

Adenosine and forskolin inhibit platelet aggregation by collagen but not the proximal signalling events

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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	D B	P C	70/EU	23	Placebo	Bisoprolol		HFr EF	32 1	32 0		R	NR	NR
CIBIS II(2)	Dargie et al.	1999	D B	P C	274/EU	15	Placebo	Bisoprolol		HFr EF	13 20	13 27		NR	NR	NR
CIBIS III(3)	Willenheimer et al.	2005	O L	A T	128/EU, Aus and Tunisia	24	Bisoprolol	Enalapril		HFr EF	55 0	55 0		R	R	6
BEST(4)	BEST Inv	2001	D B	P C	90/NA	24	Placebo	Bucindolol		HFr EF	13 54	13 54		R	PR	NR
COPERNICUS (5)	Packer et al.	2002	D B	P C	334/NA, EU, Aus	11	Placebo	Carvedilol		HFr EF	11 33	11 56		R	PR	4
PEP-CHF(6)	Cleland et al.	2006	D B	P C	53/EU	26	Placebo	Perindopril		HFr EF	42 6	42 0		R	R	12
SENIORS(7)	Flather et al.	2005	D B	P C	11/EU	21	Placebo	Nebivolol		Mix	10 61	10 67		R	R	4
V-HeFT II(8)	Cohn et al.	1991	D B	A T	13/US	30	HZ-ISD	Enalapril		HFr EF	40 1	40 3		R	R	4
ELITE I(9)	Pitt et al.	1997	D B	A T	125/US, SA, EU	11	Losartan	Captopril		HFr EF	35 2	37 0		R	NR	NR
ELITE II(10)	Pitt et al.	2000	D B	A T	289/NA, MC SA, EU	11	Losartan	Captopril		HFr EF	15 78	15 74		R	NR	NR
SOLVD(11)	SOLVD Inv	1991	D B	P C	23/NA, Belgium	48	Placebo	Enalapril		HFr EF	12 84	12 85		R	PR	NR
MERIT-HF(12)	MERIT-HF Inv	1999	D B	P C	14/US, EU	18	Placebo	Metoprolol		HFr EF	20 01	19 90		R	R	6
Val-HeFT(13)	Cohn et al.	2001	D B	P C	302/US, EU, Africa	23	Placebo	Valsartan		HFr EF	24 99	25 11		R	PR	6
RALES(14)	Pitt et al.	1999	D B	P C	195/EU, NA, SA, Asia	24	Placebo	Spirolactone		HFr EF	84 1	82 2		R	NR	NR
A-HeFT(15)	Taylor et al.	2004	D B	P C	169/US	10	Placebo	ISD/HZ		HFr EF	53 2	51 8		R	R	6

I-PRESERVE(16)	Massie et al.	2008	D B	P C	293/EU, NA, SA, AUS, Africa	50	Placebo	Irbesartan	HFpEF	20 61	20 67	R	R	6	
CHARM-Added(17)	McMurray et al.	2003	D B	P C	618/NA, EU	41	Placebo	Candesartan	HFrEF	12 72	12 76	R	PR	NR	
CHARM-Alternative(18)	Granger et al.	2003	D B	P C	618/NA, EU	42	Placebo	Candesartan	HFrEF	10 15	10 13	R	PR	6	
CHARM-Preserved(19)	Yusuf et al.	2003	D B	P C	618/NA, EU	37	Placebo	Candesartan	HFpEF	15 08	15 12	R	PR	6	
COMET(20)	Poole-Wilson et al.	2003	D B	A T	341/EU	58	Carvedilol	Metoprolol	HFrEF	15 11	15 18	R	PR	4	
EMPHASIS-HF(21)	Zannad et al.	2011	D B	P C	278/US, EU, AUS	21	Placebo	Eplerenone	HFrEF	13 73	13 64	R	PR	NS	
TOPCAT(22)	Pitt et al.	2014	D B	P C	233/NA, SA, Russia, Georgia	40	Placebo	Spironolactone	HFpEF	17 23	17 22	R	NR*	NR	
ATMOSPHERE(23)	McMurray et al.	2016	D B	A T	789/EU, NA, SA, Africa Asia	37	Enalapril	Aliskiren Combination	HFrEF	23 36	23 40	23 40	R	PR	4
PARADIGM-HF(24)	McMurray et al.	2014	D B	A T	1043/EU, America, Africa, Asia	27	Enalapril	Sacubitril/ Valsartan	HFrEF	42 12	41 87		R	PR	8
OVERTURE(25)	Packer et al.	2002	D B	A T	704/EU, America, Africa, Asia	15	Enalapril	Omapatrilat	Mix	28 84	28 86	R	PR	4	
HEAAL(26)	Konstam et al.	2009	D B	A T	255/EU, America, Africa, Asia	56	Losartan 50	Losartan 150	HFrEF	19 13	19 21	R	R	6	
PRAISE(27)	Packer et al.	1996	D B	P C	105/NA	14	Placebo	Amlodipine	HFrEF	58 2	57 1	R	PR	3	
PRAISE 2(28)	Packer et al.	2013	D B	P C	105/NA	33	Placebo	Amlodipine	HFrEF	82 7	82 7	R	PR	3	
ATLAS(29)	Packer et al.	1999	D B	A T	287/EU, Aust, NA	46	Lisinopil LD	Lisinopril HD	HFrEF	15 96	15 68	R	PR	36	
SUPPORT(30)	Sakata et al.	2015	O L	A T	17/Japan	53	ST	Olmesartan	Mix	56 8	57 8	R	NR*	12	

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

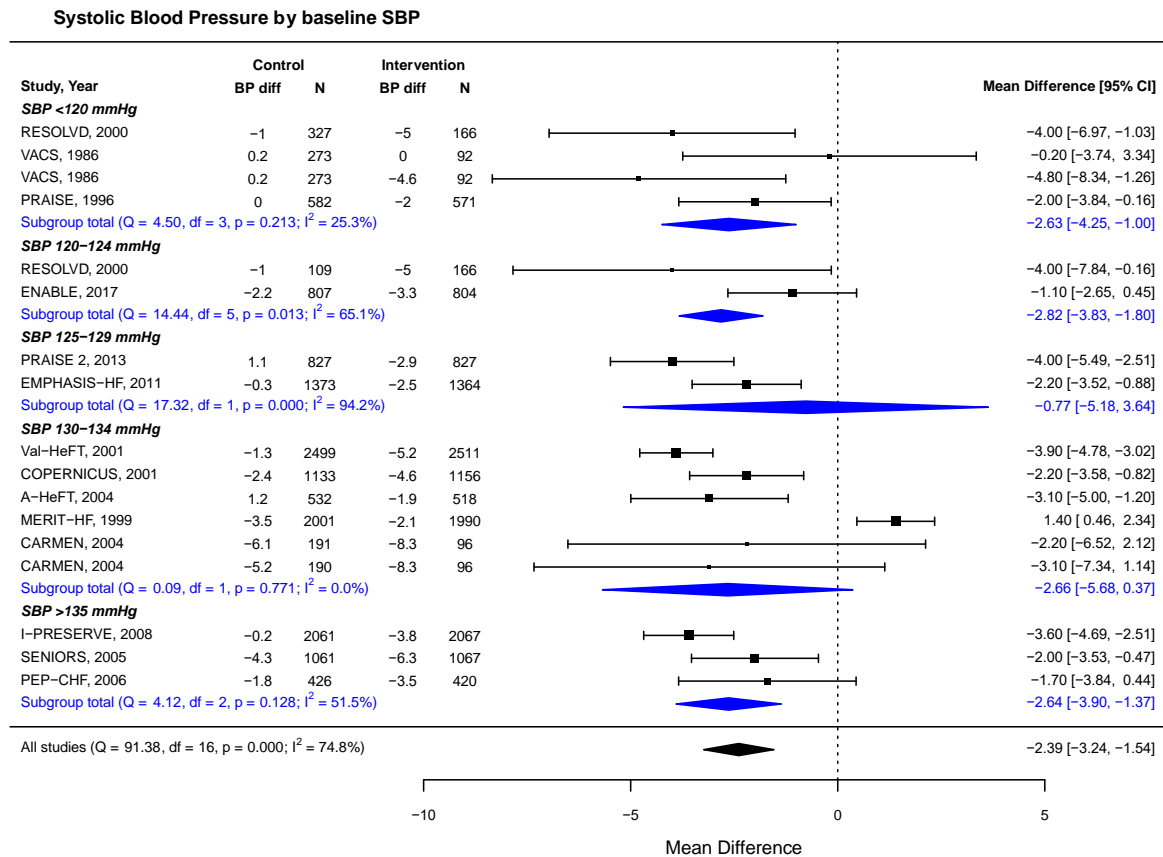
AF, atrial fibrillation; BMI, body mass index; BP, blood pressure; HF, heart failure, years, mean); HR, heart rate; HTN, hypertension; LVEF, left ventricular ejection fraction; NYHA, New York Heart Association class/II (%); NR, not reported; DM, diabetes mellitus

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

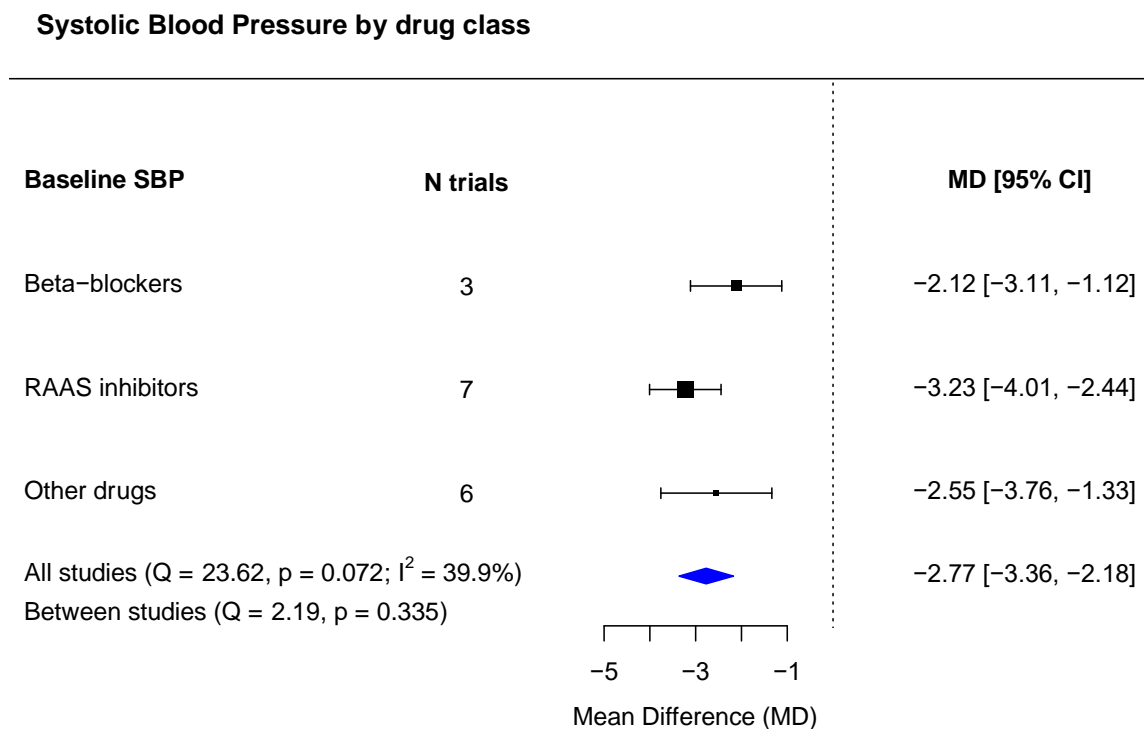
J-CHF	Okamoto et al.	2012	L	L	L	L	L	L
VACS	Cohn et al.	1986	L	L	L	L	L	L
RESOLVD	McKelvie et al.	2000	L	L	L	L	L	L

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



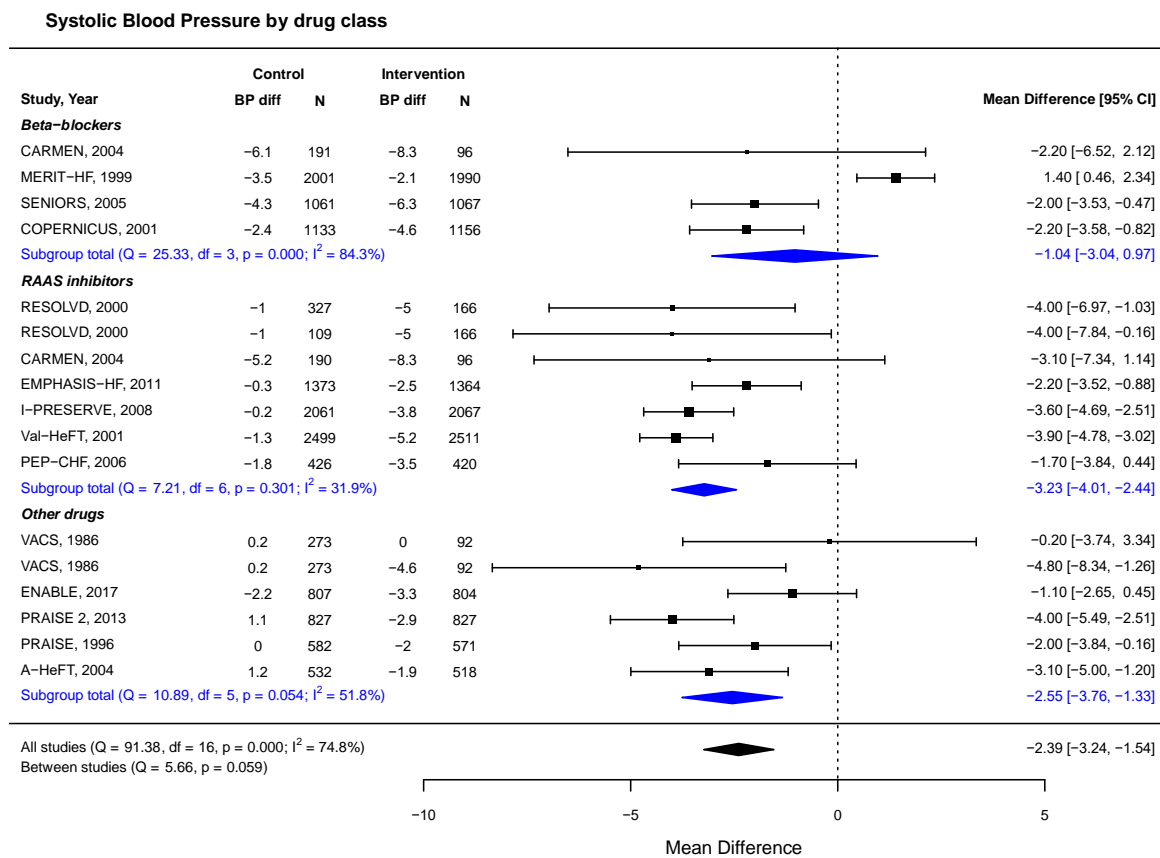
Mean differences between the change in systolic blood pressure in the intervention group versus the control group are displayed for each trial and each strata of mean baseline systolic blood pressure aggregated at trial-level. Summary measures were calculated using random effects models with REML estimators. 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



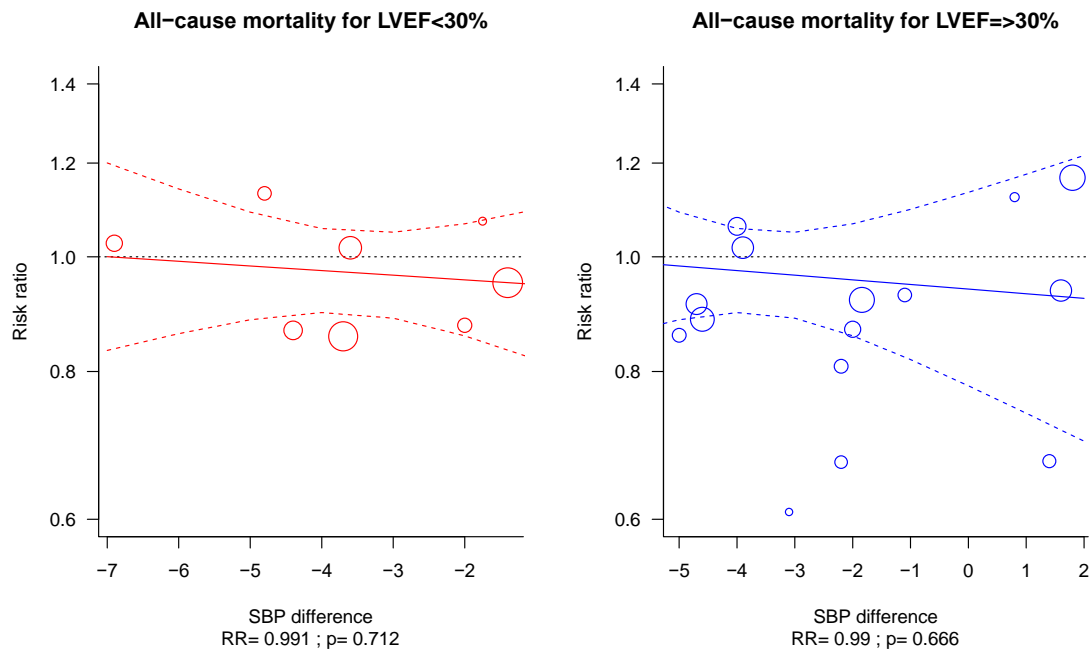
Mean differences between the change in systolic blood pressure in the intervention group versus the control group are displayed for each drug class. The outlier trial MERIT-HF was excluded from the beta-blocker subgroup to assess the impact of this trial on the subgroup estimate. Summary measures were 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



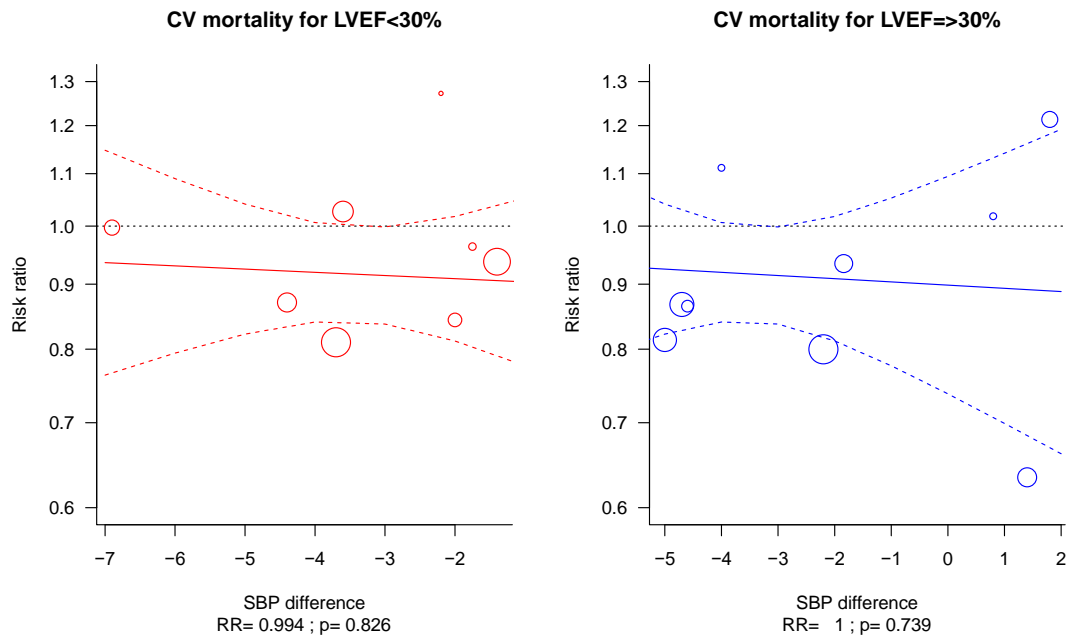
Mean differences between the change in systolic blood pressure in the intervention group versus the control group are displayed for each trial and each drug class. Summary measures were calculated using random effects models with REML estimators. Negative values mean that the reduction in systolic blood 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



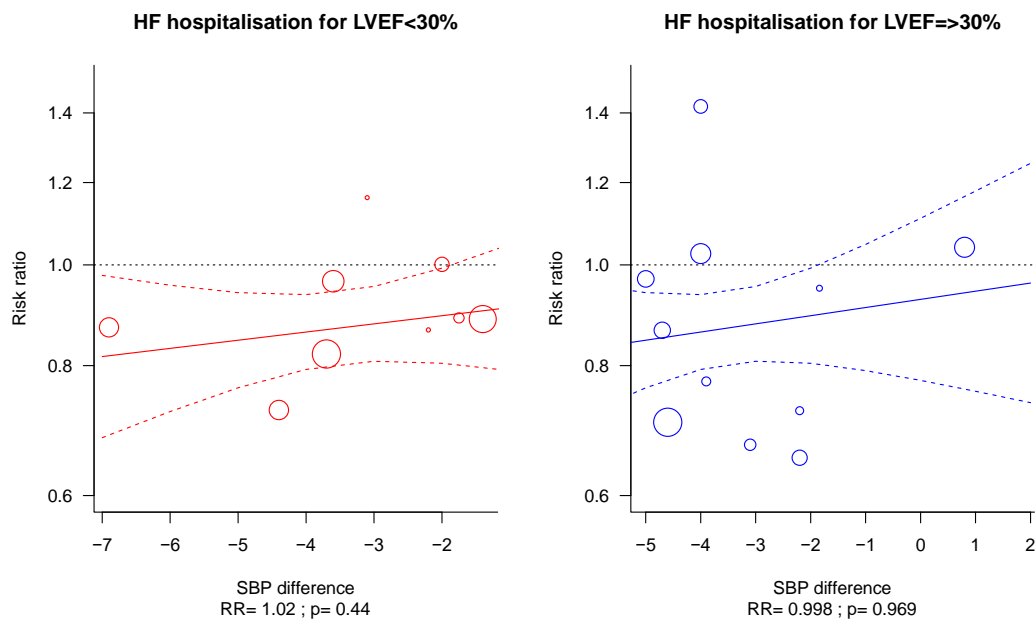
Risk ratios for all-cause mortality were regressed against the mean difference in systolic blood pressure change between the intervention and control groups in each trial and stratified by left-ventricular ejection fraction using a 30% cut-off. Negative values mean that the reduction in systolic blood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



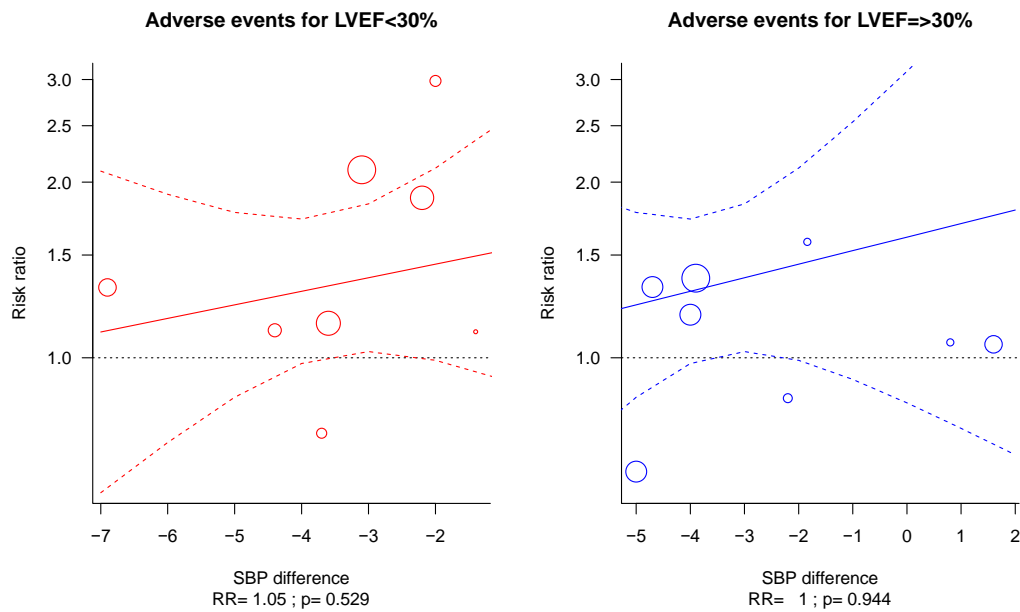
Risk ratios for cardiovascular (CV) mortality were regressed against the mean difference in systolic blood pressure change between the intervention and control groups in each trial and stratified by left-ventricular ejection fraction using a 30% cut-off. Negative values mean that the reduction in systolic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



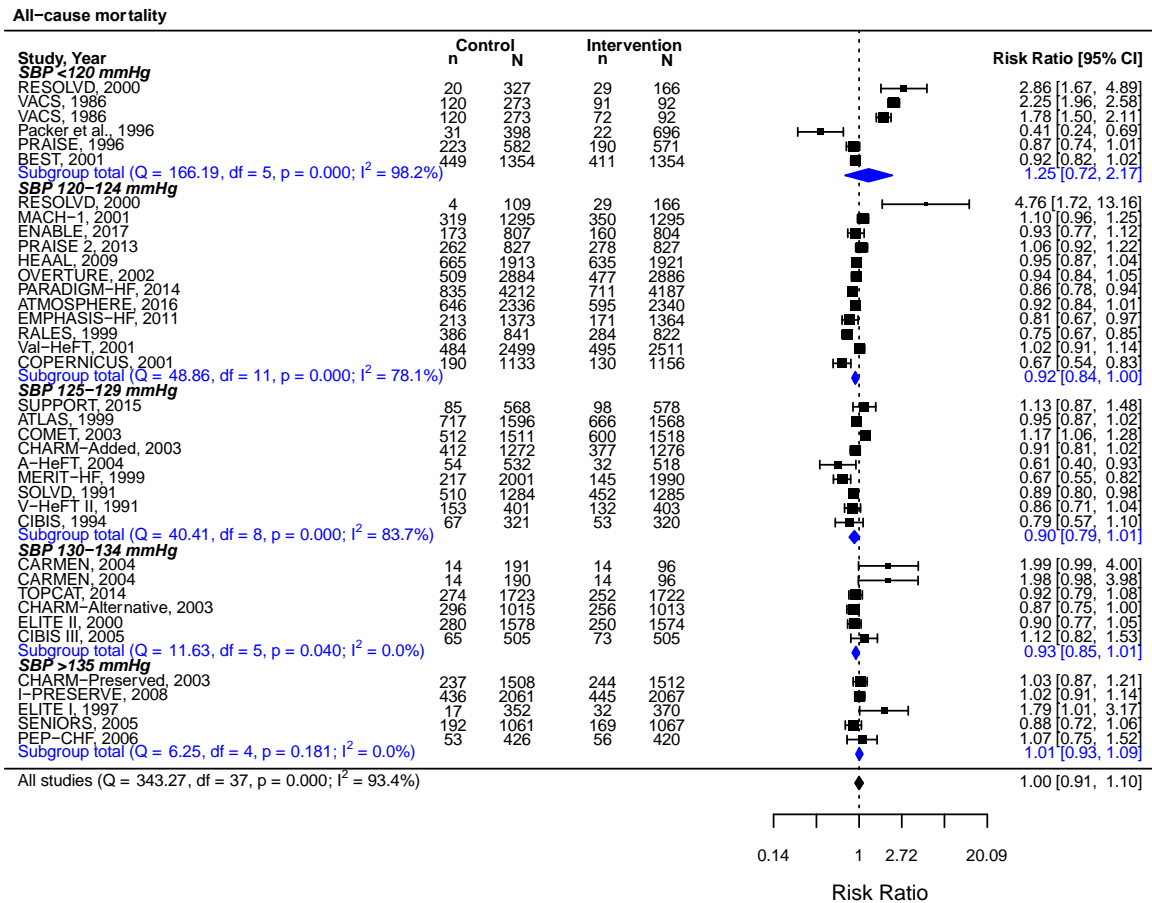
Risk ratios for heart failure (HF) hospitalisation were regressed against the mean difference in systolic blood pressure change between the intervention and control groups in each trial and stratified by left-ventricular ejection fraction using a 30% cut-off. Negative values mean that the reduction in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



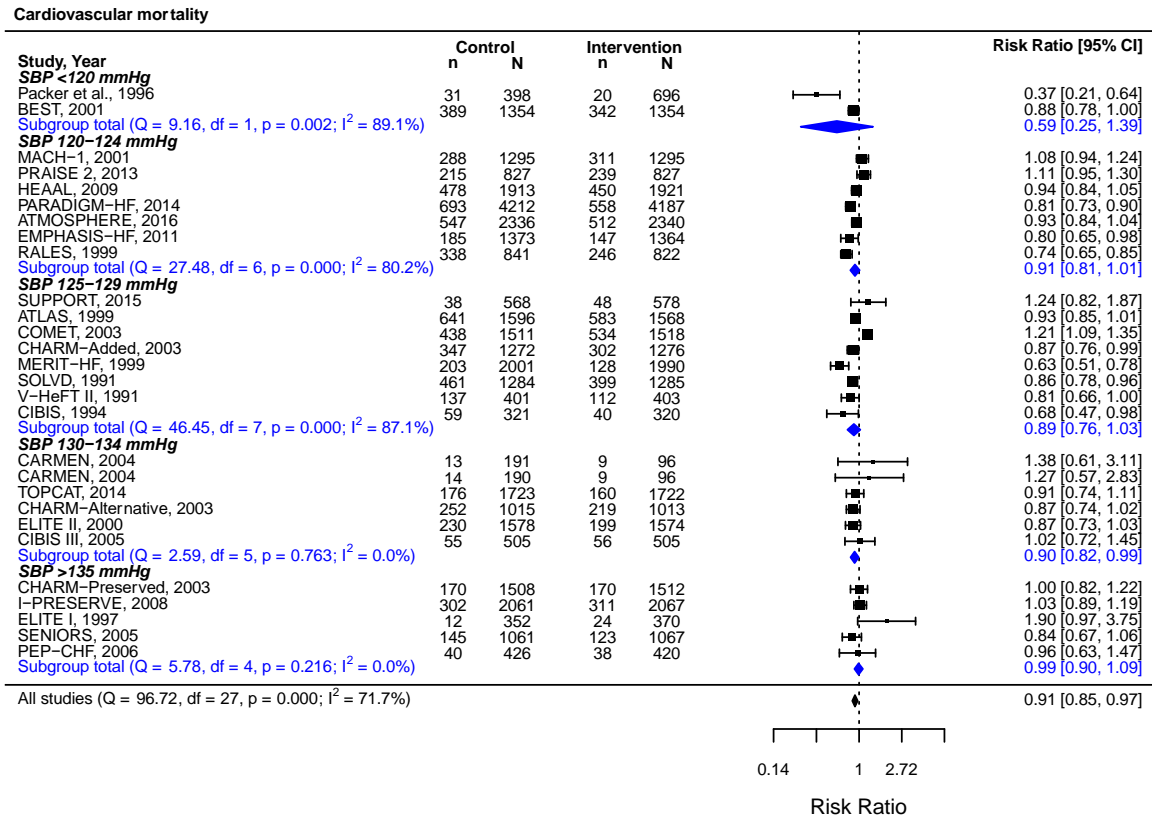
Risk ratios for adverse events leading to treatment discontinuation were regressed against the mean difference in systolic blood pressure change between the intervention and control groups in each trial and stratified by left-ventricular ejection fraction using a 30% cut-off. Negative values mean that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

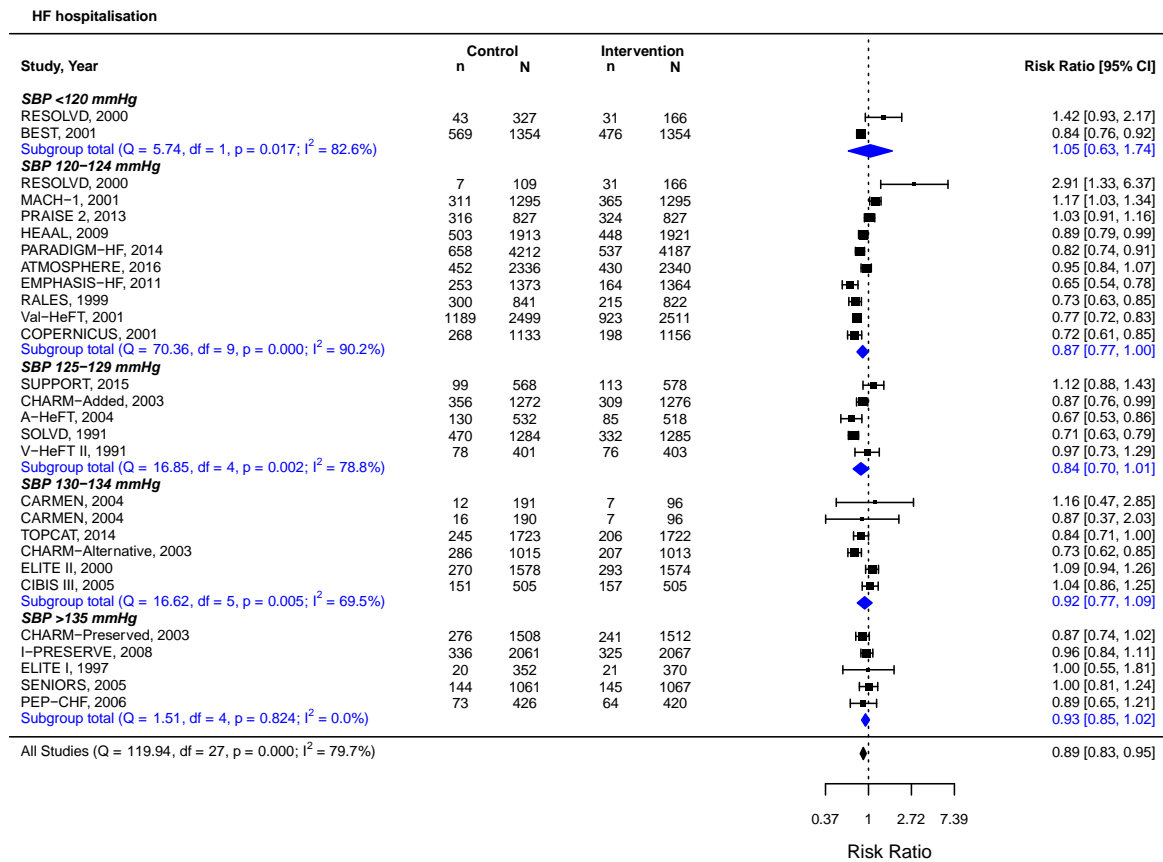
eFigure 9: Meta-analysis of the effect of blood pressure-lowering treatment on cardiovascular mortality stratified by baseline systolic blood pressure



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

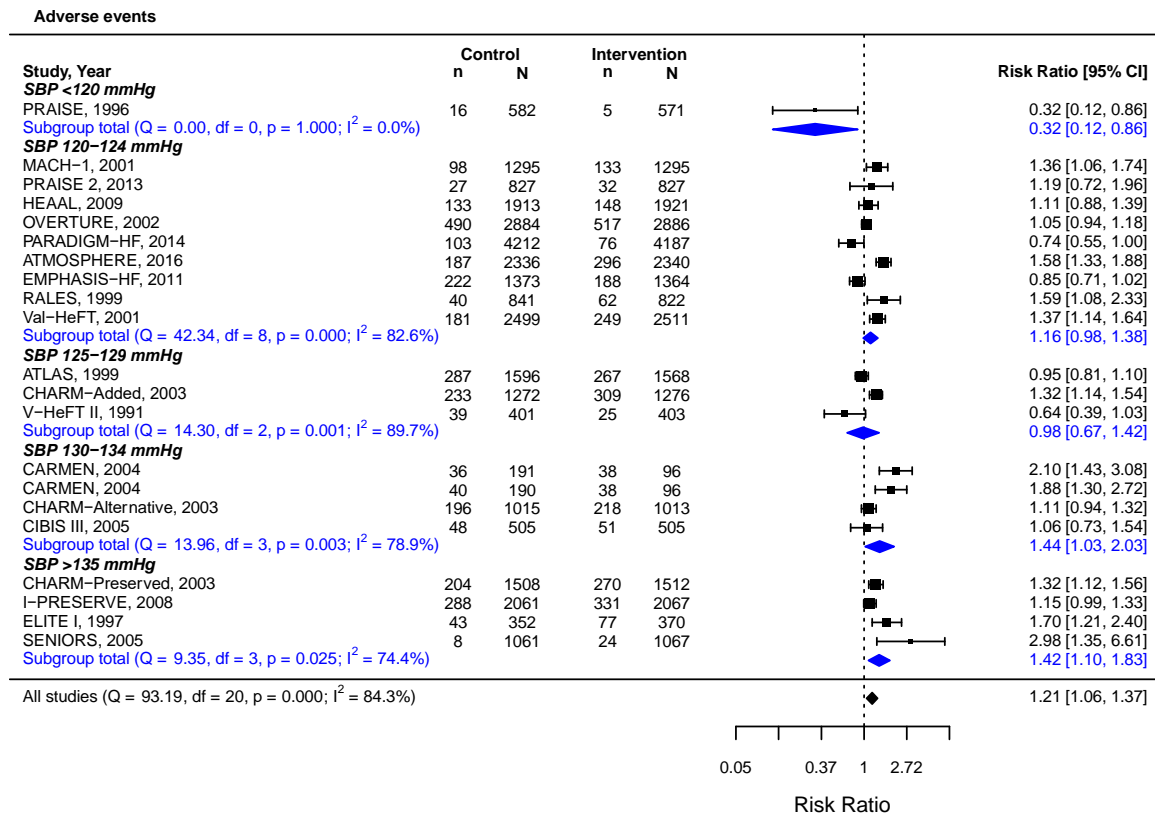
eFigure 10: Meta-analysis of the effect of blood pressure-lowering treatment on heart failure

hospitalisation stratified by baseline systolic blood pressure



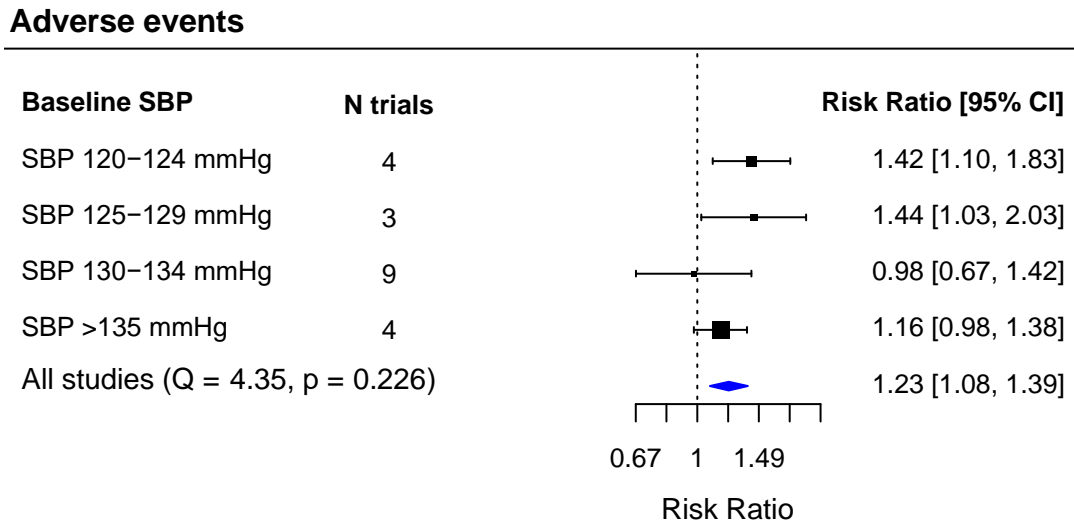
Risk ratios and 95% confidence intervals are displayed for heart failure (HF) hospitalisation for each trial and strata of mean baseline systolic blood pressure aggregated at trial-level. Summary measures were calculated using random effects models with REML estimators. n, number of events; N, total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



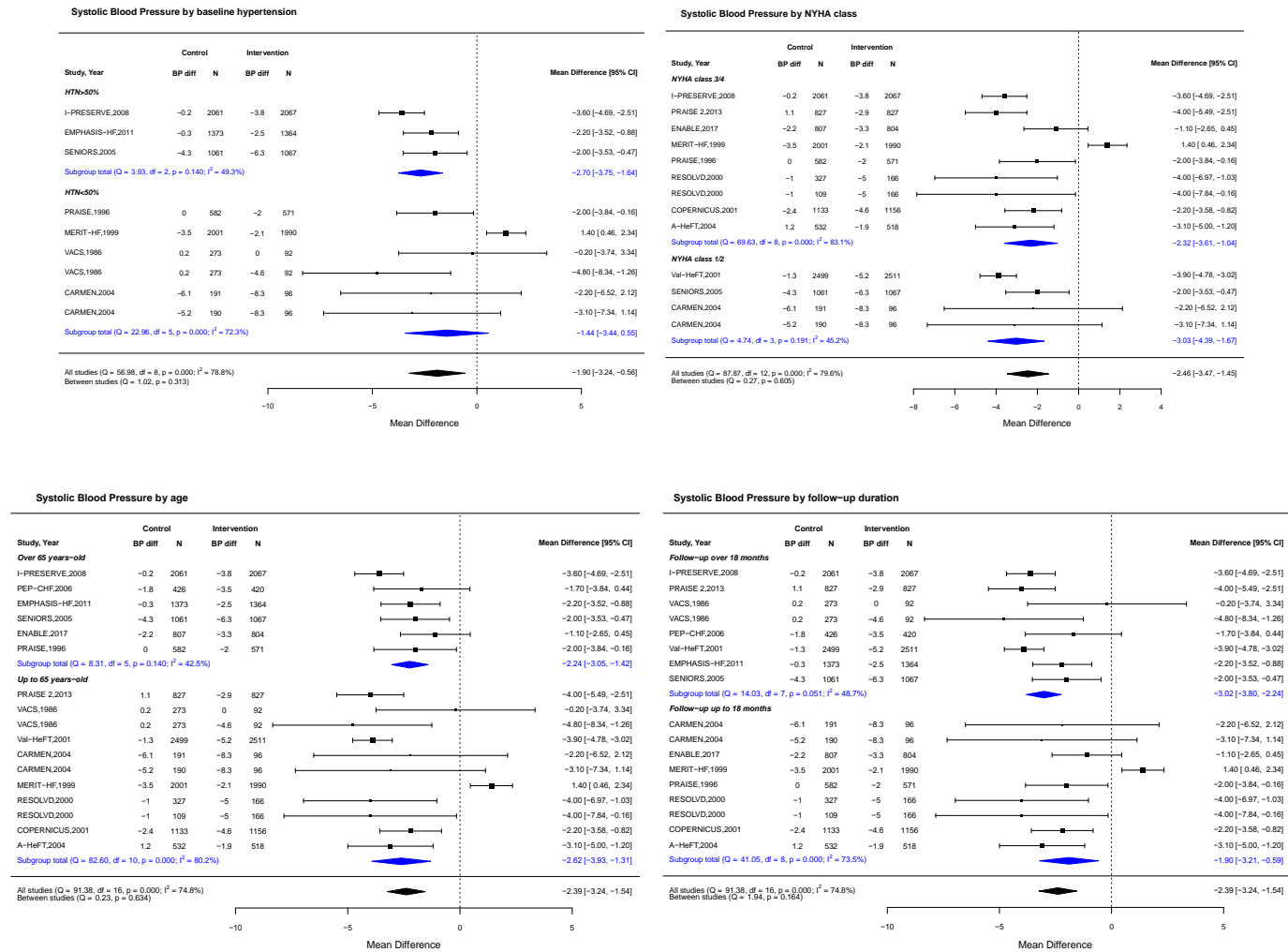
Risk ratios and 95% confidence intervals are displayed for adverse events leading to treatment discontinuation for each trial and strata of mean baseline systolic blood pressure aggregated at trial-level. Summary measures were calculated using random effects models with REML estimators. n, number of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