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Efficacy of Chinese traditional quadruple single pill combination versus valsartan/hydrochlorothiazide for the treatment of hypertension (COSPQ-BP): study protocol for randomised controlled study

Shanshan Jia, Xin Zhang, Xiangyu Yang, Runyu Ye, Yuanyuan Yao, Lu Liu, Xianghao Zuo, Yanan Li, Yu Yan, Kai Liu, Si Wang, Qingtao Meng, Xiaoping Chen

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SJ and XZ contributed equally.

SJ and XZ are joint first authors.

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Department of Cardiology, West China Hospital of Sichuan University, Chengdu, Sichuan, China

Correspondence to
Professor Xiaoping Chen;
xiaopingchen33@163.com

ABSTRACT

Introduction Hypertension constitutes the primary health burden of cardiovascular diseases, and the global control of blood pressure (BP) remains insufficient. Single pill combinations (SPCs) are employed as a means to streamline the management of poor BP control due to non-adherence and treatment inertia. The compound reserpine and triamterene tablets constitute a quadruple SPC, comprising reserpine 0.1 mg, dihydralazine 12.5 mg, hydrochlorothiazide 12.5 mg and triamterene 12.5 mg. It is widely employed in primary medical institutions and has favourable efficacy, tolerability and cost-effectiveness.

Methods and analysis The COSPQ-BP trial is a 12-week prospective randomised controlled trial to enrol 1332 patients with primary mild-to-moderate hypertension. Participants who meet the inclusion criteria will be randomly assigned to a 1:1 ratio to an intervention group (compound reserpine and triamterene tablets) or a control group (valsartan/hydrochlorothiazide). The primary outcome will be mean changes from baseline in 24-hour ambulatory systolic BP after intervention for 12 weeks. The secondary outcomes have been predetermined and will primarily encompass the following: (1) changes in other BP measures, as well as changes in blood lipids, blood glucose and uric acid at 12 weeks and (2) evaluation of the impact of starting antihypertensive therapy with compound reserpine and triamterene tablets or valsartan/hydrochlorothiazide on the depressive and anxiety statess of patients.

Ethics and dissemination The study protocol (version number: V5.0, version date: 17 January 2023) has been approved by the ethics committee (Biomedical Ethics Committee of West China Hospital of Sichuan University, approval number: Review (51) in 2023). Written informed consent will be obtained from each participant by researchers. The findings of this study will be disseminated through conference presentations and peer-reviewed publications.

Trial registration This study was registered at the Chinese Clinical Trials Registry (ChiCTR2300067920). The COSPQ-BP trial is currently enrolling. The study period will be from 1 January 2024 to 31 December 2025.

STRENGTHS AND LIMITATIONS OF THIS STUDY

⇒ This study is a multicentre randomised controlled trial, which enhances the robustness and generalisability of the findings.
⇒ The comparator in the control group is a single pill combination preparation that is recommended by clinical guidelines, thereby ensuring that the study aligns with current best practices in clinical care.
⇒ Ambulatory blood pressure (BP) monitoring is used as the primary method for out-of-office BP measurement, providing a more accurate and comprehensive assessment of BP control.
⇒ One limitation of this study is the lack of long-term cardiovascular outcomes comparison between compound reserpine and triamterene tablets and valsartan/hydrochlorothiazide. This limits the ability to assess the long-term cardiovascular benefits associated with these two antihypertensive drug regimens.

INTRODUCTION

Elevated blood pressure (BP) not only constitutes the primary health burden of cardiovascular diseases on a global scale but also gives rise to devastating consequences.[1] Over the past 30 years, in tandem with the rapid growth and ageing of the global population, the number of adult patients with hypertension aged 30–79 has increased from 650 million to 1.28 billion.[2] According to the Global Burden of Disease Study 2019, elevated systolic BP emerged as the leading risk factor associated with global mortality,

accounting for 10.8 million deaths and 9.3% of disability-adjusted life-years lost.[1] Nevertheless, BP control remains inadequate worldwide, with fewer than 14% of patients taking antihypertensive medication achieving the recommended target (140/90 mm Hg), and even less in low- and middle-income countries. Data from the China hypertension survey conducted from 2004 to 2018 revealed that the control rate of hypertension among the respondents was 12.0%, with an estimated 240 million hypertensive patients having inadequate BP control.[3] A recent meta-analysis encompassing data from 344 716 participants demonstrated that a reduction of 5 mm Hg in systolic BP was associated with a significant decrease in the risk of stroke (13%), ischaemic heart disease (7%), heart failure (14%) and cardiovascular death (5%).[4] Given the health burden entailed by hypertension, the achievement of adequate BP control stands as an effective strategy for the prevention of cardiovascular diseases.

The reasons for inadequate BP control can be attributed to various factors, including suboptimal adherence, therapeutic inertia and insufficient utilisation of combination therapies.[5 6] The proportion of antihypertensive medication nonadherence ranges from 27% to 40%, with a higher rates in low to middle-income countries and non-Western countries.[7] Enhanced adherence to antihypertensive medication not only leads to greater reductions in BP but also yields greater cardiovascular benefits compared to suboptimal adherence.[8–11] This explains why recent guidelines emphasise antihypertensive medication adherence as a major issue in the overall management of hypertension.[12 13] As evidence of cardiovascular benefit from the downregulation of antihypertensive targets accumulates, therapeutic inertia is gradually gaining widespread attention. Therapeutic inertia refers to the failure of healthcare providers to initiate or intensify treatment appropriately when a patient's BP is uncontrolled.[13] A Dutch study assessing therapeutic inertia in primary care showed that among 6400 uncontrolled hypertensive patients on one or two antihypertensive drugs, 87% of them experienced treatment inertia.[14] Augustin *et al* used a Monte Carlo simulation to confirm that the presence of therapeutic inertia during antihypertensive titration hindered the proportion of individuals who achieved long-term BP targets.[15] A current medication status survey conducted among community-dwelling adults aged 35–75 years in China revealed that treatment was irrational among individuals receiving therapy but whose BP remained uncontrolled. The study data showed that the proportion of monotherapy was as high as 81.5%, while the use of combination therapy was relatively low.[16]

To address these persistent problems, a growing number of guidelines[13 17–20] have proposed the use of single pill combinations (SPCs), also known as fixed-dose combinations (single drugs containing two or more active ingredients). SPCs are employed as a means to streamline the management of poor BP control due to non-adherence and treatment inertia. Furthermore, certain guidelines even endorse the utilisation of SPCs as a comprehensive approach in the initial treatment of hypertension. The synergistic and complementary antihypertensive mechanisms between different active ingredients enable SPCs to counteract adverse reactions and improve antihypertensive efficacy.[21] From a pharmacoeconomics perspective, SPCs are more cost-effective and seem to be a feasible solution.[22–24] Recently, there has been an increase in studies that have used low-dose combination therapy as an initial antihypertensive strategy, which involves multiple antihypertensive drugs at doses below the usual standard dose. The QUARTET trial from Australia demonstrated that ultra-low dose quadruple antihypertensive agents achieved better BP control without increasing the risk of adverse events compared with irbesartan monotherapy.[25] Moreover, significant differences in BP reduction and control rates were still observed at 52 weeks. Similarly, the recent QUARTET USA trial, conducted among the American population, has yielded similar findings. Compared with standard dose monotherapy (candesartan 8 mg), ultra-low dose quadruple antihypertensive agents showed more effective antihypertensive effects.[26] A randomised controlled trial (RCT), encompassing 300 hypertensive black African patients with uncontrolled BP, evaluated the antihypertensive efficacy of a novel low-dose triple-pill, GMRx2, including telmisartan, amlodipine and indapamide, against guideline-based standard care regimen.[27] After 6 months of follow-up, the home systolic BP (the primary effectiveness outcome) demonstrated a significantly greater reduction in the triple-pill group than in the standard care group, with a between-group difference of 5.8 mm Hg.[27] Another RCT conducted in seven countries likewise demonstrated that the antihypertensive effect and control rate of GMRx2 were significantly superior to those of dual combinations.[28] According to a secondary analysis of the TRIUMPH trial, low-dose triple therapy can significantly increase the time at the BP target, indicating BP control is more stable.[29] Moreover, a meta of 1918 patients confirmed that low-dose triple or quadruple combination therapy proved to be effective and well-tolerated as an initial treatment strategy.[30] Another meta-analysis involving 44 studies has confirmed that SPCs enhance patient adherence and persistence compared with free-equivalent combination therapy, ultimately leading to better BP control.[31] Schmieder *et al* further demonstrated that SPC reduces all-cause mortality and cardiovascular events, a result that strongly supports its application in clinical practice to improve long-term prognosis.[32]

Compound reserpine and triamterene tablets, a quadruple SPC consisting of reserpine 0.1 mg, dihydralazine 12.5 mg, hydrochlorothiazide 12.5 mg and triamterene 12.5 mg, were independently developed in China during the 1980s.[33] In addition, these four components exhibit enhanced synergy, with each medication mitigating each other's adverse effects.[34] Triamterene can alleviate hypokalaemia caused by hydrochlorothiazide, and diuretics can counteract water and sodium retention caused by reserpine and vasodilators. The excretion of

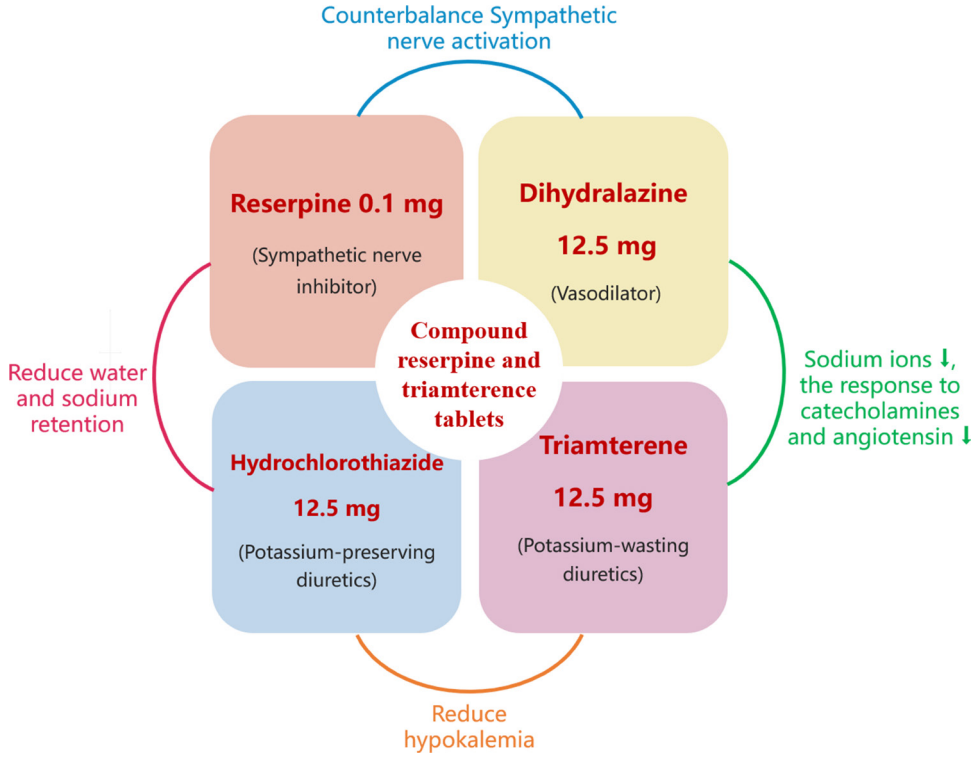

Figure 1 Synergistic mechanism between the four components.

sodium ions can reduce the concentration of sodium ions in the blood vessel wall, and the response of blood vessels to catecholamines and angiotensin is diminished, which leads to a decrease in vascular dilation and peripheral vascular resistance. Reserpine can counteract sympathetic excitation and increased heart rate caused by vasodilators and diuretics (figure 1). A meta-analysis encompassing seven RCTs confirmed that the overall effective rate (OR=2.23, 95% CI: 1.32 ~ 3.75) of compound reserpine and triamterene tablets was superior to that of other antihypertensive medications.[35] Moreover, an animal experiment demonstrated that continuous 4-week treatment with compound reserpine and triamterene tablets significantly enhanced the richness and diversity of the gut microbiota in spontaneously hypertensive rats.[36] It fostered the proliferation of beneficial bacteria such as Trichospira, Prevotaceae, Muribaculaceae and Blautia while suppressing the growth of harmful bacteria such as Clostridium.[36] A tremendous amount of data from the real world indicates that this quadruple SPC is widely used in primary medical institutions in China, with favourable efficacy, tolerability and cost-effectiveness.[33] However, due to historical reasons, previous studies conducted in the 1990s lacked accurate out-of-office BP measurements. Moreover, RCTs with dual combination therapy as a control have yet to be performed. There is a deficiency of clinical evidence regarding whether this quadruple SPC can serve as an initial antihypertensive strategy for hypertensive patients. In consideration of compound reserpine and triamterene tablets' sympathetic inhibition and diuretic effects, we selected valsartan/hydrochlorothiazide as the control group, which is recommended for initial treatment by multiple guidelines. This study will use parallel, randomised, open-label and non-inferiority involving 18 multiple tertiary medical institutions in Sichuan province, China, to evaluate the impact of quadruple combination therapy compared with dual combination therapy as initial antihypertensive regiments on BP reduction, and provide relevant clinical evidence for the preferred initial antihypertensive regiments for hypertensive patients.

METHODS

The methods described are reported in accordance with the list of recommended entries in the clinical trial protocol in the Standard Protocol Items: Recommendations for Interventional Trials statement.[37]

Study design and setting

This is a parallel, randomised, open-label and non-inferiority RCT, conducted at multiple tertiary medical institutions in China.

Eligibility criteria

All patients aged 18–75 years with mild-to-moderate essential hypertension will be screened to assess their eligibility for participation in this study. Participants meeting any of the following inclusion criteria will be recruited in this project. (1) Patients with essential hypertension, aged 18–75 years old, regardless of gender; (2) untreated patients or those who have stopped taking antihypertensive drugs for 2 weeks are eligible for the study if they meet any of the following criteria: (a) Office

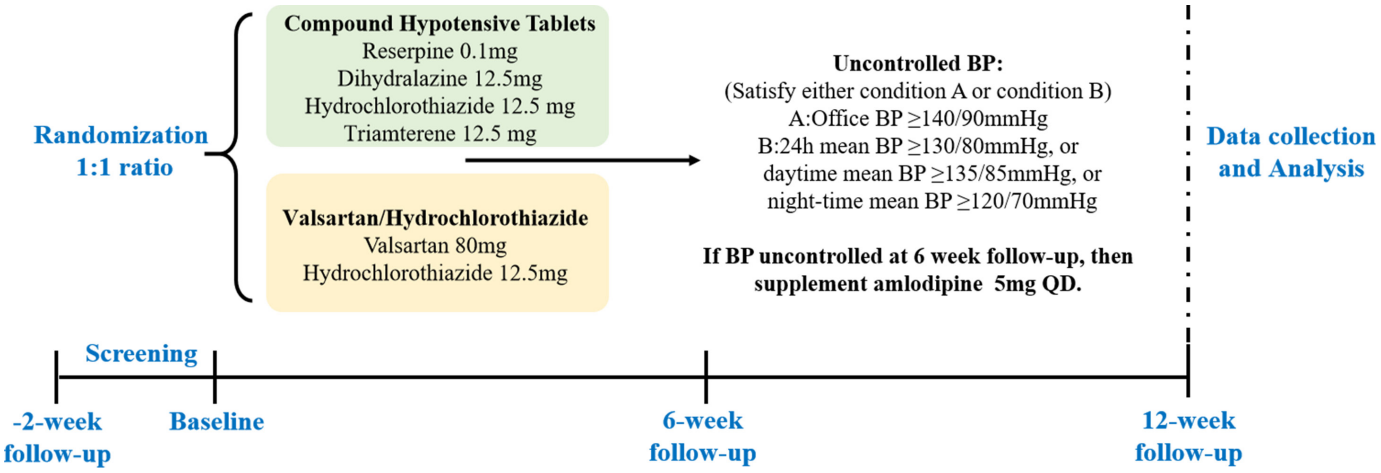

Figure 2 Follow-up time point. BP, blood pressure; QD, once daily.

BP: systolic BP 140–179 mm Hg and/or diastolic BP 90–109 mm Hg; (b) 24 hours ambulatory BP monitoring: 24 hours mean BP≥130/80 mm Hg, and/or daytime mean BP≥135/85 mm Hg and/or night-time mean BP≥120/70 mm Hg. The main exclusion criteria encompass (1) women planning a pregnancy or pregnant and breastfeeding; (2) double renal artery stenosis; (3) hyperkalaemia (serum potassium>5.5 mmol/L) and chronic renal insufficiency (creatinine>265 umol/L or estimated glomerular filtration rate<30 mL/(min·1.73m2)); (4) malignant hypertension, hypertensive emergency, hypertensive crisis and hypertensive encephalopathy; (5) history of allergy to the investigational drug or its ingredients; (6) history of alcoholism or drug addiction; (7) previous or current diagnosis of heart failure; (8) cardiovascular diseases and certain related diseases, such as unstable angina, life-threatening arrhythmias, atrial fibrillation and grade III–IV retinopathy; (9) history of depression or other mental illness; (10) active digestive tract ulcer and ulcerative colitis; and (11) inability to tolerate ambulatory BP measurement and other circumstances that preclude participation in clinical studies.

Outcomes

The primary outcome will be mean changes from baseline in 24 hours ambulatory systolic BP after intervention for 12 weeks. The secondary outcomes have been predetermined and will primarily encompass the following: (1) changes in other BP measures, as well as changes in blood lipids, blood glucose and uric acid at 12 weeks and (2) evaluation of the impact of starting antihypertensive therapy with compound reserpine and triamterene tablets or valsartan/hydrochlorothiazide on the depressive and anxiety state of patients. Safety will be evaluated based on the proportion of participants experiencing adverse events.

Safety monitoring and adverse events assessment

The pharmaceuticals employed in this RCT are drugs already on the market, substantiated as both secure and efficacious, with few adverse effects. Adverse events include falls, fall-related trauma, syncope, arrhythmia, hypotension, electrolyte disturbances, digestive reactions, drowsiness, insomnia and depressive episodes. In this study, researchers should closely observe or follow-up on the various reactions of subjects after medication, to identify adverse events or serious adverse events promptly and provide timely intervention. When adverse events occur, researchers should actively take appropriate medical measures to ensure participants' safety. Researchers should track and investigate all adverse events and record in detail the handling process and results until the adverse events are properly resolved or the subject's condition stabilises. Once the subject has an adverse event, regardless of whether it is causally related to the investigational drugs, all details will be recorded and signed in the case report form. Serious adverse events were defined as events that occurred in the course of clinical research that required hospitalisation, prolonged hospitalisation, disability, affected work ability, life threatening or death. In the event of a serious adverse event, the investigator should immediately provide the necessary emergency medical intervention, including hospitalisation, surgery and medication, to ensure the safety and health of the subject. Moreover, the researcher is obligated to furnish a report to the local ethical committee within a 24 hours timeframe following the incident.

Recruitment, randomised strategy and blinding procedures

Participants will be recruited by trained physicians from each participating hospital. Before randomisation, researchers will engage in comprehensive face-to-face discussions with potential participants, during which they will thoroughly explain the allocation process, expected benefits, and potential risks of the study to all potential participants. This process ensures that participants understand every aspect of the research, such as potential side effects, data confidentiality measures and policies for protecting personal privacy. After confirming that potential participants fully understand and voluntarily agree to participate in the study, a formal written informed consent

form (online supplemental material 1) will be signed, with a copy provided to the participant. Throughout the study, the project team will maintain regular communication with the participants to address any new questions they may have. Regardless of the reason, participants have the right to refuse participation or withdraw freely at any stage during the study.

The study aims to recruit 1332 patients from 18 hospitals in Sichuan province, China. It will be stratified by 18 subcentres and then randomly assigned within each unit. A total of 18 sets will be generated, with each set representing a distinct research unit. To ensure random assignment, a researcher from the main centre will employ the RESEARCH RANDOMIZER tool (accessible at www.randomizer.org) to generate distinct sets of random numbers ranging from 1 to 74. Based on the random numbers generated, participants within each unit will be assigned to either the compound reserpine and triamterene tablets or valsartan/hydrochlorothiazide group in a 1:1 ratio.

Considering the large sample size, and to ensure practical feasibility and enhance patient compliance, this study adopted an open-label design. The grouping will not be concealed from patients or researchers. Although the study employs an open-label design, the assessors of the primary outcome will be blinded to ensure objectivity and scientific results.

Intervention and follow-up

The trial flow diagram is presented in figure 2. The COSPQ-BP trial is a 12-week prospective RCT designed to enrol 1332 patients with primary mild-to-moderate hypertension. Participants who are eligible the inclusion criteria will be randomly assigned to a 1:1 ratio to an intervention group (compound reserpine and triamterene tablets: reserpine 0.1 mg, dihydralazine 12.5 mg, hydrochlorothiazide 12.5 mg and triamterene 12.5 mg) or a control group (valsartan 80 mg, hydrochlorothiazide 12.5 mg). Throughout the treatment period, in addition to baseline assessments, clinical and laboratory examinations will be conducted at 6 and 12 weeks following the initiation of treatment.

During the initial follow-up, researchers will collect participants' demographic data and medical history. Each participant will undergo a comprehensive physical examination, encompassing measurements of height, weight, waist circumference, heart rate, respiratory rate and office BP. Before collecting the specimens, each participant will undergo a 12 hours night fast and then provided a 10 mL fasting blood and urine sample. In addition to the aforementioned examinations, proficient researchers will conduct interviews with participants to assess medication adherence as defined by pill counts and record any adverse events encountered. To quantitatively evaluate levels of anxiety and depression before and after treatment, participants will, under the supervision of researchers, complete the Generalised Anxiety Disorder 7-Item Scale (GAD-7) and the Patient Health Questionnaire-9 (PHQ-9). All experts conducting the measurements will remain unaware of the group assignments to ensure the accuracy of the study results and minimise measurement bias. Table 1 displays the specific visit time and arrangement details.

Table 1 Study timeline and procedures

Study timeline	Baseline	6-week follow-up visit	12-week follow-up visit
Informed consent	×		
Demographics*	×		
Medical history	×		
Concomitant medications	×	×	×
Physical examination*	×	×	×
Office blood pressure measurement	×	×	×
24 hours ambulatory blood pressure monitor	×	×	×
Laboratory examination*	×		×
PHQ-9 scores*	×		×
GAD-7 scores*	×		×
Compliance with medication*		×	×
Adverse event record	×	×	×

Demographics: such as date of birth, sex, and ethnicity; **Physical examination:** including height, weight, waist circumference, breath rate, heart rate; **Laboratory examination:** including blood routine, AST, ALT, total bilirubin, direct bilirubin, indirect bilirubin, serum creatinine, triglyceride, total cholesterol, low density lipoprotein, high density lipoprotein, glucose, uric acid, sodium, potassium, chlorine, urinary albumin creatinine ratio;
Compliance with medication will be assessed by comparing the number of pills patients have left with the number of pills they have taken
GAD-7, Generalized Anxiety Disorder 7-Item Scale; PHQ-9, Patient Health Questionnaire-9.

In the second visit, the BP control of patients will be assessed using both ambulatory BP and office BP measurements. The criteria for BP control are defined as follows: the office BP<140/90 mm Hg, the 24 hours mean BP<130/80 mm Hg, the daytime mean BP<135/85 mm Hg and the night-time mean BP<120/70 mm Hg. If BP remains uncontrolled during the 6-week follow-up assessment, the researchers will supplement amlodipine 5 mg once daily as an adjunctive therapy for participants, aiming to achieve BP control. The remaining antihypertensive treatment regimen remains unchanged and the follow-up will continue until 12 weeks. In addition, during the research process, if any modifications to the

clinical study protocol, informed consent form or other documents are required, the researcher must submit an application to the ethics committee. All modifications can only be implemented after they have been formally reviewed and approved by the ethics committee.

Measurement of outcomes

Standard office blood pressure measurement

To ensure the accuracy and reliability of measurements, this study will employ standardised methods for measuring clinic BP.[31] We will use upper arm electronic BP monitors that conform to international standards and have been calibrated (HBP-9020, Omron, Kyoto, Japan). The measurements will be conducted in a quiet room with a suitable temperature. Before BP is measured, participants will be required to avoid smoking, drinking coffee, eating or exercising for 30 min. Additionally, participants will be asked to empty their bladder and maintain a seated position in a relaxed state for 5 min. During the measurement, participants will be seated in a chair with their back against the backrest, legs uncrossed and both feet flat on the floor. The participant's bare arm should be placed on the table, with the middle of the upper arm aligned with the level of the heart. Researchers will instruct participants to remain mentally relaxed, and avoid exertion, talking or moving any part of their body during the measurement process. Three separate measurements will be taken, with a 1-min interval between each measurement. The average of the last two readings will be calculated as the final BP measurement. It is important to note that during the initial measurement of office BP, both arms should be measured simultaneously, and the arm with the higher BP reading will be selected as the arm used for subsequent measurements.

Ambulatory blood pressure measurement

The project team will be using certified measuring equipment (TM2430, A&D, Tokyo, Japan) for 24 hours ambulatory BP monitoring. Prior to starting the monitoring, it is important to assess the arm circumference to determine the appropriate cuff size for the sphygmomanometer. Additionally, office BP should be measured in both upper arms before attaching the monitoring device. If there is a 10 mm Hg or greater difference between the two upper arms, the arm with the higher BP should be selected for monitoring. When the difference is less than 10 mm Hg, the non-dominant arm should be chosen. Once the monitoring device is attached, BP should be manually measured twice to ensure the sphygmomanometer is functioning properly. After the monitoring, it is recommended to confirm the normal functioning of the sphygmomanometer by manually measuring BP twice. During the daytime hours (06:00 to 22:00), BP should be measured every 20 min, and during the night-time hours (22:00 to 06:00), BP should be measured every 30 min. Patients should be informed about necessary precautions and complete a diary during the ambulatory BP monitoring period. The diary should include details such as medication usage, wake-up time, sleep time and activity. By analysing the raw data from the telemedicine platform, researchers will be able to obtain the 24 hours mean BP, daytime mean BP and night-time mean BP.

Sample size calculation

The primary observation indicator of this study is the changes in 24 hours ambulatory systolic BP from baseline after a 12-week intervention period. In this study, a non-inferiority trial design was adopted. After referring to previous research findings and consulting with statistics professionals, a threshold of 2 mm Hg was set, with a SD of 12 mm Hg. Using PASS V.15.0 software, sample size calculation was performed with a set effective mean difference of 0 for two groups, one-sided significance level α=0.025 and a power of 80%. In addition, taking into account the effect of a 15% dropout rate, a sample size of 666 participants per group was calculated, resulting in a total sample size of 1332 participants.

Statistical analysis

Descriptive statistics will be used to analyse baseline data. For continuous variables with normal distributions, the mean±SD will represent the data, while for those with non-normal distributions, the median and IQR will be used. Categorical variables will be presented as frequencies and percentages. Quantitative variables will undergo t-tests or rank-sum tests, while qualitative variables will undergo χ^2 tests or Fisher's exact tests. The primary outcome of this study, which includes changes from baseline in the mean 24 hours ambulatory systolic BP after treatment, will be analysed using analysis of covariance. The same method shall apply to analysing secondary outcomes. Data analysis will be conducted on both an intention-to-treat (ITT) and per-protocol (PP) analysis. ITT analysis refers to the follow-up, assessment and analysis of all patients initially randomised, reflecting the antihypertensive efficacy in the trial and control groups. PP analysis refers to all participants who adhered to the study protocol and completed the study. PP analysis excludes subjects who did not complete treatment as planned or whose data were missing during the trial. For subjects with missing data, we will handle it through multiple imputations. Statistical analyses will be performed using R software (V. 4.2.1).

Data management

To ensure the rigour and data quality of the study, the research team comprises healthcare professionals such as doctors, nurses and clinical research coordinators who have undergone specialised training. They will be responsible for maintaining medical records and collecting relevant data in accordance with a detailed study protocol, which will be used for subsequent analysis. Researchers will strictly adhere to the study protocol, conducting meticulous checks, collection, recording and preservation of data on schedule to minimise data missing. All raw data

collected from the study medical records will be fed into an electronic data acquisition system, the Red Shine Chronic Disease Management System,[38] developed by the Hypertension Center of West China Hospital of Sichuan University. The system will store all research-related information securely, while information involving individual study participants is kept in restricted access areas and in locked filing cabinets, where only the research team can access the data, ensuring security and privacy. During data analysis and reporting, ensure that all personally identifiable information is thoroughly anonymised to avoid any form of identification risk. In order to ensure the accuracy and comprehensiveness of the collected data, the researchers from the main centre will provide training courses to the researchers at the subcentres prior to the study's commencement. These training sessions will cover the research protocol and its related procedures. To monitor and maintain data quality, independent project experts will be assigned to oversee data evaluation, verification and cleansing on a monthly basis. During the inspection visit, project experts will compare the data submitted by the subcentres with the original data. The research data that require verification include demographics, medication adherence, protocol adherence, primary and secondary outcomes, adverse events, serious adverse events and laboratory data. Following the completion of data cleansing, the data manager and statisticians will conduct a final review to address any unresolved data issues. They will collaborate to allocate the data set according to the predetermined statistical analysis plan. Concurrently, they will review and process the records of serious adverse events, while adhering to reporting guidelines. In addition, the project team will provide regular ethics training for researchers to ensure that they understand and adhere to ethical guidelines. During the research process, the project team will designate personnel responsible for monitoring ethical issues, timely detection and resolution of potential ethical disputes, thereby safeguarding the ethical standards of the research and the rights and interests of participants. The ultimate decision to terminate the trial is rendered by the research team, statisticians and the ethics committee. These entities will assess the necessity of suspending the trial based on the findings of the interim analysis and the overall progress of the study.

DISCUSSION

The purpose of the COSPQ-BP trial was to evaluate the safety and efficacy of ultra-low dose quadruple therapy and dual combination therapy as initial treatment options for patients with hypertension to provide clinical evidence. The study was designed to explore whether compound reserpine and triamterene tablets could be used as an initial antihypertensive strategy in patients with hypertension without increasing the risk of adverse effects. Simultaneously, the results of this study can also provide scientific evidence for the clinically rational use of compound reserpine and triamterene tablets. However, several limitations exist within our study. First, the study employs an open-label design, where both doctors and patients are aware of their treatment groups. While this design ensures the feasibility of large-scale study implementation, it may still introduce biases. To mitigate this impact, we blinded the assessors of the primary outcome. Second, the study employs a non-inferiority design, which cannot confirm the efficacy of compound reserpine and triamterene tablets is superior to that of valsartan/hydrochlorothiazide. Although this design is practical in situations with limited budgets, it restricts our ability to comprehensively assess the drug's efficacy. Third, patients in the trial were only followed up for 3 months, thus limiting the capacity to evaluate their impact on long-term cardiovascular outcomes. Fourth, the study was conducted only in China, to some extent limiting the generalisability and extrapolability of the results.

Contributors All authors read and approved the final manuscript. SSJ and XZ were responsible for the conception of the study. SSJ and XZ contributed to the writing, design, revision, methodology and software of this manuscript. XYY, RYY, YYY, LL, XHZ, YNL, YY, KL, SW and QTM contributed to the design of the study. XPC serves as responsible for the overall content as guarantor.

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Competing interests None declared.

Patient and public involvement Patients and/or the public were not involved in the design, or conduct, or reporting, or dissemination plans of this research.

Patient consent for publication Consent obtained directly from patient(s).

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ORCID iDs
Xianghao Zuo http://orcid.org/0009-0009-1594-5473
Si Wang http://orcid.org/0000-0002-4456-6706
Xiaoping Chen http://orcid.org/0009-0002-6652-4328

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