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# Antihypertensive drug effects on long-term blood pressure: an individual-level data meta-analysis of randomised clinical trials

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## ABSTRACT

**Objective** Evidence from randomised trials of pharmacological treatments on long-term blood pressure (BP) reduction is limited. We investigated the antihypertensive drug effects on BP over time and across different participant characteristics.

**Methods** We conducted an individual patient-level data meta-analysis of 52 large-scale randomised clinical trials in the Blood Pressure Lowering Treatment Trialists' Collaboration using mixed models to examine treatment effects on BP over 4 years of mean follow-up.

**Results** There were 363 684 participants (42% women), with baseline mean age=65 years and mean systolic/diastolic BP=152/87 mm Hg, and among whom 19% were current smokers, 49% had cardiovascular disease, 28% had diabetes and 69% were taking antihypertensive treatment at baseline. Drugs were effective in lowering BP showing maximal effect after 12 months and gradually attenuating towards later years. Based on measures taken  $\geq 12$  months postrandomisation, mean systolic/diastolic BP difference (95% CI) between more and less intense BP-lowering treatment was  $-11.1$  ( $-11.3$  to  $-10.8$ )/ $-5.6$  ( $-5.7$  to  $-5.4$ ) mm Hg; between active treatment and placebo was  $-5.1$  ( $-5.3$  to  $-5.0$ )/ $-2.3$  ( $-2.4$  to  $-2.2$ ) mm Hg; and between active and control arms for drug comparison trials was  $-1.4$  ( $-1.5$  to  $-1.3$ )/ $-0.6$  ( $-0.7$  to  $-0.6$ ) mm Hg. BP reductions were observed across different baseline BP values and ages, and by sex, history of cardiovascular disease and diabetes and prior antihypertensive treatment use.

**Conclusion** These findings suggest that BP-lowering pharmacotherapy is effective in lowering BP, up to 4 years on average, in people with different characteristics. Appropriate treatment strategies are needed to sustain substantive long-term BP reductions.

in cardiovascular risk with more intensive BP-lowering treatment and independently of baseline BP values.<sup>8–14</sup> For most hypertensive patients, the lowered BP targets inevitably lead to a larger gap between their usual BP and the recommended target value,<sup>15 16</sup> requiring more intensive pharmacological treatment.

Attributing changes to treatment based on repeated measures of BP of an individual patient can be unreliable since measurements are subject to random fluctuations, regression to the mean, non-pharmacological effects and other sources of variability that can exceed true variability in treatment response.<sup>17–19</sup> However, it would be useful to have reliable information about the expected effects of drug treatment on BP levels over time from randomised comparisons to help interpret BP readings such as those obtained during clinical encounters. To date, randomised evidence on the effect of antihypertensive drugs on BP has come from efficacy trials with small numbers of highly selected participants and short follow-up durations.<sup>20</sup> Pooled evidence from RCTs using information from individual participants' repeated BP measurements currently does not exist, which might explain why there is no guidance on the expected magnitudes of BP reduction with the various proposed treatment strategies and whether these reductions are expected to vary among people with different characteristics.

We addressed this evidence gap by using information from 52 trials involving 363 684 participants with individual-level data on repeated BP measurements over several years<sup>21</sup> to conduct a meta-analysis to quantify the unconfounded effects of BP-lowering drugs on BP over time and examine these effects across different subgroups.

## METHODS

The design of the current phase of the Blood Pressure Lowering Treatment Trialists' Collaboration (BPLTTC) ([www.bplttc.org](http://www.bplttc.org)), including the identification of eligible trials as well as data collection and harmonisation, has been described previously,<sup>21</sup> with the protocol registered with PROSPERO (CRD42018099283). Briefly, RCTs were eligible

## INTRODUCTION

Clinical guidelines for managing hypertension have invariably lowered the recommended blood pressure (BP) targets for patients at high risk of cardiovascular disease,<sup>1–7</sup> informed by evidence from large-scale randomised clinical trials (RCTs) and their meta-analyses showing substantial reductions



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for inclusion if there was randomisation of patients between a BP-lowering agent and a placebo arm or inactive control, between various BP-lowering intensities or between various BP-lowering drugs. RCTs should have a follow-up of  $\geq 1000$  person-years in each randomly allocated arm to minimise the risk of small-study effects.<sup>22</sup> Trials without a drug comparison arm or without description of randomisation process were not eligible, nor were those conducted exclusively in patients with heart failure or investigating short-term interventions (eg, in acute care settings). The protocol for the current analyses was reviewed and approved by the BPLTTC Steering Committee prior to data analysis.

To analyse the data, we assigned each participant according to their random allocation in the individual trials, either to the active (or treatment) arm or to the control group separately for each trial design, as described in online supplemental methods and table S1, and compared BP levels between these comparison groups. Our study outcomes were mean systolic and diastolic BP differences between comparison arms.

### Statistical analysis

We used a one-stage approach to conduct the meta-analysis of repeated BP measurements over time and applied linear mixed models to estimate the effect of treatment on BP between comparison arms. We developed and compared models that accounted for clustering by trial and potential variability due to baseline BP and other trial-level and participant-level sources of heterogeneity, and determined the best fitting model for our data (online supplemental methods 1). Our primary model was based on fixed treatment effect and fixed time effect but allowing for random intercepts at trial and participant levels and a random slope for follow-up duration at participant level.

We estimated BP values and their difference between comparison groups during the course of follow-up, separately by trial design. As the early phase of the treatment may involve adjustments to optimise treatment regimens such as dosage titration,<sup>23</sup> BP difference between treatment arms may not be maximally achieved until after this period. We therefore also analysed results with and without inclusion of BP measurements taken  $< 12$  months after randomisation. We used published aggregate information on achieved BP for each comparison arm to estimate individual-level follow-up values where follow-up BP measurements were not accessible (online supplemental methods 1). We then investigated treatment effects stratified by participants' baseline BP, age, sex, body mass index, history of cardiovascular disease and diabetes and prior use of antihypertensive medication, and assessed any heterogeneity by comparing models with and without an interaction term for the characteristic of interest and treatment allocation. Models were adjusted for baseline BP, age at recruitment and sex (except when used as stratification factors). We also ran sensitivity analyses that excluded data from each trial and examined results by study period (based on the year the trial has ended).

We used likelihood ratio test (for nested models) and the Akaike information criterion (for non-nested models) to compare models and reported estimates with their 95% CI and p values that were tested at 5% significance level (two tailed). We used R (V.3.4.4)<sup>24</sup> to analyse the data.

### Patient and public involvement

There was no patient or public engagement in the design or conduct of this study.

## RESULTS

### Characteristics of trials and participants in the BPLTTC

The 52 included trials comprised of nine BP-lowering intensity trials, 21 placebo-controlled trials and 29 drug class comparison trials (table 1), mostly conducted between 1990 and 2009 (eight trials conducted after 2009). Seven trials included both comparisons between drug classes as well as either intensity of BP-lowering or between active treatment and placebo. On average, the trials had 4 years of follow-up and eight BP measurements collected after baseline.

The trials included 363 684 randomised participants (42% women) with a mean age of 65 years at baseline, including 6% aged  $\geq 80$  years. The mean baseline systolic/diastolic BP was 152/87 mm Hg (73% with  $\geq 140$  mm Hg systolic and 46% with  $\geq 90$  mm Hg diastolic BP) across all trials, with higher values for drug class comparison trials than the other designs (table 1). At baseline, 49% of all participants had had a history of cardiovascular disease and a third a history of diabetes. Baseline BP was higher for older persons, in women and among those with lower body mass index, without cardiovascular disease or diabetes and no prior use of antihypertensive medications, as compared with their counterparts (online supplemental table S2). Further details about study methods, design and risk of bias assessment for each trial are shown in online supplemental table S3 to S7).

### Temporal BP patterns by treatment allocation

The temporal patterns of BP are shown in figure 1 (additional information in online supplemental table S8). Across all trial designs, BP fell during the first few months of follow-up in both study arms. For BP-lowering intensity and placebo-controlled trials, there was divergence in BP in the early follow-up period that increased over time—BP levels in the active arm were lowest at around 2 years after baseline. For drug class comparison trials, BP levels in both comparison arms remained similar during follow-up. The mean BP achieved in the active arm of BP-lowering intensity trials was substantially lower than those achieved in the active arms of the other trial designs. Results for all BP difference trials are shown in online supplemental figure S2.

### Achieved net BP reduction by follow-up period

Figure 2 (additional details in online supplemental table S9) illustrates the varying estimates of the difference in BP between comparison groups at specific follow-up times. Consistent with the patterns of absolute BP levels, the estimated difference in BP achieved between the active and control groups tended to be lower in earlier than in later follow-up periods. For BP-lowering intensity trials, the difference in mean reductions in systolic and diastolic BP within 6 months from baseline were  $-4.2$  (95% CI  $-4.4$  to  $-4.0$ ) mm Hg and  $-2.0$  (95% CI  $-2.2$  to  $-1.9$ ) mm Hg, respectively, and over  $-10$  mm Hg and  $-5$  mm Hg reductions, respectively, based on measures taken at later follow-up periods. Similar patterns were seen for placebo-controlled trials (and BP difference trials, details shown in online supplemental figure S3), although this group achieved smaller magnitudes in mean BP reduction across all follow-up periods. Mean reductions were least for drug class comparison trials.

### Estimating overall achieved BP reduction between comparison groups

The time-related BP differences between comparison groups affected the overall achieved reduction in BP. Estimates

**Table 1** Characteristics of trials and participants

	Blood pressure (BP) difference trials			Drug class comparison trials	All trials
Characteristics	BP-lowering intensity	Placebo controlled	All BP difference trials		
Trials					
No. of trials	9	21	30	29	52*
No. of trials by year of end of study					
Before 1990	1	2	3	0	3
1990–1999	2	7	9	7	14
2000–2009	2	10	12	19	27
After 2009	4	2	6	3	8
Mean (SD) trial duration (years)	4 (2)	4 (2)	4 (2)	4 (2)	4 (2)
Mean (median) no. of follow-up BP measures	14 (13)	7 (6)	8 (8)	8 (7)	8 (8)
Participants					
No. of participants (% women)	35 934 (45)	112 934 (35)	148 873 (38)	224 038 (44)	363 684 (42)
% (n/N) Caucasian/ European ethnicity	46 (15 863/34 823)	68 (58 851/86 908)	61 (74 714/121 731)	64 (118 128/185 351)	63 (188 948/297 852)
% (N) current smoker at baseline <sup>b</sup>	22 (8238/35 908)	16 (17 702/111 190)	18 (25 940/147 098)	20 (44 173/220 708)	19 (68 360/359 719)
Mean (SD) baseline SBP/ DBP	151 (21)/88 (15)	146 (21)/83 (11)	147 (21)/84 (12)	156 (21)/90 (12)	152 (21)/87 (12)
% (N) participants by baseline SBP (mm Hg)					
<120/<70	4 (2870)/11 (3806)	8 (9176)/9 (10 037)	7 (10 650)/9 (13 843)	3 (7027)/5 (10 410)	5 (17 128)/7 (23 803)
120–129/70–79	9 (6228) / 17 (6075)	13 (15 063)/24 (26 927)	13 (18 448)/22 (33 002)	6 (12 969)/14 (31 330)	9 (30 720)/17 (63 091)
130–139/80–89	18 (11,289) / 24 (8593)	17 (19 674)/39 (43 738)	18 (26 077)/34 (50 623)	11 (23 906)/28 (62 292)	14 (48 820)/30 (109 589)
140–149/90–99	19 (11 393)/29 (14 890)	18 (20 590)/21 (24 043)	19 (27 386)/23 (34 324)	18 (41 220)/30 (67 403)	19 (66 928)/27 (98 994)
150–159/100–109	17 (10 050)/14 (6342)	14 (16 246)/7 (7355)	14 (21 107)/8 (12 264)	19 (42 509)/18 (39 839)	17 (61 495)/14 (51 014)
≥160/≥110	33 (19 050)/6 (2696)	28 (32 114)/1 (750)	30 (43 396)/2 (2994)	43 (95 833)/5 (12 188)	38 (136 226)/4 (14 810)
Mean (SD) age (years) at baseline	61 (12)	65 (10)	64 (11)	65 (9)	65 (10)
% (N) of participants by age at baseline					
<50 years	16 (7146)	5 (5596)	8 (11 256)	4 (9542)	5 (19 122)
50–59 years	34 (18 465)	22 (24 668)	25 (36 978)	24 (52 819)	24 (86 699)
60–69 years	27 (18 005)	39 (44 374)	36 (54 016)	39 (87 144)	38 (137 849)
70–79 years	18 (13 313)	26 (28 921)	24 (35 264)	28 (63 119)	27 (97 290)
≥80 years	6 (3999)	8 (9342)	8 (11 321)	5 (11 369)	6 (22 638)
% (N) with condition at baseline†					
Cardiovascular disease	16 (5617/35 934)	66 (72 209/110 020)	54 (78 738/145 945)	45 (98 944/221 993)	49 (175 519/359 357)
Coronary heart disease	11 (4120/35 934)	41 (45 591/110 008)	34 (49 711/145 942)	38 (67 766/177 363)	37 (115 562/316 125)
Stroke	3 (966/34,840)	34 (32 650/95 800)	28 (36 521/130 643)	11 (17 830/168 003)	18 (51 320/292 559)
Diabetes	24 (8540/35 934)	36 (36 179/100 697)	33 (44 719/136 631)	26 (58 404/223 654)	28 (99 375/351 357)
Chronic kidney disease	33 (4854/14 799)	9 (2845/25 789)	19 (7699/40 588)	17 (18 917/108 612)	17 (24 289/145 895)
% (N) previously on BP-lowering medication†	34 (12 141/35 934)	71 (73 833/103 766)	65 (73 237/126 502)	77 (119 454/155 069)	69 (202 428/293281)
Mean (SD) body mass index‡ (kg/m <sup>2</sup> )	29 (6)	28 (5)	28 (5)	28 (5)	28 (5)
*Some trials provided data to more than one trial design.					
†Data limited to those with relevant information and N refers to the denominator for number of participants with information on the relevant variable.					
SBP: systolic blood pressure; DBP: diastolic blood pressure.					

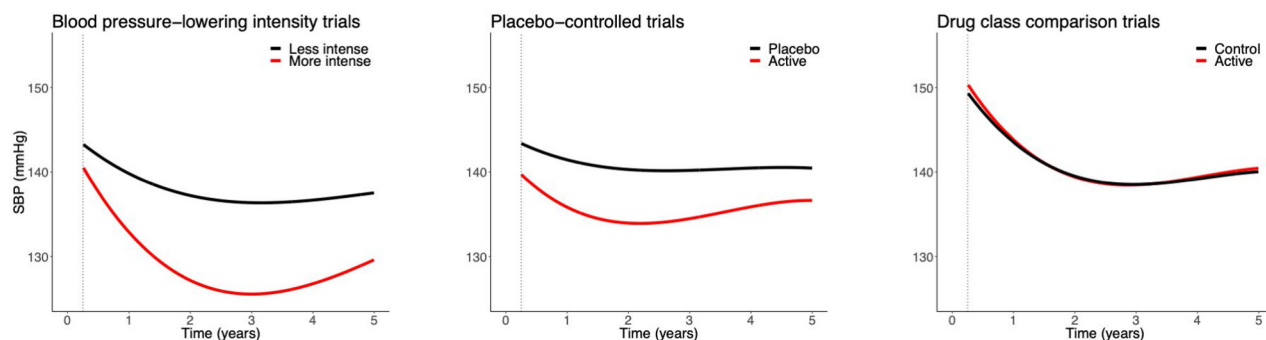
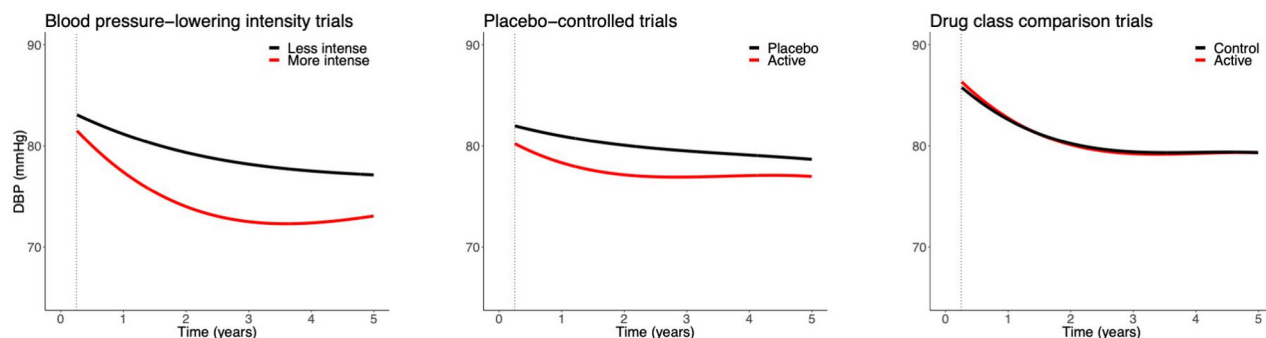
\*Some trials provided data to more than one trial design.

†Data limited to those with relevant information and N refers to the denominator for number of participants with information on the relevant variable.

SBP, systolic blood pressure; DBP, diastolic blood pressure.

based on BP measures obtained across all follow-up period were relatively smaller in magnitude than when the treatment phase of <12 months was excluded (figure 2, further details in online supplemental figure S3 and table S10). For example, for BP-lowering intensity and placebo-controlled trials, the overall mean systolic/diastolic BP reductions across the whole follow-up time were  $-7.6$  (95% CI  $-7.7$  to

$-7.4$ )/ $-3.7$  (95% CI  $-3.8$  to  $-3.6$ ) mm Hg and  $-4.0$  (95% CI  $-4.1$  to  $-3.9$ )/ $-1.9$  (95% CI  $-2.0$  to  $-1.8$ ) mm Hg, respectively; when using measurements taken  $\geq 12$  months from baseline, the achieved reductions were  $-11.1$  (95% CI  $-11.3$  to  $-10.8$ )/ $-5.6$  (95% CI  $-5.7$  to  $-5.4$ ) mm Hg and  $-5.1$  (95% CI  $-5.3$  to  $-5.0$ )/ $-2.3$  (95% CI  $-2.4$  to  $-2.2$ ) mm Hg, respectively.

**A Systolic blood pressure (SBP)****B Diastolic blood pressure (DBP)**

**Figure 1** Blood pressure (BP) trajectories according to different trial designs. Results are in red for active group and black for control group, from 3 months to 5 years of follow-up. Estimates were based on separate models for treatment and control groups, with random intercepts at individual and trial levels, a random slope for time at the individual level (see Method for details) and adjusted for baseline BP, age and sex. Baseline systolic/diastolic BP for active and control groups were: BP-lowering trials=151/88 mm Hg; placebo-controlled trials=146/83 mm Hg and drug class comparison trials=156/90 mm Hg. Estimated BP at specific time points are shown in online supplemental table S8). Results for all BP difference trials are shown in online supplemental figure S2.

### Effects of treatment on BP reduction across different subgroups

Focusing on BP differences from  $\geq 12$  months from baseline, figure 3 and online supplemental figure S4 show treatment effects by different baseline characteristics. There were some variations in the magnitudes of BP reductions, notably by body mass index categories in BP-lowering intensity trials. Some trials disproportionately contributed more data in some subgroups so the results reflected features of these trial characteristics and design. For example, the Systolic Blood Pressure Intervention Trial (SPRINT) and the Action to Control Cardiovascular Risk in Diabetes (ACCORD) trial, which achieved substantive BP reductions, included participants with higher mean baseline body mass index whereas Hypertension Objective Treatment Based on Measurement by Electrical Devices of Blood Pressure (HOMED-BP) and Valsartan in Elderly Isolated Systolic Hypertension Study (VALISH) trials, which achieved modest BP reductions, included those with lower mean baseline body mass index (online supplemental table S6). While there were variations in treatment effects across different subgroups, BP reductions were evident across these subgroups, even among those with baseline systolic BP  $< 120$  mm Hg and diastolic BP  $< 70$  mm Hg. For drug class comparison trials, BP differences overall and across subgroups were consistently small (figure 3).

### Sensitivity analyses

BP differences achieved by each trial are reported in online supplemental figure S5. Results after excluding one trial at a time largely showed similar results as the overall estimates within

each trial type (online supplemental figure S6). There were little differences in the achieved BP reductions by study period except in placebo-controlled trials that achieved greater reductions in trials that ended before 2000 than in newer trials (online supplemental table S11), due to some older trials that had far higher starting mean baseline BP values than the newer trials but with comparable treatment goals (online supplemental table S6 and figure S5). Finally, online supplemental table S12 shows how the models we used fitted the data better and gave more conservative estimates than models that did not take into account time-related variations and other individual-level factors in treatment effects.

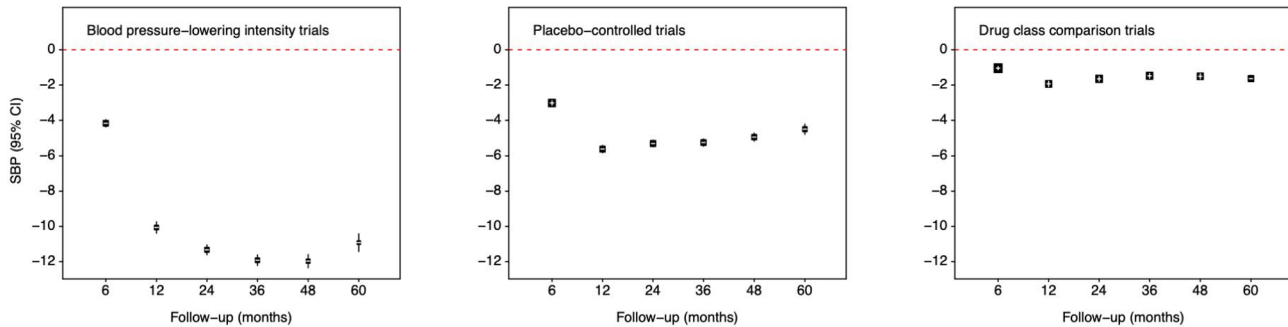
### DISCUSSION

The analysis of individual-level data of 363 684 randomised participants of 52 large-scale RCTs, the largest of such meta-analysis to date, provides evidence to the overall and stratified effects of antihypertensive treatment on relatively long-term BP reduction. The magnitude of BP reduction varied by time after randomisation and the intended trial intervention. The predicted maximum effect of intervention became apparent about a year from randomisation, with some gradual attenuation several years later during follow-up. The net achieved BP reduction varied by trial design, with BP-lowering intensity trials achieving the largest mean reduction of over 11 mm Hg systolic BP after the first year of treatment. The effects were evident across patient subgroups, as defined by their baseline BP, age, sex, body size, history of cardiovascular disease or diabetes and prior use of antihypertensive treatment.

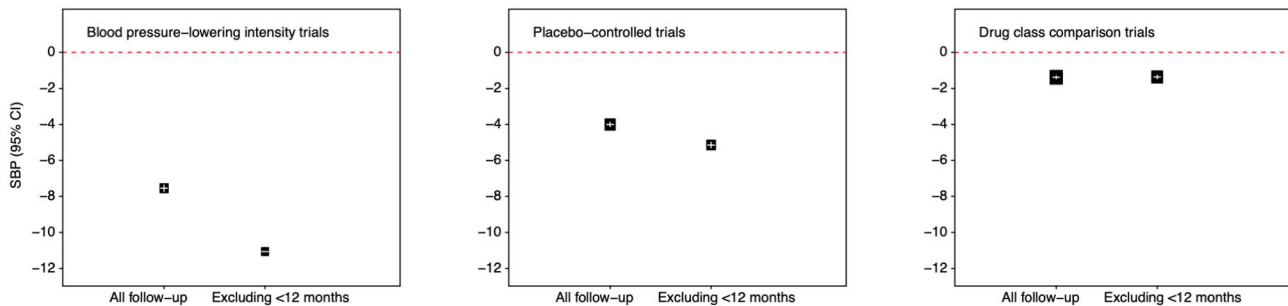


**A Systolic blood pressure (SBP)**

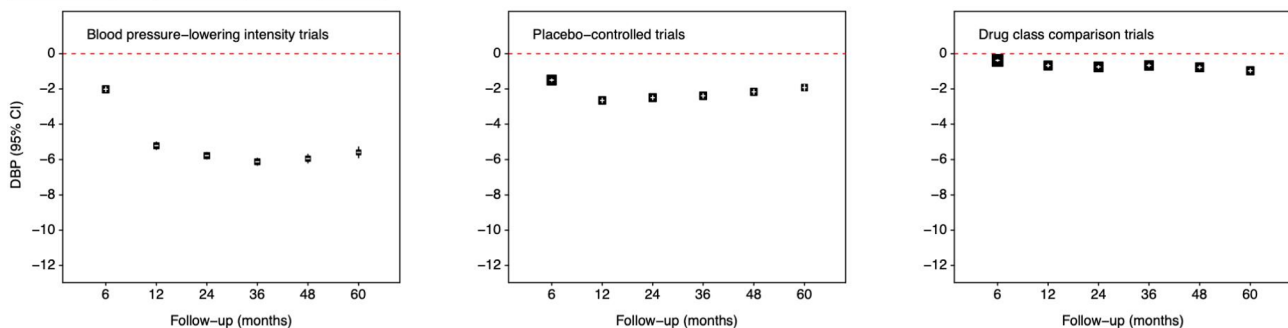
Mean difference (mmHg) at fixed time points during follow-up



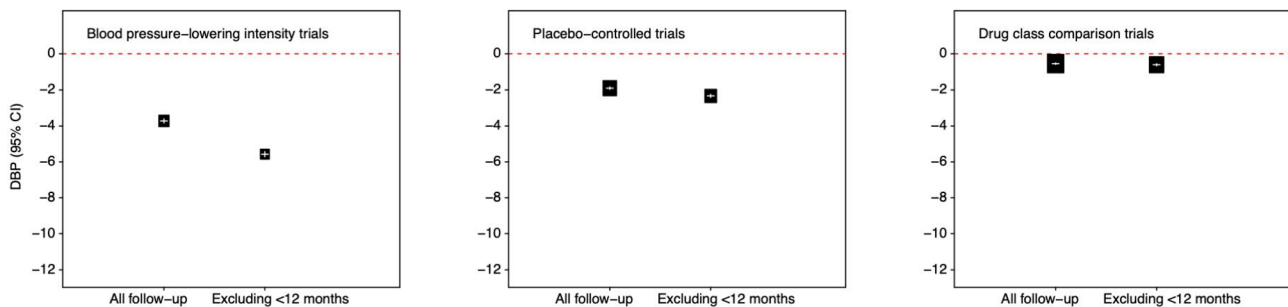
Mean difference (mmHg) achieved across all follow-up periods

**B Diastolic blood pressure (DBP)**

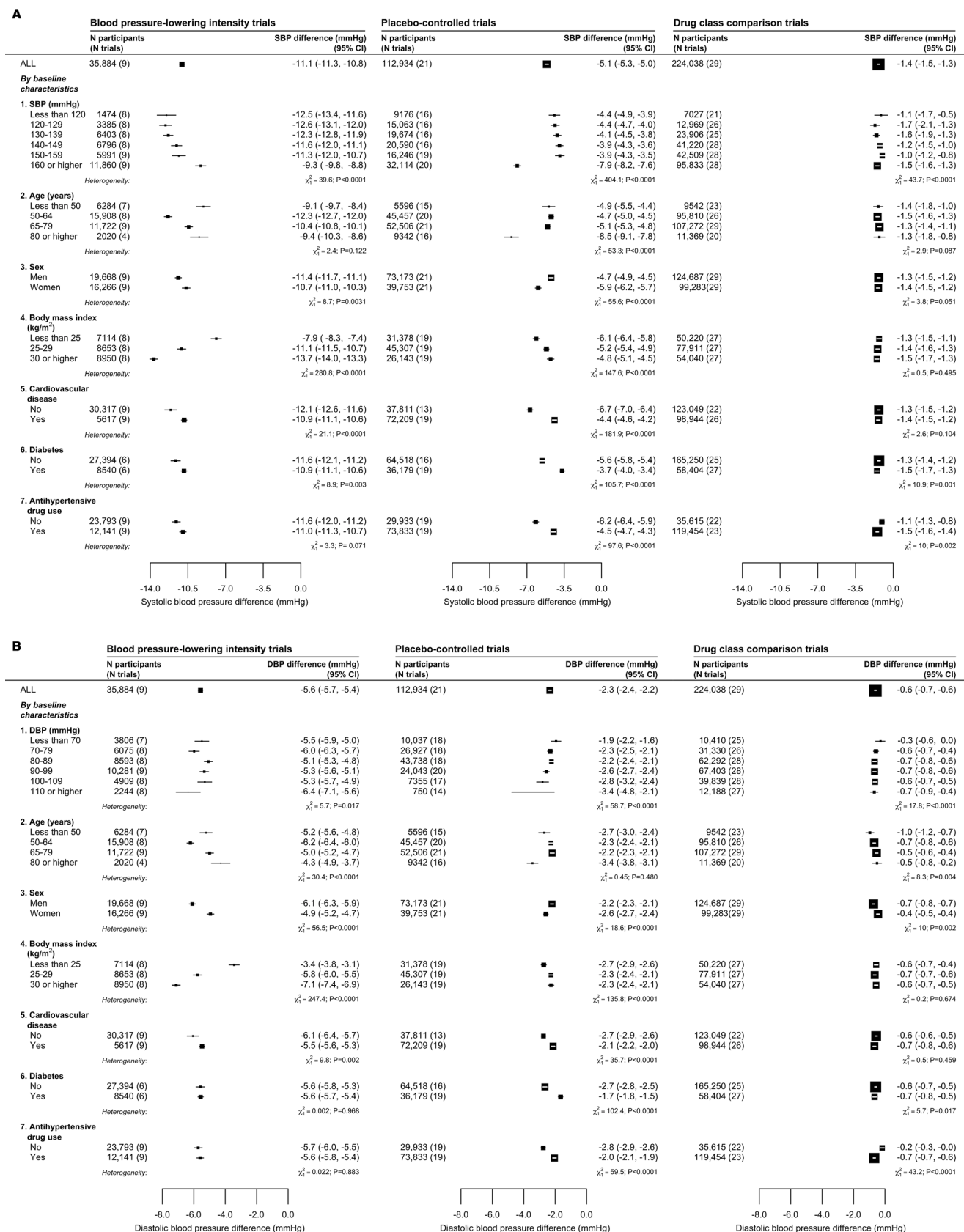
Mean difference (mmHg) at fixed time points during follow-up



Mean difference (mmHg) achieved across all follow-up periods



**Figure 2** Effects of blood pressure (BP)-lowering treatment on mean BP at fixed follow-up time points and across all follow-up period. (A) Systolic BP; (B) Diastolic BP. For mean difference at fixed follow-up time periods, estimates were based on separate models for each time period with a fixed treatment effect and random intercept for individuals. For mean difference achieved across all time period (showing results based on all follow-up BP measures and measures obtained from 12 months until end of follow-up), estimates were based on fixed treatment effect and random intercepts at individual and trial levels, a random slope for time at the individual level. All mean difference values were adjusted for baseline BP, age and sex. The area of the square is inversely proportional to the variance of the estimated difference. Negative values indicate lower BP in the active than in the control group. Additional information provided in online supplemental table S9 and S10), and results for all BP difference trials are in online supplemental figure S3.



**Figure 3** Effects of blood pressure (BP)-lowering treatment on mean BP, by baseline characteristics. (A) mean systolic BP difference; (B) mean diastolic BP difference. Estimates based on fixed treatment effect and random intercepts at individual and trial levels, a random slope for time at the individual level (see Method for details) and adjusted for baseline BP), age and sex except when these variables are used as stratification factors. The area of the square is inversely proportional to the variance of the estimated difference. Negative values indicate lower BP in the active than in the control group. Results for all BP difference trials are in online supplemental figure S4. To provide context of background BP levels, baseline BP by these subgroups are shown in online supplemental table S2.

Randomised evidence on the expected effect of antihypertensive drugs on BP has been largely based on published information from efficacy trials. In a meta-analysis of 354 trials ( $N \approx 56\,000$ ),<sup>20</sup> half-standard dosages of one, two or three antihypertensive drugs led to systolic BP reductions of 6.7 mm Hg, 13.3 mm Hg and 19.9 mm Hg, respectively, from a pretreatment systolic/diastolic BP of 150/90 mm Hg. Our study is not directly comparable with this work, but it is notable that, in our study, the mean BP reductions were less pronounced than their estimates and that the full effects became evident only after a several months after initiating therapy. This discrepancy could be due to a number of reasons. Their meta-analysis included trials with relatively short follow-up duration (around 2–16 weeks), with some trials having potentially restricted their analysis to fully adherent participants. In contrast, we included large-scale trials with 4-year mean follow-up and performed analysis as per intention to treat. By design, many trials included in our study focused on achieving a target BP level or reduction, so the maximal physiologically feasible effect on BP reduction may not have been achieved. A substantial proportion of participants were on antihypertensive drugs at baseline, which could have further underestimated the magnitude of achieved BP reduction, although it should not have an impact on the net between-group BP reductions.

Current clinical practice guidelines typically recommend a gradual intensification of antihypertensive treatment over several weeks and monitoring of its response for the treated individual.<sup>1–6</sup> However, there is no clear guidance as to the expected change in BP on initiating treatment. To gauge treatment response without a counterfactual or ‘standard’ to compare against is difficult because of the multitude of other causes of BP change.<sup>17 18</sup> Estimates of longitudinal BP changes in our study may help mitigate exaggerated attributions of change in BP to treatment, while providing reassurance about achievable reductions in various groups of ‘at-risk’ individuals. Clinical guidelines also typically define specific BP targets that should be achieved for hypertension to be considered as ‘controlled’, although target levels set by different national guidelines vary.<sup>1–6</sup> While setting a target has practical advantages, it assumes that it is achievable on full implementation of the guidelines. However, population BP follows a distribution, with mean systolic BP  $\approx 130$  mm Hg in Western populations and over 60% by age  $\geq 60$  years have values  $> 140$  mm Hg.<sup>25 26</sup> Among the most intensive treatment strategies in the clinical outcome trials were able to achieve an average of 10–15 mm Hg systolic BP reductions within a few months to several years (eg, SPRINT achieved 15 mm Hg systolic BP reduction (online supplemental figure S5)). With current evidence-based treatment recommendations, achieving a controlled BP for people with very high BP (eg,  $> 150$  mm Hg systolic), would be difficult to attain with the trialled regimens of pharmacologic treatment.<sup>27</sup> We do not imply that physiologically larger BP reductions are unachievable but rather intend to flag the limited evidence on pharmacological BP reductions of over 20 mm Hg in the long term. The achieved BP reduction estimated in our pooled analysis has implications not just for patients but also for healthcare providers whose performance will be assessed based on their patients achieving ‘controlled’ BP. Alternative monitoring strategies, such as the number of prescribed antihypertensives<sup>28</sup> for an individual as opposed to using a single BP target for all, are needed. Some translational implications of this study are described further in the online supplemental file 1– clinical perspectives.

Recommendations for BP management in specific patient groups also remains controversial. The US guidelines suggest similar recommendations for people with and without

pre-existing cardiovascular disease,<sup>1</sup> but the UK guidelines use a higher BP threshold for people without cardiovascular disease due to lack of any direct evidence of efficacy in this patient group.<sup>29</sup> Although there were some variations in the treatment effects in our stratified analyses, which were likely an artefact of trial design, BP reductions were evident across a wide range of baseline BP and other personal characteristics. Unsurprisingly, there was little difference in magnitude of BP reduction between comparison arms of drug comparison trials (overall and across subgroups). The BP values substantially fell from baseline in both arms, which is likely due to regression to the mean given the high baseline BP of patients in these trials.<sup>17</sup> The extent to which the estimated BP reductions will have an impact on existing evidence base, which have either been based on published information on average BP differences for each trial<sup>8</sup> or have not adjusted for achieved BP differences between trials,<sup>30</sup> requires further investigation.

A number of limitations need to be considered when interpreting our findings. Investigators or data custodians of some eligible trials could not be contacted (particularly for older trials) or were unwilling to take part in the collaboration. Nevertheless, the trials included in our collaboration generally have low risk of bias. Short-term effects of BP-lowering agents are well established,<sup>20</sup> and our findings extend these effects over a relatively longer period of follow-up of 4 years on average (few trials had over 5 years of follow-up). We could not compare drug classes based on standardised dosages, as most treatment interventions allowed titration or addition of other drug classes to achieve specific treatment goals (online supplemental table S3). Investigators were allowed to add non-study antihypertensive treatment in some trials, which could have led to the dilution of treatment effects between trial arms or subgroups. Adherence to

### Key messages

#### What is already known on this subject?

⇒ Randomised evidence of the effects of antihypertensive drugs on achievable blood pressure reduction has been based on trials with small sample sizes and short treatment periods of several weeks; pooled analysis of randomised evidence to provide reliable estimates of achievable long-term blood pressure reduction from pharmacological treatment is lacking.

#### What might this study add?

⇒ This large-scale individual participant-level data meta-analysis has shown that the patterns of blood pressure reduction differed over time, with the maximum effect seen in intensive treatment strategies that achieved 11 mm Hg systolic blood pressure reduction on average after the first year of treatment. Beneficial effects were demonstrable over wide ranges of baseline blood pressure, ages and body sizes, in women and men, by history of cardiovascular disease or diabetes and by prior use of antihypertensive treatment.

#### How might this impact on clinical practice?

⇒ The efficacy of antihypertensive drugs was demonstrable across different population subgroups, although the achieved blood pressure reductions, even with trialled intensive regimens, were relatively modest. These findings could guide setting realistic treatment goals in the pharmacological management of raised blood pressure.

treatment had fallen towards the end of follow-up in most trials (online supplemental table S5), which could partly explain why treatment effects were lower in these latter follow-up periods. We did not have full access to individual-level information about use of non-study drugs nor on adherence to treatment to be able to quantify their effects. Yet an important strength of our study is that it permitted comparison across subgroups while maintaining the advantage of the random allocation to treatment groups.

Our study highlights the role of pharmacological agents in effectively reducing BP over several years across individuals with a wide range of characteristics, although the achieved between-group reductions, even with the intensive BP-lowering regimens, were relatively modest. Given that large-scale trials have shown the effects of pharmacological BP reduction on improving clinical outcomes, the modest BP reductions estimated in our study should still be clinically meaningful.<sup>14</sup> Indeed, the estimates of long-term BP reduction in this study could inform treatment strategies and help in setting realistic treatment goals in the pharmacologic management of raised BP.

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# Supplementary Materials

## Antihypertensive drug effects on long-term blood pressure: an individual-level data meta-analysis of randomised clinical trials

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W H van Gilst (PREVEND-IT),  
P Verdecchia (Cardio-Sis),  
K Wachtell (LIFE),  
P Whelton (SPRINT),  
L Wing (ANBP2),  
M Woodward (ADVANCE, PROGRESS),  
Y Yui (JMIC-B),  
S Yusuf (HOPE, ONTARGET, PROfESS, TRANSCEND),  
A Zanchetti (deceased) (ELSA [European Lacidipine Study on Atherosclerosis], VHAS [Verapamil in Hypertension and Atherosclerosis Study])  
Z Y Zhang (SYST-EUR)

**Other members:** C Anderson, C Baigent, BM Brenner, R Collins, D de Zeeuw, J Lubsen, E Malacco, B Neal, V Perkovic, A Rodgers, P Rothwell, G Salimi-Khorshidi, J Sundström, F Turnbull, G Viberti, J Wang



## Supplementary Methods

### Comparison groups

For trials that compared drug(s) with placebo, we assigned those in the drug(s) and placebo arms to active and control groups, respectively. For interventions that compared effects based on blood pressure (BP)-lowering targets (e.g. more versus less intense treatment to reduce baseline BP below a pre-specified threshold or to achieve a pre-defined magnitude of reduction in BP), participants allocated to treatment arms aiming to achieve greater BP reduction were assigned to the active group, and those allocated to achieve less reduction to the control group. Both these placebo-controlled trials and trials comparing effects based on BP reduction intensity were also collectively classified as '*BP difference*' trials. Trials that compared effects between different drug classes on clinical outcomes were classified as '*drug class comparison*' trials. For these trials, we retrospectively assigned treatment allocations for the drug class achieving greater BP reduction to the active group; where the difference was null, we assigned treatment arms to the active group for those randomised to receive the novel or newer drug class and to the control group if randomised to receive standard or usual drug class therapy.

### Estimating follow-up BP level and difference between comparison arms in trials without follow-up measurements

Individual-level follow-up BP measurements were not accessible to the collaboration for two trials (IDNT<sup>1</sup> and Cardio-Sis<sup>2</sup>), and baseline BP measurements were also not available for IDNT. Mean BP values at baseline for IDNT were extracted from published literature for the treatment and control groups. For each participant of this trial, the baseline BP was imputed as the mean value for the group they were randomised to. For both Cardio-Sis and IDNT, the mean follow-up BP values at the end of the trials in the treatment and control groups were extracted from published literature. These mean values were imputed as the follow-up BP values for the relevant groups at one-year intervals for the length of the study duration. For the sensitivity analysis investigating BP difference achieved by individual trials, we extracted data on the mean BP difference (and 95% confidence interval) between treatment and control groups also from the published literature for Cardio-Sis. As such data were not available for IDNT, we estimated these values by using simple linear regression models, with follow-up BP as the outcome, and baseline BP, treatment group, age and gender as covariates.

## Model development and selection

Because the BPLTTC has individual participant-level data, we therefore made use of the full information on individual-level BP measurements in the dataset for characterising longitudinal patterns of BP, and estimating BP difference between comparison groups. Using linear mixed models, we compared models to determine potential sources of heterogeneity, and checked residual plots to help assess the best fitting model for our data.<sup>3-6</sup> Figure S1 shows the scheme for model specification and selection, using likelihood ratio test (for nested models) and the Akaike information criterion (for non-nested models), and implemented using the *nlme* package in R. The model based on random intercepts (trial and participant), fixed treatment effect and random time (participant) fitted the data better than the base model (no treatment effect), or models with random treatment effects or fixed time effect. Further model assessment showed that the best fitting model included specifying a polynomial term for time and adjusting for baseline BP, age and sex, which formed the basis for our final model as shown in Equation (1). Residual plots showed no apparent non-random patterns and indicated a good fit of the final model. We then implemented this model, and modified as appropriate, in subsequent analyses.

(1)

$$BP_{tij} = [\gamma_{000} + \gamma_{100}(\text{time})_{tij}] + [r_{0ij} + r_{1i}(\text{time})_{ti}] + \beta_1(\text{treatment}) + \beta_2(\text{time}) + \beta_3(\text{time})^2 + \beta_4(\text{time})^3 + e_{ij}$$

where:

i=individual

j=trial

BP<sub>tij</sub> = blood pressure outcome

$\gamma_{000}$  = grand mean of the intercept over all individuals and group

$\gamma_{100}(\text{time})_{tij}$  = grand mean slope over all individuals and groups

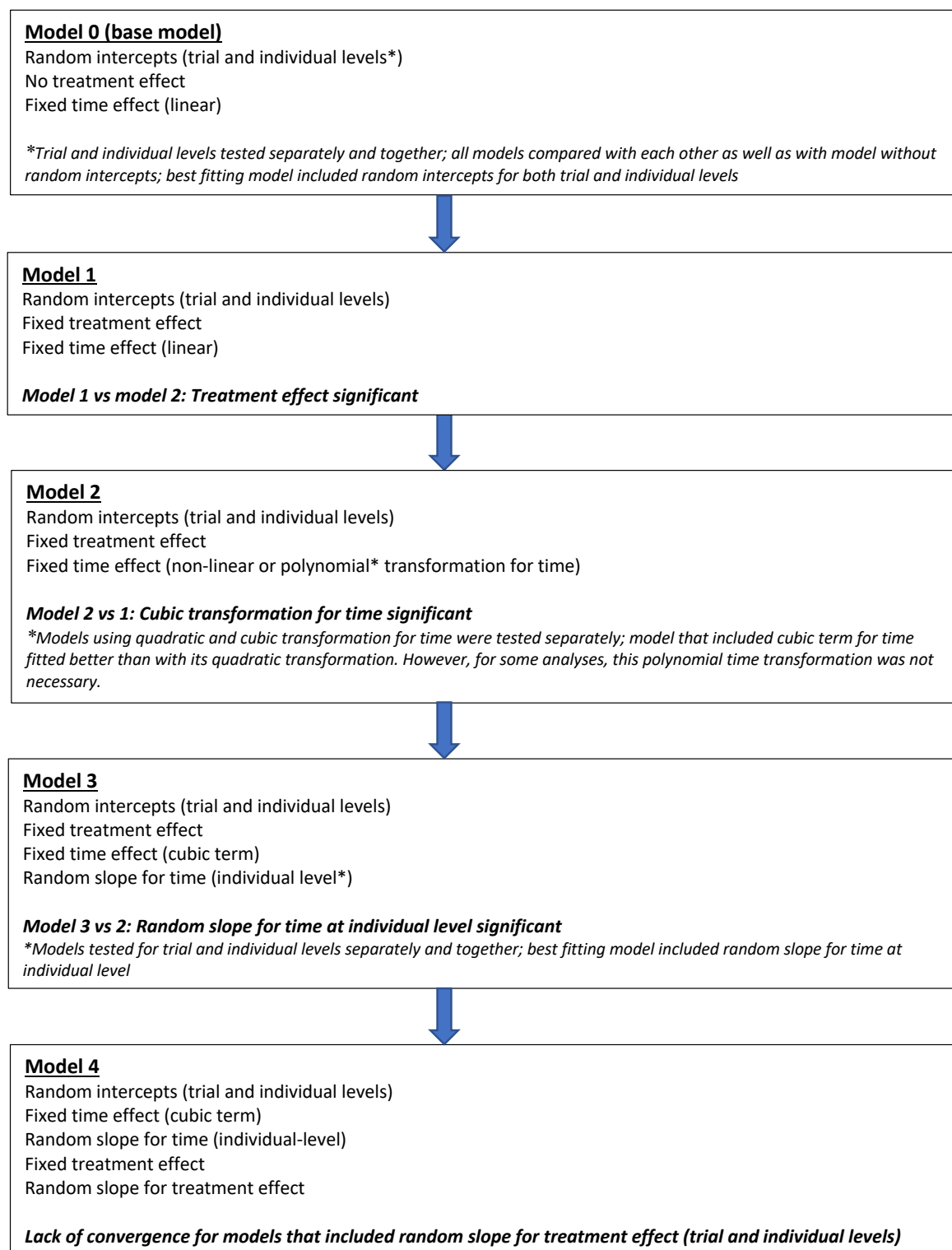
$r_{0ij}$  = random intercept (trial and individual)

$r_{1i}(\text{time})_{ti}$  = random slope (individual)

## Estimating follow-up BP level and difference between comparison arms from the linear mixed models

How to precisely measure differences in BP between treatment arms across different trials is not clear. For example, BP differences have been based on measures taken at a fixed timepoint during follow-up,<sup>7</sup> the average of all follow-up measures,<sup>8-10</sup> or the final follow-up measures.<sup>11</sup> In our analysis, we first examined how BP differed between treatment arms across specific time points during follow-up. To estimate this blood pressure difference, we first split the data into specific time periods, and ran models on each time period separately. In developing the best-fitting model for the data used in these specific analyses, Equation (1) was modified by retaining a random intercept for

individuals but excluded a random intercept for trials and random slope for time. To investigate how BP differed across all follow-up periods across all participants, by patient subgroups and trial design, we used Equation (1) to estimate this difference by showing analyses that included all follow-up BP measurements as well as by excluding follow-up measures taken <12 months from baseline, and modified the polynomial term for follow-up time accordingly. We have also illustrated how our model that took into account various potential sources of heterogeneity compared with a conventional approach based on simply obtaining the difference in BP change from baseline and follow-up between treatment arms, which assumes fixed effects for treatment over time (both at trial and participant levels) albeit allowing for random intercept at trial level, in a sensitivity analysis.

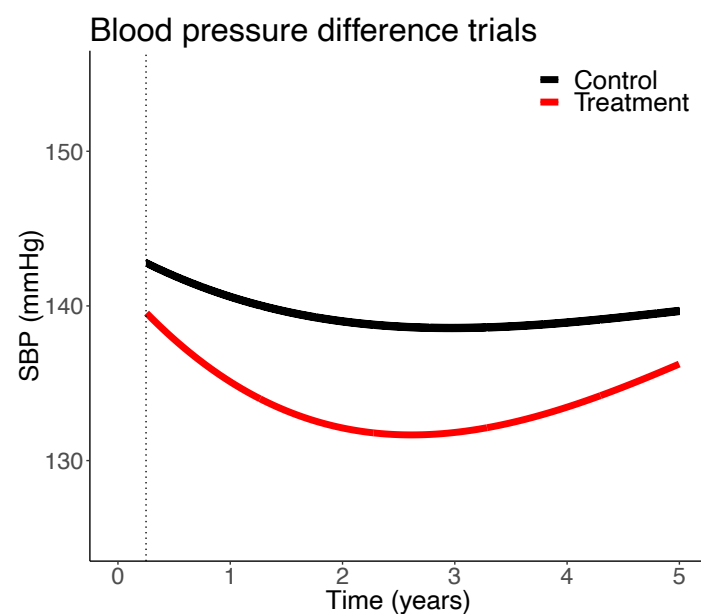
**Figure S1. Schematic diagram for model development and comparison.**

**FINAL MODEL: Random intercepts (trial and individual levels), fixed treatment effect, fixed time effect (cubic term) and random slope for time (individual level) (Model 3)**

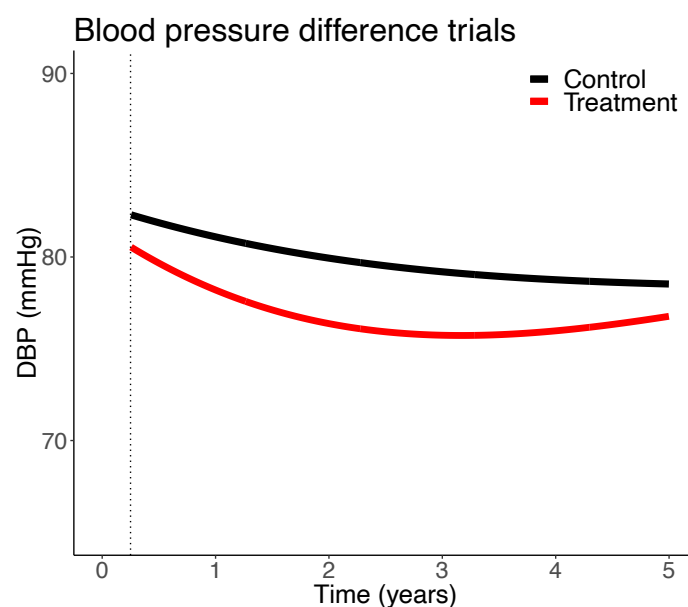


**Figure S2. Blood pressure trajectories for all blood pressure difference trials (blood pressure-lowering intensity and placebo-controlled trials combined).** Results are in red for active group and black for control group, from three months to five years of follow-up. Estimates based on separate models for treatment and control groups, with random intercepts at individual and trial levels, a random slope for time at the individual level (see **Method** for details) and adjusted for baseline blood pressure, age and sex. Baseline systolic/diastolic blood pressure for active and control groups was 147/84 mmHg. Estimated blood pressure at specific time points shown in online **Table S8**.

**A. Systolic blood pressure**



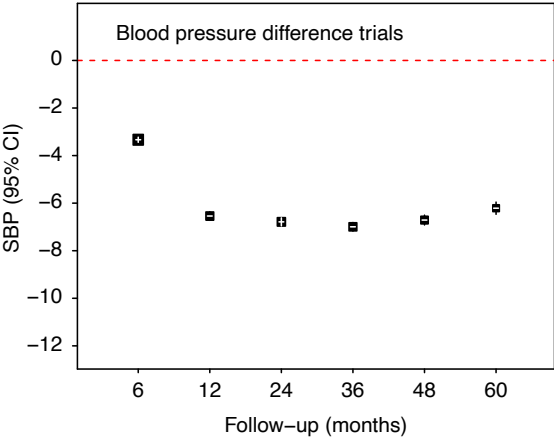
**B. Diastolic blood pressure**



**Figure S3. Effects of blood pressure-lowering treatment on mean blood pressure at fixed follow-up time points and across all follow-up period for all blood pressure difference trials (blood pressure-lowering intensity and placebo-controlled trials combined).** For mean difference at fixed follow-up time periods, estimates based on separate models for each time period with a fixed treatment effect and random intercept for individuals. For mean difference achieved across all time period (showing results based on all follow-up blood pressure measures and measures obtained from 12 months until end of follow-up), estimates based on fixed treatment effect and random intercepts at individual and trial levels, a random slope for time at the individual level. All mean difference values were adjusted for baseline blood pressure, age and sex. The area of the square is inversely proportional to the variance of the estimated difference. Negative values indicate lower blood pressure in the active than in the control group. Additional information provided in online [Table S9](#) and [Table S10](#).

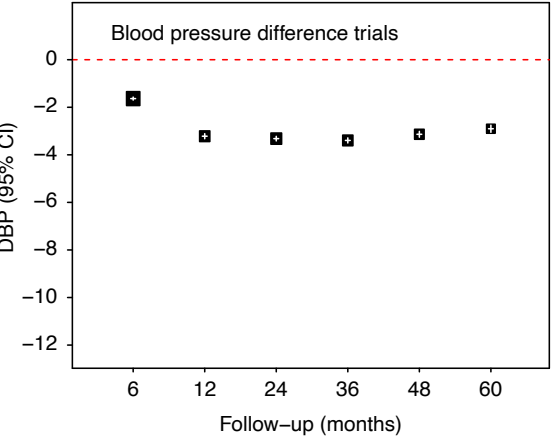
**A. Systolic blood pressure (SBP)**

Mean difference (mmHg) at fixed time points during follow-up

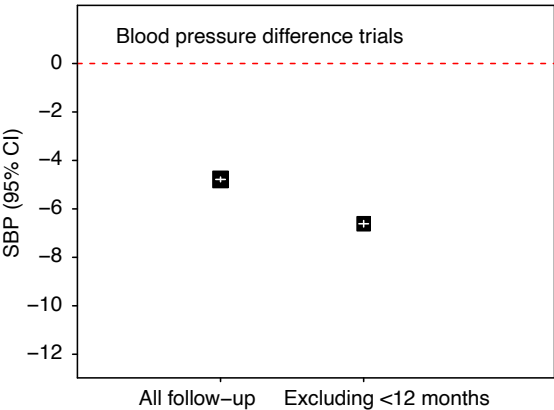


**B. Diastolic blood pressure (DBP)**

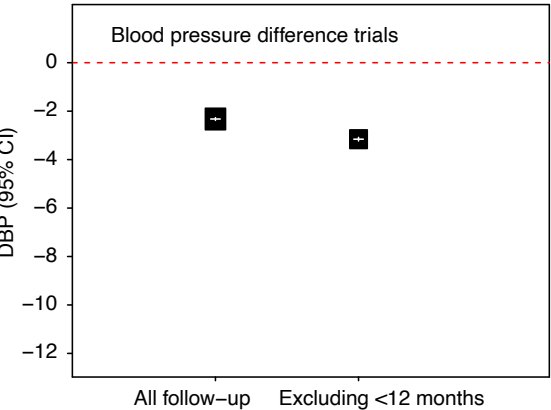
Mean difference (mmHg) at fixed time points during follow-up



Mean difference (mmHg) achieved across all follow-up periods



Mean difference (mmHg) achieved across all follow-up periods



**Figure S4. Effects of blood pressure-lowering treatment on long-term mean blood pressure, by baseline characteristics in all blood pressure difference trials (blood pressure-lowering intensity and placebo-controlled trials combined).** Estimates based on fixed treatment effect and random intercepts at individual and trial levels, a random slope for time at the individual level (see **Method** for details) and adjusted for baseline blood pressure, age and sex except when these variables are used as stratification factors

#### A. Mean systolic blood pressure difference

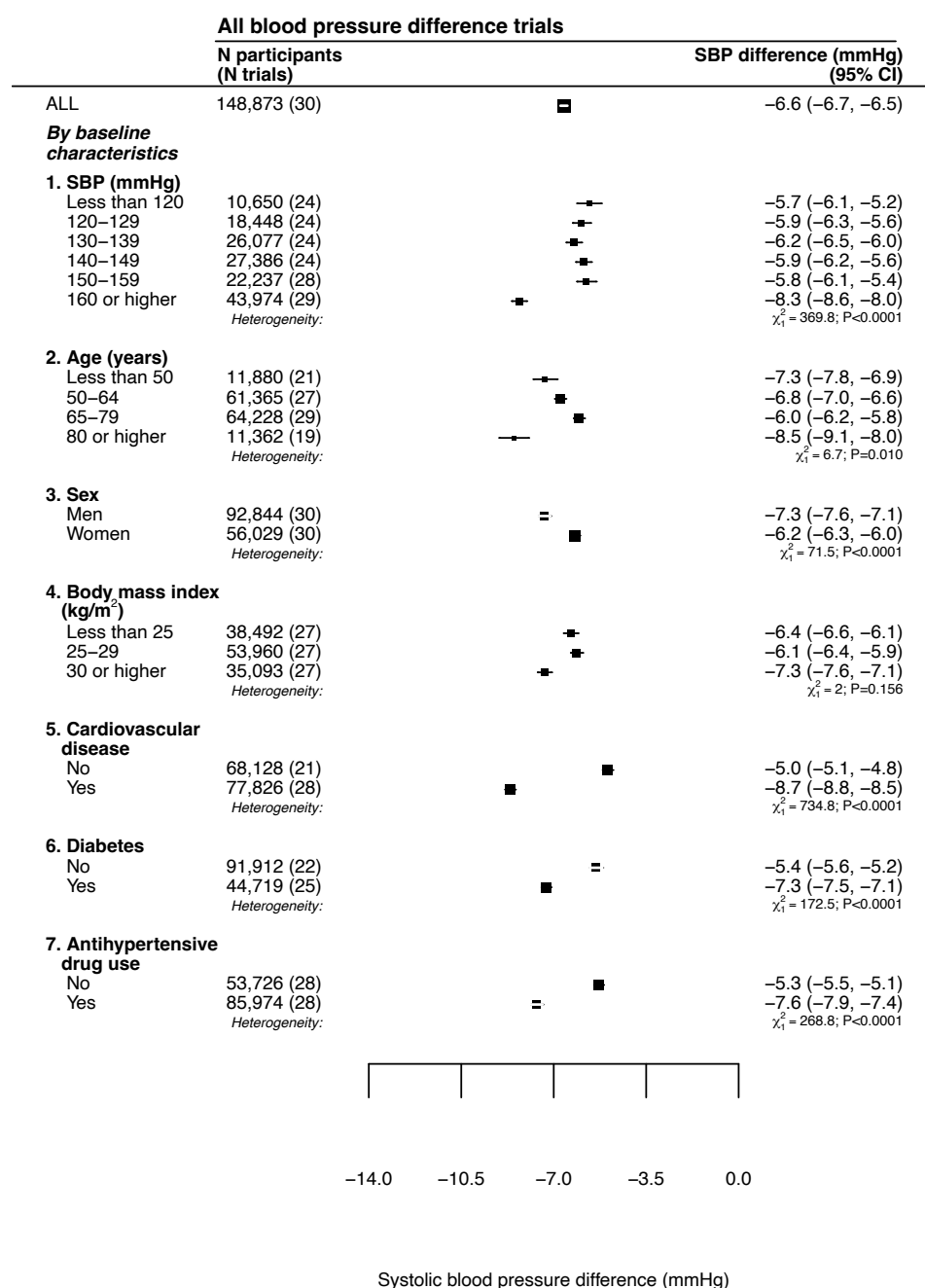
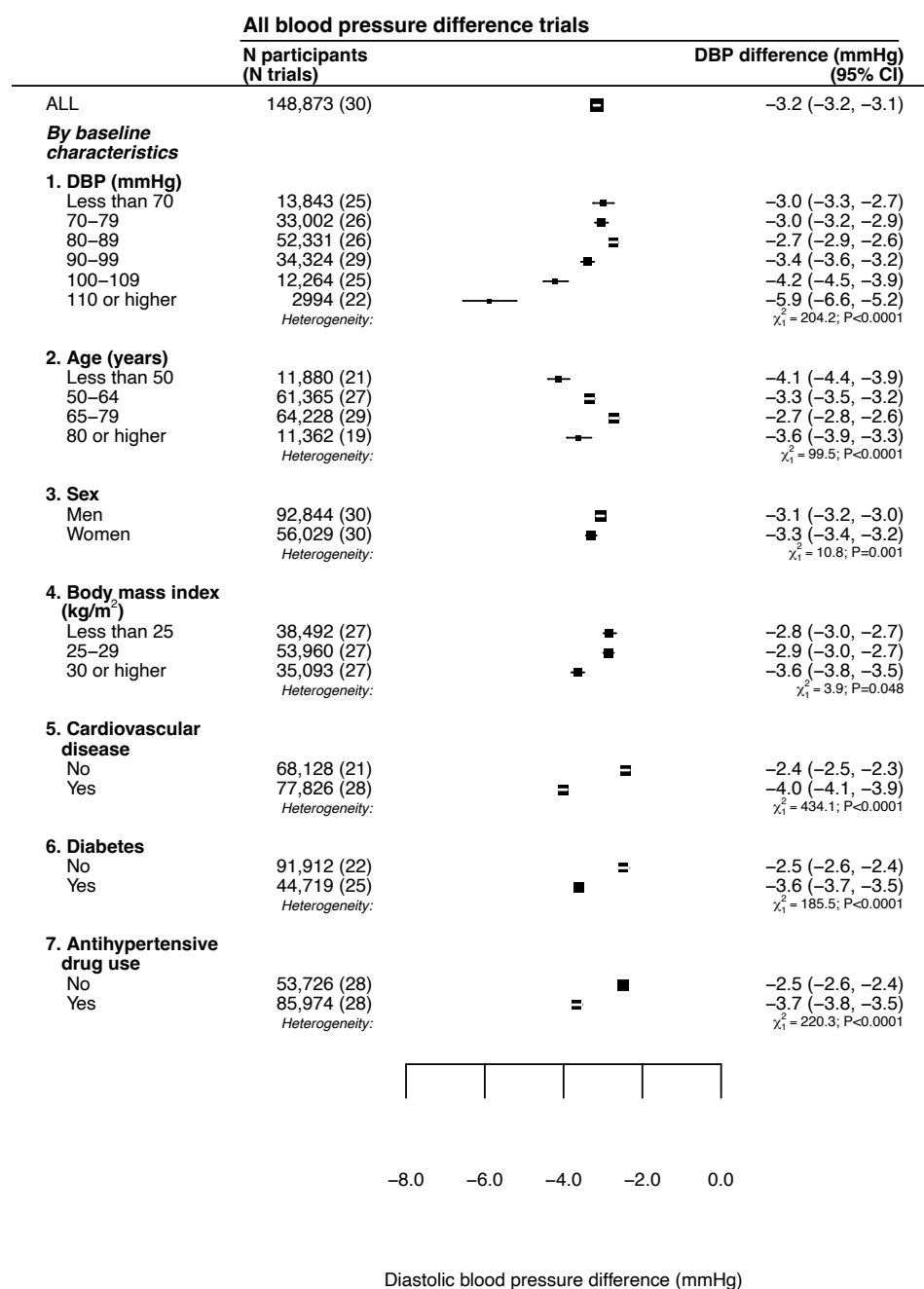


Figure S4. Effects of blood pressure-lowering treatment on long-term mean blood pressure (cont'd)

## B. Mean diastolic blood pressure difference





**Figure S5. Effects of blood pressure-lowering treatment on long-term blood pressure for each trial.** Estimates based on fixed treatment effect, a random intercept at the individual level, a random slope for time at the individual level (excluded from some trials due to non-convergence) (see **Method** for details) and adjusted for baseline blood pressure, age and sex. Acronyms described in full in **Trial acronym legend** in the Supplement.

**A. Mean systolic blood pressure difference**

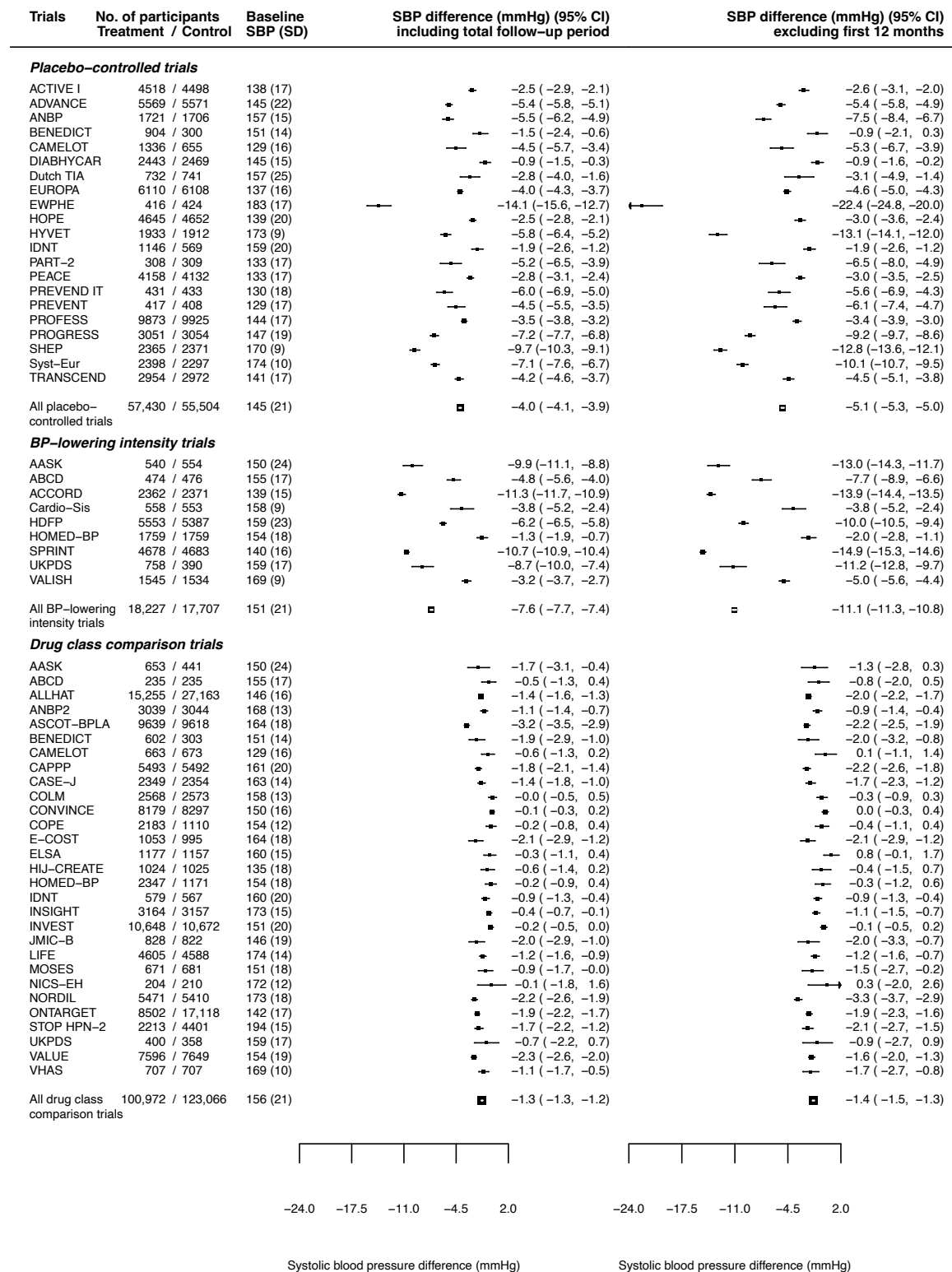
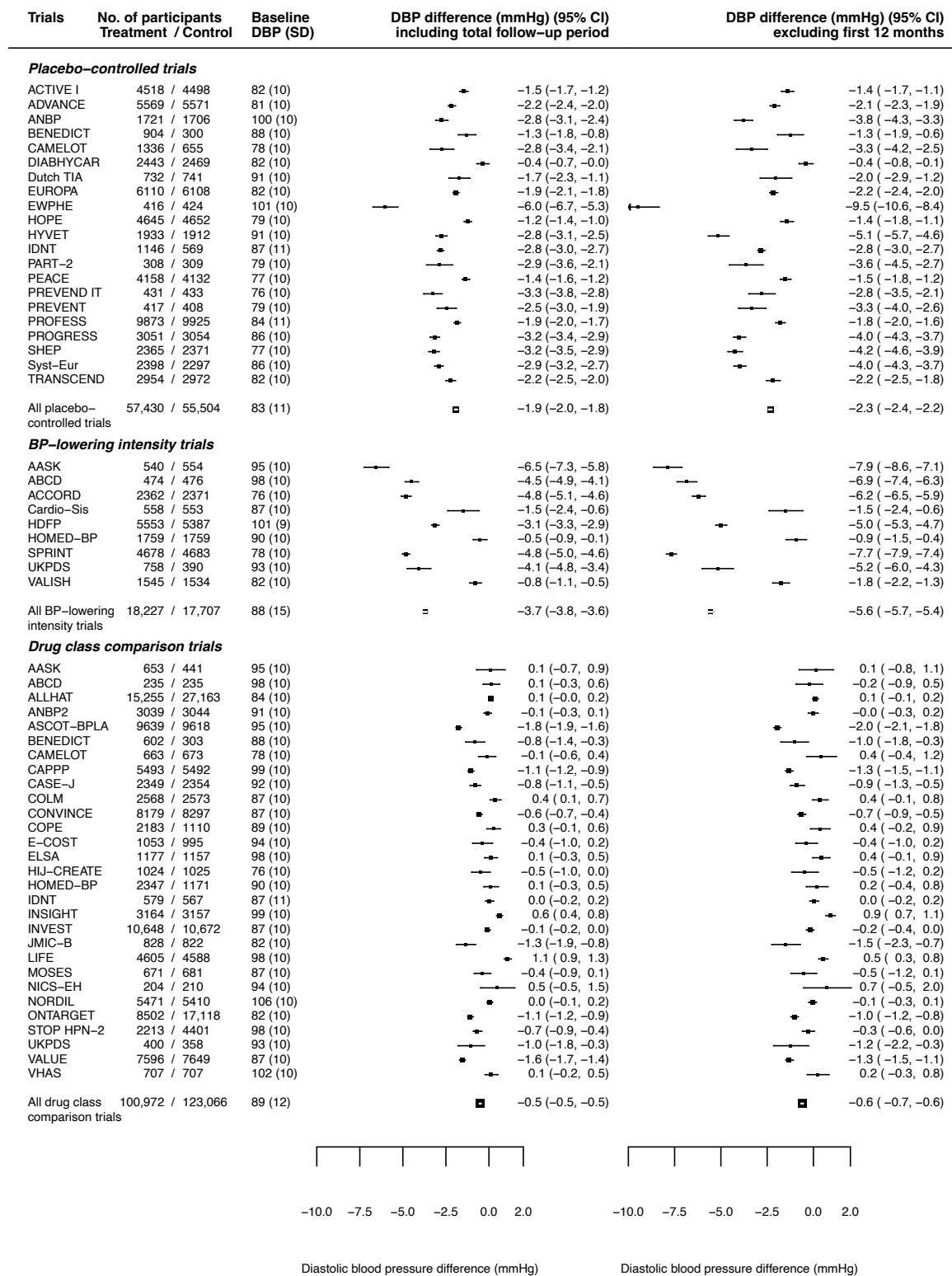


Figure S5. Effects of blood pressure-lowering treatment on long-term blood pressure for each trial (cont'd).

## B. Mean diastolic blood pressure difference



**Figure S6. Effects of blood pressure-lowering treatment on long-term mean blood pressure after excluding one trial at a time.** The estimate shown alongside a trial reflects the blood pressure difference after excluding that particular trial. Estimates based on fixed treatment effect, random intercepts at individual and trial levels, a random slope for time at the individual level (see *Method* for details) and adjusted for baseline blood pressure, age and sex and using all follow-up blood pressure measurements. Acronyms described in full in *Trial acronym legend* in the Supplement.

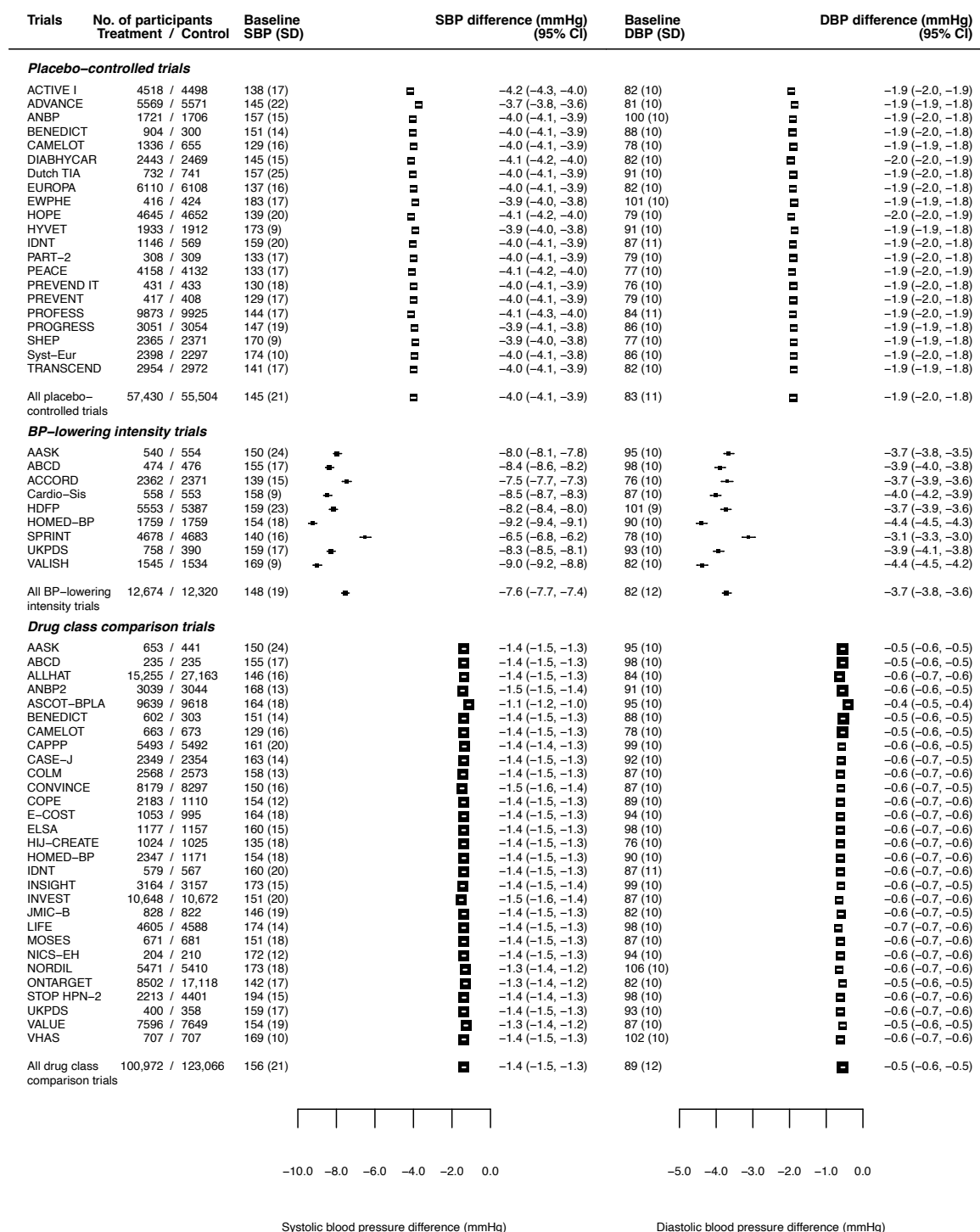


Table S1. List of trials and interventions assigned to the active and control arms in the analyses.

**A. Blood pressure difference trials (9 trials)**

<b>Trial</b>	<b>Active group</b>	<b>Control group</b>
<b><u>Trials comparing blood pressure-lowering targets (8 trials)</u></b>		
AASK	More intense treatment	Less intense treatment
ABCD	More intense treatment	Less intense treatment
ACCORD	More intense treatment	Less intense treatment
CARDIO-SIS	More intense treatment	Less intense treatment
HDFP	More intense treatment	Less intense treatment
HOMED-BP	More intense treatment	Less intense treatment
SPRINT	More intense treatment	Less intense treatment
UKPDS	More intense treatment	Less intense treatment
VALISH	More intense treatment	Less intense treatment

**Blood pressure-lowering trials comparing treatment versus placebo (21 trials)**

ACTIVE-I	ARB	Placebo
ADVANCE	ACEI and diuretic	Placebo
ANBP	Diuretic	Placebo
BENEDICT	ACEI, CCB and ACEI/CCB	Placebo
CAMELOT	CCB and ACEI	Placebo
DIABHYCAR	ACEI	Placebo
DUTCH-TIA	$\beta$ -blocker	Placebo
EUROPA	ACEI	Placebo
EWPH	Diuretic	Placebo
HOPE	ACEI	Placebo
HYVET	Diuretic	Placebo
IDNT	ARB and CCB	Placebo
PART 2	ACEI	Placebo
PEACE	ACEI	Placebo
PREVEND IT	ACEI	Placebo
PREVENT	CCB	Placebo
PROFESS	ARB	Placebo
PROGRESS	ACEI and/or diuretic	Placebo
SHEP	$\beta$ -blocker and diuretic	Placebo
SYST-EUR	CCB	Placebo
TRANSCEND	ARB	Placebo



**Table S1. List of trials and interventions assigned to the active and control arms in the analyses (cont'd).****B. Drug comparison trials (29 trials)**

<b>Trial</b>	<b>Active group</b>	<b>Control group</b>
AASK	ACEI and CCB	$\beta$ -blocker
ABCD	CCB	ACEI
ALLHAT	Diuretic	ACEI, CCB and $\alpha$ -blocker
ANBP2	Diuretic	ACEI
ASCOT-BPLA	CCB-based	$\beta$ -blocker-based
BENEDICT	ACEI and ACEI/CCB	CCB
CAMELOT	CCB	ACEI
CAPPP	$\beta$ -blocker and/or diuretic	ACEI
CASE-J	CCB	ARB
COLM	ARB and diuretic	ARB and CCB
CONVINCE	CCB	$\beta$ -blocker or diuretic
COPE	CCB/diuretic and CCB/ $\beta$ -blocker	CCB and ARB
E-COST	ARB	Conventional
ELSA	CCB	$\beta$ -blocker
HIJ-CREATE	ARB	non-ARB
HOMED-BP	CCB	ACEI and ARB
IDNT	ARB	CCB
INSIGHT	Diuretic	CCB
INVEST	CCB	non-CCB
JMIC-B	CCB	ACEI
LIFE	ARB	$\beta$ -blocker
MOSES	CCB	ARB
NICS-EH	Diuretic	CCB
NORDIL	$\beta$ -blocker and/or diuretic	CCB
ONTARGET	ARB/ACEI	ACEI and ARB
STOP HYPERTENSION-2	$\beta$ -blocker and/or diuretic	ACEI and CCB
UKPDS	$\beta$ -blocker	ACEI
VALUE	CCB-based	ARB-based
VHAS	Diuretic	CCB

Acronyms are described in full in the Trial acronym legend in the Supplement; CCB – calcium channel-blocker; ACEI – angiotensin-converting enzyme inhibitor; ARB – angiotensin II receptor blocker.

**Table S2. Mean baseline blood pressure according to baseline characteristics and trial designs.****A. Systolic blood pressure (mmHg)**

	<b>Blood pressure- lowering intensity trials</b>	<b>Placebo- controlled trials</b>	<b>All blood pressure difference trials</b>	<b>Drug class comparison trials</b>
	Mean (SD)	Mean (SD)	Mean (SD)	Mean (SD)
<b>ALL PARTICIPANTS</b>	<b>151 (21)</b>	<b>146 (20)</b>	<b>147 (21)</b>	<b>156 (21)</b>
By baseline characteristics				
1. Systolic blood pressure (mmHg)				
<120	113 (6)	112 (6)	112 (6)	112 (6)
120 to 129	125 (3)	124 (3)	124 (3)	124 (3)
130 to 139	135 (3)	133 (3)	134 (3)	134 (3)
140 to 149	144 (3)	143 (3)	143 (3)	144 (3)
150 to 159	154 (3)	153 (3)	153 (3)	154 (3)
≥160	174 (14)	171 (11)	172 (12)	175 (14)
2. Age (years)				
<50	150 (20)	138 (18)	144 (20)	155 (19)
50 to 65	151 (21)	142 (19)	144 (20)	154 (20)
65 to 79	151 (21)	147 (20)	148 (21)	157 (21)
≥80	154 (19)	160 (21)	159 (21)	160 (23)
3. Sex				
Men	149 (20)	143 (19)	144 (20)	154 (20)
Women	154 (22)	151 (21)	152 (22)	158 (21)
4. Body mass index (kg/m <sup>2</sup> )				
<25	155 (19)	147 (21)	148 (21)	158 (22)
25 to 30	147 (18)	146 (20)	146 (20)	155 (21)
≥30	142 (18)	146 (20)	145 (19)	157 (21)
5. Cardiovascular disease history				
No	148 (19)	154 (21)	153 (21)	161 (20)
Yes	144 (19)	141 (19)	141 (19)	150 (20)
6. Diabetes history				
No	152 (21)	147 (22)	149 (21)	157 (21)
Yes	147 (20)	146 (19)	145 (20)	153 (19)
7. Antihypertensive drug use				
No	150 (21)	149 (21)	149 (21)	163 (19)
Yes	152 (21)	144 (20)	145 (20)	151 (20)

Table S2. Mean baseline blood pressure according to baseline characteristics and trial designs (cont'd).

## B. Diastolic blood pressure (mmHg)

	Blood pressure- lowering intensity trials	Placebo- controlled trials	All blood pressure difference trials	Drug class comparison trials
	Mean (SD)	Mean (SD)	Mean (SD)	Mean (SD)
<b>ALL PARTICIPANTS</b>	<b>88 (15)</b>	<b>83 (11)</b>	<b>84 (12)</b>	<b>90 (12)</b>
By baseline characteristics				
1. Diastolic blood pressure (mmHg)				
<70	63 (5)	63 (5)	63 (5)	64 (5)
70 to 79	75 (3)	74 (3)	74 (3)	75 (3)
80 to 89	84 (3)	83 (3)	83 (3)	84 (3)
90 to 99	94 (3)	93 (3)	93 (3)	94 (3)
100 to 109	104 (3)	102 (3)	103 (3)	103 (3)
≥110	118 (8)	115 (7)	117 (7)	113 (5)
2. Age (years)				
<50	100 (11)	87 (12)	94 (13)	99 (11)
50 to 65	90 (13)	84 (11)	86 (12)	92 (12)
65 to 79	80 (13)	81 (10)	81 (11)	87 (12)
≥80	74 (11)	84 (11)	82 (12)	84 (12)
3. Sex				
Men	88 (15)	83 (11)	84 (12)	90 (12)
Women	88 (14)	83 (11)	85 (12)	90 (12)
4. Body mass index (kg/m <sup>2</sup> )				
<25	83 (12)	82 (11)	82 (11)	89 (12)
25 to 30	82 (13)	83 (10)	83 (11)	90 (12)
≥30	82 (13)	84 (11)	83 (11)	90 (12)
5. Cardiovascular disease history				
No	83 (12)	84 (11)	86 (13)	93 (12)
Yes	79 (14)	82 (10)	82 (11)	86 (12)
6. Diabetes history				
No	89 (15)	84 (11)	85 (13)	91 (12)
Yes	83 (13)	82 (10)	82 (11)	86 (11)
7. Antihypertensive drug use				
No	89 (15)	84 (11)	86 (13)	95 (11)
Yes	86 (15)	82 (11)	83 (11)	87 (12)

Table S3. Characteristics of trials included in the BPLTTC study.

A. Trials comparing different blood pressure-lowering targets intensity

Trial	Setting	Inclusion criteria	Exclusion criteria	Recruitment period	Randomisation groups, No. of participants (% women)			Treatment goals for blood pressure control		Treatment	Follow-up duration (y)	No. of follow-up BP measures
					All	More intense	Less intense	More intense	Less intense			
AASK <sup>12,13</sup>	USA	Age 18-70 years, African-American, hypertension, renal disease (GFR=20-65 ml/min per 1.73m <sup>2</sup> )	DBP <95 mmHg, diabetes, urine protein:creatinine ratio >25, recent malignant hypertension, secondary hypertension, non-blood pressure-related CKD, serious systemic disease, heart failure	Feb 1995 to Sept 1998	1094 (39)	540 (38)	554 (40)	Mean arterial pressure ≤92 mmHg	Mean arterial pressure 102-107 mmHg	1 of 3: β-blocker (Metoprolol), ACEI (Ramipril), CCB (Amlodipine); Plus furosemide, doxazosin, clonidine, and hydralazine or minoxidil sequentially	4.8	54
ABCD <sup>14-16</sup>	USA	Age 0-74 years, with T2D, DBP ≥80 mmHg, not on antihypertensive treatment	Recent CAD or CeVD, heart failure, renal disease	Mar 1991 to May 1993	950 (39)	474 (40)	476 (38)	DBP <75 mmHg for hypertensives (DBP ≥90 mmHg) or DBP reduction by 10 mmHg for normotensives	DBP 80-89 mmHg for hypertensives (DBP ≥90 mmHg) or no change for normotensives	Hypertensive group: CCB (Nisoldipine) and ACEI (Enalapril); plus β-blocker (Metoprolol), diuretic (HCTZ), or others but not CCB or ACEI; Normotensive group: CCB (Nisoldipine), ACEI (Enalapril) or placebo	4.7	8
ACCORD <sup>17</sup>	USA and Canada	Age ≥40y years with CVD or ≥50 years with substantial atherosclerosis, T2D, HbA1c ≥7.5%, albuminuria, LVH or ≥2 CVD risk factors (dyslipidaemia, hypertension, smoking, obesity); SBP 130-180 mmHg and taking ≤3 antihypertensive drugs, 24-hour protein excretion rate <1g	Body mass index ≥45 kg/m <sup>2</sup> , serum creatinine ≥132.6 μmol/l and other serious illness	Jan to Jun 2001, then Jan 2003 to Oct 2005	4733 (48)	2362 (48)	2371 (48)	SBP <120 mmHg	SBP <140 mmHg	Drug classes available in clinical practice	4.7	20
Cardio-Sis <sup>2,18</sup>	Italy	Age ≥55 years, SBP ≥150 mmHg, taking antihypertensive drug ≥12 weeks, ≥1 CV risk factor (smoking, dyslipidaemia, family history of premature CVD, prior TIA or stroke, established CAD or PAD	Fasting blood glucose ≥7 mmol/l, diabetes, serious conditions, renal disease, valvular heart disease, left ventricular hypertrophy, atrial fibrillation, substance misuse.	Feb 2005 to Feb 2007	1111 (59)	558 (59)	553 (59)	SBP <130 mmHg	SBP <140 mmHg	Diuretic (Furosemide), ACEI (Ramipril), ARB (Telmisartan), CCB (Amlodipine), β-blocker (Bisoprolol), Clonidine	4.7	No data
HDFP <sup>19</sup>	USA	Age 30-69 years, hypertensive with DBP ≥ 90 mmHg	None specified	Feb 1973 to Feb 1974	10,940 (46)	5485 (46)	5455 (46)	≤90 mmHg DBP if baseline DBP ≥100 mmHg or receiving antihypertensive therapy at baseline, or a reduction of 10 mmHg in DBP if baseline DBP 90-90 mmHg	Referred to community physicians for care	Diuretic (Chlorthalidone; plus triamterene or spironolactone if necessary); plus antiadrenergic drug (reserpine, alternatively, methyldopa); plus vasodilator (Hydralazine); plus antiadrenergic drug (Guanethidine); then addition or substitution of other drugs	6.7	5 (all); More intense group=24 (median)
HOMED-BP <sup>20</sup>	Japan	Self-measured SBP 135-179 mmHg or DBP 85-119 mmHg, but not if DBP <65 or SBP <110 mmHg (clinic SBP <220 mmHg and DBP <125 mmHg)	None specified	May 2001 to Oct 2009	3518 (50)	1759 (50)	1759 (50)	SBP <120 and DBP <80 mmHg	BP 125-134/80-84 mmHg	ACEI, ARB or CCB; Diuretic; β-blocker; then other drug class (avoid reaching BP <110/65 mmHg)	4.9	8

SPRINT <sup>21</sup>	USA and Puerto Rico	Age ≥50y years, SBP 130-180 mmHg, increased CVD risk (clinical/subclinical CVD other than stroke, CKD excluding polycystic kidney disease and with eGFR of 20-60 ml/min/1.73m <sup>2</sup> body surface area, 10-year Framingham CVD risk ≥15%, age ≥75y)	Diabetes or prior stroke	Nov 2010 to Mar 2013	9361 (36)	4678 (36)	4683 (35)	SBP <120 mmHg	SBP <140 mmHg	All major drug classes	3.0	13
UKPDS <sup>22-24</sup>	UK	Age 25-65 years, newly-diagnosed diabetes, and hypertension (untreated: SBP ≥160 mmHg and/or DBP ≥90 mmHg; treated: SBP ≥150 mmHg and/or DBP ≥85 mmHg)	Ketonuria, recent MI, angina, heart failure, >1 major vascular episode, serum creatinine >15 μmol/l, retinopathy, malignant hypertension, uncorrected endocrine abnormality, severe concurrent illness	1987 to 1991	1148 (45)	758 (46)	390 (42)	BP <150/85 mmHg	BP <180/105 mmHg	ACEI (Captopril) and β-blocker (Atenolol) for more intense arm; For both arms: diuretic (Furosemide), CCB (Nifedipine), methyldopa then α-blocker (Prazosin)	7.9	5
VALISH <sup>25-26</sup>	Japan	Age ≥70 to <85 years, isolated hypertension (SBP >160 mmHg and DBP <90 mmHg)	Secondary or malignant hypertension, BP ≥200/≥90 mmHg, recent CeVD or MI, recent/planned revascularisation, heart failure, aortic stenosis, valvular heart disease, atrial fibrillation/flutter, serious arrhythmia, renal/liver dysfunction	Feb 2004 to Aug 2005	3079 (62)	1545 (62)	1534 (63)	SBP <140 mmHg	SBP ≥140 to <150 mmHg	ARB (Valsartan) then other antihypertensive agents such as diuretics and CCB but not other ARB drugs	2.6	11

**Table S3. Characteristics of trials included in the BPLTTC study (cont'd).****B. Blood pressure-lowering trials comparing treatment with placebo**

Trial	Setting	Inclusion criteria	Exclusion criteria	Recruitment period	Randomisation group, No. of participants (% of women)			Drug intervention	Any additional treatment	Treatment goal for blood pressure control	Follow-up duration (years)	No. of follow-up BP measures
					All	Inter-vention	Placebo					
ACTIVE <sup>127</sup>	Multi-country	Atrial fibrillation, ≥1 risk factor (age ≥75 years, on antihypertensive treatment, history of stroke, TIA or non-CNS embolism, LVEF <45%, PVD, or age 55-74 years with either CAD or diabetes)	Use of anticoagulant, peptic ulcer disease in past 6 months, history of intracerebral haemorrhage, thrombocytopenia or mitral stenosis	Jun 2003 to May 2006	9016 (39)	4518 (39)	4498 (39)	ARB (Irbesartan)	None	None specified	4.1	9
ADVANCE <sup>28</sup>	Multi-country	Age ≥55 years T2D (diagnosed aged ≥30y), ≥1 major CVD or ≥1 CVD risk factor (microvascular disease, smoking, dyslipidaemia, microalbuminuria, T2D for ≥10 years, age ≥65 years)	HbA1c target (≤6.5%), definite indication for long-term insulin therapy	Jul 2001 to Mar 2003	11,140 (43)	5569 (42)	5571 (43)	ACEI (Perindopril) and diuretics (Indapamide) as fixed dose combination drug	At physician's discretion, but not thiazide diuretics, and only perindopril as ACEI allowed	None specified	4.2	12
ANBP <sup>29 30</sup>	Australia	Age 30-69 years with mild hypertension (DBP 95-110 mmHg and SBP <200 mmHg)	Antihypertensive treatment in past 3 months, recent angina or MI, stroke, hormone therapy, asthma, diabetes, gout, serious disease, tricyclic antidepressant use	1973 to March 1979	3427 (37)	1721 (37)	1706 (36)	Diuretic (Chlorothiazide)	Methyldopa, propranolol, or pindolol, then hydralazine or clonidine	Reduce DBP to ≤90 mmHg (after two years, further reduced to 80 mmHg)	3.6	4
BENEDICT <sup>31 32</sup>	Italy	Age ≥40 years, untreated SBP ≥130 / DBP ≥85 mmHg or needing treatment to attain below these levels, T2D for <25 years, urinary albumin excretion rate <20 µg/min, serum creatinine ≤133 µmol/l	HbA1c ≥11%, nondiabetic renal disease	Around 2000 to 2003	1209 (48)	907 (47)	302 (50)	ACEI (Trandolapril), CCB (Verapamil), both ACEI and CCB	Diuretics (HCTZ or furosemide), doxazosin, prazosin, clonidine, methyldopa or β-blocker, minoxidil, or CCB	Reduce BP to 120/80 mmHg	3.1	14
CAMELOT <sup>33</sup>	Multi-country (US, Canada, Europe)	Age 30-79 years, coronary artery stenosis >20% by angiography, DBP <100 mmHg	Left middle coronary artery obstruction >50%, LVEF <40%, heart failure	Apr 1999 to Apr 2002	1991 (26)	1336 (26)	655 (27)	CCB (Amlodipine), ACEI (Enalapril)	Allowed to continue β-blocker, α-blocker, diuretics	None specified	1.6	7
DIABHYCAR <sup>34 35</sup>	Multi-country	Age ≥50 years, T2D, urinary albumin excretion ≥20 mg/l in two consecutive urine samples	Serum creatinine >150 µmol/l, use of insulin, ACEI or ARB, heart failure, recent MI, urinary tract infection	Feb 1995 to Apr 1998	4912 (30)	2443 (30)	2469 (30)	ACEI (Ramipril)	Usual treatment	None specified	3.9	7
Dutch TIA Trial <sup>36</sup>	The Netherlands	TIA or non-disabling ischaemic stroke (Rankin Scale ≤3) in past 3 months	Cerebral ischaemia from identifiable causes other than arterial thrombosis or embolism	Feb 1986 to Mar 1989	1473 (36)	732 (34)	741 (38)	β-blocker (Atenolol)	None specified	None specified	2.3	6
EUROPA <sup>37 38</sup>	Multi-country (Europe)	Age ≥18 years, documented MI >3 months before screening, revascularisation >6 months before screening, >70% coronary obstruction	Heart failure, hypotension, uncontrolled hypertension, renal insufficiency, serum potassium >5.5 mmol/L	Oct 1997 to Jun 2000	12,218 (15)	6110 (14)	6108 (15)	ACEI (Perindopril)	None specified	None specified	4.2	9
EWPHE <sup>39 40</sup>	Multi-country	Age ≥60 years, BP 160-239/90-119 mmHg	Curable causes of high BP, retinopathy, heart failure, stroke history, hepatitis/cirrhosis, gout, malignancy, diabetes requiring insulin treatment	From 1972	840 (70)	416 (69)	424 (71)	Diuretic (HCTZ or triamterene)	Methyldopa	Reduce BP but at unspecified levels	4.6	11
HOPE <sup>41</sup>	Multi-country	Age ≥55 years, CAD, stroke, PVD or diabetes, plus ≥1 risk factor (hypertension, dyslipidaemia,	Heart failure, left ejection fraction <40%, using ACEI or Vitamin E, uncontrolled	Dec 1993 to Jun 1995	9297 (27)	4656 (28)	4652 (26)	ACEI (Ramipril)	None specified	None specified	4.5	3



		smoking, or documented microalbuminuria)	hypertension, nephropathy, or recent MI or stroke									
HYVET <sup>42</sup>	Multi-country	Age ≥80y years, sustained SBP ≥160 mmHg	Accelerated or secondary hypertension, recent haemorrhagic stroke, heart failure, serum creatinine >150 µmol/L, serum potassium <3.5 or >5.5 mmol/L, gout, and dementia	From 2000	3845 (60)	1933 (61)	1912 (60)	Diuretic (Indapamide)	ACEI (Perindopril)	Reduce BP to 150/80 mmHg	2.1	5
IDNT <sup>1</sup>	USA	Age 30-70 years, T2D, hypertension (BP ≥135/85 mmHg or taking anti-hypertensive drug), proteinuria, serum creatinine (µmol/l): 88 to 265 (women) or 106 to 265 (men)	None specified	Mar 1996 to Feb 1999	1715 (34)	1146 (36)	569 (29)	ARB (Irbesartan) and CCB (Amlodipine)	Others except ACEI, ARB and CCB	SBP <135 (10 mmHg lower if baseline value >145 mm Hg); DBP <85 mmHg	2.6	No data
PART 2 <sup>43</sup>	New Zealand	Age ≤75 years, diagnosis (in past 5 year) of MI, documented CAD, TIA or intermittent claudication	Heart failure, serious nonvascular disease, SBP >160 mmHg, DBP >100 mm Hg, DBP <100 mmHg during pre-randomisation run-in period	Not specified; Publication in 2000	617 (18)	308 (18)	309 (18)	ACEI (Ramipril)	None	None specified	4.6	5
PEACE <sup>44</sup>	Multi-country (USA, Puerto Rico, Canada and Italy)	Age ≥50 years, documented CAD	Unstable angina, severe valvular heart disease, recent revascularisation, planned elective revascularisation, limited 5-year survival, serum creatinine >177 µmol/l, serum potassium >5.5 mmol/l	Nov 1996 to Jun 2000	8290 (18)	4158 (19)	4132 (17)	ACEI (Trandolapril)	None	None specified	4.7	7
PREVEND IT <sup>45</sup>	The Netherlands	Microalbuminuria, SBP <160/100 mmHg (no previous antihypertension treatment)	Creatinine clearance <60% of normal age-adjusted value	Apr 1998 to Jun 1999	864 (35)	431 (34)	433 (36)	ACEI (Fosinopril)	None	None specified	3.8	16
PREVENT <sup>46 47</sup>	USA and Canada	Age 30-80 years, documented CAD, DBP <95 mmHg, cholesterol <325 mg/dl, fasting blood glucose <200 mg/dl	Contraindication for dihydropyridines, uncontrolled hypertension, diabetes and other major illness	Nov 1992 to Sep 1994	825 (20)	417 (20)	408 (20)	CCB (Amlodipine)	None	None specified	3.0	3
PROFESS <sup>48 49</sup>	Multi-country	Age ≥55 years with ischaemic stroke <90 days before randomisation (later modified to include age 50 to 54 years or had stroke 90 to 120 days before randomisation if with ≥2 additional risk factors: diabetes, hypertension, smoker, obesity previous CVD, end-organ damage or hyperlipidaemia) and remained stable <sup>a</sup>	Haemorrhagic stroke, severe disability after the qualifying stroke, contraindication to treatments	Sep 2003 to Jul 2006	19,798 (36)	9873 (35)	9925 (36)	ARB (Telmisartan)	At physician's discretion to control blood pressure: diuretic, then β-blocker or CCB, then ACEI but not ARB.	None specified	2.5	6
PROGRESS <sup>50 51</sup>	Multi-country (Asia, Australasia and Europe)	Stroke or TIA in past 5 years	Indication or contraindication for ACEI	Jun 1995 to Nov 1997	6105 (30)	3051 (30)	3054 (30)	ACEI (Perindopril) and/or diuretic (Indapamide)	None	Intensity of lowering based on clinical intention determined before randomisation	3.9	4
SHEP <sup>52</sup>	USA	Age ≥60 years, isolated systolic hypertension (BP 160-219/<90 mmHg, not on treatment)	Major CVD, cancer, alcoholic liver disease, renal dysfunction, competing risk of SHEP primary endpoint or presence of medical management exclusions	Mar 1985 to Jan 1988	4736 (57)	2365 (56)	2371 (57)	Diuretic (Chlorthalidone) and β-blocker (Atenolol)	None	If baseline SBP >180 mmHg: reduce to <160 mmHg; If baseline SBP 160-179 mmHg, reduce by 20 mmHg	5.0	4

SYST-EUR <sup>53</sup>	Multi-country	Age ≥60 years, sitting SBP 160-219 mmHg, sitting DBP <95 mmHg, and standing SBP ≥140 mmHg	Secondary hypertension, retinal haemorrhage/papilloedema, heart failure, dissecting aortic aneurysm, serum creatinine ≥180 μmol/l, recent severe nosebleeds, stroke or MI, dementia, disorders prohibiting standing position, severe CVD/non-CVD	Dec 1988 to Jan 1997	4695 (67)	2398 (67)	2297 (66)	CCB (Nitrendipine)	Combined with or replaced by ACEI (Enalapril), diuretic (HCTZ), or both	Reduce sitting SBP by ≥20 mmHg to <150 mmHg	2.6	3
TRANSCEND <sup>54 55</sup>	Multi-country	Intolerant to ACEI and with established CAD, PVD, CeVD or diabetes with end-organ damage	Heart failure, valvular/cardiac outflow tract obstruction, pericarditis, congenital heart disease, unexplained syncope, recent revascularisation, SBP >160 mmHg, heart transplantation, subarachnoid haemorrhage, significant renal stenosis, renal or hepatic dysfunction	Nov 2001 to May 2004	5926 (43)	2954 (43)	2972 (43)	ARB (Telmisartan)	None	None specified	4.9	9

Table S3. Characteristics of trials included in the BPLTTC study (cont'd).

C. Trials comparing different drug classes										
Trial	Country	Inclusion criteria	Exclusion criteria	Recruitment period	Randomisation groups	No. of participants (% women)	Additional (open-label) treatment	Treatment target for blood pressure control	Follow-up duration (y)	No. of follow-up BP measures
AASK <sup>12 13</sup>	USA	Age 18-70 years, African-American, hypertension, renal disease (GFR=20-65 ml/min per 1.73m <sup>2</sup> )	DBP <95 mmHg, diabetes, urine protein:creatinine ratio >25, recent malignant or hypertension, non-blood pressure-related CKD, serious systemic disease, heart failure	Feb 1995 to Sept 1998	All ACEI (Ramipril) CCB (Amlodipine) $\beta$ -blocker (Metoprolol)	1094 (39) 436 (39) 217 (39) 441 (39)	Furosemide, doxazosin, clonidine, hydralazine and minoxidil (sequentially)	None specified	4.8	54
ABCD <sup>14-16</sup>	USA	Age 0-74 years, with T2D, DBP $\geq$ 80 mmHg, not on antihypertensive treatment	Recent CAD or CeVD, heart failure, renal disease	Mar 1991 to May 1993	All CCB (Nisoldipine) ACEI (Enalapril)	470 (33) 235 (32) 235 (33)	$\beta$ -blocker (Metoprolol), diuretic (HCTZ), or others but not CCB or ACEI	None specified	4.7	8
ALLHAT <sup>56 57</sup>	Multi-country	Age $\geq$ 55y years stage 1 or 2 hypertension plus $\geq$ 1 risk factor (MI or stroke >6 months previously, left ventricular hypertrophy, T2D, smoking, HDL <0.91 mmol/l), other atherosclerotic CVD	Symptomatic or hospitalisation for heart failure, LVEF <35%	Feb 1994 to Jan 1998	All Diuretic (Chlorthalidone) CCB (Amlodipine) ACEI (Lisinopril) $\alpha$ -blocker (Doxazosin)	42,418 (47) 15,255 (47) 9048 (47) 9054 (46) 9061 (46)	Atenolol, clonidine or reserpine	BP <140/90 mmHg	4.8	3
ANBP <sup>258</sup>	Australia	Age 65-84 years, SBP $\geq$ 160 mmHg or DBP $\geq$ 90 mmHg (if SBP $\geq$ 140 mmHg), no recent CVD	Serious illness, plasma creatinine >221 $\mu$ mol/l, malignant hypertension, dementia	April 1995 to Jun 1998	All ACEI (Enalapril) Diuretic (HCTZ)	6083 (51) 3044 (50) 3039 (52)	$\beta$ -blocker, CCB and $\alpha$ -blocker	Lower SBP by 20 mmHg to <160 mmHg (<140 mmHg if tolerated,) and by 10 mmHg DBP to <90 mmHg (<80 mmHg if tolerated)	4.1	9
ASCOT-BPLA <sup>59 60</sup>	Multi-country	Age 40-79 years, untreated (SBP $\geq$ 160 or DBP $\geq$ 100 mmHg) or treated hypertension (SBP $\geq$ 140 or DBP $\geq$ 90 mmHg), $\geq$ 3 CVD risk factors (documented LVH, abnormal ECG, T2D, PAD, previous stroke or TIA, male sex, age $\geq$ 55 years, microalbuminuria or proteinuria, smoking, TC:HDL $\geq$ 6, family history of premature coronary heart disease	Previous MI, current treatment for angina, recent CeVD, fasting triglycerides >4.5 mmol/l, heart failure, arrhythmia, haematological or biochemical abnormality at screening	Feb 1998 to May 2000	All CCB (Amlodipine-based) $\beta$ -blocker (Atenolol-based)	19,257 (23) 9639 (23) 9618 (23)	For CCB arm: plus ACEI (Perindopril); For $\beta$ -blocker arm: plus diuretic (bendroflumethiazide) and potassium	With diabetes: BP <140/90 mmHg; Without diabetes: BP <130/80 mmHg	5.3	12
BENEDICT <sup>31 32</sup>	Italy	Age $\geq$ 40 years, untreated SBP $\geq$ 130 or DBP $\geq$ 85 mmHg or needing treatment to attain below these levels, T2D for <25 years, urinary albumin excretion rate <0 $\mu$ g/min on two consecutive measures, serum creatinine $\leq$ 133 $\mu$ mol/l	HbA1c $\geq$ 11%, nondiabetic renal disease	Around 2000 to 2003	All (excluding placebo) ACEI (Trandolapril) CCB (Verapamil) ACEI (Trandolapril) and CCB (Verapamil)	907 (47) 302 (48) 303 (46) 302 (45)	Diuretic (HCTZ or furosemide), then doxazosin, prazosin, clonidine, methyl dopa or $\beta$ -blocker, then minoxidil, or CCB	BP 120/80 mmHg	3.1	14
CAMELOT <sup>33</sup>	Multi-country	Age 30-79 years, coronary artery stenosis >20% by angiography and DBP <100 mmHg	Left middle coronary artery obstruction >50%, LVEF <40%, heart failure	Apr 1999 to Apr 2002	All (excluding placebo) CCB (Amlodipine) ACEI (Enalapril)	1336 (26) 663 (24) 673 (28)	Allowed to continue $\beta$ -blocker, $\alpha$ -blocker, diuretic	None specified	1.6	7
CAPPP <sup>61 62</sup>	Sweden and Finland	Age 25-66 years, DBP $\geq$ 100 mmHg on two occasions	Secondary hypertension, serum creatinine >150 $\mu$ mol/l, condition requiring $\beta$ -blocker treatment	Dec 1989 to Apr 1995	All ACEI (Captopril) Conventional: $\beta$ -blocker (Atenolol or metoprolol) and/or diuretic (HCTZ, bendofluazide)	10,985 (47) 5492 (45) 5493 (48)	Diuretic and CCB if necessary	Supine DBP <90 mmHg	5.8	6
CASE-J <sup>63 64</sup>	Japan	Age 20-85 years, $\geq$ 1 high-risk factor: SBP $\geq$ 180 or DBP $\geq$ 110 mmHg, T2D, history of angina pectoris, MI, stroke, TIA >6 months	BP $\geq$ 200/120 mmHg, T1D, heart failure, ejection fraction <40%, atrial fibrillation, cancer	Sep 2001 to Jan 2003	All ARB (Candesartan) CCB (Amlodipine)	4703 (45) 2354 (46) 2349 (43)	Allowed to continue background treatment (diuretic, $\alpha$ -blocker, $\beta$ -	BP (mmHg) by age (years): <60: <130/85; 60-69: <140/90; 70-	3.1	6

		prior to screening, LVH, proteinuria or serum creatinine ≥1.3 mg/100 ml, peripheral artery obstruction					blocker); Can add other treatment except ARB, CCB, ACEI	79: <150/90; ≥80: <160/90		
COLM <sup>65 66</sup>	Japan	Age 65-84 years, hypertension (treated: BP ≥140/90 mmHg; untreated: BP ≥160/100 mmHg), CVD history or CVD risk factors (diabetes, dyslipidaemia)	Secondary/malignant hypertension, recent major CVD, revascularisation, angina pectoris hospitalisation or severe heart failure, atrial fibrillation, hepatic or renal dysfunction	Apr 2007 to Sep 2008	All ARB (Olmesartan) and CCB (Amlodipine or azelnidipine) ARB (Olmesartan) and diuretic (HCTZ, Trichlormethiazide, or indapamide)	5141 (48) 2568 (48) 2573 (48)	β-blocker, α-blocker, ACEI	BP <140/90 mmHg	3.0	8
CONVINCE <sup>67 68</sup>	Multi-country	Age ≥55 years, hypertension, ≥1 CVD risk factor (e.g., diabetes, smoking)	Heart failure, dysrhythmia, secondary hypertension, recent MI or stroke, renal disease, other serious disease, BP ≥190/110 mmHg without treatment	Sep 1996 to Dec 1998	All CCB (Verapamil) β-blocker (Atenolol) or diuretic (HCTZ)	16,476 (55) 8179 (56) 8297 (56)	Additional treatment if necessary	BP <140/90 mmHg	2.8	4
COPE <sup>69</sup>	Japan	Age 40-85 years, BP ≥140/90 mmHg	SBP ≥200 or DBP ≥120 mmHg, secondary hypertension, diabetes, recent CVD or revascularisation, heart failure, atrial fibrillation/flutter, hepatic or renal dysfunction, congenital or rheumatic heart disease, cancer	Jun 2003 to Nov 2006	All CCB/ARB (Benidipine/ARB) CCB/β-blocker (Benidipine/β-blocker) CCB/Diuretic (Benidipine/Thiazide)	3293 (49) 1110 (49) 1089 (49) 1094 (49)	Additional treatment if necessary	BP <140/90 mmHg	3.6	5
E-COST <sup>70</sup>	Japan	Age 35-79 years, BP 140-180/90-110 mmHg	Diabetes, dysglycemia, secondary hypertension, recent MI or stroke, angina pectoris requiring β-blocker treatment, heart failure, left ventricular ejection fraction <40%	Sept to Dec 1999	All ARB (Candesartan) Conventional (mainly CCB and β/α-blocker)	2048 (52) 1053 (56) 995 (48)	Additional treatment but not ARB or ACEI	BP <140/90 mmHg	3.1	2
ELSA <sup>71 72</sup>	Multi-country	Age 45-79 years, BP 150-210/95-115 mmHg	Recent MI or stroke, and T2D	Possibly between 1994 to 1998	All CCB (Lacidipine) β-blocker (Atenolol)	2334 (45) 1177 (46) 1157 (45)	Diuretic (HCTZ)	DBP <95 mmHg	3.4	10
HIJ-CREATE <sup>73</sup>	Japan	Age 20-80 years, CAD hospitalisation and hypertension (BP ≥140/90 mmHg or antihypertensive treatment use)	Secondary hypertension, recent AMI or CeVD, severe aortic valve stenosis, cardiomyopathy, serum creatinine >2 mg/dl, serum potassium >5 mmol/l, hepatic dysfunction, malignancy	Jun 2001 to Apr 2004	All ARB (Candesartan) Non-ARB (including ACEI)	2049 (20) 1024 (18) 1025 (21)		BP <130/85 mmHg	4.0	5
HOMED-BP <sup>20</sup>	Japan	Self-measured SBP 135-179 mmHg or DBP 85-119 mmHg, but not if DBP <65 mmHg or SBP <110 mmHg (clinic SBP <220 mmHg and DBP <125 mmHg)	None specified	May 2001 to Oct 2009	All ACEI ARB CCB	3518 (50) 1172 (50) 1175 (50) 1171 (50)	Diuretic; β-blocker; then other drugs (avoid reaching BP <110/65 mmHg)	Either BP <120/80 mmHg or BP 125-134/80-84 mmHg	4.9	8
IDNT <sup>1</sup>	USA	Age 30-70 years, T2D, hypertension (BP ≥135/85 mmHg or taking antihypertensive drug), proteinuria, serum creatinine of 88 to 265 μmol/l (women) or 106 to 265 μmol/l (men)	None specified	Mar 1996 to Feb 1999	All (except placebo) ARB (Irbesartan) CCB (Amlodipine)	1146 (36) 579 (35) 567 (37)	Others except ACEI, ARB and CCB	SBP <135 mmHg (10 mmHg lower if baseline value >145 mmHg); and DBP <85 mmHg	2.6	No data
INSIGHT <sup>74</sup>	Multi-country	Age 55-80 years, hypertensive (SBP ≥150 or DBP ≥95 mmHg, or SBP ≥160 mmHg), ≥1 other risk factor (TC ≥6.43 mmol/l, smoking, family history of premature MI, CAD, other CVD)	None specified	Sep 1994 to Jun 1996	All CCB (Nifedipine) Diuretic (Co-amilofide [HCTZ + amiloride])	6321 (54) 3157 (54) 3164 (53)	β-blocker or ACEI, then others except CCB or diuretic	SBP/DBP reduction by 20/10 mmHg or SBP/DBP <140/90 mmHg	2.8	15
INVEST <sup>75</sup>	Multi-country	Age ≥50 years, documented CAD, essential hypertension requiring drug therapy, heart failure Class I-III <sup>b</sup>	Patients taking β-blocker within two weeks of randomisation or for recent MI	From Jan 1998	All CCB (Verapamil) Non-CCB (Atenolol)	21,230 (52) 10,648 (52) 10,672 (52)	ACEI (Trandolapril) and/or diuretic (HCTZ)	SBP/DBP <140/90 mmHg; <130/85 mmHg with diabetes or renal impairment	2.8	5
JMIC-B <sup>76</sup>	Japan				All	1650 (31)		BP <150/90 mmHg	2.3	5

		Age <75 years, hypertension (BP ≥160/≥95 mmHg or both SBP ≥150 and DBP ≥90 mmHg, or antihypertensive treatment), CAD or meeting both criteria: history of >2 anginal attacks per week with stable frequency and ST-segment depression of ≥1 mm on stress test (or detection of MI with myocardial scintigraphy)	MI, unstable angina, DBP ≥120 mmHg, secondary hypertension, symptomatic CeVD, heart failure, atrial fibrillation/arrhythmias, renal or hepatic dysfunction, uncontrollable diabetes and familial hypercholesterolaemia	Jan 1994 to Jul 1997	CCB (Nifedipine) ACEI (Enalapril, imidapril or lisinopril)	828 (32) 822 (30)	α-blocker (doxazosin, bunazosin or prazosin); nitrates or β-blocker for angina if needed			
LIFE <sup>77 78</sup>	Multi-country	Age 55-80 years, hypertension (SBP 160-200 mmHg; DBP 95-115 mmHg), electrocardiogram signs of LVH	Secondary hypertension, recent MI or stroke, angina pectoris requiring treatment, heart failure or left ejection fraction ≤40%	June 1995 to May 1997	All ARB (Losartan) β-blocker (Atenolol)	9193 (54) 4605 (54) 4588 (54)	Diuretic (HCTZ) and other antihypertensive treatment except ACEI, ARB and β-blocker	BP 140/90 mmHg	4.9	15
MOSES <sup>79</sup>	Germany and Austria	Hypertension requiring treatment, documented TIA, ischaemic stroke or cerebral haemorrhage	Internal carotid artery occlusion or stenosis >70%, heart failure, age >85 years, on anticoagulant for cardiac arrhythmia, high-grade aortic or mitral valve stenosis, unstable angina	Oct 1998 to Feb 2002	All ARB (Eprosartan) CCB (Nitrendipine)	1352 (46) 681 (46) 671 (45)	Diuretic, β-blocker, α-blocker or centrally-acting drugs; ACEI, ARB or CCB only if clinically necessary	BP <140/90 mmHg	3.3	7
NICS-EH <sup>80</sup>	Japan	Age ≥60 years, SBP 160-220 mmHg and DBP <115 mmHg and no cardiovascular complications	None specified	Oct 1989 to Apr 1992	All CCB (Nidardipine) Diuretic (Trichlormethiazide)	414 (67) 204 (60) 210 (74)	Titration but no additional treatment	BP response sufficient as determined by the investigator	3.2	3
NORDIL <sup>81</sup>	Norway and Sweden	Age 50-74 years, untreated hypertension (DBP ≥100 mmHg on two occasions); if previously treated, DBP ≥100 mmHg on two consecutive visits at one week apart during run-in period and no treatment was given	Age <50 or ≥70y, bradycardia, secondary hypertension, atrial fibrillation, recent CeVD or MI, heart failure	Oct 1992 to Oct 1999	All CCB (Diltiazem) β-blocker and/or diuretic (Thiazide)	10,881 (51) 5410 (51) 5471 (51)	CCB group: plus ACEI, diuretic, α-blocker or any other if necessary; β-blocker group: ACEI or α-blocker or any other drug except CCB if necessary		4.2	8
ONTARGET <sup>54 82</sup>	Multi-country	CAD, PAD, CeVD or diabetes with end-organ damage	Heart failure, pericarditis, congenital heart disease, unexplained syncope, planned revascularisation <3 months of consent, uncontrolled hypertension, heart transplant, subarachnoid haemorrhage, renal artery disease, proteinuria, hepatic dysfunction, volume or sodium depletion, primary hyperaldosteronism, hereditary fructose intolerance, other serious conditions	Jan 2002 to Aug 2003	All ACEI (Ramipril) ARB (Telmisartan) ACEI (Ramipril) and ARB (Telmisartan)	25,620 (27) 8576 (27) 8542 (26) 8502 (26)	None	None specified	4.8	9
STOP Hyper-tension-2 <sup>83</sup>	Sweden	Aged 70-84 years, SBP ≥180 mmHg and/or DBP ≥105 mmHg	Not specified	Sep 1992 to Dec 1994 1987 to 1991	All Conventional: β-blocker (Atenolol or metoprolol), diuretic (HCTZ) or both ACEI (Enalapril or lisinopril) CCB (Felodipine or isradipine)	6614 (67) 2213 (68) 2205 (66) 2196 (66)		BP <160/95 mmHg	4.5	10
UKPDS <sup>22-24</sup>	UK	Age 25-65 years, newly-diagnosed diabetes, and hypertension (untreated: SBP ≥160 mmHg and/or DBP ≥90 mmHg; treated: SBP ≥150 mmHg and/or DBP ≥85 mmHg)	Ketonuria, recent MI, angina, heart failure, >1 major vascular episode, serum creatinine >175 μmol/L, retinopathy, malignant hypertension, uncorrected endocrine abnormality, severe concurrent illness		All ACEI (Captopril) β-blocker (Atenolol)	758 (46) 400 (49) 358 (43)	Sequentially: Diuretic (furosemide), CCB (nifedipine), methylodopa, ARB (prazosin)	BP <150/85 mmHg	7.9	5
VALUE <sup>84 85</sup>	Multi-country	Age ≥50 years, hypertension, CVD, CVD risk factors (male sex, age >50 years, diabetes, current smoking, high	Renal artery stenosis, recent CAD or CeVD, severe hepatic disease or chronic renal failure, heart failure, on	Sept 1997 to Dec 1999	All ARB (Valsartan-based) CCB (Amlodipine-based)	15,245 (42) 7649 (42) 7596 (42)	Diuretic (HCTZ), then other antihypertensive drugs except ARB (ACEI)	BP <140/90 mmHg	4.2	12

		cholesterol, LVH, proteinuria, serum creatinine 150 to 265 µmol/l)	monotherapy with β-blocker for CAD and hypertension				or CCB if clinically indicated other than for hypertension)			
VHAS <sup>86</sup>	Italy	Age 40-65 years, BP ≥160/95 mmHg	Secondary hypertension, recent stroke or TIA, CAD, PAD, bradycardia, arrhythmias, heart failure, renal or hepatic dysfunction, hyperuricaemia, hypokalemia, T1D, familial dyslipidemia, serious concomitant disease	Probably early 1990s (publication in 1997)	All CCB (Verapamil) Diuretic (Chlorthalidone)	1414 (51) 707 (50) 707 (52)	ACEI (Captopril )	Sitting DBP ≤90 mmHg; ≤95 mmHg if lowered by ≥10% from baseline values	1.7	2

Trial name acronyms are described in full in the Trial acronym legend in the Supplement; Data on participant numbers and proportions, mean duration of follow-up and mean number of follow-up blood pressure measurements are from the datasets provided to the collaboration; BP – blood pressure; GFR – glomerular filtration rate; DBP – diastolic blood pressure; CKD – chronic kidney disease; T2D – type 2 diabetes; CAD – coronary artery disease; CeVD – cerebrovascular disease; CVD – cardiovascular disease; HbA1c - glycated haemoglobin; SBP – systolic blood pressure; TIA – transient ischaemic attack; PAD – peripheral artery disease; MI – myocardial infarction; CNS – central nervous system; LVEF – low ventricular ejection fraction; HDL – high-density lipoprotein; ECG – electrocardiogram; TC – total cholesterol; LVH – left ventricular hypertrophy; T1D – type 1 diabetes; CCB – calcium channel-blocker; ACEI – angiotensin-converting enzyme inhibitor; ARB – angiotensin II receptor blocker; HCTZ – hydrochlorothiazide; <sup>a</sup>Excludes 534 participants with heart failure at baseline; <sup>b</sup>Excludes 1346 participants with heart failure at baseline.



Table S4. Risk of bias assessment of each trial.

Trial	Risk of bias arising from randomisation	Risk of bias due to effect of assignment to intervention	Risk of bias due to missing outcome data	Risk of bias due to measurement of outcome	Risk of bias due to reporting of result	Overall risk of bias
AASK	Low	Low	Low	Low	Low	Low
ABCD	Low	Low	Low	Low	Low	Low
ACCORD	Low	Some	Low	Low	Low	Low
ACTIVE I	Low	Low	Low	Low	Low	Low
ADVANCE	Low	Low	Low	Low	Low	Low
ALLHAT	Low	Low	Low	Low	Low	Low
ANBP	Low	Low	Low	Low	Low	Low
ANBP2	Low	Some	Low	Low	Low	Low
ASCOT-BPLA	Low	Some	Low	Low	Low	Low
BENEDICT	Low	Low	Low	Low	Low	Low
CAMELOT	Low	Low	Low	Low	Low	Low
CAPPP	Low	Some	Low	Low	Low	Low
Cardio-Sis	Low	Some	Some	Low	Low	Some
CASE-J	Low	Some	Low	Low	Low	Low
COLM	Low	Some	Low	Low	Low	Low
CONVINCE	Low	Low	Low	Low	Low	Low
COPE	Low	Some	Low	Low	Low	Low
DIABHYCAR	Low	Low	Low	Low	Low	Low
Dutch TIA Trial	Low	Low	Low	Low	Low	Low
E-COST	High	Some	Low	Low	Low	High
ELSA	Low	Low	Low	Low	Low	Low
EUROPA	Low	Low	Low	Low	Low	Low
EWPHE	Low	Low	Low	Low	Low	Low
HDFP	Some	Some	Low	Low	Low	Low
HIJ-CREATE	Low	Some	Low	Low	Low	Low
HOMED-BP	Low	Some	Low	Low	Low	Low
HOPE	Low	Some	Low	Low	Low	Low
HYVET	Low	Low	Low	Low	Low	Low
IDNT	Low	Low	Some	Low	Low	Some
INSIGHT	Low	Low	Low	Low	Low	Low
INVEST	Low	Some	Low	Low	Low	Low
JMIC-B	Low	Some	Low	Low	Low	Low
LIFE	Low	Low	Low	Low	Low	Low
MOSES	Low	Some	Low	Low	Low	Low
NICS-EH	Low	Some	Low	Low	Low	Some
NORDIL	Low	Some	Low	Low	Low	Low
ONTARGET	Low	Some	Low	Low	Low	Low
PART 2	Low	Low	Low	Low	Low	Low
PEACE	Low	Low	Low	Low	Low	Low
PREVEND IT	Low	Low	Low	Low	Low	Low
PREVENT	Low	Low	Low	Low	Low	Low
PRoFESS	Low	Low	Low	Low	Low	Low
PROGRESS	Low	Low	Low	Low	Low	Low
SHEP	Low	Low	Low	Low	Low	Low
SPRINT	Low	Some	Low	Low	Low	Low
STOP Hypertension-2	Low	Some	Low	Low	Low	Low
SYST-EUR	Low	Some	Low	Low	Low	Low
TRANSCEND	Low	Low	Low	Low	Low	Low
UKPDS	Low	Some	Low	Low	Low	Low
VALISH	Low	Low	Low	Low	Low	Low
VALUE	Low	Low	Low	Low	Low	Low
VHAS	Low	Low	Low	Low	Low	Low

Trial name acronyms are described in full in the Trial acronym legend in the Supplement.

**Table S5. Indicators of numbers of blood pressure-lowering drug classes given and adherence to assigned treatment, separately by trial design.****A. Blood pressure-lowering intensity trials**

Trial	Comparison groups	Number of drugs given		Adherence to randomised treatment assignment during follow-up	
		No.	Description	%	Description
<b>AASK</b>	Less intense	3	Mean number of drugs given	81.7	On randomised treatment
	More intense	2.4	Mean number of drugs given	80.1	On randomised treatment
<b>ABCD<sup>†</sup></b>	Less intense	-	Not reported	-	Mean achieved SBP during last 4 years of follow-up: 137 mmHg
	More intense	-	Not reported	-	Mean achieved SBP during last 4 years of follow-up: 128 mmHg
<b>ACCORD</b>	Less intense	2.1	Mean number of drugs given after year 1 follow-up	-	Mean achieved SBP after year 1 follow-up: 134 mmHg
	More intense	3.4	Mean number of drugs given after year 1 follow-up	-	Mean achieved SBP after year 1 follow-up: 119 mmHg
<b>Cardio-Sis</b>	Less intense	2.9	Mean number of drugs given at year 2 follow-up	-	Mean achieved SBP at end of study: 136 mmHg
	More intense	2.9	Mean number of drugs given at year 2 follow-up	-	Mean achieved SBP at end of study: 132 mmHg
<b>HDFP</b>	Less intense	58%	Taking antihypertensive drugs at year 5 follow-up	43.5	Achieved at or below DBP goal
	More intense	78%	Taking antihypertensive drugs at year 5 follow-up	64.9	Achieved at or below DBP goal
<b>HOMED-BP</b>	Less intense	1.74	Mean defined daily dose at last follow-up	68.3	Meeting target SBP (125 to 134 mmHg) at end of study
	More intense	1.82	Mean defined daily dose at last follow-up	42.6	Meeting target SBP (<125 mmHg) at end of study
<b>SPRINT</b>	Less intense	1.8	Mean number of drugs given	-	Mean achieved SBP at end of study: 135 mmHg
	More intense	2.7	Mean number of drugs given	-	Mean achieved SBP at end of study: 122 mmHg
<b>UKPDS</b>	Less intense	11%	Taking $\geq 3$ drug classes at year 9 follow-up	43.0	% of total person-years not receiving treatment
	More intense	29%	Taking $\geq 3$ drug classes at year 9 follow-up	77.0	% of total person-years on assigned treatment
<b>VALISH</b>	Less intense	1.6	Mean number of drugs given at end of follow-up	-	Mean achieved SBP at end of study: 142 mmHg
	More intense	1.6	Mean number of drugs given at end of follow-up	-	Mean achieved SBP at end of study: 137 mmHg

Table S5. Indicators of numbers of blood pressure-lowering drug classes given and adherence to assigned treatment, separately by trial design (cont'd).

B. Placebo-controlled trials					
Trial	Comparison groups	Number of drugs given		Adherence to randomised treatment assignment during follow-up	
		No.	Description	%	Description
ACTIVE I	Placebo	2.15	Mean number of non-study drugs at year 2	69.7	Did not discontinue assigned treatment
	ARB	2	Mean number of non-study drugs at year 2	69.7	Did not discontinue assigned treatment
ADVANCE	Placebo	1.57	Mean number of non-study drugs by end of follow-up	74.0	On randomised treatment by end of follow-up
	ACEI and diuretic	1.28	Mean number of non-study drugs by end of follow-up	73.0	On randomised treatment by end of follow-up
ANBP	Placebo	1.52	Mean number of drugs given (calculated from numbers taking 1, 2 or ≥2 corresponding placebo)	63.3	On randomised treatment by end of study
	Diuretic	1.82	Mean number of drugs given (calculated from numbers taking 1, 2 or ≥2 drugs)	66.1	On randomised treatment by end of study
BENEDICT	Placebo	2.18	Mean number of drugs given	-	Not reported
	ACEI	1.99	Mean number of drugs given	-	Not reported
	CCB	2.03	Mean number of drugs given	-	Not reported
	ACEI and CCB	1.87	Mean number of drugs given	-	Not reported
CAMELOT	Placebo	-	NA	68.9	Did not discontinue assigned treatment
	CCB	8.6	Mean dose received (g)	70.7	Did not discontinue assigned treatment
	ACEI	17.4	Mean dose received (g)	64.9	Did not discontinue assigned drug
DIABHYCAR	Placebo	0.22	Mean number of non-study drugs given	59.0	On randomised treatment by end of study
	ACEI	0.2	Mean number of non-study drugs given	59.3	On randomised treatment by end of study
Dutch-TIA	Placebo	-	Not reported	67.7	On randomised treatment at year 3 follow-up
	β-blocker	-	Not reported	64.2	On randomised treatment at year 3 follow-up
EUROPA	Placebo	-	NA	84.0	On randomised treatment at year 3 follow-up
	ACEI	7.05	Maximum mean daily dose (mg)	81.0	On randomised treatment at year 3 follow-up
EWPHE	Placebo	0.63	Mean number of non-study drugs given	63.0	Did not discontinue assigned treatment
	Diuretic	0.35	Mean number of non-study drugs given	64.2	Did not discontinue assigned treatment
HOPE	Placebo	0.18	Mean number of non-study drugs given	87.7	On randomised treatment at final visit (12.3 % received intervention drug)
	ACEI	0.14	Mean number of non-study drugs given	78.8	On randomised treatment at final visit
HYVET	Placebo	-	NA	-	Not reported
	Diuretic	0.73	Mean number of non-study drug given at year 2	-	Not reported
IDNT	Placebo	3.3	Mean number of non-study drugs given	-	Not reported
	ARB and CCB	3	Mean number of non-study drugs given	-	Not reported

<b>PART 2</b>	Placebo	7	% given non-study drug at year 4 follow-up	75.0	On randomised treatment at year 4 follow-up
	ACEI	2.9	% given non-study drug at year 4 follow-up	72.0	On randomised treatment at year 4 follow-up
<b>PEACE</b>	Placebo	8.3	% taking non-study drug at year 3	77.7	On randomised treatment at year 3 follow-up
	ACEI	74.5	% taking study and non-study drug (same class) at year 3	68.6	On randomised treatment at year 3 follow-up
<b>PREVEND IT</b>	Placebo	-	Not reported	63.3	Compliance above 75% at year 4 follow-up
	ACEI	-	Not reported	70.7	Compliance above 75% at year 4 follow-up
<b>PREVENT</b>	Placebo	0.67	Mean number of non-study drugs given	83.0	Pill count compliance
	CCB	0.56	Mean number of non-study drugs given	79.0	Pill count compliance
<b>PRoFESS</b>	Placebo	2.5	% on non-study ARB at penultimate visit ( $\geq 30\%$ on non-study BP-lowering drugs by end of study)	70.8	% on randomised treatment at year 3 follow-up
	Telmisartan	2.3	% on non-study ARB at final visit ( $\geq 25\%$ on non-study BP-lowering drugs by end of study)	68.3	% on randomised treatment at year 3 follow-up
<b>PROGRESS</b>	Placebo	-	Not reported	87.0	On randomised treatment by end of follow-up
	ACEI and/or diuretic	-	Not reported	86.0	On randomised treatment by end of follow-up
<b>SHEP</b>	Placebo	44.4	% given study drug at year 5 follow-up	55.6	On randomised treatment at year 5 follow-up
	$\beta$ -blocker and diuretic	-	Over two-thirds given step 1 and/or step 2 drug at year 5 follow-up	89.7	On randomised treatment at year 3 follow-up
<b>SYST-EUR</b>	Placebo	-	Some given treatment but could not be estimated	47.7	On randomised treatment at year 4 follow-up
	CCB	1.35	Mean number of drugs given	60.4	On randomised treatment at year 4 follow-up
<b>TRANSCEND</b>	Placebo	1.6	Mean number of non-study drugs given by end of study	40.7	On randomised treatment by end of study (more may have received non-study drugs)
	ARB	1.4	Mean number of non-study drugs given by end of study	80.8	On randomised treatment by end of study

Table S5. Indicators of numbers of blood pressure-lowering drug classes given and adherence to assigned treatment, separately by trial design (cont'd).

C. Drug class comparison trials					
Trial	Comparison groups	Number of drugs given		Adherence to randomised treatment assignment during follow-up	
		No.	Description	%	Description
AASK	ACEI	2.7	Mean number of drugs given	76.8	On randomised treatment during follow-up
	CCB	2.7	Mean number of drugs given	83.4	On randomised treatment during follow-up
	$\beta$ -blocker	2.8	Mean number of drugs given	83.6	On randomised treatment during follow-up
ABCD <sup>‡</sup>	CCB	2.8	Mean number of drugs given	45.1	Did not discontinue assigned treatment
	ACEI	2.9	Mean number of drugs given	39.6	Did not discontinue assigned treatment
ALLHAT	Diuretic	1.8	Mean number of drugs given	71.2	On randomised treatment at year 5 follow-up
	CCB	1.9	Mean number of drugs given	72.1	On randomised treatment at year 5 follow-up
	ACEI	2	Mean number of drugs given	61.2	On randomised treatment at year 5 follow-up
	$\alpha$ -blocker <sup>87</sup>	1.2	Mean number of drugs given at year 4 follow-up	75.0	On randomised treatment at year 4 follow-up
ANBP2	ACEI	6.0%	Given $\geq 3$ drugs	58.0	On randomised treatment by end of study
	Diuretic	5.0%	Given $\geq 3$ drugs	62.0	On randomised treatment by end of study
ASCOT-BPLA	CCB-based	2.2	Mean number of drugs given	50.0	On randomised treatment (with and without other antihypertensive drugs)
	$\beta$ -blocker-based	2.3	Mean number of drugs given	55.0	On randomised treatment (with and without other antihypertensive drugs)
BENEDICT	Placebo	2.18	Mean number of drugs given	-	Not reported
	ACEI	1.99	Mean number of drugs given	-	Not reported
	CCB	2.03	Mean number of drugs given	-	Not reported
	ACEI and CCB	1.87	Mean number of drugs given	-	Not reported
CAMELOT	Placebo	-	NA	69.3	Did not discontinue assigned drug
	CCB	8.6	Mean dose received (g)	70.7	Did not discontinue assigned drug
	ACEI	17.4	Mean dose received (g)	64.9	Did not discontinue assigned drug
CAPPP	$\beta$ -blocker and/or diuretic	-	Not reported	-	Not reported
	ACEI	-	No reported	-	Not reported
CASE-J	ARB	1.5	Mean number of drugs given	96.5	Receiving >80% of assigned drug during follow-up
	CCB	1.4	Mean number of drugs given	96.0	Receiving >80% of assigned drug during follow-up
COLM	ARB and CCB	2.1	Mean number of drugs given	-	Not reported
	ARB and diuretic	2.1	Mean number of drugs given	-	Not reported
CONVINCE	CCB	-	Proportion given >1 drug increased over time	60.6	Did not discontinue assigned drug

	$\beta$ -blocker or diuretic	-	Proportion given >1 drug increased over time	60.3	Did not discontinue assigned drug
COPE	CCB and ARB	1.22	Mean number of drugs given	78.6	Did not discontinue assigned drug
	CCB and $\beta$ -blocker	1.26	Mean number of drugs given	74.1	Did not discontinue assigned drug
	CCB and diuretic	1.30	Mean number of drugs given	76.2	Did not discontinue assigned drug
E-COST	Conventional	71.5%	Taking $\geq 3$ drugs	81.9	On randomised treatment by end of study
	ARB	21.5%	Taking $\geq 3$ drugs	77.3	On randomised treatment by end of study
ELSA	CCB	31.8%	Taking additional drug (diuretic)	-	Not reported
	$\beta$ -blocker	35.9%	Taking additional drug (diuretic)	-	Not reported
HIJ-CREATE	non-ARB	2.8	Mean number of drugs given	77.0	On randomised treatment (prescribed ARB at the end of study)
	ARB	2	Mean number of drugs given	97.5	On randomised treatment (prescribed ACEI at end of study)
HOMED-BP	ACEI	-	Not reported	-	Not reported
	ARB	-	Not reported	-	Not reported
	CCB	-	Not reported	-	Not reported
IDNT	ARB	4	Mean number of drugs given	-	Not reported
	CCB	4	Mean number of drugs given	-	Not reported
INSIGHT	Diuretic	1.72	Minimum mean number of drugs given at year 3	78.1	On randomised treatment at year 3 follow-up
	CCB	1.65	Minimum mean number of drugs given at year 3	70.7	On randomised treatment at year 3 follow-up
INVEST	CCB	1.4	Mean number of drugs given at year 2 follow-up	81.5	On randomised treatment at year 2 follow-up (Step 1 drug only)
	non-CCB	1.4	Mean number of drugs given at year 2 follow-up	77.5	On randomised treatment at year 2 follow-up (Step 1 drug only)
JMIC-B	CCB	2.02	Mean number of drugs given	-	Not reported
	ACEI	1.03	Mean number of drugs given	-	Not reported
LIFE	ARB	2.15	Minimum mean number of drugs	84.0	On randomised treatment
	$\beta$ -blocker	2.11	Minimum mean number of drugs	80.0	On randomised treatment
MOSES	CCB	1.34	Minimum mean number of drugs	-	Not reported
	ARB	1.44	Minimum mean number of drugs	-	Not reported
NICS-EH	Diuretic	1.1	Mean number of drugs given	-	Not reported
	CCB	1.1	Mean number of drugs given	-	Not reported
NORDIL	CCB	1.4	Mean number of drugs given	77.0	On randomised treatment
	$\beta$ -blocker and/or diuretic	1.5	Mean number of drugs given	93.0	On randomised treatment
ONTARGET	ARB	1.1	Mean number of drugs given	85.6	On randomised treatment at year 4 follow-up
	ACEI	1	Mean number of drugs given	84.7	On randomised treatment at year 4 follow-up
	ARB and ACEI	1.1	Mean number of drugs given	73.6	On randomised treatment at year 4 follow-up



<b>STOP</b>	$\beta$ -blocker and/or	1.6	Mean number of drugs given	62.3	On randomised treatment at final visit
<b>Hypertension-2</b>	diuretic				
	ACEI	1.6	Mean number of drugs given	61.3	On randomised treatment at final visit
	CCB	1.6	Mean number of drugs given	66.2	On randomised treatment at final visit
<b>UKPDS</b>	ACEI	27%	$\geq 3$ agents in tight control	78.0	On randomised treatment at final visit
	$\beta$ -blocker	31%	$\geq 3$ agents in tight control	65.1	On randomised treatment at final visit
<b>VALUE</b>	ARB-based	2.1	Mean number of drugs given	73.7	On randomised treatment during follow-up
	CCB-based	2	Mean number of drugs given	74.9	On randomised treatment during follow-up
<b>VHAS</b>	CCB	1.2	Mean number of drugs given	44.1	On randomised treatment (staying on monotherapy) at year 2 follow-up
	Diuretic	1.3	Mean number of drugs given	38.8	On randomised treatment (staying on monotherapy) at year 2 follow-up

Trial name acronyms are described in full in the Trial acronym legend in the Supplement; SBP – systolic blood pressure; CCB – calcium channel-blocker; ACEI – angiotensin-converting enzyme inhibitor; ARB – angiotensin II receptor blocker; \*Normotensive patient cohort only; †Hypertensive patient cohort only.

Table S6. Characteristics of participants at baseline for each trial.

Trial	Participants, N (% women)	Age (years), mean (SD)	SBP (mmHg), mean (SD)	DBP (mmHg), mean (SD)	Body mass index (kg/m <sup>2</sup> ), mean (SD)	% Current smokers (N)	% Caucasian / European (N)	% Prevalent disease (N)				
								Cardiovascular disease	Coronary heart disease	Cerebrovascular disease/stroke	Chronic kidney disease	Diabetes
AASK	1094 (39)	54 (11)	150 (24)	95 (10)	30.6 (6.6)	29 (321)	0 (0)	52 (564)	52 (564)	-	100 (1094)	0 (0)
ABCD	950 (39)	58 (8)	155 (17)	98 (10)	31.7 (5.7)	14 (65)	66 (310)	9 (89)	9 (41)	2 (11)	19 (90)	100 (470)
ACCORD	4733 (48)	63 (7)	139 (15)	76 (10)	32.1 (5.5)	13 (626)	59 (2781)	34 (1593)	14 (650)	6 (307)	0 (0)	100 (4733)
ACTIVE	9016 (39)	70 (10)	138 (17)	82 (10)	29.1 (5.8)	8 (698)	75 (6769)	35 (3177)	2294 (25.4%)	14 (1230)	0 (0)	20 (1785)
ADVANCE	11,140 (43)	66 (6)	145 (22)	81 (10)	28.3 (5.2)	14 (1550)	60 (6687)	31 (3461)	2380 (21.4%)	13 (1438)	-	100 (11,140)
ALLHAT	42,418 (47)	67 (8)	146 (16)	84 (10)	29.6 (5.9)	22 (9269)	51 (21561)	46 (19,389)	-	-	-	36 (15,283)
ANBP	3427 (37)	50 (9)	157 (15)	100 (10)	26.7 (3.9)	26 (891)	-	0 (16)	0 (16)	0 (0)	7 (240)	0 (0)
ANBP2	6083 (51)	73 (5)	168 (13)	91 (10)	27.1 (4.2)	7 (431)	98 (5984)	8 (474)	4 (229)	5 (276)	0 (6)	7 (441)
ASCOT-BPLA	19,257 (23)	63 (9)	164 (18)	95 (10)	28.7 (4.6)	33 (6277)	95 (18357)	36 (7008)	27 (5284)	11 (2121)	62 (12,017)	27 (5145)
BENEDICT	1204 (47)	62 (8)	151 (14)	88 (10)	29.1 (4.7)	12 (146)	100 (1204)	-	-	-	0 (0)	100 (1209)
CAMELOT	1991 (26)	58 (10)	129 (16)	78 (10)	29.8 (5.3)	26 (528)	89 (1783)	93 (1858)	93 (1857)	4 (81)	-	18 (364)
CAPP	10,985 (47)	52 (8)	161 (20)	99 (10)	27.8 (4.4)	22 (2431)	-	3 (351)	2 (201)	1 (160)	0 (28)	5 (572)
Cardio-Sis	1111 (59)	67 (7)	158 (9)	87 (10)	27.8 (4.2)	20 (226)	-	18 (202)	11 (128)	8 (91)	0 (0)	0 (0)
CASE-J	4703 (45)	64 (11)	163 (14)	92 (10)	24.5 (3.7)	22 (1025)	0 (0)	22 (1028)	13 (596)	10 (473)	58 (2720)	43 (2018)
COLM	5141 (48)	74 (5)	158 (13)	87 (10)	24.3 (3.4)	11 (551)	0 (0)	24 (1225)	11 (563)	15 (751)	2 (108)	26 (1362)
CONVINCE	16,476 (56)	66 (7)	150 (16)	87 (10)	-	23 (3795)	84 (13845)	27 (4458)	23 (3820)	6 (1019)	0 (0)	20 (3239)
COPE	3293 (49)	64 (11)	154 (12)	89 (10)	24.5 (3.4)	21 (700)	0 (0)	7 (219)	3 (109)	4 (126)	46 (1530)	0 (0)
DIABHYCAR	4912 (30)	65 (8)	145 (15)	82 (10)	29.2 (4.6)	15 (756)	-	15 (739)	15 (739)	-	-	100 (4912)
Dutch TIA Trial	1473 (36)	64 (10)	157 (25)	91 (10)	-	47 (693)	-	100 (1473)	9 (138)	100 (1473)	100 (1711)	5 (79)
E-COST	2048 (53)	64 (11)	164 (18)	94 (10)	-	-	0 (0)	10 (213)	-	10 (213)	11 (228)	0 (0)
ELSA	2334 (46)	57 (7)	160 (15)	98 (10)	27.2 (3.8)	20 (478)	98 (2294)	13 (305)	13 (305)	-	7 (163)	4 (98)
EUROPA	12,218 (15)	61 (9)	137 (16)	82 (10)	27.4 (3.5)	15 (1862)	99 (12,064)	100 (12,218)	100 (12,218)	2 (222)	0 (0)	-
EWPHE	840 (70)	71 (8)	183 (17)	101 (10)	26.4 (4.5)	17 (143)	-	15 (124)	9 (73)	8 (63)	0 (2)	72 (8.6%)
HDFP	10,940 (45)	51 (10)	159 (23)	101 (9)	-	39 (4248)	55 (6021)	7 (780)	5 (561)	3 (274)	-	7 (772)
HU-CREATE	2049 (20)	65 (9)	135 (18)	76 (10)	24.6 (3)	25 (509)	-	100 (2049)	100 (2049)	10 (205)	0 (3)	38 (780)
HOMED-BP	3518 (50)	60 (10)	154 (18)	90 (10)	24.4 (3.5)	21 (743)	0 (0)	3 (106)	2 (61)	1 (46)	-	15 (538)
HOPE	9297 (27)	66 (7)	139 (20)	79 (10)	27.7 (4.4)	14 (1319)	90 (8343)	80 (7477)	80 (7477)	-	-	39 (3577)
HVET	3845 (60)	84 (3)	173 (9)	91 (10)	24.7 (3.7)	7 (253)	-	10 (374)	3 (121)	7 (261)	-	10 (388)
IDNT	1715 (34)	59 (8)	159 (20)	87 (11)	30.8 (5.8)	-	73 (1241)	-	-	-	100 (1715)	100 (1715)

INSIGHT	6321 (54)	65 (6)	173 (15)	99 (10)	28.2 (4.6)	28 (1793)	-	11 (671)	11 (671)	-	-	21 (1302)
INVEST	21,320 (51)	66 (10)	151 (20)	87 (10)	29.2 (7.1)	12 (2809)	48 (10,925)	100 (21,320)	100 (21,320)	7 (1629)	2 (424)	28 (6400)
JMIC-B	1650 (31)	65 (85)	146 (19)	82 (10)	24 (2.9)	34 (563)	0	100 (1650)	100 (1650)	-	-	23 (372)
LIFE	9193 (54)	67 (7)	174 (14)	98 (10)	28 (4.8)	16 (1499)	92 (8503)	19 (1771)	16 (1469)	4 (401)	-	13 (1195)
MOSES	1352 (46)	68 (10)	151 (18)	87 (10)	27.5 (4.3)	18 (247)	100 (1352)	100 (1352)	26 (355)	100 (1352)	5 (72)	37 (498)
NICS-EH	414 (67)	70 (7)	172 (12)	94 (10)	23.4 (3.1)	9 (38)	0	4 (16)	4 (0.9%)	3 (12)	-	4 (17)
NORDIL	10,881 (51)	60 (7)	173 (18)	106 (10)	27.8 (4.3)	22 (2442)	-	7 (740)	496 (4.6%)	2 (271)	0 (31)	7 (727)
ONTARGET	25,620 (27)	67 (7)	142 (17)	82 (10)	28.2 (4.8)	13 (3225)	73 (18,708)	87 (22,315)	75 (19,102)	70 (17,927)	-	38 (9612)
PART 2	617 (18)	60 (8)	133 (17)	79 (10)	26.8 (3.6)	16 (100)	100 (615)	74 (457)	68 (420)	10 (62)	-	8 (51)
PEACE	8290 (18)	64 (8)	133 (17)	77 (10)	-	14 (1177)	-	100 (8290)	100 (8290)	4 (357)	-	17 (1380)
PREVEND IT	864 (35)	51 (12)	130 (18)	76 (10)	26.4 (4.4)	40 (345)	96 (830)	3 (24)	2 (13)	2 (13)	100 (864)	3 (22)
PREVENT	825 (20)	57 (10)	129 (17)	79 (10)	28 (4.8)	25 (204)	89 (732)	100 (825)	100 (825)	7 (55)	1 (8)	12 (98)
PRoFESS	19,798 (36)	66 (8)	144 (17)	84 (11)	26.8 (5)	21 (4231)	57 (11,200)	100 (19,798)	15 (2933)	100 (19,798)	-	28 (5587)
PROGRESS	6105 (30)	64 (10)	147 (19)	86 (10)	25.7 (3.8)	21 (1279)	0 (9)	100 (6105)	16 (983)	100 (6105)	-	13 (761)
SHEP	4736 (57)	72 (7)	170 (9)	77 (10)	27.1 (4.8)	13 (597)	79 (3731)	6 (284)	5 (232)	0 (66)	0 (0)	10 (476)
SPRINT	9361 (36)	68 (9)	140 (15.6)	78 (10)	29.9 (5.8)	13 (1240)	58 (5399)	20 (1877)	20 (1877)	0 (0)	28 (2646)	0 (0)
STOP Hypertension 2	6614 (67)	76 (4)	194 (15)	98 (10)	26.7 (4)	9 (594)	-	16 (1072)	10 (647)	8 (502)	-	11 (719)
SYST-EUR	4695 (67)	70 (7)	174 (10)	86 (10)	27 (4.1)	7 (343)	-	6 (286)	3 (164)	3 (124)	0 (20)	10 (449)
TRANSCEND	5926 (43)	68 (7)	141 (17)	82 (10)	28.2 (4.8)	10 (582)	61 (3621)	88 (5222)	75 (4418)	71 (4207)	-	36 (2118)
UKPDS	1148 (45)	56 (8)	159 (17)	93 (10)	29.6 (5.5)	23 (256)	87 (1000)	3 (35)	1 (15)	2 (20)	-	100 (1148)
VALISH	3079 (62)	76 (4)	169 (9)	82 (10)	23.5 (3.4)	15 (450)	-	12 (371)	6 (194)	7 (202)	31 (944)	13 (399)
VALUE	15,245 (42)	67 (8)	154 (19)	87 (10)	28.6 (5)	24 (3664)	89 (13,617)	60 (9169)	46 (6981)	20 (3014)	-	32 (4823)
VHAS	1414 (51)	54 (7)	169 (10)	102 (10)	27.1 (4.1)	18 (256)	100 (1414)	12 (164)	-	-	3 (48)	8 (108)

Acronyms are described in full in the Trial acronym legend in the Supplement; SBP – systolic blood pressure; DBP – diastolic blood pressure.

**Table S7. Blood pressure measurement methods used in the trials included in the BPLTTC.**

Study	Specified method of blood pressure measurement
AASK	Mean of last two readings of three consecutive seated BP readings after five minutes rest. A Hawksley random zero sphygmomanometer was used.
ABCD	Determined at two separate visits.
ACCORD	Average of three measurements in the sitting position, using an automated device (Omron 907), after five minutes rest.
ACTIVE I	Measured in duplicated in five minute intervals.
ADVANCE	Mean of two measurements in the sitting position, taken using a standardized automated sphygmomanometer (Omron HEM-705CP, Tokyo, Japan), after the patient was rested for at least five minutes.
ALLHAT	Mean of four measurements, two taken at two separate visits.
ANBP	Mean of four measurements over two visits, taken using a random zero or London School of Hygiene sphygmomanometer in sitting position after 5 minutes of rest.
ANBP2	Mean of measurements at two visits, taken using a mercury sphygmomanometer in the sitting position.
ASCOT-BPLA	Measured three times using a semi-automated device in the sitting position, after five minutes of rest. Mean of last two readings used.
BENEDICT	Mean of three morning measurements.
CAMELOT	Measured using a manual cuff and stethoscope.
CAPP	Mean of two measurements taken in supine position using conventional mercury sphygmomanometer.
Cardio-Sis	Mean of three consecutive readings at every visit, taken using standard mercury sphygmomanometers after sitting for ten minutes.
CASE-J	Mean of two measurements, taken in the sitting position.
COLM	Mean of two stable measurements that differed by less than 5 mm Hg, taken at least twice at intervals of one to two minutes.
CONVINCE	Not provided.
COPE	Mean of two stable measurements (difference <5mmHg), taken using the upper arm after five minutes rest in a sitting position.
DIABHYCAR	Measured once using a mercury sphygmomanometer in the sitting position.
Dutch TIA	A single measurement in the sitting position using a mercury manometer.
E-COST	Taken in sitting position.
ELSA	Three measurements taken in sitting position using a mercury manometer.
EUROPA	Two measurements taken with a standard sphygmomanometer in sitting position, after five minutes rest.
EWPHE	Taken in sitting position.
HDFP	Four readings taken in sitting position; First and third reading taken using conventional mercury manometer; Second and fourth reading taken using Hawksley random-zero manometer
HIJ-CREATE	Measured using a standard cuff mercury sphygmomanometer in sitting position after five minutes of rest.
HOMED-BP	Clinic: Mean of two measurements taken using a validated sphygmomanometer (OMRON HEM-907IT, Omron Healthcare, Kyoto, Japan) in the sitting position after two minutes rest; Home: as with clinic but taken in the morning, 1 hour after waking up, before breakfast and before taking BP treatment, and mean of readings over 5 days prior to clinic visit.
HOPE	Mean of two measurements in the sitting position after fifteen minutes rest, taken using a mercury sphygmomanometer.
HYVET	Two measurements taken in the standing position, using a mercury sphygmomanometer or a validated automated device.
IDNT	Taken in the sitting position.
INSIGHT	Mean of three measurements after a five minute rest, taken using a mercury sphygmomanometer.
INVEST	Mean of two measurements taken in the sitting position as described in JNC VI.
JMIC-B	Average of two last measurements of three measurements, taken in sitting or supine position, whichever had been decided upon initially.
LIFE	Sitting blood pressure, measured at the trough.
MOSES	Not provided.

NICS-EH	Not provided.
NORDIL	Measured on two separate occasions.
ONTARGET	Average of two readings was used. Each blood pressure reading consisted of measurement using an automated validated device (OMRON, model HEM-757) after 3 minutes of rest while sitting.
PART 2	Average of two measurements using a standard mercury sphygmomanometer following standard protocol.
PEACE	Not provided.
PREVEND IT	Ten consecutive measurements were taken using an automatic Dinamap XL model; last two measurements were averaged to determine BP measurement.
PREVENT	Not provided.
PRoFESS	Average of two measures taken twice, at least two minutes apart, using a standard and validated Omron sphygmomanometer (Omron Healthcare Inc) with an appropriately sized cuff applied to the upper nondominant arm at heart level. <sup>49 88</sup>
PROGRESS	Two measurements of BP were taken using a mercury sphygmomanometer.
SHEP	Average of four seated BP measurements, taken using a Hawksley random zero manometer.
SPRINT	Measured after rest, preferably using an automated device, but a manual device could be used if necessary.
STOP Hypertension-2	After five minutes of rest, BP was measured in the supine position.
SYST-EUR	Average of six sitting BP measurements and six standing BP measurements, two in each position at each of three baseline visits taken one month apart.
TRANSCEND	Average of two readings was used. Each blood pressure reading consisted of measurement using an automated validated device (OMRON, model HEM-757) after 3 minutes of rest while sitting.
UKPDS	Mean of last three of four BP measurements taken after 5 minutes of rest while sitting at consecutive clinic visits using an automated validated device (Copal UA-251 or a Takeda UA-751).
VALISH	Blood pressure taken in sitting position at two separate visits within 2 to 4 weeks.
VALUE	Measured after sitting for five minutes.
VHAS	Lowest value of three measurements, taken in the sitting position after a 10-minute rest, at consecutive one-minute intervals.

Acronyms are described in full in the Trial acronym legend in the Supplement; BP – blood pressure.

**Table S8. Supplementary data for Figure 1 and online Figure S2, showing estimated mean blood pressure separately for each comparison arm at specific time points during follow-up, by trial design.**

Comparison arm	Follow-up period (months)												
	Baseline	3	6	9	12	18	24	30	36	42	48	54	60
<b>Blood pressure-lowering intensity trials</b>													
<u>Systolic blood pressure (mmHg)</u>													
More intense	151	141	138	135	133	130	127	126	126	126	127	128	130
Less intense	151	143	142	141	140	138	137	137	136	136	137	137	138
<u>Diastolic blood pressure (mmHg)</u>													
More intense	88	82	80	79	77	75	74	73	73	72	72	73	73
Less intense	88	83	82	82	81	80	79	79	78	78	78	77	77
<b>Placebo-controlled trials</b>													
<u>Systolic blood pressure (mmHg)</u>													
Active	146	140	138	137	136	135	134	134	134	135	136	136	137
Placebo	146	143	143	142	141	141	140	140	140	140	140	141	140
<u>Diastolic blood pressure (mmHg)</u>													
Active	83	80	79	79	78	78	77	77	77	77	77	77	77
Placebo	83	82	82	81	81	80	80	80	79	79	79	79	79
<b>Blood pressure difference trials</b>													
<u>Systolic blood pressure (mmHg)</u>													
Active	145	140	138	136	135	133	132	132	132	132	133	135	136
Control	145	143	142	141	141	140	139	139	139	140	140	140	140
<u>Diastolic blood pressure (mmHg)</u>													
Active	84	81	80	79	77	77	76	76	76	76	76	76	76
Control	83	82	82	81	81	80	80	80	79	79	79	79	79
<b>Drug class comparison trials</b>													
<u>Systolic blood pressure (mmHg)</u>													
Active	156	150	148	146	144	141	139	139	138	139	139	140	140
Control	155	149	147	145	144	141	140	139	139	139	139	140	140
<u>Diastolic blood pressure (mmHg)</u>													
Active	90	86	85	84	83	81	80	80	79	79	79	79	79
Control	89	86	85	84	83	81	80	80	79	79	79	79	79

Estimates based on separate models for each comparison arm, with random intercepts at individual and trial levels, a random slope for time at the individual level (see Method for details) and adjusted for baseline blood pressure, age and sex; Data concatenated at to five years of follow-up.



**Table S9. Supplementary data for Figure 2 and online Figure S3 showing mean blood pressure difference between comparison groups over follow-up time.**

Follow-up period, months	Systolic blood pressure (mmHg) difference (95% CI)	Diastolic blood pressure (mmHg) difference (95% CI)
<b>Blood pressure-lowering intensity trials (9 trials)</b>		
0 to 6	-4.2 (-4.4 to -4.0)	-2.0 (-2.2 to -1.9)
6 to 12	-10.1 (-10.4 to -9.7)	-5.2 (-5.4 to -5.0)
12 to 24	-11.3 (-11.6 to -11.0)	-5.8 (-6.0 to -5.6)
24 to 36	-11.9 (-12.2 to -11.6)	-6.1 (-6.3 to -5.9)
36 to 48	-12.0 (-12.3 to -11.6)	-6.0 (-6.2 to -5.7)
48 to 60	-10.9 (-11.4 to -10.4)	-5.6 (-5.9 to -5.3)
<b>Placebo-controlled trials (21 trials)</b>		
0 to 6	-3.0 (-3.1 to -2.9)	-1.5 (-1.6 to -1.4)
6 to 12	-5.6 (-5.8 to -5.4)	-2.7 (-2.8 to -2.5)
12 to 24	-5.3 (-5.5 to -5.1)	-2.5 (-2.6 to -2.4)
24 to 36	-5.3 (-5.5 to -5.0)	-2.4 (-2.5 to -2.3)
36 to 48	-4.9 (-5.2 to -4.7)	-2.2 (-2.3 to -2.0)
48 to 60	-4.5 (-4.8 to -4.2)	-1.9 (-2.1 to -1.8)
<b>All blood pressure difference trials (30 trials)</b>		
0 to 6	-3.3 (-3.4 to -3.2)	-1.6 (-1.7 to -1.6)
6 to 12	-6.5 (-6.7 to -6.4)	-3.2 (-3.3 to -3.1)
12 to 24	-6.8 (-7.0 to -6.6)	-3.3 (-3.4 to -3.2)
24 to 36	-7.0 (-7.2 to -6.8)	-3.4 (-3.5 to -3.3)
36 to 48	-6.7 (-6.9 to -6.5)	-3.1 (-3.3 to -3.0)
48 to 60	-6.2 (-6.5 to -6.0)	-2.9 (-3.1 to -2.8)
<b>Drug class comparison trials (29 trials)</b>		
0 to 6	-1.0 (-1.1 to -1.0)	-0.4 (-0.4 to -0.3)
6 to 12	-1.9 (-2.1 to -1.8)	-0.7 (-0.8 to -0.6)
12 to 24	-1.6 (-1.8 to -1.5)	-0.8 (-0.8 to -0.7)
24 to 36	-1.5 (-1.6 to -1.3)	-0.7 (-0.7 to -0.6)
36 to 48	-1.5 (-1.7 to -1.4)	-0.8 (-0.9 to -0.7)
48 to 60	-1.6 (-1.8 to -1.5)	-1.0 (-1.1 to -0.9)

Model based on fixed treatment effect (see Method), and estimates adjusted for baseline blood pressure, age and sex; Negative values indicate lower blood pressure in the active than in the control group.

**Table S10. Supplementary data for Figure 2 and online Figure S3 showing achieved mean blood pressure difference between active and control groups with and without taking into account early follow-up measurements.**

Follow-up period, months	Systolic blood pressure (mmHg) difference (95% CI)	Diastolic blood pressure (mmHg) difference (95% CI)
<u>Blood pressure-lowering intensity trials (9 trials)</u>		
All follow-up	-7.6 (-7.7 to -7.4)	-3.7 (-3.8 to -3.6)
From 12 months to end of follow-up	-11.1 (-11.3 to -10.8)	-5.6 (-5.7 to -5.4)
<u>Placebo-controlled trials (20 trials)</u>		
All follow-up	-4.0 (-4.1 to -3.9)	-1.9 (-2.0 to -1.8)
From 12 months to end of follow-up	-5.1 (-5.3 to -5.0)	-2.3 (-2.4 to -2.2)
<u>Blood pressure difference trials (30 trials)</u>		
All follow-up	-4.8 (-4.9 to -4.7)	-2.3 (-2.4 to -2.3)
From 12 months to end of follow-up	-6.6 (-6.7 to -6.5)	-3.2 (-3.2 to -3.1)
<u>Drug class comparison trials (29 trials)</u>		
All follow-up	-1.4 (-1.5 to -1.3)	-0.5 (-0.6 to -0.5)
From 12 months to end of follow-up	-1.4 (-1.5 to -1.3)	-0.6 (-0.7 to -0.6)

Model based on fixed treatment effect and random intercept for trials (see Method for details) and adjusted for baseline blood pressure, age and sex; Negative values indicate lower blood pressure in the active than in the control group.

**Table S11. Achieved mean blood pressure difference\* between active and control groups stratified by time period of conducting the trial.**

<b>Year of end of study</b>	<b>Systolic blood pressure (mmHg) difference (95% CI)</b>	<b>Diastolic blood pressure (mmHg) difference (95% CI)</b>
<u>Blood pressure-lowering intensity trials (9 trials)</u>		
Pre-2000 (3 trials)	-10.1 (-10.5 to -9.6)	-5.3 (-5.5 to -5.0)
2000 or later (6 trials)	-11.4 (-11.6 to -11.1)	-5.6 (-5.8 to -5.4)
<u>Placebo-controlled trials (21 trials)</u>		
Pre-2000 (9 trials)	-7.7 (-8.0 to -7.4)	-3.3 (-3.5 to -3.1)
2000 or later (12 trials)	-4.5 (-4.6 to -4.3)	-2.1 (-2.2 to -2.0)
<u>Blood pressure difference trials (30 trials)</u>		
Pre-2000 (12 trials)	-7.8 (-8.1 to -7.5)	-3.5 (-3.7 to -3.3)
2000 or later (18 trials)	-5.9 (-6.1 to -5.8)	-2.9 (-2.9 to -2.8)
<u>Drug class comparison trials (29 trials)</u>		
Pre-2000 (7 trials)	-1.1 (-1.3 to -0.8)	-0.8 (-0.9 to -0.6)
2000 or later (22 trials)	-1.4 (-1.5 to -1.3)	-0.6 (-0.6 to -0.5)

Model based on fixed treatment effect and random intercept for trials (see Method for details) and adjusted for baseline blood pressure, age and sex; Negative values indicate lower blood pressure in the active than in the control group; \*Based on blood pressure measurements from ≥12 months to end of follow-up.

Table S12. Comparison of models estimating mean blood pressure difference between comparison arms.

Model	SBP (mmHg)		DBP (mmHg)	
	Mean difference (95% CI)	AIC	Mean difference (95% CI)	AIC
<b>BLOOD PRESSURE-LOWERING INTENSITY TRIALS</b>				
<b>All follow-up</b>				
Model 1: Fixed effect (treatment and time) and random intercept (trial)	-9.7 (-9.8 to -9.6)	3,708,049	-5.0 (-5.1 to -4.9)	3,254,826
Model 2: Random intercepts (trial and individual levels), fixed treatment effect, fixed time effect (cubic term) and random slope for time (individual level)	-7.6 (-7.7 to -7.4)	3,598,296	-3.7 (-3.8 to -3.6)	3,126,973
<b>From 12 months to end of follow-up</b>				
Model 1: Fixed effect (treatment and time) and random intercept (trial)	-11.8 (-11.9 to -11.7)	2,431,042	-6.1 (-6.1 to -6.0)	2,150,542
Model 2: Random intercepts (trial and individual levels), fixed treatment effect, fixed time effect (cubic term) and random slope for time (individual level)	-11.1 (-11.3 to -10.8)	2,359,772	-5.6 (-5.7 to -5.4)	2,059,717
<b>PLACEBO-CONTROLLED TRIALS</b>				
<b>All follow-up</b>				
Model 1: Fixed effect (treatment and time) and random intercept (trial)	-4.6 (-4.6 to -4.5)	7,326,530	-2.1 (-2.1 to -2.1)	6,313,968
Model 2: Random intercepts (trial and individual levels), fixed treatment effect, fixed time effect (cubic term) and random slope for time (individual level)	-4.0 (-4.1 to -3.9)	7,101,069	-1.9 (-2.0 to -1.8)	6,114,559
<b>From 12 months to end of follow-up</b>				
Model 1: Fixed effect (treatment and time) and random intercept (trial)	-5.1 (-5.2 to -5.0)	4,224,464	-2.3 (-2.4 to -2.3)	3,642,401
Model 2: Random intercepts (trial and individual levels), fixed treatment effect, fixed time effect (cubic term) and random slope for time (individual level)	-5.1 (-5.3 to -5.0)	4,082,606	-2.3 (-2.4 to -2.2)	3,515,852
<b>ALL BLOOD PRESSURE DIFFERENCE TRIALS</b>				
<b>All follow-up</b>				
Model 1: Fixed effect (treatment and time) and random intercept (trial)	-6.0 (-6.1 to -6.0)	12,216,192	-3.0 (-3.0 to -2.9)	10,594,707
Model 2: Random intercepts (trial and individual levels), fixed treatment effect, fixed time effect (cubic term) and random slope for time (individual level)	-4.8 (-4.9 to -4.7)	11,826,496	-2.3 (-2.4 to -2.3)	10,216,192
<b>From 12 months to end of follow-up</b>				
Model 1: Fixed effect (treatment and time) and random intercept (trial)	-7.3 (-7.4 to -7.3)	7,117,093	-3.6 (-3.6 to -3.5)	6,186,156
Model 2: Random intercepts (trial and individual levels), fixed treatment effect, fixed time effect (cubic term) and random slope for time (individual level)	-6.6 (-6.7 to -6.5)	6,854,402	-3.2 (-3.2 to -3.1)	5,926,777
<b>DRUG COMPARISON TRIALS</b>				
<b>All follow-up</b>				
Model 1: Fixed effect (treatment and time) and random intercept (trial)	-1.4 (-1.4 to -1.3)	16,539,815	-0.6 (-0.6 to -0.6)	14,228,432
Model 2: Random intercepts (trial and individual levels), fixed treatment effect, fixed time effect (cubic term) and random slope for time (individual level)	-1.4 (-1.5 to -1.3)	16,078,396	-0.5 (-0.6 to -0.5)	13,790,959
<b>From 12 months to end of follow-up</b>				
Model 1: Fixed effect (treatment and time) and random intercept (trial)	-1.3 (-1.4 to -1.3)	10,516,160	-0.7 (-0.7 to -0.6)	9,069,610
Model 2: Random intercepts (trial and individual levels), fixed treatment effect, fixed time effect (cubic term) and random slope for time (individual level)	-1.4 (-1.5 to -1.3)	10,193,302	-0.6 (-0.7 to -0.6)	8,751,146

SBP – systolic blood pressure; DBP – diastolic blood pressure; AIC: Aikeke information criterion; Adjusted for baseline blood pressure, age and sex; Negative values indicate lower blood pressure in the active than in the control group.

## CLINICAL PERSPECTIVES

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Antihypertensive medications are effective in lowering blood pressure in people with a wide range of characteristics. If clinically indicated, such treatment should be considered in men and women, in relatively young and older adults, with or without a history of cardiovascular disease or diabetes, and even among those whose blood pressure levels are below the usual thresholds for defining hypertension.

Treatment strategies should consider aiming for a substantive reduction in blood pressure. Whilst setting a blood pressure target is practical, such an approach could either mean a modest reduction for some and difficult to achieve for others, depending on their baseline or usual pre-treatment blood pressure levels. The optimal treatment strategy would focus on achieving the greatest long-term blood pressure reduction possible that can be tolerated by the patient and is feasible to implement.

Monitoring of blood pressure of an individual patient is necessary to assess treatment response. However, short-term measurements, such as readings taken a few months since treatment initiation, are unlikely to be informative of the extent to which the blood pressure has been reduced. Moreover, achieved reduction in blood pressure attenuates over time, which is likely due to reduced treatment compliance. Hence, long-term monitoring of blood pressure and addressing issues on treatment adherence should form part of clinical care to maximise the benefits of pharmacologic treatment of raised blood pressure. Longitudinal data of blood pressure reduction reported in this study can also provide some guidance on achievable blood pressure reductions based on trialed regimens.

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## TRIAL ACRONYM LEGEND

<b>Trial acronym</b>	<b>Full name or description</b>
<b>AASK</b>	African American Study of Kidney Disease and Hypertension
<b>ABCD</b>	Appropriate Blood Pressure Control in Diabetes
<b>ACCORD</b>	Action to Control Cardiovascular Risk in Diabetes blood pressure trial
<b>ACTIVE I</b>	Atrial Fibrillation Clopidogrel Trial with Irbesartan for Prevention of Vascular Events
<b>ADVANCE</b>	Action in Diabetes and Vascular disease: preterAx and diamicroN-MR Controlled Evaluation
<b>ALLHAT</b>	Antihypertensive and Lipid Lowering Treatment to Prevent Heart Attack Trial
<b>ANBP</b>	Australian National Blood Pressure Study
<b>ANBP2</b>	Second Australian National Blood Pressure Study
<b>ASCOT-BPLA</b>	Anglo-Scandinavian Cardiac Outcomes Trial-Blood Pressure Lowering Arm
<b>BENEDICT</b>	BErgamo NEphrologic Diabetes Complications Trial
<b>CAMELOT</b>	Comparison of Amlodipine vs Enalapril to Limit Occurrences of Thrombosis
<b>CAPP</b>	Captopril Prevention Project
<b>Cardio-Sis</b>	Studio Italiano Sugli Effetti Cardiovascolari del Controllo della Pressione Arteriosa Sistolica
<b>CASE-J</b>	Candesartan Antihypertensive Survival Evaluation in Japan Trial
<b>COLM</b>	Combination of OLMesartan study
<b>CONVINCE</b>	Controlled ONset Verapamil INvestigation of Cardiovascular Endpoints trial
<b>COPE</b>	Combination Therapy of Hypertension to Prevent Cardiovascular Events
<b>DIABHYCAR</b>	Noninsulin-dependent diabetes, hypertension, microalbuminuria or proteinuria, cardiovascular events, and ramipril
<b>Dutch TIA Trial</b>	Dutch Transient Ischemic Attack Trial
<b>E-COST</b>	Efficacy of Candesartan on Outcome in Saitama Trial
<b>ELSA</b>	European Lacidipine Study on Atherosclerosis
<b>EUROPA</b>	EUropean trial on Reduction Of cardiac events with Perindopril in patients with stable coronary Artery disease
<b>EWPH</b>	European Working Party on High Blood Pressure in the Elderly
<b>HDFP</b>	Hypertension Detection and Follow-up Program
<b>HIJ-CREATE</b>	Heart Institute of Japan Candesartan Randomized Trial for Evaluation in Coronary Artery Disease
<b>HOMED-BP</b>	Hypertension Objective Treatment Based on Measurement by Electrical Devices of Blood Pressure
<b>HOPE</b>	Heart Outcomes Prevention Evaluation
<b>HYVET</b>	Hypertension in the Very Elderly Trial
<b>IDNT</b>	Irbesartan Diabetic Nephropathy Trial
<b>INSIGHT</b>	International Nifedipine GITS study: Intervention as a Goal in Hypertension Treatment
<b>INVEST</b>	International Verapamil-Trandolapril Study
<b>JMIC-B</b>	Japan Multicenter Investigation for Cardiovascular Diseases-B
<b>LIFE</b>	Losartan Intervention For Endpoint reduction
<b>MOSES</b>	Morbidity and Mortality After Stroke, Eprosartan Compared With Nitrendipine for Secondary Prevention
<b>NICS-EH</b>	National Intervention Cooperative Study in Elderly Hypertensives
<b>NORDIL</b>	Nordic Diltiazem Study
<b>ONTARGET</b>	Ongoing Telmisartan Alone and in Combination with Ramipril Global Endpoint Trial
<b>PART 2</b>	Prevention of Atherosclerosis with Ramipril Trial
<b>PEACE</b>	Prevention of Events with Angiotensin Converting Enzyme Inhibition
<b>PREVEND IT</b>	Prevention of Renal and Vascular Endstage Disease Intervention Trial
<b>PREVENT</b>	Prospective Randomized Evaluation of the Vascular Effects of Norvasc Trial
<b>PRoFESS</b>	Prevention Regimen for Effectively Avoiding Second Strokes
<b>PROGRESS</b>	Perindopril Protection Against Recurrent Stroke Study
<b>SHEP</b>	Systolic Hypertension in the Elderly Program
<b>SPRINT</b>	Systolic Blood Pressure Intervention Trial
<b>STOP Hypertension-2</b>	Swedish Trial in Old Patients with Hypertension-2
<b>SYST-EUR</b>	SYSTolic Hypertension in EUROpe
<b>TRANSCEND</b>	Telmisartan Randomized Assessment Study in ACE Intolerant Subjects with Cardiovascular Disease
<b>UKPDS</b>	UK Prospective Diabetes Study
<b>VALISH</b>	Valsartan in Elderly Isolated Systolic Hypertension
<b>VALUE</b>	Valsartan Antihypertensive Long-term Use Evaluation
<b>VHAS</b>	Verapamil in Hypertension and Atherosclerosis Study

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