Supplementary Information

Effect Modification by Age on the Benefit or Harm of Antihypertensive Treatment for Elderly Hypertensives: A Systematic Review and Meta-analysis

Chi-Jung Huang[1], Chern-En Chiang[2], Bryan Williams[3], Kazuomi Kario[4], Shih-Hsien Sung[5,6], Chen-Huan Chen[6,7,8], Tzung-Dau Wang[9], Hao-Min Cheng[1,6,7,8,*]

[1]Center for Evidence-based Medicine, Taipei Veterans General Hospital, Taipei, Taiwan; [2]General Clinical Research Center, Taipei Veterans General Hospital, Taipei, Taiwan; [3]Institute of Cardiovascular Sciences, University College London (UCL) and National Institute for Health Research (NIHR) UCL Hospitals Biomedical Research Centre, London, UK; [4]Division of Cardiovascular Medicine, Department of Medicine, Jichi Medical University School of Medicine, Tochigi, Japan; [5]Division of Cardiology, Department of Internal Medicine, Taipei Veterans General Hospital, Taipei, Taiwan; [6]Department of Medicine, National Yang-Ming University, Taipei, Taiwan; [7]Division of Faculty Development, Department of Medical Education, Taipei Veterans General Hospital, Taipei, Taiwan; [8]Institute of Public Health and Community Medicine Research Center, National Yang-Ming University, Taipei, Taiwan; and [9]Division of Cardiology, National Taiwan University Hospital, Taipei, Taiwan

Short title: Elderly hypertension

***Correspondence:**
Hao-Min Cheng, MD, PhD
Center for Evidence-based Medicine, Taipei Veterans General Hospital, Taipei, Taiwan
No. 201, Sec. 2, Shih-Pai Road, Beitou District, Taipei 112, Taiwan, R.O.C.
E-mail: hmcheng@vghtpe.gov.tw
Tel: (886)-2-28757434 #307
Fax: (886)-2-28757726

Supplementary Methods

Search strategy of relevant literature

Two electronic databases, MEDLINE and the Cochrane Library, were systematically searched without language restrictions.

1. MEDLINE, PreMEDLINE, and other related databases via PubMed search interface

#1 Search "Aged"[Mesh] OR "elderly" OR "geriatric"
#2 Search "Hypertension"[Mesh] OR "Hypertension, Malignant"[Mesh] OR "Prehypertension"[Mesh] OR "hypertensive patients"
#3 Search "Antihypertensive Agents"[Mesh] OR "Antihypertensive Agents" [Pharmacological Action] OR "Angiotensin II Type 1 Receptor Blockers"[Mesh]
#4 Search antihypertensive* OR "hypertension therapy" OR "hypertensive therapy" OR "hypertension treatment" OR "hypertensive treatment" OR "blood pressure lowering" OR "blood pressure reduction" OR "blood pressure control"
#5 Search (#1 AND #2)
#6 Search (#3 OR #4)
#7 Search (#5 AND #6)
#8 Search "Myocardial Ischemia"[Mesh] OR "coronary heart disease" OR "myocardial infarction"
#9 Search ("Stroke"[Mesh] OR "Brain Ischemia"[Mesh] OR "Intracranial Embolism and Thrombosis"[Mesh] OR "Intracranial Hemorrhages"[Mesh] OR stroke OR strokes)
#10 Search "Heart Failure"[Mesh] OR "heart failure"
#11 Search "Renal Insufficiency"[Mesh] OR "renal failure" OR "kidney failure"
#12 Search ("Dementia"[Mesh] OR "Dementia, Multi-Infarct"[Mesh] OR "Dementia, Vascular"[Mesh] OR dementia)
#13 Search "Cognitive Dysfunction"[Mesh]
#14 Search (#8 OR #9 OR #10 OR #11 OR #12 OR #13)
#15 Search (#7 AND #14) Filters: Clinical Trial; Controlled Clinical Trial; Randomized Controlled Trial

2. Cochrane Library via Wiley search interface

#1 MeSH descriptor: [Aged] explode all trees
#2 elderly or geriatric:ti,ab,kw (Word variations have been searched)
#3 #1 or #2
#4 MeSH descriptor: [Hypertension] explode all trees
#5 MeSH descriptor: [Prehypertension] explode all trees
#6 hypertensive patients:ti,ab,kw (Word variations have been searched)
#7 #4 or #5 or #6
#8 #3 and #7
#9 MeSH descriptor: [Antihypertensive Agents] explode all trees
#10 antihypertensive or "hypertension therapy" or "hypertensive therapy" or "hypertension treatment" or "hypertensive treatment" or "blood pressure lowering" or "blood pressure reduction" or "blood pressure control":ti,ab,kw (Word variations have been searched)
#11 #9 or #10

#12 MeSH descriptor: [Myocardial Ischemia] explode all trees
#13 coronary heart disease or "myocardial infarction":ti,ab,kw (Word variations have been searched)
#14 #12 or #13
#15 MeSH descriptor: [Stroke] explode all trees
#16 MeSH descriptor: [Brain Ischemia] explode all trees
#17 MeSH descriptor: [Intracranial Embolism and Thrombosis] explode all trees
#18 MeSH descriptor: [Intracranial Hemorrhages] explode all trees
#19 stroke or strokes:ti,ab,kw (Word variations have been searched)
#20 #15 or #16 or #17 or #18 or #19
#21 MeSH descriptor: [Heart Failure] explode all trees
#22 heart failure:ti,ab,kw (Word variations have been searched)
#23 #21 or #22
#24 MeSH descriptor: [Renal Insufficiency] explode all trees
#25 renal failure or "kidney failure":ti,ab,kw (Word variations have been searched)
#26 #24 or #25
#27 MeSH descriptor: [Dementia] explode all trees
#28 MeSH descriptor: [Dementia, Vascular] explode all trees
#29 MeSH descriptor: [Dementia, Multi-Infarct] explode all trees
#30 dementia:ti,ab,kw (Word variations have been searched)
#31 #27 or #28 or #29 or #30
#32 MeSH descriptor: [Cognition Disorders] explode all trees
#33 #14 or #20 or #23 or #26 or #31 or #32
#34 #8 and #11 and #33 in Trials

Supplementary Table 1. PRISMA Checklist

Section/topic	#	Checklist item	Reported on page #
TITLE			
Title	1	Identify the report as a systematic review, meta-analysis, or both.	1
ABSTRACT			
Structured summary	2	Provide a structured summary including, as applicable: background; objectives; data sources; study eligibility criteria, participants, and interventions; study appraisal and synthesis methods; results; limitations; conclusions and implications of key findings; systematic review registration number.	3-4
INTRODUCTION			
Rationale	3	Describe the rationale for the review in the context of what is already known.	5
Objectives	4	Provide an explicit statement of questions being addressed with reference to participants, interventions, comparisons, outcomes, and study design (PICOS).	5
METHODS			
Protocol and registration	5	Indicate if a review protocol exists, if and where it can be accessed (e.g., Web address), and, if available, provide registration information including registration number.	6
Eligibility criteria	6	Specify study characteristics (e.g., PICOS, length of follow-up) and report characteristics (e.g., years considered, language, publication status) used as criteria for eligibility, giving rationale.	6
Information sources	7	Describe all information sources (e.g., databases with dates of coverage, contact with study authors to identify additional studies) in the search and date last searched.	6
Search	8	Present full electronic search strategy for at least one database, including any limits used, such that it could be repeated.	6 & Suppl. Methods
Study selection	9	State the process for selecting studies (i.e., screening, eligibility, included in systematic review, and, if applicable, included in the meta-analysis).	6 & Suppl. Figure 1
Data collection process	10	Describe method of data extraction from reports (e.g., piloted forms, independently, in duplicate) and any processes for obtaining and confirming data from investigators.	7
Data items	11	List and define all variables for which data were sought (e.g., PICOS, funding sources) and any assumptions and simplifications made.	7
Risk of bias in individual studies	12	Describe methods used for assessing risk of bias of individual studies (including specification of whether this was done at the study or outcome level), and how this information is to be used in any data synthesis.	8
Summary measures	13	State the principal summary measures (e.g., risk ratio, difference in means).	8
Synthesis of results	14	Describe the methods of handling data and combining results of studies, if done, including measures of consistency (e.g., I^2) for each meta-analysis.	8

Supplementary Table 1. PRISMA Checklist

Section/topic	#	Checklist item	Reported on page #
Risk of bias across studies	15	Specify any assessment of risk of bias that may affect the cumulative evidence (e.g., publication bias, selective reporting within studies).	8
Additional analyses	16	Describe methods of additional analyses (e.g., sensitivity or subgroup analyses, meta-regression), if done, indicating which were pre-specified.	8-9
RESULTS			
Study selection	17	Give numbers of studies screened, assessed for eligibility, and included in the review, with reasons for exclusions at each stage, ideally with a flow diagram.	10
Study characteristics	18	For each study, present characteristics for which data were extracted (e.g., study size, PICOS, follow-up period) and provide the citations.	10 & Table 1
Risk of bias within studies	19	Present data on risk of bias of each study and, if available, any outcome level assessment (see item 12).	10 & 13
Results of individual studies	20	For all outcomes considered (benefits or harms), present, for each study: (a) simple summary data for each intervention group (b) effect estimates and confidence intervals, ideally with a forest plot.	Figure 2, Figure 4 & Suppl. Figure 6
Synthesis of results	21	Present results of each meta-analysis done, including confidence intervals and measures of consistency.	11-13
Risk of bias across studies	22	Present results of any assessment of risk of bias across studies (see Item 15).	10 & 13
Additional analysis	23	Give results of additional analyses, if done (e.g., sensitivity or subgroup analyses, meta-regression [see Item 16]).	11-13
DISCUSSION			
Summary of evidence	24	Summarize the main findings including the strength of evidence for each main outcome; consider their relevance to key groups (e.g., healthcare providers, users, and policy makers).	14-17
Limitations	25	Discuss limitations at study and outcome level (e.g., risk of bias), and at review-level (e.g., incomplete retrieval of identified research, reporting bias).	17-18
Conclusions	26	Provide a general interpretation of the results in the context of other evidence, and implications for future research.	18
FUNDING			
Funding	27	Describe sources of funding for the systematic review and other support (e.g., supply of data); role of funders for the systematic review.	20

From: Moher D, Liberati A, Tetzlaff J, Altman DG, The PRISMA Group (2009). Preferred Reporting Items for Systematic Reviews and Meta-Analyses: The PRISMA Statement. PLoS Med 6(6): e1000097. doi:10.1371/journal.pmed1000097

Supplementary Table 2. Definition of renal failure in 7 trials reporting renal outcome

Trial	Definition
EWPHE, 1985	Renal events: severe increase in serum creatinine
JATOS, 2008	Acute or chronic renal failure: doubling of the serum creatinine concentration to a value of 1.5 mg/dL or higher
SHEP, 1991	Renal dysfunction: serum creatinine concentration greater than 265.2 μmol/L
SPRINT, 2016	Chronic kidney disease (1) for participants with CKD at baseline (estimated glomerular filtration rate [eGFR] <60 ml/min/1.73 m^2): a ≥50% reduction in eGFR (measured twice at least 90 days apart), dialysis, or a kidney transplant; (2) for participants without CKD at baseline: a ≥30% reduction in eGFR from baseline to an end value of <60 mL/min/1.73m^2 (measured twice at least 90 days apart), dialysis, or a kidney transplant
Syst-China, 1998	Renal failure/renal insufficiency: on 2 consecutive visits the serum creatinine levels showed a 2-fold increase compared to initial values or reached 360 μmol/L (4.0 mg/dL)
Syst-Eur, 1997	Renal failure/renal insufficiency: at 2 consecutive visits the serum creatinine concentration reached or exceeded 360 μmol/L (4.0 mg/dL) or doubled compared with the concentration at randomization
VALISH, 2010	Renal dysfunction: doubling of serum creatinine to a level over 2.0 mg/dL or introduction of dialysis

Supplementary Table 3. Outcomes assessed during blood pressure (BP)-lowering treatment, comparing intensive versus standard blood-pressure control in hypertensive adults ≥60 years of age

		CHD (n/N)		Stroke (n/N)		HF (n/N)		CV death (n/N)		MACE (n/N)		RF (n/N)		All-cause death (n/N)		Cognitive decline (n/N)		Dementia (n/N)	
Trial	Year	Intensive	Standard	Intensive	Standard	Intensive	Standard	Intensive	Standard	Intensive	Standard	Intensive	Standard	Intensive	Standard	Intensive	Standard	Intensive	Standard
ASCOT-BPLA	2011	211/4042	219/4095	198/4042	282/4095	90/4042	113/4095	169/4042	221/4095	739/4042	886/4095			492/4042	540/4095				
EWPHE	1985	17/416	29/424	12/416	19/424	7/416	17/424	67/416	93/424	42/416	61/424	4/416	1/424	135/416	149/424				
FEVER	2011			67/1631*	122/1548*			27/1631†	50/1548†					50/1631†	74/1548†				
HEP	1986	35/419	38/465	20/419	39/465	22/419	36/465	35/419	50/465					60/419	69/465				
HYVET pilot	2003			6/426	18/426			23/426	19/426					30/426	22/426				
				12/431	18/426			22/431	19/426					27/431	22/426				
HYVET	2008	9/1933	12/1912	51/1933	69/1912	22/1933	57/1912	99/1933	121/1912	138/1933	193/1912			196/1933	235/1912				
HYVET-COG	2008															485/1687	486/1649	126/1687	137/1649
JATOS	2008	7/2212	7/2206	44/2212	42/2206	8/2212	7/2206	9/2212	8/2206	59/2212	56/2206	8/2212	9/2206	54/2212	42/2206				
MRC-2	1992	128/2183	159/2213	101/2183	134/2213			161/2183	180/2213	258/2183	309/2213			301/2183	315/2213				
SCOPE	2003	70/2477	63/2460	89/2477	115/2460			145/2477	152/2460	242/2477	268/2460			259/2477	266/2460	113/2416	125/2409	62/2477	57/2460
SHEP pilot	1989	15/443	4/108	11/443	6/108	6/443	2/108	14/443	5/108	44/443	20/108			32/443	7/108				
SHEP	1991, 2001	104/2365	141/2371	103/2365	159/2371	55/2365	105/2371	90/2365	112/2371	199/2365	289/2371	7/2365	11/2371	213/2365	242/2371	12/1368‡	17/1317‡	37/2365	44/2371
SPRINT	2016	37/1317	53/1319	27/1317	34/1319	35/1317	56/1319	18/1317	29/1319	102/1317	148/1319	44/1310	17/1309	73/1317	107/1319				
STONE§	1996	2/787	2/740	16/801	36/774	2/787	6/744	11/796	14/752	24/809	59/797			15/800	26/764				
STOP-Hypertension	1991	25/812	28/815	29/812	53/815	19/812	39/815	17/812	41/815	58/812	94/815			36/812	63/815				
Syst-China	1998	9/1253	7/1141	45/1253	59/1141	4/1253	8/1141	33/1253	44/1141	74/1253	94/1141	3/1253	1/1141	61/1253	82/1141				
Syst-Eur	1997	33/2398	45/2297	47/2398	77/2297	37/2398	49/2297	59/2398	77/2297	137/2398	186/2297	3/2398	2/2297	123/2398	137/2297				
	2002																	21/1485	43/1417
VALISH	2010	5/1545	4/1534	16/1545	23/1534			11/1545	11/1534	32/1545	37/1534	5/1545	2/1534	24/1545	30/1534				
Wei et al	2013	9/363	9/361	21/363	36/361	6/363	16/361	25/363	50/361	40/363	67/361			51/363	87/361				

CHD, coronary heart disease; CV, cardiovascular; HF, heart failure; MACE, major adverse cardiovascular events; RF, renal failure

*The number of incident cases was estimated by the incidence rate (events/1000 person-years), given participant numbers and follow-up period of the trial.

†The number of incident cases was estimated by the hazard ratio, referred to as the risk ratio, and its confidence interval, given participant numbers in the intensive and standard control groups.

‡The number of incident cases was estimated by multiplying the number of participants by the cumulative incidence in follow-up year 4.

§Total sample sizes vary among outcomes since each one considered the numbers of subjects with no terminating event that were constant.

Supplementary Table 4. Adverse side effects reported during blood pressure (BP)-lowering treatment

		Falls (n/N)		Fractures (n/N)		Syncope (n/N)		Hypotension (n/N)		Electrolyte abnormality (n/N)	
Trial	Year	Intensive	Standard	Intensive	Standard	Intensive	Standard	Intensive	Standard	Intensive	Standard
HYVET*	2010			38/1933	52/1912						
SCOPE	2003							609/2477	576/2460		
SHEP	1991	303/2365	247/2371	57/2365	47/2371	52/2365	31/2371				
SPRINT	2016	65/1317	73/1319			39/1317	32/1319	32/1317	19/1319	53/1317	36/1319
Wei et al	2013			3/363	5/361						

*Data on fracture events for HYVET was from the report in 2010[1].

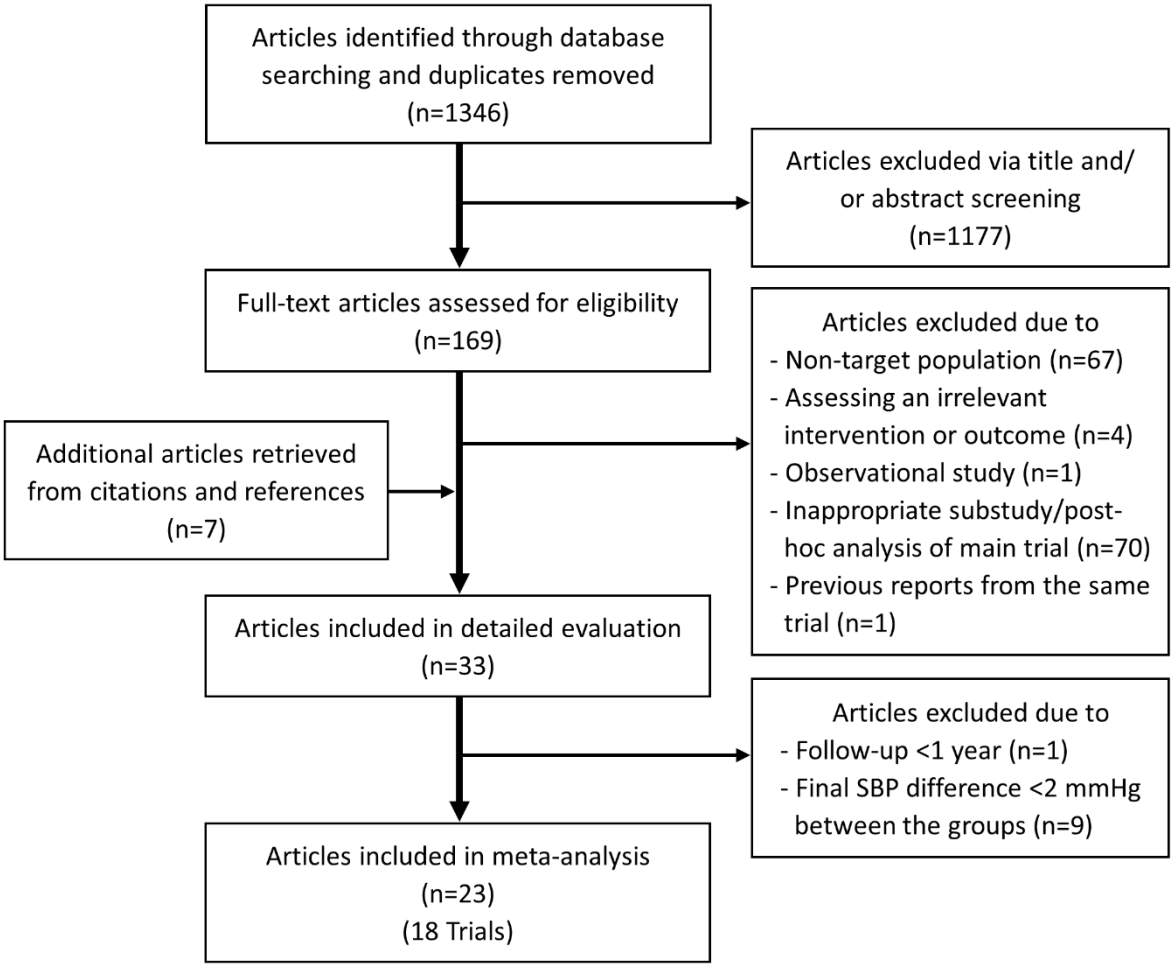
Supplementary Table 5. GRADE summary of findings: Intensive BP control of <140 mmHg compared to standard BP control of 140-150 mmHg for adverse vascular events

Outcome (studies)	No of participants (%)		Effect (95% CI)		Quality of the evidence (GRADE)†
	Intensive control	Standard control	Relative*	Absolute	
Coronary heart disease (4 RCTs) follow up: median 3.4 years	232/8162 (2.8%)	239/8196 (2.9%)	RR 0.98 (0.82 to 1.17)	1 fewer per 1,000 (from 5 fewer to 5 more)	⊕⊕⊕◯ MODERATE due to imprecision
Stroke (5 RCTS) follow up: median 3.3 years	346/9793 (3.5%)	505/9744 (5.2%)	RR 0.68 (0.55 to 0.85)	17 fewer per 1,000 (from 8 fewer to 23 fewer)	⊕⊕⊕⊕ HIGH
Heart failure (3 RCTs) follow up: median 4.0 years	104/6617 (1.6%)	136/6662 (2.0%)	RR 0.74 (0.46 to 1.18)	5 fewer per 1,000 (from 4 more to 11 fewer)	⊕⊕⊕◯ MODERATE due to imprecision
Cardiovascular death (5 RCTs) follow up: median 3.3 years	241/9793 (2.5%)	340/9744 (3.5%)	RR 0.68 (0.52 to 0.89)	11 fewer per 1,000 (from 4 fewer to 17 fewer)	⊕⊕⊕⊕ HIGH
MACE (4 RCTs) follow up: median 3.4 years	870/8162 (10.7%)	1046/8196 (12.8%)	RR 0.83 (0.69 to 0.99)	22 fewer per 1,000 (from 1 fewer to 40 fewer)	⊕⊕⊕⊕ HIGH
Renal Failure (2 RCTs) follow up: median 2.4 years	13/3757 (0.3%)	11/3740 (0.3%)	RR 1.19 (0.48 to 2.94)	1 more per 1,000 (from 2 fewer to 6 more)	⊕⊕◯◯ LOW due to very serious imprecision
All-cause death (5 RCTs) follow up: median 3.3 years)	671/9793 (6.9%)	773/9744 (7.9%)	RR 0.81 (0.63 to 1.05)	15 fewer per 1,000 (from 4 more to 29 fewer)	⊕⊕◯◯ LOW due to inconsistency and imprecision

CI, confidence interval; MACE, major adverse cardiovascular events; RCTs, randomized controlled trials; RR, risk ratio

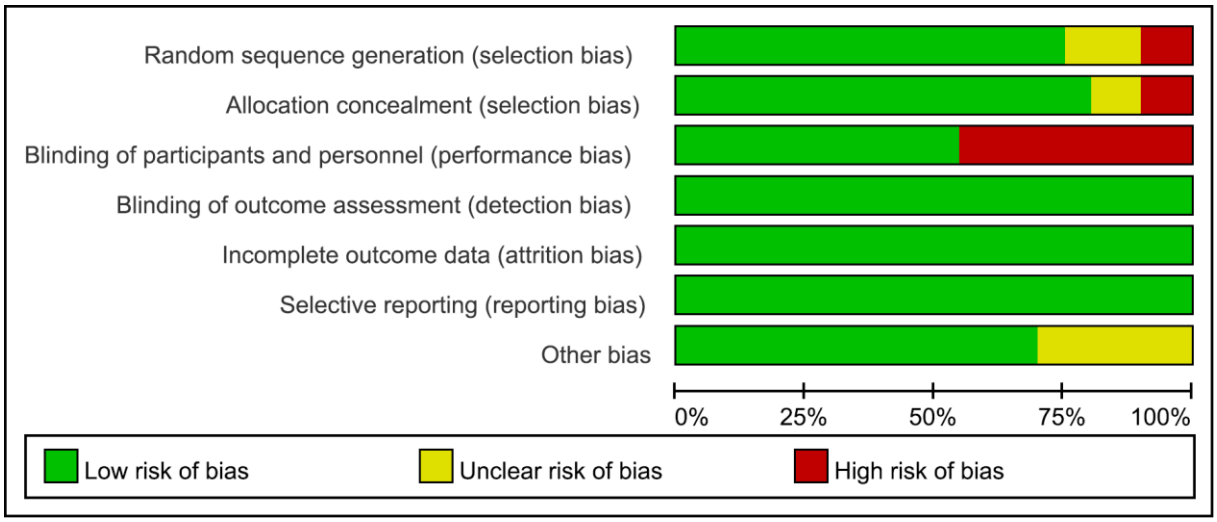
*Pooled relative risk was estimated by the random-effects model.

†GRADE system classifies the quality of evidence into four levels: high, moderate, low, and very low. High quality: we are very confident that the true effect lies close to that of the estimate of the effect. Moderate quality: we are moderately confident that the true effect is likely to be close to the estimate of the effect, but there is a possibility that it is substantially different. Low quality: our confidence in the effect estimate is limited because the true effect may be substantially different from the estimate of the effect. Very low quality: we have very little confidence in the effect estimate because the true effect is likely to be substantially different from the estimate of effect[2].

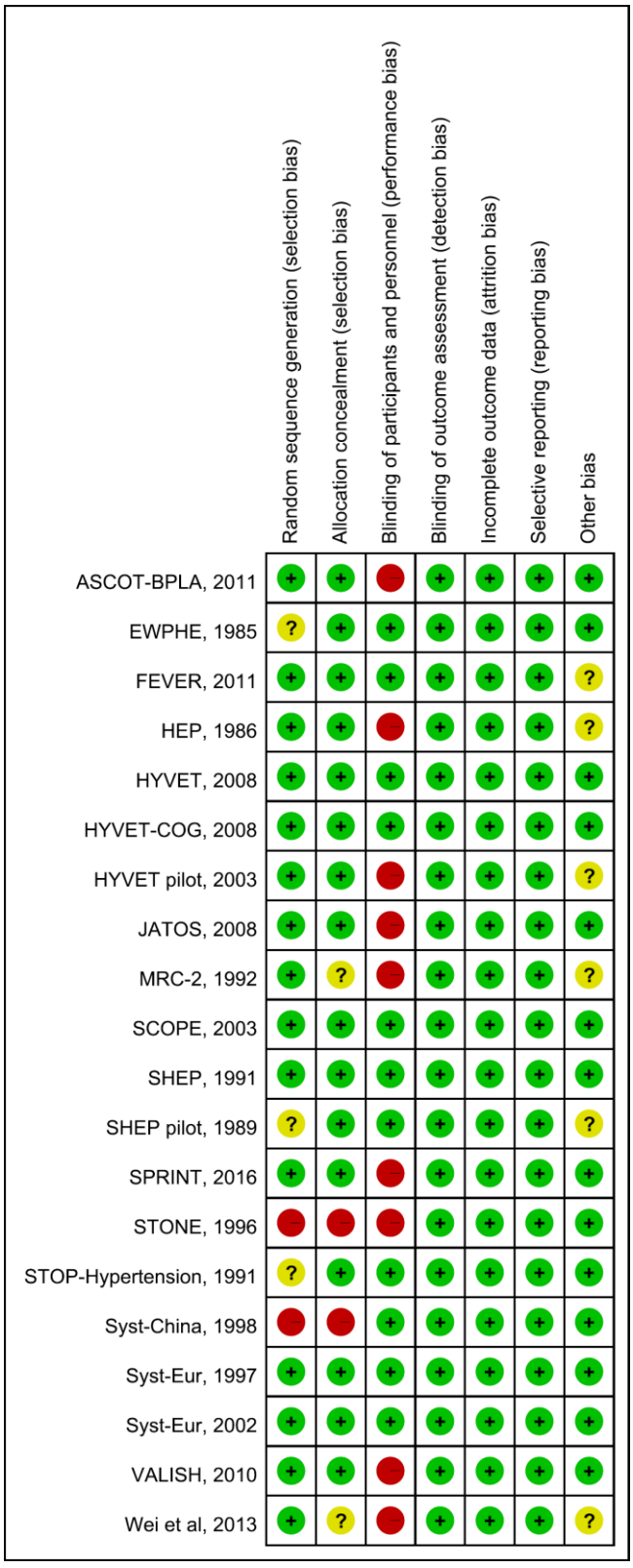


Supplementary Figure 1. Flow diagram of literature selection

The flowchart summarizes the results of database searches from inception to December 12, 2016. No further major trials were obtained in the final search (on April 20, 2017). SBP, systolic blood pressure

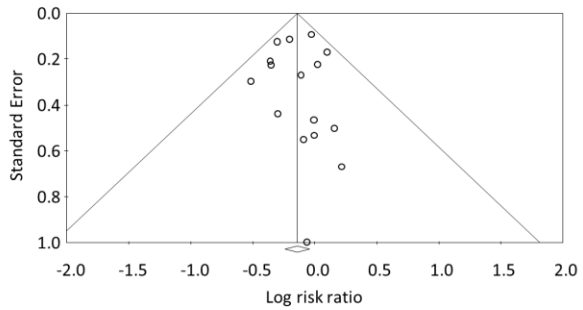


Supplementary Figure 2. Risk of bias graph for the judgement about each methodological quality item that presented as percentages across all included studies



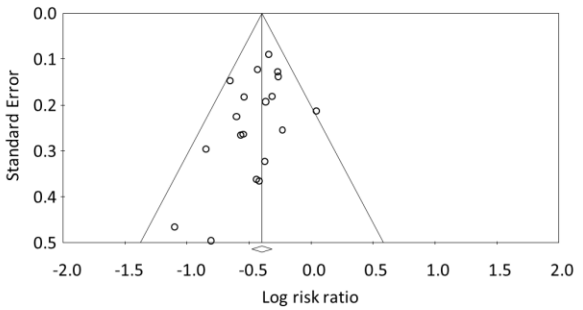
Supplementary Figure 3. Risk of bias summary for all of the judgements about methodological quality for all included studies

Coronary heart disease



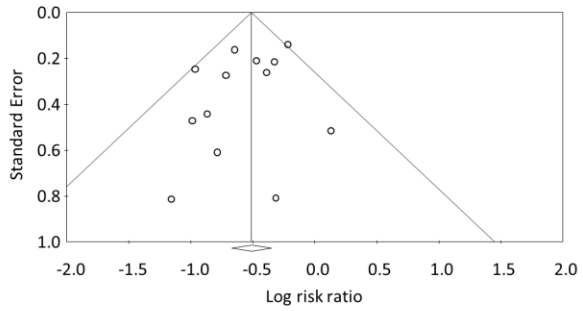
Egger's regression asymmetry test
(*P* = 0.99, intercept = 0.003, 95% CI = -0.83 to 0.84)

Stroke



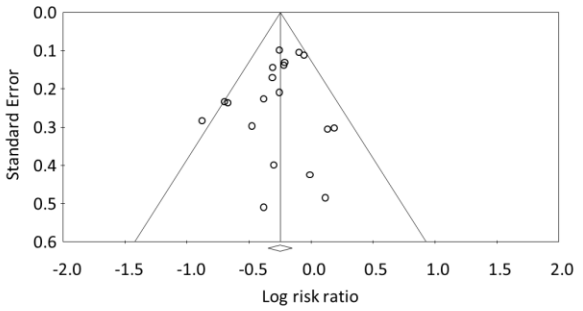
Egger's regression asymmetry test
(*P* = 0.11, intercept = -0.86, 95% CI = -1.94 to 0.22)

Heart failure



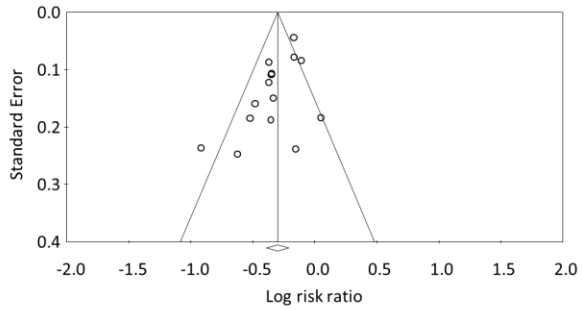
Egger's regression asymmetry test
(*P* = 0.24, intercept = -0.77, 95% CI = -2.15 to 0.61)

Cardiovascular death



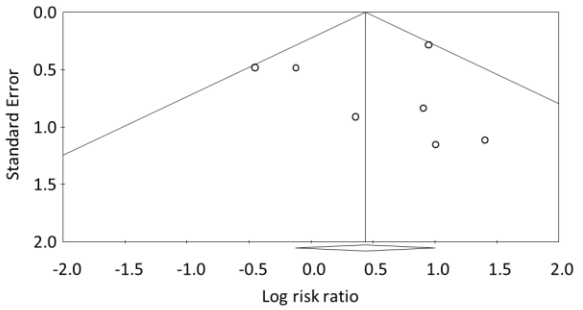
Egger's regression asymmetry test
(*P* = 0.30, intercept = -0.61, 95% CI = -1.83 to 0.60)

MACE



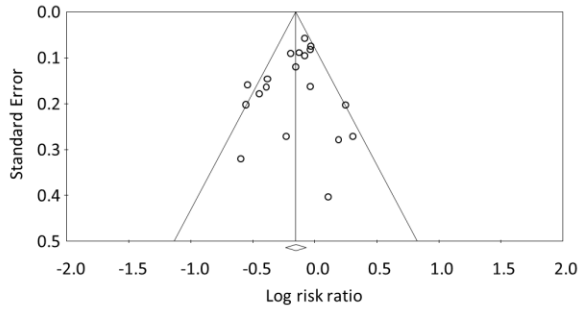
Egger's regression asymmetry test
(*P* = 0.02, intercept = -1.75, 95% CI = -3.14 to -0.37)

Renal failure



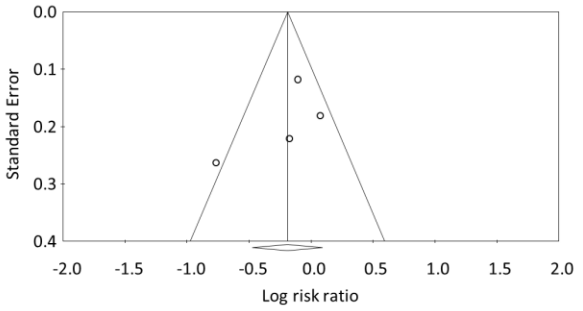
Egger's regression asymmetry test
(*P* = 0.88, intercept = -0.17, 95% CI = -2.96 to 2.61)

All-cause death



Egger's regression asymmetry test
(*P* = 0.28, intercept = -0.75, 95% CI = -2.16 to 0.67)

Dementia

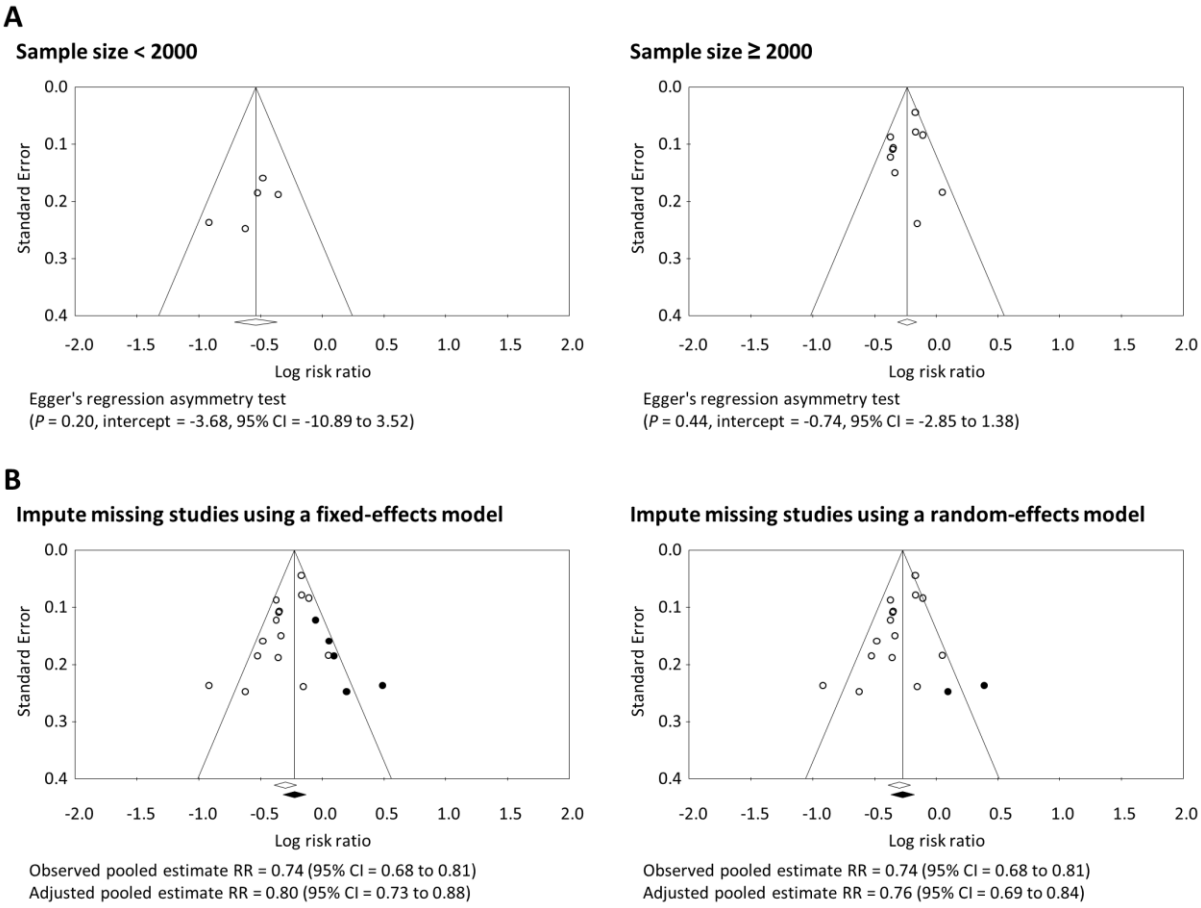


Egger's regression asymmetry test
(*P* = 0.43, intercept = -2.53, 95% CI = -13.53 to 8.48)

Supplementary Figure 4. Funnel plots and Egger's regression asymmetry test for assessing publication bias

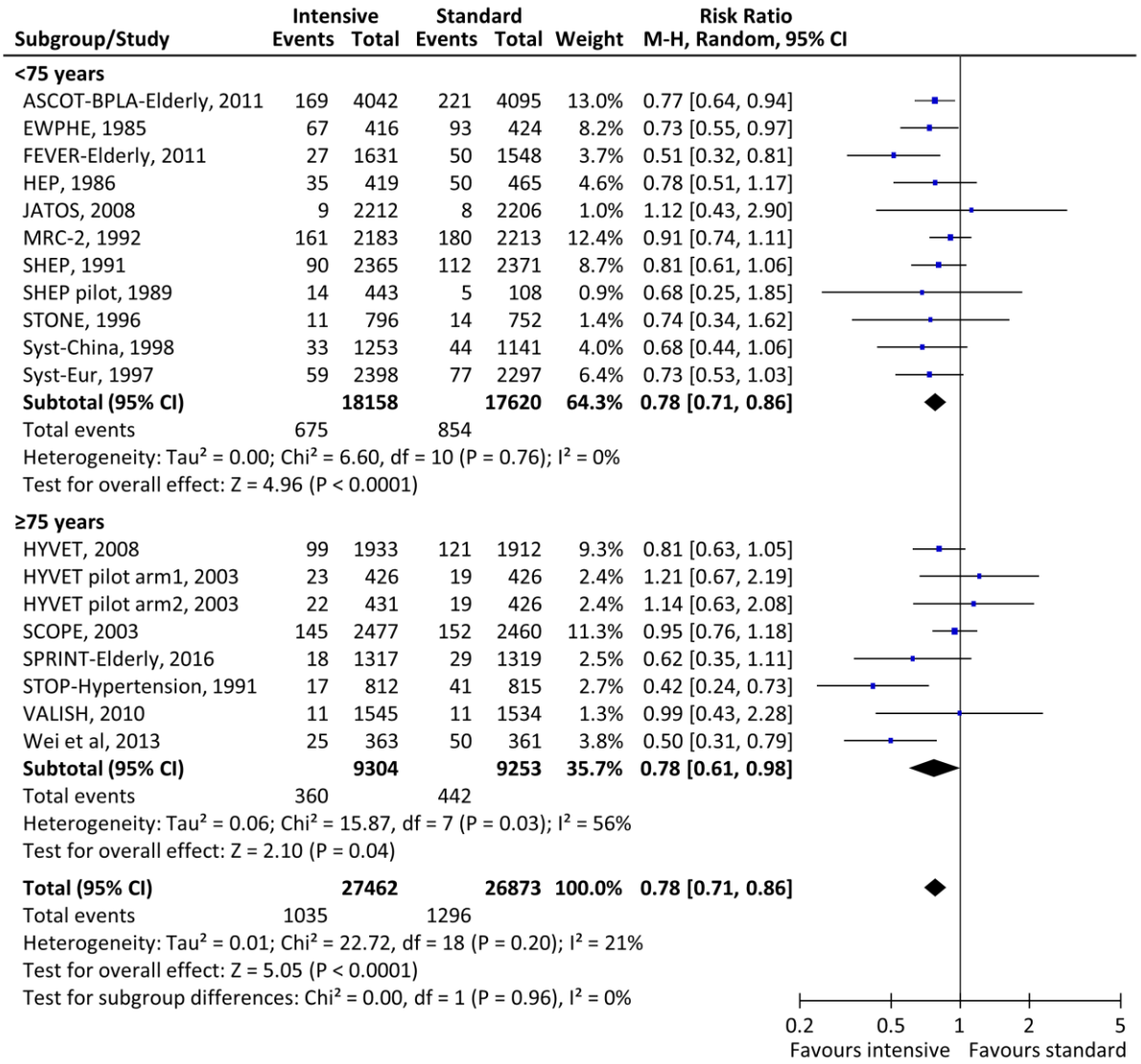
Publication bias was not evaluated for cognitive decline because of only a few trials limiting

the power to test this bias. Diamond represents the pooled estimate of log relative risks and its 95% confidence interval that was calculated by using random-effects model. MACE, major adverse cardiovascular events



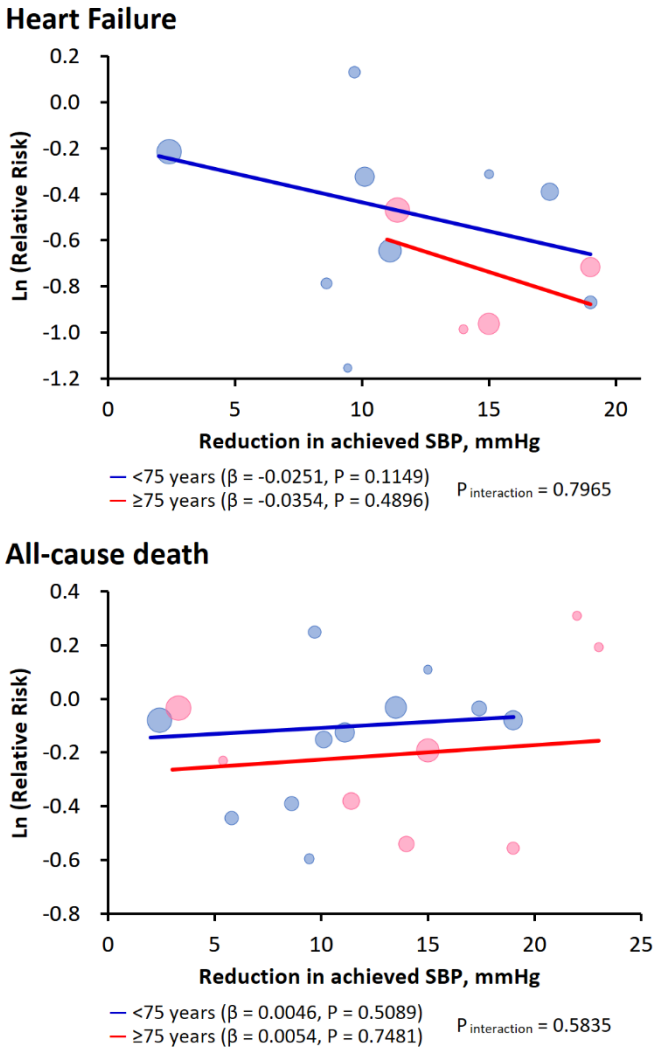
Supplementary Figure 5. Illustration of funnel plot asymmetry for major adverse cardiovascular events

Heterogeneity derived from distinct treatment effects might lead to funnel plot asymmetry (A). A nonparametric "trim and fill" method was adopted to test and adjust for publication bias and did not draw different conclusion (B). The theoretical missing studies (solid circle) were imputed on the right side of the observed mean effect (open diamond). Solid diamond represents the adjusted pooled estimate of log relative risks and its 95% confidence interval.



Supplementary Figure 6. Forest plot of pooled estimates comparing intensive versus standard BP control for cardiovascular death, stratified by baseline mean ages of the included trials

M-H, Mantel-Haenszel



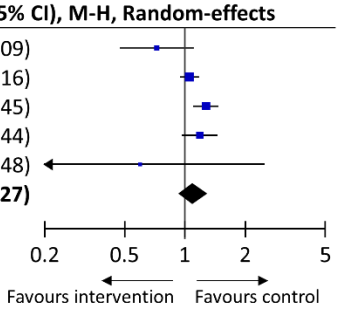
Supplementary Figure 7. Meta-regression analyses of treatment effect in relation to achieved systolic blood pressure (SBP) reduction for heart failure and all-cause death, stratified by baseline mean ages of the included trials. The regression fits for two age groups are shown. The size of the circle represents the weight of each trial and is inversely proportional to the standard error of the effect estimate. Ln, natural logarithm

A

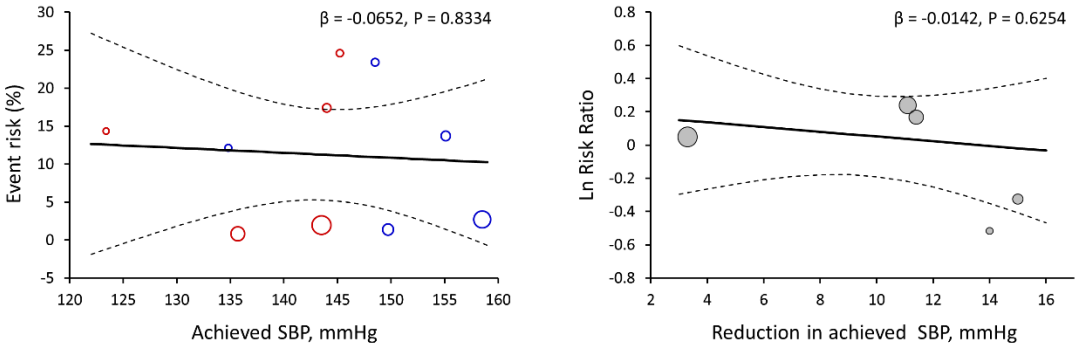
Trials	Achieved SBP I	Achieved SBP C	Intervention Events	Intervention Total	Control Events	Control Total	Weight	Risk Ratio (95% CI), M-H, Random-effects
HYVET, 2010	143.5	158.5	38	1933	52	1912	9.9%	0.72 (0.48, 1.09)
SCOPE, 2003	145.2	148.5	609	2477	576	2460	34.4%	1.05 (0.95, 1.16)
SHEP, 1991	144.0	155.1	412	2365	325	2371	30.6%	1.27 (1.11, 1.45)
SPRINT, 2016	123.4	134.8	189	1317	160	1319	23.9%	1.18 (0.97, 1.44)
Wei et al, 2013	135.7	149.7	3	363	5	361	1.1%	0.60 (0.14, 2.48)
Overall			**1251**	**8455**	**1118**	**8423**	**100.0%**	**1.10 (0.94, 1.27)**

Heterogeneity: $Tau^2 = 0.01$; $Chi^2 = 10.39$, df = 4 (P = 0.03); $I^2 = 62\%$

Test for overall effect: Z = 1.21 (P = 0.23)

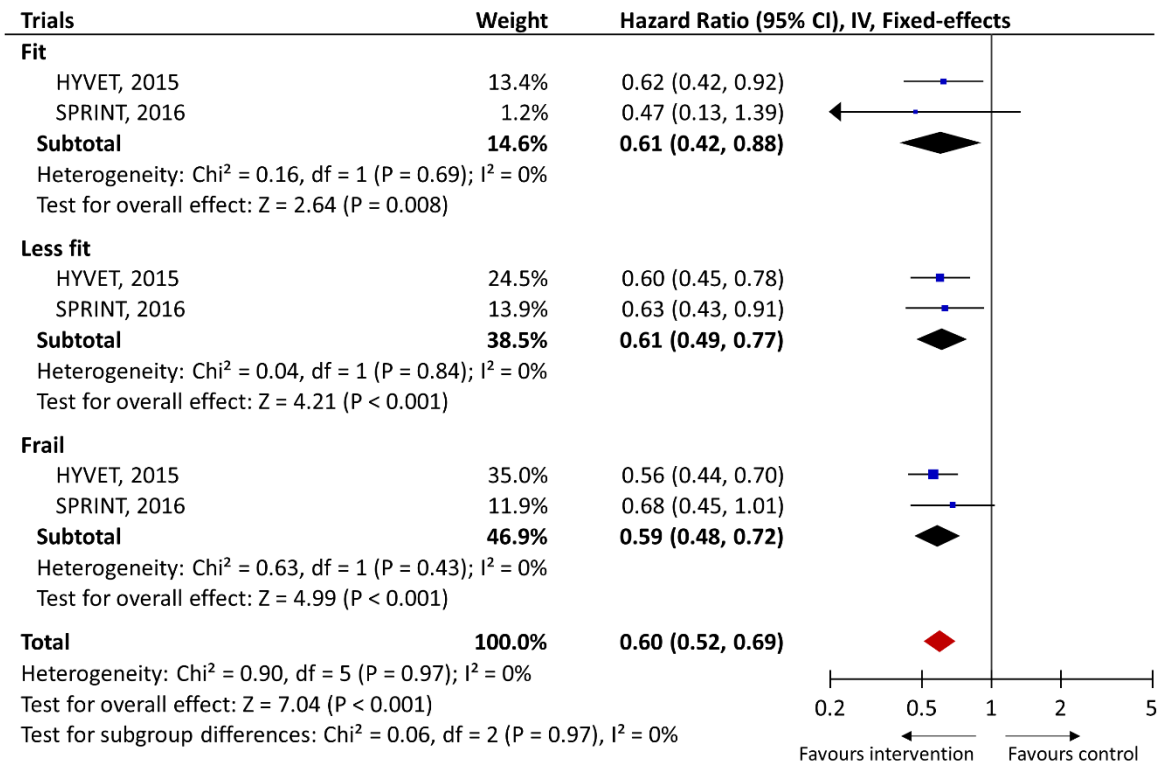


B



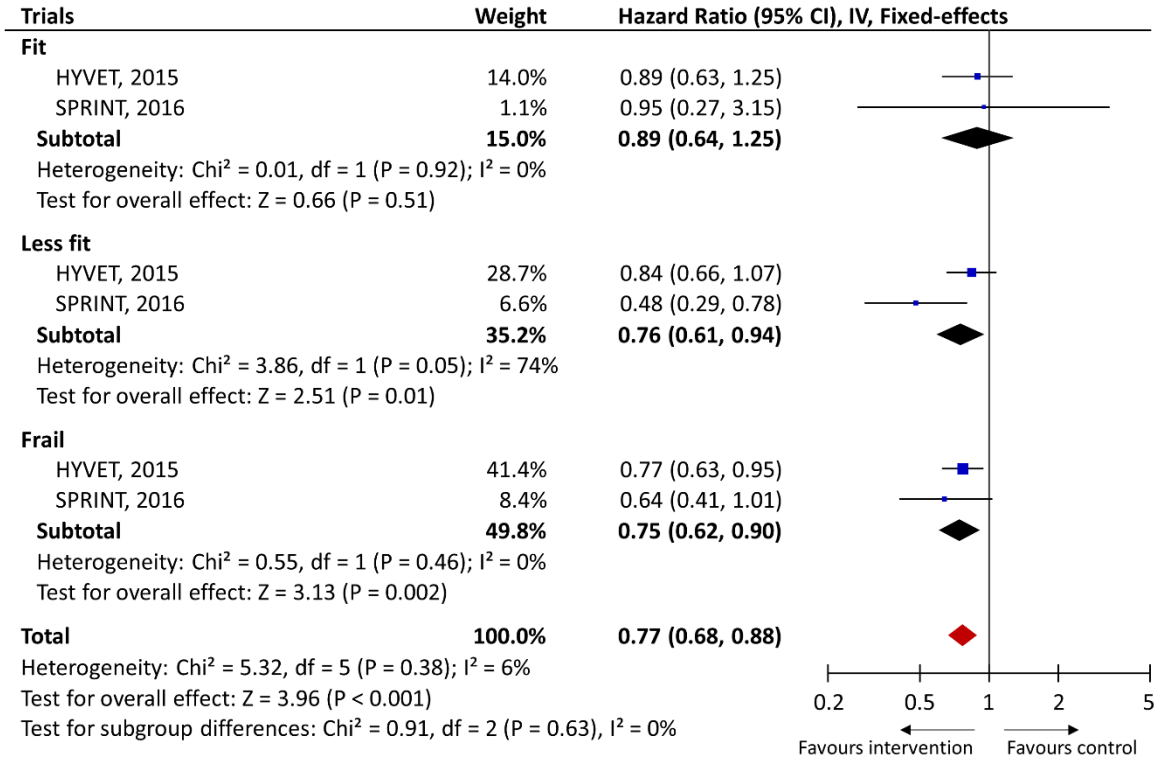
Supplementary Figure 8. Effects of antihypertensive treatment on reported side effects (A) and the relationship of the risk of reported side effects to achieved systolic blood pressure (SBP) and achieved SBP difference between intensive and standard control groups (B)

Reported side effects summarized the events of falls, fractures, syncope, hypotension, and electrolyte abnormality. Diamond denote pooled relative risk and 95% confidence interval (top panel). The bottom-left inset in this figure shows meta-regression analysis performed on the data from combining the intensive (colored in red) and standard (colored in blue) control groups, and the bottom-right inset shows meta-regression analysis that regressed the relative risk on the difference in achieved SBP between the intensive and standard control groups. The regression fit (solid line) and 95% confidence interval (dash line) are shown. The size of the circle represents the weight of each trial and is inversely proportional to the standard error of the effect estimate. C, control; I, intervention; Ln, natural logarithm; M-H, Mantel-Haenszel



Supplementary Figure 9. Effects of antihypertensive treatment on cardiovascular events, stratified by frailty status

Frailty status classified using frailty index (FI) as fit (FI≤0.10), less fit (0.10<FI≤0.21), or frail (FI>0.21). IV, Inverse Variance



Supplementary Figure 10. Effects of antihypertensive treatment on all-cause death, stratified by frailty status

Frailty status classified using frailty index (FI) as fit (FI≤0.10), less fit (0.10<FI≤0.21), or frail (FI>0.21). IV, Inverse Variance

References

1. Peters R, Beckett N, Burch L, de Vernejoul MC, Liu L, Duggan J, Swift C, Gil-Extremera B, Fletcher A, Bulpitt C. The effect of treatment based on a diuretic (indapamide) +/- ACE inhibitor (perindopril) on fractures in the Hypertension in the Very Elderly Trial (HYVET). *Age Ageing* 2010; **39**(5)**:** 609-616.
2. Balshem H, Helfand M, Schunemann HJ, Oxman AD, Kunz R, Brozek J, Vist GE, Falck-Ytter Y, Meerpohl J, Norris S, Guyatt GH. GRADE guidelines: 3. Rating the quality of evidence. *J Clin Epidemiol* 2011; **64**(4)**:** 401-406.