Heart and Kidney Interactions: what are the challenges for prevention and progression

Christoph Wanner, Würzburg, Germany

Würzburg
Daniel Meisner
1586-1626

England
Thomas Sydenham
1624-1689
‘a man is as old as his arteries’

ESC Session 232: Expanding opportunities for SGLT2i in clinical cardiology
Monday, September 2, 2019 - 13:00-14:00
EBAC Disclosures

C. Wanner

I. Institution grants: Boehringer-Ingelheim (BI)

II. Speaker honoraria: AstraZ, Bayer, BI, Lilly, MSD, Sanofi

III. Advisory Board: Bayer, BI, MSD

IV. Shares/stock: None
Cardio-Renal Syndrome
HF and CKD

Chronic Kidney Disease

Water
Salt
Glucose
Facts & Challenges

~ 40-50% of all HF patients have concomitant CKD  
EJHF 2014;16:103-11

~ 40-50% of all CKD patients have HF*  

*T2DM CKD patients have a preponderance for HeFpEF

Of all the common diseases, CKD imposes the most dramatic divergence between biological age and chronological age

Declining renal function, independent of a patient’s age, is the main driver of cardiovascular ageing

…. underlying pathophysiologic pathways, originating in the kidney and involving the cardiac and vascular system, are dominated by progressive fibrosis and degeneration, associated with altered telomerase activity …. 

Challenges

Resistance to diuretics in CKD and HF (altered dose response curve)

A recent shift in thought process regarding the interplay of cardiac and renal dysfunction suggest that renal congestion may be the primary driver of worsening renal function

Once discharged after acute decompensated HF it is advisable to transition the patients into an outpatient decompression clinic for further Decongestive therapy and follow-up
Renal function in T2D patients in the PARADIGM-HF trial
HFrEF <40/35%, symptomatic

Change in eGFR (ml/min/1.73m²)

Years since randomisation

Number at risk
No diabetes, enalapril
No diabetes, sacubitril/valsartan
Diabetes, enalapril
Diabetes, sacubitril/valsartan

Packer et al, Lancet Diabetes Endocrinol 2018;6:547-554
EMPA-REG Outcome: Long-term – chronic - eGFR slope

week 4 to last value on treatment
EMPA-REG Outcome: eGFR over 3 years

Patients analyzed
Placebo: 2323, 2205, 2121, 1927, 1763, 1262, 977, 448
Empagliflozin: 4644, 4451, 4318, 4018, 3710, 2654, 2087, 1037

Mixed model repeated measures analysis in the treated set (QC-AD)

Wanner et al, NEJM 2016; 375:323-334
## EMPA-REG Outcome: Kidney outcomes by baseline HF

<table>
<thead>
<tr>
<th>Outcome Type</th>
<th>Empagliflozin</th>
<th>Placebo</th>
<th>HR† (95% CI)</th>
<th>p-value for interaction</th>
</tr>
</thead>
<tbody>
<tr>
<td>Incident or worsening nephropathy* or CV death</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>All patients</td>
<td>675/4170</td>
<td>6497/2102</td>
<td>23.6</td>
<td>0.61 (0.55, 0.69)</td>
</tr>
<tr>
<td>HF at baseline: NO</td>
<td>579/3758</td>
<td>425/1887</td>
<td>22.5</td>
<td>0.62 (0.55, 0.70)</td>
</tr>
<tr>
<td>HF at baseline: YES</td>
<td>96/412</td>
<td>72/215</td>
<td>33.5</td>
<td>0.57 (0.42, 0.77)</td>
</tr>
<tr>
<td>Incident or worsening nephropathy*</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>All patients</td>
<td>525/4124</td>
<td>388/2061</td>
<td>18.8</td>
<td>0.61 (0.53, 0.70)</td>
</tr>
<tr>
<td>HF at baseline: NO</td>
<td>464/3723</td>
<td>339/1855</td>
<td>18.3</td>
<td>0.62 (0.54, 0.71)</td>
</tr>
<tr>
<td>HF at baseline: YES</td>
<td>61/401</td>
<td>49/206</td>
<td>23.8</td>
<td>0.53 (0.36, 0.77)</td>
</tr>
<tr>
<td>Progression to macroalbuminuria** (UA CR &gt;300 mg/g)</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>All patients</td>
<td>459/4091</td>
<td>330/2033</td>
<td>16.2</td>
<td>0.62 (0.54, 0.72)</td>
</tr>
<tr>
<td>HF at baseline: NO</td>
<td>411/3897</td>
<td>289/1828</td>
<td>15.8</td>
<td>0.64 (0.55, 0.75)</td>
</tr>
<tr>
<td>HF at baseline: YES</td>
<td>48/394</td>
<td>41/205</td>
<td>20.0</td>
<td>0.50 (0.33, 0.75)</td>
</tr>
<tr>
<td>Doubling of serum creatinine level with eGFR ≤45 ml/min/1.73 m², initiation of renal replacement therapy, or death from renal disease</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>All patients</td>
<td>81/4645</td>
<td>71/2323</td>
<td>3.1</td>
<td>0.54 (0.40, 0.75)</td>
</tr>
<tr>
<td>HF at baseline: NO</td>
<td>64/4187</td>
<td>60/2082</td>
<td>2.9</td>
<td>0.50 (0.35, 0.72)</td>
</tr>
<tr>
<td>HF at baseline: YES</td>
<td>17/458</td>
<td>11/241</td>
<td>4.6</td>
<td>0.78 (0.36, 1.67)</td>
</tr>
<tr>
<td>Sustained† eGFR decline of ≥40%, initiation of renal replacement therapy, or death from renal disease</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>All patients</td>
<td>100/4645</td>
<td>86/2323</td>
<td>3.7</td>
<td>0.55 (0.41, 0.73)</td>
</tr>
<tr>
<td>HF at baseline: NO</td>
<td>79/4187</td>
<td>72/2082</td>
<td>3.5</td>
<td>0.51 (0.37, 0.70)</td>
</tr>
<tr>
<td>HF at baseline: YES</td>
<td>21/458</td>
<td>14/241</td>
<td>5.8</td>
<td>0.78 (0.39, 1.53)</td>
</tr>
</tbody>
</table>

Butler J et al, in press 2019
Effects of Empagliflozin vs placebo on %HbA1c, by eGFR

<table>
<thead>
<tr>
<th>eGFR (mL/min/1.73m²)</th>
<th>Number of measurements</th>
<th>%HbA1c difference (95% CI)</th>
<th>p value for interaction</th>
</tr>
</thead>
<tbody>
<tr>
<td>≥90</td>
<td>Empagliflozin: 348</td>
<td>Placebo: 343</td>
<td>-0.84 (-0.95, -0.72)</td>
</tr>
<tr>
<td>≥60 to &lt;90</td>
<td>Empagliflozin: 518</td>
<td>Placebo: 516</td>
<td>-0.60 (-0.70, -0.51)</td>
</tr>
<tr>
<td>≥30 to &lt;60</td>
<td>Empagliflozin: 234</td>
<td>Placebo: 239</td>
<td>-0.38 (-0.52, -0.24)</td>
</tr>
<tr>
<td>&lt;30</td>
<td>Empagliflozin: 42</td>
<td>Placebo: 46</td>
<td>-0.04 (-0.37, 0.29)</td>
</tr>
</tbody>
</table>

Cherney et al. Kidney International 2018; 93: 231-244
Kidney function over time by baseline HF

Butler J et al, in press 2019
Renal MOA +/- Diabetes: Increased renal sodium reabsorption

1. Activation of RAAS and SNS
2. Obesity
3. Hypertension
4. Heart failure
5. Diabetes

Key drivers for RAAS and SNS activation:

- CKD
- Obesity
- Hypertension
- Heart failure
- Diabetes

Renal sodium reabsorption

Glomerular pressure

Blockade of SGLT2

Adapted from: Cherney D et al. Circulation 2014;129:587
Where to go from here?

- Managing volume overload in CKD by chronically restrict dietary sodium (no sustained success), but should include a “personal salt manager” (point of care technology) even in asymptomatic lung congestion!

- Use technology i.e. diagnostic measures such as bioimpedance spectroscopy, lung ultrasound to manage hypervolemia

- We need more data in CKD & HF: trial design with a composite of MACE and MAKE (Major Adverse Kidney Event) ?

- ‘New’ endpoints, such as HHF, eGFR slopes (and albuminuria)!

Parfrey et al, CJASN 2016;11:539-46
Zoccali & Mallamaci, CJASN 2018;13:1432-1434
Glomerular Hypertension & Single Nephron Hyperfiltration

- Normal: GFR >90 ml/min
- Glomerular Hypertension: GFR >135 ml/min, Hyperfiltration
- CKD Stage 3: GFR <60 ml/min
- CKD Stage 4: GFR <30 ml/min
Primary cardio-renal composite outcome

CV death

Kidney disease progression

„Hard“ kidney endpoints

ESKD defined as:
- Initiation of chronic dialysis
- Kidney transplant

Renal death*

Surrogate kidney endpoints

Kidney function loss defined as:
- Sustained ≥40% eGFR decline
- Sustained kidney failure (i.e. eGFR <10ml/min/1.73m²)

more non-diabetic kidney disease than DKD ! ?

Herrington et al, CKJ 2018;11:749-761
Patient education on lifestyle and diabetes management

+ Metformin

Atherosclerotic CVD?

Yes

Add a second agent proven to reduce MACE and/or cardiovascular mortality

- SGLT2i
- GLP1-RA

No
"This is not the end. It is not even the beginning of the end. But it is, perhaps, the end of the beginning”

Winston Churchill 1942