DİYALİZ HASTALARINDA MİNERAL KEMİK BOZUKLUKLARI ÖNLENEMEZ Mİ?

(FOSFOR KONTROLÜNDE VE D VİTAMİNİ TEDAVİSİNDE YENİLİKLER)

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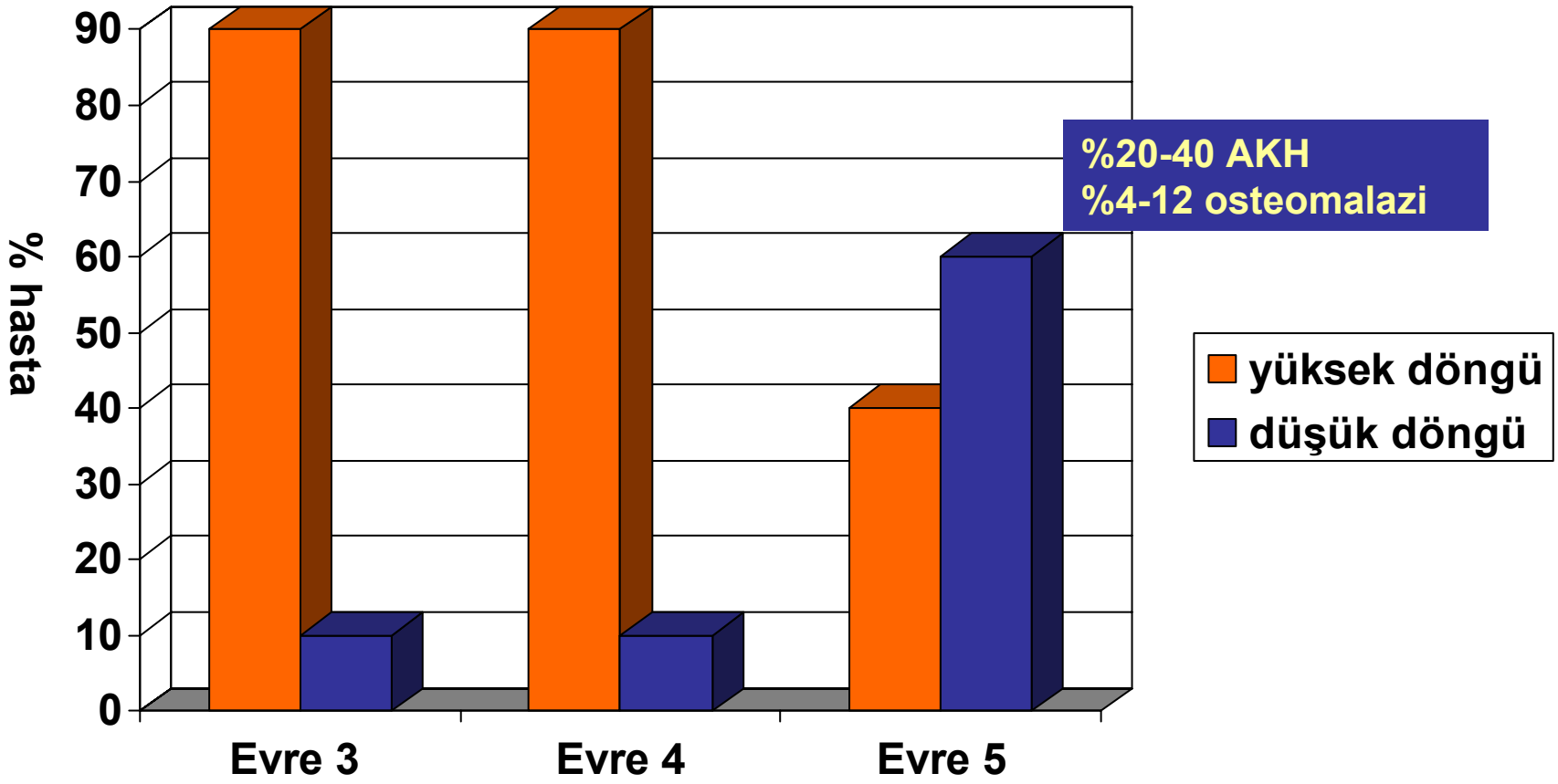
Gazi Üniversitesi Tıp Fakültesi
Nefroloji BD

KBY'de mineral kemik bozukluklarının tanımı

- Kalsiyum, fosfor, PTH ve D vitaminini ilgilendiren anormallikler
- Kemik volümü, mineralizasyonu, sağlamlığı ve kemik döngüsünde anormallikler
- Vasküler ve diğer yumuşak doku kalsifikasyonları

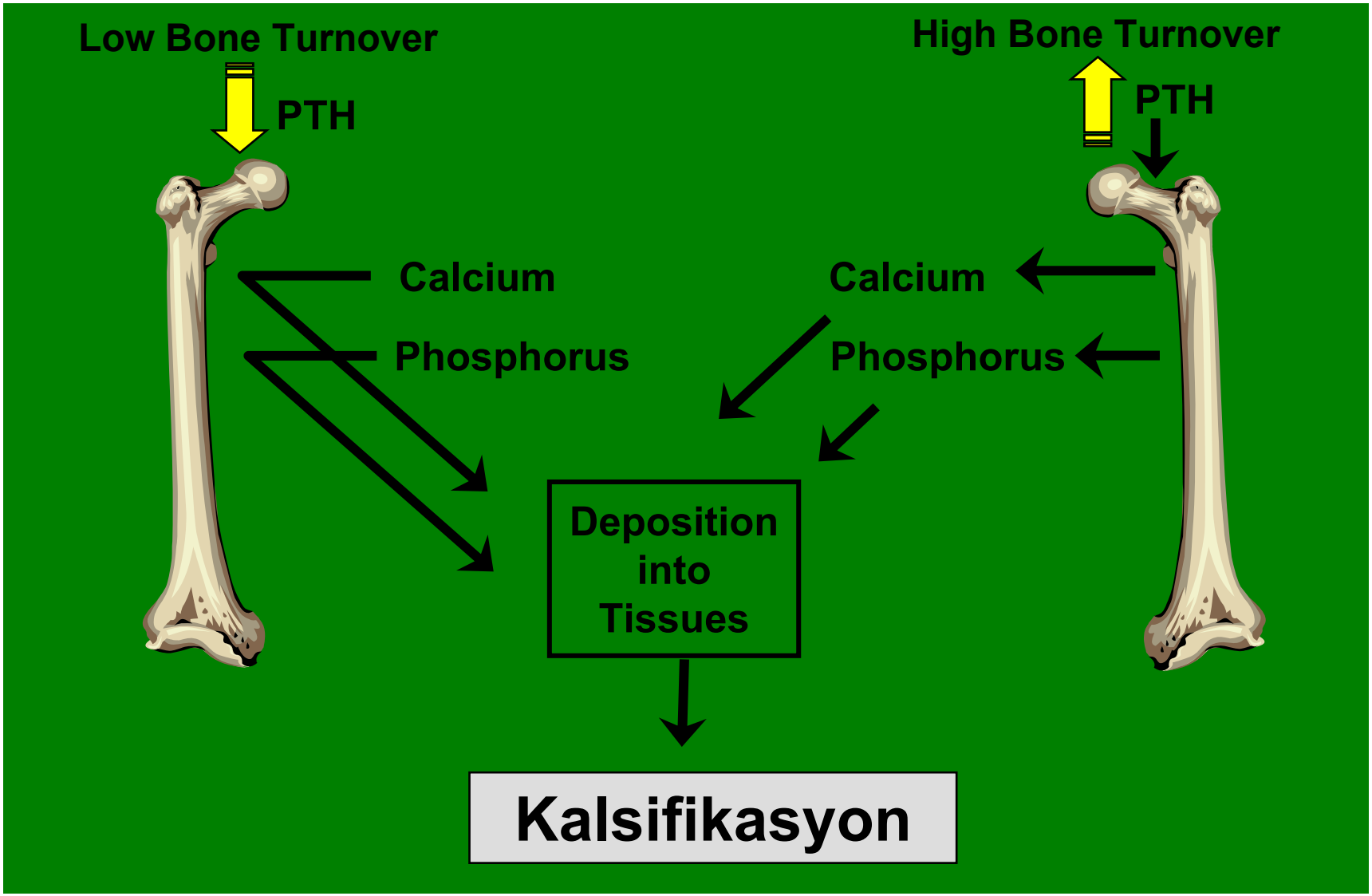
CKD-MBD, KDIGO Kidney Int 2006

KBY'li hastalarda üremik kemik hastalığı



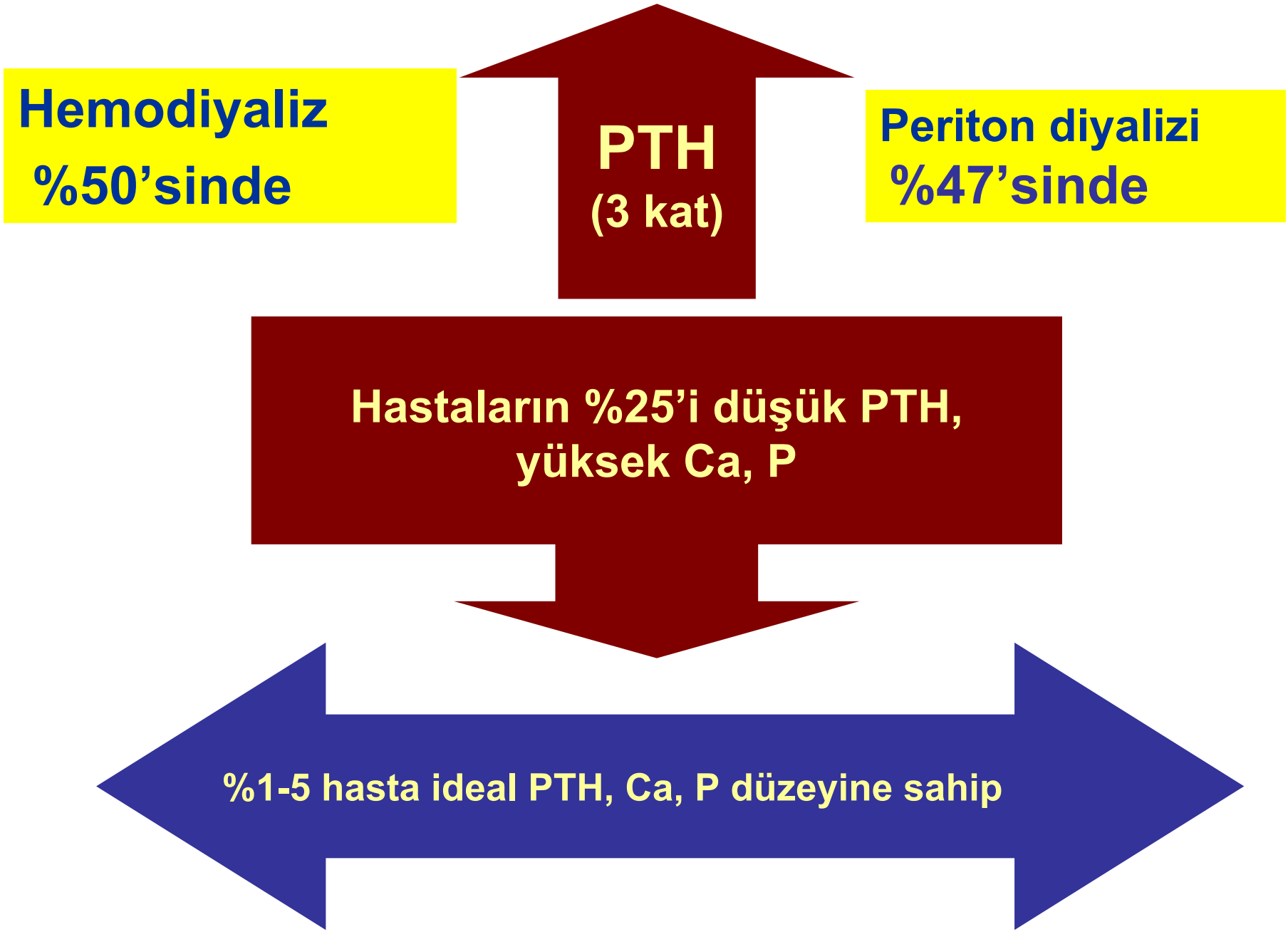
Joy SM et al. J Manag Care Pharm 2007

Extraskeletal kalsifikasyon üzerine kemik döngüsünün etkileri

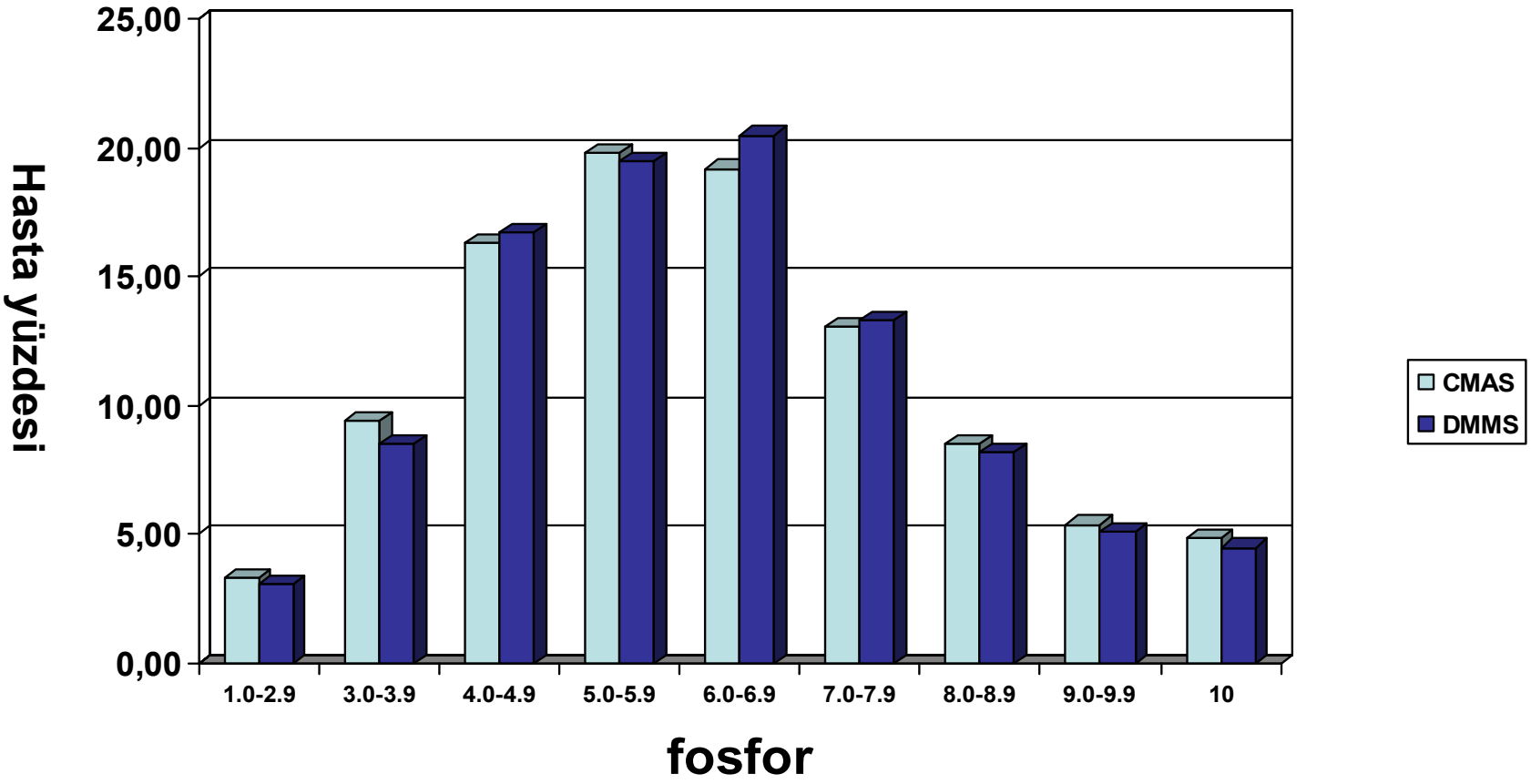


K/DOQI 2003

- ✓ Serum Ca 8.4 - 9.5 mg/dl
- ✓ Serum P 3.5 - 5.5 mg/dl
- ✓ Serum Ca X P < 55 mg^2/dl^2
- ✓ Serum PTH 150-300 pg/ml

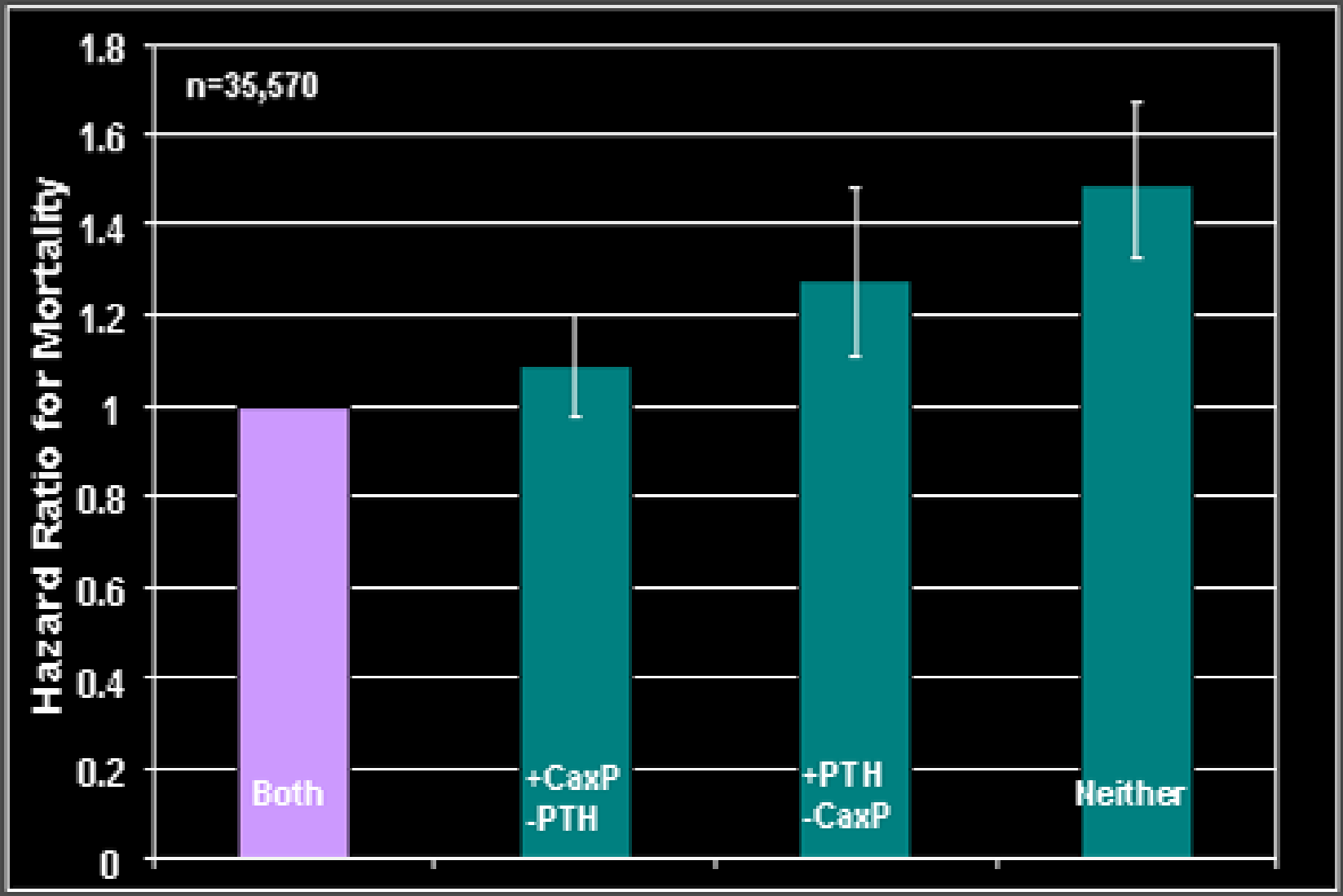

Hemodiyaliz
%50'sinde
PTH
(3 kat)
Periton diyalizi
%47'sinde
Hastaların %25'i düşük PTH,
yüksek Ca, P
%1-5 hasta ideal PTH, Ca, P düzeyine sahip

Case Mix Adequacy Study (n=3738) ort:6.2
Dialysis Morbidity Mortality Study (n=2669) Ort P:6.2



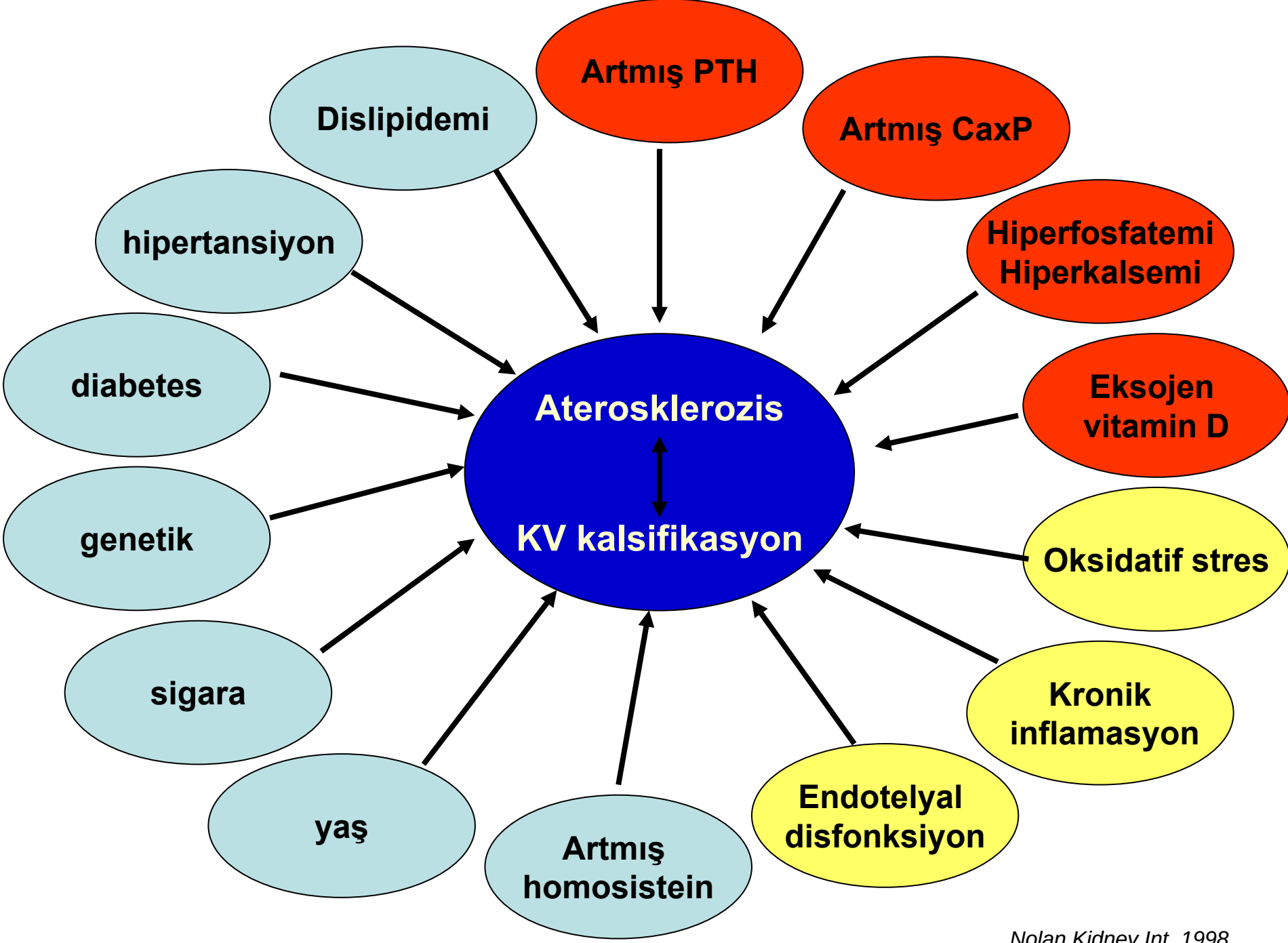
Block G AJKD 1998

K/DOQI Target Ranges (PTH and Ca x P) and Risk of Mortality

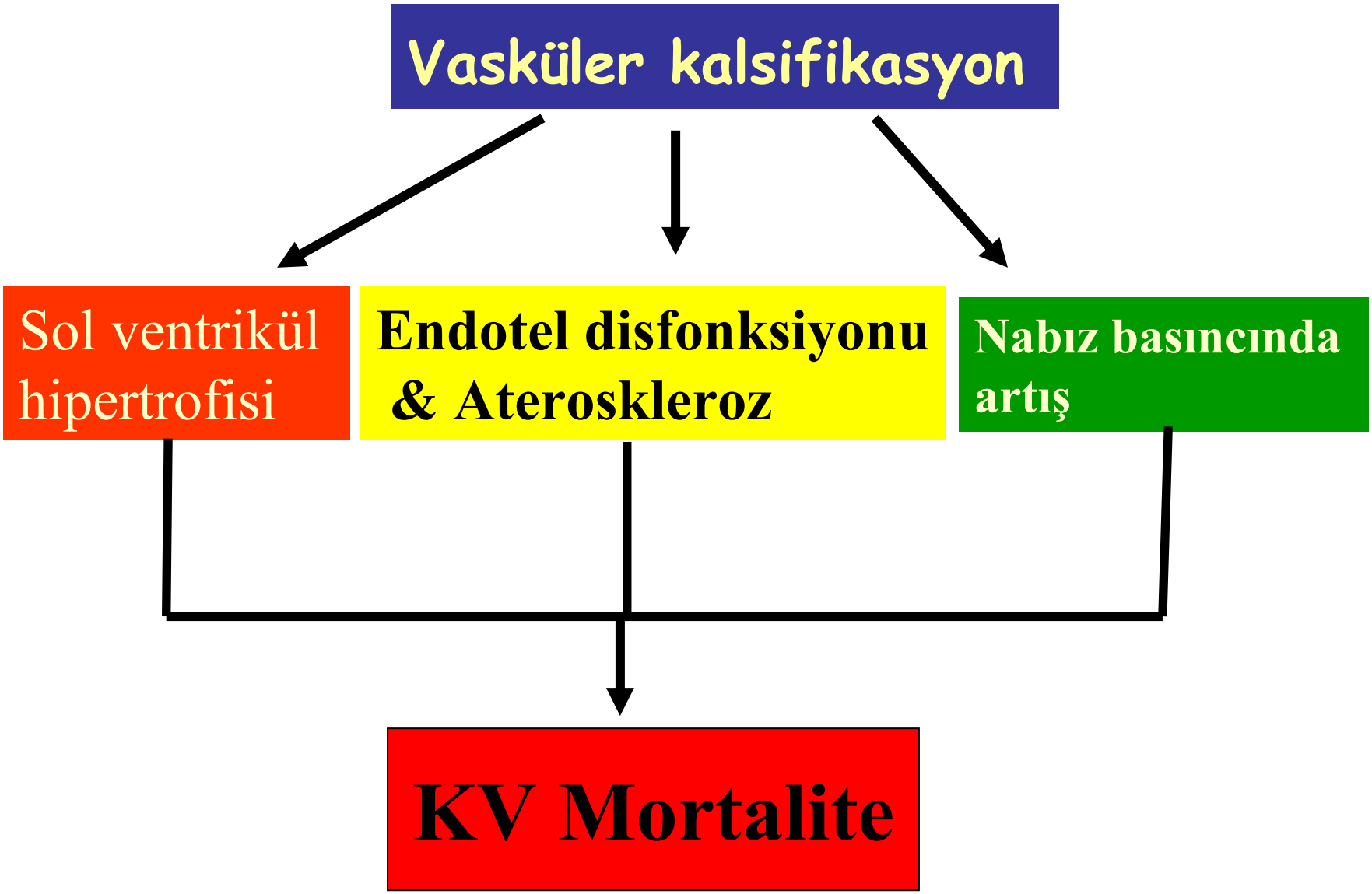


Cox model adjusted for age, sex, race, diabetes, BMI, vintage, URR, missed treatments, albumin, and hemoglobin

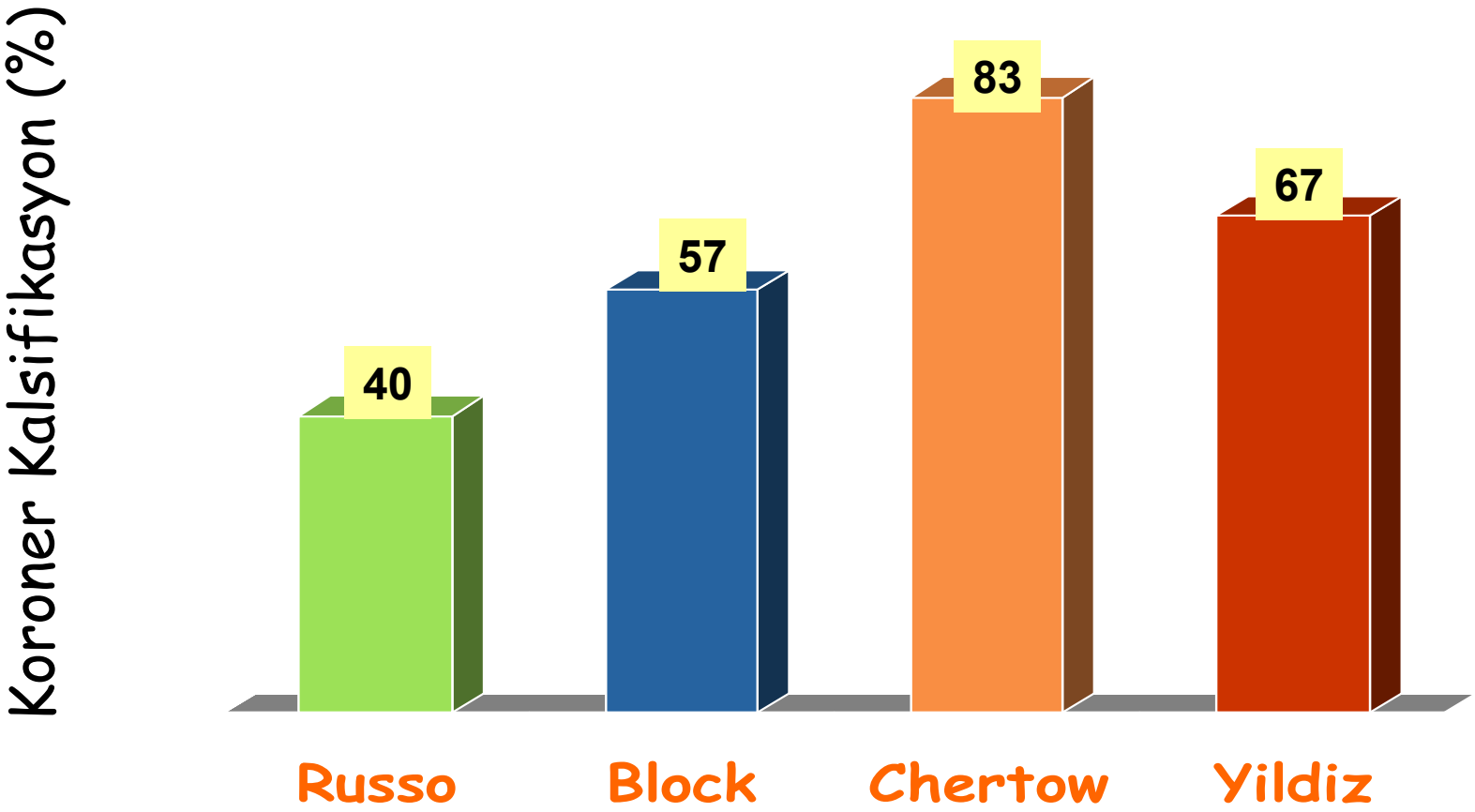
Block G, Klassen P, Danese M, et al. ASN 2003



Nolan Kidney Int 1998

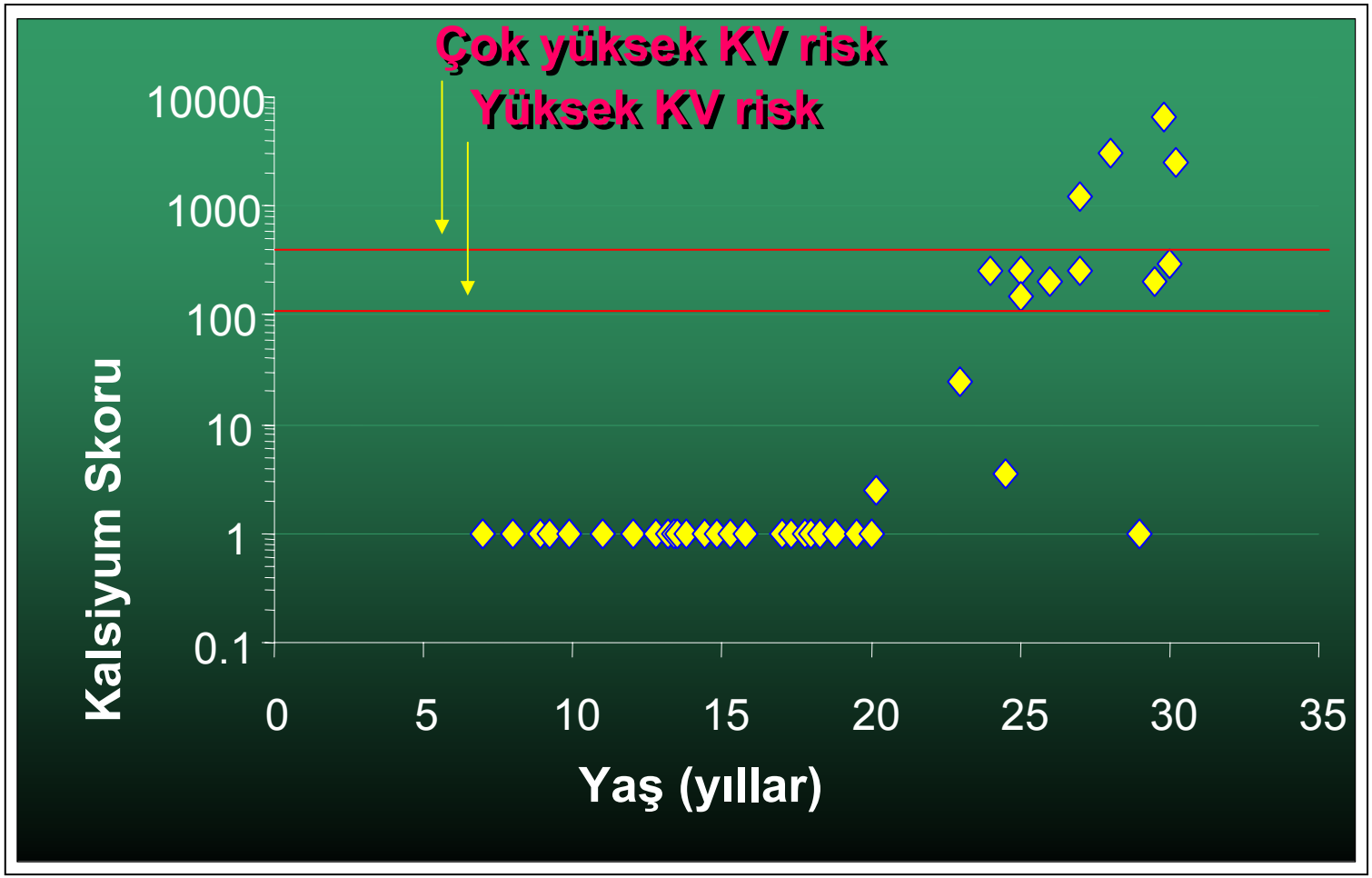

Vasküler kalsifikasyon
Sol ventrikül hipertrofisi
Endotel disfonksiyonu & Ateroskleroz
Nabız basıncında artış
KV Mortalite

SDBY hastalarında kardiyovaskuler kalsifikasyon sıklığı



1. Russo ve ark, AJKD 2004 (CrCI=33 ml/dak)
2. Block ve ark KI 2005
3. Chertow ve ark, KI 2002
4. Yildiz ve ark, NDT 2004

Hemodiyaliz ve koroner arter kalsifikasyonu



Goodman WG, et al. N Engl J Med. 2000;342:1478-1483.

Fosfor

"The shocking history of phosphorus: A biography of the Devil's element"

- 1669 yılında Hennig Brand tarafından ilk kez idrarda saptanmış
- Işık saçan anlamında, turuncu renkli element
- Vücutta kalsiyumdan sonra en yoğun olarak bulunan ikinci element (%85'i kemik ve dişlerde)

Nephrol Dial Transplant (1999) 14: 2085–2087

Hyperphosphataemia—a silent killer of patients with renal failure?

Kerstin Amann[1], Marie-Luise Gross[1], Gérard M. London[3] and Eberhard Ritz[2]

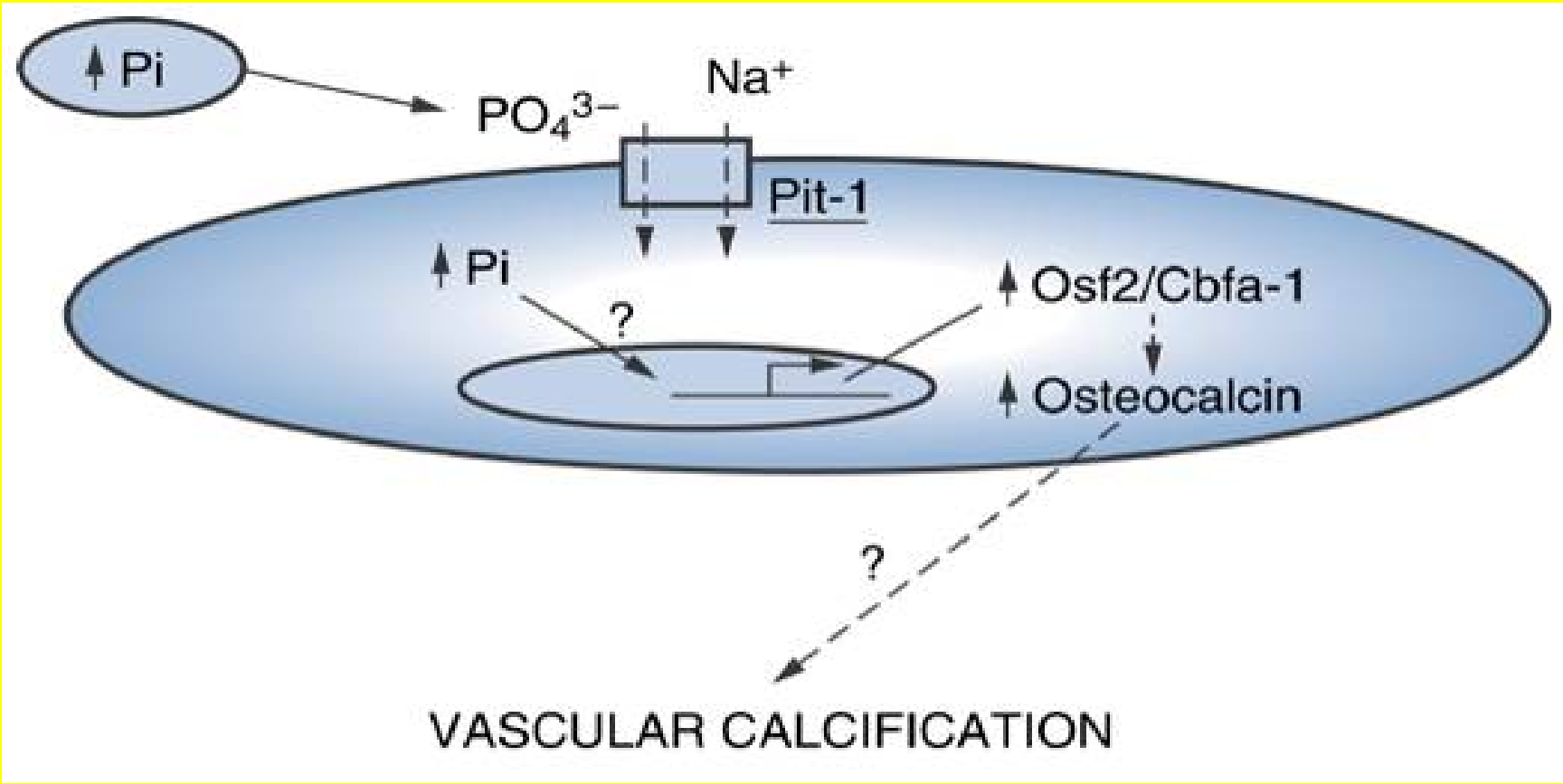
[1]Department of Pathology and [2]Department of Internal Medicine, Ruperto Carola University, Heidelberg, Germany and [3]Hôpital Manhes, Fleury Mérogis, France

Introduction

For decades, it has been known that patients with end-stage renal failure have an excessive coronary and cardiac risk. There is also widespread consensus that coronary atherosclerosis and its complications are not fully explained by classical risk factors, e.g. dyslipidaemia, elevated homocysteine concentrations, hypertension, insulin resistance, high fibrinogen etc.

Studies on uraemia spring many surprises. In an early investigation, the paradoxical finding had been made [1] that high cholesterol concentrations are predictive of better survival. This observation subsequently has been confirmed [2] and the paradox is presumably explained by the fact that high cholesterol is a surrogate marker for adequate nutrition.

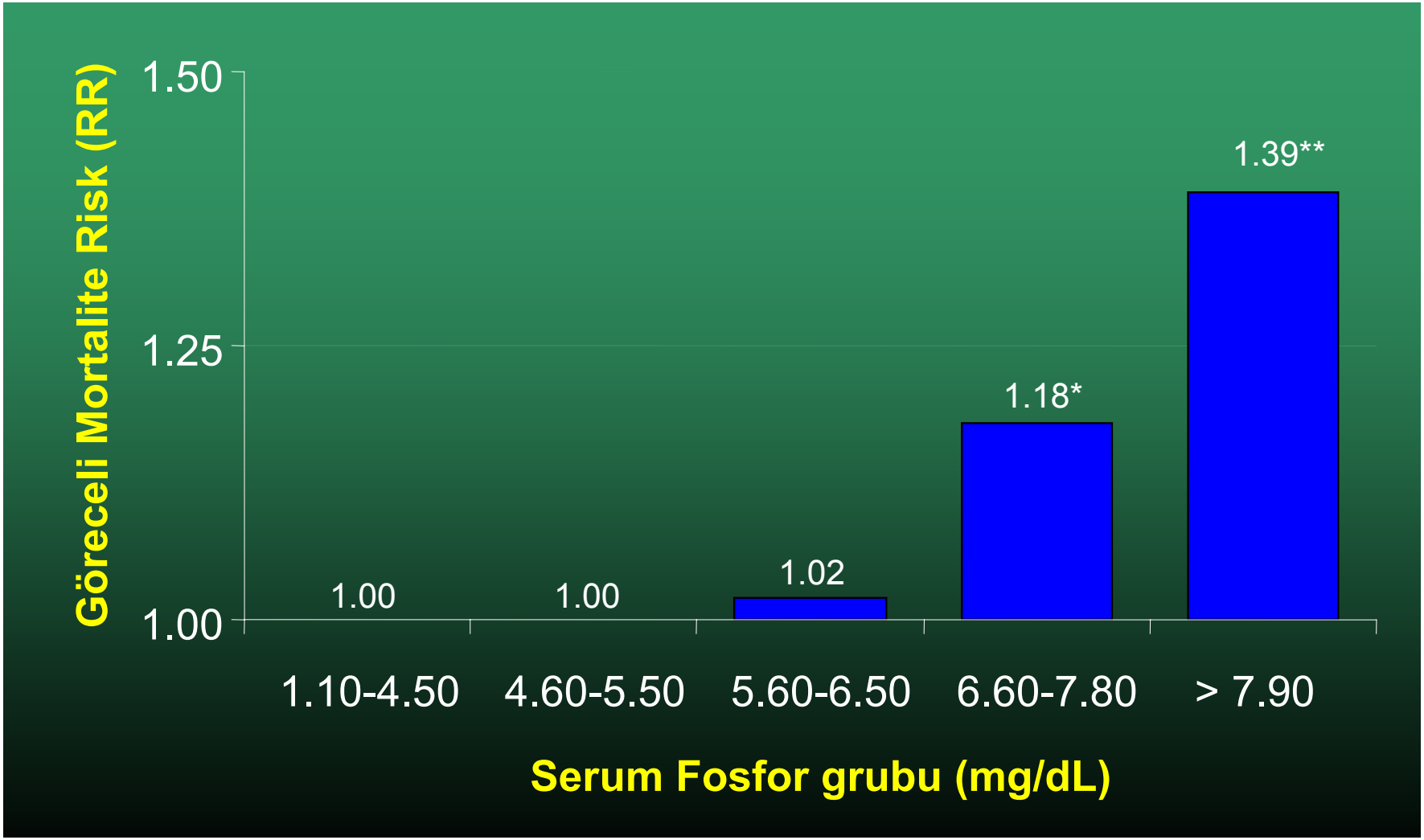
stage of plaque transformation. Recently, non-invasive technology, based on fast electron computed tomography (CT) led to the recognition that the number and the extension of calcified plaques [7] is a highly sensitive indicator of coronary atherosclerosis. The specificity of the lesions detected by fast electron CT is shown by the fact that they respond to interventions such as administration of statins [8]. Necrotic cores of plaques are known to calcify easily. This is accompanied by expression of genes which potentially play a role in calcium metabolism, e.g. osteopontin and osteocalcin, raising interesting issues about the mechanisms, direct or indirect, through which hyperphosphataemia promotes calcification. Autopsy studies [9] and clinical observations using electron-beam CT [10] showed a high prevalence of rapidly progressing calcified coron-



Cbfa:Core binding factor a

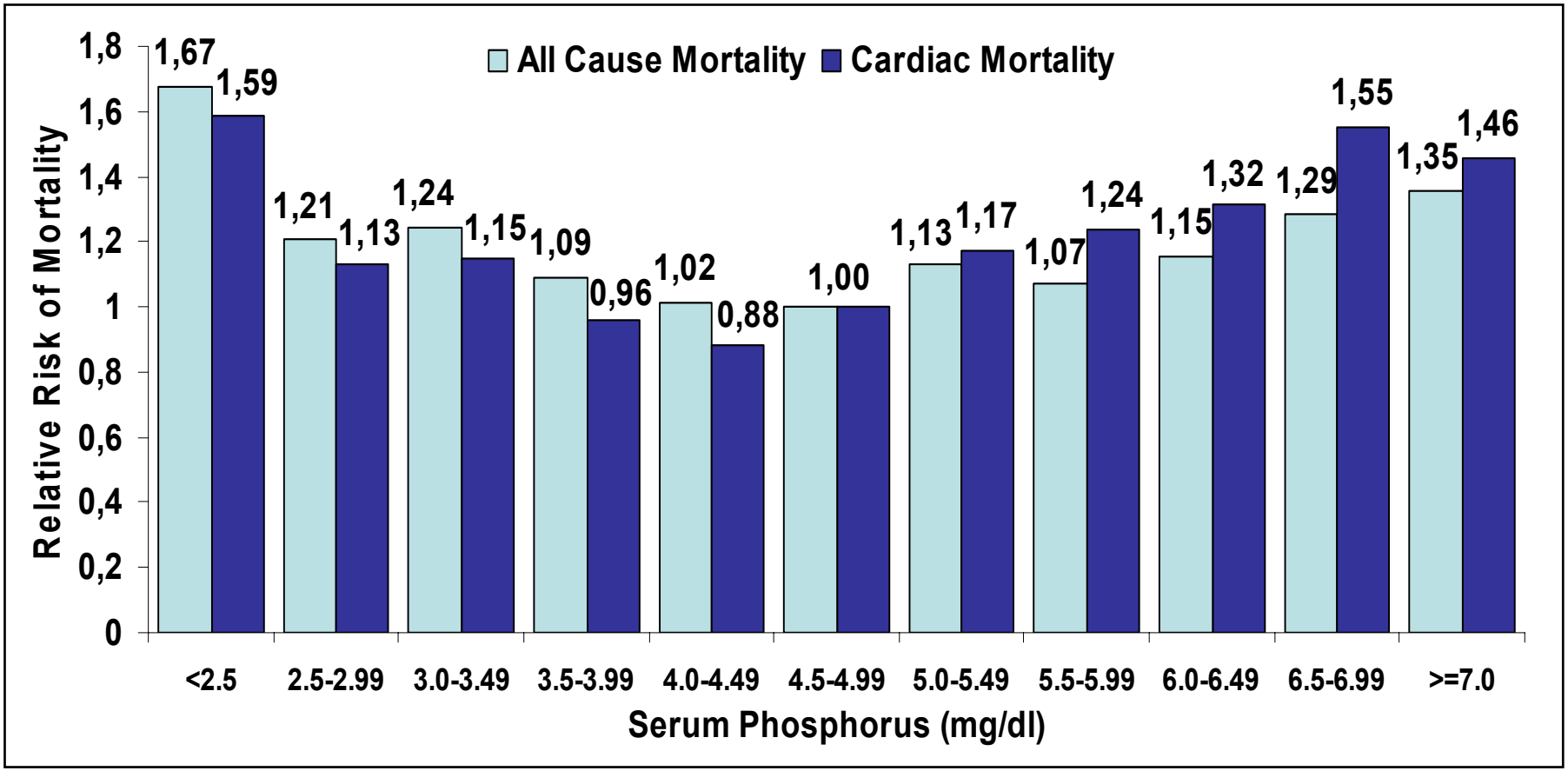
Giachelli et al. AJKD 2001

Hiperfosfatemi kardiovasküler mortaliteyi arttırır



Block GA, et al. Am J Kidney Dis. 1998;31:607-617.

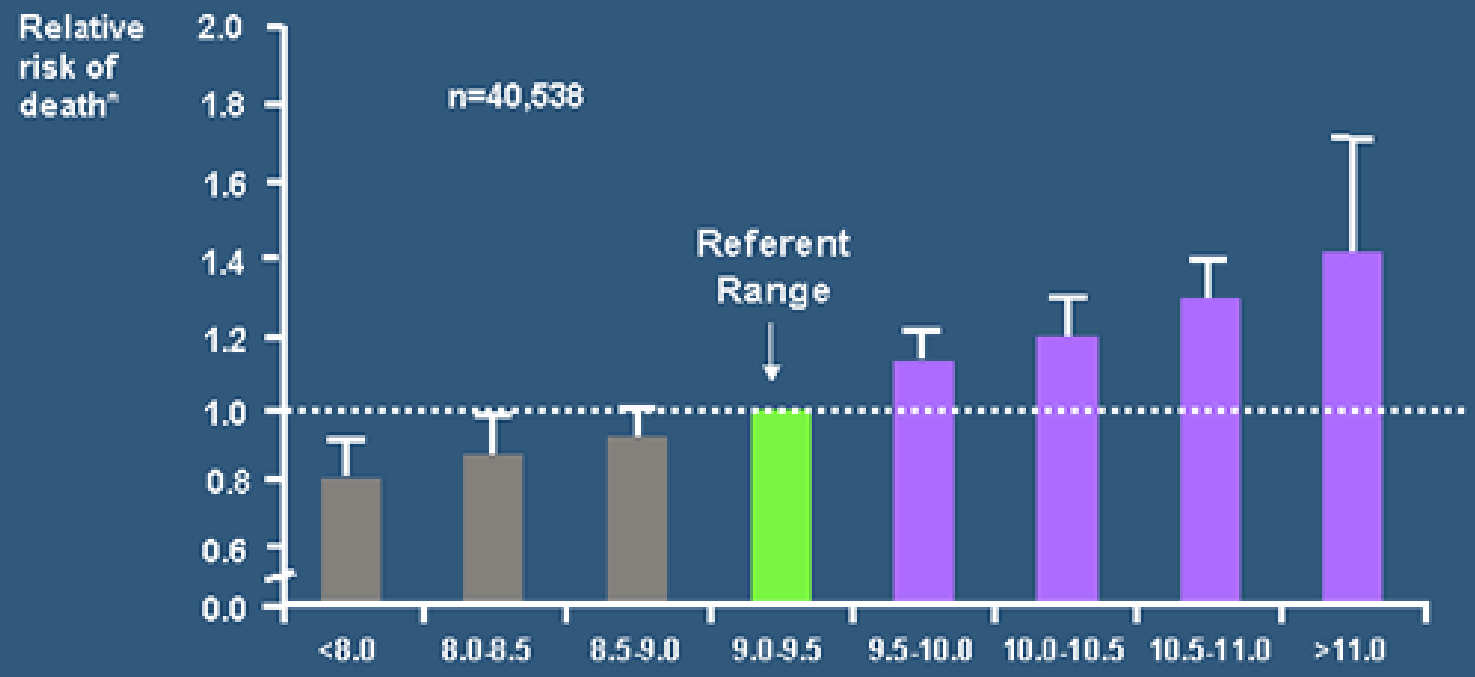
Tüm nedenlere ve kardiyak nedenlere bağlı mortalite:DOPPS



N=14298

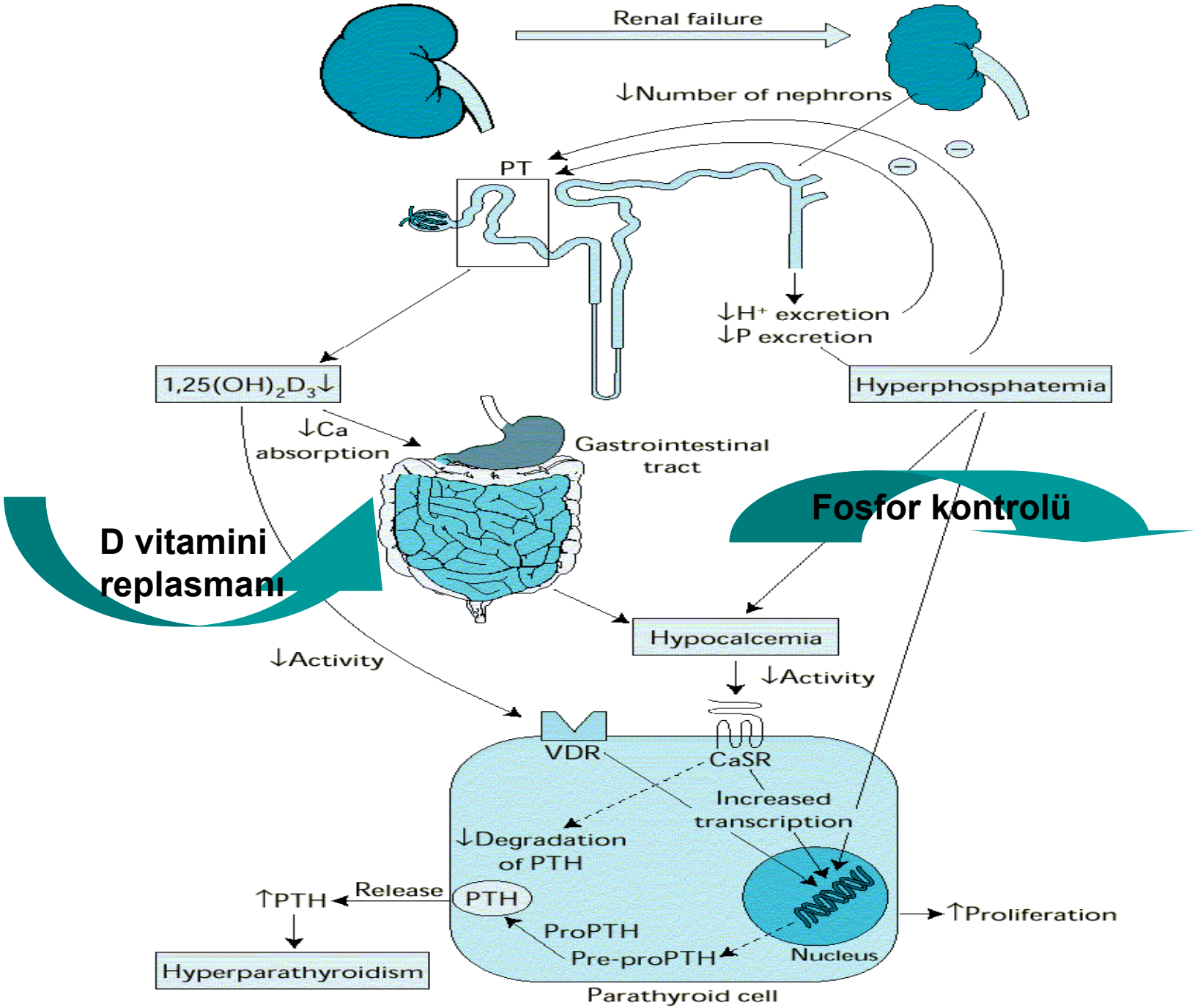
Young ve ark, KI 2005;67:1179

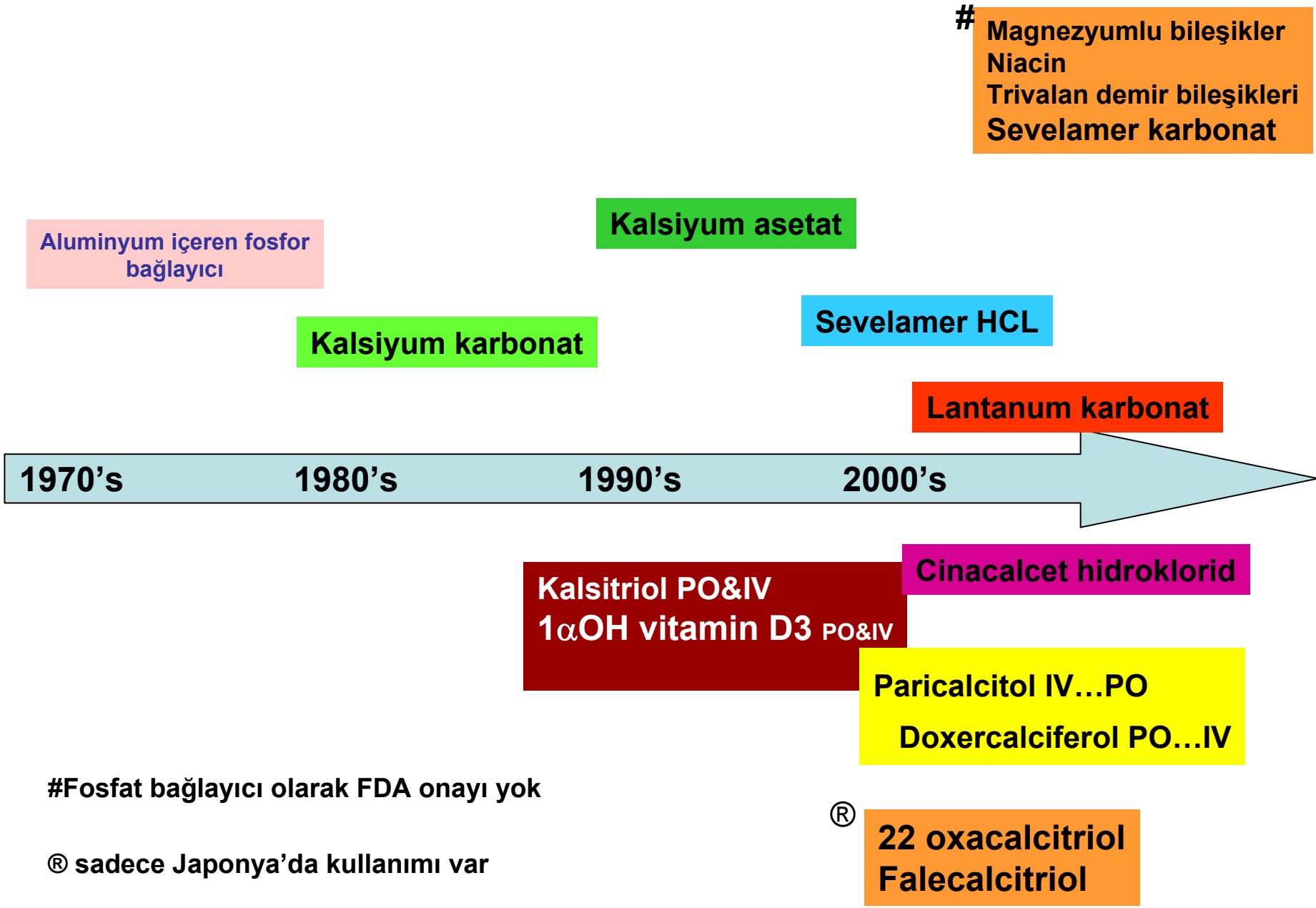
Elevated Serum Calcium Increases Mortality Risk



*Multivariable adjusted

Block GA, Klassen PS, Lazarus JM, Ofsthun N, Lowrie EG, Chertow GM. *J Am Soc Nephrol.* 2004;15:2208-2218.


Renal failure
↓Number of nephrons
PT
↓H⁺ excretion
↓P excretion
1,25(OH)2D3↓
Hyperphosphatemia
↓Ca absorption
Gastrointestinal tract
D vitamini replasmanı
Fosfor kontrolü
Hypocalcemia
↓Activity
↓Activity
VDR
CaSR
Increased transcription
↓Degradation of PTH
↑PTH
Release
PTH
ProPTH
Pre-proPTH
Nucleus
↑Proliferation
Hyperparathyroidism
Parathyroid cell



Kovesdy, C. P. et al. Clin J Am Soc Nephrol 2008;3:168-173

FOSFOR BAĞLAYICILAR

- Aluminyum hidroksit
- Magnezyum tuzları
- Demir tuzları
- Niacin (Niceritrol)
- Kalsiyum karbonat
- Kalsiyum asetat

Sevelamer hydrochloride(Renagel®)
Lanthanum carbonate (Fosrenol ®)
Sevelamer karbonat (Renvela®)

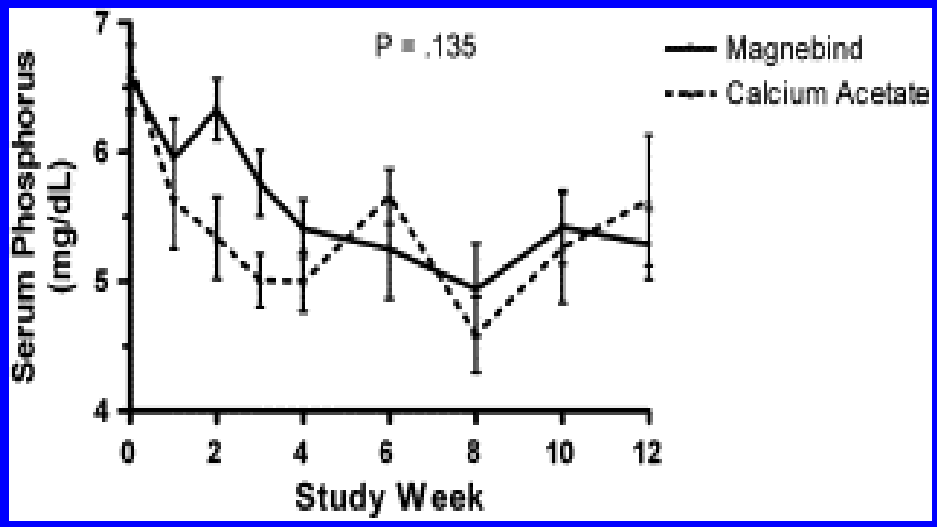
DEMİR TUZLARI

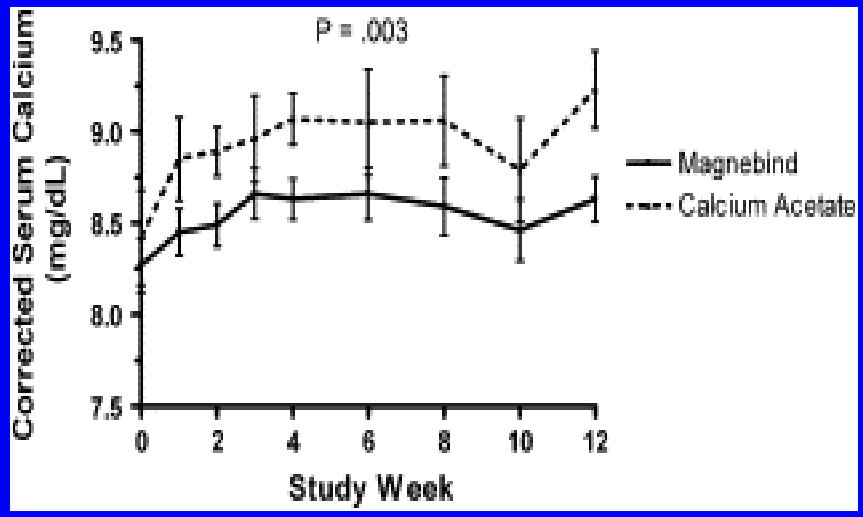
- 3 değerlikli demir tuzları diyetteki fosforu bağlar
- pH bağımlı reaksiyon olup maksimum etki pH 2-3 arasındadır
- 1 gram elementer demir ile 88-180 mg P bağlanabilmekte
- Polinuklear iron hydroxide ile ort. %20 fosfor azaltımı sağlanabilir(4 hf)
- Yüksek dozda demir kullanımı gereksinimi?
- Yeterli çalışma yok

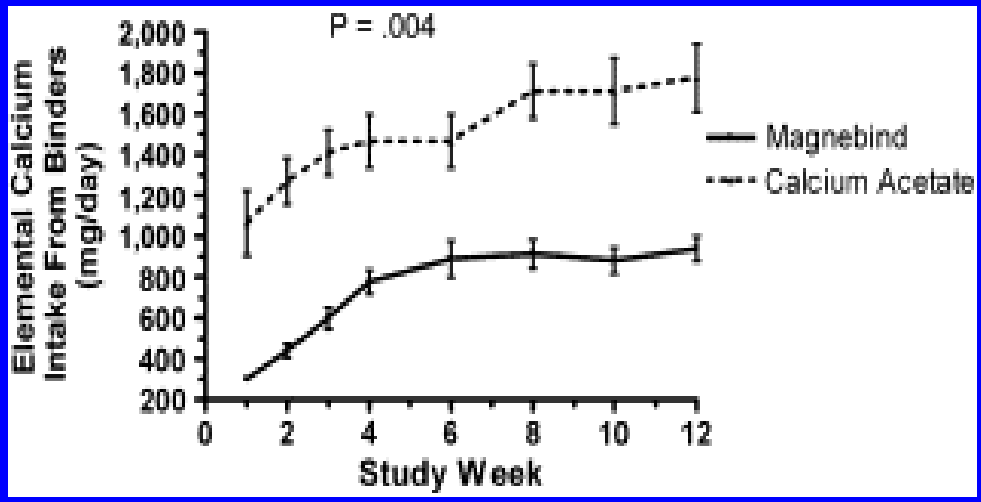
Niceritrol

- Nikotinik asid derivesi
- İncebarsak mukozasından P transportunu inhibe eder (Na-Fosfat transporter'i)
- İntestinal P absorbsiyonunu engeller,
- üriner P atılımı arttırır
- Lipid düşürücü etkisi de vardır
- Yeterli sayıda çalışma yoktur
- Trombositopeni ve anemi yan etkileri var

Magnezyum Tuzları







Kalsiyum içeren fosfor bağlayıcı dozunu azaltır

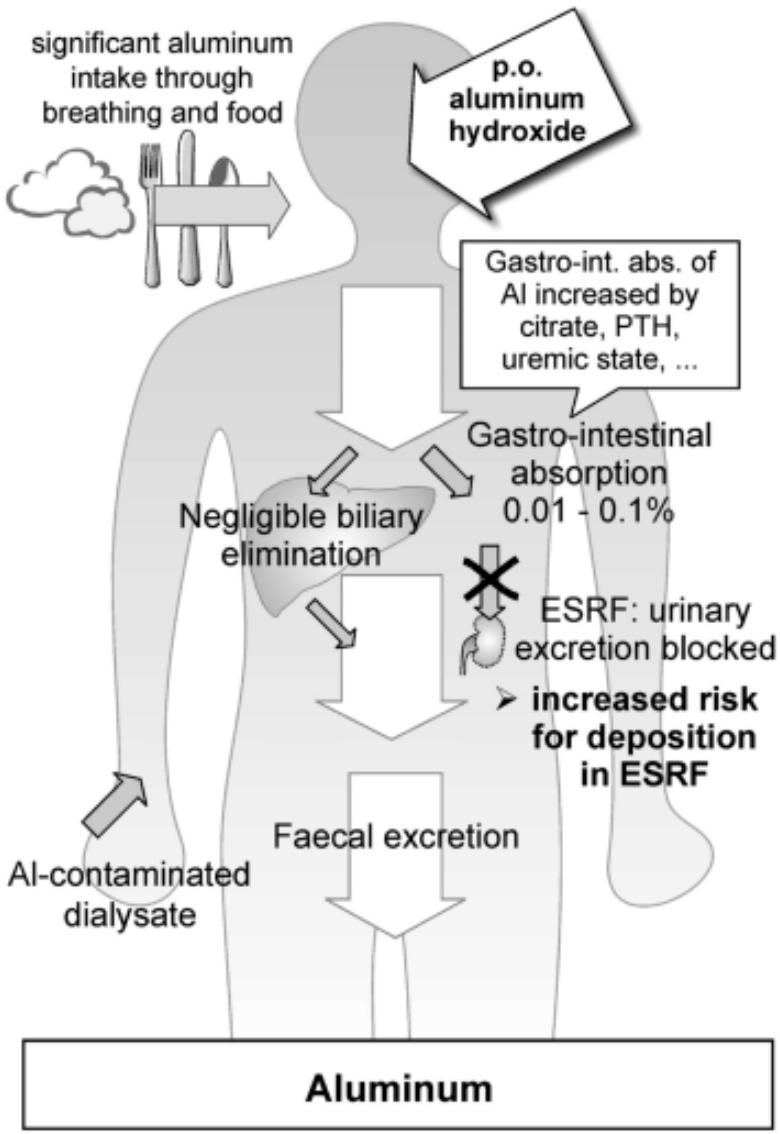
Diyalizat magnezyum konsantrasyonuna dikkat

Vasküler kalsifikasyonu azaltır??

Aritmi görülme insidansını azaltır??

Spiegel D J Renal Nutrit 2007

Aluminyum hidroksid



Avantajları

Güçlü fosfor bağlayıcı

Ucuz

Dezavantajları

Düşük döngülü kemik hst.

Eritropoietine dirençli anemi

Nörolojik bulgular

Persy et al. Seminars In Dialysis 19 (3) , 195–199

Kalsiyum içeren fosfor bağlayıcılar

Kalsiyum karbonat, kalsiyum asetat, kalsiyum ketoglutarat, kalsiyum sitrat

Aluminyuma göre daha zayıf olarak fosfor bağlarlar

Kalsiyum karbonat asidozun düzelmesine katkıda bulunur

Dezavantajları

Hiperkalsemik epizodlar
D vitamini ile birlikte kullanım zorluğu
Extraosseal kalsifikasyon artışı
GI yan etkiler nedeniyle tedaviye uyumsuzluk

- Ciddi vasküler ve/veya diğer yumuşak doku kalsifikasyonu olan diyaliz hastalarında kalsiyum içeren fosfat bağlayıcılar kullanılmamalıdır.

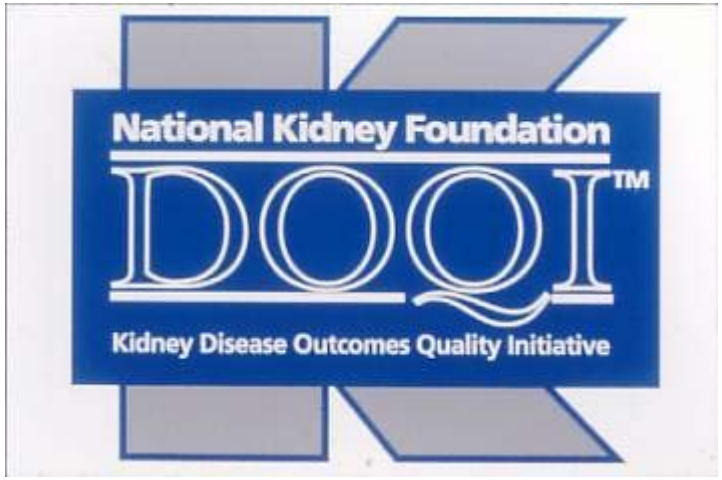
Serum P>7mg/dl olan diyaliz hastalarında Al içeren fosfat bağlayıcılar sadece bir kür olarak kısa süreli (4 hf) kullanılabilir. Bu hastalarda daha sık diyaliz düşünülmelidir.

GUIDELINE 5.7
GUIDELINE 5.8

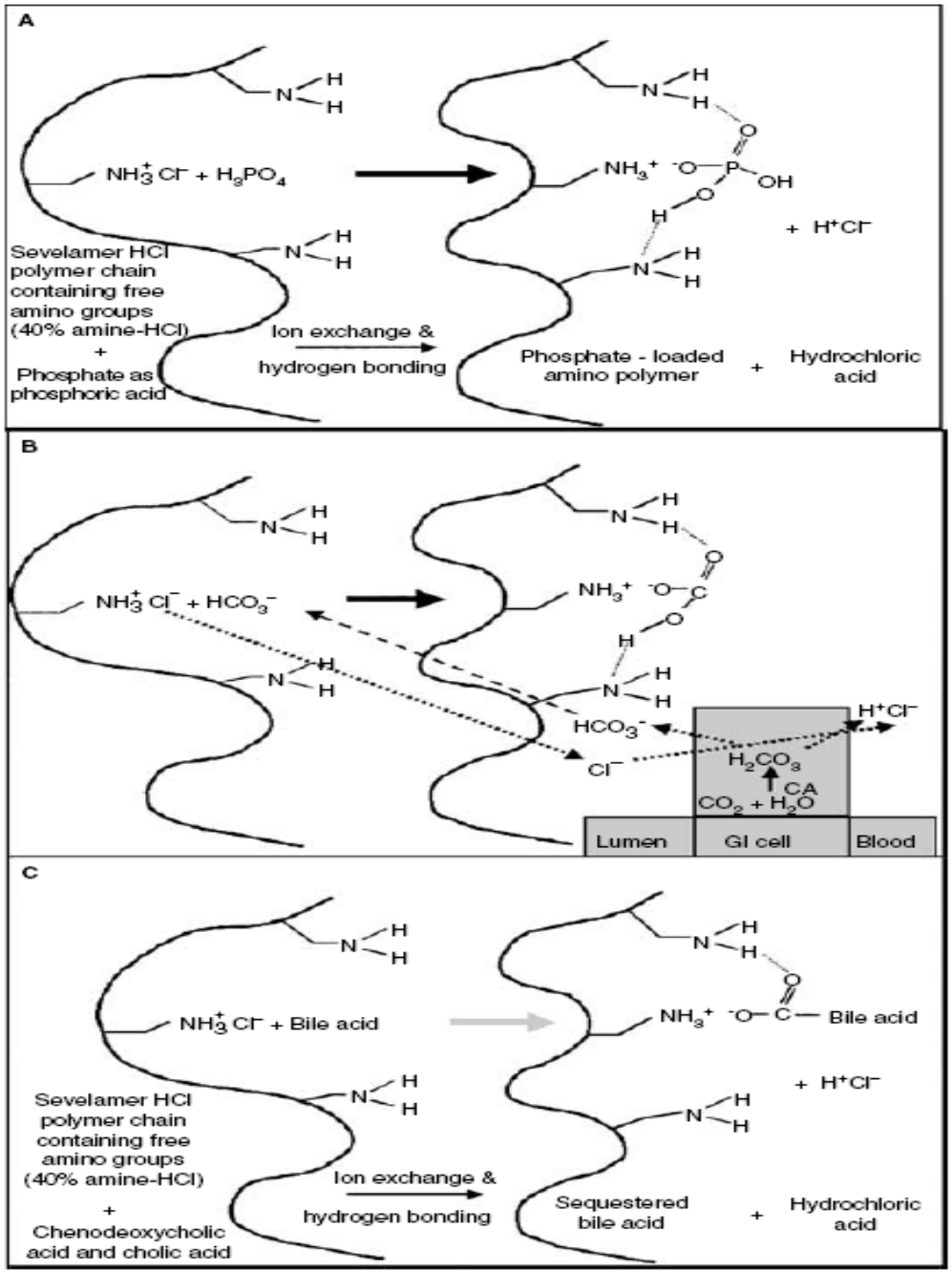
EVRE 5 Böbrek yetmezliği

- Kalsiyum içeren fosfat bağlayıcıların sağladığı elemental kalsiyumun total dozu 1500mg/gün, diyetle alım dahil 2000mg/gün' ı aşmamalıdır.

- Hiperkalsemik (düzeltilmiş total Ca>10.2 mg/dl) veya iki ardışık ölçümde plazma PTH<150 pg/ml olan diyaliz hastalarında kalsiyum içeren fosfat bağlayıcılar **kullanılmamalıdır**



GUIDELINE 5.5
GUIDELINE 5.6



Sevelamer hidroklorid

GIS den emilimi yoktur

Kalsiyum ve metal içermez

Kalsiyum tuzlarına eşdeğer etkinlik

Lipid düşürücü etkisi var

İlaç etkileşimi yoktur

Hiperkalsemi sıklığı daha az

KV kalsifikasyonu azaltır

Doz:1200-4800 mg

Dezavantajları

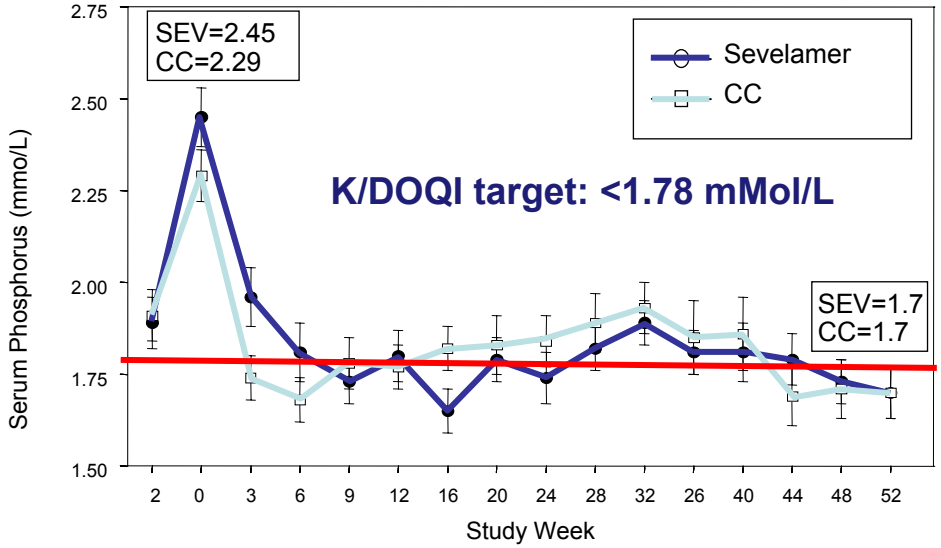
Pahalı

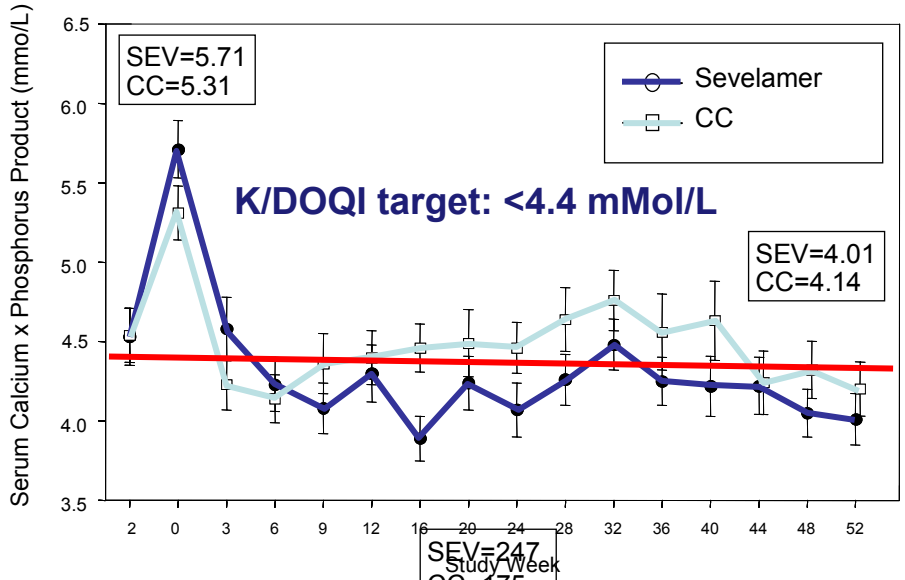
GI yan etkiler

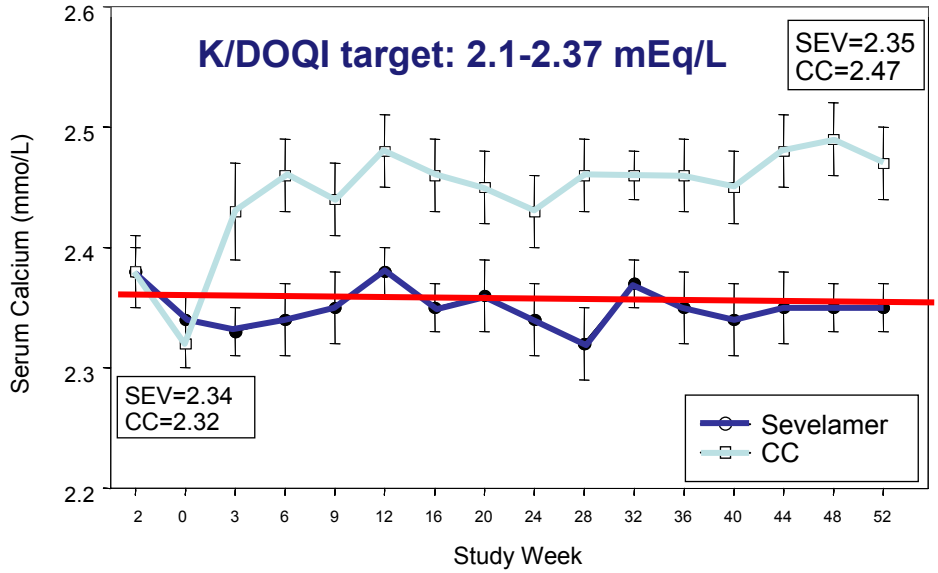
Asidoz

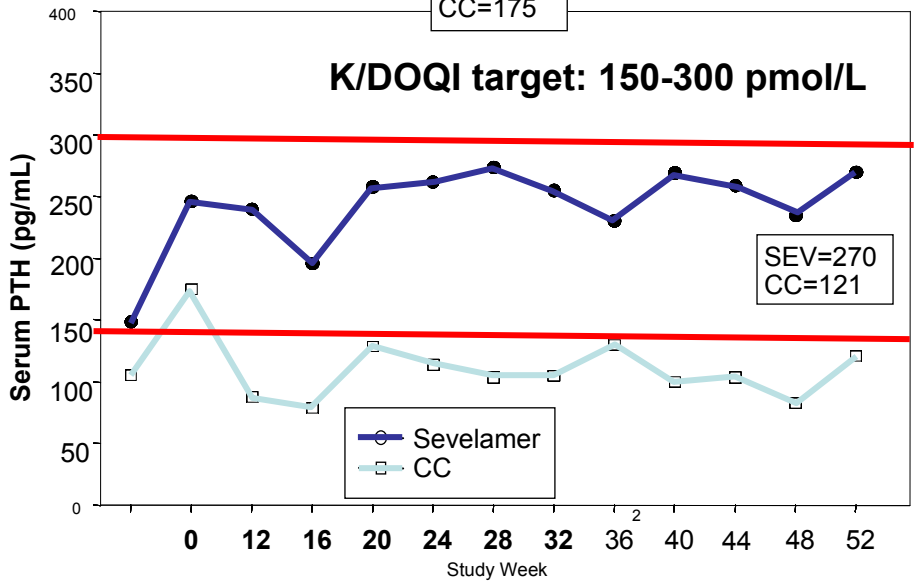
Brezina et al. NDT 2004

Sevelamer vs kalsiyum karbonat

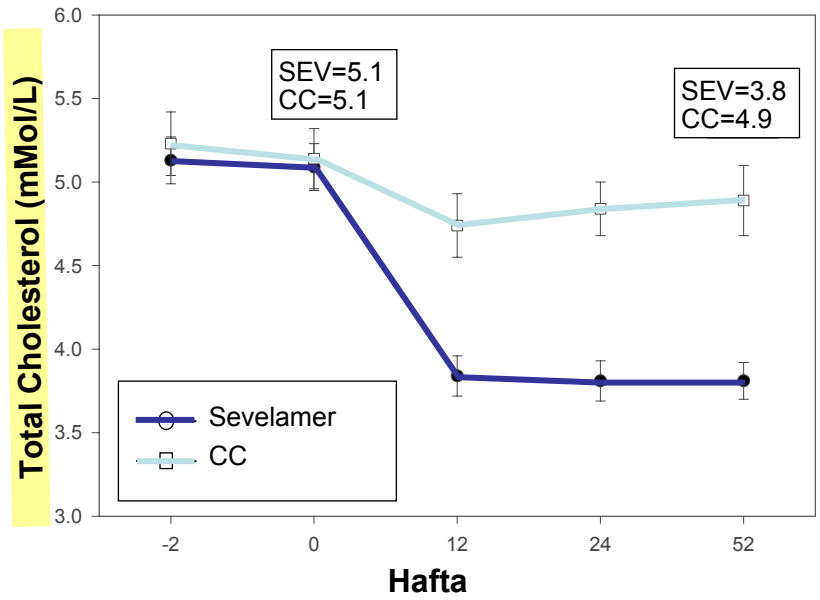


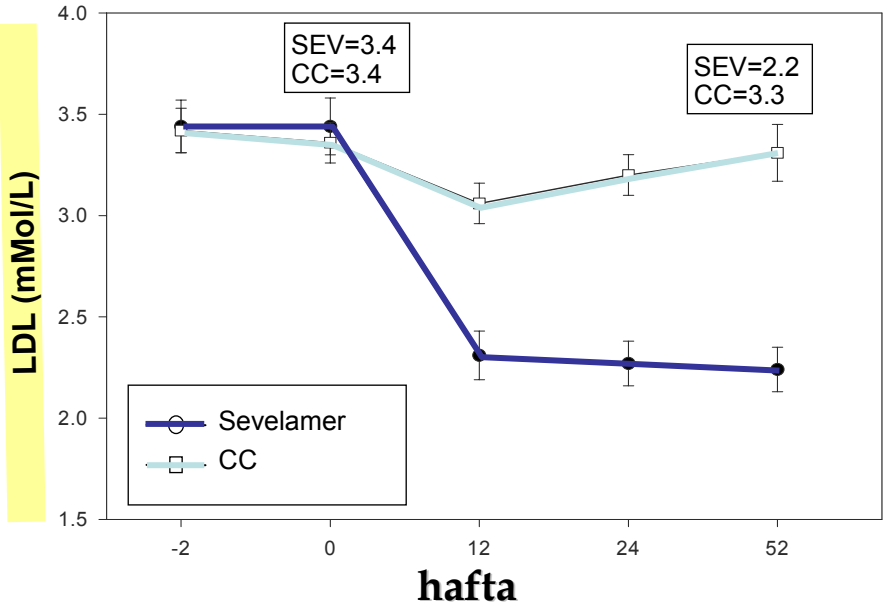


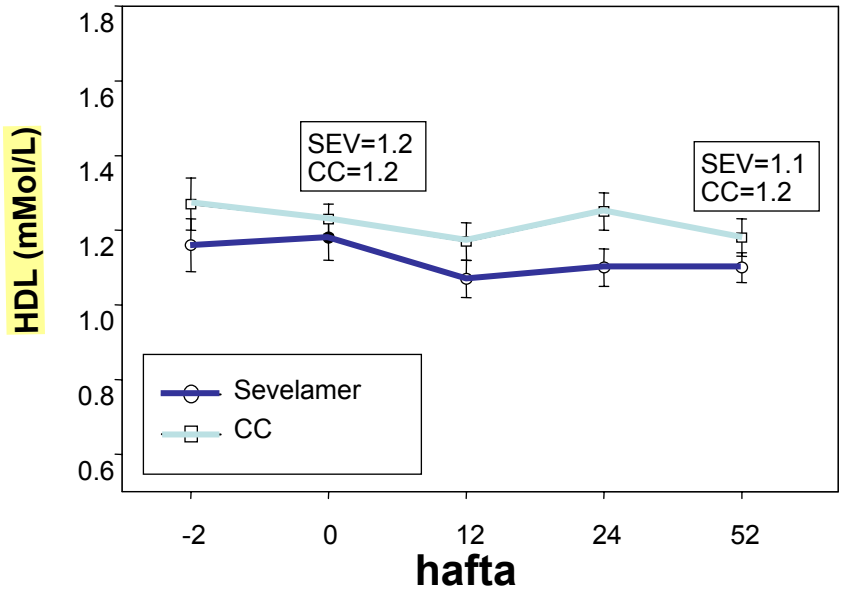




Total kolesterol, LDL, ve HDL



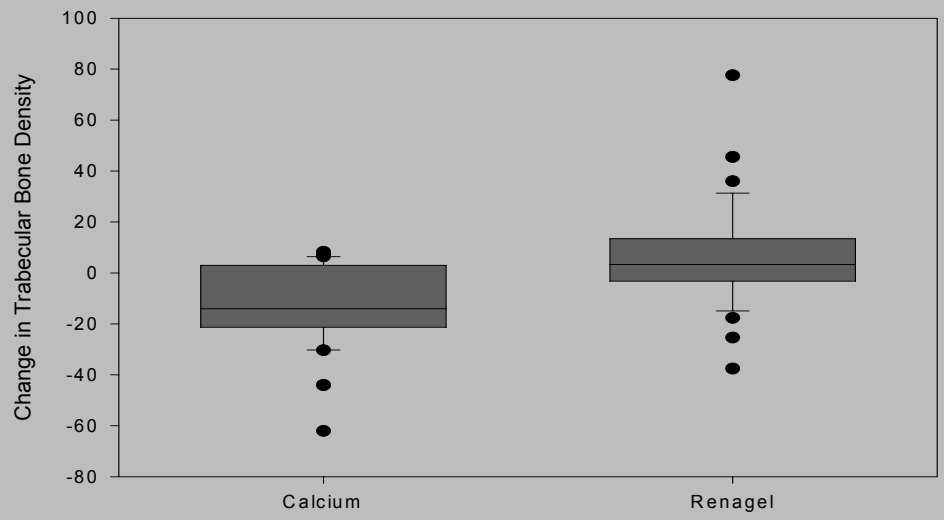


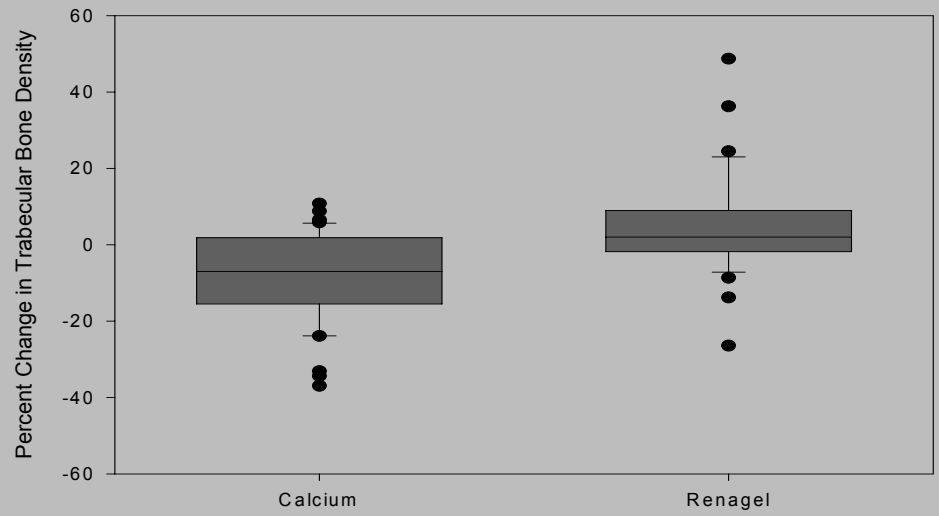


Treat to Goal study

N:202 hd hastası
52 haftalık izlem

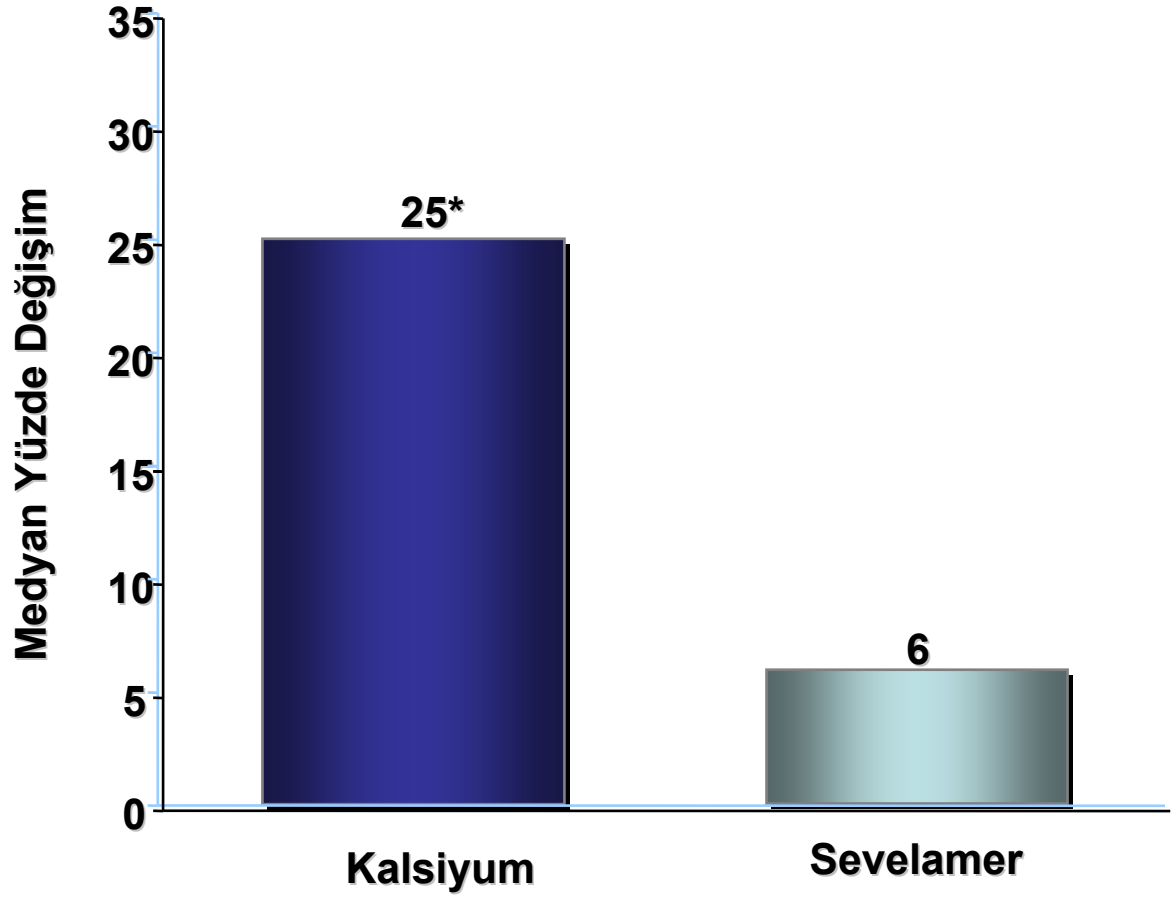
Chertow et al Kidney Int 2002





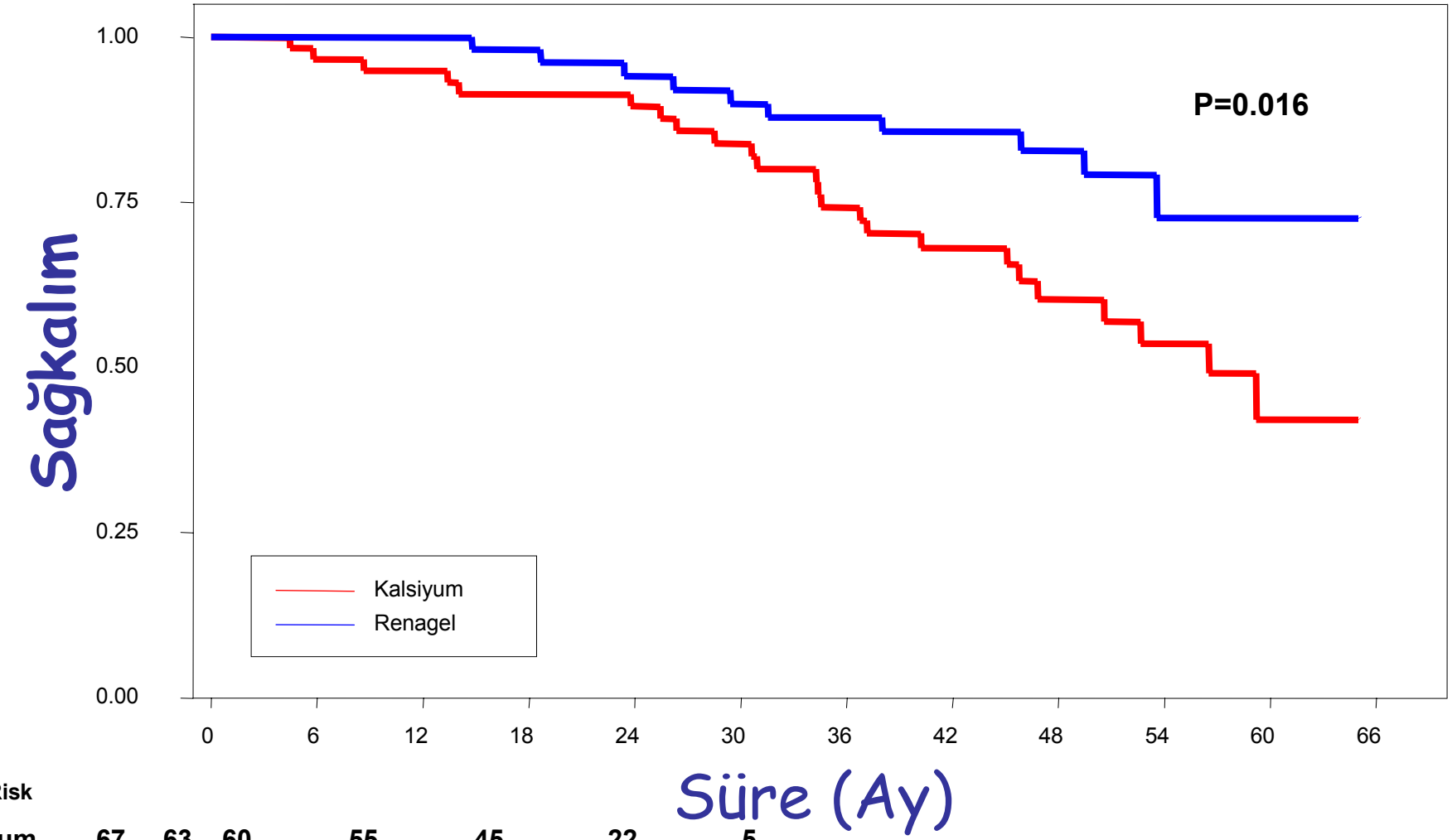
Asmus et al. NDT 2005

Koroner kalsifikasyon skorunda yüzde değişim 52. hafta



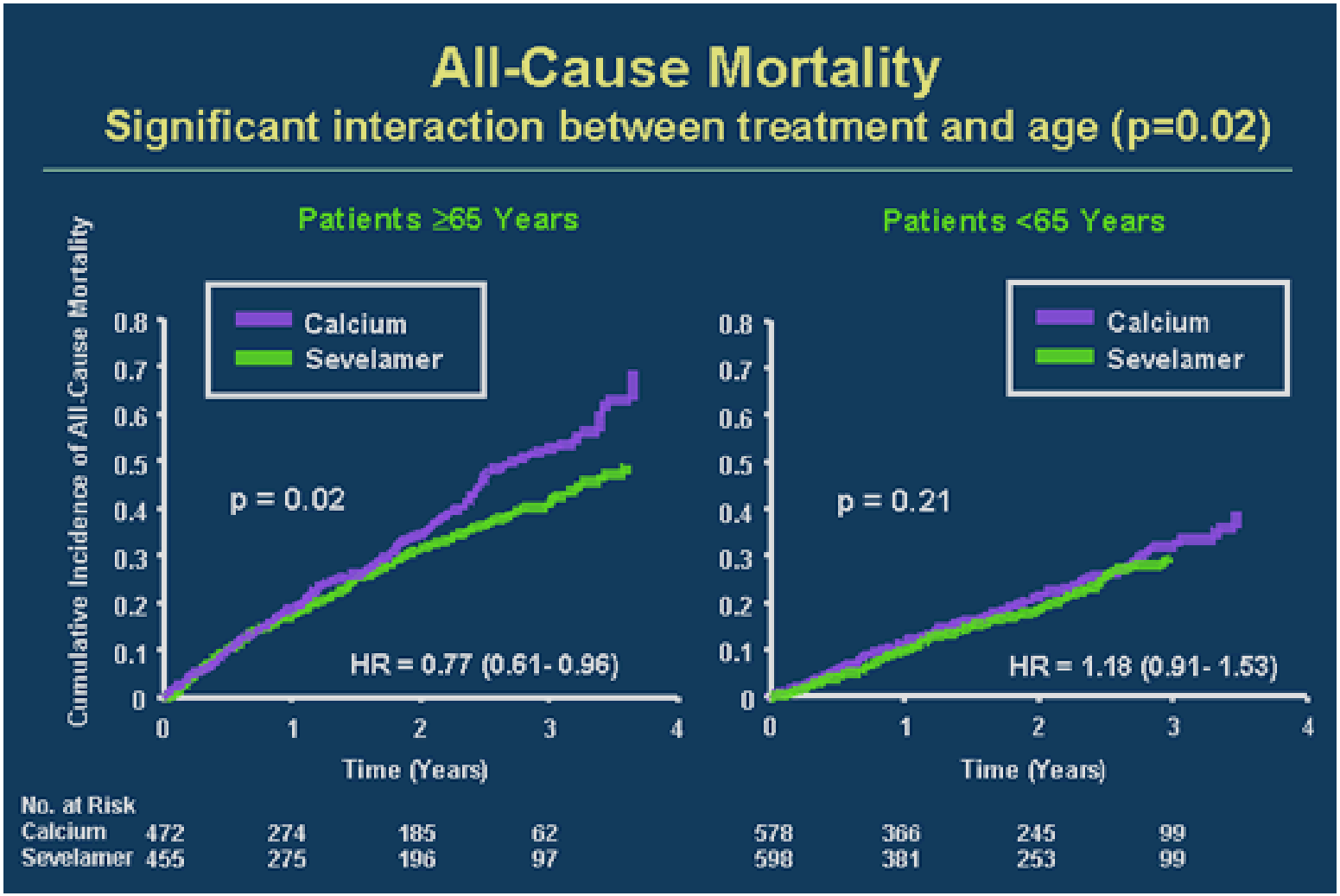
*grup içi *P*<0.0001; gruplar arası P=0.02.

RIND Çalışması: yeni diyaliz hastalarında Renagel çalşması



No. at Risk							
Kalsiyum	67	63	60	55	45	22	5
Renagel	60	57	57	51	47	25	4

DCOR study



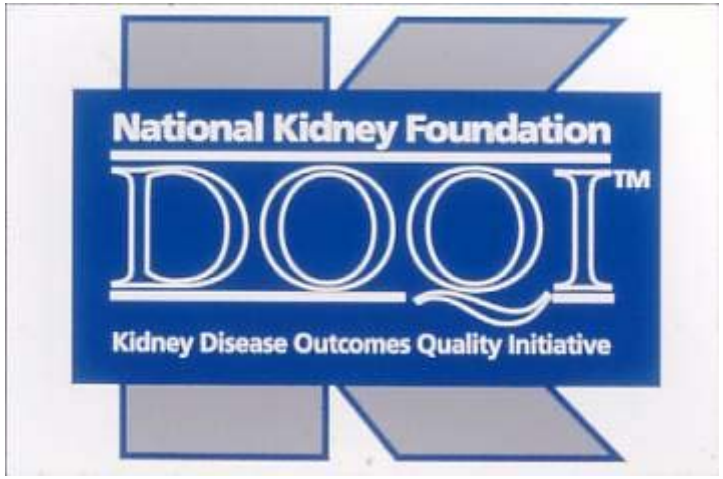
N:2103 diyaliz hastası
44 aylık izlem

Suki et al Kidney Int 2007

EVRE 5 Böbrek Yetmezliği

- *Kalsiyum içeren fosfat bağlayıcılar ya da
  *Ca, Al, Mg içermeyen diğer fosfat bağlayıcılar (*Sevelamer HCl* gibi) serum P düzeylerini düşürmede etkilidirler
  Her ikisi de primer tedavide kullanılabilir.

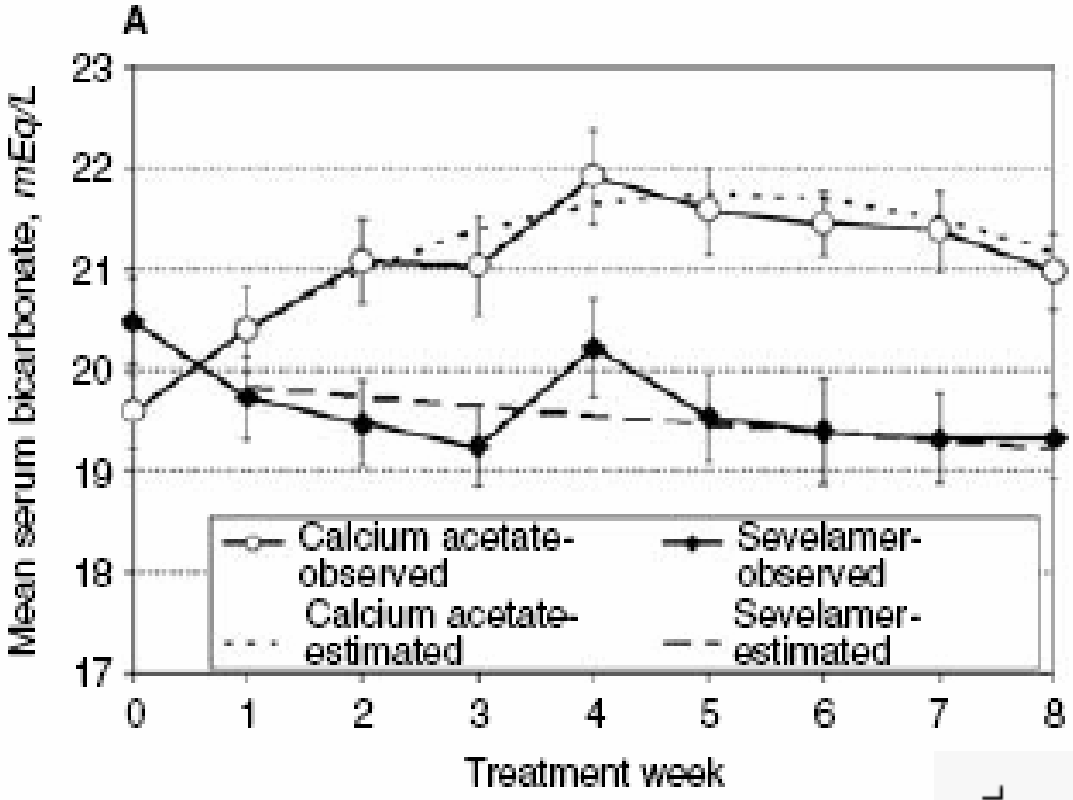
- Buna rağmen hiperfosfatemisi devam eden (P>5.5 mg/dl) diyaliz hastalarında her ikisi kombine kullanılmalıdır.

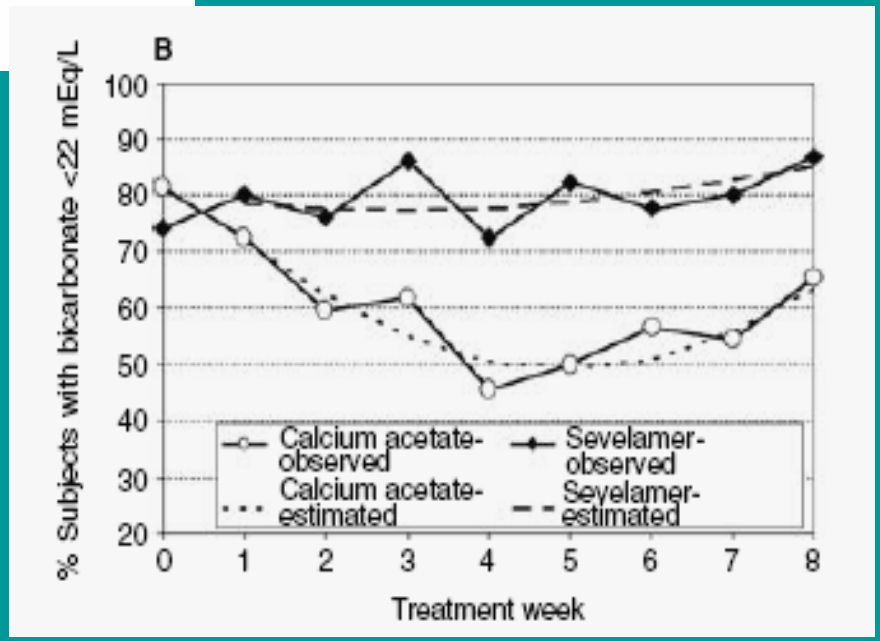


GUIDELINE 5.3
GUIDELINE 5.4

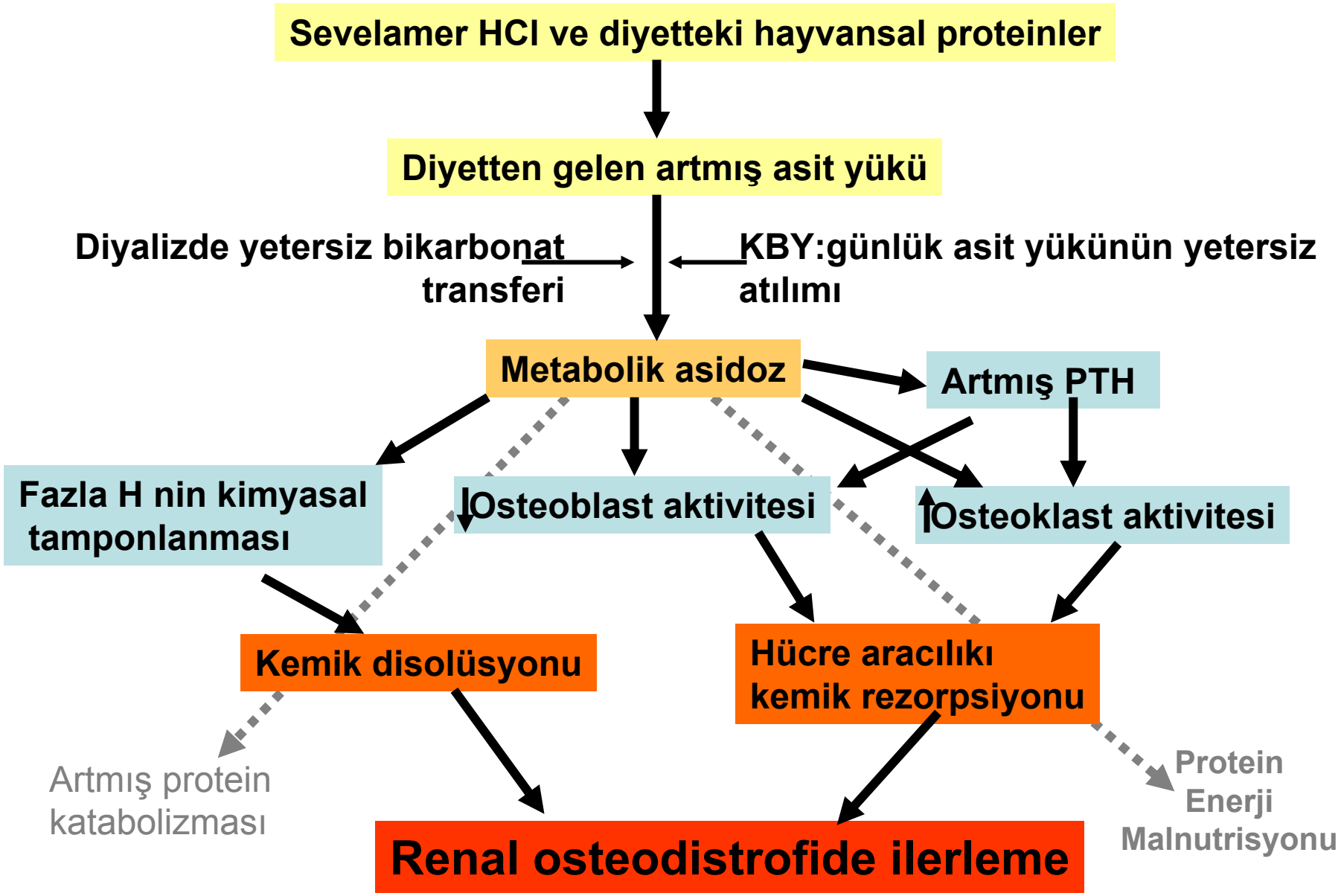
- **Hiperkalsemik**
- **CaXP>55'nin üzerinde**
- **PTH'sı 150 pg/ml altı hastalarda (Adinamik kemik hastalığı şüphesi)**

Hastalarda kalsiyumlu fosfor bağlayıcı kesilmeli, tedaviye sevelamer eklenmeli.





Brezina et al. NDT 2004



Brezina et al. NDT 2004

CJASN ePress. Published on May 1, 2008 as doi: 10.2215/CJN.05161107

Efficacy and Tolerability of Sevelamer Carbonate in Hyperphosphatemic Patients Who Have Chronic Kidney Disease and Are Not on Dialysis

Markus Ketteler,* Marianne Rix,† Stanley Fan,‡ Nicholas Pritchard,§ Ove Oestergaard,‖ Scott Chasan-Taber,¶ Jeremy Heaton,¶ Ajay Duggal,¶ and Philip A. Kalra**

Table 2. Laboratory measurements over time[a]

Laboratory (Serum)	Baseline	Day 56/ET	Change from Baseline to Day 56/ET	P^b	After Washout	Change from Day 56 to Day 70	P^b
Phosphorus (mg/dl; mean ± SD)[c]	6.2 ± 0.8	4.8 ± 1.0	−1.4 ± 1.0	<0.001	6.5 ± 1.3	1.7 ± 1.1	<0.001
Calcium-phosphorous product (mg^2/dl^2; mean ± SD)[c]	53.1 ± 7.0	42.2 ± 8.1	−10.4 ± 9.0	<0.001	55.7 ± 11.2	13.8 ± 9.5	<0.001
Total cholesterol (mg/dl; mean ± SD)[c]	173.2 ± 42.0	137.2 ± 36.4	−19.5 ± 17.1%	<0.001	165.5 ± 47.0	23.0 ± 20.9%	<0.001
LDL cholesterol (mg/dl; mean ± SD)[c]	104.7 ± 33.6	69.7 ± 25.2	−31.9 ± 18.1%	<0.001	98.4 ± 39.0	44.9 ± 34.9%	<0.001
HDL cholesterol (mg/dl; mean ± SD)[c]	47.7 ± 17.4	48.3 ± 16.1	4.4 ± 15.3%	0.139	47.2 ± 15.8	−0.9 ± 9.3%	0.440
Bicarbonate (mEq/L; mean ± SD)[d]	16.6 ± 3.6	18.2 ± 3.7	1.3 ± 2.9	0.005	18.0 ± 3.6	−0.5 ± 3.5	0.326
Calcium (mg/dl)[d]	8.5 ± 0.9	8.8 ± 0.8	0.3 ± 0.5	<0.001	8.6 ± 0.6	−0.2 ± 0.5	0.007
iPTH (pg/ml; median)[d]	341	319	−39	0.013	362	63	<0.001
25-hydroxyvitamin D (ng/ml; mean ± SD)[d]	28.9 ± 16.2	31.1 ± 12.9	2.0 ± 10.3	0.080	32.3 ± 13.7	0.2 ± 7.7	0.890

[a]iPTH, intact parathyroid hormone.
[b]Wilcoxon signed rank test.
[c]Results are based on intention-to-treat population (n = 46).
[d]Results are based on the safety set (n = 49).

Lantanum Karbonat

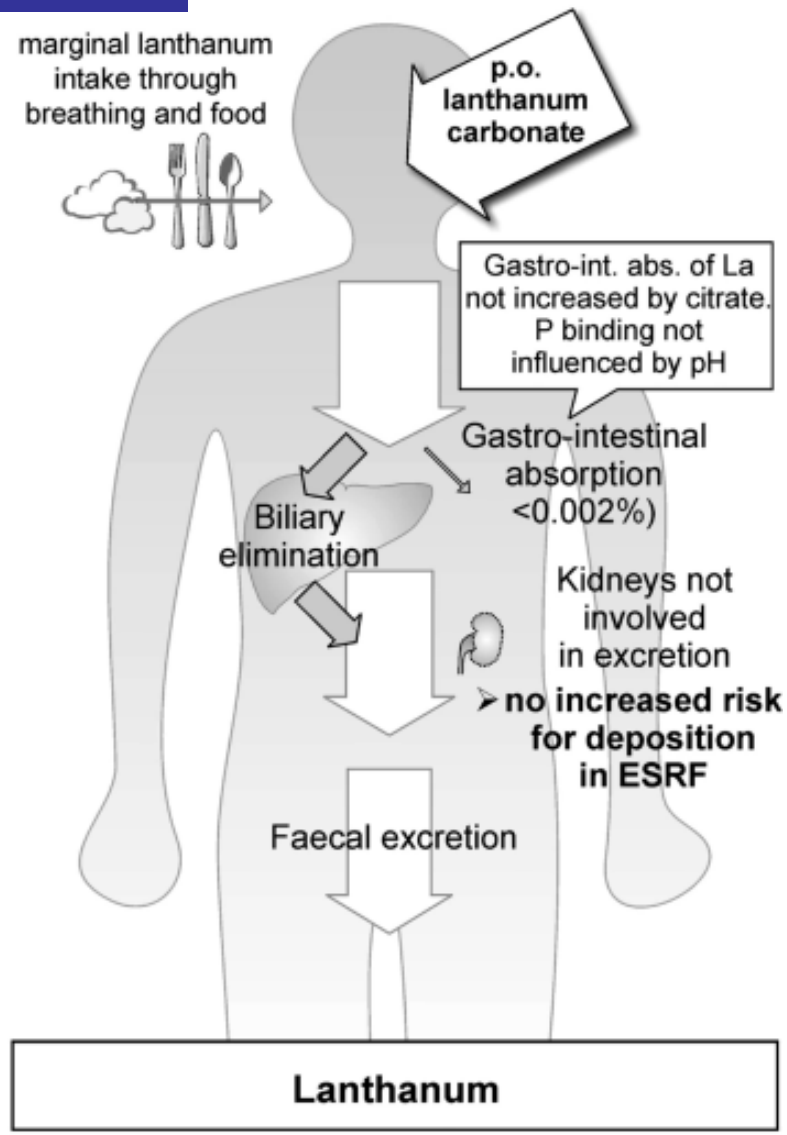
3 değerlikli katyonik, eser element

GİS emilimi çok düşük

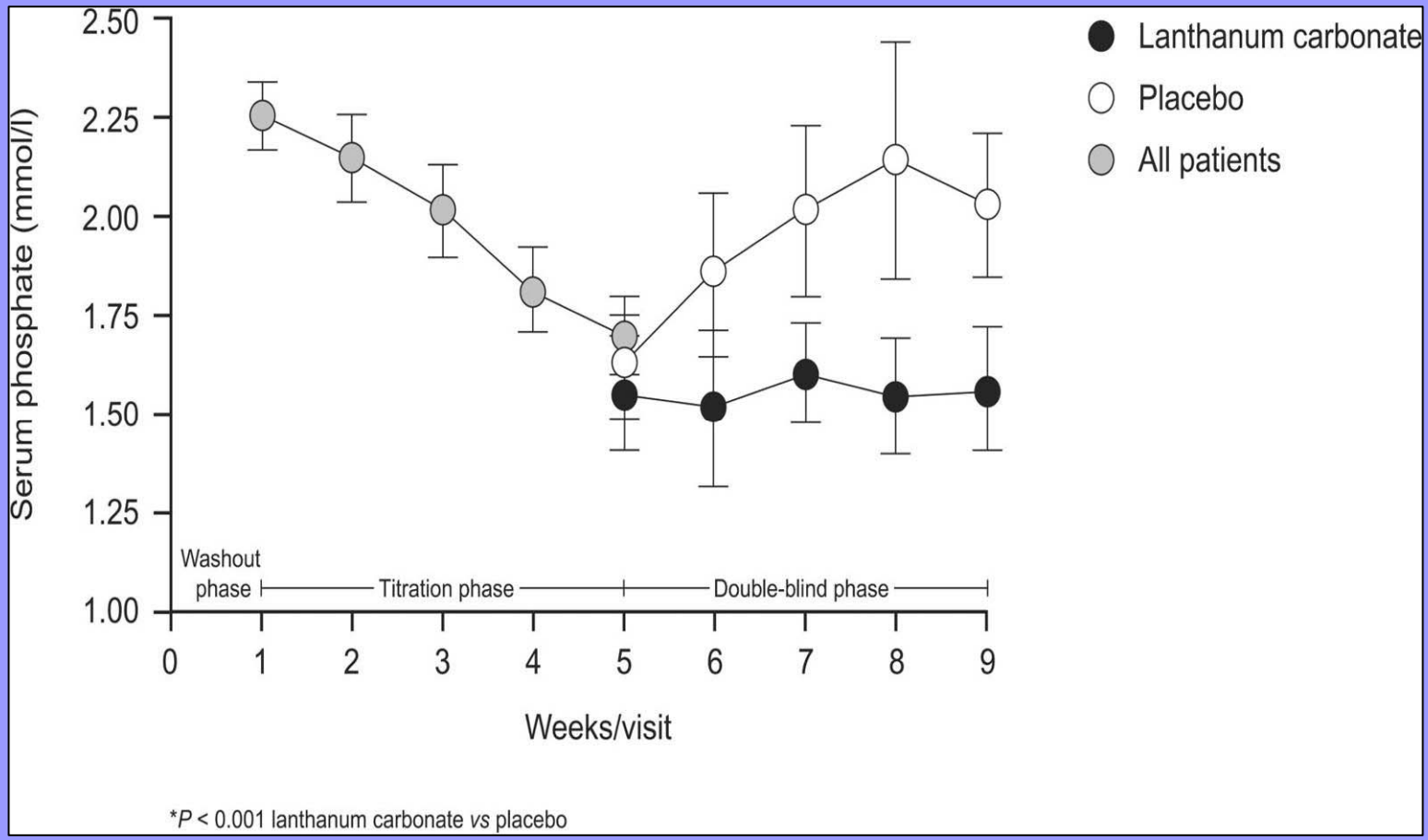
Proteinlere bağlanma > %99

%80 safra %13 barsak duvarı yoluyla atılır

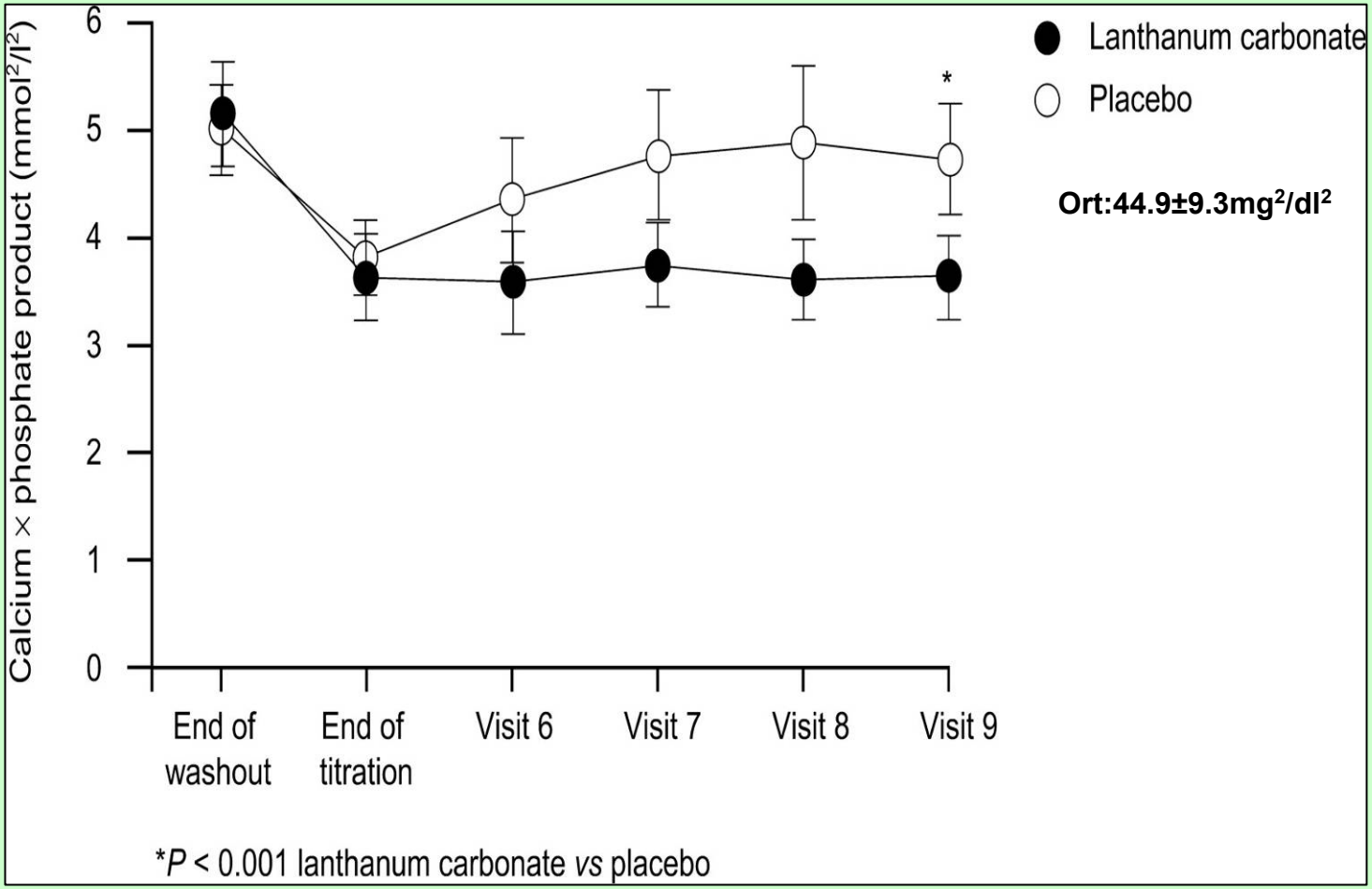
Doz:750-3000mg



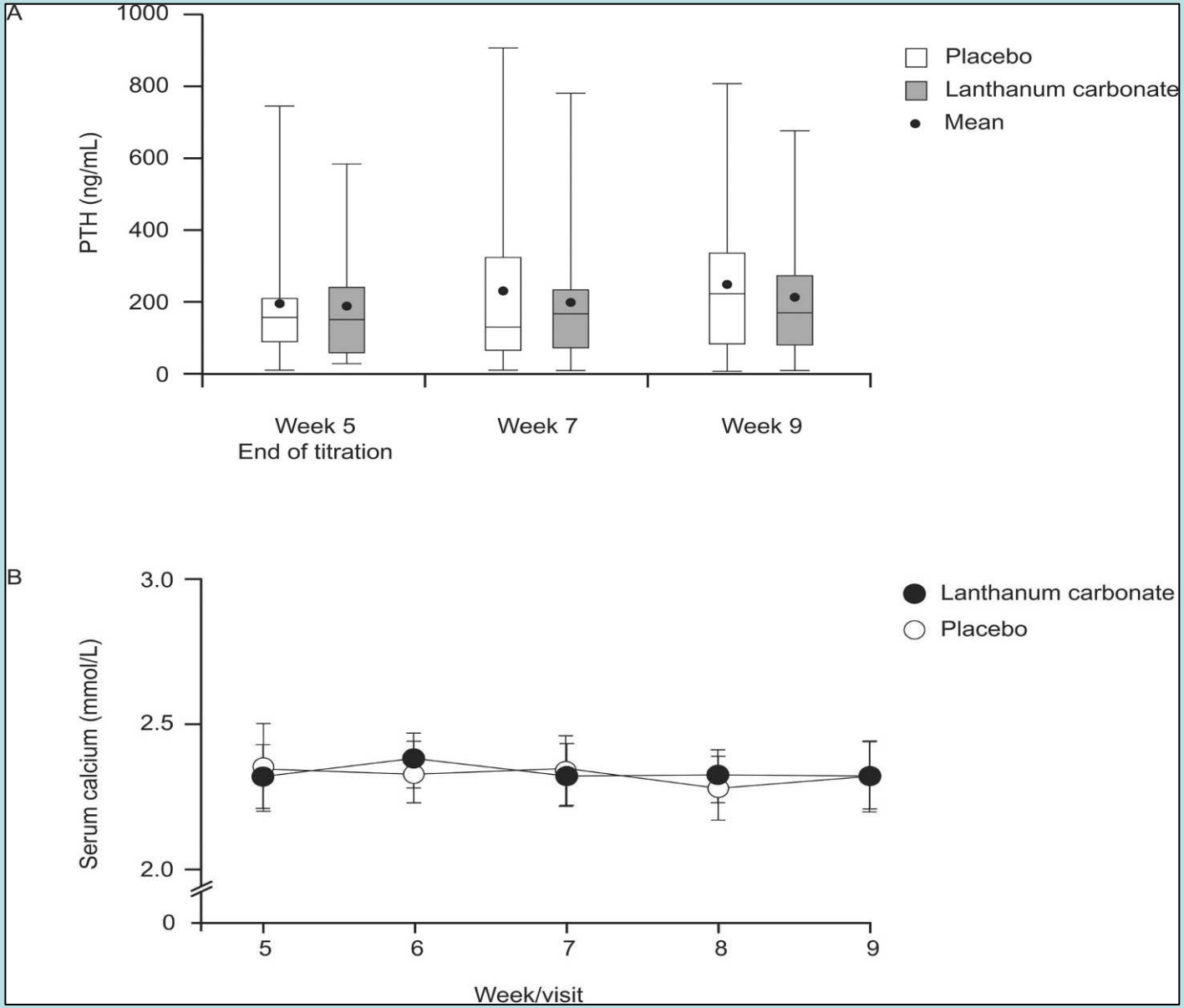
Persy et al. Seminars In Dialysis 19 (3) , 195–199



Al-Baaj, F. et al. Nephrol. Dial. Transplant. 2005 20:775-782



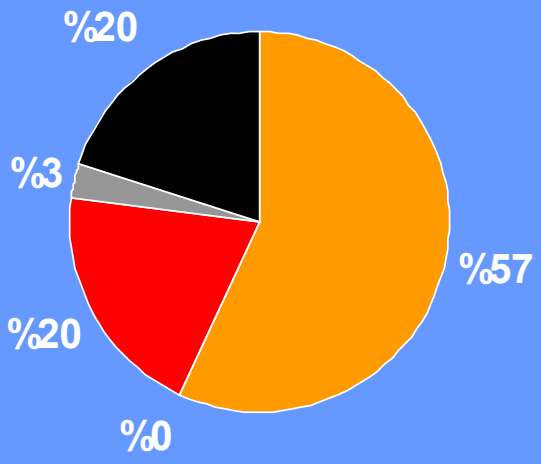
Al-Baaj, F. et al. Nephrol. Dial. Transplant. 2005 20:775-782



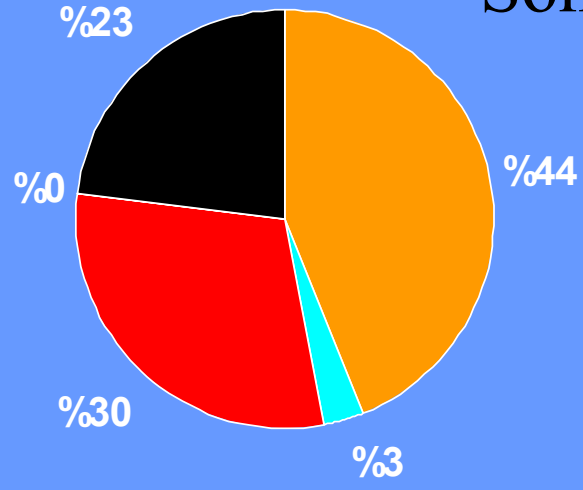
Al-Baaj, F. et al. Nephrol. Dial. Transplant. 2005 20:775-782

Calcium Carbonate

Başlangıç



Son



Mixed

Normal histoloji

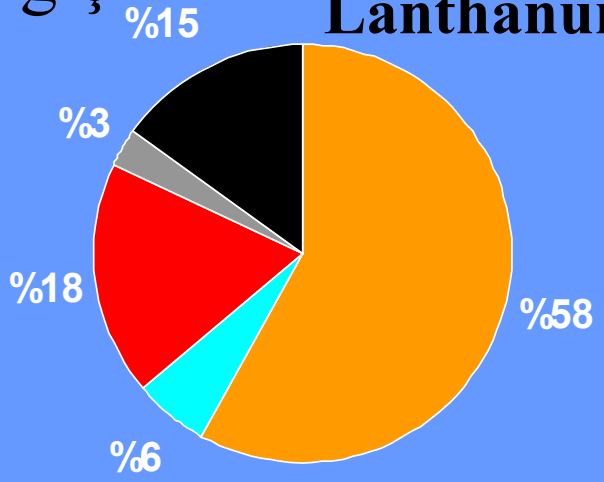
Adinamik Kemik Hast.

Osteomalazi

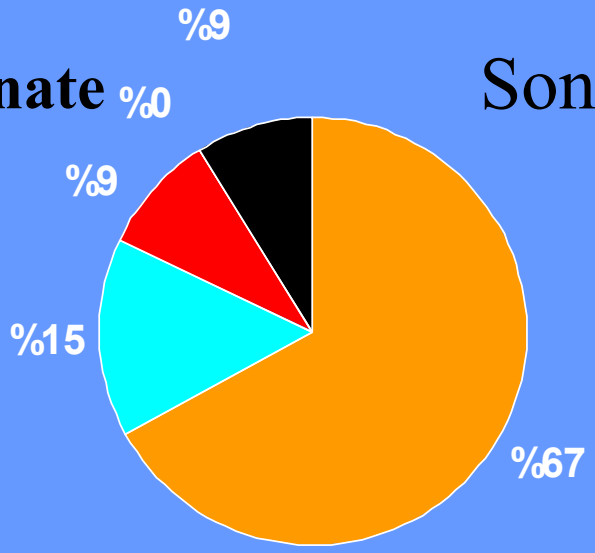
Hyperparatiroidizm

Lanthanum Carbonate

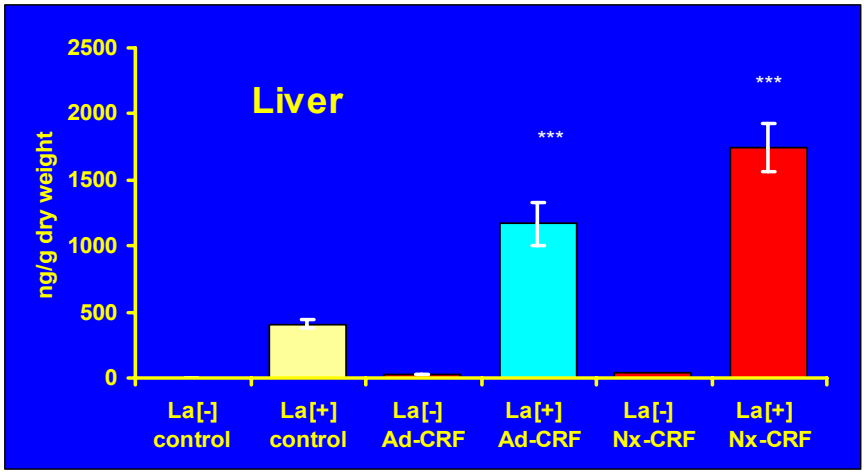
Başlangıç

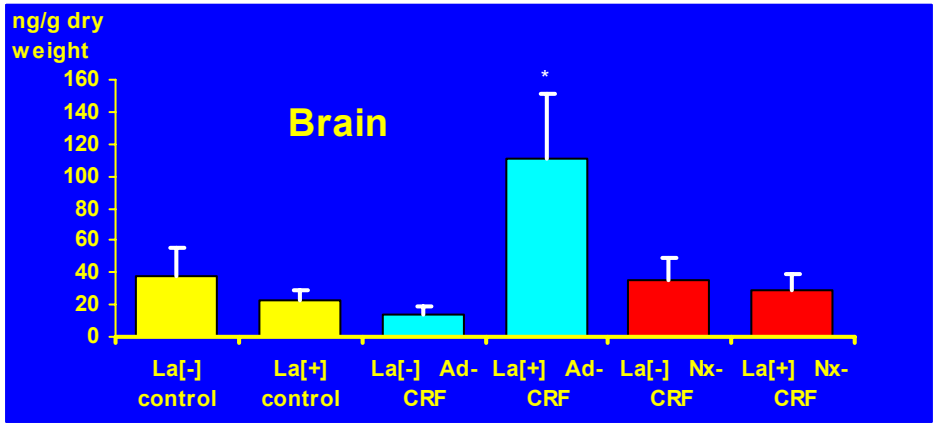


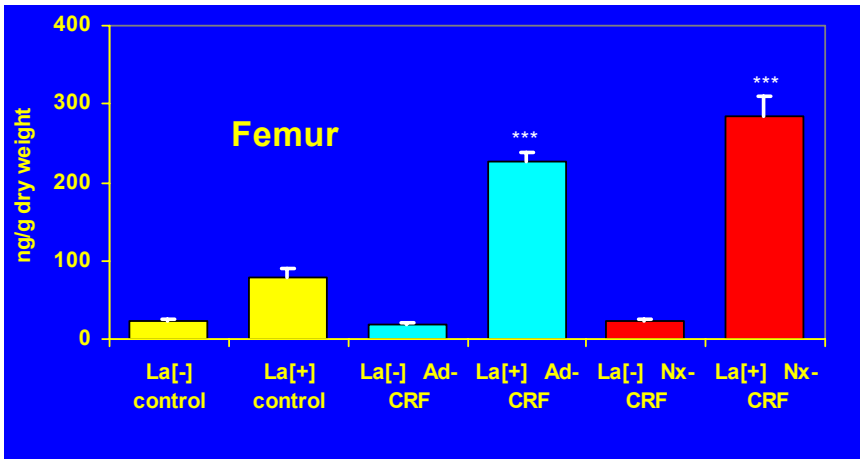
Son

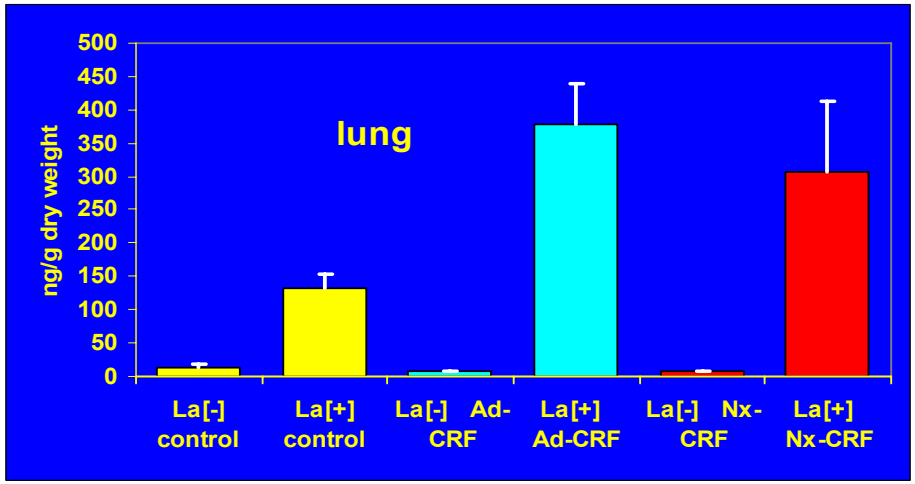


Lantanum karbonat ve plasebo ile tedaviden 28 gün sonraki organ lantanum düzeyleri



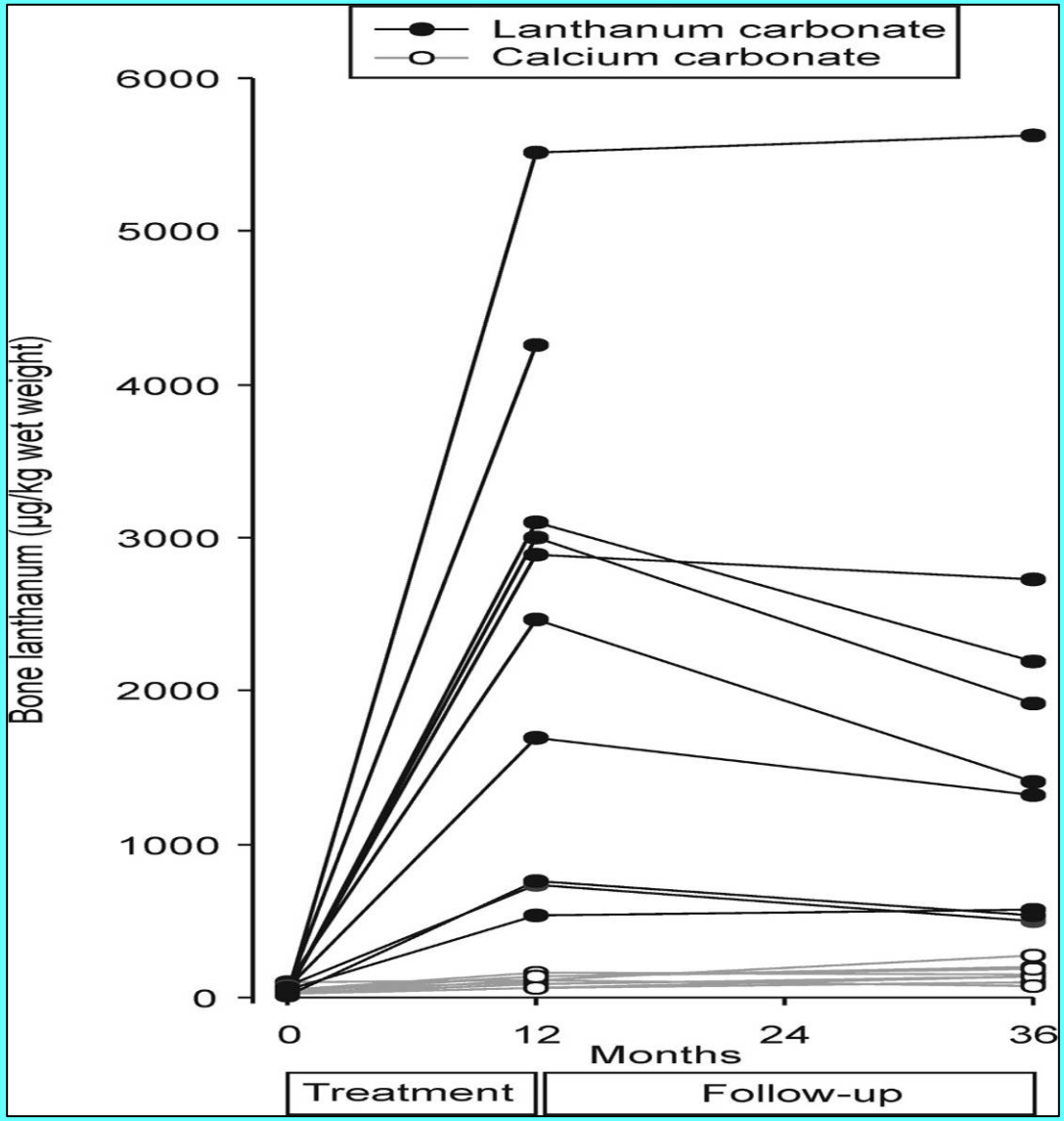






*** = p<0.05 ,*** =p<0.01**

Lacour et al, KI 2005



Spasovski, G. B. et al. Nephrol. Dial. Transplant. 2006 21:2217-2224;

Avantajları

-Güvenli
-$CaCO_3$ ile benzer P kontrolü sağlar
-Kemik histomorfometrisinde düzelme
-Adinamik kemik hastalığına dönüşüme neden olmaz
-Asidoz üzerine olumlu etkileri var

Dezavantajları

-Doku birikimi?
-Uzun dönem yan etki ve toksisitesi bilinmiyor
-Vasküler kalsifikasyon üzerine etkileri bilinmiyor

Marked suppression of secondary hyperparathyroidism by intravenous administration of 1,25-dihydroxy-cholecalciferol in uremic patients.

E Slatopolsky, C Weerts, J Thielan, R Horst, H Harter and K J Martin

J. Clin. Invest. **74**(6): 2136-2143 (1984). doi:10.1172/JCI111639.

Research Article

Evre 5 kronik böbrek yetmezliği hastalarında

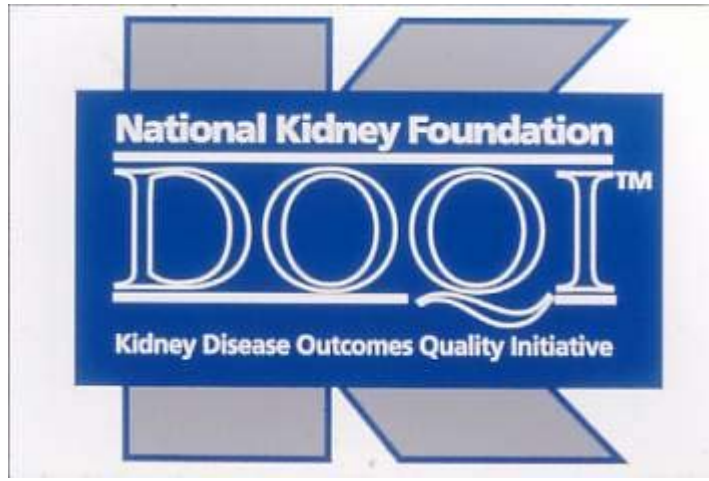
Plazma PTH > 300pg/ml ise

➡PTH' nın kemikteki etkisini(yüksek döngülü kemik hastalığı gibi) tersine döndürmek için,

➡defektif mineralizasyonu tedavi etmek için,

- *Calcitriol veya*
- *Analoglarından biri (paricalcitol, doxercalciferol veya alfacalcidol)*

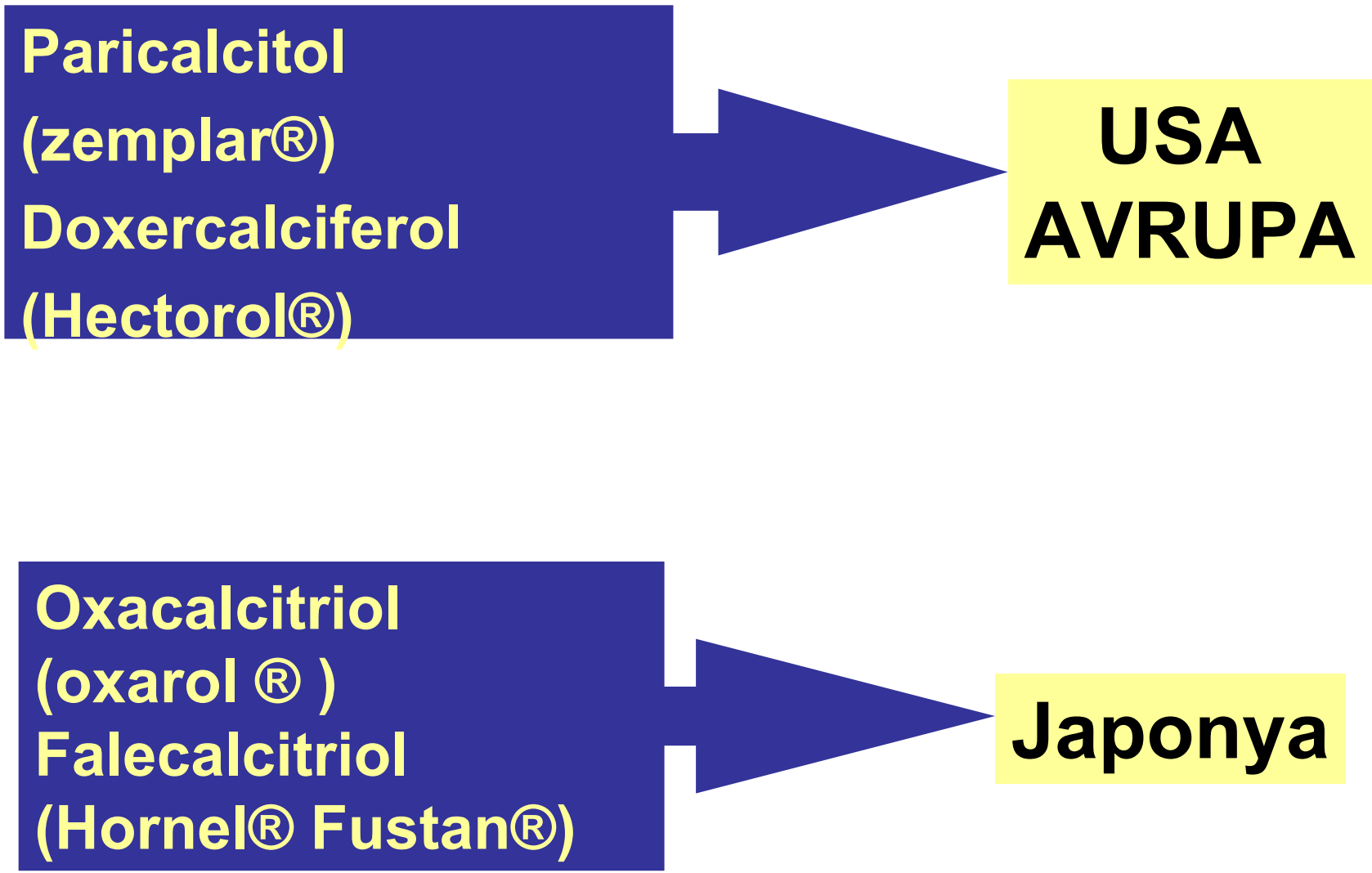
kullanılmalı



GUIDELINE 13.A.2

Vitamin D

- 1,25 dihidroksi vitamin D3 (calcitriol)
- 1 α hidroksi vitamin D3 (alfacalcidol)
- 1,25 dihidroksi 19 norvitamin D2 (19-norD2)(Paricalcitol)
- 1 α hidroksi vitamin D2 (Doxercalciferol)
- 1,25 dihidroksi-22-oxa vitamin D3 (22-oxacalcitriol, Maxacalcitol OCT)
- 1,25 dihidroksi 26,27 hexafluorovitamin D3 (falecalcitriol)

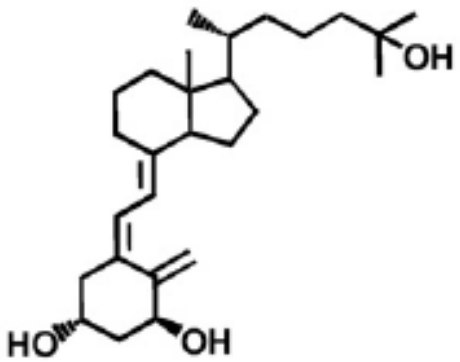

Paricalcitol
(zemplar®)
Doxercalciferol
(Hectorol®)
USA
AVRUPA
Oxacalcitriol
(oxarol ®)
Falecalcitriol
(Hornel® Fustan®)
Japonya

Vitamin D_2 ~ Vitamin D_3

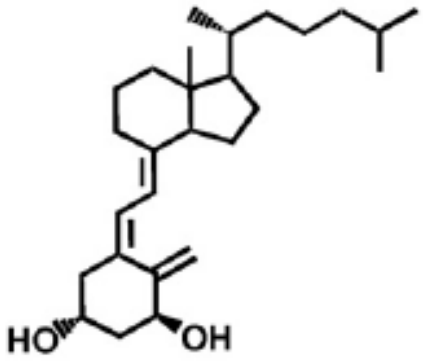
- **Vitamin D_2 (ergokalsiferol)….1 α D_2**
- **Vitamin D_3 (kolekalsiferol)….1 α D_3**
- **Yan zincirdeki küçük bir fark ile birbirlerinden ayrılırlar**
- **Vitamin D_2'nin hayvanmodellerinde daha az toksik olduğu görülmüş**
- **Hayvan modellerinde düşük dozlarda aynı etkiye sahipler (kalsiyum absorbsiyonu, kalsiyum mobilizasyonu)**
- **Farmakolojik dozlarda vitamin D_3 daha toksik**
- **1 α D_2'nin karaciğerdeki 24 hidroksilasyonu toksik etkisini azaltır.**

Frazao JM Am J Kidney Dis 2000

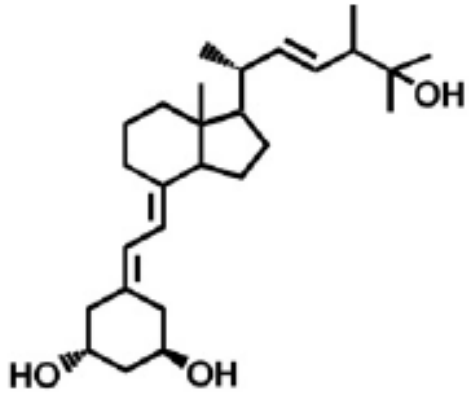
Farklı D vitaminlerinin moleküler yapısı



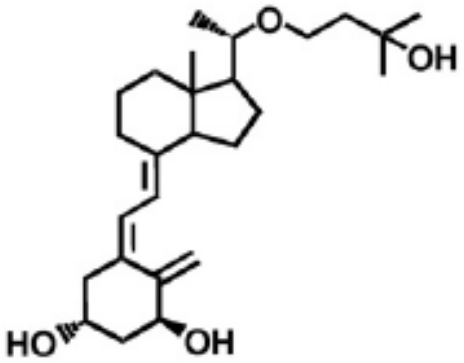
1α25 dihydroxyvitamin D3
Calcitriol



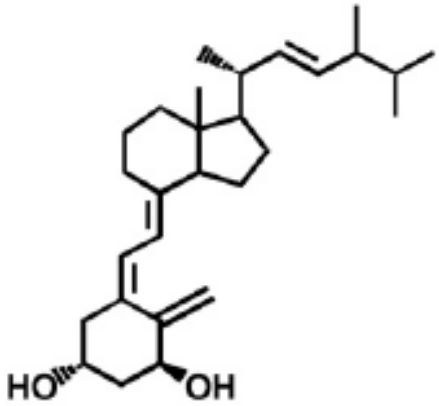
1αhydroxyvitamin D3
Alfacalcidol



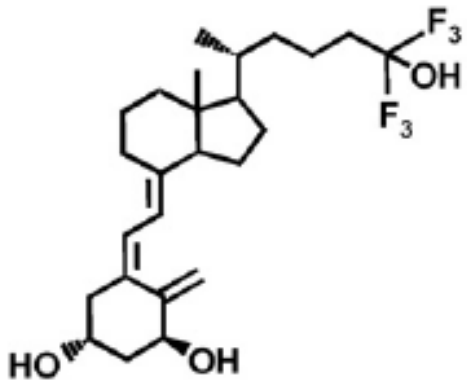
1α25 dihydroxy 19 nor vitamin D2
Paricalcitol



22-Oxacalcitriol
Maxacalcitol



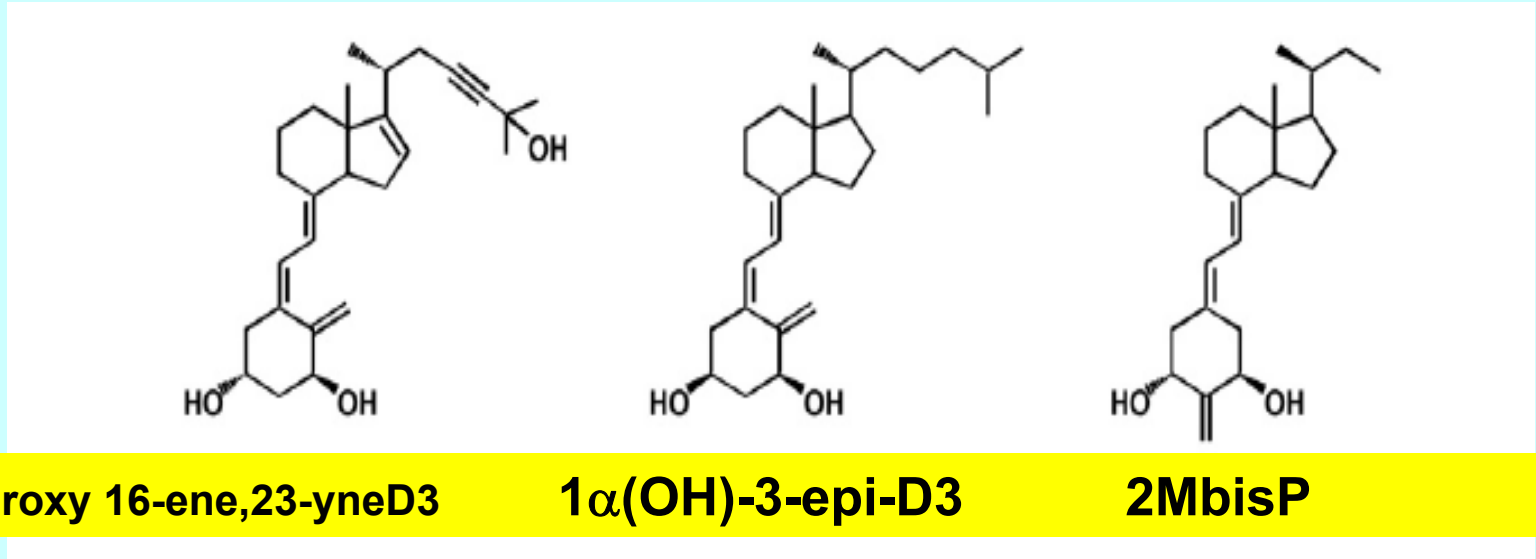
1αhydroxyvitamin D2
Doxercalciferol



1α25 dihydroxy 26-27-F6 vitamin D3
Falecalcitriol

Brown A Nephrol Dial Transplant 2002

Farklı D vitaminlerinin moleküler yapısı



1,25 dihydroxy 16-ene,23-yneD3 1α(OH)-3-epi-D3 2MbisP

$1,25\alpha(OH)_2D_3$ Calcitriol
$1\alpha(OH)_2D_3$ Alfacalcidol

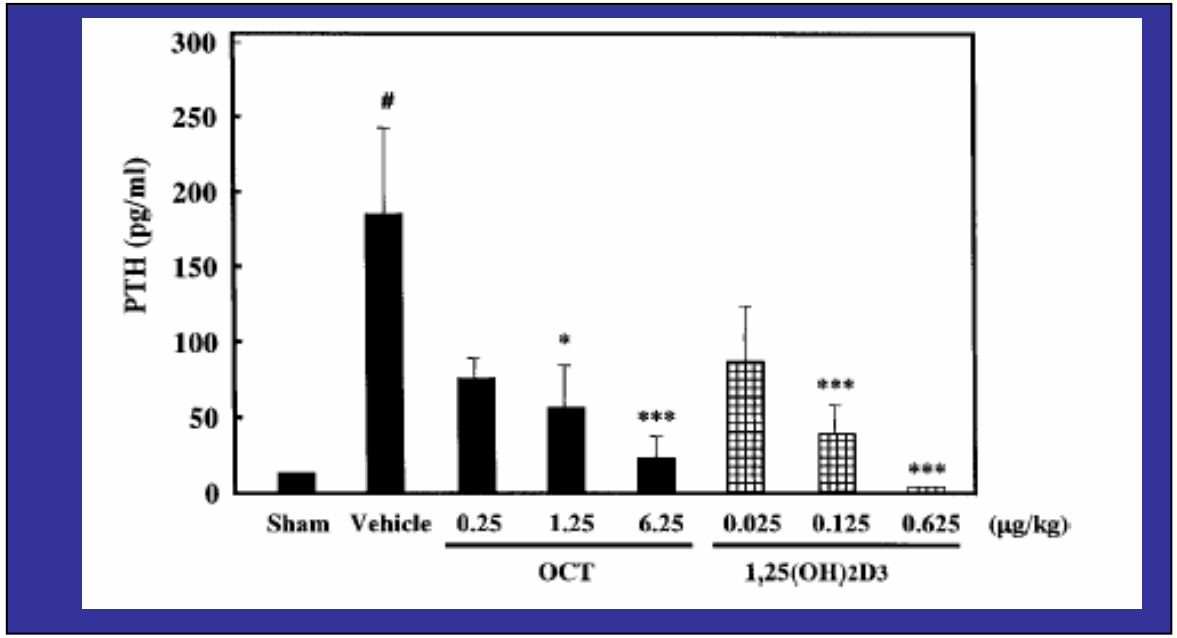
- 1, 25 (OH)2 vitamin D3
- Sekonder hiperparatiroidizmin tedavisinde ilk kullanılan vitamin D
- PTH baskılayıcı etkisi belirgin
- GIS'den kalsiyum ve fosfor absorbsiyonunu en fazla arttıran vitamin D analogu
- Kalsiyum tuzu içeren fosfor bağlayıcıları ile birlikte vasküler ve yumuşak doku kalsifikasyon riskini arttırır
- Adinamik kemik hastalığı oluşum riski yüksek

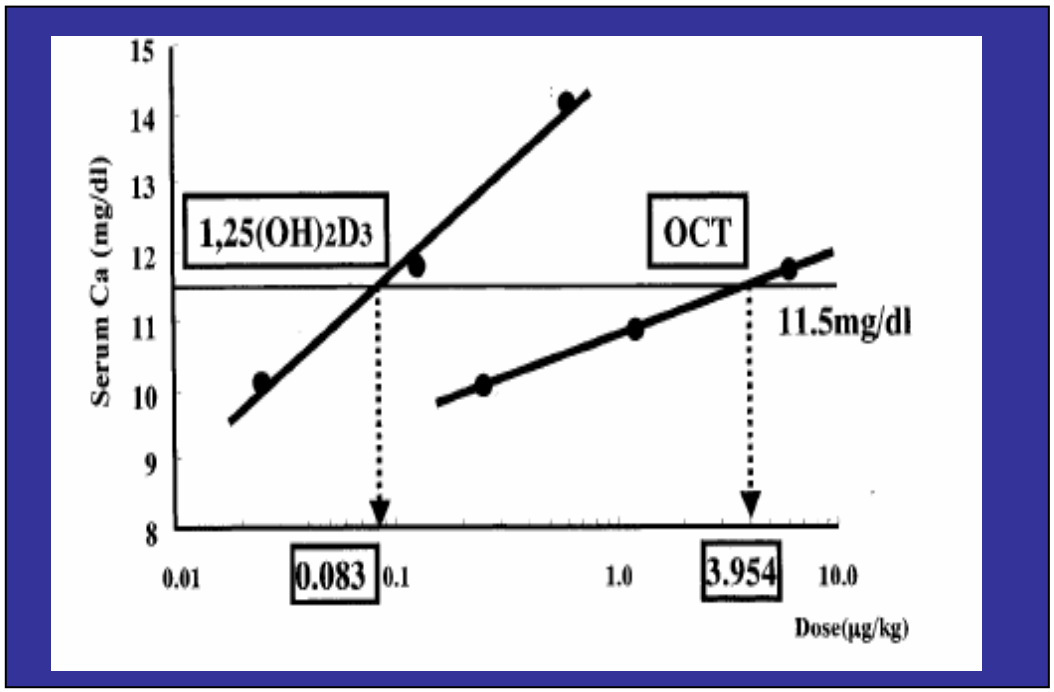
22-Oxacalcitriol

- Sadece japonya'da kullanılıyor (Oxarol®) (2000 yılından beri)
- Kalsitriole göre daha az kalsemik ve hiperfosfatemik.(doz bağımlı etki)
- PTH baskılayıcı etkisi benzer
- Vitamin D bağlayıcı proteine afinitesi kalsitriole göre düşük (500kat)
- Dolaşımdaki yarı ömrü kısa
- Enjeksiyondan kısa süre sonra hedef dokuda toplanır

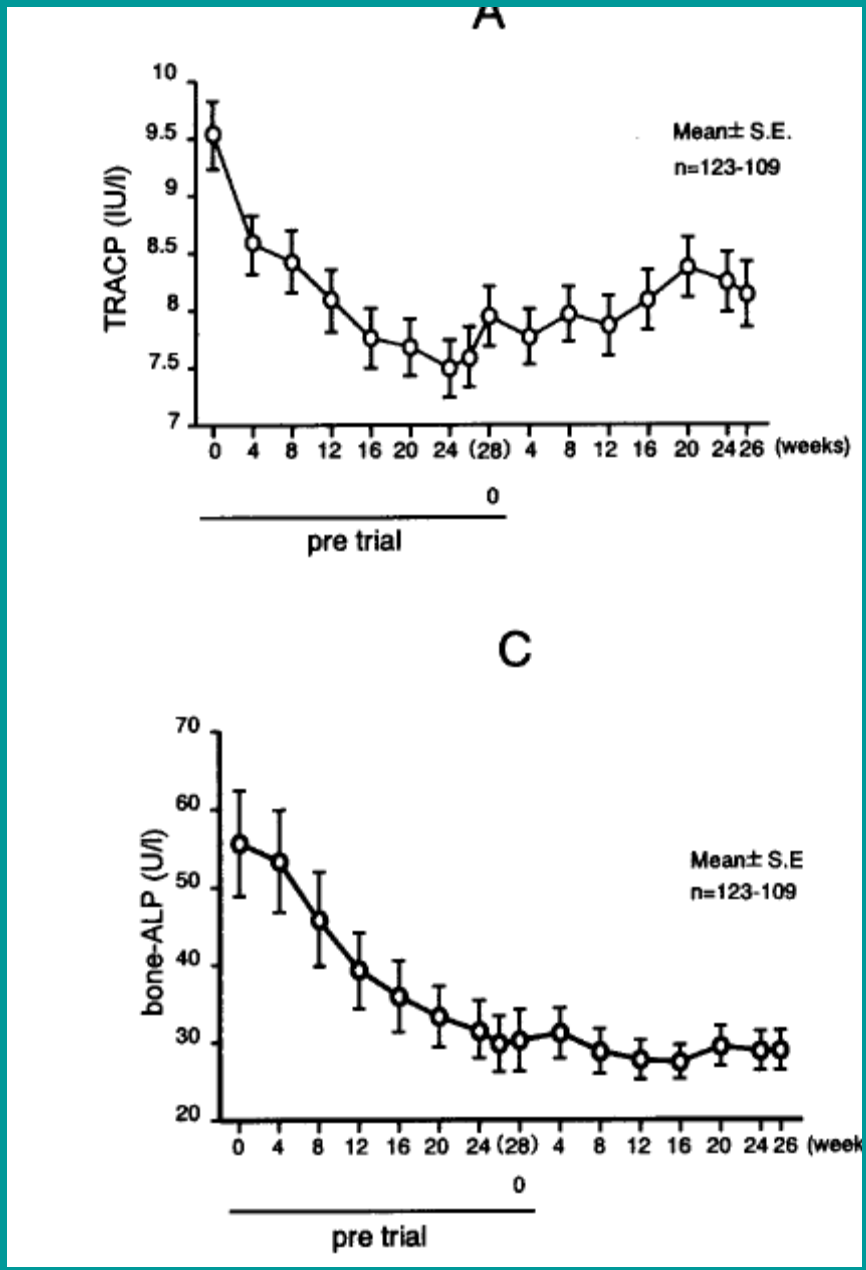
22-Oxacalcitriol

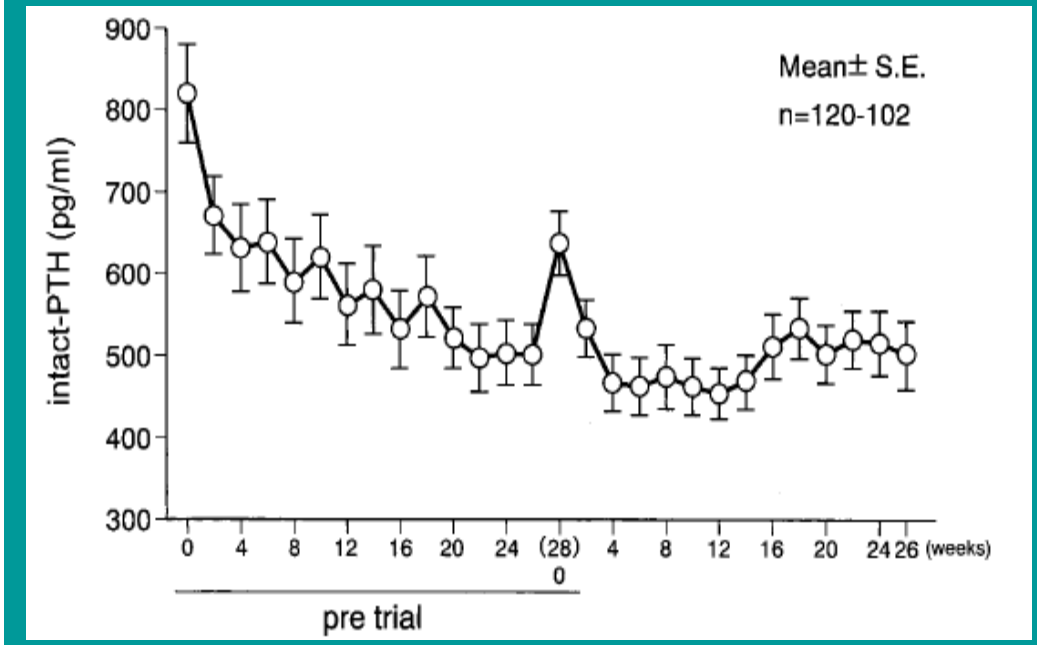
- Böbreklerdeki 1αhidroksilazı inhibe ederek endojen Calcitriol düzeylerini düşürür
- Kemik ve barsaklardaki etkisi kısa süreli
- Paratiroid gland hücre nükleuslarında kalış süresi uzun bulunmuş





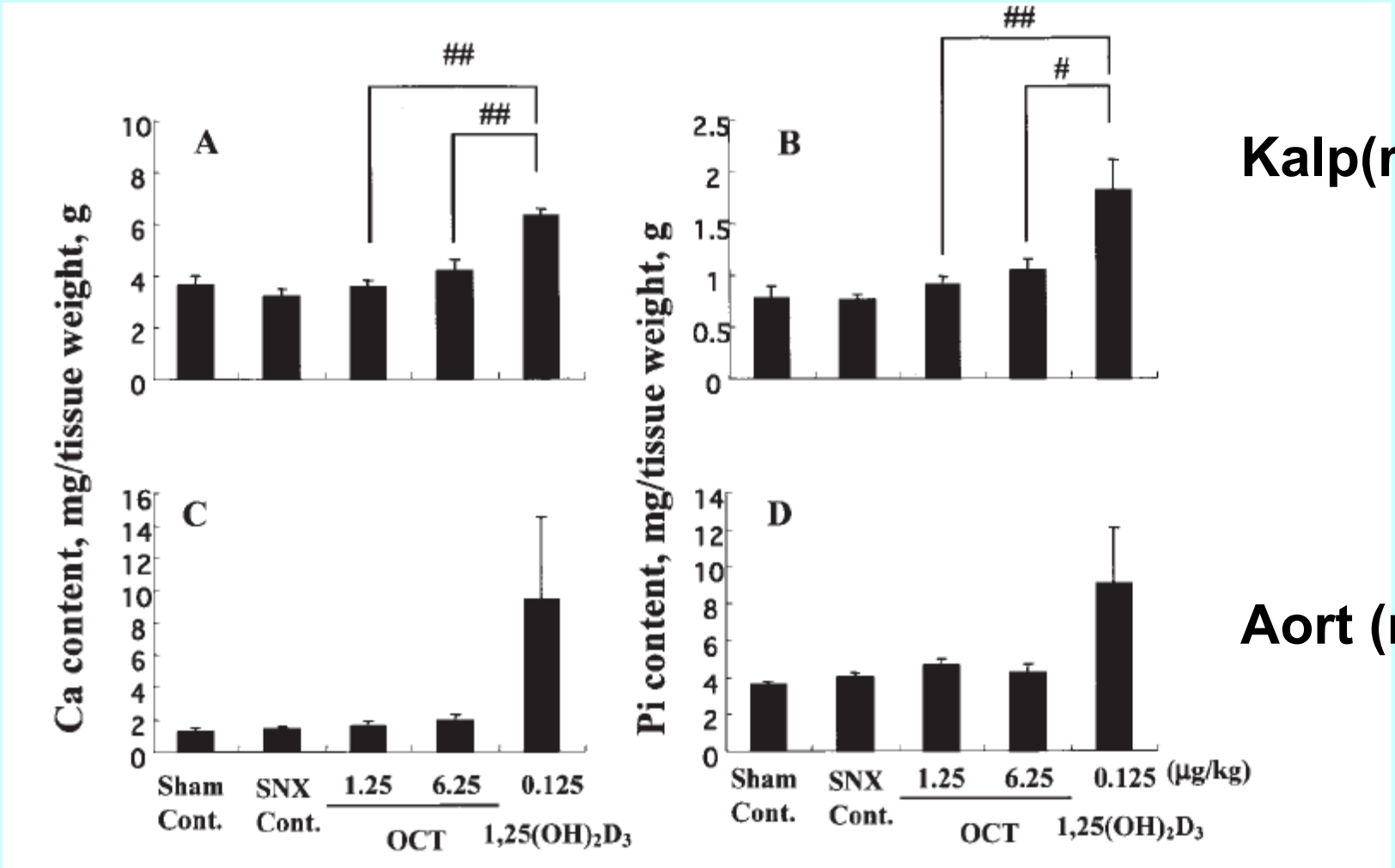
Hirata et al Nephrol Dial Transplant 2002





N:124
26 hafta

Akizawa et al Nephrol Dial Transplant 2002



Kalp(rat)

Aort (rat)

Hirata et al. Nephrol Dial Transplant 2003

19 Nor D_2 Paricalcitol

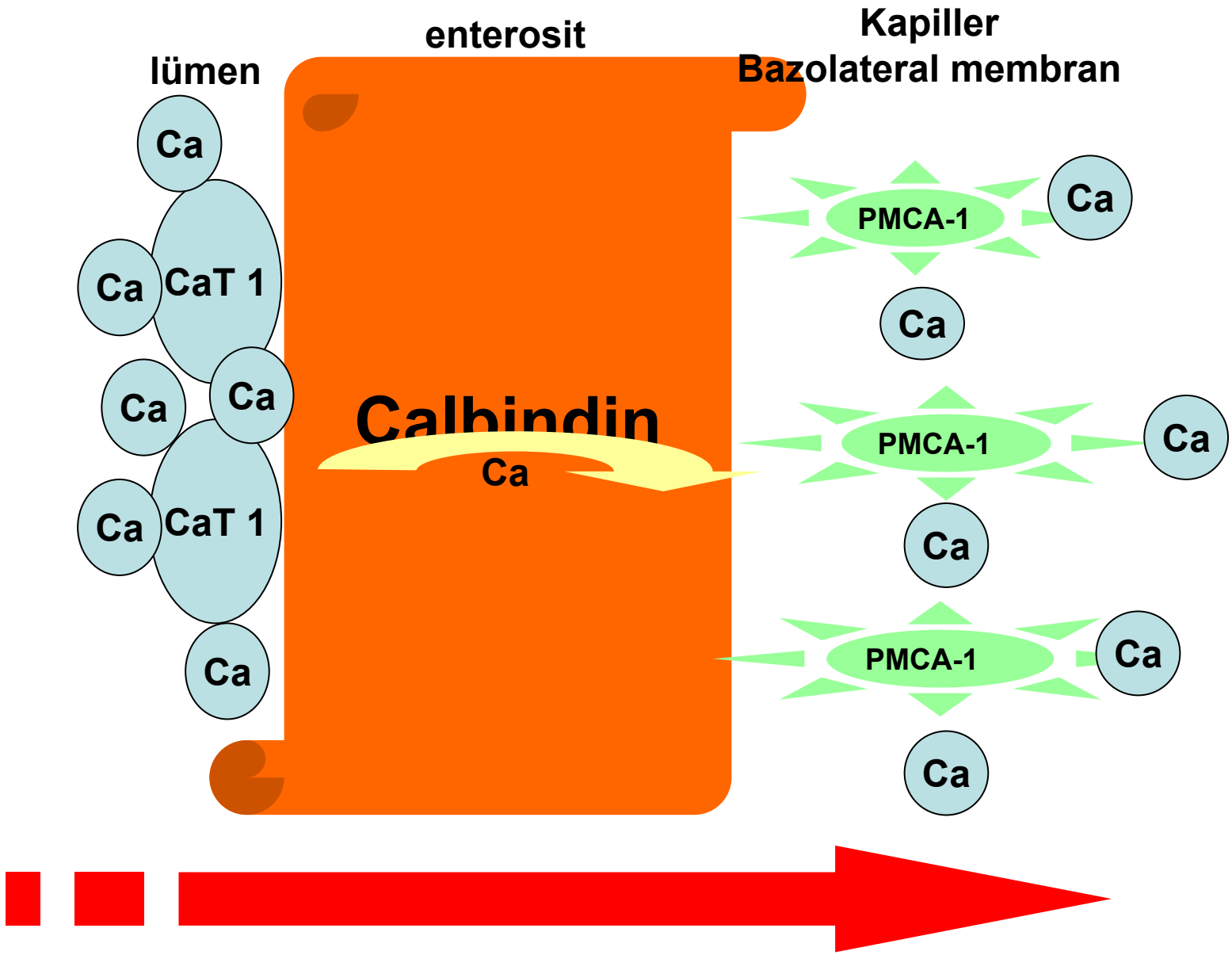
- Hipokalsemik etkisi en güçlü vitamin D analogu
- Vitamin D reseptörlerine olan afinitesi kalsitriolden 3 kat daha azdır
- Fosfatemik ve kalsemik etkisi kalsitriolden 10 kat daha azdır
- Kemiklerden kalsiyum ve fosfor mobilizasyonu 10 kat daha azdır
- Hedef PTH değerlerine ulaşma daha hızlı
- Kronik kullanımda intestinal vit D reseptör düzeylerini azaltır
- OCT gibi 1αhidroksilazı inhibe ederek endojen Calcitriol düzeylerini düşürür

Brown AJ Nephrol Dial Transplant 2002

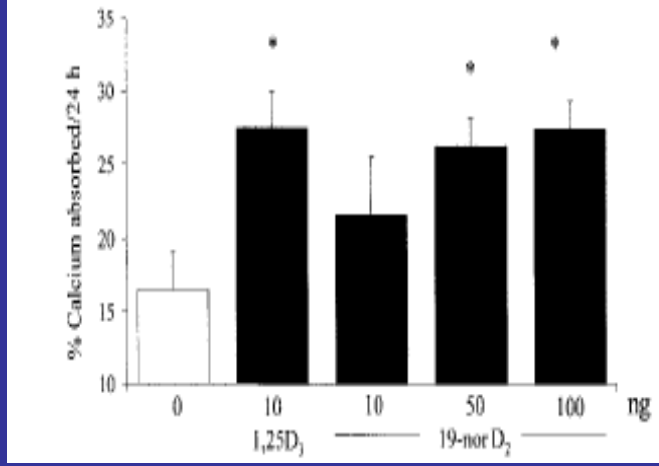
19 Nor D_2 Paricalcitol

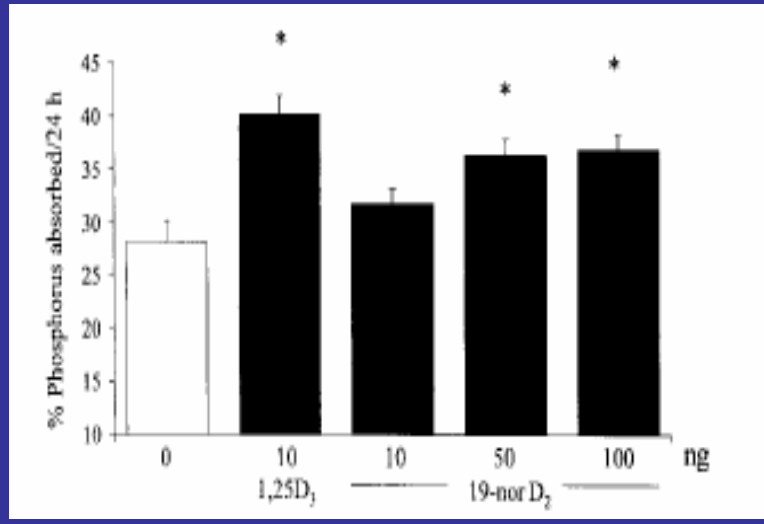
- Calcitriol gibi paratiroid gland hiperplazisini azaltır
- Calcitriol tedavisine yanıtsız olanlarda da etkili
- Kemik büyüme göstergesi olan kollagen sentezini arttırır
- IV formu 1998'de, oral formu 2005'de onay aldı.(Zemplar®)

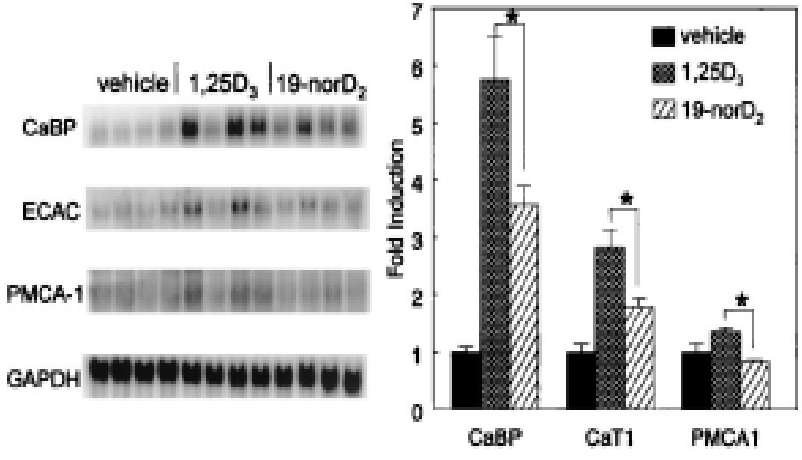
Brown AJ Nephrol Dial Transplant 2002



calcium transporter 1 (CaT1)
plasma membrane calcium ATPase-1(PMCA-1)

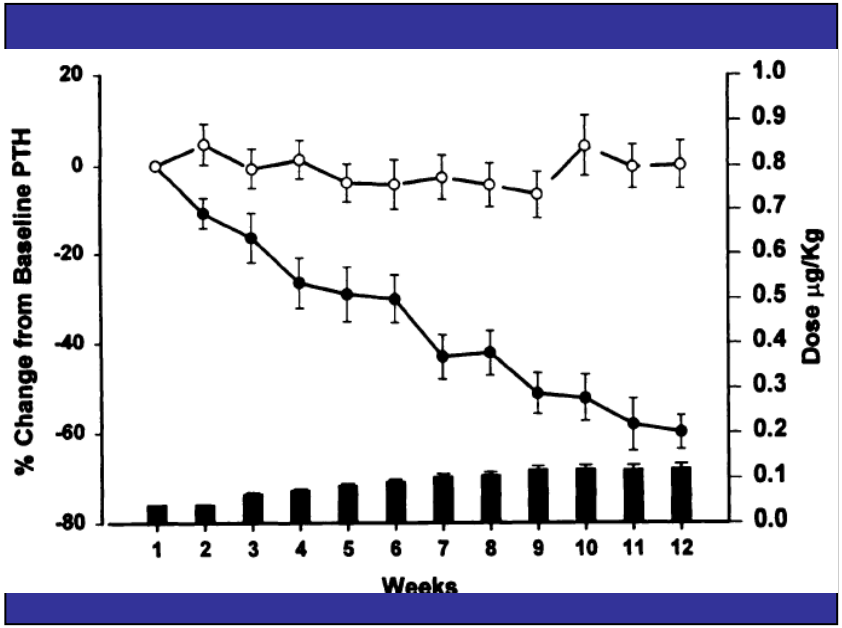


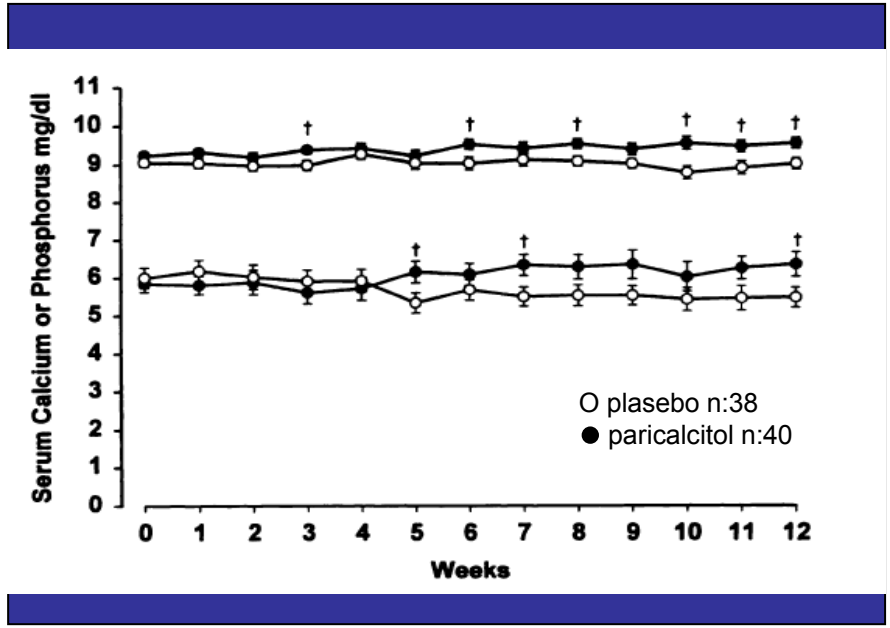




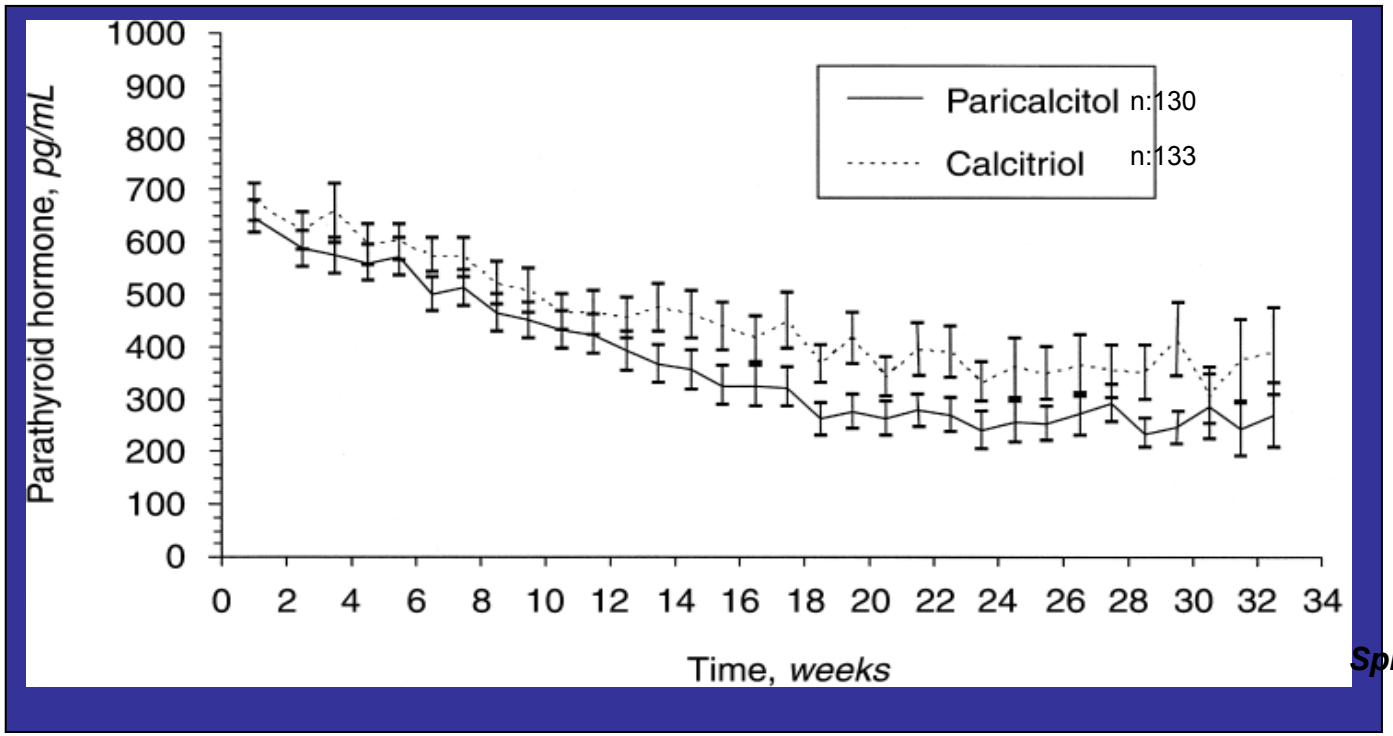
Parikalsitol ile aktiviteleri azalanlar;
Luminal membranda calcium transporter 1 (CaT1)
Sitozolde Calbindin
Enterosit bazolateral membranında plasma membrane calcium ATPase-1(PMCA-1)

Brown AJ J Lab Clin Med May 2002





Martin KJ et al JASN Aug 1998

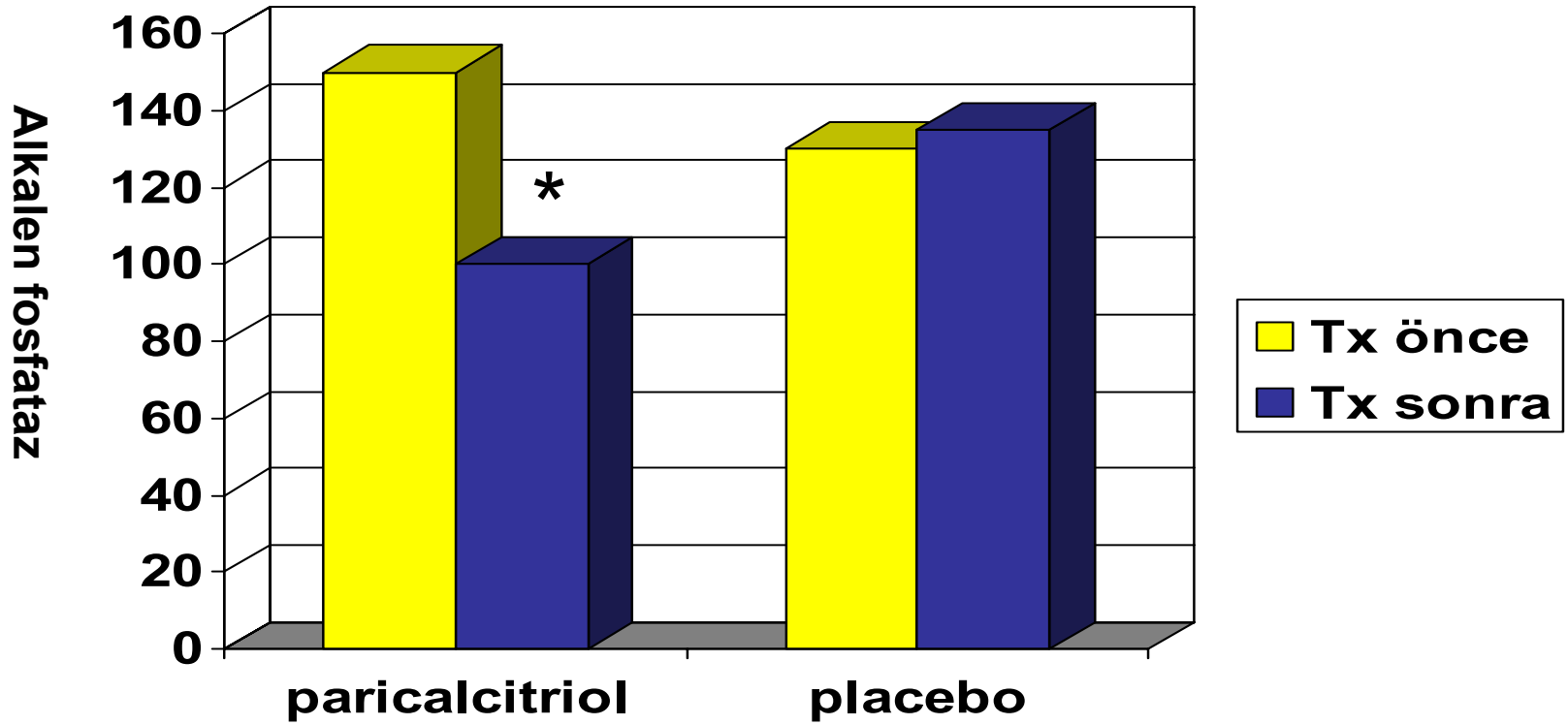


Sprague M Kidney Int 2003

J Am Soc Nephrol 9: 1427–1432, 1998

19-Nor-1-α-25-Dihydroxyvitamin D_2 (Paricalcitol) Safely and Effectively Reduces the Levels of Intact Parathyroid Hormone in Patients on Hemodialysis

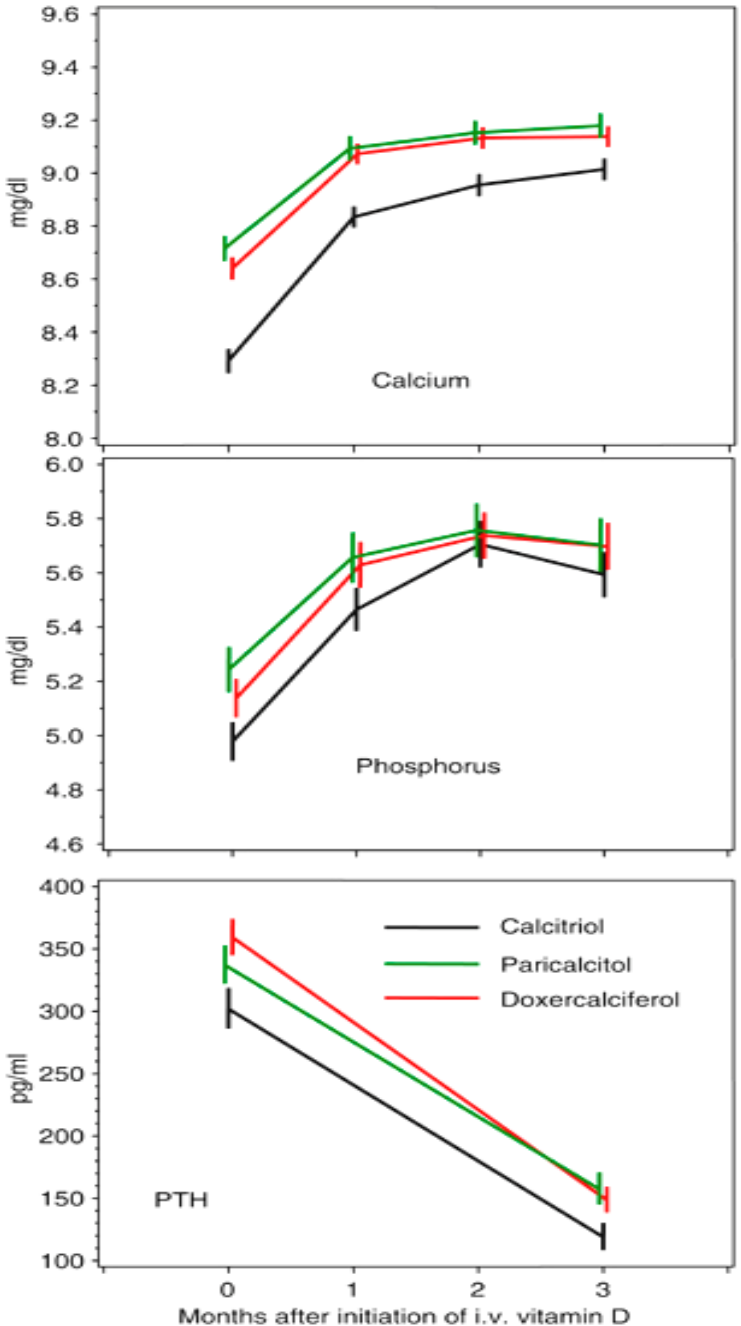
KEVIN J. MARTIN,* ESTHER A. GONZÁLEZ,* MARY GELLENS,* L. LEE HAMM,† HANNA ABBOUD.‡ and JILL LINDBERG§

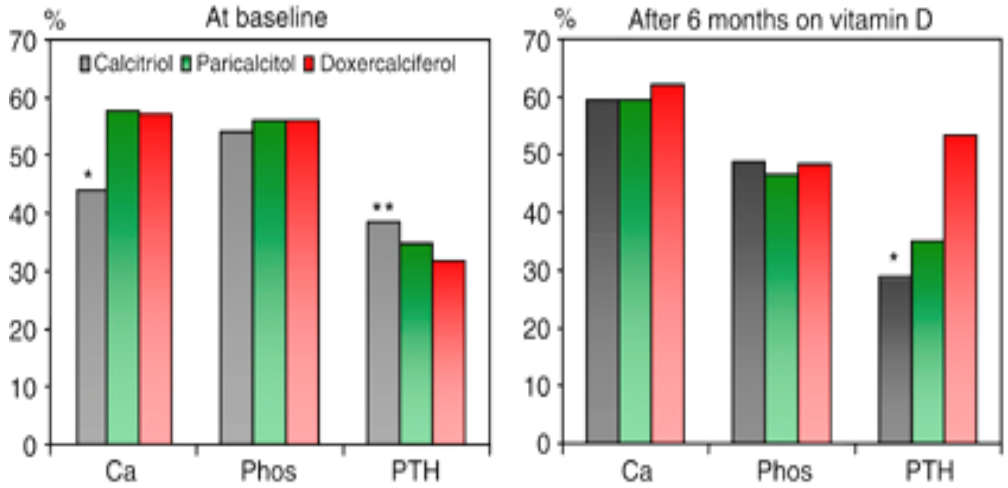


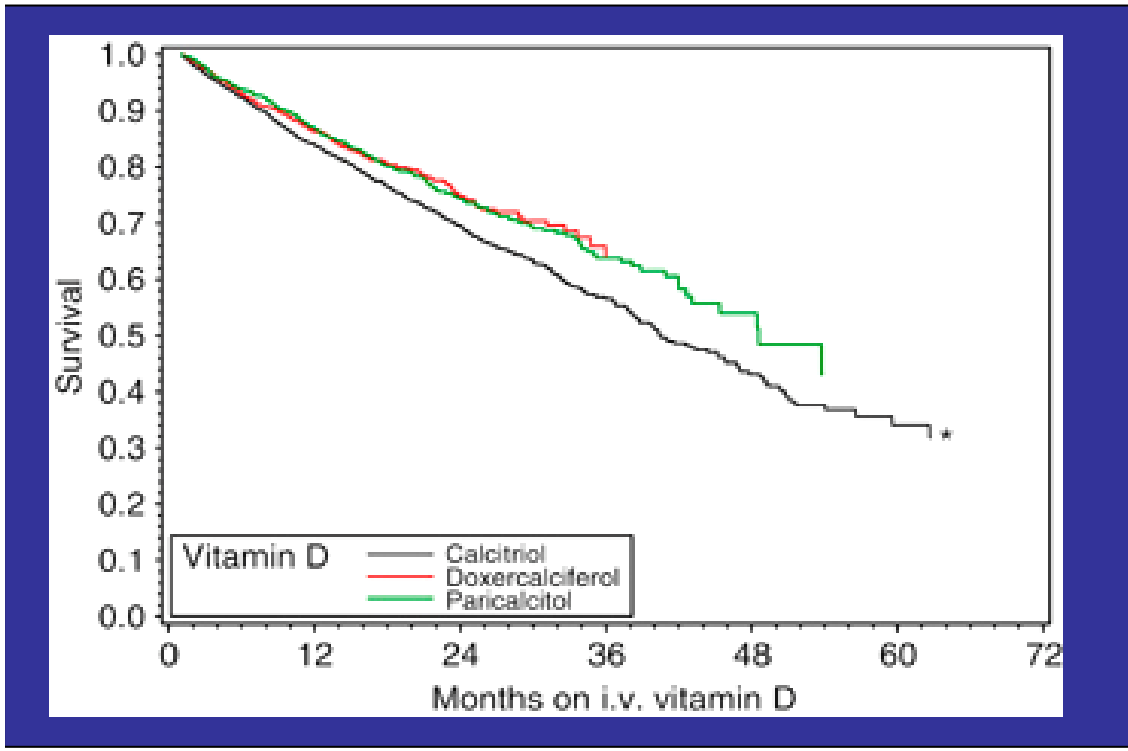
p<0.05 vs tedavi öncesi

Martin KJ et al JASN Aug 1998

N:7731,







Tentori F et al Kidney Int 2006

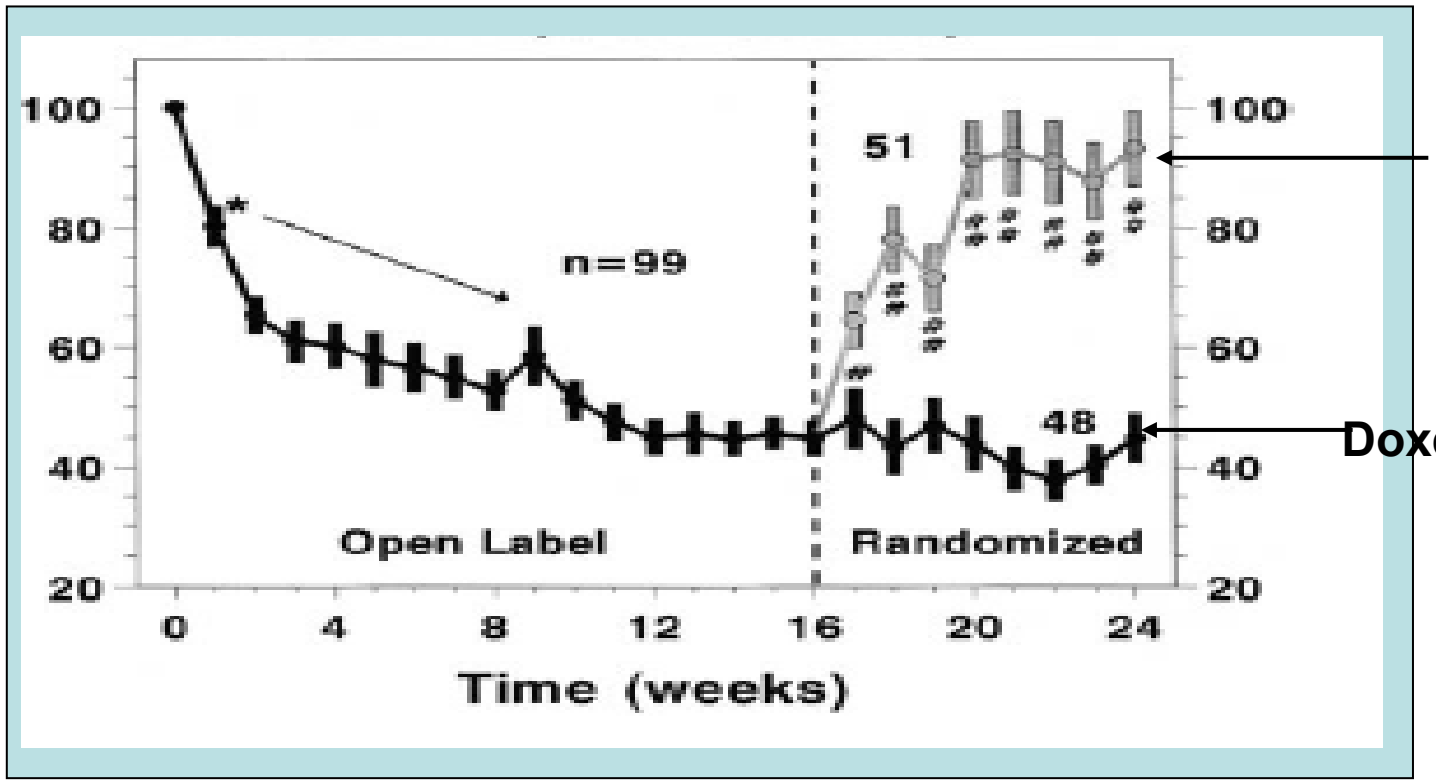
1α (OH) D_2 Doxercalciferol

- USA'de kullanımı onay alan 2. vit D analogu
- Prohormon olup 1,25$(OH)_2D_2$ ve 1,24$(OH)_2D_2$'ye dönüşerek etki gösterir
- 1,24$(OH)_2D_2$ daha az kalsemik ve hiperfosfatemik
- Kemik mobilizasyonu ve kalsiyum transportu calcitriol ile benzer
- Kronik kullanımda 1αhydroxy D3'den daha az toksik
- Önce oral formu (1999), sonra IV formu USA'da kullanım için onay almıştır (Hectorol®)

Brown AJ Nephrol Dial Transplant 2002

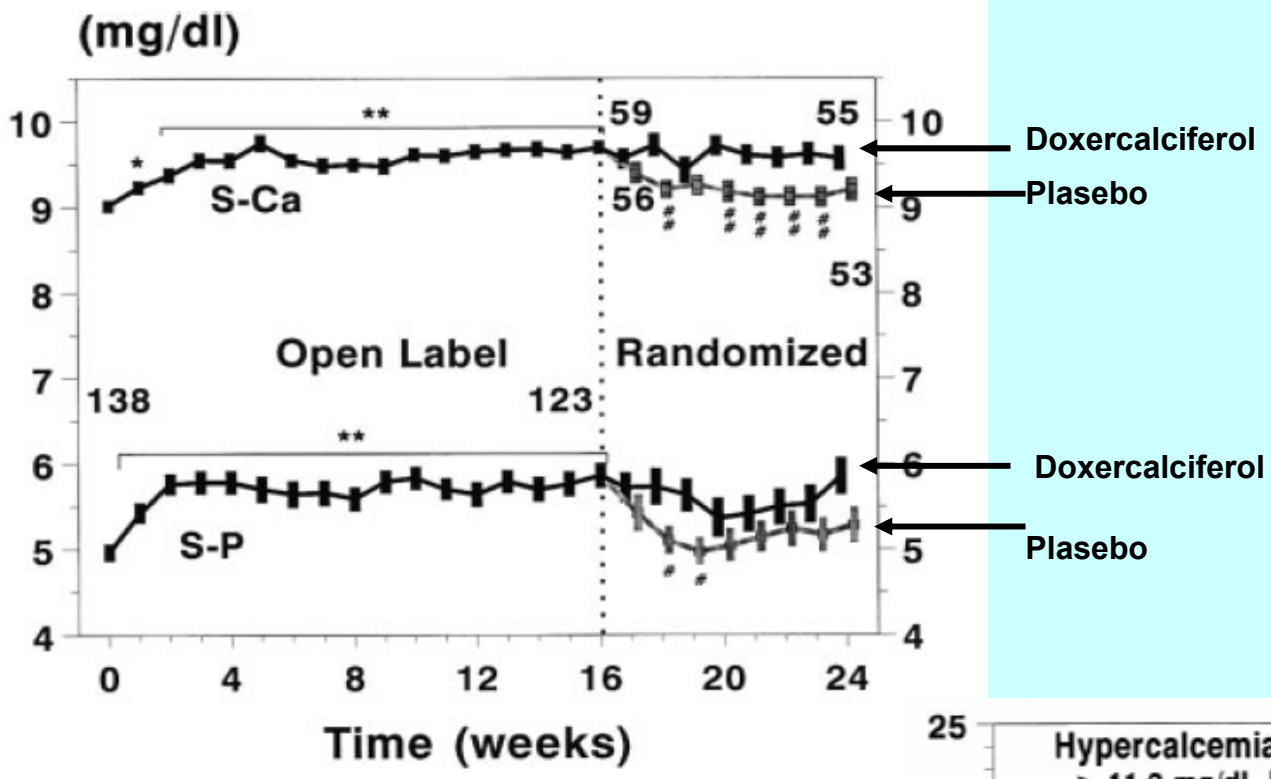
Sekonder Hpt ve Intermittan Doxercalciferol (1 α-Hydroxyvitamin D2) kullanımı

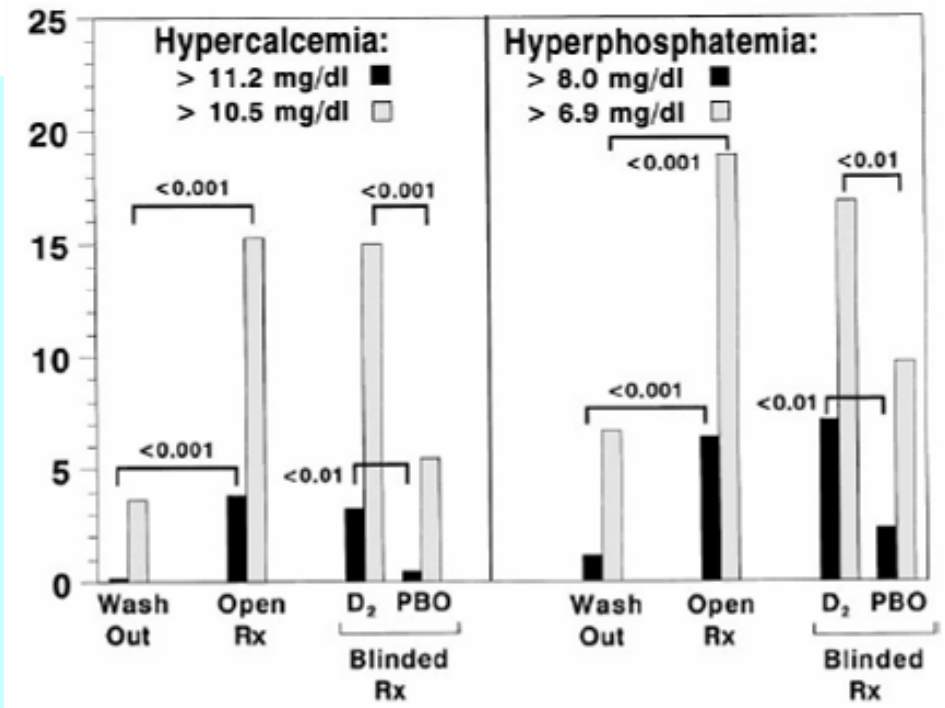
N=99 hasta
Açık etiketli, randomize plasebo kontrollü çalışma
Orta-ciddi hiperparatiroidizmi olan diyaliz hastaları



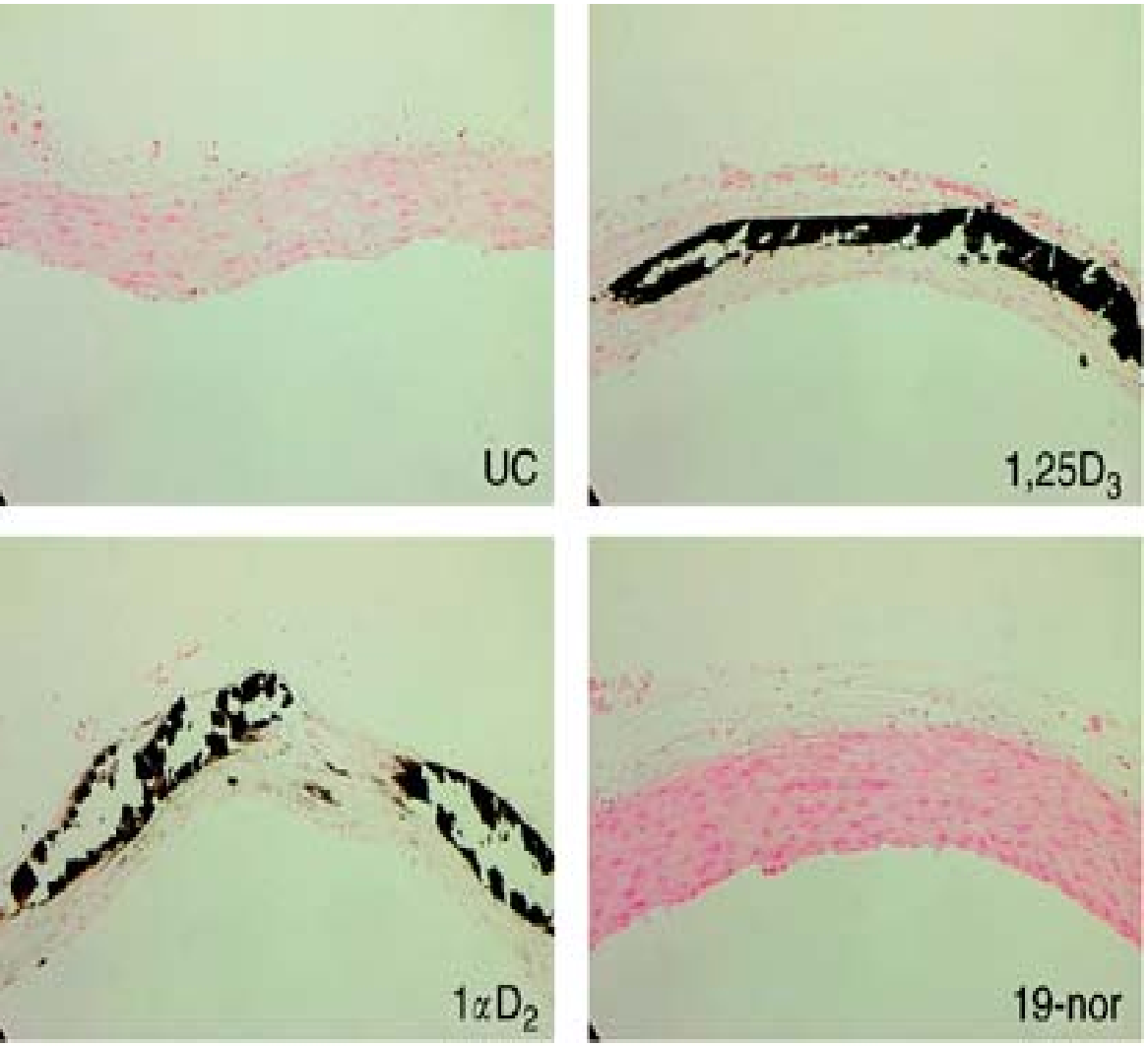
%91.9 hastada %50 den fazla PTH azalması
%79.8 hastada %70 den fazla PTH azalması
%82.8 hastada hedef PTH düzeylerine ulaşma

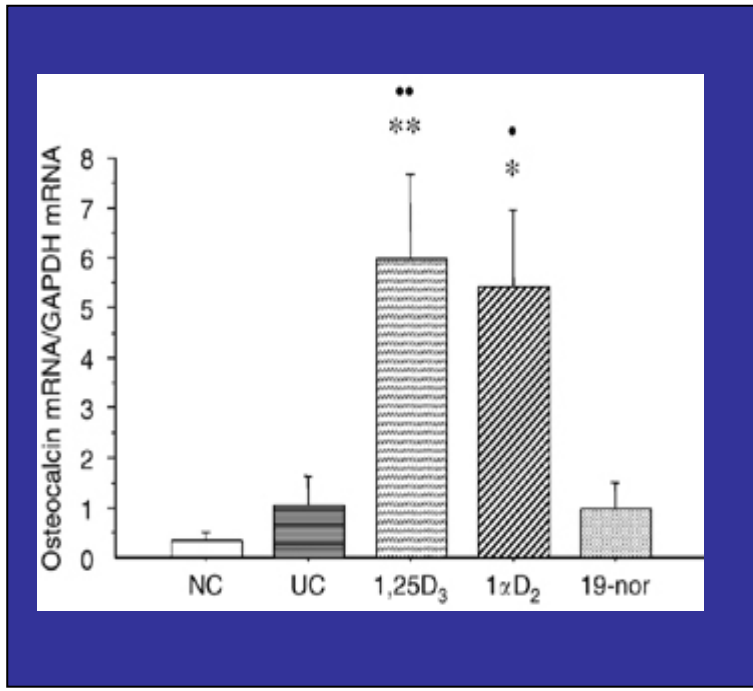
Frazao JM Am J Kidney Dis 2000





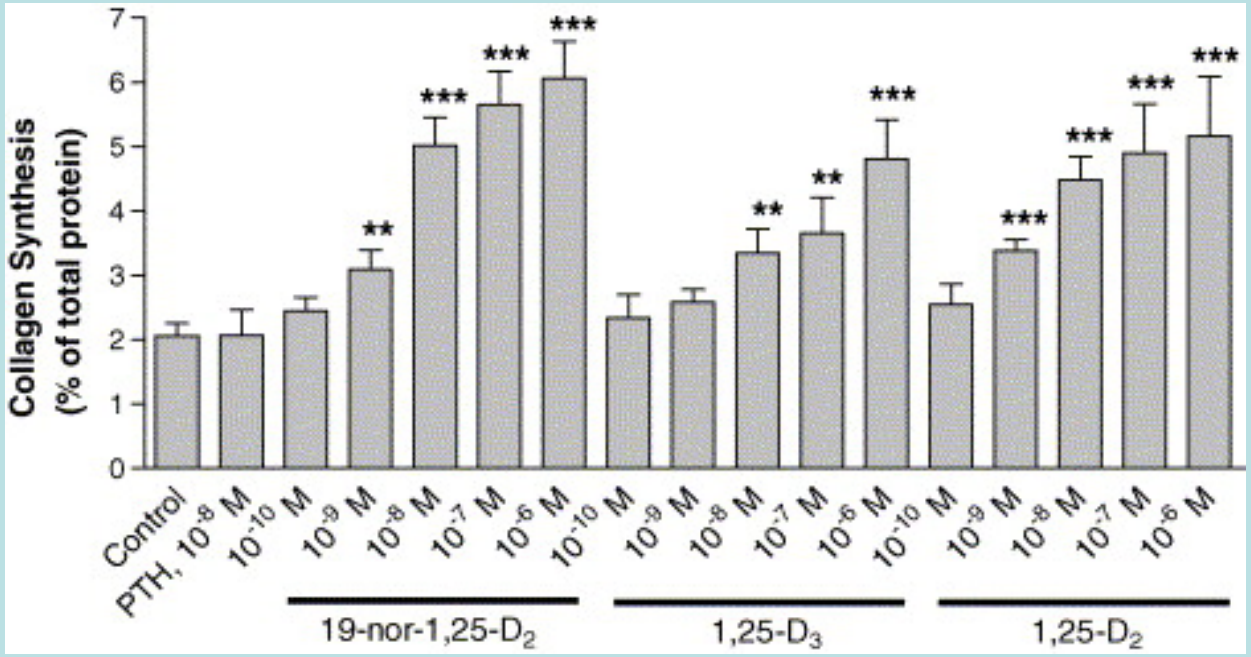
Frazao JM Am J Kidney Dis 2000

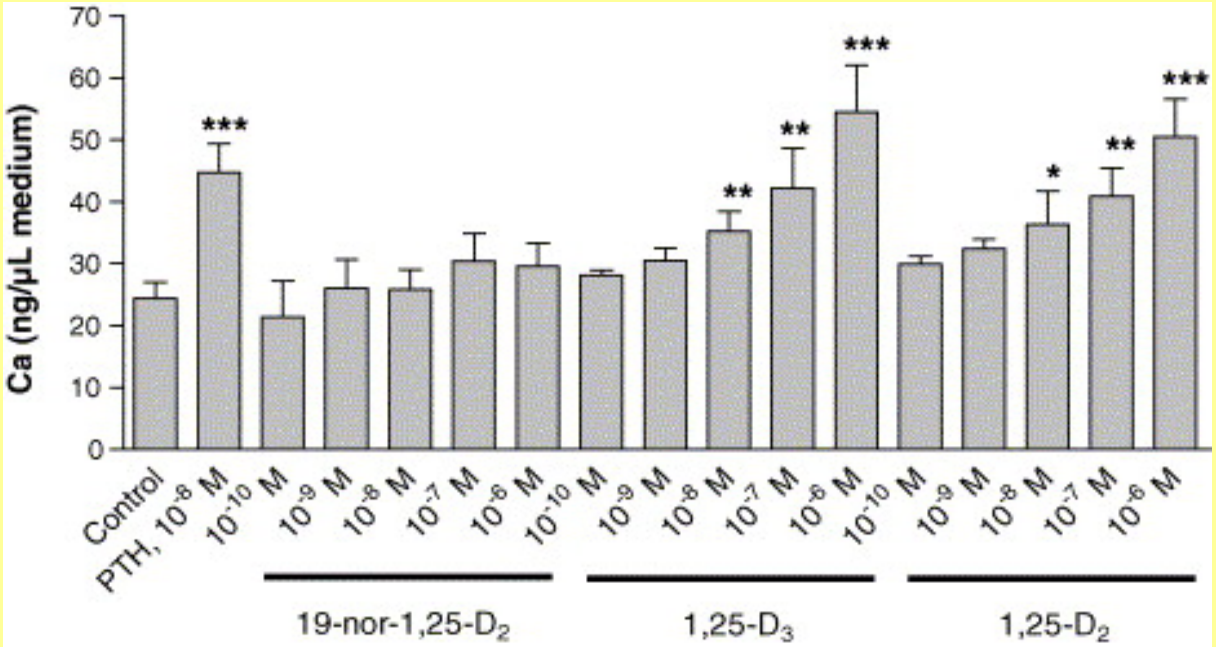




Üremik rat aortasının farklı ajanlarla tedavi sonrası görüntüleri

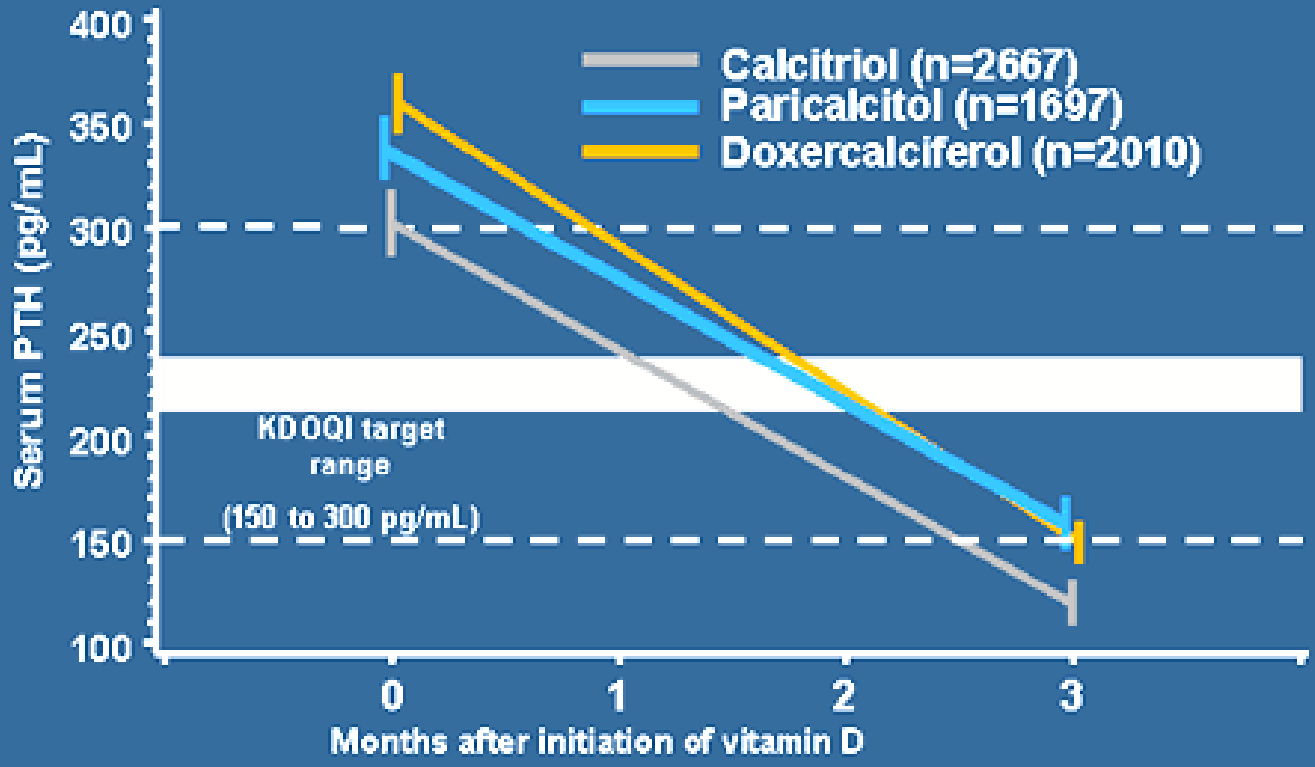
Mizobuchi and Slatapolsky Kidney Int 2007





Nakane M
J steroid Biochem Mol Biol Jan 2006

Mean Serum PTH: First 3 Months of Injectable Vitamin D Therapy



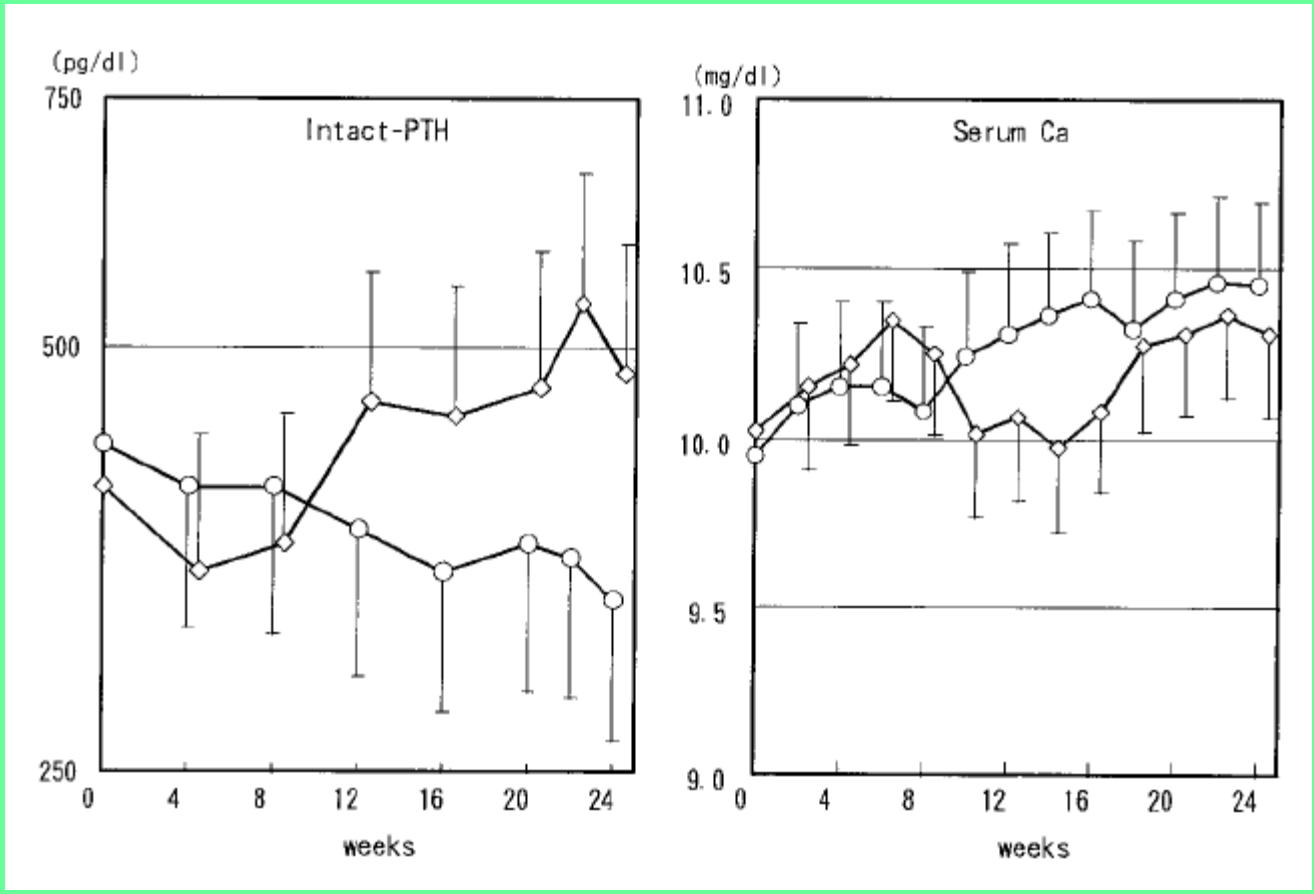
Tentori F et al. *Kidney Int.* 2006; 70(10):1858-1865

Falecalcitriol

- Japonya'da kullanılan vit D analogu
- Yan zincirinin oksidasyona dayanıklılığı nedeniyle invivo calcitriol'den daha yüksek aktiviteye sahip
- VDR'ne 3 kat daha az afinite gösterir
- Calcitriolden daha hızlı plazmadan temizlenir
- Paratiroid glandlar, böbrek ve barsaklarda 23-hidroxi metaboliti uzun süreli olarak bulunur
- Hedef doku metabolizması yavaştır
- Oral formulasyonu vardır (Hornel® Fustan®)

Komuro S Drug Metab Dispos 2003

Falecalcitriol vs Alfacalcidol



○ Falecalcitriol
◇ alfacalcidol

n:25 hd hastası

Akiba T AJKD 1998

Tissue	[1β-^{3}H]F_6-1α,25(OH)$_2$VD$_3$		
	6 h	24 h*	48 h
Parathyroid gland	73.6 ± 9.9	64.9 ± 5.4	71.3 ± 7.0
Serum	17.9 ± 1.1	4.83 ± 1.25	1.40 ± 0.13
Thyroid	10.2 ± 1.3	4.72 ± 0.59	2.94 ± 0.66
Liver	26.1 ± 3.6	11.5 ± 1.9	9.64 ± 1.46
Kidney	99.3 ± 12.5	166 ± 12	120 ± 17
Skin	4.42 ± 0.53	3.71 ± 1.16	2.24 ± 0.55
Humerus bone	4.02 ± 0.58	2.29 ± 0.69	1.91 ± 0.15
Small intestine	27.7 ± 6.1	39.5 ± 6.2	28.1 ± 9.2

Tissue	[1β-^{3}H]1α,25(OH)$_2$VD$_3$		
	6 h	24 h	48 h
Parathyroid gland	29.1 ± 2.5	7.72 ± 0.74	4.87 ± 0.45
Serum	24.0 ± 1.1	6.70 ± 0.56	2.96 ± 0.31
Thyroid	11.8 ± 2.4	3.33 ± 0.59	1.74 ± 0.21
Liver	33.1 ± 5.7	13.6 ± 2.9	7.84 ± 1.68
Kidney	15.3 ± 0.9	5.41 ± 0.62	3.67 ± 0.31
Skin	3.99 ± 1.36	1.51 ± 0.26	1.11 ± 0.81
Humerus bone	3.53 ± 0.52	0.705 ± 0.045	0.414 ± 0.053
Small intestine	8.35 ± 0.95	3.22 ± 0.56	1.93 ± 0.12

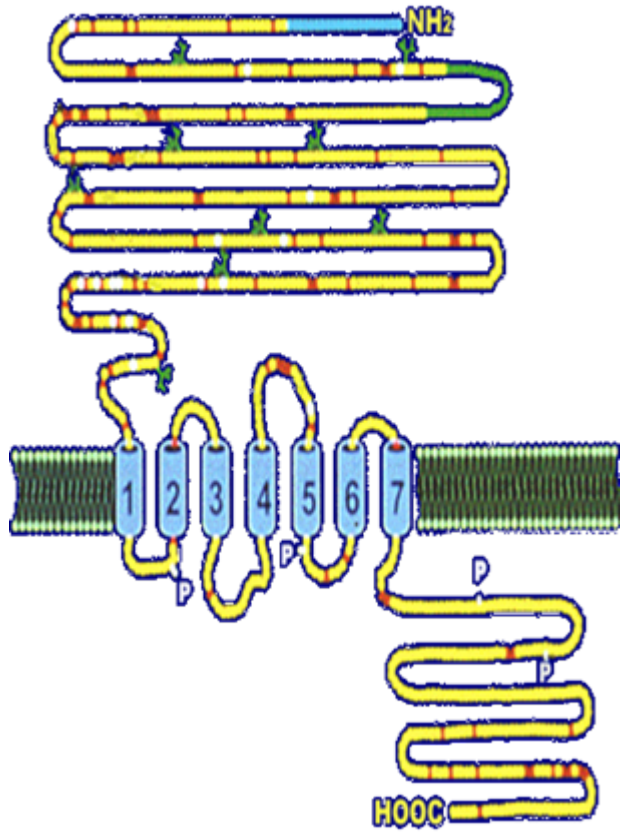
Komuro S Drug Metab Dispos 2003

Vit.D sterolleriyle tedavide önerilen başlangıç dozları (her hemodiyalizde) Serum Ca, P, PTH düzeyleri ve Ca×P

PTH (pg/ml)	Ca (mg/dl)	P (mg/dl)	Ca×P (mg^2/dl^2)	*Calcitriol* µg	*Paricalcitol* µg IV	*Doxercalciferol* µg
300-600	< 9.5	< 5.5	< 55	IV: 0.5-1.5 ORAL: 0.5-1.5	2.5-5	IV: 2 ORAL: 5
600-1000	< 9.5	< 5.5	< 55	IV: 1- 3 ORAL: 1-4	6-10	IV: 2-4 ORAL: 5-10
> 1000	< 10	< 5.5	< 55	IV: 3-5 ORAL: 3-7	10-15	IV: 4-8 ORAL: 10-20

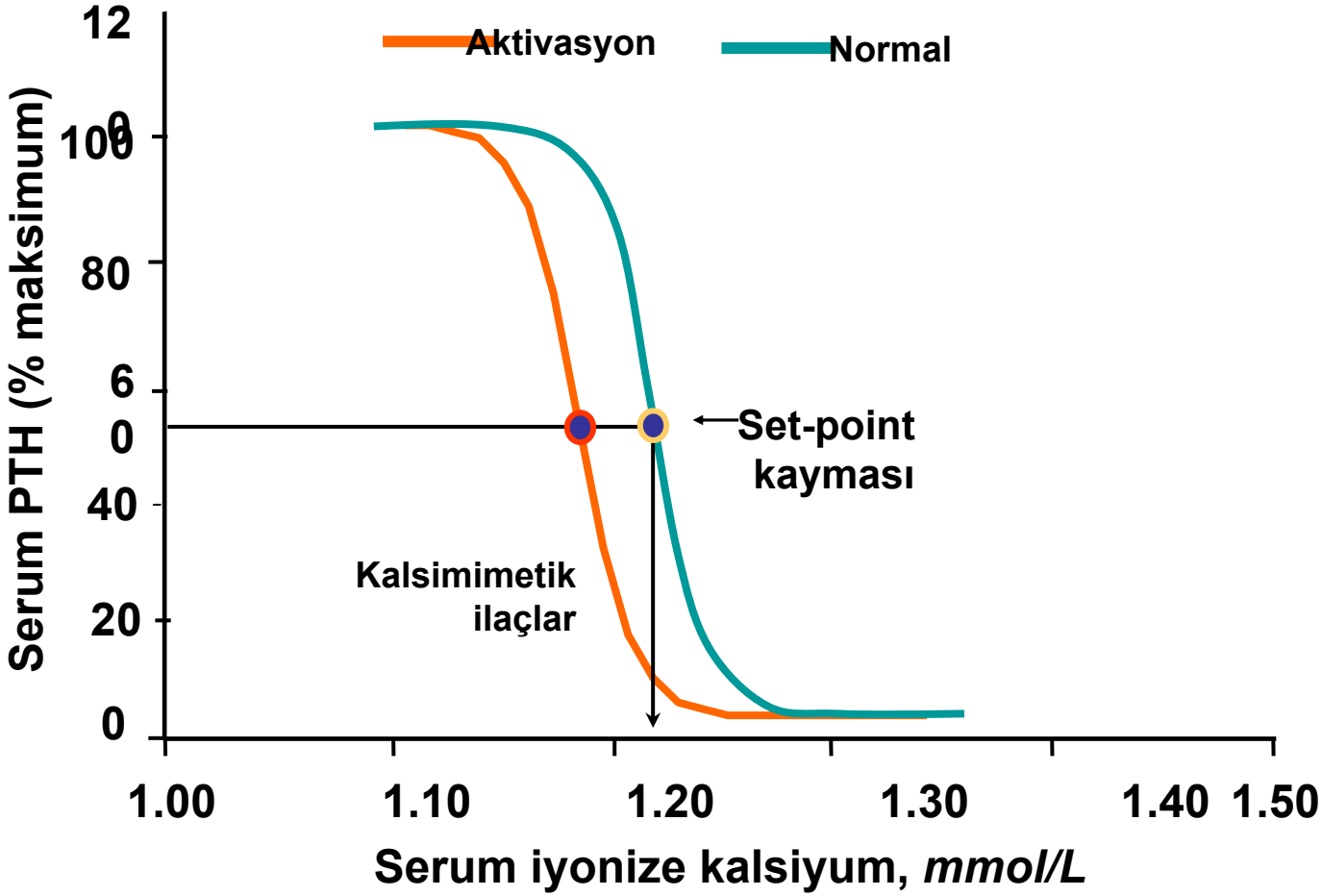
Cinacalcet (kalsimimetik)

- FDA onayı olmış tek kalsimimetik
- Renal karsinomada da kullanılıyor
- Paratiroid glandlardaki kalsiyum reseptörlerinin(CaR) transmembran domainine bağlanıyor ve kalsiyuma afinitesini arttırıyor.
- Bulantı, kusma ve hipokalsemi en önemli yan etkileri
- Uzun dönem mortalite, kemik yapı ve KV olaylar üzerine etkinliğine dair çalışma yok

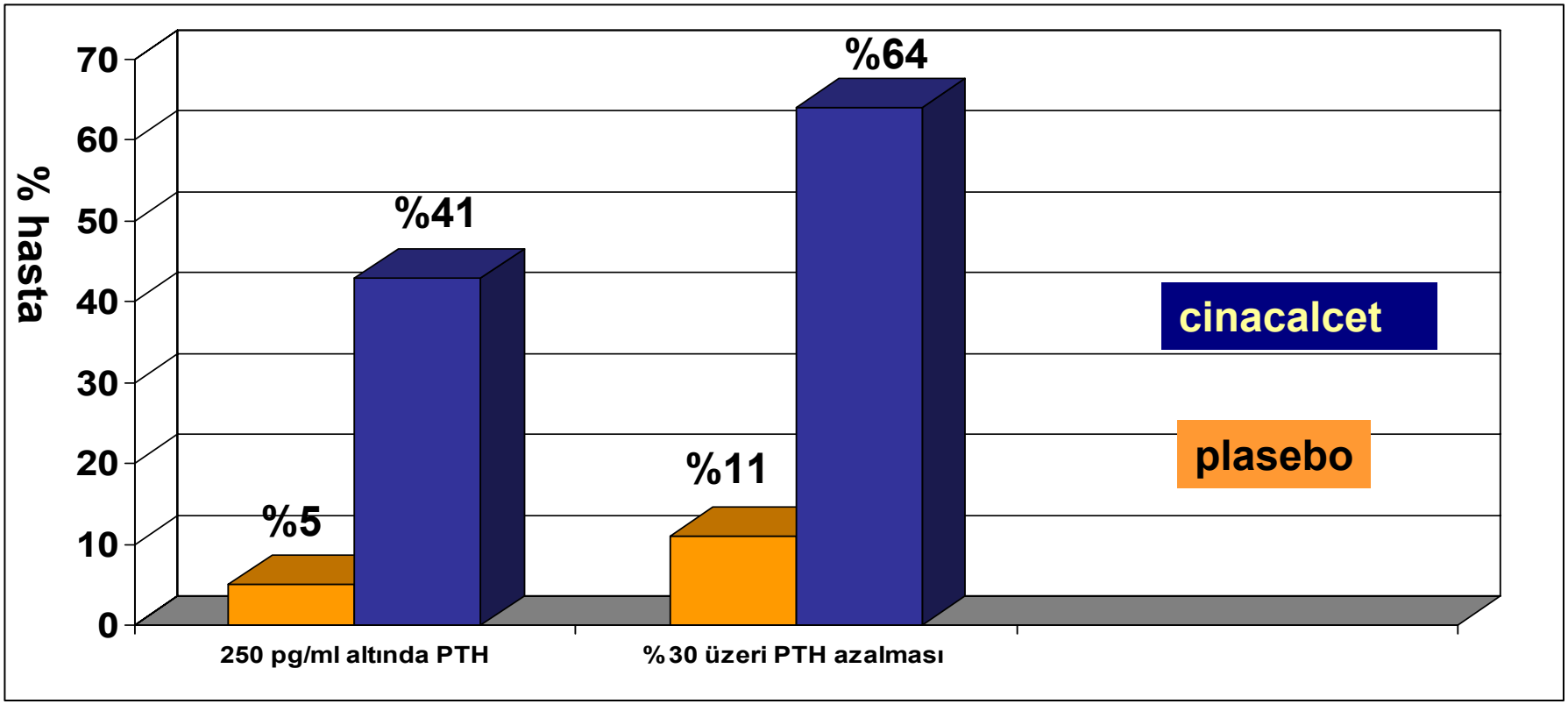


Brown et al, Nature 1993

Kalsimimetiklerin PTH-Kalsiyum ilişkisi üzerine etkisi



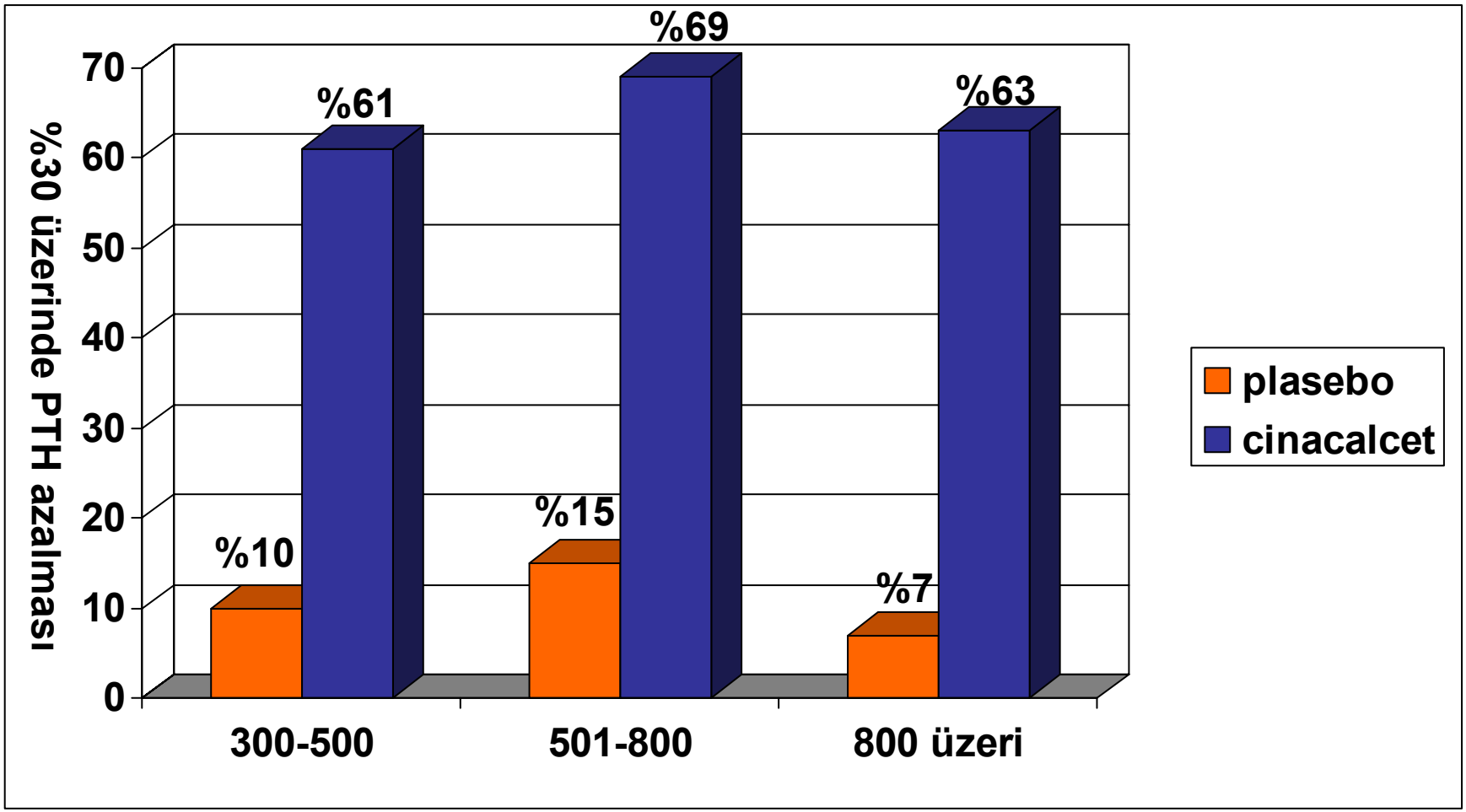
Goodman WG et al. *Kidney Int*. 1996;50:1834-1844.



Cinacalcet N= 371
Plasebo N=370
26 haftalık takip

Serum kalsiyumu %6.8
Serum fosforu %8.4
CaxP product %14.6 azalma gösterdi

Block et al. NEJM 2004

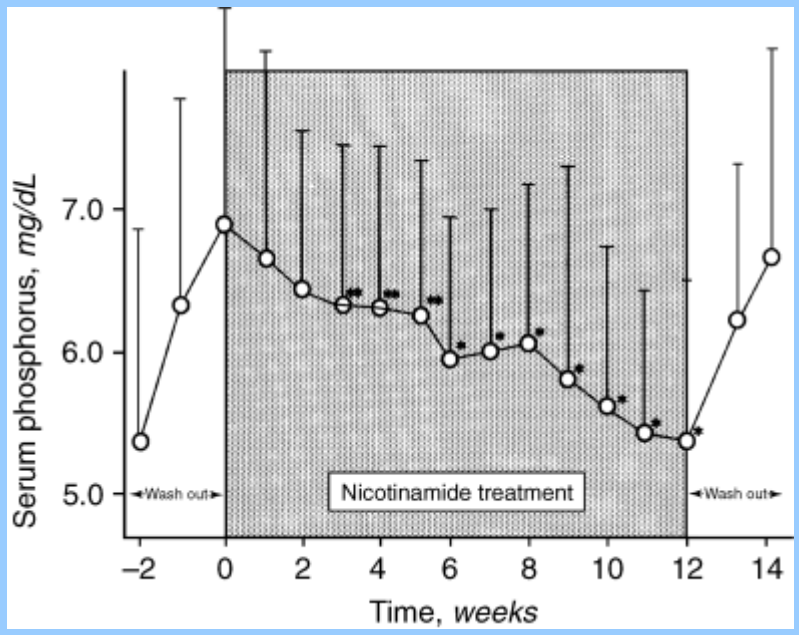


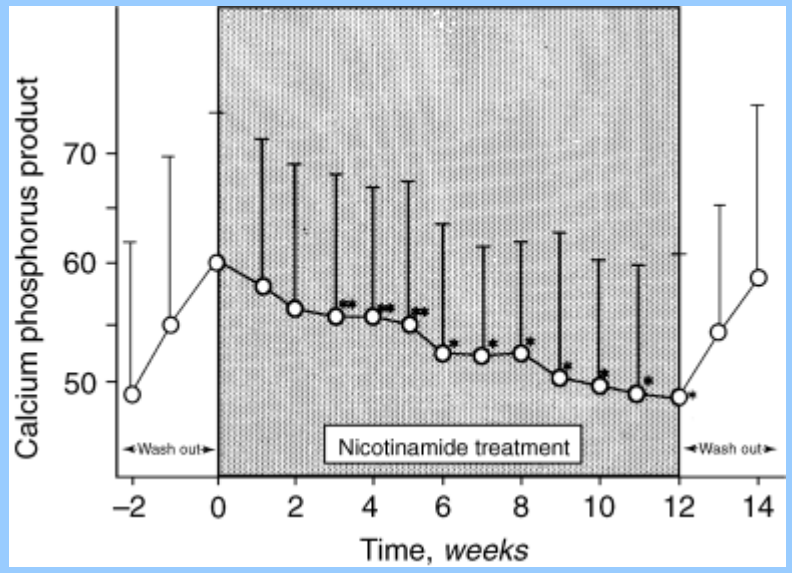
Cinacalcet N= 371
Plasebo N=370
26 haftalık takip

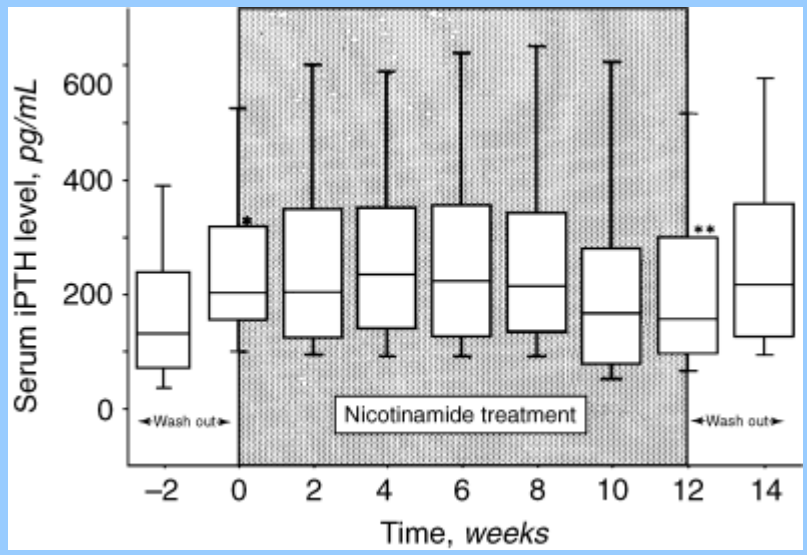
Block et al. NEJM 2004

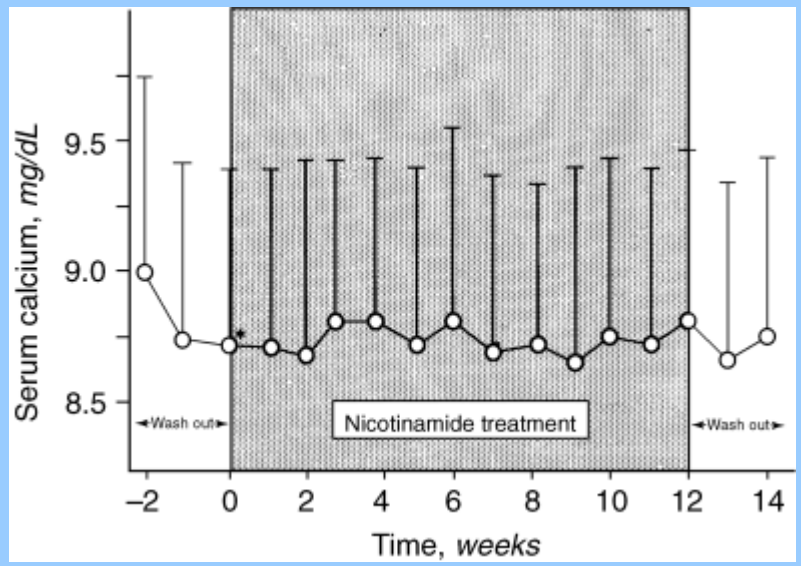

Teşekkürler

* TTG: Chertow GM. KI 2002
** Hutchison WCN 03. Berlin



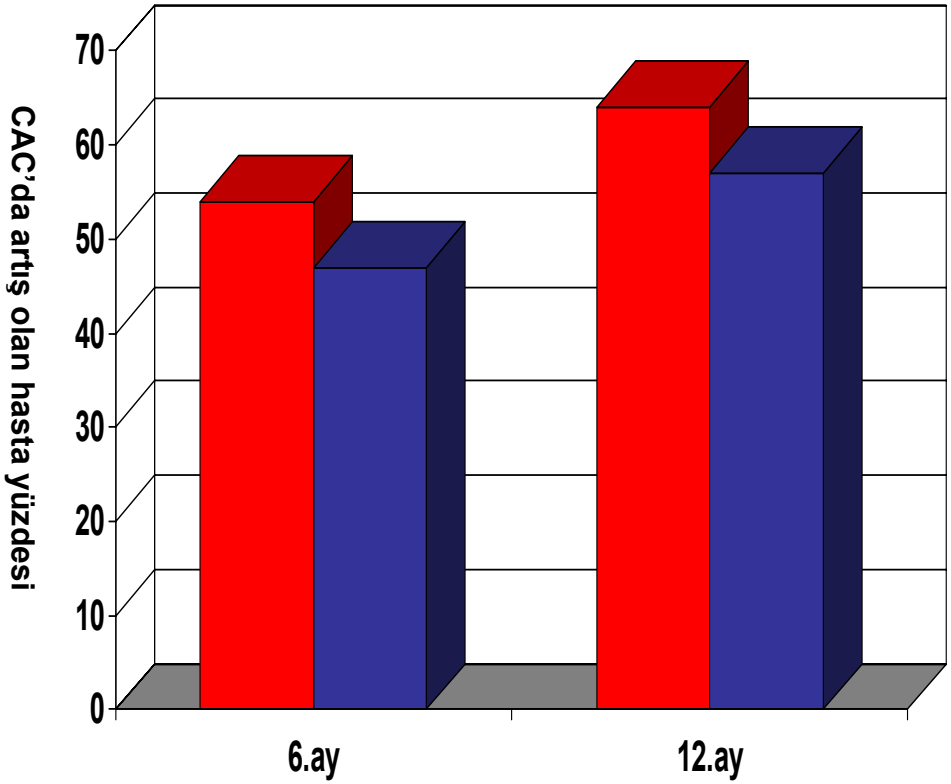


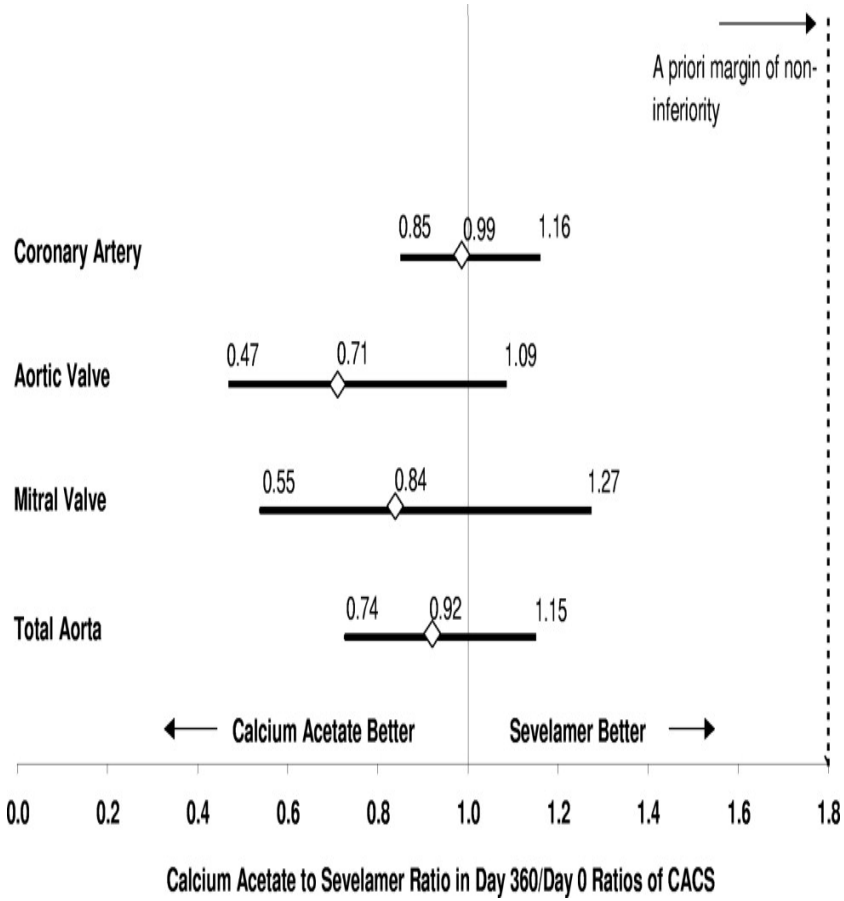




Takahashi et al. Kidney International (2004) ***65****, 1099–1104*

The Calcium Acetate Renagel Evaluation-2 (CARE-2) Study





Kalsiyum asetat n:103 hd hastası

Sevelamer HCL n:100 hd hastası

1 yıllık takip çalışması
Her iki grupta Atorvastatin ile LDL<70

Qunibi et al AJKD april 2008