Expected remaining lifetimes in adult CKD Stage 5 as compared to the General Population.

- **Europe**
- **US Whites**
- **General Population**
- **Transplant**
- **Dialysis**

ERA-EDTA Registry data and USRDS data.
Increased prevalence of CVD

TABLE 2. Approximate Prevalence of CVD in the General Population and CKD

<table>
<thead>
<tr>
<th></th>
<th>Ischemic Heart Disease (Clinical)</th>
<th>LVH (Echo)</th>
<th>Heart Failure (Clinical)</th>
</tr>
</thead>
<tbody>
<tr>
<td>General population</td>
<td>8–13*</td>
<td>20†</td>
<td>3–6‡</td>
</tr>
<tr>
<td>CKD stages 3–4 (diabetic and nondiabetic kidney disease)</td>
<td>NA</td>
<td>25–50 (varies with level of kidney function)§</td>
<td>NA</td>
</tr>
<tr>
<td>CKD stages 1–4 (kidney transplant recipients)</td>
<td>15</td>
<td></td>
<td></td>
</tr>
<tr>
<td>CKD stage 5 (hemodialysis)</td>
<td>40#</td>
<td>75**</td>
<td>40#</td>
</tr>
<tr>
<td>CKD stage 5 (peritoneal dialysis)</td>
<td>40#</td>
<td>75**</td>
<td>40#</td>
</tr>
</tbody>
</table>

Circulation 2003;108;2154-2169

Hypertension 2003;42:1050-1065
Increased prevalence of CVD

ERA-EDTA Registry data (5 countries – 1994 to 2001)

*Prevalence of cardiovascular co-morbidity at the start of dialysis*

Stel VS et al. Prevalence of co-morbidity in different European RRT populations and its effect on access to renal transplantation. NDT 2005: 2803–2811
Increased prevalence of CVD

DOPPS 1 data

Prevalence of cardiovascular co-morbidity in HD patients at ‘baseline’

- CAD
- CHF
- Other cardiac

Increased cardiovascular mortality

Cardiovascular mortality in the general population (NCHS) and in kidney failure treated by dialysis or transplant (USRDS)


Circulation 2003;108:2154-2169
Hypertension 2003;42;1050-1065
“The directly standardized cardiovascular mortality rate was 8.8 (95% CI, 8.6-9.0) times higher in patients starting dialysis than in the general population.”
Why is cardiovascular mortality so much increased?

- CKD is common in people with CVD and with CVD risk factors

- CKD is associated with an increased risk of adverse outcomes in these conditions

**TABLE 6. Traditional and Nontraditional Cardiovascular Risk Factors in CKD**

<table>
<thead>
<tr>
<th>Traditional Risk Factors</th>
<th>Nontraditional Factors</th>
</tr>
</thead>
<tbody>
<tr>
<td>Older age</td>
<td>Albuminuria</td>
</tr>
<tr>
<td>Male sex</td>
<td>Homocysteine</td>
</tr>
<tr>
<td>Hypertension</td>
<td>Lipoprotein(a) and apolipoprotein(a) isoforms</td>
</tr>
<tr>
<td>Higher LDL cholesterol</td>
<td>Lipoprotein remnants</td>
</tr>
<tr>
<td>Lower HDL cholesterol</td>
<td>Anemia</td>
</tr>
<tr>
<td>Diabetes</td>
<td>Abnormal calcium/phosphate metabolism</td>
</tr>
<tr>
<td>Smoking</td>
<td>Extracellular fluid volume overload</td>
</tr>
<tr>
<td>Physical inactivity</td>
<td>Electrolyte imbalance</td>
</tr>
<tr>
<td>Menopause</td>
<td>Oxidative stress</td>
</tr>
<tr>
<td>Family history of CVD</td>
<td>Inflammation (C-reactive protein)</td>
</tr>
<tr>
<td>LVH</td>
<td>Malnutrition</td>
</tr>
<tr>
<td></td>
<td>Thrombogenic factors</td>
</tr>
<tr>
<td></td>
<td>Sleep disturbances</td>
</tr>
<tr>
<td></td>
<td>Altered nitric oxide/endothelin balance</td>
</tr>
</tbody>
</table>

- High prevalence of traditional risk factors in CKD

- As renal function deteriorates non-traditional risk factors play an increasing role in GFR loss and cardiovascular damage
In order to be regarded as a causal risk factor there ideally needs to be

- biological plausibility as to why the factor may promote CVD risk
- demonstration that the risk factor level increases with severity of kidney disease
- demonstration of an association between the risk factor and CVD in observational studies in CKD and
- demonstration in placebo-controlled clinical trials that treatment of the risk factor decreases CVD outcomes
Negative “cardiovascular RCTs” in CKD

- **CREATE**
  failed to show a reduction of cardiovascular events by early complete correction of anemia

- **4D**
  failed to show a statistically significant effect of atorvastatin on a composite primary end point of cardiovascular death, nonfatal myocardial infarction, and stroke in patients with diabetes receiving hemodialysis

- **CHOIR**
  showed that the use of a target hemoglobin level of 13.5 g/dl (as compared with 11.3 g/dl) was associated with increased risk of a composite mainly cardiovascular endpoint and no incremental improvement in the quality of life

- **AURORA**
  failed to show a significant effect of initiation of treatment with rosuvastatin on the composite primary end point of death from cardiovascular causes, nonfatal myocardial infarction, or nonfatal stroke

- **AASK**
  failed to show an effect of intensive blood-pressure control on kidney disease progression in black patients with hypertensive chronic kidney disease
Why trials in dialysis patients may be negative

Possibility 1  
*There is a benefit (a true effect) of the intervention, but it was not detected in this specific trial*

Possibility 2  
*There is indeed no effect in the dialysis population*

---


Jager KJ, Stel VS, Zoccali C, Wanner C, Dekker FW. The issue of studying the effect of interventions in renal replacement therapy - to what extent may we be deceived by selection and competing risk? NDT 2010 – ahead of print 10 September
Why trials in dialysis patients may be negative

Possibility 1  There is a benefit (a true effect) of the intervention, but it was not detected in this specific trial

1st potential cause - ‘Flawed’ RCT design

– selected patient populations in RCTs
  • strict in- and exclusion criteria → enrollment of relatively healthy subjects
  • refusal rate usually higher in worse patients → healthy volunteer bias
    ~~ increases the risk of a study being underpowered

– unequal distribution of unmeasured confounders ~~ if so, unable to adjust

– some endpoints or other patient characteristics may be difficult to determine
  ~~ adjudication helps, but may not entirely solve the problem

– studies in prevalent dialysis patients may suffer from survivor bias
  ~~ incident patients to be preferred
Why trials in dialysis patients may be negative

Survivor bias in studies using prevalent dialysis patients

- = start of dialysis  † = death  t = time of sampling patients

- When prevalent patients are sampled at any of the time points (t1, t2 or t3), those who live longest - the survivors - (3/5 patients) will be over-represented

- Survivor bias may distort the relative risk in either direction
Possibility 1  

There is a benefit (a true effect) of the intervention, but it was not detected in this specific trial.

2nd potential cause - Mortality in this patient population is extremely high

Beneficial effects may be masked by

- increased mortality from other causes inducing a ‘dilution’ of the effect
  ~~~ ‘low signal to noise ratio’
- dilution increased by the heterogeneity of cardiac death (ischaemic / sudden death / heart failure)
Why trials in dialysis patients may be negative

Modifiable risk factors associated with sudden cardiac arrest within hemodialysis clinics

Patrick H. Fun1,2, Ruediger W. Lehrich1, Emily F. Honeycutt3, Charles A. Herzog3 and John P. Middleton1

Kidney Int advance online, 1 September 2010

• Case control study to identify dialysis-related factors associated with increased risk of sudden cardiac arrest

• 502 cases who experienced a sudden cardiac arrest and 1632 age- and dialysis-vintage-matched controls

• Sudden cardiac arrest was associated with:
  • low potassium dialysate (<2 meq/l)
  • increased ultrafiltration volumes
  • low calcium dialysate
  • predialysis serum creatinine levels

• Traditional risk factors like history of CHD and CHF were NOT significantly influential
Possibility 2  *There is indeed no effect in the dialysis population*

Dialysis patients are a ‘selected’ group compared to the general population.

‘Survival of the fittest’?
- Genetic make-up allowing better adaptation to an increasingly disadvantageous uraemic milieu over the course of decreasing renal function?
- Less vulnerable to traditional risk factors?

Problem further increased when using prevalent dialysis patients inducing survivor bias.
CKD as risk factor for other chronic diseases

CKD is also associated with an increased risk of adverse outcomes in other chronic diseases like infection and cancer

Cardiovascular Health Study - a community-based cohort of older individuals

<table>
<thead>
<tr>
<th></th>
<th>Fourth Quartile Cystatin C (&gt;1.22) versus First Quartile (&lt;0.93)</th>
<th>Fourth Quartile eGFR &lt;60.17) versus First Quartile (&gt;81.4)</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>HR (95% CI)*</td>
<td>P Value</td>
</tr>
<tr>
<td>Dementia</td>
<td>1.01 (0.58 to 1.75)</td>
<td>0.978</td>
</tr>
<tr>
<td>Pulmonary disease</td>
<td>2.67 (1.21 to 5.89)</td>
<td>0.015</td>
</tr>
<tr>
<td>Infection</td>
<td>4.65 (2.03 to 10.63)</td>
<td>&lt;0.001</td>
</tr>
<tr>
<td>Cancer</td>
<td>1.79 (1.33 to 2.42)</td>
<td>&lt;0.001</td>
</tr>
<tr>
<td>Other</td>
<td>2.71 (1.69 to 4.35)</td>
<td>&lt;0.001</td>
</tr>
</tbody>
</table>

*Adjusted for age, race, and gender.

**CKD as risk factor for non-cardiovascular mortality**

“The directly standardized NON cardiovascular mortality rate was 8.1 (95% CI, 7.9-8.3) times higher in patients starting dialysis than in the general population.”

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CKD as risk factor for non-cardiovascular mortality

Conclusions

- Compared to the general population life expectancy in adult CKD stage 5 patients is on average reduced to
  - ~ 30% in dialysis patients
  - ~ 60% in transplant patients

- Both the prevalence of CVD and cardiovascular mortality are importantly increased

- RCTs on treatment of traditional cardiovascular risk factors have frequently provided negative results
Conclusions

• A true effect of such interventions may not be detected due to
  – ‘flawed’ RCT design
  – ‘low signal to noise ratio’ due to high mortality inducing a ‘dilution’ of the effect
    increased by heterogeneity of cardiac death

• Lack of effect in this ‘selected’ population
  – ‘survival of the fittest’
  – survivor bias in studies using prevalent patients
    → both may hamper the generalizability of results in the general population to
      the dialysis population and vice versa
    → results from high quality studies in incident RRT patients with very limited
      in- and exclusion criteria are likely the ones best qualified to be extrapolated to
      other RRT populations
Conclusions

• CKD is not only associated with unfavourable cardiovascular outcomes, but also with (unfavourable outcomes of) other chronic diseases

• This underlines the importance of understanding the relationship between CKD, CVD and other chronic diseases

• Research into this area is much needed
  – Common cause?
  – Role of the immune system?
  – Causal pathway of cardiac disease in patients undergoing dialysis?
Thank you