Effects of the Selective Aldosterone Blocker Eplerenone Versus the Calcium Antagonist Amlodipine in Systolic Hypertension


Abstract—Eplerenone is a highly selective aldosterone blocker, which is under development for the treatment of hypertension and heart failure. To assess its usefulness in older patients with systolic hypertension and widened pulse pressure, we compared the effects of eplerenone with amlodipine, on clinic blood pressure (BP) and pulse pressure and in a subset of the patients, ambulatory BP, vascular compliance, and urinary albumin excretion. The study involved 269 patients ≥50 years of age who were randomly assigned to either eplerenone (50 to 200 mg daily) or amlodipine (2.5 to 10 mg daily) in a double-blind titration to effect design. After 24 weeks of therapy, reductions in clinic systolic BP were similar for both treatments (eplerenone, −20.5±1.1 mm Hg; amlodipine, −20.1±1.1 mm Hg). Reductions in clinic diastolic BP were modestly larger on amlodipine (−6.9±0.7 mm Hg) compared with eplerenone (−4.5±0.7 mm Hg) (P=0.014). Pulse pressure was also reduced similarly from baseline by the 2 treatment groups (eplerenone, −15.9 mm Hg versus amlodipine, −13.4 mm Hg, P=0.07). Changes from baseline in pulse wave velocity after 24 weeks of therapy were statistically similar for eplerenone and amlodipine. In patients with microalbuminuria at baseline (>30 mg albumin/g creatinine), eplerenone reduced the urinary albumin/creatinine ratio by 52% compared with a reduction of 10% by amlodipine (P=0.04). Thus, eplerenone was as effective as amlodipine in lowering systolic BP and pulse pressure as well as pulse wave velocity in older patients with widened pulse pressure hypertension. Furthermore, eplerenone reduced microalbuminuria to a greater extent than amlodipine in this older patient group. (Hypertension. 2003;41:1021-1026.)

Key Words: hypertension, essential ■ calcium antagonists ■ aldosterone ■ albuminuria ■ pulse pressure

Systolic blood pressure (BP) elevation has been recognized as an independent risk factor that far exceeds the risk associated with an elevated diastolic BP in patients with hypertension. Moreover, isolated systolic hypertension is a disorder characterized by a systolic BP >140 mm Hg but with a diastolic BP <90 mm Hg and has been associated with increases in stroke, coronary artery disease, heart and kidney failure, and all-cause mortality rates. This issue is especially important in older people because aging predisposes patients to development of arteriosclerosis accompanied by reduced vascular compliance with amplification of systolic BP and reduction of diastolic BP. Elevation of systolic BP in this population is a primary consequence of reduced arterial elasticity that increases the pressure with the ejection of the cardiac stroke volume. The widened pulse pressure that results from this phenomenon paves the way for cardiovascular morbidity since elevated systolic BP is associated with greater left ventricular workload and myocardial oxygen demand, whereas a decreased diastolic BP may decrease coronary perfusion pressure, resulting in decreased myocardial oxygen supply. Therapeutic data on the benefits of reduction of systolic pressure are well delineated in the cardiovascular literature, whereas less is known about the effects of antihypertensive therapy on the pulse pressure. Thus, it is of value to determine the impact of new antihypertensive therapies on these hemodynamic parameters in patients with hypertension.

In this article, we report on the comparative effects of eplerenone, a novel selective aldosterone blocker, versus the calcium antagonist amlodipine on BP, pulse wave velocity, and albuminuria in older men and women with hypertension. Eplerenone is a steroid nucleus-based antimineralocorticoid that acts as a competitive and selective inhibitor of aldosterone at aldosterone receptor sites in various tissues throughout the body. As the result of the presence of a 9,11-epoxide group in the structure of eplerenone, selectivity for the aldosterone receptor is enhanced and the drug has very low affinity for the progesterone and androgen receptors (eg, <1% and <0.1%, respectively, of the receptor binding of spironolactone, the reference drug of this class). The enhanced selectivity of eplerenone for the aldosterone receptor should maintain BP lowering with improved tolerability compared with spironolactone.

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tone. In a previous trials of eplerenone in middle-aged patients with diastolic hypertension,\textsuperscript{11,12} statistically and clinically significant reductions in clinical and ambulatory BP were observed with doses of 50 to 400 mg daily.

### Methods

#### Patient Population

Men and women at least 50 years of age with systolic hypertension (defined as seated clinic systolic BP of 150 to 165 mm Hg with a pulse pressure of ≥70 mm Hg or 165 to 200 mm Hg with a diastolic pressure of ≥95 mm Hg) were included in the trial. Patients were excluded from the trial if they had clinically significant heart, liver, or kidney disease or if the serum creatinine was >1.5 mmol/L or >1.3 mmol/L, for men and women, respectively, or if the serum potassium level was ≥5.0 mmol/L at baseline.

#### Design

The study was a multicenter, double-blind, randomized, active-controlled, titration-to-effect trial. After discontinuation of any usual antihypertensive drug therapy, patients were given single-blind placebo tablets for 2 to 4 weeks to establish the baseline BPs and laboratory parameters. At random assignment, patients received either 50 mg eplerenone once daily or 2.5 mg amlopidine once daily. If this initial dose resulted in adequate systolic BP control (<140 mm Hg), the study medication was not altered for the remainder of the 24-week double-blind period. However, if systolic BP was uncontrolled at week 2, the dose of eplerenone was increased to 100 mg daily, whereas amlopidine was increased to 5 mg daily. If the systolic BP remained elevated at week 6, eplerenone was increased to 200 mg daily and amlopidine to 10 mg daily. After 10 weeks of double-blind therapy, if the systolic BP was >170 mm Hg, the patient was removed from the trial for safety considerations. In addition, if the patient’s serum potassium level was in excess of 5.5 mmol/L on 2 consecutive occasions 1 to 3 days apart, the patient was removed from the study and placed on conventional therapy.

Patients were assessed at 4-week intervals during the trial for BP, heart rate, serum potassium, adverse events, and concomitant medications. At baseline and after 14 and 24 weeks of double-blind therapy, ambulatory BP monitoring, pulse wave velocity, and microalbuminuria were assessed at selected sites.

#### Measurements of Blood Pressure and Heart Rate

The office (or clinic) BP was measured in duplicate in both the seated and standing positions at all visits approximately 24 hours after dosing of study medication. In sites experienced in ambulatory BP monitoring, patients underwent ambulatory BP and heart rate measurements with the SpaceLabs 90207 monitor as previously described.\textsuperscript{11}

#### Measurements of Pulse Wave Velocity

At approximately half of the sites, all patients underwent pulse wave velocity that was measured from the carotid to femoral arteries and from the carotid to radial arteries with the use of the Complior (Complior Systems, Colson)\textsuperscript{13} device at baseline and 14 and 24 weeks after random assignment. This device gives an automated measurement of pulse wave velocity for 1 or 2 arterial segments simultaneously through the use of dedicated mechanotransducers. As previously described,\textsuperscript{13} pulse wave velocity values of <5.44 m/s or >28.8 m/s were excluded from the analyses.

#### Microalbuminuria Determinations

Microalbuminuria assessments were made at baseline and after 14 and 24 weeks of double-blind therapy in all sites. A first morning voided spot urine sample for microalbumin (measured as the urinary albumin-creatinine ratio or UACR)\textsuperscript{14} was collected before administration of study medication.

### Statistical Analyses

The primary efficacy end point of the trial was to establish noninferiority of eplerenone by assessing the mean change from baseline in seated systolic BP after 24 weeks of therapy with the use of one-sided 95% confidence limits. The null hypothesis was that the reduction in systolic BP on amlopidine was at least 6 mm Hg greater than on eplerenone. Treatment comparisons were based on the least-squares means obtained by SAS Type III analysis (SAS 6.09 VMS operating system, SAS Institute). The statistical analyses were performed on an intention-to-treat basis and used ANCOVA. Secondary analyses included the changes from baseline in the clinic pulse pressure and diastolic pressure, 24-hour BP, and several other ambulatory monitoring parameters including daytime mean, nighttime mean, and the changes in ambulatory heart rate. In addition, eplerenone and amlopidine were compared with respect to changes from baseline in carotid-femoral and carotid-radial pulse wave velocity and mean percent changes from baseline in microalbuminuria at week 24.

All adverse events were summarized by treatment group. The incidence of treatment-emergent adverse events were tabulated for treatment group and body system and was analyzed by treatment group with the use of the Fisher exact test. All data were analyzed on an intention-to-treat basis using the Fisher exact test.

### Results

#### Patient Characteristics and Dosing of Drugs

There were 269 patients randomly assigned into the 2 treatment arms with similar demographics and baseline clinic BP values (Table 1). Of 134 patients randomly assigned to receive eplerenone, 102 (76%) completed the trial; of the 135 patients randomly assigned to receive amlopidine, 94 (70%) completed the trial. The main reasons for withdrawal after random assignment were as follows: eplerenone, 7.5% because of adverse events, 7.5% for personal reasons, and 9% because of all other categories combined; amlopidine, 12.6% because of adverse

### Table 1. Baseline Patient Characteristics

<table>
<thead>
<tr>
<th>Characteristic</th>
<th>Eplerenone</th>
<th>Amlodipine</th>
</tr>
</thead>
<tbody>
<tr>
<td>Gender, M:F</td>
<td>61:73</td>
<td>66:69</td>
</tr>
<tr>
<td>Age, y</td>
<td>67±6</td>
<td>69±6</td>
</tr>
<tr>
<td>Ethnicity, %</td>
<td></td>
<td></td>
</tr>
<tr>
<td>White</td>
<td>89</td>
<td>89</td>
</tr>
<tr>
<td>Black</td>
<td>2</td>
<td>4</td>
</tr>
<tr>
<td>Asian</td>
<td>1</td>
<td>2</td>
</tr>
<tr>
<td>Latino</td>
<td>7</td>
<td>5</td>
</tr>
<tr>
<td>Other</td>
<td>1</td>
<td>0</td>
</tr>
<tr>
<td>Body mass index, kg/m²</td>
<td>28.8±5.3</td>
<td>28.8±6.0</td>
</tr>
<tr>
<td>Female</td>
<td>28.7±4.0</td>
<td>29.1±4.7</td>
</tr>
<tr>
<td>Male</td>
<td>166/86±11/7</td>
<td>166/86±12/8</td>
</tr>
<tr>
<td>Clinic BP, mm Hg</td>
<td>79.4±10.0</td>
<td>80.1±11.7</td>
</tr>
<tr>
<td>24-hour pulse pressure, mm Hg</td>
<td>154±8±14/9</td>
<td>150±8±8/7</td>
</tr>
<tr>
<td>24-hour pulse pressure, mm Hg</td>
<td>69±11</td>
<td>66±10</td>
</tr>
</tbody>
</table>

All comparisons between groups are \(P>0.05\).
There were no significant differences in systolic BP reductions for the 2 treatment groups.

At week 24, the number and proportion of patients on the first dose level of eplerenone (50 mg) and amlodipine (2.5 mg) was 25 (20%) and 18 (15%), respectively. The number on the second dose level of eplerenone (100 mg) and amlodipine (5 mg) was 19 (15%) and 35 (29%), respectively. Most patients were on the highest dose level of eplerenone (200 mg) and amlodipine (10 mg) at 81 (65%) and 68 (56%), respectively. Thus, the median dose for eplerenone was 200 mg and for amlodipine was 10 mg. At the end of the 24-week, double-blind treatment period, the mean daily dose of eplerenone was 155 mg and the mean dose of amlodipine was 7.4 mg.

**Clinic Blood Pressure**

The adjusted mean changes in trough systolic BP in the clinic (or office) setting are shown in Figure 1. At week 24 of double-blind therapy, there were mean reductions in systolic BP of \(-20\) mm Hg compared with baseline for both eplerenone and amlodipine. The 95% confidence interval (\(-2.8\) to 3.5) showed no significant difference between the treatment groups; noninferiority of eplerenone was established. Changes in trough diastolic BP were significant for both agents compared with baseline, and the reduction in diastolic BP on amlodipine (\(-7\) mm Hg) was modestly larger than the reduction observed with eplerenone (\(-4.5\) mm Hg) (95% confidence interval, \(-4.4\), \(-0.5\), \(P=0.014\)). Finally, the 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 Blood Pressure and Heart Rate**

A total of 27 patients in the eplerenone group and 19 patients in the amlodipine group had evaluable ambulatory BP recordings (high-quality studies at baseline and at 14 weeks and 24 weeks of therapy). Changes in ambulatory heart rate, systolic and diastolic BP, as well as pulse pressure are shown in Table 2. The treatment differences between eplerenone and amlo- dipine for changes in 24-hour diastolic BP at weeks 14 and 24 were not statistically significant. Changes in the 24-hour pulse pressure and heart rates were similar for the 2 treatment groups.

The 24-hour systolic BP profiles for eplerenone and amlodipine at weeks 14 and 24 are shown in Figure 2. Both drugs induced substantial 24-hour reductions compared with placebo baseline, with no evidence of attenuation control at the end of the dosing period. Of note, at 24 weeks, the daytime ambulatory systolic BP in the amlodipine group was moderately higher than it was at the week 14 study (see Figure 2).

**Pulse Wave Velocity**

There were 71 patients receiving eplerenone and 68 patients receiving amlodipine who had complete pulse wave velocity assessments at baseline, week 14, and week 24 of the study. At baseline, the mean carotid-femoral pulse wave velocities were similar for the 2 treatment groups (eplerenone, 15.5±2 m/s and amlodipine, 16.5±3 m/s). The baseline carotid-radial pulse wave velocities were 11.5±2.5 m/s for the eplerenone treatment group and 11.3±2.4 m/s for the amlodipine group.

**TABLE 2. Effects of Eplerenone vs Amlodipine on Clinic and Ambulatory BP, Pulse Pressure, and Heart Rate**

<table>
<thead>
<tr>
<th>Parameter</th>
<th>Eplerenone (n=27)</th>
<th>Amlodipine (n=19)</th>
<th>P</th>
</tr>
</thead>
<tbody>
<tr>
<td>Ambulatory BP</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Week 14 visit</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Δ 24-hour BP, mm Hg</td>
<td>(-10.8/-3.6±1.6/1.0)</td>
<td>(-12.2/-6.6±2.1/1.4)</td>
<td>0.57/0.08</td>
</tr>
<tr>
<td>Δ Pulse pressure, mm Hg</td>
<td>(-6.8±1.0)</td>
<td>(-5.7±1.4)</td>
<td>0.53</td>
</tr>
<tr>
<td>Δ heart rate (beats/minute)</td>
<td>(1.2±1.4)</td>
<td>(0.2±1.8)</td>
<td>0.66</td>
</tr>
<tr>
<td>Week 24 visit</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Δ 24 hour BP, mm Hg</td>
<td>(-8.5/-2.8±1.9/1.2)</td>
<td>(-12.0/-5.7±2.3/1.4)</td>
<td>0.23/0.11</td>
</tr>
<tr>
<td>Δ Pulse pressure, mm Hg</td>
<td>(-5.8±1.2)</td>
<td>(-6.1±1.4)</td>
<td>0.85</td>
</tr>
<tr>
<td>Δ heart rate, beats/min</td>
<td>(0.2±1.1)</td>
<td>(-0.7±1.4)</td>
<td>0.78</td>
</tr>
<tr>
<td>Clinic BP (Week 24)</td>
<td>(n=128)</td>
<td>(n=132)</td>
<td></td>
</tr>
<tr>
<td>Δ systolic BP, mm Hg</td>
<td>(-20.5±1.1)</td>
<td>(-20.1±1.1)</td>
<td>0.83</td>
</tr>
<tr>
<td>Δ diastolic BP, mm Hg</td>
<td>(-4.5±0.7)</td>
<td>(-6.9±0.7)</td>
<td>0.01</td>
</tr>
</tbody>
</table>

All data are from intent-to-treat populations; P values are based on a 2-sided ANCOVA test of treatment differences with baseline value as covariates and treatment and centers as factors.
Changes from baseline in pulse wave velocity were similar for both eplerenone and amlodipine (Figure 3). The reductions from baseline in carotid-femoral and carotid radial pulse wave velocity were significant within each group \((P<0.05)\), but the differences between groups were not significant. The carotid-femoral pulse wave velocity was slightly lower at week 24 compared with week 14 in the eplerenone group despite no further changes in clinic or ambulatory BP.

**Figure 2.** Effects of eplerenone (top panel) and amlodipine (bottom panel) on 24-hour BP over time at baseline and after 14 and 24 weeks of double-blind therapy.

**Figure 3.** Changes from baseline in pulse wave velocity after 14 and 24 weeks of therapy with eplerenone and amlodipine.

**Albumin to Creatinine Ratio**

There were 106 patients in the eplerenone group and 111 patients in the amlodipine group who participated in the evaluation of changes from baseline in urinary albumin to creatinine ratio. At baseline, the geometric mean for the eplerenone group was 12.3±8.8 mg/g, whereas the mean for the amlodipine group was 9.7±9.5 mg/g. These baseline differences were not statistically significant. As shown in Figure 4, the mean percent change from baseline in the urinary albumin to creatinine ratio was significantly greater \((P=0.002)\) for eplerenone \((-27\% \text{ to } -28\%)\) compared with amlodipine \((-3\% \text{ to } -7\%)\) at both 14 and 24 weeks of therapy. In the subgroup of patients who had microalbuminuria at baseline \((>30 \text{ mg/g creatinine})\), the mean percent reduction for eplerenone was 52\%, whereas for amlodipine it was 10\% \((P=0.04)\).

**Adverse Events**

Treatment emergent adverse events were reported in 64\% (86 of 134) of patients in the eplerenone group and 70\% (95 of 135) of the patients in the amlodipine group. There were no deaths during the trial and there were no serious adverse events attributed to either study drug. The most common treatment emergent adverse events in the eplerenone group were headache (16.4\%), upper respiratory tract infection (6.7\%), and nonspecific pain (6\%). In the amlodipine group, the most common adverse events were peripheral edema (25.2\%), headache (13.3\%), diarrhea (5.9\%), upper respiratory infection (5.9\%), and nausea (5.2\%). The incidence of edema in the amlodipine group (25.2\%) was significantly higher than in the eplerenone group (3.7\%) \((P<0.05)\). Elevation in the serum potassium (serum potassium >5.5 mmol/L) was reported as an adverse event in 4 patients (3.0\%) in the eplerenone group and 2 patients (1.5\%) in the amlodipine group. Gynecomastia, breast tenderness, and menstrual irregularities were not reported for either drug.

**Discussion**

**Principal Findings**

Eplerenone, a new selective aldosterone blocker, was as effective as amlodipine in reducing both systolic and pulse pressure in older hypertensive patients with a widened pulse pressure. In addition, both eplerenone and amlodipine improved arterial elasticity, based on the significant reductions from baseline in
Patients with diastolic hypertension, eplerenone significantly reduced clinic systolic pressure by 13 mm Hg in all patients (by 14 mm Hg in black patients and by 12 mm Hg in white patients). Of note is that the baseline systolic BP in that population was ≈150 mm Hg, whereas in the current study the baseline systolic BP averaged ≈165 mm Hg.

Pulse Wave Velocity
As noted in Figure 3, both eplerenone and amlodipine improved arterial elasticity, based on the significant reductions from baseline in the carotid-to-femoral and carotid to radial pulse wave velocity. The pulse wave velocity is determined by the elastic modulus of the arterial wall, arterial geometry (both thickness and radius), and blood density. Thus, a reduction in pulse wave velocity will be strongly related to a reduction in arterial stiffness associated with improvement in elasticity of the vessel.

Prior work by Duprez and coworkers demonstrated that aldosterone plays a role in reduced vascular compliance of the aorta and large arteries. Findings in hypertensive animal models suggest that aldosterone may act directly on vascular and cardiac myocytes to induce collagen synthesis and vascular inflammation. Furthermore, blockade of aldosterone with eplerenone has been shown to restore endothelium-dependent relaxation, normalize vascular endothelin-I levels, and markedly block vascular inflammation.

In the current study, eplerenone, acting as a selective aldosterone blocker, significantly improved arterial elasticity compared with baseline in these older patients over a 24-week period but was not different from a calcium antagonist. In future studies, longer-term administration should answer the question as to whether the therapy may have more prominent effects associated with reversal of vascular inflammation and collagen deposition in the arterial wall.

Albumin to Creatinine Ratios
As shown in Figure 4, eplerenone reduced the urinary albumin to creatinine ratio to a significantly greater extent than amlodipine. This finding was more striking in the 16% of patients whose baseline albumin to creatinine ratio was >30 mg/g (or 3393 μg/mmol). These results bear clinical significance, as it is well documented that microalbuminuria is associated with increased cardiovascular and renal failure risk and in patients with hypertension is highly correlated to adverse cardiovascular and metabolic risk profiles.

Reduction of albuminuria by antihypertensive agents has been associated with reduction in the rates of decline in renal function in hypertensive patients with baseline reductions in renal function.

Despite similar effects on clinic and 24-hour BP to drugs that block angiotensin (and in our study, aldosterone), the dihydropyridine calcium antagonists have typically been shown to have no effect on proteinuria reduction. The calcium antagonists such as amlodipine and felodipine dilate both afferent and efferent arterioles, which may even increase protein excretion despite the reduction in arterial pressure. Eplerenone, as a selective blocker of aldosterone, had been shown to attenuate renal damage in preclinical studies of stroke-prone spontaneously hypertensive rats, given chronic saline in the drinking water. Of note in this model is the reduction in proteinuria associated with marked reductions in vascular inflammation, vascular and glomerular sclerosis, and tubular damage, independent of BP-lowering effects. Further research is needed to...
determine the pharmacological effects of eplerenone in various types of kidney disease in humans.

Safety and Tolerability

The tolerability and safety profile of eplerenone in this older population with widened pulse pressure hypertension was good. The overall incidence of side effects was slightly lower than amloidipine in part because of a lower rate of peripheral edema. In addition, there were no male patients in the eplerenone treatment group who had gynecomastia, a finding often reported for spironolactone, a nonspecific antagonist of androgens, progestrone, and aldosterone.27

Conclusions

These data show that eplerenone, a new selective aldosterone blocker, was as effective as amloidipine in the treatment of older hypertensive patients with systolic hypertension, characterized by a widened pulse pressure. Specific attributes of this agent were 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. Taken together with an antihypertensive efficacy that was equivalent to amloidipine and with similar tolerability, these effects suggest that eplerenone will be a useful agent in the treatment of older patients with hypertension.

References

Effects of the Selective Aldosterone Blocker Eplerenone Versus the Calcium Antagonist Amlodipine in Systolic Hypertension

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In the article by White et al (Effects of the selective aldosterone blocker eplerenone versus the calcium antagonist amlodipine in systolic hypertension), which appeared in the May 2003 issue (Hypertension. 2003;41:1021–1026), the affiliations for coauthor Daniel Duprez were listed incompletely. Dr Daniel Duprez is affiliated with the following institutions: Department of Cardiovascular Diseases, University of Ghent, Belgium, and Cardiovascular Division, University of Minnesota, Minneapolis, Minn. The author regrets this error.