The "Attraction" of Phosphate Binders in Chronic Kidney Disease

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NMSHP Fall 2014

Learning Objectives

- Pharmacist
  1. Describe the role of phosphate binders in chronic kidney disease related mineral and bone disorder.
  2. Compare and contrast the different classes of phosphate binders.
  3. Discuss major safety issues associated with each class of phosphate binders.
  4. Select an appropriate phosphate binder(s) for patients with chronic kidney disease.
- Pharmacy Technician
  1. Explain the indication for phosphate binders.
  2. Identify agents used for phosphate binding.
  3. Specify available phosphate binder dosage forms.

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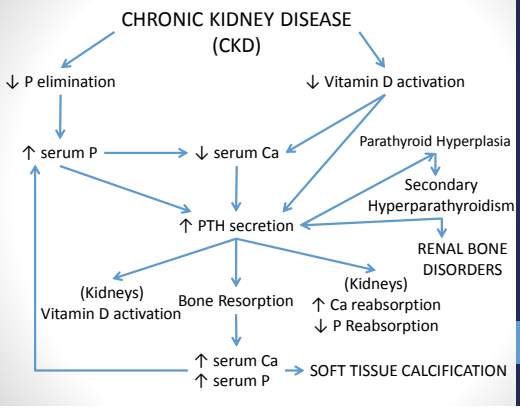

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Types of Renal Bone Disorders

- Osteitis fibrosis cystica
  - Excess PTH
  - Bone marrow fibrosis
- Osteomalacia
  - Defective mineralization
  - Vitamin D deficiency, (Al toxicity)
- Adynamic bone disease
  - Cause? Associated with lower levels of PTH
- Mixed uremic osteodystrophy

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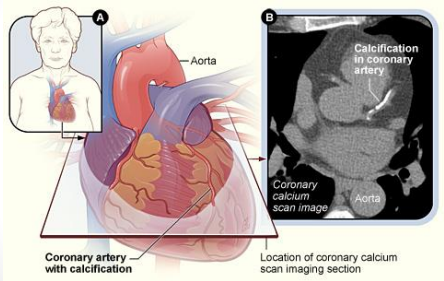
Coronary Calcification



http://www.daviddarling.info/encyclopedia/C/coronary_calcium_scan.html

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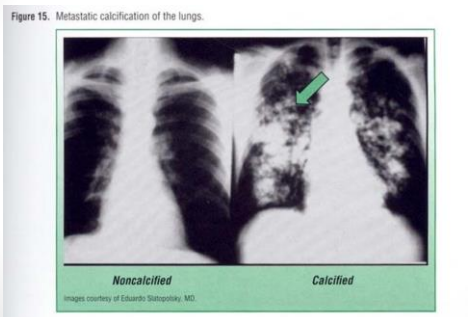
Soft Tissue Calcification



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Soft Tissue Calcification

Figure 18. Articular metastatic calcification; shoulder.

In an autopsy study of 56 patients who died while undergoing chronic dialysis and 18 nondialyzed patients with CRF, extraskeletal calcification was found in 79% of dialysis patients and 44% of nondialyzed patients.[4] Severe, generalized visceral lesions were present in 36% of dialysis patients and 11% of nondialyzed patients (Table 6). Severe calcification of the cardiac conduction system or myocardium was concluded to be the cause of death in 6 patients.

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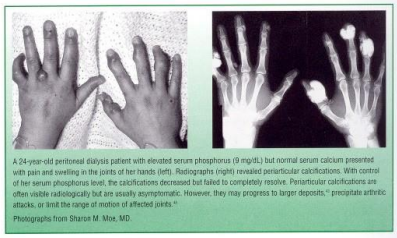
Soft Tissue Calcification

Periarticular Calcification and Generalized Calcification

Periarticular (Figures 17 and 18), ocular, and cutaneous calcification may likewise accompany kidney disease and contribute to patient morbidity, further decreasing patient mobility and quality of life.

Figure 17. Periarticular metastatic calcification; hand.



A 24-year-old peritoneal dialysis patient with elevated serum phosphorus (9 mg/dL) but normal serum calcium presented with pain and swelling in the joints of her hands (left). Radiographs (right) revealed periarticular calcifications. With control of her serum phosphorus level, the calcifications decreased but failed to completely resolve. Periarticular calcifications are often visible radiologically but are usually asymptomatic. However, they may progress to larger deposits,[1] precipitate arthritic attacks, or limit the range of motion of affected joints.[4]

Photographs from Sharon M. Moe, MD.

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Calciphylaxis

http://www.primehealthchannel.com/calciphylaxis.html

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Case 1 – T. S. 61 y.o. female

- PMH
  - DM Type 2
  - HTN
  - CKD
- Meds
  - Ramipril 5 mg PO daily
  - Ferrous fumarate 300 mg PO TID
  - Lantus 24 U SC daily
  - Humalog TIDcc
- PE
  - 1+ bilateral edema
- Labs
  - SCr 1.5 mg/dL
  - eGFR 33 mL/min/1.73m^2
  - Ca 9.2 mg/dL (8.4-10.4)
  - P 6.7 mg/dL (2.3-5.6)
  - iPTH 314 pg/mL (11-80)

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CKD Mineral and Bone Disorder Guidelines

- KDIGO (Kidney Disease Improving Global Outcomes)
  - http://kdigo.org/home/mineral-bone-disorder/
  - Kidney International 2009; 76 (Suppl 113): S1-S130.
- KDOQI (Kidney Disease Outcomes Quality Initiative)
  - http://www.kidney.org/professionals/KDOQI/guidelines_bone/index.htm
  - American Journal of Kidney Diseases 2003; 42(4) Suppl 3: S1-S201.

National Kidney Foundation®

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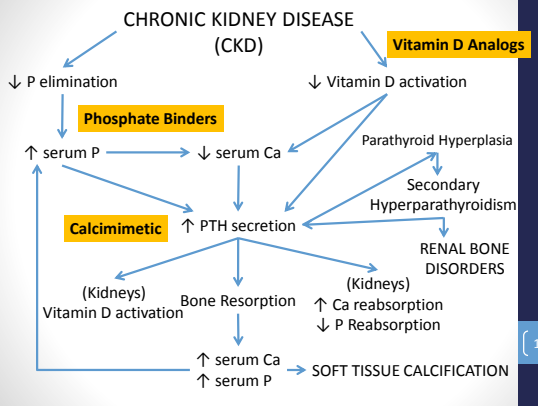

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Guideline Recommendations

Phosphorus	KDIGO	KDOQI
Stage 3 (GFR 30-59)	Normal serum P	2.7-4.6 mg/dL
Stage 4 (GFR 15-29)	Normal serum P	2.7-4.6 mg/dL
Stage 5ND (GFR <15)	Normal serum P	3.5-5.5 mg/dL
Stage 5D (PD/HD)	Lower towards normal serum P range	3.5-5.5 mg/dL

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Guideline Recommendations

Calcium	KDIGO	KDOQI
Stage 3 (GFR 30-59)	Normal serum Ca	Normal serum Ca
Stage 4 (GFR 15-29)	Normal serum Ca	Normal serum Ca
Stage 5ND (GFR <15)	Normal serum Ca	Normal serum Ca range, preferably lower end (8.4-9.5 mg/dL)
Stage 5D (PD/HD)	Normal serum Ca	Normal serum Ca range, preferably lower end (8.4-9.5 mg/dL)

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Dietary Phosphorus Restriction

- Beverages:
  - Ale
  - Beer
  - Cocoa
  - Dark colas
- Dairy products:
  - Cheese
  - Ice cream
  - Milk
  - Cream soups
  - Yogurt
- Protein:
  - Carp
  - Fish roe
  - Organ meets
  - Oysters
  - Sardines
- Dried beans & peas
- Others:
  - Bran cereals
  - Whole grain products
  - Nuts

www.kidney.org

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Phosphate Binders

	Rx	Formulations	Place in Therapy
Aluminum hydroxide	No	Liquid, tablet, capsule	Alternate
Calcium-based			Preferred
Ca acetate	Yes/no	Capsule, tablet	
Ca carbonate	No	Liquid, tablet, chewable, capsule	
Lanthanum carbonate	Yes	Chewable tablet	Alternate
Sevelamer			Preferred
Sevelamer HCl (Renagel)	Yes	Tablet	
Sevelamer carbonate (Renvela)	Yes	Tablet, powder	

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Biochemical Endpoints

Treat to Goal

(Prevalent HD)

	SVR (n=99)	Ca (n=101)	P-value
P	5.1±1.2	5.1±1.4	NS
Ca	9.5±0.6	9.7±0.7	<0.05
↑Ca	5%	16%	<0.05
iPTH	224	138	NS
↓iPTH	30%	57%	<0.05
TC	141±28	182±49	<0.05
LDL	65±21	103±43	<0.05
HDL	43±10	45±12	NS
Trig	137	150	NS

Chertow. Kidney Int 2002;62:245.

RIND

(Incident HD)

	SVR (n=54)	Ca (n=55)	P-value
P	5.2±0.9	5.1±0.8	NS
Ca	9.1±0.5	9.6±0.5	<0.05
iPTH	298±152	243±16	<0.05
TC	134±52	160±32	<0.05
LDL	60±34	81±26	<0.05
Trig	171±108	191±106	NS

Block. Kidney Int 2005;68:1815.

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Bone Histology Summary

- No major difference between calcium carbonate with lanthanum carbonate or sevelamer
- Changes in bone turnover were heterogenous
  - Some patients improved while others worsened
- Results influenced by baseline turnover rates

KDIGO. Kidney International 2009; 76 (Suppl 113): S1-S130.

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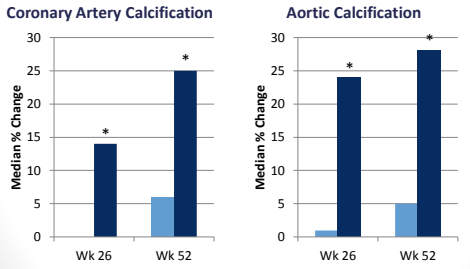
Treat to Goal

* P<0.05 Ca vs Sevelamer
* P<0.05 Ca vs Baseline

Sevelamer vs Calcium



Chertow. Kidney Int 2002;62:245-252.

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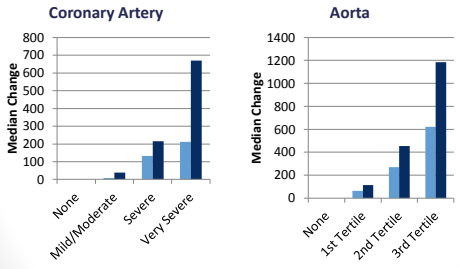
Treat to Goal

Sevelamer vs Calcium



Chertow. Kidney Int 2002;62:245-252.

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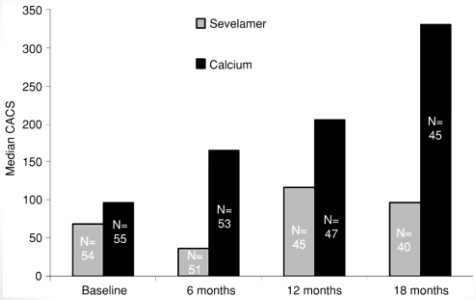
RIND



Block. Kidney Int 2005;68:1815-1824.

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RIND

- CAC = 0 at baseline, none progressed to CAC >30 by study end
- CAC >30 at baseline, progressive CAC increase (in sevelamer and Ca arm)
- Ca arm: more rapid and severe increase in CAC

	Baseline CAC = 0 (n=37)	Baseline CAC >0 (n=72)	
Mean age	45 ± 12 y	64 ± 11 y	P<0.0001

Block. Kidney Int 2005;68:1815-1824.

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RIND

- During parent study, subjects remained on their assigned phosphate binder (sevelamer vs calcium)
- After final scan, subjects given phosphate binders at discretion of primary nephrologist
- Median follow up = 44 months

Block. Kidney Int 2005;68:1815-1824.
Block. Kidney Int 2007;71:438-441.

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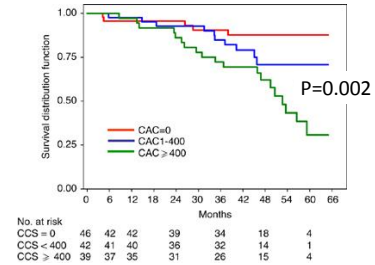
RIND Follow up



Adjusted (age, race, gender, diabetes)

Block. Kidney Int 2007;71:438-441.

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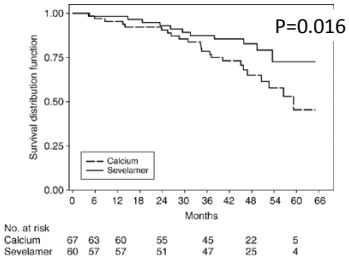
RIND Follow up



Adjusted (age, race, gender, DM, history artherosclerotic cardiovascular disease, CRP, albumin, Kt/V, baseline CAC)

Block. Kidney Int 2007;71:438-441.

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DCOR

- Prospective, multi-center, randomized, open-labeled, parallel design
- Adult HD (>3 mo)
- Required phosphate binder
- Medicare = primary insurance
- Powered to detect all-cause mortality

Suki. Kidney Int 2007;72:1130-7.

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DCOR

	Sevelamer (n=99)	Calcium (n=101)	P-value
P	5.8±1.3	5.7±1.3	<0.01
Ca	9.2±0.7	9.5±0.7	<0.0001
iPTH, median	278 (200,476)	226 (142,387)	<0.0001
TC	146±34	161±35	<0.0001
LDL	69±26	85±31	<0.0001
HDL	45±15	44±16	NS

Suki. Kidney Int 2007;72:1130-7.

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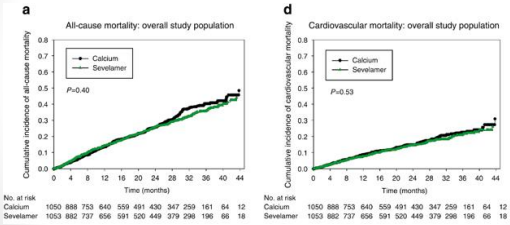
DCOR

All-cause Mortality
P=0.40

Cardiovascular Mortality
P=0.53



Calcium = black line
Sevelamer = green line

Suki. Kidney Int 2007;72:1130-7.

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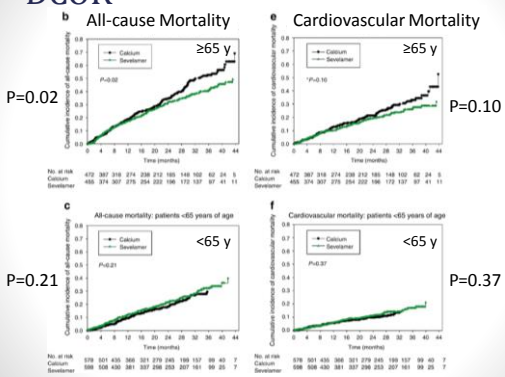
DCOR

Suki. Kidney Int 2007;72:1130-7.



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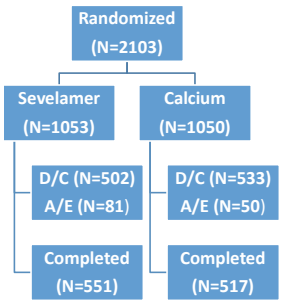
DCOR Patient disposition



Suki. Kidney Int 2007;72:1130-7.

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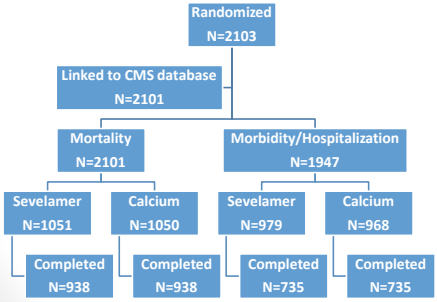
DCOR Secondary Analysis CMS Data



St. Peter. Am J Kidney Dis 2008;51:445-54.

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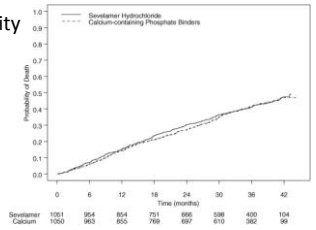
DCOR Secondary Analysis

- All-cause mortality



- Cardiovascular mortality = NS

St. Peter. Am J Kidney Dis 2008;51:445-54.

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DCOR Secondary Analysis

	Sevelamer (N=979)	Calcium (N=968)	95% CI	P
First Hospitalization				
Unadjusted RR	0.98	Reference	0.89-1.08	0.7
Adjusted RR	0.99	Reference	0.90-1.09	0.9
Multiple hospitalizations				
Unadjusted RR	0.90	Reference	0.82-0.99	0.03
Adjusted RR	0.89	Reference	0.82-0.98	0.02
Hospital days				
Unadjusted RR	0.88	Reference	0.78-1.00	0.05
Adjusted RR	0.88	Reference	0.78-0.99	0.03

Adjusted (age, race, sex, dialysis vintage, DM, comorbid cardiovascular conditions)

St. Peter. Am J Kidney Dis 2008;51:445-54.

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CARE-2

- Multicenter, randomized, controlled, open-label, non-inferiority trial
- Assess calcification progression in HD patients treated with calcium-containing vs calcium-free phosphate binders when LDL-C was decreased to <70 mg/dL.
  - P >5.5 mg/dL
  - LDL >80 mg/dL
  - CAC scores 30 to 7000 Units at baseline
- Ca acetate n=103; sevelamer n=100
  - P goal 3.5 to 5.5
  - Atorvastatin added to achieve LDL <70 mg/dL in both groups

Qunibi. Am J Kidney Dis 2008;51:952-65.

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CARE-2

	Sevelamer (n=70)	Calcium (n=59)	P-value
P	5.4±1.8	5.0±1.6	NSD
Ca	9.0±0.7	9.4±0.7	<0.05
iPTH	434±359	316±212	<0.05
TC	126±30.6	134±32.3	<0.05
LDL	62.4±23.0	68.8±22.3	NS
HDL	38.8±11.3	36.4±8.7	NS
Trig	149±69.8	157±124	NS

Qunibi. Am J Kidney Dis 2008;51:952-65.

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CARE-2 CAC Scores

	Sevelamer	Calcium Acetate	P-value
Baseline CAC	969±1,386	1,098±1,440	NS
6 mo CAC	996±1,419	1,197±1,413	NS
6 mo absolute increase	97±211 (p<0.0001)	109±374 (p<0.0001)	NS
6 mo % increase	24±39	71±365	NS
12 mo CAC	1,116±1,569	1,297±1,487	NS
12 mo absolute increase	227±485 (p<0.0001)	228±355 (p<0.0001)	NS
12 mo % increase	57±86	52±92	NS

Qunibi. Am J Kidney Dis 2008;51:952-65.

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Lanthanum Carbonate

- Effectively lowers serum phosphorous and iPTH
- Does not increase serum Ca
- Adverse effect rates comparable to other phosphate binders
- Accumulation in blood and bone below toxic levels
  - Studies were short in duration, most ≤ 1y

Zhang. BMC Nephrology 2013;14:226.

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Aluminum Hydroxide

- Al adverse effects:
  - Central nervous system toxicity (Dialysis Dementia)
  - Osteomalacia
  - Microcytic anemia
- Citrate increases intestinal Al absorption
- KDIGO Guidelines: Avoid long-term use
- KDOQI: May be used as short-term therapy (4 wk) in patients with serum P >7 mg/dL
- Safe quantity of Al phosphate binder unknown

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Phosphate Binders

	Rx	Cost	Comments
Aluminum hydroxide	No	$10/500 mL	Al content varies 100 to >200 mg (per tablet)
Calcium-based			KDOQI recommends not to exceed 2000 mg/day elemental Ca
Ca acetate	Yes/no	$100/100 tablets Medicaid formulary	25% elemental Ca
Ca carbonate	No	$10/100 tablets	40% elemental Ca
Lanthanum carbonate	Yes	$990/100 tablets	
Sevelamer			
Sevelamer HCl (Renagel)	Yes	$530/100 tablets Medicaid formulary	↓ Ciprofloxacin absorption ~50%
Sevelamer carbonate (Renvela)	Yes	$430/100 tablets $14/powder packet	

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Pipeline – Resin

- Colestilan (MCI-196)
  - Anion exchange resin
  - Locatelli. Nephrol Dial Transplant 2014;29(5):1061-73.
    - Effective phosphate and cholesterol lowering

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Pipeline – Iron based

- Sucroferric oxyhydroxide (PA21)
  - Floege. Kidney Int 2014-86(3):638-47.
    - Equivalent phosphate control with 3 pills/day compared to 8 of sevelamer
- Ferric Citrate (JTT-751)
  - Lewis. J Am Soc Nephrol 2014. [Epub ahead of print]
    - Effective phosphate binding
    - Increased iron stores, decreased IV iron and erythropoietin administration

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Case 1 – T. S. 61 y.o. female

- PMH
  - DM Type 2
  - HTN
  - CKD
- Meds
  - Ramipril 5 mg PO daily
  - Ferrous fumarate 300 mg PO TID
  - Lantus 24 U SC daily
  - Humalog TIDcc
- PE
  - 1+ bilateral edema
- Labs
  - SCr 1.5 mg/dL
  - eGFR 33 mL/min/1.73m^2
  - Ca 9.2 mg/dL (8.4-10.4)
  - P 6.7 mg/dL (2.3-5.6)
  - iPTH 314 pg/mL (11-80)

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Case 2 – QQ 54 y.o. female

- Receives hemodialysis MWF
- Medications:
  - $CaCO_3$ 1250 mg PO TIDcc & snacks
  - Epoetin alpha 4000 U with HD
  - Iron sucrose 100 mg IV q week
  - Renal vitamin PO daily

Time	iPTH	Serum Ca	Serum P	Serum albumin
3 mo ago	890	8.5	6.5	
2 mo ago	744	8.6	6.8	
Last month	789	8.5	7.2	
Today	943	8.9	6.9	2

- What is the **most** appropriate change to recommend?
  - A. Increase $CaCO_3$ to 2.5 g TIDcc & snacks
  - B. D/C $CaCO_3$, start Ca acetate 667 mg TIDcc & snacks
  - C. D/C $CaCO_3$, start $AlOH_3$ 320 mg TIDcc & snacks
  - D. D/C $CaCO_3$, start sevelamer carbonate 800 mg TIDcc & snacks

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