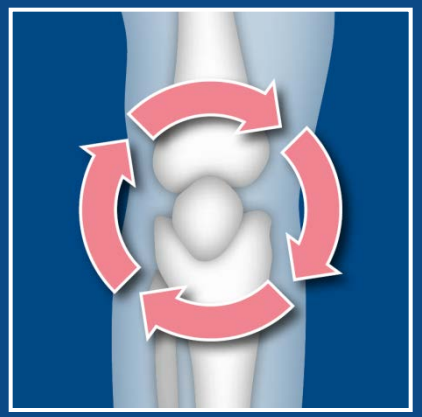
Nephro Update Europe 2018

5-6 October, Budapest

Bone and Mineral Disease



Adrian Covic, Romania

Conflicts of Interest

Research Support:

Lecturing: Vifor

Consulting activities: FMC

Renal osteodystrophy – diagnosis

Clinical case

A 62 year-old female, IDDM, hypertension and CKD – eGFR – 15 ml/min,

Presented with progressive bilateral ankle, foot, elbow and rib pain. Recent minor falls.

She had no history of trauma, swelling or stiffnessof the affected joints.

The patient was afebrile and in no acute distress. Her feet, ankles, and elbows had normal range of motion with no point tenderness, crepitus, swelling or erythema

What tests to perform?

1. Ca, P, PTH
2. Additional bone turnover markers (bALP, intact PINP, TRAP5b)
3. Dual-energy X-ray absorptiometry;
4. Bone biopsy and quantitative histomorphometry
5. High-resolution CT
6. High-resolution MRI

State of the art

Progressive decline in renal function adversely affects bone architecture, mineralization, collagen structure and marrow composition – increased risk of fractures

DXA - to assess bone mineral density and bone turnover markers - tools used to evaluate renal osteodystrophy have important limitations

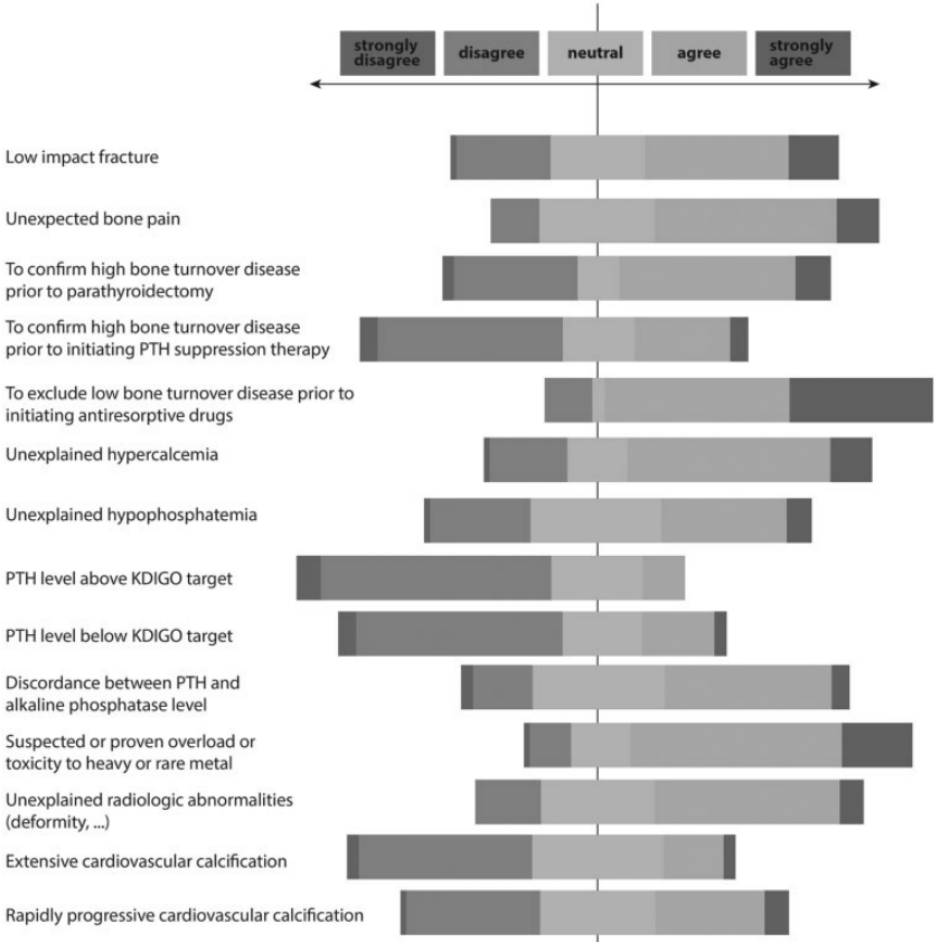
Bone biopsy and quantitative histomorphometry, the 'gold standard' is invasive, expensive, requires expertise to perform, process and interpret and is rarely used in clinical practice

This has led to a search for reliable biomarkers / high-resolution imaging to estimate bone architecture and bone strength

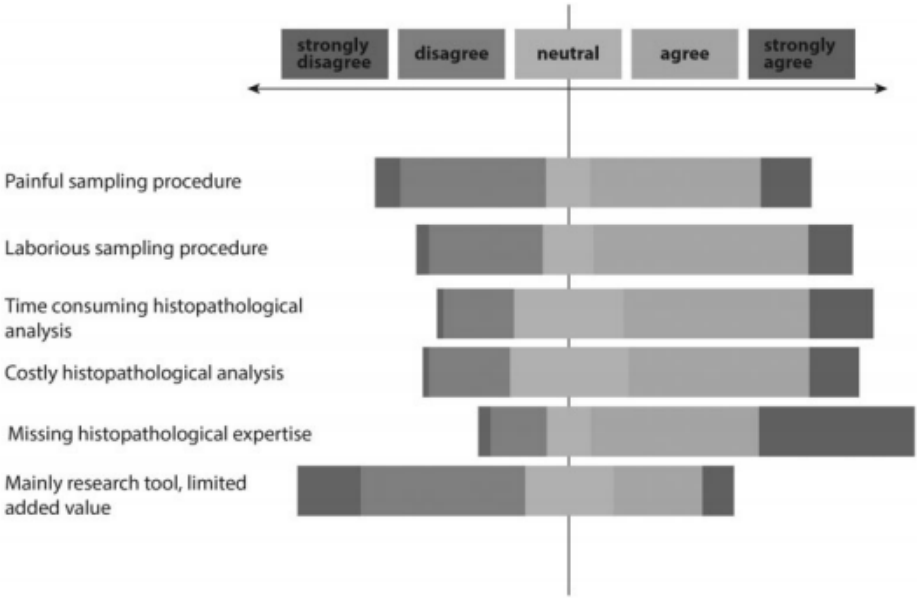
Parfitt Curr. Opin. Nephrol. Hypertens. 12 (4) (2003) 387–403. Nickolas, J. Bone Miner. Res. 28 (8) (2013) 1811–1820. Wehrli, J. Magn. Reson. Imaging 25 (2) (2007) 390–409. R. KijowskiJ. Bone Miner. Res. 27 (7) (2012) 1494–1500

Bone biopsy practice patterns across Europe: the European renal osteodystrophy initiative

Recent survey conducted among European nephrologists – diverse practice



'Potential indications to perform a bone biopsy.'
Percentage distribution



'What are in your opinion hurdles to a more widespread clinical implementation of bone biopsies in CKD patients?'
Percentage distribution

P. Evenepoel et al. NDT 2017 Oct 1;32(10):1608-1613

Association of renal function with fracture risk

N = 1477 participants aged > 65yrs from the Longitudinal Aging Study Amsterdam; 6-year fracture follow-up

eGFR Quartile (Min-Max) (ml/min/1.73 m^2)	Number of fractures /total *N*	Model 1	Model 2	Model 3
9–57	30/329	1.39 (1.19–1.63), $p < 0.01$	1.38 (1.17–1.61), $p < 0.01$	1.36 (1.15–1.60), $p < 0.01$
57–66	30/328	1.11 (0.95–1.30), $p = 0.19$	1.10 (0.94–1.29), $p = 0.24$	1.09 (0.93–1.28), $p = 0.27$
66–74	33/331	1.11 (0.95–1.30), $p = 0.23$	1.08 (0.92–1.26), $p = 0.35$	1.08 (0.92–1.26), $p = 0.36$
74–254	22/330	Reference group	Reference group	Reference group

Presented are the hazard ratios, 95% confidence intervals; model 1, adjusted for age and sex; model 2, adjusted for age, sex, BMI, smoking, alcohol, and number of chronic diseases; model 3, adjusted for age, sex, BMI, smoking, alcohol, number of chronic diseases, and PTH

From a eGFR < 60 ml/min/1.73 m² – an increased incident fracture risk

Chen H. et al. Osteoporos Int 2018 Sep;29(9):2129-2138

MRI - significant, relevant associations to bone biopsy

ESRD patients

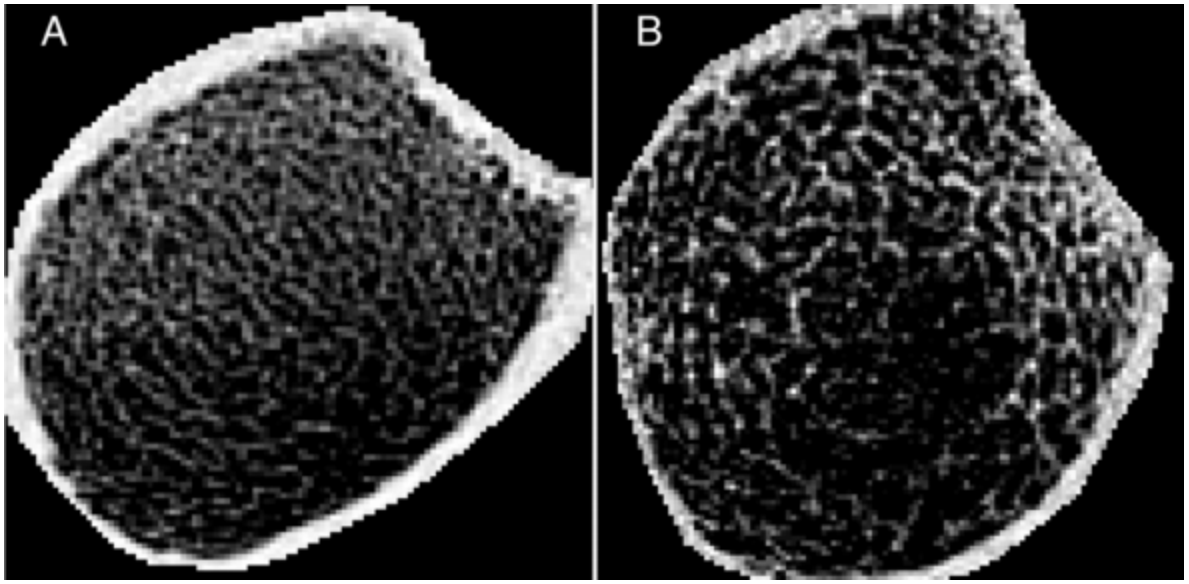
-High-resolution MRI at the distal tibia,

-BMD by dual energy X-ray absorptiometry (DXA; hip and spine)

-transiliac bone biopsies with histomorphometry

-microcomputed tomography (micro-CT)

-biomarkers of mineral metabolism



compact cortical bone and well connected trabecular bone compartment

thinned and porous cortical bone and disconnected trabecular bone regions

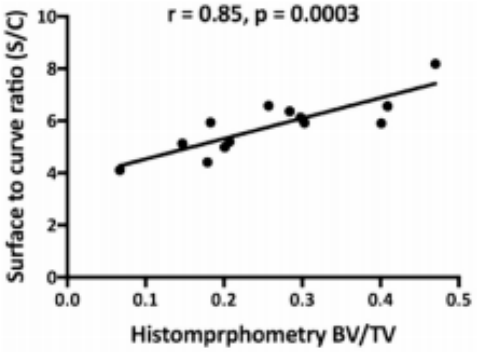
(MRI) of distal tibia

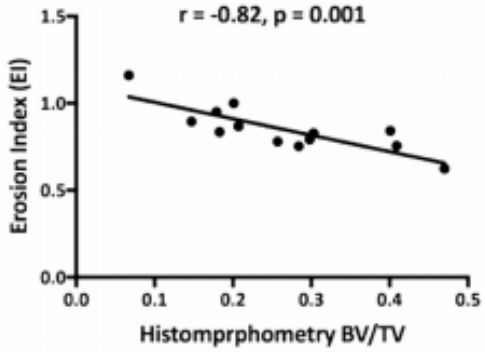
- indices of trabecular network integrity,
- surface to curve ratio
- erosion index

Sharma, Bone. 2018 Sep;114:14-21

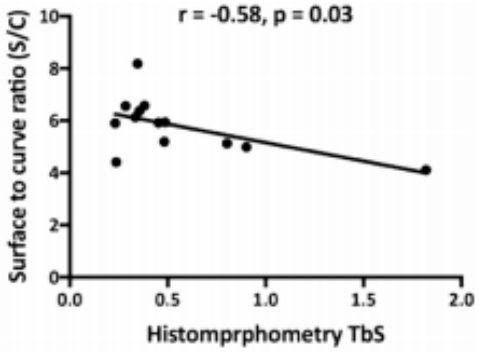
MRI - significant, relevant associations to bone biopsy

MRI vs transiliac bone biopsies and micro-CT

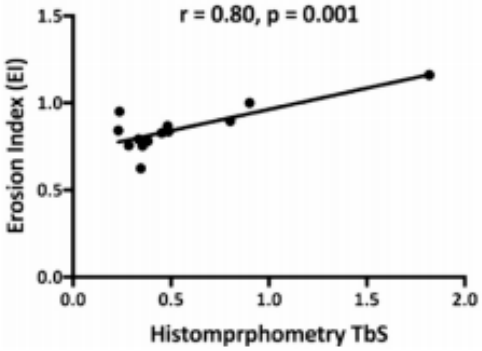


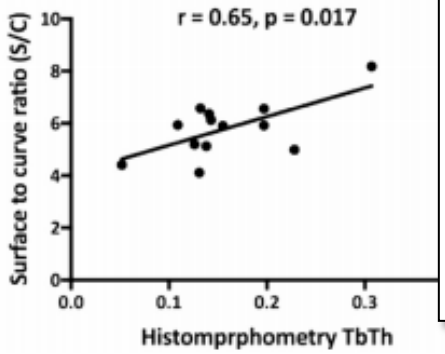


trabecular bone volume (BV/TV)



trabecular separation (TbS, µm).





MRI indices of trabecular network integrity, surface to curve ratio and erosion index correlated to histomorphometric trabecular bone volume, separation and thickness

trabecular thickness (TbTh, µm)

Sharma, Bone. 2018 Sep;114:14-21

MRI and BMD categories

MRI parameter	BMD findings at the femural neck (WHO classification) T score-1.0-2.5 (osteopenia)	T score -2.5 and below
Surface to curve ratio	5.5 ± 0.85	3.6 ± 2.1*
Erosion Index	0.90 ± 0.1	1.3 ± 0.6
Bone volume (%)	11.0 ± 2.2	7.2 ± 0.8*
Trabecular thickness (µm)	0.13 ± 0.006	0.12 ± 0.0*
Trabecular number (1/mm)	0.86 ± 0.14	0.62 ± 0.1*
Trabecular Separation (µm)	1.05 ± 0.2	1.5 ± 0.25**
Cortical thickness (µm)	2.7 ± 0.51	2.4 ± 0.46

*p≤0.05 compared to subjects without osteopenia or osteoporosis respectively
**p≤0.01 compared to subjects without osteopenia or osteoporosis respectively

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*p≤0.05 compared to subjects without osteopenia or osteoporosis respectively
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All MRI-derived trabecular parameters differed significantly for the participants with **femoral neck Tscores ≤ −2.5 versus those with T-scores > −2.5**

Sharma, Bone. 2018 Sep;114:14-21

The vexing old issue…

- If bone biomarkers could differentiate ***low / high*** bone turnover or even replace bone biopsy

bALP, intact PINP, TRAP5b and radius HR-pQCT parameters can discriminate *low* from non-low bone turnover

69 CKD patients stages 4–5, including patients on dialysis and 68 controls

Biomarker (iPTH , PINP, bALP, CTX, TRAP5b) and distal radius and tibia by HR-pQCT.

Bone biopsy (only in patients with CKD) using tetracycline bone labeling

Table 3. Diagnostic accuracy of biomarkers and radius high-resolution peripheral quantitative computed tomography for identifying patients with low bone turnover

Variables	AUC (95% CI)	Criterion	Sensitivity, %	Specificity, %	PPV, %	NPV, %
Biomarkers						
iPTH	0.563 (0.40 to 0.72)	≤183 pg/ml	70	53	32	85
Intact PINP	0.794 (0.64 to 0.90)	≤57 ng/ml	80	75	50	92
Total PINP	0.719 (0.56 to 0.85)	≤124 ng/ml	80	68	44	91
bALP	0.824 (0.67 to 0.93)	≤21 μg/L	89	77	53	96
tALP	0.753 (0.60 to 0.87)	≤88 IU/L	91	63	46	95
CTX	0.766 (0.61 to 0.88)	≤0.84 ng/ml	60	84	55	87
TRAP5b	0.799 (0.64 to 0.91)	≤4.6 U/L	89	71	47	96
Radius HR-pQCT *Z* score						
Total vBMD	0.811 (0.65 to 0.92)	>−1.0	100	59	45	100
Cortical BV/TV	0.802 (0.64 to 0.92)	>−0.2	89	63	44	94
Combined variables						
bALP and radius total vBMD *Z* score	0.797 (0.62 to 0.92)	Not available	100	58	39	100

AUC, area under the receiver operating characteristic curve; 95% CI, 95% confidence interval; PPV, positive predictive value; NPV, negative predictive value; iPTH, intact parathyroid hormone; PINP, procollagen type 1 N-terminal propeptide; bALP, bone alkaline phosphatase; tALP, total alkaline phosphatase; CTX, collagen type 1 crosslinked C-telopeptide; TRAP5b, tartrate-resistant acid phosphatase 5b; HR-pQCT, high-resolution peripheral quantitative computed tomography; vBMD, volumetric bone mineral density; BV/TV, bone volume/tissue volume.

Salam. JASN 2018 May;29(5):1557-1565

bALP, intact PINP, TRAP5b and radius HR-pQCT parameters can discriminate *low* from non-low bone turnover

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- AUCs for bALP, intact PINP, TRAP5b >0.790, each significantly better than the iPTH
- AUC for radius HR-pQCT - significantly better also
- Combined variables (HR-pOCT and bALP) did not improve the AUC

Salam. JASN 2018 May;29(5):1557-1565

iPTH can discriminate *high* bone turnover with accuracy similar to that of the other biomarkers

Table 4. Diagnostic accuracy of biomarkers for identifying patients with high bone turnover

Biomarkers	AUC (95% CI)	Criterion	Sensitivity, %	Specificity, %	PPV, %	NPV, %
iPTH	0.760 (0.60 to 0.88)	>327 pg/ml	53	96	90	75
Intact PINP	0.765 (0.61 to 0.88)	>107 ng/ml	53	92	82	74
Total PINP	0.725 (0.56 to 0.85)	>142 ng/ml	75	68	60	81
bALP	0.750 (0.59 to 0.87)	>31 μg/L	56	83	69	74
tALP	0.670 (0.51 to 0.81)	>102 IU/L	65	73	61	76
CTX	0.762 (0.61 to 0.88)	>2.39 ng/ml	53	96	90	75
TRAP5b	0.710 (0.55 to 0.84)	>4.6 U/L	81	58	57	82

AUC, area under the receiver operating characteristic curve; 95% CI, 95% confidence interval; PPV, positive predictive value; NPV, negative predictive value; iPTH, intact parathyroid hormone; PINP, procollagen type 1 N-terminal propeptide; bALP, bone alkaline phosphatase; tALP, total alkaline phosphatase; CTX, collagen type 1 crosslinked C-telopeptide; TRAP5b, tartrate-resistant acid phosphatase 5b.

Salam. JASN 2018 May;29(5):1557-1565

Take-Home Message

- MRI - based assessment of bone microstructure - may become a non-invasive alternative to histomorphometry in patients with CKD
- Validation of the role of MRI will require prospective trials, designed to assess its potential for fracture prediction and monitoring therapeutic intervention
- bALP, intact PINP, TRAP5b, and radius HR-pQCT were able to discriminate low bone turnover in patients with advanced CKD.
- Despite poor diagnostic accuracy for low bone turnover, iPTH can discriminate high bone turnover with similar accuracy to other biomarkers in this study.

Hyper/hypo P and mortality

Clinical case

54-year-old well nourished, active man, 11-year history of chronic kidney disease secondary to chronic glomerulonephritis; in august 2012 he started hemodialysis; no residual renal function, no phosphate binders or vitamin D in his current treatment;

At his monthly evaluation, P level is 6 mg/dl.

How would you treat this patient?

1. I would treat intensively
2. Only diet
3. Phosphate binder
4. I do not treat – I do not have all the necessary information;

.

State of the art

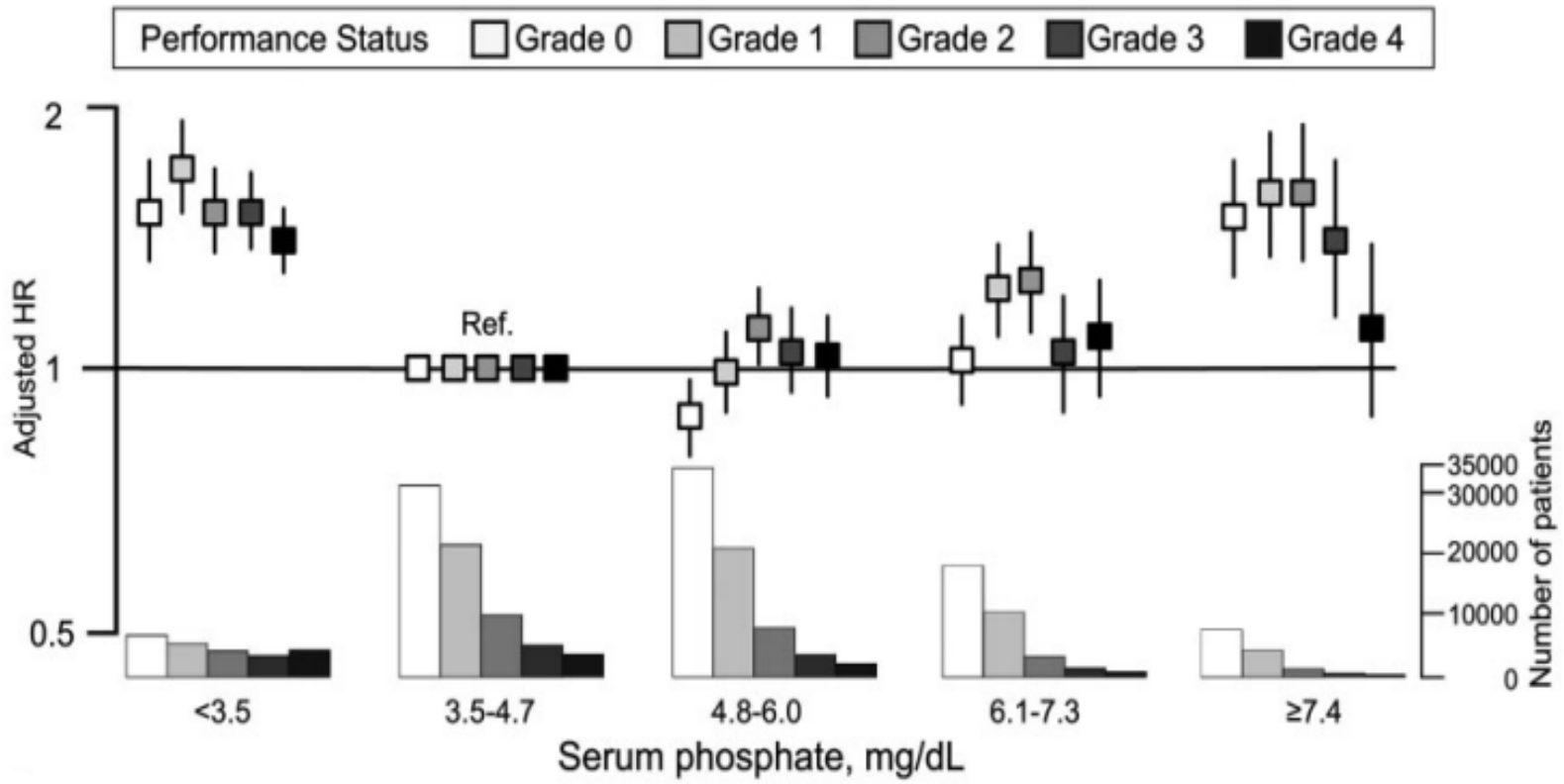
- Abnormal serum levels of phosphate, calcium and PTH are associated with increased mortality risk in dialysis patients

- The association between MBD parameters and mortality may be modified by several factors

Functional impairment attenuates the association between HP and mortality in dialysis patients

N = 220 054 prevalent dialysis patients ; data from the Japanese Society for Dialysis Therapy Renal Data Registry collected 2009 and 2010; 18.447 (8.4%) had died.

Performance status ranged from Grades 0 to 4 (Grade 0 - patients who are fully active; Grade 4 - patients completely disabled patients who cannot carry out any self-care; totally confined to a bed or chair)



Wakasugi, **Nephrol Dial Transplant 2018 Aug 13**

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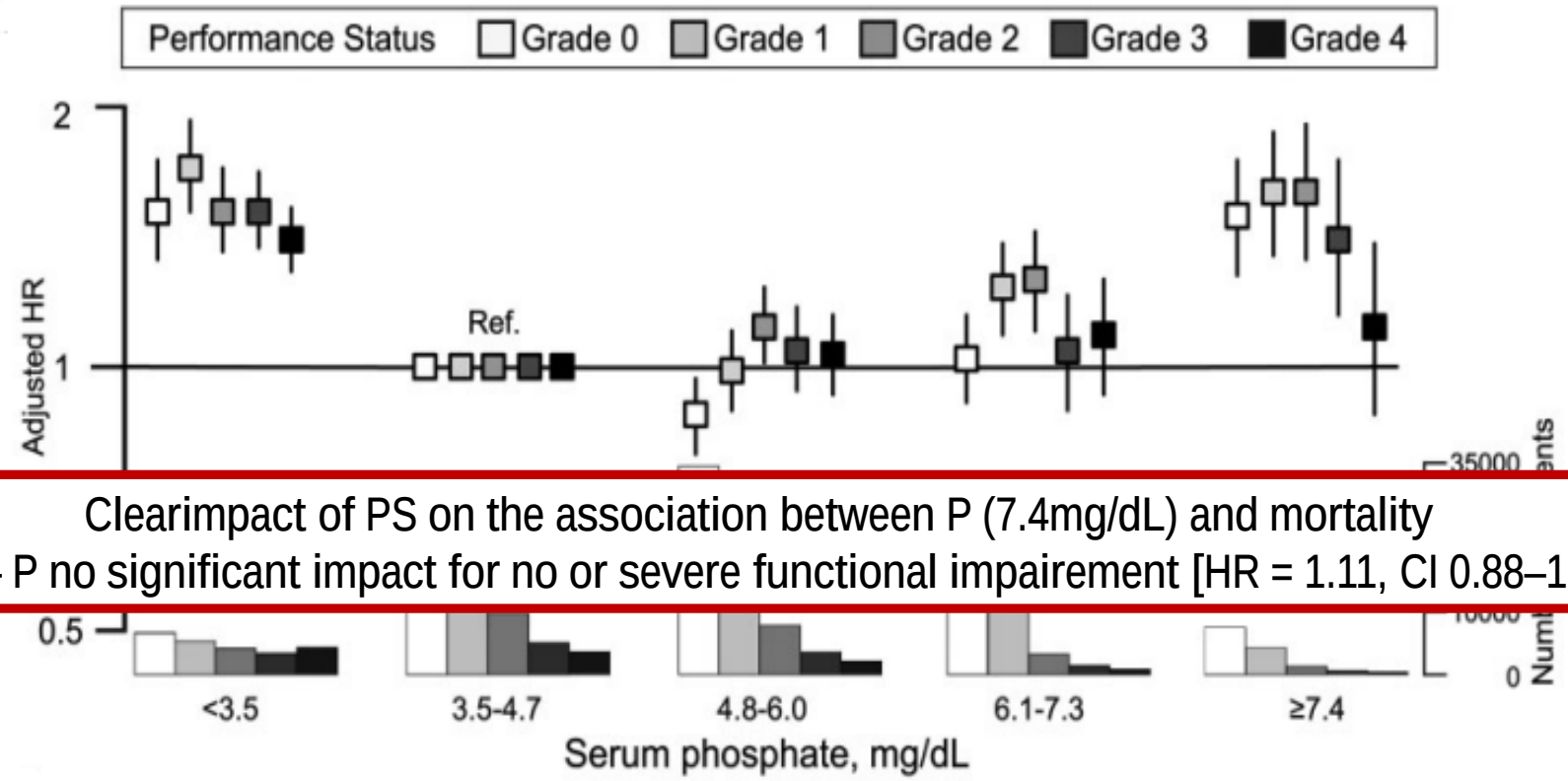
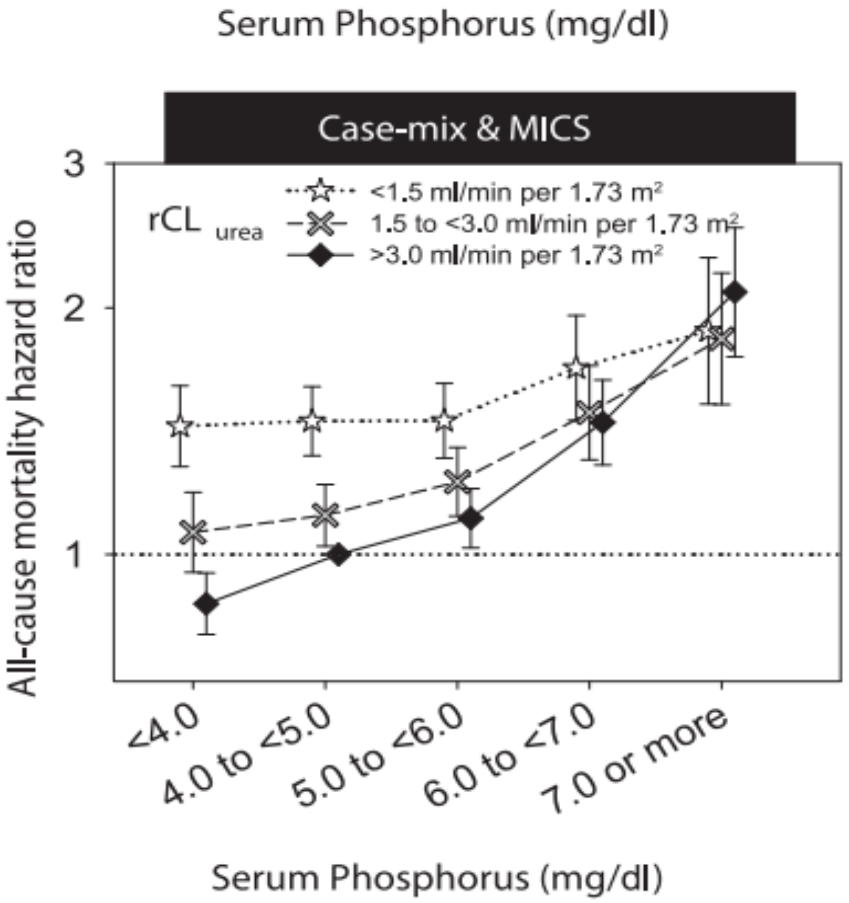


Clearimpact of PS on the association between P (7.4mg/dL) and mortality
High – P no significant impact for no or severe functional impairement [HR = 1.11, CI 0.88–1.39]

Wakasugi, ***Nephrol Dial Transplant 2018 Aug 13***

Residual kidney function modified the mortality risk associated with P among incident HD patients.

N = 35,114 incident hemodialysis patients from a large United States dialysis organization; 8102 (23%) patients died during the median follow-up of 1.3 years



1. incremental mortality risk across higher serum P concentrations

2. Steeper curves among patients with higher residual renal urea clearance **(P interaction = 0.001).**

Wang, cJASN 2017 Jul 7;12(7):1118-1127

CKD-MBD phenotypes associated with reduced hospitalization-free survival and increased mortality

EuCliD database:

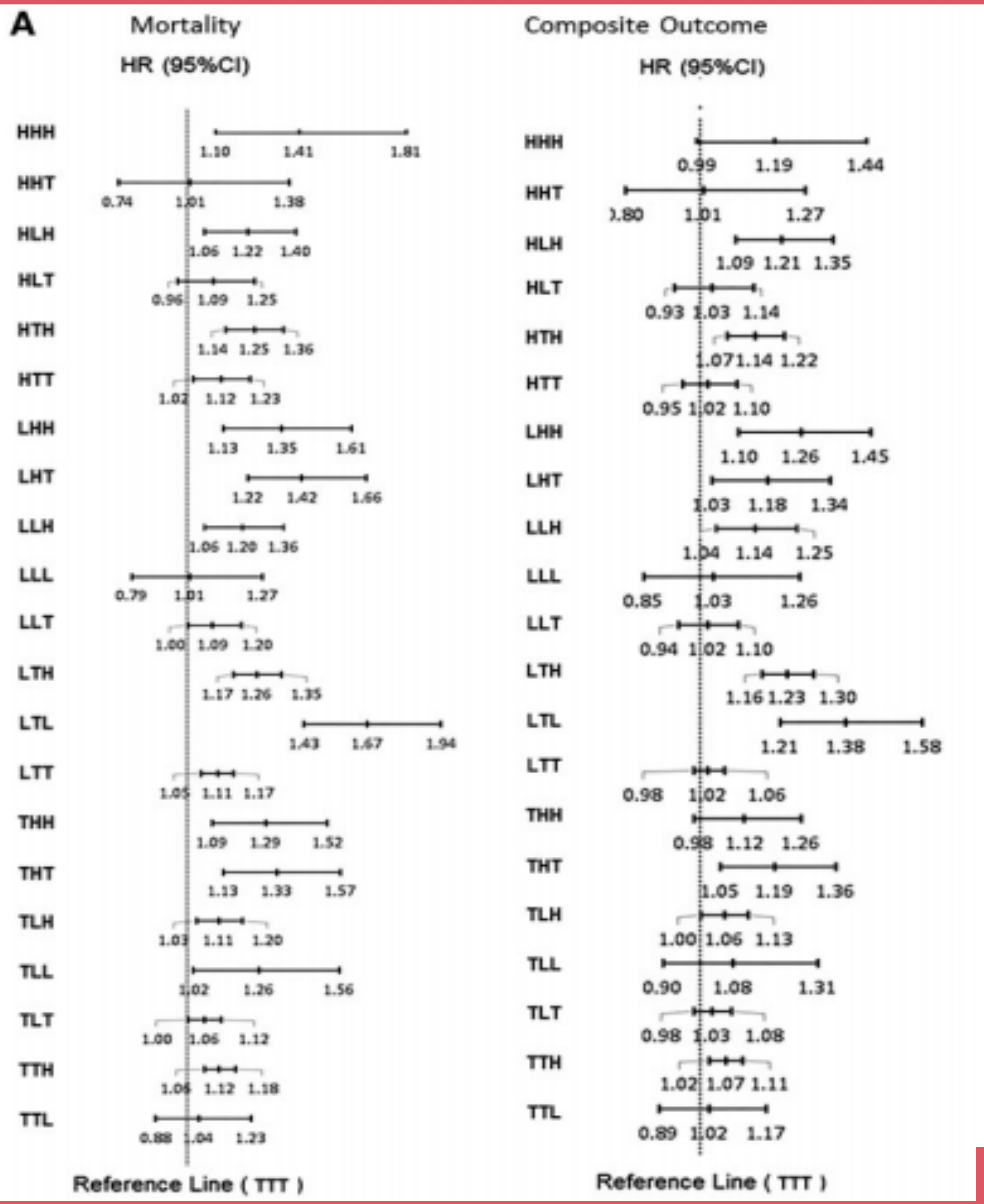
N = 35,721 HD pts.; 15,795 deaths

27 mutually exclusive phenotypes based on combinations of serum PTH, P and Ca 6-month averages

(L, low; T, target; H, high).

Tested the association between CKD-MBD phenotypes and 5-year mortality and hospitalization risk

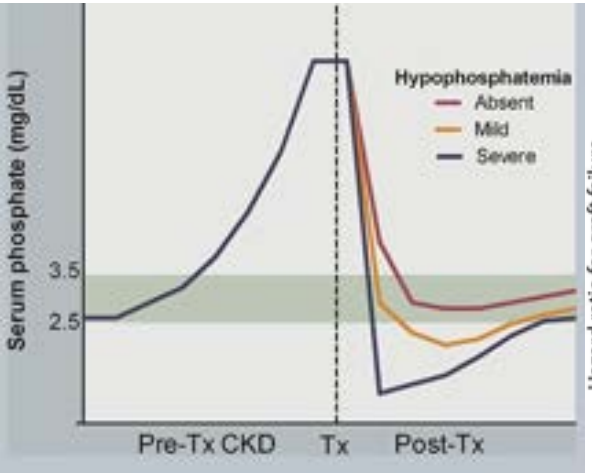
(outcome risk score-adjusted proportional hazard regression)

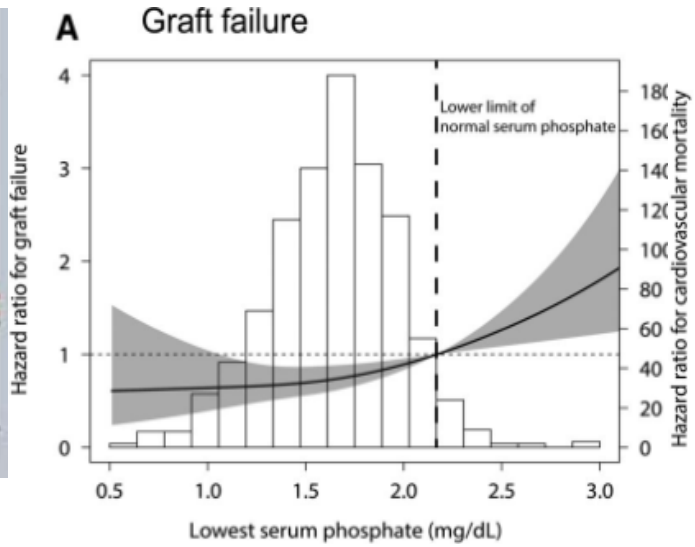


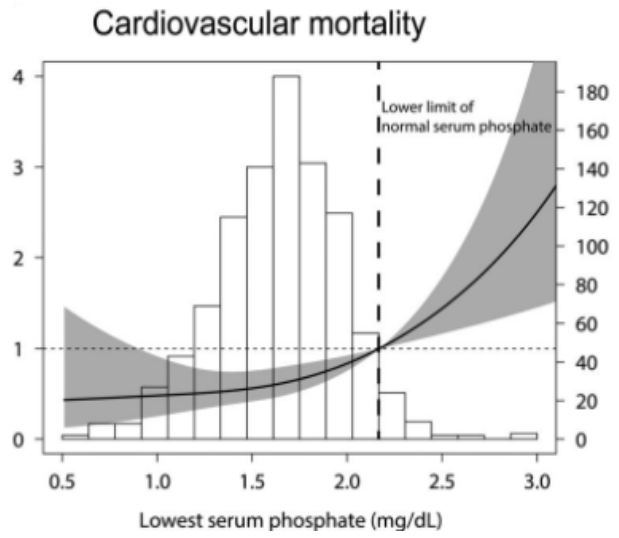
Neri et al. Nephrology Dialysis Transplantation, gfy273. 2018 August 27

Post-transplant hypophosphatemia develops early after transplantation - favourable long-term graft/patient outcomes

longitudinal cohort study in 957 renal transplant recipients







Hypo P - Lower risk of death-censored graft failure (HR 0.61; 95% CI, 0.43 to 0.88 per 1 mg/dl lower serum phosphate) and CV mortality (HR, 0.37; 95% CI, 0.22 to 0.62)

van London et al. cJASN. 2017 Aug 7;12(8):1301-1310

Take home message

- The association between HP and mortality was modified by functional status and residual renal function AND PHENOTYPE

- Hyper-P per se – should urgently be reconsidered as target!
- should be clearly interpreted by joint presence of: a) RRF; b) functional impairment & malnutrition; c) Calcium and PTH

- Hypophosphatemia - very common after kidney transplantation and associated with favorable graft and patient outcome

Secondary HPTH – medical and surgical parathyroidectomy

Clinical case

69-year-old Caucasian man with an 11-year history of hemodialysis;

developed pain in both legs, muscle weakness, pruritus;

serum calcium - 9.29 mg/dL; the serum P – 6.8 mg/dl and PTH - 1647 pg/mL;

How would you treat this patient?

1. Cinacalcet;
2. Evocalcet;
3. Parathyroidectomy

State of the Art

- Secondary hyperparathyroidism contributes to extraskeletal calcifications and is associated with all-cause and CV mortality.

"Medical parathyroidectomy" – calcimimetics

Cinacalcet is used to control SHPT, but:

- may induce hypocalcemia
- may induce GI symptoms - lower adherence and insufficient dosages

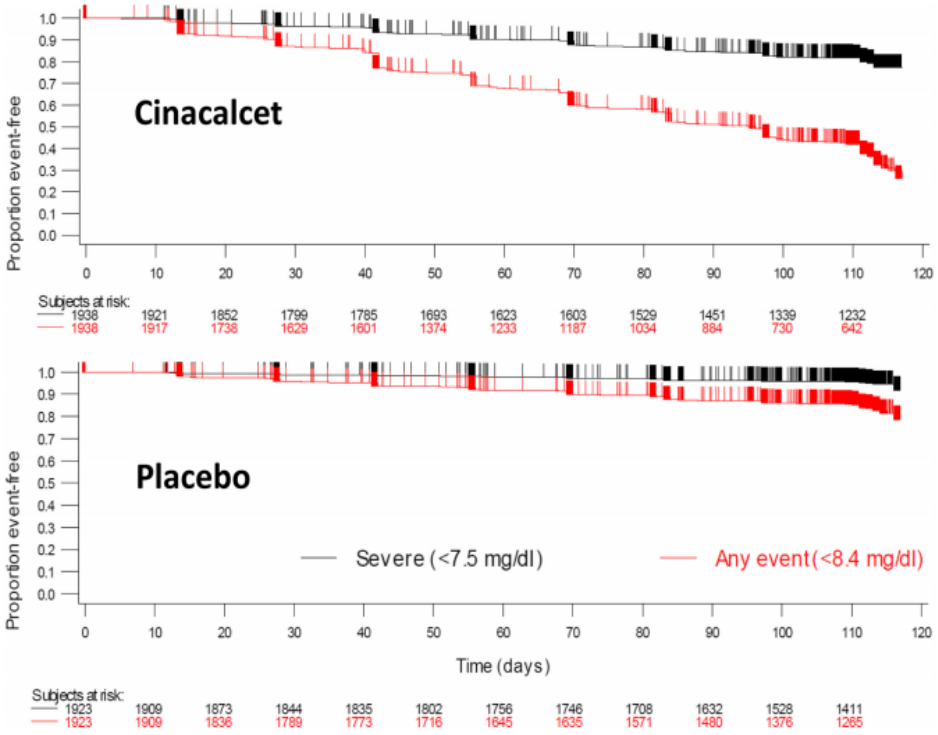
Evocalcet:

- may be different from cinacalcet

Kawata T, PLoS One. 2018;3;13:e0195316.

Cinacalcet - the occurrence of hypocalcemia is frequent and related to the severity of secondary HPTH

post hoc analysis of the EVOLVE trial



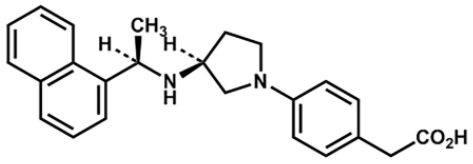
	Episodes and patients (%)	Hazard ratio (95% CI)	*P* value[b]
Region			<0.001
USA	89/430 (20.7)	Reference	
Australia	8/30 (26.7)	1.54 (0.72, 3.28)	
Canada	11/37 (29.7)	1.29 (0.65, 2.56)	
Europe	99/302 (32.8)	1.55 (1.07, 2.24)	
Latin America	100/196 (51.0)	3.29 (2.25, 4.80)	
Russia	30/76 (39.5)	2.95 (1.80, 4.84)	
Race			0.073
White	198/584 (33.9)	Reference	
Black	42/250 (16.8)	0.61 (0.41, 0.93)	
Hispanic	82/185 (44.3)	1.06 (0.75, 1.49)	
Other	15/52 (28.8)	0.92 (0.53, 1.61)	
BMI (kg/m^2)	337/1071 (31.5)	1.021 (1.003, 1.039)	0.021
History of diabetes			0.055
No	226/723 (31.3)	Reference	
Yes	111/348 (31.9)	1.29 (0.99, 1.67)	
PTH (100 pg/ml)	337/1071 (31.5)	1.04 (1.02, 1.06)	<0.001
Corrected total serum calcium (mg/dl)	337/1071 (31.5)	0.29 (0.25, 0.35)	<0.001
NTx (100 nmol/l)	337/1071 (31.5)	0.983 (0.963, 1.003)	0.090
25(OH)D (µg/l)	337/1071 (31.5)	0.990 (0.979, 1.000)	0.062
Total alkaline phosphatase (100 U/l)	337/1071 (31.5)	1.14 (1.06, 1.23)	<0.001

58.3% developed at least 1 hypocalcemia episode during the first 16 wks.
18.4% were categorized as severe hypocalcemia

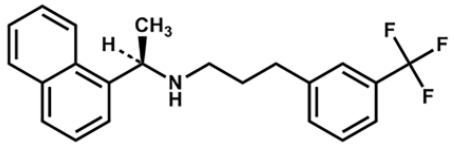
Floege et al. Kidney Int. 2018 Jun;93(6):1475-1482

State of the Art

- Evocalcet:
  - new calcimimetic agent for oral use
  - favorable profile by evaluating the effect on gastric emptying in rats
  - CYP2D6 inhibition observed in cinacalcet not seen for evocalcet.



Evocalcet



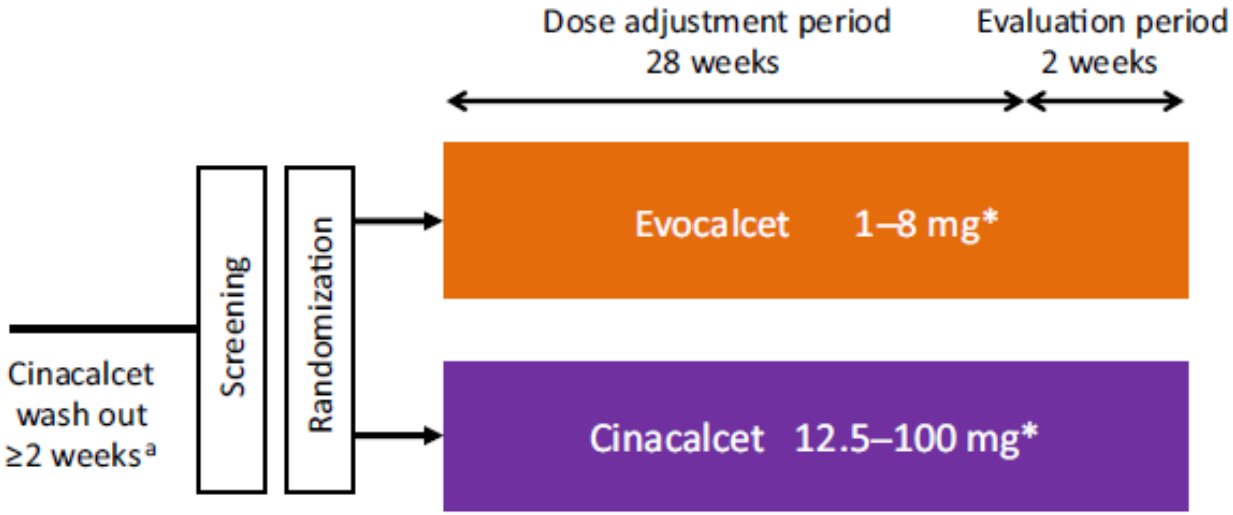
Cinacalcet

Kawata T, PLoS One. 2018;3;13:e0195316.

Head-to-head comparison of the new calcimimetic agent evocalcet with cinacalcet

N = phase 3, randomized, double-blind, double-dummy trial

Patients with SHPT on HD were randomized to receive evocalcet or cinacalcet (317 patients each) for 30 weeks



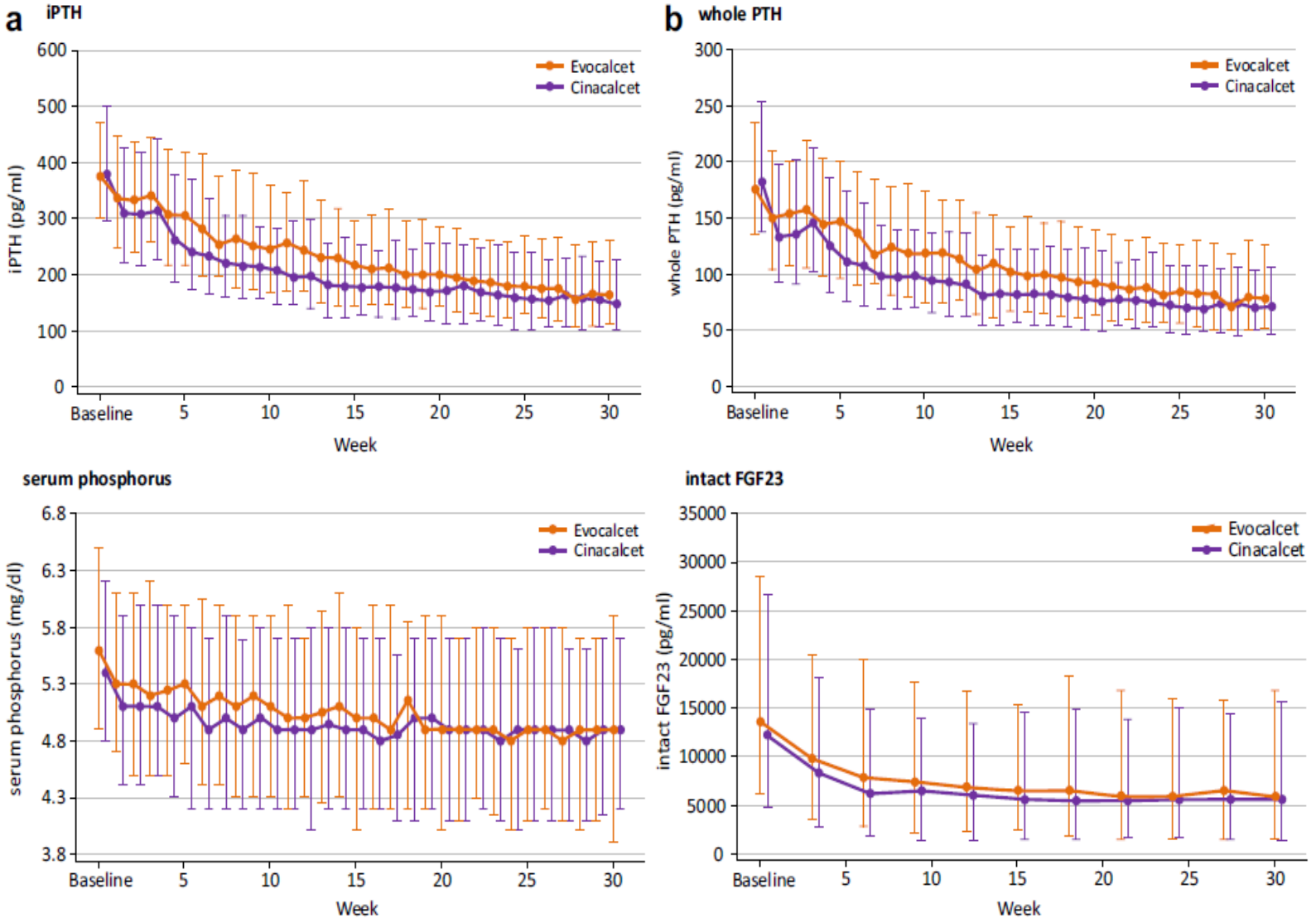
Treatment period: 30 weeks

* Initial dose

iPTH level[b]	Evocalcet	Cinacalcet
<500 pg/ml	1 mg	25 mg
≥500 pg/ml	2 mg	25 mg

Fukagawa M. Kidney Int. 2018 Jul 20

Noninferiority of evocalcet to cinacalcet in suppressing iPTH



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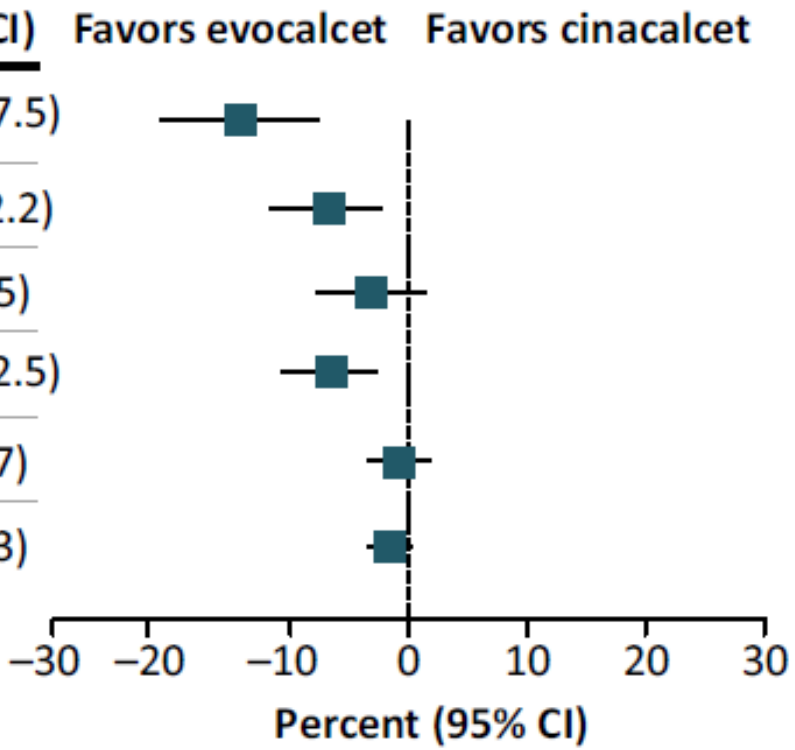
With fewer gastrointestinal-related adverse events

Adverse event	Percent	(95% CI)
Gastrointestinal-related adverse events	−14.2	(−20.9, −7.5)
Nausea	− 6.9	(−11.7, −2.2)
Vomiting	− 3.2	(−7.8, 1.5)
Abdominal discomfort	− 6.6	(− 10.7, −2.5)
Decreased appetite	− 0.9	(−3.6, 1.7)
Abdominal distension	− 1.6	(−3.4, 0.3)



Fukagawa M. Kidney Int. 2018 Jul 20

State of the art

Surgical parathyroidectomy

- PTX is required in about 15 % of patients after 10 years and 38 % of patients after 20 years of ongoing dialysis

- PTX dramatically ameliorates SHPT symptoms and signs and increases survival rates and patient quality of life.

- However a significant proportion develops recurrent SHPT following PTX, ranging between 10 and 30 %

- Most failures occur when the surgeon dose not remove all hyper functioning parathyroid tissue

Wei Ling Lau et al. Clin J Am Soc Nephrol. 2018 Jun 7

State of the art

- KDOQI “Parathyroidectomy should be recommended in patients with severe hyperparathyroidism (persistent serum levels of intact PTH >800 pg/mL[88.0 pmol/L]), associated with hypercalcemia and/or hyperphosphatemia that are refractory to medical therapy. (OPINION)”

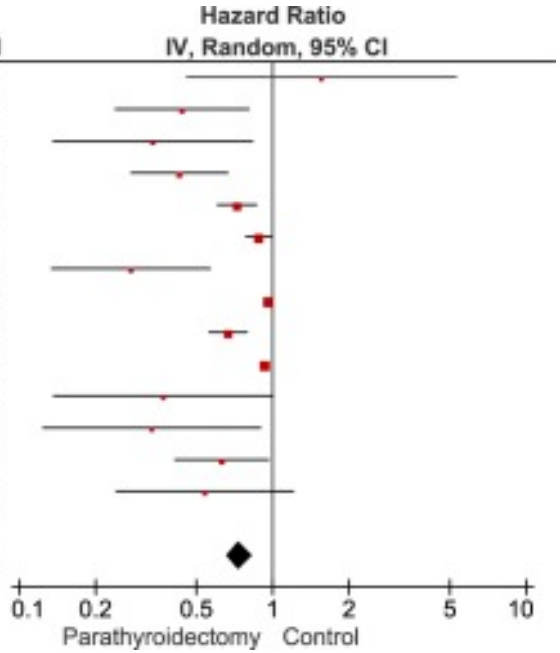
- KDIGO 2017 “In patients with CKD stages 3–5D with severe hyperparathyroidism (HPT) who fail to respond to medical/pharmacological therapy, we suggest parathyroidectomy (2B)

sPTX - decreased all-cause mortality and CV mortality

Systematic review and meta-analysis; 15 cohort studies, comprising 24,048 participants

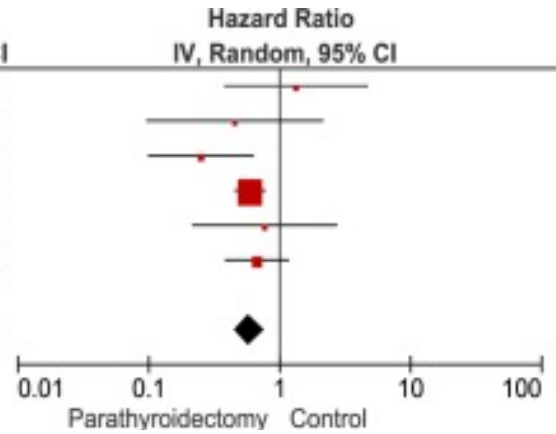
Study or Subgroup	log[Hazard Ratio]	SE	Parathyroidectomy Total	Control Total	Weight	Hazard Ratio IV, Random, 95% CI
Conzo G. et al. 2013	0.4418	0.6268	30	20	0.8%	1.56 [0.46, 5.31]
Costa-Hong V. et al. 2007	-0.8239	0.3123	50	68	3.0%	0.44 [0.24, 0.81]
Dussol B. et al. 2007	-1.0881	0.4649	19	32	1.5%	0.34 [0.14, 0.84]
Goldstein P. et al 2013	-0.8475	0.2265	123	128	4.9%	0.43 [0.27, 0.67]
Ho L-C. et al 2016	-0.324	0.0929	998	998	12.8%	0.72 [0.60, 0.87]
Ivarsson K. et al. 2015	-0.1281	0.0606	423	1234	15.7%	0.88 [0.78, 0.99]
Iwamoto N. et al 2012	-1.2879	0.3698	88	88	2.2%	0.28 [0.13, 0.57]
Kestenbaun B. et al. 2004	-0.0406	0.0191	4558	4558	18.5%	0.96 [0.92, 1.00]
Komaba H. et al 2015	-0.4055	0.0907	4428	4428	13.0%	0.67 [0.56, 0.80]
Li W. et al. 2016	-0.0726	0.0224	53	92	18.3%	0.93 [0.89, 0.97]
Ma T-L. et al 2015	-0.9939	0.5115	60	161	1.2%	0.37 [0.14, 1.01]
Moldovan D. et al 2015	-1.0986	0.5064	26	26	1.2%	0.33 [0.12, 0.90]
Sharma J. et al. 2013	-0.462	0.2192	150	1044	5.2%	0.63 [0.41, 0.97]
Trombetti A. et al 2007	-0.6162	0.4137	40	80	1.8%	0.54 [0.24, 1.21]
Total (95% CI)			**11046**	**12957**	**100.0%**	**0.74 [0.66, 0.83]**

Heterogeneity: Tau² = 0.02; Chi² = 69.92, df = 13 (P < 0.00001); I² = 81%
Test for overall effect: Z = 5.17 (P < 0.00001)



Study or Subgroup	log[Hazard Ratio]	SE	Parathyroidectomy Total	Control Total	Weight	Hazard Ratio IV, Random, 95% CI
Conzo G. et al. 2013	0.2877	0.6455	30	20	4.1%	1.33 [0.38, 4.72]
Costa-Hong V. et al. 2007	-0.7911	0.795	50	68	2.7%	0.45 [0.10, 2.15]
Iwamoto N. et al 2012	-1.3863	0.4767	88	88	7.4%	0.25 [0.10, 0.64]
Komaba H. et al 2015	-0.5255	0.1385	4428	4428	62.9%	0.59 [0.45, 0.78]
Lin H-C. et al. 2014	-0.2657	0.6505	30	23	4.0%	0.77 [0.21, 2.74]
Sharma J. et al. 2013	-0.4005	0.2893	150	1044	18.9%	0.67 [0.38, 1.18]
Total (95% CI)			**4776**	**5671**	**100.0%**	**0.59 [0.46, 0.76]**

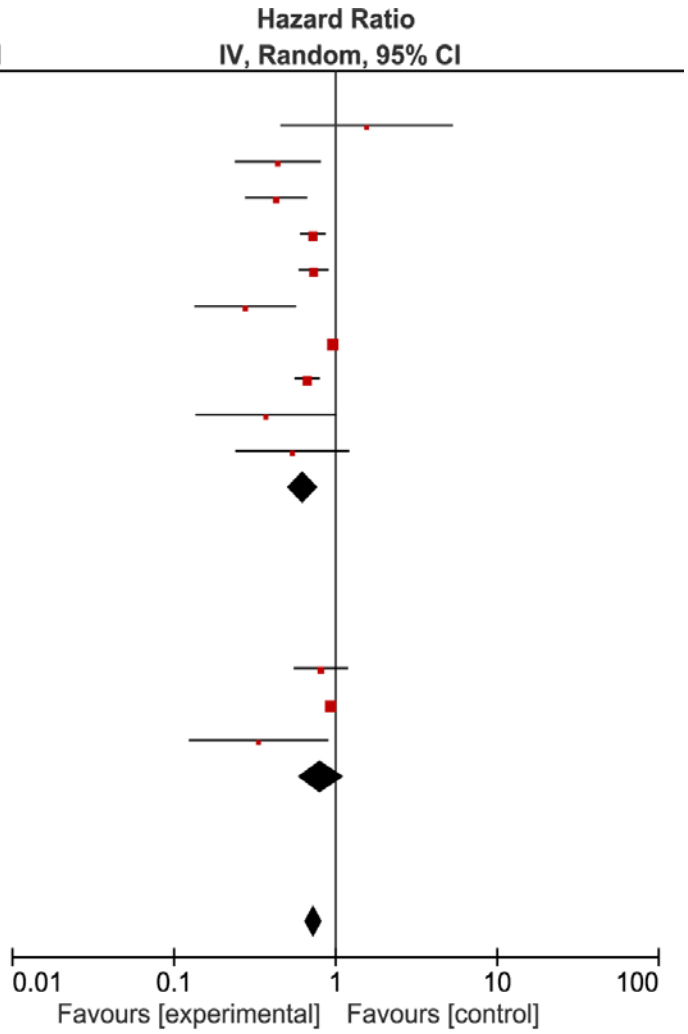
Heterogeneity: Tau² = 0.01; Chi² = 5.31, df = 5 (P = 0.38); I² = 6%
Test for overall effect: Z = 4.01 (P < 0.0001)



Apetrii, Covic, PLoS One. 2017 Nov 6;12(11):e0187025.

In the post-calcimimetics era the advantage of sPTX was smaller and lost statistical significance

Study or Subgroup	log[Hazard Ratio]	SE	Weight	Hazard Ratio IV, Random, 95% CI
1.6.1 Prior the introduction of calcimimetics				
Conzo G. et al. 2013	0.4418	0.6268	0.9%	1.56 [0.46, 5.31]
Costa-Hong V. et al. 2007	-0.8239	0.3123	3.2%	0.44 [0.24, 0.81]
Goldstein P. et al 2013	-0.8475	0.2265	5.3%	0.43 [0.27, 0.67]
Ho L-C. et al 2016	-0.324	0.0929	13.4%	0.72 [0.60, 0.87]
Ivarsson et al. pre-cinacalcet	-0.3147	0.1086	12.0%	0.73 [0.59, 0.90]
Iwamoto N. et al 2012	-1.2879	0.3698	2.4%	0.28 [0.13, 0.57]
Kestenbaun B. et al. 2004	-0.0406	0.0191	19.2%	0.96 [0.92, 1.00]
Komaba H. et al 2015	-0.4055	0.0907	13.6%	0.67 [0.56, 0.80]
Ma T-L. et al 2015	-0.9939	0.5115	1.3%	0.37 [0.14, 1.01]
Trombetti A. et al 2007	-0.6162	0.4137	1.9%	0.54 [0.24, 1.21]
Subtotal (95% CI)			**73.2%**	**0.63 [0.50, 0.79]**
Heterogeneity: Tau² = 0.08; Chi² = 62.01, df = 9 (P < 0.00001); I² = 85%				
Test for overall effect: Z = 3.98 (P < 0.0001)				
1.6.2 After the introduction of calcimimetics				
Ivarsson et al. pre-cinacalcet	-0.2107	0.1975	6.4%	0.81 [0.55, 1.19]
Li W. et al. 2016	-0.0726	0.0224	19.0%	0.93 [0.89, 0.97]
Moldovan D. et al 2015	-1.0986	0.5064	1.3%	0.33 [0.12, 0.90]
Subtotal (95% CI)			**26.8%**	**0.81 [0.59, 1.12]**
Heterogeneity: Tau² = 0.04; Chi² = 4.57, df = 2 (P = 0.10); I² = 56%				
Test for overall effect: Z = 1.27 (P = 0.20)				
Total (95% CI)			**100.0%**	**0.73 [0.65, 0.83]**
Heterogeneity: Tau² = 0.02; Chi² = 66.67, df = 12 (P < 0.00001); I² = 82%				
Test for overall effect: Z = 5.08 (P < 0.00001)				
Test for subgroup differences: Chi² = 1.61, df = 1 (P = 0.20), I² = 37.9%				



Apetrii, Covic, PLoS One. 2017 Nov 6;12(11):e0187025.

Effect of parathyroidectomy and cinacalcet on quality of life - a systematic review

Reference	Year	No. of patients	Follow-up	Main objective	Pre-PTx	Post-PTx	P-value
SF-36							
Bratucu *et al.* [26]	2015	85	6 months	SF-36			
				PCS	29.96 ± 8.11	38.50 ± 5.36	<0.0001
				MCS	45.06 ± 11.37	47.28 ± 9.30	0.01
Cheng *et al.* [8]	2013	49	12 months	SF-36			
				PCS	40.3 ± 17.1	59.0 ± 14.9	<0.0001
				MCS	47.6 ± 17.1	63.7 ± 13.0	<0.0001
Yang *et al.* [27]	2011	37	3 months	SF-36			
				PCS	31.3 (20–45.1)	42.9 (27.7–48.7)	<0.001
				MCS	39.5 (25–48.6)	42.4 (29.8–49.2)	<0.05
Chow *et al.* [28]	2003	12	6 months	SF-36			
				Physical functioning	59.2 ± 26.8	68.0 ± 28.6	0.01
				Role limitations—physical	27.1 ± 31.0	50.0 ± 46.5	0.04
				Pain	57.9 ± 27.8	83.1 ± 16.3	0.004
PAS							
Bratucu *et al.* [26]	2015	85	6 months	PAS	567 ± 136	293 ± 85	<0.0001
Cheng *et al.* [8]	2013	49	12 months	PAS	545 ± 263	284 ± 201	<0.0001
Pasieka and Parsons [4]	2000	32	12 months	Median symptom index score	572	355	<0.01
VAS							
Yang *et al.* [27]	2011	37	3 months	VAS			
				Skin itching	4.31 ± 3.33	3.0 ± 2.19	<0.001
				Joint pain	4.98 ± 3.37	2.61 ± 2.19	<0.05
				Muscle weakness	4.63 ± 2.90	3.30 ± 2.19	<0.001

PTx improved QoL in patients treated for ESRD-related HP

The difference in impact between PTx and cinacalcet on QoL has not been compared directly.

Lau et al. Nephrol Dial Transplant. 2017 Nov 1;32(11):1902-1908

Take-Home Message

- the occurrence of hypocalcemia is frequent following initiation of cinacalcet and the likelihood of developing hypocalcemia was related to the severity of secondary HPTH
- the non-inferiority of evocalcet to cinacalcet in suppressing iPTH with fewer gastrointestinal-related adverse events
- sPTX remains even in the modern nephrology era a valid and viable therapeutic intervention especially for long-term dialysis patients

FGF-23

a.FGF23 and mortality (in CKD/renal transplantation)

b.New experimental data regarding FGF 23 regulation

c. New theraphies for FGF 23 decline

FGF-23

a.FGF23 and mortality (in CKD/renal transplantation)

b.New experimental data regarding FGF 23 regulation

c. New theraphies for FGF 23 decline

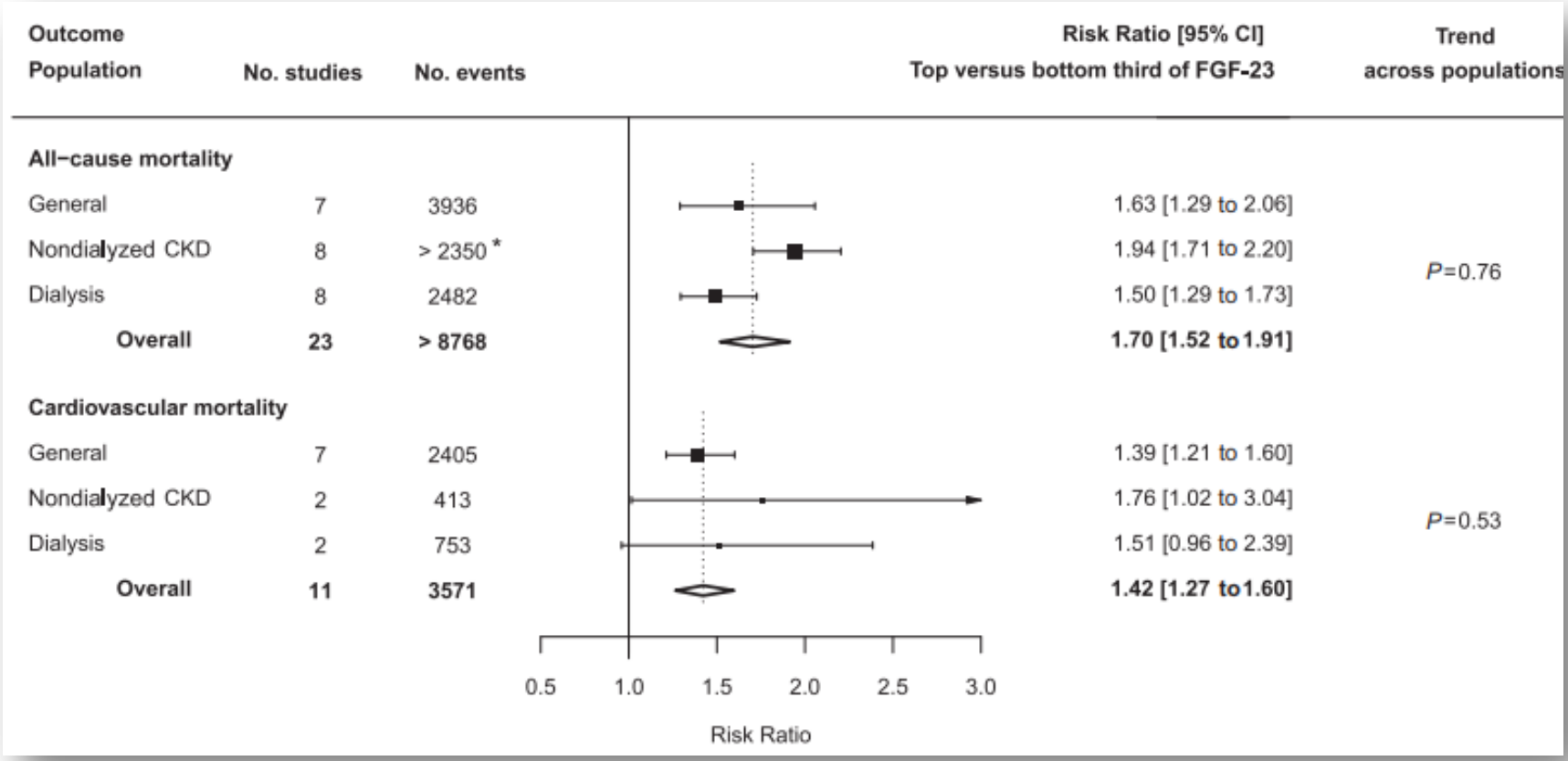
State of the art - Elevated FGF 23

- Strongly associated with CV disease and mortality
- Independently associated with left ventricular hypertrophy, heart failure, atrial fibrillation and mortality.
- If so, interventions targeting FGF-23 might hold therapeutic potential.

Palmer, JAMA 2011; 305: 1119–1127; Faul, J Clin Invest 2011; 121: 4393–4408; Isakova, JAMA 2011; 305: 2432–2439

FGF-23 was strongly associated with both CV / nonCV causes of death - *lack of specificity of the associations between raised FGF-23 and risk*

Systematic review and metanalysis – 34 prospective studies reporting associations between FGF-23 concentration and risk of cardiovascular events

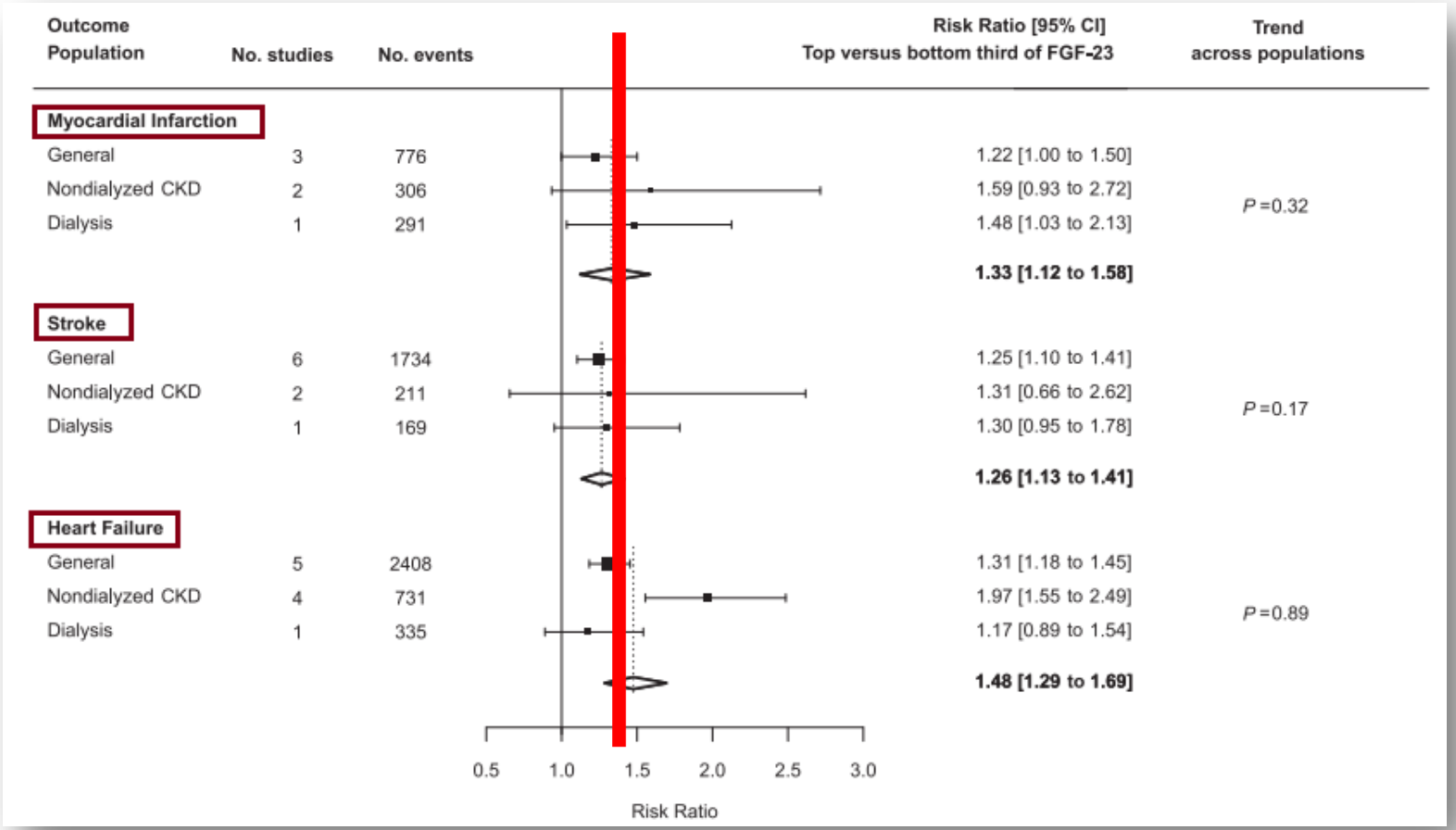


HR = 1.70 for all-cause mortality,1.42 for CV mortality, and 1.52 for non-CV mortality (calculated indirectly)

Associations - similar for CV and nonCV mortality.

Marthi et al. J Am Soc Nephrol 2018 Jul;29(7):2015-2027

Irrespective of a population's level of kidney function, a difference in FGF-23 concentration was associated with 30% increased risk of MI and stroke, and 50% increased risk of HF



OF NOTE, the size of association did not increase across these populations

Marthi et al. J Am Soc Nephrol 2018 Jul;29(7):2015-2027

THUS
Similarly-sized associations between increased FGF-23 concentration and CV and nonCV outcomes

Associations that are both nonspecific and do not exhibit an exposure–response relationship

These results do not support the hypothesis that targeting FGF-23 will reduce cardiovascular disease risk

Marthi et al. J Am Soc Nephrol 2018 Jul;29(7):2015-2027

Another dogma - Elevated FGF 23 and LVH...

- Cross-sectional studies have revealed that higher FGF23 is consistently associated with LVH

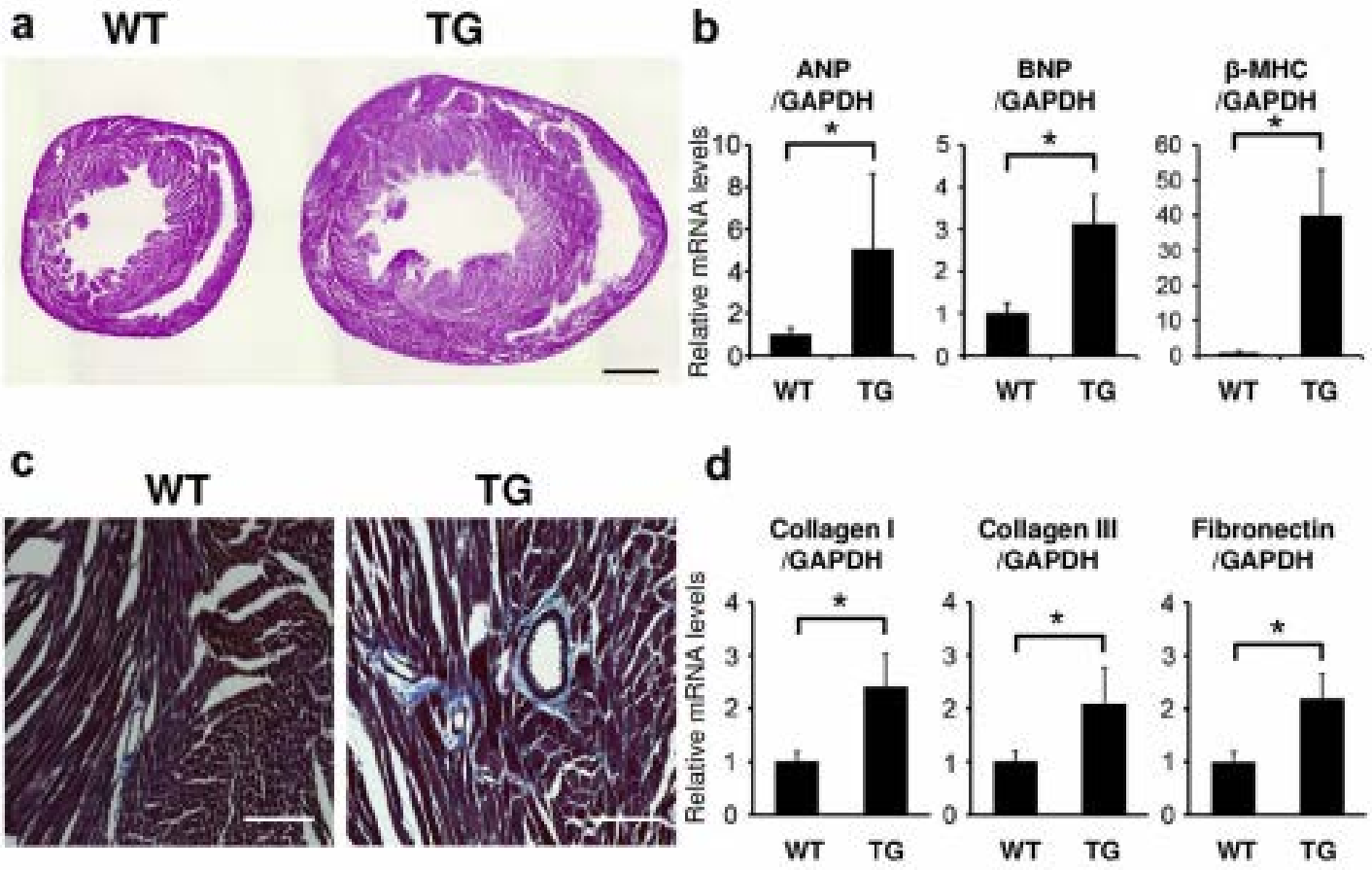
- 2 possible theories:
  - FGF23 upregulates distal tubular sodium uptake in an a-klotho–dependent manner, leading to volume expansion, hypertension, and subsequent cardiac hypertrophy.
  - FGF23 induces cardiac hypertrophy via an a-klotho–independent activation of calcineurin A (CnA)–nuclear factor of activated T cells (NFAT) in cardiomyocytes

- Preexisting LVH does have an effect on FGF 23 concentration?

Lavi-Moshayoff V. Am J Physiol Renal Physiol. 2010;299:F882–F889. Silver J Nat Rev Nephrol. 2013;9:641–649. Meir T Kidney Int. 2014;86:1106–1115. David V. Kidney Int. 2016;89:135–146. Wolf M J Bone Miner Res. 2013;28:1793–1803.

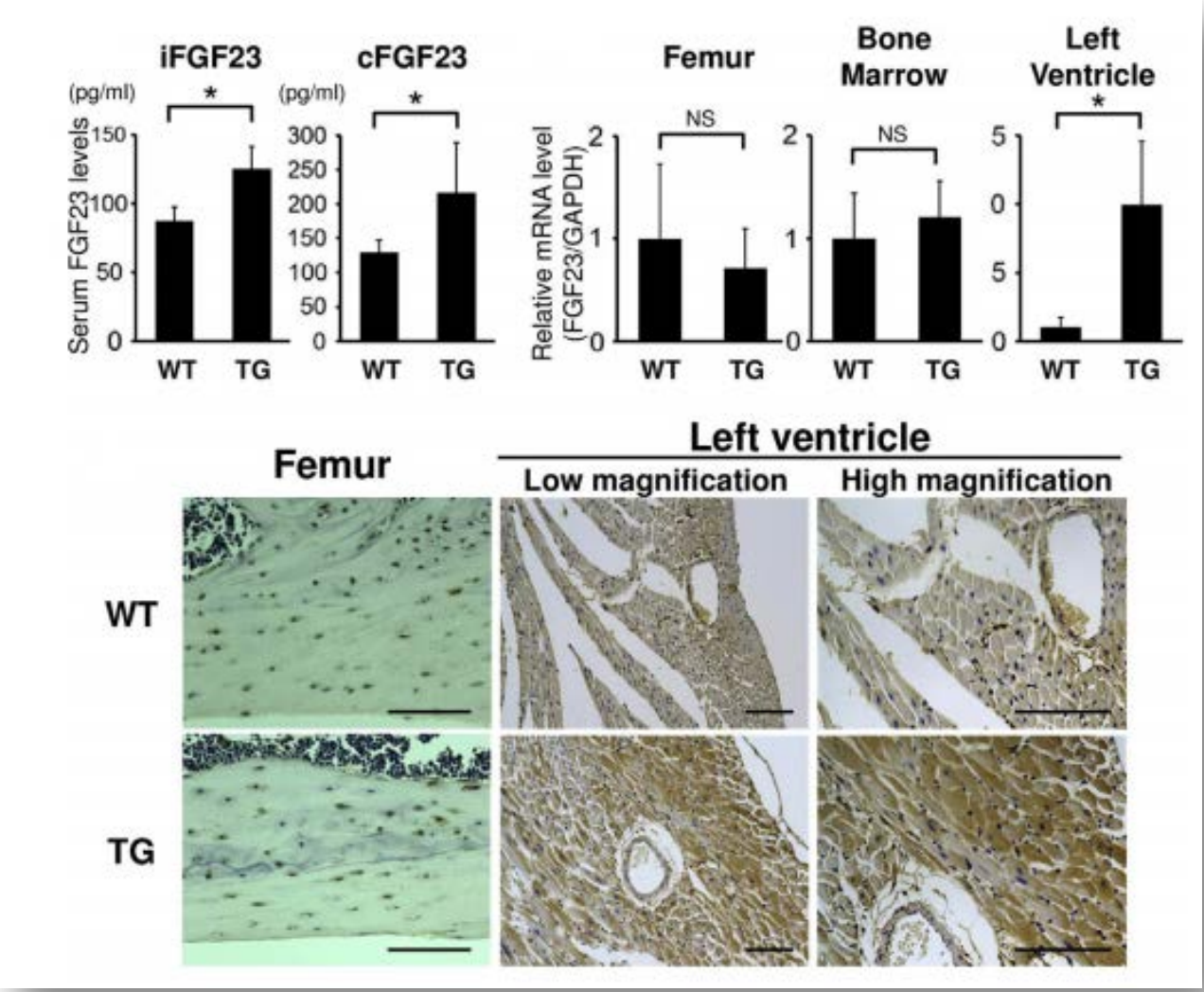
At six weeks, these mice showed severe LVH

transgenic (TG) mice that express the constitutively active form of the CnA catalytic subunit under the control of a-myosin heavy chain (a-MHC) promoter as the CnA-NFAT is the key pathway in LVH



Matsui, Kidney Int. 2018 Jul;94(1):60-71

FGF23 levels were elevated in cardiomyocytes, but not osteocytes of the transgenic animals



Matsui, Kidney Int. 2018 Jul;94(1):60-71

FGF-23

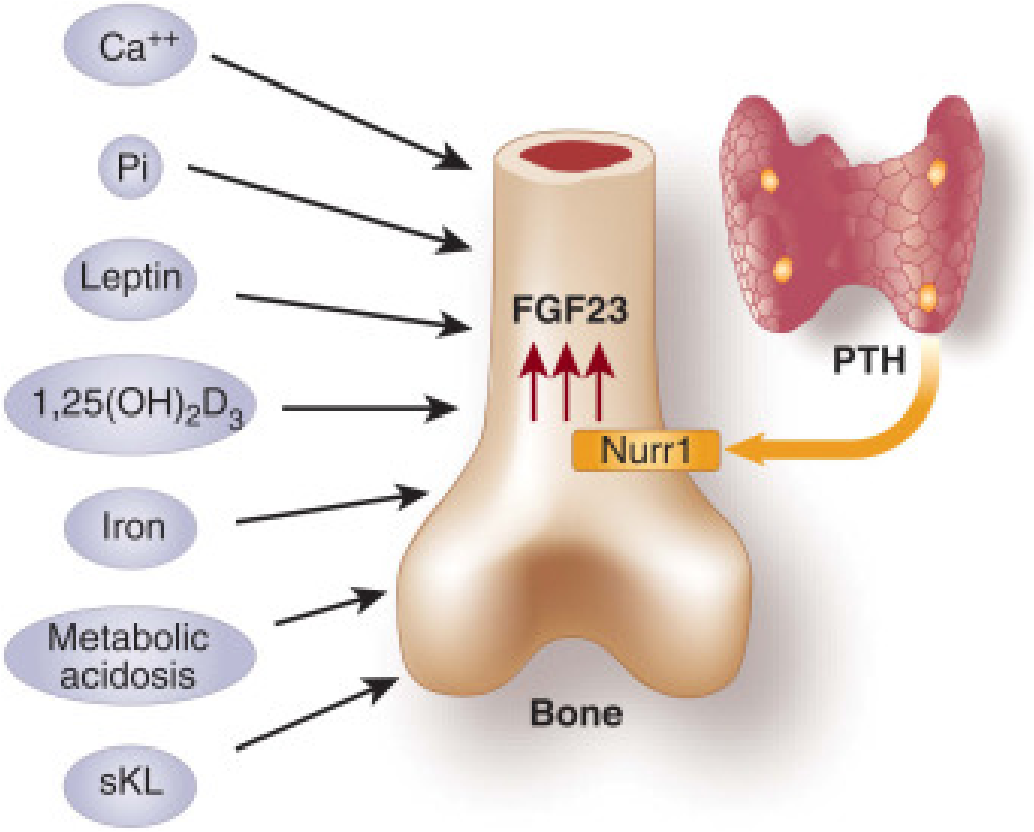
a.FGF23 and mortality (in CKD/renal transplantation)

b.New experimental data regarding FGF 23 regulation

c. New theraphies for FGF 23 decline

State of the art
FGF23 regulation – still incompletely understood

- Elevated FGF 23 - determined by several factors: phosphate retention, high serum PTH levels, acidosis, vitamin D treatment, calcium;



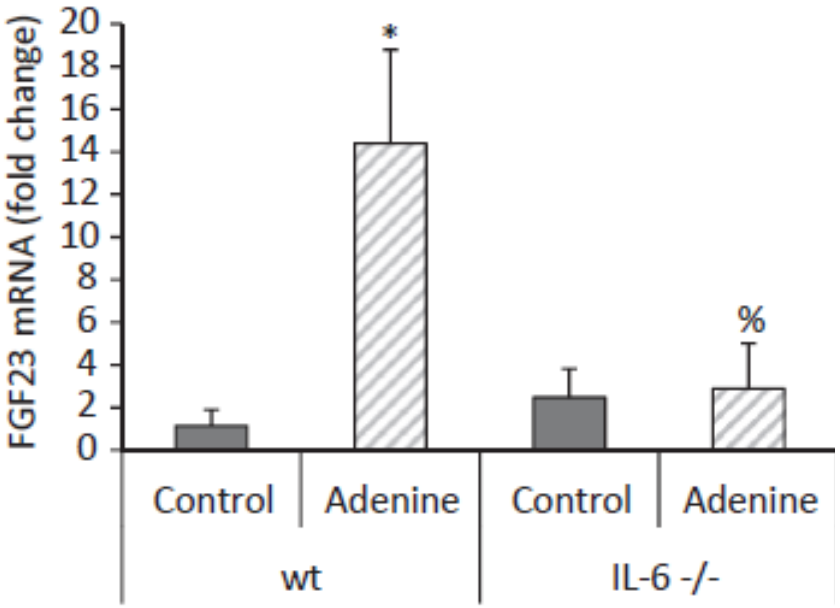
sKL - secreted Klotho

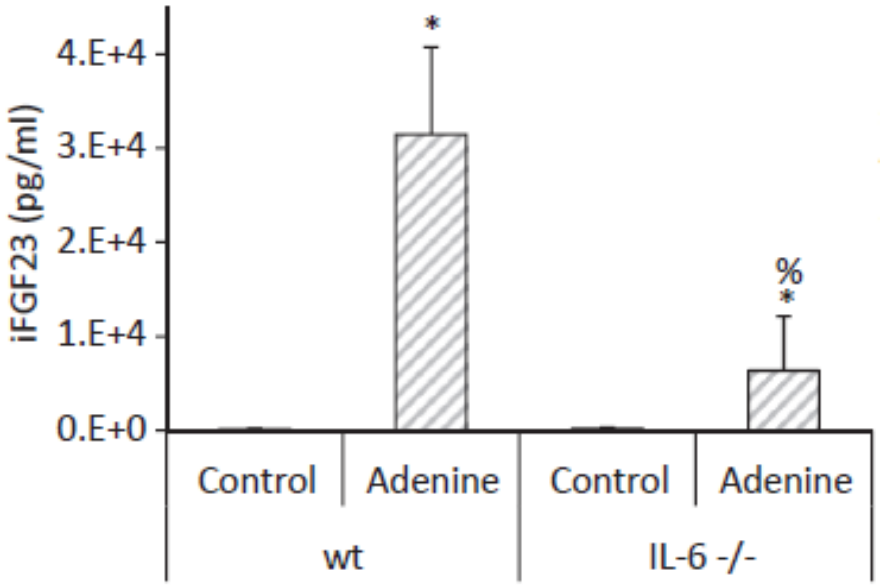
Inflammation - stimulates FGF23….therefore….
IL-6 - an essential regulator of FGF23?

Lanske et al. Kidney International 2014;86:1072-1074

IL-6 expression is necessary for the increase in FGF23 expression in prolonged uremia.

IL-6 knock-out mice fed an adenine diet to induce CKD failed to increase bone FGF23 mRNA and had a muted increase in serum FGF23 levels, compared with the increases in wild-type mice with CKD.

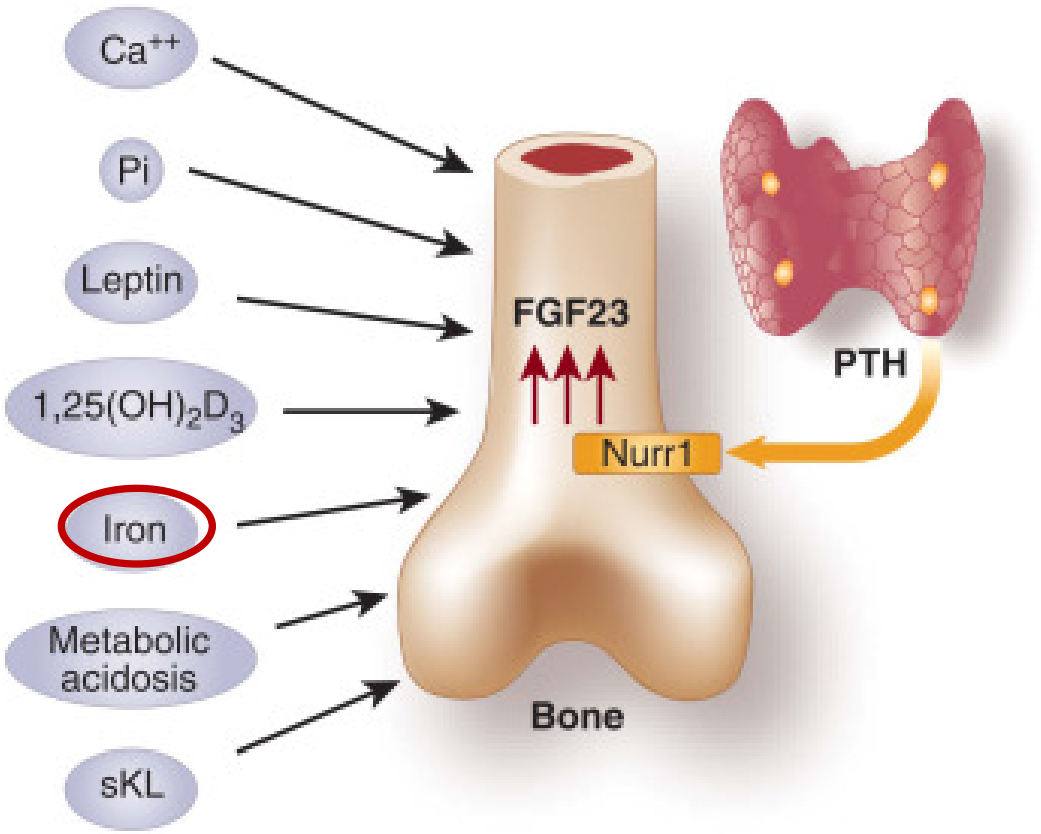




Durlacher-Betzer Kidney Int. 2018 Aug;94(2):315-325.

State of the art
FGF23 regulation – still incompletely understood

- Elevated FGF 23 - determined by several factors: phosphate retention, high serum PTH levels, acidosis, vitamin D treatment, calcium;



sKL - secreted Klotho

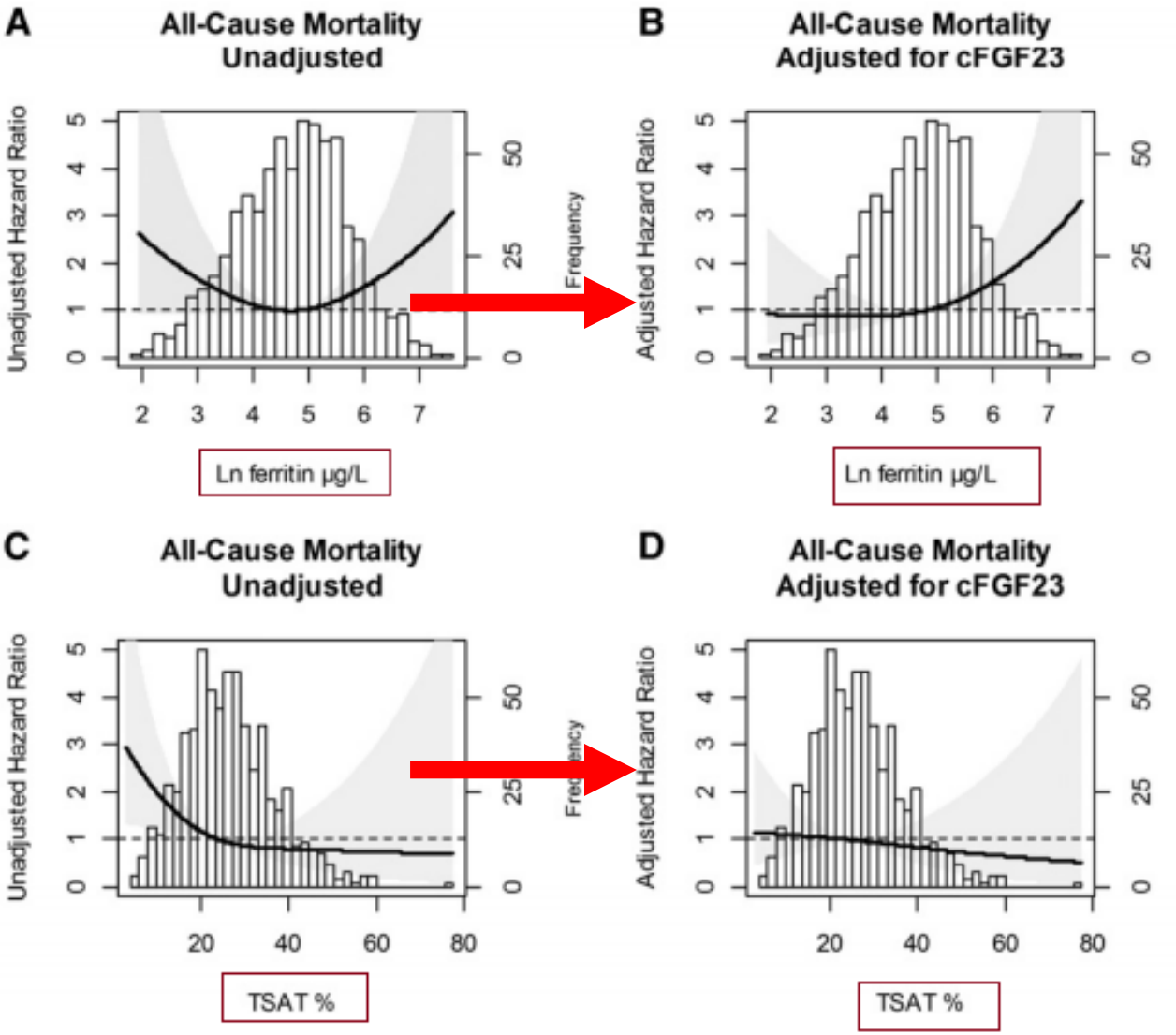
Iron - stimulates FGF23

Lanske et al. Kidney International 2014;86:1072-1074

cFGF23 - an important *mediator* of the association between iron deficiciency (ID) and mortality in renal transplantation

N = 700 stable RTRs

5.4 years after transplant



Eisenga et al. J Am Soc Nephrol. 2017 Dec;28(12):3639-3646

Mediation analysis - cFGF23 explained 46% of the association between ID and mortality

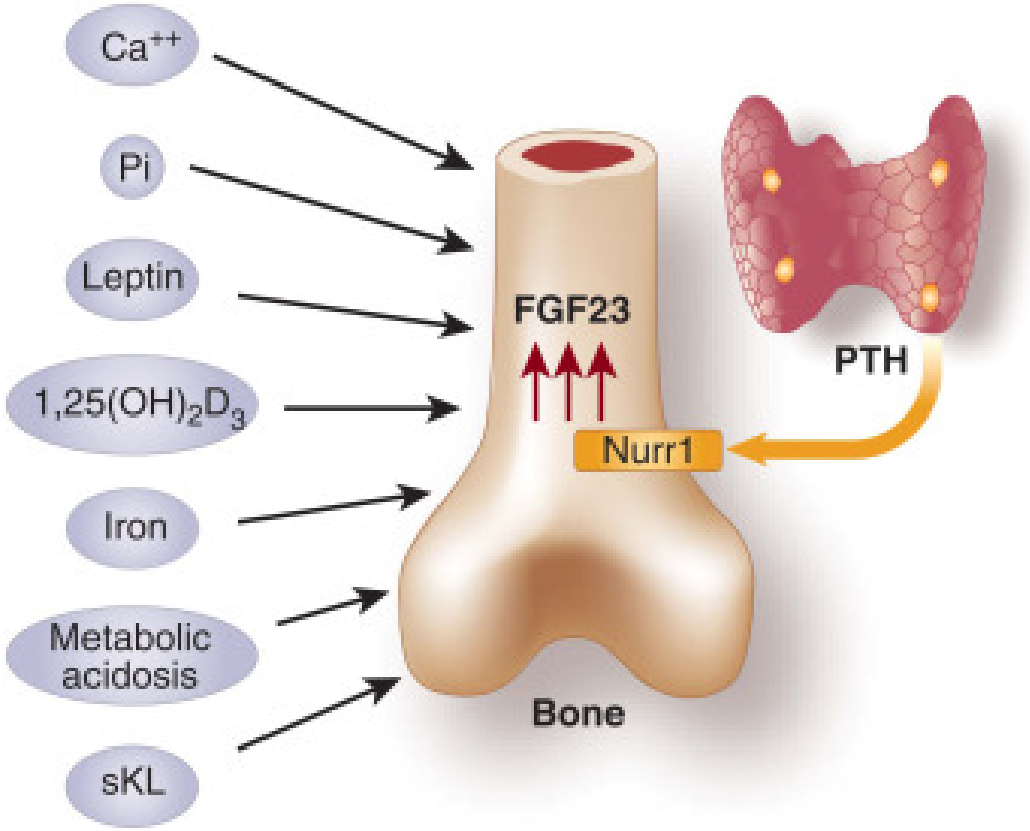
Table 3. Mediation analysis of ID with all-cause mortality through iFGF23, cFGF23, and hs-CRP

Potential Mediator	Outcome	Effect (Path)[a]	Multivariable Model[b]	
			Coefficient (95% CI, bc)[c]	Proportion Mediated[d]
iFGF23	All-cause mortality	Indirect effect (*ab* path)	0.01 (−0.01 to 0.01)	Not mediated
		Total effect (*ab* + *c*′ path)	0.14 (0.04 to 0.23)	
		Unstandardized total effect[e]	0.80 (0.26 to 1.33)	
cFGF23	All-cause mortality	Indirect effect (*ab* path)	0.06 (0.02 to 0.11)	46%
		Total effect (*ab* + *c*′ path)	0.13 (0.03 to 0.22)	
		Unstandardized total effect[e]	0.48 (−0.10 to 1.07)	
hs-CRP	All-cause mortality	Indirect effect (*ab* path)	0.01 (−0.01 to 0.04)	Not mediated
		Total effect (*ab* + *c*′ path)	0.14 (0.03 to 0.24)	
		Unstandardized total effect[e]	0.77 (0.22 to 1.32)	

Eisenga et al. J Am Soc Nephrol. 2017 Dec;28(12):3639-3646

State of the art
FGF23 regulation – still incompletely understood

- osseous tissue is the major source for circulating FGF23
- bone marrow (BM) also expresses FGF23
- However, the role of erythroid progenitor cells (EPCs) in acute changes of FGF23 has not been studied.

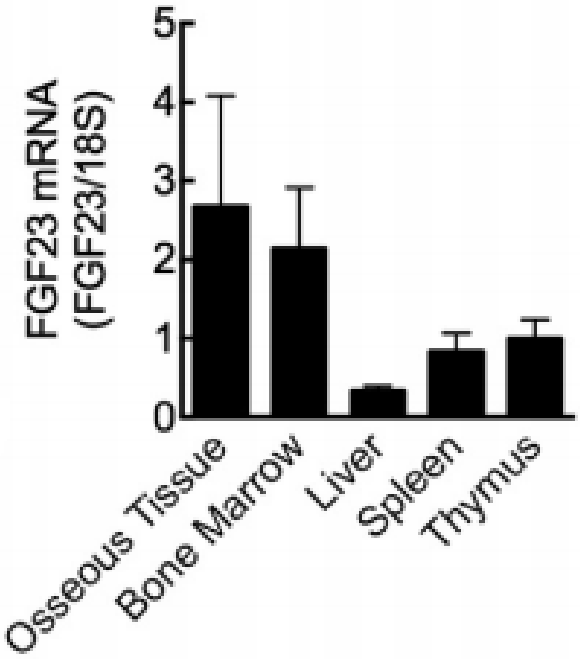


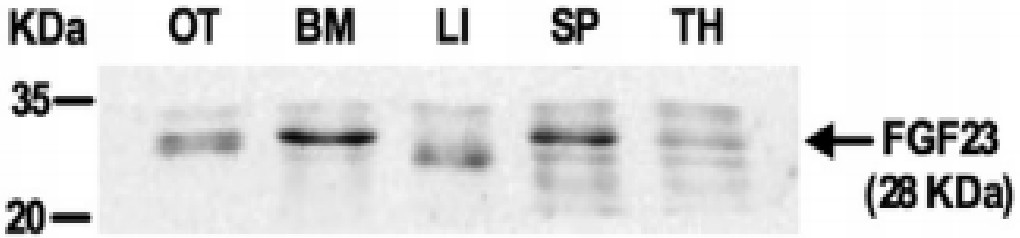
Lavi-Moshayoff V. Am J Physiol Renal Physiol. 2010;299:F882–F889. Silver J Nat Rev Nephrol. 2013;9:641–649. Meir T Kidney Int. 2014;86:1106–1115. David V. Kidney Int. 2016;89:135–146. Wolf M J Bone Miner Res. 2013;28:1793–1803.

Lanske et al. Kidney International 2014;86:1072-1074

FGF23 is synthesized in erythroid progenitor cells

FGF23 expression in bone marrow from mouse tibia and other FGF23-expressing tissues (e.g., osseous tissue, spleen, liver, thymus)





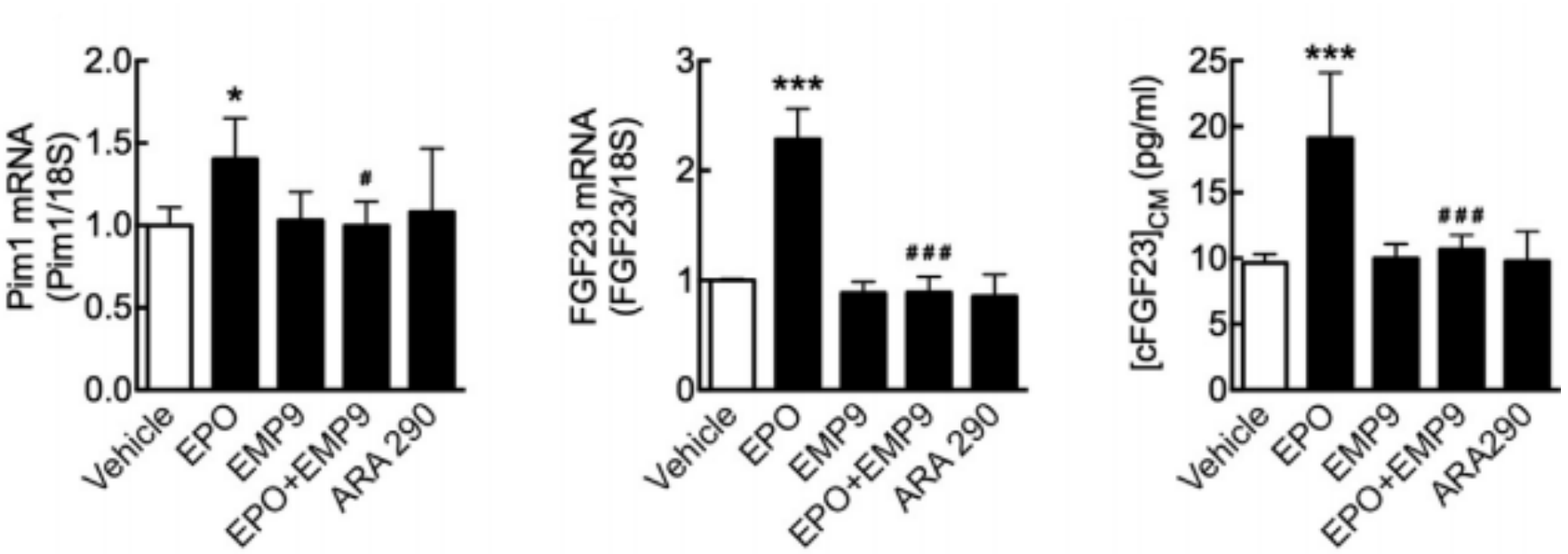
Toro et al. Kidney Int. 2018 May;93(5):1131-1141

EPO upregulated FGF23 via the homodimeric EPO receptor (EPOR) in BM – ex vivo

Mice bone marrow cells were incubated with recombinant human (rh) EPO (rhEPO) for 2 hours

ARA 209 - EPOR/CD131 heterodimeric receptor agonist

EMP9 - EPOR antagonist



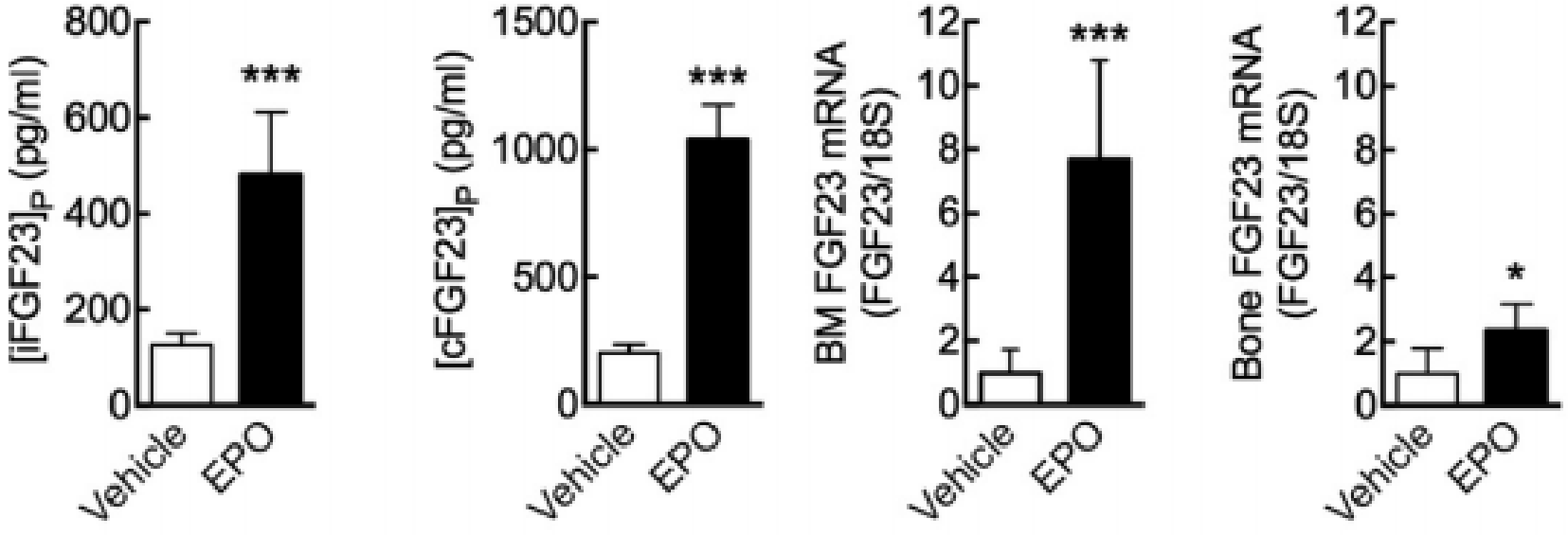
The protooncogene serine/threonine-protein kinase-1 (Pim1) mRNA transcript upregulated by EPO via EPOR served as a positive control

The induction of FGF23 by rhEPO was completely blocked by EMP9

Toro et al. Kidney Int. 2018 May;93(5):1131-1141

The same results *in vivo*

mice were injected with a single dose of rhEPO, and iFGF23 and cFGF23 in plasma were measured.



Toro et al. Kidney Int. 2018 May;93(5):1131-1141

FGF-23

a.FGF23 and mortality (in CKD/renal transplantation)

b.New experimental data regarding FGF 23 regulation

c. New theraphies for FGF 23 decline

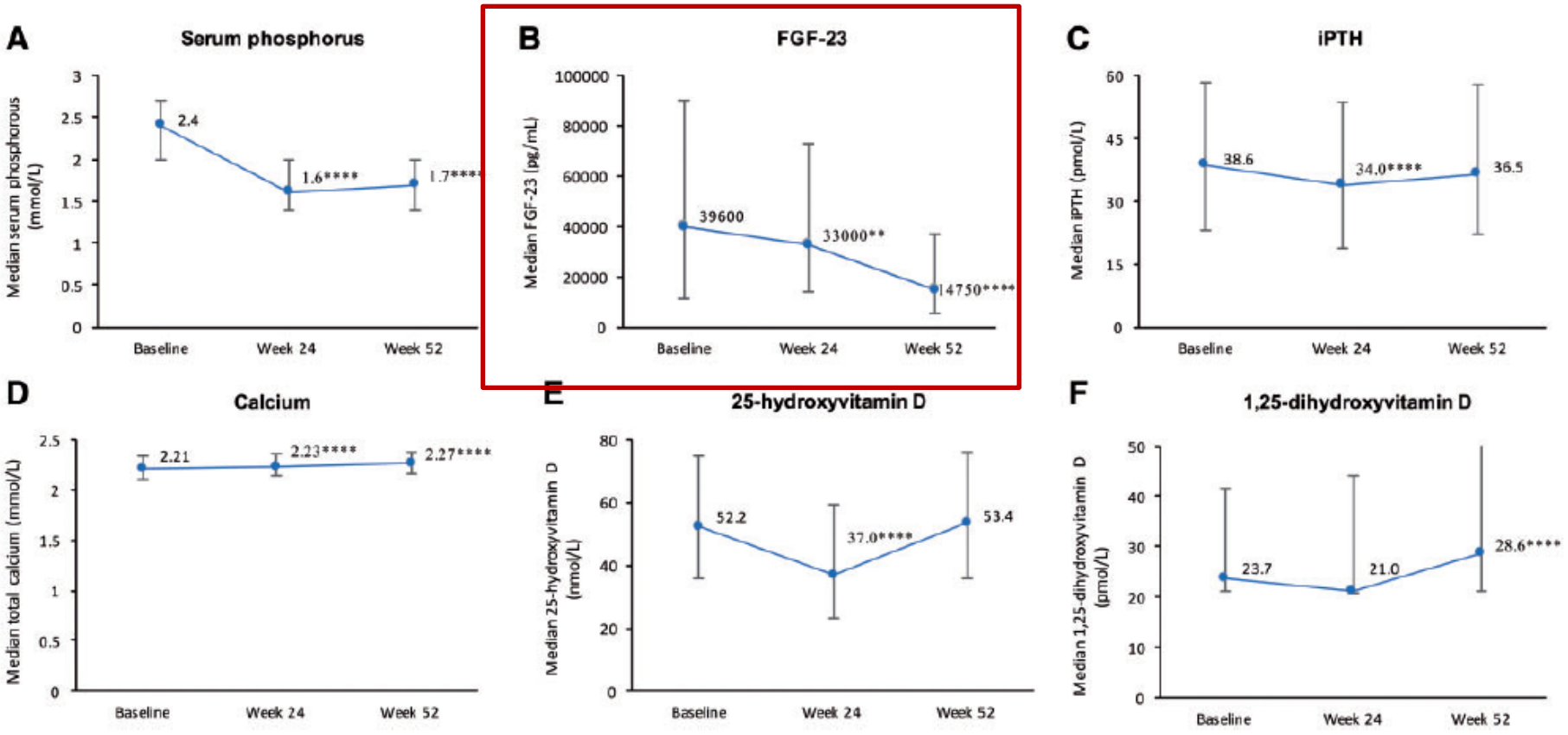
It was already showed that elevated FGF 23

- strongly associated with CV disease and mortality
- independently associated with left ventricular hypertrophy, heart failure, atrial fibrillation and mortality.
- BUT…Treatments that solely target FGF23 reduction precipitate severe hyperphosphatemia, and accelerate vascular calcification and mortality
- The need to identify therapies capable of jointly lowering both serum phosphate and FGF23 concentrations.

Palmer, JAMA 2011; 305: 1119–1127; Faul, J Clin Invest 2011; 121: 4393–4408; Isakova, JAMA 2011; 305: 2432–2439

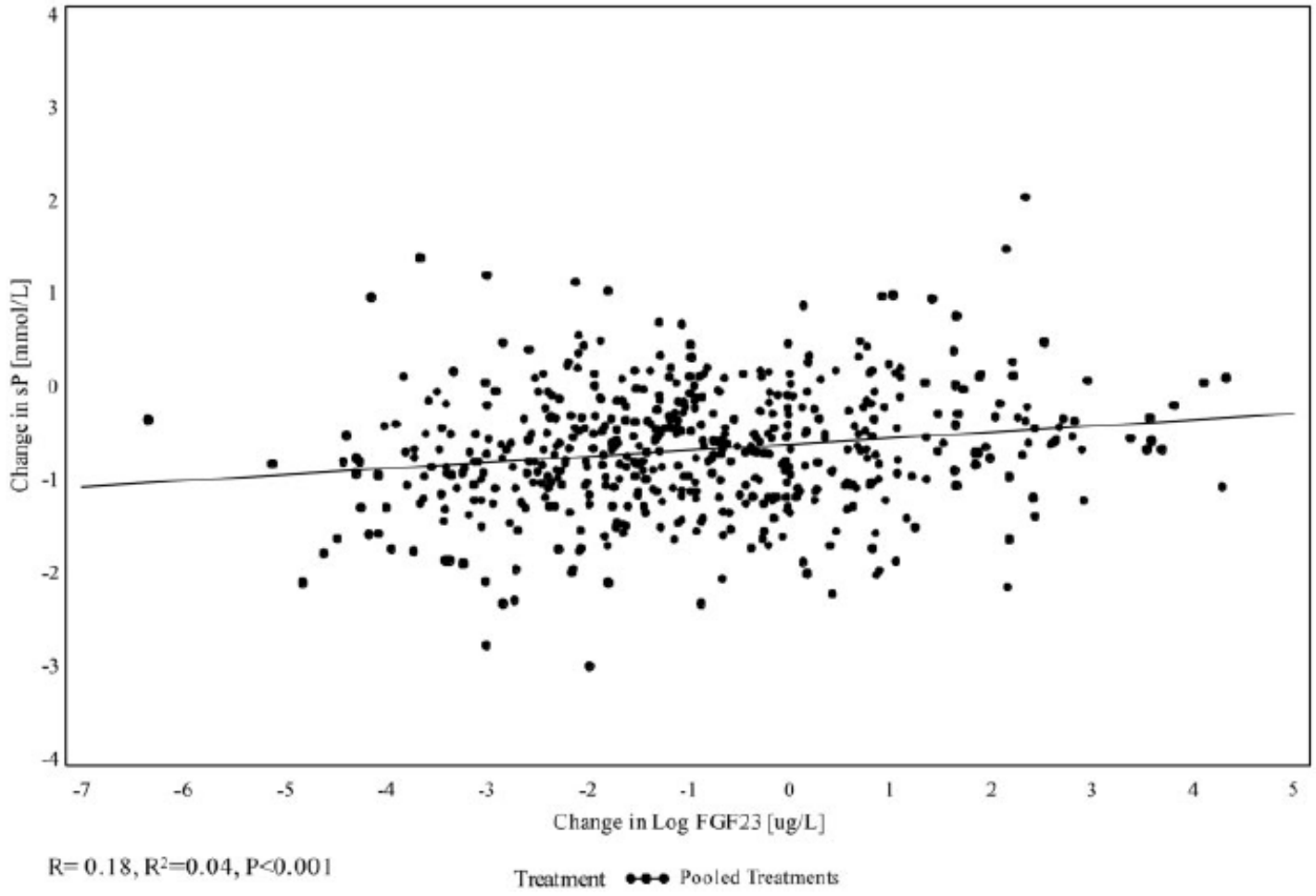
Sucroferric oxyhydroxide or sevelamer - significant 30% reductions in serum P and FGF-23 concentrations

Post-hoc analysis; 1059 patients randomized 2:1 to sucroferric oxyhydroxide or sevelamer for up to 24weeks; eligible patients enrolled in a 28-week extension



Ketteler, Covic Nephrol Dial Transplant. 2018 May 29

Only a negligible proportion of the variance in the FGF-23 change from baseline was explained by the change from baseline in serum phosphorus.



Ketteler, Covic Nephrol Dial Transplant. 2018 May 29

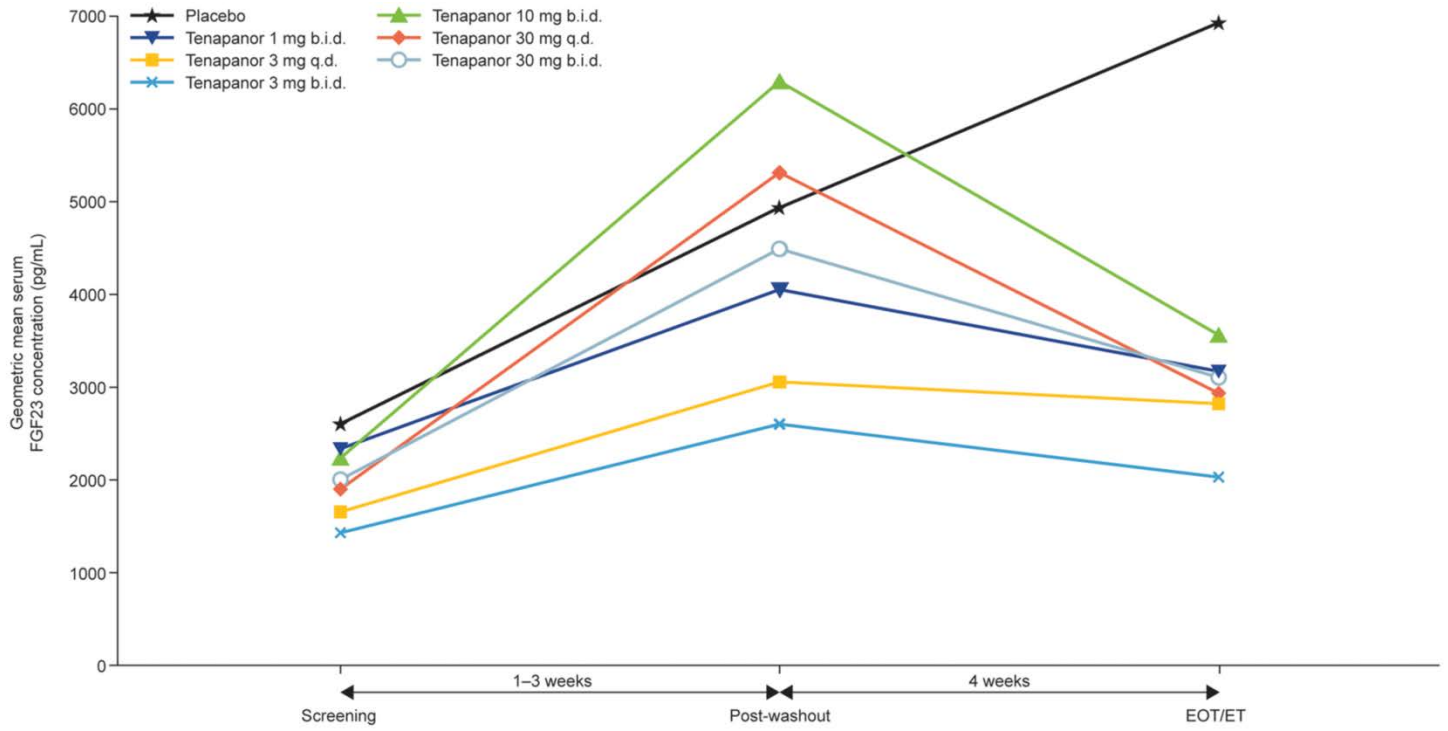
Tenapanor significantly lowered FGF23 versus placebo following just 4 weeks of treatment

- Tenapanor is a small-molecule inhibitor of the sodium/ hydrogen exchanger isoform 3 (NHE3).
- In addition to lowering gastrointestinal absorption of sodium, tenapanor also decreases gastrointestinal absorption of phosphate via a mechanism distinct from luminal phosphate binding
- Tenapanor acts in the gut, with minimal systemic drug exposure.
- In healthy volunteers, increases in stool phosphorus up to 14.2 mmol/d relative to placebo were observed with tenapanor dosing, with concomitant reductions in urinary phosphorus.

Block, Nephrol Dial Transplant. 2018 Apr 3.

Tenapanor significantly lowered FGF23 versus placebo following just 4 weeks of treatment

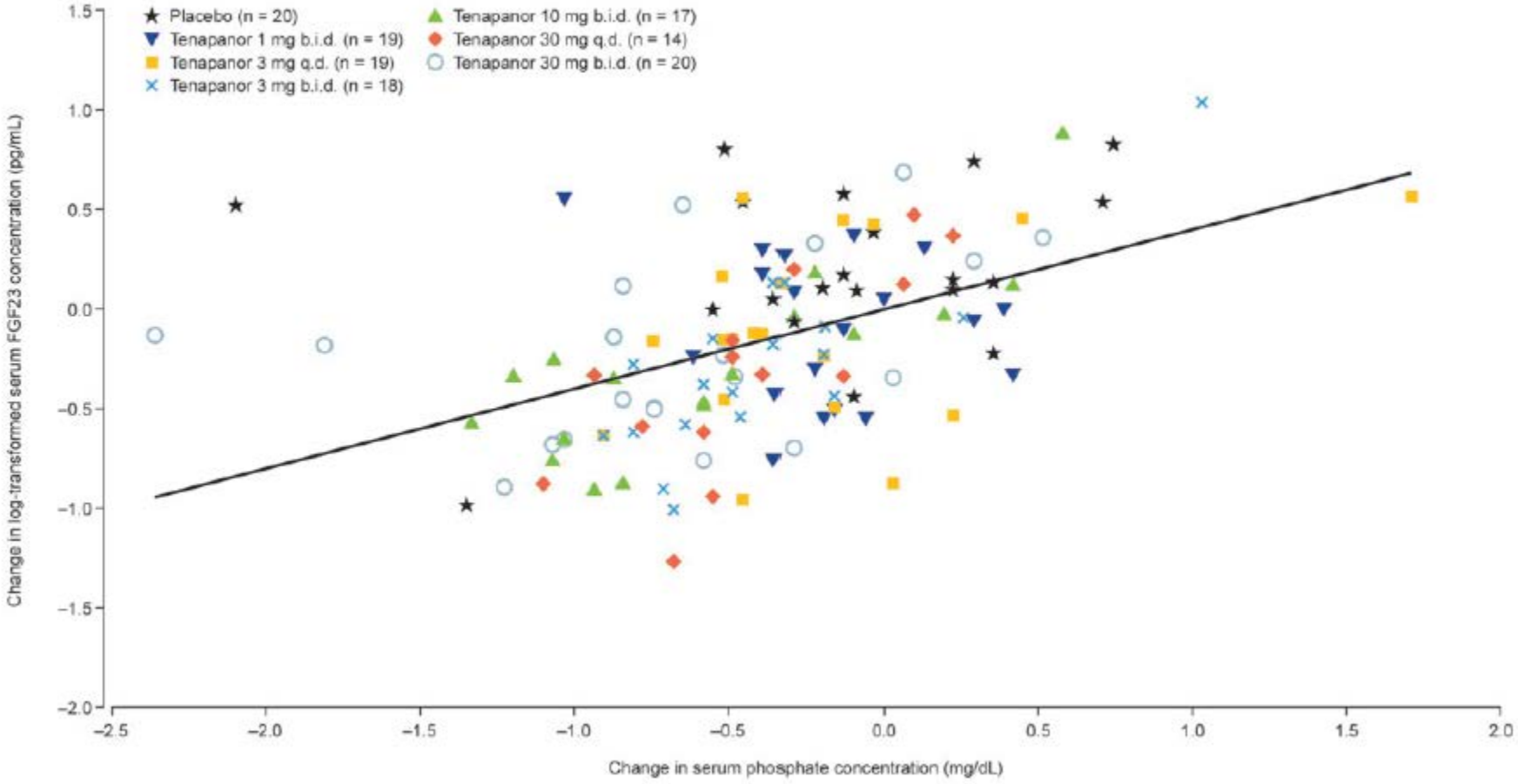
After 1–3 weeks of washout of phosphate binders 162 patients randomized to receive placebo or one of six tenapanor regimens (3 or 30 mg once daily, or 1, 3, 10 or 30 mg twice daily)



	Placebo	Tenapanor						Placebo	Tenapanor						Placebo	Tenapanor					
		1 mg b.i.d.	3 mg q.d.	3 mg b.i.d.	10 mg b.i.d.	30 mg q.d.	30 mg b.i.d.		1 mg b.i.d.	3 mg q.d.	3 mg b.i.d.	10 mg b.i.d.	30 mg q.d.	30 mg b.i.d.		1 mg b.i.d.	3 mg q.d.	3 mg b.i.d.	10 mg b.i.d.	30 mg q.d.	30 mg b.i.d.
	★	▼	■	×	▲	◆	○	★	▼	■	×	▲	◆	○	★	▼	■	×	▲	◆	○
Geometric mean, pg/mL (CV, %)	2605 (215)	2337 (251)	1655 (491)	1430 (165)	2236 (310)	1901 (296)	2004 (319)	4937 (206)	4052 (264)	3057 (255)	2601 (231)	6294 (202)	5312 (218)	4491 (347)	6930 (205)	3171 (234)	2822 (345)	2030 (226)	3563 (259)	2935 (480)	3106 (491)
Median, pg/mL (range)	2459 (133–56 825)	2634 (279–30 285)	1935 (36–31 926)	1960 (212–7308)	2423 (82–26 374)	1911 (128–21 726)	2468 (189–33 996)	4270 (202–99 001)	4154 (488–47 687)	3103 (160–32 428)	2341 (234–19 975)	7548 (153–43 283)	5354 (624–53 700)	6466 (152–73 770)	7457 (346–114 857)	3761 (409–22 261)	2331 (170–40 724)	3067 (231–22 827)	4622 (100–38 752)	2938 (112–42 193)	5714 (62–41 481)
n	23	20	22	20	21	19	22	23	21	21	21	20	18	22	22	19	20	19	22	15	21

Block, Nephrol Dial Transplant. 2018 Apr 3.

However, in this study, the magnitude of FGF23 reduction correlated with the magnitude of change in serum P



Block. Nephrol Dial Transplant. 2018 Apr 3.

Take home message – FGF 23 - mortality

- Across a wide range of levels of kidney function, higher FGF-23 concentration associated with increased risks of MI, HF, stroke, and CV death.
- However, higher FGF-23 - increased risk of non CV death
- Importantly, variation in cFGF23 explained a considerable part of the association between ID and mortality.

Take-Home Message

- New important regulators: inflammation, iron,
- New potentially relevant contributors: pre-existing LVH, EPO….
- Erythroid progenitor cells of bone marrow express FGF23.
- Sucroferric oxyhydroxide, sevelamer and tenapanor significantly decreased serum FGF23 in patients receiving hemodialysis with hyperphosphatemia

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