Cardiovascular Mortality:
General Population vs ESRD Dialysis Patients

RN Foley, PS Parfrey, and MJ Sarnak; Clinical epidemiology of cardiovascular
Causes of death in ESRD Patients

- Cardiovascular: 51% (20-64), 56% (65+)
- Infection: 21% (20-64), 14% (65+)
- Malnutrition: 3% (20-64), 3% (65+)

Courtesy Peter Stenvinkel, MD
Causes of cardiovascular disease in CKD/ESRD – A puzzle with many pieces

- Smoking
- Anemia
- Vascular calcification
- Oxidative stress
- Dyslipidemia
- Endothelial dysfunction
- Genetics
- Insulin resistance
- Sympathetic activation
- Inflammation
- Yet unknown risk factors
- Left ventricular hypertrophy
- AGE’s
- Hypertension
Pathogenesis of cardiovascular disease in CKD
Atherothrombosis is a Systemic Disease: Increase for Myocardial Infarction and Stroke as a Function of ABI Measurement

Medial calcifications

Intimal calcifications

Medicalcosis = Monckeberg

Intimal = atherosclerosis
Femoral Artery

Pelvic Arteries

Intimal Calcification

Medial Calcification

Mixed Calcification

London et al., Nephrol Dial Transplant 2003; 18: 1731-40
Calcification Status & Cardiovascular Survival in ESRD

London et al., Nephrol Dial Transplant 2003; 18: 1731-40
Frequency of calcified aortic arch*

* x-ray radiography
Atherosclerosis: causes

ACCELERATED ATHEROSCLEROSIS IN PROLONGED MAINTENANCE HEMODIALYSIS

Armando Lindner, M.D., Bernard Charra, M.D., Donald J. Sherrard, M.D., and Belding H. Scribner, M.D.

- Older age
- Hypertension
- Male gender
- Elevated LDL and Decreased HDL cholesterol
- Diabetes mellitus
- Tobacco use
- Psychosocial stress
- Family history of CVD
- ECF overload
- Anemia
- Abnormal mineral metabolism
- Malnutrition
- Inflammation/Infection
- Thrombogenic factors
- Oxidative stress
- Proteinuria
- Uremic toxins
Two types of risk factors

<table>
<thead>
<tr>
<th>Risk Factor</th>
<th>Intimal/Atherosclerotic Calcification</th>
<th>Medial/Mönkeberg’s Calcification</th>
</tr>
</thead>
<tbody>
<tr>
<td>Dyslipidemia</td>
<td>Yes</td>
<td>No</td>
</tr>
<tr>
<td>Advanced age</td>
<td>Yes</td>
<td>Yes (local)</td>
</tr>
<tr>
<td>Elevated blood pressure</td>
<td>Yes</td>
<td>Reciprocal (medial lesions worsen blood pressure)</td>
</tr>
<tr>
<td>Male</td>
<td>Yes</td>
<td>No</td>
</tr>
<tr>
<td>Smoking</td>
<td>Yes</td>
<td>No</td>
</tr>
<tr>
<td>Inflammation</td>
<td>Yes (local)</td>
<td>Yes (systemic mediators)</td>
</tr>
<tr>
<td>Diabetes/glucose intolerance</td>
<td>Yes</td>
<td>Yes</td>
</tr>
<tr>
<td>Kidney disease</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Reduced GFR</td>
<td>No</td>
<td>Yes</td>
</tr>
<tr>
<td>Calcium</td>
<td></td>
<td>Yes</td>
</tr>
<tr>
<td>Hypercalcemia</td>
<td>No</td>
<td>Yes</td>
</tr>
<tr>
<td>Positive balance</td>
<td>No</td>
<td>Yes</td>
</tr>
<tr>
<td>Hyperphosphatemia</td>
<td>Yes</td>
<td>Yes</td>
</tr>
<tr>
<td>PTH abnormalities</td>
<td>No</td>
<td>Yes</td>
</tr>
<tr>
<td>Vitamin D administration</td>
<td>No</td>
<td>Yes</td>
</tr>
<tr>
<td>Duration of treatment with dialysis</td>
<td>No</td>
<td>Yes</td>
</tr>
</tbody>
</table>

*Goodman, Am J Kidney Dis, 2004*
# Biomarkers of vascular calcification

<table>
<thead>
<tr>
<th>Promoters</th>
<th>Inhibitors</th>
</tr>
</thead>
<tbody>
<tr>
<td>- High blood glucose levels</td>
<td><strong>Circulating inhibitors</strong></td>
</tr>
<tr>
<td>- High LDL Cholesterol</td>
<td>- fetuin A</td>
</tr>
<tr>
<td>- Low HDL Cholesterol</td>
<td>- bone morphogenic protein -7</td>
</tr>
<tr>
<td>- Uremic serum</td>
<td>- PTHrP</td>
</tr>
<tr>
<td>- Hyperphosphatemia</td>
<td>- HDL</td>
</tr>
<tr>
<td>- Increased CaxP product</td>
<td>- Magnesium</td>
</tr>
<tr>
<td>- High intake of Vitamin D</td>
<td></td>
</tr>
<tr>
<td>- High iPTH levels</td>
<td><strong>Locally acting inhibitors</strong></td>
</tr>
<tr>
<td>- Hypercalcemia</td>
<td>- Matrix Gla protein</td>
</tr>
<tr>
<td>- Elevated leptin levels</td>
<td>- Osteopontin</td>
</tr>
<tr>
<td>- TNF α</td>
<td>- Pyrophosphate</td>
</tr>
<tr>
<td>- TGFβ</td>
<td>- Osteoprotegerin (OPG)</td>
</tr>
<tr>
<td>- AGEs</td>
<td></td>
</tr>
<tr>
<td>- Oxidised lipids</td>
<td></td>
</tr>
</tbody>
</table>
Distribution of 83 HD patients according to CV risk and ABI

At least one cv complication: LVH; MI; stroke; Heart failure
Established general favouring conditions

- age +++
- male gender
- hypertension
- diabetes mellitus
- vitamin D intoxication
Established favoring conditions linked to CKD

- severe 2ary hyperparathyroidism
- low bone turnover (hypoPTH, Al)
- high-dose active vitamin D metabolites
- high serum P or Ca; high Ca x P product
- excessive oral calcium intake
- duration of dialysis
Vascular calcification

Vascular calcification causes cardiac disease

VC

Vessel stiffness

↑ Pulse wave velocity
↓ Coronary perfusion

↑ Pulse pressure
↑ Afterload

Left ventricular hypertrophy

Cardiac disease events
**Vascular calcifications**

Ectopic calcification in the vessel wall is very common in ESRD

**Localization**

- **arterial calcifications**
  - atheromatous (*intima, sub-intima*)
  - medial (*media*)

- **arteriolar calcifications**
  - calcific uremic arteriolopathy (*“calciphylaxis”*)