• Active and Native Vitamin D

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Disclosures

• Member of Sanofi, Shire, Amgen and Vifor Australia advisory boards.
• Has received speaker’s fees from Amgen and Shire.
Outline

General Population Data
• Bone
• Effects outside bone
• Time to turn out the lights?

25OH-vitamin D Assays
• Seasonal variations
• Specific populations
• What should we be measuring?

Nutritional / 25OHD in CKD 3-5 and 5D

Calcitriol and Analogs in CKD 3-5 and 5D

Conclusions
Skeletal Effects of Vitamin D

- Osteomalacia / Rickets
- Myopathy
- Secondary HPT
- Reduced BMD

25OHD nmol/L

- <15 - 25
- <40 - 50
- 40 - 50
- >60 – 75

ng/ml

- 6 – 10
- 16 – 20
- 16 - 20
- 24 - 30
### Non-Skeletal Effects of Vitamin D

**Osteomalacia / Rickets**
- Myopathy
- Secondary HPT
- Reduced BMD

**Neuromuscular function:**
- Falls, tests of functional capacity

<table>
<thead>
<tr>
<th>25OHD nmol/L</th>
<th>&lt;15 - 25</th>
<th>&lt;40 - 50</th>
<th>40 - 50</th>
<th>&gt;60 – 75</th>
</tr>
</thead>
<tbody>
<tr>
<td>ng/ml</td>
<td>6 – 10</td>
<td>16 – 20</td>
<td>16 - 20</td>
<td>24 - 30</td>
</tr>
</tbody>
</table>

**Association Studies**
- CV Outcomes; RAS regulation; Myocardial cell hypertrophy;
- VSMC proliferation; Endothelial cell function;
- Diabetes types 1 and 2; Insulin resistance
- Infection; Immunomodulation; cancer
- Preeclampsia
General Population; Fracture Risk

Pooled analysis; 12 studies (30011 participants 65 or older; 91% women);
1111 incident hip and 3770 nonvertebral fractures

Vitamin D or D plus Ca vs. placebo or calcium. Median dose 800 IU (792 - 2000)

Meta-analysis of intervention studies

**Risk of hip fracture**

<table>
<thead>
<tr>
<th>Quartile of Vitamin D Intake</th>
<th>Effect</th>
</tr>
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<tbody>
<tr>
<td>TOP QUARTILE of VIT D 792-2000 IU</td>
<td>Pooled RR, 0.72 (95% CI: 0.59-0.89)</td>
</tr>
<tr>
<td>Chapuy 1992</td>
<td>Q=5.04; P=0.41</td>
</tr>
<tr>
<td>Flicker 2005</td>
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<tr>
<td>Grant A 2005</td>
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<td>Grant B 2005</td>
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<td>Jackson 2006</td>
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<tr>
<td>Bischoff-Ferrari 2010</td>
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<tr>
<td>Combined</td>
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</table>

**Risk of non vertebral fracture**

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<tr>
<td>TOP QUARTILE of VIT D 792-2000 IU</td>
<td>Pooled RR, 0.88 (95% CI: 0.74-1.04)</td>
</tr>
<tr>
<td>Chapuy 1992</td>
<td>Q=8.6; P=0.12</td>
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<td>Combined</td>
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NOTE: Effect driven by Chapuy 1992; ?prevalence of osteomalacia
Randomised to vitamin D2/D3 (calcitriol and analogs excluded) or control

Most; elderly women. Dose generally ≥800 IU/day.

High baseline falls risk (15-69%; median 50%).

26 studies; 45782 participants
Is the odds ratio of patients suffering at least 1 fall reduced with calciferol?

• Vit D deficient; Significant;
  OR; 0.53 (0.39 – 0.72)

• Non-deficient; Borderline:
  OR; 0.90 (0.81-0.99)

Similar to earlier analysis of Bischoff-Ferrari; 0.84 vs. 0.87 (BMJ 2009)

Favours Vit D     Placebo

Muscle Strength

Grip Strength

7 RCTs, n= 3648
No effect

Favours Vit D

Hip strength

17 RCTs, n = 5072

- No effect in adults with 25OHD >25 nmol/L
- Limited studies report improvement for adults with 25OHD <25 nmol/L

Favours placebo
• **Balance and Sway** (n=207)
  -0.2 (-0.39 to -0.01) P=0.04
  Not robust with removal of one low quality study.

• **TUG** (n=274)
  -0.19 (-0.35 to -0.02) P=0.03

• **Lower Extremity Strength** (n=312)
  NS; P=0.55

**Effect of Vitamin D Supplementation on Muscle Strength, Gait and Balance in Older Adults: A Systematic Review and Meta-Analysis**

Veiled Arabic Women living in Denmark with 25OHD levels <20 nmol/L Hypovitaminosis D myopathy without *biochemical* features of OM

Muscle Strength

- Improved force by single twitch electrical stimulation
- Improved; Knee extension after 3 and 6 mo. treatment

• Vitamin D3 or placebo with antituberculous therapy

Time to Negative Sputum Culture

No difference vs. placebo when added to standard therapy

Martineau Lancet 2011 377;242-50
**Effects Outside Bone**

- Vitamin D and COPD

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**Probability of 1st exacerbation**

No difference vs. placebo over 1 year in 184 patients with moderate to severe deficiency

Effects Outside Bone

• Cardiometabolic Syndrome (MI, Cardiac event or death, stroke)

  The association between vitamin D status and cardiometabolic outcomes is uncertain. Trials showed no clinically significant effect of vitamin D supplementation at the dosages given.

• Type 1 diabetes with high C-peptide

  At doses used, calcitriol is ineffective in protecting beta-cell function in subjects (including children) with recent-onset type 1 diabetes and high C-peptide at diagnosis.

Effects Outside Bone

• Vitamin D and CV outcomes; a systematic review and meta-analysis

Forest Plot representing pooled result for mortality, MI and stroke

Elamin et al; JCEM 2011 96: 1931-1942
Long-term follow-up for mortality and cancer in a randomized placebo-controlled trial of vitamin D(3) and/or calcium (RECORD trial).

- 5292 people (85% women) aged at least 70 yr with previous low-trauma fracture
- Randomly allocated to daily vitamin D3 (800 IU), calcium (1000 mg), both, or placebo for 24-62 months
- Follow-up of 3 yr

Conclusions:
- Daily vitamin D or calcium supplementation did not affect mortality, vascular disease, cancer mortality, or cancer incidence
For bone and muscle:
Benefits may be limited to
• Older individuals (>60 years)
• Those with levels are <25-50 nmol/L (10-20 ng/ml)

IOM 2011:
With the exception of measures related to bone health, the potential indicators examined are currently not supported by evidence
• Adequate 25OHD 40-50 nmol/L
• UL: 4000 IU/day

Editorial

Vitamin D
Too Soon to Turn Out the Lights?

Ravi I. Thadhani, JoAnn E. Manson
Confounding influences:

• What is the cut point for major clinical disease
• Seasonal variation
• Genetic variation and specific populations
• Assays
**Cut Points:** Serum 25-Hydroxyvitamin D Concentration and Risk for Major Clinical Disease Events in a Community-Based Population.

- 1621 participants ≥ 65 years
- 4 US communities
- Median follow-up 11 years (IQ range 6,13)
- Composite clinical outcome
  - 1018 (63%)
  - Hip fracture for 137 (8%)
  - MI for 186 (11%)
  - Cancer for 335 (21%)
  - Death for 360 (22%)

Z score less than −0.54 (29th percentile of the normal distribution) best discriminated risk for the composite outcome.
Seasonal variation: Serum 25-Hydroxyvitamin D Concentration and Risk for Major Clinical Disease Events in a Community-Based Population.

Z score less than −0.54 (29th percentile of the normal distribution) best discriminated risk for the composite outcome.

•Based on association with major clinical disease events, optimal 25OHD is ≥ 50 nmol/L (20 ng/ml)

Genetic Factors

• GWAS studies*
Differences in 25OHD between strongest genetic variants were similar to summer winter seasonal changes.
Variants in 7-DHC reductase
25-hydroxylase (CYP2R1)
CYP24A1

• GC gene polymorphisms, encoding DBP had greatest effect on 25OHD values

*Wang et al. The Lancet, 2010:376, (9736), 180 – 188
Genetic and environmental determinants of vitamin D status
Assays: Vitamin D Binding Protein

- DBP: glycosylated~58kd protein
  t½ 2-3 days
  Produced in the Liver

- Negative acute phase reactant
  Binds actin in tissue damage
  DBP-actin is rapidly cleared

- 25OHD t½ is 2-3 weeks; ligand recycling

- 1,25(OH)₂D t½ is 4-6 hours
25OHD and Circulating Proteins

- 25OHD binds to DBP in circulation
- 25OHD binds to Albumin
- 25OHD circulates in a free form

\[ \text{[Total]} = [D] + [DAlb] + [DDBP] \]
Only UNBOUND hormones cross cell membranes and have biological action.
Only UNBOUND hormones cross cell membranes and have biological action.
Albumin Bound 25OHD is Bioavailable

Yet, vitamin D deficiency is clinically defined by TOTAL 25(OH)D
TBG-bound T4 (no exchange)  

Albumin-bound T4 (bioavailable)  

Target tissue  

Free T4  

T4 deiodinase  

Thyroid hormone receptor  

Similar to T4 response
TBG-bound T4 (no exchange)  Albumin-bound T4 (bioavailable)  DBP-25OHD (no exchange)  Albumin-25OHD (bioavailable)

Target tissue  Kidney epithelium

Free T4  Free 25OHD

T4 deiodinase  1,25D

Thyroid hormone receptor  VDR

Similar to T4 response

Slide modified from Dr Thadhani
DBP Modifies the Vitamin D - BMD Relationship

- 49 healthy young adults enrolled in the Metabolic Abnormalities in College-Aged Students (MACS) study
- Free and bioavailable 25OHD levels were positively correlated to Lumbar Spine BMD
- No correlation to values of 1,25(OH)2D

Powe, J Bone Miner Res 2011; 2011: 26 (7)1609–1616
### DBP Modifies the Vitamin D - BMD Relationship

This may explain the racial paradox

<table>
<thead>
<tr>
<th></th>
<th>WHITES</th>
<th>BLACKS</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>25(OH)D</strong></td>
<td>High</td>
<td>Low</td>
</tr>
<tr>
<td><strong>PTH</strong></td>
<td>Low</td>
<td>High</td>
</tr>
<tr>
<td><strong>Bone Mineral Density</strong></td>
<td>Low</td>
<td>High</td>
</tr>
<tr>
<td><strong>Osteoporosis/Fracture</strong></td>
<td>High</td>
<td>Low</td>
</tr>
</tbody>
</table>
### Summary

- Vitamin D deficiency as is currently defined is an epidemic
- Assay quality assurance and standardisation remains a problem
- Seasonal and genetic factors influence 25OHD levels
- Determining bioavailable vitamin D may resolve some paradoxes of association and interventional studies
- Large RCTs may soon provide insight to these Qs
Practise Patterns for Vitamin D in CKD
Approximate KDIGO iPTH Range: 2-9X

DOPPS USA Data 2010 - 2013

67% in target

N Patients:
- AUG10: 3275
- DEC10: 3598
- APR11: 3644
- AUG11: 3807
- DEC11: 3582
- APR12: 1759
- AUG12: 2481
- DEC12: 2887
- APR13: 2483

Overall
23% of Patients Receive Cinacalcet
75% of Patients Receive IVI Vitamin D

40% paricalcitol, 55% doxercalciferol; 25% with cinacalcet
80-90% of Cinacalcet is prescribed with VIT D

Source: US-DOPPS Practice Monitor, August 2013
Study for the Evaluation of Early Kidney disease (SEEK):
1814 CKD 3-5 patients from USA:
48% male, 47% diabetes, 71% > age 65

Reciprocal Relationship to PTH

Calciferol therapy reduces PTH in CKD 1 to 4

Patient-level associations; 25OHD in CKD-5D

Falls, stability and muscle strength in CKD 5D

Clinical Endocrinology (2010)

Association between 25-hydroxyvitamin D, somatic muscle weakness and falls risk in end-stage renal failure

N Boudville†, C Inderjeeth‡, GJ Elder§ and P Glendinning∗∗

Cross sectional study of HD patients:

Patient-level associations; 25OHD in CKD-5D

Falls Risk, stability and muscle strength in CKD 5D

- Significant inverse relationships of 25OHD to falls
- Quadriceps strength
- Function related to falls (Modified Barthel Index)
- No relationship to 1,25(OH)2D

Patient-level associations; 25OHD in CKD-5D

Multivariate adjusted OR of 90-day all-cause and CV mortality

- **No active vitamin D therapy**
- **Active vitamin D therapy**
- Reference; *active vitamin D*+$25$(OH)$D_3 >30$ ng/ml+calcitriol $>13$ pg/ml

**Lower risk at higher 25OHD values**

<table>
<thead>
<tr>
<th>25OHD (ng/ml)</th>
<th>OR All Cause Mortality</th>
<th>OR CV Mortality</th>
</tr>
</thead>
<tbody>
<tr>
<td>&lt;10</td>
<td><img src="Diagram" alt="Diagram" /></td>
<td><img src="Diagram" alt="Diagram" /></td>
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<tr>
<td>10–30</td>
<td><img src="Diagram" alt="Diagram" /></td>
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<tr>
<td>&gt;30</td>
<td><img src="Diagram" alt="Diagram" /></td>
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**Effects of Cholecalciferol on Biochemical, Vascular, and Quality of Life Outcomes in HD**

- Double blind RCT over 6 months
- 60 satellite HD patients with 25(OH)D <60 nmol/L
- Oral cholecalciferol 50,000 IU in 10 mls weekly for 8 weeks then monthly for 4 months
- Placebo: medium chain triglyceride

| Muscle strength and hand grip |
| Functional testing and balance |
| QOL questionnaire (KDOQOL-36) |
| PWV, BP |
| Ca, P, 25(OH)D, 1,25(OH)₂D ,PTH, b-ALP and TRAcP-5b,Hb and ESA |

**Co-morbidities: ANZDATA**

- Falls diary, infections, adverse events

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Effects of Cholecalciferol on Biochemical, Vascular, and Quality of Life Outcomes in HD

Baseline characteristics well matched:
Median age 62 years (20–86), 52% women, 55% diabetes, 25(OH)D 43±13 nmol/L (17±5 ng/ml); BMI (kg/m²) 31.3 ± 9.5 (placebo) 26.6 ± 6.4 (cholecalciferol)

• 25(OH)D lower with diabetes (39±13 vs. 48±10 nmol/L; p=0.002)
  Correlated to calcitriol (r=0.27; p=0.04)
  Correlated to distance covered in the 6-min. walk
  Predicted PWV (adjusted r²=0.149; p=0.019);
  Part correlations: Age 0.306, 25(OH)D -0.266).
### Effects of Cholecalciferol on Biochemical, Vascular, and Quality of Life Outcomes in HD

At 6 months: No effect on primary end point; muscle strength testing

#### Table 4. Baseline and 6-month muscle group strength

<table>
<thead>
<tr>
<th>Muscle Group</th>
<th>Time</th>
<th>Placebo</th>
<th>Cholecalciferol</th>
<th>P Value</th>
</tr>
</thead>
<tbody>
<tr>
<td>Grip strength</td>
<td>Baseline</td>
<td>21 (17, 25)</td>
<td>23 (19, 28)</td>
<td>0.28</td>
</tr>
<tr>
<td></td>
<td>6 mo</td>
<td>21 (17, 24)</td>
<td>24 (21, 28)</td>
<td></td>
</tr>
<tr>
<td>Shoulder abduction</td>
<td>Baseline</td>
<td>5 (4, 6)</td>
<td>5 (4, 6)</td>
<td>0.53</td>
</tr>
<tr>
<td></td>
<td>6 mo</td>
<td>6 (4, 7)</td>
<td>7 (5, 9)</td>
<td></td>
</tr>
<tr>
<td>Elbow flexion</td>
<td>Baseline</td>
<td>12 (9, 14)</td>
<td>12 (9, 14)</td>
<td>0.63</td>
</tr>
<tr>
<td></td>
<td>6 mo</td>
<td>14 (11, 16)</td>
<td>15 (12, 18)</td>
<td></td>
</tr>
<tr>
<td>Elbow extension</td>
<td>Baseline</td>
<td>10 (8, 11)</td>
<td>10 (9, 12)</td>
<td>0.41</td>
</tr>
<tr>
<td></td>
<td>6 mo</td>
<td>11 (9, 13)</td>
<td>13 (11, 14)</td>
<td></td>
</tr>
<tr>
<td>Hip flexion</td>
<td>Baseline</td>
<td>12 (10, 15)</td>
<td>13 (11, 15)</td>
<td>0.83</td>
</tr>
<tr>
<td></td>
<td>6 mo</td>
<td>16 (14, 17)</td>
<td>16 (15, 18)</td>
<td></td>
</tr>
<tr>
<td>Knee flexion</td>
<td>Baseline</td>
<td>11 (9, 12)</td>
<td>12 (10, 13)</td>
<td>0.93</td>
</tr>
<tr>
<td></td>
<td>6 mo</td>
<td>14 (12, 16)</td>
<td>13 (11, 15)</td>
<td></td>
</tr>
<tr>
<td>Knee extension</td>
<td>Baseline</td>
<td>15 (12, 17)</td>
<td>14 (12, 17)</td>
<td>0.97</td>
</tr>
<tr>
<td></td>
<td>6 mo</td>
<td>19 (16, 21)</td>
<td>19 (16, 22)</td>
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</table>

Data are shown in kilograms of force (95% confidence interval). P values represent differences in strength between treatment groups over time (repeated-measures ANOVA). There were 30 patients in each group at baseline and 24 patients in the placebo group and 21 patients in the cholecalciferol group at 6 months.
Effects of Cholecalciferol on Biochemical, Vascular, and Quality of Life Outcomes in HD

At 6 months
- 25OHD and calcitriol were higher and phosphate lower (p=0.04)
- TRAcP-5b higher; p=0.04
- Reduced Ca-based P binder use
- No between group differences in levels of iPTH, ALP, b-ALP, Ca, functional tests, falls, HRQOL, PWV, ESA dose, Infections, AEs

Summary: calciferol

- PTH is inversely related to 25OHD values in CKD 3 - 4 / 5. General population data is applicable to many in this group.

- In CKD 5D, association studies suggest relationships of 25OHD to improved mortality, PWV and functional tests but no change was seen after 6 months therapy in patients with vitamin D insufficiency.

- Treatment with cholecalciferol effectively increases serum 25(OH)D and levels of calcitriol are higher; possibly supporting the concept of extra-renal conversion.

- Cholecalciferol may increase osteoclast markers.
- Cholecalciferol does not increase serum Ca or P.
Rationale for Treatment with Calcitriol and Analogs

- Control of sHPT and avoidance of PTx
- Control of sHPT effects on bone and mineral metabolism
- Avoidance of related CV events and mortality
- Pleomorphic vitamin D effects; oxidative stress, infection etc
- Physiological Replacement
Control of sHPT

- Reduced bone mass and quality
- Structural properties: micro-architecture;
  - loss of plate structures in trabecular bone
  - reduced cortical thickness
  - increased cortical porosity reduces
Control of sHPT

- Reduced bone mass and quality
- Structural properties: micro-architecture;
  - loss of plate structures in trabecular bone
  - reduced cortical thickness
  - increased cortical porosity reduces

With equal bone volume, resorption cavities cause twice the loss of stiffness as the same amount of loss due to trabecular thinning.
Avoidance of CV events and mortality

HR

>68 pmol/L

>601 pg/ml

All-Cause

Cardiovascular

PTH pg/ml

Tentori AJKD 2008
Avoidance of CV events and mortality

FRESENIUS MEDICAL CARE iPTH TARGET <300 pg/ml

SURVIVAL: Paricalcitol > Calcitriol

P < 0.001

Teng et al N Eng J Med 2003. 349;5
PTH and mortality inconsistently associated

![Graph showing the relationship between PTH and mortality, with different calcium levels and PTH ranges.]
PTH value may not reflect bone turnover

Low bone turnover is common

Turnover:
- Afro-Americans
  Low in 32%
- Caucasians
  Low in 62%

630 bone biopsies: 543 Caucasian. Dialysate Ca$^{2+}$ 1.25 mmol/L in 371, 1.75 mmol/L in 259; 429 Ca-based P binders; 4 cinacalcet

Low turnover may increase bone fragility

Microcrack frequency and bone remodeling in postmenopausal osteoporotic women on long-term bisphosphonates: a bone biopsy study

Compared to controls, reduced turnover but no increase in microcrack accumulation

Low and high turnover potentiate VC

Soft tissue Calcium Deposition

- Inappropriately Low PTH
- Reduced rapid Uptake
- Abnormal Bone Turnover

ECF

- Prescribed Ca
  - Ca ‘Spike’
  - Calcitriol and analogs

- Reduced Kidney Function

ECF many compartments interstitial, bone, CT, plasma, water ; net balance zero
1,25(OH)$_2$D actions vary with calcium balance

**Normal Ca balance**
- Maintains GI Ca absorption
- $1,25$(OH)$_2$D
- VDR
- intestinal Ca$^{2+}$ absorption

**Negative Ca balance**
- Increases Ca release from bone independent of direct PTH effect
- $1,25$(OH)$_2$D
- bone resorption
- ↓ bone mass
- ↑ mineralization inhibitors
- ↓ bone mineralization


- $1,25$(OH)$_2$D suppresses mineralisation by increasing levels of pyrophosphate
- Inhibits osteoblastogenesis and increases osteoclast activity
- BUT: Effects vary with developmental stage
  Anabolic effects on mature osteoblasts also reported
  St Arnaud J Steroid Biochem Mol Biol 2008
1,25(OH)_2D / FGF 23 interactions

- PTH
- FGF 23
  - INCREASED CELL CYCLING

- CYP 27B1
- CYP 24A1
- Pi
- Ca

1,25(OH)_2D induces FGF 23 release if normocalcaemic; ? reduced in CKD*

FGF 23 and 1,25(OH)_2D induce 24-hydroxylase; clears calcitriol, analogs and 25OHD.

Cell cycling effects

Petkovich and Jones. Current Opin Nephrol Hypertens 2011
Biphasic Dose-Response Curve for 1,25(OH)2D

Deleterious Consequences of Deficiency or Excess

- Suppressed PTH
- Reduced VSMC PTHrp
- Reduced VSMC PTHR1 signaling
- Induced TNALP
- Low Bone Turnover
- Hyperphosphataemia
- Hypercalcaemia
- Metalloproteinases

Arterial stiffness
VC
LVH

Increased Renin and ATII
Pro-inflammatory cytokines
IL-12/IL-10 ratio
Metalloproteinases
Protective factors of endothelial cells

Risk of deficiency or excess (%)

Increasing vitamin D dosage
Effect of Calcitriol and Analogs on TMV

<table>
<thead>
<tr>
<th>Turnover:</th>
<th>Mineralisation:</th>
<th>Volume:</th>
</tr>
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<tbody>
<tr>
<td>• Calcitriol IV / PO</td>
<td>↑</td>
<td>←</td>
</tr>
<tr>
<td>• Alfacalcidol</td>
<td>↑</td>
<td>↑</td>
</tr>
<tr>
<td>• Paricalcitol</td>
<td>?</td>
<td>?</td>
</tr>
<tr>
<td>• Doxercalciferol</td>
<td>?</td>
<td>?</td>
</tr>
<tr>
<td>• Maxacalcitol</td>
<td>←</td>
<td>↑</td>
</tr>
</tbody>
</table>

Reduced turnover, woven bone, fibrosis, improved mineralisation

Meta-analysis: Vitamin D Compounds in Chronic Kidney Disease

Su etonia C. Palmer, MBChB; David O. McGregor, PhD; Petra Macaskill, PhD; Jonathan C. Craig, PhD; Gra hame J. Elder, PhD; and Giovanni F.M. Strippoli, MD, MPH(Hons), MM

Purpose: To determine whether vitamin D therapy improves biochemical markers of mineral metabolism and cardiovascular and mortality outcomes in chronic kidney disease.

Data Sources: MEDLINE (January 1966 to July 2007), EMBASE (January 1980 to July 2007), and Cochrane databases were searched without language restriction.

Meta-analysis of 76 trials; 3667 patients; 40 years research!
Calcitriol and newer analogs

- Little data on patient-level outcomes

- Reciprocal relationship of calcitriol / analogs to PTH
  Newer analogs may reduce PTH more effectively

- Established vitamin D therapies were associated with increases in both Ca and P

- Newer analogs were associated with increases in Ca but not P vs. placebo

In patients with LVH and CKD, does 48-weeks treatment with paricalcitol reduce LV mass and CVD events and improve diastolic function and cardiac biomarkers?

![Graph showing changes in iPTH pg/ml over weeks for Placebo and Paricalcitol groups.](Thadhani et al. JAMA, 2012 Vol 307, No.7)
The PRIMO Randomized Controlled Trial

- NS change in LVMI at 48 weeks (primary endpoint)
- Hospitalizations from any cause NS
- Between-group differences in BNP NS
- Paricalcitol reduced left atrial volume index, a measure linked to adverse cardiovascular events, particularly CCF

ADVERSE EVENTS
- Hypercalcemia (paricalcitol, 22.6% vs placebo, 0.9%; P.001)
- Decline in GFR by creatinine and cystatin C-based methods (p=0.001 and 0.06 respectively)

COMMENTS:
- Patients may have been too well controlled: RAS inhibitors, BP, CRP
- BNP and LAVI changes may be adequate surrogates.
Summary: calcitriol and analogs

- Pharmacological doses of calcitriol and analogs suppress PTH in CKD 3-5D but increase calcium and/or phosphate levels.
- Calcitriol and analogs improve bone histomorphometry in patients with high bone turnover.
- Patients treated with calcitriol/analogos ± calcimimetics may develop low bone turnover; with increased risks for VC and possibly bone quality.
- Despite observational support for calcitriol/analogos improving CV risk and mortality, the PRIMO study did not show an overall advantage; although surrogate measures suggest subgroups may be benefited.
- Low dose calcitriol/analogos may benefit CV risk and bone