Supplementary Online Content

Bundy JD, Li C, Stuchlik P, et al. Systolic blood pressure reduction and risk of cardiovascular disease and mortality: a systematic review and network meta-analysis. *JAMA Cardiol.* Published online May 31, 2017. doi:10.1001/jamacardio.2017.1421

This supplementary material has been provided by the authors to give readers additional information about their work.

eAppendix. Methods

Network meta-analysis (NMA) compares multiple treatment groups using both direct comparisons of interventions within randomized controlled trials and indirect comparisons across trials. The objectives of NMA are twofold: to strengthen inference concerning the relative efficacy of two treatments, by including both 'direct' and 'indirect' comparisons; and to facilitate simultaneous inference regarding all treatments, in order to select the best treatment.[1] For example, we compared the effects of each of 10 achieved mean systolic blood pressure (SBP) categories with every other category of achieved SBP on risk of cardiovascular disease and mortality, pooling direct and indirect evidence into one summary measure (hazard ratio) for each possible comparison. Importantly, the randomization procedure in each individual trial is preserved, providing the typical benefits associated with randomization, namely protection against confounding and bias. Although it is often argued that indirect comparisons are needed only when direct comparisons are not available, it is important to realize that both direct and indirect evidence contribute to the total body of evidence.

Treatment nodes were defined by categorizing SBP into 10 separate achieved levels, as follows: <120, 120-124, 125-129, 130-134, 135-139, 140-144, 145-149, 150-154, 155-159, and ≥160 mmHg. For an individual trial, each randomization group was assigned to one category of achieved SBP according to the group's mean SBP level during the trial, irrespective of medications used or initial treatment target. Thus, each trial contributed to two distinct achieved SBP categories based on randomization groups (e.g. 120-124 mmHg vs. 130-134 mmHg). We constructed network diagrams for each outcome and the overall network to visualize direct and indirect comparisons.

We used a Bayesian hierarchical random effects model and a generalized linear modeling framework to conduct the analyses, in which a likelihood and link function are chosen to suit the treatment effect of interest and the type of data retrieved.[2] We chose a binomial likelihood to accommodate dichotomous outcomes (i.e. disease [death] vs. no disease [alive]) and applied a complementary log-log link function to model the probability of event. We included a log-transformation of trial duration in the model to reduce the influence of variations in trial length. In addition, to account for the baseline risk heterogeneity of clinical outcomes among included trials, we adjusted for the baseline risk (defined as the event rate or mortality in the higher achieved SBP groups of each trial) as a covariate, according to methods provided by Achana and colleagues.[3]

Our primary model is:

$$cloglog(p_{ik}) = \log(time_i) + \mu_{ib} + d_{bk} + \beta_{bk} \times (\mu_{iA} - \bar{\mu}) + \varepsilon_{ibk},$$
$$\varepsilon_{ibk} \sim N(0, {\sigma_{bk}}^2)$$

where p_{ik} indicates the probability of event in the lower achieved SBP group *k* (i.e. active treatment group in placebo-controlled trials or intensive treatment group in intensive vs. standard treatment trials) of trial *i*; $time_i$ indicates the trial duration in trial *i*; μ_{ib} indicates the trial-specific baseline event rate in the higher achieved SBP group *b* (i.e. placebo group in placebo-controlled trials or standard treatment group in intensive vs. standard treatment trials) of trial *i*; d_{bk} indicates the mean effect of lower achieved SBP group *k* relative to higher achieved SBP group *b*, adjusted for the baseline risk; β_{bk} indicates the baseline-risk covariate, defined as change in the log-hazard ratio of an event per unit change in the baseline risk, for lower achieved SBP group *k* relative to higher achieved SBP group *b*, at the mean baseline risk across trials; $(\mu_{iA} - \bar{\mu})$ is used to center the baseline-risk covariate on the mean reference achieved SBP group's event rate μ_{iA} (taken as the 130-134 mmHg group; the most frequent achieved SBP group in our study) in order to improve convergence of the model; and ε_{ibk} denotes trial-specific random effects and are normally distributed with mean 0 and between-trial variance ${\sigma_{bk}}^2$.

The mean effect of lower achieved SBP group *k* relative to higher achieved SBP group *b* (d_{bk}) is interpreted as a log-hazard ratio. We obtained pooled hazard ratios for all possible achieved SBP group comparisons using Markov Chain Monte Carlo simulation, assuming vague prior distributions for trial baseline risks (normal distribution with mean 0 and variance 100^2), achieved SBP group effects (normal distribution with mean 0 and variance 100^2), and between-trial standard deviation (uniform distribution from 0 to 5). Informative prior distributions were also considered. However, without clear justification for their use, we used standard recommendations and retained vague priors for model parameters.[2]

For each model, we used three chains of 100,000 iterations after a burn-in period of 50,000 iterations, in which initial iterations are discarded to ensure final estimates are based on stable posterior sampling. Thus, final posterior inference was based on 300,000 iterations. Convergence was assessed using trace plots and the Brooks-Gelman-Rubin statistic.[4] The median of the posterior distribution was selected as the point estimate, bounded by the 2.5th and 97.5th percentiles to form a 95% credibility interval (i.e. confidence interval).

We assessed the influence of differing baseline risks (event rates or mortality in higher achieved SBP groups) across trials using a test of the null hypothesis that the baseline-risk covariate was equal to 0 (i.e. no effect

of differing baseline risks across trials). We compared fixed-effects vs. random-effects models and assessed model fit according to clinical plausibility and the Bayesian deviance information criterion (DIC), which penalizes model complexity.[5] A lower DIC indicates a better-fitting model. Due to DIC results and clinical plausibility, our primary analyses are based on the random-effects model which suggests achieved SBP group effects come from a distribution of effects rather than one fixed effect. Results and characteristics of the different models assessed appear in eTables 14-18.

Heterogeneity in direct evidence was assessed by comparing random-effects models to fixed-effects models as well as monitoring the posterior between-trial standard deviation, which is an indicator of the variability in achieved SBP group effect among different trials. Inconsistency, defined as disagreement between direct and indirect evidence, was assessed via inconsistency model, design-by-treatment interaction, and node-splitting methods.

The standard Bayesian NMA model assumes consistency between direct and indirect evidence. By adding a random inconsistency factor that represents the discrepancy between direct and indirect evidence and comparing this model to the standard model (i.e. with no such inconsistency factor), we conducted an omnibus test of global, network-wide consistency.[6] That is, the better fitting model (indicated by lower DIC) indicates whether the consistency or inconsistency assumption better represents the data. If the standard consistency model is the better fit, it suggests consistency between direct and indirect evidence.

We used design-by-treatment interaction methods to assess inconsistency by testing the interaction of a given "treatment" (achieved SBP group) and the different possible "designs" (direct comparisons) that include that achieved SBP group.[7] This analysis provides information on both design-level inconsistency and global inconsistency via a Wald X^2 test of all the design-by-treatment interaction parameters (or inconsistency parameters; *IF*) at each design via the formula

$$\text{Wald} = \sum_{j=1}^{l} \frac{\widehat{IF}_j^{\,2}}{\hat{\sigma}_j^{\,2}} \sim \chi_l^{\,2}$$

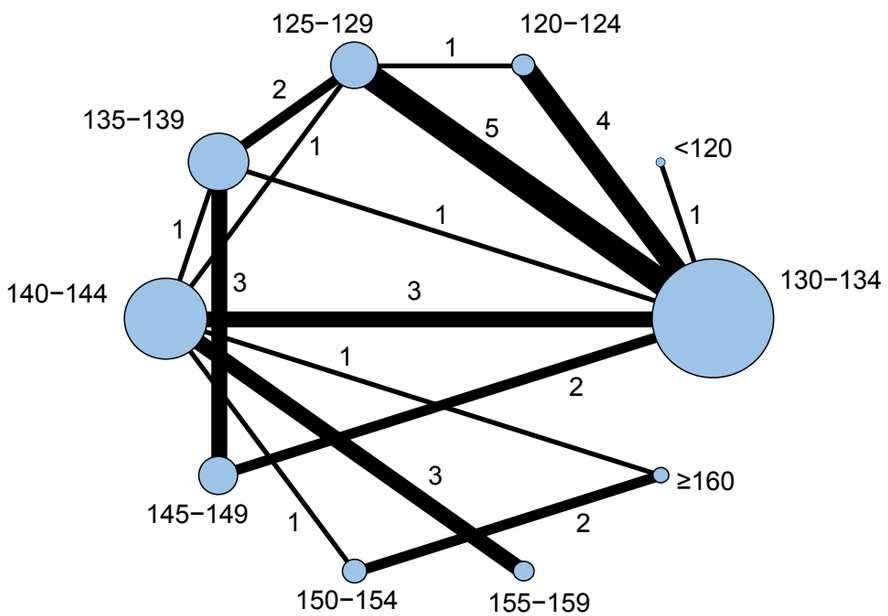
where $\widehat{IF}_j^{\,2}$ indicates the square of the inconsistency factors for each design *j* and $\hat{\sigma}_j^{\,2}$ indicates the variance of the inconsistency factors for each design *j*, which is tested with *l* degrees of freedom, or the total number of inconsistency factors.[8]

Finally, we assessed node-specific inconsistency via the node-splitting method.[9] By separating each node's summary estimate into its direct and indirect components, the agreement between direct and indirect evidence was visually and statistically assessed. eTables 19-23 provide results for these analyses which show how the evidence for each node is constructed, consisting of 1) the direct evidence portion; 2) the indirect evidence portion; and 3) the combined evidence (i.e. achieved SBP group effect estimate). A Bayesian p-value for each comparison is reported to test the null hypothesis that the estimate derived from direct evidence is equal to the estimate derived from indirect evidence. A consistency p-value of <0.05 suggests inconsistency in a given comparison.

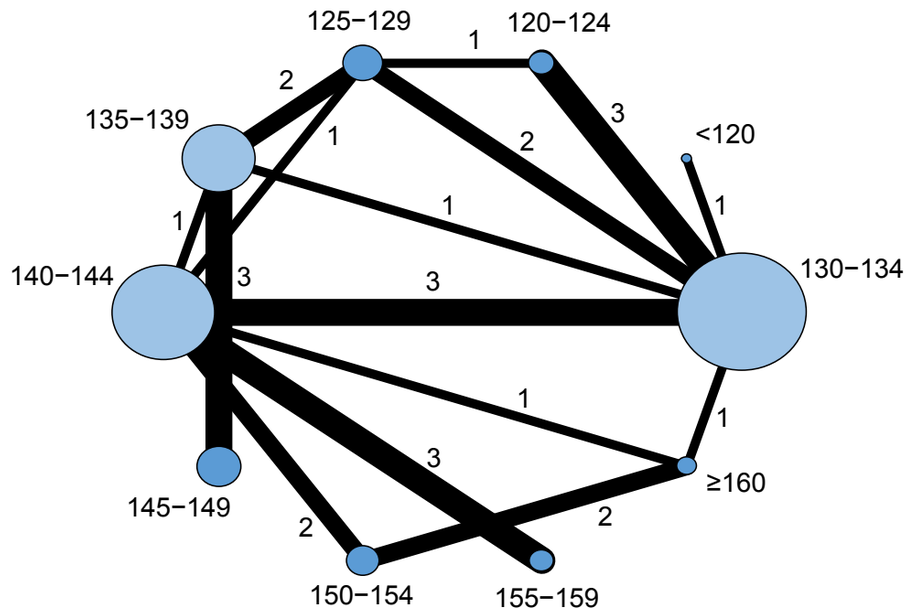
Data analysis was conducted separately for each clinical outcome, using a significance level of 0.05 in interpretation of credibility intervals. WinBUGS version 1.4.3 (Medical Research Council Biostatistics Unit, Cambridge, UK), R version 3.2.1 (R Project for Statistical Computing), and Stata version 12.1 (StataCorp LP, College Station, Texas) were used to conduct the analyses. WinBUGS and R code were adapted from publicly-available resources.[10]

eFigure 1. Networks of Treatment Comparisons for Cardiovascular Disease and Mortality According to Randomization Groups With Various Mean Levels of Achieved Systolic Blood Pressure

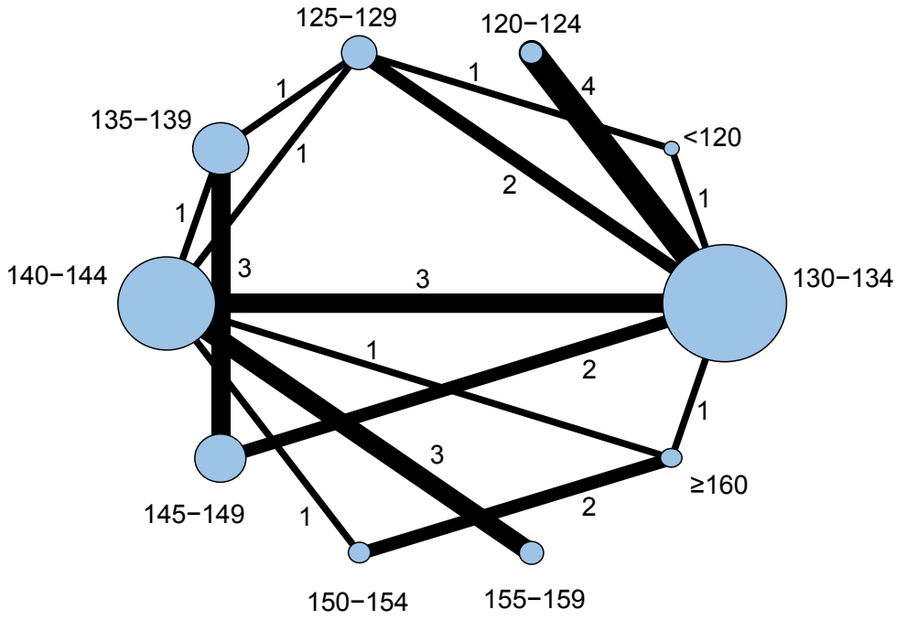
Panel A. Major Cardiovascular Disease (31 trials)



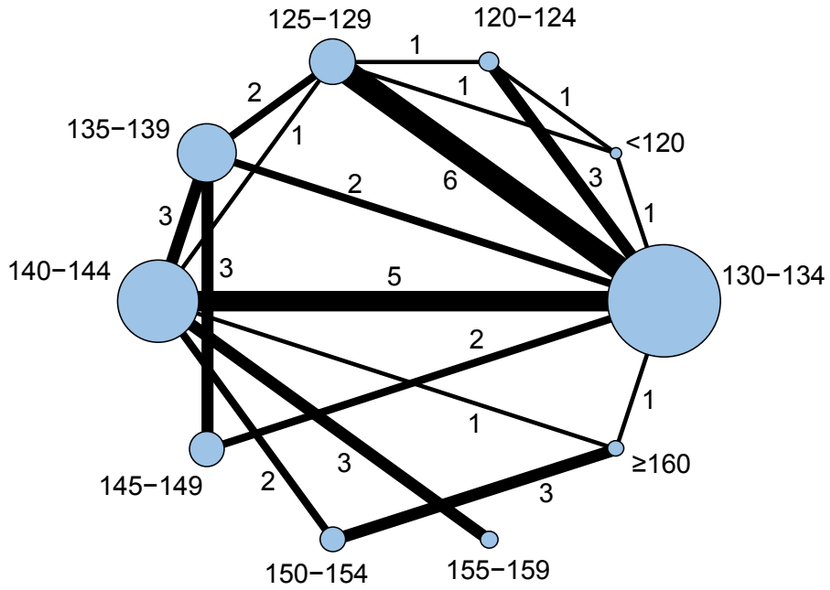
Panel B. Stroke (27 trials)



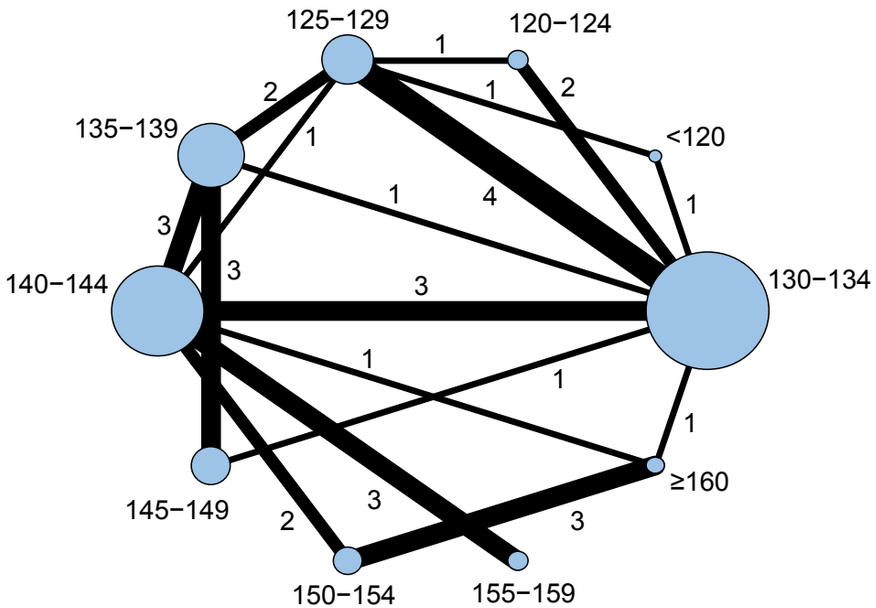
Panel C. Coronary Heart Disease (27 trials)



Panel D. All-cause Mortality (41 trials)



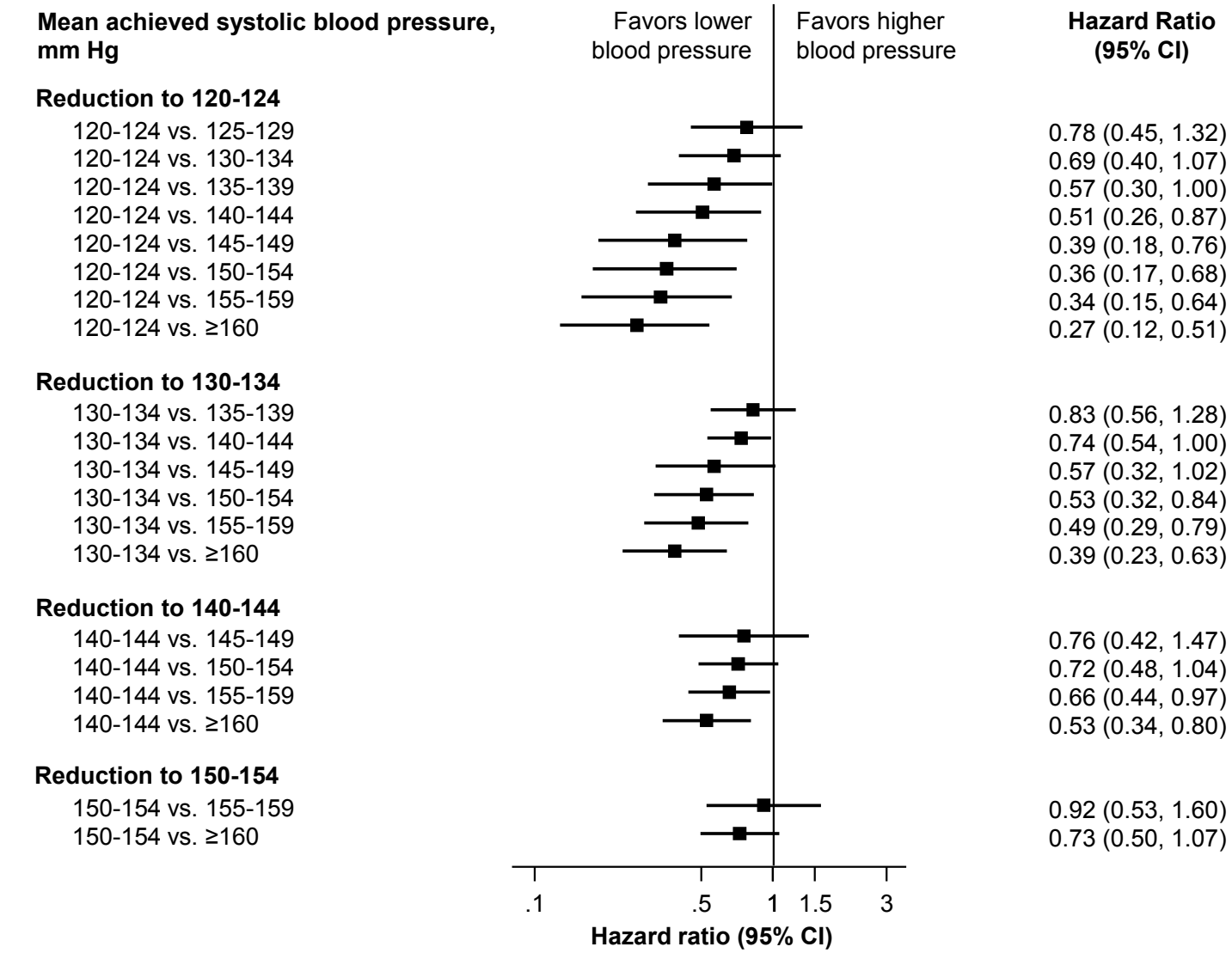
Panel E. Cardiovascular Disease Mortality (33 trials)



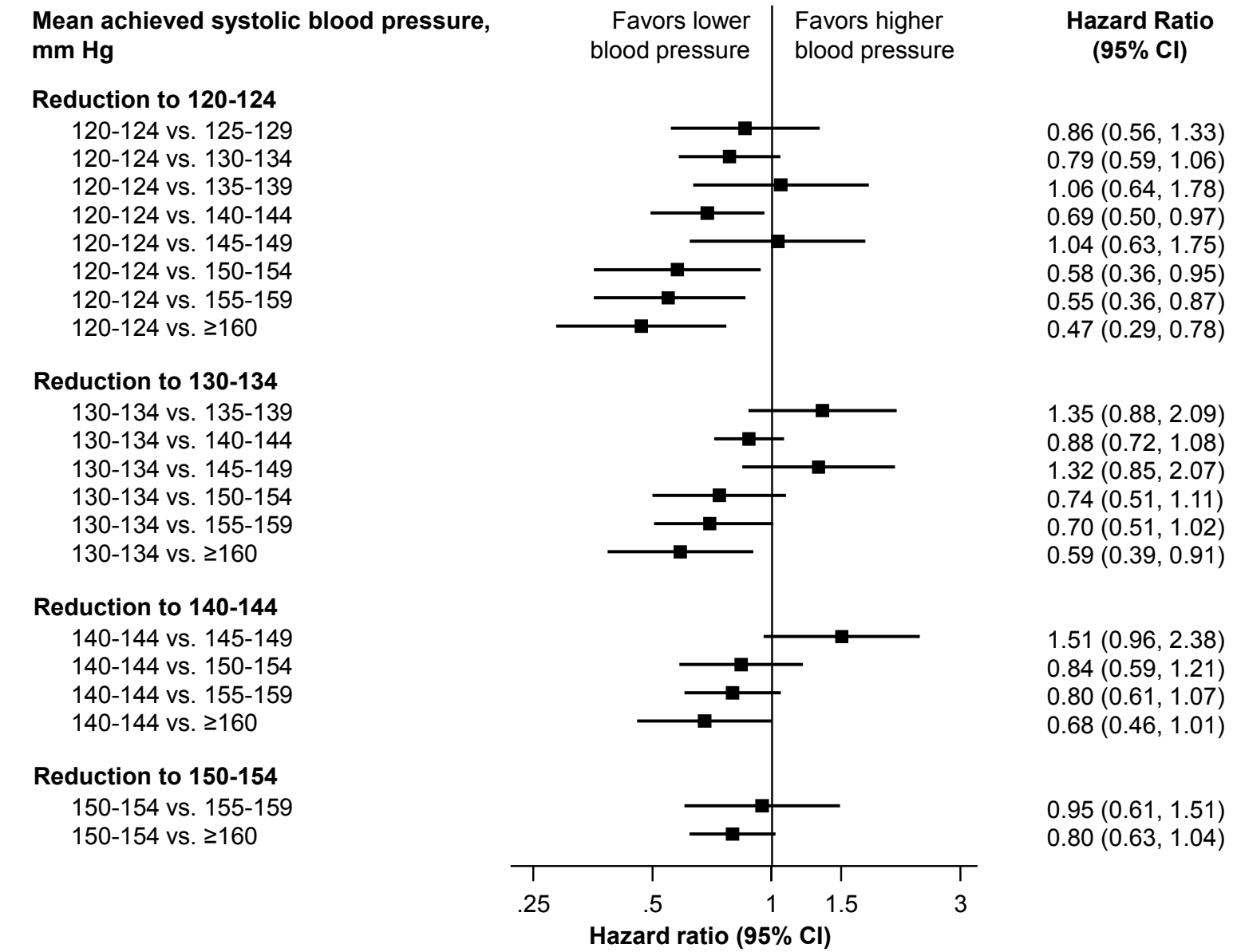
Each node (blue circle) represents a mean systolic blood pressure (mmHg) category. The size of the nodes corresponds to the number of antihypertensive treatment groups of the categories. Comparisons are linked with a line, the thickness of which corresponds to the number of trials that assessed the comparison. Numbers next to every line indicate the number of trials directly comparing the categories.

eFigure 2. Hazard Ratios and 95% CIs for Stroke, Coronary Heart Disease, and Cardiovascular Disease Mortality Associated With More Intensive Reductions in Systolic Blood Pressure

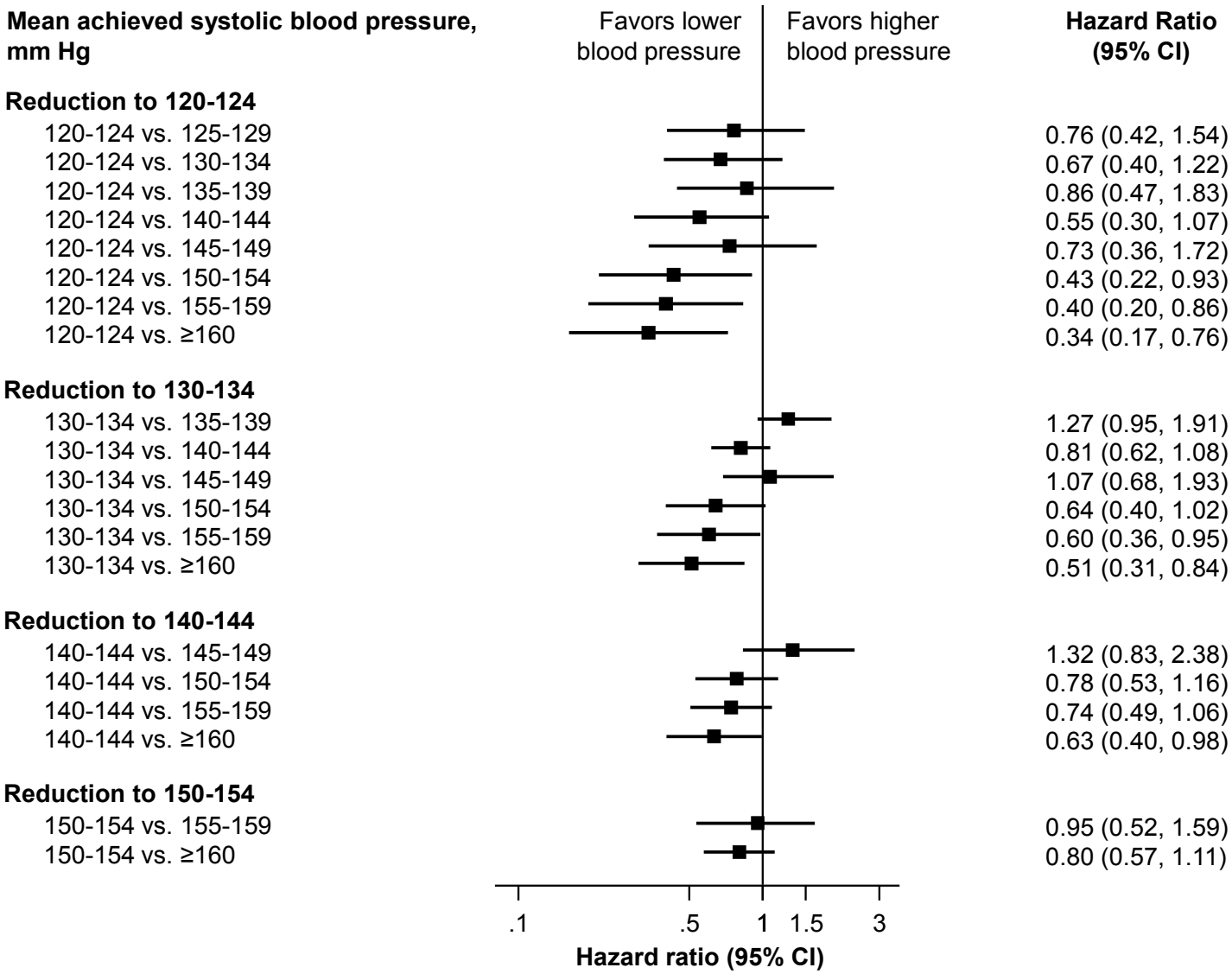
Panel A. Stroke



Panel B. Coronary heart disease



Panel C. Cardiovascular disease mortality



Panel A shows hazard ratios and 95% confidence intervals for stroke. Panel B shows hazard ratios and 95% confidence intervals for coronary heart disease. Panel C shows hazard ratios and 95% confidence intervals for cardiovascular disease mortality. Error bars indicate 95% confidence intervals. CI indicates confidence interval.

eTable 1. Characteristics of 42 Clinical Trials With 144,220 Participants

Trial	Publication Year	Mean Duration, years	Study Population	Mean age, years	Female, %	Diabetes, %	Comparison Groups					
							Treatments	Sample Sizes	Baseline Systolic BP (mm Hg)	Achieved Systolic BP (mm Hg)	Baseline Diastolic BP (mm Hg)	Achieved Diastolic BP (mm Hg)
VA Cooperative Study[11*]	1970	3.3	Hypertension	55	39	NR	Hydrochlorothiazide + reserpine vs placebo	186/194	162.1/165.1	134.9/169.3	103.8/104.7	86.4/105.9
HSCSG[12]	1974	2.3	Stroke, hypertension	59	40	36	Methyclothiazide + deserpidine vs placebo	233/219	167/167	142/167	100/100	87.7/100
USPHSH Cooperative Study[13]	1977	7.0	Hypertension	44	20	0	Chlorothiazide + rauwolfia vs placebo	193/196	147.8/145.9	131.5/147.4	98.8/99.0	88.4/98.4
HDFP[14,15]	1979	5.0	Hypertension	51	46	7	Stepped care vs usual care	5485/5455	159.0/158.5	130/140	101.1/101.1	84/89
ANBP1[16,17]	1980	4.0	Hypertension	50	37	0	Chlorothiazide vs placebo	1721/1706	157.7/157.1	140/155	100.5/100.4	91/98
Oslo Study[18]	1980	5.5	Hypertension	45	0	0	Hydrochlorothiazide vs treatment if BP≥180/110	406/379	156.2/155.3	131/148	97.4/96.2	85/93
MRCWP[19]	1985	4.9	Hypertension	52	48	0	Bendrofluazide or propranolol vs placebo	8700/8654	161.4/161.3	137/148	98.5/98.0	86/92
EWPHE[20]	1985	4.6	Hypertension, age ≥ 60	72	70	0	Hydrochlorothiazide + triamterene vs placebo	416/424	183/182	150.1/171.6	101/101	85/94
V-HeFT-I[21]	1986	2.3	Heart failure	58	0	21	Prazosin vs hydralazine-nitrate	183/186	119.2/119.6	114.6/120.2	75.7/75.0	73/74
DAVIT II[22]	1990	1.3	Myocardial infarction	60	20	6	Verapamil vs placebo	878/897	120/120	136/141	76/76	82/86
SHEP[23]	1991	4.5	Isolated systolic hypertension	72	57	10	Chlorthalidone vs placebo	2365/2371	170.5/170.1	144.5/155.1	76.7/76.4	67.7/71.9
MRCWP Older Adults[24]	1992	5.8	Hypertension, age 65-74	70	58	0	Atenolol or hydrochlorothiazide vs placebo	2183/2213	184.8/184.7	151/165	90.9/90.4	77/83

Trial	Publication Year	Mean Duration, years	Study Population	Mean age, years	Female, %	Diabetes, %	Comparison Groups					
							Treatments	Sample Sizes	Baseline Systolic BP (mm Hg)	Achieved Systolic BP (mm Hg)	Baseline Diastolic BP (mm Hg)	Achieved Diastolic BP (mm Hg)
SAVE[25]	1992	3.5	Myocardial infarction	59	18	22	Captopril vs placebo	1115/1116	112/113	119/125	70/70	74/77
TOMHS[26]	1993	4.4	Hypertension	55	38	NR	Active treatment vs placebo	668/234	140.4/141.1	124.5/132	90.5/90.5	79.4/81.9
MDRD[27]	1994	2.2	Chronic kidney disease	52	40	5	Low target vs usual target	432/408	130/131	126.2/133.8	80/80	76.9/80.7
Shanghai SPAMI[28]	1996	1.8	Myocardial infarction	64	24	12	Captopril vs conventional therapy	478/344	NR	137/144	NR	78.0/85.5
Syst-Eur[29]	1997	2.0	Hypertension, age ≥60	70	67	11	Active treatment vs placebo	2398/2297	173.8/173.9	151/161	85.5/85.5	78.5/83.5
UKPDS[30]	1998	8.4	Diabetes, hypertension	56	45	100	Tight target vs less tight target	758/390	159/160	144/154	94/94	82/87
PART-2[31]	2000	4.0	Cardiovascular disease	61	18	9	Ramipril vs placebo	308/309	133/133	127/132	79/79	74/78
PREVENT[32]	2000	3.0	Coronary artery disease	57	20	0	Amlodipine vs placebo	417/408	128.8/130.0	122/130	78.8/78.9	75/79
SCAT[33]	2000	4.0	Coronary artery disease	61	11	11	Enalapril vs placebo	229/231	128/132	122/130	77/78	74/77
ABCD-HTN[34]	2000	3.7	Diabetes, hypertension	58	33	100	Intensive target vs moderate target	234/231	156/154	132/138	98/98	78/86
PROGRESS[35]	2001	3.9	Stroke/ transient ischemic attack	64	30	13	Perindopril vs placebo	3051/3054	147/147	132.5/141.5	86/86	79/83
ABCD-NT[36]	2002	5.3	Diabetes	59	45	100	Intensive vs moderate BP target	237/243	135.6/137.2	128/137	84.4/84.4	75/81
AASK[37,38]	2002	4.1	Chronic kidney disease, hypertension	55	61	0	Low target vs high target (MAP ≤ 92)	540/554	152/149	128/141	96/95	78/85

Trial	Publication Year	Mean Duration, years	Study Population	Mean age, years	Female, %	Diabetes, %	Comparison Groups					
							Treatments	Sample Sizes	Baseline Systolic BP (mm Hg)	Achieved Systolic BP (mm Hg)	Baseline Diastolic BP (mm Hg)	Achieved Diastolic BP (mm Hg)
CHARM-Overall[39]	2003	3.1	Heart failure	66	32	29	Candesartan vs placebo	3803/3796	130.6/131.1	125/130	76.6/76.7	73/76
EUROPA[40]	2003	4.2	Coronary artery disease	60	15	12	Perindopril vs placebo	6110/6108	137/137	128/133	82/82	78/80
NICOLE[41–43]	2003	3.0	Coronary artery disease	60	21	10	Nisoldipine vs placebo	408/411	129/129	132.3/140.3	78/78	78.9/81.9
ACTION[44]	2004	4.9	Coronary artery disease	64	21	15	Nifedipine vs placebo	3825/3840	137.3/137.6	131/136	79.9/79.8	75.3/78
CAMELOT[45]	2004	2.0	Coronary artery disease	58	26	18	Amlodipine + enalapril vs placebo	1336/655	129.2/128.9	124.3/129.6	77.5/77.6	75.0/78.2
PREVEND IT[46]	2004	4.0	Microalbuminuria	51	35	3	Fosinopril vs placebo	431/433	129/131	126/131	76/76	74/77
ADVANCE[47]	2007	4.3	Diabetes	66	43	100	Perindopril + indapamide vs placebo	5569/5571	145/145	134.4/140	81/81	74.8/77.0
Tepel M[48]	2008	1.6	Chronic kidney disease, hypertension	61	37	29	Amlodipine vs placebo	123/128	140/140	130/140	80/80	76/78
HYVET[49]	2008	1.8	Hypertension, age ≥80	84	61	7	Indapamide vs placebo	1933/1912	173.0/173.0	143.5/158.5	90.8/90.8	77.9/84
JATOS[50]	2008	1.7	Hypertension, age 65-85	74	61	12	Strict target vs mild target	2212/2206	171.6/171.5	135.9/145.6	89.1/89.1	74.8/78.1
PATS[51]	2009	3.0	Stroke	60	28	0	Indapamide vs placebo	2840/2825	154.0/153.6	143/151	92.6/93.0	86.0/89.3
ACCORD[52]	2010	4.7	Diabetes	62	48	100	Intensive target vs standard target	2362/2371	139.0/139.4	119.3/133.5	75.9/76.0	64.4/70.5
VALISH[53]	2010	2.9	Hypertension, age 70-84	76	62	13	Strict target vs moderate target	1545/1534	169.5/169.6	136.6/142	81.7/81.2	74.8/76.5

Trial	Publication Year	Mean Duration, years	Study Population	Mean age, years	Female, %	Diabetes, %	Comparison Groups					
							Treatments	Sample Sizes	Baseline Systolic BP (mm Hg)	Achieved Systolic BP (mm Hg)	Baseline Diastolic BP (mm Hg)	Achieved Diastolic BP (mm Hg)
PARAMOUNT[54]	2012	0.7	Heart failure, hypertension	71	56	38	LCZ696 vs Valsartan	149/152	136/136	128.5/134.5	80/78	74.9/76.5
SPS3[55]	2013	3.7	Stroke	63	37	37	Low target vs high target	1501/1519	142/144	127/138	78/79	NR
Wei et al.[56]	2013	4.0	Hypertension, age >70	77	34	23	Intensive target vs standard target	363/361	158.8/160.3	135.7/149.7	83.7/84.8	76.2/82.1
SPRINT[57]	2015	3.3	Hypertension, age ≥50	68	36	0	Intensive treatment vs standard treatment	4678/4683	139.7/139.7	121.5/134.6	78.2/78.0	68.7/75.0

Abbreviations: CHD, coronary heart disease; CVD, cardiovascular disease; TIA, transient ischemic attack; BP, blood pressure; NR, not reported.

* VA Cooperative 90-114 mmHg group

eTable 2. Description of Blood Pressure Measurement Methods for All Included Trials

Trial	Timing of mean achieved blood pressure	Blood pressure measurement methods
VA Cooperative Study[11*]	Mean BP during the study	Three seated measurements using a Hawksley random-zero sphygmomanometer after at least 5 minutes of rest. The mean of the last two readings was recorded.
HSCSG[12]	Mean BP during the study	Three measurements taken in the right arm after 15 minutes of rest
USPHSH Cooperative Study[13]	Mean BP during the study	Measurements taken in the sitting position after resting quietly for 20 minutes without smoking
HDFP[14,15]	Mean BP at the end of intervention	Three seated measurements using a Hawksley random-zero sphygmomanometer
ANBP1[16,17]	Mean BP during the study	Mean of two measurements using either random-zero or London School of Hygiene sphygmomanometers after 5 minutes rest
Oslo Study[18]	Mean BP during the study	Two measurements with a minute interval using a conventional mercury manometer after 5 minutes rest. The last reading was used in the analyses.
MRCWP[19]	Mean BP during the study	Measurements taken by specially trained, and regularly tested, nurses using either a Hawksley random-zero or London School of Hygiene sphygmomanometer
EWPHE[20]	Mean BP during the study	Measurements taken while participant was seated
V-HeFT-I[21]	BP at termination of intervention	Not reported
DAVIT II[22]	Mean BP between the middle and end of intervention	Not reported
SHEP[23]	Mean BP during the study	Measurements taken by trained, certified technicians using standardized techniques using a Hawksley random-zero manometer
MRCWP Older Adults[24]	Mean BP during the study	Three seated measurements using a Hawksley random-zero sphygmomanometer. The mean of the last two readings was recorded.
SAVE[25]	Mean BP during the study	Not reported
TOMHS[26]	Mean BP during the study	Measurements taken with a random-zero device
MDRD[27]	Mean BP during the study	Measurements taken by trained personnel monthly using a random-zero mercury sphygmomanometer
Shanghai SPAMI[28]	Mean BP during the study	Not reported
Syst-Eur[29]	Mean BP during the study	Averages of six sitting and six standing readings
UKPDS[30]	Mean BP during the study	Four seated measurements taken by a trained nurse after 5 minutes rest. The mean of the last three readings was recorded.
PART-2[31]	Mean BP during the study	Measurements taken in duplicate at every clinic visit using a standard mercury sphygmomanometer, following a standardized protocol
PREVENT[32]	Mean BP during the study	Not reported
SCAT[33]	Mean BP during the study	Not reported
ABCD-HTN[34]	Mean BP during the study	Average of three seated measurements at each visit
PROGRESS[35]	Mean BP during the study	Measurements taken in duplicate, to the nearest 2 mm Hg, with a standard mercury sphygmomanometer

Trial	Timing of mean achieved blood pressure	Blood pressure measurement methods
ABCD-NT[36]	Mean BP in the last 4 years of follow-up	Average of three seated measurements at each visit
AASK[37,38]	Mean BP during the study	Three seated measurements using a Hawksley random-zero sphygmomanometer after at least 5 minutes of rest. The mean of the last two readings was recorded.
CHARM-Overall[39]	Mean BP during the study	Not reported
EUROPA[40]	Mean BP during the study	Two seated measurements with a standard sphygmomanometer after at least 5 minutes of rest
NICOLE[41–43]	Mean BP during the study	Not reported
ACTION[44]	Mean BP during the study	Measurements taken with a standard sphygmomanometer in the sitting position after 5 minutes rest
CAMELOT[45]	Mean BP during the study	Measurements taken using a manual cuff and stethoscope
PREVEND IT[46]	Mean BP during the study	Ten consecutive measurements with an automatic Dinamap XL model 9300 series device. The mean of the last two readings were used.
ADVANCE[47]	Mean BP during the study	Mean of two seated measurements using a standardized automated sphygmomanometer after at least 5 minutes rest
Tepel M[48]	Mean BP during the study	Measured after 10 minutes rest
HYVET[49]	BP at termination of intervention	Two measurements taken after the participant had been standing for 2 minutes using either a mercury sphygmomanometer or a validated automated device
JATOS[50]	BP at termination of intervention	Mean of at last two seated measurements per visit by the auscultatory method, using a sphygmomanometer, after 5 to 10 minutes of rest
PATS[51]	Mean BP during the study	Mean of four seated measurements over two visits after at least 5 minutes of rest
ACCORD[52]	Mean BP during the study	Mean of three seated measurements using an automated device (Omron Model 907) after 5 minutes rest
VALISH[53]	Mean BP during the study	Measurement taken in sitting position
PARAMOUNT[54]	Mean BP during the study	Not reported
SPS3[55]	Mean BP during the study	Three measurements taken at every visit using an automated device (Colin Press-Mate BP-8800C sphygmomanometer)
Wei et al.[56]	Mean BP during the study	At least two seated measurements taken per visit by the auscultatory method using a sphygmomanometer after 5 to 10 minutes of rest
SPRINT[57]	Mean BP during the study	Mean of three seated measurements using an automated device (Omron Model 907) after 5 minutes rest

Abbreviations: BP, blood pressure

* VA Cooperative Study 90-114 mmHg group

eTable 3. Quality Assessment and Risk of Bias for All Included Trials

Trial	Year	Random sequence generation	Allocation concealment	Blinding of participants/outcome assessment	Incomplete data	Selective reporting	Intention-to-treat analysis	Other sources of bias
VA Cooperative Study[11*]	1970	Unclear risk	Unclear risk	Low risk	Low risk	Low risk	Low risk	Low risk
HSCSG[12]	1974	Low risk	Low risk	Low risk	Low risk	Unclear risk	Low risk	Low risk
USPHSH Cooperative Study[13]	1977	Unclear risk	Unclear risk	Low risk	Low risk	Low risk	Unclear risk	Low risk
HDFP[14,15]	1979	Low risk	Low risk	Low risk	Unclear risk	Low risk	Unclear risk	Unclear risk
ANBP1[16,17]	1980	Low risk	Low risk	Low risk	Low risk	Low risk	Low risk	Low risk
Oslo Study[18]	1980	Low risk	Unclear risk	Low risk	Low risk	Low risk	Low risk	Low risk
MRCWP[19]	1985	Low risk	Unclear risk	Low risk	Unclear risk	Low risk	Low risk	Low risk
EWPHE[20]	1985	Unclear risk	Unclear risk	Low risk	Unclear risk	Unclear risk	Low risk	Unclear risk
V-HeFT-I[21]	1986	Low risk	Low risk	Low risk	Low risk	Unclear risk	Low risk	Low risk
DAVIT II[22]	1990	Unclear risk	Low risk	Low risk	Low risk	Low risk	Low risk	Low risk
SHEP[23]	1991	Low risk	Low risk	Low risk	Unclear risk	Low risk	Low risk	Low risk
MRCWP Older Adults[24]	1992	Low risk	Unclear risk	Low risk	Unclear risk	Low risk	Low risk	Low risk
SAVE[25]	1992	Low risk	Unclear risk	Low risk	Unclear risk	Low risk	Low risk	Low risk
TOMHS[26]	1993	Unclear risk	Unclear risk	Low risk	Low risk	Low risk	Low risk	Low risk
MDRD[27]	1994	Low risk	Low risk	High risk	Low risk	Low risk	Low risk	Low risk
Shanghai SPAMI[28]	1996	Unclear risk	Unclear risk	High risk	Low risk	Unclear risk	Unclear risk	Unclear risk
Syst-Eur[29]	1997	Low risk	Unclear risk	Low risk	Low risk	Low risk	Low risk	Low risk
UKPDS[30]	1998	Low risk	Low risk	Low risk	Low risk	Low risk	Low risk	Low risk
PART-2[31]	2000	Low risk	Low risk	Low risk	Low risk	Low risk	Low risk	Low risk
PREVENT[32]	2000	Unclear risk	Unclear risk	Low risk	Low risk	Low risk	Unclear risk	Unclear risk
SCAT[33]	2000	Unclear risk	Unclear risk	Low risk	Low risk	Low risk	Low risk	Low risk
ABCD-HTN[34]	2000	Low risk	Low risk	Low risk	Unclear risk	Low risk	Low risk	Unclear risk
PROGRESS[35]	2001	Unclear risk	Unclear risk	Low risk	Low risk	Low risk	Low risk	Low risk
ABCD-NT[36]	2002	Unclear risk	Unclear risk	Low risk	Unclear risk	Low risk	Low risk	Low risk

Trial	Year	Random sequence generation	Allocation concealment	Blinding of participants/outcome assessment	Incomplete data	Selective reporting	Intention-to-treat analysis	Other sources of bias
AASK[37,38]	2002	Low risk	Low risk	Low risk	Low risk	Low risk	Low risk	Low risk
CHARM-Overall[39]	2003	Low risk	Low risk	Low risk	Low risk	Low risk	Low risk	Low risk
EUROPA[40]	2003	Unclear risk	Unclear risk	Low risk	Low risk	Unclear risk	Low risk	Low risk
NICOLE[41–43]	2003	Unclear risk	Unclear risk	Low risk	Low risk	Unclear risk	Low risk	Low risk
ACTION[44]	2004	Low risk	Low risk	Low risk	Low risk	Low risk	Low risk	Low risk
CAMELOT[45]	2004	Unclear risk	Low risk	Low risk	Low risk	Unclear risk	Low risk	Low risk
PREVEND IT[46]	2004	Low risk	Low risk	Low risk	Unclear risk	Unclear risk	Low risk	Low risk
ADVANCE[47]	2007	Low risk	Low risk	Low risk	Low risk	Unclear risk	Low risk	Low risk
Tepel M[48]	2008	Low risk	Low risk	Low risk	Low risk	Low risk	Low risk	Low risk
HYVET[49]	2008	Low risk	Low risk	Low risk	Low risk	Low risk	Low risk	Unclear risk
JATOS[50]	2008	Low risk	Low risk	Low risk	Low risk	Unclear risk	Low risk	Low risk
PATS[51]	2009	Low risk	Low risk	Low risk	Unclear risk	Unclear risk	Low risk	Low risk
ACCORD[52]	2010	Low risk	Low risk	Low risk	Low risk	Low risk	Low risk	Low risk
VALISH[53]	2010	Unclear risk	Low risk	Low risk	Low risk	Low risk	Low risk	Low risk
PARAMOUNT[54]	2012	Low risk	Low risk	Low risk	Unclear risk	Unclear risk	Unclear risk	Unclear risk
SPS3[55]	2013	Low risk	Low risk	Low risk	Low risk	Low risk	Low risk	Low risk
Wei et al.[56]	2013	Low risk	Unclear risk	Low risk	Unclear risk	Unclear risk	Low risk	Low risk
SPRINT[57]	2015	Low risk	Low risk	Low risk	Low risk	Low risk	Low risk	Low risk

* VA Cooperative Study 90-114 mmHg group

eTable 4. Description of Cardiovascular Disease, Coronary Heart Disease, Stroke, and Cardiovascular Disease Mortality Outcomes for All Included Trials

Study	Outcome
Major Cardiovascular Events	
HSCSG[12]	Stroke recurrence, congestive heart failure, probable myocardial infarction, certain myocardial infarction, sudden death
USPHSH Cooperative Study[13]	Stroke, fatal myocardial infarction, nonfatal myocardial infarction, sudden death
HDFP[14,15]	Cardiovascular disease mortality, nonfatal stroke, nonfatal myocardial infarction
ANBP1[16,17]	Stroke, fatal ischemic heart disease, nonfatal myocardial infarction, congestive cardiac failure
Oslo Study[18]	Stroke, definite myocardial infarction, coronary events without myocardial ischemia, angina pectoris with positive exercise electrocardiogram, sudden death
MRCWP[19]	Stroke, coronary events, other relevant deaths, deaths due to other cardiovascular causes
SHEP[23]	Definite nonfatal or fatal myocardial infarction, sudden cardiac death, rapid cardiac death, coronary artery bypass graft, angioplasty, nonfatal or fatal stroke, transient ischemic attack, aneurysm, endarterectomy
MRCWP Older Adults[24]	Fatal and nonfatal stroke, fatal and nonfatal coronary events, other cardiovascular events, including deaths due to hypertension and to rupture or dissection of an aortic aneurysm
TOMHS[26]	Coronary heart disease death, nonfatal myocardial infarction, surgery for aortic aneurysm, coronary artery bypass surgery, coronary artery angioplasty, thrombolytic therapy, hospitalization for angina, nonfatal stroke, other cardiovascular disease deaths
Syst-Eur[29]	Stroke, heart failure, myocardial infarction
PART-2[31]	Myocardial infarction, unstable angina, congestive heart failure, stroke, death from cardiovascular disease
PREVENT[32]	Fatal and nonfatal myocardial infarction, fatal and nonfatal stroke, other fatal vascular events
SCAT[33]	Myocardial infarction, stroke, hospitalization for angina
PROGRESS[35]	Fatal and nonfatal stroke, fatal and nonfatal myocardial infarction, death due to any vascular cause, including unexplained sudden death
ABCD-NT[36]	Myocardial infarction, cerebral vascular accident, congestive heart failure, cardiovascular death
AASK[37,38]	Cardiovascular mortality or first cardiovascular hospitalization for myocardial infarction, stroke, heart failure, or revascularization procedure
CHARM-Overall[39]	Cardiovascular death, hospital admission for chronic heart failure, myocardial infarction, stroke, coronary revascularization procedure
EUROPA[40]	Cardiovascular mortality, nonfatal myocardial infarction, stroke, heart failure requiring hospital admission
ACTION[44]	Cardiovascular or unknown death, myocardial infarction, new overt heart failure, debilitating stroke
CAMELOT[45]	Coronary revascularization, nonfatal myocardial infarction, stroke or TIA, cardiovascular death, hospitalization for congestive heart failure
PREVEND IT[46]	Cardiovascular mortality, hospitalization for nonfatal myocardial infarction, heart failure, and cerebrovascular accident

Study	Outcome
ADVANCE[47]	Cardiovascular death, nonfatal myocardial infarction, nonfatal stroke
HYVET[49]	Death from cardiovascular causes, stroke, myocardial infarction, heart failure
JATOS[50]	Cerebral infarction, cerebral hemorrhage, subarachnoid hemorrhage, myocardial infarction, congestive heart failure, sudden death
PATS[51]	Stroke, myocardial infarction, other cardiovascular deaths
ACCORD[52]	Nonfatal myocardial infarction, nonfatal stroke, death from cardiovascular causes
VALISH[53]	Cardiovascular death, nonfatal stroke, nonfatal myocardial infarction
PARAMOUNT[54]	Cardiovascular death, heart failure, acute coronary syndrome
SPS3[55]	Stroke, myocardial infarction
Wei et al.[56]	Fatal and nonfatal stroke, acute myocardial infarction, other cardiovascular deaths
SPRINT[57]	Myocardial infarction, acute coronary syndrome, stroke, heart failure, death from cardiovascular causes
Stroke	
VA Cooperative Study[11*]	Cerebrovascular accidents diagnosed clinically as thrombosis or hemorrhage
HSCSG[12]	Cerebrovascular episode lasting more than 24 hours, marked increase in frequency of TIAs, deterioration of more than eight points in the neurological score
HDFP[14,15]	Fatal and nonfatal stroke
ANBP1[16,17]	Thrombotic or hemorrhagic cerebrovascular disease
MRCWP[19]	Fatal and nonfatal stroke
SHEP[23]	Fatal and nonfatal stroke
MRCWP Older Adults[24]	Fatal and nonfatal stroke
Syst-Eur[29]	Fatal and nonfatal stroke
UKPDS[30]	Fatal and nonfatal stroke
PREVENT[32]	Fatal and nonfatal stroke
SCAT[33]	Fatal and nonfatal stroke
PROGRESS[35]	Fatal and nonfatal stroke, including ischemic stroke and cerebral hemorrhage
ABCD-NT[36]	Fatal and nonfatal cerebral vascular accident
AASK[37,38]	Fatal and nonfatal stroke
EUROPA[40]	Fatal and nonfatal stroke
ACTION[44]	Debilitating stroke
CAMELOT[45]	Fatal stroke, nonfatal stroke or TIA

Study	Outcome
PREVEND IT[46]	Cerebrovascular accident
ADVANCE[47]	Major cerebrovascular events defined as death due to cerebrovascular disease or nonfatal stroke
HYVET[49]	Fatal and nonfatal stroke
JATOS[50]	Fatal and nonfatal cerebral infarction, cerebral hemorrhage, subarachnoid hemorrhage
PATS[51]	Fatal and nonfatal stroke
ACCORD[52]	Fatal and nonfatal stroke
VALISH[53]	Fatal and nonfatal stroke
SPS3[55]	Ischemic stroke, intracranial hemorrhages, disabling strokes, including stroke deaths
Wei et al.[56]	Fatal and nonfatal hemorrhagic and ischemic stroke
SPRINT[57]	Fatal and nonfatal stroke
Coronary Heart Disease	
VA Cooperative Study[11*]	Fatal and nonfatal myocardial infarction or sudden death
HSCSG[12]	Probable Myocardial infarction, certain myocardial infarction, sudden death
USPHSH Cooperative Study[13]	Fatal myocardial infarction, nonfatal myocardial infarction, sudden death
HDFP[14,15]	Fatal coronary heart disease, nonfatal myocardial infarction
ANBP1[16,17]	Fatal ischemic heart disease, non-fatal myocardial infarction
Oslo Study[18]	Definite myocardial infarction, coronary events without myocardial ischemia, angina pectoris with positive exercise electrocardiogram, sudden death
MRCWP[19]	Coronary events, including sudden death thought to be due to a coronary cause, fatal myocardial infarction, nonfatal myocardial infarction
SHEP[23]	Definite nonfatal or fatal myocardial infarction, sudden cardiac death, rapid cardiac death, coronary artery bypass graft, angioplasty, aneurysm, endarterectomy
MRCWP Older Adults[24]	Sudden death thought to be due to a coronary cause, death known to be due to a myocardial infarction, nonfatal myocardial infarction
SAVE[25]	Recurrence of a fatal or nonfatal myocardial infarction
TOMHS[26]	Coronary heart disease death, nonfatal myocardial infarction, surgery for aortic aneurysm, coronary artery bypass surgery, coronary artery angioplasty, thrombolytic therapy, hospitalization for angina
Syst-Eur[29]	Fatal and nonfatal myocardial infarction
UKPDS[30]	Fatal and nonfatal myocardial infarction
PART-2[31]	Death from coronary heart disease or nonfatal myocardial infarction

Study	Outcome
PREVENT[32]	Fatal and nonfatal myocardial infarction
SCAT[33]	Fatal and nonfatal myocardial infarction
PROGRESS[35]	Coronary mortality and nonfatal myocardial infarction
ABCD-NT[36]	Fatal and nonfatal myocardial infarction
AASK[37,38]	Fatal and nonfatal myocardial infarction, revascularization procedures
EUROPA[40]	Fatal and nonfatal myocardial infarction
ADVANCE[47]	Major coronary events defined as death due to coronary heart disease, including sudden death, and nonfatal myocardial infarction
HYVET[49]	Fatal and nonfatal myocardial infarction
JATOS[50]	Fatal and nonfatal myocardial infarction, sudden death
ACCORD[52]	Fatal coronary events, nonfatal myocardial infarction, unstable angina
VALISH[53]	Fatal and nonfatal myocardial infarction, sudden death
Wei et al.[56]	Acute myocardial infarction
SPRINT[57]	Fatal and nonfatal myocardial infarction
Cardiovascular Disease Mortality	
VA Cooperative Study[11*]	Deaths due to hypertensive or atherosclerotic complications
HSCSG[12]	Fatal congestive heart failure, myocardial infarction, pulmonary embolism, other cardiovascular deaths, sudden death
HDFP[14,15]	Cardiovascular cause of death, including cerebrovascular disease, myocardial infarction, other ischemic heart disease, hypertensive heart disease, and other cardiovascular diseases
ANBP1[16,17]	Fatal cerebrovascular disease, ischemic heart disease, congestive cardiac failure, other cardiovascular disease deaths
Oslo Study[18]	Coronary deaths including sudden death, cerebrovascular deaths
MRCWP[19]	All deaths from cardiovascular causes
EWPHE[20]	Cerebrovascular, cardiac, and other cardiovascular causes of death
DAVIT II[22]	Cardiac death
SHEP[23]	Total cardiovascular deaths, including stroke, coronary heart disease, and other cardiovascular deaths
MRCWP Older Adults[24]	All cardiovascular deaths, including fatal stroke and fatal coronary events
SAVE[25]	Cardiovascular causes of death, including atherosclerotic heart disease, progressive heart failure, sudden death, acute myocardial infarction, and other cardiac or vascular deaths

Study	Outcome
Shanghai SPAMI[28]	Cardiac death
Syst-Eur[29]	All cardiovascular causes of death, including stroke, cardiac mortality, and coronary mortality
UKPDS[30]	Fatal stroke, fatal myocardial infarction, sudden death
PART-2[31]	All fatal cardiovascular events
SCAT[33]	Cardiac death
PROGRESS[35]	Death due to any vascular cause, including unexplained sudden death
ABCD-NT[36]	Cardiovascular death
AASK[37,38]	Cardiovascular mortality
CHARM-Overall[39]	All deaths except deaths with an established, unequivocal non-cardiovascular cause
EUROPA[40]	Cardiovascular mortality
ACTION[44]	Cardiovascular or unknown mortality
CAMELOT[45]	Cardiovascular death
PREVEND IT[46]	Cardiovascular mortality
ADVANCE[47]	Cardiovascular death
HYVET[49]	Death from cardiovascular causes
JATOS[50]	Fatal cerebral infarction, cerebral hemorrhage, subarachnoid hemorrhage, myocardial infarction, congestive heart failure, sudden death
PATS[51]	Fatal cardiovascular endpoints, including stroke, myocardial infarction, and other cardiovascular causes
ACCORD[52]	Deaths from cardiovascular causes, including myocardial infarction and stroke
VALISH[53]	Cardiovascular death
SPS3[55]	Vascular death
Wei et al.[56]	Cardiovascular deaths, including stroke, acute myocardial infarction, and heart failure
SPRINT[57]	Death from cardiovascular causes

* VA Cooperative Study 90-114 mmHg group

eTable 5. Hazard Ratios and 95% CIs for Major Cardiovascular Disease and Stroke Associated With More Intensive Reductions in Systolic Blood Pressure*

Major Cardiovascular Disease (31 trials)

Systolic blood pressure in more intensive groups, mmHg	Systolic blood pressure in less intensive groups, mmHg: <120	120-124	125-129	130-134	135-139	140-144	145-149	150-154	155-159	≥160	Systolic blood pressure in more intensive groups, mmHg
≥160		1.32 [1.00 - 1.79]	1.08 [0.83 - 1.37]	0.93 [0.74 - 1.19]	0.90 [0.68 - 1.20]	0.77 [0.60 - 1.02]	0.72 [0.53 - 1.02]	0.61 [0.43 - 0.88]	0.54 [0.40 - 0.76]	0.48 [0.33 - 0.70]	<120
155-159	0.94 [0.58 - 1.54]		0.82 [0.67 - 0.97]	0.71 [0.60 - 0.83]	0.68 [0.55 - 0.85]	0.58 [0.48 - 0.72]	0.55 [0.42 - 0.72]	0.46 [0.34 - 0.63]	0.41 [0.32 - 0.54]	0.36 [0.26 - 0.51]	120-124
150-154	0.73 [0.50 - 1.07]	0.92 [0.53 - 1.60]		0.87 [0.77 - 0.99]	0.83 [0.71 - 1.01]	0.71 [0.61 - 0.86]	0.67 [0.53 - 0.87]	0.56 [0.43 - 0.76]	0.51 [0.40 - 0.65]	0.44 [0.33 - 0.61]	125-129
145-149	0.69 [0.31 - 1.39]	0.86 [0.40 - 1.75]	0.93 [0.43 - 1.89]		0.96 [0.83 - 1.14]	0.83 [0.74 - 0.94]	0.78 [0.63 - 0.98]	0.65 [0.51 - 0.85]	0.58 [0.48 - 0.72]	0.51 [0.39 - 0.69]	130-134
140-144	0.53 [0.34 - 0.80]	0.66 [0.44 - 0.97]	0.72 [0.48 - 1.04]	0.76 [0.42 - 1.47]		0.85 [0.71 - 1.03]	0.81 [0.68 - 0.96]	0.68 [0.51 - 0.90]	0.60 [0.47 - 0.78]	0.53 [0.39 - 0.73]	135-139
135-139	0.47 [0.24 - 0.85]	0.58 [0.31 - 1.05]	0.64 [0.34 - 1.14]	0.68 [0.46 - 1.01]	0.88 [0.54 - 1.41]		0.94 [0.74 - 1.20]	0.79 [0.63 - 0.99]	0.70 [0.60 - 0.84]	0.62 [0.48 - 0.80]	140-144
130-134	0.39 [0.23 - 0.63]	0.49 [0.29 - 0.79]	0.53 [0.32 - 0.84]	0.57 [0.32 - 1.02]	0.74 [0.54 - 1.00]	0.83 [0.56 - 1.28]		0.83 [0.60 - 1.18]	0.75 [0.56 - 1.01]	0.66 [0.47 - 0.94]	145-149
125-129	0.34 [0.17 - 0.61]	0.43 [0.22 - 0.75]	0.47 [0.24 - 0.81]	0.50 [0.27 - 0.85]	0.65 [0.38 - 0.99]	0.74 [0.47 - 1.08]	0.88 [0.57 - 1.25]		0.90 [0.68 - 1.19]	0.79 [0.66 - 0.94]	150-154
120-124	0.27 [0.12 - 0.51]	0.34 [0.15 - 0.64]	0.36 [0.17 - 0.68]	0.39 [0.18 - 0.76]	0.51 [0.26 - 0.87]	0.57 [0.30 - 1.00]	0.69 [0.40 - 1.07]	0.78 [0.45 - 1.32]		0.88 [0.65 - 1.19]	155-159
<120	0.22 [0.09 - 0.51]	0.28 [0.12 - 0.64]	0.30 [0.13 - 0.69]	0.32 [0.13 - 0.79]	0.42 [0.19 - 0.89]	0.48 [0.22 - 1.06]	0.57 [0.29 - 1.12]	0.65 [0.31 - 1.47]	0.83 [0.38 - 2.00]		≥160
	≥160	155-159	150-154	145-149	140-144	135-139	130-134	125-129	120-124	<120	

Systolic blood pressure in less intensive groups, mmHg

Stroke (27 trials)

* Hazard ratios and 95% confidence intervals for major cardiovascular disease in upper cells (blue) and stroke in lower cells (red). Cells are shaded according to hazard ratios, from light (higher hazard ratios) to dark (lower hazard ratios).

eTable 6. Hazard Ratios and 95% CIs for Coronary Heart Disease Associated With More Intensive Reductions in Systolic Blood Pressure*

Coronary Heart Disease (27 trials)										
Systolic blood pressure in less intensive groups, mmHg										
<120	120-124	125-129	130-134	135-139	140-144	145-149	150-154	155-159	≥160	Systolic blood pressure in more intensive groups, mmHg
	1.14 [0.67 - 1.89]	0.98 [0.73 - 1.30]	0.89 [0.62 - 1.28]	1.20 [0.68 - 2.17]	0.78 [0.50 - 1.25]	1.18 [0.65 - 2.17]	0.66 [0.38 - 1.16]	0.63 [0.37 - 1.10]	0.53 [0.30 - 0.95]	<120
		0.86 [0.56 - 1.33]	0.79 [0.59 - 1.06]	1.06 [0.64 - 1.78]	0.69 [0.50 - 0.97]	1.04 [0.63 - 1.75]	0.58 [0.36 - 0.95]	0.55 [0.36 - 0.87]	0.47 [0.29 - 0.78]	120-124
			0.91 [0.70 - 1.20]	1.23 [0.75 - 2.04]	0.80 [0.56 - 1.16]	1.20 [0.72 - 2.08]	0.67 [0.42 - 1.12]	0.64 [0.42 - 1.05]	0.54 [0.33 - 0.92]	125-129
				1.35 [0.88 - 2.09]	0.88 [0.72 - 1.08]	1.32 [0.85 - 2.07]	0.74 [0.51 - 1.11]	0.70 [0.51 - 1.02]	0.59 [0.39 - 0.91]	130-134
					0.65 [0.41 - 1.02]	0.98 [0.75 - 1.32]	0.55 [0.31 - 0.97]	0.52 [0.31 - 0.89]	0.44 [0.25 - 0.80]	135-139
						1.51 [0.96 - 2.38]	0.84 [0.59 - 1.21]	0.80 [0.61 - 1.07]	0.68 [0.46 - 1.01]	140-144
							0.56 [0.32 - 0.99]	0.53 [0.31 - 0.91]	0.45 [0.25 - 0.81]	145-149
								0.95 [0.61 - 1.51]	0.80 [0.63 - 1.04]	150-154
									0.84 [0.52 - 1.37]	155-159
										≥160

* Cells are shaded according to hazard ratios, from light (higher hazard ratios) to dark (lower hazard ratios).

eTable 7. Hazard Ratios and 95% CIs for All-Cause Mortality and Cardiovascular Disease Mortality Associated With More Intensive Reductions in Systolic Blood Pressure*

All-cause Mortality (41 trials)

Systolic blood pressure in more intensive groups, mmHg \ Systolic blood pressure in less intensive groups, mmHg	<120	120-124	125-129	130-134	135-139	140-144	145-149	150-154	155-159	≥160
≥160		1.27 [0.98 - 1.67]	0.93 [0.76 - 1.18]	0.93 [0.75 - 1.16]	1.00 [0.78 - 1.32]	0.75 [0.58 - 0.95]	0.90 [0.65 - 1.25]	0.65 [0.47 - 0.89]	0.63 [0.44 - 0.85]	0.60 [0.42 - 0.84]
155-159	0.85 [0.48 - 1.59]		0.74 [0.57 - 0.97]	0.73 [0.58 - 0.93]	0.79 [0.59 - 1.05]	0.59 [0.45 - 0.77]	0.71 [0.50 - 1.00]	0.51 [0.36 - 0.71]	0.49 [0.34 - 0.67]	0.47 [0.32 - 0.67]
150-154	0.80 [0.57 - 1.11]	0.95 [0.52 - 1.59]		0.99 [0.83 - 1.18]	1.08 [0.88 - 1.30]	0.81 [0.65 - 0.95]	0.96 [0.72 - 1.27]	0.70 [0.51 - 0.91]	0.67 [0.49 - 0.85]	0.64 [0.46 - 0.86]
145-149	0.47 [0.23 - 0.88]	0.56 [0.26 - 0.99]	0.59 [0.29 - 1.06]		1.08 [0.90 - 1.29]	0.82 [0.68 - 0.93]	0.97 [0.75 - 1.26]	0.71 [0.53 - 0.90]	0.68 [0.51 - 0.85]	0.65 [0.47 - 0.85]
140-144	0.63 [0.40 - 0.98]	0.74 [0.49 - 1.06]	0.78 [0.53 - 1.16]	1.32 [0.83 - 2.38]		0.75 [0.61 - 0.89]	0.90 [0.73 - 1.10]	0.65 [0.48 - 0.85]	0.63 [0.46 - 0.81]	0.60 [0.43 - 0.80]
135-139	0.40 [0.22 - 0.66]	0.47 [0.26 - 0.74]	0.50 [0.29 - 0.79]	0.85 [0.57 - 1.28]	0.64 [0.43 - 0.85]		1.20 [0.93 - 1.59]	0.87 [0.69 - 1.08]	0.83 [0.67 - 1.01]	0.80 [0.62 - 1.03]
130-134	0.51 [0.31 - 0.84]	0.60 [0.36 - 0.95]	0.64 [0.40 - 1.02]	1.07 [0.68 - 1.93]	0.81 [0.62 - 1.08]	1.27 [0.95 - 1.91]		0.72 [0.50 - 1.01]	0.69 [0.48 - 0.95]	0.67 [0.45 - 0.94]
125-129	0.45 [0.25 - 0.76]	0.53 [0.29 - 0.85]	0.56 [0.33 - 0.92]	0.94 [0.57 - 1.69]	0.71 [0.49 - 1.00]	1.12 [0.79 - 1.69]	0.88 [0.63 - 1.18]		0.96 [0.71 - 1.29]	0.92 [0.77 - 1.09]
120-124	0.34 [0.17 - 0.76]	0.40 [0.20 - 0.86]	0.43 [0.22 - 0.93]	0.73 [0.36 - 1.72]	0.55 [0.30 - 1.07]	0.86 [0.47 - 1.83]	0.67 [0.40 - 1.22]	0.76 [0.42 - 1.54]		0.96 [0.70 - 1.33]
<120	0.41 [0.21 - 0.81]	0.49 [0.25 - 0.91]	0.52 [0.28 - 0.98]	0.87 [0.47 - 1.82]	0.66 [0.39 - 1.11]	1.03 [0.63 - 1.89]	0.81 [0.51 - 1.28]	0.92 [0.60 - 1.52]	1.20 [0.56 - 2.38]	
	≥160	155-159	150-154	145-149	140-144	135-139	130-134	125-129	120-124	<120

Cardiovascular Disease Mortality (33 trials)

* Hazard ratios and 95% confidence intervals for all-cause mortality in upper cells (blue) and cardiovascular disease mortality in lower cells (red). Cells are shaded according to hazard ratios, from light (higher hazard ratios) to dark (lower hazard ratios).

eTable 8. Hazard Ratios and 95% CIs for Major Cardiovascular Disease and Stroke Associated With More Intensive Reductions in Systolic Blood Pressure in Sensitivity Analysis Excluding SPRINT*

Major Cardiovascular Disease (30 trials)

Systolic blood pressure in more intensive groups, mmHg	Systolic blood pressure in less intensive groups, mmHg: <120	120-124	125-129	130-134	135-139	140-144	145-149	150-154	155-159	≥160	Systolic blood pressure in more intensive groups, mmHg
≥160		1.41 [1.02 - 1.96]	1.09 [0.84 - 1.39]	0.93 [0.73 - 1.19]	0.89 [0.68 - 1.22]	0.76 [0.59 - 1.02]	0.72 [0.53 - 1.02]	0.60 [0.43 - 0.88]	0.54 [0.40 - 0.76]	0.48 [0.33 - 0.70]	<120
155-159	0.80 [0.44 - 1.41]		0.78 [0.61 - 0.96]	0.66 [0.52 - 0.83]	0.64 [0.49 - 0.84]	0.54 [0.42 - 0.71]	0.51 [0.38 - 0.71]	0.43 [0.31 - 0.61]	0.38 [0.28 - 0.53]	0.34 [0.24 - 0.50]	120-124
150-154	0.73 [0.50 - 1.06]	0.92 [0.53 - 1.61]		0.85 [0.75 - 0.99]	0.83 [0.70 - 1.00]	0.70 [0.60 - 0.85]	0.66 [0.53 - 0.86]	0.56 [0.42 - 0.76]	0.50 [0.40 - 0.65]	0.44 [0.33 - 0.61]	125-129
145-149	0.68 [0.31 - 1.41]	0.85 [0.40 - 1.75]	0.93 [0.44 - 1.89]		0.96 [0.83 - 1.15]	0.83 [0.74 - 0.94]	0.78 [0.63 - 0.98]	0.65 [0.51 - 0.85]	0.58 [0.48 - 0.73]	0.52 [0.39 - 0.69]	130-134
140-144	0.53 [0.34 - 0.79]	0.66 [0.44 - 0.97]	0.72 [0.48 - 1.04]	0.77 [0.42 - 1.47]		0.85 [0.70 - 1.03]	0.81 [0.68 - 0.96]	0.67 [0.50 - 0.91]	0.60 [0.47 - 0.78]	0.53 [0.39 - 0.73]	135-139
135-139	0.46 [0.24 - 0.85]	0.58 [0.30 - 1.05]	0.63 [0.33 - 1.14]	0.68 [0.46 - 1.01]	0.88 [0.54 - 1.41]		0.94 [0.74 - 1.20]	0.79 [0.63 - 0.99]	0.70 [0.60 - 0.84]	0.62 [0.48 - 0.81]	140-144
130-134	0.39 [0.23 - 0.65]	0.50 [0.29 - 0.81]	0.54 [0.33 - 0.86]	0.58 [0.33 - 1.04]	0.75 [0.54 - 1.02]	0.85 [0.56 - 1.30]		0.83 [0.60 - 1.18]	0.75 [0.56 - 1.01]	0.66 [0.46 - 0.94]	145-149
125-129	0.33 [0.16 - 0.59]	0.42 [0.21 - 0.73]	0.46 [0.23 - 0.79]	0.49 [0.26 - 0.83]	0.64 [0.37 - 0.97]	0.72 [0.45 - 1.05]	0.85 [0.54 - 1.20]		0.89 [0.68 - 1.19]	0.79 [0.66 - 0.94]	150-154
120-124	0.19 [0.08 - 0.44]	0.24 [0.10 - 0.55]	0.26 [0.11 - 0.60]	0.28 [0.12 - 0.65]	0.36 [0.17 - 0.76]	0.41 [0.19 - 0.88]	0.49 [0.23 - 0.97]	0.57 [0.28 - 1.18]		0.88 [0.65 - 1.20]	155-159
<120	0.23 [0.09 - 0.52]	0.28 [0.12 - 0.66]	0.31 [0.13 - 0.70]	0.33 [0.14 - 0.81]	0.43 [0.20 - 0.91]	0.49 [0.22 - 1.09]	0.57 [0.29 - 1.12]	0.68 [0.32 - 1.56]	1.18 [0.45 - 3.23]		≥160
	≥160	155-159	150-154	145-149	140-144	135-139	130-134	125-129	120-124	<120	

Systolic blood pressure in less intensive groups, mmHg

Stroke (26 trials)

* Hazard ratios and 95% confidence intervals for major cardiovascular disease in upper cells (blue) and stroke in lower cells (red). Cells are shaded according to hazard ratios, from light (higher hazard ratios) to dark (lower hazard ratios).

eTable 9. Hazard Ratios and 95% CIs for Coronary Heart Disease Associated With More Intensive Reductions in Systolic Blood Pressure in Sensitivity Analysis Excluding SPRINT*

Coronary Heart Disease (26 trials)										
Systolic blood pressure in less intensive groups, mmHg										
<120	120-124	125-129	130-134	135-139	140-144	145-149	150-154	155-159	≥160	
	1.12 [0.63 - 1.92]	0.98 [0.72 - 1.32]	0.88 [0.61 - 1.32]	1.22 [0.67 - 2.27]	0.79 [0.47 - 1.33]	1.18 [0.63 - 2.27]	0.64 [0.36 - 1.16]	0.65 [0.37 - 1.20]	0.51 [0.28 - 0.93]	<120
		0.88 [0.54 - 1.45]	0.80 [0.52 - 1.20]	1.10 [0.59 - 2.00]	0.71 [0.43 - 1.14]	1.06 [0.56 - 1.96]	0.58 [0.32 - 1.02]	0.59 [0.33 - 1.03]	0.46 [0.25 - 0.83]	120-124
			0.90 [0.69 - 1.20]	1.25 [0.76 - 2.08]	0.81 [0.55 - 1.22]	1.20 [0.71 - 2.13]	0.65 [0.40 - 1.10]	0.67 [0.42 - 1.12]	0.52 [0.31 - 0.88]	125-129
				1.37 [0.89 - 2.13]	0.88 [0.71 - 1.12]	1.33 [0.86 - 2.08]	0.72 [0.50 - 1.08]	0.74 [0.53 - 1.08]	0.57 [0.38 - 0.87]	130-134
					0.65 [0.42 - 0.99]	0.96 [0.72 - 1.33]	0.52 [0.30 - 0.91]	0.53 [0.32 - 0.90]	0.42 [0.24 - 0.74]	135-139
						1.49 [0.97 - 2.33]	0.81 [0.58 - 1.15]	0.83 [0.64 - 1.11]	0.65 [0.44 - 0.94]	140-144
							0.54 [0.31 - 0.93]	0.56 [0.34 - 0.93]	0.43 [0.25 - 0.76]	145-149
								1.02 [0.68 - 1.56]	0.79 [0.62 - 1.03]	150-154
									0.78 [0.50 - 1.19]	155-159
										≥160

Systolic blood pressure in more intensive groups, mmHg

* Cells are shaded according to hazard ratios, from light (higher hazard ratios) to dark (lower hazard ratios).

eTable 10. Hazard Ratios and 95% CIs for All-Cause Mortality and Cardiovascular Disease Mortality Associated With More Intensive Reductions in Systolic Blood Pressure in Sensitivity Analysis Excluding SPRINT*

All-cause Mortality (40 trials)

Systolic blood pressure in more intensive groups, mmHg	Systolic blood pressure in less intensive groups, mmHg: <120	120-124	125-129	130-134	135-139	140-144	145-149	150-154	155-159	≥160	Systolic blood pressure in more intensive groups, mmHg
≥160		1.28 [0.91 - 1.82]	0.93 [0.75 - 1.20]	0.92 [0.74 - 1.19]	0.99 [0.76 - 1.33]	0.75 [0.56 - 0.97]	0.89 [0.64 - 1.28]	0.65 [0.45 - 0.91]	0.62 [0.43 - 0.85]	0.60 [0.40 - 0.85]	<120
155-159	0.85 [0.48 - 1.56]		0.72 [0.51 - 1.06]	0.71 [0.50 - 1.05]	0.77 [0.52 - 1.16]	0.58 [0.39 - 0.85]	0.69 [0.45 - 1.10]	0.50 [0.32 - 0.78]	0.48 [0.31 - 0.74]	0.46 [0.29 - 0.73]	120-124
150-154	0.80 [0.57 - 1.10]	0.94 [0.53 - 1.59]		0.99 [0.83 - 1.19]	1.06 [0.87 - 1.32]	0.80 [0.64 - 0.95]	0.96 [0.71 - 1.28]	0.69 [0.50 - 0.92]	0.66 [0.48 - 0.86]	0.64 [0.45 - 0.87]	125-129
145-149	0.47 [0.23 - 0.87]	0.56 [0.26 - 0.99]	0.60 [0.29 - 1.05]		1.08 [0.89 - 1.30]	0.81 [0.67 - 0.93]	0.97 [0.74 - 1.27]	0.70 [0.52 - 0.90]	0.68 [0.49 - 0.85]	0.65 [0.47 - 0.85]	130-134
140-144	0.63 [0.40 - 0.97]	0.74 [0.49 - 1.06]	0.79 [0.54 - 1.16]	1.32 [0.84 - 2.38]		0.75 [0.60 - 0.89]	0.90 [0.72 - 1.11]	0.65 [0.47 - 0.86]	0.62 [0.45 - 0.81]	0.60 [0.42 - 0.81]	135-139
135-139	0.40 [0.22 - 0.66]	0.48 [0.26 - 0.74]	0.50 [0.29 - 0.79]	0.85 [0.57 - 1.28]	0.64 [0.43 - 0.85]		1.20 [0.92 - 1.64]	0.87 [0.69 - 1.09]	0.83 [0.66 - 1.02]	0.80 [0.61 - 1.04]	140-144
130-134	0.51 [0.31 - 0.83]	0.60 [0.36 - 0.93]	0.63 [0.40 - 1.00]	1.06 [0.68 - 1.92]	0.81 [0.61 - 1.06]	1.25 [0.94 - 1.89]		0.72 [0.49 - 1.02]	0.69 [0.47 - 0.96]	0.67 [0.44 - 0.96]	145-149
125-129	0.46 [0.26 - 0.76]	0.54 [0.30 - 0.88]	0.57 [0.34 - 0.93]	0.96 [0.58 - 1.75]	0.73 [0.50 - 1.02]	1.14 [0.81 - 1.72]	0.91 [0.65 - 1.20]		0.95 [0.69 - 1.30]	0.92 [0.76 - 1.11]	150-154
120-124	0.52 [0.18 - 1.56]	0.62 [0.22 - 1.79]	0.66 [0.24 - 1.92]	1.12 [0.40 - 3.45]	0.84 [0.32 - 2.27]	1.32 [0.50 - 3.70]	1.04 [0.41 - 2.78]	1.15 [0.45 - 3.13]		0.96 [0.69 - 1.35]	155-159
<120	0.41 [0.22 - 0.80]	0.49 [0.25 - 0.91]	0.52 [0.28 - 0.98]	0.87 [0.48 - 1.82]	0.66 [0.40 - 1.11]	1.02 [0.64 - 1.89]	0.81 [0.52 - 1.30]	0.90 [0.59 - 1.47]	0.79 [0.27 - 2.17]		≥160
	≥160	155-159	150-154	145-149	140-144	135-139	130-134	125-129	120-124	<120	

Systolic blood pressure in less intensive groups, mmHg

Cardiovascular Disease Mortality (32 trials)

* Hazard ratios and 95% confidence intervals for all-cause mortality in upper cells (blue) and cardiovascular disease mortality in lower cells (red). Cells are shaded according to hazard ratios, from light (higher hazard ratios) to dark (lower hazard ratios).

eTable 11. Hazard Ratios and 95% CIs for Major Cardiovascular Disease and Stroke Associated With More Intensive Reductions in Systolic Blood Pressure in Sensitivity Analysis Excluding Trials With High or Unclear Risk of Bias*

Major Cardiovascular Disease (29 trials)

Systolic blood pressure in more intensive groups, mmHg	Systolic blood pressure in less intensive groups, mmHg: <120	120-124	125-129	130-134	135-139	140-144	145-149	150-154	155-159	≥160	Systolic blood pressure in more intensive groups, mmHg
≥160		1.33 [1.00 - 1.81]	1.08 [0.83 - 1.38]	0.93 [0.73 - 1.20]	0.90 [0.68 - 1.21]	0.77 [0.59 - 1.02]	0.72 [0.52 - 1.02]	0.61 [0.43 - 0.88]	0.54 [0.40 - 0.76]	0.48 [0.33 - 0.71]	<120
155-159	0.80 [0.43 - 1.44]		0.81 [0.65 - 0.98]	0.70 [0.58 - 0.83]	0.67 [0.54 - 0.85]	0.58 [0.47 - 0.72]	0.54 [0.41 - 0.72]	0.45 [0.33 - 0.63]	0.41 [0.31 - 0.54]	0.36 [0.26 - 0.50]	120-124
150-154	0.73 [0.49 - 1.08]	0.92 [0.52 - 1.64]		0.86 [0.76 - 1.00]	0.83 [0.71 - 1.01]	0.71 [0.61 - 0.86]	0.67 [0.53 - 0.87]	0.56 [0.43 - 0.77]	0.50 [0.40 - 0.66]	0.44 [0.33 - 0.62]	125-129
145-149	0.69 [0.30 - 1.44]	0.86 [0.39 - 1.79]	0.94 [0.43 - 1.93]		0.96 [0.83 - 1.14]	0.83 [0.74 - 0.94]	0.78 [0.62 - 0.98]	0.65 [0.51 - 0.86]	0.58 [0.48 - 0.73]	0.51 [0.39 - 0.69]	130-134
140-144	0.53 [0.33 - 0.80]	0.66 [0.44 - 0.99]	0.72 [0.48 - 1.06]	0.76 [0.41 - 1.49]		0.86 [0.71 - 1.04]	0.81 [0.67 - 0.96]	0.67 [0.50 - 0.91]	0.60 [0.47 - 0.78]	0.53 [0.39 - 0.74]	135-139
135-139	0.47 [0.23 - 0.87]	0.59 [0.30 - 1.08]	0.64 [0.33 - 1.16]	0.68 [0.45 - 1.03]	0.89 [0.53 - 1.43]		0.94 [0.73 - 1.21]	0.79 [0.63 - 1.00]	0.71 [0.60 - 0.84]	0.62 [0.48 - 0.81]	140-144
130-134	0.39 [0.23 - 0.64]	0.49 [0.29 - 0.81]	0.53 [0.32 - 0.86]	0.57 [0.32 - 1.05]	0.75 [0.54 - 1.02]	0.84 [0.55 - 1.31]		0.84 [0.60 - 1.18]	0.75 [0.56 - 1.02]	0.66 [0.46 - 0.95]	145-149
125-129	0.34 [0.16 - 0.61]	0.43 [0.21 - 0.76]	0.47 [0.23 - 0.82]	0.50 [0.26 - 0.86]	0.65 [0.37 - 1.00]	0.73 [0.45 - 1.07]	0.88 [0.54 - 1.25]		0.90 [0.67 - 1.19]	0.79 [0.66 - 0.94]	150-154
120-124	0.26 [0.11 - 0.51]	0.32 [0.14 - 0.63]	0.35 [0.15 - 0.68]	0.37 [0.16 - 0.75]	0.49 [0.24 - 0.86]	0.55 [0.27 - 0.98]	0.66 [0.35 - 1.06]	0.75 [0.41 - 1.30]		0.88 [0.65 - 1.20]	155-159
<120	0.22 [0.09 - 0.53]	0.28 [0.11 - 0.67]	0.31 [0.13 - 0.72]	0.33 [0.13 - 0.83]	0.43 [0.19 - 0.92]	0.48 [0.21 - 1.10]	0.57 [0.28 - 1.16]	0.66 [0.31 - 1.56]	0.87 [0.39 - 2.29]		≥160
	≥160	155-159	150-154	145-149	140-144	135-139	130-134	125-129	120-124	<120	

Systolic blood pressure in less intensive groups, mmHg

Stroke (26 trials)

* Hazard ratios and 95% confidence intervals for major cardiovascular disease in upper cells (blue) and stroke in lower cells (red). Cells are shaded according to hazard ratios, from light (higher hazard ratios) to dark (lower hazard ratios). Trials excluded in the analysis of major cardiovascular events include PREVENT[32] and PARAMOUNT.[54] Trials excluded in the analysis of stroke include PREVENT.[32]

eTable 12. Hazard Ratios and 95% CIs for Coronary Heart Disease Associated With More Intensive Reductions in Systolic Blood Pressure In Sensitivity Analysis Excluding Trials With High or Unclear Risk of Bias*

Coronary Heart Disease (26 trials)										
Systolic blood pressure in less intensive groups, mmHg										
<120	120-124	125-129	130-134	135-139	140-144	145-149	150-154	155-159	≥160	Systolic blood pressure in more intensive groups, mmHg
	1.26 [0.68 - 2.27]	0.99 [0.73 - 1.33]	0.92 [0.62 - 1.38]	1.25 [0.68 - 2.30]	0.82 [0.50 - 1.35]	1.23 [0.65 - 2.34]	0.68 [0.38 - 1.24]	0.66 [0.38 - 1.19]	0.55 [0.30 - 1.01]	<120
		0.79 [0.48 - 1.31]	0.74 [0.53 - 1.04]	1.00 [0.58 - 1.72]	0.65 [0.46 - 0.94]	0.98 [0.58 - 1.68]	0.55 [0.33 - 0.91]	0.52 [0.33 - 0.84]	0.44 [0.26 - 0.75]	120-124
			0.93 [0.71 - 1.26]	1.27 [0.76 - 2.13]	0.82 [0.57 - 1.23]	1.25 [0.73 - 2.16]	0.69 [0.43 - 1.17]	0.66 [0.42 - 1.11]	0.55 [0.33 - 0.95]	125-129
				1.35 [0.88 - 2.11]	0.88 [0.73 - 1.09]	1.33 [0.86 - 2.08]	0.74 [0.51 - 1.12]	0.71 [0.51 - 1.03]	0.59 [0.39 - 0.91]	130-134
					0.65 [0.41 - 1.02]	0.98 [0.74 - 1.33]	0.55 [0.31 - 0.97]	0.52 [0.31 - 0.90]	0.44 [0.25 - 0.80]	135-139
						1.51 [0.97 - 2.38]	0.84 [0.59 - 1.22]	0.80 [0.61 - 1.08]	0.67 [0.45 - 1.01]	140-144
							0.55 [0.32 - 0.99]	0.53 [0.31 - 0.91]	0.44 [0.25 - 0.81]	145-149
								0.96 [0.60 - 1.53]	0.80 [0.62 - 1.04]	150-154
									0.83 [0.51 - 1.37]	155-159
										≥160

* Cells are shaded according to hazard ratios, from light (higher hazard ratios) to dark (lower hazard ratios). Trials excluded in the analysis of coronary heart disease include PREVENT.[32]

eTable 13. Hazard Ratios and 95% CIs for All-Cause Mortality and Cardiovascular Disease Mortality Associated With More Intensive Reductions in Systolic Blood Pressure in Sensitivity Analysis Excluding Trials With High or Unclear Risk of Bias*

All-cause Mortality (37 trials)

Systolic blood pressure in more intensive groups, mmHg	Systolic blood pressure in less intensive groups, mmHg: <120	120-124	125-129	130-134	135-139	140-144	145-149	150-154	155-159	≥160	Systolic blood pressure in more intensive groups, mmHg
≥160		1.27 [1.00 - 1.61]	0.93 [0.77 - 1.12]	0.92 [0.77 - 1.12]	0.94 [0.75 - 1.18]	0.78 [0.63 - 0.96]	0.85 [0.64 - 1.13]	0.67 [0.50 - 0.89]	0.65 [0.49 - 0.85]	0.62 [0.45 - 0.85]	<120
155-159	0.85 [0.58 - 1.25]		0.73 [0.58 - 0.93]	0.73 [0.59 - 0.90]	0.74 [0.57 - 0.96]	0.61 [0.48 - 0.78]	0.67 [0.49 - 0.91]	0.53 [0.39 - 0.72]	0.51 [0.38 - 0.68]	0.49 [0.35 - 0.68]	120-124
150-154	0.84 [0.67 - 1.05]	0.99 [0.70 - 1.38]		1.00 [0.86 - 1.16]	1.02 [0.85 - 1.20]	0.84 [0.71 - 0.98]	0.92 [0.71 - 1.17]	0.73 [0.56 - 0.92]	0.70 [0.55 - 0.88]	0.67 [0.50 - 0.88]	125-129
145-149	0.61 [0.39 - 0.95]	0.72 [0.48 - 1.07]	0.72 [0.48 - 1.10]		1.02 [0.86 - 1.19]	0.85 [0.74 - 0.95]	0.93 [0.72 - 1.16]	0.73 [0.58 - 0.91]	0.70 [0.56 - 0.86]	0.68 [0.51 - 0.87]	130-134
140-144	0.65 [0.47 - 0.88]	0.77 [0.60 - 0.97]	0.77 [0.60 - 0.99]	1.07 [0.77 - 1.49]		0.83 [0.70 - 0.98]	0.90 [0.75 - 1.08]	0.71 [0.55 - 0.92]	0.69 [0.54 - 0.87]	0.66 [0.50 - 0.88]	135-139
135-139	0.52 [0.36 - 0.75]	0.62 [0.44 - 0.84]	0.62 [0.45 - 0.86]	0.86 [0.66 - 1.10]	0.80 [0.64 - 0.99]		1.10 [0.86 - 1.39]	0.86 [0.71 - 1.05]	0.83 [0.70 - 0.98]	0.80 [0.63 - 1.01]	140-144
130-134	0.55 [0.39 - 0.77]	0.65 [0.49 - 0.85]	0.65 [0.50 - 0.87]	0.90 [0.66 - 1.26]	0.84 [0.73 - 0.99]	1.05 [0.87 - 1.32]		0.79 [0.58 - 1.07]	0.76 [0.57 - 1.03]	0.73 [0.52 - 1.02]	145-149
125-129	0.51 [0.35 - 0.73]	0.60 [0.43 - 0.82]	0.60 [0.44 - 0.84]	0.84 [0.59 - 1.19]	0.78 [0.63 - 0.97]	0.97 [0.77 - 1.25]	0.93 [0.76 - 1.11]		0.96 [0.74 - 1.25]	0.93 [0.78 - 1.10]	150-154
120-124	0.35 [0.21 - 0.60]	0.41 [0.26 - 0.68]	0.41 [0.26 - 0.70]	0.57 [0.35 - 0.98]	0.53 [0.35 - 0.84]	0.67 [0.43 - 1.08]	0.63 [0.43 - 0.96]	0.68 [0.44 - 1.12]		0.96 [0.72 - 1.29]	155-159
<120	0.44 [0.29 - 0.68]	0.52 [0.36 - 0.76]	0.52 [0.36 - 0.78]	0.72 [0.49 - 1.10]	0.67 [0.51 - 0.93]	0.84 [0.62 - 1.20]	0.80 [0.62 - 1.06]	0.86 [0.69 - 1.14]	1.26 [0.77 - 2.03]		≥160
	≥160	155-159	150-154	145-149	140-144	135-139	130-134	125-129	120-124	<120	

Systolic blood pressure in less intensive groups, mmHg

Cardiovascular Disease Mortality (31 trials)

* Hazard ratios and 95% confidence intervals for all-cause mortality in upper cells (blue) and cardiovascular disease mortality in lower cells (red). Cells are shaded according to hazard ratios, from light (higher hazard ratios) to dark (lower hazard ratios). Trials excluded in the analysis of all-cause mortality include EWPHE[20], Shanghai SPAMI[28], PREVENT[32] and PARAMOUNT.[54] Trials excluded in the analysis of cardiovascular disease mortality include EWPHE[20] and Shanghai SPAMI.[28]

eTable 14. Model Fit Characteristics for Major Cardiovascular Disease

SBP Treatment Group (mmHg)	Fixed Effects Model Treatment Effects					Random Effects Model Treatment Effects					Baseline Risk Adjusted Model Treatment Effects				
	Mean	SD	Median	2.5%	97.5%	Mean	SD	Median	2.5%	97.5%	Mean	SD	Median	2.5%	97.5%
<120	-0.059	0.061	-0.059	-0.180	0.060	-0.060	0.104	-0.060	-0.268	0.149	-0.066	0.118	-0.066	-0.303	0.172
120-124	-0.340	0.063	-0.340	-0.464	-0.216	-0.346	0.082	-0.345	-0.509	-0.187	-0.347	0.084	-0.347	-0.518	-0.182
125-129	-0.147	0.027	-0.147	-0.201	-0.093	-0.135	0.051	-0.136	-0.233	-0.028	-0.141	0.066	-0.143	-0.266	-0.005
135-139	0.061	0.053	0.061	-0.043	0.165	0.042	0.076	0.044	-0.116	0.187	0.036	0.079	0.039	-0.128	0.187
140-144	0.203	0.035	0.203	0.134	0.273	0.191	0.057	0.193	0.072	0.299	0.190	0.060	0.192	0.063	0.304
145-149	0.276	0.083	0.276	0.113	0.439	0.256	0.110	0.258	0.036	0.468	0.251	0.112	0.253	0.025	0.470
150-154	0.455	0.093	0.455	0.272	0.638	0.432	0.125	0.434	0.178	0.674	0.430	0.130	0.432	0.163	0.678
155-159	0.563	0.070	0.563	0.427	0.700	0.540	0.100	0.542	0.335	0.731	0.538	0.104	0.543	0.322	0.735
≥160	0.687	0.107	0.687	0.478	0.896	0.668	0.138	0.669	0.391	0.936	0.666	0.143	0.667	0.376	0.943
Bayesian deviance information criterion	505.7					503.5					504.5				
Between-trial standard deviation						0.075					0.081				
Baseline risk											0.010	0.056	0.011	-0.106	0.120

Mean treatment effects (natural logarithm of the hazard ratio) for each systolic blood pressure category with the 130-134 group taken to be the baseline treatment. Bayesian deviance information criterion is a measure of model fit (lower deviance information criterion indicates better fit). Between-trial standard deviation is a measure of between-trial heterogeneity for the random effects and baseline risk adjusted models. Baseline risk covariate is for the baseline risk adjusted model.

eTable 15. Model Fit Characteristics for Stroke

SBP Treatment Group (mmHg)	Fixed Effects Model Treatment Effects					Random Effects Model Treatment Effects					Baseline Risk Adjusted Model Treatment Effects				
	Mean	SD	Median	2.5%	97.5%	Mean	SD	Median	2.5%	97.5%	Mean	SD	Median	2.5%	97.5%
<120	-0.551	0.211	-0.549	-0.969	-0.143	-0.552	0.315	-0.549	-1.180	0.068	-0.560	0.343	-0.558	-1.247	0.117
120-124	-0.258	0.152	-0.257	-0.556	0.040	-0.353	0.226	-0.343	-0.829	0.066	-0.389	0.247	-0.377	-0.913	0.065
125-129	-0.039	0.100	-0.039	-0.235	0.157	-0.104	0.174	-0.094	-0.478	0.214	-0.135	0.198	-0.122	-0.568	0.221
135-139	0.197	0.106	0.196	-0.013	0.405	0.194	0.185	0.195	-0.176	0.561	0.179	0.207	0.182	-0.244	0.588
140-144	0.262	0.052	0.262	0.161	0.364	0.281	0.128	0.278	0.027	0.546	0.304	0.156	0.301	-0.002	0.625
145-149	0.611	0.158	0.611	0.304	0.920	0.584	0.258	0.586	0.063	1.092	0.565	0.287	0.567	-0.019	1.130
150-154	0.586	0.101	0.586	0.388	0.785	0.610	0.209	0.606	0.202	1.043	0.639	0.241	0.632	0.174	1.138
155-159	0.679	0.113	0.679	0.458	0.900	0.698	0.219	0.695	0.267	1.145	0.722	0.251	0.717	0.231	1.239
≥160	0.890	0.127	0.889	0.642	1.139	0.918	0.224	0.914	0.485	1.377	0.950	0.253	0.944	0.462	1.474
Bayesian deviance information criterion	411.1					404.2					404.1				
Between-trial standard deviation						0.211					0.248				
Baseline risk											-0.066	0.191	-0.054	-0.484	0.292

Mean treatment effects (natural logarithm of the hazard ratio) for each systolic blood pressure category with the 130-134 group taken to be the baseline treatment. Bayesian deviance information criterion is a measure of model fit (lower deviance information criterion indicates better fit). Between-trial standard deviation is a measure of between-trial heterogeneity for the random effects and baseline risk adjusted models. Baseline risk covariate is for the baseline risk adjusted model.

eTable 16. Model Fit Characteristics for All-Cause Mortality

SBP Treatment Group (mmHg)	Fixed Effects Model Treatment Effects					Random Effects Model Treatment Effects					Baseline Risk Adjusted Model Treatment Effects				
	Mean	SD	Median	2.5%	97.5%	Mean	SD	Median	2.5%	97.5%	Mean	SD	Median	2.5%	97.5%
<120	-0.131	0.069	-0.131	-0.266	0.006	-0.327	0.114	-0.329	-0.547	-0.096	-0.076	0.110	-0.078	-0.286	0.151
120-124	-0.340	0.087	-0.340	-0.510	-0.171	-0.102	0.102	-0.107	-0.292	0.113	-0.315	0.118	-0.316	-0.545	-0.075
125-129	-0.063	0.035	-0.064	-0.133	0.006	-0.053	0.065	-0.054	-0.181	0.084	-0.011	0.085	-0.011	-0.183	0.157
135-139	-0.099	0.059	-0.100	-0.215	0.016	-0.100	0.082	-0.100	-0.262	0.063	-0.078	0.090	-0.078	-0.256	0.102
140-144	0.160	0.039	0.160	0.084	0.237	0.186	0.066	0.181	0.068	0.335	0.211	0.077	0.204	0.077	0.385
145-149	-0.006	0.092	-0.006	-0.186	0.175	0.010	0.125	0.008	-0.234	0.262	0.028	0.132	0.027	-0.230	0.294
150-154	0.307	0.091	0.307	0.128	0.485	0.330	0.124	0.326	0.097	0.588	0.355	0.132	0.349	0.109	0.634
155-159	0.339	0.076	0.339	0.189	0.488	0.373	0.118	0.367	0.157	0.627	0.398	0.128	0.389	0.167	0.681
≥160	0.383	0.103	0.383	0.181	0.584	0.411	0.138	0.406	0.153	0.699	0.436	0.146	0.430	0.164	0.745
Bayesian deviance information criterion	619.5					618.7					619.6				
Between-trial standard deviation						0.091					0.103				
Baseline risk											-0.050	0.068	-0.049	-0.191	0.084

Mean treatment effects (natural logarithm of the hazard ratio) for each systolic blood pressure category with the 130-134 group taken to be the baseline treatment. Bayesian deviance information criterion is a measure of model fit (lower deviance information criterion indicates better fit). Between-trial standard deviation is a measure of between-trial heterogeneity for the random effects and baseline risk adjusted models. Baseline risk covariate is for the baseline risk adjusted model.

eTable 17. Model Fit Characteristics for Cardiovascular Disease Mortality

SBP Treatment Group (mmHg)	Fixed Effects Model Treatment Effects					Random Effects Model Treatment Effects					Baseline Risk Adjusted Model Treatment Effects				
	Mean	SD	Median	2.5%	97.5%	Mean	SD	Median	2.5%	97.5%	Mean	SD	Median	2.5%	97.5%
<120	-0.272	0.093	-0.272	-0.454	-0.091	-0.218	0.205	-0.223	-0.625	0.209	-0.211	0.228	-0.212	-0.673	0.254
120-124	-0.459	0.184	-0.458	-0.823	-0.098	-0.398	0.260	-0.405	-0.894	0.140	-0.388	0.281	-0.396	-0.921	0.196
125-129	-0.116	0.043	-0.116	-0.201	-0.032	-0.137	0.125	-0.130	-0.410	0.103	-0.134	0.157	-0.125	-0.468	0.158
135-139	-0.126	0.078	-0.126	-0.279	0.025	-0.238	0.161	-0.221	-0.601	0.036	-0.256	0.178	-0.240	-0.650	0.055
140-144	0.196	0.052	0.196	0.094	0.298	0.205	0.121	0.205	-0.042	0.452	0.208	0.138	0.209	-0.075	0.485
145-149	0.021	0.129	0.021	-0.232	0.274	-0.067	0.239	-0.050	-0.592	0.365	-0.089	0.260	-0.072	-0.656	0.385
150-154	0.443	0.117	0.443	0.214	0.674	0.447	0.206	0.449	0.029	0.859	0.449	0.229	0.451	-0.018	0.904
155-159	0.449	0.109	0.449	0.236	0.662	0.504	0.215	0.494	0.093	0.962	0.515	0.239	0.507	0.055	1.018
≥160	0.648	0.135	0.647	0.384	0.913	0.671	0.225	0.671	0.217	1.121	0.675	0.248	0.676	0.173	1.169
Bayesian deviance information criterion	500.6					494.8					494.3				
Between-trial standard deviation						0.207					0.244				
Baseline risk											-0.016	0.124	-0.020	-0.263	0.247

Mean treatment effects (natural logarithm of the hazard ratio) for each systolic blood pressure category with the 130-134 group taken to be the baseline treatment. Bayesian deviance information criterion is a measure of model fit (lower deviance information criterion indicates better fit). Between-trial standard deviation is a measure of between-trial heterogeneity for the random effects and baseline risk adjusted models. Baseline risk covariate is for the baseline risk adjusted model.

eTable 18. Model Fit Characteristics for Coronary Heart Disease

SBP Treatment Group (mmHg)	Fixed Effects Model Treatment Effects					Random Effects Model Treatment Effects					Baseline Risk Adjusted Model Treatment Effects				
	Mean	SD	Median	2.5%	97.5%	Mean	SD	Median	2.5%	97.5%	Mean	SD	Median	2.5%	97.5%
<120	-0.203	0.073	-0.203	-0.347	-0.060	-0.216	0.122	-0.214	-0.466	0.022	-0.116	0.183	-0.117	-0.475	0.250
120-124	-0.198	0.115	-0.198	-0.425	0.028	-0.207	0.140	-0.207	-0.485	0.067	-0.240	0.148	-0.241	-0.528	0.058
125-129	-0.178	0.062	-0.178	-0.300	-0.057	-0.156	0.102	-0.159	-0.355	0.055	-0.092	0.135	-0.096	-0.350	0.187
135-139	-0.290	0.204	-0.289	-0.691	0.108	-0.278	0.221	-0.276	-0.714	0.151	-0.302	0.222	-0.300	-0.738	0.133
140-144	0.178	0.054	0.178	0.072	0.283	0.167	0.086	0.169	-0.013	0.331	0.130	0.101	0.133	-0.078	0.324
145-149	-0.241	0.206	-0.239	-0.645	0.162	-0.240	0.222	-0.238	-0.681	0.192	-0.282	0.226	-0.281	-0.725	0.158
150-154	0.358	0.151	0.358	0.062	0.653	0.335	0.191	0.337	-0.053	0.703	0.300	0.199	0.303	-0.103	0.683
155-159	0.415	0.113	0.416	0.193	0.637	0.387	0.161	0.392	0.054	0.696	0.347	0.176	0.353	-0.019	0.679
≥160	0.583	0.167	0.583	0.257	0.909	0.553	0.209	0.556	0.131	0.957	0.519	0.213	0.522	0.090	0.930
Bayesian deviance information criterion	386.2					385.3					386.9				
Between-trial standard deviation						0.108					0.126				
Baseline risk											-0.173	0.227	-0.174	-0.618	0.275

Mean treatment effects (natural logarithm of the hazard ratio) for each systolic blood pressure category with the 130-134 group taken to be the baseline treatment. Bayesian deviance information criterion is a measure of model fit (lower deviance information criterion indicates better fit). Between-trial standard deviation is a measure of between-trial heterogeneity for the random effects and baseline risk adjusted models. Baseline risk covariate is for the baseline risk adjusted model.

eTable 19. Node-Splitting Results of Testing Consistency for Major Cardiovascular Disease

Reference Group (mmHg)	Comparison Group (mmHg)	IHR Combined Direct and Indirect Evidence	IHR Direct Evidence	IHR Indirect Evidence	Difference Between Direct and Indirect Evidence	*P* Value
120-124	125-129	0.207	0.254	0.167	0.086	0.68
125-129	135-139	0.177	0.108	0.256	-0.148	0.19
125-129	140-144	0.331	0.070	0.395	-0.325	0.06
130-134	<120	-0.066	-0.066	0.057	-0.123	0.50
130-134	120-124	-0.347	-0.323	-0.407	0.084	0.68
130-134	125-129	-0.141	-0.275	0.019	-0.294	0.01[a]
130-134	135-139	0.036	0.121	-0.056	0.177	0.87
130-134	140-144	0.190	0.219	-0.007	0.226	0.90
130-134	145-149	0.251	0.080	0.286	-0.206	0.25
135-139	140-144	0.153	0.161	0.153	0.009	0.51
135-139	145-149	0.215	0.236	0.038	0.197	0.74
140-144	150-154	0.240	0.275	0.111	0.165	0.73
140-144	155-159	0.349	0.350	-0.827	1.176	0.50
140-144	≥160	0.476	0.369	0.530	-0.162	0.28
150-154	≥160	0.236	0.255	0.089	0.166	0.72

Network-wide Omnibus Tests of Consistency			
Inconsistency Model Approach	Consistency Model:	DIC =	504.5
	Inconsistency Model:	DIC =	508.2
Design-by-treatment Interaction Approach	Global Wald X^2	p >	0.99

IHR is the natural logarithm of the mean hazard ratio for the comparison group vs. reference group. The network-wide omnibus tests of consistency were conducted by 1) fitting the primary model which assumes consistency and comparing it to a model assuming inconsistency, with a lower Bayesian deviance information criterion (DIC) indicating a better fitting model; and 2) a global test of the inconsistency factors in each direct comparison (design-by-treatment interaction approach).

[a] Statistically significant, $p < 0.05$

eTable 20. Node-Splitting Results of Testing Consistency for Stroke

Reference Group (mmHg)	Comparison Group (mmHg)	IHR Combined Direct and Indirect Evidence	IHR Direct Evidence	IHR Indirect Evidence	Difference Between Direct and Indirect Evidence	*P* Value
120-124	125-129	0.254	0.560	0.117	0.443	0.78
125-129	135-139	0.315	0.387	0.236	0.151	0.63
125-129	140-144	0.439	0.082	0.655	-0.573	0.12
130-134	<120	-0.560	-0.556	0.158	-0.714	0.50
130-134	120-124	-0.389	-0.306	-0.740	0.434	0.78
130-134	125-129	-0.135	-0.391	0.029	-0.419	0.15
130-134	135-139	0.179	0.220	0.143	0.077	0.58
130-134	140-144	0.304	0.288	0.358	-0.070	0.42
130-134	≥160	0.950	1.472	0.827	0.646	0.85
135-139	140-144	0.124	0.380	0.017	0.363	0.77
135-139	145-149	0.386	0.385	0.079	0.306	0.50
140-144	150-154	0.335	0.421	0.079	0.342	0.80
140-144	155-159	0.419	0.416	-0.271	0.687	0.50
140-144	≥160	0.647	0.211	0.883	-0.672	0.05[a]
150-154	≥160	0.312	0.398	0.056	0.342	0.80

Network-wide Omnibus Tests of Consistency			
Inconsistency Model Approach	Consistency Model:	DIC =	404.1
	Inconsistency Model:	DIC =	405.3
Design-by-treatment Interaction Approach	Global Wald X^2	p >	0.99

IHR is the natural logarithm of the mean hazard ratio for the comparison group vs. reference group. The network-wide omnibus tests of consistency were conducted by 1) fitting the primary model which assumes consistency and comparing it to a model assuming inconsistency, with a lower Bayesian deviance information criterion (DIC) indicating a better fitting model; and 2) a global test of the inconsistency factors in each direct comparison (design-by-treatment interaction approach).

[a] Not statistically significant, exact p = 0.052

eTable 21. Node-Splitting Results of Testing Consistency for All-Cause Mortality

Reference Group (mmHg)	Comparison Group (mmHg)	IHR Combined Direct and Indirect Evidence	IHR Direct Evidence	IHR Indirect Evidence	Difference Between Direct and Indirect Evidence	*P* Value
<120	120-124	-0.239	-0.339	-0.156	-0.183	0.24
<120	125-129	0.065	0.210	-0.128	0.338	0.96
120-124	125-129	0.304	-0.261	0.347	-0.608	0.11
125-129	135-139	-0.067	-0.034	-0.075	0.042	0.59
125-129	140-144	0.222	0.129	0.243	-0.114	0.33
130-134	<120	-0.076	0.044	-0.173	0.217	0.86
130-134	120-124	-0.315	-0.311	-0.321	0.009	0.53
130-134	125-129	-0.011	-0.078	0.024	-0.102	0.22
130-134	135-139	-0.078	0.043	-0.187	0.230	0.92
130-134	140-144	0.211	0.162	0.374	-0.212	0.08
130-134	145-149	0.028	-0.093	0.033	-0.127	0.39
130-134	≥160	0.436	0.776	0.383	0.393	0.83
135-139	140-144	0.289	0.451	0.171	0.281	0.95
135-139	145-149	0.106	0.115	-0.049	0.164	0.65
140-144	150-154	0.144	0.154	0.105	0.048	0.57
140-144	155-159	0.187	0.188	0.395	-0.207	0.50
140-144	≥160	0.225	-0.020	0.280	-0.301	0.18
150-154	≥160	0.081	0.087	0.042	0.045	0.56

Network-wide Omnibus Tests of Consistency			
Inconsistency Model Approach	Consistency Model:	DIC =	619.6
	Inconsistency Model:	DIC =	624.8
Design-by-treatment Interaction Approach	Global Wald X^2	p >	0.99

IHR is the natural logarithm of the mean hazard ratio for the comparison group vs. reference group. The network-wide omnibus tests of consistency were conducted by 1) fitting the primary model which assumes consistency and comparing it to a model assuming inconsistency, with a lower Bayesian deviance information criterion (DIC) indicating a better fitting model; and 2) a global test of the inconsistency factors in each direct comparison (design-by-treatment interaction approach).

eTable 22. Node-Splitting Results of Testing Consistency for Cardiovascular Disease Mortality

Reference Group (mmHg)	Comparison Group (mmHg)	IHR Combined Direct and Indirect Evidence	IHR Direct Evidence	IHR Indirect Evidence	Difference Between Direct and Indirect Evidence	*P* Value
<120	125-129	0.077	0.242	-0.262	0.503	0.88
120-124	125-129	0.254	-1.136	0.539	-1.674	0.03[a]
125-129	135-139	-0.122	-0.045	-0.192	0.146	0.65
125-129	140-144	0.341	-0.091	0.420	-0.511	0.15
130-134	<120	-0.211	0.053	-0.453	0.506	0.88
130-134	120-124	-0.388	-0.599	1.054	-1.653	0.03[a]
130-134	125-129	-0.134	-0.207	-0.069	-0.138	0.32
130-134	135-139	-0.256	-0.010	-0.396	0.386	0.88
130-134	140-144	0.208	0.179	0.296	-0.117	0.32
130-134	145-149	-0.089	-1.264	0.031	-1.294	0.08
130-134	≥160	0.675	0.899	0.610	0.289	0.69
135-139	140-144	0.464	0.596	0.305	0.291	0.83
135-139	145-149	0.167	0.229	-1.107	1.336	0.92
140-144	150-154	0.242	0.267	0.146	0.121	0.60
140-144	155-159	0.307	0.305	-0.208	0.514	0.50
140-144	≥160	0.467	0.077	0.544	-0.467	0.22
150-154	≥160	0.226	0.241	0.134	0.107	0.59

Network-wide Omnibus Tests of Consistency			
Inconsistency Model Approach	Consistency Model:	DIC =	494.3
	Inconsistency Model:	DIC =	495.9
Design-by-treatment Interaction Approach	Global Wald X^2	p >	0.99

IHR is the natural logarithm of the mean hazard ratio for the comparison group vs. reference group. The network-wide omnibus tests of consistency were conducted by 1) fitting the primary model which assumes consistency and comparing it to a model assuming inconsistency, with a lower Bayesian deviance information criterion (DIC) indicating a better fitting model; and 2) a global test of the inconsistency factors in each direct comparison (design-by-treatment interaction approach).

[a] Statistically significant, $p < 0.05$

eTable 23. Node-Splitting Results of Testing Consistency for Coronary Heart Disease

Reference Group (mmHg)	Comparison Group (mmHg)	IHR Combined Direct and Indirect Evidence	IHR Direct Evidence	IHR Indirect Evidence	Difference Between Direct and Indirect Evidence	*P* Value
<120	125-129	0.025	0.261	-0.342	0.604	>0.99
125-129	135-139	-0.210	-0.282	-0.143	-0.139	0.40
125-129	140-144	0.222	0.162	0.245	-0.083	0.42
130-134	<120	-0.116	0.184	-0.424	0.608	>0.99
130-134	120-124	-0.240	-0.243	0.169	-0.411	0.50
130-134	125-129	-0.092	-0.239	0.212	-0.452	0.01[a]
130-134	140-144	0.130	0.199	-0.157	0.356	0.88
130-134	145-149	-0.282	-0.408	-0.143	-0.264	0.28
130-134	≥160	0.519	0.155	0.644	-0.488	0.17
135-139	140-144	0.432	0.106	0.559	-0.453	0.19
135-139	145-149	0.020	0.051	-0.200	0.251	0.70
140-144	150-154	0.169	0.244	-0.083	0.327	0.77
140-144	155-159	0.217	0.218	-0.160	0.378	0.50
140-144	≥160	0.389	0.437	0.391	0.046	0.52
150-154	≥160	0.220	0.249	-0.092	0.342	0.79

Network-wide Omnibus Tests of Consistency			
Inconsistency Model Approach	Consistency Model:	DIC =	386.9
	Inconsistency Model:	DIC =	389.5
Design-by-treatment Interaction Approach	Global Wald X^2	p >	0.99

IHR is the natural logarithm of the mean hazard ratio for the comparison group vs. reference group. The network-wide omnibus tests of consistency were conducted by 1) fitting the primary model which assumes consistency and comparing it to a model assuming inconsistency, with a lower Bayesian deviance information criterion (DIC) indicating a better fitting model; and 2) a global test of the inconsistency factors in each direct comparison (design-by-treatment interaction approach).

[a] Statistically significant, $p < 0.05$

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