BMC Medicine

RESEARCH

Open Access

# Initial treatment with a single capsule containing half-dose quadruple therapy vs standard-dose dual therapy in hypertensive patients (QUADUAL): a randomized, blinded, crossover trial

Xiexiong Zhao[1], Tao Liu[1], Qiong Yang[1,5], Guoping Yang[2,3], Xingli Li[4], Xiaohong Tang[1], Jingle Li[1], Zhongshu Liang[1,5], Anying Li[1], Lixiong Zeng[1], Juan Wen[1], Xiaoyan Wang[1], Liping Peng[1], Wenjuan Wang[1], Jingjing Cai[1,2], Ye Chen[1], Miao Huang[1], Ruixuan Li[1], Ru Fu[1], Lin Zhao[1], Xiaogang Li[1†] and Weihong Jiang[1,5*†]

## Abstract

**Background** Guidelines recognized dual combination in initial antihypertensive therapy. Studies found that low-dose quadruple combination were superior to monotherapy. However, whether low-dose quadruple therapy is better than dual combination is unknown.

**Methods** A randomized blinded crossover trial was conducted to compare the efficacy and safety of low-dose quadruple antihypertensives (irbesartan 75 mg + metoprolol 23.75 mg + amlodipine 2.5 mg + indapamide 1.25 mg) with standard-dose dual antihypertensives (irbesartan 150 mg + amlodipine 5 mg), both in a single pill, in the initial treatment of patients with mild to moderate hypertension. Patients were randomly assigned in a 1:1 ratio to two crossover sequences. Each sequence received four-weeks of either half-dose quadruple antihypertensives or standard-dose dual antihypertensives, followed by a two-week washout and crossover for four-weeks. Participants and researchers were blinded. The main outcomes were the reduction of blood pressure and safety outcomes. Analyses were per intention to treat.

**Results** A total of 90 eligible participants were randomized between July 13, 2022, and April 20, 2023. The mean age was 43.88 years (SD 10.31), and 25.6% were women. The mean baseline 24-h blood pressure was 145.59/93.84 mm Hg. Compared to the standard-dose dual treatment, the half-dose quadruple treatment resulted in a further reduction in mean 24-h blood pressure by 4.72/4.17 mm Hg ($P < 0.001$ for both systolic and diastolic blood pressure), mean daytime blood pressure by 5.52/4.73 mm Hg ($P < 0.001$ for both), mean nighttime blood pressure by 2.37/2.25 mm Hg ($P = 0.034$ and 0.014, respectively), and mean office blood pressure by 2.91/1.73 mm Hg ($P < 0.001$ and 0.014, respectively). Apart from significant increases of fasting blood glucose ($P = 0.029$) and blood uric acid ($P < 0.001$)

†Xiaogang Li and Weihong Jiang shared last authorship.

*Correspondence:
Weihong Jiang
jiangweihongdoc@163.com
Full list of author information is available at the end of the article

in the half-dose quadruple group, no other adverse events or changes in laboratory values differed significantly between the two treatments.

**Conclusions** Initiating treatment with half-dose quadruple combination therapy was more effective in lowering blood pressure than standard-dose dual therapy. The safety of half-dose quadruple therapy was comparable.

**Trial registration** ClinicalTrials.gov Identifier: NCT05377203.

**Keywords** Hypertension, Antihypertensive, Low-dose combination, Randomized controlled trial

## Background

Hypertension is the most common cardio-cerebrovascular disease worldwide and often coexists with other cardiovascular risk factors, causing damage to important organs [1, 2]. Globally, hypertension is the leading risk factor for deaths, accounting for 10.8 million deaths in 2019 [3], and it also places a significant economic burden on China [4]. However, despite its prevalence and impact, the awareness, treatment, and control rates of hypertension remain suboptimal, with some data showing corresponding metrics to be as low as 50.0%, 38.1%, and 11.1%, respectively [5].

Current hypertension guidelines recognized the efficacy of dual combination therapy as an initial antihypertensive treatment [1, 2, 6–9]. However, hypertension involves multiple mechanisms [10, 11], and the goal of blood pressure control has become more stringent. Dual combination therapy may not be sufficient to meet the needs of patients. Several studies have investigated the use of low-dose three-drug or four-drug combinations in initial treatment [12–16], which showed promising results in terms of antihypertensive effects and safety profiles compared to monotherapy. However, these studies employed monotherapy or placebo or usual care as controls, which are not consistent with current guidelines for initial hypertension treatment or not a fixed comparison. These studies did not demonstrate whether low-dose multidrug ($\geq 3$) combinations were more effective than the current recommended dual combinations, and studies conducted in a predominantly Asian/Chinese population are still lacking.

Therefore, the QUADUAL trial aimed to address these gaps in research by evaluating the efficacy and safety of half-dose quadruple therapy compared to standard-dose dual therapy.

## Methods

### Study design

We conducted an investigator-initiated, prospective, randomized double-blind $2\times2$ crossover clinical trial, comparing the effectiveness and safety of low-dose quadruple antihypertensives with standard-dose dual drugs in initial antihypertensive treatment in patients with mild to moderate hypertension (140–179/90–109 mm Hg), in the Third Xiangya Hospital of Central South University, Hunan Province, China. The protocol (Additional file 1) and statistical analysis plan have been published previously [17, 18]. This study followed the Consolidated Standards of Reporting Trials (CONSORT) reporting guideline.

### Participants

Participants were eligible for inclusion in the trial if they were 1) $\geq 18$ and $< 80$ years old; 2) had never taken antihypertensive medications or had not taken antihypertensive medications in the past one month; 3) met the diagnostic criteria of hypertension: a) office blood pressure: systolic blood pressure $\geq 140$ mmHg and/or diastolic blood pressure $\geq 90$ mmHg, in three separate measurements on different days; and b) ABPM: 24-h average blood pressure $\geq 130/80$ mmHg or daytime average blood pressure $\geq 135/85$ mmHg or nighttime average blood pressure $\geq 120/70$ mmHg; 4) participated voluntarily and signed a written informed consent. Patients were excluded from the trial if 1) they were confirmed or highly suspected secondary hypertension; 2) had severe hypertension; 3) other conditions not appropriate for participating in this trial. Detailed inclusion and exclusion criteria were listed in the Additional file 2: Expanded Methods.

### Randomization

Randomization and blinding were established by an independent statistician using blocked randomization and individual random crossover method. Except for randomizing, blinding, and drug coding investigators, who were not involved in any other process of the trial, all others were blinded to patient grouping and drug assignment [17]. The blind allocation was sealed in opaque envelopes.

### Interventions

Participants were randomized into two crossover sequences in 1:1 ratio. One sequence was given low-dose quadruple antihypertensive drugs for four weeks, washed out with a placebo for two weeks, and then switched to standard-dose dual drugs for four weeks. The other sequence went the other way (Additional file 2: Fig. S1).

The combination drugs were put into one identical capsule. Half-dose quadruple capsule contained irbesartan 75 mg, metoprolol 23.75 mg (metoprolol tartrate sustained-release tablet), amlodipine 2.5 mg, indapamide 1.25 mg in total (referred to as "1/2 (A + B + C + D)") and standard-dose dual capsule contained irbesartan 150 mg and amlodipine 5 mg in total ("A + C" for short), advised to take once daily, in the morning on an empty stomach.

### Study outcomes

The primary outcome was established as the reduction in mean 24-h systolic blood pressure (SBP) by ABPM after four weeks of drug administration.

Secondary outcomes were the change in mean daytime and nighttime SBP in ABPM; 24-h, daytime, and nighttime mean diastolic blood pressure (DBP) in ABPM; morning blood pressure surge in ABPM; office blood pressure; home blood pressure; and heart rate after four-week treatment. Blood pressure control rate after treatment was also concerned. Time in target range (TTR) of home blood pressure = days met target / days of medication × 100% [19]. Medication compliance = (total number of dispensed medication pills—number of returned medication pills) / number of days medication should be taken * 100%.

Safety outcomes were adverse events, adverse drug reactions after treatment and changes in biochemistry results and QT interval of the electrocardiogram.

Certified medical electronic upper arm sphygmomanometer [Omron HBP-1300, OMRON (DALIAN) Co., Ltd.] was used for clinic blood pressure and certified ambulatory blood pressure monitor [DMS-ABP, DM SYSTEMS (Beijing) Co., Ltd.] for ambulatory blood pressure. Home blood pressure was measured at home by patients themselves or their family members with upper arm sphygmomanometers calibrated by physicians when enrolling. Blood pressure measurement methods were detailed in Additional file 2: Expanded Methods.

### Statistical analysis

Based on results of previous trial [16] that the 1/4 dose quadruple combination further reduced SBP by 6.9 mm Hg (95% CI 4.9–8.9) compared to single drug, with an estimated standard deviation of 15 mm Hg, and our previous clinical observation results on low-dose quadruple combination and standard-dose dual combination, it was estimated that the difference in 24-h mean SBP reduction between the two groups was 6 ± 15 mm Hg. Considering 20% loss to follow-up and the random factors of the block group, a final sample size of 90 participants with 45 in each crossover sequence would provide the trial 90% power (at a two-sided alpha level of 0.05).

Continuous variables were presented as mean and standard deviation (SD) or median and interquartile range (IQR) and categorical variables as frequencies and percentages. All efficacy results were statistically analyzed in full analysis set according to the intention-to-treat principle. The primary outcome and continuous variables of secondary outcomes were analyzed using a linear mixed-effects model that included all pre-specified covariates to analyze the treatment effect, stage effect, and sequence effect (residual carryover effect), with participant as a random effect [20, 21]. Longitudinal linear models were used to estimate the differences in home blood pressure. The proportion of participants achieving target blood pressure was analyzed by McNemar chi-square test. Safety outcomes were analyzed using chi-square tests or Fisher's exact probability method in safety set.

Prespecified subgroups included age (< 45 years or ≥ 45 years), sex, and diabetes. Prespecified sensitivity analysis were conducted 1) in per protocol set for analysis of primary and secondary outcomes; and 2) in different ways of managing missing data for analysis of home blood pressure.

All statistical significance tests were conducted using a two-sided type I error rate of 5%. All statistical analyses were performed using R Studio 2023.06.0 + 421.

## Results

### Study participants

A total of 90 eligible participants were randomized between July 13, 2022, and April 20, 2023, with final study visits completed on July 4, 2023. The mean age of the study population was 43.88 years, 25.6% were women, and 93.3% were Han Chinese. The mean baseline 24-h systolic/diastolic blood pressure was 145.59/93.84 mm Hg. Prior to randomization, median duration of hypertension was 12 months, and 4.4% of participants had ever taken blood pressure-lowering treatment. 4.4% had diabetes and 71.1% had mild sleep apnea, with no participants complicated with coronary heart disease, cerebrovascular disease, and peripheral vascular disease (Table 1). The mean duration of the trial last for 75.40 days and medication compliance was more than 95% (Additional file 2: Table S1). After excluding one participant for low blood pressure, two for using drugs that affected the trial, one for COVID-19, and two for voluntary withdrawal, a total of 84 participants completed stage one treatment (full analysis set). In stage two treatment, one participant voluntarily withdrew and one withdrew due to COVID-19, leaving 75 participants who completed the whole treatment (Fig. 1), with 63 participants included in the per protocol set.

**Table 1** Characteristics of the patients at baseline

| | Participants (*N* = 90) | | Participants (*N* = 90) |
|---|---|---|---|
| Age (years) | 43.88 (10.31) | TC (mmol/l) | 5.22 (0.93) |
| Sex (Female) | 23 (25.6%) | TG (mmol/l) | 2.47 (1.96) |
| Race or ethnicity | | LDL-C (mmol/l) | 3.02 (0.86) |
| Han | 84 (93.3%) | HDL-C (mmol/l) | 1.15 (0.28) |
| Others[a] | 6 (6.7%) | HCY (umol/l) | 12.45 [10.90, 14.80] |
| Time of HTN (months) | 12 [2, 36] | Plasma renin (pg/ml) | 13.61 [7.84, 22.39] |
| Ever treated[b] | 4 (4.4%) | Plasma aldosterone (pg/ml) | 167.40 [138.26, 219.74] |
| Family history of HTN | 73 (81.1%) | TSH (uIU/ml) | 2.37 (1.51) |
| Family history of early onset cardiovascular disease | 8 (8.9%) | Urinary protein | |
| Smoking | 26 (28.9%) | - | 70 (77.8%) |
| Alcohol | 8 (8.9%) | + | 19 (21.1%) |
| Diabetes | 4 (4.4%) | + + | 1 (1.1%) |
| Coronary heart disease | 0 | Sinus rhythm | 90 (100.0%) |
| Cerebrovascular disease | 0 | SV1 + RV5 (mv) | 2.77 (0.78) |
| Peripheral vascular disease | 0 | QT (ms) | 373.08 (29.96) |
| Sleep apnea[c] | 64 (71.1%) | QTc (ms) | 419.24 (22.83) |
| BMI (kg/m$^2$) | 25.54 (3.02) | LA (mm) | 31.57 (3.25) |
| Waistline (cm) | 88.37 (8.92) | RA (mm) | 30.16 (2.69) |
| Statin use | 21 (23.3%) | LV (mm) | 45.61 (3.63) |
| Fibrate use | 5 (5.6%) | RV (mm) | 28.40 (2.86) |
| Metformin use | 4 (4.4%) | IVS (mm) | 11.04 (1.23) |
| Serum potassium (mmol/l) | 4.07 (0.36) | LVPW (mm) | 10.62 (1.08) |
| Blood sodium(mmol/l) | 143.14 (2.09) | LVEF (%) | 68.79 (5.76) |
| FBG (mmol/l) | 5.45 (1.26) | E/A | 0.95 (0.33) |
| Glycosylated hemoglobin (%) | 5.81 (1.18) | Carotid plaque | 22 (24.4%) |
| Serum creatinine (umol/l) | 73.42 (13.24) | IMT (mm) | 0.87 (0.17) |
| Serum uric acid (umol/l) | 378.22 (86.28) | ABI | 1.17 (0.07) |
| Serum urea (mmol/l) | 4.53 (1.23) | baPWV (cm/s) | 1741.26 (273.94) |
| eGFR (ml/min/1.73m$^2$) | 103.12 (12.15) | ABPM character | |
| ALT (U/L) | 39.96 (29.90) | Dippers | 41 (45.6%) |
| AST (U/L) | 28.20 (12.24) | Non-dippers | 47 (52.2%) |
| TBL (umol/l) | 14.31 (5.29) | Reverse-dippers | 2 (2.2%) |
| DBL(umol/l) | 4.08 (1.58) | | |

Data are mean (SD) (for normal distribution) or median [$P_{25}$, $P_{75}$] (for non-normal distribution) or number of patients (%)(for categorical variables)

*ABI* Ankle brachial index, *ABPM* Ambulatory blood pressure monitoring, *ALT* Alanine transaminase, *AST* Aspartate transaminase, *baPWV*, Brachial-ankle pulse wave velocity, *BMI* Body mass index, *DBL* Direct bilirubin, *E/A* E/A ratio of mitral valve, *eGFR* Estimated glomerular filtration rate, *FBG* Fasting blood glucose, *HCY* Homocysteine, *HDL-C* High density lipoprotein cholesterol, *HTN* Hypertension, *IMT* carotid intima-media thickness, *IVS* Interventricular septum, *LA* Left atrium, *LDL-C* Low density lipoprotein cholesterol, *LV* Left ventricle, *LVEF*, Left ventricular ejection fraction, *LVPW* posterior wall of left ventricle, *RA* Right atrium, *RV* Right ventricle, *TBL* Total bilirubin, *TC*, Total cholesterol, *TG* Triglyceride, *TIA* Transient ischemic attack, *TSH* Thyroid stimulating hormone

[a] Chinese minority

[b] Ever taken blood pressure-lowering medications but not currently taking treatment for at least 1 month

[c] Mild sleep apnea which was not considered for the reason of hypertension

### Primary outcomes

After four-week treatment, the mean change in 24-h systolic blood pressure was −22.61 mm Hg (95% CI, −24.57 to −20.65 mm Hg) in half-dose quadruple treatment group and −17.94 mm Hg (95% CI, −19.99 to −15.89 mm Hg) in the standard-dose dual treatment group (Table 2). The mean 24-h systolic blood pressure difference between groups was −4.72 mm Hg (95% CI −7.60 to −1.84; $P < 0.001$). Tests for both a carry-over effect ($P = 0.656$) and a stage effect ($P = 0.484$) were not significant. The sensitivity analyses based on per protocol set also confirmed the significant difference in

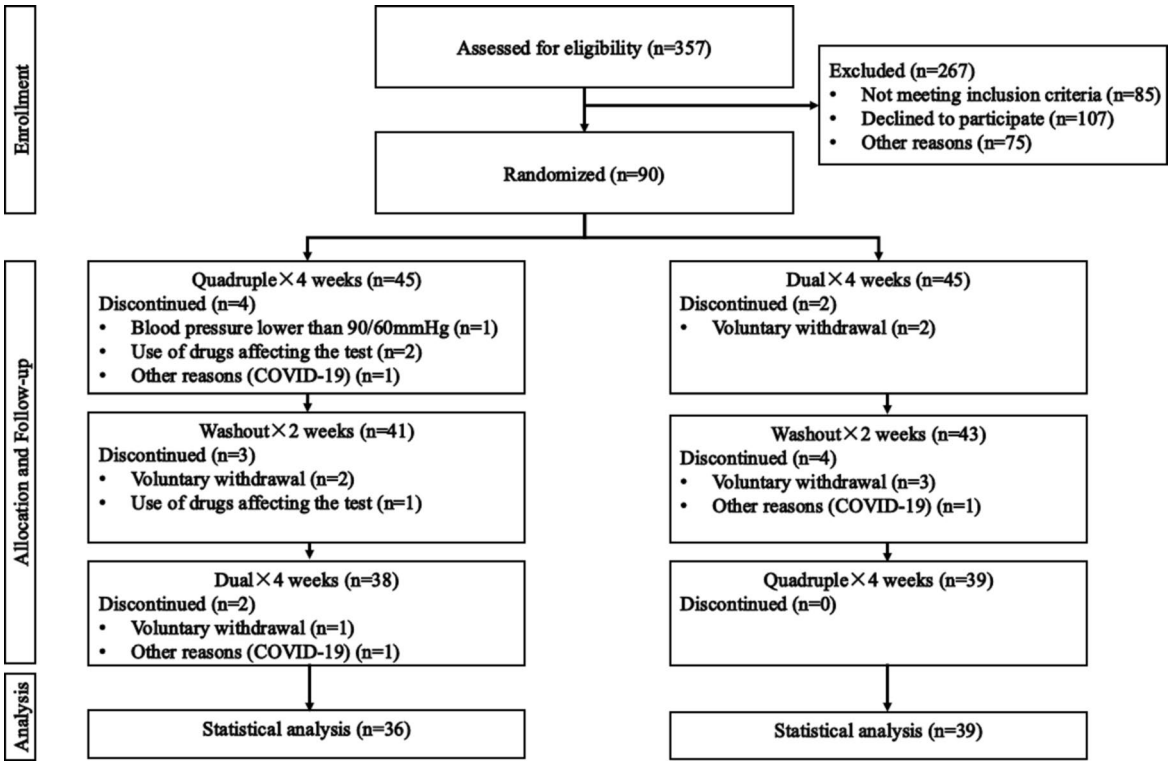


**Fig. 1** Trial profile. Only one participant withdrew in the quadruple therapy stage with a blood pressure below 90/60 mmHg and changed the treatment to losartan 50 mg per day. "Use of drugs affecting the test": one participant in quadruple treatment was hospitalized with SAE and switched to a different blood pressure medication to facilitate medication adjustment; the others were using other antihypertensive drugs by themselves

mean 24-h systolic blood pressure (Additional file 2: Table S2).

### Secondary outcomes

After four-week treatment, the mean differences of 24-h diastolic blood pressure (−17.09 mm Hg vs. −13.15 mm Hg), daytime ambulatory blood pressure (−24.16/−18.12 mm Hg vs. −18.81/−13.73 mm Hg), nighttime ambulatory blood pressure (−18.35/−13.84 mm Hg vs. −15.56/−11.43 mm Hg), and office blood pressure (−25.99/−16.20 mm Hg vs. −23.36/−14.99 mm Hg) were significantly different between the half-dose quadruple treatment group and the standard-dose dual treatment group (Table 2, Additional file 2: Fig. S2). While two treatments did not show obvious difference on home blood pressure in the fourth week (Table 2, Additional file 2: Fig. S2), half-dose quadruple treatment reduced patients' home blood pressure in longitudinal change within 4 weeks, especially systolic blood pressure, more significantly than standard-dose dual treatment (Fig. 2). The sensitivity analyses based on per protocol set confirmed the significant difference in mean 24-h diastolic blood pressure, daytime ambulatory blood pressure, office blood pressure and longitudinal home systolic blood pressure difference between groups (Additional file 2: Table S2, Fig. S3). The sensitivity analyses in home blood pressure enhanced the significant difference in mean home blood pressure difference between groups, even in home diastolic blood pressure (Additional file 2: Fig. S4-S6).

The difference between the effects of the two treatment regimens on heart rate was inconclusive and not clinically significant (Table 2). The mean morning surge differences between groups were not significant (Table 2).

A greater proportion of participants taking half-dose quadruple capsule achieved their blood pressure target at 4th week compared with taking standard-dose dual capsule (Additional file 2: Table S3, Table S4). TTR of home blood pressure was significantly higher in half-dose quadruple treatment group than standard-dose dual treatment group (56.91 ± 37.06% vs. 46.03 ± 33.70%; $P = 0.025$; Table 3). Difference of TTR between groups remained the same trend in the sensitivity analyses based on participants of per protocol set (Additional file 2: Table S5).

### Adverse events

In total, 46 adverse events in half-dose quadruple group and 17 in standard-dose dual group were reported

**Table 2** Effects of quadruple and dual treatments

| Treatment | Baseline (0th or 6th week) | End of treatment (4th or 10th) | Difference | *P*-value[†] |
|---|---|---|---|---|
| **Primary outcomes** | | | | |
| 24-h systolic blood pressure (mmHg) | | | | |
| Quadruple treatment | 143.28 (8.26) | 120.66 (8.68) | −22.61 (8.81) | < 0.001[*] |
| Dual treatment | 142.88 (9.16) | 125.04 (8.22) | −17.94 (9.15) | |
| **Secondary outcomes** | | | | |
| 24-h diastolic blood pressure (mmHg) | | | | |
| Quadruple treatment | 91.91 (8.30) | 74.83 (7.10) | −17.09 (6.26) | < 0.001[*] |
| Dual treatment | 91.64 (8.55) | 78.41 (7.87) | −13.15 (6.07) | |
| 24-h mean pulse rate (bpm) | | | | |
| Quadruple treatment | 76.28 (8.98) | 74.33 (9.23) | −1.95 (7.30) | < 0.001[*] |
| Dual treatment | 76.42 (9.94) | 77.89 (9.74) | 1.49 (6.58) | |
| Daytime ambulatory systolic blood pressure (mmHg) | | | | |
| Quadruple treatment | 147.30 (9.61) | 123.14 (9.48) | −24.16 (9.83) | < 0.001[*] |
| Dual treatment | 146.64 (9.77) | 127.91 (8.60) | −18.81 (9.42) | |
| Daytime ambulatory diastolic blood pressure (mmHg) | | | | |
| Quadruple treatment | 94.97 (9.06) | 76.85 (7.57) | −18.12 (7.17) | < 0.001[*] |
| Dual treatment | 94.52 (8.92) | 80.65 (8.15) | −13.73 (6.35) | |
| Daytime ambulatory mean pulse rate (bpm) | | | | |
| Quadruple treatment | 79.92 (9.58) | 77.47 (10.00) | −2.45 (8.28) | < 0.001[*] |
| Dual treatment | 80.44 (10.79) | 81.86 (10.47) | 1.44 (7.31) | |
| Night-time ambulatory systolic blood pressure (mmHg) | | | | |
| Quadruple treatment | 132.60 (9.24) | 114.25 (9.22) | −18.35 (10.46) | 0.034[*] |
| Dual treatment | 132.37 (10.96) | 116.95 (9.79) | −15.56 (10.98) | |
| Night-time ambulatory diastolic blood pressure (mmHg) | | | | |
| Quadruple treatment | 83.62 (8.99) | 69.79 (7.76) | −13.84 (7.59) | 0.014[*] |
| Dual treatment | 83.62 (9.85) | 72.20 (8.90) | −11.43 (7.92) | |
| Night-time ambulatory mean pulse rate (bpm) | | | | |
| Quadruple treatment | 66.31 (8.85) | 66.94 (10.76) | 0.62 (8.80) | 0.397 |
| Dual treatment | 65.23 (8.81) | 67.05 (8.77) | 1.87 (6.96) | |
| Morning Surge (mmHg) | | | | |
| Quadruple treatment | 17.65 (11.97) | 17.02 (10.87) | −0.62 (14.25) | 0.790 |
| Dual treatment | 22.07 (11.28) | 17.54 (11.78) | −4.39 (13.48) | |
| Office systolic blood pressure (mmHg) | | | | |
| Quadruple treatment | 148.52 (13.23) | 122.54 (10.94) | −25.99 (12.80) | < 0.001[*] |
| Dual treatment | 151.40 (13.02) | 128.19 (10.57) | −23.36 (12.12) | |
| Office diastolic blood pressure (mmHg) | | | | |
| Quadruple treatment | 94.43 (10.31) | 78.23 (7.91) | −16.20 (8.80) | 0.014[*] |
| Dual treatment | 95.86 (10.99) | 81.02 (8.73) | −14.99 (8.14) | |
| Office pulse rate (bpm) | | | | |
| Quadruple treatment | 78.69 (12.42) | 75.26 (12.57) | −3.42 (12.03) | 0.327 |
| Dual treatment | 79.69 (13.85) | 76.96 (11.61) | −2.70 (9.87) | |
| Home systolic blood pressure (mmHg) | | | | |
| Quadruple treatment | 144.92 (13.37) | 122.52 (10.35) | −22.40 (14.41) | 0.368 |
| Dual treatment | 147.67 (14.59) | 124.65 (10.48) | −23.02 (15.11) | |
| Home diastolic blood pressure (mmHg) | | | | |
| Quadruple treatment | 93.93 (9.22) | 80.64 (8.59) | −13.29 (8.72) | 0.312 |
| Dual treatment | 96.11 (10.86) | 82.65 (9.39) | −13.45 (9.32) | |
| Home pulse rate (bpm) | | | | |
| Quadruple treatment | 78.75 (11.55) | 76.48 (12.00) | −2.23 (9.42) | 0.122 |
| Dual treatment | 78.42 (13.10) | 78.40 (11.58) | −0.02 (10.75) | |

**Table 2** (continued)

Data are mean (SD)

† Linear mixed effect model adjusted for basic blood pressure/heart rate, stage, sequence, sex, age, nation, DM, OSAS, smoke, alcohol, ever treated, time of HTN, BMI and eGFR, with participants as randomized effect

* $P < 0.05$ for significant difference between two treatments

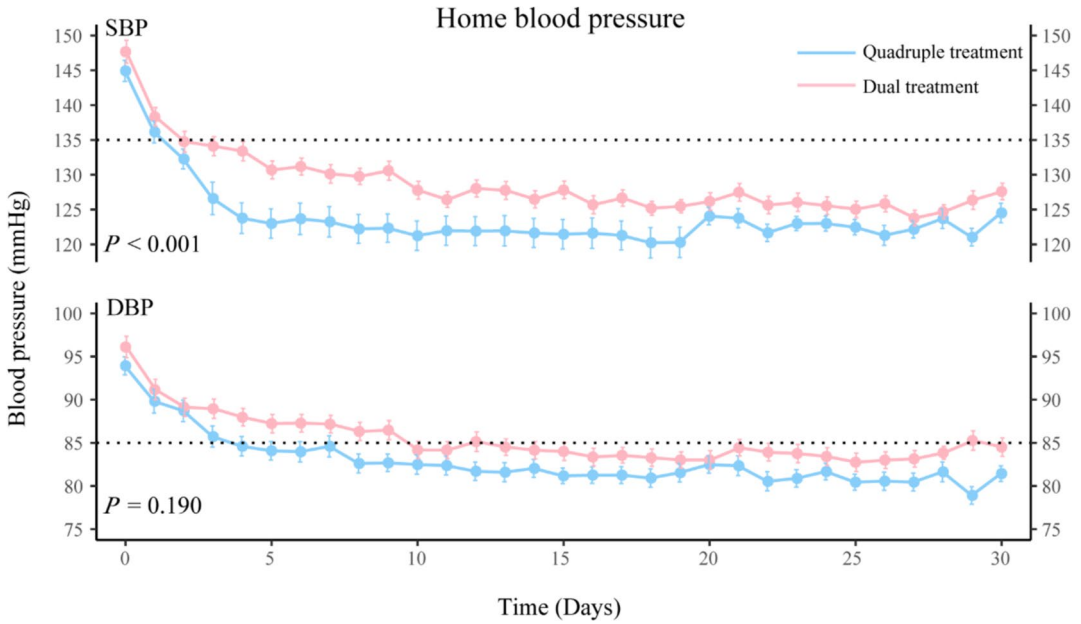


**Fig. 2** Effects on home blood pressure of two treatments. *P* was for interaction effect of treatment and days based on linear mixed effect model, adjusted for stage, sequence, sex, age, nation, diabetes, OSAS, smoke, alcohol, ever treated, time of hypertension, BMI and eGFR, with participants and treatments as randomized effect. I bars represent 95% confidence intervals

**Table 3** Effects of quadruple and dual treatments on TTR of home blood pressure

| | Quadruple treatment | Dual treatment | *P*-value† |
|---|---|---|---|
| Home systolic blood pressure | 83.68 (27.44) | 72.64 (30.24) | 0.006* |
| Home diastolic blood pressure | 58.04 (34.76) | 49.64 (35.83) | 0.041* |
| Home blood pressure | 56.91 (37.06) | 46.03 (33.70) | 0.025* |

Data are mean (SD) of TTR

*TTR* Time in target range of blood pressure

† Linear mixed effect model adjusted for basic blood pressure, stage, sequence, sex, age, nation, DM, family history of HTN, family history of early onset cardiovascular disease, OSAS, smoke, alcohol, ever treated, time of HTN, waistline, BMI, LVEF, carotid plaque, IMT, ABI, baPWV, eGFR and drugs taken, with participants as randomized effect

* $P < 0.05$ for significant difference between two treatments

during the study, in which 36 and 8 adverse events, respectively, were considered related to the treatment (definite, probable and possible relationship). The most common adverse events reported in half-dose quadruple group were investigations (especially fasting blood glucose increased and blood uric acid increased), which were significantly more than standard-dose dual group ($N=9$ vs. $N=2$, $P=0.029$; and $N=21$ vs. $N=1$, $P<0.001$; respectively; Table 4, Additional file 2: Table S6-S7). For both treatments, the total number of dropouts in two phases was four. Only one participant withdrew in the quadruple therapy stage for his blood pressure below 90/60 mmHg and changed the treatment to losartan 50 mg per day. No any other instances where participants had to change the dose of medications taken due to intolerance.

Only one participant in half-dose quadruple group reported one serious adverse event (cerebral infarction)

**Table 4** Adverse events during the study period

| | Quadruple treatment | Dual treatment |
|---|---|---|
| Flushing | 0 | 1 (1.11%) |
| Hypotension | 1 (1.11%) | 0 |
| Fatigue | 1 (1.11%) | 1 (1.11%) |
| Perspiration | 0 | 1 (1.11%) |
| Poor appetite | 1 (1.11%) | 0 |
| Cerebral infarction[a] | 1 (1.11%) | 0 |
| Headache | 0 | 1 (1.11%) |
| Dizziness | 2 (2.22%) | 2 (2.22%) |
| Palpitation | 0 | 2 (2.22%) |
| Chest distress | 2 (2.22%) | 0 |
| Gout | 0 | 0 |
| Serum potassium decreased | 5 (5.56%) | 2 (2.22%) |
| Serum sodium decreased | 0 | 0 |
| **Fasting blood glucose increased*** | **9 (10.00%)** | **2 (2.22%)** |
| Creatinine increased | 0 | 0 |
| Blood urea increased | 0 | 0 |
| **Blood uric acid increased*** | **21 (23.33%)** | **1 (1.11%)** |
| Alanine aminotransferase increased | 2 (2.22%) | 3 (3.33%) |
| Aspartate aminotransferase increased | 1 (1.11%) | 0 |
| Total bilirubin increased | 0 | 1 (1.11%) |
| Direct bilirubin increased | 0 | 0 |
| Urinary protein increased | 0 | 0 |
| QT interval prolongation | 0 | 0 |
| QTc interval prolongation | 0 | 0 |
| **Total*** | **46 (51.11%)** | **17 (18.89%)** |

Data are frequency of adverse events (%)

[a] Reported serious adverse event

* $P < 0.05$ for significant difference between two treatments

(Table 4), who was finally diagnosed with moyamoya disease by digital subtraction angiography.

### Laboratory values

There were statistically significant between-group differences in the changes of serum potassium, serum sodium, fasting blood glucose, serum creatinine, serum uric acid, and serum urea, while not for alanine transaminase, aspartate transaminase, total bilirubin, direct bilirubin, QT interval, and QTc interval (Table 5).

### Subgroup analysis

There was no evidence of heterogeneity in the treatment effect for the outcomes in the prespecified subgroups of sex and age (Additional file 2: Fig. S7, Table S8). Because only four patients had diabetes mellitus, a subgroup analysis based on this condition was not performed.

## Discussion

This crossover trial demonstrated that initiating treatment with half-dose quadruple combination therapy was more effective in lowering blood pressure than starting with standard-dose dual therapy. Apart from significant increases of fasting blood glucose and blood uric acid in the half-dose quadruple group, no other adverse events or changes in laboratory values differed significantly between the two treatments.

Early attainment of target blood pressure is known to lower cardiovascular risk and lead to better prognosis [22–25]. Aggressive treatment of patients with grade 1 and 2 hypertension could reduce 803,000 cardiovascular events per year and increase 1.2 million quality-adjusted life years compared with maintaining the status quo [26], yielding considerable socioeconomic benefits. The PURE study noted that less than 1/3 of hypertensive patients achieved target blood pressure after starting with only monotherapy [27]. Compared with monotherapy, combination therapy at the initiation of antihypertensive

**Table 5** Effects of two treatments on laboratory measurements

| Drug | | Baseline | End of treatment (4th or 10th) | Overall Difference | *P*-value from baseline | *P*-value between groups[†] |
|---|---|---|---|---|---|---|
| **Serum potassium (mmol/l)** | | | | | | |
| | Quadruple treatment | 4.07 (0.34) | 3.90 (0.33) | −0.17 (0.35) | < 0.001 | < 0.001 |
| | Dual treatment | 4.07 (0.37) | 4.12 (0.27) | 0.03 (0.34) | 0.492 | |
| **Serum sodium(mmol/l)** | | | | | | |
| | Quadruple treatment | 142.99 (1.81) | 141.84 (1.88) | −1.31 (2.42) | < 0.001 | < 0.001 |
| | Dual treatment | 143.28 (2.35) | 142.88 (1.97) | −0.26 (2.58) | 0.371 | |
| **FBG (mmol/l)** | | | | | | |
| | Quadruple treatment | 5.55 (1.44) | 5.90 (1.23) | 0.41 (0.83) | < 0.001 | 0.011 |
| | Dual treatment | 5.34 (1.05) | 5.59 (1.38) | 0.11 (0.79) | 0.224 | |
| **Serum creatinine (umol/l)** | | | | | | |
| | Quadruple treatment | 74.58 (13.62) | 75.38 (12.38) | 1.75 (7.81) | 0.049 | < 0.001 |
| | Dual treatment | 72.27 (12.89) | 71.18 (12.15) | −2.19 (6.72) | 0.005 | |
| **Serum uric acid (umol/l)** | | | | | | |
| | Quadruple treatment | 375.91 (87.49) | 419.92 (89.46) | 39.27 (82.68) | < 0.001 | < 0.001 |
| | Dual treatment | 380.53 (85.99) | 331.09 (79.27) | −45.81 (72.13) | < 0.001 | |
| **Serum urea (mmol/l)** | | | | | | |
| | Quadruple treatment | 4.31 (1.12) | 5.37 (1.21) | 0.80 (1.26) | < 0.001 | < 0.001 |
| | Dual treatment | 4.75 (1.31) | 4.75 (1.37) | 0.16 (1.25) | 0.269 | |
| **ALT (U/L)** | | | | | | |
| | Quadruple treatment | 40.02 (24.19) | 35.05 (22.24) | −4.16 (22.94) | 0.109 | 0.304 |
| | Dual treatment | 39.89 (34.97) | 37.49 (24.24) | −3.27 (21.55) | 0.182 | |
| **AST (U/L)** | | | | | | |
| | Quadruple treatment | 29.13 (9.98) | 27.20 (11.76) | −0.96 (11.64) | 0.462 | 0.106 |
| | Dual treatment | 27.27 (14.20) | 25.51 (7.96) | −2.39 (9.22) | 0.024 | |
| **TBL (umol/l)** | | | | | | |
| | Quadruple treatment | 13.33 (4.86) | 13.49 (5.99) | −0.44 (4.60) | 0.395 | 0.925 |
| | Dual treatment | 15.30 (5.56) | 13.39 (5.09) | −0.68 (4.65) | 0.201 | |
| **DBL (umol/l)** | | | | | | |
| | Quadruple treatment | 3.76 (1.45) | 4.09 (1.87) | 0.03 (1.36) | 0.863 | 0.343 |
| | Dual treatment | 4.39 (1.66) | 4.23 (1.69) | 0.15 (1.45) | 0.346 | |
| **QT interval (ms)** | | | | | | |
| | Quadruple treatment | 370.44 (29.85) | 380.52 (32.47) | 8.50 (26.92) | 0.006 | 0.097 |
| | Dual treatment | 375.71 (30.18) | 375.95 (28.21) | 3.29 (25.07) | 0.247 | |
| **QTc interval (ms)** | | | | | | |
| | Quadruple treatment | 414.98 (21.08) | 412.10 (25.47) | −7.14 (20.79) | 0.003 | 0.396 |
| | Dual treatment | 423.51 (23.93) | 413.38 (23.83) | −5.54 (22.14) | 0.029 | |

[†] Linear mixed effect model adjusted for basic values, stage, sequence, sex, age, DM, with participants as randomized effect

treatment increased magnitude of blood pressure reduction and shortened time to target blood pressure [28–30], even in patients with grade 1 hypertension [31–33].

In recent years, some researchers proposed the hypothesis that low-dose multidrug combinations (≥3) offered better antihypertensive effects and fewer side effects in initial treatment, and conducted preliminary investigations into this field [12–16], further breaking the stereotyped thought that the current antihypertensive regimen started with a combination of two drugs, based on which 2023 ESH hypertension guidelines mentioned the quadpill concept [34]. However, none of the above studies compared the dual therapy recommended by hypertension guidelines and involved the Chinese population. Our findings addressed these gaps, and strengthened the conclusion that small dose of quadruple drugs were more effective in lowering blood pressure than standard-dose dual drugs. In our study, half-dose quadruple therapy

reduced SBP by 4.72 mmHg more than standard-dose dual therapy, which is less than the QUARTET trial [16], where quadruple quarter-dose therapy lowered SBP by 6.9 mmHg more than standard-dose monotherapy. This is consistent with the current understanding that the combination of two different medications is more effective than doubling the dose of a single drug. In addition, the primary outcome of our study was 24-h SBP, which is a better metric compared to office BP [35, 36]. This is also an advantage compared to previous research. Recent years, higher TTR was found associated with a decreased risk of death from any cause and major adverse cardiovascular events [37–39]. So, we added to analysed this parameter retrospectively and found that small dose of quadruple drugs could significantly increase TTR. Though the decrease of home blood pressure at the fourth week between two treatments seemed no obvious difference, the longitudinal home blood pressure within the four weeks and TTR revealed significant advantages in small dose of quadruple drugs. The suspected reason may be nervousness on the day of visit, making the home blood pressure higher on that day.

Looking at the baseline data, we could see that it was a relatively young cohort, with only 4% having diabetes. Older hypertensive patients often visited the clinic already on medication, whereas younger hypertensive patients were typically not on any treatment when they sought care. Our study primarily focused on untreated hypertensive patients, which may be why the sample mainly consisted of younger individuals with fewer comorbidities, such as diabetes. In young people, women are generally less likely to develop hypertension and other cardiovascular diseases, due to the protective effects of estrogen [40], which may be the reason the population was predominantly male. In this trial, we chose "A + C" over "A + D" as control based on evidence-based evidence and Chinese clinical practice. 2020 ISH guidelines only recommended "A + C" [1], and there was ample evidence for "A + C" [41, 42] rather than "A + D" [42, 43] in hypertension treatment. "A + C" was also the most prescribed dual combination in China [44]. Therefore, as an exploratory attempt, we chose the more obvious advantageous "A + C" combination as control. Regarding to beta-blocker, although it was no longer recognized as a priority antihypertensive drug in American guidelines [6], it was recommended as the first-line drug in Chinese [45] and European guidelines [34]. Moreover, the sympathetic nervous system and the renin-angiotensin system were significantly activated in Chinese population especially with young and middle age [46–49], so, our quadruple combination included beta-blocker.

In this trial, the half-dose quadruple combination reported more adverse events on fasting blood glucose and blood uric acid, which may be related to beta-blockers and diuretics [50–53]. The incidence of gout induced by the quadruple combination remained zero, despite increased uric acid. In addition, half-dose quadruple combination could reduce blood potassium and sodium and elevate creatinine and urea to some extent, which may all be associated with diuretics [54, 55]. However, there was no clinical meaning for these small changes compared with baseline.

Although one participant experienced a cerebral infarction when using low-dose quadruple therapy, the blood pressure of this participant was not low (approximately 150/90 mm Hg). The diagnosis was confirmed by digital subtraction angiography with Moyamoya disease, which made the patient susceptible to stroke [56]. After comprehensive analysis by the clinical end point committee and neurological physician, this serious adverse event was more related to the patient's underlying condition. For the convenience of adjusting the medication according to blood pressure, the participant withdrew from the trial.

In general, the safety of half-dose quadruple therapy was comparable with standard-dose dual therapy, and specific adverse events were related to the type of drug combinations.

#### Strength

The strengths of this study are that: 1) the use of dual combination as control, unlike the previous trials with single drug or placebo, could illustrate the antihypertensive advantages of quadruple combinations more effectively; 2) the use of a single capsule with identical appearance and interior could effectively ensure the implementation of blinding, guarantee the participants' compliance with medication [57], and also reduced in the feeling of polypharmacy [57]; 3) crossover design is self-controls and can minimize bias and improve statistical power; 4) the use of a range of blood pressure measurement methods, including ABPM, office blood pressure and home blood pressure, made the results more convincing, and the treatment effects were consistent.

#### Limitation

Due to the single sample source and a small sample size, the study was limited in its ability to cover a broad population and geographic area, which may restrict its generalizability. The small number of patients may also make some results like target rate of blood pressure and subgroup analysis less convincing. Pill-count compliance has its limitations, including the possibility that participants may remove pills before clinic visits. In addition, the trial failed to explore the long-term antihypertensive effect and prognosis of cardiovascular outcomes for

the limitations of the crossover study. Various half-dose quadruple combinations and standard-dose dual combinations were not employed in the trial, making it difficult to generalize the conclusions to all multi-drug combinations. However, the combinations in this trial were typical and representative, at least giving the concept that half-dose quadruple combinations were more effective in lowering blood pressure than standard-dose dual combinations. Therefore, more subsequent studies are needed for further exploration of the advantages of small-dose quadruple antihypertensive drugs by including more research centers, employing more kinds of combinations of quadruple and dual drugs, and observing for a longer period for prognosis of cardiovascular outcomes.

## Conclusions

The QUADUAL study, to our knowledge, was the first trial to investigate the antihypertensive effect of low-dose quadruple drug initial treatment with standard-dose dual therapy as control, and it was also the first quadruple antihypertensive study conducted in the Chinese population. This study could provide a rich and solid theoretical basis for the development of possible low-dose quadruple antihypertensive combinations in the future, and provide a reference for the selection of antihypertensive programs in hypertension guidelines, thereby actively promoting the prevention and treatment of hypertension.

### Abbreviations

| | |
|---|---|
| ABPM | Ambulatory Blood Pressure Monitoring |
| BMI | Body Mass Index |
| DBP | Diastolic Blood Pressure |
| eGFR | Estimated Glomerular Filtration Rate |
| IDMC | Independent Data Monitoring Committee |
| OSAS | Obstructive Sleep Apnea Syndrome |
| SBP | Systolic Blood Pressure |
| TTR | Time in Target Range |

## Supplementary Information

The online version contains supplementary material available at https://doi.org/10.1186/s12916-025-03892-8.

Additional file 1. Study protocol.

Additional file 2. Expanded Methods. Table S1. Duration of medication and medication compliance. Table S2. Effects of quadruple and dual treatments in PPS population. Table S3. Blood pressure target rate of two antihypertensive treatments. Table S4. Blood pressure target rate of two antihypertensive treatments in PPS population. Table S5. Effects of quadruple and dual treatments on TTR of home blood pressure in PPS population. Table S6. List of adverse events in system organ class. Table S7. List of relationship of adverse events and treatments. Table S8. Subgroup analysis of other indicators. Figure S1. Flow diagram of the QUADUAL trial. Figure S2. Antihypertensive effects of two treatments. Figure S3. Effects on home blood pressure of two treatments in PPS population. Figure S4. Effects on home blood pressure of two treatments after LOCF imputation. Figure S5. Effects on home blood pressure of two treatments after NOCB imputation. Figure S6. Effects on home blood pressure of two treatments after linear imputation. Figure S7. Forest plot of blood pressure according to subgroups. QUADUAL team acknowledgements.

### Acknowledgements

Acknowledgements were detailed in Additional file 2: QUADUAL team acknowledgements.

### Authors' contributions

XXZ for conceptualization, writing of original draft, project administration, and supervision; TL for data curation, investigation, and writing of review & editing; QY for investigation, resources, and writing of review & editing; GPY for supervision, methodology, and writing of review & editing; XLL for formal analysis, methodology, visualization, writing of review & editing; XHT for investigation, resources, and writing of review & editing; JLL, AYL, LXZ, JW, XYW, LPP, and LZ for investigation and resources; ZSL for investigation, writing of review & editing; WJW for investigation; JJC for writing of review & editing; YC, MH, RXL, and RF for data curation; XGL for funding acquisition, writing of review & editing, and resources; WHJ for funding acquisition, supervision, and writing of review & editing. All authors read and approved the final manuscript.

### Funding

The study was supported by the Key Research and Development program of Hunan Province (NO.2022SK2029), and the National Natural Science Foundation of China Projects (NO.81800271). The funders had no role in the design and conduct of the study; collection, management, analysis, and interpretation of the data; preparation, review, or approval of the manuscript; and decision to submit the manuscript for publication.

### Data availability

Coded data (without personal identification information) used and analysed during the current study will be available to researchers one year after the publication date of the manuscript from the corresponding author on reasonable request, with the approval of the steering committee and Research Center for Clinical Trials of the Third Xiangya Hospital of Central South University, on signing of a data access agreement.

## Declarations

### Ethics approval and consent to participate

Institutional Review Board of the Third Xiangya Hospital, Central South University approved this trial (approval number R22023 and R22152). The purpose and method of the study were informed in detail and the written informed consent was obtained before enrollment from all the patients.

### Consent for publication

Not applicable.

### Competing interests

The authors declare no competing interests.

### Author details

[1]Department of Cardiology, The Third Xiangya Hospital of Central South University, Yuelu District, 138 Tongzipo Road, Changsha 410013, Hunan, China. [2]Center of Clinical Pharmacology, The Third Xiangya Hospital of Central South University, Changsha, China. [3]Department of Clinical Pharmacology, XiangYa School of Pharmaceutical Sciences, Changsha, China. [4]Department of Epidemiology, XiangYa School of Public Health, Changsha, China. [5]Hypertension Research Center of Hunan Province, Changsha, Hunan, China.

Received: 21 August 2024 Accepted: 22 January 2025
Published online: 29 January 2025

### References

1. Unger T, Borghi C, Charchar F, Khan NA, Poulter NR, Prabhakaran D, et al. 2020 International Society of Hypertension global hypertension practice guidelines. J Hypertens. 2020;38(6):982–1004.
2. Joint Committee for Guideline, Revision. 2018 Chinese guidelines for prevention and treatment of hypertension-a report of the revision committee of Chinese guidelines for prevention and treatment of hypertension. J Geriatr Cardiol. 2019;16(3):182–241.

3. G. B. D. Risk Factors Collaborators. Global burden of 87 risk factors in 204 countries and territories, 1990–2019: a systematic analysis for the global burden of disease study 2019. Lancet. 2020;396(10258):1223–49.
4. The Writing Committee of the Report on Cardiovascular Health and Diseases in China. Report on cardiovascular health and diseases burden in China: an Updated Summary of 2020. Chin Circul J. 2021;36(6):521–45.
5. Lu J, Lu Y, Wang X, Li X, Linderman GC, Wu C, et al. Prevalence, awareness, treatment, and control of hypertension in China: data from 1.7 million adults in a population-based screening study (China PEACE Million Persons Project). Lancet. 2017;390(10112):2549–58.
6. Whelton PK, Carey RM, Aronow WS, Casey DE Jr, Collins KJ, Dennison Himmelfarb C, 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. J Am Coll Cardiol. 2018;71(19):2199–269.
7. Visseren FLJ, Mach F, Smulders YM, Carballo D, Koskinas KC, Back M, et al. 2021 ESC guidelines on cardiovascular disease prevention in clinical practice. Eur Heart J. 2021;42(34):3227–337.
8. Lopez-Jaramillo P, Barbosa E, Molina DI, Sanchez R, Diaz M, Camacho PA, et al. Latin American Consensus on the management of hypertension in the patient with diabetes and the metabolic syndrome. J Hypertens. 2019;37(6):1126–47.
9. Umemura S, Arima H, Arima S, Asayama K, Dohi Y, Hirooka Y, et al. The Japanese Society of Hypertension guidelines for the management of hypertension (JSH 2019). Hypertens Res. 2019;42(9):1235–481.
10. Junbo G, Yongjian X, Chen W. Internal medicines. Beijing: People's Medical Publishing House; 2018. p. 247–50.
11. Naik P, Gandhi H, Pawar V, Giridhar R, Yadav MR. Management of hypertension-journey from single drug therapy to multitargeted ligand therapy: a clinical overview. Curr Clin Pharmacol. 2015;10(4):321–46.
12. Mahmud A, Feely J. Low-dose quadruple antihypertensive combination: more efficacious than individual agents–a preliminary report. Hypertension. 2007;49(2):272–5.
13. Chow CK, Thakkar J, Bennett A, Hillis G, Burke M, Usherwood T, et al. Quarter-dose quadruple combination therapy for initial treatment of hypertension: placebo-controlled, crossover, randomised trial and systematic review. Lancet. 2017;389(10073):1035–42.
14. Webster R, Salam A, de Silva HA, Selak V, Stepien S, Rajapakse S, et al. Fixed low-dose triple combination antihypertensive medication vs usual care for blood pressure control in patients with mild to moderate hypertension in Sri Lanka: a randomized clinical trial. JAMA. 2018;320(6):566–79.
15. Hong SJ, Sung KC, Lim SW, Kim SY, Kim W, Shin J, et al. Low-Dose triple antihypertensive combination therapy in patients with hypertension: a randomized, double-blind, phase II study. Drug Des Devel Ther. 2020;14:5735–46.
16. Chow CK, Atkins ER, Hillis GS, Nelson MR, Reid CM, Schlaich MP, et al. Initial treatment with a single pill containing quadruple combination of quarter doses of blood pressure medicines versus standard dose monotherapy in patients with hypertension (QUARTET): a phase 3, randomised, double-blind, active-controlled trial. Lancet. 2021;398(10305):1043–52.
17. Zhao X, Chen Y, Yang G, Li X, Tang X, Yang Q, et al. Initial treatment with a single capsule containing half-dose quadruple therapy vs standard-dose dual therapy in hypertensive patients (QUADUAL): study protocol for a randomized, blinded, crossover trial. Am Heart J. 2023;264:10–9.
18. Zhao X, Li X, Liu T, Yang G, Chen Y, Huang M, et al. Initial treatment with a single capsule containing half-dose quadruple therapy versus standard-dose dual therapy in hypertensive patients (QUADUAL): statistical analysis plan for a randomized, blinded, crossover trial. Trials. 2024;25(1):45.
19. Buckley LF, Baker WL, Van Tassell BW, Cohen JB, Alkhezi O, Bress AP, et al. Systolic Blood Pressure Time in Target Range and Major Adverse Kidney and Cardiovascular Events. Hypertension. 2023;80(2):305–13.
20. Lawrence X, Yu BVL. FDA Bioequivalence Standards. London: Springer, New York Heidelberg Dordrecht London; 2014.
21. Twisk JWR. Analysis of data from randomized controlled trials: a practical guide. Switzerland: Springer Nature Switzerland AG; 2021.
22. Weber MA, Julius S, Kjeldsen SE, Brunner HR, Ekman S, Hansson L, et al. Blood pressure dependent and independent effects of antihypertensive treatment on clinical events in the VALUE Trial. Lancet. 2004;363(9426):2049–51.
23. Gradman AH, Parise H, Lefebvre P, Falvey H, Lafeuille MH, Duh MS. Initial combination therapy reduces the risk of cardiovascular events in hypertensive patients: a matched cohort study. Hypertension. 2013;61(2):309–18.
24. Corrao G, Nicotra F, Parodi A, Zambon A, Heiman F, Merlino L, et al. Cardiovascular protection by initial and subsequent combination of antihypertensive drugs in daily life practice. Hypertension. 2011;58(4):566–72.
25. Yu JM, Kong QY, Shen T, He YS, Wang JW, Zhao YP. Benefit of initial dual-therapy on stroke prevention in Chinese hypertensive patients: a real world cohort study. J Thorac Dis. 2015;7(5):881–9.
26. Gu D, He J, Coxson PG, Rasmussen PW, Huang C, Thanataveerat A, et al. The cost-effectiveness of low-cost essential antihypertensive medicines for hypertension control in China: a modelling study. PLoS Med. 2015;12(8):e1001860.
27. Chow CK, Teo KK, Rangarajan S, Islam S, Gupta R, Avezum A, et al. Prevalence, awareness, treatment, and control of hypertension in rural and urban communities in high-, middle-, and low-income countries. JAMA. 2013;310(9):959–68.
28. An J, Luong T, Qian L, Wei R, Liu R, Muntner P, et al. Treatment patterns and blood pressure control with initiation of combination versus monotherapy antihypertensive regimens. Hypertension. 2021;77(1):103–13.
29. Mancia G, Rea F, Cuspidi C, Grassi G, Corrao G. Blood pressure control in hypertension. Pros and cons of available treatment strategies. J Hypertens. 2017;35(2):225–33.
30. Mancia G, Asmar R, Amodeo C, Mourad JJ, Taddei S, Gamba MA, et al. Comparison of single-pill strategies first line in hypertension: perindopril/amlodipine versus valsartan/amlodipine. J Hypertens. 2015;33(2):401–11.
31. Gradman AH, Basile JN, Carter BL, Bakris GL, Materson BJ, Black HR, et al. Combination therapy in hypertension. J Am Soc Hypertens. 2010;4(2):90–8.
32. Weir MR, Levy D, Crikelair N, Rocha R, Meng X, Glazer R. Time to achieve blood-pressure goal: influence of dose of valsartan monotherapy and valsartan and hydrochlorothiazide combination therapy. Am J Hypertens. 2007;20(7):807–15.
33. Brown MJ, McInnes GT, Papst CC, Zhang J, MacDonald TM. Aliskiren and the calcium channel blocker amlodipine combination as an initial treatment strategy for hypertension control (ACCELERATE): a randomised, parallel-group trial. Lancet. 2011;377(9762):312–20.
34. Mancia G, Kreutz R, Brunström M, Burnier M, Grassi G, Januszewicz A, et al. 2023 ESH guidelines for the management of arterial hypertension the task force for the management of arterial hypertension of the European Society of Hypertension: Endorsed by the International Society of Hypertension (ISH) and the European Renal Association (ERA). J Hypertens. 2023;41(12):1874–2071.
35. Böhm M, de la Sierra A, Mahfoud F, Schwantke I, Lauder L, Haring B, et al. Office measurement vs. ambulatory blood pressure monitoring: associations with mortality in patients with or without diabetes. Eur Heart J. 2024;45(31):2851–61.
36. Staplin N, de la Sierra A, Ruilope LM, Emberson JR, Vinyoles E, Gorostidi M, et al. Relationship between clinic and ambulatory blood pressure and mortality: an observational cohort study in 59 124 patients. Lancet. 2023;401(10393):2041–50.
37. Chung SC, Pujades-Rodriguez M, Duyx B, Denaxas SC, Pasea L, Hingorani A, et al. Time spent at blood pressure target and the risk of death and cardiovascular diseases. PLoS One. 2018;13(9):e0202359.
38. Doumas M, Tsioufis C, Fletcher R, Amdur R, Faselis C, Papademetriou V. Time in therapeutic range, as a determinant of all-cause mortality in patients with hypertension. J Am Heart Assoc. 2017;6(11):e007131.
39. Fatani N, Dixon DL, Van Tassell BW, Fanikos J, Buckley LF. Systolic blood pressure time in target range and cardiovascular outcomes in patients with hypertension. J Am Coll Cardiol. 2021;77(10):1290–9.
40. Sabbatini AR, Kararigas G. Estrogen-related mechanisms in sex differences of hypertension and target organ damage. Biol Sex Differ. 2020;11(1):31.
41. Dahlöf B, Sever PS, Poulter NR, Wedel H, Beevers DG, Caulfield M, et al. Prevention of cardiovascular events with an antihypertensive regimen of amlodipine adding perindopril as required versus atenolol adding bendroflumethiazide as required, in the Anglo-Scandinavian Cardiac Outcomes Trial-Blood Pressure Lowering Arm (ASCOT-BPLA): a multicentre randomised controlled trial. Lancet. 2005;366(9489):895–906.

42. Jamerson K, Weber MA, Bakris GL, Dahlöf B, Pitt B, Shi V, et al. Benazepril plus Amlodipine or Hydrochlorothiazide for Hypertension in High-Risk Patients. New Engl J Med. 2008;359(23):2417–28.
43. Hansson L, Lindholm LH, Niskanen L, Lanke J, Hedner T, Niklason A, et al. Effect of angiotensin-converting-enzyme inhibition compared with conventional therapy on cardiovascular morbidity and mortality in hypertension: the Captopril Prevention Project (CAPPP) randomised trial. Lancet. 1999;353(9153):611–6.
44. Lu Y, Van Zandt M, Liu Y, Li J, Wang X, Chen Y, et al. Analysis of dual combination therapies used in treatment of hypertension in a multinational cohort. JAMA Netw Open. 2022;5(3):e223877.
45. Joint Committee for Guideline R. 2018 Chinese guidelines for prevention and treatment of hypertension-a report of the revision committee of chinese guidelines for prevention and treatment of hypertension. J Geriatr Cardiol. 2019;16(3):182–241.
46. Lambert E, Dawood T, Straznicky N, Sari C, Schlaich M, Esler M, et al. Association between the sympathetic firing pattern and anxiety level in patients with the metabolic syndrome and elevated blood pressure. J Hypertens. 2010;28(3):543–50.
47. Bajkó Z, Szekeres CC, Kovács KR, Csapó K, Molnár S, Soltész P, et al. Anxiety, depression and autonomic nervous system dysfunction in hypertension. J Neurol Sci. 2012;317(1–2):112–6.
48. Pan Y, Cai W, Cheng Q, Dong W, An T, Yan J. Association between anxiety and hypertension: a systematic review and meta-analysis of epidemiological studies. Neuropsychiatr Dis Treat. 2015;11:1121–30.
49. Liu J, Lu X, Chen L, Huo Y. Expert consensus on the management of hypertension in the young and middle-aged Chinese population. Int J Clin Pract. 2019;73(12):e13426.
50. Gress TW, Nieto FJ, Shahar E, Wofford MR, Brancati FL, S ARC. Hypertension and antihypertensive therapy as risk factors for type 2 diabetes mellitus. New Engl J Med. 2000;342(13):905–12.
51. Hall JJ, Eurich DT, Nagy D, Tjosvold L, Gamble JM. Thiazide diuretic-induced change in fasting plasma glucose: a meta-analysis of randomized clinical trials. J Gen Intern Med. 2020;35(6):1849–60.
52. Ohta Y, Kamide K, Hanada H, Morimoto S, Nakahashi T, Takiuchi S, et al. Genetic factors associated with elevation of uric acid after treatment with thiazide-like diuretic in patients with essential hypertension. Hypertens Res. 2020;43(3):220–6.
53. Takahashi Y, Nishida Y, Nakayama T, Asai S. Adverse effect profile of trichlormethiazide: a retrospective observational study. Cardiovasc Diabetol. 2011;10:45.
54. Carey RM, Moran AE, Whelton PK. Treatment of hypertension: a review. JAMA. 2022;328(18):1849–61.
55. Lin Z, Li HL, Tsoi MF, Cheung BMY. Hypokalaemia associated with hydrochlorothiazide used in the treatment of hypertension in NHANES 1999–2018. J Hum Hypertens. 2023;37(5):354–62.
56. Gonzalez NR, Amin-Hanjani S, Bang OY, Coffey C, Du RS, Fierstra J, et al. Adult moyamoya disease and syndrome: current perspectives and future directions: a scientific statement from the American Heart Association/American Stroke Association. Stroke. 2023;54(10):E465–79.
57. Parati G, Kjeldsen S, Coca A, Cushman WC, Wang J. Adherence to single-pill versus free-equivalent combination therapy in hypertension: a systematic review and meta-analysis. Hypertension. 2021;77(2):692–705.


## Publisher's Note