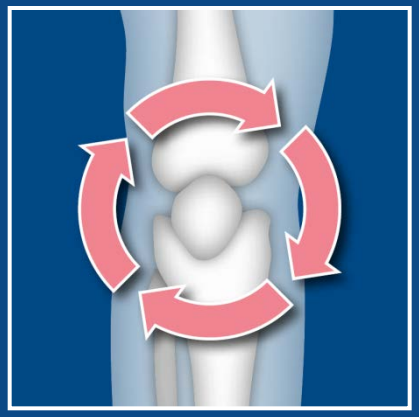
Nephro Update Europe 2017

6-7 October, Vienna

Bone and Mineral Disease



Adrian Covic, Romania

FGF 23 Regulation

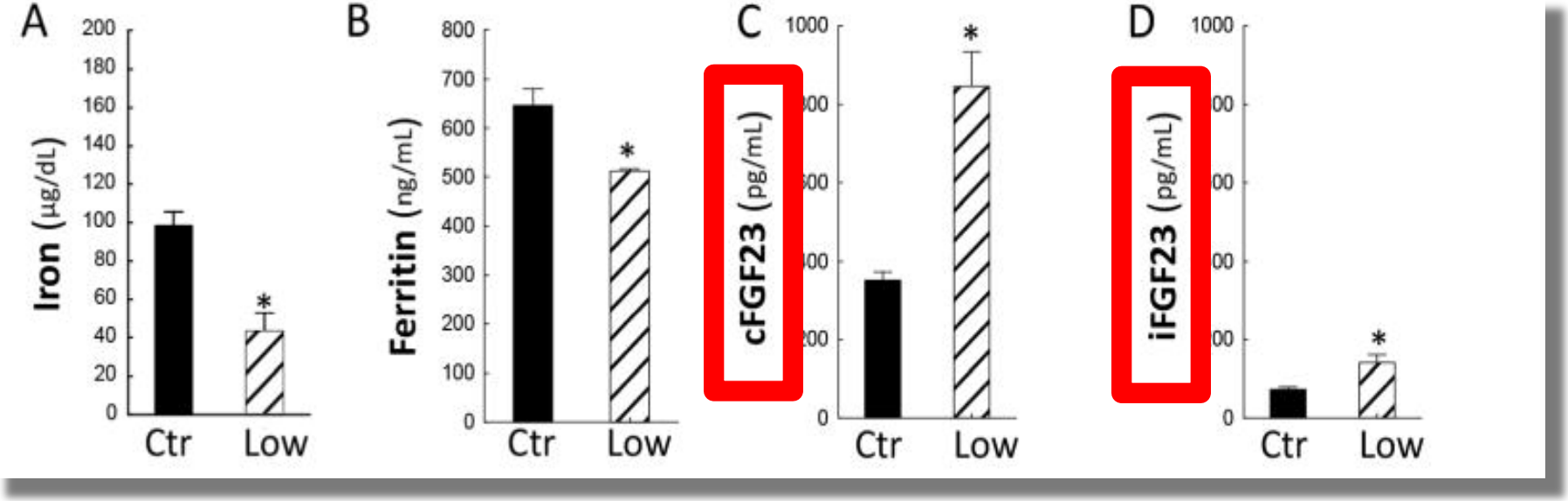
State of the Art

- FGF23 levels rises progressively in CKD
- FGF 23 regulation is incompletely understood;
- High levels of PTH, 1,25-dihydroxyvitamin D3, P and Ca stimulate FGF23 production but cannot adequately explain the increases in FGF23 levels in *early* CKD
- Iron and inflammation – two possible new regulator of FGF23 production

Gutierrez OM, The New England journal of medicine. 2008;359:584–592; Kovesdy CP. Nephron Clinical practice. 2013;123:194–201. Wolf M. JASN. 2011;22:956–966;

Iron deficiency regulates FGF23

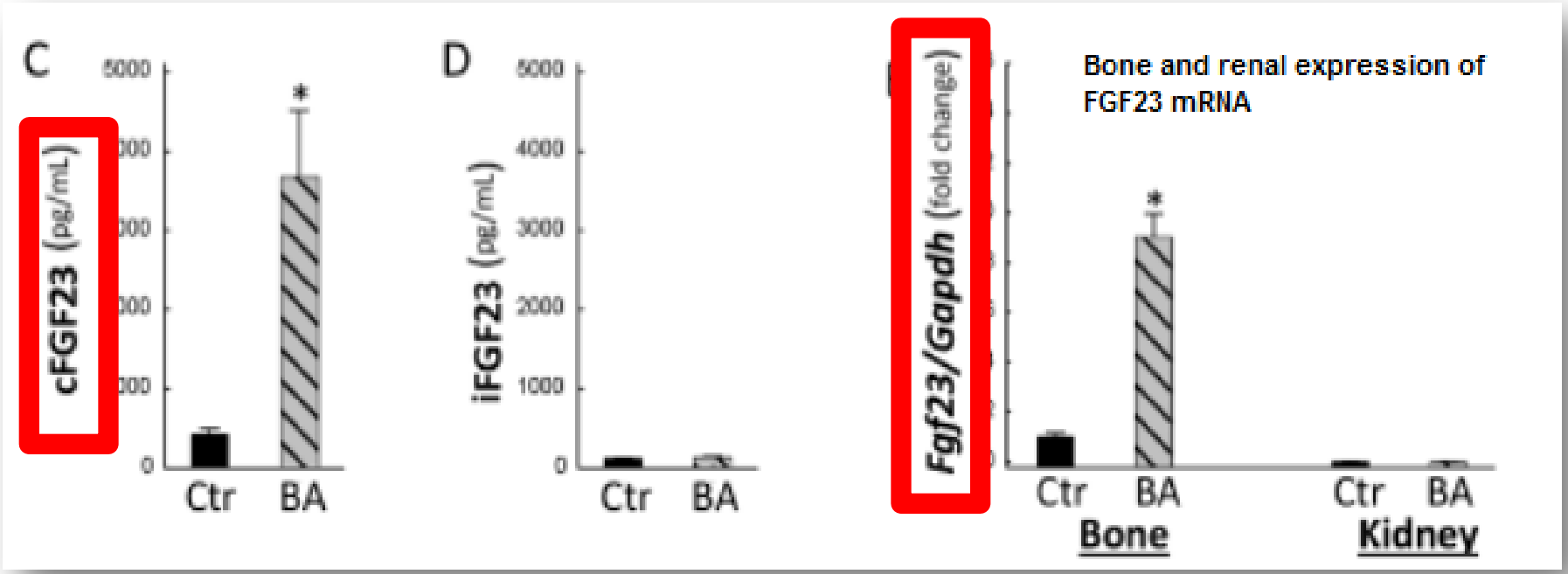
3-week-old wild-type mice a *low iron diet* for 3 weeks or control



David V. Kidney Int. 2016 ;89(1):135-46.

Acute inflammation - increases in osseous *Fgf23* mRNA and serum levels of C-terminal FGF23, but no changes in iFGF23

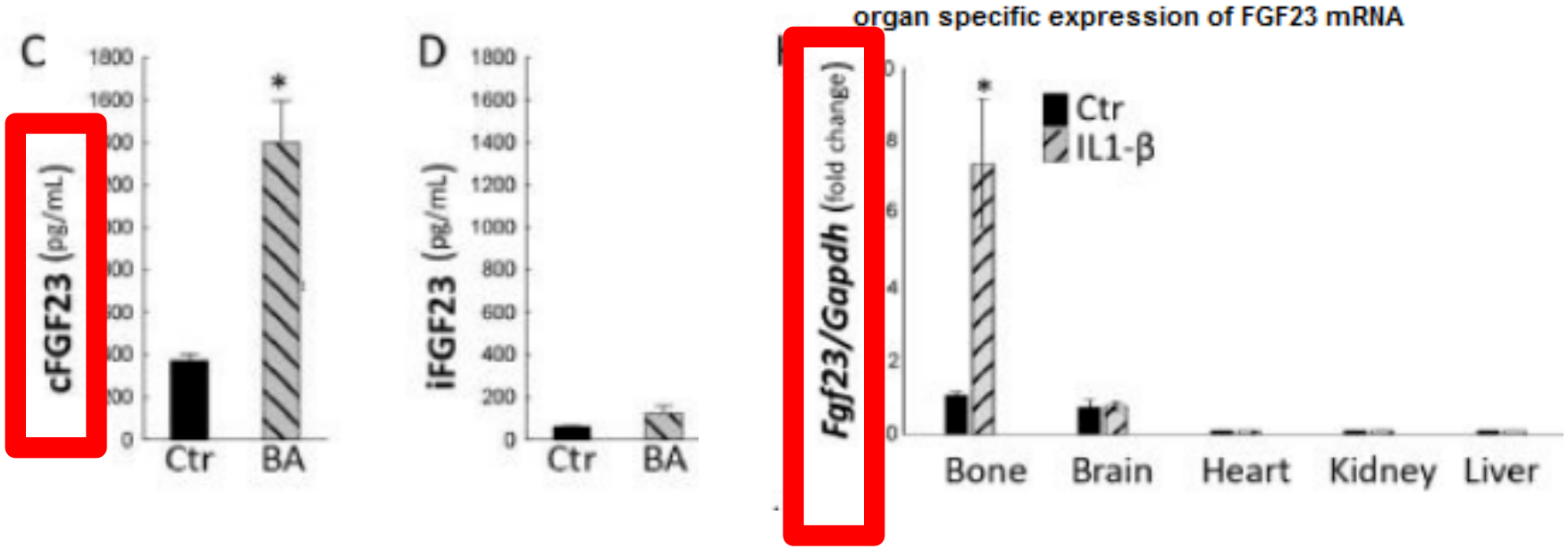
acute inflammation induced by single injections of heat-killed *Brucella abortus* or interleukin-1β (IL-1β)



David V. Kidney Int. 2016 ;89(1):135-46.

Chronic inflammation - increased osseous Fgf23 mRNA and serum C-terminal FGF23, but modestly increased iFGF23

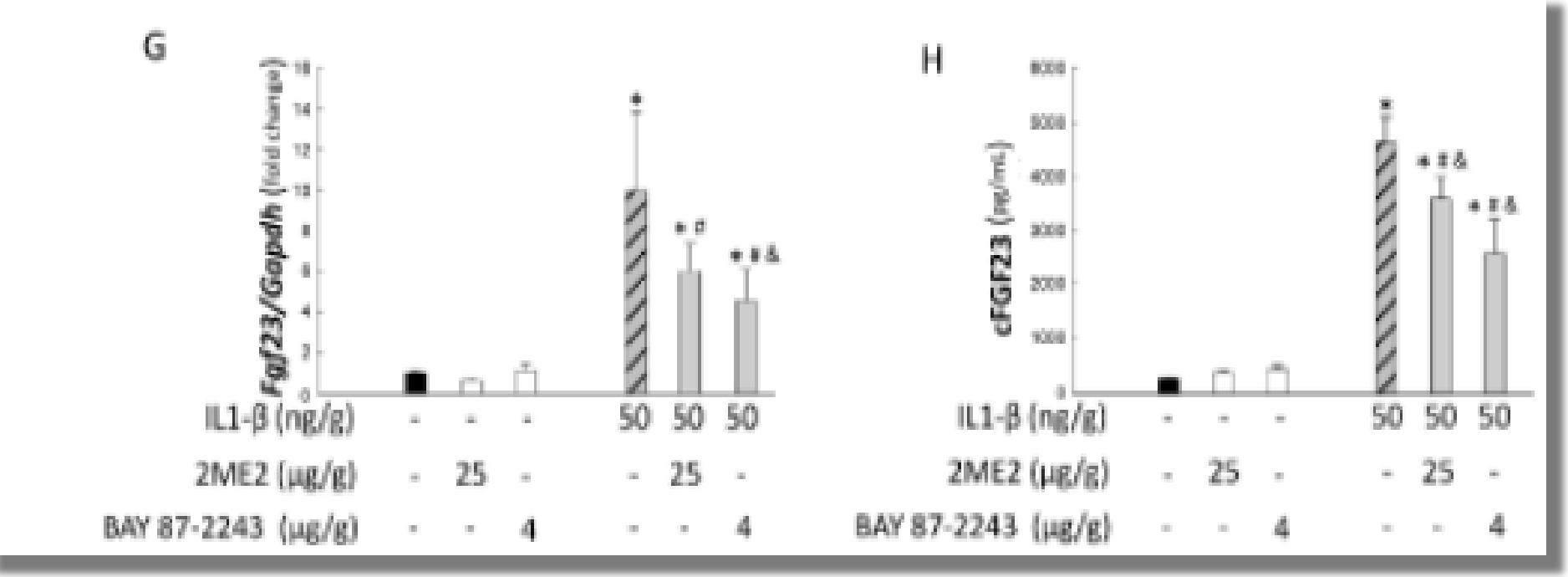
Chronic inflammation induced by repeated bacteria or IL-**1β injections**



David V. Kidney Int. 2016 ;89(1):135-46.

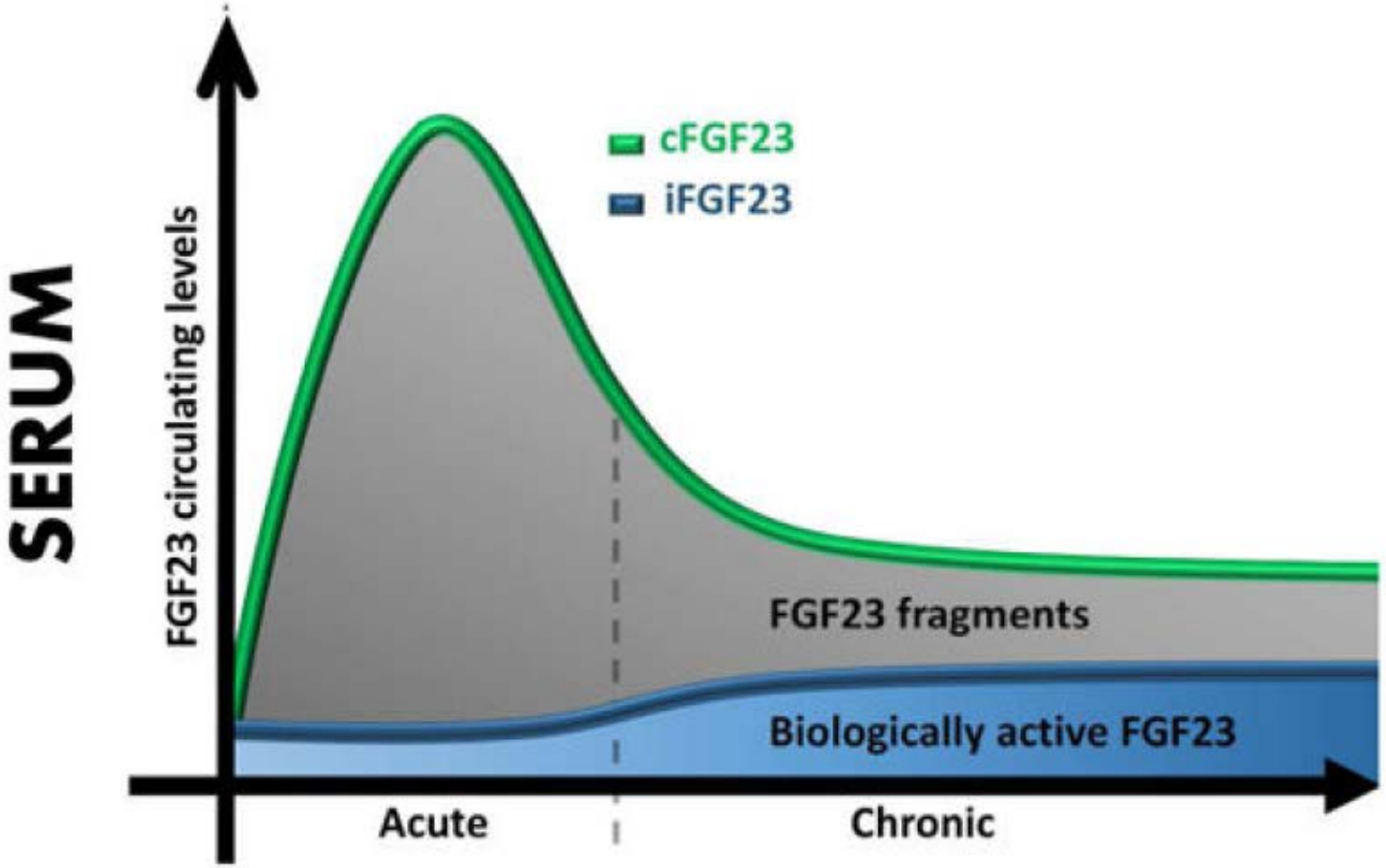
Inflammation increased Fgf23 transcription **by activating Hif1α signaling**

- **In vivo, IL-1β injection in mice pre-treated with the HIF1α inhibitors, 2ME2 and BAY 87-2243, attenuated inflammation-induced increases in *Fgf23* mRNA and cFGF23 levels**



David V. Kidney Int. 2016 ;89(1):135-46.

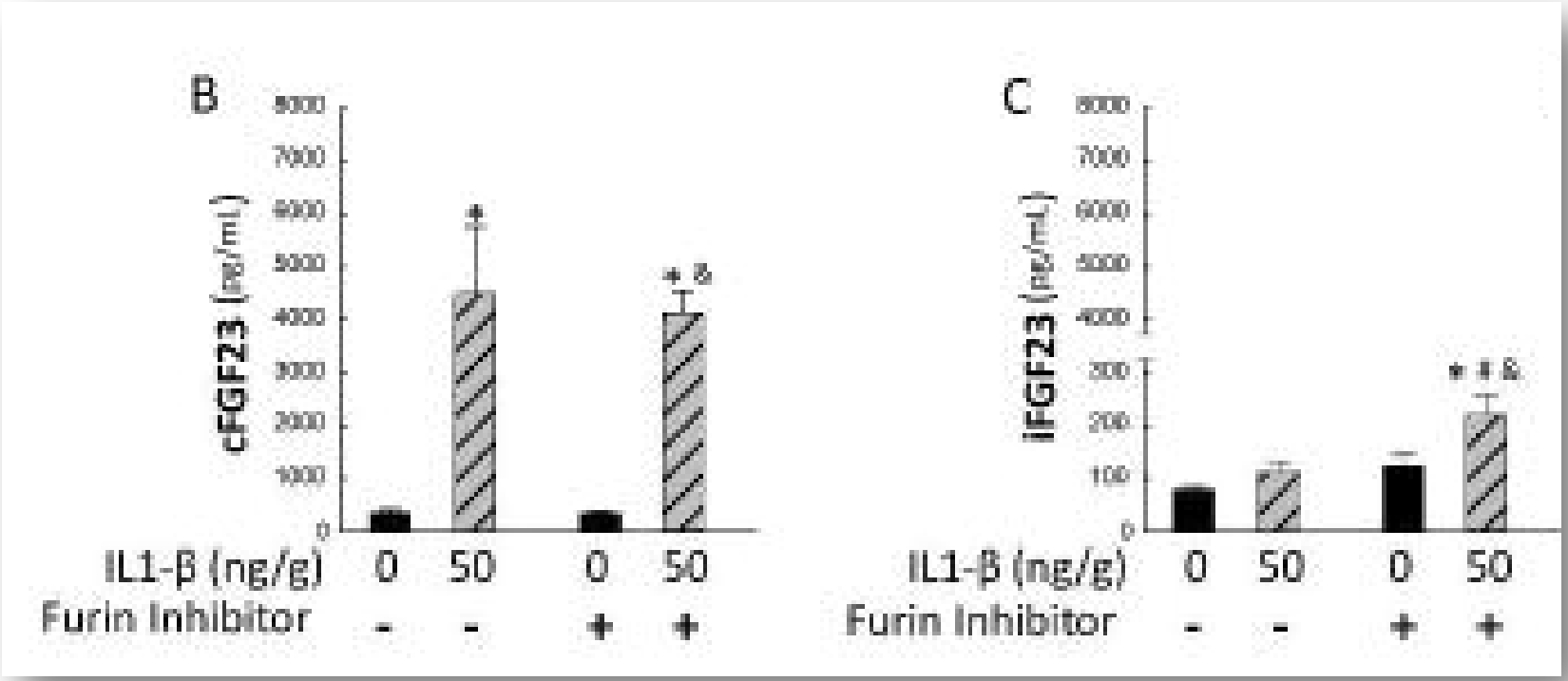
Schematic representation of FGF23 regulation by inflammation - see relative magnitude….



David V. Kidney Int. 2016 ;89(1):135-46.

The discrepancy between cFGF23 and intact FGF23 increase – concomitant increases in FGF23 production and cleavage

co-administration of IL-1β with a furin/furin-like protease inhibitor, which blocks FGF23 cleavage, significantly increased circulating iFGF23 compared to IL-1β treatment alone

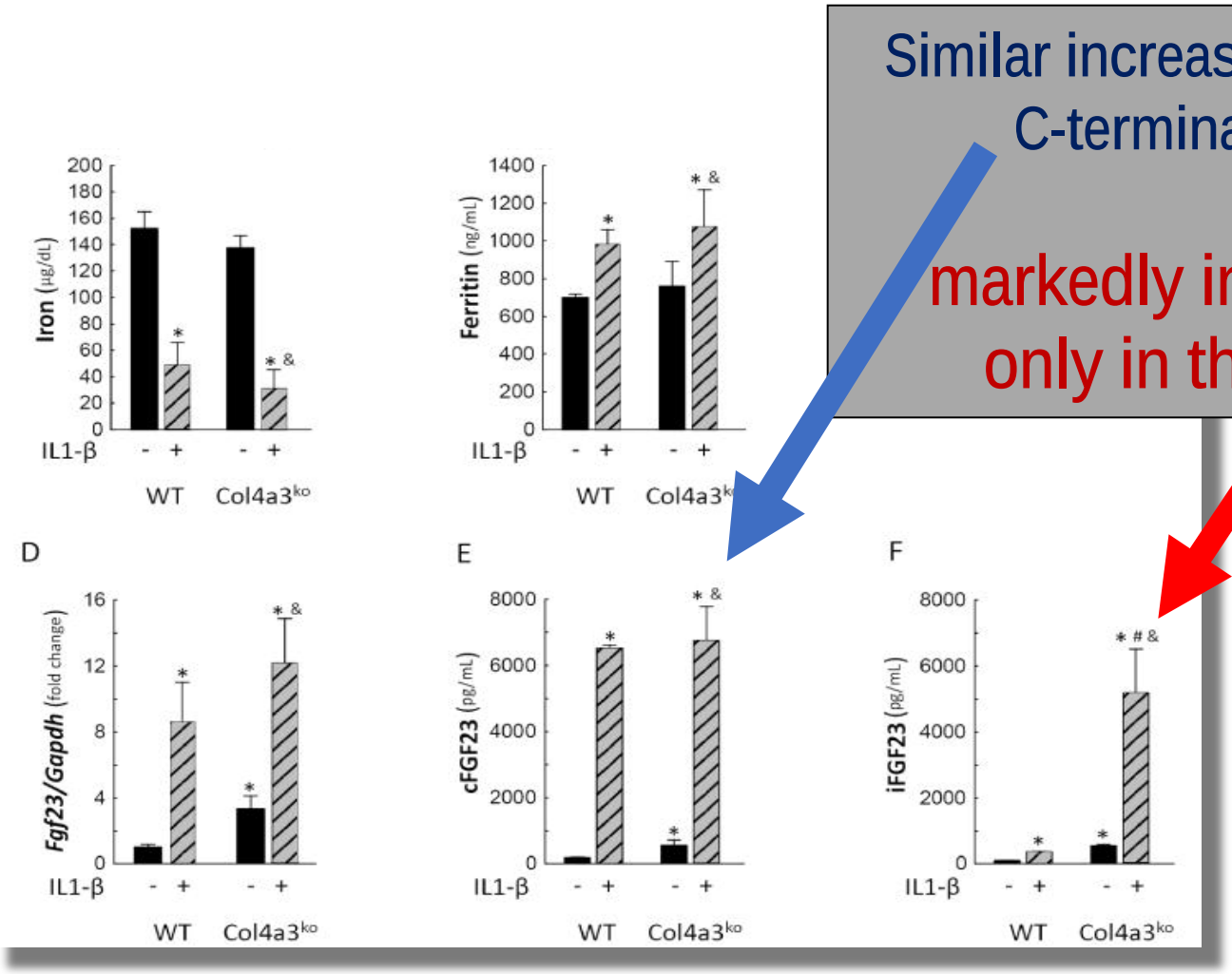


David V. Kidney Int. 2016 ;89(1):135-46.

The same response in animals with impaired kidney function ?

Renal disease impairs FGF 23 cleavage?

Wt and Col4a3^{ko} mice with moderate CKD

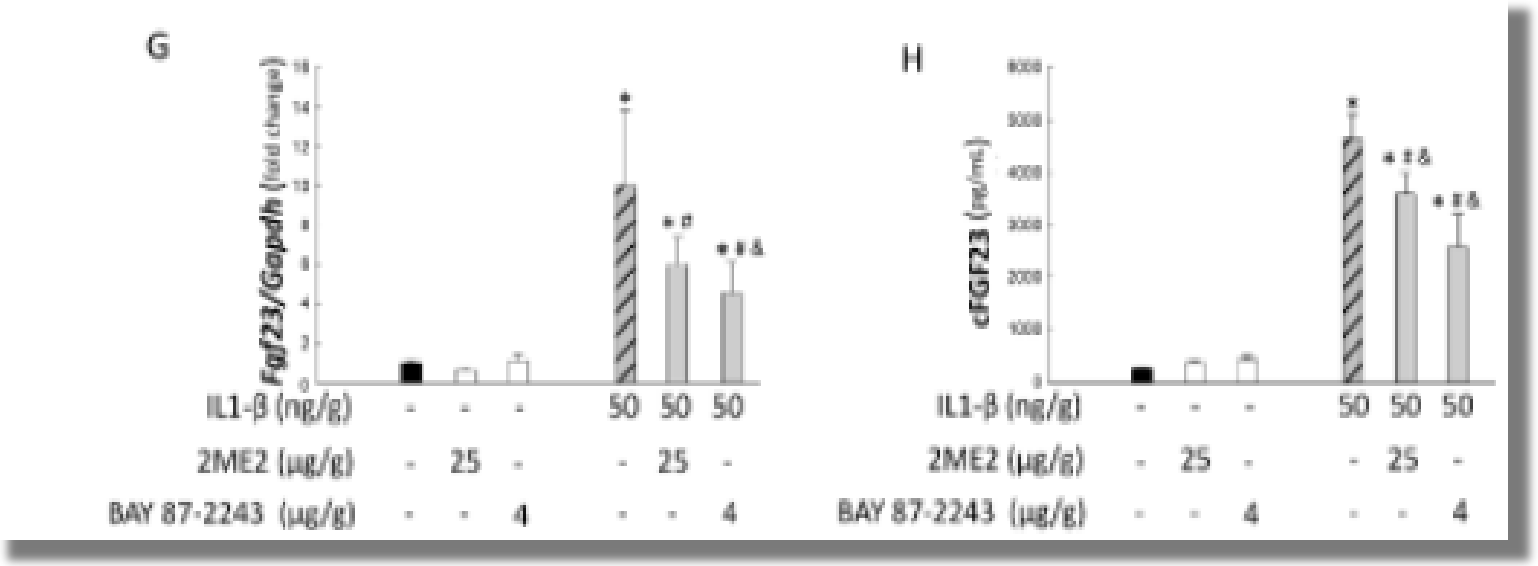


Similar increased Fgf23 mRNA and C-terminal FGF23 levels but markedly increased iFGF23 only in the CKD mice.

David V. Kidney Int. 2016 ;89(1):135-46.

Inflammation increased FGF23 transcription by activating Hif1α signaling

- **In vivo, IL-1β injection in mice pre-treated with the HIF1α inhibitors, 2ME2 and BAY 87-2243, significantly attenuated inflammation-induced increases in *Fgf23* mRNA expression and cFGF23 levels**



David V. Kidney Int. 2016 ;89(1):135-46.

- Inflammation
  1) Associated with mortality;
  2) stimulates production of FGF 23 production;

- High levels of FGF 23 - independently associated with mortality in CKD.

- interrelationships among inflammation, FGF23, and risk of death has not been studied

Munoz Mendosa. Kidney Int. 2017; 91(3):711-719

Inflammation - independently associated with risk of death. With further adjustment for FGF23, the risks of death - minimally attenuated

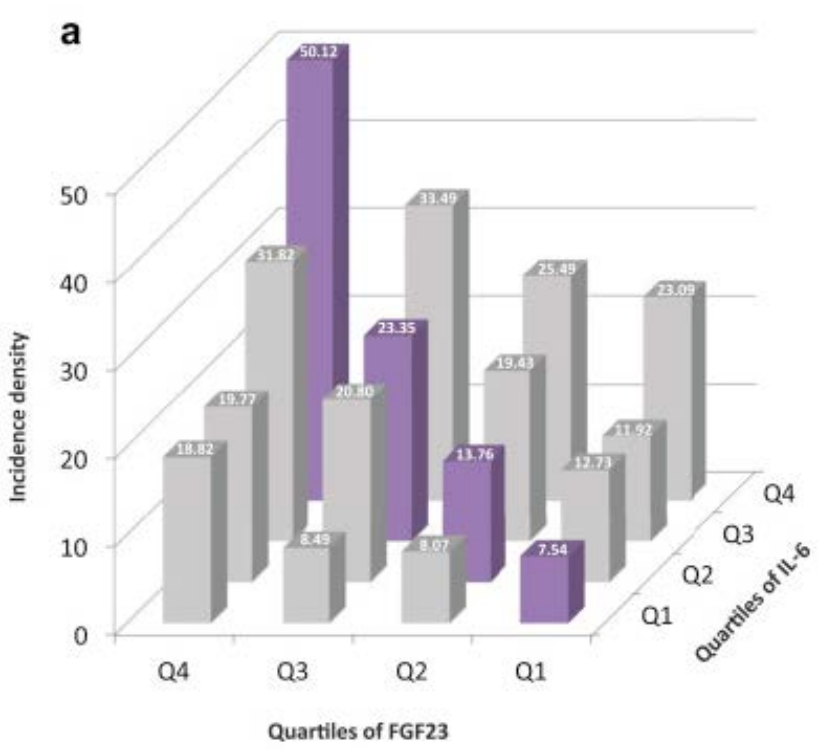
N = 3875 participants in the CRIC study with CKD stages 2 to 4

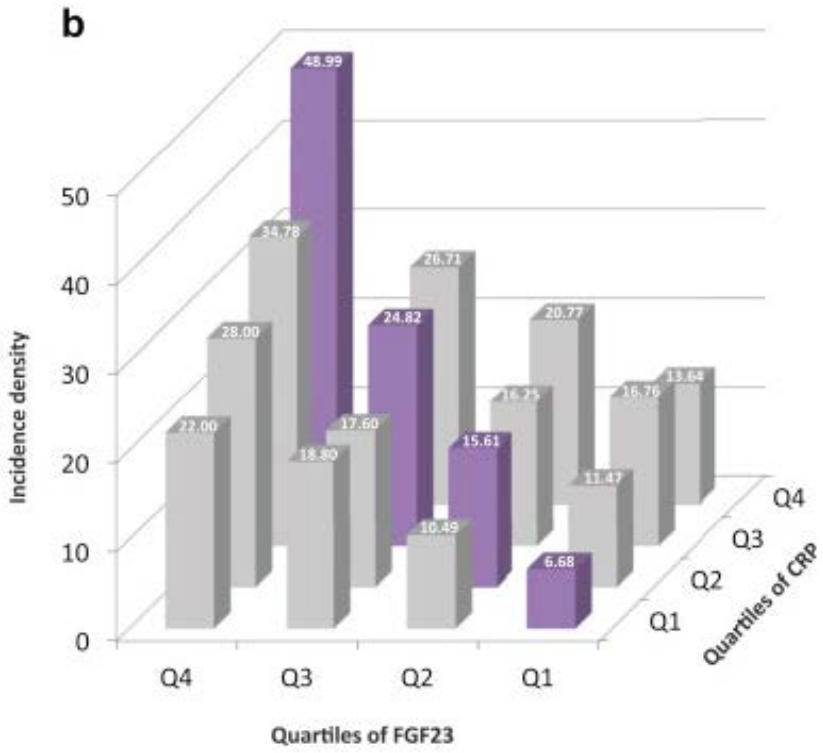
Table 3 Dual effects of inflammatory markers and FGF23 on all-cause mortality				
	HR (95% CI)			
	Unadjusted	**Model A**	**Model B**	**Model C**
Single Cox proportional hazards model that includes both IL-6 and FGF23				
Per SD of lnIL-6	1.39 (1.30–1.48)	1.30 (1.20–1.41)	1.30 (1.20–1.41)	1.29 (1.18–1.40)
Per SD of lnFGF23	1.47 (1.36–1.58)	1.42 (1.30–1.55)	1.40 (1.28–1.54)	1.36 (1.23–1.50)
Single Cox proportional hazards model that includes both CRP and FGF23				
Per SD of lnCRP	1.26 (1.15–1.37)	1.23 (1.13–1.35)	1.22 (1.11–1.33)	1.22 (1.11–1.33)
Per SD of lnFGF23	1.58 (1.46–1.70)	1.48 (1.35–1.62)	1.46 (1.34–1.60)	1.41 (1.28–1.55)

Model A is stratified by site and adjusted for age, sex, race, ethnicity, body mass index, diabetes, smoking status, history of CV, systolic BP, estimated eGFR, urine albumin-to-creatinine ratio categories, serum albumin, hemoglobin, and low-density lipoprotein.
Model B is model A plus use of aspirin, beta blockers, statins, angiotensin-converting enzyme inhibitors or angiotensin II receptor blockers, active vitamin D, nutritional vitamin D, phosphate binders, and steroids.
Model C is model B plus serum calcium, phosphate, and parathyroid hormone

Munoz Mendosa. Kidney Int. 2017; 91(3):711-719

Additive effects of elevated levels of inflammatory markers and FGF23 on risk of mortality





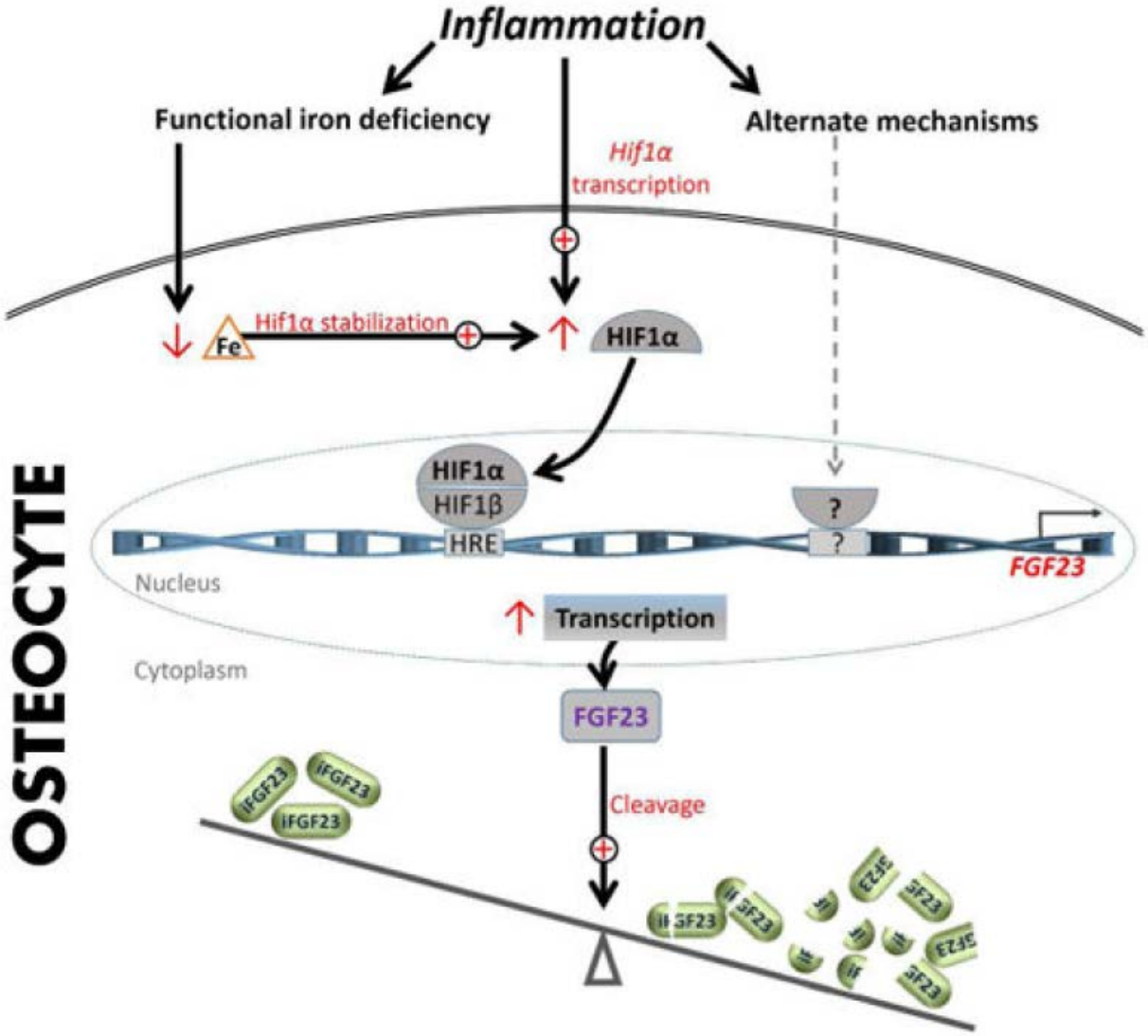
Munoz Mendosa. Kidney Int. 2017; 91(3):711-719

Take-Home Message

- Inflammation markedly increases FGF23 expression;
- Bone is the predominant source of increased FGF23 transcription relative to other organs, including the kidney, which may be a secondary source of FGF23 in CKD
- Osteocytes maintain normal serum levels of biologically active FGF23 by increasing FGF23 cleavage ➡ marked increases in circulating cFGF23 levels but normal iFGF23
- CKD acts by blocking cleavage of FGF23?
- **Increased activity of HIF1α is one mechanism through which inflammation stimulates FGF23** transcription
- FGF23 neither potentiates nor markedly attenuates the relationship between inflammation and death

David V. Kidney Int. 2016 ;89(1):135-46.

Take-Home Message



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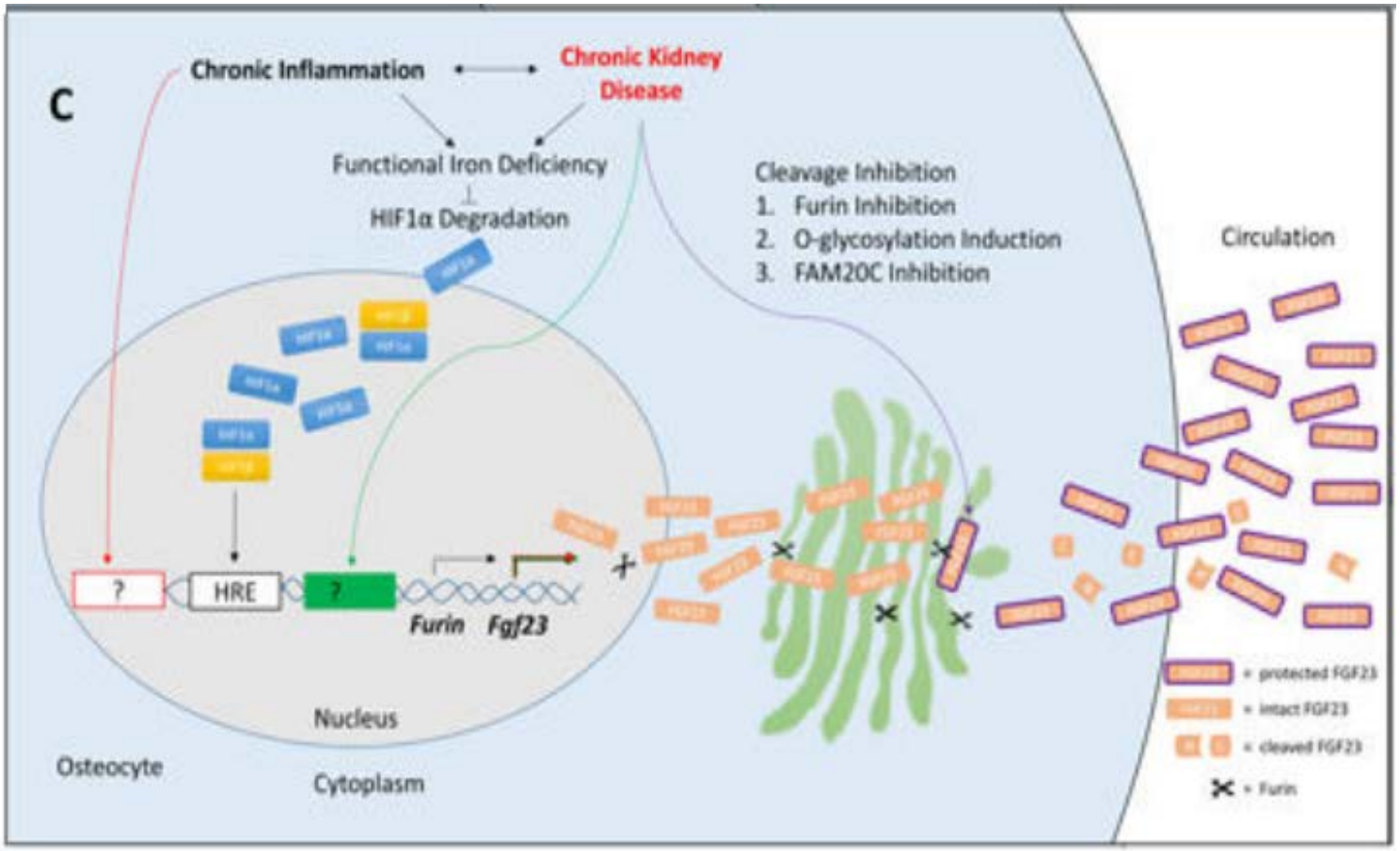
Take-Home Message



David V. Kidney Int. 2016 ;89(1):135-46.

a-Klotho as a Therapeutic Target

State of the Art

- **α**-Klotho is highly expressed in the kidney, where its extracellular domain is cleaved and released into the circulation
- CKD - is a state of **α**-Klotho deficiency

Hu MC, JASN. 2016;27:79–90; Hu MC et al. Ann Rev Physiol. 2013; 75:503–533; Bian A, et al. Clin Inter Aging. 2015; 10:1233–1243; Hu MC et al. JASN 2015;26: 1290–1302. Hu MC et al. JASN. 2011;22:124–136; Ravikumar P J Appl Physiol 2016;120:723–732. Hu MC, Kidney Int. 2010;78:1240–1251

State of the Art

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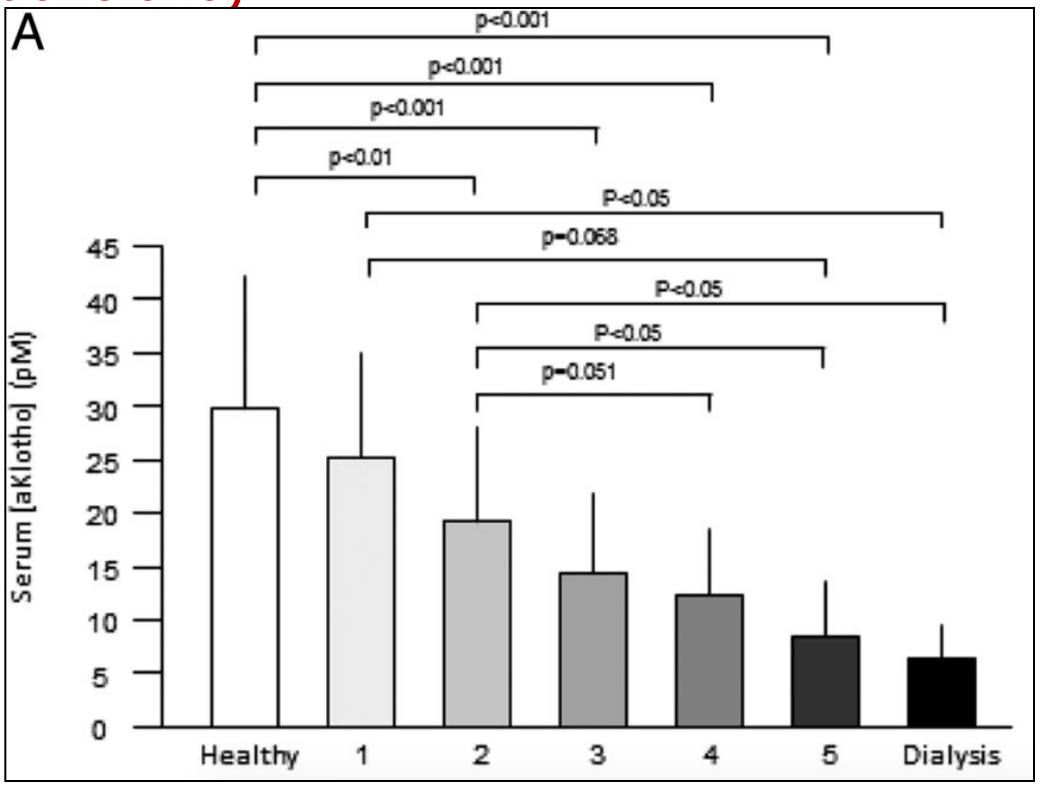

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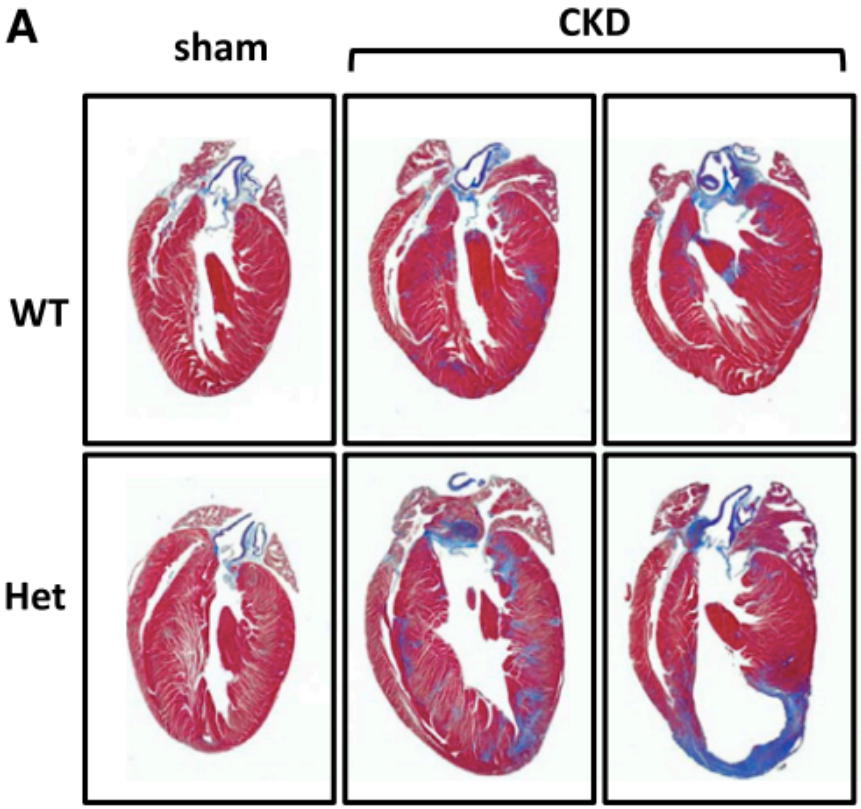
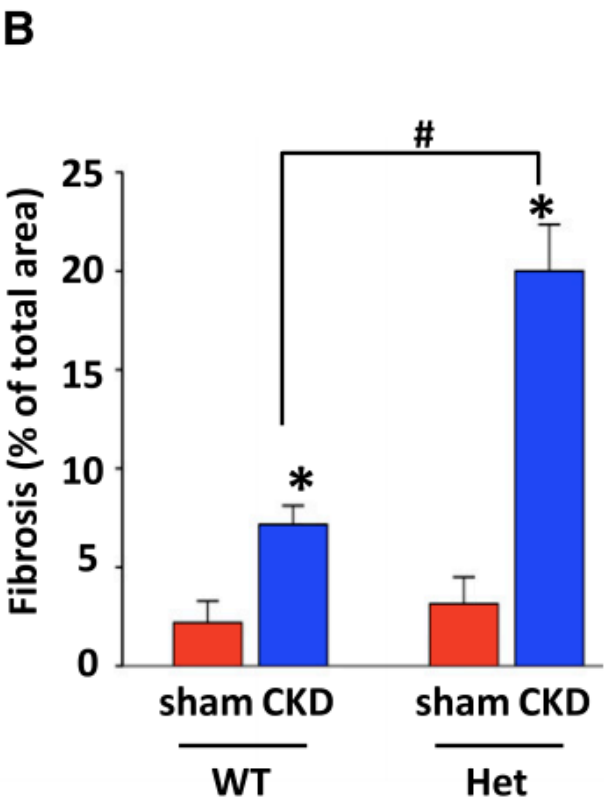
State of the Art

- **α**-Klotho is highly expressed in the kidney, where its extracellular domain is cleaved and released into the circulation
- CKD - is a state of **α**-Klotho deficiency
- Soluble **α**-Klotho exerts multiple actions, including antioxidation, antisenescence, pro-autophagy, anti-apoptosis, antifibrosis, pro–stem cell, and anti-insulin actions
- ⟹ multiple *negative systemic effects* including the CV system

Hu MC, JASN. 2016;27:79–90; Hu MC et al. Ann Rev Physiol. 2013; 75:503–533; Bian A, et al. Clin Inter Aging. 2015; 10:1233–1243; Hu MC et al. JASN 2015;26: 1290–1302. Hu MC et al. JASN. 2011;22:124–136; Ravikumar P J Appl Physiol 2016;120:723–732. Hu MC, Kidney Int. 2010;78:1240–1251

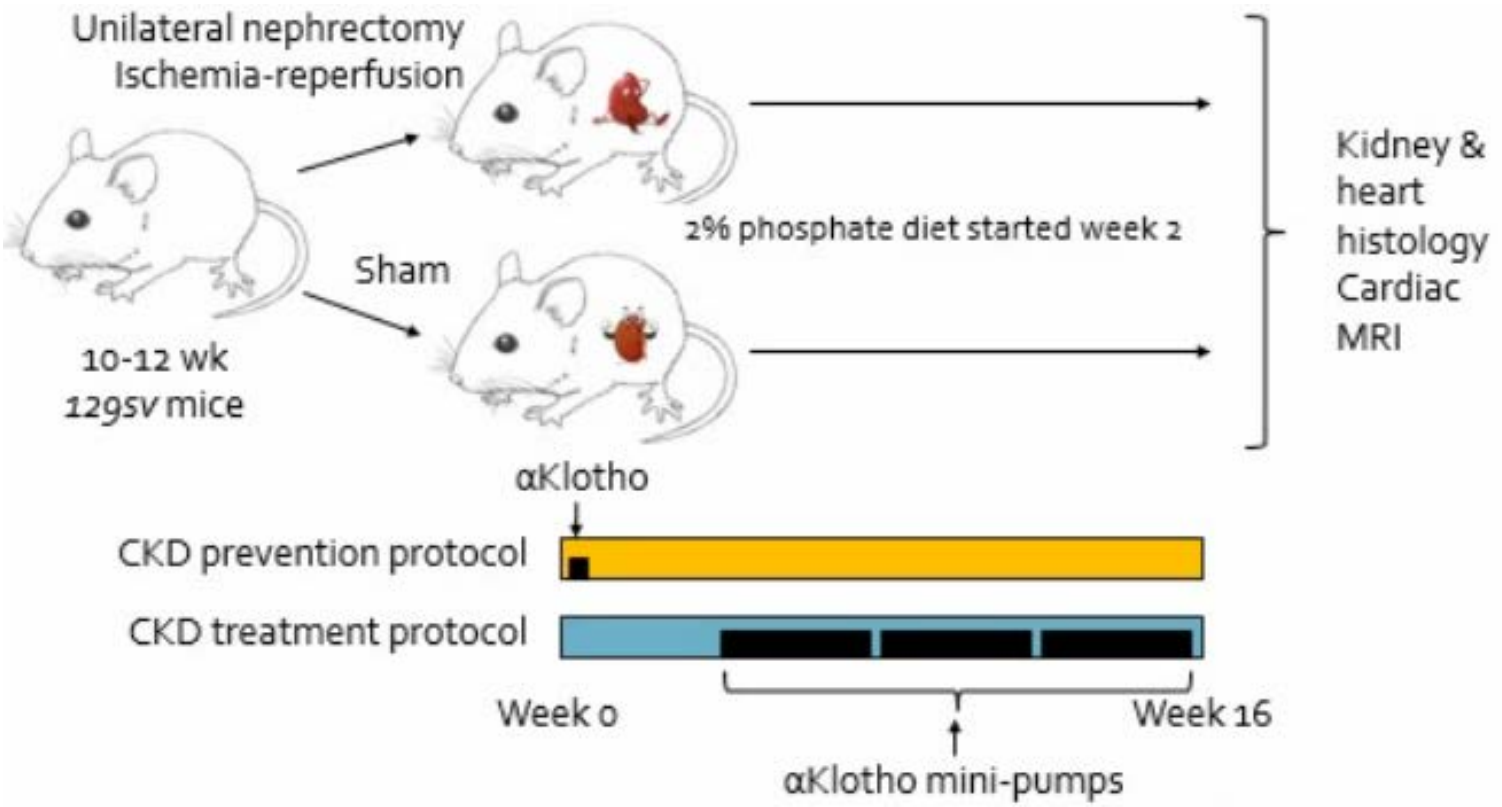
Klotho deficiency causes LVH and fibrosis (in CKD)





Xie et al, J Am Soc Nephrol. 2015;26(5):1150-60

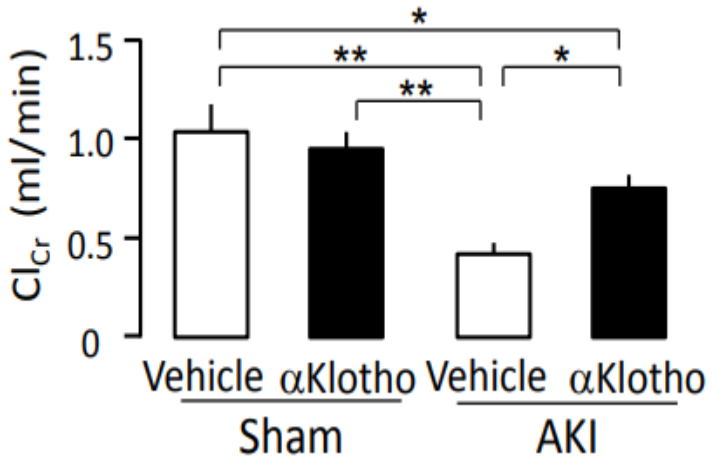
Recombinant a-Klotho may be prophylactic and therapeutic for AKI to CKD

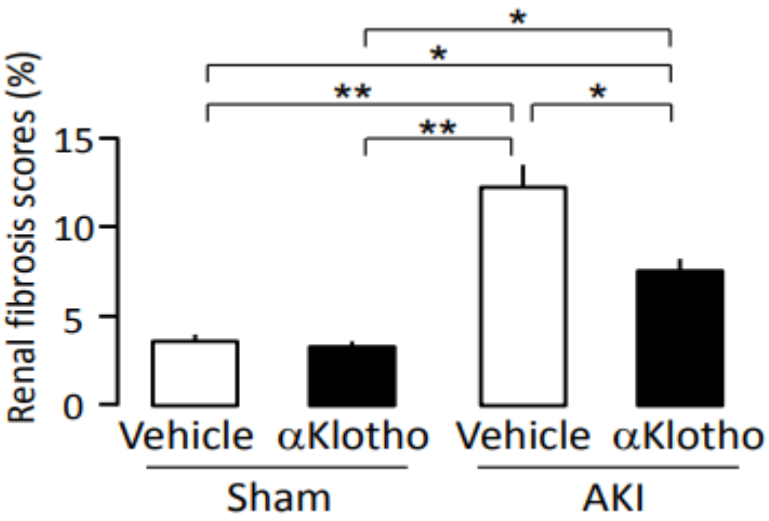


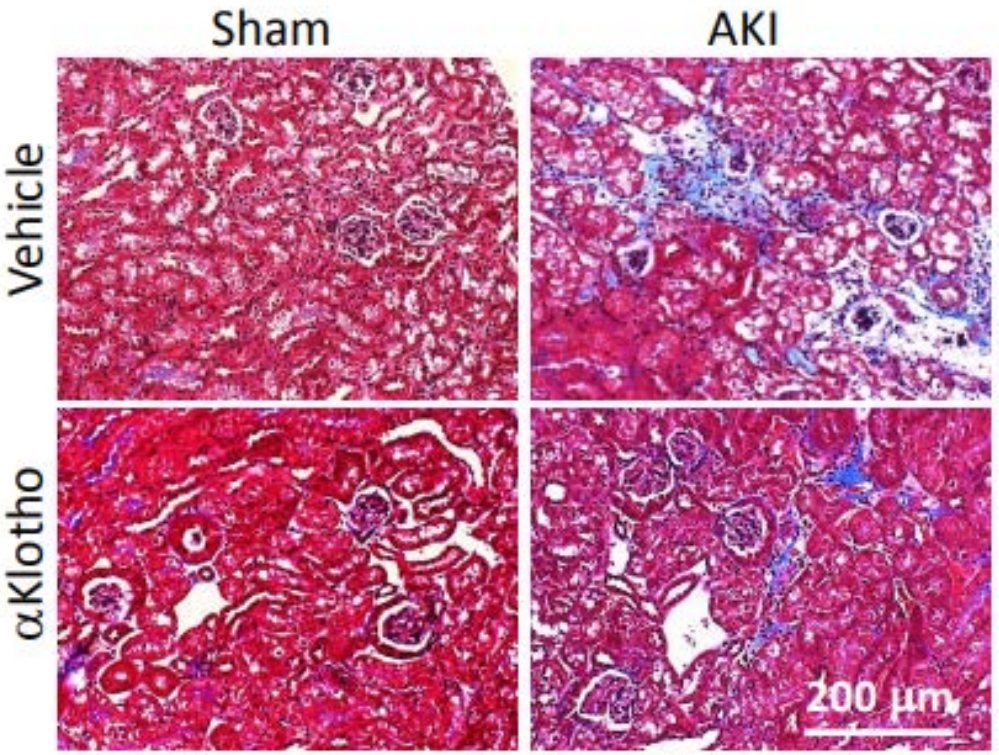
Mo HC. Kidney Int. 2017; 91(5):1104-1114

Early administration of α-Klotho prevented 1) AKI-to-CKD progression

At 20 weeks after AKI

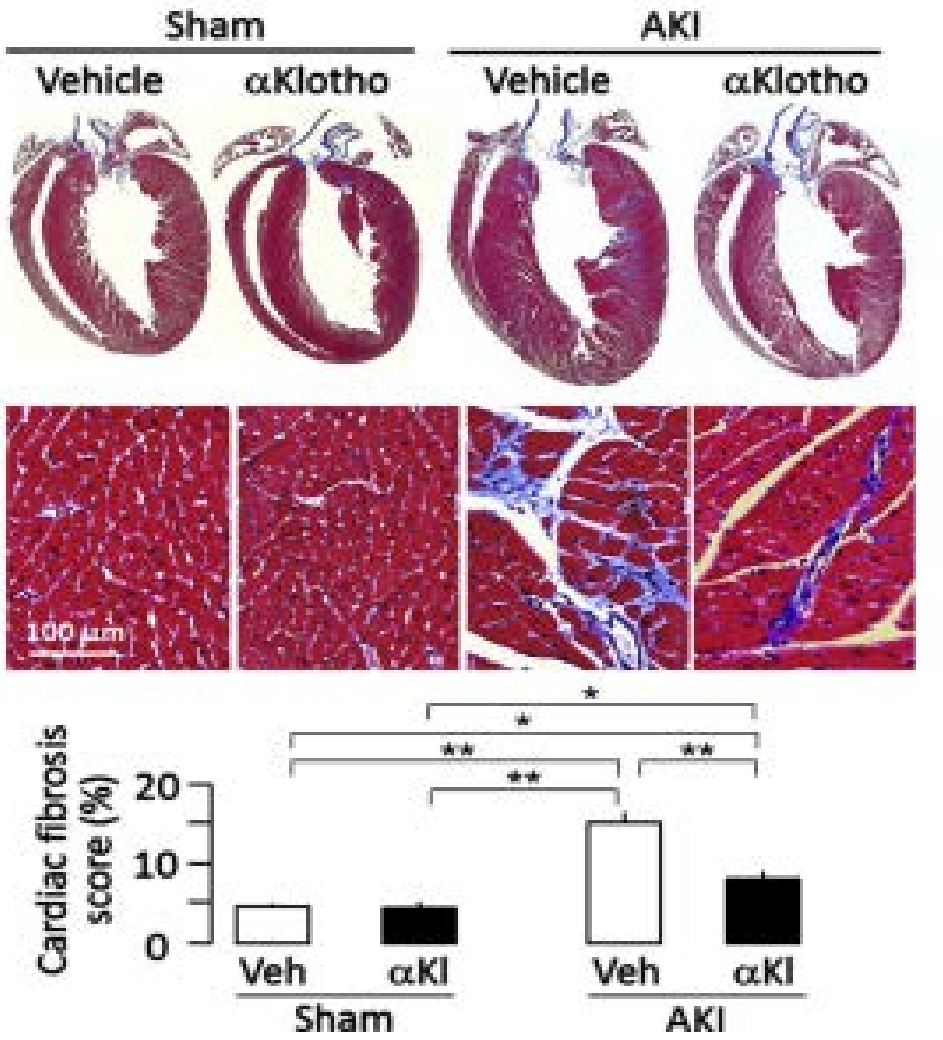






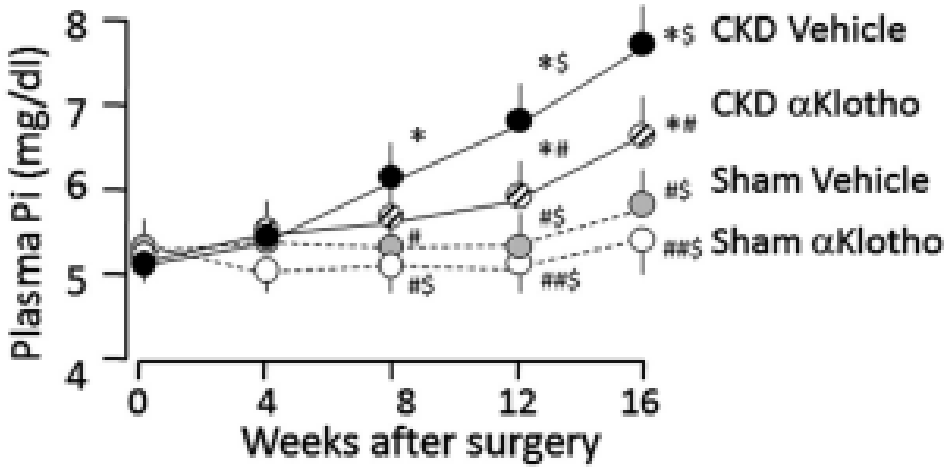
Mo HC. Kidney Int. 2017; 91(5):1104-1114

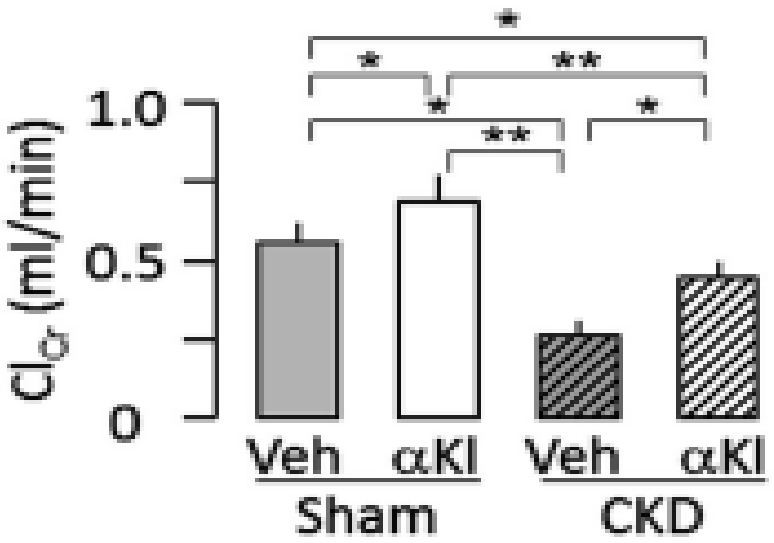
Early administration of α-Klotho prevented 2) cardiac remodeling



Mo HC. Kidney Int. 2017; 91(5):1104-1114

Chronic α-Klotho administration attenuated high phosphate diet induced renal fibrosis and improved renal function





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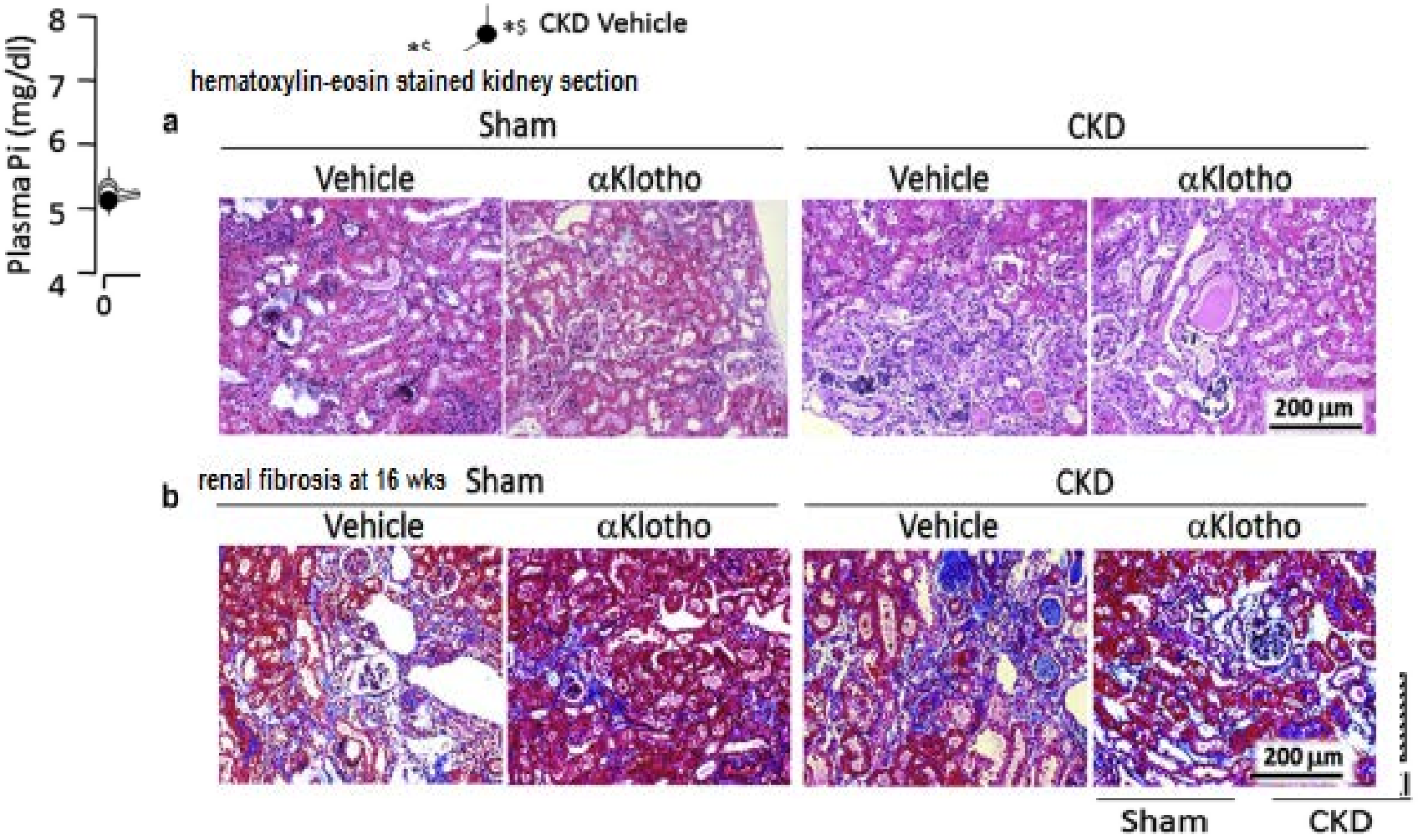

Mo HC. Kidney Int. 2017; 91(5):1104-1114

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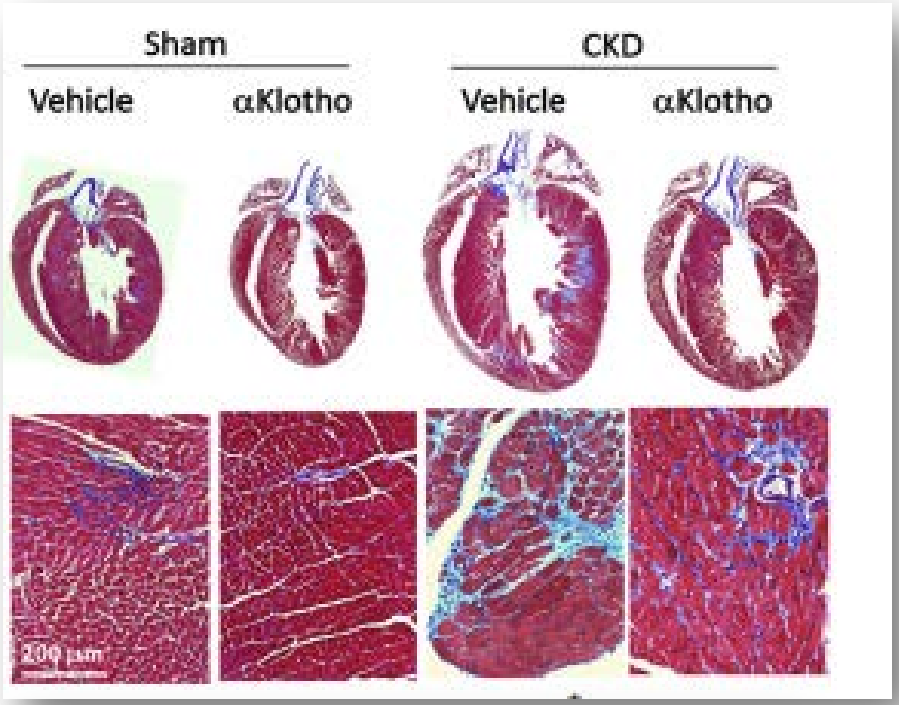
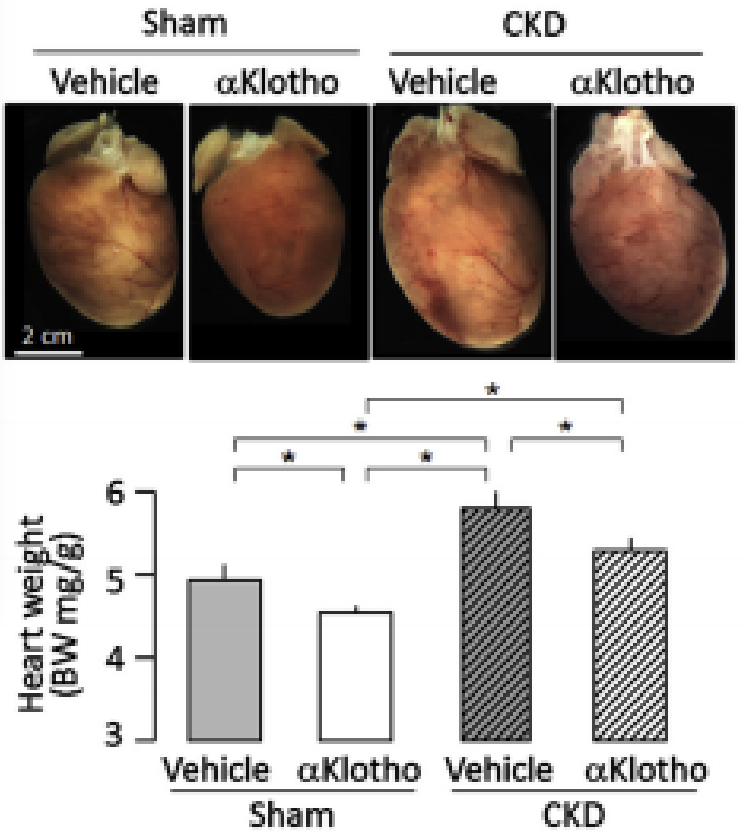
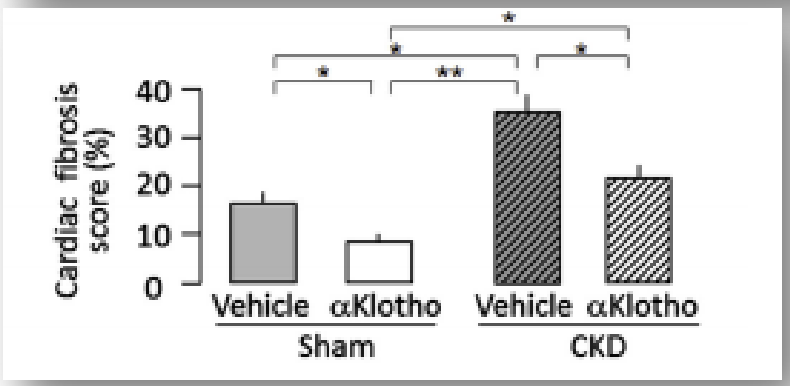






Mo HC. Kidney Int. 2017; 91(5):1104-1114

Take-Home Message

α-Klotho replacement - a promising therapeutic strategy:

- for retardation of AKI-to-CKD progression
- improvement of uremic cardiomyopathy.

Vitamin D Clinical Trials

State of the Art

- Values of serum 25-hydroxyvitamin D (25OHD) defined as insufficient or deficient are common in the CKD patients

- Observational studies have shown an association between low 25OHD levels and adverse clinical outcomes (muscle weakness, falls risk, sudden cardiac death, cerebrovascular and all-cause mortality)

- Experimental and observational studies suggest that nutritional vitamin D may enhance erythropoiesis in settings of 25OHD deficiency.

Wolf M et al. Kidney Int 2007;72:1004–1013; Elder et al. J Am Soc Nephrol. 2016 Jun;27(6):1581-4; Drechsler C, et al. Eur Heart J 31: 2253–2261, 2010; Miskulin D et al.: J Am Soc Nephrol ,2016; Hewitt et al. Clin J Am Soc Nephrol 8: 1143–1149, 2013; Marckmann Pet al. Nephrol Dial Transplant 27: 3523–3531, 2012

Ergocalciferol - had NO EFFECT on clinical outcomes

double-blind, placebo-controlled, RCT; 276 patients on HD with vitamin D insufficiency or deficiency - randomized to 6 months of ergocalciferol or placebo.

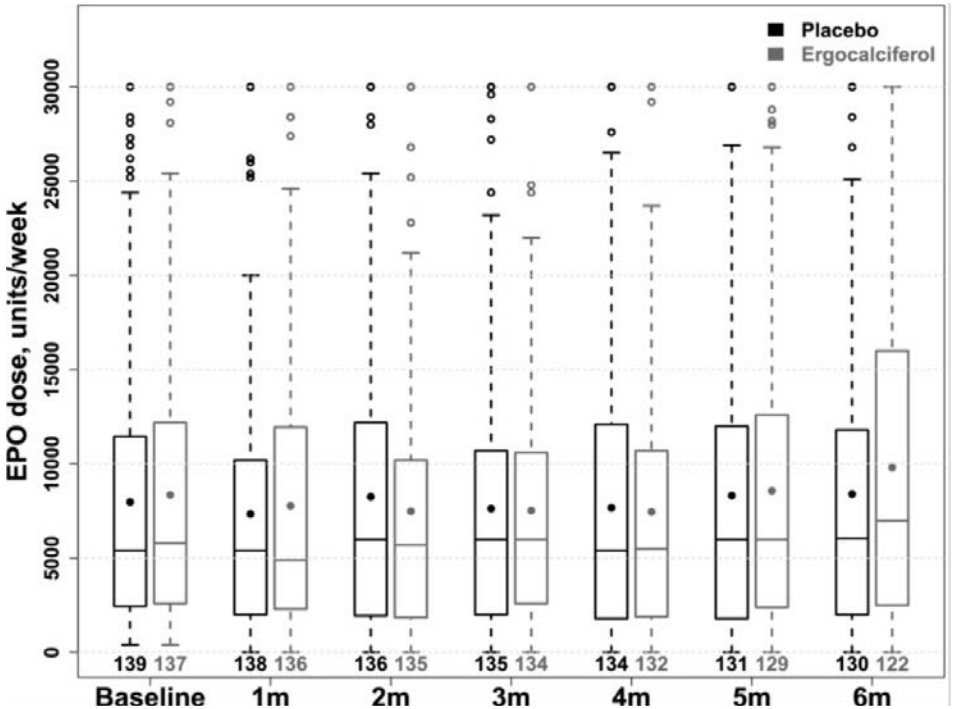
Table 3. Clinical events by treatment arm

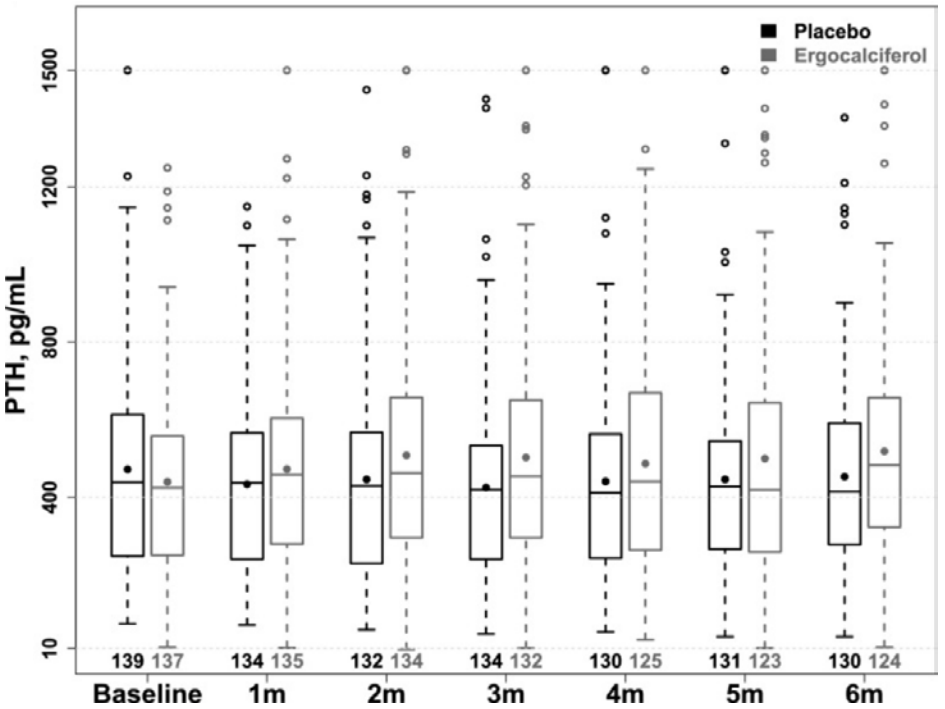
	Ergocalciferol (*n*=137)	Placebo (*n*=139)	*P* Value
All-cause hospitalization			
Events/total years at risk	70/61.1	88/62.6	
Event rate (per 100 PY) (95% CI)	114.6 (90.7 to 144.8)	140.5 (114.0 to 173.1)	
IRR (95% CI)	0.82 (0.60 to 1.12)	1.00 (Reference)	0.20
Cardiovascular disease hospitalization			
Events/total years at risk	17/61.1	29/62.6	
Event rate (per 100 PY) (95% CI)	27.8 (17.3 to 44.8)	46.3 (32.2 to 66.6)	
IRR (95% CI)	0.60 (0.33 to 1.09)	1.00 (Reference)	0.10
Infection-related hospitalization			
Events/total years at risk	15/61.1	15/62.6	
Event rate (per 100 PY) (95% CI)	24.6 (14.8 to 40.7)	23.9 (14.4 to 39.7)	
IRR (95% CI)	1.03 (0.50 to 2.10)	1.00 (Reference)	0.95
Falls			
Events/total years at risk	21/61.1	21/62.6	
Event rate (per 100 PY) (95% CI)	34.4 (22.4 to 52.7)	33.5 (21.9 to 51.4)	
IRR (95% CI)	1.03 (0.56 to 1.88)	1.00 (Reference)	0.94
Fractures			
Events/total years at risk	5/61.1	1/62.6	
Event rate (per 100 PY) (95% CI)	8.2 (3.4 to 19.7)	1.6 (0.2 to 11.3)	
IRR (95% CI)	5.13 (0.60 to 43.88)	1.00 (Reference)	0.14

PY, person-years; IRR, Incidence rate ratio is the ratio of the event rate in the ergocalciferol as compared with the placebo arm.

Miskulin D et al. JAMA 2016 Jun;27(6):1801-10

Ergocalciferol - had NO EFFECT on EPO utilization or PTH





Miskulin D et al. JAMA 2016 Jun;27(6):1801-10

Take-Home Message

Administration of ergocalciferol to 25(OH)D-deficient patients on HD:

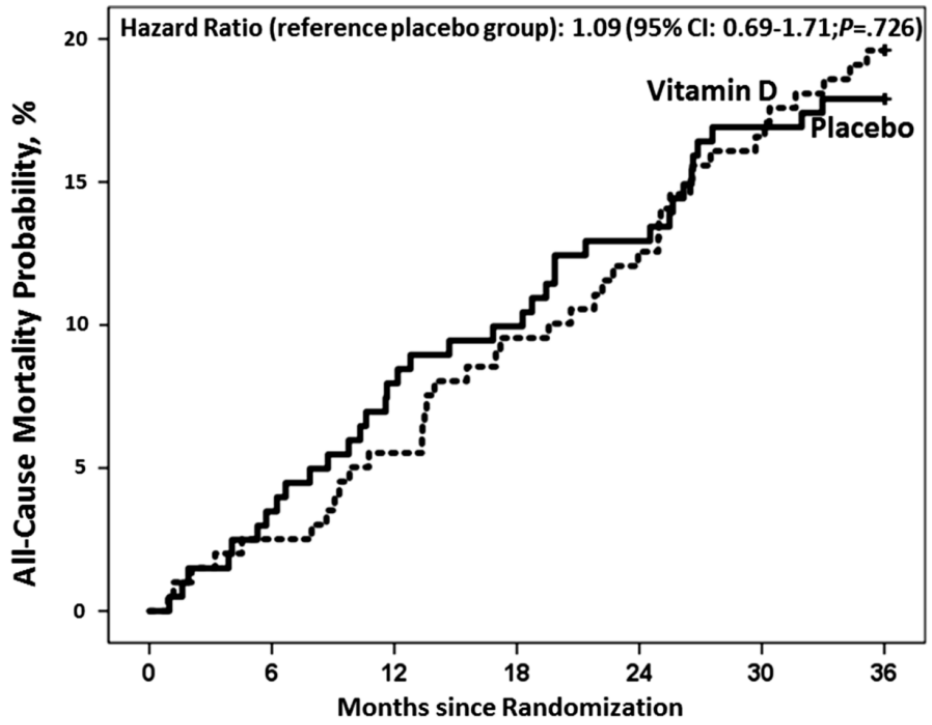
1) had no effect on clinical outcomes;

2) had no effect in the management of anemia

In addition….

Vitamin D – NO EFFECT ON FALLS

Vitamin D – NO EFFECT ON MORTALITY IN HF



Patients at risk							
Placebo	201	194	185	181	175	167	165
Vitamin D	199	194	188	180	174	166	160

Zittermann et al, Eur Heart J. 2017;38(29):2279-2286

Second Generation Calcimimetics

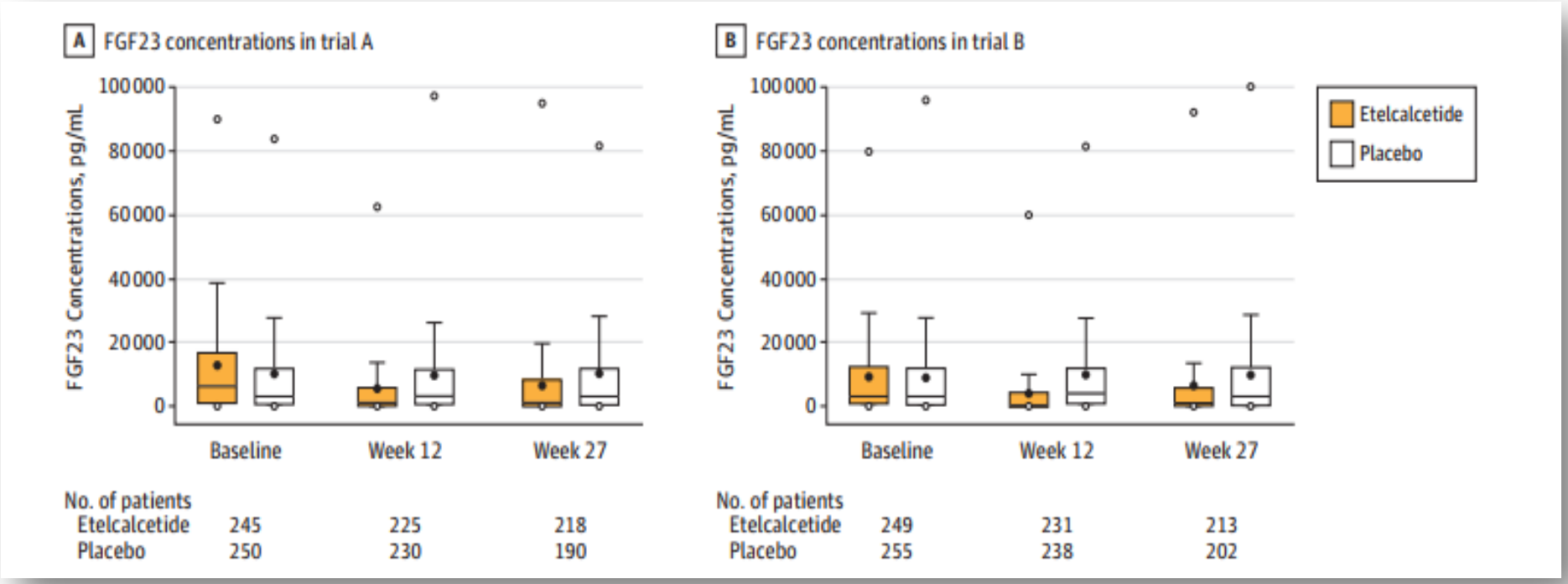
State of the Art

- Secondary hyperparathyroidism contributes to extraskeletal calcification and is associated with all-cause and cardiovascular mortality.
- Control is suboptimal in the majority of patients receiving HD
- Etelcalcetide is a synthetic peptide composed of 7 D-amino acids linked to an L-cysteine via a disulfide bond that functions as an activator of the calcium-sensing receptor.
- Etelcalcetide was developed to improve efficacy and adherence and reduce gastrointestinal adverse effects relative to cinacalcet (i.v formulation; thrice-weekly dosing at the time of dialysis)

Kidney Disease Improving Global Outcomes CKD-MBD Workgroup; Kidney Int. 2009;76 (suppl 113):1-140. 2. Tentori F et al. Clin J Am Soc Nephrol. 2015;10(1):98-109. Martin KJ et al. Nephrol Dial Transplant. 2014;29(2): 385-392. Chen P et al. J Clin Pharmacol. 2015;55(6):620-628. Block GA, et alASN ; November 5-10, 2013;

Etelcalcetide vs placebo
Treatment with etelcalcetide decreased FGF23

Two parallel, phase 3, randomized, placebo-controlled treatment trials - 1023 patients receiving hemodialysis with moderate to severe secondary hyperparathyroidism.
Iv administration of etelcalcetide (n = 503) or placebo (n = 513) after each HD session for 26 weeks



Block, JAMA. 2017 Jan 10;317(2):146-155

Etelcalcetide - vs placebo
more muscle spasms, nausea and vomiting

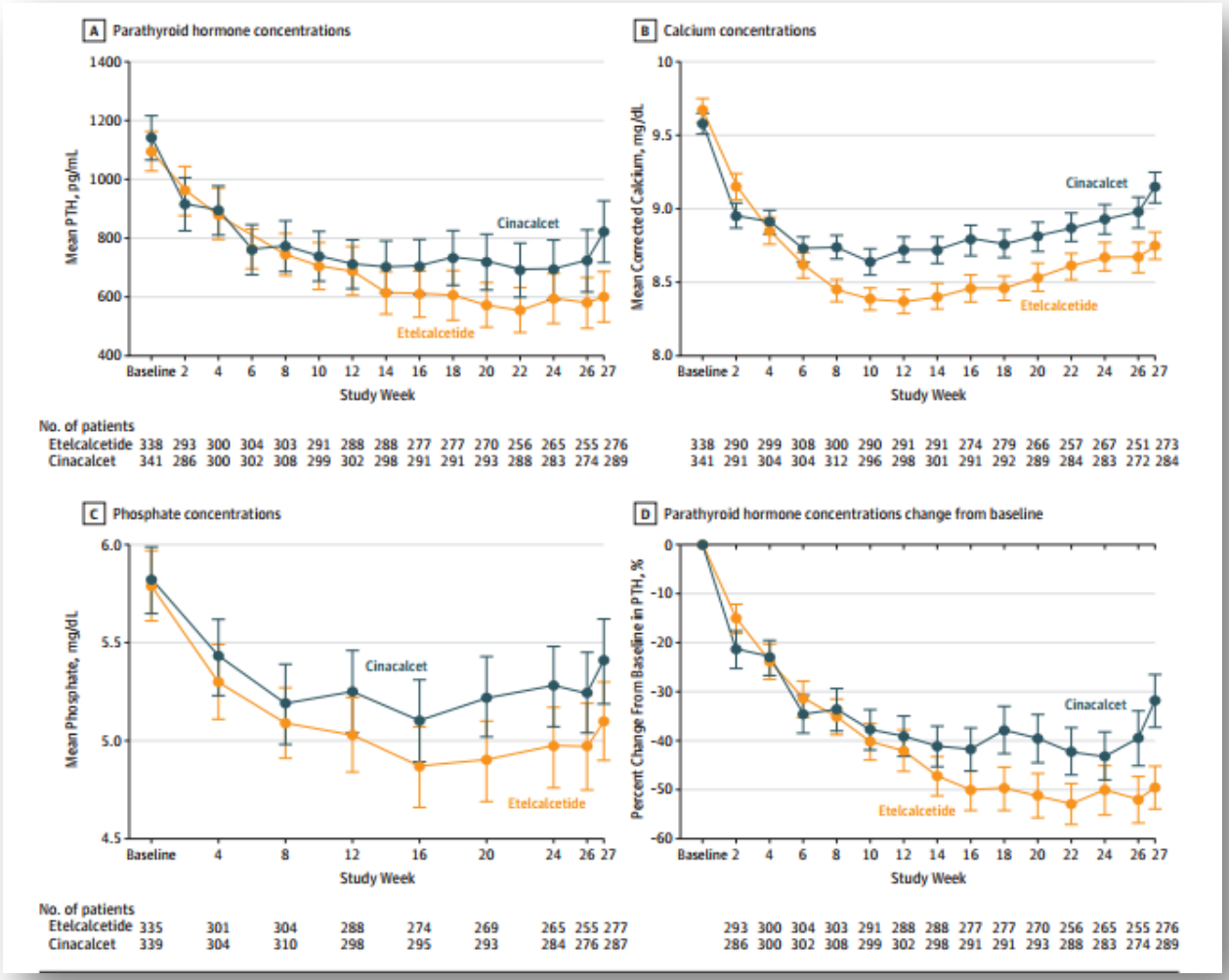
	No. (%) of Participants			
	Trial A		Trial B	
Adverse Events	Etelcalcetide (n = 251)	Placebo (n = 254)	Etelcalcetide (n = 252)	Placebo (n = 259)
Blood calcium decrease[b]	153 (61.0)	21 (8.3)	168 (66.7)	31 (12.0)
Muscle spasms	30 (12.0)	18 (7.1)	28 (11.1)	16 (6.2)
Diarrhea	18 (7.2)	18 (7.1)	36 (14.3)	26 (10.0)
Nausea	31 (12.4)	13 (5.1)	23 (9.1)	19 (7.3)
Vomiting	26 (10.4)	18 (7.1)	19 (7.5)	8 (3.1)
Headache	18 (7.2)	20 (7.9)	20 (7.9)	11 (4.2)
Hypocalcaemia	18 (7.2)	1 (0.4)	17 (6.7)	0
Hypertension	12 (4.8)	17 (6.7)	19 (7.5)	12 (4.6)
Hypotension	16 (6.4)	10 (3.9)	14 (5.6)	16 (6.2)
Arteriovenous fistula site complication	13 (5.2)	14 (5.5)	16 (6.3)	12 (4.6)
Pain in extremity	17 (6.8)	11 (4.3)	7 (2.8)	9 (3.5)
Paresthesia	13 (5.2)	3 (1.2)	11 (4.4)	0
Back pain	8 (3.2)	8 (3.1)	14 (5.6)	11 (4.2)
Upper respiratory tract infection	8 (3.2)	10 (3.9)	13 (5.2)	16 (6.2)

Block, JAMA. 2017 Jan 10;317(2):146-155

Etelcalcetide vs Cinacalcet
Superior in achieving biochemical end points

A randomized, double-blind, double-dummy active clinical trial;

N = 683 patients receiving HD with serum PTH>500 pg/mL on active therapy



Block, JAMA.2017 Jan 10;317(2):156-164

Etelcalcetide compared with cinacalcet:
1) more hypocalcemia;
2) NO difference in self-reported nausea and vomiting

Preferred Term	Patients, No. (%) Etelcalcetide (n = 338)	Cinacalcet (n = 341)
Blood calcium decreased[b]	233 (68.9)	204 (59.8)
Nausea	62 (18.3)	77 (22.6)
Vomiting	45 (13.3)	47 (13.8)
Hypotension	23 (6.8)	10 (2.9)
Headache	22 (6.5)	24 (7.0)
Muscle spasms	22 (6.5)	20 (5.9)
Diarrhea	21 (6.2)	35 (10.3)
Hypertension	21 (6.2)	23 (6.7)
Anemia	17 (5.0)	15 (4.4)
Hypocalcemia	17 (5.0)	8 (2.3)
Pain in extremity	17 (5.0)	14 (4.1)
Bronchitis	5 (1.5)	17 (5.0)

Block, JAMA.2017 Jan 10;317(2):156-164

Take-Home Message

Etelcalcetide-treated patients

- Better PTH control
- Low serum phosphate
- Low FGF23 concentrations
- Similar gastrointestinal effects (cinacalcet)

New Phosphate Binders:
-Iron based P Binders
-Inhibitor of the Sodium/Hydrogen Exchanger Isoform 3

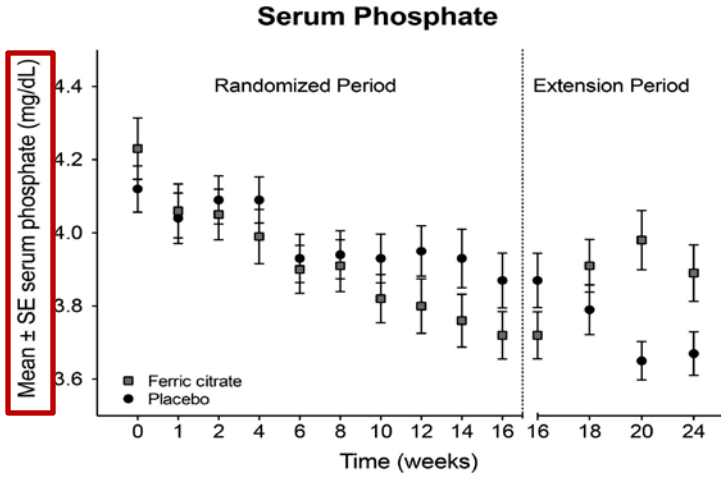
State of the Art

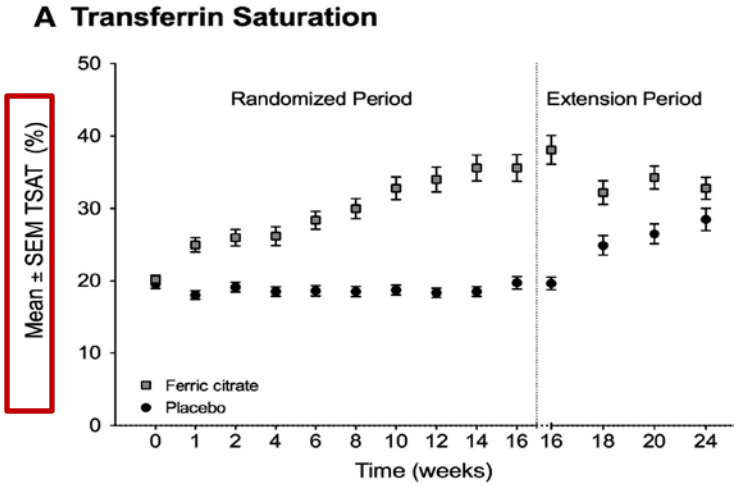
- Hyperphosphatemia is associated with mortality, fractures, and cardiovascular disease, including vascular calcification and left ventricular hypertrophy.
- Adherence to diet and phosphate binders is poor- pill burden, timing of ingestion around mealtimes, and gastrointestinal side effects
- Iron based phosphate binders - effectively repleted iron stores and partially corrected anemia
- Tenapanor - minimally absorbed small molecule inhibitor of the sodium/hydrogen exchanger isoform 3; functions in the gut to reduce sodium and phosphate absorption

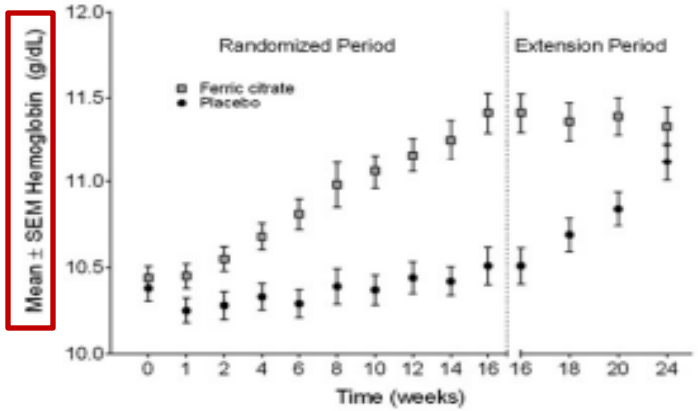
Palmer SC, et al. JAMA 2011; 305:1119; .Eddington H et al. Clin J Am Soc Nephrol 2010; 5:2251.. Fissell RB et al. Hemodial Int 2016;20:38-49; Chiu YW, et al. Clin J Am Soc Nephrol 4: 1089–1096, 2009; Block G et al. J Am Soc Nephrol 2012; 23:1407; Labonté ED et al. J Am Soc Nephrol 26: 1138–1149, 2015

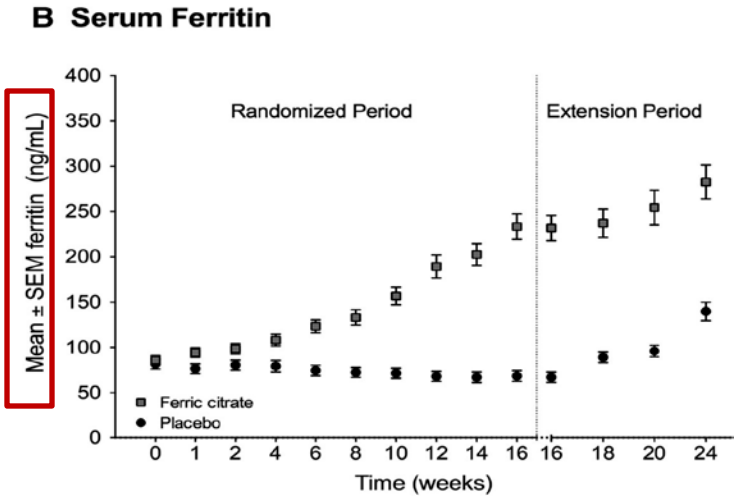
Ferric citrate replete iron stores and partially corrected anemia

Randomized double-blind clinical; NDD-CKD and iron deficiency anemia; oral ferric citrate (n=117) and placebo (n=115)





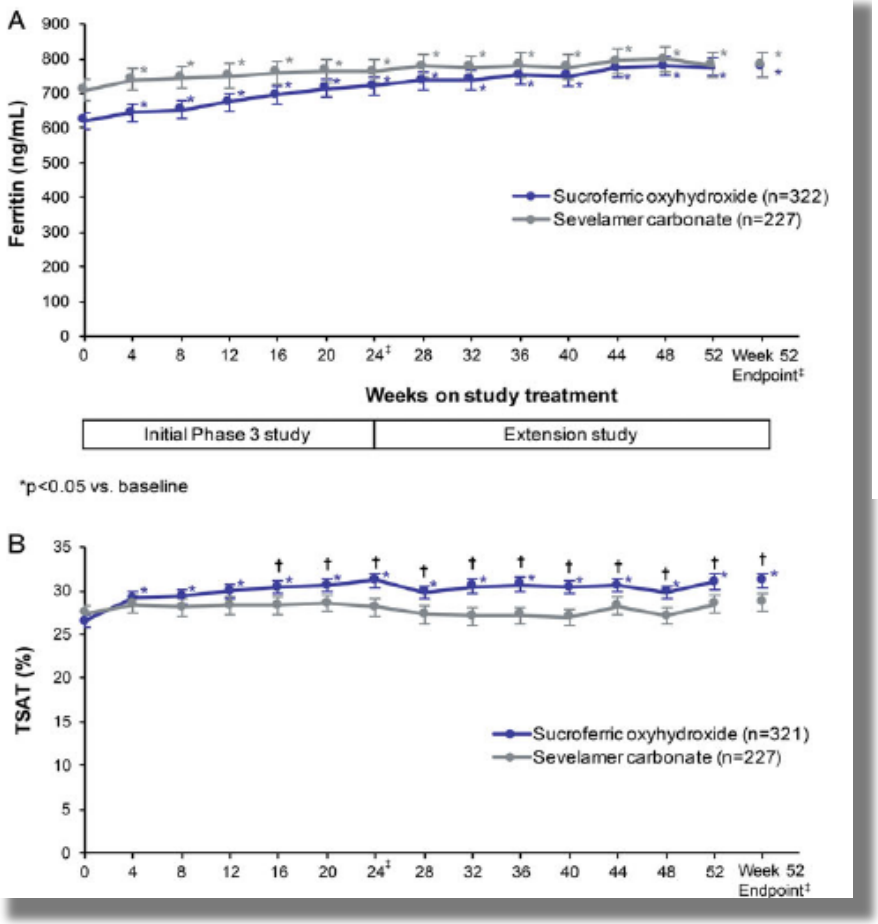


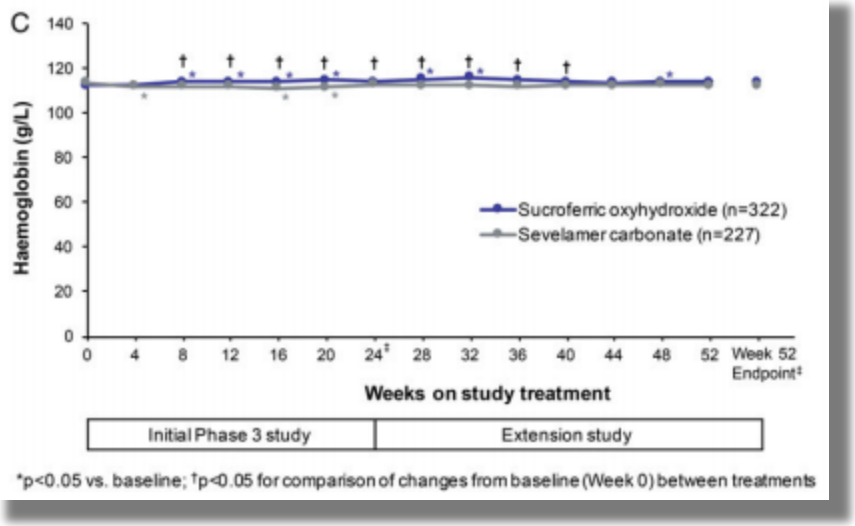


Fishbane et al. JASN 2017;28:1851-1858

The same favorable effects for sucroferric oxyhydroxide

N = 1059 patients randomized to sucroferric oxyhydroxide 1.0–3.0 g/day (*n* = 710) or sevelamer carbonate ('sevelamer') 2.4–14.4 g/day (*n* = 349) for up to 52 weeks



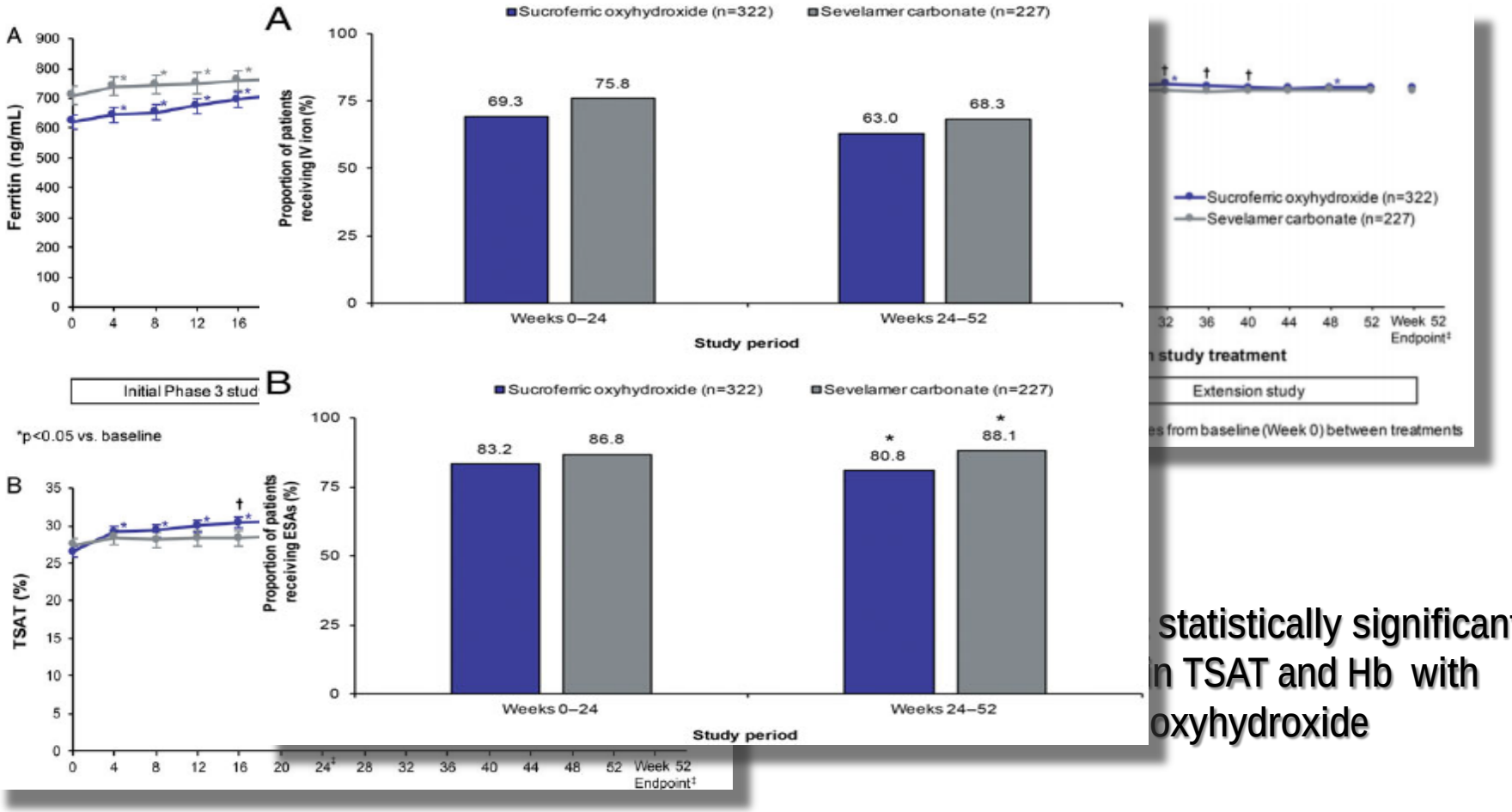


There were small, but statistically significant, greater increases in TSAT and Hb with sucroferric oxyhydroxide

Covic, NDT 2017

The same favorable effects for sucroferric oxyhydroxide

N = 1059 patients randomized to sucroferric oxyhydroxide 1.0–3.0 g/day (*n* = 710) or sevelamer carbonate ('sevelamer') 2.4–14.4 g/day (*n* = 349) for up to 52 weeks

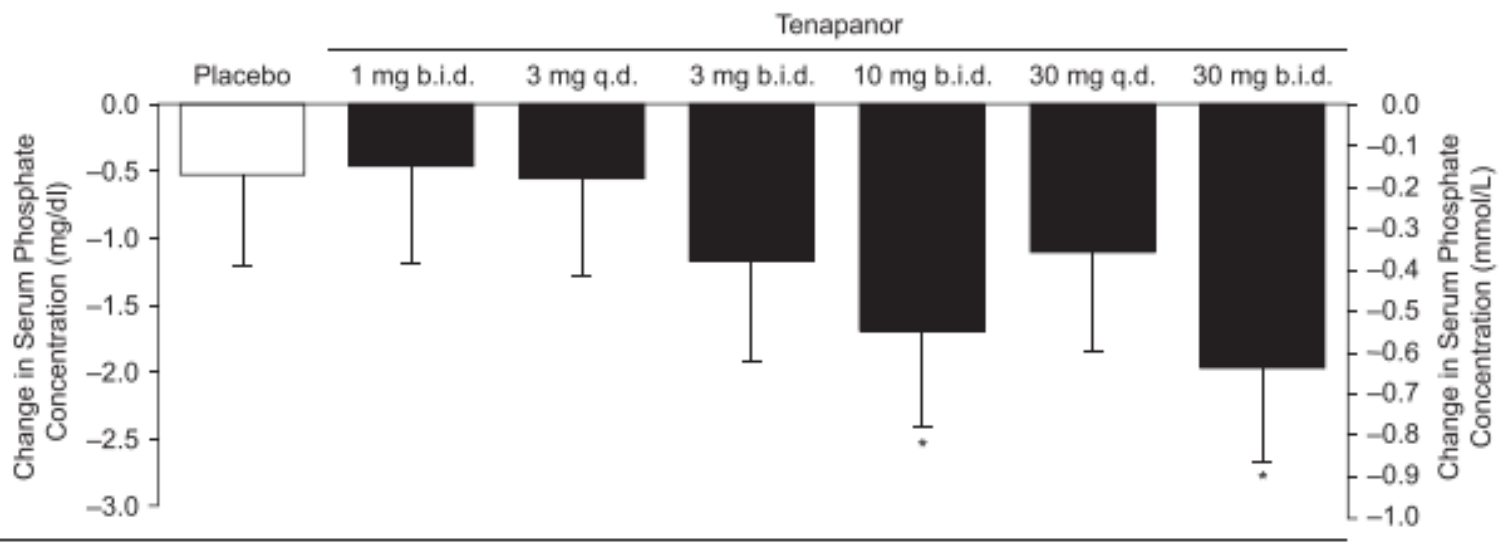


statistically significant,
n TSAT and Hb with
oxyhydroxide

Covic, NDT 2017

Tenapanor - dose-dependent reductions in serum P

Randomized, double-blind, placebo controlled; N = 162 HD patients to one of six tenapanor regimens (3 or 30 mg once daily or 1, 3, 10, or 30 mg twice daily) or placebo for 4 weeks



Serum Phosphate Concentration (mg/dl)							
Baseline[a]	7.87±1.49	7.55±1.00	7.73±1.28	7.32±1.01	7.92±1.06	7.61±0.85	7.76±1.18
Change from Baseline at EOT/ET[b]	–0.54 (–1.21, 0.13)	–0.47 (–1.18, 0.24)	–0.56 (–1.28, 0.17)	–1.18 (–1.93, –0.44)	–1.70 (–2.41, –0.99)	–1.11 (–1.85, –0.37)	–1.98 (–2.67, –1.28)
n (baseline, EOT/ET)	26, 26	23, 23	22, 22	21, 21	23, 23	21, 21	25, 24

Block, J Am Soc Nephrol. 2017 Jun;28(6):1933-1942

Diarrhea - the most common adverse event

AE Category	Placebo, *n*=26	Tenapanor					
		1 mg Twice Daily, *n*=23	3 mg Once Daily, *n*=22	3 mg Twice Daily, *n*=21	10 mg Twice Daily, *n*=23	30 mg Once Daily, *n*=21	30 mg Twice Daily, *n*=25
Any AE	11 (42)	10 (43)	13 (59)	12 (57)	16 (70)	13 (62)	19 (76)
Any serious AE	4 (15)	2 (9)[a]	1 (5)	2 (10)	3 (13)	0	2 (8)
Fatal serious AE	0	1 (4)	0	0	0	0	0
Any AE leading to discontinuation	2 (8)	3 (13)	1 (5)	3 (14)	3 (13)	7 (33)	9 (36)
Diarrhea AE leading to discontinuation	0	2 (9)	0	2 (10)	1 (4)	6 (29)	8 (32)
AEs by system organ class[b]							
Cardiac disorders	2 (8)	1 (4)	0	1 (5)	0	1 (5)	0
Ear and labyrinth disorders	0	0	0	3 (14)	0	0	0
GI disorders	5 (19)	7 (30)	5 (23)	9 (43)	15 (65)	12 (57)	19 (76)
Diarrhea	3 (12)	6 (26)	4 (18)	6 (29)	11 (48)	11 (52)	17 (68)
Nausea	1 (4)	0	2 (9)	1 (5)	1 (4)	1 (5)	1 (4)
Abdominal pain	1 (4)	0	1 (5)	0	0	0	2 (8)
Vomiting	0	0	1 (5)	1 (5)	0	2 (10)	0
Fecal incontinence	0	0	0	1 (5)	2 (9)	0	0
General disorders and administration site conditions	0	2 (9)	2 (9)	0	0	0	2 (8)
Infections and infestations	3 (12)	0	2 (9)	1 (5)	1 (4)	1 (5)	0
Injury, poisoning, and procedural complications	0	2 (9)	1 (5)	2 (10)	1 (4)	0	2 (8)
Metabolism and nutrition disorders	2 (8)	1 (4)	1 (5)	1 (5)	2 (9)	1 (5)	1 (4)
Musculoskeletal and connective tissue disorders	2 (8)	0	0	1 (5)	0	2 (10)	2 (8)
Nervous system disorders	0	1 (4)	2 (9)	1 (5)	1 (4)	3 (14)	2 (8)
Psychiatric disorders	2 (8)	0	1 (5)	0	0	0	2 (8)
Skin and subcutaneous tissue disorders	1 (4)	0	2 (9)	0	1 (4)	0	0

Block, J Am Soc Nephrol. 2017 Jun;28(6):1933-1942

Effects on FGF 23

Table 2. Effects of ferric citrate on PTH and FGF23

Variables	Ferric Citrate		Placebo		*P* Value
	Baseline	Week 16	Baseline	Week 16	
Median PTH (IQR), pg/ml	103 (67, 171)	84 (58, 173)	92 (62, 168)	89.5 (61.5, 147.5)	0.02
Median c-FGF23 (IQR), RU/ml	364.0 (198.2, 601.2)	232.5 (136.5, 397.4)	305.8 (176.6, 484.4)	309.4 (185.5, 503.1)	<0.001
Median i-FGF23 (IQR), RU/ml	134.0 (89.6, 233.1)	105.0 (66.7, 180.1)	134.3 (83.1, 201.9)	119.5 (82.2, 213.2)	<0.001

c-FGF23, c-terminal fibroblast growth factor 23; i-FGF23, intact fibroblast growth factor 23.

Tenapanor - significant reductions in FGF23 compared with placebo

Biomarker	Placebo, *n*=26	Tenapanor					
		1 mg Twice Daily, *n*=23	3 mg Once Daily, *n*=22	3 mg Twice Daily, *n*=21	10 mg Twice Daily, *n*=23	30 mg Once Daily, *n*=21	30 mg Twice Daily, *n*=26
Serum FGF23							
Baseline serum FGF23, pg/ml[c]	4937 (206)	4052 (264)	3057 (255)	2601 (231)	6294 (202)	5312 (218)	4491 (347)
Ratio of geometric least squares mean between EOT/ET and baseline[d]	1.22	0.91[e]	0.89[e]	0.76[f]	0.72[f]	0.73[f]	0.81[f]
95% CI	1.00 to 1.48	0.74 to 1.11	0.72 to 1.09	0.62 to 0.93	0.59 to 0.88	0.57 to 0.92	0.66 to 0.98

Block, J Am Soc Nephrol. 2017 Jun;28(6):1933-1942

Fishbane, J Am Soc Nephrol 28 2017.

Take-Home Message

Treatment with new phosphate binders in HD patients with hyperphosphatemia

1) statistically significant reductions in serum P in HD patients.

2) Significant reductions in serum FGF23 concentrations

3) Safe and efficacious treatment for iron deficiency anemia (for iron based)

A single pill given once or twice daily offers great potential to improve the management of CKD-related bone mineral disorders.

New CKD-MBD Guideline Summary and Comparison of 2017 Updated and 2009 KDIGO CKD-MBD Recommendations

Treatment of CKD–MBD: Targeted at Lowering High Serum P and Maintaining Serum Ca

New 4.1.1: In patients with CKD G3a-G5D, treatments …should be based on serial assessments of P, Ca, and PTH levels, considered together *(Not Graded).*

New 4.1.2: In patients with CKD G3a-G5D, we suggest lowering elevated phosphate levels toward the normal range *(2C).*

New 4.1.3: In patients with CKD G3a-G5D, we suggest avoiding hypercalcemia *(2C)*.

Old 4.1.1: In patients with CKD G3a–G5D, we suggest maintaining serum P in the normal range (2C).

In patients with CKD G5D, we suggest lowering elevated P levels toward the normal range (2C).

Old 4.1.2: In patients with CKD G3a–G5D, we suggest maintaining serum Ca in the normal range (2D).

Ketteler et al. Kidney Int 2017 Jul;92(1):26-36

Rationale for Update

4.1.2: There is an absence of data that efforts to maintain phosphate in the normal range are of benefit to CKD G3a-G4 patients, including some safety concerns. Treatment should aim at overt hyperphosphatemia.

4.1.3: Mild and asymptomatic hypocalcemia (e.g., in the context of calcimimetic treatment) can be tolerated in order to avoid inappropriate calcium loading in adults.

Ketteler et al. Kidney Int 2017 Jul;92(1):26-36

Phosphate and Calcium

New 4.1.4: In patients with CKD G5D, we suggest using a dialysate calcium concentration between 1.25 and 1.50 mmol/l (2.5 and 3.0 mEq/l) *(2C).*

…

New 4.1.6: In adult patients with CKD G3a-G5D receiving phosphate-lowering treatment, we suggest restricting the dose of calcium-based phosphate binders (2B).

Old 4.1.3: In patients with CKD G5D, we suggest using a dialysate calcium concentration between 1.25 and 1.50 mmol/l (2.5 and 3.0 mEq/l) *(2D).*

Old 4.1.5: In patients with CKD G3a–G5D and hyperphosphatemia, we recommend restricting …

- in the presence of persistent or recurrent hypercalcemia (1B).
- in the presence of arterial calcification (2C)
- and/or adynamic bone disease (2C) and/or if serum PTH levels are persistently low (2C)

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Rationale for Update

4.1.4: Additional studies of better quality are available; however, they do not allow discrimination of benefits and harm between calcium dialysate concentrations of 1.25 and 1.50 mmol/l (2.5 and 3.0 mEq/l). Hence, the wording is unchanged but evidence grade is upgraded from 2D to 2C.

....

4.1.6: New evidence from three randomized control trials (RCTs) supports a more general recommendation to restrict calcium-based phosphate binders in hyperphosphatemic patients of all severities of CKD

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Assessment of PTH

- New 4.2.1: …we suggest that patients with levels of intact PTH progressively rising or persistently above the upper normal limit for the assay should be evaluated … *(2C).*

- Old 4.2.1: In patients with CKD G3a–G5 not on dialysis…we suggest that patients with levels of intact PTH above the upper normal limit of the assay are first evaluated …(*2C*)…..

Ketteler et al. Kidney Int 2017 Jul;92(1):26-36

Rationale for Update

The Work Group felt that modest increases in PTH may represent an appropriate adaptive response to declining kidney function and have revised this statement to include "persistently" above the upper normal PTH level as well as "progressively rising" PTH levels, rather than "above the upper normal limit".

Although the optimal PTH is not known, the Work Group felt that rising PTH levels in CKD G3a-G5 warrant examination of modifiable factors:

- Vitamin D insufficiency/deficiency
- Hypocalcemia / Hyperphosphatemia
- High phosphate intake

Ketteler et al. Kidney Int 2017 Jul;92(1):26-36

Calcitriol and Vitamin D

New 4.2.2: In adult patients with CKD G3a-G5 not on dialysis, we suggest calcitriol and vitamin D analogs not be routinely used (2C).

Old 4.2.2: In patients with CKD G3a–G5 not on dialysis, in whom serum PTH is progressively rising and remains persistently above the upper limit of normal for the assay despite correction of modifiable factors, we suggest treatment with calcitriol or vitamin D analogs (*2C*).

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Rationale for Update

- Suppression of PTH via calcitriol and other vitamin D analogs have been the therapeutic mainstay for the treatment of secondary hyperparathyroidism

- Multiple RCTs cited in the 2009 Guideline reported benefits of these agents on improving biochemical endpoints, and adverse effects of hypercalcemia were also noted.

- Two trials, PRIMO and OPERA, demonstrated significantly increased risk of hypercalcemia in patients treated with paricalcitol, compared with placebo, in the absence of beneficial effects on surrogate cardiac endpoints.

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Maintaining/Lowering PTH

New 4.2.4: In patients with CKD G5D requiring PTH-lowering therapy, we suggest calcimimetics, calcitriol, or vitamin D analogs, or a combination of calcimimetics with calcitriol or vitamin D analogs *(2B).*

- Old 4.2.4: In patients with CKD G5D and elevated or rising PTH, we suggest calcitriol, or vitamin D analogs, or calcimimetics, or a combination of calcimimetics and calcitriol or vitamin D analogs

Ketteler et al. Kidney Int 2017 Jul;92(1):26-36

Rationale for Update

- Recommendation 4.2.4 originally had not been identified for an update. However, due to a subsequent series of secondary and *post-hoc* publications of the EVOLVE trial, the Work Group decided to re-evaluate it.
-
- Although EVOLVE did not meet its primary endpoint, the majority of the Work Group were reluctant to exclude potential benefits of calcimimetics for CKD G5D patients, based on subsequent prespecified analyses.

- No PTH-lowering treatment was prioritized at this time, since calcimimetics, calcitriol, and vitamin D analogs are all acceptable first-line options in CKD G5D patients.

Ketteler et al. Kidney Int 2017 Jul;92(1):26-36

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List of Abbreviations

- 25-hydroxyvitamin D (25OHD)
- AKI – acute kidney injury
- BA - *Brucella abortus*
- BMD bone mineral density
- Ca –calcium
- CKD – chronic kidney disease
- cFGF - C-terminal fibroblast growth factor
- CV – cardiovascular
- DXA dual-energy X-ray absorptiometry
- eGFR estimated glomerular filtration rate
- FGF fibroblast growth factor
- FRAX fracture risk assessment tool
- GI gastrointestinal
- HD - hemodialysis
- iFGF23 – intact fibroblast growth factor
- IL-**1β** - interleukin-**1β**
- iPTH intact parathyroid hormone
- KDIGO Kidney Disease: Improving Global Outcomes
- KDOQI Kidney Disease Outcomes Quality Initiative
- P - phosphate
- PTH parathyroid hormone
- RCT randomized controlled trial
- ROC receiver operating characteristic
- SD standard deviation
- SHPT secondary hyperparathyroidism
- VDR vitamin D receptor