CVD Prevention in Patients with Chronic Kidney Disease

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Outline

- CKD and CAD epidemiology
- Pathophysiology of accelerated calcific coronary atherosclerosis
- Clinical consequences of coronary calcification in CKD
- Response to anti-calcific and anti-atherosclerosis therapy
Relative Burden of CVD in General and CKD Populations

10-year CHD Mortality
A Continuum in Risk

Microalbuminuria and eGFR as CKD Screening Tests by Age
KEEP, N=40,013; NHANES, N=10,486

Figure 1. Relative proportions of glomerular filtration rate (eGFR) less than 60 ml/min/1.73 m², and both as positive screening tests for chronic kidney disease in the Hopkins Early Evaluation Program (KEEP) and National Health and Nutrition Examination Survey (NHANES) 1999-2004. *P < 0.001 for eGFR and ACE-I. The current eGFR is held at 30 ml/min/1.73 m² if it exceeds 30 ml/min/1.73 m².


FIGURE 88-3 Relative risks of heart and kidney outcomes in cohorts where eGFR and ACR were measured.

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Atherosclerotic Plaque Development

Hydroxyapatite is formed in vesicles which are released from apoptotic foam cells. Macrophages release protease activator protease that causes foam cell apoptosis, thereby allowing macrophage extracellular matrix for progenitor removal (Cauda, J Clin Invest, 1996). VSMCs undergo osteoblastic transformation.
Large lipid deposition and adjacent medial calcification suggests atherosclerosis.
There was a statistically significant increase in the risk of CVD with increasing P levels (p=0.02).

Patients with serum P levels > 3.5 mg/dL were 1.55 times more likely to have CVD.

**Determinants of Serum Phosphorus (mg/dL)**

- Dietary intake and absorption of P
- Urinary fractional excretion of P
- eGFR
- FGF-23
- 1,25 Dihydroxyvitamin D
- PTH

**Phosphorus and Cardiovascular Events in Framingham Heart Study: Dhingra R, et al. (2007)**

- There was a statistically significant increase in the risk of CVD with increasing P levels (p=0.02)
- Patients with serum P levels > 3.5 mg/dL were 1.55 times more likely to have CVD

**Figure 1.** Proportion of calcified sites by serum phosphate group.
FGF-23 and Mortality in ESRD: the ArMORR Cohort Study

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"Calcification Paradox"


Pulse Wave Velocity Correlates with Arterial Calcification

![Graph showing correlation between Pulse Wave Velocity (PWV) and Arterial Calcification (Agatston score).]

R = 0.664
P < 0.0001

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Mean weighted annualized progression of coronary calcification was 17.2±6.7%.
The non-CKD and CKD rates were 16.9±5.2 and 18.4±11.1%, respectively, p < 0.0001.
No therapy reduced the rate of progression.
After adjustment for baseline characteristics, the relative hazard for the primary composite endpoint was 0.88 (95% CI, 0.79 to 0.97; \( P = 0.008 \)).

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**LDL Hypothesis in CKD**

*CAD* \(\rightarrow\) \(\downarrow\) *LDL-C* \(\rightarrow\) \(\downarrow\) *MI CVD Death*

- 90% of CVD Deaths are Ischemia Related
- Precipitating event is plaque rupture

*CAD* \(\rightarrow\) \(\downarrow\) *LDL-C* \(\rightarrow\) \(\downarrow\) *MI No \(\Delta\) CVD Death*

- ? of CVD Deaths are Ischemia Related
- Underlying CAD and LVH
- Precipitating event is NOT plaque rupture
- Electrolyte disturbance, sepsis, etc
SHARP: Major Atherosclerotic Events

<table>
<thead>
<tr>
<th>Event</th>
<th>Eze/simv (n=4650)</th>
<th>Placebo (n=4620)</th>
<th>Risk ratio &amp; 95% CI</th>
</tr>
</thead>
<tbody>
<tr>
<td>Major coronary event</td>
<td>213 (4.6%)</td>
<td>230 (5.0%)</td>
<td>10.5% SE 5.4 reduction (p=0.0022)</td>
</tr>
<tr>
<td>Non-haemorrhagic stroke</td>
<td>131 (2.8%)</td>
<td>174 (3.8%)</td>
<td></td>
</tr>
<tr>
<td>Major atherosclerotic event</td>
<td>526 (11.3%)</td>
<td>619 (13.4%)</td>
<td></td>
</tr>
<tr>
<td>Other cardiac death</td>
<td>162 (3.5%)</td>
<td>182 (3.9%)</td>
<td>5.4% SE 9.4 reduction (p=0.57)</td>
</tr>
<tr>
<td>Haemorrhagic stroke</td>
<td>45 (1.0%)</td>
<td>37 (0.8%)</td>
<td></td>
</tr>
<tr>
<td>Other major vascular events</td>
<td>207 (4.5%)</td>
<td>218 (4.7%)</td>
<td></td>
</tr>
<tr>
<td>Major vascular event</td>
<td>701 (15.1%)</td>
<td>814 (17.6%)</td>
<td>15.3% SE 4.7 reduction (p=0.0012)</td>
</tr>
</tbody>
</table>

SHARP: Cause-specific mortality

<table>
<thead>
<tr>
<th>Event</th>
<th>Eze/simv (n=4650)</th>
<th>Placebo (n=4620)</th>
<th>Risk ratio &amp; 95% CI</th>
</tr>
</thead>
<tbody>
<tr>
<td>Coronary</td>
<td>91 (2.0%)</td>
<td>90 (1.9%)</td>
<td></td>
</tr>
<tr>
<td>Other cardiac</td>
<td>142 (3.1%)</td>
<td>182 (3.9%)</td>
<td>5.6% SE 8.4 reduction (p=0.38)</td>
</tr>
<tr>
<td>Subtotal: Any cardiac</td>
<td>253 (5.4%)</td>
<td>372 (5.9%)</td>
<td></td>
</tr>
<tr>
<td>Stroke</td>
<td>68 (1.5%)</td>
<td>70 (1.5%)</td>
<td></td>
</tr>
<tr>
<td>Other vascular</td>
<td>40 (0.9%)</td>
<td>36 (0.8%)</td>
<td>5.6% SE 3.0 reduction (p=0.000)</td>
</tr>
<tr>
<td>Subtotal: Any vascular</td>
<td>364 (7.8%)</td>
<td>408 (6.4%)</td>
<td></td>
</tr>
<tr>
<td>Cancer</td>
<td>150 (3.2%)</td>
<td>126 (2.7%)</td>
<td>5.3% SE 1.0 increase (p=0.04)</td>
</tr>
<tr>
<td>Renal</td>
<td>144 (3.0%)</td>
<td>173 (3.7%)</td>
<td></td>
</tr>
<tr>
<td>Other non-vascular</td>
<td>154 (3.3%)</td>
<td>151 (3.3%)</td>
<td></td>
</tr>
<tr>
<td>Subtotal: Any non-vascular</td>
<td>468 (10.4%)</td>
<td>462 (10.2%)</td>
<td></td>
</tr>
<tr>
<td>Unknown cause</td>
<td>113 (2.4%)</td>
<td>115 (2.5%)</td>
<td>1.9% SE 4.2 increase (p=0.40)</td>
</tr>
<tr>
<td>Total: Any death</td>
<td>1142 (24.6%)</td>
<td>1115 (24.4%)</td>
<td></td>
</tr>
</tbody>
</table>
Cardiovascular Calcification in CKD
A Multifactorial Pathogenesis

- Hypertension
- Dyslipidemia
- Age
- Type II Diabetes
- Genetics
- Smoking
- Duration of dialysis
- Oxidative Stress
- Calcitriol and VDA
- Chronic Inflammation
- Hyperphosphatemia
- Exogenous Ca intake
- Smoking
- Elevated Ca x P Product

Sources:
1. Qunibi QY, Nolan CA, Ayus JC.