Trials

STUDY PROTOCOL

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Design and rationale for a randomized, open-label, parallel clinical trial evaluating major adverse cardiovascular events (pharmacological treatment versus diet control) in patients with high-normal blood pressure: the PRINT-TAHA9 trial

Armin Attar[1*], Seyed Alireza Mirhosseini[1,2,3], Roham Borazjani[4], Mehrab Sayadi[5], Mahsa Ahadi[6], MohammadJavad Zibaeenezhad[3], Iman Razeghian-Jahromi[3] and Nader Parsa[3]

Abstract

Background The distinction between normal and high blood pressure remains a debated topic, with varying guidelines on when to start medication. Contemporary guidelines advocate for the initiation of antihypertensive therapy in individuals who present with high-normal blood pressure, particularly those exhibiting elevated 10-year atherosclerotic cardiovascular disease (ASCVD) risk scores. Despite these recommendations, there is a notable lack of direct evidence supporting the efficacy of treating high-normal blood pressure to prevent major adverse cardiovascular events (MACE).

Methods The PRINT-TAHA9 trial, a unicentric, randomized, open-label, controlled, parallel clinical study, seeks to explore the effects of intensive blood pressure control on MACE in participants with high-normal blood pressure. We will enroll 1620 adults aged 18 years and above with a systolic blood pressure range of 130–140 mmHg, diastolic blood pressure under 90 mmHg, and atherosclerotic cardiovascular disease (ASCVD) risk score exceeding 7.5%. The study will be executed in five distinct phases, with each phase enrolling between 300 and 400 participants. Participants will be randomly assigned to either the treatment group receiving antihypertensive medication (amlodipine/valsartan) and a low-salt/low-fat diet or to the control group receiving a similar diet. Follow-up visits are scheduled every 6 months over a 3-year period to monitor blood pressure, evaluate medication adherence, document any adverse events, and adjust the intervention as necessary. Cox proportional hazards regression analysis will be employed to examine the disparities between the two arms.

Discussion Despite guidelines promoting early treatment of elevated blood pressure, the debate continues due to insufficient evidence that such interventions significantly reduce the occurrence of MACE. This trial seeks to address this critical evidence gap.

*Correspondence:
Armin Attar
attar_armin@yahoo.com; attarar@sums.ac.ir
Full list of author information is available at the end of the article

Trial registration The PRINT-TAHA9 trial was registered in October 2019 with the Iranian Registry of Clinical Trials (IRCT.ir) under the registration number IRCT20191002044961N1. https://irct.behdasht.gov.ir/trial/43092.

Keywords Prehypertension, High-normal blood pressure, Cardiovascular outcome, Adverse events, Major adverse cardiovascular events, Intensive blood pressure control

Introduction

Background and rationale

Exploring the exact border between normotension and hypertension shows that their actual cutoff values and definitions have always been a subject of dispute. In 2017, the AHA identified hypertension as having a systolic blood pressure (SBP) ≥ 130 mmHg or a diastolic blood pressure (DBP) ≥ 80 mmHg [1]. A year later, the European Society of Cardiology (ESC) and the European Society of Hypertension (ESH) raised the hypertension threshold by 10 mmHg compared to the prior year's standard [2]. Notably, any blood pressure between the optimal and the hypertensive values was interpreted as "high-normal blood pressure" and "elevated blood pressure" by the ESC/ESH and AHA, respectively. In 2023, the ESC/ESH guidelines recommended antihypertensive drug initiation for patients with high-normal blood pressure and previous cerebrovascular disease (CVD), especially coronary artery disease (CAD) [3]. Nevertheless, according to the ACC/AHA, patients with SBP between 130 and 140 mmHg should receive pharmacological intervention if their 10-year atherosclerotic cardiovascular risk (ASCVD) is above 10% [1]. Although this recommendation is supported by some secondary analyses of large clinical trials [4, 5], there is a lack of direct evidence evaluating this recommendation, and consequently, this decision has been criticized by some experts [6]. Despite these criticisms, some other investigators claim that there are sufficient data to support this recommendation [7].

There is solid evidence available on the association between elevated blood pressure, other cardiovascular risk factors, and hypertension progression. However, the direct effect of high-normal blood pressure on long-term major adverse cardiovascular events (MACE), such as any type of acute coronary syndromes (ACS) or heart failure, and whether to treat it remain unclear [8–10]. Russel et al. reported that prehypertension (high-normal blood pressure) is associated with approximately 3.4% of hospitalizations and 9.1% of cardiovascular-related deaths while increasing the risk of end-stage renal disease (ESRD) development [11]. Moreover, prehypertension associated with other predisposing conditions, such as obesity, smoking, and diabetes, is believed to be a major risk factor for cardiovascular events [12].

Notably, the exact relationship between prehypertension and MACE has not been thoroughly evaluated. However, Qureshi et al. reported a clear association between prehypertension and ACS [13]. Additionally, a recently published cohort study in China reported a greater risk for MACE and stroke incidence, suggesting early identification of high-risk individuals [14].

Considering the importance of prehypertension on cardiovascular outcomes and the controversies in this field, we designed a study on the **PR**evention of MACE involving **INT**ensive blood pressure reduction in patients with high-normal blood pressure at the **T**raditional and **A**dvanced **H**eart **A**pproaches Clinical Center, trial **9** (PRINT-TAHA9 trial). This trial aims to evaluate the hypothesis that pharmacologically reducing blood pressure in patients with SBP between 130 and 140 mmHg would reduce MACE. This hypothesis is based on our previous study, a post hoc analysis of the Systolic Blood Pressure Intervention Trial (SPRINT), which revealed that prehypertensive patients might benefit from antihypertensive treatment, which cannot be confidently recommended because it was not exclusively designed and randomized for this specific population [5]. Furthermore, based on our other analysis, we chose to enroll patients with an ASCVD risk above 7.5% instead of 10% [15].

Objective

This trial focused on assessing the effects of intensive blood pressure control in subjects with high-normal blood pressure and ASCVD risk score of 7.5% or higher.

Methods

Study design and setting

This investigation is a unicentric, randomized, superiority, open-label, controlled, parallel clinical trial. MACE will be compared between two groups with high-normal blood pressure, defined as office SBP of 130–140 mmHg and DBP less than 90 mmHg, measured at the Imam Reza Cardiovascular Clinic in Shiraz, Iran. This protocol was conceived in accordance with the guidelines from the Standard Protocol Items: Recommendations for Interventional Trials (SPIRIT).

Study participants and eligibility criteria

The study will enroll adults aged 18 years and older without diabetes or any underlying cardiovascular conditions who had baseline SBP of 130–140 mmHg

	STUDY PERIOD (month)									
	Enrolment	Allocation	Post-allocation							Close-out
TIMEPOINT	-1	0	1	3	6	12	18	24	30	36
ENROLMENT:										
Eligibility screen*	X									
Informed consent	X									
Allocation (randomization)		X								
INTERVENTIONS**:										
[Intervention (pharmacotherapy + diet)]		←	—	—	—	—	—	—	—	→
[control (Diet)]		←	—	—	—	—	—	—	—	→
Intervention adjustment (if needed)			X	X	X	X	X	X	X	X
ASSESSMENTS:										
Medical history, Baseline variables	X									
Blood and urine sample	X									
SBP and DBP measurement	X	X	X	X	X	X	X	X	X	X
Adherence check			X	X	X	X	X	X	X	X
assessment of adverse events			X	X	X	X	X	X	X	X

Fig. 1 SPIRIT schedule of study timeline; PRINT-TAHA9 trial. *Eligibility criteria: Adults aged 18 + with no diabetes or undisclosed cardiovascular conditions, baseline SBP of 130–140 mmHg, DBP < 90 mmHg, and a 10-year ASCVD risk ≥ 7.5%. Exclusions: History of DM, CVA, HF, IHD, or prior use of statins, antiplatelets, and antihypertensives for other conditions. **The treatment group receives amlodipine/valsartan (5/80 mg daily, Valzomix®, Abidi Pharmaceutical Company) and follows a low-salt, low-fat diet for 36 months to maintain SBP below 130/80 mmHg. The control group adheres to a similar diet but receives antihypertensive medication only if SBP exceeds 140/90 mmHg, following the same protocol

and DBP under 90 mmHg, as well as a 10-year ASCVD risk of 7.5% or greater (Fig. 1). The exclusion criteria included a history of diabetes mellitus (DM), cerebrovascular accident (CVA), heart failure (HF), ischemic heart disease (IHD), or prior use of statins, antiplatelet agents, or antihypertensive agents for other conditions.

Intervention

In addition to obtaining blood and urine specimens for initial biochemical and hematological analyses, skilled nurses will collect medical histories and baseline data. Blood samples will be analyzed at the local health service laboratory following standard procedures [16]. Following the initial screening, candidates who are deemed potentially eligible will undergo further evaluation to identify possible secondary hypertension.

Blood samples will be collected for complete blood count (CBC), thyroid function test (TFT), blood urea nitrogen (BUN), and creatinine (Cr) analyses, along with measurements of serum sodium (Na), potassium (K), calcium (Ca), and phosphorus (Ph) levels. Subsequently, patients will be allocated to the treatment and control groups through permuted block randomization. The intervention group will be administered an antihypertensive regimen (amlodipine/valsartan at an initial dose of 5/80 mg; Valzomix®, Abidi Pharmaceutical Company, Tehran, Iran) taken daily for 36 months, along with a low-salt, low-fat diet aimed at maintaining SBP below 130/80 mmHg. Conversely, the control group will follow a similar diet but will receive antihypertensive medication only if their SBP exceeds 140/90 mmHg, following the same medication protocol. Uncontrolled blood pressure (defined as blood pressure greater than 130/80 mmHg in the intervention group and 140/90 mmHg in the control group) in any of the further visits will be managed by gradual increases in the antihypertensive medication dosage (such as amlodipine/valsartan 5/160 mg, 10/160 mg, and finally adding indapamide 1.5 mg (step-up approach)). If the SBP drops below 100 mmHg at one visit or below 110 mmHg at two consecutive visits, the dosage decreases (through a step-down approach), as shown in Fig. 2.

Adherence

Individuals will be provided with a comprehensive set of information about the importance and necessity of routine drug consumption and attending scheduled visits while providing informed consent. At each visit, patients will receive a complete set of checkups, and their compliance will be assessed via returned tablet counts.

Concomitant care

Participants will undergo follow-up visits at 1, 3, 6, 12, 18, 24, 30, and 36 months. At each visit, SBP and DBP will be measured following a standardized protocol. Although participants with prior use of statins or other specified drugs are excluded, medications will be prescribed based on current guidelines if prevention or treatment of other conditions necessitates it.

Outcomes

The primary endpoints of this study are the incidence of MACE, which include cardiac death, ACS, CVA, and hospitalization due to cardiovascular causes such as heart failure, arrhythmia, angina pectoris, or percutaneous coronary intervention (PCI). The measure for these outcomes will be clinical diagnosis confirmed by medical records, and the method of aggregation will be the count and proportion of events in each group. The metric used will be the difference in incidence rates between the treatment and control groups over the study period, with comparisons made at each follow-up visit up to 36 months. An independent expert will assess all measurements to ensure their accuracy. In the case of poor recordings, the expert will determine whether the measurement is of adequate quality for endpoint assessment. Measurements of inadequate quality will not be used in the analysis and will be treated as missing data. Emerging MACE will be evaluated by an independent safety committee. The secondary endpoints of the study are SBP and DBP, measured at each follow-up visit. The method of aggregation for SBP and DBP will be the mean values at each time point, and the metric will be the change from baseline in blood pressure readings. Comparisons will be made between the treatment and control groups at each follow-up visit up to 36 months.

Participant timeline

As shown in Figs. 1 and 2, participants will follow a comprehensive timeline from enrollment through various follow-up stages to evaluate the effect of intensive blood pressure management in individuals with high-normal blood pressure. Initially, potential participants will be screened for eligibility and, upon meeting the criteria, will be enrolled and randomized to receive either the intervention or control treatment. Baseline assessments included medical history, baseline variables, and blood and urine samples for biochemistry and hematologic tests. Follow-up visits at 1, 3, 6, 12, 18, 24, 30, and 36 months post-enrollment involve monitoring SBP and DBP, checking medication adherence through returned tablet counts, and recording any adverse events. The intervention may be adjusted based on blood pressure control at these visits. This study aimed to assess the primary outcome of MACE with a comprehensive approach to participant management and data collection.

Sample size

This study is a superior clinical trial that aimed to detect a difference between the anticipated 3% incidence of MACE in the intervention group and the 6% incidence in the control group based on our previous study [4]. Given a predetermined significance level (alpha) of 5% coupled with a desired study power of 80% (1 − beta) and considering an acceptable clinical difference margin set at 50% of the projected difference, adjustments were made to account for an estimated dropout rate of 10%. By utilizing Formula 1 [17] for these calculations, it is determined that each arm of the study requires an estimated sample size of approximately 730 participants to achieve the outlined objectives. A total of 1620 participants accounted

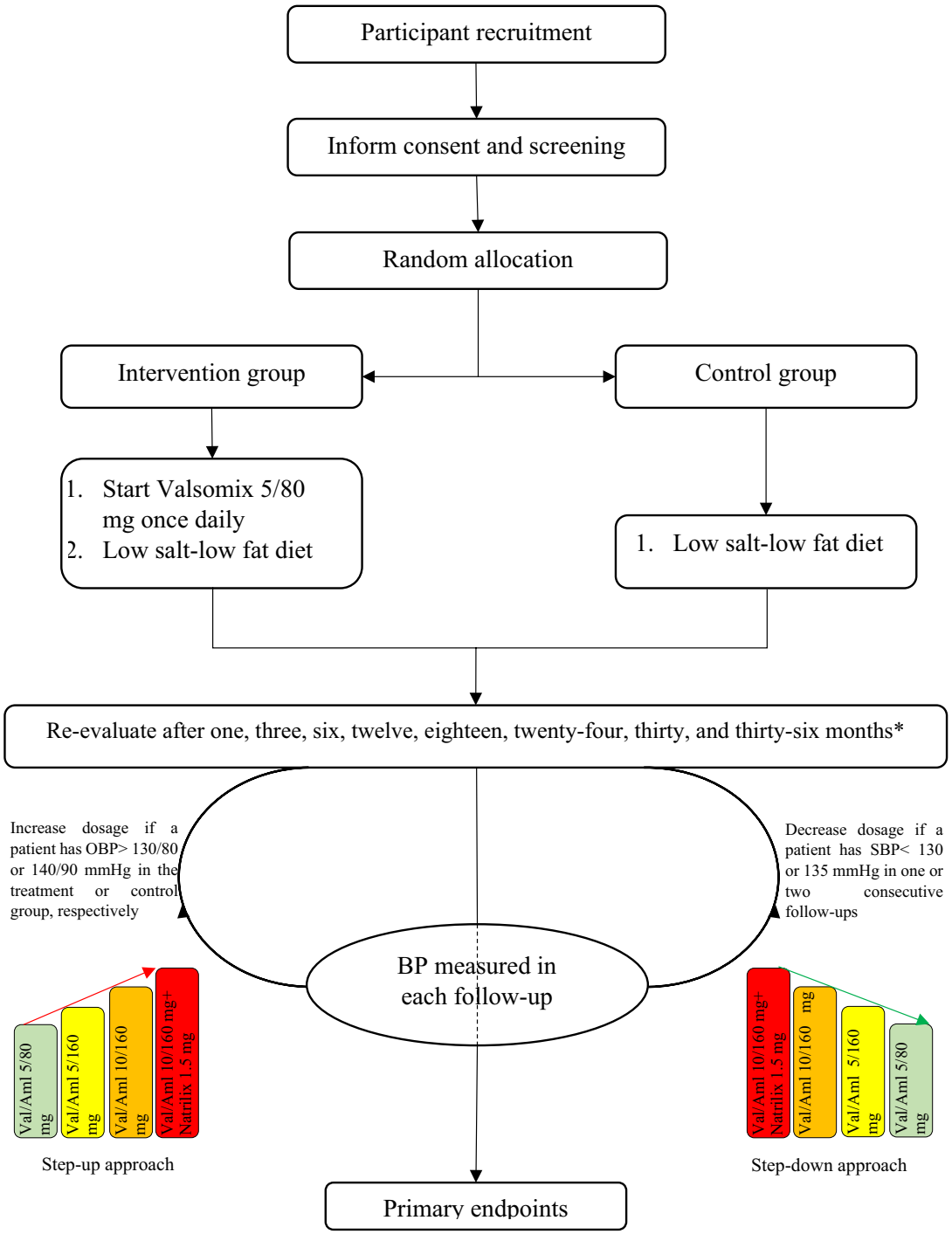

Fig. 2 SPIRIT flowchart of the study. OBP, office blood pressure; SBP, systolic blood pressure; Val/Aml, valsartan-amlodipine as a single-pill combination. *During each of the follow-up visits, if the blood pressure in the control group exceeds 140/90 mmHg, we will start the antihypertensive medications

for potential dropouts and nonadherence at a conservative rate, ensuring comprehensive data collection and analysis. Recruiting the entire sample size at once may be challenging; therefore, we decided to conduct the study in five phases. We began with the recruitment of 300 patients in phase 1 and, based on the decisions of the SC and DSMB, will proceed to complete the remaining phases.

$$N = 2 \times \left(\frac{z_{1-\alpha} + z_{1-\beta}}{d - \delta_0} \right)^2 \times p \times (1 - p) \quad (1)$$

N = size per group; p = the response rate of the control group; p_0 = the response rate of the treatment group; z_x = the standard normal deviate for a one-sided x; d = the real difference between two treatment effects; δ_0 = a clinically acceptable margin.

Recruitment

The selection of the Imam-Reza Clinic for our study is strategically justified by its high patient volume, status as a key referral center for comprehensive patient management, and proactive engagement in blood pressure screening campaigns, which are integral to our research focus. The physicians will direct patients to enroll in our study. The clinic's economic accessibility, through low consultation fees and broad insurance coverage, ensures inclusivity, enabling participation from diverse socioeconomic backgrounds. Furthermore, our initiative to educate potential participants at the clinic leverages its robust patient education framework, enhancing recruitment efforts and reinforcing the clinic's pivotal role in promoting cardiovascular health. Collectively, these attributes make the Imam-Reza Clinic an ideal setting for our study, providing a rich data pool and facilitating impactful research on blood pressure management.

Randomization method (sequence generation and concealment mechanism)

The study will utilize permuted block randomization, implemented through a web-based service (https://www.sealedenvelope.com/), to manage the allocation of 300–400 patients in each phase, ensuring an equal number of participants in the control and treatment groups per phase. The randomization schedule will be securely stored within an electronic database at Imam-Reza Clinic. Enrollment personnel will access each subsequent assignment through this database, ensuring a consistent and unbiased allocation process throughout all study phases. This randomization approach involves creating blocks by assigning various sequences to the numbers 1 through 6. The specific block sequences are as follows: 1-AABB, 2-ABAB, 3-ABBA, 4-BBAA, 5-BABA, 6-BAAB. In these sequences, "A" denotes patients allocated to the treatment group, while "B" represents those in the control group. Block numbers will be selected using a random numbers table until 36 blocks of four-letter sequences have been chosen. This method ensures a balanced allocation of participants across the two study groups.

Implementation and blinding

Patients who provide informed consent and meet the eligibility requirements will be subjected to randomization. The well-trained nursing staff, who are in charge of recruitment and conducting clinical interviews at the Imam-Reza Clinic, will initiate the randomization request. As an open-label trial, participants and physicians responsible for follow-up visits will not be blinded. The outcome assessors and data analyzers are blinded in this study.

Data collection and management

During the baseline visit, all patient information and data will be recorded and securely archived at the Imam-Reza Clinic. At each follow-up visit, a blinded staff member (a well-trained nurse) will interview the patient and record the follow-up (outcome) data. Subsequently, the patient will be examined by a physician who is not blinded to the treatment allocation. All documents and records will be securely archived. We will utilize standardized data collection methods and a secure, electronic database at Imam-Reza Clinic, managed by a specialized team that ensures data quality through regular audits and data cleaning. Access is strictly controlled, with advanced security measures such as encryption and backups to prevent unauthorized access. An independent committee conducts periodic data monitoring for safety and integrity. Following ethical and regulatory standards, data analysis will be carried out as per a predefined plan, ensuring transparent and reproducible reporting of findings, thereby maintaining research excellence and protecting participant privacy.

Statistical analysis

Data analysis will be conducted using the Stata, version 18.0 (StataCorp LLC, College Station, Texas, USA). Quantitative data are presented as the mean ± standard deviation (SD), and categorical data are presented as frequencies and percentages. For quantitative comparisons, either the independent t-test or Mann–Whitney U test will be utilized. Cox regression analysis was used to determine the specific impact of antihypertensive treatment on cardiovascular events, and a P value ≤ 0.05 will be considered to indicate statistical significance. Participants who did not complete the follow-up were censored at their last known contact. The analysis will primarily focus on the intention-to-treat population, which is determined by the initial random allocation, to test the primary hypothesis of proving superiority. Subgroup analysis will be performed, focusing on factors of clinical significance such as age, sex, existing health conditions,

and additional indicators of risk. For all hypothesis testing, a two-sided approach will be adopted, with the significance level set at 5%.

Analysis of population and missing data

In our study, the primary analysis focusing on the endpoints will proceed without adjustments for covariates, and we will not employ imputation techniques for missing baseline variable values. Patients who are lost to follow-up will be censored at the last known point of contact and considered not to have reached the primary endpoint in the calculation of Kaplan–Meier event rates. This approach ensures a straightforward and transparent analysis of the data, reflecting the true nature of the study's outcomes.

Data monitoring, harms, and auditing

Before the statistical analysis is initiated, a cardiology department expert, external to our research team, will critically assess and approve all data measurements. Measurements that fail to meet the requisite quality standards will be excluded and considered missing for analytical purposes. A neutral DSMB, unaware of participant treatment allocations, will evaluate the occurrence of significant MACE. Upon the completion of this adjudication stage, the database will be unlocked for analysis. Communication regarding any adverse incidents will be directed to an autonomous DSMB by the TMC. If the adverse event rate in the intervention group exceeds that of the control group by more than 20% at any interim analysis, the DSMB will review the data and may recommend trial termination if deemed necessary. Regular monitoring of safety data, including unexpected serious adverse events, mortality, and severe arrhythmias, will be the DSMB's responsibility, with quarterly safety reports generated for review. Additionally, all deaths will be promptly communicated to the DSMB, which will also perform audits every 6 months, functioning independently from the study researchers. In addition to MACE, we will systematically collect data on other potential harms, such as drug reactions and other adverse events, through both spontaneous reporting and structured follow-up visits. Harms will be collected, analyzed, and reported using standardized medical terminology, such as the Medical Dictionary for Regulatory Activities (MedDRA). All collected harms, regardless of their frequency, will be reported in publications to provide a comprehensive overview of the safety profile. This approach ensures transparency and allows for a detailed understanding of the potential risks associated with the interventions.

Ethical considerations

This survey was conducted in compliance with the Declaration of Helsinki [18] and received ethics approval from the Institutional Review Board and Ethics Committee of Shiraz University of Medical Sciences (SUMS) on October 2, 2019, under the approval number IR.SUMS.MED.REC.1398.420. The study has been registered with the Iranian Registry of Clinical Trials at https://www.irct.ir under the trial identifier IRCT20191002044961N1. Furthermore, all participants were required to provide informed consent, a process facilitated by experienced nurses or clinical staff.

Protocol amendments

In our research, any changes to the protocol that might affect the conduct of the study, potential patient benefits, or patient safety will require a formal amendment, which will be applied by the TMC and SC. This encompasses alterations in the study objectives, methodology, participant characteristics, sample sizes, study procedures, or significant administrative adjustments. Prior endorsement from the Ethics Committee/Institutional Review Board (IRB) of Shiraz University of Medical Sciences is mandatory for these amendments to uphold ethical guidelines and safeguard participant well-being.

Consent and assent

The process of obtaining consent or assent involves the staff introducing the trial to potential participants and providing them with detailed information sheets for thorough understanding. Following this, patients will engage in informed discussions with the consulting specialist. Written consent will then be acquired from those patients who decide to participate in the trial by a trained general practitioner. There will be no ancillary studies conducted using data collected from this trial, ensuring that all participant information is solely used for the intended research purposes as outlined in the study protocol.

Confidentiality

Participant information will be safeguarded in locked file cabinets situated in restricted-access areas. To preserve confidentiality, laboratory samples, reports, data collection sheets, processing, and administrative documents will be tagged with a coded ID rather than personal identifiers. Records containing personal identifiers, such as locator forms and consent documents, will be stored separately from those identified by code. Additionally, all local databases will be fortified with password-protected

access systems, ensuring that data security and participant privacy are maintained throughout the study.

Discussion

The latest ACC/AHA High Blood Pressure Guidelines no longer use the term "prehypertension". Instead, they classify blood pressure as either elevated (120–129/ < 80 mmHg) or hypertensive, diverging from previous guidelines that defined 140/90 mmHg as stage 1 hypertension. It further recommends addressing high blood pressure medically at an earlier threshold of 130/80 mmHg rather than the previous 140/90 mmHg standard [19]. A 2004 epidemiologic follow-up study sought to assess the impact of prehypertension on hospital admissions and mortality rates. A total of 3.4% of hospitalizations, 6.5% of nursing home admissions, and 9.1% of deaths could be directly attributed to prehypertension. The study concluded that eliminating prehypertension could significantly decrease the rates of hospitalization, nursing home entry, and early death [11]. A cross-sectional study in 2007 showed that after 10 years, 31.1% of subjects with prehypertension became hypertensive [9]. The progression of prehypertension to hypertension can increase the risk of cognitive function impairment, increased left ventricular mass, end-stage renal disease, and arteriosclerosis. Therefore, it "might" be beneficial to treat prehypertension with antihypertensive medications in addition to lifestyle modifications [12]. Despite the apparent importance of this issue, it has not been exclusively addressed in a clinical trial before.

Previous studies were conducted in the general population and did not stratify patients according to their comorbidities [20, 21]. Therefore, the authors could not clearly determine whether the MACE were directly the result of hypertension or other associated diseases, leading to selection bias. In the PRINT-TAHA9, we excluded all diabetic patients and those with other comorbidities previously described in the "Study participants and eligibility criteria" section and enrolled only nondiabetic prehypertensive adults to obtain more pure and specific results on this matter. Moreover, we excluded patients with prior use of aspirin, statins, antihypertensives, and anticoagulants prescribed for other conditions because we believe that these medications could significantly influence the outcomes and act as major confounding factors, potentially compromising the integrity of our investigation.

A post hoc secondary analysis of the SPRINT trial designed to determine the practical cutoff limit of cardiovascular risk for starting intensive blood pressure reduction showed a J-shaped relationship between intensive blood pressure control and 10-year Framingham cardiovascular risk levels at a cutoff limit of approximately < 7% [15]. In this trial, we decided to set this cutoff limit as an inclusion criterion rather than a 10-year risk of more than 10%, which was used in the SPRINT trial.

According to the latest hypertension guidelines of the ESC/ESH, the initiation of antihypertensive therapy with a two-drug combination might be recommended for high-risk individuals. In older patients (≥ 65 years old), the initiation of antihypertensive treatment with a two-drug combination, preferably a single-pill combination (SPC), is suggested [2]. Multiple studies have proven that the efficacy of SPCs is greater than that of non-combined medications, and SPCs have improved tolerability and safety profiles [22–25]. Several SPCs have been made worldwide, and the two most common SPCs available in Iran are amlodipine/valsartan and amlodipine/valsartan/hydrochlorothiazide. Other SPCs are neither widely accessible nor inexpensive. Considering these points, we chose amlodipine/valsartan 5–80 mg as the medication of choice in our study. Moreover, we did not use triple SPC to avoid hypotension and subsequent adverse events.

Due to the single-center design of our study, we were unable to recruit all desired participants at once. Consequently, we implemented a phased recruitment strategy comprising five stages. Additionally, we recognize that a 3-year follow-up period may be inadequate to fully ascertain the long-term impact of the treatment on major cardiovascular events. We intend to perform a primary analysis at the conclusion of this period and determine whether to extend the trial.

Access to data

Only the TMC members have access to patient data and files.

Ancillary and post-trial care

The Shiraz University of Medical Sciences will offer insurance coverage for any harm that participants might experience as a result of the study protocol. This insurance will encompass additional healthcare costs, compensation, or damage that is demonstrably linked to the study's procedures.

Dissemination policy

Trial results

The findings of the study will be promptly disseminated to the physicians involved in the study, those referring patients, the participants themselves, and the broader medical community to ensure timely access to the new insights gained. The results will also be published in peer-reviewed scientific journals and presented at national and international conferences.

Authorship
Authorship will be discussed and determined in TMC.

Reproducible research
The full protocol of the study will be made publicly available as soon as possible.

Appendices
Appendix 1 shows the variables and components of the medical evaluation of the enrolled patients. Informed consent materials are presented in Appendix 2.

Biological specimens
Blood samples were collected to conduct a comprehensive blood count (CBC), assess thyroid function (TFT), and measure the levels of blood urea nitrogen (BUN) and creatinine (Cr). Additionally, the serum levels of sodium (Na), potassium (K), calcium (Ca), and phosphorus (Ph) were evaluated.

Table of execution timelines
See Fig. 1.

Trial status
This document outlines protocol version number 03, finalized on July 27, 2024. The recruitment for phase 1 started on December 2019, following the trial registration on IRCT.ir, and concluded in February 2020. The follow-up for phase 1 has been completed. Recruitment for the subsequent phases is currently ongoing. We estimate that the recruitment will be completed by September 2026.

Abbreviations

SBP	Systolic Blood Pressure
DBP	Diastolic Blood Pressure
AHA	American Heart Association
MACE	Major Adverse Cardiovascular Events
SPRINT	Systolic Blood Pressure Intervention Trial
ESC/ESH	European Society of Cardiology and the European Society of Hypertension
ACS	Acute Coronary Syndromes
PCI	Percutaneous Coronary Intervention
ESRD	End-Stage Renal Disease
DM	Diabetes Mellitus
ASCVD	AtheroSclerosis CardioVascular Disease
IHD	Ischemic Heart Diseases
CVA	CerebroVascular Accident
CBC	Complete Blood Count
TFT	Thyroid Function Test
BUN	Blood Urea Nitrogen
Cr	Creatinine
SPC	Single-Pill Combination
HF	Heart Failure
SC	Steering Committee
TMC	Trial Management Committee
DSMB	Data, Safety, and Monitoring Board

Supplementary Information
The online version contains supplementary material available at https://doi.org/10.1186/s13063-024-08420-2.

Additional file 1: SPIRIT checklist
Additional file 2: Appendix 1
Additional file 3: Appendix 2

Roles and responsibilities
Principal Investigator and Research Physician: AA.
Steering Committee (SC): AA, RB, MI, MS, and SAM. This committee will convene and hold meetings before the start of recruitment and then every 6 months throughout the study. The meetings will focus on discussing trial-related issues to ensure adherence to the protocol, monitoring progress to meet objectives and timelines, making decisions about protocol amendments, resource allocation, and addressing significant issues or challenges. Additionally, they will oversee quality assurance and facilitate effective communication and coordination among all stakeholders.
Trial Management Committee (TMC): AA and SAM. This committee consists of the two main investigators of the study, who maintain close contact with the staff, workers, and all matters related to the study. They discuss all issues among themselves and compile a list of matters to be resolved by the SC.
Data, Safety, and Monitoring Board (DSMB): The DSMB is composed of SC members, two cardiologists, and an ethicist who are not part of the research team. They convene every 6 months after the study begins to review and address any safety concerns, as detailed in the "Data monitoring, harms, and auditing" section.
Data Managers: MS and SAM.
Lead Investigator: AA.

Authors' contribution
AA, RB, MA, MS, and SAM contributed to the development of the protocol, preparation of the proposal, and critical revisions. AA took the lead in conceptualizing the study design with the help of MZ, IR, and NP. All the authors agreed to bear responsibility and accountability for the entirety of the project.

Funding
We have received funding from the Office of the Vice-Chancellor for Research of Shiraz University of Medical Sciences (project number 97–01-01–17710). The funder had no role in the study, except that Shiraz University of Medical Sciences provided ethical clearance.

Data Availability
Requests for data access will be reviewed by the TMC to ensure compliance with ethical guidelines and the study's objectives. Approved requests will be granted access to the data under conditions that protect participant confidentiality and align with the trial's governance policies.

Declarations

Competing interests
The authors declare no conflicts of interest in this study.

Author details
[1]TAHA Clinical Trial Group, Department of Cardiovascular Medicine, School of Medicine, Shiraz University of Medical Sciences, Shiraz, Iran. [2]MD-MPH Department, School of Medicine, Shiraz University of Medical Sciences, Shiraz, Iran. [3]Cardiovascular Research Center, School of Medicine, Shiraz University of Medical Sciences, Shiraz, Iran. [4]Trauma Research Center, Shahid Rajaee (Emtiaz) Trauma Hospital, Shiraz University of Medical Sciences, Shiraz, Iran. [5]Non-Communicable Disease Research Center, Shiraz University of Medical Sciences, Shiraz, Iran. [6]Student Research Committee, Shiraz University of Medical Sciences, Shiraz, Iran.

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