Bone Imaging and Fracture Discrimination

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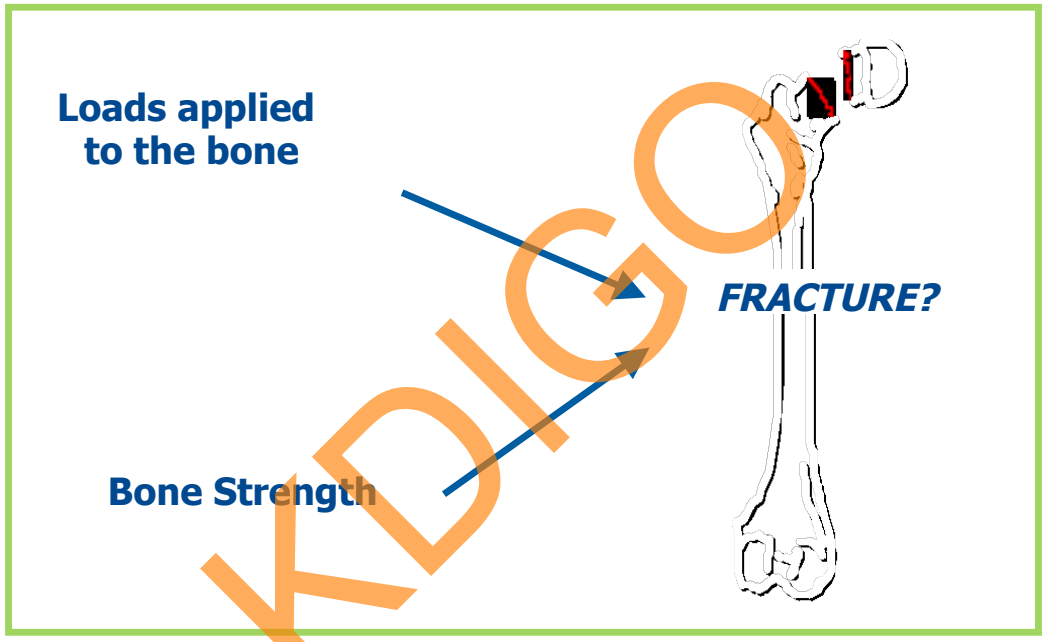
Disclosure of Interests

- Consultant: Genzyme, Novartis, Shire, Warner-Chillcott
- Speaker Bureau with: Amgen, Genzyme, Novartis, Shire, Warner-Chillcott

Objectives

- Etiology of fractures
- Epidemiology of fractures
- Bone imaging and fracture discrimination
- Potential bone quality guidelines that may need to be updated

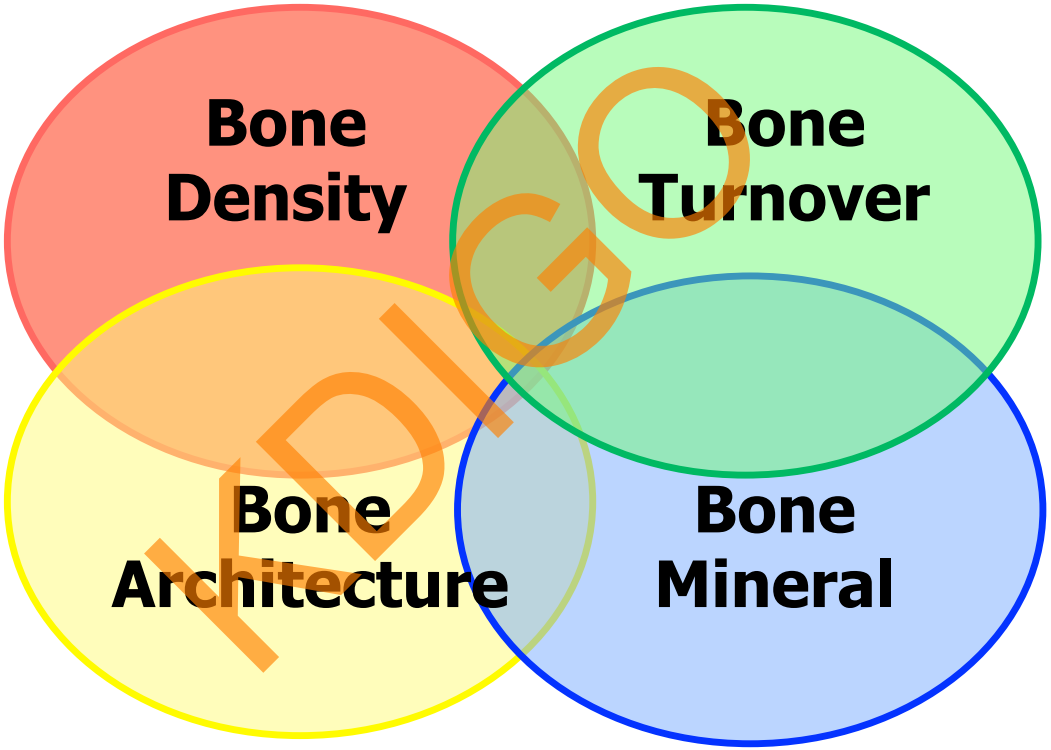
Why Bones Break



$$\frac{\text{Applied Load}}{\text{Bone Strength}} > 1, \text{ fracture will occur}$$

Bouxsein MJ Bone Joint Surg Am. 2001

Contributors to Bone Strength



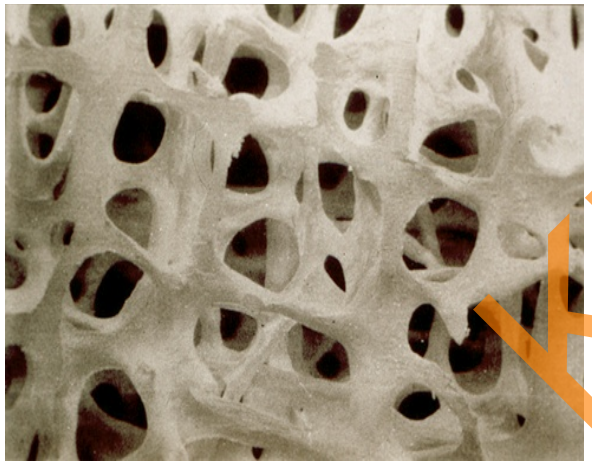
KDIGO CKD-MBD

- A systemic disorder of mineral and bone metabolism due to CKD manifested by either one or a combination of the following:
  - Vascular or other soft tissue calcification
  - Abnormalities of calcium, phosphorus, PTH or Vitamin D metabolism
  - Abnormalities in bone turnover, mineralization, volume, linear growth or strength

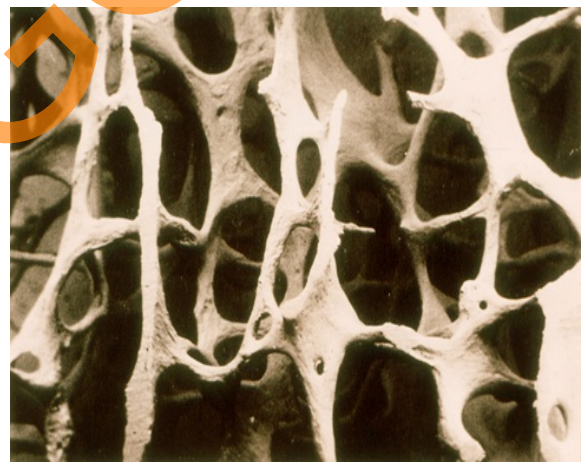
Moe et al. KI. 2006.

Definition of Osteoporosis: 2001

"a skeletal disorder characterized by compromised bone strength predisposing a person to an increased risk of fracture. Bone strength primarily reflects the integration of bone density and bone quality"



Normal bone



Osteoporosis

NIH consensus conference 2001

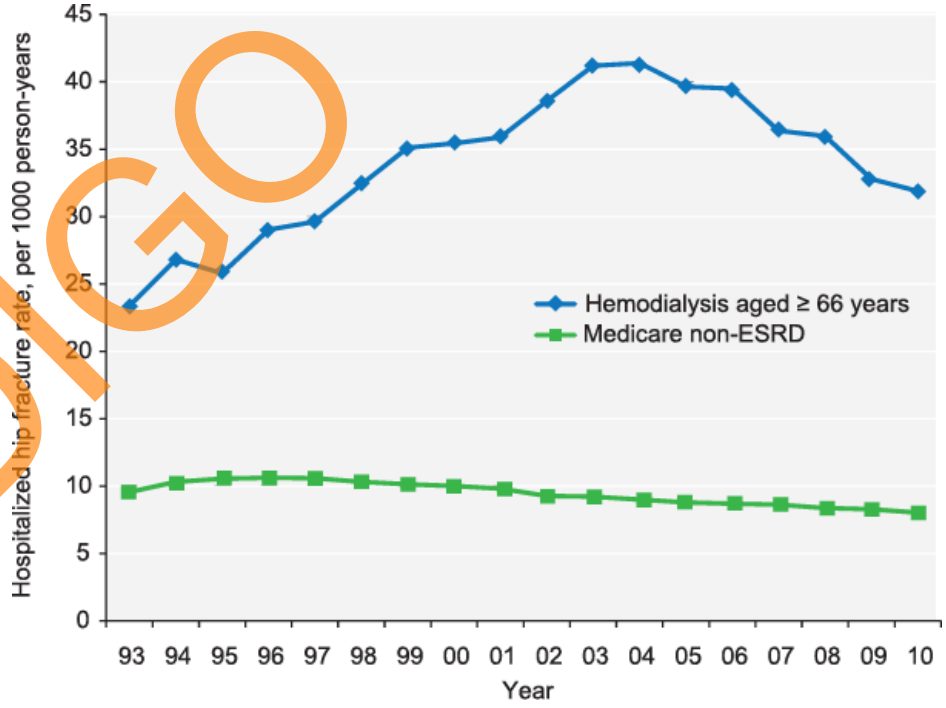
Fractures in Stage 5D

- Fracture rates /post discharge outcomes from 2000-2009 using medicare data (US Renal Data System)
- Constant rate of fracture over time; high
- Pelvis/hip: 20.6 per thousand patient years
- Higher morbidity and mortality if admitted with fracture
  - 3.8 to 5.2 more hospitalizations
  - 47% discharged to skilled nursing facility
  - Mortality 2x higher

Beaubrun A et al JASN 2013

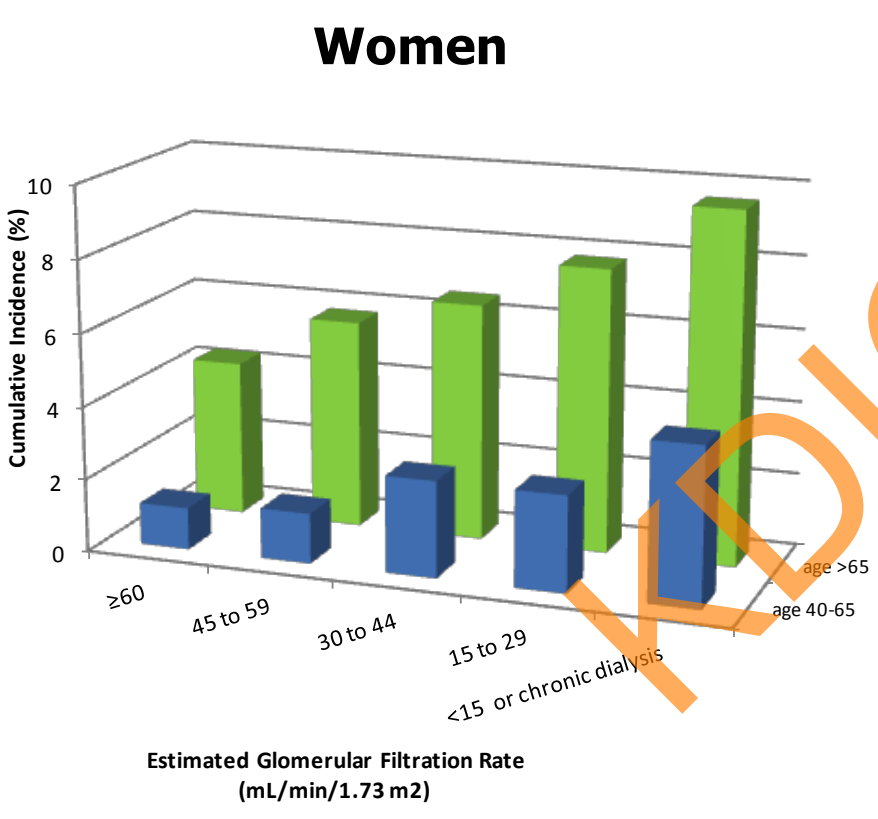
Hip Fractures in 5D

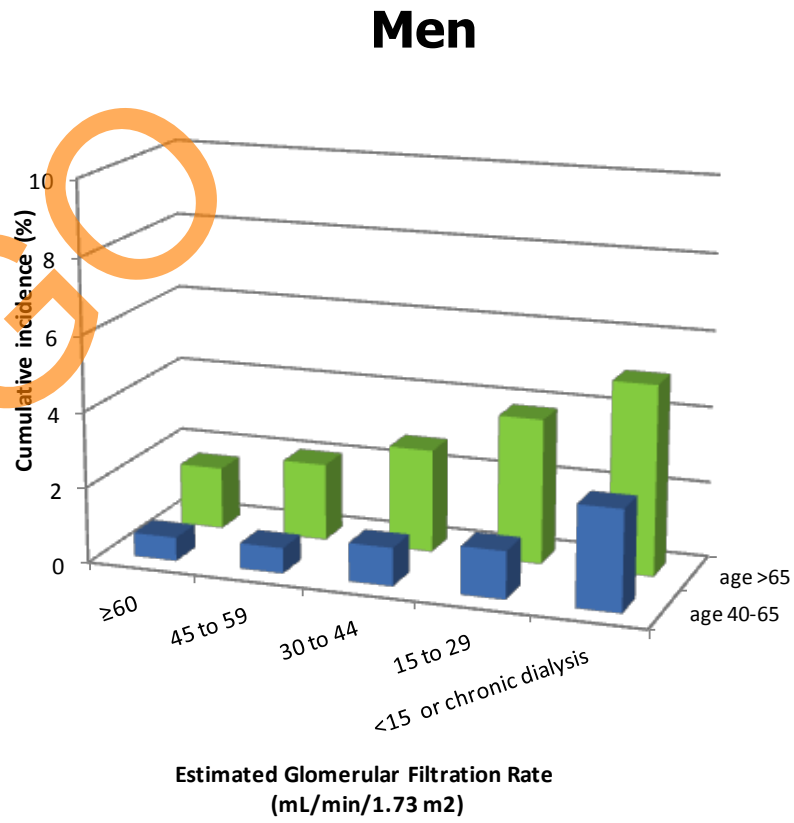
- 2 cohorts using medicare data
  - HD cohort
  - Non ESRD (age >65, medicare)
- Hip fractures 93-2010
- Decline in fractures since 2003
  - Calcium based binders
  - Cinacalcet use
  - NKF-KDOQI guidelines 2003



Areneson TJ et al AJKD 2013

Fractures Across the Spectrum of CKD





Naylor et al. 2013 ASN Abstract

Summary

- Fractures are due to impaired bone strength
- Fracture rates are higher in CKD than non CKD
- Noninvasive methods to assess fracture risk

KDIGO Recommendations

3.2.2.

In patients with CKD stages 3 - 5D with evidence of CKD-MBD we suggest that BMD testing not be performed routinely because BMD does not predict fracture risk as it does in the general population, and BMD does not predict the type of renal osteodystrophy (2B)

KDIGO RATINGS

- Level 2B: we suggest –
  - The majority of people in your situation would want the recommended course of action, but many would not (patient perspective)
  - Different choices will be appropriate for different patients (clinicians)
  - The recommendation is likely to require substantial debate and involvement of stake holders before policy can be determined (policy makers)
  - B: Moderate evidence – the true effect is likely to be close to the estimate of the effect but there is a possibility that it is substantially different

Revisit the Recommendation?

- Are there important and relevant new data?
- Do the data suggest the recommendation might or should change?

Tonelli M 2013

A Shift in the Balance

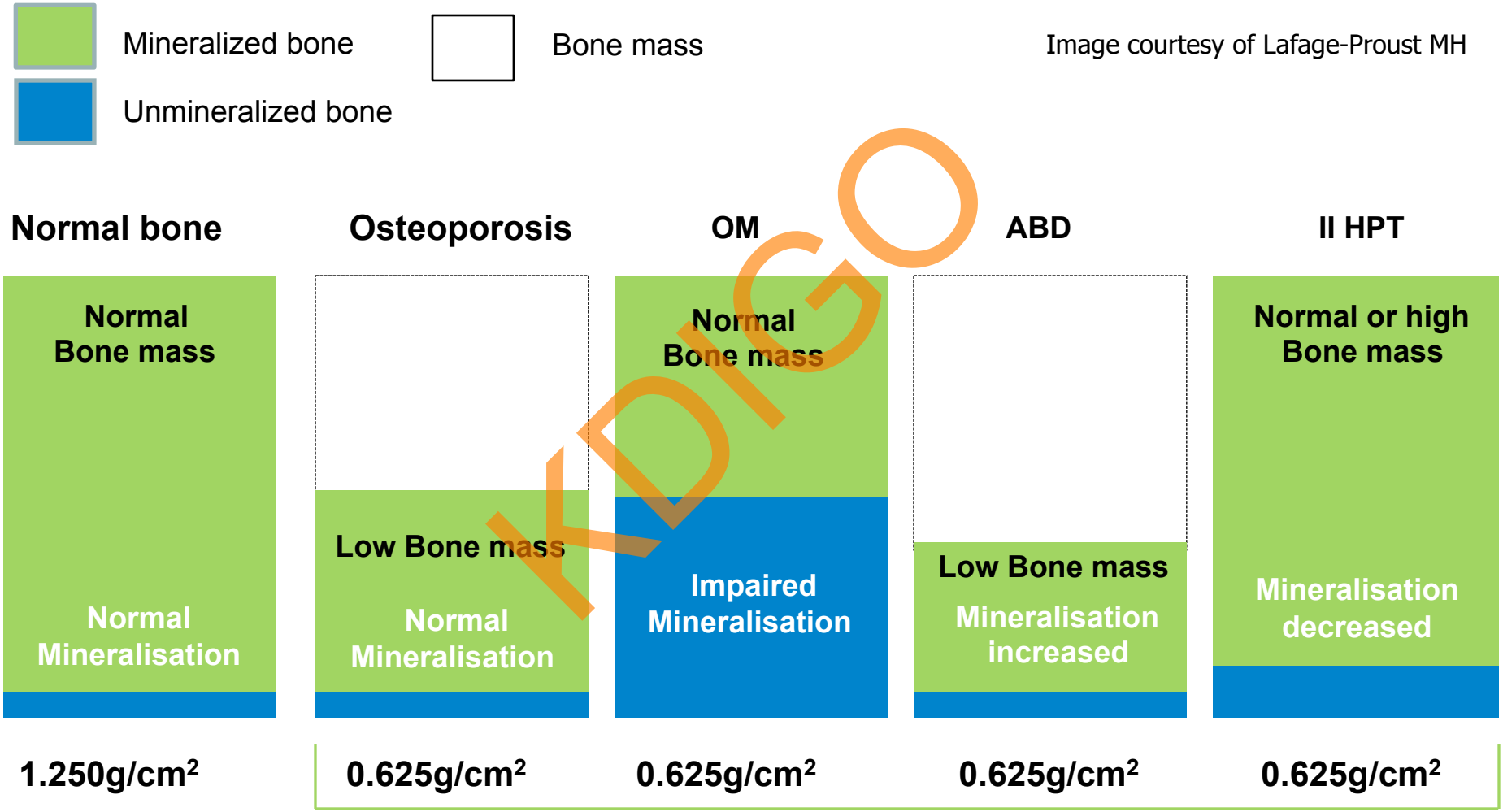
Strengths of DXA

- Quick, noninvasive
- Measurements correlate with fracture risk
- Predictive ability similar to that of BP to predict stroke
- Better than ability of cholesterol to predict coronary artery disease

Limitations of DXA

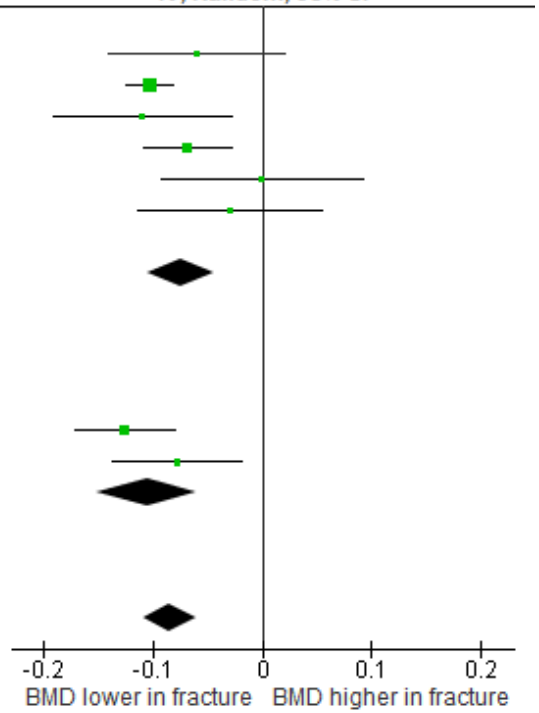
- No threshold
- Static assessment of bone
- Areal bone mineral density
- No data on microarchitecture
- Results are meant for diagnosis

Limitations with DXA in CKD

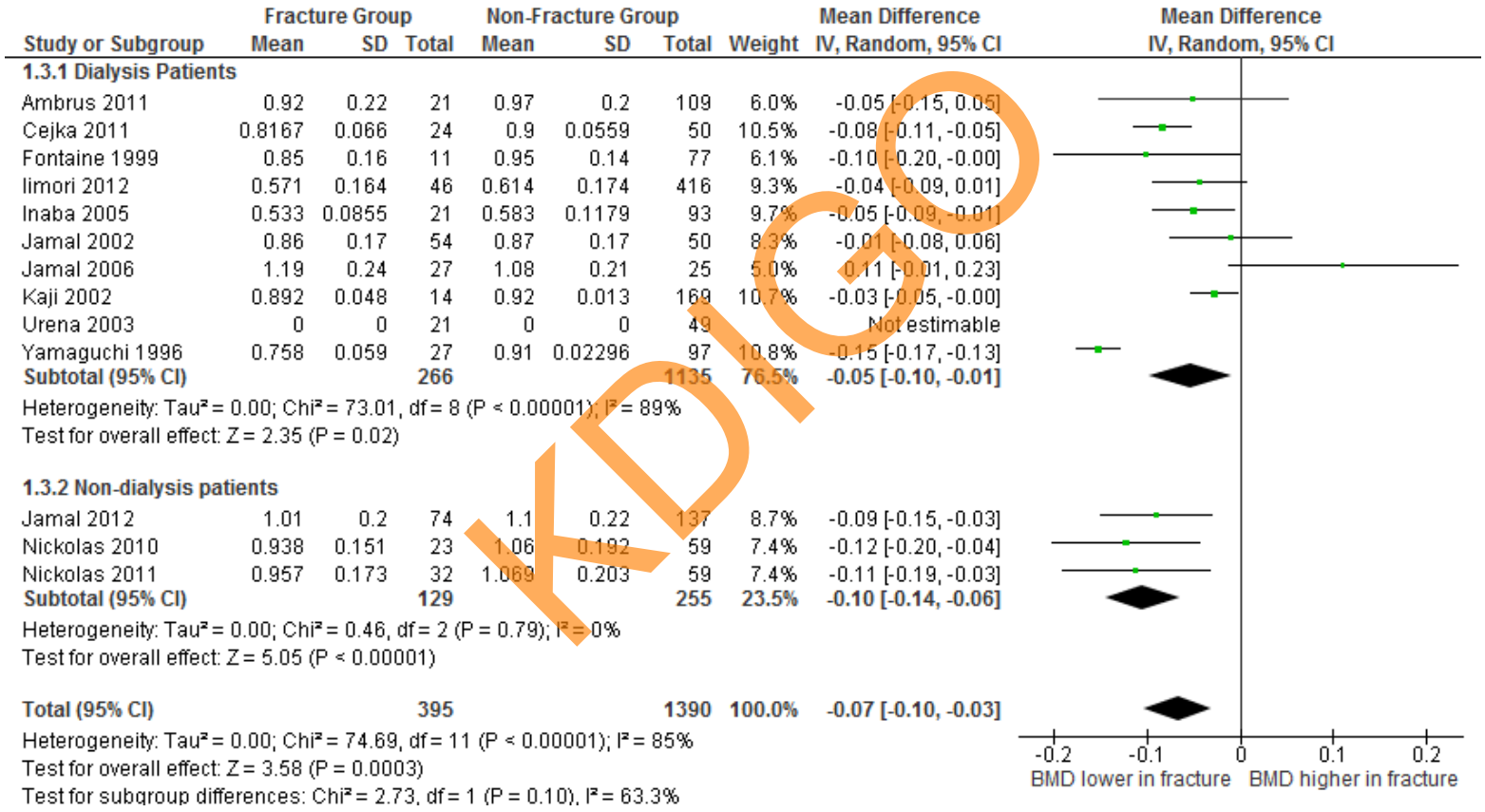


Total Hip BMD by DXA

Study or Subgroup	Fracture Group Mean	SD	Total	Non-Fracture Group Mean	SD	Total	Weight	Mean Difference IV, Random, 95% CI
1.2.1 Dialysis Patients								
Ambrus 2011	0.66	0.18	21	0.72	0.14	109	7.0%	-0.06 [-0.14, 0.02]
Cejka 2011	0.573	0.048	24	0.6764	0.037	50	28.3%	-0.10 [-0.13, -0.08]
Fontaine 1999	0.62	0.13	11	0.73	0.12	77	7.0%	-0.11 [-0.19, -0.03]
Iimori 2012	0.567	0.133	46	0.636	0.141	416	17.9%	-0.07 [-0.11, -0.03]
Jamal 2002	1.3	0.23	54	1.3	0.25	50	5.7%	0.00 [-0.09, 0.09]
Jamal 2006	0.76	0.17	27	0.79	0.14	25	6.6%	-0.03 [-0.11, 0.05]
Urena 2003	0	0	21	0	0	49		Not estimable
Subtotal (95% CI)			**204**			**776**	**72.5%**	**-0.07 [-0.11, -0.04]**
Heterogeneity: Tau² = 0.00; Chi² = 8.78, df = 5 (P = 0.12); I² = 43%								
Test for overall effect: Z = 4.81 (P < 0.00001)								
1.2.2 Non-dialysis patients								
Nickolas 2010	0.621	0.0718	23	0.747	0.134	59	16.0%	-0.13 [-0.17, -0.08]
Nickolas 2011	0.677	0.127	32	0.755	0.154	59	11.4%	-0.08 [-0.14, -0.02]
Subtotal (95% CI)			**55**			**118**	**27.5%**	**-0.11 [-0.15, -0.06]**
Heterogeneity: Tau² = 0.00; Chi² = 1.61, df = 1 (P = 0.21); I² = 38%								
Test for overall effect: Z = 4.47 (P < 0.00001)								
Total (95% CI)			**259**			**894**	**100.0%**	**-0.08 [-0.11, -0.06]**
Heterogeneity: Tau² = 0.00; Chi² = 11.33, df = 7 (P = 0.12); I² = 38%								
Test for overall effect: Z = 6.91 (P < 0.00001)								
Test for subgroup differences: Chi² = 1.21, df = 1 (P = 0.27), I² = 17.5%								

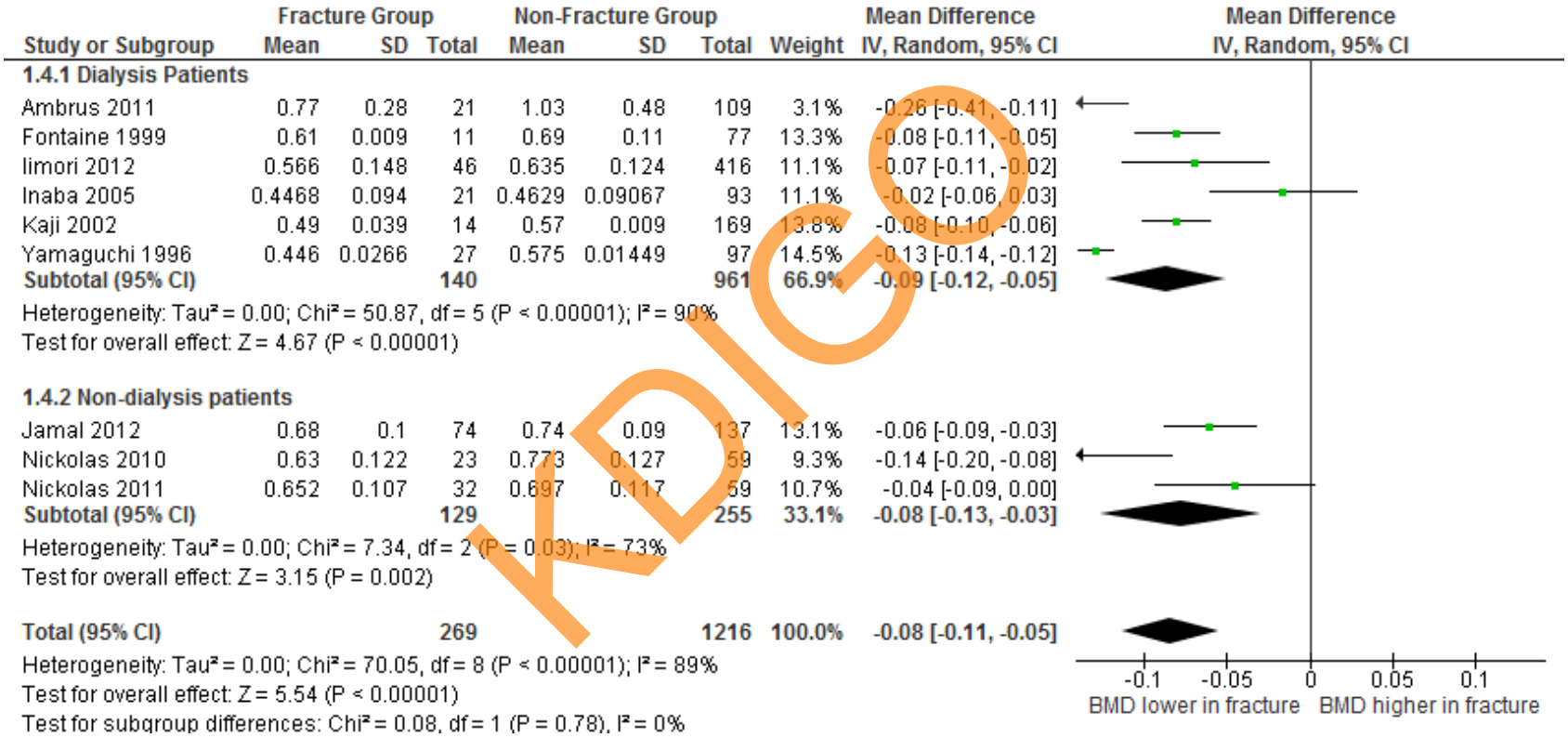


Lumbar Spine BMD by DXA



Study or Subgroup	Fracture Group Mean	SD	Total	Non-Fracture Group Mean	SD	Total	Weight	Mean Difference IV, Random, 95% CI
1.3.1 Dialysis Patients								
Ambrus 2011	0.92	0.22	21	0.97	0.2	109	6.0%	-0.05 [-0.15, 0.05]
Cejka 2011	0.8167	0.066	24	0.9	0.0559	50	10.5%	-0.08 [-0.11, -0.05]
Fontaine 1999	0.85	0.16	11	0.95	0.14	77	6.1%	-0.10 [-0.20, -0.00]
Iimori 2012	0.571	0.164	46	0.614	0.174	416	9.3%	-0.04 [-0.09, 0.01]
Inaba 2005	0.533	0.0855	21	0.583	0.1179	93	9.7%	-0.05 [-0.09, -0.01]
Jamal 2002	0.86	0.17	54	0.87	0.17	50	8.3%	-0.01 [-0.08, 0.06]
Jamal 2006	1.19	0.24	27	1.08	0.21	25	5.0%	0.11 [-0.01, 0.23]
Kaji 2002	0.892	0.048	14	0.92	0.013	169	10.7%	-0.03 [-0.05, -0.00]
Urena 2003	0	0	21	0	0	49		Not estimable
Yamaguchi 1996	0.758	0.059	27	0.91	0.02296	97	10.8%	-0.15 [-0.17, -0.13]
Subtotal (95% CI)			**266**			**1135**	**76.5%**	**-0.05 [-0.10, -0.01]**
Heterogeneity: Tau² = 0.00; Chi² = 73.01, df = 8 (P < 0.00001); I² = 89%								
Test for overall effect: Z = 2.35 (P = 0.02)								
1.3.2 Non-dialysis patients								
Jamal 2012	1.01	0.2	74	1.1	0.22	137	8.7%	-0.09 [-0.15, -0.03]
Nickolas 2010	0.938	0.151	23	1.06	0.192	59	7.4%	-0.12 [-0.20, -0.04]
Nickolas 2011	0.957	0.173	32	1.069	0.203	59	7.4%	-0.11 [-0.19, -0.03]
Subtotal (95% CI)			**129**			**255**	**23.5%**	**-0.10 [-0.14, -0.06]**
Heterogeneity: Tau² = 0.00; Chi² = 0.46, df = 2 (P = 0.79); I² = 0%								
Test for overall effect: Z = 5.05 (P < 0.00001)								
Total (95% CI)			**395**			**1390**	**100.0%**	**-0.07 [-0.10, -0.03]**
Heterogeneity: Tau² = 0.00; Chi² = 74.69, df = 11 (P < 0.00001); I² = 85%								
Test for overall effect: Z = 3.58 (P = 0.0003)								
Test for subgroup differences: Chi² = 2.73, df = 1 (P = 0.10), I² = 63.3%								

Mid 3rd Radius by DXA



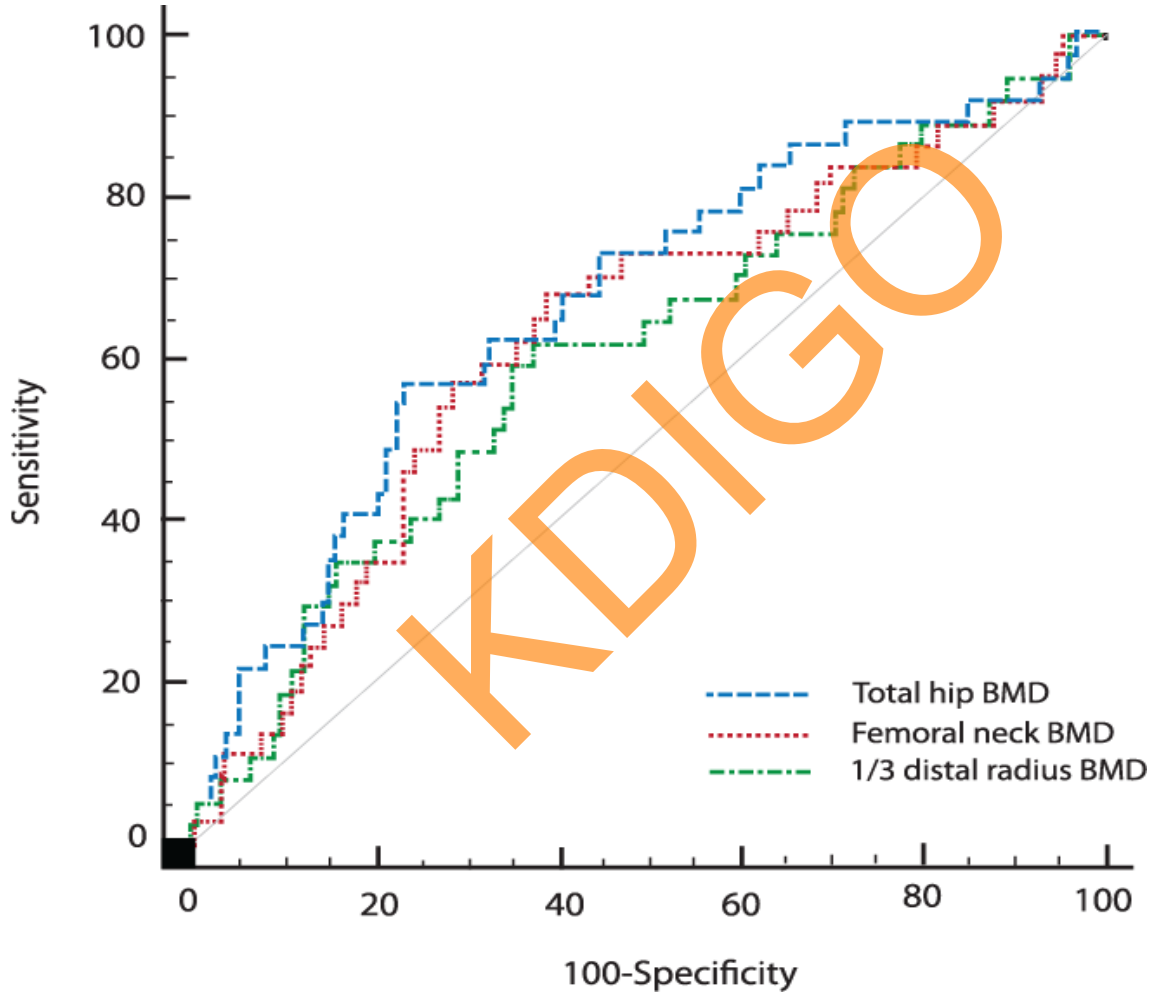
Study or Subgroup	Fracture Group Mean	SD	Total	Non-Fracture Group Mean	SD	Total	Weight	Mean Difference IV, Random, 95% CI
1.4.1 Dialysis Patients								
Ambrus 2011	0.77	0.28	21	1.03	0.48	109	3.1%	-0.26 [-0.41, -0.11]
Fontaine 1999	0.61	0.009	11	0.69	0.11	77	13.3%	-0.08 [-0.11, -0.05]
Iimori 2012	0.566	0.148	46	0.635	0.124	416	11.1%	-0.07 [-0.11, -0.02]
Inaba 2005	0.4468	0.094	21	0.4629	0.09067	93	11.1%	-0.02 [-0.06, 0.03]
Kaji 2002	0.49	0.039	14	0.57	0.009	169	13.8%	-0.08 [-0.10, -0.06]
Yamaguchi 1996	0.446	0.0266	27	0.575	0.01449	97	14.5%	-0.13 [-0.14, -0.12]
Subtotal (95% CI)			**140**			**961**	**66.9%**	**-0.09 [-0.12, -0.05]**
Heterogeneity: Tau² = 0.00; Chi² = 50.87, df = 5 (P < 0.00001); I² = 90%								
Test for overall effect: Z = 4.67 (P < 0.00001)								
1.4.2 Non-dialysis patients								
Jamal 2012	0.68	0.1	74	0.74	0.09	137	13.1%	-0.06 [-0.09, -0.03]
Nickolas 2010	0.63	0.122	23	0.773	0.127	59	9.3%	-0.14 [-0.20, -0.08]
Nickolas 2011	0.652	0.107	32	0.697	0.117	59	10.7%	-0.04 [-0.09, 0.00]
Subtotal (95% CI)			**129**			**255**	**33.1%**	**-0.08 [-0.13, -0.03]**
Heterogeneity: Tau² = 0.00; Chi² = 7.34, df = 2 (P = 0.03); I² = 73%								
Test for overall effect: Z = 3.15 (P = 0.002)								
Total (95% CI)			**269**			**1216**	**100.0%**	**-0.08 [-0.11, -0.05]**
Heterogeneity: Tau² = 0.00; Chi² = 70.05, df = 8 (P < 0.00001); I² = 89%								
Test for overall effect: Z = 5.54 (P < 0.00001)								
Test for subgroup differences: Chi² = 0.08, df = 1 (P = 0.78), I² = 0%								

BMD and Fractures in CKD

- Prospective study
- 485 patients on HD, followed for 5 years
- 46 clinical fractures and 29 prevalent spine fractures
- BMD by DXA (hip, spine, 1/3 radius) able to predict incident fractures
  - FRAX did not improve prediction

Imori S et al NDT 2012

DXA to Predict Fracture



Imori S et al NDT 2012

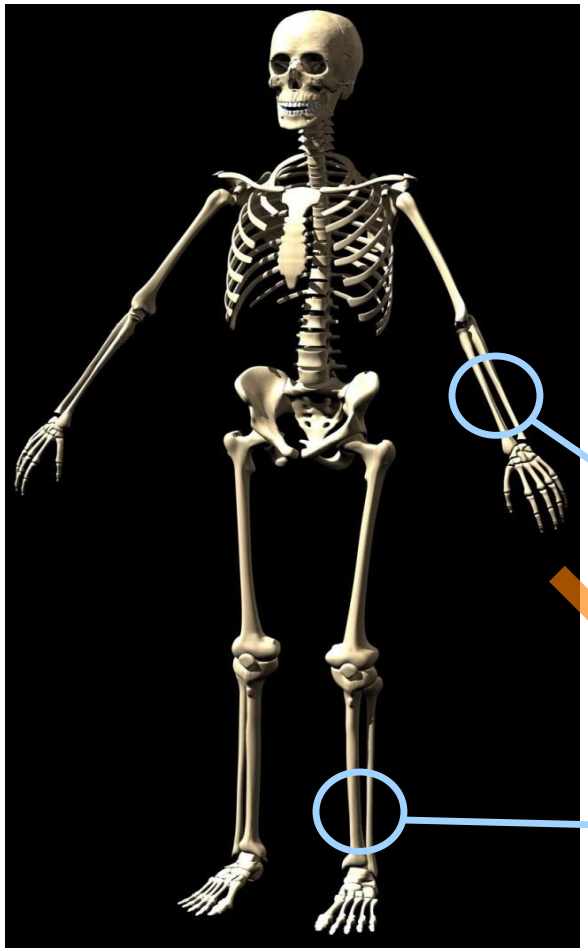
FRAX in CKD

Risk assessment tool developed by the World Health Organization to identify men and women at high fracture risk.
Uses ten clinical risk factors, combined either with or without femoral neck BMD, to estimate the 10-year probability of fracture (hip or major osteoporotic fracture).

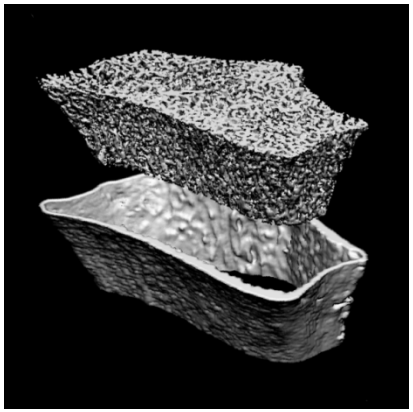
	Risk Factor	AUC	95% CI
Any Fracture	FRAX with BMD	0.71	0.65 to 0.77
	FRAX without BMD	0.67	0.61 to 0.73
	FRAX without BMD and secondary OP	0.67	0.61 to 0.73
	Age	0.64	0.58 to 0.7
	Femoral Neck BMD	0.67	0.61 to 0.73

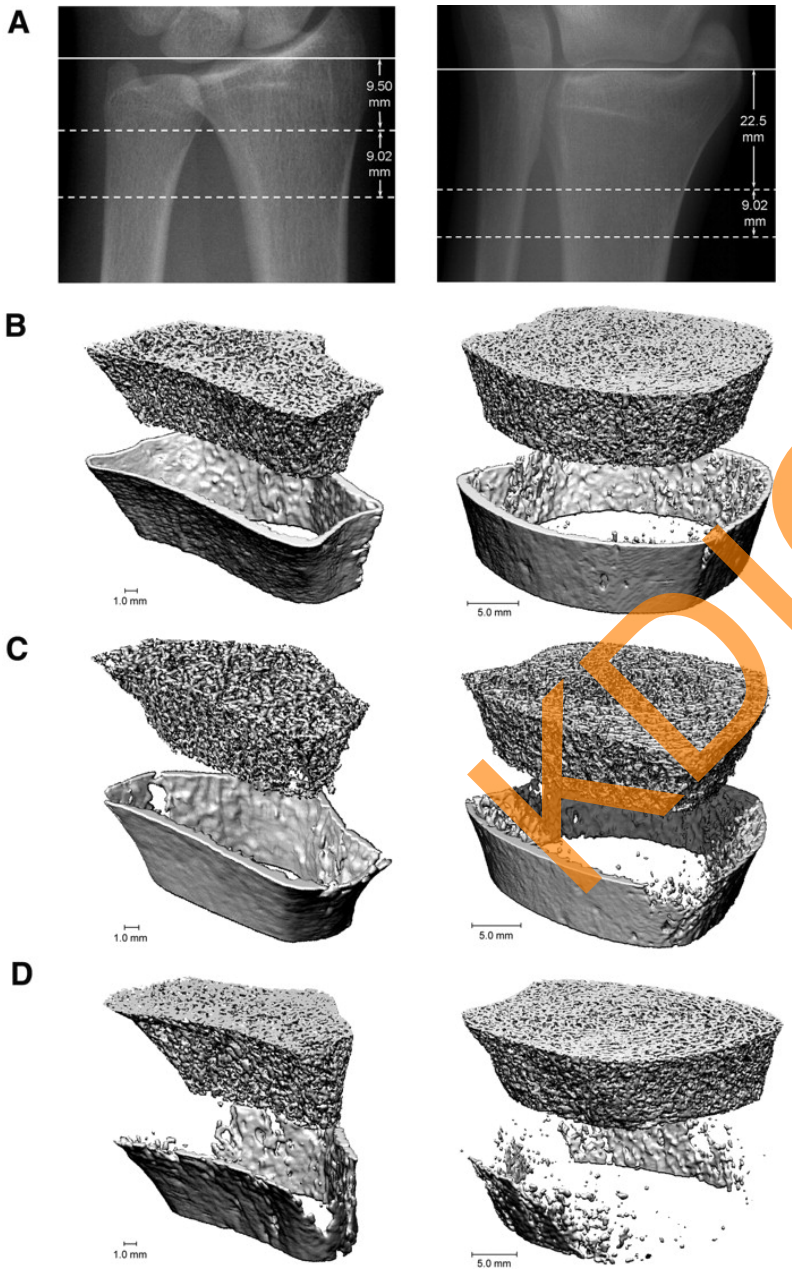
Jamal SA et al OI In Press

High Resolution Peripheral Quantitative Comput Tomography (HR-pQCT)



- Voxel size of ~82 μm^3
- Volumetric Bone Mineral Density (BMD) of the distal radius and tibia
- Distinguishes cortical and trabecular bone





Healthy postmenopausal caucasian

Predialysis CKD; no fracture

Predialysis CKD with fracture

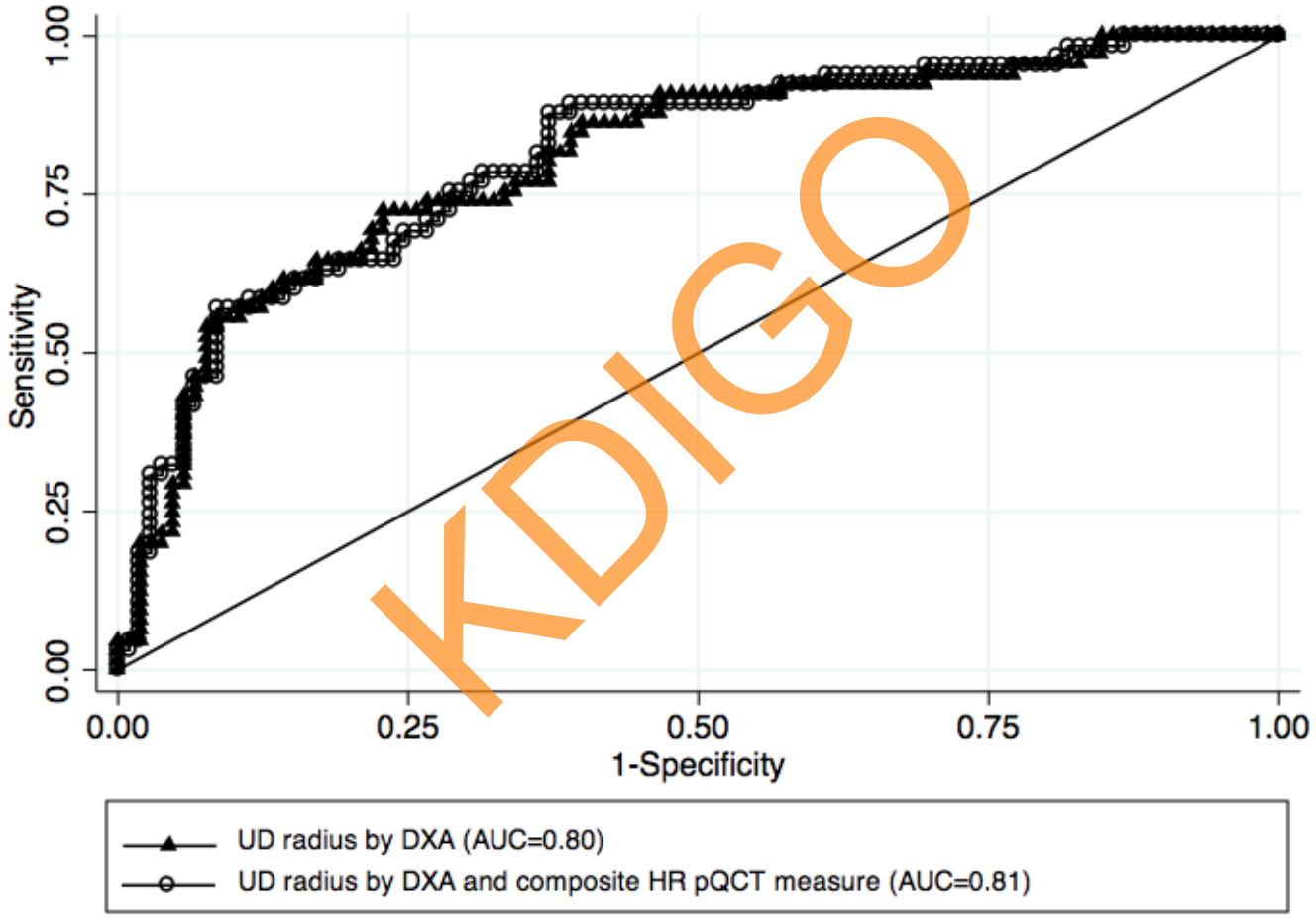
Nickolas T L et al. JASN 2010

HR pQCT Data

- Prospective data- HR pQCT and DXA
- 53 subjects
- CKD stages 2 to 5D
- Followed for mean: 1.5 yrs
- Decreases in BMD by DXA and HR PQCT
- No fracture data

Nickolas et al JBMR 2013

BMD by DXA vs. HRpQCT 3 to 5 CKD



Jamal SA et al OI 2012

KDIGO Recommendations

3.2.2.

In patients with CKD stages 3 - 5D with evidence of CKD-MBD we suggest that BMD testing not be performed routinely because BMD does not predict fracture risk as it does in the general population, and BMD does not predict the type of renal osteodystrophy (2B)

?REVISIT

KDIGO Recommendations

5.5. In patients with an estimated glomerular filtration rate greater than approximately 30ml/min per 1.73m^2, we suggest that measuring BMD in the first 3 months after kidney transplant if they receive corticosteroids, or have risk factors for osteoporosis as in the general population (2D)

D – very low quality of evidence ..the estimate is very uncertain, often will be far from the truth

DXA and Fractures Post Transplant

- 238 transplant patients ; 8 year follow up
- 53 fractures in 46 patients

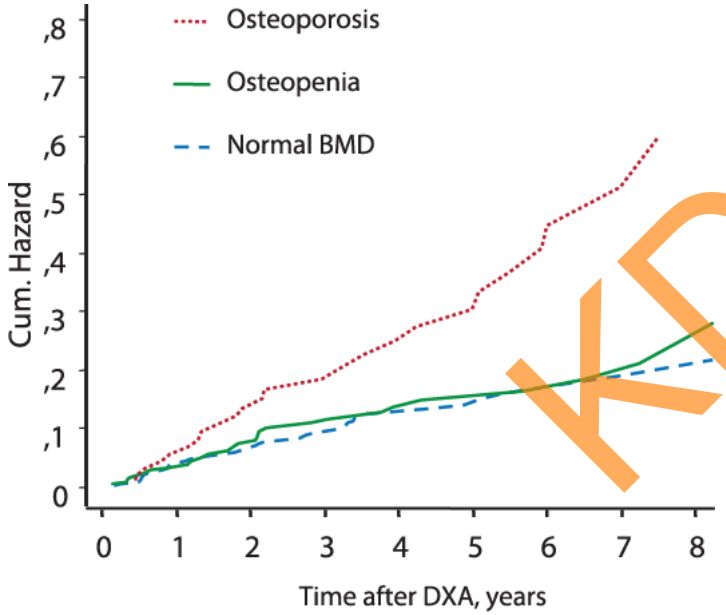


Figure 1. **Cumulative hazard plot for time to fracture after DXA, separated according to the presence of osteopenia or osteoporosis in the lumbar region.** p = 0.002.

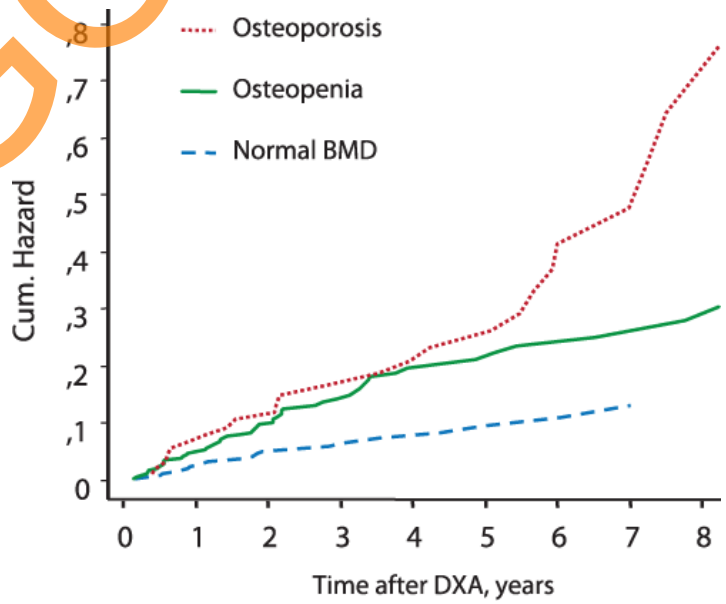
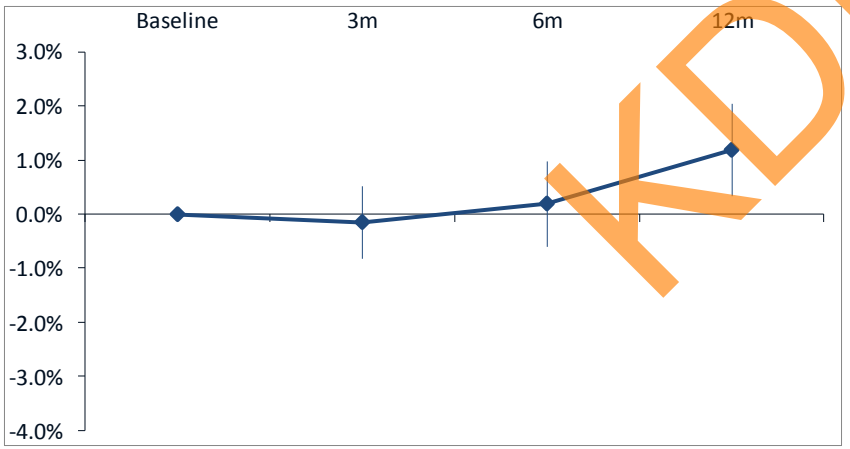


Figure 2. **Cumulative hazard plot for time to fracture after DXA, separated according to the presence of osteopenia or osteoporosis in the hip region.** p < 0.0001.

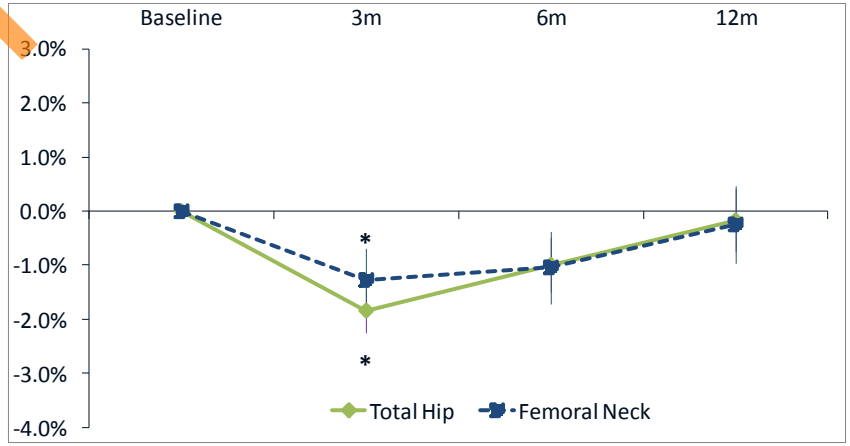
Akaberi S et al Am J Transplant 2008

ECSW* and BMD

- *Stop corticosteroids on the 4th post-transplant day and manage with a calcineurin inhibitor
- Observational studies minimal fracture protection with ECSW
- Abstract Nickolas et al (ASBMR 2013):
  - 47 recipients managed with ECSW
  - Followed for 12 months

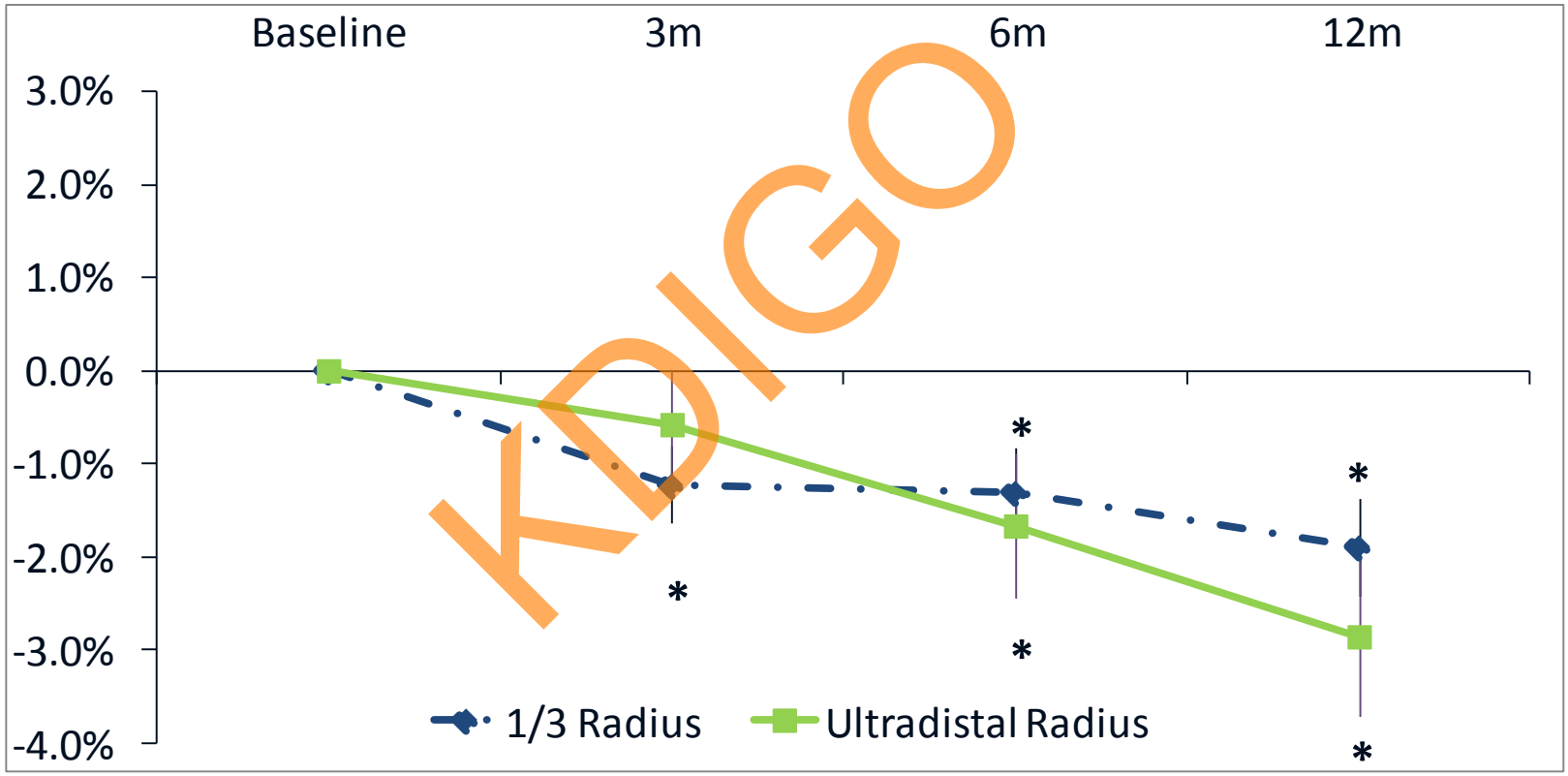


Spine BMD by DXA



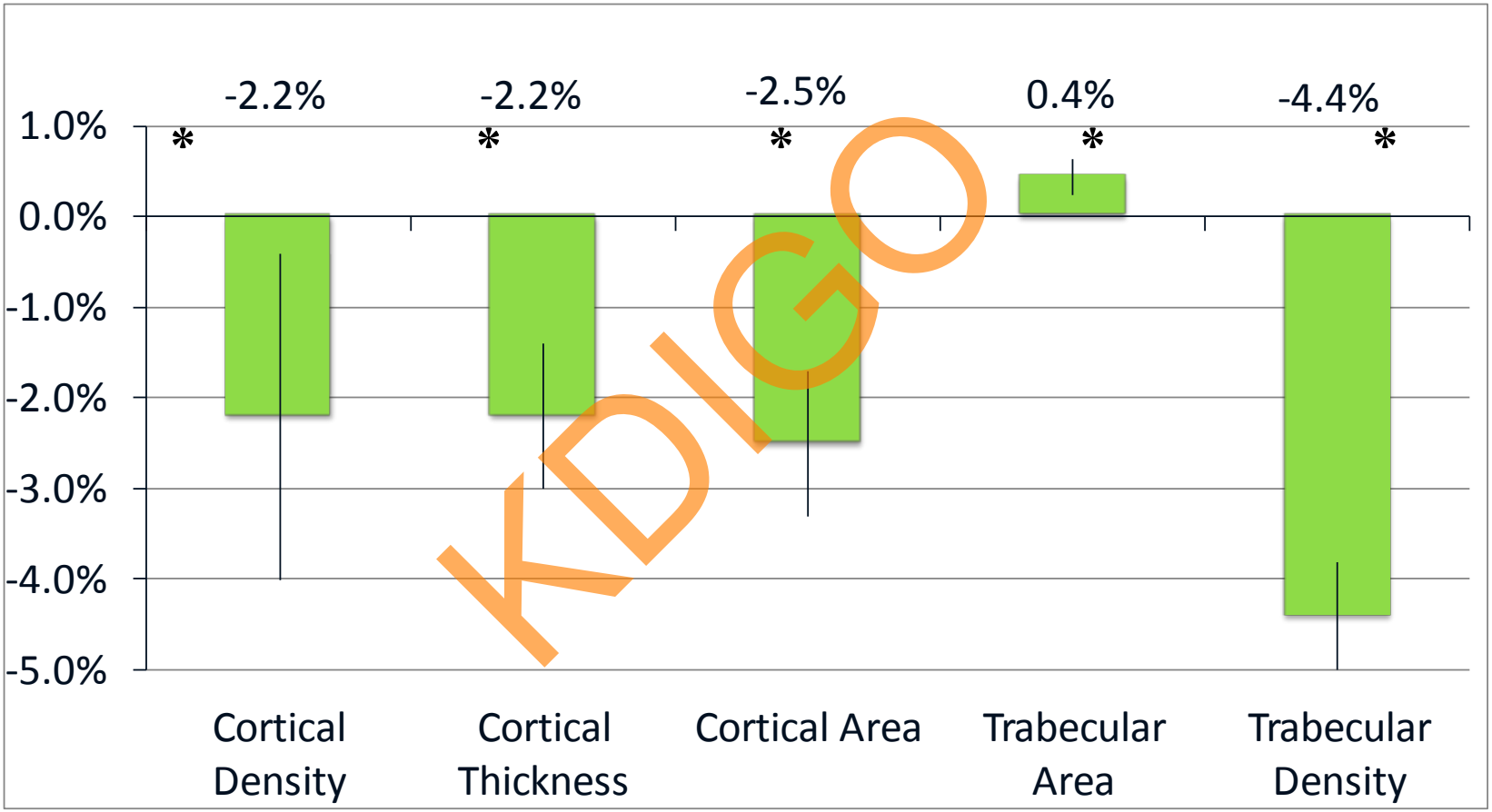
Hip BMD by DXA

Peripheral Skeletal Changes: Forearm



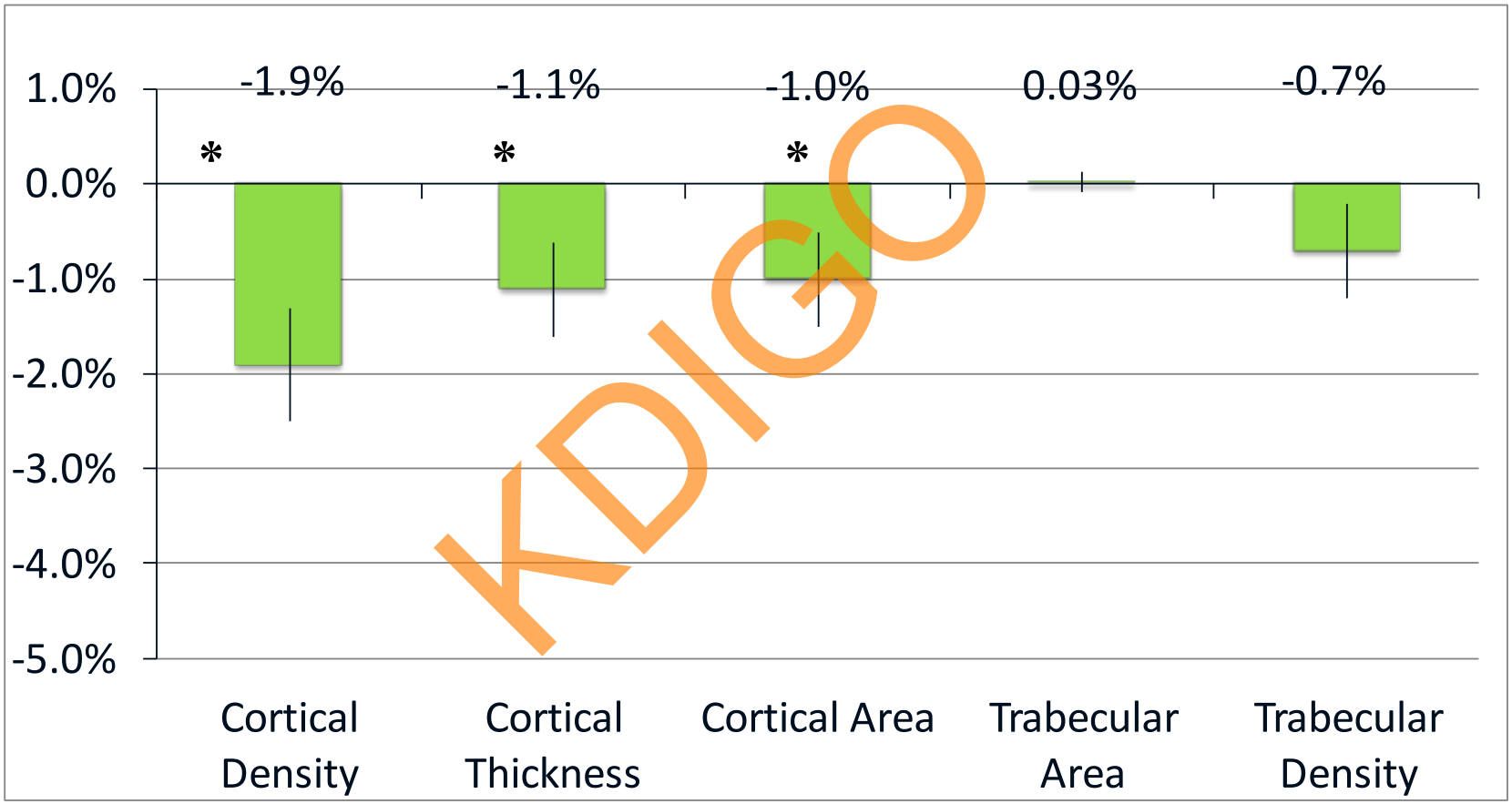
* $p < 0.05$ vs. Baseline

HR-pQCT of the Radius: 12 month changes after transplantation



* p < 0.05 vs. Baseline

HR-pQCT of the Tibia: 12 month changes after transplantation



* p < 0.05 vs. Baseline

KDIGO Recommendations

5.5.

In patients with an estimated glomerular filtration rate greater than approximately 30ml/min per 1.73m^2, we suggest that measuring BMD in the first 3 months after kidney transplant if they receive corticosteroids, or have risk factors for osteoporosis as in the general population (2D)

?REVISIT

Revisit Recommendations

- BMD by DXA can predict fractures in CKD and transplant
- Cross sectional data
  - Consistent across BMD sites, studies
- Some prospective data
- HRpQCT confirms presence of disturbance in bone microarchitecture


Did you know that men over 50 suffer from osteoporosis more than prostate cancer?
got milk?