Epidemiological insights
(or, why does CKD cause heart failure?)

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 Director, MRC Population Health Research Unit; Deputy Director, Clinical Trial Service Unit & Epidemiological Studies Unit, University of Oxford, UK
Disclosure of interests

Unrestricted grant provided by Novartis to the University of Oxford (study sponsor) to conduct the UK-HARP-3 trial of sacubitril/valsartan vs irbesartan in patients with CKD (Co-PI)
Presentation overview

- Epidemiological evidence that CKD is associated with an increased risk of heart failure (and vice versa)
- Potential problems in interpreting the evidence for risk factors for heart failure in CKD
- Suggested framework for conceptualising risk factors for heart failure in the context of CKD
- Contribution from intrinsic risk factors (defined as those that arise as a direct consequence of CKD)
- Contribution from extrinsic risk factors (defined as causal risk factors that are not a direct result of CKD)
- Implications for prevention of heart failure in CKD
Cumulative incidence of heart failure by eGFR in 14,800 ARIC study participants

No prior coronary artery disease

Prior coronary artery disease

1Kottgen et al. JASN 2007; 18:1307-15
Echocardiographic findings from 700 children\textsuperscript{1} and 3500 adults\textsuperscript{2} with CKD

Prevalence of LV hypertrophy

\begin{itemize}
\item Baseline eGFR
\item \textsuperscript{1}Schaefer et al. CJASN 2017; 12:19-28
\item \textsuperscript{2}Park et al. JASN 2012; 23:1725-34
\end{itemize}
Problems in interpreting observational studies among patients with CKD

- Kidney disease may distort associations between exposures and CV outcomes
  - Example: LDL cholesterol and CHD
- CVD is highly prevalent, but (a) may be subclinical, and (b) atherosclerotic and structural heart disease co-exist, complicating interpretation
  - Example: BP and vascular events
- Conclusion: assessment of causation by risk factors for heart failure in CKD should be informed by:
  - evidence in those without CKD (in whom reverse causality is less problematic)
  - separate consideration of atherosclerotic and non-atherosclerotic disease
  - Studies in which confounding can be minimised eg, RCTs and Mendelian Randomization studies
Association between cholesterol and risk of CHD in 350,000 healthy men

Stamler et al. *JAMA* 1986; 256: 2823-8
Inverse association between cholesterol and RR for CV mortality in dialysis patients\textsuperscript{1}

\textsuperscript{1}Baigent et al. Seminars in Dialysis 2007; 20:498-503
SHARP: reducing LDL cholesterol prevents major vascular events in CKD

<table>
<thead>
<tr>
<th>Event</th>
<th>eze/simva (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>0.83 (0.74-0.94) p=0.0021</td>
</tr>
<tr>
<td>Non-hemorrhagic stroke</td>
<td>131 (2.8%)</td>
<td>174 (3.8%)</td>
<td></td>
</tr>
<tr>
<td>Any revascularization procedure</td>
<td>284 (6.1%)</td>
<td>352 (7.6%)</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>0.94 (0.78-1.14) p=0.56</td>
</tr>
<tr>
<td>Hemorrhagic 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>0.85 (0.77-0.94) p=0.0012</td>
</tr>
</tbody>
</table>

1 Baigent C et al, for SHARP investigators. Lancet 2011; 377: 2181-92
Meta-analysis of 1 m healthy adults in 61 prospective studies: association of SBP with CHD

1 Prospective Studies Collaboration, Lancet 2002; 360: 1903-13
SHARP trial: association between systolic BP and MAJOR VASCULAR EVENTS (A) overall and (B) subdivided by evidence of prior CVD

1 Herrington et al. Hypertension 2017; 69 (in press)
Definitions

• **Intrinsic risk factors**: exposures that arise as a direct consequence of CKD

• **Extrinsic risk factors**: known causes of heart failure that are NOT a direct consequence of CKD
EXTRINSIC risk factors
- Obesity
- Diabetes mellitus
- Cigarette smoking

Suggested framework for the causation of heart failure in patients with CKD

INTRINSIC risk factors
- Blood pressure
- Dyslipidaemia
- Anaemia or iron-deficiency
- Neurohumoral activation
- Albuminuria
- CKD-Mineral Bone Disease
- Inflammation

Heart Failure ↓ Renal blood flow

Coronary Heart Disease

Myocardial ischaemia

Progressive CKD

KDIGO Controversies Conference on Heart Failure in CKD
May 25-28, 2017 | Athens, Greece
INTRINSIC RISK FACTORS: Heart failure mediated through myocardial ischaemia

- Coronary Heart Disease
- Myocardial ischaemia
- Heart Failure

INTRINSIC risk factors:
- Blood pressure
- Dyslipidaemia
- Inflammation (IL-6)
INTRINSIC RISK FACTORS and the risk of coronary heart disease (CHD)

- Blood pressure
- Dyslipidaemia
  - LDL cholesterol
  - Triglycerides
  - Lp(a)
- Inflammation
Meta-analysis of 1 m healthy adults in 61 prospective studies: association of SBP with CHD

Prospective Studies Collaboration, Lancet 2002; 360: 1903-13

Hazard ratio for Heart Disease (floating absolute risks & 95% CI)

Usual systolic blood pressure (mmHg)

Age at risk
- 80-89
- 70-79
- 60-69
- 50-59
- 40-49

\(^1\) Prospective Studies Collaboration, Lancet 2002; 360: 1903-13
## Genetic risk scores and selected CV outcomes

<table>
<thead>
<tr>
<th>Phenotype</th>
<th>Consortium</th>
<th>Total N or Cases/controls</th>
<th>SBP Effect/mmHg</th>
<th>SBP P</th>
<th>DBP Effect/1mmHg</th>
<th>DBP P</th>
</tr>
</thead>
<tbody>
<tr>
<td>Heart</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
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</tr>
<tr>
<td>CHD</td>
<td>CARDioGRAM plus4D</td>
<td>63,746/130,681</td>
<td>1.042</td>
<td>10^{-44}</td>
<td>1.069</td>
<td>10^{-38}</td>
</tr>
<tr>
<td>Heart failure</td>
<td>CHARGE</td>
<td>2,526/18,400</td>
<td>1.021</td>
<td>0.03</td>
<td>1.035</td>
<td>0.02</td>
</tr>
<tr>
<td>LV wall thickness (cm)</td>
<td>CHARGE</td>
<td>11,311</td>
<td>0.004</td>
<td>10^{-8}</td>
<td>0.007</td>
<td>10^{-8}</td>
</tr>
</tbody>
</table>

1 Ehret et al. Nature Genetics 2016; 48: 1171-84
## Genetic risk scores for lipids and CHD

<table>
<thead>
<tr>
<th>Allele score</th>
<th>HDL cholesterol</th>
<th>Log Triglycerides</th>
<th>LDL cholesterol</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>CHD (incident/prevalent)</td>
<td>P-value</td>
<td>Odds ratio (95% CI)</td>
</tr>
<tr>
<td></td>
<td>Odds ratio (95% CI)</td>
<td>P-value</td>
<td>Odds ratio (95% CI)</td>
</tr>
<tr>
<td>Unrestricted (48 SNPs)</td>
<td>0.53 (0.40-0.70)</td>
<td>8.8 x 10^{-6}</td>
<td>0.68 (0.47-0.97)</td>
</tr>
<tr>
<td>Restricted (19 SNPs)</td>
<td>0.91 (0.42-1.98)</td>
<td>0.817</td>
<td>1.33 (0.49-3.59)</td>
</tr>
<tr>
<td>Unrestricted (67 SNPs)</td>
<td>1.62 (1.24-2.11)</td>
<td>3.7 x 10^{-4}</td>
<td>1.59 (1.15-2.20)</td>
</tr>
<tr>
<td>Restricted (27 SNPs)</td>
<td>1.61 (1.00-2.59)</td>
<td>0.05</td>
<td>1.63 (0.91-2.91)</td>
</tr>
<tr>
<td>Unrestricted (42 SNPs)</td>
<td>1.78 (1.58-2.01)</td>
<td>2.0 x 10^{-21}</td>
<td>1.43 (1.24-1.66)</td>
</tr>
<tr>
<td>Restricted (19 SNPs)</td>
<td>1.92 (1.68-2.19)</td>
<td>4.6 x 10^{-22}</td>
<td>1.49 (1.26-1.75)</td>
</tr>
</tbody>
</table>

1 Holmes M et al. Eur Heart J 2015; 36: 539-550
**Characteristic serum lipid distribution at different stages of CKD**

<table>
<thead>
<tr>
<th></th>
<th>LDL-C</th>
<th>sdLDL</th>
<th>TRG</th>
<th>HDL-C</th>
<th>Lp(a)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Predialysis CKD</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td>↑*</td>
</tr>
<tr>
<td>(Stages 3-4)</td>
<td>←OR→</td>
<td>↓</td>
<td>↑</td>
<td>↓</td>
<td>↑*</td>
</tr>
<tr>
<td>Nephrotic syndrome</td>
<td>↑</td>
<td></td>
<td></td>
<td>OR↑</td>
<td>OR←OR↑</td>
</tr>
<tr>
<td>(Stages 3-4)</td>
<td></td>
<td></td>
<td></td>
<td>OR</td>
<td>↑</td>
</tr>
<tr>
<td>Hemodialysis</td>
<td>OR←OR↓</td>
<td>↑</td>
<td>↑</td>
<td>↓</td>
<td>↑</td>
</tr>
<tr>
<td>(Stage 5)</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td>↑</td>
</tr>
<tr>
<td>Peritoneal dialysis</td>
<td>↑</td>
<td>↑</td>
<td>↑</td>
<td>↓</td>
<td>↑</td>
</tr>
<tr>
<td>(Stage 5)</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td>↑</td>
</tr>
<tr>
<td>Renal transplantation</td>
<td>↑</td>
<td>↑</td>
<td>↑</td>
<td>↑</td>
<td>↓*</td>
</tr>
<tr>
<td>(Stage 5)</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
</tbody>
</table>

* Mainly in individuals with high-molecular-weight apolipoprotein(a) phenotypes.

Mendelian Randomization: potential role for Lp(a)\(^1\)

- MR studies show that Lp(a) is a cause of CHD\(^1\)
- **BUT**, risk of increased Lp(a) in general population is for low-molecular weight isoforms of Lp(a), whilst in CKD it is high-molecular weight isoforms that are increased

\(^1\) Clarke et al, for the PROCARDIS investigators. NEJM 2009; 361: 2518-28
Long term follow-up of the WOSCOPS trial: lowering LDL cholesterol prevents heart failure

20 year follow-up of WOSCOPS – pravastatin 40mg versus placebo reduced hospitalisation for heart failure by 35%

207 admissions in 123 subjects
133 admissions in 91 subjects

Ford et al. Circulation 2016; 133:1073-80
Markers of inflammation: IL6R is implicated in the causation of CHD

Among markers of inflammation (CRP, fibrinogen, IL-6, soluble IL6R), genetic risk score experiment shows that the IL6R pathway is involved in causation of CHD

Suggested framework for the causation of heart failure in patients with CKD

Progressive CKD

INTRINSIC risk factors
- Blood pressure
- Dyslipidaemia
- Anaemia or iron-deficiency
- Neurohumoral activation
- Albuminuria
- CKD-Mineral Bone Disease
- Inflammation

↓ Renal blood flow

Heart Failure
Evidence that raised blood pressure is a cause of heart failure $^{1,2}$

(a) Observational study (CALIBER)$^1$

<table>
<thead>
<tr>
<th>Blood Pressure Range</th>
<th>Heart Failure Events</th>
<th>Heart Failure Participants</th>
</tr>
</thead>
<tbody>
<tr>
<td>60-74 mm Hg</td>
<td>13209</td>
<td>137319</td>
</tr>
<tr>
<td>75-84 mm Hg</td>
<td>4862</td>
<td>136986</td>
</tr>
<tr>
<td>85-89 mm Hg</td>
<td>4635</td>
<td>136682</td>
</tr>
<tr>
<td>90-94 mm Hg</td>
<td>3284</td>
<td>115411</td>
</tr>
<tr>
<td>95-99 mm Hg</td>
<td>890</td>
<td>39888</td>
</tr>
<tr>
<td>≥100 mm Hg</td>
<td>9775</td>
<td>138298</td>
</tr>
</tbody>
</table>

(a) Meta-analysis of randomized trials$^2$

<table>
<thead>
<tr>
<th>Condition</th>
<th>Studies</th>
<th>Events</th>
<th>Intervention</th>
<th>Control</th>
<th>RR (95% CI) per 10 mm Hg reduction in systolic blood pressure</th>
</tr>
</thead>
<tbody>
<tr>
<td>Major cardiovascular events</td>
<td>55</td>
<td>13209</td>
<td>137319</td>
<td>14068</td>
<td>0.80 (0.77-0.83)</td>
</tr>
<tr>
<td>Coronary heart disease</td>
<td>56</td>
<td>4862</td>
<td>136986</td>
<td>5301</td>
<td>0.83 (0.78-0.88)</td>
</tr>
<tr>
<td>Stroke</td>
<td>54</td>
<td>4635</td>
<td>136682</td>
<td>5378</td>
<td>0.73 (0.68-0.77)</td>
</tr>
<tr>
<td>Heart failure</td>
<td>43</td>
<td>3284</td>
<td>115411</td>
<td>3760</td>
<td>0.72 (0.67-0.78)</td>
</tr>
<tr>
<td>Renal failure</td>
<td>16</td>
<td>890</td>
<td>39888</td>
<td>834</td>
<td>0.95 (0.84-1.07)</td>
</tr>
<tr>
<td>All-cause mortality</td>
<td>57</td>
<td>9775</td>
<td>138298</td>
<td>9998</td>
<td>0.87 (0.84-0.91)</td>
</tr>
</tbody>
</table>

1Rapsomaniki et al. Lancet 2014; 383: 1899-911
2Ettehad et al., Lancet 2016; 387: 957-67
## Genetic risk scores and selected CV outcomes

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1 Ehret et al. Nature Genetics 2016; 48: 1171-84
Evidence that anaemia is a cause of heart failure

Meta-analysis of ESA trials show reduced hospitalization for heart failure

A: Heart Failure Hospitalizations

<table>
<thead>
<tr>
<th></th>
<th>ESA Events</th>
<th>ESA Total</th>
<th>Control Events</th>
<th>Control Total</th>
<th>Weight</th>
<th>Peto Odds Ratio [95% CI]</th>
</tr>
</thead>
<tbody>
<tr>
<td>Cleland 2005</td>
<td>3</td>
<td>18</td>
<td>0</td>
<td>6</td>
<td>2.2%</td>
<td>4.31 [0.28, 66.37]</td>
</tr>
<tr>
<td>Ghali 2008</td>
<td>25</td>
<td>162</td>
<td>31</td>
<td>157</td>
<td>50.5%</td>
<td>0.74 [0.42, 1.32]</td>
</tr>
<tr>
<td>Kourea 2008</td>
<td>3</td>
<td>21</td>
<td>5</td>
<td>20</td>
<td>7.2%</td>
<td>0.51 [0.11, 2.36]</td>
</tr>
<tr>
<td>Mancini 2003</td>
<td>1</td>
<td>15</td>
<td>4</td>
<td>8</td>
<td>4.1%</td>
<td>0.09 [0.01, 0.67]</td>
</tr>
<tr>
<td>Palazzuoli 2006</td>
<td>4</td>
<td>20</td>
<td>8</td>
<td>18</td>
<td>9.2%</td>
<td>0.33 [0.09, 1.28]</td>
</tr>
<tr>
<td>Palazzuoli 2007</td>
<td>4</td>
<td>26</td>
<td>8</td>
<td>25</td>
<td>10.2%</td>
<td>0.40 [0.11, 1.46]</td>
</tr>
<tr>
<td>Parissis 2006</td>
<td>2</td>
<td>21</td>
<td>3</td>
<td>11</td>
<td>4.3%</td>
<td>0.27 [0.04, 1.96]</td>
</tr>
<tr>
<td>Ponikowski 2007</td>
<td>2</td>
<td>19</td>
<td>3</td>
<td>22</td>
<td>4.9%</td>
<td>0.75 [0.12, 4.80]</td>
</tr>
<tr>
<td>van Veldhuisen 2007</td>
<td>4</td>
<td>110</td>
<td>3</td>
<td>55</td>
<td>7.4%</td>
<td>0.46 [0.10, 2.05]</td>
</tr>
<tr>
<td><strong>Total:</strong> ESA (48/412) versus control (66/322)</td>
<td>0.56 [0.37, 0.84]</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
</tbody>
</table>

Heterogeneity: \( \chi^2 = 7.78, df = 8 \) \( (P = .46); I^2 = 0\%
Test for overall effect: \( Z = 2.80 \) \( (P = .005) \)

\(^1\)Kotecha at al. Am Heart J 2011; 161: 822-831e2
Lack of evidence that increasing haemoglobin reduce LV mass\(^1\) or risk of heart failure hospitalisation\(^2\) in CKD

CREATE: No effect of higher Hb target on LV mass

CHOIR: stopped early for harm in higher Hb target group (13.5 g/dL vs 11.5 g/dL)

\(^1\)CREATE investigators NEJM 2006; 355: 2071-84

\(^2\)CHOIR investigators NEJM 2006; 355: 2085-98
RED-HF: No effect of darbepoietin alfa on heart failure hospitalisation

- RED-HF trial
- 2278 patients with systolic heart failure (HFrEF)
- Darbepoietin alfa vs placebo
- Median Hb 13.0 vs 11.5 g/dL
- Mean f.u. 28 months

1Swedberg K et al. for the RED-HF group. NEJM 2013; 368: 1210-9
Associations between neurohumoral activation (sympathetic tone) and (a) CHD or (b) heart failure

- Heart rate (HR) independent risk factor for CV outcomes
- Inhibition of the $I_f$ channel with ivabradine reduces HR (but not contractility)
- SHIFT trial (6558 patients with systolic HF), ivabradine reduced risk of heart failure hospitalisation (16% vs 21%; P<0.0001 - right panel)\(^1\)
- SIGNIFY trial (19,102 patients with stable CHD), ivabradine had no effect on risk of MI (4.1% vs 3.9%; P=0.43)\(^2\)

\(^1\)Swedberg K et al. for SHIFT investigators. Lancet 2010; 376:875-85
\(^2\)Fox K et al for the SIGNIFY investigators. NEJM 2014; 371: 1091-99
EVOLVE: effect of cinacalcet on risk of heart failure

The EVOLVE Trial Investigators. NEJM 2012; 367:2482-2494
Suggested framework for the causation of heart failure in patients with CKD

**INRINSIC risk factors**
- Blood pressure
- Dyslipidaemia
- Anaemia or iron-deficiency
- Neurohumoral activation
- Albuminuria
- CKD-Mineral Bone Disease
- Inflammation

Heart Failure ➠ ↓ Renal blood flow ➠ Progressive CKD
INTRINSIC RISK FACTORS and risk of CKD progression (ie, loss of glomerular filtration)

- Blood pressure: ↑BP associated with ↑progression, BUT genetic risk scores (GRS) suggest causal association for ↑ uACR (not ↓ eGFR)
- Increased glomerular pressure/hyperfiltration: EMPA-REG demonstrated that empagliflozin ↓ progression, as have trials in which ↓ uACR (+ ↓ BP) reduce progression
- Dyslipidaemia: No evidence that ↑ LDL cholesterol ↑ progression
- Neurohumoral activation: RAAS inhibition slows progression. Animal and human studies with moxonidine suggest ↑ SNS activity a cause of glomerulosclerosis, but renal denervation trials inconclusive at best.
- Mineral bone disease: observational studies show that ↑ FGF23 independently predicts ↑ progression, but proof of causation lacking
- Inflammation: ↑ CRP, IL6 associate with ↑ progression, but proof of causation lacking
Suggested framework for the causation of heart failure in patients with CKD

EXTRANISC risk factors
- Obesity
- Diabetes mellitus
- Cigarette smoking

Progressive CKD

Heart Failure

↓ Renal blood flow

Myocardial ischaemia

Coronary Heart Disease

KDIGO Controversies Conference on Heart Failure in CKD
May 25-28, 2017 | Athens, Greece
### EXTRINSIC RISK FACTORS and risk of (a) CHD (b) heart failure & (c) CKD progression

<table>
<thead>
<tr>
<th>Risk Factor</th>
<th>CHD</th>
<th>Heart failure</th>
<th>CKD progression</th>
</tr>
</thead>
<tbody>
<tr>
<td>Diabetes mellitus</td>
<td>RR = 2.0 (1.8-2.2)(^1)</td>
<td>RR = 1.9 (1.5-2.3)(^2)</td>
<td>Renal death RR = 3.0 (2.4-3.8)(^4)</td>
</tr>
<tr>
<td>Higher body mass index</td>
<td>RR per 5 kg/m(^2) = 1.4 (1.3-1.4)(^5)</td>
<td>RR per 5 kg/m(^2) = 1.9 (1.6-2.2)(^5)</td>
<td>ESRD: RR(^*) = 6.1 (5.0-7.5)(^6)</td>
</tr>
<tr>
<td>Cigarette smoking</td>
<td>RR = 1.5 (1.3-1.8) for atherosclerotic events in CKD patients(^8)</td>
<td>RR = 1.6 (1.4-1.8)(^2)</td>
<td>RR ↑ in some observational studies(^7); no effect on progression (serial eGFRs) in SHARP(^8)</td>
</tr>
</tbody>
</table>

\(^*\) BMI 30-35 vs 18.5-25 kg/m\(^2\)

### SUMMARY: aetiological relevance of INTRINSIC RISK FACTORS

<table>
<thead>
<tr>
<th>Risk Factor</th>
<th>CHD</th>
<th>Heart failure</th>
<th>CKD progression</th>
</tr>
</thead>
<tbody>
<tr>
<td>Blood pressure</td>
<td>+++</td>
<td>+++</td>
<td>+/-</td>
</tr>
<tr>
<td>Dyslipidaemia</td>
<td>+</td>
<td>+</td>
<td>-</td>
</tr>
<tr>
<td>Anaemia/ iron-deficiency</td>
<td>+/-</td>
<td>+/-</td>
<td>-</td>
</tr>
<tr>
<td>Neurohumoral activation</td>
<td>+/-</td>
<td>++</td>
<td>++</td>
</tr>
<tr>
<td>Albuminuria</td>
<td>+/-</td>
<td>+/-</td>
<td>+/-</td>
</tr>
<tr>
<td>Mineral Bone Disease</td>
<td>+/-</td>
<td>+/-</td>
<td>+/-</td>
</tr>
<tr>
<td>Inflammation</td>
<td>+</td>
<td>+/-</td>
<td>+/-</td>
</tr>
</tbody>
</table>
## SUMMARY: aetiological relevance of EXTRINSIC RISK FACTORS (by definition, causal)

<table>
<thead>
<tr>
<th>Risk Factor</th>
<th>CHD</th>
<th>Heart failure</th>
<th>CKD progression</th>
</tr>
</thead>
<tbody>
<tr>
<td>Diabetes</td>
<td>+++</td>
<td>+++</td>
<td>+++</td>
</tr>
<tr>
<td>Higher body mass index</td>
<td>++</td>
<td>++</td>
<td>++</td>
</tr>
<tr>
<td>Cigarette smoking</td>
<td>+++</td>
<td>+++</td>
<td>+/-</td>
</tr>
</tbody>
</table>
Suggested framework for the causation of heart failure in patients with CKD

**EXTRINSIC risk factors**
- Obesity
- Diabetes mellitus
- Cigarette smoking

**INTRINSIC risk factors**
- Blood pressure
- Neurohumoral activation
- Dyslipidaemia
- Inflammation

**Heart Failure**

↓ Renal blood flow

**Progressive CKD**

**Coronary Heart Disease**

↓ Renal blood flow

Myocardial ischaemia
Conclusions: priorities for prevention of heart failure in CKD, based on current knowledge

• Treatments for extrinsic risk factors likely to be effective:
  – Quitting cigarette smoking
  – Improved diabetic control
  – Avoidance of overnutrition

• Treatments for intrinsic risk factors (based on current evidence) – treat now or conduct RCTs:
  – Intensive blood pressure reduction
  – Reduce neurohormonal activation (eg, RAAS blockade, MRAs)
  – Reduce sympathetic activity (eg, beta-blockers)

• Modification of other intrinsic risk factors more speculative and requires new RCT or convincing genetic risk score evidence
I gratefully acknowledge the generous support of the UK Medical Research Council