SUPPLEMENTARY TABLES AND FIGURES

Table S1: Search strategies

PubMed		
No	**Search Terms**	**Items found**
#9	(((((hypertens*) AND (adults OR adult OR elderly OR aged)) AND (intensive OR strict OR tight OR low OR optimal OR active) AND ("blood pressure" OR antihypertens*) AND (treatment OR management OR therapy OR target OR goal OR control) AND (("cardiovascular outcomes" OR) OR mortality OR morbidity))) AND ((Clinical Trial[ptyp] OR Controlled Clinical Trial[ptyp] OR Randomized Controlled Trial[ptyp]) AND hasabstract[text] AND Humans[Mesh] AND (middle age[MeSH] OR aged[MeSH]))))	1,282
#8	Search ((("cardiovascular outcomes" OR cardiovascular)) OR mortality) OR morbidity	4,499,760
#7	Search (((intensive OR strict OR tight OR low OR optimal OR active)) AND ("blood pressure" OR antihypertens*)) AND (treatment OR management OR therapy OR target OR goal OR control)	63,585
#6	Search ((((("randomized controlled trial"[Title]) OR "controlled clinical trial"[Title]) OR "randomized trial"[Title]) OR trial[Title]) OR randomized[Title]	261,134
#5	Search ("Cardiovascular outcomes" OR mortality OR morbidity)	3,014,437
#4	Search (treatment OR management OR therapy OR target OR goal OR control)	13,952,795
#3	Search ("blood pressure" OR antihypertens*)	476,380
#2	Search (intensive OR strict OR tight OR low OR optimal OR active)	3,841,252
#1	Search (hypertens*) AND (adults OR adult OR elderly OR aged)	261,906
Medline		
No	**Search Terms**	**Items found**
#6	#5 AND #4 Indexes=MEDLINE Timespan=All years	1,308
#5	((((TOPIC: ("randomized controlled trial") OR TOPIC: ("controlled clinical trial")) OR TOPIC: ("randomized trial")) OR TOPIC: (randomized)) OR TOPIC: (trial)) Indexes=MEDLINE Timespan=All years	1,305,048
#4	#2 AND #1 Refined by: MeSH HEADINGS: (HUMANS) Indexes=MEDLINE Timespan=All years	3,691
#3	#2 AND #1 Indexes=MEDLINE Timespan=All years	3,995
#2	(((TOPIC: (((((intensive) OR strict) OR tight) OR low) OR optimal) OR active) AND TOPIC: ("blood pressure" OR antihypertens*)) AND TOPIC: (((((treatment) OR management) OR therapy) OR target) OR goal) OR control)) AND TOPIC: (("cardiovascular outcomes") OR mortality) OR morbidity)) Indexes=MEDLINE Timespan=All years	12,486
#1	(TOPIC: (hypertens*) AND TOPIC: (((adults) OR adult) OR elderly) OR aged)) Indexes=MEDLINE Timespan=All years	277,842
Embase		
No	**Search Terms**	**Items found**
#5	#3 AND #4	409
#4	#1 AND #2	1,230
#3	'randomized controlled trial':ti,ab,kw OR 'controlled clinical trial':ti,ab,kw OR 'randomized trial':ti,ab,kw OR randomized:ti,ab,kw OR trial:ti,ab,kw	1,210,684
#2	(intensive:ti,ab,kw OR strict:ti,ab,kw OR tight:ti,ab,kw OR low:ti,ab,kw OR optimal:ti,ab,kw OR active:ti,ab,kw) AND ('blood pressure':ti,ab,kw OR antihypertens*:ti,ab,kw) AND (treatment:ti,ab,kw OR management:ti,ab,kw OR therapy:ti,ab,kw OR target:ti,ab,kw OR goal:ti,ab,kw OR control:ti,ab,kw) AND ('cardiovascular outcomes':ti,ab,kw OR mortality:ti,ab,kw OR morbidity:ti,ab,kw)	9,446
#1	hypertens*:ti,ab,kw AND (adults:ti,ab,kw OR adult:ti,ab,kw OR elderly:ti,ab,kw OR aged:ti,ab,kw)	101,293

Table S2: Stepwise drug class protocol

Study	Primary drugs	Secondary additional drugs	Tertiary additional drugs
ANBP 1981	Diuretic (T)	↑dose and/or BBs	
BBB 1994	N/R		
Cardio-Sis 2009	ARBs or ACE-Is or ABs or BBs or Diuretic or CCBs + transdermal clonidine – at investigators discretion		
COPE 2017	CCB+ (ARB or BB or Diuretic (T)) separately	↑Dose of CCB	↑dose of CCB in 3 steps of) + any drug in 4th step
FEVER 2005	CCBs	+ Diuretic (T) or any drug class but not CCBs	
HOT 1998	CCBs	+ ACE-Is or BBs	↑dose of CCB of ACE-Is/or BB - step 4 + diuretic – step 5
HYVET 2008	Diuretic (T)	+ ACE-Is or at ↑dose	
JATOS 2008	CCBs	↑dose of CCB + any dug class but not CCB	
SCOPE 2003	ARBs	↑dose	Other drug but not ACE-Is or ARBs
SHEP 1989	Diuretic (T)	Diuretic (T) or ABA or BBs + ↑dose	↑dose
SPRINT 2019	Diuretic (T) + ACE-Is or ARB + CCBs		
STOP-Hypertension 1991	BBs + Diuretic (T)	+ Diuretic or BBs	
Syst-China 1998	CCBs	+/or replaced ACE-Is and/or diuretic	
Syst-Eur 1997	CCBs	+/or replaced ACE-Is and/or Diuretic at ↑dose	
VALISH 2010	ARBs	↑dose +/or any drug class but not ARBs	
Wei et al. 2013	ACE-Is or ARBs or BBs or CCBs or Diuretic (T)	↑dose	↑dose

***ABA**: adrenergic blocking agent, **BB:** beta blocker, **CCB**: calcium channel blocker, **T**: thiazide diuretic, ↑: increasing*

Table S3: Sub-analysis for systolic versus diastolic BP treatment targets on relative risk reduction of outcome events

Follow-up Duration	Studies (Comparison)	Risk ratio	95% CI	*p*-value	Heterogeneity	
					I^2	*p*-value
Major cardiovascular events						
Systolic BP	13 (13)	**0.68**	0.59 – 0.78	0.000	70.81	0.000
Diastolic BP	3 (4)	1.06	0.88 – 1.28	0.561	36.39	0.194
Myocardial infarction						
Systolic BP	12 (12)	0.87	0.72 – 1.05	0.144	0.00	0.858
Diastolic BP	3 (4)	0.88	0.72 – 1.07	0.199	0.00	0.821
Stoke						
Systolic BP	13 (13)	**0.69**	0.61 – 0.76	0.000	3.85	0.408
Diastolic BP	3 (4)	1.00	0.80 – 1.26	0.972	0.00	0.500
Heart failure						
Systolic BP	11 (11)	**0.53**	0.43 – 0.66	0.000	1.23	0.430
Diastolic BP	0 (0)	-	-	-	-	-
Cardiovascular mortality						
Systolic BP	12 (12)	**0.72**	0.61 – 0.84	0.000	32.21	0.133
Diastolic BP	2 (3)	1.04	0.81 – 1.34	0.735	0.00	0.469
All-cause mortality						
Systolic BP	13 (13)	**0.78**	0.69 – 0.89	0.000	49.45	0.022
Diastolic BP	2 (3)	1.06	0.89 – 1.25	0.525	0.00	0.753

Table S4: Sub-analysis for follow-up duration on relative risk reduction of outcome events using systolic BP treatment targets only

Follow-up Duration	Studies (Comparison)	Risk ratio	95% CI	*p*-value	Heterogeneity	
					I^2	*p*-value
Major cardiovascular events						
< 3 years	5 (5)	**0.60**	0.44– 0.83	0.002	83.07	0.000
≥ 3 years	8 (8)	**0.74**	0.67 – 0.82	0.000	20.00	0.271
Myocardial infarction						
< 3 years	5 (5)	0.85	0.58 – 1.26	0.421	0.00	0.983
≥ 3 years	7 (7)	0.87	0.70 – 1.09	0.221	0.00	0.444
Stoke						
< 3 years	5 (5)	**0.66**	0.46 – 0.94	0.021	56.63	0.056
≥ 3 years	8 (8)	**0.68**	0.60 – 0.77	0.000	0.00	0.868
Heart failure						
< 3 years	5 (5)	**0.48**	0.35 – 0.67	0.000	0.00	0.412
≥ 3 years	6 (6)	**0.56**	0.41 – 0.76	0.000	10.15	0.351
Cardiovascular mortality						
< 3 years	5 (5)	**0.65**	0.46 – 0.91	0.012	38.84	0.162
≥ 3 years	7 (7)	**0.74**	0.61 – 0.89	0.002	33.98	0.169
All-cause mortality						
< 3 years	5 (5)	0.79	0.58 – 1.08	0.134	68.12	0.014
≥ 3 years	8 (8)	**0.79**	0.69 – 0.90	0.000	37.26	0.127

Table S5: Sub-analysis for effect of SBP targets on relative risk reduction of outcome events

SBP target	Included studies	Risk ratio	95% CI	*p*-value	Heterogeneity	
					I^2	*p*-value
Major cardiovascular events						
<120	1	0.63	0.47 – 0.83	0.001	0.00	1.000
<130	1	0.47	0.34 – 0.67	0.000	0.00	1.000
<140	5	0.76	0.64 – 0.89	0.001	31.15	0.214
<150	3	0.71	0.62 – 0.81	0.000	0.00	0.995
<160	3	0.60	0.35 – 1.03	0.065	92.89	0.000
Myocardial infarction						
<120	1	0.59	0.35 – 0.99	0.044	0.00	1.000
<130	1	0.66	0.19 – 2.33	0.519	0.00	1.000
<140	4	0.96	0.56 – 1.66	0.891	0.00	0.944
<150	3	0.76	0.53 – 1.10	0.146	0.00	0.650
<160	3	1.04	0.79 – 1.37	0.796	0.00	0.807
Stoke						
<120	1	0.50	0.25 – 1.00	0.049	0.00	1.000
<130	1	0.44	0.14 – 1.42	0.170	0.00	1.000
<140	5	0.73	0.60 – 0.89	0.002	22.77	0.269
<150	3	0.67	0.54 – 0.82	0.000	0.00	0.664
<160	3	0.60	0.41 – 0.87	0.008	53.36	0.117
Heart failure						
< 120	1	0.42	0.31 – 0.96	0.040	0.00	1.000
<130	1	0.43	0.11 – 1.63	0.213	0.00	1.000
<140	4	0.54	0.29 – 0.99	0.046	45.41	0.139
<150	3	0.52	0.33 – 0.85	0.008	48.06	0.146
<160	2	0.51	0.31 – 0.85	0.010	0.00	0.638
Cardiovascular mortality						
<120	1	0.42	0.15 – 1.18	0.100	0.00	1.000
<130	1	0.53	0.30 – 0.94	0.029	0.00	1.000
<140	4	0.70	0.52 – 0.94	0.016	21.58	0.281
<150	3	0.76	0.63 – 0.92	0.004	0.00	0.782
<160	3	0.65	0.34 – 1.24	0.189	73.61	0.023
All-cause mortality						
<120	1	0.70	0.45– 1.09	0.117	0.00	1.000
<130	1	0.52	0.33 – 0.81	0.004	0.00	1.000
<140	5	0.81	0.62 – 1.05	0.104	58.19	0.049
<150	3	0.81	0.71 – 0.92	0.001	0.00	0.479
<160	3	0.83	0.56 – 1.23	0.346	66.45	0.051

Table S6: Overall NNT and NNH for outcome events

Outcome events	**Studies (Comparison)**	**N**		**Events**		**NNT**
		ITx	**STx**	**ITx**	**STx**	
Major cardiovascular event	16 (17)	36599	29291	1892	2071	38
Myocardial infarction	15 (16)	31758	24421	447	377	502
Stroke	16 (17)	36599	29291	795	926	91
Heart failure	11 (11)	18694	17681	134	242	112
Cardiovascular mortality	14 (15)	33802	26960	688	744	113
All-cause mortality	15 (16)	35535	28228	1449	1424	85
						NNH
Hypotension related events	5 (5)	11757	11301	880	853	778

ITx: *intensive treatment,* ***N:*** *total number of participants,* ***NNH****: number needed to harm,* ***NNT****: number needed to treat,* ***STx****: standard treatment*

Table S7: Success and withdrawal rates of included studies

Included studies	**Success %**		**Weighed means**		**Withdrawal %**		**Weighed means**	
	ITx	**STx**	**ITx**	**STx**	**ITx**	**STx**	**ITx**	**STx**
ANBP 1981	70.0	28	1.85	0.80				
Cardio-Sis 2009	72.2	66.9	3.62	3.64				
COPE 2017	85.9	36.1	13.39	4.50				
HYVET 2008	48.0	19.9	8.5	3.74	3.6	7.2	1.07	0.53
JATOS 2008	64.9		12.92		3.6	3.1	0.53	0.61
SCOPE 2003					15	17	3.26	2.85
SHEP 1989	60.0	33	2.39	0.35				
Syst-Eur 1997	43.5	21.4	9.38	4.83	0.5	5.5	0.98	1.17
VALISH 2010	67.5	47.8	9.38	7.21	2.6	2.8	0.33	0.40
Wei et al. 2013					0.3	1.4	0.04	0.05
Total			61.29	25.08			5.25	7.4

ITx: *intensive treatment,* ***STx:*** *standard treatment*

Table S8: Assessment of study quality – JADAD SCORE of included studies

Study, Author, Year	**Randomization**	**Randomization described and appropriate**	**Blinding**	**Blinding described and appropriate**	**An account of all patients included**	**Total Score 5**
ANBP Report by the Management Committee, 1981	1	Not described	1	1	1	4
BBB Hansson, 1994	1	Not described	1	1	1	4
Cardio-Sis Verdecchia et al., 2009;	1	1	1	1	1	5
COPE Umemoto et al., 2017	1	1	1	1	1	5
FEVER Liu et al., 2005	1	1	1	1	1	5
HOT Hansson et al., 1998	1	1	1	1	1	5
HYVET Beckett et al., 2008	1	1	1	1	1	5
JATOS JATOS Study Group, 2008	1	1	1	1	1	5
SCOPE Lithell et al., 2003	1	1	1	1	1	5
SHEP Perry et al., 1989	1	1	1	1	1	5
SPRINT Attar et al., 2019	1	1	Not blinded	Not described	1	3
STOP-Hypertension Dahlöf et al., 1991	1	Not described	1	1	1	4
Syst-China Lui et al., 1998	1	1	1	1	1	5
Syst-Eur Staessen et al., 1997	1	1	1	1	1	5
VALISH Ogihara et al., 2010	1	1	1	1	1	5
Wei et al., 2013	1	1	1	1	1	5

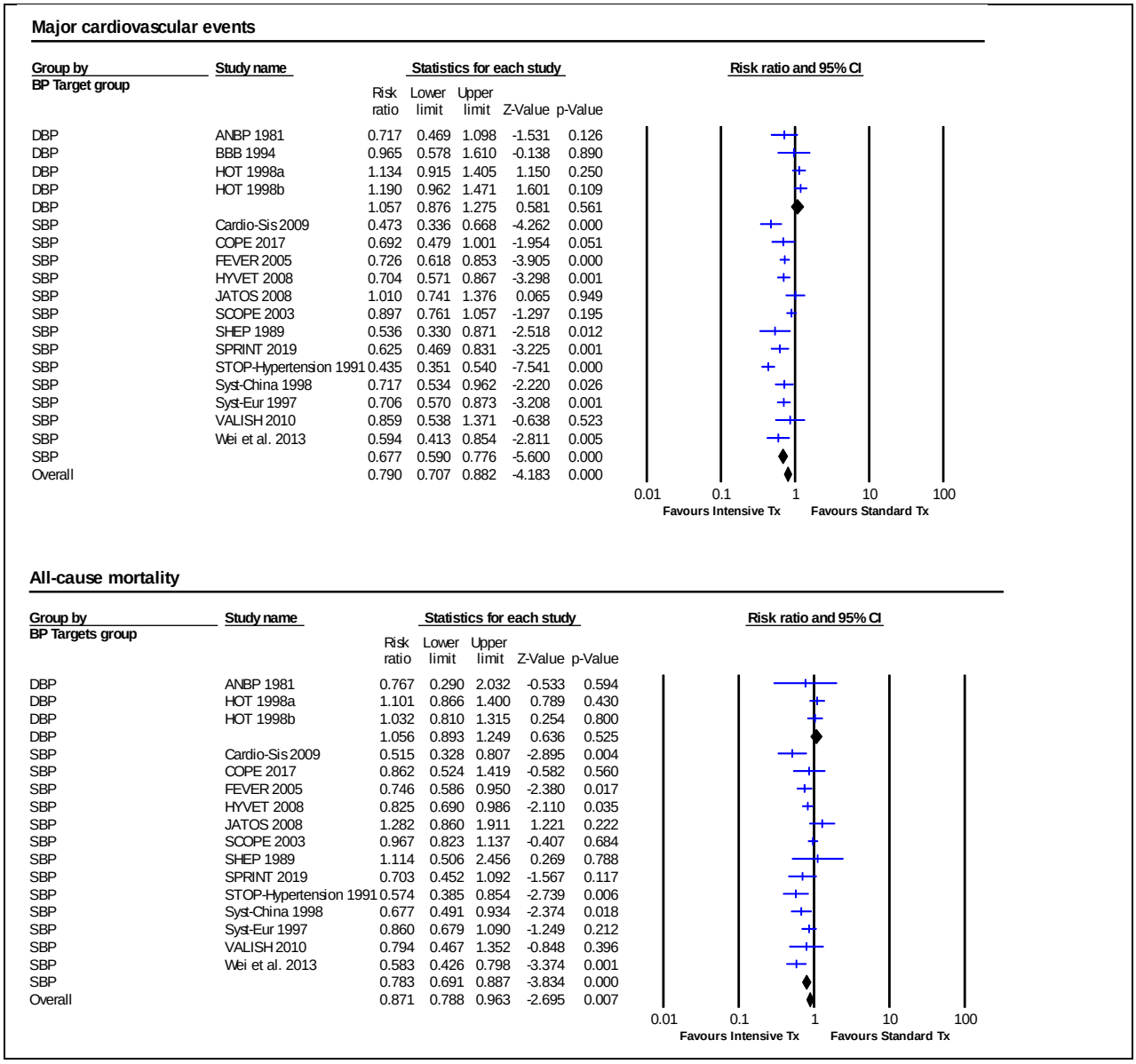

Figure S1: Sub-analysis for SBP versus DBP treatment targets on relative risk reduction of major cardiovascular events and all-cause mortality

A p-value < 0.05 represents a significant pooled point of estimate of risk ratio. Short vertical lines across each horizontal lines and horizontal lines represents risk ratio and 95% confidence interval (CI) for each study. The vertical line on the scale 1 interval across all horizontal lines represents the estimate of overall risk ratio. The diamond represents the 95% CI for pooled estimates of effect of risk ratio. Tx represent treatment.

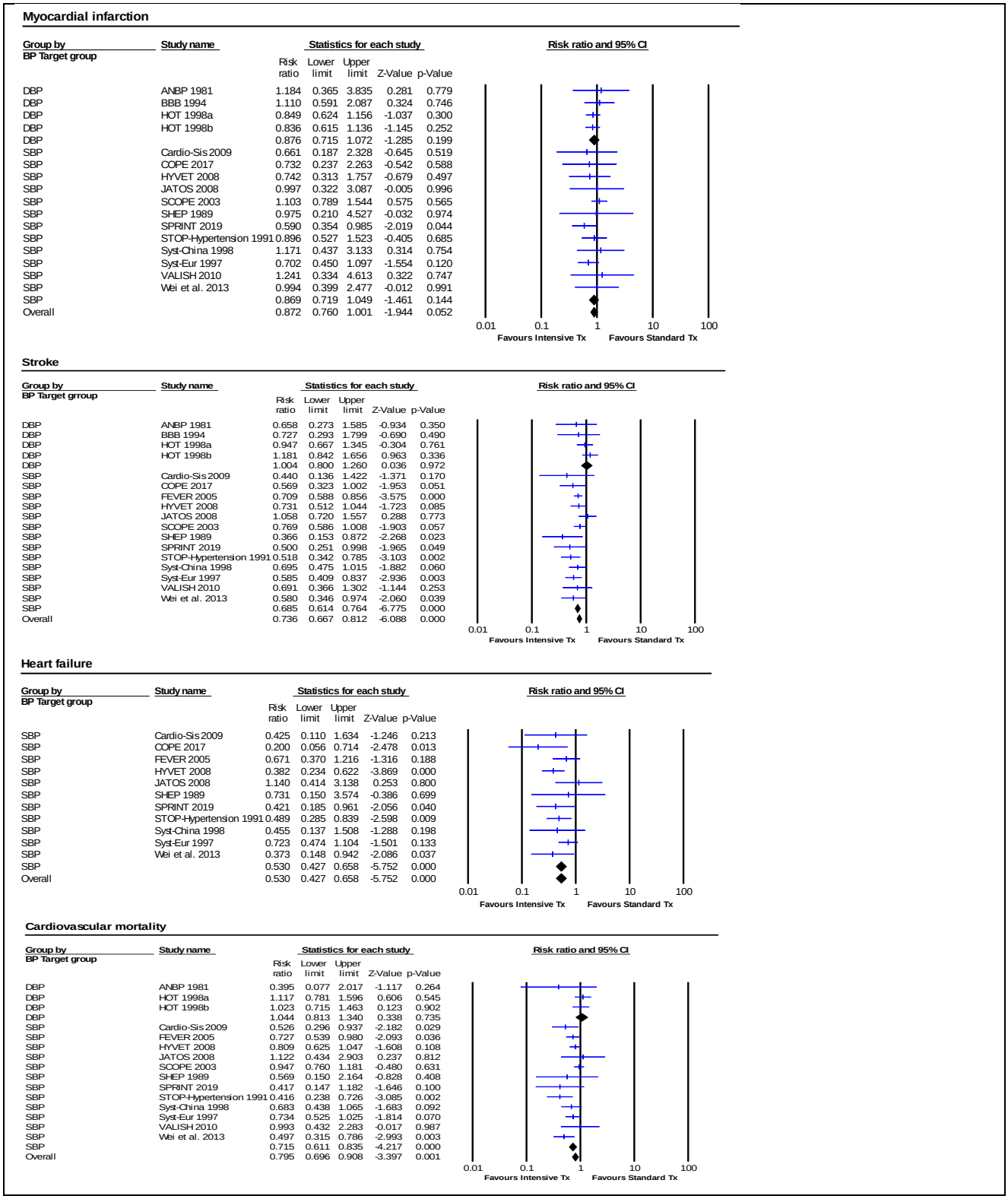

Figure S2: Sub-analysis for SBP versus DBP treatment targets on relative risk reduction of cardiovascular outcome events

A p-value < 0.05 represents a significant pooled point of estimate of risk ratio. Short vertical lines across each horizontal lines and horizontal lines represents risk ratio and 95% confidence interval (CI) for each study. The vertical line on the scale 1 interval across all horizontal lines represents the estimate of overall risk ratio. The diamond represents the 95% CI for pooled estimates of effect of risk ratio. Tx represent treatment.

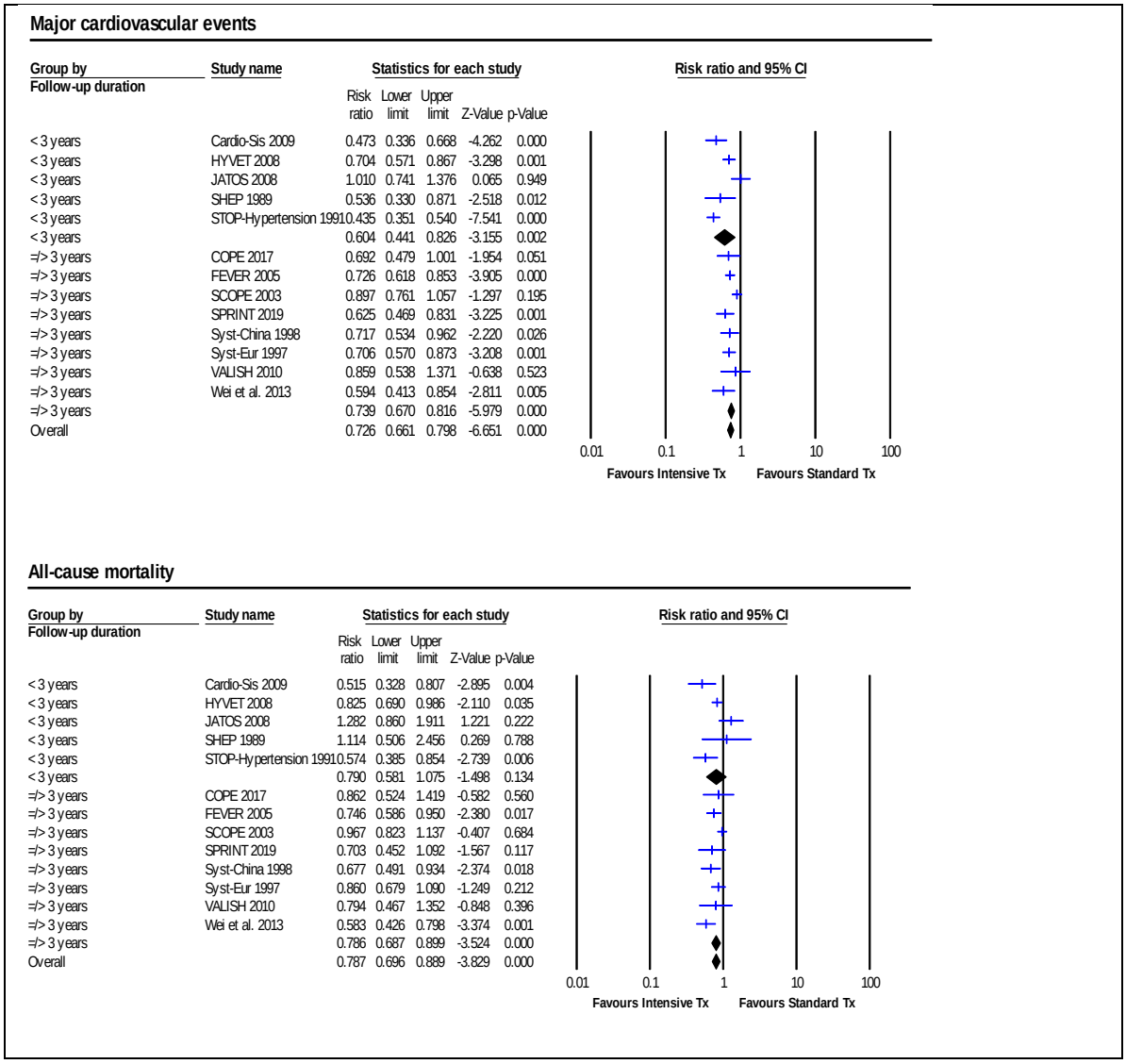

Figure S3: Sub-analysis for follow-up duration on relative risk reduction of major cardiovascular events and all-cause mortality for SBP treatment targets only

A p-value < 0.05 represents a significant pooled point of estimate of risk ratio. Short vertical lines across each horizontal lines and horizontal lines represents risk ratio and 95% confidence interval (CI) for each study. The vertical line on the scale 1 interval across all horizontal lines represents the estimate of overall risk ratio. The diamond represents the 95% CI for pooled estimates of effect of risk ratio. Tx represent treatment.

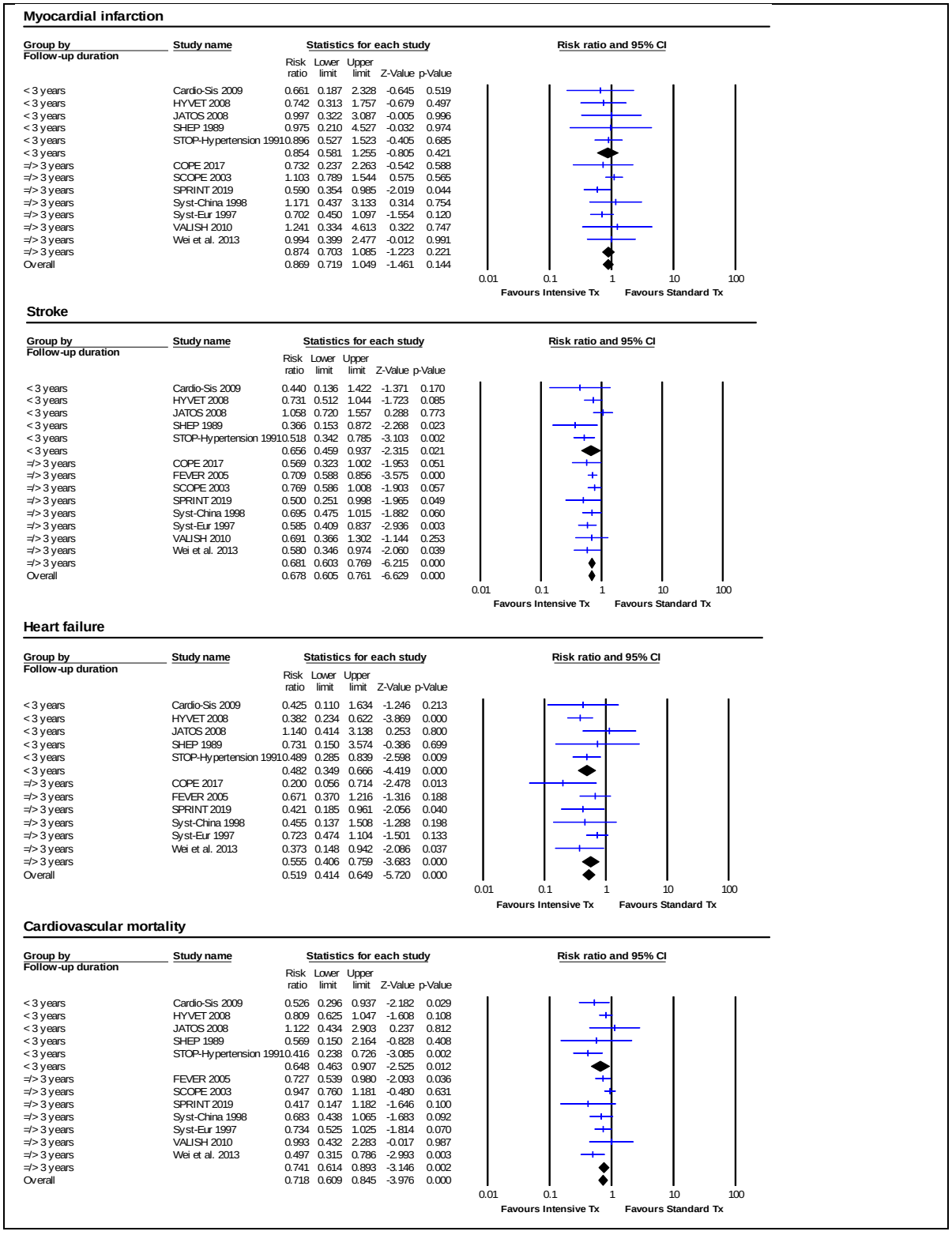

Figure S4: Sub-analysis for follow-up duration on relative risk reduction of cardiovascular outcomes events for SBP treatment targets only

A p-value < 0.05 represents a significant pooled point of estimate of risk ratio. Short vertical lines across each horizontal lines and horizontal lines represents risk ratio and 95% confidence interval (CI) for each study. The vertical line on the scale 1 interval across all horizontal lines

represents the estimate of overall risk ratio. The diamond represents the 95% CI for pooled estimates of effect of risk ratio. Tx represent treatment.

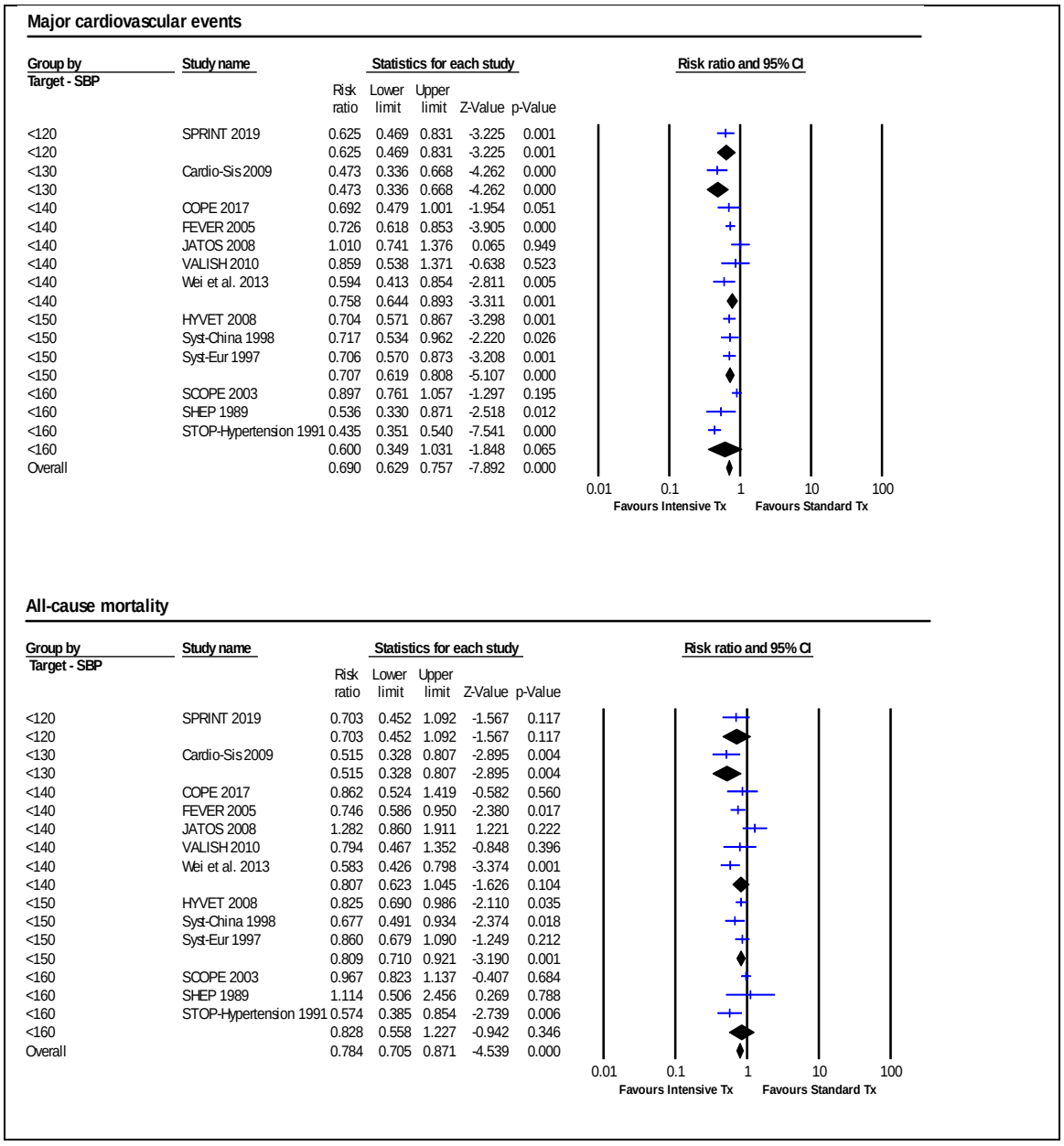

Figure S5: Sub-analysis for effect of SBP treatment targets on relative risk reduction of major cardiovascular events and all-cause mortality

A p-value < 0.05 represents a significant pooled point of estimate of risk ratio. Short vertical lines across each horizontal lines and horizontal lines represents risk ratio and 95% confidence interval (CI) for each study. The vertical line on the scale 1 interval across all horizontal lines represents the estimate of overall risk ratio. The diamond represents the 95% CI for pooled estimates of effect of risk ratio. Tx represent treatment.

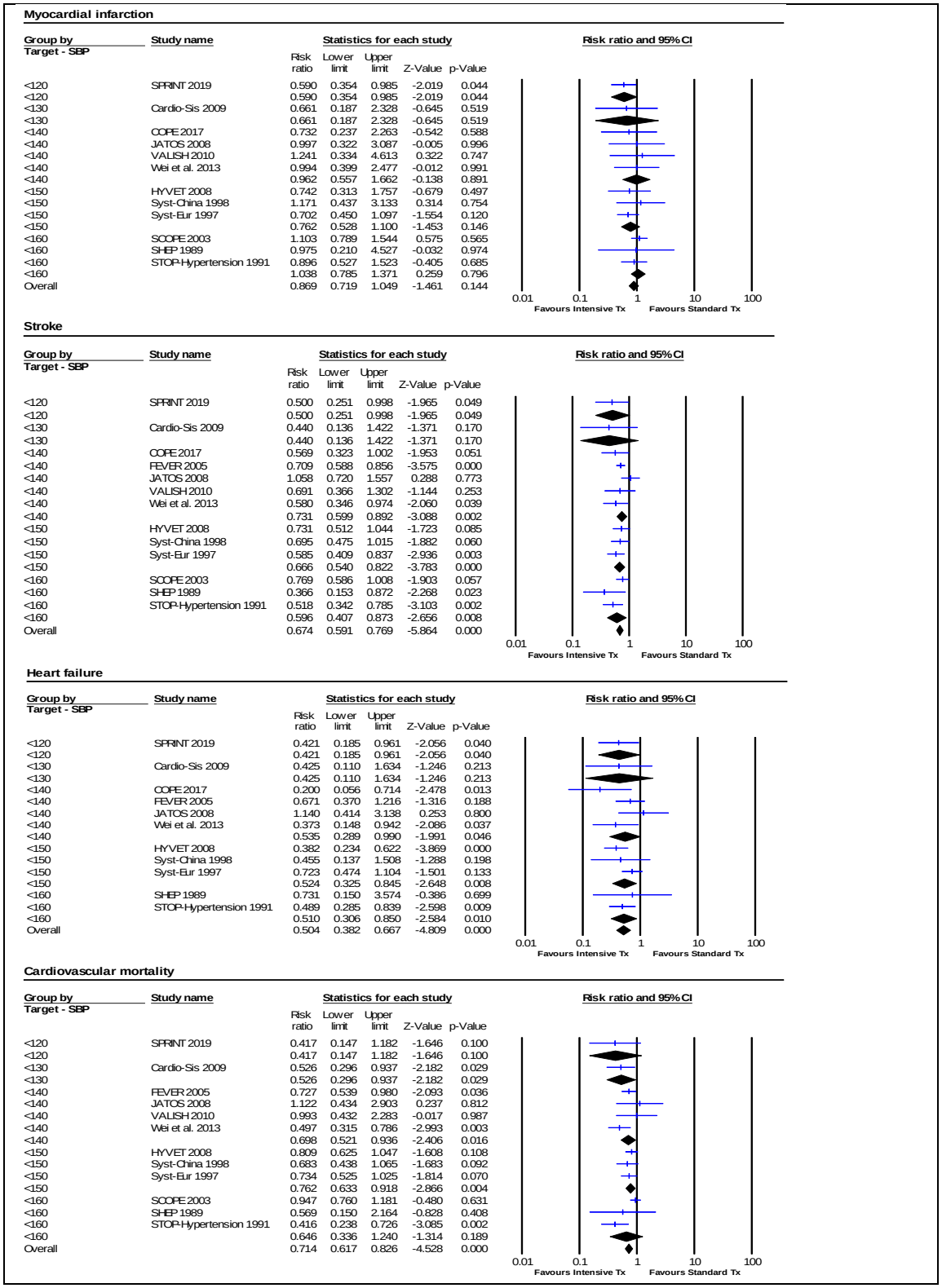

Figure S6: Sub-analysis for effect of SBP treatment targets on relative risk reduction of cardiovascular outcomes events

A p-value < 0.05 represents a significant pooled point of estimate of risk ratio. Short vertical lines across each horizontal lines and horizontal lines represents risk ratio and 95% confidence interval (CI) for each study. The vertical line on the scale 1 interval across all horizontal lines represents the estimate of overall risk ratio. The diamond represents the 95% CI for pooled estimates of effect of risk ratio. Tx represent treatment

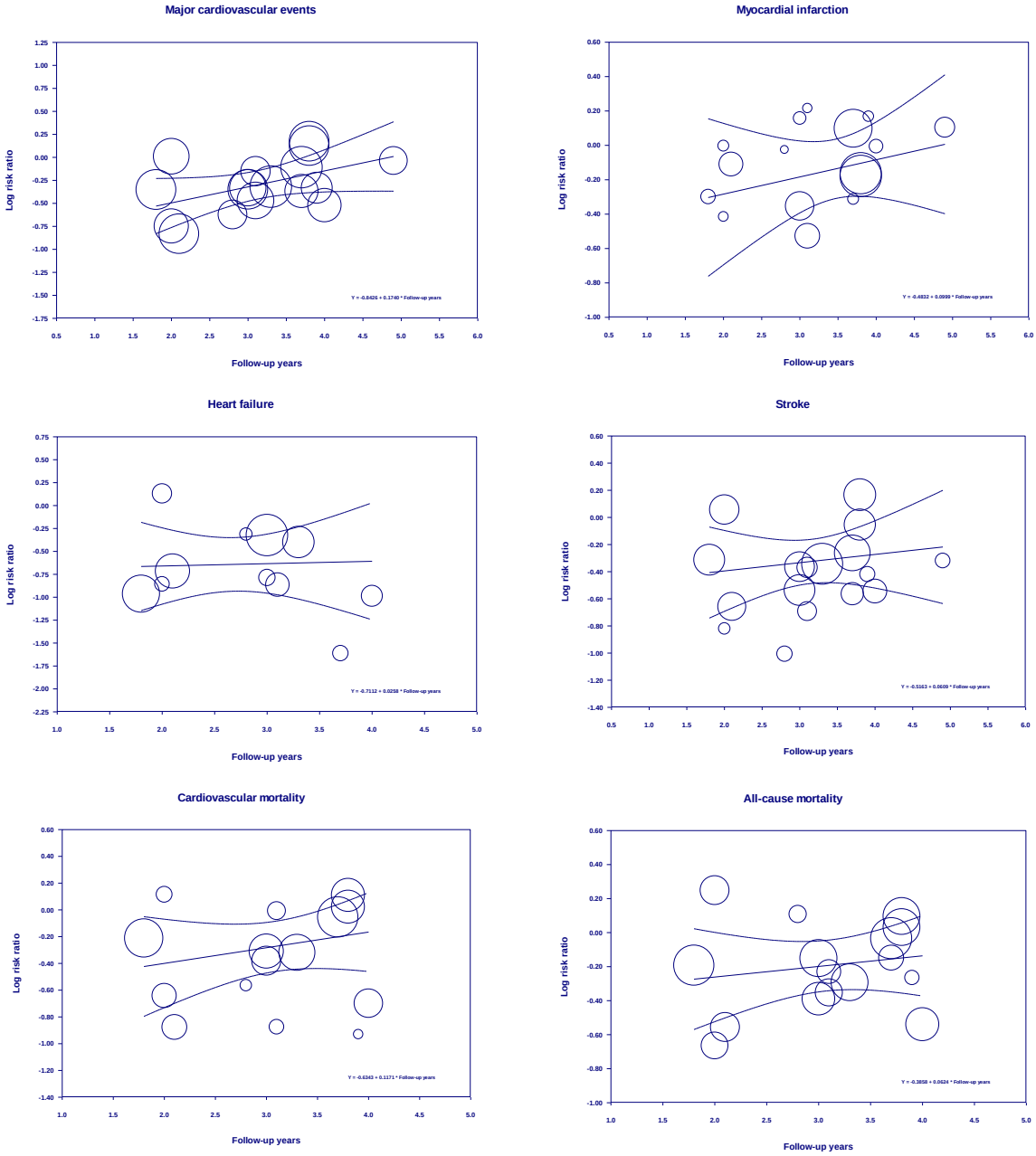

Figure S7: Meta-regression on follow-up years for relative risk reduction of outcome events

The p-value for MCEs, MI, Stoke, HF, CV mortality and All-cause motility are respectively 0.028, 0.337, 0.496, 0.884, 0.251 and 0.445.

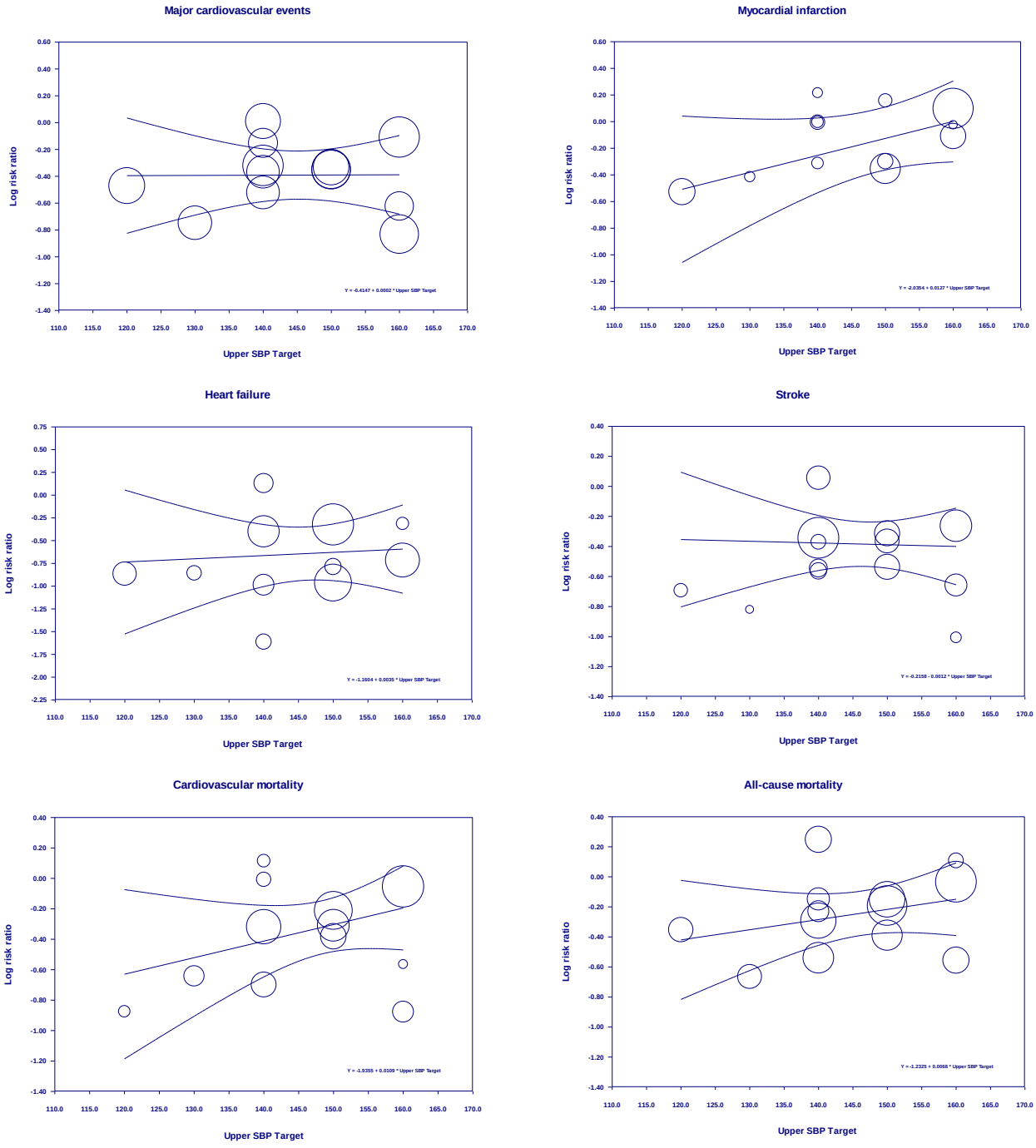

Figure S8: Meta-regression on upper SBP treatment targets for relative risk reduction of outcome measures

The p-value for MCEs, MI, Stoke, HF, CV mortality and All-cause motility are respectively 0.980, 0.070, 0.858, 0.757, 0.151 and 0.237

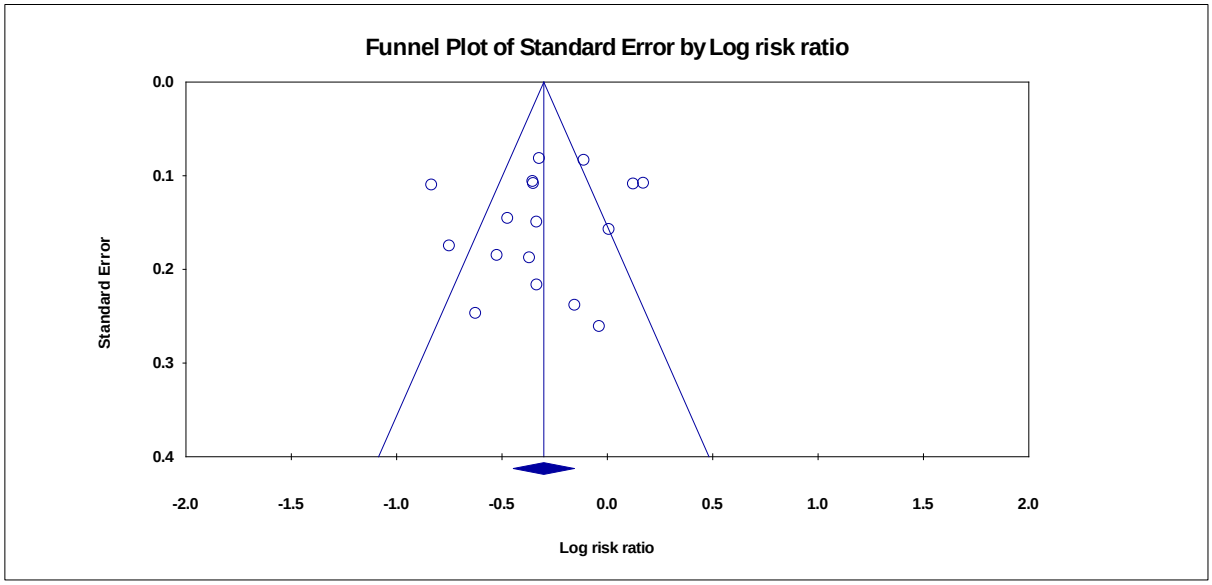

Figure S9: Funnel plot for major cardiovascular events [intercept = -1.17 (95% CI -4.62–2.28), *p*=0.481]

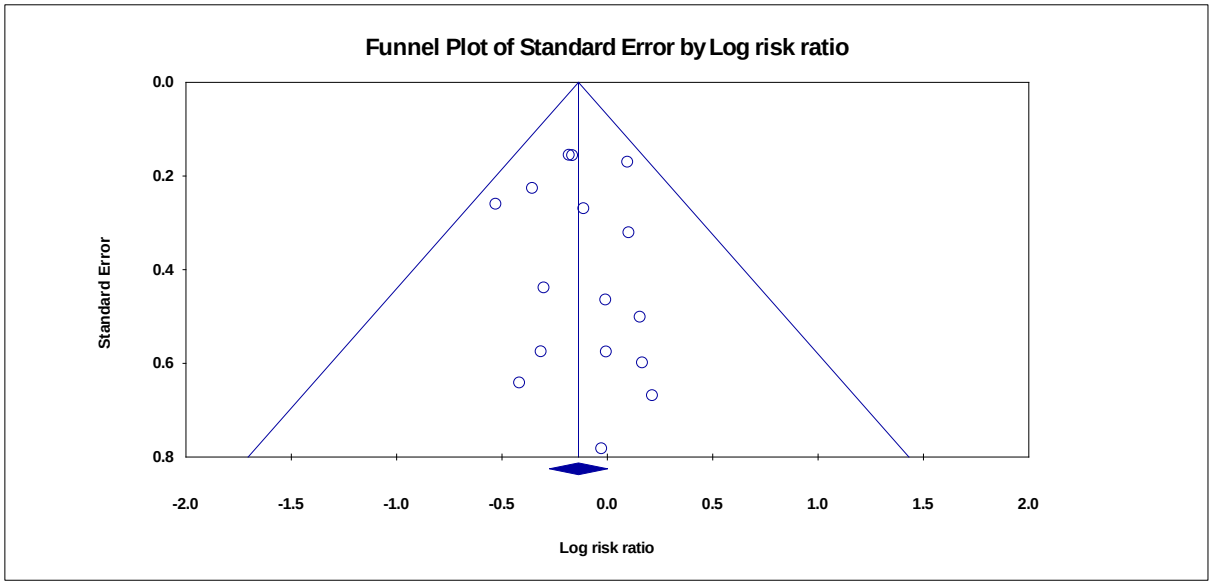

Figure S10: Funnel plot for myocardial infarction [intercept = 0.14(95% CI -0.64–0.91), *p*=0.714]

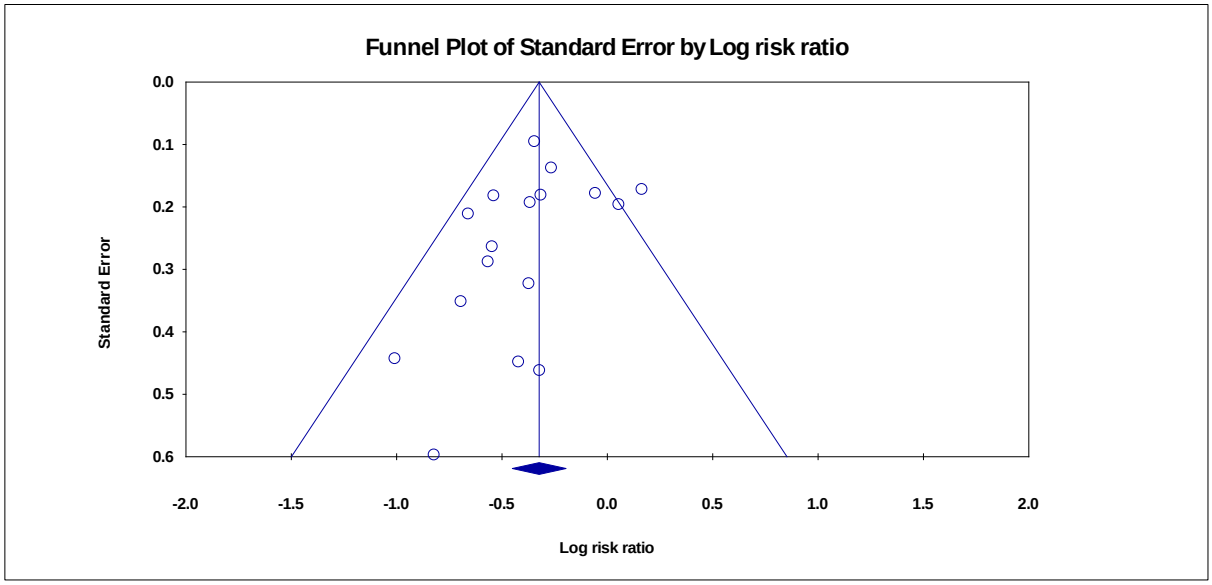

Figure S11: Funnel plot for stroke [intercept = -0.94 (95% CI -2.36–0.48), *p*=0.177]

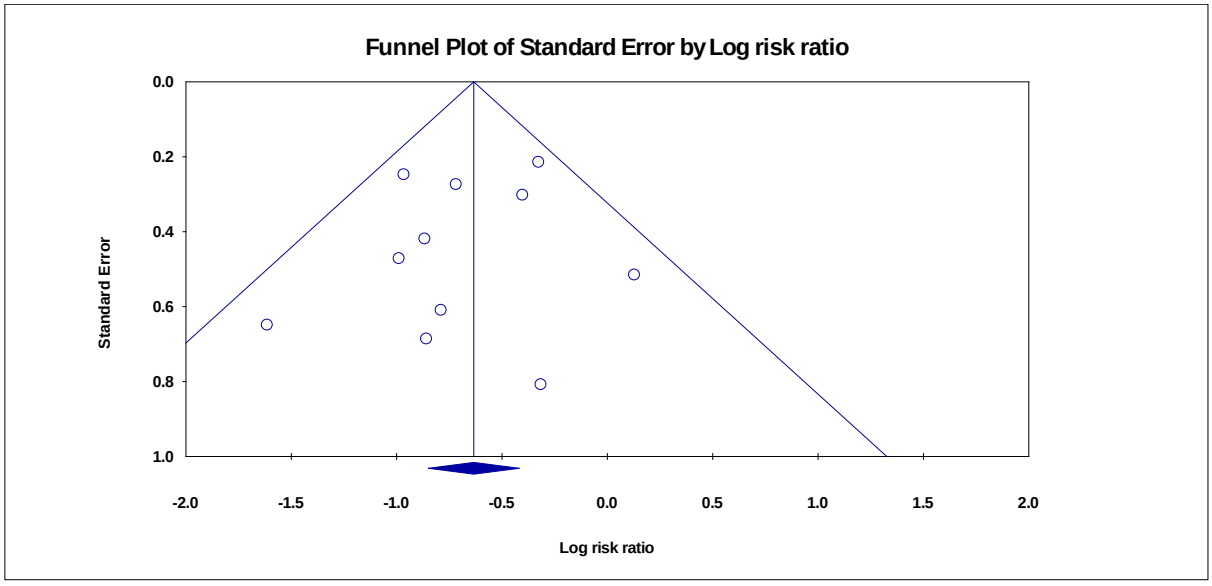

Figure S12: Funnel plot for heart failure [intercept = -0.53(95% CI -2.28–1.23), *p*=0.515]

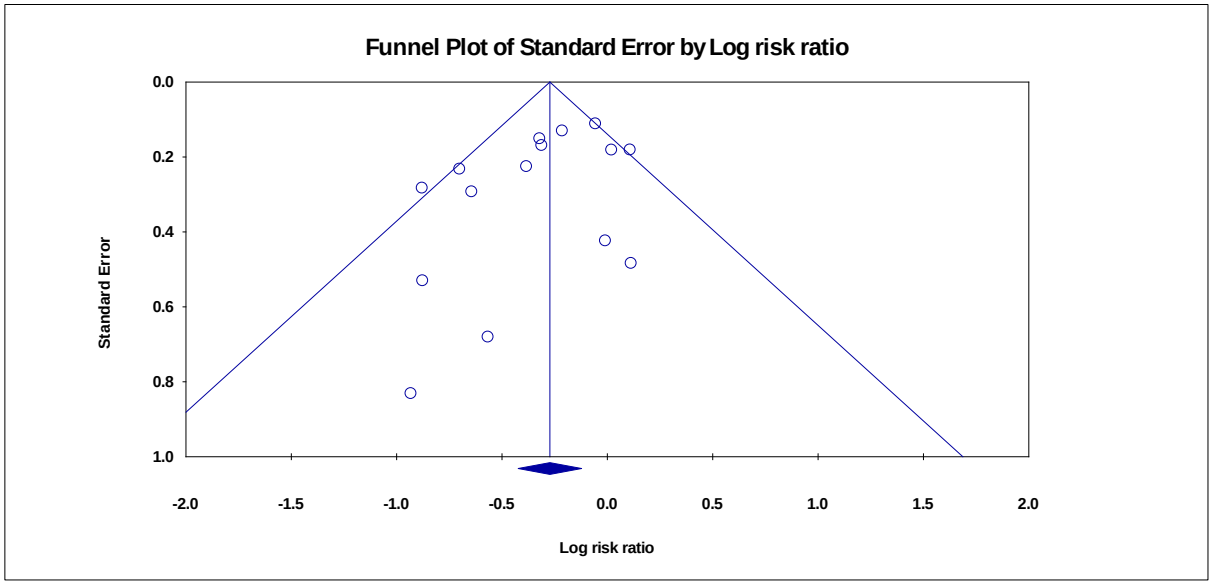

Figure S13: Funnel plot for cardiovascular mortality [intercept = -1.2(95% CI -2.63–0.24), p=0.096]

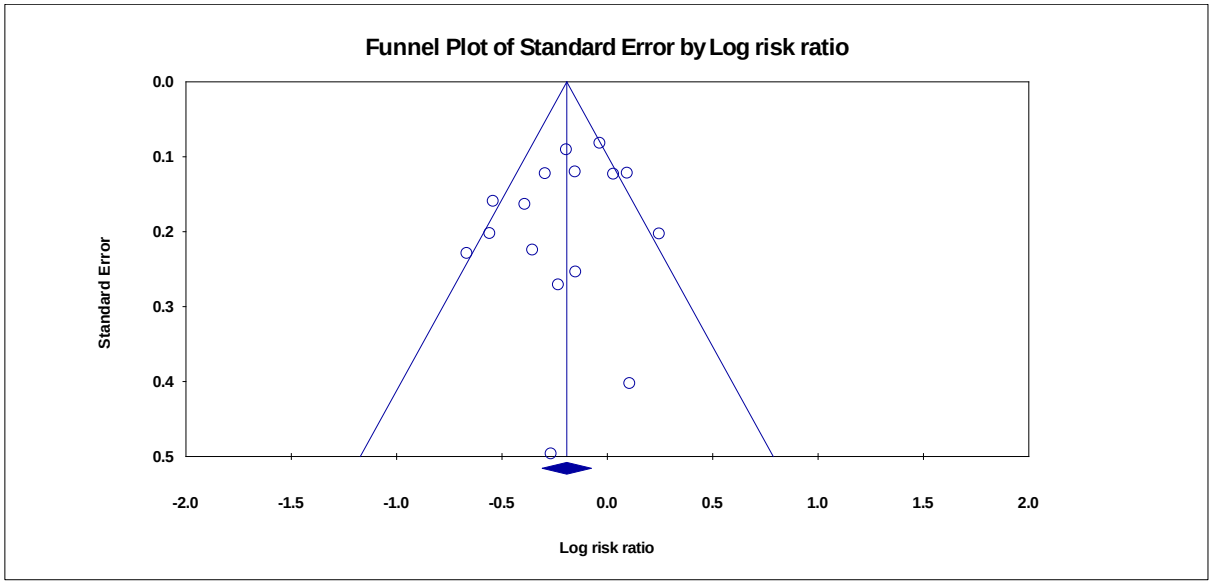

Figure S14: Funnel plot for all-cause mortality [intercept = -1.0(95% CI -2.87–0.88), p=0.273]