Endothelial Function Is Impaired in Patients Receiving Antihypertensive Drug Treatment Regardless of Blood Pressure Level

FMD-J Study (Flow-Mediated Dilation Japan)

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Abstract—Hypertension is associated with endothelial dysfunction. Blood pressure significantly correlates with endothelial function in antihypertensive drug-naive subjects. The purpose of this study was to determine whether treatment status affects the relationship between blood pressure and endothelial function. We measured flow-mediated vasodilation (FMD) in 2297 subjects, including 1822 antihypertensive drug-naive subjects and 475 treated hypertensive patients. FMD significantly decreased in relation to increase in systolic blood pressure (8.2±3.1% in subjects with systolic blood pressure of <120 mm Hg, 7.5±2.8% for 120–129 mm Hg, 7.1±2.8% for 130–139 mm Hg, and 6.7±2.6% for ≥140 mm Hg; P<0.001). Systolic blood pressure was independently associated with FMD in untreated subjects. In contrast, there was no significant relationship between systolic blood pressure and FMD in treated hypertensive patients (4.6±3.1% in treated hypertensives with systolic blood pressure of <120 mm Hg, 4.8±2.7% for 120–129 mm Hg, 4.9±2.8% for 130–139 mm Hg, and 4.5±2.3% for ≥140 mm Hg; P=0.77). Propensity score matching analysis revealed that the prevalence of endothelial dysfunction defined as FMD of less than the division point for the lowest tertile, and the middle tertile of FMD was significantly higher in treated hypertensive patients than in untreated subjects in all systolic blood pressure categories. Endothelial function

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Endothelial dysfunction is established in the initial step in the pathogenesis of atherosclerosis and plays a critical role in the development and maintenance of atherosclerosis.[1–3] In addition, endothelial function has been shown to be an independent predictor of cardiovascular events.[4] Recently, measurement of flow-mediated vasodilation (FMD) of the brachial artery has become the most widely used technique for the assessment of endothelial function in humans.[5–8]

Hypertension is associated with endothelial dysfunction.[9–11] Previous studies have shown that blood pressure significantly correlates with FMD and is independently associated with FMD in subjects without antihypertensive drug treatment, indicating that endothelial function is progressively impaired as blood pressure increases in antihypertensive drug-naive subjects.[6,12,13] Lowering blood pressure with antihypertensive drugs has been shown to improve or restore endothelial function in patients with essential hypertension.[10,14–16] However, there is little information on the relationship between blood pressure and FMD in patients receiving antihypertensive drug treatment. In addition, to our knowledge, there has been no study in which the difference in endothelial function assessed by FMD between treated and untreated subjects with similar levels of blood pressure was investigated.

We, therefore, measured FMD in subjects with and without antihypertensive drug treatment to determine whether treatment status affects the relationship between blood pressure and endothelial function.

Methods

Subjects

This study was conducted in subjects from the FMD-J study (Flow-Mediated Dilation Japan).[17] The FMD-J study was a prospective multicenter study conducted at 22 university hospitals and affiliated clinics in Japan to examine the usefulness of FMD assessment for the management of patients at risk for cardiovascular disease.[17] Detailed information on the subjects and protocol of the FMD-J study is publicly available.[17] In brief, the FMD-J study included 3 study arms: study A, study B, and study C. Patients aged 20 to 74 years who had been diagnosed as having coronary artery disease were enrolled in study A, patients aged 20 to 74 years with controlled hypertension or diabetes mellitus who had been receiving antihypertensive or antidiabetic treatment for at least 6 months were enrolled in study B, and subjects who underwent annual health checkups as mandated by the company were enrolled in study C. Some of the data from the FMD-J study were previously reported elsewhere.[18] FMD was measured using UNEXEF18G (UNEX Co., Nagoya, Japan), an ultrasound instrument specialized for FMD measurement. All of the sonographers specialized in FMD measurement at the participating institutions received training for a standard protocol of FMD measurement and training for scanning and analysis of the record at the core laboratory located in Tokyo Medial University. All recordings of brachial artery scans obtained during the measurement of FMD were sent from the participant institutions to the core laboratory in Tokyo Medical University by USB flash drives and were individually analyzed by a well-experienced reader at the core laboratory without any information about the patients. The ethical committees of the participating institutions approved the study protocol. The study was executed in accordance with the Good Clinical Practice guidelines. Informed consent for participation in the study was obtained from all subjects.

A total of 4162 Japanese adults were enrolled from the FMD-J study. Subjects with unclear images of the brachial artery interfaces (n=494), subjects who had been previously diagnosed with cardiovascular disease (n=641), subjects who were being treated with lipid-lowering or glucose-lowering drugs (n=494), subjects with C-reactive protein levels >10 mg/dL at the time of enrollment (n=9), and subjects with missing information on age (n=1), blood pressure (n=18), smoking status (n=7), and antihypertensive drugs (n=201) were excluded. Finally, 2297 subjects were enrolled in this study. We defined smokers as those who were current smokers. Diagnosis of metabolic syndrome was made using Japanese definition proposed by the Committee to Evaluate Diagnostic Standards for Metabolic Syndrome.[19] Thus, metabolic syndrome was diagnosed by a combination of waist circumference of ≥85 cm in men and of ≥90 cm in women and ≥2 of the following 3 components: (1) systolic blood pressure ≥130 or 85 mm Hg, (2) triglycerides ≥1.7 mmol/L (150 mg/dL) or high-density lipoprotein cholesterol <1.03 mmol/L (40 mg/dL), and (3) fasting blood glucose ≥6.11 mmol/L (110 mg/dL).

Study Protocol

Subjects fasted the previous night and abstained from alcohol, smoking, caffeine, and antioxidant vitamins on the day of the FMD examination. The subjects were kept in the supine position in a quiet, dark, and air-conditioned room (constant temperature of 23°C–26°C) throughout the study. A 23-gauge polyethylene catheter was inserted into the left deep antecubital vein to obtain blood samples. FMD was measured at least 20 minutes after maintaining the supine position. The observers were blind to the form of examination.

Measurement of FMD

A high-resolution ultrasonography equipment specialized to measure FMD (UNEXEF18G, UNEX Co, Nagoya, Japan) was used to evaluate FMD. Additional details are available in the online-only Data Supplement. The intraclass correlation coefficient between each participating institutions and the core laboratory has been previously described.[18]

Measurement of Blood Pressure

Blood pressure was measured in accordance with the Japanese Society of Hypertension Guidelines for the Management of Hypertension in 2014.[20] In brief, blood pressure was measured in a sitting position by the auscultation method using a mercury sphygmomanometer and was performed 2×, and the mean value of 2 measurements was used for analysis. Blood pressure was measured and determined on the same day that the FMD measurement was performed.

Statistical Analysis

Results are presented as means±SD. All reported probability values were 2 sided, and a $P<0.05$ was considered statistically significant. Categorical variables were compared by means of the χ^2 test. Continuous variables were compared by using ANOVA with Bonferroni test for post hoc comparisons for multiple groups. Univariate linear regression analyses were performed to assess the relationships among the variables. Propensity score analysis was used to generate a set of matched cases (subjects with antihypertensive drug treatment) and controls (subjects without antihypertensive drug treatment). The propensity score was calculated for each patient on the basis of logistic regression analysis of the probability of taking antihypertensive drugs within groups stratified by systolic blood

pressure (<120 mm Hg, 120–129 mm Hg, 130–139 mm Hg, and ≥140 mm Hg) using clinical variables, including age, sex, body mass index, systolic blood pressure, diastolic blood pressure, heart rate, total cholesterol, triglycerides, high-density lipoprotein cholesterol, fasting glucose, current smoking (yes or no), and metabolic syndrome (yes or no). With these propensity scores, 2 well-matched groups based on clinical characteristics were created for comparison of the prevalence of endothelial dysfunction defined as FMD of <6.0%, the division point for the lowest tertile and the middle tertile of FMD in subjects without antihypertensive drug treatment. Multivariate regression analysis was performed to identify independent variables associated with FMD among risk factors and laboratory data, including 11 variables used for the propensity score matching except for diastolic blood pressure. The data were processed using the software package Stata version 9 (Stata Co., College Station, TX).

Results

Baseline Clinical Characteristics

The baseline clinical characteristics are summarized in Table 1. Of the 2297 subjects, 1824 (79.4%) were men and 473 (20.6%) were women. Mean systolic blood pressure was 127.5±15.7 mm Hg and mean diastolic blood pressure was 81.1±10.9 mm Hg. The mean value of FMD was 6.9±3.1%. Among all subjects, 1822 (79.3%) were untreated and 475 (20.7%) were being treated with antihypertensive drugs. Among the treated subjects, 65.2% were on calcium channel blockers, 68.6% were on angiotensin II receptor blockers or angiotensin-converting enzyme inhibitors, 15.2% were on β-blockers, and 29.3% were on diuretics. The mean number of prescribed antihypertensive drugs per patient was 1.8±0.9. Characteristics of the treated and untreated subjects are summarized in Table 1. FMD was significantly smaller in subjects with antihypertensive drug treatment than in those without treatment (4.7±2.7% versus 7.5±3.0%; $P<0.001$). The division point for the lowest tertile and middle tertile of FMD was 6.0% in subjects without antihypertensive drug treatment. Therefore, endothelial dysfunction was defined as FMD of <6.0%. The prevalence of endothelial dysfunction was significantly higher in subjects with antihypertensive drug treatment than in those without treatment (70.3% versus 33.3%; $P<0.001$).

Relationship Between Systolic Blood Pressure and FMD in Subjects Without Antihypertensive Drug Treatment

Subjects without antihypertensive drug treatment were categorized into 4 groups based on systolic blood pressure: <120 mm Hg, 120 to 129 mm Hg, 130 to 139 mm Hg, and ≥140 mm Hg. The clinical characteristics of untreated subjects categorized according to systolic blood pressure are summarized in Table 2. FMD decreased significantly in relation to increase in the systolic blood pressure categories (8.2±3.1%, 7.5±2.8%, 7.1±2.8%, and 6.7±2.6%; $P<0.001$; Figure). The prevalence of endothelial dysfunction increased significantly in relation to increase in the systolic blood pressure categories (24.4%, 32.8%, 38.6%, and 43.6%; $P<0.001$). Univariate regression analysis revealed that there was a significant negative correlation between systolic blood pressure and FMD in untreated subjects ($r=-0.22$; $P<0.001$; Table S1 in the online-only Data Supplement). Multivariate analysis revealed that systolic blood pressure was independently associated with FMD in untreated subjects (see Table S2).

Relationship Between Systolic Blood Pressure and FMD in Subjects With Antihypertensive Drug Treatment

Subjects with antihypertensive drug treatment were also categorized into 4 groups based on systolic blood pressure: <120 mm Hg, 120 to 129 mm Hg, 130 to 139 mm Hg, and ≥140 mm Hg. The clinical characteristics of treated subjects categorized according to systolic blood pressure are summarized in Table 3. There was no significant difference in FMD among the 4 groups categorized according to systolic blood pressure (4.6±3.1%, 4.8±2.7%, 4.9±2.8%, and 4.5±2.3%; $P=0.77$; Figure). There was also no significant difference in the prevalence of endothelial dysfunction among the 4 groups (68.6%, 69.1%, 70.3%, and 73.3%; $P=0.85$). Univariate regression analysis revealed that there was no significant correlation between systolic blood pressure and FMD in treated hypertensives ($r=-0.02$; $P=0.69$; Table S3).

Propensity score matching analysis was used to create matched pairs between treated and untreated subjects within categories stratified by systolic blood pressure (<120 mm Hg, 120–129 mm Hg, 130–139 mm Hg, and ≥140 mm Hg). The clinical characteristics of well-matched pairs between treated and untreated subjects in each systolic blood pressure category are summarized in Tables S4 through S7. The prevalence of endothelial dysfunction was significantly higher in subjects with antihypertensive drug treatment than in those without treatment in all systolic blood pressure categories without significant differences between the 2 groups with respect to clinical parameters, including blood pressure (67.7% versus 27.9%, $P<0.001$ in the <120 mm Hg category; 69.3% versus 50.7%, $P=0.02$ in the 120–129 mm Hg category; 66.1% versus 48.4%, $P=0.04$ in the 130–139 mm Hg category; 78.9% versus 44.2%, $P<0.001$ in the ≥140 mm Hg category; Tables S4–S7). FMD was significantly smaller in subjects with antihypertensive drug treatment than in those without treatment in all systolic blood pressure categories (4.8±3.0% versus 7.4±2.6%, $P<0.001$ in the <120 mm Hg category; 4.7±2.7% versus 6.3±2.6%, $P<0.001$ in the 120–129 mm Hg category; 5.1±2.7% versus 6.7±2.9%, $P=0.002$ in the 130–139 mm Hg category; 4.0±2.1% versus 6.3±2.2%, $P<0.001$ in the ≥140 mm Hg category; Tables S4–S7).

Relationship Between Number of Prescribed Antihypertensive Drugs and FMD in Subjects With Antihypertensive Drug Treatment

We next categorized subjects with antihypertensive drug treatment into 3 groups according to the number of prescribed antihypertensive drugs: 1, 2, and ≥3. The clinical characteristics of treated hypertensives categorized according to the number of antihypertensive drugs are summarized in Table S8. FMD was significantly smaller in subjects treated with ≥3 antihypertensive drugs than in those treated with 1 or 2 antihypertensive drugs (4.0±2.5% versus 4.8±2.8% and 4.9±2.7%; $P=0.04$, respectively; Figure S1). The prevalence of endothelial dysfunction was significantly higher in subjects treated with ≥3 antihypertensive drugs than in those treated with 1 or 2 antihypertensive drugs (82.1% versus 68.7% and 66.0%; $P=0.01$). Multivariate analysis revealed that not systolic blood pressure but the number of prescribed

Table 1. Clinical Characteristics of the Subjects

Variables	All Subjects (n=2297)	Antihypertensive Drug		*P* Value
		Untreated (n=1822)	Treated (n=475)	
Age, y	49.6±10.8	46.7±9.0	60.7±9.7	<0.001
Men, n (%)	1824 (79.4)	1534 (84.2)	290 (61.1)	<0.001
Body mass index, kg/m^2	23.1±3.1	22.8±3.0	24.4±3.4	<0.001
Systolic blood pressure, mm Hg	127.5±15.7	126.6±15.7	131.0±15.1	<0.001
Diastolic blood pressure, mm Hg	81.1±10.9	81.0±11.3	81.4±9.4	0.47
Heart rate, bpm	64.3±10.6	64.1±10.6	64.8±10.6	0.20
Total cholesterol, mmol/L	5.23±0.81	5.21±0.80	5.29±0.82	0.07
Triglycerides, mmol/L	1.30±0.82	1.26±0.79	1.45±0.92	<0.001
HDL cholesterol, mmol/L	1.55±0.40	1.56±0.40	1.50±0.41	0.004
Glucose, mmol/L	5.38±0.77	5.30±0.68	5.70±1.00	<0.001
Current smokers, n (%)	765 (33.3)	699 (38.4)	66 (13.9)	<0.001
Metabolic syndrome, n (%)	279 (12.1)	168 (9.2)	111 (23.4)	<0.001
Antihypertensive drug				
Calcium channel blockers, n (%)	310 (65.2)		310 (65.2)	
ARBs/ACEIs, n (%)	326 (68.6)		326 (68.6)	
β-Blockers, n (%)	72 (15.2)		72 (15.2)	
Diuretics, n (%)	139 (29.3)		139 (29.3)	
Aldosterone antagonists, n (%)	13 (2.7)		13 (2.7)	
No. of antihypertensive drugs			1.8±0.9	
Flow-mediated vasodilation, %	6.9±3.1	7.5±3.0	4.7±2.7	<0.001
Endothelial dysfunction, n (%)	941 (41.0)	607 (33.3)	334 (70.3)	<0.001

ACEI indicates angiotensin-converting enzyme inhibitor; ARB, angiotensin receptor blocker; and HDL, high-density lipoprotein.

antihypertensive drugs (≥3) was independently associated with FMD in treated hypertensives (Table S9).

Discussion

In the present study, we demonstrated that FMD decreased significantly in relation to increase in systolic blood pressure in subjects without antihypertensive drug treatment, whereas there was no significant relationship between systolic blood pressure and FMD in subjects with antihypertensive drug treatment. Endothelial function assessed by FMD was impaired regardless of the level of blood pressure achieved by treatment in hypertensives. We also demonstrated that the prevalence of endothelial dysfunction was significantly higher and that FMD was significantly smaller in subjects with antihypertensive drug treatment than in those without treatment although the blood pressure levels were comparable in the 2 groups in analysis using propensity score matching. In addition, not systolic blood pressure but the number of prescribed antihypertensive drugs was independently associated with FMD in treated hypertensives. To our knowledge, this is the first report showing the difference in association of blood pressure levels with FMD between treated and untreated subjects and showing that the number of prescribed antihypertensive agents required for the management of blood pressure is independently associated with FMD in treated hypertensives.

Previous studies have shown that blood pressure significantly correlates with FMD and is independently associated with FMD in subjects without antihypertensive drug treatment.[12,13] Although detailed clinical data were not shown in the report, investigators in the Framingham Heart Study reported that blood pressure significantly correlated with FMD and was independently associated with FMD in analyses excluding various subject subsets, including those taking antihypertensive agents, those taking lipid medications, those undergoing hormone replacement therapy, and those with prevalent cardiovascular disease, in a large community-based population.[6] Consistent with these previous observations, our results also showed that blood pressure significantly correlated with FMD and that systolic blood pressure was independently associated with FMD in a large number of well-characterized subjects without antihypertensive drug treatment. These findings suggest that endothelial function is progressively impaired as blood pressure increases and that the degree of endothelial dysfunction is related to the severity of hypertension in subjects without antihypertensive drug treatment. Although a significant relationship between blood pressure and endothelial function in antihypertensive drug-naive subjects has been demonstrated, there is little information on the relationship between blood pressure and endothelial function in patients with hypertension who are receiving antihypertensive drug therapy. In the present study, we found that there was

Table 2. Clinical Characteristics of the Subjects Without Antihypertensive Drug Treatment According to Systolic Blood Pressure

Variables	SBP<120 (n=594)	SBP 120–129 (n=530)	SBP 130–139 (n=329)	SBP>140 (n=369)	*P* Value
Age, y	45.3±8.9	46.0±8.6	47.2±9.1	49.7±9.0	<0.001
Men, n (%)	430 (72.4)	464 (87.6)	302 (91.8)	338 (91.6)	<0.001
Body mass index, kg/m^2	21.7±2.6	23.0±3.0	23.4±2.9	23.6±3.1	<0.001
Systolic blood pressure, mm Hg	110.3±7.0	124.1±3.0	134.1±2.7	149.8±9.7	<0.001
Diastolic blood pressure, mm Hg	71.3±6.9	79.3±6.7	85.9±6.8	94.7±8.9	<0.001
Heart rate, bpm	62.0±10.0	64.2±10.9	65.2±10.9	66.4±10.4	<0.001
Total cholesterol, mmol/L	5.17±0.82	5.19±0.82	5.27±0.77	5.28±0.77	0.08
Triglycerides, mmol/L	1.12±0.71	1.26±0.78	1.36±0.98	1.37±0.73	<0.001
HDL cholesterol, mmol/L	1.62±0.41	1.54±0.38	1.51±0.38	1.56±0.40	<0.001
Glucose, mmol/L	5.13±0.61	5.27±0.56	5.43±0.80	5.50±0.74	<0.001
Current smokers, n (%)	195 (32.8)	183 (34.5)	146 (44.4)	175 (47.4)	<0.001
Metabolic syndrome, n (%)	9 (1.5)	35 (6.6)	51 (15.5)	73 (19.8)	<0.001
Antihypertensive drug					
Calcium channel blockers, n (%)	0 (0)	0 (0)	0 (0)	0 (0)	
ARBs/ACEIs, n (%)	0 (0)	0 (0)	0 (0)	0 (0)	
β-Blockers, n (%)	0 (0)	0 (0)	0 (0)	0 (0)	
Diuretics, n (%)	0 (0)	0 (0)	0 (0)	0 (0)	
Aldosterone antagonists, n (%)	0 (0)	0 (0)	0 (0)	0 (0)	
Flow-mediated vasodilation, %	8.2±3.1	7.5±2.8	7.1±2.8	6.7±2.6	<0.001
Endothelial dysfunction, n (%)	145 (24.4)	174 (32.8)	127 (38.6)	161 (43.6)	<0.001

ACEI indicates angiotensin-converting enzyme inhibitor; ARB, angiotensin receptor blocker; HDL, high-density lipoprotein; and SBP, systolic blood pressure.

no significant relationship between systolic blood pressure and FMD in patients with hypertension who were receiving antihypertensive drug therapy. In addition, in analyses using propensity score matching, the prevalence of endothelial dysfunction was significantly higher, and FMD was significantly smaller in subjects with antihypertensive drug treatment than in those without treatment although clinical parameters, including blood pressure, were comparable in the 2 groups. These findings suggest that endothelial function is impaired regardless of the level of blood pressure achieved by treatment in hypertensive patients for whom antihypertensive treatment is clinically considered necessary for blood pressure control. Recently, Asayama et al[21] evaluated the relationship between blood pressure level and cardiovascular mortality risk among Japanese subjects with and without antihypertensive drug treatment. They demonstrated that the risks of total cardiovascular mortality and death from coronary heart disease, heart failure, and stroke in subjects without antihypertensive

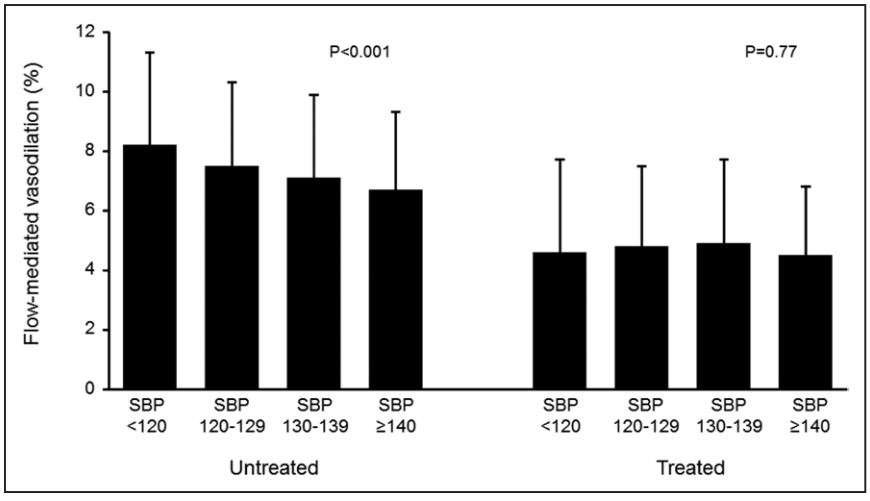

Figure. Flow-mediated vasodilation among 8 groups defined by systolic blood pressure (SBP) and use of antihypertensive drug.

Table 3. Clinical Characteristics of the Subjects With Antihypertensive Drug Treatment According to Systolic Blood Pressure

Variables	SBP<120 (n=105)	SBP 120–129 (n=139)	SBP 130–139 (n=111)	SBP>140 (n=120)	*P* Value
Age, y	59.7±9.8	60.8±9.0	59.2±10.0	63.0±9.7	0.01
Men, n (%)	64 (61.0)	92 (66.2)	76 (68.5)	58 (48.3)	0.007
Body mass index, kg/m^2	23.8±3.2	24.5±3.2	25.0±3.9	24.3±3.2	0.08
Systolic blood pressure, mm Hg	112.5±5.9	124.9±2.9	134.6±2.8	151.0±10.3	<0.001
Diastolic blood pressure, mm Hg	73.8±7.3	80.7±7.4	84.0±7.4	86.6±10.1	<0.001
Heart rate, bpm	62.3±8.9	63.7±10.3	66.2±9.4	67.0±12.5	0.002
Total cholesterol, mmol/L	5.29±0.79	5.22±0.76	5.28±0.77	5.37±0.94	0.59
Triglycerides, mmol/L	1.30±0.73	1.55±0.87	1.57±1.27	1.37±0.72	0.07
HDL cholesterol, mmol/L	1.54±0.42	1.45±0.37	1.47±0.43	1.56±0.43	0.09
Glucose, mmol/L	5.55±0.94	5.70±1.06	5.65±0.90	5.87±1.04	0.11
Current smokers, n (%)	15 (14.3)	27 (19.4)	16 (14.4)	8 (6.7)	0.03
Metabolic syndrome, n (%)	16 (15.2)	37 (26.6)	31 (27.9)	27 (22.5)	0.10
Antihypertensive drug					
Calcium channel blockers, n (%)	63 (60.0)	84 (60.4)	81 (73.0)	82 (68.3)	0.11
ARBs/ACEIs, n (%)	77 (73.3)	99 (71.2)	68 (61.3)	82 (68.3)	0.23
β-Blockers, n (%)	16 (15.2)	16 (11.5)	13 (11.7)	27 (22.5)	0.06
Diuretics, n (%)	31 (29.5)	45 (32.4)	33 (29.7)	30 (25.0)	0.63
Aldosterone antagonists, n (%)	1 (1.0)	3 (2.2)	3 (2.7)	6 (5.0)	0.29
No. of antihypertensive drugs	1.8±0.8	1.8±0.8	1.8±0.8	2.0±1.0	0.31
Flow-mediated vasodilation, %	4.6±3.1	4.8±2.7	4.9±2.8	4.5±2.3	0.77
Endothelial dysfunction, n (%)	72 (68.6)	96 (69.1)	78 (70.3)	88 (73.3)	0.85

ACEI indicates angiotensin-converting enzyme inhibitor; ARB, angiotensin receptor blocker; HDL, high-density lipoprotein; and SBP, systolic blood pressure.

drug treatment linearly increased with an increment of blood pressure category, whereas there were no stepwise increases in these cardiovascular risks in treated hypertensive patients without a history of cardiovascular disease. In accordance with results of previous epidemiological studies, they also demonstrated that subjects with antihypertensive drug treatment had a higher cardiovascular risk compared with those without treatment for a given level of blood pressure.[21–24] Following these results, recent broad-based cardiovascular risk prediction equations include treatment for hypertension as a covariate.[25,26] Although it has not been fully elucidated why antihypertensive drug treatment cannot restore cardiovascular risk to the level of untreated subjects with similar blood pressure levels, Liu et al[27] demonstrated that treated hypertensive patients had much higher cumulative blood pressure exposure over time than did untreated hypertensive patients with similar blood pressure levels, leading to a higher prevalence of end-organ damage and subclinical atherosclerosis in treated hypertensive patients than in untreated subjects. These findings raise the possibility that higher cumulative blood pressure exposure may cause irreversible damage to the endothelium that is not completely restored by antihypertensive drug treatment, resulting in a higher prevalence of endothelial dysfunction and smaller FMD in subjects with antihypertensive drug treatment than in those without treatment. Receiving antihypertensive drug treatment per se may be a sort of marker of high cardiovascular risk and endothelial dysfunction regardless of the level of blood pressure achieved by treatment. Persistence of endothelial dysfunction in treated hypertensive patients may contribute to the development of cardiovascular complications associated with essential hypertension.

Among the treated hypertensive patients, FMD was significantly smaller in patients treated with ≥3 antihypertensive drugs than in those treated with 1 or 2 antihypertensive drugs, and it was shown that not systolic blood pressure but the number of prescribed antihypertensive drugs (≥3) was independently associated with FMD. These findings also support the hypothesis that cumulative blood pressure exposure may be related to the degree of endothelial dysfunction. Treated hypertensive patients in whom multiple antihypertensive drugs are required for the management of blood pressure may have higher cumulative blood pressure exposure than those treated with 1 or 2 antihypertensive drugs, resulting in smaller FMD in patients treated with ≥3 antihypertensive drugs.

Previous studies have shown different effects of antihypertensive drugs on endothelial function measured by FMD independent of the blood pressure–lowering effect among antihypertensive drug classes in patients with essential hypertension, raising the possibility that differences in FMD and the relationship between FMD and blood pressure levels exist

among antihypertensive drug classes.[16,28] Renin–angiotensin–aldosterone inhibitors have been shown to improve or restore endothelial function,[16] whereas β-blockers could attenuate the vasodilatory response after brachial artery occlusion. However, the small sample size of hypertensive patients on monotherapy, especially patients on monotherapy with β-blockers (n=6) and diuretics (n=5), did not allow us to compare FMD and the relationship between FMD and blood pressure levels among hypertensive patients on monotherapy with calcium channel blockers, angiotensin II receptor blockers/angiotensin-converting enzyme inhibitors, β-blockers, and diuretics. Further study is needed to determine whether differences in the relationship between endothelial function and blood pressure levels exist among antihypertensive drug classes.

Although the cross-sectional design of our study did not allow us to establish a definitive causal relationship between hypertension and endothelial dysfunction, our findings raise the possibility that there are primary disturbances that impair NO activity and this in turn causes hypertension. If those patients are treated with drugs that lower blood pressure but do not target the primary disturbances that are causing the impaired NO activity, the hypertension may be corrected by the drug treatment, but the primary abnormalities causing the impaired NO activity that underlies the hypertension will not be corrected by the drug treatment.

FMD in the brachial artery, an index of endothelial function, is determined not only by functional status of the endothelium in the brachial artery but also by other functional and structural variables, including brachial artery stiffness, baseline brachial artery diameter, reactive hyperemic flow, induced shear stress, and endothelium-independent vasodilation.[29–33] We cannot deny the possibility that persistently reduced FMD in treated hypertensive patients is attributed to a stiffer brachial artery that poses a physical limit to the capability of the artery to dilate regardless of the status of endothelial function. Although data on pulse wave velocity in combination with other markers of endothelial dysfunction, such as microalbuminuria, would provide more specific insights into the mechanism underlying the persistently reduced FMD in treated hypertensive patients, we have no information on pulse wave velocity and other markers of endothelial dysfunction. In addition, we cannot deny the possibility that the ability of the arteries to dilate in response to reactive hyperemia is altered by antihypertensive drugs per se. Vasoactive medications might have certain effects on the functional and structural status of peripheral conduit and resistance arteries. Therefore, there is a possibility that the functional and structural status of the vasculature is chronically altered by long-term use of vasoactive medication, making FMD of no use for the assessment of endothelial function and for the prediction of cardiovascular risk in patients with hypertension who have been receiving long-term antihypertensive drug treatment. Further studies are warranted to evaluate the clinical role of FMD in the assessment of cardiovascular risk in treated hypertensive patients.

The duration of hypertension may play a critical role in endothelial dysfunction and may be a major confounding factor in the relationship between hypertension and endothelial dysfunction. The duration of hypertensive disease may be longer in the treated patients than in the untreated subjects. Information on the duration of hypertension would enable more specific conclusions to be drawn on the association of treatment status with the relationship between blood pressure and endothelial dysfunction. Treated hypertensive patients enrolled in this study had been receiving antihypertensive treatment for at least 6 months. However, we have no more information on the duration of hypertension.

Perspectives

FMD decreased significantly in relation to increase in systolic blood pressure in subjects without antihypertensive drug treatment, whereas there was no significant association between systolic blood pressure and FMD in subjects with antihypertensive drug treatment. Among subjects with similar blood pressure levels, the prevalence of endothelial dysfunction was higher in subjects with antihypertensive drug treatment than in those without treatment, and FMD was smaller in subjects with antihypertensive drug treatment than in those without treatment. Persistence of endothelial dysfunction regardless of the level of blood pressure achieved by treatment in hypertensives may contribute to the development of cardiovascular complications associated with essential hypertension. It is possible that early recognition and treatment of hypertension may be required to effectively protect against endothelial damage and maintain normal endothelial function.

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Disclosures

None.

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Novelty and Significance

What Is New?

- There was no significant relationship between systolic blood pressure and flow-mediated vasodilation in subjects with antihypertensive drug treatment.
- Among subjects with similar blood pressure levels, flow-mediated vasodilation was significantly smaller in subjects with antihypertensive drug treatment than in those without treatment.

What Is Relevant?

- Endothelial dysfunction cannot be completely restored by antihypertensive drug treatment to the level of untreated subjects with similar blood pressure levels.

Summary

Persistence of endothelial dysfunction regardless of the level of blood pressure achieved by antihypertensive drug treatment in hypertensives may contribute to the development of cardiovascular complications associated with essential hypertension.

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Endothelial Function Is Impaired in Patients Receiving Antihypertensive Drug Treatment Regardless of Blood Pressure Level: FMD-J Study (Flow-Mediated Dilation Japan)

Tatsuya Maruhashi, Junko Soga, Noritaka Fujimura, Naomi Idei, Shinsuke Mikami, Yumiko Iwamoto, Akimichi Iwamoto, Masato Kajikawa, Takeshi Matsumoto, Nozomu Oda, Shinji Kishimoto, Shogo Matsui, Haruki Hashimoto, Yoshiki Aibara, Farina Binti Mohamad Yusoff, Takayuki Hidaka, Yasuki Kihara, Kazuaki Chayama, Kensuke Noma, Ayumu Nakashima, Chikara Goto, Hirofumi Tomiyama, Bonpei Takase, Takahide Kohro, Toru Suzuki, Tomoko Ishizu, Shinichiro Ueda, Tsutomu Yamazaki, Tomoo Furumoto, Kazuomi Kario, Teruo Inoue, Shinji Koba, Kentaro Watanabe, Yasuhiko Takemoto, Takuzo Hano, Masataka Sata, Yutaka Ishibashi, Koichi Node, Koji Maemura, Yusuke Ohya, Taiji Furukawa, Hiroshi Ito, Hisao Ikeda, Akira Yamashina and Yukihito Higashi

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ENDOTHELIAL FUNCTION IS IMPAIRED IN PATIENTS RECEIVING ANTIHYPERTENSIVE DRUG TREATMENT REGARDLESS OF BLOOD PRESSURE LEVEL: FMD-J STUDY

Brief title: Antihypertensive Therapy and Endothelial Function

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Methods

Measurement of FMD

Vascular response to reactive hyperemia in the brachial artery was used for assessment of endothelium-dependent FMD. A high-resolution linear artery transducer was coupled to computer-assisted analysis software (UNEXEF18G, UNEX Co, Nagoya, Japan) that used an automated edge detection system for measurement of brachial artery diameter. A blood pressure cuff was placed around the forearm. The brachial artery was scanned longitudinally 5 to 10 cm above the elbow. When the clearest B-mode image of the anterior and posterior intimal interfaces between the lumen and vessel wall was obtained, the transducer was held at the same point throughout the scan by a special probe holder (UNEX Co) to ensure consistency of the image. Depth and gain setting were set to optimize the images of the arterial lumen wall interface. When the tracking gate was placed on the intima, the artery diameter was automatically tracked, and the waveform of diameter changes over the cardiac cycle was displayed in real time using the FMD mode of the tracking system. This allowed the ultrasound images to be optimized at the start of the scan and the transducer position to be adjusted immediately for optimal tracking performance throughout the scan. Pulsed Doppler flow was assessed at baseline and during peak hyperemic flow, which was confirmed to occur within 15 s after cuff deflation. Blood flow velocity was calculated from the color Doppler data and was displayed as a waveform in real time. The baseline longitudinal image of the artery was acquired for 30 s, and then the blood pressure cuff was inflated to 50 mm Hg above systolic pressure for 5 min. The longitudinal image of the artery was recorded continuously until 5 min after cuff deflation. Pulsed Doppler velocity signals were obtained for 20 s at baseline and for 10 s immediately after cuff deflation. Changes in brachial artery diameter were immediately expressed as percentage change relative to the vessel diameter before cuff inflation. FMD was automatically calculated as the percentage change in peak vessel diameter from the baseline value. Percentage of FMD [(Peak diameter-Baseline diameter)/Baseline diameter] was used for analysis. Blood flow volume was calculated by multiplying the Doppler flow velocity (corrected for the angle) by heart rate and vessel cross-sectional area ($-r^2$). Reactive hyperemia was calculated as the maximum percentage increase in flow after cuff deflation compared with baseline flow.

Table S1. Univariate Analysis of the Relationships between Flow-mediated Vasodilation and Variables in Subjects without Antihypertensive Drug Treatment

	Flow-mediated vasodilation	
Variables	r	P value
Age, y	-0.24	<0.001
Body mass index, kg/m^2	-0.17	<0.001
Systolic blood pressure, mm Hg	-0.22	<0.001
Diastolic blood pressure, mm Hg	-0.21	<0.001
Heart rate, bpm	-0.03	0.14
Total cholesterol, mmol/L	-0.12	<0.001
Triglycerides, mmol/L	-0.13	<0.001
HDL cholesterol, mmol/L	0.05	0.04
Glucose, mmol/L	-0.11	<0.001

HDL, high-density lipoprotein.

Table S2. Multiple Linear Regression Analyses of the Relationships between Flow-mediated Vasodilation and Variables in Subjects without Antihypertensive Drug Treatment

	Flow-mediated vasodilation			
Variables	Parameter Estimate	Standard Error	T value	P value
Age, yr	-0.065	0.008	-8.40	<0.001
Men	-0.091	0.097	-0.94	0.35
Body mass index, kg/m^2	-0.124	0.256	-4.86	<0.001
Systolic blood pressure, mm Hg	-0.026	0.005	-5.52	<0.001
Heart rate, bpm	0.023	0.006	3.67	<0.001
Total cholesterol, mmol/L	-0.128	0.094	-1.37	0.17
Triglycerides, mmol/L	-0.257	0.106	-2.43	0.02
HDL cholesterol, mmol/L	-0.299	0.212	-1.41	0.16
Glucose, mmol/L	-0.025	0.105	-0.24	0.81
Current smoking	-0.324	0.069	-4.67	<0.001
Metabolic syndrome	0.035	0.130	0.27	0.79

The adjusted r^2 of the model for male subjects was 0.13.

Table S3. Univariate Analysis of the Relationships between Flow-mediated Vasodilation and Variables in Subjects with Antihypertensive Drug Treatment

	Flow-mediated vasodilation	
Variables	r	P value
Age, y	-0.04	0.45
Body mass index, kg/m^2	-0.08	0.07
Systolic blood pressure, mm Hg	-0.02	0.69
Diastolic blood pressure, mm Hg	-0.02	0.60
Heart rate, bpm	0.15	0.001
Total cholesterol, mmol/L	0.05	0.26
Triglycerides, mmol/L	-0.02	0.61
HDL cholesterol, mmol/L	0.15	<0.001
Glucose, mmol/L	-0.01	0.86

HDL, high-density lipoprotein.

Table S4. Clinical Characteristics of the Subjects with Antihypertensive Drug Treatment with Systolic Blood Pressure <120 mm Hg

Variables	Untreated (n=68)	Treated (n=68)	P value
Age, yr	55.3±8.6	56.1±9.2	0.58
Men, n (%)	44 (64.7)	38 (55.9)	0.29
Body mass index, kg/m^2	23.6±2.8	23.1±3.0	0.27
Systolic blood pressure, mm Hg	112.0±7.3	112.0±6.3	0.99
Diastolic blood pressure, mm Hg	74.7±8.2	73.9±7.6	0.57
Heart rate, bpm	63.4±9.1	62.5±9.6	0.56
Total cholesterol, mmol/L	5.30±0.66	5.42±0.79	0.33
Triglycerides, mmol/L	1.34±0.69	1.25±0.77	0.44
HDL cholesterol, mmol/L	1.50±0.35	1.63±0.44	0.07
Glucose, mmol/L	5.52±1.21	5.43±0.66	0.60
Current smokers, n (%)	19 (27.9)	12 (17.7)	0.15
Metabolic syndrome, n (%)	5 (7.4)	3 (4.4)	0.46
Antihypertensive drug			
Calcium channel blockers, n (%)	0 (0)	38 (55.9)	
ARBs/ACEIs, n (%)	0 (0)	53 (77.9)	
β-blockers, n (%)	0 (0)	12 (17.7)	
Diuretics, n (%)	0 (0)	19 (27.9)	
Aldosterone antagonists, n (%)	0 (0)	1 (1.5)	
Number of antihypertensive drugs		1.9±0.9	
Flow-mediated vasodilation, %	7.4±2.6	4.8±3.0	<0.001
Endothelial dysfunction, n (%)	19 (27.9)	46 (67.7)	<0.001

HDL, high-density lipoprotein; ARB, angiotensin receptor blocker; ACEI, angiotensin-converting enzyme inhibitor.

Table S5. Clinical Characteristics of the Subjects with Antihypertensive Drug Treatment with Systolic Blood Pressure 120 to 129 mm Hg

Variables	Untreated (n=75)	Treated (n=75)	P value
Age, yr	56.7±6.2	56.2±8.4	0.68
Men, n (%)	55 (73.3)	56 (74.7)	0.85
Body mass index, kg/m^2	23.7±2.8	24.1±2.9	0.46
Systolic blood pressure, mm Hg	124.8±3.2	125.1±3.0	0.56
Diastolic blood pressure, mm Hg	82.3±6.3	81.3±8.4	0.44
Heart rate, bpm	63.5±9.0	64.4±10.5	0.54
Total cholesterol, mmol/L	5.36±0.84	5.25±0.77	0.43
Triglycerides, mmol/L	1.38±0.81	1.43±0.81	0.70
HDL cholesterol, mmol/L	1.54±0.42	1.48±0.40	0.40
Glucose, mmol/L	5.45±0.68	5.56±0.70	0.35
Current smokers, n (%)	19 (25.3)	22 (29.3)	0.58
Metabolic syndrome, n (%)	13 (17.3)	14 (18.7)	0.83
Antihypertensive drug			
Calcium channel blockers, n (%)	0 (0)	41 (54.7)	
ARBs/ACEIs, n (%)	0 (0)	57 (76.0)	
β-blockers, n (%)	0 (0)	6 (8.0)	
Diuretics, n (%)	0 (0)	29 (38.7)	
Aldosterone antagonists, n (%)	0 (0)	2 (2.7)	
Number of antihypertensive drugs		1.8±0.8	
Flow-mediated vasodilation, %	6.3±2.6	4.7±2.7	<0.001
Endothelial dysfunction, n (%)	38 (50.7)	52 (69.3)	0.02

HDL, high-density lipoprotein; ARB, angiotensin receptor blocker; ACEI, angiotensin-converting enzyme inhibitor.

Table S6. Clinical Characteristics of the Subjects with Antihypertensive Drug Treatment with Systolic Blood Pressure 130 to 139 mm Hg

Variables	Untreated (n=62)	Treated (n=62)	P value
Age, yr	54.6±9.6	54.9±9.5	0.88
Men, n (%)	48 (77.4)	49 (79.0)	0.83
Body mass index, kg/m^2	23.8±3.0	23.8±3.3	0.99
Systolic blood pressure, mm Hg	134.7±2.8	134.7±2.7	0.90
Diastolic blood pressure, mm Hg	84.3±6.8	86.1±7.0	0.16
Heart rate, bpm	64.7±8.8	67.1±8.7	0.13
Total cholesterol, mmol/L	5.29±0.81	5.26±0.79	0.85
Triglycerides, mmol/L	1.46±1.47	1.51±1.17	0.84
HDL cholesterol, mmol/L	1.47±0.39	1.47±0.46	0.95
Glucose, mmol/L	5.61±0.78	5.72±1.05	0.49
Current smokers, n (%)	13 (21.0)	14 (22.6)	0.83
Metabolic syndrome, n (%)	13 (21.0)	15 (24.2)	0.67
Antihypertensive drug			
Calcium channel blockers, n (%)	0 (0)	46 (74.2)	
ARBs/ACEIs, n (%)	0 (0)	33 (53.2)	
β-blockers, n (%)	0 (0)	7 (11.3)	
Diuretics, n (%)	0 (0)	16 (25.8)	
Aldosterone antagonists, n (%)	0 (0)	0 (0)	
Number of antihypertensive drugs		1.7±0.7	
Flow-mediated vasodilation, %	6.7±2.9	5.1±2.7	0.002
Endothelial dysfunction, n (%)	30 (48.4)	41 (66.1)	0.04

HDL, high-density lipoprotein; ARB, angiotensin receptor blocker; ACEI, angiotensin-converting enzyme inhibitor.

Table S7. Clinical Characteristics of the Subjects with Antihypertensive Drug Treatment with Systolic Blood Pressure ≥140 mm Hg

Variables	Untreated (n=52)	Treated (n=52)	P value
Age, yr	56.8±6.4	57.9±10.4	0.48
Men, n (%)	37 (71.2)	40 (76.9)	0.50
Body mass index, kg/m^2	24.4±3.7	24.2±2.8	0.83
Systolic blood pressure, mm Hg	148.8±9.1	150.9±9.5	0.26
Diastolic blood pressure, mm Hg	91.9±8.9	91.3±9.9	0.74
Heart rate, bpm	66.9±10.7	66.0±13.8	0.72
Total cholesterol, mmol/L	5.30±0.76	5.47±1.00	0.36
Triglycerides, mmol/L	1.40±0.80	1.54±0.83	0.36
HDL cholesterol, mmol/L	1.57±0.39	1.52±0.41	0.52
Glucose, mmol/L	5.83±1.20	5.95±1.02	0.59
Current smokers, n (%)	7 (13.5)	7 (13.5)	1.0
Metabolic syndrome, n (%)	12 (23.1)	14 (26.9)	0.65
Antihypertensive drug			
Calcium channel blockers, n (%)	0 (0)	36 (69.2)	
ARBs/ACEIs, n (%)	0 (0)	34 (65.4)	
β-blockers, n (%)	0 (0)	13 (25.0)	
Diuretics, n (%)	0 (0)	11 (21.2)	
Aldosterone antagonists, n (%)	0 (0)	5 (9.6)	
Number of antihypertensive drugs		1.9±1.1	
Flow-mediated vasodilation, %	6.3±2.2	4.0±2.1	<0.001
Endothelial dysfunction, n (%)	23 (44.2)	41 (78.9)	<0.001

HDL, high-density lipoprotein; ARB, angiotensin receptor blocker; ACEI, angiotensin-converting enzyme inhibitor.

Table S8. Clinical Characteristics of the Subjects with Antihypertensive Drug Treatment According to the Number of Antihypertensive Drugs

	Number of antihypertensive drugs			
	1	2	≤3	
Variables	(n=195)	(n=185)	(n=95)	P value
Age, yr	61.1±8.9	61.4±10.1	58.6±10.1	0.053
Men, n (%)	117 (60.0)	109 (58.9)	64 (67.4)	0.36
Body mass index, kg/m^2	23.8±3.2	24.1±3.4	26.1±3.4	<0.001
Systolic blood pressure, mm Hg	130.6±14.7	130.0±15.6	133.8±15.1	0.13
Diastolic blood pressure, mm Hg	81.8±9.7	81.2±9.0	81.0±9.5	0.74
Heart rate, bpm	65.3±11.1	64.9±10.3	63.8±10.2	0.51
Total cholesterol, mmol/L	5.33±0.82	5.32±0.79	5.14±0.86	0.15
Triglycerides, mmol/L	1.40±0.89	1.43±0.84	1.61±1.12	0.17
HDL cholesterol, mmol/L	1.54±0.44	1.53±0.41	1.37±0.35	0.002
Glucose, mmol/L	5.56±0.87	5.66±1.03	6.07±1.08	<0.001
Current smokers, n (%)	24 (12.3)	23 (12.4)	19 (20.0)	0.16
Metabolic syndrome, n (%)	37 (19.0)	35 (18.9)	39 (41.1)	<0.001
Antihypertensive drug				
Calcium channel blockers, n (%)	103 (52.8)	119 (64.3)	88 (92.0)	<0.001
ARBs/ACEIs, n (%)	78 (40.0)	157 (84.9)	91 (95.8)	<0.001
β-blockers, n (%)	6 (3.1)	28 (15.1)	38 (40.0)	<0.001
Diuretics, n (%)	5 (2.6)	57 (30.8)	77 (81.2)	<0.001
Aldosterone antagonists, n (%)	1 (0.5)	3 (1.6)	9 (9.5)	<0.001
Flow-mediated vasodilation, %	4.8±2.8	4.9±2.7	4.0±2.5	0.03
Endothelial dysfunction, n (%)	134 (68.7)	122 (66.0)	78 (82.1)	0.01

HDL, high-density lipoprotein; ARB, angiotensin receptor blocker; ACEI, angiotensin-converting enzyme inhibitor.

Table S9. Multiple Linear Regression Analyses of the Relationships between Flow-mediated Vasodilation and Variables in Subjects with Antihypertensive Drug Treatment

	Flow-mediated vasodilation			
Variables	Parameter Estimate	Standard Error	T value	P value
Age, yr	-0.018	0.013	-1.34	0.18
Men	-0.383	0.140	-2.73	0.007
Body mass index, kg/m^2	-0.007	0.042	-0.16	0.88
Systolic blood pressure, mm Hg	-0.008	0.008	-0.92	0.36
Heart rate, bpm	0.028	0.012	2.28	0.02
Total cholesterol, mmol/L	-0.091	0.163	-0.56	0.58
Triglycerides, mmol/L	0.154	0.162	0.95	0.34
HDL cholesterol, mmol/L	0.738	0.370	2.00	0.04
Glucose, mmol/L	0.078	0.130	0.60	0.55
Current smoking	-0.033	0.182	-0.18	0.86
Metabolic syndrome	-0.054	0.183	-0.30	0.77
Antihypertensive drugs ≥3	-0.330	0.162	-2.03	0.04

The adjusted r^2 of the model for male subjects was 0.04.

Figure S1

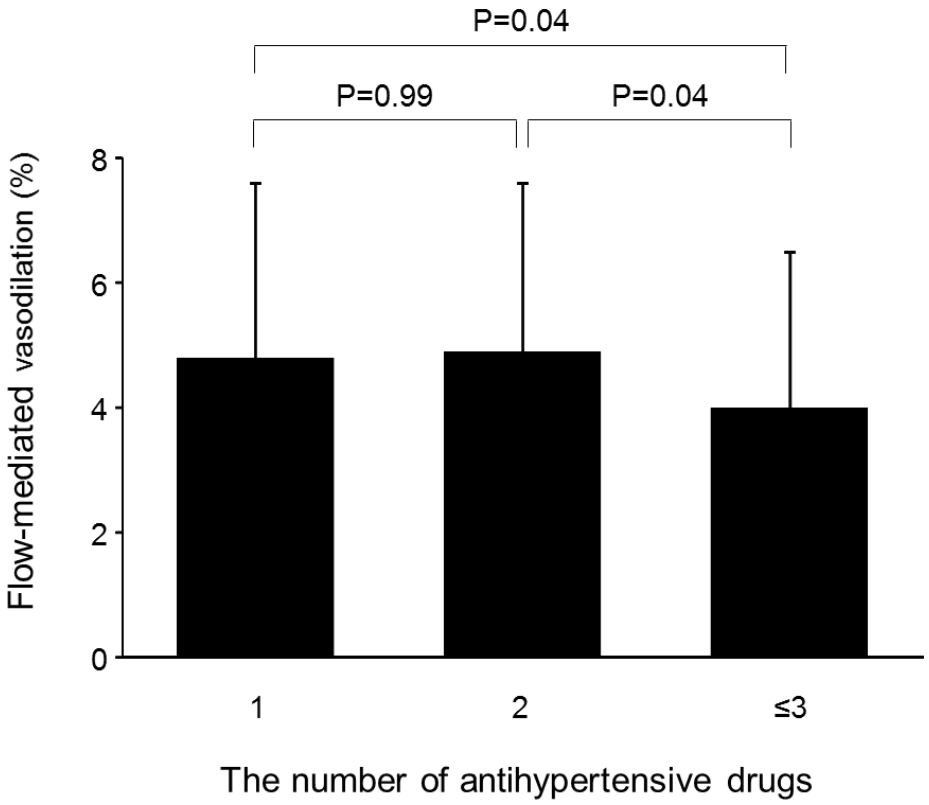

Figure legend

Figure S1. Flow-mediated vasodilation in subjects treated with 1, 2, and 3 or more antihypertensive drugs