Έχουν τα παράγωγα της Βιταμίνης D ωφέλιμη δράση στη Χρόνια Νεφρική Νόσο?

Ιωάννης Γ. Γριβέας

Επιμελητής Νεφρολογικού Τμήματος

401 ΓΣΝΑ

Kidney International, Vol. 63, Supplement 85 (2003), pp. S83–S87

New vitamin D analogs

EDUARDO SLATOPOLSKY, JANE FINCH, and ALEX BROWN

Renal Division, Department of Internal Medicine, Washington University School of Medicine, St. Louis, Missouri

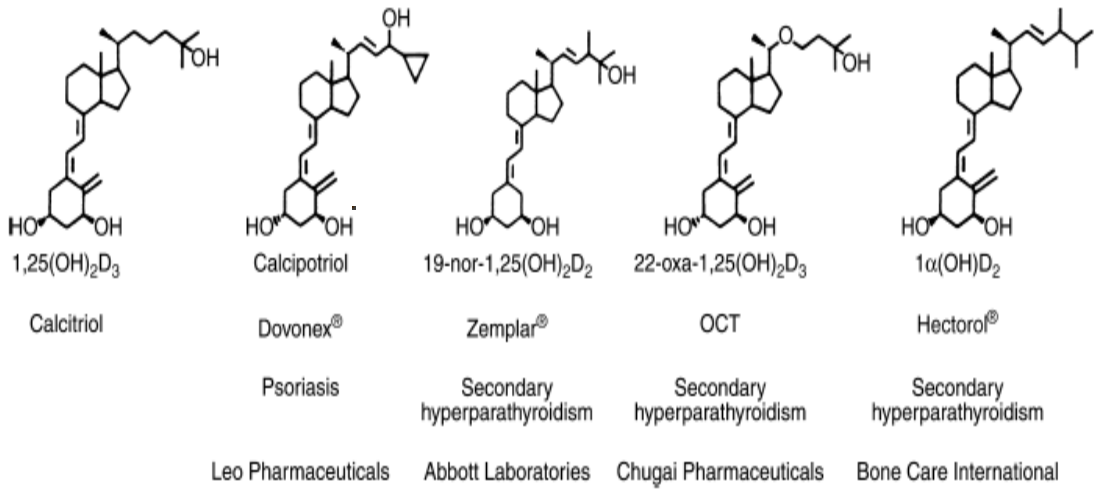
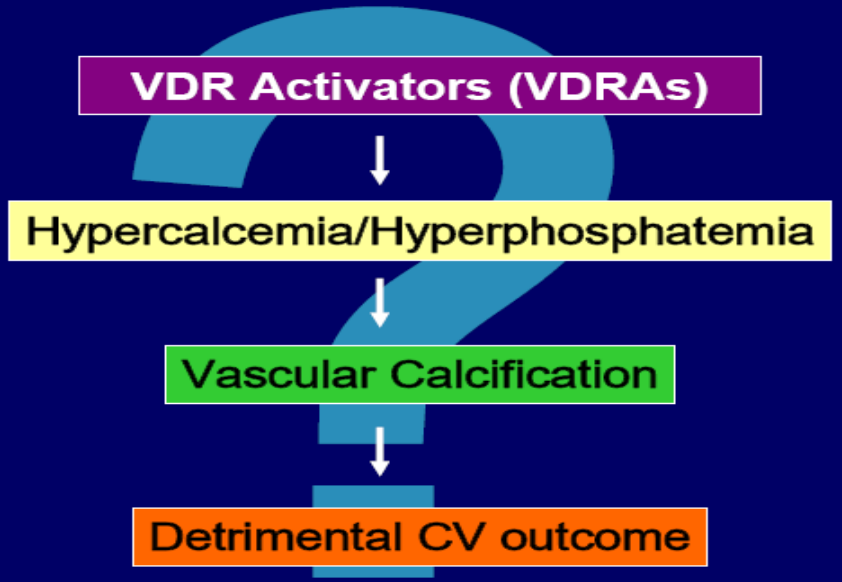


Fig. 1. Chemical structure of $1,25(OH)_2D_3$ and several vitamin D analogs. (Reproduced from reference [29]).

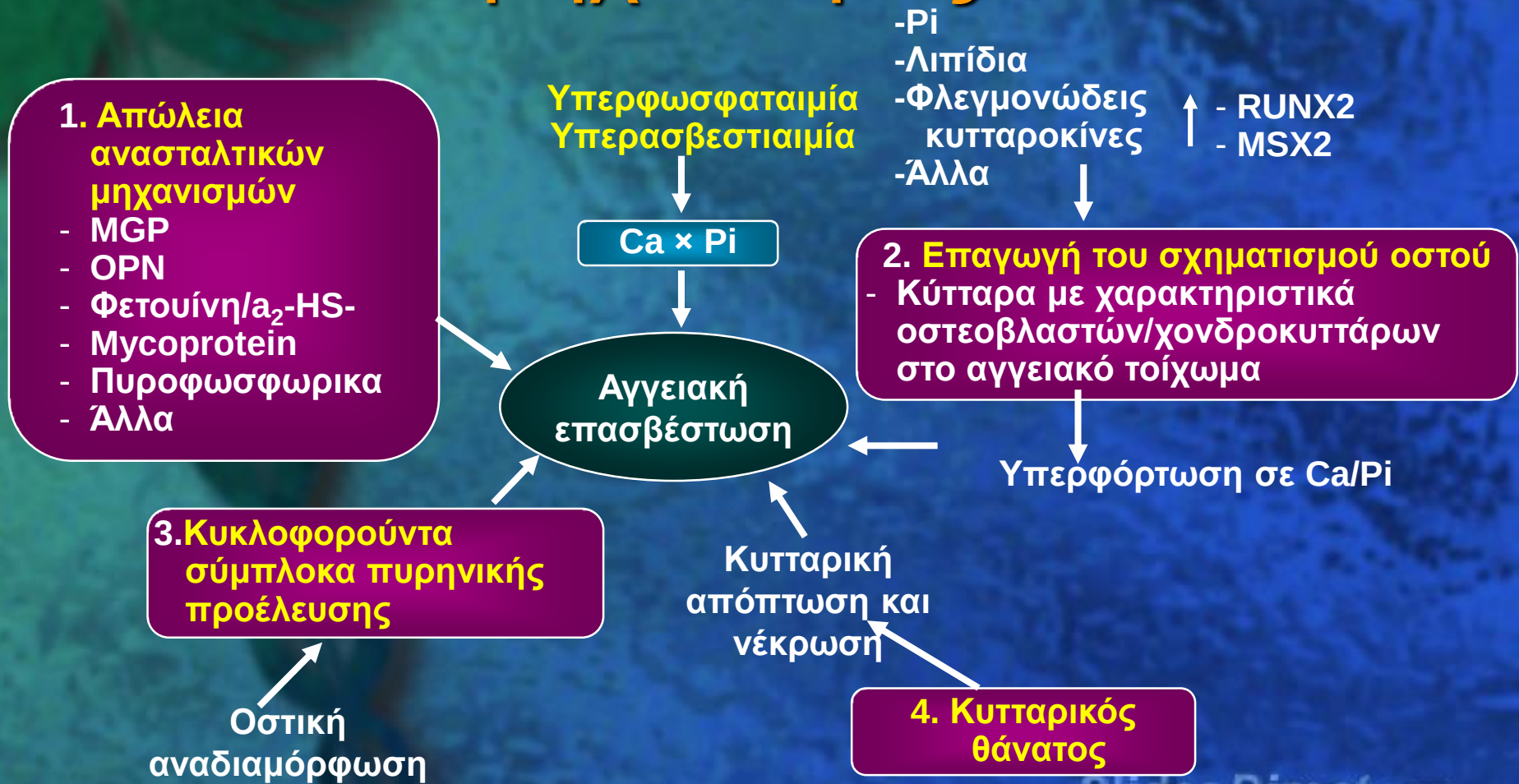
Potential calcification risk factors associated with uremia

- Hypercalcemia
- Hyperphosphatemia
- Elevated Ca x P
- PTH, vitamin D3
- Diet (vitamin K), warfarin
- Inflammation, TNFα
- Toxins AGEs

VDRAs Cause Vascular Calcification?



Αγγειακές επασβεστώσεις: μηχανισμός



Giachelli CM. J Am Soc Nephrol 2004:15:2959–64

Beyond Minerals and Parathyroid Hormone: Role of Active Vitamin D in End-Stage Renal Disease

Myles Wolf and Ravi Thadhani
Renal Unit, Department of Medicine, Massachusetts General Hospital, Harvard Medical School, Boston, Massachusetts

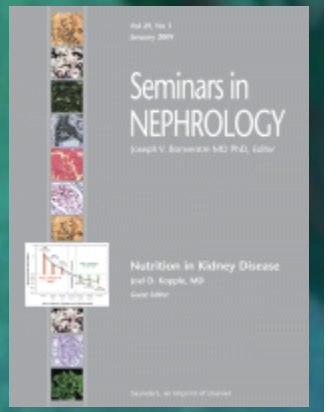


TABLE 1. Percent changes in calcium, phosphorus, and PTH levels after initiation of vitamin D[a]

		Paricalcitol		Calcitriol		
Laboratory	Months	Mean percentage change	IQR	Mean percentage change	IQR	*p*-value
Calcium	3	4.7	[−0.5–8.2]	5.7	[0.0–9.4]	< 0.001
	6	6.2	[0.0–10.6]	7.6	[1.0–12.3]	< 0.001
	12	6.7	[0.5–11.4]	8.2	[1.2–13.2]	< 0.001
Phosphorus	3	9.2	[−10.7–22.6]	11.4	[−10.2–25.9]	< 0.001
	6	11.9	[−11.2–27.9]	14.6	[−10.1–30.8]	< 0.001
	12	11.9	[−11.7–28.8]	13.9	[−10.7–31.0]	< 0.001
PTH	3	−30	[−63–14]	−22	[−65–9]	< 0.001
	6	−26	[−67–7]	−20	[−70–4]	< 0.001
	12	−15	[−63–2]	−5	[−65–8]	< 0.001

Differential effects of 19-nor-1,25-$(OH)_2D_2$ and 1α-hydroxyvitamin D_2 on calcium and phosphorus in normal and uremic rats

Eduardo Slatopolsky, Mario Cozzolino, and Jane L. Finch

Renal Division, Department of Internal Medicine, Washington University School of Medicine, St. Louis, Missouri, USA

Table 1. Blood chemistries in normal and uremic rats

Group	*N*	Cr	T Ca	ICa	P	PTH
		mg/dL				*pg/mL*
Normal	6	0.78 ± 0.05	8.96 ± 0.08	4.46 ± 0.07	5.77 ± 0.29	50.3 ± 13.2
Uremic control	9	1.16 ± 0.04	9.02 ± 0.13	4.62 ± 0.13	7.48 ± 0.93	185.4 ± 114.8
U+19-nor (50 ng)	10	1.33 ± 0.05	9.23 ± 0.09	4.61 ± 0.08	6.47 ± 0.65	76.3 ± 16.6
U+19-nor (100 ng)	10	1.28 ± 0.03	9.30 ± 0.12	4.57 ± 0.08	5.24 ± 0.24[a]	58.2 ± 9.4
U+19-nor (250 ng)	10	1.17 ± 0.06	9.51 ± 0.12[a]	4.63 ± 0.05	6.72 ± 0.70	54.6 ± 14.0
U+1α-D_2 (50 ng)	9	1.50 ± 0.20	9.79 ± 0.17[b]	4.76 ± 0.08	6.62 ± 0.71	138.9 ± 44.1[d]
U+1α-D_2 (100 ng)	9	1.44 ± 0.06	11.87 ± 0.20[c]	5.46 ± 0.09[c]	7.94 ± 0.31	<2
U+1α-D_2 (250 ng)	9	1.81 ± 0.08	12.10 ± 0.20[c]	5.34 ± 0.16[c]	9.54 ± 0.51[a]	<2

Differential effects of 19-nor-1,25-$(OH)_2D_2$ and 1α-hydroxyvitamin D_2 on calcium and phosphorus in normal and uremic rats

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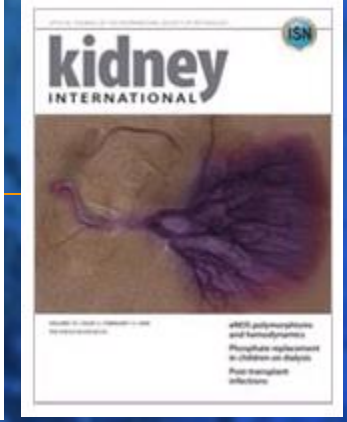
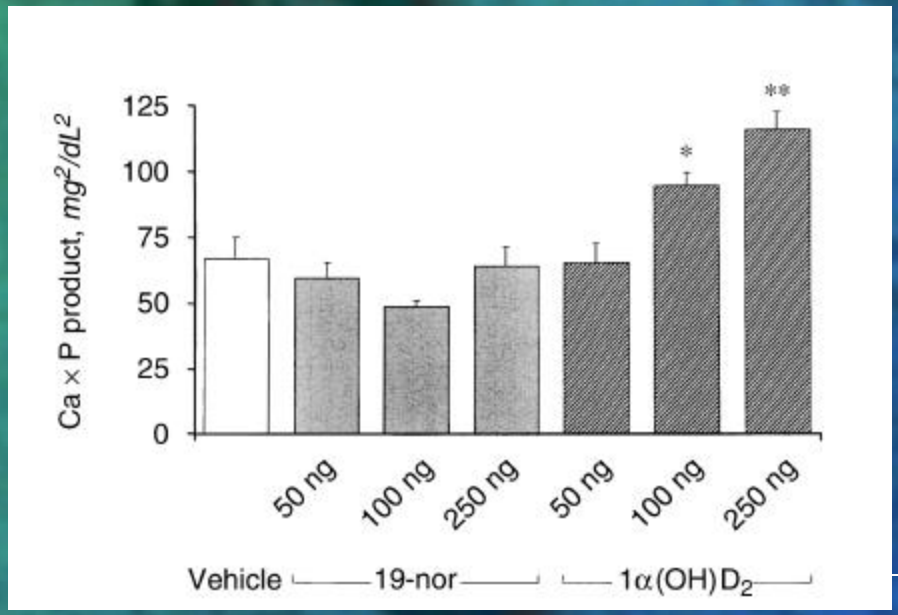
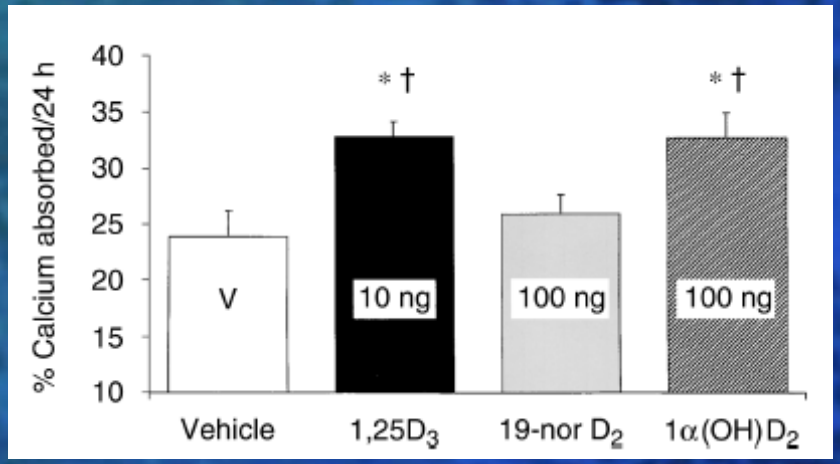
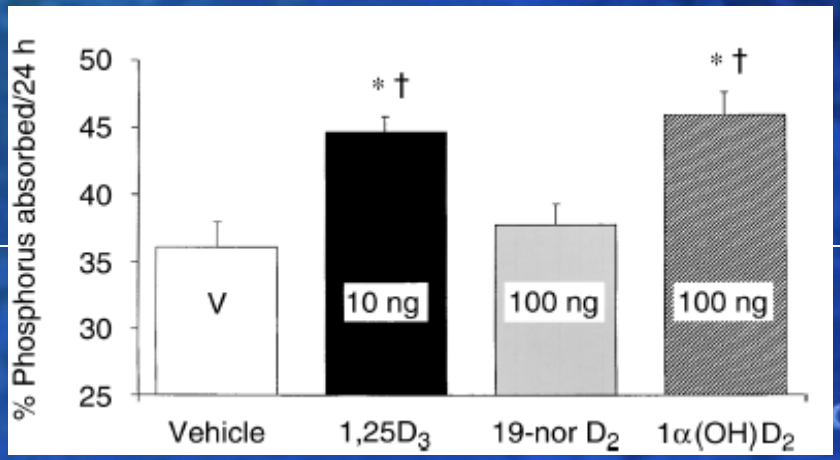
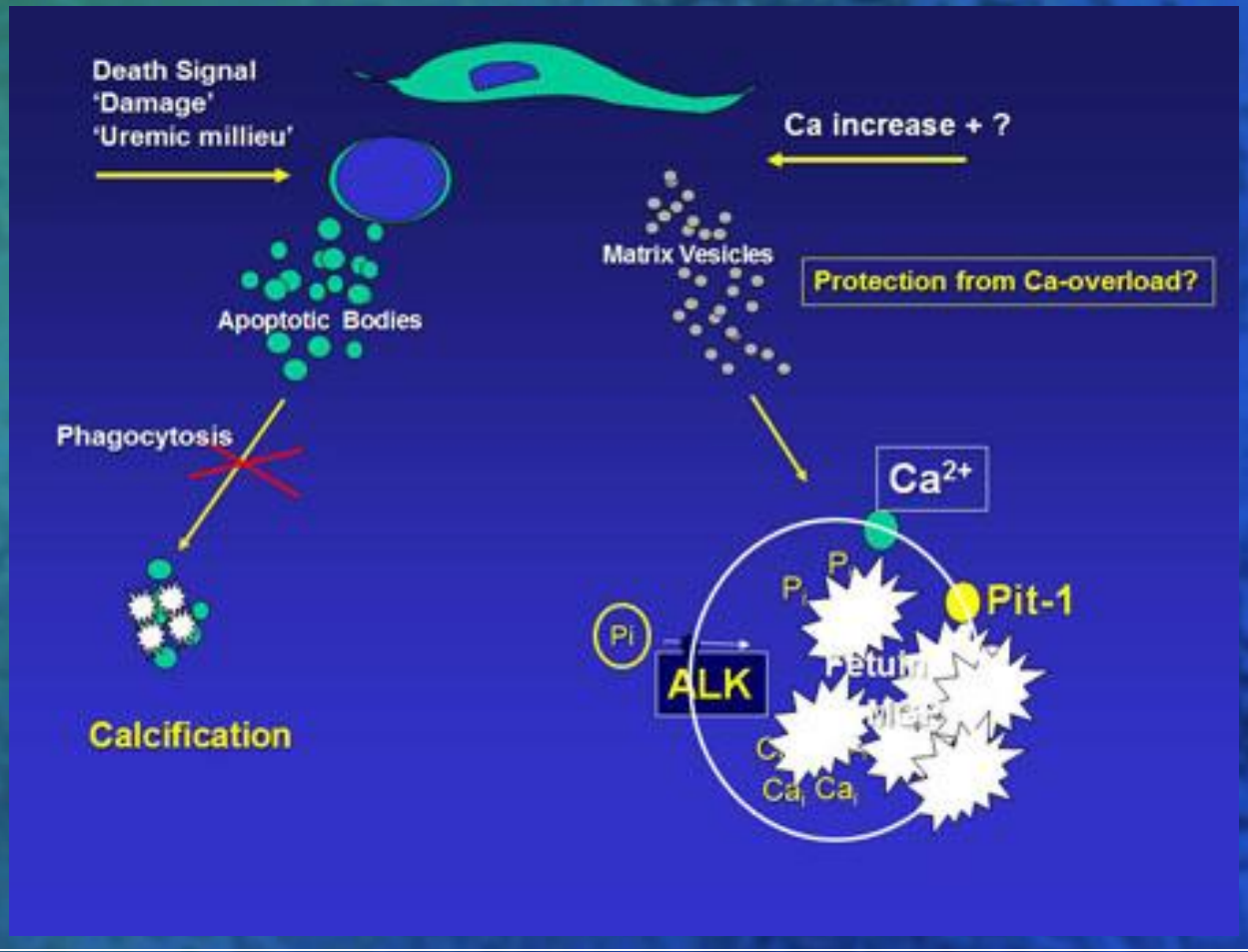










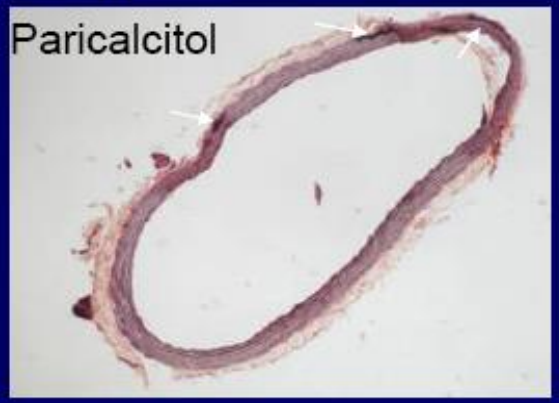
Η επίδραση στις τιμές των Ca, Ph και την εμφάνιση αγγειακών επασβεστώσεων ευνοούν την *paricalcitol*.

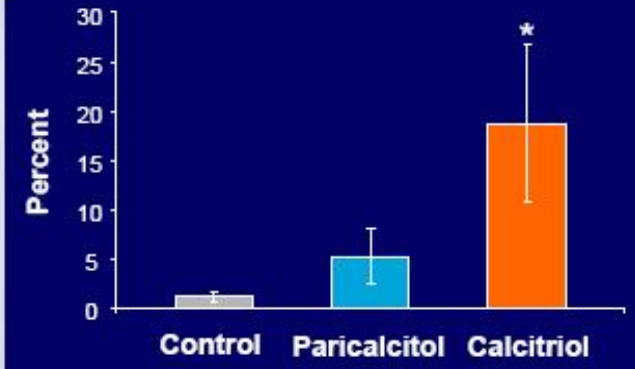
Η αύξηση ινωματώδους ιστού περιαγγειακά ευνοεί την *calcitriol*.

Repo JM, Rantala IS, Honkanen TT, et al.. Paricalcitol aggravates perivascular fibrosis in rats with renal insufficiency and low calcitriol. Kidney Int 2007;72:977-984.

Calcitriol Induces More Calcification Than Paricalcitol

- 5/6 nephrectomized rats with high doses of calcitriol (1 µg/kg) or paricalcitol (3 µg/kg) for 8 weeks

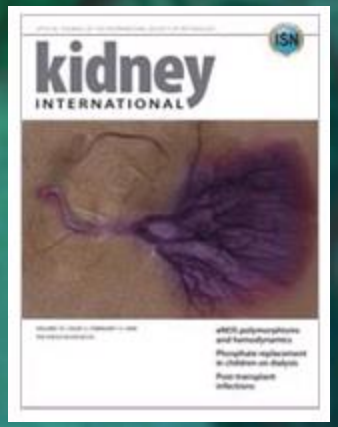


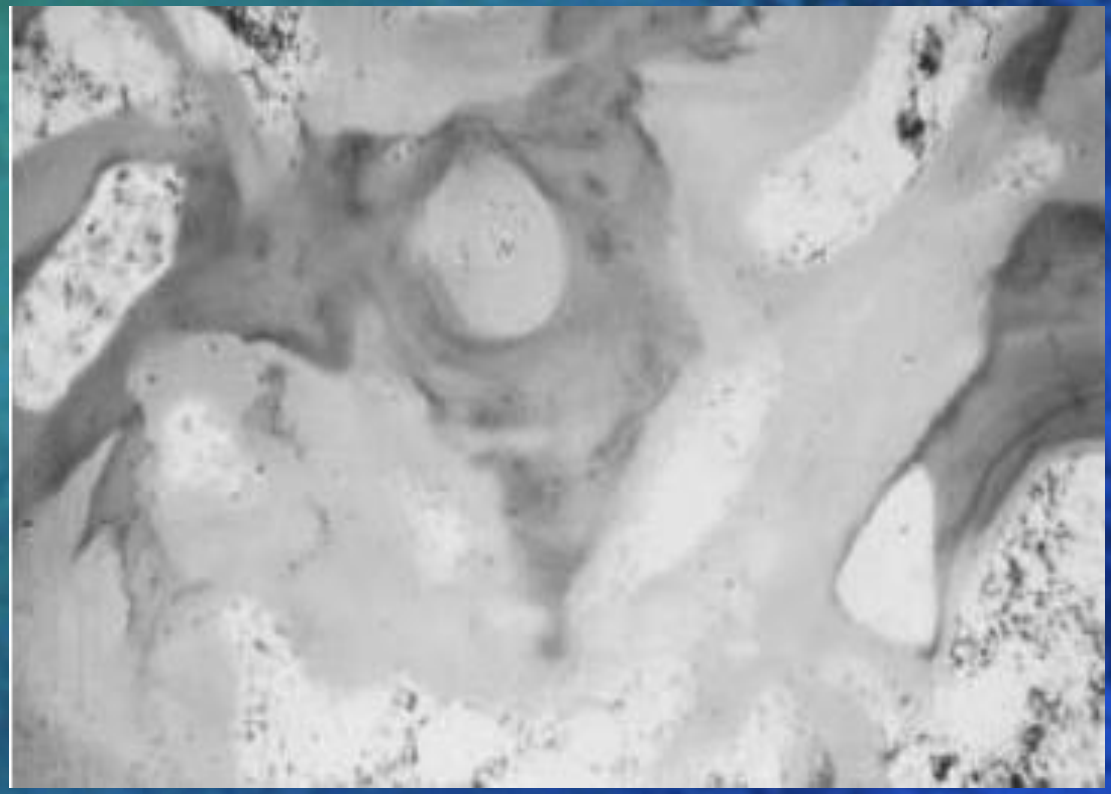


*p<0.01 vs Control

Cardus A, et al. J Bone Miner Res 2007;22:860-6

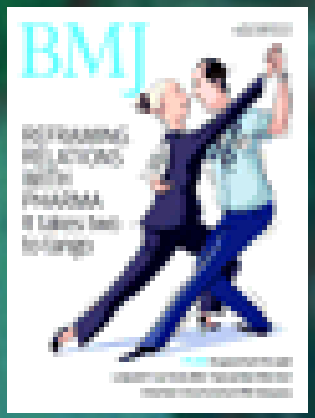
Αδυναμική Οστική Νόσος





Baker LR, Abrams L, Roe CJ, Faugere MC, Fanti P, Subayti Y, Malluche HH.
1,25(OH)2D3 administration in moderate renal failure: a prospective double-blind.
Kidney Int. 1989 ;35(2):661-9.

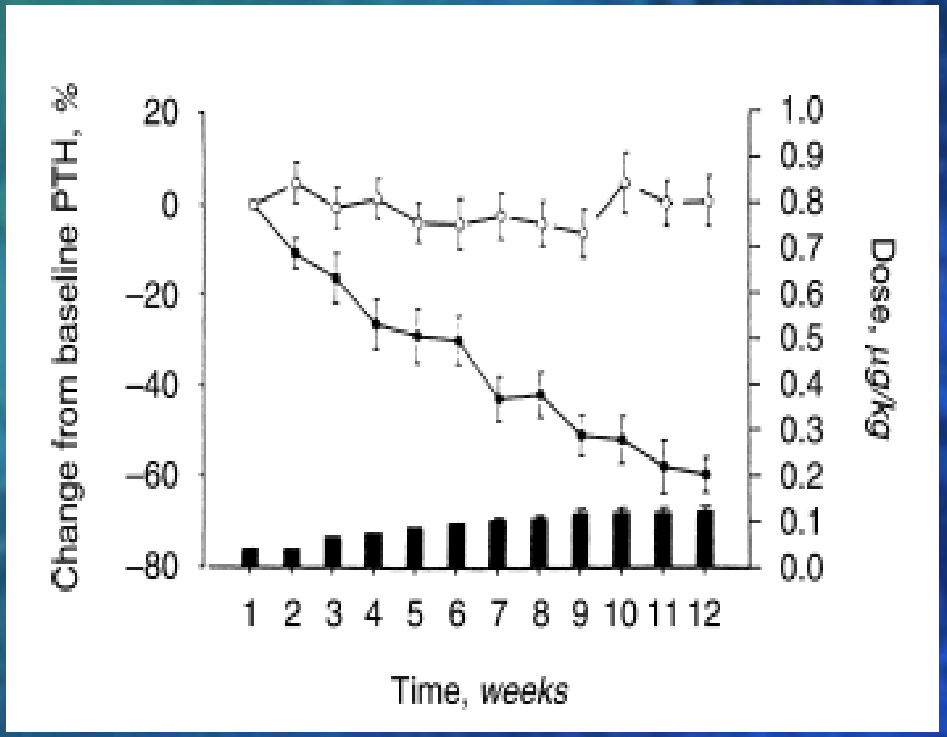
Αδυναμική Οστική Νόσος



Η πιθανότητα ανάπτυξης ελαττώνεται και πάντα σε συνδυασμό με άλλες βιοχημικές παραμέτρους

Hamdy N, Kanis J, Beneton M, et al. Effect of alfacalcidol omn natural course of disease in mild to moderate renal failure. BMJ 1995;310:358-363.

Αδυναμική οστική νόσος



MARTIN KJ, GONZALES EA, GELLENS M, *et al*: 19-nor-1-α-25-dihydroxyvitamin D_2 (Paricalcitol) safely and effectively reduces the levels of intact parathyroid hormone in patients on hemodialysis. *J Am Soc Nephrol* 9:1427–1432, 1998

Kidney International, Vol. 63, Supplement 85 (2003), pp. S83–S87

New vitamin D analogs

EDUARDO SLATOPOLSKY, JANE FINCH, and ALEX BROWN

Renal Division, Department of Internal Medicine, Washington University School of Medicine, St. Louis, Missouri

The vitamin D analogs currently used for the treatment of secondary hyperparathyroidism have less calcemic and phosphatemic activity while still effectively

Επανεξέταση του ρόλου της βιτ-D;

…It is surprising that the uncertainty and ongoing debate over vitamin D use in chronic kidney disease still relies on uncontrolled data and few randomized trials that show efficacy only for correction of bone and serum adnormalities ...

S Palmer, G Srippoli. Vitamin D compounds in chronic kidney disease: change may be needed for good! Nephrol Dial Transplant 2008;23:1786-1789

Επανεξέταση του ρόλου της βιτ-D;

Critique of Observational Data Analyses

- Differences in baseline characteristics
- Potential misclassification and bias
- Non-random assignment of therapy could have led to unequal susceptibility to the outcome
- Lack of prospective data
- Groups not contemporaneous
- Residual confounding
  - Why people get VDRA therapy in the first place accounts for the benefit even if that factor(s) remains elusive
- Need for supportive biological data

Επανεξέταση του ρόλου της βιτ-D;

REVIEW | Annals of Internal Medicine

Meta-analysis: Vitamin D Compounds in Chronic Kidney Disease

Suetonia C. Palmer, MBChB; David O. McGregor, PhD; Petra Macaskill, PhD; Jonathan C. Craig, PhD; Graham J. Elder, PhD; and Giovanni F.M. Strippoli, MD, MPH(Hons), MM

Table 2. Summary of Trial Results for Patient-Level End Points for Vitamin D Treatment in People with Chronic Kidney Disease

Outcome Analyzed (Reference)	Studies Reporting Outcome, n	Patients Enrolled, n	Relative Risk (95% CI)*	Heterogeneity (Chi-Square)	I^2, %†
Established vitamin D sterol vs. placebo or no treatment					
All-cause mortality (11, 14, 50)	3	259	1.34 (0.42 to 4.26)	1.77	0
Fracture (12, 47, 49)	3	108	1.00 (0.06 to 15.41)	–	–
Parathyroidectomy (11, 47)	2	135	0.82 (0.05 to 12.47)	2.79	64.1
Development of bone pain (42)	1	74	0.41 (0.02 to 9.25)	–	–
Newer vitamin D vs. placebo or no treatment					
All-cause mortality (24, 41)	2	250	2.40 (0.36 to 16.01)	0.05	0
Fracture	–	–	–	–	–
Parathyroidectomy	–	–	–	–	–
Development of bone pain (59)	1	35	0.20 (0.01 to 4.05)	–	–
Newer vitamin D vs. established vitamin D sterol					
All-cause mortality	–	–	–	–	–
Fracture	–	–	–	–	–
Parathyroidectomy	–	–	–	–	–
Development of bone pain	–	–	–	–	–
Vitamin D vs. calcium					
All-cause mortality (24)	1	47	5.2 (0.26 to 102.36)	–	–
Fracture	–	–	–	–	–
Parathyroidectomy	–	–	–	–	–
Development of bone pain	–	–	–	–	–
Intravenous vs. oral vitamin D					
All-cause mortality (56)	1	28	0.33 (0.01 to 7.55)	–	–
Fracture	–	–	–	–	–
Parathyroidectomy	–	–	–	–	–
Development of bone pain	–	–	–	–	–
Intraperitoneal vs. oral vitamin D					
All-cause mortality	–	–	–	–	–
Fracture	–	–	–	–	–
Parathyroidectomy	–	–	–	–	–
Development of bone pain	–	–	–	–	–
Intermittent vs. daily vitamin D					
All-cause mortality	–	–	–	–	–
Fracture	–	–	–	–	–
Parathyroidectomy	–	–	–	–	–
Development of bone pain	–	–	–	–	–

* Values <1 or >1 indicate the direction of effect for the experimental intervention vs. the control.
† I^2 >50% indicates significant heterogeneity.

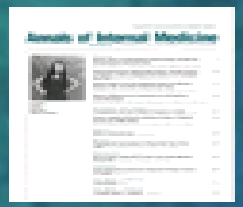
Palmer et al. Ann Intern Med 2007;147:840-853

Επανεξέταση του ρόλου της βιτ-D;

- 3500 pts
- 76 Randomized Controlled Trials

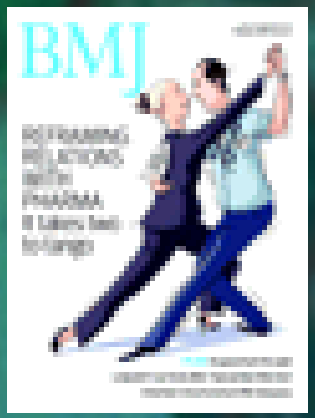
➢ Insufficient randomized evidence was available to determine the beneficial effect on mortality and clinical outcomes in chronic kidney disease.

➢ Vitamin D compounds have unproven efficacy relative to important clinical end points.



Palmer SC, McGregor DO, Macaskill P, et al. Vitamin D compounds in chronic kidney disease: a meta analysis. Ann Intern Med 2007;147:840-853

Επανεξέταση του ρόλου της βιτ-D;



…few trials bother to look…large placebo controlled trials with hard clinical end points are justified and must be done…

All you need to read in the other general journals. BMJ 2008;336:16-17

Επανεξέταση του ρόλου της βιτ-D;

Our standards have rightly changed: whereas in the past we celebrated biochemical endpoints, we now insist on improving clinical outcomes. This was certainly the impetus for our own hypothesis-generating studies.[28]

Nevertheless, until we confirm which (if any) measure is a valid surrogate, one biochemical variable cannot be corrected at the expense of worsening another.

Tradhani R. Activated vitamin D sterols in kidney disease. Lancet 2008;371: 542-544

Επανεξέταση του ρόλου της βιτ-D;

…Clinical effects of vitamin D compounds are necessarily pleiotropic and incompletely understood, because of gene transcription by vitamin D in diverse tissues, via activation of vit-D receptors…

Tradhani R. Activated vitamin D sterols in kidney disease. Lancet 2008;371: 542-544

Nephrol Dial Transplant (1998) 13 [Suppl 3]: 73–77

Nephrology
Dialysis
Transplantation

Vitamin D receptor gene (VDR) polymorphisms: effect on bone mass, bone loss and parathyroid hormone regulation

Carlos Gómez Alonso, Manuel L. Naves Díaz, Carmen Díaz-Corte, Jose L. Fernández Martín and Jorge B. Cannata Andía

Bone and Mineral Research Unit, Instituto Reina Sofía de Investigación, Hospital Central de Asturias, Oviedo, Spain

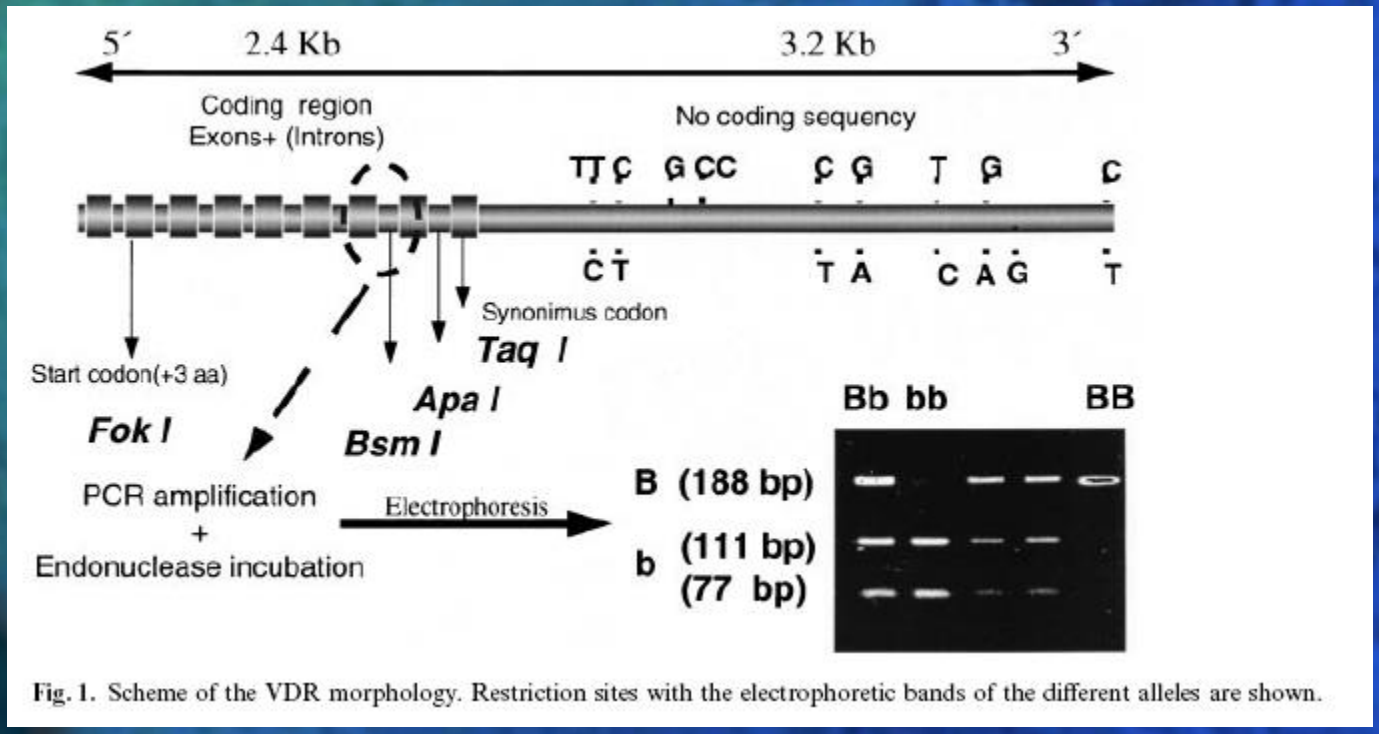


Fig. 1. Scheme of the VDR morphology. Restriction sites with the electrophoretic bands of the different alleles are shown.

Nephrol Dial Transplant (1998) 13 [Suppl 3]: 73–77

Nephrology
Dialysis
Transplantation

Vitamin D receptor gene (VDR) polymorphisms: effect on bone mass, bone loss and parathyroid hormone regulation

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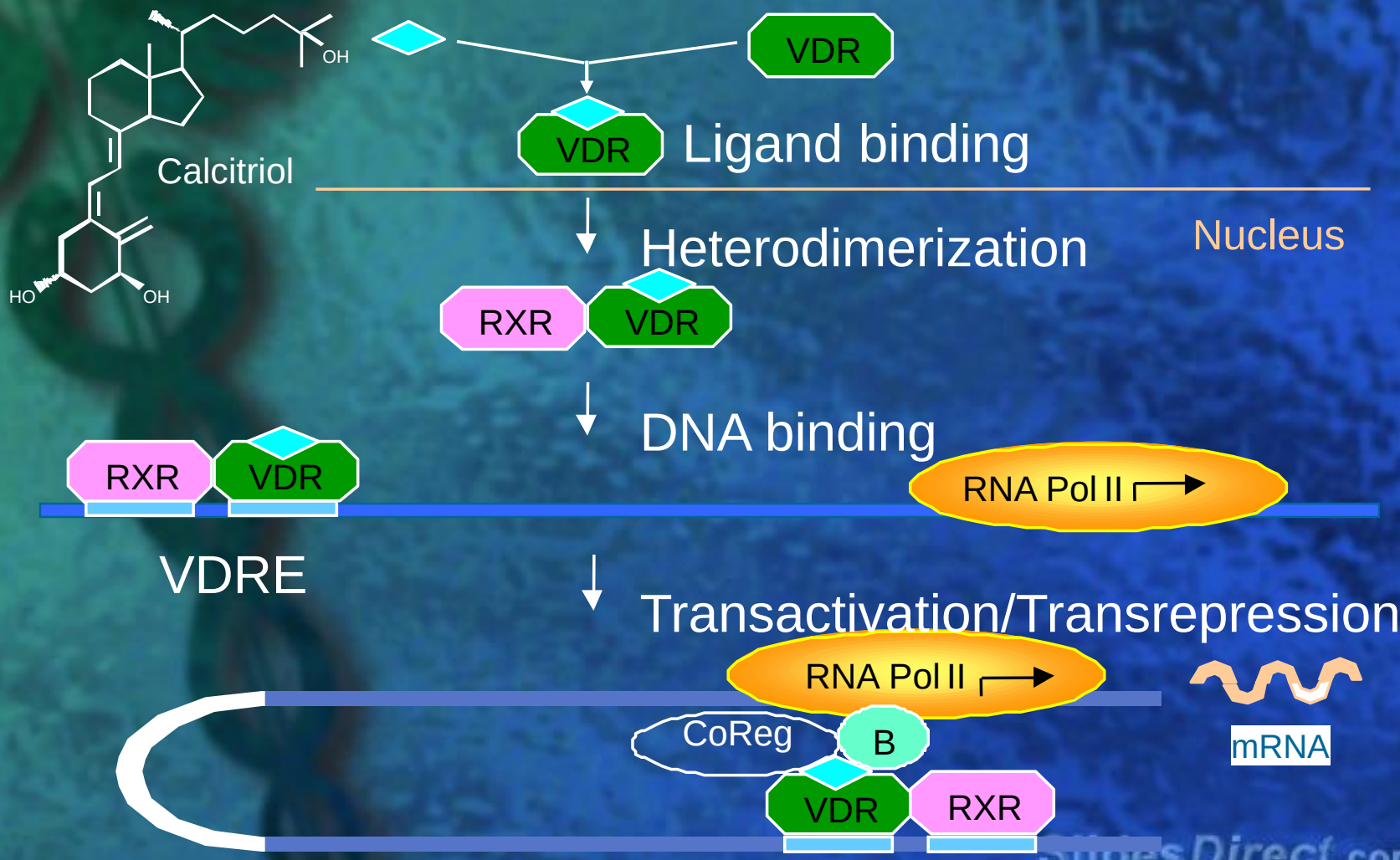
Restriction enzyme	Alleles	Genotypes
Bsm 1	B	BB
	b	Bb
		bb
Taq 1	T	TT
	t	Tt
		tt
Apa 1	A	AA
	a	Aa
		aa
Fok 1	F	FF
	f	Ff
		Ft

Cellular Action of VDR activation



- **H** Cr αυξήθηκε και η Creatinine Clearance ελαττώθηκε , η κάθαρση της ινουλίνης δεν φάνηκε να επηρεάζεται.

- Η τιμή της Cr αποκαταστάθηκε εντός 60 ημερών από τη διακοπή της θεραπείας με βιταμίνη D.

The increased Cr may be explained by an augmented release from muscular tissue, probably due to the improvement of uremic myopathy induced by calcitriol.

Bertoli M, Luisetto G, Ruffatti A, Urso M, Romagnoli G.
Renal function during calcitriol therapy in chronic renal failure.
Clin Nephrol. 1990 Feb;33(2):98-102.

Current Opinion in Nephrology and Hypertension

- **Suppression of the adaptive immune system is not without a price.**
- ***Leismania major***
- ***Toxoplasmosis***

Bikle, Daniel D. ***Vitamin D and the immune system: role in protection against bacterial infection.*** *Current Opinion in Nephrology and Hypertension:Volume 17(4)July 2008, p 348-352.*

Φάρμακα στις Νεφρικές παθήσεις

Φαρμακευτική παρέμβαση στις διαταραχές του μεταβολισμού Ca^{++} & Po_4^{---}

"trials for policy"

"lumping"

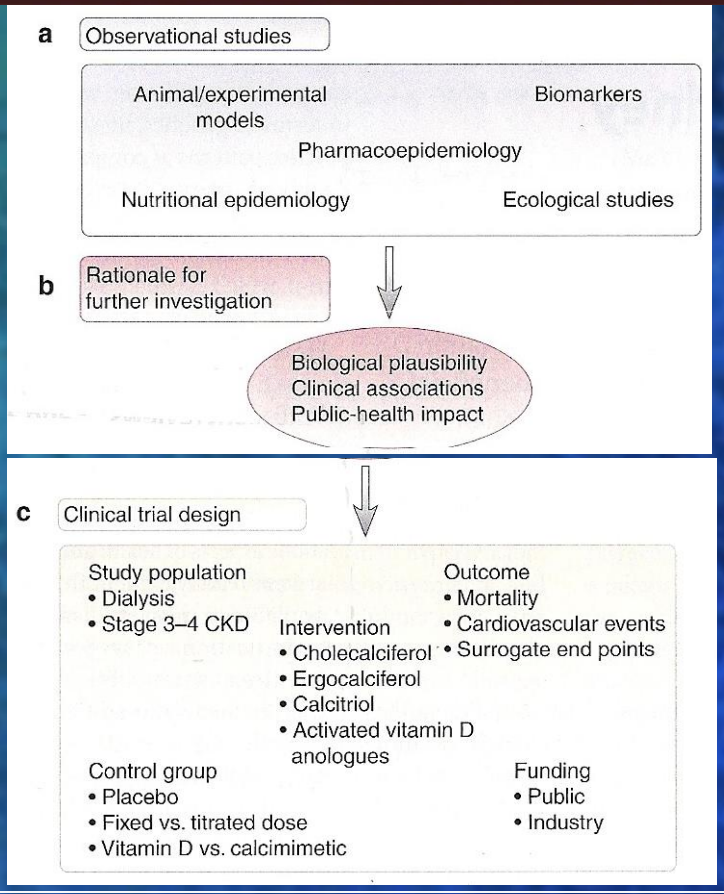
"splitting"

"confounding by indication"

S Palmer, G Srippoli. Vitamin D compounds in chronic kidney disease: change may be needed for good! Nephrol Dial Transplant 2008;23:1786-1789

Φάρμακα στις Νεφρικές παθήσεις

Φαρμακευτική παρέμβαση στις διαταραχές του μεταβολισμού Ca^{++} & Po_4^{---}



Repo JM, Rantala IS, Honkanen TT, Kidney Int 2007;72:977-984.