Benefit–harm trade-offs of intensive blood pressure control versus standard blood pressure control on cardiovascular and renal outcomes: an individual participant data analysis of randomised controlled trials

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Summary

Background Although intensive blood pressure control is recommended by major guidelines, its overall benefit–harm balance remains uncertain. In particular, it is unclear how net clinical benefit varies by blood pressure target and patient characteristics. We aimed to quantify the benefit–harm trade-offs of intensive blood pressure control versus standard blood pressure control.

Methods We conducted a post-hoc, pooled participant-level analysis of six randomised controlled trials (ACCORD BP, SPRINT, ESPRIT, BPROAD, STEP, and CRHCP). Trial selection was based on our collaborative framework, the Blood Pressure Reduction Union-Landmark Evidence, and a targeted literature search, guided by five predefined inclusion criteria: (1) comparison of intensive systolic blood pressure targets (<120 mm Hg or <130 mm Hg) versus standard treatment; (2) reporting of composite major cardiovascular outcomes; (3) enrolment of more than 2000 participants; (4) standardised reporting of treatment-related adverse events; and (5) availability of individual participant data. We also conducted a systematic review in which we searched PubMed for studies published from database inception up to June 15, 2025, with no language restrictions. We used search terms related to cardiovascular outcomes, hypertension, intensive blood pressure lowering, and randomised trials. Study screening and data extraction were independently conducted in pairs by ten reviewers, with discrepancies resolved by discussion or adjudication. Participants in the six trials were randomly assigned to intensive blood pressure treatment (systolic blood pressure target <120 mm Hg or <130 mm Hg) versus standard treatment (systolic blood pressure target <140 mm Hg, <150 mm Hg in older adults, or usual care), depending on the trial design. The primary benefit outcome was a composite of myocardial infarction, stroke, heart failure, and cardiovascular death. The primary harm outcomes were adverse events of interest (eg, hypotension and syncope) and renal-related events. Statistical analyses were performed on an intention-to-treat basis using Bayesian hierarchical models.

Findings The initial dataset included 80 676 participants, of whom 80 220 were included in our analyses (intensive blood pressure control group n=40 503; standard blood pressure control group n=39 717). The median age was 64·0 years (IQR 59·0–70·0), 39 043 (48·7%) participants were male, and 41 177 (51·3%) were female. Most participants were Asian (66 290 [82·6%]) or White (8097 [10·1%]). During a median follow-up of 3·2 years (IQR 3·0–3·5), the composite cardiovascular disease outcome occurred in 2158 (5·3%) participants in the intensive blood pressure control group and 2811 (7·1%) participants in the standard blood pressure control group (hazard ratio 0·76, 95% credible interval [CrI] 0·72–0·81; p<0·0001). Compared with standard blood pressure control, intensive blood pressure control was associated with a 1·73% absolute risk reduction (95% CrI 1·65–1·81) in cardiovascular disease (number needed to treat 58 [95% CrI 55–61]) and a 1·82% absolute risk increase (95% CrI 1·63–2·01) for adverse events of interest (number needed to harm 55 [95% CrI 49–61]). Overall, intensive blood pressure control showed a favourable benefit–harm profile, with a net benefit of 1·14 (95% CrI 1·03–1·25), using adjudicated weighting. The net benefit remained positive when considering kidney-related adverse events (1·13 [95% CrI 1·01–1·24]).

Interpretation Compared with standard blood pressure control, intensive blood pressure control provides a net benefit between the reduction in cardiovascular events and the increase in adverse events, including renal events.

Funding National Key Research and Development Program, the Ministry of Science and Technology of China; National Science and Technology Major Project; National Natural Science Foundation of China; China Academy of Chinese Medical Sciences Innovation Fund for Medical Science; and Science and Technology Program of Liaoning Province.

Lancet 2025; 406: 1009–19

Published **Online** August 31, 2025 https://doi.org/10.1016/S0140-6736(25)01391-1

See **Comment** page 980

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Research in context

Evidence before this study

We systematically searched PubMed for randomised controlled trials evaluating intensive blood pressure lowering and its effect on cardiovascular outcomes. The search strategy included comprehensive combinations of MeSH terms and keywords related to cardiovascular disease (eg, "myocardial infarction", "stroke", "heart failure", "mortality"), hypertension (eg, "high blood pressure", "prehypertension"), and treatment intensity (eg, "intensive", "strict", "tight"). Filters for randomised controlled trials were applied. The search covered studies published from database inception to June 15, 2025, with no language restrictions. Eligible studies were randomised controlled trials comparing intensive blood pressure control (defined as systolic blood pressure targets <130 mm Hg or <120 mm Hg) versus standard treatment, reporting cardiovascular events and adverse events. Our search ultimately identified six randomised controlled trials: ACCORD BP, SPRINT, ESPRIT, BPROAD, STEP, and CRHCP. These trials focused primarily on relative risk reduction without a comprehensive net-benefit assessment that accounts for both cardiovascular benefits and potential adverse events, particularly renal complications. Reliable estimates of the benefits and harms of intensive blood pressure control, and how these vary by blood pressure target and patient characteristics, are crucial for optimising treatment decisions. Emerging evidence from recent large, high-quality trials provides an opportunity to address this gap.

Added value of this study

This pooled analysis of individual participant data was conducted to contextualise the findings from existing randomised controlled trials within the broader scientific landscape and to inform guideline recommendations for hypertension management, ultimately enhancing clinical decision making. To our knowledge, this study provides the first pooled analysis of individual participant data explicitly assessing the benefit–harm trade-off of intensive blood pressure control across six pivotal randomised controlled trials, encompassing 80 220 participants. It addresses key clinical uncertainties by quantifying both the cardiovascular benefits and the potential harms, particularly renal adverse events. Net benefit varied by systolic blood pressure target (120 mm Hg *vs* 130 mm Hg) and patient characteristics, highlighting the need for individualised blood pressure management based on risk profiles. This approach provides deeper insight into treatment effects across diverse populations, supporting more precise and evidence-based clinical decision making.

Implications of all the available evidence

Our findings provide robust evidence supporting a net-benefit-based approach to hypertension management, shifting the focus from cardiovascular risk reduction alone to a more patient-centred framework that integrates both benefits and potential harms. These insights offer important implications for refining blood pressure guidelines and underscore the importance of individualised strategies to optimise outcomes while avoiding both overtreatment and undertreatment.

Introduction

The concept of intensive blood pressure lowering was first introduced by the 2017 American College of Cardiology/American Heart Association Hypertension Guidelines,[1] primarily on the basis of the Systolic Blood Pressure Intervention Trial (SPRINT).[2] Following the publication of several large randomised controlled trials, including the Strategy of Blood Pressure Intervention in the Elderly Hypertensive Patients (STEP),[3] the China Rural Hypertension Control Project (CRHCP),[4,5] the Effects of Intensive Systolic Blood Pressure Lowering Treatment in Reducing Risk of Vascular Events (ESPRIT),[6] and the Blood Pressure Control Target in Diabetes (BPROAD),[7] both the 2024 European Society of Cardiology and the Chinese Hypertension Guidelines began recommending a target of 130/80 mm Hg,[8,9] as did guidelines from Canada and Japan.[10,11] Building on the evidence from these pivotal randomised controlled trials and the revised guidelines, intensive blood pressure lowering has become increasingly supported by the global evidence base.[12]

Although recommendations have shifted towards more intensive blood pressure control, several important questions remain. First, current guidelines for intensive blood pressure control focus primarily on the relative reduction in cardiovascular risk, while associated risks are given secondary consideration. Even key evidence supporting guidelines has not provided conclusive data on the absolute net benefit of intensive blood pressure control.[13] Second, high-quality randomised controlled trials have consistently shown cardiovascular benefits with an intensive systolic blood pressure target of 120 mm Hg.[2,6,7,14,15] However, the latest European Society of Cardiology guidelines (published in 2024)[8] recommend a systolic blood pressure target of 120–129 mm Hg, citing additional considerations such as the lower blood pressure values typically observed under clinical trial conditions in comparison with those measured in routine care, the limited generalisability of trial populations to patients outside trial settings, and concerns about adverse events when targeting systolic blood below 120 mm Hg in every day clinical practice.[8] As such, the net clinical benefits of intensive blood pressure lowering, whether targeting a systolic blood pressure of 120 mm Hg or 130 mm Hg, remain uncertain

in routine clinical practice. Third, conclusions for specific populations, such as older people or those with diabetes, are largely based on subgroup analyses with small sample sizes, which can increase the risk of bias. Although some meta-analyses have attempted to increase sample size by pooling data across trials,[16–19] most are based on published aggregate data rather than individual participant data, and thus remain secondary analyses. More importantly, evaluating the net benefit in these groups, accounting for adverse events, is essential to guide clinical practice. These evidence gaps highlight key areas where actionable insights are urgently needed for better patient care.

To our knowledge, no pooled benefit–harm assessment of intensive blood pressure control has previously been conducted. Given the recent publication of high-quality randomised controlled trials on intensive blood pressure control, we believe such an analysis would be highly timely. Individual participant data meta-analyses, which combine and analyse raw data from similar studies in a single dataset, are widely regarded as the gold standard for the synthesis of clinical trial evidence.[20] We aimed to conduct a single-stage individual participant data meta-analysis of six pivotal randomised controlled trials on intensive blood pressure lowering. Our goal was fill the gaps in current guidelines by providing a comprehensive benefit–harm evaluation, including outcomes for which the benefit or harm is debated, such as renal function, and profiling the net benefit across different blood pressure targets and among diverse populations, synthesising the most up-to-date evidence to help guide global clinical practice.

Methods

Search strategy and selection criteria

For this post-hoc pooled analysis, we used participant-level data from six major randomised controlled trials, the Action to Control Cardiovascular Risk in Diabetes Blood Pressure (ACCORD BP),[21] SPRINT,[2] ESPRIT,[6] BPROAD,[7] STEP,[3] and CRHCP,[5] to comprehensively evaluate the net benefit of intensive blood pressure control. Trial selection was based on our collaborative framework, the Blood Pressure Reduction Union-Landmark Evidence (BPRULE), and on a targeted literature search guided by five predefined inclusion criteria: (1) comparison of intensive systolic blood pressure targets (<120 mm Hg or <130 mm Hg) versus standard treatment; (2) reporting of composite major cardiovascular outcomes (eg, myocardial infarction, stroke, or heart failure) to ensure cross-trial consistency and broad clinical relevance of intensive blood pressure control; (3) enrolment of at least 2000 participants; plus two essential requirements for individual participant data meta-analyses of net benefit: (4) standardised reporting of treatment-related adverse events; and (5) availability of individual participant data.

To complement this strategy and enhance transparency, we conducted a systematic review, searching PubMed on June 15, 2025 for articles published from database inception, using search terms related to cardiovascular outcomes, hypertension, intensive blood pressure lowering, and randomised trials, with no language restriction (a detailed search strategy is shown in the appendix pp 3–4). Of the 34 trials identified, 23 were excluded because they did not meet the clinical or methodological scope of the current study (eg, blood pressure targets were not sufficiently intensive, diastolic blood pressure targets were used, or cardiovascular outcome data were not available). Of the remaining 11 potentially eligible trials, five were excluded due to small sample size, absence of reporting of adverse events, or unavailability of individual participant data. The remaining six trials were included in the final individual participant data meta-analysis (figure 1). A comprehensive summary of included and excluded trials, along with reasons for exclusion, is provided in the appendix (pp 36–43).

See Online for appendix

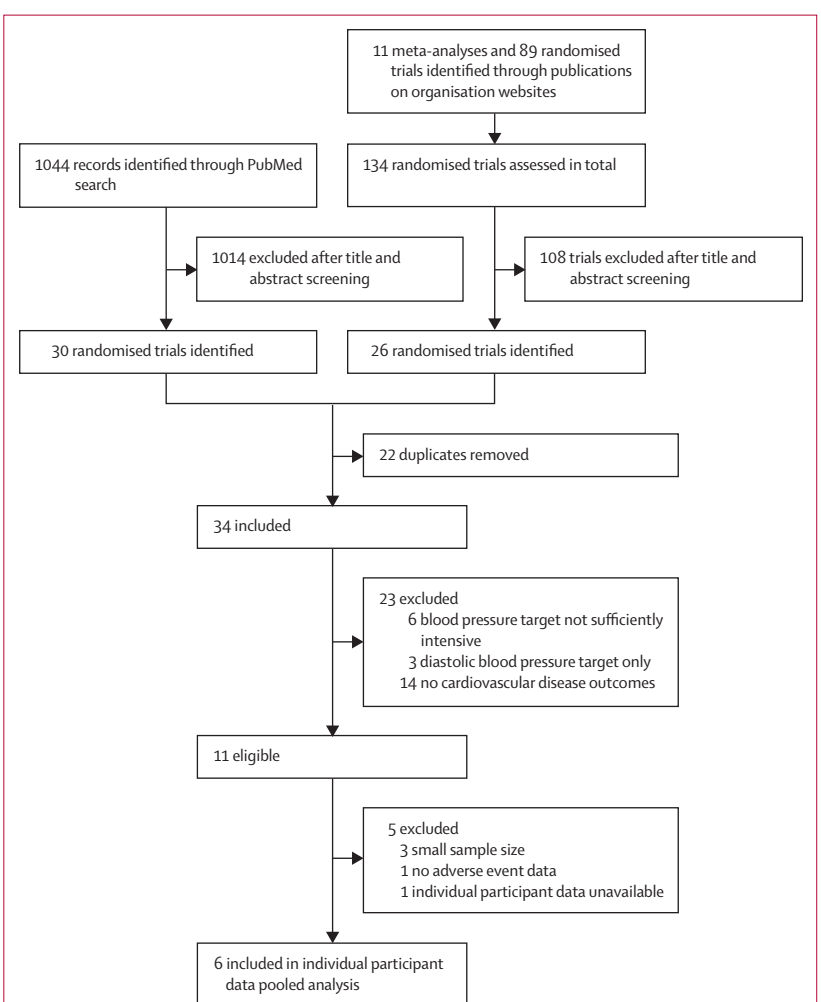

Figure 1: **Study flow diagram**

De-identified data from the SPRINT[2] and ACCORD BP[21] trials were obtained through the National Heart, Lung, and Blood Institute Biologic Specimen and Data Repository Information Coordinating Center, and data from ESPRIT,[6] BPROAD[7] and STEP[3] were accessed through direct communication with the trial lead investigators within the BPRULE collaborative framework. The CRHCP trial[5] was led by our own research team, and full access to its individual-level data was available to the authors. All six randomised controlled trials were registered with ClinicalTrials.gov (ACCORD BP, NCT00000620; SPRINT, NCT01206062; ESPRIT, NCT04030234; BPROAD, NCT03808311; STEP, NCT03015311; and CRHCP, NCT03527719). This study was conducted in accordance with the Declaration of Helsinki and received approval from the Ethics Committee of the First Hospital of China Medical University (Shenyang, Liaoning, China), with a waiver of informed consent.

Study population

We included all participants who were randomly assigned in the ACCORD BP,[21] SPRINT,[2] ESPRIT,[6] BPROAD,[7] STEP,[3] and CRHCP[5] trials. A detailed summary of these trials is shown in the appendix (pp 44–46). The original results and trial methodologies have been previously published elsewhere.[2,3–7,14,21]

The ACCORD BP trial[21] (n=4733) was a randomised, open-label study comparing intensive versus standard blood pressure control in adults aged 40 years and older with diabetes, conducted at 77 sites in the USA and Canada (2003–09; mean follow-up 4·7 years). The SPRINT trial[2] (n=9361) enrolled adults aged 50 years and older at high risk of cardiovascular disease without diabetes or stroke across 102 US sites (2010–15); the trial was stopped early after a median follow-up of 3·3 years due to a statistically significant reduction in the primary composite cardiovascular outcome of myocardial infarction, acute coronary syndrome, stroke, heart failure, and cardiovascular death in the intensive group. The ESPRIT trial[6] (n=11 255) included adults with or without diabetes or stroke and was conducted in China (2019–23; median follow-up 3·4 years [IQR 3·0–3·4]). The BPROAD trial[7] (n=12 821) focused on patients with diabetes across 145 clinical sites in China (2019–24; median follow-up 4·2 years [IQR 2·9–4·6]). All four trials randomly assigned participants (1:1) to intensive (systolic blood pressure <120 mm Hg) versus standard (systolic blood pressure <140 mm Hg) treatment.

The STEP trial[3] (n=8511) was a multicentre, randomised controlled trial conducted in China (2017–20) that enrolled adults aged 60–80 years with hypertension and randomly assigned participants to a systolic blood pressure target of 110 mm Hg to less than 130 mm Hg versus 130 mm Hg to less than 150 mm Hg (median follow-up 3·3 years [IQR 3·2–3·5]). The CRHCP trial[5] (n=33 995) was a cluster-randomised trial across 326 rural villages in three Chinese provinces (2018–23), evaluating intensive blood pressure management (<130/80 mm Hg) versus usual care in adults aged 40 years and older (median follow-up 4·0 years [IQR 4·0–4·1]). For the individual participant data meta-analysis, 3-year data from CRHCP were used due to biomarker availability for kidney outcomes.

Sex was self-reported by participants in all included trials. Detailed information on blood pressure measurement methods, intervention strategies, and medications for each trial is provided in the appendix (pp 47–49).

Benefit and harm outcomes

In alignment with the CRHCP[5] and BPROAD[7] trials, the primary benefit outcome in our analysis was defined as a composite of myocardial infarction, stroke, heart failure, and death due to cardiovascular causes. To ensure comparability, we harmonised the primary outcome across the ACCORD BP,[21] SPRINT,[2] ESPRIT,[6] and STEP[3] trials. Specifically, we incorporated heart failure into the ACCORD BP[21] dataset, excluded non-myocardial infarction acute coronary syndrome events from the SPRINT trial,[2] removed both coronary and non-coronary revascularisations from the ESPRIT trial,[6] and excluded hospitalisations for unstable angina, coronary revascularisation, and atrial fibrillation from the STEP trial.[3] The individual components of the composite cardiovascular outcome were also analysed.

The primary harm outcome was adverse events of interest, defined as the occurrence of any of the following events recorded or calculated from the six individual trials: hypotension, syncope, injurious fall, arrhythmia, angio-oedema, acute kidney injury, renal failure, end-stage renal disease or dialysis, a reduction of 50% or more in estimated glomerular filtration rate in patients with chronic kidney disease at baseline, or a reduction of 30% or more in estimated glomerular filtration rate to less than 60 mL/min per 1·73 m² in patients without chronic kidney disease at baseline. Additionally, kidney-related outcomes were analysed as a separate harm outcome. Detailed definitions of the benefit and harm outcomes are provided in the appendix (pp 50–52).

Statistical analysis

Statistical analyses were conducted using individual patient data on an intention-to-treat basis. The net difference and 95% CI of blood pressure between the intensive treatment group and the standard treatment group was estimated using a linear mixed-effects regression model and adjusted for age, sex, and random effects including cluster and trials. A one-stage Bayesian hierarchical model was used to simultaneously analyse all trials, accounting for within-trial clustering via random effects. In this model, the intervention of interest (intensive *vs* standard treatment) was included as a fixed-effect covariate, and the hierarchical structure included

random intercepts for trials and clusters nested within trials. The primary outcome was analysed by means of a Bayesian flexible parametric survival model with a non-informative prior for time-to-event data. The prior for the intervention was set as a neutral regularising normal prior (mean 0, standard deviation 0·355, which places 95% of the probability mass between a hazard ratio [HR] of 0·5 and 2·0). Treatment effects were presented as HRs for time-to-event outcomes and as odds ratios (ORs) for binary outcomes, both with a 95% credible interval (CrI). Details of the Bayesian modelling process are shown in the appendix (pp 4–5).

The benefit–harm assessment was based on a quantitative approach to estimate the incremental net clinical benefit. The Bayesian hierarchical model with Markov chain Monte Carlo sampling was used to obtain the posterior distributions. We obtained risk estimates for each outcome, whether time-to-event or dichotomous, by sampling the model posteriors. The absolute risk reduction for intensive treatment was calculated by subtracting the cumulative risk for benefit outcomes in the intensive treatment group from the control group. The absolute risk increase for harm outcomes was similarly estimated.

The weighting of benefit and harm outcomes was determined through a three-step process (see appendix pp 6–8 for full details). First, outcome weights were derived from a patient preference survey conducted among individuals with hypertension, led by Johns Hopkins University and Kaiser Permanente Colorado.[22,23] These patient preference-based weights were then used to calculate the mean weights for total cardiovascular disease outcomes, total adverse events of interest, and renal adverse events in our analysis. Second, a panel of 11 experts (including NO), comprising four cardiologists, two neurologists, one nephrologist, one epidemiologist, one health policy expert, and two patient representatives, reviewed and refined the weights, particularly for outcomes not covered in the original survey. Third, a focused literature review was conducted to ensure that the final weights aligned with published estimates of outcome severity and patient preferences, supporting their clinical relevance and validity.[24–26] The outcome weighting process and final values are detailed in the appendix (p 53). Mean weights were calculated for the cardiovascular benefit endpoint, total adverse events of interest, and renal adverse events, yielding relative weight ratios of 1·0:3·1 for cardiovascular disease benefit to total adverse events and 1·0:1·8 for cardiovascular disease benefit to renal adverse events (appendix pp 8–9).

Net benefit was calculated as absolute risk reduction minus the product of absolute risk increase and weight. Additionally, we conducted a graphical sensitivity analysis to assess the robustness of net-benefit estimates across varying harm-to-benefit weighting scenarios (ranging from 1:1 to 1:10). The CrIs of absolute risk reduction, absolute risk increase, and net benefit were estimated based on a bootstrap method with Markov chain Monte Carlo simulations, and 10 000 repetitions were made to generate a distribution of the net benefit to estimate the quantile values. Number needed to treat and number needed to harm were also estimated.

To assess the heterogeneity of net benefits across studies with different antihypertensive targets, we separately analysed trials with systolic blood pressure targets of 120 mm Hg and 130 mm Hg. Additionally, we conducted exploratory subgroup analyses based on baseline characteristics, including age (<65 years *vs* ≥65 years, <80 years *vs* ≥80 years), sex (male *vs* female), race (White *vs* non-White), education level (less than high school *vs* high school or more), antihypertensive treatment (yes *vs* no), diastolic blood pressure (<70 mm Hg *vs* ≥70 mm Hg), BMI (<28 kg/m² *vs* ≥28 kg/m²), cardiovascular disease risk (high *vs* not high), diabetes (yes *vs* no), stroke (yes *vs* no), and chronic kidney disease (yes *vs* no). To establish if the net benefits were significantly different between subgroups, we simulated 1000 random variates of the net benefit within each subgroup. We subsequently used quantile regression to estimate the p value for the differences between the groups. The Bonferroni correction method was used to account for multiple comparisons to adjust the probability of type I error of p values. Between-study heterogeneity was addressed by incorporating random effects into our hierarchical Bayesian model, allowing for flexible estimation of variation across trials.

We also did the following sensitivity analyses: (1) a two-stage approach, in which each trial was analysed separately using individual patient data, followed by combining results using a random-effects model to account for intertrial variability; (2) an adjusted model accounting for age, sex, smoking status, antihypertensive medication use, cardiovascular disease history, diabetes history, baseline systolic blood pressure, and LDL cholesterol; (3) analyses with different prior distribution (an optimistic prior favouring the belief of benefit and a pessimistic prior favouring the belief of harm); (4) exclusion of the trial involving clustered data; (5) exclusion of participants assigned to the intensive glycaemic control group in the ACCORD BP trial;[21] (6) consideration of competing risks of death using a Bayesian approach based on cause-specific hazard functions;[27] and (7) considering all-cause mortality as an independent benefit outcome, assigned the same weight as cardiovascular death, in the net-benefit analysis.

We set the significance threshold at 5% with two-sided tests. Missing data were imputed using chained random forests with predictive mean matching.[28] All analyses were done with R software version 4.4.0.

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

The initial dataset included 80 676 participants from six cohorts (ACCORD BP,[21] SPRINT,[2] ESPRIT,[6] BPROAD,[7] STEP,[3] and CRHCP[5] trials). After excluding 456 individuals due to missing cardiovascular outcome data, 80 220 participants remained in the final eligible dataset for analysis. 40 503 participants were in the intensive treatment group and 39 717 were in the standard treatment group. The median age was 64·0 years (IQR 59·0–70·0), and 39 043 (48·7%) participants were male and 41 177 (51·3%) were female. 66 290 (82·6%) participants were Asian, 8097 (10·1%) were White, 3871 (4·8%) were Black, 1303 (1·6%) were Hispanic, and 659 (0·8%) were other races or ethnicities. The median follow-up duration was 3·2 years (IQR 3·0–3·5), during which 4969 composite cardiovascular events and 5056 adverse events of interest, including 2607 kidney-related events, were reported. The baseline characteristics for the cohort are in the table. Age-stratified baseline characteristics are shown in the appendix (pp 54–55).

The net difference between the intensive and standard treatment groups in systolic blood pressure reduction was –12·6 mm Hg (95% CI –13·0 to –12·3), and the net difference in diastolic blood pressure was –5·7 mm Hg (95% CI –5·9 to –5·5; appendix pp 10–11). The composite

	Overall (n=80 220)	Intensive treatment group (n=40 503)	Standard treatment group (n=39 717)
Age, years	64·0 (59·0–70·0)	64·0 (58·5–70·0)	64·0 (59·0–70·0)
Sex			
Female	41 177 (51·3%)	20 801 (51·4%)	20 376 (51·3%)
Male	39 043 (48·7%)	19 702 (48·6%)	19 341 (48·7%)
Race or ethnic group			
Asian	66 290 (82·6%)	33 535 (82·8%)	32 755 (82·5%)
Non-Hispanic White	8097 (10·1%)	4077 (10·1%)	4020 (10·1%)
Non-Hispanic Black	3871 (4·8%)	1897 (4·7%)	1974 (5·0%)
Hispanic	1303 (1·6%)	658 (1·6%)	645 (1·6%)
Other	659 (0·8%)	336 (0·8%)	323 (0·8%)
High school education or above	27 738 (34·6%)	13 919 (34·4%)	13 819 (34·8%)
Smoking status			
Never smoked	49 129 (61·2%)	24 909 (61·5%)	24 220 (61·0%)
Former smokers	13 850 (17·3%)	6957 (17·2%)	6893 (17·4%)
Current smokers	17 241 (21·5%)	8637 (21·3%)	8604 (21·7%)
BMI, kg/m²	26·9 (4·4)	26·9 (4·4)	26·8 (4·4)
Systolic blood pressure, mm Hg	148·4 (16·9)	148·7 (17·3)	148·1 (16·6)
Diastolic blood pressure, mm Hg	82·9 (11·5)	83·1 (11·6)	82·6 (11·4)
History of major cardiovascular disease*	14 156 (17·6%)	7304 (18·0%)	6852 (17·3%)
History of stroke	11 132 (13·9%)	5768 (14·2%)	5364 (13·5%)
History of diabetes	26 362 (32·9%)	13 245 (32·7%)	13 117 (33·0%)
History of chronic kidney disease	5273 (6·6%)	2675 (6·6%)	2598 (6·5%)
Use of antihypertensive medications	63 464 (79·1%)	32 557 (80·3%)	30 907 (77·8%)
Antihypertensive medications	1·2 (0·9)	1·2 (0·9)	1·2 (0·9)
Use of aspirin	20 143 (25·1%)	10 176 (25·1%)	9967 (25·1%)
Use of statins	22 343 (27·9%)	11 139 (27·5%)	11 204 (28·2%)
Total cholesterol, mg/dL	182·1 (45·9)	182·5 (46·1)	181·6 (45·6)
LDL cholesterol, mg/dL	100·4 (34·5)	100·7 (34·7)	100·2 (34·3)
HDL cholesterol, mg/dL	48·8 (14·9)	48·9 (15·0)	48·6 (14·8)
Triglycerides, mg/dL	128·4 (90·3–189·5)	129·2 (90·3–189·6)	128·0 (89·5–188·7)
Estimated glomerular filtration rate, mL/min per 1·73 m²†	91·9 (19·7)	92·0 (19·7)	91·7 (19·6)
Atherosclerotic cardiovascular disease 10-year risk strata‡			
Low or borderline risk (<7·5%)	15 162 (18·9%)	7788 (19·2%)	7374 (18·6%)
Intermediate risk (7·5–19·9%)	30 080 (37·5%)	15 171 (37·5%)	14 909 (37·5%)
High risk (≥20%)	34 978 (43·6%)	17 544 (43·3%)	17 434 (43·9%)

Data are median (IQR), n (%), or mean (SD). *Major cardiovascular disease includes myocardial infarction, stroke, and heart failure. †Estimated glomerular filtration rate was calculated based on the 2021 Chronic Kidney Disease Epidemiology Collaboration creatinine equations. ‡Atherosclerotic cardiovascular disease risk was calculated based on the American College of Cardiology and American Heart Association Pooled Cohort Equations.

Table: **Baseline characteristics of participants in the six included trials**[2,3,5–7,21]

cardiovascular disease outcome occurred in 2158 (5·3%) of 40 503 participants in the intensive treatment group and in 2811 (7·1%) of 39717 in the standard treatment group (HR 0·76 [95% CrI 0·72–0·81]; p<0·0001; figure 2; appendix p 12). This finding was replicated in the two-stage approach (HR 0·76 [95% CI 0·69–0·84]; p<0·0001; appendix p 13). Risk reductions in the intensive treatment group versus the standard treatment group were observed across individual cardiovascular disease outcome components (figure 2, appendix pp 14–15) and were consistent across age subgroups (<65 years and ≥65 years; appendix p 16). Compared with standard blood pressure control, intensive blood pressure control was also associated with a lower risk of all-cause mortality (HR 0·87 [95% CrI 0·80–0·94]; p=0·0016). However, adverse events of interest and kidney-related outcomes occurred more frequently in the intensive treatment group compared with the standard treatment group (figure 2). These adverse events were generally more common among participants aged 65 years and older than in participants younger than 65 years (appendix p 56). Subgroup-specific HRs for major cardiovascular disease and ORs for total adverse events of interest are shown in the appendix (pp 17–18).

Over a median follow-up of 3·2 years (IQR 3·0–3·5), intensive blood pressure control resulted in an absolute risk reduction of 1·73% (95% CrI 1·65–1·81) for cardiovascular disease events (number needed to treat 58 [95% CrI 55–61]), primarily driven by stroke reduction, and in an absolute risk increase of 1·82% (95% CrI 1·63–2·01) in adverse events of interest (number needed to harm 55 [95% CrI 49–61]) compared with standard blood pressure control figure 3). Age-stratified absolute risk reductions and absolute risk increases are shown in the appendix (p 57). Overall, intensive blood pressure control showed a favourable benefit–harm profile compared with standard blood pressure control, using an adjudicated weighting in which one cardiovascular benefit was considered equivalent to 3·1 harms, resulting in a net benefit of 1·14 (95% CrI 1·03–1·25; figure 3). Net benefit for cardiovascular disease versus kidney-related adverse events was consistently positive with intensive blood pressure control compared with standard blood pressure control (1·13 [1·01–1·24]). For 1000 patients with hypertension treated with intensive blood pressure control over 3 years, 17 cardiovascular events would be prevented at the cost of 18 adverse events of interest or 11 kidney-related adverse outcomes (appendix p 19). The corresponding net benefit results for the six individual trials are shown in the appendix (p 20). Results assuming one benefit outcome is as impactful as five harm outcomes are shown in the appendix (p 21). A graphical sensitivity analysis showed how the net benefit varied under different harm-to-benefit weighting assumptions, ranging from 1:1 to 1:10 (appendix p 22). For cardiovascular disease benefit versus renal adverse events, the net benefit remained favourable across the entire range of weight ratios. For cardiovascular disease benefit versus total adverse events of interest, the net benefit remained favourable when the weight exceeded 1·00:1·05.

Mean blood pressure values during follow-up by systolic blood pressure target are shown in the appendix (pp 23–24), and net blood pressure differences between treatment groups are shown in the appendix (pp 10–11). When grouped by systolic blood pressure targets (120 mm Hg, n=37878; 130 mm Hg, n=42 342), the absolute risk reduction for cardiovascular disease with intensive treatment was 1·84% (95% CrI 1·75–1·92) for 120 mm Hg and 1·65% (1·54–1·76) for 130 mm Hg (figure 4). The corresponding relative risk reductions are shown in the appendix (p 25). Adverse events of interest occurred in 3521 (9·3%) of 37878 participants in the 120 mm Hg target trials and in 1535 (3·6%) of 42 342 participants in the 130 mm Hg target trials. The

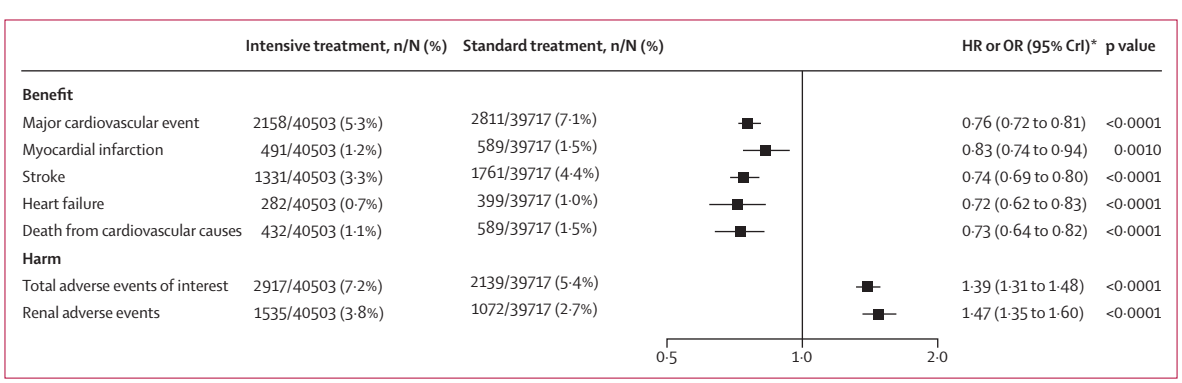

Figure 2: **Pooled estimates of treatment effects for intensive versus standard blood pressure control on benefit and harm outcomes**
Major cardiovascular events included myocardial infarction, stroke, heart failure, and cardiovascular death. Total adverse events of interest included hypotension, syncope, injurious fall, arrhythmia, angio-oedema and renal adverse events. Renal adverse events included acute kidney injury, renal failure, end-stage renal disease or dialysis, a reduction of 50% or more in estimated glomerular filtration rate in patients with chronic kidney disease at baseline, or a reduction of 30% or more in estimated glomerular filtration rate to <60 mL/min per 1·73 m² in patients without chronic kidney disease at baseline. CrI=credible interval. HR=hazard ratio. OR=odds ratio. *Benefit outcomes are accompanied by HRs, and harm outcomes by ORs.

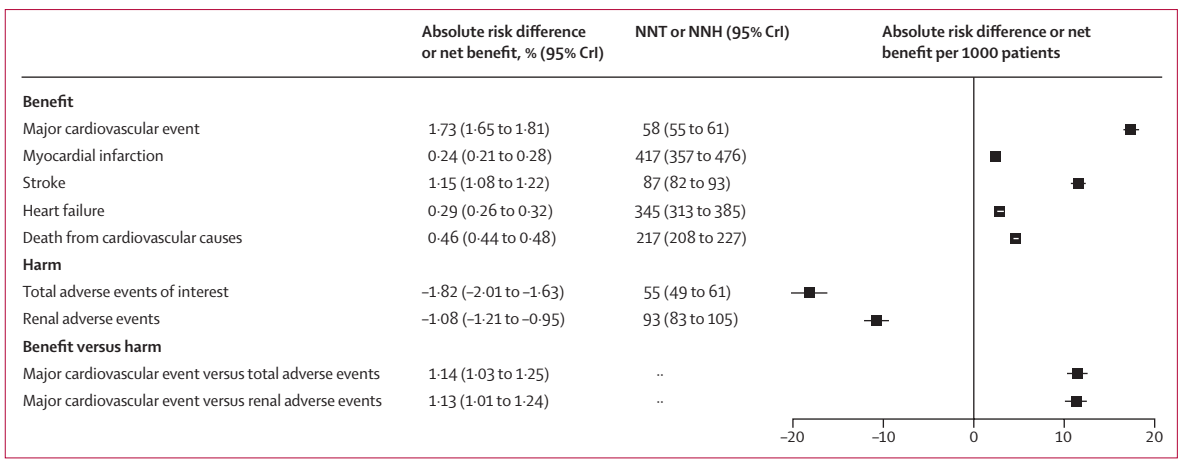

Figure 3: **Net benefit analysis comparing intensive versus standard blood pressure control**
Major cardiovascular events included myocardial infarction, stroke, heart failure, and cardiovascular death. Total adverse events of interest included hypotension, syncope, injurious fall, arrhythmia, angio-oedema and renal adverse events. Renal adverse events included acute kidney injury, renal failure, end-stage renal disease or dialysis, a reduction of 50% or more in estimated glomerular filtration rate in patients with chronic kidney disease at baseline, or a reduction of 30% or more in estimated glomerular filtration rate to <60 mL/min per 1·73 m² in patients without chronic kidney disease at baseline. All NNT and NNH values were based on a median follow-up of 3·2 years (IQR 3·0–3·5). CrI=credible interval. NNH=number needed to harm. NNT=number needed to treat.

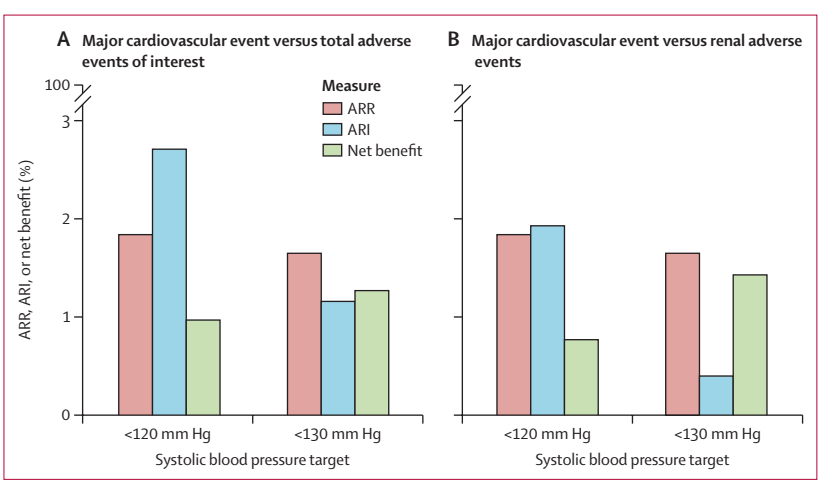

Figure 4: **Net benefits of intensive versus standard blood pressure control in trials with different systolic blood pressure targets (<120 mm Hg and <130 mm Hg)**
(A) Major cardiovascular events versus total adverse events of interest, weighted at 1·0:3·1. (B) Major cardiovascular events versus renal adverse events, weighted at 1·0:1·8. Net benefit is defined as the absolute risk reduction minus the weighted absolute risk increase, expressed as a percentage. Values greater than 0% indicate a net benefit; values of less than 0% indicate net harm. Trials with a systolic blood pressure target of <120 mm Hg were ACCORD BP,[21] SPRINT,[2] ESPRIT,[6] and BPROAD,[7] and those with a systolic blood pressure target of <130 mm Hg were STEP[3] and CRHCP.[5] ARI=absolute risk increase. ARR=absolute risk reduction.

resulting net benefit of intensive treatment over standard treatment was 0·97 (95% CrI 0·87–1·06) in the 120 mm Hg trials and 1·27 (1·16–1·37) in the 130 mm Hg trials, based on adjudicated weights. When considering only kidney-related adverse events, the net benefit was 0·77 (0·59–0·92) in the 120 mm Hg trials and 1·43 (1·32–1·53) in the 130 mm Hg trials (figure 4). Findings were consistent when the benefit-to-harm weighting was adjusted to 1:5 (appendix p 26).

Exploratory subgroup analyses showed that, for the combination of cardiovascular disease versus all adverse events of interest, net benefit of intensive versus standard blood pressure control was greater in younger patients, those with stroke, without chronic kidney disease, and with baseline diastolic blood pressure 70 mm Hg or greater (appendix p 27). Age-specific and diastolic blood pressure-specific patterns are shown in the appendix (pp 28–29). For cardiovascular disease versus renal adverse events, net benefit of intensive blood pressure control versus standard blood pressure control was higher in patients without diabetes than in those with diabetes (appendix p 30). A comprehensive benefit–harm map was developed to show net clinical benefit across patient characteristics, and a phenotype-specific summary table shows estimates for commonly encountered high-risk or clinically debated profiles (appendix pp 31, 58). Further analysis stratified by systolic blood pressure target showed similar results across different patient characteristics (appendix pp 32–33). Results from sensitivity analyses, including covariate adjustment, alternative prior distributions, trial exclusions, competing risk modelling, and considering all-cause mortality as a separate benefit outcome, were broadly consistent with the main findings (appendix p 59).

Discussion

To our knowledge, this is the first pooled individual participant data analysis of high-quality randomised controlled trials evaluating the net clinical benefit of intensive versus standard blood pressure control, and the six included trials are the most representative and rigorous studies in the intensive blood pressure control literature. Overall, intensive blood pressure lowering reduced cardiovascular events and showed a favourable net benefit, even when accounting for potential renal harm (appendix pp 34–35). Both 120 mm Hg and 130 mm Hg systolic blood pressure targets showed net

benefit, but to varying degrees. Exploratory subgroup analyses showed heterogeneity in net benefit across patient characteristics (eg, greater benefit in those with stroke), highlighting the need for further investigation.

Recommendations for intensive blood pressure control in current hypertension guidelines have not been primarily grounded in quantitative benefit–harm assessments.[1,8,9,29,30] A review reported that only 19% of comparative effectiveness studies on medications primarily focused on harm outcomes.[31] Benefit–harm analysis offers a structured framework for evaluating the balance between the benefits and risks of medications and health-care interventions.[32,33] Such assessments are essential to support shared decision making between clinicians, patients, and caregivers.[34] Several high-quality studies have provided examples for applying net benefit analysis in clinical decision making.[35–37] Although several studies have evaluated the net benefit of intensive blood pressure control,[14,38,39] they have all relied solely on data from the SPRINT trial,[2] which limits the applicability of their findings. By contrast, our study draws on data from six pivotal randomised controlled trials, encompassing diverse populations, including patients at high risk of cardiovascular disease, general populations, and patients with conditions such as diabetes, stroke, and coronary artery disease, from both hospital and community settings. This provides robust, authoritative evidence to guide the clinical practice of intensive blood pressure control.

The net clinical benefit of various intensive systolic blood pressure targets (eg, 120 mm Hg or 130 mm Hg) remains uncertain in current guidelines. Blood pressure values of less than 120/70 mm Hg are generally considered ideal.[8,9,40] Notably, the SPRINT,[2] ESPRIT,[6] and BPROAD[7] trials have consistently shown that lowering systolic blood pressure below 120 mm Hg significantly reduces cardiovascular events.[2,6,7,14] Moreover, an individual-level meta-analysis of 48 randomised controlled trials supported continued cardiovascular disease risk reduction with systolic blood pressure lowered to less than 120 mm Hg.[41] However, alternative meta-analyses suggested that targeting a systolic blood pressure of less than 130 mm Hg might be more reasonable.[42–44] An analysis of 27 414 adults with hypertension aged 60 years and older reported a numerically lower HR for cardiovascular disease with a systolic blood pressure target of less than 130 mm Hg compared with less than 120 mm Hg.[45] To inform this debate, our study pooled recent data from high-quality randomised controlled trials and showed that both 120 mm Hg and 130 mm Hg targets offer meaningful benefit, with variation by patient profile and adverse events. These findings support more individualised guideline development and decision making.

Although this individual participant data meta-analysis ensured high internal validity through harmonised randomised controlled trial data, observational studies remain valuable for complementing evidence, particularly in assessing long-term outcomes, rare events, and real-world implementation. Notably, several cohort studies have also shown cardiovascular benefits of lower blood pressure in patients with diverse characteristics.[46–48] These findings highlight the importance of integrating randomised and routine practice evidence, especially in the evaluation of net clinical benefit.

Our study acknowledges the increased risk of adverse events with intensive blood pressure control, yet weighted analyses showed that the net clinical benefit remained favourable across most scenarios. Moreover, recognising all-cause mortality as the ultimate arbiter of net clinical benefit, we additionally analysed it as an independent benefit endpoint. Although the estimated net benefit was attenuated, it remained favourable, further reinforcing the overall advantage of intensive blood pressure control.

We believe this study provides two key contributions to intensive blood pressure management in clinical practice. First, we pooled updated, high-quality randomised controlled trials using individual participant data analysis—the gold standard for evidence synthesis—to fill gaps in current guidelines. Unlike previous meta-analyses based on outdated studies and aggregate data, our study clarified the net benefit of intensive blood pressure control across diverse populations and mapped key benefit–harm profiles. Second, we proposed a net benefit-based evidence framework for guidelines recommending intensive blood pressure control, similar to the approach used by the US Preventive Services Task Force in their Recommendation Statements.[49,50] This framework offers a systematic evaluation of net benefit for patients, providing a more direct pathway for translating high-quality evidence into routine clinical care.

This study also has several limitations. First, definitions and reporting of adverse events varied across trials, and event dates were often unavailable, limiting time-to-event analyses; however, similar follow-up durations likely mitigated this effect. Second, cognitive outcomes could not be evaluated because of limited and inconsistent data across trials. Third, patient-reported outcomes such as quality of life were missing in most trials, limiting assessment of broader patient-centred benefits and highlighting a key direction for future research. Fourth, the 120 mm Hg and 130 mm Hg systolic blood pressure targets were evaluated in separate trials with different comparators, precluding direct comparison between the two strategies. Although our study did not aim to establish which target is superior, patient characteristics such as age and race were closely aligned with target assignment across trials, introducing potential confounding. In addition, given that the subgroup analyses were exploratory and involved multiple comparisons, these findings should be interpreted with caution. Finally, results should be interpreted within the context of the limitations of post-hoc analysis.

In conclusion, our pooled individual participant data analysis of six pivotal randomised controlled trials confirms that intensive blood pressure control yields net cardiovascular benefit across diverse populations. This research addresses substantial gaps in hypertension guidelines and offers robust, actionable evidence to inform clinical practice.

Contributors

XG, GS, YX, SZ, QS, YL, GN, YB, WW, JC, JL, and YS conceived and designed the study. XG, GS, YX, SZ, QS, YL, GN, YB, WW, JC, JL, and YS supervised the data collection. NO, NY, JW, YZ, HY, CS, CW, and SL collected data. SZ, GL, ZC, WZ, and AEM analysed and interpreted the data. XG, GS, and YS drafted the manuscript. All authors revised the manuscript for important intellectual content and approved the final submitted version. XG, GS, SZ, and YS accessed and verified the data. All authors vouch for the completeness and accuracy of the data and for the fidelity of the trial to the protocol, had access to all the included data, and had final responsibility for the decision to submit to publication.

Declaration of interests

We declare no competing interests.

Data sharing

Individual participant data from the ACCORD BP[21] and SPRINT[2] trials are available from the National Heart, Lung, and Blood Institute Biologic Specimen and Data Repository Information Coordinating Center, in accordance with its data sharing policy. De-identified data from the CRHCP trial[4,5] can be requested from YS (yxsun@cmu.edu.cn). De-identified data from the ESPRIT trial[6] can be requested from JL (esprit_data@fuwaihospital.org) from 2 years after the publication of the ESPRIT trial. De-identified data from the STEP trial[3] can be requested from JC (caijun7879@126. com). De-identified data from the BPROAD trial[7] can be requested from GN (gning@sibs.ac.cn) from 3 years after the publication of the BPROAD trial. All data requests must include a methodologically sound research proposal and will be subject to review by the respective study steering committee. Data access agreements may be required as applicable.

Acknowledgments

This work was funded by the National Key Research and Development Program, the Ministry of Science and Technology of China (2017YFC1307600); the National Science and Technology Major Project (2023ZD0508900); the National Natural Science Foundation of China (82088102); the China Academy of Chinese Medical Sciences Innovation Fund for Medical Science (2021-I2M-1-009); and the Science and Technology Program of Liaoning Province (2020JH1/10300002). In addition, China Medical University and the First Hospital of China Medical University provided financial and staff support for this project. AEM is affiliated with Columbia University and Resolve to Save Lives, and receives support from the US National Institutes of Health and the American Heart Association, none of which is related to the present study. We thank Duolao Wang (Liverpool School of Tropical Medicine, Liverpool, UK) for his valuable advice and assistance with statistical analyses. We are grateful to all investigators, trial staff, and participants across all six studies for their important contributions.

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