Clinical trials, where are we 10 years after RALES study?

Targeting the Aldosterone pathway in cardiovascular disease

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Nancy, France
Dr Zannad reports receiving Speaker/consultant honoraria from Alere, AstraZeneca, BG Medicine, Boston Scientific, Novartis, Pfizer, Resmed, Servier and Takeda.
Liz Taylor died this year ... from heart failure
SURVIVAL IN CANCER & HF WOMEN

Breast
MI
Bowel
Ovarian
Heart Failure
Lung

Yrs. of follow up

McMurray JVV Stewarts
EHJ 23:D50,2002
ACE inhibitors block the RAAS, including aldosterone production

MRAs act on the kidney and are diuretics with potassium-sparing effects

Combining an MRA with an ACE inhibitor is unsafe and can produce hyperkalaemia and worsening renal function

Zannad F. Am J Cardiol. 1993;71:34A-39A.
MRAs in Heart Failure Treatment: New Data

- MRAs exert an independent and additive effect to that of ACE inhibitors.
- Apart from their renal effects, MRAs exert direct cardiac and vascular effects.
- Combining an ACE inhibitor and an MRA achieves a more complete inhibition of the whole RAAS and produces further clinical benefits.

Zannad F. Am J Cardiol. 1993;71:34A-39A.
**Aldosterone/MR antagonists beneficial across the spectrum of severity**

**RALES (LVSD, CHF severe symptoms)**

**EPHESUS (LVSD + HF after MI)**
EMPHASIS-HF
Inclusion Criteria

- **Inclusion**
  - > 55 years of age
  - NYHA functional class II
  - Ejection fraction $\leq 30\%$ (or, if between $31\%$ and $35\%$, $\text{QRS} > 130 \text{ msec}$)
  - Treated with the recommended or maximally tolerated dose of ACE inhibitor (or an ARB or both) and a beta-blocker (unless contraindicated)
  - Within 6 months of hospitalization for a cardiovascular reason [or, if no such hospitalization, $\text{BNP} \geq 250 \text{ pg/ml}$ or $\text{NT-pro-BNP} \geq 500 \text{ pg/ml}$ (males) or $750 \text{ pg/ml}$ (females)]

- **Exclusion**
  - Serum potassium $> 5.0 \text{ mmol/L}$
  - $\text{eGFR} < 30 \text{ ml/min/1.73 m}^2$
  - Need for a potassium-sparing diuretic
  - Any other significant comorbid condition

Zannad F et al NEJM 2011
Aldosterone/MR antagonists beneficial across the spectrum of severity

**RALES**
- 1663 NYHA class III/IV patients
- 95% ACE-I/10% β-blocker
- RRR (95% CI) 30 (18-40)%
- *P* < 0.001

**EMPHASIS-HF**
- 2737 NYHA class II patients
- 93% ACE-I or ARB/87% β-blocker
- RRR (95% CI) 22 (5-36)%
- *P* = 0.0139

EMPHASIS-HF
Primary Endpoint Cardiovascular Death or Hospitalization for HF

Unadjusted HR 0.66; 0.56, 0.78; \( P < 0.0001 \)

HR [95% CI] = 0.63 [0.54, 0.74] \( P < 0.0001 \)

No. at Risk
Placebo     1373      848       512
Eplerenone  1364    925     562

Zannad F et al NEJM 2011
EMPHASIS-HF
Mortality From Any Cause

HR [95% CI] = 0.76 [0.62, 0.93] P = 0.0081

No. at Risk
Placebo          1373  947  587  242
Eplerenone     1364  972  625  269

Unadjusted HR 0.78; 0.64, 0.95; P = 0.01

Zannad F et al NEJM 2011
Optimization of Neurohumoral blockade
Systolic heart failure. Moderate to severe symptoms.

Optimization of Neurohumoral blockade in systolic heart failure. Mild symptoms.

Target population

- All patients with LVSD except
  - patients with CKD (eGFR < 40-30 ml/min), excluded from trials and contraindicated
  - Patients with hyperkalemia (K+ > 5mEq/ml)
  - Patients on potassium sparing agents or potassium supplements
When to initiate?

**CHF**
patients with stable conditions

**AHF**
post discharge when renal function has stabilized

**Acute MI**
+ LVSD and HF

as soon as possible after the 3rd day
(the earlier the better)
How to use?

- The evidence
- Target patient population
- Dosing
- Safety
- Class effect?
Dose-Finding in RALES

Spironolactone (mg)

Pmol/L

Nt-ANF

Pcb 12.5 25 50 75

0 100 200 300 400
RALES Dose-Ranging Study
Mean Serum Potassium Levels (Intent-To-Treat Cohort)

RALES Investigators, Am J Cardiol, 1996.
Hyperkalemia is an inherent risk in the treatment of HF with RAAS Inhibitors.
**EMPHASIS-HF**  Potassium Safety

<table>
<thead>
<tr>
<th>Outcome</th>
<th>Eplerenone (N=1360)</th>
<th>Placebo (N=1373)</th>
<th>P Value</th>
</tr>
</thead>
<tbody>
<tr>
<td>Hyperkalemia (investigator reported AE)</td>
<td>109 (8)</td>
<td>50 (3.7)</td>
<td>&lt;0.001</td>
</tr>
<tr>
<td>Hyperkalemia leading to drug discontinuation</td>
<td>15 (1.1)</td>
<td>12 (0.9)</td>
<td>0.57</td>
</tr>
<tr>
<td>Serum K+ &gt; 5.5 mmol/L</td>
<td>158 (11.8)</td>
<td>96 (7.2)</td>
<td>&lt;0.001</td>
</tr>
<tr>
<td>Serum K+ &gt; 6.0 mmol/L</td>
<td>33 (2.5)</td>
<td>25 (1.9)</td>
<td>0.29</td>
</tr>
<tr>
<td>Hospitalization for hyperkalemia (adjudicated)</td>
<td>4 (0.3)</td>
<td>3 (0.2)</td>
<td>0.85</td>
</tr>
</tbody>
</table>
Consequences of Cardiac Hypertrophy and Fibrosis

LVH FIBROSIS

STIFFNESS
- Diastolic dysfunction

HETEROGENEITY
- Systolic dysfunction
- Arrhythmias

HEART FAILURE

SUDDEN DEATH
RALES: The high-risk fibrosis group seemed to benefit from spironolactone

Survival

PIIINP < 3.85µg/l

PIIINP > 3.85µg/l

Overall

PINP

< Med

> Med

PICP

< Med

> Med

PIIINP

< Med

> Med

Aldactone (Better)    Placebo (Better)

Effect of Eplerenone on Markers of Collagen Production in Post-MI HF Patients: EPHESUS

Placebo       Eplerenone

<table>
<thead>
<tr>
<th></th>
<th>Placebo</th>
<th>Eplerenone</th>
</tr>
</thead>
<tbody>
<tr>
<td>Wk 0</td>
<td>212</td>
<td>217</td>
</tr>
<tr>
<td>Wk 4</td>
<td>197</td>
<td>197</td>
</tr>
<tr>
<td>Mo 3</td>
<td>194</td>
<td>192</td>
</tr>
<tr>
<td>Mo 6</td>
<td>188</td>
<td>87</td>
</tr>
<tr>
<td>Mo 9</td>
<td>174</td>
<td>177</td>
</tr>
</tbody>
</table>

$P = 0.007$  $P = 0.001$  $P = 0.007$  $P = 0.006$  $P = 0.002$

Change in Serum PIIINP (in EPHESUS and RALES)

**EPHESUS 0-9 Months**

*P* = 0.002

**RALES 0-6 Months**

*P* = 0.004

Consequences of Cardiac Hypertrophy and Fibrosis

- LVH FIBROSIS
  - STIFFNESS
    - Diastolic dysfunction
  - HETEROGENEITY
    - Systolic dysfunction
    - Arrhythmias

- HEART FAILURE
- SUDDEN DEATH
## Rates of sudden cardiac death
**MRA trials in HF**

<table>
<thead>
<tr>
<th></th>
<th>MRA (EPL or Spiro)</th>
<th>Placebo</th>
<th>Hazard Ratio (95%CI)</th>
<th>P Value</th>
</tr>
</thead>
<tbody>
<tr>
<td>RALES(^1)</td>
<td>82/822 (SPIRO)</td>
<td>110/841</td>
<td>0.71 (0.54–0.95)</td>
<td>0.02</td>
</tr>
<tr>
<td>EPHESUS (Post MI)(^2)</td>
<td>162/3319 (EPLERENONE)</td>
<td>201/3313</td>
<td>0.79 (0.64–0.97)</td>
<td>0.03</td>
</tr>
<tr>
<td>EMPHASIS HF(^3)</td>
<td>60/1364 (4.4%) (EPLERENONE)</td>
<td>76/1373 (5.5%)</td>
<td>0.76 (0.54–1.07)</td>
<td>0.12</td>
</tr>
</tbody>
</table>

EMPHASIS-HF
New Onset Atrial Fibrillation/Flutter

HR [95% CI] = 0.58 [0.35, 0.96] P = 0.034

No. at Risk
Placebo 883 611 345 133
Eplerenone 911 627 397 162

Swedberg et al ESC-HFA 20
EPHESUS: Effects of Eplerenone on BNP, Osteopontin and Big Endothelin

Influence of treatment, \( P = 0.02 \)
Influence of baseline value, \( P = 0.001 \)

Influence of treatment, \( P = 0.018 \)
Influence of basal value, \( P < 0.001 \)

Zannad, unpublished data
Spironolactone or Eplerenone?
Effect of eplerenone versus spironolactone on cortisol and hemoglobin A$_{1c}$ levels in patients with chronic heart failure

Masayuki Yamaji, MD, Takayoshi Tsutamoto, MD, Chiho Kawahara, MD, Keizo Nishiyama, MD, Takashi Yamamoto, MD, Masanori Fujii, MD, and Minoru Horie, MD Otsu, Japan

The rise in HbA1c was correlated to the rise in Cortisol

Do you believe in class effect?
Targeting the aldo pathway in CV disease.
Better understanding of how it works.

Aldosterone

- ↑ PAI1
- ↑ Platelet activation
- ↑ Na + reabsorption
- ↓ Cardiomyocytes
- ↑ Cardiac fibrosis
- ↑ Collagen matrix
- Modulation of MMP
- ↓ K+
- ↓ Mg++
- ↓ HR variability
- ↓ Catecholamine uptake
- ↑ Ca2+ ion current
- ↓ K+ ion current
- Hypertension
- Acute Endothelial dysfunction
- Perivascular fibrosis
- ↓ Arterial compliance

↑ Coag.
↑ Volemia
LV dysfunction & remodeling
Cardiac arrhythmias
Cardiac ischaemia

Sudden Cardiac Death
HF Progression
Targeting the aldo pathway in CV disease. 

Changing practice
Targeting the aldo pathway in CV disease. **Changing practice**

**All** symptomatic patients with **low EF**
(With eGFR > 30 ml/min and K < 5.5 mEq/l)

- ACE inhibitor
- Beta-Blocker
- MR Antagonist

+ LBBB

ICD-CRT
Targeting the aldo pathway in CV disease.
New indications

- Heart failure
  - Systolic HF
  - Diastolic HF
  - Prevention of HF
- Hypertension
  - Essential HT
  - Resistant HT
  - PHA
  - High normal blood pressure

- Acute Coronary syndromes
  - With systolic HF
  - Upon admission
- CV Prevention in Chronic Hemodialysis
  - High CV risk
- Diabetes
- Metabolic syndrome
Targeting the aldosterone pathway in CV disease.
New MR antagonists

<table>
<thead>
<tr>
<th>Generation</th>
<th>Selectivity (sex side effects)</th>
<th>potency</th>
<th>Vasculra/renal effect</th>
<th>Priamry Aldo</th>
<th>Anti-inflammatory</th>
</tr>
</thead>
<tbody>
<tr>
<td>First Spiro</td>
<td>+</td>
<td>++</td>
<td>+</td>
<td>+</td>
<td>++</td>
</tr>
<tr>
<td>Second Eplerenone</td>
<td>+++</td>
<td>++</td>
<td>+</td>
<td>+</td>
<td>++</td>
</tr>
<tr>
<td>Third Non steroidal</td>
<td>++++</td>
<td>+++</td>
<td>++</td>
<td>+</td>
<td>++</td>
</tr>
<tr>
<td>Fourth Non renal</td>
<td>0</td>
<td>+++</td>
<td>++++</td>
<td>0</td>
<td>++++</td>
</tr>
</tbody>
</table>
Targeting the aldo pathway in CV disease. Beyond MR antagonists.

Aldosterone

Cortisol

ASI

MRA

Aldo Synthase Inhibitors
- LCI
- MSD

MR antagonists
- Steroidal
  - Spironolactone
  - Potassium canrenone
  - Eplerenone
- Non steroidal
  - Bay
Targeting the aldosterone pathway in CV disease.

- Understanding pathophysiology
- Life saving drugs
- New indications
- New MR antagonists
- Beyond MR antagonists