CKD-MBD after renal transplantation

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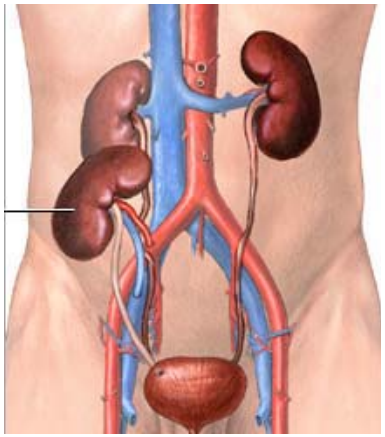
Madrid, 2013

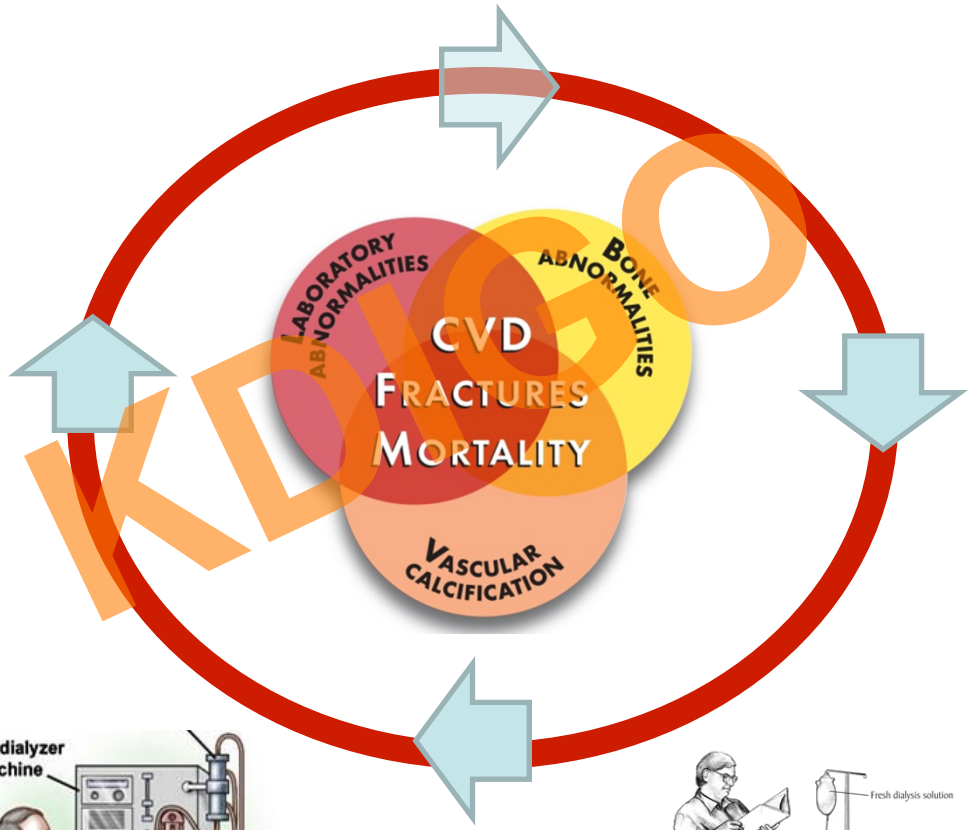
Disclosure of Interests

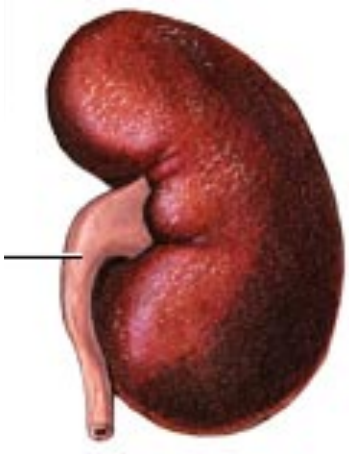
- Amgen: consultancy, research grant, honoraria, sponsored education
- Shire: honoraria, sponsored education
- Sanofi-Genzyme:research grant

CKD-MBD

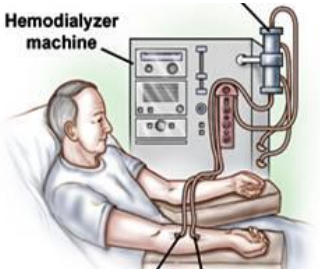


Renal Transplantation

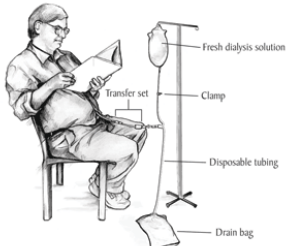




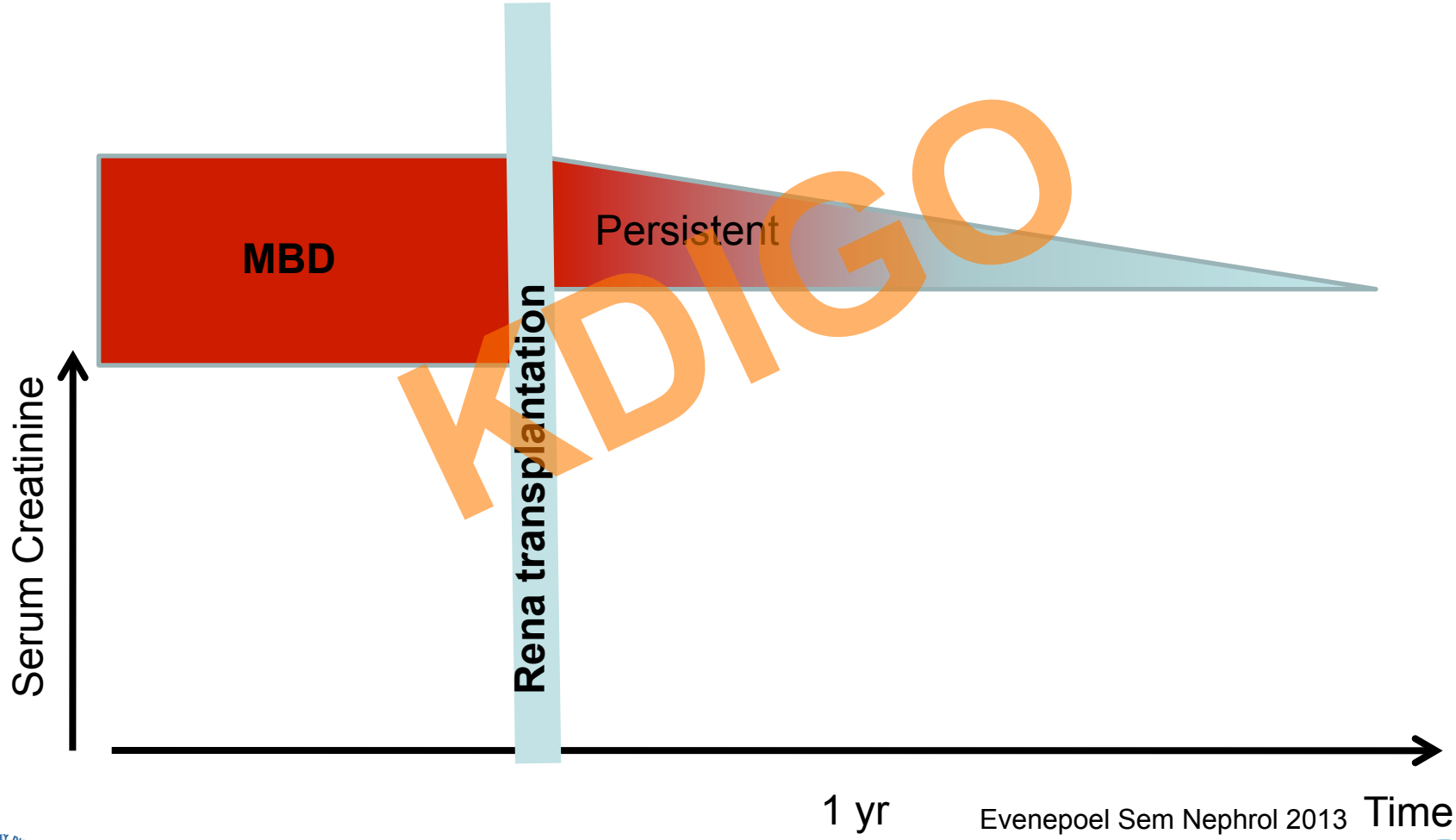
CKD stage1-5



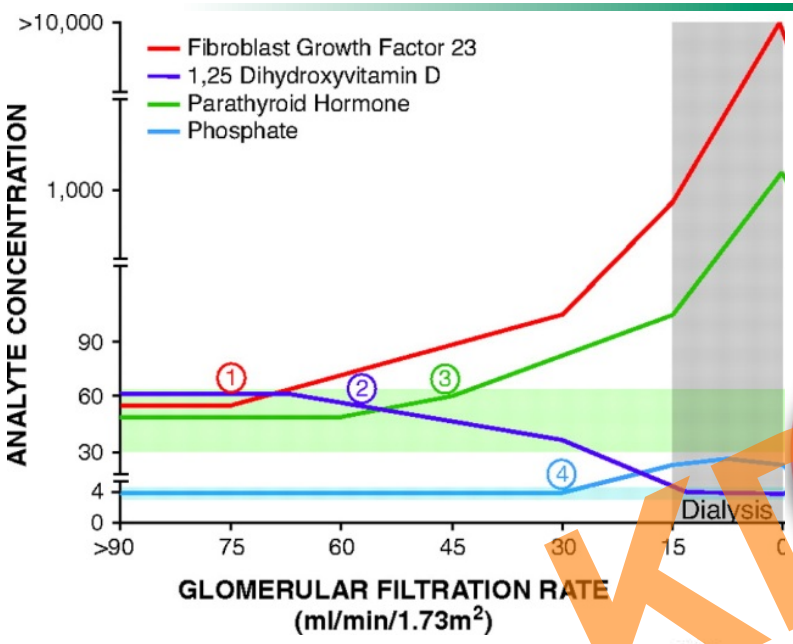
CKD stage 5D

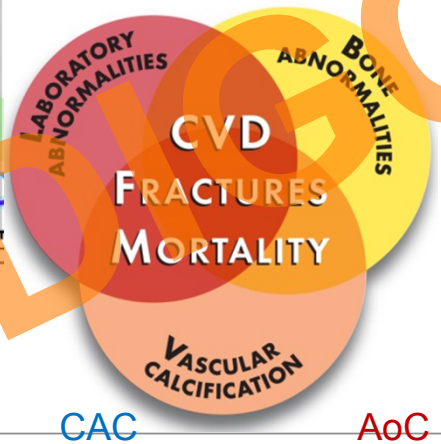


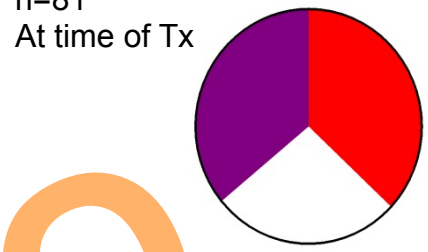
Posttransplant CKD-MBD

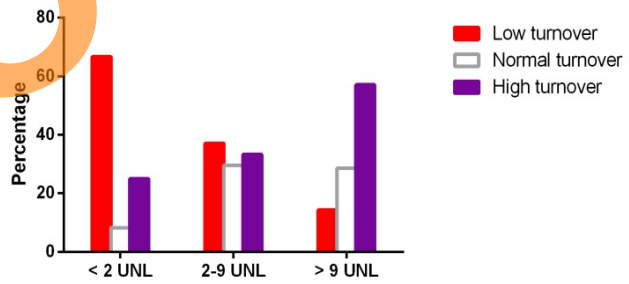


Pretransplant CKD-MBD

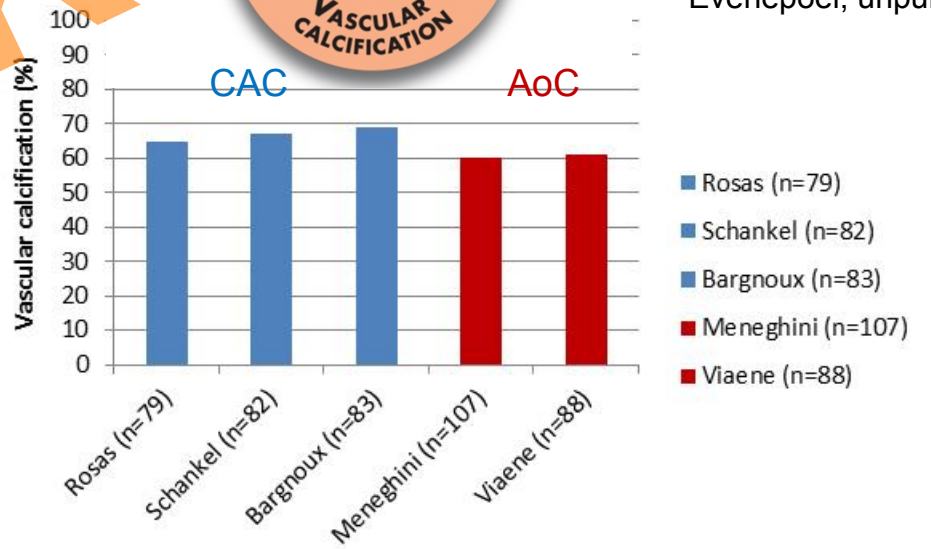




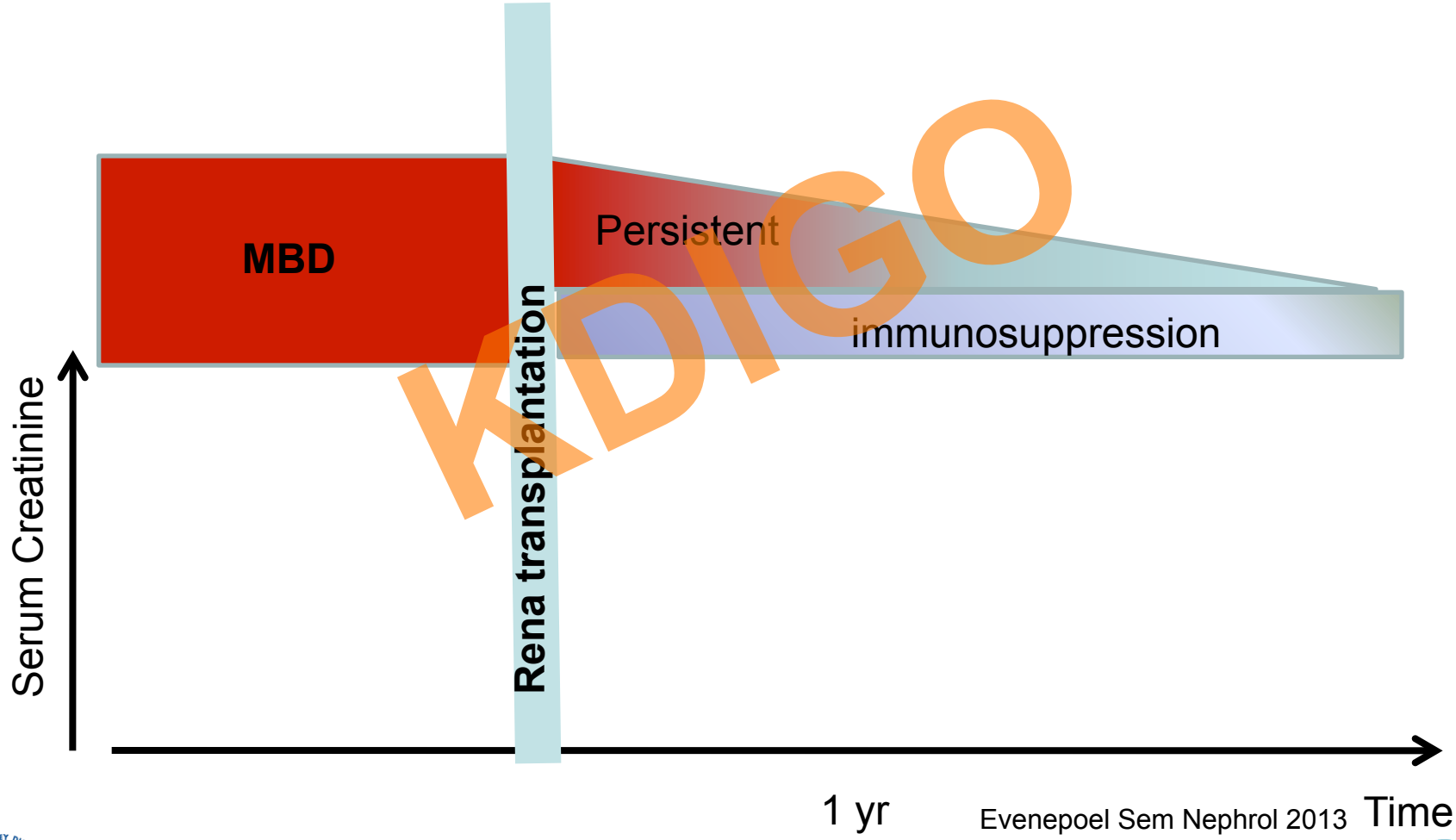




Evenepoel, unpublished data



Posttransplant CKD-MBD



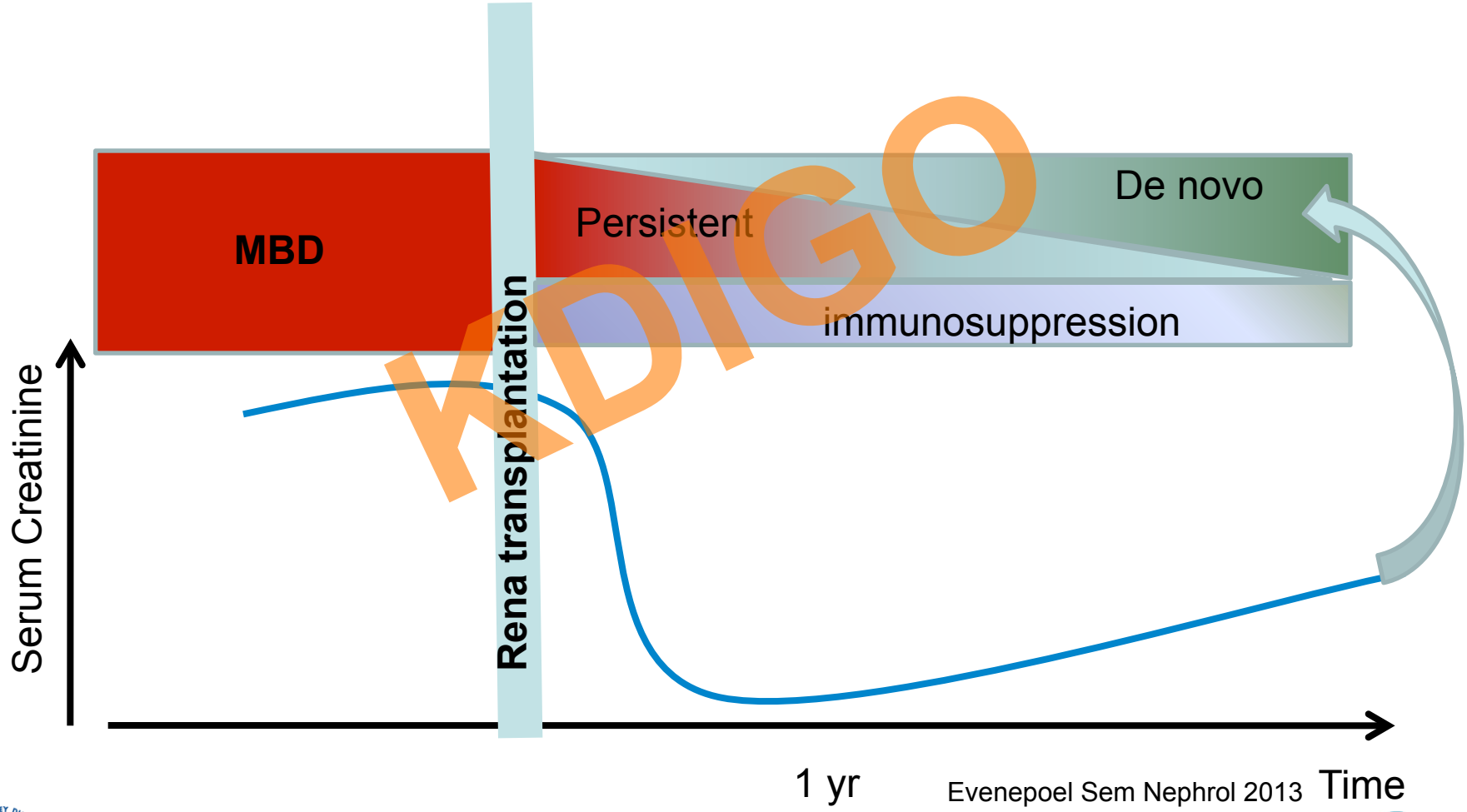
Evenepoel Sem Nephrol 2013

Immunosuppressives & bone and mineral metabolism

Immunosuppressive Agent	Effect on Bone Mineral Metabolism
Glucocorticoids	Effect on osteoblasts: decreases bone formation by inducing apopotosis, inhibiting function, and decreasing collagen synthesis. Effect on osteoclasts: increases bone resorption through osteoclast activation by upregulation of RANKL/ OPG; systemic effects include decreased gastrointestinal absorption of calcium, increased renal calcium wasting (hypogonadism, myopathy, avascular necrosis)
Calcineurin inhibitors	Controversial effect: in vitro appears to inhibit bone resorption; in vivo appears to increase bone resorption, leading to bone formation; promote renal Mg leak; promote calciuria
Mycophenolate mofetil	No effect
Azathioprine	No effect
Sirolimus	Controversial effect; in vitro appears to inhibit osteoclast differentiation; promotes renal phosphate leak
Evirolimus	Controversial effect; in vitro appears to inhibit osteoclast formation, activity, and differentiation

Adapted from Alshayeb et al. AJKD 2013

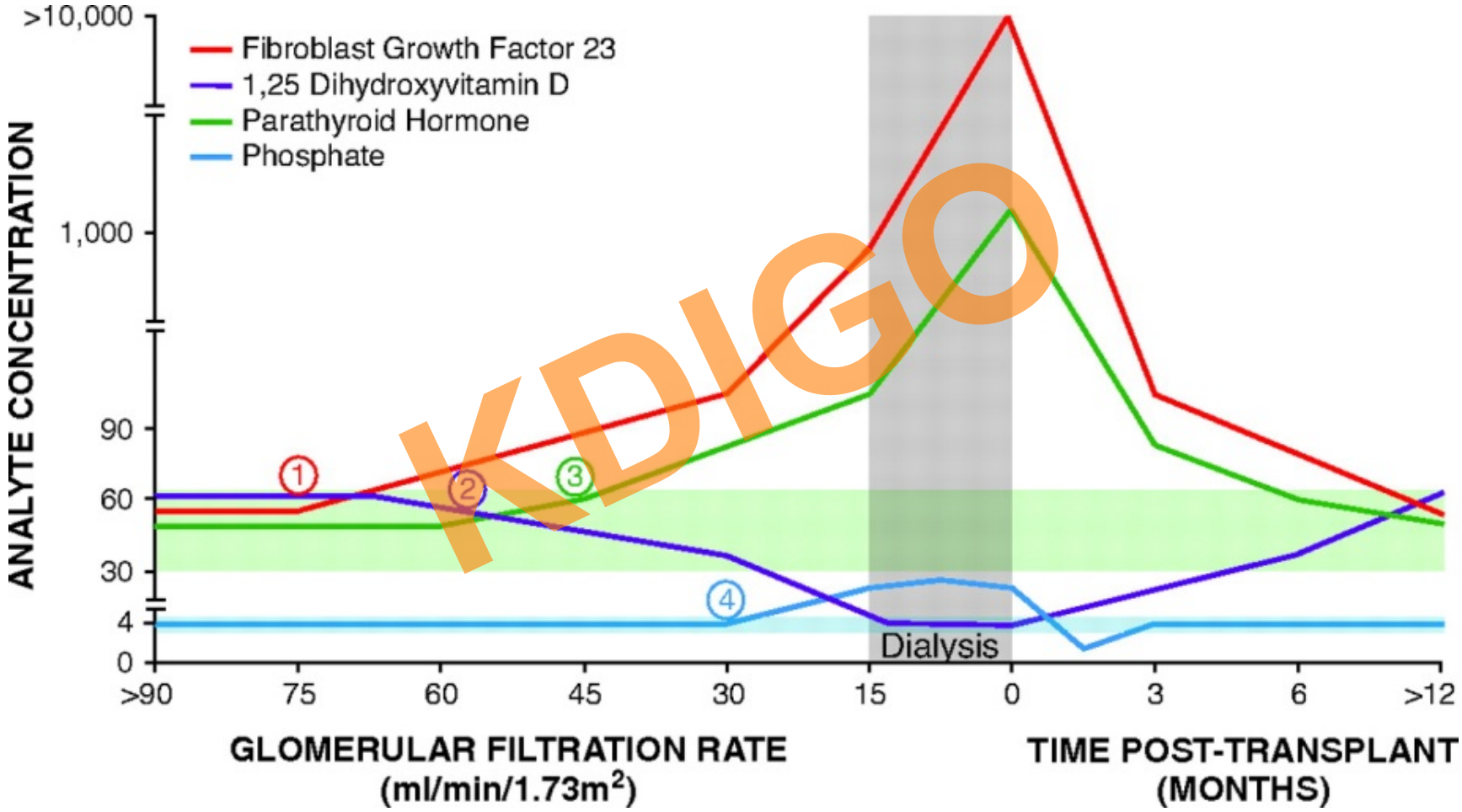
Posttransplant CKD-MBD



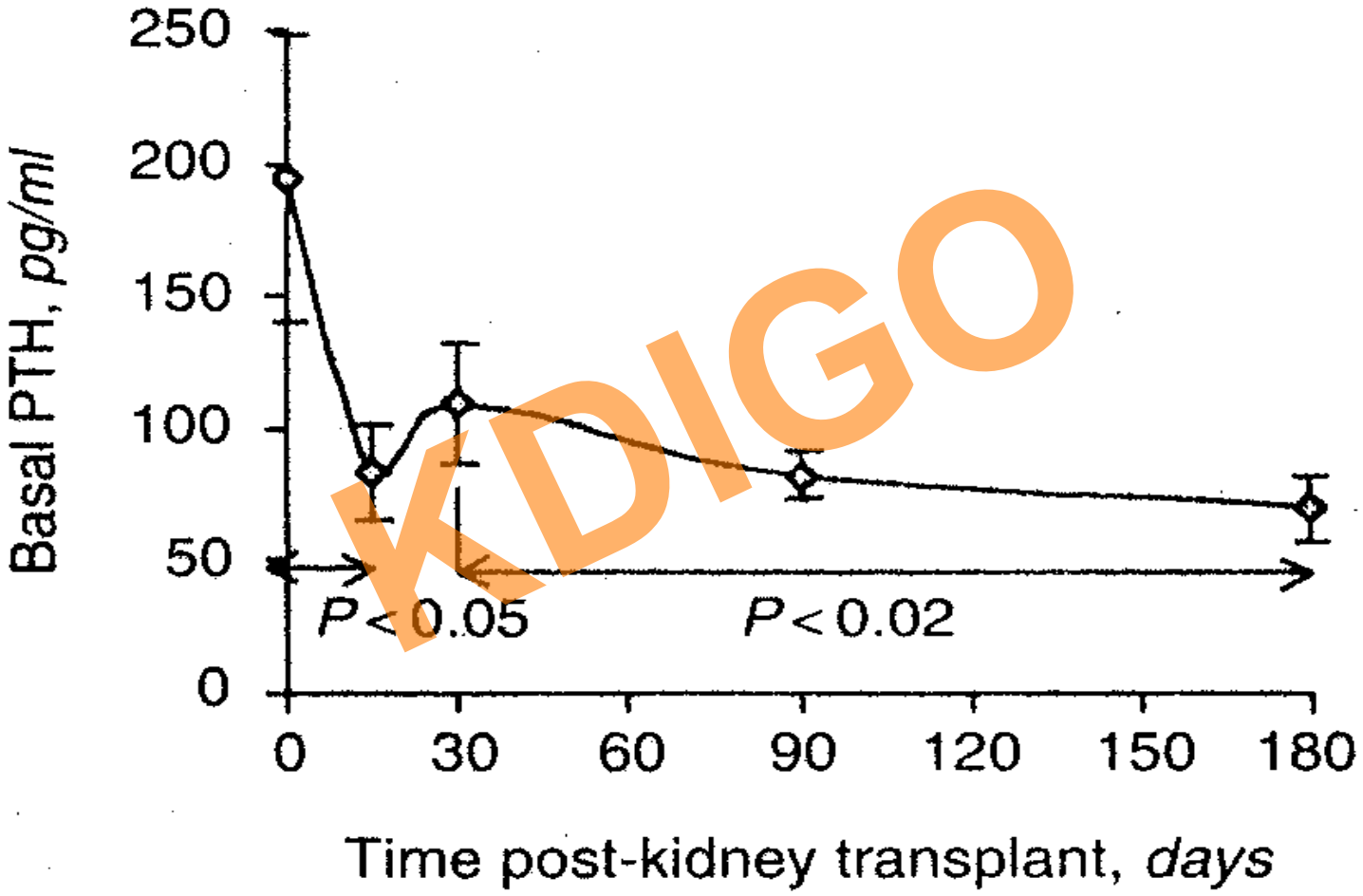
Posttransplant CKD-MBD

- Laboratory abnormalities
- Bone disease
- Vascular calcification
- Treatment

Lab abnormalities

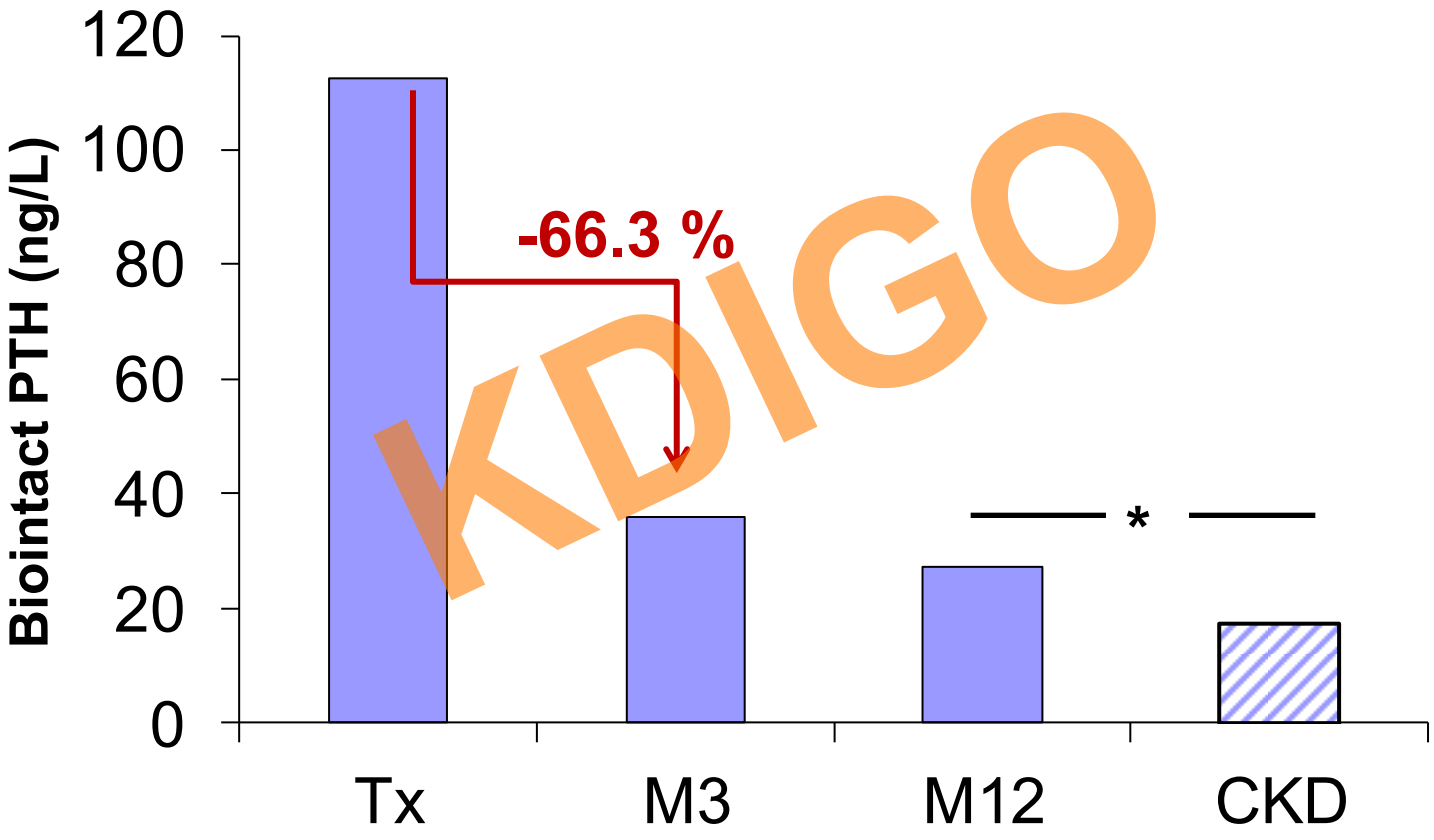


PTH



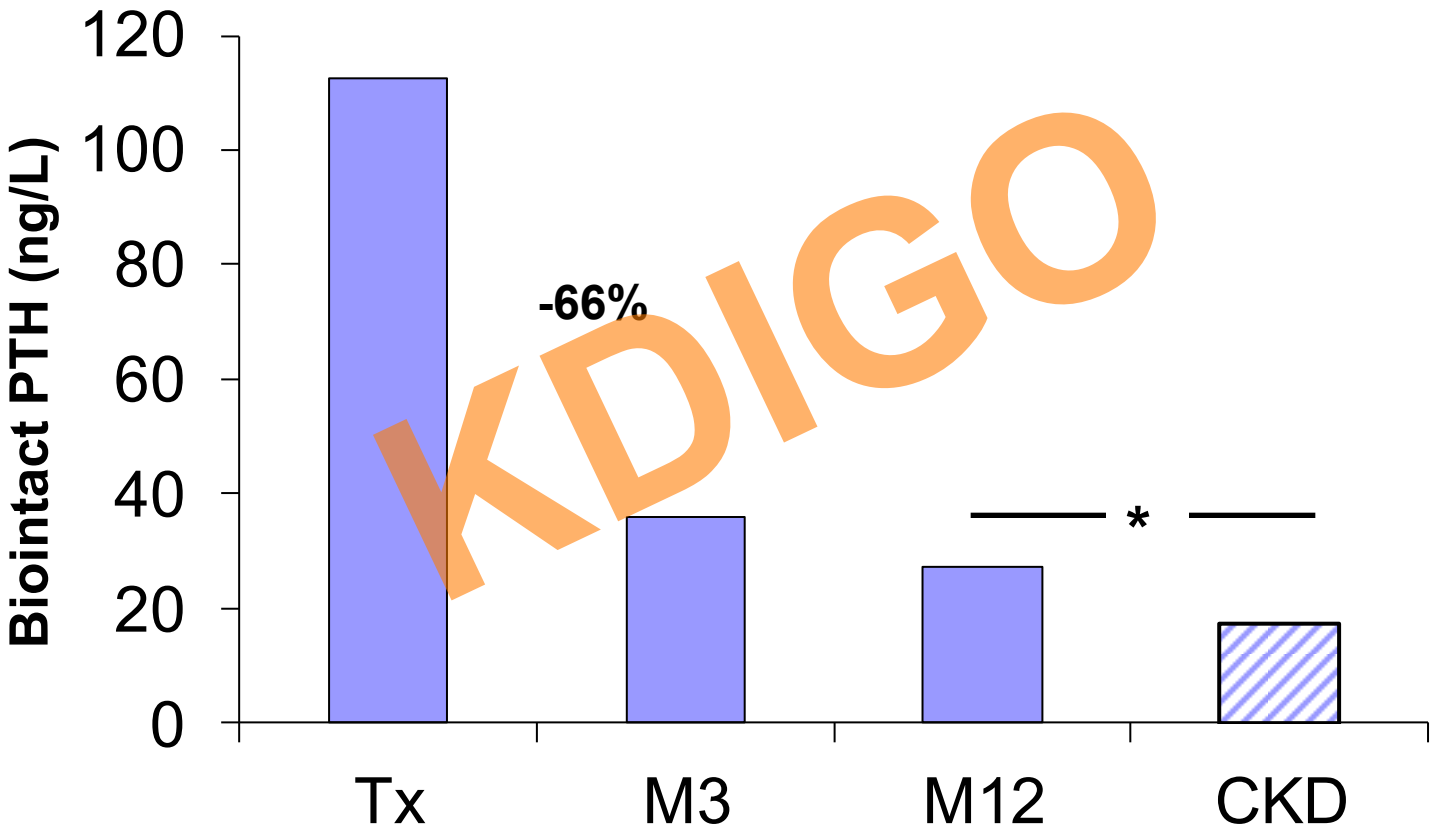
Bonarek *et al*. KI 1999 (n=11)

PTH



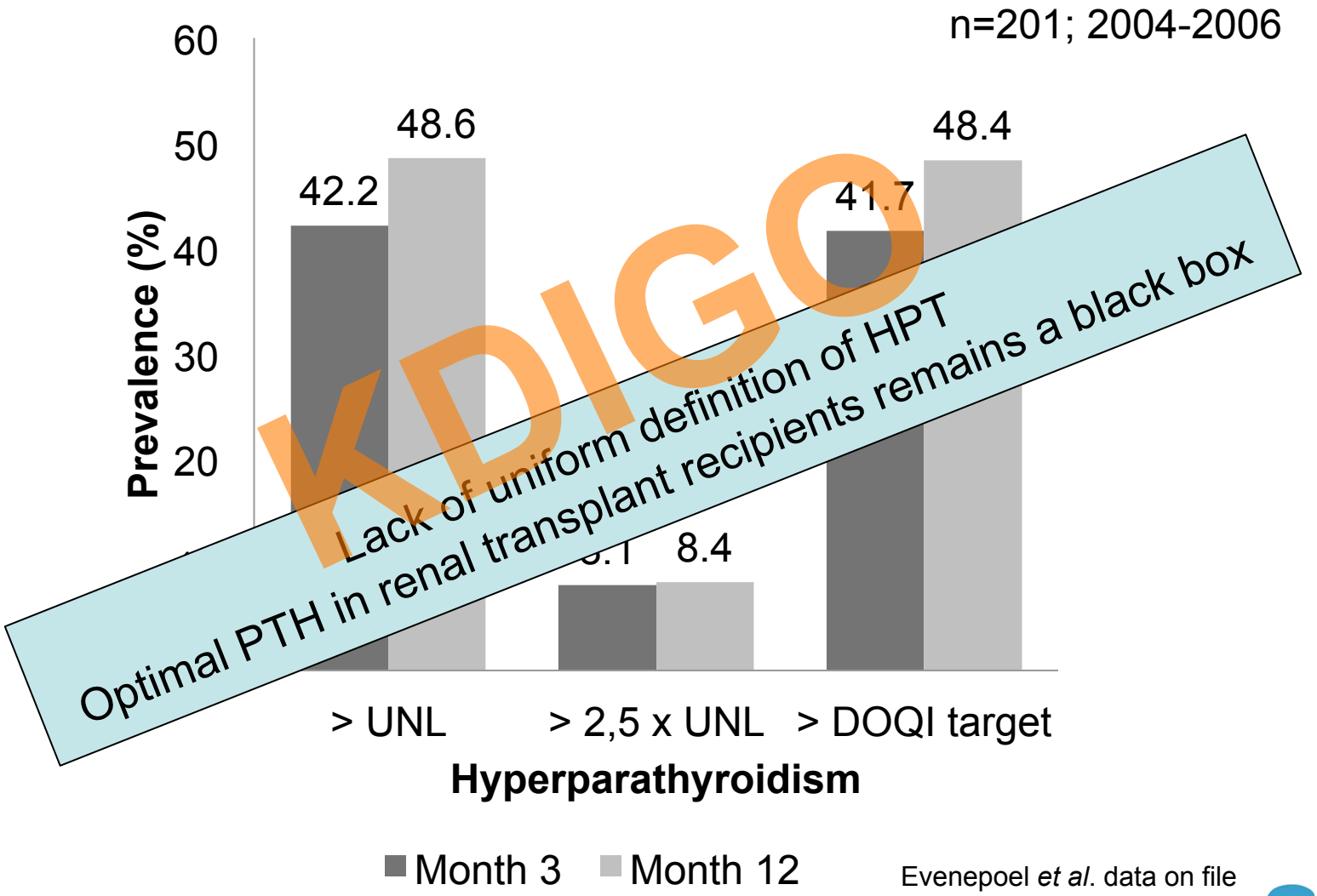
Evenepoel *et al*. Clin J Am Soc Nephrol. 2008 Nov;3(6):1829-36.

PTH



Evenepoel *et al*. Clin J Am Soc Nephrol. 2008 Nov;3(6):1829-36.

Posttransplant HPT: prevalance



Evenepoel *et al*. data on file

Pathophysiology of persistent/inappropriate HPT

- Regression of parathyroid hyperplasia is a time-consuming process (low cell turnover and long life span of parathyroid cells)
- Clonal (autonomous) growth: less sensitive to normal feed-back mechanisms
- Low/inappropriate low level of 25(OH)VitD and $1,25(OH)_2$VitD

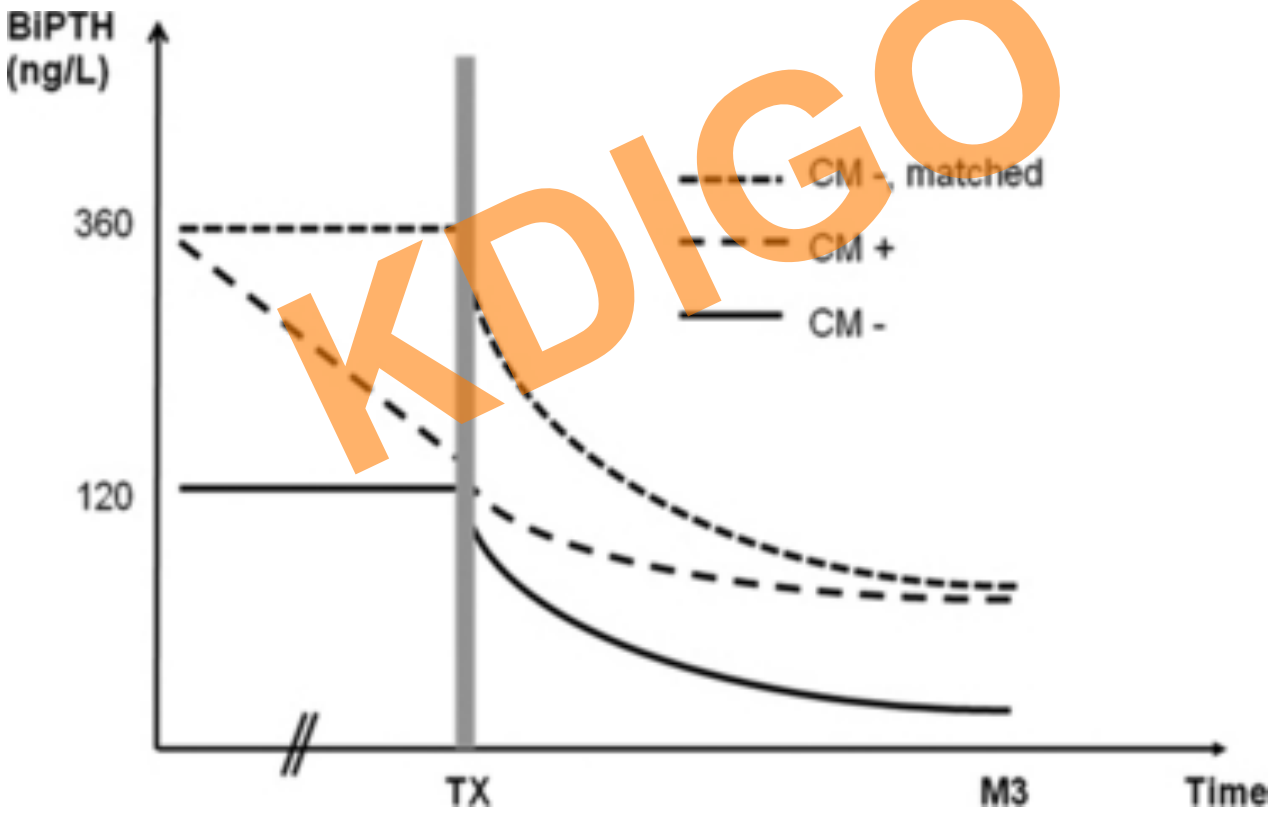
Risk factors for persistent/inappropriate HPT

- At time of transplantation:
  - Severe HPT as evidenced by high pre-transplant serum level of iPTH, calcium, phosphorus and alkaline phosphatases or therapy with cinacalcet
  - Long dialysis vintage
  - Vit D receptor polymorphisms (bb>BB)?

Torres *et al.* NDT 1998;suppl3:94-97
Evenepoel *et al*. NDT 2004;19:1281-7
Reinhardt *et al*. NDT 1998;13:436-442
Messa *et al.* Kidney Int 1998;54:1704-13
Evenepoel *et al* Clin Transplant 2012
Torregrossa *et al* Transplant Proc 2009
Certow et al. Clin Transplant 2000

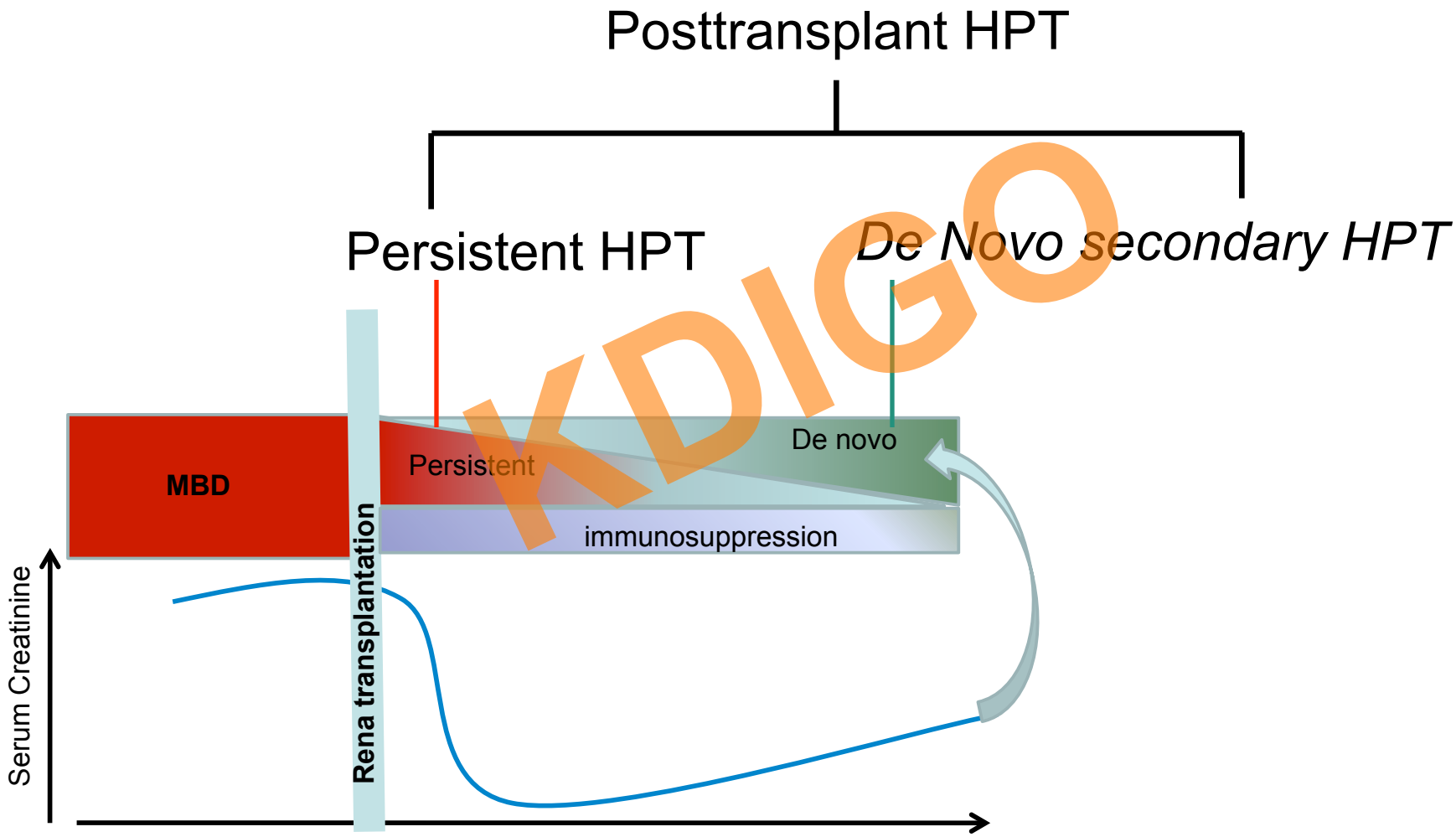
Risk factors for persistent/inappropriate HPT

Mineral metabolism in renal transplant recipients discontinuing cinacalcet at the time of transplantation: a prospective observational study



Evenepoel *et al.* Clin Transplant 2012

Posttransplant HPT



Posttransplant *de novo* sHPT

Posttransplant HPT

Persistent HPT

De Novo secondary HPT

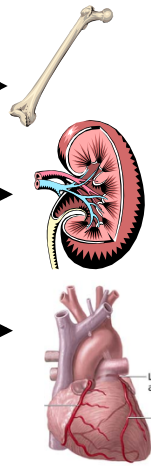
Appropriate

-To overcome endorgan resistance
-To maintain normophosphatemia
-To maintain normocalcemia

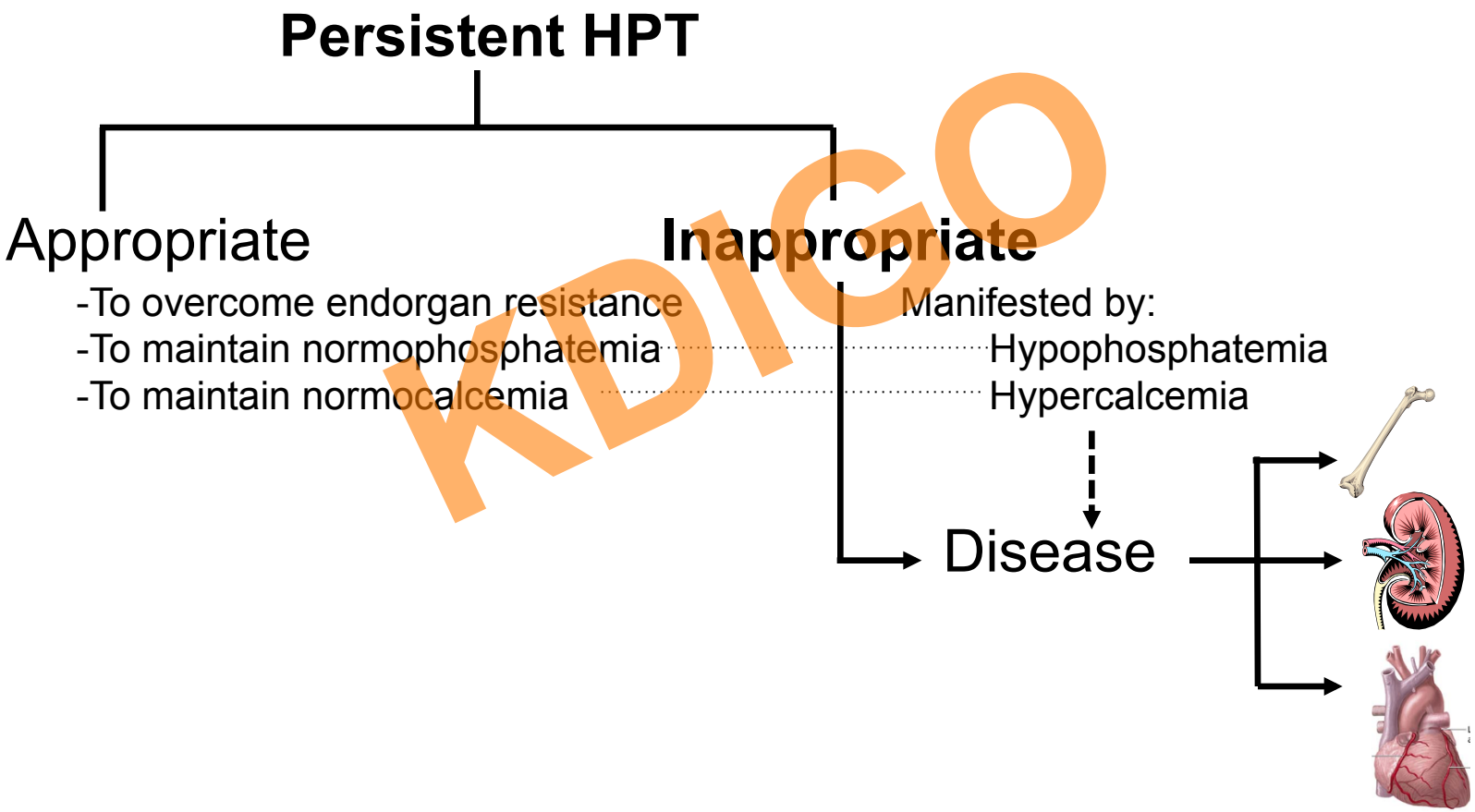
Inappropriate

?

Disease



Posttransplant persistent HPT



Posttransplant HPT & hypophosphatemia

Persistent HPT

Appropriate

-To overcome endorgan resistance
-To maintain normophosphatemia
-To maintain normocalcemia

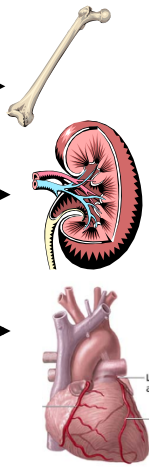
Inappropriate

Manifested by:

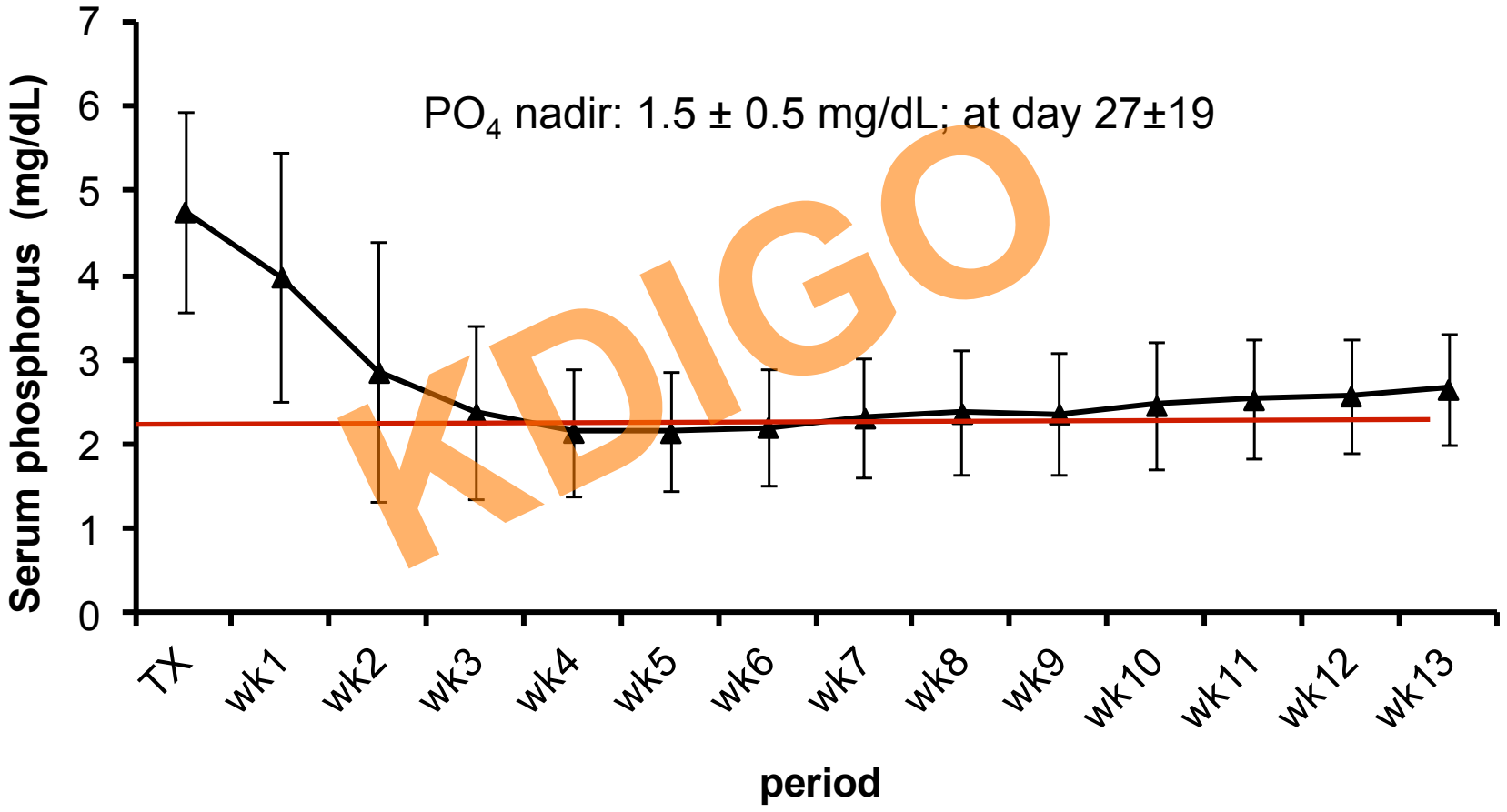
Hypophosphatemia

Hypercalcemia

Disease



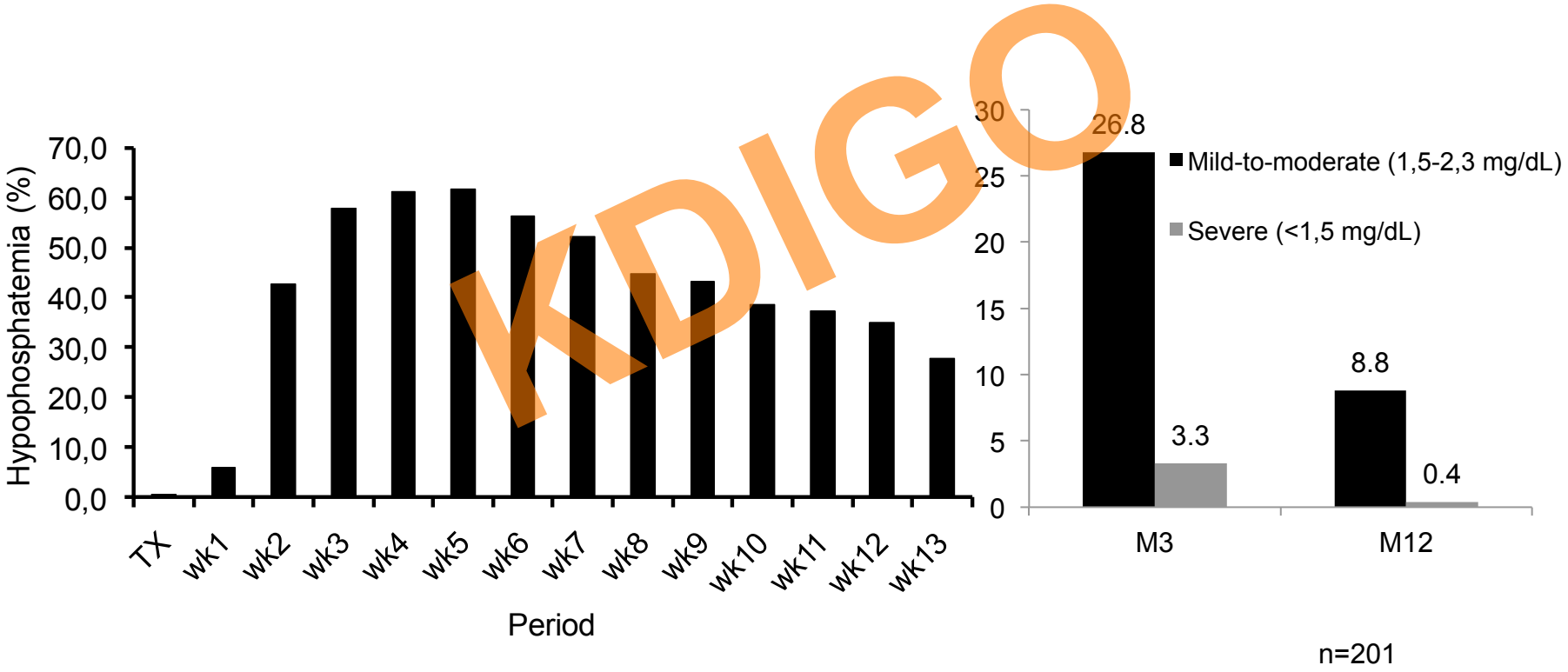
Phosphorus



Evenepoel et al. CJASN 2009

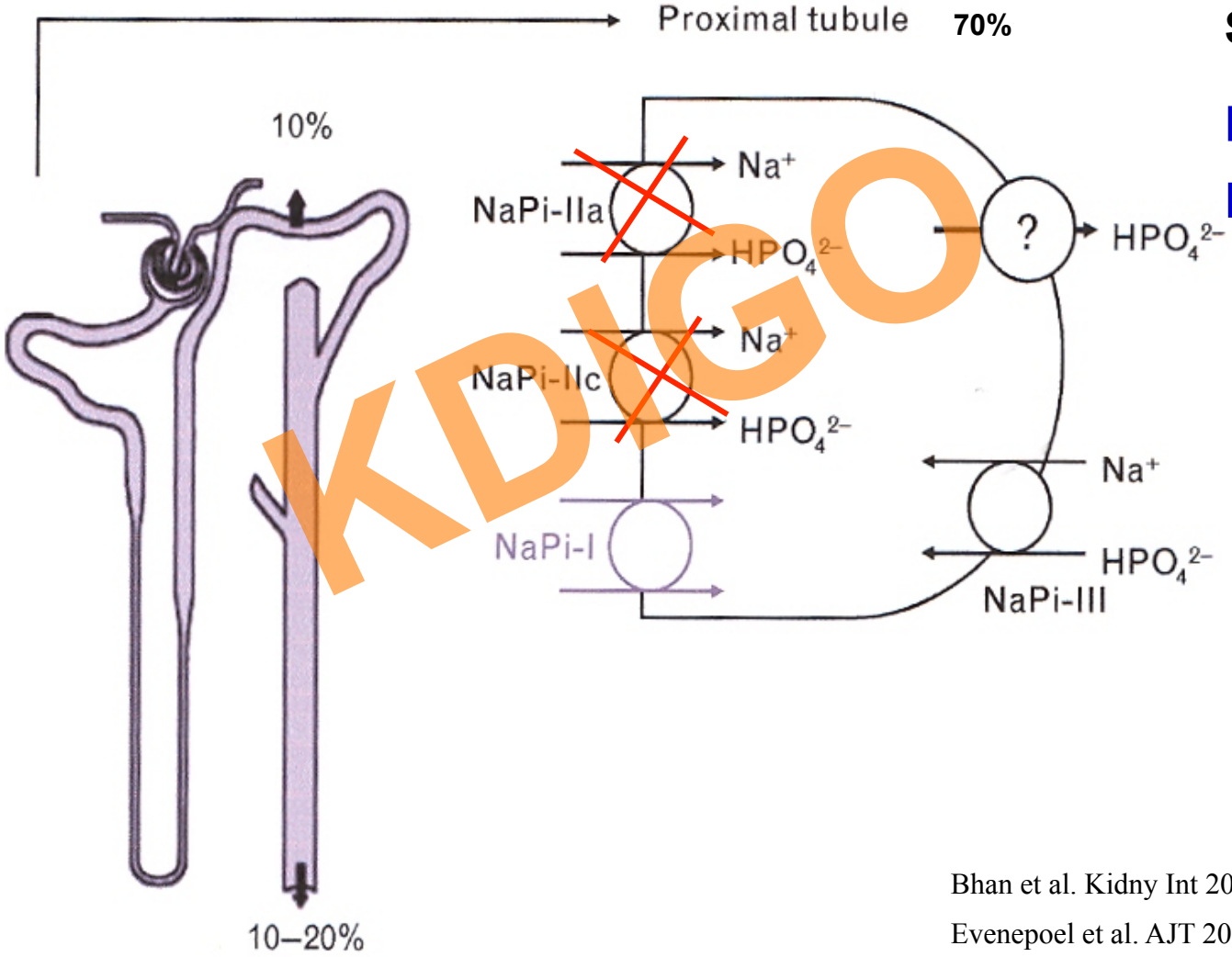
Hypophosphatemia: prevalence

Hypophosphatemia, defined as PO_4 < 2.3 mg/dL (0.74 mmol/L)



Evenepoel et al. CJASN 2008; Evenepoel data on file

Renal Phosphorus leak



Synergism

PTH

FGF23

Bhan et al. Kidny Int 2006

Evenepoel et al. AJT 2007

Posttransplant HPT & hypercalcemia

Persistent HPT

Appropriate

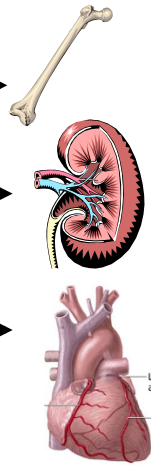
- To overcome endorgan resistance
- To maintain normophosphatemia
- To maintain normocalcemia

Inappropriate

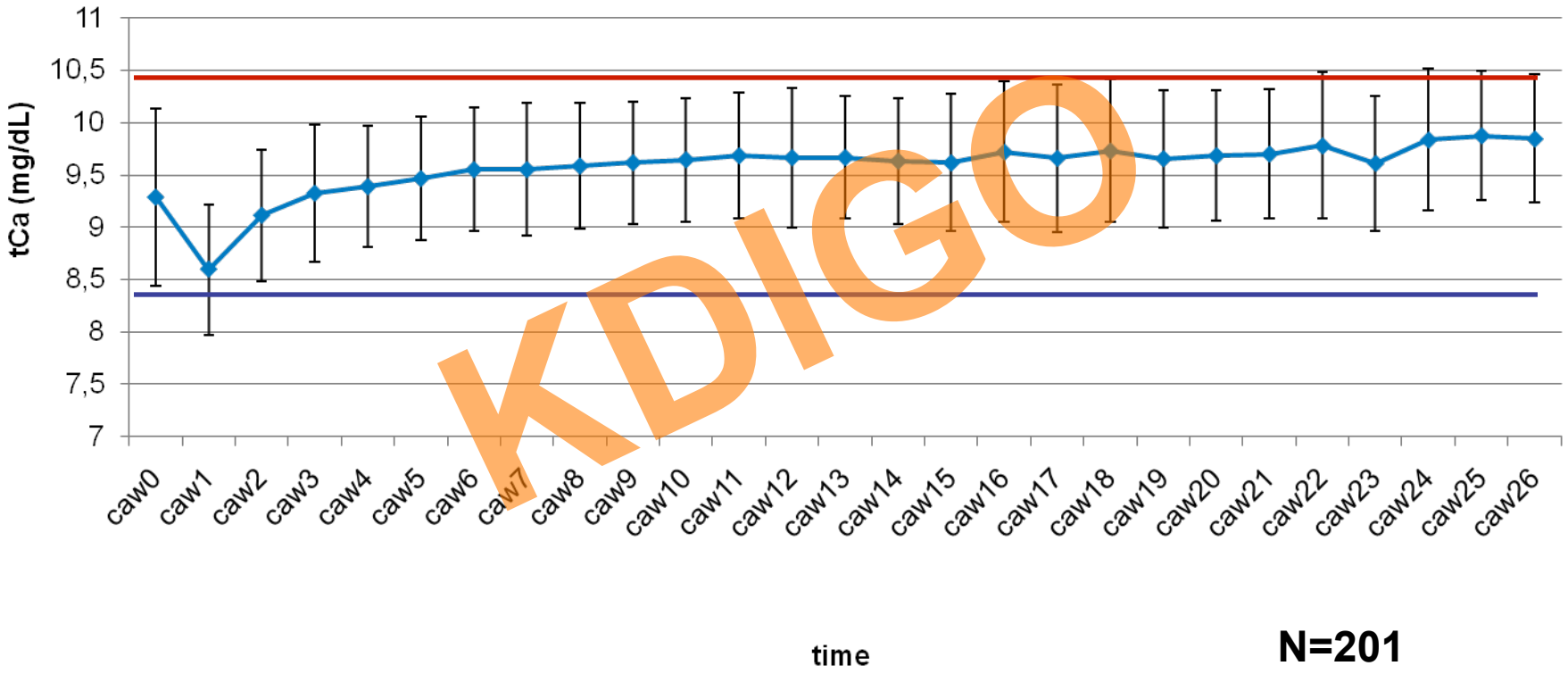
Manifested by:

- Hypophosphatemia
- **Hypercalcemia**

→ Disease



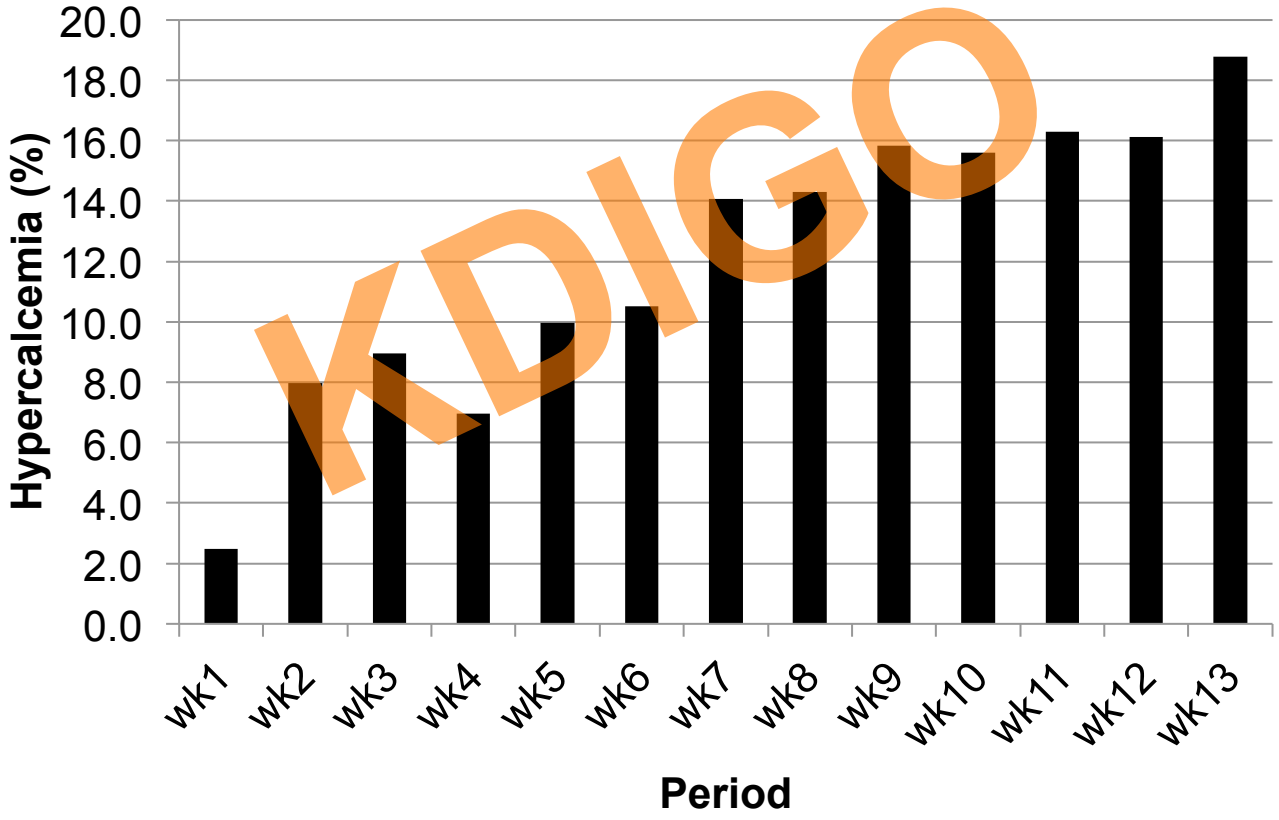
Calcium



Evenepoel et al. CJASN 2009; Evenepoel, data on file

Hypercalcemia: prevalence

Hypercalcemia, defined as Albumin corrected tCa >10.3 mg/dL; n=201



Hypercalcemia: prevalance

Author	era	n	parameter	M3	Yr1	Yr2	Yr3	Yr4
Cundy et al.	‘83	100	tCa>10.5 mg/dL	17	17	11	-	-
Reinhard et al.	‘92-’93	129	tCa>10.5 mg/dL	52	23	10	-	-
Evenepoel et al.	‘89-’00	1165	tCa>10.5 mg/dL	-	31	23	23	15
Egbuna et al.	‘96-’03	301	tCa>10.2 mg/dL	9	9	-	-	
Evenepoel et al.	‘04-’06	201	tCa>10.3 mg/dL	13				

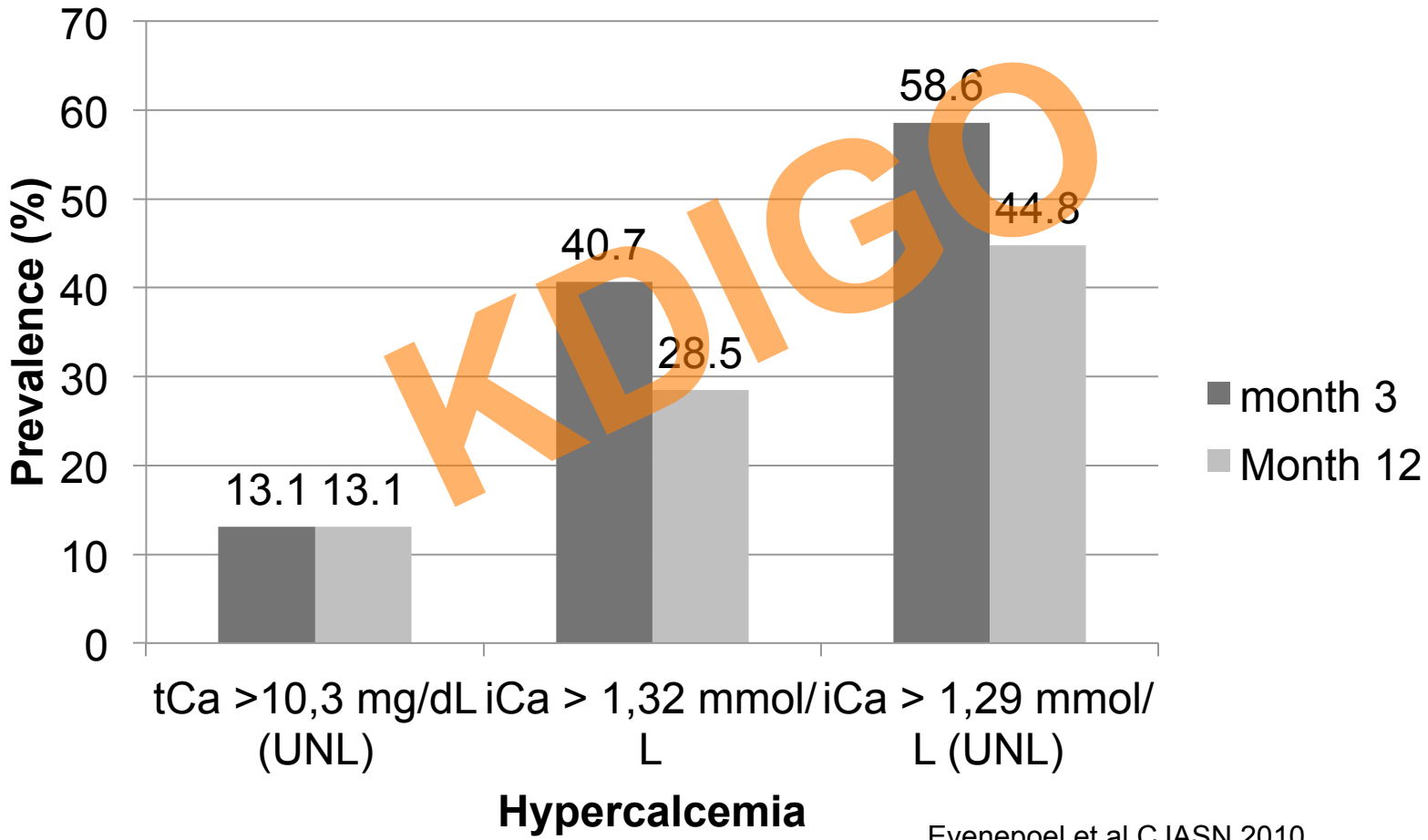
Wide variation:

- Differences in diagnostic criteria
- Differences in interval since transplantation
- Differences in study era (e.g. before and after K/DOQI guidelines on mineral metabolism)

Cundy et al. QJM 1983; Egbuna et al. Clin transplant 2007; Reinhardt et al. NDT 1998; Evenepoel et al. NDT 2004; Evenepoel et al. CJASN 2009

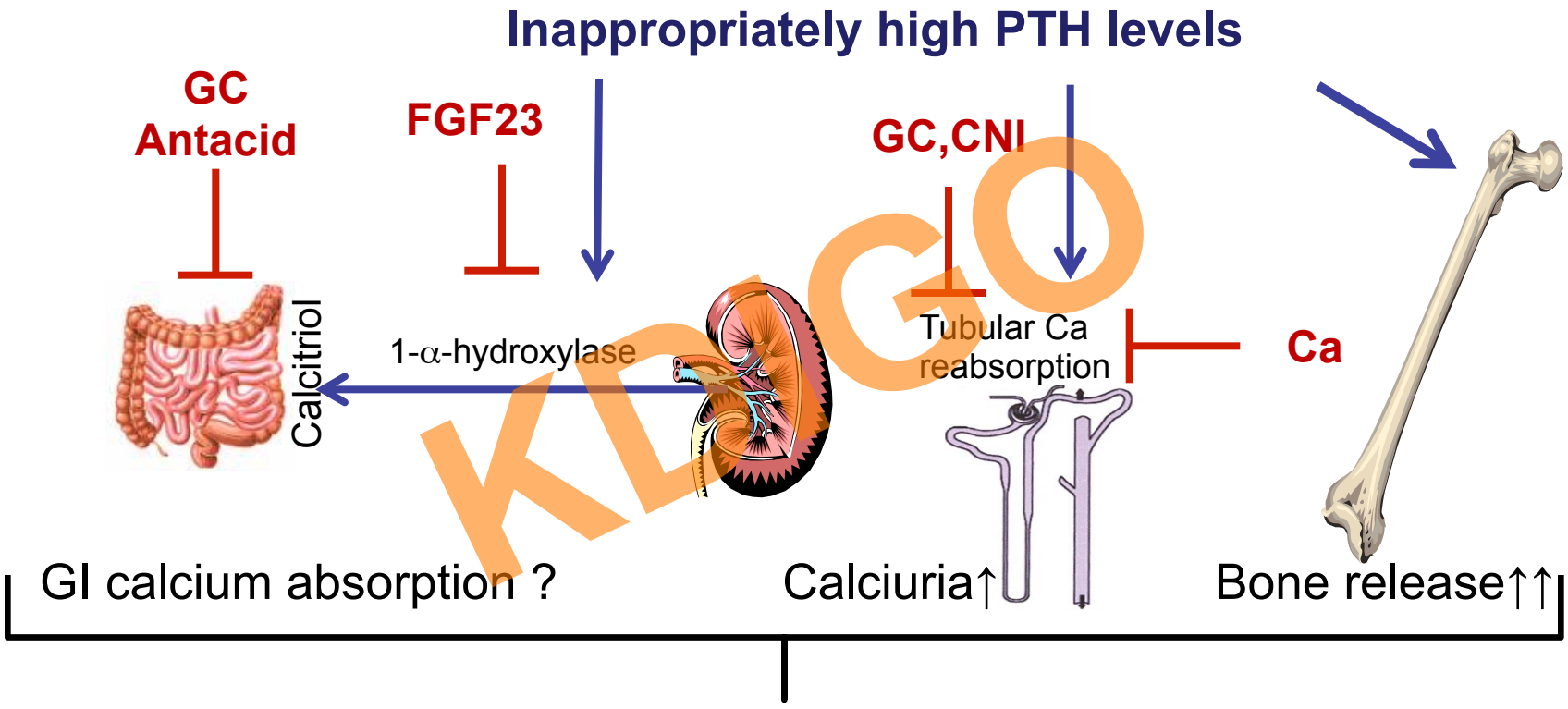
Hypercalcemia: diagnostic criteria

tCa underestimates "true" hypercalcemia



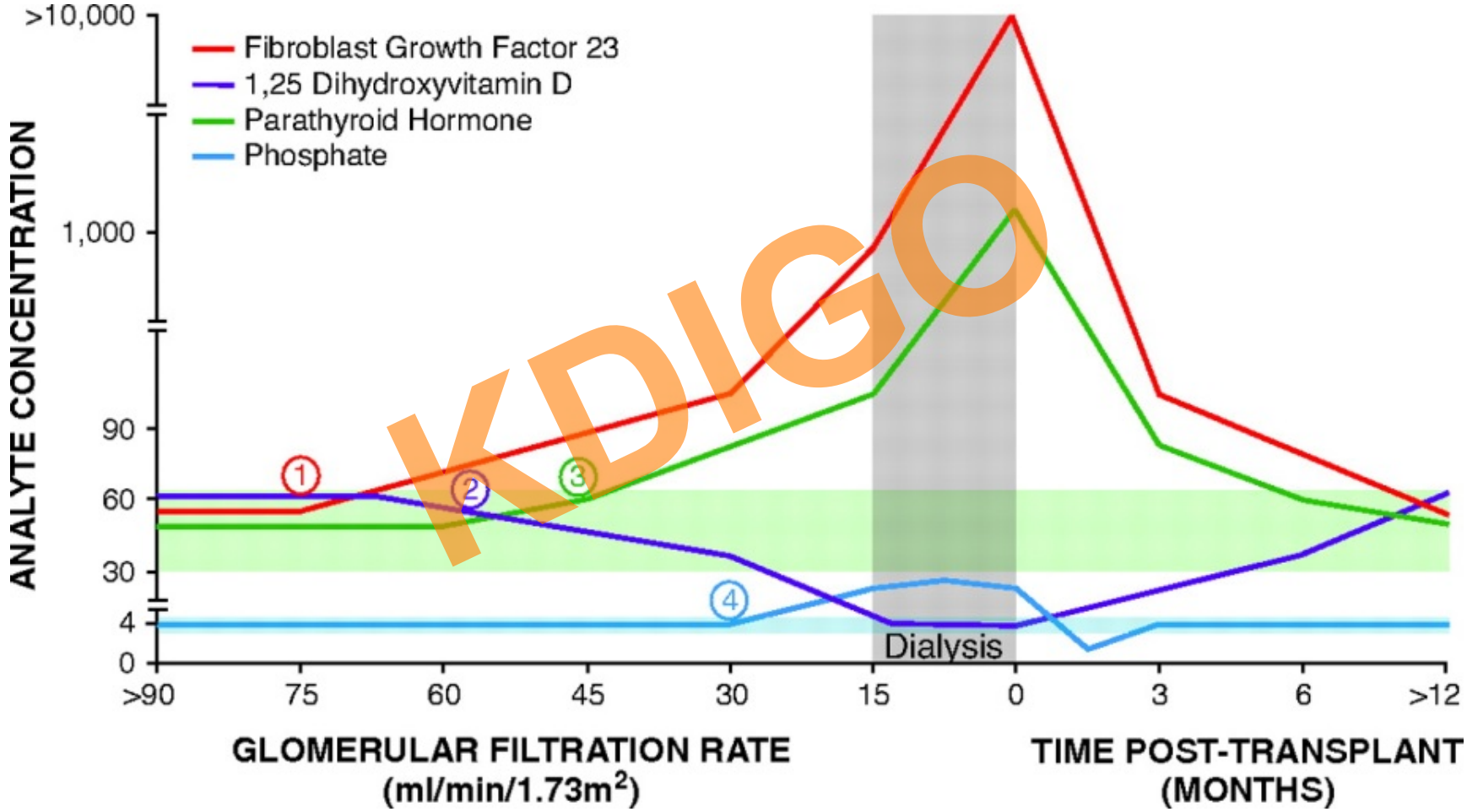
Evenepoel et al CJASN 2010

Posttransplant calcium metabolism/balance

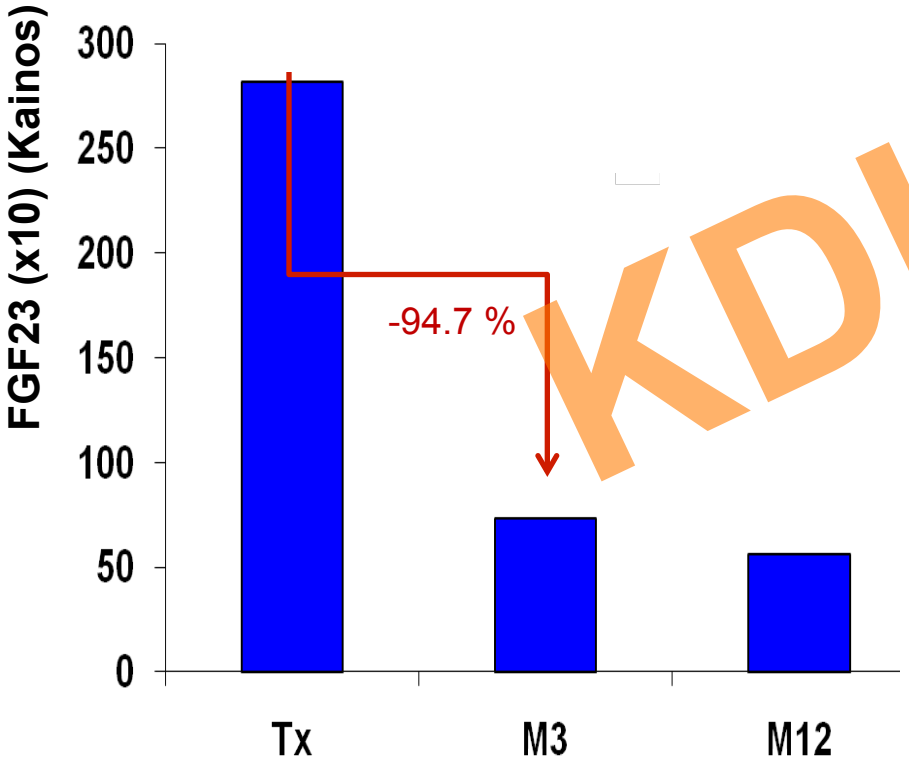


Evenepoel et al. CJASN 2009
Lee et al AJN 2011

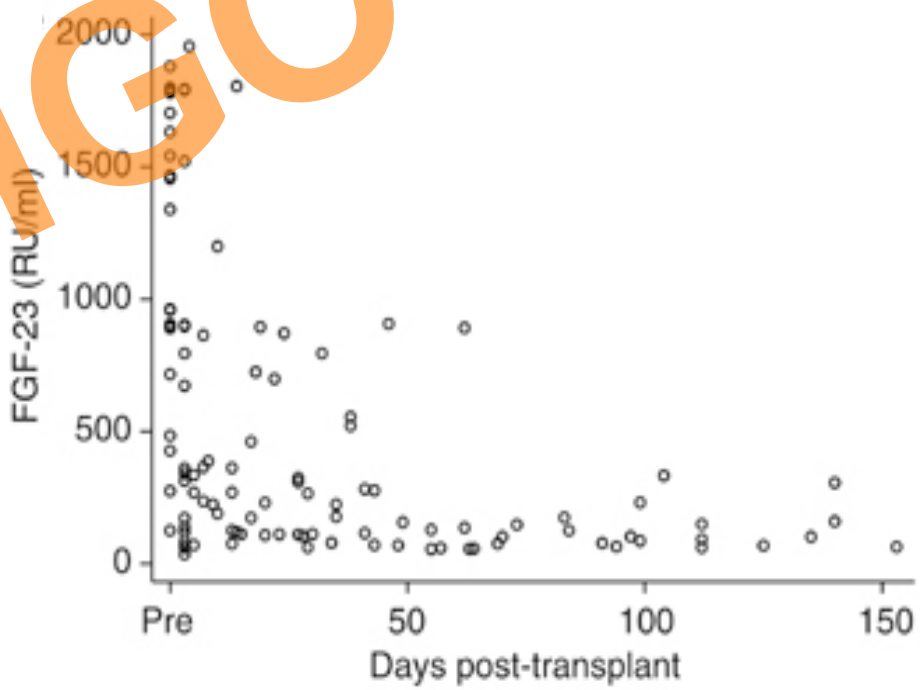
Lab abnormalities



FGF-23

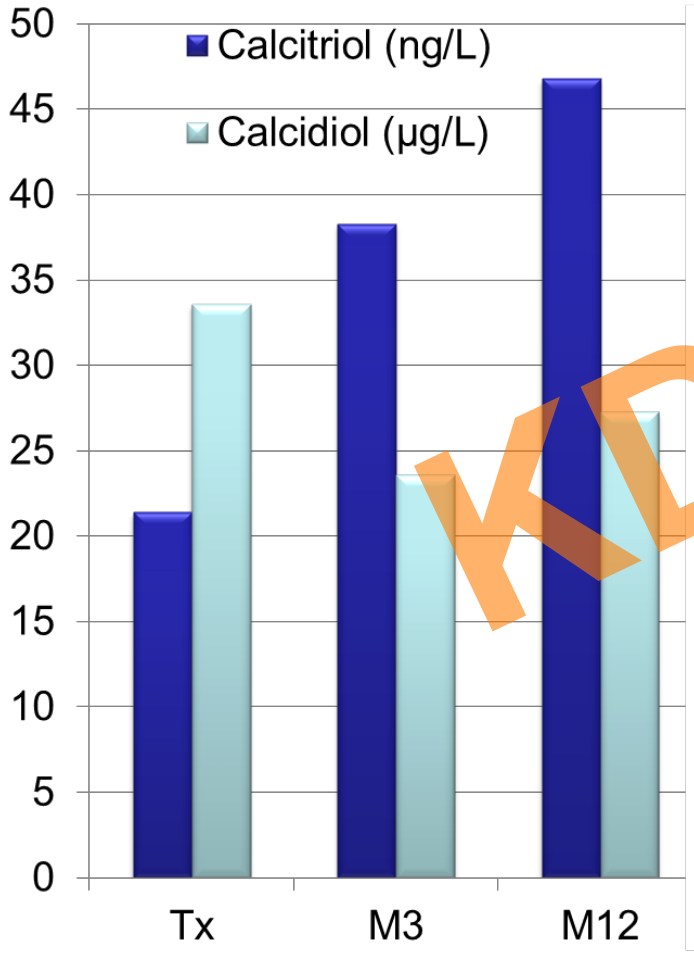


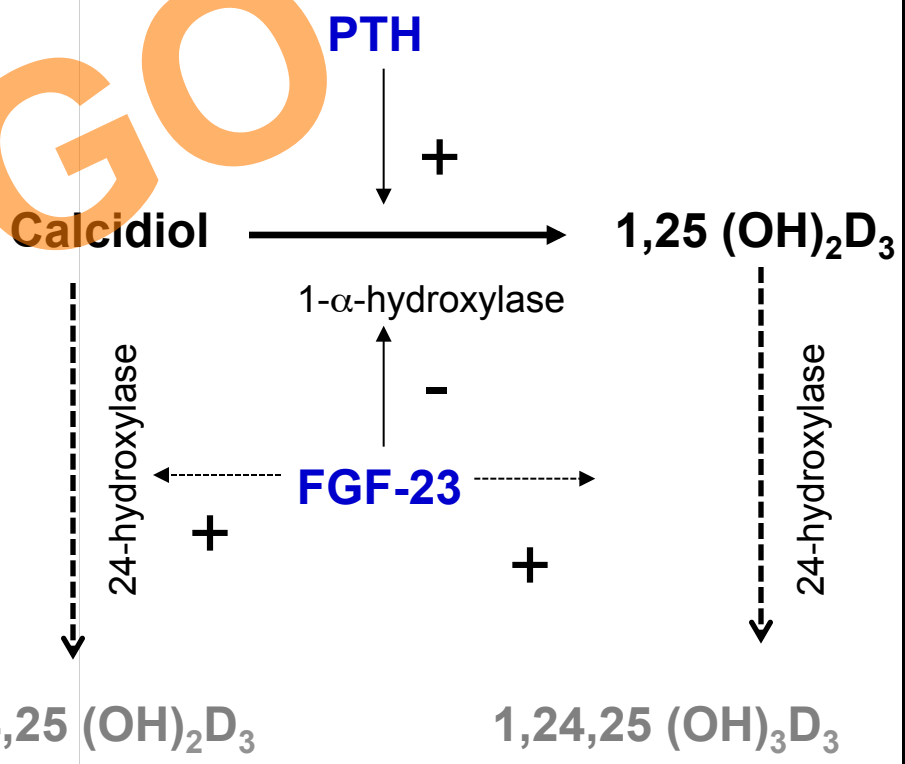
Evenepoel *et al*. cJASN 2008
Evenepoel et al. AJT 2007



Bhan *et al*. Kidney Int 2006

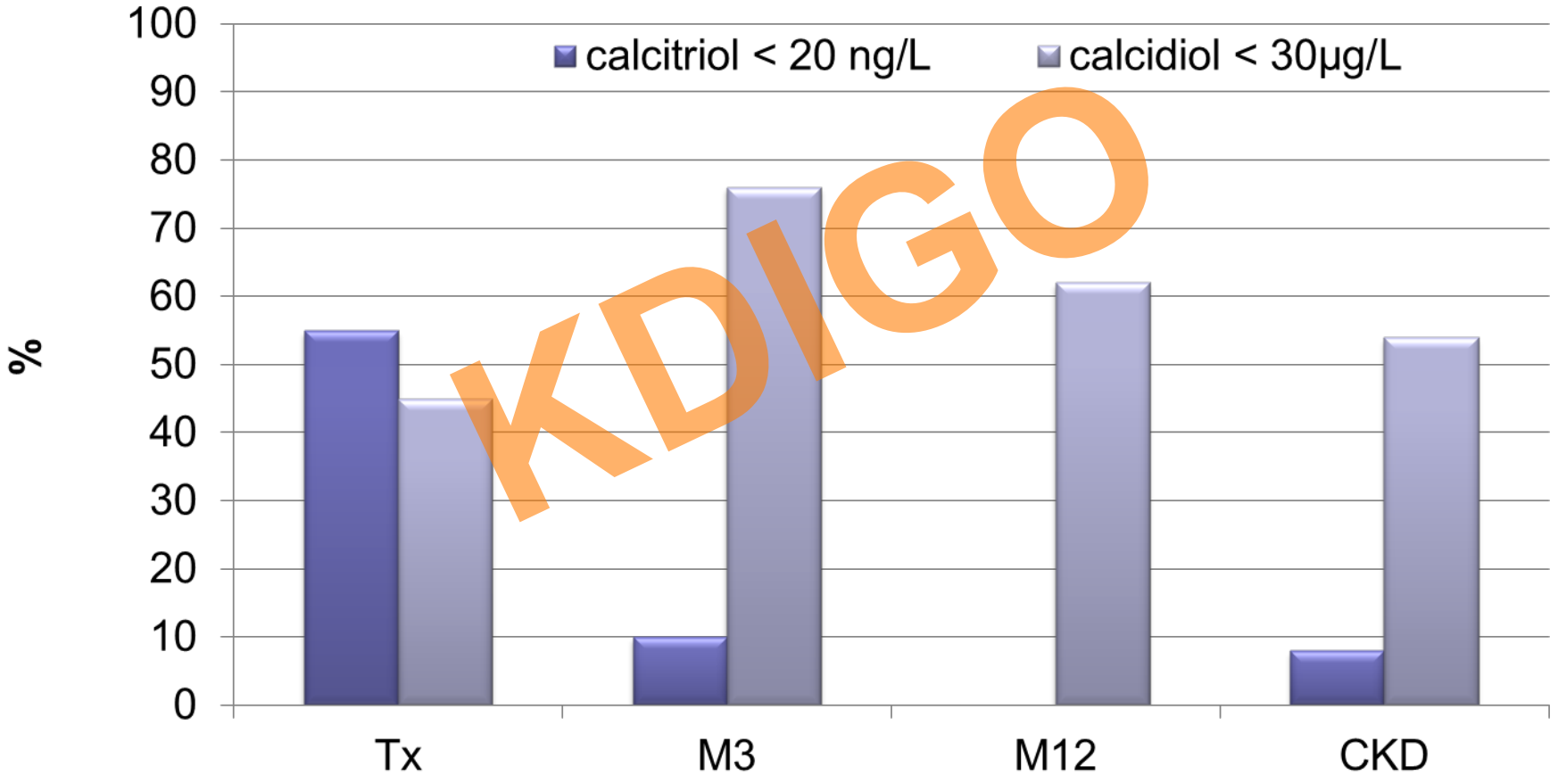
Vitamin D





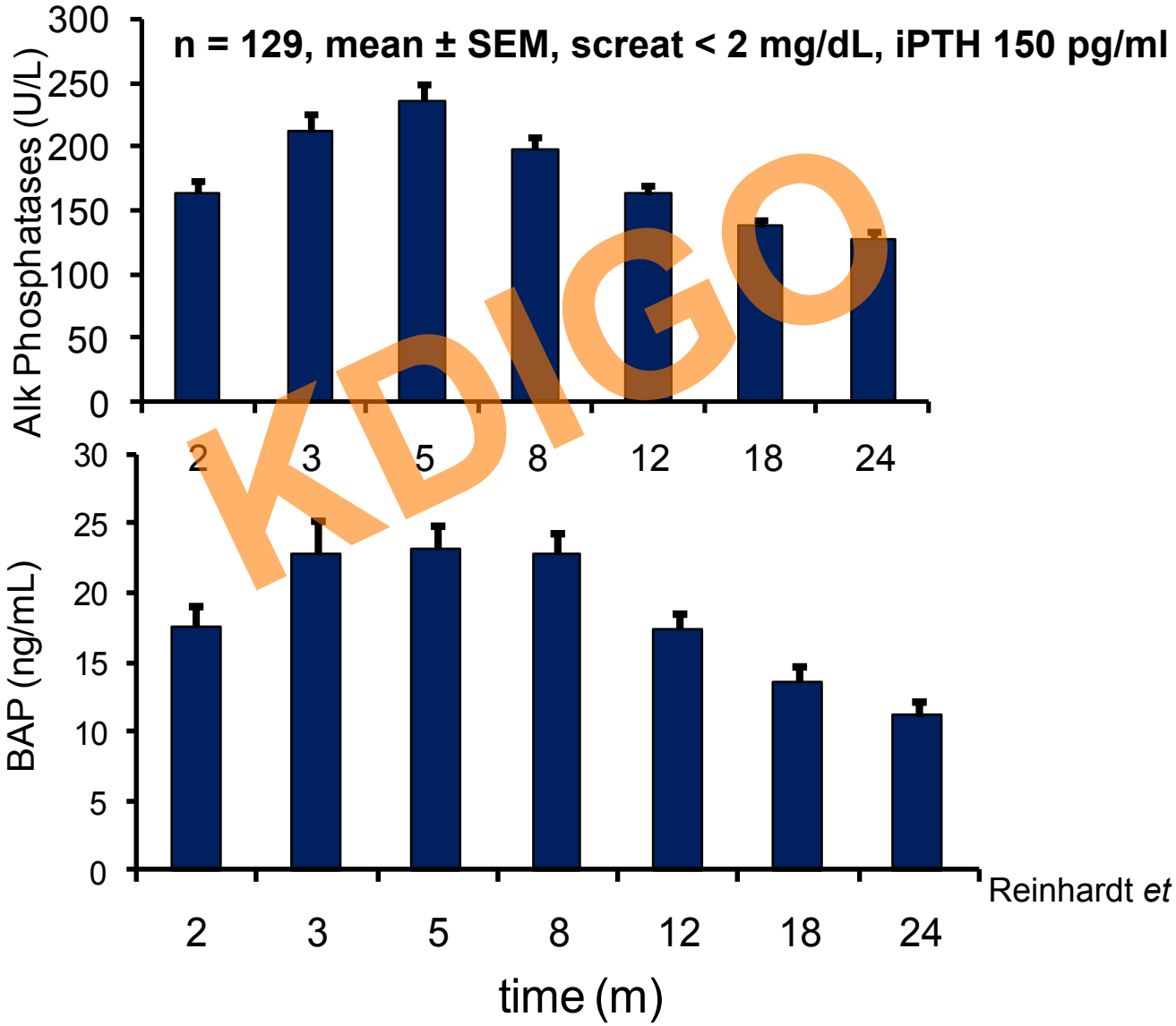
Wesseling-Perry Pedr Nephrol 2013
Evenepoel CJASN 2008 2007

Vitamin D



Evenepoel *et al.* CJASN 2008

Alkaline Phosphatases

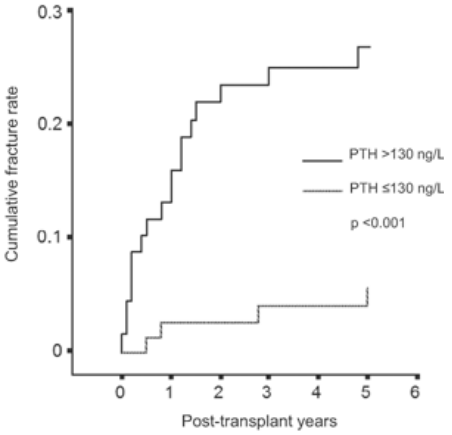


Reinhardt *et al.* NDT 1998

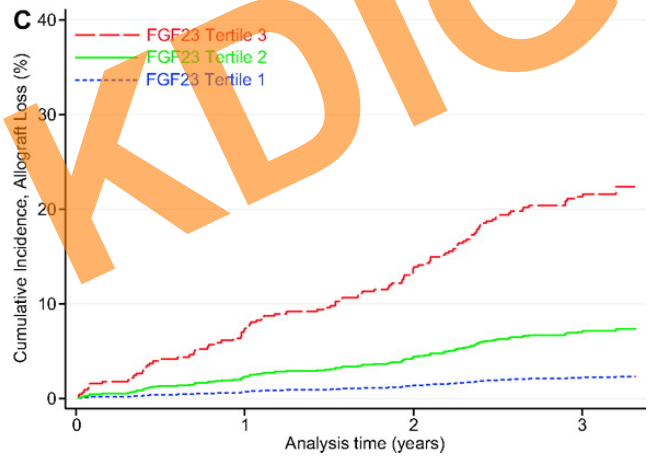
Lab abnormalities and patient-level outcomes

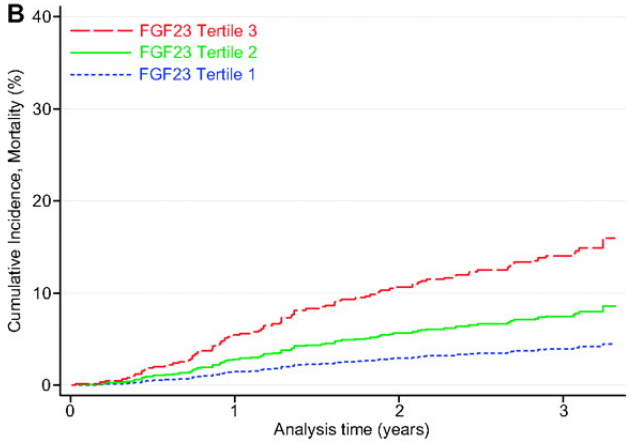
Observational data, associations:

	Fractures	Graft survival	CVD	Patient survival
PTH	pos [1, 2, 6]	0 [3,7]	Pos: IMT[4], arterial stiffness[5]	0 [3,7]
FGF23	?	neg[3]	?	neg[3]



1. Perrin et al. AJT 2013





3. Wolf et al. JASN 2011

1,Giannini *et al.* JBMR 2010; 2. Perrin et al. AJT 2013; 3. Wolf et al. JASN 2011; 4. Suwelack AJH 2001; 5.Barenbrock Kidney Int 1998; 6. Yamamoto et al. JBMR 2013; 7. Molnar CJASN 2012

Posttransplant CKD-MBD

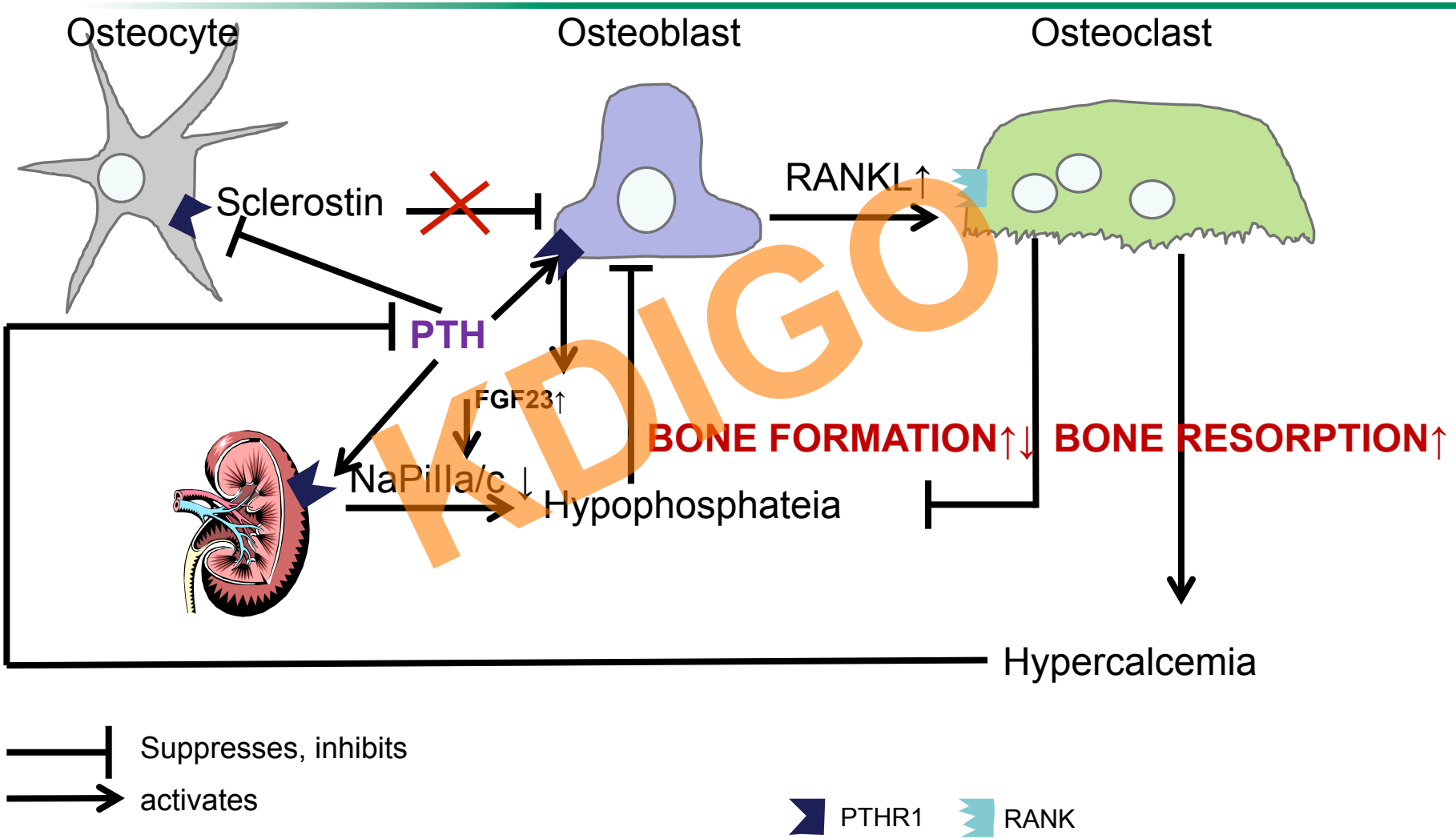
- Laboratory abnormalities
- **Bone disease**
- Vascular calcification
- Treatment

Bone histomorphometry

Author	n	interval	T (H/N/L, %)	M (L, %)	V (L, %)	Main findings
Rojas	20	1-6 m	↓			impaired osteoblastogenesis and early osteoblast apoptosis
Julian	20	6 m	↓		↓	
Rolla	20	8.3 yr	↑	↓		
Monier-Faugere	57	5,6 yr	↓	↓	↓	Gd dose correlates inversely with V and T
Carlini	25	7,5r	↕	↓		High bone resorption, coexisting with a low bone formation rate and delayed mineralisation time (uncoupling of bone resorption and formation)
Lehamn	57	4 yr	↕			
Neves	27	2 yr	26/48/26	48	37	

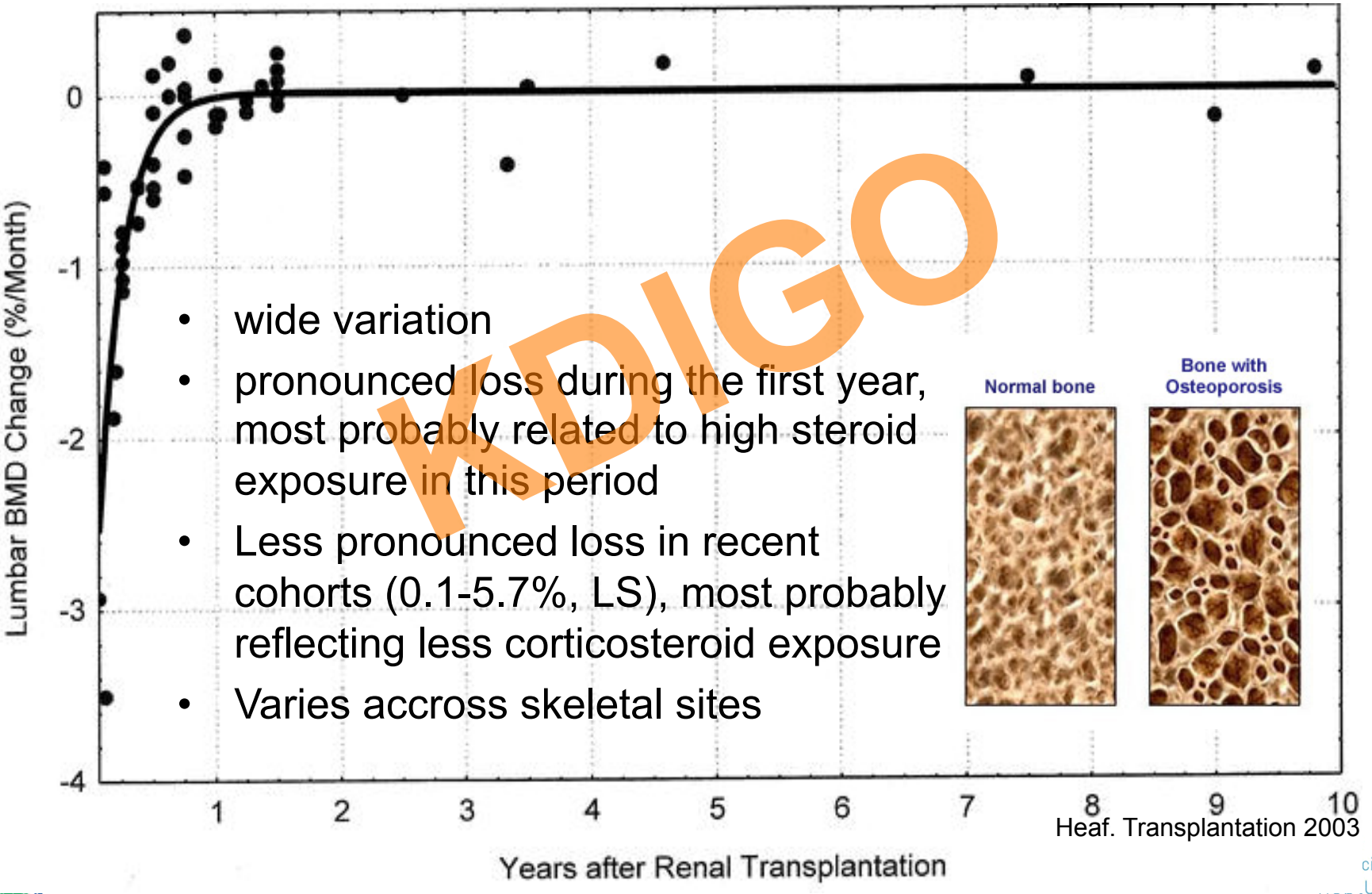
Rojas et al. Kidney Int 2003; Julian et al. NEJM; Rolla et al. Transplantation 2006; Monier-Faugère JASN 2000; Carlini et al. AJKD 2000; Lehmann *et al*. Transplant Proc 2007; Neves et al. Transplantation 2013

Posttransplant bone metabolism



Rojas *et al*., Kidney Int 2003;Evenepoel Sem Nephrol 2013

(a)BMD



- wide variation
- pronounced loss during the first year, most probably related to high steroid exposure in this period
- Less pronounced loss in recent cohorts (0.1-5.7%, LS), most probably reflecting less corticosteroid exposure
- Varies accross skeletal sites

Heaf. Transplantation 2003

Bone abnormalities and patient-level outcomes

	Fractures	Graft survival	Patient survival
Bone histomorphometry	?	?	?
(a)BMD	neg[1]	?	?
Bone biomarker	?	?	?

1. Akaberi *et al.* AJT 2008

Posttransplant CKD-MBD

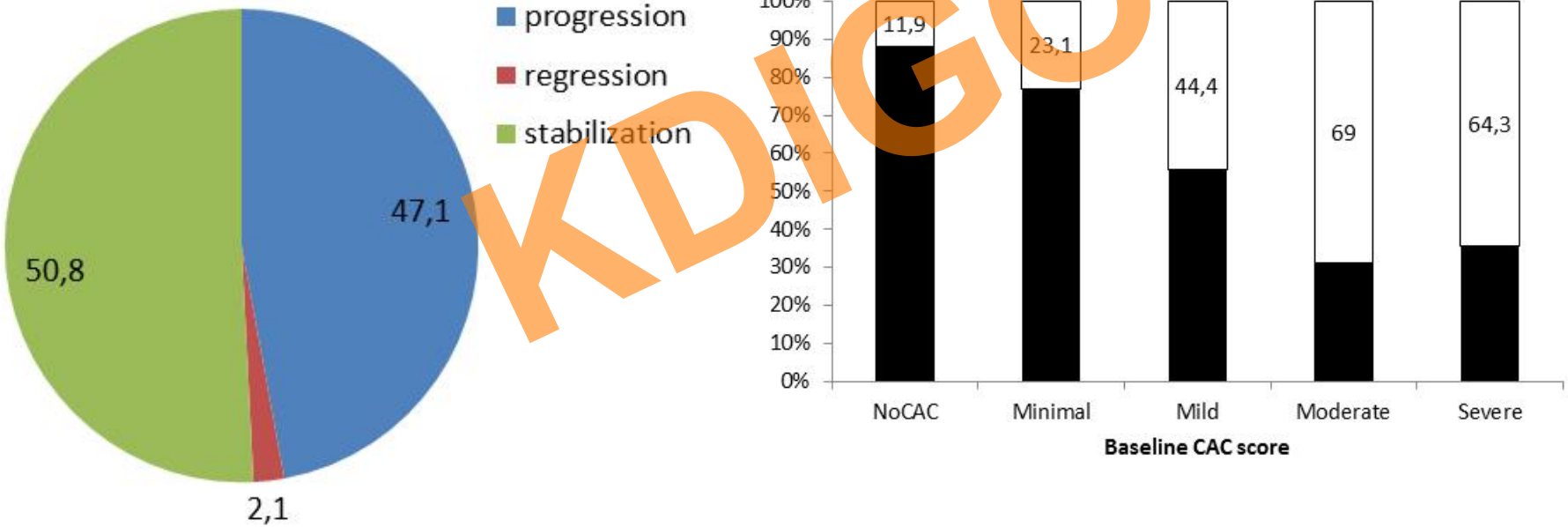
- Laboratory abnormalities
- Bone disease
- Vascular calcification
- Treatment

Vascular calcification

Author/group	Schankel	Mazzoferro	Moe	Oschatz	Seyahi	Bargnoux	Maréchal
n	82	41	23	31	150	83	189
population	incident	prevalent	incident	incident	prevalent	Incident	prevalent
Age, male (%)	50, 62%	48, 61%	NA	53, 73%	39, 67%	51, 62%	53, 61%
Exclusion	Ischemic cardiac disease	-	-	-	Ischemic cardiac disease	-	-
Baseline CAC %	67%				35%	69%	81%
Baseline CAC score (mean/ median)	392/76	660/5	269/19	716/215	60/0	388/54	1617/195
Follow-up (yrs)	1.8	2.0	1.0	1.0	2.8	1.1	4.4
ΔCACpy (units)	+ 0.5 (median)	NA	0 (median)	+	+ 0.5 (median)	0 (median)	+11 (median)
ΔCACpy (%)	1.4 (median) 67.3 (mean)	NA	25 (mean)	NA			
Progr Schankel	23%	NA	NA	NA	38%	NA	38%
Prog Hokanson	NA	NA	NA	NA	29%	26%	47%
Progr Sevrukov	NA	12%	NA	NA	28%	NA	49%
Determinants baseline	NA	NA	NA	NA	NA	NA	Age, gender, PTH, dialysis vintage
Determinants progression	Baseline CAC, race, BMI, BP	PTH, erythrocyte sedimentation rate	NA	Baseline CAC, smoking, dialysis vintage	Baseline CAC, triglyceride level, Bisphosphonate use	Baseline CAC	Baseline CAC, phosphate, calcidiol
Other relevant findings		TX favorable affects but does not halt CAC progression	Slower progression in TX as compared to HD patients	Early increase, followed by stabilisation		Progression similar to general population, slower than in HD	

Vascular calcification

Brussels Renal Transplant Cohort (BRTC) study,
n=189, FU 4,4 yrs



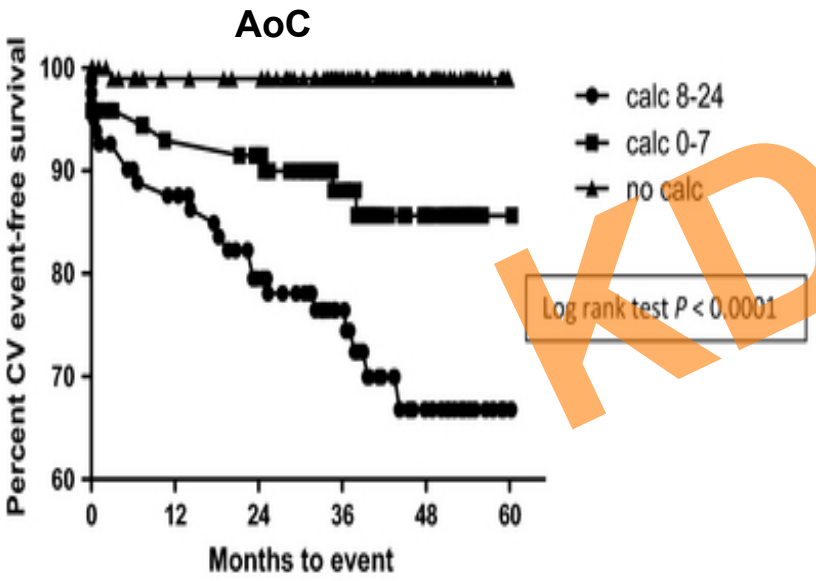
Independent determinants of progression: high age, high serum phosphate, low calcidiol, high baseline score

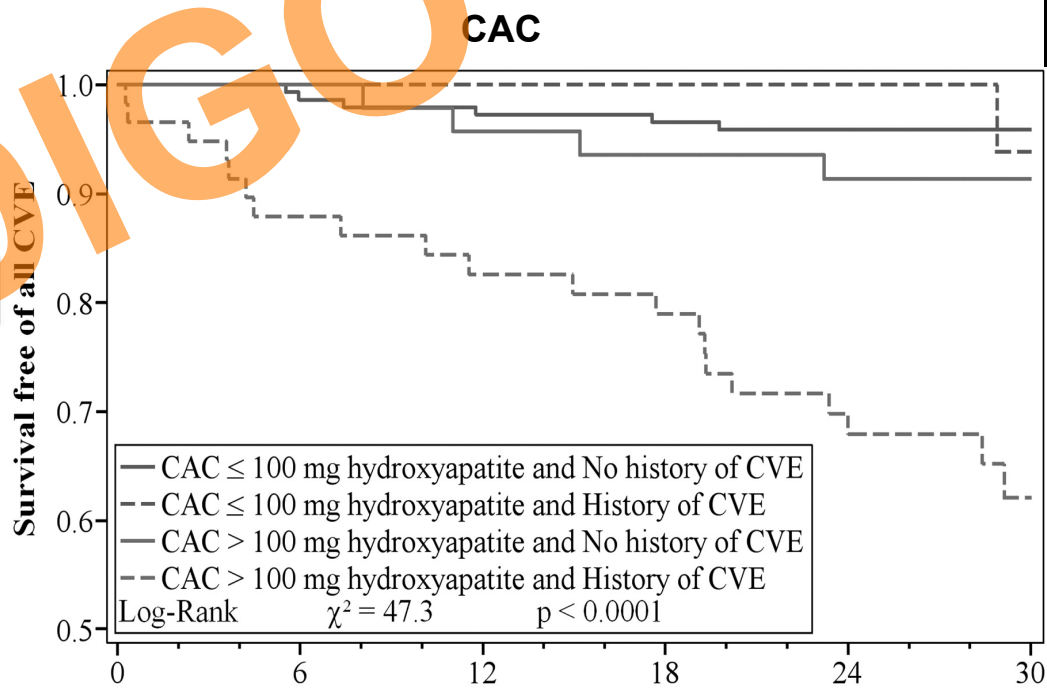
Evenepoel, Jadoul (in preparation)

Vascular calcification and patient level outcomes

Observational data, associations:

	Fractures	CVE	Patient survival
Vascular calcification	?	pos [1, 2]	?





Independent of age, gender, and CV history

1. Nguyen *et al*. NDT 2010
2. Claes *et al.* Transplant Int 2013

Posttransplant CKD-MBD

- Laboratory abnormalities
- Bone disease
- Vascular calcification
- Treatment

Treatment options

- Supplements: calcium, phosphorus, Vitamin D
- Parathyroid hormone suppression
  - Parathyroidectomy
  - Calcimimetics
- Antiresorptive agents
- Bone anabolics
- Steroid sparing/withdrawal

Treatment options: supplements

Therapy	Treatment effect	Limitations
Calcium	Replenish calcium PTH suppression	hypercalcemia?
Phosphorus	Replenish PO_4	• Large doses required • Limited efficacy (↑FGF-23 and/or PTH) • May promote nephrocalcinosis
Native Vit D	↑GI Ca absorption ↓PTH (pleiotropic effects)	• hypercalcemia (origin?) • fracture risk ?: RCTs neg

Active Vit D	↑GI Ca absorption
	↓PTH
	↑ BMD FN and LS
	(pleiotropic effects)
		• hypercalcemia (origin?)
		• fracture risk:?
		  •RCTs neg
		  •meta-analysis (pos)

Evenepoel Sem Nephrol 2013; Alshayeb, Josephson, Sprague AJKD 2013; Palmer Cochrane 2007; Stein et al. JCEM 2012 (solid organTx) ; Yu et al. Clin Tranplant 2012; Lieben *et al*. JCI 2012

Phosphate supplements

Prospective interventional study,
n=32; initiation at month 41
Single arm: Na_2HPO_4: 1500 mg/d for 2 weeks

Caravaca *et al*. NDT 1998

	Pre	Post	p
sCreat	1.23	1.23	NS
sPhos (mg/dL)	2.62	3.37	0.0001
sCa (mg/dL)	10.53	10.23	0.003
sBic (mEq/L)	24.6	23.8	0.003
sPTH (ng/L)	132	172	0.0001
uPhos (mg/d)	824	1668	0.0001
uCa (mg/d)	189	122	0.0001
FE phos (%)	29.5	48.0	0.0001

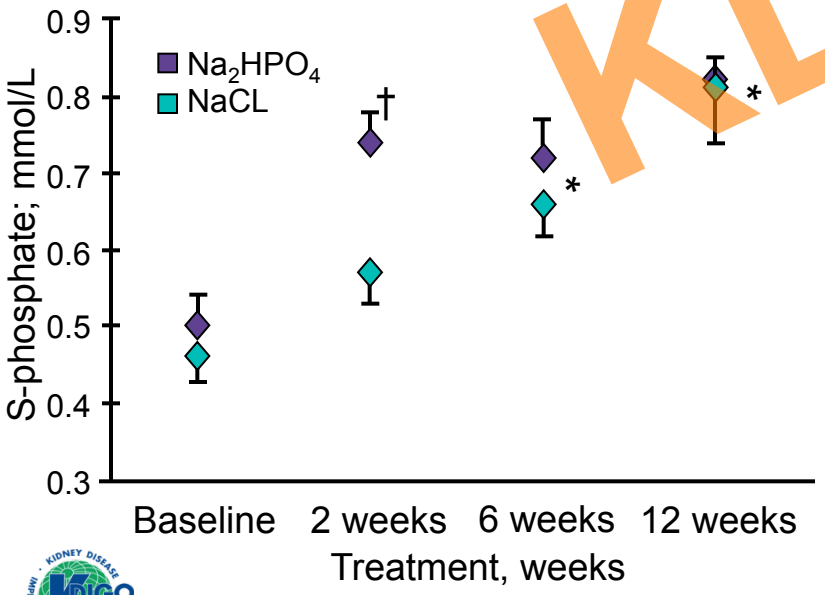
Phosphate supplements

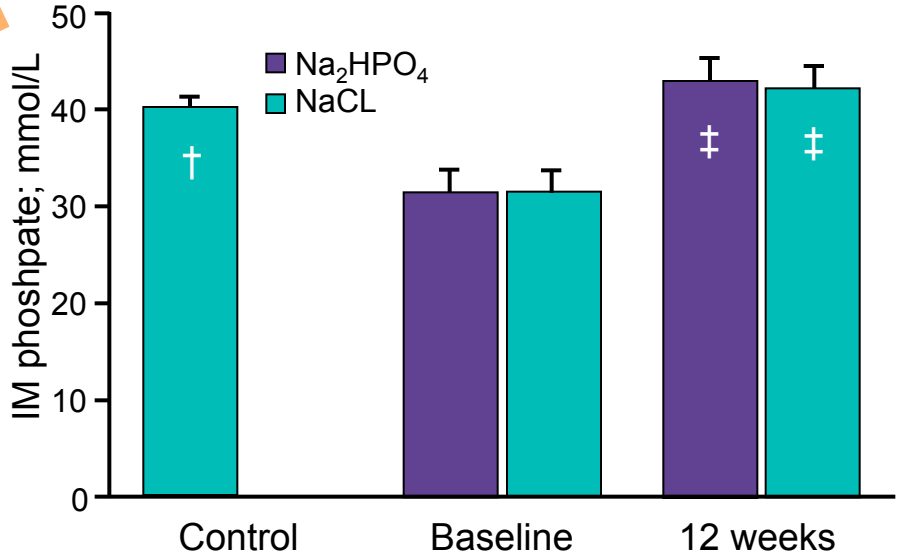
Prospective randomized controlled interventional study
n=28 (1:1); initiation at month 1;

Arm A: Nacl, 12 weeks

Arm B: Na_2HPO_4: 300-900 mg/d, 12 weeks

Ambühl et al. *AJKD* 1999



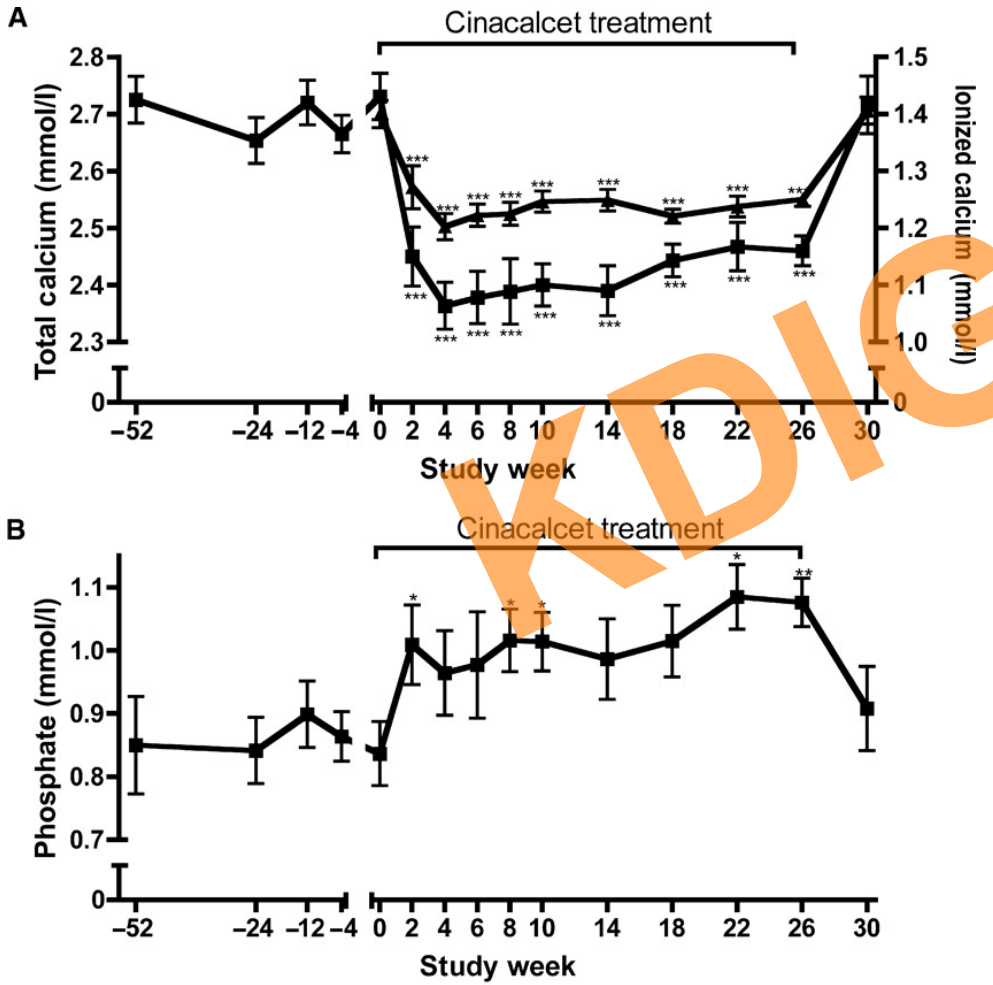


Treatment options: PTH suppression

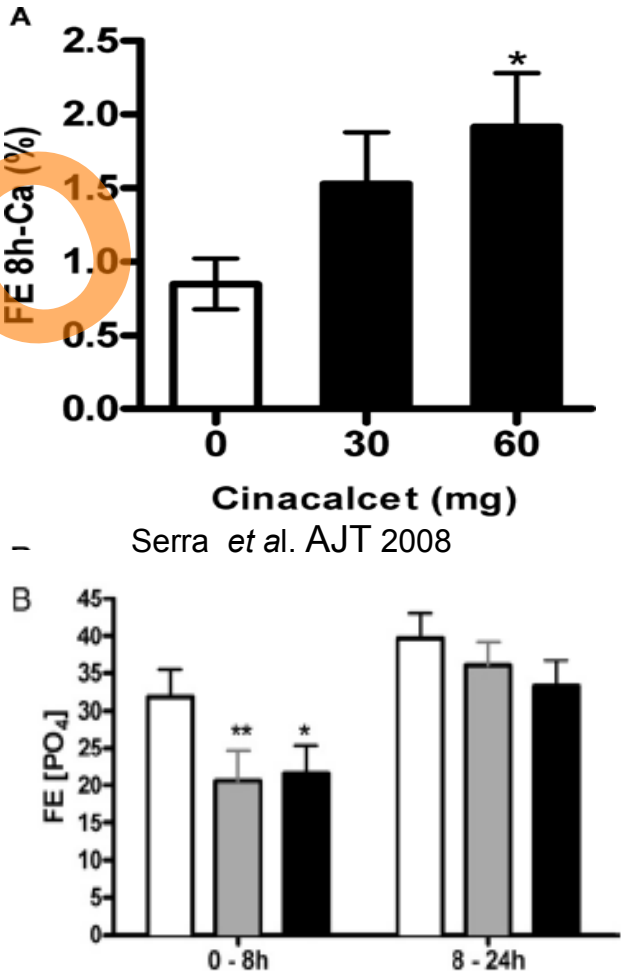
Therapy	Treatment effect	Limitations
Parathyroidectomy	↑Po_4, ↓Ca, ↓PTH (↑ BMD)	• 4-gland hyperplasia requires general anesthesia • Transient hypocalcaemia due to “hungry-bone" syndrome • Persistent hypoparathyroidism with sustained hypocalcaemia / low bone turnover • Parathyromatosis • No RCTs with hard endpoints
Calcimimetics	↑PO_4↓Ca, ↓PTH (↑ BMD)	• Risk of low bone turnover • No registration post-transplant/off-label • No RCTs with hard endpoints

Evenepoel Sem Nephrol 2013
Alshayeb, Josephson, Sprague AJKD 2013

Cinacalcet



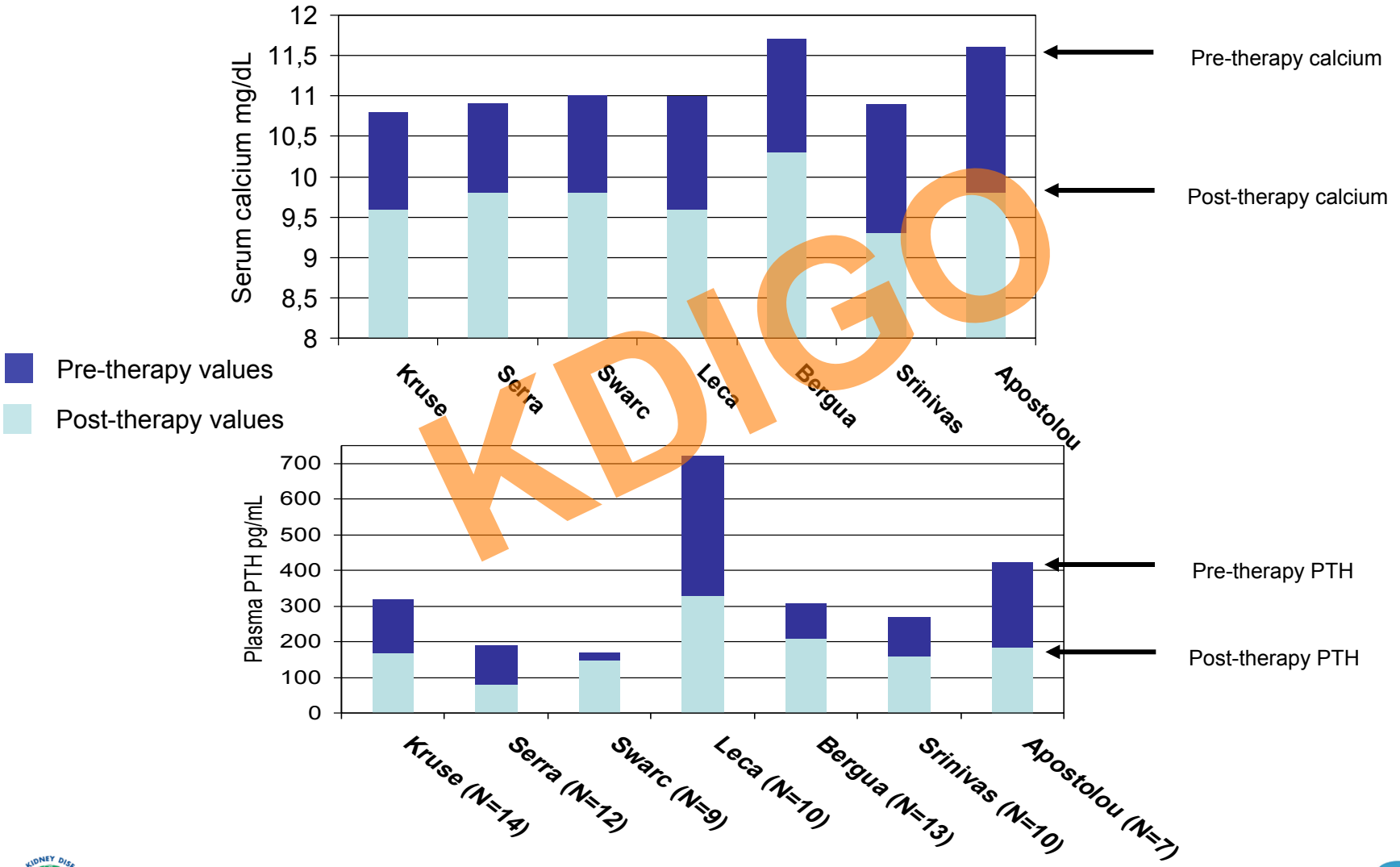
Serra *et al*. NDT 2007



Serra *et al*. AJT 2008

Serra *et al*. AJKD 2008

Cinacalcet



Treatment options: antiresorptive agents, anabolics, steroid sparing/withdrawal

Therapy	Treatment effect	Limitations

Bisphosphonates	↓Ca, (↑PTH, ↓Po4),
	↑ BMD
		• risk of low bone turnover
		• fracture risk:?
		  • RCTs neg;
		  • meta-analysis pos

Denosumab	↓Ca, (↑PTH, ↓Po4), ↑ BMD	• Risk of low bone turnover • Unknown immunological effects • No registration post-Tx
Teriparatide	↑ coritcal bone ?	• Questionable efficacy
Steroid sparing	↑GI Ca absorption ↑BMD	
Correct metabolic acidosis/Mg depletion	↑HCO3, ↑Mg	• No RCTs

Evenepoel Sem Nephrol 2013; Alshayeb, Josephson, Sprague AJKD 2013; Stein et al. JCEM 2011

Bisphosphonates

Study	No. of Patients	Design	Outcome
Grotz et al (2001)	80	Prospective placebo controlled; kidney recipients received either ibandronate or placebo at 3, 6, and 9 mo posttransplantation vs control group	Less bone loss, spinal deformation, and loss of body height in the ibandronate group during first y posttransplantation
Fan et al (2000, 2003)	26	Prospective placebo controlled; kidney recipients received either IV pamidronate or placebo at time of transplantation and 1 mo later; 17 patients had second DEXA at 4 y	Preserved BMD at lumbar spine and femoral neck in pamidronate group vs increased loss of BMD in placebo group during first y posttransplantation; preserved BMD at femoral neck in 4 y in pamidronate-treated group
Haas et al (2003)	20 (incident)	Prospective placebo controlled; kidney recipients received either zoledronic acid or placebo at baseline and 3 mo after transplantation, calcium citrate 1 g/d; creat < 2 mg/dL.	Improved BMD in lumbar spine, stable BMD in femoral neck at 6 mo, T↓in both groups without increased risk of adynamic bone disease in the zoledronic acid–treated group
Coco et al (2003)	20 (incident)	Prospective, controlled; kidney recipients received either pamidronate at baseline, 1, 2, 3, 6 mo plus daily vitamin D (400 IU) /Ca^{+2} (500mg) vs vitamin D/Ca^{+2}, no GFR limitation	Preserved BMD in vertebral spine at 6 and 12 mo with increased risk of adynamic bone disease in pamidronate-treated group (all patients in pamidronate group vs 50% in control group)
Walsh et al (2009)	93 (incident)	Prospective, controlled; kidney recipients received either pamidronate at baseline, 1, 2, 3, 6 mo plus daily vitamin D (400IU)/Ca^{+2} (500 mg) vs vitamin D/Ca^{+2}, no GFR limitation	Preserved BMD in lumbar spine, total hip at 12 mo. Lower (NS) fracture rate in pamidronate group (6.4% vs 3.3 % per year)
Jeffery et al[111] (2003)	117	Prospective, controlled; kidney recipients with osteopenia at baseline received either daily alendronate and Ca^{+2} vs calcitriol and Ca^{+2}	Improved BMD in lumbar spine and femoral neck in both groups, superior effect of alendronate on spine BMD

Bisphosphonates

El-Agroudy et al (2005)	60 (incident)	Prospective, controlled; kidney recipients with osteopenia or osteoporosis at baseline received either alendronate (5 mg/d) or alfacalcidol (0.5 µg/d) or calcitonin (100µL intranasally) vs control; calcium carbonate 0.5 g/d; creat < 2mg/dL.	Alfacalcidol and alendronate improved BMD at both lumbar spine and femoral neck, while calcitonin improved BMD in lumbar spine only (at 1 year)
Nowacka-Cieciura et al (2006)	66	Prospective, controlled; kidney recipients with osteopenia or osteoporosis at baseline received either alendronate or risendronate or were drug free	Improved BMD in femoral neck in bisphosphonate-treated group at 12 mo
Torregrosa et al (2007)	84	Prospective, controlled; kidney recipients with osteopenia at baseline received either weekly risendronate + daily vitamin D/Ca^{+2} or vitamin D/Ca^{+2} only	Increased BMD in lumbar spine at 1 y in risendronate-treated group
Abediazar & Nakhjavani[117] (2011)	43 (incident)	Prospective, controlled; kidney recipients with osteopenia at baseline were randomly assigned to either weekly alendronate (30 mg) + daily vitamin D (not specified) or daily vitamin D only	Alendronate increased BMD in distal radius and lumbar spine at 1 y (poor quality study)
Yamamoto (2013)	24 (prevalent)	Prospectice, uncontrolled; kidney recipients with low BMD were prescribed weekly oral alendronate (35 mg); mean GFR 49 ml/min 1.73m², no Vit D	Oral alendronate did not affect BMD in lumbar spine (after 2 yr) but suppressed bone turnover biomarkers
Smerud (2012)	129 (incident)	Randomized, double-blind, placebo-controlled study; kidney recipients (<4 wk) received either ibendronate iv (3 mg, every 3 mo for 12 mo) or placebo; eGFR > 30 ml/min, calcitriol (0.25 µg/d) + calcium carbonate (2.5 g)	Improved BMD in total femur and ultradistal radius but not in lumbar spine in ibendronate-treated patients at 12 mo. Suppression of bone formation markers

Abbreviations: BMD, bone mineral density; Ca^{+2}, calcium; DEXA, dual-energy x-ray absorptiometry; IV, intravenous

Adapted from Alshayeb et al. AJKD 2013

Individualized therapy

Algorithm for treatment allocation after transplantation.

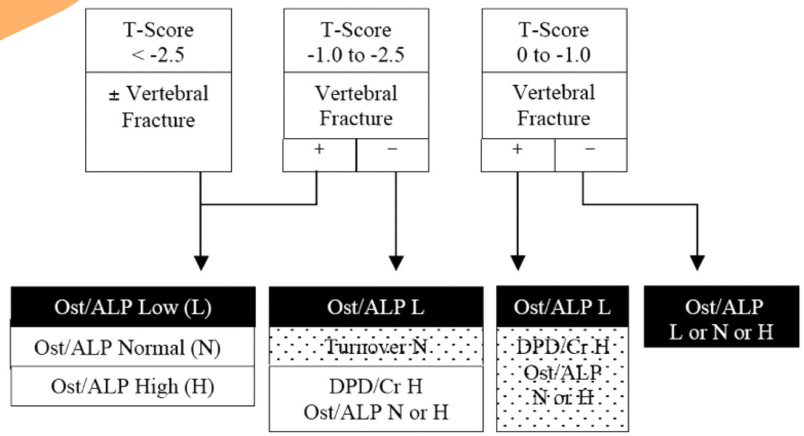
STEP ONE: Early post-transplant BMD by DXA and lateral thoracic and lumbar spine radiographs.

STEP TWO: Laboratory investigations including PTH, 25(OH)D and markers of bone turnover; osteocalcin (Ost), alkaline phosphatase (ALP) and urinary deoxypyridinoline/creatinine ratio (DPD/Cr) at 2-4 weeks as renal function stabilizes.

STEP THREE: Score risk factors for fracture.

Age >50 years	1
Hypogonadal male or female	1
Previous non-vertebral fragility fracture	1
Prolonged oral glucocorticoids pre-transplant	1
Low body mass index	1
First degree relative with osteoporosis	1
Postural instability, peripheral neuropathy, reduced visual acuity, falls	1
Pre-transplant iPTH >50 pmol/L / osteitis fibrosa on bone biopsy	1
Type 1 diabetes	2

STEP FOUR: Allocate patients to bisphosphonate □or calcitriol ■therapy. Borderline patients ⚄ prescribed bisphosphonates for risk factor scores ≥3. Unless contraindicated, all patients receive cholecalciferol until vitamin D replete plus calcium supplementation. Patients with T-scores above 0 or with prior parathyroidectomy and low bone turnover receive or continue calcitriol.



□ Bisphosphonates
■ Calcitriol
⚄ Bisphosphonates if risk factors socre ≥3

Mainra R , and Elder G J CJASN 2010;5:117-124

Summary

- Kidney transplantation does not solve the problem of CKD-MBD
- Posttransplant CKD-MBD is very heterogeneous and reflect prior MBD, de novo MBD, and the effects of immunosuppressive drugs
- The pathophysiology of posttransplant CKD-MBD is ill-defined
- Adequately designed and powered RCT addressing posttransplant CKD-MBD are scarce
- Therapy should be focussed on controlling inappropriate persistent hyperparathyroidism, as reflected by simultaneous hypercalcemia and/or hypophosphatemia, and should be causal whenever possible
- Therapy should be individualized

Research recommendations

- In depth experimental and clinical research to elucidate the pathophysiology of posttransplant CKD-MBD
- Balance studies to determine calcium, phosphorus and magnesium balance in (incident) renal transplant patients
- Adequately designed RCT to evaluate the efficacy of various established treatment strategies (and especially PTH suppression therapy) on surrogate and hard patient-level outcomes
- Define the value of laboratory abnormalities, bone imaging techniques and bone histomorphometry in predicting fractures