Antialdosterone treatment in heart failure

전남의대
윤현주
Chronic Heart Failure
Prognosis of Heart failure

- Progression
- Further damage
- Excessive wall stress
- Neurohormonal activation
- Myocardial ischemia

Mechanism of death:
- Sudden death 40%
- Worsening CHF 40%
- Other 20%

Annual mortality:
- < 5%
- 10%
- 20% to 30%
- 30 to 80%

Left ventricular dysfunction and symptoms:
- Asymptomatic
- Mild
- Moderate
- Severe

Patients surviving %
Asymptomatic LV dysfunction → Chronic heart failure → Systemic hypoperfusion

Class I → Class II → Class III → Class IV

- Neurohormonal activation
- Sodium retention
- Peripheral vasoconstriction
- Contractile failure
# Classification of Heart Failure

<table>
<thead>
<tr>
<th>Stage</th>
<th>Patient Description</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>A</strong></td>
<td>High risk for developing heart failure (HF)</td>
</tr>
<tr>
<td></td>
<td>- Hypertension</td>
</tr>
<tr>
<td></td>
<td>- CAD</td>
</tr>
<tr>
<td></td>
<td>- Diabetes mellitus</td>
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<tr>
<td></td>
<td>- Family history of cardiomyopathy</td>
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<tr>
<td><strong>B</strong></td>
<td>Asymptomatic HF</td>
</tr>
<tr>
<td></td>
<td>- Previous MI</td>
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<tr>
<td></td>
<td>- LV systolic dysfunction</td>
</tr>
<tr>
<td></td>
<td>- Asymptomatic valvular disease</td>
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<tr>
<td><strong>C</strong></td>
<td>Symptomatic HF</td>
</tr>
<tr>
<td></td>
<td>- Known structural heart disease</td>
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<tr>
<td></td>
<td>- Shortness of breath and fatigue</td>
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<td>- Reduced exercise tolerance</td>
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<tr>
<td><strong>D</strong></td>
<td>Refractory end-stage HF</td>
</tr>
<tr>
<td></td>
<td>- Marked symptoms at rest despite maximal medical therapy</td>
</tr>
<tr>
<td></td>
<td>(recurrently hospitalized or cannot be safely discharged from the hospital without specialized interventions)</td>
</tr>
</tbody>
</table>
Treatment of heart failure

• Manage other risk factors
• Manage coexisting coronary heart disease
• Avoid aggravating factors
  – Non-steroidal anti-inflammatory drugs
  – Short-acting calcium-channel blockers
  – Advise low salt diet
  – Advise a moderate alcohol intake
  – Limiting fluid intake may be appropriate in advanced heart failure, but care is needed to avoid dehydration.

• Vaccinate people against influenza annually and pneumococcus as a one-off, as they are at increased risk of infective complications.
• Consider cardiac rehabilitation, palliative care, and long-term social support if appropriate.
# Treatment of Heart Failure

<table>
<thead>
<tr>
<th>Stage A</th>
<th>Stage B</th>
<th>Stage C</th>
<th>Stage D</th>
</tr>
</thead>
<tbody>
<tr>
<td>High risk for HF without disease</td>
<td>Structural heart ds without HF signs or symptoms</td>
<td>Structural hearts ds with prior or concurrent signs, symptoms of HF</td>
<td>Refractory HF requiring specialized Tx</td>
</tr>
</tbody>
</table>

**Goals**
- **Stage A**
  - 고혈압, 치료, 금연, 이상지질 치료, 정기적 운동, 음주, 약물의 절제, 대사 증후군 조절
- **Stage B**
  - Stage A의 모든 것, 식이염분 제한
- **Stage C**
  - Stage A의 모든 것, 적정 치료 수준 결정
- **Stage D**
  - Stage A, B, C의 모든 것 적정 치료 수준 결정

**Drugs**
- **Stage A**
  - ACEI or ARB in appropriate pts
  - β-blockers in appropriate pts
- **Stage B**
  - Diuretics for fluid retention ACEI, β-blockers
- **Stage C**
  - Aldosterone antagonists
  - ARB, Digoxin
  - Hydralazine/nitrates
- **Stage D**
  - End-of-life care
  - Extraordinary Mx
  - heart transplant
  - chronic inotrope permanent
  - mechanical support experimental
  - surgery or drugs

**Devices for selected pts**
- Biventricular pacing
- Implantale defibrillator
New Therapies in the Heart Failure

Neurohumoral approaches
- Aldosterone antagonists
- Vasopressin antagonists
- Endopeptidase inhibitors
- NO enhancing therapy
- Natriuretic hormones

Gene therapy
Cell therapy

Inflammatory modulators
- Cytokine inhibitors
- Immune modulation

Inotropic agents
- Phosphodiesterase inhibitors
- Calcium sensitizers

Systemic agents
- Erythropoietin analogues
- Statins

Modulators of myocardial remodeling
- MMP inhibitors

Cardiac metabolic agents
- Partial fatty acid oxidase inhibitors
- Advanced glycation end product antagonists
Treatment of Heart Failure

Heart failure with preserved ejection fraction:
- Manage comorbid conditions such as high blood pressure, ischaemic heart disease and diabetes mellitus in line with NICE guidance.

Heart failure due to left ventricular systolic dysfunction:
- Offer both ACE inhibitors and beta-blockers licensed for heart failure as first-line treatment.
- Consider an ARB if intolerant of ACE inhibitors.

If symptoms persist despite optimal first-line treatment, seek specialist advice and for second-line treatment consider adding:
- an aldosterone antagonist licensed for heart failure (especially in moderate to severe heart failure or MI in past month) or
- an ARB licensed for heart failure (especially in mild to moderate heart failure) or
- hydralazine in combination with nitrate (especially in people of African or Caribbean origin with moderate to severe heart failure)

If symptoms persist consider:
- CRT (pacing with or without a defibrillator)
- digoxin

Specialist assessment

Offer rehabilitation and education, and diuretics for congestion and fluid retention.

Consider an ICD where appropriate.
First-line treatment for LVSD

- Offer both **ACE inhibitors** and **beta-blockers** licensed for heart failure to all patients with LVSD

Second-line treatment for LVSD

- aldosterone antagonist licensed for heart failure (especially in NYHA class III–IV or MI in past month)
- ARB licensed for heart failure (especially in NYHA class II-III)
- hydralazine in combination with nitrate (especially in people of African or Caribbean origin with NYHA class III-IV)
Cardiovascular Actions of Aldosterone

- Intravascular fluid retention, volume overload
- Endothelial dysfunction
  - impaired vascular reactivity
  - decrease vascular antioxidant capacity,
    increase oxidant stress
  - limiting bioavailable nitric oxide
- Activate inflammation
- Alter fibrinolysis
  (increasing PAI-1 expression,
   -> promote tissue fibrosis)
The effect of impaired LV function on aldosterone synthesis

Circulation. 2010;121:934-939
Aldosterone Antagonist

- Potassium sparing diuretics

- Antagonize the effects of aldosterone at the late distal tubule and cortical collecting tubule

- Direct pharmacologic antagonism of mineralocorticoid receptors

  1. Spironolactone
  2. Eplerenone
Action mechanism of aldosterone antagonist

Aldosterone

Sodium and Water Retention
Edema

Potassium and Magnesium Excretion
Arrhythmias

Collagen deposition
Myocardial and Vascular Fibrosis
# Aldosterone antagonist

<table>
<thead>
<tr>
<th>Characteristics</th>
<th>Spironolactone</th>
<th>Eplerenone</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Clinical indication</strong></td>
<td>Severe (NYHA class III–IV) CHF with LV systolic dysfunction</td>
<td></td>
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<tr>
<td></td>
<td>Essential hypertension</td>
<td></td>
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<tr>
<td></td>
<td>Primary hyperaldosteronism</td>
<td></td>
</tr>
<tr>
<td><strong>Receptor binding affinity</strong></td>
<td>$1.1 \times 10^{-1}$</td>
<td>$5.1 \times 10^{-3}$</td>
</tr>
<tr>
<td>(aldosterone=1)</td>
<td></td>
<td></td>
</tr>
<tr>
<td><strong>Sex-steroid receptor</strong></td>
<td>Yes</td>
<td>Minimal</td>
</tr>
<tr>
<td><strong>cross-reactivity</strong></td>
<td></td>
<td></td>
</tr>
<tr>
<td><strong>Metabolism</strong></td>
<td>Hepatic</td>
<td>Cytochrome P450, isoenzyme CYP3A4</td>
</tr>
<tr>
<td><strong>Conversion to metabolites for effect</strong></td>
<td>Yes</td>
<td>No</td>
</tr>
<tr>
<td><strong>Half-life, h</strong></td>
<td>1.4</td>
<td>4–6</td>
</tr>
<tr>
<td><strong>Excretion</strong></td>
<td>Renal and bile</td>
<td>Renal and GI</td>
</tr>
<tr>
<td><strong>Administration</strong></td>
<td>With food to maximize absorption</td>
<td>With or without food</td>
</tr>
<tr>
<td><strong>Recommended dose, mg/d</strong></td>
<td>Hypertension, 50–100; CHF, 25–200</td>
<td>Hypertension, 50–100; CHF, 25–50</td>
</tr>
<tr>
<td><strong>Drug interactions</strong></td>
<td>Potentiate hyperkalemia</td>
<td>Potentiate hyperkalemia</td>
</tr>
<tr>
<td></td>
<td>ACE-I</td>
<td>ACE-I</td>
</tr>
<tr>
<td></td>
<td>NSAIDs</td>
<td>NSAIDs</td>
</tr>
<tr>
<td></td>
<td>Potentiate hypotension</td>
<td></td>
</tr>
<tr>
<td></td>
<td>Narcotics</td>
<td>CYP3A4 inhibitors increase eplerenone:</td>
</tr>
<tr>
<td></td>
<td>Increase digoxin levels</td>
<td>itraconazole, ribonavir, clarithromycin</td>
</tr>
<tr>
<td><strong>Side effects</strong></td>
<td>Hyperkalemia</td>
<td>CYP3A4 inducers decrease eplerenone:</td>
</tr>
<tr>
<td></td>
<td>Gynecomastia, breast tenderness</td>
<td>St John's wort</td>
</tr>
<tr>
<td></td>
<td>Erectile dysfunction</td>
<td>Hyperkalemia</td>
</tr>
<tr>
<td></td>
<td>Dysmenorrhea, amenorrhea</td>
<td>Abdominal pain, diarrhea</td>
</tr>
</tbody>
</table>
Spironolactone

- Nonselective aldosterone antagonist
- Metabolized in liver
- Plasma half life ~1.4h
  (if hepatic congestion, duration increase x5)
- Max drug response 48h after 1\textsuperscript{st} dose
- Structurally similar to progesterone
  - sex steroid receptor cross-reactivity
  - antiprogestosterone, antiandrogen effect
Eplerenone

- Selective aldosterone receptor antagonist
- Limited affinity for the progesterone and androgen receptor
  -> lack sex-related side effect
- steady-state drug level 48h after 1st dose
- metabolized CytP450
- plasma half life 4-6h
Adverse effects

• Hyperkalemia (impairing aldosterone-mediated effects on K+ homeostasis in the principal cells in kidney)
• Hyperchloremic metabolic acidosis
• Gynecomastia
• Hirsuitism, impotence, menstrual irregularity
Aldosterone antagonist

Secondary Prevention

Aldosterone antagonist in UA/NSTEMI patients already receiving and ACE-I with LVSD (EF <0.40) and either symptomatic HF or DM

Aldosterone antagonist in those with LVSD (EF<0.35) and recent or current NYHA class IV HF symptoms*

ACE-I=Angiotensin converting enzyme inhibitor,
DM=Diabetes mellitus, EF=Ejection fraction, HF=Heart failure, LVSD=Left ventricular systolic dysfunction,
MI=Myocardial infarction, NYHA=New York Heart Association

*Contraindications include abnormal renal function (creatinine ≥2.5 mg/dL in men or ≥2.0 mg/dL in women) and hyperkalemia (K+ ≥5.0 meq/L)
Addition of an aldosterone antagonist is recommended in selected patients with moderately severe to severe symptoms of HF and reduced LVEF who can be carefully monitored for preserved renal function and normal potassium concentration. Creatinine 2.5 mg/dL or less in men or 2.0 mg/dL or less in women and potassium should be less than 5.0 mEq/L. Under circumstances where monitoring for hyperkalemia or renal dysfunction is not anticipated to be feasible, the risks may outweigh the benefits of aldosterone antagonists.
The Hospitalized Patient

**Intensifying the Diuretic Regimen**

When diuresis is inadequate to relieve congestion, as evidenced by clinical evaluation, the diuretic regimen should be intensified using either:

a. higher doses of loop diuretics;

b. addition of a second diuretic (such as metolazone, spironolactone or intravenous chlorthiazide) or

c. Continuous infusion of a loop diuretic.
### Oral Diuretics Recommended for Use in the Treatment of Chronic Heart Failure

<table>
<thead>
<tr>
<th>Drug</th>
<th>Initial Daily Dose(s)</th>
<th>Maximum Total Daily Dose</th>
<th>Duration of Action</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Loop Diuretics</strong></td>
<td></td>
<td></td>
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</tr>
<tr>
<td>Bumetanide</td>
<td>0.5 to 1.0 mg once or twice</td>
<td>10 mg</td>
<td>4 to 8 hours</td>
</tr>
<tr>
<td>Furosemide</td>
<td>20 to 40 mg once or twice</td>
<td>600 mg</td>
<td>6 to 8 hours</td>
</tr>
<tr>
<td>Torsemide</td>
<td>10 to 20 mg once</td>
<td>200 mg</td>
<td>12 to 16 hours</td>
</tr>
<tr>
<td><strong>Thiazide Diuretics</strong></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Chlorothiazide</td>
<td>250 to 500 mg once or twice</td>
<td>1000 mg</td>
<td>6 to 12 hours</td>
</tr>
<tr>
<td>Chlorthalidone</td>
<td>12.5 to 25 mg once</td>
<td>100 mg</td>
<td>24 to 72 hours</td>
</tr>
<tr>
<td>Hydrochlorothiazide</td>
<td>25 mg once or twice</td>
<td>200 mg</td>
<td>6 to 12 hours</td>
</tr>
<tr>
<td>Indapamide</td>
<td>2.5 mg once</td>
<td>5 mg</td>
<td>30 hours</td>
</tr>
<tr>
<td>Metolazone</td>
<td>2.5 mg once</td>
<td>20 mg</td>
<td>12 to 24 hours</td>
</tr>
<tr>
<td><strong>Potassium-Sparing Diuretics</strong></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Amiloride</td>
<td>5 mg once</td>
<td>20 mg</td>
<td>24 hours</td>
</tr>
<tr>
<td><strong>Spironolactone</strong></td>
<td>12.5 to 25 mg once</td>
<td>50 mg†</td>
<td>2 to 3 days</td>
</tr>
<tr>
<td>Triamterene</td>
<td>50 to 75 mg twice</td>
<td>200 mg</td>
<td>7 to 9 hours</td>
</tr>
</tbody>
</table>

### Sequential Nephron Blockade

- Metolazone
- Hydrochlorothiazide
- Chlorothiazide (IV)
- 2.5 to 10 mg once plus loop diuretic
- 25 to 100 mg once or twice plus loop diuretic
- 500 to 1000 mg once plus loop diuretic

*Eplerenone, although also a diuretic, is primarily used in chronic heart failure as a suppressor of the renin-angiotensin-aldosterone system.*

†Higher doses may occasionally be used with close monitoring.
Randomized Aldosterone Evaluation Study (RALES)

1,663 patients with NYHA Class III or IV HF and LVSD (EF < 0.35) randomized to spironolactone (25-50mg) or placebo for 24 months

Survival (%)

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

Months

RR = 0.70, P<0.001

Aldosterone inhibition reduces death in patients with advanced heart failure

Pitt B et. al. NEJM 1999;341:709-717
**Spironolactone**

- **Spironolactone**, should be considered for people with moderate to severe heart failure (NYHA grades III-IV) who are already on an ACE inhibitor and a loop diuretic [SIGN, 1999; DH, 2000; Samuel, 2003].

- The Randomised Aldactone Evaluation Study (RALES) compared treatment with low-dose spironolactone (25 mg daily) added to standard care with other diuretics, ACE inhibitors and digoxin against standard care alone, in people with moderate to severe heart failure (NYHA III-IV) [Pitt et al, 1999]. Mortality was reduced by 30%, the risk of hospitalization for worsening heart failure was reduced by 35%, and there was a significant improvement in symptoms. Over 2 years, one death was avoided for every 9 people treated with spironolactone in addition to standard therapy.

- Careful monitoring for hyperkalaemia and hypovolaemia is required. [Heart Failure Society of America, 1999; Krum, 2001; Remme et al, 2001]
Aldosterone antagonists are underused by clinicians

Jane-Lise Samuel and Claude Delcayre

Aldosterone antagonists decrease the mortality of patients with heart failure, but an observational study by Albert and colleagues has found that a surprisingly low number of patients receive aldosterone antagonists before discharge from hospital. This article highlights potential reasons for why there is such an underuse of efficient drugs in heart failure.
Aldosterone Antagonist Use

(N=12,565 Patients)

JAMA 2009;302(15):1658-65
Prescribed rates of major oral medications before admission and at discharge in the present study.
56/M Dyspnea

HTN (+), Ex-Smoker
Previous PCI due to MI 4 years ago
EF 40%
Aspirin 100mg
Dilatrend 12.5mg
Diovan 80mg
Lasix 20mg
Crestor 10mg
Effect of Spironolactone on Plasma Brain Natriuretic Peptide and Left Ventricular Remodeling in Patients with CHF

![Graphs showing changes in LVEDVI, LVESVI, LVMII, ALD, BNP, and PIINP with spironolactone and placebo treatment.](Image)

* J Am Coll Cardiol 2001;37:1228–33
Spironolactone use at discharge was associated with improved survival in hospitalized patients with systolic heart failure.

946 Pts
EF<40%
Eplerenone Post-Acute Myocardial Infarction Heart Failure Efficacy and Survival study (EPHESUS)

3,313 patients with evidence of HF and LVSD (EF < 0.40) after a MI randomized to eplerenone (25-50 mg) or placebo for 16 months

Aldosterone inhibition improves survival in patients with post-MI HF and LVSD

RR = 0.85, P=0.008

Pitt B et al. NEJM 2003;348:1309-21
Eplerenone, a Selective Aldosterone Blocker, in Patients with Left Ventricular Dysfunction after Myocardial Infarction

Bertram Pitt, M.D., Willem Remme, M.D., Faiez Zannad, M.D., James Neaton, Ph.D., Felipe Martinez, M.D., Barbara Roniker, M.D., Richard Bittman, Ph.D., Steve Hurley, B.S., Jay Kleiman, M.D., and Marjorie Gatlin, M.D., for the Eplerenone Post–Acute Myocardial Infarction Heart Failure Efficacy and Survival Study Investigators*

Death from Any Cause
Death from Cardiovascular Causes or Hospitalization for Cardiovascular Events
Sudden Death from Cardiac Causes

Eplerenone in Patients with Systolic Heart Failure and Mild Symptoms

Faiez Zannad, M.D., Ph.D., John J.V. McMurray, M.D., Henry Krum, M.B., Ph.D., Dirk J. van Veldhuisen, M.D., Ph.D., Karl Swedberg, M.D., Ph.D., Harry Shi, M.S., John Vincent, M.B., Ph.D., Stuart J. Pocock, Ph.D., and Bertram Pitt, M.D., for the EMPHASIS-HF Study Group

2737Pts
EF<35%
NYHA II

NEJM 2011;364:11
New biology of aldosterone

- Old concept:
  - Released from the adrenal cortex, ->circulated in the bloodstream,
  - Acted only on the kidney
  - Retain sodium and excrete potassium

- New concept:
  - Aldosterone is made in, including various organs: Vessels, Brain, Myocardium
  - many tissues also express mineralocorticoid receptors.
  - Aldosterone acts in a paracrine fashion in many organs.

Curr Opin Nephrol Hypertens 2008:17:44-50
Aldosterone receptor antagonist

Circulation. 2010;121:934-939
Chronic Heart Failure

Symptom Control
Improving of Heart function
  : EF, LV size
Improving prognosis
  : Survival benefit
감사합니다.