Age and blood pressure stratified effects of blood pressure-lowering pharmacotherapy for the prevention of cardiovascular disease and death: an individual-level meta-analysis of 358,707 randomised participants

The Blood Pressure Lowering Treatment Trialists' Collaboration*

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Abstract

Background: The effects of pharmacological blood pressure (BP)-lowering on cardiovascular outcomes in older individuals, particularly when BP is not substantially elevated, remains uncertain. We compared the effects of BP-lowering treatment on the risk of major cardiovascular events in groups of patients stratified by age and BP at baseline.

Methods: We conducted an individual participant-level data (IPD) meta-analysis of randomised controlled trials of pharmacological BP-lowering versus placebo or other classes of BP-lowering medications, or between more versus less intensive treatment strategies, which had at least 1000 persons-years of follow-up in each treatment arm. Data from 51 randomised clinical trials were obtained from the Blood Pressure Lowering Treatment Triallists' Collaboration involving 358,707 participants. We pooled the data and categorised participants into baseline age groups (<55, 55-64, 65-74, 75-84, and ≥85 years) and BP categories (in 10-mmHg increments from <120 to ≥170 mmHg systolic BP and from <70 to ≥110 mmHg diastolic). We used a fixed-effect one-stage IPD meta-analysis approach and applied Cox proportional hazard models, stratified by trial, to analyse the data.

Results: The age of participants at randomisation ranged from 21 to 105 years (median 65, interquartile range 59 to 75), with 42,960 (12%) of participants aged <55 years, 128,437 (35.8%) 55 to 64 years, 128,506 (35.8%) 65 to 74 years, 54,016 (15.1%) 75-84 years, and 4,788 (1.3%) ≥ 85 years. The hazard ratios for the risk of major cardiovascular events per 5-mmHg systolic BP reduction for each age group were: <55 years 0.82 (95% confidence interval 0.76-0.88), 55-64 years 0.91 (0.88-0.95), 65-75 years 0.91 (0.88-0.95), 75-84 years 0.91 (0.87-0.96), and ≥85 years 0.99 (0.87-1.12) (adjusted p for interaction=0.05). Similar patterns of proportional risk reductions were observed for a 3-mmHg diastolic BP reduction. Absolute risk reductions for major cardiovascular events varied by age and were larger in older groups (adjusted p for interaction=0.025). We did not find evidence for any clinically meaningful heterogeneity of relative treatment effects across different baseline BP categories in any age group.

Conclusions: Pharmacological BP reduction is effective into old age, with no evidence to suggest that relative risk reductions for prevention of major cardiovascular events vary by systolic or diastolic BP levels at randomization, down to less than 120/70 mmHg. It should therefore be considered an important treatment option regardless of age with removal of age-related thresholds from international guidelines.

Research in Context

Evidence before the study

We searched MEDLINE, The Cochrane Central Register of Controlled Trials and ClinicalTrials.gov covering the period between 1 January 1966 and 1 September 2019, with no language restrictions, for randomised controlled trials investigating blood pressure (BP)-lowering drug treatment. We searched MEDLINE using and expanding on the MeSH terms for “hypertension”, “blood pressure”, and “antihypertensive agents” including possible variations thereof as well as relevant antihypertensive drug classes. We identified several individual randomised controlled trials and meta-analyses with age-stratified effect of BP-lowering treatment but no reports with concurrent age and BP stratification at the level of individuals. Additionally, evidence on treatment effects in the very elderly and normal or mildly elevated BP was limited.

Added value of this study

We gathered individual participant-level data (IPD) from eligible large-scale trials of BP-lowering treatment. With access to IPD from 358,707 randomised participants from 51 trials (with 22,000 aged 80 years and older), this study enabled detailed investigation of age and BP stratified effects on major cardiovascular events and death. Participants were divided into baseline age groups (<55, 55-64, 65-74, 75-84, and ≥85 years) and BP categories (in 10-mmHg increments from <120 to ≥170 mmHg systolic BP and from <70 to ≥110 mmHg diastolic). We found pharmacological BP reduction to be effective across a wide range of ages with no evidence to suggest that relative risk reductions for prevention of major cardiovascular events varied by baseline systolic or diastolic BP levels, down to less than 120/70 mmHg. Although there was suggestive evidence for diminishing relative risk reductions with increasing age (adjusted p for heterogeneity = 0.05) and limited statistical power for detection of an effect in the oldest age group in isolation (90 years at the end of the study), absolute risk reductions did not follow the same pattern and appeared to be even larger in the older age groups. Stratified effects on all-cause death followed a similar pattern, with no evidence to suggest that treatment increases mortality in any age group.

Implications of all the available evidence

This most detailed study of age and BP stratified effect of antihypertensive medication provides compelling evidence for the effectiveness of pharmacological BP reduction into old age irrespective of baseline systolic or diastolic BP. This challenges the common approach of withholding antihypertensive treatment for older adults, in particular when their BP is not highly abnormal. Treatment should therefore be considered an important option regardless of age with removal of age-related thresholds from international guidelines.

Background

Elevated blood pressure (BP) is a well-known, modifiable risk factor for cardiovascular morbidity and mortality, and antihypertensive medications play an essential cardioprotective role.[1,2] With ageing populations, one increasingly important uncertainty of the effects of BP-lowering pharmacotherapy is whether treatment should be initiated in, and continued into, older age, mainly when BP is within the 'normal' range.[3]

Epidemiological studies have suggested that elevated BP is a major risk factor for cardiovascular events across different age categories and over a wide range of BP.[4–7] Although these studies have found some attenuation in relative risks with increasing age, older patients might still gain as much as, if not more than, younger individuals from BP-lowering because the absolute cardiovascular event rates increase with age.[5] On the other hand, other studies have challenged this observation and have reported an increased risk of cardiovascular events and death in older patients with lower BP compared to those with higher BP.[8–11] Some have even suggested a rapid decline in BP in the years preceding death, raising doubts about the value of BP-lowering treatment in older people.[12]

Thus far, robust evidence from randomised controlled trials (RCTs) has been lacking, in part because of the underrepresentation of older individuals in clinical trials. To date, HYVET remains the only large-scale trial that has exclusively recruited patients aged 80 years and older.[13] While this study found 30% and 23% reductions in risk of stroke and cardiovascular death, respectively, its 3845 participants were selected based on very high BP at baseline. Several other randomised trials and their meta-analyses have also investigated the effects of BP reduction by age.[14–16] While these studies found no evidence of heterogeneity of effects by age, individual trials have had limited statistical power to investigate this question in depth. Previous meta-analyses were also mainly based on broad age categories (e.g. <65 years vs ≥65 years) and could not investigate effects based on narrower age groups and by other important characteristics such as baseline BP.[15] This uncertainty is evident in the conflicting clinical guideline recommendations for treatment according to age (**Table S1**).[17–19]

The third cycle of the Blood Pressure Lowering Treatment Trialists' Collaboration (BPLTTC) now has access to individual participant-level data (IPD) of over 350,000 randomised patients with 22,000 patients aged 80 years and older.[20] This offered an unprecedented opportunity to conduct an IPD meta-analysis of RCTs to investigate the stratified effects of pharmacological BP-lowering treatment on the risk of major cardiovascular events and death across age, systolic and diastolic BP categories at baseline.

Methods

Study governance, data source and eligibility criteria

We used the resources provided by the BPLTTC to conduct this IPD meta-analysis. The BPLTTC is a collaboration of the principal investigators of major clinical trials of pharmacological BP-lowering treatment (www.bplttc.org). The collaboration is coordinated by the University of Oxford and, based on the last update, includes information from 52 randomised trials.[20] Details of the BPLTTC design have been reported elsewhere.[2,20,21] The initial inclusion criteria of the BPLTTC were RCTs of pharmacological BP-lowering treatment with at least 1000 persons-years of follow-up in each randomly allocated group. In the current analysis, we included trials that provided data for outcomes, including type and timing of events, as well as age and baseline BP measurements. Participants with previous history of heart failure were excluded. Ethics approval for the current phase was obtained from the Oxford Tropical Research Ethics Committee (OxTREC Reference 545–14), and the current analysis plan was approved by the BPLTTC steering committee and collaborators before releasing the data for analysis.

Definition of outcomes, randomised groups and stratification variables

The primary outcome was defined as either a composite of fatal or non-fatal stroke, fatal or non-fatal myocardial infarction or ischaemic heart disease, or heart failure causing death or requiring hospitalisation. The secondary outcomes included all-cause death, and each component of the primary outcome. For each trial, randomised arm(s) were classified into

the two arms of “intervention” and “comparator”. For placebo-controlled trials, the placebo arm was considered as the comparator and the active arm as the intervention. For trials comparing different drug classes, the arm in which the BP reduction was greater was considered as intervention and the other treatment arm(s) as comparator. Trials that compared “more intense” versus “less intense” strategy were classified as the intervention and comparator arms, respectively. Detailed information about the comparison groups, trial design and patient characteristics, and level of BP reduction for each trial have been reported elsewhere.[2,20,21]

To identify age-specific effects, we categorised participants into five groups based on their age at baseline (less than 55, 55-64 years, 65-74 years, 75-84 years and 85 years or higher). To examine the risk reduction across BP categories, we stratified the participants into seven categories of baseline systolic BP including <120 mmHg, 120-129 mmHg, 130-139 mmHg, 140-149 mmHg, 150-159 mmHg, 160-169 mmHg, ≥170 mm Hg and six categories of baseline diastolic blood pressure including <70 mmHg, 70-79 mmHg, 80-89 mmHg, 90-99 mmHg, 100-109 mmHg, ≥110 mmHg.

Statistical analysis

We conducted a one-stage IPD meta-analysis using stratified Cox proportional hazard models, with fixed treatment effects, and participants as the units of analysis.[2,22] The model was stratified by baseline hazard functions for each trial to satisfy the proportional hazards assumption.[23] We performed an intention-to-treat analysis based on the groups to which each participant had initially been assigned (intervention versus comparator). Patients entered the analysis at the date of the randomisation and were followed-up until the earliest occurrence of the outcome of interest, death, or end of the trial. The average systolic and diastolic BP reduction between randomised groups, excluding the first 12 months, among all trials that aimed at achieving a difference in BP was 6.3 mmHg (95% confidence interval [CI], 6.1 to 6.4) and 3 mmHg (CI 2.9 to 3.0), respectively.[21] Therefore, we standardised the effect sizes for each 5 mmHg reduction in systolic and 3 mmHg for diastolic BP reduction. The method used for this standardisation, and detailed description of the statistical analyses have been published elsewhere.[2]

We plotted cumulative incidence curves by treatment allocation and age categories. Hazard ratios (HR) and their 95% CI were presented using forest plots with standardisation by 5 mmHg systolic BP reduction and 3 mmHg diastolic BP reduction. To test whether treatment effects varied across prespecified subgroups of age categories and systolic and diastolic BP levels at baseline, we used likelihood-ratio tests for interactions. Likelihood-ratio tests compares models with and without interactions between treatment effect and age or blood pressure categories. The calculated p for interaction was adjusted for multiple testing using Hommel's method to avoid chance finding.[24,25] As a sensitivity analysis, we estimated the unstandardised effect, which did not consider weighting treatment effects by the achieved BP reduction for each trial. These analyses were pre-specified and followed the study protocol. In response to reviewer comments, we performed a sensitivity analysis investigating the unstandardised age-stratified effects and additionally stratified by the three types of trial designs. We further calculated the absolute risk reductions using a Poisson regression model with identity link for each stratum to investigate the heterogeneity of treatment effects on an absolute scale. For this analysis, the absolute risk difference would reflect the mean BP reduction across all trials contributing data for that each category. Analyses were performed using R (version 3.3) statistical software.

Role of funders

The funders had no role in the design or conduct of the study, data analysis, interpretation of the results, manuscript preparation, or approval to submit for publication.

Results

Of the 52 randomised trials included in the BPLTTC, one trial was excluded because it did not report the outcome of interest **(Table S2**). Therefore, 51 trials comprising 358,707 participants were included in the analysis (**Table S2**). There were no reports of heart failure outcome in six trials, no cardiovascular death outcomes in five trials, and no stroke and ischaemic heart disease outcomes in one trial (**Table S2**). Of the included participants, 42,960 (12%) were aged 55 years or younger, 128,437 (35.8%) aged 55 to 64 years, 128,506 (35.8%) aged 65 to 74 years, 54,016 (15.1%) were aged 75-84 years and 4788 (1.3%) were

aged 85 years or older (age range 21 to 105 years). The highest median follow-up time was in aged 55 years or younger (4.5 [interquartile range (IQR)=3.1] years) and the lowest median follow-up was in aged 85 and older (2.8 [IQR 2.3] years). Compared with men, the percentage of women was higher in older age groups and lower in younger age groups. The prevalence of peripheral vascular disease, atrial fibrillation and cerebrovascular disease at baseline were greater in the older age groups. Mean systolic and diastolic BP at baseline tended to be higher and lower in older age groups, respectively. Detailed characteristics of participants stratified by age categories are presented in **Table 1**.

The cumulative incidence for the primary outcome stratified by age categories at baseline and treatment allocation showed an increasing incidence by increasing age (**Figure 1**). In all age groups, event rates were lower in the intervention than in the comparator group. However, the confidence limit was widest in the group of individuals aged 85 years or higher at baseline, reflecting the limited number of participants and events in this group (**Figure 1**). The age-stratified relative and absolute risk reductions for the primary and secondary outcomes are shown in **Figure 2**. For the primary outcome of major cardiovascular events, there was suggestive evidence for heterogeneous treatment effects by age, with a pattern consistent with a greater relative risk reduction in the youngest age group and smaller effects with wider CI in those aged 85 or more at baseline (adjusted $P_{interaction}$=0.05). A 5-mmHg pharmacological systolic BP reduction lowered the risk of major cardiovascular events in participants aged 55 years or younger (hazard ratio [HR] 0.82, 95% confidence interval [CI] 0.76 to 0.88), aged 55 to 64 years (HR 0.91, 95% CI 0.88 to 0.95), aged 65 to 74 years (HR 0.91, 95% CI 0.88 to 0.95) and aged 75 to 84 (HR 0.91, 95% CI 0.87 to 0.96). The relative treatment effect in participants aged 85 years or older in isolation was not significant (HR 0.99, 95% CI 0.87 to 1.12) (**Figure 2**). However, due to the higher event rate in the older groups, we observed a somewhat higher absolute reduction in the risk of major cardiovascular events in the older groups (adjusted $P_{interaction}$=0.025) (**Figure 2**). Broadly similar patterns of absolute and relative risk reductions were observed for the secondary outcomes of stroke, ischaemic heart disease, heart failure, cardiovascular death and all-cause death. However, the effect estimates were less precise for some of these outcomes (**Figure 2**). Relative risk reductions for a 3 mmHg diastolic BP reduction are presented in **Figure S1**, and were consistent with those for a 5 mmHg systolic BP reduction.

To assess whether the average treatment effects in each age group varies by baseline BP of individuals, we further stratified individuals in each age group into 7 pre-specified subgroups of systolic BP. This analysis showed no evidence of any heterogeneous treatment effect by categories of systolic BP at baseline on the risk of major cardiovascular events in any of the age groups (all adjusted $P_{interaction}$>0.07) (**Figure 3**). In particular, while the CIs of effect estimates were less precise for those aged 85 years compared with other age groups, there was no evidence to suggest that the overall weaker effects in this age group were masking heterogenous treatment effects by baseline BP (adjusted $P_{interaction}$=1). In line with this, there was also no clear pattern of increasing proportional effects among individuals with higher baseline systolic BP on the risk of major cardiovascular events. Similarly, the effects of diastolic BP reduction stratified by baseline diastolic BP categories and age groups on the risk of major cardiovascular events showed no heterogeneity of treatment by diastolic BP at baseline (all adjusted $P_{interaction}$>0.84) (**Figure 4**). Age and BP stratified analyses of the treatment effects on the risk of all-cause mortality were broadly consistent with the results of major cardiovascular outcomes, showing no evidence of diminishing relative effects in lower systolic (**Figure S2**) or diastolic BP categories (**Figure S3**).

In a sensitivity analysis, we repeated the analysis without standardisation for BP reduction at the trial level and found that the findings were broadly similar to the main results, both overall (**Figure S4**) and when stratified by the three types of trial designs included (**Table S3**).

Discussion

This individual-level meta-analysis of 358,707 randomised participants showed that pharmacological BP reduction is effective across a wide range of ages with no evidence to suggest that relative risk reductions for prevention of major cardiovascular events vary by baseline systolic or diastolic BP levels, down to less than 120/70 mmHg. Although there was a suggestive evidence for diminishing relative risk reductions with increasing age, absolute risk reductions did not follow the same pattern and appeared to be even larger in the oldest age groups. Stratified effects on all-cause death followed a similar pattern, with no evidence

to suggest that treatment increases mortality in any age group. With only about 1000 major cardiovascular events accrued over a median follow-up duration of 2.8 years in the group of participants aged 85 or more at randomisation, the treatment effects in this highest age category in isolation were uncertain.

Representative national surveys of Western populations have shown that systolic BP increases continuously with age.[26] This pattern has traditionally been considered as a natural process of ageing that is 'essential' for maintenance of coronary and cerebral perfusion. However, the observation that in populations remote from Western lifestyle, BP levels do not increase with age,[27,28] as well as epidemiological studies showing strong associations between elevated BP and cardiovascular disease across all age groups[4,6,7] and down to a systolic BP of 90 mmHg in healthy adults[29] have gradually shifted the perception that a higher BP in older individuals is inevitable and physiologically necessary. However, randomised evidence on the effect of pharmacological BP-lowering on cardiovascular outcomes in the very elderly across a wide range of BP has been limited, leading to conflicting guideline recommendations across the world. To our knowledge, the American College of Cardiology/American Heart Association (ACC/AHA) 2017 guidelines remains an exception in not making an age distinction for their treatment recommendation.[18] By contrast, the European Society of Cardiology/European Society of Hypertension (ESC/ESH) set the threshold for consideration of drug treatment in those aged 60-79 years at ≥140/90 mmHg and in those aged 80 years or more at ≥160/90 mmHg.[17] Similarly, the National Institute for Health and Care Excellence (NICE) 2019 guidelines for England do not recommend treatment in adults over 80 years of age if their BP is lower than 150/90 mmHg.[19] The American College of Physicians/American Academy of Family Physicians (ACP/AAFP) 2017 guidelines even consider treatment above 60 years as only indicated when systolic BP is >150 mmHg.[30] The more recent guidelines by the International Society of Hypertension also make a distinction by age and recommend a target of <140/90 mmHg for those aged 65 years and more.[31]

The findings from our study close the gap in evidence for age-specific treatment effects on major cardiovascular outcomes. With access to individual-level data including detailed

systolic and diastolic BP measurements from 54,016 randomised participants aged 75-84 and 4788 participants aged 85 years or more, we were able to investigate the effects of treatment to greater depth than before, and importantly with simultaneous stratification by systolic or diastolic BP down to <120/70 mmHg at randomisation. For our primary and secondary outcomes, we found no strong evidence of heterogeneity of relative effects across a wide range of systolic or diastolic BP categories. These findings are in line with a recent report by the BPLTTC that had shown consistent effects for primary and secondary prevention of cardiovascular disease with no evidence of diminishing effects when systolic BP was normal or mildly elevated.[2] The present study extends those earlier findings to diastolic BP of <70 mmHg and challenges the differential treatment recommendation by age and BP for prevention of major cardiovascular events.

The second main finding of this study was the observation that relative risk reductions appeared to diminish with increasing age. The reasons behind this observation are not entirely clear and could be of statistical or biological nature. With a p-value for interaction of 0.05 for the primary outcome and the absence of any meaningful interaction by age for ischaemic heart disease and heart failure, a chance finding cannot be ruled out. Indeed, an alternative interpretation of our age stratified results could be that relative risk reductions for the majority of participants included in the analyses (55 to 85 years at baseline) are consistent. On the other hand, statistical tests for interaction are notoriously conservative and our results in the context of large-scale epidemiological studies,[4,6] which have also shown a pattern of diminishing relative effects with increasing age, invites consideration of different explanations. For instance, the shorter treatment duration in older participant groups and their longer longer life-time exposure to elevated BP might limit the reversibility of the vascular effects of treatment over a relatively short period of time. Of note, the average treatment duration in the oldest age group was only about half of that in the youngest age group. Furthermore, younger people are less likely to present with multiple risk factor for CVD than older people, and this difference could also explain the stronger relative contribution of a single risk factor in younger age compared with older age when overt CVD risk factor clustering tends to diminish relative risks while increasing absolute risks.

Regardless of whether the heterogeneity of relative treatment effects by age are meaningful or spurious, the absolute risk reductions afforded by the treatment more convincingly increased with age - because of the substantially increasing risk of vascular events by age. The strength of RCTs lies in their ability to provide unbiased estimates of relative treatment effects that are typically generalisable across time and place. However, estimates of absolute risks are less generalisable because trial participants are rarely representative of populations to whom the results are to be applied. Therefore, we caution against overinterpretation of our results by assuming that the absolute risk reductions reported are fixed and directly applicable to decision making. More appropriately, such estimates are to be derived from the combination of proportional effects in our study and absolute risks taken from contemporary patient registries.[32] Thus, our analyses of absolute risk differences are only useful for *internal comparisons* of effect sizes across strata. To this end, the observation of increasing absolute risk reductions in older participant groups should help overcome the clinical inertia and the common inverse care law to which many older individuals are subjected.[33]

Our analyses focused on the effects of a fixed degree of BP reduction on future risk of major cardiovascular events, including its components of stroke, heart failure, ischaemic heart disease and cardiovascular death. We also report the effects on all-cause death which might be of particular interest to guide decision making for BP-lowering pharmacotherapy in older individuals. We found that the proportional risk reduction for all-cause death is marginally larger in younger than older age, with no obvious effect in people older than 75 years. In general, treatment effects on all-cause death from targeted interventions in RCTs are to be interpreted with caution because of their sensitivity to varying fractions of outcomes that are amenable to treatment and those that are unlikely to be affected by them. For instance, in another BPLTTC report, we have shown that BP-lowering pharmacological therapy has no material effect on cancer risk.[34] But, if cancer death rate is substantially elevated in one group, then one would expect a dilution of proportional treatment effects in comparison with another group that has a higher fraction of cardiovascular death, despite consistent effects on cardiovascular events. With these considerations in mind, the lack of excess mortality risk in older groups suggests that harmful fatal effects of the treatment are very unlikely in any age group.

It could be argued that health-related quality of life and prevention of harms is of equal or even greater importance to the very elderly than prevention of fatal or non-fatal cardiovascular events. However, to our knowledge, there are no randomised comparisons to suggest that a fixed level of BP reduction in older individuals causes more harm than benefit in older people. For instance, in a subgroup analysis of SPRINT, the total serious adverse event rates were similar in the two study arms.[35] Several other age-stratified analyses of RCTs and their meta-analyses have also shown no worsening in functional status, physical wellbeing, or quality of life.[36] Concerns about worsening cognitive function in older people and low BP have been raised in some observational studies but are likely due to reverse causation[37] and have not been substantiated in randomized trial thus far.[38] Planned BPLTTC projects are investigating some of those questions in greater detail.[20]

Our study represents the most detailed analysis of BP-lowering treatment effect by age and BP to date. However, there are several limitations, which should be taken into account when interpreting our results. Our effect estimates for people aged 85 years and older at randomisation (average age 90 years at the end of the trial) were uncertain, due to the comparatively smaller number of participants developing the main outcome (1041 events). Relatedly, due to the typically restricted eligibility criteria of RCTs, other groups such as those with a high multimorbidity and polypharmacy burden and the very frail and institutionalised individuals have been underrepresented.[39] The generalisability of the findings to these highly relevant and growing patient groups remains uncertain.[40-42] Future studies such as the ATEMPT (Anti-hypertensive Treatment Evaluation in Multimorbid and Polymedicated patients Trial - ISRCTN17647940) shall address those limitations and investigate treatment effects on several additional patient-important outcomes. We acknowledge that clinical decisions cannot be deferred until such evidence emerges. However, in the absence of any strong evidence for excess harms from randomised studies, we believe that it is appropriate for patients who are on BP-lowering pharmacotherapy to continue receiving such treatment if well-tolerated and when prevention of fatal and non-fatal cardiovascular events remains of importance.

In conclusion, we found no evidence to substantiate the common approach of withholding antihypertensive treatment for older adults, in particular when their BP is not highly abnormal. Although the findings for people aged 85 years or more at study entry (average 90 years at the end of the study) were less compelling, the overall patterns were consistent and suggestive of worthwhile reductions in cardiovascular outcomes across all age groups. While clinical decision-making for initiation and continuation of pharmacological BP-lowering will continue to be based on harm-benefit trade-offs for any individual, our study does not support the common belief that such trade-offs justify the overemphasis of several clinical practice guidelines on an individual's age or starting BP. Therefore, pharmacological BP reduction should be considered as an important treatment option for prevention of cardiovascular events even in those aged 80 years or more and guidelines should be simplified to remove any differing BP thresholds by age.

Author contribution

KR was responsible for the conceptualising the study. KR, ZB, MN, EC, DC, JC, BRD, CJP and KKT were involved in developing the research protocol and investigation plan. EC, DC, ZB, MN and KR are responsible for data curation. KR drafted the original version of the manuscript. All authors contributed in writing and editing subsequent versions of the manuscript. All authors provided intellectual input and helped interpret the data. ZB was responsible for data visualisation. KR, MN and DC acquired funding for the study. The Blood Pressure Lowering Treatment Trialists' Collaboration Core Analytic group (ZB, MN, EC, DC, and KR) has full access to the study data, and takes responsibility for the integrity of the data and accuracy of the data analysis. The corresponding author has the final responsibility for the decision to submit for publication.

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Archive, and declare that those who carried out the original analysis and collection of the data bear no responsibility for the further analysis or interpretation of the data.

Declaration of interest

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Ethics approval

The BPLTTC obtained approval to conduct this collaborative research from the Oxford Tropical Research Ethics Committee (OXTREX Reference: 545-14).

Data sharing statement

The governance of the BPLTTC have been reported previously.[11] The BPLTTC is governed by the University of Oxford's policies on research integrity and codes of practice and follows the university's policy on the management of research data and records. Scientific activities based on BPLTT dataset are overseen by the BPLTT Steering Committee. All data shared with the BPLTTC are considered confidential, and will not be provided to any third party. Requests for data should be made directly to the data custodians of individual trials. Information about individual projects is posted at www.bplltc.org.

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J Kostis (SHEP [Systolic Hypertension in the Elderly Program]),

K Kuramoto (NICS-EH [National Intervention Cooperative Study in Elderly Hypertensives]),

J Lanke (STOP Hypertension-2 [Swedish Trial in Old Patients with Hypertension-2], NORDIL [Nordic Diltiazem]),

E Lewis (IDNT),

J B Lewis (IDNT),

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L H Lindholm (CAPPP [Captopril Prevention Project], STOP Hypertension-2, NORDIL),

S Lueders (MOSES [The Morbidity and Mortality After Stroke, Eprosartan Compared With Nitrendipine for Secondary Prevention]),

S MacMahon (ADVANCE, PART-2 [Prevention of Atherosclerosis with Ramipril Trial]),

G Mancia (INSIGHT)

M Matsuzaki (COPE [The Combination Therapy of Hypertension to Prevent Cardiovascular Events]),

M H Mehlum (VALUE),

S Nissen (CAMELOT [Comparison of Amlodipine vs Enalapril to Limit Occurrences of Thrombosis]),

H Ogawa (HIJ-CREATE [Heart Institute of Japan Candesartan Randomized Trial for Evaluation in Coronary Heart Disease]),

T Ogihara (CASE-J, COLM [Combinations of OLMesartan], COPE),

T Ohkubo (HOMED-BP),

C R Palmer (INSIGHT),

A Patel (ADVANCE),

C J Pepine (INVEST [International Verapamil SR-Trandolapril Study]),

M A Pfeffer (PEACE [Prevention of Events With Angiotensin- Converting Enzyme Inhibition]),

B Pitt (PREVENT)

N R Poulter (ASCOT [Anglo-Scandinavian Cardiac Outcomes Trial]),

H Rakugi (CASE-J, VALISH [Valsartan in Elderly Isolated Systolic Hypertension Study]),

G Reboldi (Cardio-Sis [CARDIOvascolari del Controllo della Pressione Arteriosa SIStolica]),

C Reid (ANBP2 [The Second Australian National Blood Pressure Study]),

G Remuzzi (BENEDICT [BErgamo NEphrologic DIabetes Complications Trial]),

P Ruggenenti (BENEDICT),

T Saruta (CASE-J),

J Schrader (MOSES),

R Schrier (deceased) (ABCD),

P Sever (ASCOT-BPLA),

P Sleight (deceased) (CONVINCE, HOPE [Heart Outcomes Prevention Evaluation], ONTARGET [Ongoing Telmisartan Alone and in Combination with Ramipril Global Endpoint Trial], TRANSCEND [Telmisartan Randomised AssessmeNt Study in ACE iNtolerant subjects with cardiovascular Disease]),

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H Suzuki (E-COST),

L Thijs (Syst-Eur),

K Ueshima (CASE-J, VALISH),

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K Wachtell (LIFE),

P Whelton (SPRINT),

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M Woodward (ADVANCE, PROGRESS)

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Table 1. Baseline characteristics of participants by age categories at baseline.

Characteristic	< 55 years (n=42960)	55-64 years (n=128437)	65-74 years (n=128506)	75-84 years (n=54016)	≥ 85 years (n=4788)
Sex					
Women	14957 (34.8)	49785 (38.8)	53696 (41.8)	27835 (51.5)	2938 (61.4)
Men	28003 (65.2)	78652 (61.2)	74810 (58.2)	26181 (48.5)	1850 (38.6)
Systolic blood pressure (mmHg)	150 (20.7)	150 (20.4)	153 (21.2)	158 (22.3)	157 (20.5)
Diastolic blood pressure (mmHg)	95 (12.4)	88 (11.9)	86 (11.8)	84 (11.9)	82 (12.1)
Categories of systolic blood pressure (mmHg)					
<120	2384 (5.6)	7151 (5.6)	5415 (4.2)	1646 (3.1)	121 (2.5)
120-129	3864 (9.1)	12537 (9.8)	10137 (7.9)	3285 (6.1)	305 (6.4)
130-139	6164 (14.5)	19212 (15.1)	16467 (12.9)	5753 (10.7)	510 (10.7)
140-149	8535 (20.1)	25058 (19.6)	23260 (18.2)	8524 (15.8)	738 (15.4)
150-159	7366 (17.3)	22798 (17.9)	21936 (17.1)	8140 (15.1)	644 (13.5)
160-169	6738 (15.9)	19539 (15.3)	22846 (17.9)	10794 (20.0)	1012 (21.1)
≥170	7433 (17.5)	21230 (16.6)	27888 (21.8)	15821 (29.3)	1458 (30.5)
Categories of diastolic blood pressure (mmHg)					
<70	945 (2.2)	6108 (4.8)	9778 (7.6)	5882 (10.9)	708 (14.8)
70-79	3270 (7.7)	20025 (15.7)	25662 (20.1)	12243 (22.7)	1091 (22.8)
80-89	7527 (17.7)	38509 (30.2)	42986 (33.6)	17808 (33.0)	1378 (28.8)
90-99	13731 (32.3)	37490 (29.4)	32556 (25.4)	12737 (23.6)	1299 (27.2)
100-109	12384 (29.1)	19969 (15.7)	13485 (10.5)	4233 (7.8)	278 (5.8)
≥110	4628 (10.9)	5425 (4.3)	3472 (2.7)	1056 (2.0)	30 (0.6)
Body mass index (kg/m^2)	28.3 (5.0)	28.7 (5.3)	27.8 (10.0)	26.4 (4.8)	25.2 (4.0)
Comorbidity					
Peripheral vascular disease	763 (5.1)	4208 (9.0)	5432 (10.6)	2287 (11.6)	207 (14.0)
Atrial fibrillation	550 (1.3)	2213 (1.7)	4356 (3.4)	3058 (5.7)	308 (6.4)
Diabetes	7257 (16.9)	40686 (31.7)	41269 (32.1)	13199 (24.4)	807 (16.9)
Chronic kidney disease	4562 (16.4)	7893 (16.1)	7725 (16.2)	3634 (19.1)	247 (16.0)
Cerebrovascular disease	3780 (9.5)	16946 (17.2)	19700 (19.6)	9484 (21.0)	737 (19.1)
Ischaemic heart disease	13035 (30.8)	42689 (33.6)	45813 (35.9)	17045 (31.6)	1414 (29.5)
Previous use of non-study medications					
ACEIs	2129 (18.1)	17478 (33.8)	19862 (34.0)	8206 (31.6)	674 (31.8)
ARBs	390 (4.1)	1961 (6.0)	3805 (9.5)	2353 (13.5)	65 (8.1)

Calcium-channel blockers	3960 (27.7)	18172 (30.0)	23400 (34.2)	9888 (33.4)	610 (28.0)
Diuretics	1696 (11.9)	10563 (18.4)	14451 (22.5)	7032 (25.1)	672 (30.9)
Beta-blockers	5565 (39.0)	22382 (36.9)	23597 (34.5)	8007 (27.0)	381 (17.5)
Alpha-blockers	321 (4.9)	1299 (3.2)	2118 (4.4)	1061 (4.8)	53 (5.3)
Anti-platelet medications	1319 (27.7)	19823 (47.1)	21431 (45.3)	7982 (36.3)	476 (25.3)
Anticoagulants medications	304 (6.0)	1519 (5.0)	2893 (8.0)	1763 (13.7)	91 (13.3)
Lipid-lowering medications	4459 (35.1)	21546 (41.5)	21674 (37.5)	6646 (27.8)	154 (8.9)
Follow-up (years)	4.5 (3.1)	4.4(2.0)	4.1 (1.9)	3.7 (2.2)	2.8 (2.3)

Data are n (%), mean (SD), or median (IQR), ACEIs: Angiotensin-converting enzyme inhibitors, ARBs: Angiotensin-receptor blockers

Figure 1. Rate of major cardiovascular events per 5-mmHg reduction in systolic blood pressure, stratified by treatment allocation and age categories at baseline.

Major cardiovascular events, defined as a composition of fatal or non-fatal stroke, fatal or non-fatal myocardial infarction or ischaemic heart disease, or heart failure causing death or requiring hospitalisation. The shaded area represents the 95% confidence intervals.

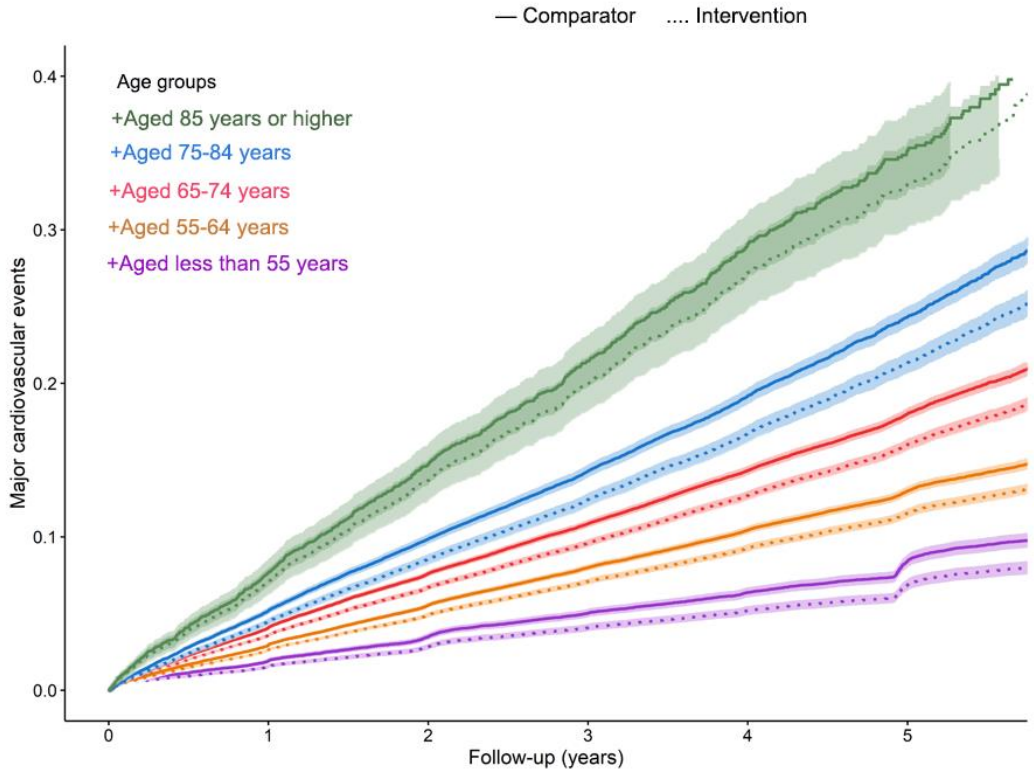

Figure 2. Age-stratified relative risk and absolute risk difference of systolic blood pressure reduction on primary and secondary outcomes.

Relative risk reductions are presented with hazard ratios (HR) and 95% confidence intervals (CI) per 5-mmHg reduction in systolic blood pressure, separately for each outcome. The absolute risk difference reflects mean of blood pressure reduction for each age category. Adjusted p interaction: adjusted for multiple testing using Hommel's method. Unadjusted p interaction: unadjusted for multiple testing.

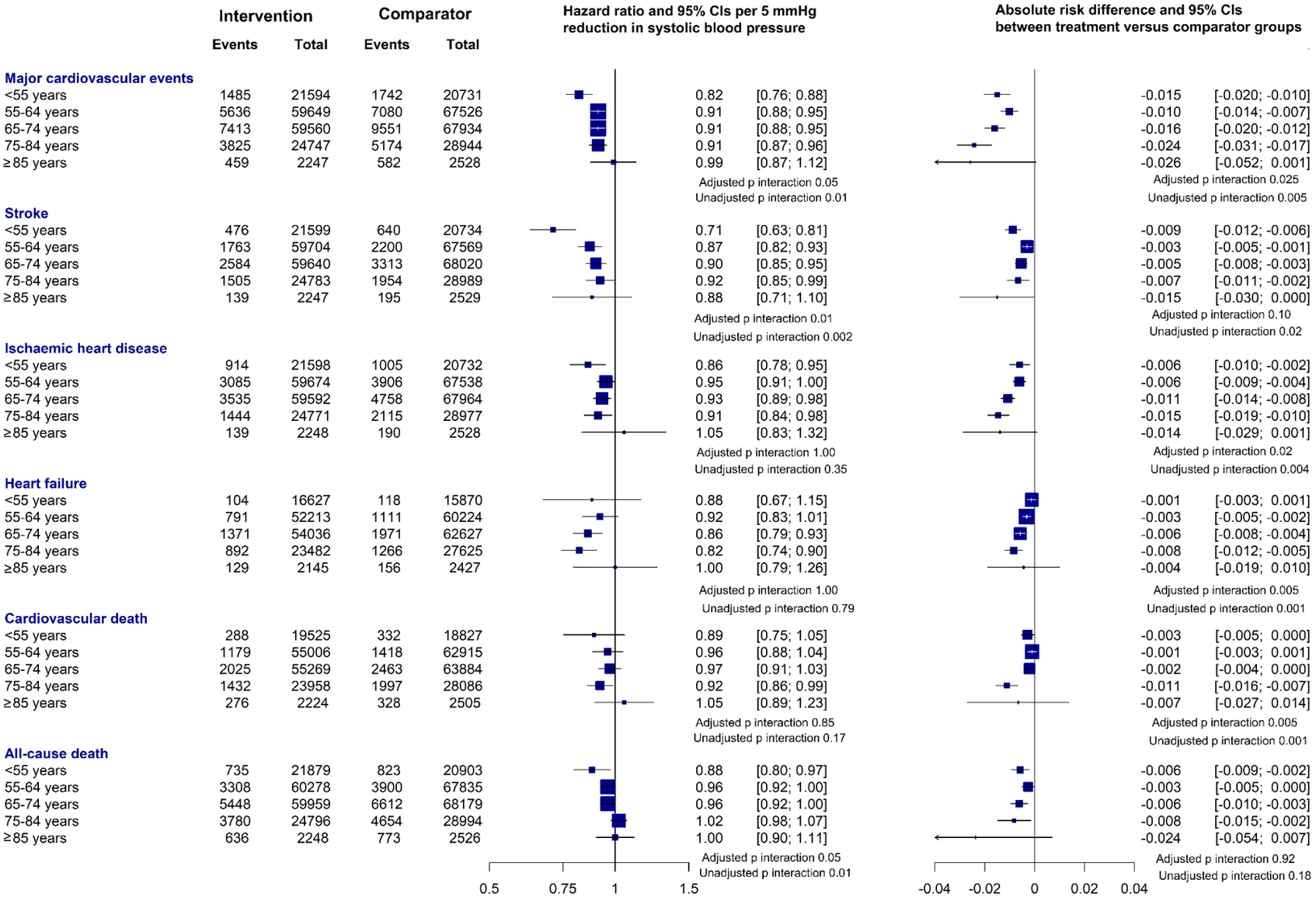

Figure 3. Age-specific relative effects of blood pressure-lowering treatment on major cardiovascular events, by systolic blood pressure categories at baseline.

Forest plot shows the hazard ratios (HR) and 95% confidence intervals (CI) per 5-mmHg reduction in systolic blood pressure. Adjusted p interaction: adjusted for multiple testing using Hommel's method. Unadjusted p interaction: unadjusted for multiple testing

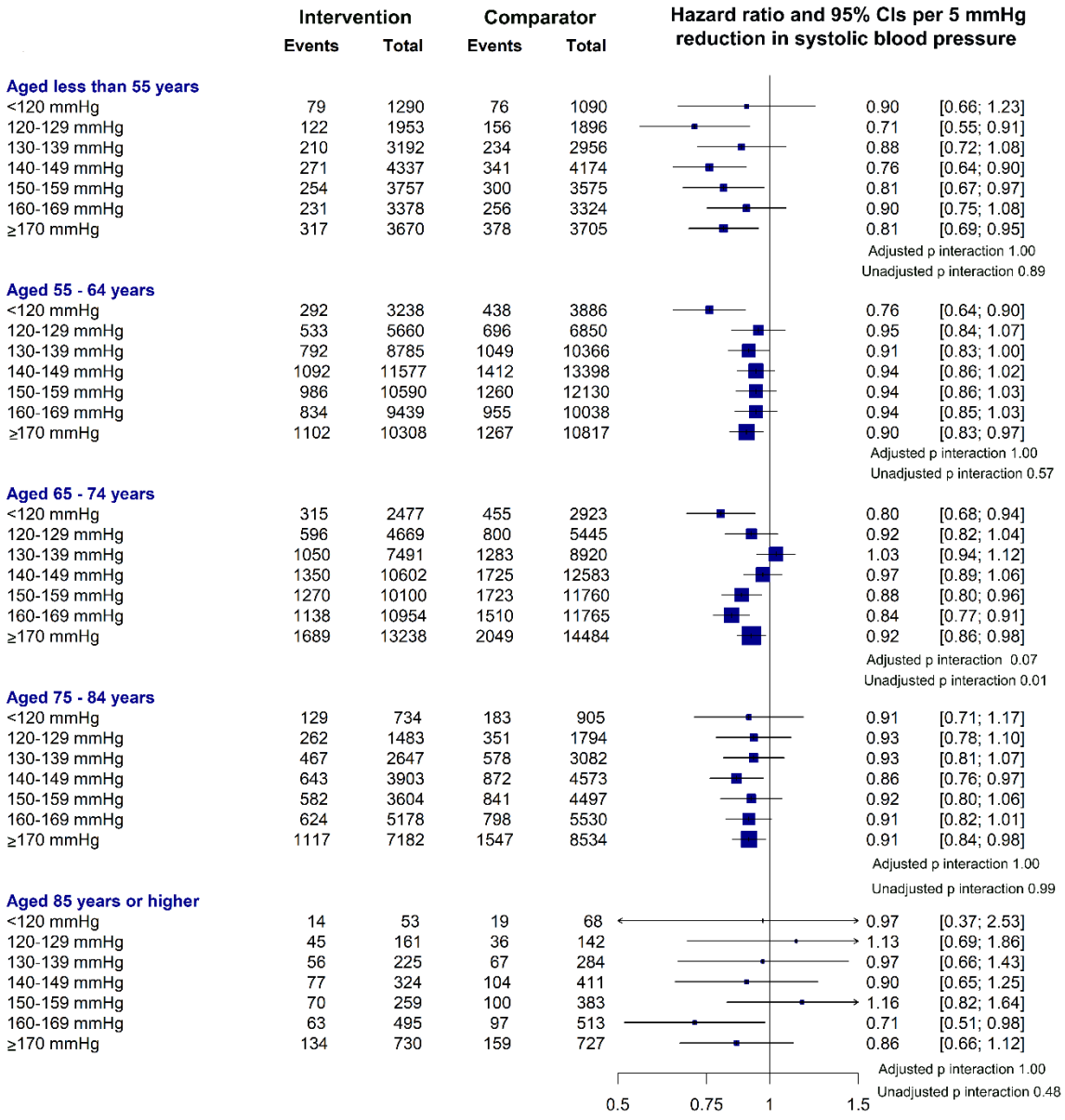

Figure 4. Relative effects of blood pressure-lowering treatment on major cardiovascular events, by diastolic blood pressure categories at baseline.

Forest plot shows the hazard ratios (HR) and 95% confidence intervals (CI) per 3-mmHg reduction in diastolic blood pressure. Adjusted p interaction: adjusted for multiple testing using Hommel's method. Unadjusted p interaction: unadjusted for multiple testing