Lowering systolic blood pressure to less than 120 mm Hg versus less than 140 mm Hg in patients with high cardiovascular risk with and without diabetes or previous stroke: an open-label, blinded-outcome, randomised trial

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Summary

Background Uncertainty exists about whether lowering systolic blood pressure to less than 120 mm Hg is superior to that of less than 140 mm Hg, particularly in patients with diabetes and patients with previous stroke.

Methods In this open-label, blinded-outcome, randomised controlled trial, participants with high cardiovascular risk were enrolled from 116 hospitals or communities in China. We used minimised randomisation to assign participants to intensive treatment targeting standard office systolic blood pressure of less than 120 mm Hg or standard treatment targeting less than 140 mm Hg. The primary outcome was a composite of myocardial infarction, revascularisation, hospitalisation for heart failure, stroke, or death from cardiovascular causes, assessed by the intention-to-treat principle. This trial was registered with ClinicalTrials.gov, NCT04030234.

Findings Between Sept 17, 2019, and July 13, 2020, 11 255 participants (4359 with diabetes and 3022 with previous stroke) were assigned to intensive treatment (n=5624) or standard treatment (n=5631). Their mean age was 64·6 years (SD 7·1). The mean systolic blood pressure throughout the follow-up (except the first 3 months of titration) was 119·1 mm Hg (SD 11·1) in the intensive treatment group and 134·8 mm Hg (10·5) in the standard treatment group. During a median of 3·4 years of follow-up, the primary outcome event occurred in 547 (9·7%) participants in the intensive treatment group and 623 (11·1%) in the standard treatment group (hazard ratio [HR] 0·88, 95% CI 0·78–0·99; p=0·028). There was no heterogeneity of effects by diabetes status, duration of diabetes, or history of stroke. Serious adverse events of syncope occurred more frequently in the intensive treatment group (24 [0·4%] of 5624) than in standard treatment group (eight [0·1%] of 5631; HR 3·00, 95% CI 1·35–6·68). There was no significant between-group difference in the serious adverse events of hypotension, electrolyte abnormality, injurious fall, or acute kidney injury.

Interpretation For hypertensive patients at high cardiovascular risk, regardless of the status of diabetes or history of stroke, the treatment strategy of targeting systolic blood pressure of less than 120 mm Hg, as compared with that of less than 140 mm Hg, prevents major vascular events, with minor excess risk.

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Introduction

Elevated blood pressure is the largest modifiable contributor for cardiovascular disease and premature death worldwide.[1,2] Lowering blood pressure is one of the most effective treatments to prevent cardiovascular events.[3] Reducing systolic blood pressure to less than 140 mm Hg is well established and considered as the standard blood pressure-lowering treatment.[4–6]

Uncertainty exists regarding whether systolic blood pressure of less than 120 mm Hg is a better target than lowering blood pressure to less than 140 mm Hg, due to limited and conflicting evidence from randomised controlled trials. SPRINT is the only trial that proved targeting systolic blood pressure of less than 120 mm Hg was more effective in reducing the risk of major vascular events than standard treatment in patients with high cardiovascular risk and without diabetes or stroke.[7] The ACCORD trial compared the two systolic blood pressure targets in patients with diabetes and the RESPECT trial in those with history of stroke, and both obtained non-significant results.[8,9] The different results, in SPRINT, ACCORD, and RESPECT, might be due to the statistical underpower of ACCORD and RESPECT, the confounding effect of factorial design, the interactions by diabetes status and history of stroke, or different blood pressure measurements. SPRINT used the unattended blood pressure measurement technique which presumably led to lower blood pressure values than those obtained in other trials.[6] The meta-analysis on individual participant-level data showed a 5 mm Hg reduction in systolic blood

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For Mandarin translation of the abstract see Online for appendix 2

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See Online for appendix 1

Research in context

Evidence before this study

We searched PubMed using the search terms ((Intensive blood pressure[Text Word]) or (Systolic blood pressure target <120 mm Hg[Text Word])) and ((Cardiovascular Diseases[MeSH Terms]) or (Myocardial infarction[MeSH Terms]) or (Stroke[MeSH Terms]) or (Revascularization[Text Word]) or (Heart failure[MeSH Terms]) or (Death[MeSH Terms])) and (Randomized Controlled Trial[Publication Type]) for randomised clinical trials published between database inception and Jan 9, 2024, with no language restrictions. We identified three randomised controlled trials that compared the effects of targeting systolic blood pressure of less than 120 mm Hg with that of less than 140 mm Hg on major vascular events, which obtained conflicting results. The ACCORD trial included diabetic patients and the RESPECT trial included patients with previous stroke; both used standard office blood pressure measurement and got non-significant results. In contrast, SPRINT included patients with high cardiovascular risk without diabetes or stroke and showed a 25% risk reduction. Since SPRINT used unattended office blood pressure measurement, there are arguments that this measurement presumably led to lower blood pressure values than those obtained in other trials. Thus, uncertainty exists about whether targeting standard office systolic blood pressure of less than 120 mm Hg is superior to that of less than 140 mm Hg, and whether patients with diabetes or previous stroke should take different blood pressure targets.

Added value of this study

To the best of our knowledge, this is the first randomised trial to assess the effects of lowering standard office systolic blood pressure to less than 120 mm Hg on major vascular events among a population with high cardiovascular risk, regardless of history of diabetes or stroke. This is also the largest randomised controlled trial to assess the effects of lowering systolic blood pressure to less than 120 mm Hg on major vascular events. We provide evidence that targeting standard office systolic blood pressure of less than 120 mm Hg prevents more major vascular events than that of less than 140 mm Hg. Our study further showed no heterogeneity of effects by diabetes status, duration of diabetes, or history of stroke. In addition, we observed fewer acute harm events than previous trials.

Implications of all the available evidence

The treatment strategy of targeting standard office systolic blood pressure of less than 120 mm Hg prevented more major vascular events compared with the treatment targeting less than 140 mm Hg, with minor excess risk. A lower blood pressure target (ie, standard office systolic blood pressure <120 mm Hg) should be considered for patients with high cardiovascular risk, regardless of diabetes status or history of stroke.

pressure lowered the risk of major cardiovascular events, even in participants with baseline systolic blood pressure of less than 120 mm Hg.[10] This beneficial effect was weaker in participants with diabetes than those without.[11] However, the proportions of participants with baseline systolic blood pressure of less than 120 mm Hg were very small in both analyses. In addition, there is scarce data about harms of lowering systolic blood pressure to less than 120 mm Hg. Given the above uncertain benefit and potential harm, most current clinical guidelines do not recommend lowering systolic blood pressure to less than 120 mm Hg.[4–6,12]

Here, we report the findings of the Effects of Intensive Systolic Blood Pressure Lowering Treatment in Reducing Risk of Vascular Events (ESPRIT) trial, which compared the efficacy and safety of intensive blood pressure-lowering treatment targeting systolic blood pressure of less than 120 mm Hg with standard treatment for over 3 years among more than 11 000 participants with high cardiovascular risk and with or without diabetes or previous stroke. We used the standard office blood pressure measurements as those used in ACCORD, RESPECT, and routine clinical practice.

Methods

Study design

We conducted an open-label, blinded-outcome, randomised controlled trial at 116 sites (103 hospitals and 13 community medical centres) in China. Details of the trial rationale and design have been reported previously.[13] The trial was designed and led scientifically by a steering committee. The central ethics committee at Fuwai Hospital and ethics committee of each participating site approved the trial. The trial protocol and the statistical analysis plan are available in appendix 1. This trial is registered with ClinicalTrials.gov, NCT04030234.

Participants

Participants who were aged at least 50 years and with 130–80 mm Hg were considered to be eligible if they had high cardiovascular risk (ie, established cardiovascular disease or at least two major cardiovascular risk factors). Major cardiovascular risk factors were aged 60 years or older for men or 65 years or older for women, diabetes, dyslipidemia, and current smoker. Major exclusion criteria were known secondary cause of hypertension, one-minute standing systolic blood pressure of less than 110 mm Hg, scheduled revascularisation within the next 6 months, left ventricular ejection fraction of less than 35%, or estimated glomerular filtration rate (eGFR) of less than 45 mL/min per 1·73 m². Details of the trial inclusion and exclusion criteria are listed in appendix 1 (pp 7–8). Participants were recruited by clinical records searching or local advertisement. Sex was recorded according to the national identity card. All participants provided written informed consent.

Randomisation and masking

Eligible participants were allocated to either intensive treatment (systolic blood pressure target <120 mm Hg) or standard treatment (systolic blood pressure target <140 mm Hg) in a 1:1 ratio using a minimised randomisation programme with site stratification. We used central randomisation via an online system. All data in the trial were processed electronically. The local investigators used an internet-based application for performing tasks (including entering participant data at study visits, minimised randomisation, distribution of appropriate study treatment, and local trial administration). Site investigators and participants were aware of the trial-group assignments, but statisticians and event adjudicators were blinded to the treatment allocation.

Procedures

After randomisation, participants in both groups were followed up at months 1, 2, and 3 and then every 3 months. Additional visits could be scheduled if necessary for blood pressure lowering titration or safety monitoring. Investigators adjusted participants' antihypertensive medications based on standard office blood pressure measurement and study-group assignment, with the guidance by unified treatment algorithms (appendix 1 pp 14–15). At each office visit, blood pressure was measured by a trained investigator using an electronic blood pressure monitor (Omron HBP-1100; Omron Corp, Dalian, China) which was connected to a computer, so that the blood pressure values were transferred into the electronic case report to avoid recording errors. Each participant was measured three times with an interval of 1 min according to the standard procedure after participant was seated and had a quiet rest for at least 5 min. The mean value of the three measurements was used as the blood pressure level.

To optimise adherence to medication, ten types of free drugs were provided, which cover the five classes of evidence-based antihypertensive medications (ie, angiotensin converting enzyme inhibitors, angiotensin receptor blockers, calcium channel blockers, thiazide-type diuretics, and β blockers; appendix 1 p 20). Other antihypertensive medications can also be used but were not provided by the trial.

Blood electrolytes and creatinine were monitored at a local laboratory at months 1, 2, 3, and 6 and every 6 months thereafter. At each follow-up visit, we collected the information about antihypertensive medication adherence, concomitant medication use, outcome events, and serious adverse events. We also collected other adverse events that could be related to the study intervention, including acute kidney injury, emergency room visits for hypotension, syncope, injurious falls, and electrolyte abnormalities.

When participants could not come to the study clinic in person, we followed them up by telephone, and asked them to maintain the previous prescription. Telephone follow-up affected up-titration rather than stable antihypertensive treatment. When the COVID-19 pandemic broke out in January, 2020, we were conducting a rapid recruitment; thus many participants were in the titration period (the first 3 months after randomisation). Although none of the sites were locked down, some sites limited the number of face-to-face interviews, and many participants became reluctant to go to study clinics. This situation lasted until early April, 2020, when all sites returned to the normal status. At months 1, 2, and 3, 16·1%, 29·3%, and 29·6% of participants in the intensive treatment group and 15·7%, 29·6%, and 29·4% in the standard treatment group were followed up by telephone (appendix 1 p 21). As reported in our published protocol, the COVID-19 pandemic interrupted titration and caused a 3-month delay of reaching the blood pressure target in the intensive treatment group because participants in the intensive treatment group needed a longer time to achieve target than those in the standard treatment group. Therefore, the effective follow-up period was 3 months shorter than that observed.[13]

Outcomes

The primary outcome was major vascular events (ie, a composite of myocardial infarction, coronary or non-coronary revascularisation, hospitalisation or emergency room visit for heart failure, stroke, or death from cardiovascular causes). The prespecified secondary outcomes included components of the primary composite outcome, death from any cause, a composite of the primary outcome or death from any cause, and composite kidney outcome (ie, end-stage renal disease, a sustained decline in eGFR to <10 mL/min per 1·73 m², death from renal causes, or a sustained decline ≥40% in eGFR from baseline). Sustained decline in eGFR referred to the measurement during two planned consecutive follow-ups; or the last planned follow-up or the last planned follow-up before death (or withdrawal of informed consent). Noticing that 25 (27·5%) of 91 participants who experienced a kidney outcome of declined eGFR in two consecutive follow-ups in the intensive treatment group and 12 (29·3%) of 41 in the standard treatment group, had their eGFR returned to at least 60 mL/min per 1·73 m² at the last follow-up, we did a post-hoc sensitivity analysis with sustained decline in eGFR referred to the measurement during two planned consecutive follow-up and remained decline at the last follow-up.

Other secondary outcomes (cognitive outcome and fundus vascular outcome) will be reported separately in other manuscripts. Prespecified subgroups for the primary outcome included diabetes status, duration of diabetes, history of stroke, and other characteristics of interest (appendix 1 p 13). We further conducted two subgroup analyses of previous cardiovascular disease and eGFR of less than 60 mL/min per 1·73 m², which were not prespecified.

All events of death, myocardial infarction, coronary or non-coronary revascularisation, hospitalisation or emergency room visit for heart failure, stroke, end-stage renal disease, and acute kidney injury were centrally adjudicated by members of the clinical event committee who were unaware of the randomisation assignment according to the prespecified criteria (appendix 1 pp 9–12). In addition, angina and transient ischaemic attack were also adjudicated by the clinical event committee to avoid missing myocardial infarction, coronary revascularisation, and stroke.

Statistical analysis

The original and modified sample sizes were reported previously.[13] Briefly, with an annual event rate of 3·4% in the standard treatment group, and a loss to follow-up of 2% per year during 3 years, we estimated that at least 10 300 participants would provide 90% power at two-sided p=0·05 to detect a 20% difference in the primary outcome risk between groups. No interim efficacy analysis was conducted. An independent data monitoring committee regularly reviewed the safety data during the trial.

All analyses were based on the intention-to-treat (ITT) principle with Kaplan–Meier estimate for the time to the primary outcome. The Cox proportional hazards regression was applied for comparing the time to the first occurrence of the outcome between the two treatment groups, with estimation of hazard ratios (HR) and 95% CIs. Although the proportional-hazards assumption assessed by Schoenfeld residuals' method was not met for the primary outcome (p=0·0082) and the composite of primary outcome or death from any cause (p=0·0049; appendix 1 p 22), the absolute difference of cumulative primary outcome rate between groups indicated a minor and non-significant cross (appendix 1 p 23). Therefore, we first used the prespecified analysis of Cox proportional hazards to provide a more conservative overall evaluation of the efficacy, and further did post-hoc analysis to estimate the HRs according to the years of follow-up. The analysis for major vascular events without revascularisation was a post-hoc analysis.

We did further sensitivity analysis. For the primary outcome, we used the Fine–Gray model to account for the competing risk of non-cardiovascular death as a prespecified sensitivity analysis. We also used the Fine–Gray model to do post-hoc sensitivity analysis accounting for competing risk of non-cardiovascular death for death from cardiovascular causes, and all-cause death for other components of the primary outcome. We also did post-hoc analysis treating 16 deaths from undetermined causes as cardiovascular death.

For the secondary outcomes, the CIs were not adjusted for multiplicity and should not be used in place of a hypothesis test. We examined the consistency of the intervention effect on the primary outcome among subgroups using statistical tests of interaction between the treatment effect and the subgroup within the Cox models. A two-sided p value of less than 0·05 was considered to indicate significance. All analyses were performed in SAS (version 9.4) and R (version 4.1.1).

Role of the funding source

The funders of the study had no role in study design, data collection, data analysis, data interpretation, or writing of the report.

Results

Between Sept 17, 2019, and July 13, 2020, a total of 11 255 participants were randomly assigned. Mean age was 64·6 years (SD 7·1), 4650 (41·3%) were women and 6605 (58·7%) were men, and a history of diabetes was reported by 4359 (38·7%) of the participants, coronary heart disease by 3252 (28·9%), and stroke by 3022 (26·9%; table 1). The median duration of follow-up was 3·4 years (IQR 3·0–3·4), 162 discontinued study intervention, and only six participants were lost to follow-up (figure 1).

The mean baseline systolic blood pressure was 146·8 mm Hg (SD 10·5) in the intensive treatment group and 147·0 mm Hg (SD 10·7) in the standard treatment group. After randomisation, both groups achieved sustained blood pressure reduction. Throughout the follow-up (except the first 3 months for titration), the mean systolic blood pressure was 119·1 mm Hg (SD 11·1) in the intensive treatment group and 134·8 mm Hg (SD 10·5) in the standard treatment group. The intensive treatment group achieved a stable systolic blood pressure of 120 mm Hg after 9 months of follow-up, and the standard treatment group achieved 135 mm Hg after 2 months (figure 2, appendix 1 pp 24–25). The diastolic blood pressure results are shown in appendix 1 (pp 16, 26–27). The intensive treatment group used more antihypertensive medications (2·7 [SD 1·0] *vs* 2·0 [SD 0·9]) than the standard treatment group (figure 2). Medications used in each group are shown in appendix 1 (p 28). At the final follow-up, 2323 (42·5%) of 5461 participants in the intensive treatment group and 837 (15·4%) of 5425 of those in the standard treatment group reported use of diuretics.

The primary outcome event occurred in 547 (9·7%) of 5624 participants from the intensive treatment group and 623 of 5631 (11·1%) from the standard treatment group (HR 0·88; 95% CI 0·78–0·99; p=0·028) (figures 3A and 4). In the exploratory analyses, the risk difference was observed after 1 year and the HR for the period of longer than 1 year was 0·78 (95% CI 0·67–0·90; figure 3B).

The individual components of primary outcome showed differential effects (figure 4). Death from cardiovascular causes occurred in 59 (1·1%) participants from the intensive treatment group and in 97 (1·7%) from the standard treatment group (HR 0·61; 95% CI 0·44–0·84). The between-group differences of myocardial infarction, heart failure, and stroke were similar with the primary outcome but not significant. However, the rates of

	Intensive treatment (n=5624)	Standard treatment (n=5631)
Age, years		
Mean	64·6 (7·1)	64·6 (7·2)
Distribution		
<60	1395 (24·8%)	1412 (25·1%)
60–69	2864 (50·9%)	2835 (50·4%)
≥70	1365 (24·3%)	1384 (24·6%)
Sex		
Female	2327 (41·4%)	2323 (41·3%)
Male	3297 (58·6%)	3308 (58·8%)
Region*		
Northern	4465 (79·4%)	4466 (79·3%)
Southern	1159 (20·6%)	1165 (20·7%)
Smoking status		
Current smoker	1739 (30·9%)	1777 (31·6%)
Former smoker	1084 (19·3%)	1086 (19·3%)
Never smoker	2801 (49·8%)	2768 (49·2%)
Alcohol consumption		
Not drinking	3831 (68·1%)	3847 (68·3%)
Moderate drinking	1148 (20·4%)	1107 (19·7%)
Excessive drinking†	645 (11·5%)	677 (12·0%)
BMI, kg/m²		
Mean	26·3 (3·3)	26·3 (3·3)
Distribution		
<24	1337 (23·8%)	1368 (24·3%)
≥24 to <28	2741 (48·7%)	2688 (47·7%)
≥28	1540 (27·4%)	1568 (27·9%)
Missing data	6 (0·1%)	7 (0·1%)
Time from hypertension diagnosis to randomisation visit, years		
Median,	10·3 (5·0–18·6)	10·4 (5·0–19·0)
Distribution		
<5	1400 (24·9%)	1347 (23·9%)
≥5 to <10	1133 (20·2%)	1118 (19·9%)
≥10 to <20	1898 (33·8%)	1932 (34·3%)
≥20	1193 (21·2%)	1234 (21·9%)
Diabetes‡	2180 (38·8%)	2179 (38·7%)
Time from diabetes diagnosis to randomisation visit, years		
Median	6·9 (2·7–12·2)	7·0 (3·0–13·0)
Distribution		
<4	725 (33·3%)	684 (31·4%)
≥4 to <10	654 (30·0%)	658 (30·2%)
≥10	801 (36·7%)	837 (38·4%)
Previous disease‡		
Coronary heart disease§	1632 (29·0%)	1620 (28·8%)
Stroke	1520 (27·0%)	1502 (26·7%)
Peripheral artery disease¶	44 (0·8%)	28 (0·5%)
Abdominal aortic aneurysm‖	3 (0·1%)	4 (0·1%)
Atrial fibrillation	113 (2·0%)	112 (2·0%)
Systolic blood pressure, mm Hg		
Mean	146·8 (10·5)	147·0 (10·7)
(Continued from previous column)		
Distribution		
<141	1871 (33·3%)	1872 (33·2%)
141–50	1833 (32·6%)	1791 (31·8%)
>150	1920 (34·1%)	1968 (35·0%)
Diastolic blood pressure, mm Hg		
Mean	82·8 (10·1)	82·9 (10·5)
Distribution		
<78	1715 (30·5%)	1693 (30·1%)
78–86	1899 (33·8%)	1851 (32·9%)
>86	2010 (35·7%)	2087 (37·1%)
eGFR, mL/min per 1·73 m²**		
Mean	83·2 (13·6)	83·5 (13·7)
<60	337 (6·0%)	340 (6·0%)
Missing data	23 (0·4%)	11 (0·2%)
Total cholesterol, mmol/L††		
Mean	4·0 (1·2)	4·0 (1·2)
Missing data	23 (0·4%)	11 (0·2%)
LDL cholesterol, mmol/L††		
Mean	2·3 (0·8)	2·3 (0·8)
Missing data	23 (0·4%)	11 (0·2%)
HDL cholesterol, mmol/L††		
Mean	0·9 (0·3)	0·9 (0·3)
Missing data	23 (0·4%)	11 (0·2%)
Total triglycerides, mmol/L††		
Mean	1·7 (1·1)	1·7 (1·1)
Missing data	23 (0·4%)	11 (0·2%)
Number of antihypertensive medications		
0	149 (2·7%)	149 (2·7%)
1	2437 (43·3%)	2451 (43·5%)
2	2154 (38·3%)	2111 (37·5%)
3	761 (13·5%)	787 (14·0%)
≥4	123 (2·2%)	133 (2·4%)
Statin use‡‡	2623 (46·6%)	2591 (46·0%)
Aspirin use	2419 (43·0%)	2398 (42·6%)

Data are n (%), mean (SD), or median (IQR). Percentages may not total 100 because of rounding. eGFR=estimated glomerular filtration rate. *Regions were divided by Qinling Mountains–Huaihe River line. †Excessive drinking was defined as drinking ≥15 g of alcohol (as ethanol) per day. ‡Based on the self-reported history. §Coronary heart disease was defined as previous myocardial infarction, percutaneous coronary intervention, coronary artery bypass grafting, at least a 50% diameter stenosis of a coronary artery, or chest pain with evidence of myocardial ischaemia. ¶Abdominal aortic aneurysm was defined as abdominal aortic aneurysm of at least 5 cm with repair. ‖Peripheral artery disease was defined as carotid endarterectomy, carotid stenting, peripheral artery disease with revascularisation. **Estimated GFR was based on central laboratory results; it differs from that reported in the published protocol which was based on local laboratory results. ††Lipids were based on central laboratory results. ‡‡Differs from the published protocol, in which a small portion of participants using amlodipine atorvastatin were not counted as statin use.

Table 1: **Characteristics of the participants at baseline**

coronary revascularisation and non-coronary revascularisation were almost the same between groups. The absolute risk differences of primary outcome and its

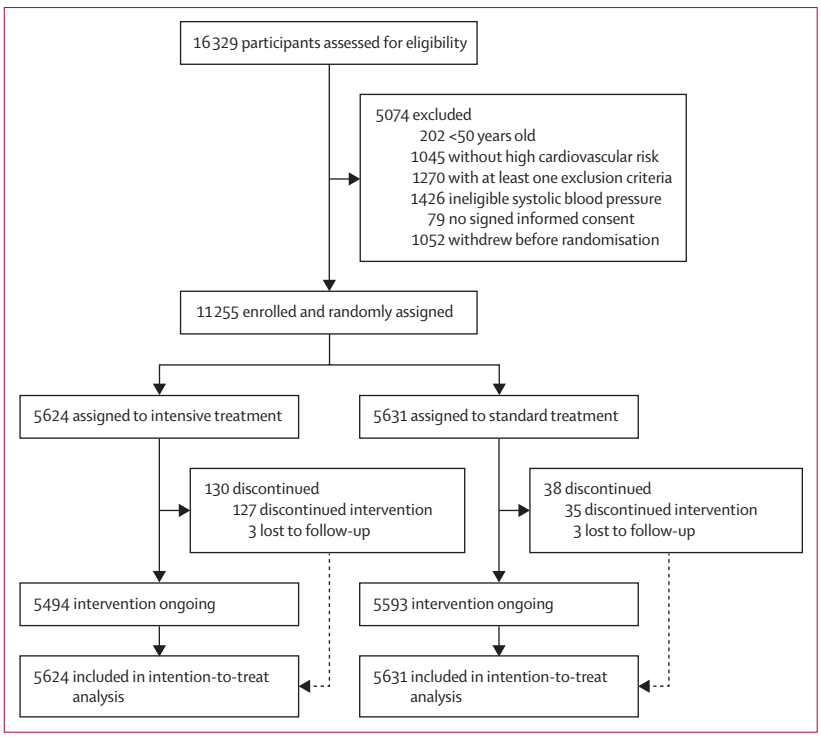

Figure 1: **Trial profile**

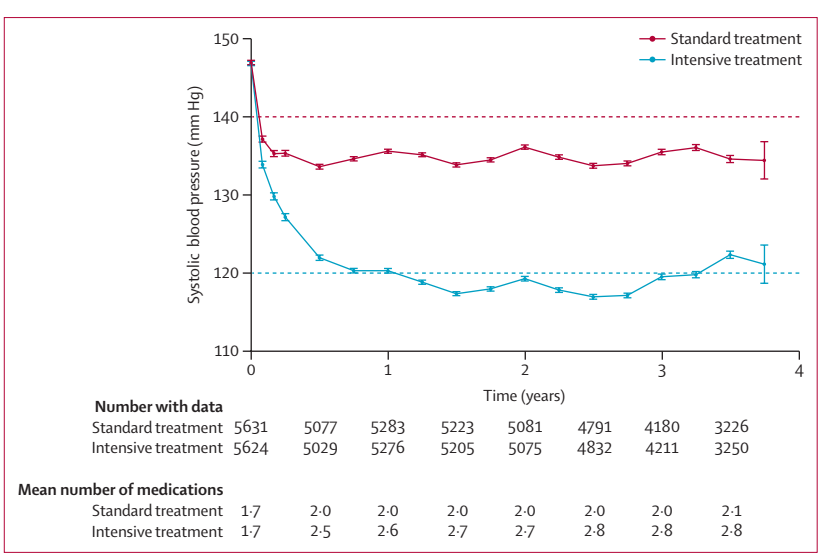

Figure 2: **Systolic blood pressure in the two treatment groups over the course of the trial**
The systolic blood pressure target in the intensive treatment group was less than 120 mm Hg, and the target in the standard treatment group was less than 140 mm Hg. The mean number of medications is the number of antihypertensive medications administered with the adherence over 80% at the exit of each visit. I bars represent 95% CIs.

individual components and the numbers of repeat events are shown in appendix 1 (pp 29–30). The risks of death from any cause (HR 0·79; 95% CI 0·64–0·97) and composite of primary outcome or death from any cause (0·89; 0·80–0·99) were lower in the intensive treatment group. The causes of death are shown in appendix 1 (p 31).

We conducted analysis of prespecified subgroups except periphery artery disease and atrial fibrillation, because both variables accounted for no more than 2% of all participants. Neither prespecified subgroups (appendix 1 pp 17–19) nor unprespecified subgroups (appendix 1 p 32) showed heterogeneity in the effect of intensive treatment on the primary outcome. The results of sensitivity analyses were similar with those of the main analyses (appendix 1 pp 33–34).

The composite kidney outcome occurred in 169 (3·0%) participants from the intensive treatment group and in 102 (1·8%) from the standard treatment group (HR 1·70; 95% CI 1·33–2·17). End-stage renal disease occurred in one participant and a sustained decline in eGFR to a value of less than 10 mL/min per 1·73 m² occurred in three participants, all from the intensive treatment group (appendix 1 p 35). When excluding participants whose eGFR returned to a value of 60 mL/min per 1·73 m² or greater at the last follow-up, or declined only at the last follow-up, the relative risk of the intensive treatment group was higher than that in the main analysis, but the absolute risk was lower (appendix 1 p 36).

Serious adverse events occurred in 2366 (42·1%) participants from the intensive treatment group and 2378 (42·2%) participants from the standard treatment group (HR 1·01; 95% CI 0·95–1·07; table 2, appendix 1 p 37). Serious adverse events of syncope occurred more frequently in the intensive treatment group (24 [0·4%] of 5624) than in the standard treatment group (eight [0·1%] of 5631; HR 3·00; 95% CI 1·35–6·68). All these participants were hospitalised and recovered, two resulting in fracture, one in each group. Among them, five in the intensive treatment group and two in the standard treatment group were caused by hypotension. There was no significant between-group difference in serious adverse events of hypotension (0·1% *vs* 0·1%), electrolyte abnormality (0·2% *vs* 0·2%), injurious fall (0·5% *vs* 0·4%), or acute kidney injury (0·1% *vs* <0·1%).

Discussion

In this large randomised trial conducted in both hospital and community settings, we showed that for patients with hypertension at high cardiovascular risk, regardless of the status of diabetes or history of stroke, the treatment strategy of targeting systolic blood pressure of less than 120 mm Hg, as compared with that of less than 140 mm Hg, prevents major vascular events, with minor excess risk. To further prevent a primary outcome event the 75 patients need to be treated with intensive treatment for 3 years and the 148 patients need to be treated with intensive treatment for 3 years to prevent cardiovascular death.

Our trial has a number of strengths to facilitate reliable assessments of moderate but important treatment effects, including large sample size, high adherence to

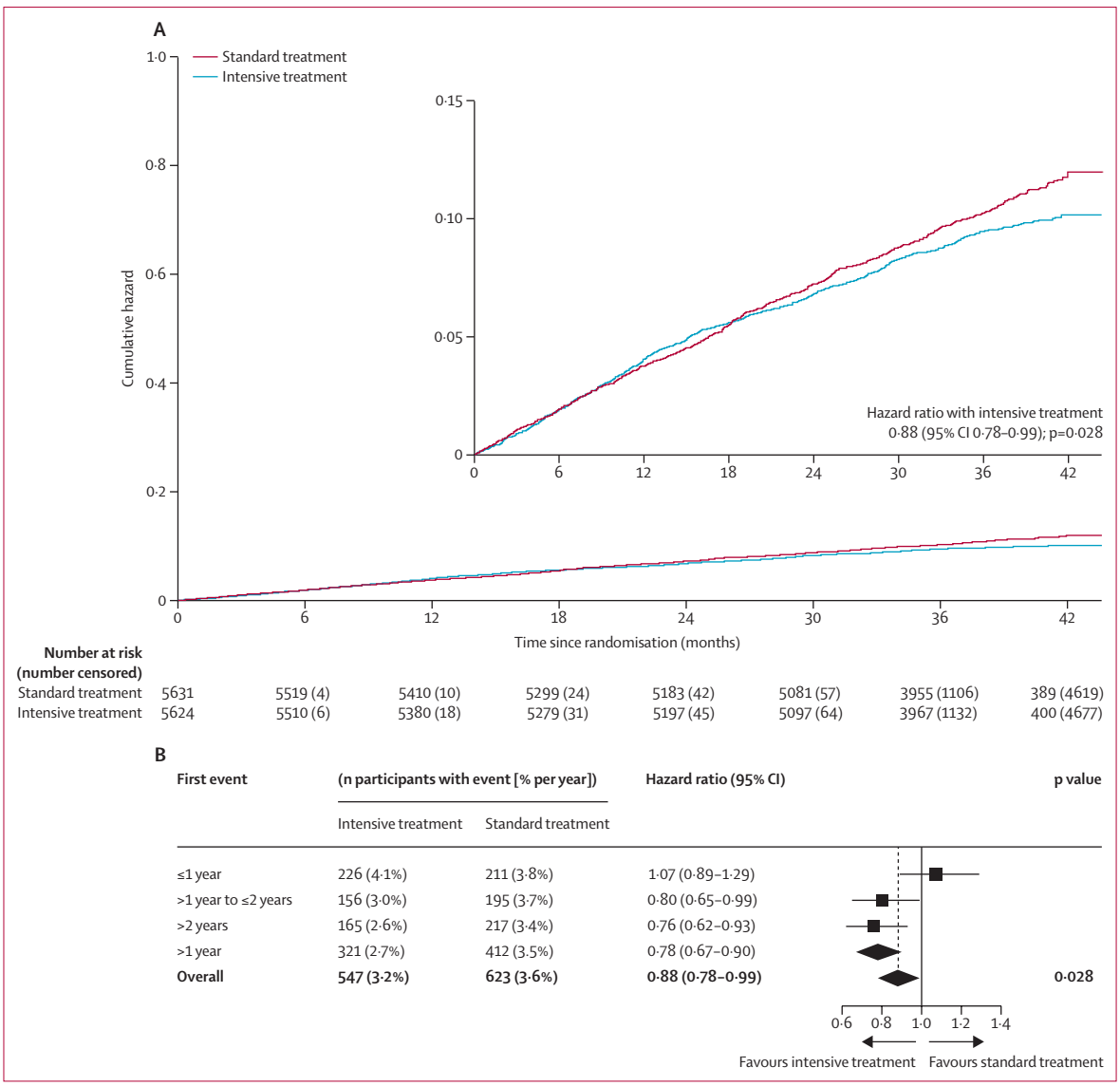

Figure 3: **Primary outcome during the follow-up**

(A) Cumulative hazards for the major vascular events (a composite of myocardial infarction, coronary or non-coronary revascularisation, hospitalisation or emergency room visits for new-onset heart failure or acute decompensated heart failure, stroke, or death from cardiovascular causes), the primary outcome in this trial; the inset in the panel shows the same data on an enlarged y axis. (B) Hazard ratios for the first major vascular event among the participants in the intensive treatment group, as compared with those in the standard treatment group, according to the period of follow-up; the numbers at risk declined with each period of follow-up because of censoring, so rates per year were calculated in the participants at risk at the start of each period; for each period of follow-up, hazard ratios are plotted as squares, with the size of each square proportional to the precision of the estimates (with larger boxes indicating a greater degree of precision); the horizontal lines represent 95% CIs (not adjusted for multiple comparisons), and the dashed vertical line indicates the overall hazard ratio; for the composite period of follow-up, the hazard ratio and corresponding 95% CIs are represented by a diamond.

intervention, few participants lost to follow-up, and a large number of clinical outcomes. We achieved a mean systolic blood pressure of 119 mm Hg with the treatment strategy targeting systolic blood pressure of less than 120 mm Hg, and 135 mm Hg with that targeting systolic blood pressure of less than 140 mm Hg. In our study, the relative risk reduction of primary outcome by the intensive treatment is smaller than that in SPRINT and the evaluation based on individual participant-level meta-analysis. But the absolute risk reduction and number needed to treat to prevent a major vascular event and cardiovascular death are similar with those of SPRINT.[7,10,14] In our trial, the relative risk reduction was diluted by revascularisation, the event rate of which was almost the same in both groups. But this did not affect the absolute risk reduction and the number needed to treat, which is more relevant for decision making than relative risk reduction. Considering the event rate in the control group, participants of SPRINT had a similar risk with those in our trial. SPRINT showed a 25% risk reduction in primary

	Intensive treatment (n=5624)	Standard treatment (n=5631)	Hazard ratio (95% CI)	p value
Myocardial infarction	82 (1·5%)	91 (1·6%)	0·90 (0·67–1·22)	0·50
Stroke	262 (4·7%)	303 (5·4%)	0·86 (0·73–1·02)	0·083
Heart failure	57 (1·0%)	78 (1·4%)	0·73 (0·52–1·03)	0·072
Death from cardiovascular causes	59 (1·1%)	97 (1·7%)	0·61 (0·44–0·84)	0·0027
Major vascular events without revascularisation	**417 (7·4%)**	**495 (8·8%)**	**0·84 (0·74–0·96)**	**0·010**
Coronary revascularisation	183 (3·3%)	182 (3·2%)	1·01 (0·82–1·24)	0·94
Non-coronary revascularisation	23 (0·4%)	22 (0·4%)	1·05 (0·58–1·88)	0·88
Major vascular events (primary outcome)	**547 (9·7%)**	**623 (11·1%)**	**0·88 (0·78–0·99)**	**0·028**
Death from any cause	160 (2·8%)	203 (3·6%)	0·79 (0·64–0·97)	0·025
Primary outcome or death from any cause	**637 (11·3%)**	**714 (12·7%)**	**0·89 (0·80–0·99)**	**0·039**

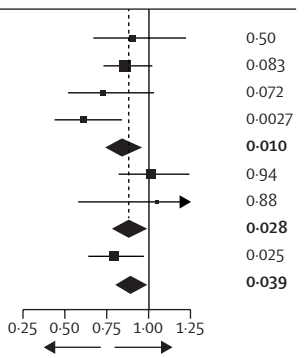

Figure 4: **Primary outcome and secondary outcomes**
The primary outcome is a composite cardiovascular outcome of myocardial infarction, coronary or non-coronary revascularisation, hospitalisation or emergency room visit for new-onset heart failure or acute decompensated heart failure, stroke, or death from cardiovascular causes. Heart failure is defined as hospitalisation or emergency room visit for new-onset heart failure or acute decompensated heart failure. The prespecified secondary outcomes included components of the primary composite outcome, death from any cause, a composite of the primary outcome or death from any cause. The analysis for the outcome of major vascular events without revascularisation was a post-hoc analysis. A single patient can have multiple events and therefore can contribute information to more than one row. The size of each square for hazard ratio is proportional to the precision of the estimates (with larger boxes indicating a greater degree of precision), the horizontal lines represent 95% CIs, and the dashed vertical line indicates the overall hazard ratio for the effect of intensive treatment on the first major vascular event. For composite outcomes, hazard ratios and their corresponding 95% CIs are represented by bold text and diamonds.

	Intensive treatment (n=5624)	Standard treatment (n=5631)	Hazard ratio (95% CI)	p value
Serious adverse event*	2366 (42·1%)	2378 (42·2%)	1·01 (0·95–1·07)	0·78
Conditions of interest				
Serious adverse event only				
Hypotension†	7 (0·1%)	3 (0·1%)	2·33 (0·60–9·02)	0·22
Syncope‡	24 (0·4%)	8 (0·1%)	3·00 (1·35–6·68)	0·0071
Electrolyte abnormality	9 (0·2%)	13 (0·2%)	0·69 (0·30–1·62)	0·40
Injurious fall§	29 (0·5%)	20 (0·4%)	1·45 (0·82–2·57)	0·20
Acute kidney injury¶	3 (0·1%)	2	1·50 (0·25–8·99)	0·66
Emergency room visit or serious adverse event				
Hypotension†	17 (0·3%)	5 (0·1%)	3·40 (1·26–9·22)	0·016
Syncope‡	26 (0·5%)	12 (0·2%)	2·17 (1·09–4·30)	0·027
Electrolyte abnormality	10 (0·2%)	13 (0·2%)	0·77 (0·34–1·76)	0·53
Injurious fall§	40 (0·7%)	33 (0·6%)	1·21 (0·77–1·92)	0·41
Acute kidney injury¶	3 (0·1%)	2	1·50 (0·25–8·99)	0·66
Monitored electrolyte disturbances‖				
Serum sodium <130 mmol/L	92 (1·6%)	60 (1·1%)	1·54 (1·11–2·14)	0·0090
Serum sodium >150 mmol/L	15 (0·3%)	21 (0·4%)	0·72 (0·37–1·39)	0·32
Serum potassium <3·0 mmol/L	97 (1·7%)	91 (1·6%)	1·07 (0·80–1·43)	0·64
Serum potassium >5·5 mmol/L	105 (1·9%)	98 (1·7%)	1·07 (0·82–1·42)	0·61

*A serious adverse event is an event that is fatal or life threatening, resulting in significant or persistent disability, requiring or prolonging a hospitalisation, a congenital anomaly or birth defect, or is an important medical event that the investigator judges to be significant hazards or harm to the participant and may have required medical or surgical intervention to prevent one of the other events listed here. †Hypotension was defined as symptomatic low blood pressure accompanied by dizziness, light headedness, feeling faint, or other symptoms, but not including syncope. ‡Syncope was defined as the temporary loss of consciousness; sensation that one is about to faint or might faint, but does not, is not syncope. §An injurious fall was defined as a fall that resulted in evaluation in an emergency room or one that resulted in hospitalisation. ¶Confirmation of acute kidney injury requires one of the following: (1) an increase in serum creatinine by at least 0·3 mg/dL (≥26·5 µmol/L) within 48 h; (2) an increase in serum creatinine to 1·5 times or more the baseline value within the previous 7 days; or (3) urine volume of 0·5 mL/kg per hour or less for 6 h. ‖Detected on routine or unscheduled tests; routine laboratory tests were performed at months 1, 2, 3, and 6, then every 6 months and at a final visit.

Table 2: **Serious adverse events, conditions of interest, and monitored electrolyte abnormality**

outcome with number need to treat of 61, and a 43% reduction in cardiovascular death with number needed to treat of 172.

In addition, the relatively shorter intervention duration could reduce the beneficial effects to some extent. In our study, the benefit of targeting systolic blood pressure of less than 120 mm Hg occurred after 1 year, and the proportional risk reduction appeared to be larger with more prolonged follow-up. A similar pattern of Kaplan–Meier curve had been observed in other two trials comparing blood pressure targets (SPRINT and ACCORD).[7,8] This finding might be mainly because both groups received good blood pressure management and had their blood pressure lowered after randomisation. Thus, the blood pressure difference between groups had not been well established before antihypertensive treatment titration completed, which usually requires 3 months.[7,8,15] In our study, the benefit could be further delayed because the titration process was extended for 3 months due to the interruption by the sudden outbreak of the COVID-19 pandemic.[13] Fortunately, the pandemic did not affect the compliance to established antihypertensive treatment. Therefore, we kept satisfactory blood pressure management after 9 months from randomisation. Before 9 months, the average systolic blood pressure in the intensive treatment group was between 120 mm Hg and 130 mm Hg. Our study was not designed to answer whether targeting systolic blood pressure of less than 120 mm Hg is superior to that of less than 130 mm Hg. However, if less than 130 mm Hg was better, we might not observe such delayed emergence of benefit.

This study evaluated the heterogeneity of efficacy regarding diabetes or stroke within one randomised

controlled trial and filled the knowledge gaps of the interactions in various subgroups. As hypothesis generating, participants with diabetes in the HOT trial showed a strong trend of major cardiovascular events risk reduction from targeting diastolic blood pressure of less than 90 mm Hg to that of less than 80 mm Hg.[16] However, the non-significant results of the ACCORD trial raised concerns that targeting systolic blood pressure of less than 120 mm Hg might not benefit patients with diabetes.[8] Inadequate randomised controlled trial data and meta-analyses that included heterogeneous trials assessing different blood pressure targets are incapable of providing reliable conclusions.[17] A rigorous individual-participant-level data meta-analysis showed that participants with diabetes had weaker relative risk reduction than those without, but similar absolute risk reduction. However, this study only included approximately 5000 participants with diabetes and 11 000 participants without diabetes with baseline systolic blood pressure of less than 120 mm Hg.[11] There is no evidence that patients with diabetes have different pathophysiological changes from those without, which leads to different optimal blood pressure targets. Our subgroup analysis showed no interaction with either history or duration of diabetes, indicating no evidence that the effects of intensive treatment differ according to diabetes status. The SPS3 trial included 3020 patients with recent lacunar stroke to compare targeting systolic blood pressure of less than 150 mm Hg with that of less than 130 mm Hg. The RESPECT trial included 1263 patients with history of stroke to compare targeting systolic blood pressure of less than 140 mm Hg with that of less than 120 mm Hg. Both trials showed non-significant risk reduction.[9,18] Our trial found no heterogeneity in patients with previous stroke or not. This is particularly important for the populations with a high stroke burden. The stronger effect among the patients who used statin might have occurred by chance, but at least it does not support the hypothesis that statin therapy reduces the benefit of blood pressure lowering, which was observed among the individuals with intermediate cardiovascular risk.[19] Antihypertensive and lipid lowering treatments, particularly when used in combination, resulted in the prevention of major cardiovascular events.[20,21] Our subgroup analysis did not identify significant heterogeneity in a wide range of patients with hypertension. However, we do not have sufficient statistical power to rule out important subgroup differences.

We extended the evidence for the benefit and harm trade-off of targeting systolic blood pressure of less than 120 mm Hg. Consistent with SPRINT, we observed that the intensive treatment increased risk of sustained renal function decline, with few participants developing end-stage renal disease.[7,22,23] People had expected end-stage renal disease, an important outcome in patients with diabetes or hypertension, to be prevented by more intensive blood pressure lowering treatment. However, there is no evidence to support either such protective or harmful effect.[3,24,25] We will continue to collect kidney outcomes in the post-trial prolonged follow-up. In our trial, intensive treatment group experienced much fewer serious adverse events of hypotension, syncope, injurious fall, acute kidney injury, or electrolyte abnormality than previous trials.[7,8] The absolute rates of these serious adverse events in our study were similar with the STEP trial, which compared targeting systolic blood pressure of less than 150 mm Hg with that of less than 130 mm Hg in older (aged 60–80 years) Chinese patients with hypertension, as well as with RESPECT and SPS3; all achieved 127 mm Hg in intensive treatment group.[9,15,18] The better safety might be attributed to study population or treatment. We excluded the patients with eGFR of less than 45 mL/min per 1·73 m², who are more likely to suffer acute kidney injury.[26] The low rates of electrolyte abnormality may be related to the relatively low use of diuretics, which is consistent with the pattern of hypertensive medication use in China.[27,28] The low incidence of serious syncope and hypotension might be attributed to cautious up-titration of antihypertensive medications. It is possible that physicians who well understand the safety issues of intensive treatment based on previous trials might therefore provide better care to avoid potential harm.

The strategy of targeting systolic blood pressure of less than 120 mm Hg should not be interpretated as lowering all patients' systolic blood pressure to less than 120 mm Hg. In our study, if participants could not tolerate systolic blood pressure of less than 120 mm Hg, they should maintain their lowest tolerable systolic blood pressure level. Our study was conducted at both hospital and community settings in diverse economic–geographic regions, and achieved a mean systolic blood pressure of 119 mm Hg with this strategy. The strategy of targeting systolic blood pressure of less than 120 mm Hg with common, accessible, and affordable drugs is feasible to benefit hypertensive patients with high risk of cardiovascular disease and prevent excess acute injury. Moreover, poor hypertension control (systolic blood pressure of less than 140 mm Hg) remains a major global challenge. People might be concerned that it is difficult to achieve systolic blood pressure of less than 120 mm Hg. This trial shows that treatment on a regular follow-up basis, with committed personnel, and availability of a good range of recommended drugs can achieve remarkable control rates for hypertension.

This study has several limitations. First, the trial is open label. It is not possible to blind investigators or participants for assessing different blood pressure targets. However, it is unlikely the awareness of intervention would affect the incidence of clinical events, particularly death. The reduction in mortality was substantial. Moreover, the blinded central adjudication further prevented potential bias in outcome measures. Second, the proportion of patients with mildly reduced renal function was small. The results of kidney outcomes could

mainly reflect the effects in people with normal renal function. Third, the effects of preventing major vascular events might be underestimated due to a short duration of follow-up. At the initiation of this study, we planned to evaluate the effects in a prolonged period and obtained consent from nearly all participants for post-trial follow-up. We will follow up these participants for another 2 years to collect data of primary outcomes, renal function, and dementia. Fourth, we did not measure standing blood pressure during follow-up and could not evaluate the effects of study intervention on standing blood pressure. Fifth, this trial only included a Chinese population, which has high sodium intake and high stroke burden.[29,30] However, considering the overlapping 95% CIs, our findings are generally consistent with studies from other ethnicities.[7,8,18]

In conclusion, targeting systolic blood pressure of less than 120 mm Hg, as compared with that of less than 140 mm Hg, prevents major vascular events and death with minor excess risk in patients with hypertension at high cardiovascular risk, regardless of the status of diabetes or history of stroke. Our findings provide new evidence about the benefit and harm of treatment targeting systolic blood pressure of less than 120 mm Hg.

Contributors

JiaL, YL, JG, XY, and JLi conceptualised the study design. JiaL, YL, and JG prepared the first draft of the report. YL and JG were involved with data curation in the trial. LL did the statistical analysis. LL and JG accessed and verified the underlying data reported in the manuscript. All authors critically reviewed the report and approved the final version before submission. All the authors guarantee the completeness and accuracy of the reported data and the fidelity of the trial to the protocol. JLi was responsible for the decision to submit the manuscript for publication.

Declaration of interests

JLi reports research grants from Servier (TIANJIN) Pharmaceutical for assessing effects of indapamide sustained release and perindopril–amlodipine, to the Fuwai Hospital, and honoraria for presentation from Servier (TIANJIN) Pharmaceutical. All other authors report no competing interests.

Data sharing

Data from this study can be requested from Prof Jing Li (ESPRIT_Data@fuwaihospital.org) 2 years after the publication of this study. De-identified participant data with identifiers, the data dictionary, and other specified data sets can be requested. Specific requests for data will require the submission of a proposal with a valuable research question as assessed by the study steering committee and might require a data access agreement to be signed.

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