What do the antagonists of aldosterone receptors have to offer in the treatment of heart failure?

Athanasios J. Manolis

Director Cardiology Department, Asclepeion Hospital, Athens, Greece

Adj. Assistant Professor, Hypertension and Atherosclerosis Section, Boston University Medical School, Boston, USA

Adj. Associate Professor of Cardiology, Emory University, Atlanta, USA
Heart Failure: Pathophysiology

**LVSD**
- CO
- Systemic perfusion
- Pulmonary pressure
- Pulmonary congestion

**Neurohormonal Adaptation**
- ↑ Sympathetic nervous system
- ↑ HR
- ↑ Contractility
- ↑ CO

**Stimulation of RAA system**
- ↑ AngII, aldosterone

**Na⁺ and H₂O retention**
- Endothelial dysfunction
- Organ fibrosis
- LV dilatation and hypertrophy
- Oxidative stress
- Vascular remodeling
- Immune system activation
Aims of Heart Failure Patient Management

- Alleviate symptoms
- Improve quality of life
- Delay disease progression
- Prolong patient survival
- Reduce sudden cardiac death
- Minimise hospital admissions/hospital care (costs)
Heart Failure Drug Treatment Options

Symptom Relieving
- Diuretics
- Digoxin

Disease Modifying
- ACE inhibitors / angiotensin II receptor antagonists
- Beta-blockers
- Aldosterone receptor antagonists
Present Challenges in Treatment

Despite use of ACE inhibitors + β-blockers

- Risk of death remains high (≥12% per year)
- Risk of death or cardiovascular hospitalization remains high (≥25% per year)
- Risk of disability remains high
What Is the Next Step?

ACE inhibitor + β-blocker

Optimize
What Is the Next Step?

Optimize

Choice of dose  Choice of drug

ACE inhibitor + β-blocker
Optimization of ACE Inhibition

ATLAS Trial
Randomized comparison of low dose (2.5 mg to 5 mg daily) and high-dose lisinopril (32.5 mg to 35 mg daily)

- 8% lower risk of death ($P=0.128$)
- 15% lower risk of death or hospitalization for heart failure ($P=0.001$)
- Greater risk of hypotension, renal insufficiency, and hyperkalemia with high dose

Effect of Different Doses of Carvedilol on Morbidity and Mortality (MOCHA)

**Mortality**

![Graph showing mortality rates for different doses of Carvedilol compared to placebo.](image)

- *P*<0.05 vs placebo
- †P=0.07 vs placebo
- ‡P<0.001 vs placebo

**Cardiovascular Hospitalization**

![Graph showing cardiovascular hospitalization rates for different doses of Carvedilol compared to placebo.](image)

- *P*=0.01

What Is the Next Step?

ACE inhibitor + \( \beta \)-blocker

Optimize

Choice of dose

Choice of drug
# ACE Inhibitors vs Angiotensin Receptor Blockers in Multicenter Trials

<table>
<thead>
<tr>
<th>Study</th>
<th>Captopril</th>
<th>Losartan</th>
<th>Hazard Ratio</th>
<th>P Value</th>
</tr>
</thead>
<tbody>
<tr>
<td>OPTIMAAL(^1) (post-MI CHF)</td>
<td>447/2,733</td>
<td>499/2,744</td>
<td>1.13 (0.99,1.28)</td>
<td>0.07</td>
</tr>
<tr>
<td>ELITE II(^2) (chronic HF)</td>
<td>250/1,574</td>
<td>280/1,578</td>
<td>1.13 (0.95,1.35)</td>
<td>0.16</td>
</tr>
</tbody>
</table>

Optimization of $\beta$-Blockade

COMET Trial
Randomized comparison of metoprolol (50 mg BID) and carvedilol (25 mg BID)

- 17% lower risk of death ($P=0.0017$)
- 11% lower risk of death or hospitalization for heart failure ($P=0.02$)
- Similar risk of adverse events

What Is the Next Step?

Add a third agent

ACE inhibitor + β-blocker
What Is the Next Step?

ACE inhibitor + β-blocker

Angiotensin receptor blocker
Aldosterone antagonist
What Is the Next Step?

ACE inhibitor + β-blocker

Angiotensin receptor blocker

Val-HeFT
CHARM
VALIANT
Val-HeFT: ARBs Added to ACE Inhibitors

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**All-Cause Mortality**

![Graph showing event-free survival for Valsartan and Placebo over months, with no significant difference (P=0.80).]

**Death or CHF Hospitalization**

![Graph showing event-free survival for Valsartan and Placebo over months, with a significant decrease (13%, P=0.009).]

CHARM Program: All-Cause Mortality

Alternative

Added

Preserved

Overall

Hazard ratio

HR=0.89 (0.77-1.02)
P=0.086

HR=0.91 (0.83-1.00)
P=0.055

CHARM-Added: Cardiovascular Death or Hospitalization for CHF

HR 0.85 (95% CI 0.75-0.96), P=0.011

The Pathophysiology of Heart Failure
Results from Neurohormonal Activation

Aldosterone

Angiotensin II

Norepinephrine

Hypertrophy, apoptosis, ischemia, arrhythmias, remodeling, fibrosis
What Is the Next Step?

- ACE inhibitor + β-blocker

EPHESUS and RALES lead to Aldosterone antagonist
Randomized Aldactone Evaluation Study: Study Design

NYHA III or IV heart failure
LVEF $\leq$ 35%
ACEI + loop diuretic ± digoxin

Spironolactone
25-50 mg/day (n=822)

Placebo (n=841)

Primary Endpoint
- All-cause mortality

Secondary Endpoints
- Cardiac mortality
- Cardiac hospitalisation
- Cardiac mortality or cardiac hospitalisation
- Changes from baseline in NYHA classification

RALES: All-Cause Mortality

RR=0.70 (0.60-0.82)
P<0.001

Survival (%)

Spironolactone

Placebo

RALES: Cardiovascular Mortality or Cardiovascular Hospitalization

Survival (%)

**Primary End Points:**
- All-cause mortality
- CV mortality/CV hospitalisation*

**Secondary End Points:**
- CV mortality
- All-cause mortality/all-cause hospitalisations
- CV hospitalisations

*CV hospitalisation = hospitalisation for heart failure, MI, stroke, or ventricular arrhythmia*

Pitt B et al. Cardiovasc Drugs and Therapy 2001; 15: 79-87

**Study Design**

**EPHESUS**

**Primary End Points:**
- All-cause mortality
- CV mortality/CV hospitalisation*

**Secondary End Points:**
- CV mortality
- All-cause mortality/all-cause hospitalisations
- CV hospitalisations
EPHESUS: All-Cause Mortality

Cumulative incidence (%)

- Placebo
- Eplerenone

Months since randomization

RR=0.85 (0.75-0.96)
P=0.008

EPHESUS: Combined Risk of Cardiovascular Mortality or Cardiovascular Hospitalization

Cumulative incidence (%)

- Placebo
- Eplerenone

RR = 0.87 (0.79-0.95)

P = 0.002

Months since randomization

Cumulative incidence (%)

0 3 6 9 12 15 18 21 24 27 30 33 36

### All-Cause Mortality Subgroup Analysis

#### Total mortality

<table>
<thead>
<tr>
<th>Variable</th>
<th>Male</th>
<th>Female</th>
<th>P-value</th>
</tr>
</thead>
<tbody>
<tr>
<td>Gender</td>
<td>Male</td>
<td>Female</td>
<td>0.44</td>
</tr>
<tr>
<td>Median age</td>
<td>≤65 yr</td>
<td>&gt;65 yr</td>
<td>0.23</td>
</tr>
<tr>
<td>Median pulse pressure</td>
<td>&lt;45 mmHg</td>
<td>≥45 mmHg</td>
<td>0.01*</td>
</tr>
<tr>
<td>Median serum potassium</td>
<td>&lt;4 mmol/L</td>
<td>≥4 mmol/L</td>
<td>0.29</td>
</tr>
<tr>
<td>Median serum creatinine</td>
<td>&lt;96 µmol/L</td>
<td>≥96 µmol/L</td>
<td>0.03*</td>
</tr>
<tr>
<td>History of diabetes</td>
<td>No history</td>
<td>Any type of diabetes</td>
<td>0.35</td>
</tr>
<tr>
<td>History of hypertension</td>
<td>No</td>
<td>Yes</td>
<td>0.05</td>
</tr>
<tr>
<td>Median ejection fraction before randomisation</td>
<td>&lt;35%</td>
<td>≥35%</td>
<td>0.25</td>
</tr>
<tr>
<td>Reperfusion within 14 days of index AMI</td>
<td>No</td>
<td>Yes</td>
<td>0.62</td>
</tr>
<tr>
<td>Use of diuretics</td>
<td>No</td>
<td>Yes</td>
<td>0.34</td>
</tr>
<tr>
<td>Use of potassium supplements</td>
<td>No</td>
<td>Yes</td>
<td>0.71</td>
</tr>
</tbody>
</table>

*Statistically significant

Objective: To assess the impact of eplerenone on mortality 30 days after randomization in patients after acute myocardial infarction (AMI) with a left ventricular ejection fraction (LVEF) $\leq 40\%$ and clinical signs of heart failure (HF)

Why Are 30-day Mortality Data Important?

Rate of Sudden Cardiac Death Post-MI

Study of 14,609 patients with LVD, HF, or both after MI to assess the timing of sudden cardiac death, using the VALIANT database.

Risk reduction in all-cause mortality seemed to occur as early as 10 days post-randomization.

All-Cause Mortality (Primary End Point)

RR=0.69 (95% CI, 0.54-0.89)

EPHESUS™: Sudden Cardiac Death at 30 Days Post-Randomization

Sudden Cardiac Death (Secondary End Point)

RR = 0.63 (95% CI, 0.40 - 1.00)

- Placebo + standard therapies (n=3313)
- Eplerenone + standard therapies (n=3319)

Cumulative Incidence (%)

P = .051

Aldosterone Antagonism

EPHESUS and RALES Trials
Placebo vs eplerenone or spironolactone added to ACE inhibitor and β-blocker in post-MI CHF or class III-IV heart failure

- 15% to 30% lower risk of death ($P<0.01$)
- 15% to 30% lower risk of death or hospitalization for heart failure in both trials, both $P<0.001$
- Higher risk of renal insufficiency and hyperkalemia
What Is the Next Step?

ACE inhibitor + \(\beta\)-blocker

- Angiotensin receptor blocker
- Aldosterone antagonist
## Should an Aldosterone Antagonist Be the Next Step After ACE Inhibitor + β-Blocker?

<table>
<thead>
<tr>
<th></th>
<th>Aldosterone Antagonist</th>
<th>Angiotensin Receptor Blocker</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Effect on mortality</strong></td>
<td>15%-30%</td>
<td>5%-10%</td>
</tr>
<tr>
<td><strong>Effect on risk of death or CHF hospitalization</strong></td>
<td>15%-30%</td>
<td>10%-15%</td>
</tr>
<tr>
<td><strong>Effect on blood pressure</strong></td>
<td>No change</td>
<td>Decrease</td>
</tr>
<tr>
<td><strong>Other safety</strong></td>
<td>Renal insufficiency Hyperkalemia</td>
<td>Renal insufficiency Hyperkalemia</td>
</tr>
</tbody>
</table>
What Is the Next Step?

ACE inhibitor + β-blocker

Aldosterone antagonist
ESC GUIDELINES FOR HEART FAILURE
(UPDATE 2005)

- Aldosterone antagonists such as eplerenone are recommended in addition to ACEi and β-blockers in post-MI LV dysfunction with or without symptoms of HF (level of evidence IB).

- Check serum potassium <5 and creatinine<2.5. Add low dose Eplerenone 25 mg. After 4-6 days if potassium is 5-5.5 reduce dose 50%. If potassium > 5.5 stop the drug. If symptoms persists and normokalaemia exists after one month, increase to 50 mg daily. Check biochemics after one week.
Post-MI LV Dysfunction: Current therapeutic strategies

- ACE inhibitors (SAVE, AIRE, TRADE)
- Carvedilol (CAPRICORN)
- ARBs alternatively to ACEi (VALIANT)
- Eplerenone (EPHESUS)

- Statins
- Aspirine
- Nitrates?