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A 48-week study of amlodipine plus amiloride/hydrochlorothiazide vs. amlodipine plus telmisartan in the treatment of hypertension

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Disclosures
None.

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SUMMARY

Background: Chinese Hypertension Intervention Efficacy (CHIEF) study is a large-scale randomised clinical trial across China, which compares the efficacy of two combination regimens in reducing cardiovascular events associated with hypertension. **Methods:** We reported the 48-week efficacy and tolerability of the two antihypertensive regimens in participants from Shandong Province, China. Eligible patients aged 50–79 years were randomised to receive amlodipine plus amiloride/hydrochlorothiazide (Group A) or amlodipine plus telmisartan (Group B). The doses of both regimens were titrated and other antihypertensive agents were added subsequently to achieve a blood pressure (BP) goal (<140/90 mmHg for general population, <130/80 mmHg for diabetics and <150/90 mmHg for elderly). Efficacy variables included the changes of BP, control rates (the proportion of patients achieving a BP goal), and response rates (the proportion of patients achieving a BP goal or a reduction of BP ≥20/10 mmHg). Safety was assessed by monitoring the incidence of adverse events (AEs). **Results:** Of the 349 patients enrolled, 314 were randomised and 291 completed the study (141 in Group A and 150 in Group B). At week 48, the BP was reduced by 28.77/15.55 mmHg in Group A and by 31.38/16.07 mmHg in Group B ($p > 0.05$ for comparisons between Group A and Group B). The control rates (71.79% vs. 77.22%; $p = 0.270$) and response rates (79.49% vs. 84.81%; $p = 0.218$) were also similar. For both regimens, the control rates in diabetic patients were relatively lower (31.91% and 32.50%), while those in elderly patients were pretty higher (90.74% and 97.62%). AEs were mild to moderate in severity (17.95% vs. 12.66%, $p = 0.193$). **Conclusion:** Both combination regimens, amlodipine plus amiloride/hydrochlorothiazide and amlodipine plus telmisartan, were effective and safe for the high-risk hypertensive patients.

What's known
- The prevalence of hypertension was alarmingly high and the control rate was unacceptably low in Shandong Province, China.
- Combination therapy with different classes of antihypertensive agents achieves an optimal blood pressure (BP) reduction and less adverse effects in short-term study.

What's new
- Long-term combination therapy with amlodipine plus amiloride/hydrochlorothiazide or amlodipine plus telmisartan was effective and safe for high-risk hypertensive patients.
- The control rate and response rate in elderly hypertensive patients were both higher than those in diabetic individuals because of a lenient BP goal and the effective treatment.

Introduction

Hypertension is one of the most common risk factors for the morbidity and mortality of cardiovascular (CV) diseases in both developed and developing countries. Prospective studies demonstrated that, at ages 40–69 years, each increment in systolic blood pressure (SBP) of 20 mmHg or in diastolic blood pressure (DBP) of 10 mmHg from 115/75 mmHg is associated with more than twofold increase in death rates from stroke, ischaemic heart disease and other vascular diseases (1). The prevalence of hypertension is nearly 20% in Chinese population over 18 years of age according to the data from China National Nutrition and Health Survey 2002 (2). Stringent control of blood pressure (BP) is associated with a significant reduction of CV events. It has been estimated by using Framingham algorithms that, if BP was controlled to normal levels, 19% of coronary heart disease events would be prevented (3). Unfortunately, an investigation from Shandong Province indicated that the control rate of hypertension was only 7.3% in Chinese rural population aged 35–74 years (4).

The Seventh Report of the Joint National Committee on Prevention, Detection, Evaluation, and Treatment of High Blood Pressure (JNC 7) (5) and 2007 Guidelines for the Management of Arterial Hypertension by European Society of Hypertension (ESH) and European Society of Cardiology (ESC)

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(6) recommended a goal BP of < 140/90 mmHg for general patients with hypertension and <130/80 mmHg for those with diabetes or chronic kidney disease. As suggested in several clinical randomised controlled trials, such as UKPDS (UK Prospective Diabetes Study) (7), RENAAL (Reduction of Endpoints in NIDDM with the Angiotensin II Antagonist Losartan) (8), ALLHAT (Antihypertensive and Lipid-Lowering Treatment to Prevent Heart Attack Trial) (9), ASCOT-BPLA (Anglo-Scandinavian Cardiac Outcomes Trial–Blood Pressure Lowering Arm) (10) and IDNT (Irbesartan type 2 Diabetic Nephropathy Trial) (11), a majority of patients require at least two classes of antihypertensive agents with complementary mechanisms of action to achieve an adequate BP control. For patients with moderate to severe hypertension, BP ≥20/10 mmHg above goal, or higher risk of a CV event, low-dose initial combination therapy with two agents is advocated to obtain maximal BP reduction and minimal adverse effects (5,6).

Combination of diuretics with renin-angiotensin-aldosterone system (RAAS) antagonists has been an attractive option to clinicians, because the compensatory effect of diuretic-induced RAAS activation can be attenuated by angiotensin-converting enzyme (ACE) inhibitors or angiotensin receptor blockers (ARBs). However in ACCOMPLISH (Avoiding Cardiovascular Events in Combination Therapy in Patients Living with Systolic Hypertension) trial, the combination of an ACE inhibitor benazepril with a long-acting dihydropyridine calcium channel blocker (CCB) amlodipine demonstrated a significant risk reduction of 19.6% in primary cardiovascular events compared with the combination of benazepril with a diuretic, hydrochlorothiazide (12). Several short-term multicentre randomised double-blind placebo-controlled factorial-design studies on the combination of amlodipine with ARBs, including olmesartan, telmisartan and valsartan, have shown a significant reduction of BP in patients with DBP ≥95 mmHg in comparison with respective monotherapy components or placebo (13–15). Therefore, CCB/ARB combination is one of the most favourable regimens for treatment of hypertension.

Chinese Hypertension Intervention Efficacy (CHIEF) study is a large-scale randomised clinical trial that recruited more than 13,000 hypertensive patients from 180 clinical centres in China (16). The BP lowering arm of CHIEF study was to compare the efficacy of two initial combination regimens, amlodipine plus amiloride/hydrochlorothiazide and amlodipine plus telmisartan, in reducing CV events associated with hypertension. Herein, we reported the 48-week efficacy and tolerability of the two antihypertensive regimens in participants from Shandong Province, China.

Methods

Participants and study design

The design and rationale of CHIEF study have been described in detail previously (16). Briefly, hypertensive patients aged 50–79 years were eligible for inclusion if they had at least one of the following CV risk factors: previous (≥ 3 months) stroke, transient ischaemic attack, myocardial infarction, or coronary revascularisation; stable angina pectoris; cardiac insufficiency (NYHA class II); peripheral arterial disease; controlled type 2 diabetes; mild or moderate chronic kidney disease; overweight or obesity; dyslipidemia; family history of premature CV events; current smoking; left ventricular hypertrophy; intimal thickening or atherosclerotic plaque in the carotid arteries; hypertensive fundus oculi grade III–IV or retinal atherosclerosis grade III–IV. Exclusion criteria included secondary hypertension; cardiac or cerebral attack within 3 months; severe cardiomyopathy or valvular heart disease; unstable angina pectoris; advanced hepatic or renal diseases; malignant tumor; gout; taking oral contraceptives or planning a pregnancy; uncontrolled diabetes; definite hypersensitivity or contraindication to the study medications; or any other clinical conditions unsuitable for this trial.

Three hundred and forty-nine patients were recruited from seven research sites (primary care practices, hospitals, or research centres) in Shandong Province between March 2008 and September 2008. This study conformed to good clinical practice guidelines and was conducted in compliance with the Declaration of Helsinki. This protocol was approved by the institutional medical ethics committee. All participants provided written informed consents.

After screening visit, potentially eligible patients discontinued any antihypertensive medications for 2 weeks. The patients with seated SBP 140–179 mmHg and/or DBP 90–109 mmHg were immediately randomly assigned to either of the two regimens once daily: group A – amlodipine 2.5 mg plus amiloride 1.25 mg/hydrochlorothiazide 12.5 mg, and group B – amlodipine 2.5 mg plus telmisartan 40 mg. Amiloride/hydrochlorothiazide is a fixed-dose single-pill combination of amiloride 2.5 mg plus hydrochlorothiazide 25 mg. The randomisation was made centrally by an internet allocation service. In order to achieve a BP goal (< 140/90 mmHg for general population, < 130/80 mmHg for diabetics, and < 150/90 mmHg for elderly) (17), investigators titrated the daily doses to 2.5 mg/25 mg for amiloride/hydrochlorothiazide and to 80 mg for telmisartan after 2 weeks. Thereafter,

the amlodipine component in both groups was increased to 5 mg daily at week 4 for an adequate BP control. Other antihypertensive agents could be added at week 8, if necessary, including an ACE inhibitor or ARB for Group A, diuretics for Group B, and a non-dihydropyridine CCB, α- or β-adrenoceptor blocker for both groups.

Efficacy and safety assessment

The efficacy variables included the BP reduction from baseline to week 48, BP control rates (the proportion of patients achieving a BP goal defined as above) and response rates (the proportion of patients achieving a BP goal or a reduction of BP ≥ 20/10 mmHg from baseline) at the end of study.

Safety was assessed by monitoring the incidence of adverse events (AEs), which were defined as any undesirable symptoms and abnormal findings of physical examination and laboratory tests that occurred after the initiation of treatment, regardless of their relation to study drugs. Compliance was determined by counting the returned capsules/tablets at scheduled visits.

Statistical analysis

Continuous variables were expressed as mean ± SD, and categorical variables as frequency counts and percentages. All data were analysed in the 'intention-to-treat (ITT)' population (i.e. all patients taking at least one dose of study medications, who had an efficacy assessment at baseline and at least one post-baseline efficacy assessment) by using SPSS version 17.0 for windows (SPSS Inc., Chicago, IL, USA). Last observation carried forward (LOCF) methodology was applied in the event of early discontinuation. Differences between treatment groups were evaluated using an analysis-of-variance model for continuous variables, including changes in BP levels, with two-sided 95% confidence interval (CI). For efficacy variables, SBP and DBP, non-inferiority was inferred if the lower bound of the 95%CI was >−5.0 mmHg, and superiority was declared if the lower bound of the interval was >0 mmHg. A Chi-square test was used for comparing categorical variables. Statistical significance was considered for a two-tailed value of $p < 0.05$.

Results

Patient characteristics

Of 349 patients who entered the washout phase, 314 (89.97%) were randomised to receive amlodipine plus amiloride/hydrochlorothiazide or amlodipine plus telmisartan, and 291 completed the study (Figure 1). The most common reasons for withdrawal during treatment were AEs (14 patients, 4.46%) and lost follow-up (9 patients, 2.87%). Among the randomised patients, 145 (46.18%) were male and 169 (53.82%) were female. Their mean age was 63.55 years, and 137 (43.63%) were elderly (aged ≥ 65 years). The average body mass index (BMI) was 26.45 kg/m^2, with 174 (55.41%) overweight (BMI ≥ 25 kg/m^2) and 42 (13.38%) obesity (BMI ≥ 30 kg/m^2). Diabetes was present in 88 (28.03%) participants. The average BP was 159.88/93.38 mmHg at baseline. The two treat-

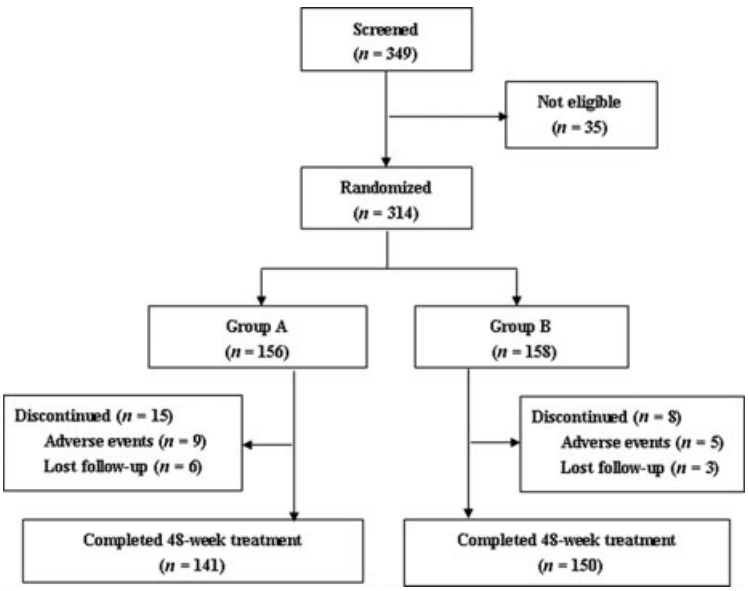

Figure 1 Disposition of patients. Group A: amlodipine plus amiloride/hydrochlorothiazide; Group B: amlodipine plus telmisartan

Table 1 Demographic and other clinical characteristics of study participants at baseline

Characteristics	Group A (*n* = 156)	Group B (*n* = 158)
Age (years)	64.19 ± 7.42	62.92 ± 7.19
Sex, *n* (%)		
Female	80 (51.28%)	89 (56.33%)
Male	76 (48.72%)	69 (43.67%)
BMI (kg/m^2)	26.71 ± 3.56	26.19 ± 3.23
Pulse rate (beats per minute)	72.04 ± 10.65	71.17 ± 10.61
SBP (mmHg)	158.94 ± 9.88	160.82 ± 10.05
DBP (mmHg)	93.12 ± 7.02	93.63 ± 7.23
Hypertension category		
Grade 1, *n* (%)	59 (37.82%)	47 (29.75%)
Grade 2, *n* (%)	97 (62.18%)	111 (70.25%)
Elderly, *n* (%)	75 (48.08%)	62 (39.24%)
SBP (mmHg)	160.35 ± 9.49	159.52 ± 9.70
DBP (mmHg)	91.13 ± 7.32	90.92 ± 7.59
Diabetes, *n* (%)	47 (30.13%)	40 (25.32%)
SBP (mmHg)	158.56 ± 9.32	161.38 ± 11.03
DBP (mmHg)	91.86 ± 7.37	90.99 ± 9.34
ISH, *n* (%)	39 (25.00%)	36 (22.78%)
SBP (mmHg)	158.99 ± 9.88	160.10 ± 10.48
DBP (mmHg)	84.35 ± 4.89	83.90 ± 4.86

Group A: amlodipine plus amiloride/hydrochlorothiazide; Group B: amlodipine plus telmisartan.
Grade 1 hypertension refers to SBP 140–159 mmHg and/or DBP 90–99 mmHg; Grade 2 hypertension, SBP 160–179 mmHg and/or DBP 100–109 mmHg; and ISH, SBP ≥ 140 mmHg and DBP < 90 mmHg. BMI, body mass index; DBP, diastolic blood pressure; ISH, isolated systolic hypertension; SBP, systolic blood pressure.

ment groups were comparable in terms of demographic and other clinical characteristics at randomisation (Table 1).

Efficacy

Blood pressure reduction

For both treatment groups, there were statistically significant reductions in SBP and DBP at week 48 in comparison with those at baseline (Figure 2). The BP in amlodipine plus amiloride/hydrochlorothiazide regimen decreased from 158.94 ± 9.88/93.12 ± 7.02 mmHg to 130.17 ± 8.89/77.57 ± 7.58 mmHg ($p < 0.001$), and that in amlodipine plus telmisartan regimen decreased from 160.82 ± 10.05/93.63 ± 7.23 mmHg to 129.44 ± 8.65/77.56 ± 7.38 mmHg ($p < 0.001$). The treatment difference in SBP was 2.58 mmHg (95%CI, −0.15∼5.32; $p = 0.064$), and that in DBP was 0.78 mmHg (95%CI, −0.97∼2.52; $p = 0.525$). Thus according to the pre-defined criterion for non-inferiority and superiority, the BP differences in amlodipine plus telmisartan regimen were neither inferior nor superior than those in amlodipine plus amiloride/hydrochlorothiazide regimen.

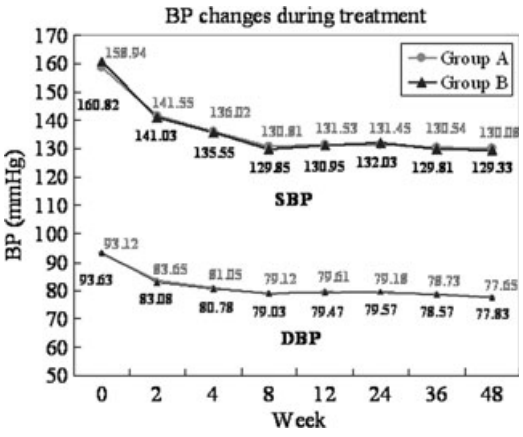

Figure 2 BP levels at each visit during 48 weeks. Group A: amlodipine plus amiloride/hydrochlorothiazide; Group B: amlodipine plus telmisartan. BP, blood pressure; DBP, diastolic blood pressure; SBP, systolic blood pressure

Blood pressure control and response rates

As demonstrated in Figure 3, no statistically significant difference was observed in the control rates and response rates between the two treatment regimens at each visit. However, more patients in the amlodipine plus telmisartan group achieved BP goal than those in amlodipine plus amiloride/hydrochlorothiazide group at the end of study (71.79% vs. 77.22%; $p = 0.270$). The response rate showed a similar pattern (79.49% vs. 84.81%; $p = 0.218$). In addition, the control rates at week 8 were 67.95% in Group A and 74.68% in Group B, which implicated that 32.05% patients in Group A and 25.32% patients in Group B received non-study medications.

Antihypertensive efficacy in subgroups

For specific subgroups receiving amlodipine plus amiloride/hydrochlorothiazide, the BP changes from baseline to week 48 were −30.08 ± 13.19/−15.63 ± 8.79 mmHg in the elderly, −28.22 ± 12.32/−14.39 ± 9.55 mmHg in the diabetics, and −27.99 ± 12.14/−9.88 ± 6.48 mmHg in the patients with isolated systolic hypertension (ISH). For specific subgroups receiving amlodipine plus telmisartan, the BP changed −29.02 ± 11.50/−15.71 ± 9.27 mmHg in the elderly, −30.85 ± 10.89/−13.11 ± 9.40 mmHg in the diabetics, and −30.93 ± 12.07/−10.43 ± 7.03 mmHg in the patients with ISH.

In comparison with general population, the control rate and response rate of diabetic patients in

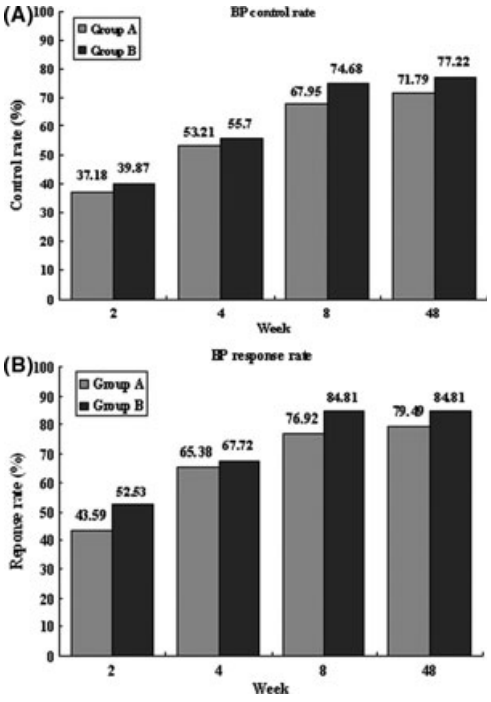

Figure 3 BP control rates and response rates. (A) Cumulative proportion of patients achieving BP goals, i.e. BP <140/90 mmHg for general population, <130/80 mmHg for diabetics, and <150/90 mmHg for elderly. (B) Cumulative proportion of patients achieving BP goals or a reduction of BP ≥20/10 mmHg from baseline. Group A: amlodipine plus amiloride/hydrochlorothiazide; Group B: amlodipine plus telmisartan. No significant between-group differences were found. BP, blood pressure

both treatment groups were lower at each visit, while the data of the elderly were higher (Table 2). However, no statistically significant between-group differences were detected in these subgroups.

Safety

Both antihypertensive regimens were generally well tolerated. A total of 48 patients (17.95% in Group A vs. 12.66% in Group B, p = 0.193) experienced AEs during follow-up, as summarised in Table 3. Most AEs were considered as mild to moderate in severity, and no serious drug-related AEs or deaths were reported. Peripheral oedema and headache were the frequent complaints during treatment in both groups. There were no significant changes in pulse rate, plasma creatinine or creatine kinase. The mean uric acid increased from 321.92 μmol/l at baseline to 326.18 μmol/l at week 48 in amlodipine plus amiloride/hydrochlorothiazide group, and decreased slightly in amlodipine plus telmisartan group from 305.41 μmol/l to 304.89 μmol/l. Hepatic enzyme, alanine transaminase (ALT), was elevated between two- to threefold of upper reference limit in one patient of each group who were treated with simvastatin concomitantly. As expected, the incidences of hypokalemia and hyponatremia occurred more frequently in amlodipine plus amiloride/hydrochlorothiazide group, whereas hyperkalemia were found

Table 2 Blood pressure control rates and response rates in diabetic or elderly patients

	Week 2	Week 4	Week 8	Week 48
Group A				
Control rates				
Diabetes	8.51%	10.64%	23.40%	31.91%
Elderly	53.70%	81.48%	88.89%	90.74%
Response rates				
Diabetes	23.40%	38.30%	44.68%	55.32%
Elderly	55.56%	83.33%	88.89%	90.74%
Group B				
Control rates				
Diabetes	10.00%	12.50%	27.50%	32.50%
Elderly	64.29%	83.33%	92.86%	97.62%
Response rates				
Diabetes	25.00%	35.00%	55.00%	57.50%
Elderly	69.05%	85.71%	95.24%	97.62%

Group A: amlodipine plus amiloride/hydrochlorothiazide; Group B: amlodipine plus telmisartan.

Table 3 Adverse events during treatment

	Group A (*n* = 156)	Group B (*n* = 158)
Overall AEs	28 (17.95%)	20 (12.66%)
Clinical manifestations		
Headache and dizziness	6 (3.85%)	2 (1.27%)
Peripheral oedema	8 (5.13%)	5 (3.16%)
Dyspepsia	3 (1.92%)	3 (1.90%)
Fatigue	4 (2.56%)	2 (1.27%)
Hypotension	2 (1.28%)	0
Paradoxical BP elevation	0	2 (1.27%)
Laboratory findings		
Hyperkalemia	0	2 (1.27%)
Hypokalemia	1 (0.64%)	0
Hyponatremia	3 (1.92%)	1 (0.63%)
ALT elevation	1 (0.64%)	1 (0.63%)
Adverse outcomes		
Frequent atrial premature beat	0	1 (0.63%)
New-onset diabetes	3 (1.92%)	2 (1.27%)
Peripheral facial paralysis	1 (0.64%)	0
Pulmonary cancer	0	1 (0.63%)
Withdrawal from treatment	15 (9.62%)	8 (5.06%)

Group A: amlodipine plus amiloride/hydrochlorothiazide; Group B: amlodipine plus telmisartan. AEs, adverse events; ALT, alanine transaminase.

in amlodipine plus telmisartan group. The most AEs leading to withdrawal during the follow-up period were peripheral oedema (3.21% vs. 1.27%), intolerant headache and dizziness (1.28% vs. 0.63%), paradoxical BP elevation (0 vs. 1.27%), and hyponatremia (1.28% vs. 0), respectively.

Discussion

Hypertension is a complex disease, and a great number of pathophysiological factors contribute to BP elevation. Combination of antihypertensive agents with different and complementary mechanisms of action provides greater BP reduction and less adverse effects in clinical practice. CCBs represent a logical choice for antihypertensive therapy in China because of their remarkable efficacy in preventing stroke. However, when used in monotherapy, vasodilation produced by CCBs activates the RAAS and increases the incidence of peripheral oedema (18), which can be counterbalanced by concomitant administration of an ARB or a diuretic. Thiazide diuretics-based combinations have been widely prescribed for patients with hypertension. ASCOT and ACCOMPLISH demonstrated that a CCB plus an ACE inhibitor exerted a greater BP reduction and resulted in less major adverse CV events than a thiazide diuretic plus a β-blocker or plus an ACE inhibitor (10,14).

In this multicentre prospective open-label active-controlled randomised clinical trial, we evaluated the efficacy and safety of combination treatment with amlodipine plus amiloride/hydrochlorothiazide compared with amlodipine plus telmisartan in hypertensive patients. The reductions in SBP and DBP were statistically pronounced in both groups. Similar changes of BP were present in the subgroups of elderly, diabetics, and patients with ISH. These findings were supported by a recent randomised double-blind study conducted by Calhoun et al (19), which evaluated the efficacy and safety of triple therapy with amlodipine/valsartan/hydrochlorothiazide in 2271 patients with moderate or severe hypertension for 8 weeks. BP reduction from baseline was 39.7/24.7 mmHg in amlodipine 10 mg/valsartan 320 mg/hydrochlorothiazide 25 mg group, 33.5/21.5 mmHg in amlodipine 10 mg/valsartan 320 mg group, 32.0/19.7 mmHg in valsartan 320 mg/hydrochlorothiazide 25 mg group, and 31.5/19.5 mg in amlodipine 10 mg/hydrochlorothiazide 25 mg group.

In our present study, the BP control rates were 37.18% in patients treated with amlodipine 2.5 mg plus amiloride 1.25 mg/hydrochlorothiazide 12.5 mg and 39.87% in patients treated with amlodipine 2.5 mg plus telmisartan 40 mg at week 2. These rates were increased to 67.95% and 74.68% respectively in the two groups at week 8 when patients were treated with amlodipine 5 mg plus amiloride 2.5 mg/hydrochlorothiazide 25 mg or amlodipine 5 mg plus telmisartan 80 mg. However, the BP control rates increased slightly to 71.79% in group A and 77.22% in group B by the end of week 48 even other classes of antihypertensive agents were added. Similar findings were observed for BP control rates and response rates. These data suggested that initial combination therapy with conventional doses of antihypertensive drugs, i.e. amlodipine 5 mg plus amiloride/hydrochlorothiazide 2.5 mg/25 mg or amlodipine 5 mg plus telmisartan 80 mg, was reasonable for treatment of mild to moderate hypertension in Chinese population and was associated with a BP control rate around 70%. Furthermore, although both regimens were comparably effective in antihypertension, amlodipine plus telmisartan seemed superior to amlodipine plus amiloride/hydrochlorothiazide for lowing BP and achieving target control. In comparison with our results, the BP reduction was greater in Calhoun's study (19) as described as above, but the control rates were much lower in the three dual antihypertensive groups (54.1%, 48.3% and 44.8% for amlodipine 10 mg/valsartan 320 mg, valsartan 320 mg/hydrochlorothiazide 25 mg and amlodipine 10 mg/hydrochlorothiazide 25 mg, respectively; all $p < 0.0001$). Such differences may be explained in most part by the dosage of medications and severity of hypertension. In our present study, the baseline BP was classified as grade 1–2 hypertension according to ESH and ESC guidelines (6), and most patients were treated with amlodipine 2.5–5 mg, amiloride/hydrochlorothiazide 1.25–2.5 mg/12.5–25 mg and/or telmisartan 40–80 mg; while the patients in Calhoun study were diagnosed as grade 2–3 hypertension and treated with higher doses of CCB, ARB and/or thiazide diuretic. In addition, ethnicity may be a confounding factor for treatment efficacy. A randomised 4×4 factorial study (20) was performed in adult patients with stage 1 or 2 hypertension, which included 79.4% Caucasians, 16.2% Blacks and only 4.4% Asians. The BP control rate was lower (65.7%) in patients treated with amlodipine 5 mg/telmisartan 80 mg than that in our study.

In subgroup analysis of this study, the higher control rate and response rate in the elderly patients may be explained partly by the lenient BP goal and the effective antihypertension; likewise, because of a stringent BP goal and poor response to antihypertensive treatment, the control rate and response rate in the hypertensive patients with diabetes were lower than those of general population. In an observational cross-sectional survey conducted in 12 European

countries, 38.8% patients with both essential hypertension and diabetes needed ≥3 different antihypertensive agents to control their BP, whereas 28.0% hypertensive patients without metabolic syndrome or diabetes did so (21). In fact, tight control of SBP among diabetic patients at high risk for CV events or with concomitant coronary artery disease was not associated with improved CV outcomes compared with usual control (22,23).

Safety and tolerability are the great concerns in most short- or long-term clinical studies. As for this study, the frequencies of overall AEs were comparable between the two treatment groups but insignificantly higher in patients treated with amlodipine plus amiloride/hydrochlorothiazide. The drug-related AEs were consistent with the known pharmacological properties of each component. Adverse metabolic effects associated with diuretics involved electrolytic disturbance, hyperuricaemia, and hyperglycaemia. Although ARBs were beneficial for patients with impaired glucose metabolism, they induced hyperkalemia potentially. Mild elevation of hepatic enzyme ALT in two patients may be because of the adverse effect of simvastatin, but this occurs very rare and most often in the first 4 month of treatment (24). Peripheral oedema was one of the most common AEs in patients treated with CCB and the leading cause of treatment discontinuation. Even if a diuretic or an ARB was administered concomitantly, it could not be eliminated but counteracted partially. These findings were supported by a 52-week, randomised, open-label, extension study (25). Fogari et al evaluated peripheral oedema by using two objective measures, ankle-foot volume (AFV) and pretibial subcutaneous tissue pressure (PSTP), in hypertensive patients treated with amlodipine, and found that the relative risk of ankle oedema would be reduced by 60%–70% when perindopril (26) or valsartan (27) was added to amlodipine monotherapy.

The compliance or adherence was satisfactory in this study, which was attributable to the robust therapeutic efficacy and less AEs of the combination strategy. Nevertheless, several limitations should be noted. First of all, no patients with grade 3 hypertension were enrolled. With increasing evidence from other clinical trials (28,29), we believe that initial combination therapy is also definitely reasonable for treatment of severe hypertension. Secondly, the major adverse CV events in each group were rarely reported herein because the follow-up period was not long enough and the study sample was relatively small. A large scale extension study is warranted. Finally, to avoid potentially increased risk of hyperkalemia, a third arm with telmisartan plus amiloride/hydrochlorothiazide was not included.

In conclusion, this study confirmed the rationale of using different classes of drugs with complementary mechanisms of action to control hypertension. The combinations therapy of amlodipine 2.5–5 mg plus amiloride 1.25–2.5 mg/hydrochlorothiazide 12.5–25 mg and amlodipine 2.5–5 mg plus telmisartan 40–80 mg produced a similarly and statistically significant BP reduction. Both treatments were well tolerated and associated with achievement of BP goals in the majority of Chinese patients with mild to moderate hypertension and at least one CV risk factor.

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Author contributions

FL contributed to the design and concept of the study; YZ and Z L analysed and interpreted the data; YZ drafted the article; FL and YZ critically revised the article; FL approved the article; HS and YZ performed Statistics; HS secured funding; YZ, SS and SW contributed to data collection.

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