Chronic Kidney Disease: why is it important for CVD and diabetes?

Professor Richard McManus
Overview

• Definitions & epidemiology
• CKD and subsequent risk
• Proteinuria
• Diabetes
• Statins
## Definitions

<table>
<thead>
<tr>
<th>Stage</th>
<th>Description</th>
<th>GFR mls/min/1.73m²</th>
</tr>
</thead>
<tbody>
<tr>
<td>1</td>
<td>Kidney damage with normal or increased GFR</td>
<td>≥ 90</td>
</tr>
<tr>
<td>2</td>
<td>Kidney damage with reduced GFR</td>
<td>60-89</td>
</tr>
<tr>
<td>3a</td>
<td>Moderately reduced GFR</td>
<td>45-59</td>
</tr>
<tr>
<td>3b</td>
<td>Moderately reduced GFR</td>
<td>30-44</td>
</tr>
<tr>
<td>4</td>
<td>Severely reduced GFR</td>
<td>15-29</td>
</tr>
<tr>
<td>5</td>
<td>Kidney Failure</td>
<td>≤ 15 or dialysis</td>
</tr>
</tbody>
</table>
WHO GETS IT?
Who gets it?

Total Population
N= 2707130

Patients with a Serum Creatinine
N= 1403422 (51.8%)

Patients with two lab EGFRs 7 days apart
N=648363 (24.0%)

Patients with CKD
N=111730 (4.1%)

Patients with readcode for CKD
N=81086 (3.0%)

Patients without a Readcode for CKD
N=30664(1.1%)

Patients with a Readcode for CKD but GFR above 60
N=46724(1.7%)

420415 patients have only single eGFR
(15.5%)

Prevalence approx double if single eGFR

<table>
<thead>
<tr>
<th>Stage</th>
<th>3a</th>
<th>3b</th>
<th>4</th>
<th>5</th>
</tr>
</thead>
<tbody>
<tr>
<td>Prevalence</td>
<td>2.86</td>
<td>0.86</td>
<td>0.180</td>
<td>0.031</td>
</tr>
<tr>
<td></td>
<td>(2.84-2.88)</td>
<td>(0.85-0.87)</td>
<td>(0.175-0.185)</td>
<td>(0.029-0.033)</td>
</tr>
<tr>
<td>Mean age</td>
<td>60.55 ± 15.03</td>
<td>74.47 ± 11.14</td>
<td>79.08 ± 10.02</td>
<td>77.23±12.62</td>
</tr>
<tr>
<td>% female</td>
<td>53.5%</td>
<td>62.1%</td>
<td>63.0%</td>
<td>55.8%</td>
</tr>
</tbody>
</table>

Jain et al Plos One 2014

Prevalence approx double if single eGFR
Much increased with age
IMPORTANCE OF CVD?
CKD patients are FAR more likely to die than progress to ESKD

5% Medicare Sample, 1996-1997 Cohort, 2-Year Follow-Up

n = 19,940,320  n = 4,007,980  n = 688,680  n = 406,800

What causes this?

Kaiser Permanente Data:

- 1.12m adults >20 yrs with SCr 1996-2000 and no ESRF
- Calculated eGFR and followed up for CVD events
- 55% women, mean age 52
- Mean FU 2.4 yrs
CKD leads to Increased CVD Risk and Mortality

Worse where rapid decline in eGFR

- CVD Health Study
- 4380 patients with repeated eGFR
- Compared decline in GFR in first 7 years with outcomes in subsequent 8 yrs
- Rapid decline defined as >3mls/min/yr

<table>
<thead>
<tr>
<th>Parameter</th>
<th>No Rapid Decline</th>
<th>Rapid Decline</th>
</tr>
</thead>
<tbody>
<tr>
<td>HF rates (events/1000 patient-years)</td>
<td>30</td>
<td>42</td>
</tr>
<tr>
<td>demographic adjusted HR</td>
<td>1.00 (reference)</td>
<td>1.40 (1.20 to 1.65)</td>
</tr>
<tr>
<td>multivariate adjusted HR</td>
<td>1.00 (reference)</td>
<td>1.24 (1.05 to 1.46)</td>
</tr>
<tr>
<td>MI rates (events/1000 patient-years)</td>
<td>16</td>
<td>24</td>
</tr>
<tr>
<td>demographic adjusted HR</td>
<td>1.00 (reference)</td>
<td>1.53 (1.24 to 1.88)</td>
</tr>
<tr>
<td>multivariate adjusted HR</td>
<td>1.00 (reference)</td>
<td>1.42 (1.14 to 1.76)</td>
</tr>
<tr>
<td>Stroke rates (events/1000 patient-years)</td>
<td>17</td>
<td>22</td>
</tr>
<tr>
<td>demographic adjusted HR</td>
<td>1.00 (reference)</td>
<td>1.29 (1.05 to 1.57)</td>
</tr>
<tr>
<td>multivariate adjusted HR</td>
<td>1.00 (reference)</td>
<td>1.11 (0.89 to 1.37)</td>
</tr>
<tr>
<td>PAD rates (events/1000 patient-years)</td>
<td>3</td>
<td>5</td>
</tr>
<tr>
<td>demographic adjusted HR</td>
<td>1.00 (reference)</td>
<td>1.86 (1.12 to 3.08)</td>
</tr>
<tr>
<td>multivariate adjusted HR</td>
<td>1.00 (reference)</td>
<td>1.67 (1.02 to 2.75)</td>
</tr>
</tbody>
</table>

Progression risk factors are all also cardiovascular risk factors

- Hypertension
- Dyslipidaemia
- Smoking
- Obesity
- Proteinuria
Evidence of reduced use of primary and secondary prevention in CKD

- Significant reduction in both medical and interventional intervention as GFR reduces
- Therapeutic nihilism?
  “Perhaps the constellation of findings in the patient with chronic kidney disease connotes a degree of debility that wrongly discourages physicians from applying useful preventative strategies”
Eg Worse CKD associated with higher \( CHADS_2 \) score but not more RX

H Reinecke et al, Kidney International 2014
Mortality increases with age and reduced eGFR

Bottom Line

• CKD common
• Mortality from CVD more important vs ESRD
• Worse with rapid decline eGFR
• Diabetes amplifies this effect
• Evidence of therapeutic nihilism
PROTEINURIA
What is proteinuria?

<table>
<thead>
<tr>
<th>Albumin:creatinine ratio</th>
<th>Protein:creatinine ratio</th>
<th>24-hour urinary protein excretion (g/day)</th>
</tr>
</thead>
<tbody>
<tr>
<td>30 mg/mmol</td>
<td>Approx. equivalent to 50 mg/mmol</td>
<td>Approx. equivalent to 0.5 g/day</td>
</tr>
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</table>

Clinically significant proteinuria = ACR > 30 mg/mmol (qv diabetes where microalbuminuria is 10% of this)
eGFR vs ACR: effects on mortality

A. All-cause mortality; eGFR

B. All-cause mortality; ACR

C. Cardiovascular mortality; eGFR

D. Cardiovascular mortality; ACR

Chronic Kidney Disease Prognosis Consortium Lancet 2010
Microalbuminuria & CHD
Third Copenhagen City Heart Study

Relative risk of death

<table>
<thead>
<tr>
<th>Urine albumin excretion</th>
<th>Relative risk</th>
</tr>
</thead>
<tbody>
<tr>
<td>&lt;25%</td>
<td>1</td>
</tr>
<tr>
<td>25% - 50%</td>
<td>1</td>
</tr>
<tr>
<td>50% - 75%</td>
<td>1</td>
</tr>
<tr>
<td>&gt;75% (ACR &gt; 0.7)</td>
<td>4</td>
</tr>
</tbody>
</table>
Increasing proteinuria increases risk of ESRD
1860 non diabetic patients with mean follow-up 2.2 yrs.

ACE inhibitor group had greater mean decrease in blood pressure and urinary protein excretion

After adjustment for patient and study characteristics at baseline and changes in SBP and urinary protein excretion relative risks in the ACE inhibitor group

- 0.69 (CI, 0.51 to 0.94) for end-stage renal disease
- 0.70 (CI, 0.55 to 0.88) for combined outcome of doubling of the baseline serum creatinine concentration or ESRF

Patients with greater urinary protein excretion at baseline benefited more from ACE inhibitor therapy
HOW LOW TO GO?
Latest data on optimal BP goal for ESRD & mortality in HT

Sim et al JACC 2014;64:588-597

398,419 treated HT-ves from Kaiser Permanante

SBP 130-139 / 60-79 was optimum in this large cohort followed for 5 yrs to 2010

Sim et al JACC 2014;64:588-597
BP target in Proteinuria

- Best evidence for effect of BP reduction to $<130/\text{in those with proteinuria}$
Change in LV mass and LV mass Index in CKD stage 3 patients on ACEi or ARB treated with spironolactone or placebo.

-20 -15 -10 -5 0 5 10

LV mass (g) LV mass index (g/m²)

†† p<0.01 spironolactone vs. placebo at week 40

Edwards NC et al JACC 2009
Bottom Line

• In uncomplicated CKD 3, treat blood pressure to usual targets – 140/90 mmHg
• In proteinuria, then treat to 130/80 mmHg
• In diabetes treat to usual targets (inc where microalbuminuria)
WHAT ABOUT DIABETES?
Diabetes and CKD

• Compelling indications for ACEI as first line antihypertensive are not affected by CKD

• Proteinuria is even more of a risk factor in DM hence microalbuminuria thresholds are much lower than the proteinuria threshold for CKD without diabetes (approx 10% of proteinuria threshold)
Don’t forget old lessons re ACEI eg T1DM

Lewis et al, 1983, NEJM 329: 1456

N=409
P’uria \leq 500\text{mg/d}
Creat < 220\mu\text{M} = \text{BP control}

Overall 46% reduction
76% in pts creat > 130\mu\text{M}
Normo + hypertensive
• Double risk of depression in DM with eGFR <30
• Risk no longer significant when adjusting for reduced Hb
• QoL not significantly related to eGFR

Bottom Line

• Main place for ACEI/ARB in CKD is in those with proteinuria and/or diabetes
• In uncomplicated CKD then normal BP lowering treatment is appropriate
• Don’t forget other issues in presence of multi morbidity
WHAT ABOUT STATINS?
Statins and CKD

- Previously some concern that statins “don’t work” in CKD
- This is mainly an issue for CKD stage 5 ie NOT most patients with CKD in PC
- AURORA study of rosuvastatin in dialysis patients was negative
- However...
Statin plus ezetimibe

- SHARP study (Baigent et al Lancet 2011)
- 2/3 eGFR < 30, primary = major atherosclerotic events
Cochrane Meta-analysis

All cause mortality
RR 0.89 (0.82-0.97)

CVD mortality
RR 0.86 (0.78-0.95)

CVD events
RR 0.78 (0.72-0.85)

MI
RR 0.76 (0.68-0.86)

Stroke
RR 0.86 (0.62-1.20)

Palmer et al Ann Int Med 2012
Bottom Line

• Use statins to reduce CVD risk in people with CKD:
  – Primary prevention, calculate risk as normal but be aware that CKD increases this risk
  – Secondary prevention – statins indicated for all
Conclusions

• CKD is common
• Main issue is cardiovascular risk unless young or CKD 3b or below
• Treat CVD risk as normal with antihypertensives and statins
• In presence of proteinuria and/or diabetes, treat blood pressure more aggressively and use ACEI
• Don’t forget other non CVD issues (depression)