In The Name of God

Treatment of Bone Mineral Disorders in CKD-ESRD

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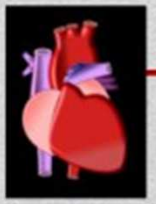
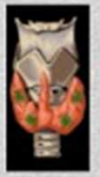
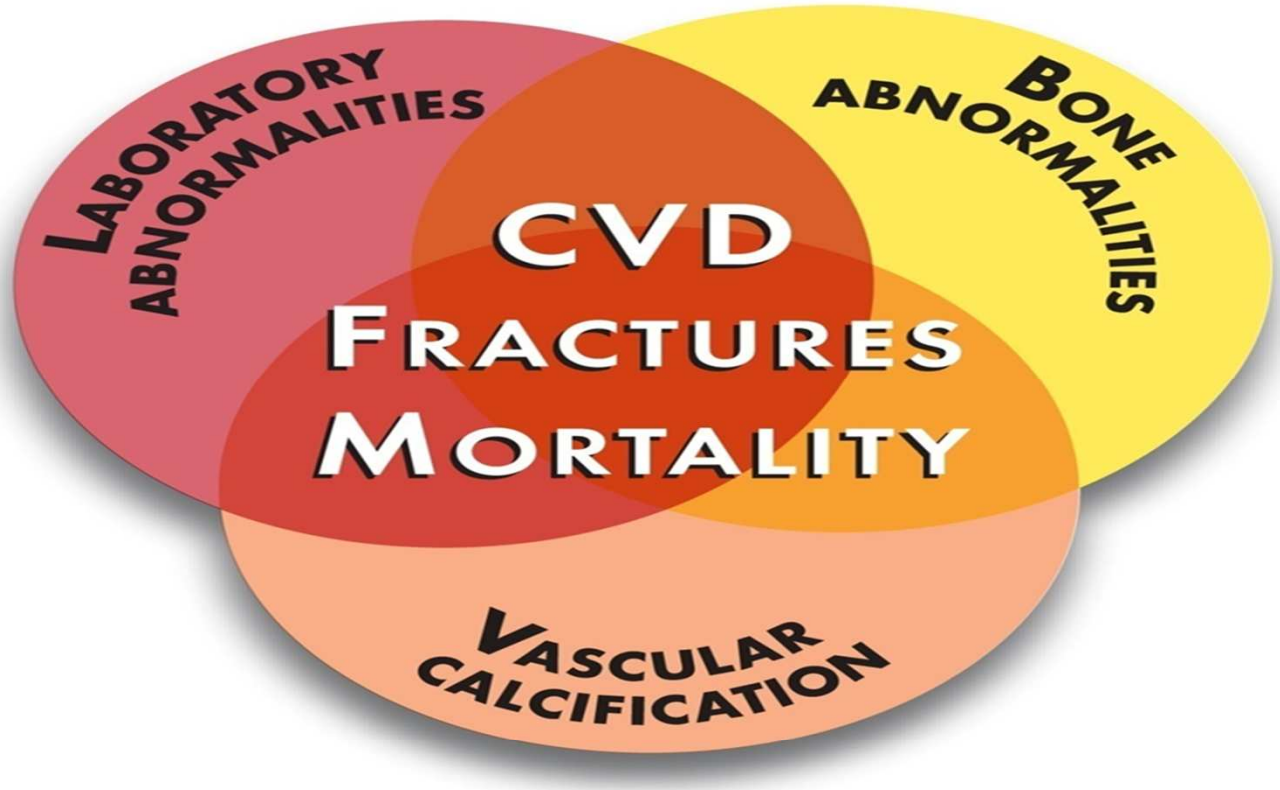
IUMS

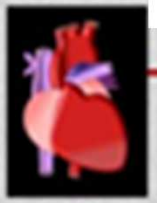


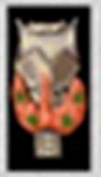


Chronic Kidney Disease—Mineral and Bone Disorder

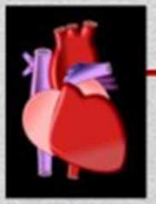


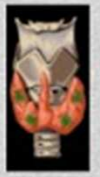
CKD-MBD



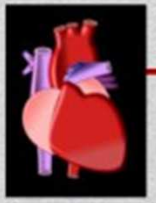


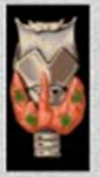
- The treatment of patients with CKD-MBD varies depending upon the prevailing metabolic abnormality, the characteristic bone disease, and the severity of underlying kidney dysfunction.





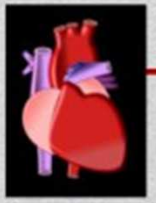
- The optimal approach for preventing and/or treating **mineral metabolism abnormalities** in predialysis patients with stage 3, 4, and 5 CKD due in part to a paucity of evidence related to therapy is unclear.
- The current management of mineral bone disease in these patients is based on the concept that patients are in positive phosphate balance, have a low circulating level of 1,25(OH)2D as well as low 25(OH)D (due to chronic illness), and have increased PTH prior to demonstrable hyperphosphatemia or hypocalcemia.

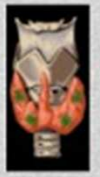




Initial treatment principally involves the administration of some combination of the following:

- Dietary phosphate restriction
- Phosphate binders (either calcium- or non-calcium-containing binders)



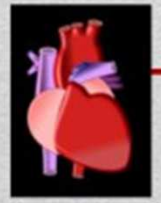


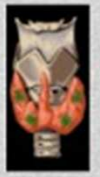
Dietary restriction

- Among predialysis patients with PTH or serum phosphate levels greater than target levels, it is suggested to restrict dietary phosphate intake to 900 mg/day.

- In dialysis patients with serum P> 4.5 mg/dL, the daily dietary P intake should be limited to < 800 mg

- P contained in vegetable-based foods, such as nuts, exhibits a low GI absorption rate (bioavailability, 20–40%), while P contained in animal-based foods, such as yogurt, demonstrates a high GI absorption rate (bioavailability, 40–60%). In particular, the bioavailability of inorganic P included as an additive and preservative in carbonated beverages reaches **80–100%**.



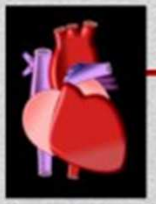


- In general, the dietary P content is proportional to protein intake, as shown in the equation below

Dietary P (mg)= 78+11.8 × protein intake(g)

Thus, it is possible that restrictions on the dietary P intake can, in turn, lead to protein deficiency

- To achieve the goal of limiting P intake while maintaining the protein intake , it is recommended that patients select diets with a low phosphorus–protein (P-P) ratio.



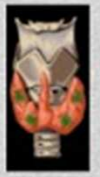
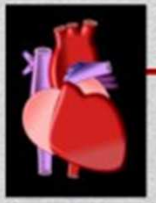
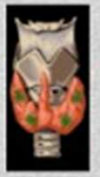


Table. Phosphorus and protein content of selected foods

Food	Common measure (g)	Phosphorus content (mg)	Protein content (g)	Phosphorus (mg) / protein (g) ratio
Chicken, leg, meat only, fried or fired	60	115.8	17.0	4.1
Chicken, breast, meat only, fried	60	148.8	20.0	4.5
Pork, ribs, roasted	60	135.6	14.0	5.8
Pork, belly	60	79.2	10.3	4.6
Beef, Korean cattle, loin	60	99.0	12.6	4.7
Beef, imported cattle, brisket, braised	60	112.2	14.0	4.8
Mackerel, broiled	60	144.0	14.5	6.0
Spanish mackerel, broiled	60	156.0	14.2	6.6
Chum salmon, smoked	60	141.0	13.8	6.1
Chicken's egg, broiled	60	123.6	7.3	10.2
Soybean curd, pressed	80	72.0	6.7	8.6
Potatoes, steamed	100	35.0	1.9	18.4
Sweet potatoes, steamed	100	40.0	1.1	36.4
Chestnuts, raw	60	40.8	1.9	12.8
Peanuts, dried	10	39.8	2.5	1.6
Milk, ordinary liquid milk	200	178.0	6.4	55.6
Yogurt, liquid type	150	93.0	2.3	62.0

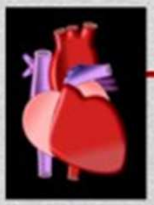
Adapted with permission from the Nutritious Food Table, 8th Revision, 2011, National Academy of Agricultural Science.

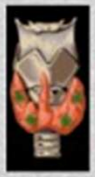




•Thus, Dietary phosphorus should be derived from sources of high biologic value, such as meats and eggs. Phosphorus from food additives should also be estimated and restricted.

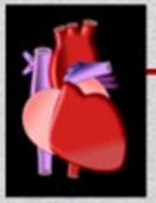
- In cases of cooking foods with a high P content, boiling the food is helpful for lowering its P content.

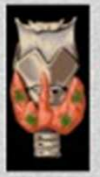




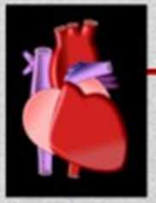
- A decrease in serum PTH levels plus improvements in bone histology with dietary phosphate restriction among patients with mild CKD was noted.

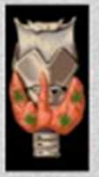
- However, hyperparathyroidism and hyperphosphatemia are unlikely to be prevented by dietary phosphorus restriction alone in the setting of progressive renal insufficiency.





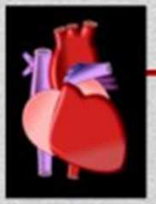
- Thus, Among predialysis patients with serum phosphate levels greater than target levels despite dietary phosphorus restriction after two to four months, recommended administration of phosphate binders(calcium- OR non-calcium-based).

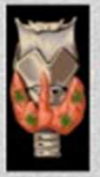




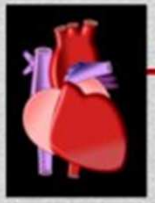
P removal through dialysis

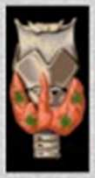
- The amount of P removed by conventional HD (3 times/wk, 4 h/session) is approximately 2.3–2.6 g/wk, and the amount of P removed by PD (4 times/d, 2-L exchanges) is 2.0–2.2 g per week
- nocturnal HD (8 hours/day) is performed, the removal of P can increase to 4.5–4.9 g
- Thus, if the daily dietary P intake is assumed to be 800 mg, the amount of P removed through weekly conventional dialysis is only half of the dietary intake. Thus, the administration of phosphate binders would be inevitable for controlling the serum P concentration in dialysis patients



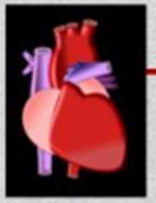


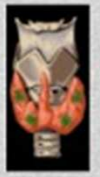
- **calcium-containing phosphate binders** for patients who are hypocalcemic and, because of their lower cost compared with non-calcium-containing phosphate binders, in many patients who are normocalcemic, particularly if they are not also being treated with active vitamin D or vitamin D analogs, with careful monitoring of calcium and phosphorous concentration.

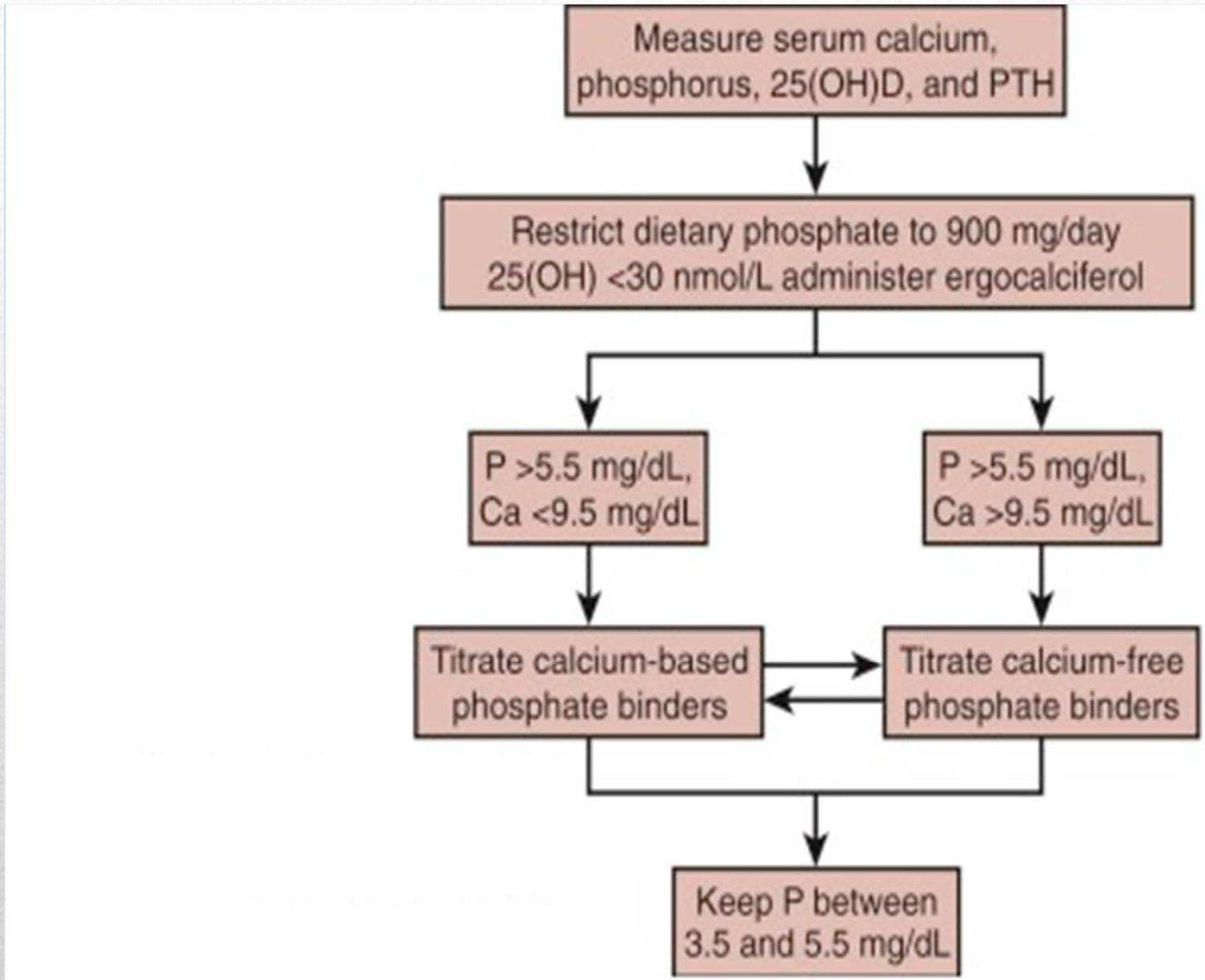




- **Non-calcium-containing phosphate binders** are used for hypercalcemic patients and are appropriate also in normocalcemic CKD patients, particularly if they are also receiving active vitamin D or vitamin D analogs



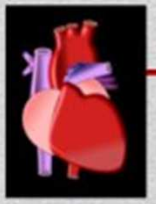


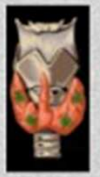

Measure serum calcium, phosphorus, 25(OH)D, and PTH
Restrict dietary phosphate to 900 mg/day
25(OH) <30 nmol/L administer ergocalciferol
P >5.5 mg/dL, Ca <9.5 mg/dL
P >5.5 mg/dL, Ca >9.5 mg/dL
Titrate calcium-based phosphate binders
Titrate calcium-free phosphate binders
Keep P between 3.5 and 5.5 mg/dL

Phosphate binders

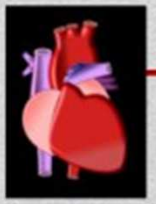
Dosing and administration

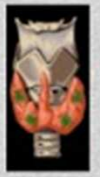
- For all phosphate buffers, the lowest dose that is effective should be used with meals.
- If calcium-containing buffers are selected, the amount of elemental calcium contained in the phosphate binder should not exceed 1500 mg per day.





Effects on Serum Biochemistries							
Agent	Target	PTH	FGF-23	Calcium	Phosphorus	Cost	Risk
Calcium-based binders		↓	⇩	↑	↓		
Calcium carbonate		↓	⇩	↑	↓	Lowest	Hypercalcemia
Calcium acetate						Low	Vascular calcifications
Calcium-free binders							
Sevelamer HCl	Intestinal	↔	⇩	↔	↓	High	Acidosis
	Phosphate						GI intolerance
Sevelamer carbonate	Absorption	↔	⇩	↔	↓	High	GI intolerance
Lanthanum carbonate		↔	⇩	↔	↓	High	Lanthanum retention *
Aluminum hydroxide		↔	⇩	↔	↓	Low	Aluminum retention
Aluminum carbonate							
Vitamin D sterols †	VDR	↓	↑	↑	↑	High	Hypercalcemia
Cinacalcet HCl	CaSR	↓	↓	↓	⇩	Highest	Hypocalcemia
							Nausea/vomiting

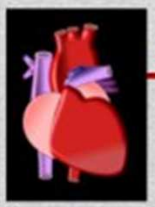


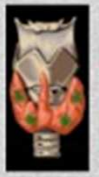


	Effective	Pill burden	Pleiotropic effects	Accumu-lation	Cost
Aluminum	yes	low	none	yes	low
Calcium-Ac/Carb	yes	high	none	yes	low
Sevelamer	yes	high	yes	no	high
Lanthanum	yes	low	none	some	high
Ca-Mg	yes	high	none	some	low
~~Colestilan~~	yes	high	yes	no	high
Fe-Citrate	yes	high	none	yes	high
Fe-Oxyhydroxide	yes	low	none	no	high

Vitamin D, calcitriol, and vitamin D analogs

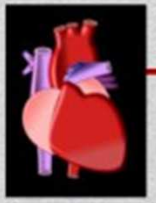
- Vitamin D includes both vitamin D2 (ergocalciferol) and vitamin D3 (cholecalciferol). Vitamin D derivatives include the naturally occurring vitamin D metabolite, calcitriol (1,25-dihydroxycholecalciferol [1,25(OH)2D]), and synthetic vitamin D analogs, such as doxercalciferol, paricalcitol, alfacalcidol, falecalcitriol, and 22-oxacalcitriol (or maxacalcitol
- Vitamin D deficiency — 25(OH)D deficiency (level<30ng/ml) is a common finding in patients with CKD, is associated with elevated PTH levels

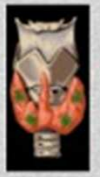




Recommended Supplementation for Vitamin D Deficiency/Insufficiency in Patients with CKD Stages 3 and4

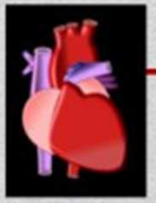
Serum 25(OH)D (ng/mL)[nmol/L]	Definition	Ergocaiciferol Dose (Vitamin D_2)	Duration (months)	Comment
<5	Severe vitamin D deficiency	50000 IU/wk orally x 12 wks; then monthly	6 months	Measure 25(OH)D Levels after 6 months
		500000 IU as single I.M. dose		Assure patient adherence; measure 25(OH)D at 6 months
5-15	Mild vitamin D deficiency	50000 IU/wk x 4 weeks, then 50000 IU/month orally	6 months	Measure 25(OH)D Levels after 6 months
16-30	vitamin D insufficiency	50000 IU/month orally	6 months	

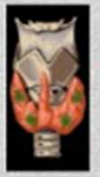




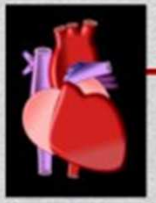
Calcitriol and synthetic vitamin D analogs

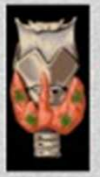
- The administration of calcitriol or synthetic vitamin D analogs in predialysis patients is not routine.
- Among patients with stage 3 to 5 CKD not yet on dialysis, the administration of such agents is suggested if correction of nutritional vitamin D deficiency, administration of calcium supplementation, and control of serum phosphate with diet and binders over a six month period are ineffective in suppressing PTH levels.



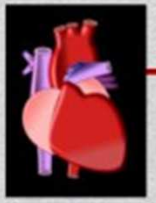


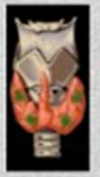
- Treatment with either calcitriol or a synthetic vitamin D analog should not be given to predialysis patients with stage 3 to 5 CKD unless the serum phosphate is in the normal range and the corrected serum total calcium concentration is <9.5 mg/dL
- In addition serum calcium and phosphate being measured at least every three months.



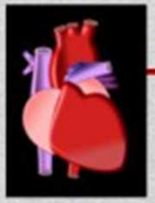


- If the serum level of corrected total calcium exceeds 10.2 mg/dL (2.54 mmol/L), ergocalciferol therapy and all forms of vitamin D therapy should be discontinued
- Vitamin D therapy should also be discontinued if intact PTH levels become persistently low.



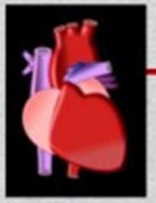


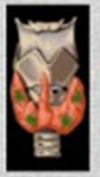
- In dialysis patients If PTH levels remain >300 pg/mL despite optimal treatment of hyperphosphatemia and hypocalcemia, further therapy for hyperparathyroidism is indicated.
- If the calcium level is near or below the lower limit of normal (calcium <9.5 mg/dL) and the phosphate is well within the normal range(Phosphorus <5.5 mg/dL), administration of calcitriol or a synthetic vitamin D analog is suggested.



- Controversies exist regarding the route (oral versus IV), the dose and frequency (intermittent higher "pulse" therapy versus lower daily therapy), and the timing of calcitriol initiation in patients with CKD.

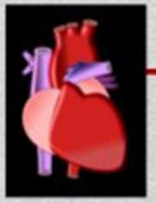
- There are no compelling data to use intravenous (IV) versus oral therapy, or to use calcitriol versus a synthetic analog. Cost and patient compliance are two considerations

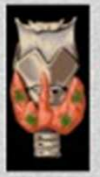




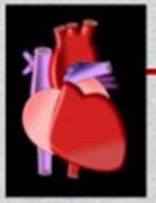
Calcimimetics

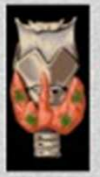
Among predialysis patients with secondary hyperparathyroidism that is refractory to therapy with vitamin D derivatives (such as calcitriol or synthetic vitamin D analogs), calcium supplements, and phosphate binders, cinacalcet may be useful. However, the use of cinacalcet in the early stages of CKD is highly controversial. Some experts and the KDIGO working group recommend not giving cinacalcet.





- If cinacalcet is administered, however, laboratory values should be monitored closely (weekly after starting therapy or after a change in dose) because of the risk of hypocalcemia and elevations of serum phosphate (predialysis patients).
- The initial dose of 30 mg/day should be cautiously titrated upwards every two weeks only if the serum calcium level is >8.4 mg/dL and PTH is higher than the target range.



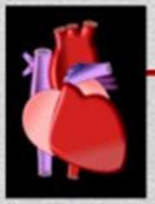


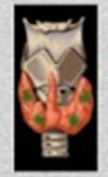
In dialysis patients If PTH levels remain >300 pg/mL despite optimal treatment of hyperphosphatemia and hypocalcemia, cinacalcet for hyperparathyroidism is indicated:

- Phosphorus >5.5 mg/dL and calcium >8.4 mg/dL
- Phosphorus <5.5 mg/dL and calcium >9.5 mg/dL

if the serum calcium level is <8.4 mg/dL, cinacalcet should not be initiated

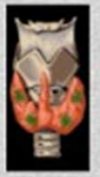
Dose — Cinacalcet is initiated at a dose of 30 mg/day, with stepwise increments to 60, 90, and 180 mg/day. The dose can be increased every four weeks until goals are achieved.





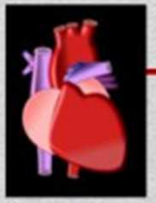
- The final step is to adjust the doses of phosphate binders, calcitriol/synthetic vitamin D analogs, and cinacalcet to attempt to attain target values.
- Among patients with inadequate reduction of PTH with initial therapies, serum phosphorus <5.5 mg/dL, and serum calcium <9.5 mg/dL, adding calcitriol or a synthetic vitamin D analog is suggested to patients who are already receiving cinacalcet.
- Among patients with inadequate reduction of PTH with initial therapies and serum calcium >8.4 mg/dL, is suggested adding cinacalcet to patients who are already receiving calcitriol or a synthetic vitamin D analog.

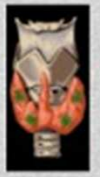




Dose

The optimal dose of calcitriol or synthetic vitamin D analogs has not been established and depends upon the concurrent use of calcimimetics, the dose of concomitant calcium-based phosphate binders, and the potency/selectivity of the vitamin D analog. Th ceurrent approach has been empiric, with the goal of administering increasing doses of calcitriol or synthetic vitamin D analogs, along with phosphate binders, to achieve a plasma iPTH level between 150 and 300 pg/mL



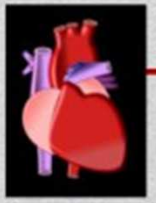


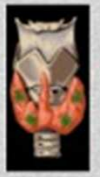
Comparative "physiologic" doses for calcitriol and synthetic vitamin D analogs in the setting of calcimimetic use are:

- Calcitriol 0.5 mcg/dialysis session
- Paricalcitol 2 mcg/dialysis session

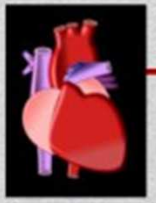
Treatment algorithms that titrate calcitriol or synthetic vitamin D analogs to reduce PTH lead to higher doses of these agents. Typical doses of currently used agents in such settings are:

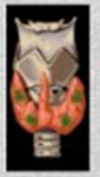
- Calcitriol 1.5 mcg/dialysis session
- Paricalcitol 6 mcg/dialysis session





- The maximal tolerated dose of intermittent calcitriol is usually approximately 7 to 8 mcg/week .
- With the availability of cinacalcet HCl to suppress PTH, it is advisable to not exceed the physiologic replacement doses of active vitamin D analogs
- This "high-dose" vitamin D strategy has been challenged with the advent of calcimimetics
- Dose adjustments typically occur at four- to eight-week intervals as the plasma calcium concentration rises



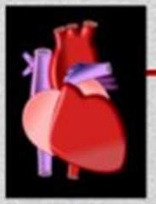


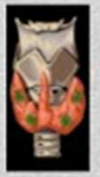
Treatment Failure

Treatment failures include:

1. dialysis patients with tertiary hyperparathyroidism, which is defined as elevated PTH levels and spontaneous hypercalcemia or

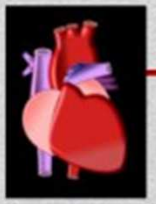
2. patients with persistent and progressive elevations of serum PTH that cannot be lowered to levels <300 pg/mL despite treatment with vitamin D analogs and cinacalcet (180 mg/day).

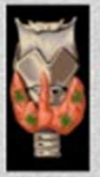




- ESRD patients who have markedly elevated, medical therapy-refractory PTH levels and related signs and symptoms are generally referred for

parathyroidectomy






Thank You