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Research Article

Effect of a fixed combination of Perindopril and Amlodipine on blood pressure control in 6256 patients with not-at-goal hypertension: the AVANT'AGE study

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Abstract

In clinical practice, general practitioners are likely to face hypertensives with uncontrolled blood pressure (BP), whose antihypertensive treatment need to be modified. In the present study, 710 general practitioners have each included the first 10 patients with not-at-goal hypertension, for whom they decided to modify their antihypertensive treatment with addition of a fixed combination of Perindopril and Amlodipine at either of its four dosages: 5/5, 5/10, 10/5, or 10/10 mg. In total, 6256 patients were included, with BP measured both at baseline and after 3 months. At the end of follow-up, a mean reduction of 20.3 ± 12.4 mm Hg in systolic BP and 11.3 ± 9.6 mm Hg in diastolic BP were observed, and 62.3% achieved successful BP control. Body mass index and waist circumference were significant determinants of both systolic and diastolic BP reductions ($P \leq .04$). Moreover, in addition to baseline BP level, body mass index was the only significant determinant of BP control of systolic, diastolic BP, and of both ($P \leq .04$). Addition of a fixed combination of Perindopril and Amlodipine to BP regimen was efficient, in terms of BP control, for 62.3% of those patients with not-at-goal hypertension. Furthermore, baseline BP level and obesity were important influential factors of BP control. J Am Soc Hypertens 2013;7(2):163–169.

Keywords: Hypertension; blood pressure control; cardiovascular risk factor.

Introduction

Arterial hypertension is a prevalent condition and the leading cause of various cerebrovascular and cardiovascular (CV) events and mortality.[1–3] Although this common CV risk factor is theoretically treatable, the reality of worldwide blood pressure (BP) control is far from perfect.[3,4] Furthermore, in routine clinical practice, it is very common for general practitioners (GPs) to find difficulty in patients' BP control with antihypertensive agents, even according to the most current guideline.[5] In this respect, a decision on the modification of chronic antihypertensive treatment needs to be made by the GPs, because of patients' uncontrolled BP or poor compliance and/or tolerance. Many studies have focussed on patients with resistant hypertension, but few studies have focused on patients with not-at-goal hypertension, especially in a nationwide survey in "real-life" clinical practice. Furthermore, characteristics of these patients, as well as the cause of their resistant condition, were largely unknown.

In literature, many studies have documented that angiotensin enzyme-converting inhibitor (ACEI) and calcium channel blocker (CCB) were beneficial in BP control in patients with resistant hypertension,[6–9] but the combined effect of these two agents on not-at-goal hypertension remained unclear.

We therefore conducted the AVANT'AGE study in 6256 patients with not-at-goal hypertension, for whom their GPs

Conflict of Interest: Jacques Blacher, principal investigator of the AVANT'AGE study, received honoraria from Servier. Servier was the unique sponsor of the AVANT'AGE study.

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decided to modify their chronic antihypertensive treatments with addition of a fixed combination of Perindopril and Amlodipine. Our goal was to investigate the combined effect of ACEI and CCB on BP control, as well as its influential factors, in these hypertensives.

Methods

Study Design

The Age Vasculaire et risqué résiduel chez I'hyperteNdu TrAité vu en médicine GénéralE (AVANT'AGE) study was an open-label clinical trial, which has focused on the BP control in patients with not-at-goal hypertension in general practice. 710 GPs, representative of the French active GPs, have each included the first 10 hypertensives with uncontrolled BP or poor compliance and/or tolerance (ie, the hypertensive patients for whom they decided to modify the chronic antihypertensive treatment). The decision of treatment modification was based on uncontrolled BP (91%) and/or poor compliance/tolerance (46%). Included in the present study were 7032 patients (58% males), with mean age ± standard deviation (SD) of 62.4 ± 11.5 years, ranged from 21 to 98 years, whose antihypertensive treatments were modified by their GPs, of whom 6256 participants (93%) were given the same modification with addition of COVERAM (a fixed combination of Perindopril and Amlodipine). Specifically, the dosages of the fixed combination of Perindopril and Amlodipine were 5/5 mg (46.4%), 5/10 mg (11.7%), 10/5 mg (24.6%), 10/10 mg (17.3%), and the specific dosage of the combination for each patient was decided by his or her GP according to the patient's BP. Written informed consent was obtained from each study participant.

Anthropometric, Clinical, and Biological Parameters

Body height, body weight and waist circumference were measured, and body mass index (BMI) was calculated as body weight in kg divided by the square of body height in meters. Overweight and obesity were defined as BMI >25 kg/m^2 and >30 kg/m^2, respectively, and abdominal obesity were defined as waist circumference >102 cm in men and >88 cm in women. Clinical data was collected from patient's medical document by GP for each participant, including smoking habit, the presence of diabetes mellitus, dyslipidemia, left ventricular hypertrophy, coronary heart disease, microalbuminuria, and renal insufficiency, as well as the use of medications, especially the use of antihypertensive agents. Biological tests were not performed in the context of our study, but data obtained previously were used for characterizing each subject.

Blood Pressure Measurement

Each participant's BP was measured by his or her GP by the electronic device currently used by the physician, after at least 5 minutes rest in the sitting position, both at baseline and at the end of the follow-up.

Follow-up Procedure

Follow-up started from the baseline examination of each individual and lasted for 3 months. Of all 6256 participants in the present study, 304 (4.9%) were lost to follow up. BP measurements were repeated during the following visit that took place 3 months later. After reviewing medical history and use of medication, target BP was set for each participant by his or her GP according to the current guideline (ie, 130/80 mm Hg for hypertensives with diabetes mellitus, renal dysfunction or established CV diseases)[5]. Controlled BP was defined as patient's BP below the target BP. However, since a small number of patients' medical documents were not complete, and their target BPs could not be set accurately, only 5677 patients had successful evaluation of systolic and diastolic BP control.

Statistical Analysis

Anthropometric, clinical, and biological parameters were compared between men and women by student's *t* test and Fisher's exact test for quantitative and qualitative variables, respectively. Student's *t* test was also applied to compare BP properties between at baseline and after treatment, and to compare the magnitude of BP reductions between patients with and without related abnormalities. Determinants of the magnitude of BP reduction and of BP control were assessed by multivariate linear and logistic regression models, respectively, with taking age, male gender, BMI, waist circumference, current smoking, plasma glucose, low-density lipoprotein (LDL) and high-density lipoprotein (HDL) cholesterol, number of previous antihypertensive agents, and baseline BP level as potential confounders. Statistical analysis was performed using SAS software, version 9.1 (SAS Institute, Cary, NC). $P < .05$ was considered statistically significant.

Results

Characteristics of participants by gender were presented in Table 1, including conventional CV risk factors, BP properties, biochemical parameters, related disorders and treatments. Men, compared with women, had significantly higher BMI (27.9 ± 4.1 vs 27.0 ± 5.4 kg/m^2; $P < .001$) and waist circumference (100.4 ± 11.9 vs 91.3 ± 13.7 cm; $P < .001$), higher diastolic BP (90.4 ± 8.7 vs 89.8 ± 8.8 mm Hg; $P < .007$), plasma glucose (7.08 ± 1.55 vs 6.86 ± 1.59 mmol/L; $P < .001$), and triglyceride (1.22 ± 0.27 vs 1.18 ± 0.27 mmol/L; $P < .001$), more frequently

Table 1
Characteristics of participants by gender

	Total (n = 6256)	Men (n = 3645)	Women (n = 2611)	*P*
Age, years	62.4 ± 11.5	61.4 ± 10.9	63.8 ± 12.0	**<.001**
Body mass index, kg/m^2	27.6 ± 4.7	27.9 ± 4.1	27.0 ± 5.4	**<.001**
Waist circumference, cm	96.7 ± 13.4	100.4 ± 11.9	91.3 ± 13.7	**<.001**
Current smoke, n (%)	950 (15.4)	686 (19.1)	264 (10.3)	**<.001**
Systolic blood pressure, mm Hg	154.9 ± 11.8	154.7 ± 11.7	155.1 ± 11.9	.16
Diastolic blood pressure, mm Hg	90.2 ± 8.8	90.4 ± 8.7	89.8 ± 8.8	**.007**
Heart rate, beats/second	75.8 ± 8.8	75.7 ± 8.9	76.0 ± 8.6	.18
Plasma glucose, mmol/L	6.99 ± 1.57	7.08 ± 1.55	6.86 ± 1.59	**<.001**
HbA1c, %	6.74 ± 1.06	6.72 ± 1.03	6.77 ± 1.09	.37
Total cholesterol, mmol/L	5.40 ± 1.04	5.37 ± 1.07	5.44 ± 1.00	**.01**
Low-density lipoprotein cholesterol, mmol/L	3.31 ± 0.95	3.30 ± 0.97	3.33 ± 0.91	.22
High-density lipoprotein cholesterol, mmol/L	1.39 ± 0.42	1.33 ± 0.41	1.46 ± 0.43	**<.001**
Triglyceride, mmol/L	1.20 ± 0.27	1.22 ± 0.27	1.18 ± 0.27	**<.001**
Diabetes mellitus, n (%)	1408 (22.9)	860 (24.0)	548 (21.3)	**.01**
Dyslipidemia, n (%)	1786 (35.1)	1113 (37.8)	673 (31.4)	**<.001**
Left ventricular hypertrophy, n (%)	687 (12.3)	429 (13.1)	258 (11.2)	**.03**
Coronary heart disease, n (%)	455 (7.7)	348 (10.1)	107 (4.3)	**<.001**
Microalbuminuria, n (%)	358 (7.1)	230 (7.7)	128 (6.2)	**.03**
Renal insufficiency, n (%)	281 (4.7)	140 (4.0)	141 (5.7)	**.002**
Antidiabetic therapy, n (%)	1377 (22.3)	848 (23.5)	529 (20.5)	**.004**
Antihyperlipidemic therapy, n (%)	2778 (44.9)	1733 (48.0)	1045 (40.5)	**<.001**
Antiplatelet therapy, n (%)	1747 (28.3)	1117 (31.1)	630 (24.5)	**<.001**

Values are means ± standard deviation or numbers in parenthesis. Diseases and treatments were defined by reading patients' medical document by general practitioners. Biochemical parameters were the last measurements of patients' medical document.

reported smoking (19.1% vs 10.3%; $P < .001$), and higher prevalence of related disorders, including diabetes mellitus, dyslipidemia, left ventricular hypertrophy, coronary heart disease, microalbuminuria, and renal insufficiency ($P \leq .03$) and the corresponding treatments, such as antidiabetic, antihyperlipidemic, and antiplatelet therapies ($P \leq .004$). Women, on the contrary, were significantly older (age, 63.8 ± 12.0 years vs 61.4 ± 10.9 years; $P < .001$), and had significantly higher total (5.44 ± 1.00 vs 5.37 ± 1.07 mmol/L; $P = .01$) and HDL cholesterol (1.46 ± 0.43 vs 1.33 ± 0.41 mmol/L; $P < .001$).

At baseline, antihypertensive monotherapy concerned 74.4%, bitherapy 19.9%, tritherapy 4.8%, and quartherapy or more 0.9% of all participants. Use of antihypertensive agents was prevalence in the present population, namely 38.6% for ACEI, 20.8% for ARB, 30.2% for CCB, 16.8% for β-blocker, 29.1% for diuretics, 3.0% for central-acting agent, and 0.8% for renin inhibitor, respectively. After 6256 patients took Perindopril and Amlodipine, in addition, there are still 627 patients (10.0%) having two antihypertensive agents, 97 (1.6%) having three antihypertensive agents, and 11 (0.2%) having four or more antihypertensive agents, with 562 patients (75.3%) taking β-blocker, 227 (30.4%) taking diuretics, and 64 (8.6%) taking central-acting agent.

At the end of follow-up, after addition of a fixed combination of Perindopril and Amlodipine, systolic BP, diastolic BP, and pulse pressure changed by -20.3 ± 12.4, -11.3 ± 9.6, and -9.0 ± 12.3 mm Hg, respectively ($P < .001$, Table 2). Of all patients, 4342 (76.4%) had successful BP

Table 2
Modifications in blood pressure after addition of a fixed combination of Perindopril and Amlodipine

	Baseline	After Treatment with COVERAM	*P**	Difference	*P*†
Systolic blood pressure, mm Hg	154.9 ± 11.8	134.6 ± 9.7	**<.001**	-20.3 ± 12.4	**<.001**
Diastolic blood pressure, mm Hg	90.2 ± 8.8	78.9 ± 7.8	**<.001**	-11.3 ± 9.6	**<.001**
Pulse pressure, mm Hg	64.7 ± 11.8	55.7 ± 9.1	**<.001**	-9.0 ± 12.3	**<.001**

COVERAM is the brand name of the fixed combination of Perindopril and Amlodipine.
* Indicates *P* value for interclass comparison.
† Indicates *P* value for comparison between absolute difference and zero.

control in either systolic or diastolic BP, with 3537 (62.3%) in both, 606 (10.7%) only in systolic BP, and 199 (3.5%) only in diastolic BP.

In Figure 1, the magnitude of BP reductions were compared between patients with and without related disorders, such as obesity, abdominal obesity, diabetes, and dyslipidemia. As compared with non-obese patients, patients with obesity and overweight had significantly lower BP reductions (20.6 ± 11.9 and 20.5 ± 11.3 vs 21.7 ± 11.9 mm Hg in systolic BP; 11.7 ± 8.9 and 11.9 ± 8.7 vs 12.9 ± 9.0 mm Hg in diastolic BP; $P = .003$ and $P < .001$). Similarly, patients with abdominal obesity had lower BP reductions than non-abdominal-obese patients, with a reduction of 20.6 ± 11.5 vs 21.1 ± 11.6 mm Hg and 11.7 ± 8.6 vs 12.5 ± 8.9 mm Hg in systolic and diastolic BP, respectively, but only the difference in diastolic BP reached statistical significance ($P = .001$). On the other hand, patients with diabetes had significant lower BP reductions than the normal (19.9 ± 11.6 vs. 21.1 ± 11.7 mm Hg in systolic BP and 11.4 ± 8.6 vs 12.4 ± 8.9 mm Hg in diastolic BP; both $P < .001$).

As shown in Table 3, determinants of the magnitude of BP reduction were investigated in multivariate linear regression models, with taking age, male gender, BMI, waist circumference, current smoking, plasma glucose, LDL and HDL cholesterol, number of previous antihypertensive agents,

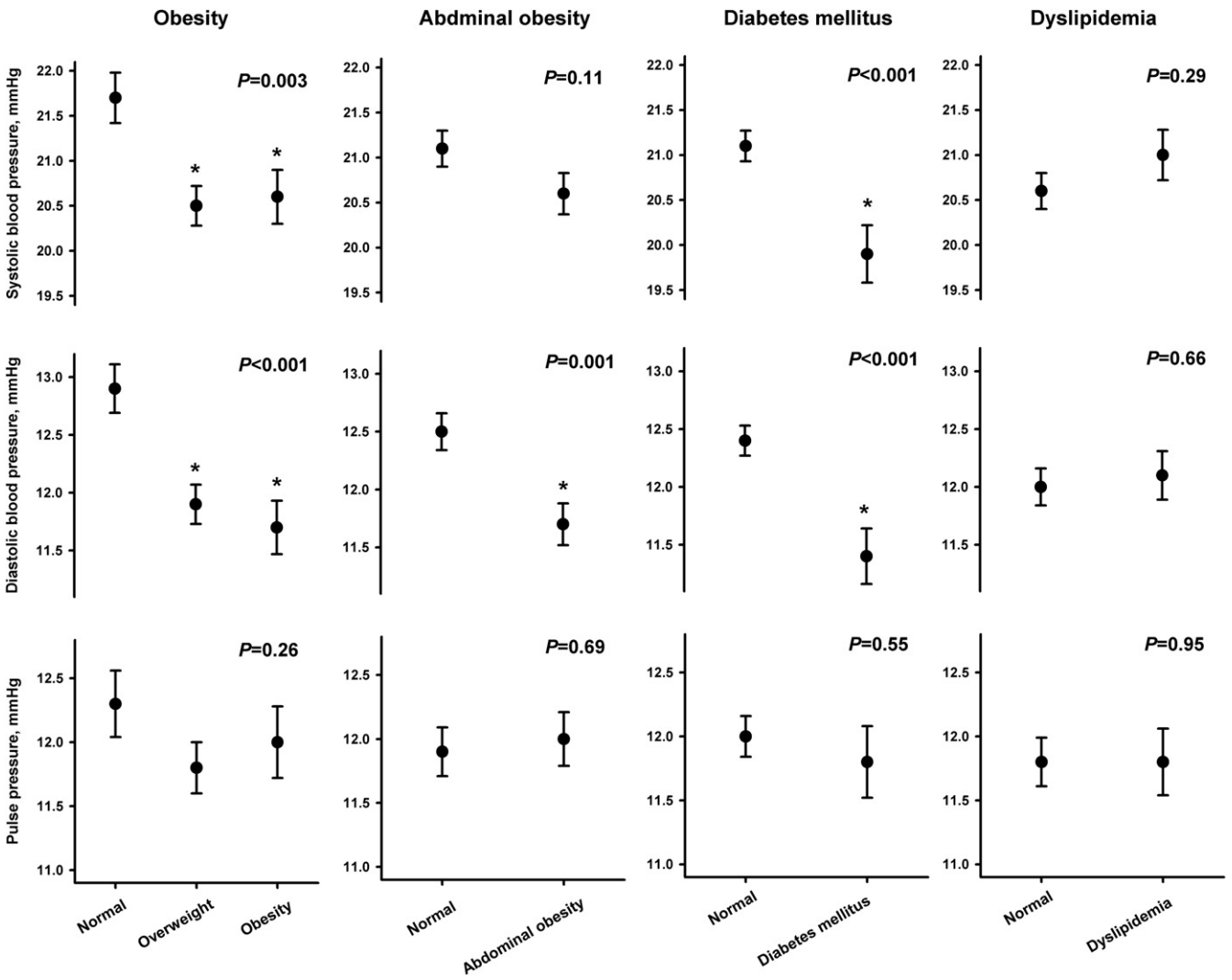

Figure 1. Comparison of the magnitude of blood pressure reduction between patients with and without related abnormalities. The magnitude of reductions in systolic and diastolic blood pressure and pulse pressure (mean and standard errors) were shown in patients with and without related abnormalities, such as obesity, abdominal obesity, diabetes mellitus, and dyslipidemia. Normal weight, overweight, and obesity were defined as body mass index <25 kg/m^2, 25 to 30 kg/m^2, and >30 kg/m^2, respectively. Abdominal obesity was defined as waist circumference >102 cm in men and >88 cm in women, respectively. Diabetes mellitus and dyslipidemia were defined by reviewing patients' medical document. *Indicates the difference in blood pressure reduction reached statistical significance between patients with and without related abnormalities.

Table 3
Determinants of the magnitude of blood pressure reduction

	Systolic Blood Pressure		Diastolic Blood Pressure		Pulse Pressure	
	$\beta \pm$ SE	*P*	$\beta \pm$ SE	*P*	$\beta \pm$ SE	*P*
Corresponding blood pressure, +10 mm Hg*	7.15 ± 0.11	<.001	6.52 ± 0.13	<.001	6.28 ± 0.11	<.001
Age, +10 years	-0.54 ± 0.11	<.001	-0.21 ± 0.10	.03	-0.29 ± 0.11	.007
Male gender, (1 = men, 0 = women)	–	–	–	–	–	–
Body mass index, kg/m^2	-0.08 ± 0.04	.04	-0.07 ± 0.03	.03	–	–
Waist circumference, +10 cm	-0.37 ± 0.14	.009	-0.51 ± 0.12	<.001	–	–
Current smoker, (1 = smoker, 0 = non-smoker)	–	–	–	–	–	–
Plasma glucose, mmol/L	–	–	–	–	–	–
Low-density lipoprotein cholesterol, mmol/L	-0.37 ± 0.13	.006	-0.31 ± 0.11	.006	–	–
High-density lipoprotein cholesterol, mmol/L	–	–	0.61 ± 0.25	.01	–	–
Number of previous antihypertensive agents	-0.62 ± 0.21	.004	–	–	-0.48 ± 0.20	.02

β, Estimated parameter; SE, standard error.
Multivariate linear regression models were applied to define the determinants of the magnitude of blood pressure reduction.
–Indicates non-significant.
* Indicates the corresponding blood pressure components at baseline.

and baseline BP level as potential confounders. Age and baseline BP level were the most pronounced determinants of the magnitude of BP reduction, and explained 47%, 36%, and 46% of the variation of BP reductions in systolic and diastolic BP and pulse pressure, respectively. In addition, only BMI, waist circumference, and LDL cholesterol stayed in the models accounting for the magnitude of BP reduction in systolic and diastolic BP ($P \leq .04$), while the impact of plasma glucose on the BP reduction became nonsignificant ($P \geq .08$).

With similar adjustment, determinants of BP control were investigated by multivariate logistic regression models. Older age, increased BMI, waist circumference, plasma glucose and baseline systolic BP, decreased HDL cholesterol, and more previous antihypertensive agents were in favor of not-at-goal systolic BP, with hazard ratios of 0.93 (0.87-0.99), 0.91 (0.83-1.00), 0.85 (0.77-0.93), 0.88 (0.82-0.94), 0.77 (0.73-0.83), 1.08 (1.02-1.16), and 0.81 (0.73-0.90), respectively (Figure 2). Increased BMI and baseline diastolic BP, and more frequently current smoking were in favor of not-at-goal diastolic BP, with hazard ratios of 0.89 (0.81-0.98), 0.74 (0.69-0.79), and 0.82 (0.68-0.98), respectively. Increased BMI and baseline diastolic BP were in favor of unsuccessful BP control in both systolic and diastolic BP, with hazard ratios of 0.90 (0.82-0.98) and 0.80 (0.55-0.86), respectively. Of note, in addition to baseline

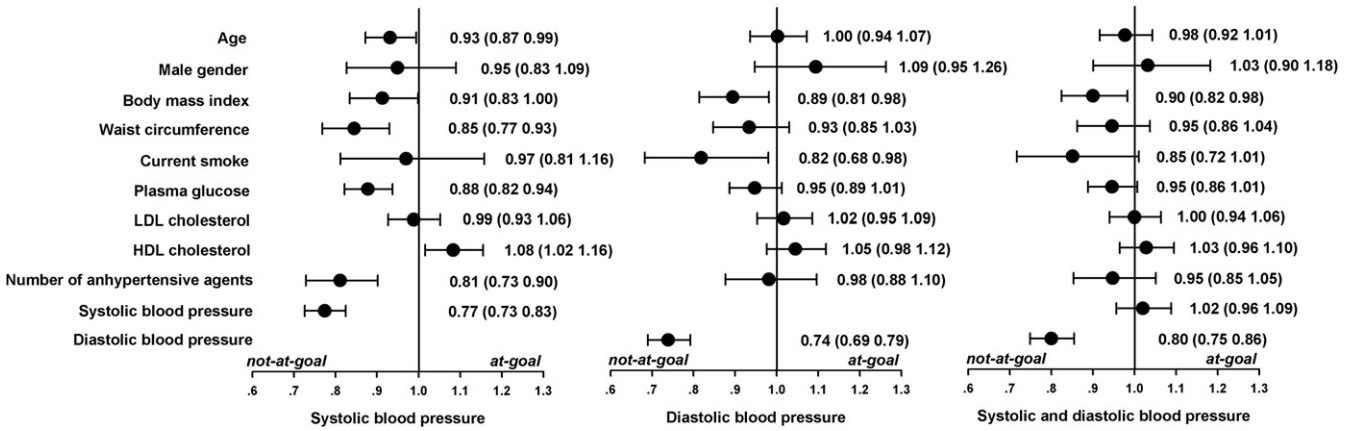

Figure 2. Determinants of blood pressure control of systolic and diastolic blood pressure and of both. Multivariate logistic regression models were applied to define the determinants of blood pressure control of systolic and diastolic blood pressure. Multivariate ordinal logistic regression model was applied to define the determinants of blood pressure control of both systolic and diastolic blood pressure, with 0 = blood pressure control of neither systolic nor diastolic blood pressure, 1 = blood pressure control of either systolic or diastolic blood pressure, and 2 = blood pressure control of both systolic and diastolic blood pressure. Odds ratio and 95% confidential interval were present on the right side of each plot, and calculated per 1-SD unit in quantitative variables and presence versus absence in qualitative variables.

BP level, BMI was the only factor in three models to influence successful BP control of either systolic or diastolic BP, and of both ($P \leq .04$).

Discussion

Major Findings

The present study contains two major findings: 1) after addition of a fixed combination of Perindopril and Amlodipine, 4342 (76.4%) patients had successful BP control of either systolic or diastolic BP, and 3537 (62.3%) of both; 2) in addition to baseline BP level, obesity was an independent determinant of BP reduction and of BP control.

Aggregation of Cardiovascular Risk in Patients With not-at-Goal Hypertension

Patients with not-at-goal hypertension, as observed in the present study, had quite high prevalence of many CV risk factors, namely 15.3% were current smokers, 25.6% were obese, 39.3% of men and 53.5% of women had abdominal obesity, 22.8% were diabetic, 35.1% had dyslipidemia, 12.0% had left ventricular hypertrophy, and 7.1% had microalbuminuria. Cuspidi et al also reported that, compared with patients with controlled BP, patients with resistant hypertension had a significant higher prevalence of left ventricular hypertrophy, increased carotid intima-media thickness, and microalbuminuria.[10] Similar findings could also be observed in other studies.[11,12] All these findings indicated that, no matter in patients with resistant or not-at-goal hypertension, the aggregation of CV risk factors was frequently reported, which indicated that the resistant condition of BP control in these patients was partly attributable to the risk aggregation.

Effect of Perindopril and Amlodipine on Blood Pressure Reduction

After addition of a fixed combination of Perindopril and Amlodipine, a reduction of about 20 mm Hg in systolic BP and 11 mm Hg in diastolic BP were observed, and about three-quarters of these patients had achieved successful BP control of either systolic or diastolic BP. This remarkable reduction in BP level, as well as a significant improvement in BP control, indicated that addition of a fixed combination of Perindopril and Amlodipine was efficient in most patients with not-at-goal hypertension.

Influential Factors for Blood Pressure Reduction

We found that, in the present study, patients with either obesity (overall or abdominal) or diabetes had significant lower BP reduction, as compared with patients without related abnormalities, but the similar finding was absent in patients with dyslipidemia, which indicated that obesity and diabetes, but not dyslipidemia, would have a negative impact on BP reduction. However, in multivariate analysis, we noted that, in addition to baseline BP level and age, only BMI and waist circumference, as well as LDL cholesterol, stayed in the models influencing the magnitude of BP reduction in systolic and diastolic BP, but the impact from plasma glucose was non-significant. Similarly, in multivariate analysis of BP control, in addition to baseline BP level, BMI was the only influential factor staying three models to affect BP control of systolic and diastolic BP, and of both, which highlighted the importance of obesity in the risk reduction strategy for successful BP control. In consistence with our finding, in the Framingham study, it was reported that the strongest predictor of lack of BP control was obesity, baseline BP level, and age.[13,14] In the Antihypertensive and Lipid-Lowering Treatment to Prevent Heart Attack Trial (ALLHAT) study, the predictors of resistant BP included obesity, older age, high baseline BP, and left ventricular hypertrophy.[15] In this respect, from a practical point of view, strengthened strategy for body weight reduction would be strongly recommended for a better BP control in patients with not-at-goal hypertension and obesity.

On the other hand, we also noted that, in the present study, the impact of diabetes on BP reduction was significant in univariate analysis, but became neglectable after full adjustment. This finding raised a question about whether patients with diabetes had poorer BP control only because of their obese stature. In order to test this hypothesis, we compared the magnitude of BP reductions after treatment in patients without obesity or diabetes ($n = 1661$), with obesity but no diabetes ($n = 3268$), and with both obesity and diabetes ($n = 1205$), and found that the reductions were 21.8 ± 12.1, 20.8 ± 11.4, and 19.8 ± 11.8 mm Hg in systolic BP ($P < .001$), and 12.9 ± 9.0, 11.9 ± 8.7, and 11.7 ± 8.9 mm Hg in diastolic BP (both $P < .001$), respectively. Furthermore, after adjustment for age and gender, the above-mentioned trend remained significant (both $P < .001$). This finding indicated that, even with a remarkable weight reduction, a better management of plasma glucose would remain beneficial for a better BP control. However, this hypothesis needs to be further confirmed by prospective interventional studies.

Strength and Limitations

A strength of the present study is its nationwide survey in patients with not-at-goal hypertension. On the other hand, as an open-label study without a control group, findings in the present study need to be carefully interpreted. The magnitude of BP control could be partly attributed to regression to the mean effect or to improved compliance in relation to participation to a clinical research protocol.

In summary, we found that addition of a fixed combination of Perindopril and Amlodipine to BP regimen was efficient, in terms of BP control, for 62.3% of those patients with not-at-goal hypertension. Furthermore, in addition to baseline BP level, obesity was an independent and significant influential factor of BP control.

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