



Twenty-four-hour ambulatory blood pressure changes in older patients with essential hypertension receiving monotherapy or dual combination antihypertensive drug therapy

Pei-Pei LU^{1,2,4}, Xu MENG^{1,2}, Ying ZHANG^{1,2}, Yan-Qi LI², Shu WANG², Li-Sheng LIU^{1,2},
Wen WANG^{1,2}, Yu-Ling LI³, Yu-Qing ZHANG¹, Ai-Hua HU², Xian-Liang ZHOU¹, Li-Hong MA⁴

¹Department of Cardiology, Fuwai Hospital, National Center for Cardiovascular Diseases, Chinese Academy of Medical Science and Peking Union Medical College, Beijing, China

²Clinical Trial and Research Center, Beijing Hypertension League Institute, Chinese Hypertension League, Beijing, China

³Xinjiekou Community Health Service Center, Beijing, China

⁴Department of Traditional Chinese Medicine, Fuwai Hospital, National Center for Cardiovascular Diseases, Chinese Academy of Medical Sciences and Peking Union Medical College, Beijing, China

Abstract

Objective To evaluate the differences in 24-hour ambulatory blood pressure (BP) in older patients with hypertension treated with the five major classes of antihypertensive drugs, as monotherapy or dual combination therapy, to improve daytime and nighttime BP control. **Methods** We enrolled 1920 Chinese community-dwelling outpatients aged ≥ 60 years and compared ambulatory BP values and ambulatory BP control (24-hour BP $< 130/80$ mmHg; daytime mean BP $< 135/85$ mmHg; and nighttime mean BP $< 120/70$ mmHg), as well as nighttime BP dip patterns for monotherapy and dual combination therapy groups. **Results** Patients' mean age was 71 years, and 59.5% of patients were women. Calcium channel blockers (CCBs) constituted the most common (60.3% of patients) monotherapy, and renin-angiotensin system (RAS) blockers combined with CCBs was the most common (56.5% of patients) dual combination therapy. Monotherapy with beta-blockers (BB) provided the best daytime BP control. The probabilities of having a nighttime dip pattern and nighttime BP control were higher in patients receiving diuretics compared with CCBs (OR = 0.52, $P = 0.05$ and OR = 0.41, $P = 0.007$, respectively). Patients receiving RAS/diuretic combination therapy had a higher probability of having controlled nighttime BP compared with those receiving RAS/CCB (OR = 0.45, $P = 0.004$). Compared with RAS/diuretic therapy, BB/CCB therapy had a higher probability of achieving daytime BP control (OR = 1.27, $P = 0.45$). **Conclusions** Antihypertensive monotherapy and dual combination drug therapy provided different ambulatory BP control and nighttime BP dip patterns. BB-based regimens provided lower daytime BP, whereas diuretic-based therapies provided lower nighttime BP, compared with other antihypertensive regimens.

J Geriatr Cardiol 2019; 16: 354–361. doi:10.11909/j.issn.1671-5411.2019.04.005

Keywords: Aging; Ambulatory blood pressure monitoring; Antihypertensive drugs; Beta-blockers; Diuretics

1 Introduction

Ambulatory blood pressure monitoring (ABPM) has become a valuable tool to assess blood pressure (BP) because

it provides more accurate blood pressure assessment and better prognosis for cardiovascular morbidity and mortality compared with office BP.^[1,2] Another advantage of ABPM is that it provides nighttime BP measurements and identifies nighttime BP dipping, which are both more closely associated with future cardiovascular complications than daytime BP, in population-based trials.^[3,4] Previous trials have also reported that lowering nighttime BP with antihypertensive drugs may improve cardiovascular prognosis.^[5,6]

The benefits of antihypertensive drugs in terms of preventing cardiovascular events are well established in patients with hypertension, based on several clinical trials reporting the BP-lowering effects of these drugs, assessed using office BP.^[7] A previous systematic review evaluating

Correspondence to: Xian-Liang ZHOU & Li-Hong MA, Department of Cardiology, Fuwai Hospital, National Center for Cardiovascular Diseases, Chinese Academy of Medical Science and Peking Union Medical College, Beijing, China (ZHOU XL) and Department of Traditional Chinese Medicine, Fuwai Hospital, National Center for Cardiovascular Diseases, Chinese Academy of Medical Sciences and Peking Union Medical College, Beijing, China (MA LH). E-mails: zhouxianliang0326@hotmail.com (ZHOU XL) & mlh8168@163.com (MA LH)

Received: March 1, 2019

Revised: March 4, 2019

Accepted: April 18, 2019

Published online: April 28, 2019

differences in antihypertensive treatment-induced changes between office BP and ambulatory BP showed that the measured treatment effect was greater with office BP than with ambulatory BP.^[8] However, data are limited for ambulatory BP changes in patients with hypertension treated with different classes and combinations of antihypertensive drugs based on recommended by international guidelines to achieve BP targets.

Nighttime BP is an independent predictor of cardiovascular outcomes.^[4,9] However, few studies have evaluated the optimal treatment to control nighttime BP, and abnormal nocturnal BP is more prevalent in older than in younger patients.^[10,11] Therefore, we aimed to investigate differences in ambulatory BP, especially nighttime BP, in older patients with hypertension treated with monotherapy *vs.* dual combination therapy with antihypertensive drugs.

2 Methods

2.1 Patients

The Beijing Hypertension League Institute developed a new BP management tool that uses ABPM and home BP monitoring with remote BP monitoring technology to improve BP control in Chinese patients with hypertension. The development of this tool was funded by the Chinese Ministry of Sciences and Technology and supported technologically by Kang Information Technology Co., Ltd. (Beijing, China). The devices were approved by the Chinese Food and Drug Administration.

This study involved 58 centers in 16 provinces of China, and was performed from April 2017 to August 2018. We recruited 15000 patients aged ≥ 60 years who had ABPM data and defined monotherapy and dual combined antihypertensive drug therapy regimens. Among the 15000 potential patients, we enrolled community-dwelling outpatients to undergo 24-h ABPM if they had an office BP $\geq 140/90$ mmHg or were taking antihypertensive drugs ($n = 1920$, combined). We excluded patients with disability, dementia, and conditions for which their physicians considered them unsuitable to participate in the study. To avoid the effect of metabolic disorders, we included only patients with body mass index (BMI) ≥ 18 kg/m² in the final analyses. All included patients were encouraged to measure their BP at home. At the same time, this study protocol was approved by the ethics committees in each center. All patients provided informed consent.

2.2 BP measurements

Following complete physical examinations, we asked patients to measure their 24-h ABPMs using the ABPM de-

vice that we provided (KC2300A; Kang Information Technology Co., Ltd.), which were programmed to record BP at 15-minute intervals during the day and at 30-minute intervals during the night. The default daytime hours were from 6:00 am to 10:00 pm, and the default nighttime hours were from 10:00 pm to 6:00 am. The ABPM devices were equipped with a General Packet Radio Service wireless transmission module that transmitted BP values in real time to the Hypertension Management Cloud Platform using mobile internet. The Cloud Platform stored and analyzed the ABPM data and then created standardized analysis reports. We asked patients to perform their usual daily activities and to return the following morning to have the device removed. We also asked patients to keep their arm still during cuff inflation.

To account for patients' nighttime involuntary movements, ABPM records were considered valid if there were more than 80% successful systolic BP (SBP) and diastolic BP (DBP) recordings in the 24-h period. Daytime and nighttime durations were defined according to patients' self-reported times for waking and retiring.

Nocturnal dip was defined as the relative decline in mean nighttime SBP compared with mean daytime values. We defined patients with extreme dip, expected dip, no dip, and risers as $> 20\%$, $10\%–20\%$, $0\%–10\%$, or $< 0\%$ relative decline, respectively. Among patients receiving antihypertensive treatment, those with a mean daytime BP $< 135/85$ mmHg, mean 24-h BP $< 130/80$ mmHg, and mean nighttime BP $< 120/70$ mmHg were considered to have controlled BP.

2.3 Statistical analysis

Data were presented as means \pm SD for continuous variables and as percentages for categorical variables. Differences in BP values between different drug classes and for dual combinations of these classes were assessed by one-way analysis of variance. We performed post-hoc analyses using the Bonferroni method to compare differences between any two groups and the χ^2 test to analyze differences between categorical variables. Logistic regression was performed to assess the odds ratios (ORs) of the association between the different antihypertensive drugs and combination therapies, and the BP dip pattern and BP control after adjusting for age, sex, and BMI. We used SPSS software for Windows (version 22.0, IBM SPSS, Inc., Armonk, NY) for all statistical analyses, and two-tailed $P < 0.05$ was considered statistically significant.

3 Results

3.1 Patient characteristics

The included 1920 patients had a mean age of 71 years,

59.5% were women, and 164 patients (8.5%) received no antihypertensive drugs. Among treated patients, 1243 patients (64.7%) were receiving monotherapy with an antihypertensive drug, while 513 (26.7%) were taking dual combination therapy. The mean 24-h, daytime, and nighttime BPs were similar between the monotherapy group and the dual combination therapy group (Table 1).

3.2 Differences between antihypertensive drug class

Seventy-seven patients were taking beta-blockers (BBs), namely, metoprolol (66.2%) and bisoprolol (27.3%). In the diuretic-treated group, 29 (64.4%) patients were taking hydrochlorothiazide, and 16 patients (35.6%) were taking indapamide as monotherapy. The main angiotensin-converting enzyme inhibitors were perindopril (25.0% of patients), fosinopril (22.5%), enalapril (21.3%), benazepril (18.8%), and captopril (11.3%). The main angiotensin receptor blockers were valsartan (32.3% of patients), irbesartan (24.4%), telmisartan (18.2%), and losartan (16.8%). The largest group receiving monotherapy comprised patients treated with calcium channel blockers (CCBs) ($n = 750$), namely, amlodipine (58.1% of patients), nifedipine (33.6%), and felodipine (6.4%).

Table 2 shows the mean BPs, circadian BP patterns, and BP control rates in groups stratified by the five major drug classes. Although patients treated with antihypertensive drugs had significant BP reduction compared with untreated patients, different drug classes were associated with different BP-lowering effects. Patients treated with BBs had lower BP for all BP categories and better daytime BP control (59.7% of patients), but a lower percentage of patients

had a dip pattern (16.9%) compared with other monotherapies. For nighttime BP, patients treated with diuretics had the highest rate of nighttime BP control (33.3%) and tended to have a dip pattern (33.3%), whereas CCB-treated patients had the lowest rate of nighttime BP control (18.0%).

Compared with the diuretic group, patients treated with all other antihypertensive drug classes tended to have lower probabilities of having a dip pattern, and patients treated with BBs had the lowest probability (OR = 0.38, 95% CI: 0.16–0.91), as shown in Figure 1A. Regarding BP control, BBs had better effects on daytime BP control compared with diuretics (OR = 2.22, 95% CI: 1.04–4.73) (Figure 2A), while diuretics were more likely to increase nighttime BP control compared with the CCB group (OR = 0.41, 95% CI: 0.21–0.79; diuretic group as reference) (Figure 2B).

3.3 Differences between dual combination therapies

We analyzed data for 513 patients taking dual combination therapy, namely, renin–angiotensin system (RAS) blockers/BB: 55 patients; RAS/diuretics: 80 patients; RAS/CCB: 290 patients; and BB/CCB: 88 patients. We excluded patients receiving CCB/diuretics, BB/diuretics, and α -blocker-based combinations because of low patient numbers (each therapy included less than 20 patients).

Table 3 shows the mean BPs, circadian BP patterns, and BP control rates in patients stratified by the different dual combination therapies. Antihypertensive dual combination therapy significantly lowered office and ambulatory BP. Among the four combinations, patients treated with RAS/CCB had higher ambulatory BP, and patients treated with BB/CCB had lower daytime BP, compared with other

Table 1. Patients' characteristics stratified according to monotherapy or dual combination antihypertensive therapy.

	Total ($n = 1920$)	Untreated ($n = 164$)	Single drug ($n = 1243$)	Two-drug combination ($n = 513$)	<i>P</i> -value*
Age, yrs	70.9 ± 7.8	70.7 ± 8.0	71.0 ± 7.8	70.9 ± 7.7	0.89
Female	59.5%	56.7%	60.9%	57.1%	0.25
BMI, kg/m ²	25.8 ± 4.9	25.4 ± 3.6	25.8 ± 5.2	26.0 ± 4.7	0.38
SBP, mm Hg					
Office	147.7 ± 18.7	157.0 ± 9.9	145.5 ± 19.4	145.0 ± 20.4	< 0.001
24-h	135.8 ± 15.3	145.4 ± 11.7	134.6 ± 15.3	135.5 ± 15.4	< 0.001
Daytime	137.0 ± 15.5	147.1 ± 11.6	135.9 ± 15.6	136.6 ± 15.4	< 0.001
Nighttime	131.8 ± 18.3	139.5 ± 16.7	130.8 ± 18.3	131.8 ± 18.3	< 0.001
DBP, mm Hg					
Office	83.0 ± 13.2	86.8 ± 12.4	82.0 ± 12.7	82.0 ± 14.3	< 0.001
24-h	76.4 ± 10.1	80.7 ± 10.4	76.0 ± 9.9	76.0 ± 10.2	< 0.001
Daytime	77.7 ± 10.4	82.2 ± 10.6	77.3 ± 10.2	77.2 ± 10.5	< 0.001
Nighttime	71.9 ± 11.1	75.5 ± 11.7	71.6 ± 11.0	71.6 ± 11.2	< 0.001

Data are presented as means ± SD or n (%). **P*-value indicates differences for all groups. BMI: body mass index; DBP: diastolic blood pressure; SBP: systolic blood pressure.

Table 2. Differences in blood pressure values and control rates stratified by the different classes of antihypertensive drugs.

	Untreated (n = 164)	BB (n = 77)	Diuretic (n = 45)	ACEI (n = 80)	ARB (n = 291)	CCB (n = 750)	P-value [§]
Age, yrs	70.7 ± 8.0	70.4 ± 7.3	72.2 ± 7.9	70.5 ± 7.7	70.5 ± 7.7	71.2 ± 7.9	0.62
Female	56.7%	57.1%	51.1%	63.7%	61.2%	61.5%	0.59
BMI, kg/m ²	25.4 ± 3.6	26.1 ± 3.9	25.6 ± 5.4	25.2 ± 6.2	25.6 ± 4.3	26.0 ± 5.4	0.59
SBP, mm Hg							
Office	157.0 ± 9.9*	140.0 ± 14.6	146.3 ± 19.9	141.0 ± 17.3	147.4 ± 21.2	145.6 ± 19.2	<0.001
24-h	145.4 ± 11.7**	130.0 ± 12.8	135.0 ± 14.0	134.4 ± 18.2	135.0 ± 15.5	135.0 ± 15.1	<0.001
Daytime	147.1 ± 11.6**	131.1 ± 12.9	136.4 ± 14.3	135.3 ± 18.0	136.1 ± 15.5	136.3 ± 15.6	<0.001
Nighttime	139.5 ± 16.7**	126.5 ± 16.5	130.4 ± 19.4	131.8 ± 21.4	131.1 ± 19.2	131.1 ± 17.6	<0.001
DBP, mm Hg							
Office	86.8 ± 12.4*	77.4 ± 14.0	90.6 ± 11.4*	81.2 ± 11.9	82.4 ± 11.8	81.9 ± 12.7	<0.001
24-h	80.7 ± 10.4**	74.0 ± 9.2	78.1 ± 9.3	76.4 ± 10.0	75.4 ± 10.0	76.2 ± 9.9	<0.001
Daytime	82.2 ± 10.6**	75.3 ± 9.3	79.5 ± 9.4	77.3 ± 9.9	76.6 ± 10.5	77.7 ± 10.3	<0.001
Nighttime	75.5 ± 11.7*	70.1 ± 11.3	73.3 ± 11.4	73.6 ± 12.3	71.1 ± 11.0	71.7 ± 10.7	<0.001
Dipping type							0.19
Extreme dipper	2.4%	2.6%	4.4%	0	2.1%	1.9%	0.47
Dipper	29.9%	16.9%	33.3%	21.3%	24.7%	21.3%	0.06
Nondipper	38.4%	46.8%	31.1%	42.5%	38.8%	44.5%	0.23
Riser	29.3%	33.8%	31.1%	36.3%	34.4%	32.3%	0.87
Control rate [†]							
24-h BP	0	46.8%	33.3%	40.0%	37.1%	32.8%	<0.001
Daytime BP	6.7%**	59.7%	40.0%	53.8%	47.4%	47.3%	<0.001
Nighttime BP	4.3% ^{##}	27.3%	33.3%	20.0%	26.1%	18.0% [#]	<0.001

Data are presented as means ± SD or n (%). [§]P-value indicates differences for all groups; [†]Defined as 24-h BP < 130/80 mmHg; daytime BP < 135/85 mmHg; and nighttime BP < 120/70 mmHg. **P < 0.001 and *P < 0.05 compared with BBs; ^{##}P < 0.001 and [#]P < 0.05 compared with diuretics. ACEI: angiotensin-converting enzyme inhibitor; ARB: angiotensin receptor blocker; BB: beta-blockers; BMI: body mass index; BP: blood pressure; CCB: calcium channel blockers; DBP: diastolic blood pressure; SBP: systolic blood pressure.

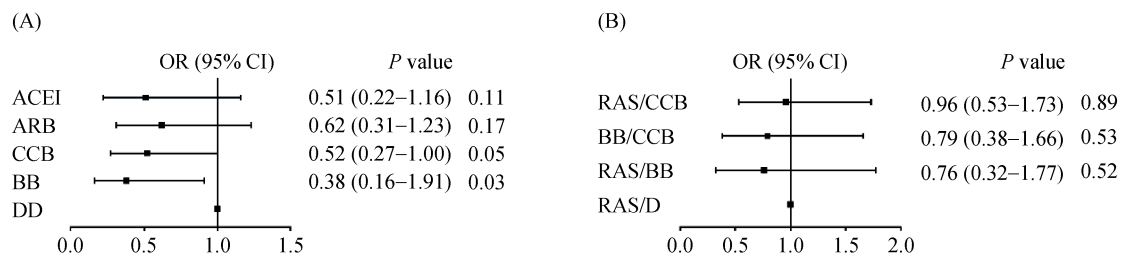


Figure 1. Associations between monotherapy and dual combination antihypertensive drug therapy, and the probability of a nighttime blood pressure dip pattern. (A): Dip pattern for each drug class; and (B): dip pattern with dual combination therapy. Diuretics and RAS/D were used as the reference group for the monotherapy groups and dual combination groups, respectively. RAS therapy included angiotensin-converting enzyme inhibitors and angiotensin receptor blockers. ACEI: angiotensin-converting enzyme inhibitor; ARB: angiotensin receptor blocker; BB: beta-blockers; CCB: calcium channel blockers; DD/D: diuretics; DBP: diastolic blood pressure; OR: odd ratio; RAS: renin-angiotensin system.

groups. Although there was no significant difference in the percentage of patients with a dip pattern between the four groups, patients treated with RAS/BB tended to have lower probabilities of having a dip pattern compared with other dual combination therapy groups (Figure 1B).

Significant differences in ambulatory BP control were

seen between the dual combination therapy groups. In Table 3, patients treated with BB/CCB had higher probabilities of achieving daytime BP control and a higher control rate (55.7%). [OR = 1.27, 95% CI: 0.69–2.35 (Figure 2C), with RAS/diuretics as the reference group] Patients with RAS/D were more likely to have controlled nighttime BP compared

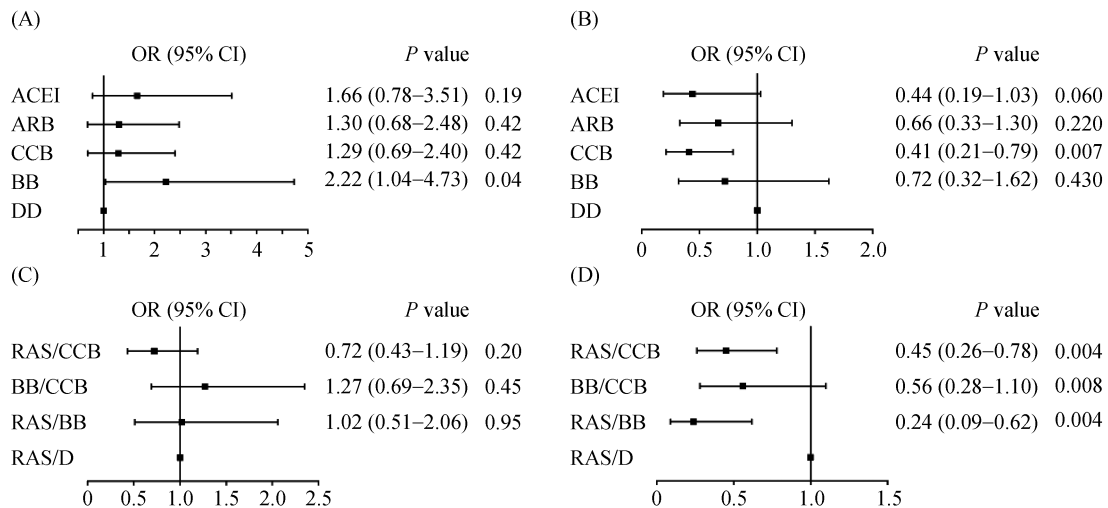


Figure 2. Associations between monotherapy and dual combination antihypertensive drug therapy, and the probability of controlled blood pressure. (A): Daytime BP control (< 135/85 mmHg) for each drug class; (B): nighttime BP control (< 120/70 mmHg) for each drug class; (C): daytime BP control with dual combination therapy; and (D): nighttime BP control with dual combination therapy. Diuretic therapy and RAS/D therapy were used as the reference groups for the monotherapy and dual combination groups, respectively. RAS therapy included angiotensin-converting enzyme inhibitors and angiotensin receptor blockers. ACEI: angiotensin-converting enzyme inhibitor; ARB: angiotensin receptor blocker; BB: beta-blockers; BP: blood pressure; CCB: calcium channel blockers; DD/D: diuretics; OR: odd ratio; RAS: renin-angiotensin system.

Table 3. Differences in blood pressure values and control rates stratified by the different dual antihypertensive combinations.

	Untreated (n = 164)	RAS ^a /BB (n = 55)	RAS/D (n = 80)	RAS/CCB (n = 290)	BB/CCB (n = 88)	P-value [§]
Age, yrs	70.7 ± 8.0	70.1 ± 7.6	72.2 ± 7.9	70.6 ± 7.3	71.1 ± 8.7	0.47
Female	56.7%	52.7%	61.3%	57.6%	54.5%	0.87
BMI, kg/m ²	25.4 ± 3.6	26.8 ± 5.1	25.3 ± 4.0	26.2 ± 5.0	25.6 ± 3.6	0.12
SBP, mm Hg						
Office	157.0 ± 9.9 ^a	140.0 ± 14.2	142.7 ± 23.6	145.4 ± 19.1	149.0 ± 22.6	< 0.001
24-h	145.4 ± 11.7 ^b	133.0 ± 13.9	133.1 ± 15.2	137.7 ± 15.8 ^b	132.2 ± 14.1	< 0.001
Daytime	147.1 ± 11.6 ^b	134.1 ± 14.4	134.3 ± 15.0	138.9 ± 15.8 ^b	132.9 ± 14.2	< 0.001
Nighttime	139.5 ± 16.7 ^c	130.4 ± 15.7	128.6 ± 19.0	133.6 ± 18.8	129.5 ± 17.0	< 0.001
DBP, mm Hg						
Office	86.8 ± 12.4	85.5 ± 12.0	78.7 ± 15.4	82.1 ± 15.2	84.0 ± 11.2	0.003
24-h	80.7 ± 10.4 ^c	78.0 ± 11.2	74.7 ± 10.5	76.1 ± 9.9	75.4 ± 10.1	< 0.001
Daytime	82.2 ± 10.6 ^c	79.1 ± 11.7	76.1 ± 10.9	77.4 ± 10.2	76.4 ± 10.2	< 0.001
Nighttime	75.5 ± 11.7 ^c	74.2 ± 11.9	69.2 ± 10.8	71.7 ± 11.1	71.4 ± 11.2	< 0.001
Dipping type						0.19
Extreme dipper	2.4%	1.8%	2.5%	1.0%	1.1%	0.77
Dipper	29.9%	20.0%	23.8%	23.8%	20.5%	0.40
Nondipper	38.4%	34.5%	40.0%	42.4%	45.5%	0.66
Riser	29.3%	43.6%	33.8%	32.8%	33.0%	0.42
Control rate [†]						
24-h BP	0	32.7%	38.8%	30.3%	42.0%	< 0.001
Daytime BP	6.7% ^b	49.1%	51.2%	41.7% ^b	55.7%	< 0.001
Nighttime BP	4.3% ^c	10.9% ^c	35.0%	29.3%	22.7%	< 0.001

Data are presented as means ± SD or n (%). [§]P-value indicates differences for all groups; ^aRAS therapy included angiotensin-converting enzyme inhibitors and angiotensin receptor blockers. [†]Defined as 24-h BP < 130/80 mmHg; daytime BP < 135/85 mmHg; and nighttime BP < 120/70 mmHg. ^aP < 0.05 compared with RAS/BB; ^bP < 0.05 compared with BB/CCB; ^cP < 0.05 compared with RAS/D. ACEI: angiotensin-converting enzyme inhibitor; ARB: angiotensin receptor blocker; BB: beta-blockers; BMI: body mass index; BP: blood pressure; CCB: calcium channel blockers; DD/D: diuretics; DBP: diastolic blood pressure; RAS: renin-angiotensin system; SBP: systolic blood pressure.

with patients treated with other dual combinations (OR = 0.45, 95% CI: 0.26–0.78 for RAS/CCB; and OR = 0.24, 95% CI: 0.09–0.62 for RAS/BB; both compared with RAS/diuretics) (Figure 2D).

4 Discussion

Our results showed that even with similar ambulatory BP, differences in BP dip patterns and ambulatory BP control occurred in older patients treated with different classes of antihypertensive drugs and their dual combinations. Although patients treated with BBs had lower BPs compared with other monotherapy groups, these patients' nighttime BP was difficult to lower, with these patients showing lower probabilities of having a dip pattern and nighttime BP control. In contrast, patients receiving only diuretics were more likely to have a dip pattern and controlled nighttime BP. Among patients receiving dual combination therapy, patients receiving BB/CCB had lower ambulatory BP and higher probabilities of daytime BP control, whereas patients receiving RAS/diuretics had higher probabilities of having a dip pattern and nighttime BP control, both compared with the RAS/BB combination.

Recommendations vary in different international hypertension guidelines for selecting optimal antihypertensive drug classes and different class combinations for patients with hypertension. The European guidelines^[2,12] recommend the five major classes of antihypertensive drugs (diuretics, BBs, CCBs, angiotensin-converting enzyme inhibitors, or angiotensin receptor- blockers) for initial treatment, mainly considering the drug BP-lowering effects regardless of drug class. However, the latest American College of Cardiology (ACC) and the American Heart Association (AHA) guidelines^[13] changed from a strong preference for thiazide diuretics^[14] to a wide consideration of the four major classes, as recommended in the European guidelines, except for BBs. Because most patients require two or more drugs to achieve the target BP, the ACC/AHA guidelines recommend combining different classes for initial treatment. The European guidelines recommend all possible combinations of the five major classes of drugs except the angiotensin-converting enzyme inhibitor/RAS combination. The ACC/AHA guidelines recommend combination therapy, but do not specify the possible class combinations.

The main benefits of antihypertensive drugs in preventing cardiovascular events are attributed to lowered BP.^[2] Although a large number of clinical trials have compared the BP-lowering effects of different monotherapy^[15–18] or dual combined therapy,^[19,20] information is limited regarding the effects of the major drug classes and their combina-

tions on daily ABPM changes in older patients, and no studies have evaluated remotely-monitored ABPM. In a previous trial,^[21] comparing the difference between office BP and ambulatory BP in patients receiving monotherapy, results showed differences for ambulatory BP, but no differences for office BP, among the five major drug classes. The authors of the trial also reported that patients receiving CCBs had higher ambulatory BPs, blunted nighttime BP dip, and less BP control compared with patients receiving diuretics. However, in our trial, we found similar ambulatory BPs among patients receiving the four major classes except in those receiving BBs, and patients receiving only CCBs had less nighttime BP control compared with patients receiving diuretics. In addition, diuretic therapy increased the probabilities of an abnormal BP dip status and nocturnal BP control, while BB therapy was associated with a blunted nocturnal BP dip. Our results were consistent with a previous prospective randomized controlled trial comparing the effects of hydrochlorothiazide and atenolol on nighttime BP response.^[22]

There is little direct evidence available to compare the effects of BP reduction and cardiovascular outcomes between different antihypertensive combination regimens because most trials used monotherapy as their initial intervention. The Avoiding Cardiovascular Events through Combination Therapy in Patients Living with Systolic Hypertension (ACCOMPLISH) trial is the only trial that directly assessed the relative efficacy of dual combination therapy. The trial evaluated RAS/CCB and RAS/diuretic combinations from the beginning of the trial, and showed lower rates of cardiovascular events with RAS/CCB therapy without noticeable differences in mean office BP. However, in our trial, patients treated with RAS/CCB had higher ambulatory BP and poorer BP control compared with other dual combination therapy groups, while patients receiving RAS/diuretics had better nighttime BP control compared with patients receiving RAS/CCB. A possible explanation for the BP-lowering difference between the ACCOMPLISH trial and our trial is that the effects of antihypertensive drugs on ambulatory BP may not match the effects on office BP, as shown in a previous meta-analysis.^[8] Another possible reason is that our trial was not a prospective randomized controlled trial, and the drug dose and individual patient differences may have confounded our results.

4.1 Limitations

There are several limitations in our study. Firstly, this was an observational study without baseline BP information, which can influence both selection of the initial antihypertensive drugs and patients' BP values. Secondly, the lack of

data for clinical factors that may influence drug class selection, namely, comorbidities and medication doses and frequency of administration. Last but not least, patients in our trial were exclusively older Chinese patients; therefore, our results might not apply to younger patients and other ethnic groups. However, our trial evaluated patients aged ≥ 60 years with hypertension, and age is the most important risk factor affecting BP values and comorbidities in this group. Moreover, we found no significant difference in patients' demographics when comparing the results of monotherapy or dual combination therapy.

To our knowledge, ours is the first study to evaluate the different BP-lowering effects of the major antihypertensive drug classes and monotherapy vs dual combination therapy using ABPM data from a remote monitoring system transmitting real-time BP values. Our results suggested that diuretic therapy had greater effects on nighttime BP control, and that BB-based therapies had greater effects on daytime BP compared with newer antihypertensive drug classes.

4.2 Conclusion

Patients treated with monotherapy or dual combined antihypertensive drugs have different ambulatory BP control and nocturnal BP dip patterns. BB-based regimens provided better daytime BP reduction, whereas diuretic-based therapies provided better nocturnal BP control and dip status compared with other antihypertensive regimens. Our results showed that older classes of antihypertensive drugs are not inferior to the newer classes in achieving better BP control.

Acknowledgments

We thank Kang Information Technology Co., Ltd. for providing the ABPM devices and technological support. This study was supported by a grant from the Chinese Ministry of Sciences and Technology (2016YFC1300100). The authors had no conflicts of interest to disclose.

References

- 1 Conen D, Bamberg F. Noninvasive 24-h ambulatory blood pressure and cardiovascular disease: a systematic review and meta-analysis. *J Hypertens* 2008; 26: 1290–1299.
- 2 Mancia G, Fagard R, Narkiewicz K, *et al.* 2013 ESH/ESC guidelines for the management of arterial hypertension: the Task Force for the Management of Arterial Hypertension of the European Society of Hypertension (ESH) and of the European Society of Cardiology (ESC). *Eur Heart J* 2013; 34: 2159–2219.
- 3 Harshfield GA, Wilson ME, Treiber FA, *et al.* A comparison of ambulatory blood pressure patterns across populations. *Blood Press Monit* 2002; 7: 265–269.
- 4 Fagard RH, Celis H, Thijs L, *et al.* Daytime and nighttime blood pressure as predictors of death and cause-specific cardiovascular events in hypertension. *Hypertension* 2008; 51: 55–61.
- 5 Svensson P, de Faire U, Sleight P, *et al.* Comparative effects of ramipril on ambulatory and office blood pressures: a HOPE Substudy. *Hypertension* 2001; 38: E28–E32.
- 6 Hermida RC, Ayala DE, Mojón A, *et al.* Decreasing sleep-time blood pressure determined by ambulatory monitoring reduces cardiovascular risk. *J Am Coll Cardiol* 2011; 58: 1165–1173.
- 7 Etehad D, Emdin CA, Kiran A, *et al.* Blood pressure lowering for prevention of cardiovascular disease and death: a systematic review and meta-analysis. *Lancet* 2016; 387: 957–967.
- 8 Mancia G, Parati G. Office compared with ambulatory blood pressure in assessing response to antihypertensive treatment: a meta-analysis. *J Hypertens* 2004; 22: 435–445.
- 9 Perez-Lloret S, Toblli JE, Cardinali DP, *et al.* Nocturnal hypertension defined by fixed cut-off limits is a better predictor of left ventricular hypertrophy than non-dipping. *Int J Cardiol* 2008; 127: 387–389.
- 10 Deng M, Chen DW, Dong YF, *et al.* Independent association between age and circadian systolic blood pressure patterns in adults with hypertension. *J Clin Hypertens (Greenwich)* 2017; 19: 948–955.
- 11 de la Sierra A, Redon J, Banegas JR, *et al.* Prevalence and factors associated with circadian blood pressure patterns in hypertensive patients. *Hypertension* 2009; 53: 466–472.
- 12 Mancia G, De Backer G, Dominiczak A, *et al.* 2007 guidelines for the management of arterial hypertension: The Task Force for the Management of Arterial Hypertension of the European Society of Hypertension (ESH) and of the European Society of Cardiology (ESC). *Eur Heart J* 2007; 28: 1462–1536.
- 13 Whelton PK, Carey RM, Aronow WS, *et al.* 2017 ACC/AHA/AAPA/ABC/ACPM/AGS/APhA/ASH/ASPC/NMA/PCNA guideline for the prevention, detection, evaluation, and management of high blood pressure in adults: executive summary: a report of the American College of Cardiology/American Heart Association Task Force on Clinical Practice Guidelines. *Hypertension* 2018; 71: 1269–1324.
- 14 Chobanian AV, Bakris GL, Black HR, *et al.* The seventh report of the Joint National Committee on Prevention, Detection, Evaluation, and Treatment of High Blood Pressure: the JNC 7 report. *JAMA* 2003; 289: 2560–2572.
- 15 Dahlöf B, Devereux RB, Kjeldsen SE, *et al.* Cardiovascular morbidity and mortality in the Losartan Intervention For Endpoint reduction in hypertension study (LIFE): a randomised trial against atenolol. *Lancet* 2002; 359: 995–1003.
- 16 ALLHAT officers and coordinators for the ALLHAT collaborative research group. Major outcomes in high-risk hypertensive patients randomized to angiotensin-converting en-

- zyme inhibitor or calcium channel blocker vs diuretic: The Antihypertensive and Lipid-Lowering Treatment to Prevent Heart Attack Trial (ALLHAT). *JAMA* 2002; 288: 2981–2997.
- 17 Brown MJ, Palmer CR, Castaigne A, *et al.* Morbidity and mortality in patients randomised to double-blind treatment with a long-acting calcium-channel blocker or diuretic in the International Nifedipine GITS study: Intervention as a Goal in Hypertension Treatment (INSIGHT). *Lancet* 2000; 356: 366–372.
- 18 Beckett NS, Peters R, Fletcher AE, *et al.* Treatment of hypertension in patients 80 years of age or older. *N Engl J Med* 2008; 358: 1887–1898.
- 19 Jamerson K, Weber MA, Bakris GL, *et al.* Benazepril plus amlodipine or hydrochlorothiazide for hypertension in high-risk patients. *N Engl J Med* 2008; 359: 2417–2428.
- 20 Liu L, Zhang Y, Liu G, *et al.* The Felodipine Event Reduction (FEVER) study: a randomized long-term placebo-controlled trial in Chinese hypertensive patients. *J Hypertens* 2005; 23: 2157–2172.
- 21 de la Sierra A, Gorostidi M, Banegas JR, *et al.* Ambulatory blood pressures in hypertensive patients treated with one antihypertensive agent: differences among drug classes and among drugs belonging to the same class. *J Clin Hypertens (Greenwich)* 2015; 17: 857–865.
- 22 Chapman AB, Cotsonis G, Parekh V, *et al.* Night blood pressure responses to atenolol and hydrochlorothiazide in black and white patients with essential hypertension. *Am J Hypertens* 2014; 27: 546–554.