IMPLEMENTATION OF THE CKD-MBD GUIDELINES INTO CLINICAL PRACTICE

Goce Spasovski, R. Macedonia

Antalya, Turkey, September 16 2012
Session Objectives

- **Guidelines** – *needs and controversy*
  - Evidence level
  - Dissemination
  - Implementation

- Definition of the problem of CKD-MBD
  - *clinically relevant definition and classification*
  - CKD-MBD guidelines (KDOQI / KDIGO)

- Treatment options
  - *hyperphosphatemia under a constant debate*
  - Phosphate binders

- Implementation results?!
European best practice quo vadis? From European best practice guidelines (EBPG) to European renal best practice (ERBP)

Carmine Zoccali¹, Daniel Abramowicz², Jorge B Cannata-Andia³, Pierre Cochat⁴, Adrian Covic⁵, Kai-Uwe Eckardt⁶, Denis Fouque⁷, Olof Heimburger⁸⁹, Alison McLeod¹⁰, Elizabeth Lindley¹¹, Francesco Locatelli¹², Goce Spasovski¹³, James Tattersall¹⁴, Wim Van Biesen¹⁵, Christopher Wanner¹⁶ and Raymond Vanholder¹⁵

● **Guidelines – healthcare improvement**
  – **Evidence level**
    • High & low (perceived as equal?)
  – **Dissemination**
    • Global – the whole community
  – **Implementation**
    • Funding
    • Audits
Renal best practice guidance/guidelines and implementation controversy

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**Evidence level**

- The difficulties in measuring hard outcomes are directly attributed to a specific guideline related change in the patient outcome

**Implementation**

- Frequently neglected issue!?
- Ideally optimize the limited health care resources
- Development of implementation tools
Evidence level

- Various institutions - a plethora of often parallel recommendations on similar topics - different messages
- **KDIGO** - global nephrology guidelines on a worldwide basis
  - Whole spectrum – 2006: selected topics – GRADE eval.*
  - quality of evidence
  - balance of health benefits and harms
  - **balance of net financial benefits and costs**

Implementation - Guidelines debate

*Increasing knowledge - education*

- Presentations at meetings (*Congresses & CME courses*)
- Publications and availability on websites (*Free text online*)
- Email blasts
- Quiz allotting CME points
- Educational materials, systematic reviews of guideline & implementation strategies

*The obstacles to changing practices*

- in the professional setting
- in the patient
- the organisation of care processes
  - *Economic conditions*
  - *Legal, political or cultural constraints*

Implementation

Changing attitudes

Audits - measuring the progress based at regular intervals
- the application of the recommendations (supra/national level)
- feedback system:
  - Neutral (simple statement)
  - Rewarding (bonus)
  - Punitive

Changing outcomes by improving patient health and quality of care

- Organisations to be contacted to achieve these aims:
  - professional bodies & scientific/clinical associations
  - specialty representative groups
  - Funding bodies
  - CME groups
  - bodies representative for education of pts & health professionals
Implementation (prerequisites)

- Recognised need for marketing, advertising, increased visibility of the particular GUIDELINE recommendation (R)

- Each GUIDELINE (R) should be accompanied by the proposal on the anticipated possibilities for its implementation
  - Target group to focus upon
    - National Societies/individual physician
    - Patients associations/individual patient
    - Governmental bodies
    - Professional associations
CKD-MBD consensus definition & classification

Mineral
Hormonal
Bone abnormalities,
Vascular calcifications
Soft tissue calcifications

CVD, fractures, mortality
What is ‘Precise P & Ca Management’?

K-DOQI Guidelines
GB Renal Association Guidelines
EDTA Guidelines

KDIGO Guidelines on CKD-MBD
K/DOQI* guidelines for Bone Metabolism and Disease / Dislipidemia in Chronic Kidney Disease

<table>
<thead>
<tr>
<th>Parameter</th>
<th>K/DOQI Guidelines</th>
</tr>
</thead>
<tbody>
<tr>
<td>P</td>
<td>3.5 – 5.5 mg/dL (1.1 – 1.8 mmol/l)</td>
</tr>
<tr>
<td>Ca x P</td>
<td>&lt; 55 mg²/dL² (&lt; 4.4 mmol²/l²)</td>
</tr>
<tr>
<td>PTH</td>
<td>150 – 300 pg/mL</td>
</tr>
<tr>
<td>LDL cholesterol</td>
<td>&lt; 100 mg/dL (&lt; 2.56 mmol/l)</td>
</tr>
<tr>
<td>Total cholesterol</td>
<td>&lt; 200 mg/dL (&lt; 5.12 mmol/l)</td>
</tr>
</tbody>
</table>

*National Kidney Foundation K/DOQI (Kidney Disease Outcome Initiative)

The K/DOQI guidelines have become widely accepted and are basis of many national treatment guidelines in Eastern Europe

Sevelamer remains first line treatment option (Lanthanum, MCI 196)

Ca based binders contraindicated in low PTH, high Ca, severe calcifications

Mortality Risk Varies According to Number of Laboratory Targets* Achieved Concurrently

<table>
<thead>
<tr>
<th>Parameter</th>
<th>KDIGO Guidelines</th>
</tr>
</thead>
<tbody>
<tr>
<td>Serum phosphate</td>
<td>Normal range – no evidence for targets</td>
</tr>
<tr>
<td>Serum calcium</td>
<td>Normal range – no evidence for targets</td>
</tr>
<tr>
<td>Ca x PO₄ product</td>
<td>Not a useful construct</td>
</tr>
<tr>
<td>Target PTH level</td>
<td>From 2 to 9 x ULN</td>
</tr>
<tr>
<td>Calcium dosage</td>
<td>No evidence to favour any specific binder</td>
</tr>
</tbody>
</table>
In patients with CKD stages 3-5D and hyperphosphatemia, the recommendation\textsuperscript{a} is to:

- Restrict calcium based phosphate binders in the presence of:
  - Arterial calcification
  - Adynamic bone disease (ABD)
  - Persistently low serum PTH levels

- Restrict the dose of calcium based phosphate binders and/or restrict the dose of calcitriol or vitamin D analog are suggested\textsuperscript{b}, in the presence of:
  - Persistent or recurrent hypercalcemia
Endorsement

KDIGO (CKD-MBD) Commentary

David J.A. Goldsmith, Mariano Rodriguez and Raymond Van sco Locatelli, Klaus Olgaard, Zoccoli, Gerard Michel London, to benefits in the prevention of osteodystrophy.

Global Outcomes and Bone Disorder (ERBP) Best Practice (ERBP)
Why not aim for ‘normal’ serum phosphate (professionals)?

Explanations and Excuses ...

- Perceived as difficult to achieve
- Time consuming in a busy clinic
- Need regular dietician input
- Binders are difficult to take, so...
- Patients find adherence difficult

- Our results are OK, no one else is doing any better!
Can we do better (patients)?

Patients need time and explanation

- Need to be engaged ...
- Need to understand what they are aiming for
- Need to understand what phosphate binders do
- Need to understand timing and dosage of binders
- Need to know what to do if adherence difficult

Also need to know if phosphate control is beneficial!
Hyperphosphatemia is the most frequent abnormality.

Around 90% of dialysis patients on phosphate binders, still 35% out of KDOQI targets.

Mineral Metabolism and Mortality Risk in the DOPPS

Disorders of mineral metabolism are associated with increased mortality

Vascular events in healthy older women on calcium supplementation

## Risk Factors Associated With Cardiac Calcification in Young Dialysis Patients

<table>
<thead>
<tr>
<th>Factor</th>
<th>Coronary Calcification (n=14)</th>
<th>No Calcification (n=25)</th>
<th>P - value</th>
</tr>
</thead>
<tbody>
<tr>
<td>Ca from calcium binders (mg/day)</td>
<td>6456 ± 4278</td>
<td>3325 ± 1490</td>
<td>0.02</td>
</tr>
<tr>
<td>Serum Ca (mmol/L)</td>
<td>2.4 ± 0.2</td>
<td>2.28 ± 0.23</td>
<td>0.25</td>
</tr>
<tr>
<td>Serum P (mmol/L)</td>
<td>2.2 ± 0.3</td>
<td>2.0 ± 0.4</td>
<td>0.06</td>
</tr>
<tr>
<td>Ca × P (mmol²/L²)</td>
<td>5.2 ± 0.9</td>
<td>4.5 ± 1.0</td>
<td>0.04</td>
</tr>
<tr>
<td>Age (years)</td>
<td>26 ± 3</td>
<td>15 ± 5</td>
<td>&lt;0.001</td>
</tr>
<tr>
<td>Mean duration of dialysis (years)</td>
<td>14 ± 5</td>
<td>4 ± 4</td>
<td>&lt;0.001</td>
</tr>
</tbody>
</table>

- 39 HD patients 7 – 30 years
- 60 controls 20-30 years
- EBT scans at baseline and after 18-24 months

PREVENTION OF COMPLICATIONS OF THERAPY OF HYPERPHOSPHATEMIA & MBD & ROD & VC IN CKD PATIENTS
Reducing Calcium Load With a Calcium-free Phosphate Binder


Data on file, Genzyme Corporation


Phosphate binder: 3-5 g/day (20-30% resorption) ≈ 1300 mg/day

Dialysate: 1.25 moll/L - net influx ≈ 100-150 mg calcium / HD

Diet: intake ≈ 600 mg calcium per day

Calcium Binder*

Calcium-Free, Metal-Free Binder
Mortality effect of coronary calcification and phosphate binder choice (Sevelamer)

Follow up of a randomized, prospective, open label, multicenter study over a median of 44 months (RIND). 127 patients randomized to either sevelamer or Ca. Prespecified secondary endpoint. Block GA et al. *Kidney Int* 2007;71:438-441

Treatment with sevelamer was associated with a significant survival benefit. There were 11 deaths in the sevelamer and 23 in the Calcium group.
Results of the DCOR trial were inconclusive for the primary end-point of all-cause mortality across the entire patient cohort (RR 0.91; p = 0.3)

A mortality benefit for patients treated with Renagel® was shown in subgroups: Patients older than 65 (predefined) and patients on study for more than 2 years.

### Hospitalisation rate by binder choice

<table>
<thead>
<tr>
<th>Rate per patient-year</th>
<th>Sevelamer</th>
<th>Calcium</th>
<th>HR*</th>
<th>p*</th>
</tr>
</thead>
<tbody>
<tr>
<td>First hospitalisations</td>
<td>0.96</td>
<td>0.97</td>
<td></td>
<td>ns</td>
</tr>
<tr>
<td>Multiple hospitalisations</td>
<td>1.70</td>
<td>1.91</td>
<td>0.89</td>
<td>0.02</td>
</tr>
<tr>
<td>Days in hospital</td>
<td>12.3</td>
<td>13.9</td>
<td>0.88</td>
<td>0.03</td>
</tr>
</tbody>
</table>

Almost every patient was hospitalised once per year. Renagel® treated patients were hospitalized less frequently and spent less time in the hospital.


*Adjusted for demographic variables and prestudy cardiovascular comorbidity*
**Cost-effectiveness** - Good value for money!?


  Lack of outcome data favorable enough to justify widespread utilisation


The yearly cost of implementation of the K/DOQI guidelines for 416 pts. at this center (University of Ottawa) was estimated at $500,605 (American dollars). Given the significant cost, widespread adoption of the K/DOQI CPGs for Bone Metabolism and Disease should await the publication of compelling data demonstrating significant improved outcomes in patients treated with sevelamer.
Economic evaluation of sevelamer in patients with end-stage renal disease

Conclusions. The cost per QALY gained for treating all dialysis patients with sevelamer exceeds what would usually be considered good value for the money. While the high cost per QALY was in part due to the inclusion of the costs of dialysis and transplant in the analysis, the cost per QALY gained remained relatively unattractive even when these costs were excluded. Although a lower cost per QALY gained is realized when only patients older than 65 years are treated, this strategy remains economically unattractive, particularly given the uncertainty of clinical benefit in this group.
The effects of calcium-based versus non-calcium-based phosphate binders on mortality among patients with chronic kidney disease: a meta-analysis

Sophie A. Jamal¹, David Fitchett², Charmaine E. Lok³, David C. Mendelssohn⁴ and Ross T. Tsuyuki⁵

Background. The effects of calcium compared with non-calcium-based phosphate binders on mortality, cardiovascular events and vascular calcification in patients with chronic kidney disease (CKD) are unknown.

Methods. To address this question, we conducted a systematic review. We electronically searched MEDLINE, EMBASE, Cochrane Central Register of Controlled Trials and CINAHL. We identified 160 potential studies and included 8 randomized trials. Eligible studies, determined by consensus using predefined criteria, were reviewed, and data were extracted onto a standard form.

Conclusion. Despite the trends observed, we did not find a statistically significant difference in cardiovascular mortality and coronary artery calcification in patients receiving calcium-based phosphate binders compared to non-calcium-based phosphate binders. However, the data are limited by the small number of studies and the confidence intervals do not exclude a potentially important beneficial effect. Therefore, further randomized trials are required.
The primary advantage for more recently developed phosphate binders (lanthanum carbonate and sevelamer) is a DECREASE IN HYPERCALCEMIA IN DIALYSIS PATIENTS.

Full adoption of sevelamer and lanthanum by government drug reimbursement agencies in place of calcium salts would lead to a LARGE INCREASE IN HEALTH CARE EXPENDITURE.

This can be justified only by presenting evidence for improved clinical outcomes of these agents compared with calcium salts. Additionally, it should be remembered that to date NO CLINICAL TRIAL HAS SHOWN A SURVIVAL ADVANTAGE FOR CALCIUM SALTS (COMPaRED WITH PLACEBO OR OTHER AGENTS)
A Review of Sevelamer Hydrochloride in End-Stage Renal Disease Patients on Dialysis

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Although KDOQI and KDIGO published CKD—MBD guidelines has clearly stated where calcium-based phosphate binders should not be used in D patients (hypercalcemia and low PTH) and where non calcium-containing phosphate binders are preferred (patients with severe vascular and/or other soft tissue calcifications), the greatest controversy and disagreements within the nephrological community still exists upon the cost-effectiveness of non calcium binder (sevelamer) use. Indeed, despite the evidence and recognised trend towards both a decrease in VC and CVD associated with sevelamer use, it is still an ongoing matter of debate. The magnitude of this controversy is increased when the issue of advanced medical and/or budgetary evaluation related to the implementation of clinical guidelines for CKD—MBD treatment is considered. Despite advocated use of sevelamer across a range of common clinical scenarios in CKD, its widespread utilization is challenged as exceeding what would usually be considered good value for money. If so, it is questionable whether the recommendations and suggestions from the guidelines should be followed, and further, do we need guidelines and innovative drugs for treatment of hyperphosphatemia? While awaiting the answer, as clinicians we should proceed with a treatment to “do no harm”, trying to at least limit the calcium exposure of our dialysis patients.
IMPLEMENTATION STRATEGIES
Reduction of Calcium Load and successful P control

“Individualized program” – do not harm!

Dose reduction of the calcium phosphate binders 1-2 gr/day
(single therapy or in combination)
Low-calcium dialysis bath 1.25 mmol/l
Precautious use of Vit. D
<table>
<thead>
<tr>
<th>Parameters</th>
<th>2009</th>
<th>2005</th>
<th>P</th>
</tr>
</thead>
<tbody>
<tr>
<td>Number of HD population</td>
<td>1,282</td>
<td>1,026</td>
<td></td>
</tr>
<tr>
<td>Study cohort—Number (%)</td>
<td>742 (57.8)</td>
<td>588 (57.3)</td>
<td></td>
</tr>
<tr>
<td>Age (years)</td>
<td>56.9 ± 12.9</td>
<td>53.3 ± 13.1</td>
<td>&lt;0.01</td>
</tr>
<tr>
<td>Dialysis duration (years)</td>
<td>6.8 ± 9.2</td>
<td>6.8 ± 6.1</td>
<td>n.s.</td>
</tr>
<tr>
<td>Male (%)</td>
<td>55</td>
<td>62.4</td>
<td>n.s.</td>
</tr>
<tr>
<td>Ca (mM/l) range</td>
<td>2.30 ± 0.24</td>
<td>2.36 ± 0.33</td>
<td>&lt;0.01</td>
</tr>
<tr>
<td>(1.6–3.4)</td>
<td>1.6–3.4</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Ca (2.1–2.6)</td>
<td>79.0</td>
<td>67.4</td>
<td>&lt;0.05</td>
</tr>
<tr>
<td>Ca (&lt;2.1)</td>
<td>13.8</td>
<td>15.1</td>
<td>n.s.</td>
</tr>
<tr>
<td>Ca (&gt;2.6)</td>
<td>7.2</td>
<td>17.5</td>
<td>n.s.</td>
</tr>
<tr>
<td>P (mM/l) range</td>
<td>1.49 ± 0.41</td>
<td>1.64 ± 0.61</td>
<td>&lt;0.01</td>
</tr>
<tr>
<td>(0.5–3.0)</td>
<td>0.5–3.0</td>
<td></td>
<td></td>
</tr>
<tr>
<td>P (1.1–1.8)</td>
<td>64.9</td>
<td>59</td>
<td>n.s.</td>
</tr>
<tr>
<td>P (&lt;1.1)</td>
<td>16.1</td>
<td>12.5</td>
<td>&lt;0.05</td>
</tr>
<tr>
<td>P (&gt;1.8)</td>
<td>19.0</td>
<td>28.5</td>
<td>n.s.</td>
</tr>
<tr>
<td>Ca × P (mM²/l²)</td>
<td>3.44 ± 1.05</td>
<td>3.79 ± 1.62</td>
<td>&lt;0.01</td>
</tr>
<tr>
<td>Ca × P (&lt;4.4 mM²/l²)</td>
<td>80.6</td>
<td>71.1</td>
<td>n.s.</td>
</tr>
<tr>
<td>iPTH (pg/ml) range</td>
<td>323.3 ± 363.8</td>
<td>437.3 ± 611.2</td>
<td>&lt;0.01</td>
</tr>
<tr>
<td>(5–1,702)</td>
<td>5–1,702</td>
<td></td>
<td></td>
</tr>
<tr>
<td>iPTH (150–300 pg/ml)</td>
<td>35.1</td>
<td>17.3</td>
<td>n.s.</td>
</tr>
<tr>
<td>iPTH (&gt;300 pg/ml)</td>
<td>22.9</td>
<td>38.6</td>
<td>n.s.</td>
</tr>
<tr>
<td>iPTH (&lt;150 pg/ml)</td>
<td>42.0</td>
<td>44.1</td>
<td>n.s.</td>
</tr>
<tr>
<td>Parathyroidectomy (%)</td>
<td>4.2</td>
<td>7.0</td>
<td>n.s.</td>
</tr>
</tbody>
</table>

Data are expressed as mean ± SD and percentage (of the study population).
Improved P control through a sustained education, monitoring & evaluation process

Conclusion:
The guidelines implementation process should be a continuous and self-monitored process, with the help of periodic surveys.
CKD-MBD Guidelines - Is there any confusion?

- Evidence
- Guidelines
- Implementation
- Data from systematic reviews & meta analysis
Continuous education through interactive sessions, and monitoring & evaluation of the stuff is essential as an implementation strategy.

“Mild and stepwise treatment" could be a better option than overzealous treatment in order to "do no harm" for patients’ health.

The individualization of the CKD-MBD management should be successful even in the absence of modern new treatments.

Nephrologists in developing countries should ask for advanced treatment options in accordance with the guidelines at least for a small subset of patients where standard therapy does not work.

Professionals should be dedicated to implement the knowledge into the clinical practice and to convince the authorities for best treatment options as main goal for our patients.
Implementation of the CKD-MBD guidelines could save Bones, Blood vessels & the Heart!

Thank You!