The Perceived vs Real Importance of Hyperkalemia in Cardiovascular Practice

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• Consultant
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What we know about novel potassium binders

• Effective in treating hyperkalemia
• Well-tolerated
• Safety and efficacy data for up to 1 year
• Dose response
• DDI issues ‘manageable’
• Aldosterone-lowering effects
• Hypokalemia is uncommon
• Rebound hyperkalemia when stopped
• Enablement possible
## What we know about RAASi therapy in heart failure

**rEF, pEF, and post-MI**

<table>
<thead>
<tr>
<th></th>
<th>Post-MI low EF</th>
<th>Mild–mod HF low EF</th>
<th>Severe HF low EF</th>
<th>Preserved EF HF</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>ACEi</strong>¹</td>
<td>AIRE SAVE</td>
<td>SOLVD</td>
<td>CONSENSUS</td>
<td>PEP-CHF (perindopril)</td>
</tr>
<tr>
<td><strong>MRA</strong></td>
<td>EPHESUS¹ (eplerenone)</td>
<td>EMPHASIS¹ (eplerenone)</td>
<td>RALES¹ (spironolactone)</td>
<td>TOPCAT² (spironolactone)</td>
</tr>
<tr>
<td><strong>ARB</strong>¹</td>
<td>OPTIMAAL VALIANT</td>
<td>ELITE-II HEALL VAL-HeFT CHARMM</td>
<td>CHARM-Preserved</td>
<td>I-PRESERVE</td>
</tr>
<tr>
<td><strong>ARNI</strong>³</td>
<td></td>
<td>PARADIGM-HF</td>
<td></td>
<td>PARAGON-HF</td>
</tr>
</tbody>
</table>

Guidelines recommendation for Stage C HFrEF


In patients with chronic symptomatic HFrEF NYHA class II or III who tolerate an ACE inhibitor or ARB, replacement by an ARNI is recommended to further reduce morbidity and mortality (19).
Angiotensin II and aldosterone antagonism

Class I recommended therapies

• If the patient is unable to take them
  – strategies to make treatment possible are needed
• If the patients can only take one
  – strategies to make treatment possible are needed
• What if the patient can take one or both medications but only at low doses?
What we know about RAASi dose response?

<table>
<thead>
<tr>
<th>Trial</th>
<th>Drug</th>
<th>Groups</th>
<th>N</th>
<th>Age, years</th>
<th>Male, %</th>
<th>F-up, months</th>
</tr>
</thead>
<tbody>
<tr>
<td>ATLAS(^1)</td>
<td>Lisinopril</td>
<td>LD=2.5–5.0 mg daily, HD=32.5–35 mg daily</td>
<td>1,596/1,568</td>
<td>64</td>
<td>79</td>
<td>46</td>
</tr>
<tr>
<td>HEAAL(^2)</td>
<td>Losartan</td>
<td>LD=50 mg daily, HD=150 mg daily</td>
<td>1,919/1,927</td>
<td>66</td>
<td>71</td>
<td>56</td>
</tr>
</tbody>
</table>

Comparative Effects of Low and High Doses of the Angiotensin-Converting Enzyme Inhibitor, Lisinopril, on Morbidity and Mortality in Chronic Heart Failure

Milton Packer, MD; Philip A. Poole-Wilson, MD; Paul W. Armstrong, MD; John G.F. Cleland, MD; John D. Horowitz, MD; Barry M. Massie, MD; Lars Rydén, MD; Kristian Thygesen, MD; Barry F. Uretsky, MD; on behalf of the ATLAS Study Group*

### TABLE 2. Effect of Treatment on Major Clinical Events

<table>
<thead>
<tr>
<th>Event</th>
<th>Low-Dose</th>
<th>High-Dose</th>
<th>Hazard Ratio</th>
<th>P</th>
</tr>
</thead>
<tbody>
<tr>
<td>All-cause mortality</td>
<td>717 (44.9)</td>
<td>666 (42.5)</td>
<td>0.92 (0.82–1.03)</td>
<td>0.128</td>
</tr>
<tr>
<td>Cardiovascular mortality</td>
<td>641 (40.2)</td>
<td>583 (37.2)</td>
<td>0.90 (0.81–1.01)</td>
<td>0.073</td>
</tr>
<tr>
<td>All-cause mortality + hospitalization for any reason</td>
<td>1338 (83.8)</td>
<td>1250 (79.7)</td>
<td>0.88 (0.82–0.96)</td>
<td>0.002</td>
</tr>
<tr>
<td>All-cause mortality + hospitalization for cardiovascular reason</td>
<td>1182 (74.1)</td>
<td>1115 (71.1)</td>
<td>0.92 (0.84–0.99)</td>
<td>0.036</td>
</tr>
<tr>
<td>All-cause mortality + hospitalization for heart failure*</td>
<td>964 (60.4)</td>
<td>864 (55.1)</td>
<td>0.85 (0.78–0.93)</td>
<td>&lt;0.001</td>
</tr>
</tbody>
</table>

### Effects of high-dose versus low-dose losartan on clinical outcomes in patients with heart failure (HEAAL study): a randomised, double-blind trial

Marvin A Konstam, James D Neaton, Kenneth Dickstein, Helmut Drexler, Michel Komajda, Felipe A Martinez, Gunter A J Riegger, William Malbecq, Ronald D Smith, Soneil Gupta, Philip A Poole-Wilson,† for the HEAAL Investigators†

<table>
<thead>
<tr>
<th>Event Type</th>
<th>Losartan 150 mg (n=1921)</th>
<th>Losartan 50 mg (n=1913)</th>
<th>HR (95% CI)†</th>
<th>p value†</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>Number with event</td>
<td>Rate*</td>
<td>Number with event</td>
<td>Rate*</td>
</tr>
<tr>
<td>All-cause death or heart failure admission</td>
<td>828</td>
<td>11·1</td>
<td>889</td>
<td>12·4</td>
</tr>
<tr>
<td>All-cause death or cardiovascular admission</td>
<td>1037</td>
<td>15·6</td>
<td>1085</td>
<td>17·0</td>
</tr>
<tr>
<td>All-cause death</td>
<td>635</td>
<td>7·6</td>
<td>665</td>
<td>8·2</td>
</tr>
<tr>
<td>Heart failure admission</td>
<td>450</td>
<td>6·0</td>
<td>503</td>
<td>7·0</td>
</tr>
<tr>
<td>Cardiovascular admission</td>
<td>762</td>
<td>11·5</td>
<td>826</td>
<td>12·9</td>
</tr>
</tbody>
</table>

*Per 100 patient-years of follow-up. †Hazard ratio (HR) and p value from Cox regression, with region and baseline β-blocker use as covariates.

Table 2: Hazard ratios for the primary and major secondary endpoints and components
RAASi doses and mortality

Adjusted mortality rate for patients (A) receiving recommended dose; (B) reached less than recommended dose due to symptoms, side effects or non-cardiac organ failure; and (C) reached less than recommended dose for other reasons; together with the risk set sizes at each time point.

MRA dose response

• No efficacy data

• Common clinical practice to
  – Not initiate at all
  – One strike (hyper-K) and you are out
    • Irrespective of other circumstances
  – Use unusual doses common
    • 12.5 mg every 2nd or 3rd day
    • Unknown efficacy
Spironolactone causes hyperkalemia in a dose-dependent fashion

Dose-finding study pre-RALES

Optimal dosing of MRA in HF is limited by hyperkalemia

Angiotensin II and aldosterone antagonism

Class I recommended therapies in HF

- If the patient is unable to take them due to hyperkalemia, then strategies to make treatment possible are necessary
- If the patients can only take one but not the other class of drugs, then strategies to make treatment possible are necessary

- What if the patient can take medications but only at low doses?
  - Strategies to optimize doses are necessary
  - Practice guidelines recommend attempting clinical trial doses
Is this a relevant clinical problem?
Renal function, spironolactone and hyperkalemia in heart failure

RALES analysis*

Impaired renal function and spironolactone use are associated with increased hyperkalemia (>5.5 mEq/L) rates in patients with heart failure

*Double-blind trial in 1,658 patients with New York Heart Association functional Class III or IV heart failure and ejection fraction <35% randomized to spironolactone 25mg (which could be titrated to 50mg) or placebo daily.

Real-world RAASi use

- Retrospective analysis of EMR database (>7 million patients)
  (i) RAASi prescriptions according to treatment guidelines
  (ii) RAASi prescriptions after hyperkalemia events
  (iii) Clinical outcomes in patients whose RAASi are discontinued or down-titrated lower than the guidelines recommend
- Substantial gap between recommendations in treatment guidelines and real-world prescribing patterns for RAASi
- Sub-therapeutic RAASi dosing is common
- Hyperkalemia is a common cause of RAASi down-titration and discontinuation

Nearly half of patients on maximum dose of RAASi had down-titrated or discontinued RAASi therapy after a hyperkalaemia event.
MRA-eligible HF Patients are undertreated

Get With the Guidelines-HF Registry

• Among 12,565 patients eligible for MRA therapy, 4087 (32.5%) received a mineralocorticoid receptor antagonist at discharge, and there was a modest increase in treatment from 28% to 34% over the study period
CHAMP-HF Registry: Use of GDMT Among Patients with HFrEF

Hyperkalemia continues to be an issue in heart failure: PARADIGM-HF

PARADIGM-HF selected a population at low risk for hyperkalemia prior to randomization

- Excluded patients with eGFR < 30 mL/min/1.73 m²
- Excluded patients with a serum K⁺ of more than 5.2 mEq/L at screening (or more than 5.4 mEq/L at randomization)
- Had a run-in phase on ACEi that excluded 6% of patients due to AE, then a run-in phase on LCZ-696 that excluded another 6% of patients due to AE, which selected a population that would be at low risk for hyperkalemia

Hyperkalemia rates remained high despite a carefully selected population

- > 5.5 mEq/L: 16.1% LCZ-696 vs 17.3% ACEi (P=0.15)

Management of hyperkalemia

Reduce/stop/don’t start RAASi

Serum K⁺ (mEq/L)

>5.0

>5.5

>6.0

<table>
<thead>
<tr>
<th>Serum K⁺ Threshold Before Change in RAASi Guideline Recommendation</th>
</tr>
</thead>
<tbody>
<tr>
<td>K/DOQI[^5]: if 5.1-5.5, take measures to lower K⁺ when initiating RAASI</td>
</tr>
<tr>
<td>NICE[^4]: don’t start RAASI if &gt;5.0</td>
</tr>
<tr>
<td>HFSA HF[^3]: AA not recommended &gt;5.0</td>
</tr>
<tr>
<td>ACCF/AHA HF[^1]: don’t start if &gt;5.0</td>
</tr>
<tr>
<td>ESC HF[^2], ACCF/AHA HF[^1], K/DOQI[^5]: reduce dose of/stop ACEi/ARB, AA if &gt;5.5</td>
</tr>
<tr>
<td>NICE[^4]: Stop RAASI if &gt;6.0</td>
</tr>
</tbody>
</table>

Is enablement possible?
PEARL-HF: Majority of patients had spironolactone dose increased

*Patients with heart failure with reduced ejection fraction.
† P=0.015; ‡ P=0.019

AMBER

Primary Endpoint: Patients Who Remained on Spironolactone at Week 12

LS mean (95% CI) difference between groups: 20% (95% CI 10, 29)

$P < 0.0001$

Patients Who Remained on Spironolactone at Week 12, % (95% CI)

Placebo 98/148

Patiromer 126/147
OPAL-HK: RAASi enablement with patiromer in hyperkalemic HF-CKD patients

*P<0.001. †Requiring any adjustment of RAASi (i.e., down-titration or discontinuation) or patiromer dose increase due to hyperkalaemia at any time during Part B. ‡Receiving any dose of a RAASi at the end of Part B. RAASi, renin–angiotensin–aldosterone system inhibitors

Do they work in all patient sub-groups?
Treatment for hyperkalemia in HF patients receiving maximal, submaximal or no RAASi
Pooled analysis from two Phase III trials

Proportion of HF patients achieving normokalemia

Distribution of RAASi therapy classes among HF patients receiving maximal and submaximal RAASi therapy

Mean Serum Potassium in Patients With Heart Failure Over 52 Weeks

All serum K⁺ analyses are based on central lab values; 2 patients (1 in the mild HK group and 1 in the moderate HK group) did not have a central lab serum K⁺ value at baseline and therefore are not included in the analysis at this time point. *P<0.001 change in least square mean from baseline. †P<0.05 change in least square mean from last dose of patiromer. ‡Last available serum K⁺ value on or prior to the last dose received over the entire course of study treatment.
Specific Groups

No. of patients

<table>
<thead>
<tr>
<th>Baseline Potassium Level, mEq/L</th>
<th>0 hours</th>
<th>48 hours</th>
</tr>
</thead>
<tbody>
<tr>
<td>&lt;5.5</td>
<td>258</td>
<td>251</td>
</tr>
<tr>
<td>5.5-&lt;6.0</td>
<td>169</td>
<td>163</td>
</tr>
<tr>
<td>≥6.0</td>
<td>179</td>
<td>172</td>
</tr>
</tbody>
</table>

Do we worry about mild hyperkalemia?
Do we worry about mild hyperkalemia?

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Serum potassium concentration between

• 5.0-5.5 meq/L

Elevated serum potassium is associated with an increase in all-cause mortality in at-risk populations

- All-cause mortality was significantly elevated for every 0.1 mEq/L change in sK⁺ <4.0 mEq/L and ≥5.0 mEq/L

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Adjusted mortality (95% CI*) by sK⁺ level

Fear matters

• Don't start
• One strike (hyper-K) and you are out
  • Irrespective of other circumstances
• Use unusual doses common
  • 12.5 every 2nd or 3rd day
  • Unknown efficacy

• Patient factors
  – Compliance
  – Distance
  – Social support
So it stands to reason...

- Use novel $K^+$ binders to optimize RAASi therapy

- Enabling therapy not new in medicine
  - Antiemetic and chemotherapy
  - Diuretics and ACEi
Precedence

• Dexrazoxane
  – Chelating agent interferes with iron-mediated free radical generation - anthracycline induced cardiomyopathy
  – ASCO recommends dexrazoxane for cardio-protection in metastatic breast cancer patients who have received more than 300 mg/m² of doxorubicin to reduce the risk of developing HF and thus permitting longer duration of treatment.

• PPI – DAPT
  – ACC AHA 2008 guidelines recommended use
The questions is

• NOT discussing patients not studied (e.g. GFR <30 or HFpEF)
• In those population where RAASi proven to be efficacious
  – Those who develop hyperkalemia likely older, more comorbid, and lower GFR (still over 30) etc.
  – Is this group unresponsive? Hyper-responsive?
Maybe benefit is due to hyperkalemia?
Incidence, Predictors, and Outcomes Related to Hypo- and Hyperkalemia in Patients With Severe Heart Failure Treated With a Mineralocorticoid Receptor Antagonist

Orly Vardeny, PharmD, MS; Brian Claggett, PhD; Inder Anand, MD; Patrick Rossignol, MD, PhD; Akshay S. Desai, MD, MPH; Faiez Zannad, MD, PhD; Bertram Pitt, MD; Scott D. Solomon, MD; for the Randomized Aldactone Evaluation Study (RALES) Investigators

**Figure 3.** Rates of death after visit 2 (4 weeks) by treatment, based on serum potassium levels at visit 2. Mortality rates were higher in participants randomized to placebo when compared with those taking spironolactone at all potassium levels. $P<0.0001$ for comparison between spironolactone and placebo. Shaded areas represent 95% confidence intervals.
Why not used? Why do guidelines don’t recommend it?

• Should cost be included in guidelines decision making?
Will RAASi enablement with PATIROMER through potassium control in HFrEF patients potentially result in better CV outcomes?

**INCLUSION CRITERIA**
- ~2400 Patients with Heart Failure (HFrEF)
- With or without CKD (eGFR >30 mL/min/1.73m²)
- ~ 418 sites across the globe
- sK+ > 5.0 mEq/L
- History of HK in the past 12 months =>RAASi discontinuation
- Hospitalization for HF (or equivalent) within 12 months

**RUN-IN PHASE**
- (single blindered, up to 12 weeks)
- Initiate patiromer
- Start at 8.4 g/day and up-titrate as necessary up to 25.2 g/day
- Optimise ACEi/ARB/ARNi
- Initiate/optimise MRA†

**TREATMENT PHASE**
- (double blindered)
- Patiromer Continued
- Placebo (withdraw patiromer)

*Start at 8.4 g/day and up-titrate as necessary up to 25.2 g/day. Subject must return within 1 week (± 3 days) after patiromer initiation or dose adjustment to assess potassium levels.

†Initiate selected MRA; up-titrate to 50 mg/day. † = If there are changes to ACEi, ARB, ARNi and/or MRA dose or serum potassium varies outside the intended range, unscheduled weekly or monthly visits should occur until stability returns.

§ = If the potassium Assessment Visit is at 2 weeks after the EOS Visit, then follow-up Phone call is not required.
Worse outcomes with worsening comorbidity related to sub-optimal therapy due to real or perceived risk or history of hyperkalemia should be attributed to hyperkalemia.
Future need and opportunities

- Prevention vs. treatment
- Safety and efficacy in populations excluded from previous trials
  - e.g. eGFR <30 (more in need?)
- Doses not used in previous trials
  - e.g. diuretic resistance