"Osteoporosis" in CKD the dilemmas in management

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October 2013

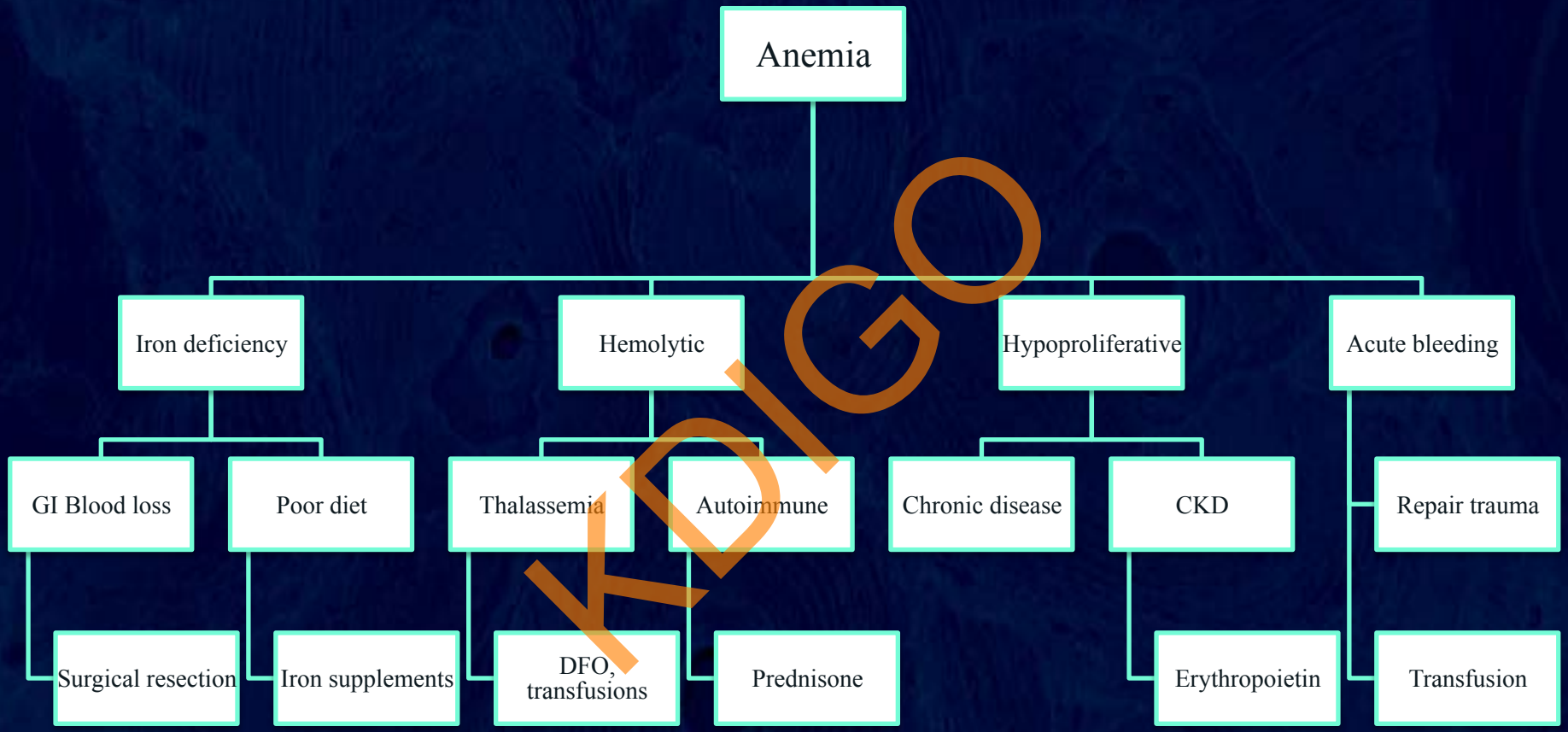
*"**Dilemma** should be reserved for reference to a predicament in which a difficult choice must be made between undesirable alternatives" (Apple dictionary)*

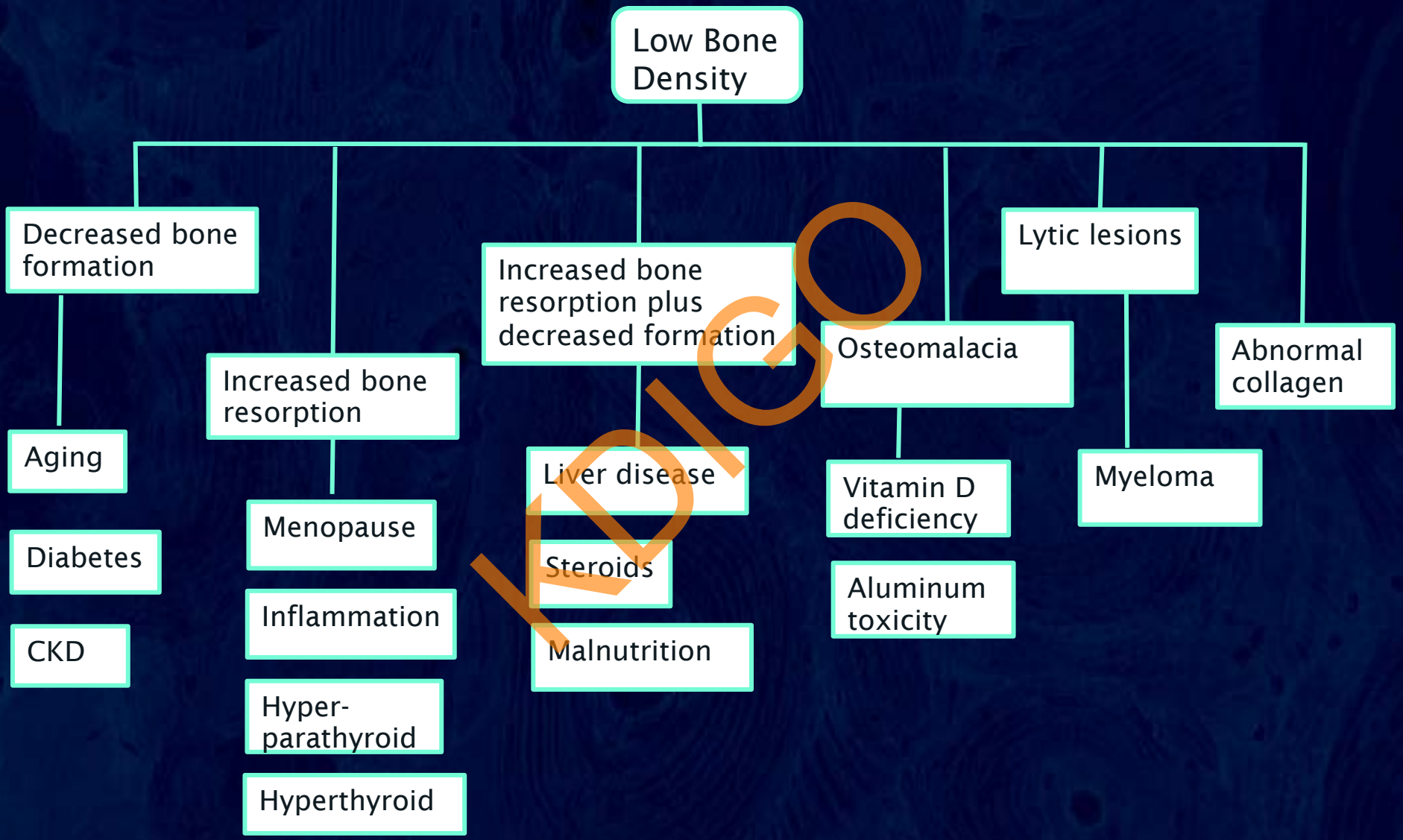
No conflicts of interest

KDIGO

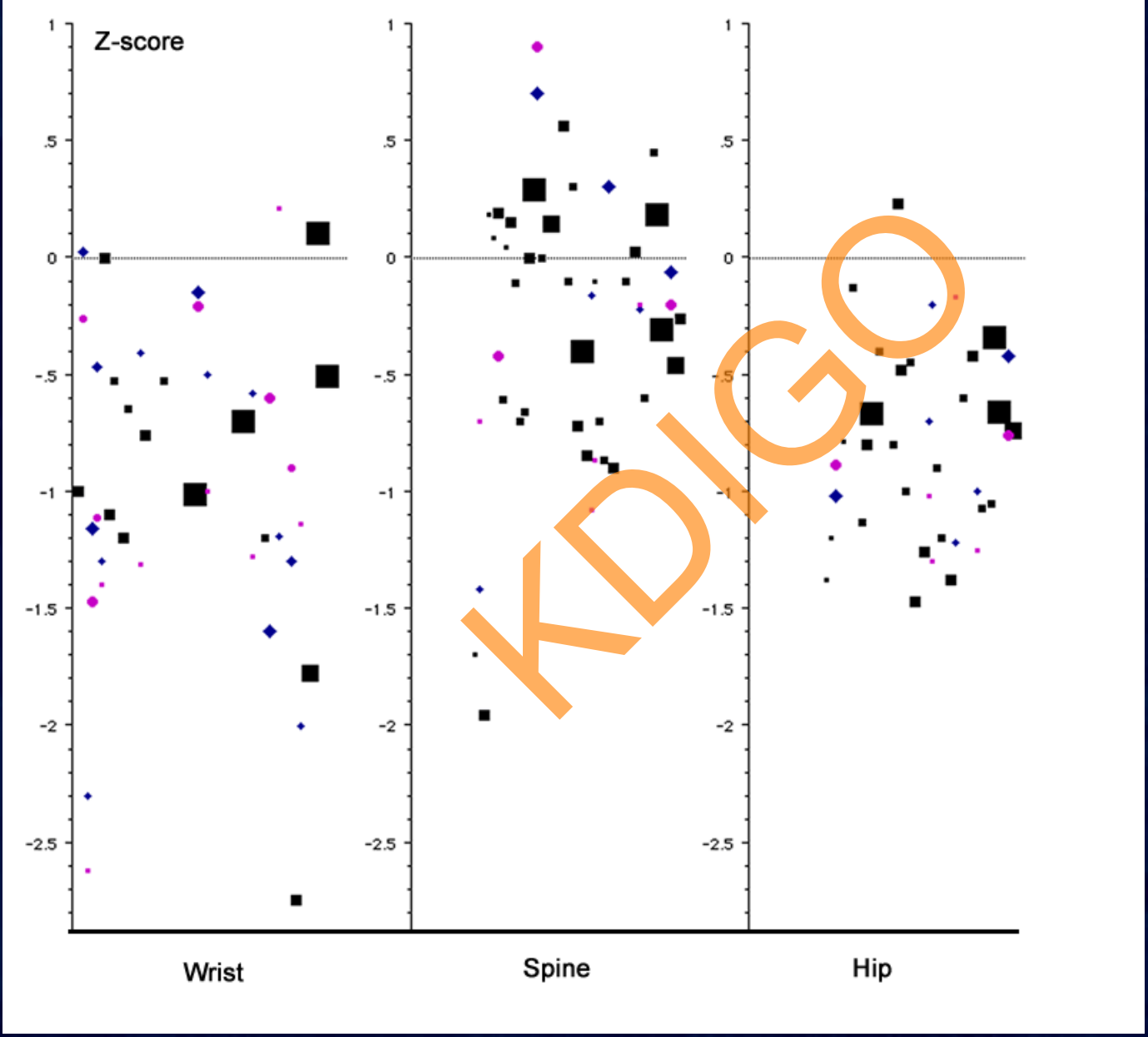
“Osteoporosis” is a
measurement on a bone density
and not a diagnosis.

Similar to anemia which
is a measurement on a blood sample
but not a diagnosis.


Anemia
Iron deficiency
Hemolytic
Hypoproliferative
Acute bleeding
GI Blood loss
Poor diet
Thalassemia
Autoimmune
Chronic disease
CKD
Repair trauma
Surgical resection
Iron supplements
DFO, transfusions
Prednisone
Erythropoietin
Transfusion

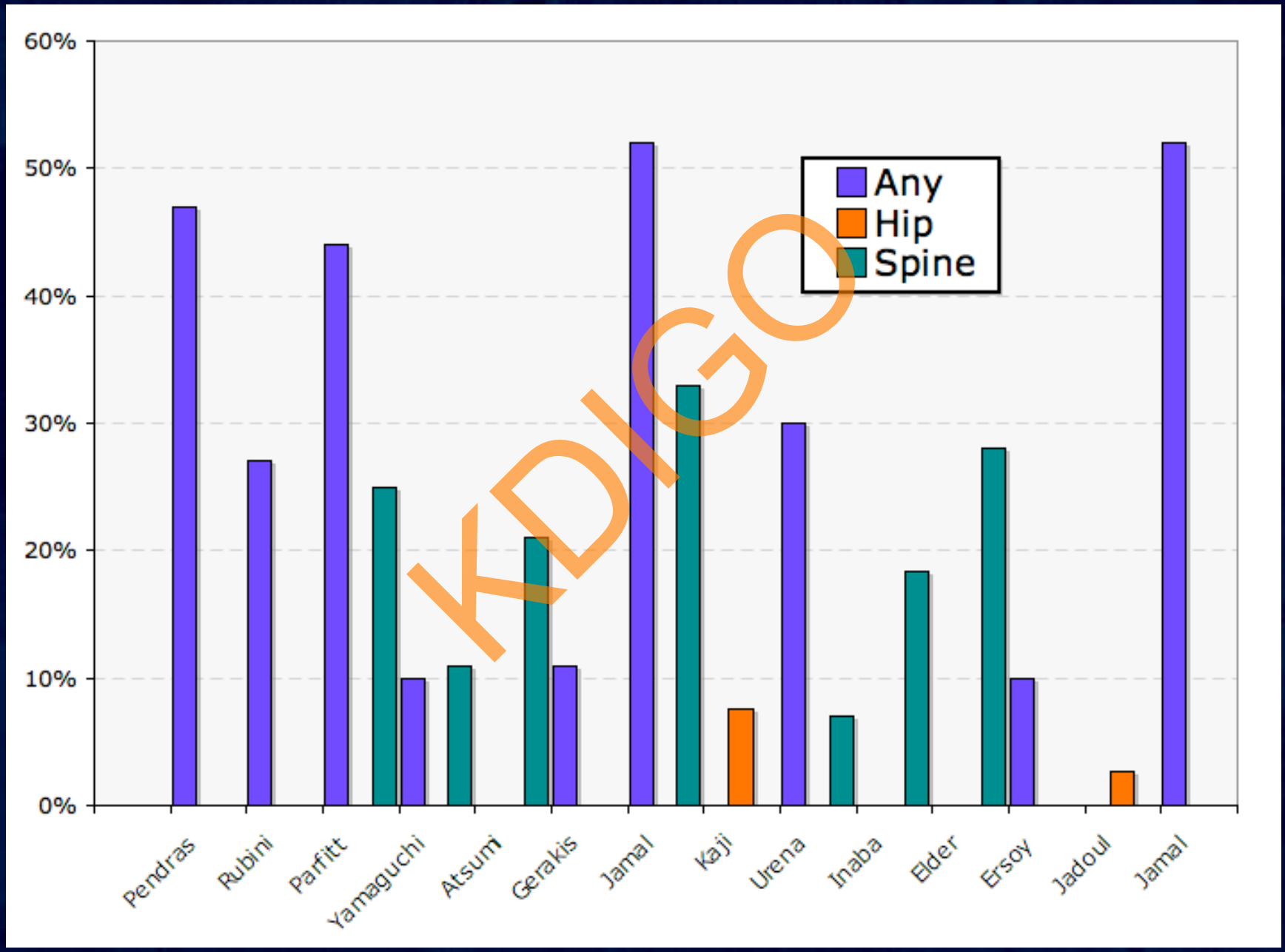

Low Bone Density
Decreased bone formation
Aging
Diabetes
CKD
Increased bone resorption
Menopause
Inflammation
Hyper-parathyroid
Hyperthyroid
Increased bone resorption plus decreased formation
Liver disease
Steroids
Malnutrition
Osteomalacia
Vitamin D deficiency
Aluminum toxicity
Lytic lesions
Myeloma
Abnormal collagen
KDIGO

Bone density in Dialysis Patients



Ott, Nephrology, 2009

Fracture Prevalence in CKD 5D



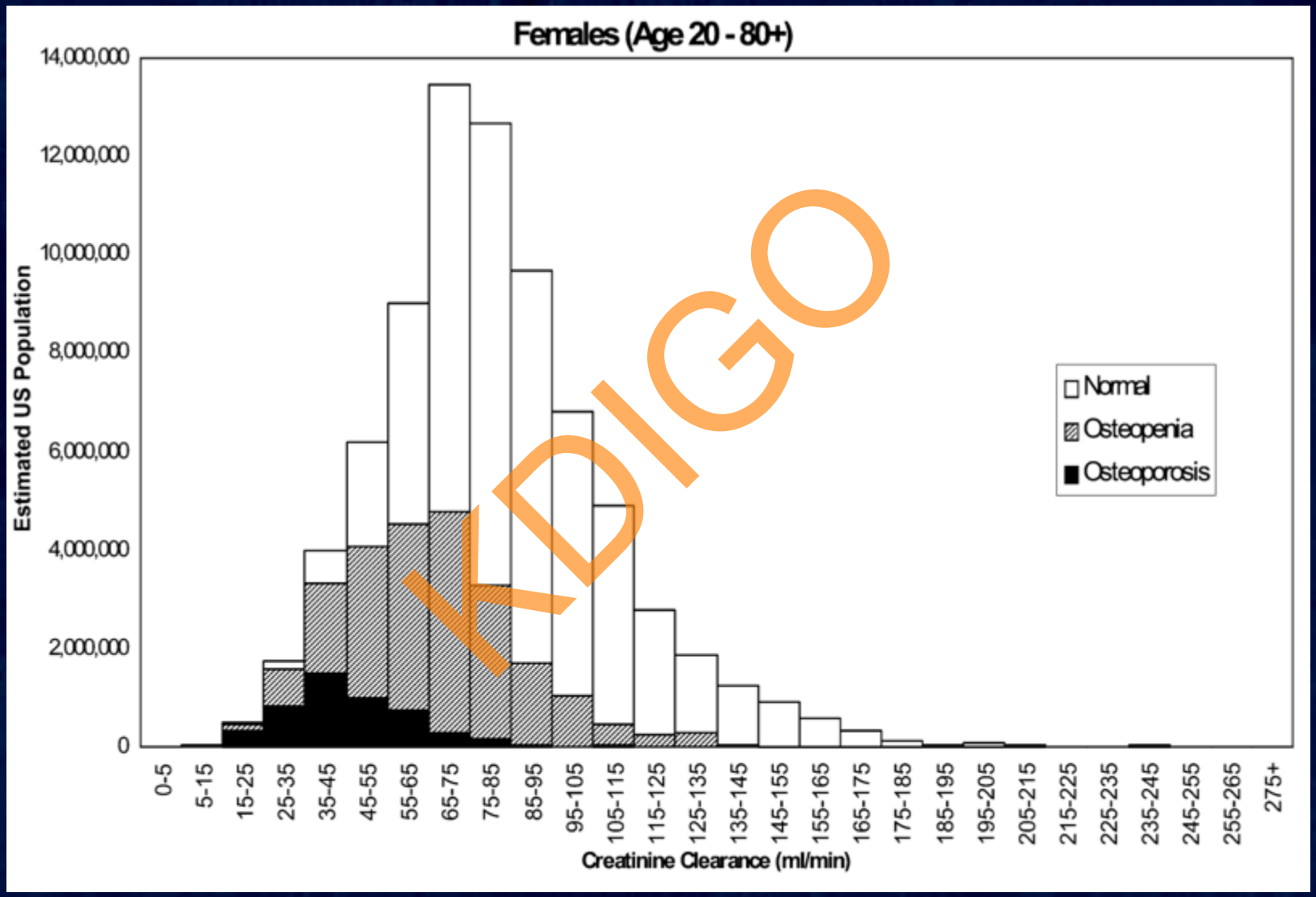
Bone density in Dialysis Patients

Author	Yr	N	N Fx	Fracture	BMD: Skeletal Site			
					Spine	Hip	Wrist	Body
Yamaguchi	96	124	27	Clinical, vertebral	NO*		YES*	
Atsumi	99	187	39	Vertebral	YES*			YES*
Gerakis	00	62	7	Clinical	NO	NO		
Fontaine	00	88	11	Clinical, vertebral	YES	YES	YES	
Jamal	02	104	54	Clinical, vertebral	NO*	NO*		
Kaji	02	183	14	Hip	NO*		YES*	
Urena	03	70	21	Clinical, vertebral	NO*	NO*	NO*	YES*
Negri	04	65	6	Clinical	NO	NO		
Inaba	05	114	21	Vertebral	NO*		NO*	
Elder	06	242	89	Clinical, vertebral	NO	YES	nr	
Ersoy	06	292	24	Clinical	NO	NO		
Jamal	06	52	27	Clinical, vertebral	NO	NO	YES*	
Dolgos	08	133	38	Clinical	nr	nr		YES
Mares	09	73	15	Vertebral	NO*			
Iimori	12	485	46	Clinical	NO*	YES*	NO*	YES*

New studies with HRpQCT

- With these research tools patients with CKD have lower bone density than normal controls.

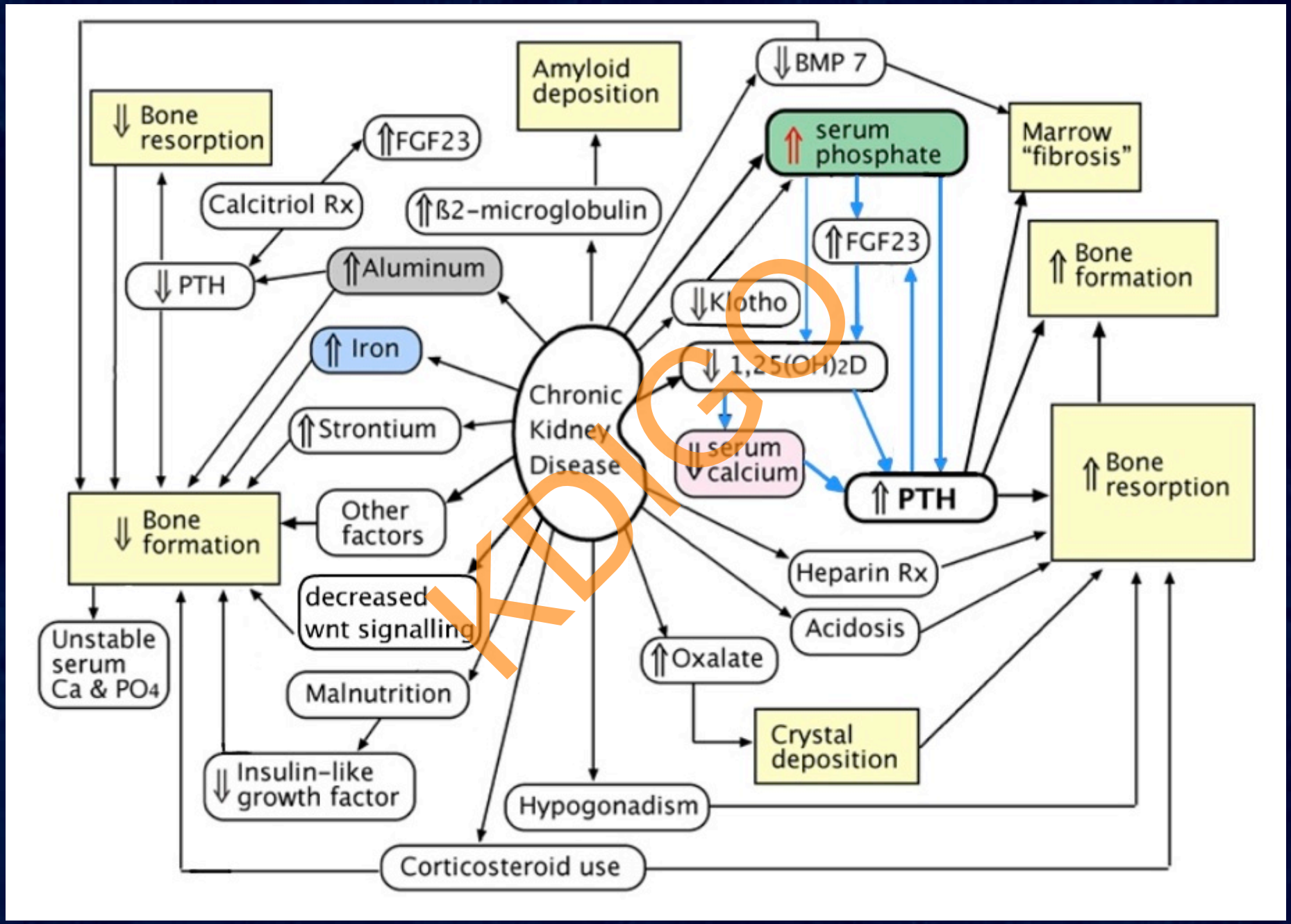
Bone density by eGFR



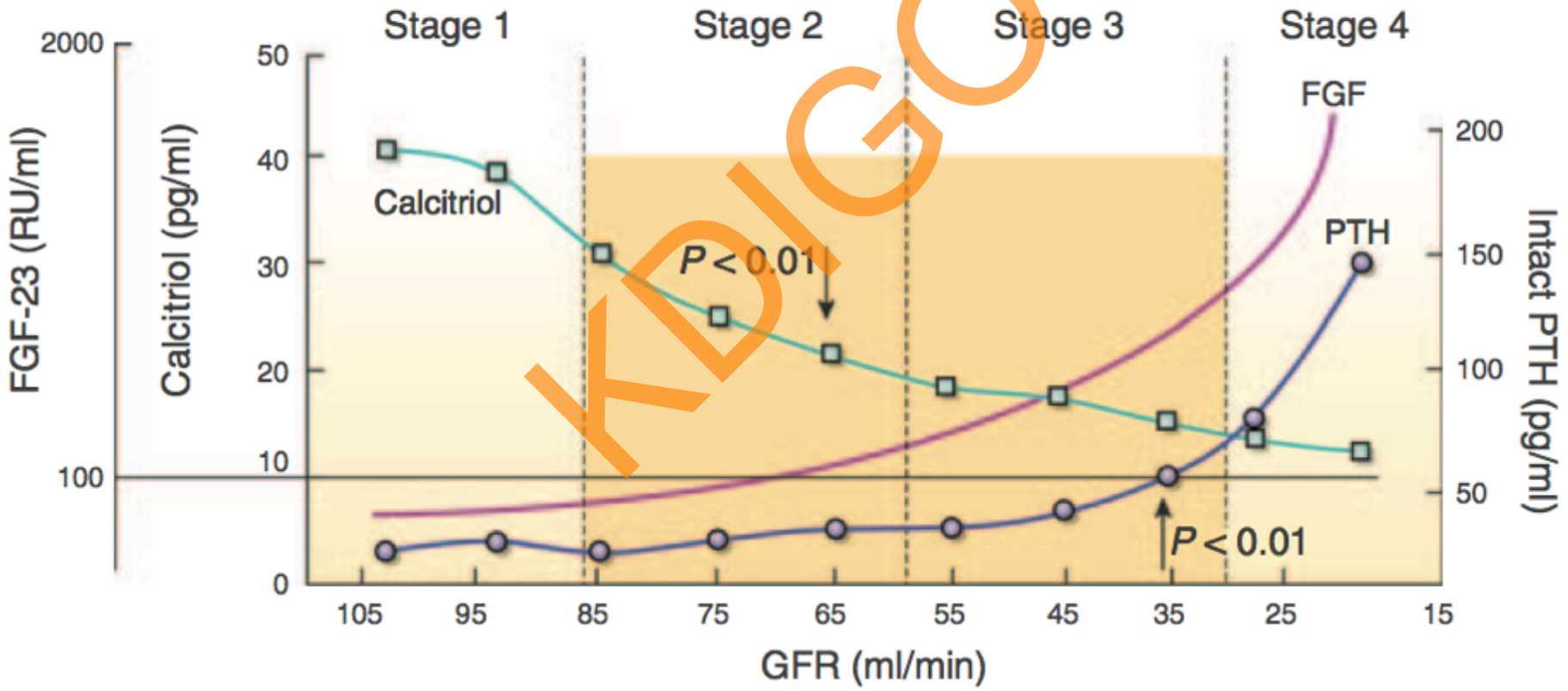
data from NHANES

Klawansky, Osteo Int, 2003

CKD-MBD	Ordinary osteoporosis
Increased PTH and alkaline phosphatase	Normal PTH and alkaline phosphatase
Bone density weakly related to fractures	Bone density predicts fractures
Bone loss mostly in cortical bone	Bone loss in trabecular and cortical bone
High prevalence of adynamic bone or very high bone formation	Bone formation generally normal to slightly high
Associated with vascular calcifications	Weakly associated with vascular calcifications
Abnormal calcium, phosphate, FGF23, BMP7, Klotho, 1,25-vitamin D, iron, bicarbonate, sclerostin, and cytokines	Normal or mildly abnormal

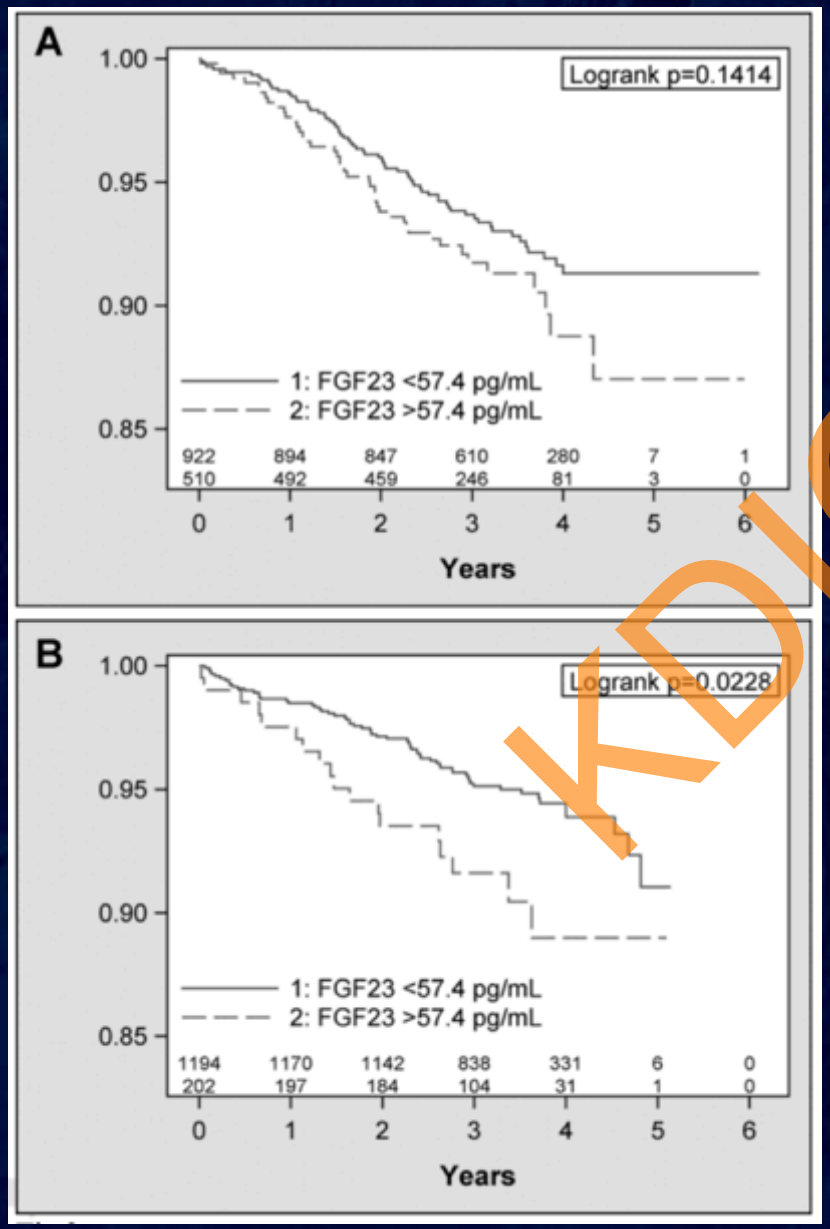

Chronic Kidney Disease
⇓ Bone resorption
⇑FGF23
Calcitriol Rx
⇓ PTH
⇑Aluminum
⇑ Iron
⇑Strontium
⇓ Bone formation
Other factors
Unstable serum Ca & PO4
decreased wnt signalling
Malnutrition
⇓ Insulin-like growth factor
Amyloid deposition
⇑ß2-microglobulin
⇓BMP 7
⇑ serum phosphate
⇑FGF23
⇓Klotho
⇓ 1,25(OH)2D
⇓ serum ⇓ calcium
⇑ PTH
Marrow "fibrosis"
⇑ Bone formation
⇑ Bone resorption
Heparin Rx
Acidosis
⇑Oxalate
Crystal deposition
Hypogonadism
Corticosteroid use

Progressive abnormalities in CKD



Gal-Moscovici, KI 2010

FGF23 and fractures



eGFR > 71

eGFR < 71

Mirza, JBMR, 2010

Treatment of Bone Disease in CKD patients

CKD stage 3

Post-hoc analysis of studies of osteoporosis medications (bisphosphonates, raloxifene, teriparatide and denosumab) that included subjects with age-related CKD stage 3 found fracture benefit, similar to patients with normal eGFR

These studies excluded sick patients. The subjects had normal calcium, PTH, and alkaline phosphatase.

JOURNAL OF BONE AND MINERAL RESEARCH
Volume 22, Number 4, 2007
Published online on January 22, 2007; doi: 10.1359/JBMR.070112

Alendronate Treatment in Women With Normal to Severely Impaired Renal Function: An Analysis of the Fracture Intervention Trial*

Sophie A Jamal,[1] Douglas C Bauer,[2] Kristine E Ensrud,[3] Jane A Cauley,[4] Marc Hochberg,[5] Areef Ishani,[3] and Steven R Cummings[2]

N = 6458 Age 55 to 80 with low bone density

Exclusion: creat>144µmol/L

Normal serum PTH, calcium, vitamin D, thyroid, alk. phos.

Patients with stage 4 CKD were excluded

Using a modified Cockcroft-Gault, 581 (9.9%) had eGFR <45

Women with eGFR <45 had greater number of fractures

With alendronate (3 to 4.5 years) vs. placebo:

Similar odds ratio for clinical fracture (0.80 with CKD vs. 0.78)

Odds ratio for Spine fracture not significantly different

(0.72 with CKD vs. 0.50)

FRACTURE INTERVENTION TRIAL

Jamal, JBMR 2007

Treatment of bone disease
Stage 4-5 CKD

Pharmacokinetics of bisphosphonates

Cleared only by kidney

Very poor oral absorption

About 50% of dose deposited in the skeleton

Deposits in calcified tissues

Remains in skeleton for longer than 10 years

Pamidronate clearance 69 ml/min

A Pervasive Myth:
bone formation with bisphosphonates is normal

"Reduction of bone turnover . . . without any signs of adynamic bone" – Recker, 2007

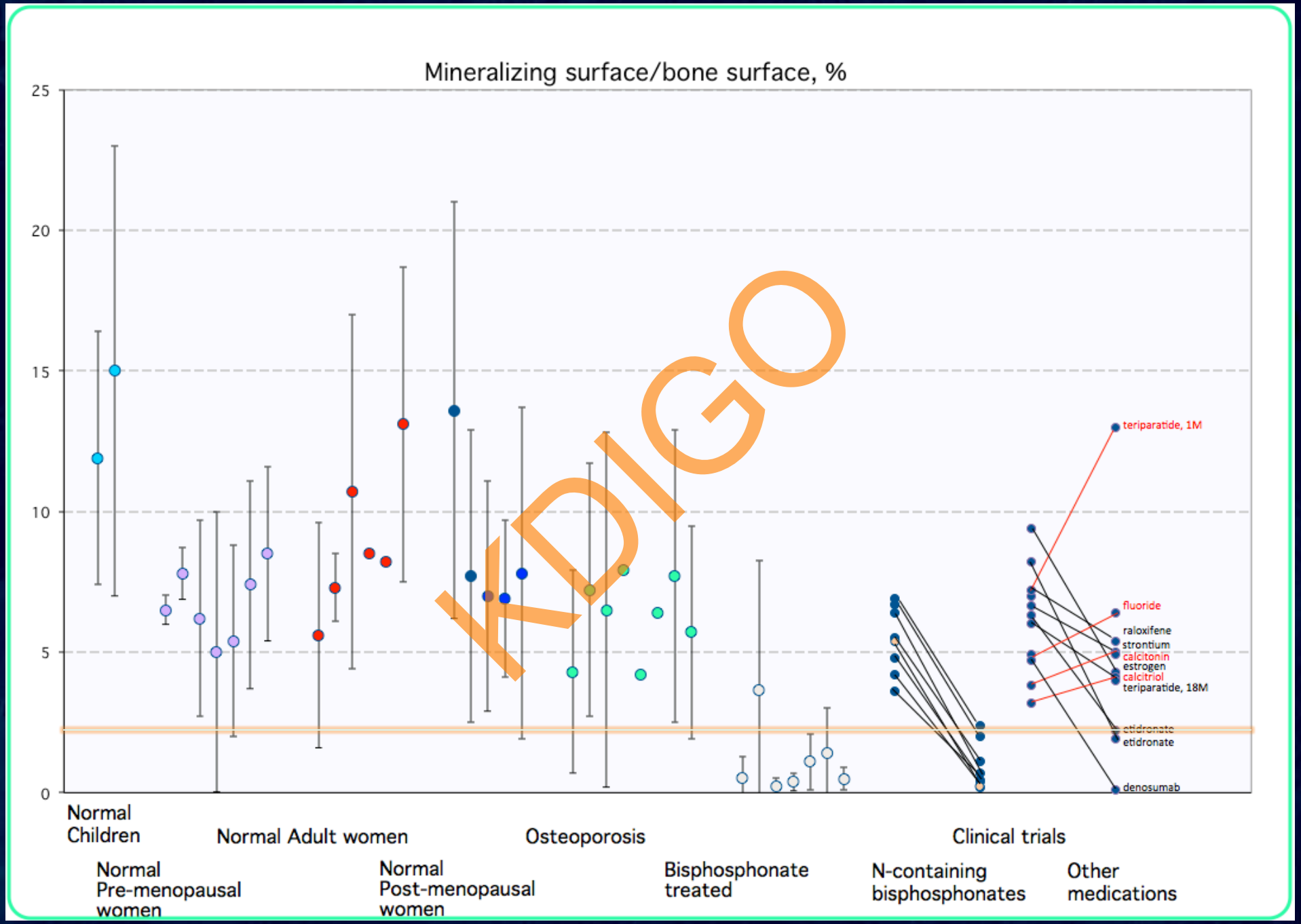
"Most patients on bisphosphonates show reductions in remodeling to the range seen in healthy premenopausal women" – Khosla et al, 2012

"BPs decrease the rate of bone turnover into the premenopausal range" – Papapoulos 2008

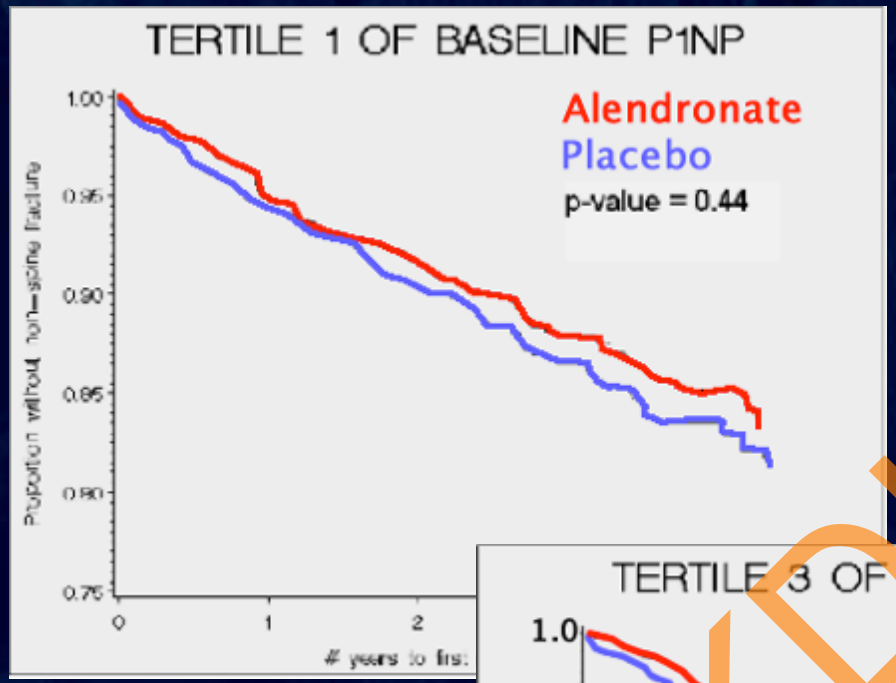
"reducing bone turnover to premenopausal levels – the level of bone resorption seen in many users of bisphosphonates" – Abrahamsen, 2012

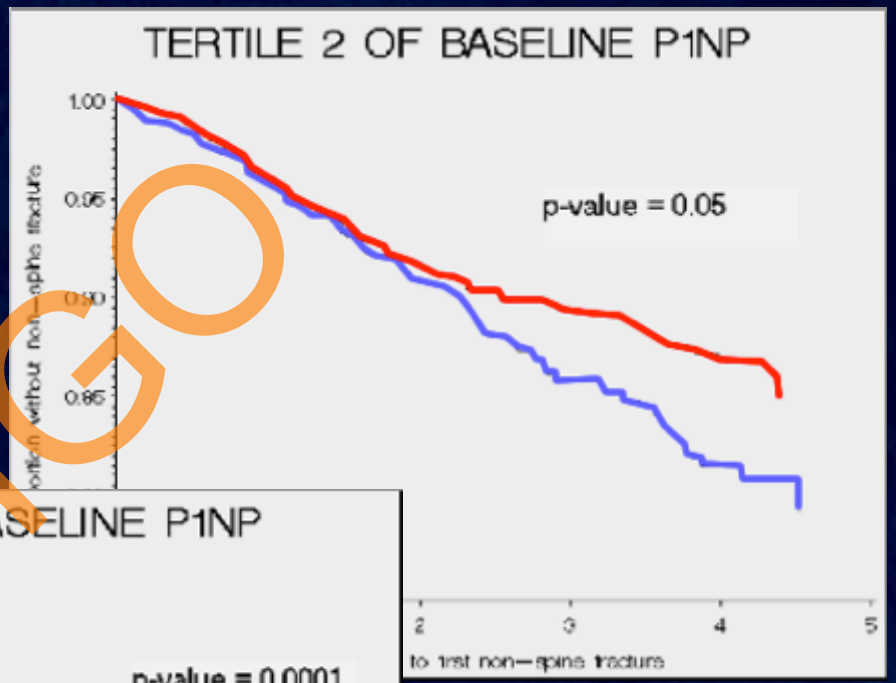
"I find the key point statement "Bisphosphonates severely reduce bone formation and cause adynamic bone disease" too strong." – 2013 reviewer

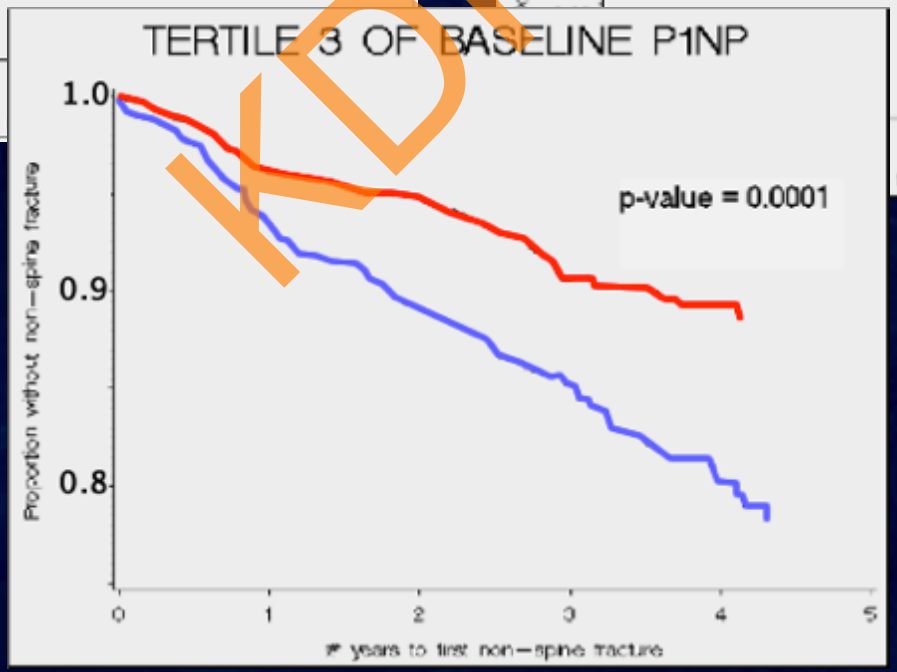
"The statement that bisphosphonates cause adynamic bone disease is unproven" – 2013 reviewer


Mineralizing surface/bone surface, %
25
20
15
10
5
0
KDIGO
teriparatide, 1M
fluoride
raloxifene
strontium
calcitonin
estrogen
calcitriol
teriparatide, 18M
etidronate
etidronate
denosumab
Normal Children
Normal Adult women
Osteoporosis
Clinical trials
Normal Pre-menopausal women
Normal Post-menopausal women
Bisphosphonate treated
N-containing bisphosphonates
Other medications

Alendronate vs placebo: baseline P1NP tertiles



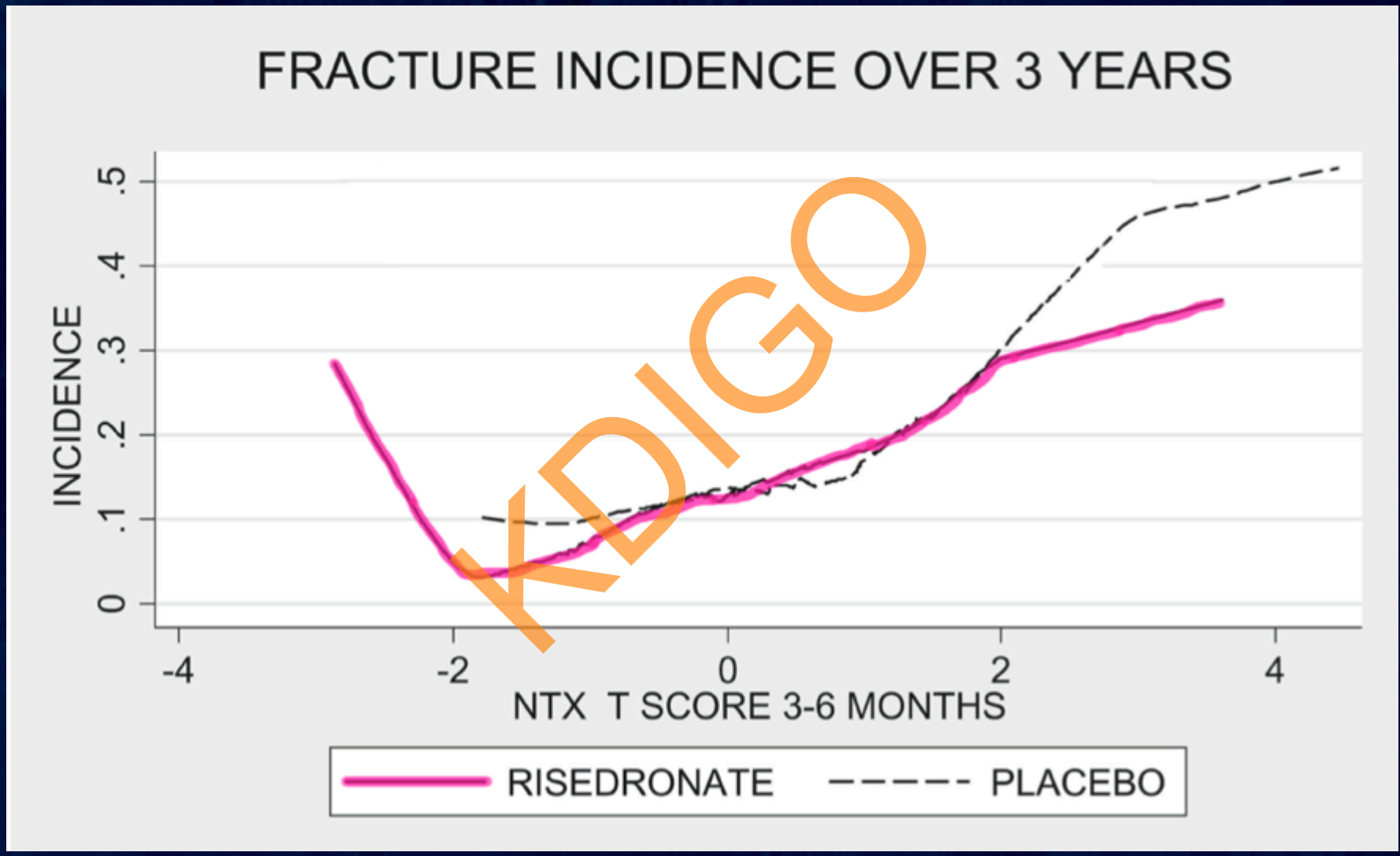




Non-spine fractures

Bauer, JBMR, 2006

NTX and fracture incidence

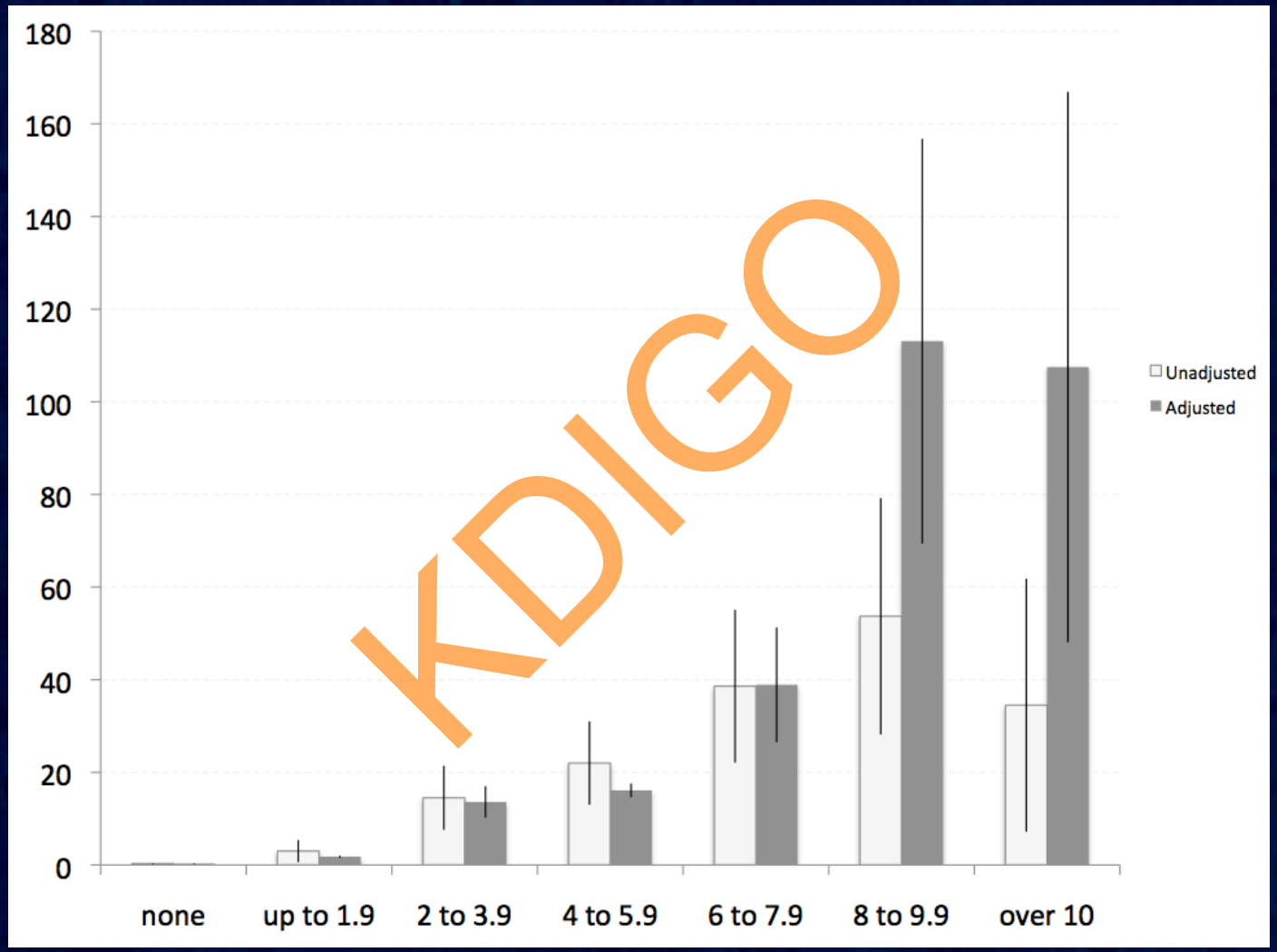


Below a 35-40% decrease in NTX there was no further decrease in vertebral fracture risk

Eastell, JBMR,2007

Incidence of atypical femur fracture

Rate/ 100,000/ yr



Duration bisphosphonate use, yrs

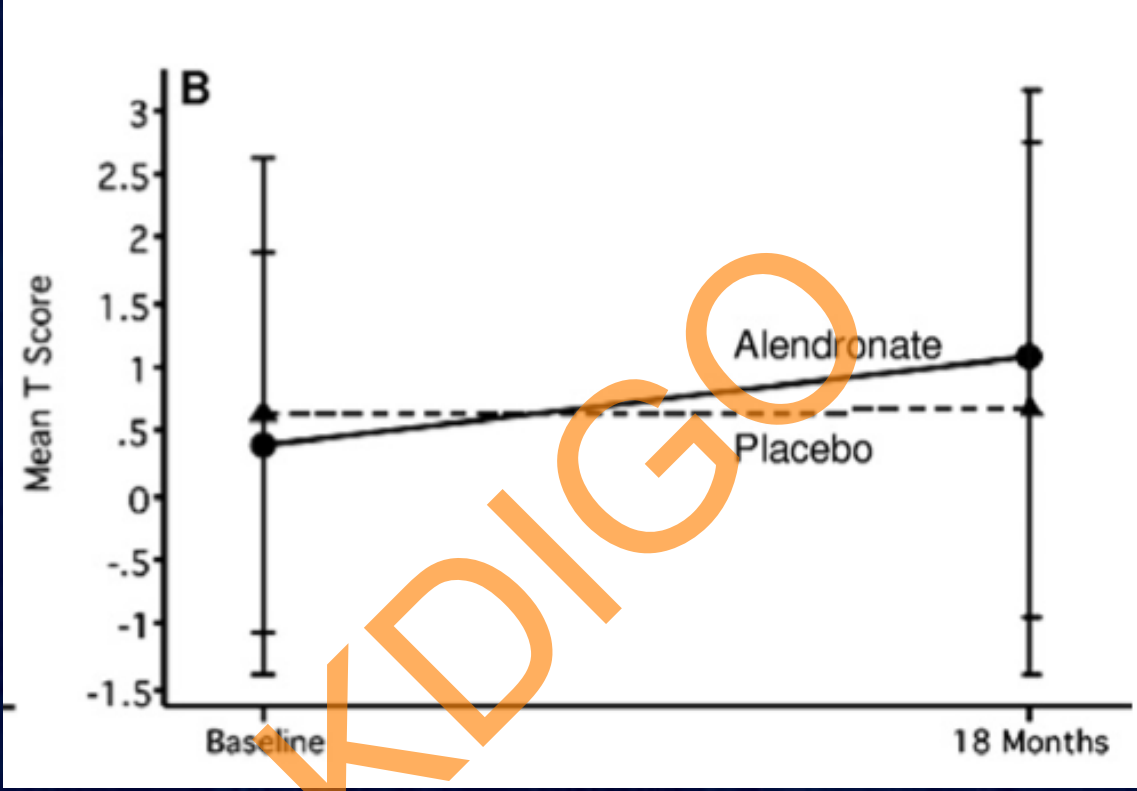
Dell, JBMR, 2012

Alendronate in CKD stage 3-4

- RCT of 51 patients, mean eGFR 34
- 18 months duration
- NO difference in progression of cardiovascular calcification
- Higher PTH with alendronate

Toussaint, AJKD 2010

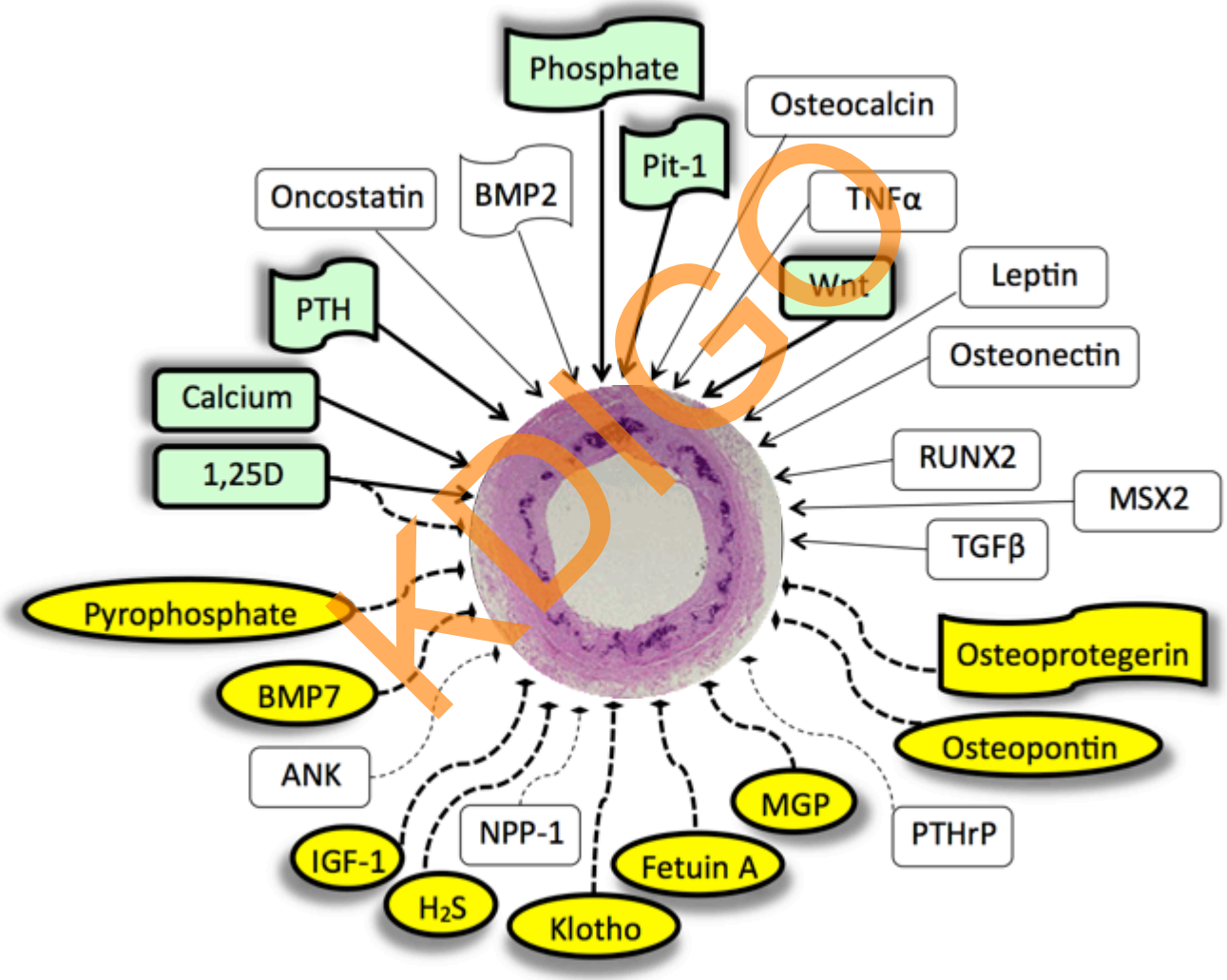
Alendronate in CKD stage 3-4

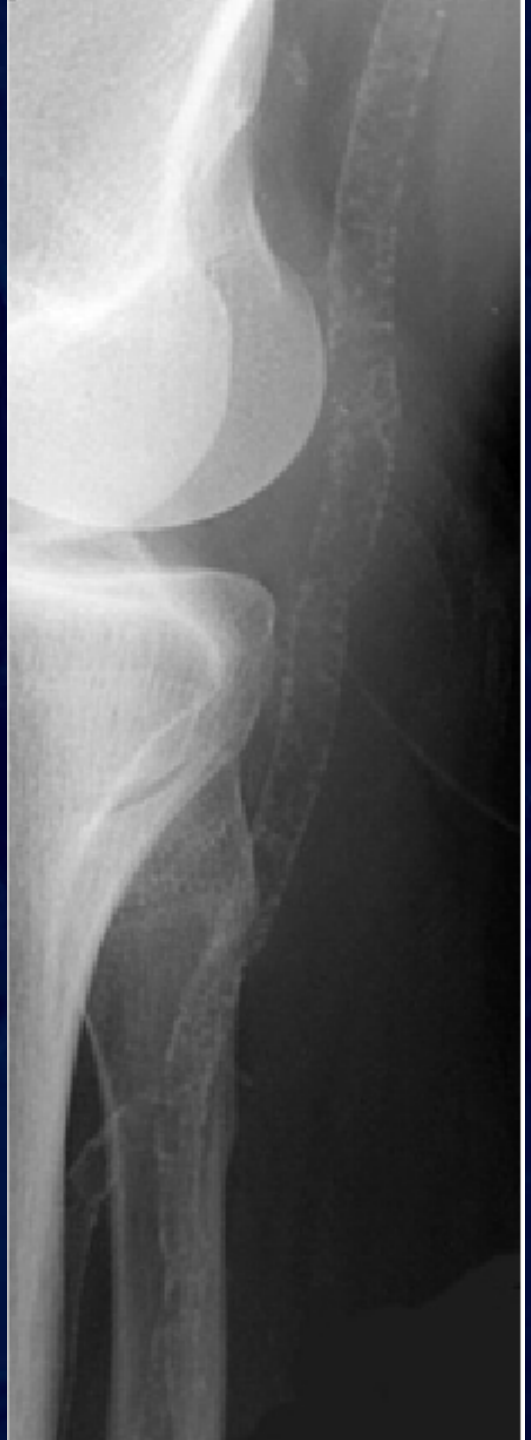


- Spine increase 0.3 T-score units more with alendronate than with placebo.
- Fem neck 0.03 T-score units higher (not significant)

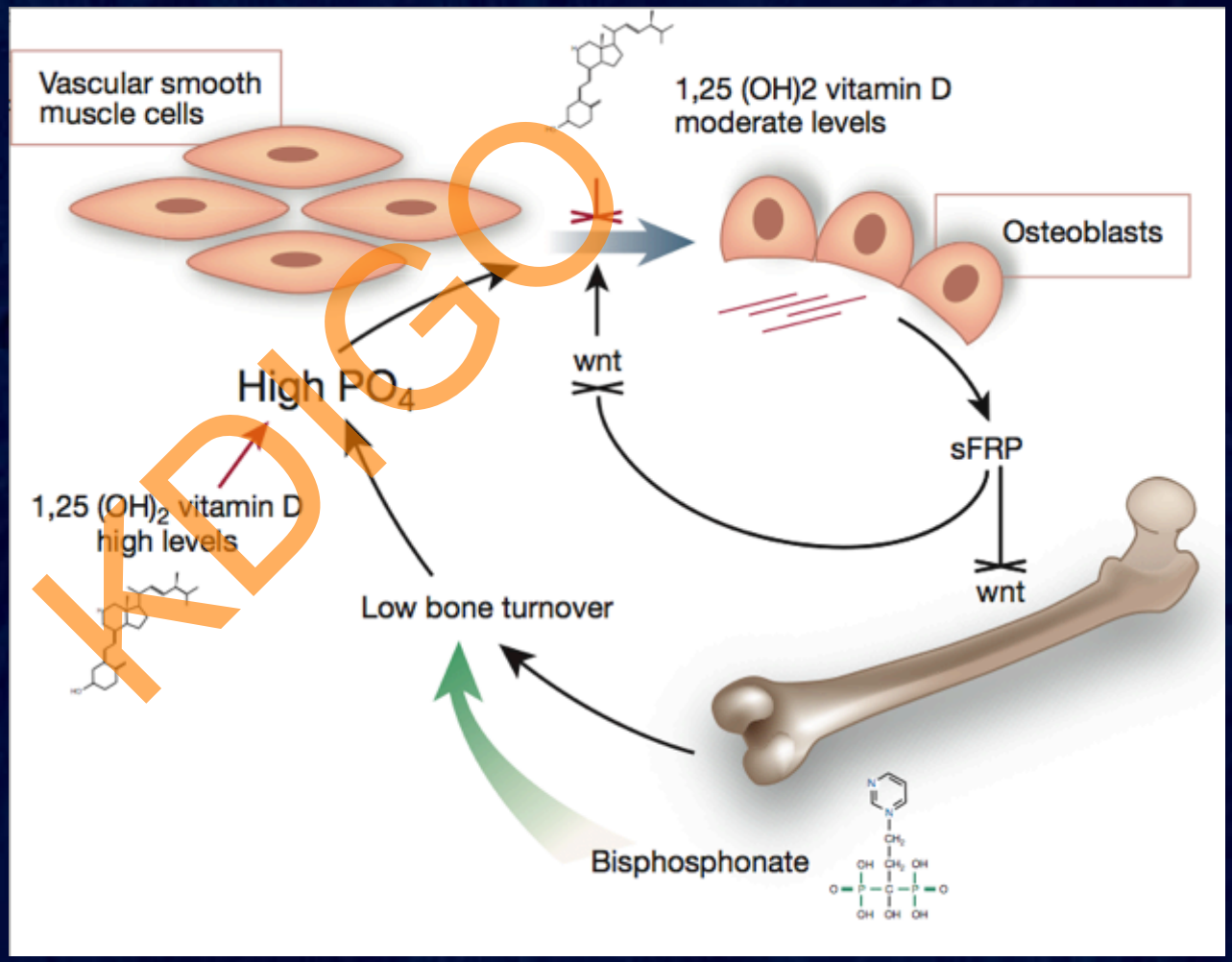
Toussaint, AJKD 2010

Vascular Calcification





Vascular calcifications and bone turnover



Model proposed by Cannata & Hruska

Bisphosphonates and vascular calcification

- Etidronate directly inhibits mineralization
- In some animal models bisphosphonates inhibit development of vascular calcifications
- If bone resorption is high, treatment can lower calcium and phosphate by decreasing bone resorption
- However, these drugs severely decrease bone formation and this will lead to unstable serum mineral levels because bone can not buffer calcium or phosphate

Bisphosphonates and vascular calcification

- In women with osteoporosis, vascular calcifications increased after treatment with alendronate or ibandronate, but this was not different from controls.

- In the MESA study, bisphosphonate users younger than 65 yrs had higher prevalence of vascular calcifications than non-users, but those older than 65 yrs had lower prevalence than non-users. There was no reason found to explain this difference.

- Studies of cardiovascular adverse effects in bisphosphonate users are inconsistent.

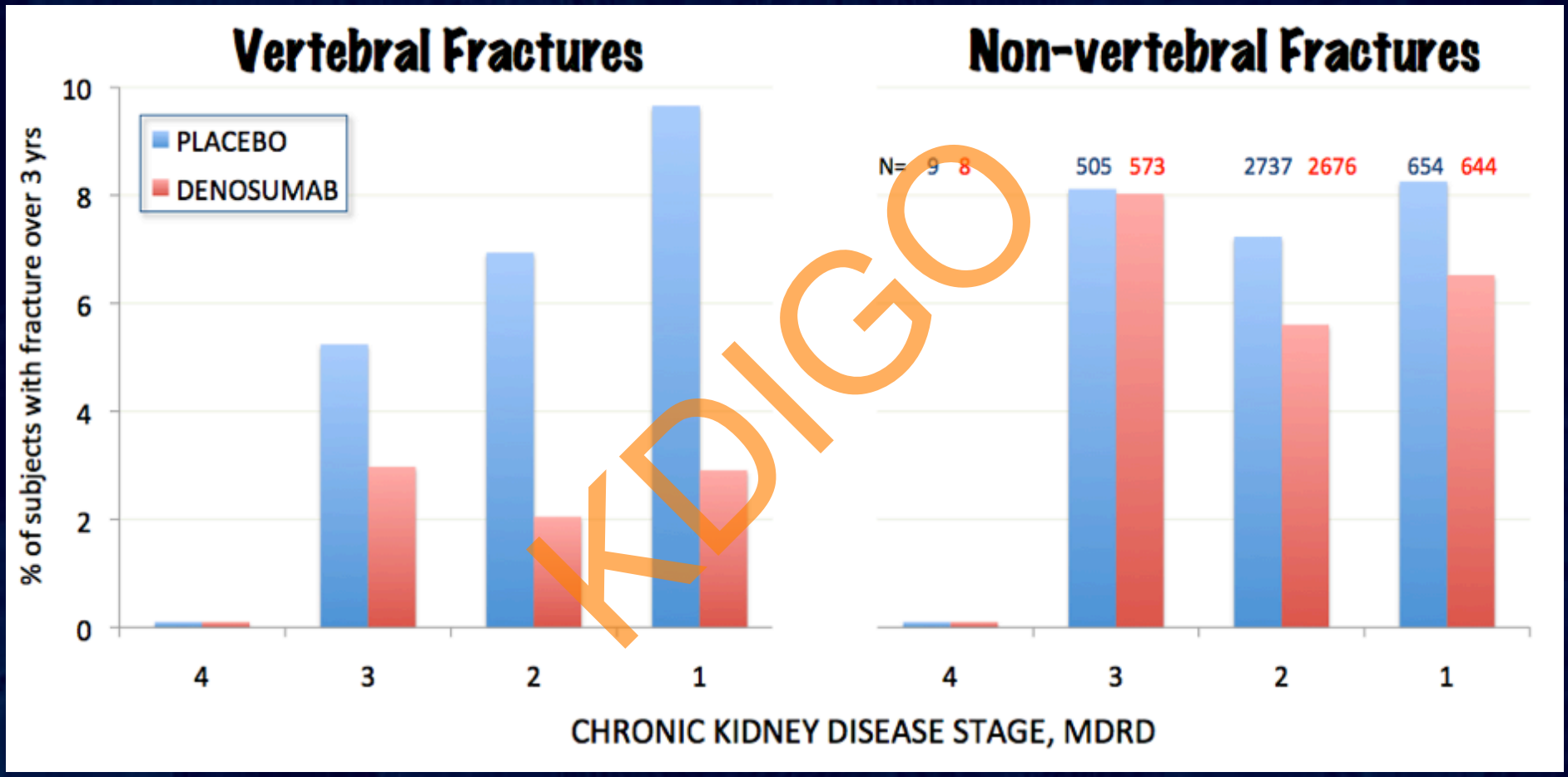
Cardiovascular events (MI) in bisphosphonate users: Mixed results

Author	Yr	Population	N on bis	Design	Duration	Risk of heart disease
Harris	2000	PMOP	1638	letter about RCT results	3 yrs	MI placebo 1.6% rise 1.5%
Bunch	2009	Utah health plan	7489	users vs controls (4:1)	~ 4 yrs	MI: 1% in both
Bunch	2009	Utah cath. pts	9623	retrospective database review	~ 4 yrs	MI: 8% nonusers, 10% users; HR CV mortality 1.38 (.96-1.99)
Camm	2010	PMOP	4916	post-hoc of RCT	3 yrs	No difference in MI Zol vs. placebo
Huang	2010	Taiwan	21,037	retrospecitive cohort	x 1 yr	RR MI 2.24 in users >1 yr with hx CV disease; 1.20 in all women vs. raloxifene
Lu	2011	Taiwan OP pts	6949	retrospective cohort	1 yr	Alendronate 10mg/day worse than 70mg/day
Kang	2012	OP pts Taiwan	1548	matched cohort	2 yr	HR 0.37 vs. untreated fracture patients
Vestergaard	2012	Denmark	57,221	cohort study	2.8 yrs	RR 1.36 (1.18-1.57)
Hartle	2012	CKD stage 3-4	3234	cohort	x 3.9 yrs	overall HR mortality 0.78 (0.67-0.91) but CV mortality 1.17 (0.96-1.42)

Be cautious about bisphosphonates in patients with CKD stages 4-5

1) Inadequate studies in this population.
2) Data from patients with early stages of CKD may not reliably be extrapolated to later stages because many features of bone disease appear in stages 4-5.
3) Bisphosphonates can increase PTH.
4) Bisphosphonates markedly reduce the bone formation rates.
5) Some rare but serious side effects have been reported with prolonged use.

Denosumab in CKD



Jamal, JBMR, 2011

Denosumab lowers serum calcium in CKD

Number with calcium <7.5

	Normal	Stage 2	Stage 3	Stage 4	Stage 5
N	12	13	13	9	8
# with low Ca	0	1	0	2	2

FDA

Raloxifene in women on dialysis

One year BMD results	Placebo N = 25	Raloxifene N = 25
Spine	.952 - .949	.942 - .973*
Hip	.745 - .753	.722 - .727

Hernandez, 2003, Kidney Int

Raloxifene : Cross-links

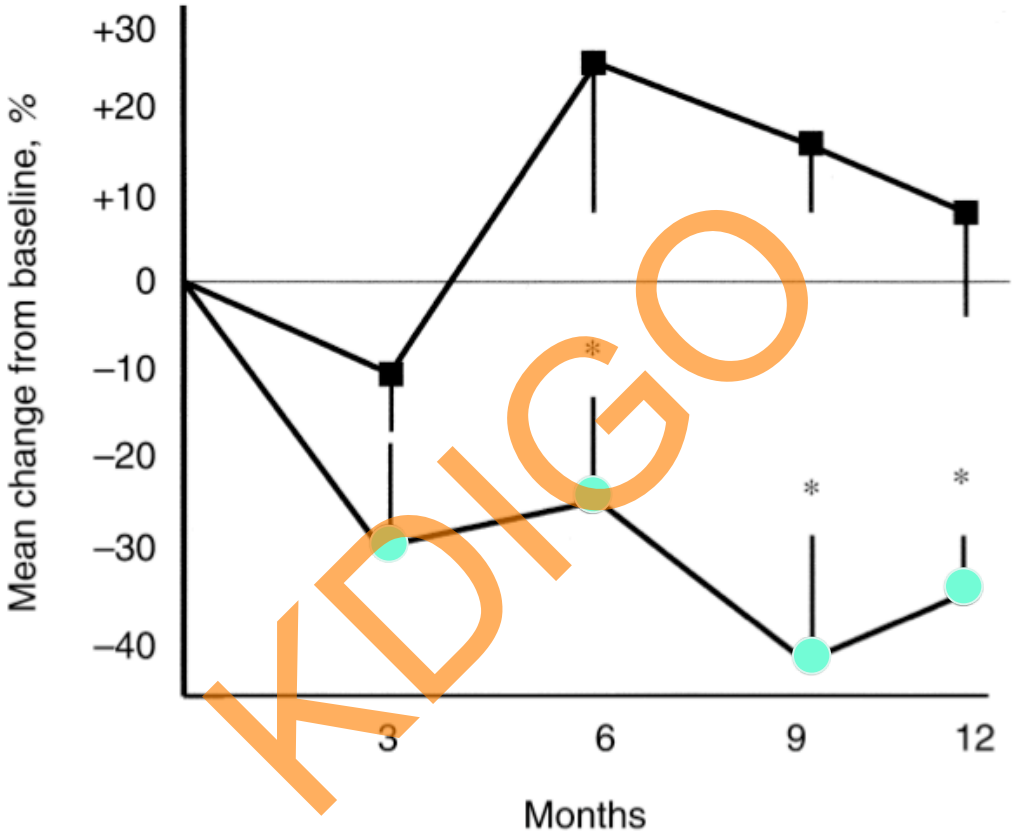
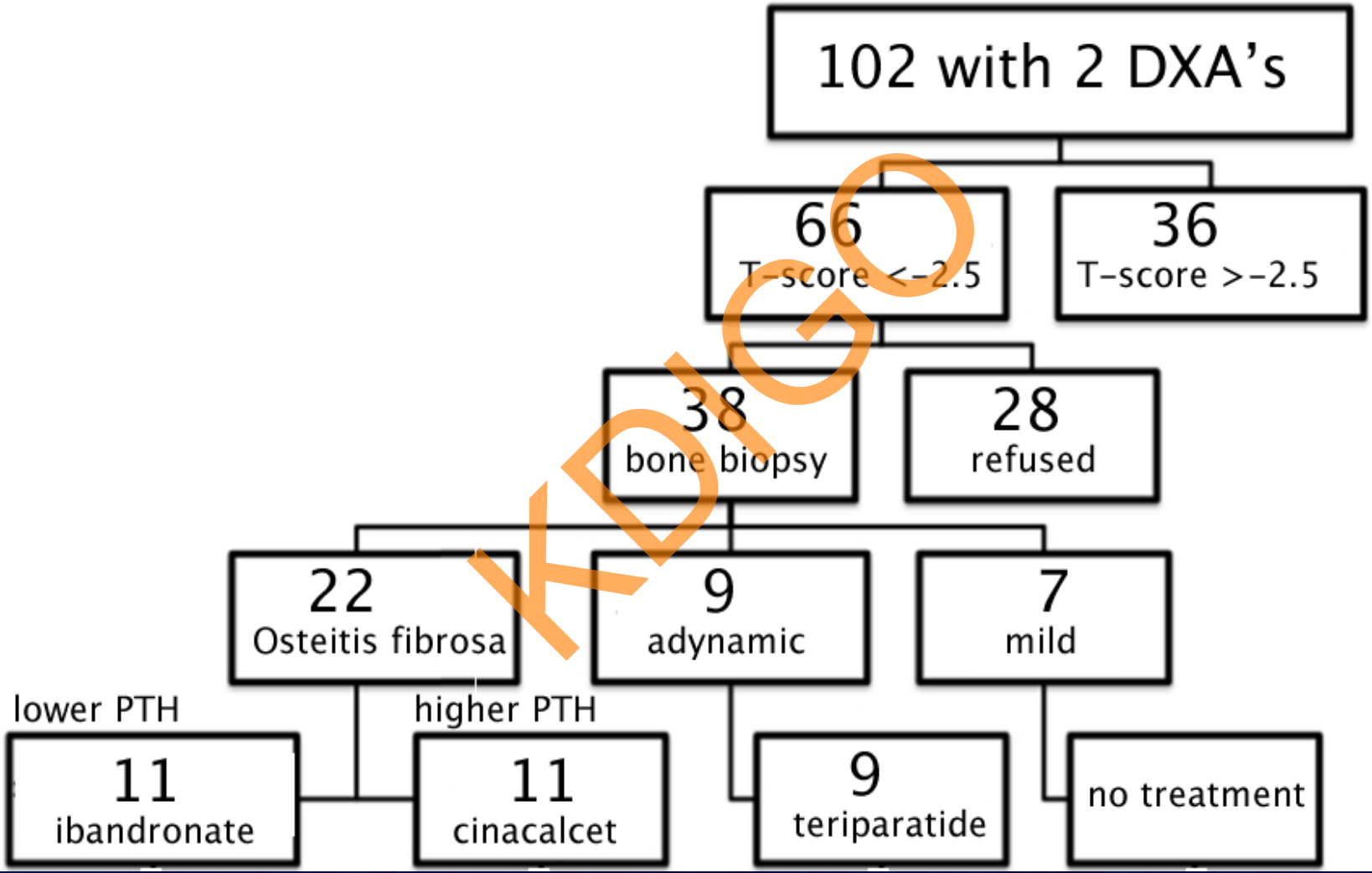


Fig. 1. Mean (SD) percentage changes from baseline in serum pyridinoline crosslinks levels in postmenopausal hemodialyzed women given raloxifene (60 mg/day) (●) or placebo (■) for 1 year. *$P < 0.01$ vs. placebo.

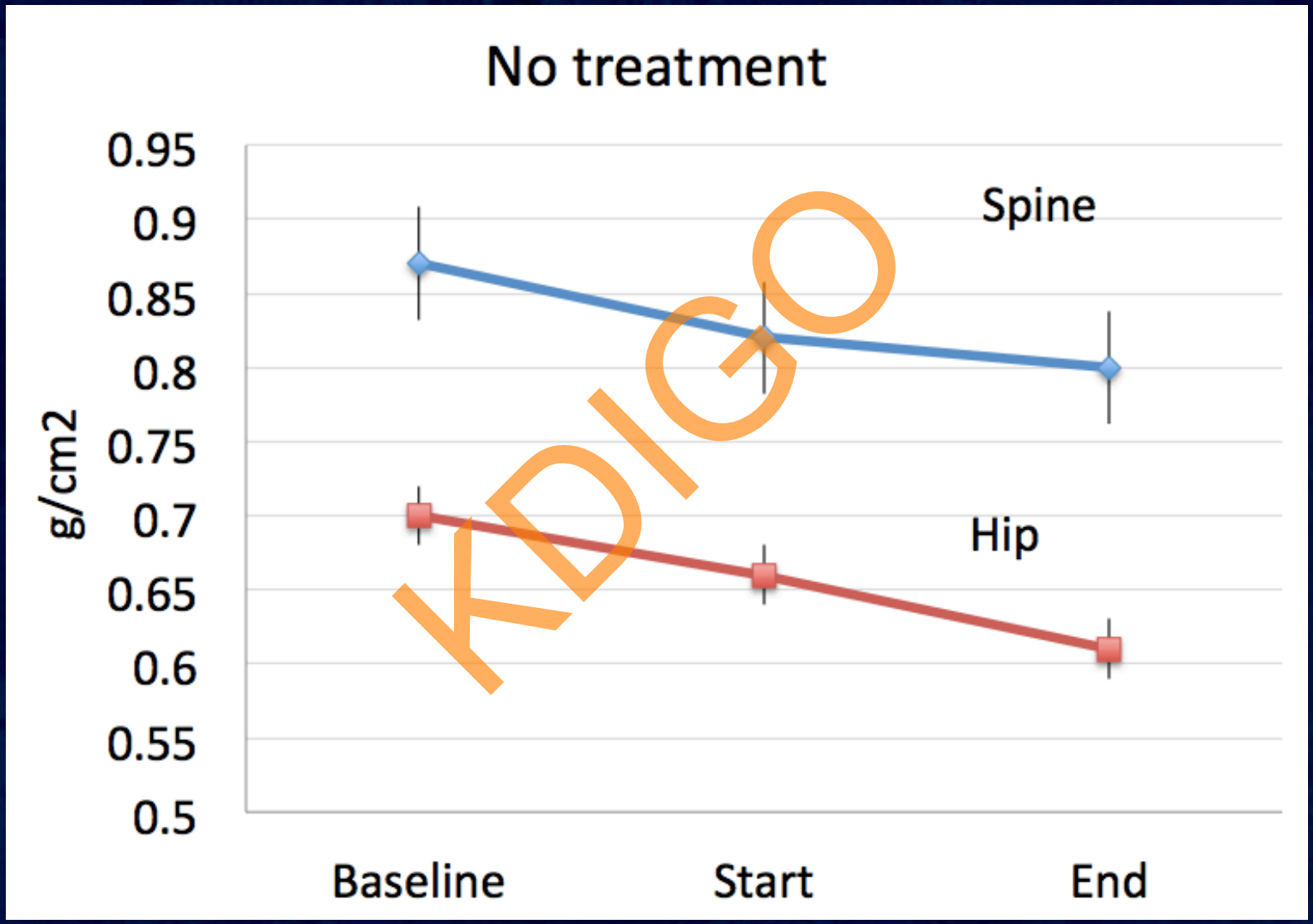
Hernandez, 2003, Kidney Int

Osteoporosis medicines in CKD-MBD



Mitsopoulos AJN 2012

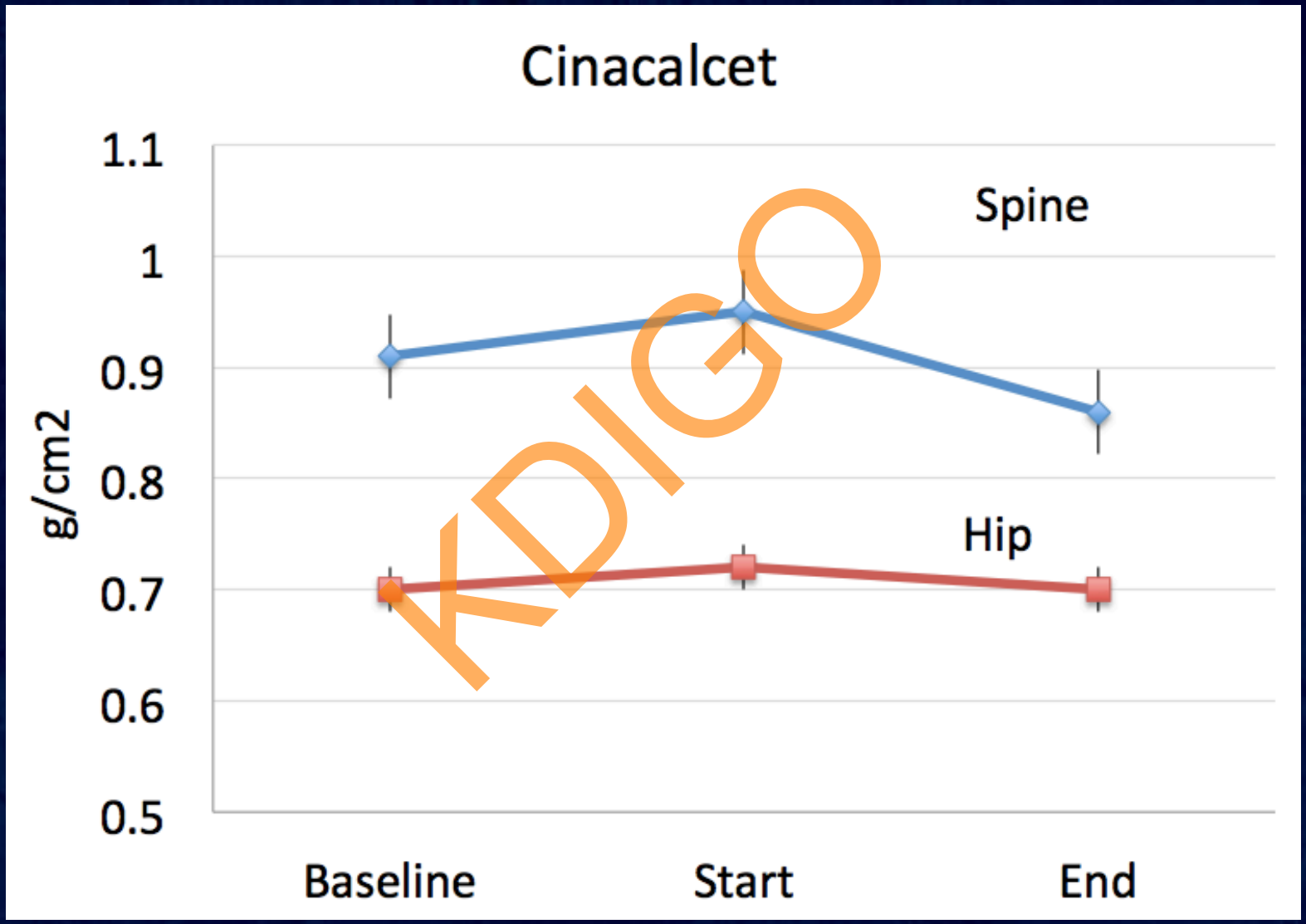
Osteoporosis medicines in CKD-MBD



N = 5; PTH = 267

Mitsopoulos AJN 2012

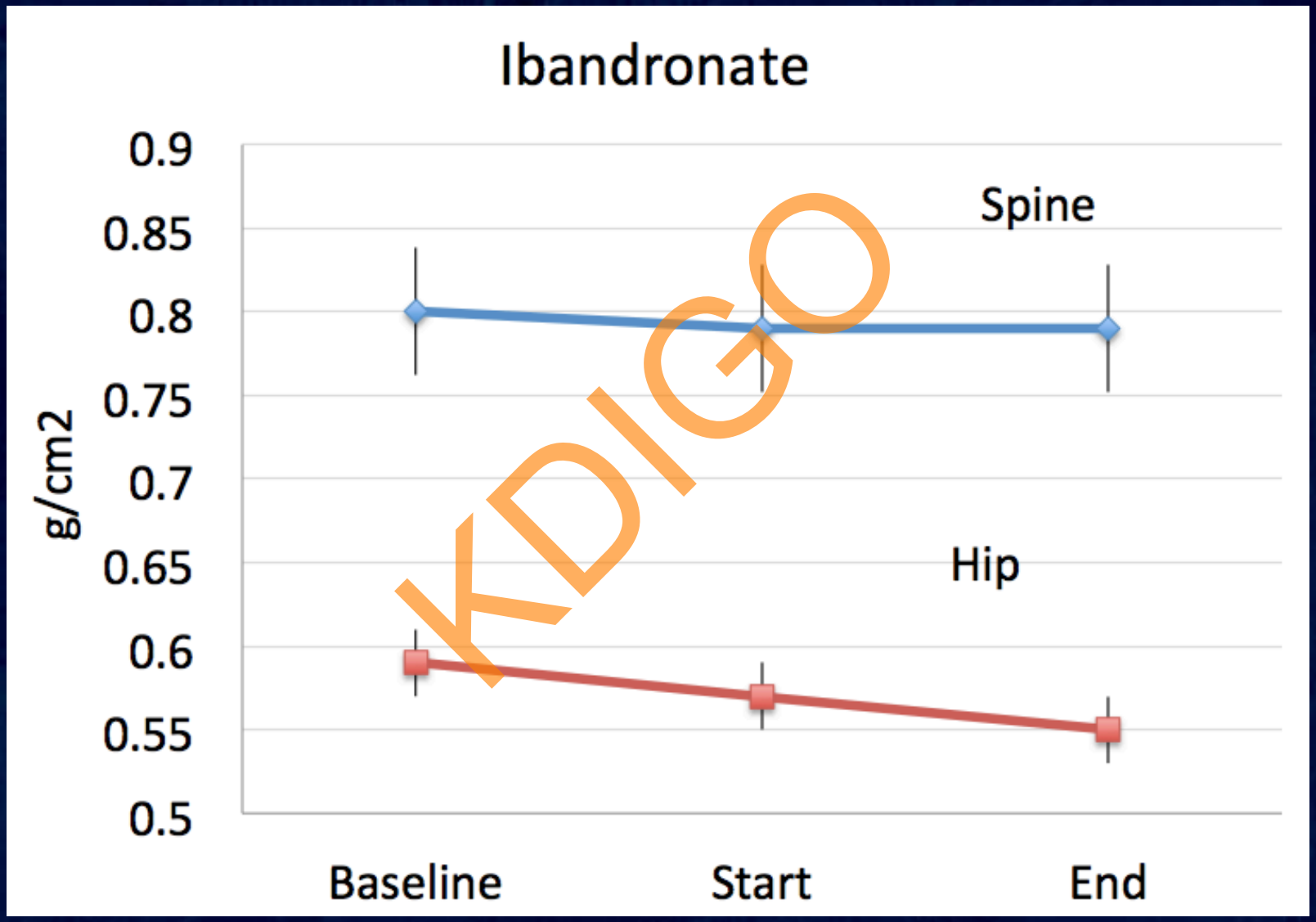
Osteoporosis medicines in CKD-MBD



N = 8; PTH = 487

Mitsopoulos AJN 2012

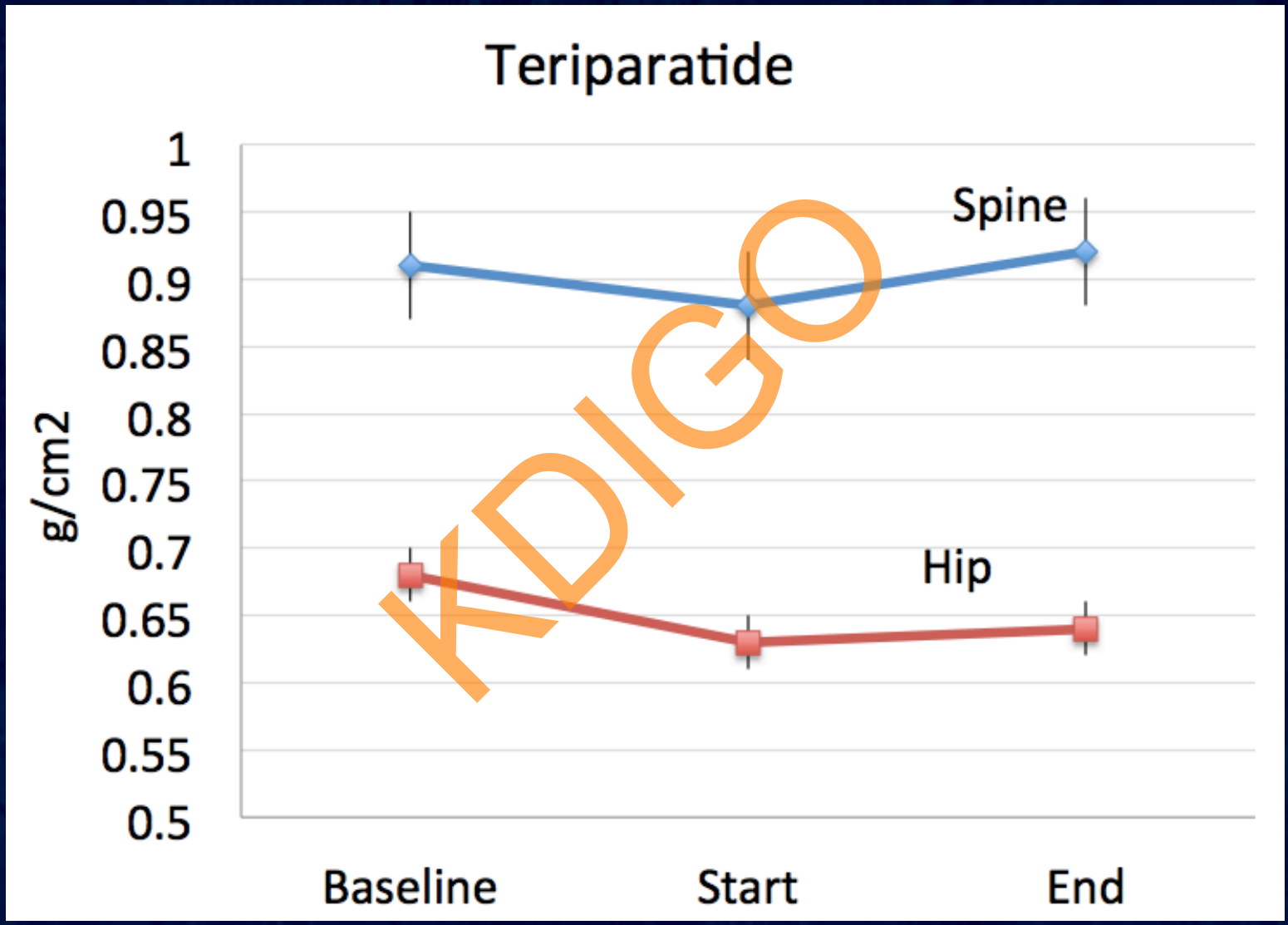
Osteoporosis medicines in CKD-MBD



N = 7; PTH = 250 pg/ml

Mitsopoulos AJN 2012

Osteoporosis medicines in CKD-MBD

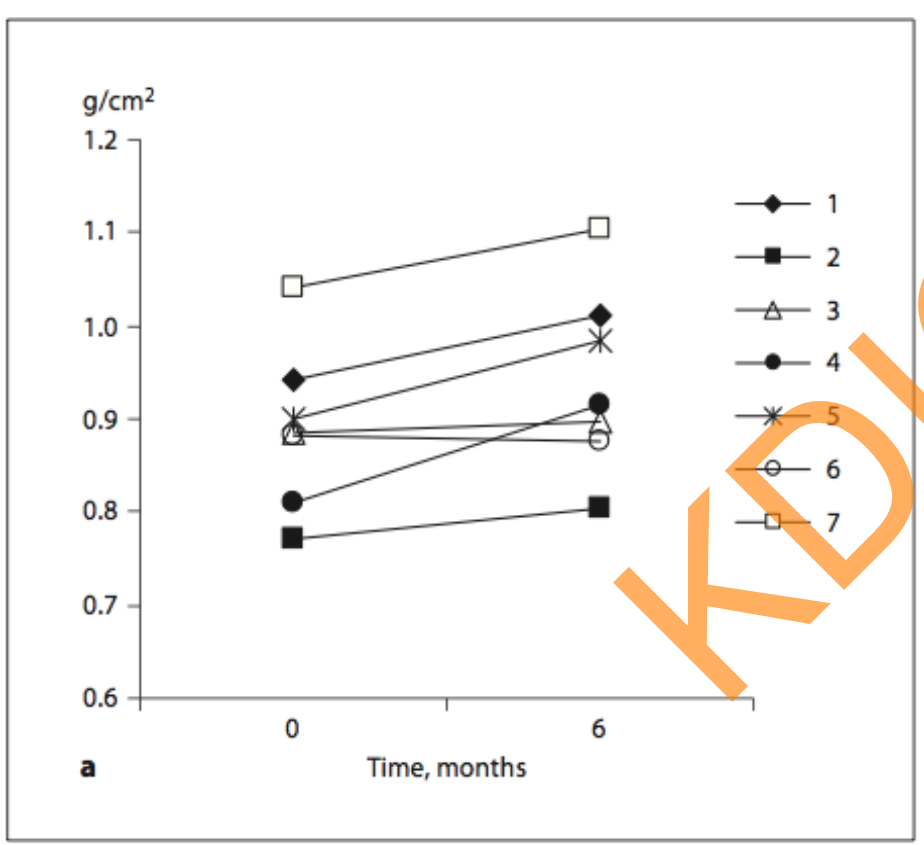


N = 8; mean PTH = 150 pg/ml

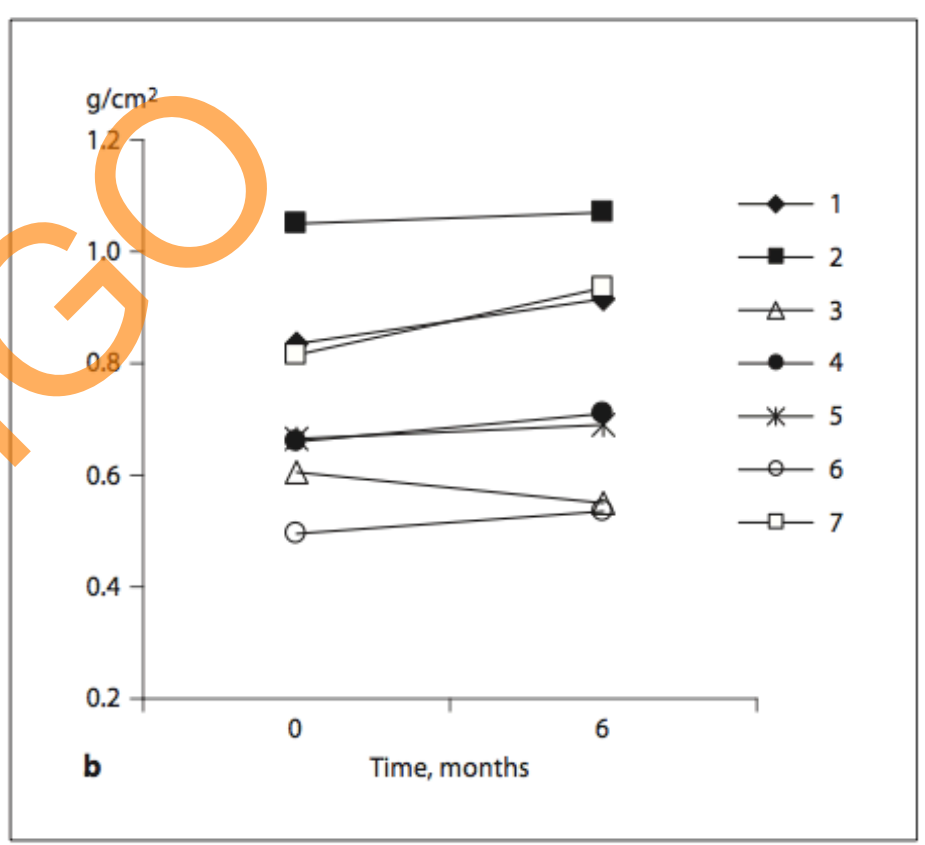
Mitsopoulos AJN 2012

Teriparatide in CKD-MBD

SPINE



HIP



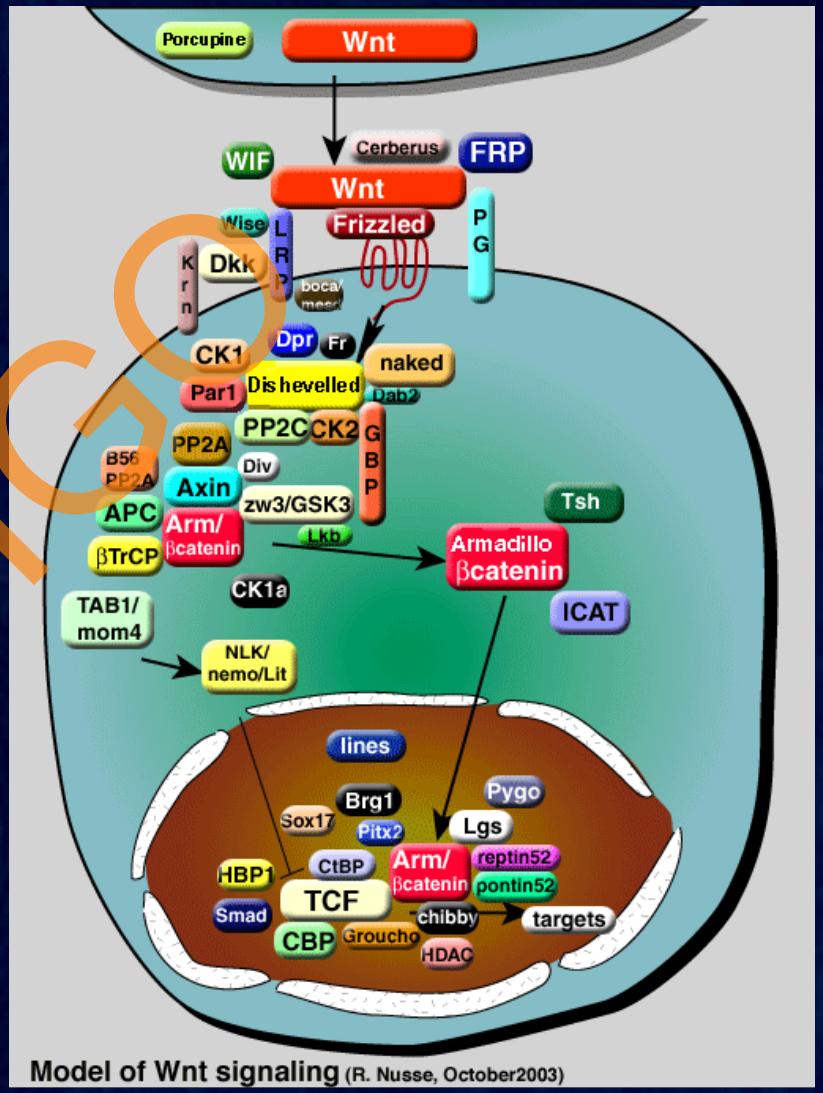
N = 7; hx PTX in 6

Cejka, Kidney BP Res 2010

Wnt signalling pathway

Wnt-signalling pathway is necessary for osteoblastic cell differentiation

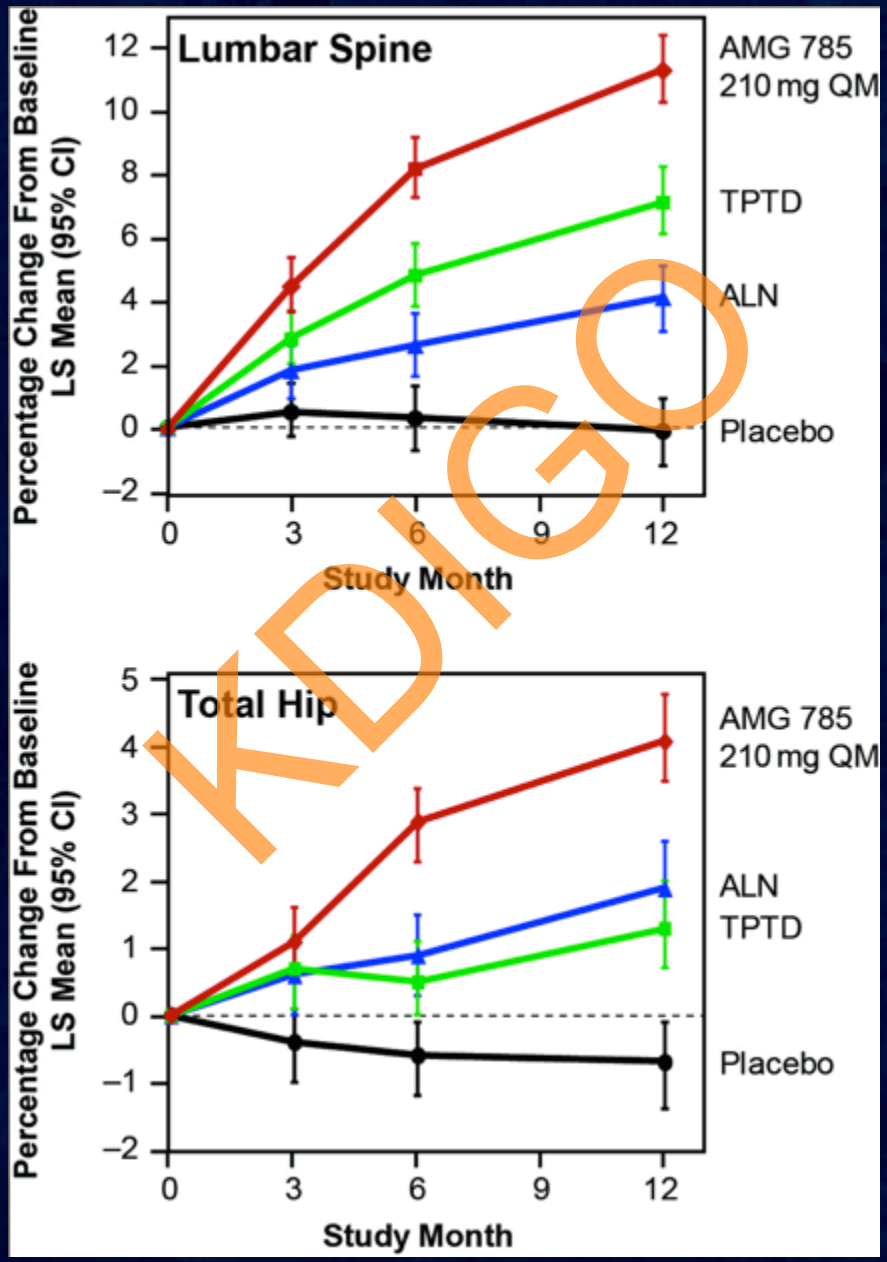
Inhibitors of this pathway include sclerostin, dickkopf, wnt-inhibitory factor and secreted frizzled related protein.



Sclerostin antibodies increase formation of normal bone

Li, JBMR, 2009

Romosozumab



Presented 2012
ASBMR

SOST inhibits prostate cancer invasion

Bryan Hudson, Gabriela Loots, Nick Hum, Cindy Thomas.
Lawrence Livermore National Laboratory: ASBMR 2012

SOST did not change the proliferation of prostate cells in culture.

In a double-chamber system, adding SOST decreased the invasiveness of the prostate cancer cells.

Bone from *Sost* k/o mice had increased invasion of prostate cancer cells.

Sost k/o mice had more tumor formation when injected with prostate cancer cells;
Lrp5 k/o mice had decreased tumor formation.

Wnt signalling: potential concerns

- Sclerostin involved in FGF23 secretion
- Wnt signalling increases conversion of vascular smooth muscle cells into osteoblasts
- Some β catenin activated mice get AML
- Wnt signalling may worsen renal disease and cause podocyte dysfunction, proteinuira and epithelial damage.

Neuromuscular function and fracture in CKD

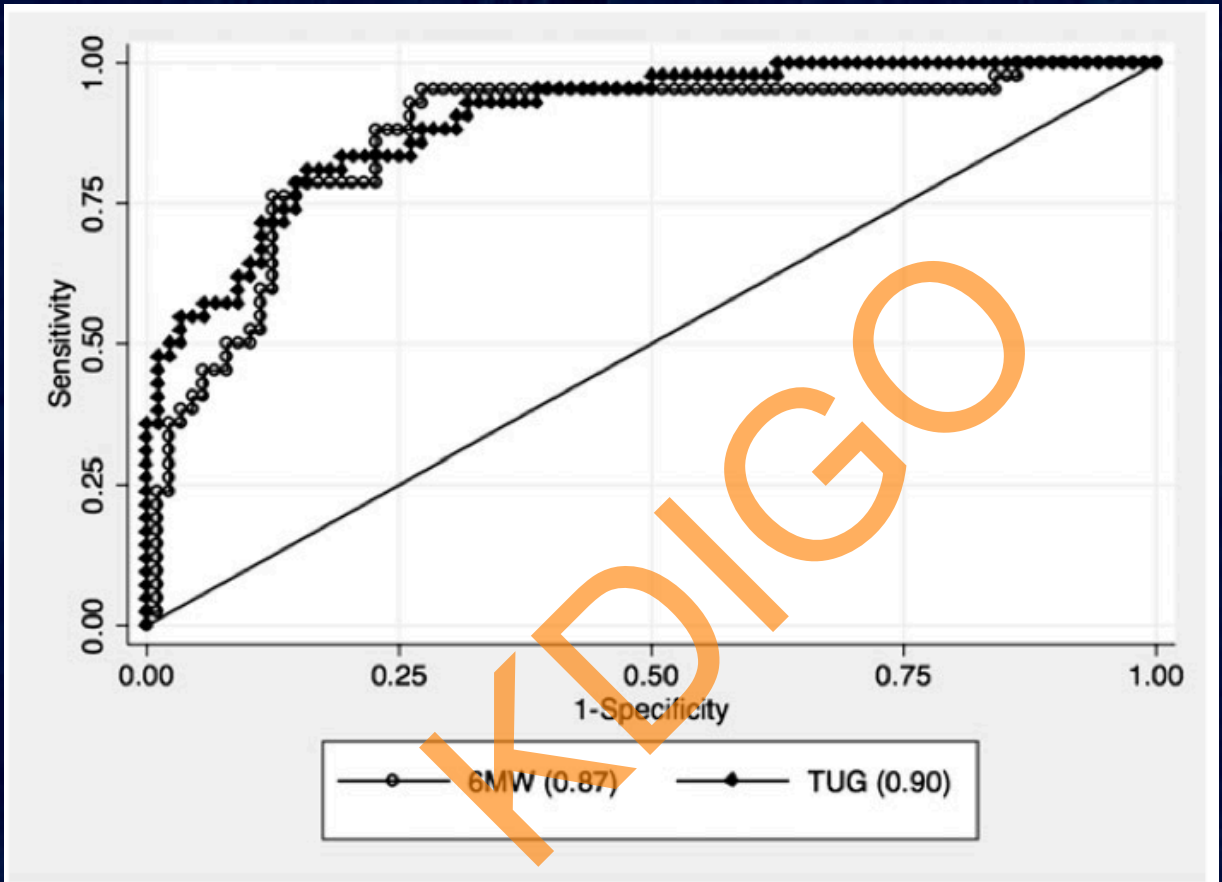


Fig. 1. Relationship between sensitivity and specificity of the 6MW and the TUG and the ability to identify patients with fracture (Fracture defined as self-reported low-trauma fracture since age 40 and/or prevalent vertebral fracture by morphometry at study entry). The area under the receiver operating characteristic curve for the 6MW was 0.87 and for TUG was 0.90 ($P > 0.05$).

N = 211
CKD 3-5

West, Nephrol Dial Tx, 2012

Exercise

Don’t forget about falls!