Effects of Add-on Therapy Consisting of a Selective Mineralocorticoid Receptor Blocker on Arterial Stiffness in Patients with Uncontrolled Hypertension

Takahiro Shibata¹, Joshi Tsutsumi¹, Jun Hasegawa¹, Nobutaka Sato¹, Eitatsu Murashima¹, Chikara Mori¹, Kenichi Hongo² and Michihiro Yoshimura²

Abstract

Objective  Aldosterone plays an important role in the pathogenesis of atherosclerosis; however, the significance of mineralocorticoid receptor blockade for atherosclerosis has not been fully elucidated. In this study, the effect of add-on eplerenone on the degree of arterial stiffness was examined in patients with uncontrolled hypertension.

Methods  Forty-seven uncontrolled hypertensive patients who had previously been treated with antihypertensive drugs were examined retrospectively. Thirty-two patients received add-on therapy consisting of eplerenone (Group E) and 15 patients received add-on therapy with a Calcium channel blocker (CCB) or an increased dose of CCB (Group C) in addition to their baseline medications. Both the systolic blood pressure (SBP) and diastolic blood pressure (DBP) values were significantly decreased at two and 12 months in Group C. In contrast, neither the SBP nor DBP values were significantly changed at two months and eventually decreased at 12 months in Group E. The degree of arterial stiffness, as evaluated according to the cardio-ankle vascular index (CAVI), did not improve at either two or 12 months in Group C, whereas the CAVI values improved as early as at two months and the improvement was sustained at 12 months in Group E. The extent of change in the CAVI was not associated with the level of changes in the SBP or DBP values in Group E.

Conclusion  Treatment with eplerenone added to the patient’s baseline medications improves the degree of arterial stiffness as early as at two months after the beginning of treatment, independent of the blood pressure-lowering actions of these drugs in patients with uncontrolled hypertension.

Key words: mineralocorticoid receptor blocker, Calcium channel blocker, arterial stiffness, cardio-ankle vascular index

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Introduction

Several large-scale clinical studies, including the Randomized ALdactone Evaluation Study (RALES) (1), Eplerenone Post-acute myocardial infarction Heart failure Efficacy and Survival Study (EPHESUS) (2) and Eplerenone in Mild Patients Hospitalization and Survival Study in Heart Failure (EMPHASIS-HF) (3) trials, have shown that mineralocorticoid receptor (MR) blockers significantly reduce the incidence of cardiovascular events in patients with heart failure. The clinical significance of MR blocker therapy for the treatment of heart failure is widely recognized, and many other clinical and basic studies have shed light on the potential future uses of MR blockers in a variety of cardiovascular diseases. One potential use of MR blockers is to prevent atherosclerotic processes or improve the degree of arterial stiffness in patients with hypertension.

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MR blockers have been shown to inhibit atherosclerosis in non-human primates (4). Several animal studies have suggested that aldosterone is involved in the onset of vascular inflammation (5, 6) and vascular fibrosis (7, 8), and MR blockade has been reported to result in the attenuation of both inflammation and fibrosis. However, there remains controversy regarding the inhibitory effects of MR blockers on atherosclerosis in humans (9-12). Therefore, the accumulation of more clinical evidence is required to examine the effects of MR blockers in preventing atherosclerosis and/or ameliorating arterial stiffness in patients with hypertension.

In the present study, we investigated the effects of adding eplerenone (13, 14), a selective MR blocker, to other anti-hypertensive drugs on the blood pressure and arterial stiffness in comparison to that observed with escalating the dose or newly adding a Calcium channel blocker (CCB). The study population was retrospectively recruited among patients, who exhibited uncontrolled hypertension, even under baseline treatment with other anti-hypertensive drugs. That is, in this study, we examined the add-on effects of eplerenone on the degree of arterial stiffness in patients with relatively advanced stages of atherosclerosis.

Materials and Methods

Study patients

Among the outpatients with hypertension who visited the Division of Cardiology, Department of Internal Medicine, Jikei Daisan Hospital between June 2010 and May 2012, we retrospectively selected the study patients based on the following criteria.

Patients who newly received eplerenone with other anti-hypertensive drugs after failing to attain their therapeutic goals with regard to blood pressure were assigned to Group E. Patients who received add-on therapy with CCBs or an increased dose of CCB compared to their baseline medications given for blood pressure control were classified into Group C. The diagnosis of hypertension and the therapeutic goals for blood pressure were determined in each patient based on the Japanese Society of Hypertension Guidelines for the Management of Hypertension (JSH 2009) (15). Patients with secondary hypertension were excluded from this study. In Group E, the dose of eplerenone was successively escalated up to 50 mg without side effects, such as hyperkalemia. In Group C, the dose of CCB was escalated or other CCBs were additionally added; new CCBs (amlodipine or nifedipine) were added in four patients and the dose of amlodipine was escalated from 5 to 10 mg in 11 patients. The patients in Group C did not receive MR blockers. The final study population comprised 47 patients (26 men and 21 women), including 32 patients in Group E and 15 patients in Group C. The study protocol was approved by the Ethics Committee of the Jikei University School of Medicine (approval number 23-268 6729).

Blood pressure measurement and blood sampling

Blood pressure was measured by trained physicians using a conventional mercury sphygmomanometer after five-minutes of rest in the outpatient clinic. Blood samples were collected from the antecubital vein, and routine hematology and biochemistry studies were performed immediately using an autoanalyzer. The serum creatinine levels were determined according to a standard enzymatic method. The plasma B-type natriuretic peptide (BNP) levels were measured using an enzyme-linked immunosorbent assay. The blood pressure values, and serum creatinine, serum potassium and plasma BNP levels were determined at baseline, and after two and 12 months of treatment.

Measurement of the arterial stiffness according to the cardio-ankle vascular index (CAVI)

The degree of arterial stiffness was evaluated according to the CAVI. Blood pressure, pulse wave velocity, electrocardiograms and heart sounds were simultaneously monitored using a VaSera VS-1000 instrument (Fukuda Denshi, Tokyo, Japan). The pulse wave velocity was calculated by dividing the distance from the aortic valve to the ankle artery by the sum of the time between the aortic valve closing sound and the notch of the brachial pulse wave, and the time between the rise of the brachial pulse wave and the ankle pulse wave (16). The CAVI was determined based on the following equation: \[ \text{CAVI} = \frac{a}{\Delta \rho} \times \frac{\ln(P_s/P_d) \times PWV^2 + b}{\rho} \] where \(P_s\) and \(P_d\) are the systolic and diastolic blood pressures, respectively, \(PWV\) is the pulse wave velocity between the heart and ankle, \(\Delta P\) is \(P_s - P_d\), \(\rho\) is the blood density, and \(a\) and \(b\) are constants (17). The CAVI values included the factors of blood pressure, and the average of the right and left CAVI values was used for the analysis.

Statistical analysis

The results are presented as the means ± standard deviation, unless stated otherwise. Continuous variables were analyzed using Student’s t-test, and categorical data were analyzed using the Chi-square test. Pearson correlation coefficients (r) were calculated in the univariate correlation analyses. The level of statistical significance was set at a p value of <0.05.

Results

Patients’ characteristics at baseline

The patients’ characteristics at baseline are shown in Tables 1 and 2. The baseline characteristics were not significantly different between the two groups, with the exception of the existence of dyslipidemia, and diabetes mellitus (DM) and the use of statins. The prevalence of smoking, body mass index values and numbers of antihypertensive drugs were not significantly different between the two groups. The triglyceride levels were significantly higher in Group C than...
Table 1. Characteristics of the Patients.

<table>
<thead>
<tr>
<th>Variable</th>
<th>Group E (n=32)</th>
<th>Group C (n=15)</th>
<th>p value</th>
</tr>
</thead>
<tbody>
<tr>
<td>Male gender (%)</td>
<td>17 (53.1)</td>
<td>9 (60.0)</td>
<td>0.75</td>
</tr>
<tr>
<td>Age (mean ±SD)</td>
<td>71.4 ± 6.2</td>
<td>72.8 ± 7.3</td>
<td>0.43</td>
</tr>
<tr>
<td>Smoking</td>
<td>2 (6.2)</td>
<td>1 (6.7)</td>
<td>0.96</td>
</tr>
<tr>
<td>BMI (Body mass index)</td>
<td>24.6±3.3</td>
<td>24.8±3.7</td>
<td>0.84</td>
</tr>
<tr>
<td>Numbers of anti HT drug</td>
<td>2.5±0.7</td>
<td>2.4±0.5</td>
<td>0.79</td>
</tr>
<tr>
<td>Underlying diseases</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Dislipidemia (%)</td>
<td>15 (46.8)</td>
<td>13 (81.3)</td>
<td>0.01</td>
</tr>
<tr>
<td>LDL-C (mg/dL)</td>
<td>92.6±24.2</td>
<td>100.0±25.2</td>
<td>0.4</td>
</tr>
<tr>
<td>HDL-C (mg/dL)</td>
<td>63.9±17.5</td>
<td>69.5±21.3</td>
<td>0.4</td>
</tr>
<tr>
<td>TG (mg/dL)</td>
<td>132.3±75.9</td>
<td>200.4±80.1</td>
<td>0.02</td>
</tr>
<tr>
<td>Diabetes mellitus (%)</td>
<td>6 (18.8)</td>
<td>1 (6.7)</td>
<td>0.04</td>
</tr>
<tr>
<td>HbA1c (%)</td>
<td>6.27±0.60</td>
<td>5.91±0.61</td>
<td>0.1</td>
</tr>
<tr>
<td>Ischemic heart disease (%)</td>
<td>8 (25.0)</td>
<td>4 (26.7)</td>
<td>0.95</td>
</tr>
<tr>
<td>Valvular disease (%)</td>
<td>1 (3.1)</td>
<td>0 (0.0)</td>
<td>0.94</td>
</tr>
<tr>
<td>Medications</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>ACE inhibitor/ARB (%)</td>
<td>17 (53.1)</td>
<td>6 (40.0)</td>
<td>0.41</td>
</tr>
<tr>
<td>β blocker (%)</td>
<td>8 (25.0)</td>
<td>4 (26.7)</td>
<td>0.96</td>
</tr>
<tr>
<td>CCB (%)</td>
<td>20 (62.5)</td>
<td>15 (100)</td>
<td>p&lt;0.01</td>
</tr>
<tr>
<td>Statin (%)</td>
<td>12 (37.5)</td>
<td>13 (81.3)</td>
<td>p&lt;0.01</td>
</tr>
</tbody>
</table>

ACE: angiotensin converting enzyme
ARB: angiotensin receptor blocker
CCB: calcium channel blocker
Statin: HMG-CoA reductase inhibitor
LDL-C: low density lipoprotein cholesterol
HDL-C: high density lipoprotein cholesterol
TG: triglyceride
HbA1c: glycosylated hemoglobin A1c
Group E: the hypertensive patients with eplerenone added to the basal therapy
Group C: the hypertensive patients with an increase in the Ca channel antagonist or a new Ca channel antagonist added to the basal therapy

Table 2. The Baseline BP, CAVI and BNP.

<table>
<thead>
<tr>
<th>Variables</th>
<th>Group E (n=32)</th>
<th>Group C (n=15)</th>
<th>p value</th>
</tr>
</thead>
<tbody>
<tr>
<td>Systolic BP (mmHg)</td>
<td>143.9±21.5</td>
<td>146.7±7.9</td>
<td>0.73</td>
</tr>
<tr>
<td>Diastolic BP (mmHg)</td>
<td>86.9±13.5</td>
<td>79.8±9.6</td>
<td>0.04</td>
</tr>
<tr>
<td>CAVI</td>
<td>9.7±1.0</td>
<td>9.5±1.1</td>
<td>0.55</td>
</tr>
<tr>
<td>BNP (pg/mL)</td>
<td>56.0±57.9</td>
<td>44.4±39.4</td>
<td>0.56</td>
</tr>
</tbody>
</table>

BP: blood pressure
CAVI: cardio-ankle vascular index
BNP: B-type natriuretic peptide
Group E: the hypertensive patients with eplerenone added to the basal therapy
Group C: the hypertensive patients with an increase in the Ca channel antagonist or a new Ca channel antagonist added to the basal therapy

in Group E (p<0.05), while the rates of DM and use of statins were significantly higher in Group E than in Group C (p<0.05 and p<0.01). The systolic blood pressure (SBP) values at baseline were not significantly different between the two groups, whereas the diastolic blood pressure (DBP) values were significantly lower in Group C than in Group E (p<0.05). Neither the CAVI values nor plasma BNP levels at baseline were significantly different between the two groups.

Changes in blood pressure

As shown in Fig. 1a, the SBP values significantly decreased from 146.7 ± 7.9 mmHg at baseline to 128.3 ± 12.1 mmHg at two months and 126.7 ± 10.3 mmHg at 12 months (p<0.001, respectively) in Group C. In contrast, the SBP values did not change significantly at two months, with data of 143.9 ± 21.5 mmHg at baseline and 141.5 ± 19.2 mmHg at two months (p=NS), although they significantly decreased to 129.9 ± 13.8 mmHg at 12 months (p<0.001), in Group E. As shown in Fig. 1b, the DBP values significantly decreased from 79.8 ± 9.6 mmHg at baseline to 73.2 ± 6.3 mmHg at two values months (p<0.05), and 72.0 ± 7.7 mmHg at 12 months (p<0.001) in Group C. Meanwhile the DBP values did not change significantly from 86.9 ± 13.5 mmHg at baseline to 84.3 ± 9.0 mmHg at two months (p=NS), whereas significant decrease to 73.2 ± 8.9 mmHg was observed at 12 months (p<0.001), in Group E.

Changes in the CAVI values

As shown in Fig. 2, the CAVI values did not change significantly in Group C, with data of 9.5 ± 1.2 at baseline, 9.5 ± 1.1 at two months and 9.6 ± 1.3 at 12 months (p=NS, respectively). However, the CAVI values significantly decreased from 9.7 ± 1.0 at baseline to 9.2 ± 1.1 at two months and 9.1 ± 1.2 at 12 months (p<0.001, respectively) in Group E.

We subsequently investigated the correlations between the changes in the SBP values and the changes in the CAVI values from baseline to two months (Fig. 3a) and 12months (Fig. 3b) in all cases. A similar analysis was performed to assess the associations between the changes in the DBP and CAVI values at two months (Fig. 3c) and 12 months (Fig. 3d). Consequently, no significant correlations were observed in any of these analyses. Therefore, the CAVI values were confirmed to be independent of blood pressure.
reduced both the SBP and DBP values as early as at two
months after the beginning of treatment and continued to
show an effect at 12 months, whereas eplerenone gradu-
ally reduced both the SBP and DBP values by 12 months,
although a significant reduction was not observed at two
months. 2) CCBs did not significantly reduce the CAVI val-
ues, and there were no significant differences between the
baseline values and the values obtained at either two or 12
months after the start of treatment, whereas eplerenone re-
duced the CAVI values as early as two months after start of
treatment, and the significant reduction continued at 12
months, suggesting that the changes in the CAVI values in-
duced by eplerenone were not associated with the changes in
blood pressure.

The degree of arterial stiffness is commonly evaluated ac-
cording to the pulse wave velocity (PWV), which can be
monitored in a quantitative manner using a basically non-
invasive procedure. However, as the PWV is known to be
largely affected by blood pressure, it is not suitable for
evaluating the effects of anti-hypertensive medications on ar-
terial stiffness. In order to address this issue, the CAVI was
developed as an indicator of arterial stiffness based on pa-
rameters that are independent of blood pressure at the time of
measurement (17-19). We herein demonstrated that the
CAVI values decreased at two months after the start of
eplerenone treatment, while no significant changes were ob-
served in either the SBP or DBP values. In addition, there
were no associations between the changes in blood pressure
and the changes in the CAVI values. These results suggest
that treatment with eplerenone improves the CAVI, inde-
pendent of any effects on blood pressure.

In the present study, we recruited patients with uncon-
trolled hypertension even under baseline treatment with anti-
hypertensive drugs. It is likely that these patients would
have progressed to the advanced stage of atherosclerosis.
Suzuki et al. (20) reported that treatment with eplerenone re-
duces the development of atherosclerosis lesions by attenuat-

Changes in the plasma BNP levels

Fig. 4 shows the changes in the plasma BNP levels. In
Group C, the plasma BNP levels did not change signifi-
cantly, from 44.4 ± 39.4 pg/mL to 42.1 ± 35.6 pg/mL at
baseline at two months and 51.3 ± 50.8 pg/mL at 12 months
(p=NS, respectively). In Group E, the plasma BNP levels
also did not decrease significantly at two months, from 56.0
± 58.0 pg/mL at baseline to 45.9 ± 56.9 pg/mL (p=NS),
whereas a significant decrease to 36.1 ± 32.6 pg/mL was
observed at 12 months (p<0.01).

Changes in the serum creatinine and potassium levels

The changes in the serum creatinine and potassium levels
during the study period are shown in Table 3. Although the
serum creatinine concentrations increased significantly, no
patients displayed an abnormal serum creatinine level over
the upper limit of the normal range.

Discussion

The major findings of this study are as follows: 1) CCBs
reduced both the SBP and DBP values as early as at two
months after the beginning of treatment and continued to
show an effect at 12 months, whereas eplerenone gradu-
ally reduced both the SBP and DBP values by 12 months,
although a significant reduction was not observed at two
months. 2) CCBs did not significantly reduce the CAVI val-
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duces the development of atherosclerosis lesions by attenuat-
Recombinant human growth hormone (rhGH) may also occur in humans. In addition, many reports have shown that DM is a risk factor or progressive atherosclerosis. In the current study, there were more DM patients in Group E than in Group C (p<0.05). Furthermore, statins have been reported to inhibit atherosclerosis. In the present cohort, more patients in Group C used statins than in Group E (p<0.01). Therefore, atherosclerosis may have been more severe in the DM patients with eplerenone added to the basal therapy compared with the group with an increase in the Ca channel antagonist or a new Ca channel antagonist added to the basal therapy.

Table 3. The Changes in the Serum Creatinine and Potassium Level.

<table>
<thead>
<tr>
<th></th>
<th>Cr mg/dL</th>
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<tbody>
<tr>
<td></td>
<td>pre</td>
<td>2M</td>
<td>12M</td>
</tr>
<tr>
<td>Group C</td>
<td>0.85±0.21</td>
<td>0.85±0.20</td>
<td>0.83±0.20</td>
</tr>
<tr>
<td>Group E</td>
<td>0.77±0.23</td>
<td>0.83±0.21</td>
<td>0.86±0.24</td>
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</table>

<table>
<thead>
<tr>
<th></th>
<th>K mEq/L</th>
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<tbody>
<tr>
<td></td>
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<td></td>
<td></td>
</tr>
<tr>
<td>Group C</td>
<td>4.23±0.30</td>
<td>4.33±0.44</td>
<td>4.16±0.24</td>
</tr>
<tr>
<td>Group E</td>
<td>4.24±0.35</td>
<td>4.23±0.34</td>
<td>4.36±0.37</td>
</tr>
</tbody>
</table>

* p<0.05: compared with the baseline data

Cr: serum creatinine level
K: serum potassium level
Group E: the hypertensive patients with eplerenone added to the basal therapy
Group C: the hypertensive patients with an increase in the Ca channel antagonist or a new Ca channel antagonist added to the basal therapy

**Figure 3.** Relationships between the changes in the blood pressure and CAVI values. a: Relationship between the changes in the systolic blood pressure and CAVI values at two months after treatment. b: Relationship between the changes in the systolic blood pressure and CAVI values at 12 months after treatment. c: Relationship between the changes in the diastolic blood pressure and the CAVI values at two months after treatment. d: Relationship between the changes in the diastolic blood pressure and CAVI values at 12 months after treatment. Correlations between the changes in the SBP and CAVI values at two months (2M) and 12 months (12M) and correlations between the changes in the DBP and CAVI values at two months (2M) and 12 months (12M). A linear regression analysis was conducted to assess the two parameters, and Pearson correlation coefficients were calculated.

**Table 3.** The Changes in the Serum Creatinine and Potassium Level.

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<td>0.83±0.20</td>
</tr>
<tr>
<td>Group E</td>
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<td>0.83±0.21</td>
<td>0.86±0.24</td>
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<thead>
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<th></th>
<th>K mEq/L</th>
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</tr>
<tr>
<td>Group C</td>
<td>4.23±0.30</td>
<td>4.33±0.44</td>
<td>4.16±0.24</td>
</tr>
<tr>
<td>Group E</td>
<td>4.24±0.35</td>
<td>4.23±0.34</td>
<td>4.36±0.37</td>
</tr>
</tbody>
</table>

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Cr: serum creatinine level
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Group E: the hypertensive patients with eplerenone added to the basal therapy
Group C: the hypertensive patients with an increase in the Ca channel antagonist or a new Ca channel antagonist added to the basal therapy

**Figure 4.** Changes in the plasma BNP levels. The data are presented as the mean±standard deviation. * statistically significant difference from the baseline value. Group E: hypertensive patients who received eplerenone in addition to their baseline therapy. Group C: hypertensive patients treated with an increased dose of a Ca channel blocker or the addition of a new Ca channel blocker to their baseline therapy.
likely to advance in Group E than in Group C in this study. Hence, the current results are particularly important, in that add-on eplerenone successfully reduced the incidence of atherosclerosis or restored the patient’s arteries to a nearly normal condition, even in those with advanced atherosclerosis.

The mechanisms underlying these effects are still not clear at present. Increased arterial stiffness is known to be closely related to arteriosclerosis (21, 22), which is characterized by reduced arterial compliance (i.e., reduced elasticity of the arteries) due to increased fibrosis, the loss of elastic fibers, and extensive vessel wall calcification (23). It is thus possible that eplerenone may directly act on the vascular wall to attenuate these processes, independent of its blood pressure-lowering actions. Previous studies have also shown that aldosterone is pro-fibrotic and its receptor antagonist, eplerenone, attenuates the progression of fibrosis in various tissues including the heart and arteries (8, 9).

In this study, the plasma BNP levels decreased after treatment with eplerenone. This effect is similar to previous findings (24–26). Although the current patients did not clinically present with symptoms of overt heart failure, the present findings suggest that eplerenone may help to prevent the future progression of heart failure in such patients.

The applied dose of eplerenone merits was discussed. In this study, we included patients who received 50 mg of eplerenone; however, it remains unclear what dose of eplerenone is required to improve arterial stiffness. Based on the present results, eplerenone appears to be highly tolerable in severely hypertensive patients with a normal serum creatinine level; however, MR blockers are known to induce hyperkalemia (2–4). It is thus necessary to carefully monitor patients for the onset of hyperkalemia and elevation of the creatinine level when administering eplerenone. The application of a lower dose, such as 25 mg, may still be useful, and further studies should therefore be performed to determine the lowest dose that provides benefits.

In this study, we treated the patients with L-type CCBs, such as nifedipine and amlodipine. Recent studies have suggested that other CCBs, including L/N-type CCBs and L/T-type CCBs, inhibit aldosterone synthesis (27, 28); therefore, future analyses using these types of CCBs may show different findings in terms of arterial stiffness.

In conclusion, the blood pressure-lowering actions of eplerenone are relatively lower than those of CCBs in patients with uncontrolled hypertension. However, in this study, the degree of arterial stiffness, as evaluated according to the CAVI, rapidly improved following treatment with eplerenone, independent of its blood pressure-lowering effects. The administration of combination therapy with eplerenone and other anti-hypertensive drugs is expected to improve the degree of arterial stiffness, even in patients with uncontrolled hypertension.

The major limitations of this study are that a small number of patients were included and we did not measure or evaluate several markers of arterial stiffness and/or inflammation. In addition, the patients’ characteristics were not adjusted for in the analysis, which may have biased the outcomes. Therefore, additional larger studies are needed to confirm our results.

### Conclusion

The present findings indicate that treatment with a selective MR blocker, eplerenone, is superior to CCBs in terms of improving arterial stiffness. In the current study, the addition of eplerenone to the patients’ baseline medications improved the degree of arterial stiffness as early as at two months after the beginning of treatment, independent of the blood-lowering actions of this drug in patient with uncontrolled hypertension. We have no conflicts of interest or any relationships with industry members with respect to this study.

### The authors state that they have no Conflict of Interest (COI).

### References


