Ruth
Ruth Rappaport Children's Hospital
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Cinacalcet in pediatric CKD secondary hyperparathyroidism

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בן 7 שנים עם אי"ס כליות

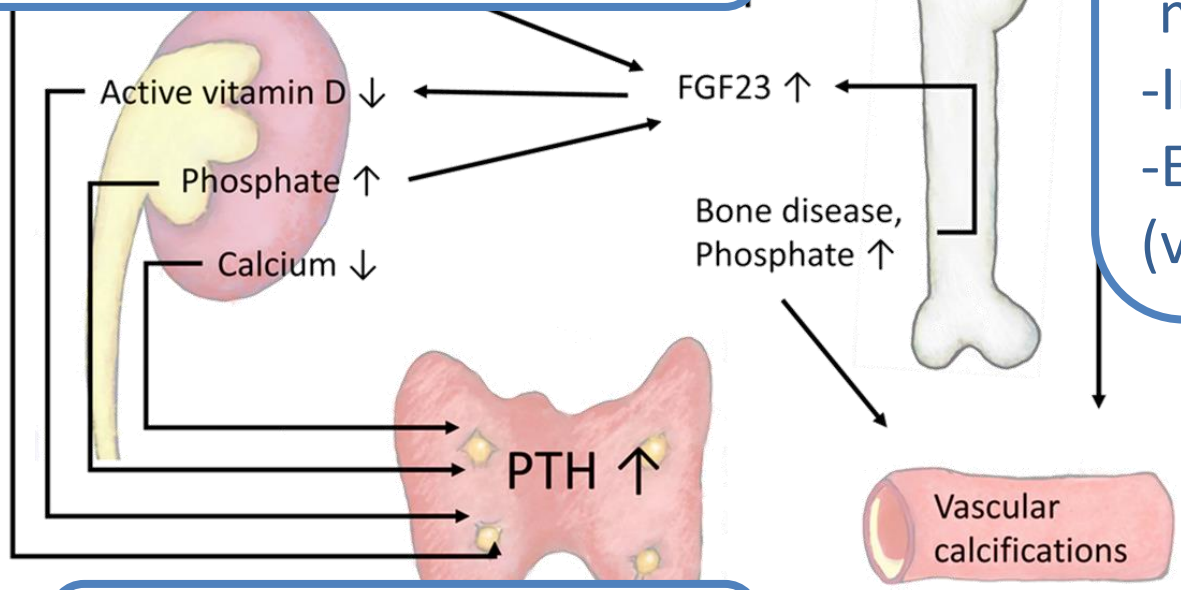
- ברקע כליות דיספלסטיות
- דיאליזה צפקית כרונית
- היפרפאראתירואידזם ומחלת עצם קשה
- למרות טיפול בסידן, ויטמין D, ויט.D פעיל וסופחי זרחן - רמת PTH 2900ng/l (נורמה15-65)
- במעבדה: סידן 9.4מג%, זרחן 6מג%, ויט. D תקין

- **האם לתת סינקלצט?**
- **קריטריונים לטיפול?**
- **מינון?**
- **מעקב?**

- החל טיפול
- כעבור חודש: PTH בירידה, היפוקלצמיה
- **איך להמשיך?**

Secondary hyperparathyroidism - a compensatory complication of ESRD

Disturbances in serum Ca, P, vit. D



High PTH & parathyroid hyperplasia

Major manifestations:
-Abnormal bone & mineral metabolism
-Impaired linear growth
-Ectopic calcifications (vascular, soft tissue)

Almquist et al. *2020;27(1)*

Secondary hyperparathyroidism – Treatment goals in children

- Improve control of PTH concentrations
- Maintain normal serum Ca and P levels
- Improve growth velocity and final adult height
- Prevent complications

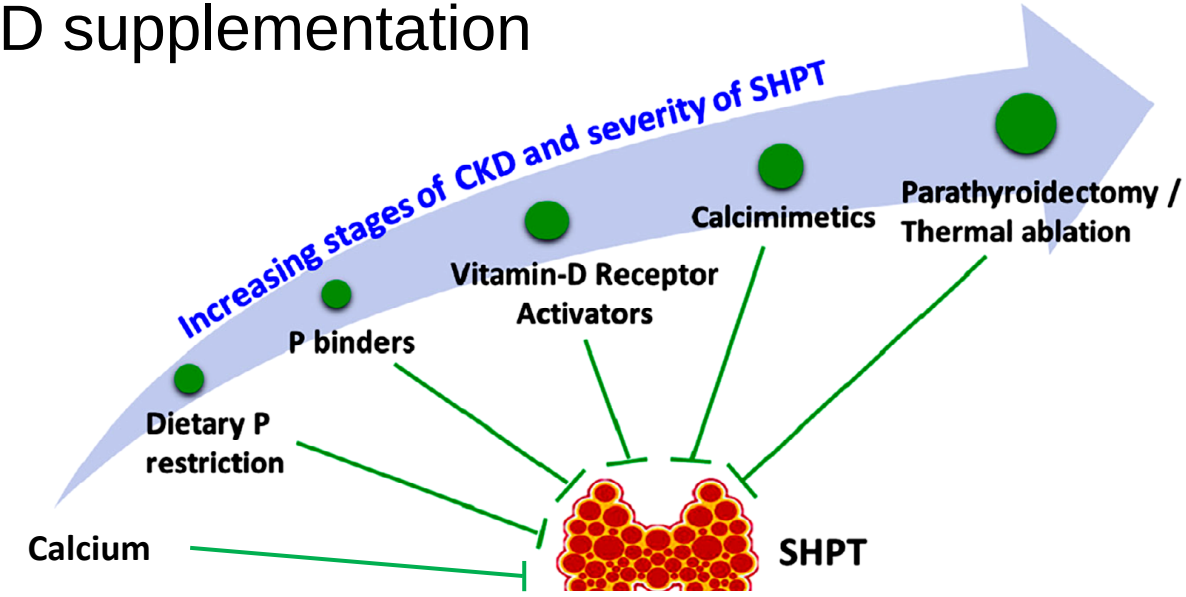
****no consensus regarding target PTH levels (normal, 2-3 times normal)**

Secondary hyperparathyroidism – therapeutic approaches

<u>Traditional therapies</u>:
Calcium: nutritional & supplements
Phosphate: intake control, P binders, intensification of dialysis

Vit. D & active vit. D supplementation

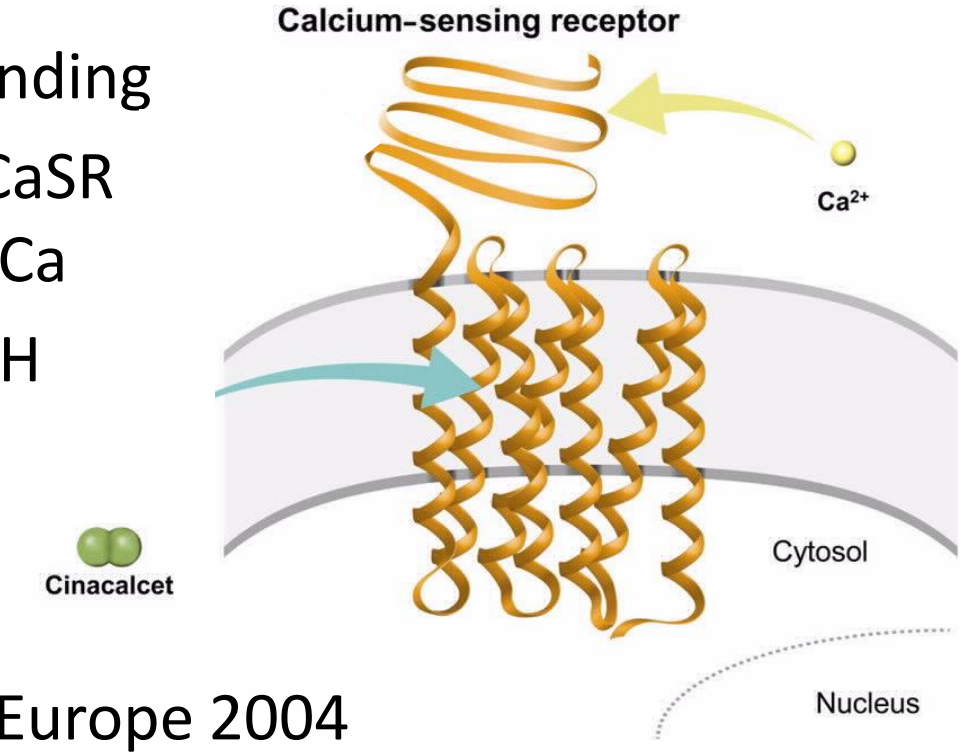
<u>Calcimimetics</u>:
activate the calcium-sensing receptor



Tsai et al. Clinical Medicine 24 (2024)

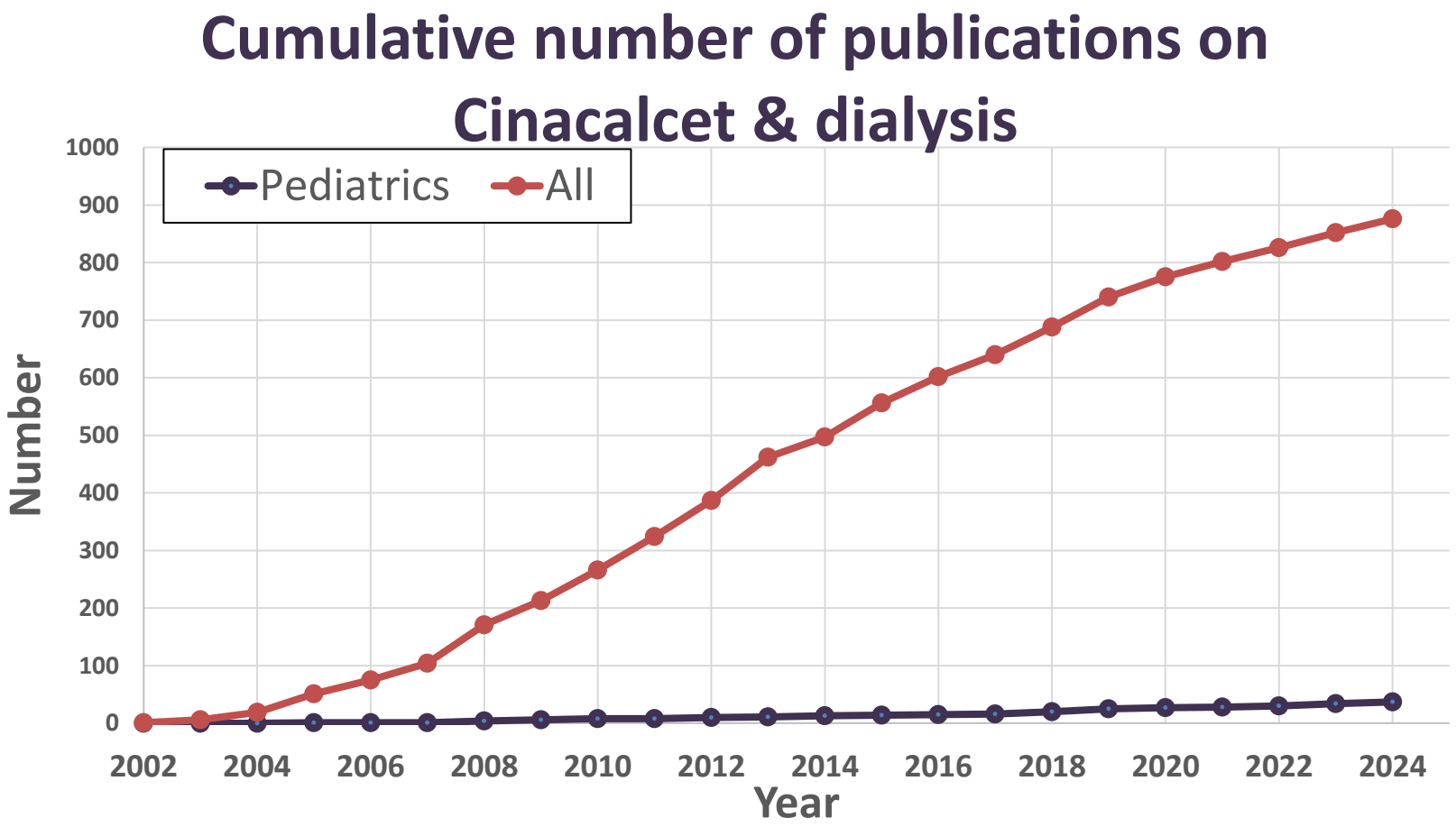
Cinacalcet - a calcimimetic

- An allosteric activator of the CaSR
- Transmembrane domain binding
- Enhances the parathyroid CaSR sensitivity for extracellular Ca
- Leads to reduced serum PTH



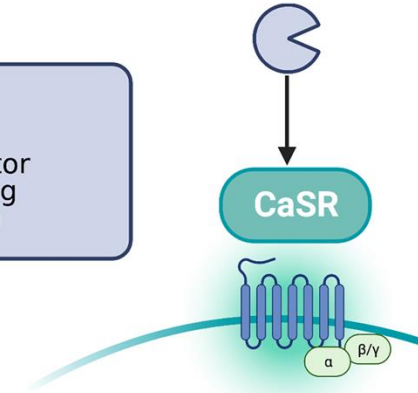
- Approved in adults: US and Europe 2004
- Approved in children aged >3yrs: Europe 2017

What is known?

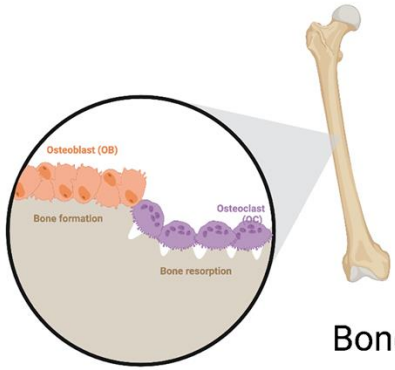


Potential beneficial effects of Cinacalcet

Cinacalcet
First generation
Positive allosteric CaSR modulator
Transmembrane domain binding
Once daily oral administration



Simultaneously reduces PTH **and** serum Ca & P
Different from vit. D analogs
→ stimulate Ca & P GI absorption



Bone

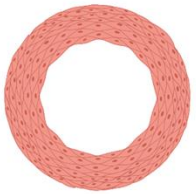
↓

Improvement of bone remodeling
↑osteoblast activity
↓osteoclast differentiation
↓resorptive activity

Parathyroid

↓

↓parathyroid hyperplasia
↓ PTH level
↓ Calcium and Phosphate levels



Vessel

↓

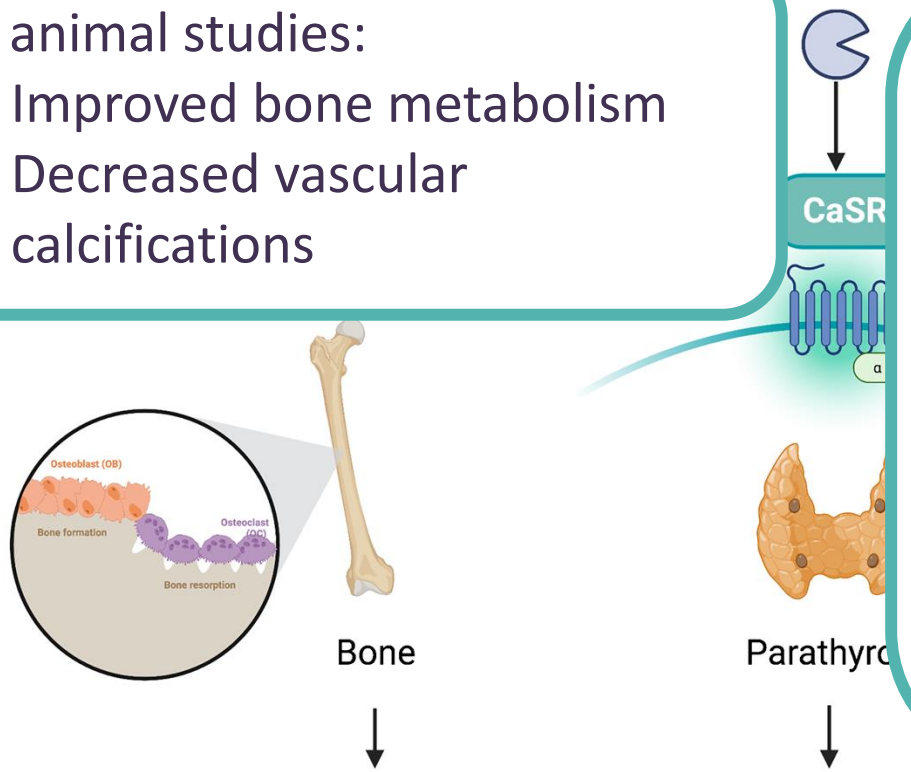
Modest effect on progression of vascular calcification
↓ serum calcification propensity
↓ serum calciprotein particles levels

Current Osteoporosis Reports (2023) 21

Potential beneficial effects of Cinacalcet

In animal studies:

- Improved bone metabolism
- Decreased vascular calcifications



In adults:

- Effective & safe suppressing PTH
- Some evidence for reduction in cardiovascular events and aortic calcifications
- No clear effect on: fractures, bone turnover markers, all-cause mortality

Improvement of bone remodeling
↑osteoblast activity
↓osteoclast differentiation
↓resorptive activity

↓parathyroid hyperplasia
↓ PTH level
↓ Calcium and Phosphate levels

Modest effect on progression of vascular calcification
↓ serum calcification propensity
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Current Osteoporosis Reports (2023) 21

Cinacalcet in pediatric ESRD – mostly data regarding PTH and safety

- Effect on PTH varied: PTH reduced by ≥ 30% in 22-100% patients
- Ca and P mostly slight decrease within normal

- Little data regarding:
  - Bone metabolism, fractures
  - Linear growth
  - Cardiovascular events

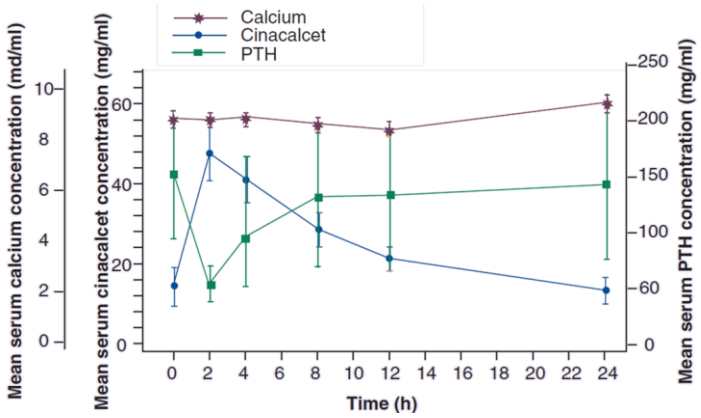
Limited by:

- Multiple sources, not directly comparable
- Variable doses
- Variable duration
- Variable ages
- Small numbers
- A period of FDA hold d/t fatality

PTH & Calcium after cinacalcet treatment

Following a single-dose of cinacalcet:

- **Calcium** nadir at ~8h (4-24h), normalizes within 48 h
- **PTH** Nadir at 2 hrs, return to baseline at 8-12 hrs, secondary decrease at 48 hrs



With daily treatment:

- Ca nadir at 4mon, overall a 1mg% decrease from baseline
- Stabilization of Ca levels thereafter

Locatelli et al. *Expert Rev. Endocrinol. Metab. 2006* (1)

Nephrol Dial Transplant (2020) 35: 47–64
doi: 10.1093/ndt/gfz159
Advance Access publication 22 October 2019

ndt
Nephrology Dialysis Transplantation

Cinacalcet use in paediatric dialysis: a position statement from the European Society for Paediatric Nephrology and the Chronic Kidney Disease-Mineral and Bone Disorders Working Group of the ERA-EDTA

- Developed to provide guidance to healthcare professionals on the use of cinacalcet in paediatric dialysis patients
- Reflect: evidence from clinical studies, expert opinion and extrapolation from adult studies

The 22 consensus statements:

Considerations before starting Cinacalcet

Indications & contraindications

Treatment schedule

Monitoring during treatment

Treatment of persistent severe SHPT despite conventional therapy & cinacalcet

Considerations before starting Cinacalcet

- Monitor serum Ca, P, PTH, 25OH vitD regularly → address combined trend
- Ca & P levels kept within normal ranges

- Perform ECG, calculate QTc

- Address other metabolic and clinical abnormalities: metabolic acidosis, anaemia

Cinacalcet indications & contraindications

- Age >3 yrs on dialysis

- Severe hyperparathyroidism despite optimized conventional management
- High/high-normal Ca levels ≥ 9.6mg/dl (2.40mmol/L) , no clear PTH threshold

- **CI:** Prolonged QT interval
- **Caution:** seizure history, cardiac arrhythmia, significant liver disease, poor medication adherence

Cinacalcet treatment schedule

- Starting dose: 0.2mg/kg/d
- 0.2mg/kg/d increments, at least Q 4weeks
- Max 2.5mg/kg/d (up to 60-180mg daily)
- Titration by PTH level, most aim for X2-3 upper normal
- Maintain Ca> 8.8mg/dl (albumin corrected)
- Once daily dose, use minimal effective dose

- **Decrease:** Ca < 8.8 mg/dl **or** PTH 100-150 pg/ml, low for the individual or declining too rapidly
- **Discontinue:** Ca<8mg/dl, iCa<1.0mmol/l OR PTH <100pg/ml
- **Restart** a lower dose when Ca returns to high-normal

Monitoring during cinacalcet therapy

- Serum Ca:
  - Within 1 week of starting, Weekly during titration
  - At least monthly on maintenance
- Serum PTH - Monthly

- Children & caregivers informed of: symptoms of hypocalcaemia, importance of adherence, monitoring, caution about other medications that may prolong QTc or interact with cinacalcet

Treatment of persistent severe SHPT despite conventional therapy & cinacalcet

- Lack of data

- Parathyroidectomy considered
- Timing: after 6months of appropriate dose, at the physician's discretion

- Some studies suggest response after 8 months of treatment

KI REPORTS
KIReports.org

Cinacalcet: Addressing the Unmet Clinical Need in the Management of CKD-Mineral and Bone Disorder in Infants on Dialysis

Evelien Snauwaert[1] and Agni

[1]Department of Pediatric Nephrology
ERKNet Center, Ghent, Belgium

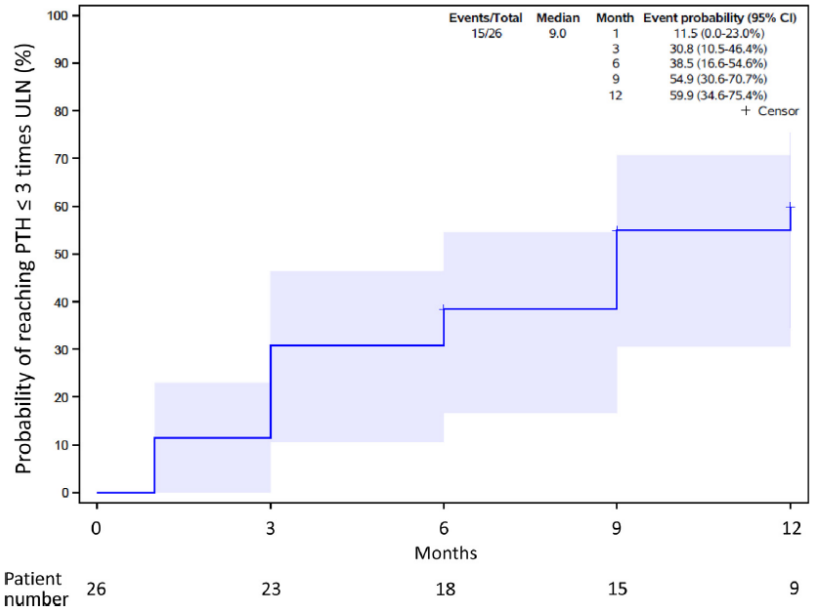
Kidney Int Rep (2024) **9**, 2332–2334; h

Infants and young children on dialysis constitute a small, but very challenging group of patients:

- Intensive skeletal growth & specific dietary requirements
- The most rapid bone turnover and mineralization → the most challenging MBD control

The European experience of cinacalcet in infants <3y of age on dialysis

- 2009-2021, 35 ped. dialysis centers, 26 children
- The probability of achieving PTH <3 times the upper limit of normal increased over time
- > 50% after 9 months



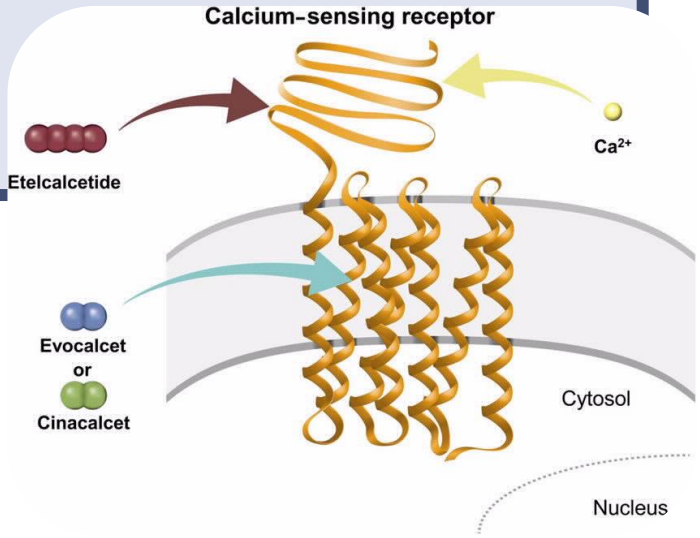
Adverse events:

- Hypocalcemia in 27% - similar to older children
- Precocious puberty in 3/26 (11%)

Bernardor-Kidney Int Rep (2024)

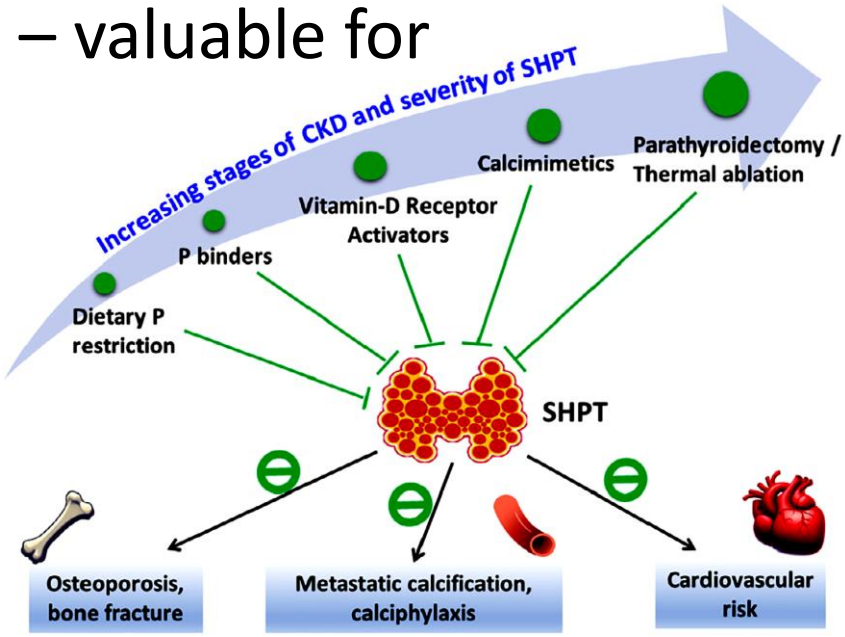
Etelcalcetide
A “second generation” calcimimetic

- Binds to the CaSR extracellular domain
- A positive allosteric activator, mechanism distinct from that of cinacalcet
- Does not require extracellular calcium binding to CaSR for its’ activation
- IV thrice weekly administration



Summary – cinacalcet in pediatric ESRD

- Effective in reducing PTH levels
- Safe and well tolerated
- However, data is variable and limited in scope
- Sharing clinical experience – valuable for optimizing treatment



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