]
Mathur et al. [51]
Phisitkul et al. [52]
Jara et al. [48]
none
cMA in CKD most likely affects protein metabolism negatively
no homogenous evidence that cMA in CKD affects bone stability
cMA in CKD aggravates CKD progression

- Chez les patients avec MRC, considérer les interventions diététiques et/ou un traitement pharmacologique pour prévenir l'acidose sévère (Bicarbonate <16 mmol/L)

KDIGO 2024

- Chez les patients avec MRC, considerer les interventions diététiques et/ou un traitement pharmacologique pour prévenir l’acidose sévère (Bicarbonate <16 mmol/L)
- Mesurer le Bicarbonate si on corrige pour ne pas sur-corriger (effet sur la TA, le K et la surcharge hydrique)

KDIGO 2024

KI REPORTS
KIReports.org
CLINICAL RESEARCH

A Systematic Review and Meta-Analysis on Effects of Bicarbonate Therapy on Kidney Outcomes

Check for updates

Sebastian Hultin[1,2,3], Chris Hood[1,4], Katrina L. Campbell[1,5], Nigel D. Toussaint[1,6], David W. Johnson[1,7,8] and Sunil V. Badve[1,3,9]

[1]Australasian Kidney Trials Network, The University of Queensland, Brisbane, Australia; [2]University of Sydney, Sydney, Australia; [3]Department of Nephrology, St George Hospital, Sydney, Australia; [4]Department of Nephrology, Middlemore Hospital, Auckland, New Zealand; [5]Healthcare Excellence and Innovation, Metro North Hospital and Health Service, Brisbane, Australia; [6]Department of Nephrology, The Royal Melbourne Hospital, Parkville, Australia; [7]Department of Nephrology, Princess Alexandra Hospital, Brisbane, Australia; [8]Translational Research Institute, Brisbane, Australia; and [9]The George Institute for Global Health, University of New South Wales Medicine, Sydney, Australia

Kidney Int Rep (2021) 6, 695–705;

- 15 études, 2445 participants, suivi 12 mois
- RCT, eGFR<60 et/ou protéinurie, au moins 3 mois
- Bicarbonate de Sodium
- 6 vs placebo

Table 1. Summary of studies included in the systematic review

Study (reference no.)	Inclusion criteria	*n*	Experimental intervention	Control intervention	Jadad score	Male sex, %	Age, y	Diabetes mellitus, %	Baseline kidney function	Baseline proteinuria	Baseline serum bicarbonate, mmol/l	Follow-up, mo
Mathur 2006 (46)	Serum creatinine <4 mg/dl	40	Sodium bicarbonate 1.2 mEq/kg/d; target serum bicarbonate 22–26 mmol/l	Placebo	3	63	40.5	NR	Serum creatinine 2.9 mg/dl	NR	19.4	3
de Bristo-Ashurst 2009 (42)	CrCl 15 to 30 ml/min per 1.73 m^2, serum bicarbonate 16–20 mmol/l	134	Sodium bicarbonate 600 mg thrice daily; target serum bicarbonate ≥23 mmol/l	No study medication	3	52	54.8	36	CrCl 20.4 ml/min per 1.73 m^2	1.75 g/d	19.9	24
Mahajan 2010 (33)	Hypertension, urine ACR 200–2000 mg/g; eGFR 60–90 ml/min per 1.73 m^2, serum bicarbonate >24.5 mmol/l	80	Sodium bicarbonate 0.5 mEq/kg/d	Placebo	1	48	51.3	0	eGFR 75.5 ml/min per 1.73 m^2	Urine ACR 421 mg/g	26.1	60
Disthabanchong 2010 (36)	eGFR ≤60 ml/min per 1.73 m^2, serum bicarbonate ≤22 mmol/l	44	Sodium bicarbonate 1.8 to 3.6 g/d; target serum bicarbonate 21–43 mmol/l	No study medication	2	48	62.8	49	eGFR 18.8 ml/min per 1.73 m^2	NR	20.9	3 to 4
Jeong 2014 (43)	eGFR <30 ml/min per 1.73 m^2, serum bicarbonate <22 mmol/l	80	Sodium bicarbonate 1000 mg thrice daily; target serum bicarbonate >22 mmol/l	No study medication	1	71	54.6	26	eGFR 16.9 ml/min per 1.73 m^2	NR	18.7	12
Bellasi 2016 (35)	eGFR 15–44 ml/min per 1.73 m^2, serum bicarbonate <24 mmol/l	145	Sodium bicarbonate 0.5 mmol/kg twice daily; target serum bicarbonate 24–28 mmol/l	No study medication	3	57	65.5	100	CrCl 33.5 mL/min	NR	21.4	12
Yan 2017 (39)	eGFR 15–59 ml/min per 1.73 m^2, serum bicarbonate 16–20 mmol/l, non-thyroid illness syndrome	84	Sodium bicarbonate 1–2 g/d; target serum bicarbonate 22–27 mmol/l	Placebo	3	58	53.1	39	eGFR 18.8 ml/min per 1.73 m^2	NR	16.3	5
Dubey 2018 (37)	eGFR 15–59 ml/min per 1.73 m^2, serum bicarbonate <22 mmol/l	188	Sodium bicarbonate 0.5 mEq/kg/d; target serum bicarbonate 24–26 mmol/l	No study medication	3	71	50.2	15	eGFR 30.6 ml/min per 1.73 m^2	NR	18.1	6
Alva 2019 (40)	eGFR 15–30 ml/min per 1.73m^2, serum bicarbonate 10–20 mmol/l	67	Sodium bicarbonate 1.8 g/d; target serum bicarbonate >23 mmol/l	No study medication	2	71	72.6	3	eGFR 21.8 ml/min per 1.73 m^2	NR	16.7	9
DiLorio 2019 (45)	eGFR 15–59 ml/min per 1.73m^2, serum bicarbonate 18–24 mmol/l	795	Sodium bicarbonate up escalated by 25%/wk; target serum bicarbonate 24–28 mmol/l	No study medication	3	62	67.6	30.7	eGFR 33.4 ml/min per 1.73 m^2	Urine ACR 208 mg/g	21.7	36
Goraya 2019 (30)	eGFR 30–59 ml/min per 1.73 m^2, urine ACR >200 mg/g; hypertension, serum bicarbonate 22–24 mmol/l	72	Sodium bicarbonate 0.3 mEq/kg/d	No study medication	1	44	53.8	0	eGFR 42.6 ml/min per 1.73 m^2	Urine ACR 316 mg/g	23	60
Witham 2020 (44)	eGFR 15–30 ml/min per 1.73 m^2, serum bicarbonate <2 mmol/l, age >60 y	300	Sodium bicarbonate 500–1000 mg thrice daily; target serum >22mmol/l	Placebo	5	57	73.9	50.5	eGFR 18.9 ml/min per 1.73 m^2	Urine ACR 79.9 mg/g	20.4	24
Melamed 2020 (41)	eGFR 15–59 ml/min per 1.73m^2, serum bicarbonate 20–26 mEq/l	149	Sodium bicarbonate 0.4 mEq/l/kg/d	Placebo	5	54	61	62	eGFR 36.2 ml/min per 1.73m^2	NR	24	24
Raphael 2020 (34)	eGFR 15–89 ml/min per 1.73m^2, urine ACR <30 mg/g, serum bicarbonate 22–28 mEq/l	74	Sodium bicarbonate 0.5 mEq/kg/d in 2 divided doses	Placebo	5	97	72	100	eGFR 51 ml/min per 1.73 m^2	Urine ACR 121 mg/g	24	6
Raphael 2020 (18)	eGFR 20–44 ml/min per 1.73 m^2 or eGFR 45–59 with urine ACR >50 mg/g, serum bicarbonate 20–28 mEq/l	192	Sodium bicarbonate 0.8 mEq/kg/d (high dose) or 12 mEq/d (low dose)	Placebo	5	68	66	54	eGFR 35 ml/min per 1.73 m^2	NR	24	7

ACR, albumin-creatinine ratio; CrCl, creatinine clearance; eGFR, estimated glomerular filtration rate; NR, not reported

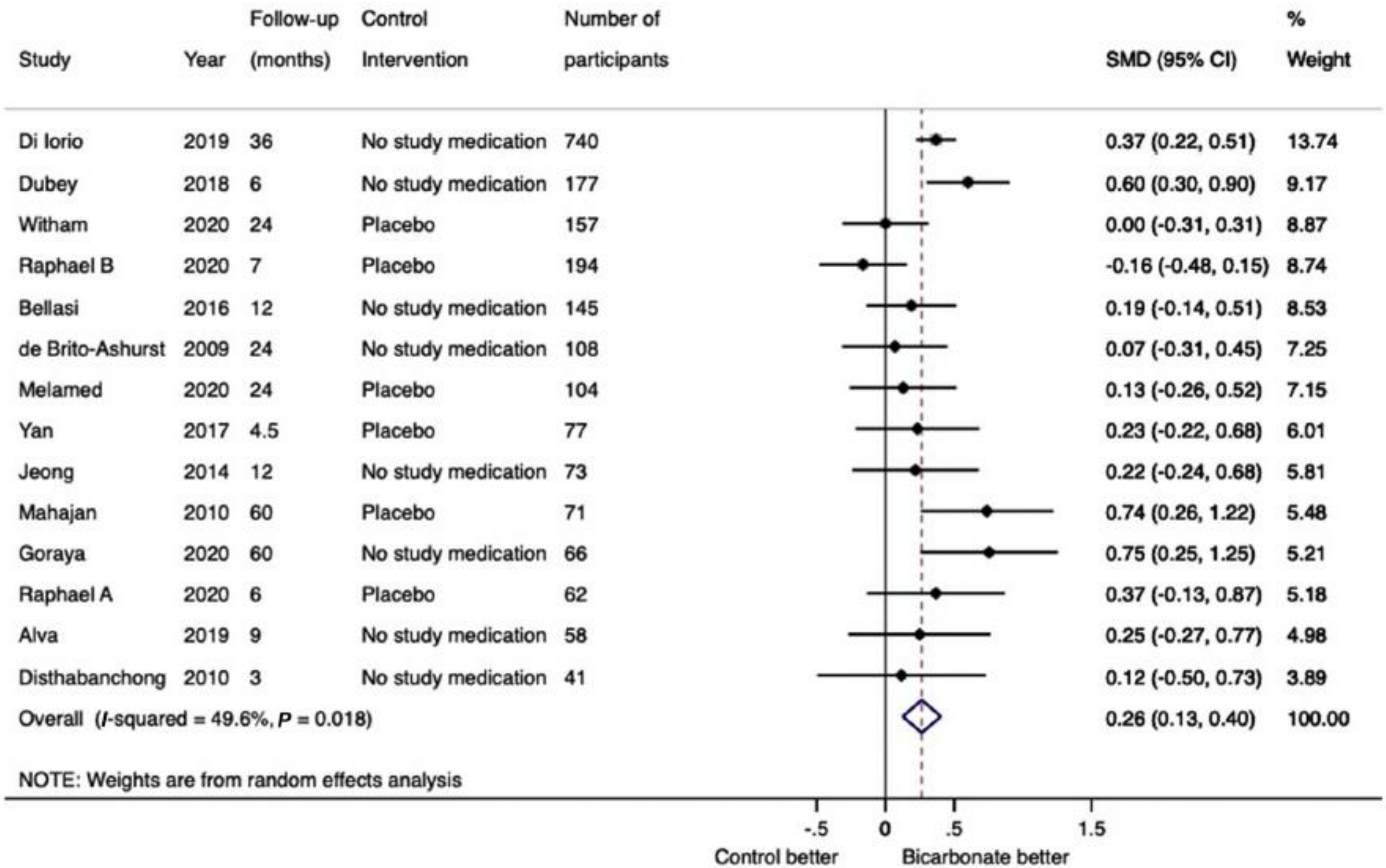


Figure 3. Forest plot showing the effect of bicarbonate therapy on change in kidney function (eGFR or creatinine clearance) from baseline to last measurement. CI, confidence interval; SMD, standardized mean difference.

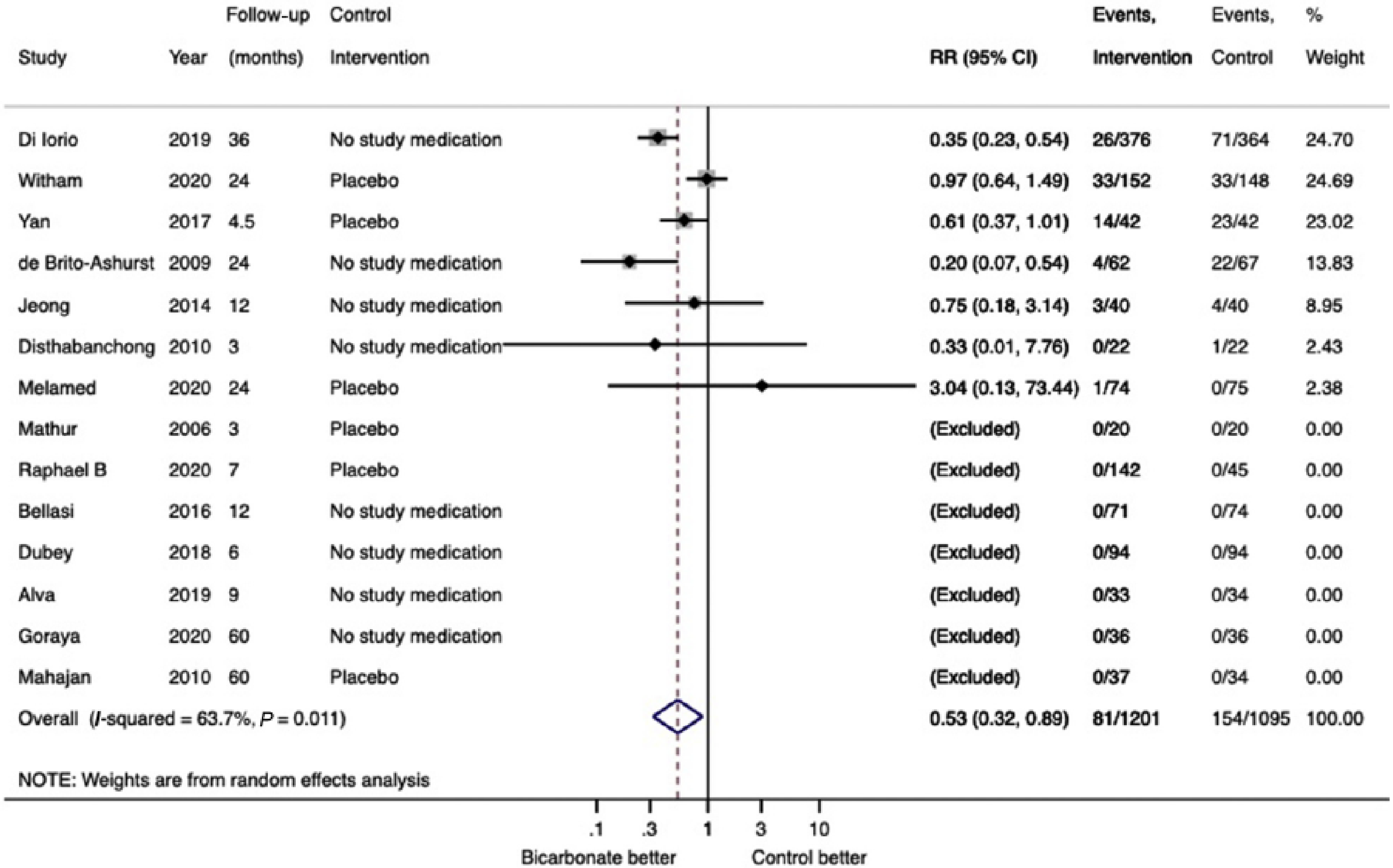


Figure 4. Forest plot showing the effect of bicarbonate therapy on progression to kidney failure. CI, confidence interval; RR, risk ratio.

Figure S1. Subgroup analysis of the effect of bicarbonate therapy on change in kidney function 1: according to the use of placebo or no study medication in the control arm.

Forest plot showing subgroup analysis according to the use of placebo or no study medication on the effect of bicarbonate therapy on the change in kidney function. Interaction p-value 0.22.

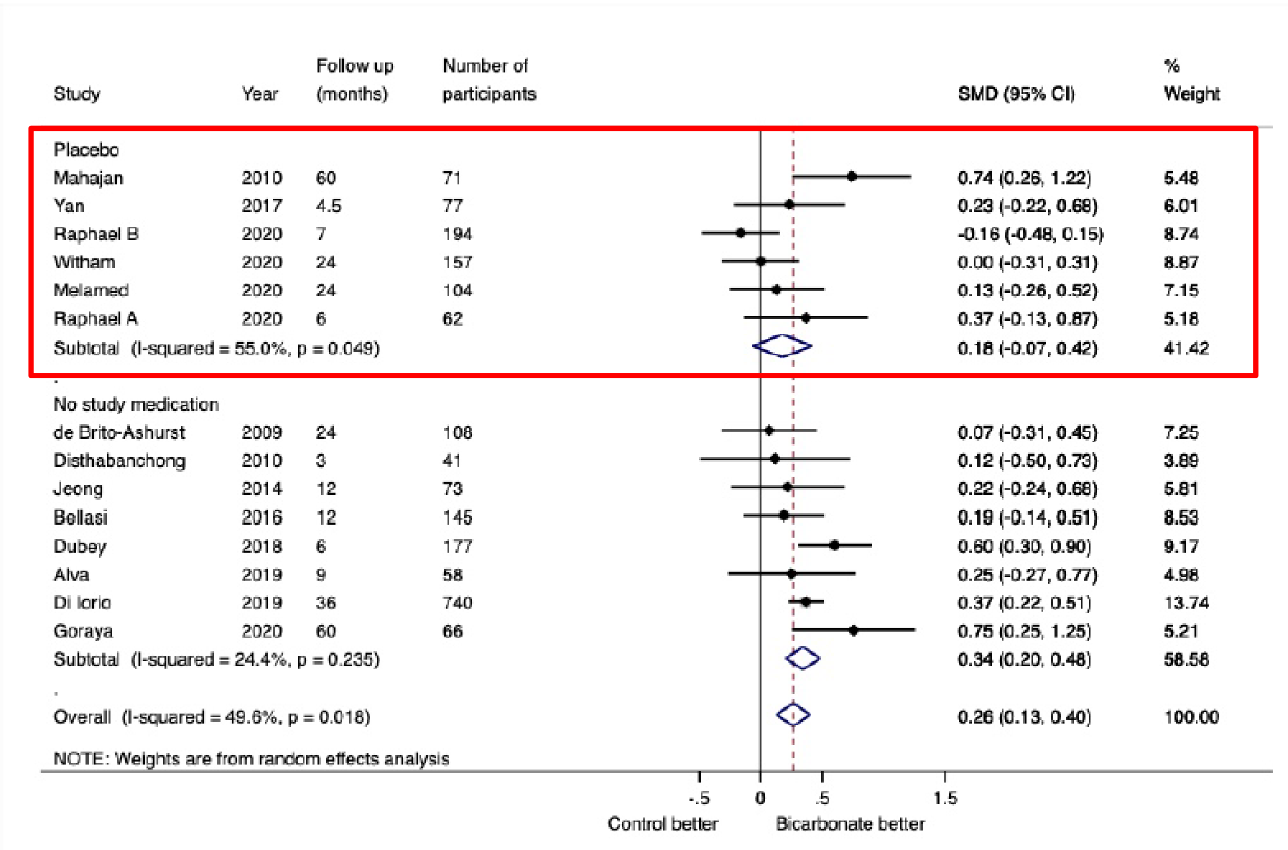
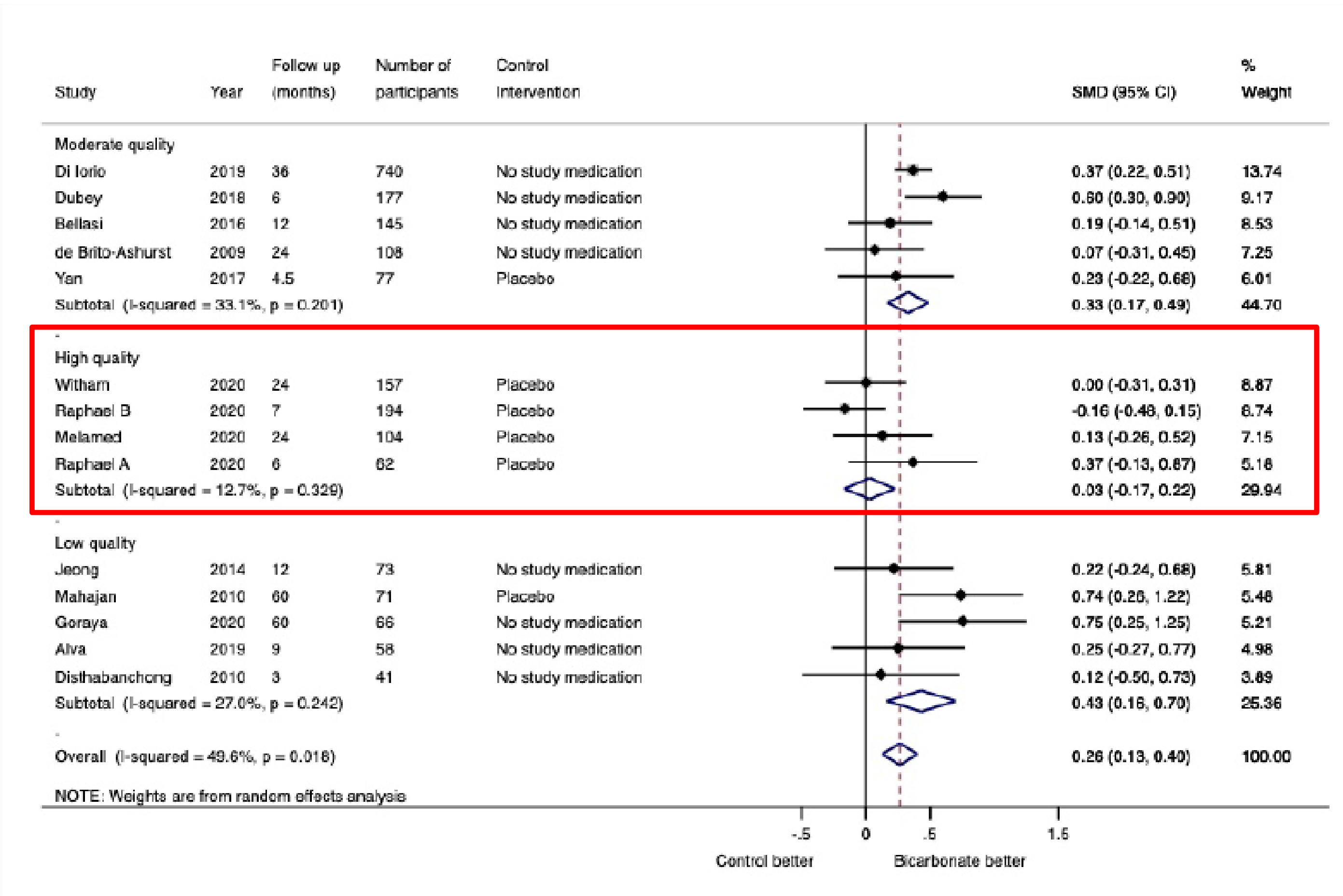


Figure S3. Subgroup analysis of the effect of bicarbonate therapy on the change in kidney function 3: according to trial quality.

Forest plot showing subgroup analysis according to trial quality on the effect of bicarbonate therapy on the change in kidney function. Interaction p-value 0.03.



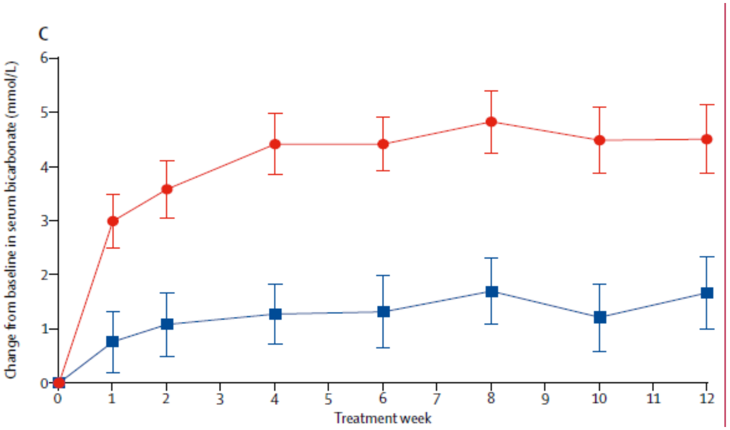
Nephrol Dial Transplant (2023) 38: 1448–1458
https://doi.org/10.1093/ndt/gfac289
Advance Access publication date 4 November 2022

Design and population of the VALOR-CKD study: a multicenter, randomized, double-blind, placebo-controlled trial evaluating the efficacy and safety of veverimer in slowing progression of chronic kidney disease in patients with metabolic acidosis

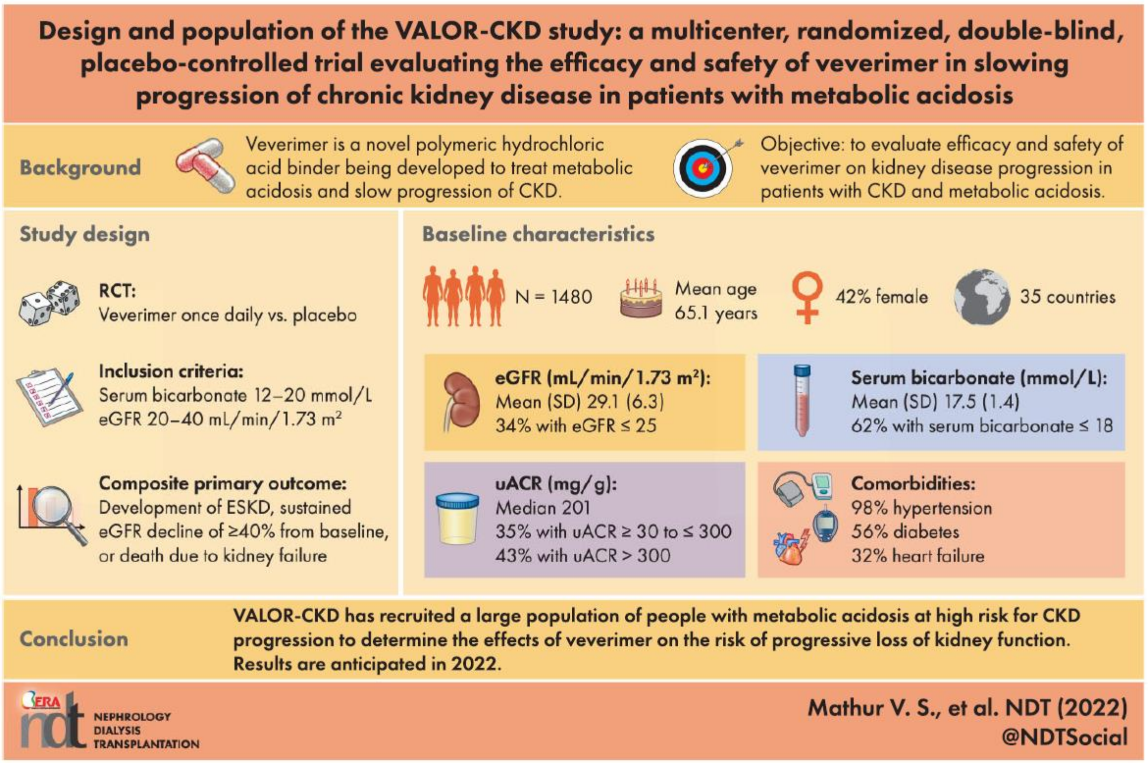
Vandana S. Mathur[1], David A. Bushinsky[2], Lesley Inker[3], Gerrit Klaerner[4], Elizabeth Li[5], Dawn Parsell[6], Vlado Perkovic[7], Yuri Stasiv[8], Michael Walker[9], Donald E. Wesson[10], David C. Wheeler[11] and Navdeep Tangri[12]

Veverimer versus placebo in patients with metabolic acidosis associated with chronic kidney disease: a multicentre, randomised, double-blind, controlled, phase 3 trial

Donald E Wesson, Vandana Mathur, Navdeep Tangri, Yuri Stasiv, Dawn Parsell, Elizabeth Li, Gerrit Klaerner, David A Bushinsky



Lancet 2019; 393: 1417–27

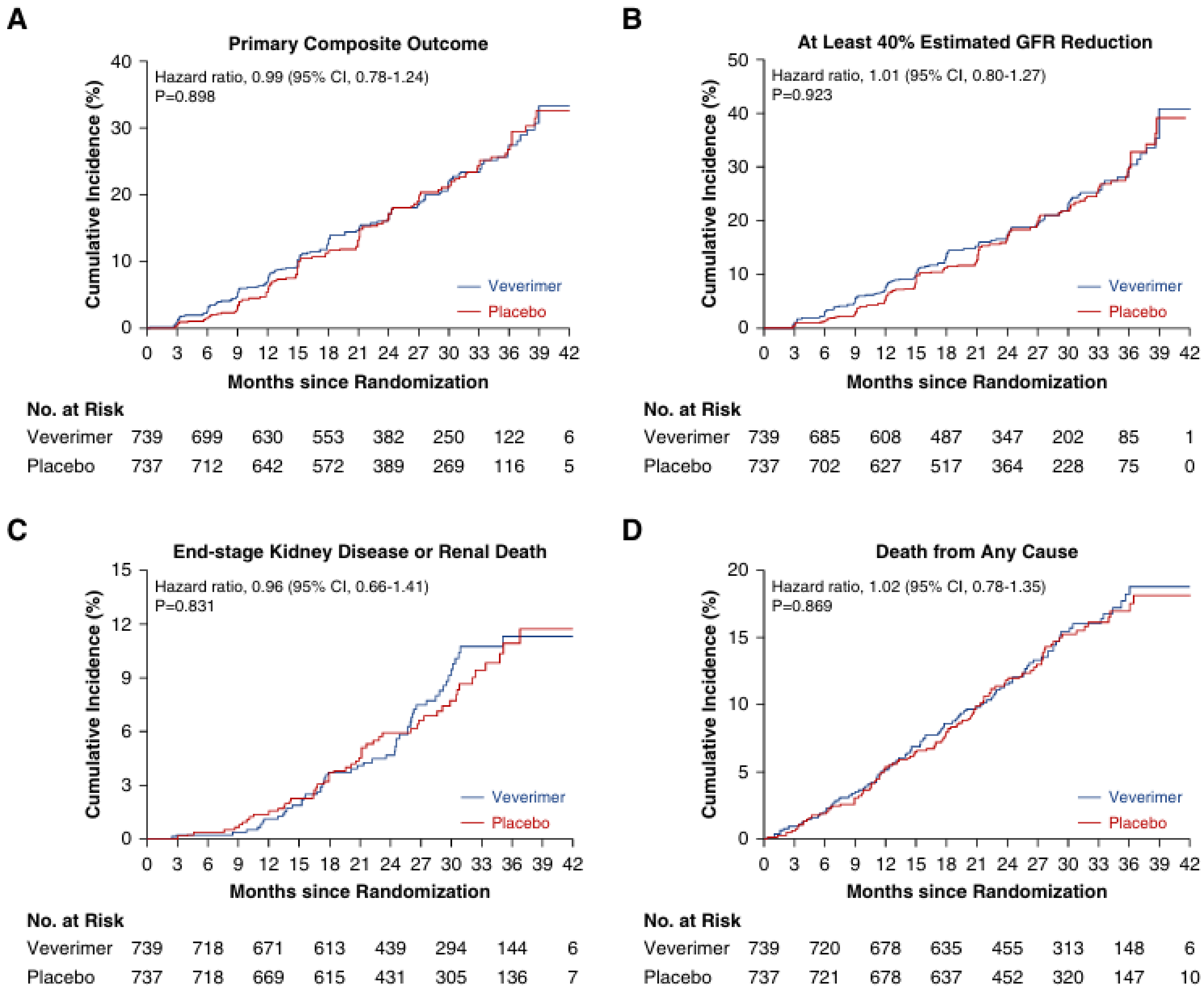


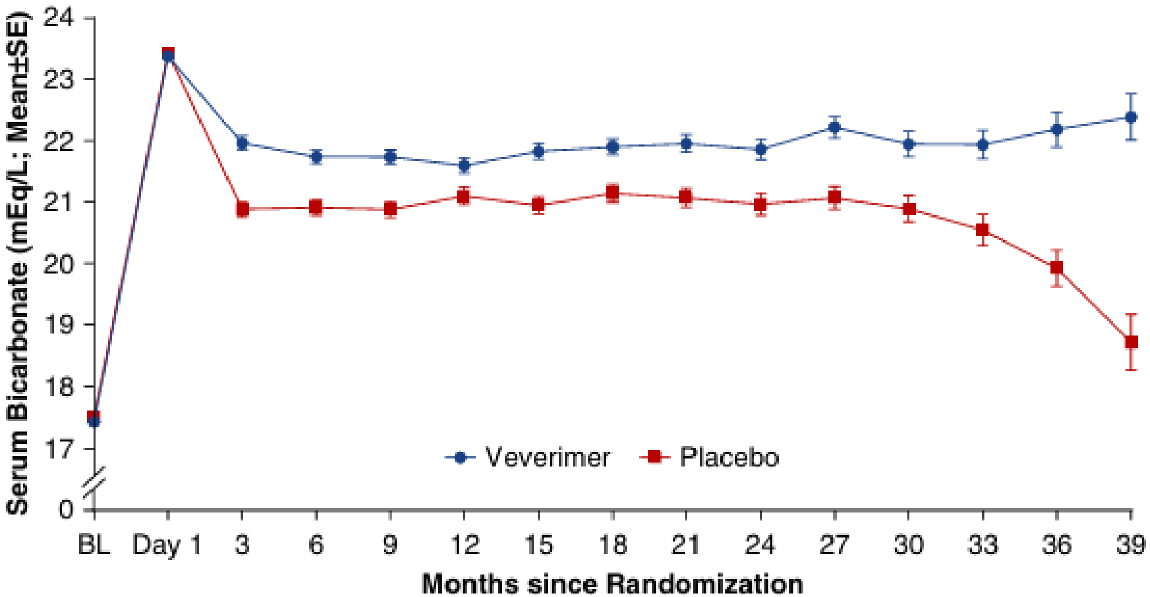
CLINICAL RESEARCH www.jasn.org

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

Navdeep Tangri,[1] Vandana S. Mathur,[2] David A. Bushinsky,[3] Gerrit Klaerner,[4] Elizabeth Li,[5] Dawn Parsell,[4] Yuri Stasiv,[4] Michael Walker,[6] Donald E. Wesson,[7,8] David C. Wheeler,[9] Vlado Perkovic,[10] and Lesley A. Inker[11]

JASN 35: 311–320, 2024.


A
Primary Composite Outcome
Hazard ratio, 0.99 (95% CI, 0.78-1.24)
P=0.898
Cumulative Incidence (%)
Months since Randomization
Veverimer
Placebo
No. at Risk
Veverimer 739 699 630 553 382 250 122 6
Placebo 737 712 642 572 389 269 116 5
B
At Least 40% Estimated GFR Reduction
Hazard ratio, 1.01 (95% CI, 0.80-1.27)
P=0.923
Cumulative Incidence (%)
Months since Randomization
Veverimer
Placebo
No. at Risk
Veverimer 739 685 608 487 347 202 85 1
Placebo 737 702 627 517 364 228 75 0
C
End-stage Kidney Disease or Renal Death
Hazard ratio, 0.96 (95% CI, 0.66-1.41)
P=0.831
Cumulative Incidence (%)
Months since Randomization
Veverimer
Placebo
No. at Risk
Veverimer 739 718 671 613 439 294 144 6
Placebo 737 718 669 615 431 305 136 7
D
Death from Any Cause
Hazard ratio, 1.02 (95% CI, 0.78-1.35)
P=0.869
Cumulative Incidence (%)
Months since Randomization
Veverimer
Placebo
No. at Risk
Veverimer 739 720 678 635 455 313 148 6
Placebo 737 721 678 637 452 320 147 10



No. of Participants

Veverimer	739	739	709	688	650	598	595	561	475	387	348	261	188	123	67
Placebo	737	736	712	682	662	602	595	574	471	390	352	284	197	120	64

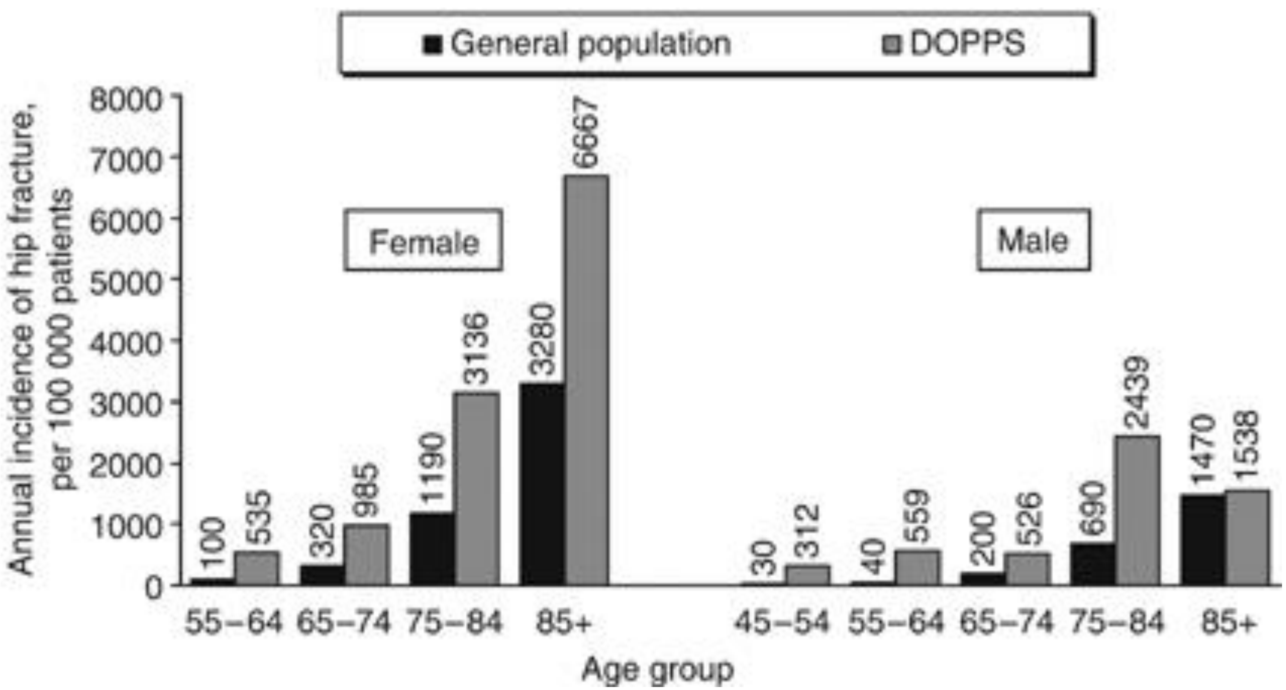
Figure 3. Change in serum bicarbonate. Mean serum bicarbonate during the study. The I bars indicate SEM. BL denotes baseline. Day 1 is the day of randomized withdrawal to veverimer or placebo, following an active treatment run-in period. Figure 3 can be viewed in color online at www.jasn.org.

Si traiter, comment faire?

- Bicarbonate de Sodium
- Régime végétarien (fruits et légumes)

Hyperparathryoidie

Incidence de la fracture de la hanche chez le patient dialysé vs. en population générale



Jadoul M, KI ,2006, p1358

Kidney Int. 2014 January ; 85(1): 166–173. doi:10.1038/ki.2013.279.

High rates of death and hospitalization follow bone fracture among hemodialysis patients

Francesca Tentori, MD[1,2], **Keith McCullough, MS**[1], **Ryan D. Kilpatrick, PhD**[3], **Brian D. Bradbury, DSc**[3,4], **Bruce M. Robinson, MD**[1,5], **Peter G. Kerr, MD**[6], and **Ronald L. Pisoni, PhD**[1]

N=34579
3% de
fractures

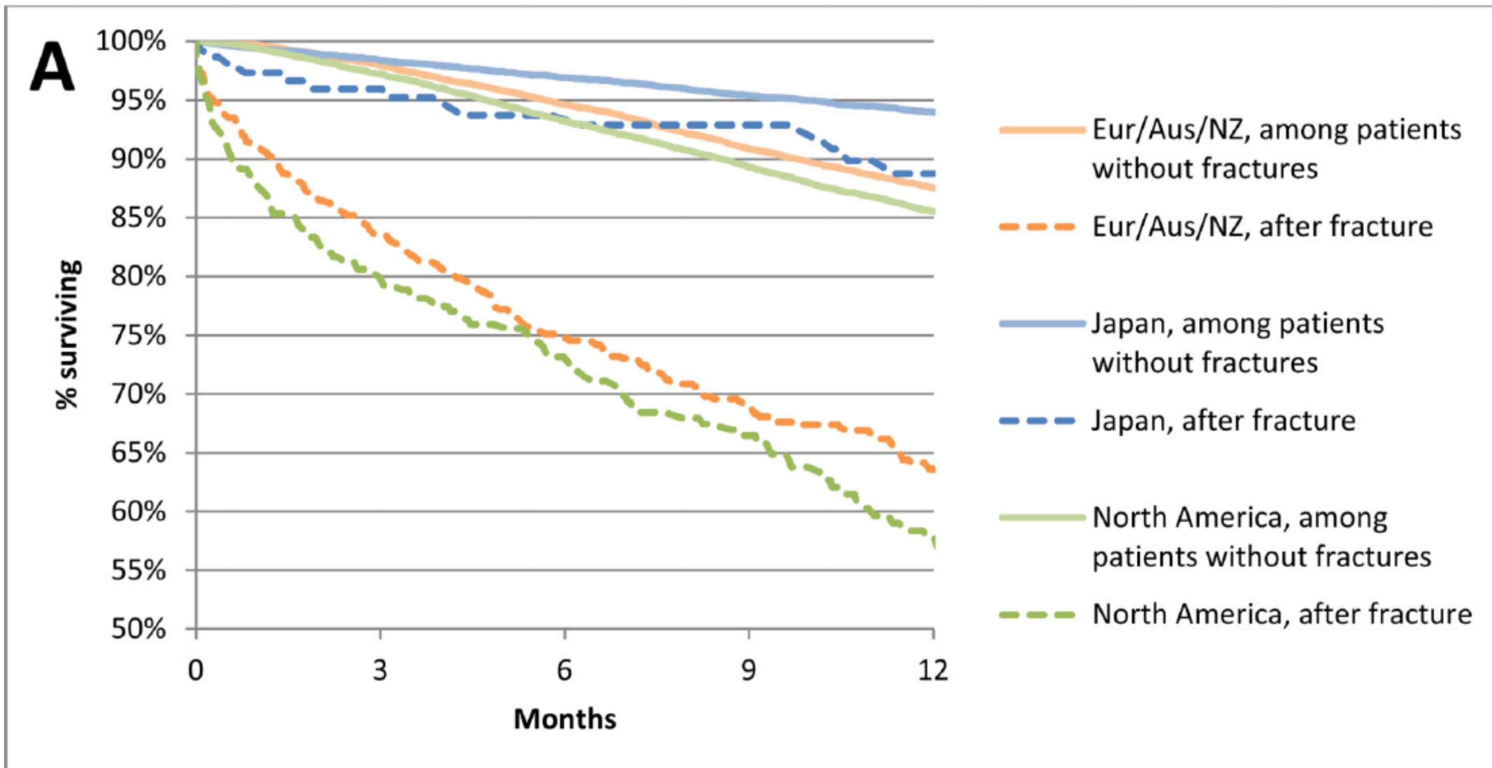
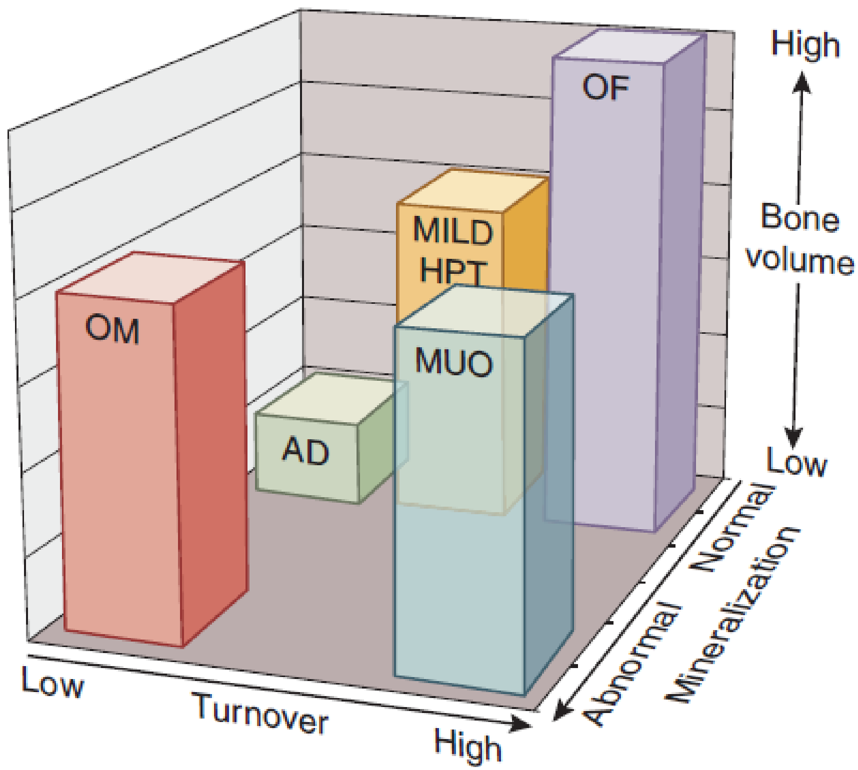


Figure 5A & 5B. Time to death and hospitalization among DOPPS participants who experienced and those who did not experience a fracture requiring hospitalization, by DOPPS region
Panel A: Unadjusted survival (time to death) by DOPPS region.

La santé osseuse en MRC en 3D
(volume versus turnover versus minéralisation)



Moorthi N, Kidney Int, 2013, p886

Diagnostic et suivi

KDIGO Guidelines
August 2009

4.2.3. In patients with CKD stage 5D, we suggest maintaining iPTH levels in the range of approximately two to nine times the upper normal limit for the assay (2C). We suggest that marked changes in PTH levels in either direction within this range prompt an initiation or change in therapy to avoid progression to levels outside of this range (2C).

see commentary on page 240

Inter-method variability in PTH measurement: Implication for the care of CKD patients

J-C Souberbielle[1], A Boutten[2], M-C Carlier[3], D Chevenne[4], G Coumaros[5], E Lawson-Body[1,6], C Massart[7], M Monge[8], J Myara[9], X Parent[10], E Plouvier[11] and P Houillier[12], Working group on PTH and vitamin D, Société Française de Biologie Clinique (SFBC)

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Assay	PTH (ng/l)	PTH (ng/l)	PTH (ng/l)	Median bias (%)
Allegro intact PTH	150	300	1000	0
N-tact PTH IRMA	83	160	517	−44.9 (−68.0; −26.2)
PTH IRMA Immunotech	188	369	1216	23.9 (−6.1; 108.3)
ELISA-PTH	149	290	948	−1.6 (−24.3; 47.2)
Total intact PTH IRMA	134	262	857	−14.5 (−41.5; 23.5)
DSL PTH IRMA	323	638	2108	123.0 (53.1; 188.9)
DSL PTH ELISA	264	523	1734	79.6 (−8.0; 180.9)
Elecsys PTH	161	311	1011	7.3 (−13.8; 80.3)
Immulite 2000 intact PTH	212	410	1334	37.8 (3.8; 130.8)
PTH-ACS 180	185	374	1256	18.8 (−9.9; 69.4)
PTH AdviaCentaur	168	342	1154	9.5 (27.6; 55.6)
Intact PTH advantage	174	339	1109	14.6 (−10.4; 72.2)
LIAISON N-tact PTH	111	223	748	−23.4 (−68.2; −1.9)
Ca-PTH IRMA	84	165	543	−44.8 (−65.6; −22.8)
BioIntact PTH advantage	109	214	704	−27.6 (−53.0; 12.5)

DSL, diagnostic system laboratories; ELISA, enzyme-linked immunosorbent assay; IRMA, immunoradiometric assay; PTH, parathyroid hormone.
These values were calculated according to the equations presented in Table 2. The median bias value (right column), expressed in %, is, for a given method (*A*), the median (minimum–maximum) of the ratios, ((value measured with *A*–value measured with the Allegro assay)/value measured with the Allegro assay) in the 47 serum pools. As we considered the Allegro-intact PTH as the reference, the bias with this method is, by definition, 0.

La PTH chez les patients dialysés

☑ PTH n'est pas un marqueur de turnover osseux car ce dernier est un processus long alors que la concentration de PTH varie rapidement en fonction du Ca^{++}

☑ Des valeurs élevées sont associées à un haut remodelage osseux

☑ Des valeurs basses sont associées à un faible remodelage osseux

Pas parfait: Bonafide *Behets GJ, 2014, KI, 2015, p846*

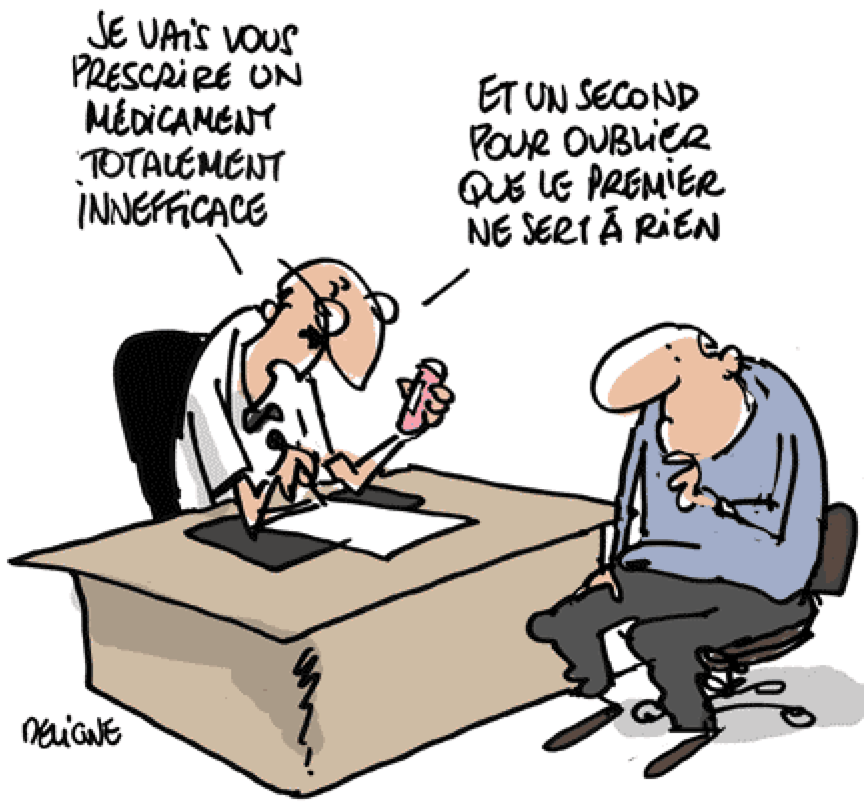
17% (25/146) des sujets avec PTH>300 pg/mL (Advia Centaur) et PALO>21 ng/mL <u>exclus</u> car turnover normal (mais pas d'OA!)

3.1.4 In patients with CKD stages 3–5D, we recommend that therapeutic decisions be based on trends rather than on a single laboratory value, taking into account all available CKD–MBD assessments (1C).

Diagnostic

- Pas si simple en dialyse…
- En MRC, quelle est la valeur normale de PTH=?
- Collaboration clinico-biologique
- Place de la PBO Torres PU, Sem Nephrol, 2014, p612
- Place de l'échographie et de la scintigraphie

Comment traiter?



Choix thérapeutique pour hyperPTH

- Calcium
- Vitamine D native
- Vitamine D active
- Vitamine D active “modifiée”
- Cinacalcet
- PTHx

Qu’est ce qui va guider notre choix?

- Individualisé
- Tendance
- Calcémie (bilan calcique)
- Phosphorémie
- (PBO, QDR, Calcifications, autres biomarqueurs)

Vitamine D native/Calcium

- Vitamine D native à tout le monde Delanaye P, Nephrol Ther, 2015
- …puis je monitorise (mais on peut probablement s'en passer)
- Calcium comme traitement de l'hyperPTH:

Soit si hypocalcémie

Soit pour chélater le phosphore

- Dose maximale de calcium?
- Dose minimale même en cas de "normocalcémie" (patient dénutri)?
- Bain en calcium a un effet sur PTH aussi

Jean G, NDT, 2013 et Ok E, JASN, 2016

Cholecalciferol in haemodialysis patients: a randomized, double-blind, proof-of-concept and safety study

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Keywords: vitamin D, calcification, parathormone

Nephrol Dial Transplant (2013) 28: 1779–1786

Table 1. Clinical and biological characteristics of patients that have completed the study. Data are expressed as mean ± SD if the distribution is normal and median (IQR) if not specified

	Placebo $n = 14$	Cholecalciferol $n = 16$	P
Age (years)	73 ± 12	75 ± 9	0.50*
Sex ratio (% female)	36	25	0.52
Dialysis vintage (month)	56 ± 39	44 ± 46	0.47*
K_t/V	1.36 ± 0.17	1.37 ± 0.17	0.87*
Calcium (mmol/L)	2.16 ± 0.15	2.18 ± 0.12	0.75*
Phosphorus (mg/L)	45 ± 11	46 ± 13	0.79*
Parathormone (pg/mL) Median (IQR)	240 [195–410]	312 [206–447]	0.36**
25-Hydroxyvitamin D(ng/mL)	12 ± 6	12 ± 5	0.90*
Use of phosphate binder (all) (%)	58	38	0.28
Use of phosphate binder (calcium-based) (%)	43	32	0.51
Use of phosphate binder (sevelamer) (%)	36	50	0.43
Use of calcitriol analogue (%)	57	31	0.15
Caltriol analogue doses (μg/week)	0.88 ± 1.05	0.59 ± 1.04	0.5*
Abdominal calcification score	8 ± 8	8 ± 5	0.52*

Baseline characteristics of patients randomized in the study who completed the study. These values were compared between placebo and vitamin D-treated patients with Student's *t*-test (*), Mann–Whitney *U*–test (**) or χ^2 test. Values are expressed as mean ± SD, if not specified.

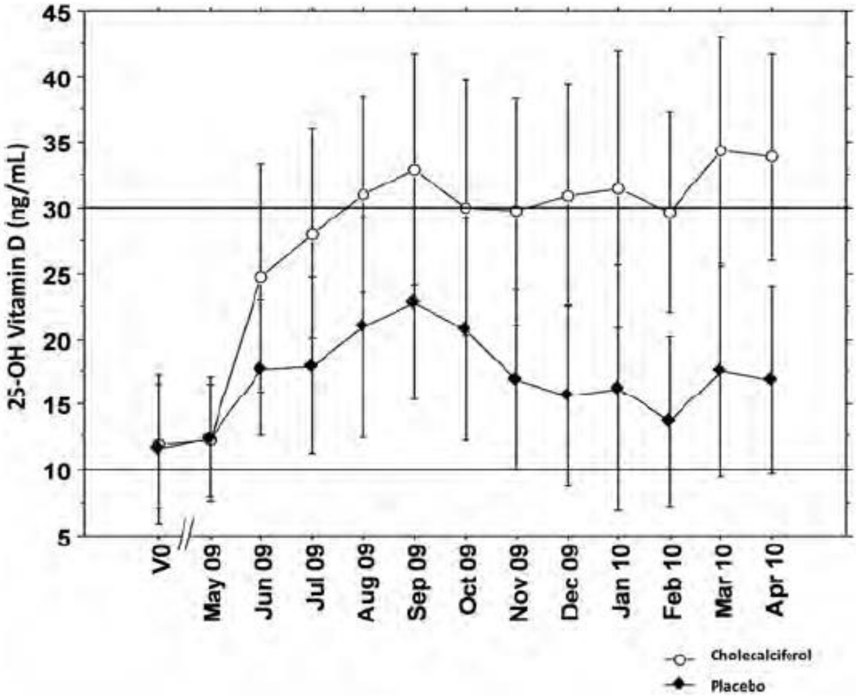

FIGURE 2: 25-Hydroxyvitamin D (ng/mL) levels over a 1-year period in the placebo and cholecalciferol groups. Data are expressed as mean ± SD.

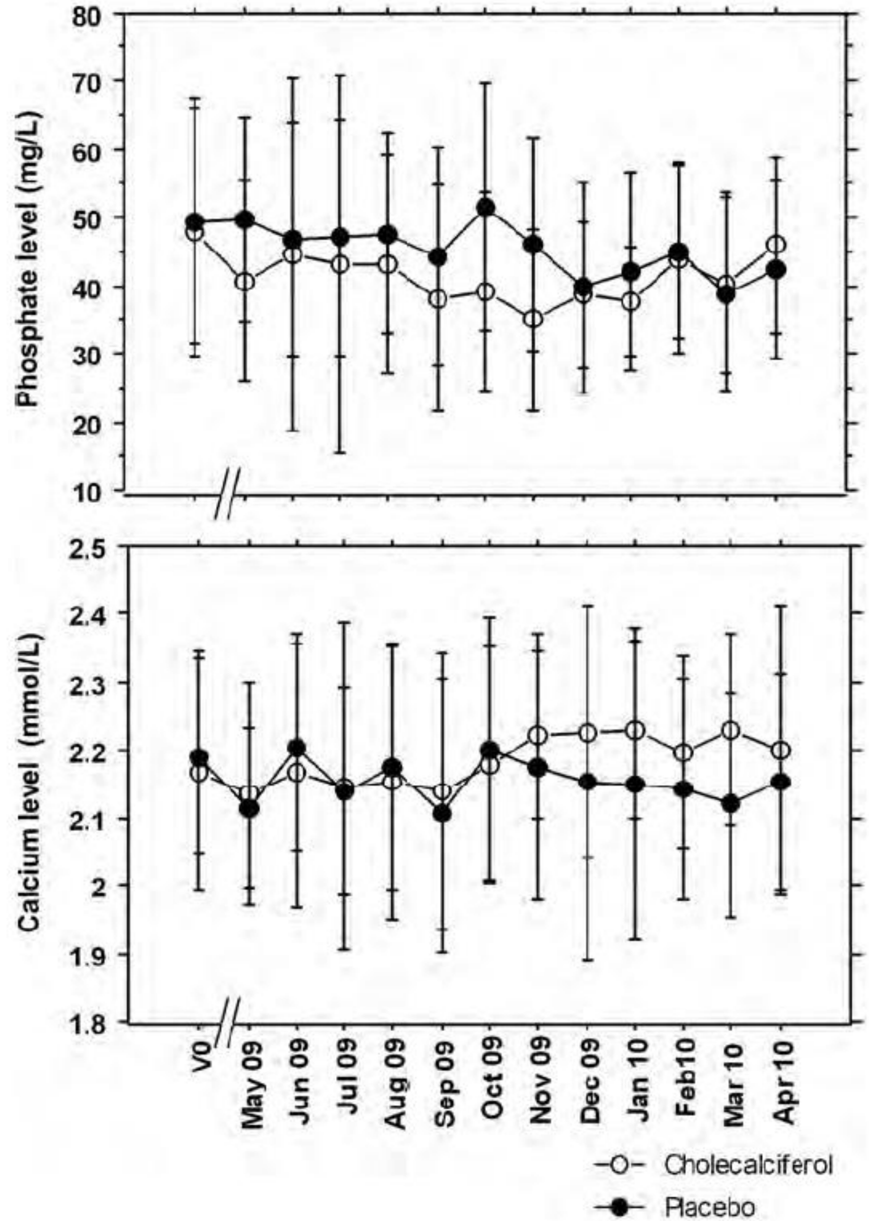

Table 2. Changes in the main safety variables over the 1-year study period

	Placebo			Cholecalciferol (25 000 IU, every 2 weeks)			
	Baseline	Delta over 1 year	P[a]	Baseline	Delta over 1 year	P[a]	P[b]
N	14			16			
Parathormone (pg/mL) Median (IQR)	240 (195–410)	80 (−58 to 153)	–	312 (206–447)	−115 [−192 to 81]	–	0.02*
Calcium (mmol/L)	2.16 ± 0.11	−0.01 ± 0.14	0.79	2.18 ± 0.15	0.02 ± 0.21	0.71	0.65
Phosphorus (mg/L)	45 ± 11	−3 ± 10	0.35	46 ± 13	0 ± 13	0.94	0.59
Calcification score	8 ± 8	2 ± 3	0.03	8 ± 5	2 ± 2	0.0003	0.89

Values are given as mean ± SD or as median (interquartile range).
[a]P-value for a paired *t*-test for within treatment groups variation over 1 year.
[b]P-value for the *t*-test or *Mann–Whitney test comparing the change from baseline to 1 year between treatment groups. Values are expressed as mean ± SD, if not specified.

Vitamine D active(s)

Vitamine D active

- Premières études chez l'homme au début des années 70
  Brickman AS, NEJM, 1972, p891

The New England
Journal of Medicine

Volume 287 NOVEMBER 2, 1972 Number 18

ACTION OF 1,25-DIHYDROXYCHOLECALCIFEROL, A POTENT, KIDNEY-PRODUCED METABOLITE OF VITAMIN D_3, IN UREMIC MAN

Arnold S. Brickman, M.D., Jack W. Coburn, M.D., and Anthony W. Norman, Ph.D.

Abstract Only the kidney is capable of producing 1,25-dihydroxycholecalciferol (1,25diOHC), the probable active form of vitamin D. The possibility that parenchymal damage in chronic renal disease impairs production of 1,25diOHC and accounts for "vitamin-D-resistant" uremia prompted our evaluation of its effect in uremic man. Three patients with advanced renal failure showed significant responses to daily treatment with only 100 U (2.7 μg) of 1,25diOHC for six to 10 days: serum calcium and phosphorus rose; intestinal radioactive calcium (^{47}Ca) absorption increased by 30 to 220 per cent; and fecal calcium decreased by 25 to 71 per cent in those undergoing balance studies. In contrast, 40,000 U (1 mg) of vitamin D_3 caused no change in serum calcium and phosphorus and had negligible effects on ^{47}Ca absorption. Thus, 1,25diOHC is highly active in uremic man, and its impaired production may account for certain abnormalities of calcium homeostasis in uremia. The agent may hold future promise in management of disordered calcium metabolism in uremia.

Références	Echantillon	Comparateurs	Calcium	Phosphore	PTH	Commentaires
Maxwell, 1978 [1]	13 9 Dialysés	D_3 : 1200 U/J PO Calcitriol : jusque 1,5 µg/j PO (dose moyenne 0.5 µg/j)	Stable Augmente 5 patients avec au moins une fois >2.63 mmol/L	ND	ND	Randomisé, double aveugle 11 semaines 400 U D_3/J 8 semianes avant dans les 2 groupes
Berl, 1978 [2]	16 15 Dialysés	D_3 : 400 U/J PO et augmentation jusqu'à 1200 Calcitriol : 0,5 µg/j PO et augmentation jusqu'à 1.5	Stable Augmente de 2.26 à 2.56 mmo/L 5 patients avec au moins une fois >2.88 mmol/L	Stable Stable	Mesuré chez 15 et 13 patients Stable Diminution chez 11/13	Randomisé, double aveugle 12 semaines 400 U D_3/J 8 semianes avant dans les 2 groupes
Baker, 1986 [3]	38 38 Dialysés	Placebo Calcitriol : 0,5 µg/j PO (max 1 µg/j)	Stable Fréquemment > 2.75 mmol/L	ND	Augmente Diminue	Randomisé 5 ans (plus que 7 patients à 5 ans)
Nordal, 1989	14 14 MRC	Placebo Calcitriol: 0.25 µg/j PO	Diminue Augmente 7 patients au moins une fois hypercalcémie	Stable Stable	Stable Diminue	Randomisé, double aveugle Amélioration de la biospie osseuse (high turneover)
Baker, 1989 [3]	6 7 MRC	Placebo Calcitriol : 0,2 à 0.5 µg/j PO	Stable Augmente 4 patients au moins une fois hypercalcémie	Stable Stable		Randomisé, double aveugle 12 mois Amélioration de la biospie osseuse (high turneover)
Hamdy, 1995 [7]	87 89 MRC	Placebo Alphacalcidol 0.25 à 1 µg/j	Stable Augmentation >3 mmol/L 1 fois chez 3 patients	Stable Stable	Augmente Diminue puis stable	Randomisée, double aveugle 2 ans Effet positif de l'alfacalcidol sur l'os

Vitamine D active

- Le calcitriol et l’alfacalcidol sont efficaces!!!
- Efficacité surtout si P contrôlé !
- Risque d’hypercalcémie (mais à l’époque…)
- Risque d’os adynamique

IV ou PO ?

- Premières études IV dans les années 80

Andress, NEJM, 1989, p274 Slatoposky, J Clin Invest, 1984, p2136

- Plus efficace? Moins d'hypercalcémie?

INTRAVENOUS CALCITRIOL IN THE TREATMENT OF REFRACTORY OSTEITIS FIBROSA OF CHRONIC RENAL FAILURE

DENNIS L. ANDRESS, M.D., KEITH C. NORRIS, M.D., JACK W. COBURN, M.D., EDUARDO A. SLATOPOLSKY, M.D., AND DONALD J. SHERRARD, M.D.

Abstract Osteitis fibrosa, a frequent complication of chronic renal failure, is characterized by increased rates of bone formation and bone resorption due to increased secretion of parathyroid hormone (PTH). Effective treatment with oral calcitriol is often impossible in patients with osteitis fibrosa, because low doses may cause hypercalcemia. Because short-term infusions of intravenous calcitriol are capable of suppressing the secretion of parathyroid hormone in patients with uremia without causing hypercalcemia, we evaluated the effectiveness of long-term intermittent calcitriol infusions (1.0 to 2.5 μg three times weekly, during dialysis) in treating severe osteitis fibrosa in 12 consecutive patients on hemodialysis whose disease was refractory to conventional therapy.

After a mean (±SE) treatment period of 11.5±1.4 months, the mean bone-formation rate declined from 1642±277 to 676±106 μm^2 per square millimeter per day (P<0.01) in the 11 patients who successfully completed the study. Similar reductions occurred in the osteoblastic osteoid (18±3 to 9±2 percent; P<0.01) and the degree of marrow fibrosis (6.2±1.7 to 3.5±1.3 percent; P = 0.01). Concomitant serum biochemical changes included increased calcium levels (2.55±0.03 to 2.67±0.05 mmol per liter; P<0.01), decreased alkaline phosphatase levels (489±77 to 184±32 U per liter; P<0.001), and decreased levels of PTH (amino-terminal, 172±34 to 69±16 ng per liter in five patients, P<0.03; and carboxy-terminal, 1468±467 to 1083±402 ml-eq per liter in six patients, P not significant). Although the majority of the patients had transient episodes of asymptomatic hypercalcemia, this complication could be quickly reversed by temporarily halting treatment or decreasing the dose of calcitriol.

We conclude that long-term intermittent infusions of intravenous calcitriol are effective in ameliorating osteitis fibrosa in patients on dialysis. Patients whose osteitis fibrosa is refractory to oral calcitriol and who are candidates for parathyroidectomy should be considered first for intravenous calcitriol therapy. (N Engl J Med 1989; 321:274-9.)

IV *versus* PO

Références	Echantillon	Comparateurs	Calcium	Phosphore	PTH	Commentaires
Fischer, 1993 [4]	11 Dialysés	Calcitriol IV 3X/sem 2 µg Calcitriol PO 3X/sem 2 µg	Augmente et 11 épisodes d'hypercalcémie (>2.7 mmol/L) chez 8 patients Augmente et 10 épisodes d'hypercalcémie (>2.7 mmol/L) chez 7 patients	Stable Stable	Diminue Diminue	Crossover (IV puis PO chez 6, inverse chez 5) 4 mois Effet identique sur la PTH, le calcium et le phosphore
Mazzaferro, 1994 [5]	12 Dialysés	Calcitriol IV 3X/sem 0.015 µg/Kg (1 µg pour 70 kg) Calcitriol PO 3X/sem 0.015 µg/Kg (1 µg pour 70 kg)	Stable Stable	Diminue Stable		Randomisé 8 mois Modification du bain en calcium dans le groupe IV Effet plus important du groupe IV sur PTH Amélioration des paramètres d'ostéite fibreuse à la biospie dans le groupe IV
Quarles, 1994 [6]	9 10 Dialysés	Calcitriol IV 3X/sem 2 à 4 µg Calcitriol PO 3X/sem 2 à 4 µg	Augmente et 80% avec au moins une fois >2.6 mmol/L Augmente et 56% avec au moins une fois >2.6 mmol/L	Diminue Diminue	Diminue Diminue	Randomisé, double aveugle 36 semaines Même diminution de PTH Même fréquence d'hypercalcémie et d'hyperphosphatémie (>7 mg/dL) Echec du traitement sur la PTH si hyperP
Indridason, 2000 [8]	11 20 21 Dialysés	Calcium Calcitriol PO, 0.5 µg/j Calcitriol IV, 1 µg IV 3x/sem But=calcémie à 2.5-2.6 mmol/L	Augmente et 2 épisodes d'hypercalcémie/patient /an Augmente et 3 épisodes d'hypercalcémie/patient /an Augmente et 3.4 épisodes d'hypercalcémie/patient /an	Diminue et 0.9 épisodes d'hyperP/patient/an Augmente et 4.2 épisodes d'hyperP/patient/an Augmente et et 4.9 épisodes d'hyperP/patient/an	Diminue Diminue Diminue	Randomisé 40 semaines Doses moyennes à la fin : Calcium : 5.6 g, calcitriol PO : 3.9 µg/sem, IV : 4.6 µg/sem (2.2g de calcium constant dans les 2 groupes calcitriol) Effet sur calcémie idem dans 3 groupes Effet sur P idem entre PO et IV Effet sur PTH idem (surtout si compliance prise en compte)

Bolus IV

- Efficace: oui
- Plus efficace: moins sûr
- Moins hyperCa et moins hyperP: probablement pas
- Plus cher
- Compliance

Les dérivés de la vitamine D active

- Paricalcitol
- Maxacalcitol
- Doxercalciferol
- Oxacalcitriol
- Falecalcitriol

- Physio: Activateur sélectif du VDR, à savoir action au niveau du R des parathyroides mais pas (ou moins) de l'intestin

- Nombreuses études animales: moins d'hyperCa, moins d'hyperP, moins de calcifications, moins d'HVG
- <u>Etudes versus placebo: Diminution PTH de 42% à 6 mois et 2% d'hypercalcémie</u>

Dérivés de la vitamin D active

- Peu d’hypercalcémie: c’est possible si titrage de la dose avec le paricalcitol et le calcitriol
- Efficacité comparable
- Paricalcitol agit plus vite
- Un peu plus d’objectif atteint mais au prix d’un peu plus d’”oversuppression”
- Coût-bénéfice?

Vitamine D active(s)

- Jamais d'analogues
- Jamais d'IV
- (quasi) Jamais en dehors d'une stratégie de **<u>traitement</u>** d'hyperPTH (sauf si hypoCa post PTHx)
- Pour le traitement de l'hyperPTH si

La 25-OH est normale

Il n'y a pas d'hyperP

Il n'y a pas d'hyperCa

- Titration des doses (+Delivery Observed Treatment)
- Pas de monitoring

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journal homepage: www.elsevier.com/locate/cca

Monitoring 25-OH and 1,25-OH vitamin D levels in hemodialysis patients after starting therapy: Does it make sense?

Pierre Delanaye[a,b,*], Antoine Lanot[c,d,e], Antoine Bouquegneau[a], Xavier Warling[f], Luc Radermacher[f], Catherine Masset[f], Jean-Marie Krzesinski[a], Olivier Moranne[b], Etienne Cavalier[g]

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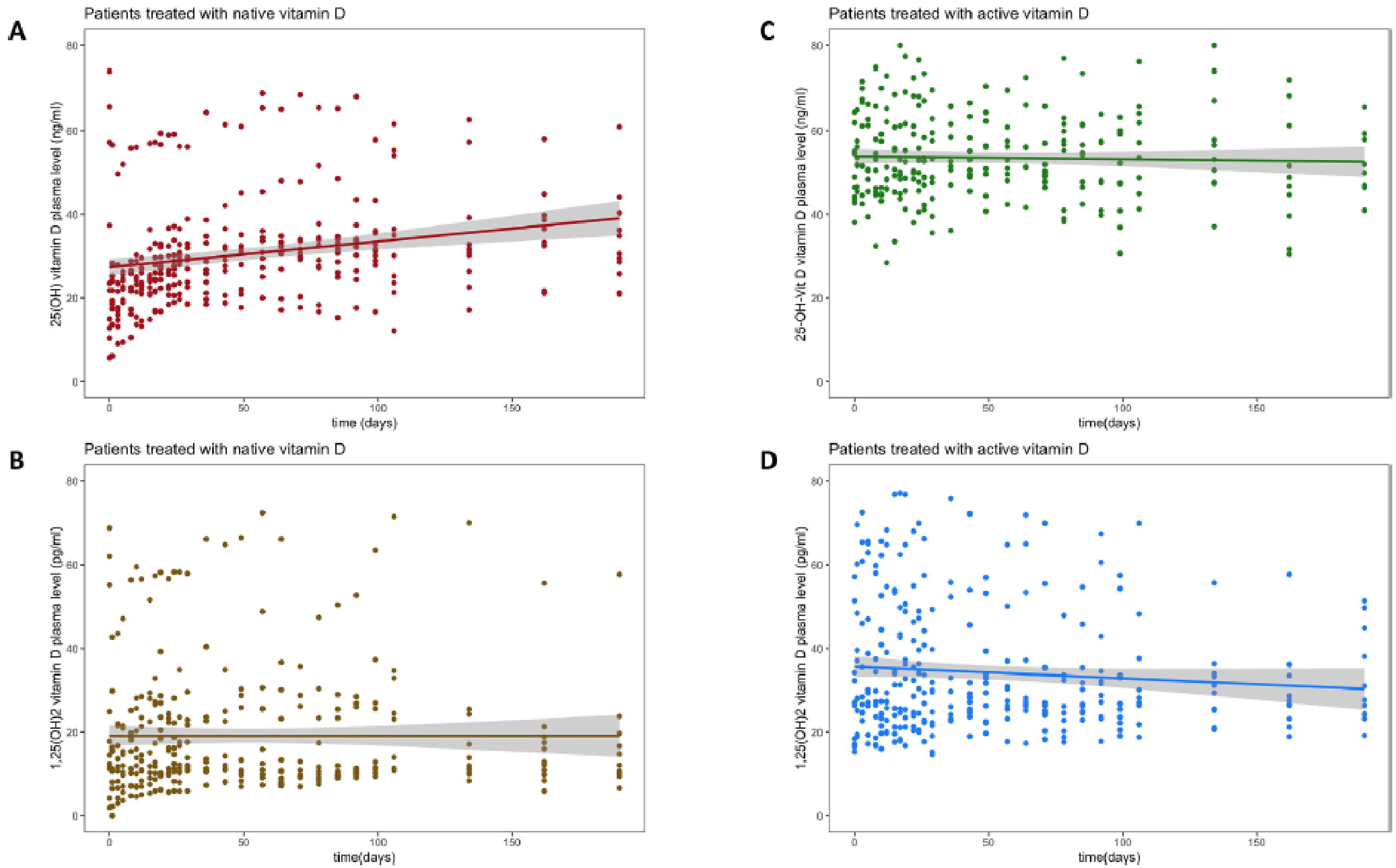


Fig. 2. Scatter plot and linear regression modeling the evolution of serum levels of: A. 25(OH) vitamin D in the group of patients treated with native vitamin D. B. 1,25$(OH)_2$ vitamin D in the group of patients treated with native vitamin D. C. 25(OH) vitamin D in the group of patients treated with active vitamin D. D. 1,25$(OH)_2$ vitamin D in the group of patients treated with active vitamin D.

Cinacalcet

The NEW ENGLAND JOURNAL of MEDICINE

ORIGINAL ARTICLE

Effect of Cinacalcet on Cardiovascular Disease in Patients Undergoing Dialysis

The EVOLVE Trial Investigators*

ABSTRACT

N Engl J Med 2012.

Table 1. Characteristics of the Patients at Baseline.*

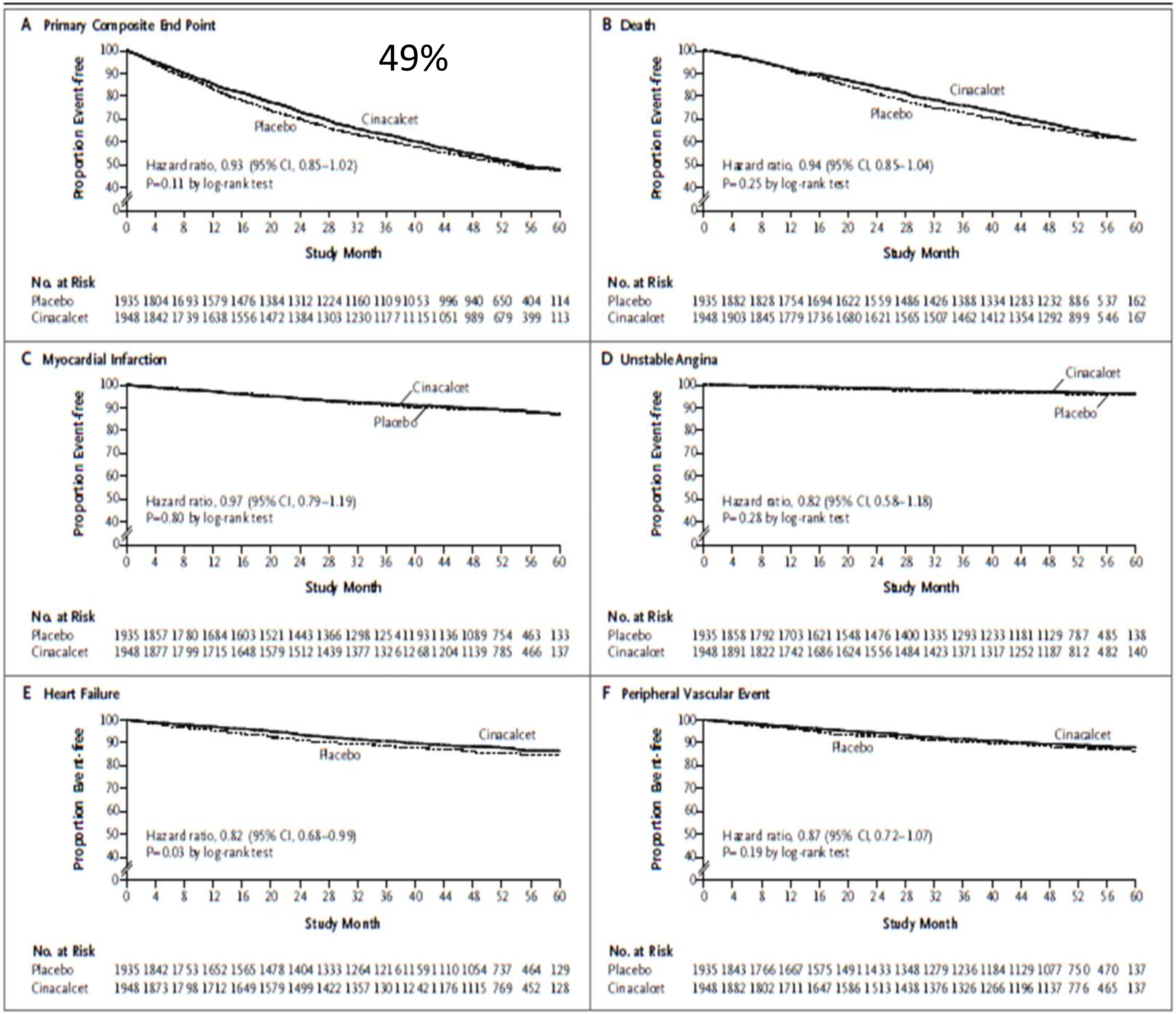
Characteristic	Cinacalcet (N=1948)	Placebo (N=1935)
Age (yr)		
Median	55.0	54.0
10th to 90th percentile	35.0–74.0	35.0–73.0
Female sex (%)	41.5	39.7
Race (%)†		
White	57.7	57.7
Black	21.0	22.1
Other	21.3	20.2
Body-mass index‡		
Median	26.3	26.4
10th to 90th percentile	20.4–36.4	20.6–36.7
Duration of dialysis (mo)		
Median	45.4	45.1
10th to 90th percentile	8.5–142.0	9.9–149.6
Blood pressure (mm Hg)		
Systolic		
Median	140	141
10th to 90th percentile	110–176	111–177
Diastolic		
Median	80	80
10th to 90th percentile	60–100	60–100
Medical history (%)		
Diabetes	33.6	33.5
Type 1	3.7	4.2
Type 2	29.8	29.4
Cardiovascular disease	95.4	94.6
Hypertension	92.5	91.7
Heart failure	23.1	23.6
Peripheral vascular disease	16.1	16.6
Coronary-artery bypass grafting	6.9	8.0
Percutaneous coronary intervention	6.7	6.8
Myocardial infarction	12.3	12.6
Stroke	8.3	10.0
Transient ischemic attack	5.1	3.8
Amputation	6.2	6.7
Atrial fibrillation	10.4	11.6

* There were no significant differences between the two groups except for mean diastolic blood pressure (P=0.02) and transient ischemic attack (P<0.05).

† Race was self-reported.

‡ The body-mass index is the weight in kilograms divided by the square of the height in meters.

	Cinacalcet (N=1948)	Placebo (N=1935)
Laboratory parameters		
iPTH (pg/mL)		
Median	695	690
p10, p90	362, 1707	363, 1683
Corrected calcium (mg/dL)		
Median	9.8	9.8
p10, p90	9.0, 10.7	9.0, 10.7
Phosphorus (mg/dL)		
Median	6.3	6.2
p10, p90	4.9, 8.3	4.9, 8.4
Ca x P (mg^2/dL^2)		
Median	60.9	60.3
p10, p90	48.0, 81.8	47.5, 82.3
25(OH) D (ng/mL) *		
Median	17	18
p10, p90	8, 37	8, 38
Bone-specific alkaline phosphatase (µg/L)		
Median	23.12	22.90
p10, p90	11.46, 71.03	11.53, 66.55

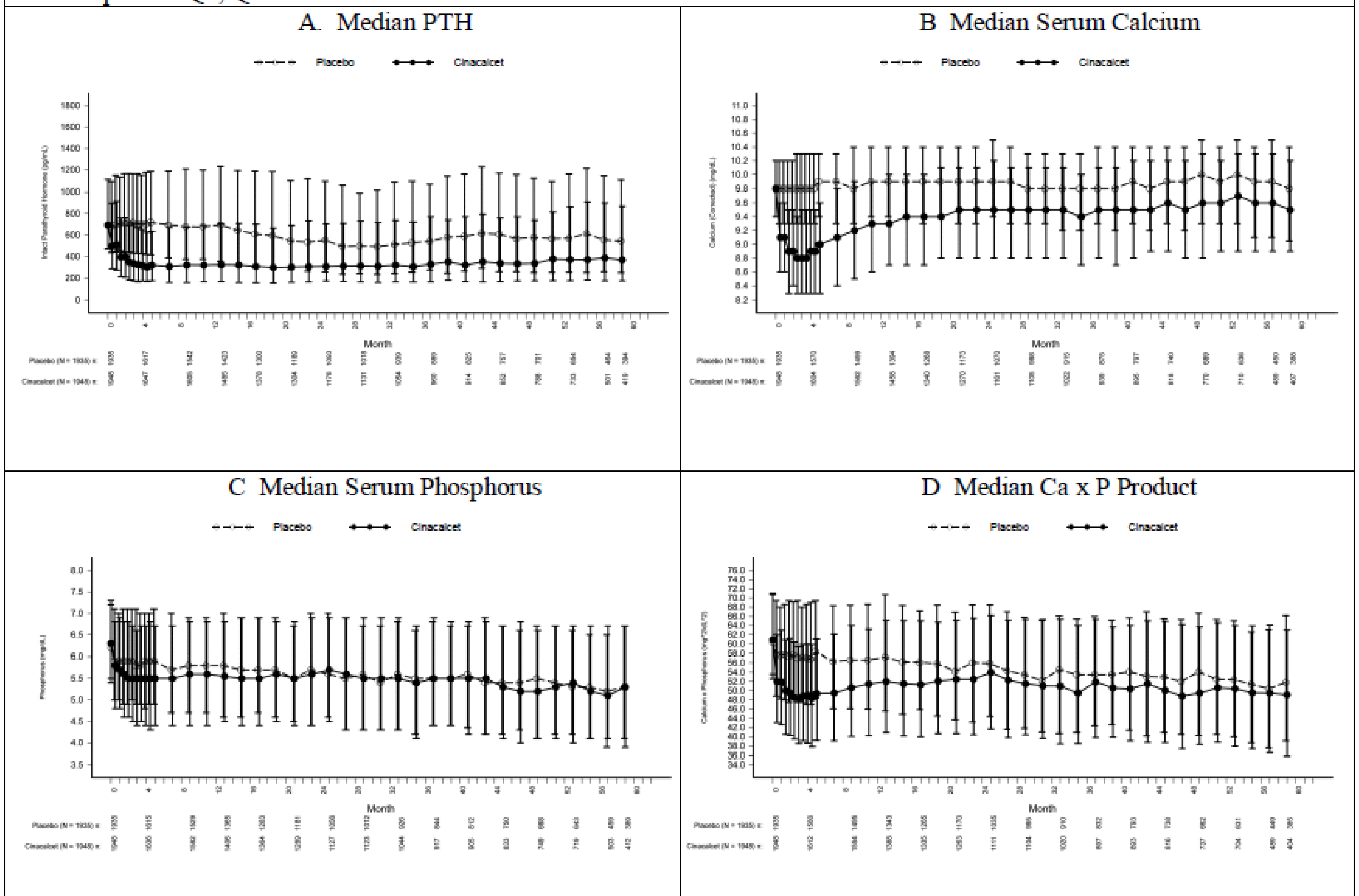


49%
A Primary Composite End Point
Proportion Event-free
Cinacalcet
Placebo
Hazard ratio, 0.93 (95% CI, 0.85–1.02)
P=0.11 by log-rank test
Study Month
No. at Risk
Placebo 1935 1804 1693 1579 1476 1384 1312 1224 1160 1109 1053 996 940 650 404 114
Cinacalcet 1948 1842 1739 1638 1556 1472 1384 1303 1230 1177 1115 1051 989 679 399 113
B Death
Proportion Event-free
Cinacalcet
Placebo
Hazard ratio, 0.94 (95% CI, 0.85–1.04)
P=0.25 by log-rank test
Study Month
No. at Risk
Placebo 1935 1882 1828 1754 1694 1622 1559 1486 1426 1388 1334 1283 1232 886 537 162
Cinacalcet 1948 1903 1845 1779 1736 1680 1621 1565 1507 1462 1412 1354 1292 899 546 167
C Myocardial Infarction
Proportion Event-free
Cinacalcet
Placebo
Hazard ratio, 0.97 (95% CI, 0.79–1.19)
P=0.80 by log-rank test
Study Month
No. at Risk
Placebo 1935 1857 1780 1684 1603 1521 1443 1366 1298 1254 1193 1136 1089 754 463 133
Cinacalcet 1948 1877 1799 1715 1648 1579 1512 1439 1377 1326 1268 1204 1139 785 466 137
D Unstable Angina
Proportion Event-free
Cinacalcet
Placebo
Hazard ratio, 0.82 (95% CI, 0.58–1.18)
P=0.28 by log-rank test
Study Month
No. at Risk
Placebo 1935 1858 1792 1703 1621 1548 1476 1400 1335 1293 1233 1181 1129 787 485 138
Cinacalcet 1948 1891 1822 1742 1686 1624 1556 1484 1423 1371 1317 1252 1187 812 482 140
E Heart Failure
Proportion Event-free
Cinacalcet
Placebo
Hazard ratio, 0.82 (95% CI, 0.68–0.99)
P=0.03 by log-rank test
Study Month
No. at Risk
Placebo 1935 1842 1753 1652 1565 1478 1404 1333 1264 1216 1159 1110 1054 737 464 129
Cinacalcet 1948 1873 1798 1712 1649 1579 1499 1422 1357 1301 1242 1176 1115 769 452 128
F Peripheral Vascular Event
Proportion Event-free
Cinacalcet
Placebo
Hazard ratio, 0.87 (95% CI, 0.72–1.07)
P=0.19 by log-rank test
Study Month
No. at Risk
Placebo 1935 1843 1766 1667 1575 1491 1433 1348 1279 1236 1184 1129 1077 750 470 137
Cinacalcet 1948 1882 1802 1711 1647 1586 1513 1438 1376 1326 1266 1196 1137 776 465 137

Résultats négatifs mais…

Figure S4: Biochemical parameters during the study (intent-to-treat analysis)

I bars represent Q1, Q3

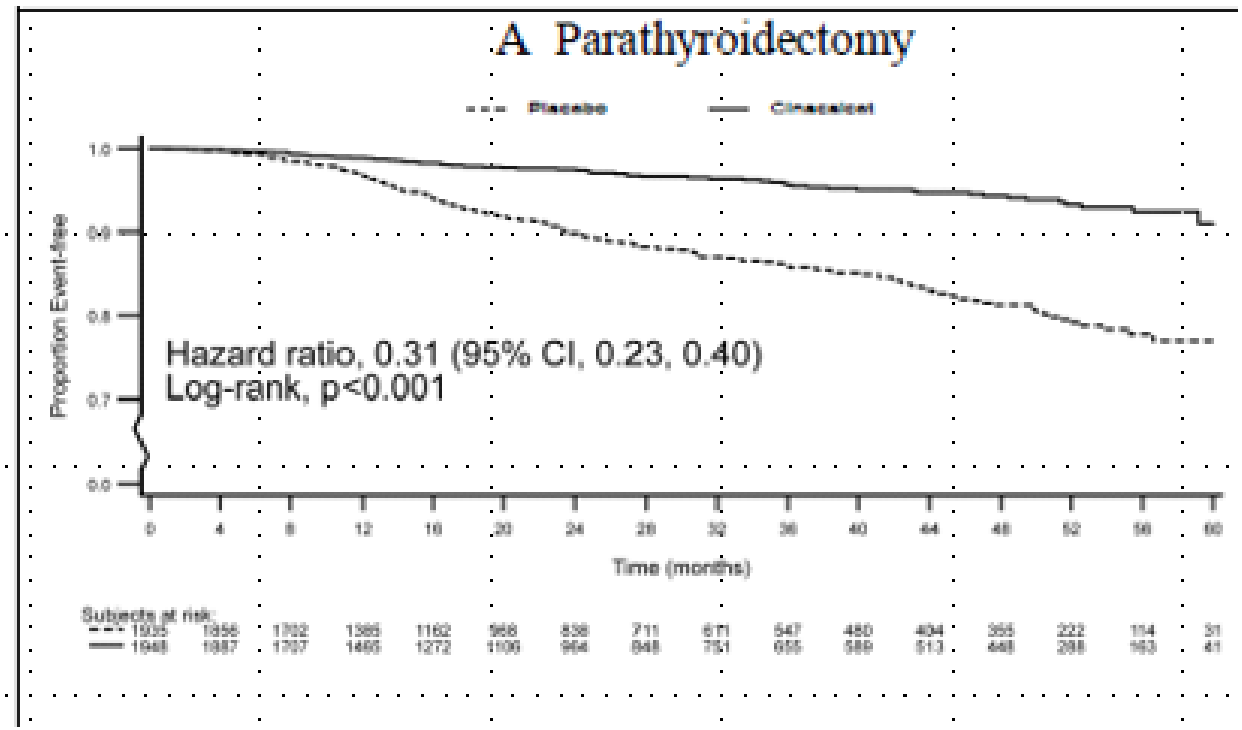


N = Number of patients in the intent-to-treat analysis set

n = Number of patients with laboratory value at the study visit

PTH = plasma intact parathyroid hormone

Résultats négatifs mais…



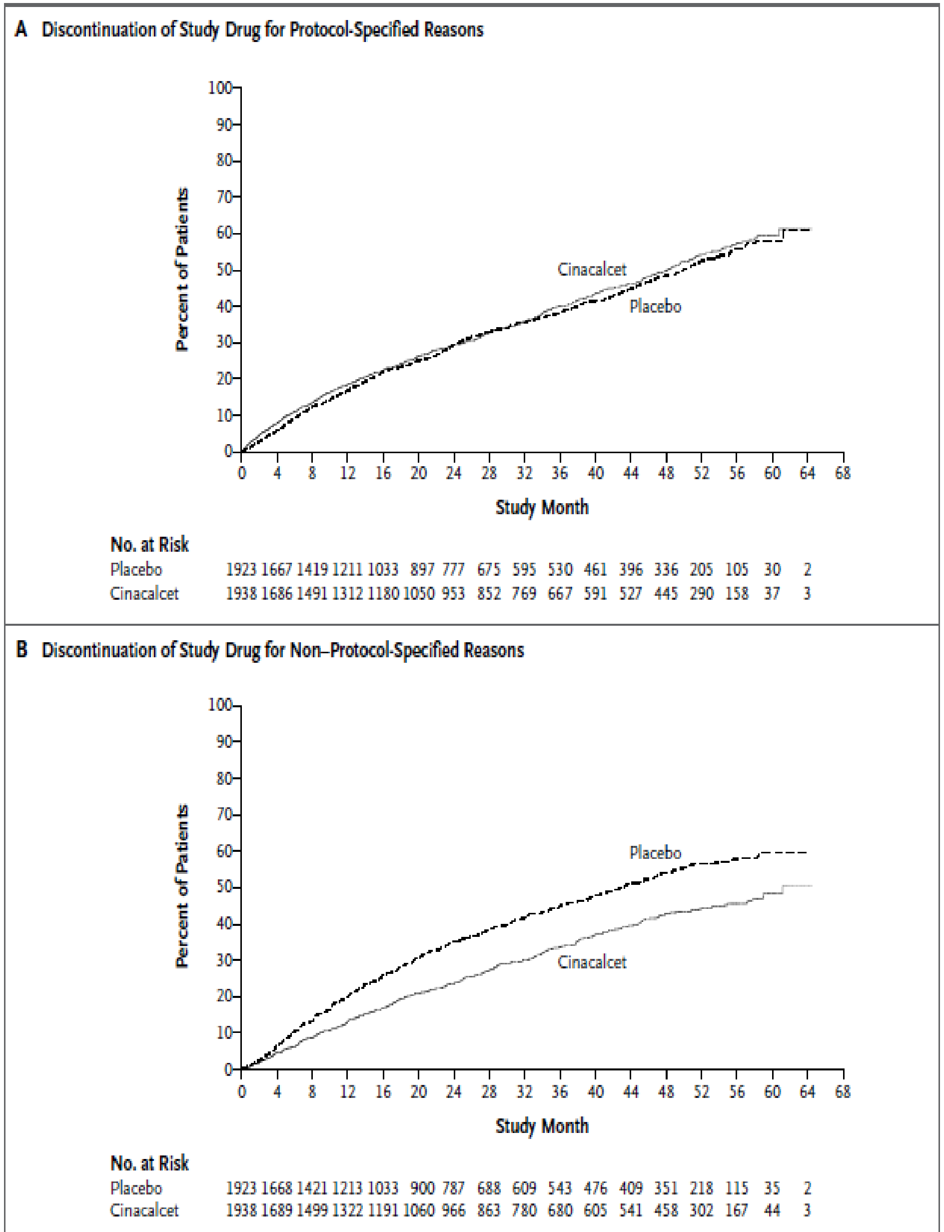


Figure 2. Cumulative Incidence of Study-Drug Discontinuation in the As-Treated Population.
Shown are Kaplan–Meier curves comparing cinacalcet with placebo with respect to the time to discontinuation of a study drug for protocol-specified reasons (Panel A) and non–protocol-specified reasons (Panel B).

Cinacalcet stoppé:
66,7%
16% pour ES, 21% pour raisons « administratives » ou souhait du patient et 22% selon protocole

Placebo stoppé:
70,5%
12% pour ES, 31% pour raisons « administratives » ou souhait du patient et 20% selon protocole

Cinacalcet débuté dans le groupe placebo: 19.8%

Effets secondaires

Table 2. Adverse Events.*

Event	Cinacalcet (N=1938)			Placebo (N=1923)		
	No. of Patients	Exposure-Adjusted Rate†	Crude Incidence‡	No. of Patients	Exposure-Adjusted Rate†	Crude Incidence‡
		no. of patients/ 100 patient-yr	*% of patients*		*no. of patients/ 100 patient-yr*	*% of patients*
All adverse events§	1806	273.2	93.2	1748	217.8	90.9
Nausea§	563	18.3	29.1	299	9.1	15.5
Vomiting§	497	15.4	25.6	264	8.0	13.7
Diarrhea	397	12.0	20.5	360	11.5	18.7
Serious adverse events	1338	53.3	69.0	1351	56.9	70.3
Treatment-related events						
Adverse events§	890	35.3	45.9	363	11.3	18.9
Serious adverse events¶	69	1.8	3.6	44	1.2	2.3
Events associated with important identified risk						
Convulsions	48	1.2	2.5	30	0.8	1.6
Hypocalcemia§	240	6.7	12.4	33	0.9	1.7
Hypersensitivity reaction	183	4.9	9.4	160	4.6	8.3
Additional adverse events of interest						
Acute pancreatitis	20	0.5	1.0	20	0.5	1.0
Possibly drug-related hepatic disorder	45	1.1	2.3	50	1.4	2.6
Nervous system disorder‖	711	24.3	36.7	586	20.5	30.5
Ventricular arrhythmia	18	0.4	0.9	23	0.6	1.2
Neoplastic event††						
Any	115	2.9	5.9	90	2.5	4.7
Fatal	25	0.6	1.3	23	0.6	1.2
Calciphylaxis‖	6	0.1	0.3	18	0.5	0.9
Hypercalcemia	32	0.8	1.7	36	1.0	1.9
Hyperphosphatemia	28	0.7	1.4	30	0.8	1.6

CONCLUSIONS

In an unadjusted intention-to-treat analysis, cinacalcet did not significantly reduce the risk of death or major cardiovascular events in patients with moderate-to-severe secondary hyperparathyroidism who were undergoing dialysis. (Funded by Amgen; EVOLVE ClinicalTrials.gov number, NCT00345839.)

JAMA | Original Investigation

Effect of Etelcalcetide vs Placebo on Serum Parathyroid Hormone in Patients Receiving Hemodialysis With Secondary Hyperparathyroidism

Two Randomized Clinical Trials

JAMA. 2017;317(2):146-155.

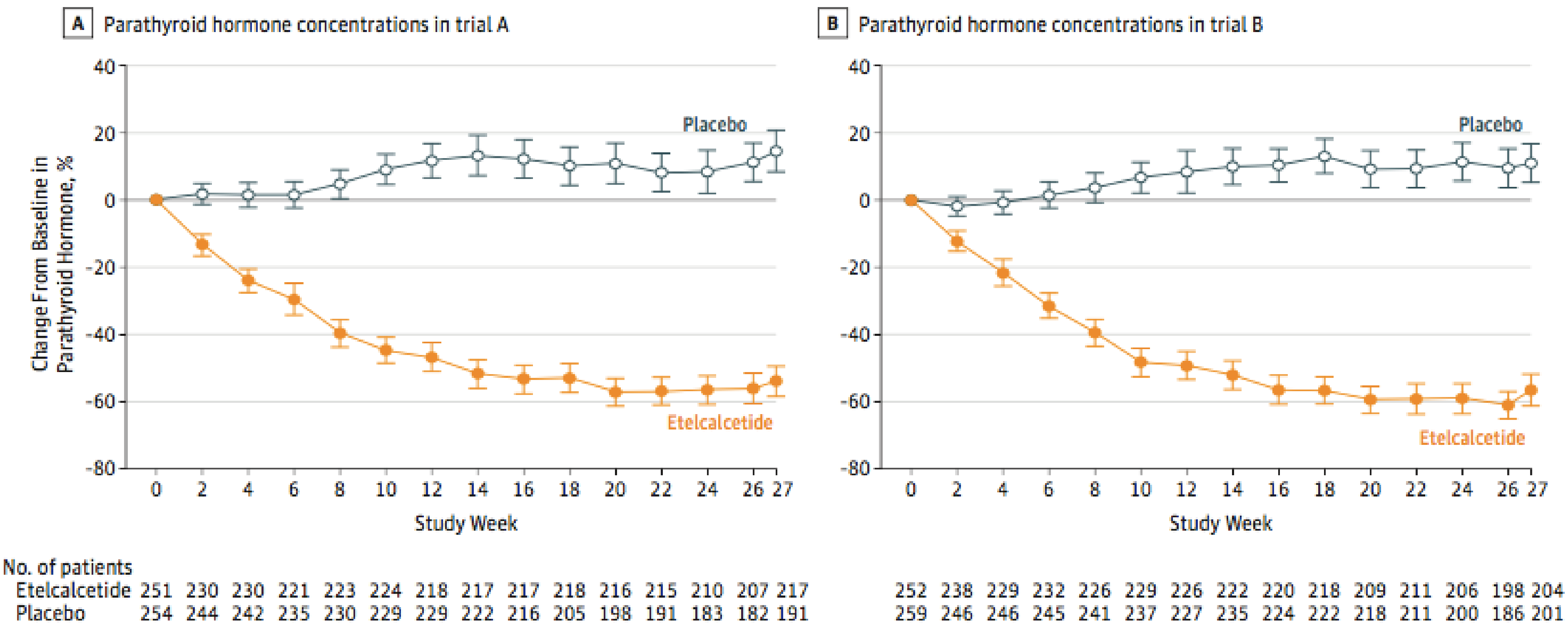
Geoffrey A. Block, MD; David A. Bushinsky, MD; John Cunningham, DM; Tilman B. Drueke, MD; Markus Ketteler, MD; Reshma Kewalramani, MD; Kevin J. Martin, MB, BCh; T. Christian Mix, MD; Sharon M. Moe, MD; Uptal D. Patel, MD; Justin Silver, MD; David M. Spiegel, MD; Lulu Sterling, PhD; Liron Walsh, MD; Glenn M. Chertow, MD, MPH

COMBINAISON DE 2 ESSAIS CONTROLES RANDOMISES EN DOUBLE AVEUGLE, DE PHASE 3

OBJECTIF PRIMAIRE:
% de pts ayant une réduction de PTH initiale >30%

OBJECTIFS SECONDAIRES:
% de patients ayant une PTH < ou égale à 300 pg/ml
% de réduction PTH, calcium et phosphore

OBJECTIF PRINCIPAL



PROPORTION DE PATIENTS AYANT UNE REDUCTION >3O% PTH

74-75,3% vs 8,3-9,6% (p<0,001)

JAMA | Original Investigation

Effect of Etelcalcetide vs Cinacalcet on Serum Parathyroid Hormone in Patients Receiving Hemodialysis With Secondary Hyperparathyroidism
A Randomized Clinical Trial

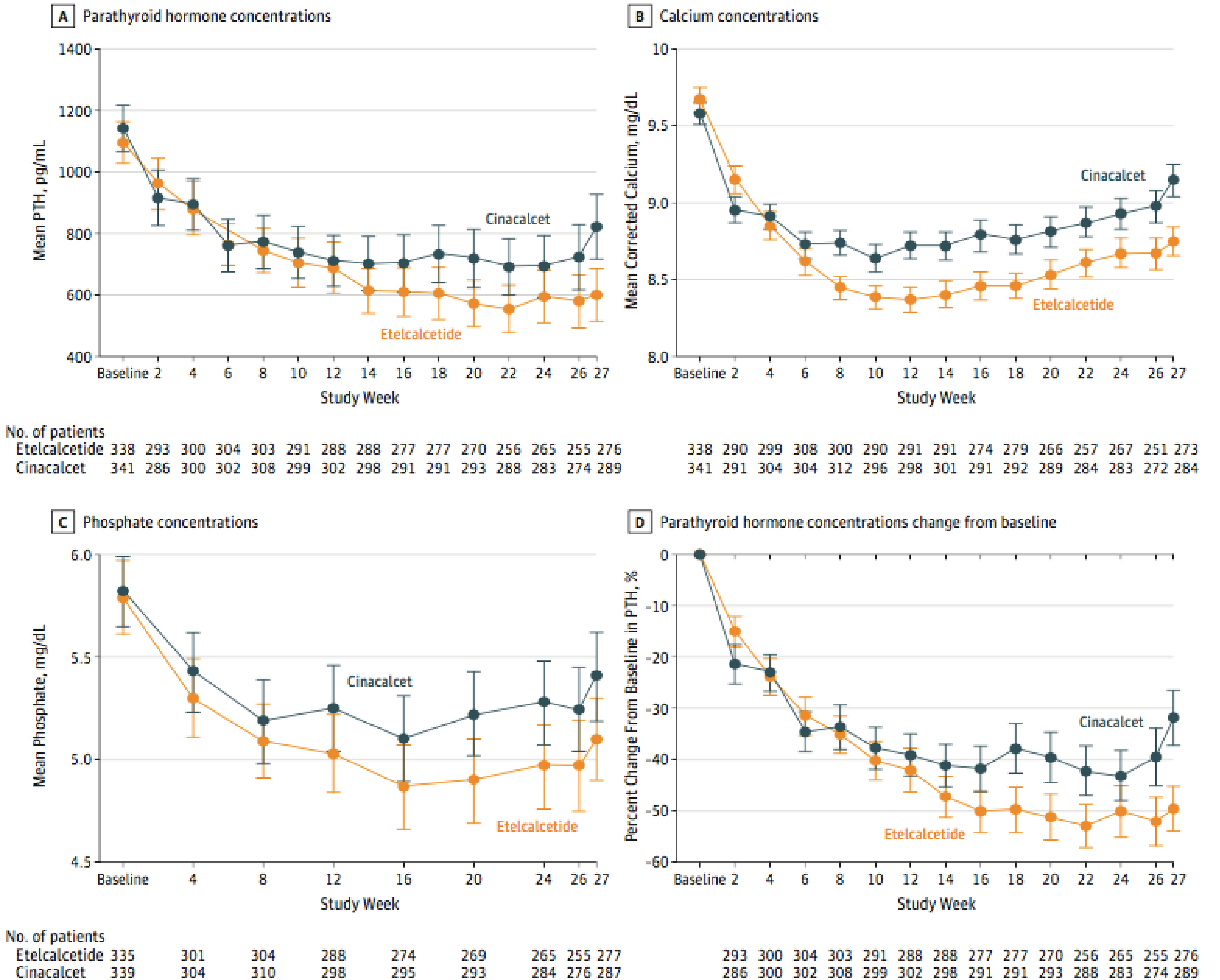
JAMA. 2017;317(2):156-164.

Geoffrey A. Block, MD; David A. Bushinsky, MD; Sunfa Cheng, MD; John Cunningham, MD; Bastian Dehmel, MD; Tilman B. Drueke, MD; Markus Ketteler, MD; Reshma Kewalramani, MD; Kevin J. Martin, MB, BCh; Sharon M. Moe, MD; Uptal D. Patel, MD; Justin Silver, MD; Yan Sun, MS; Hao Wang, PhD; Glenn M. Chertow, MD, MPH

ESSAI CONTROLE RANDOMISE EN DOUBLE AVEUGLE et DOUBLE PLACEBO, DE PHASE 3

OBJECTIF PRIMAIRE:
% de pts ayant une réduction de PTH initiale >30%
NON INFERIORITE

OBJECTIFS SECONDAIRES:
% de patients ayant une réduction > 50% de PTH
% de patients ayant une réduction > 30% de PTH
Nombre de jours /semaine de nausées/vomissements (2 mois)
SUPERIORITE


A Parathyroid hormone concentrations
Mean PTH, pg/mL
1400
1200
1000
800
600
400
Cinacalcet
Etelcalcetide
Baseline 2 4 6 8 10 12 14 16 18 20 22 24 26 27
Study Week
No. of patients
Etelcalcetide 338 293 300 304 303 291 288 288 277 277 270 256 265 255 276
Cinacalcet 341 286 300 302 308 299 302 298 291 291 293 288 283 274 289
B Calcium concentrations
Mean Corrected Calcium, mg/dL
10
9.5
9.0
8.5
8.0
Cinacalcet
Etelcalcetide
Baseline 2 4 6 8 10 12 14 16 18 20 22 24 26 27
Study Week
338 290 299 308 300 290 291 291 274 279 266 257 267 251 273
341 291 304 304 312 296 298 301 291 292 289 284 283 272 284
C Phosphate concentrations
Mean Phosphate, mg/dL
6.0
5.5
5.0
4.5
Cinacalcet
Etelcalcetide
Baseline 4 8 12 16 20 24 26 27
Study Week
No. of patients
Etelcalcetide 335 301 304 288 274 269 265 255 277
Cinacalcet 339 304 310 298 295 293 284 276 287
D Parathyroid hormone concentrations change from baseline
Percent Change From Baseline in PTH, %
0
-10
-20
-30
-40
-50
-60
Cinacalcet
Etelcalcetide
Baseline 2 4 6 8 10 12 14 16 18 20 22 24 26 27
Study Week
293 300 304 303 291 288 288 277 277 270 256 265 255 276
286 300 302 308 299 302 298 291 291 293 288 283 274 289

Effets secondaires

Pas moins d'effets secondaires digestifs!

Nombre de patients (%)	**Etelcalcétide N = 338**	**Cinacalcet N = 341**
Ostéopathie adynamique	0	0
Insuffisance cardiaque	10 (3,0)	2 (0,6)
Convulsions	3 (0,9)	2 (0,6)
Hypersensibilité	19 (5,6)	17 (5,0)
Hypocalcémies	240 (71,0)	207 (60,7)
Diminution de la calcémie asymptomatique	233 (68,9)	204 (59,8)
Hypocalcémie symptomatique	17 (5,0)	8 (2,3)
Hypophosphatémie	5 (1,5)	3 (0,9)
Réaction à l'injection	68 (20,1)	53 (15,5)
Torsades de pointes / allongement QT	1 (0,3)	0
Tachyarythmies ventriculaires	0	0

Etelcalcetide: IV

est-ce que l’efficacité de l’etelcalcetide n’est pas due, du moins en partie, à la compliance meilleure (vu que le traitement est administré en dialyse) ?

Cinacalcet/etelcacétide

- Traitement de l’hyperPTH
- Sans hésiter si hypercalcémie et/ou hyperphosphatémie
- Facteur “limitant”: hypocalcémie
- Titration des doses (dans les deux sens)
- Je m’autorise l’hypocalcémie

Cinacalcet ou vitamin D active

- Traitements vraiment concurrents?
- NON!

PTHx

- Solution extrême et irréversible
- De moins en moins pratiquée en Europe
- Pas anodin
- Attention dans le post-op immédiat car “bone-hungry syndrome” et risque +++ d’hypocalcémie

Clinical Outcomes after Parathyroidectomy in a Nationwide Cohort of Patients on Hemodialysis

Areef Ishani,†‡ Jiannong Liu,* James B. Wetmore,* Kimberly A. Lowe,§ Thy Do,§ Brian D. Bradbury,§ Geoffrey A. Block,‖ and Allan J. Collins**

- USRDS
- N=4435
- 2007-2009
- Suivi 1 an

- Mortalité postop-30 jours = 2%

(post-op de néphrectomie pour don: 0.031% à 90 jours, post-op de néphrectomie pour néo: 2.6%)

(Mortalité à 30 jours de PTHx en population générale = 0.11%)

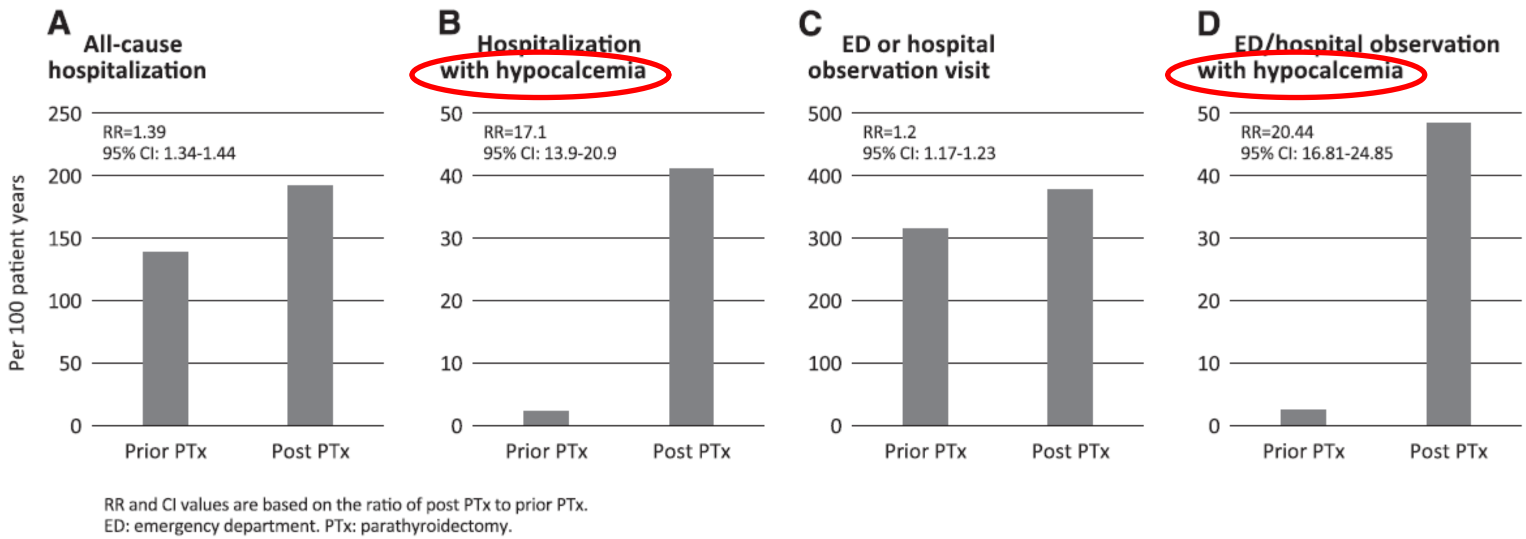


Figure 2. | Event rates in the 1 year before and 1 year after parathyroidectomy. (A) Total hospitalizations. (B) Total hospitalizations with hypocalcemia. (C) Total emergency department or observation visits. (D) Total emergency department or observation visits with hypocalcemia. RR and 95% CI values are based on the ratio of postparathyroidectomy to prior parathyroidectomy. 95% CI, 95% confidence interval; ED, emergency department; PTx, parathyroidectomy; RR, rate ratio.

Hyperphosphatémie

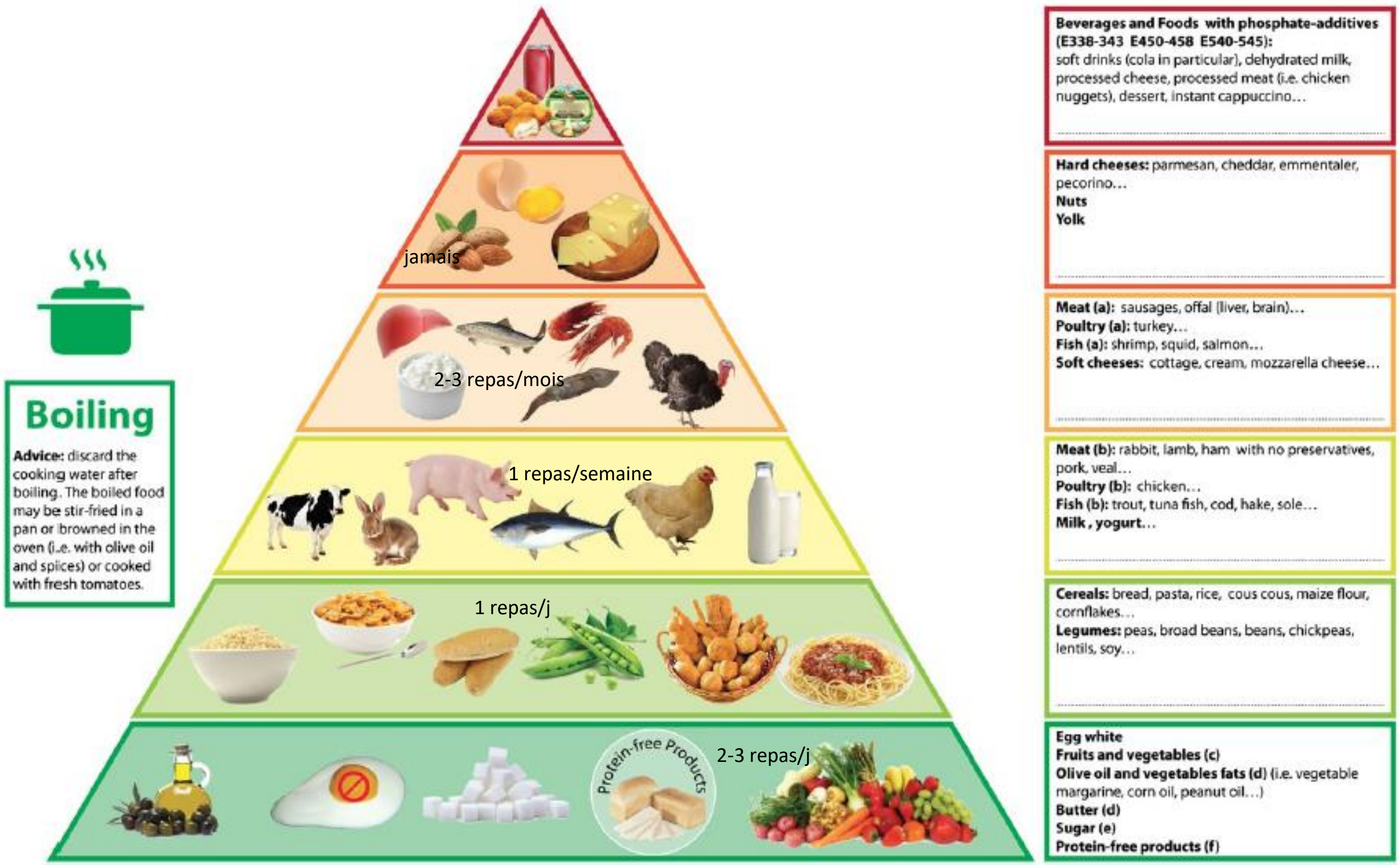
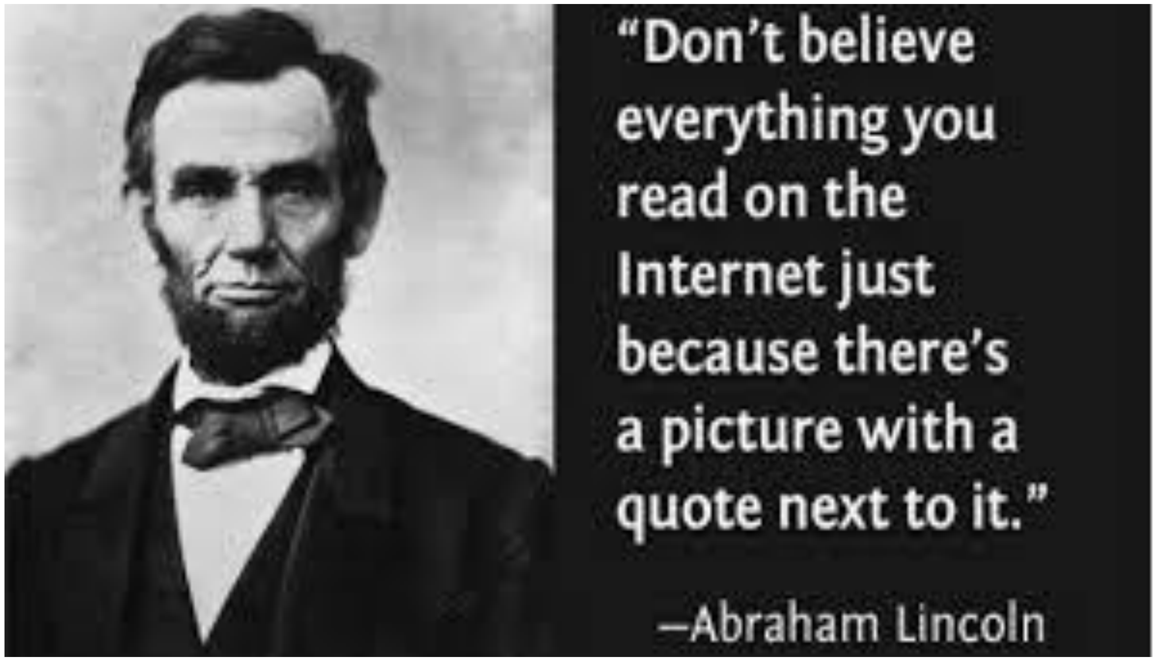


Figure 1 The phosphorus pyramid. Foods are distributed on six levels on the basis of their phosphorus content, phosphorus to protein ratio and phosphorus bioavailability. Each level has a colored edge (from green to red, through yellow and orange) that corresponds to recommended consumption frequency, 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 »

- Peu de preuves de l’utilité des chélateurs en pré-dialyse…

Les chélateurs…



Calcium / Sevelamer / Lanthanum/Magnesium/Dérivés du fer

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

HYPERKALIEMIE

- Définition pour les KDIGO: K> 5 mmol/l
- Pas de traitement avant 5,5 mmol/L
- Prélèvements…

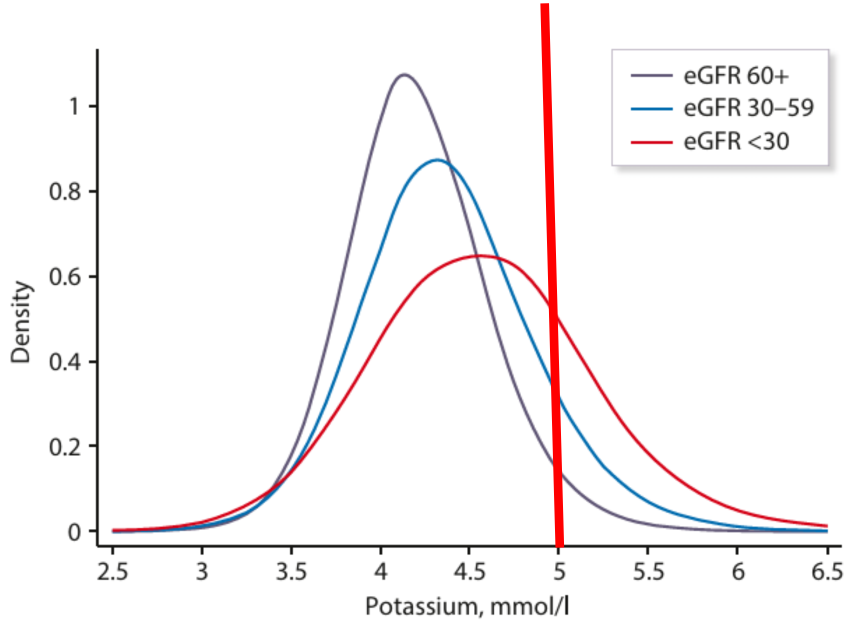


Figure 29 | Distribution of blood potassium in general population and high-risk cohorts from the Chronic Kidney Disease Prognosis Consortium, by estimated glomerular filtration rate (eGFR). Density refers to the proportion of the population experiencing serum potassium level (e.g., 0.08 of the population with a GFR >60 have a potassium of 3.8; conversely, 0.2 of the population with a GFR <30 have a potassium of 5.5). Reproduced from Kovesdy CP,

Table 26 | Medications associated with increased risk of hyperkalemia

Class	Mechanism	Example
ACEi	Inhibit conversion of angiotensin I to angiotensin II	Captopril, lisinopril, perindopril, etc.
ARB	Inhibit activation of angiotensin I receptor by angiotensin II	Losartan, irbesartan, candesartan, etc.
Aldosterone antagonist	Block aldosterone receptor activation	Spironolactone, eplerenone, and finerenone
β-Adrenergic receptor blocker	Inhibit renin release	Propranolol, metoprolol, and atenolol
Digitalis glycoside	Inhibit Na^+-K^+-ATPase, necessary for collecting duct K^+ secretion	Digoxin
Heparin	Reduced production of aldosterone	Heparin sodium
Potassium-sparing diuretic	Block collecting duct apical Na^+ channel, decreasing gradient for K^+ secretion	Amiloride and triamterene
NSAIDs	Inhibit synthesis of prostaglandin E and prostacyclin, inhibiting renin release	Ibuprofen, naproxen, diclofenac, etc.
CNI	Inhibit Na^+-K^+-ATPase, necessary for collecting duct K^+ secretion	Cyclosporine and tacrolimus
ns-MRA	Block MR-mediated Na^+ reabsorption	Finerenone
Other	Block collecting duct apical Na^+ channel, decreasing gradient for K^+ secretion	Trimethoprim and pentamidine

ACEi, angiotensin-converting enzyme inhibitor; ARB, angiotensin II receptor blocker; ATP, adenosine triphosphate; CNI, calcineurin inhibitor; K^+, potassium; Na^+, sodium; NSAID, nonsteroidal anti-inflammatory drug; ns-MRA, nonsteroidal mineralocorticoid receptor antagonist.
Data from Weiner *et al.*[576] and Kidney Disease: Improving Global Outcomes Diabetes Work Group.[23]

Résines

Table 27 | A comparison of potassium exchange agents

	(Polystyrene sulfonates) sodium or calcium	Patiromer	Sodium zirconium cyclosilicate (SZC)
Mechanism of action	Sodium-potassium exchange resin (SPS) or calcium-potassium exchange resin (CPS)	Calcium-potassium exchange polymer	Crystalline compound that traps K^+ in exchange for hydrogen and sodium cations
Counterion content	SPS: Suspension contains 65 mmol/60 ml (15 g) of sodium and powder approximately 4.1 mmol/g of sodium. CPS: 1.6–2.4 mmol/g of calcium.	1600 mg of calcium per 8.4 g of patiromer	Approximately 400 mg of sodium per 5 g of SZC
Cations bound	Potassium, magnesium, and calcium	Potassium, magnesium, and phosphate (bound by calcium release)[582]	Potassium
Formulation of route of administration	Powder for reconstitution (oral), suspension (oral), and enema (rectal)	Powder for reconstitution (oral)	Powder for reconstitution (oral suspension)
Dosage and titration	Oral: 15–60 g/d (up to 4 times per day) Rectal: 30 g/d (for SPS up to a maximum of 50 g/d)	Initial: 8.4 g orally once per day (maximum 25.2 g orally once per day); dose can be increased by 8.4 g increments at 1-week intervals	Initial: 10 g orally 3 times per day for up to 48 hours
Maintenance dosing	15–60 g/d orally per day depending on potassium level and level of tolerability	8.4–25.2 g orally once per day	5 g every second day to 10 g once per day
Onset of effect	Variable, hours to days	4–7 hours	Starts to reduce potassium within 1 hour with normokalemia typically at 24–48 hours
Duration of effect	Variable, 6–24 hours	24 hours	Not studied; not systematically absorbed and excreted fecally
Administration pearls	Separate from oral medications by at least 3 hours before or 3 hours after administration; if gastroparesis, separate other medications by 6 hours	Separate from oral medications by at least 3 hours before or 3 hours after administration except for those drugs to not have a clinically important interaction	No dose adjustments or separation of time of dosing is required for any medication that does not have pH-dependent bioavailability. However, SZC should be administered at least 2 hours before or 2 hours after oral medicinal products with clinically meaningful gastric pH-dependent bioavailability
Adverse effects	GI events (nausea, vomiting, diarrhea, constipation), electrolyte disturbances (hypokalemia, hypocalcemia, and hypomagnesemia), edema, and potentially serious GI adverse events (intestinal necrosis, bleeding, ischemic colitis, and perforation)	GI events (nausea, diarrhea, and flatulence), electrolyte disturbances (hypokalemia, hypercalcemia, and hypomagnesemia) Insufficient postmarketing surveillance at present to evaluate long-term/rare events	Hypokalemia and edema events are the most common. Milder reports of GI events (nausea, diarrhea, and constipation) Insufficient postmarketing surveillance at present to evaluate long-term/rare events

GI, gastrointestinal.

Modified from Bridgeman MB, Shah M, Foote E. Potassium-lowering agents for the treatment of nonemergent hyperkalemia: pharmacology, dosing and comparative efficacy. *Nephrology Dialysis Transplantation*, Volume 34, Supplement 3, pages iii45–iii50.[581]

1st line: **Address correctable factors**	• Review non-RASi medications (e.g. NSAIDs, trimethoprim) • Assess dietary potassium intake (dietary referral) and consider appropriate moderation of dietary potassium intake
2nd line: **Medications**	Consider: • Appropriate use of diuretics • Optimize serum bicarbonate levels • Licensed potassium exchange agents
3rd line: **Last resort**	• Reduce dose or discontinue RASi/MRA (Discontinuation is associated with increased cardiovascular events. Review and restart RASi or MRA at a later date if patient condition allows.)

Figure 32 | Actions to manage hyperkalemia (potassium >5.5 mmol/l) in chronic kidney disease. MRA, mineralocorticoid receptor antagonists; NSAID, nonsteroidal anti-inflammatory drug; RASi, renin-angiotensin system inhibitors.

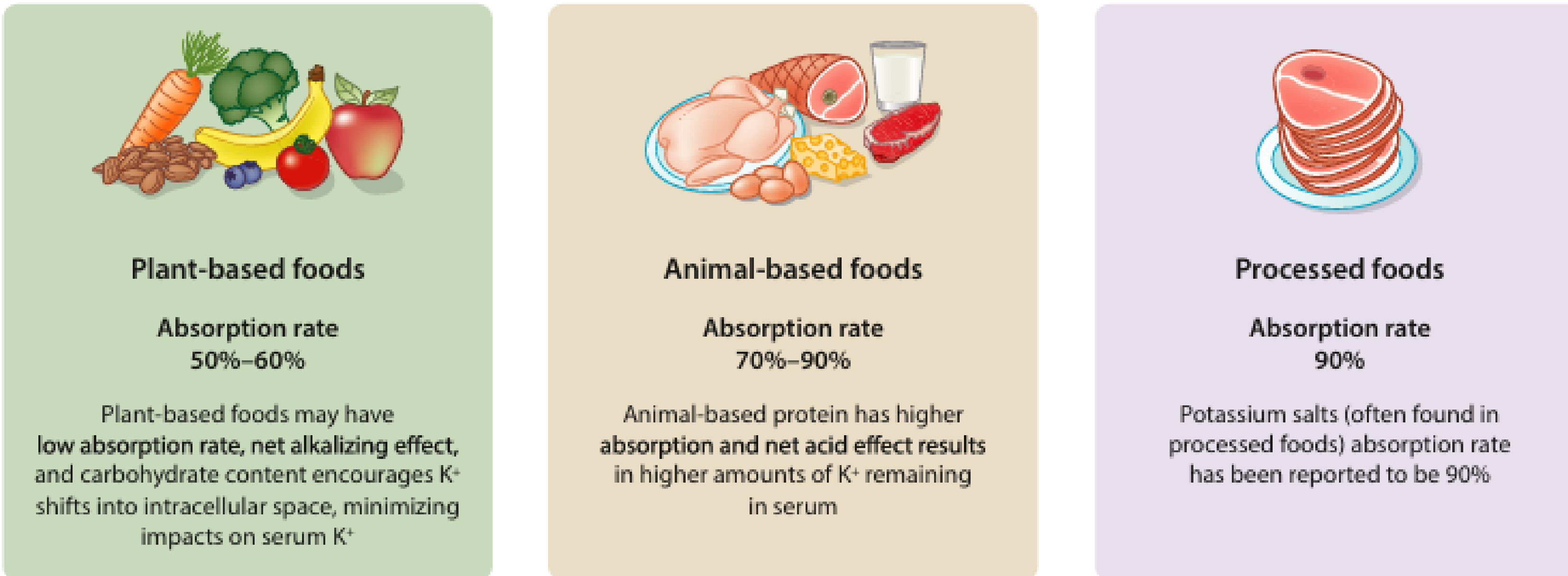


Figure 33 | Potassium absorption rates of plant-based, animal-based, and processed foods. Data from Picard K, Griffiths M, Mager DR, Richard C. Handouts for low-potassium diets disproportionately restrict fruits and vegetables. *J Ren Nutr.* 2021;31:210–214.[592]

Potassium_Management_in_Kidney_Disease.pdf

MERCI

de

votre attention