National PBM Drug Monograph

Eplerenone (Inspra™)

VHA Pharmacy Benefits Management Strategic Healthcare Group
and the Medical Advisory Panel
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Executive Summary

- Aldosterone has been linked to hypertension, cardiac hypertrophy, cardiac and vascular fibrosis, and ventricular arrythmias[1-3].
- The cardioprotective benefits of aldosterone blockade have been demonstrated in Class III/IV CHF patients treated with spironolactone (Aldactone®) when added to standard therapy[1,2,5]. However, spironolactone treatment may be accompanied by several endocrine side effects including a loss of libido, menstrual irregularities, gynecomastia, and impotence[1,2,4,8].
- Eplerenone (Inspra®) was designed to be a selective aldosterone receptor antagonist with the hope of minimizing the adverse effects associated with spironolactone[1-4,7].
- Eplerenone is currently FDA approved for the treatment of hypertension (alone or in combination with other antihypertensive agents) and Post-MI CHF[8].
- Contraindications and warnings associated with eplerenone usage are primarily concerned with the risk of hyperkalemia[8,11,12]. Drug interactions with eplerenone include those drugs which inhibit the CYP450 3A4 mediated metabolism (ketoconazole, erythromycin, verapamil, and saquinavir) of eplerenone and those that increase the risk of hyperkalemia (ACEIs, ARBs, and potassium sparing diuretics)[8,11,12].
- Eplerenone appears to have lower incidence rates of gynecomastia, breast pain, and menstrual irregularity related side effects than spironolactone. However this comparison may be misleading as the doses of spironolactone used in heart failure are lower than those used in hypertension and there are not head to head studies in similar populations as equipotent doses.
- Both once and twice daily dosing regimens of eplerenone have been shown to significantly reduce BP compared to placebo in mild-to-moderate hypertensive patients[7]. Eplerenone has also been shown to lower BP in poorly controlled hypertensive patients as an add-on to a fixed dose ACEI or ARB[3].
- Studies have suggested that eplerenone may reduce BNP in CHF patients, reduce left ventricular mass in patients with essential hypertension, and lower BP more than losartan or placebo in African American patients with hypertension[1,2,4,8,13,15-18].
- Eplerenone reduced overall mortality by 15% and significantly decreased cardiovascular morbidity and mortality in post-MI CHF patients in the EPHESUS trial[21] when used with traditional therapy
- The relative efficacy of spironolactone and eplerenone in CHF patients is unknown due to the lack of head-to-head trials between these two agents, differences in study design in the CHF trials and weaknesses in study design relating to use of other agents to treat CHF.
- A cost-analysis between eplerenone and spironolactone showed spironolactone is more cost-effective in treating hypertension.
- For essential hypertension, due to its high cost and lack of demonstrated clinical outcomes Eplerenone should be highly restricted only to those individuals who require treatment with an aldosterone blocker and cannot tolerate an adequate trial of spironolactone due to endocrine related adverse events.
- For treatment of Post-MI CHF eplerenone should be reserved for patients whom are maximally treated with all other medications known to affect the outcome of CHF (ACEIs, ARBs, Beta-blockers, Diuretics) and are unable to tolerate spironolactone due to documented endocrine adverse effects.
- Although no clinical studies exist Eplerenone might be considered as an alternative in patients who develop ADR's on spironolactone, who have hyperaldosterone states such as primary hyperaldosteronism or liver disease syndromes.

Introduction

Aldosterone is an effector hormone, which has been linked to hypertension, cardiac hypertrophy, cardiac and vascular fibrosis, and ventricular arrythmias[1-3]. Sodium retention, hypokalemia, and hypomagnesaemia are also associated with aldosterone[1,2]. The renin-angiotensin-aldosterone system (RAAS) is the most important physiological system involved in the development and progression of hypertension[1,3]. In addition, the RAAS is theorized to be an essential causative link between hypertension and the development of end-stage renal disease[4]. A number of the commonly utilized medications for the treatment of hypertension and heart failure are inhibitors of this system[1,5,6]. Angiotensin-converting enzyme inhibitors (ACEIs) and angiotensin II receptor blockers (ARBs) are upstream inhibitors of the RAAS that are commonly employed to prevent the aforementioned complications[1,4,6]. These upstream agents initially cause a significant drop in aldosterone levels; over time the level will rise returning to pretreatment values[1,2,7]. This "aldosterone escape" phenomenon has suggested the value of using aldosterone receptor antagonist agents as adjunctive therapy.

The cardioprotective benefits of aldosterone blockade were demonstrated in the Randomized Aldactone Evaluation Study (RALES) in which Class III/IV CHF patients were treated with spironolactone (Aldactone®) in addition to standard therapy[1,2,5]. The positive effects on mortality seen with spironolactone were accompanied by several endocrine side effects. The nonselective binding of spironolactone to androgen and progesterone receptors was associated with a loss of libido, menstrual irregularities, gynecomastia, and impotence[1,2,4,8]. Eplerenone (Inspra®) was designed to be a selective aldosterone receptor antagonist (SARA) with the hope of minimizing these adverse effects[1-4,7]. This agent was approved by the FDA for the treatment of essential hypertension in September of 2002.

Pharmacology/Pharmacokinetics

Eplerenone is a selective blocker of aldosterone at the mineralocorticoid receptor[1-4,8]. Formerly known under as epoxymexrenone, eplerenone is a 9-α, 11-α epoxy derivative of spironolactone[1,2,9]. This agent was designed to minimize the adverse effects seen with spironolactone due to androgen and progesterone receptor binding[1-4,7]. Eplerenone exerts its effects by binding to the mineralocorticoid receptor and blocking the binding of aldosterone. This prevents the induction of sodium reabsorption within the kidney nephrons and subsequent increases in blood pressure[8]. It is classified as a potassium sparing diuretic. Most studies suggest that eplerenone is a 20-fold less potent antagonist at the mineralocorticoid receptor than spironolactone.[1,2]. However, some literature suggests that eplerenone may have greater anti-mineralocorticoid activity than sprionolactone[4].

Spironolactone is an antagonist of aldosterone, acting primarily through competitive binding of receptors at the aldosterone-dependant sodium-potassium exchange site in the distal convoluted renal tubule[10]. Spironolactone causes increased excretion of sodium and water, while retaining potassium[10]. It is through this antagonism that spironolactone exerts its antihypertensive and diuretic effects[10].

Pharmacokinetics[2,8,10]:

Agent	F (%)	Vd	% PB	Tmax	Tss	T 1/2	Metabolism/Elimination
Eplerenone	98	43-90L	49	1-2hr	2 D	3.8hr	By liver to **inactive** metabolites. Primarily mediated by CYP3A4. Excretion: 66% urine, 32% feces.
Spironolactone	73	-	90	1-3hr	-	1.3-1.4hr	By liver to **active** metabolites. Excretion: 53% urine, 20% feces.

FDA Approved Indications and Off-Label Uses[8,10]

Drug	Indication
Eplerenone	-Tx of hypertension alone or in combination with other antihypertensive agents -Tx of patients with left ventricular systolic dysfunction (ejection fraction ≤40%) and clinical evidence of congestive heart failure after an acute myocardial infarction
Spironolactone	-Primary hyperaldosteronism -Edematous conditions: CHF, nephrotic syndrome, or cirrhosis with edema and/or ascites -Essential hypertension -Hypokalemia.

Current VA National Formulary Status

- **Spironolactone (Aldactone®) –** formulary unrestricted
- **Eplerenone (Inspra®) –** not yet evaluated

Dosage and Administration[8,10]

Drug	Formulations	Dosage	Comment
Eplerenone	Tablets: 25, 50 mg	Post MI CHF: 25-50mg QD Hypertension: Start: 50mg QD Max: 50mg BID	-Patients receiving erythromycin, saquinavir, verapamil, fluconazole, or other CYP3A4 inhibitors should use a starting dose of 25mg QD. Hypertension: Doses >100mg/D have not shown a greater effect on BP and may be associated with hyperkalemia.
Spironolactone	Tablets: 25, 50, 100mg	Varies with indication. Hypertension: Start: 50mg/d in single or divided doses (Usual 50-100mg/d)	-Doses >100mg/D have not shown a greater effect on BP and may be associated with hyperkalemia.

Dose Adjustment in CHF patients for eplerenone

Serum potassium (mEq/L)	Action	Dose Adjustment
< 5.0	Increase	25 mg QOD to 25 mg QD 25 mg QD to 50 mg QD
5.0 – 5.4	Maintain	No adjustment
5.5 – 5.9	Decrease	50 mg QD to 25 mg QD 25 mg QD to 50 mg QOD
≥ 6.0	Withhold	

Adverse Effects (Safety Data) [8,11-14]

CHF-Post MI

Eplerenone has been evaluated for safety in 3307 patients. In placebo-controlled studies, the overall rates of adverse events were 78.9% with eplerenone and 79.5% with placebo. Adverse events occurred at a similar rate regardless of age, gender, or race. Therapy was discontinued due to an adverse event in 4.4% of patients treated with eplerenone and 4.3% of patients given placebo. The adverse events that were reported more frequently in elperenone than placebo patients were hyperkalemia (3.4% vs 2.0%) and elevated creatinine (2.4% vs 1.5%). 6.5% of patients treated with eplerenone reported an increase of 0.5mg/dL or greater in creatinine compared to 4.9% in placebo patients.

Rates of Sex Hormone Related Adverse Events in a CHF-Post MI Clinical Study

	Rates in Males			Rates in Females
	Gynecomastia	**Mastodynia**	**Either**	**Abnormal Vaginal Bleeding**
Eplerenone	0.4%	0.1%	0.5%	0.4%
Placebo	0.5%	1.1%	0.6%	0.4%

Hypertension

In 3091 patients treated for hypertension, the most common reasons for discontinuation of eplerenone were headache, dizziness, angina pectoris/myocardial infarction, and increased gamma glutamyl transpeptidase (GGT).

Rates (%) of Adverse Events Occurring in Placebo-Controlled Studies in =1% of Patients Treated With Eplerenone (25-400 mg) and at a More Frequent Rate Than in Placebo-Treated Patients

	Eplerenone (n=945)	**Placebo (n=372)**
Metabolic		
Hypercholesterolemia	1%	0%
Hypertriglyceridemia	1%	0%
Digestive		
Diarrhea	2%	1%
Abdominal pain	1%	0%
Urinary		
Albuminuria	1%	0%
Respiratory		
Coughing	2%	1%
Central/Peripheral Nervous System		
Dizziness	3%	2%
Body as a Whole		
Fatigue	2%	1%
Influenza-like symptoms	2%	1%

Note: Adverse events that are too general to be informative or are very common in the treated population are excluded.

Gynecomastia and abnormal vaginal bleeding were reported with eplerenone but not with placebo. The rates of these sex hormone related adverse events are shown in the table below. The rates increased slightly with increasing duration of therapy. In females, abnormal vaginal bleeding was also reported in 0.8% of patients on antihypertensive medications (other than spironolactone) in active control arms of the studies with eplerenone.

Rates of Sex Hormone Related Adverse Events in Hypertension Clinical Studies				
	Rates in Males			Rates in Females
	Gynecomastia	Mastodynia	Either	Abnormal Vaginal Bleeding
All controlled Studies	0.5%	0.8%	1.0%	0.6%
Controlled studies lasting ≥6 months	0.7%	1.3%	1.6%	0.8%
Open label, long term study	1.0%	0.3%	1.0%	2.1%

Spironolactone:
The rates of some sex hormone related adverse events have been studied with spironolactone as well. An efficacy and tolerance study of spironolactone for use in the treatment of essential hypertension, by Jeunemaitre X, et al provides some comparative incidence data[33].

- A total of 2,051 patients with essential hypertension were studied. Of these, 699 men were followed for at least 2 months.
- Overall 91 (13%) cases of gynecomastia were observed.
- In men treated with greater than 150mg daily, 52% developed gynecomastia.
- The interval between the initiation of treatment and the onset of gynecomastia varied considerably from 2 to 100 months.
- Development of gynecomastia was highly significantly dose-related.
- In nearly all cases, gynecomastia disappeared when spironolactone treatment was interrupted.

Potassium

- CHF-Post MI

Incidence of hypokalemia (<3.5 mEq/L) or hyperkalemia (>5.5 or =6.0 mEq/L)

Potassium (mEq/L)	Eplerenone (n=3251) n (%)	Placebo (n=3237) n (%)
< 3.5	273 (8.4)	424 (13.1)
>5.5	508 (15.6)	363 (11.2)
≥ 6.0	180 (5.5)	126 (3.9)

Incidence of hyperkalemia (>5.5 mEq/L) in CHF-Post MI patients by proteinuria and history of diabetes

	Eplerenone	Placebo
Proteinuria, no diabetes	16 %	11 %
Diabetes, no proteinuria	18 %	13 %
Proteinuria and diabetes	26 %	16%

- Hypertension

In placebo-controlled fixed-dose studies, the mean increases in serum potassium were dose related and are shown in the table below along with the frequencies of values >5.5 mEq/L.

Changes in Serum Potassium in the Placebo-Controlled, Fixed-Dose Studies of Eplerenone			
Daily Dosage	n	Mean Change mEq/L	>5.5 mEq/L
Placebo	194	0	1%
25	97	0.08	0%
50	245	0.14	0%
100	193	0.09	1%
200	139	0.19	1%
400	104	0.36	8.7%

Patients with both Type 2 diabetes and microalbuminuria are at increased risk of developing persistent hyperkalemia. In a study in such patients taking eplerenone 200 mg, the frequencies of maximum serum potassium levels >5.5 mEq/L were 33% with eplerenone given alone and 38% when eplerenone was given with enalapril.

Rates of hyperkalemia increased with decreasing renal function. In all studies serum potassium elevations >5.5 mEq/L were observed in 10.4% of patients treated with eplerenone with baseline calculated creatinine clearance <70 ml/min, 5.6% of patients with baseline creatinine clearance of 70-100 ml/min, and 2.6% of patients with baseline creatinine clearance of >100 ml/min.

Sodium
Serum sodium decreased in a dose-related manner. Mean decreases ranged from 0.7 mEq/L at 50 mg daily to 1.7 mEq/L at 400 mg daily. Decreases in sodium (<135 mEq/L) were reported for 2.3% of patients administered eplerenone and 0.6% of placebo-treated patients.

Triglycerides
Serum triglycerides increased in a dose-related manner. Mean increases ranged from 7.1 mg/dl at 50 mg daily to 26.6 mg/dl at 400 mg daily. Increases in triglycerides (above 252 mg/dl) were reported for 15% of patients administered eplerenone and 12% of placebo-treated patients.

Cholesterol
Serum cholesterol increased in a dose-related manner. Mean changes ranged from a decrease of 0.4 mg/dl at 50 mg daily to an increase of 11.6 mg/dl at 400 mg daily. Increases in serum cholesterol values greater than 200 mg/dl were reported for 0.3% of patients administered eplerenone and 0% of placebo-treated patients.

Liver Function Tests
Serum alanine aminotransferase (ALT) and gamma glutamyl transpeptidase (GGT) increased in a dose-related manner. Mean increases ranged from 0.8 U/L at 50 mg daily to 4.8 U/L at 400 mg daily for ALT and 3.1 U/L at 50 mg daily to 11.3 U/L at 400 mg daily for GGT. Increases in ALT levels greater than 120 U/L (3 times upper limit of normal) were reported for 15/2259 patients administered eplerenone and 1/351 placebo-treated patients. Increases in ALT levels greater than 200 U/L (5 times upper limit of normal) were reported for 5/2259 of patients administered eplerenone and 1/351 placebo-treated patients. Increases of ALT greater than 120 U/L and bilirubin greater than 1.2 mg/dl were reported 1/2259 patients administered eplerenone and 0/351 placebo-treated patients. Hepatic failure was not reported in patients receiving eplerenone.

BUN/Creatinine
Serum creatinine increased in a dose-related manner. Mean increases ranged from 0.01 mg/dl at 50 mg daily to 0.03 mg/dl at 400 mg daily. Increases in blood urea nitrogen to greater than 30 mg/dl and serum creatinine to greater than 2 mg/dl were reported for 0.5% and 0.2%, respectively, of patients administered eplerenone and 0% of placebo-treated patients.

Uric Acid
Increases in uric acid to greater than 9 mg/dl were reported in 0.3% of patients administered eplerenone and 0% of placebo-treated patients

Pregnancy Category & Breastfeeding [8]:

Eplerenone is pregnancy category B. There are no adequate and well-controlled studies in pregnant women. Eplerenone should be used during pregnancy only if the potential benefit justifies the potential risk to the fetus. The concentration of eplerenone in human breast milk after oral administration is unknown.

PRECAUTIONS/CONTRAINDICATIONS [8,11,12]

Contraindications:
- Prior hypersensitivity to eplerenone
- Serum potassium > 5.5 mEq/L
- Creatinine clearance ≤ 30 mL/min
- In patients currently treated with strong inhibitors of CYP450 3A4 (e.g., ketoconazole, itraconazole, nefazodone, clarithromycin, ritonavir, and nelfinavir)
- Hypertension- eplerenone is also contraindicated for the following:
  - Creatinine clearance ≤ 50 mL/min
  - Type 2 diabetes with microalbuminuria
  - Serum creatinine > 2.0 mg/dL in males or >1.8 mg/dL in females
  - In patients treated concomitantly with potassium supplements or potassium-sparring diuretics (amiloride, spironolactone, or triamterene)

Warnings:
- Hyperkalemia may occur with eplerenone
  - Can lead to serious, sometimes fatal, arrhythmias
  - Periodic monitoring is recommended
  - Increased risk with concomitant use of ACEI or ARB
  - Dose reduction had shown decreased potassium levels

Precautions:
- CHF post-MI patients
  - Patients who develop hyperkalemia (>5.5 mEq/L) may still benefit from eplerenone with dose adjustment
  - Patients with diabetes, serum creatinine > 2.0 mg/dL (males) or >1.8 mg/dL (females) or creatinine clearance ≤ 50 mL/min should be treated with caution
- CHF post-MI and hypertension patients
  - The use of eplerenone in patients with severe hepatic impairment has not been evaluated
  - The use of eplerenone in patients with renal impairment (see contraindications; warnings; and precautions)
  - Patients should not use potassium supplements or salt substitutes containing potassium without consulting the prescribing physician
- Drug interactions (see contraindications and below)
  - Eplerenone has not been studied with lithium or NSAIDs.
- Patients with prior hypersensitivities to spironolactone
- Patients who are pregnant (Category B) or breast feeding (0.85:1 [milk:plasma] AUC ratio)
- Patients in metabolic or respiratory acidosis may have potentiation of hyperkalemic effects
- Eplerenone has been studied in pediatric patients

DRUG INTERACTIONS[8,11,12]

Drug Interactions With Eplerenone		
Agent	**Effect**	**MOA/Clinical Comments**
Ketoconazole (Azole antifungals)	1.7-fold increase in Cmax 5.4-fold increase in AUC of eplerenone	Pharmacokinetic, Due to inhibition of CYP450 3A4
Other CYP450 3A4 Inhibitors (erythromycin, verapamil, and saquinavir)	Result in increases of 1.4-1.6-fold in eplerenone Cmax and 2.0-2.9-fold in AUC	Pharmacokinetic, Due to inhibition of CYP450 3A4

ACEIs and ARBs	Increased risk of hyperkalemia	Pharmacodynamic
Potassium-sparing diuretics (amiloride, spironolactone, and triamterene)	Increased risk of hyperkalemia	Pharmacodynamic

EFFICACY MEASURES

Eplerenone has been primarily studied as an antihypertensive agent. Therefore, in most studies the primary endpoint was reduction in systolic blood pressure (SBP) or diastolic blood pressure (DBP). Systolic blood pressure coincides with the time of ventricular contraction (when pressure is the highest). Diastolic blood pressure occurs when the ventricles are relaxing (lowest point pressure). Commonly used secondary measures included the measurement of blood levels of aldosterone and renin. These neurohormones act as surrogate markers for the degree of aldosterone blockade due to the use of an aldosterone-blocking agent (i.e., eplerenone or spironolactone). Increases in aldosterone and renin are seen with aldosterone receptor antagonists due to physiologic feedback mechanisms.

CLINICAL TRIALS

Citation # 1	Weinberger MH, Roniker B, Krause SL, et al. Eplerenone, a selective aldosterone blocker, in mild-to-moderate hypertension. Am J Hypertens 2002;15:709-16[7].
Goal/ Objective	To evaluate the efficacy, safety, and tolerability of eplerenone as compared to placebo in the treatment of hypertensive patients over the course of an 8-week trial.
Methods	◆ **Study Design**: ➢ Randomized, double-blind trial ➢ Spironolactone as an "aldosterone receptor antagonist positive control" ➢ Dose-ranging, parallel group, multicenter clinical trial (48 sites within the U.S.) ➢ 417 randomized: 53 patients received placebo ➢ 54, 49, and 56 patients received eplerenone 50, 100, or 400mg once daily respectively ➢ 55, 54, and 48 patients received eplerenone 25, 50, or 200mg twice daily respectively ➢ 48 patients received spironolactone 50mg twice daily ➢ Subjects were screened for 2-week, followed by a 4-week single-blind placebo period, and then an 8-week double blind treatment period **Primary endpoint:** ➢ The adjusted mean change from baseline in seated and standing, cuff assessed diastolic blood pressure (DBP), measured at trough compared to placebo **Secondary endpoints:** ➢ The adjusted mean change from baseline in seated, cuff-assessed systolic blood pressure (SBP); 24-hr ABPM mean SBP and DBP; total and active plasma renin; and serum aldosterone levels. ◆ **Safety and Tolerability Assessments** ➢ Adverse events were recorded based on patient report. The manner in which this data was collected was not defined. ➢ Venous blood samples were collected for assessment of plasma total renin, active renin, aldosterone, potassium, liver enzymes, and thyroid-stimulating hormone levels. ◆ **Statistics**: ➢ The intent-to-treat population included all patients who had at least one evaluation in addition to the baseline evaluation. ➢ All analyses were two-tailed at the $p< 0.05$ level. ➢ A sample of 50 patients per group was planned to provide 80% power to detect a mean

	change of 4.5mm Hg in cuff DBP between each eplerenone dose and the placebo group after 8 weeks of treatment (assumes a SD of 8mm Hg). ➢ Treatment groups were compared for continuous variables using a two-way analysis of variance (ANOVA) including treatment and investigator as factors. ➢ Pearson chi-squared tests were used to evaluate categorical data such as gender and ethnicity. ➢ The change from baseline in cuff-assessed DBP measured at 8 weeks (or the final visit) was evaluated using an analysis of covariance (ANCOVA), which included treatment and center as factors and baseline DBP as covariate. ➢ Specific dosage comparisons within primary and secondary measures of efficacy were made using contrast-based t tests within a linear model. ➢ Changes from baseline in RAAS hormonal data were analyzed using ANCOVA. Pairwise comparisons based on the linear trend-testing approach were replaced with conventional pairwise comparisons. ➢ Placebo versus eplerenone comparisons were performed using contrast based t tests. ➢ All randomized patients who took at least one dose of study medication were included in the safety analyses. Changes in adverse effects from baseline to end of study were evaluated within treatment group using paired t tests and compare among treatment groups using Kruskal-Wallis tests.
Criteria	◆ **Inclusion**: ➢ Subjects were 21-80 years of age. ➢ Men and women. ➢ White, African American, Hispanic, Asian/other. ➢ Seated DBP by cuff-assessment ≥95 and <114 mm Hg. ➢ A mean 24-Hr DBP ≥85 mm Hg by ABPM. ➢ Medication compliance of ≥80% during the single-blind placebo lead-in period. ◆ **Exclusion**: ➢ Secondary, severe, or malignant hypertension with or without retinopathy. ➢ Regular use of systemic medications known to influence BP. ➢ Regular use of nonsteroidal anti-inflammatory drugs. ➢ Myocardial infarction, percutaneous transluminal coronary angioplasty, coronary artery bypass graft, angina pectoris, or intermittent claudication within the previous 6 months. ➢ Severe aortic or mitral valvular disease and cardiac arrhythmia requiring medical treatment or causing hemodynamically relevant disturbances. ➢ Hypertrophic cardiomyopathy or congestive heart failure requiring digoxin or diuretic therapy. ➢ Stroke or transient ischemic attack within the previous 6 months. ➢ Insulin-dependent diabetes mellitus. ➢ Acute or chronic hepatic disease. ➢ Serum creatinine >1.5 mg/dL or serum potassium > 5.0 mEq/L. ➢ Known history of alcohol or drug abuse. ➢ Known hypersensitivity to spironolactone or steroids. ➢ Use of any other investigational medication 30 days before this study. ➢ Night-shift employment. ➢ Upper arm circumference >42cm.
Results	➢ 417 randomized patients, 409 patients were included in the efficacy analysis ➢ No significant differences were noted among groups with baseline characteristics ➢ Mean baseline seated and standing SBP/DBP among the groups at were similar **Primary endpoint:** **Mean change from baseline to final visit for eplerenone versus placebo**

Seated SBP	-4.4 to -15.0mm Hg (in a dose-response manner)
Seated DBP	-4.4 to -8.9mm Hg
Standing SBP	-3.6 to -14.5mmHg
Standing DBP	-3.7 to –8.0mm Hg
Adj mean ABPM DBP	-6.2 to -16.1mm Hg
Adj mean ABPM SBP	-4.1 to -9.0mm Hg
Trough ABPM SBP	-5.2 to -20.4mmHg
Trough ABPM DBP	-4.1 to -12.1mm Hg

- Reductions in mean seated and standing SBP and DBP from baseline to final visit were demonstrated in all eplerenone-treated groups compared to placebo except in standing DBP in the daily 100mg group
- In most instances, there were no significant differences between twice daily and daily dosing of eplerenone, with respect to reductions in sitting and standing DBP
- The exception being the greater reductions seen with the 50mg BID group when compared to the 100mg QD group (p= 0.036 seated, p=0.012 standing)

Secondary endpoints:

- Significant reductions in SBP and DBP were seen in 24-hr ABPM for all eplerenone doses used
- Reductions in trough ABPM DBP from baseline to final visit between the eplerenone and placebo groups were observed for all but two eplerenone treated groups (50mg QD and 25mg BID were p=NS)
- No significant differences were observed between the QD and BID dosing regimens in ambulatory SBP and DBP, except for a difference ($p<0.033$) between the 200mg BID and 400mg QD groups
- Spironolactone caused reductions ($P<0.001$) in SBP and DBP compared to placebo
- The adjusted mean changes from baseline to final visit in SBP and DBP for twice-daily 50mg and daily 100mg of eplerenone dosing were approximately 50% to 75% of those observed with the twice-daily 50mg spironolactone group

RAAS Hormone Profile:

Mean adjusted change in serum aldosterone, total plasma renin, and active plasma renin:

Group	Serum Aldosterone	Active Plasma Renin	Total Plasma Renin
Placebo	1.0±2.3 ng/dL	-4.0±4.9 mU/L	-0.3±17.4 mU/L
Epl 50mg QD	6.1±2.3	10.3.0±5.0	42.9±17.4
Epl 100mg QD	10.3±2.5	8.7±5.3	57.3±18.5
Epl 400mg QD	19.3±2.3	15.6±4.8	132.7±16.9
Epl 25mg BID	7.1±2.3	9.5±4.9	56.4±17.1
Epl 50mg BID	10.4±2.4	19.0±4.9	105.9±17.4
Epl 200mg BID	32.9±2.4	24.8±5.4	166.2±18.7
Spr 50mg BID	19.7±2.5	14.6±5.4	140.3±18.8

- Differences in adjusted mean changes from baseline to final visit were observed in total plasma renin between all doses of eplerenone and placebo ($p\leq 0.05$)
- Adjusted mean changes from baseline to final visit in active plasma renin levels of 50mg BID, 200mg BID, and 400mg QD groups differed compared to placebo but not between twice daily and daily eplerenone regimens
- With the exception of the 200mg BID eplerenone group, all increases in total plasma renin were smaller in the eplerenone treated groups than in those receiving spironolactone
- Active plasma renin levels were lower in the twice daily 25mg, daily 50mg, and daily 100mg eplerenone groups compared to the spironolactone group
- Aldosterone serum levels were significantly increased in the 50mg BID, 200mg BID, 100mg

	QD, and 400mg QD eplerenone groups compared to placebo ➢ Increases in aldosterone levels in the 50mg and 100mg QD and 25mg and 50mg BID eplerenone groups were less than those observed in the twice daily 50mg spironolactone group **Tolerability:** ➢ 190 (46% overall) of patients reported at least one adverse event ➢ 11 patients discontinued treatment because of adverse events (groups not specified) ➢ The incidence of adverse events in eplerenone treated patients was similar to placebo ➢ There were no reports of gynecomastia, increased incidence of impotence, or menstrual abnormalities in eplerenone treated patients compared to placebo ➢ One patient in the spironolactone group reported treatment related intermenstrual bleeding ➢ An increase ($p \leq 0.05$) in mean thyroid-stimulating hormone levels was observed in the daily 400mg eplerenone group. ➢ Seventeen patients had potassium levels ≥5.5mEq/L. Of these, three were reported as adverse events (one in the placebo, 100mg and 400mg QD eplerenone groups).
Conclusions	➢ Eplerenone in daily doses of 50, 100, and 400mg for 8 weeks significantly reduced BP compared to placebo. ➢ This reduction occurred in a dose-dependant manner. ➢ No consistent clinically significant differences in lowering BP were noted between once and twice daily dosing regimens. ➢ Dose related increases in serum aldosterone, total renin, and active renin levels were seen due to the blockade of aldosterone receptors by eplerenone. ➢ Changes in these hormones and in BP were greater with twice-daily 50mg spironolactone than with twice daily 50mg or daily 100mg eplerenone. ➢ The incidence of adverse effects was similar in the eplerenone and placebo groups and no cases of gynecomastia or menstrual abnormalities were reported. ➢ Eplerenone doses of 50 to 400mg once daily are well tolerated and effective in reducing BP in patients with mild-to-moderate hypertension during a 24-hour period.
Critique	**Strengths** ➢ Randomized, double-blind, active-controlled study ➢ Spironolactone as a positive control was used ➢ Implemented adequate wash period **Limitations** ➢ The study population was not well defined, and the age demographics were not given. Therefore, the mean age of patients in the study cannot be reliably compared to that of VA patients. ➢ More males enrolled than females, which is representative of the VA population. ➢ The assessments of adverse effects and tolerability were not well defined. It is unclear how the AEs were measured and when these measurements were recorded/reported. ➢ The study excluded those with hypertrophic cardiomyopathy or CHF requiring digoxin or diuretic therapy. These groups are among the most likely target patients to receive an aldosterone blocker. ➢ The study assessed the baseline to endpoint changes in BP but did not show the change over time or the change at any intermediate time point. As "snapshot" data, the reliability of the presented efficacy data may not be as good. ➢ The study was only for 8 weeks of active treatment. Hypertension is a longstanding disorder, which requires long-term treatment. Long-term outcomes in terms of event reduction or adverse events remain unknown. ➢ The optimal dose range of eplerenone was not specified or determined by this study. Several of the doses used exceeded the FDA recommended maximum dose of 100mg/day.
Sponsorship	• Study was sponsored by Pharmacia.

Citation # 2	Krum H, Nolly H, Workman D, et al. Efficacy of eplerenone added to renin-angiotensin blockade in hypertensive patients. Hypertension 2002;40:117-23[3].
Goal/ Objective	To evaluate the antihypertensive efficacy, safety, and tolerability of eplerenone, as compared to placebo, when added to fixed-dose therapy with a single ACEI or ARB in patients with mild-to-moderate hypertension.
Methods	◆ **Study Design**: ➢ Randomized, double-blind, placebo-controlled trial ➢ Multi-center, 45 sites in the US, Australia, Canada, Argentina, Brazil, and Mexico ➢ The study consisted of three stages: a 1 to 2 week pretreatment screening period, a 2 to 4 week single-blind placebo run-in period, and an 8 week double-blind treatment period ➢ Patients were stratified by ACEI or ARB treatment and then were allocated within each group to receive eplerenone or placebo in a 1:1 ratio (computer randomized) ➢ The pretreatment screening allowed patients on multiple antihypertensives therapy regimens an opportunity to withdraw additional therapy while remaining on monotherapy with an ACEI or ARB ➢ All eligible patients then entered the single-blind placebo run-in period (on monotherapy). ➢ If patients met the BP criteria (see inclusion criteria) at the end of the run-in period, they were entered into the 8 week treatment period and received eplerenone or placebo by random assignment ➢ Treated patients received 50mg eplerenone or placebo once daily for 2 weeks ➢ If their DBP was < 90mm Hg throughout the study, then they remained on this dose ➢ If BP was still uncontrolled at the end of week 2 or became uncontrolled by weeks 4 or 6, the dose was increased 100mg daily ➢ If BP remained uncontrolled at week 6 in patients who had received the increased dose at weeks 2 or 4, they were withdrawn from the study **Study (Efficacy) Assessments:** ➢ BP, heart rate, hematology, and biochemistry values were assessed at the initial screening ➢ Subsequently, BP, HR, concomitant medications, adverse events, and serum potassium levels were assessed at weeks 0, 2, 4, 6, 8, and 9 after randomization ➢ Hematology and biochemistry evaluations and urinalysis were conducted at weeks 0, 8, and 9 after randomization ➢ Plasma renin and serum aldosterone were determined at weeks 0 and 8 after randomization. ➢ BP was measured using a calibrated manual mercury sphygmomanometer. **Primary Efficacy Endpoints:** ➢ mean change from baseline of trough cuff seated DBP and SBP at week 8 ➢ These were evaluated separately for those treated with ACEIs and ARBs. **Secondary Efficacy Assessment:** ➢ Incidence of adverse events ➢ Mean change from baseline in hematology, biochemistry, and urinalysis parameters. ➢ Mean change in plasma renin and serum aldosterone at week 8 ➢ The percentage of responders was also assessed. Responders were defined as patients with DBP < 90mmHg or a ≥ 10mm Hg reduction from baseline ◆ **Safety and Tolerability Assessments** ➢ Adverse events were assessed at weeks 0, 2, 4, 6, 8, and 9 after randomization. ➢ Method of data collection not explicitly stated but appears to be by patient report. ➢ Safety also assessed based on incidences of hyperkalemia in the treated groups. ◆ **Statistics**: ➢ A sample size of 60 patients per group was planned to provide a 90% power to detect a difference of at least 4.8mm Hg in seated cuff-assessed DBP at trough plasma levels between baseline and week 8.

	➢ A SD of 8mm Hg was assumed and differences were detected with a 2-sided test at the 5% level. ➢ Intent-to-treat population included all patients who had at least 1 post-baseline assessment. ➢ Missing values were computed using the last-observation-carried-forward method. ➢ All statistical analyses were conducted separately for the ACEI and ARB groups. ➢ Treatment groups were compared for continuous variables using a 1-way ANOVA model. ➢ Categorical variables were evaluated with Pearson chi-squared tests. ➢ Changes between baseline and week 8 in seated trough cuff-assessed DBP and SBP, plasma renin, serum aldosterone, and in laboratory test results between groups were evaluated using a 2-way ANCOVA with baseline as the covariate and with treatment and center as cofactors. ➢ Within the treatment group, changes between baseline and endpoint were analyzed using a paired t-test. ➢ Response rates were compared with the Cochran-Mantel-Haenszel test stratified by center. ➢ Results from small centers were pooled to prevent artificial effects of severe imbalances in patient counts among centers.
Criteria	◆ **Inclusion**: ➢ Men and nonpregnant women b/w 18-85 years. ➢ Patients must have been taking a fixed dose of an ACEI or ARB. ➢ Have a history of mild to moderate hypertension or current hypertension defined as DBP ≥ 95 and < 110mm Hg and SBP <180mm Hg. ➢ ECG without arrhythmia. ➢ No clinically significant abnormal laboratory values. ➢ Serum potassium between ≥ 3.0 and ≤ 5.0 mEq/L. ➢ Demonstrated 80% to 120% medication compliance during the single-blind placebo period. ➢ Women of child bearing age with a negative pregnancy test. ◆ **Exclusion**: ➢ Failure to meet with any of the above inclusion criteria. ➢ Secondary, severe, or malignant hypertension. ➢ Hx of MI, coronary revascularization, unstable angina pectoris or arrhythmias requiring treatment during the previous 6 months. ➢ A history of class II through IV CHF or severe aortic or mitral valvular disease requiring medical treatment or causing hemodynamically significant disturbances. ➢ Stroke or transient ischemic attack in the previous six months. ➢ Concurrent use of other antihypertensives, including – diuretics, α-blockers, β-blockers, or calcium channel blockers. ➢ Insulin dependent or uncontrolled diabetes mellitus. ➢ Evidence of alcohol or drug abuse. ➢ Known hypersensitivity to eplerenone, ACEIs, or ARBs. ➢ A gastrointestinal disorder that may interfere with the phramacokinetics of eplerenone, ACEIs, or ARBs. ➢ A serious comorbid condition. ➢ The use of any other investigational medication 30 days before the study.
Results	◆ **Patients:** ➢ There were no significant differences in the characteristics and demographics between the four treatment groups at baseline. ➢ 341 patients were entered into the study ➢ 177 were receiving ACEIs and 164 were receiving ARBs ➢ The doses of ACEI and ARB were similar in those randomized to eplerenone and placebo ➢ Eplerenone dose increases from 50mg to 100mg were performed in 48/85 (56%) of ACEI patients and 40/82 (49%) of ARB patients ➢ There were no significant differences in the numbers of patients within each of the 4 study

groups requiring up-titration with eplerenone

- 96 patients did not complete the study (59 from the ACEI group, 37 from ARB):
  - Treatment failure - 66 patients
  - Adverse events - 5 patients
  - Lost to follow-up - 4 patients
  - Protocol noncompliance - 5patients
  - Preexisting protocol violation - 5 patients
  - Other - 11 patients
- There was no difference between any of the treatment groups in the rate of withdrawal for any of these reasons.

Primary Efficacy Endpoint (BP Changes):

Changes from baseline (week 0) to weak 8

Epl/ACEI SBP*	-13.4±1.35mm Hg
Epl/ACEI SBP*	-13.4±1.35mm Hg
Placebo/ACEI SBP	-7.5±1.31mm Hg
Epl/ACEI DBP^{+}	-9.9±0.88mm Hg
Plc/ACEI DBP	-8.0±0.86mm Hg
Epl/ARB SBP*	-16.0±1.37mm Hg
Plc/ARB SBP	-9.2±1.41mm Hg
Epl/ARB DBP*	-12.7±0.81mm Hg
Plc/ARB DBP	-9.3±0.83mm Hg

*P ≤ 0.05 vs. corresponding value for Plc/ACEI or Plc/ARB.

$^{+}$P=NS vs. corresponding value

- There were no comparisons made between the ACEI and ARB groups with or without eplerenone.
- At week 8, 87.8% of Epl/ARB patients and 73.8% of Plc/ARB patients were classified as responders (p=0.003).
- There was no significant difference in the number of responders was seen between the Epl/ACEI and Plc/ACEI patients.

Secondary Efficacy Endpoints:

Neurohormonal Parameters (changes from week 0 to week 8):

- Minor changes in neurohormonal levels from week 0 were observed in the Plc/ACEI and Plc/ARB groups.
- Total plasma renin concentrations were increased by 71.7% in Epl/ACEI patients and 67.3% in Epl/ARB patients.
- Mean serum aldosterone concentrations increased *5.3% in the Epl/ACE group and 60.5% in the Epl/ARB group.

- **Safety and tolerability:**
  - 136 (40%) of patients reported at least 1 AE.
  - Most mild to moderate.
  - 4 (2.3% of ACEI treated patients) in ACEI group were serious (aggravated hypertension, syncope, inguinal hernia w/ hospitalization, and myocardial infarction leading to death).
  - The MI did occur in an eplerenone treated individual but was not believed to be related to eplerenone treatment.
  - No significant differences were observed in the total adverse events or severe adverse events between those groups that received eplerenone and those which received placebo in addition to an ACEI or ARB.
  - There were no reports of gynecomastia, menstrual disturbances, or hypotension in any study patient.
  - However, there were two patients who withdrew from the Epl/ARB group due to possible hormonal adverse effects.

	➢ One withdrew because of headache and moderate orchitis and one because of impotence. ➢ Eplerenone, in combination with an ACEI or ARB, had no significant effect on heart rate during the study. **Laboratory values:** ➢ The mean changes in plasma levels of potassium, sodium, magnesium, BUN, creatinine, and uric acid were compared from week 0 to week 8. ➢ No statistically significant differences were observed between Plc/ACEI and Epl/ACEI groups for any of these laboratory values. ➢ Statistically significant ($p < 0.05$) differences between Plc/ARB and Epl/ARB group lab values were seen. These were: potassium (0.20±0.04 mmol/L), sodium (-0.7±0.4 mmol/L), BUN (0.73±0.20 mmol/L), creatinine (4.4±1.5 umol/L), and uric acid (25.4±7.3 umol/L). ➢ All of these changes remained within the normal ranges (not clinically significant but numerically significant). ➢ 1 patient in the Epl/ACEI group developed a mild hyperkalemia (5.5mmol/L) which resolved before the end of the study without medication adjustment.
Conclusions	➢ This study demonstrated that in patients whose BP was not controlled with an ACEI or ARB, the addition of eplerenone over an 8-week period significantly lowered SBP in both groups and DBP in ARB patients. ➢ Therefore, BP can be further reduced when eplerenone is added to either an ACEI or ARB. ➢ The effect of eplerenone on SBP was even more notable than its effect on DBP. ➢ The addition of eplerenone to ACEIs or ARBs was associated with increased levels of total renin, active renin, and serum aldosterone. ➢ Adverse events were generally not severe and not significantly different between eplerenone and placebo. ➢ There were no reports of gynecomastia, menstrual disorders, or hypotension during the 8-week treatment period.
Critique	**Strengths** ➢ Randomized, double-blind, placebo-controlled study ➢ Implemented adequate wash period **Limitations** ➢ The criteria by which responders were assessed (DBP < 90mm Hg or Δ 10mm Hg reduction from baseline) may not have provided an accurate assessment of clinical efficacy. ➢ Only mild-to-moderate hypertensive patients were included which limits the applicability of this study to other more severely hypertensive patients. ➢ The average age of the patients in this trial was younger than that of VA patients. These mean ages were 54.7 ACEI/Plc, 55.7 ACEI/Epl, 55.1 ARB/Plc, and 54.2 for ARB/Epl. ➢ In most of the treatment groups there were more women than men, which is not representative of the VA population. ➢ The study used the last-observation-carried-forward method to replace missing values. This may have introduced bias depending on the rate of onset of BP reductions, or other measured endpoints. ➢ No long-term benefits to morbidity or mortality were assessed. The NNT and cost measures were not taken into account in this study. This makes the therapy groups difficult to assess with respect to treatment benefit versus cost. ➢ The study excluded those patients with a history of MI or CHF class II-IV. These individuals are among the patients most frequently treated with an aldosterone blocker.
Sponsorship	• Study was sponsored by Pharmacia.

Citation # 3	Pitt B, Reichek N, Willenbrock R, et al. Effects of eplerenone, enalapril, and eplerenone/enalapril in patients with essential hypertension and left ventricular hypertrophy. Circulation 2003;108:1831-1838[15].
Goal/ Objective	To compare left ventricular hypertrophy (LVH) regression with eplerenone, enalapril, and eplerenone/enalapril.

Methods	◆ **Study Design**: ➢ 9 month randomized, double-blind, parallel group study ➢ After a 14-day washout period, 202 patients were randomized to either eplerenone 200mg/day, enalapril 40mg/day, and eplerenone 200mg/day plus enalapril 10mg/day ➢ Add-on antihypertensive therapy with hydrochlorothiazide and/or amlodipine was permitted for uncontrolled BP at week 8 ➢ Patients were discontinued due to treatment failure if: o Symptomatic hypotension, sustained DBP ≥90 mm Hg or SBP >180 on or after week 16, DBP >115 mm Hg or SBP > 200 mm Hg at 2 consecutive visits, or need other BP meds not included in the protocol. **Primary endpoint:** ➢ Changes in left ventricular mass from baseline **Secondary endpoints:** ➢ Changes from baseline in SBP and DBP, urinary albumin-creatinine ratio, RAAS hormones and safety events ◆ **Statistics**: ➢ Analysis of LVH regression (MRI cohort) included patients treated least 3 months with a baseline and an end point MRI within 21 days after starting medication. ➢ 1-way ANOVA or the chi-square test was used to compare baseline characteristics ➢ Primary and secondary endpoints were evaluated with analysis of covariance ➢ Needs 55 patients per group (165 total) to provide 94% power to detect an average LV mass reduction within 15 g between the eplerenone and enalapril groups (one-sided, alpha =0.05)
Criteria	◆ **Inclusion**: ➢ Patients diagnosed with LVH (either by ECG or echocardiogram), history of hypertension (seated DBP <110 mm Hg and seated SBP≤ 180 mm Hg who is taking BP meds, or DBP 90-114 mmHg and SBP 141-200 mm Hg if not on BP meds) and in sinus rhythm ◆ **Exclusion**: ➢ Pregnant ➢ Orthostatic hypotension, ➢ Use of guanethidine, spironolactone, or reserpine 30 days prior ➢ Serum potassium <3.0 or > 5.0 mEq/L ➢ Serum creatinine >1.5 mg/dL for men and >1.3 mg/dL for woman ➢ Contraindication to MRI ➢ Left ventricular ejection fraction < 40% ➢ NYHA Class III to IV CHF or unstable angina ➢ A history of Q-wave MI, stroke, TIA, PTCA, coronary artery bypass graft in last 6 months ➢ Secondary hypertension ➢ Contraindication or hypersensitivity to any study medication ➢ DMI or uncontrolled DMII ➢ Acute or chronic hepatic disease ➢ Impaired renal function ➢ Drug or alcohol abuse problems ➢ Terminal illness ➢ Use of investigational drug 30 days prior
Results	◆ **Patients:** ➢ There were no significant differences between the groups in baseline characteristics other than heights between the female groups. ➢ 153 of 202 patients met the criteria for the MRI cohort (patients who received treatment for at least 3 months with a baseline and an end point MRI within 21 days after starting medication).

Primary Efficacy Endpoints:

- Changes in left ventricular mass from baseline:
  - -14.5± 3.36 g in eplerenone group (P<0.001 versus baseline),
  - -19.7± 3.20 g in enalapril group (P<0.001 versus baseline),
  - -27.2±3.39 g in eplerenone/enalapril group (P<0.001 versus baseline).
    - eplerenone versus enalapril (P=0.258)
    - eplerenone/enalapril versus eplerenone (P=0.007)
    - eplerenone/enalapril versus enalapril (P=0.107)

Secondary Efficacy Endpoints:

- Changes from baseline in mean SBP and DBP, respectively:
  - –23.8± 1.8 and –11.9±1.0 mm Hg for eplerenone group
  - –24.7± 1.7 and –13.4±1.0 mm Hg for enalapril group
  - –28.7± 1.8 and –14.4±1.0 mm Hg for eplerenone/enalapril group
    - eplerenone/enalapril versus eplerenone (P=0.048)
- Urinary albumin-creatinine ratio:
  - Baseline means were similar for the 3 groups.
  - Changes from baseline: -24.9% in eplerenone, -37.4% in enalapril, and –52.6% in eplerenone/enalapril group.
    - eplerenone/enalapril versus eplerenone (P=0.038)
    - eplerenone/enalapril versus enalapril (P=0.001)
- RAAS hormones:
  - Baseline levels of active plasma renin and serum aldosterone were within limits and similar between the 3 groups
  - Renin and aldosterone levels increased in the eplerenone and eplerenone/enalapril groups.
  - In the enalapril group, rennin increased but aldosterone levels remained unchanged.

◆ **Safety and tolerability:**

Events	eplerenone	enalapril	eplerenone/ enalapril
	n (%)	n (%)	n (%)
Dropout rates	(21.9%)	(19.7%)	(16.4%)
Serious adverse events	7	5	9
Gynecomastia	1	0	1
Impotence	3	0	1
Serious hyperkalemia (≥6.0 mmol/L)	7 (10.9%)	2 (2.8%)	3 (4.5%)

Conclusions

- Eplerenone was as effective as enalapril in LVH regression
- Eplerenone used with enalapril was more effective in reducing LV mass and systolic blood pressure than eplerenone monotherapy

Critique

Strengths

- Randomized, double-blind study
- Evaluation of changes in ventricular mass

Limitations

- Sample size for each group was not reached to provide 94% power to detect an average LV mass reduction within 15 g between the eplerenone and enalapril groups
- The study excluded those patients with a history of MI or CHF class III-IV. These individuals are among the patients most frequently treated with an aldosterone blocker.
- Only mild-to-moderate hypertensive patients were included which limits the applicability of this study to other more severely hypertensive patients.

Sponsorship

- Study was sponsored by Pharmacia.

Citation # 4	Flack J, Oparil S, Pratt H, et al. Efficacy and tolerability of eplerenone and losartan in hypertensive black and white patients. Journal of the American College of Cardiology 2003;41(7):1148-55[16].
Goal/ Objective	The purpose of this study was to evaluate the efficacy and tolerability of monotherapy with the selective aldosterone blocker eplerenone in both black and white patients with hypertension.
Methods	◆ **Study Design**: ➢ Randomized, double-blind, active controlled, placebo run-in, parallel group trial ➢ Multi-center, 42 sites in the United States and 8 in South Africa ➢ Physical examination and laboratory testing at the screening visit ➢ Patients entered into a 2-4 week placebo run-in period if they were o Able to withdrawn from antihypertensive medication, without arrhythmia requiring treatment, without clinically significant laboratory abnormality, and with a serum potassium level of 3.5 to 5.0 mmol/l ➢ After the placebo period, eligible patients (DBP 95 –110 mm Hg and SBP <180 mm Hg) were randomized (stratified by race) to eplerenone, losartan, or placebo. ➢ Dosing of study medications o Initiated with daily doses of eplerenone 50 mg, losartan 50 mg, or placebo o If DBP was ≥90 mm Hg or SBP was ≥140 mm Hg at weeks 4, 8, or 12, the dose was increased to 100 mg/day of eplerenone or losartan o If BP remained ≥140/90 mm Hg, the dose was increased to eplerenone 200 mg/day or continued at losartan 100 mg/day ➢ Patients were withdrawn from the study if: o DBP was ≥95 mm Hg or SBP was ≥150 mm Hg after week 12 at the highest dose of study drug o DBP was ≥110 mm Hg or SBP was ≥180 mm Hg at two consecutive visits taking place 1 to 3 days apart o Symptomatic hypotension (lightheadedness, dizziness, or syncope) o Hyperkalemia (>5.5 mmol/l) on 2 consecutive occasions 1 to 3 days apart ➢ HR, BP, serum potassium level, and adverse events were assessed every 2 weeks ➢ Active renin and serum aldosterone was measured at week 0 and final visit **Primary Endpoints:** ➢ The mean change in DBP from baseline **Secondary Endpoints:** ➢ The mean change for SBP and DBP within and between racial groups ➢ Urinary protein excretion as measured by changes in the urinary albumin/creatinine ratio (UA/CR) ➢ The effect of eplerenone in subgroups: women, obese patients, patients with SBP ≥160 mm Hg, elderly patients, and patients with microalbuminuria ◆ **Statistics**: ➢ A priori power calculations determined the sample size of black and white patients that was required to detect a 4.5 mm Hg difference in DBP from baseline between eplerenone and placebo with power of 99%, 97%, and 80%, respectively, in all patients, black patients, and white patients. ➢ Powered 90% for all patients and 75% for black patients to show a 3 mm Hg difference in DBP between the eplerenone and losartan groups ➢ Intent-to-treat population included all patients who had at least 1 post-baseline assessment ➢ Missing values were computed using the last-observation-carried-forward method. ➢ Baseline characteristics were compared using 1-way ANOVA for continuous variables or Pearson chi-square tests for categorical variables. ➢ BP data were evaluated using a 2-way ANCOVA. ➢ Response rates were compared with the Cochran-Mantel-Haenszel test ➢ Adverse events were analyzed using Fisher exact test.

Criteria

- **Inclusion:**
  - Self-identified as black or white patients
  - BP < 140-90 mm Hg and on 1-2 antihypertensive medications

- **Exclusion:**
  - Known secondary hypertension
  - Insulin dependent DM
  - Hepatic disease
  - Elevated serum creatinine
  - Evidence of alcohol or drug abuse
  - Could not be withdrawn from antihypertensive
  - Regularly used corticosteroids
  - History of NYHA Class II, III, or IV CHF, MI, coronary revascularization, stroke or TIA within the past 6 months
  - Current unstable angina
  - Any serious medical condition

Results

- **Patients:**
  - 551 patients were randomized and 352 completed 16 weeks of treatment
  - 535 patients were included in the cohort for efficacy analysis because 16 patients (4 placebo, 8 eplerenone, and 4 losartan) had no post-baseline assessment.
  - Compliance was 90.5% in the placebo group, 91.5% in the eplerenone group, and 88.6% to 89.1% in the losartan group.
  - There were no significant differences in the characteristics and demographics between the three treatment groups at baseline.
  - 63% of patients were black and 37% were white in all 3 groups
  - There was a difference in active renin concentration between black and white patients
    - Black (n = 243) versus white (n = 156) patients, active renin was 10.3 mU/l versus 13.8 mU/l, respectively ($p < 0.001$)

Primary Efficacy Endpoint:
Mean Changes in SBP and DBP at End Point (week 16)

	Placebo	Eplerenone	Losartan	Eplerenone Vs. Placebo	Eplerenone vs. Losartan
All Patients	N = 177	N = 174	N = 184		
SBP	-3.4±1.05	-12.8±1.06	-6.3±1.04	P<0.001	P<0.001
DBP	-5.3±0.65	-10.3±0.65	-6.9±0.64	P<0.001	P<0.001
Black	N = 110	N = 108	N = 117		
SBP	-3.7±1.48	-13.5±1.43	-5.3±1.43	P<0.001	P<0.001
SBP	-4.8±0.96	-10.2±0.94	-6.0±0.94	P<0.001	P<0.001
White	N = 67	N = 66	N = 67		
SBP	-3.2±1.78	-12.3±1.79	-8.5±1.76	P=0.001	P=0.126
DBP	-6.4±1.04	-11.1±1.05	-8.4±1.03	P=0.001	P=0.068

  - Mean change in DBP from baseline were significantly greater with eplerenone than placebo or losartan in all patients ($p < 0.001$) and in black patients ($p \leq 0.001$)

Secondary Efficacy Endpoints:
  - Mean changes in DBP and SBP from baseline were significantly greater with eplerenone than placebo or losartan in all patients ($p < 0.001$) and in black patients ($p \leq 0.001$)
  - Among white patients, mean changes in DBP and SBP were
    - Significantly greater with eplerenone than placebo ($p = 0.001$)
    - Similar between eplerenone and losartan
  - Response rates (defined as % of patients with DBP <90 mm Hg or DBP ≥90 mm Hg but ≥10 mm Hg below baseline)

	○ placebo, eplerenone, and losartan were 41.2%, 64.5%, and 48.3%, respectively ($p < 0.001$ for eplerenone vs. placebo, $P = 0.003$ for eplerenone vs. losartan) ➢ The mean change in the UA/CR was determined in a smaller population (n = 118, 132, and 133 for placebo, eplerenone, and losartan, respectively). ○ 5.2% (95% CI -8.4 to 20.8) for placebo ○ -21.6% (95% CI -31.3 to -10.7) for eplerenone ($p = 0.003$ vs. placebo) ○ -18.2% (95% CI -28.3 to -6.7) for losartan ($p = 0.003$ vs. placebo) ○ No difference between the eplerenone and losartan groups ($p = 0.652$) ➢ No significant differences in subgroup analysis regarding efficacy for eplerenone in women, men, and patients with baseline SBP ≥160 mm Hg ➢ Eplerenone was also effective in both obese and non-obese patients (data not shown) ◆ **Safety and tolerability:** ➢ 6 (3.3%) patients in the placebo and eplerenone groups and eight (4.3%) in the losartan group withdrew from the study due to adverse events ➢ Most frequently reported events included headache, respiratory system disorders, and gastrointestinal disorders ➢ No significant differences were observed in the adverse events between the groups received eplerenone, placebo or losartan ➢ 2 patients in eplerenone group reported menstrual disorder and 2 reported decreased libido ➢ Serum creatinine levels were similar between all groups ➢ Changes in serum potassium at study end were ○ -0.01 ± 0.03, +0.09 ± 0.03, and +0.03 ± 0.03 mmol/l in the placebo, eplerenone, and losartan groups, respectively ($p < 0.001$ for eplerenone vs. placebo, $P = 0.003$ for eplerenone vs. losartan) ➢ Hyperkalemia (>5.5 mmol/l) in 3, 4, and 3 patients in the placebo, eplerenone, and losartan groups, respectively. ➢ One eplerenone-treated patient was withdrawn due to an elevated potassium level
Conclusions	• Eplerenone significantly reduced DBP and SBP compared with placebo in both black and white patients with mild-to-moderate hypertension. • Eplerenone significantly reduced DBP and SBP compared with losartan in all patients and black, and was comparable to losartan in white patients with mild-to-moderate hypertension. • Adverse events were generally not severe and not significantly different between all three groups
Critique	• **Strengths** ➢ Randomized, double-blind, active controlled, placebo run-in trial ➢ Comparing efficacy (stratified by race) between racial groups ➢ Implemented adequate wash period • **Limitations** ➢ The "all patients combined" group is influenced by more blacks due to 63% of patients were black and 37% were white ➢ Did not provide mean doses of study medications at the end of the trial ➢ Did not show data for the obese and non-obese subgroups analysis regarding efficacy ➢ The study excluded those patients with a history of MI or CHF class II-IV. These individuals are among the patients most frequently treated with an aldosterone blocker. ➢ Only mild-to-moderate hypertensive patients were included which limits the applicability of this study to other more severely hypertensive patients.
Sponsorship	• Study was sponsored by Pharmacia.

Citation # 5	White WB, Carr AA, Krause S, et al. Assessment of the novel selective aldosterone blocker eplerenone using ambulatory and clinical blood pressure in patients with systemic hypertension. Am J Cardiol 2003;92:38-42[17].
Goal/ Objective	To assess the efficacy and safety of eplerenone for the treatment of hypertension

Methods	◆ **Study Design**: ➢ Multi-center, randomized, double-blind, placebo-controlled trial. ➢ Patient discontinued all antihypertensive agents and received a placebo tablet for 3-4 weeks to establish baseline BP readings ➢ Patients were randomized to placebo, or eplerenone (25, 50, 100, or 200 mg once daily) for 12 weeks ➢ Patients were withdrawn form the study if: o Systolic BP was >180 mm Hg or diastolic BP was >110 mm Hg at any time o Hyperkalemia (>5.5 mmol/L) on 2 consecutive occasions 1 to 3 days apart ➢ Office seated BPs (24 hours after taking medication), heart rate, serum potassium, adverse events, and concomitant medications were assessed every 2 weeks ➢ Clinic and ambulatory BP monitoring were assessed at baseline and after 12 weeks ➢ During the 24-hour ambulatory monitoring study, BP and heart rate were measured every 15 -20 minutes. **Primary Endpoint:** ➢ Mean change from baseline in seated clinic DBP **Secondary Endpoints:** ➢ Changes from baseline in: clinic systolic pressure, 24-hour systolic and diastolic BPs, heart rate, and active renin and serum aldosterone levels ◆ **Safety:** ➢ Serum chemistries, active renin, and serum aldosterone levels were determined at baseline and after 12 weeks ➢ Incidents of hyperkalemia, hypotension, impotence, gynecomastia, menstrual abnormalities, female breast pain, and hyperuricemia ◆ **Statistics**: ➢ Efficacy were performed on an intention-to-treat basis ➢ Treatment groups were compared with respect to change from baseline to the 12-week clinic BP end point using 2-way ANCOVA ➢ Laboratory values were analyzed using Fisher's exact test ➢ The biochemical variables were log-transformed and analyzed by ANCOVA ➢ The safety analyses included all patients who received ≥1 dose of medication ➢ Assuming 1-sided testing at the 0.025 level, the study is powered to detect a difference in adjusted mean change in baseline between the placebo and the treatment groups: o 100% in eplerenone 200-mg arm (n = 90) o 99% in eplerenone 100-mg arm (n = 90) o 80% in eplerenone 50-mg arm (n = 90) o 19% in eplerenone 25-mg arm (n = 45) vs. placebo (n=90)
Criteria	◆ **Inclusion**: ➢ Adult men and women were included if they had untreated hypertension ➢ Seated clinic SBPs were <180 mm Hg, the clinic DBP was between 95 - 110 mm Hg, and the 24-hour mean diastolic BP was ≥85 mm Hg ◆ **Exclusion**: ➢ Recent myocardial infarction or unstable angina ➢ Congestive heart failure ➢ Clinically significant liver or renal disease ➢ Known secondary hypertension ➢ Uncontrolled diabetes mellitus (glycohemoglobin >10%) ➢ Serum creatinine was >1.5 (for men) or >1.3 mmol/L (for women) ➢ Serum potassium was >5.0 mmol/L at baseline

Results

- **Patients:**
  - 400 patients randomized into the 5 treatment arms by 47 sites in the US and Brazil
  - Patient characteristics were similar among the groups
  - Percent of patients withdrawn (main reason is treatment failure):
    - 22% placebo group
    - 27%, 21%, 11%, 14% for eplerenone 25, 50, 100, 200 mg group, respectively
  - Other reasons included lost to follow-up, protocol violations, noncompliance, adverse events, or patient withdrawal of consent.

Primary Endpoint:

- Mean reductions in DBP at the week 12:

Placebo	-1.7 mm Hg	
Eplerenone		vs. placebo
25 mg	-3.7 mm Hg	($p = 0.10$)
50 mg	-4.6 mm Hg	($p \leq 0.01$)
100 mg	-6.3 mm Hg	($p \leq 0.01$)
200 mg	-5.4 mm Hg	($p \leq 0.01$)

Secondary Endpoints:

- Mean reductions in SBP at the week 12:

Placebo	0 mm Hg	
Eplerenone		vs. placebo
25 mg	-5.7 mm Hg	($p \leq 0.01$)
50 mg	-6.7 mm Hg	($p \leq 0.01$)
100 mg	-10.4 mm Hg	($p \leq 0.01$)
200 mg	-8.8 mm Hg	($p \leq 0.01$)

  - Significant reductions from baseline in mean 24-hour SBP and DBP ($p \leq 0.006$ for SBP and $p \leq 0.005$ for DBP) in all of the eplerenone groups compared with placebo.
  - The reductions in ambulatory BP were dose-dependent for the 25- to 200-mg doses of eplerenone (range 6.4/4.4 mm Hg for 25 mg daily to 10.3/5.7 mm Hg for 200 mg daily)
  - Changes in 24-hour mean heart rate from baseline were similar in all eplerenone groups compared to placebo

- **Safety and tolerability:**
  - There were small increases in potassium with each dose level of eplerenone compared to placebo (i.e., 200 mg of eplerenone was 0.20 ± 0.05 mmol/L, $p<0.001$)
  - 1 patient from placebo and eplerenone 200 mg group had a serum potassium >5.5 mmol/L
  - Significant dose-dependent increases from baseline in active plasma renin and serum aldosterone for all eplerenone treatment groups at week 12 compared with placebo
  - No significant relations between the reductions in ambulatory BP and increases in active renin or serum aldosterone
  - Treatment emergent adverse events were similar between groups: 48% of patients in the eplerenone groups and 49% in placebo.
  - The most common (>5% incidence) treatment emergent adverse events in the elperenone group were headache (11.6%), upper respiratory tract infection (8.1%), and nonspecific pain (6%). In the placebo group, the most common adverse events were headache (13.3%) and accidental injury (5.6%). No statistically significant between groups
  - 1 incident of impotence in the placebo and eplerenone 100-mg group
  - No reports of sexual dysfunction, gynecomastia or menstrual irregularities

Conclusions	➢ Eplerenone was effective in reducing clinic and 24-hour BP in patients with systemic hypertension at doses of 25 to 200 mg/day. ➢ Eplerenone was well tolerated with statistical, but not clinical significant changes from baseline in mean serum potassium. The increase in serum potassium was not in a dose-related manner. ➢ Similar number of patients experienced hyperkalemia (>5.5 mmol/L) and impotence compared to placebo. ➢ The reductions from baseline in the clinic versus ambulatory BP were similar for the various doses. ➢ Increases in serum aldosterone and active plasma renin did not correlate with reductions in ambulatory BP.
Critique	• Strengths ➢ Randomized, double-blind, placebo controlled trial ➢ Compared clinical versus ambulatory blood pressure across different doses ➢ Efficacy were performed on an intention-to-treat basis ➢ Implemented adequate wash period • Limitations ➢ No discussion of what concomitant medications patients were taking ➢ The study excluded those patients with a history of MI or CHF. These individuals are among the patients most frequently treated with an aldosterone blocker. ➢ Only mild-to-moderate hypertensive patients were included which limits the applicability of this study to other more severely hypertensive patients.
Sponsorship	• Study was sponsored by Pharmacia.

Citation # 6	Burgess ED, Lacourciere Y, Ruilope-Urioste LM, et al. Long-term safety and efficacy of the selective aldosterone blocker eplerenone in patients with essential hypertension. Clin Ther. 2003 Sep;25(9):2388-404[18].
Goal/ Objective	To assess the long-term safety profile and efficacy of eplerenone
Methods	◆ **Study Design**: ➢ Multicenter, open-label, uncontrolled trial ➢ 77 sites in North America, South America, and Europe between 1999 and 2000 ➢ A 1-week washout period of previous antihypertensive therapy, a open-label dose-titration period 10-weeks and a maintenance period of 14 months ➢ After the washout period, eligible patients received eplerenone 50 mg daily ➢ Office visits biweekly until month 3, then monthly until month 14. ➢ Dose based on mean DBP and SBP taken during the first 3 months ➢ Dosing of study medications o If BP was uncontrolled (DBP ≥90 mm Hg or SBP ≥140 mm Hg), eplerenone was increased to 100 mg daily and then 200 mg daily o If BP remained uncontrolled at the maximum daily dose of eplerenone (200 mg), another antihypertensive agent could be added o The second antihypertensive agent could be increased once, or switch to at week-8, week-10, or month-3 visit o A third antihypertensive agent was not allowed ➢ Mean trough cuff BP, heart rate, adverse events (AEs), and serum potassium levels were measured at each visit, laboratory tests every 3 months, and a physical examination every 6 months ➢ Patients were not allow to take sildenafil, theophylline, or papaverine within 24 hours before a study visit; glucocorticoids for longer than 2 weeks; nitrates (except at stable, long-term doses); immunosuppressive or cytotoxic agents; or antihypertensive agents (e.g., alpha-blockers for benign prostatic hypertrophy) other than the ones allowed in the study ➢ Withdrawn for treatment failure if patients is: o Severe hypertension (DBP ≥110 mm Hg or SBP ≥180 mm Hg)

	○ Uncontrolled hypertension (DBP ≥90 mm Hg or SBP ≥140 mm Hg on 2 consecutive occasions 3 to 5 days apart on or after month 4 ➢ Additional causes for withdrawal were: ○ Inability to tolerate study treatment, symptomatic hypotension, a serum potassium level >5.5 mmol/L at 2 consecutive measurements, uncontrolled arrhythmia, pregnancy, administrative reasons, investigators decision, or patient's request **Primary Endpoint:** ➢ Cumulative withdrawal rate due to uncontrolled DBP **Secondary Endpoints:** ➢ The withdrawal rate due to treatment failure at or after month 4 ➢ The mean change in SBP and DBP from baseline ➢ Responder rates (defined as SBP <140 mm Hg and DBP <90 mm Hg or a decrease in DBP of ≥10 mm Hg from baseline) ◆ **Safety:** ➢ Safety was assessed in terms of the rate of withdrawals due to AEs ➢ Treatment emergent AEs included new or increased signs or symptoms, or clinically significant findings on clinical laboratory tests, physical examination, or ECG ➢ Not specified in the protocol, events that may be associated with aldosterone blocking agents were collected ○ hyperkalemia hypotension, impotence, gynecomastia, menstrual abnormalities, female breast pain, and hyperuricemia. ➢ Compliance was assessed with patient administered diary card ◆ **Statistics**: ➢ Efficacy analyses were performed on the intent-to-treat (ITT) population (all patients with a baseline assessment and ≥l assessment during treatment) ➢ Safety analyses included all patients who took ≥1 dose of eplerenone. ➢ Descriptive statistics were used for demographic and baseline characteristics, and for efficacy and safety measurements.
Criteria	◆ **Inclusion**: ➢ Patients aged ≥18 years with essential hypertension (DBP ≥90 and <110 mm Hg, or SBP ≥140 and <180 mm Hg) ➢ Women of childbearing potential could be enrolled only if they were incapable of becoming pregnant or were using an oral contraceptive, hormonal implant, diaphragm, or intrauterine device to prevent pregnancy ◆ **Exclusion**: ➢ Secondary, severe, or malignant hypertension ➢ Regular use of other antihypertensive agents (e.g., beta-blockers for prevention of migraine or arrhythmias) ➢ A history of stroke, TIA, MI, coronary revascularization, unstable angina, or arrhythmia requiring treatment in the 6 months before enrollment ➢ Valve disease or class II-IV CHF requiring treatment ➢ Type 1 diabetes or uncontrolled type 2 diabetes ➢ Hepatic disease ➢ Impaired renal function ➢ Serum potassium >5.0 mmol/L ➢ Substance abuse ➢ Hypersensitivity to eplerenone ➢ Any clinical laboratory value or medical/behavioral condition that might affect the patient's ability to participate ➢ Use of spironolactone, reserpine, guanethidine, or an investigational medication in the preceding 30 days

Results	**Patients:** ➢ 586 patients were enrolled in the study: 407 patients completed >6 months; 98 completed >12 months ➢ Patients demographics: 80.4% white, 51.5% male, mean age of 55 ➢ The mean baseline SBP/DBP were 149.8/96.1mm Hg ➢ Acceptable compliance with study treatment was reported for 89.2% patients ➢ 41.5% patients needed another antihypertensive agent with the most common classes were: o Calcium channel blockers (12.5%) o ACE inhibitors (11.3%) o Diuretics (7.6%) **Primary Endpoint:** ➢ 98 (16.8%) of the 582 patients were withdrawn because of treatment failure **Secondary Endpoints:** ➢ A total of 433 patients (74.4%) responded to eplerenone monotherapy or combination of eplerenone and another antihypertensive agent: o 68 (11.7%) receiving eplerenone 50 mg o 89 (15.3%) receiving eplerenone 100 mg o 104 (17.9%) receiving eplerenone 200 mg o 172 (29.6%) receiving a combination of eplerenone and an additional antihypertensive agent ◆ **Safety and tolerability:** ➢ 68.8% of patients experienced a treatment-emergent AE o An association with study medication was considered probable in 8.4% patients ➢ Impotence and gynecomastia occurred in a respective 3.0% and 0.7% of men ➢ Breast pain and menstrual abnormalities occurred in a respective 0.7% and 2.5% of women ➢ Only 1 (0.4%) case of female breast pain and 2 (0.7%) cases of male impotence were likely to be related to study medication ➢ 40 patients (6.8%) were withdrawn from the study because of an AE. ➢ Elevations in ALT/AST and fatigue were the most common AEs leading to discontinuation. ➢ 14 patients (2.4%), 8 monotherapy with eplerenone 200 mg and 3 on eplerenone 200 mg plus another antihypertensive, had an AE of hyperkalemia or were withdrawn hyperkalemia ➢ There were no clinically significant mean changes in other laboratory values, vital signs, or findings on physical examination
Conclusions	➢ Eplerenone, either as monotherapy or in combination with another antihypertensive agent, was efficacious and tolerated in the management of hypertension
Critique	• **Strengths** ➢ Multi-center, randomized, double-blind trial ➢ Compliance was followed with compliance cards ➢ Implemented adequate wash period • **Limitations** ➢ Descriptive statistics were used for demographic and baseline characteristics, and for efficacy and safety measurements ➢ The study excluded those patients with a history of MI or CHF class II-IV. These individuals are among the patients most frequently treated with an aldosterone blocker ➢ Only mild-to-moderate hypertensive patients were included which limits the applicability of this study to other more severely hypertensive patients
Sponsorship	• Study was sponsored by Pharmacia.

Citation # 7	White, WB, Duprez D, St Hillaire R, et al. Effects of the selective aldosterone blocker eplerenone versus the calcium antagonist amlodipine in systolic hypertension. Hypertension 2003;41:1021-26[19].
Goal/ Objective	To assess its usefulness in older patients with systolic hypertension
Methods	◆ **Study Design**: ➢ Multi-center, randomized, double-blind, active-controlled trial ➢ Patient discontinued all antihypertensive agents and received a placebo tablet for 2-4 weeks to establish baseline BP readings ➢ Patients were randomized to eplerenone 50 mg once daily or 2.5 mg amlodipine once daily for 24 weeks ➢ Dosing of medications o If SBP was uncontrolled (>140 mm Hg) at week 2, eplerenone was increased to 100 mg daily, and amlodipine was increased to 5 mg daily o If the SBP still uncontrolled at week 6, eplerenone was increased to 200 mg daily and amlodipine to 10 mg daily ➢ Withdrawn from the study if: o SBP was >170 mm Hg after 10 weeks for safety considerations o Hyperkalemia (> 5.5 mmol/L) on 2 consecutive occasions 1 to 3 days apart ➢ Office seated BP (after 24 hours of taking medication), heart rate, serum potassium, adverse events, and concomitant medications were assessed every 4 weeks ➢ Ambulatory BP monitoring, pulse wave velocity, and microalbuminuria were assessed at baseline and after 14 and 24 weeks **Primary Endpoints:** ➢ Mean change from baseline in seated SBP **Secondary Endpoints:** ➢ Changes from baseline in: o Clinic pulse pressure and diastolic pressure o 24-hour BP o Ambulatory parameters: daytime and nighttime mean, and heart rate o Carotid-femoral and carotid-radial pulse wave velocity o Microalbuminuria ◆ **Safety:** ➢ Serum chemistries, active renin, and serum aldosterone levels were determined at baseline and after 12 weeks of therapy ➢ Incidents of hyperkalemia, hypotension, impotence, gynecomastia, menstrual abnormalities, female breast pain, and hyperuricemia. ◆ **Statistics**: ➢ Efficacy were performed on an intention-to-treat basis and used ANCOVA ➢ Adverse events were analyzed by the Fisher exact test ➢ 100 patients per group was needed for 94% power to detect (non-inferiority) a difference of at least 6mm Hg in mean change from baseline in seated SBP
Criteria	◆ **Inclusion**: ➢ Men and women at least 50 years of age with systolic hypertension (defined as seated clinic systolic BP of 150-165 mm Hg with a pulse pressure of ≥70 mm Hg or 165-200 mm Hg with a diastolic pressure of ≤95 mm Hg) ◆ **Exclusion**: ➢ Clinically significant heart, liver, or kidney disease ➢ Serum creatinine was >1.5 mmol/L or >1.3 mmol/L, for men and women, respectively, ➢ Serum potassium was ≥5.0 mmol/L at baseline
Results	**Patients:** ➢ 269 patients were randomized with similar baseline characteristics

- At the end of the 24-week, the mean daily dose of eplerenone was 154 mg and the mean dose of amlodipine was 7.4 mg
- 76% of eplerenone patients and 70% of amlodipine patients completed the trial
- The main reasons for withdrawal (not statistical significant):

Reasons for withdrawal	Eplerenone	Amlodipine
Adverse events	7.5%	12.6%
Personal reasons	7.5%	5.9%
All other categories combined	9%	11%

Primary Endpoint:

- Compared to baseline at week 24, there were mean reductions in SBP of 20 mm Hg for both eplerenone and amlodipine with no significant difference between the treatment groups (95% CI, -2.8 to 3.5)

Secondary Endpoints:

- Reduction in DBP were significant for both agents compared with baseline (95% CI, -4.4, -0.5, P =0.014)
  - amlodipine (-7 mm Hg) vs. eplerenone (-4.5 mm Hg) (P=0.01)
- Mean reductions in pulse pressure were not significantly different between the groups (-16 mm Hg for eplerenone versus -13 mm Hg for amlodipine, P =0.07)
- Ambulatory BP recordings
  - 27 patients in the eplerenone group and 19 in amlodipine
  - changes in 24-hour diastolic BP were not statistically significant
- Changes in the 24-hour pulse pressure and heart rates were similar for the 2 groups
- Pulse wave velocity assessments
  - 71 patients on eplerenone and 68 amlodipine assessed
  - Both eplerenone and amlodipine had significant ($p < 0.05$) and similar reduction from baseline in pulse wave velocity
- Albumin to Creatinine Ratio
  - 106 patients in the eplerenone group and 111 in amlodipine assessed
  - Similar baseline: eplerenone (12.3±8.8 mg/g), and amlodipine (9.7±9.5 mg/g)
  - Greater mean change for eplerenone (P =0.002) at both 14 and 24 weeks
    - eplerenone (-27% to -28%) vs. amlodipine (-3% to -7%)

◆ **Safety and tolerability:**

- Treatment emergent adverse events
  - 64% (86 of 134) of patients in the eplerenone group
  - 70% (95 of 135) of the patients in the amlodipine group
- **The most common treatment emergent adverse events:**

Eplerenone	Amlodipine
Headache (16.4%) Upper respiratory tract infection (6.7%) Nonspecific pain (6%)	Peripheral edema (25.2%) Headache (13.3%) Diarrhea (5.9%) Upper respiratory infection (5.9%) Nausea (5.2%)

- The incidence of edema in the amlodipine group (25.2%) was significantly higher than in the eplerenone group (3.7%) ($P < 0.05$).
- Hyperkalemia (>5.5 mmol/L):4 patients in the eplerenone group and 2 in amlodipine
- No reports of deaths, serious adverse events, gynecomastia, breast tenderness, and menstrual irregularities attributed to either study drug

Conclusions	➢ Eplerenone was as effective as amlodipine in the treatment of older hypertensive patients with systolic hypertension ➢ Eplerenone has the ability to reduce pulse wave velocity, a determinant of arterial elasticity, and to induce a substantial reduction in microalbuminuria, a marker for microvascular disease in the kidney.
Critique	• **Strengths** ➢ Multi-center, randomized, double-blind, active-controlled trial ➢ Measured clinical and ambulatory blood pressure ➢ Implemented adequate wash period • **Limitations** ➢ Ambulatory BP recordings and pulse wave velocity assessments were not performed at all sites and sample size were small ➢ The study excluded those patients with clinically significant heart disease. These individuals are among the patients most frequently treated with an aldosterone blocker ➢ Only mild-to-moderate hypertensive patients were included which limits the applicability of this study to other more severely hypertensive patients.
Sponsorship	• Study was sponsored by Pharmacia.

Citation # 8	Pitt B, Remme W, Zannad F, et al. Eplerenone, a selective aldosterone blocker in patients with left ventricular dysfunction after myocardial infarction. NEJM 2003;348(4):1309-21[20].
Goal/ Objective	To evaluate the effect of eplerenone on morbidity and mortality among patients with acute myocardial infarction complicated by left ventricular dysfunction and heart failure.
Methods	◆ **Study Design**: ➢ International, multi-center, randomized, double-blind, placebo-controlled study ➢ Continue until 1,012 deaths occur, which require 6,200 randomized patients followed for up to 2.5 years. ➢ Patients were randomized 3 to 14 days after acute myocardial infarction (AMI) to eplerenone (25 mg/day) or placebo for four weeks, then increased to 50mg/day ➢ If hyperkalemia (> 5.5 mmol/L), eplerenone was reduced or temporarily discontinued until serum potassium concentration is < 5.5 mmo/L ➢ Optimal medical therapy including ACEIs, ARBs, diuretics, and beta-blockers, as well as coronary reperfusion therapy were allowed (but not required) ➢ Follow-up visits at 1 and 4 weeks, 3 months, and every 3 months until the end of the study ➢ Serum potassium concentration were measured at 48 hours, week 1, 4, and 5 weeks after randomization, at visits and within 1 week after any change of dose ➢ Vital status and hospitalizations were followed every 3 months **Primary endpoints:** ➢ All cause mortality ➢ Cardiovascular (CV) mortality and CV hospitalization o CV hospitalizations: those due to HF, recurrent non-fatal AMI, and stroke or arrhythmia **Secondary endpoints:** ➢ CV mortality – sudden cardiac death, death due to progressive HF, fatal AMI and stroke ➢ All-cause mortality plus all-cause hospitalizations ◆ **Statistics**: ➢ Cox proportional-hazards regression was used for evaluating primary and secondary end points according to the intention-to-treat principle and to summarize the time to first hospitalization for a cardiovascular event ➢ Time-to-event distributions were summarized with Kaplan-Meier curves ➢ 88.3 % power to detect an 18.5 % difference between the two groups in the rate of death from any cause

Criteria

- **Inclusion**:
  - An AMI documented by – abnormal cardiac enzymes, evolving ECG diagnostic of AMI, typical chest pain and enzyme changes if patient has pre-existing left bundle branch block on ECG, LV dysfunction documented by EF ≤ 40%by echocardiogram
  - HF documented by – pulmonary congestion manifested by pulmonary rales, chest X-ray showing pulmonary venous congestion, auscultatory evidence of a third heart sound (S_3)
- **Exclusion**:
  - HF of primary valvular or congenital etiology
  - Current evidence of clinical instability (e.g., arrhythmias other than atrial fibrillation, cardiogenic shock, etc.)
  - PTCR during screening must be clinically stable for a minimum of 24 hours following the procedure and prior to randomization
  - CABG during the screening period must be clinically stable for a minimum of 72 hours following the procedure and before randomization
  - An implanted cardiac defibrillator (ICD)
  - Uncontrolled hypotension (SBP<90 mmHg)
  - Requires the use of potassium-sparing diuretics or spironolactone
  - Serum creatinine level >2.5 mg/dL during the screening period
  - Serum potassium level >5.0 mEq/L during the screening period
  - Planned cardiac transplantation
  - Current evidence of alcohol or drug abuse problems
  - Any condition, which the Investigator makes participation in this study not in the best interest of the patient
  - Known hypersensitivity to eplerenone or spironolactone
  - Severe organic disorder or has had surgery or disease of the gastrointestinal tract, which in the opinion of the investigator, may interfere with the absorption, pharmacokinetics, or elimination of the study medication
  - Chronic psychoses or behavioral conditions, which in the opinion of the Investigator would limit the ability of the patient to comply with the requirements of this study
  - Comorbid condition that would be expected to result in death during the next three years (e.g., terminal cancer, AIDS, etc.), including patients receiving immunosuppressive or antineoplastic therapy
  - Received any investigational medication or investigational device within 30 days prior to the first dose of study medication, or is actively participating in any investigational drug or device study, or is scheduled to receive an investigational drug other than eplerenone or be treated with an investigational device during the course of this study
  - Previously admitted to the study

Results

Patients:

- 6642 patients were randomized at 674 centers in 37 countries between 1999 and 2001
- 3313 patients received placebo and 3319 received eplerenone
- No significant differences between the groups in baseline characteristics

Characteristic	Eplerenone (N=3319)	Placebo (N=3313)
Age-yr	64	64
Race (%) White	90	90
Sex (%) Male	72	70
Blood Pressure (mm Hg)	119/72	119/72
LVEF (%)	33	33
Reperfusion therapy or revascularization (%)	45	45
Symptoms of heart failure (%)	90	90

- At baseline, 87% of patients were on ACEIs or ARBs, 75% on beta-blockers, 88 % on aspirin, and 60% on diuretics
- 1021 patients dropped out (493 in the placebo and 538 in the eplerenone group)
  - Request by the patient (204 in the placebo and 231 in the eplerenone group)
  - Adverse events (149 in the placebo and 147 in the eplerenone group)
  - Unknown status (7 in the placebo and 10 in the eplerenone group)

Primary Efficacy Endpoints:

	Eplerenon (N=3319)	Placebo (N=3313)	Relative Risk (95% CI)	P Value
Death from any cause	478	554	0.85 (0.75-0.96)	0.008
CV mortality and CV hospitalization	885	993	0.87 (0.79-0.95)	0.002

Secondary Efficacy Endpoints:

	Eplerenon (N=3319)	Placebo (N=3313)	Relative Risk (95% CI)	P Value
CV mortality Sudden death	407 162	483 201	0.83 (0.72-0.94) 0.79 (0.64-0.97)	0.005 0.03
All-cause mortality & all-cause hospitalizations	1730	1829	0.92 (0.86-0.98)	0.02

- Hospitalization for cardiovascular events compared to placebo
  - 15% relative risk reduction (P=0.03) in number of patients for heart failure
  - 23% relative risk reduction (P=0.002) in episodes of heart failure

- **Safety and tolerability:**
  - Serum creatinine concentration had increased by 0.02 mg/dL in the placebo group and by 0.06 mg/dL in the eplerenone group (P<0.001) at one year
  - Serious hyperkalemia (≥ 6.0 mmol/L) occurred in 5.5% of patients in the eplerenone group compared to 3.9% placebo (P=0.002)
  - 15 patients (12 from eplerenone group and 3 placebo) were hospitalized for serious hyperkalemia
  - Patients with creatinine clearance <50ml/min had greater incidence of serious hyperkalemia (10.1% in the eplerenone group and 5.9% placebo (P=0.006))
  - Incidence of gynecomastia and impotence were similar between the two groups of men
    - Gynecomastia: 0.5% eplerenone vs 0.6% placebo
    - Impotence: 0.9% for both groups

Conclusions

- Eplerenone (25-50 mg) given to patients after AMI with left ventricular dysfunction reduced overall risk of death, and death and hospitalization from cardiovascular causes
- The reduction in cardiovascular mortality was mostly due to reduction in the rate of sudden death from cardiac causes.
- The reduction in the rate of hospitalization for cardiovascular events was largely due to reduction in the risk of hospital for heart failure and episodes of hospitalization for heath failure.
- The major adverse event of eplerenone is hyperkalemia, especially in patients with impaired renal function.

Critique

Strengths

- Randomized, double-blind, placebo-controlled study
- Primary endpoints were mortality and hospitalization

Limitations

- No active control. Eplerenone was not compared to spironolactone for efficacy.
- No discussion of patient population classification according NYHA.
- No discussion of titrating ACE inhibitors to their target doses before adding the investigational agent

	➢ No discussion of the dose of standard therapy medications (e.g., ACE inhibitors, beta furosemide and digoxin) used or comparisons of Tx group vs control group with regard to balance of standard therapies which can have a major impact on trial results ➢ No independent risk factor analysis was done
Sponsorship	• Study was sponsored by Pharmacia.

Citation # 9	Pitt B, Zannad F, Remme W, et al. The Effect of Spironolactone on Morbidity and Mortality in Patients with Severe Heart Failure. NEJM 1999;341(10):709-17[21].
Goal/ Objective	To evaluate spironolactone in the reduction of the risk of death from all causes among patients who had severe heart failure as a result of systolic left ventricular dysfunction
Methods	◆ **Study Design**: ➢ Multi-center, randomized, double-blind, placebo-controlled study ➢ Randomized to spironolactone (25 mg/day) or placebo ➢ After 8 weeks, increased dose to 50 mg QD if patient has signs or symptoms of progression of heart failure without hyperkalemia ➢ If hyperkalemia, decreased dose to 25 mg QOD or adjust the doses of concomitant medications ➢ Follow-up visits and laboratory measurements were scheduled every 4 weeks for the 1st 12 weeks, then every 3 months for a year and every 6 months thereafter ➢ Study medication could be withheld for o Serious hyperkalemia, a serum creatinine >4.0 mg/dL illness, or any condition deemed medically necessary ➢ Adding digitalis and vasodilators were allowed, but potassium-sparing diuretics ➢ Oral potassium supplements were allow for hypokalemia (serum potassium < 3.5 mmol/dL) ➢ The effect of spironolactone was also assessed with the use of six pre-randomization variables: left ventricular ejection fraction, the cause of heart failure, the serum creatinine concentration, age, the use of ACE inhibitors, and the use of digitalis **Primary Endpoint:** ➢ Death from any cause **Secondary endpoints:** ➢ Death from cardiac causes ➢ Hospitalization for cardiac causes ➢ Combined incidence of death from cardiac causes or hospitalization for cardiac causes ➢ Change in the NYHA class ◆ **Statistics**: ➢ Kaplan–Meier methods were used for cumulative survival curves ➢ The primary comparison between the two groups was based on a log-rank test ➢ Cox proportional-hazards regression models were developed to explore the effects of base-line variables on the estimated effect of spironolactone ➢ The power of the study to detect a difference between treatment groups was set at 90 percent (with a two-tailed α level of 0.05)
Criteria	◆ **Inclusion**: ➢ NYHA class IV heart failure within the 6 months before enrollment and were in NYHA class III or IV at the time of enrollment ➢ A diagnosis of heart failure at least 6 weeks before enrollment ➢ Treated with an ACE inhibitor (if tolerated) and a loop diuretic, and had a left ventricular ejection fraction <35 % within the 6 months before enrollment ◆ **Exclusion**: ➢ Primary operable valvular heart disease (other than mitral or tricuspid regurgitation with clinical symptoms due to left ventricular systolic heart failure)

- Congenital heart disease
- Unstable angina
- Primary hepatic failure
- Active cancer
- Any life-threatening disease (other than heart failure)
- Undergone heart transplantation or were awaiting the procedure
- A serum creatinine > 2.5 mg/dL
- A serum potassium concentration >5.0 mmol/dL

Results

Patients:

- The study was stopped earlier, after a mean follow-up of 24 months, due to the greater reduction in the risk of death from all causes
- 1663 patients were randomized at 195 centers in 15 countries between 1995 and 1996: 841 received placebo and 822 spironolactone.
- No significant differences between the groups in baseline characteristics
- Baseline medications characteristics
  - Mean ejection fraction was 25%
  - NYHA Class III/IV: 72%/ 27% for spironolactone and 69%/ 31% for placebo
- 414 patients (200 in the placebo group and 214 in spironolactone) discontinued treatment because of a lack of response, adverse events, or administrative reasons
- The mean daily dose of study medication was 31 mg in the placebo group and 26 mg in the spironolactone group
- Baseline medications characteristics (%)

	Placebo group	Spironolactone group
Loop Diuretics	100	100
ACE inhibitors	94	95
Digitalis	72	75
Aspirin	37	36
Potassium supplements	27	29
Beta-blockers	10	11

Primary Efficacy Endpoints:

	Placebo (N=841)	Spironolactone (N=822)	Relative Risk (95% CI)	P Value
Death from any cause	386	284	0.70 (0.60-0.82)	< 0.001

Secondary Efficacy Endpoints:

	Placebo (N=841)	Spironolactone (N=822)	Relative Risk (95% CI)	P Value
Death attributed to cardiac causes*	314	226	0.69 (0.58-0.82)	< 0.001
Hospitalization for cardiac causes	753	515	0.70 (0.59-0.82)	< 0.001

*Attributed to lower risks of both deaths from progressive heart failure and sudden death from cardiac causes

- The combined incidence of death or hospitalization for cardiac causes
  - 32% reduction in risk with spironolactone (relative risk, 0.68; 95% CI= 0.59 to 0.78; P<0.001)
- A change in the NYHA class: (P<0.001 between all groups)

NYHA class	Placebo	spironolactone

<table>
<tr><td></td><td>
<table>
<tr><td></td><td colspan="2">% of Patients</td></tr>
<tr><td>Improved</td><td>33%</td><td>41%</td></tr>
<tr><td>No change</td><td>18%</td><td>21%</td></tr>
<tr><td>Worsened</td><td>48%</td><td>38%</td></tr>
</table>
Similar reduction in death was seen when analyzed in prespecified subgroups: sex, NYHA class, baseline serum potassium concentration, use of potassium supplements, and use of beta-blockers
◆ Safety and tolerability:

Serum creatinine and median potassium concentration had increased by 0.05 to 0.10 mg/dL (P<0.001) and 0.30 mg/L (P<0.001), respectively in the spironolactone group compared to no changes for both in the placebo group at one year
Serious hyperkalemia occurred in 10 patients in the placebo group (1%) and 14 patients in the spironolactone group (2%, P=0.42)
Gynecomastia or breast pain in men was reported in 10% of the spironolactone group and 1% of the placebo group (P<0.001), resulting more spironolactone patients to discontinue treatment (10 vs. 1, P=0.006)

</td></tr>
<tr><td>Conclusions</td><td>

Spironolactone used in combination with standard therapy reduced the risk of death from all causes, and death and hospitalization from cardiac causes among patients who had severe heart failure
Spironolactone also improved the symptoms of heart failure measured by changes in the NYHA functional class
The results were consistent among subgroups
There was a significant increase from base line in serum creatinine and potassium concentrations in the patients in the spironolactone group, this change was not clinically important

</td></tr>
<tr><td>Critique</td><td>
Strengths

Randomized, double-blind, placebo-controlled study
Primary endpoints were mortality and hospitalization

Limitations

ACE inhibitors were not titrated to their target doses before adding the investigational agent
No discussion of the dose of standard therapy medications (e.g., furosemide and digoxin) used

</td></tr>
<tr><td>Sponsorship</td><td>• Study was sponsored by Searle.</td></tr>
</table>

ACQUISITION COSTS

Spironolactone*	COST/tablet ($)	COST/day ($)+	COST/year ($)+
25mg (#100)	0.03	0.06-0.12	21.90-43.80
25mg (#1000)	0.027	0.054-0.108	19.71-39.42
50mg	NA**	NA**	NA**
100mg	NA**	NA**	NA**

*Spironolactone is available as Aldactone ® but is currently ordered as generic made by Geneva.
**NA indicates that this dosage form is not applicable since it is not ordered by VASDHS.
+ Spironolactone dose of 50mg/D-100mg/D.

Eplerenone	COST/tablet ($)	Daily Dose	COST/day ($)	COST/year ($)
25mg	2.25	25 mg QD	2.25	821.25
50 mg	2.25	50 mg QD	4.50	1,642.50

COST ANALYSIS

Thus far there has been only one head-to-head trial comparing monotherapy of eplerenone and spironolactone in the treatment of hypertension[7]. There have been no long-term trials addressing morbidity or mortality to date. At this time it is only possible to include a cost analysis based on cost per unit reduction in SBP and DBP. This study used several efficacy variables including: change in seated and standing SBP and DBP, 24-hr ambulatory SBP and DBP, total and active plasma renin, and serum aldosterone levels. The analysis below is based on the change from baseline in seated SBP and DBP only. This analysis is based on the cost per year per reduction of mm Hg in SBP/DBP.

DRUG	DAILY DOSE	# OF PTS/LENGTH (WKS)	COST/DAY ($)	ANNUAL COST ($)	Δ FROM BASELINE IN SEATED SBP/DBP (mm Hg)	COST PER YEAR/REDUCTION IN mmHg OF SBP/DBP ($)
Spironolactone	50mg BID	48/8weeks	0.108	39.42	-16.7/-9.5	2.36/4.15
Eplerenone	50mg QD	54/8weeks	2.25	821.25	-4.4/-4.5	186.65/182.50
Eplerenone	100mg QD	49/8weeks	4.50	1642.50	-7.9/-4.4	207.91/373.30
Eplerenone	50mg BID	54/8weeks	4.50	1642.50	-11.7/-7.8	140.39/210.58

CONCLUSIONS

Hypertension

Eplerenone is currently FDA approved for essential hypertension and post-MI CHF.[8,11,12]. Several studies have shown eplerenone to be successful in reducing both SBP and DBP in patients with moderate-to-severe hypertension[1-3,7,8]. The dose of eplerenone is not recommended in doses greater than 100 mg daily because it has not shown a greater effect on BP and may be associated with dose-related risks of hyperkalemia[8, 11]. Studies have also demonstrated that BP can be further reduced when eplerenone is added to either an ACEI or ARB[2,3]. However, long-term clinical trials will be required to determine if any additional morbidity or mortality benefit results from this combination treatment[2].

Heart Failure

Spironolactone, in relatively low doses has been shown in the RALES trial to significantly reduce mortality in moderate-to-severe heart failure when combined with standard therapy[1,2,5,11]. Eplerenone's theoretical advantage over spironolactone is in its potential for lower incidences of endocrine-related adverse effects, due to its greater selectivity[1-4,7,11]. In August of 2003, eplerenone was approved for Post-MI CHF patients based on a significant (15%) reduction compared to placebo in the risk of death from the EPHESUS trial. Since there are no head-to-head trials of spironolactone and eplerenone, relative efficacy of these two agents is unknown. In addition, it is difficult to compare efficacy between the two agents for CHF because patient populations were different in the RALES trial with 72%/27% of the patients classified as NYHA Class III/IV and 90% of the patients classified as experiencing heart failure symptoms in EPHESUS trial. Until further studies with similar patient populations to determine

superior efficacy between the two agents, eplerenone may be considered in heart failure patients who cannot tolerate spironolactone.

Adverse Effects/Safety

Caution should be used when administering eplerenone to patients with diabetes, renal failure or other hyperkalemia risk factors (i.e., taking ACE inhibitors or ARBs)[2,8]. There is a dose related increase in potassium effect demonstrated in a fixed-dose hypertension study[8]. In CHF patients, the incidence of serious hyperkalemia (≥ 6.0 mmol/L) was 5.5% with eplerenone in EPHESUS trial and 2% with spironolactone in RALES trial. In one 9 month study by Pitt et al[17] eplerenone was seen to have significant higher rates of hyperkalemia with respect to enalapril. In terms of sex hormone-related adverse events, gynecomastia and abnormal vaginal bleeding was reported for patients treated with eplerenone and not with placebo in the hypertension trials and the risk for these adverse events increased marginally with longer use[8]. The rate of gynecomastia was 0.5% with eplerenone in the EPHESUS study noticeably lower than 10% with spironolactone in the RALES trial. However population differences and dosing differences may limit interpretation of such results.

RECOMMENDATIONS

Recommendations:

Due to its lack of demonstrated clinical outcomes and high cost, eplerenone should be highly restricted only to those individuals who require treatment with an aldosterone blocker for essential hypertension and are unable to tolerate spironolactone due to documented endocrine adverse effects. Because there are numerous agents for the treatment of hypertension this should be a rare indication for use. For treatment of Post-MI CHF eplerenone should be reserved for patients whom are maximally treated with all other medications known to affect the outcome of CHF (ACE, ARB, Beta-blockers, Diuretics) and are unable to tolerate spironolactone due to documented endocrine adverse effects. The use of eplerenone for edema, hypokalemia or hyperaldosteronism has not yet been adequately studied and should be discouraged at this time but might be considered in cases where aldosterone antagonism is considered essential and spironolactone has resulted in endocrine adverse events. It has been shown to have some efficacy in the management of hypertension as monotherapy or as an add-on agent for patients who are already on an ACEI or ARB but are poorly controlled but its cost effectiveness compared to other antihypertensive agents is poor. For information on when aldosterone blockers are considered appropriate for essential hypertension or heart failure, refer to the VHA/DoD hypertension guideline and pharmacologic supplement and PBM/MAP CHF treatment guidelines for use located at http://vaww.pbm.med.va.gov/pbm/treatment.htm.

All providers who wish to prescribe eplerenone should have documented that:

- Their patient is being treated for essential hypertension or Post-MI CHF and meets criteria for an aldosterone-blocking agent for post-MI CHF, or for advanced systolic CHF (advanced class III or IV), or for hypertension with documented (or strongly suspected) hyperaldosteronism but is unable to tolerate spironolactone due to an endocrine-related adverse event or other plausible adverse drug reaction
- Has a specific requirement for treatment of their hypertension or Post-MI CHF with an aldosterone-blocking agent as outlined in the PBM/MAP guidelines and cannot tolerate an adequate trial with spironolactone.
- Have failed a course of spironolactone due to a specific, documented, endocrine adverse event (gynecomastia, menstrual irregularities, etc).

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