



Senior Medicine Rotation: Evidence-Based Medicine Project

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Block: October

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Case SIGNOUT:

50 yo African American male with PMH HTN and non-ischemic CHF (last EF 25% per patient) s/p AICD who presents with SOB. He has had progressive SOB on exertion over the last week, which by the day PTA resulted in a decrease in his exercise tolerance from a baseline of ~3 blocks to <1 block and increase in pillow orthopnea from 2 to 3 pillows. He denies any f/c, n/v, cough, or cp and reports compliance with all medications, but notes that his furosemide was decreased from 60 mg BID to 20 mg BID by his PMD one week ago secondary to worsening renal function. Exam is notable for bilateral crackles, troponins negx3. Patient is diuresed with IV furosemide for likely CHF exacerbation with prompt relief of symptoms. TTE subsequently shows estimated EF 30-35% with moderately decreased LV systolic function and global hypokinesis. On admission, patient's medication regimen included carvedilol 25mg BID, ibersartan 70mg daily, and furosemide 20 mg daily.

Clinical Question: Given his cardiac function and functional status, would this patient benefit from the addition of an aldosterone antagonist to his medication regimen?

Background:

Evidence from several randomized, placebo-controlled trials supports that ACE inhibitors and beta-blockers can reduce morbidity and mortality in all patients with CHF EF \leq 35%:

SOLVD trial: Addition of enalapril to conventional therapy significantly reduced mortality and hospitalizations for heart failure in patients with CHF with EF \leq 35% and NYHA classes II and III. Enalapril significantly reduced incidence of heart failure and rate of hospitalizations for heart failure compared to placebo in patients with asymptomatic left ventricular dysfunction with EF \leq 35%.

CONSENSUS trial: Addition of enalapril to conventional therapy in patients with severe CHF (NYHA class IV) significantly reduced mortality compared to placebo.

MERIT-HF: Metoprolol CR/XL added to standard regimen improved survival in patients with NYHA Class II-IV and EF \leq 40% vs placebo.

COPERNICUS: Carvedilol reduced morbidity and mortality in patients with mild (EF \leq 35%) to severe (EF <25%) heart failure.

With regards to aldosterone antagonist therapy, the placebo-controlled trial RALES (Randomized Aldactone Evaluation Study) showed that adding spironolactone to recommended therapy in patients with EF \leq 35% systolic CHF and moderate-to-severe (NYHA functional class III or IV) symptoms reduces mortality and risk of hospitalization for cardiovascular causes. The EPHEsus (Eplerenone Post-Acute Myocardial Infarction Heart Failure Efficacy and Survival Study) additionally showed that addition of eplerenone to recommended medical therapy reduced mortality from any cause and hospitalization for CV causes in patients with heart failure following acute MI. Though this patient has an EF ~30-35%, he would be considered NYHA functional class II, a group that was not studied in the RALES trial. In addition, he never suffered from an acute MI, which was the population of focus in the EPHEsus trial.

Search Strategy

Database: Pubmed

Search terms: "aldosterone antagonists" [MeSH Major Topic] AND "heart failure" [MeSH Major Topic] AND "mortality" [MeSH Subheading]) "randomized controlled trial" [Publication Type]

Results: 14

1. [Spironolactone use at discharge was associated with improved survival in hospitalized patients with systolic heart failure.](#)

Hamaguchi S, Kinugawa S, Tsuchihashi-Makaya M, Goto K, Goto D, Yokota T, Yamada S, Yokoshiki H, Takeshita A, Tsutsui H.

Am Heart J. 2010 Dec;160(6):1156-62. PMID: 21146672

2. [Eplerenone in patients with systolic heart failure and mild symptoms.](#)

Zannad F, McMurray JJ, Krum H, van Veldhuisen DJ, Swedberg K, Shi H, Vincent J, Pocock SJ, Pitt B; EMPHASIS-HF Study Group.

N Engl J Med. 2011 Jan 6;364(1):11-21. Epub 2010 Nov 14. PMID: 21073363

3. [Rationale and design of the Eplerenone in Mild Patients Hospitalization And Survival Study in Heart Failure \(EMPHASIS-HF\).](#)

Zannad F, McMurray JJ, Drexler H, Krum H, van Veldhuisen DJ, Swedberg K, Shi H, Vincent J, Pitt B.

Eur J Heart Fail. 2010 Jun;12(6):617-22. Epub 2010 Apr 13. PMID: 20388647

4. [Timing of eplerenone initiation and outcomes in patients with heart failure after acute myocardial infarction complicated by left ventricular systolic dysfunction: insights from the EPHEsus trial.](#)

Adamopoulos C, Ahmed A, Fay R, Angioi M, Filippatos G, Vincent J, Pitt B, Zannad F; EPHEsus Investigators.

Eur J Heart Fail. 2009 Nov;11(11):1099-105. PMID: 19875410

5. [Cost-effectiveness analysis of aldosterone blockade with eplerenone in patients with heart failure after acute myocardial infarction in the French context: the EPHEsus study.](#)

de Povourville G, Solesse A, Beillat M.

Arch Cardiovasc Dis. 2008 Sep;101(9):515-21. Epub 2008 Nov 6. PMID: 19041835

6. [History of hypertension and eplerenone in patients with acute myocardial infarction complicated by heart failure.](#)

Pitt B, Ahmed A, Love TE, Krum H, Nicolau J, Cardoso JS, Parkhomenko A, Aschermann M, Corbalán R, Solomon H, Shi H, Zannad F.

Hypertension. 2008 Aug;52(2):271-8. Epub 2008 Jun 16. PMID: 18559720

7. [\[Eplerenone Post-AMI Heart Failure Efficacy and survival study \(EPHEsus\)\].](#)

Takata Y, Asano K, Yamashina A.

Nihon Rinsho. 2005 Mar;63 Suppl 3:336-41. Japanese. No abstract available. PMID: 15813091

8. [Economic evaluation of the randomized aldactone evaluation study \(RALES\): treatment of patients with severe heart failure.](#)

Glick HA, Orzol SM, Tooley JF, Remme WJ, Sasayama S, Pitt B.

Cardiovasc Drugs Ther. 2002 Jan;16(1):53-9. PMID: 12085979

9. [Expanding the outcomes in clinical trials of heart failure: the quality of life and economic components of EPHEsus \(Eplerenone's neuroHormonal Efficacy and SURvival Study\).](#)

Spertus JA, Tooley J, Jones P, Poston C, Mahoney E, Deedwania P, Hurley S, Pitt B, Weintraub WS.

Am Heart J. 2002 Apr;143(4):636-42. PMID: 11923800

10. [Limitation of excessive extracellular matrix turnover may contribute to survival benefit of spironolactone therapy in patients with congestive heart failure: insights from the randomized aldactone evaluation study \(RALES\). Rales Investigators.](#)

Zannad F, Alla F, Dousset B, Perez A, Pitt B.

Circulation. 2000 Nov 28;102(22):2700-6. Erratum in: Circulation 2001 Jan 23;103(3):476. PMID: 11094035

11. [\[Blocking of aldosterone receptors reduces the risk of events in patients with severe cardiac failure\].](#)

Opasich C.

Ital Heart J Suppl. 2000 Mar;1(3):425-6. Italian. No abstract available. PMID: 10815276

12. [\[Study of the month. The RALES study \(randomized aldactone evaluation study\)\].](#)

Kulbertus H.

Rev Med Liege. 1999 Sep;54(9):770-2. French. PMID: 10589274

13. [What's old is new again. Spironolactone and heart failure.](#)

Lock M, Chun R.

Can Fam Physician. 1999 Nov;45:2621-2. No abstract available. PMID: 10587769

14. [The effect of spironolactone on morbidity and mortality in patients with severe heart failure. Randomized Aldactone Evaluation Study Investigators.](#)

Pitt B, Zannad F, Remme WJ, Cody R, Castaigne A, Perez A, Palensky J, Wittes J.

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Senior Medicine Rotation: Based Medicine Project (Cont)

EMPHASIS-HF Trial

Group	Criteria or definition	n
Population screened.	Patients at 278 centers in 29 countries	N/A
Inclusion criteria	Age \geq 55, NYHA functional class II, EF \leq 30% or $>$ 30 to 35% with QRS $>$ 130 msec, and treatment with ACE inhibitor and/or ARB plus beta-blocker at recommended or max tolerated dose; if enrollment did not occur within 6 months of hospitalization for cardiovascular reason, BNP \geq 250 or pro-BNP \geq 500 in men and 750 in women required	2737
Exclusion criteria	Acute MI, NYHA class III or IV, serum K ⁺ $>$ 5 mmol/L, estimated GFR $<$ 30 ml/min/1.73m ² , need for potassium-sparing diuretic, or any other clinically significant, coexisting condition	unknown
Treatment group	Eplerenone starting at 25 mg daily and increased to 50mg after 4 weeks with adjustment of dose based on K ⁺ levels	1364
No treatment group	Placebo	1373

Primary endpoint: Death from cardiovascular causes or first hospitalization for heart failure

Secondary endpoints: Hospitalization for heart failure or death from any cause; death from any cause; death from CV causes; hospitalization for any reason; hospitalization for HF; hospitalization for CV causes; fatal or nonfatal MI; death from any cause of hospitalization for any reason; death from HF or hospitalization for HF; fatal or nonfatal stroke; implantation of a cardioverter-defibrillator; implantation of a cardiac-resynchronization device; hospitalization for worsening renal function; hospitalization for hyperkalemia

- Are the Results of the Trial Valid?

- Randomized? YES
- All patients accounted for at end? 17 patients (1.2%) in eplerenone group and 15 patients (1.1%) in placebo group were lost to follow-up. 188 patients (13.8%) in eplerenone group and 222 patients (16.2%) in placebo group discontinued study due to adverse event, but difference was not significant between two groups (p=0.09).
- Intention to treat? YES
- Blinding? YES, double-blinded
- Groups similar at start of trial? YES
- Equal treatment of groups? YES. Eplerenone group was started at dose of 25mg daily (25mg every other day for those with GFR 30-49 and placebo group given matching placebo. After 4 weeks, dose was increased to 50 mg daily for eplerenone group. Thereafter, every 4 months, serum potassium levels were checked in all patients and doses adjusted based on results. Eplerenone or placebo pill was decreased if potassium 5.5 to 5.9 and held if potassium 6.0 or greater. If dose adjusted, potassium remeasured within 72 hours and restarted if level below 5.0. Followed for 21 months, at which time trial was stopped.
- Did randomization work? YES. Eplerenone and placebo groups were similar with respect to all of the following: age, sex, race, heart rate, BP, LVEF, QRS duration, BMI, principal

cause of heart failure, duration of heart failure, medical history, Hg, Cr, GFR, serum potassium, device therapy, medications at randomization visit.

- **Are the Results of the Trial important?** Yes. After a follow-up period of 21 months, treatment with eplerenone vs. placebo significantly reduced both risk of death from cardiovascular causes or hospitalization for heart failure (18.3% in eplerenone group vs. 25.9% in placebo group, $p < 0.001$). Eplerenone also significantly reduced death from any cause ($p = 0.008$), hospitalization for any reason ($p < 0.001$), and hospitalization for heart failure ($p < 0.001$) as compared to placebo.
 - Size of treatment effect?
 - Primary outcome: Risk of death from cardiovascular causes or hospitalization for heart failure, Hazard ratio = 0.63
 - Secondary outcomes: Death from any cause, HR = 0.76; hospitalization for any reason, HR = 0.77; hospitalization for heart failure, HR = 0.58
 - Precision of the estimate of the effect? Effect was precise, with 95% CIs not crossing 1.0
 - Primary outcome: 95% CI, 0.54 – 0.74
 - Secondary outcomes: 95% CI for death from any cause, 0.62 – 0.93; hospitalization for any reason, 0.67 – 0.88; hospitalization for heart failure, 0.47 – 0.70

Table 2. Primary Outcome, Component Events, and Key Secondary Outcomes.*

Outcome	Eplerenone (N=1364) <i>no. of patients (%)</i>	Placebo (N=1373) <i>no. of patients (%)</i>	Adjusted Hazard Ratio (95% CI)	Adjusted P Value	Unadjusted Hazard Ratio (95% CI)	Unadjusted P Value
Primary outcome: death from cardiovascular causes or hospitalization for heart failure	249 (18.3)	356 (25.9)	0.63 (0.54–0.74)	<0.001	0.66 (0.56–0.78)	<0.001
Prespecified adjudicated secondary outcomes						
Death from any cause or hospitalization for heart failure	270 (19.8)	376 (27.4)	0.65 (0.55–0.76)	<0.001	0.68 (0.58–0.79)	<0.001
Death from any cause	171 (12.5)	213 (15.5)	0.76 (0.62–0.93)	0.008	0.78 (0.64–0.95)	0.01
Death from cardiovascular causes	147 (10.8)	185 (13.5)	0.76 (0.61–0.94)	0.01	0.77 (0.62–0.96)	0.02
Hospitalization for any reason	408 (29.9)	491 (35.8)	0.77 (0.67–0.88)	<0.001	0.78 (0.69–0.89)	<0.001
Hospitalization for heart failure	164 (12.0)	253 (18.4)	0.58 (0.47–0.70)	<0.001	0.61 (0.50–0.75)	<0.001
Hospitalization for cardiovascular causes	304 (22.3)	399 (29.1)	0.69 (0.60–0.81)	<0.001	0.72 (0.62–0.83)	<0.001
Fatal or nonfatal myocardial infarction	45 (3.3)	33 (2.4)	1.32 (0.84–2.06)	0.23	1.34 (0.86–2.10)	0.20
Death from any cause or hospitalization for any reason	462 (33.9)	569 (41.4)	0.75 (0.66–0.85)	<0.001	0.76 (0.68–0.86)	<0.001
Death from heart failure or hospitalization for heart failure	170 (12.5)	262 (19.1)	0.58 (0.48–0.70)	<0.001	0.61 (0.51–0.74)	<0.001
Fatal or nonfatal stroke	21 (1.5)	26 (1.9)	0.79 (0.44–1.41)	0.42	0.78 (0.44–1.39)	0.40
Implantation of a cardioverter–defibrillator	61 (4.5)	59 (4.3)	0.99 (0.69–1.42)	0.98	1.01 (0.71–1.45)	0.95
Implantation of a cardiac-resynchronization device	33 (2.4)	41 (3.0)	0.77 (0.49–1.22)	0.27	0.78 (0.49–1.23)	0.28
Hospitalization for worsening renal function†	9 (0.7)	8 (0.6)	0.97 (0.37–2.58)	0.95	1.09 (0.42–2.82)	0.86
Hospitalization for hyperkalemia†	4 (0.3)	3 (0.2)	1.15 (0.25–5.31)	0.85	1.31 (0.29–5.87)	0.72
Other outcomes‡						
Sudden cardiac death	60 (4.4)	76 (5.5)	0.76 (0.54–1.07)	0.12	0.77 (0.55–1.08)	0.12
Death from worsening heart failure	45 (3.3)	61 (4.4)	0.68 (0.46–1.00)	0.05	0.71 (0.48–1.04)	0.08

* Adjusted results were adjusted for prespecified baseline characteristics (see the Statistical Analysis section). CI denotes confidence interval.

† No death was attributed to hospitalization for worsening renal function or hyperkalemia.

‡ “Other outcomes” were secondary outcomes that were adjudicated but not prespecified.

Number needed to treat (per year) to prevent one event:

- 1) Primary outcome: 19 (95% CI, 15 – 27)
- 2) Death from any cause: 51 (95% CI, 32 – 180)

- Can I apply these results to my patient? Maybe.
 - Comparison of my patient to trial patients.

This trial was applicable to my patient in that my patient met several important inclusion criteria, including that he had heart failure with NYHA Class II functional status, was on recommended heart failure therapy (beta-blocker, ARB, and diuretic), and was hospitalized in the last 6 months for a cardiovascular cause. He also did not meet any of the exclusion criteria. In addition, his medical history is similar to that of the trial patients in that he has hypertension, which was present in more than half (66%) of the trial patients. Meanwhile, he did not have a history of diabetes, CABG, atrial fibrillation, or LBBB, which were all present in a minority (<35%) of the trial patients. Though this patient has non-ischemic heart failure and >68% of this cohort had ischemic heart failure, reduction in primary outcome (hospitalization for heart failure or death from CV causes) was shown to be significant in the pre-specified subgroup of non-ischemic heart failure patients. Similarly, although only a minority (~18%) of patients had a cardiac defibrillator, this pre-specified subgroup was also found to have a significant reduction in primary outcome. Given that single-lead, shock-only the defibrillator itself has been shown to decrease mortality (SCD-HeFT trial) in patients with NYHA class II or III CHF with LVEF of $\leq 35\%$ and that sudden cardiac death (studied as a secondary endpoint in this trial) did not differ between the eplerenone and placebo groups, it appears that that eplerenone might contribute to mortality reduction via other mechanisms in patients with device therapy such as this one.

Despite the above characteristics that make this trial applicable to my patient, he technically would not have qualified for the study because he was younger than 55 years of age and though he reported an EF of <30% in the past, his TTE on this admission showed an EF of 30-35% , which would have required him to have a QRS duration of >130msec to qualify for this study, a finding he did not have on EKG. The average age was 69 and LVEF 26%. In addition, in terms of baseline characteristics, the study patients were predominantly white males, with only <3% blacks, the demographic of this patient.

- All clinically important outcomes considered? Yes

Many important clinical outcomes were considered, including overall mortality, mortality from cardiovascular cause, hospitalization for heart failure, and hospitalization for any reason, all of which are important in patients with CHF and all of which were significantly reduced. Incidence of fatal or nonfatal stroke and death from worsening heart failure were not significantly reduced. Importantly, given hyperkalemia as a drawback to aldosterone antagonist therapy, the authors studied rates of hospitalization for worsening renal function or hospitalization for hyperkalemia and found that these outcomes did not differ significantly between the two groups.
- Likely benefits outweigh potential harms and cost? Yes

The benefits of eplerenone therapy include reduced all-cause mortality, CV mortality, all-cause hospitalization, and CV related hospitalization. Also, unlike spironolactone, eplerenone is more selective and does not have affinity for androgen and progesterone receptors, making side effects of sexual dysfunction, gynecomastia, and menstrual irregularities uncommon with this aldosterone antagonist. An important potential harm of eplerenone therapy is hyperkalemia, which was significantly more frequent in the treatment group versus the control group. Serum potassium >5.5 mmol/L was found in 11.8% of patients in the eplerenone group vs 7.2% in the placebo group (p<0.001). However, the rates of hospitalization for hyperkalemia and withdrawal from the study for hyperkalemia or any other cause did not differ between the two groups. Since this patient has good renal function, is on an ARB (less likely to cause hyperkalemia than ACE inhibitors), and appears reliable to follow-up for monitoring of serum potassium, the benefits may outweigh the harms of eplerenone in this patient.