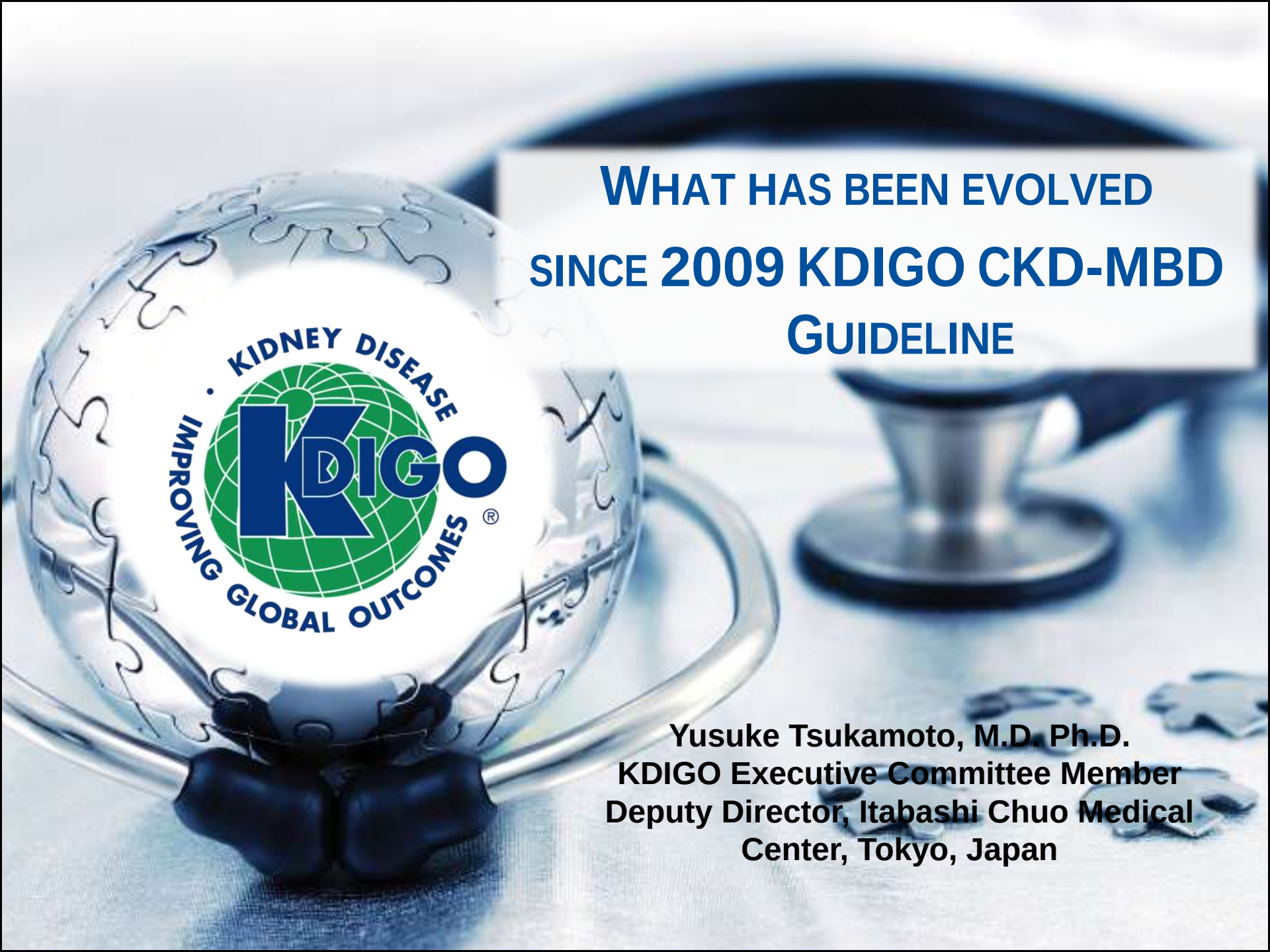


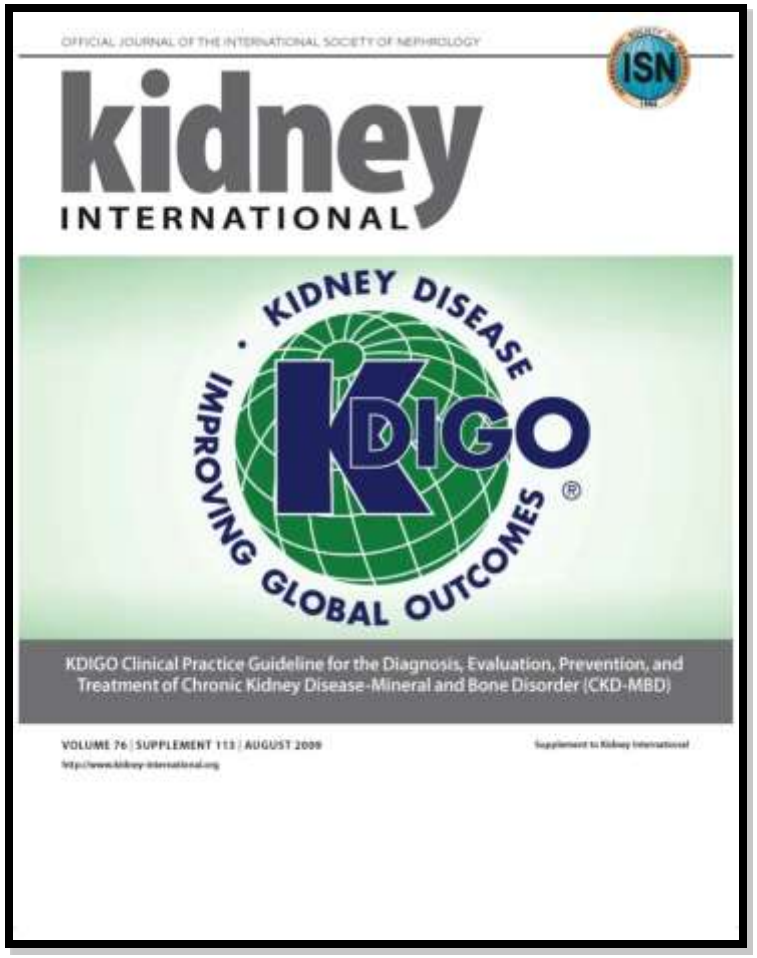
WHAT HAS BEEN EVOLVED SINCE 2009 KDIGO CKD-MBD GUIDELINE

Yusuke Tsukamoto, M.D. Ph.D.
KDIGO Executive Committee Member
Deputy Director, Itabashi Chuo Medical Center, Tokyo, Japan

C.O.I

- Honorarium for lecture
  - Otsuka Pharm, Kyowahakko-Kirin Pharm, Chugai Pharm, Dainippon-Sumitomo Pharm, Bayer Japan

Publishing the CKD-MBD Guideline



The first KDIGO clinical practice guideline on CKD-MBD was published in August 2009.

2nd KDIGO Controversy Conference on CKD-MBD

- **74 attendees** from **5 continents** and **19 countries**

- **Divided into four Breakout Groups**
  - **Vascular Calcification**
  - **Bone Quality**
  - **Calcium and Phosphorus**
  - **Vitamin D and PTH**

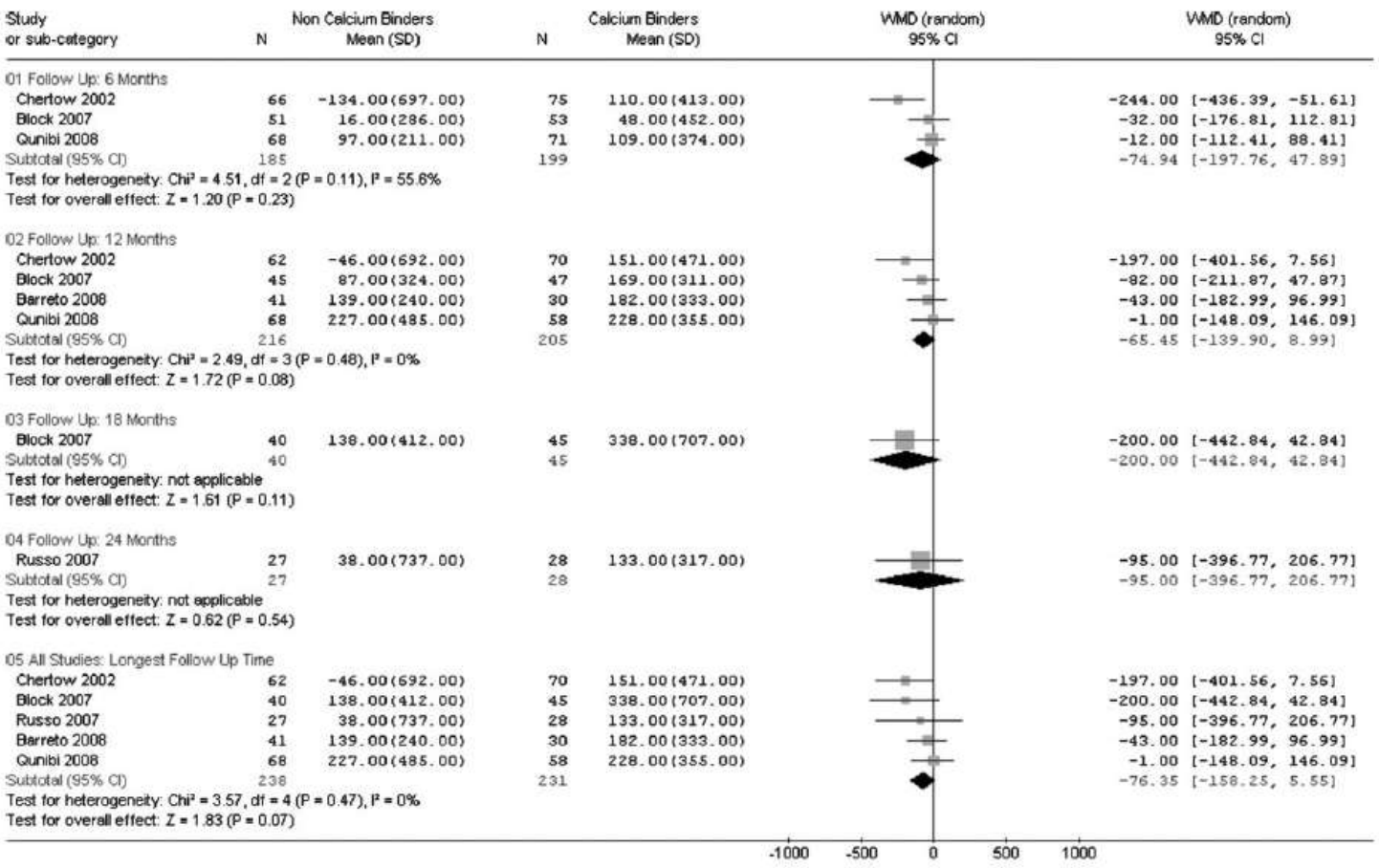
Topic #1: Vascular Calcification

- **3.3.1 In patients with CKD stages 3–5D, we suggest that a lateral abdominal radiograph can be used to detect the presence or absence of vascular calcification, and an echocardiogram can be used to detect the presence or absence of valvular calcification, as reasonable alternatives to computed tomography based imaging (2C).**

- **3.3.2 We suggest that patients with CKD stages 3–5D with known vascular/valvular calcification be considered at highest cardiovascular risk (2A). It is reasonable to use this information to guide the management of CKD–MBD (not graded).**

New Studies: Sevelamer vs Ca P binder -coronary calcification-

Change in Agatston Score

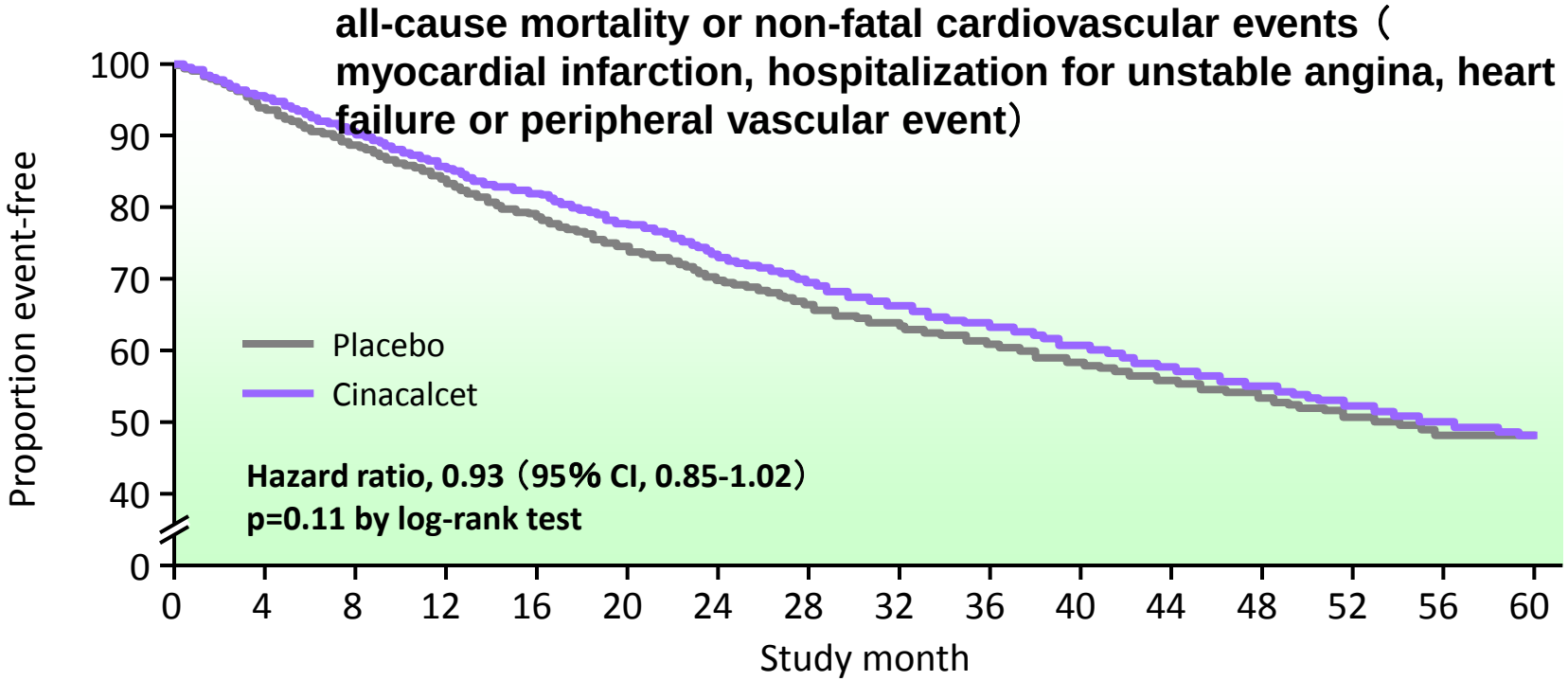


Favors sevelamar ***Favors calcium***

Jamal, et al. NDT 2009

EVOLVE: ITT analysis of the primary composite outcome and its components.

(A) Primary composite end point



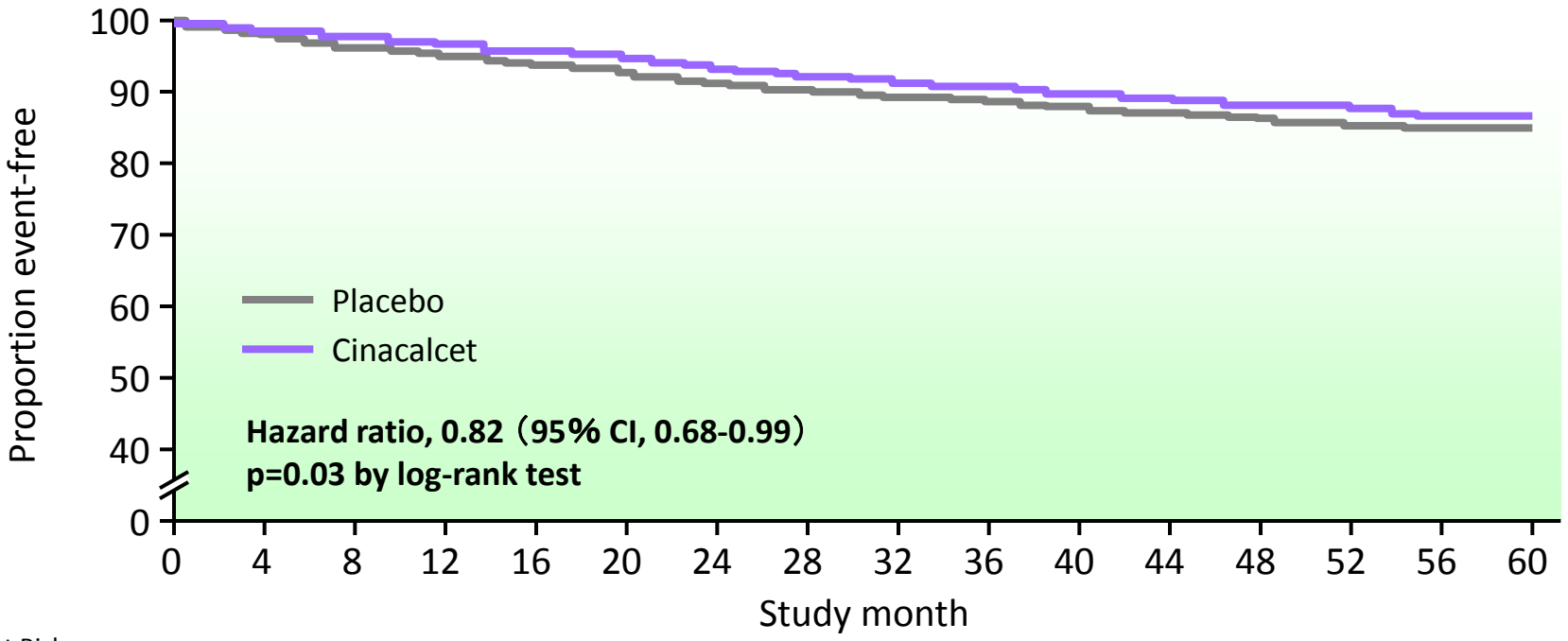
No. at Risk																
Placebo	1,935	1,804	1,693	1,579	1,476	1,384	1,312	1,224	1,160	1,109	1,053	996	940	650	404	114
Cinacalcet	1,948	1,842	1,739	1,638	1,556	1,472	1,384	1,303	1,230	1,177	1,115	1,051	989	679	399	113

Shown are Kaplan-Meier curves comparing cinacalcet with placebo for the time to the first primary composite outcome（Panel A）, death（Panel B）, first myocardial infarction（Panel C）, first hospitalization for unstable angina（Panel D）, first episode of heart failure（Panel E）, and first episode of a peripheral vascular event（Panel F）.

Chertow GM, et al. *N Engl J Med* 2012; November 3, Epub

EVOLVE: ITT analysis of the primary composite outcome and its components.

(E) Heart failure

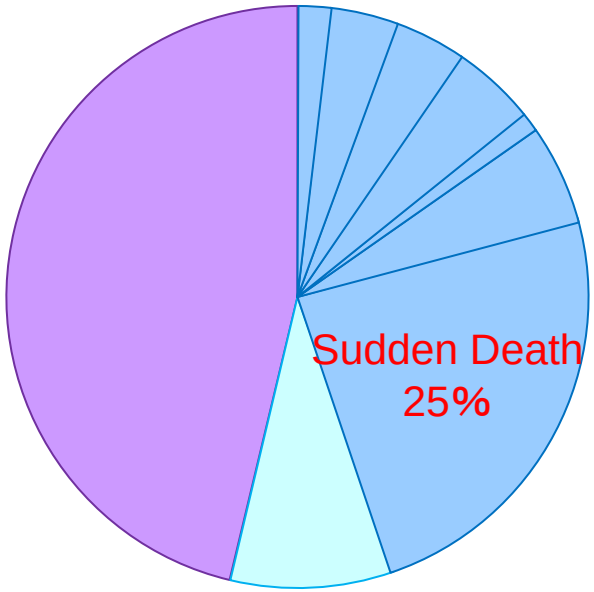


No. at Risk																
Placebo	1,935	1,842	1,753	1,652	1,565	1,478	1,404	1,333	1,264	1,216	1,159	1,110	1,054	737	464	129
Cinacalcet	1,948	1,873	1,798	1,712	1,649	1,579	1,499	1,422	1,357	1,301	1,242	1,176	1,115	769	452	128

Shown are Kaplan-Meier curves comparing cinacalcet with placebo for the time to the first primary composite outcome（Panel A）, death（Panel B）, first myocardial infarction（Panel C）, first hospitalization for unstable angina（Panel D）, first episode of heart failure（Panel E）, and first episode of a peripheral vascular event（Panel F）.

Chertow GM, et al. *N Engl J Med* 2012; November 3, Epub

Adjudicated causes of death in the EVOLVE study population



- ✓ 768 (54%)of 1421 death were adjudicated as being due to cardiovascular cause.
- ✓ 25 % were sudden death and 4% were heart failure / cardiogenic shock.

Wheeler DC, et al. *J Am Heart Assoc*. 2014; 3(6): e001363

Post hoc analysis: Different effect of cinacalcet can be investigated between atherosclerotic and nonatherosclerotic event

Cardiovascular Events

Nonatherosclerotic Events

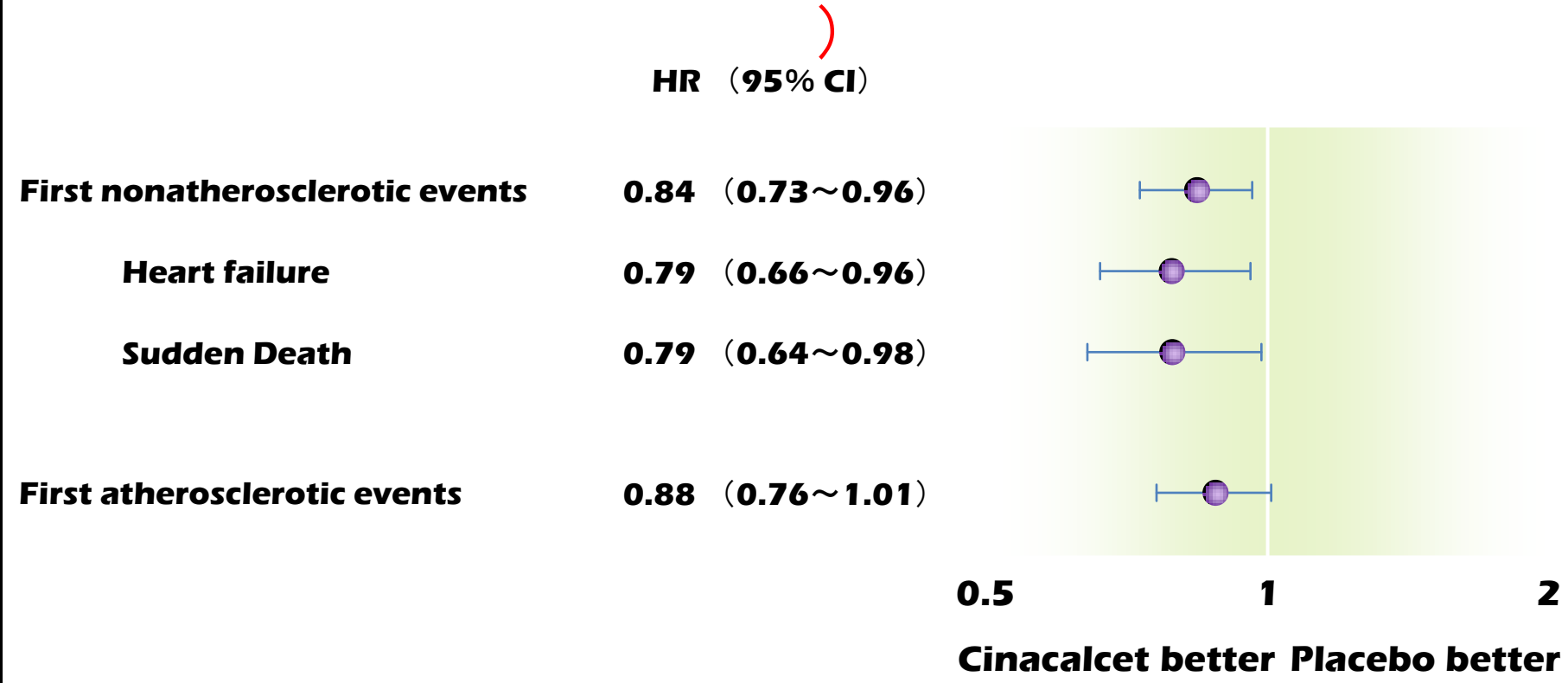
- Heart Failure
- Sudden
- Hemorrhagic stroke
- Fatal pulmonary stroke
- Other fatal cardiovascular events
- Unknown cardiovascular death cause

Atherosclerotic Events

- Peripheral vascular events
- Myocardial Infarction
- Nonhemorrhagic stroke
- Hospitalization for unstable angina
- Death from cardiovascular procedure
- Other fatal cardiovascular

Wheeler DC, et al. *J Am Heart Assoc*. 2014; 3(6): e001363

Time to the First Cardiovascular Events （Multivariable Cox Regression Model, ITT analysis ）



- ✓ There was a 16% (95% CI 4% to 26%) lower hazard of nonatherosclerotic events in patients randomized to cinacalcet.
- ✓ The relative hazard ratio for heart failure and sudden death was reduced with statistically significant by 21%.

Wheeler DC, et al. *J Am Heart Assoc*. 2014;

Topic #1: Vascular Calcification

- **3.3.1 In patients with CKD stages 3–5D, we suggest that a lateral abdominal radiograph can be used to detect the presence or absence of vascular calcification, and an**

The group was unanimous in their assessment of the clinical significance of cardiovascular calcification and the conclusion that cardiovascular calcification should be considered for guidance of CKD-MBD management.

- **(not graded).**

Topic #2: Calcium + Phosphate

4.1.4 In patients with CKD stages 3–5 (2D) and 5D (2B), we suggest using phosphate-binding agents in the treatment of hyperphosphatemia. It is reasonable that th… CKD st… co… gr…

Can we recommend non-calcium containing Pi binders than calcium containing more specifically?

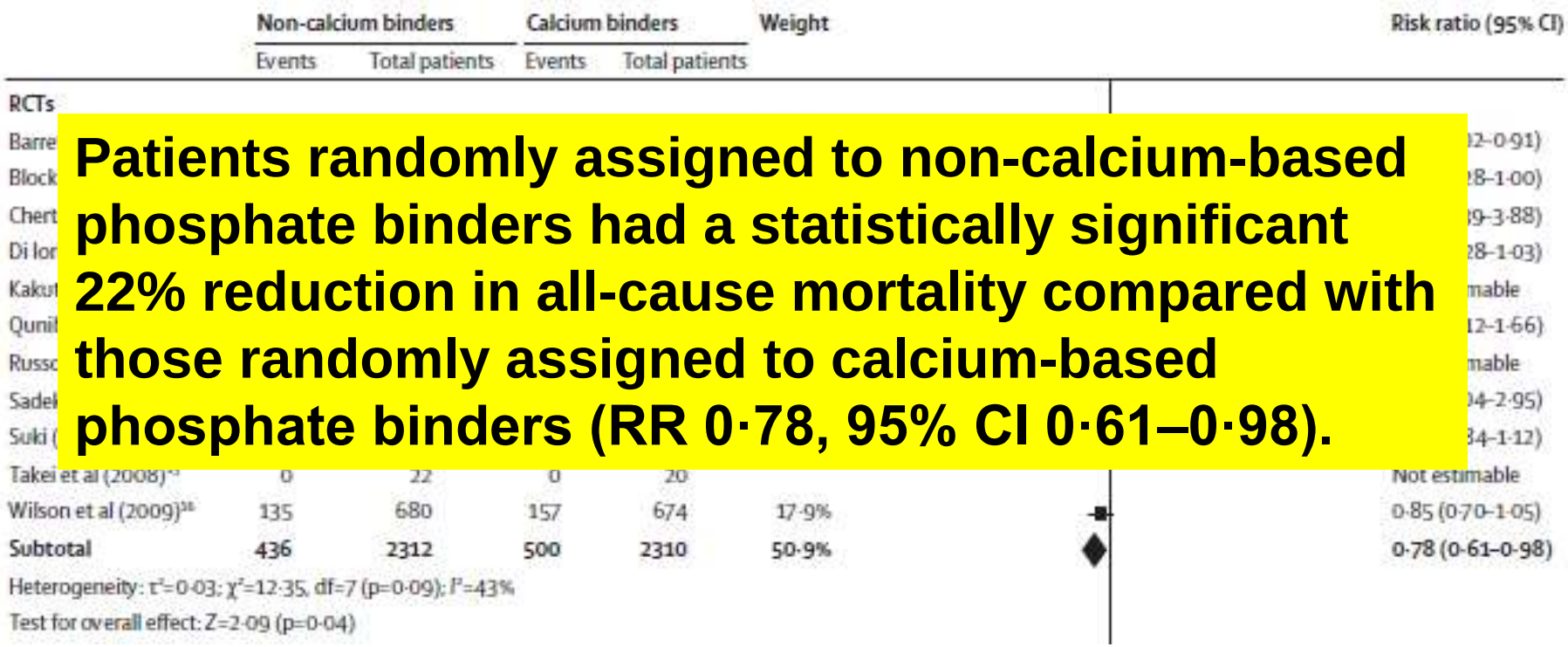
Arguments:

New data from RCTs, safety data

Distinguish pre-dialysis and dialysis

New Studies: Non-Ca vs Ca P binders

All Cause Mortality

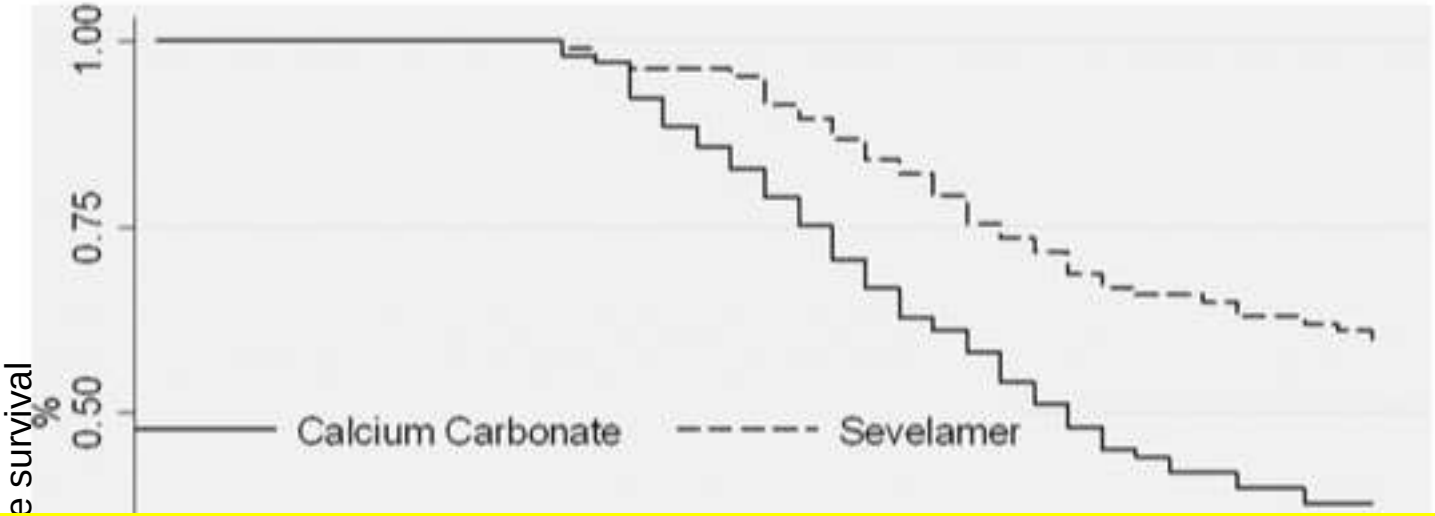


Patients randomly assigned to non-calcium-based phosphate binders had a statistically significant 22% reduction in all-cause mortality compared with those randomly assigned to calcium-based phosphate binders (RR 0·78, 95% CI 0·61–0·98).

Favors non-calcium ***Favors calcium***

Jamal, et al. Lancet 2013

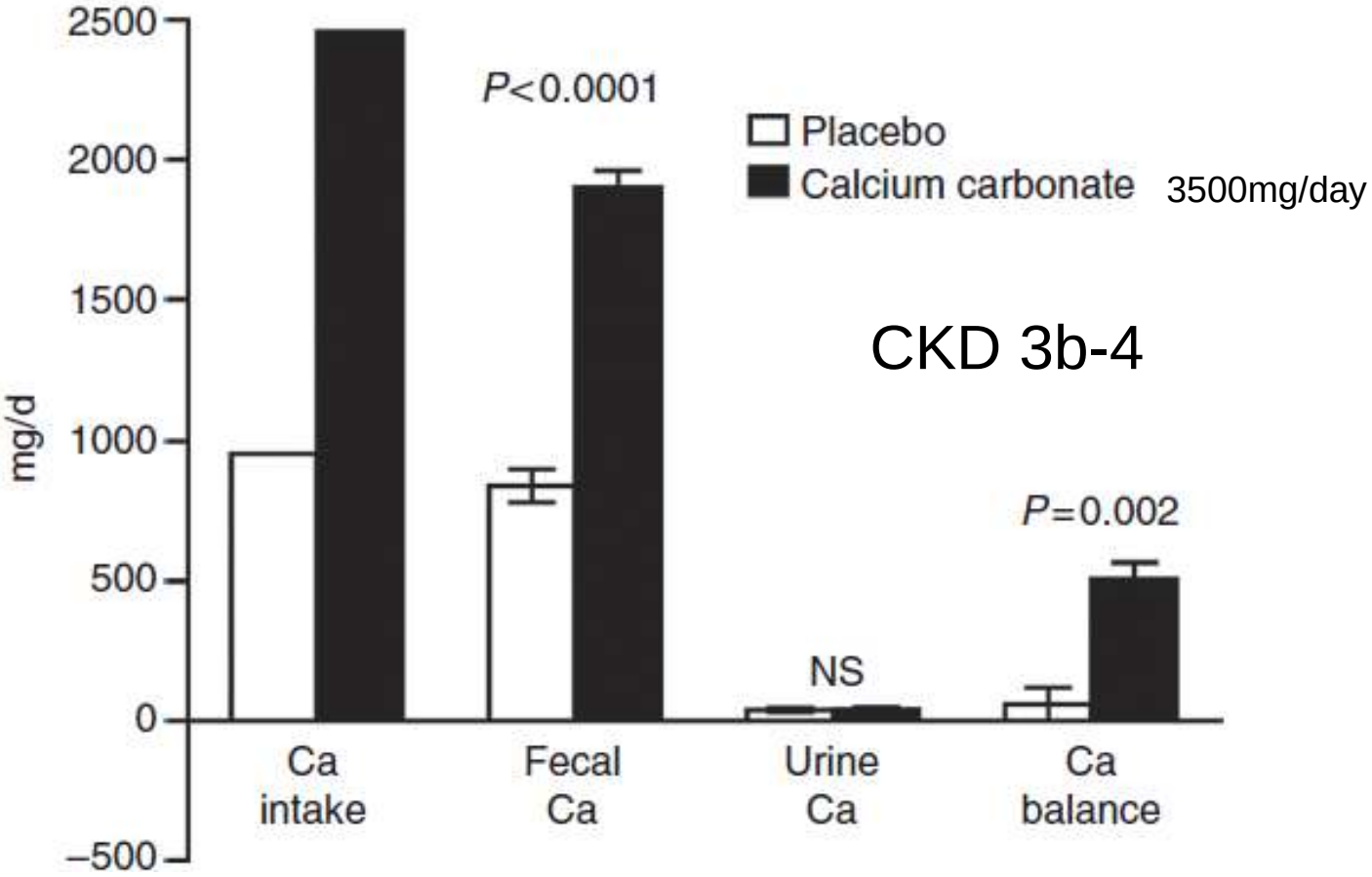
INDEPENDENT STUDY



Event-free survival from the composite end point of all-cause mortality and dialysis inception among patients treated either with sevelamer (n=107) or calcium carbonate (n=105) in CKD 3-4. (log-rank test = 11.46; P,0.01)

Iorio BD, et a;. Clin J Am Soc Nephrol 7, 2012.

New Studies-Calicium overload by $CaCO_3$



Hill et al, Kidney International 2013

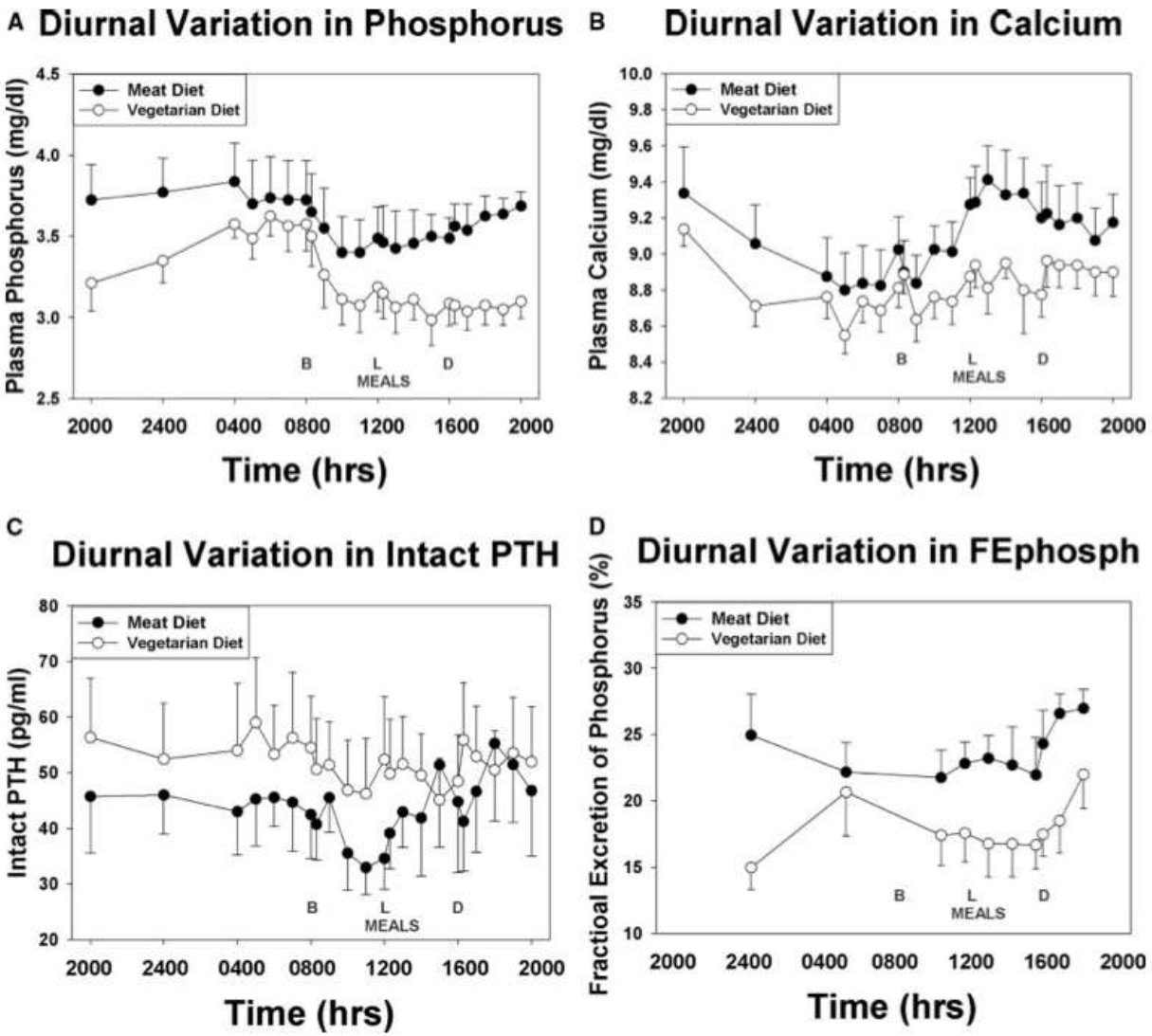
Topic #2: Calcium + Phosphate

4.1.7 In patients with CKD stages 3–5D, we suggest limiting dietary phosphate intake in the treatment of hyperphosphatemia alone or in combination with other treatments (*2D*).

Argument:

Data on food additives and differences in protein source

Vegetarian Compared with Meat Dietary Protein Source and Phosphorus Homeostasis in CKD



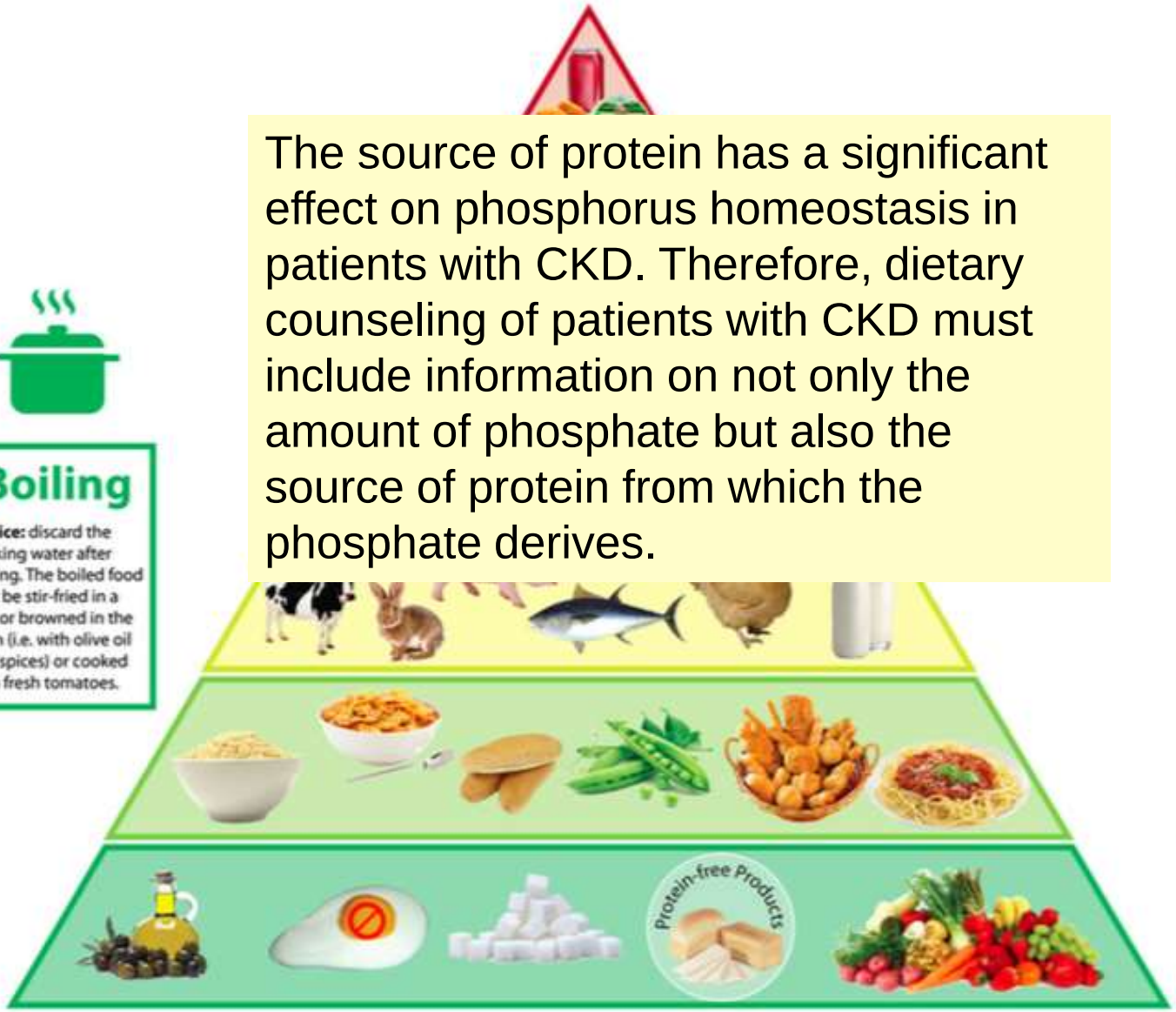
2200Cal
Protein
18%(78g)
P 800-850mg

Moe SM, et al. Clin J Am Soc Nephrol. 2011;6:257

The source of protein has a significant effect on phosphorus homeostasis in patients with CKD. Therefore, dietary counseling of patients with CKD must include information on not only the amount of phosphate but also the source of protein from which the phosphate derives.

Boiling

Advice: discard the cooking water after boiling. The boiled food may be stir-fried in a pan or browned in the oven (i.e. with olive oil and spices) or cooked with fresh tomatoes.



Beverages and Foods with phosphate-additives (E338-343 E450-458 E540-545): soft drinks (cola in particular), dehydrated milk, processed cheese, processed meat (i.e. chicken nuggets), dessert, instant cappuccino....

Hard cheeses: parmesan, cheddar, emmentaler, pecorino....
Nuts
Yolk

Meat (a): sausages, offal (liver, brain)....
Poultry (a): turkey....
Fish (a): shrimp, squid, salmon....
Soft cheeses: cottage, cream, mozzarella cheese....

Meat (b): rabbit, lamb, ham with no preservatives, pork, veal....
Poultry (b): chicken....
Fish (b): trout, tuna fish, cod, hake, sole....
Milk , yogurt....

Cereals: bread, pasta, rice, cous cous, maize flour, cornflakes....
Legumes: peas, broad beans, beans, chickpeas, lentils, soy....

Egg white
Fruits and vegetables (c)
Olive oil and vegetables fats (d) (i.e. vegetable margarine, corn oil, peanut oil....)
Butter (d)
Sugar (e)
Protein-free products (f)

D'Alessandro et al. BMC Nephrology 2015, 16:9

Topic #4: Bone Quality

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).

Argument:

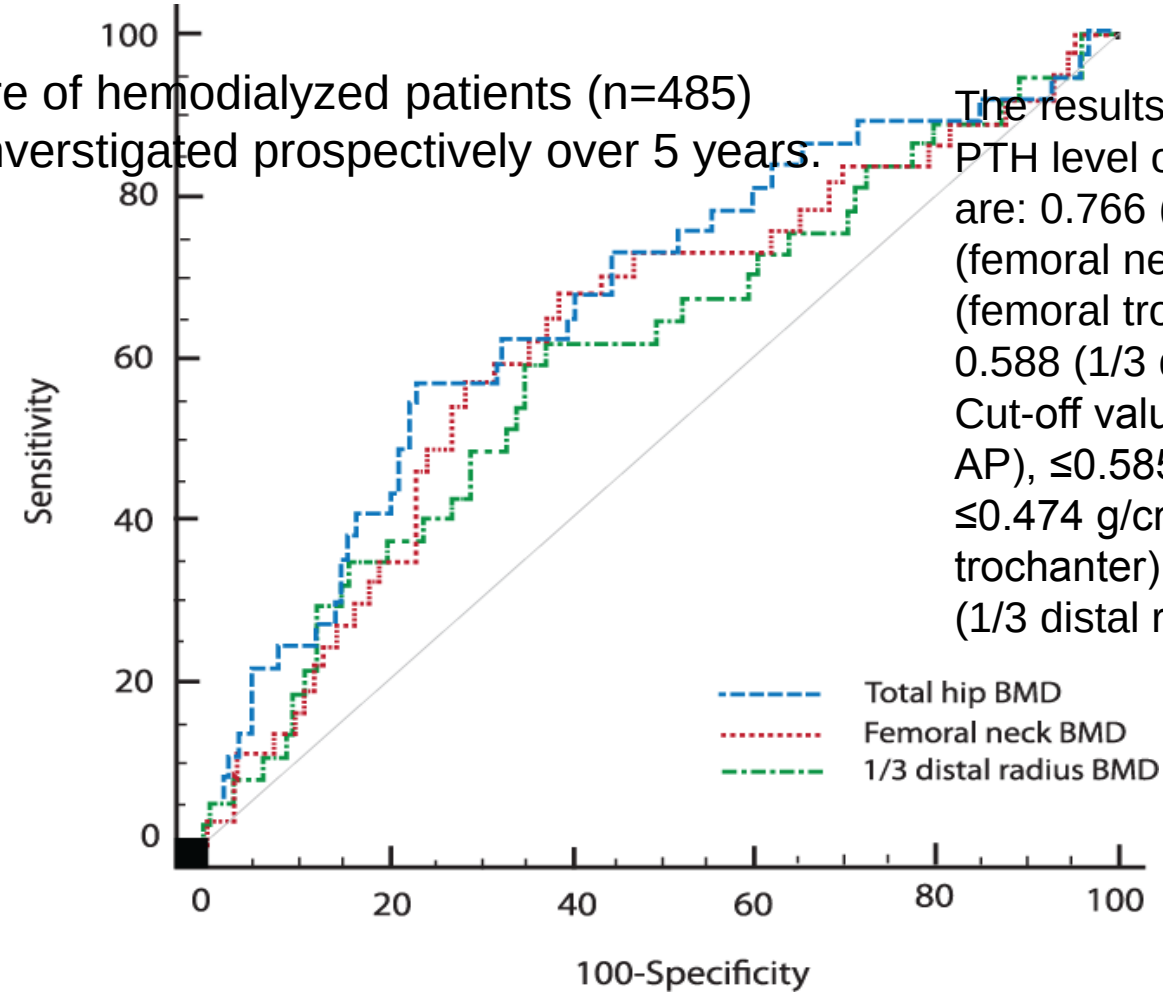
Data on usefulness of DXA to predict bone fracture in CKD, 5D and Tx.

Secondary analyses in osteoporosis trials

New therapies – denosumab and teriparatide

New Data-Usefulness of testing in predicting fracture risk.

Fracture of hemodialyzed patients (n=485) were inverstigated prospectively over 5 years.



The results without stratifying PTH level or gender for AUCs are: 0.766 (b-AP, $p<0.0001$), 0.61 (femoral neck, $p<0.05$), 0.616 (femoral trochanter, $p<0.01$) and 0.588 (1/3 distal radius, $p<0.05$). Cut-off values are >20.1 µg/L (b-AP), ≤0.585 g/cm^2 (femoral neck), ≤0.474 g/cm^2 (femoral trochanter), and ≤0.589 g/cm^2 (1/3 distal radius).

Imori S et al NDT 2012

Mean predicted 5-year fracture risk from the Canadian FRAX and observed 5-year major osteoporotic fracture risk according to eGFR.

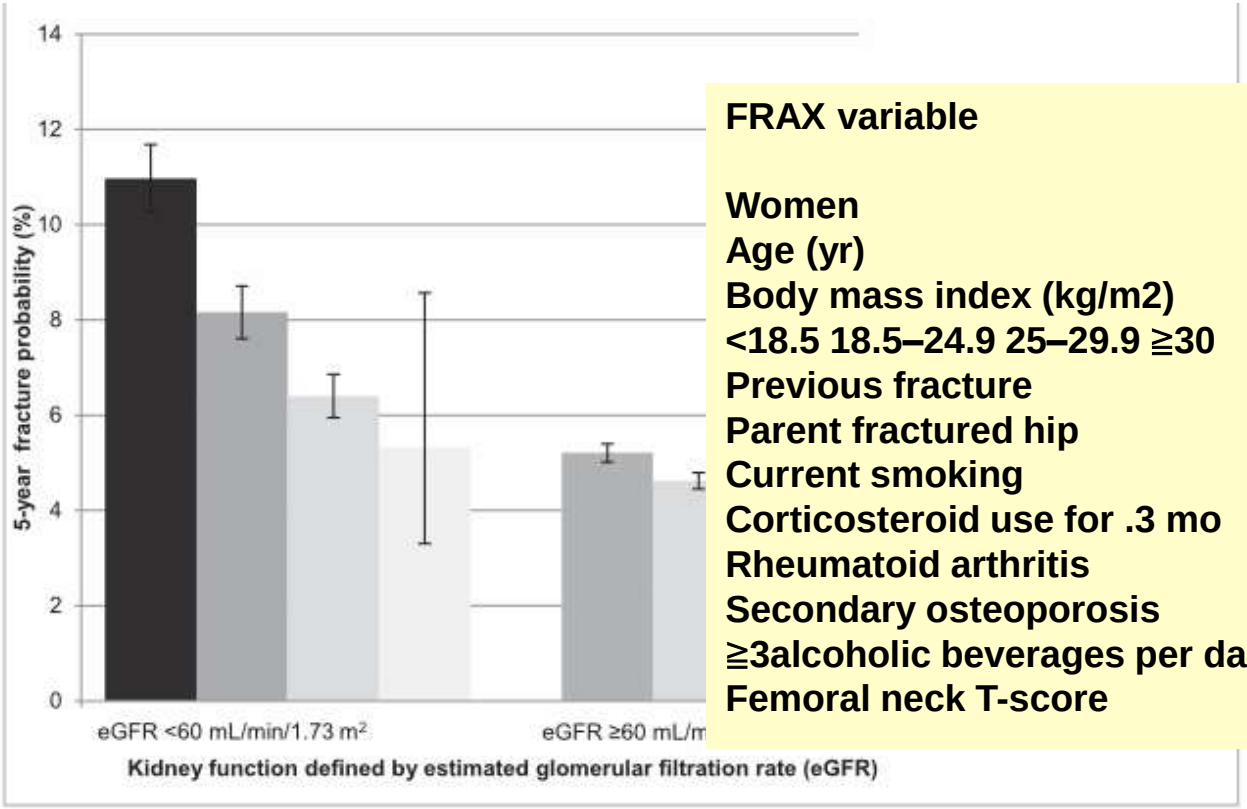
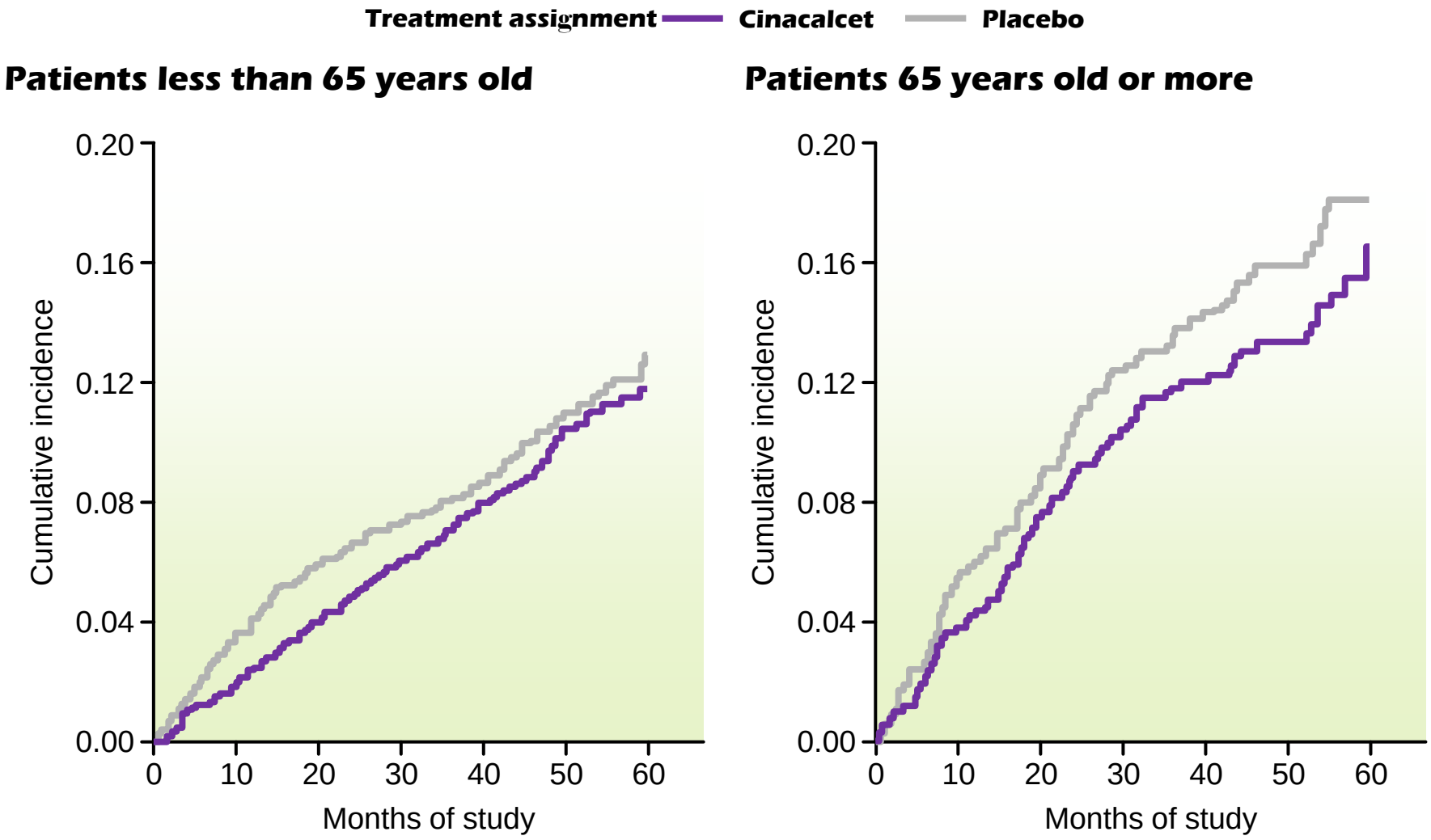


Figure 2. | Mean predicted 5-year fracture risk from the Canadian FRAX tool (with and without BMD) and observed 5-year major osteoporotic fracture risk (Kaplan–Meier) according to eGFR. Error bars are 95% confidence intervals. BMD, bone mineral density; FRAX, Fracture Risk Assessment Tool

Naylor et al. Clin J Am Soc Nephrol 10: 646–653, April, 2015

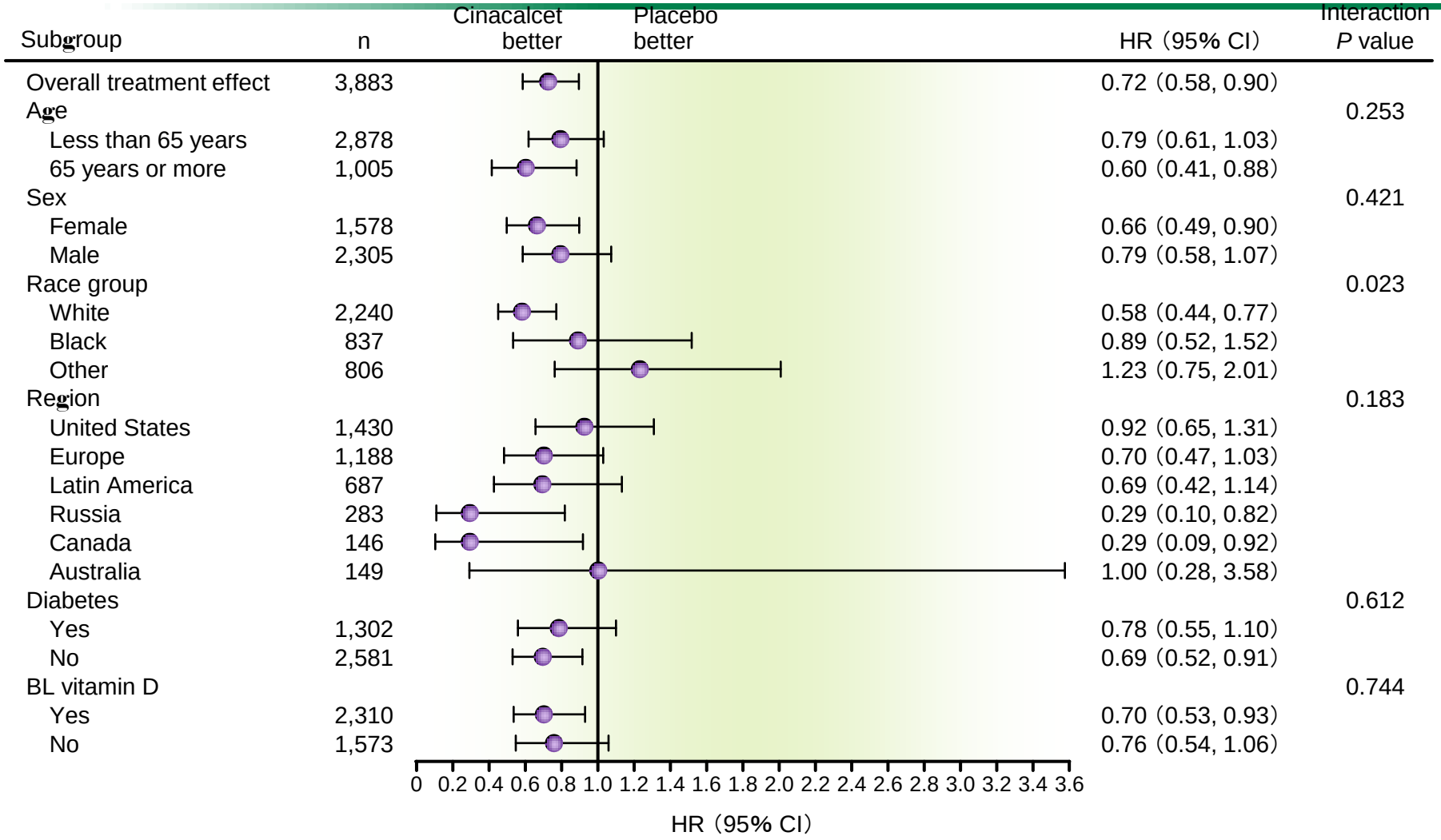
Cinacalcet reduced fracture in elderly patiensts -from post-hoc analysis of EVOLVE-



Cumulative incidence of clinical fractures in patients aged ＜65 years（left）and aged ≥65 years（right）.

Moe SM, et al. *J Am Soc Nephrol* 2014 Dec 11. pii: ASN.2014040414.

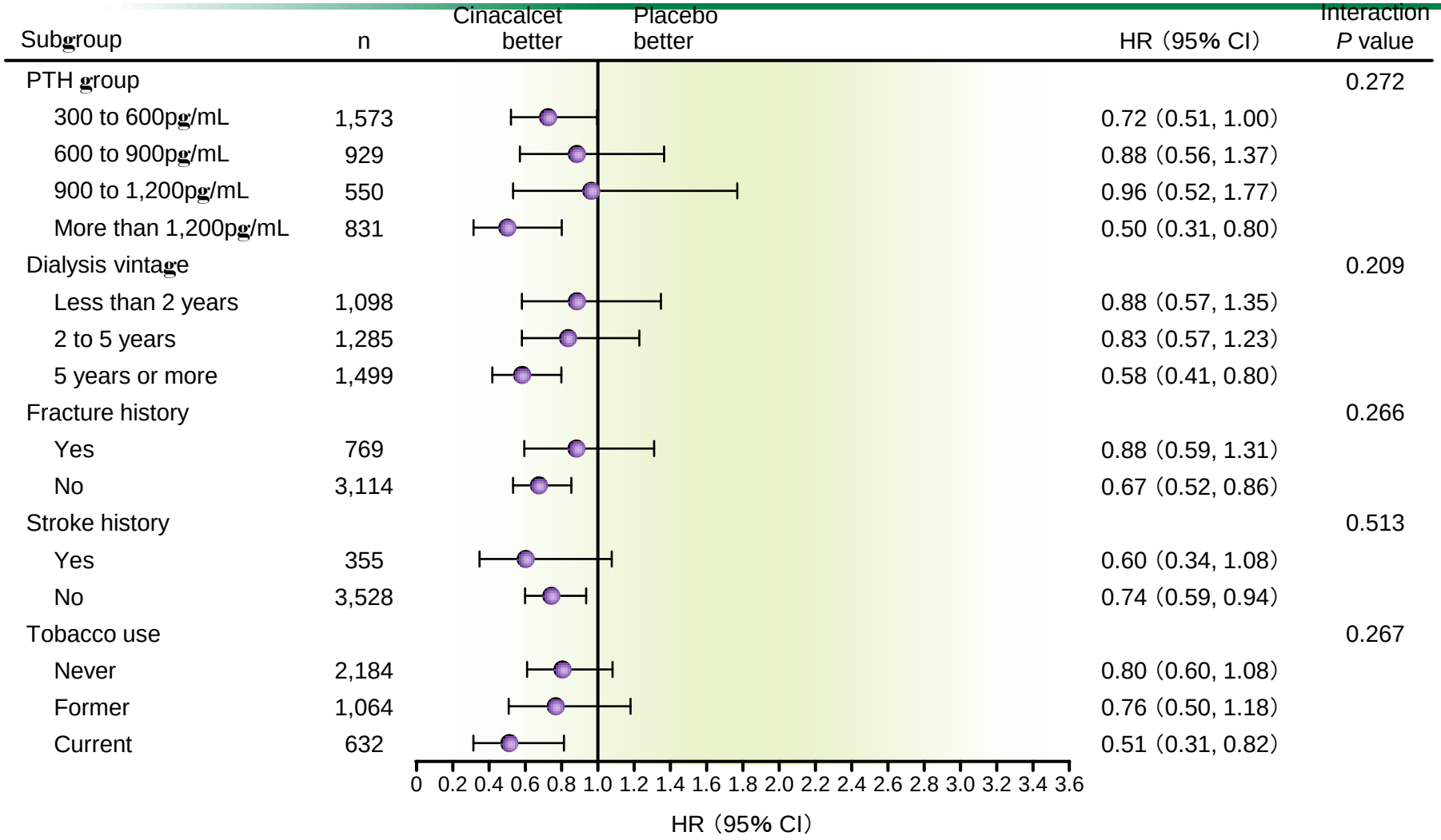
Forest plot of treatment effect of cinacalcet on clinical fracture rate by prespecified baseline characteristics using lag-censoring analysis①



HR, hazard ratio.

Moe SM, et al. *J Am Soc Nephrol* 2014 Dec 11. pii: ASN.2014040414.

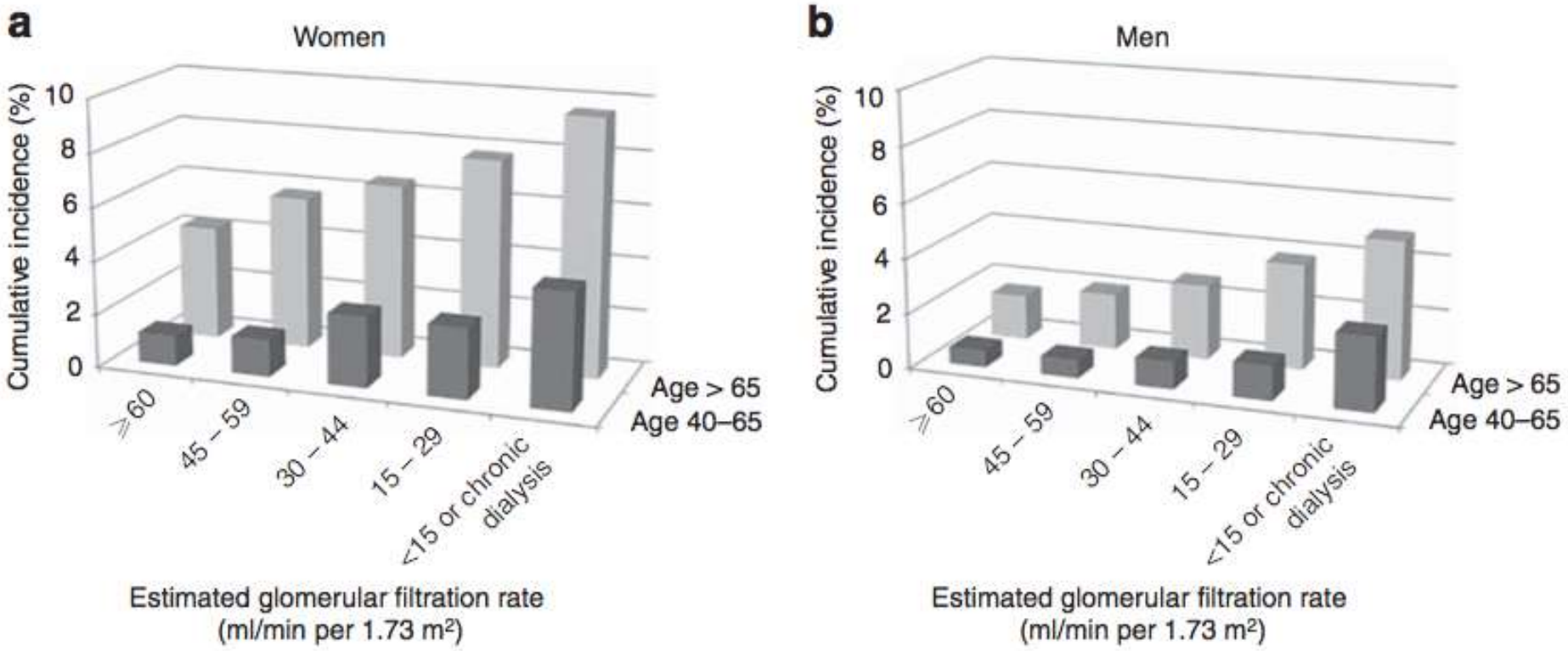
Forest plot of treatment effect of cinacalcet on clinical fracture rate by prespecified baseline characteristics using lag-censoring analysis②



HR, hazard ratio.

Moe SM, et al. *J Am Soc Nephrol* 2014 Dec 11. pii: ASN.2014040414.

Three-year cumulative incidence of fracture.



KL Naylor et al.: Fracture in chronic kidney disease. Kidney International (2014) 86, 810–818

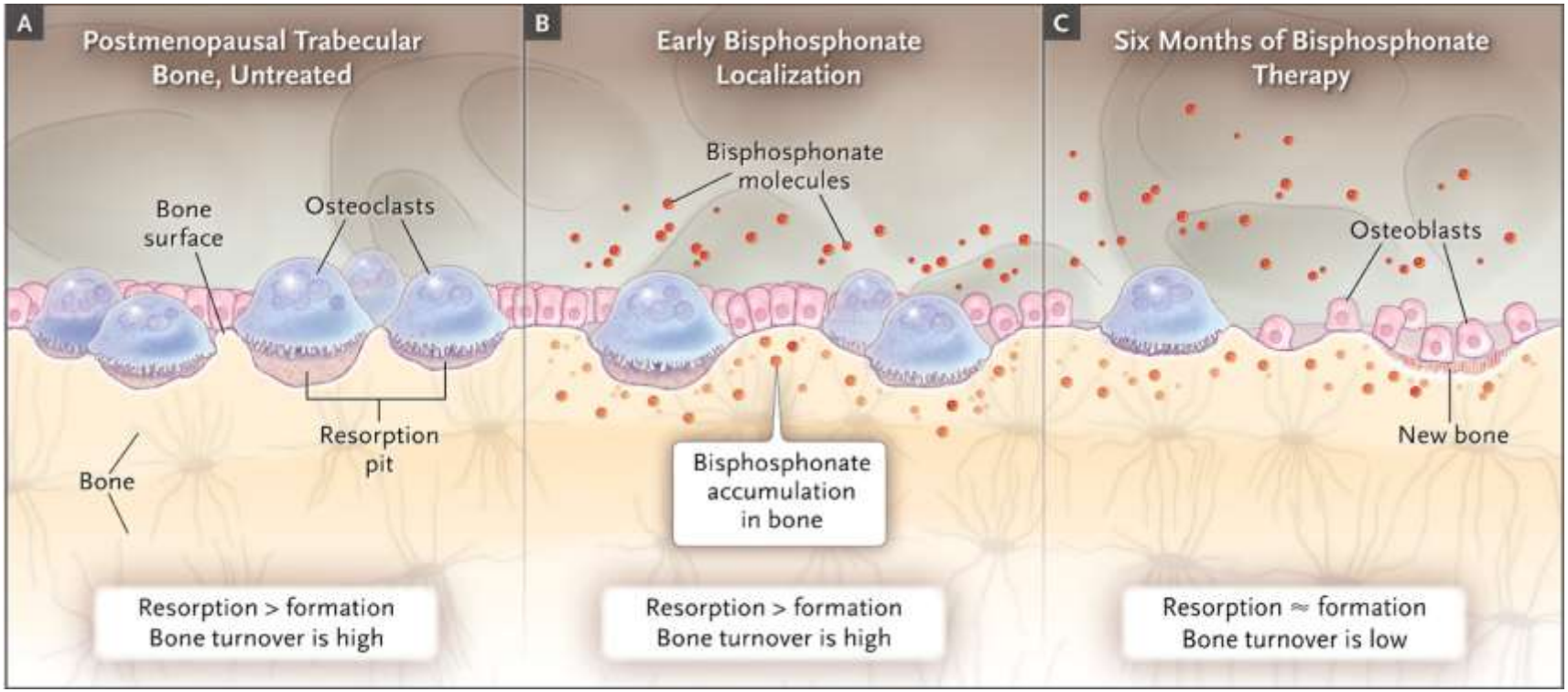
New strategy to treat osteoporosis in CKD

FDA approved bisphosphonate in 2013

Name	FDA label year	Concerns for use in patients with CKD	Author's commentary
Alendronate	2013	Not recommended for CrCl <35 ml/min	Agree with the FDA recommendations
Risedronate	2013	Not recommended for CrCl <30 ml/min	Agree with the FDA recommendations
Ibandronate	2013	Not recommended for CrCl <30 ml/min	Agree with the FDA recommendations
Zoledronic acid	2013	Contraindicated with CrCl <35 ml/min or acute renal impairment	Agree with the FDA recommendations

adapted fromOtt, S. M. *Nat. Rev. Nephrol.* 9, 681–692 (2013)

Cellular Elements Involved in Postmenopausal Trabecular Bone Turnover before and during Bisphosphonate Therapy.



Favus MJ. N Engl J Med 2010;363:2027-2035.

Effect of Ibandronate on BMD of Hemodialyzed Patients

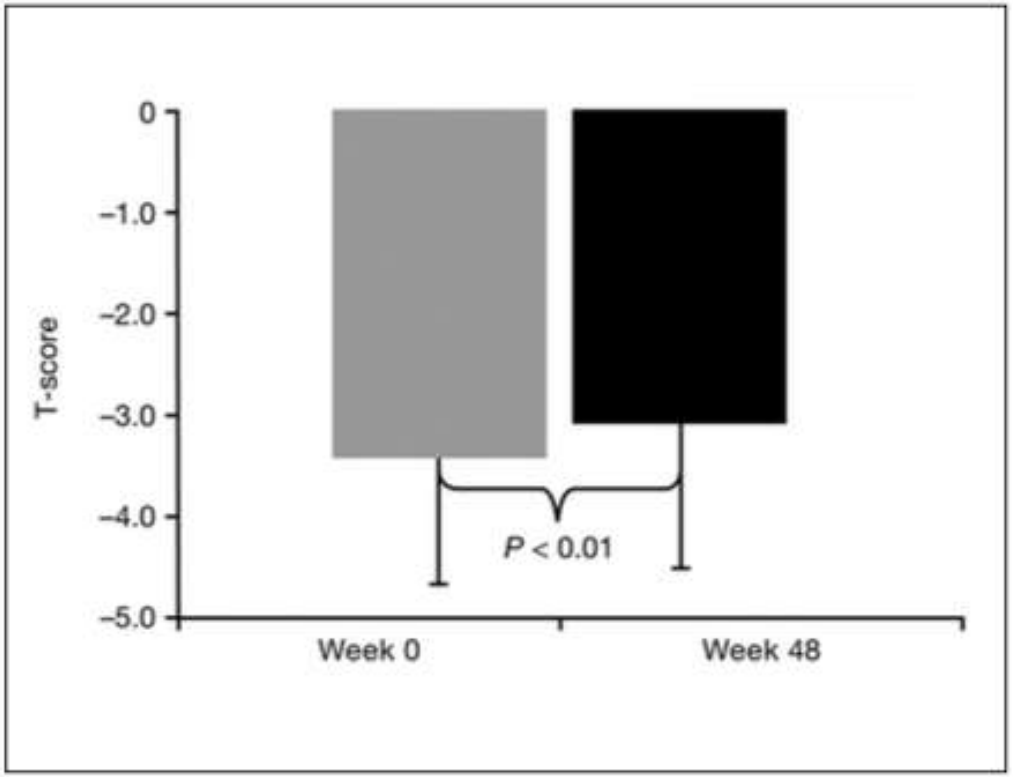


Fig. 2 - Mean spine bone densitometry T-score at week 0 and week 48 following treatment with intravenous ibandronate 2 mg every 4 weeks.

Bergner R., et al. J Nephrol 2008; 21: 510-516

New strategy to treat osteoporosis in CKD

FDA approved regimens for osteoporosis in 2013

Oestrogen	2011	None	Data limited in women with stage 4–5 CKD; use in younger women with amenorrhoea and BMD in the osteoporotic range or fracture
Raloxifene	2007	None	Pilot data in women on haemodialysis suggests beneficial effects; this agent is the best current choice in women with CKD who do not have coagulation problems
Teriparatide	2009	Use with caution in patients with recent urolithiasis	Preliminary data suggest a benefit in patients with CKD, low parathyroid hormone levels and BMD in the osteoporotic range
Calcitonin	2012	None	Probably safe, but concerns regarding cancer not resolved; effects on osteoporosis weaker than those of other drugs, and no data in patients with CKD
Denosumab	2013	Risk of hypocalcaemia in patients with CrCl <30 ml/min	Might be useful to treat hypercalcaemia but risky in patients with CKD and osteoporosis, owing to hypocalcaemia and suppressed bone formation

*Source, Drugs@FDA. Abbreviations: BMD, bone mineral density; CKD, chronic kidney disease; CrCl, creatinine clearance.[122]

adapted fromOtt, S. M. *Nat. Rev. Nephrol.* 9, 681–692 (2013)

Effect of Denosumab on BMD in CKD-FREEDOM STUDY

The increases in BMD did not differ by level of kidney function, and the magnitude of increase in BMD was not substantially different by stage of CKD compared with the overall increase in BMD at all sites.

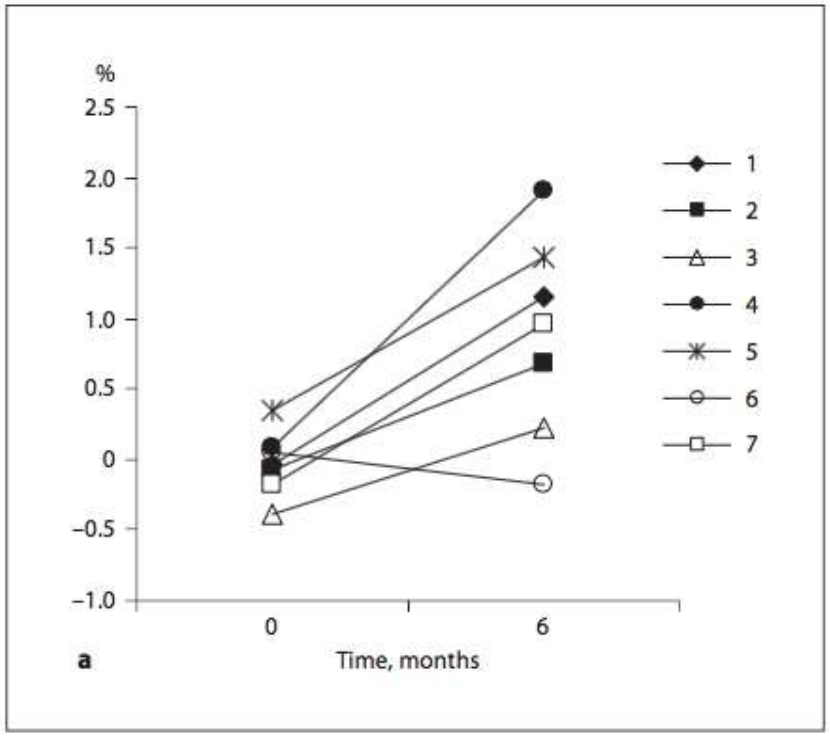
Ta

Outcome	Stage 4 CKD eGFR 15 to 29 mL/min ($N = 73$)	Stage 3 CKD eGFR 30 to 59 mL/min ($N = 2817$)	Stage 2 CKD eGFR 60 to 89 mL/min ($N = 4069$)	Stage 1 CKD/normal eGFR $\geq$ 90 mL/min ($N = 842$)
Lumbar spine BMD, % change	5.0 (−0.8–10.8)	8.9 (8.4–9.3)*	9.0 (8.6–9.4)*	8.1 (7.2–8.9)*
Femoral neck BMD, % change	5.9 (3.3–8.5)*	5.1 (4.7–5.5)*	5.2 (4.9–5.5)*	5.6 (4.9–6.3)*
Total-hip BMD, % change	5.9 (3.0–8.7)*	6.4 (6.1–6.7)*	6.4 (6.2–6.7)*	5.8 (5.2–6.3)*

N = number of randomized subjects. A difference in BMD% change > 0 in favor of denosumab.
*$p \leq .0002$.

Jamal SA, et al. J Bone Miner Res. 2011;26:1829

Treatment of Hemodialysis-Associated Adynamic Bone Disease with Teriparatide



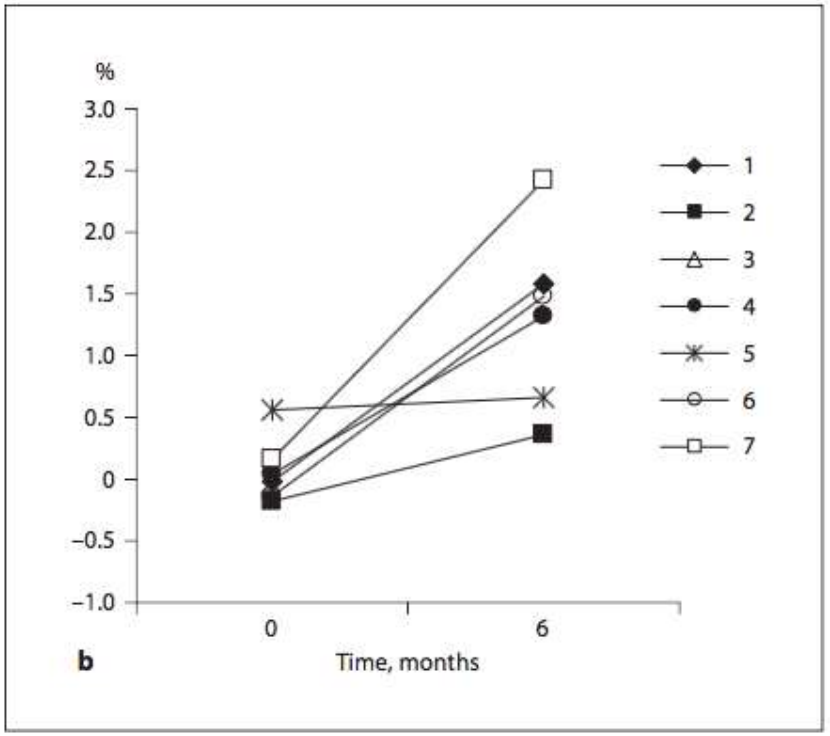
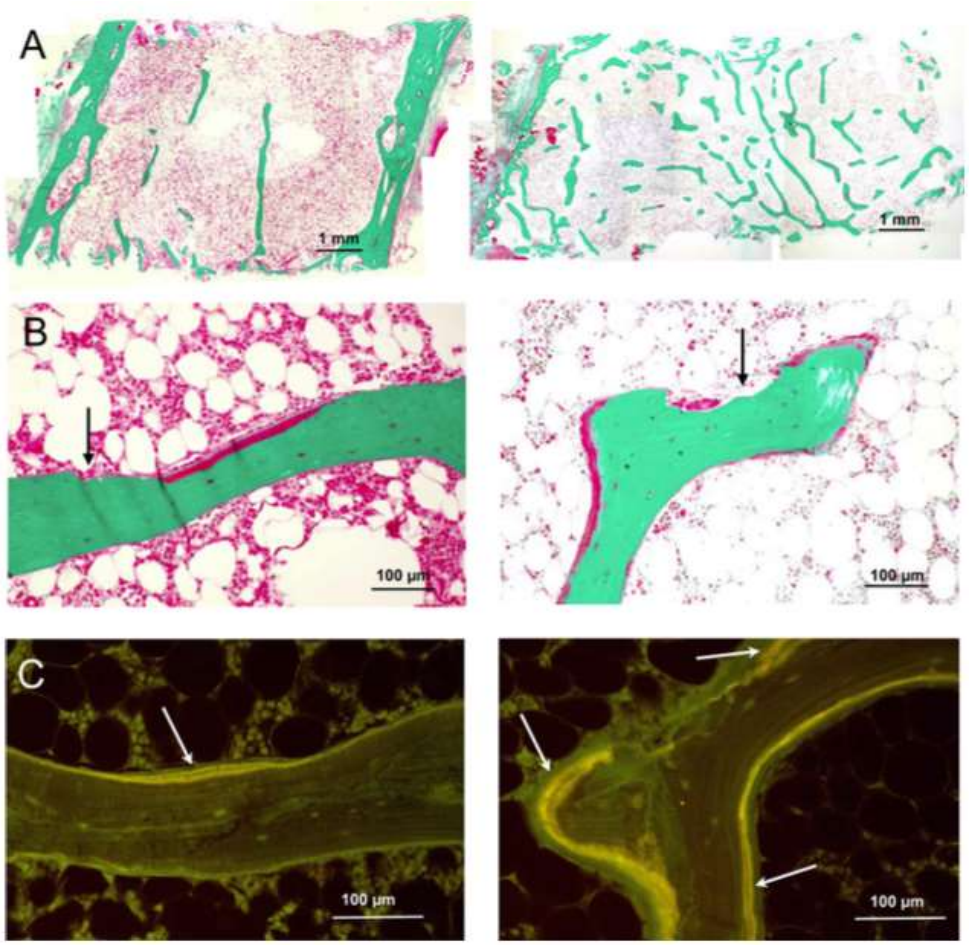


Fig. 2. Calculated percentage of monthly change in bone mineral density based on serial DEXA measurements of lumbar spine (**a**) and femoral neck (**b**) before and during therapy with teriparatide in individual patients.

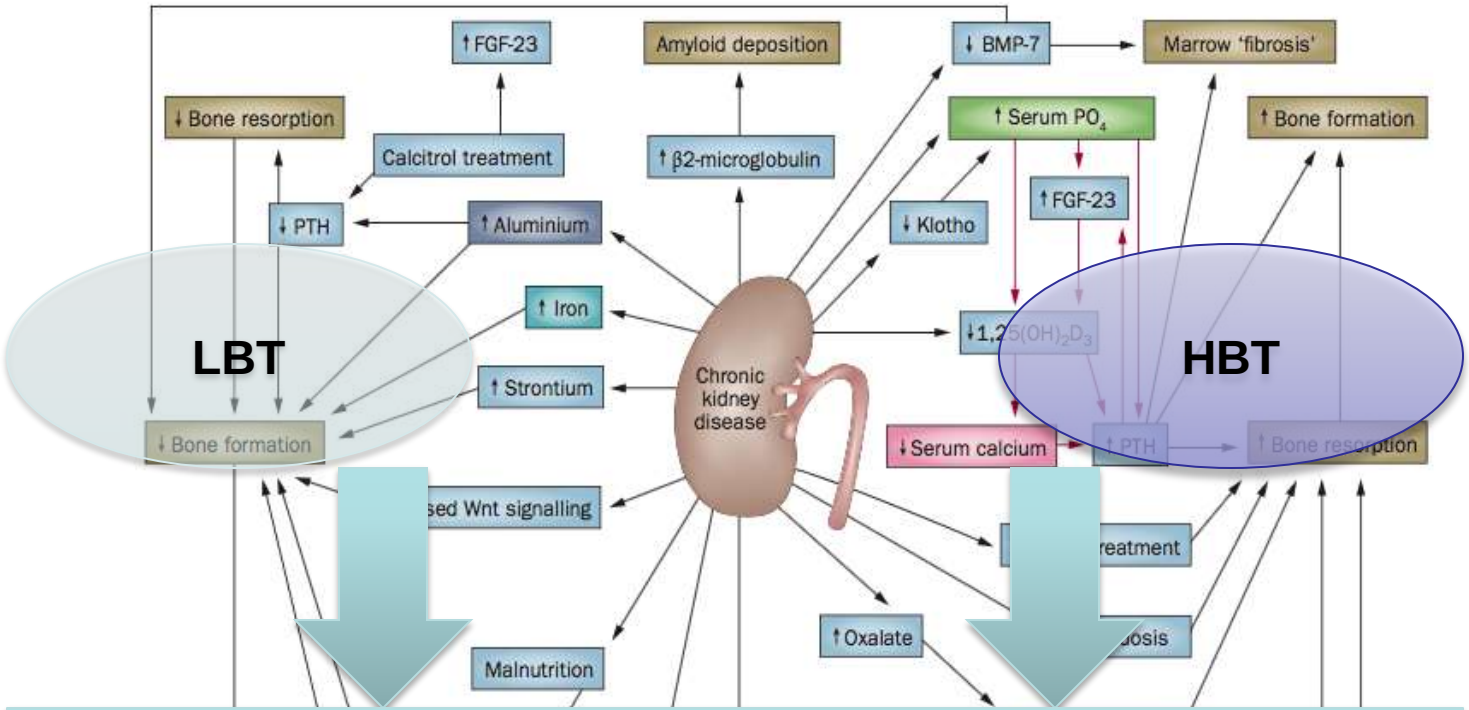
Cejka, D. et al. Kidney Blood Press Res 2010;33:221

Effect of Teriparatide on histology of adanyamic bone



Palcu, D. et al. Am J Kidney Dis. 65:933

Factors determining bone quality in CKD



Choice of regimens according to patient's bone turnover

parathyroid hormone. Permission obtained from American Society of Nephrology © Ott, S. M. *Clin. J. Am. Soc. Nephrol.* **3**, S151–S156 (2008) and adapted from Ott, S. M. *Semin. Nephrol.* **29**, 122–132, which is published under an open-access licence by Elsevier Inc.

Expected Guideline Update in 2015

Overview of proposed changes

- Selective update in **red**
- Minor tweaking in **dark grey**
- No changes **in black**