Losartan/hydrochlorothiazide combination is safe and effective for morning hypertension in very elderly patients

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Abstract

Morning hypertension is an independent risk for cerebrovascular and cardiovascular events. Although the prevalence of morning hypertension increases with age, treatment of morning hypertension has not been established, particularly in very elderly patients. We compared the safety and efficacy of a losartan/ hydrochlorothiazide (HCTZ) combination in controlling morning hypertension between Very-Elderly (≥75 years) and Young/Elderly patients (<75 years). This study was a subanalysis of the Morning Hypertension and Angiotensin Receptor Blocker/Hydrochlorothiazide Combination Therapy study, in which patients with morning hypertension (≥135/85 mmHg) received a 50-mg losartan/12.5-mg HCTZ combination tablet (combination therapy) or 100-mg losartan (high-dose therapy) for 3 months. High adherence rates and few adverse effects were observed in Very-Elderly patients receiving combination (n=32) and high-dose (n=34) therapies and in Young/Elderly patients receiving combination (n=69) and high-dose (n=66) therapies. Baseline morning systolic BP (SBP) was similar in both age groups receiving either therapy. Morning SBP was reduced by 20.2 mmHg and 18.1 mmHg with combination therapy and by 7.1 mmHg and 9.1 mmHg with high-dose therapy in the Very-Elderly and Young/Elderly patients, respectively. Morning BP target

(<135/85 mmHg) was achieved in 40.6% and 55.1% by combination therapy and in 14.7% and 24.2% by high-dose therapy in the Very-Elderly and Young/Elderly patients, respectively. Neither therapy changed renal function and serum potassium in Very-Elderly patients. In conclusion, the losartan/HCTZ combination was safe and effective in controlling morning hypertension in Very-Elderly as well as Young/Elderly patients. In addition, combination therapy was also superior to high-dose therapy for lowering morning SBP in Very-Elderly patients.

Introduction

Morning hypertension, which is defined as the elevation of blood pressure (BP) in the early morning based on BP self-measurements performed at home, is an independent risk factor for cerebrovascular and cardiovascular events (1). As the incidence of morning hypertension increases with age (2), its management is becoming increasingly important in our current aging society. However, morning hypertension treatment has not been established, especially in very elderly patients.

Combinations of two or more antihypertensive agents are required in the majority of hypertensive patients (3). As it has been shown that the combination of an angiotensin receptor blocker (ARB) and a small dose of hydrochlorothiazide (HCTZ) have complementary mechanisms of action, effectively reduce BP, and are generally well tolerated, these drugs are often administered together (4,5). Our previous multicenter, prospective, randomized clinical trial Morning Hypertension and Angiotensin Receptor Blocker/Hydrochlorothiazide Combination Therapy (MAPPY) study demonstrated that a 3-month treatment of losartan/ HCTZ combination therapy was superior to high-dose losartan therapy in reducing morning systolic BP (SBP) (6). However, it remains unknown whether a losartan/HCTZ combination would be safe and

effective for morning hypertension treatments in very elderly patients. Therefore, this study investigated the safety and efficacy of losartan/HCTZ combination therapy in patients with morning hypertension (≥135/85 mmHg) aged <75 years (Young/Elderly group) and those aged ≥75 years (Very-Elderly group), who were registered in the MAPPY study.

Patients and methods

Study population

The MAPPY study was a 3-month prospective, randomized, open-labeled, parallel-group, multicenter trial, with a blinded end-point assessment (Clinical Trials Registration-Unique Identifier: NCT00795847). A total of 201 patients were enrolled in this subanalysis of the MAPPY study. Patients who were ≥75 years were allocated to the Very-Elderly group (n=66), while patients who were <75 years were allocated to the Young/Elderly group (n=135). This study was performed in accordance with the Declaration of Helsinki and was approved by the institutional review boards or the ethics committees of all of the participating institutions. All of the patients provided written informed consent.

Data collection and measurements

The design, trial management, and primary results of the MAPPY study have been described elsewhere (6). Briefly, this previous study enrolled on-treatment outpatients who had morning hypertension. Morning hypertension was defined as a morning SBP ≥135 mmHg, diastolic BP (DBP) ≥85 mmHg or both (7) on 7 consecutive days of the home BP self-measurements during the run-in period (at least 1 month). Patients were excluded from the study if they had secondary hypertension, malignant hypertension or uncontrolled hypertension, uncontrolled diabetes mellitus with an HbA1c ≥9.0%, a history of gout or serum uric acid ≥8.0 mg•dL^{-1}, serum creatinine ≥2.0 mg•dL^{-1}, serum potassium (K) ≥5.5 mmol•L^{-1}, liver damage (for example, alanine aminotransferase or γ-GTP level >3× the upper normal limit), administration of a thiazide diuretic, administration of an ARB or angiotensin-converting enzyme inhibitor (ACEI) exceeding the standard doses approved in Japan, and the presence of contraindications for thiazides or ARBs. After randomization, an antihypertensive agent was switched to a 50 mg losartan/12.5 mg HCTZ fixed-dose combination tablet (combination therapy) or to 100 mg losartan (high-dose therapy) once every morning without any washout period. If patients were receiving either an ARB or ACEI, it was changed to the appropriate test

drug. Once the 3-month treatment was started, there were no further changes in the antihypertensive agents prescribed. Patients were instructed to perform home BP self-measurement every day in the early morning (within 1 h after waking up, after urination, before dosing in the morning, before breakfast and after resting for 1-2 min in a sitting position) and in the evening (before bedtime, after resting for 1 to 2 min in a sitting position), in accordance with the Japanese Society of Hypertension Guidelines for the Management of Hypertension 2009 (8). Cuff oscillometry was applied through the use of electronic upper arm cuff devices. Each patient used the same type of home BP monitoring device throughout the study. On the day of the randomization, the initial evaluation (i.e., medical history, medications) and laboratory tests were performed after obtaining written informed consent. After the 3-month treatment, the follow-up evaluation and laboratory tests were repeated (6). The adherence rate to the medication was qualitatively assessed by asking the patient if he/she took the test drugs for $\geq$85%, 50-84%, or <50% of the time during each of the 28-day visit intervals (6).

Statistical analysis

Statistical analysis was performed using commercially available software (IBM SPSS Statistics 21.0J, IBM Japan). Data are expressed as the mean±SD. Because of the

skewed distributions, a geometric mean (95% confidence interval) was expressed and a natural logarithmic transformation was performed for the triglycerides and the B-type natriuretic peptide (BNP). Natural logarithm-transformed values were used for the statistical analyses and then reconverted to antilogarithm forms. Analysis of variance (ANOVA) followed by a post-hoc Scheffe's test for continuous variables or the chi-square test for categorized data was used for comparisons of baseline demographics and characteristics among the 4 groups. A chi-square test was used to compare the ratios of adverse events, medication adherence, and the target BP achievement among the groups. Repeated-measures two-way ANOVA followed by post-hoc Scheffe's tests were performed to compare the morning SBP, estimated glomerular filtration rate (eGFR), and serum K levels between the baseline and post-treatment. Changes in the morning SBP were compared using two-way ANOVA followed by post-hoc Scheffe's tests among the 4 groups. A $p<0.05$ was considered as statistically significant.

Results

Baseline characteristics and demographics

Table 1 shows the baseline characteristics and demographics for the 66 Very-Elderly

and 135 Young/Elderly patients. In the Very-Elderly group, 32 subjects were administered the losartan/HCTZ combination therapy and 34 were given high-dose losartan therapy. In the Young/Elderly group, 69 subjects were administered the combination therapy and 66 received the high-dose therapy. The baseline morning, evening, and office SBP did not differ among the 4 groups. Although the Very-Elderly patients had a lower baseline morning, evening, and office DBP compared to the Young/Elderly patients, there were no differences found between the 2 treatment groups. Baseline eGFR and triglycerides were lower and BNP was higher in the Very-Elderly patients compared to the Young/Elderly patients, whereas the levels did not differ between the losartan/HCTZ combination and the high-dose therapies. There were no differences in the other baseline parameters, comorbidity, and the number of administered antihypertensive agents among the 4 groups. In each group, more than 90% of the patients received either an ARB or an ACEI.

Safety assessment

During the 3-month treatment, most individuals in the two treatment groups of the Very-Elderly or Young/Elderly patients exhibited a medication adherence rate of 85% or more (Table 2). There were 5 (7.8%) Very-Elderly and 4 (3.0%) Young/Elderly patients

who experienced adverse events. There was no significant difference in the incidence of adverse events. Moreover, the incidence did not differ between the losartan/HCTZ combination and the losartan high-dose therapies in the Very-Elderly as well as in the Young/Elderly patients. There were no documented serious adverse effects, such as severe hyperkalemia, marked serum creatinine elevation, and symptomatic hypotension, in either of the patient groups.

Effects on morning SBP

The intention-to-treat analysis was performed to determine the effects of the losartan/HCTZ combination and the high-dose losartan therapies on the morning SBP levels. After the 3-month treatment, the combination therapy reduced the morning SBP from 154.0±11.5 to 133.8±14.9 mmHg ($p<0.01$), while the high-dose losartan therapy decreased the morning SBP from 152.6±10.0 to 145.5±16.2 mmHg ($p<0.01$) in the Very-Elderly patients (Figure 1). In the Young/Elderly patients, the combination therapy reduced the morning SBP from 148.8±9.3 to 130.6±9.8 mmHg ($p<0.01$), while the high-dose therapy reduced the morning SBP from 150.1±8.7 to 141.1±12.3 mmHg ($p<0.01$). The combination therapy decreased the post-treatment morning SBP to levels that were lower than the high-dose therapy in the Very-Elderly and Young/Elderly

patients ($p<0.05$ and $p<0.01$, respectively).

In the Very-Elderly patients, the target achievement rates for the morning BP after the 3-month treatment were 40.6% for the losartan/HCTZ combination therapy and 14.7% for the high-dose losartan therapy. In the Young/Elderly patients, the achievement rates were 55.1% for the combination therapy and 24.2% for the high-dose therapy. The combination therapy exhibited higher target achievement rates in both the Very-Elderly and Young/Elderly patients ($p<0.05$ and $p<0.001$, respectively). However, there was no significant difference noted for the target achievement rates between the Very-Elderly and Young/Elderly patients.

Effects on morning SBP reduction

Changes in the morning SBP (Δmorning SBP) during the 3-month treatment were investigated on the basis of the available-case analysis, i.e., an analysis that examined subjects with available data for both the morning SBP measurements before and after the 3-month treatment. The Δmorning SBP values were -20.2±14.8 mmHg for the combination therapy and -7.1±12.7 mmHg for the high-dose therapy in the Very-Elderly patients (Figure 2). The Δmorning SBP values in the Young/Elderly patients were -18.1±11.7 mmHg for the combination therapy and -9.1±12.4 mmHg for the high-dose

therapy. Combination therapy induced a greater SBP reduction compared to the high-dose therapy in both age groups ($p<0.01$ for both). However, there was a similar efficacy of the two therapies for the morning SBP reduction between the Young/Elderly and Very-Elderly patients.

Effects on eGFR and serum K levels

Baseline eGFR was lower in the Very-Elderly patients versus the Young/Elderly patients of either therapy group, whereas the serum K levels were similar among the 4 groups at baseline (Table 1). The intention-to-treat analysis showed that neither treatment caused any significant changes in the eGFR and serum K levels in either of the age groups (Figure 3).

Effects on evening and office SBP

Baseline values for the evening and office SBP did not differ among the Very-Elderly combination, Very-Elderly high-dose, Young/Elderly combination, and Young/Elderly high-dose groups (Table 1). Both the combination and high-dose therapies significantly reduced the evening and office SBP in the Very-Elderly and Young/Elderly patients ($p<0.01$ for all) (Figure 4A). The combination therapy induced a greater office SBP reduction versus the high-dose therapy in the Very-Elderly and Young/Elderly patients

($p<0.01$ and $p<0.05$, respectively) (Figure 4B). A similar trend was observed for the effects on the evening SBP, although the changes did not reach statistical significance. There was no difference observed for the combination or high-dose therapy with regard to the extent of the induced reduction in the evening and office SBP between the Very-Elderly and Young/Elderly patients.

Discussion

The present study demonstrated that the losartan/HCTZ combination therapy was superior to the high-dose losartan therapy in controlling morning hypertension in the Very-Elderly patients (Figure 1). In addition, the combination therapy reduced morning SBP in the Very-Elderly patients to levels that were similar to those of the Young/Elderly patients (Figure 2). Moreover, both the combination and high-dose therapies were found to be safe and tolerable for the Very-Elderly as well as the Young/Elderly patients (Table 2).

Morning hypertension, which is a characteristic feature of elderly hypertension, is associated with an increased cerebrovascular and cardiovascular event risk (9-11). Since low-renin essential hypertension and hypertension with increased

salt-sensitivity are often found in elderly patients (12), salt and water retention are believed to be involved in the mechanism of morning hypertension in this patient group. Thus, it has been suggested that HCTZ would be effective in the treatment of morning hypertension in the elderly. In addition, since HCTZ has a very long duration of action and a large trough/peak ratio, it is also considered to be suitable for stably lowering the BP over a 24-hour period. The current guidelines for the management of hypertension in Europe, the United States and Japan recommend the use of a low dose of thiazide diuretics as one of the first-line drugs for the treatment of elderly hypertension (13-15). As we found that more than 90% of the Very-Elderly patients in the present study had received an ARB at baseline (Table 1), this suggests that the addition of HCTZ or an increased dose of ARB might be a practical option as the next step in controlling morning hypertension. However, due to concern for potential adverse effects, e.g., dehydration, electrolyte abnormality, and excess BP lowering, diuretics are underused in the treatment of elderly hypertension in Japan. Although our previous MAPPY study demonstrated that the losartan/HCTZ combination was both safe and superior to high-dose losartan in treating morning hypertension (6), this study did not determine if these results were also applicable to the very elderly patient population.

In the present study, our safety assessment indicated that both the 3-month losartan/HCTZ combination and the high-dose losartan therapies were safe and tolerable in the Very-Elderly as well as the Young/Elderly patients. Also, it was noteworthy that the combination therapy did not induce any serious adverse effects or affect the renal function and serum K in the Very-Elderly patients.

The most important finding of the present study was that the losartan/HCTZ combination therapy induced a greater reduction in the morning SBP and a higher target achievement rate of the morning BP, as compared with the high-dose losartan therapy in the Very-Elderly patients (Figures 1 and 2). In addition, the beneficial effects found for the Very-Elderly patients were comparable to those observed in the Young/Elderly patients. These observations are in line with the Hypertension in the Very-Elderly Trial (HYVET), which demonstrated that indapamide-based therapy effectively reduced all-cause mortality and cardiovascular events in hypertensive patients who were ≥80 years (16).

Although our results suggested that one of the beneficial effects of the losartan/HCTZ combination therapy was control of the evening and office SBP, these changes were less consistent than those found for the morning SBP, especially in the

Very-Elderly patients (Figure 4). The reason for the differences observed remains unknown at the present. However, these observations might be related to the fact that older subjects are known to have larger fluctuations of their office BP (i.e., visit-to-visit BP variability) (17) and that the evening SBP is strongly influenced by the measurement conditions, such as drinking alcohol and bathing (18).

In the present study, most subjects received an ARB or ACEI before being switched to the losartan/HCTZ combination or high-dose losartan (Table 1). While it would have been interesting to be able to determine the possible difference in the effects on the safety and efficacy of the test drugs between the preceding ARB and ACEI, the small number of patients receiving ACEI precluded any further analysis of this in our study. It has also been shown that the administration of an α-blocker prior to going to bed is useful in the management of morning hypertension (19). Thus, co-administration with an α-blocker might have an impact on the efficacy of the losartan/HCTZ combination and the high-dose losartan. However, the number of patients taking an α-blocker in our study was too small for a statistical evaluation. Moreover, there were no data available on whether an α-blocker was prescribed in the morning or in the evening in these patient groups. Therefore, the potential differential effects between

ARB and ACEI and potential effects of α-blockers will need to be further investigated in future studies.

There were several limitations for the current study. First, there were only a small number of patients in each group, as this was a subanalysis of our previous MAPPY study. Therefore, we need to be careful in interpreting the results of the present study due to the low statistical power of the analysis. Second, high-dose losartan was only administered once every morning in the current study. It is possible that the administration of high-dose losartan would be more effective for controlling morning hypertension if it was administered once in the evening or if the dose was halved and then administered both in the morning and in the evening. This issue will need to be addressed in a future study. Third, the majority of the patients enrolled in this study were not observed during the summer season. Thus, we cannot deny the possibility that there would be an increased prevalence of adverse effects for the combination therapy during the summer, such as dehydration, fainting, symptomatic hypotension, and renal dysfunction. Finally, a further randomized study with a larger patient number and longer observation period will need to be undertaken in order to determine the long-term safety and efficacy of the losartan/HCTZ combination therapy for cardiovascular morbidity

and mortality in very elderly patients.

In conclusion, losartan/HCTZ combination therapy was safe and effective in controlling morning hypertension in very elderly patients with ages ≥75 years, as well as in young/elderly patients who were <75 years. In addition, losartan/HCTZ combination therapy was superior to high-dose losartan therapy in lowering the morning SBP in very elderly patients. These findings suggest that the addition of HCTZ may be a desirable option even in very elderly patients when the target morning BP cannot be achieved by only an ARB.

Declaration of interest

The authors report no conflicts of interest. The authors alone are responsible for the content and writing of the paper.

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Figure legends

Figure 1. Effects of a 3-month treatment with 50 mg losartan/12.5 mg hydrochlorothiazide combination therapy (Combination) or high-dose (100 mg) losartan therapy (High-dose) on the systolic blood pressure (BP). The intention-to-treat analysis was performed for the combination therapy (n=69) and high-dose therapy (n=66) groups in the Young/Elderly (<75 years) and for the combination therapy (n=32) and high-dose therapy (n=34) in the Very-Elderly patients (≥75 years). Bar=1 x SD. **p<0.01 vs. Baseline. #p<0.05 and ##p<0.01 vs. High-dose.

Figure 2. Effects of a 3-month treatment with losartan/hydrochlorothiazide combination therapy (Combination) and high-dose losartan therapy (High-dose) on the changes in the morning SBP (Δmorning SBP). The Δmorning SBP change was calculated on the basis of the available-case analysis in the subjects who had paired data available for both the morning SBP values at baseline and post-treatment (Young/Elderly combination, n=53; Young/Elderly high-dose, n=47; Very-Elderly combination, n=21; Very-Elderly high dose, n= 24). NS, not significant.

Figure 3. Effects of 3-month treatment with losartan/hydrochlorothiazide combination therapy (Combination) and high-dose losartan therapy (High-dose) on estimated glomerular rate (eGFR) (A) and serum potassium (K) (B). The intention-to-treat analysis was performed as described in Figure 1. *$p<0.05$ vs. Baseline. #$p<0.05$ vs. High-dose.

Figure 4. Effects of 3-month losartan/hydrochlorothiazide combination therapy (Combination) and high-dose losartan therapy (High-dose) on the evening and office SBP levels (A, the intention-to-treat analysis) and on the evening and office SBP changes (Δevening SBP and Δoffice SBP) (B, the available-case analysis). Bar=1 x SD. **$p<0.01$ vs. Baseline. ##$p<0.01$ vs. High-dose.

Table 1. Baseline characteristics and demographic

	Young/elderly		Very elderly		
	Patients <75 years old		Patients ≥75 years old		
	Combination	High dose	Combination	High dose	P-value
Number, n	69	66	32	34	-
Age, year	62.6 ± 9.0	62.7 ± 8.7	79.1 ± 4.1	78.2 ± 3.1	0.000
Male, n (%)	42(58.8)	29(42.9)	19(62.1)	12(34.4)	0.039
BMI, kgm^{-2}	24.0 ± 3.0	24.6 ± 3.1	23.9± 3.1	22.6 ± 3.1	0.068
Morning BP					
Systolic BP, mmHg	148.9 ± 9.2	150.9 ± 10.0	153.8 ± 11.2	153.3 ± 10.4	0.142
Diastolic BP, mmHg	85.7 ± 9.6	86.9 ± 9.4	80.6 ± 5.5	79.3 ± 7.3	0.001
Evening BP					
Systolic BP, mmHg	140.3 ± 12.1	139.8 ± 10.4	145.0 ± 15.9	140.1 ± 12.0	0.497
Diastolic BP, mmHg	78.9 ± 10.0	77.4 ± 8.1	73.6 ± 7.6	73.4 ± 8.9	0.052
Office BP					
Systolic BP, mmHg	146.1± 13.2	148.7 ± 13.6	150.1 ± 17.0	146.5 ± 15.3	0.622
Diastolic BP, mmHg	82.5 ± 11.8	81.6± 10.4	75.7 ± 7.8	75.9 ± 9.3	0.006
eGFR, ml per min per $1.73m^2$	70.3 ± 12.5	76.0 ± 16.6	60.8 ± 14.6	62.1 ± 15.1	0.000
K, $mmoll^{-1}$	4.3 ± 0.3	4.3 ± 0.4	4.4 ± 0.4	4.3 ± 0.4	0.322
Uric acid, mg dl^{-1}	5.6 ± 1.4	5.7 ± 1.5	6.1 ± 2.2	5.7 ± 1.4	0.608
LDL cholesterol, mg dl^{-1}	108.8 ± 30.8	120.8 ± 28.6	103.6 ± 28.5	111.6 ± 22.8	0.069
HDL cholesterol, mg dl^{-1}	59.6 ± 14.4	57.0 ± 14.6	56.1 ± 12.9	58.1 ± 15.9	0.724
Triglycerides, mg dl^{-1a}	110 [55-290]	123 [37-270]	93 [44-241]	94 [41-166]	0.030
HbA1c, %	5.6 ± 0.6	5.5 ± 0.4	5.9 ± 0.6	5.5 ± 0.6	0.163
BNP, pg ml^{-1a}	22.1 [4.0-229.4]	28.1 [2.1-188.0]	42.6 [5.9-284.0]	60.7 [16.6-222.2]	0.002
Comorbidity n (%)					
Diabetes	11(16.4)	7(11.1)	9(31.0)	6(18.9)	0.134
Dyslipidemia	25(37.3)	27(42.9)	12(41.4)	14(43.8)	0.906
CAD	5(7.5)	4(3.2)	5(17.2)	5(12.5)	0.501
CVD	3(5.8)	2(4.3)	5(17.2)	4(12.5)	0.235
Smoking	5(8.1)	11(19.0)	3(10.3)	4(12.5)	0.339
Treatment during the run-in period					
No. of antihypertensive drug	1.63 ± 0.93	1.41 ± 0.62	1.95 ± 0.74	1.79 ± 0.78	
ACEi	1(1.6)	4(6.6)	1(3.6)	1(3.2)	0.879
ARB	56(88.9)	53(86.9)	26(92.9)	29(90.6)	0.936
Ca channel blockers	24(37.5)	24(39.3)	13(46.4)	20(62.5)	0.087

α-blockers	6(9.4)	0(0.0)	2(7.1)	1(3.1)	0.092
β-blockers	15(23.4)	5(8.2)	7(25.0)	5(15.6)	0.092
Loop diuretics	0(0.0)	1(1.6)	1(3.6)	1(3.1)	0.524
Spironolactone	1(1.6)	1(1.6)	1(3.6)	0(0.0)	0.758

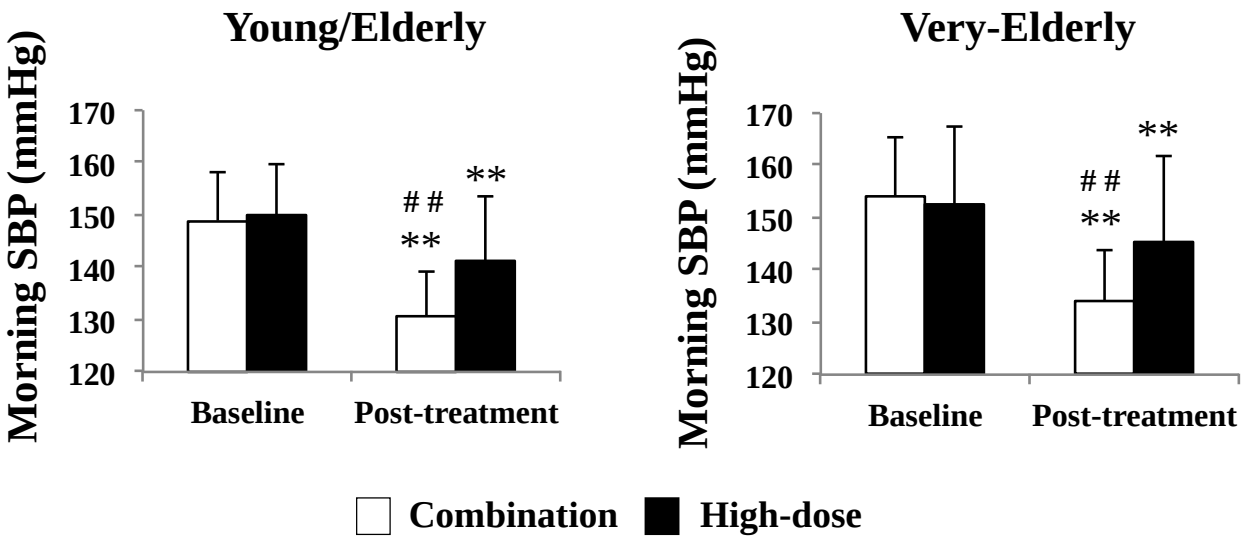
BMI, body mass index; BP, blood pressure; eGFR, estimated glomerular filtration rate; LDL, low-density lipoprotein; HDL, low-density lipoprotein; BNP, brain-type natriuretic peptide; CAD, coronary artery disease; CVD, cerebrovascular disease; ARB, angiotensin receptor blocker; ACEi, angiotensin-converting enzyme inhibitor.

Data are described as n (%), mean±SD, or geographic mean (95% confidence interval).

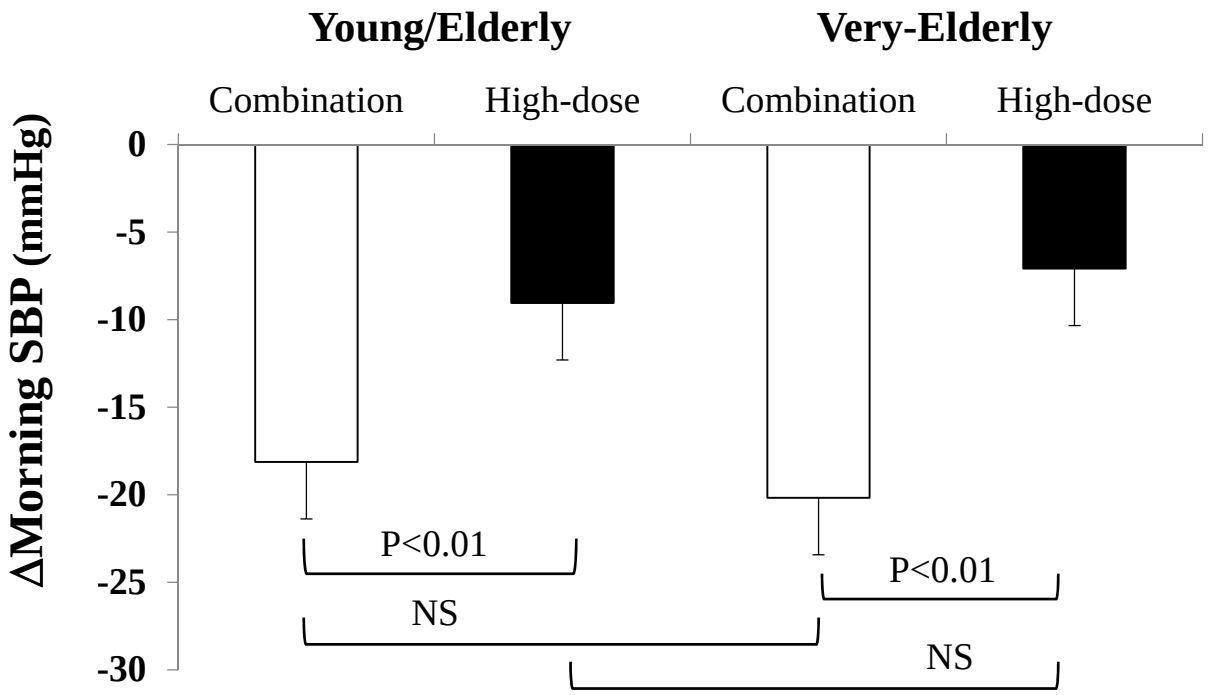
Table 2. Medication Adherence and Adverse Events

Medication adherence, %	1 month	2 month	3 month
Young/Elderly (<75)			
Combination			
≥80 %	98	100	97
50-80 %	2	0	2
<50 %	0	0	2
High -dose (%)			
≥80 %	98	98	100
50-80 %	2	2	0
<50 %	0	0	0
Very-Elderly (≥75)			
Combination (%)			
≥80 %	100	100	100
50-80 %	0	0	0
<50 %	0	0	0
High -dose (%)			
≥80 %	96	96	97
50-80 %	4	2	3
<50 %	0	0	0

Adverse events, n (%)	N	Intractable high BP	Headache	Hot flash	itchy eye	Urticaria	Palpitation	Creatinine elevation	Total
Young/Elderly (<75)									
Combination	69	1 (1.4)	0	0	0	0	0	0	1 (1.4)
High -dose	66	1 (1.5)	1 (1.5)	0	0	1 (1.5)	0	0	3 (4.5)
Very-Elderly (≥75)									
Combination	32	0	1 (3.1)	0	1(3.1)	0	0	1 (3.1)	3 (9.4)
High -dose	34	0	0	1 (2.9)	0	0	1 (2.9)	0	2 (5.9)

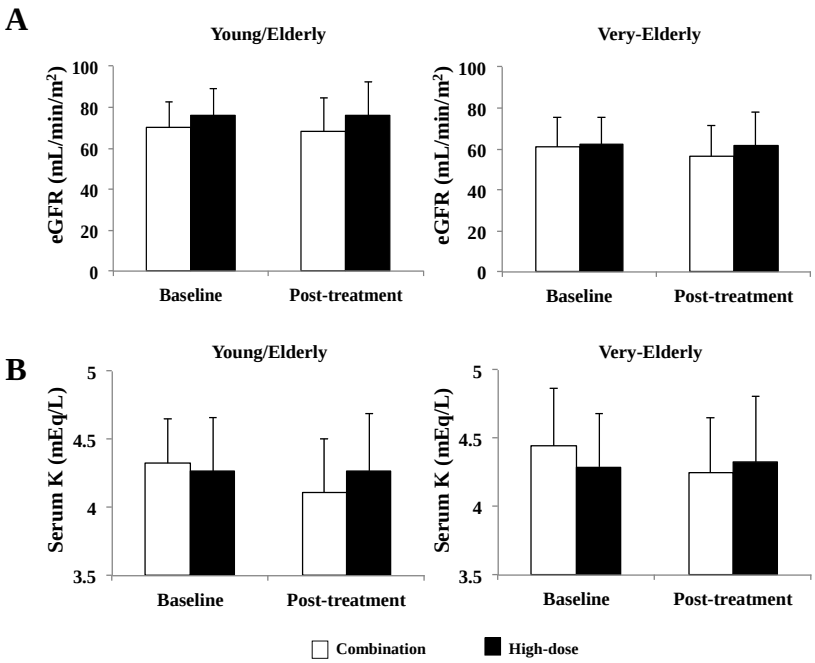

Young/Elderly
Very-Elderly
Morning SBP (mmHg)
170
160
150
140
130
120
Baseline
Post-treatment
# #
**
Combination
High-dose

New Figure 1


Young/Elderly
Very-Elderly
Combination
High-dose
Combination
High-dose
ΔMorning SBP (mmHg)
0
-5
-10
-15
-20
-25
-30
P<0.01
P<0.01
NS
NS

New Figure 2

New Figure 3


A
Young/Elderly
Very-Elderly
eGFR (mL/min/m2)
100
80
60
40
20
0
Baseline
Post-treatment
B
Serum K (mEq/L)
5
4.5
4
3.5
Combination
High-dose

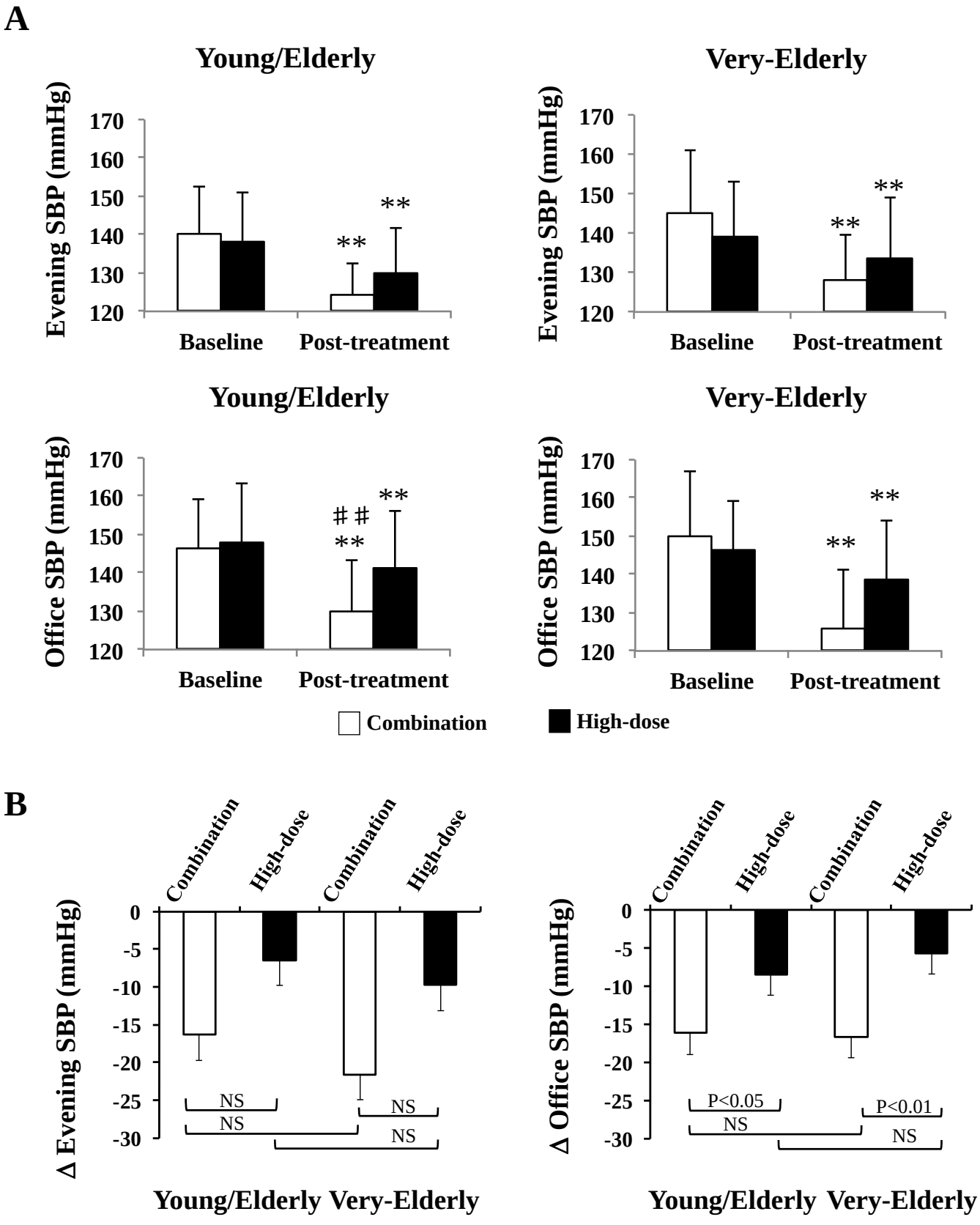

A
Young/Elderly
Very-Elderly
Evening SBP (mmHg)
Office SBP (mmHg)
170
160
150
140
130
120
**
##
Baseline
Post-treatment
Combination
High-dose
B
Δ Evening SBP (mmHg)
Δ Office SBP (mmHg)
0
-5
-10
-15
-20
-25
-30
NS
P<0.05
P<0.01
Young/Elderly
Very-Elderly

Figure 4