APPENDIX A. SEARCH STRATEGIES

Databases Searched:

- Ovid Medline
- PubMed [Publisher status segment]
- Embase
- Cochrane Library (Ovid EBM Reviews): Cochrane Central Register of Controlled Trials; Cochrane Database of Systematic Reviews; Database of Abstracts of Reviews of Effects; Health Technology Assessment; NHS Economic Evaluation Database

Grey Literature Sources:

- ClinicalTrials.gov
- World Health Organization International Clinical Trials Registry Platform (WHO ICTRP)
- International Standard Randomised Controlled Trials Number registry (ISRCTN)
- Conference Papers Index

Ovid MEDLINE(R) and Ovid OLDMEDLINE(R) 1946 to January Week 4 2015
Ovid MEDLINE(R) In-Process & Other Non-Indexed Citations January 29, 2015
Date of search: January 30, 2015

1	Hypertension/	193547
2	hypertension, malignant/	2172
3	hypertension, renal/	12991
4	hypertension, renovascular/	6296
5	(hypertensive or hypertension or ((high or elevated or raised) adj2 blood pressure)).ti,ab.	333658
6	blood pressure/	238359
7	systole/	16952
8	diastole/	14899
9	(blood pressure* or arterial pressure* or systole* or (systol* and (pressure* or mm Hg or mm Hg)) or diastole* or (diastol* and (pressure* or mm Hg or mm Hg)) or BP or DBP or (SBP not spontaneous bacterial peritonitis)).ti,ab.	401649
10	or/1-9	757490
11	antihypertensive agents/ or acebutolol/ or alprenolol/ or amlodipine/ or atenolol/ or bendroflumethiazide/ or bepridil/ or betaxolol/ or bethanidine/ or bisoprolol/ or bupranolol/ or captopril/ or carteolol/ or celiprolol/ or chlorisondamine/ or chlorothiazide/ or chlorthalidone/ or cilazapril/ or clonidine/ or cyclopenthiazide/ or diazoxide/ or dihydralazine/ or diltiazem/ or doxazosin/ or enalapril/ or enalaprilat/ or felodipine/ or fosinopril/ or guanabenz/ or guanfacine/ or hydralazine/ or hydrochlorothiazide/ or hydroflumethiazide/ or indapamide/ or indoramin/ or isradipine/ or labetalol/ or lisinopril/ or losartan/ or methyldopa/ or metipranolol/ or metolazone/ or metoprolol/ or mibefradil/ or minoxidil/ or nadolol/ or nicardipine/ or nimodipine/ or nisoldipine/ or nitrendipine/ or oxprenolol/ or pempidine/ or penbutolol/ or perindopril/ or pinacidil/ or pindolol/ or polythiazide/ or prazosin/ or propranolol/ or ramipril/ or reserpine/ or timolol/ or todralazine/ or trichlormethiazide/ or xipamide/ or (antihypertensive or anti-hypertensive).ti,ab.	191932

12	adrenergic alpha-antagonists/ or adrenergic alpha-1 receptor antagonists/ or doxazosin/ or indoramin/ or labetalol/ or prazosin/ or adrenergic alpha-2 receptor antagonists/ or adrenergic beta-antagonists/ or alprenolol/ or bunolol/ or bupranolol/ or carteolol/ or dihydroalprenolol/ or iodocyanopindolol/ or levobunolol/ or metipranolol/ or nadolol/ or oxprenolol/ or penbutolol/ or pindolol/ or propranolol/ or sotalol/ or timolol/ or adrenergic beta-1 receptor antagonists/ or acebutolol/ or atenolol/ or betaxolol/ or bisoprolol/ or celiprolol/ or metoprolol/ or practolol/ or adrenergic beta-2 receptor antagonists/ or adrenergic beta-3 receptor antagonists/ or (adrenergic alpha-antagonist* or adrenergic alphaantagonist*).ti,ab.	93013
13	angiotensin-converting enzyme inhibitors/ or captopril/ or cilazapril/ or enalapril/ or enalaprilat/ or fosinopril/ or lisinopril/ or perindopril/ or ramipril/ or angiotensin-converting enzyme inhibitor*.ti,ab.	43990
14	angiotensin receptor antagonists/ or angiotensin ii type 1 receptor blockers/ or losartan/ or saralasin/ or angiotensin ii type 2 receptor blockers/ or angiotensin receptor antagonist*.ti,ab.	17586
15	calcium channel blockers/ or amlodipine/ or amrinone/ or bencyclane/ or bepridil/ or cinnarizine/ or diltiazem/ or felodipine/ or fendiline/ or flunarizine/ or gallopamil/ or isradipine/ or lidoflazine/ or mibefradil/ or nicardipine/ or nifedipine/ or nimodipine/ or nisoldipine/ or nitrendipine/ or tiapamil hydrochloride/ or verapamil/ or calcium channel blocker*.ti,ab.	70143
16	diuretics/ or acetazolamide/ or amiloride/ or bendroflumethiazide/ or bumetanide/ or chlorothiazide/ or chlorthalidone/ or clopamide/ or cyclopenthiazide/ or ethacrynic acid/ or ethoxzolamide/ or furosemide/ or hydrochlorothiazide/ or hydroflumethiazide/ or indapamide/ or mefruside/ or methazolamide/ or methyclothiazide/ or metolazone/ or muzolimine/ or polythiazide/ or spironolactone/ or ticrynafen/ or triamterene/ or trichlormethiazide/ or xipamide/ or diuretics, osmotic/ or isosorbide/ or diuretics, potassium sparing/ or epithelial sodium channel blockers/ or mineralocorticoid receptor antagonists/ or sodium chloride symporter inhibitors/ or sodium potassium chloride symporter inhibitors/ or diuretic*.ti,ab.	77139
17	vasodilator agents/ or acetylcholine/ or adenosine/ or "adenosine-5'-(n-ethylcarboxamide)"/ or alprostadil/ or amiodarone/ or amrinone/ or amyl nitrite/ or bencyclane/ or bepridil/ or betahistine/ or bradykinin/ or calcitonin gene-related peptide/ or celiprolol/ or chromonar/ or colforsin/ or cromakalim/ or cyclandelate/ or diazoxide/ or dihydroergocristine/ or dihydroergocryptine/ or dilazep/ or diltiazem/ or dipyridamole/ or dyphylline/ or enoximone/ or ergoloid mesylates/ or erythritol/ or erythrityl tetranitrate/ or flunarizine/ or hexobendine/ or iloprost/ or isosorbide dinitrate/ or isoxsuprine/ or isradipine/ or khellin/ or lidoflazine/ or mibefradil/ or milrinone/ or minoxidil/ or molsidomine/ or moxisylyte/ or nafronyl/ or niacin/ or nicardipine/ or nicergoline/ or nicorandil/ or nicotinyl alcohol/ or nifedipine/ or nimodipine/ or nisoldipine/ or nitrendipine/ or nitroglycerin/ or nitroprusside/ or nonachlazine/ or nylidrin/ or oxprenolol/ or oxyfedrine/ or papaverine/ or pentaerythritol tetranitrate/ or pentoxifylline/ or perhexiline/ or phenoxybenzamine/ or pinacidil/ or pindolol/ or pituitary adenylate cyclase-activating polypeptide/ or polymethyl methacrylate/ or prenylamine/ or s-nitroso-n-acetylpenicillamine/ or s-nitrosoglutathione/ or s-nitrosothiols/ or sodium azide/ or suloctidil/ or theobromine/ or theophylline/ or thiouracil/ or tolazoline/ or trapidil/ or trimetazidine/ or vasoactive intestinal peptide/ or verapamil/ or xanthinol niacinate/ or endothelium-dependent relaxing factors/ or nitric oxide/ or vasodilator*.ti,ab.	350538
18	Aldosterone/	21964
19	Chlorisondamine/	543
20	Mineralocorticoids/ or Desoxycorticosterone/ or Desoxycorticosterone Acetate/	8175
21	Pempidine/	163
22	Renin-Angiotensin System/	14256
23	or/11-22	632178
24	exp Cardiovascular Diseases/	1901992
25	exp Heart Failure/	88568
26	exp Kidney Diseases/ or exp Kidney Failure, Chronic/	415035
27	hypotension/	17869

28	stroke/ or brain infarction/ or brain stem infarctions/ or lateral medullary syndrome/ or cerebral infarction/ or dementia, multi-infarct/ or infarction, anterior cerebral artery/ or infarction, middle cerebral artery/ or infarction, posterior cerebral artery/ or stroke, lacunar/	88131
29	polypharmacy/	2517
30	exp cognition disorders/	63655
31	exp dementia/	121166
32	accidental falls/	15941
33	exp fractures, bone/	142161
34	"quality of life"/	121510
35	(death* or mortalit* or morbidit* or comorbidit* or co-morbidit* or multimorbidit* or multi-morbidit* or coexist* or co-exist* or stroke* or infarct* or multiinfarct* or multi-infarct* or transient ischemic attack* or TIA or cerebrovascular or (heart adj (disease* or failure*)) or ((renal or nephro* or kidney) adj2 (disease* or failure* or disorder* or injury or injuries)) or AKI or fracture* or falls or cognit* or dementia* or hypotension or hypotensive or polypharm* or "quality of life").ti,ab.	2265610
36	or/24-35	3913057
37	and/10,23,36	120955
38	limit 37 to "all aged (65 and over)"	30492
39	(elder* or aged or old or older or oldest or senior* or geriatric* or gerontolog* or sexagenarian* or septuagenarian* or octogenarian* or nonagenarian*).ti,ab.	1436775
40	37 and 39	15236
41	38 or 40	38096
42	cohort studies/ or follow-up studies/ or longitudinal studies/ or prospective studies/ or retrospective studies/ or ((cohort* or trial*) adj3 extension*).ti,ab.	1387757
43	and/41-42	7501
44	limit 43 to (comment or editorial or letter)	77
45	43 not 44	7424
46	limit 45 to english language [OBSERVATIONAL STUDY RESULTS]	6655
47	limit 41 to (meta analysis or systematic reviews)	643
48	47 not 46	541
49	limit 48 to english language [META-ANALYSIS AND SYSTEMATIC REVIEW RESULTS]	474
50	and/10,23	162820
51	(201212* or 2013* or 2014* or 2015*).ed. or (201212* or 2013* or 2014* or 2015*).dc.	2570599
52	and/50-51	10390
53	limit 52 to (clinical trial, phase iii or clinical trial, phase iv or controlled clinical trial or pragmatic clinical trial or randomized controlled trial)	1037
54	limit 53 to english language	988
55	remove duplicates from 54 [RCT/CCT RESULTS]	956

EMBASE (Elsevier)
http://embase.com
Date of search: January 30, 2015

Search Strategy		Results
44	#41 OR #42 OR #43	2,594
43	#39 AND ([controlled clinical trial]/lim OR [randomized controlled trial]/lim) AND [english]/lim NOT [medline]/lim	1,138
42	#39 AND [english]/lim AND ([cochrane review]/lim OR [systematic review]/lim OR [meta analysis]/lim) NOT [medline]/lim	186
41	#40 AND [english]/lim NOT ([editorial]/lim OR [letter]//lim OR [medline]/lim)	1,475
40	#39 AND ('cohort analysis'/de OR 'observational study'/de OR 'prospective study'/de OR 'retrospective study'/de OR 'longitudinal study'/de OR 'follow-up study':ab,ti OR 'follow-up studies':ab,ti OR ((cohort* OR trial*) NEAR/3 extension*):ab,ti)	6,637
39	#37 OR #38	65,498
38	#7 AND #22 AND #35 AND (elder*:ab,ti OR aged:ab,ti OR old:ab,ti OR older:ab,ti OR oldest:ab,ti OR senior*:ab,ti OR geriatric*:ab,ti OR gerontolog*:ab,ti OR sexagenarian*:ab,ti OR septuagenarian*:ab,ti OR octogenarian*:ab,ti OR nonagenarian*:ab,ti)	37,068
37	#7 AND #22 AND #35 AND ([aged]/lim OR [very elderly]/lim)	42,220
36	#7 AND #22 AND #35	251,536
35	#23 OR #24 OR #25 OR #26 OR #27 OR #28 OR #29 OR #30 OR #31 OR #33 OR #34	5,706,843
34	death*:ab,ti OR mortalit*:ab,ti OR morbidit*:ab,ti OR comorbidit*:ab,ti OR 'co-morbidity':ab,ti OR 'co-morbidities':ab,ti OR multimorbidit*:ab,ti OR 'multi-morbidity':ab,ti OR 'multi-morbidities':ab,ti OR coexist*:ab,ti OR 'co-existing':ab,ti OR stroke*:ab,ti OR infarct*:ab,ti OR multiinfarct*:ab,ti OR 'multi-infarction':ab,ti OR 'multi-infarctions':ab,ti OR 'transient ischemic attack':ab,ti OR 'transient ischemic attacks':ab,ti OR tia:ab,ti OR cerebrovascular:ab,ti OR (heart NEXT/1 (disease* OR failure*)):ab,ti OR ((renal OR nephro* OR kidney) NEAR/2 (disease* OR failure* OR disorder* OR injury OR injuries)):ab,ti OR aki:ab,ti OR fracture*:ab,ti OR falls:ab,ti OR cognit*:ab,ti OR dementia*:ab,ti OR hypotension:ab,ti OR hypotensive:ab,ti OR polypharm*:ab,ti OR 'quality of life':ab,ti	2,969,107
33	'quality of life'/de	268,408
32	'fracture'/exp	215,542
31	'falling'/de	25,824
30	'dementia'/exp	238,471
29	'disorders of higher cerebral function'/exp	553,733
28	'polypharmacy'/de	7,732
27	'cerebrovascular disease'/exp	480,125
26	'hypotension'/exp	106,487
25	'kidney disease'/exp	707,514
24	'heart failure'/exp	322,750
23	'cardiovascular disease'/exp	3,134,649
22	#8 OR #9 OR #10 OR #11 OR #12 OR #13 OR #14 OR #15 OR #16 OR #17 OR #18 OR #19 OR #20 OR #21	1,125,178
21	'renin angiotensin aldosterone system'/de	31,112
20	'pempidine'/de	283
19	'deoxycorticosterone acetate'/de	2,712
18	'deoxycorticosterone'/de	7,177
17	'mineralocorticoid'/exp	71,060
16	'chlorisondamine'/de	1,025
15	'aldosterone'/de	31,797
14	'vasodilator agent'/exp OR vasodilator*:ab,ti	430,197
13	'diuretic agent'/exp OR diuretic*:ab,ti	310,799
12	'calcium channel blocking agent'/exp OR 'calcium channel blocker':ab,ti OR 'calcium channel blockers':ab,ti	187,980
11	'angiotensin 2 receptor antagonist'/exp OR 'angiotensin ii receptor antagonist':ab,ti OR 'angiotensin ii receptor antagonists':ab,ti	8,252
10	'angiotensin receptor antagonist'/exp OR 'angiotensin receptor antagonist':ab,ti OR 'angiotensin receptor antagonists':ab,ti	63,456
9	'adrenergic receptor blocking agent'/exp OR 'adrenergic alpha-antagonist':ab,ti OR 'adrenergic alpha-antagonists':ab,ti OR 'adrenergic alphaantagonist':ab,ti	342,302

8	'antihypertensive agent'/exp OR antihypertensive:ab,ti OR 'anti hypertensive':ab,ti	593,629
7	#1 OR #2 OR #3 OR #4 OR #5 OR #6	1,115,118
6	'blood pressure':ab,ti OR 'arterial pressure':ab,ti OR systole*:ab,ti OR (systol*:ab,ti AND (pressure*:ab,ti OR mm Hg:ab,ti OR 'mm hg':ab,ti)) OR diastole*:ab,ti OR (diastol*:ab,ti AND (pressure*:ab,ti OR mm Hg:ab,ti OR 'mm hg':ab,ti)) OR bp:ab,ti OR dbp:ab,ti OR (sbp:ab,ti NOT 'spontaneous bacterial peritonitis':ab,ti)	505,982
5	'diastole'/de	14,230
4	'systole'/de	13,554
3	'blood pressure'/exp	415,778
2	hypertensive:ab,ti OR hypertension:ab,ti OR (((high OR elevated OR raised) NEAR/2 blood):ab,ti AND pressure:ab,ti)	458,732
1	'hypertension'/exp	513,148

Cochrane Library (Ovid EBM Reviews)

- **Cochrane Central Register of Controlled Trials** December 2014
- **Cochrane Database of Systematic Reviews** 2005 to December 2014
- **Database of Abstracts of Reviews of Effects** 4th Quarter 2014
- **Health Technology Assessment** 4th Quarter 2014
- **NHS Economic Evaluation Database** 4th Quarter 2014

Date of search: January 30, 2015

1	(hypertensive or hypertension or ((high or elevated or raised) adj2 blood pressure)).ti,ab.	29303
2	(blood pressure* or arterial pressure* or systole* or (systol* and (pressure* or mm Hg or mm Hg)) or diastole* or (diastol* and (pressure* or mm Hg or mm Hg)) or BP or DBP or (SBP not spontaneous bacterial peritonitis)).ti,ab.	44700
3	and/1-2	16149
4	(antihypertensive or anti-hypertensive).ti,ab.	8074
5	(adrenergic alpha-antagonist* or adrenergic alphaantagonist*).ti,ab.	0
6	angiotensin-converting enzyme inhibitor*.ti,ab.	2444
7	angiotensin receptor antagonist*.ti,ab.	74
8	calcium channel blocker*.ti,ab.	1575
9	diuretic*.ti,ab.	4287
10	vasodilator*.ti,ab.	2596
11	or/4-10	16071
12	(death* or mortalit* or morbidit* or comorbidit* or co-morbidit* or multimorbidit* or multi-morbidit* or coexist* or co-exist* or stroke* or infarct* or multiinfarct* or multi-infarct* or transient ischemic attack* or TIA or cerebrovascular or (heart adj (disease* or failure*)) or ((renal or nephro* or kidney) adj2 (disease* or failure* or disorder* or injury or injuries)) or AKI or fracture* or falls or cognit* or dementia* or hypotension or hypotensive or polypharm* or "quality of life").ti,ab.	155570
13	(elder* or aged or old or older or oldest or senior* or geriatric* or gerontolog* or sexagenarian* or septuagenarian* or octogenarian* or nonagenarian*).ti,ab.	70846
14	and/3,11-13	536
15	limit 14 to medline records [Limit not valid in CDSR,DARE,CLHTA,CLEED; records were retained]	407
16	14 not 15	129
17	limit 16 to english language [Limit not valid in CDSR,DARE; records were retained]	84

APPENDIX B. STUDY SELECTION

Table 9. Inclusion Codes, Code Definitions, and Criteria Corresponding to the Key Questions

Code	Definition	KQ1.What are the health outcome effects of differing blood pressure targets?	KQ2. How does age modify the benefits of differing blood pressure targets?	KQ3a. How does the patient burden of comorbidities modify the benefits of differing blood pressure targets? KQ3b. In patients who have suffered a TIA/stroke, does treatment of blood pressure to specific targets affect outcomes?	KQ4. Do the harms of targeting lower blood pressure vary with age?	KQ5. Do the harms of targeting lower blood pressure vary with patient burden of comorbidities?
I – Trial	Trials with ≥ 6 months of follow-up that address any of KQs 1-5.	Population: Adults aged ≥60 with hypertension Intervention: Pharmacologic treatment of hypertension Comparator: Usual care, or another specified SBP target. Primary outcomes: · All-cause mortality · Mortality related to stroke, CHD, CHF, and renal disease · Morbidity including stroke, CHD, CHF, and renal disease Timing: Published 2012 or later. Incidence of outcomes ≥ 6 months of hypertension treatment. Study design: Controlled trials (randomized or non-randomized) with ≥ 6 months of follow-up.			PICTS as for KQs 1-3, but with harms outcomes: · Changes in cognition · Falls · Changes to quality of life · Hypotension · Acute kidney injury *Code B: large (n>10k) cohort studies that only report* · *All-cause mortality* · *Cardiovascular outcomes*	
I – Cohort	Cohort studies are included for KQs 4-5 only if they report harms. · Large (N>10,000) multi-center cohort studies. · Cohort extensions of major trials.	Data on the primary outcomes listed above will not be abstracted from cohort studies.			· Controlled study designs (RCT and non-randomized controlled clinical trials used for KQs 1-3) · Cohort extensions of trials that examined specific blood pressure targets · Cohort studies that examined the effects of lower blood pressure in the context of antihypertensive medication · Cohort studies that reported the effects of lower blood pressure despite that hypertension management was not the primary objective of the intervention studied.	
I – Stroke	Trials of any duration that address KQ3a.	*Population KQ3b:* Aged ≥60 with hypertension and recent cerebrovascular accident (≤ 6 months). *Intervention KQ3b:* Pharmacologic treatment of hypertension within the first 6 months post-stroke. *Additional outcomes of interest for KQ3b:* Recurrent cerebrovascular accident; Functional status; Disability				
I – SR	Systematic review or meta-analysis on any of the KQs					

Table 10. Exclusion Codes, Code Definitions, and Criteria Corresponding to the Key Questions

Code	Definition	**KQ1.**What are the health outcome effects of differing blood pressure targets?	**KQ2**. How does age modify the benefits of differing blood pressure targets?	**KQ3a**. How does the patient burden of comorbidities modify the benefits of differing blood pressure targets? **KQ3b**. In patients who have suffered a TIA or stroke, does treatment of blood pressure to specific targets affect outcomes?	**KQ4.** Do the harms of targeting lower blood pressure vary with age?	**KQ5.** Do the harms of targeting lower blood pressure vary with patient burden of comorbidities?
X1	Non-English publication	Note: most foreign language studies will be filtered out during initial library cleaning.				
X2	Article does not pertain in any way to hypertension -Rx treatment in older adults					
X3	Study population is not in scope for any of the KQs	Include: Adults with hypertension aged ≥ 60 or mean age ≥60. For KQ3: existing comorbidity or recent cerebrovascular accident (≤ 6 months). Exclude: Studies with mean age < 60.				
X4	No primary data, or study design not in scope	Exclude: · Controlled before/after studies · Case reports/case series · RCTs with less than 6 month follow-up				
X5	Intervention modality or study objectives are not in scope	Exclude: · Trials for which hypertension management was not the primary objective, despite that secondary effects on hypertension may be reported, *eg*, TNT for the j-curve effect. · Non-pharmacologic interventions for blood pressure control · Blood pressure interventions during the acute phase post-stroke (KQ3a).			Note: For KQs 4- 5, cohort studies that report harms of lower blood pressure may be included even if hypertension management was not the primary objective of the intervention studied.	
X6	None of the reported outcomes are in scope	Primary outcomes of interest: · All-cause mortality · Mortality related to stroke, CHD, CHF, and renal disease · Morbidity including stroke, CHD, CHF, and renal disease			Harms of interest: · Changes in cognition · Falls · Changes to quality of life · Polypharmacy	
X7	Other reason, specify					
B	Background	Add ‘B’ any of the above X codes (*eg*, ‘X6–B’) if the article contains information that may be useful for the introduction, discussion, limitations, future research, or other contextual purposes. Add comments or keywords as needed.				

B = background; KQ = key question; CHD = congenital heart disease; CHF = congestive heart failure; RCT = randomized controlled trials; TIA = transient ischemic attack; TNT = treat to new targets

APPENDIX C. QUALITY ASSESSMENT

Table 11. Assessment of Randomized Controlled Trials for Potential Risk of Bias

Study	Allocation sequence adequately generated?	Allocation adequately concealed?	Knowledge of the allocated intervention adequately prevented during the study?	Incomplete outcome data adequately addressed?	Free of suggestion of selective outcome reporting?	Free of other problems that could put it at a high risk of bias?	Summary assessment High/Low/ Unclear Risk of Bias	Funder
ACCORD[22]	Yes: central, computer-based randomization	Yes	Yes: non-blinded study, but they used dual, blinded outcome adjudicators	Missing data assumed to be random, sensitivity analysis performed and outcome measures not significantly changed	Yes	Yes	Low	National Heart, Lung, Blood Institute; NIH agencies
ADVANCE[27]	Yes: central, computer-based, randomization	Yes	Yes: participants, providers, outcome assessors all blinded	Yes: extremely low loss-to follow-up, 15 patients in a sample of >11,000	Yes	Yes	Low	Servier; National Health and Medical Research Council of Australia
BENEDICT-B[28]	Yes: central, computer-based randomization	Yes	Yes: participants, providers, outcome assessors all blinded	Yes: all censored events included in analysis, power and statistical significance were adequate	Yes	Yes	Low	Mario Negri Institute for Pharmacologic Research/Institute for Rare Diseases
Cardio-Sis[23]	Yes: central, computer-based randomization	Yes	Yes: open-label study, but outcome adjudicators were blinded	Yes: only one patient lost to follow-up	Yes: Primary outcome was left ventricular hypertrophy, but cardiovascular and mortality endpoints were prespecified secondary outcomes	Yes	Low	Heart Care Foundation; Boehringer-Ingelheim, Sanofi-Aventis; Pfizer

Study	Allocation sequence adequately generated?	Allocation adequately concealed?	Knowledge of the allocated intervention adequately prevented during the study?	Incomplete outcome data adequately addressed?	Free of suggestion of selective outcome reporting?	Free of other problems that could put it at a high risk of bias?	Summary assessment High/Low/ Unclear Risk of Bias	Funder
EWPHE[29]	Probably: patients were randomized and allocated by a central coordinating center, but exact method of randomization was not reported	Yes: central allocation	Yes: providers, patients, and outcome assessors all blinded	Yes: similar loss to follow-up in both groups (14 vs 16%), ITT analysis for mortality outcome	Yes, though ITT analysis was only performed for mortality outcome	Yes	Low	Belgian National Research Foundation; Merck, Sharp and Dohme and Smith; Kline and French
FEVER[30]	Yes: central, computer-based randomization	Yes	Yes	Yes: life-status could not be obtained at study end but number was low (0.3%)	Yes	Yes	Low	National Science and Technology Ministry; Beijing Hypertension League Institute and Shanxi Kangbao Pharmaceutical Company
HOT[17]	Yes: central, computer-based randomization	Yes	Yes: open-label but outcome adjudicators were blinded	Yes: 2.6% of patients lost to follow-up; total of 1.8% of all patient-years analyzed contained in censored group; analysis conducted up to time of loss and BP or prior morbidity not found to be significantly different	Yes	Yes	Low	Astra AB, Sweden; Astra Merck Inc, USA; TEVA, Israel; Hoechst, Argentina

Study	Allocation sequence adequately generated?	Allocation adequately concealed?	Knowledge of the allocated intervention adequately prevented during the study?	Incomplete outcome data adequately addressed?	Free of suggestion of selective outcome reporting?	Free of other problems that could put it at a high risk of bias?	Summary assessment High/Low/ Unclear Risk of Bias	Funder
HYVET[6]	Yes: central, computer-based randomization	Yes	Yes: providers, patients, outcome assessors blinded	Yes: very low loss to follow-up (0.3% overall); ITT analysis	Yes	Yes: though of note inclusion criteria changed over time	Low	British Heart Foundation; Institut de Recherches Internationales Servier
JATOS[24]	Yes: central, computer-based randomization	Yes	Yes: outcome assessors blinded; providers and patients likely not blinded but not clearly reported	Yes: censored events reported but no sensitivity analysis performed; ITT analysis	Yes	Unclear: there was not enough precision in protocol information describing outcome definitions	Low	Shionogi and Co. LTD
PRO-GRESS[31]	Yes: central computer-based randomization	Yes	Yes: providers, patients, and outcome assessors blinded	Yes: very low loss to follow-up, though it is unclear whether this refers to vital status outcome or patients attending follow-up visits; ITT analysis	Yes	Yes	Low	Servier; Health Research Council of New Zealand; National Health and Medical Research Council of Australia
RENAAL[32]	Yes: central, computer-based randomization	Yes	Yes: providers, patients, outcome assessors blinded	Yes: very low loss to follow-up; ITT analysis	Yes	Unclear - study was stopped early because of new data that ACE inhibitors were beneficial for population similar to that under study (considered unethical to continue)	Low	Merck

Study	Allocation sequence adequately generated?	Allocation adequately concealed?	Knowledge of the allocated intervention adequately prevented during the study?	Incomplete outcome data adequately addressed?	Free of suggestion of selective outcome reporting?	Free of other problems that could put it at a high risk of bias?	Summary assessment High/Low/ Unclear Risk of Bias	Funder
SCOPE[33]	Yes: central randomization by fax	Yes	Yes: placebo control	Yes: losses to follow-up accounted for, multiple outcomes reported, ITT analysis	Yes	Yes: dual independent qualitative assessment reviews; sufficiently powered; prospective	Low	AstraZeneca
SHEP[8]	Yes: central randomization and allocation	Yes	Yes: providers, patients, outcome assessors blinded	Yes: only 5 patients in each group were unavailable for follow-up; ITT analysis	Yes	Yes	Low	National Heart, Lung, Blood Institute; National Institute on Aging
SPRINT[11]	Yes: central computer-based randomization	Yes	Yes: open-label, but outcomes were centrally adjudicated by blinded assessors	Yes: losses to follow-up accounted for, multiple outcomes reported, ITT analysis	Yes	Unclear: trial was stopped early by DSMB for benefit	Low	National Institutes of Health
SPS3[25]	Yes: central, computer-based randomization	Yes	Yes: open-label, but outcome assessors blinded	Yes: though details on those lost to follow-up not available, overall rate low (3%); ITT analysis	Yes	Yes	Low	NIH-NINDS
STONE[19]	No: patients were allocated alternately by entry order number	No	Yes: placebo control, but patients in placebo whose DBP >110 after the run-in period were switched by their physicians to active treatment	Yes: 2% loss to follow-up; ITT analysis	Yes: outcomes appear to be fully reported, but with methodological flaws earlier in study protocol	Yes: none others detected; randomization issues are serious	High	Ministry of Health of People's Republic of China; Bayer Canada

Study	Allocation sequence adequately generated?	Allocation adequately concealed?	Knowledge of the allocated intervention adequately prevented during the study?	Incomplete outcome data adequately addressed?	Free of suggestion of selective outcome reporting?	Free of other problems that could put it at a high risk of bias?	Summary assessment High/Low/ Unclear Risk of Bias	Funder
Syst-China[20]	No: eligible patients at each center were alternatingly assigned to type A or type B medication	No	Yes: placebo control	Yes: ITT analysis; patients who withdrew remained in open follow-up; patients without any report within the year before the trial ended classified as lost to follow-up, but included in analysis up to the most recent evaluation of health status	Yes	Yes: randomization and allocation flaws have unclear effect on effectiveness estimates; methodological flaws significant	High	State Planning Commission of the People's Republic of China
Syst-Eur[34]	Yes: central randomization and allocation	Yes	Yes: patients, providers, outcome assessors blinded	No: losses to follow-up and adverse events incompletely discussed, no illustrating figures	Yes	Yes	Low	Bayer; National Fund for Scientific Research
TRANS-CEND[35]	Yes: central, computer-based randomization	Yes	Yes: patients, providers, outcome assessors blinded	Yes: 99.7% had vital status ascertained; primary analysis included all patients, used time-to-event approach, counting the first occurrence of any component of the composite outcome	Yes	Yes	Low	Boehringer Ingelheim
VALISH[26]	Yes: Centralized computer randomization	Yes	No: open label	Yes: 181 (5.5%) patients lost to follow-up; censored patients analyzed up to censoring event; ITT analysis	Yes	Yes	Low	Japan Cardiovascular Research Foundation

Study	**Allocation sequence adequately generated?**	**Allocation adequately concealed?**	**Knowledge of the allocated intervention adequately prevented during the study?**	**Incomplete outcome data adequately addressed?**	**Free of suggestion of selective outcome reporting?**	**Free of other problems that could put it at a high risk of bias?**	**Summary assessment** High/Low/ Unclear Risk of Bias	**Funder**
Wei, 2013[21]	Yes: random numbers table computer-generated	Unclear whether allocation itself was concealed	No: open label and not enough detail about outcome adjudication procedure	No: concerning that those lost-to-follow-up are not mentioned in analysis; ITT analysis	Yes	No: small sample size, generalizability; no limitations section; inadequate description of how they obtained outcome information such as mortality or how they assessed cardiac events	High	Not disclosed

APPENDIX D. DATA SUPPLEMENT

Table 12. Detailed Results of Trials that Conducted Age-stratified Analyses

Study Comparison, T vs C	Age groups (N patients)	Results comparing T vs C, by outcome and age group
Studies that compared BP targets (mm Hg)		
ACCORD[37] SBP < 120 vs < 140	< 65 ≥ 65 (Total N = 4733; n per age group not reported)	Unadjusted HR for combined nonfatal MI, nonfatal stroke, and cardiovascular death (95% CIs not reported, but were not statistically significant, interpreted from graph): < 65: 0.90 ≥ 65: 0.91 Age interaction P-value = .98
HOT[38] DBP ≤ 80 vs ≤ 85 vs ≤ 90	< 65 (n = 12803) ≥ 65 (n = 5987)	Events/1000 patient-years by DBP group ≤ 80 vs ≤ 85 vs ≤ 90 mm Hg (P-value for trend; HR calculated from event rates, 95% CI not reported): Total mortality: < 65: 5.7 vs 5.5 vs 4.5 (P = .13) HR ≤ 80 vs ≤ 85: 1.04 HR ≤ 80 vs ≤ 90: 1.27 ≥ 65: 15.4 vs 13.9 vs 15.7 (P =.89) HR ≤ 80 vs ≤ 85: 1.11 HR ≤ 80 vs ≤ 90: 0.98 Cardiovascular death: < 65: 2.2 vs 2.9 vs 1.9 (P = .52) HR ≤ 80 vs ≤ 85: 0.76 HR ≤ 80 vs ≤ 90: 1.16 ≥ 65: 8.0 vs 5.7 vs 7.6 (P = .81) HR ≤ 80 vs ≤ 85: 1.40 HR ≤ 80 vs ≤ 90: 1.05 MI: < 65: 2.3 vs 2.9 vs 3.2 (P = .13) HR ≤ 80 vs ≤ 85: 0.79 HR ≤ 80 vs ≤ 90: 0.72 ≥ 65: 3.2 vs 2.4 vs 4.4 (P = .22) HR ≤ 80 vs ≤ 85: 1.33 HR ≤ 80 vs ≤ 90: 0.73 Stroke: < 65: 2.4 vs 3.8 vs 2.3 (P = .77) HR ≤ 80 vs ≤ 85: 0.63 HR ≤ 80 vs ≤ 90: 1.04 ≥ 65: 6.7 vs 6.6 vs 7.8 (P = .41)

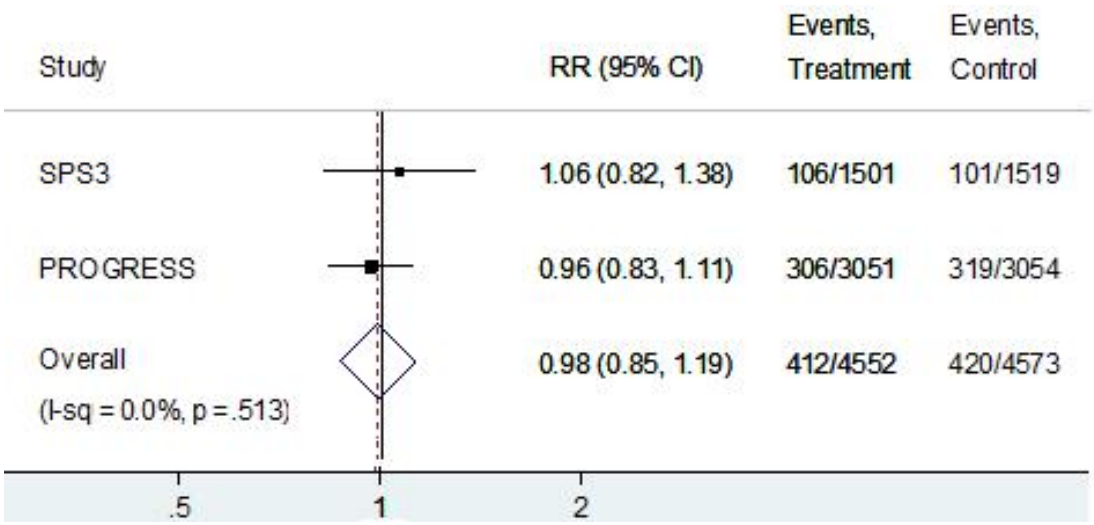
Study Comparison, T vs C	Age groups (N patients)	Results comparing T vs C, by outcome and age group
		HR ≤ 80 vs ≤ 85: 1.02 HR ≤ 80 vs ≤ 90: 0.86
JATOS[24] SBP < 140 vs < 160	< 75 (n = 2549) ≥ 75 (n = 1869)	RR (95% CI) P-value for interaction term in Cox regression with treatment, age, sex, and interaction between treatment and age as covariates: Cerebrovascular disease: < 75: 0.65 (0.29 to 1.45) ≥ 75: 1.52 (0.77 to 3.00) P = .03 Cardiovascular disease: < 75: 0.77 (0.26 to 2.25) ≥ 75: 1.07 (0.43 to 2.67) P = .50 Renal failure: < 75: 0.60 (0.09 to 3.91) ≥ 75: 1.25 (0.22 to 7.00) P = .75
SPS3[39] SBP < 130 vs 130-149	< 75 (n = 2526) ≥ 75 (n = 494)	HR (95% CI) Total mortality < 75: 1.13 (0.80 to 1.59) ≥ 75: 0.83 (0.53 to 1.29) Vascular death < 75: 1.17 (0.68 to 2.01) ≥ 75: 0.42 (0.18 to 0.98) MI: < 75: 0.91 (0.56 to 1.48) ≥ 75: 0.77 (0.23 to 2.52) Recurrent stroke: < 75: 0.77 (0.59 to 1.01) ≥ 75: 1.01 (0.59 to 1.73)
VALISH[26] SBP < 140 vs < 150	< 75 (n = 1233) ≥ 75 (n = 1846)	Combined sudden death; stroke; MI; death due to CHF; other cardiovascular death; unplanned hospitalization for cardiovascular disease; and renal dysfunction, HR (95% CI): < 75: 0.74 (0.35 to 1.56) ≥ 75: 0.95 (0.60 to 1.51)
Studies that compared more vs less intensive treatment for hypertension		
ADVANCE[27]	< 65 (n = 4536)	Major macrovascular or microvascular events combined, unadjusted RR (95% CI):

Study Comparison, T vs C	Age groups (N patients)	Results comparing T vs C, by outcome and age group
(Perindopril + indapamide) vs placebo	≥ 65 (n = 6604)	< 65: 0.95 (0.82 to 1.09) ≥ 65: 0.90 (0.81 to 1.00)
HYVET[36] Indapamide vs placebo	80-84 (n = 2807) ≥ 85 (n = 1038)	HR (95% CI): Total mortality: 80-84: 0.76 (0.60 to 0.97) ≥ 85: 0.88 (0.64 to 1.20) Cardiovascular mortality: 80-84: 0.75 (0.55 to 1.05) ≥ 85: 0.82 (0.53 to 1.32) Cardiac events: 80-84: 0.64 (0.49 to 0.83) ≥ 85: 0.75 (0.50 to 1.12) Stroke: 80-84: 0.70 (0.46 to 1.06) ≥ 85: 0.59 (0.27 to 1.29)
SHEP[8] Chlorthalidone vs placebo	60-69 (n = 1963) 70-79 (n = 2124) ≥ 80 (n = 649)	Stroke RR (95% CI): 60-69: 0.74 (0.48 to 1.14) 70-79: 0.65 (0.46 to 0.92) ≥ 80: 0.53 (0.32 to 0.88)
Syst-China[20] (Nitrendipine ± Captopril ± Hydrochlorothiazide) vs placebo	< 65 (n = 1079) 65-69 (n = 699) ≥ 70 (n = 616)	Unadjusted HR (P-values interpreted from graph): Cardiovascular mortality: < 65: 0.34 (P < .05) 65-69: 0.67 (P = ns) ≥ 70: 0.89 (P = ns) Fatal + nonfatal cardiovascular events: < 65: 0.54 (P < .05) 65-69: 0.80 (P = ns) ≥ 70: 0.62 (P = ns)
Syst-Eur[40,69] Nitrendipine vs placebo	60-69 (n = 2501) 70-79 (n = 1753) ≥ 80 (n = 441)	Unadjusted HR (95% CIs not reported; P-values interpreted from graph):[69] Total mortality: 60-69: 0.59 (P = *ns*) 70-79: 0.58 (P < .05) ≥ 80: 1.11 (P = ns) Cardiovascular death: 60-69: 0.58 (P = ns) 70-79: 0.49 (P < .05) ≥ 80: 0.97 (P = ns) Cardiac events:

Study Comparison, T vs C	Age groups (N patients)	Results comparing T vs C, by outcome and age group
		60-69: 0.64 (P = ns) 70-79: 0.69 (P = ns) ≥ 80: 0.79 (P = ns) Stroke: 60-69: 0.46 (P < .05) 70-79: 0.54 (P < .05) ≥ 80: 0.67 (P = ns) "In Cox regression with adjustment applied for significant covariates, the treatment-by-age interaction term was significant (P = .009) for total mortality and nearly significant (P = .09) for cardiovascular mortality, indicating that the benefit of treatment was lost after the age of about 75 years. In contrast, the treatment-by-age interaction for the combined fatal and nonfatal events was not statistically significant."[40]
TRANSCEND[35] Telmisartan vs placebo	< 65 (n = 2375) 65-74 (n = 2576) ≥ 75 (n = 975)	Composite outcome of cardiovascular death, myocardial infarction, or stroke: No significant age interaction (P = .80)

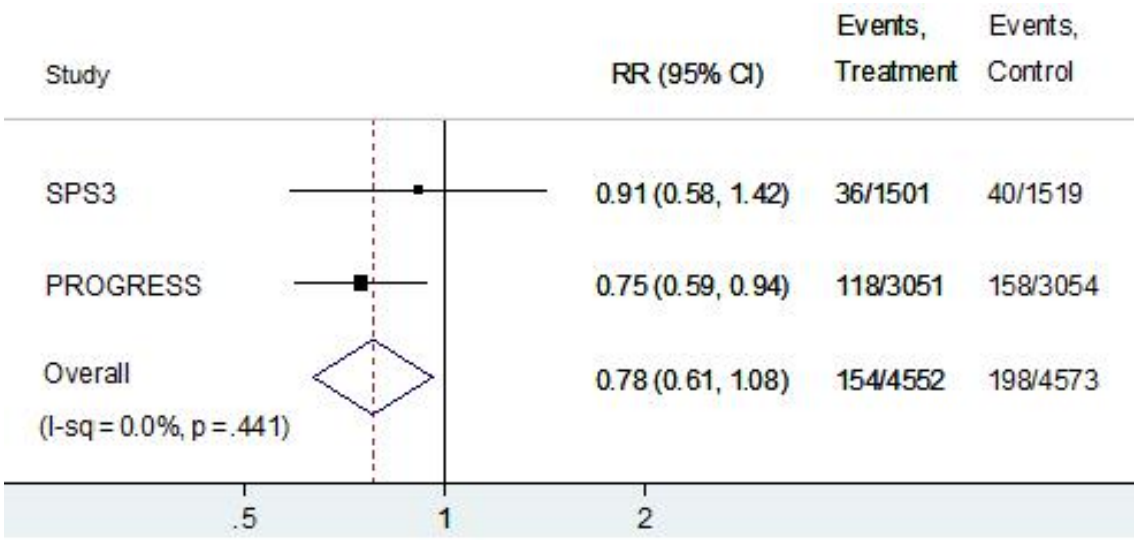
Abbreviations: ACCORD = Action to Control Cardiovascular Risk in Diabetes; ADVANCE = Action in Diabetes and Vascular Disease; C = comparator/control; CHF = congestive heart failure; CI = Confidence interval; DBP = Diastolic blood pressure; HOT = Hypertension Optimal Treatment; HR = hazard ratio; HYVET = Hypertension in the Very Elderly Trial; JATOS = Japanese Trial to Assess Optimal Systolic Blood Pressure in Elderly Hypertensive Patients; MI = myocardial infarction; N = Number randomized; ns = not statistically significant; RR = relative risk; SBP = systolic blood pressure; SHEP = Systolic Hypertension in the Elderly Program; SPS3 = Secondary Prevention of Small Subcortical Strokes; Syst-China = Systolic Hypertension in China; Syst-Eur = Systolic Hypertension in Europe; T = treatment; TRANSCEND = Telmisartan Randomized Assessment Study in ACE Intolerant Subjects with Cardiovascular Disease; VALISH = Valsartan in Elderly Isolated Systolic Hypertension.

Figure 8. Relative risk of mortality in trials of patients with history of stroke



CI = confidence interval; PROGRESS = Perindopril Protection Against Recurrent Stroke Study; SPS3 = Secondary Prevention of Small Subcortical Strokes

Figure 9. Relative risk of major cardiac events in trials of patients with history of stroke



CI = confidence interval; PROGRESS = Perindopril Protection Against Recurrent Stroke Study; SPS3 = Secondary Prevention of Small Subcortical Strokes

APPENDIX E. PEER REVIEWER COMMENTS AND AUTHOR RESPONSES

Question Text	Reviewer Number	Comment	Response
Are the objectives, scope, and methods for this review clearly described?	2-10, 12, 15, 16	All responded: Yes	
Is there any indication of bias in our synthesis of the evidence?	2-10, 12, 15, 16	All responded: No	
Are there any published or unpublished studies that we may have overlooked?	2, 3, 5, 6, 9, 10, 12, 15, 16	No	
	4	Yes - I'm sure it wasn't overlooked, it just hasn't been published yet. SPRINT. NIH held press conference today. because it has not yet been published it cannot be included in the meta-analysis, but it could and probably should be mentioned in the narrative as being a study to consider when results are published.	SPRINT has been included
	7	Yes - The SHEP study did report a significant increase in falls in the intervention vs control group (which you note in your table but not the text).	We added this information in the text.
		There is a very small observational study (JAMA Int Med, Mosello, 2015) finding that the combination of multiple blood pressure medications and lowest tertile of BP among patients with dementia was associated with greater loss of MMSE points.	This was published after our search. The results are in line with several other observational studies that fell within our search dates. All of the observational studies of cognition, including this one, have some issues with confounding. Given that there were 7 RCTs examining cognitive outcomes and that we've already included several obs studies with similar findings as this one, it is unlikely that the addition of the Mosello study would alter results.
		There is a very recent trial of withdrawal of blood pressure medications in Leiden (the DANTE trial) Annals Internal Medicine 2015 (last week), by Noonen et al, that did not find short term improvements in cognition.	Interesting study – falls out of the scope of our key questions.
	8	Yes - I would not say overlooked, but the SPRINT study is obviously going to be influential.	SPRINT has been included
Additional suggestions or comments can be provided below. If applicable, please indicate the page and line numbers from the draft report.	2	See comments in the attached file.	
		A matter not addressed in this review is the important but controversial issue of BP management in the subacute period after stroke. In general, there is fear that dropping BP in the first hours post-stroke (when collaterals may be perfusing at-risk brain) can extend damage in stroke and worsen outcomes, yet a few studies using ACE-I or ARB drugs begun within 24- to 48-hours of stroke decreased recurrence or mortality. I would urge caution in applying the results of long-term trials to the acute post-stroke period.	We have added some language to the methods and results to clarify that we did not examine management of acute stroke.
		While no suggestive signal was seen in this review, the issue remains as to whether some anti-hypertensive individual drugs or classes of drugs might have superior outcomes independent of BP targets or actual reduction in BP achieved. This has been suggested for ACE-Is and ARBs for the outcome of initial or recurrent stroke.	Noted. We were not able to identify a clear pattern, but one would really need to look at comparative effectiveness studies and individual level data to answer this question.

Question Text	Reviewer Number	Comment	Response
	3	P31 line 21: I would add that the SPS 3 trial showed a statistically significant reduction in intracerebral hemorrhage, a type of stroke with high mortality.	Noted. We've reported the outcome of all strokes. SPS3 reports 5 different stroke outcomes including a variety of hemorrhagic stroke outcomes. The intracerebral hemorrhage outcome was the only one with $p < 0.05$. Moreover, the rate of disabling or fatal strokes with similar in both groups. It would be misleading for us to report one secondary outcome and not all others.
		P 46, line 52: Discussion: Did any of the studies report sex differences in the benefits of BP lowering?	We did not systematically evaluate this question.
		P 46, line 47: Would add that even though the absolute benefit may be small, the population and health system benefits may be worthwhile	noted
	6	Table on page 5,line 11 comment on mortality says "more moderate targets (SBP<140mm Hg). Shouldn't it say (SBP>140)? Page 6: list of abbreviations under the table (line 33) does not include ROB nor is ROB listed in the abbreviations list on pages 8-9. Page 20, line 15 "monotherapy with benzene"--should that be benazepril instead of benzene? page 32, line 33,"described and increased risk" should be "described an increased risk"	Appreciated – all noted and corrected.
	8	I am including these as attachments.	
	9	The report is well-written.	Thank you
		Page 2, line 39, did cough and hypotension vary with age?	There were no data on this.
		Table 10 provides information about risk of bias, but little text is provided about how these assessments were made.	We followed standard methods for assessment (ref included). We revised table to include more detail, especially for areas in which we noted flaws.
		Page 31, line 9, SPS3 had a "rigorous" definition of stroke as stated, but it was also restrictive to one type of ischemic stroke (namely only lacunar infarcts); therefore, results may not be generalizable to other stroke types (e.g., hemorrhagic stroke or large artery atherosclerotic ischemic stroke). How may the results be applicable to Veterans with a history of transient ischemic attack?	We've revised the language to be more clear about the inclusion criteria in both the SPS3 and PROGRESS trials. The progress trial did include a broader definition of stroke and TIA.
		Page 45, line 18 (typographical error, errant 6).	noted
		General comment: consider hyphenating "treat-to-target" studies throughout (there are occasions without use of hyphens.	done
		Limitations Section: consider including a statement that the included trials used pharmacologic treatment of hypertension and therefore excluded trials that focused on non-pharmacologic approaches to hypertension management.	We have added this.
		A statement about domains where additional research is needed would be of interest.	We have added a brief future research section.
	10	Although a few studies are of questionable quality, they are adequately handled and don't bias the conclusions. Although this was written before SPRINT was announced, if not mentioned, you could add that it may address this question, or you could comment that it is unpublished at this time, but shows benefots for a population average age 68 years.	SPRINT has been included
	15	see attachment for comments	

Question Text	Reviewer Number	Comment	Response
	16	A thorough review of evidence regarding intensity of treatment for hypertension that provides guidance but perhaps more notably identifies the need for additional investigation. 1. Would encourage consistency in the use of abbreviations (i.e. once define use consistently thereafter - risk of bias/ROB). 2. Would also recommend more consistent use of symbols (i.e. < & >) to define blood pressure targets rather than prose ((i.e. 140 mm HG or less). 3. Forest plots are somewhat blurred and would benefit from sharpening. 4. Please include justification for exclusion of comparative effectiveness studies.	Noted and revised accordingly

Additional comments – Reviewer #2	Response
Page 3, Line 6: It would be useful to state whether the difference was significant or not, and by what p value, given the rather high NNTs. (**also insert comma after NNT ##)**	As above, all the #'s have changed. We present CI and NNT throughout
Page 11, Line 54: An interesting and controversial topic is whether some anti-hypertensive individual drugs or classes of drugs have superior outcomes independent of BP target or actual reduction in BP. This has been suggested for ACE-Is and ARBs for the outcome of initial or recurrent stroke. I understand this was outside the scope of your review, but did you find enough in the literature to suggest this as a future topic for exploration?	Agree an interesting topic, but outside scope – as we note in limitations partly this would be answered by comparative effectiveness studies which we did not include.
Page 11, Line 59: We surmised the **(change "the" to "that")**	Noted
Page 15, Line 37: I gather from the below that no studies were excluded if they targeted DBP rather than SBP?	Correct, we have clarified inclusion/exclusion criteria
Page 15 Line 53: In an effort to better understand treatment effects among different age subgroups, we explored the possibility of gathering data to conduct analysis (**change to analyses**) based on individual patient data from blood pressure treatment trials.	Noted
Page 16, Line 6: "We anticipate using data from these six trials to conduct meta-analyses examining blood pressure treatment benefits and harms in those age 60-69, 70-79, 80-89, and over age 90." Will the results be disseminated in a subsequent report?	We anticipate writing up a separate manuscript of these results.
Page 18, Line 11: "Overall, there was little to no consistent evidence of a clinically significant incremental benefit of treating blood pressures to levels substantially below current guideline recommend (**change to recommended**) levels of 150/90 in patients over age 60."	Noted
Page 18, Line 41: "The remaining studies had primary outcomes related to renal disease or microalbuminuria27,31 or additional outcomes not specified **(delete specified)** of interest for this review (LVH regression).20"	Noted
Page 18, Line 43: Among trials which specified a particular medication as first-line therapy, seven used ace (**ACE - term should be defined at first use)** inhibitors or angiotensin-receptor blockers, 5 used calcium channel blockers, and six used diuretics (Tables 2 and 3).	Noted
Page 23, Line 25: You might want to comment on reduced significance (p value) with population subset. However, it's confusing that CI does not include 1 yet $p > 0.05$. Is this a mult. comparisons adjustment?	Again, all #'s have changed. We use CI preferentially throughout.
Just a note that all of the figures appear blurry (out of focus) in my copy.	Noted – we have tried to improve the appearance of the figures.
Page 51, Line 18: Another issue not addressed is the important but controversial issue of BP management in the subacute period after stroke. In general, there is fear that dropping BP in the first hours post-stroke (when collaterals may be perfusing at-risk brain) can extend damage in stroke and worsen outcomes, yet a few studies using ACE-I or ARB drugs begun within 24- to 48-hoours of stroke decreased recurrence or mortality. Perhaps a subject for a future ESP review?	Agree – interesting topic, but out of scope (and we added statement clarifying that we did not include acute stroke).

Additional comments – Reviewer #4	**Response**
Overall, this is an excellent review of the evidence. These are comments that may help make the review more useful to clinicians:	
- It is very helpful that the achieved BPs in the trials has been included.	
- The lack of evidence about effect of comorbidity burden is striking and should be a call to clinical trialists to gather more information in that area.	We added this to future research section
- Possibly more could be done with the available information about ADE rates, for example, in one place there is mention that 4 of 10 trials found increased withdrawals due to ADEs in older individuals (particularly cough and hypotension, with hypotension being potentially serious). Page 7 could use more cautions re the ADE statements.	We have added a statement in discussion about potential seriousness of hypotension given the increased rate of syncope in 2 studies.
- There is mention that HYVET study excluded patients with dementia or nursing home; however, my recollection (should be checked with source data) is that the individuals in HYVET were quite healthy for age (not just "not frail" but healthier than average). Since this group is a major contributor to information about lack of impact on adverse events in those over 75, it is important to provide more detail about how health this group was.	We have created a new table focused on exclusion criteria of each trial to better examine this issues of applicability
- In general, I think it would be good to make more visible the issue of to whom the findings may be generalized. Clinicians are looking for guidance. It is important, for example, not to assume that because HYVET had certain findings that these findings would apply to all patients over age 80.	See above
o It would be helpful to have information in the tables with more detailed descriptions of the study populations at baseline, to make it clearer what where the characteristics of the study populations, so that clinicians managing older Veterans and other older adults can more easily compare the patients in the studies to the patient about whom they are making clinical decisions, to understand how similar (or not) their patient may be to the patients in the clinical trials that form the evidence base.	See above
o Further along those lines, it would be helpful to describe in the narrative some comparisons of the baseline characteristics and the events in the study groups with the typical prevalence among Veterans (who receive their care in VA) in comparable age groups. For example, there is mention of low stroke or other event rates, but the expected rates in the typical Veteran population are not shown so it is hard to make the comparison.	We have included more about study event rates. The rates in Veterans will vary markedly depending on their risk factor profile. We have added more discussion about risk factor profile and study inclusion in the treat to target trial section
o Although there were no studies with evidence about the role of comorbidity, it would be helpful at least to describe to the extent the data are available in the study reports the baseline extent of comorbidity.	See above
o Where ADEs are at low rates, comparison of the rates in general population , or ideally in VA patient population, over time would be helpful for comparison	We have noted comparison of ADEs within trials, but do not have data on these ADEs in general population
- A large study of BP targets is underway in the SPRINT trial. A press briefing by NIH today (9/11/2015) released results. The paper has not yet been peer-reviewed and published, so it cannot be included in the meta-analysis, but some mention of this study should be in this report. Some information from the trial that we would hope to see in the published report:	SPRINT has been included
o subgroup analysis for the older patients (by decades within the older age groups), with outcomes, length of time in trial, achieved BPs, variability in SBPs, pulse pressures, etc, length of time in trial and at target BP and/or on final number of drugs (i.e., how much time for ADEs to become apparent), quality of life reports, intolerance rates for drugs	These analyses would require individual patient level data – we are working on individual patient data meta-analyses with data from 6 trials to get at some of these issues (eg - outcomes by age decile)
o baseline data on comorbidities broken down by age group	Most studies did not report comorbidities in this way.
o analyses of interactions of age and comorbidity and ADEs: - It may be hard for some clinical readers to understand why some studies were included by the criterion of comparing more intensive to less intensive therapy, but other studies were not. There are several studies that compare drug therapy to placebo, so appear to be studies of impact of treating HTN, or studies of impact of a particular drug, rather than specifically more vs less intensive treatment (although drug therapy vs placebo is certainly more intense vs less intense). Without pulling all the studies and looking at the underlying study design, it isn't easily clear to the reader why these studies of drug vs placebo are included while other studies of drug vs placebo are not.	We have tried to clarify this in the methods section under study selection. We did not exclude any studies of drug vs placebo that met other criteria (age and hypertensive population).

Additional comments – Reviewer #4	Response
- the Limitations section acknowledges that there may be specific medication effects that are not part of the analyses in this ESP. this is an important point. There are specific drugs with more effect on outcomes (as in ALLHAT) and there are specific drugs that may, at least theoretically, have lower rates of particular ADEs (for example, thiazide diuretics may block calcium loss and may theoretically decrease risk of osteopenia). I agree that with the already limited number of studies with which to examine the key questions it would seem to be impossible to disentangle the effects of particular drugs.	Noted
- In addition to evidence regarding comorbidities, it would be useful to have evidence about the impact of the total number of medications that patient has apart from antihypertensives. As another descriptive factor about the study populations, information about total number of meds at baseline, as compared with total number of meds for VA patients of same age, would help clinicians with knowing how well the study patients resemble the patients they are seeing every day.	Most studies did not report this information.
- with the NNT of 10,000 given on page 28, seems that any conclusions about stroke should be very cautious.	We have re-run analyses as noted elsewhere and these numbers have changed.

Additional comments – Reviewer #8	Response
I appreciate the concise executive summary. I was surprised that there was no discussion of how to handle HOT, which used DBP targets and the emphasis on achieved BP rather than target BP. In many cases, the studies were described as not having a target BP, but usually there was some information about the approach, though it was not used in this summary, presumably because the details were not precisely defined. I also did not find a justification for combining very disparate intervention and control interventions. Beyond the general idea that one arm achieved at least a tiny bit lower BP than the other in every study, there seems little justification for combining a placebo controlled study where the control arm had only a target SBP of less than 219 mm Hg to a study like HOT, where everyone targeted a DBP below 90, and some lower still. It does not appear the authors considered generating a more qualitative summary or at least some discussion of the implications of combining these very different studies. I did appreciate they looked at a number of more homogeneous subgroups, but the criteria were limited to baseline characteristics or achieved control in the intervention group, it seems. The fact that some of the studies had almost no difference in achieved BP, or had very different BP goals/permitted levels for the less intensive group was not addressed.	Appreciate the insightful comments. We have markedly changed much of the results section and the summary of evidence table both because we re-ran all analyses with SPRINT and in part to respond to these comments. Most of the RR/ARR have changed. We have clarified the rationale for synthesizing the data the way we did – hopefully it will be clear that we examined the data from different directions and that we clarified that the treat to target trials are distinct from the others. We revamped the way we analyzed and discussed the HOT trial. We also, hopefully, more clearly present the rationale and results of the numerous sensitivity analyses which should get at some of the issues noted here. For instance, we ran analyses excluding trials with minimal achieved differences in BP. We also included more detail under the "trial characteristics" section. Finally, we agree that the combination of all studies is relatively meaningless – we've explained this in results and deleted the combined analysis.
The table on page 5 has some useful numbers, though I found some confusing. In the first, mortality, row the point estimates of RR are actually very significant, even though they are not statistically significant. I think that the large N of the studies suggests that they pretty definitively ruled out an important benefit, but actually, the ARR seen in the subset is a pretty important change – the idea of preventing one death for every 100 persons treated is huge. It is a little hard to interpret since you use % when most people would have events per 100 pt – years. Here I can't tell if is 1% a year, or 1% over 20 years of treatment – pretty different things.	See above - these numbers have changed with new analyses
The stroke row is a really confusing one. The apparently statistically significant RR of 0.72 seems like it would be clinically important – a 28% RR reduction is as good as or better than we see with statins and MI in people with CVD!! But then the ARR is 0.01% - that is 1/10000. For me to reconcile these two numbers, I have to have an event rate of 3.6/10,000 compared to an event rate of 2.6/10,000. This seems like the stroke rate per week in some high risk groups and makes the NNT of 10,000 not so unimpressive after all!!! Again, the use of percentages is confusing in an ARR presentation. I think that a statistical explanation of these numbers would help me. I recognize that they likely come from different approaches to synthesizing data, and therefore can't be quite as simplistically interpreted as if they came from a single trial, but the relationship between ARR and RR needs to be transparent.	See above – numbers have changed.

Additional comments – Reviewer #8	Response
Overall, it seems very hard to say that the evidence justifies the conclusion "Overall, we found moderate-strength evidence that using a systolic blood pressure target of 140 mm Hg or less did not appreciably improve outcomes in older patients compared to slightly higher targets." Rather, I would say you "found little evidence that using a target of 140 mm Hg or less appreciably improve outcomes, but (you) cannot exclude as much as a 1/3 reduction in most important cardiovascular outcomes." If you disagree, you need to reconcile your point estimates and 95% CI with the conclusions in some way that I don't see in the current version.	See above – we have revised the conclusions based on newer analyses
I think the conclusion on stroke is not very useful because it does nto discuss a target but a range. And the range is wide enough that people are going to wonder – "so what do you mean? Do you want them below 130 or do you want them below 140?" It is going to take an extra drug to get someone from 139 to 129, in most cases. So you need to describe what the data say iin a little more detail. Are you saying that <130 was better than < 150 and < 140 was better than < 150, but we can't tell if 130 or 140 are any different? Then it seems to me you are saying you can't tell if any further reduction below 140 is worth it. When you discussed the overall numbers, it seems you would not endorse < 140 as better because there was no studies where you took people in the 140-160 range and pushed some lower and left some above 140. So to me, you should say you don't have any studies of people < 140 that showed any additional benefit. So the benefit of <130 is not shown at all.	Agree – we have tried to clarify exactly what each trial showed.
FULL SYNTHESIS	
I won't complain about the summary or the referring to the 'rate' of events without any evidence of a time frame, since I already said I found it confusing. I think that given the persistent references to the relative unimportance of a relative risk reduction of 25% some discussion of why they have that opinion is appropriate. It is greater than the benefit seen in some statin trials for primary and even secondary prevention, and similar to that seen with treatment in younger individuals. I can't account for some of the ARR calculations that suggest a remarkably small ARR in the setting of a significant event rate and a reasonably large summary estimate of RRR. But at least a reasonable approach would be to apply the observed RRR to a typical event rate in the target population and consider whether that would be considered a little more important than they consider the statistically significant drops in mortality and stroke, based solely on the quantitative combined analysis.	As above, we have redone our analyses with SPRINT and with the HOT subgroups combined differently so the RR and ARR have changed substantially as a result.
The comment on less heterogeneity in mortality among the 3 trials comparing <140 to higher targets, while I assume is mathematically true, is counterintuitive, since they include both the study with highest RR and the study with the lower RR among the 6 in Table 2. It really reflects the fact that with these smaller trials the fact that the results are quite disparate is not as statistically unlikely. Maybe you could tone that comment down. And the summary OR is really just the impact of the Wei study, which has 138 of the 164 deaths. I wonder if you should be making some comment on the Wei study, which is quite influential both in this analysis, and in the overall comparison of less intensive to more intensive trgets. The Wei study has a mortality in the less intensive arm that is more than 20% over 4 years. In contrast, the VALISH study has lower than 2% mortality over 3 years. The ages are roughly comparable, the amount of CAD is comparable, and the baseline BP is actually higher in VALISH. There is 10% more DM in the Wei study. But the difference in mortality is ENORMOUS. And the control group ends up with mean SBP around 150 in Wei, but 142 in VALISH even though both are trying to keep the control below 150 mm Hg (to keep a person reliably below 150, one must have a mean quite a bit below 150). The delta in SBP between the groups is 14 compared to less than 5 mm Hg.	We have revised this section substantially and no longer include this statement. Also, there were several peer review comments about the Wei study – we agreed that it seems an unusual study and and was an outlier. We conducted sensitivity analyses with and without this study.
The surprising stroke ARR versus RR numbers are again seen here, again without comment. I can't figure out the math on the ARR. Being a simple person, I see VALISH, a study in Japan, where in 3 years of follow up, in people mean age 76 years old, all with hypertension, the stroke rate is 1/100. Here, the ARR is 7/1000, about 10 times the estimated summary ARR – in the other studies the ARR is even higher, often much higher, except in JATOS, a study of 4000 participants, also from Japan, where there is no benefit for stroke. Yet the summary estimate is < 1/10,000? This makes no sense. The funny treatment of HOT, where you throw the <85 people in the <90 group makes it a little harder to interpret. As I recalled, when I looked up the actual hot numbers, the <85 did the worst of anyone, so it did not obscure a big benefit of BP lowering to put them in the <90 group – just the opposite – but it does not make sense, since it is targeting a number less than current guidelines, which is what you said you wanted to count as the intensive group.	As above, we have revamped our analyses of HOT. Agree that it made more sense to dichotomize 80/85 vs 90. We also conducted additional analyses without the middle group. Because the HOT was such a large trial, these changes had a large impact on results. We added a paragraph to results focused on HOT and the different analyses.

Additional comments – Reviewer #8	Response
The table 3 would benefit from some information about the targets in the intervention group versus controls. Thus, in SHEP the comparison is a target SBP of 140 versus no target SBP, but both groups were treated for a target DBP of <90 – i.e., no matter how high the SBP don't treat the control group unless DBP > 90 mm Hg. In the Sys-Eur study, the control group was treated if they got above 219/99. In other studies in this table, e.g., TRANSCEND, all patients were fairly well controlled and the intervention simply added a drug. Thus, I don't see this analysis as very amenable to combination.	See above. We have examined the data quantitatively from several different angles, and added more description of the differences in studies and how these prompted various sensitivity analyses.
The cardiac event data (Figure 8) is also kind of interesting in that the three Asian studies have zero benefit in reducing an already incredibly low cardiac event rate – again, note how old they are and still very few events. In the American/European studies, lots of benefit. ACCORD is harder to interpret and also had a really low SBP target. Recall that recently we learned that high risk Japanese people don't benefit from aspirin in primary prevention of MI. Although you note the heterogeneity, you don't try to interpret it. I think you have a little freedom, and perhaps obligation to think about why there is heterogeneity, even though you are trying to make this part of the review a quantitative synthesis.	We have added a paragraph to the results and statements to the discussion describing the differences in event rates and speculating whether or not these may have accounted for some of the heterogeneity.
I am not sure why the DBP< 85 group is included with the DBP < 90 group in the HOT study. I would just drop the <85 people if you don't want to consider them separately.	See above
The ARR being greater with greater age is an artifact of higher event rates, not a bigger effect – note the RR are essentially the same.	See above
In the discussion of the results of the trials comparing more and less intensive therapy rather than competing targets, they note that the trials showing the largest ARR are ones with achieved SBP > 140. I would have noted that they are the ones with the largest delta SBP and the ones with the highest even rate in the control groups.	These #'s have changed. We focus now on the baseline BP subgroups (which overlap substantially with achieved BP groups) – the event rates are actually not higher in the higher baseline BP groups (overall).
The analysis of post stroke intensive versus less intensive is interesting in that it is positive and the ARR is considered nontrivial by the authors. I note that the event rate in both trials was over 10% for stroke alone and the delta SBP was 9 mm Hg and 11 mm Hg in the PROGRESS and SPS3 respectively	Noted
I found that the discussion of Key Question 2 was much more forthcoming about the difficulty of quantitatively combining very different studies and (perhaps consequently) very different results.	Noted
The discussion of KQ 3 found that ARR is higher when event rates are higher. This seems consistent with what one sees if one looks at BP Rx in general. Studies like STOP (Swedish Trial in Old People) and EWPHE (included in this review), with high event rates and studies like the MRC I and II trials, with low event rates, have similar RR (and RRR) but STOP and EWPHE had much larger ARR.	Noted
I found the discussions of KQ 4 and 5 similarly well calibrated to the relatively scant evidence.	Noted

Additional comments – Reviewer #15	Response
General comments: This is an excellent and helpful report. Very well written.	Thank you.
Executive summary:	
Next to last line intro---leave out "proposed" since it is done	Done
Last line-----I would be more specific about what older is in this report (eg age> 60)	done
Quality assessment---were observational studies reviewed for quality?	We noted methodologic deficiencies of the few included observational studies in the cognitive study section.
Key findings---line 2----need "with" between compared and more	done
Line7---leave out "more" and state direction (what is the effect?)	done
Introduction:	
~ line 8---I think it should read "age" rather than "ages" groups	done
Table 1---GREAT TABLE	Thank you
Data synthesis:	
I would rewrite 2nd sentence----"We do not present CVD mortality data in this report since ….."	done

Additional comments – Reviewer #15	Response
Study level meta-analysis sxn----last line 2nd p---what currently defines mild htn? Do you want to include a lower boundary? I thought mild was 160-180?	Done
Detailed study results:	
1st p---I think you should say something like "Among 20 studies, X showed benefit from treating more intensely/to target. When data from these studies was combined in meta-analysis, more intensive……"	We revised the results section and have added some more detail to overview section re: # studies showing benefit
I don't understand how you can have a RR of 0.89 with CI 0.83-0.96 and 0 ARR	These #'s have changed with re-analysis
3rd paragraph, last sentence----would be helpful to add the range of bp's (160, range 166-174). Also in 3rd p, how much absolute risk difference do these 4 studies acct for?	We've revamped the entire results section and have included more information about the sensitivity analyses and resultant changes in ARR.
I think adding a figure/forrest plot for CVA and CAD for those younger/older than 70 as you do for total mortality would be very helpful (like figure 2)	We have revised KQ2 and included the age meta-analysis results here. However, because of concerns for ecologic fallacy we did not include the forest plots as we can't really use them to examine age-treatment effects with any degree of confidence
The Wei study stands out both for its results and control event rate. Note that the number of cardiovascular events is similar, the number of strokes 15 less in the I group and 36 total differences in death between the 2 groups. I am worried about the randomization. What are they dying of? Review of the quality ratings doesn't suggest this has low risk of bias to me.	Agree. We have revised accordingly. We also re-ran analyses without 2 other high risk of bias studies (we had overlooked this in first draft)
Page 28----the ARR of 1% for total mortality seems fairly big.	Numbers have all changed with SPRINT and additional analyses
Figure 9----title----add in "comparing x to x"	Done
Note the format of KQ 2 differs from KQ1	We've added subheaders to make more similar
3rd p, line 3 - "an" rather than "and"	Noted
SHEP description in p 3. I might state this: "conversely, the SHEP trial identified a decreased risk of stroke when the treated systolic blood pressures in patients with baseline bp's above 170 was less than 150 (mean X)" to be really clear.	Done
Renal outcomes-----I am uncertain about this but it might be helpful to provide some numbers for changes in creatinine/GFR since this is such a common occurrence in practice.	Specific renal outcomes and numbers are presented in Table 6
Cognitive outcomes-----in general (and this is true throughout) I recommend being more specific about bps rather than stating "moderately tight" as in first P of this section. Similarly, in the last paragraph "large proportion"----what % - this might matter.	The specific BPs are listed in following sentence. Re: large proportion with missing data – these numbers are in table –added the numbers into paragraph as well.
Falls/fractures----thoughts on the non-spine fractures? NSS but interesting. ? thiazides?	Unclear – mainly looking at this as potential harm – the trend towards benefit was seen in 2 studies but not in a third. Not sure we can much of the potential reduction in fracture risk.
The orthostatic hypotension stuff d/n make sense to me. Thoughts?	As we note, a number of trials found increased rates of hypotension. Three trials looked at syncope and 2 found a higher rate. We added sentence to discussion suggesting that the hypotension has potential to be serious given the excess rate of syncope in 2 trials.
Summary/discussion:	
Line 2 "compared *with*…."	Noted
Need to discuss the 1% absolute mortality reduction a little bit more when you note that move aggressive treatment didn't "appreciably" improve outcomes	As above, all numbers have changed
Mid paragraph 1-----can you be more explicit rather than say "modest" effect?	We have put in NNT throughout
Paragraph 3. It would be interesting to find out usual stroke rates in the general age specific population given the low event rates you note.	Added a paragraph to discussion about event rates.
Tables 2 and 3----it might be helpful to add publication dates in column 1. I think there is a wide range	Agree. Done.