Effects of blood pressure lowering drugs in heart failure

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Contents

eTable 1: Methodological characteristics of the included trials

Trial	Author	Y	B	C	N centres/Location	Follow-up (mean)	Control	Int 1	Int 2	HF type	N C	N Int 1	N Int 2	Baseline BP	Achieved BP	BP time (months)
CIBIS(1)	Lechat et al.	1994	DB	PC	70/EU	23	Placebo	Bisoprolol		HFrEF	321	320		R	NR	NR
CIBIS II(2)	Dargie et al.	1999	DB	PC	274/EU	15	Placebo	Bisoprolol		HFrEF	1320	1327		NR	NR	NR
CIBIS III(3)	Willenheimer et al.	2005	OL	AT	128/EU, Aus and Tunisia	24	Bisoprolol	Enalapril		HFrEF	550	550		R	R	6
BEST(4)	BEST Inv	2001	DB	PC	90/NA	24	Placebo	Bucindolol		HFrEF	1354	1354		R	PR	NR
COPERNICUS(5)	Packer et al.	2002	DB	PC	334/NA, EU, Aus	11	Placebo	Carvedilol		HFrEF	1133	1156		R	PR	4
PEP-CHF(6)	Cleland et al.	2006	DB	PC	53/EU	26	Placebo	Perindopril		HFpEF	426	420		R	R	12
SENIORS(7)	Flather et al.	2005	DB	PC	11/EU	21	Placebo	Nebivolol		Mix	1061	1067		R	R	4
V-HeFT II(8)	Cohn et al.	1991	DB	AT	13/US	30	HZ-ISD	Enalapril		HFrEF	401	403		R	R	4
ELITE I(9)	Pitt et al.	1997	DB	AT	125/US, SA, EU	11	Losartan	Captopril		HFrEF	352	370		R	NR	NR
ELITE II(10)	Pitt et al.	2000	DB	AT	289/NA, MC SA, EU	11	Losartan	Captopril		HFrEF	1578	1574		R	NR	NR
SOLVD(11)	SOLVD Inv	1991	DB	PC	23/NA, Belgium	48	Placebo	Enalapril		HFrEF	1284	1285		R	PR	NR
MERIT-HF(12)	MERIT-HF Inv	1999	DB	PC	14/US, EU	18	Placebo	Metoprolol		HFrEF	2001	1990		R	R	6
Val-HeFT(13)	Cohn et al.	2001	DB	PC	302/US, EU, Africa	23	Placebo	Valsartan		HFrEF	2499	2511		R	PR	6
RALES(14)	Pitt et al.	1999	DB	PC	195/EU, NA, SA, Asia	24	Placebo	Spironolactone		HFrEF	841	822		R	NR	NR
A-HeFT(15)	Taylor et al.	2004	DB	PC	169/US	10	Placebo	ISD/HZ		HFrEF	532	518		R	R	6

I-PRESERVE(16)	Massie et al.	2008	DB	PC	293/EU, NA, SA, AUS, Africa	50	Placebo	Irbesartan		HFpEF	2061	2067		R	R	6
CHARM-Added(17)	McMurray et al.	2003	DB	PC	618/ NA, EU	41	Placebo	Candesartan		HFrEF	1272	1276		R	PR	NR
CHARM-Alternative(18)	Granger et al.	2003	DB	PC	618/NA, EU	42	Placebo	Candesartan		HFrEF	1015	1013		R	PR	6
CHARM-Preserved(19)	Yusuf et al.	2003	DB	PC	618/NA, EU	37	Placebo	Candesartan		HFpEF	1508	1512		R	PR	6
COMET(20)	Poole-Wilson et al.	2003	DB	AT	341/EU	58	Carvedilol	Metoprolol		HFrEF	1511	1518		R	PR	4
EMPHASIS-HF(21)	Zannad et al.	2011	DB	PC	278/US, EU, AUS	21	Placebo	Eplerenone		HFrEF	1373	1364		R	PR	NS
TOPCAT(22)	Pitt et al.	2014	DB	PC	233/NA, SA, Russia, Georgia	40	Placebo	Spironolactone		HFpEF	1723	1722		R	NR*	NR
ATMOSPHERE(23)	McMurray et al.	2016	DB	AT	789/EU, NA, SA, Africa Asia	37	Enalapril	Aliskiren	Combination	HFrEF	2336	2340	2340	R	PR	4
PARADIGM-HF(24)	McMurray et al.	2014	DB	AT	1043/EU, America, Africa, Asia	27	Enalapril	Sacubitril/Valsartan		HFrEF	4212	4187		R	PR	8
OVERTURE(25)	Packer et al.	2002	DB	AT	704/EU, America, Africa, Asia	15	Enalapril	Omapatrilat		Mix	2884	2886		R	PR	4
HEAAL(26)	Konstam et al.	2009	DB	AT	255/EU, America, Africa, Asia	56	Losartan 50	Losartan 150		HFrEF	1913	1921		R	R	6
PRAISE(27)	Packer et al.	1996	DB	PC	105/NA	14	Placebo	Amlodipine		HFrEF	582	571		R	PR	3
PRAISE 2(28)	Packer et al.	2013	DB	PC	105/NA	33	Placebo	Amlodipine		HFrEF	827	827		R	PR	3
ATLAS(29)	Packer et al.	1999	DB	AT	287/EU, Aust, NA	46	Lisinopil LD	Lisinopril HD		HFrEF	1596	1568		R	PR	36
SUPPORT(30)	Sakata et al.	2015	OL	AT	17/Japan	53	ST	Olmesartan		Mix	568	578		R	NR*	12

ENABLE(31)	Packer et al.	2017	DB	PC	151/EU, Aus, NA	18	Placebo	Bosentan		HFrEF	807	804		R	PR	78
MACH-1(32)	Levine et al.	2001	DB	PC	NR/EU, NA, Israel	50	Placebo	Mibefradil		HFrEF	1295	1295		NR	NR	NR
PRECISE(33)	Packer et al.	1996	DB	PC	NR/US	12	Placebo	Carvedilol		HFrEF	398	626		R	NR*	NR
CARMEN(34)	Remme et al.	2004	DB	AT	65/EU	18	Carvedilol+ Placebo	Enalapril+Placebo	Carvedilol+ Enalapril	HFrEF	191	190	191	R	R	8
J-CHF(35)	Okamoto et al.	2012	DB	AT	Japan	36	Carvedilol LD	Carvedilol MD	Carvedilol HD	HFrEF	118	116	118	R	NR	NR
VACS(36)	Cohn et al.	1986	DB	PC	US	28	Placebo	HZN-ISD	Prazosin	HFrEF	273	186	183	R	R	2
RESOLVD(37)	McKelvie et al.	2000	DB	PC	60/NA, Italy	11	Enalapril	Candesartan	Combination	HFrEF	109	327	332	R	R	11

AT, active treatment; Aus, Australia; B, blinding; BP, blood pressure; BP time, time point when achieved BP was reported; C, type of control; Can, Canada; DB, double blind; EU, Europe; HD, high dose; HFpEF, heart failure with preserved ejection fraction; HFrEF, heart failure with reduced ejection fraction; Int, intervention; LD, low dose; LEVF, left ventricular ejection fraction used as inclusion criteria; N, number; NA, North America; NR, not reported; NS, not specified**;** PC, placebo controlled; PR, partially-reported; R, reported; SA, South America; SB, single blind; ST, standard therapy; US, United States of America; Y, year.

*indicates that trial mentioned there was no difference in achieved blood pressure between study arms, but exact values were not reported.

eTable 2: Baseline characteristics of the included trials

Trial	Author	Sex (% male)	Age (years, mean)	NYHA I/II (%)	NYHA III/IV (%)	Ischaemic HF (%)	AF (%)	DM (%)	HTN (%)	HR (bpm, mean)	LVEF (%, mean)	BMI (kg/m^2, mean)
CIBIS(1)	Lechat et al.	83	60	0	100	36	55	6	NR	82	25	NR
CIBIS II(2)	Dargie et al.	80	61	0	100	50	12	NR	NR	NR	NR	NR
CIBIS III(3)	Willenheimer et al.	68	72	49	51	NR	NR	NR	66	79	29	NR
BEST(4)	BEST Inv	78	60	0	100	58	27	11	NR	81	23	NR
COPERNICUS(5)	Packer et al.	80	63	0	0	67	NR	NR	NR	83	20	NR
PEP-CHF(6)	Cleland et al.	45	76	75	25	NR	NR	NR	NR	74	65	NR
SENIORS(7)	Flather et al.	43	76	59	41	NR	NR	NR	62	79	34	NR
V-HeFT II(8)	Cohn et al.	100	61	57	43	NR	NR	NR	47	78	29	NR
ELITE I(9)	Pitt et al.	67	74	65	35	68	NR	NR	59	74	30	NR
ELITE II(10)	Pitt et al.	70	71	52	48	79	NR	NR	49	75	31	NR
SOLVD(11)	SOLVD Inv	80	61	68	32	71	18	NR	42	80	25	NR
MERIT-HF(12)	MERIT-HF Inv	78	64	41	59	66	NR	NR	44	82	28	NR
Val-HeFT(13)	Cohn et al.	80	63	62	38	57	31	7	NR	NR	27	NR
RALES(14)	Pitt et al.	73	65	0	100	55	4	NR	NR	81	25	NR
A-HeFT(15)	Taylor et al.	60	57	0	100	23	26	39	NR	NR	24	NR
I-PRESERVE(16)	Massie et al.	40	72	21	79	25	NR	64	89	72	60	NR
CHARM-Added(17)	McMurray et al.	78	64	24	76	63	26	7	48	74	28	NR
CHARM-Alternative(18)	Granger et al.	68	67	48	52	69	20	7	50	75	30	NR
CHARM-Preserved(19)	Yusuf et al.	60	67	61	39	56	9	23	65	71	54	NR
COMET(20)	Poole-Wilson et al.	80	62	48	52	52	44	18	37	81	26	NR
EMPHASIS-HF(21)	Zannad et al.	78	69	0	0	69	NR	NR	66	72	26	NR
TOPCAT(22)	Pitt et al.	49	69	67	33	NR	NR	NR	NA	68	56	NR
ATMOSPHERE(23)	McMurray et al.	79	63	64	36	56	NR	NR	62	72	28	27
PARADIGM-HF(24)	McMurray et al.	78	64	75	25	60	NR	NR	71	73	30	28

OVERTURE(25)	Packer et al.	79	64	48	52	56	NR	NR	NR	NR	24	NR
HEAAL(26)	Konstam et al.	71	66	69	31	64	NR	NR	60	72	33	27
PRAISE(27)	Packer et al.	76	65	0	100	63	NR	NR	56	83	21	NR
PRAISE 2(28)	Packer et al.	66	59	0	100	0	62	16	NR	81	21	NR
ATLAS(29)	Packer et al.	80	64	0	84	NR	NR	NR	NR	80	23	NR
SUPPORT(30)	Sakata et al.	75	66	0	7	48	21	NR	NR	71	54	24
ENABLE(31)	Packer et al.	74	67	0	100	69	NR	NR	NR	74	25	NR
MACH-1(32)	Levine et al.	79	63	0	74	68	NR	NR	29	78	25	NR
PRECISE(33)	Packer et al.	77	58	0	57	48	NR	NR	NR	84	23	NR
CARMEN(34)	Remme et al.	81	62	7	29	68	NR	NR	32	78	NR	26
J-CHF(35)	Okamoto et al.	89	60	0	17	29	NR	NR	NR	81	30	24
VACS(36)	Cohn et al.	100	58		0	44	NR	NR	40	82	30	NR
RESOLVD(37)	McKelvie et al.	85	63	0	38	72	NR	NR	NR	76	28	NR

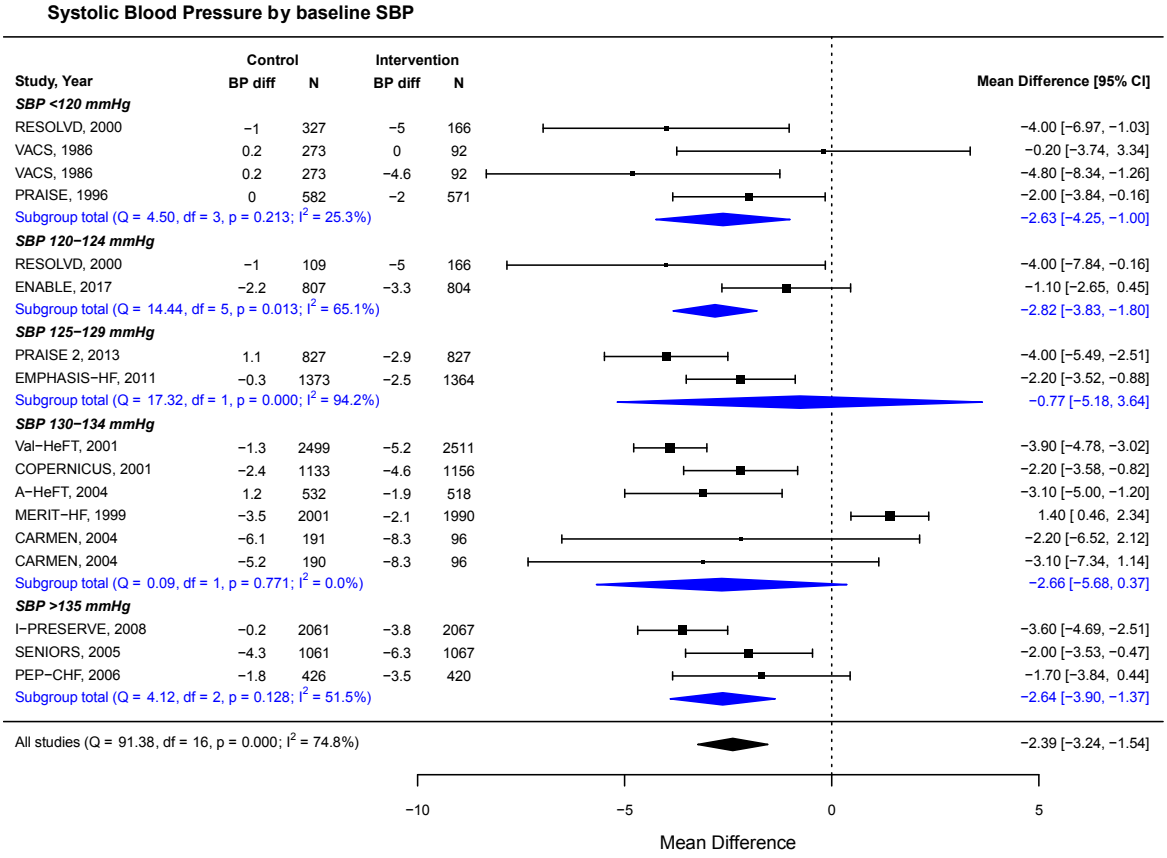
AF, atrial fibrillation; BMI, body mass index; BP, blood pressure; HF, heart failure, years, mean); HR, heart rate; HTN, hypertension; LVEF, left ventricular ejection fraction; NYHA, New York Heart Association class/II (%); NR, not reported; DM, diabetes mellitus

eTable3: Risk of bias assessment

Trial	Author	Year	Selection bias	Performance bias	Detection bias	Attrition bias	Reporting bias	Summary
CIBIS	Lechat et al.	1994	L	L	L	L	L	L
CIBIS II	Dargie et al.	1999	L	L	L	L	L	L
CIBIS III	Lechat et al.	2005	L	H	L	L	L	M
BEST	BEST Inv	2001	L	L	L	L	L	L
COPERNICUS	Packer et al.	2001	L	L	L	L	L	L
PEP-CHF	Cleland et al.	2006	L	L	L	L	L	L
SENIORS	Flather et al.	2005	L	L	L	L	L	L
V-HeFT II	Cohn et al.	1991	L	L	L	L	L	L
ELITE I	Pitt et al.	1997	U	L	L	L	L	U
ELITE II	Pitt et al.	2000	L	L	L	L	L	L
SOLVD	SOLVD Inv	1991	L	L	L	L	L	L
MERIT-HF	MERIT-HF Inv	1999	L	L	L	L	L	L
Val-HeFT	Cohn et al.	2001	L	L	L	L	L	L
RALES	Pitt et al.	1999	U	L	L	L	L	U
A-HeFT	Taylor et al.	2004	L	L	L	L	L	L
I-PRESERVE	Massie et al.	2008	L	L	L	L	L	L
CHARM-Added	McMurray et al.	2003	L	L	L	L	L	L
CHARM-Alternative	Granger et al.	2003	L	L	L	L	L	L
CHARM-Preserved	Yusuf et al.	2003	L	L	L	L	L	L
COMET	Wilson et al.	2003	L	L	L	L	L	L
EMPHASIS-HF	Zannad et al.	2011	L	L	L	L	L	L
TOPCAT	Pitt et al.	2014	L	L	L	L	L	L
ATMOSPHERE	McMurray et al.	2016	L	L	L	L	L	L
PARADIGM-HF	McMurray et al.	2014	L	L	L	L	L	L
OVERTURE	Packer et al.	2002	L	L	L	L	L	L
HEAAL	Konstam et al.	2009	L	L	L	L	L	L
PRAISE	Packer et al.	1996	L	L	L	L	L	L
PRAISE 2	Packer et al.	2013	L	L	L	L	L	L
ATLAS	Packer et al.	1999	L	L	L	L	L	L
SUPPORT	Sakata et al.	2015	L	H	H	L	L	M
ENABLE	Packer et al.	2017	L	L	L	L	L	L
MACH-1	Levine et al.	2001	L	L	L	L	L	L
Packer M, et al. 1996	Packer et al.	1996	L	L	L	L	L	L
CARMEN	Komadja et al.	2004	L	L	L	L	L	L

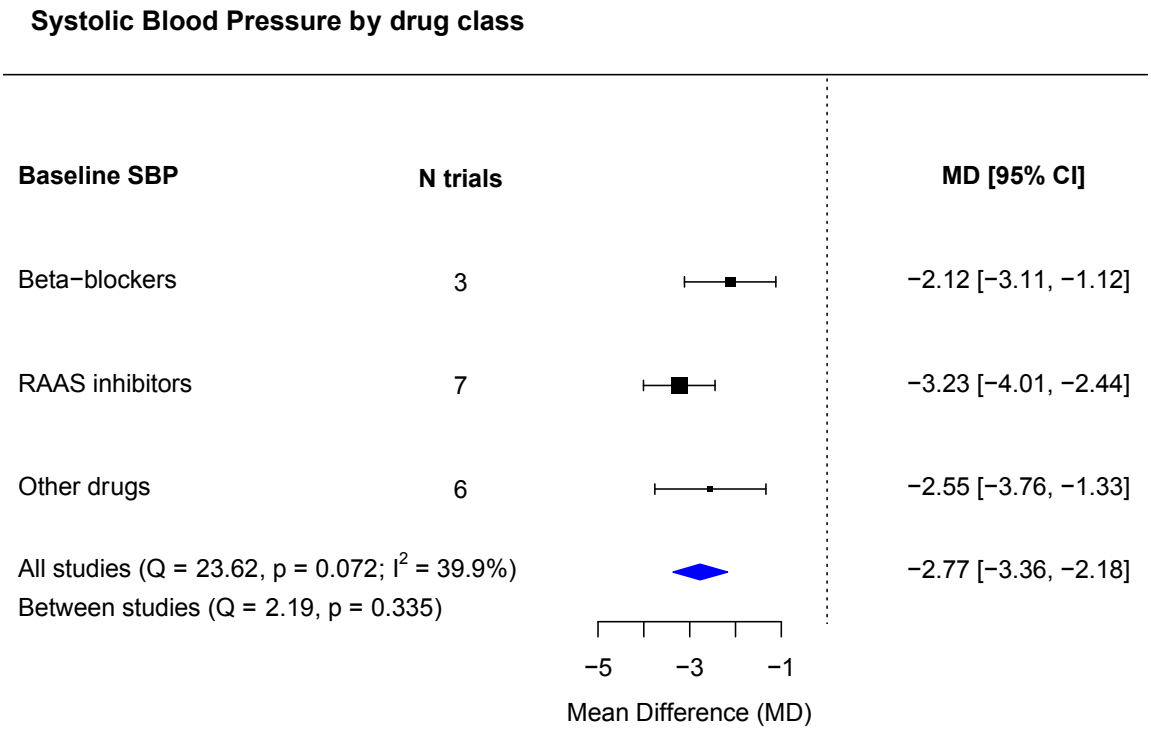
J-CHF	Okamoto et al.	2012	L	L	L	L	L	L
VACS	Cohn et al.	1986	L	L	L	L	L	L
RESOLVD	McKelvie et al.	2000	L	L	L	L	L	L

eFigure 1: Meta-analysis of the effect of blood pressure-lowering treatment on systolic blood pressure stratified by mean of baseline systolic blood pressure



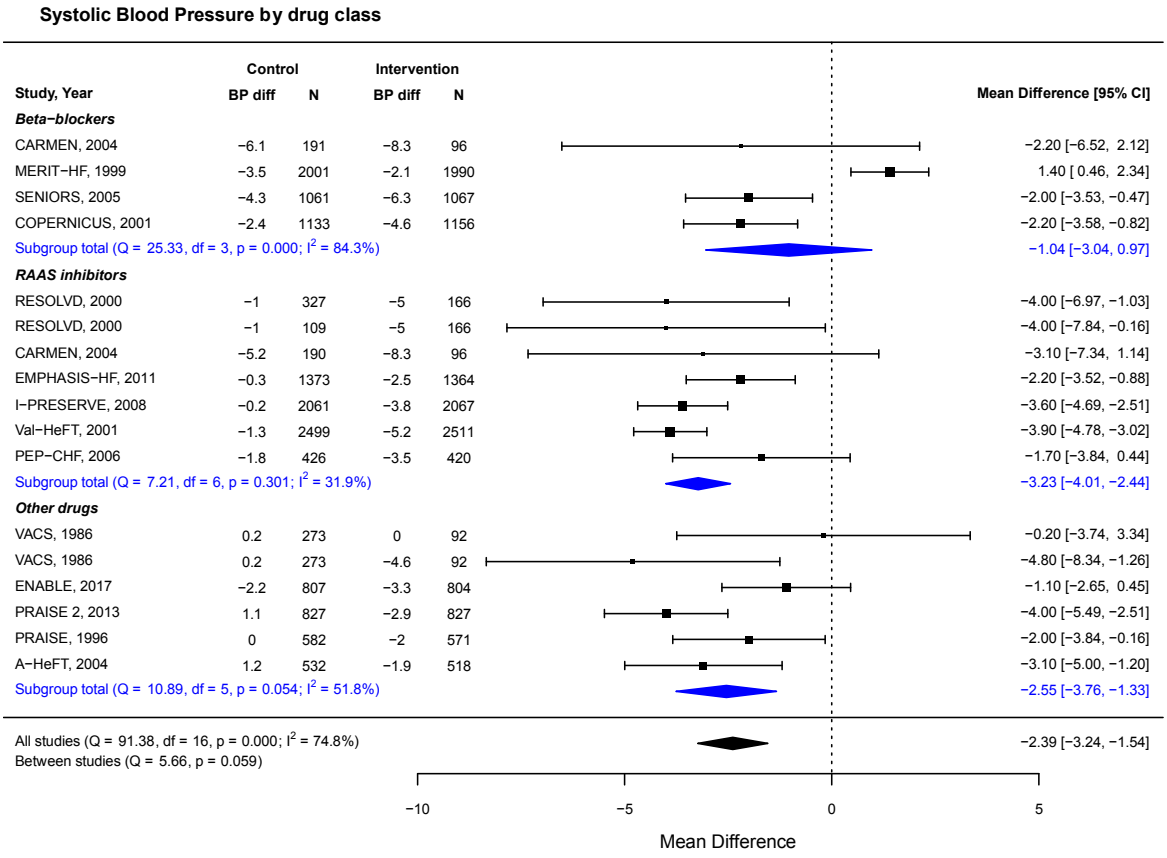
Mean differences between the change in systolic blood pressure in the intervention group versus the control group are displayed for each trial and each strata of mean baseline systolic blood pressure aggregated at trial-level. Summary measures were calculated using random effects models with REML estimators. Negative values mean that the reduction in systolic blood pressure was greater in the intervention group and vice-versa. Only studies that compared active treatment with placebo were included. BP diff, difference between achieved and baseline systolic blood pressure; SBP, systolic blood pressure

eFigure2: Meta-analysis of the effect of blood pressure-lowering treatment on systolic blood pressure stratified by drug class excluding the MERIT-HF trial



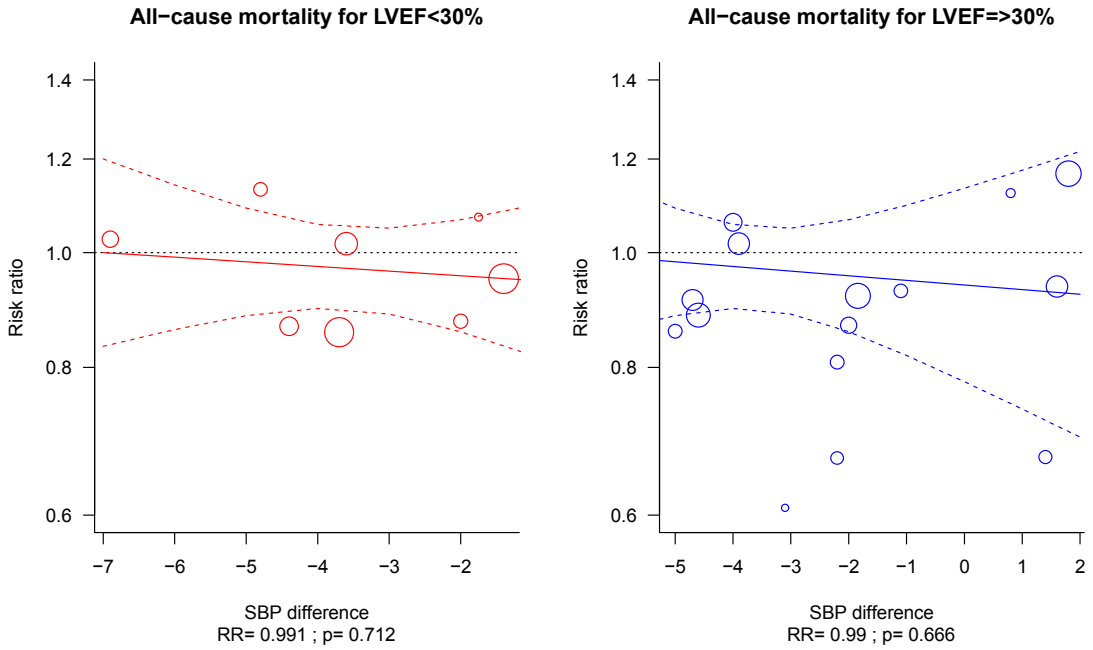
Mean differences between the change in systolic blood pressure in the intervention group versus the control group are displayed for each drug class. The outlier trial MERIT-HF was excluded from the beta-blocker subgroup to assess the impact of this trial on the subgroup estimate. Summary measures were calculated using random effects models with REML estimators. Negative values mean that the reduction in systolic blood pressure was greater in the intervention group and vice-versa. Other drugs include calcium-channel blockers, alpha-blockers, and hydralazine-isosorbide dinitrate. Only studies that compared active treatment with placebo were included. SBP, systolic blood pressure; RAAS, renin-angiotensin-aldosterone system

eFigure 3: Meta-analysis of the effect of blood pressure-lowering treatment on systolic blood pressure stratified by drug class



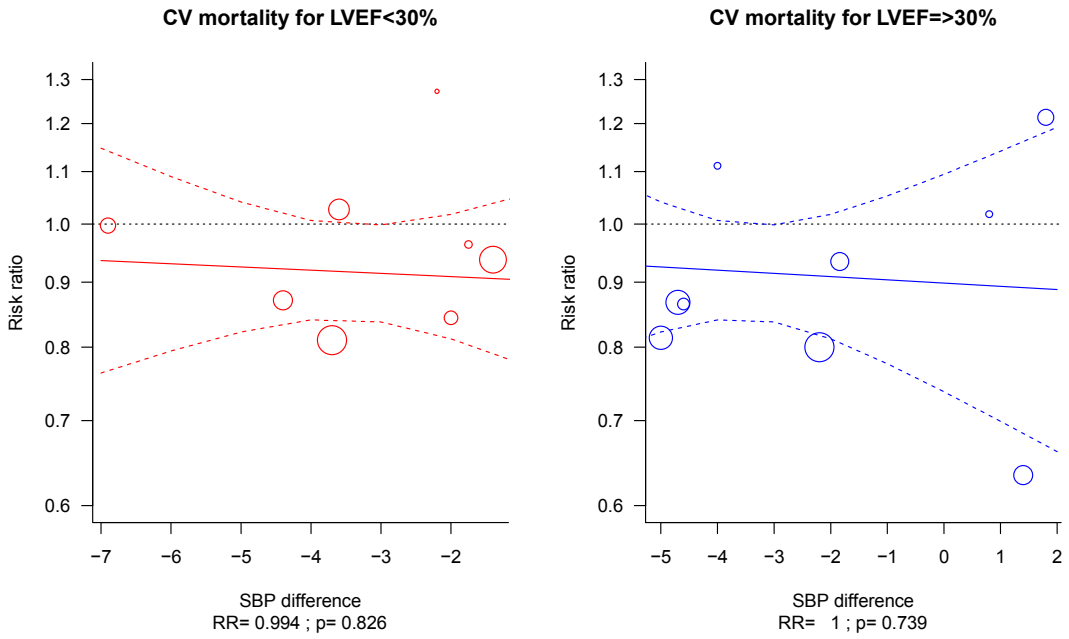
Mean differences between the change in systolic blood pressure in the intervention group versus the control group are displayed for each trial and each drug class. Summary measures were calculated using random effects models with REML estimators. Negative values mean that the reduction in systolic blood pressure was greater in the intervention group and vice-versa. Other drugs include calcium-channel blockers, alpha-blockers, and hydralazine-isosorbide dinitrate. Only studies that compared active treatment with placebo were included. BP diff, difference between achieved and baseline systolic blood pressure; SBP, systolic blood pressure; RAAS, renin-angiotensin-aldosterone system

eFigure 4: Meta-regression of risk ratio for all-cause mortality according to the difference in systolic blood pressure between study groups stratified by left-ventricular ejection fraction



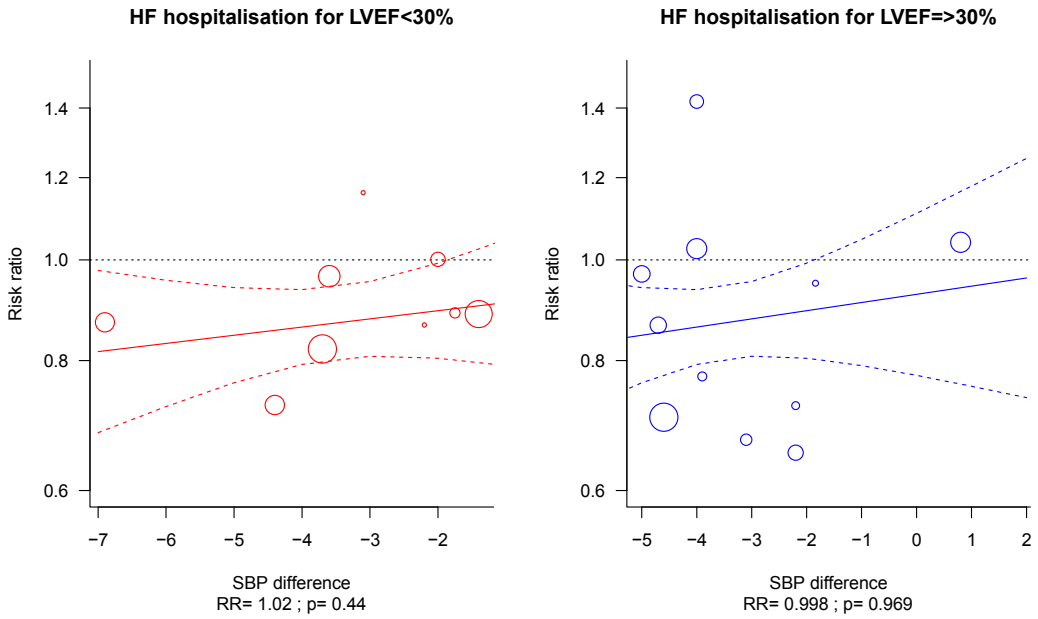
Risk ratios for all-cause mortality were regressed against the mean difference in systolic blood pressure change between the intervention and control groups in each trial and stratified by left-ventricular ejection fraction using a 30% cut-off. Negative values mean that the reduction in systolic blood pressure was greater in the intervention group and vice-versa. SBP, systolic blood pressure

eFigure 5: Meta-regression of risk ratio for cardiovascular mortality according to the difference in systolic blood pressure between study groups stratified by left-ventricular ejection fraction



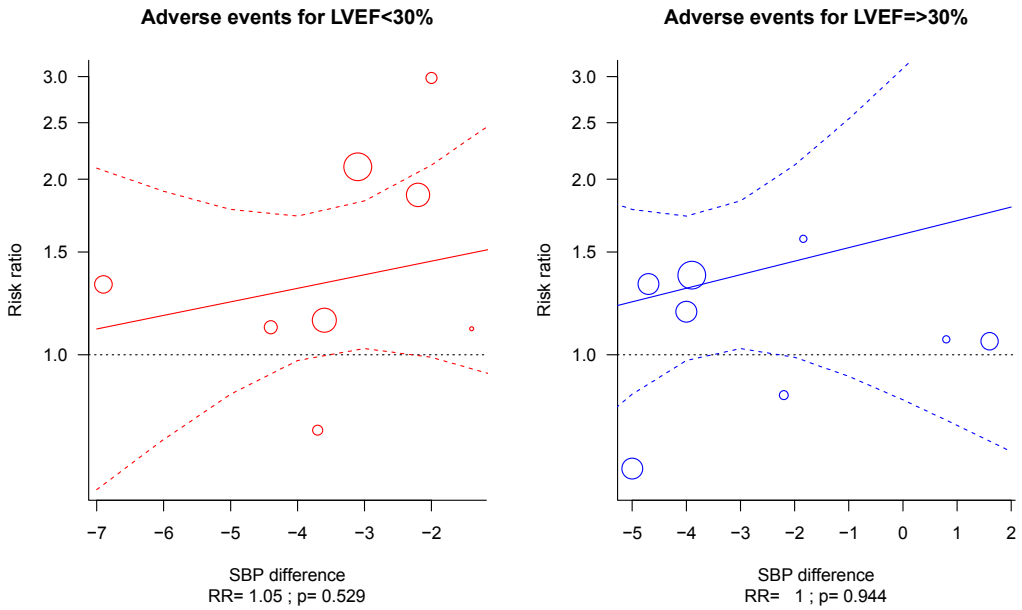
Risk ratios for cardiovascular (CV) mortality were regressed against the mean difference in systolic blood pressure change between the intervention and control groups in each trial and stratified by left-ventricular ejection fraction using a 30% cut-off. Negative values mean that the reduction in systolic blood pressure was greater in the intervention group and vice-versa. SBP, systolic blood pressure

eFigure 6: Meta-regression of risk ratio for heart failure hospitalisation according to the difference in systolic blood pressure between study groups stratified by left-ventricular ejection fraction



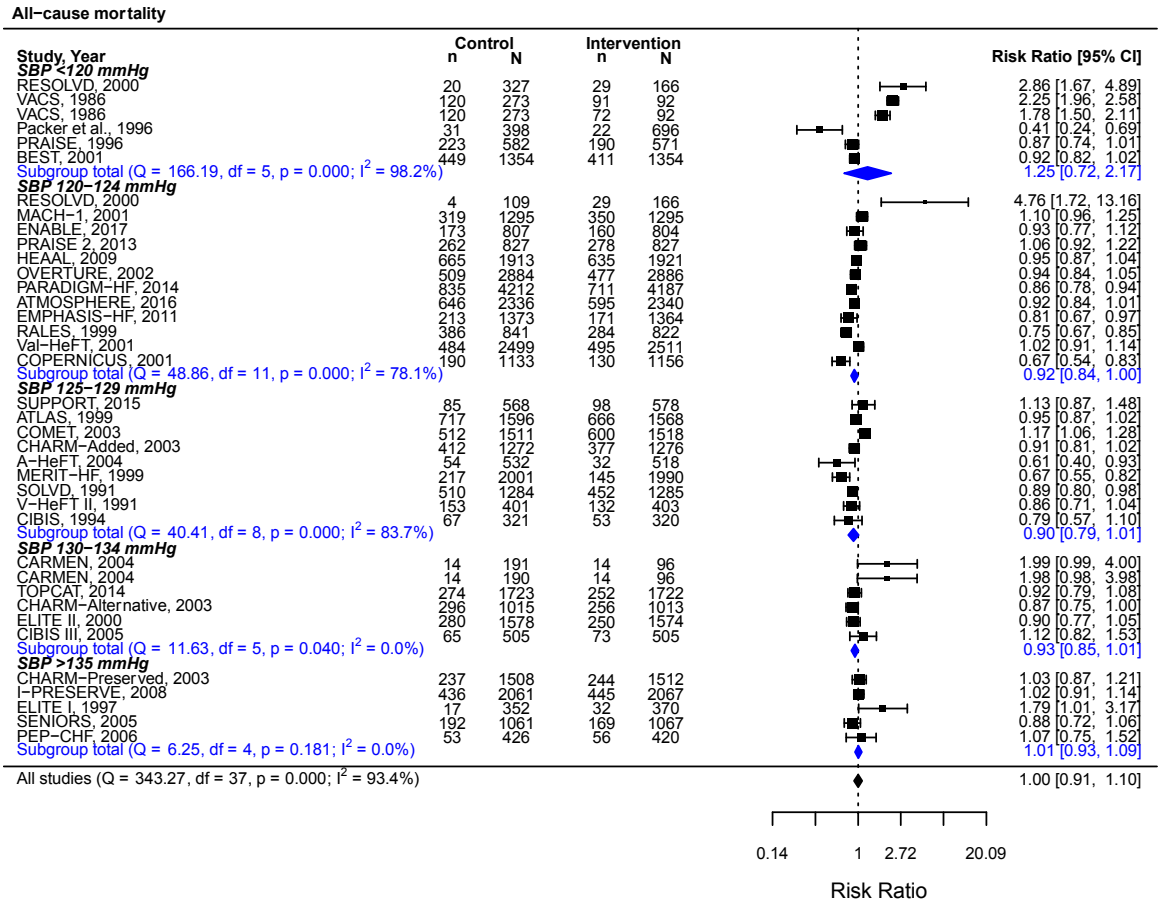
Risk ratios for heart failure (HF) hospitalisation were regressed against the mean difference in systolic blood pressure change between the intervention and control groups in each trial and stratified by left-ventricular ejection fraction using a 30% cut-off. Negative values mean that the reduction in systolic blood pressure was greater in the intervention group and vice-versa. SBP, systolic blood pressure

eFigure 7: Meta-regression of risk ratio for adverse events leading to treatment discontinuation according to the difference in systolic blood pressure between study groups stratified by left-ventricular ejection fraction



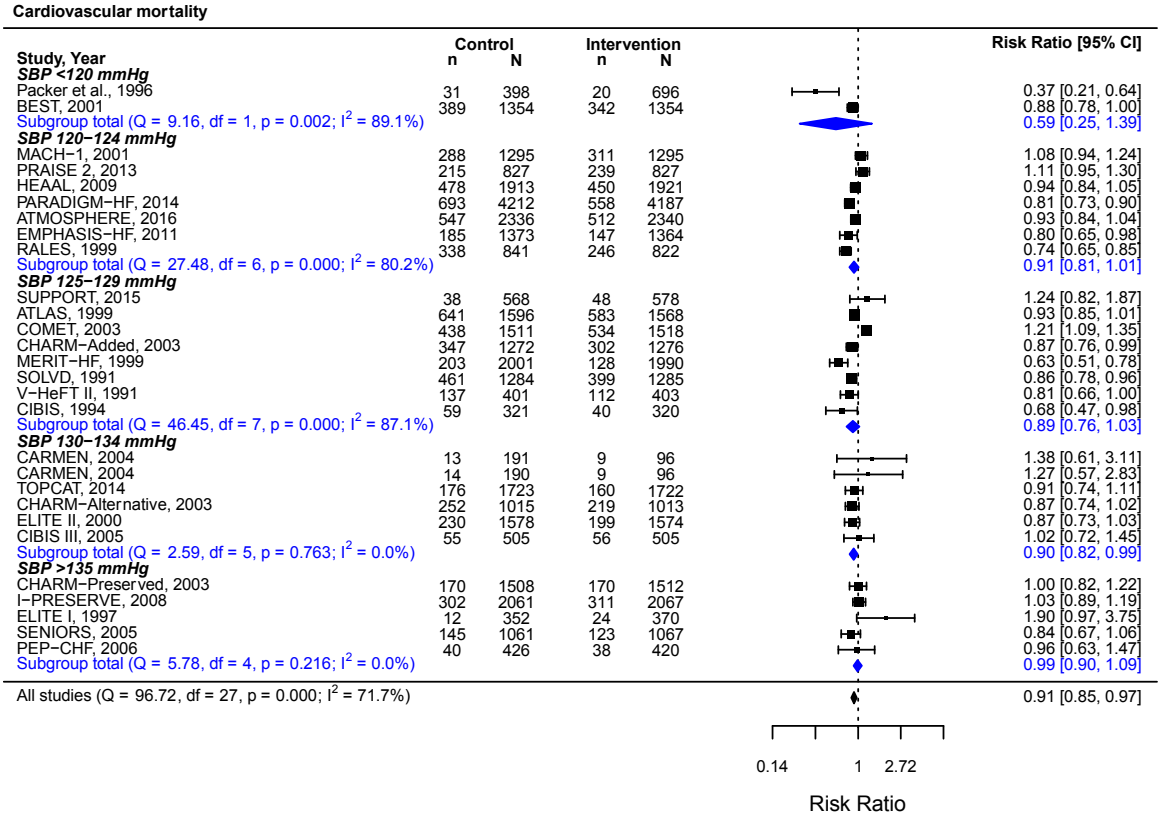
Risk ratios for adverse events leading to treatment discontinuation were regressed against the mean difference in systolic blood pressure change between the intervention and control groups in each trial and stratified by left-ventricular ejection fraction using a 30% cut-off. Negative values mean that the reduction in systolic blood pressure was greater in the intervention group and vice-versa. SBP, systolic blood pressure

eFigure 8: Meta-analysis of the effect of blood pressure-lowering treatment on all-cause mortality stratified by baseline systolic blood pressure



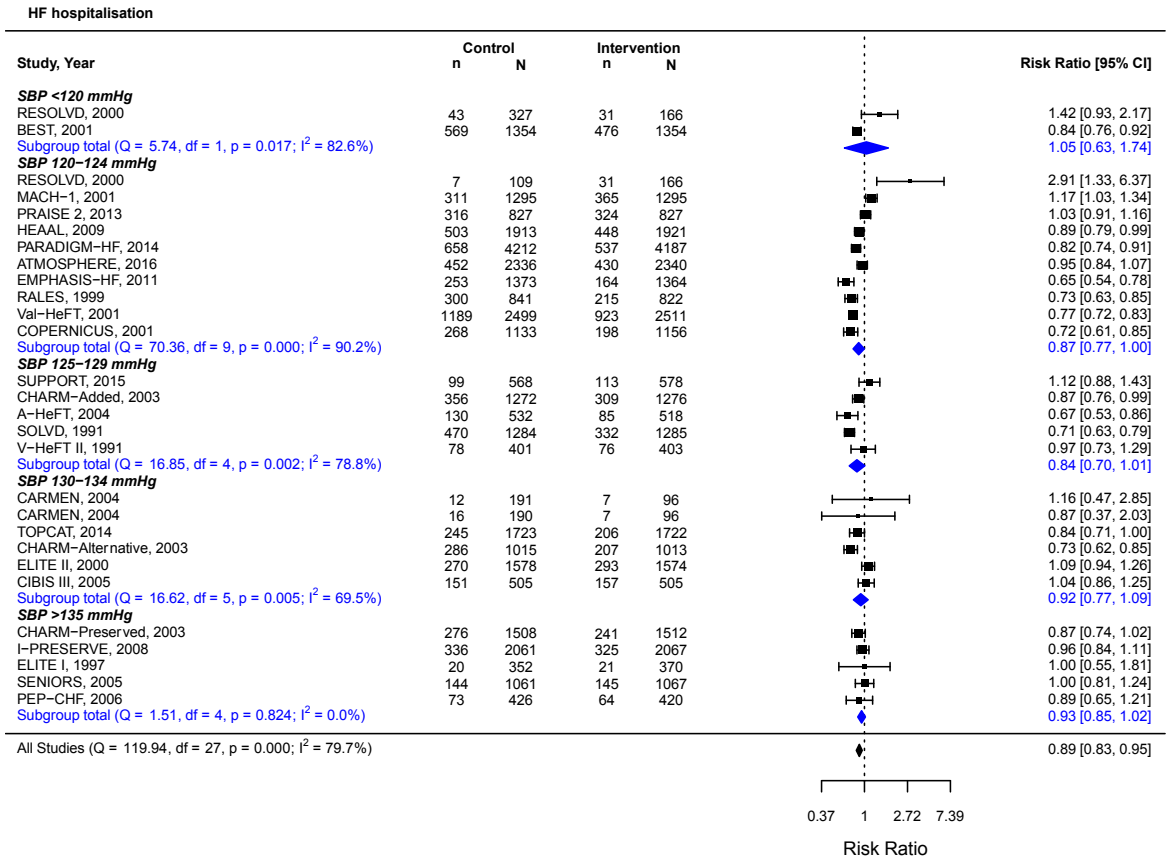
Risk ratios and 95% confidence intervals are displayed for all-cause mortality for each trial and strata of mean baseline systolic blood pressure aggregated at trial-level. Summary measures were calculated using random effects models with REML estimators. SBP, systolic blood pressure

eFigure 9: Meta-analysis of the effect of blood pressure-lowering treatment on cardiovascular mortality stratified by baseline systolic blood pressure



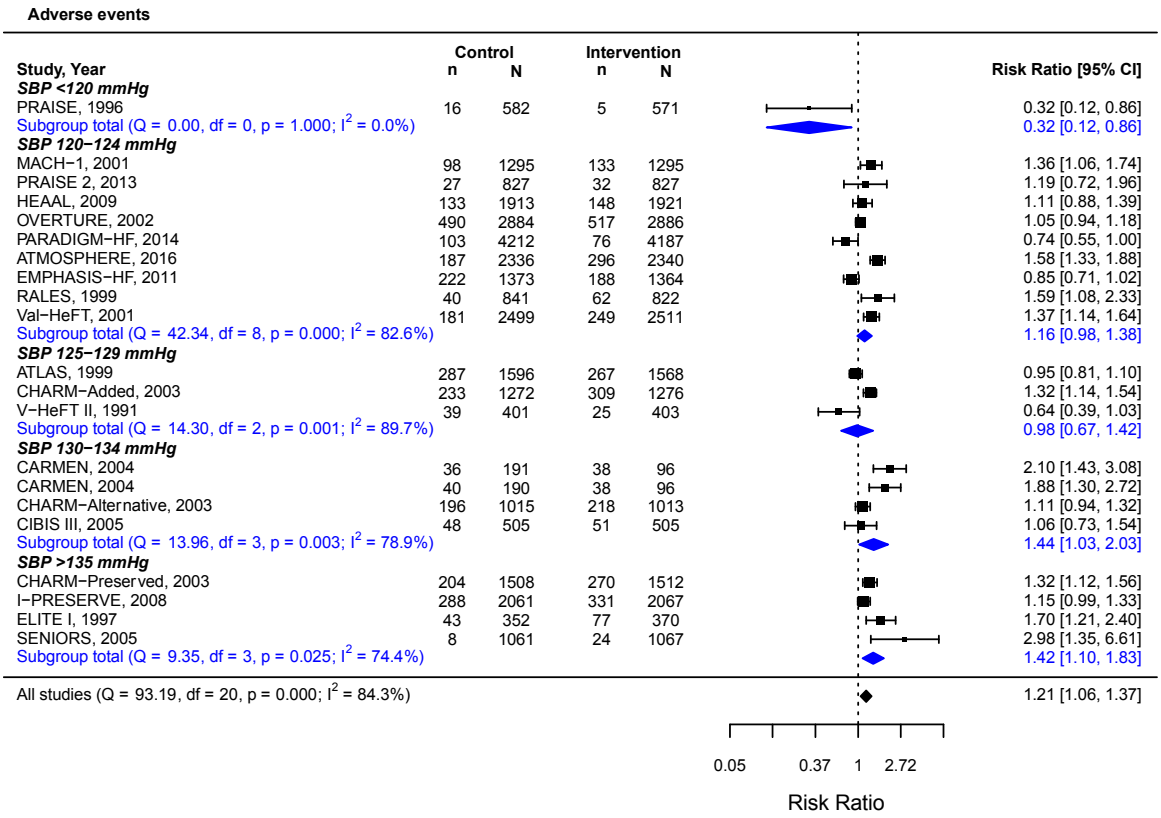
Risk ratios and 95% confidence intervals are displayed for cardiovascular mortality for each trial and strata of mean baseline systolic blood pressure aggregated at trial-level. Summary measures were calculated using random effects models with REML estimators. n, number of events; N, total number of patients; SBP, systolic blood pressure

eFigure 10: Meta-analysis of the effect of blood pressure-lowering treatment on heart failure hospitalisation stratified by baseline systolic blood pressure



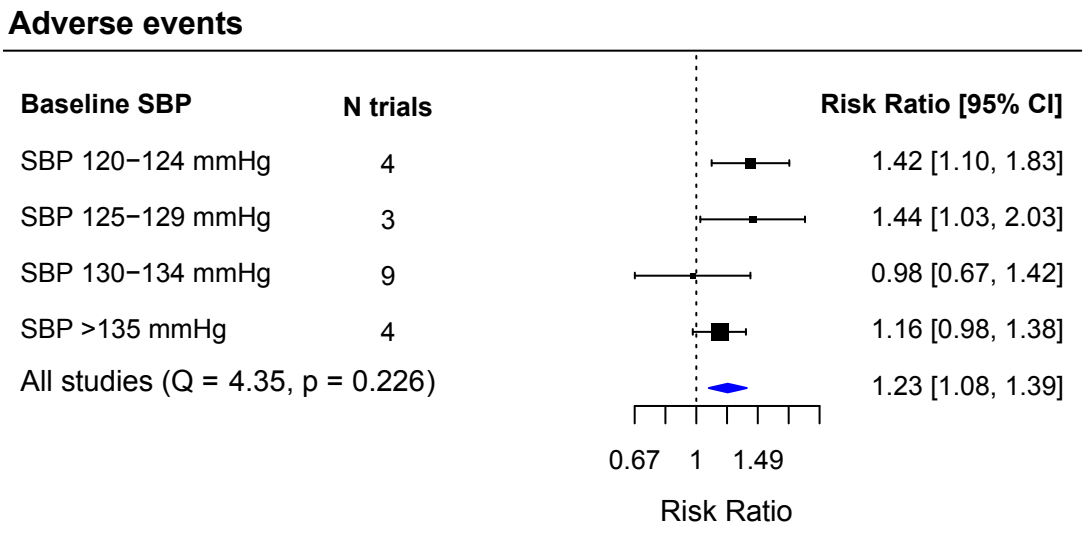
Risk ratios and 95% confidence intervals are displayed for heart failure (HF) hospitalisation for each trial and strata of mean baseline systolic blood pressure aggregated at trial-level. Summary measures were calculated using random effects models with REML estimators. n, number of events; N, total number of patients; SBP, systolic blood pressure

eFigure 11: Meta-analysis of the effect of blood pressure-lowering treatment on adverse events leading to treatment discontinuation stratified by baseline systolic blood pressure



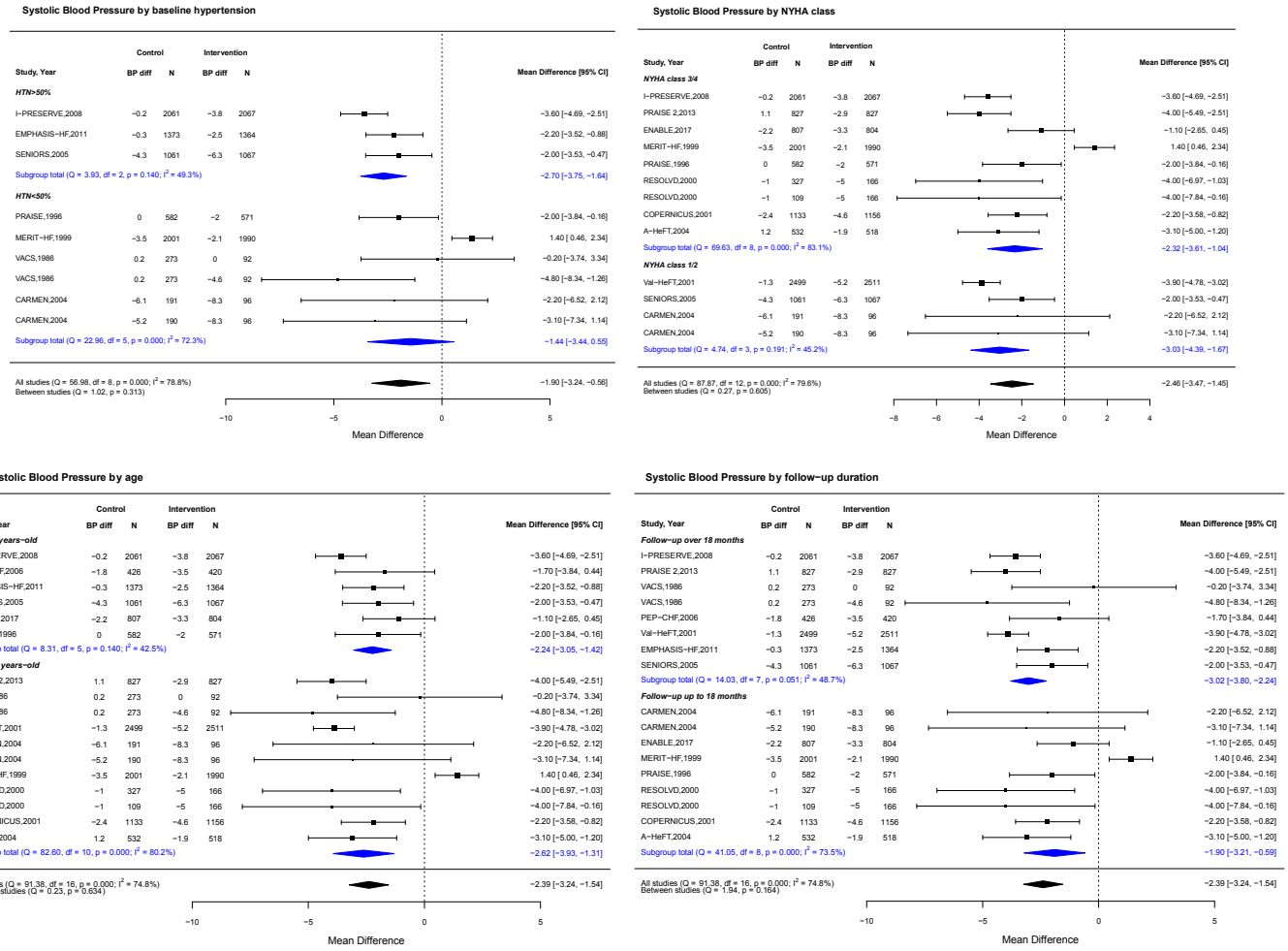
Risk ratios and 95% confidence intervals are displayed for adverse events leading to treatment discontinuation for each trial and strata of mean baseline systolic blood pressure aggregated at trial-level. Summary measures were calculated using random effects models with REML estimators. n, number of events; N, total number of patients; SBP, systolic blood pressure

eFigure 12: Meta-analysis of the effect of blood pressure-lowering treatment on adverse events leading to treatment discontinuation stratified by baseline systolic blood pressure excluding the trial with systolic blood pressure below 120 mmHg



Risk ratios and 95% confidence intervals are displayed for adverse events leading to treatment discontinuation for each strata of mean baseline systolic blood pressure aggregated at trial-level, excluding the lowest stratum (<120 mmHg) which included only a single trial. This stratum had a significantly lower risk and when it was excluded the heterogeneity across strata of baseline systolic blood pressure was no longer statistically significant. Summary measures were calculated using random effects models with REML estimators. SBP, systolic blood pressure

eFigure 13: Meta-analysis of the effect of blood pressure-lowering treatment on systolic blood pressure stratified by hypertension at baseline, NYHA class at baseline, age and duration of follow-up.



Mean differences between the change in systolic blood pressure in the intervention group versus the control group are displayed for each trial and each subgroup. Top left: subgroup analysis for hypertension at baseline, with trials categorised as under or over 50% prevalence of baseline hypertension. Top right: subgroup analysis for NYHA class at baseline, with trials split into two categories according to the predominant NYHA class. Bottom left: subgroup analysis for age, with trials split according to patients' mean age. Bottom right: subgroup analysis for duration of follow-up with trials split into two categories according to mean duration of follow-up. Summary measures were calculated using random effects models with REML estimators. Negative values mean that the reduction in systolic blood pressure was greater in the intervention group and vice-versa. Only studies that compared active treatment with placebo were included. BP diff, difference between achieved and baseline systolic blood pressure; SBP, systolic blood pressure

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