Effects of Angiotensin II–Receptor Blockers on Soluble Cell Adhesion Molecule Levels in Uncomplicated Systemic Hypertension: An Observational, Controlled Pilot Study in Taiwanese Adults*

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ABSTRACT

Background: Controversy exists as to whether individuals with hypertension without risk factors for atherosclerosis (eg, diabetes mellitus, dyslipidemia, obesity) have elevated levels of cell adhesion molecules (CAMs).

Objective: The aim of this study was to determine whether (1) levels of soluble CAMs (sCAMs) (soluble E-selectin [sE-selectin], soluble intercellular adhesion molecule-1 [sICAM-1], soluble vascular cell adhesion molecule-1 [sVCAM-1], and von Willebrand factor [vWF]) are elevated in Taiwanese adults with uncomplicated essential hypertension without other risk factors; (2) CAM levels increase with severity (stage) of hypertension; and (3) monotherapy with the angiotensin II–receptor blocker (ARB) irbesartan modulates CAM expression in a subgroup of these patients.

Methods: This observational, controlled pilot study was conducted at the Hypertension Clinic, Department of Internal Medicine, Kaohsiung Medical University Hospital, Kaohsiung, Taiwan. Adult patients with uncomplicated essential hypertension without other risk factors (eg, diabetes mellitus, dyslipidemia, obesity) and normotensive controls were eligible. Blood pressure (BP) was determined using 24-hour ambulatory BP monitoring (ABPM) in all participants, and the staging of hypertension was classified based on criteria in The Seventh Report of the Joint National Committee on Prevention, Detection, Evaluation, and Treatment of High Blood Pressure (normotensive, prehypertension, stage I hypertension, and stage II hypertension). The sCAM levels and
24-hour ABPM were measured before and after 8 weeks of open-label irbesartan monotherapy in a subgroup of the patients with hypertension. Patients who had difficulty achieving the target BP values on irbesartan monotherapy were treated with combination therapy (2 or 3 antihypertensive agents); levels of sCAMs were not measured in these patients. Plasma levels of sE-selectin, the sCAMs, and vWF were measured using enzyme-linked immunosorbent assay.

**Results:** The study comprised 61 patients with uncomplicated essential hypertension (33 men and 28 women; mean [SD] age, 51 [12] years) and 17 normotensive controls (11 men, 6 women; mean [SD] age, 52 [11] years). The mean (SD) dose of irbesartan was 243 (63) mg. Hypertensive patients had significantly higher circulating levels of sICAM-1 compared with normotensive controls ($P = 0.009$). No significant differences in levels of sVCAM-1, sE-selectin, or vWF were found between hypertensive patients and controls. The mean sICAM-1 level was significantly higher in the prehypertensive patients compared with normotensive controls ($P = 0.03$). The mean sE-selectin level was significantly higher in the patients with stage I hypertension compared with the prehypertensive group ($P = 0.01$). The 18 patients given 8 weeks of irbesartan monotherapy showed a significant decrease from baseline in systolic and diastolic BP (both, $P = 0.001$) and sE-selectin ($P = 0.006$), but not in sVCAM-1 or sICAM. Forty-three patients did not reach target BP on irbesartan monotherapy and thus were treated with combination therapy.

**Conclusions:** Based on the results of this observational, controlled pilot study in Taiwanese patients, we suggest that ARB therapy, in addition to reducing BP, has the potential to suppress CAM expression and to improve endothelial dysfunction in hypertension. (Curr Ther Res Clin Exp. 2005;66:181-194) Copyright © 2005 Excerpta Medica, Inc.

**Key words:** soluble cell adhesion molecule, ambulatory blood pressure monitoring, systemic hypertension, angiotensin II–receptor blockers.

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**INTRODUCTION**

Hypertension is one of the main risk factors for cardiovascular disease and atherosclerosis. The formation of atherosclerotic lesions and subsequent development of coronary heart disease (CHD) result from the activation and expression of cell adhesion molecules (CAMs).$^1$ Soluble CAMs (sCAMs), which lack cytoplasmic- and membrane-spanning domains, are present in circulation.$^2$ Little is known about cell-surface shedding and clearance of these molecules; however, their levels in serum and plasma can be readily determined,$^2,^3$ making clinical investigation possible.$^3,^4$

Because the expression of CAMs is tightly regulated, uncontrolled cell immigration is avoided.$^5$ Consequently, the levels of CAMs in circulation may reflect endothelial inflammation/activation.$^6-^8$

Previous studies have demonstrated that the soluble isoforms of intercellular adhesion molecule-1 (sICAM-1), vascular cell adhesion molecule-1 (sVCAM-1),
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and E-selectin (sE-selectin) are present in the circulation and elevated in idiopathic pulmonary fibrosis,\textsuperscript{9} diabetes mellitus,\textsuperscript{10} dyslipidemia,\textsuperscript{6} acute ischemic cerebral infarction,\textsuperscript{11} CHD\textsuperscript{12-14} and its risk factors (eg, obesity), and atherosclerosis.\textsuperscript{14-19}

However, controversy exists as to whether individuals with hypertension without other risk factors for atherosclerosis have elevated levels of CAMs.\textsuperscript{16,20-24} Moreover, even in population-based studies, the relationships between CAMs and blood pressure (BP) are inconsistent.\textsuperscript{19,25-27}

The aim of this study was to determine whether (1) levels of sCAMs (sE-selectin, sICAM-1, sVCAM-1, and von Willebrand factor [vWF]) are elevated in Taiwanese adults with uncomplicated essential hypertension without other risk factors; (2) CAM levels increase with severity (stage) of hypertension; and (3) monotherapy with the angiotensin II-receptor blocker (ARB) irbesartan modulates CAM expression in a subgroup of these patients.

**PATIENTS AND METHODS**

**Study Participants**

Taiwanese patients aged ≥18 years with uncomplicated essential hypertension without other risk factors for atherosclerosis (eg, diabetes mellitus, dyslipidemia, obesity) and healthy volunteers (normotensive control group) were enrolled in the study. All participants were recruited for this observational, controlled pilot study from the Hypertension Clinic, Department of Internal Medicine, Kaohsiung Medical University Hospital, Kaohsiung, Taiwan. The study was approved by the ethics committee at the hospital, and all eligible patients gave verbal informed consent.

Hypertensive patients were enrolled after 2 clinical visits at which diastolic BP (DBP) was >95 mm Hg as measured using a mercury sphygmomanometer (REX, Tokyo, Japan). Patients with hypertension receiving antihypertensive agents were asked to discontinue medication for 2 weeks before entry. Normotensive subjects were eligible if they had no history of cardiac disease and had normal cardiac function, as assessed using cardiac ultrasonography (HP SONOS 5500 Image System, Hewlett-Packard Development Company, LP, Andover, Massachusetts). They were excluded if they were receiving medical therapy.

Hypertensive individuals were excluded from the study if they had diabetes mellitus, stroke, elevated (>1.3 mg/dL) serum creatinine levels, or abnormal findings on resting electrocardiography. Additional exclusion criteria were serious concomitant disease (eg, autoimmune disease), recent acute infection, or inflammatory disease. Patients who were pregnant, possibly pregnant, or breastfeeding also were excluded.

**Laboratory Testing and Clinical Assessments**

On the morning of the study day, after a 12-hour overnight fast, all hypertensive patients and controls underwent thorough physical examination and fast-
ing blood chemistry analysis (urinalysis, blood urea nitrogen measurement, serum lipid profile, and plasma glucose and serum creatinine measurements). Blood samples were also collected by a laboratory technician for the determination of CAM levels. Lipids and lipoproteins were determined using electrophoresis. Low-density lipoprotein cholesterol levels were calculated using the Friedewald formula. Other examinations included chest radiography (posteroanterior view); electrocardiography; M-mode and 2-dimensional cardiac ultrasonography; and studies to exclude secondary hypertension, diabetes mellitus, and renal disease.

To determine whether monotherapy with irbesartan modulates the expression of these sCAMs in relation to systemic hypertension, a subset of patients with hypertension enrolled in the late stage of this project received open-label irbesartan monotherapy, 150 to 300 mg QD (depending on BP) for 8 weeks. In these patients, blood chemistry analysis and measurement of sCAMs were repeated after treatment. In patients receiving irbesartan monotherapy, the dose was titrated to a maximum of 300 mg QD regardless of whether target BP was achieved.

**Ambulatory Blood Pressure Monitoring**

BP was measured using 24-hour ambulatory BP monitoring (ABPM). On the morning of the study day, after blood sampling, each participant underwent ABPM (model 90207 sphygmomanometer, SpaceLabs Medical, Inc., Redmond, Washington). This portable device uses a standard cuff placed around the left upper arm and inflated at regular intervals (every 30 minutes between 6 AM and 6 PM and every hour between 6 PM and 6 AM). Systolic BP (SBP) and DBP were estimated using oscillometry. At the end of the 24-hour monitoring period, BP measurement and heart rates were downloaded to a microcomputer for further analysis. Recordings showing an inconsistent increase or decrease in SBP or DBP of >50 mm Hg without changes in heart rate or a calculated pulse pressure <10 mm Hg were excluded from the analysis. Hypertension was defined as sitting office SBP/DBP >140/>90 mm Hg and a mean 24-hour ambulatory BP ≥135/≥85 mm Hg. Patients with prehypertension or stage I or II hypertension were enrolled. The staging of hypertension was classified using the criteria in The Seventh Report of the Joint National Committee on Prevention, Detection, Evaluation, and Treatment of High Blood Pressure, as follows: prehypertension (SBP 120–139 mm Hg or DBP 80–89 mm Hg), stage I hypertension (SBP 140–159 mm Hg or DBP 90–99 mm Hg), and stage II hypertension (SBP ≥160 mm Hg or DBP ≥100 mm Hg). Mean 24-hour SBP <120 mm Hg or DBP <80 mm Hg was defined as normotensive. However, when a patient's SBP and DBP fell into different categories, the patient was classified in the higher category. In patients receiving irbesartan monotherapy, irbesartan 150 mg/d was given. This dose could be doubled at week 4 if DBP was >90 mm Hg or DBP was reduced by <10 mm Hg.
Measurement of Soluble Cell Adhesion Molecule Levels

On the morning of the study day, blood samples for determining circulating levels of sICAM-1, sVCAM-1, sE-selectin, and vWF were collected after a 12-hour overnight fast with minimal venostasis. Plasma levels of sCAMs and sE-selectin were determined in duplicate using a monoclonal antibody–based enzyme-linked immunosorbent assay (ELISA) kit (R&D Systems, Minneapolis, Minnesota). Plasma vWF level was measured using the ELISA kit, which contained specific rabbit-human vWF antibodies.

Statistical Analysis

Between-group differences were analyzed using the Mann-Whitney $U$ test. The differences between baseline and posttreatment values were analyzed using the Wilcoxon rank sum test. The correlation between 24-hour SBP/DBP and sCAMs was assessed using the Spearman rank correlation test. All values are reported as mean (SD). $P < 0.05$ was considered significant. All statistical analyses were performed using SPSS version 11.0 (SPSS Inc., Chicago, Illinois).

RESULTS

Study Population

Eighty-five individuals were enrolled in the study; the data from 7 of these were excluded from the study—4 because of diabetes mellitus and 3 because serum creatinine level was >2.0 mg/dL. Thus, 78 individuals completed the study, including 61 patients (78.2%) with uncomplicated essential hypertension (33 men, 28 women; mean [SD] age, 51 [12] years) and 17 normotensive controls (21.8%) (11 men, 6 women; mean [SD] age, 52 [11] years) (Table 1).

Ambulatory Blood Pressure

Mean (SD) 24-hour SBP/DBP values were significantly higher in the hypertensive patients compared with normotensive controls (143 [15]/91 [10] mm Hg vs 119 [8]/75 [7] mm Hg; both, $P < 0.001$). No significant between-group differences in fasting plasma glucose level or in serum levels of creatinine, cholesterol, or triglycerides were observed (Table 1).

Of the 61 hypertensive patients, 20 (32.8%) were classified as having prehypertension (mean [SD] 24-hour SBP/DBP, 131 [5]/83 [6] mm Hg); 27 (44.3%), as stage I hypertension (142 [10]/96 [6] mm Hg); and 14 (23.0%), as stage II hypertension (162 [13]/103 [10] mm Hg).

Soluble Cell Adhesion Molecule Levels

Compared with the normotensive group, the hypertensive group had significantly higher levels of sICAM-1 (318 [118] vs 236 [61] ng/mL; $P = 0.009$) (Table II). There were no significant differences in sVCAM-1, sE-selectin, or vWF levels between patients classified in any hypertensive stage and the control group.
Table I. Baseline demographic and clinical characteristics of the study population (N = 78).

<table>
<thead>
<tr>
<th>Characteristic</th>
<th>Hypertensive (n = 61)</th>
<th>Control (n = 17)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Age, y</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Mean (SD)</td>
<td>51 (12)</td>
<td>52 (11)</td>
</tr>
<tr>
<td>Sex, no. (%)</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Male</td>
<td>33 (54)</td>
<td>11 (65)</td>
</tr>
<tr>
<td>Female</td>
<td>28 (46)</td>
<td>6 (35)</td>
</tr>
<tr>
<td>24-h Ambulatory BP, mean (SD), mm Hg</td>
<td></td>
<td></td>
</tr>
<tr>
<td>SBP</td>
<td>143 (15)*</td>
<td>119 (8)</td>
</tr>
<tr>
<td>DBP</td>
<td>91 (10)*</td>
<td>75 (7)</td>
</tr>
<tr>
<td>Hypertension stage</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Prehypertension</td>
<td></td>
<td></td>
</tr>
<tr>
<td>No. of patients (%)</td>
<td>20 (33)</td>
<td>–</td>
</tr>
<tr>
<td>SBP, mean (SD), mm Hg</td>
<td>131 (5)</td>
<td>–</td>
</tr>
<tr>
<td>DBP, mean (SD), mm Hg</td>
<td>83 (6)</td>
<td>–</td>
</tr>
<tr>
<td>Stage I</td>
<td></td>
<td></td>
</tr>
<tr>
<td>No. of patients (%)</td>
<td>27 (44)</td>
<td>–</td>
</tr>
<tr>
<td>SBP, mean (SD), mm Hg</td>
<td>142 (10)</td>
<td>–</td>
</tr>
<tr>
<td>DBP, mean (SD), mm Hg</td>
<td>96 (6)</td>
<td>–</td>
</tr>
<tr>
<td>Stage II</td>
<td></td>
<td></td>
</tr>
<tr>
<td>No. of patients (%)</td>
<td>14 (23)</td>
<td>–</td>
</tr>
<tr>
<td>SBP, mean (SD), mm Hg</td>
<td>162 (13)</td>
<td>–</td>
</tr>
<tr>
<td>DBP, mean (SD), mm Hg</td>
<td>103 (10)</td>
<td>–</td>
</tr>
<tr>
<td>Biochemistry, mean (SD), mg/dL</td>
<td></td>
<td></td>
</tr>
<tr>
<td>FPG</td>
<td>97 (17)</td>
<td>101 (11)</td>
</tr>
<tr>
<td>Creatinine</td>
<td>1.0 (0.3)</td>
<td>0.9 (0.2)</td>
</tr>
<tr>
<td>TC</td>
<td>201 (35)</td>
<td>193 (38)</td>
</tr>
<tr>
<td>LDL-C</td>
<td>134 (29)</td>
<td>131 (38)</td>
</tr>
<tr>
<td>VLDL-C</td>
<td>32 (19)</td>
<td>26 (14)</td>
</tr>
<tr>
<td>HDL-C</td>
<td>41 (10)</td>
<td>41 (10)</td>
</tr>
<tr>
<td>TG</td>
<td>116 (55)</td>
<td>107 (60)</td>
</tr>
</tbody>
</table>

BP = blood pressure; SBP = systolic blood pressure; DBP = diastolic blood pressure; FPG = fasting plasma glucose; TC = total cholesterol; LDL-C = low-density lipoprotein cholesterol; VLDL-C = very low-density lipoprotein cholesterol; HDL-C = high-density lipoprotein cholesterol; TG = triglycerides.

*P < 0.001 versus control group.
Table II. Baseline mean (SD) plasma cell adhesion molecule levels in the study population (N = 78).

<table>
<thead>
<tr>
<th>Component</th>
<th>Hypertensive (n = 61)</th>
<th>Control (n = 17)</th>
</tr>
</thead>
<tbody>
<tr>
<td>slCAM-1, ng/mL</td>
<td>318 (118)*</td>
<td>236 (61)</td>
</tr>
<tr>
<td>sVCAM-1, ng/mL</td>
<td>565 (243)</td>
<td>523 (130)</td>
</tr>
<tr>
<td>sE-selectin, ng/mL</td>
<td>51.0 (23.7)</td>
<td>38.7 (16.2)</td>
</tr>
<tr>
<td>vWF, mU/mL</td>
<td>790 (182)</td>
<td>770 (238)</td>
</tr>
</tbody>
</table>

slCAM-1 = soluble intercellular adhesion molecule-1; sVCAM-1 = soluble vascular cell adhesion molecule-1; sE-selectin = soluble E-selectin; vWF = von Willebrand factor.

*P = 0.009 versus control group.

Compared with normotensive controls, the patients classified as prehypertensive had significantly higher levels of slCAM-1 (P = 0.03); however, no significant differences in slCAM-1 level were found between prehypertensive patients and those with stage I and II hypertension (Figure 1A).

The levels of sE-selectin were significantly higher in patients with stage I hypertension compared with the prehypertensive group (P = 0.01), but there were no differences in sE-selectin levels between patients with stage I and II hypertension (Figure 1B). No differences in levels of sVCAM-1 and vWF were observed between groups by hypertension stage.

Correlation Analysis

With hypertensive patients and normotensive controls considered together as a group, the pooled scatter plots of slCAM-1 and sE-selectin versus mean 24-hour SBP and DBP are shown in Figure 2. By regression analysis, both slCAM-1 (r = 0.295 and P = 0.009; Figure 2A) and sE-selectin (r = 0.333 and P = 0.003; Figure 2B) showed positive correlations with mean 24-hour SBP. Although no correlation between slCAM-1 versus mean 24-hour DBP was noted (Figure 2C), there was a positive correlation between sE-selectin (r = 0.291, P = 0.010) and mean 24-hour DBP (Figure 2D). In contrast, sVCAM-1 and vWF were not correlated with either mean 24-hour SBP or DBP (data not shown).

Effects of Angiotensin Receptor Blockade Therapy

In the 18 patients who received 8 weeks of monotherapy with the ARB irbesartan, the mean (SD) dose was 243 (63) mg. The mean 24-hour SBP/DBP decreased significantly from pretreatment to week 8 (142 [14]/88 [9] vs 125 [1]/78 [8] mm Hg; both, P < 0.001). sE-selectin levels also decreased significantly (55.3 [29.0] vs 44.2 [28.1] ng/mL; P = 0.006). No significant changes in the levels of slCAM-1, sVCAM-1, or vWF were seen in the irbesartan-treated patients (Table III).
Figure 1. Comparison of plasma levels of (A) soluble intercellular adhesion molecule-1 (sICAM-1) and (B) soluble E-selectin (sE-selectin) between each stage of hypertension and with normotensive controls. *P = 0.03 versus normotensive controls; †P = 0.01 versus prehypertension group.
Figure 2. Correlation between mean 24-hour systolic blood pressure (SBP) and (A) soluble intercellular adhesion molecule-1 (sICAM-1) and (B) soluble E-selectin (sE-selectin) (N = 78).

(continued)
Figure 2. (Continued) Correlation between mean 24-hour diastolic blood pressure (DBP) and (C) soluble intercellular adhesion molecule-1 (sICAM-1) and (D) soluble E-selectin (sE-selectin) (N = 78).

C

D

\[ r = 0.221, P = 0.054 \]

\[ r = 0.291, P = 0.010 \]
Table III. Mean (SD) and ambulatory blood pressure (BP) and plasma cell adhesion molecule levels before and after irbesartan monotherapy for hypertension. *

<table>
<thead>
<tr>
<th>Parameter</th>
<th>Irbesartan (n = 18)</th>
<th>Control (n = 17)</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>Before</td>
<td>After</td>
</tr>
<tr>
<td>24-h Ambulatory BP, mm Hg</td>
<td></td>
<td></td>
</tr>
<tr>
<td>SBP</td>
<td>142 (14)</td>
<td>125 (11)</td>
</tr>
<tr>
<td>DBP</td>
<td>88 (9)</td>
<td>78 (8)</td>
</tr>
<tr>
<td>sICAM-1, ng/mL</td>
<td>298 (133)</td>
<td>275 (86)</td>
</tr>
<tr>
<td>sVCAM-1, ng/mL</td>
<td>504 (162)</td>
<td>484 (124)</td>
</tr>
<tr>
<td>sE-selectin, ng/mL</td>
<td>55.3 (29.0)</td>
<td>44.2 (28.1)</td>
</tr>
<tr>
<td>vWF, mU/mL</td>
<td>813 (190)</td>
<td>797 (177)</td>
</tr>
</tbody>
</table>

SBP = systolic BP; DBP = diastolic BP; sICAM-1 = soluble intercellular adhesion molecule-1; sVCAM-1 = soluble vascular cell adhesion molecule-1; sE-selectin = soluble E-selectin; vWF = von Willebrand factor.

* No significant between-group differences were found.
† P < 0.001 versus before therapy.
‡ P = 0.006 versus before therapy.

DISCUSSION

Based on the results of this study, we suggest that even mildly elevated BP (pre-hypertension and stage I hypertension) is sufficient to activate CAM expression, particularly sICAM-1 and sE-selectin. An increase in severity (stage) of hypertension was not associated with a change in the expression of the 2 CAMs. This observation is, at least in part, consistent with those in the study by Preston et al., in which the strong positive correlation between sICAM-1, sVCAM-1, and vWF levels versus BP in patients with normotension or mild hypertension was not found in patients with severe hypertension (mean SBP/DBP, 195 [26]/127 [7] mm Hg).

The mechanisms by which systemic hypertension leads to an increase in levels of particular CAMs is not fully understood. Hemodynamics (e.g., shear stress, mechanical stress, stretching, and humoral changes) play an important role in endothelial function. Clinical interest regarding sCAMs is increasing due to their association with atherosclerosis and their possible use as biochemical markers of atherogenic risk.

Systolic hypertension is more likely to induce hypertension-related endothelial damage and dysfunction than is diastolic hypertension. An association between SBP and sICAM-1 and sE-selectin, and DBP and sE-selectin was observed in our study. These relationships may help to explain why SBP is a better predictor of cardiovascular events than DBP, particularly in elderly (age, >65 years) hypertensive patients.

We observed a linear association between sE-selectin and SBP and DBP. This finding is in agreement with some but not all previous studies. These
discrepancies may reflect the different characteristics of different ethnic groups. The levels of sE-selectin might be related to vascular damage and might be a marker for endothelial damage.\textsuperscript{34}

Two months of open-label irbesartan monotherapy in a subgroup of 18 patients resulted in a decrease in sE-selectin level and BP. It is still unclear whether ARB therapy modulates the expression of sCAMs in hypertensive individuals and its mechanism. In addition to their antihypertensive effect, the ARBs telmisartan and irbesartan also function as partial peroxisome-proliferator–activated receptor–gamma agonists.\textsuperscript{35,36} In the present study, however, we did not find a correlation between reduced SBP and DBP and changes in sE-selectin level with irbesartan monotherapy, which might suggest that the effect of ARBs on sE-selectin and/or CAM expression in hypertension is independent of their BP-lowering effect. We suggest that ARB therapy, in addition to reducing BP, has the potential to suppress CAM expression and improve endothelial dysfunction.

This preliminary study had some limitations. Due to difficulty in achieving target BP with monotherapy, combination antihypertensive therapy (2 or 3 drugs) was needed in 43 hypertensive patients, which reduced the subgroup receiving irbesartan monotherapy to 18 patients. Because the CAM levels were not measured in these 43 patients, we could not compare them between different classes of antihypertensive agents. Additional limitations of our study included the relatively small number of normotensive subjects compared with the number of hypertensive patients and the short treatment period, which limited the power of our study to detect changes in CAM levels after therapy.

A long-term, randomized, blinded, placebo-controlled follow-up ARB study is warranted.

CONCLUSION
Based on the results of this observational, controlled pilot study in Taiwanese patients, we suggest that ARB therapy, in addition to reducing BP, has the potential to suppress CAM expression and improve endothelial dysfunction in hypertension.

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