LIÈGE université

1er CONGRÈS DE LA SOCIÉTÉ CONGOLAISE DE NEPHROLOGIE
DU 19 AU 21 NOVEMBRE 2025 A BRAZZAVILLE

# Gestion des troubles phosphocalciques chez l'IRC

Pierre DELANAYE,
Université de Liège
BELGIQUE

# Physiopathologie

# Timing of Onset of CKD-Related Metabolic Complications

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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.

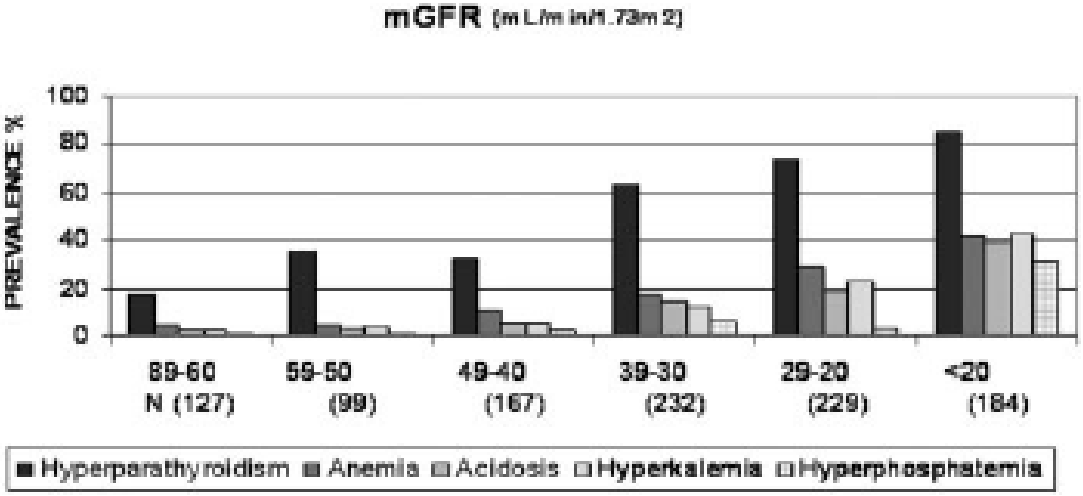


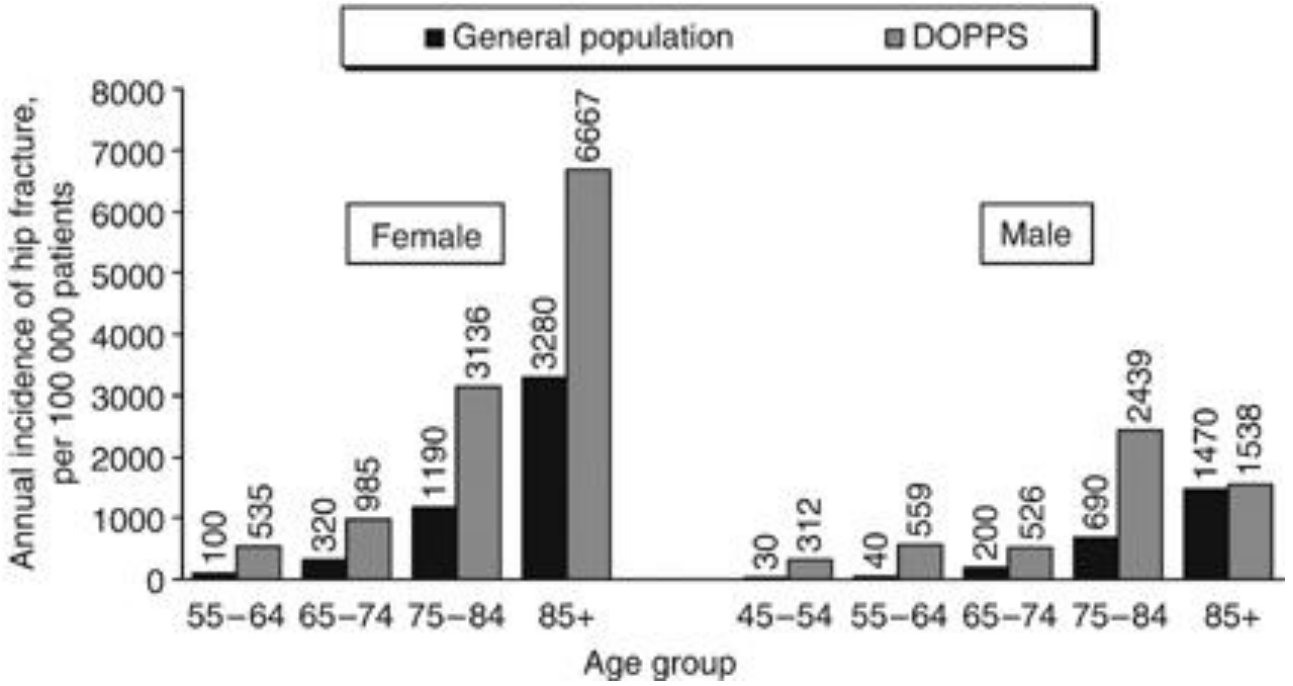

**Table 2.** Prevalence of metabolic complications[a] in the cohort

| | 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.

# 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

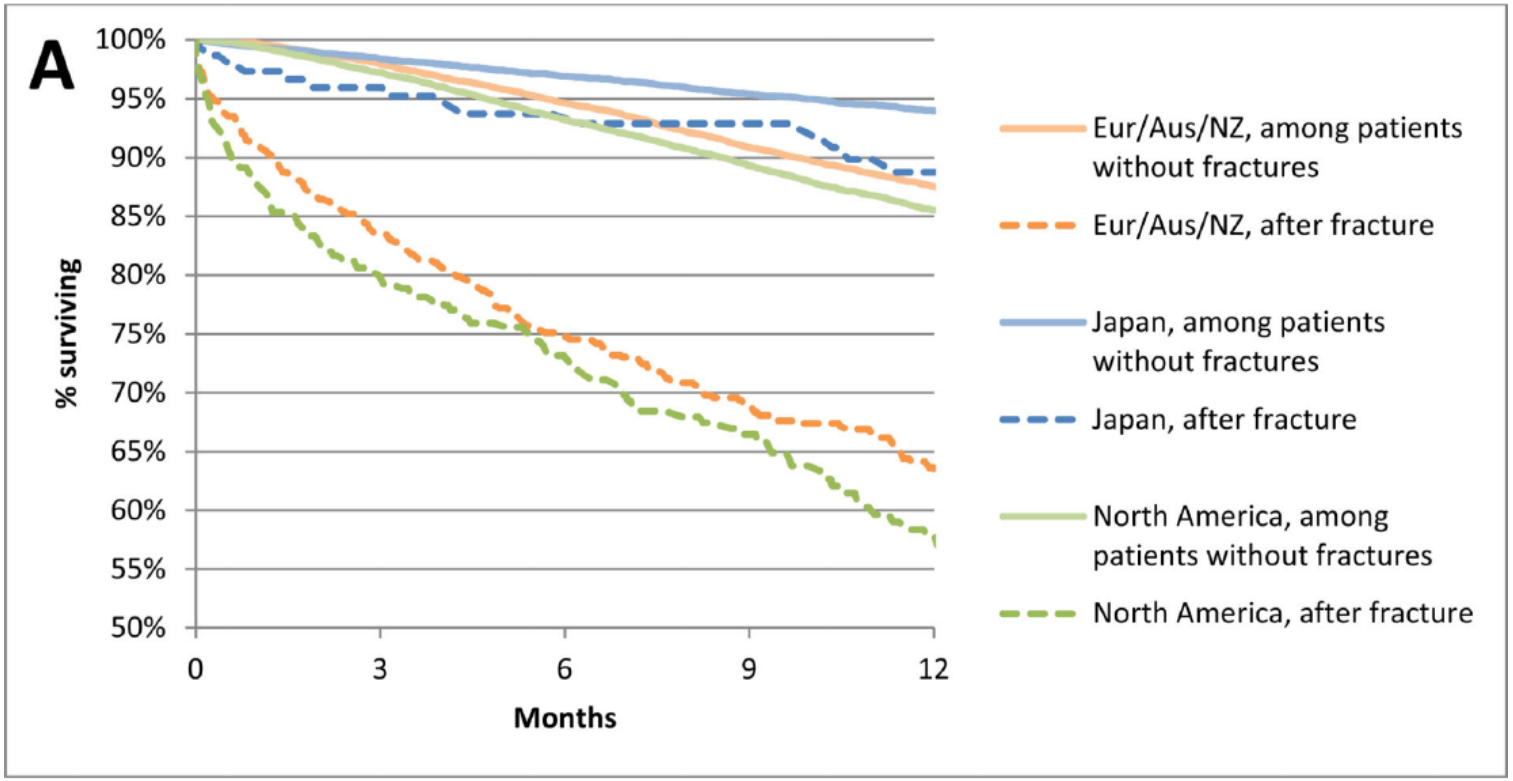
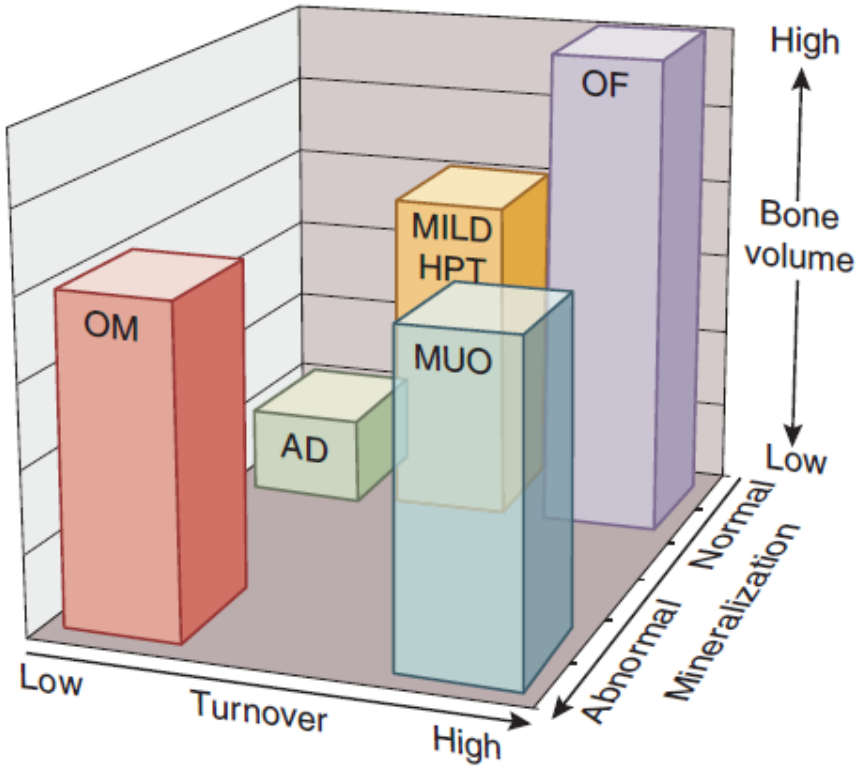



**Figure 5A & 5B. Time to death and hospitalization among DOPPS participants who experienced and those who did not experience a fracture requiring hospitalization, by DOPPS region**

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 exclus 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

Pierre Delanaye[1],
Laurent Weekers[1],
Xavier Warling[2],
Martial Moonen[2],
Nicole Smelten[3],
Laurent Médart[4],
Jean-Marie Krzesinski[1]
and Etienne Cavalier[5]

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[4]Radiology, Centre Hospitalier "La Citadelle", Liège, Belgium and
[5]Clinical Chemistry, University of Liège, CHU Sart Tilman, Liège, Belgium

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 $\chi^2$ test. Values are expressed as mean ± SD, if not specified.

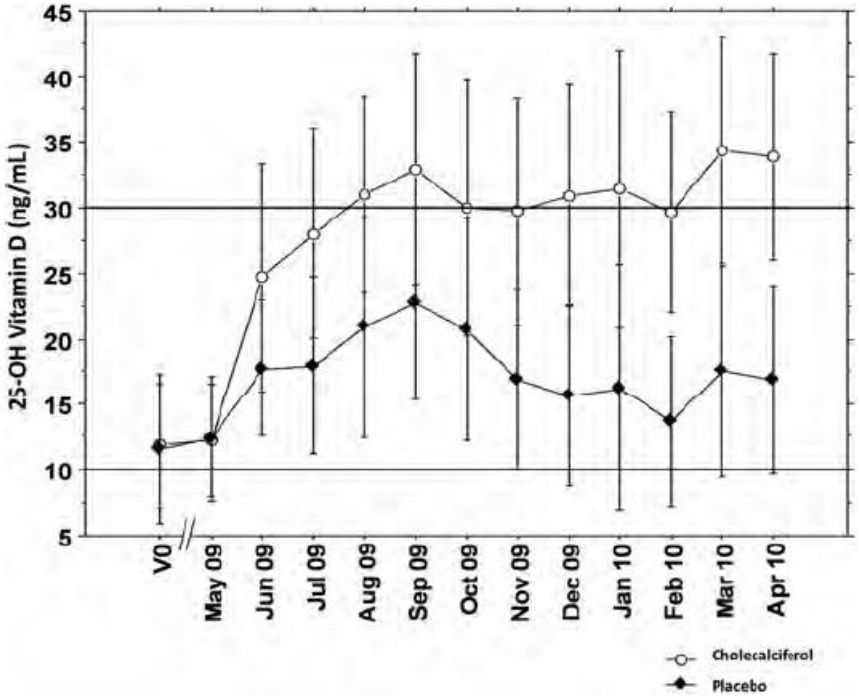
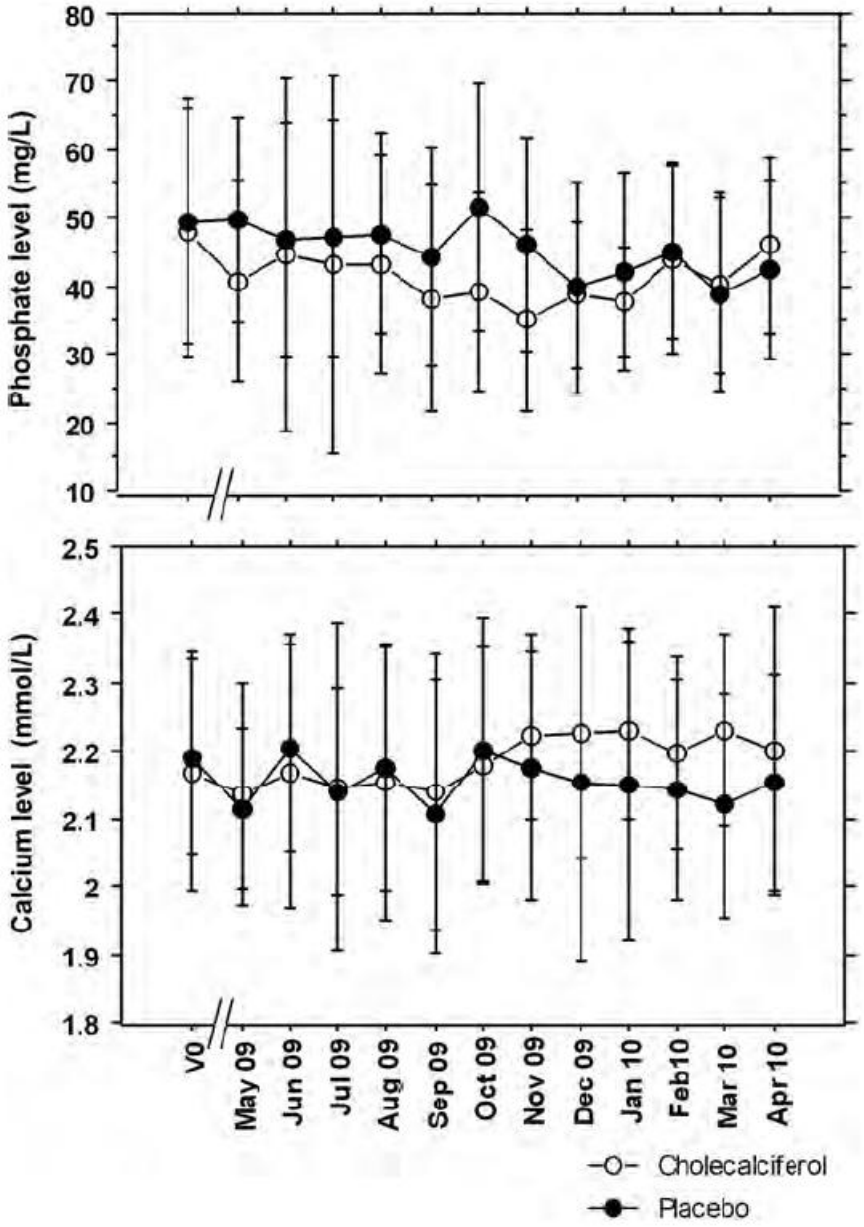



FIGURE 2: 25-Hydroxyvitamin D (ng/mL) levels over a 1-year period in the placebo and cholecalciferol groups. Data are expressed as mean ± SD.



## 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<br>9<br>Dialysés | $D_3$ : 1200 U/J PO<br>Calcitriol : jusque 1,5 µg/j PO (dose moyenne 0.5 µg/j) | Stable<br>Augmente<br>5 patients avec au moins une fois >2.63 mmol/L | ND | ND | Randomisé, double aveugle<br>11 semaines<br>400 U $D_3$/J 8 semianes avant dans les 2 groupes |
| Berl, 1978 [2] | 16<br>15<br>Dialysés | $D_3$ : 400 U/J PO et augmentation jusqu'à 1200<br>Calcitriol : 0,5 µg/j PO et augmentation jusqu'à 1.5 | Stable<br>Augmente de 2.26 à 2.56 mmo/L<br>5 patients avec au moins une fois >2.88 mmol/L | Stable<br>Stable | Mesuré chez 15 et 13 patients<br>Stable<br>Diminution chez 11/13 | Randomisé, double aveugle<br>12 semaines<br>400 U $D_3$/J 8 semianes avant dans les 2 groupes |
| Baker, 1986 [3] | 38<br>38<br>Dialysés | Placebo<br>Calcitriol : 0,5 µg/j PO (max 1 µg/j) | Stable<br>Fréquemment > 2.75 mmol/L | ND | Augmente<br>Diminue | Randomisé<br>5 ans (plus que 7 patients à 5 ans) |
| Nordal, 1989 | 14<br>14<br>MRC | Placebo<br>Calcitriol: 0.25 µg/j PO | Diminue<br>Augmente<br>7 patients au moins une fois hypercalcémie | Stable<br>Stable | Stable<br>Diminue | Randomisé, double aveugle<br>Amélioration de la biospie osseuse (high turneover) |
| Baker, 1989 [3] | 6<br>7<br>MRC | Placebo<br>Calcitriol : 0,2 à 0.5 µg/j PO | Stable<br>Augmente<br>4 patients au moins une fois hypercalcémie | Stable<br>Stable | | Randomisé, double aveugle<br>12 mois<br>Amélioration de la biospie osseuse (high turneover) |
| Hamdy, 1995 [7] | 87<br>89<br>MRC | Placebo<br>Alphacalcidol 0.25 à 1 µg/j | Stable<br>Augmentation >3 mmol/L 1 fois chez 3 patients | Stable<br>Stable | Augmente<br>Diminue puis stable | Randomisée, double aveugle<br>2 ans<br>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 $\mu$g 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 $\mu m^2$ 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<br>Calcitriol PO 3X/sem 2 µg | Augmente et 11 épisodes d'hypercalcémie (>2.7 mmol/L) chez 8 patients<br>Augmente et 10 épisodes d'hypercalcémie (>2.7 mmol/L) chez 7 patients | Stable<br>Stable | Diminue<br>Diminue | Crossover (IV puis PO chez 6, inverse chez 5)<br>4 mois<br>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)<br>Calcitriol PO 3X/sem 0.015 µg/Kg (1 µg pour 70 kg) | Stable<br>Stable | Diminue<br>Stable | | Randomisé<br>8 mois<br>Modification du bain en calcium dans le groupe IV<br>Effet plus important du groupe IV sur PTH<br>Amélioration des paramètres d'ostéite fibreuse à la biospie dans le groupe IV |
| Quarles, 1994 [6] | 9<br>10<br>Dialysés | Calcitriol IV 3X/sem 2 à 4 µg<br>Calcitriol PO 3X/sem 2 à 4 µg | Augmente et 80% avec au moins une fois >2.6 mmol/L<br>Augmente et 56% avec au moins une fois >2.6 mmol/L | Diminue<br>Diminue | Diminue<br>Diminue | Randomisé, double aveugle<br>36 semaines<br>Même diminution de PTH<br>Même fréquence d'hypercalcémie et d'hyperphosphatémie (>7 mg/dL)<br>Echec du traitement sur la PTH si hyperP |
| Indridason, 2000 [8] | 11<br>20<br>21<br>Dialysés | Calcium<br>Calcitriol PO, 0.5 µg/j<br>Calcitriol IV, 1 µg IV 3x/sem<br>But=calcémie à 2.5-2.6 mmol/L | Augmente et 2 épisodes d'hypercalcémie/patient/an<br>Augmente et 3 épisodes d'hypercalcémie/patient/an<br>Augmente et 3.4 épisodes d'hypercalcémie/patient/an | Diminue et 0.9 épisodes d'hyperP/patient/an<br>Augmente et 4.2 épisodes d'hyperP/patient/an<br>Augmente et et 4.9 épisodes d'hyperP/patient/an | Diminue<br>Diminue<br>Diminue | Randomisé<br>40 semaines<br>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)<br>Effet sur calcémie idem dans 3 groupes<br>Effet sur P idem entre PO et IV<br>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
- Etudes versus placebo: Diminution PTH de 42% à 6 mois et 2% d'hypercalcémie

# 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 **traitement** 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

Clinica Chimica Acta 539 (2023) 50–54

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Clinica Chimica Acta

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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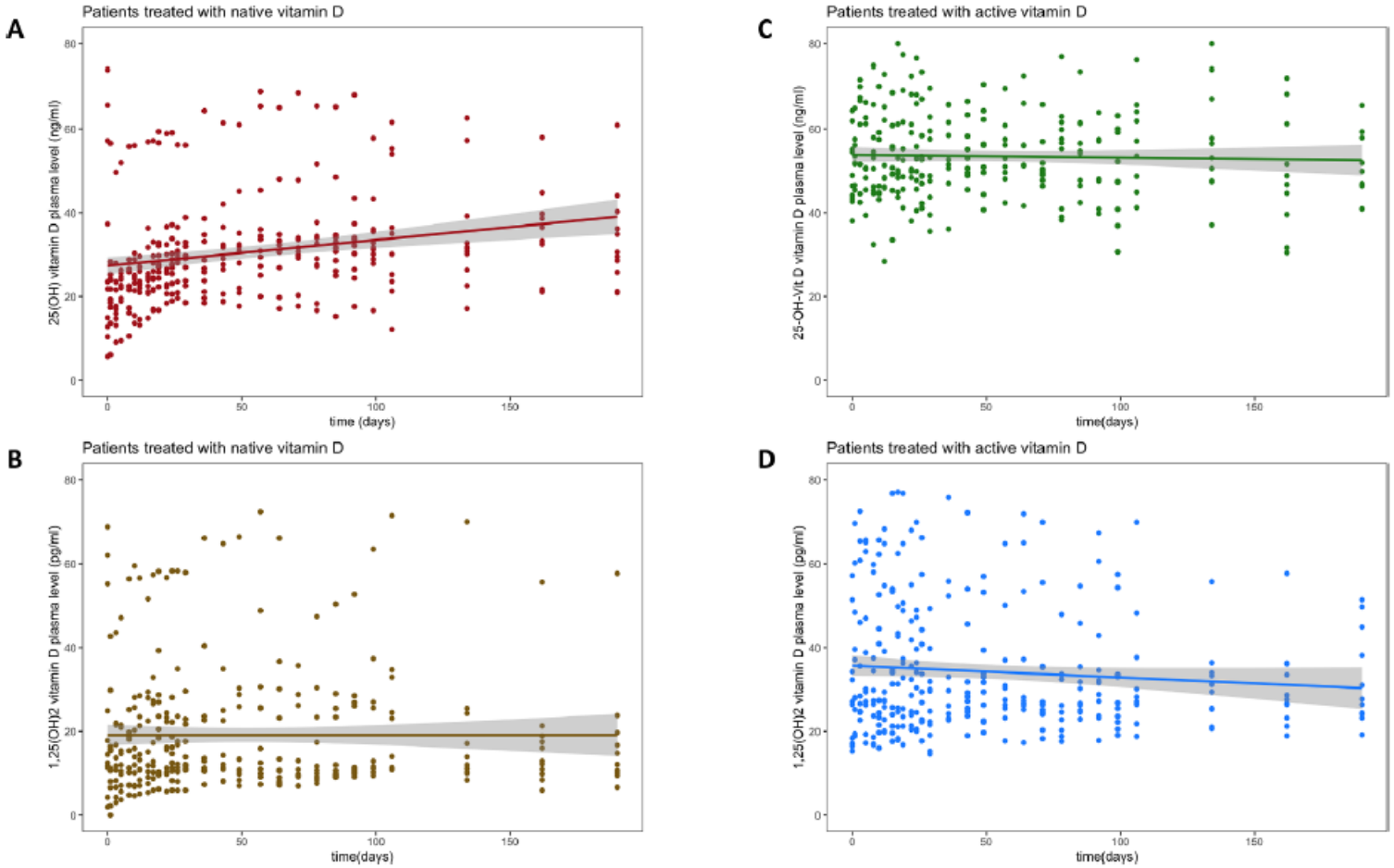



**Fig. 2.** Scatter plot and linear regression modeling the evolution of serum levels of: A. 25(OH) vitamin D in the group of patients treated with native vitamin D. B. $1,25(OH)_2$ vitamin D in the group of patients treated with native vitamin D. C. 25(OH) vitamin D in the group of patients treated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

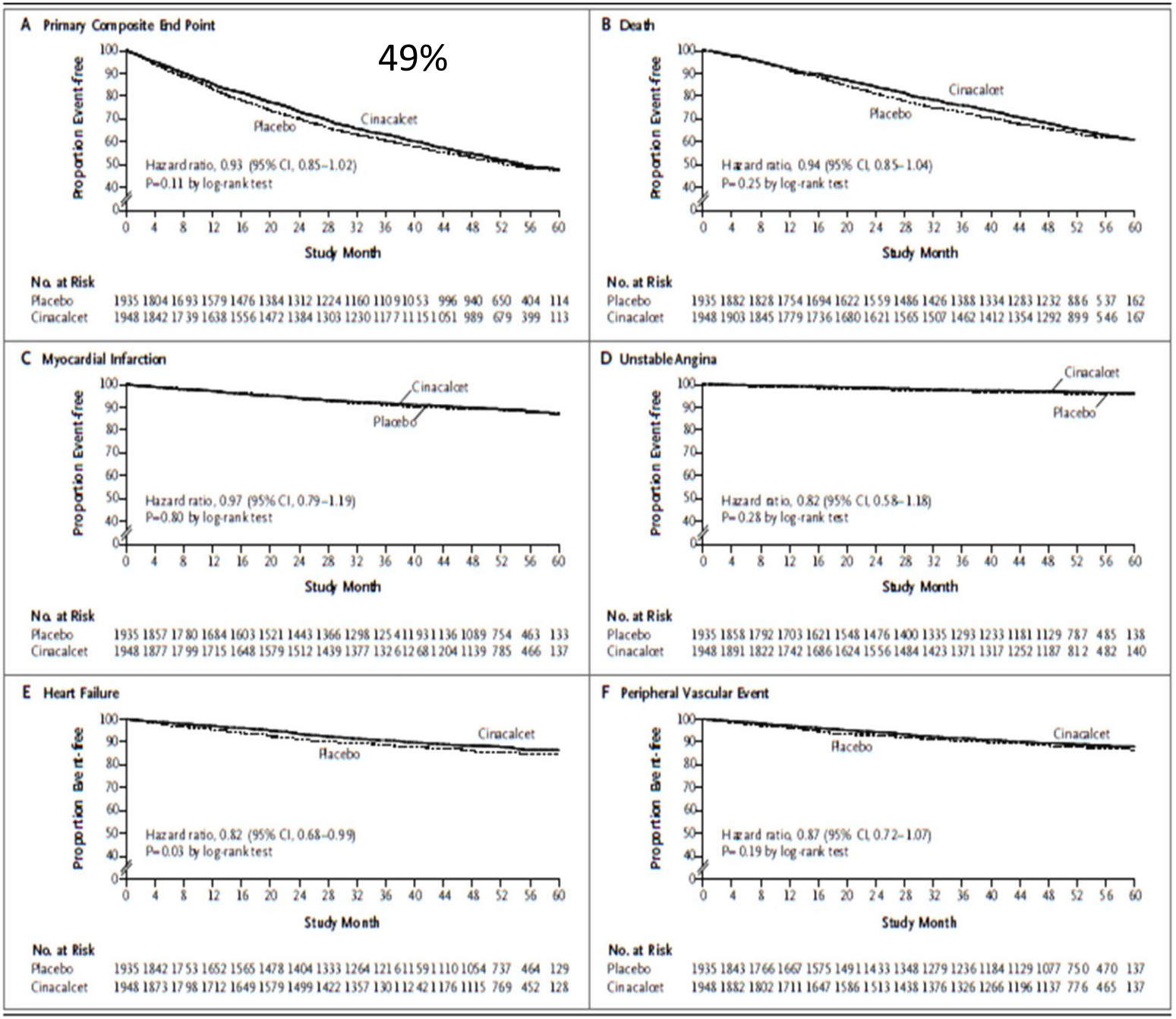
N Engl J Med 2012.

**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.

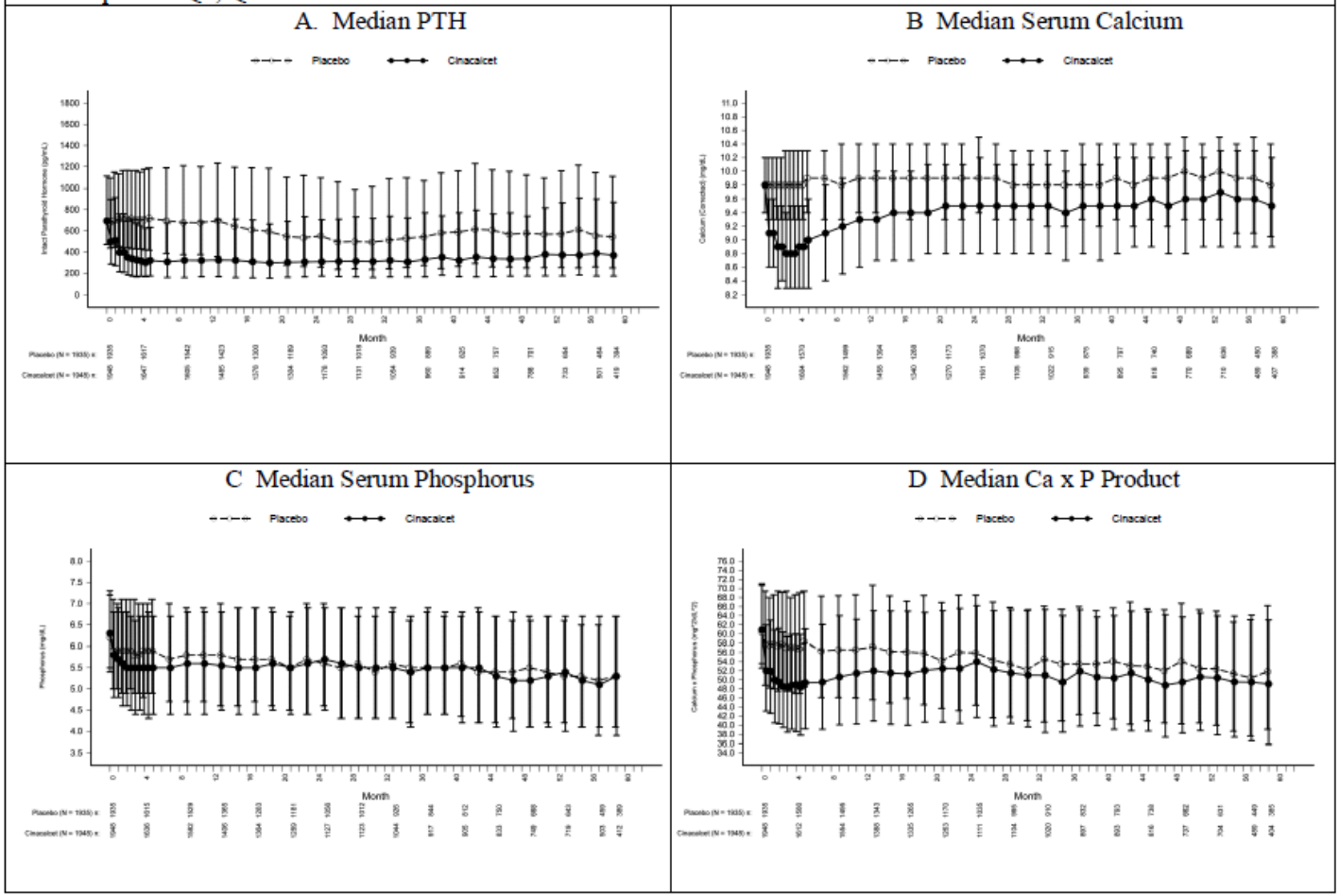
| | Cinacalcet (N=1948) | Placebo (N=1935) |
|---|---|---|
| **Laboratory parameters** | | |
| iPTH (pg/mL) | | |
| Median | 695 | 690 |
| p10, p90 | 362, 1707 | 363, 1683 |
| Corrected calcium (mg/dL) | | |
| Median | 9.8 | 9.8 |
| p10, p90 | 9.0, 10.7 | 9.0, 10.7 |
| Phosphorus (mg/dL) | | |
| Median | 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 |


A Primary Composite End Point
49%
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

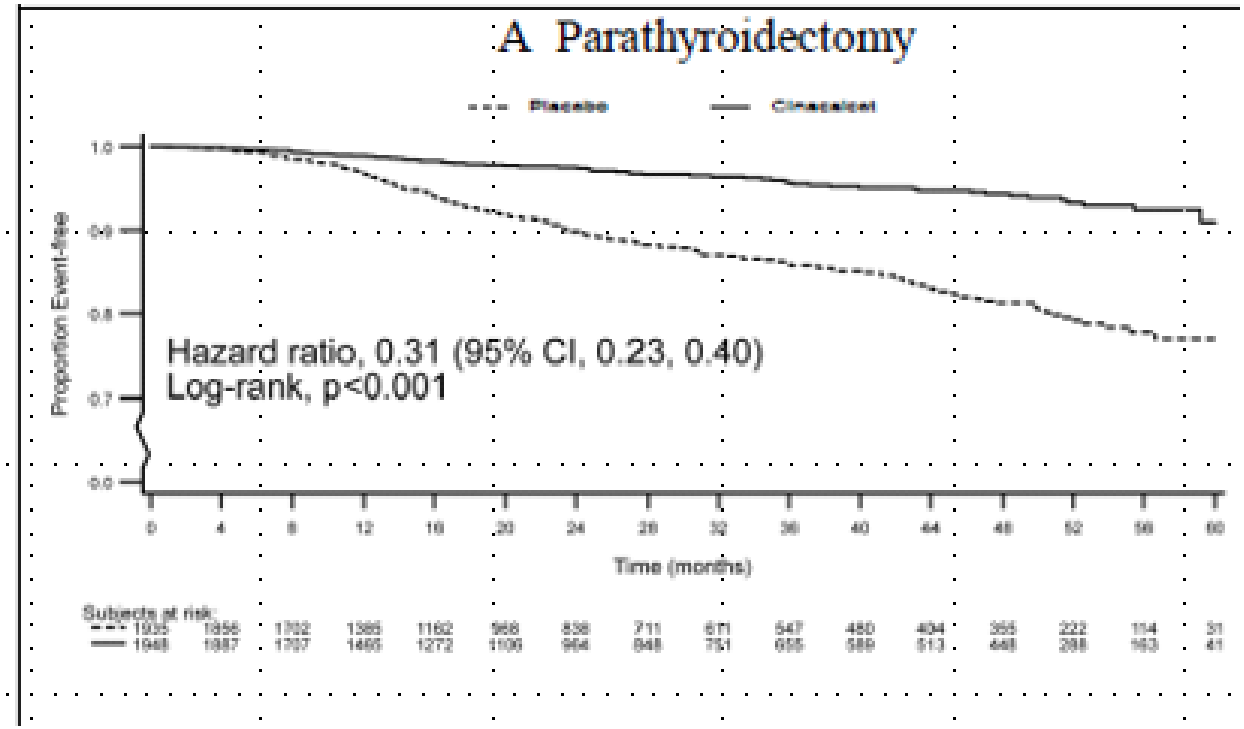



N = Number of patients in the intent-to-treat analysis set

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

PTH = plasma intact parathyroid hormone

# Résultats négatifs mais…



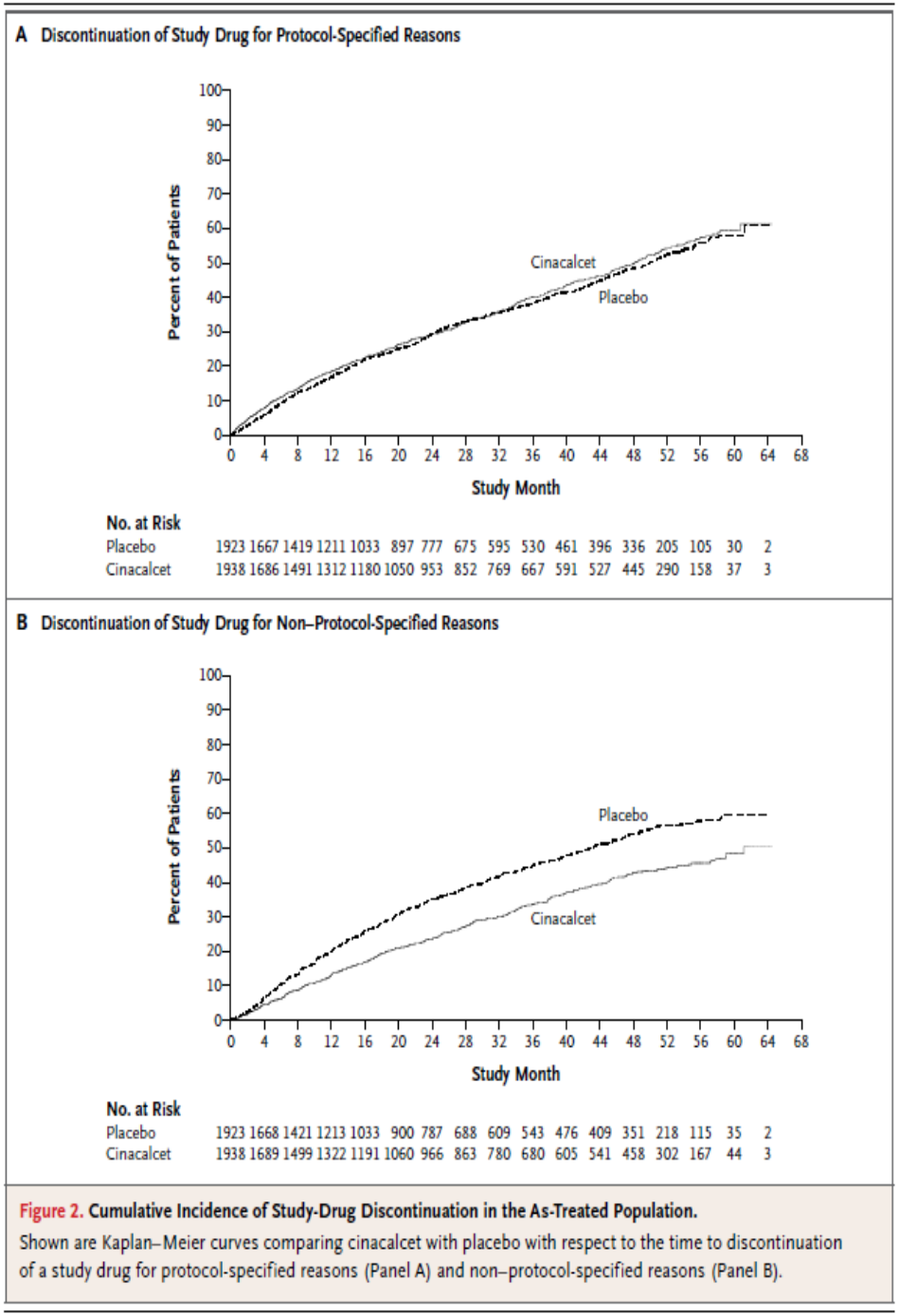



**Figure 2. Cumulative Incidence of Study-Drug Discontinuation in the As-Treated Population.**
Shown are Kaplan–Meier curves comparing cinacalcet with placebo with respect to the time to discontinuation of a study drug for protocol-specified reasons (Panel A) and non–protocol-specified reasons (Panel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

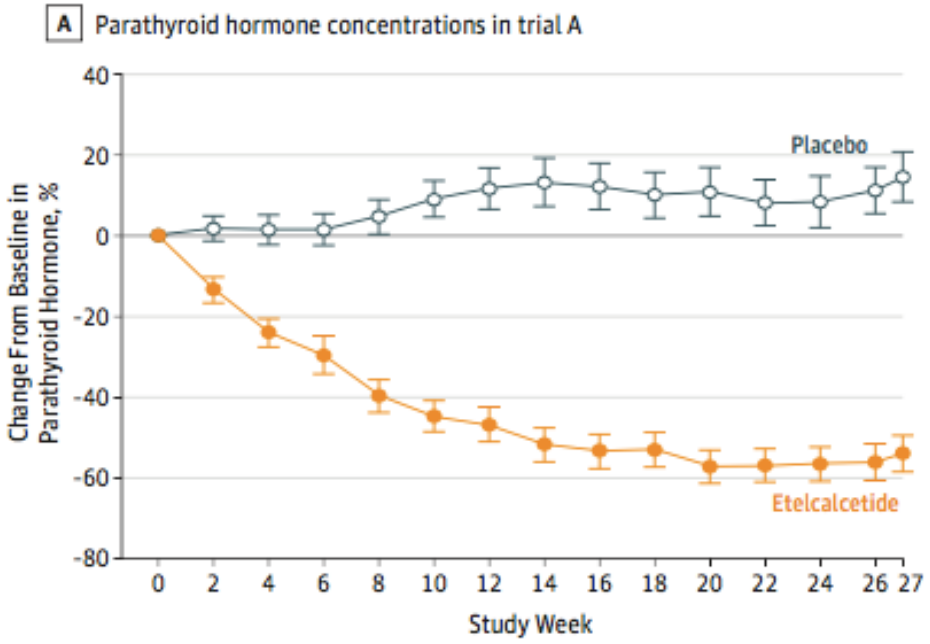
Geoffrey A. Block, MD; David A. Bushinsky, MD; John Cunningham, DM; Tilman B. Drueke, MD; Markus Ketteler, MD; Reshma Kewalramani, MD; Kevin J. Martin, MB, BCh; T. Christian Mix, MD; Sharon M. Moe, MD; Uptal D. Patel, MD; Justin Silver, MD; David M. Spiegel, MD; Lulu Sterling, PhD; Liron Walsh, MD; Glenn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

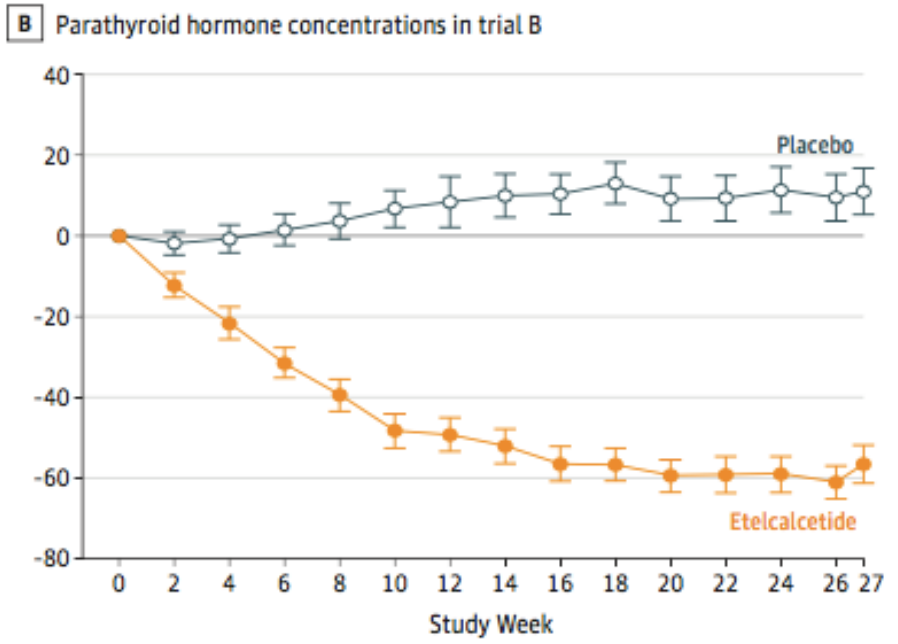
**COMBINAISON DE 2 ESSAIS CONTROLES RANDOMISES EN DOUBLE AVEUGLE, DE PHASE 3**

**<u>OBJECTIF PRIMAIRE</u>:**
**% de pts ayant une réduction de PTH initiale >30%**

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

# OBJECTIF PRINCIPAL




No. of patients

| | | | | | | | | | | | | | | | |
|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|
| Etelcalcetide | 251 | 230 | 230 | 221 | 223 | 224 | 218 | 217 | 217 | 218 | 216 | 215 | 210 | 207 | 217 |
| Placebo | 254 | 244 | 242 | 235 | 230 | 229 | 229 | 222 | 216 | 205 | 198 | 191 | 183 | 182 | 191 |

| | | | | | | | | | | | | | | | |
|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|
| Etelcalcetide | 252 | 238 | 229 | 232 | 226 | 229 | 226 | 222 | 220 | 218 | 209 | 211 | 206 | 198 | 204 |
| Placebo | 259 | 246 | 246 | 245 | 241 | 237 | 227 | 235 | 224 | 222 | 218 | 211 | 200 | 186 | 201 |

**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**

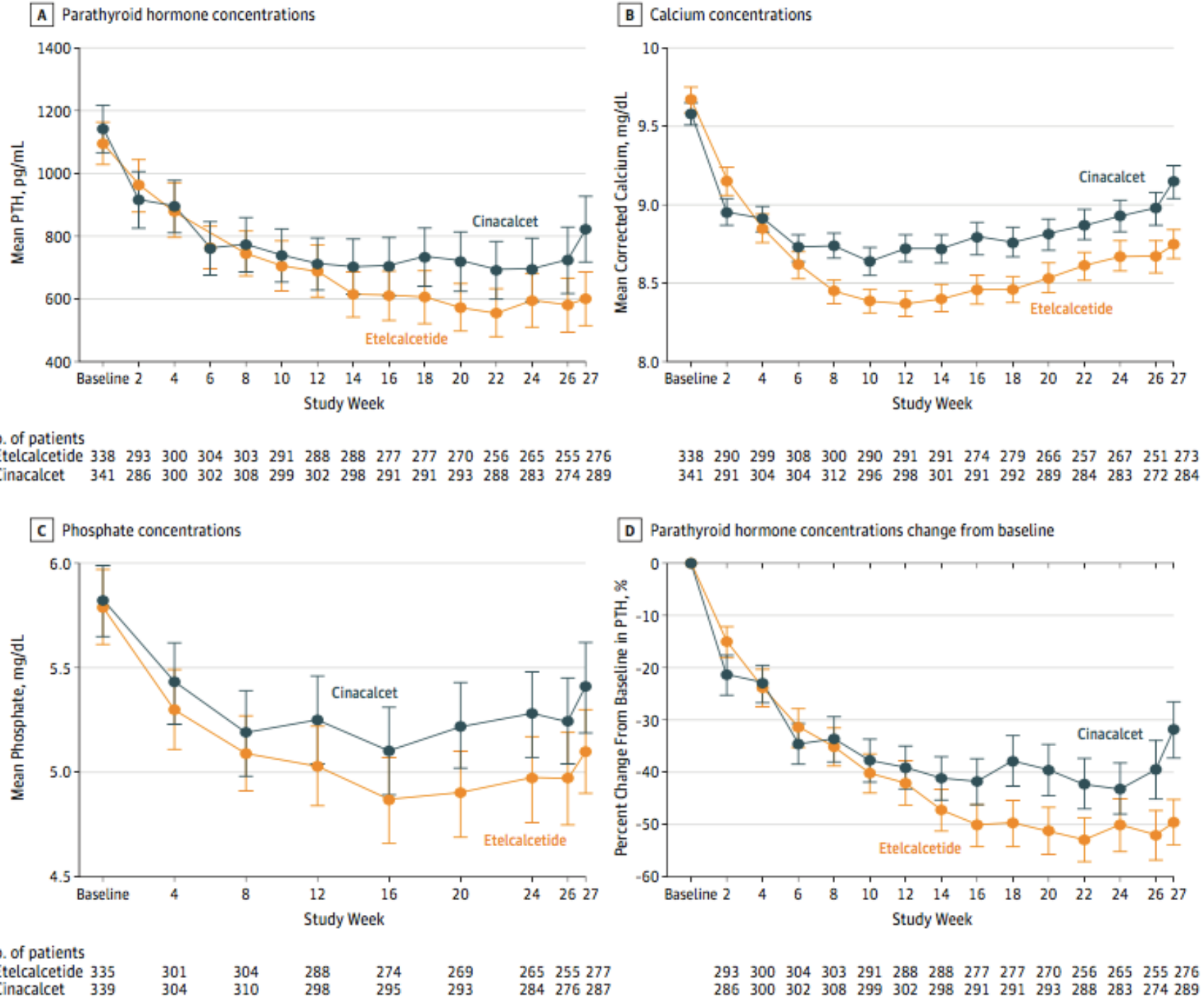
**OBJECTIFS SECONDAIRES:**

**% 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
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
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
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
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
No. of patients
Etelcalcetide 335 301 304 288 274 269 265 255 277
Cinacalcet 339 304 310 298 295 293 284 276 287
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%)

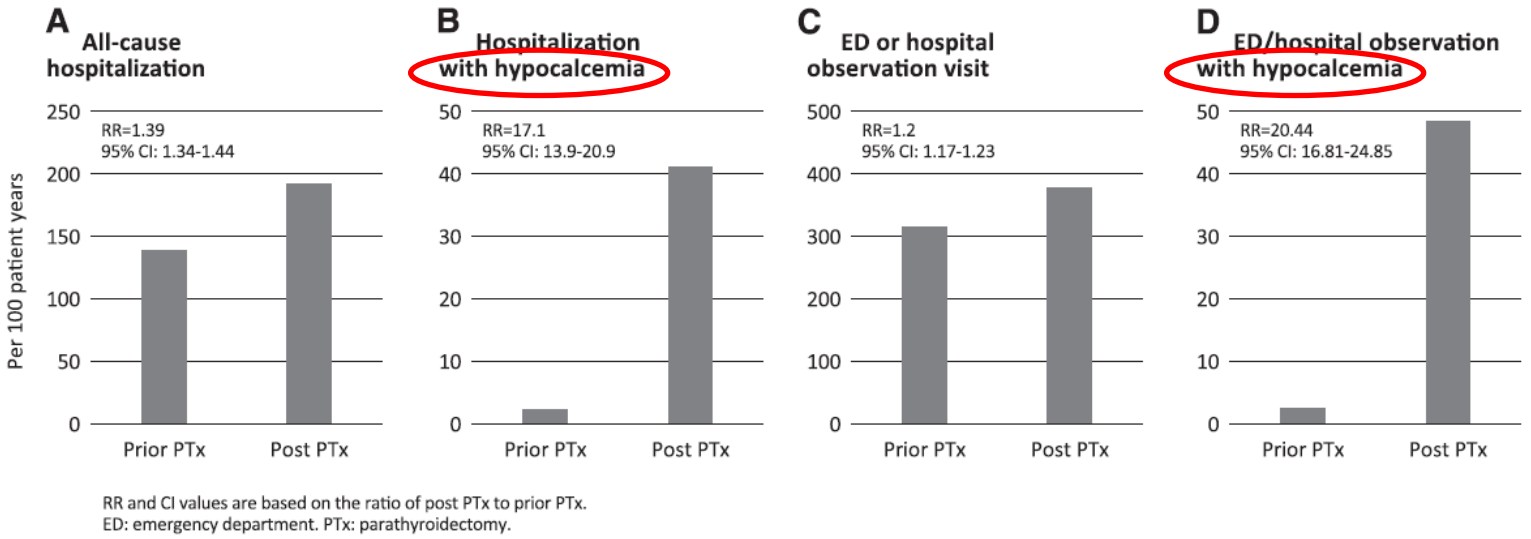



**Figure 2. | Event rates in the 1 year before and 1 year after parathyroidectomy.** (A) Total hospitalizations. (B) Total hospitalizations with hypocalcemia. (C) Total emergency department or observation visits. (D) Total emergency department or observation visits with hypocalcemia. RR and 95% CI values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

# Hyperphosphatémie

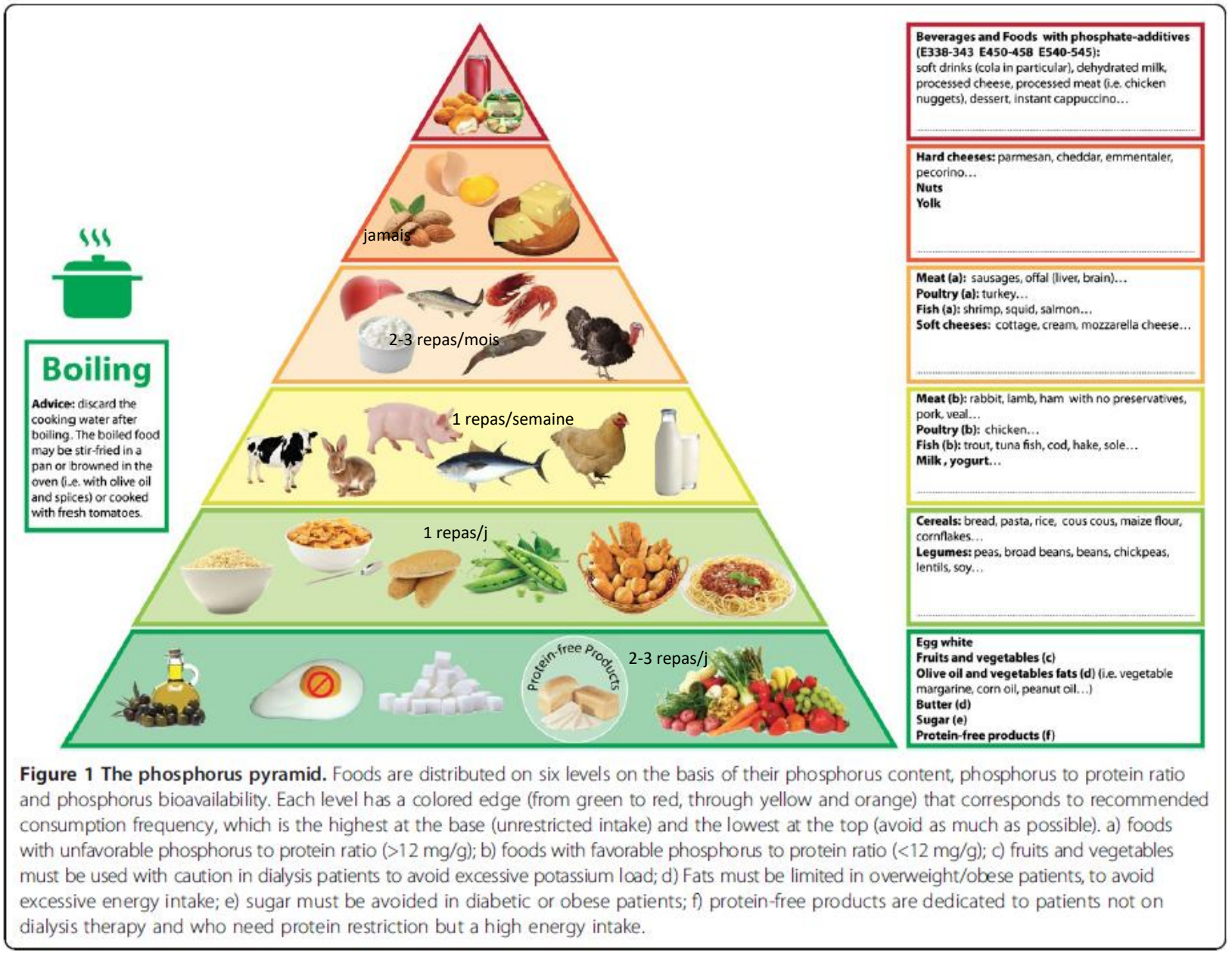
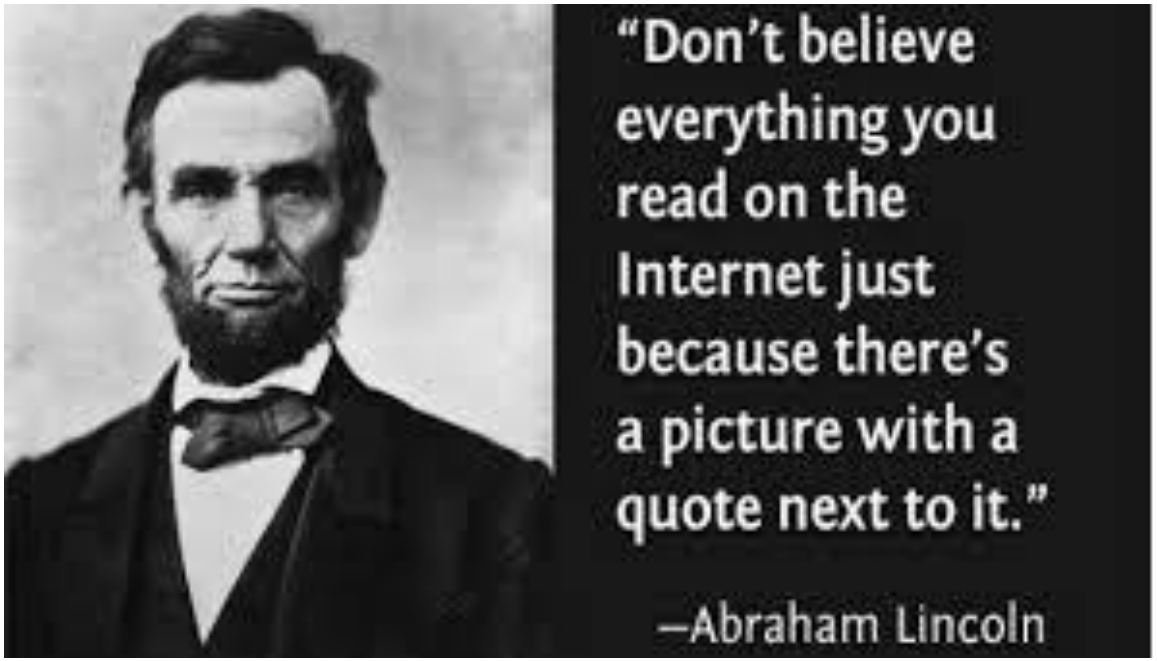



**Figure 1 The phosphorus pyramid.** Foods are distributed on six levels on the basis of their phosphorus content, phosphorus to protein ratio and phosphorus bioavailability. Each level has a colored edge (from green to red, through yellow and orange) that corresponds to recommended consumption frequency,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

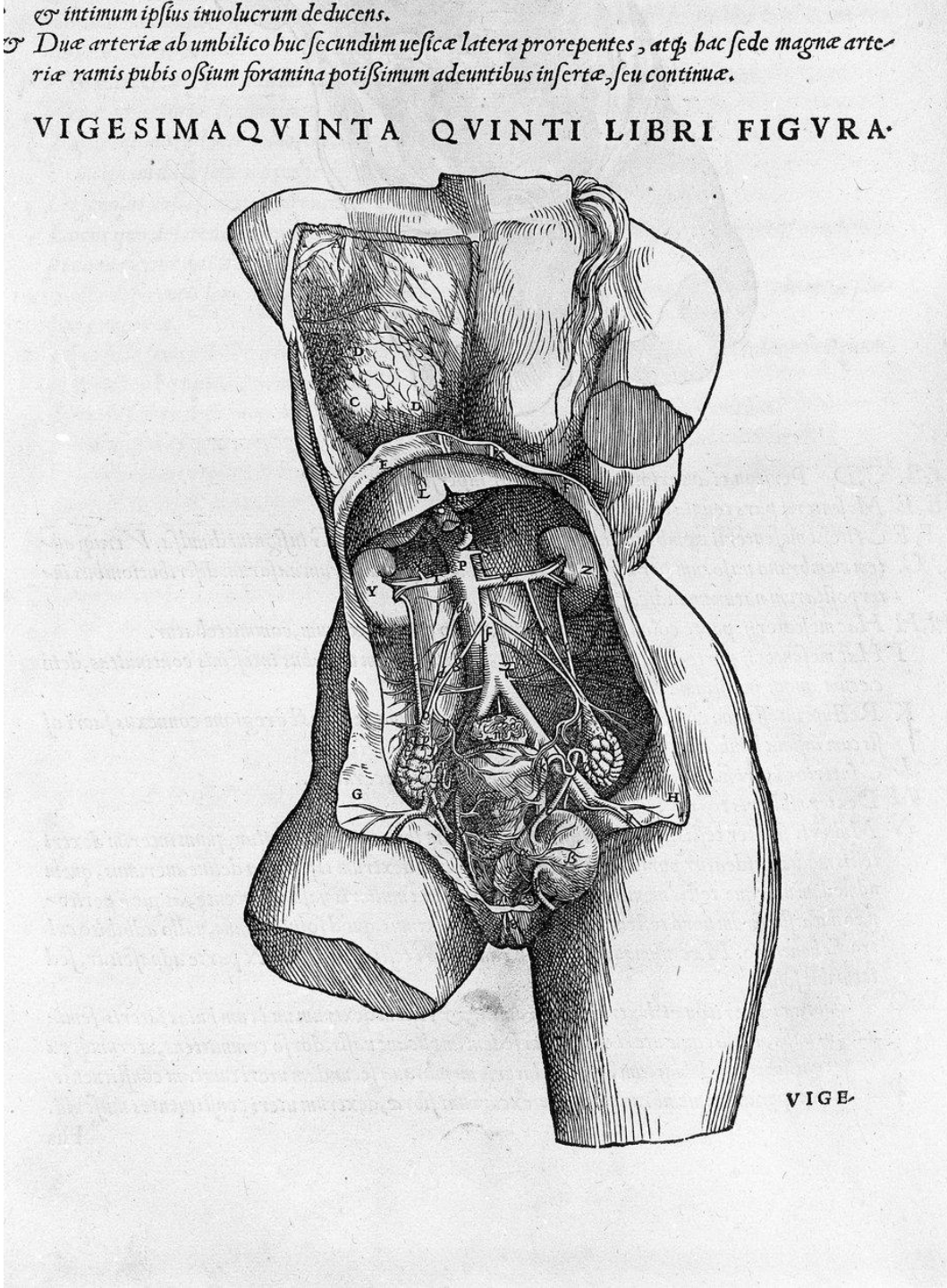
# Chélateurs non calciques

- Il se valent tous…
- Prix
- Utiliser ceux disponibles et ceux que le patient tolère/préfère

MERCI

de

votre attention

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***De Humani Corporis Fabrica***
(1543)