Coronary artery disease in patients with Diabetes- Focus on Chronic Kidney Disease

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Lars G Weiss, MD. PhD
Dept of Nephrology, Central Hospital
Karlstad Sweden
Prevention of Chronic kidney disease.

1. What is CKD?
2. How common is CKD?
3. Cardiovascular risk in CKD-patients.
4. Can CKD be prevented (Renoprotection)?
5. Can CVD in CKD-3-5 be prevented (cardioprotection)? nephropathy?
5. Conclusion.
Diabetic nephropathy vs chronic kidney disease (CKD)

- Diabetic nephropathy
  - Is defined as macroalbuminuria in two out of three samples during three months

- CKD
  - Is defined according to estimated GFR.
  - STAGE I-V
Not a sensitive marker for changes in GFR when renal function is normal. Indeed, people may lose 50% of GFR and have a borderline high Creatinine.
Commonly used formulas for estimating renal function. MDRD = modification of diet in renal disease

Cockroft and Gault equation
Estimated creatinine clearance (Cl\textsubscript{cr}) = \frac{(140 - \text{age}) \times \text{weight} \times 1.2}{\text{SCR}} \times (0.85 \text{ if female})
where age is expressed in years, SCR in \mu\text{mol/l}, and weight in kg\textsuperscript{10}

6-variable MDRD\textsuperscript{15}
170 \times (S\textsubscript{Cr}/88.4)\textsuperscript{-0.999} \times \text{age}^{-0.176} \times (\text{SU}/0.357)\textsuperscript{-0.170} \times (\text{SAlb} \times 10)^{0.318} \times (0.762 \text{ if female}) \times (1.180 \text{ if black})
where S\textsubscript{Cr} = serum creatinine in \mu\text{mol/l}, SU = serum urea in mmol/l, SAlb = serum albumin in g/l,
and age is expressed in years

4-variable MDRD\textsuperscript{16}
186.3 \times (S\textsubscript{Cr}/88.4)\textsuperscript{-1.154} \times \text{age}^{-0.203} \times (0.742 \text{ if female}) \times (1.21 \text{ if black})
where S\textsubscript{Cr} = serum creatinine in \mu\text{mol/l}, and age is expressed in years

Modified 4-variable MDRD (traceable by isotope dilution mass spectrometry)\textsuperscript{19}
F \times 175 \times (S\textsubscript{Cr}/88.4)\textsuperscript{-1.154} \times \text{age}^{-0.203} \times (0.742 \text{ if female}) \times (1.21 \text{ if black})
where F = correction factor, S\textsubscript{Cr} = serum creatinine in \mu\text{mol/l}, and age is expressed in years
Estimated Glomerular Filtration rate

- 4 variable MDRD-formula is used for CKD classification in most studies.

\[
eGFR \ (mL/\text{min}/1.73m^2) = 186 \times \left[ \text{SerumCreatinine(umol/L)} \times 0.0113 \right]^{-1.154} \times \text{Age(years)}^{-0.203} \times 0.742 \text{ if female} \times 1.21 \text{ if Afro-american}
\]
Association of estimated glomerular filtration rate (GFR) with GFR measured by an isotopic reference method. Below 60 ml/min/1.73 m² the two methods are tightly associated.

Stages of Chronic kidney disease

Numbers calculated from NHANES III-data and verified by HUNT data.

% of population

<table>
<thead>
<tr>
<th>CKD Stages</th>
<th>1</th>
<th>2</th>
<th>3</th>
<th>4</th>
<th>5</th>
</tr>
</thead>
<tbody>
<tr>
<td>GFR (ml/min/1.73m²)</td>
<td>120</td>
<td>90</td>
<td>60</td>
<td>30</td>
<td>15</td>
</tr>
<tr>
<td>Kidney disease</td>
<td>Normal GFR</td>
<td>Mild ↓ Kidney-function</td>
<td>Moderate ↓ Kidney-function</td>
<td>Severe ↓ Kidney-function</td>
<td>Kidney-failure</td>
</tr>
<tr>
<td>% of population</td>
<td>3,3</td>
<td>3,0</td>
<td>4,3</td>
<td>0,2</td>
<td>0,1</td>
</tr>
</tbody>
</table>
## Definition of normal and abnormal urine albumin leakage

<table>
<thead>
<tr>
<th></th>
<th>Morning Urine</th>
<th>24h Urine</th>
<th>Overnight urine</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Normal</strong></td>
<td>&lt; 20</td>
<td>&lt;3</td>
<td>&lt;30</td>
</tr>
<tr>
<td></td>
<td>Albumin (mg/l)</td>
<td>Albumin/Creatinine ratio* (mg/mmol)</td>
<td>Albumin (mg/24h)</td>
</tr>
<tr>
<td></td>
<td>&lt;25 M &lt;2.5 F &lt;3.5</td>
<td>&lt;25 M &lt;20 F &lt;30</td>
<td>&lt;30</td>
</tr>
<tr>
<td><strong>Microalbuminuria</strong></td>
<td>20-200</td>
<td>3-30</td>
<td>25-250</td>
</tr>
<tr>
<td></td>
<td>M 2.5-25 F 3.5-35</td>
<td>M 20-200 F 30-300</td>
<td></td>
</tr>
<tr>
<td><strong>Macroalbuminuria</strong> (proteinuria)</td>
<td>&gt;200</td>
<td>&gt;30</td>
<td>&gt;250</td>
</tr>
<tr>
<td></td>
<td>M &gt;25 F &gt;35</td>
<td>M &gt;200 F &gt;300</td>
<td></td>
</tr>
</tbody>
</table>

* The creatinine corrected values as well as the sex corrections vary between guidelines; we chose the above close to the varies recommendations, but rounded to figures that are close to the threshold given in mg/l, mg/day, and μg/min
Prevalence of albuminuria in the general population

- **Normal**
  - 0-10 mg/l
  - 75%

- **Micro-albuminuria**
  - 20-200 mg/l
  - 7.2%

- **Macro-albuminuria**
  - >200 mg/l
  - 0.7%

High-normal albuminuria
- 10-20 mg/l
- 16.6%

n=40,856

Hillege et al; J Int Med 2001;249:519-526
Prevention of Chronic kidney disease.

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Approximately 40% of T2DM patients have renal complications

- Typical progression of CKD†

<table>
<thead>
<tr>
<th>CKD stage</th>
<th>eGFR (mL/min)</th>
<th>% of T2DM pts</th>
</tr>
</thead>
<tbody>
<tr>
<td>Missing data</td>
<td>–</td>
<td>~9.5%</td>
</tr>
<tr>
<td>No CKD</td>
<td>≥90*</td>
<td>~50.8%</td>
</tr>
<tr>
<td>1</td>
<td>≥90**</td>
<td>~9%</td>
</tr>
<tr>
<td>2</td>
<td>60–89</td>
<td>~11%</td>
</tr>
<tr>
<td>3</td>
<td>30–59</td>
<td>~18%</td>
</tr>
<tr>
<td>4–5</td>
<td>&lt;29</td>
<td>~2%</td>
</tr>
</tbody>
</table>

* No signs of kidney damage
** Albuminuria – kidney damage

†Based on data from 1462 patients aged ≥20 years with T2DM who participated in the Fourth National Health and Nutrition Examination Survey (NHANES IV) in the years 1999 through 2004

Diabetes is a primary cause of incident ESRD: Comparing rates in different countries

Renal function distribution (Szummers Kidn Int 2011)

- eGFR ≥90 (n=11,947): 22.5%
- eGFR 60-89 (n=24,764): 46.6%
- eGFR 30-58 (n=14,079): 26.5%
- eGFR 15-29 (n=1,712): 3.2%
- eGFR <15/dialysis (n=592): 1.1%

Renal function:
- Normal
- Mild
- Moderate
- Severe
- Renal 51.5% on dialysis

eGFR mean±SD: 73±28 ml/min/1.73 m²
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Age-adjusted rates of any cardiovascular event by level of estimated GFR among 1,120,195 adults with known kidney function.

Go et al. NEJM 2004;351:1296-1305
PREVEND; Baseline albuminuria associated with CV mortality *in the general population* (n=40,548; 3 yr follow-up)

Hillege *et al*; *Circulation* 2002
Proteinuria and Risk of Stroke and CHD Events in Type 2 Diabetes

U-Prot, urinary protein concentration.
Cardiovascular Disease Mortality
General Population vs ESRD Patients

GP: General Population.

Uraemic Arteriopathy vs. Atherosclerosis

Chalk

Cheese
Temporal aspects of disordered phosphorus metabolism in CKD
Prevention of Chronic kidney disease.

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Albuminuria prevention and reduction
The Holy Grail for kidney protection
• This study investigated whether an angiotensin-receptor blocker (olmesartan) would delay microalbuminuria in patients with type 2 diabetes and normoalbuminuria.

• Olmesartan was associated with a delayed onset of microalbuminuria, even though blood pressure control in both groups was excellent.
Occurrence of Microalbuminuria during the 48-Month Follow-up Period in the Two Study Groups.

Lowering blood pressure reduces renal events in type 2 diabetes (Advance)

Galan : Journal of American Society of Nephrology 2009
Progression of Diabetic Renal Disease in Patients with Type 2 Diabetes

- **Normoalbuminuria**: Δ GFR 1 ml/min/year
- **Microalbuminuria**: Δ GFR 2-4 ml/min/year
- **Overt nephropathy**: Δ GFR 4-20 ml/min/year

Diagram shows changes in Albuminuria (µg/min) over time (Years): 2000, 200, 20, 2.
Regression to normoalbuminuria preserves kidney function in type 2 diabetes


Graph showing the change in glomerular filtration rate (ΔGFR) in ml/min/year for different albuminuria categories:
- **Normoalbuminuria** (n=46): ΔGFR = -2.3 ml/min/year, p=0.03
- **Microalbuminuria** (n=58): ΔGFR = -3.7 ml/min/year, p=0.007
- **Macroalbuminuria** (n=47): ΔGFR = -5.4 ml/min/year, p<0.001
RENAAL
End Stage Renal Disease

Risk Reduction: 28%
p = 0.002

Baseline proteinuria as a determinant for renal events. RENAAL-study.

Change in albuminuria (baseline compared to month 6). Versus the hazard ratio of renal endpoint. RENAAL
ALTITUDE: effect of aliskiren on cardiovascular and renal events in a high-risk type 2 diabetic population

Randomization

- Aliskiren 150 mg
- Aliskiren 300 mg once daily
- Placebo

Conventional treatment

4–12 weeks  4 weeks  total follow-up ~4 years*

ALTITUDE is an event driven study and will conclude when ~1628 patients meet the primary endpoint
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How to reduce CVD in CKD patients?

- No published RCT in patients with CKD 3-5 (CI <60 ml/min) have shown a reduction in CVD as primary endpoint.

1. Statintreatment in Dialysis patients (4D and AURURA NEJM 2005, 2009.) vs placebo both NS.

2. Treatment with ESA. TREAT-study NEJM 2009 (Darbepoetin in diabetic patients with CI<60 vs. Placebo) Hb 130 vs 90 g/l. NS.
The results of the Study of Heart and Renal Protection (SHARP)

Colin Baigent, Martin Landray
on behalf of the SHARP Investigators

Disclosure: SHARP was sponsored, designed, run, and analysed by the University of Oxford. Funding was received from Merck, the UK MRC, British Heart Foundation, and Australian NHMRC.
SHARP: Eligibility

- History of chronic kidney disease
  - not on dialysis: elevated creatinine on 2 occasions
    - Men: ≥1.7 mg/dL (150 µmol/L)
    - Women: ≥1.5 mg/dL (130 µmol/L)
  - on dialysis: haemodialysis or peritoneal dialysis
- Age ≥40 years
- No history of myocardial infarction or coronary revascularization
SHARP: Assessment of LDL-lowering
SHARP: Main outcomes

- **Key outcome**
  - Major atherosclerotic events (coronary death, MI, non-haemorrhagic stroke, or any revascularization)

- **Subsidiary outcomes**
  - Major vascular events (cardiac death, MI, any stroke, or any revascularization)
  - Components of major atherosclerotic events

- **Main renal outcome**
  - End stage renal disease (dialysis or transplant)
SHARP: Major Atherosclerotic Events

Risk ratio 0.83 (0.74 – 0.94)
Logrank 2P=0.0022

Placebo

Eze/simv
SWEDEHEART
Statin use at discharge

- eGFR ≥90: 84% (n=11947)
- 60-89: 77% (n=24764)
- 30-59: 58% (n=14079)
- 15-29: 44% (n=1712)
- <15/Dialysis: 52% (n=592)
## SWEDEHEART

### 1-year mortality and renal function

<table>
<thead>
<tr>
<th>eGFR</th>
<th>No statin n/N (%)</th>
<th>With statin n/N (%)</th>
<th>Adjusted HR</th>
<th>p-value</th>
</tr>
</thead>
<tbody>
<tr>
<td>≥90</td>
<td>249/1756 (14%)</td>
<td>272/9206 (3%)</td>
<td>0.59</td>
<td>&lt;0.001</td>
</tr>
<tr>
<td>60-89</td>
<td>844/5053 (17%)</td>
<td>703/17466 (4%)</td>
<td>0.64</td>
<td>&lt;0.001</td>
</tr>
<tr>
<td>30-59</td>
<td>1520/5252 (29%)</td>
<td>845/7370 (12%)</td>
<td>0.72</td>
<td>&lt;0.001</td>
</tr>
<tr>
<td>15-29</td>
<td>403/853 (47%)</td>
<td>183/663 (28%)</td>
<td>0.75</td>
<td>0.013</td>
</tr>
<tr>
<td>&lt;15/dialysis</td>
<td>107/230 (47%)</td>
<td>109/268 (41%)</td>
<td>1.13</td>
<td>0.545</td>
</tr>
</tbody>
</table>
What did he say? 1

- CKD is defined by eGFR in stages 1-5.
- Definition of nepropathy is repeated macroalbuminuria in 2 of 3 samples >300mg/24 hour or Alb/Creatininratio > 30 mg/mmol.
- In Western populations the prevalence of micro and macroalbuminuria is 8% and for CKD 3-5 4,5%.
- In diabetic populations this is 30-40%.
- Albuminuria and low eGFR are strong predictors for both renal and cardiovascular risc.
- Nephropathy can be prevented or at least halted by bloodpressure control, metabolic control and RAS-inhibition Targets bloodpressure <130/80 mmHg.
In patients with nephropathy important to reduce albuminuria to protect kidneys and perhaps reduce CVD. Will be studied in the ALTITUDE-study.

The first RCT to show reduction in cardiovascular disease in CKD3-5 population is the SHARP-study.

Due to different mechanisms of disease (vascular calcifications) alternative treatments need to be tested in RCT. Eg. calcimimetics in the ongoing EVOLVE-study.