Systematic Review for the 2017 ACC/AHA/AAPA/ABC/ACPM/AGS/APhA/ASH/ASPC/NMA/PCNA Guideline for the Prevention, Detection, Evaluation, and Management of High Blood Pressure in Adults: Supplemental Tables and Figures

Part 1: Self-Measured Compared to Office-Based Measurement of Blood Pressure in the Management of Adults With Hypertension

Table 1.1 Electronic search terms used for the current meta-analysis (Part 1 – Self-Measured Compared to Office-Based Measurement of Blood Pressure in the Management of Adults With Hypertension).

PubMed Search

1	(Blood Pressure Monitoring, Ambulatory [mesh] OR self care [mesh] OR telemedicine [mesh] OR patient participation [tiab] OR ambulatory [tiab] OR kiosk [tiab] OR kiosks [tiab] OR self-monitor* [tiab] OR self-measure* [tiab] OR self-care* [tiab] OR self-report* [tiab] OR telemonitor* [tiab] OR tele-monitor* [tiab] OR home monitor* [tiab] OR telehealth [tiab] OR tele-health [tiab] OR telemonitor* [tiab] OR tele-monitor* [tiab] OR telemedicine [tiab] OR patient-directed [tiab] OR “patient directed” [tiab] OR HMBP [tiab] OR SMBP [tiab] OR home [tiab] OR white coat [tiab] OR ((patient participation [ot] OR ambulatory [ot] OR kiosk [ot] OR kiosks [ot] OR self-monitor* [ot] OR self-measure* [ot] OR self-care* [ot] OR self-report* [ot] OR telemonitor* [ot] OR tele-monitor* [ot] OR home monitor* [ot] OR telehealth [ot] OR tele-health [ot] OR telemonitor* [ot] OR tele-monitor* [ot] OR telemedicine [ot] OR patient-directed [tiab] OR “patient directed” [tiab] OR HMBP [tiab] OR SMBP [tiab] OR home [ot] OR white coat [ot])	Blood pressure monitoring concept + Self Care concept
2	(office [tiab] OR clinic [tiab] OR primary care [tiab] OR usual care [tiab] OR physician [tiab] OR doctor [tiab] OR clinician [tiab] OR standard care [tiab] OR office [ot] OR clinic [ot] OR primary care [ot] OR usual care [ot] OR physician [ot] OR doctor [ot] OR clinician [ot] OR standard care [ot])	Office / Usual Care concept
3	(Hypertension [mesh] OR Hypertension [tiab] OR hypertensive [tiab] OR blood pressure [tiab] OR BP [tiab] OR hypertension [ot] OR hypertensive [ot] OR blood pressure [ot] OR BP [ot])	Hypertension concept
4	1 AND 2 AND 3	Combine Above

5	(review[pt] OR review[ti] OR comment[pt] OR editorial[pt] OR meta-analysis[pt] OR meta-analysis[ti] OR letter[pt] OR In Vitro Techniques [Mesh] OR guideline[pt] OR case reports[pt] OR case report[ti] OR news[pt] NOT ((review[pt] AND clinical trial[pt]) OR (meta-analysis[pt] AND clinical trial[pt])))	Remove non-trial publications
6	4 NOT 5	
7	(animals[mh] NOT humans[mh])	Remove animal studies
8	6 NOT 7	
9	(randomized controlled trial[pt] OR random*[tiab])	Limit to RCTs
10	8 AND 9	
	Limit to English and 1966-	Add Language and Date Limits

Embase Search

1	Self care/	Self Care concept
2	Telemedicine/	
3	(patient participation OR ambulatory OR kiosk OR kiosks OR self-care$ OR self-monitor$ OR self-measure$ OR self-report$ OR telemonitor$ OR tele-monitor$ OR telemedicine OR home monitor$ OR telehealth OR tele-health OR telemonitor$ OR tele-monitor$ OR telemedicine OR patient-directed OR patient directed OR HMBP OR SMBP OR home OR white coat).ti,ab.	
4	1 or 2 or 3	
5	(office OR clinic OR primary care OR usual care OR physician OR doctor OR clinician OR standard care).ti,ab.	Office / Usual Care concept
6	4 and 5	Combine Above
7	Blood pressure monitoring/	Add Blood Pressure Monitoring concept
8	6 or 7	
9	(Hypertension OR hypertensive OR blood pressure OR BP).ti,ab.	Add Hypertension concept
10	Hypertension/	
11	9 or 10	
12	8 and 11	
13	Random$.ti,ab	Limit to RCTs

14	Randomized controlled trial/	
15	13 or 14	
16	12 and 15	
17	(book or book series or conference abstract or conference paper or conference proceeding or "conference review" or editorial or letter or note or "review").pt.	Remove non-trial publications
18	16 NOT 17	
19	limit 18 to (human and english language and exclude medline journals and yr="1966 -Current)	Add Limits

Table 1.2. Summary of included studies

Study (Author, year)	Inclusion criteria	Exclusion criteria	Sample size	Participant characteristics	Protocol
Midanik et al. 1991(1)	Untreated mild hypertension (average of 2 consecutive office SBP <180 mm Hg and DBP 90-99 mmHg	none	204	Mean age 47 52% women 48% black Mean baseline SBP 144.4 (15.7) mm Hg Mean baseline DBP 91.3 (9.1) mm Hg	- SMBP participants asked to measure BP twice a week, send their logs to study every 4 weeks - told to contact their providers if SBP>220, DBP>120 or <50 mm Hg
Soghikhian et al, 1992(2)	Adults being treated for HTN or with office BP >140/90 mm Hg	Cardiovascular complications (not further defined)	430	Mean age 54 50% women 39% black Mean baseline SBP 137.4 (1.2) mm Hg Mean baseline DBP 86.1 (0.6) mm Hg	- Participants in SMBP arm asked to check their BP twice a week, then mail a log once a month to study investigators. - Investigators mailed the log to patients' physicians
Staessen et al., 2004(3)	Office DBP >95 mm Hg untreated or on no more than 2 BP medications	Heart failure, unstable angina, stage 3-4 hypertensive retinopathy, severe comorbid illness, serum creatinine>2 mg/dl, MI or stroke within 1 year	400	Mean age 54 52% women Mean baseline SBP 160.8 (18.6) mm Hg Mean baseline DBP 101.8 (7.4) mm Hg	-follow-up visits scheduled for both groups at 1 and 2 months, then every 2 months until 1 year -SMBP group measured home BP twice a day for 1 week prior to each visit -goal DBP for both groups 80-89 mm Hg

					-medication titrated according to protocol by study investigators -office BP used for control group, home BP used for SMBP group -if DBP<80 mm Hg then medication decreased, if 80-89 mm Hg no change, if ≥90 mm Hg then increased
McManus et al., 2005(4)	Adults ages 35-75 on treatment for HTN Office BP between140/85 and 200/100 mm Hg	none	441	Mean age 62 48% women 4% black Mean baseline SBP 157.9 (15.7) mm Hg Mean baseline DBP 88.7 (7.3) mm Hg	-SMBP asked to measure their BP in the primary care doctor's office once a month -instructed to contact their physicians for BP outside of range -control group had visits at primary doctor's discretion
Marquez-Contreras et al. 2006(5)	Age 18-80 Newly diagnosed HTN or already on medication but not controlled	Requiring ≥2 medications to control BP, living with someone taking the same medication	200	Mean age 59 49% women Mean baseline SBP 159 (16.6) mm Hg Mean baseline DBP 92.4 (10.8) mm Hg	-SMBP participants asked to measure BP 3 times a week -SMBP and control groups had study visits at 4, 12, and 24 weeks for medication titration - both groups used a monitoring events medication system (MEMS) to track adherence
Verberk et al., 2007(6)	Office SBP >139 mm Hg and/or DBP >89 mm Hg	none	430	Mean age 55 45% women Mean baseline SBP 166.2 (19.3) mm Hg Mean baseline DBP 97.1 (9.9) mm Hg	-SMBP participants asked to measure their BP daily for 7 days prior to each clinic visit -medication for SMBP and control patients determined based on stepped titration protocol

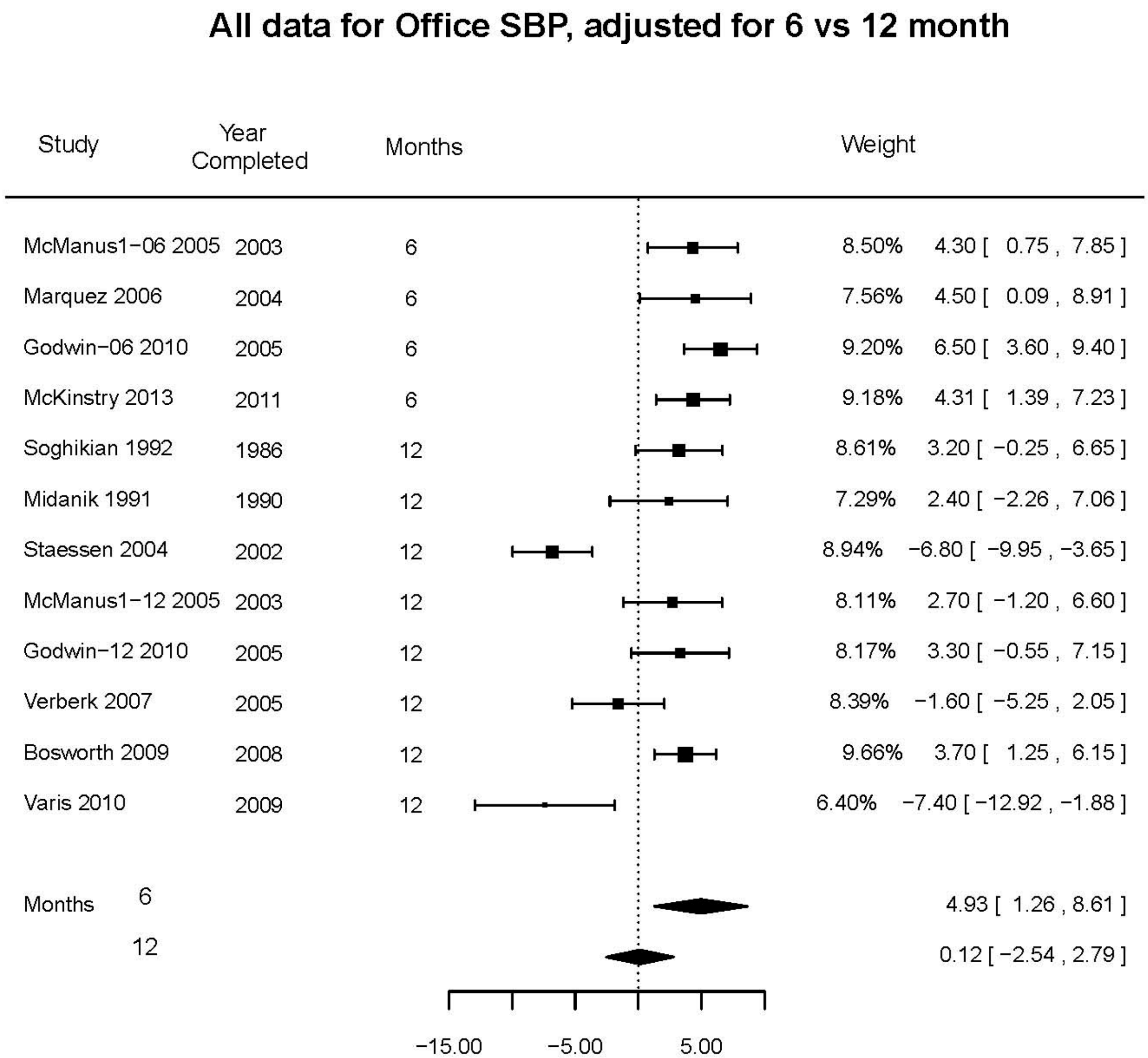
					-treating physicians blinded to patients' groups, told only mean BP from study staff
Bosworth et al., 2009 (7)	Diagnosis of HTN and treatment at least 12 months prior	Comorbidities that would interfere with self-measurement of BP	317 (an additional 319 were randomized to either behavioral intervention or behavioral intervention plus SMBP)	Mean age 62 66% women 49% black Mean baseline BP 125/71	- Patients randomized to SMBP asked to measure BP 3 days a week - mailed BP logs to study team every 2 months - clinic visits for both arms every 6 months
Godwin et al., 2010(8)	On antihypertensive medication but not controlled (SBP≥140 mm Hg or DBP≥90 mm Hg), then underwent ABPM, required SBP≥135 mmHg or DBP 85 mmHg	none	552	Mean age 68.8 51% women Mean baseline SBP 147.3 (9.0) mm Hg Mean baseline DBP 81.2 (8.2) mm Hg	-SMBP participants asked to measure their BP weekly and to bring their log to regularly scheduled visits with their primary doctor
Varis et al., 2010(9)	Initial eligibility based on office BP>140/90 mm Hg, Then all eligible patients measured home BPx3 weeks, those on medication had a washout period. Final eligibility based on home DBP 85-110 mm Hg	malignant hypertension, mean home DBP>110 mmHg during the washout period, stroke or MI within 12 months prior to randomization, unstable angina, uncontrolled or symptomatic CHF, insulin-treated diabetes mellitus, serious hepatic failure (liver enzymes 2x normal values), renal insufficiency (fS-creatinine >140 □mol/l), atrial fibrillation or having	189	Mean age not reported 61% women Mean baseline SBP 159.4 (18.3) mm Hg Mean baseline DBP 97.4 (8.9) mm Hg	-SMBP measured BP 3 times a week, mailed results to their doctors every 5 weeks

		other serious comorbidities			
Oliver et al., 2011(10)*	Uncontrolled HTN on 3 medications, defined as untreated SBP 159-200 mm Hg and/or DBP 99-120 mm Hg; treated SBP 140-200 mm Hg and/or DBP 90-120 mm Hg; current treatment with a statin for LDL>100 mg/dL	Unstable angina, CV event (MI, angina, revascularization, arrhythmia) in the past 6 months, TIA or stroke in the past 6 months, creatinine >2.0 mg/dl or calculated glomerular filtration rate<40 mL/min	62	Mean age 55 68% women 75% black Mean baseline SBP 155 mm Hg Mean baseline DBP 88 mm Hg (SD not reported)	-focused on a high-risk underserved population with HTN and dyslipidemia -both usual care and SMBP groups started on amlodipine/atorvastatin combination pill -antihypertensives added in stepwise manner according to protocol for both groups -both groups seen monthly for BP checks -SMBP group measured home BP daily for 1 week prior to clinic visit -the higher of home or office BP was used for medication titration
Hebert et al., 2011(11)*	Self-described black or Hispanic with uncontrolled HTN (≥140/90 or ≥130/80 for patients with diabetes or CKD) for the last 2 clinic visits, ≥150/95 (≥140/85 with diabetes or CKD) confirmed at recruitment	Medical conditions that prevented interaction with a nurse, including blindness, deafness, cognitive impairment	296	Mean age not reported 59% non-Hispanic black 37% Hispanic 4% black Hispanic	-protocol did not specify frequency of BP monitoring or how often results were transmitted to the study team or providers
McKinstry et al., 2013(12)	Initially screened if office SBP >145 or DBP >85 mm Hg; then further screened with ABPM. Mean ambulatory blood pressure >135/85 mm Hg	BP ≥210/135 mm Hg, atrial fibrillation, receiving care for HTN by a specialist, recent cardiovascular event or other life-threatening illness in last 6 months	401	Mean age 60 50% women Mean baseline ABPM SBP 146 (10.6) mm Hg DBP 87.1 (10.0) mm Hg	- participants asked to measure BP twice a day for a week, then weekly - automatic transmission of BP readings through mobile phone - participants could receive optional reports

					based on the last 10 BP readings with feedback on the readings - MDs given access to patients' BP logs, and encouraged to check weekly
Hosseininasab et al. 2014 (13)*	Age>18 Office SBP 140/90–159/99 mm Hg without medication or those already on antihypertensive treatment but not controlled	Severe cardiovascular comorbidities, serum creatinine >1.5 mg/dl	196	Mean age 60 60% women Mean baseline SBP 144.4 (7.4) mm Hg DBP 85.5 (6.9) mm Hg	-participants asked to measure their BP once daily -clinic visits for all participants at 4, 12 and 24 weeks - pill counts performed at each visit

BP indicates blood pressure; HTN, hypertension; SMBP, self-monitored blood pressure; MI, myocardial infarction; CHF, congestive heart failure; TIA, transient ischemic attack; CV, cardiovascular; CKD, chronic kidney disease
*studies were excluded from the primary analysis of mean SBP because blood pressure variability was not reported

Figure 1.1. All data for systolic blood pressure, adjusted for study duration*



← Office-measured BP better **Difference in systolic blood pressure** Self measured BP better →

Figure 1.2 Funnel plot for differences in systolic blood pressure among studies with a 6- vs 12-month duration

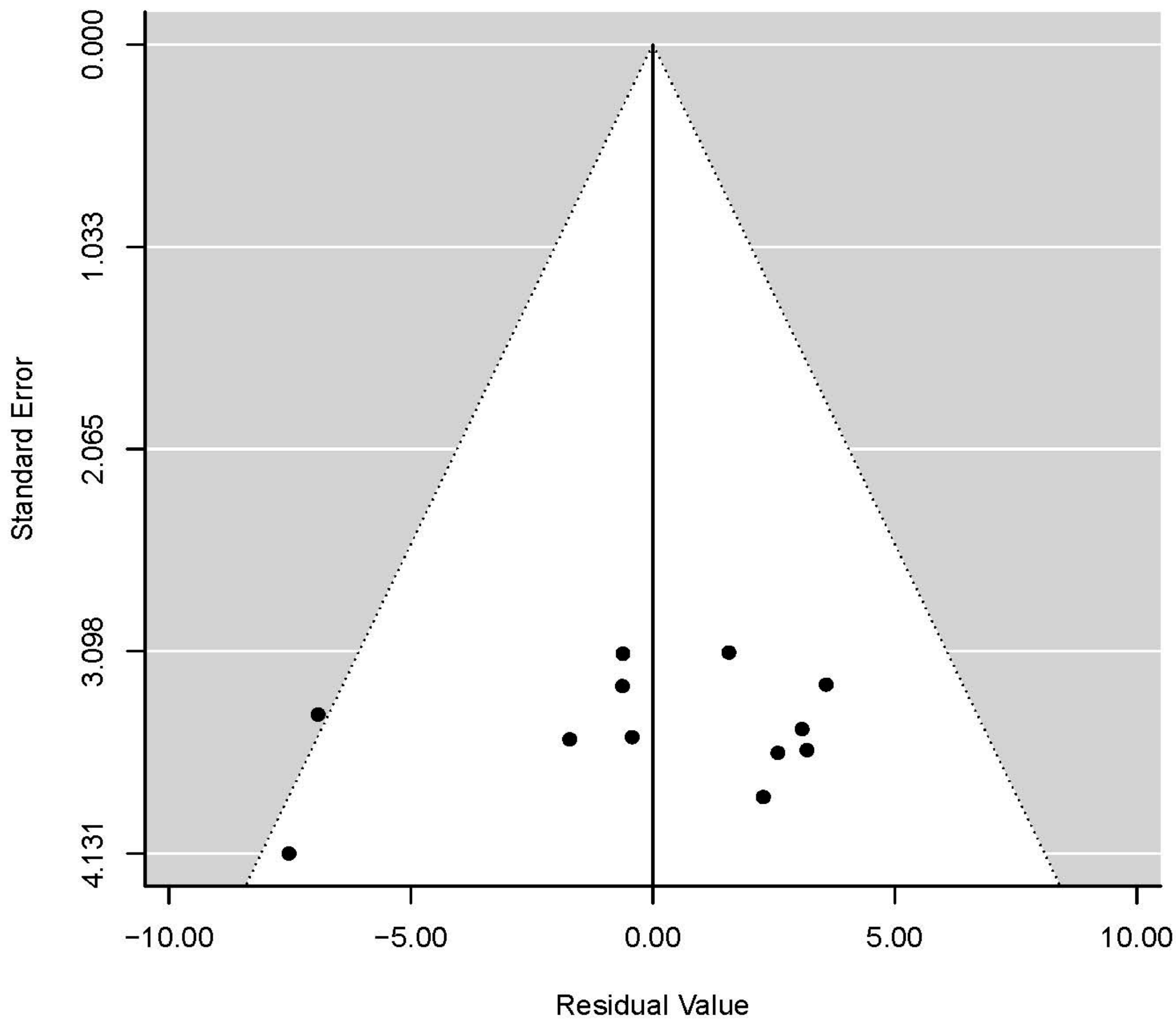
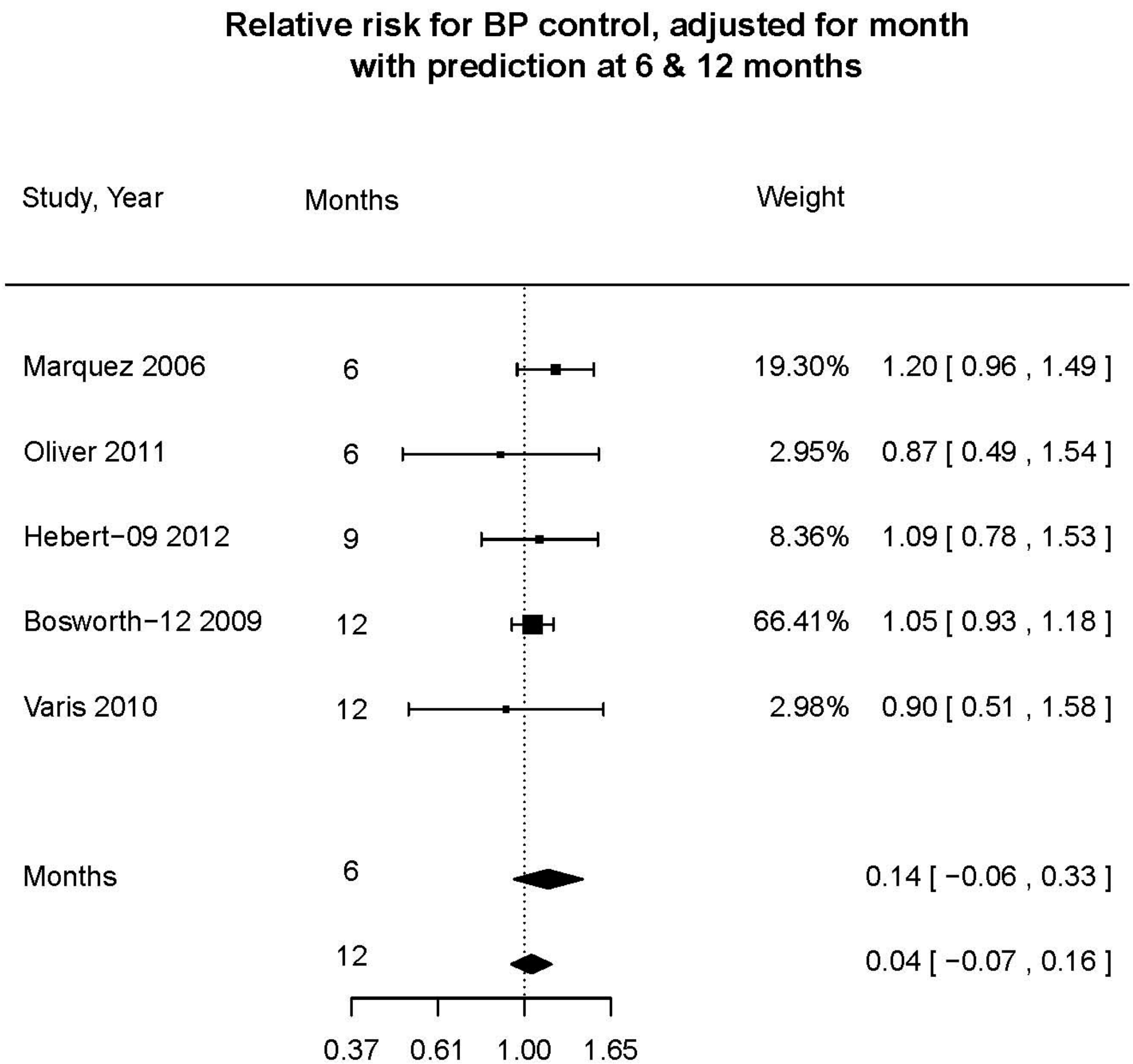
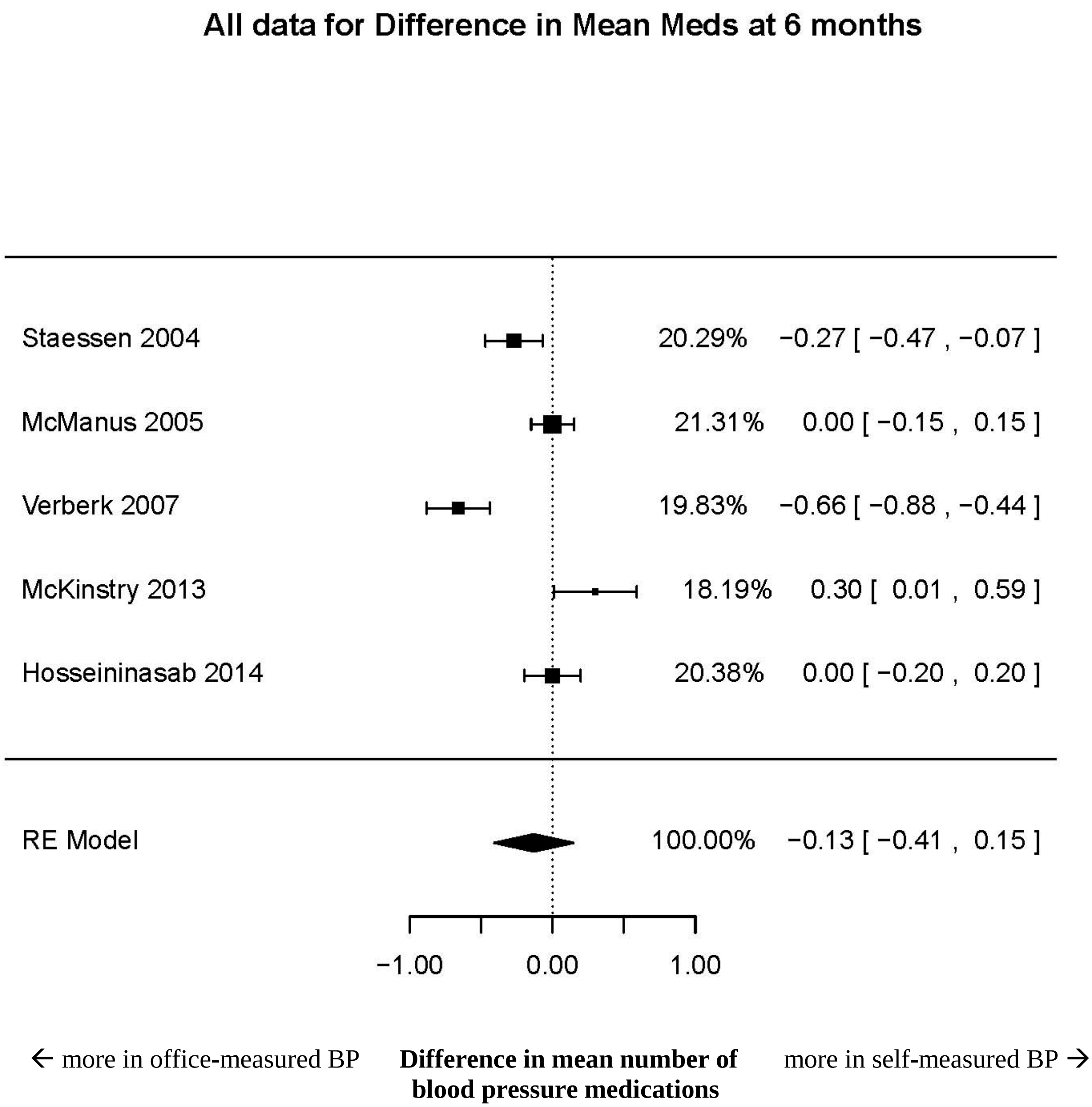


Figure 1.3. Relative Risk for BP Control, Adjusted for Study Duration



← Office measured BP better **Relative risk (log scale)** Self measured BP better →

Figure 1.4. All Data Difference in Mean Medications at 6 Months



Part 2: Targets for Blood Pressure Lowering During Antihypertensive Therapy in Adults

Table 2.1 Electronic search terms used for the current meta-analysis (Part 2 –Targets for blood pressure lowering).

PubMed Search	
(hypertension[mh] OR hypertension[tiab] OR hypertensive[tiab] OR Prehypertension[mh] OR pre-hypertens*[tiab] OR prehyperten*[tiab] OR borderline hyperten*[tiab] OR borderline blood pressure[tiab] OR antihypertensive agents[mh] OR blood pressure/drug effects[mh] OR blood pressure[ti])	Population concept
AND	Target Concept
(strict[tiab] OR tight[tiab] OR intensive[tiab] OR goal*[tiab] OR target*[tiab] or placebo[tiab] OR placebo[mh])	
AND	Limit to english
eng[la]	
AND	Limit to RCTs
(randomized controlled trial[pt] OR controlled clinical trial[pt] OR randomized[tiab] OR randomised[tiab] OR placebo[tiab] OR randomly[tiab] OR trial[tiab] OR groups[tiab])	
NOT	Remove Animal Studies
(animals[mh] NOT human[mh])	
NOT	Remove clearly irrelevent populations
(pregnan*[tiab] OR pre-eclampsia[tiab] OR preeclampsia[tiab] OR ocular[tiab] OR glaucoma[tiab])	
Limit: 2008 - present	Date Limit

Additional PubMed Search	
(hypertension[mh] OR hypertension[tiab] OR hypertensive[tiab] OR Prehypertension[mh] OR pre-hypertens*[tiab] OR prehyperten*[tiab] OR borderline hyperten*[tiab] OR borderline blood pressure[tiab] OR antihypertensive agents[mh] OR blood pressure/drug effects[mh] OR blood pressure[ti])	Population concept
AND	"intesity of therapy" concept
(add* [tiab] OR concomitant[tiab] OR multipl*[tiab] OR polytherap*[tiab] OR drug therapy, combination[mh] OR "drug combination"[all fields] OR combined[tiab] OR dual therapy[tiab] OR triple therapy[tiab] OR combination*[tiab] OR combining[tiab] OR add-on[tiab] OR adjunct*[tiab] OR plus[tiab] OR "based therapy"[tiab] OR "based treatment"[tiab] OR combination therapy[ot] OR combination treatment[ot] OR monotherapy[tiab] OR single agent[tiab])	

AND	
(no therapy[tiab] OR no treatment[tiab] OR usual care[tiab] OR standard care[tiab] OR observation[tiab] OR placebo[tiab] OR placebo[mh])	
AND	Limit to english
eng[la]	
AND	Limit to RCTs
(randomized controlled trial[pt] OR controlled clinical trial[pt] OR randomized[tiab] OR randomised[tiab] OR placebo[tiab] OR randomly[tiab] OR trial[tiab] OR groups[tiab])	
NOT	Remove Animal Studies
(animals[mh] NOT human[mh])	
NOT	Remove clearly irrelevent populations
(pregnan*[tiab] OR pre-eclampsia[tiab] OR preeclampsia[tiab] OR ocular[tiab] OR glaucoma[tiab])	
No date limit	

Embase Search

1	(*hypertension/ OR *diabetic hypertension/ OR *essential hypertension/ OR *resistant hypertension/ or *systolic hypertension/ OR *borderline hypertension/ OR exp *antihypertensive agent/ OR *blood pressure/ OR *Prehypertension/)	Population Concept
2	(hypertension OR hypertensive OR pre-hypertens$ OR prehyperten$ OR borderline blood pressure).ti	
3	blood pressure.ti.	
4	or/1-3	
5	(strict OR tight OR intensive OR goal$ OR target$ OR placebo).ti,ab.	Target Concept
6	4 and 5	
7	((exp animal/ or nonhuman/) NOT exp human/)	Remove Animal Studies
8	6 NOT 7	
9	(controlled clinical trial/ OR randomized controlled trial/)	Limit to RCTs
10	(randomized OR randomised OR placebo OR randomly OR trial OR groups).ti,ab.	
11	9 or 10	
12	8 and 11	

13	(pregnan$ OR pre-eclampsia OR preeclampsia OR ocular OR glaucoma).ti,ab.	Remove clearly irrelevent populations
14	12 not 13	
	2008 - present date limit	Date Limit

Table 2.2 *PICO(TSS) FRAMEWORK* **(Part 2–Targets for blood pressure lowering)**

	Inclusion Criteria	**Exclusion criteria**
Participants/ population	Adults (>=18 years) with Primary Hypertension or Hypertension due to Chronic Kidney Disease. Trials will not be limited by concomitant or comorbid disease (i.e., studies of persons with hypertension and diabetes will be included).	
Interventions/ exposure	"Lower" target systolic/diastolic/mean arterial blood pressure	Studies in which the primary intent of the treatment (and target blood pressure randomization) was not specifically to treat or lower blood pressure (e.g., use of ACE/ARB to treat or prevent heart failure)
Comparators/ control	"Standard" or "higher" target systolic/diastolic/mean arterial blood pressure	
Outcomes	Mortality All-Cause Cardiovascular Chronic Kidney Disease Myocardial Infarction (MI) Stroke Heart Failure Renal Outcomes End-Stage Renal Disease (ESRD) Doubling of Creatinine Halving of eGFR	All other outcomes Outcomes only reported at < 12 months or without enough detail to estimate variability
Timing (of outcomes)	Any	Any
Setting/context	Any	NA
Study design	Randomized Controlled Trials	Observational Studies
Additional criteria	>=100 randomized patients or >=400 person-years of follow-up	<100 randomized patients or <400 person-years of follow-up

Table 2.3. Publications meeting inclusion criteria and excluded from primary analyses (Part 2 –Targets for blood pressure lowering)

Author, Journal (Year)	Study Acronym	BLOOD PRESSURE (BP) TARGETS Intensive (lower) vs standard (higher) BP target	Notes (Exclusion reasons)
		Systolic BP, mm Hg	
Margolis KL, Diabetes Care (2014)	ACCORD (14)	<120 vs < 140	Subgroup analysis; standard vs intensive glycemic control of the composite primary outcome (deaths due to CVD, nonfatal myocardial infarction, and nonfatal stroke)
Margolis KL, J Gen Intern Med (2014)	ACCORD (15)	<120 vs < 140	Wrong outcome(s); No outcomes of interest
Reboldi G, Hypertension (2014)	Cardio-Sys (16)	<130 vs <140	Subgroup analysis; those with vs those without established CVD
White, J Am Geriatr Soc (2015)	SPS3 (17)	<130 vs 130-149	Subgroup analysis; aged ≥75 vs <75 yrs
Palacio, Stroke (2014)	SPS3 (18)	<130 vs 130-149	Subgroup analysis; results presented for participants with vs those without DM but not by blood pressure target
Pearce, Lancet Neurol (2014)	SPS3 (19)	<130 vs 130-149	Wrong outcome(s); Not an outcome of interest; change in cognitive function as measured by CASI Z scores
Rakugi H, Hypertens Res (2010)	JATOS (20)	<140 vs ≥ 140 to <160	Wrong analysis reported; Intent-to-treat analysis not reported; Per protocol analysis only
		Systolic/diastolic BP, mm Hg	
Holman RR, NEJM (2008)	UKPDS (21)	<150/85 vs <180/105	Not in-trial results reported, long-term follow-up only
		Diastolic BP, mm Hg	
Kjeldsen SE, J Hypertens (2000)	HOT (22)	≤80 Hg vs ≤90	Wrong analysis reported; Event counts not available
Zanchetti A, J Hypertension (2003)	HOT (23)	≤80 Hg vs ≤90	Subgroup analyses; smoking, high/lower serum cholesterol, higher/lower serum creatinine, with/without diabetes, ischaemic heart disease,
		Mean Arterial Pressure, mm Hg	
Contreras G, Hypertension (2005)	AASK (24)	≤ 92 vs 102-107	Wrong analysis reported; Results are presented by BP medication

Appel LJ, NEJM (2010)	AASK (25)	≤ 92 vs 102-107	Duplicate publication; renal outcomes results presented in other publication
Davis EM, Hypertension (2011)	AASK (26)	≤ 92 vs 102-107	Duplicate publication; renal outcomes results presented in other publication
Ku E, Kidney Intl (2015)	MDRD (27)	≤ 92 vs <107 (age ≤60 y) or 98 vs <113 (age ≥61 y)	Not in-trial results reported, long-term follow-up only

Table 2.4. Inclusion and exclusion criteria of study populations for randomized clinical trials of blood pressure targets.

First Author, Journal, Year (Year)	Study Acronym	Patient Population			BP Target Groups, mm Hg	
		Inclusion criteria	**Exclusion criteria**	**N**	**Intensive [lower], (n)**	**Standard [higher], (n)**
					SBP	
Ismail-Beigi F, Kidney International (2012) Cushman WC, NEJM (2010)	ACCORD [28] [29]	• Men and women aged 40-79 years • Type 2 DM • HbA1c ≥7.5% • Hypertension (SBP 130-160 mmHg and taking 0, 1, 2, or 3 antihypertensive medications, or SBP 161-170 mmHg and taking 0, 1 or 2 antihypertensive medications, or SBP 171-180 mmHg and taking 0 or 1 antihypertensive medications) • High-risk for CVD events • 77 clinical sites in the U.S. and Canada	• BMI >45 kg/m^2 or weight loss >10% in past 6 mo • Serum creatinine >1.5 mg/dL (132.6 µmol/L) within the previous 2 mo • History of hypoglycemic coma/seizure within past 12 mo • History consistent with type 1 diabetes • Transaminase >2 times the upper limit of normal or active liver disease • Any ongoing medical therapy with known adverse interactions with the glycemic interventions (eg, corticosteroids, protease inhibitors) • Cardiovascular event, procedure or hospitalization for unstable angina (past 3 mo) • Current symptomatic CHF, history of NYHA class III or IV CHF at any time, or ejection fraction (by any method) < 0.25 • Other serious illness	4733	SBP <120 mm Hg (2362)	SBP <140 mm Hg (2371)
Wright JT, NEJM (2015)	SPRINT [30]	• ≥50 yrs of age • SBP: 130 – 180 mm Hg on 0 or 1 medication; SBP: 130 – 170 mm Hg on up to 2 medications; SBP: 130 – 160 mm Hg on up to 3 medications; SBP: 130 – 150 mm Hg on up to 4 medications • Increased risk for CV events	• Diabetes mellitus • Prior stroke • Diagnosis of polycystic kidney disease • eGFR < 20 ml/min /1.73m2 or end-stage renal disease (ESRD) • Cardiovascular event or procedure or hospitalization for unstable angina (past 3 months) • Symptomatic heart failure (past 6 mo) or LVEF < 35% • Any indication for a specific BP lowering medication	9361	SBP <120 mm Hg (4678)	SBP <140 mm Hg (4683)

			• Arm circumference too large or small to allow accurate measurement with available devices • Other serious illness			
Verdecchia P, Lancet (2009)	Cardio-Sis (31)	• Aged ≥55 years • Hypertension (SBP≥ 150 mm Hg, receiving antihypertensive treatment for ≥12 weeks) • Non-diabetic • ≥1 additional risk factor as described in the guidelines of the European Society of Hypertension [Cigarette smoking, total cholesterol ≥5.2 mmol/L, HDL-C <1.0 mmol/L, LDL-C ≥3.4 mmol/L, family history of premature CVD in first degree relative, previous TIA or stroke, or established CAD or PAD	• History of diabetes (fasting glucose of >=7.0 mmol/L) • Any disease reducing life expectancy • Renal dysfunction (serum creatinine >176.8 µmol/L) • Clinically relevant hepatic disorders or hematological disorder • Valvular heart disease • Disorders confusing the electrocardiographic diagnosis of left ventricular hypertrophy • Complete right bundle block • Complete left bundle block • Wolff-Parkinson-White syndrome • Previous Q-wave myocardial infarction • Paced heart rhythm • Atrial fibrillation • Substance misuse	1111	SBP <130 mm Hg (558)	SBP <140 mm Hg (553)
Benavente OR, Lancet (2013)	SPS3 (32)	• Symptomatic small subcortical strokes (S3) with MRI confirmation (randomization must occur within 6 months of qualifying S3) • Clinical lancunar stroke syndrome • Absence of signs or symptoms of cortical dysfunction • No ipsilateral cervical carotid stenosis (≥50%) if the qualifying event is hemispheric • No major-risk cardioembolic sources • Patients from 81 centers in North America, Latin America and Spain	• Disabling stroke (modified Rankin score ≥ 4) • Previous intracranial haemorrhage from non-traumatic causes • Cortical ischaemic stroke	3020	SBP <130 mm Hg (1501)	SBP 130-149 mm Hg (1519)
Ogihara T, Hypertension (2010)	VALISH (33)	• Male or female • ≥70 and <85 years of age • Isolated systolic hypertension (SBP >160 mm Hg and DBP <90 mm Hg) • Sitting SBP 160-199 mm Hg	• Not reported	3260	SBP <140 mm Hg (1627)	SBP ≥140 to <150 mm Hg (1633)

		• Previously untreated or are on other therapy that can be converted to valsartan. • Patients from 461 centers in Japan				
JATOS, Hypertens Res (2008) Hayashi K, Hypertens Res (2010)	JATOS (34) (35)	• Male or female • 65-85 years of age • Essential hypertension [Persistent SBP≥ 160 mm Hg during a run-in period while receiving no antihypertensive drugs or receiving the same drug(s) for ≥ 4 weeks] • Intent to treat analysis • Japanese	• DBP >= 120 mm Hg • Secondary hypertension • Recent stroke, MI, coronary angioplasty (< 6 months prior) • Signs or symptoms of stroke • Angina pectoris requiring hospitalization • CHF of NYHA ≥ class II • Persistent arrhythmia (atrial fibrillation, dissecting aneurysm of the aorta, occlusive arterial disease, hypertensive retinopathy, serum aspartate aminopeptidase or serum alanine aminotransferase levels more than double the respective upper limit of normal) • Poorly controlled diabetes mellitus (Fasting blood sugar ≥ 200 mg/dL, HbA1c of 8% or higher) • Renal disease (Serum creatinine of 1.5 mg/dL or higher) • Malignant disease • Collagen disease • Considered unsuitable as subjects	4418	SBP <140 mm Hg (2212)	SBP 140-160 mm Hg (2206)
					SBP/DBP	
Schrier RW, NEJM (2014)	HALT-PKD (36)	• 15 to 49 years of age • Autosomal dominant polycistic kidney disease • Estimated GFR >60 ml per minute per 1.73 m^2 of body-surface area • Relatively preserved kidney function • At risk for progression to ESRD	• Documented renal vascular disease • Albumin to creatinine ratio ≥0.5 (study a) or ≥1.0 (study b) • Diabetes requiring insulin or oral hypoglycemic agents or a fasting serum glucose of ≥126 mg/dl or a random nonfasting glucose of ≥200 mg/dl	558	SBP/DBP 95/60-110/75 mm Hg (274)	SBP/DBP 120/70-130/80 mm Hg (284)
Asayama K, Hypertens Res (2012)	HOMED-BP (37)	• Mild-to-moderate hypertension • ≥40 years of age • Treatment naive or previously treated patients whose antihypertensive drug	• DBP <65 mm Hg • SBP <110 mm Hg	3518	SBP/DBP <125/<80 mm Hg (1759)	SBP/DBP 125-134/ 80-84 mm Hg (1759)

		treatment could be discontinued for ≥2 weeks • Maintained self-measured home BP of 135-179 mm Hg SBP or 85-119 mm Hg DBP off treatment • Clinic BP off treatment: <220 mm Hg SBP and <125 mm Hg DBP				
Ruggenenti P, Lancet (2005)	REIN-2 (38)	• Men or Women • Age 18-70 years • Non-diabetic nephropathy • Persistent proteinuria • Urinary protein excretion exceeding 1 g per 24 h for at least 3 months without evidence of urinary-tract infection or overt heart failure (NYHA Class III-IV). • Had not received ACE-I therapy for ≥ 6 weeks • Proteinuria of 1-3 g per 24 h with creatinine clearance < 45 mL/min per 1.73m^2 or proteinuria of ≥3g per 24 h with creatinine clearance <70 ml/min per 1.73m^2	• Treatment with corticosteroids, NSAIDs, immunosuppressive drugs • Acute MI or cerebrovascular accident (in the previous 6 months) • Severe uncontrolled hypertension • Suspicion or evidence of renovascular disease • Obstructive uropathy • Comorbid conditions including: Type 1 diabetes mellitus, collagen disease, cancer • Higher serum aminotransferase concentrations • Chronic cough or history of allergy • Poor tolerance to ACEI, or dihydropyridine CCB • Drug or alcohol abuse • Pregnancy or breastfeeding • Ineffective contraception	338	SBP/DBP <130/80 mm Hg (169)	DBP <90 mm Hg (169)
Wei Y, J Clin Hypertens (2013)	NR (39)	• 70 years of age • Hypertensive (SBP ≥150 mm Hg and/or DBP ≥90 mm Hg, measured twice in different days) or diagnosed with hypertension and currently receiving antihypertensive treatment • Chinese	• Secondary hypertension • Valvular heart disease • Chronic kidney dysfunction • Serum creatinine >=3.0 mg/dL • Recent stroke or MI (previous 6 months) • ≥NYHA class III CHF or • Echocardiography determining left ventricular ejection fraction (LVEF) <40% • Hepatic dysfunction • Autoimmune disorders • Malignant tumor • Alzheimer's disease	724	SBP/DBP ≤140/90 mm Hg (363)	SBP/DBP ≤150/90 mm Hg (361)

			• Non-cardiovascular diseases potentially causing death before the end of the study			
UKPDS Group, BMJ (1998)	UKPDS (40)	• Type 2 diabetes • Aged 25-65 years • Hypertension (SBP/DBP ≥160/90 mm Hg or ≥150/85 mm Hg if the patient was receiving antihypertensive treatment)	• Ketonuria >3 mmol/l • Recent MI (previous year) • Current angina or heart failure ➢ one major vascular episode • Serum creatinine concentration >175 µmol/l • Retinopathy requiring laser treatment • Malignant hypertension • Uncorrected endocrine abnormality • Occupation which would preclude insulin treatment or as heavy goods vehicle driver • Severe concurrent illness likely to limit life or to require extensive systemic treatment • Inadequate understanding or unwillingness to enter the study		SBP/DBP <150/85 mm Hg (798)	SBP/DBP <180/105 mm Hg (390)
						DBP
Estacio RO, Diabetes Care (2000)	ABCD – Hypertensive cohort (41)	• Hypertensive (DBP ≥ 90 mm Hg) • Off all antihypertensive medications • Type 2 diabetes • Ages 40-74 years at the time of recruitment	• Known allergy to dihydropyridines or ACEIs • Recent MI, CVA, or unstable angina pectoris (previous 6 months) or CABG surgery (previous 3 months) • CHF ≥ Class III NYHA • Demonstrated an absolute need for ACE inhibitors or CCBs • Received hemodialysis or • peritoneal dialysis • Serum creatinine level >3 mg/dl		DBP 75 mm Hg (237)	DBP 80-89 mm Hg (233)
Schrier RW, Kidney Intl (2002) Savage, J Curr Clin Trials (1993)	ABCD – Normotensive cohort (42) (43)	• Normotensive (DBP 80-89 mm Hg) • Type 2 diabetic subjects • Ages of 40-74 years at the time of recruitment • Not receiving antihypertensive medications at the randomization visit	• Known allergy to dihydropyridines or ACEIs • Recent MI, CVA, or unstable angina pectoris (previous 6 months) or CABG surgery (previous 3 months) • CHF ≥ Class III NYHA • Demonstrated an absolute need for ACE inhibitors or CCBs • Received hemodialysis or • peritoneal dialysis		DBP 10 mm Hg Decrease (237)	DBP 80-89 mm Hg (243)

			• Serum creatinine level >3 mg/dl			
Hannson L, Lancet (1998)	HOT (44)	• Aged 50-80 years • Hypertension • DBP 100 - 115 mm Hg	• Not reported		DBP ≤80 mm Hg (6262)	DBP ≤90 mm Hg (6264) ≤85 mm Hg (6264)
					MAP	
Wright JT Jr., JAMA (2002) Norris K, Am J Kidney Dis (2006)	AASK (45, 46)	• Aged 18 to 70 years • African Americans (self-identified) • Hypertensive CKD • GFR 20- 65 mL/min per 1.73 m^2 • No other identified causes of renal insufficiency	• DBP < 95 mm Hg • Known history of diabetes mellitus (Fasting glucose >=140 mg/dL, Random glucose >200 mg/dL, Urinary protein to creatinine ratio > 2.5) • Accelerated or malignant hypertension within 6 months • Secondary hypertension • Non–BP-related causes of CKD • Serious systemic disease • Clinical CHF • Specific indication for or contraindication to a study drug or study procedure		MAP ≤92 mm Hg (equivalent to a BP <125/75 mmHg) (540)	MAP 102-107 mm Hg (equivalent to a BP < 140/90 mm Hg) (554)
Sarnak MJ, Ann Intern Med (2005)	MDRD (47)	• Age 18 to 70 years • Chronic kidney disease • Serum creatinine concentration of 123.8-618.8 µmol/L (1.4- 7.0 mg/dL) in men or 106.1- 618.8 µmol/L (1.2-7.0 mg/dL) in women • GFR 13-55 mL/min/1.73 m^2	• Diabetes requiring therapy with insulin • CHF of ≥ NYHA Class III • Renal artery stenosis • History of kidney transplantation • Frequent hospitalizations		MAP <92 mm Hg (Age ≤60; equivalent to a BP <125/75 mmHg) & <98 mm Hg (Age ≥61) (432)	107 mm Hg (Age ≤ 60; equivalent to a BP < 140/90 mm Hg) & <113 mm Hg (Age ≥61)

Abbreviations: AASK: African American Study of Kidney Disease and Hypertension Trial; ABCD, Appropriate Blood Pressure Control in Diabetes Trial; ACCORD: Action to Control Cardiovascular Risk in Diabetes Trial; ACEI, angiotensin-converting-enzyme inhibitor, BP, blood pressure; CABG, Coronary artery bypass graft; CAD, coronary artery disease; Cardio-Sis, Studio Italiano Sugli Effetti CARDIOvascolari del Controllo della Pressione Arteriosa SIStolica; CCB, calcium channel blocker; CHF, congestive heart failure; CKD, Chronic kidney disease; CV, cardiovascular; CVA, cerebral vascular accident; CVD, cardiovascular disease; DBP, diastolic blood pressure; DM, diabetes mellitus; GFR, Glomerular Filtration Rate; HALT-PDK, Halt Progression of Polycystic Kidney Disease Study; HbA1c, Glycated hemoglobin level; HDL-C, density lipoprotein cholesterol; HOME-BP, Hypertension Objective Treatment Based on Measurement by Electrical Devices of Blood Pressure; HOT, Hypertension Optimal Treatment Study; JATOS, Japanese Trial to Assess Optimal Systolic Blood Pressure in Elderly Hypertensive Patients; LDL-C, low density lipoprotein cholesterol; MAP, mean arterial pressure; MDRD, Modification of Diet in Renal Disease Trial; MI, myocardial infarction; NR, Study name Not Reported; NYHA, New York Heart Association; NSAID, non-steroidal anti-inflammatory drug; PAD, peripheral artery disease; REIN-2, Rampiril Efficacy in Nephropathy-2; SBP, systolic blood pressure; SPRINT, Systolic Blood Pressure Intervetion Trial; TIA, transient ischemic attack; UKPDS, United Kingdom Prospective Diabetes Study; VALISH, Valsartan in Elderly Isolated Systolic Hypertension Study; WHO, World Health Organization.

Table 2.5. Table of study characteristics at baseline.

Study Acronym	Study N	Mean follow-up (y)	Mean Age (SD), y	% Male	% White	Mean Blood Pressure		Comorbid conditions, %				
						Systolic, mm Hg (SD)	Diastolic, mm Hg (SD)	HTN	DM	CKD	Prior CAD	CVD
Blood pressure target: systolic blood pressure (SBP)												
ACCORD [29] [28]	4733	4.7	62.2 (6.9)	52.3	60.5	139.2 (15.8)	76.0 (10.4)	NR	100	NR	NR	33.7[b]
SPRINT [30]	9361	3.3[a]	67.9 (9.4)[c] 67.9 (9.5)[d]	64.4[b]	57.7[b]	139.7 (15.8)[c] 139.7 (15.4)[d]	78.2 (11.9)[c] 78.0 (12.0)[d]	NR	0	28.2[b]	NR	20.1[b]
Cardio-Sis [31] [48]	1111	2.0[a]	67.0 (7.0)	41.4[b]	NR	163.3 (11.1)[c] 163.3 (11.1)[d]	89.7 (8.8)[c] 89.6 (8.8)[d]	100	0	NR	11.5[b]	19.4[b]
SPS3 [32] [49]	3020	3.7	63.0 (11)	63.0	50.9[b]	144 (19)[c] 142 (19)[d]	79 (11)[c] 78 (10)[d]	75.0	36.6[b]	NR	10.5[b]	NR
VALISH [33, 50]	3079	2.9	76.1 (NR)	37.5	0	169.5 (7.9)[c] 169.6 (7.9)[d]	81.7 (6.6)[c] 81.2 (6.8)[d]	100	13.0[b]	NR	5.0[b]	NR
JATOS [34, 35]	4418	NR	73.6 (5.3)[c] 73.6 (5.2)[d]	38.9[b]	0	171.6 (9.7)[c] 171.5 (9.8)[d]	89.1 (9.5)[c] 89.1 (9.5)[d]	100	11.8[b]	0	NR	3.0[b]
Blood pressure target: Systolic blood pressure/diastolic blood pressure (SBP/DBP)												
HALT-PKD [36] [51]	558	5.7	36.9 (8.2)[c] 36.3 (8.4)[d]	50.7[b]	92.7[b]	121.8 (13.8)[c] 122.6 (14.9)[d]	77.1 (11.7)[c] 78.1 (11.7)[d]	100	NR	NR	NR	NR
HOMED-BP [37] [52]	3518	5.3[a]	59.6 (10.2)[c] 59.6 (9.9)[d]	50.0	0	154.3 (17.5)[c] 154.1 (17.5)[d]	90.4 (12.2)[c] 90.0 (12.1)[d]	100	15.3[b]	NR	NR	3.0[b]
REIN-2 [38]	338	1.6[a]	54.6 (14.7)[c] 53.1 (15.8)[d]	75.0[b]	NR	137.0 (16.7)[c] 136.4 (17.0)[d]	84.3 (9.0)[c] 83.9 (10.4)[d]	NR	0	100	NR	NR
NR [39]	724	4.0	76.6 (NR)	66.3[b]	0	158.8 (16.0)[c] 160.3 (16.9)[d]	83.7 (9.6)[c] 84.8 (9.5)[d]	100	23.0	0	NR	NR
UKPDS [40] [53]	1148	8.4[a]	56.4 (8.1)	55.5[b]	86.7[b]	159 (20.0) [c] 160 (18.0)[d]	94.0 (10.0)[c] 94.0 (9.0)[d]	100	100	NR	NR	NR
Blood pressure target: diastolic blood pressure (DBP)												
ABCD- Hypertensive cohort [43] [41]	470	5.3	58.0 (8.4)[c] 57.7 (8.3)[d]	67.4[b]	NR	156 (16.1)[c] 154 (16.9)[d]	98 (6.4) [c] 98 (6.4) [d]	100	100	NR	NR	22.6[b]
ABCD – Normotensive cohort [41, 43] [42]	480	5.3	58.5 (0.6)[c] 59.6 (0.5)[d]	54.6[b]	73.5[b]	135.6 (0.8)[c] 137.2 (0.9)[d]	84.4 (0.2)[c] 84.4 (0.2)[d]	0	100	NR	24.2[b]	NR
HOT [44]	18790	3.8	61.5 (NR)	53.0	NR	169.7 (14.1)[c] 169.8 (14.4)[d]	105.4 (3.4)[c,d]	100	8.0	NR	6.0[b]	NR
Blood pressure target: Mean Arterial Pressure (MAP)												
AASK [45] [54] [46, 55] [56]	1094	4.1	55.0 (11.0)	61.0	0	152 (25)[c] 149 (23)[d]	96 (15)[c] 95 (14)[d]	100	0	100	52.0[b]	NR
MDRD [29] [47]	840	6.2	52.0	61.0	NR	130 (16)[c]	131 (18)[c]	NR	5.0	100	NR	NR

						80 (10)[d]	80 (10)[d]					

a. Median value
b. Total population data calculated from BP target group data.
c. Intensive [lower] target blood pressure group
d. Standard [higher] target blood pressure group.
Abbreviations: CAD, coronary artery disease; CKD, chronic kidney disease; CVD, cardiovascular disease; DM, diabetes mellitus; HTN, hypertension; NR, not reported.

Table 2.6. Comparison of protocols across studies (Part 2 –Targets for blood pressure lowering).

Study Acronym	Blood Pressure Measurement	Frequency of contact during follow up (monitoring and/or changes in antihypertensive medication treatment)		
		Intensive BP Goal [lower BP target]	**Standard BP Goal [higher BP target]**	**Notes on medication management**
Blood pressure target: systolic blood pressure (SBP)				
ACCORD [28, 29]		BP and glycemic treatments begin at randomization At least monthly visits until month 4 and achieving BP goal then every 2 months. "Milepost" visits at 4-month intervals for 2 years then annually. Action required at each milepost for participants who remain above SBP goal of <120 mmHg. Between designated visits, therapy may be intensified for those not at goal.	BP and glycemic treatments begin at randomization Clinical visits months 1, 4, and every 4 months thereafter. Medication dose titration or the addition of another drug is indicated if systolic blood pressure is ≥160 mm Hg at a single visit or ≥140 mm Hg at 2 successive visits Down titration permitted if SBP <135 mmHg at 2 successive clinic visits or <130 mmHg at any single visit	Medication doses may be decreased or changed whenever an ACCORD therapist considers it clinically indicated, such as when symptoms are reported that could be secondary to an antihypertensive medication
SPRINT [30]	Seated BP measured at each clinic visit using an automated measurement system (Model 907, Omron Healthcare)	Post-randomization visits at months 1,2, 3, 6, and every 3 months thereafter 2 or 3 drug therapy using a combination of thiazide-type diuretic, and/or an ACEI, or ARB (but not both) and/or a CCB initiated at randomization (an ACE inhibitor or ARB plus a CCB initiated if diuretic contraindicated or not tolerated) Drug doses increased and/or additional antihypertensive medications added at each visit (usually monthly intervals) until participant's SBP goal of <120 mmHg had been reached or the investigator decided no further antihypertensive medications may be added	Post-randomization visits at months 1,2, 3, 6, and every 3 months thereafter Participants may not be on ≥1 antihypertensive medications Use of thiazide-type diuretic initially if antihypertensive medication indicated Treatment should not be intensified at the randomization visit unless SBP ≥160 mm Hg or there was a compelling reason to add medication Medications were adjusted to target SBP of 135 - 139 mmHg, and dose reduced if SBP was <130 mmHg on a single visit or < 135 mmHg on two consecutive visits	Study physician may add, increase or reduce the dose, stop, or change antihypertensive drugs (temporarily or permanently) in the interest of participant safety
Cardio-Sis [31]	Seated BP through standard mercury sphygmomano-meter	After randomization, visits every 4 months for 2 years Anti-hypertensive therapy was open-label and tailored to the single subjects One or more SBP >130 mmHg is enough to intensify treatment	After randomization, visits every 4 months for 2 years Anti-hypertensive therapy was open-label and tailored to the single subjects	

			Achievement of SBP goal of <130 mmHg does not imply down titration of treatment	
SPS3 [32]	Automated Colin Press-Mate BP-8800C sphygmomanometers (Colin Medical Instruments, San Antonio, TX, USA)	Patients are seen at least monthly for adjustment of antihypertensive medications to achieve the assigned target blood pressure. Once the systolic blood pressure is in the assigned target range at two consecutive visits, the participant continues with quarterly follow-ups.	Same as intensive group	
VALISH [33, 50]	Seated BP	Visits every 3 months at a minimum for 2 years Valsartan, 40 to 80 mg once daily, administrated as first-step therapy. If target BP in each group was not achieved within 1 to 2 months, the dose of valsartan was increased ≤160 mg, and/or other antihypertensive agents except other angiotensin II type 1 receptor blockers were added (e.g. low-dose diuretics, Ca antagonists, and so on) to maintain the target BP Target BP level reached over 3 months	Same as intensive group	Not described
JATOS [34] [35]	Seated BP measured at least twice per visit using a sphygmomanometer	Untreated subjects – received daily 20-40 mg dose efonidipine Treated subjects – similar dose of efonidipine was added or substituted for one of the drugs being received before study entry without a washout period, efondipine could be increased to 60 mg (once or twice daily). Visits with physician every 2 or 4 weeks Investigators titrated doses of antihypertensive drugs in order to reach target BP by about 3 months after start of treatment.	Same as intensive group	
Blood pressure target: Systolic blood pressure/diastolic blood pressure (SBP/DBP)				
HALT-PKD [36, 51]	Office BP measured three times sitting and once while standing; Home BP measurements obtained every 3 days until	Treatment initiated after randomization Medication doses were adjusted in a stepwise fashion to achieve the desired BP targets (with the use of home BP	Same as intensive group	

	BP targets achieved (based on home BP measurements twice daily for 14 days)	measures) while the plasma levels of creatinine and potassium were monitored. Second-, third-, and fourth-line antihypertensive agents were added as needed Patients evaluated through PCC and telephone visits		
HOMED-BP [37] [52]	Seated BP measured twice using the oscillometric OMRON HEM-907IT device (OmronHealthcare, Kyoto,Japan) Participants self-measured sitting BP daily throughout study using the oscillometric OMRON HEM-747IC-N monitors(OmronHealthcare)	After randomization, participants were followed at intervals of 2–4 wks in general practice and 4–8 wks at hospital outpatient clinics Home BP was used to determine treatment adjustments Advice for treatment adjustment was based on computerized algorithm following 1997 recommendations of the JNC, and 1999 WHO and ISH guidelines – 4 steps including changing dosage or addition of medications	Same as intensive group	When the Home BP was <110 mmHg systolic or 65 mmHg diastolic, treatment was tailored down to avoid orthostatic hypotension
REIN-2 [38]	Seated resting BP measured 3 times, 2 minutes apart by a standard sphygmomanometer	After randomization, BP was measured at 1 wk, 2 wks, 3 mos, and every 3 mos thereafter. Additional BP measurements done within 1 wk after any change in antihypertensive therapy and whenever deemed clinically appropriate. After baseline evaluation, participants given Ramipril 2.5 mg/d after previous diurectic therapy withdrawn for 24 hours. Up-titrated to 5 mg/d concomitant antihypertensive therapy was down-titrated to maintain DBP at <90 mm Hg Felodipine 5 mg/day as an add-on to previous treatment with ramipril and concomitant BP response.	After randomization, BP was measured at 1 wk, 2 wks, 3 mos, and every 3 mos thereafter. Additional BP measurements done within 1 wk after any change in antihypertensive therapy and whenever deemed clinically appropriate. After baseline evaluation, participants given Ramipril 2.5 mg/d after previous diurectic therapy withdrawn for 24 hours. Up-titrated to 5 mg/d concomitant antihypertensive therapy was down-titrated to maintain DBP at <90 mm Hg Continued treatment with ramipril and concomitant antihypertensive drugs.	Up- and down-titration of treatments permitted to maintain the target BP and to avoid symptomatic hypotension
NR (Wei et al)[39]	Sitting BP measured by auscultatory method using a sphygmomanometer	BP was measured in the follow-up period at 4 wks, 3 mos, 6 ms, and every 6 ms thereafter (all patients followed an average of 10 times) Randomized patients were started with single-drug treatment of an ACE-I, BB, CCB, or a diuretic	Same as intensive group	

		To achieve the target BP, 1, 2, or 3 additional antihypertensive drugs could be added stepwise. If quadruple antihypertensive therapy failed to achieve BP goal, increasing dose was recommended		
UKPDS [40] [53]	Seated office BP measurement, Copal UA-251 or a Takeda UA-751 electronic, automatic, auscultatory BP reading machine (Andrew Stephens Co., Brighouse, West Yorkshire, UK)	therapy was usually started with captopri125 mg twice daily or atenolo150 mg once daily (diuretic, stopped at least 24 h before captopril was introduced at a dose of 6.25 rag) The first dose being given in hospital with a 6-h observation period. If BP remained ≥150 and/or ≥ 85 mm Hg on a single reading, the dose was increased to the maximum of atenolol 100 mg daily or captopril 50 mg twice daily Other drugs (frusemide, long-acting nifedipine,methyldopa, prazosin) added in sequence until the target BP control criteria were met.	At randomization, if a patient was already being treated with an ACE-I or a BB, this was stopped if feasible. If the BP remained at or became ≥ 200 and/or ≥ 105 mmHg, other drugs (frusemide, nifedipine, methyldopa, prazosin) were given sequentially, until the target control criteria were met. If possible, ACE-I and BB were not used.	If symptoms occurred on any drug, physicians could use their clinical judgement on choice of therapies
Blood pressure target: diastolic blood pressure (DBP)				
ABCD [41, 43]	Mean DBP determined at 2 separate visits	Participants randomized to initial antihypertensive medication (nisoldipine 10 mg/d titrated to 20, 40, then 60 mg/d or enalapril titrated to 10, 20, then 40 mg/d) plus placebo. If single study medication did not achieve target BP, then ope-label antihypertensive medications were added in step-wise fashion until target BP achieved.	Same as intensive group	Additional antihypertensive medications added at discretion of medical director but did not include CCB or ACE-I.
HOT[44]	Seated resting BP, measured three times with an oscillometric semiautomatic device (Visomat OZ, D2, International, Hestia, Germany) at randomization, 3 mos, 6 mos, and twice a year thereafter.	Antihypertensive therapy, with the long-acting CCB (felodipine, 5 mg once a day) Additional therapy and dose increments in four further steps were prescribed to reach target BP. Step two: ACE-I or BB were added Step three: dosage titrations (felodipine 10 mg once a day) Step four: (doubling the dose of either the ACE-I or the BB) Step five: adding a diuretic	Same as intensive group	

Blood pressure target: Mean Arterial Pressure (MAP)				
AASK [45, 56]	Seated resting BP measured 3 times using Hawksley random zero sphygmomanometer	Treatment with 1 of 3 antihypertenstive study drugs – sustained release BB (metoprolol 50 to 200 mg/d), ACE-I (ramapril, 2.5 to 10 mg/d), CCB (amlodipine, 5 to 10 mg/d) If target BP not achieved on study drug, additional unmasked drugs added. The dosage of each drug was increased to maximum tolerated dose before adding a subsequent agent.	Same as intensive group.	
MDRD [47]	BP measured monthly using random-zero mercury sphygmomanometer	After randomization, Nonpharmacologic therapy consisted of recommendations for exercise and weight loss and reductions in intake of dietary sodium and alcohol For pharmacologic therapy, use of all agents was allowed, to achieve BP goals. ACEI and CCB, both with or without diuretic, were encouraged as first choice and second choice agents respectively.	Same as intensive group.	
Abbreviations: ACE-I, angiotensin-converting enzyme inhibitor; BB, beta blocker; BP, blood pressure; CCB, calcium channel blocker; ISH, International Society of Hypertension; JNC, Joint National Committee; PCC, participating clinical center; WHO, World Health Organization.				

Table 2.7. Relative Risk (95% Confidence Interval) for a Given Outcome for any Intensive [Lower] Blood Pressure Target Versus any Standard [Higher] Blood Pressure Target.

Outcome	Studies included, N	Study participants included, N	Events, N (%)		RR	(95% CI)	Heterogeneity		Funnel Plot Asymmetry	
			Intensive BP target	Standard BP target			I^2 (%)	*P*-value	P-value for Kendall's Tau	P-value for Egger's Regression Test
All-cause mortality	15	49,934	952 (4.0)	1,001 (4.3)	0.89	(0.77, 1.02)	49.30	0.02	0.24	0.50
CVD mortality	10	40,266	268 (1.3)	504 (2.5)	0.86	(0.67, 1.12)	46.44	0.06	0.38	0.38
Major Cardiovascular Disease Events	7[a]	23,617	682 (5.8)	828 (7.0)	0.81	(0.70, 0.94)	41.34	0.12	0.56	0.55
Fatal or non-fatal myocardial infarction	11	31,926	415 (2.6)	419 (2.7)	0.86	(0.76, 0.99)	0.00	0.99	0.76	0.28
Fatal or non-fatal stroke	12	33,018	389 (2.3)	475 (2.9)	0.77	(0.65, 0.91)	26.43	0.18	0.74	0.41
Fatal or non-fatal heart failure	8	23,066	222 (1.9)	278 (2.4)	0.75	(0.56, 0.99)	49.12	0.06	0.55	0.72
Renal Events	8[b]	18,286	334 (3.8)	353 (4.2)	1.01	(0.89, 1.15)	0.00	0.80	1.00	0.68

Note: Detailed information about studies included for each specific outcome may be found in Tables 2.9-2.15.
a. Major cardiovascular disease events were included in the analysis only if defined and reported as a composite outcome by each trial, it included cardiovascular death, stroke, myocardial infarction, and heart failure.
b. Renal events include the following: doubling of serum creatinine, end stage renal disease, a decline in glomerular filtration rates >50% or 25 mL/min per 1.73 m^2 reduction in GFR from baseline, progression of chronic kidney disease (CKD), renal failure, renal failure in absence of acute reversible cause.

Table 2.8. Relative Risk (95% Confidence Interval) for a Given Outcome for Intensive [Lower] Blood Pressure Target <130 mm Hg Systolic Versus any Standard [Higher] Blood Pressure Target

Outcome	Studies included, N	Study participants included, N	Events, N (%)		RR	(95% CI)	Heterogeneity		Funnel Plot Asymmetry	
			Intensive BP target	Standard BP target			I^2 (%)	*P*-value	P-value for Kendall's Tau	P-value for Egger's Regression Test
All-cause mortality	9[a]	24,569	493 (4.0)	546 (4.4)	0.92	(0.79, 1.06)	15.59	0.30	0.12	0.91
CVD mortality	5[b]	19,039	117 (1.2)	145 (1.5)	0.81	(0.58, 1.14)	31.42	0.21	0.82	0.79
Major Cardiovascular Disease Events	5[a]	19,814	610 (6.2)	724 (7.3)	0.84	(0.73, 0.99)	40.70	0.15	0.82	0.82
Fatal or non-fatal myocardial infarction	6	22,077	269 (2.4)	316 (2.9)	0.85	(0.73, 1.00)	0.00	0.99	0.47	0.45
Fatal or non-fatal stroke	7	23,169	274 (2.4)	339 (2.9)	0.82	(0.70, 0.96)	0.00	0.45	1.00	0.90
Fatal or non-fatal heart failure	4	16,296	175 (2.2)	220 (2.7)	0.81	(0.58, 1.14)	53.42	0.09	1.00	0.92
Renal Events	5[b]	9,641	347 (7.4)	346 (7.0)	1.01	(0.89, 1.16)	0.00	0.99	1.00	0.48

Note: Detailed information about studies included for each specific outcome may be found in Tables 2.9-2.15.

a. Major cardiovascular disease events were included in the analysis only if defined and reported as a composite outcome by each trial, it included cardiovascular death, stroke, myocardial infarction, and heart failure.

b. Renal events include the following: doubling of serum creatinine, end stage renal disease, a decline in glomerular filtration rates >50% or 25 mL/min per 1.73 m^2 reduction in GFR from baseline, progression of chronic kidney disease (CKD), renal failure, renal failure in absence of acute reversible cause.

Table 2.9. Relative risk of all-cause mortality in the intensive [lower] versus the standard [higher] blood pressure group.

Comparison Groups Intensive (lower) vs standard (higher) BP target	Study	Author, Journal (Year)	N	Events, N (%) Intensive BP target	Standard BP target	RR (95% CI)
SBP Target (mm Hg)						
<120 vs <140	ACCORD (28)	Cushman WC, N Engl J Med (2010)	4,733	150 (6.4)	144 (6.1)	1.05 (0.84, 1.30)
<120 vs <140	SPRINT(30)	Wright JT, NEJM (2015)	9,361	155 (3.3)	210 (4.5)	0.74 (0.60, 0.91)
<130 vs <140	Cardio-Sis (31)	Verdecchia P, Lancet (2009)	1,111	4 (0.7)	5 (0.9)	0.79 (0.21, 2.94)
<130 vs 130-149	SPS3 (32)	Benavente, Lancet (2013)	3,020	106 (7.1)	101 (6.6)	1.06 (0.82, 1.38)
<140 vs ≥140 to <150	VALISH (33)	Ogihara T, Hypertension (2010)	3,260	24 (1.6)	30 (2.0)	0.79 (0.47, 1.35)
<140 vs ≥ 140 to <160	JATOS (35)	JATOS, Hypertens Res (2008)	4,418	54 (2.4)	42 (1.9)	1.28 (0.86, 1.91)
SBP/DBP Target (mm Hg)						
95/60-110/75 vs 120/70 – 130/80	HALT-PKD (36)	Schrier RW, NEJM (2014)	480	0 (0.0)	2 (0.7)	0.21 (0.01, 4.30)
<125/<80 vs 125-134/80-84	HOMED-BP (37)	Asayama K, Hypertens Res (2012)	3,518	27 (1.5)	31 (1.8)	0.87 (0.52, 1.45)
<130/80 vs <90	REIN-2 (38)	Ruggenenti P, Lancet (2005)	338	2 (1.2)	3 (1.8)	0.67 (0.11, 3.96)
≤140/90 vs ≤150/90	NR (39)	Wei Y, J Clin Hypertens (2013)	724	51 (14.0)	87 (24.1)	0.58 (0.43, 0.80)
<150/85 vs <180/105	UKPDS (40)	UKPDS Group, BMJ (1998)	1,148	134 (17.7)	83 (21.3)	0.83 (0.65, 1.06)
DBP Target (mm Hg)						
75 vs 80-89	ABCD (41)	Estacio RO, Diabetes Care (2000)	470	13 (5.5)	25 (10.7)	0.51 (0.27, 0.97)
≤80 Hg vs ≤90	HOT (44)	Hansson L, Lancet (1998)	12,528	207 (3.3)	188 (3.0)	1.10 (0.91, 1.34)
MAP Target (mm Hg)						
≤ 92 vs 102-107	AASK (45)	Wright JT Jr., JAMA (2002)	1,094	37 (6.9)	43 (7.8)	0.88 (0.58, 1.35)
≤ 92 vs <107 (age ≤60 y) or < 98 vs <113 (age ≥61 y)	MDRD (47)	Sarnak MJ, Ann Intern Med (2005)	840	12 (2.8)	7 (1.7)	1.60 (1.00, 2.55)
Meta-analyses	**I^2 (%)**	**Q Test for Heterogeneity**				**RR (95% CI)**
Any SBP target (n=6)	49.21	Q (df = 5) = 9.84, P = 0.08	25,721	493 (3.8)	532 (4.1)	0.95 (0.79, 1.15)
Any SBP/DBP target (n=5)	3.77	Q (df = 4) = 4.16, P = 0.39	6,283	212 (6.7)	203 (7.3)	0.74 (0.61, 0.89)
Intensive SBP target <130 (n= 9)[a]	15.59	Q (df = 8) = 9.48, P = 0.30	24,569	493 (4.0)	546 (4.4)	0.92 (0.79, 1.06)
All studies (n=15)	49.30	Q (df = 14) = 27.61, P = 0.02	46,934	952 (4.0)	1,001 (4.3)	0.89 (0.77, 1.02)
Sensitivity analyses						
100% Diabetic populations (n=3)[b]	60.87	Q (df = 2) = 5.11, P = 0.08	6351	297 (8.8)	252 (3.7)	0.85 (0.64, 1.14)
100% CKD populations (n=3)[c]	0.00	Q (df = 2) = 1.54 , P = 0.46	2269	51 (4.5)	53 (4.7)	0.96 (0.66, 1.40)
Study populations with mean age ≥60y (n=8)[d]	67.11	Q (df = 7) = 21.28 , P = 0.003	38,971	751 (3.9)	807 (4.1)	0.92 (0.76, 1.11)

Note: This table lists studies which fit inclusion criteria and identified all cause mortality as an outcome. Separate random effects meta-analyses for this outcome were conducted using the studies referenced above and based on blood pressure (BP) targets. Sensitivity analyses were conducted to further understand the effect of a lower target BP versus any higher target BP on populations of interest which included 1) only patients with diabetes, 2) only patients with CKD, or 3) a study population with mean age ≥60 years at baseline. Studies included in these analyses are listed in the footnotes. Additional information on study characteristics may be found in Table 2.5.

a. ACCORD, SPRINT, Cardio-Sys, SPS3, HALT-PDK, HOMED-BP, REIN-2, AASK, and MDRD.
b. ACCORD, UKPDS, ABCD.
c. REIN-2, AASK, and MDRD.
d. ACCORD, SPRINT, Cardio-Sis, SPS3, VALISH, JATOS, Wei et al, and HOT.

Table 2.10. Relative risk of cardiovascular disease mortality in the intensive [lower] versus the standard [higher] blood pressure group.

Comparison Groups Intensive (lower) vs standard (higher) BP target	Study	Author, Journal (Year)	N	Events, N (%) Intensive BP target	Events, N (%) Standard BP target	RR (95% CI)
SBP Target (mm Hg)						
<120 vs <140	ACCORD (28)	Cushman WC, N Engl J Med (2010)	4,733	60 (2.5)	58 (2.4)	1.04 (0.73, 1.48)
<120 vs <140	SPRINT (30)	Wright JT, NEJM (2015)	9,361	37 (0.8)	65 (1.4)	0.57 (0.38, 0.85)
<140 vs ≥140 to <150	VALISH (33)	Ogihara T, Hypertension (2010)	3,260	11 (0.7)	11 (0.7)	0.99 (0.43, 2.28)
<140 vs ≥ 140 to <160	JATOS (35)	JATOS, Hypertens Res (2008)	4,418	6 (0.3)	4 (0.2)	1.50 (0.42, 5.29)
SBP/DBP Target (mm Hg)						
<125/<80 vs 125-134/80-84	HOMED-BP (37)	Asayama K, Hypertens Res (2012)	3,518	3 (0.2)	5 (0.3)	0.60 (0.14, 2.51)
<130/80 vs <90	REIN-2 (38)	Ruggenenti P, Lancet (2005)	338	1 (0.6)	2 (1.2)	0.50 (0.05, 5.49)
≤140/90 vs ≤150/90	NR (39)	Wei Y, J Clin Hypertens (2013)	724	25 (6.9)	50 (13.9)	0.50 (0.31, 0.79)
DBP Target (mm Hg)						
75 vs 80-89	ABCD (42)	Schrier RW, Kidney Intl (2002)	480	13 (5.4)	9 (3.7)	1.48 (0.65, 3.40)
≤80 vs ≤90	HOT (44)	Hansson L, Lancet (1998)	18,790	96 (1.5)	90 (1.4)	1.03 (0.77, 1.39)
MAP Target (mm Hg)						
≤ 92 vs 102-107	AASK (46)	Norris K, Am J Kidney Dis (2006)	1,094	16 (3.0)	15 (2.7)	1.09 (0.54, 2.18)
Meta-analyses	**I^2 (%)**	**Q Test for Heterogeneity**				RR (95% CI)
Any SBP Targets (n=4)	49.14	Q (df = 3) = 5.90, *P* = 0.12	21,591	114 (1.1)	138 (1.3)	0.86 (0.57, 1.29)
Intensive SBP target <130 (n=5)[a]	31.42	Q (df = 4) = 5.83, P = 0.21	19,039	117 (1.2)	145 (1.5)	0.81 (0.58, 1.14)
All studies (n=10)	46.44	Q (df = 9) = 16.17, *P* = 0.06	40,266	268 (1.3)	504 (2.5)	0.86 (0.67, 1.12)
Sensitivity analyses						
100% Diabetic populations	--	--	--	--	--	--
100% CKD populations	--	--	--	--	--	--
Study populations with mean age ≥60y (n=6)[b]	63.34	Q(df=5) = 13.6370, *P*=0.02	34,841	235 (1.4)	278 (1.6)	0.82 (0.59, 1.13)

Note: This table lists studies which fit inclusion criteria and identified cardiovascular mortality as an outcome. Separate random effects meta-analyses for this outcome were conducted using the studies referenced above and based on blood pressure (BP) targets. Sensitivity analyses were conducted to further understand the effect of a lower target BP versus any higher target BP on populations of interest which included 1) only patients with diabetes, 2) only patients with CKD, or 3) a study population with mean age ≥60 years at baseline. Studies included in these analyses are listed in the footnotes. Additional information on study characteristics may be found in Table 2.5.

a. Includes ACCORD, SPRINT, HOMED-BP, REIN-2, and AASK.

b. Includes ACCORD, SPRINT, Cardio-Sis, SPS3, VALISH, JATOS, Wei et al, and HOT.

Table 2.11. Relative risk of major cardiovascular disease[a] event in the intensive [lower] versus the standard [higher] blood pressure group.

Comparison Groups Intensive (lower) vs standard (higher) BP target	Study	Author, Journal (Year)	N	Events, N (%) Intensive BP target	Standard BP target	RR (95% CI)
SBP Target (mm Hg)						
<120 vs <140	ACCORD (28)	Cushman WC, N Engl J Med (2010)	4,733	253 (10.7)	270 (11.4)	0.94 (0.80, 1.11)
<120 vs <140	SPRINT (30)	Wright JT, NEJM (2015)	9,361	243 (5.2)	319 (6.8)	0.76 (0.65, 0.90)
<130 vs <140	Cardio-Sis (31)	Verdecchia P, Lancet (2009)	1,111	17 (3.0)	32 (5.8)	0.79 (0.21, 2.94)
<140 vs ≥140 to <150	VALISH (33)	Ogihara T, Hypertension (2010)	3,260	32 (2.1)	37 (2.4)	0.86 (0.54, 1.37)
SBP/DBP Target (mm Hg)						
<125/<80 vs 125-134/80-84	HOMED-BP (37)	Asayama K, Hypertens Res (2012)	3,518	26 (1.5)	25 (1.4)	1.04 (0.60, 1.79)
≤140/90 vs ≤150/90	NR (39)	Wei Y, J Clin Hypertens (2013)	724	40 (11.0)	67 (18.6)	0.59 (0.41,0.85)
MAP Target (mm Hg)						
≤ 92 vs 102-107	AASK (46)	Norris K, Am J Kidney Dis (2006)	1,094	71 (13.1)	78 (14.1)	0.93 (0.69, 1.25)
Meta-analyses	**I^2 (%)**	**Q Test for Heterogeneity**				**RR (95% CI)**
Any SBP Target (n=4)	47.76	Q (df = 3) = 5.74, *P* = 0.12	18,283	545 (6.0)	658 (7.2)	0.81 (0.68, 0.98)
Intensive SBP target <130 (n= 5)[b]	40.70	Q (df = 4) = 6.75, *P* = 0.15	19,814	610 (6.2)	724 (7.3)	0.85 (0.73, 0.99)
All studies (n=7)	41.43	Q (df = 6) = 10.23, *P* = 0.12	23,617	682 (5.8)	828 (7.0)	0.81 (0.70, 0.94)
Sensitivity analyses						
100% Diabetic populations (n=1)	--	--	--	--	--	--
100% CKD populations (n=2)	--	--	--	--	--	--
Study populations with mean age ≥60y (n=5)[c]	54.59	Q (df=4)= 8.81, *P*=0.07	19,007	585 (6.2)	725 (7.6)	0.77 (0.64, 0.93)

Note: This table lists studies which fit inclusion criteria and identified major cardiovascular disease as an outcome. Separate random effects meta-analyses for this outcome were conducted using the studies referenced above and based on blood pressure (BP) targets. Sensitivity analyses were conducted to further understand the effect of a lower target BP versus any higher target BP on populations of interest which included 1) only patients with diabetes, 2) only patients with CKD, or 3) a study population with mean age ≥60 years at baseline. Studies included in these analyses are listed in the footnotes. Additional information on study characteristics may be found in Table 2.5.

a. Major cardiovascular disease events were included in the analysis only if defined and reported as a composite outcome by each trial, it included cardiovascular death, stroke, myocardial infarction, and heart failure.

b. Includes ACCORD, SPRINT, Cardio-Sis, HOMED-BP, and AASK.

c. Includes ACCORD, SPRINT, VALISH, JATOS, and Wei et al.

Table 2.12. Relative risk of fatal or non-fatal myocardial infarction in the intensive [lower] versus the standard [higher] blood pressure group.

Comparison Groups Intensive (lower) vs standard (higher) BP target	Study	Author, Journal (Year)	N	Events, N (%)		RR (95% CI)
				Intensive BP target	Standard BP target	
SBP Target (mm Hg)						
<120 vs <140	ACCORD [28]	Cushman WC, N Engl J Med (2010)	4,733	126 (5.3)	146 (6.2)	0.87 (0.69, 1.09)
<120 vs <140	SPRINT [30]	Wright JT, NEJM (2015)	9,361	97 (2.1)	116 (2.5)	0.84 (0.64, 1.09)
<130 vs <140	Cardio-Sis [31]	Verdecchia P, Lancet (2009)	1,110	4 (0.7)	6 (1.1)	0.66 (0.19, 2.33)
<130 vs <140	SPS3 [32]	Benavente, Lancet (2013)	3,020	36 (2.4)	40 (2.6)	0.91 (0.58, 1.42)
<140 vs ≥140 to <150	VALISH [33]	Ogihara T, Hypertension (2010)	3,079	5 (0.3)	4 (0.3)	1.24 (0.33, 4.61)
<140 vs ≥ 140 to <160	JATOS [35]	JATOS, Hypertens Res (2008)	4,418	6 (0.3)	6 (0.3)	1.00 (0.32, 3.09)
SBP/DBP Target (mm Hg)						
<125/<80 vs 125-134/80-84	HOMED-BP [37]	Asayama K, Hypertens Res (2012)	3,518	5 (0.3)	7 (0.4)	0.71 (0.23, 2.25)
<130/80 vs <90	REIN-2 [38]	Ruggenenti P, Lancet (2005)	338	1 (0.6)	1 (0.6)	1.01 (0.06, 16.0)
≤140/90 vs ≤150/90	NR [39]	Wei Y, J Clin Hypertens (2013)	724	9 (2.5)	9 (2.5)	0.99 (0.40, 2.48)
<150/85 vs <180/105	UKPDS [40]	UKPDS Group, BMJ (1998) [a]	1,148	107 (14.1)	69 (17.7)	0.80 (0.60, 1.05)
DBP Target (mm Hg)						
75 vs 80-89	ABCD [42]	Schrier RW, Kidney Intl (2002)	480	19 (8.0)	15 (6.2)	1.30 (0.68, 2.49)
Meta-analyses	**I^2 (%)**	**Q Test for Heterogeneity**				**RR (95% CI)**
Any SBP target (n=6)	0.00	Q (df = 5) = 0.63, *P* = 0.99	25,721	274 (2.1)	318 (2.5)	0.86 (0.74, 1.01)
Intensive SBP target <130 (n=6) [b]	0.00	Q (df = 5) = 0.38, *P* = 0.99	22,077	269 (2.4)	316 (2.9)	0.85 (0.73, 1.00)
All studies (n=11)	0.00	Q (df = 10) = 2.66, *P* = 0.99	31,926	415 (2.6)	419 (2.7)	0.86 (0.76, 0.99)
Sensitivity analyses						
100% Diabetic populations (n=3) [c]	0.00	Q (df = 2) = 1.82, *P* = 0.40	6351	252 (7.5)	230 (7.7)	0.86 (0.73, 1.02)
100% CKD populations (n=1)	--	--	--	--	--	--
Study populations with mean age ≥60y (n=7) [d]	0.00	Q(df=6) = 0.72, P= 0.99	26,445	283 (2.1)	327 (2.5)	0.87 (0.74, 1.01)

Note: This table lists studies which fit inclusion criteria and identified fatal or nonfatal myocardial infarction as an outcome. Separate random effects meta-analyses for this outcome were conducted using the studies referenced above and based on blood pressure (BP) targets. Sensitivity analyses were conducted to further understand the effect of a lower target BP versus any higher target BP on populations of interest which included 1) only patients with diabetes, 2) only patients with CKD, or 3) a study population with mean age ≥60 years at baseline. Studies included in these analyses are listed in the footnotes. Additional information on study characteristics may be found in Table 2.5.

a. Includes fatal or non-fatal myocardial infarction or sudden death.
b. Includes ACCORD, SPRINT, Cardio-Sys, SPS 3, HOMED-BP, and REIN-2.
c. Includes ACCORD, UKPDS, ABCD.
d. Includes ACCORD, SPRINT, Cardio-Sis, SPS3, VALISH, JATOS, and Wei et al.

Table 2.13. Relative risk of fatal or non-fatal stroke in in the intensive [lower] versus the standard [higher] blood pressure group.

Comparison Groups Intensive (lower) vs standard (higher) BP target	Study	Author, Journal (Year)	N	Events, N (%) Intensive BP target	Standard BP target	RR (95% CI)
SBP Target (mm Hg)						
<120 vs <140	ACCORD [28]	Cushman WC, N Engl J Med (2010)	4,733	36 (1.5)	62 (2.6)	0.58 (0.39, 0.88)
<120 vs <140	SPRINT [30]	Wright JT, NEJM (2015)	9,361	62 (1.3)	70 (1.5)	0.89 (0.63, 1.24)
<130 vs <140	Cardio-Sis [31]	Verdecchia P, Lancet (2009) [a]	1,111	4 (0.7)	9 (1.6)	0.44 (0.14, 1.42)
<130 vs <140	SPS3 [32]	Benavente, Lancet (2013)	3,020	125 (8.3)	152 (10.0)	0.83 (0.66, 1.04)
<140 vs ≥140 to <150	VALISH [33]	Ogihara T, Hypertension (2010)	3,260	16 (1.0)	23 (1.5)	0.69 (0.37, 1.30)
<140 vs ≥ 140 to <160	JATOS [35]	JATOS, Hypertens Res (2008)	4,418	36 (1.6)	30 (1.4)	1.20 (0.74, 1.94)
SBP/DBP Target (mm Hg)						
<125/<80 vs 125-134/80-84	HOMED-BP [37]	Asayama K, Hypertens Res (2012) [b]	3,518	20 (1.1)	16 (0.9)	1.25 (0.65, 2.40)
<130/80 vs <90	REIN-2 [38]	Ruggenenti P, Lancet (2005) [c]	338	1 (0.6)	1 (0.6)	1.01 (0.06, 15.95)
≤140/90 vs ≤150/90	NR [39]	Wei Y, J Clin Hypertens (2013)	724	21 (5.8)	36 (10.0)	0.58 (0.35, 0.97)
<150/85 vs <180/105	UKPDS [40]	UKPDS Group, BMJ (1998)	1,148	38 (5.0)	34 (8.7)	0.42 (0.18, 1.01)
DBP Target (mm Hg)						
75 vs 80-89	ABCD [42]	Schrier RW, Kidney Intl (2002)	480	4 (1.7)	13 (5.4)	0.32 (0.10, 0.95)
MAP Target (mm Hg)						
≤ 92 vs 102-107	AASK [46]	Norris K, Am J Kidney Dis (2006)	1,094	26 (4.8)	29 (5.3)	0.92 (0.55, 1.54)
Meta-analyses	**I^2 (%)**	**Q Test for Heterogeneity**				**RR (95% CI)**
Any SBP target (n=6)	24.76	Q (df = 5) = 6.65, *P* = 0.25	25,721	279 (2.2)	346 (2.7)	0.81 (0.66, 0.98)
Intensive SBP target <130 (n=7) [d]	0.00	Q (df = 6) = 5.79, P = 0.45	23,169	274 (2.4)	339 (2.9)	0.82 (0.70, 0.96)
All studies (n=12)	26.43	Q (df = 11) = 14.95, *P* = 0.18	33,018	389 (2.3)	475 (2.9)	0.77 (0.65, 0.91)
Sensitivity analyses						
100% Diabetic populations (n=3) [e]	0.00	Q (df = 2) = 1.08, *P* = 0.58	6361	78 (2.3)	109 (3.6)	0.56 (0.42, 0.74)
100% CKD populations (n=2)	--	--	--	--	--	--
Study populations with mean age ≥60y (n=7) [f]	26.35	Q(df=6) = 8.15, *P*=0.23	26,445	300 (2.3)	382 (2.9)	0.78 (0.64, 0.94)

Note: This table lists studies which fit inclusion criteria and identified fatal or nonfatal stroke as an outcome. Separate random effects meta-analyses for this outcome were conducted using the studies referenced above and based on blood pressure (BP) targets. Sensitivity analyses were conducted to further understand the effect of a lower target BP versus any higher target BP on populations of interest which included 1) only patients with diabetes, 2) only patients with CKD, or 3) a study population with mean age ≥≥60 years at baseline. Studies included in these analyses are listed in the footnotes. Additional information on study characteristics may be found in Table 2.5.

a. Composite outcome included fatal or non-fatal stroke or transient ischemic attack.
b. Non-fatal stroke only.
c. Fatal stroke only.
d. Includes ACCORD, SPRINT, Cardio-Sys, HOMED-BP, REIN-2, AASK, and SPS3.
e. Includes ACCORD, UKPDS, and ABCD.
f. Includes ACCORD, SPRINT, Cardio-Sis, SPS3, VALISH, JATOS, and Wei et al.

Table 2.14. Relative risk of fatal or non-fatal heart failure in the intensive [lower] versus the standard [higher] blood pressure group.

Comparison Groups Intensive (lower) vs standard (higher) BP target	Study	Author, Journal (Year)	N	Events, N (%)		
				Intensive BP target	Standard BP target	RR (95% CI)
SBP Target (mm Hg)						
<120 vs <140	ACCORD [28]	Cushman WC, N Engl J Med (2010)	4,733	83 (3.5)	90 (3.8)	0.93 (0.69, 1.24)
<120 vs <140	SPRINT [30]	Wright JT, NEJM (2015)	9,361	62 (1.3)	100 (2.1)	0.62 (0.45, 0.85)
<130 vs <140	Cardio-Sis [31]	Verdecchia P, Lancet (2009)	1,111	3 (0.5)	7 (1.3)	0.43 (0.11, 1.64)
<140 vs ≥ 140 to <160	JATOS [35]	JATOS, Hypertens Res (2008)	4,418	8 (0.4)	7 (0.3)	1.14 (0.41, 3.14)
SBP/DBP Target (mm Hg)						
≤140/90 vs ≤150/90	NR [39]	Wei Y, J Clin Hypertens (2013)	724	6 (1.7)	16 (4.4)	0.37 (0.15, 0.94)
<150/85 vs <180/105	UKPDS [40]	UKPDS Group, BMJ (1998)	1,148	21 (2.8)	24 (2.6)	0.45 (0.25, 0.80)
DBP Target (mm Hg)						
10 mm Hg below baseline vs 80-89	ABCD [42]	Schrier RW, Kidney Intl (2002)	480	12 (5.1)	11 (4.5)	1.12 (0.50, 2.49)
MAP Target (mm Hg)						
≤ 92 vs 102-107	AASK [46]	Norris K, Am J Kidney Dis (2006)	1,094	27 (5.0)	23 (4.2)	1.20 (0.70, 2.07)
Meta-analyses	**I^2 (%)**	**Q Test for Heterogeneity**				**RR (95% CI)**
Any SBP target (n=4)	35.48	Q(df = 3) = 4.65, P = 0.20	19,622	156 (1.6)	204 (2.1)	0.77 (0.56, 1.04)
Intensive SBP target <130 (n=4)[a]	53.42	Q(df = 3) = 6.44, P = 0.09	16,296	175 (2.2)	220 (2.7)	0.81 (0.58, 1.14)
All studies (n=8)	49.12	Q(df = 7) = 13.76, P = 0.06	23,066	222 (1.9)	278 (2.4)	0.75 (0.56, 0.99)
Sensitivity analyses						
100% Diabetic populations (n=3)[b]	63.30	Q(df = 2) = 5.45, P = 0.07	6361	116 (3.3)	125 (4.2)	0.77 (0.46, 1.28)
100% CKD populations (n=2)	--	--	--	--	--	--
Study populations with mean age ≥60y (n=5)[c]	41.98	Q(df= 4) = 6.8937, P=0.14	20,346	162 (1.6)	220 (2.2)	0.71 (0.51, 0.99)

Note: This table lists studies which fit inclusion criteria and identified fatal or nonfatal heart failure as an outcome. Separate random effects meta-analyses for this outcome were conducted using the studies referenced above and based on blood pressure (BP) targets. Sensitivity analyses were conducted to further understand the effect of a lower target BP versus any higher target BP on populations of interest which included 1) only patients with diabetes, 2) only patients with CKD, or 3) a study population with mean age ≥60 years at baseline. Studies included in these analyses are listed in the footnotes. Additional information on study characteristics may be found in Table 2.5.

a. Includes ACCORD, SPRINT, Cardio-Sys, and AASK.

b. Includes ACCORD, UKPDS, and ABCD.

c. Includes ACCORD, SPRINT, Cardio-Sis, JATOS, and Wei et al.

Table 2.15. Relative risk of renal events [a] in the intensive [lower] versus the standard [higher] blood pressure group.

Comparison Groups Intensive (lower) vs standard (higher) BP target	Study	Author, Journal (Year)	N	Events, N (%) Intensive BP target	Events, N (%) Standard BP target	RR (95% CI)
SBP Target (mm Hg)						
<120 vs <140	ACCORD (29)	Ismail-Beigi F, Kidney Intl (2012)	4,733	61 (2.6)	64 (2.7)	0.96 (0.68, 1.36)
<120 vs <140	SPRINT (30)	Wright JT, NEJM (2015)	9,361	14 (1.1)	15 (1.1)	0.92 (0.45, 1.91)
<140 vs ≥140 to <150	VALISH (33)	Ogihara T, Hypertension (2010)	3,260	5 (0.3)	2 (0.1)	2.48 (0.48,12.77)
<140 vs ≥ 140 to <160	JATOS (34)	Hayashi K, Hypertens Res (2010)	4,418	8 (0.4)	9 (0.4)	0.89 (0.34, 2.29)
SBP/DBP Target (mm Hg)						
<130/80 vs <90	REIN-2 (38)	Ruggenenti P, Lancet (2005)	338	38 (23.0)	34 (20.0)	1.12 (0.75, 1.69)
<150/85 vs <180/105	UKPDS (40)	UKPDS Group, BMJ (1998)	1,148	8 (1.1)	7 (1.8)	0.59 (0.21, 1.61)
MAP Target (mm Hg)						
≤ 92 vs 102-107	AASK (45)	Wright, JAMA (2002)	1,094	173 (32.0)	167 (30.1)	1.06 (0.89, 1.27)
≤ 92 vs <107 (age ≤60 y) or < 98 vs <113 (age ≥61 y)	MDRD (47)	Sarnak, Ann Intern Med (2005)[b]	840	61 (14.1)	66 (16.2)	0.87 (0.63, 1.20)
Meta-analyses	**I^2 (%)**	**Q Test for Heterogeneity**				**RR (95% CI)**
Intensive SBP target <130 (n=5)[c]	0.00	Q(df = 4) = 1.52, *P* = 0.82	9,641	313 (7.4)	335 (7.9)	1.01 (0.89, 1.16)
All studies (n=8)	0.00	Q(df = 7) = 3.86, *P* = 0.80	18,286	334 (3.8)	353 (4.2)	1.01 (0.89, 1.15)
Sensitivity analyses						
100% Diabetic populations (n=2)	--	--	--	--	--	--
100% CKD populations (n=3)[d]	0.00	Q (df = 2), = 1.32, *P*=0.52	2269	272 (23.9)	267 (23.6)	1.03 (0.89, 1.19)
Study populations with mean age ≥60y (n=4)[e]	0.00	Q (df = 3), = 1.32, *P*=0.72	14,869	88 (1.2)	90 (1.2)	0.97 (0.73, 1.31)

Note: This table lists studies which fit inclusion criteria and identified renal events as an outcome. Separate random effects meta-analyses for this outcome were conducted using the studies referenced above and based on blood pressure (BP) targets. Sensitivity analyses were conducted to further understand the effect of a lower target BP versus any higher target BP on populations of interest which included 1) only patients with diabetes, 2) only patients with CKD, or 3) a study population with mean age ≥60 years at baseline. Studies included in these analyses are listed in the footnotes. Additional information on study characteristics may be found in Table 2.5.

a. Renal events include the following composite of outcomes: end stage renal disease or death, doubling of serum creatinine, reduction in glomerular filtration rate (GFR) of 50%, long-term dialysis, kidney transplantation, progression of chronic kidney disease (CKD), renal failure, and renal failure in absence of acute reversible cause.

b. In-trial results presented.

c. Includes: ACCORD, SPRINT, REIN-2, AASK, and MDRD.

d. Includes REIN-2, AASK, and MDRD.

e. Includes ACCORD, SPRINT, VALISH, and JATOS.

Table 2.16. Renal outcomes data including data from the longest available follow-up in AASK and MDRD, not in-trial data.

Comparison Groups Intensive (lower) vs standard (higher) BP target	Study	Author, Journal (Year)	N	Events, N (%)		
				Intensive BP target	Standard BP target	RR (95% CI)
SBP Target (mm Hg)						
<120 vs <140	ACCORD [29]	Ismail-Beigi F, Kidney Intl (2012)	4,733	61 (2.6)	64 (2.7)	0.96 (0.68, 1.36)
<120 vs <140	SPRINT [30]	Wright JT, NEJM (2015)	9,361	14 (1.1)	15 (1.1)	0.92 (0.45, 0.99)
<140 vs ≥140 to <150	VALISH [33]	Ogihara T, Hypertension (2010)	3,260	5 (0.3)	2 (0.1)	2.48 (0.48,12.77)
<140 vs ≥ 140 to <160	JATOS [34]	Hayashi K, Hypertens Res (2010)	4,418	8 (0.4)	9 (0.4)	0.89 (0.34, 2.29)
SBP/DBP Target (mm Hg)						
<130/80 vs <90	REIN-2 [38]	Ruggenenti P, Lancet (2005)	338	38 (23.0)	34 (20.0)	1.12 (0.75, 1.69)
<150/85 vs <180/105	UKPDS [40]	UKPDS Group, BMJ (1998)	1,148	8 (1.1)	7 (1.8)	0.59 (0.21, 1.61)
MAP Target (mm Hg)						
≤ 92 vs 102-107	AASK [25]	Appel LJ, NEJM (2010)*	1,094	238 (44.1)	256 (46.2)	1.02 (0.91, 1.14)
≤ 92 vs <107 (age ≤60 y) or < 98 vs <113 (age ≥61 y)	MDRD [27]	Ku E, Kidney Intl (2014)*	840	308 (71.3)	319 (78.2)	0.91 (0.84, 0.99)
Meta-analyses	**I^2 (%)**	**Q Test for Heterogeneity**				**RR (95% CI)**
Intensive SBP target <130 (n=5)[a]	0.00	Q (df = 2) = 0.01, P = 0.99	9,641	313 (7.4)	335 (7.9)	0.95 (0.89, 1.01)
All studies (n=8)	0.00	Q (df = 7) = 5.19, *P* = 0.64	18,286	334 (3.8)	353 (4.2)	0.95 (0.89, 1.01)

Note: This table lists studies which fit inclusion criteria and identified fatal or nonfatal myocardial infarction as an outcome. Separate random effects meta-analyses for this outcome were conducted using the studies referenced above and based on blood pressure (BP) targets. Sensitivity analyses were conducted to further understand the effect of a lower target BP versus any higher target BP on populations of interest which included 1) only patients with diabetes, 2) only patients with CKD, or 3) a study population with mean age ≥≥60 years at baseline. Studies included in these analyses are listed in the footnotes. Additional information on study characteristics may be found in Table 2.5.

Renal events include the following: composite renal end points, renal events, progression of chronic kidney disease (CKD), renal failure, renal failure in absence of acute reversible cause.

a. Includes: ACCORD, SPRINT, REIN-2, AASK, and MDRD.

* Longest follow up selected, follow up after the intervention phase of the trial

Table 2.17. Sensitivity Analyses Examining the Relative Risk (95% Confidence Interval) for a Given Outcome for Intensive [Lower] Blood Pressure Target Versus any Standard [Higher] Blood Pressure Target Outcomes Among Studies in Patients with Diabetes Mellitus, Chronic Kidney Disease, or Mean Population Age ≥60 Years.

Outcome Subpopulation of interest	Studies included, N	Study participants included, N	Events, N (%)		RR	(95% CI)	Heterogeneity		Funnel Plot Asymmetry	
			Intensive BP target	Standard BP target			I^2 (%)	*P*-value	P-value for Kendall's Tau (rank correlation)	P-value for Egger's Regression Test
All-cause mortality										
100% diabetes	3	6351	297 (8.8)	252 (3.7)	0.85	(0.64, 1.14)	60.87	0.08	0.33	0.34
100% CKD	3	2269	51 (4.5)	53 (4.7)	0.96	(0.66, 1.40)	0.00	0.46	1.00	0.82
Mean age ≥60y	8	38,971	751 (3.9)	807 (4.1)	0.92	(0.76, 1.11)	67.11	0.003	0.55	0.80
CVD mortality										
100% diabetes	2	--	--	--	--	--	--	--	--	--
100% CKD	2	--	--	--	--	--	--	--	--	--
Mean age ≥60y	6	34,841	235 (1.4)	278 (1.6)	0.82	(0.59, 1.13)	63.34	0.02	0.47	0.89
Major Cardiovascular Disease Events										
100% diabetes	1	--	--	--	--	--	--	--	--	--
100% CKD	2	--	--	--	--	--	--	--	--	--
Mean age ≥60y	5	19,007	585 (6.2)	725 (7.6)	0.77	(0.64, 0.93)	54.59	0.07	0.48	0.29
Fatal or non-fatal myocardial infarction										
100% diabetes	3	6351	252 (7.5)	230 (7.7)	0.86	(0.73, 1.02)	0.00	0.40	1.00	0.35
100% CKD	1	--	--	--	--	--	--	--	--	--
Mean age ≥60y	7	26,445	283 (2.1)	327 (2.5)	0.87	(0.74, 1.01)	0.00	0.99	0.38	0.32
Fatal or non-fatal stroke										
100% diabetes	3	6351	78 (2.3)	109 (3.6)	0.56	(0.42, 0.74)	0.00	0.58	0.33	0.04
100% CKD	2	--	--	--	--	--	--	--	--	--
Mean age ≥60y	7	26,445	300 (2.3)	382 (2.9)	0.78	(0.64, 0.94)	26.35	0.23	0.77	0.37
Fatal or non-fatal heart failure										
100% diabetes	3	6351	116 (3.3)	125 (4.2)	0.77	(0.46, 1.28)	63.30	0.07	1.00	0.78
100% CKD	1	--	--	--	--	--	--	--	--	--
Mean age ≥60y	5	20,346	162 (1.6)	220 (2.2)	0.71	(0.51, 0.99)	41.98	0.14	0.84	0.55
Renal Events										
100% diabetes	2	--	--	--	--	--	--	--	--	--

100% CKD	3	2269	272 (23.9)	267 (23.6)	1.03	(0.89, 1.19)	0.00	0.52	1.00	0.81
Mean age ≥60y	4	14,869	88 (1.2)	90 (1.2)	0.97	(0.73, 1.31)	0.00	0.72	0.75	0.41

Note: Sensitivity analyses were conducted to further understand the effect of a lower target BP versus any higher target BP on populations of interest which included 1) only patients with diabetes, 2) only patients with CKD, or 3) a study population with mean age ≥60 years at baseline. Sensitivity analyses were conducted if three or more studies included the outcome and population of interest. Studies included in these analyses are listed in the footnotes. Additional information on study characteristics may be found in Table 2.5.

a. ACCORD (28), UKPDS (40), and ABCD (41).
b. REIN-2 (38), AASK (54), and MDRD (47)
c. ACCORD (28), SPRINT (30), Cardio-Sis (31), SPS3 (32), VALISH (33), JATOS (35), Wei et al (39), and HOT (44).
d. ACCORD (28), SPRINT (30), VALISH (33), JATOS (35), and Wei et al (39).
e. ACCORD (28), SPRINT (30), Cardio-Sis (31), VALISH (33), and Wei et al (39).
f. ACCORD (28), SPRINT (30), Cardio-Sis (31), SPS3 (32), VALISH (33), JATOS (35), and Wei et al (39).
g. ACCORD (28), SPRINT (30), JATOS (35), and Wei et al (39).
h. ACCORD (34), SPRINT (30), VALISH (33), and JATOS (34).

Table 2.18. Effect estimates and subgroup analyses reported by each study included in this meta-analysis: Relative risk (95% confidence interval) for a given outcome for any intensive [lower] blood pressure target vs any standard [higher] blood pressure target.

Outcome	Study Acronym	Overall or Subgroup	N		Events, N (%/yr) or (%*)		Effect Estimate (95% CI)	*P*-value
			Intensive BP target	Standard BP target	Intensive BP target	Standard BP target		
All-cause mortality	ACCORD [28]	Overall	2362	2371	150 (1.28)	144 (1.19)	HR: 1.07 (0.85-1.35)	0.55
	SPRINT [30]	Overall	4678	4683	155 (1.03)	210 (1.40)	HR: 0.73 (0.60-0.90)	0.003
	Cardio-Sis [31]	Overall	557	553	4 (0.7*)	5 (0.9*)	HR: 0.77 (0.21-2.88)	0.70
	SPS3 [32]	Overall	1501	1519	106 (1.80)	101 (1.74)	HR: 1.03 (0.79-1.35)	0.82
	SPS3 [17]	≥75 years	248	246	37 (3.89)	40 (4.53)	HR: 0.83 (0.53-1.29)	0.41
	SPS3 [17]	<75 years	1253	1273	69 (1.40)	61 (1.24)	HR: 1.13 (0.80-1.59)	0.49
	JATOS [35]	Overall	2212	2206	54 (2.44*)	42 (1.90*)	HR: NR	0.22
	HALT-PDK [36]	Overall	274	284	0 (0.00)	2 (0.70)	HR: NR	NR
	HOMED-BP [37]	Overall	1759	1759	27 (1.53)	31 (1.76)	HR: 1.25 (0.97–1.60)	0.08
	REIN-2 [38]	Overall	167	168	2 (1.20)	3 (1.79)	NR	NR
	Wei et al. [39]	Overall	363	361	51 (14.05)	87 (24.10)	NR	NR
	UKPDS [40]	Overall	758	390	134 (17.67*)	83 (21.28*)	RR: 0.82 (0.63 - 1.08)	0.17
	ABCD [41]	Overall	237	233	13 (5.5*)	25 (10.7*)	HR: NR	0.037
	HOT [44]	Overall	6262	6264	207 (3.30*)	188 (3.00*)	RR: 0.91 (0.74-1.10)	NR
	HOT [44]	Diabetes at baseline	499	501	17 (3.4*)	30 (6.0*)	RR: 1.77 (0.98-3.21)	NR
	AASK [54]	Overall	540	554	37 (6.85*)	43 (7.76*)	NR	NR
	MDRD [47]	Overall	432	408	12 (2.8)	7 (1.7)	HR: NR	NR
CVD mortality	ACCORD [28]	Overall	2362	2371	60 (0.52)	58 (0.49)	HR: 1.06 (0.74-1.52)	0.74
	SPRINT [30]	Overall	4678	4683	37 (0.25)	65 (0.43)	HR: 0.57 (0.38-0.85)	0.005
	VALISH [33]	Overall	1545	1534	11 (0.71)	11 (0.72)	HR: 0.97 (0.42-2.25)	0.95
	JATOS [35]	Overall	2212	2206	6 (0.27)	4 (0.18)	HR: NR	0.53
	HOMED-BP [37]	Overall	1759	1759	3 (0.17)	5 (0.28)	HR: 1.46 (0.77–2.74)	0.24
	REIN-2 [38]	Overall	167	168	1 (0.60)	2 (1.19)	HR: NR	NR
	Wei et al. [39]	Overall	363	361	25 (6.89)	50 (13.85)	HR: NR	0.002
	ABCD [42]	Overall	237	243	13 (5.4*)	9 (3.7*)	OR: 0.66 (0.28 – 1.58)	0.35
	HOT [44]	Overall	6262	6264	96 (1.53*)	87 (1.39*)	OR: 0.90 (0.68-1.21)	NR
	HOT[44]	Diabetes at baseline	499	501	7 (1.4*)	21 (4.2*)	RR: 3.0 (1.28-7.08)	NR
	AASK [46]	Overall	540	554	16 (3.0*)	15 (2.7*)	HR: 0.98 (0.48-2.01)	0.96
Major Cardiovascular Disease Events	ACCORD [28]	Overall	2362	2371	208 (1.87)	237 (2.09)	HR: 0.88 (0.73-1.06)	0.20
	ACCORD [28]	Male	1234	1241	1234 (2.15)	1241 (2.41)	See below, figure 1.	0.98
	ACCORD [28]	Female	1128	1130	1128 (1.56)	1130 (1.75)	Summary: Subgroup analyses were reported for the primary outcome (composite of nonfatal myocardial infarction, nonfatal stroke, or death from cardiovascular	
	ACCORD [28]	<65 yrs	1568	1548	1568 (1.54)	1548 (1.72)		0.98
	ACCORD [28]	≥65 yrs	794	823	794 (2.53)	823 (2.79)		
	ACCORD [28]	White	1452	1414	1452 (1.97)	1414 (2.34)		0.44
	ACCORD[28]	Nonwhite	910	957	910 (1.72)	957 (1.74)		
	ACCORD [28]	HbA1c ≤8.0	1050	1160	1050 (1.34)	1160 (1.82)		0.11
	ACCORD [28]	HbA1c >8.0	1309	1201	1309 (2.31)	1201 (2.35)		

	ACCORD [28]	Prior CVD, No	1558	1582	1558 (1.33)	1582 (1.46)	causes). Although intensive intervention appeared to provide better results for all subgroups for the primary outcome, none of the subgroup analyses reached statistical significance.	0.78
	ACCORD [28]	Prior CVD, Yes	804	789	804 (2.98)	789 (3.43)		
	SPRINT [30]	Overall	4678	4683	243 (1.65)	319 (6.8)	HR: 0.75 (0.64-0.89)	<0.001
	SPRINT [30]	Male	2994	3035	166 (5.5*)	230 (7.6*)	HR: 0.72 (0.59-0.88)	0.45
	SPRINT [30]	Female	1684	1648	77 (4.6*)	89 (5.4*)	HR: 0.84 (0.62-1.14)	
	SPRINT [30]	<75 yrs	3361	3364	142 (4.2*)	175 (5.2*)	HR: 0.80 (0.64–1.00)	0.32
	SPRINT [30]	≥75 yrs	1317	1319	101 (7.7*)	144 (10.9*)	HR: 0.67 (0.51–0.86)	
	SPRINT [30]	Black	1454	1493	62 (4.3*)	85 (5.7*)	HR: 0.77 (0.55–1.06)	0.83
	SPRINT [30]	Nonblack	3224	3190	181 (5.6*)	234 (7.3*)	HR: 0.74 (0.61–0.90)	
	SPRINT [30]	Prior CVD, No	3738	3746	149 (4.0*)	208 (5.6*)	HR: 0.71 (0.57–0.88)	0.39
	SPRINT [30]	Prior CVD, Yes	940	937	94 (10.0*)	111 (11.8*)	HR: 0.83 (0.62–1.09)	
	SPRINT [30]	Prior CKD, No	3348	3367	135 (4.0*)	193 (5.7*)	HR: 0.70 (0.56-0.87)	0.36
	SPRINT [30]	Prior CKD, Yes	1330	1316	108 (8.1*)	126 (9.6*)	HR: 0.82 (0.63-1.07)	
	VALISH [33]	Overall	1545	1534	32 (2.07)	37 (2.41)	HR: 0.84 (0.53-1.36)	0.48
	HOMED-BP [37]	Overall	1759	1759	26 (1.48)	25 (1.42)	HR: 1.44 (1.21–1.72)	<0.001
	Wei et al. [39]	Overall	363	361	40 (11.02)	67 (18.56)	HR: NR	0.004
	HOT [44]	Overall	6262	6264	217 (3.47*)	232 (3.70*)	RR: 1.07 (0.89-1.28)	NR
	HOT [44]	Diabetes at baseline	499	501	22 (4.4*)	45 (9.0*)	RR: 2.06 (1.24-3.44)	NR
	AASK [46]	Overall	540	554	71 (13.1*)	78 (14.1*)	HR: 0.84 (0.61-1.16)	0.29
Fatal or non-fatal myocardial infarction	ACCORD [28]	Overall	2362	2371	126 (1.13)	146 (1.28)	HR: 0.87 (0.68-1.10)	0.25
	SPRINT [30]	Overall	4678	4683	97 (0.65)	116 (0.78)	HR: 0.83 (0.64-1.09)	0.19
	Cardio-Sis [31]	Overall	557	553	4 (0.7*)	6 (1.1*)	HR: 0.66 (0.19-2.34)	0.52
	SPS3 [32]	Overall	1501	1519	36 (0.62)	40 (0.70)	HR: 0.88 (0.56-1.39)	0.59
	SPS3 [17]	≥75 years	248	246	5 (0.53)	6 (0.69)	HR: 0.77 (0.23-2.52)	0.66
	SPS3[17]	<75 years	1253	1273	31 (0.64)	34 (0.70)	HR: 0.91 (0.56-1.48)	0.71
	VALISH [33]	Overall	1545	1534	5 (0.32)	4 (0.26)	HR: 1.23 (0.33-4.56)	0.76
	JATOS [35]	Overall	2212	2206	6 (0.27)	6 (0.27)	HR: NR	NR
	HOMED-BP [37]	Overall	1759	1759	5 (0.28)	7 (0.40)	HR: 1.57 (0.98–2.50)	0.06
	REIN-2 [38]	Overall	167	168	1 (0.60)	1 (0.60)	HR: NR	NR
	Wei et al. [39]	Overall	363	361	9 (2.48)	9 (2.49)	HR: NR	0.99
	UKPDS [40]	Overall	758	390	107 (14.12*)	69 (17.69*)	RR: 0.79 (0.59 - 1.07)	0.13
	ABCD [42]	Overall	237	243	19 (8.0*)	15 (6.2*)	OR: 0.75 (0.37-1.52)	0.43
	HOT [44]	Overall	6262	6264	61 (0.97*)	84 (1.34*)	RR: 1.37 (0.99-1.91)	NR
	HOT [44]	Diabetes at baseline	499	501	7 (1.4*)	14 (2.8*)	RR: 2.01 (0.81-4.97)	NR
Fatal or non-fatal stroke	ACCORD [28]	Overall	2362	2371	36 (0.32)	62 (0.53)	HR: 0.59 (0.39-1.35)	0.55
	SPRINT [30]	Overall	4678	4683	62 (0.41)	70 (0.47)	HR: 0.89 (0.63-1.25)	0.50
	Cardio-Sis [31]	Overall	557	553	4 (0.7*)	9 (1.6*)	HR: 0.44 (0.13-1.42)	0.16
	SPS3 [32]	Overall	1501	1519	125 (2.25)	152 (2.77)	HR: 0.81 (0.64-1.03)	0.08

	SPS3 [32]	Male (n=1902)	NR	NR	80 (2.41)	111 (3.09)	HR: 0.78 (0.59-1.04)	0.50
	SPS3 [32]	Female (n=1118)	NR	NR	45 (2.01)	41 (2.17)	HR: 0.93 (0.61-1.43)	
	SPS3 [32]	<65 yrs (n=1757)	NR	NR	68 (2.05)	87 (2.71)	HR: 0.76 (0.55-1.05)	0.53
	SPS3 [32]	≥65 yrs (n=1263)	NR	NR	57 (2.53)	67 (2.86)	HR: 0.89 (0.62-1.26)	
	SPS3[32]	Hispanic (n=916)	NR	NR	29 (1.83)	36 (2.23)	HR: 0.82 (0.51-1.34)	0.85
	SPS3 [32]	White (n=1538)	NR	NR	63 (2.22)	72 (2.56)	HR: 0.86 (0.62-1.21)	
	SPS3 [32]	Black (n=492)	NR	NR	30 (3.04)	37 (4.09)	HR: 0.75 (0.47-1.22)	
	SPS3 [32]	Other/mixed Race (n=74)	NR	NR	3 (2.11)	7 (4.53)	HR: 0.48 (0.12-1.85)	
	SPS3 [32]	Non-diabetic (n=1914)	NR	NR	59 (1.64)	78 (2.15)	HR: 0.76 (0.54-1.07)	0.64
	SPS3 [32]	Diabetes (n=1106)	NR	NR	66 (3.37)	74 (3.97)	HR: 0.85 (0.61-1.19)	
	SPS3 [17]	≥75 years	248	246	27 (3.07)	26 (3.07)	HR: 1.01 (0.59-1.73)	0.98
	SPS3 [17]	<75 years	1253	1273	98 (2.09)	126 (2.72)	HR: 0.77 (0.59-1.01)	0.06
	VALISH [33]	Overall	1545	1534	16 (1.04)	23 (1.50)	HR: 0.68 (0.36-1.29)	0.24
	JATOS [35]	Overall	2212	2206	36 (1.63)	30 (1.35)	HR: NR	NR
	HOME-BP [37]	Overall	1759	1759	20 (1.14)	16 (0.91)	HR: 1.53 (1.14–2.05)	0.005
	REIN-2 [38]	Overall	167	168	0 (0.00)	1 (0.60)	HR: NR	NR
	Wei et al. [39]	Overall	363	361	21 (5.79)	36 (9.97)	HR: NR	0.87
	UKPDS [40]	Overall	758	390	38 (5.01*)	34 (8.72*)	RR: 0.56 (0.35 – 0.89)	0.013
	ABCD [42]	Overall	237	243	4 (1.7*)	13 (5.4*)	OR: 3.29 (1.06 – 10.25)	0.03
	HOT [44]	Overall	6262	6264	89 (1.42*)	94 (1.50*)	RR1.37 (0.99-1.91)	NR
	HOT[44]	Diabetes at baseline	499	501	12 (4.4*)	17 (9.0*)	RR: 1.43 (0.68- 2.99)	NR
	AASK [46]	Overall	540	554	26 (4.8*)	29 (5.3*)		
Fatal or non-fatal heart failure	ACCORD [28]	Overall	2362	2371	83 (0.73)	90 (0.78)	HR: 0.94 (0.70-1.26)	0.67
	SPRINT [30]	Overall	4678	4683	62 (0.41)	100 (0.67)	HR: 0.62 (0.45-0.84)	0.002
	Cardio-Sis [31]	Overall	557	553	3 (0.5*)	7 (1.3*)	HR: 0.42 (0.11-1.63)	0.21
	JATOS [35]	Overall	2212	2206	8 (0.36)	7 (0.32)	HR: NR	NR
	Wei et al. [39]	Overall	363	361	6 (1.65)	16 (4.43)	HR: NR	0.03
	UKPDS [40]	Overall	758	390	21 (2.77*)	24 (6.15*)	RR: 0.44 (0.20 – 0.94)	0.004
	ABCD [42]	Overall	237	243	12 (5.1*)	11 (4.5*)	OR: 0.89 (0.38 – 2.06)	0.78
	AASK [46]	Overall	540	554	27 (5.0*)	23 (4.2*)	NR	NR
Renal Events	ACCORD [28]							
	SPRINT [30]	Participants with CKD at baseline	1330	1316	14 (0.33)	15 (0.36)	HR: 0.89 (0.42-1.87)	0.76
	VALISH [33]	Overall	1545	1534	5 (0.32)	2 (0.13)	HR: 2.45 (0.48-12.64)	0.27
	JATOS [35]	Overall	2212	2206	8 (0.36*)	9 (0.41*)	HR: NR	NR
	JATOS [34]	Males	874	843	3 (0.34*)	5 (0.59*)	HR: NR	0.45
	JATOS [34]	Age ≥75 yrs	935	934	5 (0.53*)	4 (0.43*)	HR: NR	0.74
	JATOS[34]	Diabetes	264	257	1 (0.38*)	3 (1.17*)	HR: NR	0.33
	JATOS [34]	eGFR<60 mL/min/1.73 m2	1230	1269	5 (0.38*)	8 (1.17*)	HR: NR	0.44
	JATOS [34]	Proteinuria	224	230	2 (0.89*)	4 (1.73*)	HR: NR	0.44
	REIN-2 [38]	Overall	167	168	38 (22.75*)	34 (20.24*)	HR: 1.00 (0.61-1.64)	0.99
	REIN-2 [38]	Baseline proteinuria ≥3g/24h	NR	NR	NR	NR	HR: 1.09 (0.55-2.19)	0.81

	REIN-2 [38]	Baseline proteinuria of 1-3g/24hr	NR	NR	NR	NR	HR: 1.06 (0.51-2.20)	0.81
	UKPDS [40]	Overall	758	390	8 (1.06*)	7 (1.79*)	RR: 0.58 (0.15 – 2.21)	0.29
	AASK [46]	Overall	540	554	173 (32.0*)	167 (30.1*)	% Risk Reduction: 2 (-22 to 21)	0.85
	MDRD [47]	Overall	432	408	61 (14.1*)	66 (16.2*)	HR: 0.78 (0.66–0.93)	0.0056

Note: Effect estimates and subgroup analyses reported by each study included in this meta-analysis are shown in the table above for each outcome for any intensive [lower] blood pressure target vs any standard [higher] blood pressure target

Table 2.19. Comparison of relative risk reductions for intensive (lower) versus standard (higher) blood pressure targets for seven outcomes across recently published meta- analyses.

Author, Journal, Year	Intensive Treatment Target BP	Less Intensive Target BP	All-cause Mortality	CV Mortality	Major CV events	Myocardial Infarction [a]	Stroke [a]	Heart Failure [a]	Renal Events
Current meta-analysis	Any intensive BP	Less intensive target BP	0.89 (0.77, 1.02)	0.87 (0.67, 1.13)	**0.83 (0.75, 0.92)**	**0.86 (0.76, 0.99)**	**0.77 (0.65, 0.91)**	**0.75 (0.56, 0.99)**	1.01 (0.89, 1.15)
Current meta-analysis	SBP target <130 mm Hg	Less intensive target BP	0.92 (0.79, 1.06)	0.81 (0.58, 1.14)	**0.83 (0.74, 0.92)**	0.85 (0.73, 1.00)	**0.82 (0.70, 0.96)**	0.81 (0.58, 1.14)	1.01 (0.89, 1.16)
LV, PLOS Medicine, 2012 [57]	More intensive target BP	Less intensive target BP	…		**0.89 (0.99, 0.79)**	0.87 (0.75, 1.00)	**0.76 (0.63, 0.92)**	…	**0.89 (0.82, 0.97)** [b]
Brunstrom, BMJ, 2016 [58]	Attained SBP >140 mm Hg		0.96 (0.86, 1.06)	0.87 (0.71, 1.07)	…	**0.82 (0.72, 0.92)**	0.90 (0.76, 1.06)	0.83 (0.68, 1.00)	0.88 (0.76, 1.03) [b]
Brunstrom, BMJ, 2016 [58]	Attained SBP 130-140 mm Hg		**0.86 (0.79, 0.93)**	0.86 (0.72, 1.04))	…	**0.88 (0.79, 0.97)**	0.91 (0.83, 1.00)	0.81 (0.70, 0.94)	0.84 (0.66, 1.07) [b]
Brunstrom, BMJ, 2016 [58]	Attained SBP <130 mm Hg		1.10 (0.91, 1.33)	1.26 (0.89, 1.77)	…	0.94 (0.76, 1.15)	**0.65 (0.42, 0.99)**	0.93 (0.71, 1.21)	1.01 (0.71, 1.43)[b]
Ettehad, Lancet, 2016 [59]	Outcomes per 10 mm Hg reduction in SBP		**0.87 (0.77, 0.83)**	…	**0.80 (0.77, 0.83)**	…	**0.73 (0.68, 0.77)**	**0.72 (0.67-0.78)**	0.95 (0.84, 1.07)[c]
Thomopolous, J Hypertens, 2016 [60]	More intensive target BP	Less intensive target BP	0.83 (0.69, 1.03)	**0.79 (0.63, 0.97)**	…	…	**0.71 (0.60, 0.84)**	0.80 (0.49, 1.31)	…
Verdecchia, Hypertension, 2016 [61]	More intensive target BP	Less intensive target BP	0.89 (0.77, 1.02)	**0.82 (0.67, 0.99)**	…	**0.85 (0.76, 0.96)**	**0.80 (0.68, 0.95)**	**0.75 (0.57, 0.99)**	…
Xie, Lancet, 2016 [62]	Intensive (any lower BP)	Standard (any higher BP)	0.91 (0.81, 1.03)	0.91 (0.74-1.11)	**0.86 (0.78- 0.96)**	0.87 (0.76, 1.00)	**0.78 (0.68, 0.90)**	0.85 (0.66, 1.11)	0.90 (0.77, 1.06)[b]
Bangalore, Am J Med, 2017 [63]	SBP <120 mmHg	SBP <140 mmHg	0.89 (0.63, 1.24)	0.78 (0.46, 1.31)	…	0.85 (0.71, 1.02)	0.73 (0.48, 1.11)	0.76 (0.38, 1.51)	…
Bangalore, Am J Med, 2017 [63]	SBP <130 mmHg	SBP <140 mmHg	0.98 (0.73, 1.31)	1.02 (0.62, 1.67)	…	0.95 (0.68, 1.34)	0.83 (0.58, 1.18)	0.98 (0.42, 2.26)	…
Bangalore, Am J Med, 2017 [63]	SBP <120 mmHg	SBP <160 mmHg	0.88 (0.52, 1.50)	0.69 (0.29, 1.60)	…	0.68 (0.47, 1.00)	0.54 (0.29, 1.00)	0.48 (0.14, 1.62)	…
Bavishi, JACC, 2017 [64]	Intensive (any lower BP)	Standard (any higher BP)	…	**0.67 (0.45, 0.98)**	**0.71 (0.60, 0.84)**	0.79 (0.56, 1.12)	0.80 (0.61, 1.05)	**0.63 (0.40, 0.99)**	1.81 (0.86, 3.80)[c]
Weiss, Ann Intern Med, 2017 [65]	SBP <160 mm Hg	Less intensive target BP	**0.85 (0.72, 0.99)**	…	**0.86 (0.72, 0.96)**	…	0.80 (0.62, 1.01)	…	…
Weiss, Ann Intern Med, 2017 [65]	SBP <140 or DBP <85 mmHg	Less intensive target BP	0.86 (0.69, 1.06)	…	0.82 (0.64, 1.00)	…	**0.79 (0.59, 0.99)**	…	…

Abbreviations: BP, blood pressure; CV, cardiovascular; SBP, systolic blood pressure.

a. Fatal or nonfatal. b. End-stage renal disease c. Renal failure

Part 3: First-Line Antihypertensive Drug Class Comparisons in Adults

Table 3.1 Electronic search terms used for the current meta-analysis (Part 3 – First-Line Antihypertensive Drug Class Comparisons in Adults

	PubMed Search	
3	Search ((hypertension[Mesh Terms] OR hypertension[tiab] OR hypertensive[tiab] OR blood pressure[ti] OR blood pressure[mh]))	Hypertension
4	Search ((Randomized controlled trial[pt] OR controlled clinical trial[pt] OR randomized[tiab] OR randomised[tiab] OR placebo[tiab] OR clinical trials as a topic[mesh:noexp] OR randomly[tiab] OR trial[ti]))	Randomized trials
5	Search ((Angiotensin-Converting Enzyme Inhibitors[mh] OR captopril[mh] OR cilazapril[mh] OR enalapril[mh] OR enalaprilat[mh] OR fosinopril[mh] OR Lisinopril[mh] OR perindopril[mh] OR Ramipril[mh]) OR Angiotensin-Converting Enzyme Inhibitors [Pharmacological Action] OR (angiotensin converting enzyme inhibit*[tiab] OR angiotensin converting enzyme antagon*[tiab] OR acei[tiab] OR ace inhibit*[tiab] OR kininase II antagon*[tiab] OR kininase II inhibit*[tiab] OR angiotensin I converting enzyme inhibit*[tiab] OR angiotensin I converting enzyme antagon*[tiab] OR dipeptidyl carboxypeptidase inhibitor [tiab]) OR (alacepril OR altiopril OR ancovenin OR benazepril OR benazeprilat OR captopril OR ceranapril OR ceronapril OR cilazapril OR deacetylalacepril OR delapril OR derapril OR enalapril OR enalaprilat OR epicaptopril OR fasidotril OR fosinopril or gemopatrilat or idrapril or imidapril OR indolapril or libenzapril or Lisinopril OR moexipril OR moveltipril or omapatrilat OR pentopril or perindopril OR pivopril OR quinapril OR Ramipril OR rentiapril or saralasin or s nitrosocaptopril OR spirapril OR temocapril OR teprotide OR utibapril or zabicipril OR trandolapril OR zofenopril))	ACE inhibitors
6	Search (Angiotensin Receptor Antagonists[mh] OR Angiotensin II Type 1 Receptor Blockers[mh] OR Angiotensin II Type 2 Receptor Blockers[mh] OR Losartan[mh] OR Saralasin[mh] OR Angiotensin Receptor Antagonists[pharmacological action] OR Angiotensin II Type 1 Receptor Blockers[pharmacological action] OR Angiotensin II Type 2 Receptor Blockers[pharmacological action] OR angiotensin receptor antagon*[tiab] OR angiotensin receptor block*[tiab] OR angiotensin II type 1 receptor block*[tiab] OR angiotensin II type 1 receptor antagon*[tiab] OR angiotensin II type 2 receptor block*[tiab] OR angiotensin II type 2 receptor antagon*[tiab] OR angiotensin II receptor antagon*[tiab] OR angiotensin II receptor block*[tiab] OR sartan[tiab] OR sartans[tiab] OR arbs[tiab] OR arb[tiab] OR Abitesartan OR Azilsartan OR candesartan OR elisartan OR embusartan OR eprosartan OR forasartan OR irbesartan OR KT3-671 OR losartan OR milfasartan OR olmesartan OR saralasin OR saprisartan or tasosartan or telmisartan OR tasosartan OR valsartan OR zolasartan)	Angiotensin receptor blockers

7	Search ((Adrenergic beta-Antagonists[mh] OR adrenergic beta-1 receptor antagonists[mh] OR adrenergic beta-2 receptor antagonists[mh] OR adrenergic beta-3 receptor antagonists[mh] OR acebutolol[mh] OR atenolol[mh] OR betaxolol[mh] OR bisoprolol[mh] OR bupranolol[mh] OR celiprolol[mh] OR labetalol[mh] OR metoprolol[mh] OR nadolol[mh] OR oxprenolol[mh] OR penbutolol[mh] OR pindolol[mh] OR propranolol[mh]) OR (Adrenergic beta-Antagonists[pharmacological action] OR adrenergic beta-1 receptor antagonists[pharmacological action] OR adrenergic beta-2 receptor antagonists[pharmacological action] OR adrenergic beta-3 receptor antagonists[pharmacological action]) OR (adrenergic beta antagon*[tiab] OR adrenergic beta-1 receptor antagon*[tiab] OR adrenergic beta-2 receptor antagon*[tiab] OR adrenergic beta-3 receptor antagon*[tiab] OR beta adrenergic receptor block*[tiab] OR beta adrenergic block*[tiab] OR adrenergic beta receptor block*[tiab] OR beta atagon*[tiab] OR beta adrenergic antagon*[tiab] OR beta adrenoreceptor antagon*[tiab] OR beta block*[tiab]) OR (acebutolol OR adimolol OR afurolol OR alprenolol OR amosulalol OR arotinolol OR atenolol OR befunolol OR betaxolol OR bevantolol OR bisoprolol OR bopindolol OR bornaprolol OR brefanolol OR bucindolol OR bucumolol OR bufetolol OR bufuralol OR bunitrolol OR bunolol OR bupranolol OR butofilolol OR butoxamine OR carazolol OR carteolol OR carvedilol OR celiprolol OR cetamolol OR chlortalidone OR cloranolol OR cyanoiodopindolol OR cyanopindolol OR deacetylmetipranolol OR diacetolol OR dihydroalprenolol OR dilevalol OR epanolol OR esmolol OR exaprolol OR falintolol OR flestolol OR flusoxolol OR hydroxybenzylpindolol OR hydroxycarteolol OR hydroxymetoprolol OR indenolol OR iodocyanopindolol OR iodopindolol OR labetalol OR landiolol OR levobunolol OR levomoprolol OR medroxalol OR mepindolol OR methylthiopropranolol OR metipranolol OR metoprolol OR moprolol OR nadolol OR oxprenolol OR penbutolol OR pindolol OR nadolol OR nebivolol OR nifenalol OR nipradilol OR oxprenolol OR pafenolol OR pamatolol OR penbutolol OR pindolol OR practolol OR primidolol OR prizidilol OR procinolol OR pronethalol OR propranolol OR proxodolol OR ridazolol OR soquinolol OR sotalol OR spirendolol OR talinolol OR tertatolol OR tienoxolol OR tilisolol OR timolol OR tolamolol OR toliprolol OR tribendilol OR xibenolol))	Beta blockers
8	Search (Calcium channel blockers[mh] OR amlodipine[mh] OR Diltiazem[mh] OR Felodipine[mh] OR Isradipine[mh] OR Nicardipine[mh] OR Nifedipine[mh] OR Nisoldipine[mh] OR Verapamil[mh] OR Calcium Channel Blockers [Pharmacological Action] OR Calcium channel block*[tiab] OR Calcium Channel Antagon*[tiab] OR CCB[tiab] OR Exogenous Calcium Inhibit*[tiab] OR Exogenous Calcium Antagon*[tiab] OR Exogenous Calcium Block*[tiab] OR Calcium Antagon*[tiab] OR amlodipine OR amrinone OR aranidipine OR Azelnidipine or barnidipine or bencyclane or benidipine or bepridil OR clevidipine OR cilnidipine or cinnarizine or clentiazem or conotoxin* OR darodipine OR Diltiazem or efonidipine or elgodipine or etafenone or fantofarone OR Felodipine or fendiline or flunarizine or gallopamil OR Isradipine OR lacidipine OR lercanidipine or lidoflazine or lomerizine OR manidipine OR mibefradil or Nicardipine OR Nifedipine OR niguldipine or nilvadipine or nimodipine or Nisoldipine OR nitrendipine or perhexiline or prandipine OR prenylamine or semotiadil or terodiline or tiapamil OR Verapamil)	Calcium channel blockers
9	Search (Sodium Chloride Symporter Inhibitors[mh] OR bendroflumethiazide[mh] OR Benzothiadiazines[mh] OR Chlorothiazide[mh] OR chlorthalidone[mh] OR cyclopenthiazide[mh] OR hydrochlorothiazide[mh] OR hydroflumethiazide[mh] OR indapamide[mh] OR methyclothiazide[mh] OR metolazone[mh] OR polythiazide[mh] OR trichlormethiazide[mh] OR xipamide[mh] OR Sodium Chloride Symporter Inhibitors [Pharmacological Action] OR Sodium Chloride Symporter Inhibit*[tiab] OR sodium chloride cotransporter inhibit*[tiab] OR sodium chloride co-transporter inhibit*[tiab] OR Thiazide*[tiab] OR benzothiadiazine[tiab] OR benzo-thiadiazine[tiab] OR thiazide-like[tiab] OR bendroflumethiazide OR clofenamide OR clopamide OR Chlorothiazide OR chlorthalidone OR chlortalidone OR cyclopenthiazide OR cyclothiazide OR fenquizone OR hydrochlorothiazide OR hydroflumethiazide OR indapamide OR medfruside OR methyclothiazide OR metolazone OR polythiazide OR quinethazone OR trichlormethiazide OR xipamide)	Thiazide & thiazide-like diuretics
10	Search (#5 AND (#6 OR #7 OR #8 OR #9))	ACE AND (ARB or BB or Calcium OR Thiazide)
11	Search (#6 AND (#7 OR #8 OR #9))	ARB AND (BB or calcium or thiazide)
12	Search (#7 AND (#8 OR # 9))	Beta Blockers AND (calcium or thiazide)
13	Search (#8 AND #9)	Calcium Channel Blockers and Diuretics

14	Search (#10 OR #11 OR #12 OR #13)	All drug pairings together
15	Search (#14 AND #3 AND #4)	Htn + drug pairings + randomized
16	Search (#15 AND eng[la] NOT (animals[mh] NOT human[mh]))	Remove animal studies + limit to English
17	Search (#16 NOT (review[pt] OR review[ti] OR comment[pt] OR editorial[pt] OR meta-analysis[pt] OR meta-analysis[ti] OR letter[pt] OR in vitro techniques[mh] OR guideline[pt] OR case reports[pt] OR case report[ti] OR news[pt] NOT ((review[pt] AND clinical trial[pt]) OR (meta-analysis[pt] AND clinical trial[pt]) OR (case reports[pt] AND (clinical trial[pt] OR series[tiab])))))	Remove obvious non-trial publications
18	Search (#17 NOT (pregnan*[tw] OR ocular hypertension[tw] OR preeclampsia[tw] OR pre-eclampsia[tw]))	Remove pregnancy-induced hypertension and ocular hypertension

	Embase Search	
1	exp hypertension/	Hypertension Concept
2	(hypertension or hypertensive).ti,ab.	
3	Blood pressure.ti.	
4	1 or 2 or 3	
5	exp dipeptidyl carboxypeptidase inhibitor/	ACE Inhibitors
6	(angiotensin converting enzyme inhibit$ or angiotensin converting enzyme antagon$ or acei or ace inhibit$ or kininase II antagon$ or kininase II inhibit$ or angiotensin I converting enzyme inhibit$ or angiotensin I converting enzyme antagon$ or dipeptidyl carboxypeptidase inhibit$).ti,ab.	
7	(alacepril or altiopril or ancovenin or benazepril or benazeprilat or captopril or ceranapril or ceronapril or cilazapril or deacetylalacepril or delapril or derapril or enalapril or enalaprilat or epicaptopril or fasidotril or fosinopril or gemopatrilat or idrapril or imidapril or indolapril or libenzapril or Lisinopril or moexipril or moveltipril or omapatrilat or pentopril or perindopril or pivopril or quinapril or Ramipril or rentiapril or saralasin or s nitrosocaptopril or spirapril or temocapril or teprotide or utibapril or zabicipril or trandolapril or zofenopril).ti,ab.	
8	5 or 6 or 7	
9	exp Angiotensin Receptor Antagonist/ or Saralasin/	Angiotensin receptor blockers
10	(angiotensin receptor antagon$ or angiotensin receptor block$ or angiotensin II type 1 receptor block$ or angiotensin II type 1 receptor antagon$ or angiotensin II type 2 receptor block$ or angiotensin II type 2 receptor antagon$ or angiotensin II receptor antagon$ or angiotensin II receptor block$ or sartanOR sartansOR arbs or arb).ti,ab.	
11	(Abitesartan or Azilsartan or candesartan or elisartan or embusartan or eprosartan or forasartan or irbesartan or KT3-671 or losartan or milfasartan or olmesartan or saralasin or saprisartan or tasosartan or telmisartan or tasosartan or valsartan or zolasartan).ti,ab.	
12	9 or 10 or 11	
13	exp beta adrenergic receptor blocking agent/	Beta Blockers
14	(adrenergic beta antagon$ or adrenergic beta 1 receptor antagon$ or adrenergic beta 2 receptor antagon$ or adrenergic beta 3 receptor antagon$ or beta adrenergic receptor block$ or beta adrenergic block$ or adrenergic beta receptor block$ or beta atagon$ or beta adrenergic antagon$ or beta adrenoreceptor antagon$ or beta block$).ti,ab.	

15	(acebutolol or adimolol or afurolol or alprenolol or amosulalol or arotinolol or atenolol or befunolol or betaxolol or bevantolol or bisoprolol or bopindolol or bornaprolol or brefanolol or bucindolol or bucumolol or bufetolol or bufuralol or bunitrolol or bunolol or bupranolol or butofilolol or butoxamine or carazolol or carteolol or carvedilol or celiprolol or cetamolol or chlortalidone or cloranolol or cyanoiodopindolol or cyanopindolol or deacetylmetipranolol or diacetolol or dihydroalprenolol or dilevalol or epanolol or esmolol or exaprolol or falintolol or flestolol or flusoxolol or hydroxybenzylpindolol or hydroxycarteolol or hydroxymetoprolol or indenolol or iodocyanopindolol or iodopindolol or labetalol or landiolol or levobunolol or levomoprolol or medroxalol or mepindolol or methylthiopropranolol or metipranolol or metoprolol or moprolol or nadolol or oxprenolol or penbutolol or pindolol or nadolol or nebivolol or nifenalol or nipradilol or oxprenolol or pafenolol or pamatolol or penbutolol or pindolol or practolol or primidolol or prizidilol or procinolol or pronethalol or propranolol or proxodolol or ridazolol or soquinolol or sotalol or spirendolol or talinolol or tertatolol or tienoxolol or tilisolol or timolol or tolamolol or toliprolol or tribendilol or xibenolol).ti,ab.	
16	13 or 14 or 15	
17	exp calcium channel blocking agent/	Calcium channel blockers
18	(Calcium channel block$ or Calcium Channel Antagon$ or CCB$ or Exogenous Calcium Inhibit$ or Exogenous Calcium Antagon$ or Exogenous Calcium Block$ or Calcium Antagon$).ti,ab.	
19	(amlodipine or amrinone or aranidipine or Azelnidipine or barnidipine or bencyclane or benidipine or bepridil or clevidipine or cilnidipine or cinnarizine or clentiazem or conotoxin* or darodipine or Diltiazem or efonidipine or elgodipine or etafenone or fantofarone or Felodipine or fendiline or flunarizine or gallopamil or Isradipine or lacidipine or lercanidipine or lidoflazine or lomerizine or manidipine or mibefradil or Nicardipine or Nifedipine or niguldipine or nilvadipine or nimodipine or Nisoldipine or nitrendipine or perhexiline or prandipine or prenylamine or semotiadil or terodiline or tiapamil or Verapamil).ti,ab.	
20	17 or 18 or 19	
21	exp thiazide diuretic agent/ or Benzothiadiazine derivative/ or indapamide/	Thiazide & thiazide-like diuretics
22	(Sodium Chloride Symporter Inhibit$ or sodium chloride cotransporter inhibit$ or sodium chloride co-transporter inhibit$ or Thiazide$ or benzothiadiazine or benzo-thiadiazine or thiazide-like).ti,ab.	
23	(bendroflumethiazide or clofenamide or clopamide or Chlorothiazide or chlorthalidone or chlortalidone or cyclopenthiazide or cyclothiazide or fenquizone or hydrochlorothiazide or hydroflumethiazide or indapamide or mefruside or methyclothiazide or metolazone or polythiazide or quinethazone or trichlormethiazide or xipamide).ti,ab.	
24	21 or 22 or 23	
25	8 and (12 or 16 or 20 or 24)	ACE AND (ARB or BB or Calcium OR Thiazide)
26	12 and (16 or 20 or 24)	ARB AND (BB or calcium or thiazide)
27	16 and (20 or 24)	Beta Blockers AND (calcium or thiazide)
28	20 and 24	Calcium Channel Blockers and Diuretics
29	25 or 26 or 27 or 28	All drug pairings together
30	Randomized controlled trial/ or Randomization/ or Single blind procedure/ or Double blind procedure/ or Crossover procedure/ or Placebo/	Randomized Trials
31	(Randomi?ed controlled trial$ or Rct or Random allocation or Randomly allocated or Allocated randomly or Single blind$ or Double blind$ or Placebo$).tw.	

32	(allocated adj2 random).tw.	
33	((treble or triple) adj blind$).tw.	
34	30 or 31 or 32 or 33	
35	Case study/ or Abstract report/ or letter/	Remove case reports
36	Case report.tw.	
37	35 or 36	
38	34 not 37	
39	4 and 29 and 38	Htn + drug pairings + randomized
40	limit 39 to (human and english language and article)	Remove animal studies and non-trial publications

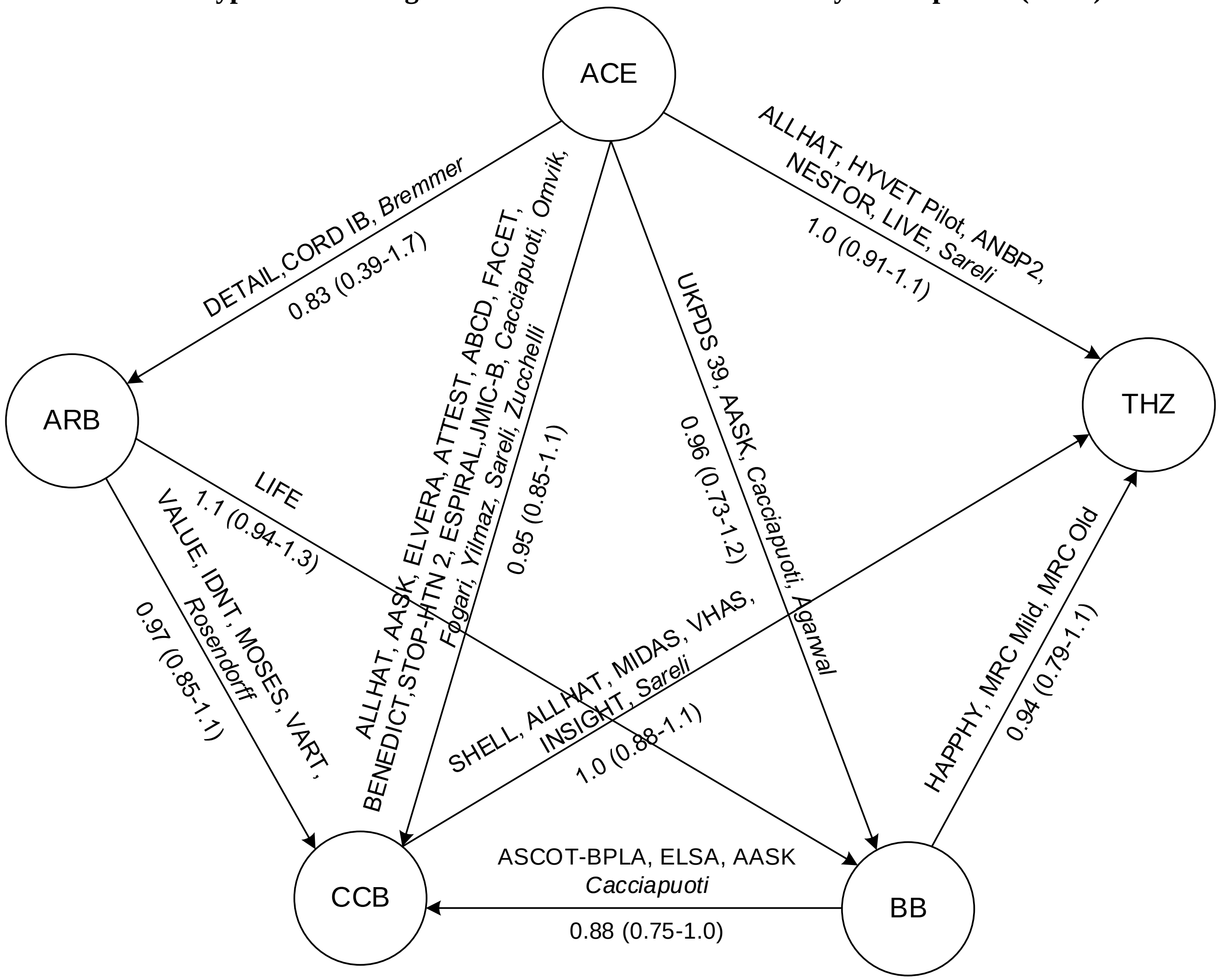
Table 3.1.1 PICO(TSS) Framework

	Inclusion Criteria	Exclusion criteria
Participants/ population	Adults (>=18 years) with Primary Hypertension or Hypertension due to Chronic Kidney Disease	Adults with secondary hypertension (other than hypertension caused by CKD)
Interventions/ exposure	Used as first-line therapy for hypertension: • Thiazide and thiazide-like diuretics • Angiotensin converting enzyme (ACE) inhibitors • Angiotensin Receptor Blockers (ARB) • Calcium Channel Blockers (CCB) • Beta-Blockers	• Central Adrenergic Agonists • Direct Vasodilators • Alpha-Receptor Blockers • Mineralocorticoid Receptor Antagonists • Renin Inhibitors • 2nd line therapy • Interventions not being used to treat hypertension/high blood pressure
Comparators/ control	All above in scope interventions as long as representative of a different class than intervention	• Central Adrenergic Agonists • Direct Vasodilators • Alpha-Receptor Blockers • Mineralocorticoid Receptor Antagonists • Renin Inhibitors • Combinations of a mix of classes • Comparison of drugs within the same class

Outcomes	• **Mortality**
	  o **All-Cause**
	  o **Cardiovascular**
	• **Heart Failure**
	• **Stroke**
	• **Composite CVD events**
	• **Myocardial Infarction (MI)**
	• Ruptured Aortic Aneurysm
	• Coronary Revascularization
	• Peripheral Revascularization
	• End-Stage Renal Disease (ESRD)
	• Doubling of Creatinine
	• Halving of eGFR
	• Cognitive Impairment
	• Dementia
	  o Total Withdrawals from study
	  o Withdrawals from study due to adverse events
	  o Hypotension
	  o Electrolyte abnormalities
	  o Angioedema
	  o Cough
	  o Adverse events resulting in intervention
	    ▪ Hypotension-related hospitalizations, ED or clinic visits
		All other outcomes

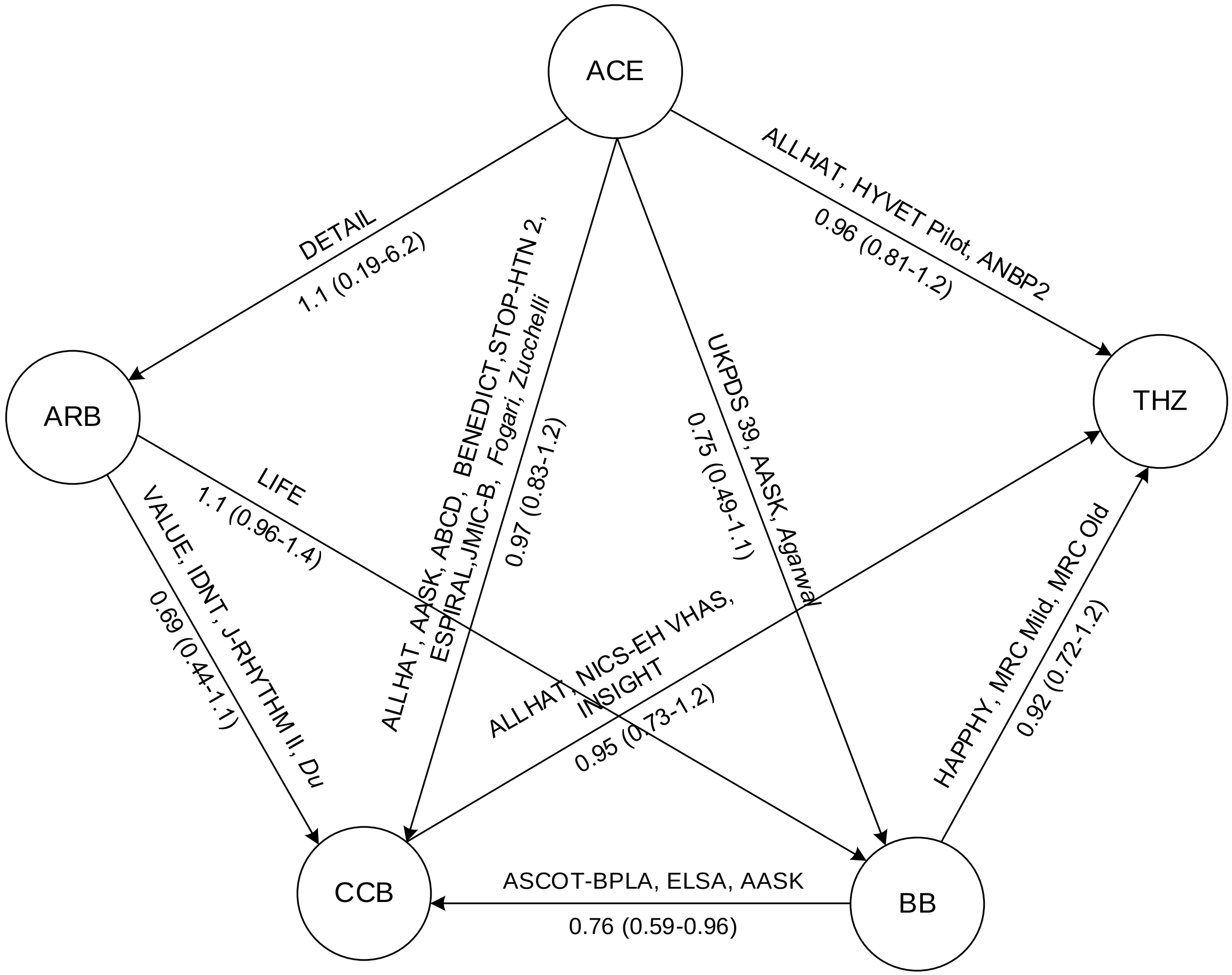
	▪ AEs resulting in discontinuation of medication • Achieved mean level of BP change • Proportion of patients achieving a target blood pressure • of hypertension • Dysglycemia including development of new-onset DM	
Timing (of outcomes)	≥48 weeks of follow-up	<48 weeks of follow-up
Setting/context	Any	NA
Study design	Randomized Controlled Trials	Observational Studies
Additional criteria	≥100 randomized patients or >=400 patient-years of follow-up	<100 randomized patients or ≥400 patient-years of follow-up

Figure 3.1 Network of clinical trials of antihypertensive drug classes in which all-cause mortality was reported (N=40). *



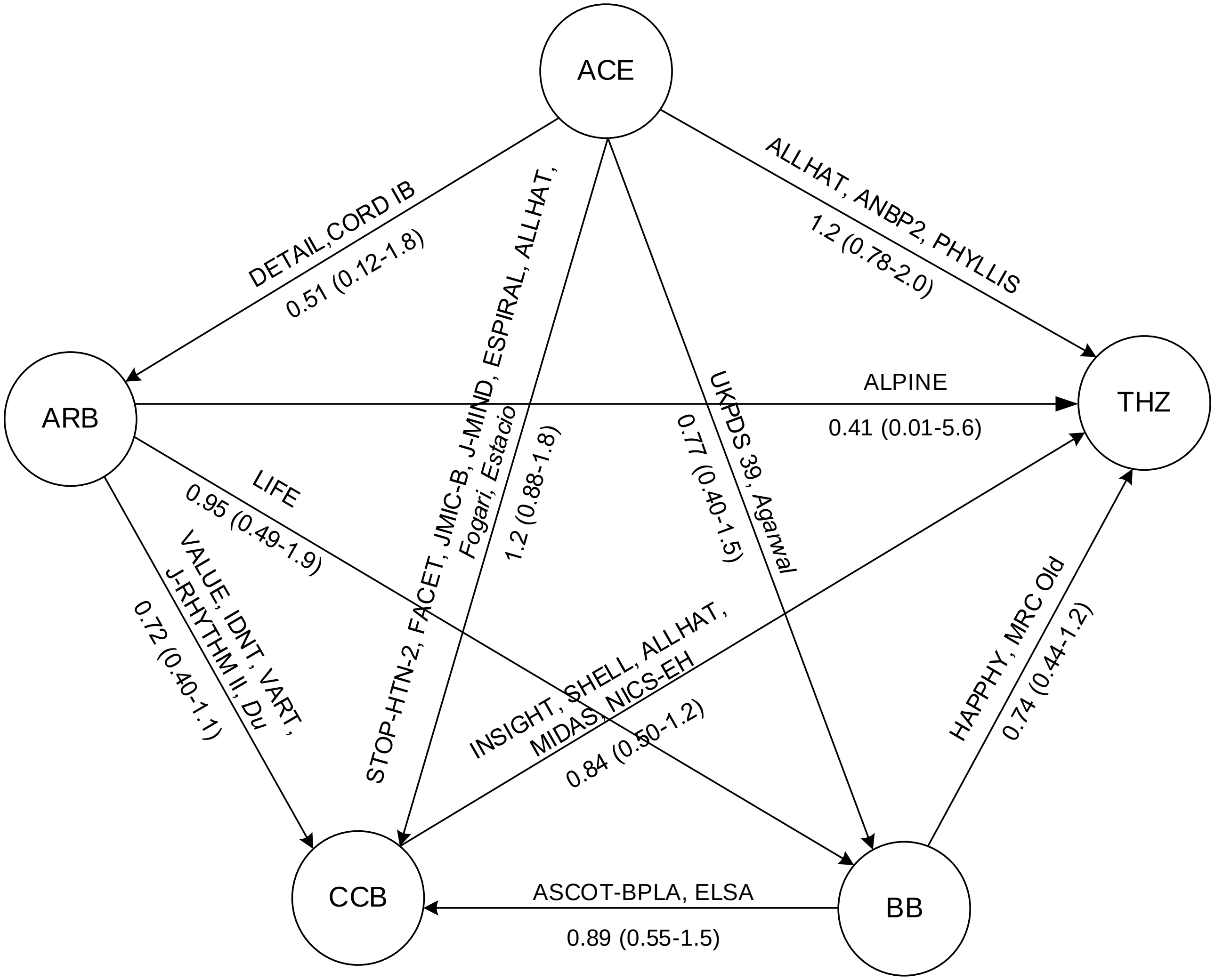
*The trials included in each pair-wise comparison are labeled above the arrow. Summary of relative risk (RR) and 95% CIs for the direct comparisons are shown below the arrow. For each pair-wise comparison, the line starts at the reference group and points towards the comparison group. Thus, the arrowhead points to a class of antihypertensive drugs for which a higher RR would signify an increased risk of mortality.

Figure 3.2 Network of clinical trials of antihypertensive drug classes in which CV mortality was reported (N=25) *



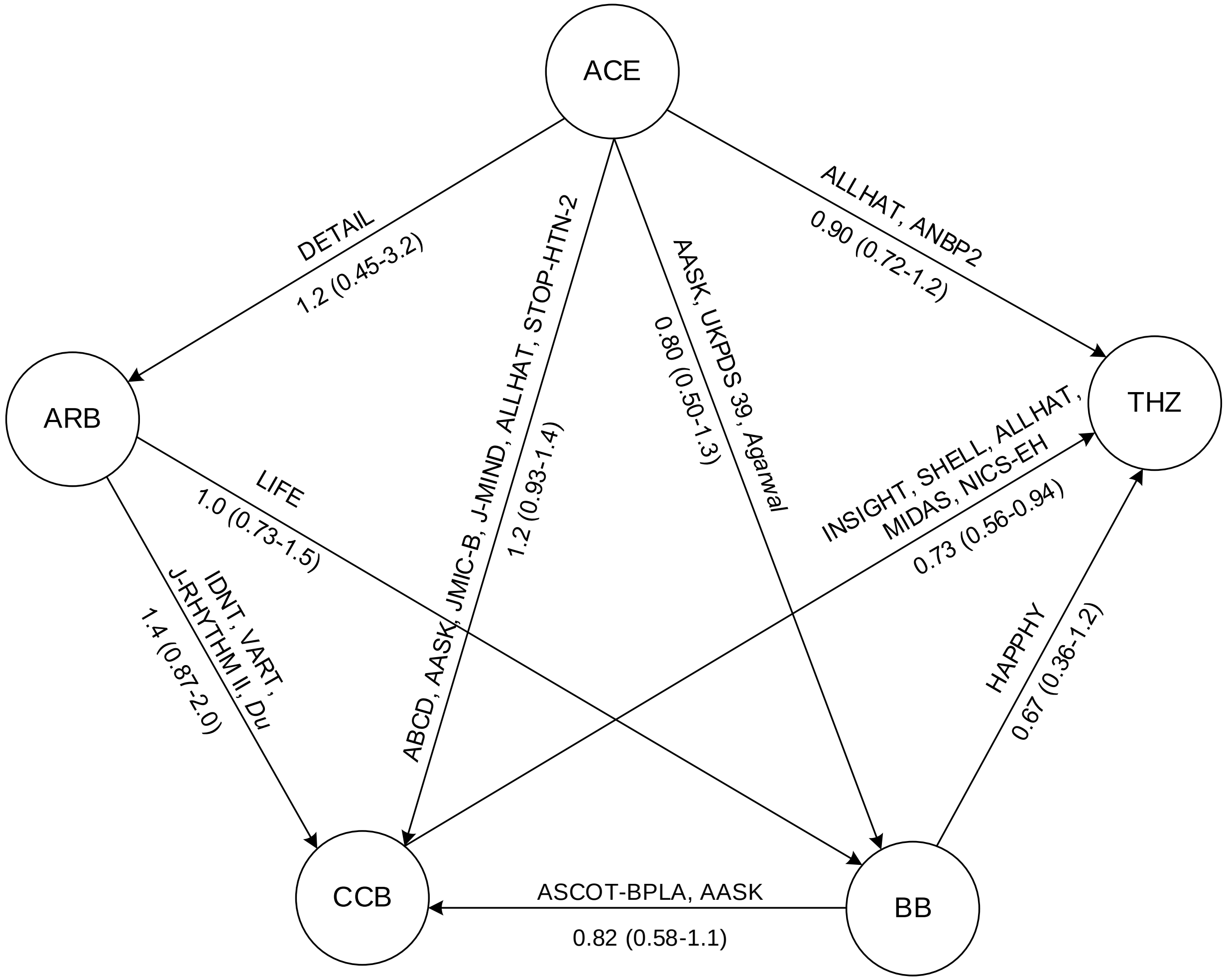
*****. *****The trials included in each pair-wise comparison are labeled above the arrow. Summary of relative risk (RR) and 95% CIs for the direct comparisons are shown below the arrow. For each pair-wise comparison, the line starts at the reference group and points towards the comparison group. Thus, the arrowhead points to a class of antihypertensive drugs for which a higher RR would signify an increased risk of CV mortality.

Figure 3.3 Network of clinical trials of antihypertensive drug classes in which myocardial infarction was reported (N=29). *



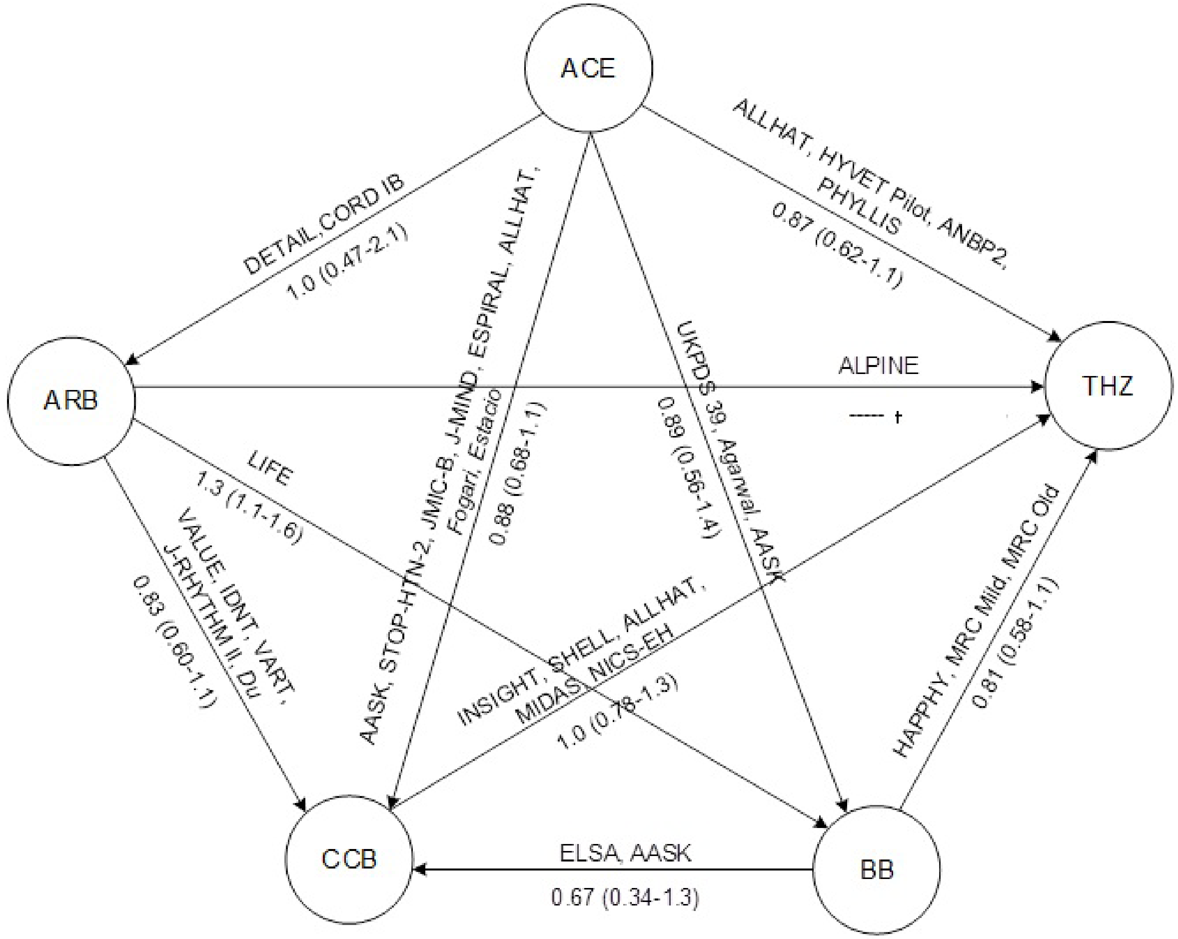
***The trials included in each pair-wise comparison are labeled above the arrow. Summary of relative risk (RR) and 95% CIs for the direct comparisons are shown below the arrow. For each pair-wise comparison, the line starts at the reference group and points towards the comparison group. Thus, the arrowhead points to a class of antihypertensive drugs for which a higher RR would signify an increased risk of myocardial infarction.

Figure 3.4. Network of clinical trials of antihypertensive drug classes in which heart failure was reported (N=21).



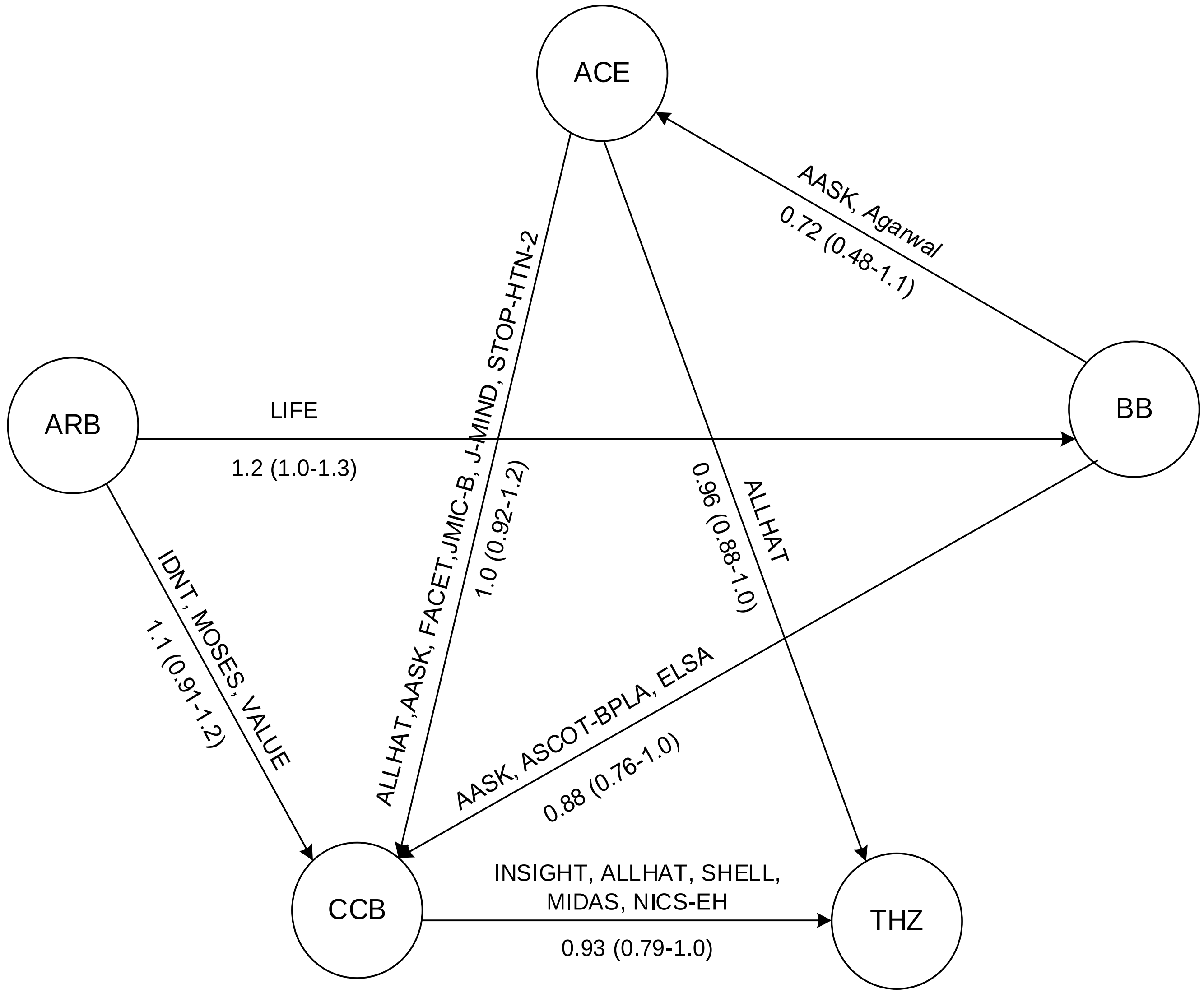
* The trials included in each pair-wise comparison are labeled above the arrow. Summary of relative risk (RR) and 95% CIs for the direct comparisons are shown below the arrow. For each pair-wise comparison, the line starts at the reference group and points towards the comparison group. Thus, the arrowhead points to a class of antihypertensive drugs for which a higher RR would signify an increased risk of heart failure.

Figure 3.5 Network of clinical trials of antihypertensive drug classes in which fatal and non-fatal stroke outcomes were reported (N=30)*



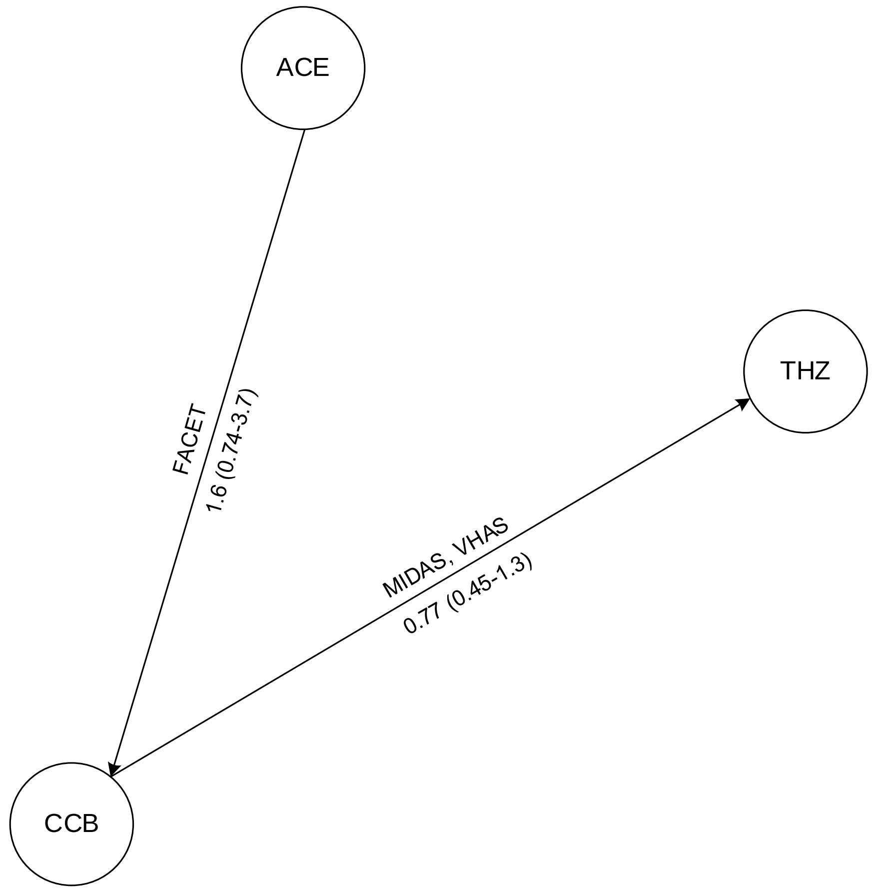
***The trials included in each pair-wise comparison are labeled above the arrow. Summary of relative risk (RR) and 95% CIs for the direct comparisons are shown below the arrow. For each pair-wise comparison, the line starts at the reference group and points towards the comparison group. Thus, the arrowhead points to a class of antihypertensive drugs for which a higher RR would signify an increased risk of stroke outcomes. † The dash represents the relative risk for THZ and ARB, which was extreme due to zeros. The value could not be calculated based on a direct comparison.

Figure 3.6 Network of clinical trials of antihypertensive drug classes in which major CV event outcomes were reported (N=17) *



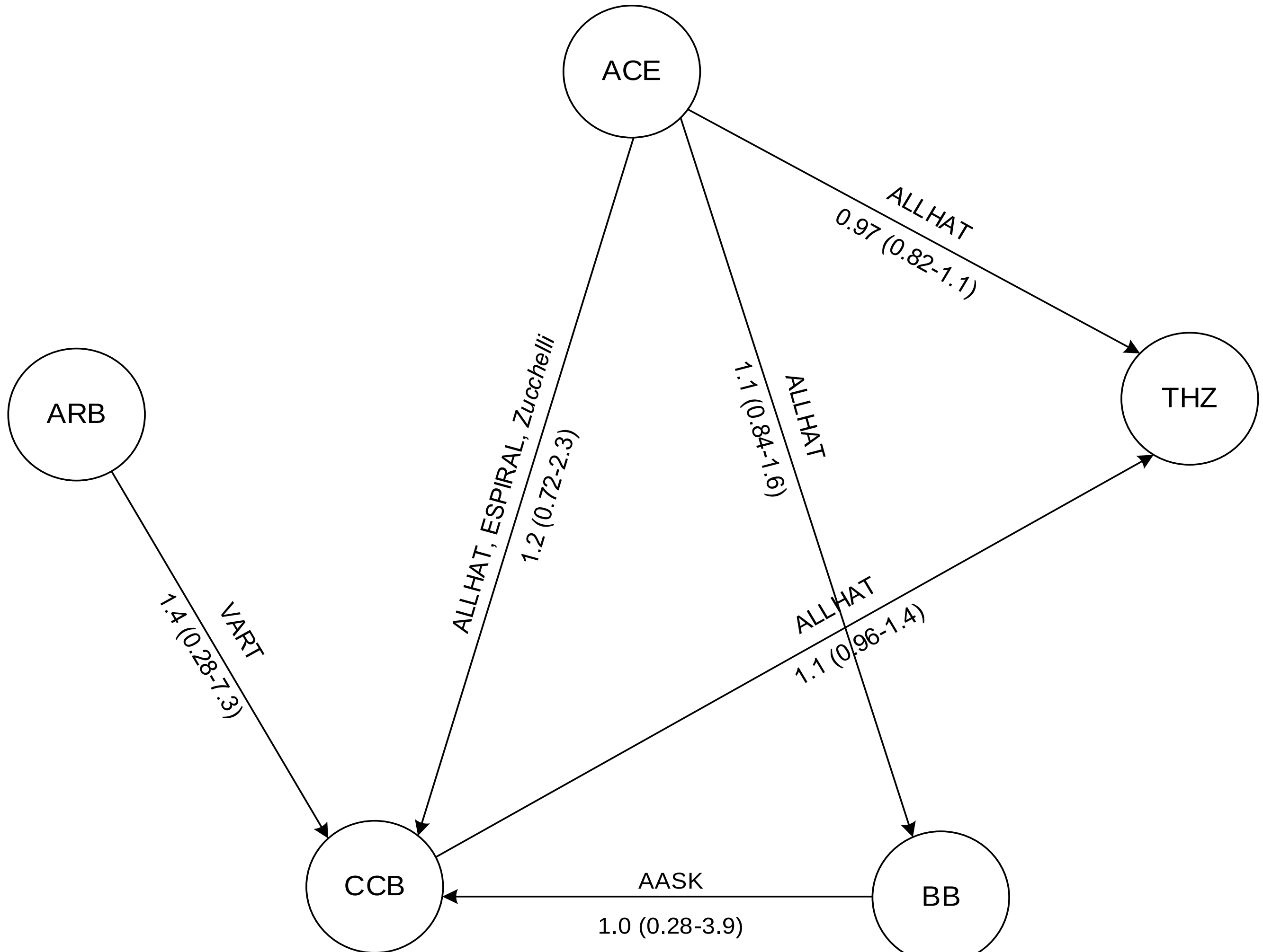
*The trials included in each pair-wise comparison are labeled above the arrow. Summary of relative risk (RR) and 95% CIs for the direct comparisons are shown below the arrow. For each pair-wise comparison, the line starts at the reference group and points towards the comparison group. Thus, the arrowhead points to a class of antihypertensive drugs for which a higher RR would signify an increased risk of major CV events.

Figure 3.7 Network of clinical trials of antihypertensive drug classes in which MACE was reported (N=3). *



***The trials included in each pair-wise comparison are labeled above the arrow. Summary of relative risk (RR) and 95% CIs for the direct comparisons are shown below the arrow. For each pair-wise comparison, the line starts at the reference group and points towards the comparison group. Thus, the arrowhead points to a class of antihypertensive drugs for which a higher RR would signify an increased risk of MACE.

Figure 3.8. Network of clinical trials of antihypertensive drug classes in which renal event outcomes were reported (N=5) *



***The trials included in each pair-wise comparison are labeled above the arrow. Summary of relative risk (RR) and 95% CIs for the direct comparisons are shown below the arrow. For each pair-wise comparison, the line starts at the reference group and points towards the comparison group. Thus, the arrowhead points to a class of antihypertensive drugs for which a higher RR would signify an increased risk of renal outcomes.

Table 3.2 Characteristics of studies

Acronym	Author	Year	Patient status /condition	Tx Comparison	Follow-up (years)	Randomized	Age (yrs)	% Female	% Caucasian	% African-American	% Asian	% Race, Other	% Hispanic	BMI	% DM	% CKD	% CHD	% Cerebrovascular Disease	% Prior MI
AASK	Wright Jr. J.T. [45]	2002	CKD, Non-Diabetic	ACE vs. CCB vs. BB	6.4	1094	54.6	38.8	0	100	0	0	NR	NR	0	100	NR	NR	NR
ABCD	Estacio RO. [66, 67]	1998	Diabetic	CCB vs. ACE	5.0	470	57.5	32.6	83.6	13.8	0	2.6	66.8	31.6	100	NR	NR	NR	7
ALLHAT	ALLHAT Res Grp [68]	2002	Hypertensive	THZ vs. CCB vs. ACE	8.0	33357	67	47.0	59.7	35.4	0	4.9	19	29.8	36	NR	25.2	NR	NR
ANBP2	Wing LM. [69]	2003	Hypertensive	ACE vs. THZ	4.1	6083	71.9	51.0	95	NR	NR	NR	NR	27	7	NR	8	5	NR
ASCOT-BPLA	Dahlof B. [70]	2005	Hypertensive	CCB vs. BB	5.5	19257	63	23.4	95.3	NR	NR	NR	NR	28.7	26.7	NR	NR	NR	0
BENEDICT	Ruggenenti P [71]	2004	DM	CCB vs. ACE	3.6	1209	62.1	46.9	NR	NR	NR	NR	NR	29.3	100	NR	NR	NR	NR
CORD IB	Spinar J [72]	2009	Hypertensive	ACE vs. ARB	1.0	3813	60.5	50.5	NR	NR	NR	NR	NR	NR	29.3	NR	NR	NR	11.7
DETAIL	Barnett AH [73]	2004	DM	ARB vs. ACE	5.0	250	60.6	27.2	98.4	NR	NR	NR	NR	30.7	100	NR	NR	NR	NR
ELSA	Zanchetti A [74]	2002	Hypertensive	BB vs. CCB	4.1	2334	56	39.4	98.2	NR	NR	NR	NR	27.2	NR	NR	NR	NR	NR
ELVERA	Terpstra W.F. [75]	2004	Non-DM	CCB vs. ACE	2.0	166	67	44.6	NR	NR	NR	NR	NR	28	0	NR	0	NR	NR
ESPIRAL	Marin R [76]	2001	Non-DM	ACE vs. CCB	3.1	241	56	41.0	NR	NR	NR	NR	NR	NR	0	NR	NR	NR	NR
FACET	Tatti P. [77]	1998	DM	ACE vs. CCB	3.5	380	63.1	40.5	NR	NR	NR	NR	NR	30.6	100	NR	0	0*	NR
HAPPHY	Wilhelmsen L [78]	1987	Non-DM	THZ vs. BB	3.8	6569	52.2	0	99	NR	NR	NR	NR	27.2	0	NR	NR	0*	0
HYVET-Pilot	Bulpitt CJ [79]	2003	Elderly	THZ vs. ACE	1.1	1283	83.8	63.5 [$]	NR	NR	NR	NR	NR	25.4 [$]	NR	NR	NR	4.5*	3
IDNT	Lewis EJ [80]	2001	DM	ARB vs. CCB	2.6	1715	59.2 [$]	33.5 [$]	72.2 [$]	13.1 [$]	5.1 [$]	4.7 [$]	5 [$]	31 [$]	100	NR	NR	NR	NR
JMIC-B	Yui Y [81, 82]	2004	Hypertensive	CCB vs. ACE	3.0	1650	65	31.2	NR	NR	NR	NR	NR	24.05	22.5	NR	NR	NR	2.5
LIFE	Dahlof B. [83]	2002	LV Hypertrophy	ARB vs. BB	4.8	9193	66.9	54	92	6	0.5	0.2	1	28	13	NR	16	8	NR
LIVE	Gosse P [84]	2000	Non-DM	THZ vs. ACE	1.0	505	54.5	43.6	77.8	NR	NR	NR	NR	26.7	0	NR	0	NR	NR
MOSES	Schrader J [85]	2005	Hypertensive	ARB vs. CCB	4.0	1405	67.9	45.8	NR	NR	NR	NR	NR	27.6	36.8	NR	26.3	61*	8.1
MRC	MRC Working Party [86]	1985	Non-DM	THZ vs. BB	5.5	17354	51.9	47.9	NR	NR	NR	NR	NR	NR	0	NR	NR	NR	NR
MRC Old	MRC Working Party [87]	1992	Elderly	THZ vs. BB	5.8	4396	NR	58 [$]	NR	NR	NR	NR	NR	NR	NR	NR	NR	NR	NR
INSIGHT	Brown MJ [88]	2000	Hypertensive	CCB vs THZ	3.5	6321	65	53.7	NR	NR	NR	NR	NR	28.2	20.6	NR	6.4 [$]	NR	6.1 [$]

Acronym	Author	Year	Patient status /condition	Tx Comparison	Follow-up (years)	Random-ized	Age (yrs)	% Female	% Caucasian	% African-American	% Asian	% Race, Other	% Hispanic	BMI	% DM	% CKD	% CHD	% Cerebrovascular Disease	% Prior MI
	Fogari R [89]	2002	DM	CCB vs. ACE	4.1	309	62.8 $	43.4	NR	NR	NR	NR	NR	27.7	100	NR	0*	0	NR
	Rosendorff C [90]	2009	LV Hypertrophy	ARB vs CCB	1.1	102	63.9	1	10.8	71.6	0	2.9	14.7	NR	16.7	NR	NR	5.9*	3.9
	Cacciapuoti F [91]	1993	Non-DM	CCB vs. ACE vs. BB	5.0	237	48	29.1	NR	NR	NR	NR	NR	NR	0	NR	0	NR	NR
	Zucchelli P [92]	1995	Non-DM	ACE vs. CCB	4.0	121	55	40.5	NR	NR	NR	NR	NR	NR	0	NR	NR	NR	NR
	Yilmaz R [93]	2010	End Stage Renal Disease	ACE vs. CCB	1.0	112	51.5	46.4	NR	NR	NR	NR	NR	22.6	NR	NR	0	NR	0
	Agarwal R [94]	2014	End Stage Renal Disease, LV Hypertrophy	BB vs. ACE	1.0	200	52.7	34.5	NR	86	NR	NR	0.5	27.9	NR	NR	26.5	16.5	NR
	Omvik P [95]	1993	Hypertensive	CCB vs. ACE	1.1	461	54.4	48.2	NR	NR	NR	NR	NR	NR	NR	NR	NR	NR	NR
	Bremner AD [96]	1997	Hypertensive	ARB vs. ACE	1.0	501	71.8	55.4	99	0.4	0.6	0.4	NR	NR	NR	NR	NR	NR	NR
	Sareli P [97]	2001	African-American	CCB_NIF vs. CCB_VER vs. THZ vs. ACE	1.1	409	53.3	77.0	0	100	0	0	NR	31.2	NR	NR	NR	NR	NR
NESTOR	Marre Michel [98]	2004	DM	THZ vs. ACE	1.1	570	60	36	85.6	4.4	2.5	8.6	NR	29.5	100	NR	NR	NR	NR
SHELL	Malacco E [99]	2003	Hypertensive	THZ vs. CCB	5.0	1882	72.3	61.3	NR	NR	NR	NR	NR	NR	13.2	NR	NR	NR	NR
STOP-HTN-2	Hansson L [100]	1999	Hypertensive	ACE vs. CCB	5.0	6614	76	66.8	NR	NR	NR	NR	NR	26.7	10.9	NR	8	3.9	3.1
UKPDS 39	UKPDS 39 [101]	1998	DM	ACE vs. BB	9.0	1148	56	45.0	85.9	8	5	1	NR	29.8	100	NR	NR	NR	NR
VALUE	Julius S [102]	2004	Hypertensive	ARB vs. CCB	6.0	15245	67.2	53	89.3	4.2	3.5	3	NR	28.6	NR	NR	45.8	19.8*	4.5
VART	Narumi H [103]	2011	Asian	ARB vs. CCB	NR	1021	60	42.8	0	0	100	0	NR	24.5	8.1	NR	3.4	0	NR
VHAS	Rosei E.A. [104]	1997	Non-DM	THZ vs. CCB	2.1	1414	53.2	51	NR	NR	NR	NR	NR	27.1	0	NR	NR	NR	NR
MIDAS	Borhani N.O. [105]	1996	Non-DM	CCB vs. THZ	3.2	883	58.5	22.2	72	22	0	6	NR	27.8	0	NR	NR	NR	1.9
ATTEST	Katayama S [106]	2008	DM	CCB vs. ACE	1.2	223	59.3	31.4	NR	NR	NR	NR	NR	26.14	100	NR	NR	NR	0
SHELL	Malacco E [99]	2003	Hypertensive	THZ vs. CCB	5.0	1882	72.3	61.3	NR	NR	NR	NR	NR	NR	13.2	NR	NR	NR	NR

NR= not reported, tx=treatment, BMI=body mass index, DM=diabetes mellitus, CKD=chronic kidney disease, CHD=coronary heart disease
$ Study reported additional groups that were not in scope. Data was calculated using interventions of interest.
* Stroke was used as surrogate for Cerebrovascular Disease

Table 3.3. All-Cause mortality events by study and antihypertensive class

Study Acronym	Author	Year	CCB		BB		ACE		ARB		THZ	
			N	Outcomes	N	Outcomes	N	Outcomes	N	Outcomes	N	Outcomes
ASCOT-BPLA	Dahlof B. (70)	2005	9,639	738 (8%)	9,618	820 (9%)						
ELSA	Zanchetti A (74)	2002	1,023	13 (1.1%)	1,012	17 (1.5%)						
AASK	Wright Jr. J.T. (45)	2002	217	13 (6%)	441	38 (8.6%)	436	29 (6.7%)				
-	Cacciapuoti F (91)	1993	82	1 (1.2%)	79	0 (0%)	76	1 (1.3%)				
-	Agarwal (94)	2014			100	4 (4%)	100	4 (4%)				
ABCD	Estacio RO. (66, 67)	1998	235	17 (7.2%)			235	13 (5.5%)				
-	Fogari R (89)	2002	103	4 (3.9%)			102	3 (2.9%)				
STOP-HTN-2	Hansson L (100)	1999	2,196	362 (16.5%)			2,205	380 (17.2%)				
ATTEST	Katayama S (106)	2008	107	0 (0%)			103	0 (0%)				
ESPIRAL	Marin R (76)	2001	112	6 (5.4%)			129	4 (3.1%)				
-	Omvik P (95)	1993	231	1 (0.4%)			230	1 (0.4%)				
BENEDICT	Ruggenenti P (71)	2004	303	2 (0.7%)			301	3 (1%)				
FACET	Tatti P. (77)	1998	191	5 (2.6%)			189	4 (2.1%)				
ELVERA	Terpstra W.F. (75)	2004	81	1 (1.2%)			85	0 (0%)				
-	Yilmaz R (93)	2010	47	1 (2.4%)			45	0 (0%)				
JMIC-B	Yui Y (81, 82)	2004	828	12 (1.4%)			822	15 (1.8%)				
-	Zucchelli P (92)	1995	61	0 (0%)			60	1 (1.7%)				
ALLHAT	ALLHAT Res Grp (68)	2002	9,048	1,256 (13.9%)			9,054	1,314 (14.5%)			15,255	2,203 (14.4%)
-	Sareli P* (97)	2001	233	0 (0%)			60	0 (0%)			58	1 (1.7%)
VALUE	Julius S (102)	2004	7596	818 (10.8%)					7649	841 (11%)		
IDNT	Lewis EJ (80)	2001	567	83 (14.6%)					579	87 (15%)		
VART	Narumi H (103)	2011	511	21 (4.1%)					510	21 (4.1%)		
-	Rosendorff C (90)	2009	38	0 (0%)					36	0 (0%)		
MOSES	Schrader J (85)	2005	671	52 (7.7%)					681	57 (8.4%)		
MIDAS	Borhani N.O (105)	1996	442	8 (1.8%)							441	9 (2.1%)
SHELL	Malacco E (99)	2003	942	145 (15.4%)							940	122 (13%)
VHAS	Rosei E.A. (104)	1997	707	5 (0.7%)							707	4 (0.6%)
UKPDS 39	UKPDS 39 (101)	1998			358	59 (16.5%)	400	75 (18.8%)				
LIFE	Dahlof B. (83)	2002			4588	431 (9%)			4605	383 (8%)		

MRC	MRC Working Party [86]	1985			4403	120 (2.7%)					4297	128 (3%)
HAPPHY	Wilhelmsen L [78]	1987			3297	96 (2.9%)					3272	101 (3.1%)
INSIGHT	Brown [88]	2000			3157	60 (1.9)			3164	52 (1.6)		
MRC-old	MRC Working Party [87]	1992							1081	66 (6.2)	1102	95 (8.6)
DETAIL	Barnett AH [73]	2004					130	6 (4.6%)	120	6 (5%)		
-	Bremner AD [96]	1997					164	2 (1%)	332	2 (1%)		
CORD IB	Spinar J [72]	2009					1926	4 (0.2%)	1887	5 (0.3%)		
HYVET-Pilot	Bulpitt CJ [79]	2003					431	27 (6.3%)			426	30 (7%)
LIVE	Gosse P [84]	2000					250	1 (0.4%)			255	0 (0%)
NESTOR	Marre Michel [98]	2004					286	1 (0.3%)			283	2 (0.7%)
ANBP2	Wing LM. [69]	2003					3044	195 (6.4%)			3039	210 (6.9%)
	**Nifedipine arm was chosen to represent CCB class as it was larger than VER* *Cacciapouti was not included in final analyses as the model could not converge when included; results were not different when Cacciapouti was included.*											

Figure 3.9 Relative risks of all-cause mortality associated with first line antihypertensive medication classes compared to Thiazides

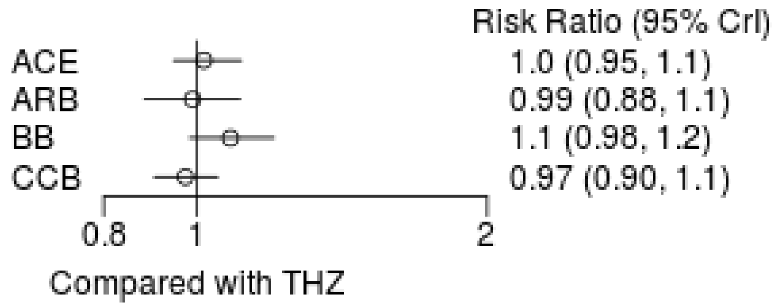


Figure 3.9.1 Pooled Network Relative risks associated with first line antihypertensive medication classes compared to THZ

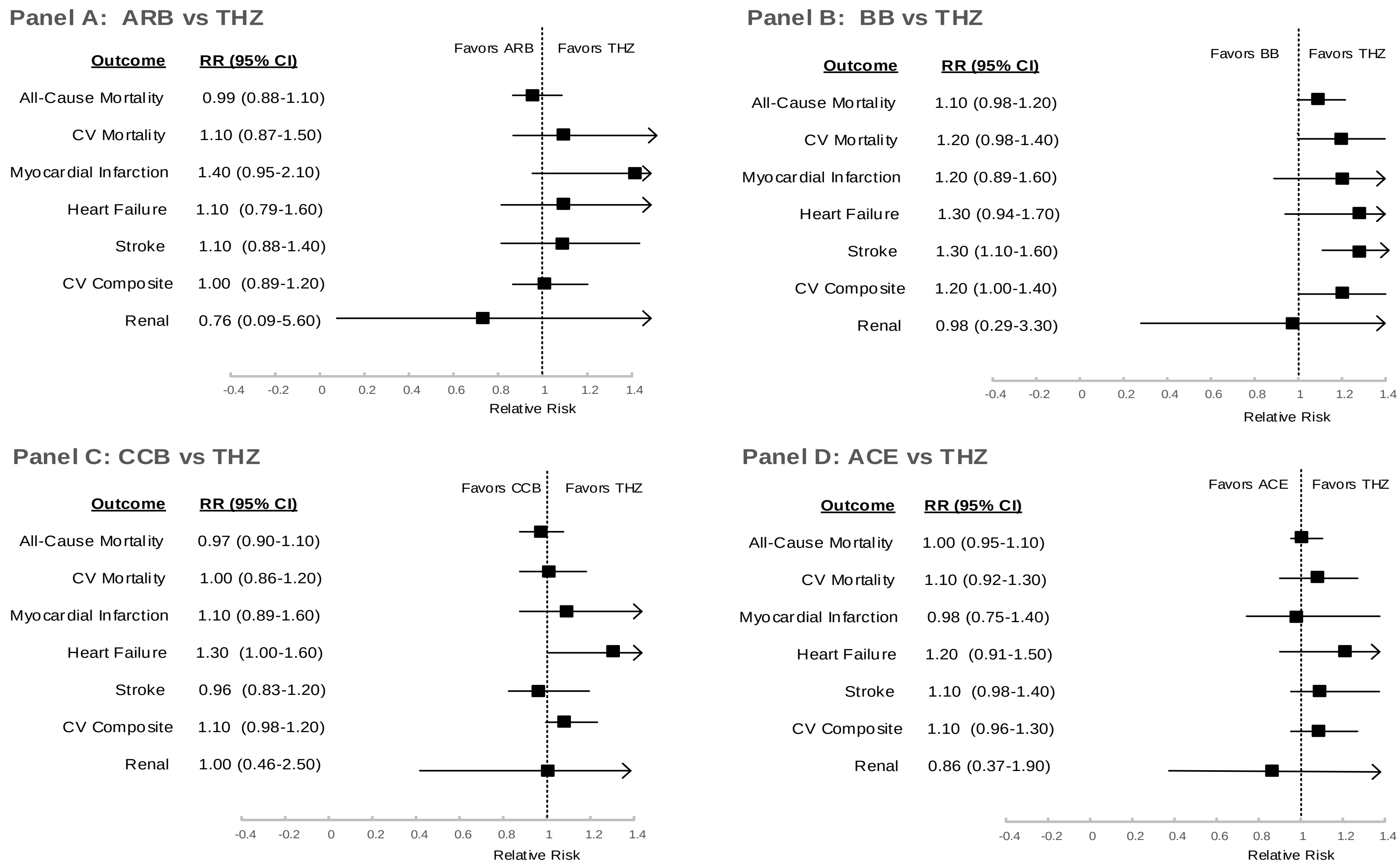


Figure 3.10 Pooled Network Relative risks of CV mortality associated with first line antihypertensive medication classes compared to THZ

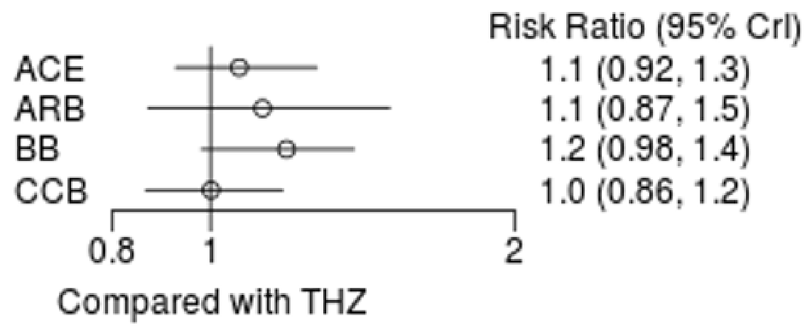


Table 3.4 Relative Treatment Effect of the Pooled Network Comparisons Expressed as RR (95% Credible Interval) of CV Mortality Associated with Antihypertensive Drug Class Comparisons

	ACE	**ARB**	**BB**	**CCB**	**THZ**
ACE	**ACE**	1.1 (0.8, 1.4)	1.1 (0.89, 1.3)	0.94 (0.8, 1.1)	0.94 (0.78, 1.1)
ARB	0.95 (0.72, 1.3)	**ARB**	1.1 (0.8, 1.3)	0.89 (0.68, 1.1)	0.89 (0.66, 1.2)
BB	0.9 (0.77, 1.1)	0.95 (0.76, 1.3)	**BB**	0.84 (0.73, 1)	0.84 (0.72, 1)
CCB	1.1 (0.92, 1.2)	1.1 (0.87, 1.5)	1.2 (0.98, 1.4)	**CCB**	1 (0.85, 1.2)
THZ	1.1 (0.92, 1.3)	1.1 (0.87, 1.5)	1.2 (0.98, 1.4)	1 (0.86, 1.2)	**THZ**

Figure 3.11. Relative risks of heart failure associated with first line antihypertensive medication classes compared to Thiazides

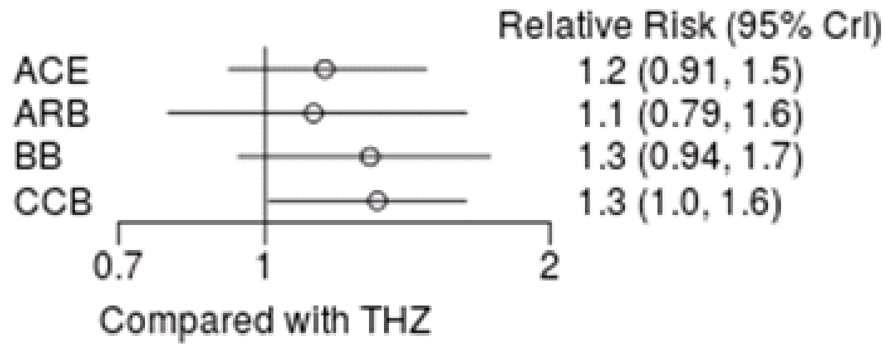


Figure 3.12. Relative Treatment Effects of Indirect Comparison Expressed as RR (95% Credible Interval) of fatal and non-fatal stroke associated with first line antihypertensive medication classes compared to THZ

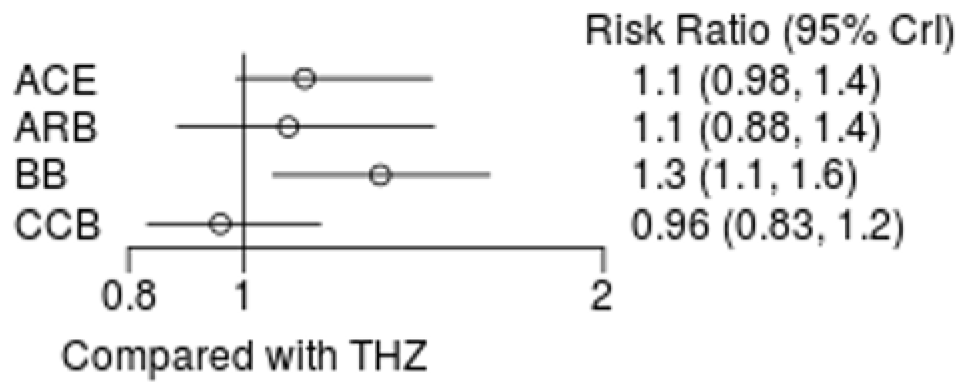


Table 3.5 Relative Treatment Effect of Pooled Network Comparisons Expressed as RR (95% Credible Interval) of Stroke Associated with Antihypertensive Drug Class Comparisons

	ACE	ARB	BB	CCB	THZ
ACE	**ACE**	0.97 (0.76, 1.2)	1.2 (0.88, 1.4)	0.85 (0.71, 0.98)	0.89 (0.7, 1)
ARB	1 (0.83, 1.3)	**ARB**	1.2 (0.91, 1.5)	0.88 (0.71, 1.1)	0.92 (0.69, 1.1)
BB	0.86 (0.71, 1.1)	0.84 (0.68, 1.1)	**BB**	0.73 (0.6, 0.93)	0.77 (0.62, 0.95)
CCB	1.2 (1, 1.4)	1.1 (0.93, 1.4)	1.4 (1.1, 1.7)	**CCB**	1 (0.86, 1.2)
THZ	1.1 (0.98, 1.4)	1.1 (0.88, 1.4)	1.3 (1.1, 1.6)	0.96 (0.83, 1.2)	**THZ**

Figure 3.13 Relative Treatment Effects of Indirect Comparison Expressed as RR (95% Credible Interval) of major CV events associated with first line antihypertensive medication classes compared to THZ

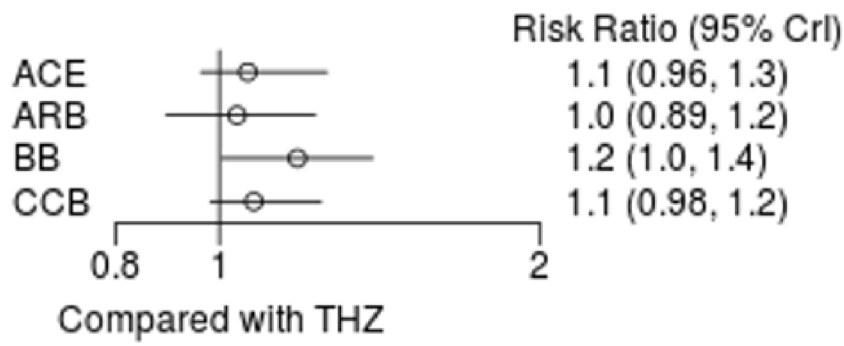


Table 3.6 Relative Treatment Effect of Pooled Network Comparisons Expressed as RR (95% Credible Interval) of Major CV Events Associated with Antihypertensive Drug Class Comparisons

	ACE	ARB	BB	CCB	THZ
ACE	**ACE**	0.98 (0.82, 1.1)	1.1 (0.92, 1.3)	1 (0.91, 1.1)	0.94 (0.79, 1)
ARB	1 (0.9, 1.2)	**ARB**	1.1 (0.98, 1.3)	1 (0.94, 1.2)	0.96 (0.81, 1.1)
BB	0.9 (0.8, 1.1)	0.88 (0.78, 1)	**BB**	0.91 (0.83, 1.1)	0.84 (0.72, 0.99)
CCB	0.99 (0.89, 1.1)	0.97 (0.85, 1.1)	1.1 (0.95, 1.2)	**CCB**	0.93 (0.8, 1)
THZ	1.1 (0.96, 1.3)	1 (0.89, 1.2)	1.2 (1, 1.4)	1.1 (0.98, 1.2)	**THZ**

Table 3.7. All-Cause mortality events by study and antihypertensive class among Blacks

Study Acronym	Author	Year	CCB		BB		ACE		ARB		THZ	
			N	Outcomes	N	Outcomes	N	Outcomes	N	Outcomes	N	Outcomes
ALLHAT	Wright JT [107]	2005	3213	481 (15%)			3210	520 (16.2%)			5369	821 (15.3%)
---	Agarwal R [94]	2014			100	4 (4%)	100	4 (4%)				
AASK	Wright Jr. J.T. [45]	2002	217	13 (6%)	441	38 (8.6%)	436	29 (6.7%)				
---	Sareli P [97]	2001	233	0 (0%)			60	0 (0%)			58	1 (1.7%)

Table 3.8 Cardiovascular mortality outcomes among Blacks by antihypertensive class and study

Study Acronym	Author	Year	ACE		CCB		ARB		THZ		BB	
			N	Outcome N (%)	N	Outcome N (%)	N	Outcome N (%)	N	Outcome N (%)	N	Outcome N (%)
AASK	Norris K [46]	2006	436	12 (2.8)	217	7 (3.2)					441	12 (2.7)
LIFE	Julius S [108]	2004					270	22 (8.1)			263	15 (5.7)
ALLHAT	Wright [107]	2005	3210	224 (7.0)	3213	215 (6.7)			5369	362 (6.7)		
-	Agarwal [94]	2014	100	3 (3.0)							100	2 (2.0)

Table 3.9 MI outcomes among Blacks by antihypertensive class and study

Study Acronym	Author	Year	ACE		CCB		ARB		THZ		BB	
			N	Outcome N (%)	N	Outcome N (%)	N	Outcome N (%)	N	Outcome N (%)	N	Outcome N (%)
LIFE	Julius S [108]	2004					270	13 (4.8)			263	6 (2.3)
ALLHAT	Wright [107]	2005	3210	260 (8.1)	3213	243 (7.6)			5369	400 (7.5)		
-	Agarwal [94]	2014	100	3 (3.0)							100	2 (2.0)

Table 3.10 CHF outcomes among Blacks by antihypertensive class and study

Study Acronym	Author	Year	ACE N	ACE Outcome N (%)	CCB N	CCB Outcome N (%)	ARB N	ARB Outcome N (%)	THZ N	THZ Outcome N (%)	BB N	BB Outcome N (%)
AASK	Norris [46]	2006	436	20 (4.5)							441	22 (5.0)
ALLHAT	Wright [107]	2005	3210	220 (6.8)	3213	248 (7.7)			5369	283 (5.3)		
-	Agarwal [94]	2014	100	10(10)							100	5 (5)

*note for Wright the direct comparison for CCB vs ACE was not included due to a difference in time periods for comparison

Table 3.11 Stroke outcomes among Blacks by antihypertensive class and study

Study Acronym	Author	Year	ACE N	ACE Outcome N (%)	CCB N	CCB Outcome N (%)	ARB N	ARB Outcome N (%)	THZ N	THZ Outcome N (%)	BB N	BB Outcome N (%)
AASK	Norris K [46]	2006	436	23 (5.3)	217	9 (4.1)					441	23 (5.2)
LIFE	Julius S [108]	2004					270	24 (8.9)			263	12 (4.6)
ALLHAT	Yamal [109]	2017	3210	214 (6.7)	3213	146 (4.5)			5369	260 (4.8)		
-	Agarwal [94]	2014	100	2 (2.0)							100	2 (2.0)

Table 3.12 composite event outcomes among Blacks by antihypertensive class and study

Study Acronym	Author	Year	ACE N	ACE Outcome N (%)	CCB N	CCB Outcome N (%)	ARB N	ARB Outcome N (%)	THZ N	THZ Outcome N (%)	BB N	BB Outcome N (%)
AASK	Norris K [46]	2006	436	20 (4.6)	217	8 (3.7)					441	22 (5.0)
LIFE	Julius S [108]	2004					270	46 (17.0)			263	29 (11.0)
ALLHAT	Wright [107]	2005	3210	444 (13.8)	3213	407 (12.7)			5369	655 (12.2)		
-	Agarwal [94]	2014	100	28 (28.0)							100	16 (16.0)

Figure 3.14. Pooled Network Relative risks among Blacks of All-Cause mortality associated with first line antihypertensive medication classes compared to THZ

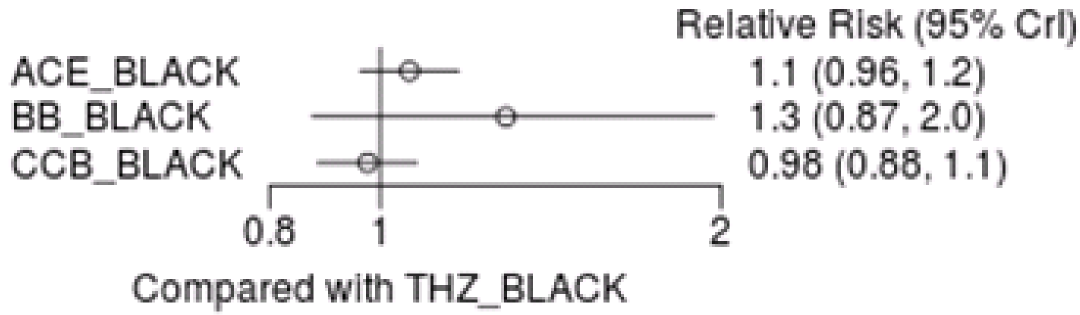


Figure 3.15 Pooled Network Relative risks among Blacks of CV mortality associated with first line antihypertensive medication classes compared to THZ

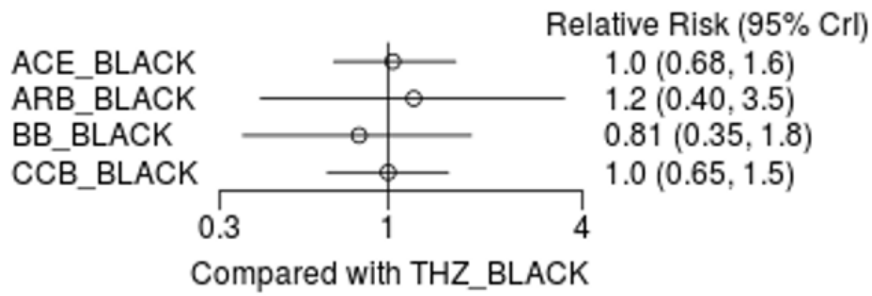


Figure 3.16 Pooled Network Relative risks among Blacks of MI associated with first line antihypertensive medication classes compared to THZ

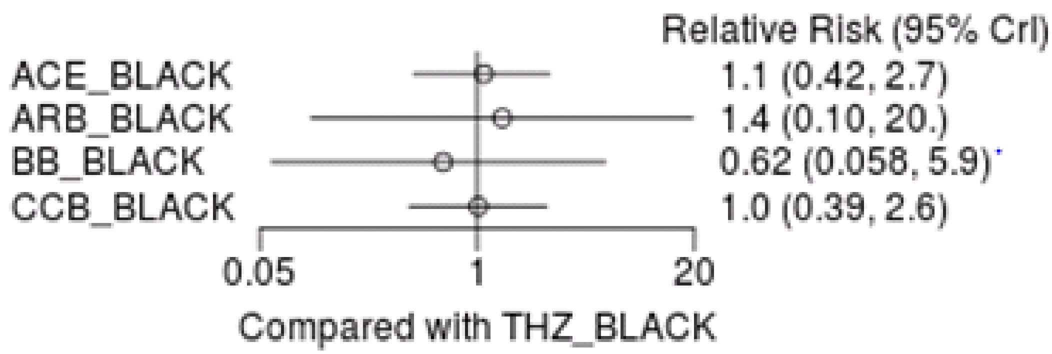


Figure 3.17. Pooled Network Relative risks among Blacks of CHF associated with first line antihypertensive medication classes compared to THZ

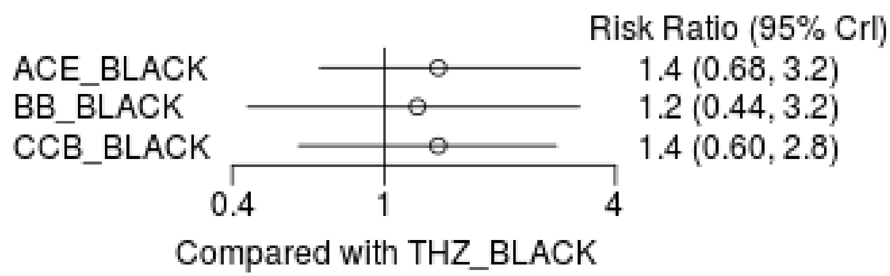


Figure 3. 18 Pooled Network Relative risks among Blacks of fatal or non-fatal stroke associated with first line antihypertensive medication classes compared to THZ

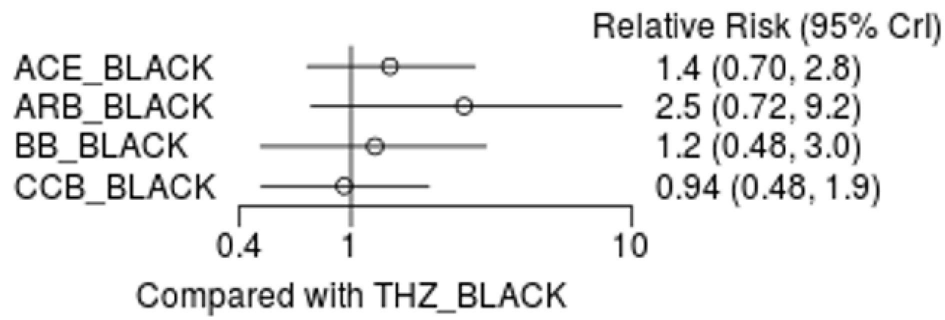
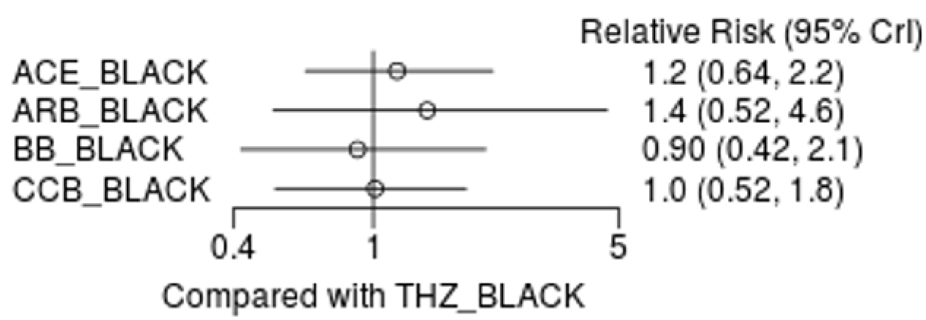


Figure 3.19 Pooled Network Relative risks among Blacks of CV events associated with first line antihypertensive medication classes compared to THZ



ADDITIONAL TABLES NOT REFERENCED IN THE TEXT (BY OUTCOME) FOR PART 3: FIRST-LINE ANTIHYPERTENSIVE DRUG CLASS COMPARISONS IN ADULTS

ALL-CAUSE MORTALITY OUTCOMES

Table 3.13 Relative Treatment Effect of Pairwise Comparisons Expressed as RR (95% Credible Interval) of All-Cause Mortality Associated with Antihypertensive Drug Class Comparisons (read top to left)

	ACE	ARB	BB	CCB	THZ
ACE	**ACE**	0.97 (0.86, 1.1)	1.1 (0.96, 1.2)	0.96 (0.88, 1)	0.98 (0.9, 1.1)
ARB	1 (0.92, 1.2)	**ARB**	1.1 (0.99, 1.2)	0.98 (0.9, 1.1)	1 (0.9, 1.1)
BB	0.94 (0.84, 1)	0.91 (0.82, 1)	**BB**	0.9 (0.82, 0.97)	0.92 (0.83, 1)
CCB	1 (0.97, 1.1)	1 (0.93, 1.1)	1.1 (1, 1.2)	**CCB**	1 (0.95, 1.1)
THZ	1 (0.95, 1.1)	0.99 (0.88, 1.1)	1.1 (0.98, 1.2)	0.97 (0.9, 1.1)	**THZ**

Table 3.14 All-Cause mortality events by study and antihypertensive class among Blacks

Study Acronym	Author	Year	CCB		BB		ACE		ARB		THZ	
			N	Outcomes	N	Outcomes	N	Outcomes	N	Outcomes	N	Outcomes
ALLHAT	Wright JT [107]	2005	3213	481 (15%)			3210	520 (16.2%)			5369	821 (15.3%)
	Agarwal R [94]	2014			100	4 (4%)	100	4 (4%)				
AASK	Wright Jr. J.T. [45]	2002	217	13 (6%)	441	38 (8.6%)	436	29 (6.7%)				
-	Sareli P [97]	2001	233	0 (0%)			60	0 (0%)			58	1 (1.7%)

Table 3.15 Relative Treatment Effect of the Pooled Network Comparisons Among Blacks Expressed as RR (95% Credible Interval) of All-Cause Mortality Associated with Antihypertensive Drug Class Comparisons

	ACE_BLACK	BB_BLACK	CCB_BLACK	THZ_BLACK
ACE_BLACK	**ACE_BLACK**	1.22 (0.824, 1.85)	0.918 (0.819, 1.02)	0.942 (0.852, 1.04)
BB_BLACK	0.82 (0.539, 1.21)	**BB_BLACK**	0.754 (0.493, 1.12)	0.774 (0.507, 1.15)
CCB_BLACK	1.09 (0.977, 1.22)	1.33 (0.891, 2.03)	**CCB_BLACK**	1.03 (0.927, 1.14)
THZ_BLACK	1.06 (0.961, 1.17)	1.29 (0.87, 1.97)	0.976 (0.881, 1.08)	**THZ_BLACK**

Table 3.16 All-Cause mortality events by study and antihypertensive class among Men

Study Acronym	Author	Year	CCB		BB		ACE		ARB		THZ	
			N	Outcomes	N	Outcomes	N	Outcomes	N	Outcomes	N	Outcomes
ALLHAT	Oparil [110]	2013	4768	763 (16%)			4867	797 (16.4%)			8084	1345 (16.6%)
MRC Mild	MRC Working Group [86]	1985			2285	75 (3.3%)					2238	82 (3.7%)
LIFE	Os [111]	2008			2112	224 (10.6%)			2118	224 (10.6%)		
HAPPHY	Wilhelmsen [78]	1987			3297	285 (8.6%)					3272	299 (9.1%)

Table 3.17 Relative Treatment Effect of the Pooled Network Comparisons Among Men Expressed as RR (95% Credible Interval) of All-Cause Mortality Associated with Antihypertensive Drug Class Comparisons

	ACE_MALE	ARB_MALE	BB_MALE	CCB_MALE	THZ_MALE
ACE_MALE	**ACE_MALE**	0.96 (0.7, 1.3)	0.95 (0.77, 1.2)	0.97 (0.83, 1.1)	1 (0.87, 1.2)
ARB_MALE	1 (0.77, 1.4)	**ARB_MALE**	1 (0.8, 1.2)	1 (0.75, 1.4)	1.1 (0.81, 1.4)
BB_MALE	1 (0.83, 1.3)	1 (0.81, 1.2)	**BB_MALE**	1 (0.82, 1.3)	1.1 (0.9, 1.3)
CCB_MALE	1 (0.87, 1.2)	0.99 (0.72, 1.3)	0.98 (0.78, 1.2)	**CCB_MALE**	1 (0.89, 1.2)
THZ_MALE	0.99 (0.85, 1.1)	0.95 (0.72, 1.2)	0.94 (0.79, 1.1)	0.96 (0.83, 1.1)	**THZ_MALE**

Figure 3.20 Pooled Network Relative risks among Men of All-Cause mortality associated with first line antihypertensive medication classes compared to THZ

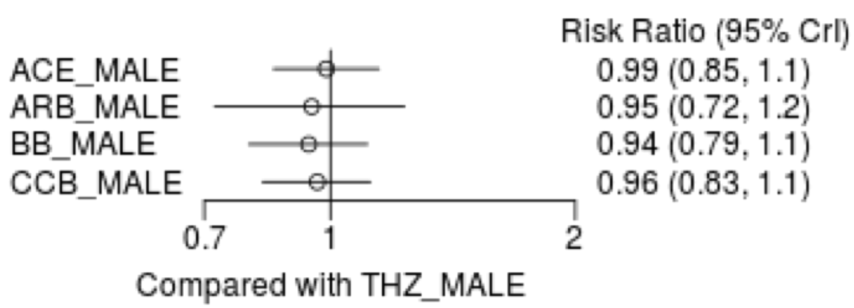


Table 3.18 All-Cause mortality events by study and antihypertensive class among Women

Study Acronym	Author	Year	CCB		BB		ACE		ARB		THZ	
			N	Outcomes	N	Outcomes	N	Outcomes	N	Outcomes	N	Outcomes
ALLHAT	Oparil [110]	2013	4280	491 (11.5%)			4187	499 (11.9%)			7171	867 (12.1%)
LIFE	Os [111]	2008			2476	207 (8.4%)			2487	159 (6.4%)		
MRC Mild	MRC Working Party [86]	1985			2118	45 (2.1%)					2059	46 (2.1%)

Table 3.19 Relative Treatment Effect of the Pooled Network Comparisons Among Women Expressed as RR (95% Credible Interval) of All-Cause Mortality Associated with Antihypertensive Drug Class Comparisons

	ACE_FEMALE	ARB_FEMALE	BB_FEMALE	CCB_FEMALE	THZ_FEMALE
ACE_FEMALE	**ACE_FEMALE**	0.76 (0.37, 1.6)	0.98 (0.54, 1.9)	0.96 (0.67, 1.4)	1 (0.72, 1.4)
ARB_FEMALE	1.3 (0.64, 2.7)	**ARB_FEMALE**	1.3 (0.89, 1.9)	1.3 (0.62, 2.5)	1.3 (0.71, 2.5)
BB_FEMALE	1 (0.54, 1.9)	0.77 (0.53, 1.1)	**BB_FEMALE**	0.97 (0.52, 1.8)	1 (0.62, 1.7)
CCB_FEMALE	1 (0.74, 1.5)	0.79 (0.39, 1.6)	1 (0.55, 1.9)	**CCB_FEMALE**	1.1 (0.74, 1.5)
THZ_FEMALE	0.99 (0.7, 1.4)	0.75 (0.4, 1.4)	0.98 (0.58, 1.6)	0.95 (0.66, 1.3)	**THZ_FEMALE**

Figure 3.21 Pooled Network Relative risks among Women of All-Cause mortality associated with first line antihypertensive medication classes compared to THZ

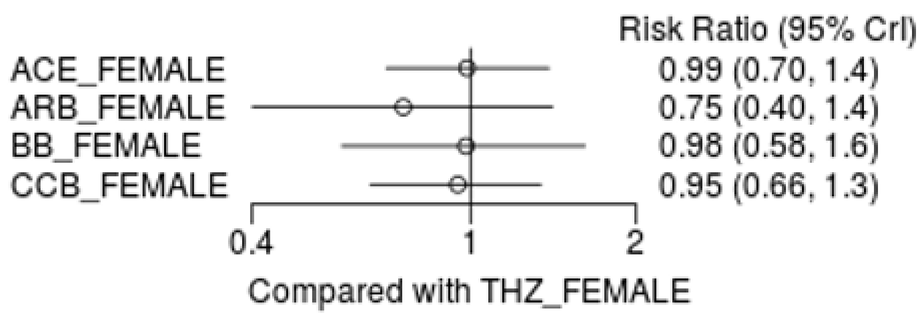


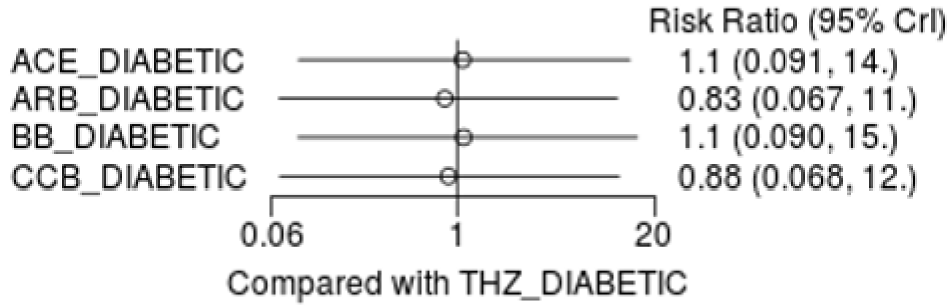
Table 3.20 All-Cause mortality events by study and antihypertensive class among Diabetics

Study Acronym	Author	Year	CCB		BB		ACE		ARB		THZ	
			N	Outcomes	N	Outcomes	N	Outcomes	N	Outcomes	N	Outcomes
DETAIL	Barnett [73]	2004					130	6 (4.6%)	120	6 (5%)		
	Fogari [89]	2002	103	4 (3.9%)			102	3 (2.9%)				
ATTEST	Katayama [106]	2008	112	0 (0%)			111	0 (0%)				
STOP-HTN-2	Lindholm [112]	2000	231	50 (21.7%)			235	56 (23.8%)				
LIFE	Lindholm [113, 114]	2002			609	104 (17.1%)			586	63 (10.8)		
UKPDS 39	UKPDS 39 [101]	1998			358	59 (16.5%)	400	75 (18.8%)				
ABCD	Estacio [66, 67]	1998	235	17 (7.2%)			235	13 (5.5%)				
FACET	Tatti [77]	1998	191	5 (2.6%)			189	4 (2.1%)				
IDNT	Lewis [80]	2001	567	83 (14.6%)					579	87 (15%)		
JMIC-B	Yui [81, 82]	2004	199	2 (1%)			173	5 (2.9%)				
BENEDICT	Ruggenenti [71]	2004	303	2 (0.7%)			301	3 (1%)				
NESTOR	Marre Michel[98]	2004					286	1 (0.3%)			283	2 (0.7%)

Table 3.21 Relative Treatment Effect of the Pooled Network Comparisons Among Diabetics Expressed as RR (95% Credible Interval) of All-Cause Mortality Associated with Antihypertensive Drug Class Comparisons

	ACE_DIABETIC	ARB_DIABETIC	BB_DIABETIC	CCB_DIABETIC	THZ_DIABETIC
ACE_DIABETIC	**ACE_DIABETIC**	0.76 (0.44, 1.4)	1 (0.57, 1.8)	0.81 (0.52, 1.2)	0.92 (0.073, 11)
ARB_DIABETIC	1.3 (0.73, 2.3)	**ARB_DIABETIC**	1.4 (0.75, 2.4)	1.1 (0.58, 1.8)	1.2 (0.088, 15)
BB_DIABETIC	0.98 (0.54, 1.8)	0.74 (0.42, 1.3)	**BB_DIABETIC**	0.79 (0.41, 1.5)	0.91 (0.065, 11)
CCB_DIABETIC	1.2 (0.82, 1.9)	0.94 (0.55, 1.7)	1.3 (0.67, 2.4)	**CCB_DIABETIC**	1.1 (0.086, 15)
THZ_DIABETIC	1.1 (0.091, 14)	0.83 (0.067, 11)	1.1 (0.09, 15)	0.88 (0.068, 12)	**THZ_DIABETIC**

Figure 3.22 Pooled Network Relative risks among Diabetics of All-Cause mortality associated with first line antihypertensive medication classes compared to THZ



CARDIOVASCULAR MORTALITY OUTCOMES

Table 3.22 Cardiovascular mortality outcomes by antihypertensive class and study

Study Acronym	Author	Year	ACE		CCB		ARB		THZ		BB	
			N	Outcome N (%)	N	Outcome N (%)	N	Outcome N (%)	N	Outcome N (%)	N	Outcome N (%)
AASK	Norris K [46]	2006	436	12 (2.8)	217	7 (3.2)					441	12 (2.7)
HYVET-Pilot	Bulpitt CJ [79]	2003	431	22 (5.1)					426	23 (5.4)		
-	Fogari R [89]	2002	102	3 (2.9)	103	4 (3.9)						
-	Zucchelli P [92]	1995	60	1 (1.7)	61	0 (0)						
STOP-HTN-2	Hansson [100]	1999	2205	226 (10.3)	2196	212 (9.7)						
UKPDS 39	UKPDS 39 [101]	1998	400	47 (11.8)							358	32 (8.9)
ANBP2	Wing LM [69]	2003	3044	84 (2.8)					3039	82 (2.7)		
BENEDICT	Ruggenenti P [71]	2004	301	1 (0.3)	303	1 (0.3)						
JMIC-B	Yui Y [81, 82]	2004	822	6 (0.7)	828	6 (0.7)						
ASPIRAL	Marin R [76]	2001	129	3 (2.3)	112	6 (5.4)						

-	Agarwal [94]	2014	100	3 (3.0)							100	2 (2.0)
ALLHAT	ALLHAT Res Grp [68]	2002	9054	618 (6.8)	9048	603 (6.7)			15255	996 (6.5)		
DETAIL	Barnett AH [73]	2004	130	2 (1.5)			120	3 (2.5)				
ASCOT-BPLA	Dahlof B [70]	2005			9639	263 (2.7)	4605	204 (4.4)			9618	342 (3.6)
IDNT	Berl T. [115]	2003			567	37 (6.5)	579	52 (8.9)				
ELSA	Zanchetti [74]	2002			1177	4 (0.3)					1157	8 (0.7)
J-RHYTHM II	Yamashita T [116]	2001			160	0 (0)	158	0 (0.0)				
-	Du Y [117]	2013			75	0 (0)	74	0 (0.0)				
NICS-EH	Kuramoto K (118)	1999			204	2 (1.0)			210	0 (0.0)		
VHAS	Rosei EA [104]	1997			707	5 (0.7)			707	4 (0.6)		
HAPPHY	Wilhelmsen L [78]	1987							3272	60 (1.8)	3297	57 (1.7)
MRC	MRC Working Party [86]	1985							4297	69 (1.6)	4403	65 (1.5)
LIFE	Dahlof [83]	2002					4605	204 (4.4)			4588	234 (5.1)
INSIGHT	Brown [88]	2000			3157	153 (4.8)			3164	152 (4.8)		
MRC-old	MRC Working Party [87]	1992							1081	134 (12.4)	1102	167 (15.2)

Table 3.23 Cardiovascular mortality outcomes among Blacks by antihypertensive class and study

Study Acronym	Author	Year	ACE		CCB		ARB		THZ		BB	
			N	Outcome N (%)	N	Outcome N (%)	N	Outcome N (%)	N	Outcome N (%)	N	Outcome N (%)
AASK	Norris K [46]	2006	436	12 (2.8)	217	7 (3.2)					441	12 (2.7)
LIFE	Julius S [108]	2004					270	22 (8.1)			263	15 (5.7)
ALLHAT	Wright [107]	2005	3210	224 (7.0)	3213	215 (6.7)			5369	362 (6.7)		
-	Agarwal [94]	2014	100	3 (3.0)							100	2 (2.0)

Table 3.24 Relative Treatment Effect of the Pooled Network Comparisons Among Blacks Expressed as RR (95% Credible Interval) of CV Mortality Associated with Antihypertensive Drug Class Comparisons

	ACE_BLACK	ARB_BLACK	BB_BLACK	CCB_BLACK	THZ_BLACK
ACE_BLACK	**ACE_BLACK**	1.17 (0.421, 3.27)	0.785 (0.365, 1.58)	0.971 (0.658, 1.41)	0.968 (0.618, 1.48)
ARB_BLACK	0.855 (0.306, 2.38)	**ARB_BLACK**	0.675 (0.325, 1.44)	0.831 (0.292, 2.45)	0.833 (0.284, 2.49)
BB_BLACK	1.27 (0.634, 2.74)	1.48 (0.695, 3.07)	**BB_BLACK**	1.23 (0.587, 2.78)	1.23 (0.552, 2.83)
CCB_BLACK	1.03 (0.708, 1.52)	1.2 (0.408, 3.42)	0.811 (0.359, 1.7)	**CCB_BLACK**	1 (0.651, 1.55)
THZ_BLACK	1.03 (0.677, 1.62)	1.2 (0.401, 3.53)	0.812 (0.353, 1.81)	0.999 (0.647, 1.54)	**THZ_BLACK**

Table 3.25 CV mortality events by study and antihypertensive class among Men

Study Acronym	Author	Year	ACE		CCB		ARB		THZ		BB	
			N	Outcome N (%)	N	Outcome N (%)	N	Outcome N (%)	N	Outcome N (%)	N	Outcome N (%)
HAPPY	Wilhelmsen [78]	1987							3272	60 (1.8)	3297	57 (1.7)
LIFE	Os [111]	2008					2118	116 (5.5)			2112	130 (6.2)
ALLHAT	Oparil [110]	2013	4867	362 (7.4)	4768	370 (7.8)			8084	581 (7.2)		

Table 3.26 Relative Treatment Effect of the Pooled Network Comparisons Among Men Expressed as RR (95% Credible Interval) of CV Mortality Associated with Antihypertensive Drug Class Comparisons

	ACE_MALE	ARB_MALE	BB_MALE	CCB_MALE	THZ_MALE
ACE_MALE	ACE_MALE	0.82 (0.49, 1.4)	0.91 (0.6, 1.4)	1 (0.85, 1.3)	0.96 (0.8, 1.2)
ARB_MALE	1.2 (0.74, 2)	ARB_MALE	1.1 (0.85, 1.5)	1.3 (0.76, 2.1)	1.2 (0.73, 1.9)
BB_MALE	1.1 (0.72, 1.7)	0.9 (0.68, 1.2)	BB_MALE	1.1 (0.74, 1.7)	1.1 (0.73, 1.5)
CCB_MALE	0.96 (0.79, 1.2)	0.79 (0.48, 1.3)	0.88 (0.58, 1.4)	CCB_MALE	0.93 (0.77, 1.1)
THZ_MALE	1 (0.85, 1.2)	0.85 (0.53, 1.4)	0.95 (0.66, 1.4)	1.1 (0.89, 1.3)	THZ_MALE

Figure 3.23 Pooled Network Relative risks among Men of CV mortality associated with first line antihypertensive medication classes compared to THZ

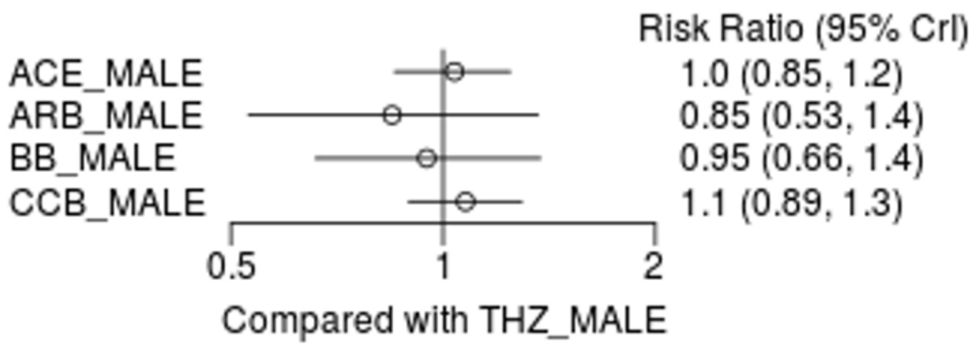


Table 3.27 CV mortality events by study and antihypertensive class among Women

Study Acronym	Author	Year	ACE		CCB		ARB		THZ		BB	
			N	Outcome N (%)	N	Outcome N (%)	N	Outcome N (%)	N	Outcome N (%)	N	Outcome N (%)
LIFE	Os [111]	2008					2487	88 (3.5)			2476	104 (4.2)
ALLHAT	Oparil [110]	2013	4187	246 (5.9)	4280	244 (5.7)			7171	416 (5.8)		
MRC Mild	MRC Working Group [86]	1985							2059	13 (0.6)	2118	17 (0.8)

Table 3.28 Relative Treatment Effect of the Pooled Network Comparisons Among Women Expressed as RR (95% Credible Interval) of CV Mortality Associated with Antihypertensive Drug Class Comparisons

	ACE_FEMALE	ARB_FEMALE	BB_FEMALE	CCB_FEMALE	THZ_FEMALE
ACE_FEMALE	**ACE_FEMALE**	1.1 (0.44, 2.9)	1.3 (0.58, 3.1)	0.97 (0.69, 1.4)	0.98 (0.72, 1.3)
ARB_FEMALE	0.89 (0.35, 2.3)	**ARB_FEMALE**	1.2 (0.8, 1.8)	0.86 (0.33, 2.2)	0.88 (0.35, 2.1)
BB_FEMALE	0.76 (0.33, 1.7)	0.85 (0.57, 1.3)	**BB_FEMALE**	0.74 (0.31, 1.7)	0.75 (0.34, 1.6)
CCB_FEMALE	1 (0.74, 1.5)	1.2 (0.46, 3)	1.4 (0.6, 3.2)	**CCB_FEMALE**	1 (0.74, 1.4)
THZ_FEMALE	1 (0.74, 1.4)	1.1 (0.48, 2.8)	1.3 (0.63, 3)	0.98 (0.72, 1.4)	**THZ_FEMALE**

Figure 3.24 Pooled Network Relative risks among Women of CV mortality associated with first line antihypertensive medication classes compared to THZ

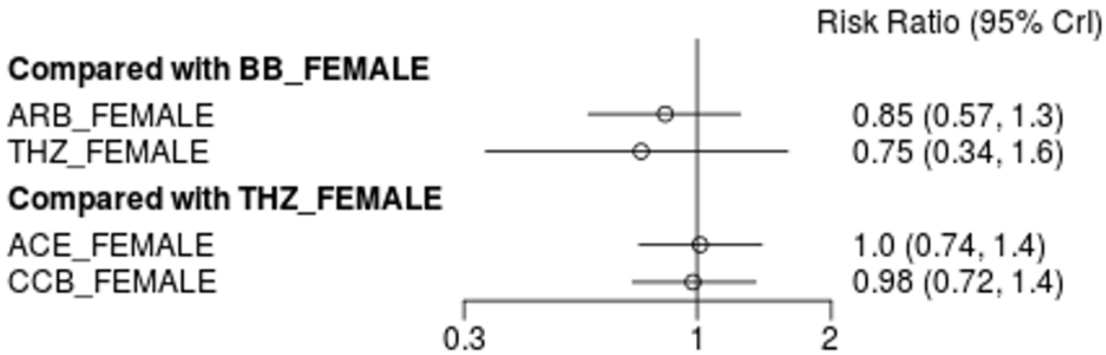


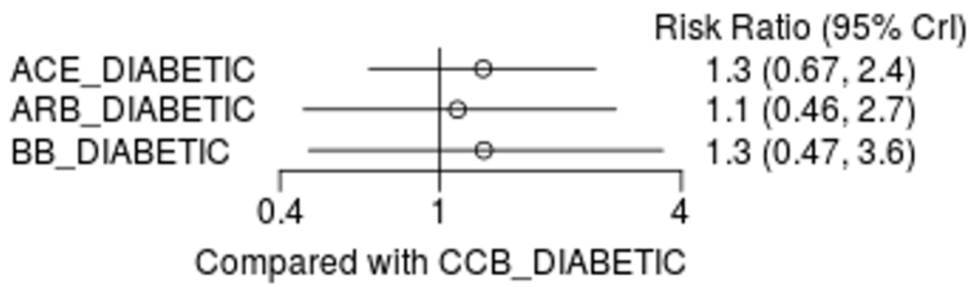
Table 3.29 CV mortality events by study and antihypertensive class among persons with Diabetes

Study Acronym	Author	Year	ACE		CCB		ARB		THZ		BB	
			N	Outcome N (%)	N	Outcome N (%)	N	Outcome N (%)	N	Outcome N (%)	N	Outcome N (%)
DETAIL	Barnett [73]	2004	130	2 (1.5)			120	3 (2.5)				
--	Fogari [89]	2002	102	3 (2.9)	103	4 (3.9)						
STOP-HTN-2	Lindholm [112]	2000	235	39 (16.6)	231	33 (14.3)						
LIFE	Lindholm [113, 114]	2002					586	38 (6.5)			609	61 (10.0)
UKPDS	UKPDS 39 [101]	1998	400	47 (11.8)							358	32 (8.9)
IDNT	Berl [115]	2003			567	37 (6.5)	579	52 (9.0)				
JMIC-B	Yui [81, 82]	2004	173	3 (1.7)	199	1 (0.5)						
BENEDICT	Ruggenenti [71]	2004	301	1 (0.3)	303	1 (0.3)						
ABCD	Estacio [66, 67]	1998										

Table 3.30 Relative Treatment Effect of the Pooled Network Comparisons Among Persons with Diabetes Expressed as RR (95% Credible Interval) of CV Mortality Associated with Antihypertensive Drug Class Comparisons

	ACE_DIABETIC	ARB_DIABETIC	BB_DIABETIC	CCB_DIABETIC
ACE_DIABETIC	**ACE_DIABETIC**	0.86 (0.36, 2.2)	1 (0.41, 2.5)	0.78 (0.41, 1.5)
ARB_DIABETIC	1.2 (0.46, 2.8)	**ARB_DIABETIC**	1.2 (0.47, 2.9)	0.9 (0.36, 2.2)
BB_DIABETIC	1 (0.39, 2.4)	0.87 (0.35, 2.1)	**BB_DIABETIC**	0.78 (0.28, 2.1)
CCB_DIABETIC	1.3 (0.67, 2.4)	1.1 (0.46, 2.7)	1.3 (0.47, 3.6)	**CCB_DIABETIC**

Figure 3.25 Pooled Network Relative risks among Persons with Diabetes of CV mortality associated with first line antihypertensive medication classes compared to THZ



MYOCARDIAL INFARCTION OUTCOMES

Table 3.31 Myocardial Infarction events by study and antihypertensive class

Study Acronym	Author	Year	CCB		BB		ACE		ARB		THZ	
			N	Outcomes	N	Outcomes	N	Outcomes	N	Outcomes	N	Outcomes
DETAIL	Barnett [73]	2004	130	2 (1.5%)					120	1 (0.8%)		
	Fogari [89]	2002	103	1 (1.9%)			102	1 (1.0%)				
STOP-HTN-2	Hansson [100]	1999	2,196	59 (2.7%)			2,205	48 (2.2%)				
ALPINE	Lindholm [119]	2003							196	1 (0.5%)	196	1 (0.5%)
VALUE	Julius [102]	2004	7,596	313 (4.1%)					7,649	369 (4.8%)		
UKPDS	UKPDS [101]	1998			358	46 (12.9%)	400	61 (15.3%)				
ANBP2	Wing [69]	2003					3,044	58 (1.9%)			3,039	82 (2.7%)
LIFE	Dahlof [83]	2002			4,588	188 (4.1%)			4,605	198 (4.3%)		
FACET	Tatti [77]	1998	191	13 (6.8%)			189	10 (5.4%)				
IDNT	Berl [115]	2003	567	27 (4.8%)					579	44 (7.6%)		

	Estacio [66]	1998	235	25 (10.6%)			235	5 (2.1%)				
PHYLISS	Zanchetti [120]	2004					127	0 (0%)			127	3 (2.4%)
HAPPHY	Wilhelmsen [78]	1987			3,297	84 (2.5%)					3,272	75 (2.3%)
JMIC-B	Yui [82]	2004	828	16 (1.9%)			822	13 (1.6%)				
J-MIND	Baba [121]	2001	228	1 (0.4%)			208	1 (0.5%)				
CORD IB	Spinar [72]	2009					1,926	4 (0.2%)	1,887	3 (0.2%)		
ESPIRAL	Marin [76]	2001	112	1 (0.9%)			129	2 (1.6%)				
ASCOT-BPLA	Collier [122]	2011	9,639	390 (4.0%)	9,618	444 (4.6%)						
J-RHYTHM II	Yamashita [116]	2011	160	0 (0%)					158	0 (0%)		
VART	Narumi [103]	2011	511	1 (0.2%)					510	2 (0.4%)		
	Agarwal [94]	2014			100	2 (2%)	100	3 (3%)				
SHELL	Malacco [99]	2003	942	12 (1.3%)							940	14 (1.5%)
	Du [117]	2013	75	0 (0%)					74	0 (0%)		
ALLHAT	ALLHAT Res Grp [68]	2002	9,048	798 (8.8%)			9,054	796 (8.8%)			15,255	1,362 (8.9%)
MIDAS	Borhani [105]	1996	442	6 (1.4%)							441	5 (1.1%)
NICS-EH	Kuramoto [118]	1999	204	2 (1.0%)							210	2 (1.0%)
INSIGHT	Brown [88]	2000	3157	16 (0.51%)							3164	5 (0.16%)
MRC old*	MRC Working Party [87]	1992			1102	80 (7.3%)					1081	48 (4.4%)
ELSA	Zanchetti [74]	2002	1,177	18 (1.5%)	1,157	17 (1.5%)						

**included all CHD event*

Figure 3.26 Relative risks of myocardial infarction associated with first line antihypertensive medication classes compared to Thiazides

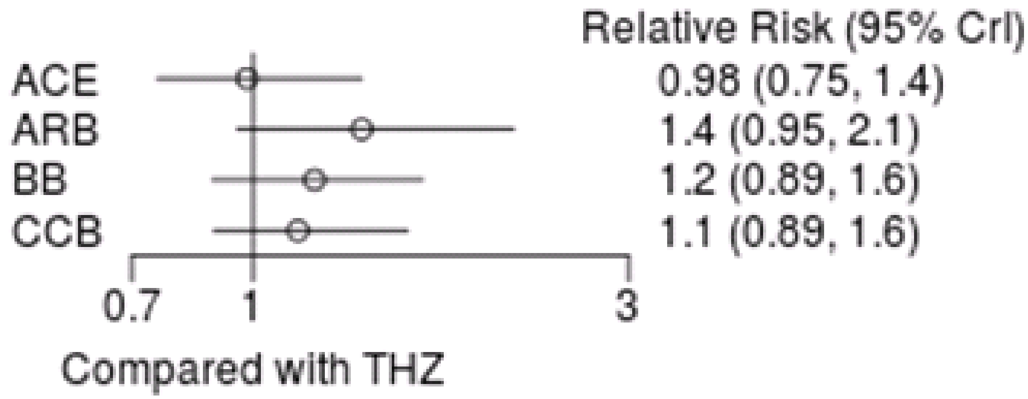


Table 3.32 Relative Treatment Effect of Pairwise Comparisons Expressed as RR (95% Credible Interval) of Myocardial Infarction Associated with Antihypertensive Drug Class Comparisons (read top to left)

	ACE	**ARB**	**BB**	**CCB**	**THZ**
ACE	**ACE**	1.39 (0.941, 2.12)	1.22 (0.864, 1.63)	1.15 (0.902, 1.5)	1.02 (0.727, 1.32)
ARB	0.717 (0.472, 1.06)	**ARB**	0.875 (0.581, 1.22)	0.829 (0.596, 1.16)	0.728 (0.466, 1.05)
BB	0.823 (0.612, 1.16)	1.14 (0.82, 1.72)	**BB**	0.947 (0.727, 1.31)	0.836 (0.608, 1.13)
CCB	0.867 (0.666, 1.11)	1.21 (0.865, 1.68)	1.06 (0.763, 1.38)	**CCB**	0.877 (0.636, 1.12)
THZ	0.982 (0.755, 1.37)	1.37 (0.953, 2.14)	1.2 (0.887, 1.64)	1.14 (0.891, 1.57)	**THZ**

Table 3.33 MI outcomes among Blacks by antihypertensive class and study

Study Acronym	Author	Year	ACE		CCB		ARB		THZ		BB	
			N	Outcome N (%)	N	Outcome N (%)	N	Outcome N (%)	N	Outcome N (%)	N	Outcome N (%)
LIFE	Julius S [108]	2004					270	13 (4.8)			263	6 (2.3)
ALLHAT	Wright [107]	2005	3210	260 (8.1)	3213	243 (7.6)			5369	400 (7.5)		
-	Agarwal [94]	2014	100	3 (3.0)							100	2 (2.0)

Table 3.34 Relative Treatment Effect of the Pooled Network Comparisons Among Blacks Expressed as RR (95% Credible Interval) of MI Associated with Antihypertensive Drug Class Comparisons

	ACE_BLACK	ARB_BLACK	BB_BLACK	CCB_BLACK	THZ_BLACK
ACE_BLACK	**ACE_BLACK**	1.26 (0.107, 15.6)	0.577 (0.0645, 4.66)	0.929 (0.361, 2.39)	0.911 (0.368, 2.4)
ARB_BLACK	0.792 (0.0642, 9.31)	**ARB_BLACK**	0.455 (0.118, 1.66)	0.721 (0.0507, 10.5)	0.707 (0.051, 9.91)
BB_BLACK	1.73 (0.215, 15.5)	2.2 (0.604, 8.46)	**BB_BLACK**	1.61 (0.171, 16.9)	1.6 (0.17, 17.1)
CCB_BLACK	1.08 (0.419, 2.77)	1.39 (0.0953, 19.7)	0.622 (0.059, 5.86)	**CCB_BLACK**	0.985 (0.384, 2.55)
THZ_BLACK	1.1 (0.417, 2.71)	1.41 (0.101, 19.6)	0.625 (0.0585, 5.88)	1.02 (0.392, 2.61)	**THZ_BLACK**

HEART FAILURE OUTCOMES

Table 3.35 Heart Failure events by study and antihypertensive class

Study Acronym	Author	Year	CCB		BB		ACE		ARB		THZ	
			N	Outcomes	N	Outcomes	N	Outcomes	N	Outcomes	N	Outcomes
DETAIL	Barnett [73]	2004	130	7 (5.4%)					120	9 (7.5%)		
AASK	Norris [46]	2006	217	8 (3.7%)	441	22 (5.0%)	436	20 (4.6%)				
VALUE	Julius [102]	2004	7,596	400 (5.3%)					7,649	354 (4.6%)		
	UKPDS [101]	1998			358	9 (2.5%)	400	12 (3%)				
ABCD	Estacio [66, 67]	1998	235	6 (2.6%)			235	5 (2.1%)				
ASCOT-BPLA	Dahlof [70]	2005	9,639	134 (1.4%)	9,618	159 (1.7%)						
ANBP2	Wing[69]	2003					3,044	69 (2.3%)			3,039	78 (2.6%)
LIFE	Dahlof [83]	2002			4,588	161 (3.5%)			4,605	153 (3.3%)		
IDNT	Berl [115]	2003	567	93 (16.4%)					579	60 (10.4%)		
HAPPHY	Wilhelmsen [78]	1987			3,297	32 (1.0%)					3,272	22 (0.7%)
JMIC-B	Yui [81, 82]	2004	828	12 (1.4%)			822	9 (1.1%)				
J-MIND	Baba [121]	2001	228	1 (0.4%)			208	0 (0%)				
J-RHTHYM II	Yamashita [116]	2011	160	0 (0%)					158	0 (0%)		
VART	Narumi [103]	2011	511	1 (0.2%)					510	3 (0.6%)		
	Agarwal [94]	2014			100	5 (5%)	100	10 (10%)				
SHELL	Malacco [99]	2003	942	23 (2.4%)							940	19 (2.0%)
INSIGHT	Brown [88]	2000	3157	2 (0.06%)							3164	1 (0.03%)
	Du [117]	2013	75	0 (0%)					74	0 (0%)		
ALLHAT	ALLHAT Res Grp [68]	2002	9,048	578 (6.4%)			9,054	471 (5.2%)			15,255	724 (4.7%)
MIDAS	Borhani [105]	1996	442	2 (0.5%)							441	0 (0%)
NICS-EH	Kuramoto [118]	1999	204	0 (0%)							210	3 (1.4%)

Table 3.36 Relative Treatment Effect of Pairwise Comparisons Expressed as RR (95% Credible Interval) of Heart Failure Associated with Antihypertensive Drug Class Comparisons (read top to left)

	ACE	ARB	BB	CCB	THZ
ACE	**ACE**	0.972 (0.706, 1.36)	1.12 (0.836, 1.44)	1.13 (0.903, 1.33)	0.865 (0.676, 1.09)
ARB	1.03 (0.736, 1.42)	**ARB**	1.15 (0.805, 1.52)	1.17 (0.819, 1.54)	0.889 (0.613, 1.27)
BB	0.897 (0.694, 1.2)	0.869 (0.659, 1.24)	**BB**	1.01 (0.786, 1.31)	0.775 (0.578, 1.07)
CCB	0.881 (0.75, 1.11)	0.858 (0.651, 1.22)	0.987 (0.766, 1.27)	**CCB**	**0.762 (0.613, 0.992)**
THZ	1.16 (0.915, 1.48)	1.12 (0.789, 1.63)	1.29 (0.936, 1.73)	**1.31 (1.01, 1.63)**	**THZ**

Table 3.37 HF outcomes among Blacks by antihypertensive class and study

Study Acronym	Author	Year	ACE		CCB		ARB		THZ		BB	
			N	Outcome N (%)	N	Outcome N (%)	N	Outcome N (%)	N	Outcome N (%)	N	Outcome N (%)
AASK	Norris [46]	2006	436	20 (4.5)							441	22 (5.0)
ALLHAT	Wright [107]	2005	3210	220 (6.8)	3213	248 (7.7)			5369	283 (5.3)		
-	Agarwal [94]	2014	100	10(10)							100	5 (5)

*note for Wright the direct comparison for CCB vs ACE was not included due to a difference in time periods for comparison

Table 3.38 Relative Treatment Effect of the Pooled Network Comparisons Among Blacks Expressed as RR (95% Credible Interval) of HF Associated with Antihypertensive Drug Class Comparisons

	ACE_BLACK	BB_BLACK	CCB_BLACK	THZ_BLACK
ACE_BLACK	**ACE_BLACK**	0.87 (0.4, 1.7)	1 (0.47, 1.7)	0.72 (0.31, 1.5)
BB_BLACK	1.1 (0.59, 2.5)	**BB_BLACK**	1.1 (0.48, 2.5)	0.82 (0.31, 2.3)
CCB_BLACK	1 (0.6, 2.1)	0.89 (0.4, 2.1)	**CCB_BLACK**	0.72 (0.36, 1.7)
THZ_BLACK	1.4 (0.68, 3.2)	1.2 (0.44, 3.2)	1.4 (0.6, 2.8)	**THZ_BLACK**

Table 3.39 HF events by study and antihypertensive class among Men

Study Acronym	Author	Year	CCB		BB		ACE		ARB		THZ	
			N	Outcomes	N	Outcomes	N	Outcomes	N	Outcomes	N	Outcomes
ALLHAT	Oparil [110]	2013	4768	38 (0.8%)			4867	33 (0.7%)			8084	51 (0.6%)
LIFE	Os [111]	2008			2112	81 (3.8%)			2118	78 (3.7%)		
HAPPHY	Wilhelmsen [78]	1987			3297	32 (1%)					3272	22 (0.7%)

Table 3.40 Relative Treatment Effect of the Pooled Network Comparisons Among Men Expressed as RR (95% Credible Interval) of HF Associated with Antihypertensive Drug Class Comparisons

	ACE_MALE	ARB_MALE	BB_MALE	CCB_MALE	THZ_MALE
ACE_MALE	**ACE_MALE**	1.3 (0.47, 3.8)	1.4 (0.55, 3.4)	1.1 (0.61, 2.1)	0.91 (0.49, 1.6)
ARB_MALE	0.75 (0.26, 2.1)	**ARB_MALE**	1 (0.6, 1.7)	0.86 (0.3, 2.4)	0.68 (0.29, 1.6)
BB_MALE	0.74 (0.3, 1.8)	0.98 (0.58, 1.7)	**BB_MALE**	0.84 (0.34, 2)	0.67 (0.34, 1.3)
CCB_MALE	0.88 (0.47, 1.6)	1.2 (0.41, 3.3)	1.2 (0.49, 3)	**CCB_MALE**	0.79 (0.44, 1.4)
THZ_MALE	1.1 (0.61, 2)	1.5 (0.62, 3.5)	1.5 (0.76, 3)	1.3 (0.7, 2.3)	**THZ_MALE**

Figure 3.27 Pooled Network Relative risks among Men of HF associated with first line antihypertensive medication classes compared to THZ

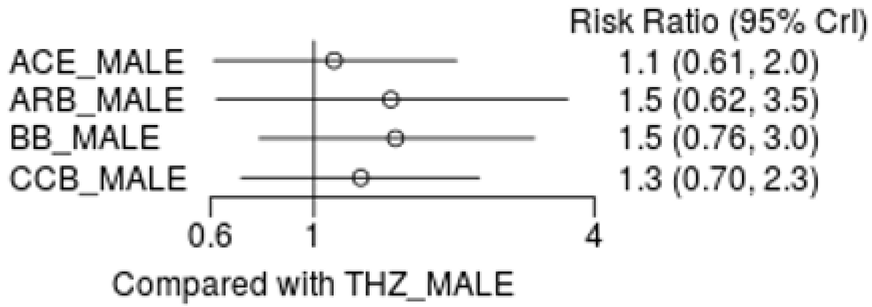


Table 3.41 HF events by study and antihypertensive class among Women

Study Acronym	Author	Year	CCB		BB		ACE		ARB		THZ	
			N	Outcomes	N	Outcomes	N	Outcomes	N	Outcomes	N	Outcomes
ALLHAT	Oparil [110]	2013	4280	45 (1%)			4187	37 (0.9%)			7171	63 (0.9%)
LIFE	Os [111]	2008			2476	80 (3.2%)			2487	74 (3%)		

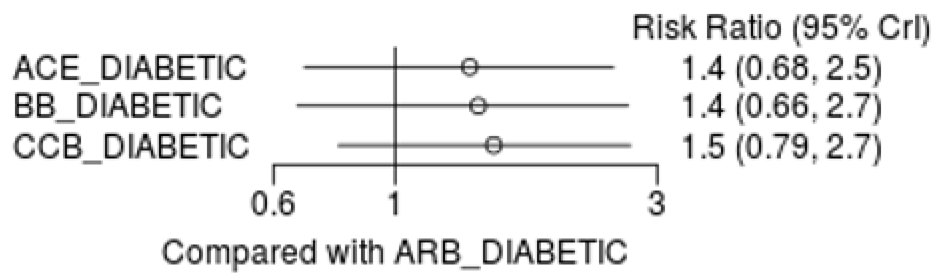
Table 3.42 HF events by study and antihypertensive class among Diabetics

Study Acronym	Author	Year	CCB		BB		ACE		ARB		THZ	
			N	Outcomes	N	Outcomes	N	Outcomes	N	Outcomes	N	Outcomes
DETAIL	Barnett [73]	2004					130	7 (5.4%)	120	9 (7.5%)		
	Lindholm [113, 114]	2002			609	55 (9%)			586	32 (5.5%)		
STOP-HTN-2	Lindholm [112]	2000	231	24 (10.4%)			235	22 (9.4%)				
UKPDS 39	UKPDS 39 [101]	1998			358	9 (2.5%)	400	12 (3%)				
ABCD	Estacio [66, 67]	1998	235	6 (2.6%)			235	5 (2.1%)				
IDNT	Berl [115]	2003	567	93 (16.4%)					579	60 (10.4%)		
JMIC-B	Yui [81, 82]	2004	199	8 (4%)			173	5 (2.9%)				
J-MIND	Baba [121]	2001	228	1 (0.4%)			208	0 (0%)				

Table 3.43 Relative Treatment Effect of the Pooled Network Comparisons Among Diabetics Expressed as RR (95% Credible Interval) of HF Associated with Antihypertensive Drug Class Comparisons

	ACE_DIABETIC	ARB_DIABETIC	BB_DIABETIC	CCB_DIABETIC
ACE_DIABETIC	**ACE_DIABETIC**	0.73 (0.4, 1.5)	1 (0.48, 2.2)	1.1 (0.67, 1.9)
ARB_DIABETIC	1.4 (0.68, 2.5)	**ARB_DIABETIC**	1.4 (0.66, 2.7)	1.5 (0.79, 2.7)
BB_DIABETIC	0.97 (0.46, 2.1)	0.71 (0.38, 1.5)	**BB_DIABETIC**	1.1 (0.49, 2.4)
CCB_DIABETIC	0.9 (0.52, 1.5)	0.66 (0.37, 1.3)	0.94 (0.41, 2)	**CCB_DIABETIC**

Figure 3.28 Pooled Network Relative risks among Diabetics of HF associated with first line antihypertensive medication classes compared to ARB (No Studies had a THZ Arm)



STROKE OUTCOMES

Table 3.44 Fatal and non-fatal stroke outcomes by antihypertensive class and study

Study Acronym	Author	Year	ACE N	ACE Stroke N (%)	CCB N	CCB Stroke N (%)	ARB N	ARB Stroke N (%)	THZ N	THZ Stroke N (%)	BB N	BB Stroke N (%)
DETAIL	Barnett AH [73]	2004	130	6 (4.6)			120	6 (5.0)				
AASK	Norris K [46]	2006	436	23 (5.3)	217	9 (4.1)					441	23 (5.2)
HYVET-Pilot	Bulpitt CJ [79]	2003	431	7 (1.6)					426	6 (1.4)		
--	Fogari R [89]	2002	102	1 (0.98)	103	0 (0.0)						
STOP-HTN-2	Hansson L [100]	1999	2205	50 (2.3)	2196	46 (2.1)						
UKPDS	UKPDS 39 [101]	1998	400	21 (5.3)							358	17 (4.7)
ABCD	Estacio RO [66, 67]	1998	235	7 (3.0)	235	11 (4.7)						
ANBP2	Wing LM [69]	2003	3044	112 (3.7)					3039	107 (3.5)		
PHYLLIS	Zanchetti A [102]	2004	127	0 (0.0)					127	0 (0.0)		
JMIC-B	Yui Y [81, 82]	2004	822	16 (1.9)	828	16 (1.9)						
J-MIND	Baba S [121]	2001	208	5 (2.4)	228	2 (0.88)						
CORD IB	Spinar J [72]	2009	1926	8 (0.42)			1887	9 (0.48)				
ESPIRAL	Marin R [76]	2001	129	0 (0.0)	112	2 (1.8)						
--	Agarwal R [94]	2014	100	2 (2.0)							100	2 (2.0)
ALLHAT	Yamal JM [109]	2014	9054	460 (5.1)	9048	382 (4.2)			15255	683 (4.5)		
ALPINE	Lindholm LH [119]	2003					196	0 (0.0)	196	0 (0.0)		
VALUE	Julius S [28, 102]	2004			7596	281 (3.7)	7649	322 (4.2)				
LIFE	Dahlof B [83]	2002					4605	232 (5.0)			4588	309 (6.7)
IDNT	Berl T [115]	2003			567	15 (2.6)	579	28 (4.8)				
J-RHYTHM II	Yamashita T [116]	2011			160	3 (1.9)	158	0 (0.0)				
VART	Narumi H [103]	2011			511	10 (2.0)	510	10 (2.0)				
--	Du H [117]	2013			75	0 (0.0)	74	1 (1.4)				
ELSA	Zanchetti A [74]	2002			1177	9 (0.76)					1157	14 (1.2)
HAPPHY	Wilhelmsen L [78]	1987							3272	41 (1.3)	3297	32 (0.97)
SHELL	Malacco E [99]	2003			942	37 (3.9)			940	38 (4.0)		
MIDAS	Borhani N.O [105]	1996			442	6 (1.4)			441	3 (0.68)		
NICS-EH	Kuramoto K [118]	1999			204	12 (5.9)			210	8 (3.8)		
INSIGHT	Brown [88]	2000			3157	55 (1.7)			3164	63 (2.0)		

MRC-old	MRC Working Party [87]	1992							1081	44 (4.1)	1102	51 (4.6)
MRC-mild	MRC Working Party [86]	1985							4297	18 (0.42)	4403	42 (0.95)

Table 3.45 Relative Treatment Effect of Pooled Network Comparisons Expressed as RR (95% Credible Interval) of Stroke Associated with Antihypertensive Drug Class Comparisons

	ACE	ARB	BB	CCB	THZ
ACE	**ACE**	0.97 (0.76, 1.2)	1.2 (0.88, 1.4)	0.85 (0.71, 0.98)	0.89 (0.7, 1)
ARB	1 (0.83, 1.3)	**ARB**	1.2 (0.91, 1.5)	0.88 (0.71, 1.1)	0.92 (0.69, 1.1)
BB	0.86 (0.71, 1.1)	0.84 (0.68, 1.1)	**BB**	0.73 (0.6, 0.93)	0.77 (0.62, 0.95)
CCB	1.2 (1, 1.4)	1.1 (0.93, 1.4)	1.4 (1.1, 1.7)	**CCB**	1 (0.86, 1.2)
THZ	1.1 (0.98, 1.4)	1.1 (0.88, 1.4)	1.3 (1.1, 1.6)	0.96 (0.83, 1.2)	**THZ**

Table 3.46 Stroke outcomes among Blacks by antihypertensive class and study

Study Acronym	Author	Year	ACE		CCB		ARB		THZ		BB	
			N	Outcome N (%)	N	Outcome N (%)	N	Outcome N (%)	N	Outcome N (%)	N	Outcome N (%)
AASK	Norris K [46]	2006	436	23 (5.3)	217	9 (4.1)					441	23 (5.2)
LIFE	Julius S [108]	2004					270	24 (8.9)			263	12 (4.6)
ALLHAT	Yamal [109]	2017	3210	214 (6.7)	3213	146 (4.5)			5369	260 (4.8)		
-	Agarwal [94]	2014	100	2 (2.0)							100	2 (2.0)

Table 3.47 Relative Treatment Effect of the Pooled Network Comparisons Among Blacks Expressed as RR (95% Credible Interval) of Fatal or Non-Fatal Stroke Associated with Antihypertensive Drug Class Comparisons

	ACE_BLACK	ARB_BLACK	BB_BLACK	CCB_BLACK	THZ_BLACK
ACE_BLACK	**ACE_BLACK**	1.83 (0.574, 5.84)	0.886 (0.433, 1.78)	0.691 (0.383, 1.2)	0.727 (0.362, 1.43)
ARB_BLACK	0.548 (0.171, 1.74)	**ARB_BLACK**	0.486 (0.187, 1.26)	0.374 (0.114, 1.23)	0.395 (0.108, 1.39)
BB_BLACK	1.13 (0.561, 2.31)	2.06 (0.792, 5.34)	**BB_BLACK**	0.778 (0.353, 1.77)	0.823 (0.33, 2.1)
CCB_BLACK	1.45 (0.836, 2.61)	2.68 (0.814, 8.79)	1.29 (0.565, 2.83)	**CCB_BLACK**	1.06 (0.529, 2.1)
THZ_BLACK	1.37 (0.698, 2.76)	2.53 (0.719, 9.24)	1.22 (0.475, 3.03)	0.944 (0.477, 1.89)	**THZ_BLACK**

Table 3.48 Stroke events by study and antihypertensive class among Men

Study Acronym	Author	Year	ACE		CCB		ARB		THZ		BB	
			N	Outcome N (%)	N	Outcome N (%)	N	Outcome N (%)	N	Outcome N (%)	N	Outcome N (%)
HAPPY	Wilhelmsen [78]	1987							3272	41 (1.3)	3297	32 (1.0)
LIFE	Os [111]	2008					2118	123 (5.8)			2112	155 (7.3)
ALLHAT	Yamal [109]	2014	4867	259 (5.3)	4768	237 (5.0)			8084	395 (4.9)		
MRC Mild	MRC Working Group [123]	1987							2238	11 (0.5)	2285	26 (1.1)

Table 3.49 Relative Treatment Effect of the Pooled Network Comparisons Among Men Expressed as RR (95% Credible Interval) of Stroke Associated with Antihypertensive Drug Class Comparisons

	ACE_MALE	ARB_MALE	BB_MALE	CCB_MALE	THZ_MALE
ACE_MALE	**ACE_MALE**	0.93 (0.15, 6.3)	1.2 (0.27, 5.4)	0.93 (0.28, 3)	0.9 (0.27, 2.9)
ARB_MALE	1.1 (0.16, 6.6)	**ARB_MALE**	1.2 (0.39, 3.9)	0.99 (0.15, 5.8)	0.98 (0.21, 4)
BB_MALE	0.86 (0.19, 3.7)	0.8 (0.26, 2.6)	**BB_MALE**	0.81 (0.18, 3.3)	0.79 (0.3, 1.8)
CCB_MALE	1.1 (0.34, 3.5)	1 (0.17, 6.5)	1.2 (0.3, 5.6)	**CCB_MALE**	0.99 (0.31, 3)
THZ_MALE	1.1 (0.35, 3.7)	1 (0.25, 4.7)	1.3 (0.56, 3.3)	1 (0.33, 3.2)	**THZ_MALE**

Figure 3.29 Pooled Network Relative risks among Men of Stroke associated with first line antihypertensive medication classes compared to THZ

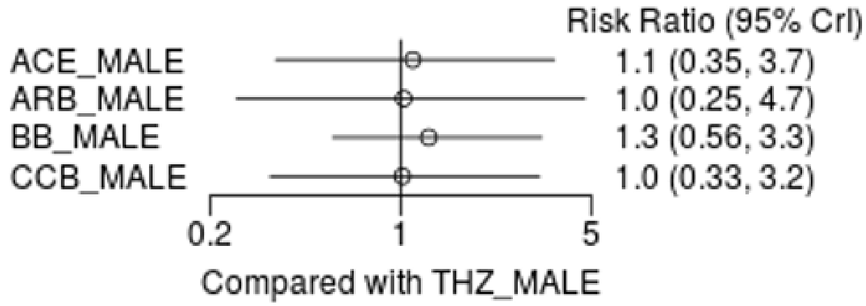


Table 3.50 Stroke events by study and antihypertensive class among Women

Study Acronym	Author	Year	ACE		CCB		ARB		THZ		BB	
			N	Outcome N (%)	N	Outcome N (%)	N	Outcome N (%)	N	Outcome N (%)	N	Outcome N (%)
LIFE	Os [111]	2008					2487	109 (4.4)			2476	154 (6.2)
ALLHAT	Yamal [109]	2014	4187	201 (4.8)	4280	145 (3.4)			7171	288 (4.0)		
MRC Mild	MRC Working Group [86]	1985							2059	14 (0.7)	2118	25 (1.1)

Table 3.51 Relative Treatment Effect of the Pooled Network Comparisons Among Women Expressed as RR (95% Credible Interval) of Stroke Associated with Antihypertensive Drug Class Comparisons

	ACE_FEMALE	ARB_FEMALE	BB_FEMALE	CCB_FEMALE	THZ_FEMALE
ACE_FEMALE	**ACE_FEMALE**	1.1 (0.28, 3.9)	1.5 (0.49, 4.7)	0.7 (0.33, 1.4)	0.83 (0.41, 1.7)
ARB_FEMALE	0.93 (0.26, 3.6)	**ARB_FEMALE**	1.4 (0.7, 2.9)	0.65 (0.18, 2.5)	0.77 (0.26, 2.5)
BB_FEMALE	0.65 (0.21, 2)	0.71 (0.35, 1.4)	**BB_FEMALE**	0.46 (0.15, 1.5)	0.55 (0.21, 1.4)
CCB_FEMALE	1.4 (0.71, 3)	1.5 (0.4, 5.6)	2.2 (0.68, 6.9)	**CCB_FEMALE**	1.2 (0.59, 2.4)
THZ_FEMALE	1.2 (0.59, 2.4)	1.3 (0.4, 3.9)	1.8 (0.73, 4.7)	0.85 (0.42, 1.7)	**THZ_FEMALE**

Figure 3.30 Pooled Network Relative risks among Women of Stroke associated with first line antihypertensive medication classes compared to THZ

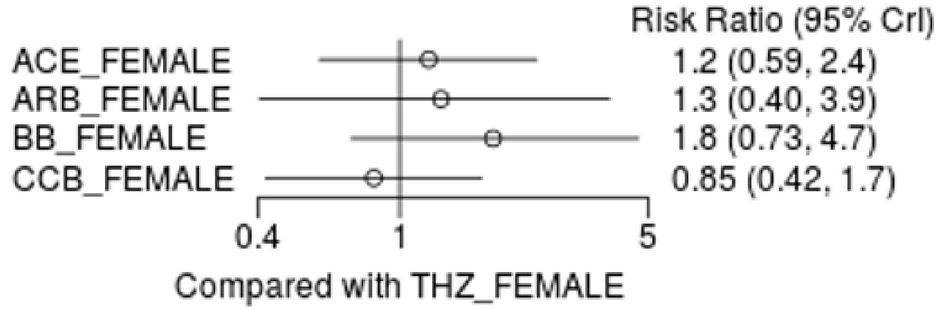


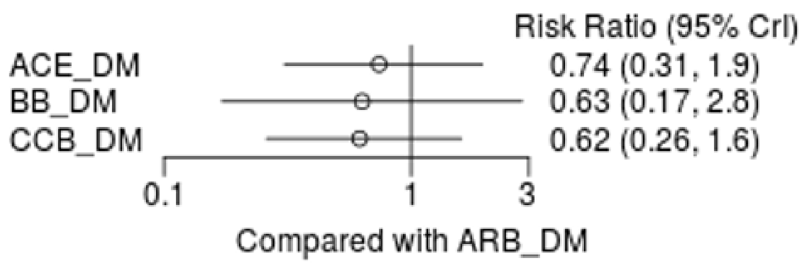
Table 3.52 Stroke events by study and antihypertensive class among persons with Diabetes

Study Acronym	Author	Year	ACE		CCB		ARB		THZ		BB	
			N	Outcome N (%)	N	Outcome N (%)	N	Outcome N (%)	N	Outcome N (%)	N	Outcome N (%)
DETAIL	Barnett [73]	2004	130	6 (4.6)			120	6 (5.0)				
--	Fogari [89]	2002	120	2 (2.0)	103	2 (1.9)						
ALPINE	Lindholm [112]	2000	235	34 (14.5)	231	29 (12.6)					358	17 (3.0)
UKPDS	UKPDS 39 [101]	1998	400	21 (5.3)								
ABCD	Estacio [66, 67]	1998	235	7 (3.0)	235	11 (4.7)						
FACET	Tatti [77]	1998	189	4 (2.1)	191	10 (5.2)						
IDNT	Berl [115]	2003			567	15 (2.6)	579	28 (4.8)				
JMIC-B	Yui [81, 82]	2004	173	6 (3.5)	199	4 (2.0)						
J-MIND	Baba [121]	2001	208	5 (2.4)	228	2 (0.9)						

Table 3.53 Relative Treatment Effect of the Pooled Network Comparisons Among Persons with Diabetes Expressed as RR (95% Credible Interval) of Stroke Associated with Antihypertensive Drug Class Comparisons

	ACE_DM	ARB_DM	BB_DM	CCB_DM
ACE_DM	**ACE_DM**	1.3 (0.51, 3.3)	0.86 (0.3, 2.8)	0.83 (0.49, 1.4)
ARB_DM	0.74 (0.31, 1.9)	**ARB_DM**	0.63 (0.17, 2.8)	0.62 (0.26, 1.6)
BB_DM	1.2 (0.36, 3.3)	1.6 (0.35, 5.8)	**BB_DM**	0.97 (0.26, 3.1)
CCB_DM	1.2 (0.72, 2.1)	1.6 (0.62, 3.8)	1 (0.32, 3.9)	**CCB_DM**

Figure 3.31 Pooled Network Relative risks among Persons with Diabetes of Stroke associated with first line antihypertensive medication classes compared to THZ



CARDIOVASCULAR COMPOSITE EVENTS

Table 3.54 Major CV events by antihypertensive class and study

Study Acronym	Author	Year	ACE N	ACE CV events N (%)	CCB N	CCB CV events N (%)	ARB N	ARB CV events N (%)	THZ N	THZ CV events N (%)	BB N	BB CV events N (%)
--	Agarwal R [94]	2014	100	28 (28.0)							100	16 (16.0)
ALLHAT	Cushman WC [124]	2012	5845	1075 (18.4)	5864	1081 (18.4)			9914	1745 (17.6)		
J-MIND	Baba S [121]	2001	208	8 (3.8)	228	5 (2.2)					4588	588 (12.8)
JMIC-B	Yui Y [81, 82]	2004	822	106 (12.9)	828	116 (14.0)					9618	852 (8.9)
STOP-HTN-2	Hansson L [100]	1999	2205	437 (19.8)	2196	450 (20.5)						
AASK	Norris K [46]	2006	436	20 (4.6)	217	8 (3.7)					441	22 (5.0)
MOSES	Schrader J [85]	2005			671	84 (12.5)	681	60 (8.8)				
IDNT	Berl T [115]	2003			567	161 (28.4)	579	172 (29.7)				
LIFE	Dahlof B [83]	2002					4605	508 (11.0)			4588	588 (12.8)

NICS-EH	Kuramoto K [118]	1999			204	21 (10.3)			210	18 (8.6)		
MIDAS	Borhani N.O. [105]	1996			442	54 (12.2)			441	33 (7.5)		
SHELL	Malacco E [99]	2003			942	90 (9.6)			940	88 (9.4)		
ELSA	Zanchetti A [74]	2002			1177	69 (5.9)					1157	73 (6.3)
ASCOT-BPLA	Dahlof B [70]	2005			9639	753 (7.8)						
VALUE	Julius S [102]	2004			7596	578 (7.6)	7649	586 (7.7)				
INSIGHT	Brown MJ [88]	2000			3157	383 (12.1)			3164	397 (12.6)		
FACET	Tatti P [77]	1998	189	14 (7.4)	191	27 (14.1)						

Table 3.55 Outcome names for composite CV event outcomes

Study Acronym	Author	Year	Outcome Name
--	Agarwal R [94]	2014	Composite, Myocardial Infarction or Composite, Stroke or Composite, Heart Failure, Congestive or Composite, Angina or Composite, Arrhythmia or Composite, Cardiac Arrest or Composite, Coronary Revascularization or Composite, Heart Valve Replacement
ALLHAT	Cushman WC [124]	2012	Composite, Mortality, Cardiovascular or Composite, Myocardial Infarction, Non-Fatal, Requiring Hospitalization or Composite, Stroke, Non-Fatal, Requiring Hospitalization or Composite, Heart Failure, Non-Fatal, Requiring Hospitalization
J-MIND	Baba S [121]	2001	Composite, Stroke, Ischemic or Composite, Angina or Composite, Myocardial Infarction or Composite, Heart Failure or Composite, Atrial Fibrillation
JMIC-B	Yui Y [81, 82]	2004	Composite, Mortality, Cardiovascular or Composite, Mortality, Sudden Death or Composite, Myocardial Infarction, Non-Fatal or Composite, Angina, Requiring Hospitalization or Composite, Heart Failure, Non-Fatal, Requiring Hospitalization or Composite, Arrhythmia, Serious or Composite, Coronary Revascularization
STOP-HTN-2	Hansson L [100]	1999	Composite, Stroke, Fatal or Non-Fatal or Composite, Myocardial Infarction, Fatal or Non-Fatal or Composite, Mortality, Cardiovascular, Other
AASK	Norris K [46]	2006	Composite, Mortality, Cardiovascular or Composite, Hospitalization, Cardiovascular, First
MOSES	Schrader J [85]	2005	Composite, Acute Coronary Syndrome, First or Composite, Heart Failure, Fatal or Non-Fatal, First or Composite, Arrhythmia, Fatal, First or Composite, Embolism, Pulmonary, Fatal or Non-Fatal, First or Composite, Myocardial Infarction, Fatal or Non-Fatal, First
IDNT	Berl T [115]	2003	Composite, Mortality, Cardiovascular or Composite, Myocardial Infarction, Non-Fatal or Composite, Heart Failure, Congestive, Non-Fatal or Composite, Stroke, Non-Fatal or Composite, Coronary Revascularization
LIFE	Dahlof B [83]	2002	Composite, Mortality, Cardiovascular or Composite, Stroke, Non-Fatal or Composite, Myocardial Infarction, Non-Fatal
NICS-EH	Kuramoto K [118]	1999	Composite, Myocardial Infarction, Non-Fatal or Composite, Angina or Composite, Heart Failure, Non-Fatal or Composite, Arrhythmia
MIDAS	Borhani N.O. [105]	1996	Composite, Stroke, Fatal or Non-Fatal or Composite, Myocardial Infarction, Fatal or Non-Fatal or Composite, Mortality, Sudden Death or Composite, Heart Failure, Congestive, Fatal or Non-Fatal or Composite, Angina or Composite, Mortality, Cardiovascular, Other or Composite, Coronary Revascularization or Composite, Stroke, Transient Ischemic Attack, Non-Fatal or Composite, Atrial Fibrillation or Composite, Premature Ventricular

			Contractions or Composite, Peripheral Revascularization or Composite, Heart Valve Replacement, Aortic or Composite, Palpitations
SHELL	Malacco E [99]	2003	Composite, Stroke, Fatal or Non-Fatal or Composite, Mortality, Sudden Death or Composite, Myocardial Infarction, Fatal or Non-Fatal or Composite, Heart Failure, Congestive, Fatal or Non-Fatal or Composite, Coronary Revascularization
ELSA	Zanchetti A [74]	2002	Composite, Myocardial Infarction, Non-Fatal or Composite, Stroke, Non-Fatal or Composite, Mortality, Cardiovascular or Composite, Heart Failure, Requiring Hospitalization or Composite, Angina or Composite, Atrial Fibrillation or Composite, Claudication
ASCOT-BPLA	Dahlof B [70]	2005	Composite, Coronary Heart Disease, Fatal or Composite, Myocardial Infarction, Non-Fatal or Composite, Myocardial Infarction, Non-Fatal, Silent or Composite, Angina, Unstable or Composite, Angina, Chronic, Stable or Composite, Heart Failure, Fatal or Non-Fatal
VALUE	Julius S [102]	2004	Composite, Heart Failure, Congestive, Requiring Hospitalization or Composite, Heart Failure, Congestive, Newly Diagnosed, Requiring Hospitalization or Composite, Myocardial Infarction, Non-Fatal or Composite, Thrombolysis, Emergency Procedure or Composite, Intervention to Prevent Myocardial Infarction
INSIGHT	Brown MJ [88]	2000	Composite, Myocardial Infarction, Fatal or Non-Fatal or Composite, Mortality, Sudden Death or Composite, Stroke, Fatal or Non-Fatal or Composite, Heart Failure, Fatal or Non-Fatal or Composite, Mortality, Cardiovascular
FACET	Tatti P [77]	1998	Composite, Stroke, Fatal or Non-Fatal or Composite, Myocardial Infarction, Fatal or Non-Fatal or Composite, Angina, Requiring Hospitalization or Composite, Adverse Events, Cardiovascular, Other or Composite, Coronary Revascularization

Table 3.56 CV composite event outcomes among Blacks by antihypertensive class and study

Study Acronym	Author	Year	ACE		CCB		ARB		THZ		BB	
			N	Outcome N (%)	N	Outcome N (%)	N	Outcome N (%)	N	Outcome N (%)	N	Outcome N (%)
AASK	Norris K [46]	2006	436	20 (4.6)	217	8 (3.7)					441	22 (5.0)
LIFE	Julius S [108]	2004					270	46 (17.0)			263	29 (11.0)
ALLHAT	Wright [107]	2005	3210	444 (13.8)	3213	407 (12.7)			5369	655 (12.2)		
-	Agarwal [94]	2014	100	28 (28.0)							100	16 (16.0)

Table 3.57 Relative Treatment Effect of the Pooled Network Comparisons Among Blacks Expressed as RR (95% Credible Interval) of CV Events Associated with Antihypertensive Drug Class Comparisons

	ACE_BLACK	ARB_BLACK	BB_BLACK	CCB_BLACK	THZ_BLACK
ACE_BLACK	**ACE_BLACK**	1.22 (0.488, 3.24)	0.769 (0.442, 1.37)	0.864 (0.468, 1.38)	0.856 (0.457, 1.56)
ARB_BLACK	0.821 (0.309, 2.05)	**ARB_BLACK**	0.636 (0.299, 1.3)	0.706 (0.231, 1.86)	0.702 (0.216, 1.93)
BB_BLACK	1.3 (0.73, 2.26)	1.57 (0.77, 3.35)	**BB_BLACK**	1.11 (0.513, 2.16)	1.11 (0.478, 2.39)
CCB_BLACK	1.16 (0.723, 2.14)	1.42 (0.537, 4.32)	0.899 (0.463, 1.95)	**CCB_BLACK**	0.989 (0.544, 1.91)
THZ_BLACK	1.17 (0.641, 2.19)	1.42 (0.518, 4.64)	0.901 (0.419, 2.09)	1.01 (0.524, 1.84)	**THZ_BLACK**

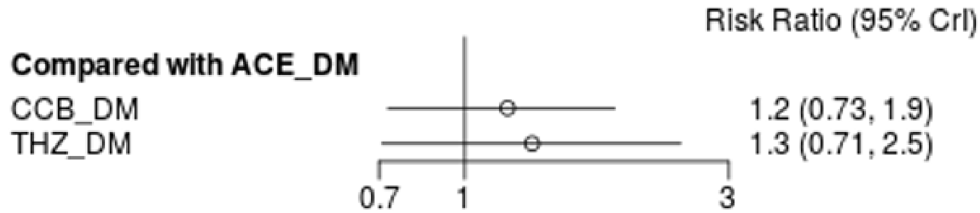
Table 3.58 CV Events by study and antihypertensive class among persons with Diabetes

Study Acronym	Author	Year	ACE		CCB		ARB		THZ		BB	
			N	Outcome N (%)	N	Outcome N (%)	N	Outcome N (%)	N	Outcome N (%)	N	Outcome N (%)
ABCD	Estacio [66, 67]	1998	235	47 (20.0)	235	50 (21.2)						
INSIGHT	Brown [88]	2000			649	54 (8.3)			653	55 (8.4)		
FACET	Tatti [77]	1998	189	14 (7.4)	191	27 (14.1)						
J-MIND	Baba [121]	2001	208	8 (3.8)	228	5 (2.2)						
ANBP2	Chowdury [125]	2014	229	32 (14.0)					212	46 (21.7)		

Table 3.59 Relative Treatment Effect of the Pooled Network Comparisons Among Persons with Diabetes Expressed as RR (95% Credible Interval) of CV Events Associated with Antihypertensive Drug Class Comparisons

	ACE_DM	CCB_DM	THZ_DM
ACE_DM	**ACE_DM**	1.2 (0.73, 1.9)	1.3 (0.71, 2.5)
CCB_DM	0.84 (0.54, 1.4)	**CCB_DM**	1.1 (0.62, 2)
THZ_DM	0.76 (0.41, 1.4)	0.91 (0.49, 1.6)	**THZ_DM**

Figure 3.32 Pooled Network Relative risks among Persons with Diabetes of CV Events associated with first line antihypertensive medication classes compared to THZ



MAJOR ADVERSE CARDIOVASCULAR EVENTS OUTCOMES

Table 3.60 Study-Specific Definitions of Major Adverse Cardiovascular Events (MACE)

Acronym	Author	Year	MACE Definition
FACET	Tatti P. (77)	1998	Any death or any vascular event or any procedure. The prospectively defined events were categorized as follows: 1) all-cause mortality, 2) fatal or nonfatal stroke, 3) fatal or nonfatal acute myocardial infarction, 4) hospitalized angina, 5) any major vascular event described in 2, 3, or 4, 6) coronary artery bypass, 7) percutaneous transluminal coronary angioplasty, and 8) any major vascular event or procedure described in 5, 6 or 7.
VHAS	Rosei E.A. (104)	1997	Events including deaths by any cause, cardiovascular deaths (cardiac or cerebrovascular), major nonfatal cardiovascular events (myocardial infarction and stroke), and minor cardiovascular events (TIA, Angina, CHF, Claudication, revascularization procedures)
MIDAS	Borhani N.O. (105)	1996	Composite, Stroke, Fatal or Non-Fatal or Composite, Myocardial Infarction, Fatal or Non-Fatal or Composite, Mortality, Sudden Death or Composite, Heart Failure, Congestive, Fatal or Non-Fatal or Composite, Angina or Composite, Mortality, Cardiovascular, Other or Composite, Coronary Revascularization or Composite, Stroke, Transient Ischemic Attack, Non-Fatal or Composite, Atrial Fibrillation or Composite, Premature Ventricular Contractions or Composite, Peripheral Revascularization or Composite, Heart Valve Replacement, Aortic or Composite, Palpitations

Table 3.61 Major Adverse Cardiovascular Events (MACE) by study and antihypertensive class

Study Acronym	Author	Year	CCB		BB		ACE		ARB		THZ	
			N	Outcomes	N	Outcomes	N	Outcomes	N	Outcomes	N	Outcomes
FACET	Tatti [77]	1998	191	34 (17.8%)			189	20 (10.6%)				
MIDAS	Borhani [105]	1996	442	54 (12.2%)							441	33 (7.5%)
VHAS	Rosei [104]	1997	707	39 (5.5%)							707	40 (5.7%)

Figure 3.33 Relative risks of MACE associated with first line antihypertensive medication classes compared to Thiazides

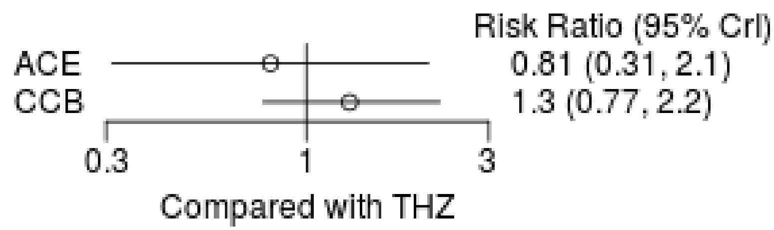


Table 3.62 Relative Treatment Effect of Pairwise Comparisons Expressed as RR (95% Credible Interval) of MACE Associated with Antihypertensive Drug Class Comparisons (read top to left)

	ACE	CCB	THZ
ACE	**ACE**	1.6 (0.71, 3.7)	1.2 (0.48, 3.2)
CCB	0.61 (0.27, 1.4)	**CCB**	0.77 (0.45, 1.3)
THZ	0.81 (0.31, 2.1)	1.3 (0.77, 2.2)	**THZ**

RENAL EVENT OUTCOMES

Table 3.63 Renal events by antihypertensive class and study

Study Acronym	Author	Year	ACE		CCB		ARB		THZ		BB	
			N	CV events N (%)	N	CV events N (%)	N	CV events N (%)	N	CV events N (%)	N	CV events N (%)
ALLHAT	Rahman [126]	2005	9054	300 (3.3)	9048	256 (2.8)			15255	493 (3.2)		
-	Zuchelli [127]	1992	60	7 (11.7)	61	14 (23.0)						
ESPIRAL	Marin [76]	2001	129	27 (20.9)	112	40 (35.7)						
VART	Narumi [103]	2011			511	4 (0.78)	510	2 (0.39)				
AASK	Wright [45]	2002			217	59 (27.2)					441	117 (26.5)

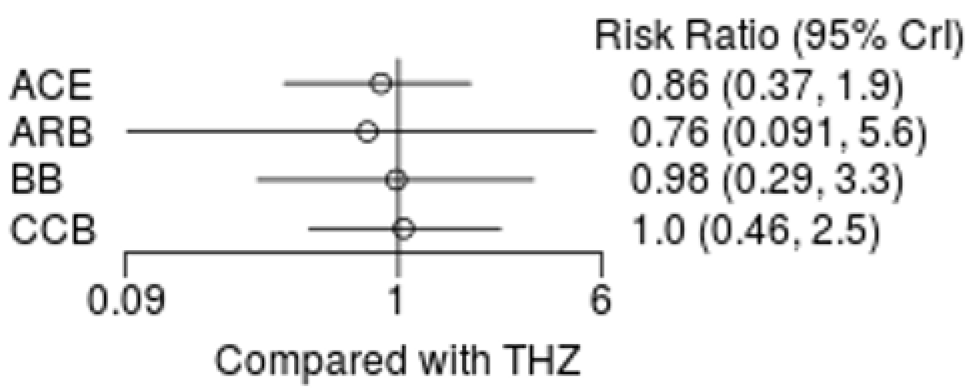
Table 3.64 Outcome descriptions for renal events

Study Acronym	Author	Year	Outcome Name
ALLHAT	Rahman [126]	2005	Composite, End-Stage Renal Disease or Composite, Halving of Estimated Glomerular Filtration Rate
-	Zuchelli [127]	1992	Dialysis
ESPIRAL	Marin [76]	2001	Composite, Doubling of Creatinine Levels or Composite, Dialysis
VART	Narumi [103]	2011	Composite, Doubling of Creatinine Levels or Composite, Dialysis
AASK	Wright [45]	2002	Composite, Halving of Estimated Glomerular Filtration Rate or Composite, Glomerular Filtration Rate 25 mL/min/1.73m², Decrease or Composite, End-Stage Renal Disease or Composite, Mortality, All-Cause

Table 3.65 Relative Treatment Effect of Pooled Network Comparisons Expressed as RR (95% Credible Interval) of Major CV Events Associated with Antihypertensive Drug Class Comparisons

	ACE	ARB	BB	CCB	THZ
ACE	**ACE**	0.9 (0.12, 6.2)	1.1 (0.47, 2.9)	1.2 (0.72, 2.2)	1.2 (0.53, 2.7)
ARB	1.1 (0.16, 8.7)	**ARB**	1.3 (0.16, 12)	1.4 (0.22, 9.9)	1.3 (0.18, 11)
BB	0.87 (0.34, 2.1)	0.79 (0.082, 6.4)	**BB**	1.1 (0.37, 3.1)	1 (0.3, 3.5)
CCB	0.81 (0.45, 1.4)	0.73 (0.1, 4.4)	0.94 (0.32, 2.7)	**CCB**	0.95 (0.41, 2.2)
THZ	0.86 (0.37, 1.9)	0.76 (0.091, 5.6)	0.98 (0.29, 3.3)	1 (0.46, 2.5)	**THZ**

Figure 3.34 Relative Treatment Effects of Indirect Comparison Expressed as RR (95% Credible Interval) of major CV events associated with first line antihypertensive medication classes compared to THZ



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