Mineralocorticoid Receptor Antagonist in HF

Introduction

• Mineralocorticoid receptor antagonist (MRA or aldosterone antagonist) has been shown to reduce morbidity and mortality in patients with chronic HFrEF.
• But MRA is commonly underused due to concern for adverse effects.
• Only 1/3 of eligible patients are prescribed MRA. (jama 2009;21:1658-65).
• MRA include spironolactone, eplerenone (not available in Thailand).

Pathophysiology

• Aldosterone is synthesized by the adrenal glands (stimulated by angiotensin II)
• Regulate Na^+, K^+ and water homeostasis.
• Aldosterone upregulates Na^+-K^+-ATPase pump - via minerocorticoid receptor within principal cells at the collecting duct - results in
  - Na^+ retention
  - Intra/extravascular volume expansion
  - K^+ excretion, Mg^+ excretion
• Aldosterone antagonist is a K-sparing diuretic, but main benefits of spironolactone in HF are not from being a diuretic or antihypertensive.
• Aldosterone directly promotes fibrosis and adverse remodeling of the heart.
• Other adverse mechanisms of hyperaldosteronism include
  - ↑ Vascular inflammation
  - ↑ cardiac apoptosis
  - ↑sympathetic tone
  - Endothelial dysfunction
  - Impairs vascular reactivity (↑ oxidant stress, ↓ available nitric oxide),
• "Aldosterone Breakthrough" - In patients with HF who are already on ACEI/ARB, aldosterone level is still 60-fold higher than normal subjects. (NEJM 2001;345:1689-97).

RCT of MRA in chronic HFrEF (all compare with placebo)

Study	Drug N	Inclusion (EF, NYHA)	Background Rx	All-cause death F/U time	Note
RALES NEJM 1999	Spironolactone (12.5 →50 mg) N = 1663	≤35% III-IV	100% Diuretics 95% ACEI 74% Digoxin 11% BB	35 vs 46% RRR = 30% 2yr	NNT = 9 to save 1 life in 2 yrs Sig ↓ SCD Prior to BB use
EPHESUS NEJM 2003	Eplerenone (25 → 50mg) N= 6642	3-14 d post MI < 40%	87% ACEI/ARB 75% BB 60% Diuretics	14.4 vs 16.7% RRR = 15% 16mo	Need to have symptoms of HF or DM to be enrolled. Mean of 7 days from MI
EMPHASIS-HF NEJM 2010	Eplerenone (25 → 50mg) N = 2737	≤30% II +CVhosp	93% ACEI/ARB 86% BB 85% Diuretics 26% Digoxin	12.5 vs 15.5% RRR = 24% 21 mo	Stop early EF 30-35% with QRS > 130 ,sec also included. K >6 in 2.5%

RALES = Randomized aldactone evaluation study trial
EPHESUS = Eplerenone in patients with left ventricular dysfunction after myocardial infarction.
EMPHASIS-HF = Eplerenone in mild patients hospitalization and survival study in HF

Clinical point

• MRAs are associated with ↑survival and
  - Improve structural remodeling (↑ LVEF, ↓ LVEDV, ↓ LVESV)
  - ↑ QoL, ↑ peak VO2
  - ↓ HF hosp, and ↓ hospital stay durations.
• Spironolactone should not be started if K > 5 mEq/L, Cr > 2.5 mg/dL (men) or > 2 mg/dL (women).
• Spironolactone should be initiated at a dose of 12.5 to 25 mg daily.
• Eplerenone should be initiated at a dose of 25 mg/d, increasing to 50 mg daily.
• Efficacy of spironolactone and eplerenone are thought to be the same (but no head-to-head RCT).
• Potassium supplements should be decreased or discontinued. If K > 5.5 should stop meds.
• Spironolactone is structurally similar to progesterone so it causes breast tenderness and gynecomastia in 7-10% of men (reported in RCT), usually resolve with drug cessation. Other s/e include erectile dysf, menstrual irregularities.
• Eplerenone is more selective so no sex steroid receptor cross-reactivity but still the same hyperK. Note, Eplerenone is metabolized via cytochrome P450 (CYP3A4)

Hyperkalemia

• Most fearful complication of MRAs
• In RALES trial, serious hyperkalemia (K^+ > 6 mmol/L) occurred only 2% in spironolactone group (vs. 1% in placebo group; p = 0.42).
• The hyperkalemia rate was much higher in community. After publication of RALES trial, the rate of hyperkalemia related hospitalization increased from 2.4 to 11 per 1000 patients and the hyperkalemia related death increased from 0.3 to 2 per 1000 patients. (nejm 2004;6:543-51).
• Guideline recommend K and electrolyte check at day 3, 7, then monthly for 3 month.

Table 17. Strategies to Minimize the Risk of Hyperkalemia in Patients Treated With Aldosterone Antagonists

1. Impaired renal function is a risk factor for hyperkalemia during treatment with aldosterone antagonists. The risk of hyperkalemia increases progressively when serum creatinine is >1.6 mg/dL.* In elderly patients or others with low muscle mass in whom serum creatinine does not accurately reflect glomerular filtration rate, determination that glomerular filtration rate or creatinine clearance is >30 mL/min/1.73 m² is recommended.
2. Aldosterone antagonists would not ordinarily be initiated in patients with baseline serum potassium >5.0 mEq/L.
3. An initial dose of spironolactone of 12.5 mg or eplerenone 25 mg is typical, after which the dose may be increased to spironolactone 25 mg or eplerenone 50 mg if appropriate.
4. The risk of hyperkalemia is increased with concomitant use of higher doses of ACE inhibitors (captopril ≥75 mg daily; enalapril or lisinopril ≥10 mg daily).
5. In most circumstances, potassium supplements are discontinued or reduced when initiating aldosterone antagonists.
6. Close monitoring of serum potassium is required; potassium levels and renal function are most typically checked in 3 d and at 1 wk after initiating therapy and at least monthly for the first 3 mo.

*Although the entry criteria for the trials of aldosterone antagonists included creatinine <2.5 mg/dL, the majority of patients had much lower creatinine; in 1 trial,[425] 95% of patients had creatinine ≤1.7 mg/dL.

Other indication

• HFpEF
  - No survival benefit. (TOPCAT. NEJM 2014)
• HFrEF stage C, NYHA I
  - No study enrolled patient with NYHA class I. Guideline correctly recommend MRA in NYHA II-IV.
• HFrEF stage B
  - Some patients in EPHESUS were actually stage B HF (Post MI + EF < 40% + DM)
  - This was not mentioned in the ACC 2013 Guideline.

Recommend reading

• Aldosterone Receptor Antagonists: Effective but Often Forgotten (Circulation 2010;121:934-939)
• Aldosterone Antagonists in Heart Failure (J Cardiovasc Pharm and Ther 16(2) 150-159)