Workshop: The patient with heart failure, renal failure and hypertension: what strategy?

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Cases

• The patient with diabetic nephropathy and hypertension
• The patient with heart failure, renal failure and hypertension
Clinical Case no 1

• Man 52 years old, obese, with type 2 diabetes for 5 years.
• Office BP: 138/88 mmHg (mean of 2 measures).
• Serum Creatinine: 123 µmol/L (eGFR 58 ml/min/1.73m²). HbA1c: 6.8%
• Urine stix: normal; Ualbumin: 78 mg/mmol
• ECG: sinus rythm, no signs of HVG
• Treatment: metformin 500 mg 1-0-1
What would be your first choice?

1. Echocardiography
2. ABPM
3. ARB
4. Diuretic
Diastolic Dysfunction in Normotensive Men with Well-Controlled Type 2 Diabetes

Poirier P. et al. Diabetes Care 2001 Jan; 24(1): 5-10
High frequency of masked hypertension in patients with CKD (AASK study)

66%
As renal function decreases the rate of cardiovascular events increases

N=1’120’295

Presence of microalbuminuria predicts the occurrence of renal and CV events

- Renal events
  - Urine albumin excretion (mg/24h)
  - Relative risk (%)
  - *P < 0.05 vs. UAE <15 mg/24h.

- Cardiovascular events
  - Urine albumin excretion (mg/24h)
  - Relative risk (%)
  - *P < 0.05 vs. UAE <15 mg/24h.

Shaded areas represent 95% CIs. Models included spline eGFR, categorical albuminuria, and their interaction terms as well as adjustment for age, sex, ethnic origin, history of CV disease, SBP, diabetes, smoking, and total cholesterol. The reference (diamond) was eGFR 95 mL/min/1.73 m² plus ACR less than 3.4 mg/mmol (30 mg/g) or dipstick test result negative or trace. Circles represent statistically significant and triangles represent not significant.
Microalbuminuria and risk of cardiovascular events, congestive heart failure and death in the HOPE trial.

(adjusted for age, sex, systolic/diastolic blood pressure, waist-hip ratio, diabetes or HbA1c)

Gerstein HC et al., JAMA 286: 421-426, 2001
What would be your first choice of drug?

- Amlodipine
- Irbesartan
- Torasemide
- Metoprolol
IDNT Primary Endpoint
Time to Doubling of Serum Creatinine, ESRD, or Death

If blood pressure was not at target with a monotherapy what would be your second line therapy?

- Amlodipine
- Ramipril
- Torasemide
- Hydrochlorothiazide
- Metoprolol
ACCOMPLISH: RAS-blocker/CCB combined therapy offers benefits in higher-risk patients

11,506 patients with hypertension who were at high risk for cardiovascular events.

No. at risk:
- Benazepril / AML: 5512, 5317, 5141, 4959, 4739, 2826, 1447
- Benazepril / HCTZ: 5483, 5274, 5082, 4892, 4655, 2749, 1390

20% lower

Renal outcomes with different fixed-dose combinations in patients with hypertension at high risk for cardiovascular events (ACCOMPLISH)

Kaplan-Meier curves for progression of chronic kidney disease for the intention-to-treat population. Progression of chronic kidney disease was defined as doubling of serum creatinine concentration, estimated glomerular filtration rate less than 15 ml/min/1.73m2.

Are there any new drugs that may worth giving?
Empagliflozin, Cardiovascular Outcomes, and Mortality in Type 2 Diabetes

A Primary Outcome

Hazard ratio, 0.86 (95% CI, 0.74–0.99)
P = 0.04 for superiority

No. at Risk
Empagliflozin 4687, 4580, 4455, 4328, 3851, 2821, 2359, 1534, 370
Placebo 2333, 2256, 2194, 2112, 1875, 1380, 1161, 741, 166

Month

B Death from Cardiovascular Causes

Hazard ratio, 0.62 (95% CI, 0.49–0.77)
P = 0.001

No. at Risk
Empagliflozin 4687, 4651, 4608, 4556, 4128, 3079, 2617, 1722, 414
Placebo 2333, 2303, 2280, 2243, 2012, 1503, 1281, 825, 177

Month

C Death from Any Cause

Hazard ratio, 0.68 (95% CI, 0.57–0.82)
P = 0.001

No. at Risk
Empagliflozin 4687, 4651, 4608, 4556, 4128, 3079, 2617, 1722, 414
Placebo 2333, 2303, 2280, 2243, 2012, 1503, 1281, 825, 177

Month

D Hospitalization for Heart Failure

Hazard ratio, 0.65 (95% CI, 0.50–0.85)
P = 0.002

No. at Risk
Empagliflozin 4687, 4614, 4523, 4427, 3988, 2950, 2487, 1634, 395
Placebo 2333, 2271, 2226, 2173, 1932, 1424, 1202, 775, 168

Month
Pathophysiological interactions between heart and kidney in type 4 cardiorenal syndrome (CRS)

- Anemia
- Uremic toxins
- Ca and Phosphate abnormalities
- Nutritional status
- Na +H2O overload
- Chronic inflammation
- EPO resistance

Cardiac remodeling
Neurohormonal abnormalities
Increased ischemic risk
Left ventricular hypertrophy
Left diastolic dysfunction
Decreased coronary perfusion
Inflammation
Coronary and tissue calcification

Smoking
Obesity
Hypertension
Dyslipidemia
Hypertension
Chronic inflammation

Genetic risk factors
Acquired risk factors
Primary nephropathy
Diabetes mellitus

Anemia, Uremic toxins
Ca and Phosphate abnormalities
Natriuretic status, BMI
Na + H2O overload
Chronic inflammation

Artificial surfaces
Contaminated fluid

Endothelial dysfunction
Smooth muscle proliferation
LDL oxidation
Vascular calcification
Oxidant stress
Accelerated atherosclerosis

Insulin resistance
Muscle metabolism

Adipocytokine production
Conclusion 1

- Blockade of the renin-angiotensin system is the main stay of diabetic nephropathy
- In high risk patients the combination with a CCB seems to be protective (CV and renal)
- SGLT-2 inhibitors may offer CV protection beyond glucose reduction
Clinical case no 2

- Women aged 62 yo, with New York Heart Association (NYHA) III and an ejection fraction of 35%
- Previous MI at age of 60
- Office BP 156/93 mmHg, ABPM day 154/91 mmHg
- eGFR 36 ml/min/1.73 m², A/C : 4.0 mg/mmol
- Na 138 mmol/L, K: 5.1 mmol/L, NT-pro-BNP 900 pg/ml
- Treatment: Perindopril 10 mg, Amlodipine 5 mg, Carvedilol 12.5 mg bid, Aspirine 100mg, Atorvastatine 40 mg
Could we do better?

• Aldosterone
• Chlorthalidone
• LCZ696 (valsartan/neprilysin inhibitor)
• Torasemide
Mechanism of Action of LCZ696
PARADIGM-HF: Patient Disposition

10,521 patients screened at 1043 centers in 47 countries

Did not fulfill criteria for randomization (n=2079)

Randomized erroneously or at sites closed due to GCP violations (n=43)

8399 patients randomized for ITT analysis

LCZ696
400 mg od (n=4187)
At last visit
375 mg daily
11 lost to follow-up

Enalapril 20 mg od (n=4212)
At last visit
18.9 mg daily
9 lost to follow-up

median 27 months of follow-up
Neprilysin in heart failure: effect on hard endpoints

despite cardiovascular causes or a first hospitalization for heart failure

<table>
<thead>
<tr>
<th>Prospectively identified adverse events</th>
<th>LCZ696 (n=4187)</th>
<th>Enalapril (n=4212)</th>
<th>P Value</th>
</tr>
</thead>
<tbody>
<tr>
<td>Symptomatic hypotension</td>
<td>588</td>
<td>388</td>
<td>&lt; 0.001</td>
</tr>
<tr>
<td>Serum potassium &gt; 6.0 mmol/l</td>
<td>181</td>
<td>236</td>
<td>0.007</td>
</tr>
<tr>
<td>Serum creatinine ≥ 2.5 mg/dl</td>
<td>139</td>
<td>188</td>
<td>0.007</td>
</tr>
<tr>
<td>Cough</td>
<td>474</td>
<td>601</td>
<td>&lt; 0.001</td>
</tr>
<tr>
<td>Discontinuation for adverse event</td>
<td>449</td>
<td>516</td>
<td>0.02</td>
</tr>
<tr>
<td>Discontinuation for hypotension</td>
<td>36</td>
<td>29</td>
<td>NS</td>
</tr>
<tr>
<td>Discontinuation for hyperkalemia</td>
<td>11</td>
<td>15</td>
<td>NS</td>
</tr>
<tr>
<td>Discontinuation for renal impairment</td>
<td>29</td>
<td>59</td>
<td>0.001</td>
</tr>
<tr>
<td>Angioedema (adjudicated)</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Medications, no hospitalization</td>
<td>16</td>
<td>9</td>
<td>NS</td>
</tr>
<tr>
<td>Hospitalized; no airway compromise</td>
<td>3</td>
<td>1</td>
<td>NS</td>
</tr>
<tr>
<td>Airway compromise</td>
<td>0</td>
<td>0</td>
<td>----</td>
</tr>
</tbody>
</table>
Changes in effective renal plasma flow (ERPF) and filtration fraction induced by omapatrilat

Frédéric Regamey et al. Hypertension. 2002;40:266-272
Effect of LCZ on BP and eGFR in heart failure patients (preserved EF)

The PARAMOUNT phase 2 study
Conclusion

• ARNI have a potential of target organ protection in the heart which may be superior to that of ACEI or ARBs alone

• The protective effects of ARNI on the kidney remain to be demonstrated in specific trials with CKD patients

• These effects should compared the an ARB/or ACE/diuretic combination or eventually against an ACE/ or ARB/CCB combination