Disclosures Vervloet

• Pharmaceutical Industries
  • Lecture fees, scientific support and advisor for: Amgen, VFMCRP and Vifor, Shire, Medice, Bayer, Kissei, Cablon Medical; all companies involved in marketing or developing phosphate lowering drugs.
  • Scientific support from: AbbVie, Amgen and FMC.
  • Advisory board of: Otsuka, Astra-Zeneca, Medice.

• Member of
  • ERA-EDTA working group on CKD-MBD
  • KDIGO committee on CKD-MBD.
GOALS OF THIS MEETING

• Recap this 2 year old guideline

• Obtain input from you on the most debated statement

• For the discussion: which novel publications might change or reinforce the guidelines? (Three examples if time allows)
ITEMS HEAVILY DISCUSSED

• **Phosphate control:** What is the meaning of “towards the normal range”?

• **Phosphate control:** Calcium-containing binders: yes or no?

• **PTH control in predialysis:** Wait with treatment until it’s severe?

• **PTH control in dialysis:** Why did this range remain so very wide (2-9 times ULN)
How up to date is a guideline?

Selected update

KDIGO 2009

KDIGO 2017

2015 Guidelines Selected for update

2017 Guidelines Release

2019-2010 Today?

2016 Literature lock
SELECTED UPDATE...

- Decided at Controversies conference Madrid 2015, but reconsidered later on

Overview of recommended changes
- Selective Update in Red
- Minor Adaptation in Grey
- No changes left uncoloured
KDIGO 2017 GUIDELINE UPDATE CONTRIBUTORS

Guideline Work Group
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Mary B. Leonard (USA) – Co-chair

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Evidence Review Team
Johns Hopkins University
Karen A. Robinson, Casey Rebholz, Lisa M. Wilson, Ermias Jirru, Marisa Chi Liu, Jessica Gayleard, Allen Zhang
CHAPTER 4.1:

• TREATMENT OF CKD–MBD: TARGETED AT LOWERING HIGH SERUM PHOSPHATE AND MAINTAINING SERUM CALCIUM
PHOSPHATE AND CALCIUM

• **NEW 4.1.1:** In patients with CKD G3a–G5D, treatments of CKD-MBD should be based on serial assessments of phosphate, calcium and PTH levels, considered together (NOT GRADED)
CKD-MBD PHENOTYPE AND ADJUSTED RISK OF DEATH OR CV HOSPITALISATION

Comparison of 2016 vs 2009 Recommendations

- **New 4.1.2.** In patients with CKD Stages 3a-5D, we suggest lowering elevated phosphorus levels towards the normal range. (2C)

- **Old 4.1.1.** In patients with CKD stages 3–5, we suggest maintaining serum phosphorus in the normal range (2C).

In patients with CKD stage 5D, we suggest lowering elevated phosphorus levels toward the normal range (2C).
RATIONALE FOR UPDATE

• There is an absence of data demonstrating that efforts to maintain phosphate in the normal range are of benefit to CKD G3a–G4 patients.

• Moreover, there even are some safety concerns related to this approach.

• Treatment should aim at overt hyperphosphataemia.

• The update emphasises the perception that early “preventive” treatment of hyperphosphataemia is currently not supported by data.
PHOSPHATE BINDERS IN MODERATE CKD

Comparison of 2016 vs 2009 Recommendations

- In adult patients with CKD Stages 3A-5D receiving phosphate-lowering treatment, we suggest restricting the dose of calcium-based phosphate binders. (2B)
- In children with CKD Stages 3A-5D, it is reasonable to base the choice of phosphate-lowering treatment on serum calcium levels. (Not Graded)

Old 4.1.5. In patients with CKD stages 3–5D and hyperphosphatemia, we recommend restricting the dose of calcium-based phosphate binders and/or the dose of calcitriol or vitamin D analog in the presence of persistent or recurrent hypercalcemia (1B). In patients with CKD stages 3–5D and hyperphosphatemia, we suggest restricting the dose of calcium-based phosphate binders in the presence of arterial calcification (2C) and/or adynamic bone disease (2C) and/or if serum PTH levels are persistently low (2C).
RATIONALE FOR UPDATE

• New evidence from three randomised control trials (RCTs) supports a more general recommendation to restrict calcium-based phosphate binders in hyperphosphataemic patients of all severities of CKD
**Phosphate Binders and Mortality Predialysis**

All-cause mortality

Dialysis inception

**Sevelamer vs. Calcium Dialysis**

**Mortality due to arrhythmias**

- Calcium carbonate
- Sevelamer

**Cardiovascular mortality**

- Calcium carbonate
- Sevelamer

Log-Rank test: p<0.001

# Meta-analysis Ca-based versus non-calcium based binders

<table>
<thead>
<tr>
<th></th>
<th>Non-calcium binders</th>
<th>Calcium binders</th>
<th>Weight</th>
<th>Risk ratio (95% CI)</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>Events</td>
<td>Total patients</td>
<td>Events</td>
<td>Total patients</td>
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<td>RCT only</td>
<td></td>
<td></td>
<td></td>
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<td>Barreto et al (2008)</td>
<td>1</td>
<td>52</td>
<td>8</td>
<td>49</td>
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<tr>
<td>Block et al (2007)</td>
<td>11</td>
<td>60</td>
<td>23</td>
<td>67</td>
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<td>Chertow et al (2002)</td>
<td>6</td>
<td>99</td>
<td>5</td>
<td>101</td>
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<tr>
<td>Di Iorio et al (2012)</td>
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<td>107</td>
<td>22</td>
<td>105</td>
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<td>Kakuta et al (2011)</td>
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<td>91</td>
<td>0</td>
<td>92</td>
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<tr>
<td>Qunibi et al (2008)</td>
<td>3</td>
<td>100</td>
<td>7</td>
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<td>Russo et al (2007)</td>
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<td>21</td>
<td>3</td>
<td>21</td>
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<td>Suki (2008)</td>
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<td>1050</td>
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<td>Takei et al (2008)</td>
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<td>0</td>
<td>20</td>
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<tr>
<td>Wilson et al (2009)</td>
<td>135</td>
<td>680</td>
<td>157</td>
<td>674</td>
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<tr>
<td><strong>Subtotal</strong></td>
<td><strong>436</strong></td>
<td><strong>2312</strong></td>
<td><strong>500</strong></td>
<td><strong>2310</strong></td>
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</tbody>
</table>

Jamal, Lancet 2013
CHAPTER 4.2:

• TREATMENT OF ABNORMAL PTH LEVELS IN CKD-MBD

TARGET RANGE: 2-9 UPPER LIMIT OF NORMAL?
MAINTAINING/LOWERING PTH IN DIALYSIS

• **4.2.3**: In patients with CKD G5D, we suggest maintaining intact PTH levels in the range of approximately 2–9 times the upper normal limit for the assay (2C)

• We suggest that marked changes in PTH levels in either direction within this range prompt an initiation or change in therapy to avoid progression to levels outside of this range (2C)
**PTH AND BONE TURNOVER**

London GM et al., JASN 2008; 19:1927-35; + data from Portugal, Brasil and Turkey

- **iPTH >500 pg/ml:** "Active" Bone
- **iPTH 100-500 pg/ml:** Undetermined range
- **iPTH <100 pg/ml:** Adynamic Bone

Bone histology

<table>
<thead>
<tr>
<th>PTH [pg/ml]</th>
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<tbody>
<tr>
<td>900</td>
</tr>
<tr>
<td>750</td>
</tr>
<tr>
<td>600</td>
</tr>
<tr>
<td>450</td>
</tr>
<tr>
<td>300</td>
</tr>
<tr>
<td>150</td>
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<tr>
<td>0</td>
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</table>
PTH AND MORTALITY

KDOQI Target Range

<table>
<thead>
<tr>
<th>PTH (pg/mL)</th>
<th>Frequency (No. of patients)</th>
</tr>
</thead>
<tbody>
<tr>
<td>0-75</td>
<td>75</td>
</tr>
<tr>
<td>75-200</td>
<td>300</td>
</tr>
<tr>
<td>200-400</td>
<td>200</td>
</tr>
<tr>
<td>400-800</td>
<td>600</td>
</tr>
<tr>
<td>800-1000</td>
<td>1000</td>
</tr>
</tbody>
</table>

Mortality Hazard Ratio

Floege et al., Nephrol Dial Transplant 2011;26:1948-1955
Lamina, Nephrol Dial Transplant 2019; 45(6):1051-1058

KDOQI KDIGO
PTH targets in dialysis

- **EVOLVE trial**
- **Bone turnover**
- **KDIGO**
- **KDOQI**
- **Healthy**

*Absolute value
†Central, assay ref range?

Area of uncertainty ≠ Target range
Comparison of 2016 vs 2009 Recommendations: Active Vitamin D in Predialysis

**NEW 4.2.2.** In adult patients with CKD Stages 3a-5 not on dialysis, we suggest *calcitriol and vitamin D analogs not be routinely used* (2C). It is reasonable to reserve the use of calcitriol and vitamin D analogs for patients with CKD Stages 4-5 with severe and progressive hyperparathyroidism (*Not Graded*).

- In children, calcitriol and vitamin D analogs may be considered to maintain serum calcium levels in the age-appropriate normal range (*Not Graded*).

**OLD 4.2.2.** In patients with CKD stages 3–5 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).
RATIONALE FOR UPDATE

• Recent RCTs of vitamin D analogs failed to demonstrate improvements in clinically relevant outcomes but did demonstrate increased risk of hypercalcemia.

• Two trials, PRIMO and OPERA, demonstrated significantly increased risk of hypercalcaemia in patients treated with paricalcitol, compared with placebo, in the absence of beneficial effects on surrogate cardiac endpoints.
**PARICALCITOL IN STAGE 3–4 CKD**

- **PRIMO trial**
  - eGFR 31 (24-43) ml/min/1.73m²
  - N=227
  - Primary endpoint: LVMI

- **OPERA trial**
  - eGFR 20 (16-31) ml/min/1.73m²
  - N=60
  - Primary endpoint: LVMI

---

**PTH**

**Calcium and Phosphate**

Wang A et al, JASN 2014; 25:125

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NEW 4.2.4. In patients with CKD Stage 5D requiring PTH-lowering therapy, we suggest calcimimetics, calcitriol, or vitamin D analogs, or a combination of calcimimetics and calcitriol, or vitamin D analogs. (2B)

OLD 4.2.4. In patients with CKD stage 5D 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 be used to lower PTH (2B).

• It is reasonable that the initial drug selection for the treatment elevated PTH be based on serum calcium ofand phosphorus levels and other aspects of CKD–MBD (not graded).

Unchanged, after the EVOLVE trial
EVOLVE: LOWERING PTH

**EVOLVE: PRIMARY ENDPOINT, SECONDARY ANALYSIS**

**Primary analysis**
- Hazard ratio, 0.93 (95% CI, 0.85, 1.02)
- Log-rank, $p = 0.112$

**Adjusted for baseline differences (age mainly)**
- Hazard ratio: 0.85 (95% CI, 0.76, 0.95)
- Log-rank, $P = 0.003$

Subjects at risk:
- Placebo
- Cinacalcet

EVOLVE:
TIME TO FIRST EPISODE OF SEVERE UNREMITTING HPT

Severe, unremitting HPT
- Prespecified and defined as
  - PTH > 1000 pg/ml (106.0 pmol/l) with serum calcium > 10.5 mg/dl (2.6 mmol/l) on 2 consecutive occasions OR
  - PTH > 1000 pg/ml with serum calcium >10.5 mg/dl on a single occasion and subsequent commercial cinacalcet use within 2 months of the laboratory assessment OR
  - parathyroidectomy

CONCLUSIONS: PHOSPHATE AND SHPT

• **Phosphate in predialysis**: Don’t treat with P-binders if it’s concentration is not increased

• **Phosphate in dialysis**: Aim towards normal range

• **Phosphate binders**: Limit dose of calcium-containing binders

• **PTH range**: In dialysis unchanged (2-9 ULN)

• **PTH in predialysis**: Avoid aiming to normalize, do not routinely use active vitamin D

• **PTH in dialysis**: Active vitamin D, calcimimetics, or combinations are reasonable as first line
ALFACALCIDOL IN HD PATIENTS WITHOUT SHPT

J-DAVID investigators; JAMA. 2018;320(22):2325-2334.
Results: cardiovascular events (full analysis set)

Cardiovascular events

- Median observation period: 3.16 years
- 13.8% in the LC group
- 12.5% in the CC group
Hazard ratio: 1.11 (95% CI: 0.88–1.41)
P=0.386 by log-rank test

Cardiovascular event-free survival

A. Crude

<table>
<thead>
<tr>
<th>Treatment</th>
<th>Hazard ratio</th>
<th>95% CI</th>
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<tbody>
<tr>
<td>LC</td>
<td>1.11</td>
<td>0.88–1.41</td>
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<tr>
<td>CC</td>
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</table>

B. Adjustment for age, gender, diabetes

<table>
<thead>
<tr>
<th>Treatment</th>
<th>Hazard ratio</th>
<th>95% CI</th>
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<tr>
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<tr>
<td>CC</td>
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C. Adjustment for covariates

<table>
<thead>
<tr>
<th>Treatment</th>
<th>Hazard ratio</th>
<th>95% CI</th>
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</table>

LOCAL DIFFERENCES


Angela Yee-Moon Wang¹, Tadao Akizawa², Sunita Bavanandan³, Takayuki Hamano⁴, Adrian Liew⁵, Kuo-Cheng Lu⁶, Dusit Lumlertgul⁷, Kook-Hwan Oh⁸, Ming-Hui Zhao⁹,¹⁰, Samuel Ka-Shun Fung¹¹, Yoshitsugu Obi¹², Keiichi Sumida¹³, Lina Hui Lin Choong¹⁴, Bak Leong Goh¹⁵, Chuan-Ming Hao¹⁶, Young-Joo Kwon¹⁷, Der-Cherng Tarn⁸,¹⁸, Li Zuo¹⁹, David C. Wheeler²⁰, Yusuke Tsukamoto²¹ and Masafumi Fukagawa²²
THANK YOU AGAIN