Diuretic Resistance

Dr TA McDonagh
Consultant Cardiologist
Royal Brompton Hospital

• The Royal College of Physicians and Surgeons of Glasgow
  Symposium and Ceremony of Admission
  Wednesday 24th February 2010
  • Rock and Blue Canyon
Les Liaisons Dangereuses....?

Simple Clinical Markers of Prognosis
Loop Diuretic Dose

- 1,354 - advanced systolic HF
- Co-variate adjustment (age, gender, IHD, LVEF, BMI, PACWP, peak VO2, BB, RAAS inhibitor, digoxin, statin, serum Na, urea, creatinine, Hb, cholesterol, SBP and smoking history)
- Diuretic quartile - independent predictor of mortality (Q4 vs Q1 HR 4.0, 95% CI 1.9 to 8.4).

Eshaghian S et al
Am J Cardiol 2006;97:1759
Diuretics and the RAAS

- 12 HF patients
- Before and after diuretics

*Bayliss J et al Br Heart J 1987;57:17*
Diuretic Resistance

- **Definition**
  - “oedema despite adequate diuretic therapy”

- **Not well studied**

  - **Prevalence**
    - Retrospective analysis of 1153 patients with advanced CHF - 34% had doses of furosemide or equivalent > 80mg
    - Predicts mortality

  *Neuberg GW et al Am Heart J 2002;144:31–8*

Causes; Multiple

- **CKD**
- **Drugs-NSAIDS**
- **Chronic admin of loop diuretics**

  - diminished natriuretic effect - the "braking phenomenon"
  - afferent arteriolar constriction (adenosine receptors)
  - hypertrophy and hyperplasia in epithelial cells of the distal convoluted tubule, leading to an increased reabsorption of sodium in this segment

  - *tubuloglomerular feedback*
What to do?

Management
Adherence issues

- **Fluid Restriction**
- **Na restriction < 100mmols/day**
- **? NSAIDs**
  - interfere with PG synthesis by inhibiting cyclooxygenase and thereby antagonise the natriuretic response to loop diuretics
Management
Dose Adjustment

- **Increase dose**
- **More frequent administration**
  - loop diuretics are short acting, postdiuretic salt retention is an important mechanism contributing to diuretic resistance
- **Try changing furosemide to bumetanide**
  - >bioavailability (80% vs 40%)

IV Administration

- **Overcomes bioavailability problems**
- **Continuous IV infusion may be more effective**
  - prevent postdiuretic salt retention completely
  - Some small studies
    - Dose of furosemide: 3 mg/hour - 200 mg/hour, (median 10–20 mg/hour);
    - Bumetanide was administered as 0.5 mg bolus followed by a continuous infusion of 0.5 mg/hour.
    - Same daily dose caused excretion of a > volume of urine and electrolytes when given as a continuous infusion.
    - The maximal plasma furosemide concentration was significantly lower and this resulted in a reduced risk for ototoxic side effects

Combining Diuretics
Sequential Nephron Blockade

• 3 studies with addition of thiazides
  - significant weight loss
  - improvement in NYHA class
  - side effects; hypokalaemia, hyponatraemia, dehydration, and renal failure
  - no advantage to metolozonene

Dormans TPJ et al, Eur Heart J 1996;17:1867–74

Which ?

- As single agents-loop diuretics
  - Furosemide, bumetanide, torasemide

- Thiazides-usually adjunctive

- Metolozon-thiazide like

- Potassium sparing
  - Triameterene
  - Amiloride
  - Sprionolactone
Other options

- **In decompensated HF or cardiogenic shock**
- **If SBP low, add an inotrope on the short term**
- **“Renal dose dopamine”**
  - Low doses (<2 µg/kg/min iv)
    - peripheral dopaminergic (DA1) receptors
    - ↓ peripheral VR
    - vasodilation: renal, splanchnic, coronary, and cerebral vascular beds
    - ↑ renal blood flow, GFR, diuresis, and Na excretion,
    - ↑ response to diuretic agents, in renal hypoperfusion and failure
  - Class of recommendation IIb, level of evidence C

ACEI/ARB/AAA and Worsening Renal Function

Some in ↑ urea/creatinine/ K⁺ expected. Small ↑ and asymptomatic-no action

- ↑ in creatinine up to 50% above baseline or to 266µmol/l
- ↑ K⁺ ≤5.5mmol/l

Caution-seek specialist advice if baseline K⁺ ≥5.0mmol/l or ≥221µmol/l
Monitor more frequently in CKD

Excessive rise: stop nephrotoxic drugs—NSAIDs, non-essential vasodilators, K⁺ supplements/sparing diuretics, recheck, reduce diuretic

Persist if ACEI and recheck
K⁺ ≥5.5mmol/l or if creatinine ↑100% or to >310µmol/l, stop ACEI/ARB

Monitor U&Es closely until creatinine and K⁺ stable

McMurray et al Eur J Heart Fail 2005 7:710
Novel Approaches...

Nesiritide
Primary Amino Acid Sequence of (hBNP)

Effect of Short-Term Nesiritide vs Dobutamine on 6-Month Survival

Log-rank test:
Dobutamine vs nesiritide, 0.015 µg/kg/min: \( P = 0.040 \)
Dobutamine vs nesiritide, 0.030 µg/kg/min: \( P = 0.366 \)

Dobutamine (n = 58)
Nesiritide, 0.030 µg/kg/min (n = 103)
Nesiritide, 0.015 µg/kg/min (n = 100)


But....

Heart Failure

Risk of Worsening Renal Function With Nesiritide in Patients With Acutely Decompensated Heart Failure

Jonathan D. Sackner-Bernstein, MD; Hal A. Skopicki, MD, PhD; Keith D. Aaronson, MD, MS

Background—Renal function is an important prognostic factor for patients with acutely decompensated heart failure (ADHF). We investigated the renal effects of nesiritide as treatment for ADHF.

Methods and Results—Randomized clinical trials comparing nesiritide with either placebo or active control for ADHF

Sackner-Bernstein JD et al. *Circulation* 2005;111:1487-1491
And... REVIEW

Short-term Risk of Death After Treatment With Nesiritide for Decompensated Heart Failure
A Pooled Analysis of Randomized Controlled Trials

Jonathan D. Sackner-Bernstein, MD
Marek Konurowski, MD
Marshall Fox, MD
Keith Aaronson, MD, MS

Context: Nesiritide improves symptoms in patients with acutely decompensated heart failure compared with placebo and appears to be safer than dobutamine. Its short-term safety relative to standard diuretic and vasodilator therapies is less clear.

Objective: To investigate the safety of nesiritide relative to noninotropic-based control therapies, primarily consisting of diuretics or vasodilators.


Ultrafiltration?
RAPID HF
Acute Decompensated Heart Failure

- Peripheral veno-venous ultrafiltration
- 40 hospitalised patients
  - Fluid retention
  - 20 randomised to 8 hours of ultrafiltration plus usual care
  - Improved symptoms

<table>
<thead>
<tr>
<th>End point</th>
<th>Ultrafiltration (n=20)</th>
<th>Usual care (n=20)</th>
<th>p</th>
</tr>
</thead>
<tbody>
<tr>
<td>Weight loss 24 h (kg)</td>
<td>2.5</td>
<td>1.86</td>
<td>0.240</td>
</tr>
<tr>
<td>Fluid removal 24 h (mL)</td>
<td>4650</td>
<td>2838</td>
<td>0.001</td>
</tr>
</tbody>
</table>


UNLOAD

- 200 patients, ADHF
- Randomised to ultrafiltration/iv diuretic
- Ultrafiltration
  - significantly > fluid loss over 48 hours (p=0.001)
  - Similar effects of creatinine

Costanzo M et al. JACC 2007; 49:675
Adenosine A1 Receptor Antagonist
IV KW-3902 (Rolofylline) in ADHF (146) with renal
dysfunction

<table>
<thead>
<tr>
<th>Parameter</th>
<th>2.5 mg, n=29</th>
<th>15 mg, n=31</th>
<th>30 mg, n=30</th>
<th>60 mg, n=29</th>
<th>Placebo, n=27</th>
</tr>
</thead>
<tbody>
<tr>
<td>6-hour urine output on day 1</td>
<td>445</td>
<td>531</td>
<td><strong>631</strong></td>
<td>570</td>
<td>374</td>
</tr>
<tr>
<td>(mL)</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Creatinine, baseline (mg/dL)</td>
<td>1.63</td>
<td>1.81</td>
<td><strong>1.69</strong></td>
<td>1.77</td>
<td><strong>1.86</strong></td>
</tr>
<tr>
<td>Creatinine, change from</td>
<td>-0.07</td>
<td>-0.04</td>
<td><strong>-0.09</strong></td>
<td>+0.03</td>
<td><strong>-0.01</strong></td>
</tr>
<tr>
<td>baseline (mg/dL)</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Total furosemide dose (mg)</td>
<td>397</td>
<td>331*</td>
<td><strong>342</strong></td>
<td>229*</td>
<td><strong>606</strong></td>
</tr>
<tr>
<td>Early withdrawal of therapy</td>
<td>14</td>
<td>39</td>
<td><strong>30</strong></td>
<td>38</td>
<td>4</td>
</tr>
<tr>
<td>due to adequate diuresis (%)</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
</tbody>
</table>

*p<0.05 vs placebo

Givertz MM, JACC 2007;50;1551

PROTECT: Primary end point

<table>
<thead>
<tr>
<th>Outcome</th>
<th>Placebo (%)</th>
<th>Rolofylline (%)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Success</td>
<td>36.0</td>
<td>40.6</td>
</tr>
<tr>
<td>Unchanged</td>
<td>44.2</td>
<td>37.5</td>
</tr>
<tr>
<td>Failure</td>
<td>19.8</td>
<td>21.8</td>
</tr>
</tbody>
</table>

2033 patients, increased seizure rate

Metra M. European Society of Cardiology 2009 Congress; September 1, 2009; Barcelona, Spain.
AVP-V₂ Antagonist Tolvaptan
“EVEREST”

- RCT, n=4133, LVEF<40%
- Admitted with HF-persistent “congestion” after standard Rx
- Primary: all-cause mortality (superiority and noninferiority) and CV death or hospitalization for HF (superiority only).
- Secondary: changes in dyspnoea, body weight, and oedema


“EVEREST”

Konstam, M. A. et al. JAMA 2007;297:1319-1331
### EVEREST

**Table 3. Effects of Telaplatin on Change From Baseline in Secondary End Points: Body Weight, Patient-Assessed Dyspnea, Serum Sodium Concentration, Etdema, and KCCQ Overall Summary Score**

<table>
<thead>
<tr>
<th></th>
<th>Telaplatin</th>
<th>Placebo</th>
<th>P Value</th>
</tr>
</thead>
<tbody>
<tr>
<td>Change in body weight at 1 day, mean (SD), kg</td>
<td>-1.76 (1.91) (n = 1999)</td>
<td>-0.97 (1.84) (n = 1999)</td>
<td>&lt;.001*</td>
</tr>
<tr>
<td>Change in dyspnea at 1 day, % showing improvement in dyspnea score</td>
<td>74.3 (n = 1938)</td>
<td>66.0 (n = 1920)</td>
<td>&lt;.001*</td>
</tr>
<tr>
<td>Change in serum sodium at 7 days or discharge (if earlier), mean (SD), mEq/L</td>
<td>5.49 (5.77) (n = 162)</td>
<td>1.05 (5.10) (n = 161)</td>
<td>&lt;.001*</td>
</tr>
<tr>
<td>Change in edema at 7 days or discharge, % showing at least a 2-grade improvement</td>
<td>73.8 (n = 1600)</td>
<td>70.8 (n = 1595)</td>
<td>.003*</td>
</tr>
<tr>
<td>Change in KCCQ overall summary score at postdischarge week 1, mean (SD)</td>
<td>10.90 (16.71) (n = 872)</td>
<td>16.53 (10.92) (n = 860)</td>
<td>&lt;.001*</td>
</tr>
</tbody>
</table>

Abbreviations: KCCQ, Kansas City Cardiomyopathy Questionnaire.
*Based on analysis of covariance model.
16 Among patients with symptoms at baseline.
17 Based on van Elteren test. 18 Among participants with baseline sodium levels of less than 134 mEq/L.

---

**Kонстам, М. А. et al. JAMA 2007;297:1319-1331**

---

### Hypertonic Saline ??

- **94 patients randomised to iv diuretic or iv diuretic and hypertonic saline infusions**
- **HSS group—more diuresis, higher sodium, lower creatinine and BNP at discharge**
- **No deaths and lower readmission rates!**

**Paterna S et al, JACC 2005;45:1977**
Diuretic Resistance in Heart Failure

- **Common problem**
- **Difficult to manage**
  - Standard measures inadequate
- **Newer therapies promising**
  - A1-adenosine receptor antagonists
  - Ultrafiltration
  - AVP antagonists

Diuretic Resistance and HF