

Research Article



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Intensive blood pressure control to prevent major cardiovascular events in individuals with high-normal blood pressure (prehypertension): PRINT-TAHA9 randomized clinical trial

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ABSTRACT

Background: The optimal treatment for individuals with high-normal blood pressure (BP, systolic BP 130–139 mmHg and diastolic BP < 90 mmHg) is debated. This study evaluates whether pharmacologically reducing systolic BP to below 130 mmHg could prevent major adverse cardiovascular events (MACE) in high-normal BP cases with no comorbidities and 10-year atherosclerotic cardiovascular disease (ASCVD) risk $\geq 7.5\%$.

Methods: In this randomized, controlled, parallel, unicentric trial, participants were assigned to either an intervention group (pharmacotherapy plus diet control) or a control group (diet control only). The study aimed for 1,600 participants but was terminated after the first phase due to limited resources and recruitment challenges. Fixed-dose combinations of valsartan and amlodipine were administered as BP-lowering agents. Follow-up visits every 3 months adjusted pharmacotherapy to maintain systolic BP < 130 mmHg in the intervention group and < 140 mmHg in the control group. MACE was the primary endpoint, with its components (cardiovascular death, myocardial infarction, stroke, and heart failure) as secondary endpoints. Multivariable Cox regression analysis was utilized to compare the group endpoints.

Results: Of 14,562 screened individuals, 231 in the intervention and 235 in the control group were included in the final intention-to-treat analysis. At baseline, the control group had a slightly higher mean age than the intervention group (67.7 vs. 66.1 years; $P = 0.013$). Females comprised a minority in both groups (19.5% in intervention vs. 16.2% in control; $P = 0.397$). The mean 10-year ASCVD risk was slightly higher in the control group (17.4% vs. 15.9%; $P = 0.013$). The MACE occurred in 9 participants (1.57 per 100 person-year) in the intensive treatment group vs. 24 (4.16 per 100 person-year) in the control group (adjusted hazard ratio [aHR], 0.26; 95% confidence interval [CI], 0.11–0.62; $P = 0.003$). The incidence of serious adverse events (hypotension, syncope, injurious falls, electrolyte

Abbreviations

ACC, American College of Cardiology; AHA, American Heart Association; aHR, adjusted hazard ratio; AKI, acute kidney injury; ASCVD, atherosclerotic cardiovascular disease; BMI, body mass index; BP, blood pressure; CI, confidence interval; CVA, cerebrovascular accident; CVD, cardiovascular disease; DBP, diastolic blood pressure; DSMB, Data Safety and Monitoring Board; eGFR, estimated glomerular filtration rate; HDL, high-density lipoprotein; HF, heart failure; HR, hazard ratio; MACE, major adverse cardiovascular events; MI, myocardial infarction; SAE, serious adverse event; SBP, systolic blood pressure; TMC, trial management committee.

Trial Registration

Iranian Registry of Clinical Trials Identifier: IRCT20191002044961N1

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Competing interest

The authors declare that no competing interests.

Availability of data and materials

The data supporting this study's findings will be available from the corresponding author upon reasonable request.

Ethics approval and consent to participate

The study protocol conforms to the Declaration of Helsinki and is approved by the ethical committee of Shiraz University of Medical Sciences and is registered with the Iranian National Committee for Ethics in Biomedical Research by number IR.SUMS.MED.REC.1398.420.

Consent for publication

All participants signed the informed consent form.

Authors' contributions

Conceptualization: Attar A; Data curation: Sayadi M, Attar A; Formal analysis: Mirhosseini SA, Sayadi M; Investigation: Mirhosseini SA, Attar A; Methodology: Mirhosseini SA, Attar A; Project administration: Attar A; Resources: Attar A; Supervision: Attar A; Validation: Attar A; Visualization: Mirhosseini SA; Writing -

imbalances, or acute kidney injury) was similar between the groups (aHR, 1.47; 95% CI, 0.82–2.62; $P = 0.195$).

Conclusions: PRINT-TAHA9 findings suggest that pharmacological BP reduction may benefit healthy asymptomatic individuals with high-normal BP and ASCVD risk $\geq 7.5\%$.

Trial Registration: Iranian Registry of Clinical Trials Identifier: IRCT20191002044961N1

Keywords: High normal blood pressure; Elevated blood pressure; Hypertension; High risk; SPRINT; Prehypertension; Intensive blood pressure reduction

BACKGROUND

Hypertension represents the most significant modifiable risk factor for cardiovascular disease (CVD) and premature death, affecting more than 1 billion individuals [1]. The classification thresholds for hypertension have evolved across guidelines over time. Blood pressure (BP) levels with a systolic (SBP) range of 130–139 mmHg and a diastolic (DBP) < 90 mmHg are referred to as high-normal or elevated BP in European guidelines [2]. In contrast, earlier American guidelines (before 2017) categorized this range as prehypertension (SBP 120–139 mmHg and DBP 80–89 mmHg), while the 2017 American College of Cardiology (ACC)/American Heart Association (AHA) update redefined it as Stage 1 hypertension [3,4]. Evidence suggests that prehypertension often precedes the onset of hypertension and serves as a significant independent risk factor for CVD, distinct from the impact of hypertension itself [5–7]. Moreover, prehypertension is commonly associated with major adverse cardiovascular events (MACE) and its established common risk factors, such as obesity, smoking, and diabetes [8–10].

The long-term impact of high-normal BP on MACE, as well as the question of whether it should be actively treated, remains controversial [11–13]. A risk-based approach is advised for managing high-normal BP, with pharmacotherapy initiation recommended when the 10-year cardiovascular risk exceeds 10% [2,14]. This approach is widely supported by experts, yet it has faced criticism for the absence of randomized controlled trials that specifically isolate the impact of BP control from other contributing risk factors [15–17]. Our secondary analysis of the SPRINT trial showed that intensive pharmacotherapy benefits patients with high-normal BP [18]. In a separate analysis, we found that individuals with a 10-year cardiovascular risk as low as 7.5% also benefit from intensive BP control [19]. Notably, this 7.5% atherosclerotic cardiovascular disease (ASCVD) risk (intermediate to high risk) threshold aligns with the established cutoff for initiating statins in dyslipidemia, making it a clinically validated benchmark for guiding BP treatment.

Based on this rationale and the absence of direct evidence supporting the benefits of intensive treatment for high-normal BP, we developed a clinical trial on the prevention of MACE involving intensive BP reduction in patients with high-normal BP as the 9th trial of traditional and advanced heart approaches clinical center (PRINT-TAHA9 trial). This trial aims to directly compare the effects of pharmacotherapy combined with dietary control to those of dietary control alone in managing high-normal BP patients with ASCVD risk $\geq 7.5\%$ and no underlying comorbidities.

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METHODS

Study design and setting

PRINT-TAHA9 is a randomized, open-label, controlled, parallel, and unicentric clinical trial comparing the MACE in 2 groups with high-normal BP. High-normal BP was defined as an office SBP between 130 and 140 mmHg and a DBP between 80 and 90 mmHg. Any office BP in the study was determined as the mean of 3 measurements taken before randomization during the participant's first clinic visit. This study was conducted at the Imam Reza Cardiovascular Clinic, a tertiary referral center for cardiovascular care in southern Iran. The detailed protocol of the study is published elsewhere [20]. All participants gave written informed consent. The study complied with the Declaration of Helsinki and received approval from the Institutional Review Board and Ethics Committee of Shiraz University of Medical Sciences (ethics code: IR.SUMS.MED.REC.1398.420). It is also registered with the Iranian Registry of Clinical Trials under the identifier IRCT20191002044961N1.

Study participants

We enrolled adult individuals with high-normal BP and a 10-year ASCVD risk of 7.5% or higher with no comorbidity. Patients with any history of diabetes mellitus, cerebrovascular accident (CVA), heart failure (HF), ischemic heart diseases, including acute or chronic coronary syndrome, arrhythmias, obstructive sleep apnea, and those taking statins, antiplatelets, anticoagulants, and antihypertensive medications for other reasons were excluded from the study.

Intervention

After random allocation to either the treatment or control group, the treatment group received a daily antihypertensive regimen of amlodipine/valsartan (initial dose 5/80 mg, Valzomix®; Abidi Pharmaceutical Company, Tehran, Iran), combined with a low-salt, low-fat diet, to maintain BP below 130/80 mmHg. In cases of uncontrolled BP (above 130/80 mmHg in the treatment), the dosage was gradually increased to 5/160 mg or 10/160 mg of amlodipine/valsartan, with the option of adding 1.5 mg of indapamide (step-up approach). If SBP fell below 100 mmHg at one visit or below 110 mmHg at 2 consecutive visits, the medication dosage would be reduced using a step-down approach. The control group adhered to the same diet but only received antihypertensive medication (the same initial dose) if their BP exceeded 140/90 mmHg. The medication dosage would be adjusted using the same step-up approach to maintain BP below the specified threshold.

Sample size, randomization, and analysis plan

As previously described [20], the PRINT-TAHA9 trial was designed originally as a superiority clinical trial with 80% power to detect a 3% difference in event rates between the treatment and control groups (anticipated MACE incidence of 6% in the control group vs. 3% in the intervention group), assuming a 10% dropout rate. The study aimed to recruit 1,620 participants in multiple phases to achieve this. Interim analyses were planned after the completion of each phase, and the Data Safety and Monitoring Board (DSMB) reviewed safety data quarterly, including adverse events and mortality. The DSMB was authorized to terminate the trial if the adverse event rate in the intervention group exceeded that of the control group by more than 20%. After enrolling 550 patients in phase 1, the trial management committee (TMC) decided to terminate the trial based on limited resources and the difficult recruitment of the specific target population. A post hoc power analysis was conducted to estimate the final statistical power of the study, which was approximately 35%.

Enrolled patients were randomly assigned to the treatment or control groups using permuted block randomization via a web-based platform (<https://www.sealedenvelope.com/>). While the trial was open-label, meaning neither participants nor physicians were blinded, outcome assessors and data analysts remained blinded to the assigned groups to ensure unbiased evaluation of the results.

Outcome and follow-up

The primary endpoint of the study was MACE, a composite of cardiovascular death, myocardial infarction (MI), stroke (CVA), and hospitalization due to HF. These outcomes were identified through clinical diagnoses using International Classification of Diseases codes and summarized as event counts and proportions within each group, with comparisons between the treatment and control groups conducted throughout the 36-month follow-up period. The secondary endpoints included the components of the primary endpoint, SBP, and DBP, with measurements at each follow-up visit (every 3 months). Adherence to medication and diet was assessed during each visit through a structured interview between the patient and the physician. If the physician identified non-adherence to the assigned treatment during any visit, the patient was censored from the study at their last visit, where adherence was confirmed. Additionally, after excluding participants who withdrew consent, refused to initiate pharmacotherapy, or opted not to attend the first scheduled follow-up visit after allocation, the remaining patients were included in the analysis based on their last confirmed follow-up visit. Patients were censored at their previous adherent visit when follow-up data were missing.

Adverse events

The incidence of adverse events, including hypotension, syncope, injurious falls, electrolyte imbalances, and acute kidney injury (AKI), was assessed and compared between intervention and control groups. Hypotension was defined as a SBP below 100 mmHg, resulting in clinical symptoms severe enough to require a physician consultation. Syncope was identified when patients experienced a sudden, temporary loss of consciousness due to transient cerebral hypoperfusion, followed by spontaneous recovery, as self-reported by participants and confirmed by a physician. Injurious falls were classified as falls resulting in an emergency department visit or hospitalization. Electrolyte imbalance was recognized when sodium, potassium, calcium, magnesium, and phosphorus levels fell outside clinically accepted ranges, as documented by a physician during checkups or requiring medical evaluation based on the patient's condition. AKI was recorded if it was listed as a diagnosis in the hospital discharge summary and deemed by the physician among the top 3 reasons for admission or continued hospitalization. The occurrence of serious adverse events (SAE) was considered the primary ancillary endpoint and was defined as any of the aforementioned adverse events that were fatal, life-threatening, resulted in significant or persistent disability, or required/prolonged hospitalization. An event was classified as an SAE if a physician determined it posed a clinically substantial risk or harm to the participant and necessitated medical or surgical intervention to prevent recurrence. All adverse events were recorded using the Medical Dictionary for Regulatory Activities and were independently reviewed and adjudicated by the DSMB.

Covariates

Considering that participants with underlying comorbidity were excluded from the study, we assessed baseline measurements, including age, sex, SBP, DBP, ASCVD risk, smoking status, body mass index (BMI), estimated glomerular filtration rate (eGFR), fasting serum glucose,

triglyceride, total cholesterol, and high-density lipoprotein (HDL) levels as covariates. Sex (male and female) and smoking status (never, current, and former smoker) were treated as categorical covariates, while all other variables were analyzed as continuous covariates. eGFR was calculated using the Modification of Diet in Renal Disease formula, and ASCVD risk was determined using the ACC risk calculator. We did not categorize continuous variables using predefined cut-off values to optimize model accuracy and statistical power.

Statistical analysis

Continuous variables are presented as mean $\pm$ standard deviation, while categorical variables are reported as frequencies (numbers and percentages). Differences between groups were assessed using independent *t*-tests or Mann-Whitney *U* tests for continuous variables, depending on normality. Fisher's exact test or the χ^2 test was applied for categorical variables. Kaplan-Meier curves were used to compare event rates between groups. To evaluate the effect of antihypertensive treatment on cardiovascular events, we conducted Cox proportional hazards regression analysis using an intention-to-treat approach. Event rates were reported as percentages and per 100 person-years for the intervention and control groups. Crude hazard ratios (HRs) were calculated for the primary endpoint, secondary outcomes, and adverse events, comparing the intervention and control groups. For further adjustment, we developed multivariable Cox regression models for primary and secondary outcomes, incorporating relevant covariates to adjust for potential confounders. The proportional hazards assumption was assessed using the scaled Schoenfeld residuals test to validate the Cox model. All statistical analyses were performed using Stata version 18 (StataCorp LLC, College Station, TX, USA). When some HRs show vast confidence intervals (CIs), which is typically observed when the number of events is very small, leading to convergence issues, to estimate the HR, we used Firth's penalized likelihood method (R software, version 4.3.2; R Foundation for Statistical Computing, Vienna, Austria) to obtain more reliable estimates. A 2-sided *P*-value ≤ 0.05 was considered statistically significant.

RESULTS

Fourteen thousand five hundred sixty-two individuals were screened for eligibility between December 2019 and August 2021, of whom 14,012 were excluded. The remaining 550 participants were randomized 1:1 between the intervention and control groups. After excluding participants who declined pharmacotherapy, withdrew consent, or failed to attend follow-up visits from the outset despite contact attempts, 231 individuals in the intervention group and 235 in the control group were included in the final modified intention-to-treat analysis. The Consolidated Standards of Reporting Trials flow diagram depicting participant flow throughout the study is shown in **Fig. 1**. The mean follow-up duration was 900 ± 175 days, with the last follow-up in September 2024.

Baseline characteristics

As shown in **Table 1**, the mean age of participants was slightly higher in the control group (67.72 ± 6.9 years) compared to the intervention group (66.1 ± 7.1 years). Females constituted a minority in both groups (19.5% and 16.2% in the intervention and the control group, respectively). Baseline values for SBP and ASCVD risk scores were higher in the control group than in the intervention group. Current smoking is more prevalent among the control group patients. Other baseline variables, including serum creatinine level, eGFR, BMI, total cholesterol, HDL, and triglyceride levels, were well-matched between the intervention and control groups.

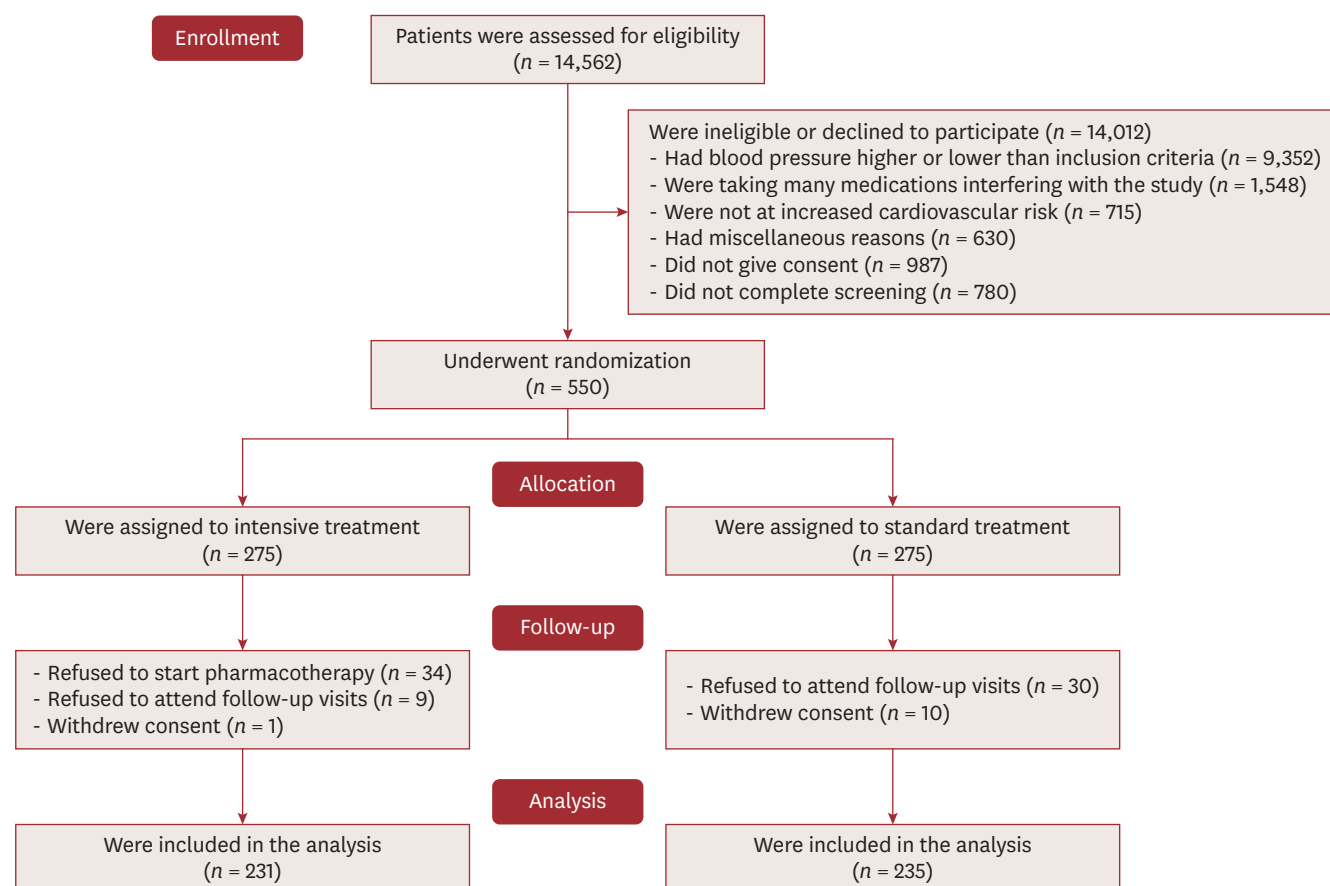


Fig. 1. Consolidated Standards of Reporting Trials flow diagram of the PRINT-TAHA9 trial participants.

Table 1. Baseline characteristics of the study participants

Characteristics	Intervention (n = 231)	Control (n = 235)	P-value
Age (yr)	66.09 ± 7.05	67.72 ± 6.99	0.013*
Female (%)	19.5	16.2	0.397
SBP (mmHg)	133.37 ± 2.80	134.81 ± 3.10	0.001*
DBP (mmHg)	77.52 ± 8.10	77.02 ± 7.90	0.499
ASCVD risk (%)	15.86 ± 6.46	17.45 ± 7.19	0.013*
Creatinine (mg/dL)	1.05 ± 0.28	1.03 ± 0.30	0.394
eGFR (mL/min/1.73 m ²)	61.94 ± 24.15	62.92 ± 23.32	0.655
Total cholesterol (mg/dL)	201.73 ± 43.76	195.73 ± 36.08	0.110
HDL (mg/dL)	50.35 ± 13.31	51.29 ± 13.40	0.451
Triglyceride (mg/dL)	124.84 ± 62.20	122.11 ± 72.54	0.665
BMI ^a (kg/m ²)	28.54 ± 5.20	28.00 ± 4.75	0.246
Smoking			
Never	82 (36.0)	102 (43.8)	0.088
Former	94 (41.2)	100 (42.9)	0.798
Current	52 (22.8)	33 (14.2)	0.011*

Values are presented as means ± standard deviation or number (%).

eGFR calculated using Modification of Diet in Renal Disease formula. To convert the values for creatinine to micromoles per liter, multiply by 88.4. To convert the values for cholesterol to millimoles per liter, multiply by 0.02586. To convert the values for triglycerides to millimoles per liter, multiply by 0.01129.

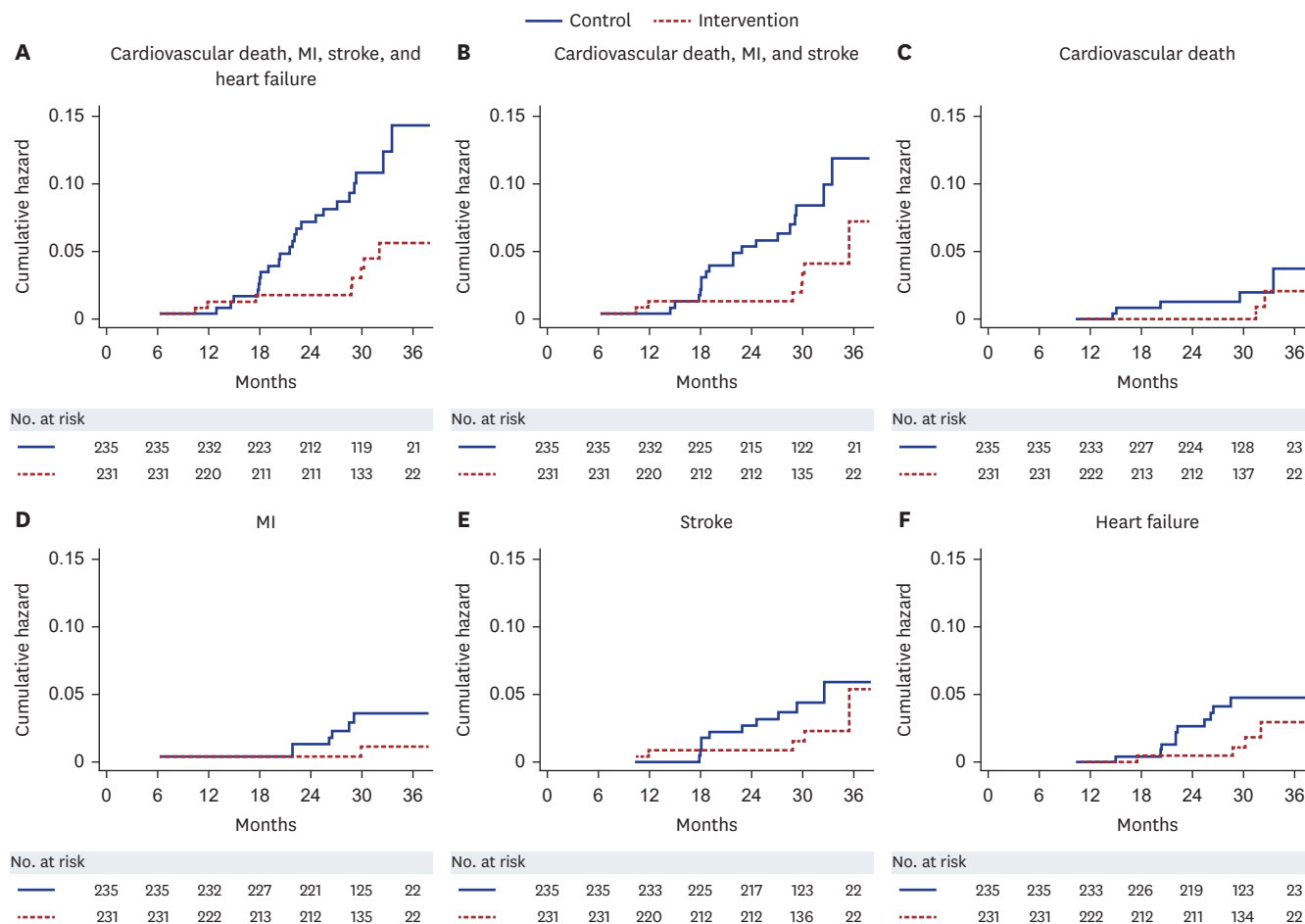
SBP, systolic blood pressure; DBP, diastolic blood pressure; ASCVD, atherosclerotic cardiovascular disease; eGFR, estimated glomerular filtration rate; HDL, high-density lipoprotein; BMI, body mass index.

^aThe BMI is the weight in kilograms divided by the square of the height in meters.

*Two-sided P-value ≤ 0.05 is considered as statistical significance.

Clinical outcomes

The primary outcome event occurred in 9 participants (1.57% per year) in the intervention group and 24 participants (4.16% per year) in the control group, yielding a crude HR of 0.37 (95% CI, 0.17–0.79; $P = 0.011$; **Fig. 2A**). These findings remained significant after excluding



Outcome	Intervention (n = 231)		Control (n = 235)		Crude HR ^a (95% CI)	P-value
	Events No. (%)	Events per 100 person-years	Events No. (%)	Events per 100 person-years		
Primary endpoint						
Cardiovascular death, MI, stroke, and heart failure	9 (3.9)	1.57	24 (10.2)	4.16	0.37 (0.17–0.79)	0.011
Secondary endpoints						
Cardiovascular death, MI, and stroke	8 (3.5)	1.39	19 (8.1)	3.28	0.41 (0.18–0.93)	0.033
Cardiovascular death	2 (0.9)	0.35	5 (2.1)	0.85	0.38 (0.07–1.95)	0.244
MI	2 (0.87)	0.35	7 (29.8)	1.19	0.29 (0.06–1.40)	0.124
Stroke	5 (2.2)	0.87	10 (4.3)	1.72	0.49 (0.17–1.43)	0.189
Heart failure	4 (1.7)	0.70	10 (4.3)	1.71	0.40 (0.13–1.29)	0.127

Fig. 2. Primary and secondary outcomes analysis. (A) The cumulative hazards for the primary outcome (a composite of cardiovascular mortality, MI, stroke, and hospitalization due to heart failure). (B) The cumulative hazards for the composite endpoint of cardiovascular mortality, MI, and stroke. (C–F) The cumulative hazards for each component of the secondary outcome including cardiovascular mortality (C), MI (D), stroke (E), and heart failure (F).

MI, myocardial infarction; HR, hazard ratio; CI, confidence interval.

^aCrude HR from Cox regression analysis comparing intensive pharmacotherapy combined with dietary blood pressure control (intervention) to dietary control alone (control).

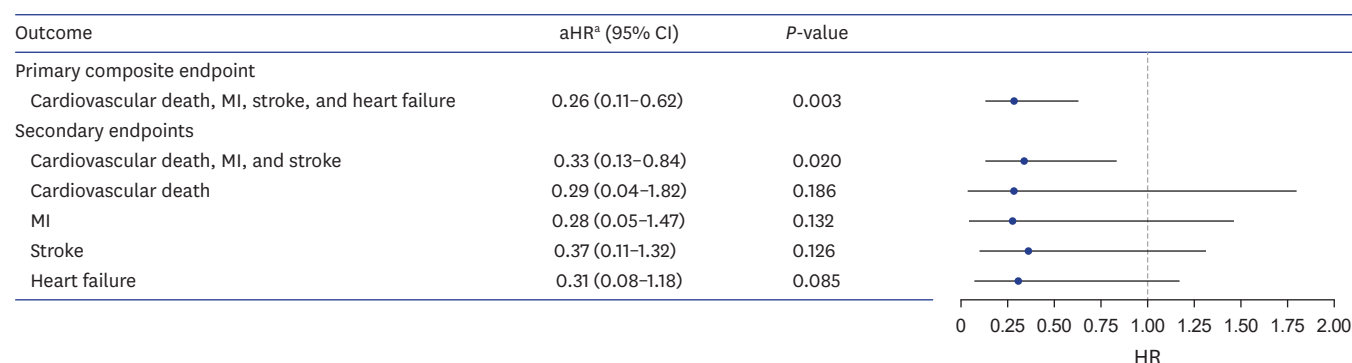


Fig. 3. Adjusted models of Cox regression analysis for primary and secondary endpoints. aHR, adjusted hazard ratio; CI, confidence interval; HR, hazard ratio; MI, myocardial infarction.

^aAdjusted Cox regression model for age, sex (female and male), baseline atherosclerotic cardiovascular disease risk score, body mass index, systolic blood pressure, diastolic blood pressure, smoking status (never, current, and former), estimated glomerular filtration rate, total cholesterol, fasting serum glucose, high-density lipoprotein, and triglyceride levels.

patients with newly diagnosed HF (HR, 0.41; 95% CI, 0.18–0.93; $P = 0.033$). The secondary outcomes did not show statistically significant differences between the groups (**Fig. 2**). After adjusting for covariates, the preventive effect of pharmacotherapy remained statistically significant for the occurrence of the primary endpoint (adjusted HR [aHR], 0.26; 95% CI, 0.11–0.62; $P = 0.003$) and the composite endpoint of cardiovascular mortality, MI, and stroke (aHR, 0.33; 95% CI, 0.13–0.84; $P = 0.020$) (**Fig. 3**). The proportional hazards assumption was held across all analyses.

Adverse events

As presented in **Fig. 4**, SAE were reported in 27 participants (11.7%) in the intensive treatment group and 24 participants (10.2%) in the standard treatment group (HR for intervention, 1.18; 95% CI, 0.68–2.05; $P = 0.55$). The intensive-treatment group showed a higher risk of hypotension (HR, 11.49; 95% CI, 1.48–89.01; $P = 0.019$) and a trend toward increased risk of syncope (HR, 3.16; 95% CI, 0.85–11.67; $P = 0.085$). Conversely, injurious falls were more frequent in the control group (HR, 0.46; 95% CI, 0.22–0.97; $P = 0.043$). After adjusting for covariates, syncope was the only adverse event with a significantly higher incidence in the intensive pharmacotherapy group (aHR, 4.43; 95% CI, 1.06–18.44; $P = 0.041$). Details of the adjusted (multivariate) analyses for all outcomes and adverse events are provided in the **Supplementary Tables 1–13**. The proportionality assumption was not violated in any analysis.

BP

The intervention group experienced a rapid and sustained reduction in SBP compared to the control group (**Fig. 5**). Over the follow-up period, the mean SBP was 122.41 ± 13.21 mmHg in the intensive treatment group, compared with 138.19 ± 11.78 mmHg in the standard treatment group, resulting in an average difference of 15.77 mmHg ($P < 0.001$). In the standard treatment group, 100 patients (42.5%) required pharmacological intervention to maintain SBP below 140 mmHg, with an annual incidence rate of 14.8%.

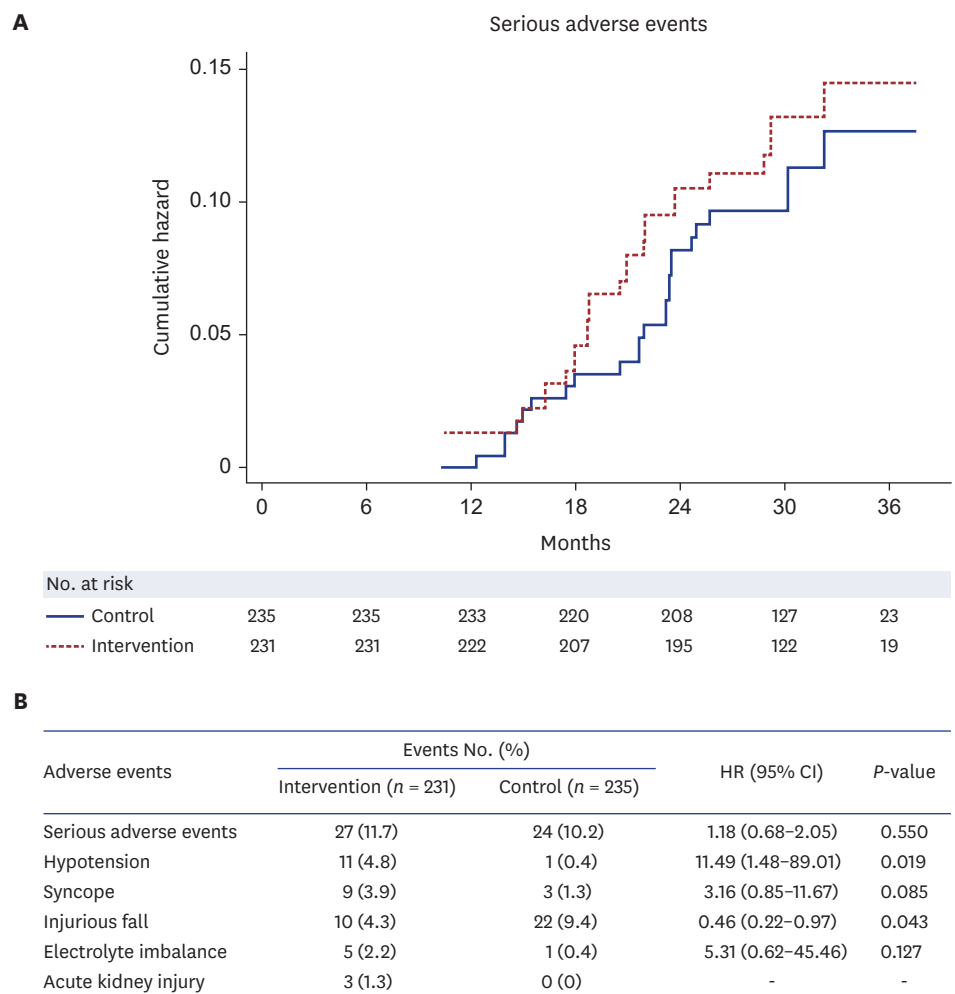


Fig. 4. Cox regression analysis for adverse events. (A) The cumulative hazard of serious adverse events in participants receiving intensive vs. standard antihypertensive treatment over time. Serious adverse events were defined as adverse events that were fatal, life-threatening, resulted in clinically significant or persistent disability, required or prolonged hospitalization, or were judged by the investigator to represent a clinically significant hazard or harm. (B) The incidence and Cox regression analysis of adverse events, including hypotension, syncopal, injurious falls, electrolyte abnormalities, and AKI. Hypotension was defined as a systolic blood pressure below 100 mmHg, leading to clinical symptoms significant enough to require a physician consultation. Syncopal was identified when patients experienced a sudden, temporary loss of consciousness due to transient cerebral hypoperfusion, followed by spontaneous recovery, as self-reported by participants and confirmed by a physician. Injurious falls were classified as falls resulting in an emergency department visit or hospitalization. Electrolyte imbalance was recognized when sodium, potassium, calcium, magnesium, or phosphorus levels fell outside clinically accepted ranges, as documented by a physician during checkups or when requiring medical evaluation based on the patient's condition. AKI was recorded if it was listed as a diagnosis in the hospital discharge summary and deemed by the physician among the top 3 reasons for admission or continued hospitalization. HR, hazard ratio; CI, confidence interval; AKI, acute kidney injury.

DISCUSSION

The PRINT-TAHA9 trial, although not reaching the ultimate sample size, demonstrated that pharmacologically lowering SBP to below 130 mmHg in healthy individuals with high-normal BP and an intermediate to high cardiovascular risk (ASCVD risk $\geq 7.5\%$) may reduce the likelihood of MACE without altering the incidence of SAE. The results of this trial support a lower threshold for initiating pharmacotherapy in patients with high-normal BP and provide insights for future trials in this area.

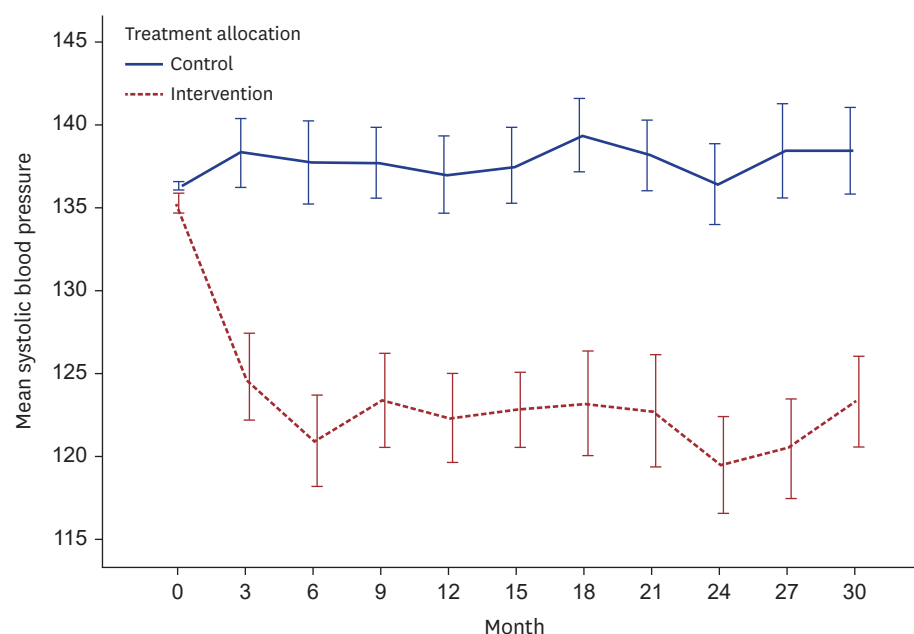


Fig. 5. Systolic and diastolic blood pressure in the 2 treatment groups throughout the follow-up. The systolic blood pressure target in the intervention group was below 130 mmHg, and the target in the standard treatment group was less than 140 mmHg. 'I' bars represent 95% confidence intervals.

The BP range of this study's target population has been described using various terms over time, including high-normal BP and prehypertension in earlier guidelines, and more recently updated to elevated BP and Stage 1 hypertension in the European and American guidelines, respectively [2-4]. The ongoing debate extends beyond classification and terminology to the optimal treatment approach for individuals within this range. Currently, ACC/AHA guidelines recommend pharmacological treatment for patients with SBP ≥ 130 mmHg and an ASCVD risk above 10% [14]. However, this recommendation has been criticized for lacking direct evidence and instead relies on secondary and meta-analyses [16]. A meta-analysis of 48 randomized trials found that BP-lowering pharmacotherapy in patients with SBP between 130–140 mmHg reduced the risk of MACE (HR, 0.89; 95% CI, 0.81–0.97), aligning with our findings [21]. It also revealed that among the components of MACE, BP-lowering treatment is effective in preventing stroke (HR, 0.73; 95% CI, 0.60–0.89) and HF (HR, 0.75; 95% CI, 0.62–0.91). However, no significant benefit was observed in those with pre-existing CVD (HR, 0.99; 95% CI, 0.92–1.07). These results may be attributed to the lack of consideration of CVD risk and DBP levels in the analysis, emphasizing the need for a risk-based approach in this target population. Another meta-analysis, focusing on individuals with SBP of 120–140 mmHg and DBP below 90 mmHg, revealed that BP-lowering treatment effectively prevents stroke and coronary heart disease, but only in high-risk patients [22]. However, these results included individuals with a history of CVD, potentially influencing the outcomes. Due to our study's limited sample size, we could not demonstrate a statistically significant preventive effect of pharmacotherapy on individual MACE components, though our analysis showed a trend toward benefit. Future larger trials are needed to confirm these findings and to explore potential differences in treatment effects between intermediate- and high-risk individuals by subgroup analysis.

The conclusion regarding the benefits of pharmacotherapy should consider not only its impact on clinical outcomes but also the occurrence of adverse events in the intervention

versus control groups. SAE, defined as those leading to disability or hospitalization, were similar between groups. Hypotension was more frequent in the intervention group, which is expected when treating individuals with high-normal BP. However, after adjusting for covariates, this difference was insignificant, suggesting that other confounders, such as lower baseline SBP and ASCVD risk in the intervention arm, were at play. Interestingly, injurious falls were higher in the control group, but this effect disappeared after adjustment, potentially due to baseline differences such as the control group's older age. After adjusting for baseline variables, the only significant adverse event in the intervention group was syncope (aHR, 4.43; 95% CI, 1.06–18.44; $P = 0.041$), though this result was borderline significant. Larger trials are needed to further evaluate this potential side effect. Other notable baseline variables include sex and smoking distribution. Females were a minority in both groups, reflecting their generally lower cardiovascular risk in the absence of comorbidities compared to males. Additionally, while most participants were never or former smokers, the control group had a significantly higher proportion of current smokers, contributing to its higher ASCVD risk. Although analyses were adjusted for all baseline characteristics, the lower SBP, younger age, higher creatinine levels, lower prevalence of current smoking, and consequently lower ASCVD risk score in the intervention group compared to the control group at the baseline should be considered when interpreting the results of both primary outcome and adverse events analyses.

The future of BP management will rely on individualized decision-making that considers each patient's unique risk factors. A risk-based approach is crucial in guiding this transition, and determining the optimal risk threshold for initiating pharmacotherapy remains a key element. Various cardiovascular risk calculators and cut-offs have been introduced based on different study designs and objectives. For example, a secondary analysis of the SPRINT trial categorized 4,298 patients based on their 10-year Framingham risk score: low risk ($< 10\%$), intermediate risk ($10\text{--}15\%$), and high risk ($\geq 15\%$). Intensive treatment significantly reduced primary outcome events in high-risk and intermediate-risk patients but not in low-risk individuals [15]. Another secondary analysis of SPRINT examined 289 high-risk, prehypertensive patients without prior CVD who were not on antihypertensive medications. The primary outcome event rate was lower in the intensive-treatment group (0.74% per year) compared to the standard treatment group (1.61% per year) (HR, 0.19; $P = 0.045$), supporting the benefits of intensive SBP reduction in high-risk prehypertensive patients [18]. Although these findings suggest that intensive SBP reduction may be beneficial for primary prevention in those with a cardiovascular risk above 10%, our post-hoc analysis of the SPRINT trial revealed that a 7.5% risk threshold for initiating pharmacotherapy is more appropriate [19]. These findings showed that even individuals with an ASCVD risk score as low as 7.5% benefit from antihypertensive pharmacotherapy. Moreover, current guidelines for initiating statins in primary cardiovascular prevention also use the 7.5% threshold. These considerations, along with the broader availability and familiarity of the ASCVD risk score (also known as the Pooled Cohort Equation) among practitioners, led us to choose it over other cardiovascular risk assessment tools, such as the Framingham risk score. The PRINT-TAHA9 results supported selecting a 7.5% ASCVD risk threshold, confirming its validity for initiating pharmacotherapy in individuals with high-normal BP. In planning the trial, the mentioned SPRINT secondary analyses, published reports of relatively high MACE incidence in Iran [23,24], and the tendency of the ASCVD score to classify a larger proportion of Iranians as intermediate/high risk [25] was the basis for anticipated event rate in sample size estimation (1% per year in the intervention and 2% per year in the control group). The observed event rates in the PRINT-TAHA9 were 1.57% per year in the intervention arm

and 4.16% per year in the control arm. The discrepancies between anticipated and observed event rates across populations should be carefully considered when interpreting results and designing future studies. Notably, our findings showed that despite the similar event rate in the intensive BP control group compared to prior trials, the event rate in our control group exceeded twice the event rates observed in the control groups of the SPRINT [26] and the ACCORD [27] study (which involved diabetic patients), which were conducted in Western populations. This may reflect the higher prevalence of cardiovascular risk factors, less healthy diets, and more sedentary lifestyles in our population [24,28]. These findings highlight not only the urgent need for enhanced primary-prevention strategies, such as community-based education, promotion of physical activity, and early interventions in childhood and schools, but also the importance of developing a region-specific cardiovascular risk calculator tailored to the study population.

In addition to reducing the risk of MACE, pharmacotherapy in prehypertensive patients prevents progression to hypertension, which is associated with significant morbidity and mortality. In our study, throughout the 3-year follow-up, 48.6% of participants in the control group transitioned from high-normal BP to a hypertensive state, necessitating ongoing antihypertensive therapy, with an annual incidence rate of 11.49%. These findings align with the TROPY trial, where Julius et al. [29] reported that nearly two-thirds of untreated prehypertensive patients developed hypertension over 4 years, and treatment with candesartan resulted in a 66.3% relative risk reduction for preventing hypertension. In the PHARAO study, Lüders and colleagues [30] reported an annual incidence rate of 18.8% for the progression from high-normal BP to hypertension, and treatment with Ramipril reduced this rate to 13%, representing a relative risk reduction of 34.4%. Moreover, in the PREVER-Prevention trial, Fuchs et al. [31] demonstrated that treatment with thiazide diuretics significantly reduced the annual incidence of hypertension development from 19.5% to 11.7%, with an HR of 0.56. These trials, alongside other studies [32], have demonstrated a significant delay in the onset of hypertension during, but not after, antihypertensive drug treatment in patients with high-normal BP. Nevertheless, the cost-effectiveness of such interventions and their ability to prevent cardiovascular events have not been clearly established. Among these trials focused on hypertension prevention as a primary endpoint, only the PHARAO study included MACE outcomes as secondary endpoints. These secondary outcomes encompassed a reduction in cerebrovascular and cardiovascular events, such as stroke, transient ischemic attack, intracerebral bleeding, MI, new onset HF requiring hospitalization, and deaths, with none showing a statistically significant difference between the groups. The lack of clinical benefit in the PHARAO study may be attributed to its design, as a fixed dose of ramipril was administered to all patients without dose adjustments to maintain SBP within a specific range. In contrast, the SPRINT trial employed dynamic medication adjustments to consistently maintain SBP below 130 mmHg, likely contributing to its positive outcomes. Considering these findings and our study results, which demonstrate the prevention of both MACE and hypertension onset through pharmacotherapy, we believe that pharmacotherapy has a strong preventive effect on morbidity and mortality, both directly and indirectly related to high BP.

Considering our findings and the fact that patients with an ASCVD risk above 7.5% and an low-density lipoprotein level above 70 mg/mL require treatment with high-dose statins, a cut-off value of 7.5% may serve as a consideration for revisions to the ACC/AHA preventive guidelines for both hypertension and hyperlipidemia treatment, potentially simplifying the recommendations [3]. While the European Society of Cardiology did not recommend

treating high-normal BP in their 2018 guidelines, the 2024 update revised this stance, now recommending pharmacological treatment for high-normal BP in patients with a 10-year ASCVD risk of $\geq 10\%$, especially if lifestyle modifications over 3 months fail to achieve adequate control [2,33]. Moreover, the target BP for hypertension treatment has been revised to below 130/80 mmHg. The results of the PRINT-TAHA9 trial highlight that even without a primary lifestyle modification period, a pharmacotherapy approach may be beneficial, supporting the effectiveness of intensive BP control in reducing cardiovascular risk across a broader population.

Our study faces important limitations. Despite the ideal sample size initially calculated to be approximately 1,600 participants, the limitations of a single-center study design necessitated a multi-phase recruitment strategy, aiming to include 400–500 participants in each phase. Analyzing less than one-third of the ideal sample size significantly reduced the statistical power of our study and resulted in wide CIs, limiting the strength of our conclusions. As such, this trial should be considered primarily hypothesis-generating and intended to provide insights for future randomized studies. Additionally, identifying healthy individuals within the strict BP range of prehypertension (SBP 130–140 mmHg, DBP < 90 mmHg) with an ASCVD risk score greater than 7.5% and without any comorbidities (including diabetes and CVD) or prior medication use (e.g., statins), proved highly challenging. To address these challenges, we leveraged the resources and facilities of Shiraz University of Medical Sciences as the funder of the study and a leading medical university in Iran. The university's task force for non-communicable diseases organizes prevention campaigns in public areas, such as walking paths near university facilities, to screen individuals for conditions like hypertension and diabetes. By collaborating with these campaigns, we integrated our screening process and screen 14,562 individuals to identify eligible participants. Despite these extensive efforts, only 466 participants were included in the final analysis (3% of the screened population), representing only one-third of the initially planned sample size. Due to these difficulties in recruitment and resource constraints, the TMC decided to terminate the trial prematurely. Another limitation of our study is the use of the ACC/AHA ASCVD risk calculator, though widely accepted in our clinical practice, has not been specifically designed, validated, or calibrated for the Iranian population and may misestimate the true cardiovascular risk [34]. Although we reached the clinical significance endpoint, our study serves as an important pilot study for future multicenter trials in diverse populations to generate sufficient evidence for a consensus statement. This would help address the limitations of the single-center design, some wide CIs, and borderline levels of significance observed in our study.

CONCLUSIONS

In healthy prehypertensive individuals without underlying disease, early pharmacological reduction of BP to normal levels (SBP below 130 mmHg) at an ASCVD risk above 7.5% may offer greater benefits for the primary prevention of fatal and nonfatal major cardiovascular events than deferring treatment until risk further increase.

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SUPPLEMENTARY MATERIALS

Supplementary Table 1

Details of adjusted Cox regression analysis for primary composite endpoint: cardiovascular death, myocardial infarction, stroke, and heart failure

Supplementary Table 2

Details of adjusted Cox regression analysis for secondary composite endpoint: cardiovascular death, myocardial infarction, and stroke

Supplementary Table 3

Details of adjusted Cox regression analysis for secondary endpoint: cardiovascular death

Supplementary Table 4

Details of adjusted Cox regression analysis for secondary endpoint: myocardial infarction

Supplementary Table 5

Details of adjusted Cox regression analysis for secondary endpoint: stroke

Supplementary Table 6

Details of adjusted Cox regression analysis for secondary endpoint: heart failure

Supplementary Table 7

Summary of Cox regression adjusted models for adverse events

Supplementary Table 8

Details of adjusted Cox regression analysis for serious adverse events

Supplementary Table 9

Details of adjusted Cox regression analysis for hypotension

Supplementary Table 10

Details of adjusted Cox regression analysis for syncope

Supplementary Table 11

Details of adjusted Cox regression analysis for injurious fall

Supplementary Table 12

Details of adjusted Cox regression analysis for electrolyte imbalance

Supplementary Table 13

Details of adjusted Cox regression analysis for acute kidney injury

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