

## Supplemental Online Content

Juraschek SP, Hu J, Cluett JL, et al. Orthostatic hypotension, hypertension treatment, and cardiovascular disease: an individual participant meta-analysis. *JAMA*. Published online October 17, 2023. doi:10.1001/jama.2023.18497

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

## eAppendix. Details of search strategies

### PUBMED SEARCH:

Hypertension, Orthostatic Hypotension (RCTs / mortality)

Search update May 13, 2022

Medline / PubMed (National Library of Medicine, NCBI)

("Hypertension"[Mesh:NoExp] OR "Essential Hypertension"[Mesh] OR "Prehypertension"[Mesh] OR hypertension[tiab] OR high blood pressure[tiab] OR prehypertension[tiab])

AND

("Hypertension/drug therapy"[Mesh] OR "Antihypertensive Agents" [Pharmacological Action] OR "Antihypertensive Agents"[Mesh] OR anti hypertensive\*[tiab] OR antihypertensive\*[tiab] OR blood pressure lowering[tiab] OR BP lowering[tiab] OR drug therapy[tiab] OR acetazolamide[tiab] OR amiloride[tiab] OR amlodipine[tiab] OR atenolol[tiab] OR benazepril[tiab] OR bisoprolol[tiab] OR bumetanide[tiab] OR candesartan[tiab] OR captopril[tiab] OR carvedilol[tiab] OR chlorthalidone[tiab] OR clonidine[tiab] OR diltiazem[tiab] OR doxazosin[tiab] OR ethacrynic acid[tiab] OR enalapril[tiab] OR felodipine [tiab] OR fosinopril[tiab] OR furosemide[tiab] OR hydralazine[tiab] OR hydrochlorothiazide[tiab] OR indapamide[tiab] OR irbesartan[tiab] OR lisinopril[tiab] OR losartan[tiab] OR metoprolol[tiab] OR metolazone [tiab] OR minoxidil[tiab] OR moexipril[tiab] OR nadolol[tiab] OR nebivolol[tiab] OR nifedipine[tiab] OR olmesartan[tiab] OR perindopril[tiab] OR pindolol[tiab] OR prazosin[tiab] OR propranolol[tiab] OR quinapril[tiab] OR ramipril[tiab] OR spironolactone[tiab] OR terazosin[tiab] OR torsemide[tiab] OR telmisartan[tiab] OR timolol[tiab] OR trandolapril[tiab] OR triamterene[tiab] OR verapamil[tiab])

AND

("Orthostatic Intolerance"[Mesh:NoExp] OR "Hypotension, Orthostatic"[Mesh] OR "Syncope, Vasovagal"[Mesh] OR orthostatic hypotension[tiab] OR orthostatic intolerance[tiab] OR postural hypotension[tiab] OR standing blood pressure[tiab] OR standing hypotension [tiab] OR syncope[tiab])

AND

("Randomized Controlled Trials as Topic"[Mesh] OR "Randomized Controlled Trial" [Publication Type] OR "Random Allocation"[Mesh] OR "Placebos"[Mesh] OR random\*[tiab] OR placebo[tiab])

366 results May 13, 2022

## Embase (Elsevier, Embase-com)

Advanced Search

Remove mapping options

Source: Embase (1974-)

Restrict to Publication Types: Article, Conference Paper

#1)

'hypertension'/de OR 'borderline hypertension'/de OR 'diabetic hypertension'/de OR 'essential hypertension'/de OR 'orthostatic hypertension'/de OR 'prehypertension'/de OR 'systolic hypertension'/de OR hypertension:ab,ti OR 'high blood pressure':ab,ti OR prehypertension:ab,ti

#2)

'antihypertensive agent'/exp/mj OR 'anti hypertensive\*':ab,ti OR antihypertensive\*:ab,ti OR 'blood pressure lowering':ab,ti OR 'BP lowering':ab,ti OR acetazolamide:ab,ti OR amiloride:ab,ti OR amlodipine:ab,ti OR atenolol:ab,ti OR benazepril:ab,ti OR bisoprolol:ab,ti OR bumetanide:ab,ti OR candesartan:ab,ti OR captopril:ab,ti OR carvedilol:ab,ti OR chlorthalidone:ab,ti OR clonidine:ab,ti OR diltiazem:ab,ti OR doxazosin:ab,ti OR 'ethacrynic acid':ab,ti OR enalapril:ab,ti OR felodipine:ab,ti OR fosinopril:ab,ti OR furosemide:ab,ti OR hydralazine:ab,ti OR hydrochlorothiazide:ab,ti OR indapamide:ab,ti OR irbesartan:ab,ti OR lisinopril:ab,ti OR losartan:ab,ti OR metoprolol:ab,ti OR metolazone:ab,ti OR minoxidil:ab,ti OR moexipril:ab,ti OR nadolol:ab,ti OR nebivolol:ab,ti OR nifedipine:ab,ti OR olmesartan:ab,ti OR perindopril:ab,ti OR pindolol:ab,ti OR prazosin:ab,ti OR propranolol:ab,ti OR quinapril:ab,ti OR ramipril:ab,ti OR spironolactone:ab,ti OR terazosin:ab,ti OR torsemide:ab,ti OR telmisartan:ab,ti OR timolol:ab,ti OR trandolapril:ab,ti OR triamterene:ab,ti OR verapamil:ab,ti

#3)

'orthostatic intolerance'/de OR 'orthostatic hypotension'/de OR 'faintness'/de OR 'orthostatic hypotension':ab,ti OR 'orthostatic intolerance':ab,ti OR 'postural hypotension':ab,ti OR 'standing blood pressure':ab,ti OR 'standing hypotension':ab,ti OR syncope:ab,ti

#4)

'randomized controlled trial'/exp OR 'randomized controlled trial (topic)'/de OR 'randomization'/exp OR 'placebo'/de OR random\*:ab,ti OR placebo:ab,ti

(#1 AND #2 AND #3 AND #4)

746 results May 13, 2022

**Cochrane Central Register of Controlled Trials (Cochrane Library, Wiley)**

Advanced Search

search in title abstract keywords:

hypertension OR "high blood pressure" OR prehypertension

AND

"anti hypertensive" OR "anti hypertensives" OR antihypertensive\* OR "blood pressure lowering" OR "BP lowering" OR acetazolamide OR amiloride OR amlodipine OR atenolol OR benazepril OR bisoprolol OR bumetanide OR candesartan OR captopril OR carvedilol OR chlorthalidone OR clonidine OR diltiazem OR doxazosin OR "ethacrynic acid" OR enalapril OR felodipine OR fosinopril OR furosemide OR hydralazine OR hydrochlorothiazide OR indapamide OR irbesartan OR lisinopril OR losartan OR metoprolol OR metolazone OR minoxidil OR moexipril OR nadolol OR nebivolol OR nifedipine OR olmesartan OR perindopril OR pindolol OR prazosin OR propranolol OR quinapril OR ramipril OR spironolactone OR terazosin OR torsemide OR telmisartan OR timolol OR trandolapril OR triamterene OR verapamil

AND

"orthostatic hypotension" OR "orthostatic intolerance" OR "postural hypotension" OR "standing blood pressure" OR "standing hypotension" OR syncope

475 results May 13, 2022

*Note there were fewer articles identified from Cochrane Central due to a refinement in the search strategy that removed the "AND random\* OR placebo" line.*

## **Summary**

PubMed 366

Embase 746

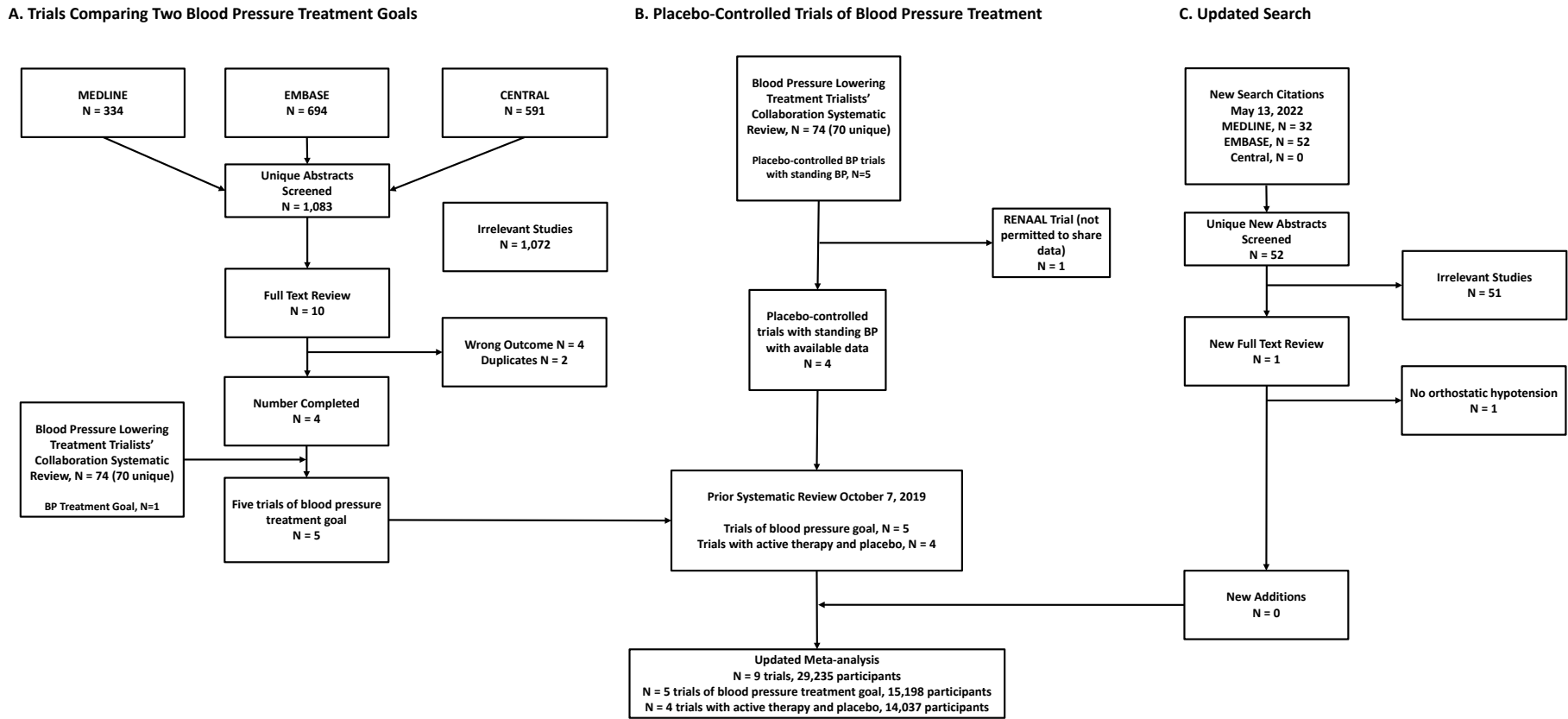
Cochrane Central 475

1587 references across all databases

52 new unique references retrieved from search May 13, 2022.

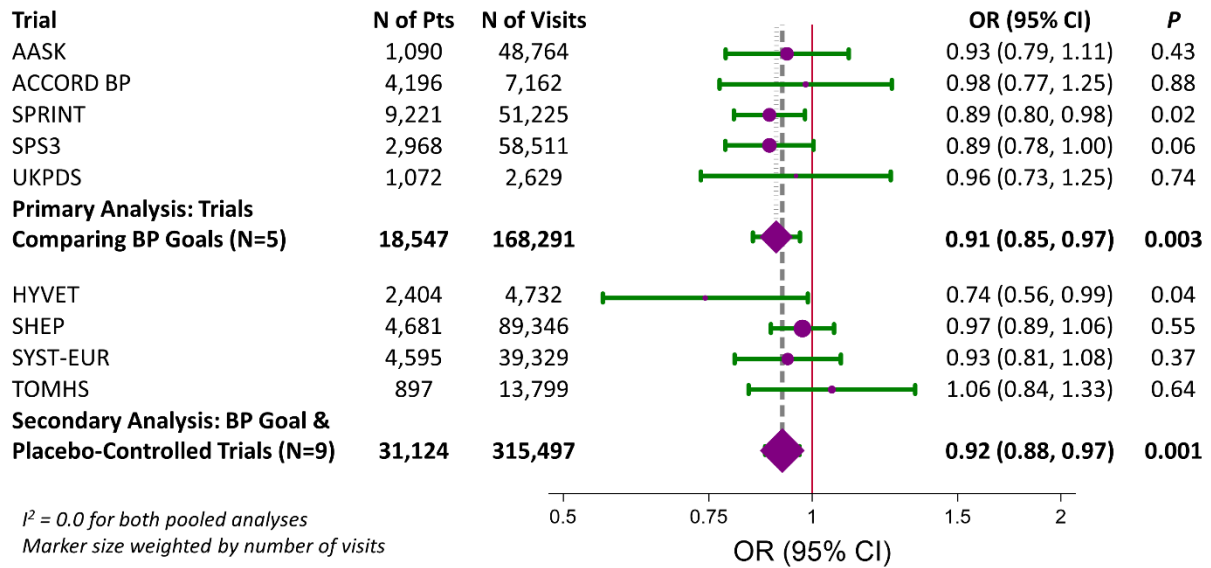
7 duplicates identified during import to Covidence: 45 new references for screening at title and abstract level

**eFigure 1.** PRISMA diagram of the updated systematic review





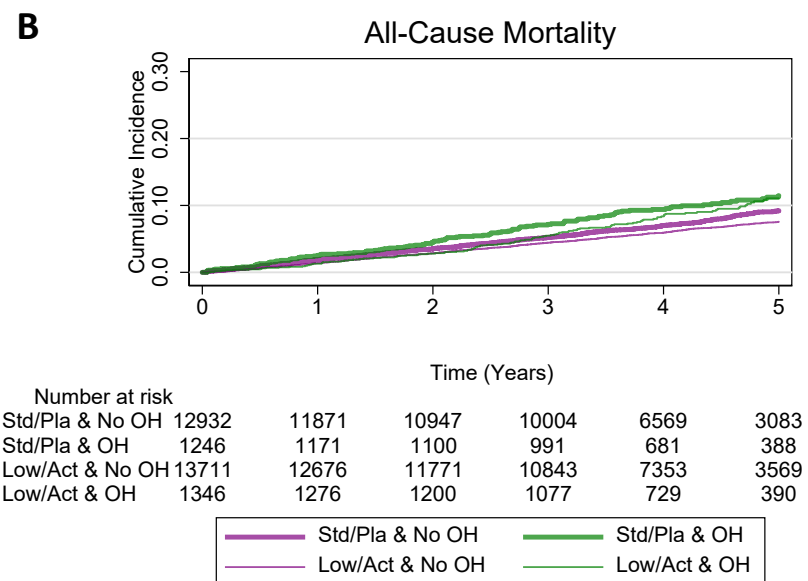
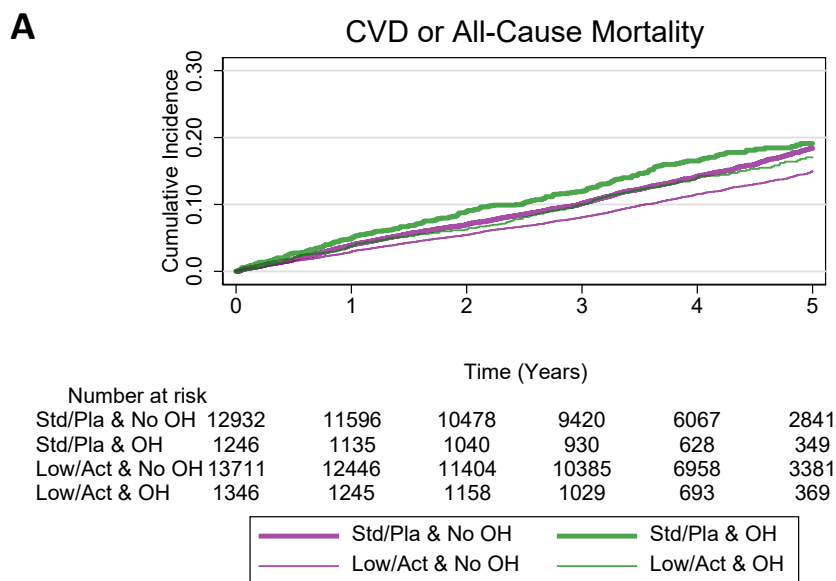
**eFigure 2.** Updated meta-analysis of the effects of hypertension treatment on orthostatic hypotension



This was updated from the Juraschek et al, *Annals of Internal Medicine* 2020 manuscript. Note that an additional visit file was found for the SPS3 trial, which increased the total number of assessments included in the meta-analysis.

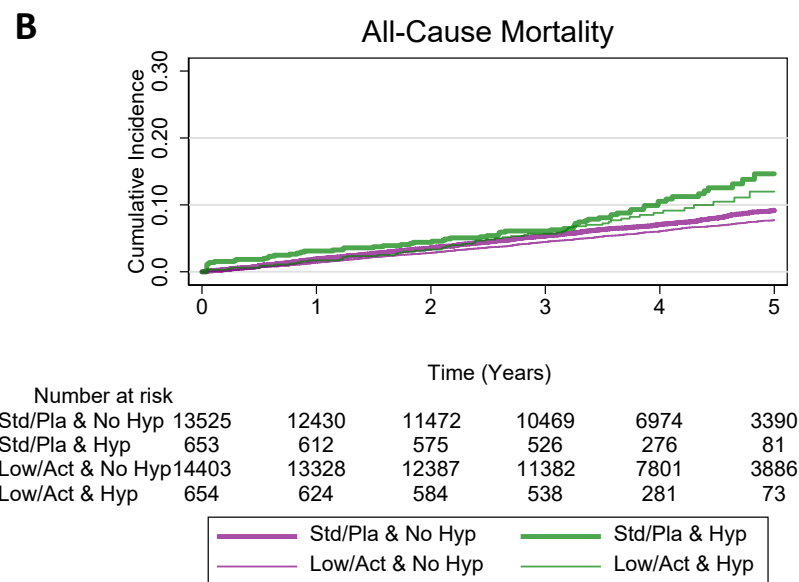
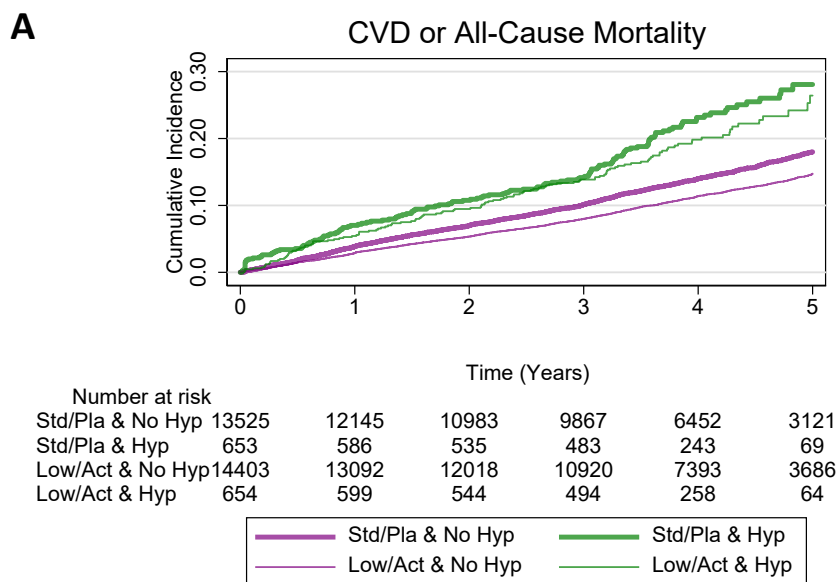
**eFigure 3.** Cumulative incidence of cardiovascular disease or all-cause mortality by treatment assignment and orthostatic hypotension status

Follow-up data across the 9 trials censored at 5-years for **(A)** CVD or all-cause mortality or **(B)** All-cause mortality. The number at risk each year of follow-up is tabulated below each figure. Abbreviations: CVD, cardiovascular disease; Low/Act represents a low blood pressure goal or active treatment assignment; OH represents orthostatic hypotension; Std/Pla represents a standard goal or placebo assignment



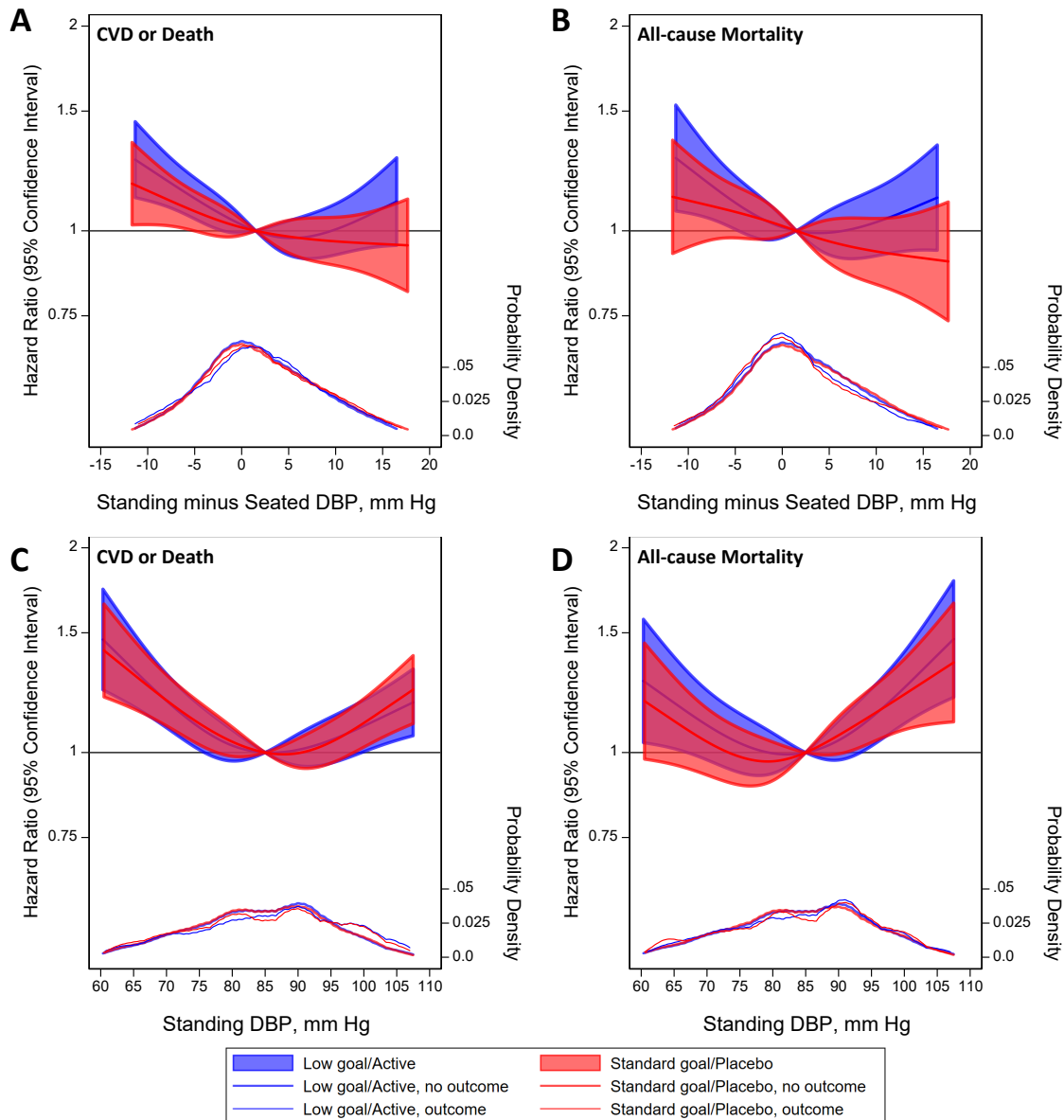
**eFigure 4.** Cumulative incidence of cardiovascular disease or all-cause mortality by treatment assignment and orthostatic hypotension status

Follow-up data across the 9 trials censored at 5-years for **(A)** CVD or all-cause mortality or **(B)** All-cause mortality. The number at risk each year of follow-up is tabulated below each figure. Abbreviations: CVD, cardiovascular disease; HYP represents standing hypotension; Low/Act represents a low blood pressure goal or active treatment assignment; Std/Pla represents a standard goal or placebo assignment



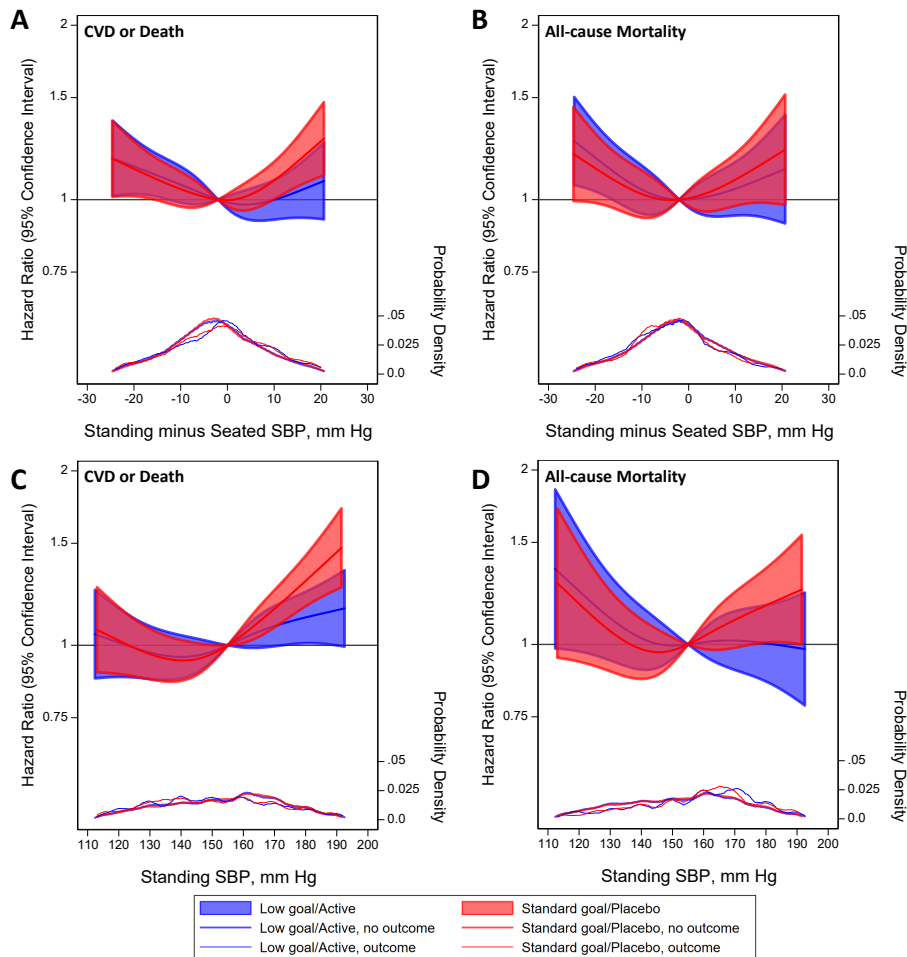
**eFigure 5.** Restricted cubic spline of difference in diastolic blood pressure or standing blood pressure

Adjusted hazard ratios by treatment status for change in diastolic blood pressure (DBP) with (A) cardiovascular disease or death or (B) all-cause mortality as well as for standing systolic blood pressure with (C) cardiovascular disease or death or (D) all-cause mortality, using a restricted cubic spline with 4 knots determined by Harrell’s method. Figures are based on data from all nine trials. Shade represents 95% confidence intervals. Both models were expressed relative to the median value and were truncated at the 2.5<sup>th</sup> and 97.5<sup>th</sup> percentiles. Models were adjusted for age, sex, and study. The hazard ratios are shown on a natural log scale. Included are kernel density plots, representing the distribution of change in DBP or standing DBP by treatment and by outcome status: low goal/active treatment, no outcome (blue, thick), low goal/active treatment outcome (blue, thin), standard goal/placebo, no outcome (red, thick), and standard goal/placebo, outcome (red, thin).



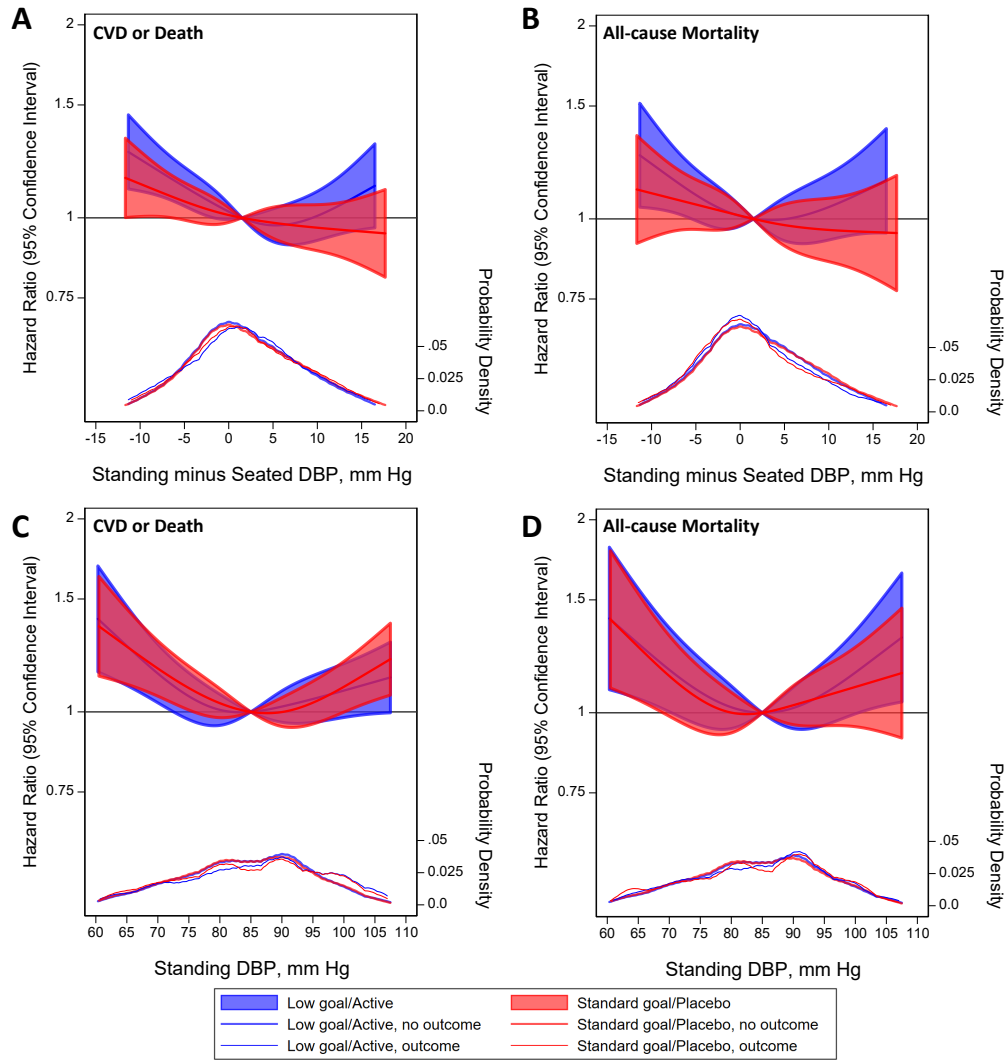
**eFigure 6.** Fully adjusted splines of difference in systolic blood pressure or standing blood pressure

Adjusted hazard ratios by treatment status for change in systolic blood pressure (SBP) with (A) cardiovascular disease or death or (B) all-cause mortality as well as for standing systolic blood pressure with (C) cardiovascular disease or death or (D) all-cause mortality, using a restricted cubic spline with 4 knots determined by Harrell’s method. Figures are based on data from all nine trials. Shade represents 95% confidence intervals. Both models were expressed relative to the median value and were truncated at the 2.5<sup>th</sup> and 97.5<sup>th</sup> percentiles. Models were adjusted for age, sex, study, baseline systolic blood pressure, baseline diastolic blood pressure, body mass index, estimated glomerular filtration rate <60 mL/min per 1.73 m<sup>2</sup> or self-reported kidney disease, and history of diabetes. There were 10,707 participants contributing to all standard goal/placebo curves and 11,227 participants for the difference curves among those assigned low goal/active therapy and 11,228 participants for the standing SBP curves among those assigned log goal/active therapy. The hazard ratios are shown on a natural log scale. Included are kernel density plots, representing the distribution of change in SBP or standing SBP by treatment and by outcome status: low goal/active treatment, no outcome (blue, thick), low goal/active treatment outcome (blue, thin), standard goal/placebo, no outcome (red, thick), and standard goal/placebo, outcome (red, thin).



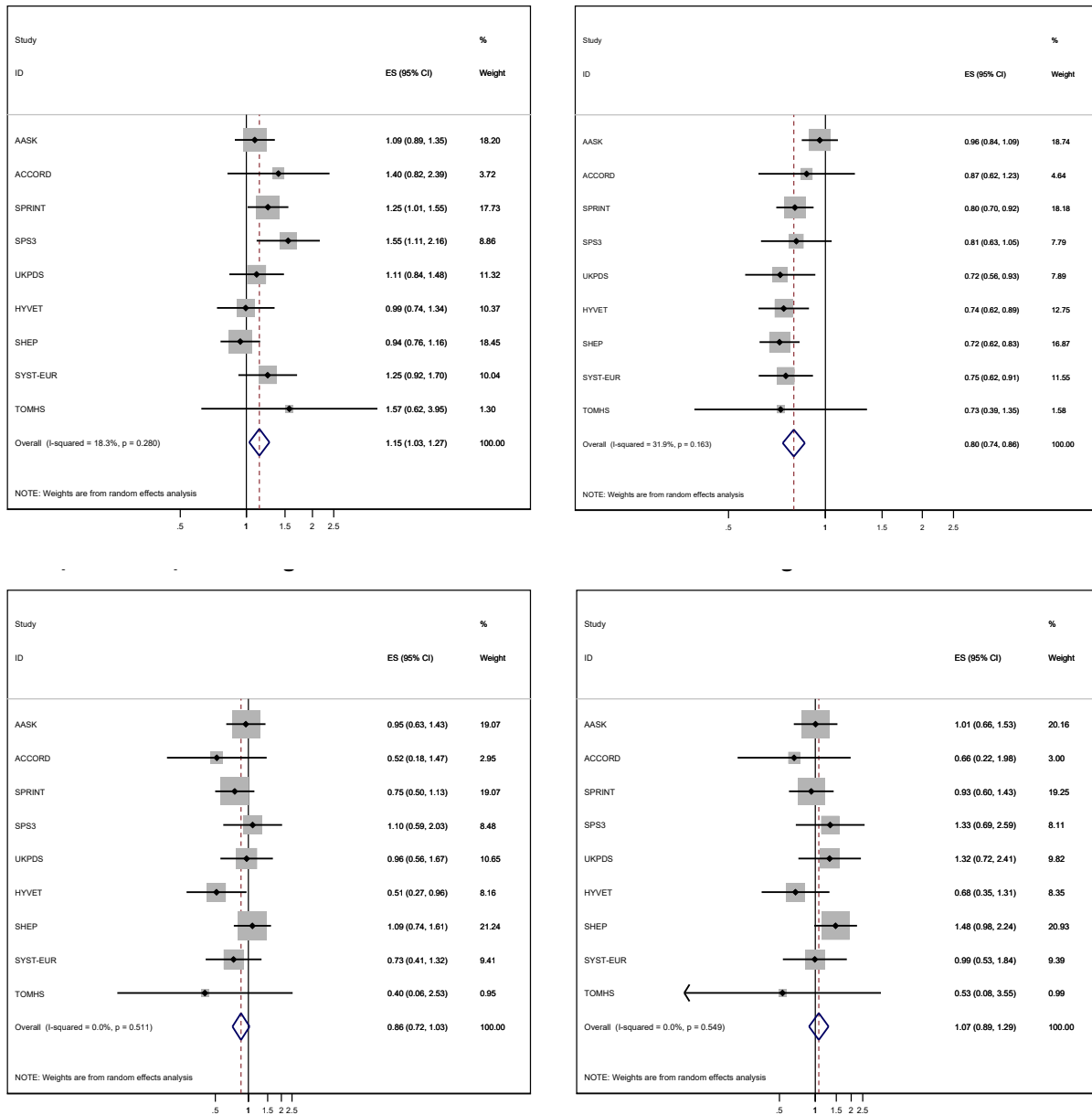
**eFigure 7.** Fully adjusted splines of difference in diastolic blood pressure or standing blood pressure

Adjusted hazard ratios by treatment status for change in diastolic blood pressure (DBP) with (A) cardiovascular disease or death or (B) all-cause mortality as well as for standing systolic blood pressure with (C) cardiovascular disease or death or (D) all-cause mortality, using a restricted cubic spline with 4 knots determined by Harrell's method. Figures are based on data from all nine trials. Shade represents 95% confidence intervals. Both models were expressed relative to the median value and were truncated at the 2.5<sup>th</sup> and 97.5<sup>th</sup> percentiles. Models were adjusted for age, sex, study, baseline systolic blood pressure, baseline diastolic blood pressure, body mass index, estimated glomerular filtration rate <60 mL/min per 1.73 m<sup>2</sup> or self-reported kidney disease, and history of diabetes. There were 10,707 participants contributing to all standard goal/placebo curves and 11,229 participants contributing to all low goal/active therapy curves. The hazard ratios are shown on a natural log scale. Included are kernel density plots, representing the distribution of change in DBP or standing DBP by treatment and by outcome status: low goal/active treatment, no outcome (blue, thick), low goal/active treatment outcome (blue, thin), standard goal/placebo, no outcome (red, thick), and standard goal/placebo, outcome (red, thin).



**eFigure 8.** Two-stage meta-analysis, orthostatic hypotension and cardiovascular disease or all-cause mortality

Two-stage meta-analysis examining the associations with cardiovascular disease or all-cause mortality of (A) orthostatic hypotension (OH, yes versus no), (B) a low or active treatment assignment (Low/Act) versus standard or placebo assignment (Std/Pla) among participants without OH, (C) Low/Act versus Std/Pla among participants with OH, and (D) the interaction between OH and treatment assignment. Individual effects were determined based on Cox models adjusted for age and sex. The pooled effect from the 9 trials were weighted with the inverse variance, using a random effects model.

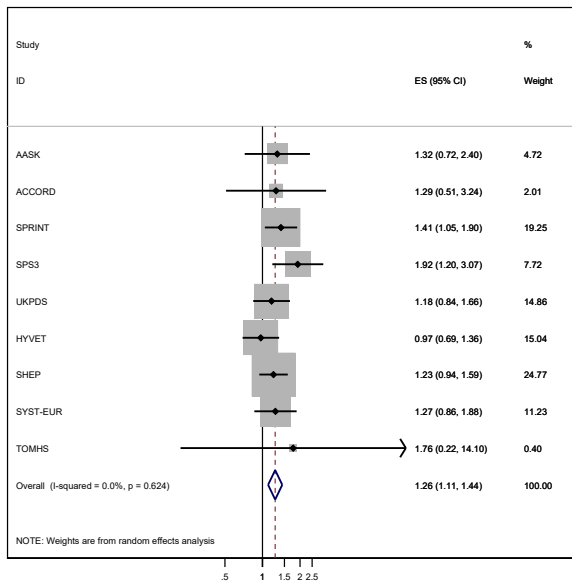




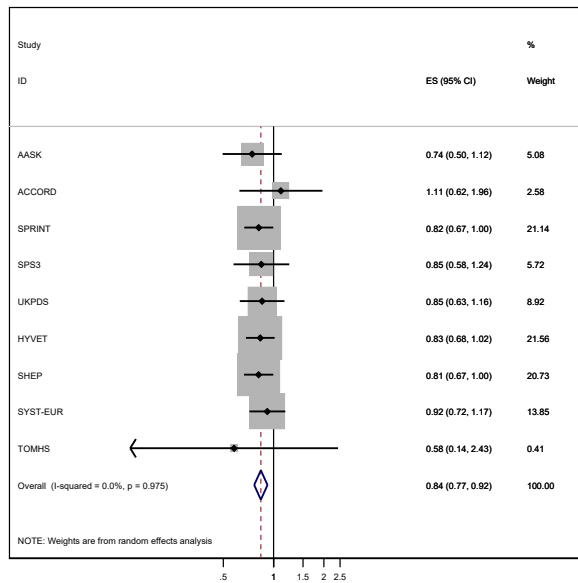
**eFigure 9.** Two-stage meta-analysis, orthostatic hypotension and all-cause mortality

Two-stage meta-analysis examining the associations with all-cause mortality of (A) orthostatic hypotension (OH, yes versus no), (B) a low or active treatment assignment (Low/Act) versus standard or placebo assignment (Std/Pla) among participants without OH, (C) Low/Act versus Std/Pla among participants with OH, and (D) the interaction between OH and treatment assignment. Individual effects were determined based on Cox models adjusted for age and sex. The pooled effect from the 9 trials were weighted with the inverse variance, using a random effects model.

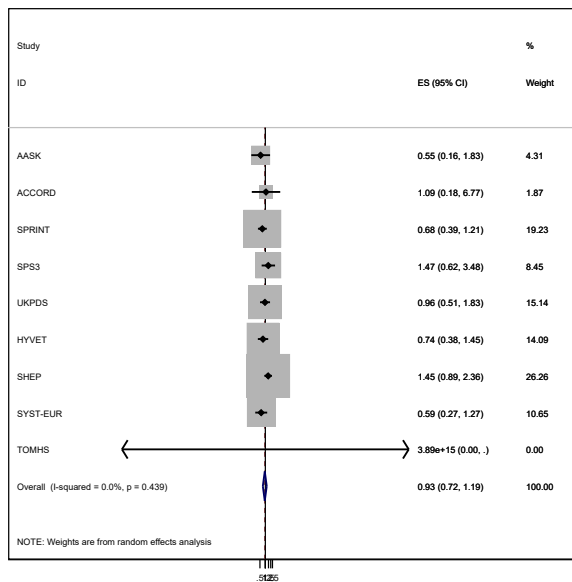
**A. Observational association: OH & Outcome**



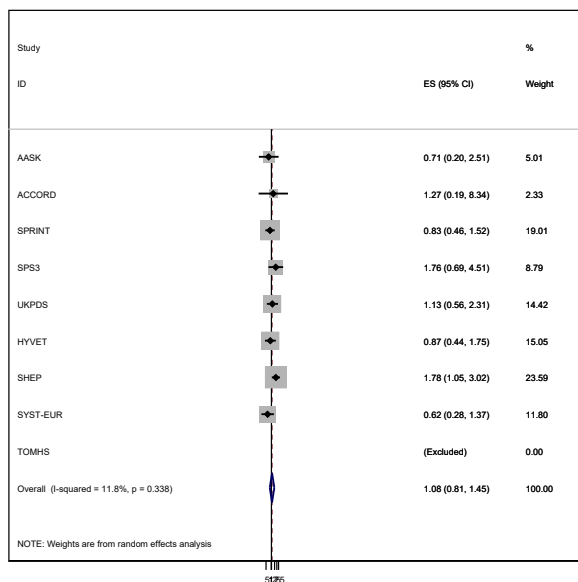
**B. Low/Act vs Std/Pla among those without OH**



**C. Low/Act vs Std/Pla among those with OH**



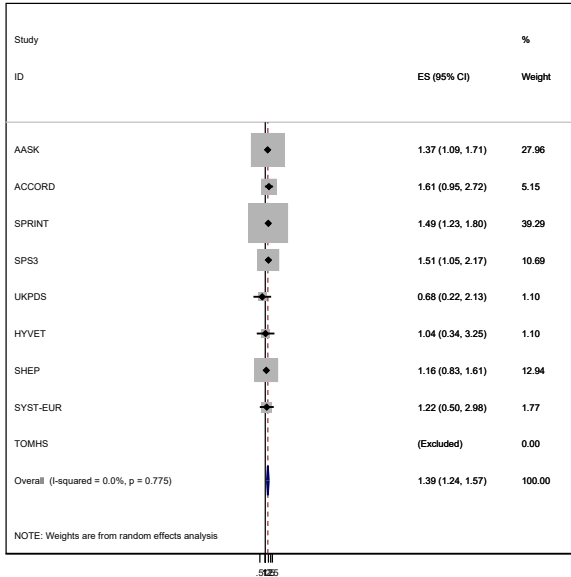
**D. Interaction of Assignment and OH**



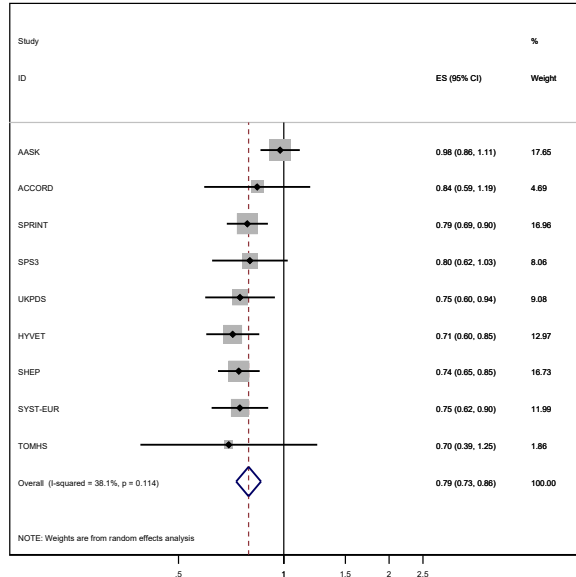
**eFigure 10.** Two-stage meta-analysis, standing hypotension and cardiovascular disease or all-cause mortality

Two-stage meta-analysis examining the associations with cardiovascular disease or all-cause mortality of (A) standing hypotension (HYP, yes versus no), (B) a low or active treatment assignment (Low/Act) versus standard or placebo assignment (Std/Pla) among participants without HYP, (C) Low/Act versus Std/Pla among participants with HYP, and (D) the interaction between HYP and treatment assignment. Individual effects were determined based on Cox models adjusted for age and sex. The pooled effect from the 9 trials were weighted with the inverse variance, using a random effects model.

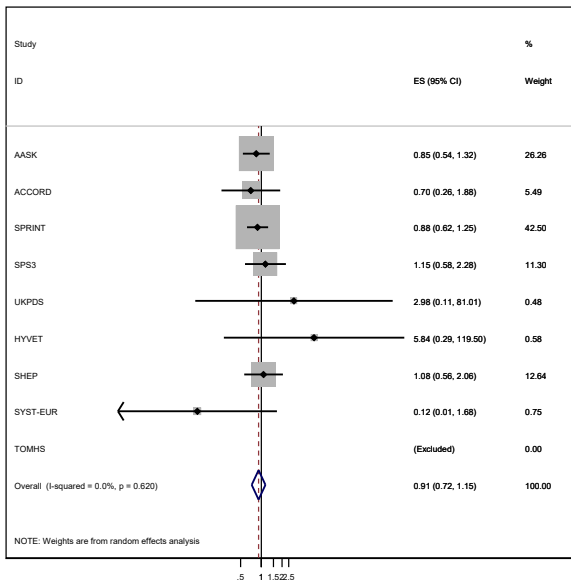
**A. Observational association: HYP & Outcome**



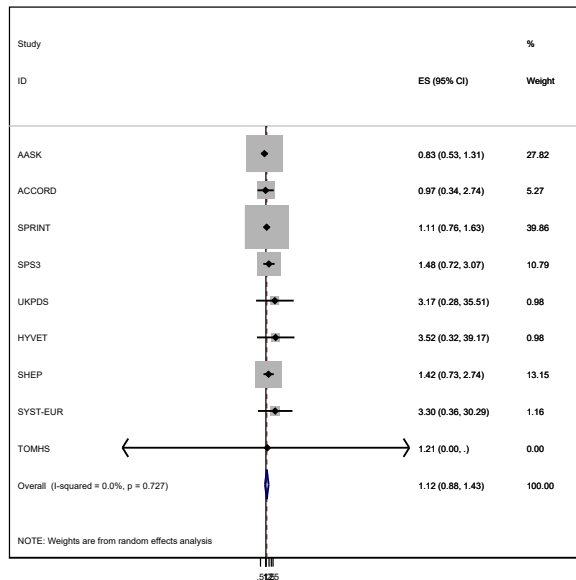
**B. Low/Act vs Std/Pla among those without HYP**



**C. Low/Act vs Std/Pla among those with HYP**



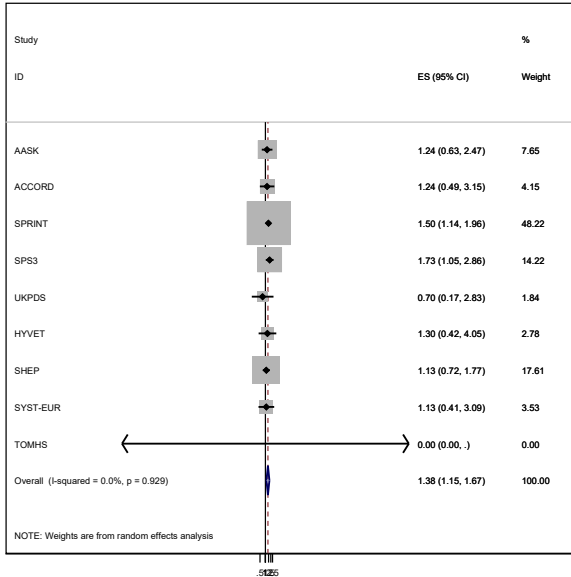
**D. Interaction of Assignment and HYP**



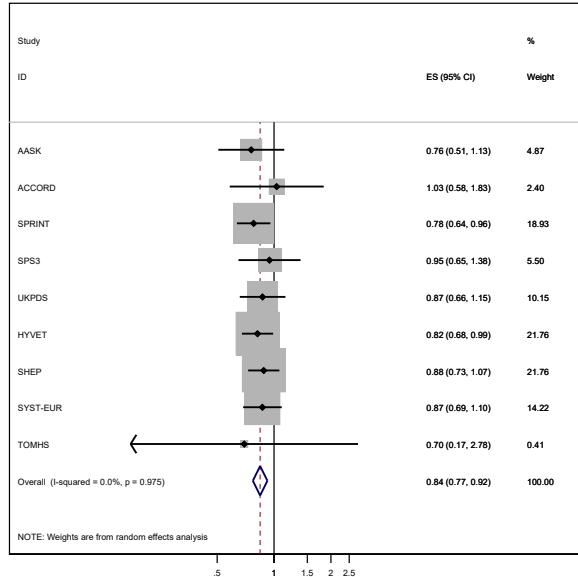
**eFigure 11.** Two-stage meta-analysis, standing hypotension and all-cause mortality

Two-stage meta-analysis examining the associations with all-cause mortality of (A) standing hypotension (HYP, yes versus no), (B) a low or active treatment assignment (Low/Act) versus standard or placebo assignment (Std/Pla) among participants without HYP, (C) Low/Act versus Std/Pla among participants with HYP, and (D) the interaction between HYP and treatment assignment. Individual effects were determined based on Cox models adjusted for age and sex. The pooled effect from the 9 trials were weighted with the inverse variance, using a random effects model.

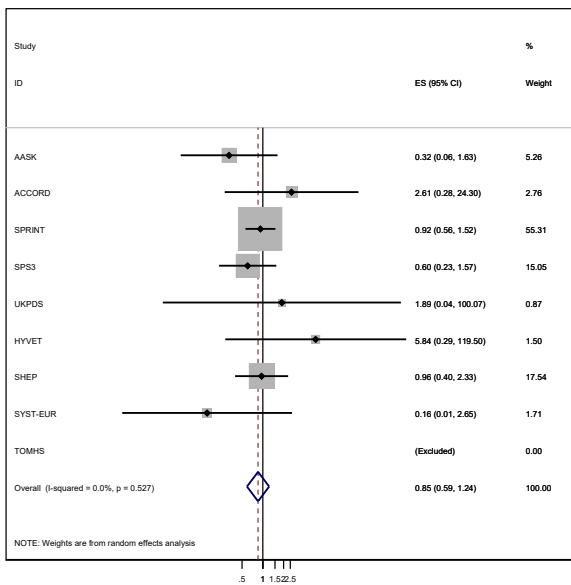
**A. Observational association: HYP & Outcome**



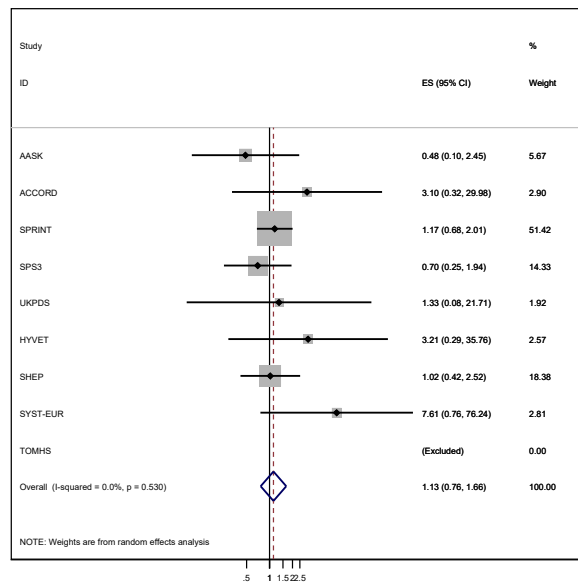
**B. Low/Act vs Std/Pla among those without HYP**



**C. Low/Act vs Std/Pla among those with HYP**



**D. Interaction of Assignment and HYP**



**eTable 1. Comparison of covariate definitions across blood pressure treatment goal trials**

	AASK	ACCORD BP	SPRINT	SPS3	UKPDS
<b>Age</b>	Reported <u>Inclusion:</u> 18-70 years	Reported <u>Inclusion:</u> 40-79 years	Reported <u>Inclusion:</u> ≥50 years	Reported <u>Inclusion:</u> ≥30 years	Reported <u>Inclusion:</u> 25-65 years
<b>Female</b>	Reported	Reported	Reported	Reported	Reported
<b>Black</b>	All participants (inclusion criterion)	Reported	Reported	Reported	Afro-Caribbean
<b>BMI</b>	Measured height and weight	Measured height and weight	Measured height and weight	Measured height and weight	Measured height and weight
<b>CKD</b>	Measured creatinine, CKD EPI equation, <60	Measured creatinine, CKD EPI equation eGFR <60 mL/min per 1.73 m <sup>2</sup>	Measured creatinine, CKD EPI equation eGFR <60 mL/min per 1.73 m <sup>2</sup>	Measured creatinine, CKD EPI equation eGFR <60 mL/min per 1.73 m <sup>2</sup> ; <u>Exclusion:</u> Participants with an estimated GFR <40 mL/min per 1.73 m <sup>2</sup>	Measured creatinine, CKD EPI equation eGFR <60 mL/min per 1.73 m <sup>2</sup> . <u>Exclusion:</u> serum creatinine concentration > 175 mmol/l
<b>Diabetes</b>	Baseline fasting glucose ≥ 126 mg/dL . AASK excluded adults with a fasting glucose ≥140 mg/dL or random glucose >200 mg/dL	<u>Inclusion:</u> 1. Type 2 diabetes mellitus defined according to the 1997 ADA criteria for 3 mo 2. An HbA1c level (obtained 3 mo before anticipated date of randomization) of a. 7.5%–11%: (i) If on insulin 1 U/kg and on 0 or 1 oral agent or (ii) If not on insulin, and on 0, 1, or 2 oral agents b. 7.5%–9%: (i) If on insulin 1 U/kg and on 2 oral agents, (ii) If on insulin 1 U/kg and 0 oral agents, or (iii) If not on insulin and on 3 oral agents) Oral agents included: insulin secretagogues, biguanides, insulin enhancers	<u>Exclusion:</u> Participants taking medications for diabetes at any time in the last 12 months are excluded. Participants were also excluded if they had a fasting plasma glucose ≥126 mg/dL, A1C ≥6.5%, a 2-hour OGTT (2-h PG) ≥200 mg/dL or a random plasma glucose concentration ≥200 mg/dL.	Chronic elevation of fasting serum glucose, >120 mg/dL or chronic requirement for glucose lowering medications (insulin secretagogues, biguanides, insulin enhancers)	<u>Inclusion:</u> Newly diagnosed diabetes with fasting plasma glucose 6.1-15.0 mmol/l without diabetic symptoms  <u>Exclusion:</u> Ketonuria >3 mmol/l Retinopathy requiring laser treatment

<b>Stroke</b>	Not reported at baseline	Not reported at baseline	<u>Exclusion:</u> History of stroke	<u>Inclusion:</u> A recent (within 180 days), symptomatic, MRI-confirmed lacunar stroke (>24 hours), and were without surgically amenable ipsilateral carotid artery stenosis or high-risk cardioembolic sources. Main exclusion criteria included disabling stroke (modified Rankin score of 4 or higher), previous intracranial hemorrhage from non-traumatic causes, retinal stroke, or cortical ischemic stroke	Self-reported
<b>CVD</b>	Not reported at baseline	History of CVD (prior MI, stroke, arterial revascularization, angina with ischemic changes on ECG at rest, changes on a graded exercise test, or positive cardiac imaging test results)	<u>Inclusion:</u> Clinical CVD (other than stroke): a) Previous myocardial infarction, percutaneous coronary intervention, CABG, carotid endarterectomy (CE), carotid stenting b) Peripheral artery disease with revascularization c) Acute coronary syndrome with or without resting ECG change, ECG changes on a graded exercise test, or positive cardiac imaging study d) At least a 50% diameter stenosis of a coronary, carotid, or lower extremity artery e) Abdominal aortic aneurysm $\geq$ 5 cm with or without repair	MI, angina, CHF, or revascularization procedure (e.g. CABG)	Self-reported history of stroke, MI, or heart failure

Abbreviations: ADA: American Diabetes Association; BMI: body mass index; CABG: coronary artery bypass graft; CHF: congestive heart failure; CKD: chronic kidney disease; CKD EPI: chronic kidney disease epidemiology collaboration; CVD: cardiovascular disease; ECG: electrocardiogram; eGFR: estimated glomerular filtration rate; ICD: international classification of disease; MRI: magnetic resonance imaging

Note this Table was adapted from Juraschek et al, *Annals of Internal Medicine*, 2020.

**eTable 2. Comparison of covariate definitions across placebo-controlled trials**

	<b>HYVET</b>	<b>SHEP</b>	<b>SYST-EUR</b>	<b>TOMHS</b>
<b>Age</b>	Reported <u>Inclusion:</u> ≥80 years	Calculated using difference of birthdate from randomization visit <u>Inclusion:</u> ≥60 years	Reported <u>Inclusion:</u> ≥60 years	Reported <u>Inclusion:</u> 45-69 years
<b>Female</b>	Reported	Reported	Reported	Reported
<b>Black</b>	Not Reported	Reported	Not Reported	Reported
<b>BMI</b>	Measured height and weight	Measured height and weight	Measured height and weight	Measured height and weight
<b>CKD</b>	Measured creatinine, CKD EPI equation eGFR <60 mL/min per 1.73 m <sup>2</sup>	Reported history of kidney disease or protein or blood in urine (Note: creatinine only available in a subset of the population and thus was not used)	Measured creatinine, CKD EPI equation eGFR <60 mL/min per 1.73 m <sup>2</sup>	Measured creatinine, CKD EPI equation eGFR <60 mL/min per 1.73 m <sup>2</sup>
<b>Diabetes</b>	Self-reported prevalent cases, antidiabetic treatment, or blood sugar >11.1 mmol/l (irrespective of fasting or nonfasting)	Reported history of non-insulin dependent diabetes <u>Exclusion:</u> Insulin dependent diabetes	Investigator reported diabetes or antidiabetic drug intake	Fasting glucose ≥ 126 mg/dL
<b>Stroke</b>	Reported history of stroke	Reported history of stroke	History of stroke (ICD9 4300-4329, 4340-4349, 4360-4369)	<u>Exclusion:</u> Reported history of stroke
<b>CVD</b>	Reported history of stroke, myocardial infarction, or heart failure	Reported history of a heart attack	Reported history of stroke, myocardial infarction, or heart failure	<u>Exclusion:</u> Reported history of cardiovascular disease

Abbreviations: BMI: body mass index; CKD: chronic kidney disease; CKD EPI: chronic kidney disease epidemiology collaboration; CVD: cardiovascular disease; eGFR: estimated glomerular filtration rate; ICD: international classification of disease; MRI: magnetic resonance imaging

Note this Table was adapted from Juraschek et al, *Annals of Internal Medicine*, 2020.

**eTable 3. Participant characteristics for all trials, trials of blood pressure treatment goal, and placebo-controlled trials**

<b>Characteristic</b>	<b>All Trials, N=29,235 Mean (SD) or %</b>	<b>Treatment Goal Trials, N=15,198 Mean (SD) or %</b>	<b>Placebo-Controlled Trials, N=14,037 Mean (SD) or %</b>
<b>Demographic Information</b>			
Age, years	69.0 (10.9) [N=29235]	64.8 (10.4) [N=15198]	73.5 (9.5) [N=14037]
Age >75 years, %	9057/29235 (31.0)	2696/15198 (17.7)	6361/14037 (45.3)
Women, %	14120/29235 (48.3)	5705/15198 (37.5)	8415/14037 (59.9)
Men, %	15115/29235 (51.7)	9493/15198 (62.5)	5622/14037 (40.1)
Black*, %	5517/20702 (26.6)	4705/15198 (31.0)	812/5504 (14.8)
<b>Past Medical Conditions</b>			
Diabetes, %	4817/29231 (16.5)	3457/15196 (22.7)	1360/14035 (9.7)
Prior stroke, %	2812/26818 (10.5)	2398/12783 (18.8)	414/14035 (2.9)
History of CVD, %	3657/28134 (13.0)	2550/14109 (18.1)	1107/14025 (7.9)
<b>Blood Pressure Measures</b>			
Pre-randomization seated SBP, mm Hg	155.1 (21.4) [N=29235]	141.6 (17.9) [N=15198]	169.8 (13.9) [N=14037]
Pre-randomization seated DBP, mm Hg	81.9 (11.6) [N=29235]	79.8 (12.6) [N=15198]	84.3 (9.9) [N=14037]
Pre-randomization standing SBP, mm Hg	153.0 (21.1) [N=29235]	142.1 (19.7) [N=15198]	164.9 (15.4) [N=14037]
Pre-randomization standing DBP, mm Hg	84.1 (12.0) [N=29235]	83.0 (13.4) [N=15198]	85.4 (10.1) [N=14037]
Pre-randomization postural change in SBP**, mm Hg	-2.1 (11.3) [N=29235]	0.5 (12.4) [N=15198]	-5.0 (9.3) [N=14037]
Pre-randomization postural change in DBP**, mm Hg	2.2 (7.4) [N=29235]	3.2 (7.8) [N=15198]	1.1 (6.8) [N=14037]
Pre-randomization seated BP $\geq 130/\geq 80$ mm Hg, %	26288/29235 (89.9)	12260/15198 (80.7)	14028/14037 (99.9)
Pre-randomization OH, %	2592/29235 (8.9)	1310/15198 (8.6)	1282/14037 (9.1)
Standing SBP $\leq 110$ or DBP $\leq 60$ mm Hg pre-randomization, %	1307/29235 (4.5)	1094/15198 (7.2)	213/14037 (1.5)
<b>Physical Measures &amp; Laboratory Values</b>			

Body mass index, kg/m <sup>2</sup>	28.4 (5.5) [N=29054]	30.0 (5.8) [N=15112]	26.7 (4.5) [N=13942]
Obese, %	9285/29054 (32.0)	6569/15112 (43.5)	2716/13942 (19.5)
eGFR <sup>***</sup> , mL/min per 1.73 m <sup>2</sup>	70.0 (19.6) [N=23134]	72.7 (21.6) [N=13706]	66.1 (15.5) [N=9428]
Stage III CKD (eGFR < 60 mL/min per 1.73 m <sup>2</sup> ) <sup>***</sup> , %	8837/28719 (30.8)	4185/14811 (28.3)	4652/13908 (33.4)

For all trials, the N for the following characteristics was: 20,702 for Black race, 26,818 for prior stroke, 28,134 for history of cardiovascular disease, 29,054 for body mass index and obesity, 23,134 for eGFR, and 28,719 for stage 3 CKD.

Among the blood pressure treatment goal trials, the N for the following characteristics was: 15,196 for diabetes, 12,783 for prior stroke, 14,109 for history of cardiovascular disease, 15,112 for body mass index and obesity, 13,706 for eGFR, and 14,811 for stage 3 CKD.

Among the placebo-controlled trials, the N for the following characteristics was: 5,504 for Black race, 14,035 for diabetes, 14,035 for prior stroke, 14,025 for history of cardiovascular disease, 13,942 for body mass index and obesity, 9,428 for eGFR, and 13,908 for stage 3 CKD.

Abbreviations: BP, blood pressure; CKD, chronic kidney disease; CVD, cardiovascular disease; DBP, diastolic blood pressure; eGFR, estimated glomerular filtration rate; SBP, systolic blood pressure

\*Self-reported

\*\*Standing minus seated blood pressure. Note that since orthostatic hypotension is defined based on either systolic or diastolic thresholds, the means for systolic and diastolic blood pressure are less than the orthostatic hypotension threshold of -20 or -10 mm Hg.

\*\*\*Based on the CKD EPI 2021 race-free, creatinine equation. eGFR was not available from UKPDS or SHEP. UKPDS provides stage III CKD categories based on the 2021 CKD-EPI race-free, creatinine equation. For SHEP we relied on a self-reported history of kidney disease.



**eTable 4. Cross-tabulation of orthostatic hypotension and standing hypotension  
N=29,235**

	No standing hypotension, N=27,928	Standing hypotension, N=1,307
No orthostatic hypotension, N=26,643	25,763	880
Orthostatic hypotension, N=2,592	2,165	427

**eTable 5. Baseline characteristics of each blood pressure treatment goal trial**

Characteristic	AASK		ACCORD		SPRINT		SPS3		UKPDS	
	N	Mean (SD) or %	N	Mean (SD) or %	N	Mean (SD) or %	N	Mean (SD) or %	N	Mean (SD) or %
<b>Demographic Information</b>										
Age, years	1089	54.6 (10.7)	1321	62.0 (6.5)	9326	67.9 (9.4)	2345	62.9 (10.8)	1117	56.9 (8.1)
Age >75 years, %	1089	0	1321	4	9326	25	2345	14	1117	0
Women, %	1089	39	1321	46	9326	36	2345	37	1117	45
Men, %	1089	61	1321	54	9326	64	2345	64	1117	55
Black*, %	1089	100	1321	20	9326	32	2345	14	1117	8
<b>Past Medical Conditions</b>										
Diabetes, %	1089	7	1321	100	9324	2	2345	34	1117	100
Prior stroke, %	1089	NA	1321	NA	9321	1	2345	100	1117	0
History of CVD, %	1089	NA	1321	35	9326	20	2345	9	1117	1
<b>Blood Pressure Measures</b>										
Pre-randomization seated SBP, mm Hg	1089	143.9 (22.5)	1321	138.1 (16.3)	9326	139.7 (15.6)	2345	142.0 (18.4)	1117	158.6 (21.9)
Pre-randomization seated DBP, mm Hg	1089	88.8 (13.5)	1321	76.2 (10.7)	9326	78.1 (11.9)	2345	77.9 (10.5)	1117	92.8 (11.2)
Pre-randomization standing SBP, mm Hg	1089	143.2 (23.5)	1321	139.5 (16.9)	9326	140.3 (17.9)	2345	144.1 (22.3)	1117	155.2 (21.7)
Pre-randomization standing DBP, mm Hg	1089	91.6 (14.6)	1321	79.0 (11.2)	9326	81.8 (12.9)	2345	81.0 (12.8)	1117	93.8 (10.9)
Pre-randomization postural change in SBP**, mm Hg	1089	-0.6 (10.8)	1321	1.3 (13.0)	9326	0.6 (11.8)	2345	2.1 (14.0)	1117	-3.3 (13.1)
Pre-randomization postural change in DBP**, mm Hg	1089	2.8 (8.2)	1321	2.9 (7.8)	9326	3.7 (7.5)	2345	3.1 (8.6)	1117	1.0 (7.3)
Pre-randomization seated BP ≥130/≥80 mm Hg, %	1089	86	1321	75	9326	80	2345	76	1117	98
Pre-randomization OH, %	1089	9	1321	8	9326	7	2345	10	1117	17

Standing SBP≤110 or  
DBP≤60 mm Hg pre-  
randomization, %

1089	8	1321	7	9326	8	2345	8	1117	1
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**Physical Measures &  
Laboratory Values**

Body mass index, kg/m <sup>2</sup>	1089	30.6 (6.6)	1321	32.5 (5.5)	9267	29.9 (5.8)	2340	28.8 (5.6)	1095	29.7 (5.5)
Obese, %	1089	47	1321	64	9267	43	2340	34	1095	40
eGFR***, mL/min per 1.73 m <sup>2</sup>	1087	42.4 (13.8)	1317	86.5 (16.8)	9287	72.4 (20.0)	2015	81.1 (18.8)	0	NA
Stage III CKD (eGFR < 60 mL/min per 1.73 m <sup>2</sup> )***, %	1087	90	1317	8	9287	27	2015	15	1105	26

Abbreviations: BP, blood pressure; CKD, chronic kidney disease; CVD, cardiovascular disease; DBP, diastolic blood pressure; eGFR, estimated glomerular filtration rate; SBP, systolic blood pressure

\*Self-reported

\*\*Standing minus seated blood pressure. Note that since orthostatic hypotension is defined based on either systolic or diastolic thresholds, the means for systolic and diastolic blood pressure are less than the orthostatic hypotension threshold of -20 or -10 mm Hg.

\*\*\*Based on the CKD EPI 2021 race-free, creatinine equation. eGFR was not available from UKPDS. UKPDS provided stage III CKD categories based on the 2021 CKD-EPI race-free, creatinine equation.

**eTable 6. Baseline characteristics of each placebo-controlled trial**

Characteristic	HYVET		SHEP		SYST-EUR		TOMHS	
	N	Mean (SD) or %	N	Mean (SD) or %	N	Mean (SD) or %	N	Mean (SD) or %
<b>Demographic Information</b>								
Age, years	3845	83.5 (3.2)	4602	72.1 (6.7)	4688	70.2 (6.7)	902	54.8 (6.4)
Age >75 years, %	3845	100	4602	33	4688	22	902	0
Women, %	3845	61	4602	57	4688	67	902	38
Men, %	3845	40	4602	43	4688	33	902	62
Black*, %	3845	NA	4602	14	4688	NA	902	20
<b>Past Medical Conditions</b>								
Diabetes, %	3845	10	4600	10	4688	10	902	6
Prior stroke, %	3845	7	4600	2	4688	1	902	0
History of CVD, %	3845	12	4590	9	4688	6	902	0
<b>Blood Pressure Measures</b>								
Pre-randomization seated SBP, mm Hg	3845	173.5 (9.4)	4602	169.7 (11.6)	4688	172.8 (11.8)	902	139.2 (13.7)
Pre-randomization seated DBP, mm Hg	3845	90.8 (9.1)	4602	77.1 (9.2)	4688	84.9 (6.9)	902	89.7 (4.8) 137.9 (14.8)
Pre-randomization standing SBP, mm Hg	3845	167.9 (11.0)	4602	164.4 (14.7)	4688	168.0 (14.1)	902	90.1 (6.6)
Pre-randomization standing DBP, mm Hg	3845	88.7 (9.3)	4602	80.2 (10.6)	4688	86.9 (8.4)	902	-1.3 (9.6)
Pre-randomization postural change in SBP**, mm Hg	3845	-5.5 (7.0)	4602	-5.4 (10.9)	4688	-4.8 (9.0)	902	0.4 (5.5)
Pre-randomization postural change in DBP**, mm Hg	3845	-2.1 (5.2)	4602	3.1 (8.1)	4688	2.0 (5.7)	902	99
Pre-randomization seated BP ≥130/≥80 mm Hg, %	3845	100	4602	100	4688	100	902	7
Pre-randomization OH, %	3845	9	4602	12	4688	7	902	2
Standing SBP≤110 or DBP≤60 mm Hg pre-randomization, %	3845	1	4602	4	4688	0	902	
<b>Physical Measures &amp; Laboratory Values</b>								
Body mass index, kg/m <sup>2</sup>	3837	24.7 (3.6)	4549	27.6 (5.1)	4654	27.0 (4.1)	902	28.9 (3.6)

Obese, %	3837	8	4549	26	4654	20	902	36
eGFR***, mL/min per 1.73 m <sup>2</sup>	3845	64.9 (16.1)	0	NA	4681	66.0 (15.1)	902	72.2 (13.6)
Stage III CKD (eGFR < 60 mL/min per 1.73 m <sup>2</sup> )***, %	3845	42	4480	25	4681	38	902	19

Abbreviations: BP, blood pressure; CKD, chronic kidney disease; CVD, cardiovascular disease; DBP, diastolic blood pressure; eGFR, estimated glomerular filtration rate; SBP, systolic blood pressure

\*Self-reported

\*\*Standing minus seated blood pressure. Note that since orthostatic hypotension is defined based on either systolic or diastolic thresholds, the means for systolic and diastolic blood pressure are less than the orthostatic hypotension threshold of -20 or -10 mm Hg.

\*\*\*Based on the CKD EPI 2021 race-free, creatinine equation. eGFR was not available from SHEP. In SHEP, participants self-reported history of kidney disease.

**eTable 7. Number of participants by distribution**  
**N=29,235**

	Low/Active, no outcome	Low/Active, outcome	Standard/placebo, no outcome	Standard/placebo, outcome
<b>Cardiovascular disease or all-cause mortality</b>				
<b>Change in SBP</b>	<b>N</b>	<b>N</b>	<b>N</b>	<b>N</b>
≤-30	134	42	125	38
>-30 to ≤-20	613	114	513	128
>-20 to ≤-10	2223	366	1946	428
>-10 to <10	8210	1326	7523	1502
≥10 to <20	1295	240	1243	271
≥20 to <30	324	59	283	88
≥30	90	21	75	15
<b>Standing SBP</b>				
<110	217	54	183	70
110 to <130	1665	270	1507	295
130 to <150	3537	554	3148	608
150 to <170	4742	714	4375	888
≥170	2728	576	2495	609
<b>Change in DBP</b>				
≤-20	53	15	41	12
>-20 to ≤-10	457	109	429	128
>-10 to <10	10585	1697	9447	1921
≥10 to <20	1608	303	1617	363
≥20	186	44	174	46
<b>Standing DBP</b>				
<70	1333	266	1268	320
70 to <80	2771	428	2634	489
80 to <90	4313	622	3929	737
90 to <100	3462	529	2984	611
≥100	1010	323	893	313

**All-cause mortality****Change in SBP**

≤-30	144	32	136	27
>-30 to ≤-20	666	61	578	63
>-20 to ≤-10	2401	188	2171	203
>-10 to <10	8932	604	8352	673
≥10 to <20	1444	91	1426	88
≥20 to <30	361	22	337	34
≥30	99	12	83	7

**Standing SBP**

<110	258	13	230	23
110 to <130	1856	79	1715	87
130 to <150	3879	212	3534	222
150 to <170	5092	364	4829	434
≥170	2962	342	2775	329

**Change in DBP**

≤-20	59	9	45	8
>-20 to ≤-10	519	47	498	59
>-10 to <10	11464	818	10493	875
≥10 to <20	1799	112	1843	137
≥20	206	24	204	16

**Standing DBP**

<70	1464	135	1438	150
70 to <80	3006	193	2909	214
80 to <90	4653	282	4340	326
90 to <100	3719	272	3300	295
≥100	1205	128	1096	110

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**eTable 8. Association of baseline orthostatic hypotension with cardiovascular disease or all-cause mortality**

Cardiovascular disease or all-cause mortality	Baseline Orthostatic Hypotension			
	Orthostatic hypotension, n/N	No orthostatic hypotension, n/N	HR (95% CI)	P
AASK	96/100	926/989	1.09 (0.89, 1.35)	0.41
ACCORD	15/101	130/1220	1.40 (0.82, 2.39)	0.22
SPRINT	93/683	881/8643	1.26 (1.01, 1.55)	0.04
SPS3	41/239	243/2106	1.55 (1.11, 2.16)	0.009
UKPDS	58/187	253/930	1.11 (0.84, 1.48)	0.46
<i>Treatment Goal Trials</i>	303/1310	2433/13888	1.24 (1.10, 1.40)	<0.001
HYVET	46/336	480/3509	0.99 (0.73, 1.35)	0.97
SHEP	102/554	765/4048	0.94 (0.76, 1.15)	0.55
SYST-EUR	45/333	413/4355	1.25 (0.92, 1.70)	0.15
TOMHS	5/59	46/843	1.57 (0.62, 3.95)	0.34
<i>Placebo-controlled Trials</i>	198/1282	1704/12755	1.00 (0.86, 1.16)	0.99
<i>All Trials**</i>	501/2592	4137/26643	1.14 (1.04, 1.26)	0.005
All-Cause Mortality	Baseline Orthostatic Hypotension			
	Orthostatic hypotension, n/N	No orthostatic hypotension, n/N	HR (95% CI)	P
AASK	12/100	94/989	1.32 (0.72, 2.40)	0.37
ACCORD	5/101	47/1220	1.29 (0.51, 3.24)	0.59
SPRINT	49/683	390/8643	1.41 (1.05, 1.90)	0.02
SPS3	21/239	105/2106	1.92 (1.20, 3.07)	0.007
UKPDS	42/187	172/930	1.18 (0.84, 1.66)	0.33
<i>Treatment Goal Trials</i>	129/1310	808/13888	1.39 (1.15, 1.68)	<0.001
HYVET	37/336	394/3509	0.97 (0.69, 1.36)	0.86
SHEP	66/554	377/4048	1.23 (0.94, 1.59)	0.13
SYST-EUR	28/333	257/4355	1.27 (0.86, 1.88)	0.23
TOMHS	1/59	8/843	1.76 (0.22, 14.12)	0.59
<i>Placebo-controlled Trials</i>	132/1282	1036/12755	1.11 (0.93, 1.33)	0.25
<i>All Trials***</i>	261/2592	1844/26643	1.24 (1.09, 1.41)	0.001

Abbreviations: CI, confidence interval; HR, hazard ratio; n represents number of events; n/N represents number of events/number of participants at risk

Cox proportional hazards models adjusted for age, sex, and study (as a categorical variable).

There was no evidence for an interaction by treatment arm for individual studies or pooled study groupings with the exception of the SHEP trial for baseline orthostatic hypotension with respect to all-cause mortality ( $P$ -interaction = 0.032).

\*Could not be calculated due to small numbers.

\*\*Egger's test found no statistical evidence of bias ( $P > 0.05$ ).

\*\*\*Egger's test found no statistical evidence of bias ( $P > 0.05$ ).



**eTable 9. Association of baseline standing hypotension with cardiovascular disease or all-cause mortality**

Cardiovascular disease or all-cause mortality	Baseline Standing Hypotension			
	Hypotension, n/N	No Hypotension, n/N	HR (95% CI)	P
AASK	83/84	939/1005	1.37 (1.09, 1.72)	0.006
ACCORD	16/86	129/1235	1.61 (0.95, 2.72)	0.08
SPRINT	124/718	850/8608	1.49 (1.23, 1.80)	<0.001
SPS3	33/191	251/2154	1.51 (1.05, 2.17)	0.03
UKPDS	3/15	308/1102	0.68 (0.22, 2.13)	0.51
<i>Treatment Goal Trials</i>	259/1094	2477/14104	1.50 (1.32, 1.71)	<0.001
HYVET	3/22	523/3823	1.04 (0.34, 3.25)	0.94
SHEP	37/162	830/4440	1.16 (0.83, 1.61)	0.39
SYST-EUR	5/15	453/4673	1.21 (0.50, 2.98)	0.67
TOMHS	0/14	51/888	*	*
<i>Placebo-controlled Trials</i>	45/213	1857/13824	1.11 (0.83, 1.50)	0.48
<i>All Trials**</i>	304/1307	4334/27928	1.39 (1.24, 1.57)	<0.001
All-Cause Mortality	Baseline Standing Hypotension			
	Hypotension, n/N	No Hypotension, n/N	HR (95% CI)	P
AASK	9/84	97/1005	1.24 (0.63, 2.47)	0.53
ACCORD	5/86	47/1235	1.24 (0.49, 3.15)	0.64
SPRINT	62/718	377/8608	1.50 (1.14, 1.97)	0.004
SPS3	18/191	108/2154	1.73 (1.05, 2.86)	0.03
UKPDS	2/15	212/1102	0.70 (0.17, 2.83)	0.62
<i>Treatment Goal Trials</i>	96/1094	841/14104	1.50 (1.21, 1.85)	<0.001
HYVET	3/22	428/3823	1.30 (0.42, 4.06)	0.65
SHEP	20/162	423/4440	1.13 (0.72, 1.77)	0.60
SYST-EUR	4/15	281/4673	1.13 (0.41, 3.09)	0.81
TOMHS	0/14	9/888	*	*
<i>Placebo-controlled Trials</i>	27/213	1141/13824	1.17 (0.79, 1.72)	0.43
<i>All Trials***</i>	123/1307	1982/27928	1.38 (1.14, 1.66)	<0.0001

Abbreviations: CVD, cardiovascular disease; CI, confidence interval; HR, hazard ratio; n represents number of events; N represents overall number of participants.

Cox proportional hazards models adjusted for age, sex, and study (as a categorical variable).

There was no evidence for an interaction by treatment arm for individual studies or pooled study groupings.

\*Could not be calculated due to small numbers.

\*\*Egger's test found no statistical evidence of bias ( $P > 0.05$ ).

\*\*\*Egger's test found no statistical evidence of bias ( $P > 0.05$ ).

**eTable 10. Association of baseline orthostatic hypotension with cardiovascular disease or all-cause mortality adjusted for additional cardiovascular risk factors**

Cardiovascular disease or all-cause mortality	Baseline Orthostatic Hypotension			
	Orthostatic hypotension, n/N	No orthostatic hypotension, n/N	HR (95% CI)	P
AASK	96/100	924/987	1.09 (0.88, 1.34)	0.44
ACCORD	15/101	129/1216	1.29 (0.75, 2.25)	0.36
SPRINT	91/675	874/8553	1.16 (0.93, 1.45)	0.18
SPS3	35/199	227/1811	1.32 (0.92, 1.89)	0.14
UKPDS	54/178	247/905	0.95 (0.70, 1.29)	0.72
<i>Treatment Goal Trials</i>	291/1253	2401/13472	1.18 (1.04, 1.33)	0.01
HYVET	46/336	479/3501	0.99 (0.73, 1.34)	0.94
SHEP	96/533	724/3894	0.92 (0.74, 1.13)	0.42
SYST-EUR	45/331	402/4316	1.20 (0.88, 1.64)	0.25
TOMHS	5/59	46/843	1.45 (0.57, 3.69)	0.43
<i>Placebo-controlled Trials</i>	192/1259	1651/12554	0.99 (0.85, 1.15)	0.88
<i>All Trials</i>	483/2512	4052/26026	1.11 (1.01, 1.22)	0.04
All-Cause Mortality	Baseline Orthostatic Hypotension			
	Orthostatic hypotension, n/N	No orthostatic hypotension, n/N	HR (95% CI)	P
AASK	12/100	94/987	1.32 (0.72, 2.41)	0.37
ACCORD	5/101	47/1216	1.25 (0.48, 3.23)	0.65
SPRINT	47/675	385/8553	1.23 (0.90, 1.67)	0.19
SPS3	18/199	97/1811	1.60 (0.96, 2.66)	0.07
UKPDS	41/178	168/905	1.06 (0.74, 1.51)	0.77
<i>Treatment Goal Trials</i>	123/1253	791/13472	1.25 (1.03, 1.52)	0.02
HYVET	37/336	393/3501	0.95 (0.68, 1.34)	0.77
SHEP	63/533	353/3894	1.23 (0.94, 1.61)	0.14
SYST-EUR	28/331	248/4316	1.15 (0.77, 1.72)	0.49
TOMHS	1/59	8/843	1.91 (0.23, 15.61)	0.54
<i>Placebo-controlled Trials</i>	129/1259	1002/12554	1.10 (0.91, 1.33)	0.31
<i>All Trials</i>	252/2512	1793/26026	1.18 (1.03, 1.35)	0.02

Abbreviations: CI, confidence interval; HR, hazard ratio; n represents number of events; n/N represents number of events/number of participants at risk

Cox proportional hazards models adjusted for age, sex, seated systolic blood pressure, seated diastolic blood pressure, eGFR<60 mL/min per 1.73 m<sup>2</sup>, body mass index, and diabetes status

Pooled estimates were additionally adjusted for study (as a categorical variable).

There was no evidence for an interaction by treatment arm for individual studies or pooled study groupings.

**eTable 11. Association of baseline standing hypotension with cardiovascular disease or all-cause mortality adjusted for additional cardiovascular risk factors**

Cardiovascular disease or all-cause mortality	Baseline Standing Hypotension			
	Hypotension, n/N	No Hypotension, n/N	HR (95% CI)	P
AASK	83/84	937/1003	1.53 (1.20, 1.97)	<0.001
ACCORD	16/86	128/1231	1.67 (0.94, 2.95)	0.08
SPRINT	124/713	841/8515	1.53 (1.24, 1.89)	<0.001
SPS3	28/162	234/1848	1.53 (1.00, 2.35)	0.05
UKPDS	3/15	298/1068	1.10 (0.34, 3.51)	0.88
<i>Treatment Goal Trials</i>	254/1060	2438/13665	1.63 (1.41, 1.88)	<0.001
HYVET	3/22	522/3815	2.34 (0.72, 7.57)	0.16
SHEP	37/160	783/4267	1.09 (0.76, 1.56)	0.64
SYST-EUR	5/15	442/4632	1.14 (0.45, 2.92)	0.78
TOMHS	0/14	51/888	*	*
<i>Placebo-controlled Trials</i>	45/211	1798/13602	1.28 (0.94, 1.76)	0.12
<i>All Trials</i>	299/1271	4236/27267	1.55 (1.36, 1.76)	<0.001
All-Cause Mortality	Baseline Standing Hypotension			
	Hypotension, n/N	No Hypotension, n/N	HR (95% CI)	P
AASK	9/84	97/1003	1.55 (0.72, 3.30)	0.26
ACCORD	5/86	47/1231	1.02 (0.38, 2.78)	0.96
SPRINT	62/713	370/8515	1.67 (1.23, 2.26)	0.001
SPS3	15/162	100/1848	2.27 (1.24, 4.16)	0.01
UKPDS	2/15	207/1068	1.18 (0.28, 4.90)	0.82
<i>Treatment Goal Trials</i>	93/1060	821/13665	1.71 (1.35, 2.17)	0.008
HYVET	3/22	427/3815	2.83 (0.87, 9.25)	0.08
SHEP	20/160	396/4267	0.98 (0.60, 1.60)	0.93
SYST-EUR	4/15	272/4632	1.19 (0.41, 3.46)	0.75

TOMHS	0/14	9/888	*	*
<i>Placebo-controlled Trials</i>	27/211	1104/13602	1.38 (0.92, 2.08)	0.12
<i>All Trials</i>	120/1271	1925/27267	1.61 (1.31, 1.98)	<0.001

Abbreviations: CVD, cardiovascular disease; CI, confidence interval; HR, hazard ratio; n represents number of events; N represents overall number of participants.

Cox proportional hazards models adjusted for age, sex, seated systolic blood pressure, seated diastolic blood pressure, eGFR<60 mL/min per 1.73 m<sup>2</sup>, body mass index, and diabetes status

Pooled estimates were additionally adjusted for study (as a categorical variable).

There was no evidence for an interaction by treatment arm for individual studies or pooled study groupings.

\*Could not be calculated due to small numbers.

**eTable 12. Association between orthostatic or standing hypotension and outcomes among those assigned a more intensive blood pressure goal or active treatment**

Cardiovascular disease or all-cause mortality	Baseline Orthostatic Hypotension				Baseline Standing Hypotension			
	Orthostatic hypotension, n/N	No orthostatic hypotension, n/N	HR (95% CI)	P	Hypotension, n/N	No Hypotension, n/N	HR (95% CI)	P
	AASK	45/47	457/491	1.09 (0.80, 1.48)	0.58	37/38	465/500	1.23 (0.88, 1.73)
ACCORD	6/56	59/602	1.13 (0.49, 2.63)	0.77	8/49	57/609	1.57 (0.74, 3.30)	0.24
SPRINT	40/344	396/4319	1.20 (0.87, 1.66)	0.28	59/361	377/4302	1.59 (1.20, 2.10)	0.001
SPS3	19/114	110/1043	1.81 (1.11, 2.96)	0.02	17/94	112/1063	1.86 (1.12, 3.11)	0.02
UKPDS	39/126	149/615	1.24 (0.87, 1.76)	0.24	2/7	186/734	1.11 (0.28, 4.50)	0.88
<i>Treatment Goal Trials</i>	149/687	1171/7070	1.24 (1.05, 1.47)	0.01	123/549	1197/7208	1.58 (1.31, 1.90)	<0.001
HYVET	14/153	209/1780	0.77 (0.45, 1.32)	0.33	2/10	221/1923	1.92 (0.48, 7.74)	0.36
SHEP	51/279	333/2029	1.15 (0.86, 1.55)	0.34	18/76	366/2232	1.40 (0.87, 2.25)	0.17
 							3.67	
SYST-EUR	21/180	186/2211	1.25 (0.80, 1.96)	0.33	1/7	206/2384	(0.51, 26.40)	0.20
TOMHS	3/47	31/621	1.31 (0.40, 4.29)	0.65	0/12	34/656	*	*
<i>Placebo-controlled Trials</i>	89/659	759/6641	1.06 (0.85, 1.32)	0.63	21/105	827/7195	1.30 (0.84, 2.01)	0.25
<i>All Trials**</i>	238/1346	1930/13711	1.17 (1.02, 1.34)	0.02	144/654	2024/14403	1.49 (1.25, 1.77)	<0.001
All-Cause Mortality	Baseline Orthostatic Hypotension				Baseline Standing Hypotension			
	Orthostatic hypotension, n/N	No orthostatic hypotension, n/N	HR (95% CI)	P	Hypotension, n/N	No Hypotension, n/N	HR (95% CI)	P
	AASK	4/47	41/491	1.06 (0.38, 2.96)	0.92	2/38	43/500	0.71 (0.17, 2.93)
ACCORD	3/56	24/602	1.30 (0.38, 4.38)	0.68	4/49	23/609	1.67 (0.57, 4.94)	0.35
SPRINT	20/344	175/4319	1.26 (0.79, 2.01)	0.33	30/361	165/4302	1.63 (1.10, 2.42)	0.02
SPS3	11/114	49/1043	2.55 (1.32, 4.92)	0.005	7/94	53/1063	1.43 (0.65, 3.14)	0.38
UKPDS	28/126	106/615	1.24 (0.82, 1.88)	0.32	1/7	133/734	0.80 (0.11, 5.74)	0.82

<i>Treatment Goal Trials</i>	66/687	395/7070	1.38 (1.06, 1.80)	0.02	44/549	417/7208	1.54 (1.12, 2.12)	0.008
HYVET	14/153	182/1780	0.89 (0.52, 1.53)	0.67	2/10	194/1923	2.24 (0.56, 9.05)	0.26
SHEP	37/279	173/2029	1.62 (1.14, 2.32)	0.008	9/76	201/2232	1.15 (0.59, 2.24)	0.69
SYST-EUR	11/180	126/2211	0.98 (0.53, 1.82)	0.95	1/7	136/2384	8.91 (1.22,65.16)	0.03
TOMHS	1/47	5/621	2.73 (0.32,23.36)	0.36	0/12	6/656	*	*
<i>Placebo-controlled Trials</i>	63/659	486/6641	1.20 (0.92, 1.56)	0.17	12/105	537/7195	1.25 (0.70, 2.23)	0.45
<i>All Trials***</i>	129/1346	881/13711	1.29 (1.07, 1.55)	0.008	56/654	954/14403	1.41 (1.07, 1.87)	0.01

Abbreviations: CI, confidence interval; HR, hazard ratio; n represents number of events; N represents overall number of participant at risk.

Cox proportional hazards models adjusted for age, sex, and study.

Pooled estimates were additionally adjusted for study (as a categorical variable).

\*Could not be calculated due to small numbers.

**eTable 13. Association between orthostatic or standing hypotension and outcomes among those assigned a standard blood pressure goal or placebo**

**Cardiovascular disease  
or all-cause mortality**

	Baseline Orthostatic Hypotension				Baseline Standing Hypotension			
	Orthostatic hypotension, n/N	No orthostatic hypotension, n/N	HR (95% CI)	P	Hypotension, n/N	No Hypotension, n/N	HR (95% CI)	P
AASK	51/53	469/498	1.10 (0.82, 1.47)	0.53	46/46	474/505	1.50 (1.11, 2.03)	0.009
ACCORD	9/45	71/618	1.69 (0.84, 3.39)	0.14	8/37	72/626	1.72 (0.82, 3.61)	0.15
SPRINT	53/339	485/4324	1.31 (0.98, 1.74)	0.07	65/357	473/4306	1.41 (1.09, 1.84)	0.01
SPS3	22/125	133/1063	1.37 (0.87, 2.15)	0.17	16/97	139/1091	1.26 (0.75, 2.12)	0.39
UKPDS	19/61	104/315	0.95 (0.58, 1.55)	0.82	1/8	122/368	0.35 (0.05, 2.54)	0.30
<i>Treatment Goal Trials</i>	154/623	1262/6818	1.25 (1.05, 1.48)	0.01	136/545	1280/6896	1.43 (1.20, 1.71)	<0.001
HYVET	32/183	271/1729	1.12 (0.78, 1.62)	0.54	1/12	302/1900	0.53 (0.07, 3.78)	0.53
SHEP	51/275	432/2019	0.78 (0.58, 1.04)	0.09	19/86	464/2208	0.98 (0.62, 1.56)	0.94
SYST-EUR	24/153	227/2144	1.27 (0.83, 1.93)	0.27	4/8	247/2289	1.15 (0.41, 3.18)	0.79
TOMHS	2/12	15/222	2.70 (0.60, 12.13)	0.20	0/2	17/232	*	*
<i>Placebo-controlled Trials</i>	109/623	945/6114	0.95 (0.78, 1.16)	0.62	24/108	1030/6629	0.98 (0.65, 1.48)	0.93
<i>All Trials**</i>	263/1246	2207/12932	1.12 (0.98, 1.27)	0.09	160/653	2310/13525	1.31 (1.11, 1.54)	0.001

**All-Cause Mortality**

	Baseline Orthostatic Hypotension				Baseline Standing Hypotension			
	Orthostatic hypotension, n/N	No orthostatic hypotension, n/N	HR (95% CI)	P	Hypotension, n/N	No Hypotension, n/N	HR (95% CI)	P
AASK	8/53	53/498	1.48 (0.70, 3.11)	0.30	7/46	54/505	1.52 (0.69, 3.35)	0.30
ACCORD	2/45	23/618	1.04 (0.24, 4.41)	0.96	1/37	24/626	0.53 (0.07, 3.98)	0.54
SPRINT	29/339	215/4324	1.54 (1.04, 2.27)	0.03	32/357	212/4306	1.39 (0.96, 2.03)	0.08
SPS3	10/125	56/1063	1.51 (0.77, 2.96)	0.23	11/97	55/1091	1.99 (1.03, 3.81)	0.04
UKPDS	14/61	66/315	1.09 (0.61, 1.96)	0.76	1/8	79/368	0.60 (0.08, 4.30)	0.61
<i>Treatment Goal Trials</i>	63/623	413/6818	1.40 (1.07, 1.83)	0.01	52/545	424/6896	1.45 (1.08, 1.94)	0.01
HYVET	23/183	212/1729	1.01 (0.66, 1.56)	0.96	1/12	234/1900	0.69 (0.10, 4.90)	0.71

SHEP	29/275	204/2019	0.91 (0.62, 1.35)	0.64	11/86	222/2208	1.12 (0.61, 2.06)	0.71
SYST-EUR	17/153	131/2144	1.57 (0.94, 2.60)	0.08	3/8	145/2289	1.05 (0.32, 3.43)	0.93
TOMHS	0/12	3/222	*	*	0/2	3/232	*	*
<i>Placebo-controlled Trials</i>	69/623	550/6114	1.04 (0.81, 1.33)	0.78	15/108	604/6629	1.12 (0.66, 1.87)	0.68
<i>All Trials***</i>	132/1246	963/12932	1.19 (0.99, 1.43)	0.06	67/653	1028/13525	1.34 (1.04, 1.72)	0.02

Abbreviations: CI, confidence interval; HR, hazard ratio; n represents number of events; N represents overall number of participants at risk.

Cox proportional hazards models adjusted for age, sex, and study.

Pooled estimates were additionally adjusted for study (as a categorical variable).

\*Could not be calculated due to small numbers.



**eTable 14. Treatment effects on cardiovascular disease or all-cause mortality by baseline orthostatic hypotension, unadjusted**

<b>Orthostatic Hypotension</b>							
<b>Cardiovascular Disease or All-cause Mortality</b>							
	<b>Orthostatic Hypotension</b>			<b>No Orthostatic Hypotension</b>			<b>P-</b>
	<b>n/N (Low/Act)</b>	<b>n/N (Std/Pla)</b>	<b>HR (95% CI)</b>	<b>n/N (Low/Act)</b>	<b>n/N (Std/Pla)</b>	<b>HR (95% CI)</b>	<b>interaction</b>
<b>AASK</b>	45/47	51/53	0.95 (0.63, 1.43)	457/491	469/498	0.96 (0.84, 1.09)	0.97
<b>ACCORD</b>	6/56	9/45	0.48 (0.17, 1.35)	59/602	71/618	0.86 (0.61, 1.21)	0.31
<b>SPRINT</b>	40/344	53/339	0.74 (0.49, 1.11)	396/4319	485/4324	0.81 (0.71, 0.92)	0.68
<b>SPS3</b>	19/114	22/125	1.08 (0.58, 1.99)	110/1043	133/1063	0.81 (0.63, 1.04)	0.41
<b>UKPDS</b>	39/126	19/61	0.96 (0.55, 1.65)	149/615	104/315	0.71 (0.55, 0.92)	0.35
<b>Treatment Goal Trials</b>	149/687	154/623	0.77 (0.62, 0.97)	1171/7070	1262/6818	0.80 (0.74, 0.87)	0.55
<b>HYVET</b>	14/153	32/183	0.50 (0.27, 0.93)	209/1780	271/1729	0.75 (0.62, 0.89)	0.22
<b>SHEP</b>	51/279	51/275	1.06 (0.72, 1.57)	333/2029	432/2019	0.73 (0.64, 0.85)	0.11
<b>SYST-EUR</b>	21/180	24/153	0.75 (0.42, 1.36)	186/2211	227/2144	0.77 (0.64, 0.94)	0.94
<b>TOMHS</b>	3/47	2/12	0.35 (0.06, 2.10)	31/621	15/222	0.73 (0.39, 1.35)	0.42
<b>Placebo-Controlled Trials</b>	89/659	109/623	0.78 (0.59, 1.03)	759/6641	945/6114	0.71 (0.65, 0.78)	0.59
<b>All Trials</b>	238/1346	263/1246	0.80 (0.67, 0.95)	1930/13711	2207/12932	0.78 (0.73, 0.83)	0.87
<b>All-cause Mortality</b>							
	<b>Orthostatic Hypotension</b>			<b>No Orthostatic Hypotension</b>			<b>P-</b>
	<b>n/N (Low/Act)</b>	<b>n/N (Std/Pla)</b>	<b>HR (95% CI)</b>	<b>n/N (Low/Act)</b>	<b>n/N (Std/Pla)</b>	<b>HR (95% CI)</b>	<b>interaction</b>
<b>AASK</b>	4/47	8/53	0.52 (0.16, 1.74)	41/491	53/498	0.75 (0.50, 1.13)	0.59
<b>ACCORD</b>	3/56	2/45	1.22 (0.20, 7.34)	24/602	23/618	1.09 (0.61, 1.93)	0.94
<b>SPRINT</b>	20/344	29/339	0.67 (0.38, 1.18)	175/4319	215/4324	0.81 (0.66, 0.99)	0.53
<b>SPS3</b>	11/114	10/125	1.43 (0.61, 3.37)	49/1043	56/1063	0.85 (0.58, 1.25)	0.28
<b>UKPDS</b>	28/126	14/61	0.93 (0.49, 1.76)	106/615	66/315	0.83 (0.61, 1.13)	0.73

<b>Treatment Goal Trials</b>	66/687	63/623	0.83 (0.59, 1.18)	395/7070	413/6818	0.84 (0.73, 0.96)	0.85
<b>HYVET</b>	14/153	23/183	0.71 (0.37, 1.38)	182/1780	212/1729	0.84 (0.69, 1.02)	0.64
<b>SHEP</b>	37/279	29/275	1.40 (0.86, 2.28)	173/2029	204/2019	0.83 (0.68, 1.02)	0.06
<b>SYST-EUR</b>	11/180	17/153	0.55 (0.26, 1.18)	126/2211	131/2144	0.93 (0.73, 1.19)	0.21
<b>TOMHS</b>	1/47	0/12	*	5/621	3/222	0.59 (0.14, 2.48)	*
<b>Placebo-Controlled Trials</b>	63/659	69/623	0.89 (0.63, 1.26)	486/6641	550/6114	0.80 (0.71, 0.90)	0.57
<b>All Trials</b>	129/1346	132/1246	0.87 (0.68, 1.11)	881/13711	963/12932	0.82 (0.75, 0.90)	0.76

Abbreviations: CI, confidence interval; HR, hazard ratio; Low/Act, randomized assignment of low blood pressure goal or active therapy; n represents number of events; N represents overall number of participants; Std/Pla, randomized assignment to standard blood pressure goal or placebo.

All models were unadjusted.

\*Could not be calculated due to small numbers.

**eTable 15. Treatment effects on cardiovascular disease or all-cause mortality by baseline standing hypotension, unadjusted**

<b>Cardiovascular Disease or All-cause Mortality</b>							
	<b>n/N (Low/Act)</b>	<b>n/N (Std/Pla)</b>	<b>Hypotension HR (95% CI)</b>	<b>n/N (Low/Act)</b>	<b>n/N (Std/Pla)</b>	<b>No Hypotension HR (95% CI)</b>	<b>P-interaction</b>
<b>AASK</b>	37/38	46/46	0.82 (0.53, 1.27)	465/500	474/505	0.97 (0.86, 1.11)	0.46
<b>ACCORD</b>	8/49	8/37	0.72 (0.27, 1.91)	57/609	72/626	0.81 (0.57, 1.15)	0.81
<b>SPRINT</b>	59/361	65/357	0.89 (0.62, 1.26)	377/4302	473/4306	0.79 (0.69, 0.90)	0.55
<b>SPS3</b>	17/94	16/97	1.18 (0.59, 2.33)	112/1063	139/1091	0.80 (0.62, 1.02)	0.29
<b>UKPDS</b>	2/7	1/8	2.20 (0.20,24.33)	186/734	122/368	0.74 (0.59, 0.93)	0.29
<b>Treatment Goal Trials</b>	123/549	136/545	0.89 (0.70, 1.14)	1197/7208	1280/6896	0.79 (0.73, 0.86)	0.35
<b>HYVET</b>	2/10	1/12	2.35 (0.21,25.89)	221/1923	302/1900	0.72 (0.60, 0.85)	0.31
<b>SHEP</b>	18/76	19/86	1.04 (0.55, 1.99)	366/2232	464/2208	0.75 (0.66, 0.86)	0.33
<b>SYST-EUR</b>	1/7	4/8	0.29 (0.03, 2.65)	206/2384	247/2289	0.78 (0.65, 0.94)	0.43
<b>TOMHS</b>	0/12	0/2	*	34/656	17/232	0.69 (0.39, 1.24)	*
<b>Placebo-Controlled Trials</b>	21/105	24/108	0.89 (0.50, 1.61)	827/7195	1030/6629	0.72 (0.65, 0.78)	0.43
<b>All Trials*</b>	144/654	160/653	0.89 (0.71, 1.12)	2024/14403	2310/13525	0.77 (0.73, 0.82)	0.27
<b>All-cause Mortality</b>							
	<b>n/N (Low/Act)</b>	<b>n/N (Std/Pla)</b>	<b>Hypotension HR (95% CI)</b>	<b>n/N (Low/Act)</b>	<b>n/N (Std/Pla)</b>	<b>No Hypotension HR (95% CI)</b>	<b>P-interaction</b>
<b>AASK</b>	2/38	7/46	0.32 (0.07, 1.53)	43/500	54/505	0.78 (0.52, 1.16)	0.29
<b>ACCORD</b>	4/49	1/37	2.64 (0.29,23.95)	23/609	24/626	1.00 (0.56, 1.77)	0.36
<b>SPRINT</b>	30/361	32/357	0.92 (0.56, 1.52)	165/4302	212/4306	0.78 (0.63, 0.95)	0.54
<b>SPS3</b>	7/94	11/97	0.65 (0.25, 1.69)	53/1063	55/1091	0.96 (0.66, 1.40)	0.46
<b>UKPDS</b>	1/7	1/8	1.07 (0.07,17.12)	133/734	79/368	0.84 (0.64, 1.11)	0.72
<b>Treatment Goal Trials</b>	44/549	52/545	0.83 (0.56, 1.24)	417/7208	424/6896	0.84 (0.73, 0.96)	0.99
<b>HYVET</b>	2/10	1/12	2.35 (0.21,25.89)	194/1923	234/1900	0.82 (0.68, 0.99)	0.37
<b>SHEP</b>	9/76	11/86	0.95 (0.39, 2.30)	201/2232	222/2208	0.89 (0.74, 1.08)	0.92

<b>SYST-EUR</b>	1/7	3/8	0.45 (0.05, 4.35)	136/2384	145/2289	0.90 (0.71, 1.14)	0.52
<b>TOMHS</b>	0/12	0/2	*	6/656	3/232	0.70 (0.18, 2.81)	*
<b><i>Placebo-Controlled Trials</i></b>	12/105	15/108	0.84 (0.40, 1.81)	537/7195	604/6629	0.81 (0.72, 0.91)	0.87
<b><i>All Trials**</i></b>	56/654	67/653	0.83 (0.58, 1.19)	954/14403	1028/13525	0.83 (0.76, 0.90)	0.87

Abbreviations: CI, confidence interval; HR, hazard ratio; Low/Act, randomized assignment of low blood pressure goal or active therapy; n represents number of events; N represents overall number of participants; Std/Pla, randomized assignment to standard blood pressure goal or placebo.

Standing hypotension defined as SBP≤110 mm Hg or DBP≤60 mm Hg

All models were unadjusted.

**eTable 16. Treatment effects on cardiovascular disease or all-cause mortality by baseline orthostatic hypotension, adjusted for additional cardiovascular risk factors**

**Orthostatic Hypotension**

**Cardiovascular Disease or All-cause Mortality**

			<b>Orthostatic Hypotension</b>			<b>No Orthostatic Hypotension</b>	
	<b>n/N (Low/Act)</b>	<b>n/N (Std/Pla)</b>	<b>HR (95% CI)</b>	<b>n/N (Low/Act)</b>	<b>n/N (Std/Pla)</b>	<b>HR (95% CI)</b>	<b>P-interaction</b>
<b>AASK</b>	45/47	51/53	0.92 (0.59, 1.44)	455/489	469/498	0.96 (0.84, 1.09)	0.89
<b>ACCORD</b>	6/56	9/45	0.47 (0.17, 1.36)	59/601	70/615	0.89 (0.63, 1.26)	0.31
<b>SPRINT</b>	40/343	51/332	0.78 (0.51, 1.18)	392/4279	482/4274	0.79 (0.70, 0.91)	0.93
<b>SPS3</b>	16/89	19/110	1.25 (0.64, 2.45)	103/897	124/914	0.80 (0.62, 1.04)	0.24
<b>UKPDS</b>	37/119	17/59	0.94 (0.52, 1.69)	146/600	101/305	0.73 (0.56, 0.94)	0.48
<b>Treatment Goal Trials</b>	144/654	147/599	0.88 (0.70, 1.11)	1155/6866	1246/6606	0.85 (0.79, 0.92)	0.79
<b>HVET</b>	14/153	32/183	0.48 (0.25, 0.90)	208/1776	271/1725	0.75 (0.62, 0.90)	0.21
<b>SHEP</b>	49/268	47/265	1.15 (0.77, 1.73)	307/1940	417/1954	0.68 (0.59, 0.79)	0.02
<b>SYST-EUR</b>	21/178	24/153	0.74 (0.41, 1.33)	181/2190	221/2126	0.74 (0.61, 0.90)	0.97
<b>TOMHS</b>	3/47	2/12	0.32 (0.04, 2.37)	31/621	15/222	0.73 (0.40, 1.36)	0.54
<b>Placebo-Controlled Trials</b>	87/646	105/613	0.81 (0.61, 1.08)	727/6527	924/6027	0.72 (0.65, 0.79)	0.38
<b>All Trials</b>	231/1300	252/1212	0.85 (0.71, 1.02)	1882/13393	2170/12633	0.80 (0.75, 0.85)	0.52
<b>All-cause Mortality</b>							
	<b>n/N (Low/Act)</b>	<b>n/N (Std/Pla)</b>	<b>Orthostatic Hypotension HR (95% CI)</b>	<b>n/N (Low/Act)</b>	<b>n/N (Std/Pla)</b>	<b>No Orthostatic Hypotension HR (95% CI)</b>	<b>P-interaction</b>
<b>AASK</b>	4/47	8/53	0.34 (0.09, 1.27)	41/489	53/498	0.75 (0.49, 1.12)	0.50
<b>ACCORD</b>	3/56	2/45	0.73 (0.10, 5.20)	24/601	23/615	1.12 (0.63, 1.99)	0.99
<b>SPRINT</b>	20/343	27/332	0.75 (0.42, 1.34)	172/4279	213/4274	0.80 (0.66, 0.98)	0.81
<b>SPS3</b>	9/89	9/110	1.54 (0.58, 4.08)	47/897	50/914	0.88 (0.59, 1.31)	0.23
<b>UKPDS</b>	27/119	14/59	0.89 (0.46, 1.72)	103/600	65/305	0.83 (0.60, 1.13)	0.93

<b>Treatment Goal</b>							
<b>Trials</b>	63/654	60/599	0.85 (0.59, 1.23)	387/6866	404/6606	0.84 (0.73, 0.96)	0.99
<b>HYVET</b>	14/153	23/183	0.70 (0.36, 1.37)	181/1776	212/1725	0.84 (0.69, 1.02)	0.65
<b>SHEP</b>	36/268	27/265	1.54 (0.93, 2.56)	159/1940	194/1954	0.79 (0.64, 0.97)	0.02
<b>SYST-EUR</b>	11/178	17/153	0.57 (0.26, 1.24)	121/2190	127/2126	0.86 (0.67, 1.11)	0.32
<b>TOMHS</b>	1/47	0/12	*	5/621	3/222	0.60 (0.14, 2.56)	*
<b>Placebo-Controlled</b>							
<b>Trials</b>	62/646	67/613	0.96 (0.68, 1.36)	466/6527	536/6027	0.82 (0.72, 0.93)	0.35
<b>All Trials</b>	125/1300	127/1212	0.91 (0.71, 1.17)	853/13393	940/12633	0.83 (0.76, 0.91)	0.52

Abbreviations: CI, confidence interval; HR, hazard ratio; Low/Act, randomized assignment of low blood pressure goal or active therapy; n represents number of events; N represents overall number of participants; Std/Pla, randomized assignment to standard blood pressure goal or placebo.

\*Could not be calculated due to small numbers.

Cox proportional hazards models adjusted for age, sex, seated systolic blood pressure, seated diastolic blood pressure, eGFR<60 mL/min per 1.73 m<sup>2</sup>, body mass index, and diabetes status. Pooled estimates are additionally adjusted for study.

**eTable 17. Treatment effects on cardiovascular disease or all-cause mortality by baseline standing hypotension, adjusted for additional cardiovascular risk factors**

**Cardiovascular Disease or All-cause Mortality**

			Hypotension			No Hypotension	
	n/N (Low/Act)	n/N (Std/Pla)	HR (95% CI)	n/N (Low/Act)	n/N (Std/Pla)	HR (95% CI)	P-interaction
<b>AASK</b>	37/38	46/46	0.91 (0.57, 1.46)	463/498	474/505	0.97 (0.86, 1.11)	0.45
<b>ACCORD</b>	8/49	8/37	0.67 (0.25, 1.86)	57/608	71/623	0.84 (0.59, 1.19)	0.95
<b>SPRINT</b>	59/360	65/353	0.86 (0.60, 1.22)	373/4262	468/4253	0.78 (0.68, 0.90)	0.65
<b>SPS3</b>	16/78	12/84	1.26 (0.59, 2.71)	103/908	131/940	0.79 (0.61, 1.03)	0.13
<b>UKPDS</b>	2/7	1/8	*	181/712	117/356	0.75 (0.60, 0.95)	0.42
<b>Treatment Goal Trials</b>	122/532	132/528	0.95 (0.74, 1.22)	1177/6988	1261/6677	0.85 (0.78, 0.92)	0.43
<b>HYVET</b>	2/10	1/12	97.19 (0.02, 4.4e+05)	220/1919	302/1896	0.72 (0.60, 0.85)	0.37
<b>SHEP</b>	18/76	19/84	1.07 (0.55, 2.08)	338/2132	445/2135	0.71 (0.62, 0.82)	0.36
<b>SYST-EUR</b>	1/7	4/8	*	201/2361	241/2271	0.74 (0.61, 0.89)	0.53
<b>TOMHS</b>	0/12	0/2	*	34/656	17/232	0.70 (0.39, 1.25)	*
<b>Placebo-Controlled Trials</b>	21/105	24/106	0.99 (0.55, 1.80)	793/7068	1005/6534	0.72 (0.66, 0.80)	0.42
<b>All Trials*</b>	143/637	156/634	0.94 (0.75, 1.18)	1970/14056	2266/13211	0.79 (0.75, 0.84)	0.14
<b>All-cause Mortality</b>							
			Hypotension			No Hypotension	
	n/N (Low/Act)	n/N (Std/Pla)	HR (95% CI)	n/N (Low/Act)	n/N (Std/Pla)	HR (95% CI)	P-interaction
<b>AASK</b>	2/38	7/46	0.36 (0.05, 2.72)	43/498	54/505	0.75 (0.50, 1.12)	0.44
<b>ACCORD</b>	4/49	1/37	2.35 (0.23, 23.71)	23/608	24/623	1.05 (0.59, 1.86)	0.35
<b>SPRINT</b>	30/360	32/353	0.92 (0.56, 1.51)	162/4262	208/4253	0.78 (0.63, 0.96)	0.61
<b>SPS3</b>	6/78	9/84	0.45 (0.15, 1.36)	50/908	50/940	0.98 (0.66, 1.45)	0.42
<b>UKPDS</b>	1/7	1/8	*	129/712	78/356	0.83 (0.63, 1.11)	0.91
<b>Treatment Goal Trials</b>	43/532	50/528	0.85 (0.57, 1.29)	407/6988	414/6677	0.84 (0.73, 0.96)	0.96
<b>HYVET</b>	2/10	1/12	97.19 (0.02, 4.4e+05)	193/1919	234/1896	0.82 (0.68, 1.00)	0.42
<b>SHEP</b>	9/76	11/84	0.85 (0.35, 2.07)	186/2132	210/2135	0.87 (0.72, 1.06)	0.93

<b>SYST-EUR</b>	1/7	3/8	*	131/2361	141/2271	0.83 (0.65, 1.05)	0.26
<b>TOMHS</b>	0/12	0/2	*	6/656	3/232	0.71 (0.18, 2.88)	*
<b>Placebo-Controlled Trials</b>	12/105	15/106	0.93 (0.43, 2.02)	516/7068	588/6534	0.84 (0.74, 0.94)	0.88
<b>All Trials**</b>	55/637	65/634	0.83 (0.58, 1.19)	923/14056	1002/13211	0.84 (0.77, 0.92)	0.88

Abbreviations: CI, confidence interval; HR, hazard ratio; Low/Act, randomized assignment of low blood pressure goal or active therapy; n represents number of events; N represents overall number of participants; Std/Pla, randomized assignment to standard blood pressure goal or placebo.

Standing hypotension defined as SBP $\leq$ 110 mm Hg or DBP $\leq$ 60 mm Hg

Cox proportional hazards models adjusted for age, sex, seated systolic blood pressure, seated diastolic blood pressure, eGFR $<$ 60 mL/min per 1.73 m<sup>2</sup>, body mass index, and diabetes status. Pooled estimates are additionally adjusted for study.



**eTable 18. Association of baseline orthostatic hypotension with cardiovascular disease or all-cause mortality, using an alternate definition of orthostatic hypotension based on a drop in systolic blood pressure of at least 30 mm Hg or a drop in diastolic blood pressure of at least 10 mm Hg**

Cardiovascular disease or all-cause mortality	Baseline Orthostatic Hypotension (Using Alternate Definition)			
	Orthostatic hypotension, n/N	No orthostatic hypotension, n/N	HR (95% CI)	P
AASK	71/74	951/1015	1.17 (0.92, 1.49)	0.20
ACCORD	10/71	135/1250	1.29 (0.68, 2.45)	0.44
SPRINT	56/393	918/8933	1.34 (1.02, 1.76)	0.03
SPS3	29/169	255/2176	1.56 (1.06, 2.29)	0.02
UKPDS	36/116	275/1001	1.09 (0.77, 1.55)	0.62
<i>Treatment Goal Trials</i>	202/823	2534/14375	1.28 (1.10, 1.47)	<0.001
HYVET	38/246	488/3599	1.15 (0.82, 1.59)	0.42
SHEP	53/254	814/4348	1.07 (0.81, 1.41)	0.63
SYST-EUR	16/91	442/4597	1.50 (0.91, 2.47)	0.11
TOMHS	4/37	47/865	2.04 (0.73, 5.67)	0.17
<i>Placebo-controlled Trials</i>	111/628	1791/13409	1.16 (0.96, 1.41)	0.13
<i>All Trials*</i>	313/1451	4325/27784	1.23 (1.10, 1.38)	<0.001
All-Cause Mortality	Baseline Orthostatic Hypotension (Using Alternate Definition)			
	Orthostatic hypotension, n/N	No orthostatic hypotension, n/N	HR (95% CI)	P
AASK	8/74	98/1015	1.17 (0.57, 2.41)	0.66
ACCORD	3/71	49/1250	1.07 (0.33, 3.45)	0.90
SPRINT	26/393	413/8933	1.29 (0.87, 1.92)	0.20
SPS3	15/169	111/2176	1.93 (1.12, 3.31)	0.02
UKPDS	29/116	185/1001	1.31 (0.88, 1.93)	0.18
<i>Treatment Goal Trials</i>	81/823	856/14375	1.37 (1.09, 1.73)	0.007
HYVET	31/246	400/3599	1.14 (0.79, 1.64)	0.48
SHEP	37/254	406/4348	1.54 (1.10, 2.16)	0.01
SYST-EUR	12/91	273/4597	1.81 (1.01, 3.23)	0.05
TOMHS	1/37	8/865	2.99 (0.37, 23.96)	0.30
<i>Placebo-controlled Trials</i>	81/628	1087/13409	1.37 (1.09, 1.72)	0.007
<i>All Trials**</i>	162/1451	1943/27784	1.37 (1.17, 1.61)	<0.001

Abbreviations: CVD, cardiovascular disease; CI, confidence interval; HR, hazard ratio; n represents number of events; N represents overall number of participants.

Cox proportional hazards models adjusted for age, sex, and study (as a categorical variable).

There was no evidence for an interaction by treatment arm for individual studies or pooled study groupings.

**eTable 19. Treatment effects on cardiovascular disease or all-cause mortality by baseline orthostatic hypotension, using an alternate definition of orthostatic hypotension based on a drop in systolic blood pressure of at least 30 mm Hg or a drop in diastolic blood pressure of at least 10 mm Hg**

Cardiovascular Disease or All-cause Mortality	Orthostatic Hypotension			No Orthostatic Hypotension			<i>P</i> -interaction
	n/N (Low/Act)	n/N (Std/Pla)	HR (95% CI)	n/N (Low/Act)	n/N (Std/Pla)	HR (95% CI)	
<b>Treatment Goal Trials</b>	102/433	100/390	0.88 (0.66, 1.16)	1218/7324	1316/7051	0.85 (0.79, 0.92)	0.88
<b>Placebo-Controlled Trials</b>	50/311	61/317	0.87 (0.59, 1.26)	798/6989	993/6420	0.74 (0.67, 0.81)	0.33
<b>All Trials</b>	152/744	161/707	0.88 (0.70, 1.10)	2016/14313	2309/13471	0.81 (0.76, 0.86)	0.45
<b>All-cause Mortality</b>							
<b>Treatment Goal Trials</b>	44/433	37/390	1.03 (0.66, 1.62)	417/7324	439/7051	0.82 (0.72, 0.94)	0.44
<b>Placebo-Controlled Trials</b>	35/311	46/317	0.84 (0.54, 1.31)	514/6989	573/6420	0.85 (0.76, 0.96)	0.94
<b>All Trials</b>	79/744	83/707	0.93 (0.68, 1.27)	931/14313	1012/13471	0.84 (0.77, 0.92)	0.56

Abbreviations: CI, confidence interval; HR, hazard ratio; Low/Act, randomized assignment of low blood pressure goal or active therapy; n represents number of events; N represents overall number of participants; Std/Pla, randomized assignment to standard blood pressure goal or placebo.

All models were adjusted for age and sex. Pooled estimates are adjusted for age, sex, and study (as a categorical variable).

**eTable 20. Treatment effects on cardiovascular disease or all-cause mortality by baseline standing hypotension, defined using distinct thresholds for systolic or diastolic blood pressure**

Standing systolic blood pressure with threshold of 110 mm Hg							
	Standing SBP ≤110 mm Hg			Standing SBP >110 mm Hg			
	n/N (Low/Act)	n/N (Std/Pla)	HR (95% CI)	n/N (Low/Act)	n/N (Std/Pla)	HR (95% CI)	P-interaction
<b>Cardiovascular Disease or Mortality</b>							
Treatment Goal Trials	65/305	83/308	0.80 (0.58, 1.11)	1255/7452	1333/7133	0.86 (0.79, 0.93)	0.80
Placebo-Controlled Trials	0/13	0/2	*	848/7287	1054/6735	0.74 (0.68, 0.81)	*
All Trials	65/318	83/310	0.80 (0.58, 1.11)	2103/14739	2387/13868	0.81 (0.76, 0.86)	1.00
<b>All-cause Mortality</b>							
Treatment Goal Trials	14/305	27/308	0.52 (0.27, 0.99)	447/7452	449/7133	0.85 (0.75, 0.97)	0.17
Placebo-Controlled Trials	0/13	0/2	*	549/7287	619/6735	0.85 (0.76, 0.96)	*
All Trials	14/318	27/310	0.52 (0.27, 0.99)	996/14739	1068/13868	0.85 (0.78, 0.93)	0.15
Standing systolic blood pressure with threshold of 100 mm Hg							
	Standing SBP ≤100 mm Hg			Standing SBP >100 mm Hg			
			HR (95% CI)			HR (95% CI)	P-interaction
<b>Cardiovascular Disease or Mortality</b>							
Treatment Goal Trials	12/70	20/68	0.41 (0.19, 0.89)	1308/7687	1396/7373	0.86 (0.80, 0.93)	0.19
Placebo-Controlled Trials	0/1	0/1	*	848/7299	1054/6736	0.74 (0.68, 0.81)	*
All Trials	12/71	20/69	0.41 (0.19, 0.89)	2156/14986	2450/14109	0.81 (0.77, 0.86)	0.31
<b>All-cause Mortality</b>							
Treatment Goal Trials	3/70	5/68	0.29 (0.06, 1.51)	458/7687	471/7373	0.84 (0.74, 0.95)	0.64
Placebo-Controlled Trials	0/1	0/1	*	549/7299	619/6736	0.85 (0.76, 0.95)	*
All Trials	3/71	5/69	0.29 (0.06, 1.51)	1007/14986	1090/14109	0.85 (0.78, 0.92)	0.65
Standing diastolic blood pressure with threshold of 60 mm Hg							
	Standing DBP ≤60 mm Hg			Standing DBP >60 mm Hg			
			HR (95% CI)			HR (95% CI)	P-interaction
<b>Cardiovascular Disease or Mortality</b>							
Treatment Goal Trials	68/330	73/314	1.00 (0.71, 1.40)	1252/7427	1343/7127	0.85 (0.79, 0.92)	0.30
Placebo-Controlled Trials	21/92	24/106	1.02 (0.57, 1.85)	827/7208	1030/6631	0.74 (0.67, 0.81)	0.22
All Trials	89/422	97/420	1.00 (0.75, 1.34)	2079/14635	2373/13758	0.80 (0.76, 0.85)	0.10

<b>All-cause Mortality</b>							
<b>Treatment Goal Trials</b>	33/330	29/314	1.26 (0.76, 2.10)	428/7427	447/7127	0.82 (0.71, 0.93)	0.15
<b>Placebo-Controlled Trials</b>	12/92	15/106	0.96 (0.44, 2.06)	537/7208	604/6631	0.85 (0.75, 0.95)	0.62
<b>All Trials</b>	45/422	44/420	1.18 (0.77, 1.81)	965/14635	1051/13758	0.84 (0.77, 0.91)	0.15
<b>Standing diastolic blood pressure with threshold of 50 mm Hg</b>							
			<b>Standing DBP ≤50 mm Hg</b>			<b>Standing DBP &gt;50 mm Hg</b>	
<b>Cardiovascular Disease or Mortality</b>			<b>HR (95% CI)</b>			<b>HR (95% CI)</b>	<b>P-interaction</b>
<b>Treatment Goal Trials</b>	8/44	13/46	0.71 (0.28, 1.79)	1312/7713	1403/7395	0.86 (0.80, 0.93)	0.28
<b>Placebo-Controlled Trials</b>	5/22	5/18	1.07 (0.28, 4.05)	843/7278	1049/6719	0.74 (0.68, 0.81)	0.71
<b>All Trials</b>	13/66	18/64	0.76 (0.36, 1.58)	2155/14991	2452/14114	0.81 (0.77, 0.86)	0.46
<b>All-cause Mortality</b>							
<b>Treatment Goal Trials</b>	6/44	5/46	1.53 (0.42, 5.60)	455/7713	471/7395	0.83 (0.73, 0.95)	0.61
<b>Placebo-Controlled Trials</b>	4/22	2/18	2.54 (0.38, 17.05)	545/7278	617/6719	0.85 (0.75, 0.95)	0.24
<b>All Trials</b>	10/66	7/64	1.87 (0.66, 5.30)	1000/14991	1088/14114	0.84 (0.77, 0.92)	0.28

Abbreviations: CI, confidence interval; HR, hazard ratio; Low/Act, randomized assignment of low blood pressure goal or active therapy; n represents number of events; N represents overall number of participants; Std/Pla, randomized assignment to standard blood pressure goal or placebo.

All models were adjusted for age and sex. Pooled estimates are adjusted for age, sex, and study (as a categorical variable).

\*Numbers too few to calculate

**eTable 21. Treatment effects among participants with baseline orthostatic hypotension or baseline standing hypotension in strata of baseline characteristics**

		Cardiovascular Disease or All-cause Mortality			All-Cause Mortality		
	n/N	HR (95% CI)	P-interaction	n/N	HR (95% CI)	P-interaction	
<b>Orthostatic hypotension</b>							
<b>Age</b>							
≤75 years	329/1719	0.86 (0.69, 1.08)	0.67	140/1719	1.04 (0.74, 1.46)	0.36	
>75 years	172/873	0.77 (0.56, 1.04)		121/873	0.80 (0.56, 1.15)		
<b>Sex</b>							
Men	288/1280	0.78 (0.62, 0.99)	0.49	144/1280	0.81 (0.58, 1.13)	0.44	
Women	213/1312	0.92 (0.70, 1.21)		117/1312	1.05 (0.73, 1.52)		
<b>Pre-randomization SBP ≥140 or DBP ≥90 mm Hg*</b>							
No	31/128	0.68 (0.32, 1.45)	0.74	9/128	0.40 (0.09, 1.89)	0.42	
Yes	470/2464	0.84 (0.70, 1.01)		252/2464	0.94 (0.73, 1.21)		
<b>Diabetes</b>							
No	374/2053	0.84 (0.68, 1.03)	0.99	179/2053	0.91 (0.67, 1.22)	0.91	
Yes	127/539	0.85 (0.59, 1.21)		82/539	0.95 (0.61, 1.49)		
<b>Stage III chronic kidney disease*</b>							
≥60 mL/min per 1.73 m <sup>2</sup>	348/1839	0.83 (0.67, 1.03)	0.98	198/1839	0.89 (0.67, 1.18)	0.62	
<60 mL/min per 1.73 m <sup>2</sup>	148/734	0.83 (0.60, 1.15)		61/734	0.97 (0.58, 1.62)		
<b>Body Mass Index</b>							
<30 kg/m <sup>2</sup>	241/1686	0.83 (0.64, 1.07)	0.62	124/1686	0.94 (0.65, 1.34)	0.95	
≥30 kg/m <sup>2</sup>	247/845	0.87 (0.67, 1.12)		130/845	0.91 (0.64, 1.29)		
<b>Standing hypotension</b>							
<b>Age</b>							
≤75 years	193/828	0.90 (0.67, 1.19)	0.99	62/828	0.75 (0.45, 1.25)	0.59	
>75 years	111/479	0.89 (0.61, 1.30)		61/479	0.92 (0.55, 1.52)		
<b>Sex</b>							

Men	193/744	0.95 (0.71, 1.26)	0.85	80/744	0.86 (0.55, 1.35)	0.68
Women	111/563	0.97 (0.66, 1.41)		43/563	1.01 (0.55, 1.86)	
<b>Pre-randomization SBP <math>\geq</math>140 or DBP <math>\geq</math>90 mm Hg*</b>						
No	138/633	0.88 (0.62, 1.23)	0.66	40/633	0.60 (0.31, 1.15)	0.12
Yes	166/674	0.99 (0.73, 1.35)		83/674	1.06 (0.68, 1.64)	
<b>Diabetes</b>						
No	254/1075	0.95 (0.74, 1.22)	0.78	98/1075	0.94 (0.63, 1.40)	0.55
Yes	50/232	1.01 (0.56, 1.80)		25/232	0.82 (0.36, 1.88)	
<b>Stage III chronic kidney disease*</b>						
$\geq$ 60 mL/min per 1.73 m <sup>2</sup>	204/874	0.98 (0.74, 1.29)	0.45	94/874	0.86 (0.57, 1.29)	0.95
<60 mL/min per 1.73 m <sup>2</sup>	100/428	0.84 (0.56, 1.26)		29/428	0.91 (0.44, 1.92)	
<b>Body Mass Index</b>						
<30 kg/m <sup>2</sup>	124/765	1.11 (0.78, 1.58)	0.23	52/765	0.97 (0.56, 1.68)	0.66
$\geq$ 30 kg/m <sup>2</sup>	175/511	0.84 (0.62, 1.14)		68/511	0.81 (0.50, 1.31)	

Abbreviations: CI, confidence interval; DBP, diastolic blood pressure; n, the number of events; HR, hazard ratio; N, the number at risk; SBP, systolic blood pressure

\*Based on the CKD EPI 2021 race-free, creatinine equation. eGFR was not available from UKPDS or SHEP. UKPDS provided stage III CKD categories based on the 2021 CKD-EPI race-free, creatinine equation. For SHEP we relied on a self-reported history of kidney disease.