2017 Hypertension Guideline Data Supplements

(Section numbers correspond to the full-text guideline.)

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Search Terms:

An extensive evidence review, which included literature derived from research involving human subjects, published in English, and indexed in MEDLINE (through PubMed), EMBASE, the Cochrane Library, the Agency for Healthcare Research and Quality, and other selected databases relevant to this guideline, was conducted between February and August 2015. Key search words included but were not limited to the following: *adherence; aerobic; alcohol intake; ambulatory care; antihypertensive: agents, drug, medication, therapy; beta adrenergic blockers; blood pressure: arterial, control, determination, devises, goal, high, improve, measurement, monitoring, ambulatory; calcium channel blockers; diet; diuretic agent; drug therapy; heart failure: diastolic, systolic; hypertension: white coat, masked, ambulatory, isolated ambulatory, isolated clinic, diagnosis, reverse white coat, prevention, therapy, treatment, control; intervention; lifestyle: measures, modification; office visits; patient outcome; performance measures; physical activity; potassium intake; protein intake; renin inhibitor; risk reduction: behavior, counseling; screening; sphygmomanometers; spironolactone; therapy; treatment: adherence, compliance, efficacy, outcome, protocol, regimen; weight.* Additional relevant studies published through June 2016, during the guideline writing process, were also considered by the writing committee, and added to the evidence tables when appropriate.

Abbreviations:

1°, primary; 2º, secondary; AASK, African American Study of Kidney Disease and Hypertension; ABI, ankle-brachial index; ABCD, Appropriate Blood Pressure Control in Diabetes; ABPM, ambulatory blood pressure monitoring; ACCESS, Acute Candesartan Cilexetil Evaluation in Stroke Survivors; ACCOMPLISH, Avoiding Cardiovascular Events Through Combination Therapy in Patients Living With Systolic Hypertension; ACCORD, Action to Control Cardiovascular Risk in Diabetes; ACE, angiotensin-converting enzyme; ACEI, angiotensin-converting enzyme inhibitor; ACS, acute coronary syndrome; ADVANCE, Action in Diabetes and Vascular Disease; AF, atrial fibrillation; AFL, atrial flutter; AHR, adjusted hazard ratio; AIPRD, Angiotensin-Converting Enzyme Inhibition in Progressive Renal Disease; ALLHAT, Antihypertensive Lipid Lowering Treatment to Prevent Heart Attack Trial; AMI, acute myocardial infarction; ARB, angiotensin-receptor blocker; ARIC, Atherosclerosis Risk in Communities; ASCOT, Anglo-Scandinavian Cardiac Outcomes Trial; BB, beta blocker; BMI, body mass index; BP, blood pressure; BPLTTC, Blood Pressure Lowering Treatment Trialists' Collaboration; bpm, beats per minute; BUN, blood urea nitrogen; CABG, coronary artery bypass graft; CAD, coronary artery disease; CATIS, China Antihypertensive Trial in Acute Ischemic Stroke; CCB, calcium-channel blocker; CCU, coronary care unit; CHD, coronary heart disease; CHF, congestive heart failure; CHHIPS, Controlling Hypertension and Hypotension Immediately Post-Stroke; CI, confidence interval; CKD, chronic kidney disease; COMFORT, Combination Pill of Losartan Potassium and Hydrochlorothiazide for Improvement of Mediation Compliance Trial; COSSACS, the Continue or Stop Post-Stroke Antihypertensives Collaborative Study; CPAP, continuous positive airway pressure; Cr, creatinine; CrCL, creatinine clearance; CRP, c-reactive protein; CR/XL, metoprolol controlled release/extended release; CT, computed tomography; CV, cardiovascular; CVD, cardiovascular disease; DASH, Dietary Approaches to Stop Hypertension; DBP, diastolic blood pressure; DM, diabetes mellitus; DM-1, diabetes mellitus type-1; DM-2, diabetes mellitus type-2; ECG, electrocardiogram; ED, emergency department; EF, ejection fraction; eGFR, estimated glomerular filtration rate; ESKD, end-stage kidney disease; ESRD, end-stage renal disease; FC, functional class; FDC, fixed dose combination; FEVER, Felodipine EVent Reduction; GITS, gastrointestinal therapeutic system; GFR, glomerular filtration rate; HBPM, home blood pressure monitoring; HCTZ, hydrochlorthiazide; HDL, high-density lipoprotein; HDL-C, high-density lipoprotein cholesterol; HEDIS, Healthcare Effectiveness Data and Information Set; HF, heart failure; HF*r*EF, reduced ejection fraction; HF*p*EF, heart failure with preserved ejection fraction; HIV, human immunodeficiency virus; HR, hazard ratio; HTN, hypertension; ICD, implantable cardioverter-defibrillator; ICH, intracerebral hemorrhage; IDACO, International Database of Ambulatory Blood Pressure in relation to Cardiovascular Outcome; IHD, ischemic heart disease; IMT, intimal media thickness; INDANA, Individual Data Analysis of Antihypertensive drug intervention trials; INTERACT2, the second Intensive Blood Pressure Reduction in Acute Cerebral Hemorrhage Trial; INVEST, International Verapamil-Trandolapril Study; INWEST, the Intravenous Nimodipine West European Stroke Trial; IQI, interquartile interval; IQR, interquartile range; IRR, incident rate ratio; ISDN, isosorbide dinitrate; IV, intravenous; JNC-7, 7th Report of the Joint National Committee; KPNC, Kaiser Permanente Northern California; LDL, low-density lipoprotein; LGSAS, low-gradient severe aortic stenosis; LIFE, Losartan Intervention For Endpoint Reduction in Hypertension; LVEF, left ventricular ejection fraction; LVH, left ventricular hypertrophy; LVMI; left ventricular mass index; MACCE, major adverse cardiac and cerebrovascular events; MACE, major adverse cardiac events; MAP, mean arterial pressure; MD, mean difference; MDPIT, Multicenter Dilitiazem Postinfarction Research Group; MDRD, Modification of Diet in Renal Disease; MERIT, Metoprolol CR/XL Randomised Intervention Trial; MESA, Multi-Ethnic Study of Atherosclerosis; MH, masked hypertension; MI, myocardial infarction; MOSES, The Morbidity and Mortality After Stroke, Eprosartan Compared With Nitrendipine for Secondary Prevention; MPR, medication possession ratio; MRFIT, Multiple Risk Factor Intervention Trial; MRI, magnetic resonance imaging; N/A, not available; NCQA, National Committee for Quality Assurance; NEMESIS, North East Melbourne Stroke Incidence Study; NHANES, National Health and Nutrition Examination Surveys; NIH, National Institute of Health; NNT, number needed to treat; NR, not relative;

NS, nonsignificant; NSAID, nonsteroidal anti-inflammatory drug; NUTRICODE, Nutrition and Chronic Diseases Expert Group; NYHA, New York Heart Association; ONTARGET, Ongoing Telmisartan Alone and in Combination With Ramipril Global Endpoint Trial; OR, odds ratio; OSA, obstructive sleep apnea; P4P, pay for performance; PA, pulmonary artery; PAD, peripheral artery disease; PAMELA, Pressione Arteriose Monitorate E Loro Associazioni; PCP, primary care provider; periop, perioperative; PREDIMED, Prevention with a Mediterranean Diet; PRISMA, Preferred Reporting Items for Systematic Reviews and Meta-Analyses; PROBE, Prospective, randomized, open, blinded endpoint; PROGRESS, The perindopril protection against recurrent stroke study; PRONTO, Prospective Optical Coherence Tomography Imaging of Patients with endovascular Age-Related Macular Degeneration Treated with Intraocular Ranibizumab; pt, patient; PTCA, percutaneous transluminal coronary angioplasty; PVD, peripheral vascular disease; QI, quality improvement; RAAS, renin angiotensin aldosterone system; RCT, randomized controlled trial; REIN-2, Blood Pressure Control for Renoprotection in Patients with Non-diabetic Renal Disease; RH, relative hazard; ROADMAP, Randomized Olmesartan and Diabetes Microalbuminuria Prevention; RR, relative risk; Rx, medical prescription; SAE, severe adverse event; SBP, systolic blood pressure; SCOPE-AS, Symptomatic Cardiac Obstruction – Pilot Study of Enalapril in Aortic Stenosis; SD, standard deviation; SE, stress echocardiography; SH, sustained hypertension; SHEP, Summer Health Enrichment; SITS-ISTR, Safe Implementation of Thrombolysis in Stroke-International Stroke Thrombolysis Register; SKIPOGH, Swiss Kidney Project on Genes in Hypertension; SPC, single pill combination; SPRINT, Systolic Blood Pressure Intervention Trial; Syst-Eur, Systolic Hypertension in Europe; t-PA, tissue plasminogen activator; TIA, transient ischemic attack; TOHP, Trials of Hypertension Prevention; TOMHS, Treatment of Mild Hypertension Study; TONE, Trial of Nonpharmacologic Intervention in the Elderly; TOPCAT, Treatment of Preserved Cardiac Function Heart Failure With Aldosterone Antagonist; TR, target range; UA, unstable angina; U.K., United Kingdom; UKPDS, United Kingdom Prospective Diabetes Study; U.S., United States; VA, Veterans Affairs; VA Coop; Veterans Administration Cooperative Study Group on Antihypertensive Agents; VA NEPHRON-D, Veterans Affairs Nephropathy in Diabetes; VALIANT, Valsartan in Acute Myocardial Infarction Trial; VALUE, Valsartan Antihypertensive Long-term Use Evaluation; WCH, white coat hypertension; and WPW; Wolff-Parkinson-White syndrome.

Data Supplement 1. Coexistence of Hypertension and Related Chronic Conditions (Section 2.4)

Study Acronym; Author; Year Published	Study Type/Design; Study Size (N)	Patient Population	Primary Endpoint and Results (include P value; OR RR; & 95% CI)	Summary/Conclusion Comment(s)
Wilson PW, et al., 1999 (1) 10335688	Study type: Nonrandomized Size: 2,406 men, 2,569 women (1,759 men, 1,818 women with follow-up)	Inclusion criteria: Men and women 18–74 y and free of CHD at baseline, from the Framingham Offspring Study Exclusion criteria: N/A	1° endpoint: Total CHD (first occurrence of angina, UA, MI, and coronary death), Hard CHD (first MI and coronary death) Results: Presence of ≥3 risk factors was associated with a 2.39 times greater risk of CHD in men (95% CI: 1.56–3.36; p<0.001) and a 5.90 increased risk of CHD in women (95% CI: 2.54–13.73; p<0.001)	• CVD risk factors infrequently occur in isolation (only 28%–30% of the time); presence of ≥3 risk factors occurred 17% of the time in both men and women; presence of ≥3 risk factors associated with high risk of CHD and coronary death (attributable risk of 20% in men and 48% in women)
Berry JD, et al., 2012 (2) 22276822	Study type: Nonrandomized Size: 257,384 black and white men and women, including 67,890 pts (from 17 meta-analysis) and 189,494 pts (from MRFIT)	Inclusion criteria: Meta-analysis of 18 cohort studies Exclusion criteria: N/A	1° endpoint: Fatal CHD, nonfatal MI, fatal or nonfatal stroke Results: Participants with optimal RF profile (total cholesterol <180 mg/dL, untreated BP <120 mm Hg systolic, and <80 mm Hg diastolic, nondiabetic, nonsmoker) compared to participants with ≥2 risk factors had lower risk of CVD through the age of 80 y (4.7% vs. 29.6% for men, 6.4% vs. 20.5% for women), lower lifetime risk of fatal heart disease and nonfatal MI (3.6% vs. 37.5% for men, <1% vs. 18.3% for women), and lower lifetime risk of fatal or nonfatal stroke (2.3% vs. 8.3% for men, 5.3% vs. 10.7% for women)	• Increased burden of 80 risk factors associated with higher lifetime risk of CVD

Data Supplement 2. Definition of High BP (Section 3.1)

Study Acronym; Author; Year Published	Study Type/Design; Study Size (N)	Patient Population	Primary Endpoint and Results (include P value; OR or RR; and CI; & 95% CI)	Summary/Conclusion Comment(s)
Lewington S, et al., 2002 12493255	Study type: Meta-analysis of 61 observational cohort studies	Inclusion criteria: Men and women with no history of previous CVD and record of key study variables. Exclusion criteria: Prior CVD	1° endpoint: Cause-specific mortality Results: 958,074 persons followed for a mean of 12 y to death (12.7 million person-y at risk. Number of deaths attributed to: -Stroke: 11960 -IHD: 34,283 -Other vascular:10092 -Non-vascular: 60797 Above a SBP ≥115 mm Hg and DBP ≥75 mm Hg, there was a progressive rise in vascular death with progressively high BP with no evidence of a J-curve (approximately doubling of stroke and IHD mortality for a 20 mm Hg higher level of SBP or 10 mm Hg higher level of DBP, in those 40–69 y). With progressively higher age, the BP-related proportional risk of vascular mortality was somewhat reduced but the corresponding absolute risk was much higher.	• In adults aged 40–89 y, usual BP is strongly related to vascular (and overall) mortality, without evidence of a threshold down to at least an SBP/DBP of 115/75 mm Hg.
Rapsomaniki E, et al., 2014 24881994	Study type: Observational cohort study Size: 1.25 million patients, in 225 primary care practices in the UK, followed for a median of 5.2 y using electronic medical records.	Inclusion criteria: Men and women ≥30 y, with no previous diagnosis of CVD, who had been registered at their practices for ≥1 year. Exclusion criteria: N/A	1° endpoint: 12 acute and chronic CVD outcomes Results: 83,098 initial CVD events recorded. Within each of 3 age groups (30–59, 60–79, and ≥80 y), the lowest risk for CVD was in those with a SBP 90–114 mm Hg and DBP 60–74 mm Hg. There was a direct relationship between level of BP and most CVD outcomes, with no evidence of J-curve, with the strongest relationship for SBP and stroke and weakest for abdominal aneurysm.	• Despite modern treatments, the lifetime burden of BP-related CVD was substantial.
Wilson PW, et al., 1999 (1) 10335688	Study type: Nonrandomized	Inclusion criteria: Men and women 18–74 y and free of CHD at baseline, from the Framingham Offspring Study	1° endpoint: Total CHD (first occurrence of angina, UA, MI, and coronary death), Hard CHD (first MI and coronary death)	• CVD risk factors infrequently occur in isolation (only 28%–30% of the time)

	Size: 2,406 men, 2,569 women (1,759 men, 1,818 women with follow-up)	Exclusion criteria: N/A	Results: Presence of ≥3 risk factors was associated with a 2.39 times greater risk of CHD in men (95% CI: 1.56–3.36; p<0.001) and a 5.90 increased risk of CHD in women (95% CI: 2.54–13.73; p<0.001)	• Presence of ≥3 risk factors occurred 17% of the time in both men and women • Presence of ≥3 risk factors associated with high risk of CHD and coronary death (attributable risk of 20% in men and 48% in women)
Guo X, et al., 2013 (3) 23634212	Study type: Meta-analysis of nonrandomized studies Size: 870,678 pts	Inclusion criteria: Studies reporting adjusted risk for CVD or mortality with pre-HTN Exclusion criteria: N/A	1° endpoint: CVD and all-cause mortality Results: SBP/DBP 120–129/80–84 mm Hg compared to <120/80 mm Hg: • All-cause mortality: RR: 0.91; 95% CI: 0.81–1.02) • CVD mortality: RR: 1.10 (95% CI: 0.92, 1.30) SBP/DBP 130–139/85–89 mm Hg compared to <120/80 mm Hg: • All-cause mortality: 1.00; 95% CI: 0.95–1.06 • CVD mortality: RR: 1.26; 95% CI: 1.13–1.41	• SBP/DBP of 120–129/80–84 mm Hg associated with increased risk for all-cause or CVD mortality. • SBP/DBP of 130–139/85–89 mm Hg associated with an increased risk for CVD mortality.
Guo X, et al., 2013 (4) 24234576	Study type: Meta-analysis of nonrandomized studies Size: 1,010,858 pts	Inclusion criteria: Studies reporting adjusted risk for fatal and nonfatal stroke, CHD, MI and total CVD events with pre-HTN, 120–129/80–84 mm Hg or 130–139/85–89 mm Hg Exclusion criteria: N/A	1° endpoint: Fatal and nonfatal stroke, CHD, MI and total CVD events Results: SBP/DBP 120-129/80-84 mm Hg compared to <120/80 mm Hg: • CVD RR: 1.24; 95% CI: 1.10–1.39 • MI RR: 1.43; 95% CI: 1.10–1.86 • Stroke: RR: 1.35; 95% CI: 1.10–1.66 SBP/DBP 130–139/85–89 mm Hg compared to <120/80 mm Hg: • CVD RR: 1.56; 95% CI: 1.36–1.78 • MI RR: 1.99; 95% CI: 1.59–2.50 • Stroke RR: 1.95; 95% CI: 1.69–2.24	• Compared to pts with SBP/DBP<120/80 mm Hg, the RR for CVD, MI and stroke were larger for pts with SBP/DBP of 130–139/85–89 mm Hg vs. SBP/DBP of 120–129/80–84 mm Hg.
Huang Y, et al., 2013 (5) 23915102	Study type: Meta-analysis of nonrandomized studies Size: 468,561 pts from 18 prospective cohort studies	Inclusion criteria: Studies reporting risk for CVD, CHD and stroke, with 120–139/80–89 mm Hg, 120–129/80–84 mm Hg or130–139/85–89 mm Hg Adults ≥18 y BP evaluated at baseline	1° endpoint: CVD, CHD, and stroke Results: Comparing SBP/DBP 120–129/80–84 mm Hg to <120/80 mm Hg: • CVD RR: 1.46; 95% CI: 1.32–1.62	• Compared to pts with SBP/DBP <120/80 mm Hg, the RR for CVD was larger for pts with SBP/DBP of 130–139/85–89 mm Hg vs.

		≥2 y follow-up for outcomes Results reported with adjustment Exclusion criteria: N/A	Comparing SBP/DBP RR: 130–139/85–89 mm Hg to <120/80 mm Hg: • CVD RR: 1.63; 95% CI: 1.47–1.80; p value comparing these risk ratios=0.02 • The RR comparing CHD and stroke by levels of SBP/DBP: 130–139/85–89 mm Hg and SBP/DBP of 120–129/80–84 mm Hg vs. <120/80 mm Hg were not reported.	SBP/DBP of 120–129/80–84 mm Hg
Huang Y, et al., 2014 (6) 24074825	Study type: Meta-analysis of nonrandomized studies Size: 1,003,793 pts were derived from 6 prospective cohort studies	Inclusion criteria: Studies reporting adjusted risk for ESRD with 120–139/80–89 mm Hg, 120–129/80–84 mm Hg or130–139/85–89 mm Hg Adults ≥18 y BP evaluated at baseline ≥ 1 y follow-up for ESRD Results reported with adjustment Exclusion criteria: 1) enrollment depended on having a condition or risk factor, 2) the study reported only age- and sex-adjusted RRs, and 3) data were derived from the same cohort or from a 2º analysis	1° endpoint: ESRD Results: Comparing SBP/DBP 120–129/80–84 mm Hg to <120/80 mm Hg: • ESRD RR: 1.44; 95% CI: 1.19–1.74 Comparing SBP/DBP 130–139/85–89 mm Hg to <120/80 mm Hg: • ESRD RR: 2.02; 95% CI: 1.70–2.40; • p value comparing these risk ratios=0.01	• Compared to pts with SBP/DBP <120/80 mm Hg, the RR for ESRD was larger for pts with SBP/DBP of 130–139/85–89 mm Hg vs. SBP/DBP of 120–129/80–84 mm Hg
Huang Y, et al., 2013 (7) 24623843	Study type: Meta-analysis of nonrandomized studies Size: 762,393 pts from 19 prospective cohort studies	Inclusion criteria: Studies reporting adjusted risk for stroke with 120–139/80–89 mm Hg, 120–129/80-84 mm Hg or130–139/85–89 mm Hg • Adults ≥18 y • BP evaluated at baseline • ≥1 y follow-up for stroke • Results reported with adjustment Exclusion criteria: • Enrollment depended on having a specific risk factor condition (e.g., DM or other baseline chronic diseases) • The RR was unadjusted or only adjusted for age and sex • Data were derived from the same cohort or meta-analysis of other cohort studies.	1° endpoint: Stroke Results: Comparing SBP/DBP 120–129/80–84 mm Hg to <120/80 mm Hg: • Stroke: RR: 1.44; 95% CI: 1.27–1.63 Comparing SBP/DBP 130–139/85–89 mm Hg to <120/80 mm Hg: • Stroke: RR: 1.95; 95% CI: 1.73–2.21 • p value comparing these risk ratios ≤0.001	• Compared to pts with SBP/DBP <120/80 mm Hg, the RR for stroke was larger for pts with SBP/DBP of 130–139/85–89 mm Hg vs. SBP/DBP of 120–129/80–84 mm Hg

Huang Y, et al., 2014 (8) 24439976	Study type: Meta-analysis of nonrandomized studies Size: 1,129,098 pts from 20 prospective cohort studies	Inclusion criteria: • Studies reporting adjusted risk for all-cause/CVD mortality with 120–139/80–89 mm Hg, 120-129/80–84 mm Hg or 130–139/85–89 mm Hg • Adults ≥18 y • BP evaluated at baseline • ≥2 y follow-up for mortality • Results reported with adjustment Exclusion criteria: • Enrollment depended on having a specific risk factor condition (e.g., DM or other baseline chronic diseases) • The RR was unadjusted or only adjusted for age and sex • Data were derived from the same cohort or meta-analysis of other cohort studies.	1° endpoint: All-cause and CVD mortality Results: Comparing SBP/DBP 120–129/80-84 mm Hg to <120/80 mm Hg: • All-cause mortality RR: 0.96; 95% CI: 0.85–1.08 • CVD mortality RR: 1.08; 95% CI: 0.98–1.18 Comparing SBP/DBP 130-139/85-89 mm Hg to <120/80 mm Hg: • All-cause mortality RR: 1.03; 95% CI: 0.95–1.12 • CVD mortality RR: 1.28; 95% CI: 1.16–1.41 • p value comparing these risk ratios: • All-cause mortality p=0.33 • CVD mortality p=0.01	• Compared to pts with SBP/DBP <120/80 mm Hg, the RR for CVD mortality was larger for pts with SBP/DBP of 130–139/85-89 mm Hg vs. SBP/DBP of 120–129/80-84 mm Hg. • The RR for not all-cause mortality was similar for these 2 BP levels.
Huang Y, et al., 2015 (9) 25699996	Study type: Meta-analysis of nonrandomized studies Size: 591,664 pts from 17 prospective cohort studies	Inclusion criteria: • Studies reporting adjusted risk for CHD with 120–139/80–89 mm Hg, 120–129/80–84 mm Hg or130–139/85–89 mm Hg • Adults ≥18 y • BP evaluated at baseline • Results reported with adjustment Exclusion criteria: • Enrollment depended on having a specific risk factor condition (e.g., DM or other baseline chronic diseases) • The RR was unadjusted or only adjusted for age and sex • Data were derived from the same cohort or meta-analysis of other cohort studies.	1° endpoint: CHD Results: Comparing SBP/DBP 120–129/80–84 mm Hg to <120/80 mm Hg: • CHD RR: 1.27; 95% CI: 1.07–1.50 Comparing SBP/DBP 130-139/85-89 mm Hg to <120/80 mm Hg: • CHD RR: 1.58; 95% CI: 1.24–2.02 • p value comparing these RR: 0.15	• Compared to pts with SBP/DBP<120/80 mm Hg, the RR for CHD was larger for pts with SBP/DBP of 130–139/85–89 mm Hg vs. SBP/DBP of 120-129/80–84 mm Hg. • However, this difference was not statistically significant.
Lee M, et al., 2011 (10) 21956722	Study type: Meta-analysis of nonrandomized studies	Inclusion criteria: • Studies reporting adjusted risk for stroke with 120–139/80–89 mm Hg, 120–129/80–84 mm Hg or130–139/85–89 mm Hg • Adults ≥18 y	1° endpoint: Incident stroke Results: Comparing SBP/DBP 120–129/80–84 mm Hg to <120/80 mm Hg: • Stroke RR: 1.22; 95% CI: 0.95–1.57	• Compared to pts with SBP/DBP <120/80 mm Hg, the RR for stroke was larger for pts with SBP/DBP of 130–139/85–89 mm Hg vs.

	Size: 518,520 pts from 18 prospective cohort studies	• BP evaluated at baseline • Results reported with adjustment Exclusion criteria: • Cross-sectional, case-control or retrospective cohort • The RR was unadjusted or only adjusted for age and sex • 95% CI not reported • Data were derived from the same cohort or meta-analysis of other cohort studies • Results from trial of antihypertensive medication	Comparing SBP/DBP 130–139/85–89 mm Hg to <120/80 mm Hg: • Stroke RR: 1.79; 95% CI: 1.49–2.16	SBP/DBP of 120–129/80–84 mm Hg
Shen L, et al., 2013 (11) 23608614	Study type: Meta-analysis of nonrandomized studies Size: 934,106 pts from 18 prospective cohort studies	Inclusion criteria: • Studies reporting adjusted risk for CHD with 120–139/80–89 mm Hg, 120–129/80–84 mm Hg or 130–139/85–89 mm Hg • BP evaluated at baseline • 95% CI was reported Exclusion criteria: N/A	1° endpoint: CHD Results: Comparing SBP/DBP 120–129/80–84 mm Hg to <120/80 mm Hg: • CHD RR: 1.16; 95% CI: 0.96–1.42 Comparing SBP/DBP 130–139/85–89 mm Hg to <120/80 mm Hg: • CHD RR: 1.53; 95% CI: 1.19–1.97)	• Compared to pts with SBP/DBP <120/80 mm Hg, the RR for CHD was larger for pts with SBP/DBP of 130–139/85–89 mm Hg vs. SBP/DBP of 120–129/80–84 mm Hg
Wang S, et al., 2013 (12) 23932039	Study type: Meta-analysis of nonrandomized studies Size: 396,200 pts from 13 prospective cohort studies	Inclusion criteria: • Prospective cohort studies reporting risk for outcomes with 120–139/80–89 mm Hg • Pts free of CVD at baseline, • Follow-up ≥5 y • Adjusted results reported • 95% CI was reported Exclusion criteria: N/A	1° endpoint: CVD, CVD mortality, all-cause mortality Results: Comparing SBP/DBP 120-129/80-84 mm Hg to <120/80 mm Hg: • CVD RR: 1.41; 95% CI: 1.25–1.59 • CVD mortality RR: 1.18; 95% CI: 0.98–1.42 • All-cause mortality RR: 0.99; 95% CI: 0.88–1.13 Comparing SBP/DBP 130–139/85–89 mm Hg to <120/80 mm Hg: • CVD RR: 1.74; 95% CI: 1.51–2.01 • CVD mortality RR: 1.33; 95% CI: 1.13–1.58 • All-cause mortality RR: 1.02; 95% CI: 0.97–1.08	• Compared to pts with SBP/DBP<120/80 mm Hg, RR for CVD and CVD mortality were larger for pts with SBP/DBP of 130–139/85–89 mm Hg vs. SBP/DBP of 120–129/80–84 mm Hg. • No difference in all-cause mortality was present across BP levels.
Cushman WC, et al., 2002 (13) 12461301	Study type: 2º analysis of an RCT Size: 33,357 pts in the ALLHAT	Inclusion criteria: Men and women ≥55 y with HTN and 1 additional CHD risk factor Exclusion criteria: Pts randomized to doxazosin.	1° endpoint: Achieving SBP/DBP<140/90 mm Hg, use of ≥2 drug classes	• BP control (<140/90 mm Hg) can be achieved in most pts ≥2 or more drug classes are often required.

			Results: SBP/DBP control was achieved by 66% at 5 y of follow-up and 63% of pts were on ≥2 drug classes.	
Dalhof B, et al., 2002 (14) 11937178	Study type: RCT Size: 9,193 pts 55–80 y in the Losartan Intervention For Endpoint reduction in HTN	Inclusion criteria: Men and women with ECG signs of LVH. Trough sitting SBP 160–200 mm Hg or DBP 95–115 mm Hg after 1–2 wk of placebo. Exclusion criteria: 2º HTN, MI/stroke within 6 mo, angina, HF or LVEF <40%.	1° endpoint: Following a titration schedule to reach a target SBP/DBP<140/90 mm Hg Results: Mean SBP/DBP at baseline was 174/98 mm Hg. Over 90% of pts required ≥2 drug classes during follow-up.	• Pts with a mean SBP/DBP of 160–200/95–115 mm Hg will need ≥2 classes of antihypertensive medication to achieve SBP/DBP <140/90 mm Hg.
Wald DS, et. al., 2009 (15) 19272490	Study type: Meta-analysis of RCT Size: 10,968 pts in 42 trials of factorial designs comparing monotherapy, combination therapy and placebo.	Inclusion criteria: Randomized placebo-controlled trials comparing 2 of 4 (thiazides, BB s, ACEIs, and CCB) drug classes. Exclusion criteria: Trials <2 wk duration, no placebo group, nonrandomized order of treatment.	1° endpoint: Mean BP reduction. Results: Combination therapy vs. monotherapy produced larger SBP reductions: • Thiazide alone (7.3 mm Hg) • Thiazide+second drug class (14.6 mm Hg) • BB alone (9.3 mm Hg) • BB +second drug class (18.9 mm Hg) • ACE-inhibitor alone (6.8 mm Hg) • ACE-inhibitor+second drug class (13.9 mm Hg) • CCB alone (8.4 mm Hg) • CCB +second drug class (14.3 mm Hg)	• Combination therapy results in substantially larger SBP and DBP reductions compared with monotherapy, even after dose titration.
Lewington S, et al., 2002 (16) 12493255	Aim: To describe the age-specific relevance of BP to cause-specific mortality Study type: Meta-analysis of cohort studies Size: 61 prospective studies with 12.7 million person-y of observation, 56,000 vascular deaths in 40–89 y.	Inclusion criteria: Collaboration was sought from the investigators of all prospective observational studies in which data on BP, blood cholesterol, date of birth (or age), and sex had been recorded at a baseline screening visit, and in which cause and date of death (or age at death) had been routinely sought for all screens during more than 5,000 person-y of follow-up (see appendix A). Relevant studies were identified through computer searches of Medline and Embase, by hand-searches of meeting abstracts, and by extensive discussions with investigators. Exclusion criteria: To minimize the effects of reverse causality (whereby	1° endpoint: • Not completely clear, but for our purposes, stroke and IHD death would be co-1°. Also looked at other vascular deaths. • HRs for stroke mortality for a 20 mm Hg lower SBP by age-group 40–49: 0.36 (95% CI: 0.32–0.40) 50–59: 0.38 (95% CI: 0.35–0.40) 60–69: 0.43 (95% CI: 0.41–0.45) 70–79: 0.50 (95% CI: 0.48–0.52) 80–89: 0.67 (95% CI: 0.63–0.71) • HRs for IHD mortality for a 20 mm Hg lower SBP by age-group 40–49: 0.49 (95% CI: 0.45–0.53) 50–59: 0.50 (95% CI: 0.49–0.52) 60–69: 0.54 (95% CI: 0.53–0.55) 70–79: 0.60 (95% CI: 0.58–0.61)	• Throughout middle and old age, usual BP is strongly and directly related to vascular (and overall) mortality, without any evidence of a threshold down to at least 115/75 mm Hg.

		established disease could change the usual BP), studies were excluded if they had selected pts on the basis of a positive history of stroke or heart disease, and individuals from contributing studies were excluded from the present analyses if they had such a history recorded at baseline.	80–89: 0.67 (95% CI: 0.64–0.70) • HRs for other vascular mortality for a 20 mm Hg lower SBP by age-group 40–49: 0.43 (95% CI: 0.38–0.48) 50–59: 0.50 (95% CI: 0.47–0.54) 60–69: 0.53 (95% CI: 0.51–0.56) 70–79: 0.64 (95% CI: 0.61–0.67) 80–89: 0.70 (95% CI: 0.65–0.75) • Similar results for DBP also in figure 1. • Similar results for men and women separately for stroke, figure 3, and IHD, figure 5.	
Ettehad D, et al., 2016 (17) 26724178	Aim: This systematic review and meta-analysis aims to combine data from all published large-scale BP-lowering trials to quantify the effects of BP reduction on CV outcomes and death across various baseline BP levels, major comorbidities, and different pharmacological interventions. Study type: Meta-analysis of RCTs Size: 123 studies with 613,815 pts	Inclusion criteria: • RCTs of BP-lowering treatment that included a minimum of 1,000 pt-y of follow-up in each study arm. No trials were excluded because of presence of baseline comorbidities, and trials of antihypertensive drugs for indications other than HTN were eligible. • Eligible studies fell into 3 categories: 1st, random allocation of pts to a BP-lowering drug or placebo; 2nd, random allocation of pts to different BP-lowering drugs; and third, random allocation of pts to different BP-lowering targets. Exclusion criteria: <1,000 pt y of follow-up in each treatment group. Intervention: BP-lowering meds Comparator: Placebo, active comparator or less intensive treatment	1° endpoint: • CVD. • Major CVD events, CHD, stroke, HF, renal failure, and all-cause mortality. • Standardized RR for 10 mm Hg difference in SBP • CVD RR: 0.80 (95% CI: 0.77–0.83) Other endpoints: CHD RR: 0.83 (95% CI: 0.78–0.88) Stroke RR: 0.73 (95% CI: 0.68–0.77) HF RR: 0.72 (95% CI: 0.67–0.78) Total deaths RR: 0.87 (95% CI: 0.84–0.91) Other results: • Benefit for CVD and other endpoints not different by baseline SBP, including <130 mm Hg fig 4 in paper CVD: 0.63; 95% CI: 0.50–0.80; p=0.22 CHD: 0.55; 95% CI: 0.42–0.72; p=0.93 Stroke: 0.65; 95% CI: 0.27–1.57; p=0.38 HF: 0.83; 95% CI: 0.41–1.70; p=0.27 Total deaths: 0.53; 95% CI: 0.37–0.76; p=0.79 • More precision around estimates of benefits in SBP 130–139 at baseline, fig 4 in paper • Results similar in trials of people with and without CVD at baseline figure 5 CVD+ 0.77 (95% CI: 0.71–0.81)	• BP-lowering significantly reduces vascular risk across various baseline BP levels and comorbidities. Our results provide strong support for lowering BP to SBP<130 mm Hg and providing BP-lowering treatment to individuals with a history of CVD, CHD, stroke, DM, HF, and CKD. • In stratified analyses, we saw no strong evidence that proportional effects were diminished in trials that included people with lower baseline SBP (<130 mm Hg), and major CV events were clearly reduced in high-risk pts with various baseline comorbidities. Both of these major findings—the efficacy of BP-lowering below 130 mm Hg and the similar proportional effects in high risk populations—are consistent with and extend the findings of the SPRINT trial. Limitations:

			CVD- 0.74 (95% CI: 0.67–0.83) Total deaths CVD+ 0.90 (95% CI: 0.83–0.98) CVD- 0.84 (95% CI: 0.75–0.93) Other outcomes similarly in figure 5 • In appendix, in general, benefits for CVD prevention seen in groups with and without baseline CHD, Stroke, DM, CKD and HF when examined separately, but no absolute risks provided to enable estimation of how far down the absolute risk curve these findings have been demonstrated. • Some evidence of BB inferiority to other med classes in figure 6. • Did not report absolute risks so do not know lower level of risk in treated populations.	• Lack of individual pt data, which would have allowed a more reliable assessment of treatment effects in different pt groups. • Interpretation: Lowering of BP into what has been regarded the normotensive range should therefore be routinely considered for the prevention of CVD among those deemed to be of sufficient absolute risk.
Law MR, et al., 2009 (18) 19454737	Study type: Meta-analysis of use of BP-lowering drugs in prevention of CVD from 147 randomized trials Size: Of 147 randomized trials of 464,000 pts, 37 trials of BBs in CAD included 38,892 pts, and 37 trials of other antihypertensive drugs in CAD included 85,395 pts	Inclusion criteria: The database search used Medline (1966 to Dec. 2007) to identify randomized trials of BP-lowering drugs in which CAD events or strokes were recorded. The search also included the Cochrane Collaboration and Web of Science databases and the citations in trials and previous meta-analyses and review articles. Exclusion criteria: Trials were excluded if there were <5 CAD events and strokes or if treatment duration was <6 mo.	1° endpoint: CAD events; stroke Results: In 37 trials of pts with a history of CAD, BB reduced CAD events 29% (95% CI: 22%–34%). In 27 trials in which BBs were used after acute MI, BB reduced CAD events 31% (95% CI: 24%–38%), and in 11 trials in which BB were used after long-term CAD, BB insignificantly reduced CAD events 13%. In 7 trials, BB reduced stroke 17% (95% CI: 1%–30%). CAD events were reduced 14% (95% CI: 2%–25%) in 11 trials of thiazide diuretics, 17% (95% CI: 11%–22%) in 21 trials of ACEIs, insignificantly 14% in 4 trials of angiotensin receptor blockers, and 15% (95% CI: 8%–22%) in 22 trials of CCB. Stroke was reduced 38% (95% CI: 28%–47%) in 10 trials of thiazide diuretics, 22% (95% CI: 8%–34%) in 13 trials of ACEI, and 34% (95% CI: 25%–42%) in 9 trials of CCB.	• With the exception of the extra protective effect of BB given shortly after a MI and the minor additional effect of CCBs in preventing stroke, all the classes of BP-lowering drugs have a similar effect in reducing CAD events and stroke for a given reduction in BP.
Sundstrom J, et al., 2015 (19) 25531552	Aim: To investigate whether pharmacologic BP reduction prevents CV events and deaths in pts with grade 1 HTN.	Inclusion criteria: RCTs of at least 1 y duration; pts ≥18 y, at least 80% of whom had grade 1 HTN and no previous CVD (MI, angina pectoris, CABG, PCI, stroke, TIA, carotid surgery, peripheral arterial	1° endpoint: Total major CV events, comprising stroke (nonfatal stroke or death from cerebrovascular disease), coronary events (nonfatal MI or death from CHD, including sudden death), HF (causing death or resulting in	• BP-lowering therapy is likely to prevent stroke and death in pts with uncomplicated grade 1 HTN.

	Study type: Meta-analysis of RCTs Size: 10 RTCs with 15,266 pts	surgery, intermittent claudication, or renal failure); and compared an antihypertensive drug provided as monotherapy or a stepped-care algorithm vs. placebo or another control regimen. Exclusion criteria: Excluded trials did not contribute an event for any of the outcomes of interest.	hospitalization), or CV death; OR: 0.86 (95% CI: 0.74–1.01) Other endpoints: Each of the above outcomes independently; and total deaths. CHD 0.91 (95% CI: 0.74–1.12) Stroke 0.72 (95% CI: 0.55–0.99) HF 0.80 (95% CI: 0.57–1.12) CVD deaths 0.75 (95% CI: 0.57–0.98) Total deaths 0.78 (95% CI: 0.67–0.92) Only the first event for a pt was used for the analysis of each outcome, but a pt who had >1 outcome type could contribute to more than 1 analysis. They also tabulated overall withdrawals and withdrawals due to adverse events.	• 5 y risks in BPLTTC control groups CVD events 7.4%, CVD deaths 3.1%
Thomopoulos C, et al., 2014 (20) 25259547	Aim: Investigating whether all grades of HTN benefit from BP-lowering treatment and which are the target BP levels to maximize outcome reduction. Study type: Meta-analysis of RCTs Size: 32 RCTs with 104,359 pts	Inclusion criteria: Intentional BP-lowering comparing active drug treatment with placebo, or less active treatment (intentional BP-lowering trials), or comparison of an active drug with placebo over baseline antihypertensive treatment, resulting in a BP difference of at least 2 mm Hg in either SBP or DBP (nonintentional BP-lowering trials); enrolling of hypertensive individuals only or a high proportion (at least 40%) of them. Exclusion criteria: N/A	1° endpoint: • As some trials were done on low-risk pts, others on higher risk pts, no evaluation of absolute risk-reduction was made. However, a 2º analysis was done including trials or trial subgroups with mean baseline SBP/DBP values in grade 1 range and a low-to-moderate risk (<5% CV deaths in 10 y in controls): FEVER stratum with baseline SBP below the median (<153 mm Hg); HTN Detection and Follow-up Program stratum with baseline DBP 90–94 mm Hg and no CVD; OSLO (e17); TOMHS (e28) and USPHS. Risks of stroke, CHD, the composite of stroke and CHD, and all-cause death were significantly reduced by BP-lowering in these low-to-moderate risk pts (control group: average CV mortality 4.5% in10 y) with a moderate BP elevation (average SBP/DBP 145.5/91 mm Hg) at randomization. Standardized RR associated with 10/5 reduction in BP: stroke 0.33 (95% CI: 0.11–0.98) CHD 0.68 (95% CI: 0.48–0.95)	• Meta-analyses favor BP-lowering treatment even in grade 1 HTN at low-to-moderate risk, and lowering SBP/DBP to <140/90 mm Hg. • Achieving <130/80 mm Hg appears safe, but only adds further reduction in stroke.

			CVD death 0.57 (95% CI: 0.32–1.02) total death 0.53 (95% 0.35–0.80) • Compared outcomes of achieved on study SBP <130 vs. ≥130 Standardized Risk ratio associated with 10/5 reduction in BP: stroke 0.68 (95% CI: 0.57, 0.83) CHD 0.87 (95% CI: 0.76, 1.00) HF 0.92 (95% CI: 0.47, 1.77) CVD 0.81 (95% CI: 0.67, 1.00) CVD death 0.88 (95% CI: 0.77, 1.01) total death 0.88 (95% CI: 0.77, 0.99) • Outcomes of achieved on study SBP 130-139 vs. ≥140 Standardized RR associated with 10/5 reduction in BP: stroke 0.63 (95% CI: 0.52, 0.77) CHD 0.77 (95% CI: 0.70, 0.86) HF 0.76 (95% CI: 0.47, 1.25) CVD 0.74 (95% CI: 0.62, 0.88) CVD death 0.81 (95% CI: 0.67, 0.97) total death 0.87 (95% CI: 0.75, 1.00) • Similar pattern of results for on treatment DBP.	
Xie X, et al., 2015 (21) 26559744	Aim: To assess the efficacy and safety of intensive BP-lowering strategies. Study type: Meta-analysis of RCTs Size: 19 RCTs with 44,989 pts	Inclusion criteria: RCTs with at least 6 mo follow-up that randomly assigned pts to more intensive vs. less intensive BP-lowering treatment, with different BP targets or different BP changes from baseline. Reference lists from identified trials and review articles were manually scanned to identify any other relevant studies. Exclusion criteria: N/A Intervention: BP-lowering meds Comparator: • Less intensive treatment • BP difference 6.8/3.5 • The mean follow-up BP levels in the less intensive BP-lowering	1° endpoint: • CVD, other major CV events, defined as a MI, stroke, HF, or CV death, separately and combined; nonvascular and all-cause mortality; ESKD, and adverse events. Progression of albuminuria (defined as new onset of micro-albuminuria/macro-albuminuria or a change from micro-albuminuria to macro-albuminuria) and retinopathy (retinopathy progression of 2 or more steps) were also recorded for trials that were done in pts with DM • CVD RR: 0.86 (95% CI: 0.78–0.96) Other endpoints: MI RR: 0.87 (95% CI: 0.76–1.00) p=0.042 Stroke RR: 0.78 (95% CI: 0.68–0.90) HF RR: 0.85 (95% CI: 0.66–1.11) CVD death RR: 0.91 (95% CI: 0.74–1.11) Total deaths RR: 0.91 (95% CI: 0.81–1.03)	• Intensive BP-lowering, including to <130 mm Hg, provided greater vascular protection than standard regimens. • In high-risk pts, there are additional benefits from more intensive BP-lowering, including for those with SPB <140 mm Hg at baseline. • The net absolute benefits of intensive BP-lowering in high-risk individuals are large. Limitations: • Lack of individual pt data, which would have allowed a more reliable assessment of

		regimen group were 140/81 mm Hg, compared with 133/76 mm Hg in the more intensive treatment group.	Other results: • Benefit for CVD not different by baseline SBP 120–139: 0.89 (95% CI: 0.76–1.05) 140–160: 0.83 (95% CI: 0.68–1.00) >160: 0.89 (95% CI: 0.73–1.09) p-heterogeneity: 0.60 • Benefit for CVD not different for more intensive and less intensive targets in intensive group <140 or <150 mm Hg: 0.76 (95% CI: 0.60–0.97) <120– <130 mm Hg: 0.91 (95% CI: 0.84–1.00; p-hetero: 0.06) • Absolute benefits were proportional to absolute risk. • For trials in which all pts had vascular disease, renal disease, or DM at baseline, the average control group rate of major vascular events was 2·9% per y compared with 0·9% per y in other trials, and the numbers needed to treat were 94 (95% CI: 44–782) in these trials vs. 186 (95% CI: 107–708) in all other trials. • Increase in Severe hypotension: 0.3% vs. 0.1% per person y OR: 2.68 (95% CI: 1.21–5.89)	treatment effects in different pt groups. • Interpretation: Supports treating pt with and without CVD at threshold of 130 to <130. Supports treating at threshold of about 130 even down to a CVD event rate of 0.9% per y.

Data Supplement 3. Out-of-Office and Self-Monitoring of BP (Section 4.2)

Study Acronym; Author; Year Published	Study Type/Design; Study Size (N)	Patient Population (N)	Primary Endpoint and Results (include P value; OR or RR; & 95% CI)	Summary/Conclusion Comment(s)
Pickering TG, et al., 1988 (22) 3336140	Study type: ● Observational Cohort ● 24-h ABPM <134/90 ● Systematic review ● Office vs. ABPM or HBPM Size: 292 pts	N/A	1° endpoint: WCH=21%	● Multiple methodologies used to define MH. Prevalence 8.5%–16.6% (general population), 14.7%–30.4% (nonelevated clinic population)

Uhlig K, et al., 2012 (23) 22439158	Study type: ● Systematic review ● Self-monitoring vs. usual care vs. self-monitoring+support	N/A	1° endpoint: Change in clinic SBP/DBP	• Self-monitoring vs. usual care resulted in lower SBP/DBP (-3.1/-2.0 mm Hg) at 6 mo • Self-monitoring + support vs. usual care resulted in lower SBP/DBP SBP/DBP -3.4– -8.9/-1.9– -4.4 mm Hg up to 12 mo. • Self-monitoring may confer a small benefit for BP control.
McManus RJ, et al., 2014 (24) 25157723	Study type: ● RCT ● Self-monitoring with self-titration vs. usual care. Size: 552 pts	Inclusion criteria: SBP/DBP ≥130/85 mm Hg	1° endpoint: Change in SBP/DBP at 12 mo	• Self-monitoring with self-titration was associated with SBP and DBP differences of 9.2 mm Hg and 3.4 mm Hg, respectively.
Margolis KL, et al., 2013 (25) 23821088	Aim: Assess impact of follow-up and monitoring system including home BP tele-monitoring and pharmacist case management on BP control in pts treated for HTN Study type: Cluster RCT Size: 450 pts	Inclusion criteria: Pts from 16 clinics in integrated health system in Minneapolis, MN	222 pts randomized to 8 usual care clinics and 228 randomized to 8 intervention clinics Intervention included 12 mo of home BP tele-monitoring and pharmacist case management, with 6 mo of follow-up afterward	• Intervention group achieved better BP control compared to usual care during 12 mo of intervention and persisting during 6 mo of follow-up • SBP was <140/90 in 57.2% (95% CI: 44.8%, 68.7%) of intervention pts at 6 and 12 mo vs. 30% (95% CI: 23.2%, 37.8%) in usual care (p=0.001) • Combination of home BP tele-monitoring and pharmacist case management helped control HTN better than usual care at 6, 12, and 18 mo.24
Margolis KL, et al., 2013 (25) 23821088	Study type: ● RCT ● Home BP telemonitoring with pharmacist case management vs. usual care. Size: 450 pts	Inclusion criteria: Uncontrolled BP	1° endpoint: SBP/DBP <140/90 mm Hg (<130/80 mm Hg in DM or CKD) at 6 and 12 mo. 2° endpoint: Change in BP, pt satisfaction, and BP control at 18 mo (6 mo after intervention stopped).	● Telemonitoring resulted in better BP control (57% vs. 30%) at 6 and 12 mo and larger SBP declines at 6, 12, and 18 mo. ● Some aspects of pt satisfaction (e.g., clinicians listening carefully) improved with telemonitoring.
McManus RJ, et al., 2014 (24) 25157723	Study type: ● RCT ● Self-monitoring with self-titration vs. usual care. Size: 552 pts	Inclusion criteria: SBP/DBP ≥130/85 mm Hg	1° endpoint: Change in SBP/DBP at 12 mo	● Self-monitoring with self-titration was associated with SBP and DBP differences of 9.2 mm Hg and 3.4 mm Hg, respectively.

Siu AL, et al., 2015 26458123	Study type: U.S. Preventive Services Task Force commissioned systematic review and meta-analysis of office and out of office BP relationships for diagnostic accuracy of diagnosing high BP after an initial office-based classification of high BP.	Inclusion criteria: ● Adults ≥18 y. ● 24 studies based on "confirmation" by means of ABPM and 6 by means of HPBM.	1° endpoint: ABPM or HBPM conformation of office-based diagnosis of high BP. ● CVD risk-relationships for ABPM, HBPM and office-based BPs also reviewed. ● ABPM was recommended as the best method to confirm an office-based diagnosis of high BP, with HBPM an acceptable alternative, based on "over diagnosis" of high BP with office BP measurements (White coat hypertension) and stronger relationships between out of office BP measurements (especially ABPM) with vascular events.	● Screen for high BP in adults ≥18 y and confirm office-based high BP using out of office BP measurements 9preferably ABPM).
Uhlig K, et al., 2012 (23) 22439158	Study type: ● Systematic review ● Self-monitoring vs. usual care vs. self-monitoring+support	N/A	1° endpoint: Change in clinic SBP/DBP	● Self-monitoring vs. usual care resulted in lower SBP/DBP (-3.1/-2.0 mm Hg) at 6 mo ● Self-monitoring + support vs. usual care resulted in lower SBP/DBP SBP/DBP -3.4– -8.9/-1.9– -4.4 mm Hg up to 12 mo. Self-monitoring may confer a small benefit for BP control.
Yi SS, et al., 2015 (26) 25737487	Study type: ● RCT ● Self-monitoring of BP vs. usual care. Size: 900 pts	N/A	1° endpoint: ● Change in clinic SBP/DBP and HTN control (SBP/DBP <140/90 mm Hg) ● Decline in SBP at 9 mo was 14.7 mm Hg and 14.1 mm Hg in the intervention and usual care groups (p=0.70); HTN was controlled in 38.9% and 39.1% in the intervention and control groups (p=0.91)	● Self-monitoring of BP by itself does not improve BP above usual care.
Agarwal R, et. al., 2011 (27) 21115879	Study type: ● Systematic review	N/A	1° endpoint: ● Change in clinic SBP/DBP and MAP	● Self-monitoring is associated with a reduction in BP. This effect is larger when accompanied by telemonitoring.

	● Self-monitoring vs. usual care vs. self-monitoring+telemonitoring Size: 9,446 pts		● Mean reduction in SBP, DBP and MAP with home monitoring was 2.63 mm Hg (95% CI: 4.24–1.02), 1.68 (95% CI: 2.58–0.79), 4.0 (95% CI: 1.79–6.22). The effect for SBP was larger when accompanied by telemonitoring (3.20; 95% CI: 4.66–1.73 vs. 1.26; 95% CI: 2.20–0.31).	
Fagard RH, et. al., 2007 (28) 17921809	Study type: ● Systematic review ● MH and WCH vs. sustained normotension Size: 11,502 pts	N/A	1° endpoint: CVD events. The adjusted HR for CVD events was 1.12 (95% CI: 0.84–1.50) for WCH vs. sustained normotension (p=0.59) and 2.00 (95% CI: 1.58–2.52) for MH vs. sustained normotension (p<0.001)	● MH is associated with increased CVD risk but WCH is not associated with increased risk.

Data Supplement 4. White Coat Hypertension (Section 4.4)

Study Acronym; Author; Year Published	Study Type/Design; Definitions	Patient Population (N)	HBPM (%)	Daytime ABPM (%)	24-h ABPM (%)	Results/Comments
Viera AJ, et al., 2010 (29) 20671718	• Office BP ×3 • Duplicate measures of: 24-h ABPM >130/80 Daytime ABPM>135/85 HBPM >135/85	• 50 pts • Untreated • Borderline HTN and BP >110/70 and <160/110	• MH=43/35	• MH=54/53	• MH=51/45	• For MH diagnosis • 95% agreement daytime and 24-h ABPM • Only 47%–53% agreement between HBPM and either daytime or 24-h ABPM
Viera AJ, et al., 2014 (30) 24842491	• Office BP ×3 • Duplicate measures of: 24-h ABPM >130/80 Daytime ABPM >135/85 HBPM >135/85	• 420 pts • Untreated • Borderline HTN and BP >120/80 and <149/95	• MH=15–17	• MH=43–44	• MH=48–50	• For MH Diagnosis • 92%–94% agreement daytime and 24-h ABPM • 70% agreement between HBPM and either daytime K=0.3–0.36
Bayo B, et al., 2006 (31) 16534404	• Office BP ×3 • HBPM ×3 d	• 190 untreated pts • Spanish • Borderline	• WCH=35 (95% CI: 28–42)		• WCH=42 (95% CI: 34, 48)	● Compared to ABPM, HBPM pulse pressure variation: 59% negative predictive value: 69%

Asayama K, et al., 2015 (32) 25135185	• Obs (IDACO) database • CV outcomes risk by WCH, MH, NTN ABPM measured: Office BP ×2 >140/90 (office) >130/80 (24-h ABPM) >135/85 (daytime ABPM) >120/70 (nighttime ABPM	• 8,237 untreated pts	N/A	• WCH=9.1 • MH=13.4	• WCH=10.7 • MH=9.7	• Overlap from daytime to 24-h ABPM: WCH=86% MH=61%
Conen D, et al., 2014 (33) 25185130	• Obs 13 IDACO Cohorts • Office ×2 • Awake ABPM >135/85 • 24-h ABP >130/80 • Analyzed by decade in y	• 7,506 untreated pts	• WCH=2.2% age 18–30, increasing to 19.5% in both sexes age >70 y • MH=inverted U distribution (13% and 11% in 18–30 y 18% and 20% in those 30–50 y • Increased prevalence in men		• WCH=3.0 in age 18–30 increasing to 19.1% both sexes age >70 y • MH=inverted U distribution (12% and 9% in youngest and oldest, 19% and 17% in those 30–50 y • Increase prevalence in men	• Similar prevalence using either 24-h or awake ABPM
Nasothimiou EG, et al., 2012 (34) 22357523	• Office BP ×3 × >140/90 • HBPM >135/85 • Daytime ABPM >135/85	• 613 pts (66% untreated, 34% treated)	• WCH=15% • MH=15%	• WCH=14% • MH=16%	N/A	• WCH: 89% agreement daytime ABPM and HBPM, kappa=0.79 • MH: 88% agreement, kappa=0.56
Coll de TG, et al., 2011 (35) 21183853	• Office ×2 >140/90 • Daytime ABPM >135/85 • HBPM >135/85	• 403 untreated pts	• WCH=24%	• WCH=8.1%	N/A	N/A
Stergiou GS, et al., 2005 (36) 15925734	• Office ×3 ×2 >140/90 • HBPM ≥135/85 awake • ABPM ≥135/85	• 438 untreated/ treated pts	• MH=12% • WCH=16%	• MH=14% • WCH=15%	N/A	• No difference in proportions of pts Dx with MH or WCH by HBPM or awake ABPM • No difference between treated and untreated. However, only 44% overlap for MH, but 90%–95% if 5 mm Hg zone of uncertainty added.

Sega R, et al., 2001 (37) 11560854	• Population-based PAMELA Study • Office ×3 >140/90 • HBPM >132/83 • ABPM >125/79 • LVMI by echo	• 2,051 pts	• WCH=12% • MH=9%	• WCH=12% • MH=9%	N/A	• 70% agreement between ABPM and HBPM for WCH and 57% for MH

Data Supplement 5. White Coat Hypertension (Prevalence) (Section 4.4)

Study Acronym; Author; Year Published	Study Type/Design; Study Size	Patient Population	Primary Endpoint and Results (include P value; OR or RR; & 95% CI)	Summary/Conclusion Comment(s)
Vinyoles E et al., 2008 (38) 18300853	Study type: • Cross-sectional, comparative multicenter descriptive study Size: 6,176 pts	N/A	1° endpoint: WCH=21%	• Multiple methodologies used to define MH. • Prevalence 8.5%–16.6% (general population), 14.7%–30.4% (nonelevated clinic population)
Pickering TG, et al., 1988 (22) 3336140	Study type: • Observational cohort • 24-h ABPM <134/90 • Systematic review • Office vs. ABPM or HBPM Size: 292 pts	N/A	1° endpoint: WCH=21%	• Multiple methodologies used to define MH. • Prevalence 8.5%–16.6% (general population), 14.7%–30.4% (nonelevated clinic population)
Piper MA, et al., 2015 (39) 25531400	Study type: • Systematic review • Office vs. ABPM or HBPM	N/A	1° endpoint: •WCH=5–35% (ABPM) • WCH conversion to SH ~1%–5% y	• Prevalence of WCH sufficiently high to require ABPM confirmation of SH in those with elevated clinic BP
Asayama K, et al., 2014 (32) 25135185	Study type: • Observational (IDACO) database • ABPM measured: • Office BP ×2 • >140/90 (office) • >130/80 (24-h ABPM) • >135/85 (daytime ABPM) • >120/70 (nighttime ABPM) Size: 8,237	Inclusion criteria: Untreated, >18 y	1° endpoint: • WCH=6.3%–12.5% • MH=9.7%–19.6%	• Variable prevalence of both WCH and MH based on method of defining

Conen D, et al., 2014 (33) 25185130	Study type: ● Observational ● 13 IDACO cohorts ● Office ×2 ● Awake ABPM >135/85 ● 24-h ABP >130/80 ● Analyzed by decade in y Size: 7,506 pts	Inclusion criteria: >18 y, untreated	1° endpoint: ● WCH=2.2% age 18–30 y, increasing to 19.5% both sexes age >70 y ● MH=inverted U distribution (13% and 11% in youngest and oldest, 18% and 20% in those 30–50 y) Increase prevalence in males	● Increase in WCH prevalence with increasing age in both sexes ● Peak MH prevalence age 30–50 y with drop at age extremes. Greater prevalence of MH in males. ● Similar prevalence when 24-h vs. awake ABPM used
Alwan H, et al., 2014 (40) 24663506	Study type: ● Observational ● SKIPOGH ● Office BP ×4 ● Daytime ABPM ● Office >140/90 ● Daytime >135/85 Size: 652	Inclusion criteria: >18 y, untreated	1° endpoint: ● WCH=2.6% ● MH=15.8%	● Pts with pre-HTN had 7 times higher rate of MH
Stergiou GS, et al., 2014 (41) 24420553	Study type: ● Observational ● 5 IDACO cohort Studies ● Office ×2 >140/90 ● Home >135/85 ● Median 8.3-y follow-up Size: 5,007 pts	Inclusion criteria: >18 y, untreated	1° endpoint: Long-term follow-up for CVD events	● WCH=13.8% ● MH=8.1%
Pierdomenico SD, et al., 2011 (42) 20847724	Study type: Meta-analysis of observational cohort studies (8 WCH, 5 MH) 24-h ABPM >130/80 Daytime >135/85 Size: 7,961 pts	Inclusion criteria: >18 y, untreated	1° endpoint: Long-term follow-up for CVD events	● WCH=16.1% ● MH=5.8%
Hansen TW, et al., 2007 (43) 17620947	Study type: ● 4 observational studies ● Office <140/90 ● 24-h ABPM >135/85 Size: 7,030 pts	● 78% untreated	Study endpoints: ● F/NF CVD ● Median follow-up =9.5 y 1° Results: ● Adj HR vs. NTN ● WCH=1.22 (CI: 0.96–1.53), p=0.09 ● MH=1.62 (CI: 1.35–1.96), p<0.001	N/A

			• SH=1.80 (CI: 1.59–2.03), p<0.001	

Data Supplement 6. White Coat Hypertension (Correlation with Clinical Outcomes) (Section 4.4)

Study Acronym; Author; Year Published	Study Type/Design; Study Size (N)	Patient Population	Study Endpoints and Length of Follow-up	Endpoint Results (Absolute Event Rates, P value; OR or RR; & 95% CI)	Summary/Conclusions/ Comment
NICE 2011 (44) 22855971	Study type: • Systematic Review • 3 Meta-analyses • 11 observational studies "best method" comparison of office vs. HBPM or ABPM that best predicted (i.e., statistically significant predictors and higher HR values) clinical outcomes (after adjustment for covariates in multivariate analyses)	• Home vs. office (n=7,685) • ABPM vs. office (n=33,158) • Home vs. ABPM vs. Office (n=2,442)	• Outcomes of interest: mortality, stroke, MI, HF, DM, vascular procedures, hospitalization for angina, and other MACCE	For predicting clinical outcomes: ABPM vs. office (9 studies): • ABPM superior to office (8 studies) • No difference between ABPM and office (1 study) HBPM vs. office (3 studies): • HBPM superior to office (2 studies) • No difference between HBPM and office (1 study) HBPM vs. ABPM vs. office (2 studies): • HBPM similar to ABPM and both superior to office (1 study) • No difference between HBPM, ABPM and office (1 study)	• Overall recommendation for ABPM to confirm HTN diagnosis (HBPM recommended if ABPM not practical)
Pierdomenico SD, et al., 2011 (42) 20847724	Study type: Meta-analysis (8 studies) • NTN vs. WCH or MH based mostly on daytime ABPM <135/85 Size: 7,961	Inclusion criteria: Untreated	• Follow-up 3.2–12.8 y • Composite CVD	• WCH vs. NTN: OR: 0.96; 95% CI: 0.65–1.42 • MH vs. NTN: OR: 2.09; 95% CI: 1.55–2.81 • SH vs. NTN: OR: 2.59; 95% CI: 2.00–3.35	N/A
Asayama K, et al., 2014 (32) 25135185	Study type: Observational (IDACO) database • CV outcomes risk by WCH, MH, NTN • ABPM measured: Office BP ×2 >140/90 (office)	Inclusion criteria: >18 y, untreated	• F/NF CVD/stroke, 729 CV events • Follow-up 10.6 y	• WCH adjusted HR: 1.2; 95% CI: 0.93–1.54; p=0.16 • MH adjusted HR: 1.81; 95% CI: 1.41–2.32; p<0.0001 • SH adjusted HR: 2.31; 95% CI: 1.91–2.80; p<0.0001	N/A

	(24-h ABPM) >130/80 (daytime ABPM) >135/85 (nighttime ABPM) >120/70 Size: 8,237				
Verdecchia P, et al., 2005 (45) 15596572	Study type: Population-based (4 international cohorts) • Office ×3 >140/90 • Awake ABPM >130/80 Size: 5,955	• 26% NTN	• Stroke • Follow-up 5.4 y	• WCH adjusted HR: 1.15; 95% CI: 0.61–2.16; p=0.66 • SH adjusted HR: 2.01; 95% CI: 1.31–3.08; p<0.001	• Stroke not increased in WCH but tended to approach systolic HTN risk 6 y after baseline ABPM.
Hansen TW, et al., 2007 (43) 17620947	Study type: Observational 4 studies • Office <140/90 • 24-h ABPM >135/85 Size: 7,030	• 78% untreated	• F/NF CVD • Median follow-up=9.5 y	• WCH adjusted HR: 1.22 (95% CI: 0.96, 1.53), p=0.09 • MH adjusted HR: 1.62; 95% CI: 1.35–1.96; p<0.001 • SH adjusted HR: 1.80; 95% CI: 1.59–2.03; p<0.001	N/A
Fagard RH, et al., 2007 (28) 17921809	Study type: Meta-analysis 7 studies • Office <140/90 • 24-h ABPM or HBPM Size: 11,502	• Treated and untreated	• F or F/NF CVD • Follow-up 3.2–12.3 y (mean=8 y)	• WCH adjusted HR: 1.12 (95% CI: 0.84–1.50), p=0.59 • MH adjusted HR: 2.0; 95% CI: 1.58–2.52; p<0.001 • Systolic HTN adjusted HR: 2.28; 95% CI: 1.87–2.78; p<0.001	N/A
Mancia G, et al., 2013 (46) 23716584	Study type: Observational PAMELA Study • Office ×3<140/90 • HBPM>135/85 and-24-h • ABPM>130/80 Size: 2,051	• 22% treated	• CV and all-cause mortality • Follow-up 16 y	• CV mortality in WCH adjusted HR: 2.04 (95% CI: 0.87–4.78), p=0.10 • All-cause mortality in WCH adjusted HR: 1.50; 95% CI: 1.03–2.18; p=0.03	• Trend but insignificant increase in CV mortality and significant increase in total mortality in WCH • Risk of developing systolic HTN greater in those with WCH
Tomiyama M, et al., 2006 (47) 16942927	Study type: Cross-sectional study assessing target organ damage by BP control status. Control: Office <140/90, daytime <135/85. Size: 332	• Treated pts	• LVMI, carotid IMT, UAE • Cross-sectional	• LVMI, carotid IMT and UAE increased in masked uncontrolled HTN compared to controlled HTN. LVMI and UAE increased in SH	• SH and masked uncontrolled HTN but not WCE associated with increased target organ damage

Ohkubo T, et al., 2005 (48) 16053966	Study type: Observational cohort • Office ×2 >140/90 • Awake ABPM >135/85 Size: 1,332	• Untreated (70%) • Treated (30%)	• CVD mortality/stroke • Follow-up 10 y	• WCH RH: 1.28; 95% CI: 0.76–2.14); p=0.4 • MH RH: 2.13; 95% CI:1.38–3.29; p<0.001 • SH RH: 2.26; 95% CI:1.77–4.54; p<0.0001	• Similar results treated and untreated, males, and females
Tientcheu D, et al., 2015 (49) 26564592	Study type: Observational cohort • Home readings ×5 ×2 visits taken by research staff • Office readings ×5 Size: 3,027	• Dallas Heart Study • 54% African American• 30%–39% treated	• Clinical CVD incl TIA, • UA	• WCH adj HR: 2.09; 95% CI: 1.05–4.15; p=0.035 • MH adj HR: 2.03; 95% CI: 1.36–3.03; p<0.001 SH adj HR: 3.12; 95% CI: 2.13–4.56; p<0.001	• Higher CVD with SH, MH and WCH (African Americans only). CVD risk not increased in whites with WCH

Data Supplement 7. Renal Artery Stenosis (Section 5.4.3)

Study Acronym (if applicable) Author Year Published	Study Type/Design; Study Size (N)	Patient Population	Primary Endpoint and Results (include P value; OR or RR; & 95% CI)	Summary/Conclusion Comment(s)
Lawes CM, et al., 2003 (50) 12658016	Study type: Meta-analysis of RCTs of BP drugs recording CHD events and strokes Size: 464,000 pts	N/A	• CHD RR or 46% Stroke 64%	• All classes of BP meds confer benefit while BB confer greater benefit in those with CAD
Riaz IB, et al., 2014 (51) 25145333	Study type: 540 studies and 7 RCTs Size: 2,139 pts	N/A	• Incidence of nonfatal MI 6.74% in both the stenting and medical therapy groups: OR: 0.99; 95% CI: 0.70–1.43; p=0.99, incidence of renal events in stenting population was found to be 19.58% vs. 20.53% in medical therapy OR: 0.95; 95% CI: 0.76–1.18; p=0.62.	• BP effect, CV accident not specifically reported
Cooper CJ, et al., 2014 (52) 24245566	Study type: Residential treatment center medical therapy with or without renal stent Size: 947 pts	Inclusion criteria: Atherosclerotic renal artery stenosis	• Composite endpoint of death from CV or renal causes, MI, stroke, hospitalization for congestive HF, progressive renal insufficiency, or the need for renal-replacement therapy. 35.1% and 35.8%, respectively; HR with stenting: 0.94; 95% CI: 0.76–1.17; p=0.58 Difference in SBP favoring the stent group: -2.3 mm Hg; 95% CI: -4.4– -0.2; p=0.03.	N/A

Xie X, et al., 2015 (21) 26559744	Study type: MA of RTC that randomly assigned individuals to different target BP levels Size: 44,989 pts	• 19 trials	• Achieved BP 133/76 mm Hg (intensive) 140/81 (less intense) • Major CV events: 14%; 95% CI: 4%–22% • MI: 13%; 95% CI: 0%–24% • Stroke: 22%; 95% CI: 10%–32% • Albuminuria: 10%; 95% CI: 3%–16% • Retinopathy progression: 19%; 95% CI: 0%–34%. • More intensive had no effects on HF: 15%; 95% CI: -11%–34% • CV death: 9%; 95% CI: –11%–26% • Total mortality: 9%; 95% CI: -3%–19% • ESKD: 10%; 95% CI: -6%–23%	• More intensive approach reduced major CV events (stroke and MI) except heat failure, CVD, ESRD, and total mortality.
Brunström M, et al., 2016 (53) 26920333	Study type: Meta-analysis of levels of BP control in DM hypertensives. Size: 73,738 pts	• 49 trials (most pts with DM-2)	Baseline SBP >150 RR for • All death: 0.89; 95% CI:0.80–0.99 • CVD: 0.75; 95% CI: 0.57–0.99 • MI: 0.74; 95% CI: 0.63–0.87 • Stroke: 0.77; 95% CI: 0.65–0.91 • ESRD: 0.82; 95% CI: 0.71–0.94 Baseline SBP140–150 RR of • Death: 0.87; 95% CI: 0.78–0.98) • MI: 0.84; 95% CI: 0.76–0.9 • HF: 0.80; 95% CI: 0.66–0.97 If baseline SBP,140 mm Hg, however, further treatment increased the risk of CV mortality (1.15; 95% CI: 1.00–1.32	• BP lowering reduces major CV events in DM. Caution for initiating treatment in diabetics with SBP <140/90
Ettehad D, et al., 2015 (17) 26724178	Study type: Meta-analysis of large RTCs of antihypertensive treatment Size: 613,815 pts	• 123 studies	Every 10 mm Hg reduction in SBP RR: • Major CV events: 0.80; 95% CI: 0.77–0.83 • CHD: 0.83; 95% CI: 0.78–0.88 • Stroke: 0.73; 95% CI: 0.68–0.77), HF (0.72, 0.67–0.78 • All-cause mortality: 0.87; 95% CI: 0.87; 0.84–0.91 • ESRD: 0.95; 0.84–1.07	• BP lowering reduces CV risk across various baseline BP levels and comorbidities. Suggest lowering SBP <130 mm Hg and BP-lowering treatment to pts with a history of CVD, CHD, stroke, DM, HF, and CKD.

Thomopolous C, et al., 2016 (54) 26848994	Study type: Meta-analysis of RTCs of more vs. less intense BP control	• 16 trials (52,235 pts) compared more vs. less intense treatment 34 (138,127 pts) active vs. placebo	More intense BP • Stroke RR: 0.71; 95% CI: 0.60–0.84) • CHD RR: 0.80; 95% CI: 0.68–0.95) • Major CV events RR: 0.75; 95% CI: 0.68–0.85 • CV mortality RR: 0.79; 95% CI: 0.63–0.97 Stratification of SBP cutoffs (150,140 and 130 mm Hg) showed that a SBP/DBP difference of 10/5 mm Hg across each cutoff reduced risk of all outcomes	• Intensive BP reduction improves CV outcomes compared to less intense Achieved BP <130/80 may be associated with CV benefit.
Julius S, et al., 2006 (55) 16537662	Study type: RCT in pre-HTN; 16 mg candesartan vs. placebo Size: 809 pts	• 58% men	• During the first 2 y, HTN developed in 154 (40.4%) pts in the placebo group compared with only 53 (13.6%) of those in the candesartan group, for RR: 66.3% (p<0.0001). After 4 y, HTN developed in 240 (63.0%) in the placebo group vs. only 208 (53.2%) in the candesartan group RR: 15.6% (p<0.0069).	• 2/3 of those with pre-HTN develop HTN within 4 y. Candesartan interrupts the onset and reduced by 15.6%
Ference BA, et al., 2014 (56) 24591335	Study type: Evaluated the effect of 12 polymorphisms (associated with BP) on the odds of CHD and compared it with the effect of lower SBP observed in both prospective cohort studies and BP-lowering randomized trials Size: 199,477 pts	• 63 studies	• 12 polymorphisms were associated with a 0.32 mm Hg lower SBP ($p=1.79\times10^{-7}$) and a 0.093-mm Hg/decade slower age-related rise in SBP ($p=3.05\times10^{-5}$). The effect of long-term exposure to lower SBP on CHD mediated by these polymorphisms was 2-fold greater than that observed in prospective cohort studies (p=0.006) and 3-fold greater than that observed in short-term BP treatment trials (p=0.001).	• SBP may be causally associated with the rate of rise in SBP with age and has a cumulative effect on the risk of CHD.

Data Supplement 8. RCTs Comparing Obstructive Sleep Apnea (Section 5.4.4)

Study Acronym; Author; Year Published	Aim of Study; Study Type; Study Size (N)	Patient Population	Study Intervention (# patients) / Study Comparator (# patients)	Endpoint Results (Absolute Event Rates, P value; OR or RR; & 95% CI)	Relevant 2° Endpoint (if any); Study Limitations; Adverse Events; Summary
Barb F, et al., 2010 (57) 20007932	Aim: Assess the effect on BP of 1 y of treatment with CPAP in nonsleepy pts with HTN and OSA.	Inclusion criteria: Pts with HTN (on medications or ≥140/90) and	Intervention: CPAP Comparator: Conservative treatment	1° endpoint: Decrease in BP Results: At 12 mo, CPAP decreased SBP by 1.89 mm Hg (95% CI: 3.90–0.11 mm Hg; p=0.065) and DBP 2.19 mm Hg	Limitations: Not blinded; both groups consisted of pts with severe sleep-apnea.

	Study type: RCT Size: 359 pts; 12 mo of follow-up	apnea-hypopnea index >19.	(dietary counseling and sleep hygiene advice).	(95% CI: 3.46– -0.93 mm Hg; p=0.001). The most significant reduction in BP was in pts who used CPAP for more than 5.6 h/night.	Conclusions: CPAP induced a significant reduction in BP, albeit small, in hypertensive pts with OSA.
Martinez-Garcia MA, et al., 2013 (58) 24327037	Aim: Assess the effect of CPAP on BP in pts with OSA and resistant hypertension. Study type: RCT Size: 194 pts; 3 mo follow-up	Inclusion criteria: Pts with resistant hypertension and OSA.	Intervention: CPAP Comparator: No therapy	1° endpoint: Change in 24-h ABPM from baseline to 12 wk. Results: • When the changes in BP were compared between groups by intent to treat, the CPAP group achieved a greater decrease in 24-h mean BP (3.1 mm Hg (95% CI: 0.6, 5.6); p=0.02) and 24-h DBP (3.2 mm Hg (95% CI: 1.0, 5.4; p=0.005) but not in 24-h SBP (3.1 mm Hg (95% CI: -0.6–6.7; p=0.10) compared to control. • There was also a greater nocturnal BP dipping pattern in CPAP treated pts than control (35.9% vs. 21.6%; adjusted OR: 2.4; CI: 1.2–5.1; p=0.02). • There was a significant positive correlation between h of CPAP use and the decrease in mean 24-h BP (r=0.29; 0.006), SBP (r=0.25; p=0.02) and DBP (r=0.30; p=0.005).	Limitations: Did not use sham CPAP as placebo; open-label; short follow-up. Conclusions: Among pts with resistant hypertension and OSA, CPAP treatment for 12 wk compared with control resulted in a decrease in 24-h mean and DBP and improvement in nocturnal pressure pattern.
Lozano L, et al., 2010 (59) 20577130	Aim: Assess effect of CPAP on pts with OSA and resistant hypertension. Study type: RCT Size: 96 pts; 3 mo of follow-up	Inclusion criteria: Pts with resistant hypertension and OSA.	Intervention: CPAP + conventional drug treatment Comparator: Conventional drug treatment alone	1° endpoint: Decrease in 24-h ABPM from baseline to 12 wk. Results: Pts with ABPM confirmed resistant hypertension treated with CPAP, unlike those treated with conventional therapy, showed a decrease in 24-h DBP (-4.9±6.4 vs. 0.1±7.3 mm Hg; p=0.027). Pts who used CPAP >5.8 h showed a greater reduction in daytime DBP (-6.12 mm Hg; 95% CI: -1.45–10.82; p=0.004), 24-h DBP (-6.98 mm Hg; 95% CI: -1.86– -12.1; p=0.009) and 24-h SBP (-9.71 mm Hg; 95% CI: -0.20– -19.22; p=0.46).	Limitations: Small study; only 3 mo follow-up; lack of sham control. Conclusions: CPAP as a complement to usual treatment improved mean 24-h DBP in pts with OSA and ABPM-confirmed resistant hypertension.

Muxfeldt ES, et al., 2015 (60) 25601933	Aim: Evaluate the effect of CPAP on pts with resistant hypertension and OSA. Study type: RCT Size: 434 pts; 6 mo of follow-up	Inclusion criteria: Pts with resistant hypertension and OSA	Intervention: CPAP + conventional antihypertensive therapy Comparator: Antihypertensive therapy alone. Conventional antihypertensive therapy included spironolactone.	1° endpoint: BP reduction at 6 mo via ABPM Results: • On an intention-to-treat analysis, there was no significant difference in any BP change, neither in nocturnal BP fall, between CPAP and control groups. The best effect of CPAP was on night-time SBP in per-protocol analysis, with greater reduction of 4.7 mm Hg (95% CI: -1.6%–5.8%; p=0.25, in comparison with the control group. • Median use of CPAP was 4.8 h.	Limitations: Nonblinded design; per protocol analysis underpowered to show the prespecified outcome of 6–7 mm Hg SBP differences between CPAP and control groups. Conclusions: CPAP had no significant effect on clinic or ambulatory BP in pts with resistant hypertension and moderately severe to severe OSA. However, in the specific subgroup of pts with uncontrolled ambulatory BP, CPAP may modestly reduce night-time SBP and improve the nocturnal BP fall pattern. The reason for lack of BP reduction in the overall study may have been due to excellent control of BP with median 5 medications, including spironolactone, in the majority of pts.
Pedrosa RP, et al., 2013 (61) 23598607	Aim: Evaluate the effect of CPAP on pts with resistant hypertension and OSA. Study type: RCT with Size: 40 pts; 6 mo follow-up	Inclusion criteria: Pts with resistant hypertension and OSA	Intervention: CPAP + conventional antihypertensive therapy (n=20) Comparator: Antihypertensive therapy alone (n=20).	1° endpoint: BP reduction at 6 mo by ABPM. Results: BP was 162±4/97±2 mm Hg prior to randomization. CPAP was used for 6 h/night. Compared with the control group, awake SBP/DBP decreased significantly in the CPAP group (-6.5±3.3/-4.5±1.9 vs. +3.1±3.3/2.1±2/7 mm Hg; p<0.05). BP changes were significant only when pts were awake but not at night by ABPM.	Limitations: Small; but strength was rigorous exclusion of pts who were nonadherent; control arm did not undergo placebo treatment; nonblinded. Conclusions: Treatment of OSA with CPAP significantly reduces daytime BP in pts with resistant hypertension.

Data Supplement 9. RCTs Studying the Effect of Nonpharmacologic Interventions on BP (Dietary Fiber Intake) (Section 6.2)

Study Acronym; Author; Year Published	Aim of Study; Study Type; Study Size (N)	Patient Population	Study Intervention (# patients) / Study Comparator (# patients)	Endpoint Results (Absolute Event Rates, P value; OR or RR; & 95% CI)	Relevant 2° Endpoint (if any); Study Limitations; Adverse Events

Whelton SP, et al., 2005 (62) 15716684	Aim: Study the effect of dietary fiber intake on BP Study type: Systematic review and meta-analysis Size: • 21 RCTs (25 comparisons) with 1,477 pts • 20 of the RCTs were conducted in nonhypertensive persons • 13 double-blind; 3 single blind and 9 open label	Inclusion criteria: • RCT • ≥16 y • English language publication before Feb. 2004 • No concurrent interventions Exclusion criteria: Missing key data	Intervention: Fiber supplementation, either as a pill (8 trials), cereal/fruit/veg (15 trials), Pectin (1 trial), Guar gum (1 trial) Comparator: Placebo or no fiber supplementation	1° endpoint: In a pooled analysis of the overall group (hypertensive and normotensive persons), the mean for change in SBP was -1.15 mm Hg; 95% CI: -2.68–0.39 mm Hg and for DBP was -1.65 mm Hg; 95% CI: -2.70– -0.61 mm Hg. In the subgroup of 20 trials conducted in nonhypertensives, the mean change in SBP was -0.14 mm Hg; 95% CI: -1.10–0.86 mm Hg. In the subgroup of 5 trials conducted in hypertensives, the mean change in BP was -5.95 mm Hg; 95% CI: -9.50– -2.40) mm Hg. 1° Safety endpoint: N/A	● This is the most detailed and comprehensive review of the topic. ● It provides limited evidence, overall, that fiber supplementation results in a significant in BP and suggests no evidence in support of an effect in normotensives.
Streppel MT, et al., 2005 (63) 15668359	Aim: Study the effect of fiber supplementation on BP Study type: Systematic review and meta-analysis Size: • 23 RCTs (25 comparisons) in 1,404 pts • Mean duration=9 wk • Mean age=42 y • 16 double-blind, with 14 (67%) of the 21 comparisons conducted in normotensive pts • 3 trials based on plant protein and 4 trials based on animal protein	Inclusion criteria • Human RCT • BP 1° or 2° outcome • Publications between January 1966–January 2003 Exclusion criteria: • Inadequate reporting of the data • Concurrent intervention	Intervention: Fiber supplementation (average dose=11.5 g/d); soluble fiber in 11 trials, insoluble fiber in 7 trials, and a mixture in the remaining trials Comparator: Placebo or no fiber supplementation	1° endpoint: In the overall group (hypertensive and normotensive pts), a pooled analysis identified a MD for change in SBP of -1.13 mm Hg; 95% CI: -2.49–0.23. In a subgroup of 17 trials conducted in “nonhypertensives” (mean baseline BP<140/90 mm Hg or <50% receiving antihypertensive medication), the mean treatment effect was -0.23 mm Hg; 95% CI: -1.43–0.98 in univariate analysis and -1.00 mm Hg; 95% CI: -1.94– -0.06 mm Hg in multivariate analysis that adjusted for age, sex, study design, duration of intervention, and fiber dose. The corresponding effects in 8 trials conducted in hypertensives were -4.53 mm Hg; 95% CI: -6.69– -2.38 mm Hg; and -2.42 mm Hg; 95% CI: -5.28–0.45 mm Hg. Safety endpoint: N/A	● Findings consistent with experience in the meta-analysis by Whelton et al.

Evans CE, et al., 2011 (64) 25668347	Aim: Study the effect of fiber supplementation on BP Study type: Systematic review and meta-analysis Size: 28 trials met the inclusion criteria and reported fiber intake and SBP and/or DBP. 18 trials were included in a meta-analysis.	Inclusion criteria • RCTs, in humans of at least 6 wk duration • Fiber isolate or fiber-rich diet against a control or placebo • Published between 1 January 1990 and 1 December 2013. Exclusion criteria: N/A	Intervention: Fiber supplementation (average dose =11.5 g/d) -soluble fiber in 11 trials, insoluble fiber in 7 trials, and a mixture in the remaining trials Comparator: Placebo or no fiber supplementation	1° endpoint: Studies were categorized into 1 of 12 fiber-type categories. The pooled estimates for all fiber types were -0.9 mm Hg (95% CI: -2.5–0.6 mm Hg) and -0.7 mm Hg (95% CI: -1.9–0.5 mm Hg) for SBP and DBP, respectively. The median difference in total fiber was 6 g. Analyses of specific fiber types concluded that diets rich in beta-glucans reduce SBP by 2.9 mm Hg (95% CI: 0.9, 4.9 mm Hg) and DBP by 1.5 mm Hg (95% CI: 0.2–2.7 mm Hg) for a median difference in beta-glucans of 4 g. Heterogeneity for individual fiber types was generally low. Safety endpoint: N/A	• Higher consumption of beta-glucan fiber is associated with lower SBP and DBP. • The results of this review are consistent with recommendations to increase consumption of foods rich in dietary fiber, but some additional emphasis on sources of beta-glucans, such as oats and barley, may be warranted.

Data Supplement 10. RCTs Studying the Effect of Nonpharmacologic Interventions on BP (Fish Oil) (Section 6.2)

Study Acronym; Author; Year Published	Aim of Study; Study Type; Study Size (N)	Patient Population	Study Intervention (# patients) / Study Comparator (# patients)	Endpoint Results (Absolute Event Rates, P value; OR or RR; & 95% CI)	Relevant 2° Endpoint (if any); Study Limitations; Adverse Events
Campbell F, et al., 2012 (65) 22345681	Aim: Study the effect of fish oil supplementation on BP Study type: Systematic review and meta-analysis Size: • 17 RCTs (25 comparisons) with 1,524 pts. • 9 trials were conducted in normotensives (1,049	Inclusion criteria: • RCT • English language publication before January 2011 • Duration ≥8 wk Exclusion criteria: N/A	Intervention: Fish oil given in capsule form, with doses varying from 0.8–13.33 g/d. Comparator: Placebo (usually corn oil, olive oil, or safflower oil).	1° endpoint: In a pooled analysis of the 8 trials conducted in hypertensive pts, the mean for change in SBP was -2.56 mm Hg; 95% CI: -4.53– -0.58 mm Hg. The corresponding SBP change for the 9 trials conducted in normotensives was -0.50 mm Hg; 95% CI: -1.44– 0.45.	• This is the most recent of many that have been published. • Previous meta-analyses have been conducted by Appel et al (1993), Morris et al. (1993), Geleijnse et al (2002) and Dickinson et al. (2006). • In general, the findings have been fairly consistent in demonstrating a relatively small (2 3/4 mm Hg SBP) but significant effect, with most of this being attributable to the results in trials conducted in hypertensive pts.

	pts with mean age of 47 y). Follow-up varied 2–26 wk.				
Rodriguez-Leyva D, et al., 2013 (66) 24126178	Aim: Study the effect of flaxseed on BP in hypertensive pts Study type: RCT Size: 110 pts with PAD	Inclusion criteria: • >40 y • PAD for >6 mo, ABI <0.9 Exclusion criteria: Inability to walk, bowel disease, moderate to severe renal failure, life expectancy <2 y with high cardiac risk, allergy to any of the study products, pts who plan to undergo surgery during the course of the trial, and no more than 2 fish meals per wk	Intervention: Pts given 1 food item per day for 6 mo, containing either 30 g of milled flax seed or placebo. Flaxseed contains omega-3 fatty acids, lignans, and fiber. Comparator: Placebo	1° endpoint: SBP and DBP consistently decreased in the flaxseed group over the course of the study. After 6 mo, SBP in the flaxseed group dropped significantly to 136±22 mm Hg (p=0.04). On the contrary, in the placebo group, SBP rose slightly to 146±21 mm Hg. After 6 mo of intervention, DBP in the flaxseed group fell to 72±11 mm Hg (p=0.004), whereas DBP in the placebo group remained the same (79±10 mm Hg).	• Based on this 1 RCT, flaxseed appeared to have a significant BP lowering effect

Data Supplement 11. RCTs Studying the Effect of Nonpharmacologic Interventions on BP (Potassium Supplementation to Placebo or Usual Diet) (Section 6.2)

Study Acronym; Author; Year Published	Aim of Study; Study Type; Study Size (N)	Patient Population	Study Intervention (# patients) / Study Comparator (# patients)	Endpoint Results (Absolute Event Rates, P value; OR or RR; & 95% CI)	Relevant 2° Endpoint (if any); Study Limitations; Adverse Events
Whelton PK, et al., 1997 (67) 9168293	Aim: Study the effect of potassium supplementation on BP Study type: Systematic review and meta-analysis Size:	Inclusion criteria: • Human RCT • Without HTN • Potassium supplementation vs. control • No concurrent interventions Exclusion criteria: Missing key data	Intervention: Potassium supplementation in 1,049 pts (potassium chloride tabs in 10 RCTs with 618 pts and diet in 2 RCT with 431 pts) Comparator: No potassium supplementation	1° endpoint: • Significant reduction in BP. • Overall (hypertensives and normotensives), mean: 3.11 mm Hg; 95% CI: -4.32– -1.91 mm Hg. • In the 12 trials conducted in normotensives, mean: -1.8 mm Hg; 95% CI: -2.9– -0.6 mm Hg for SBP and -1.0 mm Hg; 95% CI: -2.1–0.0 for DBP	• This is the most comprehensive presentation of the effects of potassium on BP, including experience in normotensives. • Significant reduction in SBP overall and in the subgroups with and without HTN. • In a subsequent meta-analysis of 23 trials, Geleijnse JM, Kok FJ, and Grobbee DE (J Hum Hypertens. 2003;17:471-480) reported a similar effect of potassium on SBP in both hypertensives and nonhypertensives (mean of -3.2 and -1.4 mm Hg, respectively).

	• Overall, 33 RCT (n=2,609) • 2 RCTs (n=1,049) in normotensives		(placebo in 10 RCT and usual diet in 2 RCT)	• In the 20 trials conducted in hypertensives, mean: -4.4 mm Hg; 95% CI: -6.6– -2.2 for SBP and -2.5 mm Hg; 95% CI: -4.9– -0.1 for DBP Safety endpoint: N/A	• The 1 RCT conducted in African-Americans (n=87) identified a mean treatment effect size of -6.9 mm Hg; 95% CI: -9.3– -4.4 for SBP (p<0.001) and -2.5 mm Hg; 95% CI: -4.3– -0.8 for DBP (p=0.004). • In the entire cohort (trials conducted in pts with HTN and normotension), net changes in SBP and DBP were directly related to level of urinary sodium excretion during the trial.
Aburto NJ, et al., 2013 (68) 23558164	Aim: Study the effect of potassium supplementation on BP Study type: Systematic review and meta-analysis Size: 21 RCTs (n=1,892); 16 in pts with HTN (n=818) and 3 RCTs in pts without HTN (n=757)	Inclusion criteria: • RCT in humans • Duration ≥4 wk • 24-h collections of urinary potassium • No concomitant interventions Exclusion criteria: Pts who were acutely ill, HIV positive, hospitalized, or had impaired urinary excretion of potassium	Intervention: Potassium supplementation in 20 trials, supplements plus diet/education in 1 trial, and diet/education alone in 2 trials. Comparator: No potassium supplementation (placebo or usual diet)	1° endpoint: • Overall change in SBP=-5.93; 95% CI: -10.15– -1.70. After removing outlier trials, the change was -3.49 mm Hg; 95% CI: -5.15– -1.82 mm Hg. • In 16 trials conducted in hypertensives, change in SBP was -5.32 mm Hg; 95% CI: -7.20– -3.43. • In the 3 trials conducted in persons without HTN, change in SBP was 0.09 mm Hg; 95% CI: -0.77–0.95. Safety endpoint: N/A	• 1 trial (TOHP Phase I) incorrectly entered twice so only 2 trials really available. However, this does not change overall finding. • The negative results for normotensives in this meta-analysis (and difference with the findings by Whelton et al) probably reflects the requirement for a duration of ≥4 wk and the fact that few trials of this duration have been conducted in normotensives.
Geleijnse JM, et al., 2003 (69) 12821954	Aim: Study the effect of potassium supplementation on BP Study type: Systematic review and meta-regression analysis Size: 27 RCTs; 19 in pts with HTN and 11 RCTs in pts without HTN	Inclusion criteria: • RCT in adults • Published after 1966 • Duration ≥2 wk • No concomitant interventions Exclusion criteria: • Disease • Outlier results (1 trial)	Intervention: Potassium supplementation Comparator: No potassium supplementation	1° endpoint: • Overall change in SBP=-2.42; 95% CI: -3.75– -1.08 • In the 19 trials conducted in hypertensives, change in SBP was -3.51 mm Hg; 95% CI: -5.31– -1.72 • In the 3 trials conducted in persons without HTN, change in SBP was 0.97 mm Hg; 95% CI: -3.07–1.14 Safety endpoint: N/A	• Imputation for missing data • In addition to the treatment effect difference by presence/absence of HTN, there was a trend toward a larger treatment effect in older age (≥45 y), and to a lesser extent higher baseline urinary Na (>150 mmol/24 h) and greater increase in urinary K (>44 mmol/24 h)

Data Supplement 12. RCTs Studying the Effect of Nonpharmacologic Interventions on BP (Protein Intake on BP) (Section 6.2)

Study Acronym; Author; Year Published	Aim of Study; Study Type; Study Size (N)	Patient Population	Study Intervention (# patients) / Study Comparator (# patients)	Endpoint Results (Absolute Event Rates, P value; OR or RR; & 95% CI)	Relevant 2° Endpoint (if any); Study Limitations; Adverse Events
Rebholz CM, et al., 2012 (70) 23035142	Aim: Study the effect of protein intake on BP Study type: Systematic review and meta-analysis Size: • 40 RCTs (44 comparisons) with 3,277 pts • 32 comparisons of protein vs. carbohydrate • 12 comparisons of vegetable vs. animal protein • 35 of the RCTs were conducted in normotensive persons (28 with SBP in the prehypertensive range)	Inclusion criteria: • RCT in humans • ≥18 y • Publication between January 1,1950 and April 1, 2011 • No concurrent interventions • No more than 10% difference in calories, sodium, potassium, fiber between the treatment arms • Duration ≥1 wk Exclusion criteria: Missing key data	Intervention: • Protein intake • 1st meta-analysis: any source of protein, with a median protein supplementation dose of 40 g/d (20–66 g/d) • 2nd meta-analysis: specifically vegetable or animal protein Comparator: • 1st meta-analysis: carbohydrate • 2nd meta-analysis: vegetable or animal protein	1° endpoint: • 1st meta-analysis There was a fairly consistent trend for a small BP lowering effect of protein compared to carbohydrate intake (86% of the trials). In a pooled analysis of the overall group (hypertensive and normotensive persons), the mean for change in SBP was -1.76 (95% CI: -2.33– -1.20). In a subgroup of 15 trials in which none of the participants were receiving antihypertensive medication, the mean change in SBP was -1.95 (95% CI: -2.62– -1.29). • 2nd meta-analysis For the comparison of vegetable vs. animal protein, there was no evidence of a difference in BP. In a pooled analysis of the overall group (hypertensive and normotensive pts) the mean change in SBP was -0.10 (95% CI: -2.31–2.11) mm Hg. In a subgroup of 8 trials in which none of the pts were receiving antihypertensive medication, the mean change in SBP was -0.55 (95% CI: -3.06–1.96). 1° Safety endpoint: N/A	• This is the most detailed and comprehensive review of the topic. • It provides strong evidence that protein supplementation results in a significant but modest reduction in BP and suggests that the effect size is similar following supplementation with protein from vegetables or animals.
Tielemans SM, et al., 2013 (71) 23514841	Aim: Study the effect of protein intake on BP	Inclusion criteria • RCTs, in "generally healthy adults"	Intervention: Protein intake	1° endpoint: • At baseline, the mean for age and SBP were 50 (range: 31–74) and 128	• Findings consistent with experience in the meta-analysis by Rebholz et al.

	Study type: Systematic review and meta-analysis Size: 16 RCT (210 comparisons) of protein vs. carbohydrate in 1,449 pts, with 14 (67%) of the 21 comparisons conducted in normotensive pts. -3 trials based on plant protein and 4 trials based on animal protein	• Publications between January 1966–January 2012 Exclusion criteria: • Inadequate reporting of the data • Concurrent intervention	Comparator: Carbohydrate intake	(range: 112–144). During the trials, the MD in protein intake was 48 g/d (range: 26–74 g/d). • In the overall group (hypertensive and normotensive participants), a pooled analysis of comparisons from 14 trials (1,208 pts) identified a MD for change in SBP of -2.11 (95% CI: -2.8– -1.37) for protein vs. carbohydrate. In 3 RCTs that employed plant protein (327 pts), the mean treatment effect was -1.95 (95% CI: -3.21– -0.69) and in 4 RCTs that employed animal protein (574 pts), the corresponding difference was -2.20 (95% CI: -3.36– -1.03). Safety endpoint: N/A	
Dong JY, et al., 2013 (72) 23829939	Aim: Study the effect of protein intake on BP in DM-2 Study type: Systematic review and meta-analysis Size: 9 RCTs with 418 pts	Inclusion criteria: • RCTs in adults with DM-2 • Publications up to August 2012 • High protein diet intervention and ≥5% difference in dietary protein intake between intervention and control groups • Trial duration ≥4 wk Exclusion criteria: Inadequate reporting of key data	Intervention: High protein diet intervention and ≥5% difference in dietary protein intake between intervention and control groups Comparator: N/A	1° endpoint: Pooled experience in the 14 trials identified a nonsignificant reduction in mean SBP of -3.10 (95% CI: -4.63– -1.56). Safety endpoint: N/A	● Heterogeneous group of open label trials with a range of duration from 4–24 wk (median of 12 wk). In addition to DM-2, all of the participants were overweight or obese. ● The quality of the trials varied, drop-out rates ranged from 0%–0%, and only 1 trial was analyzed using an intent to treat approach.
Dong JY, et al., 2013 (73) 23823502	Aim: Study the effect of probiotic fermented milk on BP. Study type: Systematic review and meta-analysis. All but 1	Inclusion criteria: • RCTs • Placebo controlled • Published prior to March 2012 Exclusion criteria:	Intervention: Probiotic fermented milk (100–450 g/d) Comparator: Not specified but all of the trials reported to be	1° endpoint: Pooled experience in the 9 trials identified a nonsignificant reduction in mean SBP of -3.59 (95% CI: -7.58–0.40). Safety endpoint: N/A	● The most recent of several meta-analyses conducted by different groups of investigators that have reported a similar effect size following administration of lactopeptides, especially the

	(cross-over) trial said to use a parallel design. Antihypertensive drug use reported in 3 trials and in an additional 3 trials mean SBP exceeded 150 mm Hg at baseline. Size: 14 RCTs with 702 pts (median size=40).	• Intervention with enzymatically hydrolysed milk • Cointervention	placebo controlled. However, 2 were single blind and 1 was open label.		lactotripeptides Valine-Proline-Proline and Isolucine-Proline-Proline. ● These findings may have special relevance for countries, like Japan, where consumption of fermented milk products is common.

Data Supplement 13. RCTs Studying the Effect of Nonpharmacologic Interventions on BP (Sodium Reduction to Placebo or Usual Diet) (Section 6.2)

Study Acronym; Author; Year Published	Aim of Study; Study Type; Study Size (N)	Patient Population	Study Intervention (# patients) / Study Comparator (# patients)	Endpoint Results (Absolute Event Rates, P value; OR or RR; & 95% CI)	Relevant 2° Endpoint (if any); Study Limitations; Adverse Events
NUTRICODE Mozaffarian D, et al., 2014 (74) 25119608	Aim: Study the effect of sodium reduction on BP and CVD mortality Study type: Meta-regression analysis Size: 103 RCTs (107 comparisons) with 6,970 pts; 38 of the 107 comparisons were conducted in normotensive pts	Inclusion criteria: RCT in 2 previous Cochrane meta-analyses Exclusion criteria: • Duration <1 wk • Mean 24-h collections or estimates of urinary sodium reduced <20 mmol in the intervention group compared to control • Concomitant interventions	Intervention: Sodium reduction Comparator: No sodium reduction	1° endpoint: • Strong evidence for a linear relationship between reduction in sodium intake and lower levels of SBP throughout the entire distribution of sodium studied, with larger reductions in older persons, blacks (compared to whites) and hypertensives (compared to normotensives). For a white, normotensive population at age 50 y, each reduction of 100 mmol/d (2.3 g/d) in dietary sodium lowered SBP by a mean: 3.74 (95% CI: 5.18–2.29). • Modeling based on global estimates of sodium intake, effect of sodium reduction on BP, and effect of BP reduction on CVD mortality attributed 1.65 million CVD deaths annually due sodium intake >2 g/d. this would represent 9.5% (95% CI: 6.4–12.8) of all CVD mortality. Estimates were not	● RCT meta-regression analysis that provides evidence for BP lowering following a reduction in dietary sodium intake, overall and in normotensive persons, with a more pronounced effect in those who were older, black and had a higher starting level of BP. ● These findings are consistent with other reports. ● The modeling analysis suggested sodium reduction would yield important population health benefits but did not specify the magnitude of the potential benefit for pts within the normal BP range.

				provided separately for hypertensive and normotensive persons. 1° Safety endpoint: N/A	
Aburto NJ, et al., 2013 (68) 23558164	Aim: Study the effect of sodium reduction on BP Study type: Systematic review and meta-analysis Size: Overall study included 36 trials (49 comparisons) conducted in 6,736 pts. Of these, 3,263 were nonhypertensive. The results in normotensives in this table are based on experience in 7 RCTs conducted in 3,067 normotensive pts.	Inclusion criteria: ● RCT in humans ● Trial duration ≥4 wk ● 24-h urinary sodium ≥40 mmol/d less in treatment compared to control group ● No concurrent interventions ● Not acutely ill Exclusion criteria: Lack of above	Intervention: Sodium reduction Comparator: No sodium reduction	1° endpoint: In pooled analysis, the overall change in SBP was -3.39 (95% CI: -4.31– -2.46) mm Hg. In the pts with HTN, the change was -4.06 (95% CI: -5.15– -2.96). In the normotensives, the change was -1.38 (95% CI: -2.74–0.02). Safety endpoint: In the small number of relevant trials, there was no significant effect of sodium reduction on lipid levels (Total cholesterol, LDL-cholesterol, HDL-cholesterol, triglyceride levels; 11 trials) or on plasma (7 trials) or urinary catecholamine levels (2 trials). Experience in 4 trials (3 which could not be included in the meta-analysis) suggested a beneficial effect of sodium reduction on urinary protein excretion.	● Study inclusion/exclusion criteria designed to yield a group of trials that would provide results that have relevance for clinical practice and public health. In this context, reduced sodium intake resulted in a statistically significant but small reduction in SBP.
He FJ, et al., 2013 (75) 22437256	Aim: Study the effect of sodium reduction on BP Study type: Systematic review, meta-analysis and meta-regression analysis Size: Overall study included 34 trials (37 comparisons) conducted in 3,230	Inclusion criteria: ● RCTs ● Healthy adults ≥18 y ● Trial duration ≥4 wk ● Sodium intake only difference between treatment and control group ● 24-h urine sodium ≥40 mmol less in treatment compared to control Exclusion criteria: Lack of above	Intervention: Sodium reduction Comparator: No sodium reduction	1° endpoint: In an overall pooled analysis, the change for SBP was -4.18 (95% CI: -5.18– -3.18) mm Hg. In the trials of persons with HTN, the mean change was -5.39 (95% CI: -6.62– -4.15) mm Hg. In the trials conducted in normotensives, the change in SBP was -2.42 (95% CI: -3.56– -1.29) mm Hg. ● In meta-regression analysis, change in 24-h urinary sodium was significantly associated with reduction in SBP (4.3 mm Hg for a 100 mmol reduction in 24-h urinary sodium).	● Study inclusion/exclusion criteria designed to yield a group of trials that would provide results that have relevance for clinical practice and public health. In this context, reduced sodium intake resulted in a significant and potentially important reduction in SBP. ● The meta-regression results were consistent with a dose-response relationship in normotensive pts

	pts. 12 of the RCTs (14 comparisons) were conducted in 2,240 normotensive pts.			Safety endpoint: In the small number of relevant trials (which included both hypertensive and normotensive pts) that provided safety endpoint measurements (4–14 trials), there was no change in total, LDL- or HDL-cholesterol, or triglyceride levels. There were small significant increases in plasma renin activity, aldosterone, and noradrenaline levels but these were consistent with expected physiologic responses to sodium reduction.	
Graudal NA, et al., 2012 (76) 22068710	Aim: Study the effect of sodium reduction on BP Study type: Systematic review and meta-analysis Size: Overall study included 167 trials. Of these, 71 RCTs were conducted in 5,577 normotensive pts, with the following characteristics: ● Median age: 27 y (13–67 y) ● Median trial duration: 7 d (4–1,100 d) ● 5,292 Whites (71 studies) ● 268 Blacks (7 studies) ● 215 Asians (3 studies)	Inclusion criteria: ● RCTs ● 24-h collections or estimates from ≥8 h collections of urinary sodium excretion Exclusion criteria: Systematic studies in unhealthy pts with diseases other than HTN	Intervention: Sodium reduction Comparator: No sodium reduction	1° endpoint: The overall effect of sodium reduction was not presented. A forest plot of 71 comparisons (from 61 trials) in the 4,919 normotensive whites assigned to sodium reduction compared to usual sodium intake identified a trend towards lower SBP in 50 (70%), no difference in 8 (11%), and higher SBP in 13 (19%). In a pooled analysis, sodium reduction compared to usual sodium intake in the normotensives yielded the following MDs in SBP: ● Whites: -1.27 (95% CI: -1.88– -0.66) ● Blacks: -4.02 (95% CI: -7.37– -0.68) ● Asians: -1.27 (95% CI: -3.07– -0.54) A corresponding analysis in the hypertensives yielded the normotensives yielded the following MDs in SBP: ● Whites: -5.48 (95% CI: -6.53– -4.43) ● Blacks: -6.44 (95% CI: -8.85– -4.03) ● Asians: -10.21 (95% CI: -16.98– -3.44) Safety endpoint: In the relevant trials (all cross-over studies and including	● Heterogeneous group of trials that included many small studies of short duration in young persons. ● Overall finding of lower BP in those assigned to a reduced intake of dietary sodium, with an apparently greater effect in Blacks compared to Whites and Asians. ● The hormone changes in this meta-analysis likely reflect a physiologic response to sodium reduction, especially in studies of short duration and rapid changes in sodium intake. The increases in total cholesterol and triglyceride levels were not noted in the meta-analyses conducted by Aburto et al. and He et al.

				comparisons in both hypertensive and normotensive participants) that provided safety endpoint measurements, significant increases in the standard MD for plasma renin activity (70 trials), aldosterone (51 trials), noradrenaline (31 trials), adrenaline (14 trials), and weighted MD for total cholesterol (24 trials), and triglyceride (18 trials) levels. There was no significant effect of sodium reduction on LDL-cholesterol (15 trials) and HDL-cholesterol (17 trials).	
DASH-Sodium Trial Sacks FM, et al., 2001 (77) 11136953	Aim: Study the effect of sodium reduction on BP Study type: Randomized, controlled crossover trial Size: Overall study based on 412 pts, of whom 243 were normotensive	Inclusion criteria: Adults ≥22 y Exclusion criteria: Taking antihypertensive medication, heart disease, renal disease, poorly controlled hyperlipidemia or DM, DM requiring insulin, special dietary requirements, >14 drinks/wk	Intervention: Feeding study in which pts were randomized to a DASH or control diet at 3 levels of assigned dietary sodium intake (High=210 mmol/d; Intermediate=100 mmol/d; Low=50 mmol/d) Comparator: Each pt served as their own control (crossover design)	1° endpoint: ● Reduced sodium intake resulted in a significant reduction in SBP, with a greater reduction during assignment to the Low compared to the Intermediate sodium intake diet. At every level of sodium intake, the achieved reduction in SBP was greater on the control group compared to the DASH diet and for Blacks compared to other pts. ● Reducing sodium intake from the high to intermediate level decreased SBP by 2.1 mm Hg (p<0.001) during the control diet and 1.3 mm Hg (p=0.03) during the DASH diet. ● Reducing sodium intake from the intermediate low level decreased SBP by a further 4.6 mm Hg (p<0.001) during the control diet and 1.7 mm Hg (p<0.01) during the DASH diet. Safety endpoint: N/A	● This trial provides the best (direct) evidence for a dose-response treatment relationship between sodium intake and level of BP. ● It also suggests the relative effect of reduced sodium intake is greater in persons with a typical U.S. diet but the combination of sodium reduction and consumption of a DASH-type diet results in a lower level of BP than can be achieved with either dietary modification on its own. ● Consistent with other trials and meta-analyses, it suggests the effect of a reduced sodium intake is greater in Blacks compared to others, especially for those consuming a typical U.S. diet.
TOHP II Trial (Sodium component) Kumanyika SK, et al., 2005 (78) 15372064	Aim: Study the effect of sodium reduction on BP and prevention of HTN. Study type: Randomized,	Inclusion criteria: ● Healthy community-dwelling adults 30–54 y ● BMI between 110% and 165% of desirable body weight	Intervention: Behavior change intervention aimed at studying the effects of modest (25%–30%) reductions in dietary sodium intake during	1° endpoint: Change in SBP ● Compared to usual care, the sodium reduction group experienced a significant mean reduction of 51 mmol for 24-h urinary excretion and -2.9 (SD: 0.5) mm Hg (p<0.001) in SBP at 6 mo (-5.1 mm Hg in	● This was the largest trial of sodium reduction in HTN prevention and also provides the longest duration of follow. ● The assumptions for a main effects factorial analysis (independence of the

	controlled factorial trial. Size: 2,382 pts, of whom 594 were randomized to sodium reduction (alone) and 596 were randomized to usual care.	• Not taking BP-lowering medication • Mean SBP <140 mm Hg and DBP 83–89 mm Hg Exclusion criteria: Taking antihypertensive medication, Heart disease, renal disease, poorly controlled hyperlipidemia or DM, DM requiring insulin, special dietary requirements, >14 drinks/wk.	up to 48 mo (minimum 36 mo) of follow-up. Comparator: Usual care group	the sodium reduction group and -2.2 mm Hg in the usual care group). • A progressive reduction in effect size for urinary sodium excretion and BP was noted over time, with mean for SBP at 18, 36 mo and termination of -2.0 (SD: 0.5) mm Hg (p<0.001), -1.2 (SD: 0.5) mm Hg (p=0.02), and -1.0 (SD: 0.5) mm Hg (p=0.5). Prevention of HTN • At 6 mo of follow-up the incidence of new onset HTN was 39% lower in the pts randomized to reduced dietary sodium intake compared to the usual care group (p=0.04). • During more prolonged follow-up, the effect size decreased but remained significant after 48 mo of follow-up (14% reduction; p=0.04). Overall, the incidence of HTN was reduced by 18% (p=0.048). Safety endpoint: N/A	interventions) were not demonstrated. Given this finding, the most reliable analysis of this trial was comparison of the experience in each active intervention group with the usual care group. This results in a reduction in statistical power. • Consistent with the pattern in the proceeding TOHP I trial sodium reduction reduced BP and the incidence of HTN but the effect sizes for sodium reduction and BP as well as the difficulty of maintaining the intervention in highly motivated and extensively counselled participants underscores the difficulty of achieving sodium reduction in the general population without changes in food processing and restaurant/fast food preparation practices.
TOHP Phase I 1992 (79) 1586398	Aim: Study the effect of sodium reduction on BP and prevention of HTN Study type: Randomized, controlled factorial trial. Size: Overall, 2,182 adults, with the 327 assigned to sodium reduction compared	Inclusion criteria: • Community-dwelling adults 30–54 y • Not on antihypertensive medication • DBP 80-89 mm Hg • Healthy Exclusion criteria: • Disease • Inability to comply with the protocol	Intervention: Behavior change intervention Comparator: Usual care	1° endpoint: Change in DBP 2° endpoint: Change in SBP Safety endpoint: CVD events, symptoms and general and well being	• Significantly lower DBP (0.9 mm Hg; p<0.05) and SBP (1.7 mm Hg; p<0.01) in the sodium reduction group compared to usual care • Few CVD events • No difference in symptoms • Significant improvement in general well-being at 6 and 18 mo (p<0.05)

	to 417 usual care controls				
Cook NR, et al., 2007 (80) 17449506	Aim: Study the effect of sodium reduction on CVD morbidity and mortality. Study type: 10–15 y post-trial follow-up of TOHP I and TOPH II pts that took advantage of the randomized trial design. Vital status was obtained for 100% of the pts and information on morbidity was obtained from 2,415 (77%) of the pts. Size: 744 TOHP Phase I and 2,382 TOHP Phase II pts	Inclusion criteria: Assigned to dietary sodium reduction or control in TOHP Phase I or TOHP Phase II. Exclusion criteria: None	Intervention: Behavior change intervention aimed at studying the effects of modest (25%–30%) reductions in dietary sodium intake during TOHP Phase I or TOHP Phase II. Comparator: No sodium reduction intervention.	1° endpoint: ● 200 CVD events and 77 deaths during follow-up ● Kaplan-Meier plots identified trends toward less morbidity and mortality in those who had been randomized to sodium reduction compared to usual care, with a consistent pattern for the TOHP I and TOHP II participants ● Risk of a CVD event was 30% lower (RR: 0.70; 95% CI: 0.53–0.94; p=0.018) among those randomized to sodium reduction compared to usual care, after adjustment for trial, clinic, age, race, sex, baseline weight and sodium excretion ● RR for total mortality was 0.80 (95% CI: 0.51–1.26). Safety endpoint: N/A	● Dietary sodium reduction, previously shown to reduce BP and prevent HTN in the TOHP I and TOHP II trials, appeared to reduce CVD events during extended post-trial follow-up of the pts from these 2 trials.

Data Supplement 14. RCTs Studying the Effect of Nonpharmacologic Interventions on BP (Stress Reduction) (Section 6.2)

Study Acronym; Author; Year Published	Aim of Study; Study Type; Study Size (N)	Patient Population	Study Intervention (# patients) / Study Comparator (# patients)	Endpoint Results (Absolute Event Rates, P value; OR or RR; & 95% CI)	Relevant 2° Endpoint (if any); Study Limitations; Adverse Events
Canter PH, et al., 2004 (81) 15480084	Aim: Study the effect of transcendental meditation on BP Study type: Systematic review Size:	Inclusion criteria: ● RCT in humans ● Publication in any language until May 2004 ● No concurrent interventions	Intervention: ● Use of transcendental meditation techniques as taught by Maharishi Mahesh Yogi ● Practiced on a regular basis over an extended period	1° endpoint: Statistically significant reduction in SBP reported in 3 of 5 trials that provided such information. 1° Safety endpoint: N/A	● Only a handful of RCTs available from the large number of publications on this topic. ● Trials had methodological weaknesses and were subject to potential bias due to the affiliation of authors to the transcendental meditation organization.

	• 6 RCTs with wide range of pts: young to elderly; healthy volunteers to Blacks with HTN. • HTN: 2 trials • High normal BP: 2 trials • Normotensive: 1 trial • Not stated: 1 trial • Sample sizes ranging from 34–156 pts • Follow-up from 2 mo–1 y	Exclusion criteria: N/A	Comparator: No treatment, sham, alternative treatment		● A few trials reported small reductions in SBP but clinical relevance of findings is unclear. ● Most of the trials were underpowered and could have missed a significant finding. ● The authors concluded that "there is at present insufficient good quality information to conclude whether or not transcendental meditation has a cumulative positive effect on BP"

Data Supplement 15. RCTs and Meta-analyses Studying the Effect of Nonpharmacologic Interventions on BP (Dietary Patterns) (Section 6.2)

Study Acronym; Author; Year Published	Aim of Study; Study Type; Study Size (N)	Patient Population	Study Intervention (# patients) / Study Comparator (# patients)	Endpoint Results (Absolute Event Rates, P value; OR or RR; & 95% CI)	Relevant 2° Endpoint (if any); Study Limitations; Adverse Events
Appel LJ, et al., 1997 (82) 9099655	Aim: Study the effect of dietary patterns on BP Study type: • Multicenter RCT • 3 arm parallel design • 3 wk pre-randomization run-in phase • Feeding study with 8 wk of intervention Size: 459 adults, mean age 44 y. (326 normotensive)	Inclusion criteria: • Adults ≥22 y • SBP<160 mm Hg and DBP 80–95 mm Hg • No antihypertensive medication Exclusion criteria: • CVD event within 6 mo • Poorly controlled DM or hyperlipidemia • BMI ≥35 • Pregnancy or lactation • Chronic illness that would interfere with participation • Unwillingness to stop taking vitamins, mineral supplements, Ca++ antacids	Intervention: • Diet high in fruits and vegetables • "Combination" diet high in fruits, vegetables, low-fat dairy products, and reduced total fat, saturated fat and cholesterol. Comparator: Usual U.S. diet	1° endpoint: Compared to the control diet, both intervention diets reduced BP, with an overall mean (95% CI) reduction of: • Fruits and Veg. Diet: SBP: -2.8 (95% CI: -4.7– -0.9) DBP: -1.1 (95% CI: -2.4– -0.3) • Combination Diet: SBP: -5.5 (95% CI: -7.4– -3.7) DBP: -3.0 (95% CI: -4.3– -1.6) The BP changes in the subgroup with HTN were: • Fruits and Veg. Diet: SBP: -7.2 (-11.4, -3.0) DBP: -2.8 (-5.4, -0.3) • Combination Diet: SBP: -11.4 (-15.9, -6.9) DBP: -5.5 (-8.2, -2.7)	● This trial was the first of several to document the value of the combination diet (later renamed the DASH diet). ● The BP reductions noted with the DASH (combination) diet were substantial and well maintained. ● Generalizability was limited due to the nature of the intervention (feeding study) and the relatively short period of intervention experience (8 wk)

		• Consuming ≥14 alcoholic drinks with • Renal insufficiency		The corresponding changes in the subgroup of normotensives were: • Fruits and Veg. Diet: SBP: -0.8 (-2.7, 1.1) DBP: -0.3 (-1.9, 1.3) • Combination Diet: SBP: -3.5 (-5.3, -1.6) DBP: -2.1 (-3.6, -0.5) 1° Safety endpoint: Infrequent and similar occurrence of gastrointestinal symptoms in each group	
Sacks FM, et al., 2001 (77) 11136953	Aim: Study the effect of different levels of sodium intake on BP during consumption of a DASH or usual U.S. diet Study type: • Multicenter RCT with 2 parallel diet arms (DASH diet or usual U.S. diet) • Within each arm, randomized cross-over trial with 3 periods testing different levels of sodium intake (no washout) Size: 412, with 59% (243) being normotensive	Inclusion criteria: • Adults ≥22 y • Average SBP between 120–159 mm Hg and average DBP between 80–95 mm Hg • No use of antihypertensive medication Exclusion criteria: Heart disease, renal insufficiency, poorly controlled hyperlipidemia or DM, DM requiring insulin, special dietary requirements, >14 alcoholic drinks /wk.	Intervention: 3 levels of dietary sodium while consuming a DASH or usual U.S. diet. The target sodium intake levels for a daily energy intake of 2,100 kcal were: High: 150 mmol (3,450 mg)/d Intermediate: 100 mmol (2,300 mg)/d Low: 50 mmol (1,150 mg)/d The mean achieved levels of sodium during the high, intermediate and low sodium periods were 144, 107 and 67 mmol/d in the DASH diet group and 141, 106, and 64 mmol/d in the usual U.S. diet group. Comparator: See description above	1° endpoint: • At each level of sodium intake, SBP and DBP were lower during consumption of the DASH diet compared to the usual U.S. diet, the difference being greatest with high sodium intake and lowest with low sodium intake, with the mean SBP difference between the DASH and usual US diets during high, intermediate and low sodium intake being -5.9 (95% CI: -8.0– -3.7), -5.0 (95% CI: -7.6– -2.5), and -2.2 (95% CI: -4.4– -0.1). The corresponding differences for DBP were -2.9 (95% CI: -4.3– -1.5), -2.5 (95% CI: -4.1– -0.8), and -1.0 (95% CI: -2.5, 0.4). • In both the DASH and usual U.S. diet arms, SBP and DBP were significantly lower during intermediate compared to high sodium intake, and during low compared to intermediate sodium intake, with the decrement being greater for the latter change. • In comparison to consumption of a usual U.S. diet at the high level of	● This trial provided additional documentation of the effectiveness of a DASH diet in lowering BP in normotensives (and hypertensives) and the complementary benefit of consuming a reduced intake of sodium.

				sodium intake, the normotensive group consuming the DASH diet at the low level of sodium intake had a mean SBP difference of 7.1 mm Hg ($p<0.001$). 1° Safety endpoint: Participants tended to report less symptoms during periods of reduced sodium intake, with a statistically significant reduction in reports of headache ($p<0.05$) consistent with prior experience in the TONE trial.	
PREMIER Appel LJ, et al., 2003 (83) 12709466	Aim: Study the effect of 2 behavioral interventions, aimed at dietary change, on BP Study type: • Multicenter RCT with 3 parallel arms: • Established • Established plus DASH diet • Advice only Size: 810 adults, with 62% (506) normotensive. At baseline, mean age, BMI and SBP/DBP were 50 y, 33 kg/m^2, and 135/85 mm Hg, respectively. Duration: 6 mo, with observations at 3 and 6 mo.	Inclusion criteria: • Adults ≥25y • Average SBP between 120–159 mm Hg and average DBP between 80–95 mm Hg • No use of antihypertensive medication • BMI between 18.5 and 45 kg/m^2 Exclusion criteria: • Regular use of drugs that affect BP • Target organ damage or DM • Use of weight-loss meds • Hx CVD event • HF, angina, cancer, within 2 y • Consumption of >21 alcoholic drinks /wk • Pregnancy, planned pregnancy, lactation	Intervention: • Structured behavioral interventions that used an identical format (4 individual and 14 group sessions) to facilitate adoption of "established" dietary recommendations for reduction in BP or "established" plus the DASH diet. The "established" dietary recommendations used in PREMIER were a) weight loss in overweight participants, b) sodium reduction, increased physical activity, reduced alcohol intake in pts consuming alcohol. • Compared to experience in the advice only (control) group, there was only modest achievement of	1° endpoint • Compared to control (advice only), SBP and DBP were significantly reduced with both active interventions but there was no significant difference in the effect size between the 2 active intervention groups. This was true for both the normotensive and hypertensive pts, with the effect size being larger in the hypertensive group. In the normotensives, the MD for change in SBP was identical for the "established" compared to "established plus DASH Diet" groups: -3.1 (95% CI: -5.1– -1.1) mm Hg The corresponding changes for DBP were -1.6 (95% CI: -2.9– -0.2) for the "established" intervention group and -2.0 (95% CI: -3.4– -0.6) for the "established intervention plus DASH Diet) group. • Overall, the incidence of HTN was lowest and the percent with optimal BP was highest in the "established plus DASH" diet but the incidence of	● This was an interesting trial which employed a behavior change approach to implement both active interventions. ● The investigators goal was to determine the additive value of the DASH Diet in persons already following key elements of conventional (established) recommendations for nonpharmacologic intervention to lower BP. ● The intervention approach in this trial was less effective in achieving weight loss and reduction in dietary sodium compared to the corresponding experience in the TOHP and TONE trials and the DASH Diet effects on intermediate variables (such as fruit and vegetable consumption) was less than that achieved in the DASH Diet feeding studies. ● Despite the modest intervention effects, both SBP and DBP were significantly reduced with the conventional intervention approach (in normotensives as well as overall) and addition of the DASH diet did not have a

			intervention goals in the "established" group, with a MDs of 3.8 kg (8.4 lbs) for body weight, 11.6 mmol (267 mg)/d) for urinary sodium excretion, no change in physical activity (but better fitness), and no change in alcohol consumption (but very low alcohol consumption at baseline). • Weight loss was somewhat greater in the "established" plus DASH diet group, with a MD of 4.8 kg (10.6 lbs) for body weight. This group also manifested expected effects of the DASH diet, with significantly higher urinary potassium and phosphorous levels, greater consumption of fruits and vegetables, dietary calcium, dairy products, and a lower consumption of total fat and saturated fat. Comparator: Advice only	HTN was significantly less and the percent with optimal BP was higher in both active intervention groups compared to advice only. The difference between the 2 active intervention groups was not significant. In the normotensives, there was a nonsignificant trend towards less HTN and a significantly higher percent with optimal BP in both active intervention groups compared to advice only, with no significant difference for percent with optimal BP in the 2 active intervention groups. 1° Safety endpoint: N/A	significant effect on reduction of SBP or DBP. ● There were some nonsignificant trends for slightly lower BP, less HTN, and more optimal BP in the "established plus DASH Diet" group compared to "established" group. The authors also cited use of the DASH Diet as a means to beneficially influence CVD risk factors in addition to BP.
Appel LJ, et al., 2005 (84) 16287956	Aim: Compare effects of 3 diets, each with a reduced intake of saturated fats, on BP and serum lipids	Inclusion criteria: • Adults ≥30 y • Average SBP between 120–159 mm Hg and	Intervention: • High protein with reduced fat/saturated fat content	1° endpoint Compared with the high carbohydrate diet, the high protein diet:	● This clinical trial demonstrated that substituting either protein or monounsaturated fat in place of carbohydrate resulted in a small

	Study type: • 2 center RCT • 3 period crossover design • Each 8 wk period was separated by a 2–4 wk wash-out phase Size: 161–164 included in analyses (191 pts randomized). 132 (80.5%) of the 164 included in the BP analyses were normotensive. Mean age and BMI were 54 y and 30.2 kg/m^2, respectively.	average DBP between 80–95 mm Hg • No use of antihypertensive medication Exclusion criteria: DM, CVD (current or H/O), LDL cholesterol >220 mg/dL, fasting triglycerides >750 mg/dL, weight >350 lb., taking that effect BP or lipids, unwillingness to stop vitamin/mineral supplements, >14 alcoholic drinks/wk.	• High unsaturated fats (predominantly monounsaturated fat) with low saturated fat content Comparator: High carbohydrate with reduced fat/saturated fat content	• Reduced SBP by -1.4 mm Hg (p=0.002) overall and by -0.9 mm Hg (p=0.047) in the normotensives • Reduced LDL cholesterol by 3.3 mg/dL (p=0.01) overall and by -2.1 mg/dL (p=0.14) in the normotensives • Reduced HDL-C by -1.3 mg/dL (p=0.02) overall • Reduced serum Triglycerides by -15.7 mg/dL (p<0.001) overall Compared with the high carbohydrate diet, the high unsaturated fat diet: • Reduced SBP by -1.3 mm Hg (p=0.005) overall and by -0.9 (p=0.06) in the normotensives • Reduced LDL cholesterol by -1.5 mg/dL (p=0.01) and by -2.1 (p=0.14) in the normotensives • Increased HDL-C by 1.1 mg/dL (p=0.03) overall • Reduced serum Triglycerides by -9.6 (p=0.02) overall	reduction in SBP and improvement in lipid profile.
Bazzano LA, et al., 2014 (85) 25178568	Aim: Compare the effects of a low-carbohydrate and a low-fat diet on body weight and CVD risk factors (including BP) Study type: Single center parallel arm RCT that compared the 2 diets over 12 mo of intervention. Size: 148 pts, with a mean age of 46.8 y at	Inclusion criteria: • 22–75 y • BMI: 30–45 kg/m^2 Exclusion criteria: • CVD • DM-2 • Kidney disease • Use of prescription weight loss meds/surgery • Weight loss >6.8 kg during prior 6 mo	Intervention: • Low-carbohydrate diet, with digestible carbohydrate (total carbohydrate minus total fiber) <40 g/d • Behavioral counselling that employed a mix of 20 individual and group meetings Comparator: • Low fat diet, with <30% of daily energy	1° endpoint: • Compared to the low-fat diet group, the low-carbohydrate diet group had a mean decrease at 12 mo of: Body weight: -3.5 (95% CI: -5.6– -1.4) kg Fat mass: -1.5 (95% CI: -2.6– -0.4) HDL-C: 7.0 (11.0–3.0) mg/dL Ratio total/HDL-C: -0.44 (95% CI: -0.71– -0.16) Sr. triglyceride: -14.1 (95% CI: -27.4– -0.8) mg/dL	● This clinical trial provides 1 of the longest follow-up experiences related to the topic. ● It suggests low carbohydrate diets may be somewhat better than traditional low fat diets in achievement of weight loss, improvement of lipid profile, inflammation, and CHD risk. ● Although the BP differences were not significant, there was a consistent trend toward lower BPs in the low-carbohydrate diet group.

	baseline. Mean SBP/DBP at baseline were 124.9/79.4 and 120.3/77.5 mm Hg in the low-fat and low-carbohydrate groups, respectively. The corresponding BMIs were 97.9 and 96.3 kg/m^2. All 148 pts were included in the analysis (intention to treat)		intake from fat (<7% from saturated fat) • Behavioral counselling that used identical format to that employed in the low carbohydrate group	• At 3, 6, and 12 mo, BP tended to be lower in the low-carbohydrate group but none of the differences in SBP or DBP were significant. • CRP was reduced in both diet groups but to a significantly greater extent in the low-carbohydrate group. • At 6 and 12 mo pts in the low carbohydrate group experienced a significant improvement in their 10-y Framingham CHD risk score. In contrast, there was no change in Framingham CHD risk in the low-fat diet group. 1° Safety endpoint: No serious side effects noted	
Nordmann AJ, et al., 2006 (86) 16476868	Aim: Compare effects of low-carbohydrate and low-fat diets on weight loss and CVD risk factors Study type: • Systematic review and meta-analysis • Cochrane Collaboration strategy Size: 5 trials (447 pts)	Inclusion criteria: • RCT • Adults ≥16 y • Low-carbohydrate diet and low-fat diet interventions • BMI ≥25 kg/m^2 • Follow-up ≥6 m Exclusion criteria: • Cross-over or sequential design • Missing data	Intervention: Low-carbohydrate diet: maximum of 60 g/d carbohydrate Comparator: Low-fat diet: maximum of 30% energy from fat	1° endpoint: At 6 mo, the low-carbohydrate diet pts, compared to the low-fat diet participants, had a mean reduction in body weight that was greater by -3.3 (95% CI: -5.3– -1.4) kg, and a more favorable profile for HDL-cholesterol and triglyceride levels. In contrast, the profile for total-cholesterol and HDL-cholesterol was more favorable in those assigned to a low-fat diet. The profile for SBP tended to be better in the low carbohydrate diet pts but the differences were not significant: MD at 6 mo: -2.4 (95% CI: -4.9–0.1) mm Hg. 1° Safety endpoint: N/A	● This systematic review/meta-analysis tends to suggest low-carbohydrate diets are somewhat more effective in reducing body weight compared to the traditionally recommended low-fat diets. ● Although the BP differences were not significant they would probably have reached a conventional level of significance had subsequent clinical trials (including the Bazzano et al. trial) been included in the analysis.

Nordmann AJ, et al., 2011 (87) 21854893	Aim: Compare effects of Mediterranean and low-fat diets on weight loss and CVD risk factors Study type: • Systematic review and meta-analysis • Cochrane Collaboration strategy Size: 6 trials (2,650 pts)	Inclusion criteria: • RCT • Intent to treat analysis • Overweight/obese with at least 1 additional CVD risk factor • Follow-up ≥6 mo Exclusion criteria: N/A	Intervention: Mediterranean diet: moderate fat intake (main sources olive oil and nuts), rich in vegetables, and low in red meat. Comparator: Low fat diet: ≤30% of energy intake from fat	1° endpoint: Compared to the low-fat diet, the Mediterranean diet resulted in MDs of: • Body weight: -2.2 (95% CI: -3.9 – -0.6) kg • BMI: -0.6 (95% CI: -1.0– -0.1) kg/m^2 • SBP: -1.7 (95% CI: -3.3– -0.05) mm Hg • DBP: -1.5 (95% CI: -2.1– -0.8) • Fasting Plasma Glucose: -3.8 (95% CI: -7.0– -0.6) mg/dL • Total-Cholesterol.: -7.4 (95% CI: -10.3– -4.4) • CRP: -1.0 (95% CI: -1.5– -0.5) 1° Safety endpoint: N/A	● Overall, this study suggests the Mediterranean diet compared to the traditional low fat diet results in greater weight loss, a better CVD risk factor profile (including better BP control), and less inflammation. ● The number of eligible trials was small and the study samples were heterogeneous (2 2º and 4 1° prevention trials).
Yokoyama Y, et al., 2014 (88) 24566947	Aim: Compare the effects of vegetarian and omnivorous diets on BP Study type: Systematic review and meta-analysis Size: • 7 trials (n=311). • 6 were RCT (n=198) • 4 parallel and 3 cross-over designs • All were open • Follow-up ≥6 wk (mean=15.7 wk) • Mean age=44.5 y	Inclusion criteria: • Adults ≥20 y • English language publications between Jan 1946-Nov 2013 Exclusion criteria: • Twin pt studies • Multiple interventions • Only categorical BP results	Intervention: • Lacto-ovo in 4 trials • Lacto in 1 trial • Vegan in 2 trials Comparator: Omnivorous diet in all trials	1° endpoint: Compared to the omnivorous diet, the vegetarian diet resulted in MDs of: • SBP: -4.8 (95% CI: -6.6– -3.1) mm Hg • DBP: -2.2 (95% CI: -3.5– -1.0) SBP was lower in the vegetarian diet group in 5 of the 7 trials (significant in 3) and DBP was lower in 6 of the 7 trials (significant in 2). 1° Safety endpoint: N/A	● Overall, this meta-analysis of clinical trials suggested BP was lower in those who consumed a vegetarian diet compared to their counterparts who consumed an omnivorous diet. ● However, the trials were generally small, heterogeneous in their design and conduct, and of questionable quality. ● Even greater reductions in SBP and DBP were noted in a MA of 32 observational studies.
PREDIMED Toledo E, et al., 2013 (89) 24050803	Aim: Compare the effects of a Mediterranean and lower-fat diet on BP	Inclusion criteria: • Adults, men 5,580 y, women 60–80 y • Free from CVD	Intervention: Pts assigned to a control group or to 1 of 2 Mediterranean diets.	1° endpoint: The percentage of pts with controlled BP increased in all 3 intervention groups (p-value for within-group changes: p<0.001). Pts	● Both the traditional Mediterranean diet and a low-fat diet exerted beneficial effects on BP and could be part of advice to pts for controlling BP.

	Study type: RCT, single-blinded, in Spanish primary healthcare centers Size: 7,447 men (55–80 y) and women (60–80 y) at high risk for CVD.	• DM or at least 3 major CVD risk factors (smoking, HTN, elevated LDL cholesterol, low HDL, overweight/obese, family history of early CHD) Exclusion criteria: Do not meet criteria listed above	The control group received education on following a low-fat diet, while the groups on Mediterranean diets received nutritional education and also free foods; either extra virgin olive oil, or nuts. Comparator: Lower fat diet	allocated to either of the 2 Mediterranean diet groups had significantly lower DBP than the pts in the control group (-1.53 mm Hg (95% CI: -2.01– -1.04) for the Mediterranean diet supplemented with extra virgin olive oil, and -0.65 mm Hg (95% CI: -1.15– -0.15) mm Hg for the Mediterranean diet supplemented with nuts). No between-group differences in changes of SBP were seen	● However, lower values of DBP were noted in the 2 groups following the Mediterranean diet with extra virgin olive oil or with nuts than in the control group.

Data Supplement 16. RCTs and Meta-analysis RCTs Studying the Effect of Nonpharmacologic Interventions on BP (Alcohol Reduction) (Section 6.2)

Study Acronym; Author; Year Published	Aim of Study; Study Type; Study Size (N)	Patient Population	Study Intervention (# patients) / Study Comparator (# patients)	Endpoint Results (Absolute Event Rates, P value; OR or RR; & 95% CI)	Relevant 2° Endpoint (if any); Study Limitations; Adverse Events
Xin X, et al., 2001 (90) 11711507	Aim: Study the effect of alcohol reduction on BP Study type: Systematic review and meta-analysis Size: • 15 RCTs (25 comparisons) with 2,234 pts. • 6 trials were conducted in normotensives (269 pts with a mean age ranging from 26.5–45.5 y). Average	Inclusion criteria: • RCT in humans • Publication between 1966-1999 • Duration ≥1 wk • Only pts regularly consuming alcohol • Only difference between the comparison groups was alcohol intake Exclusion criteria: Comparison of different doses of alcohol intake	Intervention: Reduction in alcohol consumption. In most trials this was achieved by randomization to "light" alcohol but some RCT were based on a behavioral intervention aimed at reducing the number of drinks consumed. Comparator: Usual consumption of alcohol	1° endpoint: • Overall, alcohol reduction was associated with a significant reduction in mean SBP of -3.31 (95% CI: -4.10– -2.52) and DBP of -2.04 (95% CI: -2.58– -1.49). • In the subgroup of 7 RCTs in persons with HTN, the mean changes in SBP and DBP were -3.9 (95% CI: -5.04– -2.76) and -2.41 (95% CI: -3.25– -1.57). • In the subgroup of 6 RCTs in normotensives the corresponding changes in SBP and DBP were -3.5 (95% CI: -4.61– -2.51) and -1.80 (95% CI: -3.03– -0.58).	• This is the most recent meta-analysis of this topic. Although this meta-analysis reports % reduction in alcohol intake, most trials aimed at reducing the number of alcoholic drinks consumed achieved a reduction of about 3 drinks/d. • The intervention results were consistent with the relationship alcohol and BP in observational epidemiology – about a 1 mm Hg higher SBP per alcoholic drink consumed. In observational studies, type of alcohol does not seem to matter and at lower levels of alcohol consumption (<1 standard size alcoholic drink per day in women and <2 in men) there does not

	consumption of alcohol at baseline was not reported. Follow-up varied from 1–18 wk			• In a meta-regression analysis, a dose-response was noted between % reduction in alcohol consumption and mean reduction in BP. 1° Safety endpoint: N/A	seem to be an important biological effect of alcohol on BP. • The relationship between alcohol consumption and BP is predictable and consistent in observational and RCT studies. However, the relationship between alcohol consumption and CVD is more complex as alcohol is associated with an apparently beneficial effect on CVD risk, possibly mediated by an increase in HDL-cholesterol. • Pregnant women, pts with HTN and those at risk of a drinking problem should not drink alcohol. Established light drinkers (<2 standard drinks/d in men and <1/d in women) who are normotensive are in a favorable risk category for CVD.
Stewart SH, et al., 2008 (91) 18821872	Aim: Study the effect of reduced alcohol intake on BP. Study type: Randomized, controlled factorial trial. Size: 1,383 pts.	Inclusion criteria: • Alcohol dependence. • 4—21 d of abstinence. • Men: >21 drinks/wk; Women >14 drinks/wk. • At least 2 heavy drinking days within a consecutive 30-d period during 90 d prior to baseline. Exclusion criteria: • Other substance abuse. • Psychiatric disorder requiring medication. • Unstable medical condition	Intervention: Pharmacotherapy (naltrexone, acamprosate, or both) and counseling strategies (behavioral and/or medical management). Comparator: Placebo.	Change in BP: • Based on up to 5 repeated measures of BP over 16 wk. Data modeled to estimate change in BP over time. • For pts with higher than average baseline SBP (>132 mm Hg), SBP declined by an average of 12 mm Hg (149—137) in the intervention arm compared to placebo, with a corresponding decline in DBP of 8 mm Hg. For those with a baseline SBP ≤132 mm Hg there was no change in SBP (120—121 mm Hg) or DBP. Safety endpoint: N/A	• This trial was designed to evaluate interventions for treatment of alcohol dependence. • BP measurements were not standardized. • About 20% of the observations were missing and assumed to be random.
Dickenson HO, et al., 2006 (92) 16508562	Aim: Study effectiveness of lifestyle	Inclusion criteria: • Only parallel trials	Intervention: Lifestyle change aimed at reduced consumption of alcohol	1° endpoint: -Net reduction (95% CI): SBP -3.8 (-6.1— -1.4)	• Relatively small number of trials • Limited details provided

	interventions, including reduced alcohol intake, for treatment of HTN. Study type: 1 of 10 meta-analyses. Size: 4 trials which collectively studied 305 pts	• SBP ≥140 mm Hg and/or DBP ≥85 mm Hg • ≥8 wk duration • BP outcome Exclusion criteria: • 2º HTN or renal disease • Pregnant women • Change in BP meds during trial	Comparator: Usual care	DBP -3.2 (-5.0— -1.4) Safety endpoint: N/A	
Wallace P, et al., 1988 (93) 3052668	Aim: Study effectiveness of general practitioner advice to reduce heavy drinking. Study type: • RCT Size: 909 adults (641 men and 268 women)	Inclusion criteria: Heavy drinking during wk prior to screening interview. Exclusion criteria: None mentioned	Intervention: Physician counselling aimed at reduced consumption of alcohol. Comparator: Usual care	Endpoints: • 1° outcome was reduction in percent with heavy consumption of alcohol (mean net change=46%). Liver enzymes and BP also measured at 6 and 12 mo. • Pretreatment SBP/DBP=133.5/79.9 mm Hg. • Net reduction SBP=-2.12 (95% CI: -4.19– -0.00) Safety endpoint: N/A	● The goal was to blind those conducting the outcome assessment to treatment assignment but by 6 mo assignment was known in 20-30% of the participants. ● A reduction in SBP was noted despite use of a modest intervention.
Lang T, et al., 1995 (94) 8596098	Aim: Worksite study of reduced alcohol intake effect on BP in heavy drinkers with HTN. Study type: RCT Size: 14 site physicians; 129 adults (95% men)	Inclusion criteria: • Heavy drinking (documented by history and liver enzyme elevation). • HTN (SBP/DBP >140/90 mm Hg) Exclusion criteria: • 2º HTN • Severe liver disease • Planned move/retirement.	Intervention: Physician and worker counselling aimed at reduced consumption of alcohol. Comparator: Usual care. Duration: Follow-up visits at 1, 3, 6, and 18 mo.	Endpoints: • Baseline SBP/DBP=162.5/98.0. Although all of the workers had HTN, only about 20% were being treated with antihypertensive medications at baseline. • At 1 y, the net change in SBP=-5.5 ($p<0.05$). When 5 sites with <5 workers/site were excluded, the net change in SBP=-7.3 mm Hg ($p<0.01$). • At 2 y, the net change in SBP=-6.6 ($p<0.05$).	● Behavioral intervention state of the art for its time ● Careful measurements of BP using Hawksley RZ sphygmomanometer. ● Main analyses do not seem to have accounted for cluster design.

				Safety endpoint: N/A	
Roerecke M, et al., 2017 Lancet Public Health. 2017;2:e108-120.	Aim: Study the effect of reduced alcohol intake on BP. Study type: Systematic review and meta-analysis. Size: 36 RCT with 2865 participants. Design: • 15 parallel-arm trials • 21 crossover trials Setting: • 13 in hypertension • 13 in normotension • 12 HTN and NT • Only 3 trials presented data for women.	Inclusion criteria: • RCT in adult humans • Publication on or before July 13, 2016. • Full text articles. • Change in alcohol intake for ≥1 wk	Intervention: Reduction in alcohol consumption. Strategy varied from controlled inpatient administration to randomization to "light" alcohol to pragmatic primary care trials with counselling to reduce alcohol intake. Duration: Follow-up from 1 wk to 2 y (median 4 wk).	1° endpoint: • Overall, alcohol reduction was associated with a significant reduction in mean SBP of -3.31 (95% CI: -4.10– -2.52) and DBP of -2.04 (95% CI: -2.58– -1.49). • In the subgroup of 7 RCTs in persons with HTN, the mean changes in SBP and DBP were SBP: -3.13 (95% CI: -3.93– -2.32) DBP: -2.00 (95% CI: -2.65– -1.35). • In meta-regression analysis, there was a strong relationship between the extent of BP reduction and change in BP, with no reduction in BP for those consuming 2 or less drinks at baseline but increasing reductions in BP for those with progressively higher intakes of alcohol at baseline. For instance, in those consuming ≥6 drinks/day and reducing their alcohol intake by approximately 50%, the estimated reduction in SBP and DBP were: SBP: -5.5 (95% CI: -6.70– -4.30) DBP: -3.97 (95% CI: -4.70– -3.25). Similar patterns of the effect of baseline alcohol intake on treatment effect were noted for a variety of subgroups. 1° Safety endpoint: N/A	N/A

Data Supplement 17. RCTs and Meta-analysis RCTs Studying the Effect of Nonpharmacologic Interventions on BP (Calcium Supplementation) (Section 6.2)

Study Acronym; Author; Year Published	Aim of Study; Study Type; Study Size (N)	Patient Population	Study Intervention (# patients) / Study Comparator (# patients)	Endpoint Results (Absolute Event Rates, P value; OR or RR; & 95% CI)	Relevant 2° Endpoint (if any); Study Limitations; Adverse Events
Van Mierlo LA, et al., 2006 (95) 16673011	Aim: Study the effect of calcium supplementation on BP Study type: Systematic review and meta-analysis Size: • 40 RCTs with 2,492 pts. • 27 RCTs in pts <140/90 mm Hg (n=1,728) • Follow-up varied from 3–208 wk (median=8.5 wk) • Age range 11–77 y (mean=43.7 y)	Inclusion criteria: • RCT in humans • Publication between 1996 and 2003 • Nonpregnant normotensive pts or hypertensive pts • Only difference between the comparison groups was magnesium intake • Follow-up ≥2 wk Exclusion criteria: Study pts having renal disease or hyperparathyroidism	Intervention: Increased calcium intake, with a range from 355–2,000 mg/d (mean=1,200 mg/d; median=1,055 mg/d), primarily as a gluconate or carbonate salt. Comparator: Placebo or usual intake – 32 double-blind.	1° endpoint: • Overall, increased calcium intake was associated with a significant reduction in mean SBP of -1.86 (95% CI: -2.91– -0.81) and DBP of -0.99 (95% CI: -1.61– -0.37). • The reduction was slightly less but still significant in the subset of 32 double-blind trials, with a mean SBP of -1.67 (95% CI: -2.87– -0.47) and DBP of -0.93 (95% CIL -1.64– -0.22). • There was no significant difference between the effect size in those with a baseline BP ≥ or<140/90 mm Hg. - The mean change in SBP and DBP for those with a baseline BP≥140/90 mm Hg (23 comparisons) was -2.17 (95% CI: -3.78– -0.55) and -0.95 (95% CI: -1.89– -0.01), respectively. - The mean in SBP and DBP for those with a baseline BP <140/90 mm Hg was -1.67 (95% CI: -3.01– -0.27) and -1.02 (95% CI: -1.85– -0.19) mm Hg, respectively. • The authors reported slightly larger effect sizes in those with a lower initial calcium intake, in trials that employed a dietary	• This is the most recent SR/MA on this topic to include RCT conducted in both normotensive and hypertensive pts. The authors interpreted their results as being consistent with a beneficial effect of calcium supplementation on BP, with about a 2 mm Hg reduction in SBP for a 1 g increase in calcium intake. This is slighter larger effect size than noted in several earlier meta-analyses. • A subsequent Cochrane Collaboration meta-analysis was confined to 13 RCT in 485 adults (≥18 y) with HTN studied for ≥8 wk (Dickinson HO et al. Cochrane Database of Systematic Reviews. 2006; CD004639). The authors noted a significant reduction in mean of -2.5 (95% CI: -4.5– -0.6) for SBP but a more modest insignificant change of -0.8 (95% CI: -2.1– 0.4) for DBP. Due to the poor quality of the RCT and heterogeneity of the results, the authors concluded the reduction in SBP was likely an artifact due to bias. • Although not included in most meta-analyses, calcium supplementation has been effective as a treatment in pregnant women at risk for pre-eclampsia. • Several of the meta-analyses (including the 1 by van Mierlo et al) have suggested a bigger effect size in persons with a lower intake of calcium at baseline and in trials that utilized a dietary intervention.

				intervention (compared to a supplement), and in the 4 trials conducted in Asians. 1° Safety endpoint: N/A	• Most of the trials were of short duration and did not (have the capacity) report on potential adverse effects such renal stones. • In addition to being small, several trials were of uncertain quality. • Overall, RCT experience provides limited and inconsistent evidence from trials of variable quality in support of calcium supplementation for prevention (or treatment) of HTN. Better evidence supports the role of calcium supplements, in conjunction with vitamin D, in strengthening bone density.

Data Supplement 18. RCTs and Meta-analyses RCTs Studying the Effect of Nonpharmacologic Interventions on BP (Physical Activity) (Section 6.2)

Study Acronym; Author; Year Published	Aim of Study; Study Type; Study Size (N)	Patient Population	Study Intervention (# patients) / Study Comparator (# patients)	Endpoint Results (Absolute Event Rates, P value; OR or RR; & 95% CI)	Relevant 2° Endpoint (if any); Study Limitations; Adverse Events
Whelton SP, et al., 2002 (96) 11926784	Aim: Study the effect of aerobic exercise on BP Study type: Systematic review and meta-analysis Size: 38 reports (54 comparisons) with 2,419 pts; 27 of the comparisons were conducted in normotensive pts	Inclusion criteria: • English language publication between 1966–2001 • RCT in adults ≥18 y • Duration ≥2 wk • No concurrent interventions Exclusion criteria: Missing BP data	Intervention: Aerobic exercise Comparator: No exercise prescribed	1° endpoint: • For the overall group, a pooled analysis of experience in 53 trials identified a mean net change in SBP of -3.84 (95% CI: -4.97– -2.72). In subgroup analysis, the effect was noted in different ethnic groups, in trials that employed different designs, durations, and sample sizes, in trials with obese, overweight or normal weight pts, and in trials that employed different types, intensity levels, and duration of aerobic exercise. • In the subgroup of 15 trials in hypertensives, the mean net change in SBP was -4.94 (95% CI: -7.17– -2.70).	• This meta-analysis provides the most comprehensive analysis of the effect of aerobic exercise on BP and provides strong evidence in support of aerobic exercise as an intervention to lower BP in normotensives. • Recognizing this, many of the trials were small and of short duration.

				• In the subgroup of 27 trials conducted in normotensives, the mean net change in SBP was -4.04 (95% CI: -5.32– -2.75). 1° Safety endpoint: N/A	
Cornelissen VA, et al., 2013 (97) 23525435	Aim: Study the effect of different types of physical activity on BP • Dynamic aerobic endurance • Resistance training - Dynamic - Static (Isometric) Study type: Systematic review and meta-analysis Size: Overall, 93 studies (>5,000 pts) • 59 Dynamic Aerobic Endurance studies • 13 Dynamic Resistance Training studies • 5 Combined Dynamic Aerobic and Resistance training • 4 Static (Isometric) Resistance • 12 Different interventions within 1 trial	Inclusion criteria: • Parallel arm RCTs • Adults≥18 y • Peer reviewed journals up to February 2012 • Trial duration ≥4 wk Exclusion criteria: Inadequate reporting of the data	Intervention: Physical activity Comparator: No prescription of physical activity	1° endpoint: Overall (trials in hypertensives and normotensive), pooled experience identified a significant reduction in BP with all forms of physical activity (aerobic and both forms of resistance training), with mean reductions in SBP of -3.5 mm Hg following aerobic endurance training, -1.8 mm Hg following dynamic resistance training, and -10.9 mm Hg following static (isometric) resistance training ($p<0.001$ for the difference between the effect size following static [isometric] and other forms of physical activity). In subgroup analysis, dynamic aerobic endurance and dynamic resistance training resulted in mean SBP changes of -2.1 (95% CI: -3.3– -0.83) and -4.3 (95% CI: -7.7– -0.90), respectively, in the pts with pre-HTN and smaller, nonsignificant reductions in the remaining pts with a normal BP. Safety endpoint: N/A	• Most recent in a series of progressively updated publications from Dr. Cornelissen and her colleagues. • The findings suggest a beneficial effect of all forms of physical activity on BP, with a disproportionately large effect of resistance training on BP. • Many of the available RCTs have been small, of short duration, and of uncertain quality.
Rossi AM, et al., 2013 (98) 23541664	Aim: Study the effect of resistance exercise on BP Study type: Systematic review and meta-analysis	Inclusion criteria: • RCTs in adults (≥18 y) • BP-lowering 1° outcome	Intervention: Dynamic resistance training but overall reporting of the details was poor.	1° endpoint: Pooled experience (hypertensive and normotensive pts) identified a small, nonsignificant reduction in mean SBP of -1.03 (95% CI: -3.44–0.39). The corresponding finding	• Suggests resistance training is effective in lowering BP and was the basis for recommending this intervention in the Canadian HTN Education Program recommendations.

	Size: 9 RCTs (11 intervention groups and 14 comparisons) conducted in 452 pts. 10 (71%) of the 14 comparisons were conducted in normotensives	• Trial duration ≥4 wk • Resistance training only intervention Exclusion criteria: Handgrip/isometric exercise	Comparator: No resistance training but not detailed in this article	for DBP was -2.19 (95% CI: -3.87– -0.51). Safety endpoint: N/A	• The discrepancy in effect size between this meta-analysis and the 1 conducted by Cornelisson et al may have been due to the more restrictive requirement by Rossi et al that change in BP be the 1° outcome.
Garcia-Hermosa A, et al., 2013 (99) 23786645	Aim: Study the effect of exercise on BP in obese children. Study type: Systematic review and meta-analysis. Size: 9 RCTs (410 pts).	Inclusion criteria: • Children ≤14 y with obesity • RCT • Duration ≥8 wk • 1° outcome: change in BP Exclusion criteria: Concomitant intervention	Intervention: Physical activity, principally aerobic exercise. Comparator: No physical exercise, nutrition, education, or dietary restriction intervention	1° endpoint: Change in SBP: In pooled analysis, mean change in SBP was -0.4 (95% CI: -0.66– -0.24). Safety endpoint: N/A	• This meta-analysis focused specifically on the effect of physical activity on BP in children with obesity. Although it is not stated explicitly, it seems likely that all of the participants were normotensive and not receiving medication that could influence level of BP. • The findings are consistent with other meta-analyses of the effect of physical activity on BP. • Only limited information regarding study details is provided in this publication. The interventions were heterogeneous in type, duration, and quality.
Carlson DJ, et al., 2014 (100) 24582191	Aim: Study the effect of physical activity on BP in children with obesity. Study type: Systematic review and meta-analysis. Size: 9 RCTs (223 pts: 127 intervention and 96 controls): 6 were conducted in normotensives.	Inclusion criteria: • Adults ≥18 y • RCT, including cross-over trials. • Duration ≥4 wk • Published in a peer reviewed journal between January 1, 1966 and July 31, 2013 Exclusion criteria: Studies that employed any intervention other	Intervention: Pure isometric exercise. Comparator: Use of a control group was a requirement but no additional specific information provided.	1° endpoint: • In the overall pooled analysis (hypertensive and normotensive trials), mean change in SBP was -6.77 (95% CI: -7.93– -5.62) mm Hg. • In the subgroup of 3 trials with hypertensive pts (all on antihypertensive medication), the mean change in SBP was -4.31 (95% CI: -6.42– -2.21) mm Hg. • In the subgroup of 6 trials with normotensive pts, the mean change in SBP was -7.83 (95% CI: -9.21– -6.45) mm Hg.	• This study provides information regarding the effect of pure isometric exercise interventions on BP in adults. • The BP reductions reported in this meta-analysis are surprisingly large but the overall effect pattern is quite consistent with other meta-analyses of isometric exercise.

		than pure isometric exercise (e.g., dynamic resistance)		Safety endpoint: N/A	
Cornelissen VA, et al., 2011 (101) 21896934	Aim: Study the effect of resistance training on BP. Study type: Meta-analysis Size: 28 randomized, controlled trials, involving 33 study groups and 1,012 pts.	Inclusion criteria: • Adults ≥18 y • RCT, including cross-over trials. • Duration ≥4 wk • Published in a peer reviewed journal up to June 2010 Exclusion criteria: Interventions other than pure isometric exercise (e.g. dynamic resistance)	Intervention: Resistance training, including isometric and dynamic modalities. Comparator: Use of a control group was a requirement but no additional specific information provided.	1° endpoint: Resistance training induced a significant SBP/DBP reduction in 28 normotensive or prehypertensive study groups of -3.9 (-6.4, -1.2)/-3.9 (-5.6, -2.2] mm Hg). In the 5 hypertensive study groups, the change in mean SBP/DBP was -4.1 (95% CI: -0.63–1.4)/-1.5 (95% CI: -3.4–0.40) mm Hg. When the study groups were divided according to the mode of training, isometric handgrip training in 3 groups resulted in a larger decrease in SBP/DBP (-13.5 [95% CI: -16.5– -10.5]/-6.1[95% CI: -8.3– -3.9] mm Hg) than dynamic resistance training in 30 groups (-2.8 [95% CI: -4.3– -1.3]/-2.7 [95% CI: -3.8– -1.7] mm Hg). Safety endpoint: N/A	• This meta-analysis supports the BP-lowering potential of dynamic resistance training and isometric handgrip training. • Results further suggest that isometric handgrip training may be more effective for reducing BP than dynamic resistance training. • However, given the small amount of isometric studies available, additional studies are warranted to confirm this finding.

Data Supplement 19. RCTs and Meta-analysis RCTs Studying the Effect of Nonpharmacologic Interventions on BP (Magnesium Supplementation) (Section 6.2)

Study Acronym; Author; Year Published	Aim of Study; Study Type; Study Size (N)	Patient Population	Study Intervention (# patients) / Study Comparator (# patients)	Endpoint Results (Absolute Event Rates, P value; OR or RR; & 95% CI)	Relevant 2° Endpoint (if any); Study Limitations; Adverse Events
Kass L, et al., 2012 (102) 22318649	Aim: Study the effect of magnesium supplementation on BP Study type: Systematic review and meta-analysis	Inclusion criteria: • RCT in humans • Parallel or cross-over design • Publication before July 2010 • Adults >18 y • Only difference between the	Intervention: Increased magnesium intake, with a range in elemental magnesium of 120 to 973 mg/d and a mean of 410 mg/d. Comparator: Placebo or usual intake	1° endpoint: • Overall, increased magnesium intake was associated with a small nonsignificant reduction in mean SBP of -0.32 (95% CI: -0.41– -0.23) and DBP of -0.36 (95% CI: -0.44– -0.27).	• This is the most recent systematic review/meta-analysis on this topic. The authors interpreted their results as being consistent with a beneficial effect of magnesium supplementation on BP. However, this interpretation seems at odds with the data. • In an earlier meta-analysis of 20 RCT (6 in normotensives) by Jee Systolic

	Size: 22 RCTs (23 comparisons) with 1,173 pts. Data for RCTs conducted in normotensive pts were not presented. However, most RCTs were conducted in normotensives and only 6 of the RCTs included some (or all) pts who were being treated with antihypertensive medication. Overall mean age was ~50 y. Follow-up varied from 3–24 wk, with a mean of 11.3 wk.	comparison groups was magnesium intake Exclusion criteria: Comparison of different doses of alcohol intake		• Forest plots revealed considerable heterogeneity in effect size. • The authors reported slightly larger effect sizes in subgroup analysis of cross-over RCT and RCT that employed a dose of magnesium >370 mg/d. 1° Safety endpoint: N/A	HTN et al (Am J Hyperts. 2002;15:691-696) magnesium supplementation resulted in small mean NS reductions of -0.6 (95% CI: -2.2–1.0) mm Hg in SBP and -0.8 (95% CI: -1.9–0.4) in DBP. In meta-regression analysis, there was an apparent dose-response with SBP and DBP reductions of -4.3 (95% CI: -6.3– -2.2) and -2.3 (95% CI: -4.9–0) mm Hg for each 10 mmol/d higher level of magnesium intake. • A Cochrane systematic review/meta-analysis of magnesium supplementation for treatment of HTN in adults (Dickinson HO et al. Cochrane Database Systematic Review 2006: CD 004640) included 12 RCT (n=545) with follow-up of 8–26 wk. Overall, mean SBP and DBP were reduced by -1.3 (95% CI: -4.0–1.5) and -2.2 (95% CI: -3.4– -0.9) mm Hg, respectively. The authors noted the studies were of poor quality, with considerable heterogeneity, and felt the results were likely biased. • Some authors have suggested there may be a greater BP effect when the intervention is by means of diet change but there is insufficient RCT evidence to support this position. • Magnesium sulfate is the drug of choice for prevention of seizures in the pre-eclamptic woman, or prevention of recurrence of seizures in the eclamptic woman, as demonstrated in RCT and a 2010 Cochrane review (Duley L et al. Cochrane Database of Systematic Reviews. CD000127, 2010). • Overall, RCT experience provides insufficient evidence to recommend oral

					magnesium supplementation as a means to prevent (or treat) HTN.

Data Supplement 20. RCTs Studying the Effect of Nonpharmacologic Interventions on BP (Weight Loss) (Section 6.2)

Study Acronym; Author; Year Published	Aim of Study; Study Type; Study Size (N)	Patient Population	Study Intervention (# patients) / Study Comparator (# patients)	Endpoint Results (Absolute Event Rates, P value; OR or RR; and 95% CI)	Relevant 2° Endpoint (if any); Study Limitations; Adverse Events
Neter JE, et al., 2003 (103) 12975389	Aim: Study the effect of weight loss on BP Study type: Systematic review and meta-analysis Size: 25 RCTs (34 comparisons) with 4,874 pts; 17 of the comparisons were conducted in normotensive pts	Inclusion criteria: • RCT in humans • English language publication between 1966–2002 • Nonpharmacologic intervention Exclusion criteria: • Duration <8 wk • Missing data • Objective not weight loss • Concomitant intervention(s)	Intervention: Weight loss (calorie reduction, physical activity, or combination of both) Comparator: No weight loss prescription	1° endpoint: • For the overall group, mean baseline body weight was 88.3 kg and mean change in body weight following the application of the weight loss intervention was -5.1 (95% CI: -6.03– -4.25) kg. This represents a mean percent change of -5.8%. • There was strong evidence for a BP lowering effect of weight loss on BP, overall and in normotensive subgroup. In the normotensive group, the mean for change in SBP was 4.08 (95% CI: -6.01– -2.16). • Overall, a 1 kg reduction in body weight was associated with a mean change in SBP of -1.05 (95% CI: -1.43– -0.66) mm Hg. 1° Safety endpoint: N/A	• Substantial evidence for a reduction in BP, overall and in normotensives. • With the exception of the mean (95% CI) changes in BP, this paper provides limited data for the normotensive group
Ho M, et al., 2012 (104) 23166346	Aim: Study the effect of lifestyle weight loss interventions in obese/overweight children on weight	Inclusion criteria: • RCTs, in obese/overweight children and adolescents ≤18 y	Intervention: Lifestyle weight loss program with a dietary component Comparator: No treatment, usual care or	1° endpoint: Pooled experience in the 7 RCTs with BP experience identified a significant reduction in mean SBP of -3.40 (95% CI: -5.19– -1.61). The pooled SBP MD was -3.72 (95% CI: -4.74– -2.69) in the 3 RCTs with a duration >1 y	• Findings in children are consistent with experience in adult normotensives and with experience in hypertensive pts.

	change and cardio-metabolic risk factors Study type: Systematic review and meta-analysis Size: • Overall, 38 studies • 33 included in various meta-analyses • Effect on SBP studied in 7 RCTs that included 554 pts	•English language publications between 1975–2010 • Trial duration ≥2 mo Exclusion criteria: • Studies that targeted prevention/weight maintenance • Drug trials • Trials in persons with an eating disorder • Inadequate reporting of the data	written education materials	Safety endpoint: N/A	• Considerable heterogeneity in the data
Cai L, et al., 2014 (105) 24552832	Aim: Study the effect of childhood obesity prevention programs on BP Study type: Systematic review and meta-analysis Size: Overall study included 23 studies (28 comparisons) conducted in 18,925 pts.	Inclusion criteria: • RCTs, quasi-experimental studies, and natural experiments in humans • Children and adolescents 2–18 y • Conducted in a developed country • English language publications • Trial duration ≥1 y (≥6 mo for school-based intervention studies) Exclusion criteria: • Studies that only targeted obese/overweight children or those with a medical condition • Inadequate reporting of the data	Intervention: • Weight loss • 15 school-based • 12 some combination of school, home and/or community-based • 1 child care Comparator: No weight loss	1° endpoint: Pooled experience in 19 studies (20 comparisons) identified a small but significant reduction in mean SBP of -1.65 (95% CI: -2.56– -0.71). The effect size was greater in studies that employed an intervention that combined diet and physical activity (mean change in SBP of -2.11 mm Hg). Safety endpoint: N/A	• Study included a mix of RCTs (13), quasi-experimental studies (9), and natural experiments (1). • Included studies conducted over several decades (1985–2012). A significant reduction in BP was only noted in the studies conducted between 2000–2009: mean change in SBP of -3.73 (95% CI: -5.37– -2.09) • Findings of a BP reduction in childhood consistent with evidence from the publications by Neter and Ho.
TOHP, Phase II Hypertension Prevention Collaborative Research Group,	Aim: Study the effect of weight loss on BP and prevention of HTN.	Inclusion criteria: • Healthy community-dwelling adults 30–54 y	Intervention: Behavior change intervention (combination of diet change and physical activity) aimed at	1° endpoint: Change in SBP • Compared to usual care, the weight loss group experienced a significant mean reduction of -4.5 kg in body	• Largest trial of weight loss in prevention of HTN and also provides the longest duration of follow-up

1997 (106) 9080920	Study type: Randomized, controlled factorial trial. Size: 2,382 pts, of whom 1,192 were randomized to a weight loss intervention and 1,190 were randomized to a no weight loss intervention.	• BMI between 110% and 165% of desirable body weight • Not taking BP-lowering medication • Mean SBP <140 mm Hg and DBP 83-89 mm Hg Exclusion criteria: • Taking antihypertensive medication • Heart disease, renal disease, poorly controlled hyperlipidemia or DM, DM requiring insulin, special dietary requirements • >14 drinks/wk	studying the effects of a modest reduction in body weight during up to 48 mo (minimum 36 mo) of follow-up. Comparator: Usual care group	weight and -3.7 (SD: 0.5; p<0.001) mm Hg in SBP at 6 mo (-6.0 mm Hg in the weight loss group and -2.2 mm Hg in the usual care group). • A progressive reduction in the effect sizes for body weight and BP was noted over time, with mean for SBP at 18, 36 mo and termination of -1.8 (SD: 0.5; p<0.001), -1.3 (SD: 0.5; p=0.01), and -1.1 (SD: 0.5; p=0.04). Prevention of HTN • At 6 mo of follow-up the incidence of new onset HTN was 42% lower in the participants randomized to weight loss compared to the usual care group (p=0.02). • During more prolonged follow-up, the effect size decreased but remained borderline significant after 48 mo of follow-up (13% reduction; p=0.06). Overall, the incidence of HTN was reduced by 21% (p=0.02). Safety endpoint: N/A	• The assumptions for a main effects factorial analysis (independence of the interventions) were not demonstrated. Given this finding, the most reliable analysis of this trial was comparison of the experience in each active intervention group with the usual care group. This results in a reduction in statistical power. • Consistent with the pattern in the proceeding TOHP I trial weight loss reduced BP and the incidence of HTN but the effect sizes for weight loss and BP as well as the difficulty of maintaining the intervention in highly motivated and extensively counselled participants underscores the difficulty of achieving and maintaining ideal body weight in the general population by means of lifestyle change.
TOHP, Phase I 1992 (79) 1586398	Aim: Study the effect of weight loss on BP and prevention of HTN Study type: Randomized, controlled factorial trial. Size: Overall, 2,182 adults, with the 308	Inclusion criteria: • Community-dwelling adults 30–54 y • Not on antihypertensive medication • DBP 80-89 mm Hg • Healthy Exclusion criteria: • Disease	Intervention: Behavior change intervention (combination of diet change and physical activity) Comparator: Usual care	1° endpoint: Change in DBP 2° endpoint: Change in SBP Safety endpoint: CVD events, symptoms and general and well being	• Significantly lower DBP (2.3 mm Hg; p<0.01) and SBP (2.9 mm Hg; p<0.01) in the weight loss group compared to usual care • Few CVD events • No difference in symptoms • Significant improvement in general well-being at 6 and 18 mo (p<0.05)

	assigned to weight loss compared to 256 usual care controls	• Inability to comply with the protocol			
TONE Whelton PK, et al., 1998 (107) 9515998	Aim: Study the effect of weight loss on BP and need for antihypertensive drug therapy Study type: RCT, factorial design Size: 585 (obese) participants	Inclusion criteria: • Community-dwelling adults 60–80 y • SBP <145 mm Hg and DBP <85 mm Hg on 1 antihypertensive medication Exclusion criteria: • Heart attack or stroke within 6 mo • Current angina, HF, insulin-dependent DM • Inability to comply with protocol	Intervention: Behavior change intervention (combination of diet change and physical activity) Comparator: Usual care, with similar level of contact compared to active intervention group	1° endpoint: Recurrence of HTN following withdrawal of antihypertensive medication (or CVD event) 2° endpoint: BP (while still on antihypertensive medication prior to tapering of medication) Safety endpoint: CVD events, symptoms (including headaches), dietary composition	• Significant reduction in SBP prior to withdrawal of antihypertensive medication (mean±SE=-4.0±1.3 mm Hg) • 1° outcome significantly less common in weight loss group compared to usual care – Rel. HR: 0.70; 95% CI, 0.57–0.87; p<0.001 • No overt evidence for adverse effects of intervention

Data Supplement 21. RCTs and Systematic Reviews for RCTs Studying the Effect of Nonpharmacologic Interventions on BP (Section 6.2)

Study Acronym; Author; Year Published	Aim of Study; Study Type; Study Size (N)	Patient Population	Study Intervention (# patients) / Study Comparator (# patients)	Endpoint Results (Absolute Event Rates, P value; OR or RR; & 95% CI)	Relevant 2° Endpoint (if any); Study Limitations; Adverse Events
TOHP, Phase II (Weight Loss component) 1997 (1) 9080920	Aim: Study the effect of weight loss on BP and prevention of HTN. Study type: Randomized, controlled factorial trial.	Inclusion criteria: • Healthy community-dwelling adults 30–54 y • BMI between 110% and 165% of desirable body weight • Not taking BP-lowering medication • Mean SBP <140 mm Hg and DBP 83-89 mm Hg	Intervention: Behavior change intervention (combination of diet change and physical activity) aimed at studying the effects of a modest reduction in body weight during up to 48 mo (minimum 36 mo) of follow-up.	1° endpoint: Change in SBP • Compared to usual care, the weight loss group experienced a significant mean (standard error) reduction of -4.5 kg in body weight and -3.7 (0.5) (p<0.001) mm Hg in SBP at 6 mo (-6.0 mm Hg in the weight loss group and -2.2 mm Hg in the usual care group). • A progressive reduction in the effect sizes for body weight and BP	• This was the largest trial of weight loss in prevention of HTN and also provides the longest duration of follow-up • The assumptions for a main effects factorial analysis (independence of the interventions) were not demonstrated. Given this finding, the most reliable analysis of this trial was comparison of the experience in each active intervention group with the usual care group. This results in a reduction in statistical power.

	Size: 2,382 pts, of whom 1,192 were randomized to weight loss and 1,190 were randomized to no weight loss intervention	Exclusion criteria: • Taking antihypertensive medication • Heart disease, renal disease, poorly controlled hyperlipidemia or DM, DM requiring insulin, special dietary requirements • >14 drinks/wk.	Comparator: Usual care group	was noted over time, with mean (SD) for SBP at 18, 36 mo and termination of -1.8 (0.5) (p<0.001), -1.3 (0.5) (p=0.01), and -1.1 (0.5) (p=0.04). Prevention of HTN • At 6 mo of follow-up the incidence of new onset HTN was 42% lower in the participants randomized to weight loss compared to the usual care group (p=0.02). • During more prolonged follow-up, the effect size decreased but remained borderline significant after 48 mo of follow-up (13% reduction; p=0.06). Overall, the incidence of HTN was reduced by 21% (p=0.02). Safety endpoint: N/A	• Consistent with the pattern in the proceeding TOHP I trial weight loss reduced BP and the incidence of HTN but the effect sizes for weight loss and BP as well as the difficulty of maintaining the intervention in highly motivated and extensively counselled participants underscores the difficulty of achieving and maintaining ideal body weight in the general population by means of lifestyle change.
TONE (Weight Loss component) Whelton PK, et al., 1998 (3) 9515998	Aim: Study the effect of weight loss on BP and need for antihypertensive drug therapy Study type: RCT, factorial design Size: 585 (obese) participants	Inclusion criteria: • Community-dwelling adults 60-80 y • SBP <145 mm Hg and DBP <85 mm Hg on 1 antihypertensive medication Exclusion criteria: • Heart attack or stroke within 6 mo • Current angina, HF, insulin-dependent DM • Inability to comply with protocol	Intervention: Behavior change intervention (combination of diet change and physical activity) Comparator: Usual care, with similar level of contact compared to active intervention group	1° endpoint: Recurrence of HTN following withdrawal of antihypertensive medication (or CVD event) 2° endpoint: BP (while still on antihypertensive medication prior to tapering of medication) Safety endpoint: CVD events, symptoms (including headaches), dietary composition	• Significant reduction in SBP prior to withdrawal of antihypertensive medication (mean±standard error=-4.0±1.3 mm Hg) • 1° outcome significantly less common in weight loss group compared to usual care – Rel. HR: 0.70; 95% CI: 0.57– 0.87; p<0.001 • No overt evidence for adverse effects of intervention
TOHP, Phase I (Weight Loss component) 1992 (4) 1586398	Aim: Study the effect of weight loss on BP and prevention of HTN	Inclusion criteria: • Community-dwelling adults 30–54 y	Intervention: Behavior change intervention (combination of diet change and physical activity)	1° endpoint: Change in DBP 2° endpoint: Change in SBP	• Significantly lower DBP (2.3 mm Hg; p<0.01) and SBP (2.9 mm Hg; p<0.01) in the weight loss group compared to usual care • Few CVD events

	Study type: Randomized, controlled factorial trial. Size: Overall, 2,182 adults, with the 308 assigned to weight loss compared to 256 usual care controls	• Not on antihypertensive medication • DBP 80-89 mm Hg • Healthy Exclusion criteria: • Disease • Inability to comply with the protocol	Comparator: Usual care	Safety endpoint: CVD events, symptoms and general and well being	• No difference in symptoms • Significant improvement in general well-being at 6 and 18 mo

Data Supplement 22. Observational Studies of CV Target Organ Damage Including LVH (Section 7.2)

Study Acronym; Author; Year Published	Study Type/Design; Study Size (N)	Patient Population	Primary Endpoint and Results (include P value; OR or RR; & 95% CI)	Summary/Conclusion Comment(s)
LIFE Devereux RB, et al., 2004 (108) 15547162	Study type: Sub-study of pts with HTN and ECG LVH Size: 941	Inclusion criteria: • 55–80 y • BP 160–200/95–115 mm Hg • No MI or stroke within 6 mo • Had echo • Did not require treatment with BB, ACE or AT-1 antagonist for other reasons Intervention: Treatment to BP of 140/90 mm Hg beginning with pts randomized to losartan or atenolol	1° endpoint: Change in LV mass assessed by echo and change in BP in relation to CVD events Results: • Composite endpoint of CV death, MI, or stroke reached in 104 in 4.8 y of follow-up • Reduction in 1° endpoint per SD reduction in LV mass independent of BP change OR: 0.74 (95% CI: 0.6–0.91; p=0.003) • Reductions for each composite endpoint component and total mortality were also significant; results independent of change in ECG LVH	• Reduction in LV mass by echo independently related to CVD outcomes
CARDIA Armstrong AC, et al., 2014 (109) 24507735	Study type: Observational study of population-based cohorts	Inclusion criteria: African American and white men and women stratified by education (above/below high school) 18–30 y at study start and followed for over 20 y; previously healthy	1° endpoint: Composite of hard CVD events Results: • LV mass indexed to body surface area or to height predicted CV events independently of the Framingham risk score (HR: 1.21; 95% CI: 1.05–1.39; p<0.007)	• LV mass measured at age 18–30 y leads to modest risk reclassification later in life • Low number of events limits generalizability

	Size: 3,980		• Net reclassification improvement for LVM/height was 0.13 (p<0.01) and for LVM/BSA was 0.11 (p=0.02).	
ARIC Okwuosa TM, et al., 2015 (110) 25497261	Study type: Observational study of population-based cohorts Size: 14,489	Inclusion criteria: African American and white men and women population-based cohort mean age 54.7 ± 5.7 y at study start and followed for over 25 y; previously healthy	1° endpoint: Pooled cohort CV events and 10-y Framingham CVD events Results: • 792 (5.5%) 10-y Pooled Cohort CV events and 690 (4.8%) 10-y Framingham CHD events. • LVH was associated with CVD events (HR: 1.62; 95% CI: 1.38–1.90) and CHD events (HR: 1.56; 95% CIL 1.32–1.86. • LVH by ECG did not significantly reclassify or improve C statistic compared with Framingham risk score (C statistics 0.767/0.719; net reclassification index =0.001 [p=not significant]), compared with (C statistics 0.770/0.718), respectively.	• ECG LVH does not improve risk reclassification
MESA Zalawadiya SK, et al., 2015 (111) 24699336	Study type: Observational study of population-based cohorts Size: 4,921	Inclusion criteria: Multi-ethnic cohort of men and women followed for a mean follow-up of 4.5 y	1° endpoint: Hard CVD endpoints Results: MRI calculated LVH (indexed to BSA or height; >95th percentile) predicted hard CVD events (LVH-BSA: HR: 2.36; 95% CI: 1.37–4.04; p=0.002; LVH-height [1.7]: HR: 1.95; 95% CI: 1.17–3.26; p=0.01). but did not improve risk reclassification beyond conventional risk factors	• Though LVH predicted events it did not improve risk reclassification

Data Supplement 23. RCTs on Use of Risk Estimation to Guide Treatment of Hypertension (Section 8.1.2)

Study Acronym; Author; Year Published	Aim of Study; Study Type; Study Size (N)	Patient Population	Study Intervention (# patients) / Study Comparator (# patients)	Endpoint Results (Absolute Event Rates, P value; OR or RR; & 95% CI)	Relevant 2° Endpoint (if any); Study Limitations; Adverse Events Summary
Sundstrom J, et al., 2014 (112) 25131978	Aim: We aimed to investigate whether the benefits of BP-lowering drugs are proportional to baseline CV risk, to	Inclusion criteria: BPLTTC: trials were eligible if they met the original inclusion criteria specified in the protocol, 11 and were part of the subset of studies that randomly allocated	Intervention: BP-lowering meds Comparator: Placebo or less intensive treatment	1° endpoint: • Total major CV events, consisting of stroke (nonfatal stroke or death from cerebrovascular disease), CHD (nonfatal MI or death from CHD	Summary: • Lowering BP provides similar relative protection at all levels of baseline CV risk, but progressively greater absolute risk reductions as baseline risk

	establish whether absolute risk could be used to inform treatment decisions for BP-lowering therapy, as is recommended for lipid-lowering therapy. Study type: Meta-analysis of RCTs Size: 11 trials and 26 randomized groups with 67,475 pts (51,917 pts data available for the calculation of the risk equations)	pts to either a BP-lowering drug or placebo, or to a more intensive or less intensive BP regimen. Trials had to have a minimum of 1,000 pt-y of planned follow-up in each randomized group, and should not have presented their main results before the protocol was finalized in July, 1995. Exclusion criteria: Not stated		including sudden death), HF (resulting in death or admission to hospital), or CV morbidity. • The mean estimated baseline levels of 5-y CV risk for each of the 4 risk groups were 6.0% (SD: 2–0), 12.1% (1–5), 17.7% (1–7), and 26.8% (5–4). • In each consecutive higher risk group, BP-lowering treatment reduced the risk of CV events relatively by 18% (95% CI: 7–27), 15% (95% CI: 4–25), 13% (95% CI: 2–22), and 15% (95% CI: 5–24), respectively (p=0·30 for trend) in each group with BP-lowering treatment for 5 y would prevent 14 (95% CI: 8–21), 20 (95% CI: 8–31), 24 (95% CI: 8–40), and 38 (95% CI: 16–61) CV events, respectively (p=0.04 for trend).	increases. These results support the use of predicted baseline CVD risk equations to inform BP-lowering treatment decisions. • Lowest risk group had >83% with a risk that exceeds 4%.
Sundstrom J, et al., 2015 (19) 25531552	Aim: To investigate whether pharmacologic BP reduction prevents CV events and deaths in pts with grade 1 HTN. Study type: Meta-analysis of RCTs Size: 10 RTCs with 15,266 pts	Inclusion criteria: RCTs of at least 1 y duration; pts ≥18 y, at least 80% of whom had grade 1 HTN and no previous CVD (MI, angina pectoris, CABG, PCI, stroke, TIA, carotid surgery, peripheral arterial surgery, intermittent claudication, or renal failure); and compared an antihypertensive drug provided as monotherapy or a stepped-care algorithm vs. placebo or another control regimen. Exclusion criteria: Excluded trials did not contribute an event	Intervention: BP-lowering meds Comparator: • Placebo or less intensive treatment • The difference in average achieved BP between the active and control groups was 3.6/2.4 mm Hg in the BPLTTC (Appendix Table 2, available at www.annals.org) but is unknown for the other contributing trial subgroups.	1° endpoint: Total major CV events, comprising stroke (nonfatal stroke or death from cerebrovascular disease), coronary events (nonfatal MI or death from CHD, including sudden death), HF (causing death or resulting in hospitalization), or CV death; OR: 0.86 (95% CI: 0.74–1.01) Other endpoints: Each of the above outcomes independently; and total deaths. • CHD 0.91 (95% CI: 0.74–1.12) • Stroke 0.72 (95% CI: 0.55–0.99) • HF 0.80 (95% CI: 0.57–1.12) • CVD deaths 0.75 (95% CI: 0.57–0.98)	Summary: • BP-lowering therapy is likely to prevent stroke and death in pts with uncomplicated grade 1 HTN. • 5 y risks in BPLTTC control groups CVD events 7.4% CVD deaths 3.1%

		for any of the outcomes of interest.		• Total deaths 0.78 (95% CI: 0.67–0.92) Only the first event for a pt was used for the analysis of each outcome, but a pt who had >1 outcome type could contribute to more than 1 analysis. They also tabulated overall withdrawals and withdrawals due to adverse events.	
Thompson AM, et al., 2011 (113) 21364140	Aim: To evaluate the effect of antihypertensive treatment on 2º prevention of CVD events and all-cause mortality among pts without clinically defined HTN. Study type: Meta-analysis of RCTs Size: 25 RCTs with 64,162 pts	Inclusion criteria: Studies were eligible for inclusion if they were RCTs of antihypertensive treatment among pts with BP <140 mm Hg systolic or <90 mm Hg diastolic for the prevention of CVD events (fatal or nonfatal stroke, fatal or nonfatal MI, CHF, or CVD mortality). Exclusion criteria: Studies were excluded if CVD events were not reported by HTN status in studies that included pts with and without HTN; the study population did not include pts with BP in the normal or prehypertensive ranges; the study population did not include pts with preexisting CVD or CVD equivalents, such as diabetes; antihypertensive treatment was not part of the intervention; treatment allocation was not random; a measure of variance (p-value or CI) was not reported or could not be calculated from the information provided; pts <18 y; or there were differences between	Intervention: BP-lowering meds, the majority were studies of ACEI, next most common were BBs. Comparator: Placebo or active comparator	1° endpoint: • Composite CVD (fatal or nonfatal stroke, fatal or nonfatal MI, CHF, or CVD mortality): • CVD RR: 0.85 (95% CI: 0.80–0.90), absolute risk reduction: 27.1/1,000. • This implies that a 2.7% absolute risk reduction reflects a 15% RR reduction, so the baseline risk for CVD would have been about 18%, but the follow-up interval is unclear. Other endpoints: • Stroke RR: 0.77 (95% CI: 0.61, 0.98) • MI RR: 0.80 (95% CI: 0.69, 0.93) • HF RR: 0.71 (95% CI: 0.65, 0.77) • CVD death RR: 0.83 (95% CI: 0.69, 0.99) • Total deaths RR: 0.87 (95% CI: 0.80, 0.95) Other results: Table 4 shows similar results for CVD from studies of pts with CAD vs. other, HF vs. other, and DM vs. non-DM. Similar results from studies of ACEI vs. other. These results support the	Summary: Among pts with clinical history of CVD but without HTN, antihypertensive treatment was associated with decreased risk of stroke, CHF, composite CVD events, and all-cause mortality. Limitations: • Difference in achieved BP was not reported. • Average baseline SBP not reported. No information on the entry levels of BP other than not hypertensive. Difficult to use to establish a treatment threshold or goal. • Many of these studies were designed to try to demonstrate specific drug benefits rather than BP-lowering benefits. Can we attribute the benefits to BP-lowering? We know these pts did not have HTN but we do not know the lower limit of the BP inclusion ranges or the treatment associated difference in SBP between groups making it difficult to

		intervention and control groups other than antihypertensive treatment.		conclusion that the effect is not a drug effect, but is a BP-lowering effect, and that the effect is seen in people with CVD broadly defined, not just in HF pts.	establish a treatment initiation threshold or goal.
Xie X, et al., 2015 (21) 26559744	Aim: To assess the efficacy and safety of intensive BP-lowering strategies. Study type: Meta-analysis of RCTs Size: 19 RCTs with 44,989 pts	Inclusion criteria: RCTs with at least 6 mo follow-up that randomly assigned pts to more intensive vs. less intensive BP-lowering treatment, with different BP targets or different BP changes from baseline. Reference lists from identified trials and review articles were manually scanned to identify any other relevant studies. Exclusion criteria: N/A	Intervention: BP-lowering meds Comparator: • Less intensive treatment • BP difference 6.8/3.5 • The mean follow-up BP levels in the less intensive BP-lowering regimen group were 140/81 mm Hg, compared with 133/76 mm Hg in the more intensive treatment group.	1° endpoint: • CVD, other major CV events, defined as a MI, stroke, HF, or CV death, separately and combined; nonvascular and all-cause mortality; ESKD, and adverse events. Progression of albuminuria (defined as new onset of micro-albuminuria/macro-albuminuria or a change from micro-albuminuria to macro-albuminuria) and retinopathy (retinopathy progression of 2 or more steps) were also recorded for trials that were done in pts with DM • CVD RR: 0.86 (95% CI: 0.78–0.96) Other endpoints: MI RR: 0.87 (95% CI: 0.76–1.00; p=0.042) Stroke RR: 0.78 (95% CI: 0.68–0.90) HF RR: 0.85 (95% CI: 0.66–1.11) CVD death RR: 0.91 (95% CI: 0.74–1.11) Total deaths RR: 0.91 (95% CI: 0.81–1.03) Other results: • Benefit for CVD not different by baseline SBP 120–139: 0.89 (95% CI: 0.76–1.05) 140–160: 0.83 (95% CI: 0.68–1.00) >160: 0.89 (95% CI: 0.73–1.09)	Summary: Intensive BP-lowering, including to <130 mm Hg, provided greater vascular protection than standard regimens. In high-risk pts, there are additional benefits from more intensive BP-lowering, including for those with SPB <140 mm Hg at baseline. The net absolute benefits of intensive BP-lowering in high-risk individuals are large. Limitations: • Lack of individual pt data, which would have allowed a more reliable assessment of treatment effects in different pt groups. • Interpretation: Supports treating pt with and without CVD at threshold of 130 to <130. Supports treating at threshold of about 130 even down to a CVD event rate of 0.9% per y.

				p-heterogeneity: 0.60 • Benefit for CVD not different for more intensive and less intensive targets in intensive group <140 or <150 mm Hg: 0.76 (95% CI: 0.60–0.97) <120– <130 mm Hg: 0.91 (95% CI: 0.84–1.00) p-hetero: 0.06 • Absolute benefits were proportional to absolute risk. • For trials in which all pts had vascular disease, renal disease, or DM at baseline, the average control group rate of major vascular events was 2·9% per y compared with 0·9% per y in other trials, and the numbers needed to treat were 94 (95% CI: 44–782) in these trials vs. 186 (95% CI: 107–708) in all other trials. • Increase in severe hypotension: 0.3% vs. 0.1% per person y OR: 2.68 (95% CI: 1.21–5.89)	
Ettehad D, et al., 2015 (17) 26724178	Aim: This systematic review and meta-analysis aims to combine data from all published large-scale BP-lowering trials to quantify the effects of BP reduction on CV outcomes and death across various baseline BP levels, major comorbidities, and different pharmacological interventions.	Inclusion criteria: • RCTs of BP-lowering treatment that included a minimum of 1,000 pt-y of follow-up in each study arm. No trials were excluded because of presence of baseline comorbidities, and trials of antihypertensive drugs for indications other than HTN were eligible. • Eligible studies fell into 3 categories: 1st, random allocation of pts to a BP-lowering drug or placebo; 2nd, random allocation of pts to different BP-	Intervention: BP-lowering meds Comparator: Placebo, active comparator or less intensive treatment	1° endpoint: • CVD. • Major CVD events, CHD, stroke, HF, renal failure, and all-cause mortality. • Standardized RR for 10 mm Hg difference in SBP • CVD RR: 0.80 (95% CI: 0.77–0.83) Other endpoints: • CHD RR: 0.83 (95% CI: 0.78–0.88) • Stroke RR: 0.73 (95% CI: 0.68–0.77)	Summary: • BP-lowering significantly reduces vascular risk across various baseline BP levels and comorbidities. Our results provide strong support for lowering BP to SBP <130 mm Hg and providing BP-lowering treatment to individuals with a history of CVD, CHD, stroke, DM, HF, and CKD. • In stratified analyses, we saw no strong evidence that proportional effects were diminished in trials that included people with lower

	Study type: Meta-analysis of RCTs Size: 123 studies with 613,815 pts	lowering drugs; and third, random allocation of pts to different BP-lowering targets. Exclusion criteria: <1,000 pt-y of follow-up in each treatment group.		• HF RR: 0.72 (95% CI: 0.67–0.78) • Total deaths RR: 0.87 (95% CI: 0.84–0.91) Other results: • Benefit for CVD and other endpoints not different by baseline SBP, including <130 mm Hg fig 4 in paper CVD: 0.63; 95% CI: 0.50–0.80; p=0.22 CHD: 0.55; 95% CI: 0.42–0.72; p=0.93 Stroke: 0.65; 95% CI: 0.27–1.57; p=0.38 HF: 0.83; 95% CI: 0.41–1.70; p=0.27 Total deaths: 0.53; 95% CI: 0.37–0.76; p=0.79 • More precision around estimates of benefits in SBP 130–139 at baseline, fig 4 in paper • Results similar in trials of people with and without CVD at baseline figure 5 CVD+ 0.77 (95% CI: 0.71–0.81) CVD- 0.74 (95% CI: 0.67–0.83) Total deaths CVD+ 0.90 (95% CI: 0.83–0.98) CVD- 0.84 (95% CI: 0.75–0.93) Other outcomes similarly in figure 5 • In appendix, in general, benefits for CVD prevention seen in groups with and without baseline CHD, Stroke, DM, CKD and HF when examined separately, but no absolute risks provided to enable estimation of how far down the absolute risk curve these findings have been demonstrated.	baseline SBP (<130 mm Hg), and major CV events were clearly reduced in high-risk pts with various baseline comorbidities. Both of these major findings—the efficacy of BP-lowering below 130 mm Hg and the similar proportional effects in high risk populations—are consistent with and extend the findings of the SPRINT trial. Limitations: • Lack of individual pt data, which would have allowed a more reliable assessment of treatment effects in different pt groups. • Interpretation: Lowering of BP into what has been regarded the normotensive range should therefore be routinely considered for the prevention of CVD among those deemed to be of sufficient absolute risk.

				• Some evidence of BB inferiority to other med classes in figure 6. • Did not report absolute risks so do not know lower level of risk in treated populations.	
SPRINT Wright JT Jr, et al., 2015 (114) 26551272	Aim: To test the effectiveness of a goal SBP<120 mm Hg vs. a goal SBP<140 mm Hg for the prevention of CVD in pts with SBP≥130 mm Hg at baseline. Study type: RCT Size: 9361 pts followed median of 3.26 y.	Inclusion criteria: SBP≥130 mm Hg, with upper limit varying as number of pre-trial BP-lowering meds increased. age ≥50 y Presence of at least 1 of the following: • Clinical or subclinical CVD • CKD stage ≥3 • Age≥75 • Framingham General CVD risk≥15% in 10 y Exclusion criteria: DM, history of stroke, ESRD (eGFR <20)	Intervention: Intensive BP-lowering treatment to goal SBP <120 mm Hg Comparison: • Standard BP-lowering treatment to goal SBP<140 mm Hg • Net treatment difference ~3 drugs (2.8) on average vs. 2 drugs (1.8) on average • During the trial, mean SBP was 121.5 vs. 134.6.	1° endpoint: CVD (MI, ACS, stroke, HF, CVD death) HR: 0.75 (95% CI: 0.64, 0.89) Other endpoints: • Total deaths HR: 0.73 (95% CI: 0.60–0.90) • 1° or death HR: 0.78 (95% CI: 0.67–0.90) • Components of 1° composite mostly consistent in direction other than ACS – no difference. CKD outcomes: • 1° in CKD pts: reduction in GFR of ≥50% or ESRD HR: 0.89 (95% CI: 0.42, 1.87) • Incident albuminuria HR: 0.72 (95% 0.48, 1.07) • In pts without CKD: reduction in GFR ≥30% and to <60 • HR: 3.49 (95% CI: 2.44–5.10) • Incident albuminuria HR: 0.81 (95% CI: 0.63–1.04) Adverse events: • SAEs: 1.04; p=0.25 • Significant absolute increases seen in intensive group for hypotension (1%), syncope (0.6%), electrolyte abnormality (0.8%), acute kidney injury/acute renal failure (1.6%) over the study period.	Summary: • More intensive SBP lowering to a goal of <120 mm Hg with achieved mean of approximately 121 mm Hg resulted in less CVD and lower total mortality over 3.26 y in comparison with a goal SBP <140 mm Hg and achieved SBP of ~135 mm Hg. • There were small increases in some expected SAEs. Perhaps unexpected, a sizable increase in reduced eGFR in the non-CKD group and AKI/ARF overall was observed in the intensive group. While of uncertain etiology and significance, there is speculation this could be an acute hemodynamic effect, especially given the findings regarding albuminuria. Limitations: Few pts were untreated at baseline ~9%, so SPRINT provides little if any insight at present regarding BP-lowering medication initiation for untreated people with SBP 130–139.

				• 1.7% fewer pts had orthostatic hypotension in intensive group; p=0.01.	
Lawes MR, et al., 2009 (115) 16222626	Aim: • To determine the quantitative efficacy of different classes of BP-lowering drugs in preventing CHD and stroke, and who should receive treatment. • 5 questions encapsulate this uncertainty. 1st, do BBs have a special effect over and above lowering BP in preventing CHD events in people with a history of CHD? 2nd, does the effect of BP-lowering drugs in preventing CHD and stroke differ in people with and without a history of CVD (i.e., is there a different effect in 2° and 1° prevention)? 3rd, does BP reduction alone explain the effect of BP-lowering drugs in preventing CHD and stroke? 4th, should the use of BP-lowering drugs be limited to people with high BP and not given to those at high risk of CVD	Inclusion criteria: The database search (by MRL) used Medline (1966 to December 2007; any language) to identify randomized trials of BP-lowering drugs in which CHD events or strokes were recorded (irrespective of whether BP reduction was considered the mechanism of action). Search terms were "antihypertensive agents" or "HTN" or "diuretics, thiazide" or "adrenergic beta-antagonists" or "angiotensin-converting enzyme inhibitors" or "receptors, angiotensin/antagonists & inhibitors" or "tetrazoles" or "CCB s" or "vasodilator agents" or the names of all BP-lowering drugs listed in the British National Formulary as keywords or text words. Limits were Medline publication type "clinical trial" or "controlled clinical trial" or "RCT" or "meta-analysis". We also searched the Cochrane Collaboration and Web of Science databases and the citations in trials and previous meta-analysis and review articles. Exclusion criteria: We excluded nonrandomized trials and trials in which treated groups but not control groups	Intervention: BP-lowering medications Comparison: Placebo or less intensive treatment	1° endpoint: • CHD and stroke co-1° • Standardized to a 10/5 mm Hg BP reduction Overall CHD: 0.78 (95% CI: 0.73–0.83) Stroke: 0.59 (95% CI: 0.52–0.67) • In absence of vascular disease CHD: 0.79 (95% CI: 0.72–0.86) Stroke: 0.54 (95% CI: 0.45–0.65) • History of CHD CHD: 0.76 (95% CI: 0.68–0.86) Stroke: 0.65 (95% CI: 0.53–0.80) • History of stroke CHD: 0.79 (95% CI: 0.62–1.00) Stroke: 0.66 (95% CI: 0.56–0.79) • No big drug class effects except more benefit for BBs shortly after MI. • Treatment benefits seen down to pre-treatment SBP of 110–119 mm Hg for CHD events RR: 0.78 (95% CI: 0.63–0.96) and 130–139 mm Hg for stroke RR: 0.75 (95% CI: 0.63–0.89)	Summary: The effect of BP-lowering drugs in reducing the risk of disease is entirely or largely due to BP reduction, with 1 main exception, a special extra effect of BBs in people who have had a recent MI The proportional reduction in CHD events and stroke for a given reduction in BP, an approximate halving in risk for each 10 mm Hg diastolic reduction, is the same in people with and without a history of vascular disease and in people without high BP as well as in those with high BP There is benefit in lowering BP in anyone at sufficient CV risk whatever their BP, so avoiding the need to measure BP routinely. Limitation: • Most of the pts without HTN were in the trials of people with pre-existing CVD; hence, most of the results of BP lowering in people with SBP<140 are in people with CVD. • No absolute risks or benefits provided. Not possible to estimate how far down the risk curve these results apply. Interpretation: This MA provides stronger support for

	who have a lower BP? A corollary is whether BP should be reduced to a limited extent only, a treat to target approach. Although cohort (prospective\observational) studies do not show a lower BP limit below which risk ceases to decline ("the lower the better"), this has not been shown in randomized trials across a wide range of BP. Finally, what is the quantitative effect of taking ≥1 BP-lowering drugs in lowering BP and preventing CHD events and stroke according to dose, pretreatment BP, and age? To date no such quantitative summary of effect, taking account of these determining factors, has been made. Study type: Meta-analysis of RCTs Size: 147 RCTs of BP-lowering meds and CHD events (22,000) and stroke (12,000).	had other interventions as well as BP reduction, such as cholesterol reduction. We excluded trials in pts with chronic renal failure because these pts typically have high BP and high rates of CVD and their response to standard BP-lowering therapy may differ from other people. We also excluded trials in which fewer than 5 CHD events and strokes were recorded or the duration of treatment was less than 6 mo, as these data would contribute little to the overall results and substantially increase the complexity of the analyses. RCTs were otherwise included irrespective of pt age, disease status, BP before treatment, or use of other drugs.			treating at levels <140 for people with CVD than for people without CVD.

Lewington S, et al., 2002 (16) 12493255	Aim: To describe the age-specific relevance of BP to cause-specific mortality Study type: Meta-analysis of cohort studies Size: 61 prospective studies with 12.7 million person-y of observation, 56,000 vascular deaths in 40–89 y.	Inclusion criteria: Collaboration was sought from the investigators of all prospective observational studies in which data on BP, blood cholesterol, date of birth (or age), and sex had been recorded at a baseline screening visit, and in which cause and date of death (or age at death) had been routinely sought for all screens during more than 5,000 person-y of follow-up (see appendix A; http://image.thelancet.com/extras/01art8300webappendixA.pdf). Relevant studies were identified through computer searches of Medline and Embase, by hand-searches of meeting abstracts, and by extensive discussions with investigators. Exclusion criteria: To minimize the effects of reverse causality (whereby established disease could change the usual BP), studies were excluded if they had selected pts on the basis of a positive history of stroke or heart disease, and individuals from contributing studies were excluded from the present analyses if they had such a history recorded at baseline.	Intervention: N/A Comparator: N/A • The exposures of interest were the level of SBP and DBP and age-group.	1° endpoint: • Not completely clear, but for our purposes, stroke and IHD death would be co-1°. Also looked at other vascular deaths. • HRs for stroke mortality for a 20 mm Hg lower SBP by age-group 40–49: 0.36 (95% CI: 0.32–0.40) 50–59: 0.38 (95% CI: 0.35–0.40) 60–69: 0.43 (95% CI: 0.41–0.45) 70–79: 0.50 (95% CI: 0.48–0.52) 80–89: 0.67 (95% CI: 0.63–0.71) • HRs for IHD mortality for a 20 mm Hg lower SBP by age-group 40–49: 0.49 (95% CI: 0.45–0.53) 50–59: 0.50 (95% CI: 0.49–0.52) 60–69: 0.54 (95% CI: 0.53–0.55) 70–79: 0.60 (95% CI: 0.58–0.61) 80–89: 0.67 (95% CI: 0.64–0.70) • HRs for other vascular mortality for a 20 mm Hg lower SBP by age-group 40–49: 0.43 (95% CI: 0.38–0.48) 50–59: 0.50 (95% CI: 0.47–0.54) 60–69: 0.53 (95% CI: 0.51–0.56) 70–79: 0.64 (95% CI: 0.61–0.67) 80–89: 0.70 (95% CI: 0.65–0.75) • Similar results for DBP also in figure 1. • Similar results for men and women separately for stroke, figure 3, and IHD, figure 5.	Summary: Throughout middle and old age, usual BP is strongly and directly related to vascular (and overall) mortality, without any evidence of a threshold down to at least 115/75 mm Hg.
Thomopoulos C, et al., 2014 (20) 25259547	Aim: Investigating whether all grades of HTN benefit from BP-lowering treatment and which are the target	Inclusion criteria: Intentional BP-lowering comparing active drug treatment with placebo, or less active treatment (intentional BP-lowering trials), or comparison of an active drug	Intervention/Comparator: Criteria of eligibility were intentional BP-lowering comparing active drug treatment with placebo, or less active treatment	1° endpoint: • As some trials were done on low-risk pts, others on higher risk pts, no evaluation of absolute risk-reduction was made. However, a 2º analysis was done including	Summary: Meta-analyses favor BP-lowering treatment even in grade 1 HTN at low-to-moderate risk, and lowering SBP/DBP to <140/90 mm Hg. Achieving <130/80 mm Hg

	BP levels to maximize outcome reduction. Study type: Meta-analysis of RCTs Size: 32 RCTs with 104,359 pts	with placebo over baseline antihypertensive treatment, resulting in a BP difference of at least 2 mm Hg in either SBP or DBP (nonintentional BP-lowering trials); enrolling of hypertensive individuals only or a high proportion (at least 40%) of them. Exclusion criteria: N/A	(intentional BP-lowering trials), or comparison of an active drug with placebo over baseline antihypertensive treatment, resulting in a BP difference of at least 2 mm Hg in either SBP or DBP (nonintentional BP-lowering trials); enrolling of hypertensive individuals only or a high proportion (at least 40%) of them. Other inclusion criteria can be found in the preceding paper. 51 trials were found eligible either for assessing BP-lowering effects in different HTN grades or for assessing the effects of achieving different BP levels	trials or trial subgroups with mean baseline SBP/DBP values in grade 1 range and a low-to-moderate risk (<5% CV deaths in 10 y in controls): FEVER stratum with baseline SBP below the median (<153 mm Hg) (e7); HTN Detection and Follow-up Program stratum with baseline DBP 90–94 mm Hg and no CVD (e9); OSLO (e17); TOMHS (e28) and USPHS (e29). Risks of stroke, CHD, the composite of stroke and CHD, and all-cause death were significantly reduced by BP-lowering in these low-to-moderate risk pts (control group: average CV mortality 4.5% in10 y) with a moderate BP elevation (average SBP/DBP 145.5/91 mm Hg) at randomization. Standardized risk ratio associated with 10/5 reduction in BP: stroke 0.33 (95% CI: 0.11–0.98) CHD 0.68 (95% CI: 0.48–0.95) CVD death 0.57 (95% CI: 0.32–1.02) total death 0.53 (95% 0.35–0.80) • Compared outcomes of achieved on study SBP <130 vs. ≥130 Standardized Risk ratio associated with 10/5 reduction in BP: stroke 0.68 (95% CI: 0.57, 0.83) CHD 0.87 (95% CI: 0.76, 1.00) HF 0.92 (95% CI: 0.47, 1.77) CVD 0.81 (95% CI: 0.67, 1.00) CVD death 0.88 (95% CI: 0.77, 1.01) total death 0.88 (95% CI: 0.77, 0.99) • Outcomes of achieved on study SBP 130–139 vs. ≥140	appears safe, but only adds further reduction in stroke.

				Standardized Risk ratio associated with 10/5 reduction in BP: stroke 0.63 (95% CI: 0.52–0.77) CHD 0.77 (95% CI: 0.70–0.86) HF 0.76 (95% CI: 0.47–1.25) CVD 0.74 (95% CI: 0.62–0.88) CVD death 0.81 (95% CI: 0.67–0.97) total death 0.87 (95% CI: 0.75–1.00) • Similar pattern of results for on treatment DBP.	
Lonn EM, et al., 2016 (116) 27041480	Aim: To assess efficacy of fixed-dose antihypertensive therapy in adults with intermediate CVD risk. Study type: Double-blind, placebo-controlled RCT, factorial design Size: 12,705 pts	Inclusion criteria: Men ≥55 y and women ≥60 y at intermediate risk for CVD. No BP restrictions. Exclusion criteria: • Known CVD • Indications or contraindications to study meds • Mod/advanced CKD • Symptomatic hypotension	Intervention: FDC of ARB (candesartan 16 mg/d) and diuretic (hydrochlorothiazide 12.5 mg/d) or placebo Follow-up: Median=5.6 y	1° endpoint: 1 co-1° CVD composite outcomes • CVD mortality, nonfatal MI, nonfatal stroke • Above plus cardiac arrest, HF, revascularization	Summary: • SBP/DBP reduction of 6.0/3.0 mm Hg • No difference in treatment effect • 1st co-1° 0.93 (0.79–1.10) • 2nd co-1° 0.95 (0.81–1.11) • Suggestion of a subgroup effect in tertile with the highest baseline BP and increased CVD risk.
Neaton JD et al., 1993 (117) 8336373	Aim: To compare 6 antihypertensive drugs (representing different drug classes) Study type: Double-blind, placebo-controlled RCT Size: 902 pts with stage 1 HTN	Inclusion criteria: • Men and women 45–69 y • Not taking antihypertensive medications, with DBP 90–99 mm Hg • Taking 1 antihypertensive medication, with DBP <95 mm Hg and between 85–99 mm Hg after withdrawal of BP medications	Intervention: Treatment (number): Once daily (AM): • Placebo (234) • Chlorthalidone 15 mg/d (136) • Acebutolol 400 mg/d (132) • Doxazosin 2 mg/d (134) • Amlodipine 5 mg/d (131) • Enalapril 5 mg/d (135) Follow-up: Median=4.4 y	1° endpoint: BP, QoL, side effects, chemistries, ECG, clinical events	Summary: • Drugs (plus diet) more effective compared to placebo (plus diet) for control of BP. • Minimal differences between drug regimens

Van Dieren S, et al., 2012 (118) 22677192	Aim: To assess differences in treatment effects of a fixed combination of perindopril–indapamide on major clinical outcomes in pts with type 2 DM across subgroups of CV risk. Study type: RCT Size: 11,140 pts with DM-2, from the ADVANCE trial	Inclusion criteria: DM-2, aged ≥55 y, with a history of major macrovascular or microvascular disease, or at least 1 other risk factor for vascular disease Exclusion criteria: A definite indication for, or contraindication to, any of the study treatments, a definite indication for long-term insulin treatment or were participating in any other clinical trial.	Intervention: Perindopril–indapamide or matching placebo	1° endpoint: • The Framingham equation was used to calculate 5-y CVD risk and to divide participants into 2 risk groups, moderate-to-high risk (<25% and no history of macrovascular disease), very high risk (>25% and/or history of macrovascular disease). • Endpoints were macrovascular and microvascular events.	Summary: Relative effects of BP-lowering with perindopril–indapamide on CV outcomes were similar across risk groups whilst absolute effects trended to be greater in the high-risk group.
Montgomery AA, et al., 2003 (119) 12923409	Aim: To estimate the effectiveness and cost-effectiveness of BP-lowering treatment over a lifetime. Study type: Markov decision analysis model comparing treatment and nontreatment of HTN. Size: Hypothetical cohorts for 20 different strata of sex, age (30–79 y, in 10-y bands), and CV risk (low and high)	Inclusion criteria: We created models for 20 different strata of sex, age (age 30–70 y in 10-y bands), and 2 risk profiles (designated as 'low' and 'high' risk). These example risk profiles represent the extremes of absolute CV risk, based on data from the Health Survey for England and using a Framingham risk function. We recognize that the risk of most individuals seen in primary care will be somewhere between the examples presented here. The data included were as follows: age- and sex-specific mean SBP of untreated individuals with SBP>0.160 mm Hg were used for both high-risk and low-risk profiles. In addition, low-risk profile was defined as nonsmoker, 10th percentile total cholesterol 90th percentile HDL	Intervention: Treatment and nontreatment of HTN.	1° endpoint: Life expectancy, and incremental cost: effectiveness ratios for treatment and nontreatment strategies	• Probabilities of clinical events were obtained from published literature. Summary: • Incremental cost per quality-adjusted life y among low-risk groups ranged from £1,030 to £3,304. Cost-effectiveness results for low-risk pts were sensitive to the utility of receiving antihypertensive treatment. Treatment of high-risk individuals was highly cost-effective, such that it was the dominant strategy in the oldest age group, and resulted in incremental costs per quality-adjusted life y ranging from £34–£265 in younger age groups. • Policy decisions about which pts to treat depend on whether a life-expectancy or cost-

		cholesterol, no DM, and no LVH, and high-risk profile was defined as smoker, 90th percentile total cholesterol, 10th percentile HDL cholesterol, DM, and LVH. Exclusion criteria: N/A			effectiveness perspective is taken. Treatment increases life expectancy in all strata of age, sex, and CV risk. However, younger individuals stand to gain proportionately more from BP treatment than do the elderly. In terms of cost-effectiveness, pts at high risk of CVD are a highly cost-effective group to treat. In pts at lower risk of CVD, consideration should be given to issues of pt preference and cost.
Kassai B, et al., 2005 (120) 17315403	Aim: Consideration of absolute risk has been recommended for making decisions concerning preventive treatment in HTN. Aim to estimate the benefit of antihypertensive therapy over a life-time. Study type: Meta-analysis on individual data in HTN and specific cause of death from national statistics. Disease-free survival curves until all pts have died were built using the "life-table" method. The treatment effect estimated from INDANA was applied to this curve to obtain the disease-free	Inclusion criteria: To estimate the rate of cv and non-CV deaths in a hypothetical U.S. population of untreated hypertensive pts, we used the following procedure: age-specific death rates in the U.S. general population were obtained from national vital statistics (1994), and in untreated hypertensive population they were obtained from the control groups of the INDANA database. This latter group represents a unique cohort of 14 942 untreated or placebo-treated hypertensive pts, 26–96 y with an average follow-up of 5 y Exclusion criteria: N/A	Intervention: The gain in life expectancy without stroke, CHD, and CV events was estimated from the area between the 2 survival curves of treated and control groups. The relative gain in life expectancy was defined as the ratio of gain in life expectancy to life expectancy.	1° endpoint: Stroke and CHD co-1° Results: CHD Age Y RRa ABb (%) NNTc RGLEe GLEd (%) 40 0.86 0.3 333 20 4.1 50 0.88 1.0 100 17 4.3 60 0.90 1.9 53 13 3.4 70 0.91 3.9 26 10 5.4 Stroke Age Y RRa ABb (%) NNTc RGLEe GLEd (%) 40 0.80 0.4 250 32 5.9 50 0.84 1.0 100 26 5.7 60 0.86 2.3 44 21 7.1 70 0.87 5.7 18 17 9.1 a RR at 10 y b Absolute benefit at 10 y c NNT to avoid 1 event. d Gain in life expectancy in mo without events.	Summary: Absolute gains in life expectancy are likely to be greater for younger, lower risk people with HTN than for older, higher risk people with HTN. However, the NNT to prevent an event will likely be greater especially in the short term in younger, lower risk people. This modeling analysis provides support for treating younger, lower risk individuals with HTN, but relies on the assumption that the relative benefits of treatments observed in short-term trials of higher risk individuals applies over a longer term to lower risk individuals.

	survival curve of the life-long treated population. Gains in event-free life expectancy were estimated from survival curves. A sensitivity analysis was performed to assess the impact of possible death misclassifications. Size: 6 RCTs, ~30,000 pts			e Relative gain in life expectancy without events.	
Czernichow S et al., 2011 (121) 20881867	Aim: The objective of this systematic review and meta-analysis was to compare the relative reductions in risk achieved with different starting levels of BP (and treatment regimens). Study type: Meta-analysis of RCTs Size: 32 trials with 201,566 pts (20,079 1° outcome events)	Inclusion criteria: RCTs of BP-lowering (drug vs. control or less intensive treatment) or different classes of drug therapy that included a minimum of 1,000 pt-y of follow-up in each study arm. Exclusion criteria: <1,000 pt-y of follow-up in each treatment group.	Intervention: BP-lowering meds Comparator: Placebo, active comparator or less intensive treatment	1° endpoint: • Major CVD events (stroke, CHD, and HF. • No evidence of differences in the ratio of risk across varying levels of baseline BP (with all classes of BP-lowering medications).	Summary: • Effectiveness of BP-lowering regiments in reducing RR of major CVD events does not seem to be influenced by starting level of BP. Limitations: • The majority of the participants studied were at high risk for CVD. • Information pertaining to the effect of treatment on absolute risk was not presented in this manuscript.

Data Supplement 24. Follow-Up After Initial BP Evaluation (Section 8.1.3)

Study Acronym; Author; Year Published	Aim of Study; Study Type; Study Size (N)	Patient Population	Study Intervention (# patients) / Study Comparator (# patients)	Endpoint Results (Absolute Event Rates, P value; OR or RR; & 95% CI)	Relevant 2° Endpoint (if any); Study Limitations; Adverse Events; Summary

Ambrosius WT, et al., 2014 (122) 24902920	Aim: To describe the study design of the SPRINT Study type: SPRINT RCT	Inclusion criteria: Adults ≥50 y, average SBP ≥130 mm Hg and evidence of CVD, CKD, or 10-y Framingham risk score ≥15%, or ≥75 y	Intervention: 9,361 pts randomized to 2 treatment groups: • Standard treatment group, SBP target <140 mm Hg • Intensive treatment group: SBP target <120 mm Hg.	1° endpoint: MI, ACS, stroke, HF, or CVD death.	Relevant 2° endpoint: All-cause mortality, decline in kidney function or development of ESRD, incident dementia, decline in cognitive function, and small-vessel cerebral ischemic disease Summary: This paper describes the protocol followed in the SPRINT trial that was successful in helping participants to attain and maintain BP targets in the study groups. Once treated, participants had follow-up visits to assessment BP control monthly until BP was at target. Medications were titrated and added as per protocol, when target BP was not attained.
Cushman WC, et al., 2007 (123) 17599425	Aim: To describe the study design of the BP trial of the ACCORD Trial Study type: Description of study design and protocol for the ACCORD RCT	Inclusion criteria: Adults with a diagnosis of DM-2 for at least 3 mo and at high risk for CVD events, who meet the following BP criteria: (1) SBP 130–160 mm Hg and taking 0–3 antihypertensive medications; (2) SBP 161–170 and on 0–2 antihypertensive medications; or (3) SBP 171-180 and taking 0-1 antihypertensive medication. Other entry criteria included spot urine sample <2+, protein–Cr ratio <700 mg protein/1 g Cr, or 24-h protein excretion <1.0 g/24 h.	Intervention: • Unmasked, open-label, factorial design, randomized trial with a sample size of 4,733 pts • Pts randomized to intensive SBP control (<120 mm Hg) or standard control (<140 mm Hg)	1° endpoint: Major CVD event (nonfatal MI or stroke, or CV death)	Relevant 2° endpoint: Expanded macrovascular outcome (1° outcome plus coronary revascularization or HF hospitalization), total mortality, each of the separate components of the 1° outcome, HF death or hospitalization, and composite microvascular disease outcome (kidney and eye disease). Summary: This paper describes the protocol followed in the ACCORD trial that was successful in helping participants to attain and maintain BP targets in the study groups. Once treated, participants had follow-up visits to assessment BP control monthly until BP was at target. Medications were titrated and added as per protocol, when target BP was not attained.

Data Supplement 25. RCTs for General Principles of Drug Therapy (Combination Therapies that Inhibit the RAAS) (Section 8.1.4)

Study Acronym; Author; Year Published	Aim of Study; Study Type; Study Size (N)	Patient Population	Study Intervention (# patients) / Study Comparator (# patients)	Endpoint Results (Absolute Event Rates, P value; OR or RR; & 95% CI)	Relevant 2° Endpoint (if any); Study Limitations; Adverse Events
VA NEPHRON-D Fried LF, et al., 2013 (124) 24206457	Aim: Assess the efficacy of combination of an ACEI and an ARB vs. ARB monotherapy in reducing the progression of proteinuric diabetic nephropathy Study type: Multicenter, double-blind, RCT at 32 VA Medical Centers Size: 1448 pts	Inclusion criteria: Pts with type 2 DM, a urinary albumin-to-creatinine ratio of ≥300, and an eGFR 30.0–89.9 mL/min/1.73 m^2 Exclusion criteria: • Subjects with known nondiabetic kidney disease • Serum K+ >5.5 mmol/L • Current treatment with sodium polystyrene sulfonate • Inability to stop prescribed medication that increases the risk of hyperkalemia	Intervention: Losartan 100 mg daily plus lisinopril 10–40 mg daily (n=724) Comparator: Losartan 100 mg daily plus placebo (n=724)	1° endpoint: After a median follow-up of 2.2 y, the study was stopped early due to safety concerns. There was no difference in the 1° outcome of first occurrence of change in eGFR (decrease of ≥30 mL/min/1.73 m^2 if initial GFR was ≥60 mL/min/1.73 m^2 or a decline of ≥50% if initial eGFR was <60 mL/min/1.73 m^2), ESRD, or death (HR with combination therapy: 0.88; 95% CI: 0.70–1.12; p=0.30). Safety endpoint: Combination therapy increased the risk of hyperkalemia (HR: 2.8; 95% CI: 1.8–4.2; p<0.001) and acute kidney injury (HR: 1.7; 95% CI: 1.3–2.2; p<0.001).	2° endpoint: There was no difference in the 2º endpoint of first occurrence of change in eGFR or ESRD (HR: 0.78; 95% CI: 0.58–1.05; p=0.10). There were no differences between combination therapy or losartan monotherapy for the endpoints of ESRD, death, composite of MI, HF, or stroke, MI, CHF, and stroke (p>0.05 for all). Summary: Combination therapy of losartan plus lisinopril did not improve renal outcomes compared to losartan alone, and was associated with greater risk of acute kidney injury and hyperkalemia.
ALTITUDE Parving HH, et al., 2012 (125) 23121378	Aim: Determine if addition of aliskiren as an adjunct to an ACEI or ARB reduces the risk of CV and renal events in pts with type 2 DM	Inclusion criteria: • ≥35 y with type 2 DM • On ACEI or ARB • At least 1 of the following: persistent macroalbuminuria (urine microalbumin to creatinine ratio ≥200 mg/g) and eGFR ≥30 mL/min/1.73 m^2, persistent microalbuminuria (≥20 mg/g and <200 mg/g) and a mean eGFR ≥30 and <60	Intervention: Aliskiren 300 mg daily added to conventional treatment with an ACEI or ARB (n=4,274) Comparator: Placebo (n=4,287)	1° endpoint: After a median follow-up of 32.9 mo the study was stopped early. There was no difference in the 1° composite outcome death from CV causes or first occurrence of cardiac arrest with resuscitation; nonfatal MI; nonfatal stroke;	2° endpoint: • There was no difference between aliskiren and placebo for the individual components of the composite 1° outcome (all p>0.05) other than cardiac arrest with resuscitation, which was increased significantly with aliskiren (HR: 2.40; 95% CI: 1.05–5.48; p=0.04).

	Study type: Doubled-blind, multicenter RCT Size: 8561	mL/min/1.73 m^2, or history of CVD (e.g., MI, stroke, HF, or CAD) and a mean eGFR ≥30 and <60 mL/min/1.73 m^2 Exclusion criteria: • Serum K+ >5.0 mmol/L • Type 1 DM • Unstable serum Cr • CV history (NYHA Class III or IV, SBP ≥170 mm Hg or DBP ≥110 mm Hg or SBP ≥135 and <170 mm Hg or DBP ≥82 and <100 mm Hg with at least 3 agents, 2nd or third degree heart block, renal artery stenosis • Surgical or medical conditions (malignancy in last 5 y, <2 y life expectancy, renal transplant or immunosuppressive therapy, drug/alcohol abuse, hypersensitivity/allergy/contraindication to study drugs, pregnancy) • Concomitant treatment with ≥2 agents blocking RAAS or K^+-sparing diuretics.		unplanned hospitalization for HF; ESRD; death attributable to kidney failure or need for renal-replacement therapy with no dialysis or transplantation available or initiated; or doubling of the baseline serum Cr between aliskiren or placebo (HR: 1.08; 95% CI: 0.98–1.20; p=0.12). Safety endpoint: The combination of aliskiren added to an ACEI or an ARB was associated with greater risk of hyperkalemia and hypotension (11.2% vs. 7.2% and 12.8% vs. 8.3%; p<0.001 for both, respectively).	• There was no differences in CV composite outcome, renal composite outcome, or death from any cause (p>0.05 for all) Summary: Aliskiren added to background treatment of an ACEI or ARB did not decrease CV or renal outcomes, and was associated with increased risk of cardiac arrest with resuscitation, hyperkalemia, and hypotension.
ONTARGET Yusuf S, et al., 2008 (126) 18378520	Aim: Evaluate whether use of an ARB was noninferior to ACEI, and whether the combination was superior to ACE alone in the prevention of vascular events in pts with CVD or DM but not HF. Study type: Multi-center, double-blind, RCT	Inclusion criteria: • ≥55 y • Coronary, peripheral, or cerebrovascular disease or DM with end-organ damage Exclusion criteria: • Inability to discontinue ACEI or ARB • Known hypersensitivity or intolerance to ACEI or ARB • Selected CVDs (congestive HF, hemodynamically significant valvular or outflow tract obstruction, constrictive pericarditis, complex congenital heart disease, syncopal episodes of unknown etiology <3 mo, planned cardiac surgery	Intervention: Ramipril 10 mg daily (n=8,576) Comparator: • Telmisartan 80 mg daily (n=8,542) • Combination of telmisartan and ramipril (n=8,502)	1° endpoint: After a median follow-up of 56 mo, there was no difference between ramipril vs. telmisartan or combination therapy vs. ramipril in the 1° composite outcome of death from CV causes, MI, stroke, or hospitalization for HF (RR: 1.01; 95% CI: 0.94–1.09 and RR: 0.99; 95% CI: 0.92–1.07, respectively) Safety endpoint: • Combination therapy was associated with greater risk of hyperkalemia than	2° endpoint: • There was no difference in composite of death from CV causes, MI, or stroke in the ramipril vs. telmisartan groups RR: 0.99; 95% CI: 0.9–1.07); p=0.001 or ramipril vs. combination RR: 1.00; 95% CI: 0.93–1.09 • There were no differences between ramipril vs. telmisartan or ramipril vs. combination therapy in 2º outcomes including MI, stroke, hospitalization for HF, death from CV causes, death from non-CV causes, or death from any cause (p>0.05 for all).

	Size: 25,620	or PTCA <3 mo, uncontrolled HTN on treatment [e.g., BP >160/100 mm Hg], heart transplant recipient, stroke due to subarachnoid hemorrhage) • Other conditions (significant renal artery disease, hepatic dysfunction, uncorrected volume or sodium depletion, 1° hyperaldosteronism, hereditary fructose intolerance, other major noncardiac illness or expected to reduce life expectancy or significant disability interfere with study participation, simultaneously taking another experimental drug, unable to provide written informed consent).		ramipril monotherapy (480 pts vs. 283 pts; p<0.001) • Hypotensive symptoms were cited as reason for permanent discontinuing more in telmisartan vs. ramipril (RR: 1.54; p<0.001) and combination therapy vs. ramipril monotherapy (RR: 2.75; p<0.001) • Renal impairment was more common in combination therapy vs. ramipril monotherapy RR: 1.33; 95% CI: 1.2–1.44	Summary: Combination therapy with telmisartan and ramipril did not decrease the risk of CV events in pts at high risk compared to monotherapy with ramipril. In addition, combination therapy was associated with increased risk of hypotension, hyperkalemia, and renal impairment.

Data Supplement 26. BP Goal for Patients with Hypertension (Section 8.1.5)

Study Acronym (if applicable) Author Year Published	Study Type/Design; Study Size (N)	Patient Population	Study Intervention (# patients) Study Comparator (# patients)	Primary Endpoint and Results (include P value; OR or RR; & 95% CI)	Summary/Conclusion Comment(s)
Lawes CM, et al., 2003 (50) 12658016	Study type: Meta-analysis of RCTs of BP drugs recording CHD events and strokes Size: 464,000 pts	N/A	N/A	• CHD RR or 46% Stroke 64%	• All classes of BP meds confer benefit while BB confer greater benefit in those with CAD
LV J, et al., 2013 (127) 23798459	Study type: MA of RTC that randomly assigned individuals to different target BP levels Size: 15 trials including a total of 37,348 pts	N/A	N/A	7.5/4.5 mm Hg BP difference. Intensive BP lowering achieved. RR for • Major CV events: 11%; 95% CI: 1%–21%) • MI: 13%; 95% CI: 0%–25%	• More intensive strategy for BP control reduced cardio-renal endpoint

				• Stroke: 24%; 95% CI: 8%–37% • ESRD: 11%; 95% CI: 3%–18% • Albuminuria: 10%; 95% CI: 4%–16% • Retinopathy 19%; 95% CI: 0%–34% p=0.051	
Xie X, et al., 2015 (21) 26559744	Study type: MA of RTC that randomly assigned individuals to different target BP levels Size: 19 trials (n=44,989)	N/A	N/A	Achieved BP 133/76 mm Hg (intensive) 140/81 (less intense) • Major CV events: 14%; 95% CI: 4%–22% • MI: 13%; 95% CI: 0%–24% • Stroke: 22%; 95% CI: 10%–32% • Albuminuria: 10%; 95% CI: 3%–16% • Retinopathy progression: 19%; 95% CI: 0%–34%. • More intensive had no effects on HF: 15%; 95% CI: -11%–34% • CV death: 9%; 95% CI: -11%–26% • Total mortality: 9%; 95% CI: -3%–19% • ESKD: 10%; 95% CI: -6%–23%	• More intensive approach reduced major CV events (stroke and MI) except heat failure, CVD, ESRD, and total mortality.

Verdecchia P et al., 2016 27456518	Study type: Cumulative meta-analysis of RCTs to study benefit of more vs. less intensive BP lowering Size: 18 trials (n=53,405)	N/A	N/A	• Stroke, MI, HF, CVD mortality, and all-cause mortality • Difference in achieved SBP/DBP=7.6/4.5 mm Hg • For stroke and MI the cumulative Z score crossed the efficacy boundary after addition of the SPRINT results • For CVD mortality and HF, the cumulative Z curve crossed the conventional significance boundary (but not the sequential monitoring boundary) • For all-cause mortality, the cumulative Z curve did not reside in the futility are but did not cross the conventional significance boundary	• The results strongly supported the benefit of intensive BP reduction for prevention of stroke and MI and suggested benefit for prevention of CVD mortality and HF
Bangalore S, et al., 2017 28109971	Study type: Network meta-analysis in which the authors attempted to compare the benefits and adverse effects resulting from intensive reduction in SBP Size: 17 trials (n=55,163)	N/A	N/A	• There was a significant reduction in stroke (RR: 0.54) and MI (RR: 0.68) • The point estimate favored all-cause mortality, CVD mortality and HF but the results did not achieve significance • SBP targets <120 and <130 mm Hg ranked #1 and #2 as the most efficacious • Serious adverse effects were more common at a lower SBP (120 vs. 150 or 140 mm Hg)	• Overall, the beneficial effects of treatment were consistent with other reports. The cluster plots of treatment benefit vs. risk are difficult to interpret due to limitations of the available data base and the authors' decision to weight treatment benefits and potential adverse effects equally.

				• Cluster plots for combined efficacy and safety suggested a SBP <130 mm Hg as the optimal target for SBP reduction during treatment	
Bundy JD, et al., 2017 28564682	Study type: Systematic review and network meta-analysis to assess the benefits of intensive SBP reduction during treatment of hypertension Size: 42 trials (n=144,220)	N/A	N/A	• In general, there were linear associations between achieved SPB and risk of CVD and all-cause mortality, with the lowest risk at a SBP of 120–124 mm Hg.	• This was by far the largest and best powered meta-analysis to assess the relationship between SBP reduction and major outcomes during treatment of hypertension. The findings provided strong evidence for the "lower is better" approach to treatment in patients with a high SBP who are at high risk for CVD.
Lawes CMM, et al., 2002 16222626	Study type: Review of observational reports and randomized controlled trials	N/A	N/A	• The relative benefits of BP lowering for CHD prevention likely to be consistent across a wide range of different populations • Likely to be considerable benefit for BP lowering beyond traditional thresholds, especially in those at high risk for CVD • BP lowering is likely to be more important than choice of initial agent • A large majority of patients being treated for	• Strongly supports lower BPs during BP treatment, especially in those at high risk of CVD

				hypertension have suboptimal BPs. Initiatives to lower their BP further are essential	

Study Acronym; Author; Year Published	Aim of Study; Study Type; Study Size (N)	Patient Population	Study Intervention (# patients) / Study Comparator (# patients)	Endpoint Results (include Absolute Event Rates, P value; OR or RR; and 95% CI)	Relevant 2° Endpoint (if any); Study Limitations; Adverse Events
Xie X, et al., 2015 (21) 26559744	Aim: To assess the efficacy and safety of intensive BP-lowering strategies. Study type: Meta-analysis of RCTs Size: 19 RCTs with 44,989 pts	Inclusion criteria: RCTs with at least 6 mo follow-up that randomly assigned pts to more intensive vs. less intensive BP-lowering treatment, with different BP targets or different BP changes from baseline. Reference lists from identified trials and review articles were manually scanned to identify any other relevant studies. Exclusion criteria: N/A	Intervention: BP-lowering meds Comparator: • Less intensive treatment • BP difference 6.8/3.5 • The mean follow-up BP levels in the less intensive BP-lowering regimen group were 140/81 mm Hg, compared with 133/76 mm Hg in the more intensive treatment group.	1° endpoint: • CVD, other major CV events, defined as a MI, stroke, HF, or CV death, separately and combined; nonvascular and all-cause mortality; ESKD, and adverse events. Progression of albuminuria (defined as new onset of micro-albuminuria/macro-albuminuria or a change from micro-albuminuria to macro-albuminuria) and retinopathy (retinopathy progression of 2 or more steps) were also recorded for trials that were done in pts with DM • CVD RR: 0.86 (95% CI: 0.78–0.96)	Summary: Intensive BP-lowering, including to <130 mm Hg, provided greater vascular protection than standard regimens. In high-risk pts, there are additional benefits from more intensive BP-lowering, including for those with SPB <140 mm Hg at baseline. The net absolute benefits of intensive BP-lowering in high-risk individuals are large. Limitations: • Lack of individual pt data, which would have allowed a more reliable assessment of

				<u>Other endpoints:</u> • MI RR: 0.87 (95% CI: 0.76–1.00) p=0.042 • Stroke RR: 0.78 (95% CI: 0.68–0.90) • HF RR: 0.85 (95% CI: 0.66–1.11) • CVD death RR: 0.91 (95% CI: 0.74–1.11) • Total deaths RR: 0.91 (95% CI: 0.81–1.03) <u>Other results:</u> • Benefit for CVD not different by baseline SBP 120–139: 0.89 (95% CI: 0.76–1.05) 140–160: 0.83 (95% CI: 0.68–1.00) >160: 0.89 (95% CI: 0.73–1.09) p-heterogeneity: 0.60 • Benefit for CVD not different for more intensive and less intensive targets in intensive group <140 or <150 mm Hg: 0.76 (95% CI: 0.60–0.97) <120– <130 mm Hg: 0.91 (95% CI: 0.84–1.00; p-hetero: 0.06) • Absolute benefits were proportional to absolute risk. • For trials in which all pts had vascular disease, renal disease, or DM at baseline, the average control group rate of major vascular events was 2·9% per y compared with 0·9% per y in other trials, and the numbers needed to treat were 94 (95%	treatment effects in different pt groups. • Interpretation: Supports treating pt with and without CVD at threshold of 130 to <130. Supports treating at threshold of about 130 even down to a CVD event rate of 0.9% per y.

				CI: 44–782) in these trials vs. 186 (95% CI: 107–708) in all other trials. • Increase in severe hypotension: 0.3% vs. 0.1% per person y OR: 2.68 (95% CI: 1.21–5.89)	
Julius S, et al., 2006 (55) 16537662	Study type: RCT in pre-HTN16 mg candesartan vs. placebo Size: 809 pts	• 58% men	N/A	• During the first 2 y, HTN developed in 154 (40.4%) pts in the placebo group compared with only 53 (13.6%) of those in the candesartan group, for a RR of 66.3% (p<0.0001). After 4 y, HTN developed in 240 (63.0%) in the placebo group vs. only 208 (53.2%) in the candesartan group RR 15.6% (p<0.0069).	• 2/3 of those with pre-HTN develop HTN within 4 y. Candesartan interrupts the onset and reduced by 15.6%
Lawes CM, et al., 2003 (50) 12658016	Study type: Meta-analysis of RCTs of BP drugs recording CHD events and strokes Size: 464,000 pts	N/A	N/A	• CHD RR or 46% Stroke 64%	• All classes of BP meds confer benefit while BB confer greater benefit in those with CAD
Lonn EM, et al., 2016 (116) 27041480	Aim: To assess efficacy of fixed-dose antihypertensive therapy in adults with intermediate CVD risk. Study type: Double-blind, placebo-controlled RCT, factorial design	Inclusion criteria: Men ≥55 y and women ≥60 y at intermediate risk for CVD. No BP restrictions. Exclusion criteria: • Known CVD • Indications or contraindications to study meds • Mod/advanced CKD • Symptomatic hypotension	Intervention: FDC of ARB (candesartan 16 mg/d) and diuretic (hydrochlorothiazide 12.5 mg/d) or placebo Follow-up: Median=5.6 y	1° endpoint: 1 co-1° CVD composite outcomes • CVD mortality, nonfatal MI, nonfatal stroke • Above plus cardiac arrest, HF, revascularization	Summary: • SBP/DBP reduction of 6.0/3.0 mm Hg • No difference in treatment effect • 1st co-1° 0.93 (0.79–1.10) • 2nd co-1° 0.95 (0.81–1.11)

	Size: 12,705 pts				• Suggestion of a subgroup effect in tertile with the highest baseline BP and increased CVD risk.
Neaton JD, et al., 1993 (117) 8336373	Aim: To compare 6 antihypertensive drugs (representing different drug classes) Study type: Double-blind, placebo-controlled RCT Size: 902 pts with stage 1 HTN	Inclusion criteria: • Men and women 45–69 y • Not taking antihypertensive medications, with DBP 90–99 mm Hg • Taking 1 antihypertensive medication, with DBP <95 mm Hg and between 85–99 mm Hg after withdrawal of BP medications	Intervention: Treatment (number): Once daily (AM): • Placebo (234) • Chlorthalidone 15 mg/d (136) • Acebutolol 400 mg/d (132) • Doxazosin 2 mg/d (134) • Amlodipine 5 mg/d (131) • Enalapril 5 mg/d (135) Follow-up: Median=4.4 y	1° endpoint: BP, QoL, side effects, chemistries, ECG, clinical events	Summary: • Drugs (plus diet) more effective compared to placebo (plus diet) for control of BP. • Minimal differences between drug regimens

Data Supplement 27. Choice of Initial Medication (Section 8.1.6)

Study Acronym Author Year Published	Aim of Study; Study Type; Study Size (N)	Patient Population	Study Intervention (# patients) / Study Comparator (# patients)	Endpoint Results (Absolute Event Rates, P value; OR or RR; & 95% CI)	Relevant 2° Endpoint (if any); Study Limitations; Adverse Events; Summary
Psaty BM, et al., 2003 12759325	Study type: Network meta-analysis to compare value of different first-line antihypertensive drugs in prevention of major CVD and all-cause mortality Size: 42 trials (n=192,478)	N/A	• For all outcomes, low-dose diuretics were better than placebo • None of the other first-line agents (β-blockers, ACEI, CCBs, α-receptor blockers and ARBs) were superior to low-dose diuretics • For several outcomes, low-dose diuretics were superior to other agents	• Low-dose diuretics were identified as the most effective first-line treatment for prevention of CVD and all-cause mortality during treatment of hypertension	N/A

Brunström M, et al., 2016 (53) 26920333	Study type: Meta-analysis of levels of BP control in DM hypertensives. Size: 73,738 pts	• 49 trials (most pts with DM-2)	Baseline SBP >150 RR for • All death: 0.89; 95% CI:0.80–0.99 • CVD: 0.75; 95% CI: 0.57–0.99 • MI: 0.74; 95% CI: 0.63–0.87 • Stroke: 0.77; 95% CI: 0.65–0.91 • ESRD: 0.82; 95% CI: 0.71–0.94 Baseline SBP140–150 RR of • Death: 0.87; 95% CI: 0.78–0.98) • MI: 0.84; 95% CI: 0.76–0.9 • HF: 0.80; 95% CI: 0.66–0.97 If baseline SBP,140 mm Hg, however, further treatment increased the risk of CV mortality (1.15; 95% CI: 1.00–1.32	• BP lowering reduces major CV events in DM. Caution for initiating treatment in diabetics with SBP <140/90	N/A
Ettehad D, et al., 2015 (17) 26724178	Study type: Meta-analysis of large RTCs of antihypertensive treatment Size: 123 studies (613,815 pts)	N/A	Every 10 mm Hg reduction in SBP RR: • Major CV events: 0.80; 95% CI: 0.77–0.83 • CHD: 0.83; 95% CI: 0.78–0.88 • Stroke: 0.73; 95% CI: 0.68–0.77), HF (0.72, 0.67–0.78 • All-cause mortality: 0.87; 95% CI: 0.87; 0.84–0.91 • ESRD: 0.95; 0.84–1.07	• BP lowering reduces CV risk across various baseline BP levels and comorbidities. Suggest lowering SBP <130 mm Hg and BP-lowering treatment to pts with a history of CVD, CHD, stroke, DM, HF, and CKD.	N/A
Thomopolous C, et al., 2016 (54) 26848994	Study type: Meta-analysis of RTCs of more vs. less intense BP control	• 16 trials (52,235 pts) compared more vs. less intense treatment 34 (138,127 pts) active vs. placebo	More intense BP • Stroke RR: 0.71; 95% CI: 0.60–0.84) • CHD RR: 0.80; 95% CI: 0.68–0.95)	• Intensive BP reduction improves CV outcomes compared to less intense • Achieved BP <130/80 may be associated with CV benefit.	N/A

			• Major CV events RR: 0.75; 95% CI: 0.68–0.85 • CV mortality RR: 0.79; 95% CI: 0.63–0.97 Stratification of SBP cutoffs (150,140 and 130 mm Hg) showed that a SBP/DBP difference of 10/5 mm Hg across each cutoff reduced risk of all outcomes		
Julius S, et al., 2006 (55) 16537662	Study type: RCT in pre-HTN 16 mg candesartan vs. placebo Size: 809 pts	• 58% men	• During the first 2 y, HTN developed in 154 (40.4%) pts in the placebo group compared with only 53 (13.6%) of those in the candesartan group, for a RR of 66.3% ($p<0.0001$). After 4 y, HTN developed in 240 (63.0%) in the placebo group vs. only 208 (53.2%) in the candesartan group RR 15.6% ($p<0.0069$).	• 2/3 of those with pre-HTN develop HTN within 4 y. Candesartan interrupts the onset and reduced by 15.6%	N/A
Ference BA, et al., 2014 (56) 24591335	Study type: Evaluated the effect of 12 polymorphisms (associated with BP) on the odds of CHD and compared it with the effect of lower SBP observed in both prospective cohort studies and BP-lowering randomized trials Size: 199,477 pts in 63 studies	N/A	•12 polymorphisms were associated with a 0.32 mm Hg lower SBP ($p=1.79\times10^{-7}$) and a 0.093-mm Hg/decade slower age-related rise in SBP ($p=3.05\times10^{-5}$). The effect of long-term exposure to lower SBP on CHD mediated by these polymorphisms was 2-fold greater than that observed in prospective cohort studies ($p=0.006$) and 3-fold greater than that observed in short-term BP treatment trials ($p=0.001$).	• SBP may be causally associated with the rate of rise in SBP with age and has a cumulative effect on the risk of CHD.	N/A

Data Supplement 28. Follow-Up After Initiating Antihypertensive Drug Therapy (Section 8.3.1)

Study Acronym Author Year Published	Aim of Study; Study Type; Study Size (N)	Patient Population	Study Intervention (# patients) / Study Comparator (# patients)	Endpoint Results (Absolute Event Rates, P value; OR or RR; & 95% CI)	Relevant 2° Endpoint (if any); Study Limitations; Adverse Events; Summary
Ambrosius WT, et al., 2014 (122) 24902920	Aim: To describe the study design of the SPRINT trial Study type: description of study design and protocol for the SPRINT RCT	Inclusion criteria: Adults ≥50 y, average SBP ≥130 mm Hg and evidence of CVD, CKD, or 10-y Framingham risk score ≥15%, or age ≥75 y	Intervention: 9361 participants randomized to 2 treatment groups: (1) Standard treatment group, SBP target <140 mm Hg, and (2) Intensive treatment group: SBP target <120 mm Hg.	1° endpoint: MI, ACS, stroke, HF, or CVD death.	Relevant 2° endpoint: All-cause mortality, decline in kidney function or development of ESRD, incident dementia, decline in cognitive function, and small-vessel cerebral ischemic disease Summary: This paper describes the protocol followed in the SPRINT trial that was successful in helping participants to attain and maintain BP targets in the study groups. Once treated, participants had follow-up visits to assessment BP control monthly until BP was at target. Medications were titrated and added as per protocol, when target BP was not attained.
Cushman WC, et al., 2007 (123) 17599425	Aim: To describe the study design of the BP trial of the ACCORD trial. Study type: description of study design and protocol	Inclusion criteria: Adults with a diagnosis of type 2 DM for at least 3 mo and at high risk for CVD events, who meet the following BP criteria: (1) SBP 130–160 mm Hg and taking 0–3 antihypertensive medications; (2) SBP 161–170 and on 0–2 antihypertensive	Intervention: • Unmasked, open-label, factorial design, randomized trial with a sample size of 4,733 pts • Patients were randomized to intensive SBP control (<120 mm Hg) or standard control (<140 mm Hg)	1° endpoint: Major CVD event (nonfatal MI or stroke, or CV death)	Relevant 2° endpoint: Expanded macrovascular outcome (1° outcome plus coronary revascularization or HF hospitalization), total mortality, each of the separate components of the 1° outcome, HF death or hospitalization, and

	for the ACCORD RCT	medications; or (3) SBP 171–180 and taking 0–1 antihypertensive medication. Other entry criteria included spot urine sample <2+, protein–Cr ratio <700 mg protein/1 g creatinine, or 24-h protein excretion <1.0 g/24 h.			composite microvascular disease outcome (kidney and eye disease). Summary: This paper describes the protocol followed in the ACCORD trial that was successful in helping pts to attain and maintain BP targets in the study groups. Once treated, pts had follow-up visits to assessment BP control monthly until BP was at target. Medications were titrated and added as per protocol, when target BP was not attained.
Xu W, et al., 2015 (128) 25655523	Aim: Retrospective assessment of the impact of follow-up intervals and treatment intensification thresholds on CVD events Study type: Retrospective cohort Size: 88,756 adult pts with HTN from The Health Improvement Network database	Inclusion criteria: Primary care practices in the U.K., 1986–2010.	N/A	• Median follow-up of 37.4 mo after the treatment strategy assessment period • 9,985 (11.3%) pts had an acute CV event or died. • No difference in risk of the outcome with systolic intensification thresholds 130–150 mm Hg, but HR: 1.21 for thresholds >150 mm Hg • Outcome risk increased progressively from the lowest (0–1.4 mo) to the highest 5th of time to medication intensification (HR: 1.12; 95% CI: 1.05–1.20; p=0.009) for intensification between 1.4 and 4.7 mo after detection of elevated BP). The highest fifth of time to follow-up (>2.7 mo) was also associated with increased outcome risk HR:	• Increased risk of acute CVD event or death with: • Systolic intensification thresholds >150 mm Hg • Delays of >1.4 mo before medication intensification after SBP elevation • Delays of >2.7 mo before BP follow-up after antihypertensive medication intensification • Timely medical management and follow-up impacts outcomes in the treatment of pts with HTN. • Retrospective study, but still sheds important light on the impact of follow-up actions

				1.18; 95% CI: 1.11–1.25; p<0.001	
Birtwhistle RV, et al., 2004 (129) 14726370	Aim: Assess impact of follow-up intervals on BP control in stable, treated pts with HTN Study type: RCT Size: 609 pts, 30–74 y with essential HTN, on drug treatment, with HTN controlled for ≥3 mo prior to entry into study.	Inclusion criteria: 50 family practices in southeastern Ontario, Canada.	• 302 pts randomized to follow-up every 3 mo, 307 randomized to follow-up every 6 mo.	• Pts in both groups visited doctor more frequently than their assigned interval. • Mean BP was similar in the groups, as was control of HTN. • Pt satisfaction and adherence to treatment were similar in the groups. • About 20% of pts in each group had BPs that were out of control during the study.	• Study addresses follow-up interval for pts with treated, stable, and controlled HTN. No difference in BP control or pt satisfaction between 3 and 6 mo follow-up groups. • May be helpful with recommendations for pts with treated, stable HTN.

Data Supplement 29. Monitoring Strategies to Improve Control of BP in Patients on Drug Therapy for High BP (Section 8.3.2)

Study Acronym Author Year Published	Aim of Study; Study Type; Study Size (N)	Patient Population	Study Intervention (# patients) / Study Comparator (# patients)	Endpoint Results (include Absolute Event Rates, P value; OR or RR; & 95% CI)	Relevant 2° Endpoint (if any); Study Limitations; Adverse Events; Summary
Brennan T, et al., 2010 (130) 20415618	Aim: Assess impact of follow-up and monitoring system including home BP monitoring and telephonic nurse case management on BP control in pts treated for HTN Study type: RCT Size: 638 African American pts with high BP from a national health maintenance organization plan	Inclusion criteria: HTN	Intervention: Intervention group received telephonic nurse case management, pt education materials, lifestyle counseling, and a home BP monitor Comparator: Control group received a home BP monitor only	• Intervention group achieved lower SBP (123.6 vs. 126.7 mm Hg, p=0.03) and was 50% more likely than the control group to achieve BP control OR: 1.50; 95% CI: 0.997–2.27; p=0.052	• Combination of home BP monitoring and nurse case management controlled HTN better than home BP alone

Bosworth, et al., 2009 (131) 19920269	Aim: Assess impact of telephone follow-up intervention and/or home BP monitoring on BP control in pts with treated HTN Study type: RCT Size: 636 pts were randomized; 475 pts completed the trial, including 24-mo follow-up period.	Inclusion criteria: Pts with HTN, from 2 university-affiliated primary care clinics.	• 636 pts randomized to usual care or 1 of 3 intervention groups: (1) Nurse-administered telephone intervention targeting HTN -related behaviors, (2) home BP monitoring 3 times weekly, and (3) both interventions	• 475 pts (75%) completed the 24-mo BP follow-up. • At 24 mo, improvements in the proportion of pts with BP control relative to the usual care group were 4.3% (95% CI: -4.5%, 12.9%) in the behavioral intervention group, 7.6% (95% CI: -1.9%, 17.0%) in the home BP monitoring group, and 11.0% (95% CI: 1.9%, 19.8%) in the combined intervention group. • Relative to usual care, the 24-mo difference in SBP was 0.6 mm Hg (95% CI: -2.2, 3.4 mm Hg) for the behavioral intervention group, -0.6 mm Hg (95% CI: -3.6, 2.3 mm Hg) for the BP monitoring group, and -3.9 mm Hg (95% CI: -6.9– -0.9 mm Hg) for the combined intervention group; patterns were similar for DBP	• Home BP monitoring and tailored behavioral telephone intervention improved BP control, SBP, and DBP at 24 mo relative to usual care. Combined therapy was significantly better than either therapy alone.
Bosworth, et al., 2011 (132) 21747013	Aim: Assess impact of telephone follow-up interventions on BP control in pts with treated HTN Study type: RCT Size: Of 1551 eligible pts, 593 randomized	Inclusion criteria: Primary care clinics at a VA Medical Center	• 593 pts randomized to either usual care or to 1 of 3 telephone follow-up groups: (1) nurse-administered behavioral management, (2) nurse- and physician-administered medication management, or (3) a combination of both	• 1° endpoint: BP control measured every 6 mo for 18 mo • Behavioral management and medication management alone showed significant improvements at 12 mo-12.8% (95% CI: 1.6%, 24.1%) and 12.5% (95% CI: 1.3%, 23.6%), respectively-but not at 18 mo. • In subgroup analyses, among those with poor baseline BP control, SBP decreased in the combined intervention group by 14.8 mm Hg (95% CI: -21.8– -7.8 mm Hg) at 12 mo and 8.0 mm Hg (95% CI: -15.5– -0.5 mm Hg) at 18 mo, relative to usual care.	• Telephone-based case management for high BP control effectively lowers BP for up to 1 y, but then BP control slackens. • Interventions had the most impact on pts with worst BP control at study entry. • Study carried out in the Veteran's Administration outpatient practice; unclear if results would apply to other practice settings.

Green BB, et al., 2008 (133) 18577730	Aim: Assess impact of follow-up and monitoring system including home BP monitoring, Internet-based BP management tool, and pharmacist care management on BP control in pts treated for HTN Study type: Cluster RCT Size: 778 pts from 16 clinics in integrated group practice in Washington state.	Inclusion criteria: Uncontrolled HTN and Internet access	• 2 intervention groups: one with home BP monitoring and Internet tool, and the other with home BP monitoring, Internet tool, and pharmacist care management • Compare to usual care • 1 y follow-up	• Intervention group with all components achieved better BP control vs. usual care • 56% (95% CI: 49%–62%) or combination intervention group achieved BP control vs. usual care (p<0.001) and intervention with only home BP monitor and Internet tool (p<0.001)	• Combination of home BP monitoring, Internet-based BP management tools, and pharmacist case management helped control HTN better than usual care and better than BP monitoring and Internet-based tool alone.
Heisler M, et al., 2012 (134) 22570370	Aim: Assess impact of follow-up pharmacist care management system on BP control in pts treated for HTN Study type: Cluster RCT Size: 1797 intervention and 2303 control pts from 16 primary care clinics at 5 medical centers (3 VA and 2 Kaiser Permanente)	Inclusion criteria: Uncontrolled HTN and Internet access	• 14-mo intervention period • BP 6 mo prior to and 6 mo after intervention period were compared in intervention and control groups	• Mean SBP was 2.4 mm Hg lower (95% CI: -3.4– -1.5), p<0.001 in the intervention group immediately after the intervention period, compared to the control group BP decrease was the same in the intervention and control groups (9 mm Hg).	• Pharmacist care management system in a “real world” setting was more effective than usual care in lowering BP in the short-term, but in the longer-term follow-up did not differ significantly from usual care. • This study is one of very few studies to show no significant longer term impact of a care management system on BP control in pts with HTN.
Margolis KL, et al., 2013 (25) 23821088	Aim: Assess impact of follow-up and monitoring system including home BP tele-monitoring and pharmacist case management on BP control in pts treated for HTN Study type: Cluster RCT Size: 450 pts from 16 clinics in integrated health system in Minneapolis, MN	Inclusion criteria: Uncontrolled HTN	• 222 pts randomized to 8 usual care clinics and 228 randomized to 8 intervention clinics • Intervention included 12 mo of home BP tele-monitoring and pharmacist case management, with 6 mo of follow-up afterward	• Intervention group achieved better BP control compared to usual care during 12 mo of intervention and persisting during 6 mo of follow-up • SBP was <140/90 in 57.2% (95% CI: 44.8%, 68.7%) of intervention pts at 6 and 12 mo vs. 30% (95% CI: 23.2%, 37.8%) in usual care (p=0.001)	• Combination of home BP tele-monitoring and pharmacist case management helped control HTN better than usual care at 6, 12, and 18 mo

Data Supplement 30. RCTs Comparing Stable Ischemic Heart Disease (Section 9.1)

Study Acronym; Author; Year Published	Aim of Study; Study Type; Study Size (N)	Patient Population	Study Intervention (# patients) / Study Comparator (# patients)	Endpoint Results (Absolute Event Rates, P value; OR or RR; & 95% CI)	Relevant 2° Endpoint (if any); Study Limitations; Adverse Events; Summary
INVEST Bangalore S, et al., 2014 (135) 25145522	Aim: To investigate optimal BP in pts ≥60 y with CAD and SBP >150 mm Hg treated with antihypertensive drugs Study type: Post-hoc analysis of PROBE trial (INVEST study—atenolol/HCTZ or verapamil-SR/trandolapril) Size: 8,354 pts	Inclusion criteria: Pts ≥60 y with CAD and SBP >150 mm Hg treated with antihypertensive therapy Exclusion criteria: N/A	Intervention: • 4,787 pts (57%) achieved SBP<140 mm Hg (group 1) • SBP achieved was <140 mm Hg (group 1) Comparator: • 1,747 pts (21%) achieved SBP of 140–149 mm Hg (group 2); 1,820 pts (22%) achieved SBP ≥150 mm Hg (group 3) • SBP achieved was 140–149 mm Hg (group 2) and 150 mm Hg or higher (group 3)	1° endpoint: All-cause death, nonfatal MI, or nonfatal stroke. Multiple propensity score-adjusted 1° outcome showed that compared with group 1, the risk of 1° outcome adjusted HR: 1.12 (95% CI: 0.95–1.32; p=0.19); for group 2 adjusted HR: 1.85 (95% CI: 1.59, 2.14), p<0.0001; for group 3 adjusted HR: 1.64 (95% CI: 1.40, 1.93), p<.0001 1° Safety endpoint: No significant difference between the 3 groups	Relevant 2° endpoint: Multiple propensity score-adjusted analysis: •Compared with group 1, no significant difference in all-cause mortality in group 2 but increased all-cause mortality in group 3 (HR: 1.64; 95% CI: 1.40–1.93; p<0.0001). • Compared with group 1, increase CV mortality in group 2 (HR: 1.34; 95% CI: 1.01–1.77; p=0.04) and in group 3 (HR: 2.29; 95% CI: 1.79–2.93; p<0.0001). • Compared with group 1, total MI was in group 2 (HR: 1.20; 95% CI: 0.90–1.60; p=0.21) but was increased in group 3 (HR: 2.39; 95% CI: 1.87-3.05; p<0.0001). • Compared with group 1, no significant difference with group 2 but an increase in nonfatal MI in group 3 (adjusted HR: 2.45; 95% CI: 1.02–3.71; p<0.0001). • Compared with group 1, an increase in total stroke in group 2 (HR: 1.89; 95% CI: 1.26–2.82; p=0.002) and in group 3 (HR: 2.93; 95% CI: 2.01–4.27; p<0.001). • Compared with group 1, an increase in nonfatal stroke in group 2 (HR: 1.70; 95% CI: 1.06–2.72; p=0.03) and in group 3 (HR: 2.78; 95% CI: 1.80–4.30; p<0.001). • HF and revascularization not significant Study limitations and adverse events: The present study was not designed to test whether pts ≥60 y with CAD and a SBP of 140–149 mm Hg would benefit

					from antihypertensive treatment. No adverse events were reported. Summary: The optimal SBP in pts ≥60 y with CAD and SBP >150 mm Hg treated with antihypertensive therapy was <140 mm Hg
Law MR, et al., 2009 (18) 19454737	Study type: Meta-analysis of use of BP-lowering drugs in prevention of CVD from 147 randomized trials Size: Of 147 randomized trials of 464,000 pts, 37 trials of BBs in CAD included 38,892 pts, and 37 trials of other antihypertensive drugs in CAD included 85,395 pts	Inclusion criteria: The database search used Medline (1966 to Dec. 2007) to identify randomized trials of BP-lowering drugs in which CAD events or strokes were recorded. The search also included the Cochrane Collaboration and Web of Science databases and the citations in trials and previous meta-analyses and review articles. Exclusion criteria: Trials were excluded if there were <5 CAD events and strokes or if treatment duration was <6 mo.	N/A	1° endpoint: CAD events; stroke Results: In 37 trials of pts with a history of CAD, BBs reduced CAD events 29% (95% CI: 22%, 34%). In 27 trials in which BBs were used after acute MI, BBs reduced CAD events 31% (95% CI: 24%–38%), and in 11 trials in which BBs were used after long-term CAD, BBs insignificantly reduced CAD events 13%. In 7 trials, BBs reduced stroke 17% (95% CI: 1%–30%). CAD events were reduced 14% (95% CI: 2%–25%) in 11 trials of thiazide diuretics, 17% (95% CI: 11%–22%) in 21 trials of ACEIs, insignificantly 14% in 4 trials of angiotensin receptor blockers, and 15% (95% CI: 8%–22%) in 22 trials of CCBs. Stroke was reduced 38% (95% CI: 28%–47%) in 10 trials of thiazide diuretics, 22% (95% CI: 8%–34%) in 13 trials of ACEIs, and 34%	• With the exception of the extra protective effect of BBs given shortly after a MI and the minor additional effect of CCBs in preventing stroke, all the classes of BP-lowering drugs have a similar effect in reducing CAD events and stroke for a given reduction in BP.

				(95% CI: 25%–42%) in 9 trials of CCBs.	
HOPE Yusuf S, et al., 2000 (136) 10639539	Aim: To investigate effect of ACE-I (Ramipril 10 mg) on CV events in high risk pts. over 5y with a mean entry BP of 139/79 mm Hg in both groups Study type: RCT, 2×2 factorial design Size: 9,297	Inclusion criteria: Pts ≥55 y with history of CAD, stroke, PVD or DM with either HTN, elevated total cholesterol, low LDL cholesterol, smoking, or micro albuminuria. Exclusion criteria: HF, <0.40 EF, on ACE-I or Vitamin E, uncontrolled HTN /overt nephropathy, Had MI or stroke <4 wk	Intervention: Ramipril (10 mg) (4,645) Comparator: Placebo (4,652)	1° endpoint: Composite of MI, stroke, or mortality from CV causes. Results: Endpoint reduction Ramipril group vs. Placebo (14% vs. 17.8%; RR: 0.78; CI: 0.70–0.86; p<0.001)	• Death from cardiac causes reduced (6.1% vs. 8.1%; p<0.001) • Death from MI reduced (9.9% vs. 12.3%; p<0.001) • Death from any cause (10.4 % vs. 12.2%; p=0.005)
SAVE Pfeffer M., et al., 1992 (137) 1386652	Aim: To assess if captopril decrease morbidity and mortality in pts with LV dysfunction after MI. Study type: RCT Size: 2,231	Inclusion criteria: Pts (21–80 y) surviving 3 d after MI, EF≤40%. Exclusion criteria: Pts not randomized within 16 d after MI, contra. to ACE-I use, Serum Cr. >2.5 mg/dL, severe comorbidities, unstable infarction, need for revascularization	Intervention: Captopril (titrated doses) (115) Comparator: Placebo (1116)	1° endpoint and results: All-cause mortality: 20% vs. 25%, RR: 19%; 95% CI: 3%–32%; p=0.019 Other endpoints: Fatal and nonfatal major CV events were reduced in the captopril group.	• Captopril vs. Placebo group BP at 1 y (125±18 / 77±10 mm Hg for placebo vs. 119±18/74±10 mm Hg for captopril; p<0.001) • Dizziness, alteration in taste, cough and diarrhea were reported significantly more in the captopril group • Ventricular size on Echo studies was independent predictor of adverse CV outcomes
EUROPA Fox KM, et al., 2003 (138) 13678872	Aim: To investigate efficacy of perindopril in CV events in pts with stable CAD. Study type: RCT	Inclusion criteria: Pts ≥18 y (women) with CAD >mo before screening, revascularization >6 mo before screening, ≥70% narrowing of major	Intervention: Perindopril (6,110) Comparator: Placebo (6,108)	1° endpoint: Composite of CV death, nonfatal MI, cardiac arrest with successful CPR Results: RR 20%; 95% CI: 9%–29; p=0.0003	• Perindopril resulted reduction in all these outcomes: composite of total mortality, nonfatal MI, hospital admission for UA, and cardiac arrest with successful CPR; CV mortality and nonfatal MI, the individual components these outcomes and revascularization, stroke, and admission for HF

	Size: 12,218 pts	coronary artery. Men with history of chest pain, positive ECG, echo or nuclear test Exclusion criteria: HF, planned revascularization, <110 mm Hg SBP, uncontrolled HTN, >100 mm Hg DBP, <I mo use of ACEI or ARB, Cr>150 µmol/L, serum K>5.5 mmol/L			
MERIT-HF Goldstein S, et al., 1999 (139) 10526701	Aim: To investigate if metoprolol (CR/XL) once daily with std. treatment lowers mortality in pts with HF*r*EF Study type: RCT Size: 3,991 pts	Inclusion criteria: Pts 40–80 y with NYHA class II-IV HF for 3 mo before randomization and on standard treatment 2 wk before entry, Stable clinical condition during 2 wk run-in phase, EF ≤0.40. Exclusion criteria: Acute MI, UA <28 d of entry, contra to beta blockade <6 mo, HF due to systemic disease/alcohol abuse, heart transplant candidate, ICD, planned revascularization in past 4 mo, decompensated heart, SBP <100 mm Hg, CCB treatment, amiodarone use within 6 mo	Intervention: Metoprolol CR/XL (1,990) Comparator: Placebo (2,001)	1° endpoint: All-cause mortality in the intent to treat Results: 145 vs. 217 deaths [11.0 %], RR: 0.66 (95% CI: 0.53–0.81; p=0.00009) or adjusted for interim analyses p=0.0062.	• Fewer sudden deaths in the metoprolol group (p=0.0002) • Lesser deaths from HF*r*EF in the metoprolol group (p=0.002) • Metoprolol improved survival and was well tolerated

Packer M, et al., 2001 (140) 11386263	Aim: To assess survival in severe chronic HF pts by the use of carvedilol. Study type: RCT Size: 2,289 pts	Inclusion criteria: HF pts with dyspnea/exertion for 2 mo at least and left EF<25% despite treatment clinically euvolemic; allowed on digitalis, nitrates, hydralazine, spironolactone, or amiodarone. Hospitalized pts with no acute illness. Exclusion criteria: HF due to uncorrected prim. valvular disease or reversible cardiomyopathy cardiac transplant pts., coronary revasc. <2 mo, acute MI or stroke, ventricular tachycardia, on alpha blocker or CCB or on antiarrythmics class I <4 wk, SBP <85 mm Hg, serum Cr >2.8 mg/dL, change in body weight >1.5 kg during screening.	Intervention: Carvedilol (1,156) Comparator: Placebo (1,133)	1° endpoint: ● Death from any cause 130 vs. 190 deaths RR: 35%; 95% CI: 19%–48%; p=0.00013 ● Combined risk of death/hospitalization (24% lower risk in the carvedilol; (95% CI: 13%–33%; p<0.001 Safety endpoint: Lesser pts in carvedilol group required permanent discontinuation because of adverse events or for reasons other than death (p=0.02)	• Study stopped early (1.3-y follow-up) due to benefit on survival • Long-term treatment is very valuable. • Not all the pts with severe HF were allowed in the study
CAPRICORN Dargie HJ, et al., 2001 (141) 11356434	Aim: To investigate outcomes after carvedilol after MI in pts with LV dysfunction. Study type: RCT Size: 1,959 pts	Inclusion criteria: Pts ≥18 y, MI within 3–21 d of entry, LVEF≤40%, concurrent ACEI stable dose for at least 24 h, HF pts treated and controlled with ACEI and diuretics but not inotropes.	Intervention: Carvedilol (975) Comparator: Placebo (984)	1° endpoint: All-cause mortality or hospital admissions for CV issues Results: 12% vs. 15%; RR: 23%; 95% CI: 0.60–0.98; p=0.03 No difference between groups for death or CV hospital admissions	• CV mortality, nonfatal MI reduced in the carvedilol group • No difference between groups SCD and admission due to HF

		Exclusion criteria: SBP<90 mm Hg, uncontrolled HTN, bradycardia, insulin-dependent DM, BBs not for HF, Beta-2 agonists and steroids			
MERIT-HF HTN Herlitz J, et al., 2002 (142) 11862577	Aim: To assess metoprolol CR/XL influence on mortality and hospitalizations in HF and HTN pts. Study type: RCT Size: 1,747 pts	Inclusion criteria: Same as above MERIT-HF, 1999 study (HTN subgroup) Exclusion criteria: Same as above MERIT-HF	Intervention: Metoprolol CR/XL (871) Comparator: Placebo (876)	1° endpoint: Total mortality Results: RR: 0.61; 95% CI: 0.44–0.84; p=0.0022	• Total mortality reduction was driven by reduction in the SCD and death from worsening HF • 12.5% pts had earlier discontinuation due to any cause. Lesser no. of pts in the metoprolol group (n=21) discontinued due to worsening HF The mean reduction in BP (adjusted) was 1.7 mm Hg in the metoprolol group vs. 4.8 mm Hg in placebo group (p=0.0001)
CIBIS-II 1999 (143) 10023943	Aim: To determine efficacy of bisoprolol in reducing mortality in chronic HF. Study type: RCT Size: 2,647 pts	Inclusion criteria: 18–80 y, LVEF≤35%, dyspnea, orthopnea, fatigue, NYHA class III-IV Exclusion criteria: Uncontrolled HTN, MI, UA <3 mo revascularization. treatment, heart transplant, AV block <1 degree, SBP <100 mm Hg, renal failure, reversible obstructive lung disease	Intervention: Bisoprolol (1,327) Comparator: Placebo (1,320)	1° endpoint: All-cause mortality Results: 11.8% vs. 17.3% deaths with a RR: 0.66; 95% CI: 0.54–0.81; p<0.0001	• The trial stopped early due to benefit. Bisoprolol group had significantly fewer SCDs. • Mean age was 61 y so more data on elderly pts is needed
Elkayam U, et al., 1990 (144) 2242521	Aim: To assess comparative efficacy and safety of nifedipine and ISDN alone and the combination for treating for chronic CHF.	Inclusion criteria: 18–75 y HF pts, NYHA class II and III, LVEF<40%, clinically stable, maintenance dose of Digitalis and diuretics.	Intervention: Nifedipine (21), ISDN (20), Nifedipine+ISDN (23) Comparator: Placebo	Endpoints and Results: HF-worsening: 9 in Nifedipine group vs. 3 in ISDN group (p<0.09); and 21 in nifedipine-ISDN group (p<0.001 vs. nifedipine, p<0.0001 vs. ISDN)	• In clinical deterioration nifedipine pts (8) vs. rest of the pts (No difference in LVEF or VO^2 max) • Although all the 3 drug regimens improved exercise capacity, nifedipine treatment alone or in combination resulted in clinical deterioration and worsening of CHF

	Study type: RCT with a crossover design Size: 28 pts	Exclusion criteria: Pregnancy, nursing, history of MI <1 mo before entry, valvular disease, Angina, significant pulmonary, hepatic, renal and hematologic disease, unable to walk on the treadmill, noncompliance		Clinical deterioration discontinuation: Nifedipine 29% vs. ISDN group 5% (p<0.05) DBP: Nifedipine alone or combination with ISDN (reduction, p<0.05)	
The Multicenter Dilitiazem Postinfarction Research Group 1988 (145) 2899840	Aim: To assess dilitiazem effect on recurrent infarction and death after acute MI Study type: RCT Size: 2,466 pts	Inclusion criteria: 25–75 y admitted to CCU, MI with enzyme confirmation. Exclusion criteria: • Cardiogenic shock, • Symptomatic hypotension, • PH with right HF, • 2nd/3rd degree heart block, • HR <50 bpm, • Contraceptives, • WPW syndrome, • CCBs, • Severe comorbidities or • Cardiac surgery	Intervention: Dilitiazem 240 mg (1,234) Comparator: Placebo (1,232)	1° endpoints and results: • Total mortality: identical in both groups • Cardiac death and nonfatal MI: 11% fewer in dilitiazem but difference was NS	• No combined benefit from dilitiazem on mortality or cardiac events
MDPIT Goldstein RE, et al., 1991 (146) 1984898	Aim: To determine if dilitiazem increases late onset CHF in post-MI pts with early decline in EF. Study type: RCT Size: 2,466 pts	Inclusion criteria: Same as above Exclusion criteria: Same as above	Intervention: Dilitiazem 240 mg (1,234) Comparator: Placebo (1,232)	1° endpoint and results: Same as above Follow-up Results: Pts with BL EF<0.40, late CHF in Dilitizam group (21%) vs. Placebo (12%) [p=0.004].	• Life table analysis confirmed increased frequency of late CHF in pts taking dilitiazem (p=0.0017) • Dilitiazem related CHF exclusively associated with systolic LVD with or without BBs

Freemantle N, et al., 1999 (147) 10381708	Aim: To evaluate BBs effectiveness for short-term treatment and long-term 2° prevention in acute MI. Study type: Meta-analysis of RCTs Size: 54,234 pts (82 RCTs)	Inclusion criteria: RCTs with treatment lasting >1 d and with follow-ups on clinical effectiveness in pts with MI Exclusion criteria: Cross-over RCTs	Intervention: BBs (mostly propranolol, timolol, metoprolol) Comparator: Controls (placebo/other treatment)	1° endpoint: All-cause mortality Results: • Long-term trials RR reduction: 23% (95% CI: 15%–31%) • Short-term trials RR reduction: 4%; 95% CI: -8%–5%	• Meta-regression in long-term trials indicated a near significant trend for decreased benefit in drugs with ISA. • NS in withdrawal between BBs of different cardio selectivity.
de Peuter OR, et al., 2009 (148) 19841485	Aim: To determine influence of beta-2 blockade in addition to beta-1 blockade for preventing vascular events in pts with ACS or HF. Study type: Meta-analysis of RCTs Size: 34,360 pts (33 RCTs)	Inclusion criteria: • RCTs comparing Beta-1 blockers vs. BBs 1 + 2 directly (5) • RCTs comparing Beta-1 blockers vs. Beta 1 + 2 blockers with a control group (28) Exclusion criteria: Studies not pre-specifying total mortality and vascular event as outcomes <3 mo follow-up, duplicate data, sub studies.	Intervention: Beta-1 blockers Comparator: BBs 1+2 with or without control group	1° endpoint: Total mortality, vascular events. Results: ACS Population: 1 study with different BBs underpowered to detect difference. Beta-1 vs. Placebo NS reduced mortality or vascular events HF population: Beta 1 + 2 blockers vs. Beta 1 blockers decreased mortality RR: 0.86; 95% CI: 0.78–0.94 Beta 1 and Beta 1+2 decreased total mortality. Only Beta 1+2 blockers reduced vascular events.	• Supplementary beta 2 blockade may be more beneficial. • Indirect comparisons and heterogeneity among studies
Leon MB, et al., 1981 (149) 7246435	Aim: To evaluate effectiveness of verapamil as a single agent and in combination with propranolol in pts with stable AP.	Inclusion criteria: Symptomatic angina pectoris pts, 1) not sufficiently controlled on BBs and nitrates and noncardiac	Intervention: Propranolol, verapamil, Combination of propranolol and verapamil	Results: Large dose verapamil significantly lowered BP. Propranolol and verapamil combined (at best dose) further lowered BP, improved	• HR and pressure-rate product lowered significantly on combination therapy • PR interval increased on combination treatment Regarding antianginal properties, verapamil seemed to be more effective than propranolol.

	Study type: RCT (triple crossover) Size: 11 pts	effects from propranolol hindering treatment 2) who could stay 4 wk in hospital Exclusion criteria: LVD with CHF or LVEF<30% at rest and <25% for exercise, HR<50 b/min, ≥first degree heart block	Comparator: Placebo	exercise time by 4.7 ± 0.7 min (p<0.001)	
Staessen JA, et al., 1997 (150) 9297994	Aim: To determine if active treatment reduces complications from isolated systolic HTN in the elderly. Study type: RCT Size: 4,965 pts	Inclusion criteria: Pts ≥60 y, sitting SPB 160–219 mm Hg, sitting DBP 95 mm Hg, and standing SBP ≥140 mm Hg. Exclusion criteria: Systolic HTN 2nd to a disorder, retinal hemorrhages/papilledema, CHF, aneurysms, serum Cr ≥180 µmol/L, history of nosebleed, stroke, MI <1 y, dementia, substance abuse, severe comorbidities	Intervention: Active treatment (2,398) Comparator: Placebo (2,297)	1° endpoint: Fatal and nonfatal strokes combined. Results: 13.7 vs. 7.9 endpoints/ 1,000 pts-y (42% reduction; p=0.003)	• All fatal and nonfatal cardiac endpoints (with sudden death) decreased in the active treatment group (p=0.03) • Cardiac mortality was lower in active treatment (-27%; p=0.07). All-cause mortality was not different. • Nitrendipine used for active arm.
Wright JT, et al., 2015 (114) 26551272	Aim: To compare in pts with a SBP of 130–180 mm Hg and an increased CV risk but without DM the effect of a target SBP of <140 mm Hg vs. a target SBP of <120 mm Hg on the 1° composite outcome of MI, other ACSs,	Inclusion criteria: 9,361 pts, mean 67.9 y (28.2% ≥75 y; 35.6% women; 57.7% non-Hispanic white; 31.5% African American; 10.5% Hispanic) with a SBP of 130–180 mm Hg and an increased CV risk but without DM, history of stroke, symptomatic HF within	Intervention: 4,678 pts were randomized to intensive BP treatment Comparator: 4,683 pts were randomized to standard BP treatment	1° endpoint: • At 1 y, the mean SBP was 121.4 mm Hg with intensive treatment (mean number of antihypertensive drugs was 2.8) and 136.2 mm Hg with standard treatment (mean number of antihypertensive drugs was 1.8)	• At 3.26-y median follow-up, compared with standard BP treatment, intensive BP treatment reduced all-cause mortality 27% (p=0.003), HF 38% (p=0.002), CV mortality 43% (p=0.005), and the 1° composite outcome or death 22% (p<0.001) • Intensive BP treatment reduced the 1° composite endpoint 33% (14% to 49%) in pts aged 75 y and older and 20% (0% to 36%) in pts 50–74 y • Serious adverse events were similar in both treatment groups. However, intensive BP treatment caused more hypotension (2.4% vs. 1.4%; p=0.001), more syncope (2.3% vs. 1.7%; p=0.05), more

	stroke, HF, or CV death	past 6 mo, LVEF <35%, and eGFR <20 mL/min/1.73 mm^2; CVD was present in 20.1%, and the Framingham 10-y CVD risk score was ≥15% in 61.3% of pts		• At 3.26-y median follow-up, the 1° composite outcome was reduced 25% (p<0.001) by intensive BP treatment	electrolyte abnormality (3.1% vs. 2.3%; p=0.02), and more acute kidney injury or acute renal failure (4.1% vs. 2.5%; p<0.001). The incidence of bradycardia, injurious falls, and orthostatic hypotension with dizziness was similar in both treatment groups
ALLHAT Collaborative Research Group, 2003 12925554	Aim: In a follow-up analysis, to compare diuretic vs. alpha-blocker as first step treatment of hypertension.	Inclusion criteria: Men and women ≥ 55 y with BP ≥140/90 mm Hg or on medications for hypertension with at least one additional risk factor for coronary heart disease.	Intervention: 15,255 patients were randomized to chlorthalidone and 9,061 to doxazosin and followed for 3.2 y.	Primary endpoint: Combined fatal coronary heart disease or non-fatal MI, analyzed by intention to treat.	• There was no difference in primary outcome between the arms (RR: 1.02; 95% CI: 0.94–1.13). • However, the doxazosin arm compared with the chlorthalidone arm had a higher risk for stroke (RR: 1.26; 95% CI: 1.10–1.46) and combined cardiovascular disease (RR: 1.20; 95% CI: 1.13–1.27). • The findings confirmed the superiority of diuretic-based over alpha blocker based antihypertensive treatment in the prevention of cardiovascular disease.
Zanchetti A, et al., 2006 17053536	Aim: To provide additional analyses of the primary endpoint in the VALUE trial, including sex, age, race, geographic region, smoking status, type 2 diabetes, total cholesterol, left ventricular hypertrophy, proteinuria, serum creatinine, history of coronary heart disease, stroke or transient ischemic attack and history of peripheral artery disease.	Inclusion criteria: The 15,245 patients participating in VALUE were divided into subgroups according to baseline characteristics.	Statistical analysis: Subgroup interaction analyses were conducted by the Cox proportion hazard model. Within each subgroup, treatment effects were assessed by hazard ratios and 95% CIs.		• For cardiac morbidity and mortality, the only significant subgroup by treatment interaction was of sex (p=0.016) with HR indicating a relative excess of cardiac events in women but not in men, but SBP differences in favor of amlodipine were greater in women. • In the VALUE cohort, in no subgroup of patients were there differences in the incidence of the composite cardiac endpoint with valsartan and amlodipine treatment despite greater BP reduction in the amlodipine group.

Leenen FHH, et al., 2006 16864749	Aim: To compare the long-term relative safety and outcomes of ACE inhibitor- and CCB-based regimens in older hypertensive individuals in ALLHAT.	Inclusion criteria: men and women age ≥55 y with untreated (BP 140–180/90–110 mm Hg) or treated hypertension (BP ≤160/100 mm Hg on ≤2 antihypertensive drugs) with ≥ 1 additional risk factor for coronary heart disease.	Intervention: Patients (were randomized to amlodipine (9,048) or Lisinopril (9,054).	Primary outcome: Combined fatal coronary heart disease or non-fatal MI, analyzed by intention to treat. Follow-up: 4.9 y	• Risk of coronary heart disease was similar between amlodipine and Lisinopril • For stroke, combined cardiovascular disease, gastrointestinal bleeding and angioedema, risks are higher with Lisinopril compared to amlodipine. • For heart failure, risks are higher with amlodipine compared to Lisinopril.

Data Supplement 31. Meta-analyses of ischemic heart disease (Section 9.1)

Study Acronym; Author; Year Published	Study Type/Design; Study Size	Patient Population	Primary Endpoint and Results (include P value; OR or RR; and CI)	Summary/Conclusion Comment(s)
Bundy JD, et al., 2017 28564682	Study type: Network meta-analysis Size: 144,220 patients in 42 RCTs.	Inclusion criteria: • Random allocation into an antihypertensive medication, control or treatment target • Allocation to antihypertensive Antihypertensive treatment was independent of other treatment regimens • ≥100 patients in each treatment group • Trial duration ≥ 6 mo • One or more events for each treatment group reported • Minimum 5 mm Hg difference in SBP level between the 2 treatment groups • Outcomes included major CVD, stroke, CHD, CVD mortality or all-cause mortality	• There were linear associations between mean achieved SBP and risk of cardiovascular disease and mortality, with the lowest risk at 120 to 124 mm Hg. Randomized groups with a mean achieved SBP of 120 to 124 mm Hg had a hazard ratio (HR) for major cardiovascular disease of 0.71 (95% CI: 0.60–0.83) compared with randomized groups with a mean achieved SBP of 130 to 134 mm Hg, an HR of 0.58 (95% CI: 0.48–0.72) compared with those with a mean achieved SBP of 140 to 144 mm Hg, an HR of 0.46 (95% CI: 0.34–0.63) compared with those with a mean achieved SBP of 150 to 154 mm Hg, and an HR of 0.36 (95% CI: 0.26–0.51) compared with those with a mean achieved SBP of 160 mm Hg or more.	• This study suggests that reducing SBP to levels below currently recommended targets significantly reduces the risk of cardiovascular disease and all-cause mortality and strongly support more intensive control of SBP among adults with hypertension.

Data Supplement 32. Nonrandomized Trials, Observational Studies, and/or Registries of Ischemic Heart Disease (Section 9.1)

Study Acronym; Author; Year Published	Study Type/Design; Study Size (N)	Patient Population	Primary Endpoint and Results (include P value; OR or RR; and 95% CI)	Summary/Conclusion Comment(s)
PROVE IT-TIMI 22 Bangalore S, et al., 2010 (151) 21060068	Study type: Nonrandomized trial of optimal BP after ACS Size: 4,162 pts	Inclusion criteria: Pts with acute MI or high-risk UA within 10 d randomized to pravastatin or atorvastatin and to gatifloxacin or placebo treated with standard medical and interventional treatment for ACS Exclusion criteria: N/A	1° endpoint: Composite of all-cause death, MI, UA requiring rehospitalization, revascularization after 30 d, and stroke with a mean follow-up of 24 mo Results: The relationship between SBP and DBP followed a J- or U-shaped curve association with the 1° outcome with increased events rates at both low and high BP values. A nonlinear Cox proportional hazards model showed a nadir of 136/85 mm Hg (range 130–140/80–90 mm Hg) at which the incidence of 1° outcome was lowest. There was a relatively flat curve for SBP of 110–130 mm Hg and for DBP of 70–90 mm Hg, suggesting a BP <110/70 mm Hg may be dangerous.	• After an ACS, a J- or U-shaped association existed between BP and the incidence of new CV events. The lowest incidence of CV events occurred with a BP of 130–140/80–90 mm Hg and a relatively flat curve for SBP of 110–130 mm Hg and of DBP of 70–90 mm Hg, suggesting a BP <110/70 mm Hg may be dangerous.
Law MR, et al., 2009 (18) 19454737	Study type: Meta-analysis of use of BP-lowering drugs in prevention of CVD from 147 randomized trials Size: Of 147 randomized trials of 464,000 pts, 37 trials of BBs in CAD included 38,892 pts, and 37 trials of other antihypertensive drugs in CAD included 85,395 pts	Inclusion criteria: The database search used Medline (1966 to Dec. 2007) to identify randomized trials of BP-lowering drugs in which CAD events or strokes were recorded. The search also included the Cochrane Collaboration and Web of Science databases and the citations in trials and previous meta-analyses and review articles. Exclusion criteria: Trials were excluded if there were <5 CAD events and strokes or if treatment duration was <6 mo.	1° endpoint: CAD events; stroke Results: In 37 trials of pts with a history of CAD, BBs reduced CAD events 29% (95% CI: 22%, 34%). In 27 trials in which BBs were used after acute MI, BBs reduced CAD events 31% (95% CI: 24%–38%), and in 11 trials in which BBs were used after long-term CAD, BBs insignificantly reduced CAD events 13%. In 7 trials, BBs reduced stroke 17% (95% CI: 1%–30%). CAD events were reduced 14% (95% CI: 2%–25%) in 11 trials of thiazide diuretics, 17% (95% CI: 11%–22%) in 21 trials of ACEIs, insignificantly 14% in 4 trials of angiotensin receptor blockers, and 15% (95% CI: 8%–22%) in 22 trials of CCBs. Stroke was reduced 38% (95% CI: 28%–47%) in 10 trials of thiazide diuretics, 22% (95% CI: 8%–34%) in 13 trials of ACEIs, and 34% (95% CI: 25%–42%) in 9 trials of CCBs.	• With the exception of the extra protective effect of BBs given shortly after a MI and the minor additional effect of CCBs in preventing stroke, all the classes of BP-lowering drugs have a similar effect in reducing CAD events and stroke for a given reduction in BP.

Data Supplement 33. RCTs Comparing Heart Failure (Section 9.2)

Study Acronym (if applicable) Author Year Published	Study Type/Design; Study Size (N)	Patient Population	Primary Endpoint and Results (include P value; OR or RR; and 95% CI)	Summary/Conclusion Comment(s)
LV J, et al., 2013 (127) 23798459	Study type: MA of RTC that randomly assigned individuals to different target BP levels Size: 37,348 pts	•15 trials	7.5/4.5 mm Hg BP difference. Intensive BP lowering achieved. RR for • Major CV events: 11%; 95% CI: 1%–21%) • MI: 13%; 95% CI: 0%–25% • Stroke: 24%; 95% CI: 8%–37% • ESRD: 11%; 95% CI: 3%–18% • Albuminuria: 10%; 95% CI: 4%–16% • Retinopathy 19%; 95% CI: 0%–34% p=0.051	• More intensive strategy for BP control reduced cardio-renal endpoint
Xie X, et al., 2015 (21) 26559744	Study type: MA of RTC that randomly assigned individuals to different target BP levels Size: 44,989 pts	• 19 trials	Achieved BP 133/76 mm Hg (intensive) 140/81 (less intense) • Major CV events: 14%; 95% CI: 4%–22% • MI: 13%; 95% CI: 0%–24% • Stroke: 22%; 95% CI: 10%–32% • Albuminuria: 10%; 95% CI: 3%–16% • Retinopathy progression: 19%; 95% CI: 0%–34%. • More intensive had no effects on HF: 15%; 95% CI: -11%–34% • CV death: 9%; 95% CI: -11%–26% • Total mortality: 9%; 95% CI: -3%–19% • ESKD: 10%; 95% CI: -6%–23%	• More intensive approach reduced major CV events (stroke and MI) except heat failure, CVD, ESRD, and total mortality.
Thomopolous C, et al., 2016 (54) 26848994	Study type: Meta-analysis of RTCs of more vs. less intense BP control	• 16 trials (52,235 pts) compared more vs. less intense treatment 34 (138,127 pts) active vs. placebo	More intense BP • Stroke RR: 0.71; 95% CI: 0.60–0.84) • CHD RR: 0.80; 95% CI: 0.68–0.95) • Major CV events RR: 0.75; 95% CI: 0.68–0.85 • CV mortality RR: 0.79; 95% CI: 0.63–0.97 Stratification of SBP cutoffs (150,140 and 130 mm Hg) showed that a SBP/DBP difference of 10/5 mm Hg across each cutoff reduced risk of all outcomes	• Intensive BP reduction improves CV outcomes compared to less intense Achieved BP <130/80 may be associated with CV benefit.

Data Supplement 34. RCTs Comparing HF*r*EF (Section 9.2.1)

Study Acronym; Author; Year Published	Aim of Study; Study Type; Study Size (N)	Patient Population	Study Intervention (# patients) / Study Comparator (# patients)	Endpoint Results (Absolute Event Rates, P value; OR or RR; & 95% CI)	Relevant 2° Endpoint (if any); Study Limitations; Adverse Events; Summary
Herlitz J, et al., 2002 (142) 11862577	Aim: To see effect of metoprolol vs. placebo on mortality and hospitalizations among pts with history of HTN and HF with reduced LVEF Study type: RCT Size: 1,747 pts	Inclusion criteria: NYHA class II–IV HF with LVEF ≤40% within 3 mo of enrollment; supine resting HR ≥68 bpm; stable clinical condition Exclusion criteria: Acute MI or UA within 28 d of randomization; indication or contraindication for treatment with BBs or drugs with beta-blocking properties; poor compliance; CABG surgery or PTCA in past 4 mo	Intervention: • Administration of metoprolol • 871 pts randomized to metoprolol Comparator: • Administration of placebo • 876 pts randomized to placebo	1° endpoint: At 1-y follow-up, compared with placebo, metoprolol reduced all-cause mortality 39% (95% CI: 16%–56%; p=0.002) and all-cause mortality or all-cause hospitalization 24% (95% CI: 11%–35%; p=0.0007) 1° Safety endpoint: Early permanent cessation of drug was 12.5% for metoprolol and 15.9% for placebo (p=0.048); 21 pts on metoprolol and 35 pts on placebo had early cessation because of worsening	Relevant 2° endpoint: At 1-y follow-up, compared with placebo, metoprolol reduced CV death 41% (95% CI: 17%–57%; p=0.002), death from HF: 51% (95% CI: 1%–75%; p=0.042), sudden cardiac death 49% (95% CI: 21%–67%; p=0.002), all-cause mortality or HF hospitalization 28% (95% CI: 11%–42%; p=0.002), and cardiac death or nonfatal acute MI 44% (95% CI: 23%–60%; p=0.0003) Study limitations and adverse events: Early permanent cessation of drug was 12.5% for metoprolol and 15.9% for placebo (p=0.048); 21 pts on M and 35 pts on placebo had early cessation because of worsening HF; all-cause withdrawals were 22% less with metoprolol; (p=0.048); adverse events were 28% less with metoprolol (p=0.026); worsening HF was 41% less with metoprolol (p=0.056) Summary: In an RCT of pts with HF with reduced EF and a history of HTN, compared with placebo, metoprolol succinate reduced all-cause mortality and all-cause mortality or all-cause hospitalization
Packer M, et al., 2001 (140) 11386263	Aim: To assess survival in severe	Inclusion criteria: HF pts with dyspnea/exertion for 2 mo at least and left EF<25% despite	Intervention: Carvedilol (1,156)	1° endpoint: ● Death from any cause 130 vs. 190 deaths (RR: 35%;	• Study stopped early (1.3 y follow-up) due to benefit on survival

	chronic HF pts by the use of carvedilol. Study type: RCT Size: 2,289 pts	treatment clinically euvolemic; allowed on digitalis, nitrates, hydralazine, spironolactone, or amiodarone. Hospitalized pts with no acute illness. Exclusion criteria: HF due to uncorrected prim. valvular disease or reversible cardiomyopathy, cardiac transplant pts., coronary revasc. <2 mo, acute MI or stroke, ventricular tachycardia, on alpha blocker or CCB or on antiarrythmics class I <4 wk, SBP <85 mm Hg, serum Cr >2.8 mg/dL, change in body weight >1.5 kg during screening.	Comparator: Placebo (1,133)	95% CI: 19%–48%; p=0.00013) ● Combined risk of death/hospitalization (24% lower risk in the carvedilol; 95% CI: 13%–33%; p<0.001) Safety endpoint: Lesser pts in carvedilol group required permanent discontinuation because of adverse events or for reasons other than death (p=0.02)	● Long-term treatment is very valuable. ● Not all the pts with severe HF were allowed in the study
CAPRICORN Dargie HJ, et al., 2001 (141) 11356434	Aim: To investigate outcomes after carvedilol after MI in pts with LV dysfunction. Study type: RCT Size: 1,959 pts	Inclusion criteria: Pts ≥18 y, MI within 3–21 d of entry, LVEF ≤40%, concurrent ACEI stable dose for at least 24 h, HF pts treated and controlled with ACEI and diuretics but not inotropes. Exclusion criteria: SBP <90 mm Hg, uncontrolled HTN, bradycardia, insulin-dependent DM, BBs not for HF, Beta-2 agonists, and steroids	Intervention: Carvedilol (975) Comparator: Placebo (984)	1° endpoint: All-cause mortality or hospital admissions for CV issues Results: 12% vs. 15%; RR: 23% (95% CI: 0.60–0.98; p=0.03) No difference between groups for death or CV hospital admissions	● CV mortality, nonfatal MI reduced in the carvedilol group ● No difference between groups sudden death and admission due to HF
Elkayam U, et al., 1990 (144) 2242521	Aim: To assess comparative efficacy and safety of nifedipine and ISDN alone and the combination for treating for chronic CHF.	Inclusion criteria: 18–75 y old HF pts, NYHA class II and III, LVEF<40%, clinically stable, maintenance dose of Digitalis and diuretics. Exclusion criteria: Pregnancy, nursing, history of MI <1 mo before entry, valvular disease, angina, significant pulmonary,	Intervention: Nifedipine (21), ISDN (20), Nifedipine+ISDN (23) Comparator: Placebo	Endpoints and Results: ● HF-worsening: 9 in Nifedipine group vs. 3 in ISDN group (p<0.09); and 21 in nifedipine-ISDN group (p<0.001 vs. nifedipine, p<0.0001 vs. ISDN) ● Clinical deterioration discontinuation:	● In clinical deterioration nifedipine pts (8) vs. rest of the pts (No difference in LVEF or VO^2 max.) ● Although all the 3 drug regimens improved exercise capacity, nifedipine treatment alone or in combination resulted in clinical deterioration and worsening of CHF

	Study type: Crossover RCT Size: 28 pts	hepatic, renal and hematologic disease., unable to walk on the treadmill, noncompliance		Nifedipine 29% vs. ISDN group 5% (p<0.05) ● DBP: Nifedipine alone or combination with ISDN (reduction, p<0.05)	
MDPIT Goldstein RE, et al., 1991 (146) 1984898	Aim: To determine if dilitiazem increases late onset CHF in post-MI pts with early decline in EF. Study type: RCT Size: 2,466 pts	Inclusion criteria: 18–75 y HF pts, NYHA class II and III, LVEF <40%, clinically stable, maintenance dose of digitalis and diuretics. Exclusion criteria: Pregnancy, nursing, history of MI <1 mo before entry, valvular disease, Angina, significant pulmonary, hepatic, renal and hematologic disease., unable to walk on the treadmill, noncompliance	Intervention: Dilitiazem 240 mg (1,234) Comparator: Placebo (1,232)	1° endpoint and results: ● HF-worsening: 9 in Nifedipine group vs. 3 in ISDN group (p<0.09); and 21 in nifedipine-ISDN group (p<0.001 vs. nifedipine, p<0.0001 vs. ISDN) ● Clinical deterioration discontinuation: Nifedipine 29% vs. ISDN group 5% (p<0.05) ● DBP: Nifedipine alone or combination with ISDN (reduction, p<0.05) Follow-up Results: Pts with BL EF<0.40, late CHF in Dilitizam group (21%) vs. Placebo (12%) p=0.004.	● Life table analysis confirmed increased frequency of late CHF in pts taking dilitiazem (p=0.0017) ● Dilitiazem related CHF exclusively associated with systolic LVD with or without BB s
Cohn JN, et al., 2001 (152) 11759645	Aim: To determine the effect of valsartan vs. placebo on mortality plus morbidity in pts with HF*r*EF	Inclusion criteria: 5,010 pts, mean age 63 y, with NYHA class II-IV HF*r*EF	Intervention/Comparator: 5,010 pts on standard therapy for HF were randomized to valsartan or placebo	1° endpoint and results: ● At 23-mo follow-up, mortality was similar in pts treated with valsartan or placebo ● The combined endpoint of mortality plus morbidity was reduced 13.2% (p=0.009) by valsartan because of a lower rate of HF hospitalization for HF (13.8% vs. 18.2%; p<0.001)	● Treatment with valsartan resulted in improvements in NYHA class, LVEF, signs and symptoms of HF, and quality of life compared with placebo (p<0.01).
SOLVD Investigators, 1991 (153) 2057034	Aim: To determine the effect of enalapril vs. placebo on mortality and on mortality plus	Inclusion criteria: 2,569 pts, mean age 61 y, with HF*r*EF (90% with NYHA class II and III HF)	Intervention/Comparator: 2,569 pts on standard therapy for	1° endpoint and results: At 41.4-mo follow-up, compared with placebo, enalapril	● At 41.4-mo follow-up, compared with placebo, enalapril reduced mortality by 16% (p=0.0036)

	hospitalization for HF in pts with HF*r*EF		HF were randomized to enalapril or placebo	reduced mortality or hospitalization for worsening HF by 26% (p<0.0001)	
1993 (154) 8104270	Aim: To determine the effect of ramipril vs. placebo on mortality in pts with HF*r*EF	Inclusion criteria: 2,006 pts, mean age 65 y, with HF*r*EF after MI and without NYHA class0HF	Intervention/Comparator: 2,006 pts were randomized to ramipril or placebo	1° endpoint and results: At 15-mo mean follow-up, compared with placebo, ramipril reduced all-cause mortality 27% (p=0.002)	• Analysis of prespecified 2º outcomes showed that ramipril reduced the first validated outcome (death, severe/resistant HF, MI, or stroke) by 19% (p=0.008).
Garg R, et al., 1995 (155) 7654275	Aim: A meta-analysis was performed to determine the effect of ACEIs vs. placebo on mortality and on mortality plus hospitalization for HF in pts with HF*r*EF	Inclusion criteria: The meta-analysis included 32 trials of 7,105 pts with HF*r*EF treated with ACEIs vs. placebo	Intervention/Comparator: In 25 trials, pts were treated with digoxin and/or diuretics, 4 trials only used diuretics, 1 trial used only digoxin, and 2 trials used no background therapy	1° endpoint and results: Compared with placebo, ACEIs reduced all-cause mortality 23% (p<0.001) and all-cause mortality or hospitalization for HF 35% (p<0.001).	• The reduction in mortality was primarily due to a 31% (17%–42%) reduction in death from progressive HF.
Pfeffer MA, et al., 2003 (156) 14610160	Aim: To determine the effect of valsartan, captopril, or both on mortality in pts with MI complicated by HF, LV dysfunction, or both	Inclusion criteria: 14,703 pts, mean age 65 y, with MI complicated by HF, LV dysfunction, or both	Intervention: 4,909 pts were randomized to valsartan, 4,909 pts were randomized to captopril Comparator: 4,885 pts were randomized to valsartan plus captopril.	1° endpoint and results: At 24.7-mo median follow-up, mortality was similar in the 3 treatment groups.	• The incidence of adverse events causing discontinuation of drug was 5.8% with valsartan, 7.7% with captopril, and 9.0 % with valsartan plus captopril (p<0.05 comparing valsartan with captopril and valsartan plus captopril with captopril).
Maggioni AP, et al., 2002 (157) 12392830	Aim: A subgroup analysis of the Val-HeFT study was performed to determine the effect of valsartan vs. placebo on mortality and on mortality plus morbidity in pts with HF*r*EF not receiving ACEIs	Inclusion criteria: 366 pts, mean age 67 y, with HF*r*EF not receiving ACEIs	Intervention/Comparator: 185 pts were randomized to valsartan and 181 pts were randomized to placebo	1° endpoint and results: Compared with placebo, valsartan reduced mortality 33% (p=0.017) and mortality plus morbidity 44% (p<0.001).	• Compared with placebo, valsartan reduced first hospital admission for HF 53% (p=0.0006).

Granger CB, et al., 2003 (158) 13678870	Aim: To determine the effect of candesartan vs. placebo on mortality in pts with HF*r*EF intolerant to ACEIs	Inclusion criteria: 2,028 pts, mean age 67 y, with HF*r*EF intolerant to ACEIs	Intervention/Comparator: 1,013 pts were randomized to candesartan and 1,015 pts were randomized to placebo	1° endpoint and results: At 33.7-mo median follow-up, compared with placebo, the 1° endpoint of CV death or hospital admission for HF was reduced 30% by candesartan (p<0.0001).	• Compared with placebo, candesartan reduced CV death, hospital admission for HF, MI, stroke, or coronary revascularization 24% (p<0.0001).
Pitt B, et al., 2003 (159) 12668699	Aim: To determine the effect of eplerenone vs. placebo on mortality and on CV death or hospitalization for CV events in pts with MI complicated by HF*r*EF	Inclusion criteria: 6,632 pts, mean age 64 y, with HF*r*EF after MI	Intervention/Comparator: 3,313 pts were randomized to eplerenone and 3,319 pts were randomized to placebo	1° endpoint and results: At 16-mo mean follow-up, eplerenone reduced mortality 15% (p=0.008) and CV death or hospitalization for CV events 17% (p=0.005).	• Compared with placebo, eplerenone reduced death from any cause or any hospitalization 8% (p=0.02) and sudden cardiac death 21% (p=0.03), reduced hypokalemia from 13.1% to 8.4% (p<0.001), and increased serious hyperkalemia from 3.9%–5.5% (p=0.002).
Taylor AL, et al., 2004 (160) 15533851	Aim: To determine the effect of ISDN plus hydralazine vs. placebo on mortality, first hospitalization for HF, and change in quality of life in black pts with HF*r*EF	Inclusion criteria: 1,050 African American pts, mean age 57 y, with HF*r*EF and NYHA class III or IV HF.	Intervention/Comparator: 518 pts were randomized to ISDN plus hydralazine and 532 pts were randomized to placebo	1° endpoint and results: At 10-mo mean follow-up, compared with placebo, the mean 1° endpoint of mortality, first hospitalization for HF, and change in quality of life was reduced by ISDN plus hydralazine (p=0.01).	• Compared with placebo, ISDN plus hydralazine reduced mortality from 10.2%–6.2% (p=0.02) causing cessation of the study. • Compared with placebo, ISDN plus hydralazine reduced all-cause mortality 43% (first hospitalization for HF 33% (p=0.001), and improved quality of life (p=0.02).
The Multicenter Diltiazem Postinfarction Research Group, 1988 (145) 2899840	Aim: To assess dilitiazem effect on recurrent infarction and death after acute MI Study type: RCT Size: 2,466 pts	Inclusion criteria: 25–75 y admitted to CCU, MI with enzyme confirmation. Exclusion criteria: Cardiogenic shock, symptomatic hypotension, PH with right HF, 2nd/3rd degree heart block, HR <50 bpm, contraceptives, WPW syndrome, CCBs, severe comorbidities or cardiac surgery	Intervention: Dilitiazem 240 mg (1,234) Comparator: Placebo (1,232)	1° endpoints and results: • Total mortality: identical in both groups • Cardiac death and nonfatal MI: 11% fewer in dilitiazem but difference was NS	• No combined benefit from dilitiazem on mortality or cardiac events
ONTARGET Investigators, et al., 2008 (126) 18378520	Aim: Evaluate whether use of an ARB was noninferior to ACEI, and whether the combination was	Inclusion criteria: • ≥55 y • Coronary, peripheral, or cerebrovascular disease or DM	Intervention: Ramipril 10 mg daily (n=8,576) Comparator:	1° endpoint: After a median follow-up of 56 mo, there was no difference between ramipril vs. telmisartan or combination therapy vs. ramipril in the 1°	• Telmisartan was equivalent to ramipril in pts with vascular disease or high-risk DM and was associated with less angioedema. The combination of the 2 drugs was associated with more

	superior to ACE alone in the prevention of vascular events in pts with CVD or DM but not HF. Study type: Multi-center, double-blind, RCT Size: 25,620 pts	with end-organ damage Exclusion criteria: • Inability to discontinue ACEI or ARB • Known hypersensitivity or intolerance to ACEI or ARB • Selected CVDs (congestive HF, hemodynamically significant valvular or outflow tract obstruction, constrictive pericarditis, complex congenital heart disease, syncopal episodes of unknown etiology <3 mo, planned cardiac surgery or PTCA <3 mo, uncontrolled HTN on treatment [e.g., BP >160/100 mm Hg], heart transplant recipient, stroke due to subarachnoid hemorrhage) • Other conditions (significant renal artery disease, hepatic dysfunction, uncorrected volume or sodium depletion, 1° hyperaldosteronism, hereditary fructose intolerance, other major noncardiac illness or expected to reduce life expectancy or significant disability interfere with study participation, simultaneously taking another experimental drug, unable to provide written informed consent).	• Telmisartan 80 mg daily (n=8,542) • Combination of telmisartan and ramipril (n=8,502)	composite outcome of death from CV causes, MI, stroke, or hospitalization for HF (RR: 1.01; 95% CI: 0.94–1.09 and RR: 0.99; 95% CI: 0.92–1.07, respectively) Safety endpoint: • Combination therapy was associated with greater risk of hyperkalemia than ramipril monotherapy (480 pts vs. 283 pts; p<0.001) • Hypotensive symptoms were cited as reason for permanent discontinuing more in telmisartan vs. ramipril (RR: 1.54; p<0.001) and combination therapy vs. ramipril monotherapy (RR: 2.75; p<0.001) • Renal impairment was more common in combination therapy vs. ramipril monotherapy (RR: 1.33; 95% CI: 1.22–1.44)	adverse events without an increase in benefit

Data Supplement 35. RCTs Comparing HF*p*EF (Section 9.2.2)

Study Acronym; Author; Year Published	Aim of Study; Study Type; Study Size (N)	Patient Population	Study Intervention (# patients) / Study Comparator (# patients)	Endpoint Results (Absolute Event Rates, P value; OR or RR; & 95% CI)	Relevant 2° Endpoint (if any); Study Limitations; Adverse Events; Summary
TOPCAT Pfeffer MA, et al., 2015 (161) 25406305	Aim: To investigate variation in pts and outcome in TOPCAT between pts from the Americas vs. Russia/Georgia Study type: Post-hoc analysis of prospective, double-blind, RCT Size: 3,445 pts	Inclusion criteria: NYHA class II–IV HF with LVEF ≤40% within 3 mo of enrollment; supine resting heart rate ≥68 bpm; stable clinical condition Exclusion criteria: Acute MI or UA within 28 d of randomization; indication or contraindication for treatment with BBs or drugs with beta-blocking properties; poor compliance; CABG surgery or PTCA in past 4 mo	Intervention: • Americas 886 on spironolactone • Russia/Georgia 836 on spironolactone • Spironolactone 15–45 mg daily Comparator: • Americas 881 on placebo • Russia/Georgia 842 on placebo • Placebo	1° endpoint: Composite of CV death, aborted cardiac arrest, or HF hospitalization at 3.3 y follow-up was: Americas: 27.3% for spironolactone and 31.8% for placebo HR: 0.82; 95% CI: 0.69–0.98; p=0.026; Russia/Georgia 9.3% for spironolactone and 8.4% for placebo HR: 1.10; 95% CI: 0.79–1.51; p=0.58 1° Safety endpoint: • Doubling of serum creatinine: Americas: 17.8% for spironolactone and 11.6% for placebo HR: 1.60; 95% CI: 1.25–2.05; p<0.001 • Russia/Georgia 2.0% for S and 2.1% for p HR: 0.95; 95% CI: 0.49–1.85; p=0.89 • Creatinine >3.0 mg/dL • Americas 9.8% for spironolactone and 9.1% for placebo HR: 1.10; 95% CI: 0.81–1.49; p=0.55 • Russia/Georgia 0.2% for spironolactone and 0.4% for placebo HR: 0.5; 95% CI: 0.09–2.75; p=0.43 • Hyperkalemia (potassium >5.5 mmol/L) • Americas 25.2% for spironolactone and 8.9% for placebo OR: 3.46; 95% CI: 2.62–4.56; p<0.001	Relevant 2° endpoint: CV mortality: Americas 10.8% for spironolactone and 14.4% for placebo HR: 0.74; 95% CI 0.57–0.97; p=0.027; Russia/Georgia 7.7% for spironolactone and 5.8% for placebo HR: 1.31; 95% CI: 0.91–1.90; p=0.15. Aborted cardiac arrest: NS between groups. HF hospitalization: 20.8% for spironolactone and 24.5% for placebo HR: 0.82; 95% CI: 0.67–0.99; p=0.042; Russia/Georgia 2.6% for spironolactone and 3.4% for placebo HR: 0.76; 95% CI: 0.44–1.32; p=0.327; Recurrent HF: 361 events for spironolactone and 438 events for placebo (IRR: 0.75; 95% CI: 0.58–0.96; p=0.024) Russia/Georgia 33 events for spironolactone and 37 events for placebo (IRR: 0.83; 95% CI: 0.42–1.62; p=0.58) All-cause mortality: NS between groups in Americas and Russia/Georgia. All-cause hospitalization: NS between groups in Americas and Russia/Georgia. MI: NS between groups; Stroke: NS between groups Study limitations and adverse events: The pts enrolled in Russia/Georgia in the TOPCAT trial did not demonstrate either the expected morbidity and mortality associated with symptomatic HF or

				• Russia/Georgia 11.8% for spironolactone and 9.4% for placebo OR: 1.30; 95% CI: 0.95–1.77; p=0.10 • Hypokalemia (potassium <3.5 mmol/L) Americas 15.2% for spironolactone and 26.2% for placebo) 0.51 (95% CI: 0.40–0.64; p<0.001) • Russia/Georgia 17.2% for S and 19.4% for p OR: 0.87 (95% CI: 0.68–1.11; p=0.26)	most pharmacological responses to spironolactone Summary: In pts with HF with preserved EF, spironolactone reduced the 1° endpoint of composite of CV death, aborted cardiac arrest, or HF hospitalization in the Americas group but not in the Russia/Georgia group. The pts enrolled in the Russia/Georgia group did not demonstrate either the expected morbidity and mortality associated with symptomatic HF with preserved EF or most pharmacological responses to spironolactone
Aronow WS, et al., 1997 (162) 9230162	Aim: To determine effect of propranolol vs. no propranolol on mortality plus nonfatal MI in pts with prior MI and HF*p*EF	Inclusion criteria: Pts ≥62 y with MI and LVEF ≥40% and HF NYHA class II or III treated with diuretics and ACEIs for 2 mo	Intervention: 79 pts were randomized to treatment with propranolol Comparator: 79 pts were randomized to no propranolol. • All pts continued diuretic and ACEI therapy.	1° endpoint: At 32-mo mean follow-up, multivariate Cox regression analysis showed that compared with no propranolol, propranolol reduced mortality 35% (p=0.03) and mortality plus nonfatal MI 37% (p=0.018)	Relevant 2° endpoint: At 1-y follow-up, LVEF was increased by propranolol from 57% to 63% (p<0.001) and LV mass was decreased by propranolol from 312 grams to 278 grams (p=0.001) Propranolol was stopped because of adverse effects in 11 of 79 pts (14%)
Kostis JB, et al., 1997 (163) 9218667	Aim: To determine the effect of antihypertensive drug therapy vs. placebo in prevention of HF in pts with isolated systolic HTN	Inclusion criteria: Pts ≥60 y with isolated systolic HTN in the SHEP program	Intervention/Comparator: 4,736 pts were randomized to antihypertensive drug therapy or placebo	1° endpoint: At 4.5-y follow-up, fatal or nonfatal HF was reduced 49% (p<0.001) by antihypertensive drug therapy (NNT to prevent 1 event =48)	Relevant 2° endpoint: CV mortality and nonfatal hospitalized HF was reduced 30% (p=0.002) by antihypertensive drug therapy
Beckett NS, et al., 2008 (164) 18378519	Aim: To determine the effect of antihypertensive drug therapy on fatal or nonfatal stroke in pts ≥80 y	Inclusion criteria: Pts ≥80 y with a SBP≥160 mm Hg	Intervention/Comparator: 3,845 pts were randomized to antihypertensive drug therapy or placebo	1° endpoint: The 1° endpoint of fatal or nonfatal stroke was reduced 30% (p=0.06) by antihypertensive drug therapy	Relevant 2° endpoint: Antihypertensive drug therapy reduced HF 64% (p<0.001) all-cause mortality 21% (p=0.02), and CV death 23% (p=0.06)

Van Veldhuisen DJ, et al., 2009 (165) 19497441	Aim: To determine the effect of nebivolol vs. placebo in pts with HF*r*EF and HF*p*EF	Inclusion criteria: Pts ≥70 y, history of HF, and HF*r*EF or HF*p*EF	Intervention/Comparator: 1,359 pts with a history of HF*r*EF and 752 pts with a history of HF*p*EF were randomized to nebivolol or to placebo	1° endpoint: At 21-mo follow-up, the 1° endpoint of all-cause mortality or CV hospitalization was reduced by nebivolol 14% (95% CI: 0.72–1.04) in pts with HF*r*EF and 19% (95% CI: 0.63, 1.04) in pts with HF*p*EF	Relevant 2° endpoint: HR for reduction of all-cause mortality by nebivolol: 0.84 (95% CI: 0.86–1.08) for HF*r*EF and 0.91 (95% CI: 0.62–1.33) for HF*p*EF
Yusef S, et al., 2003 (166) 13678871	Aim: To determine the effects of candesartan vs. placebo in pts with HF*p*EF	Inclusion criteria: 3,032 pts, mean age 67 y, with HF*p*EF and NYHA class II-IV HF	Intervention/Comparator: 3,032 pts were randomized to candesartan or placebo	1° endpoint: At 36.6 m follow-up, the 1° outcome of CV death or hospitalization for HF was reduced 11% (p=0.118) by candesartan	Relevant 2° endpoint: Hospitalization was reduced 16% (p=0.047) by candesartan
Massie BM, et al., 2008 (167) 19001508	Aim: To determine the effect of irbesartan vs. placebo on all-cause mortality or hospitalization for a CV cause in pts with HF*p*EF	Inclusion criteria: Pts 60 y and older with HF*p*EF and NYHA class II, III, or IV HF	Intervention/Comparator 4,128 pts were randomized to irbesartan or placebo	1° endpoint: At 49.5-mo follow-up, the 1° outcome of all-cause mortality or hospitalization for CV cause was reduced 5% by irbesartan (p=0.35)	Relevant 2° endpoint: Irbesartan did not significantly reduce the 2º outcomes of death from HF or hospitalization for HF, death from any cause and from CV causes, and quality of life
Piller LB, et al., 2011 (168) 21969009	Aim: To determine mortality rates in pts who developed HF in ALLHAT	Inclusion criteria: 1,761 pts, mean age 70 y, developed HF during ALLHAT	Intervention/Comparator At 8.9-y mean follow-up, 1,348 of 1,761 pts (77%) with HF died	1° endpoint: Post-HF all-cause mortality was similar for pts treated with chlorthalidone, amlodipine, and lisinopril. 10-y adjusted rates for mortality were 86% for amlodipine, 87% for lisinopril, and 83% for chlorthalidone	Relevant 2° endpoint: All-cause mortality rates were similar for those with HF*r*EF (84%) and for those with HF*p*EF (81%) with no significant differences by randomized treatment arm
Law MR, et al., 2009 (18) 19454737	Study type: Meta-analysis of use of BP-lowering drugs in prevention of CVD from 147 randomized trials Size: Of 147 randomized trials of 464,000 pts, 37 trials of BBs in CAD included 38,892 pts, and 37 trials of	Inclusion criteria: The database search used Medline (1966-Dec. 2007 in any language) to identify randomized trials of BP-lowering drugs in which CAD events or strokes were recorded. The search also included the Cochrane Collaboration and	1° endpoint: CAD events; stroke Results: In 37 trials of pts with a history of CAD, BBs reduced CAD events 29% (95% CI: 22%–34%). In 27 trials in which BBs were used after acute MI, BBs reduced CAD events 31% (95% CI: 24%–38%), and in 11 trials in which BBs were used after long-term CAD, BBs	• With the exception of the extra protective effect of BBs given shortly after a MI and the minor additional effect of CCBs in preventing stroke, all the classes of BP-lowering drugs have a similar effect in reducing CAD events and stroke for a given reduction in BP.	N/A

	other antihypertensive drugs in CAD included 85,395 pts	Web of Science databases and the citations in trials and previous meta-analyses and review articles. Exclusion criteria: Trials were excluded if there were <5 CAD events and strokes or if treatment duration was <6 mo.	insignificantly reduced CAD events 13%. In 7 trials, BBs reduced stroke 17% (95% CI: 1%–30%). CAD events were reduced 14% (95% CI: 2%–25%) in 11 trials of thiazide diuretics, 17% (95% CI: 11%–22%) in 21 trials of ACEIs, insignificantly 14% in 4 trials of angiotensin receptor blockers, and 15% (95% CI: 8%–22%) in 22 trials of CCBs. Stroke was reduced 38% (95% CI: 28%–47%) in 10 trials of thiazide diuretics, 22% (95% CI: 8%–34%) in 13 trials of ACEIs, and 34% (95% CI: 25%–42%) in 9 trials of CCBs.		

Data Supplement 36. Nonrandomized Trials, Observational Studies, and/or Registries of HF*p*EF (Section 9.2.2)

Study Acronym; Author; Year Published	Study Type/Design; Study Size (N)	Patient Population	Primary Endpoint and Results (include P value; OR or RR; & 95% CI)	Summary/Conclusion Comment(s)
Law MR, et al., 2009 (18) 19454737	Study type: Meta-analysis of use of BP-lowering drugs in prevention of CVD from 147 randomized trials Size: Of 147 randomized trials of 464,000 pts, 37 trials of BBs in CAD included 38,892 pts, and 37 trials of other antihypertensive drugs in CAD included 85,395 pts	Inclusion criteria: The database search used Medline (1966–Dec. 2007 in any language) to identify randomized trials of BP-lowering drugs in which CAD events or strokes were recorded. The search also included the Cochrane Collaboration and Web of Science databases and the citations in trials and previous meta-analyses and review articles.	1° endpoint: CAD events; stroke Results: In 37 trials of pts with a history of CAD, BBs reduced CAD events 29% (95% CI: 22%, 34%). In 27 trials in which BBs were used after acute MI, BBs reduced CAD events 31% (95% CI: 24%, 38%), and in 11 trials in which BBs were used after long-term CAD, BBs insignificantly reduced CAD events 13%. In 7 trials, BBs reduced stroke 17% (95% CI: 1%–30%). CAD events were reduced 14% (95% CI: 2%–25%) in 11 trials of thiazide diuretics, 17% (95% CI: 11%–22%) in 21 trials of ACEIs, insignificantly 14% in 4 trials of angiotensin receptor blockers, and 15% (95% CI: 8%–22%) in 22 trials of CCBs. Stroke was reduced 38% (95% CI: 28%–47%) in 10 trials of	• With the exception of the extra protective effect of BBs given shortly after a MI and the minor additional effect of CCBs in preventing stroke, all the classes of BP-lowering drugs have a similar effect in reducing CAD events and stroke for a given reduction in BP.

		Exclusion criteria: Trials were excluded if there were <5 CAD events and strokes or if treatment duration was <6 mo.	thiazide diuretics, 22% (95% CI: 8%–34%) in 13 trials of ACEIs, and 34% (95% CI: 25%–42%) in 9 trials of CCBs.	

Data Supplement 37. RCTs Comparing CKD (Section 9.3)

Study Acronym; Author; Year Published	Aim of Study; Study Type; Study Size (N)	Patient Population	Study Intervention (# patients) / Study Comparator (# patients)	Endpoint Results (Absolute Event Rates, P value; OR or RR; & 95% CI)	Relevant 2° Endpoint (if any); Study Limitations; Adverse Events; Summary
MDRD Klahr S, et al., 1994 (169) 8114857	Aim: To determine whether restricted protein intake or tighter HTN control would delay progression of CKD Study type: Randomized management to low or usual BP goal and usual, low or very low protein intake Size: • Total n=840 Study 1 n=585 Study 2 n=255 • Mean follow-up 2.2 y • Mean MAP, mm Hg (SD): Study 1: 98 (11) Study 2: 98 (11) • Mean SBP, mm Hg (SD): Study 1: 131 (18) Study 2: 133 (18)	Inclusion criteria: Adults 18–70 y, with renal insufficiency (serum Cr 1.2–7.0 mg/dL in women and 1.4–7.0 mg/dL in men or CrCl <70 mL/min per 1.73 m²) and MAP≤125 mm Hg (normotensives included) Exclusion criteria: Pregnancy, body weight <80% or >160% of standard, DM requiring insulin, urine protein >10 g/d, history of renal transplant, chronic medical conditions, doubts regarding compliance.	Intervention: • Study 1 included subjects with GFR 25–55 mL/min 1.73 m² (n=585); • Study 2 included subjects with GFR 13–24 mL/min 1.73 m² (n=255) • Low MAP goal ≤92 mm Hg for those 18–60 y; ≤98 for those ≥61 y • Usual: MAP goal ≤107 mm Hg for those 18–60; MAP ≤113 for subjects ≥61 • 2 studies: Study 1: above BP goals plus usual or low protein diet (1.3 or 0.58 g protein per kg of body weight/d) Study 2: above BP goals plus low or very low protein diet (0.58 or 0.28 g per kg/d) • Between group difference in MAP, mm Hg 4.7; p<0.001	1° endpoint: Rate of decline in GFR, mL/min (95% CI) • Study 1 From baseline to 4 mo Low: 3.4; 95% CI: 2.6–4.1 Usual: 1.9; 95% CI: 1.1–2.7 p=0.010 4 mo to study end, Low: 2.8; 95% CI: 2.2–3.3 Usual: 3.9; 95% CI: 3.3–4.5 p=0.006 Baseline to 3 y, Low: 10.7; 95% CI: 9.1–12.4 Usual: 12.3; 95% CI: 10.6–14.0 p=0.18 • Study 2 From baseline to end of study, Low: 3.7; 95% CI: 3.1–4.3 Usual: 4.2; 95% CI: 3.6–4.9 p=0.28 ESRD or death: • Study 2 RR for low vs. usual: 0.85; 95% CI: 0.60–1.22 p=NR	Limitations: • Drug therapy was not randomized. Recommended ACEI ± diuretic then CCB and others. More subjects in the low BP goal groups received ACEIs (48%, 51% also reported elsewhere) compared to the usual BP goal group (28%, 32% also reported e/w) (not noted in 1° manuscript but reported in Peterson JC, et al., 1995 (170)). 1.9% study 1, 1.2% study 2 lost to follow-up. • Rate of GFR decline was slower than expected in the control groups and was not constant. Summary: No significant benefits overall from either low protein or lower BP target. There was a significant interaction between baseline urinary protein excretion and BP interventions (p=0.01) indicating that low BP was of benefit to subjects with >1 g proteinuria with slower progression of loss of GFR

	• Mean DBP, mm Hg (SD): Study 1: 81 (10) Study 2: 81 (10)		Comparator: By BP and protein intake goals		
REIN-2 Ruggeneti P, et al., 2005 (171) 15766995	Aim: To determine whether intensive BP control will achieve further renoprotection (delayed progression to ESRD) compared to standard BP control in pts with chronic nephropathies Study type: Multicenter RCT of pts all placed on ACEI (ramipril) at maximum dose tolerated to achieve DBP <90 then assigned to conventional or intensified BP control. Add-on drug was dihydropyridine felodipine 5–10 mg/d Size: 335 (median time 19 mo)	Inclusion criteria: • Adults, age 18–70 y, with nondiabetic nephropathy, persistent proteinuria (urinary protein excretion >1 g/24 h for ≥3 mo) and not on ACEIs in previous 6 wk • Pts with proteinuria 1–3 g/24 h included if CrCl <70 mL/min/1.73 m^2 • For overall population, mean SBP, mm Hg (SD): Intensive: 137.0 (16.7) Conventional: 136.4 (17.0) • For overall population, mean DBP, mm Hg (SD): Intensive: 84.3 (9.0) Conventional: 83.9 (10.4) Exclusion criteria: Urinary tract infection, CHF class III–IV, treatment with corticosteroids, NSAIDs, immunosuppression, acute MI or stroke in prior 6 mo, severe uncontrolled HTN,	Intervention: • Intensive: BP goal <130/80 mm Hg • Conventional: DBP goal <90 mm Hg, irrespective of SBP • For baseline proteinuria subgroups, result BP values NR • For the overall population, achieved BP, mm Hg (SD) Intensive: 129.6/79.5 (10.9/5.3) Conventional: 133.7/82.3 (12.6/7.1) p=0.0019/<0.0001 • For the overall population, change in BP, mm Hg Intensive: -7.4/-4.8 Conventional: -2.7/-1.6 p=NR • For the overall population, BP difference between groups, mm Hg 4.1/2.8 p=NR	1° endpoint • Time to ESRD; over 36 mo follow-up, median 19 mo 1° outcome: ESRD in pts with baseline proteinuria 1–3 g/24 h HR (95% CI): 1.06 (95% CI: 0.51–2.20) p=0.89 • ESRD in pts with baseline proteinuria >3 g/24 h HR (95% CI): 1.09 (95% CI: 0.55–2.19) p=0.81 • 23% of intensive and 20% of conventional control groups progressed to ESRD. • Median rate of GFR decline, mL/min/1.73 m^2/mo (IQR) in pts with baseline proteinuria <3 g/24: Intensive: 0.18 (95% CI: 0.03–0.49) Conventional: 0.21 (95% CI: -0.03–0.40) p=0.89 • Median rate of GFR decline, mL/min/1.73 m/mo (IQR) in pts with baseline proteinuria ≥3 g/24: Intensive: 0.51; 95% CI: 0.16–1.05 Conventional: 0.39; 95% CI: 0.030.98 p=0.39	Limitations: The study was stopped at the 1st interim analysis for futility. Median time 19 mo Summary: In pts with non-DM proteinuric nephropathies receiving background ACEI therapy, no additional benefits from further BP reduction by felodipine could be shown. Dihydropyridine CCBs do not offer additional renoprotection to ACEIs or ARBs.

		suspicion for renovascular disease, obstructive uropathy, DM-1, collagen vascular disease, cancer, elevated aspartate transaminase, chronic cough, history of allergy or poor tolerance to study meds, alcohol abuse, pregnancy, breastfeeding, ineffective contraception.	Comparator: By BP goals		
AASK Wright JT, et al., 2002 (172) 12435255	Aim: To compare the effects of 2 levels of BP and 3 antihypertensive drug classes on GFR decline in HTN Study type: • Randomized 3×2 factorial trial • Measured GFR with iothalamate Size: 1,094	Inclusion criteria: • Adult African-Americans,18–70 y, with HTN (DBP ≥95) and GFR of 20–65 mL/min/1.73 m^2, no DM • At entry: mean MAP, mm Hg: Low: 115 (27) Usual: 113 (15) • Mean SBP, mm Hg (SD): Low:152 (25) Usual: 149 (23) • Mean DBP, mm Hg: Low: 96 (15) Usual: 95 (14) Exclusion criteria: DBP<95, history of DM, Urinary protein/creatinine ratio >2.5, accelerated or malignant HTN, non-BP related cause of CKD, serious systemic disease, clinical CHF, specific indication or contraindication for a	Intervention: • Low: MAP goal ≤92 mm Hg Usual: MAP goal 102–107 mm Hg • Initial treatment with a B Blocker (metoprolol), and ACEI (ramipril) or a dihydropyridine (amlodipine) with open label agents added to achieve BP goals • Study duration: 3–6.4 y • BP similar across drug groups except 2 mm Hg lower in amlodipine group • Mean from 3 mo to study end • MAP, mm Hg (SD) Low: 95.8 (8) Usual: 104 (7) • SBP/DBP, mm Hg (SD) Low: 128/78 (12/8) Usual: 141/85 (12/7) • MAP change, mm Hg Low: -20	1° endpoint: • 1° outcome: difference in mean slopes, acute GFR slope, mL/min/1.73 m^2/3 mo (SE): • 1.82 (0.54) in low BP group p<0.001 • 1° outcome: difference in mean slopes, chronic GFR slope, mL/min/1.73 m^2/y (SE): 0.21 (0.22) p=0.33 NS • Difference in mean slopes, total GFR slope, mL/min/1.73 m^2/y (SE): -0.25 (0.22) p=0.24 • Main 2º clinical composite outcome: GFR event, ESRD, or death, % risk reduction (95% CI): 2 (95% CI: -22–21) p=0.85 • GFR event or ESRD, % Risk Reduction: -2; 95% CI: -31–20; p=0.87 • ESRD or death, % risk reduction: 12; 95% CI: -13–32; p=0.31 • ESRD alone, % risk reduction: 6; 95% CI: -29–31; p=0.72	Limitations: • Based on DSMD recommendation, amlodipine arm halted early and those pts switched to open label Rx, continued study schedule and same BP goals Summary: • No difference in GFR decline with lower BP goal and no difference in composite clinical endpoints • Average rate of GFR decline 2 mL/min/y is similar or slower than previous reports • There was a trend favoring the lower BP goal in subjects with higher baseline proteinuria and the opposite trend for those without proteinuria • Ramipril treatment group had slower progression compared with metoprolol and amlodipine combined, less evident between ramipril and metoprolol

		study drug or procedure	Usual: -9 • SBP/DBP change, mm Hg Low: -24/-8 Usual: -18/-10 • Achieved mean BP difference between groups, mm Hg MAP: 11 SBP: 16 DBP: 8 Comparator: N/A	• 2º outcome: urine protein excretion Safety endpoint: • Acute and chronic rate of change in GFR (slope): NS for chronic and total slope in subgroup analyses by baseline proteinuria strata • Acute slope: p=0.08 for interaction • Total slope: p=0.04 for interaction • Chronic slope: p=0.16 for interaction • Clinical composite outcome: includes reduction in GFR by 50% or by 25 mL/min/m², ESRD, death, NS in subgroup analyses by baseline proteinuria strata; p=0.007 for interaction • For above outcomes, trends favored the lower BP goal over the usual goal in participants with higher baseline proteinuria and opposite trends in participants with little or no proteinuria Within each drug group, risk reductions for any 2º clinical outcome of the low vs. usual BP goal were not significantly different between pts with baseline urine protein to creatinine ratio ≤0.22 and >0.22 (p=NS)	
Contreras G, et al., 2005 (173) 15897360	Aim: Within AASK to examine the effect of BP intervention separately in the 3 drug treatment groups Study type: • Randomized 3×2 factorial trial • Measured GFR with iothalamate Size: 1,094	Inclusion criteria: • Adult African Americans, ages 18–70, with HTN (DBP ≥95) and GFR of 20–65 mL/min/1.73 m², no DM Mean MAP, mm Hg: Low, Amlodipine: 115.3 (18.3) Usual, Amlodipine: 112.7 (14.7) Low, Metoprolol: 114.5 (17.5)	Intervention: • Analysis by initial drug treatment group • Low, Amlodipine: MAP goal ≤92 mm Hg, Amlodipine (5–10 mg/d) Usual, Amlodipine: MAP goal 102–107 mm Hg, Amlodipine (5–10 mg/d) • Low, Metoprolol: MAP goal ≤92 mm Hg, Metoprolol (50–200 mg/d)	1° endpoint: • GFR event, ESRD, or death prior to dialysis, Amlodipine, Low vs. Usual Goal RR: 32%; 95% CI: -14–60; p=0.14 • Metoprolol, Low vs. Usual Goal RR: 4%; 95% CI: -39–33; p=0.84 • Ramipril, Low vs. Usual Goal RR: -8%; 95% CI: -93–15; p=0.24 p for interaction=0.17 • GFR event or ESRD, Amlodipine, Low vs. Usual Goal RR: 26%; 95% CI: -33–58; p=0.32	Limitations: Post-hoc analysis, effects on GFR may have been obscured by early rise and later fall with amlodipine, follow-up only 3–6.4 y, many comparisons so risk for type I error, unable to test ACEI – DHP CCB combination. Summary: • BP effect was similar among drug groups for GFR slope and main clinical composite.

		Usual, Metoprolol: 112.4 (14.1) Low, Ramipril: 115.2 (15.2) Usual, Ramipril: 114.0 (16.7) ● Mean SBP, mm Hg: Low, Amlodipine: 152.2 (28.2) Usual, Amlodipine: 147.7 (21.9) Low, Metoprolol: 152.0 (25.7) Usual, Metoprolol: 147.7 (21.4) Low, Ramipril: 151.0 (22.5) Usual, Ramipril: 150.9 (24.1) ● Mean DBP, mm Hg: Low, Amlodipine: 96.55 (15.1) Usual, Amlodipine: 94.87 (12.9) Low, Metoprolol: 95.45 (15.4) Usual, Metoprolol: 94.47 (12.5) Low, Ramipril: 96.90 (13.6) Usual, Ramipril: 95.12 (15.3) <u>Exclusion criteria:</u> DBP<95, history of DM, Urinary protein/creatinine ratio >2.5, accelerated or malignant HTN, non-BP related cause of CKD, serious systemic	Usual, Metoprolol: MAP goal 102–107 mm Hg, Metoprolol (50–200 mg/d) ● Low, Ramipril: MAP goal ≤92 mm Hg, Ramipril (2.5–10 mg/d) Usual, Ramipril: MAP goal 102–107 mm Hg, Ramipril (2.5–10 mg/d) ● Note: Amlodipine arms terminated 1 y early ● Achieved MAP difference between groups, mm Hg Amlodipine, Low vs. Usual:12.89 Metoprolol, Low vs. Usual: 11.11 Ramipril, Low vs. Usual: 10.12 p=NR ● Achieved SBP difference between groups, mm Hg Amlodipine, Low vs. Usual: 18.4 Metoprolol, Low vs. Usual: 15.4 Ramipril, Low vs. Usual: 12.6 p=NR ● Achieved DBP difference between groups, mm Hg Amlodipine, Low vs. Usual: 10.14 Metoprolol, Low vs. Usual: 8.86	● Metoprolol, Low vs. Usual Goal RR: 7%; 95% CI: -42–39; p=0.74 ● Ramipril, Low vs. Usual Goal RR: -42%; 95% CI: -126–11; p=0.14 p for interaction=0.20 ● ESRD or death prior to dialysis, Amlodipine, Low vs. Usual Goal RR: 51%; 95% CI: 13–73; p=0.016 ● Metoprolol, Low vs. Usual Goal RR: 11%; 95% CI: -40–44; p=0.61 ● Ramipril, Low vs. Usual Goal RR: -32%; 95% CI: -114–18; p=0.26 p for interaction=0.035 ● Death alone (prior to dialysis), Amlodipine, Low vs. Usual Goal RR: 48%; 95% CI: -59–83; p=0.25 ● Metoprolol, Low vs. Usual Goal RR: -1; 95% CI: -110–5; p=0.97 ● Ramipril, Low vs. Usual Goal RR: 21%; 95% CI: -92–67; p=0.61; p for interaction=0.61 <u>Safety endpoint</u>: ● ESRD alone, Amlodipine, Low vs. Usual Goal: RR: 54%; 95% CI: 8–77; p=0.028 ● Metoprolol, Low vs. Usual Goal RR: 11%; 95% CI: -60–50; p=0.70 ● Ramipril, Low vs. Usual Goal RR: -65%; 95% CI: -195–8; p=0.09; p for interaction=0.021 ● Death alone (prior to dialysis), Amlodipine, Low vs. Usual Goal: RR: 48%; 95% CI: -59–83; p=0.25 ● Metoprolol, Low vs. Usual Goal: RR: -1; 95% CI: -110–5; p=0.97 ● Ramipril, Low vs. Usual Goal RR: 21%; 95% CI: -92–67; p=0.61; p for interaction=0.61	● BP effect differed among drug groups for composite of ESRD or death and ESRD alone. ● Higher event rates for amlodipine and usual BP goal compared with other groups. ● Low BP goal associated with reduced risk of ESRD or death and ESRD for amlodipine but not for other drug groups (in the absence of ACEI treatment).

		disease, clinical CHF, specific indication or contraindication for a study drug or procedure	Ramipril, Low vs. Usual: 8.96 p=NR Comparator: N/A	● Proteinuria within each drug group, risk reductions for any 2° clinical outcome of the low vs. usual BP goal were not significantly different between pts with baseline urine protein to creatinine ratio ≤0.22 and >0.22 (p=NS)	
Norris K, et al., 2006 (174) 17059993	Aim: Compared effect of treatment on CV event rate during mean follow-up of 4.1 y by drug class and level of BP control. Determined baseline factors that predict CV outcomes Study type: Randomized 3×2 factorial trial Measured GFR with iothalamate Size: 1,094	Inclusion criteria: ● Adult African Americans, 18–70 y, with HTN (DBP ≥95) and GFR of 20–65 mL/min/1.73 m², no DM ● Mean MAP, mm Hg: 114 (16) ● Mean SBP, mm Hg: 150 (24) ● Mean DBP, mm Hg: 96 (14) Exclusion criteria: N/A	Intervention: ● Achieved SBP/DBP, mm Hg (SD) Low: 128/78 Usual: 141/85 p=NR ● SBP/DBP change, mm Hg Low: -23/-19 Usual: -8/-9 p=NR ● Achieved mean BP difference between groups, mm Hg SBP: 15 DBP: 10 p=NR Comparator: N/A	1° endpoint: ● Number of deaths before ESRD, n of events Low: 38 Usual: 47; p=NR ● Major CAD events, n of events (rate per person-y) Low: 19 (0.008) Usual: 23 (0.010); p=NS ● Stroke events, number of events (rate per person-y) Low: 26 (0.011) Usual: 29 (0.013); p=NS ● HF events, n of events (rate per person-y) Low: 27 (0.012) Usual: 23 (0.010) p=NS ● CV composite outcome, n of events (rate per person-y) Low: 71 (0.032) Usual: 78 (0.035); p=NS ● Composite outcome or ESRD, n of events (rate per person-y) Low: 143 (0.064) Usual: 159 (0.072) p=NS ● Overall rate of CV events, n of events (rate per person-y) Low: 108 (0.048) Usual: 94 (0.042); p=NS ● CV death, n of events (rate per person-y) Low: 16 (0.007)	Limitations: ● Limited power, only 202 CV events – low incidence. CV outcomes were 2º endpoints of high priority (prespecified). ● >50% had a history of heart disease at entry, 40% with LVH by ECG. 1/3 smokers, almost 50% had income <15K. Summary: ● CV outcome rate was not related to randomized interventions, either drug or BP target. ● 7 baseline risk factors were independently associated with increased risk for CV composite outcome in multivariable analyses after controlling for age, sex, baseline GFR, baseline proteinuria: PP, duration of HTN, protein/creatinine ratio, urine sodium-potassium ratio and annual income <15,000.

				Usual: 15 (0.006); p=NS	
Amlodipine Versus Enalapril in Renal Failure (AVER trial) Esnault VL, et al., 2008 (175) 18405787	Aim: To compare GFR decline in nondiabetic, nonnephrotic adults with HTN and estimated CrCl 20–60 mL/min/1.73 m² when randomized to a CCB (amlodipine, 5–10 mg/d) or an ACEI (enalapril, 5–20 mg/d). Study type: RCT Size: Amlodipine: 132 Enalapril: 131	Inclusion criteria: ● 18–80 y ● CrCl 20–60 mL/min/1.73 m² (Cockcroft-Gault) ● Nondiabetic ● Enrollment confirmed at end of 4-wk placebo run-in if sitting DBP between 90 and 119 mm Hg ● Mean SBP, mm Hg (SD): Amlodipine: 165.1 (15.4) Enalapril: 165.2 (16.6) ● Mean DBP, mm Hg (SD): Amlodipine: 102.0 (6.7) Enalapril: 102.5 (7.1) ● Mean serum Cr, mg/dL (SD): Amlodipine: 2.00 (0.8) Enalapril: 2.05 (0.7) Exclusion criteria: ● Nephrotic proteinuria ● 2º or malignant HTN (DBP >120 mm Hg) ● A major CV event within 3 mo ● Angina pectoris ● Congestive heart disease (NYHA II-IV) ● Uncontrolled arrhythmias ● II-III AV block ● Need for serious steroids, NSAIDS or cytotoxic drugs	Intervention: ● Amlodipine: 5–10 mg/d ● Enalapril: 5–20 mg/d Therapy initiated with amlodipine 5 mg/d or enalapril 5 mg/d. Drugs up-titrated to amlodipine 10 mg/d or enalapril 20 mg/d at wk 8 and 12 if DBP >90 mm Hg. After 18 wk, if maximal tolerated dose of study drug did not decrease BP to target, add on anti-HTN treatments were the following: atenolol (50–100 mg/d), loop diuretics (furosemide 20–500 mg/d or torsemide, 5–200 mg/d), alpha blockers (prazosin, 2.4–5 mg/d or doxazosin, 1–16 mg/d) and centrally acting drugs (rilmenidine (1–2 mg/d or methyldopa, 250–500 mg/d). ● BP goal: Amlodipine: <130/85 mm Hg Enalapril: <130/85 mm Hg Duration of treatment: Median follow-up 2.93 y in amlodipine group; 2.95 y in enalapril group	1° endpoint: Change in GFR from baseline to final assessment 2° Outcome: Clinical composite of renal replacement therapy, discontinuation due to deterioration of renal function, 50% decrease in GFR, doubling of serum Cr, hospitalization for transient renal failure. "Other 2º outcome measures" included: changes in serum Cr, sitting DBP and SBP, heart rate, total and HDL cholesterol, 24-h urinary protein excretion, ambulatory BP monitoring, and safety measures. Composite Outcomes: 2º clinical composite Safety endpoint: Proteinuria subgroup, >1 g/d: protein excretion rate decreased significantly in pts taking enalapril plus diuretic (median -270 mg/d; p<0.001) but not in pts taking amlodipine plus diuretic (-25 mg/d) at last obs	Summary: ● No difference in GFR change or serum creatinine at trial end Last observation: mean change in GFR, mL/min/1.73 m² Amlodipine -4.92, Enalapril -3.98; p=NS ● Last observation: mean change in Serum Cr from baseline (mg/d) Amlodipine +0.57, Enalapril +0.47; p=NS ● No difference in composite 2º endpoints. ● Mean BP (mm Hg): baseline to last observation Amlodipine 164.8/101.8 to 140.1/85.4, delta -24.7/16.4 Enalapril 165.0/102.5 to 140.3/86.4, delta -24.7/16.1

		● Women of child-bearing potential not using appropriate contraceptives ● Any disease that could limit the ability of pts to comply with protocol requirements			
ESPIRAL Marin R, et al., 2001 (176) 11593109	Aim: To investigate in a random comparison the capacity of an angiotensin converting enzyme inhibitor (fosinopril), and that of a long-acting dihydropiridine (nifedipine GITS) to modify the decay in renal function in pts with primary renal disease, exhibiting a progressive increase in serum Cr during the previous 2 y. Study type: Randomized open label trial Size: 241 Nifedipine GITS: 112 Fosinopril: 129	Inclusion criteria: ● 18–75 y ● Serum Cr between 1.5 and 5 mg/dL (133–442 µmol/l) ● HTN defined as BP >140/90 mm Hg or by the use of antihypertensive agent(s) ● Proven progression of chronic renal failure in the previous 2 y, defined by increase by >25% or >0.5 mg/dL (44.2 µmol/l) in serum Cr ● Mean SBP, mm Hg (SD): Nifedipine GITS: 157.5 (20) Fosinopril: 155 (17) ● Mean DBP, mm Hg (SD): Nifedipine GITS: 96 (11) Fosinopril: 96 (8) Exclusion criteria: ● DM ● Previous recent history of CVD (stroke, MI, or HF) ● Taking concomitant medications that could	Intervention: ● Nifedipine GITS: 30–60 mg QD ● Fosinopril: 10–30 mg QD ● Drugs added in step-wise fashion to achieve BP goal. ● Step 1: Randomized drug ● Step 2: Furosemide (up to 100 mg) ● Step 3: Atenolol (up to 100 mg) ● Step 4: Doxazosin (up to 12 mg) ● BP goal: Nifedipine GITS: <140/90 mm Hg Fosinopril: <140/90 mm Hg ● Duration of treatment: mean follow-up NR; authors report minimum follow-up of 3 y and this is when most outcome measures reported	1° endpoint: ● 1° Outcome: Time elapsed until serum Cr values doubled, or the need to enter a dialysis program ● 2º Outcome: CV events (including MI, stroke, angina, and death), proteinuria evolution and serum Cr Safety endpoint: N/A	Limitations: ● SBP was 4–6 mm Hg lower with ACEI which may have impacted improved outcomes. Still positive effects remained from fosinopril after adjusted for BP levels. ● Sodium restriction may have favored the ACEI group. Summary: ● Renal survival was significantly better if fosinopril used as first agent, unrelated to the primary renal disease. ● Proteinuria decreased by 57% in the fosinopril group and increased by 7% in the nifedipine GITS group while BP control did not differ between treatment groups for DBP. ● 3-y follow-up Doubling of serum Cr or entering dialysis N (%) Nifedipine GITS 40 (36%) Fosinopril 27 (21%) OR: 0.47 (0.26–0.84); p=0.01 ● Decrease in SBP, mm Hg (SD) Nifedipine GITS 14.0 (22.5) Fosinopril 19.8 (19.6), p NR Decrease in DBP, mm Hg (SD) Nifedipine GITS 14.9 (11.8)

		interfere with study results (steroids, immunosuppressant drugs, or NSAIDS) ● Presenting intolerance to fosinopril or nifedipine			Fosinopril 12.7 (11.6); p=NS
ACCOMPLISH Bakris GL, et al., 2010 (177) 20170948	Aim: To examine the effect of initial antihypertensive therapy with benazepril plus amlodipine compared to benazepril plus hydrochlorothiazide on progression of CKD Study type: RCT, forced drug titration Size: ● Overall benazepril plus amlodipine n=5,744 benazepril plus hydrochlorothiazide n=5,762 ● Pts with CKD benazepril plus amlodipine n=561 benazepril plus hydrochlorothiazide n=532 ● Pts without CKD benazepril plus amlodipine n=5,171 benazepril plus hydrochlorothiazide n=5,218	Inclusion criteria: ● Males or females ≥55 y, with HTN, high CV risk (history of coronary events, MI, revascularization, stroke, CKD, PAD, LVH, DM) ● Entry BP for pts with CKD benazepril plus amlodipine: 145.1/78.6 (20.2/11.2) benazepril plus hydrochlorothiazide: 145.0/78.1 (20.5/10.7) ● Rate of DM same in CKD and non-CKD pts (58.9% vs. 60.5%; p=0.302 Exclusion criteria: N/A	Intervention: ● Initial antihypertensive therapy with benazepril plus amlodipine compared to benazepril plus hydrochlorothiazide ● BP after dose adjustment benazepril plus amlodipine: 131.6/73.3 (18.2/10.3 SD), 4119 (75%) controlled ● Benazepril plus hydrochlorothiazide: 132.5/74.4 (17.9/11.2 SD), 3963 (72%) controlled p<0.0013 Target <140/90 and <130/80 for DM or CKD Comparator: N/A	1° endpoint: ● Overall: time to first event of composite CV morbidity and mortality ● Progression of CKD, a prespecified endpoint, was defined as doubling of serum creatinine concentration or ESRD (estimated glomerular filtration rate <15 mL/min/1·73 m² or need for dialysis). ● All randomized pts were included in the intention-to-treat analysis. There were 113 (2.0% x 0%) events of CKD progression in the benazepril plus amlodipine group compared with 215 (3.7% x 7%) in the benazepril plus hydrochlorothiazide group HR: 0.52, (95% CI: 0.41–0.65), p<0.0001 ● 2º endpoints: CKD plus death, change in albuminuria, change in eGFR ● Subset with more advanced CKD analyzed for rate of progression Safety endpoint: N/A	Limitations: ● Trial terminated early (mean follow-up 2.9 y [SD 0.4]) because of superior efficacy of benazepril plus amlodipine compared with benazepril plus hydrochlorothiazide with 20% lower CV risk. ● Very small proportion of study population had albuminuria above 33.9 mg/mmol combined with early trial termination to reduce renal events. ● Funded by Novartis. Summary: ● Initial antihypertensive treatment with benazepril plus amlodipine slowed progression of nephropathy to a greater extent compared to benazepril plus hydrochlorothiazide.
AVOID Parving HH, et al.,	Aim: Compare effects of dual blockade of	Inclusion criteria: Pts with HTN, 18–85 y,	Intervention: All on losartan then aliskiren or	1° endpoint: ● Ratio of albumin to creatinine at 6 mo	Limitations: No renal endpoints regarding function, survival, CV

2008 (178) 18525041	RAAS by aliskiren 300 mg/d added to maximal dose losartan 100 mg/d and optimal HTN therapy Study type: RCT, double-blinded, duration was 6 mo Size: 805 entered open label, 599 randomized, 524 completed.	and DM-2 and nephropathy (early morning alb/creat >300 mg/g or >200 mg/g in on RAAS blocker already Exclusion criteria: Non-DM kidney disease, >3,500 mg/g alb/ Cr ratio, eGFR, 30 mL/min/BSA, chronic urinary tract infections, baseline serum potassium >5.1, severe HTN, major CVD in prior 6 mo	placebo added Comparator: All on losartan, aliskiren or placebo added	● 2º: decline in eGFR, development of renal dysfunction (serum creatinine >176.8 micromol/l (2.0 mg/dL) Safety endpoint: Hyperkalemia 5% in aliskiren group, 5.7% in placebo group but more frequent individual elevations >5.5 in aliskiren group	events, BP 2/1 mm Hg lower in aliskiren group; supported by Novartis Summary: ● Outcome was degree of albuminuria. Aliskiren reduced urinary alb/creat ratio by 20% (95% CI 9–30; p<0.001) ● From post hoc analysis: Antiproteinuric effects consistent across CKD stages (19%, 22%, and 18% for stages 3, 2, and 1). For CKD 3, renal dysfunction more frequent in placebo group (29.3 vs. 13.6%; p=0.032) ● No differences in deaths or acute renal failure by treatment group (0.7% in both)
VA NEPHRON-D Fried LF, et al., 2010 (124) 20728887	Aim: To test the efficacy of the combination of losartan with lisinopril as compared with standard treatment with losartan alone in slowing the progression of proteinuric diabetic kidney disease Study type: RCT, multi-center, double-blind Size: 1448 were randomized	Inclusion criteria: Pts without adverse events on full dose losartan DM-2, eGFR 30–89.9 mL/min/1.73 m² by 4 variable MDRD formula, urinary albumin/creatinine ratio of ≥300 in a random sample Exclusion criteria: Known non-DM kidney disease, serum potassium >5.5 mmol/L, current treatment with sodium polystyrene sulfonate or inability to stop prescribed medications increasing risk of hyperkalemia.	Intervention: ● Pts with DM-2 already taking losartan 100 mg/d with albumin to creatinine ratio of ≥300 were randomized to either lisinopril 10–40 mg/d or placebo. ● 132 1° endpoints in the combination therapy group; No benefit to mortality or CV events. Combination therapy increase risk of hyperkalemia 6.3 events/100 person-y vs. 2.6 events/100 person-y (p<0.001) and acute kidney injury 12.2 vs. 6.7 events/100 person-y (p<0.001)	1° endpoint: First occurrence of a change in eGFR (a decline of ≥30 mL/min/1.73 m² if initial GFR ≥60 or a decline of ≥50% if initial eGFR <60, ESRD or death 2° endpoint: First occurrence of decline in eGFR or ESRD Safety endpoint: mortality, hyperkalemia, acute kidney injury	Summary: Study stopped early due to safety concerns. Combination of ACEI and ARB was associated with increased risk of adverse events among pts with diabetic nephropathy

			Comparator: 152 primary endpoints in monotherapy group		

Data Supplement 38. Nonrandomized Trials, Observational Studies, and/or Registries of CKD (Section 9.3)

Study Acronym; Author; Year Published	Study Type/Design; Study Size (N)	Patient Population	Primary Endpoint and Results (include P value; OR or RR; & 95% CI)	Summary/Conclusion Comment(s)
Upadhyay A, et al., 2011 (179) 21403055	Aim: To summarize trials comparing lower vs. higher BP targets in pts with CKD; focus on proteinuria as an effect modifier Study type: Systematic review Size: 2,272	Inclusion criteria: >50 pts/group, 1 y follow-up, outcomes of death, kidney failure, CV events, change in kidney function, number of antihypertensive agents, adverse events. 3 trials (MDRD, AASK, REIN-2; 8 reports)	Results: Overall trials did not show that BP target of <125/75–130/80 is more beneficial than a target of <140/90. Lower quality evidence suggests a low target may be beneficial in subgroups with proteinuria >300–1,000/d	Limitations: No pts with DM-1 included. Duration (mean follow-up 2–4 y) may be too short to detect differences in clinically important outcomes. Reporting of adverse events not uniform. Summary: Available evidence is inconclusive but does not prove a BP target <130/80 improves clinical outcomes more than a target of <140/90 in adults with CKD.
Lv, et al., 2013 (127) 23798459	Aim: To assess the renal and CV effects of intensive BP lowering in people with CKD Study type: Systematic review Size: 9,287 pts with CKD and 1,264 kidney failure events	Inclusion criteria: • Randomized trials of pts with CKD assigned to different target BP that reported kidney failure and CV events. • 11 trials on 9,287 pts with CKD and 1,264 kidney failure events (doubling of serum creatinine, 50% decline in GFR or ESKD) • Included AASK, REIN-2, MDRD, Wuhl (children), Toto, Schrier plus 5 trials with CKD subgroups, also included the late nonrandomized follow-up studies for AASK and MDRD • BP targets varied substantially between trials. 2 trials targeted mean BP <92 mm Hg for the intensive treatment arm, and 107 mm Hg in the standard treatment arm. 1 trial aimed for BP<130/80 mm Hg vs. a DBP of 90 mm Hg, 1 study targeted <120/80 mm Hg vs.	Results: Compared with standard regimens, more intensive BP lowering reduced risk of composite endpoint HR: 0.82; 95% CI: 0.68–0.98, and ESKD HR: 0.79; 95% CI: 0.67–0.93. Effect was modified by proteinuria (p=0.006) and markers of trial quality. Intensive BP lowering reduced the risk of kidney failure HR: 0.73; 95% CI: 0.62–0.86 but not in pts without proteinuria at baseline HR: 1.12; 95% CI: 0.67–1.87. No clear effect on CV events or death.	Limitations: All trials used open label, in 2 pts were blinded, substantial variability in design quality. There was substantial variability in BP targets by MAP, systolic and DBP or only DBP. Most trials did not include pts with diabetic kidney disease Summary: • Renal outcomes: 7 trials (N=5,308) recorded a total of 1,264 kidney failure events. A -7.7 mm Hg difference in SBP and a -4.9 mm Hg difference in DBP seen between treatment arms. Overall, a more intensive regimen reduced risk of composite kidney failure events by 17% HR: 0.82; 95% CI: 0.68–0.98, reduced the risk of ESKD alone by 18% (pooled HR for composite outcomes: 0.79; 95% CI: 0.67–0.93). • Intensive BP lowering had no effect on kidney failure in pts who did not have proteinuria (3 trials involving 1,218 pts HR: 1.12; 95% CI: 0.67–1.87), but it did reduce the risk of progressive kidney failure by 27% (5 trials involving 1,703 pts HR: 0.73; 95% CI: 0.62–0.86 in people who did have proteinuria at baseline.

		135–140/85–90 mm Hg, and 4 studies had DBP<75–80 mm Hg vs. from 80–90 mm Hg. A trial involving pediatric pts targeted a 24-h mean BP<the 50th percentile, compared with the 50th to 95th percentiles in the control group. 2 trials had more liberal targets for intensive treatment (<140–150 mm Hg systolic, 85 mm Hg diastolic)		• CV outcomes: major CV events reported in 5 trials (472 CV events in 5,308 pts with CKD). Intensive BP lowering did not reduce risk of CV events in pts with CKD, but the CIs remained wide RR: 1.09; 95% CI: 0.83–1.42. 6 trials reported stroke outcomes (197 events in 5,411 pts), 5 trials reported MI (138 events in 4,317 pts), and 5 trials reported HF (118 events in 5,308 pts). They saw no clear effect of intensive treatment on any of these vascular outcomes. • Death: 10 trials involving 6,788 participants reported 846 deaths. There was no clear effect of intensive BP lowering on risk of all-cause death RR: 0.94; 95% CI: 0.84–1.05) or CV death RR: 1.20; 95% CI: 0.82–1.75
Jafar TH, et al., 2003 (180) 12965979	Aim: To determine the levels of BP and urine protein excretion associated with lowest risk for progression of CKD during antihypertensive therapy with and without ACEIs. Study type: 11 RCTs in pts with predominantly nondiabetic kidney disease Size: 1,860 pooled in pt level meta-analysis; mean duration of follow-up 2.2 y	Inclusion criteria: • Pt-level meta-analysis using data from the AIPRD Study Group database to assess relationships among pts with nondiabetic kidney disease across a wide range of urine protein excretion values during antihypertensive therapy with and without ACEIs. • The AIPRD Study Group database included 1,860 pts with nondiabetic kidney disease enrolled in 11 RCTs of ACEIs to slow the progression of kidney disease. The database contained information on BP, urine protein excretion, serum creatinine, and onset of kidney failure during 22,610 visits. • Included only randomized trials (with a minimum 1 y follow-up) that compared the effects of antihypertensive regimens that included ACEIs with the effects of regimens that did not include ACEIs. HTN or decreased kidney function was required for entry into all studies. Exclusion criteria: Common to all studies: acute kidney failure, treatment with immunosuppressive meds, clinically significant chronic HF, obstructive uropathy, renal artery stenosis, active systemic disease, DM-1, history of transplantation, history of allergy to	1° endpoint: Progression of CKD defined as doubling of serum creatinine or onset of kidney failure Results: Kidney disease progression documented in 311 pts, 124 (13.2%) in the ACEI group and 187 (20.5%) in the control group (p=0.001). 176 (9.5%) developed kidney failure: 70 (7.4%) in the ACEI group and 106 (11.6%) in the control group (p=0.002). SBP of 110–129 mm Hg and urine protein excretion <2.0 g/d were associated with lowest risk for kidney disease progression. ACEI beneficial after adjustment for BP and urine protein excretion (RR: 0.67; 95% CI: 0.53–0.84). The increased risk for kidney progression at higher SBP levels was greater in pts with urine protein excretion >1.0 g/d (p<0.006).	Limitations: Studies included were not designed to assess the effect of lowering BP and urine protein excretion on kidney disease progression. Conclusions: Although reverse causation cannot be excluded with certainty, SBP goal between 110 and 129 mm Hg may be beneficial in pts with urine protein excretion >1.0 g/d. SBP <110 mm Hg may be associated with higher risk for kidney disease progression.

		ACEIs, and pregnancy.		
Giatras I, et al., 1997 (181) 9273824	Aim: To use meta-analysis to assess effects if ACEIs on development of ESRD in nondiabetic pts Study type: Meta-analysis Size: 1,594 pts from 10 studies	Inclusion criteria: All randomized studies comparing ACEIs with other antihypertensive agents, with at least 1 y of follow-up Exclusion criteria: Studies of diabetic renal disease and renal transplants were excluded.	Results: • Among 806 pts receiving ACEIs, 52 (6.4%) developed ESRD and 17 (2.1%) died. • In 788 controls, 72 (9.1%) developed ESRD and 12 (1.5%) died. The pooled RR were 0.70; 95% CI: 0.51–0.97 for ESRD and 1.24; CI: 0.55–2.83 for death. • The decreases in weighted mean systolic and DBPs during follow-up were 4.9 and 1.2 mm Hg greater, respectively, in the pts who received ACEIs.	Limitations: Included studies through 5/1996, published (7) and nonpublished (3) study results. Did not require that pts have HTN or renal insufficiency at baseline. Did not report results by severity of proteinuria related to the diseases included many of which are not characterized by proteinuria. Summary: ACEIs are more effective than other antihypertensive agents in reducing the development of end-stage nondiabetic renal disease, and they do not increase mortality. It could not be determined whether this beneficial effect is due to the greater decline in BP or to other effects of ACE inhibition.
ONTARGET Investigators, et al., 2008 (126) 18378520	Aim: Evaluate whether use of an ARB was noninferior to ACEI, and whether the combination was superior to ACE alone in the prevention of vascular events in pts with CVD or DM but not HF. Study type: Multi-center, double-blind, RCT Size: 25,620 pts	Inclusion criteria: • ≥55 y • Coronary, peripheral, or cerebrovascular disease or DM with end-organ damage Exclusion criteria: • Inability to discontinue ACEI or ARB • Known hypersensitivity or intolerance to ACEI or ARB • Selected CVDs (congestive HF, hemodynamically significant valvular or outflow tract obstruction, constrictive pericarditis, complex congenital heart disease, syncopal episodes of unknown etiology <3 mo, planned cardiac surgery or PTCA <3 mo, uncontrolled HTN on treatment [e.g., BP >160/100 mm Hg], heart transplant recipient, stroke due to subarachnoid hemorrhage) • Other conditions (significant renal artery disease, hepatic dysfunction, uncorrected volume or sodium depletion,	Intervention: Ramipril 10 mg daily (n=8,576) Comparator: • Telmisartan 80 mg daily (n=8,542) • Combination of telmisartan and ramipril (n=8,502)	1° endpoint: After a median follow-up of 56 mo, there was no difference between ramipril vs. telmisartan or combination therapy vs. ramipril in the 1° composite outcome of death from CV causes, MI, stroke, or hospitalization for HF RR: 1.01; 95% CI: 0.94–1.09 and RR: 0.99; 95% CI: 0.92–1.07, respectively Safety endpoint: • Combination therapy was associated with greater risk of hyperkalemia than ramipril monotherapy (480 pts vs. 283 pts; p<0.001) • Hypotensive symptoms were cited as reason for permanent discontinuing more in telmisartan vs. ramipril RR: 1.54; p<0.001 and combination therapy vs. ramipril monotherapy RR: 2.75; p<0.001 • Renal impairment was more common in combination therapy vs. ramipril monotherapy RR: 1.33; 95% CI: 1.22–1.44).

		1° hyperaldosteronism, hereditary fructose intolerance, other major noncardiac illness or expected to reduce life expectancy or significant disability interfere with study participation, simultaneously taking another experimental drug, unable to provide written informed consent).		
VALIANT White HD, et al., 2005 (182) 16301343	Aim: Evaluate whether use of an ARB or the combination of an ACEI and an ARB was superior to a proven effective dose of an ACEI after AMI in pts with HF and/or LVEF <40%. Study type: Multi-center, double-blind, RCT Size: 14,703 pts	Inclusion criteria: • ≥18 y • Between 12 h and 10 d after AMI • Clinical or radiological signs of HF and/or evidence of depressed LV systolic function with EF<40% or reduced echo wall motion index Exclusion criteria: • Cardiogenic shock • Serum creatinine >2.5 mg/dL • Known hypersensitivity or intolerance to ACEI or ARB • SBP<100 mm Hg • Known or suspected bilateral renal artery stenosis • Stroke or TIA within previous 3 mo • Refractory ventricular arrhythmia • Refractory angina • Right ventricular MI • Mitral stenosis, mitral regurgitation, aortic stenosis, aortic regurgitation of hemodynamic significance • Obstructive cardiomyopathy • Previous major organ transplant • Conditions likely to lead to poor adherence	Intervention: Valsartan 160 mg bid Comparator: • Captopril 50 mg tid • Combination of captopril 50 mg tid and valsartan 160 mg bid • Analyzed by prespecified age groups of <65 y (n=6988) 65–74 y (n=4555) 75–84 y (n=2777) ≥85 y (n=383)	1° endpoint: All-cause mortality 2° endpoint: • Composite of CV mortality or emergency treatment or hospitalization for new or worsening HF, reinfarction, stroke, and resuscitated cardiac arrest • On 3-y multivariable analysis, each 10-y age increase was associated with HR: 1.49; 95% CI: 1.43–1.56); p<0.0001 for mortality and an OR: 1.38; 95% CI: 1.31–1.46; p<0.0001 for readmission with HF. • Similar but slightly smaller trend for composite endpoint, higher mainly in the oldest group. Valsartan was at least as effective as captopril in reducing mortality and other adverse outcomes in all age groups and combination therapy with both agents added no incremental benefit. • Combination therapy increased the incidence of adverse effects leading to discontinuation in all age groups Safety endpoint: • Adverse events associated with captopril and valsartan were more common in the elderly and in pts receiving combination therapy. • Renal dysfunction was more common with older age and combination therapy.

Data Supplement 39. RCTs Comparing Hypertension after Renal Transplantation (Section 9.3.1)

Study Acronym; Author; Year Published	Aim of Study; Study Type; Study Size (N)	Patient Population	Study Intervention (# patients) / Study Comparator (# patients)	Endpoint Results (Absolute Event Rates, P value; OR or RR; & 95% CI)	Relevant 2° Endpoint (if any); Study Limitations; Adverse Events; Summary
Midtvedt K, et al., 2001 (183) 11468543	Aim: To compare the effect of an ACEI (lisinopril) with a CCB (controlled release nifedipine) in the treatment of post-transplant HTN focusing on changes in LVH. Study type: prospective RCT Size:154 pts 123 completed 1 y good quality echo data for 116 at 2 and 12 mo post treatment	Inclusion criteria: All RTx pts with HTN by DBP ≥95 in first 3 wk after transplant Exclusion criteria: Normotensive, isolated systolic HTN, refusal, requirement of ACEI for HF.	Intervention: Renal transplant recipients with HTN (DBP ≥95 mm Hg) in the first 3 wk after Transplant were randomized to double-blind nifedipine CR 30 mg or lisinopril 10 mg daily. Comparator: 2 treatment arms	1° endpoint: BP controlled in both groups (mean 140 ± 16/87 ± 8 with nifedipine, 136 ± 17/85 ± 8 with lisinopril, NS). LV mass reduced by 15% ($p<0.001$) in both groups (from 153 ± 43 to 131 ± 38 g/m^2 with nifedipine and from 142 ± 35 to 121 ± 34 g/m^2 with lisinopril) with no difference between groups at baseline or at follow-up.	Summary: In renal transplant pts with HTN with well-controlled BP, there is regression of LV mass after renal transplantation which is observed to be similar in pts treated with lisinopril or nifedipine.
Midtvedt K, et al., 2001 (184) 11740389	Aim: To examine whether graft function as determined by GFR was better maintained with a CCB (controlled release nifedipine) as compared to an ACEI (lisinopril) in hypertensive renal transplant recipients treated with cyclosporine. Study type: Prospective RCT Size:154 pts ● 123 completed 1 y good quality echo data for 116 at 2 and 12 mo post-Transplant ● 64 recruited to complete a 2nd y	Inclusion criteria: All renal transplant pts with HTN by DBP ≥95 in first 3 wk after transplant Exclusion criteria: Normotensive, isolated systolic HTN, refusal, requirement of ACEI for HF.	Intervention: Renal transplant pts with HTN (DBP ≥95 mm Hg) in the first 3 wk after transplant were randomized to double-blind nifedipine CR 30 mg or lisinopril 10 mg daily. Comparator: 2 treatment arms	1° endpoint: ● GFR baseline at 3–5 wk after entry, and at 1 and 2 y ● Nifedipine: baseline GFR 46 mL/min, at 1 y 56 ● Lisinopril: baseline GFR 43, at 1 y 44 ● delta N vs. L: 9.6 at 1 y (95% CI: 5.5–13.7 mL/min; p=0.0001), 10.3 at 2 y (95% CI: 4.0–16.6 mL/min; p=0.0017) ● Baseline GFR similar, change in GFR significant after 1 y and remained statistically significant after 2 y	Summary: Both nifedipine and lisinopril were safe and effective in treatment of HTN in renal transplant pts treated with cyclosporine. Pts receiving nifedipine but not lisinopril had improved renal function over 2 y.

Suwelack B, et al., 2000 (185) 11009288	Aim: To compare the structural and functional cardiac changes of quinapril vs. atenolol administered to hypertensive kidney transplant recipients Study type: Prospective RCT Size: 31 cyclosporine treated stable function recipients with HTN 6–12 wk after transplant	Inclusion criteria: Cyclosporine-based immunosuppression, stable graft function with serum creatinine <2.5 mg/dL. Exclusion criteria: Pts with severe aortic or mitral regurgitation or with heart rates >100 beats/min	Intervention: ● Cyclosporine treated stable function pts with HTN 6–12 wk after transplant randomized to double-blinded quinapril or atenolol to target DBP<90. ● Echo within 24 h of first dose and at 24 mo ● Stepwise increase in dose, could then add furosemide 40–80 mg/d, third-line CCB Comparator: 2 treatment arms	1° endpoint: ● BP was lower in the atenolol group, delta 10.7 ± 3.4 mm Hg vs. 4.5 ± 2.9 mm Hg with quinapril ● E/A ratio (impaired relaxation) increased (improved) only in quinapril group (+0.11; p<0.05) and decreased by 0.03 (p>0.05 vs. start of treatment) in the atenolol group. Difference in E/A ratio alterations was significant (p<0.05). ● LV mass index decreased only in quinapril group (p<0.05) from entry to 24 mo.	Summary: ● In hypertensive renal allograft recipients, quinapril in contrast to atenolol provided a sufficient reduction in LVH and a concomitant improvement in LV diastolic cardiac relaxation and these effects occurred independently from BP reduction. ● While the conclusion was that quinapril showed a benefit not seen with atenolol, the actual numbers are very close (14.1 ± 10.1 atenolol, 15.8 ± 7.7 quinapril). ● BP reduction was twice as great in the atenolol group as in the quinapril group. Arterial BP did not correlate with cardiac mass reduction.
Paoletti E, et al., 2007 (186) 17591533	Aim: To assess the effectiveness of ACEIs in regressing LVH persisting after renal transplantation during an 18-mo observation period. To assess the impact of cyclosporine vs. tacrolimus in affecting LVH outcome. Study type: Prospective RCT Size: 70 renal transplant recipients at 3–6 mo after transplant.	Inclusion criteria: ● Renal transplant pts with serum creatinine <2.5 mg/dL, urine protein excretion not exceeding 1 g/d and with persistent LVH at 3–6 mo after transplant. ● Previously randomized to either cyclosporine or tacrolimus immunosuppression. ● All were pts of deceased donor transplants. Exclusion criteria:	Intervention: ● RCT Lisinopril (n=36) vs. placebo (n=34), also used other agents to treat HTN ● Endpoint LVMI at 18 mo ● Echo at 3–6 mo and at 18 mo Comparator: Treatment vs. placebo	1° endpoint: ● Change in LV mass index at 18 mo. ● BP decreased in both groups (p=NS, between group differences SBP -1.7 ± 3.3 mm Hg; 95% CI: -4.8–8.2; and DBP 0.3 ± 2.2 mm Hg; 95% CI: -4.8–4.1). ● LVMI regressed more in ACEI group (-9.1 ± 13.3 g/m 2.7; p<0.001) but only in those on cyclosporine immunosuppression. Interaction of LVMI effect and	Summary: LVMI regressed more in ACEI group but only in those on cyclosporine immunosuppression. Interaction of LVMI effect and cyclosporine in post hoc analysis.

		● No DM, HF, severe valvular disease, previous renal artery stenosis blocking agents, acute rejections in prior 3 mo or significant renal artery stenosis. ● Pts receiving a preemptive 2nd transplant or a living donor transplant were excluded.		cyclosporine in post hoc analysis. ● 74/104 had LVMI above normal. ● Change in LVMI ACEIs vs. controls p<0.001 Number of meds comparable ● Number using CCB/BBs/diuretic/others was 17/21/2/9 for ACEI, 24/26/3/15 controls	
VA NEPHRON-D Fried LF, et al., 2010 (124) 20728887	Aim: To test the efficacy of the combination of losartan with lisinopril as compared with standard treatment with losartan alone in slowing the progression of proteinuric diabetic kidney disease Study type: RCT, multi-center, double-blind Size: 1,448 were randomized	Inclusion criteria: Pts without adverse events on full dose losartan DM-2, eGFR 30–89.9 mL/min/1.73 m² by 4 variable MDRD formula, urinary albumin/creatinine ratio of ≥300 in a random sample Exclusion criteria: Known nondiabetic kidney disease, serum potassium >5.5 mmol/L, current treatment with sodium polystyrene sulfonate or inability to stop prescribed medications increasing risk of hyperkalemia.	Intervention: ● Pts with DM-2 already taking losartan 100 mg/d with albumin to creatinine ratio of ≥300 were randomized to either lisinopril 10–40 mg/d or placebo. ● 132 1° endpoints in the combination therapy group No benefit to mortality or CV events. ● Combination therapy increase risk of hyperkalemia 6.3 events/100 person-y vs. 2.6 events/100 person-y (p<0.001) and acute kidney injury 12.2 vs. 6.7 events/100 person-y (p<0.001) Comparator: 152 1° endpoints in monotherapy group	1° endpoint: First occurrence of a change in eGFR (a decline of ≥30 mL/min/1.73 m² if initial GFR ≥60 or a decline of ≥50% if initial eGFR <60, ESRD or death 2° endpoint: First occurrence of decline in eGFR or ESRD Safety endpoint: Mortality, hyperkalemia, acute kidney injury	Summary: Study stopped early due to safety concerns. Combination of ACEI and ARB was associated with increased risk of adverse events among pts with diabetic nephropathy

Data Supplement 40. Nonrandomized Trials, Observational Studies, and/or Registries for Hypertension after Renal Transplantation (Section 9.3.1)

Study Acronym; Author; Year Published	Study Type/Design; Study Size (N)	Patient Population	Primary Endpoint and Results (include P value; OR or RR; & 95% CI)	Summary/Conclusion Comment(s)
Cross NB, et al., 2009 (187) 19588343	Study type: Comparative assessment by drug class using RCTs and quasi-RCTs lasting at least 2 wk in kidney transplant pts Size: ● 60 studies, 3,802 pts, most taking cyclosporine based immunosuppression ● 29 studies (n=2,262) compared CCB to placebo, 10 (n=445) ACEI to placebo, 7 (n=405) CCB to ACEI	Inclusion criteria: 21 studies for HTN, 6 for erythrocytosis, 2 CAN, 2 LVH, 30 not specified Exclusion criteria: N/A	1° endpoint: To assess comparative effects of antihypertensive agents in kidney transplant pts Results: Used random effects meta-analysis, risk ratios for dichotomous outcomes and MD for continuous outcomes, both with 95% CI. Stratified analyses and meta-regression to investigate heterogeneity.	● CCBs vs. placebo or no treatment had strongest results: improved GFR MD: 4.45 mL min (95% CI: 2.22–6.68), reduced graft loss RR: 0.75, (95% CI: 0.57–0.99). ● ACEI vs. placebo inconclusive for GFR MD: -8.07 mL/min (95% CI: -18.57–2.43) and variable for graft loss. ● Compared to CCB, ACEI decreased GFR MD: -11.48 mL/min; 95% CI: -5.75– -7.21), proteinuria MD: -0.28 g/24 h (95% CI: -0.47– -0.10), also reduced hemoglobin MD: -12.96 g/L (95% CI: -5.72– -10.21) and increased hyperkalemia RR: 3.74 (95% CI: 1.89– 7.43). Graft loss data were inconclusive. ● CCB may be preferred as first line for HTN after kidney transplant. ACEI may have some detrimental effects. There were not enough studies with other agents.
Jennings DL, et al., 2008 (188) 18094340	Study type: Literature review Size: 5 studies with 3 reporting safety endpoints and 2 reporting clinical efficacy endpoints	Inclusion criteria: Studies using either ACEI or ARB initiated within the first 12 wk after renal transplant	1° endpoint: Safety or efficacy Results: ● No significant increase in serum creatinine or potassium after up to 9 mo Rx ● Early initiation of ACEI may be more effective than BB in reducing LVH and proteinuria after 24 mo treatment	Conclusion: Reasonable to consider RAAS inhibitors as first-line treatment in pts with HTN and compelling indications i.e., DM, HF in first 12 wk after renal transplant.
Ninomiya T, et al., 2013 (189) 24092942	Aim: To define CV effects of lowering BP in pts with CKD Study type:	Inclusion criteria: Had to meet 1 of the following criteria: Pts randomized to a BP-lowering drug/regimen or a control group (placebo or less intensive BP lowering regimen) or pts randomized	Results: Compared with placebo, BP lowering regimens reduced the risk of major CV events by about a sixth per 5 mm Hg reduction in SBP in individuals with (HR: 0.83; 95% CI	Limitations: ● Limited numbers with CKD and most were stage 3a: ● There were 121,995 pts (80%) with eGFR ≥60 mL/min/1.73 m^2 (mean eGFR 81 (SD 17)

	● Meta-analysis of RCTs ● Individual pt data available for 23 trials, with summary data from another 3. Meta-analysis was performed according to baseline kidney function. Size: 26 trials (152,290 pts), including 30,295 pts with reduced eGFR, defined as eGFR <60 mL/min/1.73 m^2.	between regimens based on different classes of drugs to lower BP. Trials required to have at least 1,000 pt-y of planned follow-up in each randomized arm and not to have presented or published their main results before finalization of the overview protocol in July 1995. Exclusion criteria: Trials prior to July 1995.	0.76–0.90) and without reduced eGFR (HR: 0.83; 95% CI: 0.79–0.88), with no evidence for any difference in effect (p=1.00 for homogeneity). The results were similar irrespective of whether BP was reduced by regimens based on ACEIs, calcium antagonists, or diuretics/BBs. There was no evidence that the effects of different drug classes on major CV events varied between pts with different eGFR (all p>0.60 for homogeneity).	mL/min/1.73 m^2) and 30,295 pts (20%) with eGFR <60 mL/min/1.73 m^2 (mean 52 (SD 7) mL/min/1.73 m^2) at baseline (table 4⇓). Only 439 pts (0.3%) had eGFR <30 mL/min/1.73 m^2 at baseline. ● Limited numbers had proteinuria, present in 2,500 (7%) of 37161 pts with data available. Summary: ● These analyses provided compelling evidence for the CV benefits of reduction in BP in pts with stage 1–3 CKD. The proportional reductions in risk of major CV events were similar in pts with and without evidence of CKD, however those with CKD stood to gain larger absolute benefits because their baseline risk was much higher. ● BP-lowering is an effective strategy for preventing CV events among pts with moderately reduced eGFR. There is little evidence from these overviews to support the preferential choice of particular drug classes for the prevention of CV events in CKD.
ONTARGET Investigators, et al., 2008 (126) 18378520	Aim: Evaluate whether use of an ARB was noninferior to ACEI, and whether the combination was superior to ACE alone in the prevention of vascular events in pts with CVD or DM but not HF. Study type: Multi-center, double-blind, RCT Size: 25,620	Inclusion criteria: • ≥55 y • Coronary, peripheral, or cerebrovascular disease or DM with end-organ damage Exclusion criteria: • Inability to discontinue ACEI or ARB • Known hypersensitivity or intolerance to ACEI or ARB • Selected CVDs (congestive HF, hemodynamically significant valvular or outflow tract obstruction, constrictive pericarditis, complex congenital heart disease, syncopal episodes of unknown etiology <3 mo, planned cardiac surgery or PTCA <3 mo, uncontrolled HTN on treatment [e.g., BP >160/100 mm Hg], heart transplant recipient,	Intervention: Ramipril 10 mg daily (n=8,576) Comparator: • Telmisartan 80 mg daily (n=8,542) • Combination of telmisartan and ramipril (n=8,502)	1° endpoint: After a median follow-up of 56 mo, no difference between ramipril vs. telmisartan or combination therapy vs. ramipril in the 1° composite outcome of death from CV causes, MI, stroke, or hospitalization for HF RR: 1.01 (95% CI: 0.94–1.09) and RR: 0.99 (95% CI: 0.92–1.07), respectively. Safety endpoint: • Combination therapy was associated with greater risk of hyperkalemia than ramipril monotherapy (480 pts vs. 283 pts; p<0.001) • Hypotensive symptoms were cited as reason for permanent discontinuing more in telmisartan vs. ramipril RR: 1.54, p<0.001; and combination therapy vs. ramipril monotherapy RR: 2.75, p<0.001 • Renal impairment was more common in combination therapy vs. ramipril monotherapy RR: 1.33; 95% CI: 1.22–1.44

		stroke due to subarachnoid hemorrhage) • Other conditions (significant renal artery disease, hepatic dysfunction, uncorrected volume or sodium depletion, 1° hyperaldosteronism, hereditary fructose intolerance, other major noncardiac illness or expected to reduce life expectancy or significant disability interfere with study participation, simultaneously taking another experimental drug, unable to provide written informed consent).		
VALIANT White HD, et al., 2005 (182) 16301343	Aim: Evaluate whether use of an ARB or the combination of an ACEI and an ARB was superior to a proven effective dose of an ACEI after AMI in pts with HF and/or LVEF <40%. Study type: Multi-center, double-blind, RCT Size: 14,703	Inclusion criteria: • ≥18 y • Between 12 h and 10 d after AMI • Clinical or radiological signs of HF and/or evidence of depressed LV systolic function with EF<40% or reduced echo wall motion index Exclusion criteria: • Cardiogenic shock • Serum creatinine >2.5 mg/dL • Known hypersensitivity or intolerance to ACEI or ARB • SBP<100 mm Hg • Known or suspected bilateral renal artery stenosis • Stroke or TIA within previous 3 mo • Refractory ventricular arrhythmia • Refractory angina • Right ventricular MI • Mitral stenosis, mitral regurgitation, aortic stenosis, aortic regurgitation of hemodynamic significance • Obstructive cardiomyopathy • Previous major organ transplant	Intervention: Valsartan 160 mg bid Comparator: • Captopril 50 mg tid • Combination of captopril 50 mg tid and valsartan 160 mg bid • Analyzed by prespecified age groups of <65 (n=6,988) 65 to 74 (n=4,555) 75 to 84 (n=2,777) ≥85 y (n=383)	1° endpoint: All-cause mortality 2° endpoint: • Composite of CV mortality or emergency treatment or hospitalization for new or worsening HF, reinfarction, stroke, and resuscitated cardiac arrest • On 3-y multivariable analysis, each 10-y increase was associated with HR: 1.49 (95% CI: 1.43–1.56), p<0.0001 for mortality and OR: 1.38 (95% CI: 1.31–1.46; p<0.0001) for readmission with HF. • Similar but slightly smaller trend for composite endpoint, higher mainly in the oldest group. Valsartan was at least as effective as captopril in reducing mortality and other adverse outcomes in all age groups and combination therapy with both agents added no incremental benefit. Combination therapy increased the incidence of adverse effects leading to discontinuation in all age groups Safety endpoint: • Adverse events associated with captopril and valsartan were more common in the elderly and in pts receiving combination therapy. • Renal dysfunction was more common with older age and combination therapy.

		• Conditions likely to lead to poor adherence			
SPRINT Senior Williamson JD, et al., 2016 (190) 27195814	Aim: Intensive SBP goal <120 mm Hg) vs. standard (SBP goal <140) Study type: RCT Size: 2,636; 30% met criteria for being classified as ambulatory frail Mean follow-up:3.1 y	Inclusion criteria: Men and women age 75+; mean age 79.8 y; 38% women; 17% black, 74% Caucasian Exclusion criteria: Nursing home residents; prevalent DM, stroke, Class III/IV HF, dementia	Intervention: Medications and dietary advice to achieve SBP of <120 mm Hg Comparator: Medications and dietary advice to achieve SBP of <140 mm Hg Achieved SBP: Intensive= 123.4 mm Hg Standard= 134.8 mm Hg	1° endpoint: Composite CVD outcome (AMI, non-MI ACS, Stroke, HF, CVD death. Results: • 102 events in the intensive treatment group vs. 148 events in the standard treatment group; HR: 0.66; 95% CI: 0.51–0.85 and all-cause mortality (73 deaths vs. 107 deaths, respectively; HR: 0.67; 95% CI: 0.49–0.91. No difference in falls, orthostatic hypotension, or overall SAEs. • NNT for 1° outcome=27 and NNT for all-cause mortality=41	Limitations: Does not apply to nursing home pts or those with dementia or advance Conclusions: Intensive SBP is safe and effective for lowering CVD events and total mortality in adults ≥75 y

Data Supplement 41. RCTs Comparing Acute Intracerebral Hemorrhage Outcomes (Section 9.4.1)

Study Acronym; Author; Year Published	Aim of Study; Study Type; Study Size (N)	Patient Population	Study Intervention (# patients) / Study Comparator (# patients)	Endpoint Results (Absolute Event Rates, P value; OR or RR; & 95% CI)	Relevant 2° Endpoint (if any); Study Limitations; Adverse Events; Summary
INTERACT2 Anderson CS, et al., 2013 (191) 23713578	Aim: To assess whether rapid lowering of elevated BP would improve the outcome in pts with ICH. Study type: Phase III RCT Study size: 2,839 pts	Inclusion criteria: Pts with spontaneous ICH within the previous 6 h with elevated SBP	Design: Intensive treatment to lower BP (with a target systolic level of <140 mm Hg within 1 h) vs. guideline-recommended treatment (with a target SBP <180 mm Hg) among pts with SBP between 150 and 220 mm using agents of the physician's choosing.	1° outcome: Death or major disability (score of 3 to 6 on the modified Rankin scale) at 90 d. Pre-specified 2º outcome: Ordinal analysis of the modified Rankin score. Key findings: ● Among the 2,794 pts for whom the 1° outcome could be determined, 719 of 1,382 participants (52.0%) receiving	Summary: ● In pts with ICH, intensive lowering of BP did not result in a significant reduction in the rate of death or severe disability. ● However, there may be improved functional outcomes with intensive lowering of BP. ● INTERACT-2 is so far the largest (and only phase 3) RCT evaluating efficacy of intensive BP lowering.

				intensive treatment, vs. 785 of 1,412 (55.6%) receiving guideline-recommended treatment, had a 1° outcome event; intensive treatment OR: 0.87; 95% CI: 0.75–1.01; p=0.06. ● The ordinal analysis showed significantly lower modified Rankin scores with intensive treatment. OR for greater disability: 0.87; 95% CI: 0.77–1.00; p=0.04. ● Mortality was 11.9% in the group receiving intensive treatment and 12.0% in the group receiving guideline-recommended treatment. ● Nonfatal serious adverse events occurred in 23.3% and 23.6% of the pts in the 2 groups, respectively.	● No clear relationship between outcome and time from onset of ICH to commencing treatment and no significant effect of intensive BP-lowering treatment on hematoma growth. ● Of note, only1 third of pts achieved the target SBP level within 1 h (half achieved the target by 6 h), and most (75%) presented with mild to moderate size (<20 mL) hematomas.
ATACH-1 2010 (192) 19770736	Aim: To determine the feasibility and acute (i.e., within 72 h) safety of 3 levels of SBP reduction in subjects with supratentorial ICH treated within 6 h after symptom onset. Study type: Phase I, dose-escalation, multicenter prospective study. Study size: 60	Inclusion criteria: Pts with ICH with elevated SBP ≥170 mm Hg who presented to the ED within 6 h of symptom onset.	Design: ● IV nicardipine to reduce SBP to a target of: #1: 170–200 mm Hg in the first cohort of pts #2: 140–170 mm Hg in the 2nd cohort #3: 110–140 mm Hg in the third cohort. ● Each subject was followed-up for 3 mo to preliminarily assess mortality and the clinical outcomes. A total of 18, 20, and 22 pts were enrolled in the respective 3 tiers of SBP treatment goals.	1° outcome: Treatment feasibility (achieving and maintaining the SBP goals for 18–24 h) 2° outcomes: #1: Neurologic deterioration within 24 h; #2: Serious adverse events within 72 h. Key findings: ● Overall, 9 of 60 pts had treatment failures (all in the last tier). A total of 7 subjects with neurologic deterioration were observed: 1 (6%), 2 (10%), and 4 (18%) in tier 1, 2, and 3, respectively. ● Serious adverse events were observed in1 subject (5%) in tier 2 and in 3 subjects (14%) in tier 3. However, the safety stopping rule was not activated in any of the tiers. ● 3 (17%), 2 (10%), and 5 (23%) subjects in tiers1, 2, and 3, respectively, died within 3 mo	Summary: ● Observed proportions of neurologic deterioration and serious adverse events were below the prespecified safety thresholds, and the 3-mo mortality rate was lower than expected in all SBP tiers.
INTERACT-1	Aim: To assess the safety and efficiency of	Inclusion criteria: Pts with	Design: Early intensive lowering of BP (target SBP	1° outcome: Proportional change in hematoma volume at 24 h.	Summary: Early intensive BP-lowering treatment is clinically

Anderson CS, et al., 2008 (193) 18396107	this treatment, as a run-in phase to a larger trial. Study type: Randomized pilot trial Study size: 404	acute spontaneous ICH diagnosed by CT within 6 h of onset, elevated SBP (150–220 mm Hg), and no definite indication or contraindication to treatment	140 mm Hg; n=203) vs. standard guideline-based management of BP (target SBP 180 mm Hg; n=201).	2° outcomes: Measurements of hematoma volume. Safety and clinical outcomes: Assessed for up to 90 d. Key findings: ● Mean hematoma volumes were smaller in the guideline group (12.7 mL, SD 11.6) than in the intensive group (14.2 mL, SD 14.5). ● From randomization to 1 h, mean SBP was 153 mm Hg in the intensive group and 167 mm Hg in the guideline group (difference 13.3 mm Hg (95% CI: 8.9–17.6) mm Hg; p<0.0001); from 1 h to 24 h, BP was 146 mm Hg in the intensive group and 157 mm Hg in the guideline group (10.8 mm Hg; 95% CI: 7.7–13.9 mm Hg; p<0.0001). ● Mean proportional hematoma growth was 36.3% in the guideline group and 13.7% in the intensive group (difference 22.6%; 95% CI: 0.6%–44.5%; p=0.04) at 24 h. ● After adjustment for initial hematoma volume and time from onset to CT, median hematoma growth differed between the groups with p=0.06; the absolute difference in volume between groups was 1.7 mL (95% CI: -0.5–3.9; p=0.13). RR of hematoma growth ≥33% or ≥12.5 mL was 36% lower (95% CI: 0%–59%; p=0.05) in the intensive group than in the guideline group. Adjusted RR: 8% (95% CI: -1.0%–17%; p=0.05). ● Intensive BP-lowering treatment did not alter the risks of adverse events or 2° clinical outcomes at 90 d.	feasible, well tolerated, and might reduce hematoma growth in ICH.

Tsivgoulis G, et al., 2014 (194) 25239836	Aim: To evaluate the safety and efficacy of intensive BP reduction in pts with acute-onset ICH Study type: Systematic review and meta-analysis of RCTs. Study size: 4 eligible studies, including a total of 3,315 pts	Inclusion criteria: Pts with acute ICH randomized to either intensive or guideline BP-reduction protocols.	● Intensive early BP lowering after acute ICH onset compared with guideline-based treatment	Key findings: ● Death rates similar between pts randomized to intensive BP-lowering treatment and those receiving guideline BP-lowering treatment OR: 1.01; 95% CI: 0.83–1.23; p=0.914 ● Intensive BP-lowering treatment associated with strong trend towards lower 3-mo death or dependency vs. guideline treatment OR: 0.87; 95% CI: 0.76–1.01; p=0.062. ● Intensive BP reduction was also associated with a greater attenuation of absolute hematoma growth at 24 h (standardized MD± standard error: -0.110 ± 0.053; p=0.038).	Summary: ● Intensive BP management in pts with acute ICH is safe. ● Intensively treated ICH pts tended to have more favorable 3-mo functional outcome. ● Intensive BP reduction associated with a greater attenuation of absolute hematoma growth at 24 h. ● Starting antihypertensive treatment in the initial 5–10 d after ICH may have a different outcome from that seen after an ischemic stroke because of 2º edema formation and hemodynamic changes
ATACH2 Qureshi AI, et al., 2016 27276234	Aim: To determine the relative efficacy of intensive vs. standard antihypertensive treatment that was initiated within 4.5 H after symptom onset and continued for the next 24 H in patients with spontaneous supratentorial intracerebral hemorrhage Study type: Phase III RCT Study size: 1,000 pts	Inclusion criteria: Pts with spontaneous ICH (volume, <60 cm3) and a Glasgow Coma Scale (GCS) score of 5 or more	Design: Intravenous nicardipine administered within 4.5 H after symptom onset and continued for the next 24 H to lower BP	1° outcome: Moderately severe or severe disability or who had died (modified Rankin scale score, 4 to 6) at 3 months Key findings: ● Among 1,000 participants with a mean (±SD) systolic BP of 200.6±27.0 mm Hg at baseline, 500 were assigned to intensive treatment and 500 to standard treatment. Enrollment was stopped because of futility ● Death or disability occurred in 38.7% of patients in the intensive-treatment group and 37.7% in the standard-treatment group. RR: 1.04; 95%CI: 0.85–1.27. ● Serious adverse events occurring within 72 H after randomization were reported in 1.6% of the patients in the intensive-treatment group and 1.2% of those in the standard-treatment group. ● Renal adverse events within 7 d after randomization were significantly higher in the intensive-treatment group than in the	Summary: Treatment of patients with spontaneous ICH to achieve a target systolic BP of 110 to 139 mm Hg did not result in a lower rate of death or disability compared to conventional reduction to a target of 140–179 mm Hg. Furthermore, there was more than twice the frequency of renal adverse events in the more intensively treated arm within a week of treatment initiation.

				standard-treatment group (9.0% vs. 4.0%, p=0.002).	

Data Supplement 42. RCTs Comparing Acute Ischemic Stroke Outcomes (Section 9.4.2)

Study Acronym; Author; Year Published	Aim of Study; Study Type; Study Size (N)	Patient Population	Study Intervention (# patients) / Study Comparator (# patients)	Endpoint Results (Absolute Event Rates, P value; OR or RR; & 95% CI)	Relevant 2° Endpoint (if any); Study Limitations; Adverse Events; Summary
COSSACS Robinson TG, et al., 2010 20621562	Aim: Assess the efficacy and safety of continuing or stopping pre-existing antihypertensive drugs in patients with acute stroke Study type: RCT Size: 763	Inclusion criteria: Acute ischemic stroke (or ICH) within previous 48 h Exclusion criteria: • Impaired level of consciousness • Unable to swallow •Hypertensive emergency • BP >200/120 mm Hg • Premorbid disability • Intravenous alteplase	Intervention: Continue previous antihypertensive medication/s (n=379) Comparator: Stop previous antihypertensive medication/s (n=384)	1° endpoint: Death or major disability (mRS 3–6) at 14 d: RR: 0.86 (95% CI: 0.65–1.14; p=0.3) Safety endpoint: Adverse events, minor and serious: p>0.05 for all	Relevant 2° endpoint • 2-wk NIHSS: p=0.46 and 2-wk Barthel Index: p=0.30 • 2-wk BP: significantly lower in the continue arm (mean difference of -13 mm Hg in SBP and -8 mm Hg in DBP) p<0.0001 • 6-month mortality: p=0.98; 6-month disability p<0.05 Study limitations • Trial was terminated early because of slow recruitment, and consequently it was underpowered • Treatment was not homogeneous (different drugs, no specific BP target) • No differences when analysis restricted to patients with ischemic stroke Summary/conclusions • Early reinitiation of antihypertensive medications was safe but ineffective to prevent death or dependency • Early reinitiation of antihypertensives was associated with better BP control at 2 wk

CATIS He J, et al., 2014 24240777	Aim: Evaluate whether immediate blood pressure reduction in patients with acute ischemic stroke would reduce death and major disability at 14 d or hospital discharge Study type: RCT Size: 4071	Inclusion criteria: • Age >22 y • Acute ischemic stroke within previous 24 h Exclusion criteria: • Impaired level of consciousness • Hypertensive emergency • BP >220/120 • Atrial fibrillation • Intravenous alteplase	Intervention: Antihypertensive medication to maintain BP <140/90 for the first wk (n=2038) Comparator: No antihypertensive medication for the first wk (n=2033)	1° endpoint: Death or major disability (mRS 3–6) at 14 d: OR: 1.0 (95% CI: 0.88–1.14; p=0.98) Safety endpoint: • Vascular disease events p=0.28 • Recurrent stroke p=0.07	Relevant 2° endpoint • Death or major disability (mRS 3–5) at 90 d: OR: 0.99 (95% CI: 0.86–1.15; p=0.93) • Lower blood pressure at 14 d (mean difference of -8.6 mm Hg in SBP and -3.9 mm Hg in DBP; p<0.001) and at 90 d (mean difference of -2.9 mm Hg in SBP and -1.4 mm Hg in DBP; p<0.001) in the active arm Study limitations Antihypertensive regimen was not standardized Summary/conclusions • Early treatment of hypertension was safe but ineffective to prevent death or dependency • Early initiation of anti-hypertensives was associated with better BP control at 2 wk
Wang H, et al., 2014 (195) 24853087	Aim: To assess the effects of early BP lowering on early and long-term outcomes after acute stroke. Study type: Systematic review and meta-analysis of RCTs. Study size: 17 trials (n=13,236 pts)	Inclusion criteria: Prospective RCTs of pts ≥18 y with acute ischemic or hemorrhagic stroke; intervention compared with placebo was initiated within 7 d of stroke onset; intervention aimed to lower BP or intervention achieved BP reduction;1 or more functional outcomes reported, such as death or dependency.	● Early BP lowering after acute stroke onset compared with placebo	1° outcomes: Early (within 30 d) and long-term (from 3–12 mo). Key findings: ● Early BP lowering after acute stroke onset associated with more death within 30 d compared with placebo RR: 1.34; 95% CI: 1.02–1.74; p=0.03. ● Early BP lowering after acute stroke onset not associated with early neurological deterioration, early death within 7 d, long-term death, early and long-term dependency, early and long-term combination of death or dependency, long-term stroke recurrence, long-term MI and long-term CVE.	Summary: Results do not support early BP lowering after acute stroke. Early BP lowering may be associated with greater risk of death within 30 d after acute stroke.

		Exclusion criteria: Studies with the pts of subarachnoid hemorrhage, studies without available full-text or relevant data, studies about ongoing trials and those written in languages other than English.			
Zhao R, et al., 2015 (196) 26061309	Aim: To determine whether lowering BP during the acute phase of an ischemic stroke improves short- and long-term outcomes. Study type: Systematic review and meta-analysis of RCTs. Study size: 22 RCTs	Inclusion criteria: Pts with acute stroke (ischemic or hemorrhagic) treated with an antihypertensive agent or placebo. Groups: Treatment groups were n=5,672 (range, 6–2,308), and in the control groups was 5,416 (range, 6–2033). Follow-up: Ranged from 5 d–12 mo	● Early BP lowering after acute stroke onset compared with placebo	1° outcomes: Change in SBP and DBP after treatment and short- and long-term dependency and mortality rates. Key findings: ● Treatment groups had a greater decrease in BP than control groups, and this effect was seen with different classes of antihypertensive drugs. ● Short-term and long-term dependency rates were similar between treatment and control groups (short-term dependency: pooled OR:1.041; 95% CI: 0.936–1.159; p=0.457; long-term dependency: pooled OR:1.013; 95% CI: 0.915–1.120; p=0.806). ● Short-term or long-term mortality was similar between the treatment and control groups (short-term mortality: pooled OR: 1.020 (95% CI: 0.749–1.388; p=0.902); long-term mortality: pooled OR: 1.039 (95% CI: 0.883–1.222; p=0.644).	Summary: Antihypertensive agents effectively reduce BP during the acute phase of an ischemic stroke, but seem to confer no benefit with regard to short- and long-term dependency and mortality.
Ahmed N, et al., 2000 (197) 10835440	Aim: To investigate outcome in INWEST subgroups with increasing levels of BP reduction.	Inclusion criteria: Pts with a diagnosis of ischemic stroke in the carotid artery territory within 24 h.	Interventions: ● Nimodipine as IV infusion of 1 mg/h for 5 d followed by oral dose of 120 mg daily for a total treatment period of 21 d (n=101)	1° outcomes: Neurological outcome per the Orgogozo scale and functional outcome per the Barthel scale at d 21 Key findings: ● Nimodipine treatment resulted in a significant reduction in BP from baseline vs. placebo during the first few d.	Summary: ● DBP, but not SBP, reduction was associated with neurological worsening after the IV high-dose nimodipine after acute stroke. ● For low-dose nimodipine, the results were inconclusive.

	Study type: Post-hoc analysis of RCT Size: 265		● Nimodipine as IV infusion of 2 mg/h for 5 d followed by oral dose of 120 mg daily for a total treatment period of 21 d (n=94) Comparator: Placebo (n=100)	● A significant correlation between DBP reduction and worsening of the neurological score was found for the high-dose group (beta=0.49; p=0.048). ● Pts with a DBP reduction of ≥20% in the high-dose group had a significantly increased adjusted OR for death or dependency (n/N=25/26, OR: 10.16; 95% CI: 1.02–101.74) and death alone (n/N=9/26, OR: 4.336; 95% CI: 1.131–16.619) vs. all placebo pts (n/N=62/92 and 14/92, respectively). No correlation between SBP change and outcome.	
Bath PM, et al., 2014 (198) 25353321	Aim: To assess the clinical effectiveness of altering BP in pts with acute stroke, and the effect of different vasoactive drugs on BP in acute stroke. Update of previously published Cochrane reviews (1997, 2001, and 2008). Study type: Meta-analysis of RCTs of interventions that aimed to alter BP vs. control in pts within 1 wk of acute ischemic or hemorrhagic stroke.	Inclusion criteria: RCTs of interventions that aimed to alter BP compared with control in pts with 1 wk of acute ischemic or hemorrhagic stroke	● BP lowering after acute stroke onset compared with placebo	1° outcome: Functional outcome Key findings: ● At 24 h after randomization #1: Oral ACEIs reduced SBP MD: -8 mm Hg (95% CI: -17–1) and DBP MD: -3 mm Hg (95% CI: -9–2), sublingual ACEIs reduced SBP MD: -12.00 mm Hg (95% CI: -26–2) and DBP MD: -2 (95% CI: -10–6). ● Oral angiotensin receptor antagonists reduced SBP MD: -1 mm Hg (95% CI: -3–2) and DBP MD: -1 mm Hg (95% CI: -3–1). ● Oral BBs reduced SBP MD: -14 mm Hg (95% CI: -27– -1) and DBP MD: -1 mm Hg (95% CI: -9–7), IV BBs reduced SBP MD: -5 mm Hg (95% CI: -18–8) and DBP MD: -5 mm Hg (95% CI: -13–3). ● Oral CCBs reduced SBP MD: -13 mm Hg (95% CI: -43–17) and DBP MD: -6 mm Hg (95% CI: -14–2), IV CCBs reduced SBP MD: -32 mm Hg (95% CI: -65–1) and DBP MD: -13 (95% CI: -31–6). ● Nitric oxide donors reduced SBP MD: -12 mm Hg (95% CI: -19– -5) and DBP MD: -3 (95% CI: -4– -2).	Summary: ● No current evidence showing that lowering BP during the acute phase of stroke improves functional outcome. ● It seems reasonable to withhold BP-lowering drugs until pts are medically and neurologically stable, after which drugs can then be reintroduced. ● CCBs, ACEI, angiotensin receptor antagonists, BBs and nitric oxide donors each lower BP in acute stroke while phenylephrine appears to increase BP.

	Size: 26 trials involving 17,011 pts (8,497 pts were assigned active therapy and 8,514 pts received placebo/control). Not all trials contributed to each outcome.			● Phenylephrine, nonsignificantly increased SBP MD: 21 mm Hg (95% CI: -13–55) and DBP MD: 1 mm Hg (95% CI: -15–16). ● BP lowering did not reduce death or dependency either by drug class OR: 0.98 (95% CI: 0.92–1.05), stroke type OR: 0.98 (95% CI: 0.92–1.05) or time to treatment OR: 0.98 (95% CI: 0.92–1.05). ● Treatment within 6 h of stroke appeared effective in reducing death or dependency OR: 0.86 (95% CI: 0.76–0.99) but not death OR: 0.70 (95% CI: 0.38–1.26) by trial end. ● While death or dependency did not differ between pts who continued pre-stroke antihypertensive treatment vs. those who stopped it temporarily (worse outcome with continuing treatment OR: 1.06; 95% CI: 0.91–1.24), disability scores at the end of the trial were worse in pts randomized to continue treatment (Barthel Index MD: -3.2 (95% CI: -5.8– -0.6).	
SITS-ISTR Ahmed N, et al., 2009 (199) 19461022	Aim: To determine the association of BP and antihypertensive therapy with clinical outcomes after thrombolysis for acute ischemic stroke Study type: Retrospective analysis of prospectively maintained thrombolysis registry.	Inclusion criteria: ● Pts with acute ischemic stroke treated with IV rtPA ● BP values were recorded at baseline, 2 h, and 24 h after thrombolysis. Categories: By history of HTN and antihypertensive therapy within 7 d after thrombolysis: ● Group 1, HTN treated with antihypertensives (n=5,612)	● Various categories of HTN treatments	1° outcomes: Symptomatic (National Institutes of Health Stroke Scale score deterioration ≥4) ICH Type 2, mortality, and independence at (modified Rankin Score 0 to 2) 3 mo. Key findings: ● High SBP 2–24 h after thrombolysis as a continuous variable was associated with worse outcome ($p<0.001$) and as a categorical variable had a linear association with symptomatic hemorrhage and a U-shaped association with mortality and independence with SBP 141–150 mm Hg associated with most favorable outcomes. ● No difference in symptomatic hemorrhage OR: 1.09 (95% CI: 0.83–1.51; p=0.58) and independence OR: 1.03 (95% CI: 0.93–1.10; p=0.80) but lower mortality OR: 0.82 (95%	Summary: ● Strong association of high SBP after thrombolysis with poor outcome. ● Higher BPs during the initial 24 h were associated with greater risk of ICH in a linear fashion. ● U-shaped relation found between BP during initial 24 h and death or dependency at 3 mo, with best outcomes associated with SBP of 141–150 mm Hg.

	Study size: 11,080 pts from 2002–2006.	● Group 2, HTN withholding antihypertensives (n=1,573) ● Group 3, without history of HTN treated with antihypertensives (n=995) ● Group 4, without history of HTN not treated with antihypertensives (n=2,632).		CI: 0.73–0.92; p=0.0007) for Group 1 vs. Group 4. ● Group 2 had a higher symptomatic hemorrhage (OR: 1.86; 95% CI: 1.34–2.68; p=0.0004) and mortality (OR: 1.62; 95% CI: 1.41–1.85; p<0.0001) and lower independence (OR: 0.89; 95% CI: 0.80–0.99; p=0.04) vs. with Group 4. Group 3 had similar results as Group 1.	
ACCESS Schrader J, et al., 2003 (200) 12817109	Aim: To assess safety of modest BP reduction by candesartan in early treatment of stroke; and provide an estimate of the number of cases required to perform a larger phase III efficacy study. Study type: Prospective, double-blind, RCT; multicenter phase II study. Size: 342 pts	Inclusion criteria: Motor deficit, a cerebral CT scan excluding ICH, and necessity to treat HTN per prevailing recommendation Exclusion criteria: >85 y, disorders in consciousness preventing acquisition of consent, occlusion or >70% stenosis of the internal carotid artery, malignant HTN, manifest cardiac failure, high-grade aortic or mitral stenosis, UA pectoris, or contraindications against candesartan.	Design: 4 mg candesartan daily or placebo on d 1. On d 2, dosage was increased to 8 or 16 mg candesartan or placebo if BP >60 mm Hg SPB or 100 mm Hg DBP. Treatment was targeted to a 10%–15% BP reduction within 24 h.	1° outcome: Trial was stopped prematurely when 342 pts (339 valid) had been randomized because of an imbalance in endpoints. Key findings: Cumulative 12 mo mortality and the number of vascular events differed significantly in favor of the candesartan cilexetil group (OR: 0.475; 95% CI: 0.252–0.895).	Summary: Early antihypertensive therapy with candesartan might be a safe therapeutic option in acute stroke, but study sample size very small.
SCAST Sandset EC, et al., 2011 (201) 21316752	Aim: To examine whether careful BP-lowering treatment with the candesartan is	Inclusion criteria: Pts >18 y with acute stroke (ischemic or hemorrhagic) and SBP of ≥140 mm Hg were	Design: Pts randomized to candesartan (n=1,017) or placebo (1,012) (1:1) for 7 d, with doses	1° effect variables: Composite of vascular death, MI, or stroke during the first 6 mo; and functional outcome at 6 mo, as measured by the modified Rankin Scale.	Relevant 2° endpoint: ● Similar effects for all prespecified 2º endpoints. ● During follow-up, 9 (1%) pts on candesartan and 5 (<1%) on

	beneficial in pts with acute stroke and raised BP. Study type: Double-blind RCT Study size: 2,029 pts	included within 30 h of symptom onset.	increasing from 4 mg on d 1–16 mg on d 3–7.	Data for status at 6 mo were available for 2,004 pts (99%; 1,000 candesartan, 1,004 placebo). Key findings: ● BPs significantly lower in pts allocated candesartan vs. placebo (mean 147/82 mm Hg [SD 23/14] in the candesartan group on d 7 vs. 152/84 mm Hg [22/14] in the placebo group; p<0.0001). ● Risk of the composite vascular endpoint did not differ between treatment groups (candesartan, 120 events, vs. placebo, 111 events; adjusted HR: 1.09; 95% CI: 0.84–1.41; p=0.52. ● Analysis of functional outcome suggested a higher risk of poor outcome in the candesartan group (adjusted OR: 1.17; 95% CI: 1.00–1.38; p=0.048.	placebo had symptomatic hypotension, and renal failure was reported for 18 (2%) pts taking candesartan and 13 (1%) allocated placebo. Summary: Careful BP-lowering treatment with candesartan was not beneficial in pts with acute stroke and raised BP. Indeed, there was the suggestion of a harmful effect.
CATIS He J, et al., 2014 (202) 24240777	Aim: To evaluate whether immediate BP reduction in pts with acute ischemic stroke would reduce death and major disability at 14 d or hospital discharge. Study type: Single-blind, blinded end-points RCT. Study size: 4,071 pts	Inclusion criteria: Pts with nonthrombolysed ischemic stroke within 48 h of onset and elevated SBP	Design: Pts (n=2,038) randomized to antihypertensive treatment (aimed at lowering SBP by 10% to 25% within first 24 h, achieving BP <140/90 mm Hg within 7 d, and maintaining this level during hospitalization) vs. to discontinue all antihypertensive medications (control) during hospitalization (n=2,033).	1° outcome: Combination of death and major disability (modified Rankin Scale score ≥3) at 14 d or hospital discharge. Key findings: ● Mean SBP was reduced from 166.7 mm Hg to 144.7 mm Hg (-12.7%) within 24 h in the antihypertensive treatment group and from 165.6 mm Hg to 152.9 mm Hg (-7.2%) in the control group within 24 h after randomization (difference, -5.5% (95% CI: -4.9– -6.1%); absolute difference, -9.1 mm Hg (95% CI: -10.2– -8.1), p<0.001). ● 1° outcome did not differ between treatment groups (OR: 1.00; 95% CI: 0.88–1.14; p=0.98) at 14 d or hospital discharge. ● BP at 14 d and 90 d: significantly lower in the active arm (mean difference of -2.9 mm Hg in systolic BP and -1.4 mm Hg in diastolic BP)	Relevant 2° endpoint: Death and major disability at 3-mo posttreatment follow-up did not differ between treatment groups (500 events [antihypertensive treatment] vs. 502 events [control]; OR: 0.99; 95% CI: 0.86–1.15; p=0.93). Summary: Among pts with acute ischemic stroke, BP reduction with antihypertensive medications, vs. absence of hypertensive medication, did not reduce the likelihood of death and major disability at 14 d or hospital discharge. ● Early initiation of antihypertensives was associated with better BP control at 2 wk

COSSACS Robinson TG, et al., 2010 (203) 20621562	Aim: To assess the efficacy and safety of continuing or stopping pre-existing antihypertensive drugs in pts who recently had a stroke. Study type: Multicenter, prospective, randomized, open, blinded-endpoint trial. Study size: 763 pts	Inclusion criteria: Pts >18 y taking antihypertensive drugs enrolled within 48 h of stroke and last dose of antihypertensive drug.	Design: Continue (n=379) or stop (n=384) pre-existing antihypertensive drugs for 2 wk.	1° outcome: Death or dependency at 2 wk. Key findings: ● 72 of 379 pts in the continue group and 82 of 384 pts in the stop group reached the 1° endpoint RR: 0.86; 95% CI: 0.65–1.14; p=0.3. ● Difference in SBP at 2 wk between the continue group and the stop group was 13 mm Hg (95% CI: 10–17) and the difference in DBP was 8 mm Hg (6–10; difference between groups; p<0.0001). ● No substantial differences were observed between groups in rates of serious adverse events, 6-mo mortality, or major CV events.	Summary: ● Continuation of antihypertensive drugs did not reduce 2-wk death or dependency, CV event rate, or mortality at 6 mo ● Early reinitiation of antihypertensives was associated with better BP control at 2 wk ● Lower BP levels in those who continued antihypertensive treatment after acute mild stroke were not associated with an increase in adverse events. ● Of note, COSSACS was likely underpowered due to early termination of the trial.
CHHIPS Potter JF, et al., 2009 (204) 19058760	Aim: To assess feasibility, safety, and effects of 2 regimens for lowering BP in pts who with acute stroke. Study type: Double-blind pilot trial. Study size: 179 pts	Inclusion criteria: Pts with cerebral infarction or cerebral hemorrhage who were hypertensive SBP >160 mm Hg)	Design: ● Within 36 h of symptom onset: #1: Oral labetalol, lisinopril vs. placebo if they were nondysphagic; #2: IV labetalol, sublingual lisinopril, or placebo if they had dysphagia. ● Labetalol (n=58), lisinopril (n=58), or placebo (n=63). ● Doses were titrated up if target BP was not reached.	1° outcome: Death or dependency at 2 wk. Key findings: ● 1° outcome occurred in 61% (69) of the active vs. 59% (35) of the placebo group (RR: 1.03; 95% CI: 0.80–1.33; p=0.82) ● No evidence of early neurological deterioration with active treatment (RR: 1.22; 95% CI: 0.33–4.54; p=0.76) despite greater drop in SBP within the first 24 h in this group vs. placebo (21 [17–25] mm Hg vs. 11 [5–17] mm Hg; p=0.004). ● No rise in serious adverse events with active treatment (RR: 0.91; 95% CI: 0.69–1.12; p=0.50) but 3-mo mortality was halved (9.7% vs. 20.3%; HR: 0.40; 95% CI: 0.2–1.0; p=0.05).	Summary: ● Labetalol and lisinopril are effective antihypertensive drugs in acute stroke that do not raise risk of serious adverse events. ● Early lowering of BP with lisinopril and labetalol after acute stroke may be a promising approach to lower mortality and disability. ● However, pilot nature and very small sample size limit generalizability.
Bath PM, et al., 2015 (205) 25465108	Aim: To assess outcomes after stroke in pts given	Inclusion criteria: Pts admitted to hospital with an acute ischemic	Design: ● 7 d of transdermal glyceryl trinitrate (5 mg	1° outcome: Function, assessed with the modified Rankin Scale at 90 d	Summary: ● In pts with acute stroke and high BP transdermal glyceryl trinitrate

	drugs to lower their BP. Study type: Multicenter, randomized partial-factorial trial Study size: 4,011 pts	or hemorrhagic stroke and raised SBP (140–220 mm Hg)	per d), started within 48 h of stroke onset vs. No glyceryl trinitrate (control group). ● Pts taking antihypertensive drugs before index stroke randomly assigned to continue vs. stop taking these drugs.	Key findings: ● Mean BP was 167 (SD: 19) mm Hg/90 (13) mm Hg at baseline (median 26 h (16–37) after stroke onset), and was significantly reduced on d 1 in 2,000 pts allocated to glyceryl trinitrate vs. 2,011 controls (difference -7.0 (95% CI: -8.5– -5.6) mm Hg/-3.5 [-4·4– -2·6] mm Hg; both p<0.0001), and on d 7 in 1,053 pts allocated to continue antihypertensive drugs compared with 1,044 pts randomized to stop them (difference: -9·5 (95% CI: -11.8– -7.2) mm Hg/-5.0 [-6.4– -3.7] mm Hg; both p<0.0001). ● D-90 functional outcome did not differ in either treatment comparison-glyceryl trinitrate vs. no glyceryl trinitrate (OR: 1.01; 95% CI 0.91–1.13; p=0·83), and with continue vs. stop antihypertensive drugs (OR: 1.05; 95% CI: 0.90–1.22; p=0.55).	lowered BP with acceptable safety but did not improve functional outcome. ● Continuing prestroke antihypertensive drugs in acute stroke pts in the first few d did not confer benefit.
ATACH-1 2010 (192) 19770736	Aim: To determine the feasibility and acute (i.e., within 72 h) safety of 3 levels of SBP reduction in subjects with supratentorial ICH treated within 6 h after symptom onset. Study type: Phase I, dose-escalation, multicenter prospective study. Study size: 60	Inclusion criteria: Pts with ICH with elevated SBP ≥170 mm Hg who presented to the ED within 6 h of symptom onset.	Design: ● IV nicardipine to reduce SBP to a target of: #1: 170–200 mm Hg in the first cohort of pts #2: 140–170 mm Hg in the 2nd cohort #3: 110–140 mm Hg in the third cohort. ● Each subject was followed-up for 3 mo to preliminarily assess mortality and the clinical outcomes. A total of 18, 20, and 22 pts were enrolled in the respective 3 tiers of SBP treatment goals.	1° outcome: Treatment feasibility (achieving and maintaining the SBP goals for 18–24 h) 2° outcomes: #1: Neurologic deterioration within 24 h; #2: Serious adverse events within 72 h. Key findings: ● Overall, 9 of 60 pts had treatment failures (all in the last tier). A total of 7 subjects with neurologic deterioration were observed: 1 (6%), 2 (10%), and 4 (18%) in tier 1, 2, and 3, respectively. ● Serious adverse events were observed in1 subject (5%) in tier 2 and in 3 subjects (14%) in tier 3. However, the safety stopping rule was not activated in any of the tiers. ● 3 (17%), 2 (10%), and 5 (23%) subjects in tiers1, 2, and 3, respectively, died within 3 mo	Summary: ● Observed proportions of neurologic deterioration and serious adverse events were below the prespecified safety thresholds, and the 3-mo mortality rate was lower than expected in all SBP tiers. ● Results formed the basis of an ongoing larger randomized trial (ATACH-2) addressing the efficacy of SBP reduction in pts with ICH.

INTERACT-1 Anderson CS, et al., 2008 (193) 18396107	Aim: To assess the safety and efficiency of this treatment, as a run-in phase to a larger trial. Study type: Randomized pilot trial Study size: 404	Inclusion criteria: Pts with acute spontaneous ICH diagnosed by CT within 6 h of onset, elevated SBP (150–220 mm Hg), and no definite indication or contraindication to treatment	Design: Early intensive lowering of BP (target SBP 140 mm Hg; n=203) vs. standard guideline-based management of BP (target SBP 180 mm Hg; n=201).	1° outcome: Proportional change in hematoma volume at 24 h. 2° outcomes: Measurements of hematoma volume. Safety and clinical outcomes: Assessed for up to 90 d. Key findings: ● Mean hematoma volumes were smaller in the guideline group (12.7 mL, SD 11.6) than in the intensive group (14.2 mL, SD 14.5). ● From randomization to 1 h, mean SBP was 153 mm Hg in the intensive group and 167 mm Hg in the guideline group (difference 13.3 mm Hg (95% CI: 8.9–17.6) mm Hg; p<0.0001); from 1 h to 24 h, BP was 146 mm Hg in the intensive group and 157 mm Hg in the guideline group (10.8 mm Hg; 95% CI: 7.7–13.9 mm Hg; p<0.0001). ● Mean proportional hematoma growth was 36.3% in the guideline group and 13.7% in the intensive group (difference 22.6%; 95% CI: 0.6%–44.5%; p=0.04) at 24 h. ● After adjustment for initial hematoma volume and time from onset to CT, median hematoma growth differed between the groups with p=0.06; the absolute difference in volume between groups was 1.7 mL (95% CI: -0.5–3.9; p=0.13). RR of hematoma growth ≥33% or ≥12.5 mL was 36% lower (95% CI: 0%–59%; p=0.05) in the intensive group than in the guideline group. Adjusted RR: 8% (95% CI: -1.0%–17%; p=0.05). ● Intensive BP-lowering treatment did not alter the risks of adverse events or 2° clinical outcomes at 90 d.	Summary: Early intensive BP-lowering treatment is clinically feasible, well tolerated, and appears to reduce hematoma growth in ICH.
Hack W, et al., 2008 (206)	Aim: To assess the efficacy and	Inclusion criteria: Pts 18–80 y, who had	Design:	1° outcome: Disability at 90 d, dichotomized as a favorable outcome (a score of 0 or 1 on	Summary: Compared with placebo, IV alteplase administered between 3

18815396	safety of alteplase administered between 3 and 4.5 h after the onset of a stroke. Study type: RCT Study size: 821 pts	received a clinical diagnosis of acute ischemic stroke, and were able to receive the study drug within 3–4 h after the onset of symptoms. Exclusion criteria: SBP >185 mm Hg or DBP >110 mm Hg or aggressive treatment (IV medication) necessary to reduce BP to these limits	● Eligible pts were randomly assigned 1:1 to receive 0.9 mg of alteplase per kg, administered IV (with an upper limit of 90 mg), or placebo. ● 418 pts were assigned to receive alteplase and 403 pts were assigned to receive placebo	the modified Rankin scale, which has a range of 0–6, with 0 indicating no symptoms at all and 6 indicating death) or an unfavorable outcome (a score of 2–6 on the modified Rankin scale). 2º outcome: global outcome analysis of 4 neurologic and disability scores combined. Safety outcomes: death, symptomatic intracranial hemorrhage, and other serious adverse events. Key findings: ● More pts had a favorable outcome with alteplase than with placebo (52.4% vs. 45.2%; OR: 1.34; 95% CI: 1.02–1.76; p=0.04. ● Incidence of ICH was higher with alteplase than with placebo (for any ICH, 27.0% vs. 17.6%; p=0.001; for symptomatic intracranial hemorrhage, 2.4% vs. 0.2%; p=0.008). ● Mortality did not differ significantly between the alteplase and placebo groups (7.7% and 8.4%, respectively; p=0.68). ● No significant difference in the rate of other serious adverse events.	and 4.5 h after the onset of symptoms significantly improved clinical outcomes in pts with acute ischemic stroke; alteplase was more frequently associated with symptomatic ICH.
NINDS rt-PA Stroke Study Group, 1995 (207) 7477192	Aim: To assess the difference in clinical efficacy between IV t-PA and placebo among pts with an acute ischemic stroke Study type: Double-blind RCT	Inclusion criteria: Pts with an ischemic stroke with a clearly defined time of onset (<3 h), a deficit measurable on the NIH stroke scale, and a base-line CT scan of the brain that showed no evidence of ICH. Exclusion criteria:	Design: RCT with acute ischemic stroke pts randomized to t-PA vs. placebo	1° outcome: Clinical outcome at 3 mo, according to scores on the Barthel index, modified Rankin scale, Glasgow outcome scale, and NIH stroke scale: Key findings: ● As compared with pts given placebo, pts treated with t-PA were at least 30% more likely to have minimal or no disability at 3 mo on the assessment scales. ● Symptomatic ICH within 36 h after the onset of stroke occurred in 6.4% of pts given	Summary: Despite an increased incidence of symptomatic ICH, treatment with IV t-PA within 3 h of the onset of ischemic stroke improved clinical outcome at 3 mo

	Study size: 624 pts	SBP >185 mm Hg or DBP >110 mm Hg		t-PA but only 0.6% of pts given placebo (p<0.001). ● Mortality at 3 mo was 17% in the t-PA group and 2% in the placebo group (p=0.30).	

Data Supplement 43. RCTs Comparing Secondary Stroke Prevention (Section 9.4.3)

Study Acronym; Author; Year Published	Aim of Study; Study Type; Study Size (N)	Patient Population	Study Intervention (# patients) / Study Comparator (# patients)	Endpoint Results (Absolute Event Rates, P value; OR or RR; & 95% CI)	Relevant 2° Endpoint (if any); Study Limitations; Adverse Events; Summary
Post-stroke Antihypertensive Treatment Study (PATS) 1995 (208) 8575241	Aim: To assess whether lowering BP prevents the recurrence of stroke in Chinese pts with history of cerebrovascular disease Study type: Double-blind RCT Size: 5,665 pts	Inclusion criteria: Pts with history of stroke or TIA Exclusion criteria: N/A	Intervention: Indapamide 2.5 mg daily (n=2,840 pts) Comparator: Placebo (n=2,825 pts)	1° outcome: Recurrence of fatal or nonfatal stroke. Key findings: Average SBP/DBP at randomization was 153.8/92.8 mm Hg. At median follow-up (2 y), BP was 6.8/3.3 mm Hg lower in pts on active treatment. 143 pts on indapamide vs. 219 pts on placebo had recurrent strokes (HR: 0.69; 95% CI: 0.54–0.89; p<0.001).	2° outcome: ● Major fatal and nonfatal CV events In addition, 199 pts on indapamide and 258 pts on placebo had a CV event (HR: 0.75; 95% CI: 0.89–0.62; p=0.002). ● 2,825 pts received a placebo and 2,840 pts received. Summary: For pts with a history of stroke or TIA, BP reduction of 5/2 mm Hg with 2.5 mg of indapamide lowered the first incidence of fatal and nonfatal stroke by 29%, with 3-y absolute benefit of 29 events per 1,000 pts.
PROGRESS 2001 (209) 11589932	Aim: To determine effects of a BP-lowering regimen in hypertensive and nonhypertensive pts with a history of stroke or TIA. Study type: Double-blind, placebo-controlled trial Size: 6,105	Inclusion criteria: Pts with history of stroke (evidence of an acute disturbance of focal neurological function with symptoms lasting more than 24 h and	Intervention: Active treatment comprised a flexible regimen based on the ACEI perindopril (4 mg daily), with addition of diuretic indapamide at discretion of treating physicians (n=3,051) Comparator: Placebo (n=3,054)	1° outcome: Total stroke (fatal or nonfatal) Key findings: ● Over 4 y of follow-up, active treatment reduced BP by 9/4 mm Hg. 307 (10%) pts assigned active treatment suffered a stroke, vs. 420 (14%) assigned placebo (RR reduction: 28% (95% CI: 17, 38), p<0.0001). ● Combination therapy with perindopril plus indapamide reduced BP by 12/5 mm Hg and stroke risk by 43% (95% CI: 30%–54%). Single-drug therapy reduced	Relevant 2° endpoint: Active treatment also reduced the risk of total major vascular events (26% [16–34]). There were similar reductions in the risk of stroke in hypertensive and nonhypertensive subgroups (all p<0.01). Summary: ● This BP-lowering regimen reduced the risk of stroke among both hypertensive and nonhypertensive pts with a history of stroke or TIA. Combination therapy with perindopril and indapamide produced larger BP

		thought to be due to ICH or ischemia) or TIA within the previous 5 y. Exclusion criteria: N/A ● Pts clinically stable for at least 2 wk after their most recent vascular event before entry to the study.		BP by 5/3 mm Hg and produced no discernable reduction in the risk of stroke.	reductions and larger risk reductions than single drug therapy with perindopril alone. ● This trial showed the benefits of BP lowering in both hypertensive pts. However, based on older definitions, presence of baseline HTN in the trial was defined as ≥160/90 mm Hg.
MOSES Schrader J, et al., 2005 (210) 15879332	Aim: To assess among hypertensive stroke pts, whether for the same level of BP control, eprosartan would be more effective than nitrendipine in reducing cerebrovascular and CV morbidity and mortality. Study type: PROBE design Size: 1,405	Inclusion criteria: High-risk hypertensives with cerebral event during the last 24 mo (proven by cerebral CT scan or nuclear magnetic resonance) Exclusion criteria: Internal carotid artery occlusion or stenosis >70%, manifest HF (NYHA grade III–IV), age >85 y at the time of	Intervention: Eprosartan 600 mg (n=681) Comparator: Nitrendipine 10 mg (n=671)	1° endpoint: Composite of total mortality and all CV and cerebrovascular events, including all recurrent events. Key findings: BP reduced to comparable extent without significant differences between 2 groups during study period (150.7/84 mm Hg vs. 152.0/87.2 mm Hg with eprosartan and nitrendipine therapy to 137.5/80.8 mm Hg and 136.0/80.2 mm Hg, respectively). 75.5% reached values <140/90 mm Hg with eprosartan regimen and 77.7% with nitrendipine. During follow-up, 461 1° events occurred: 206 eprosartan and 255 nitrendipine (IDR: 0.79; 95% CI: 0.66–0.96; p=0.014.	Relevant 2° endpoint: CV events were: 77 eprosartan and 101 nitrendipine (IDR: 0.75; 95% CI: 0.55–1.02; p=0.06); cerebrovascular events: 102 eprosartan and134 nitrendipine (IDR: 0.75; 95% CI: 0.58–0.97; p=0.03). Summary: ● The combined 1° endpoint was significantly lower in the eprosartan group. ● However, it was a reduction in TIAs that accounted for most of the benefit in cerebrovascular events, with no significant difference in ischemic strokes. ● Also a more traditional analysis of time to first cerebrovascular event did not show a benefit of eprosartan.

		the cerebrovascular event, pts treated with anticoagulants for a cardiac arrhythmia, high-grade aortic or mitral valve stenosis, or UA pectoris.			
PROFESS Yusuf S, et al., 2008 (211) 18753639	Aim: To evaluate the effects of therapy with an ARB, telmisartan, initiated early after a stroke Study type: Double-blind RCT Size: 20,332 pts	Inclusion criteria: Pts ≥55 y with an ischemic stroke <90 d before randomization Exclusion criteria: 1° hemorrhagic stroke, severe disability after the qualifying stroke	Intervention: Telmisartan 80 mg daily (n=10,146) Comparator: Placebo (n=10,186)	1° endpoint: Recurrent stroke Key findings: During mean follow-up of 2.5 y, mean BP was 3.8/2.0 mm Hg lower in telmisartan group vs. placebo group. 880 pts (8.7%) in telmisartan group vs. 934 pts (9.2%) in placebo group had a subsequent stroke (HR: 0.95; 95% CI: 0.86–1.04; p=0.23).	Relevant 2° endpoint: Major CV events (death from CV causes, recurrent stroke, MI, or new or worsening HF) occurred in 1,367 pts (13.5%) in telmisartan group vs. 1,463 pts (14.4%) in placebo group (HR: 0.94; 95% CI: 0.87–1.01; p=0.11). Summary: ● Therapy with telmisartan initiated soon after ischemic stroke and continued for 2.5 y did not significantly lower Rate of recurrent stroke, or major CV events. ● Impact of treatment with telmisartan may have been affected by the high rate of discontinuation of treatment medication because of hypotensive symptoms, syncope, diarrhea, and nausea experienced in the telmisartan arm and the more aggressive treatment with other standard antihypertensive therapies in the placebo arm. Thus, adverse side effects from treatment medications may affect quality of life and thus medication adherence after stroke.
SPS-3 Benavente OR, et al., 2013 (212) 23726159	Aim: To investigate effects of different BP targets on rate of recurrent stroke in pts	Inclusion criteria: Pts with recent, MRI-defined symptomatic	Intervention: SBP target of 130–149 mm Hg (n=1,519)	1° outcome: All stroke (including ischemic strokes and intracranial hemorrhages). Key findings:	2° outcomes: No difference between target groups in disabling or fatal stroke 0.81, (95% CI: 0.53–1.23; p=0.32) or composite outcome of MI or vascular death 0.84 (95% CI: 0.68–1.04; p=0.32). However,

	with recent lacunar stroke. Study type: Randomized open-label trial Size: 3,020 pts	lacunar infarctions. Exclusion criteria: Pts with cortical strokes, cardioembolic disease, or carotid stenosis were excluded.	Comparator: SBP target of <130 mm Hg (n=1,501)	● After 1 y, mean SBP was 138 mm Hg (95% CI: 137–139) in the higher-target group and 127 mm Hg (95% CI: 126–128) in the lower-target group. ● Recurrent stroke was observed in 152 pts assigned to higher-target group (2.8% per y) vs. 125 assigned to the lower-target group (2.3% per y; HR: 0.81; 95% CI: 0.64–1.03).	hemorrhagic stroke occurred in 16 pts assigned to the higher-target group (0.29% per y) vs. 6 assigned to the lower-target group (0.11% per y; HR: 0.37 (95% CI: 0.15–0.95). Serious complications of hypotension were observed in 15 pts assigned to the higher-target group (0.26% per y) and 23 assigned to the lower-target group (0.40% per y; HR: 1.53; 95% CI: 0.80–2.93). Summary: Use of a SBP target of less than 130 mm Hg was not significantly better than a target of 130–149 mm Hg for preventing any recurrent stroke. However, the lower target appeared to confer benefit for prevention of hemorrhagic stroke.

Data Supplement 44. Nonrandomized Trials, Observational Studies, and/or Registries of Secondary Stroke Prevention (Section 9.4.3)

Study Acronym; Author; Year Published	Study Type/Design; Study Size (N)	Patient Population	Primary Endpoint and Results (include P value; OR or RR; & 95% CI)	Summary/Conclusion Comment(s)
Rashid P, et al., 2003 (213) 14576382	Study type: Meta-analysis of RCTs Size: 7 RCTs	Inclusion criteria: Pts with a history of ischemic stroke, TIA, or ICH Exclusion criteria: N/A	1° outcome: Recurrent stroke Key findings: Antihypertensive drug therapy associated with a 24% reduction in recurrent stroke risk (RR: 0.76; 95% CI: 0.63–0.92) Recurrent stroke risk reduction seen in both hypertensive and normotensive (as defined by the respective trials) pts and linked to magnitude of reduction in SBP	2° outcomes: Nonfatal stroke OR: 0.79 (95% CI: 0.65–0.95), MI OR: 0.79 (95% CI: 0.63, 0.98), and total vascular events OR: 0.79 (95% CI: 0.66–0.95). No effect seen on vascular or all-cause mortality. ACEIs and diuretics separately, and particularly together, reduced vascular events, while beta-receptor antagonists had no discernable effect. Summary: Use of antihypertensive agents to lower BP for the prevention of vascular events in pts with previous stroke or TIA is efficacious.
Lakhan SE, et al., 2009 (214) 19843330	Aim: To examine the role of BP reduction using antihypertensive	Inclusion criteria: Pts with a history of ischemic stroke, TIA, or ICH Exclusion criteria: N/A	1° outcome: Recurrent stroke BP-lowering agents reduced recurrent stroke OR: 0.71 (95% CI: 0.59–0.86; p=0.0004) and	2°outcomes: BP-lowering agents did not affect the rate of MI or all-cause mortality.

	agents to prevent recurrent stroke. Study type: Systematic review and meta-analysis Size: 10 RCTs		CV events OR: 0.69 (95% CI: 0.57–0.85; p=0.0004) in pts with a prior stroke or TIA.	Summary: BP lowering agents reduced the occurrence of subsequent stroke and CV events. Rate of MI and all-cause mortality was unchanged.
Liu L, et al., 2009 (215) 19798097	Aim: To examine role of BP reduction using antihypertensive agents to prevent recurrent stroke. Study type: Systematic review and meta-analysis Size: 10 RCTs	Inclusion criteria: Pts with a history of ischemic stroke, TIA, or ICH Followed up 2 to 5 y. Exclusion criteria: N/A	1° outcome: Recurrent stroke Key findings: Antihypertensive drugs associated with significant reduction in recurrent strokes (RR: 0.78; 95% CI: 0.68–0.90). Impact of antihypertensive treatment after ischemic stroke was similar in a restricted group of subjects with HTN and when all subjects, including those with and without HTN, were included. Pooled OR: 0.63 (95% CI: 0.54–0.73; p<0.0001) for trials involving diuretics as a component of therapy and 0.93 (95% CI: 0.87–1.01; p=0.086) for trials in which treatment included renin system inhibitors (p<0.0001 for heterogeneity).	2° outcomes: Significant reduction in recurrent stroke seen with diuretics (alone or in combination with ACEIs) but not with renal artery stenosis inhibitors, BBs, or CCBs used alone; however, statistical power was limited, particularly for the assessment of BBs and CCBs. Summary: In conclusion, BP lowering by indapamide treatment reduced the recurrence of stroke and the incidence of CV events in Chinese pts with cerebrovascular disease. Whether prevention of stroke recurrence depends on drug class, degree of BP lowering or both requires further investigation.
Lee M, et al., 2012 (216) 21796663	Aim: To compare impact of achieving tight vs. usual SBP control on stroke prevention Study size: 11 studies with 42,572 pts and 794 stroke events.	Inclusion criteria: (1) Achieved SBP<130 mm Hg in an active treatment group and SBP 130 to 39 mm Hg in a comparator group by trial; (2) trial duration at least 6 mo; (3) total pts and number of stroke events reported separately for active treatment and comparator groups. Exclusion criteria: (1) Nonrandomized trials; (2) trials in which either the	1° outcome: Association of future stroke risk and achieved level of different SBP (intensive vs. usual) Key findings: • Final SBPs, weighted for trial size, were a mean of 126.5 mm Hg in the intensive treatment arms and 132.6 mm Hg in the conventional arms (mean SBP reduction, 6.1 mm Hg). • In subgroup analyses, those with established (symptomatic) CVD at entry did not experience stroke risk reduction with tight control (0.92; 95% CI: 0.83–1.03).	Summary: Achieving an SBP <130 mm Hg vs. 130–139 mm Hg appears to provide additional stroke protection only among pts with risk factors but no established CVD.

		comparator or the active therapy group received additional treatment that other group did not; (3) majority of participants had ESRD; (4) <10 stroke events in a trial, because stroke was not a major endpoint; (5) SBP not significantly different between active and comparator groups at trial end; (6) Achieved SBP<130 mm Hg in a comparator group.		
Lee M, et al., 2012 (217) 22052520	Aim: To evaluate whether use of ACEIs or ARB reduces future vascular events in persons with prior stroke. Size: 8 RCTs with 29,667 pts	Inclusion criteria: (1) RCT design; (2) pts had a history of stroke or TIA; (3) active treatment consisted of ACEIs or ARBs; (4) follow-up duration at least 6 mo; (5) total pts and number of future major vascular events and/or recurrent stroke were reported separately for active treatment and comparator groups. Exclusion criteria: (1) mandatory ACEI or ARB use in control groups; (2) study purpose was to examine efficacy of ACEIs or ARBs in pts with acute stroke	1° outcome: Major vascular event (nonfatal stroke, nonfatal MI, or death from CV causes) or stroke (ischemic or hemorrhagic) Key findings: Use of ACEIs or ARBs in persons with prior stroke was associated with lower risks of future major vascular events RR: 0.91 (95% CI: 0.87–0.97; p=0.001); NNT=71 and recurrent stroke RR: 0.93 (95% CI: 0.86–0.99; p=0.03); NNT=143.	Summary: Treatment with an ACEI or ARB has a clear but rather modest effect on reducing vascular risk in persons with prior stroke.
Arima H, et al., 2006 (218) 16685221	Aims: #1: To investigate the effects of randomized treatment on recurrent stroke by baseline BP levels #2: To investigate association	Inclusion criteria: Pts with history of cerebrovascular event (stroke or TIA) within the previous 5 y Groups: Defined by baseline BP of <120, 120–139, 140–159, and 160 mm Hg or greater	1° outcome: Total stroke (fatal or nonfatal) Key findings: ● Smaller BP differences between active vs. placebo groups (p<0.0001) and corresponding lesser risk reductions (p trend=0.05) with lower baseline BPs Association of stroke incidence with achieved	Summary: ● These analyses provide no evidence of a J-curve relationship between BP level and stroke risk among pts with cerebrovascular disease. However, ischemic stroke, TIA, and hemorrhagic pts were all enrolled and within 5 y of the index event suggesting that these pts were generally neurologically stable and not acknowledging the

	between achieved follow-up BP levels and recurrent stroke risk. Study type: Post-hoc analysis of PROGRESS trial. Size: 6,105 pts		follow-up SBP level was strong and continuous with no evidence of a J-curve in the range of achieved follow-up SBP from 112–168 mm Hg (p trend <0.0001 RR of study treatment on the discontinuation of randomized treatment increased progressively across the subgroups with lower baseline SBP levels at entry (p trend=0.04), but there was no corresponding difference in effects of randomized treatment on the risks of death or hospital admission (both p trend >0.2) or hypotension, renal dysfunction, electrolyte disturbance, hip fracture, or depression between pts with different levels of baseline BP at baseline (all p trend >0.1) ● Minor side-effects were progressively more common at lower BP levels (p homogeneity=0.04).	differences in pathophysiologic mechanism between stroke types. ● First analysis showed that the effectiveness of antihypertensive treatment for 2º stroke prevention diminished as baseline BP declined (relative RRs were 39%, 31%, 14%, and 0%, respectively, in the groups defined previously). This trend of decreasing effect was despite successful reduction of mean SBP in each active-treatment group compared with placebo (11.1, 9.2, 7.6, and 7.4 mm Hg reductions, respectively, in the groups defined previously). Also of note, 40% of pts with a baseline BP<140 mm Hg were taking antihypertensive therapy at baseline.
White CL, et al., 2015 (219) 25850462	Aim: To determine safety and tolerability of lowering BP in older adults with lacunar stroke Study type: Post-hoc analysis of randomized trial Study Size: 494 pts	Inclusion criteria: Pts with lacunar stroke ≥75 y	1° outcome: Rates of side effects related to lowering SBP 2° outcome: Stroke recurrence and death from vascular causes Key findings: ● Older pts achieved SBP levels similar to younger pts (mean SBP of 125 mm Hg in lower SBP target group and 137 mm Hg in higher target group) ● 3.5 y of follow-up 21% reported dizziness and 15% reported lightheadedness when standing; only significant difference between younger and older groups was unsteadiness when standing (23% vs. 32%, p<0.001). No difference in recurrent stroke by target SBP level among the older subjects (HR: 1.01; 95% CI: 0.59–1.73), but the	Summary: Pts ≥75 y with a recent lacunar stroke who achieved a lower SBP target (<130 mm Hg) were significantly more likely to report unsteadiness on standing than their younger counterparts. Lower SBP was not related to a decrease in recurrent stroke risk in elderly pts with lacunar stroke but there was a potential protective advantage from vascular death.

			lower target SBP group in older pts was linked to a significant reduction in vascular death (HR: 0.42; 95% CI: 0.18–0.98; p=0.049).	
Ovbiagele B, et al., 2011 (220) 22089721	Aim: To assess the association of maintaining low-normal vs. high-normal SBP levels with risk of recurrent stroke. Study type: Post hoc analysis of a multicenter trial involving 20,330 pts (age ≥50 y) with recent noncardioembolic ischemic stroke followed up for 2.5 y Study Size: 20,330 pts	Inclusion criteria: Pts 55 y or older with an ischemic stroke <90 d before randomization Categories: Based on mean SBP level was very low-normal (<120 mm Hg), low-normal (120≤130 mm Hg), high-normal (130≤140 mm Hg), high (140≤150 mm Hg), and very high (≥150 mm Hg). ● 1° outcome was recurrent stroke and the 2º outcome was a composite of recurrent stroke, MI, and death due to vascular causes	1° outcome: First recurrence of stroke of any type 2° outcome: Composite of stroke, MI, or death from vascular causes. Key findings: Recurrent stroke rates were 8.0% (95% CI: 6.8%–9.2%) for the very low-normal SBP level group, 7.2% (95% CI: 6.4%–8.0%) for the low-normal SBP group, 6.8% (95% CI: 6.1%–7.4%) for the high-normal SBP group, 8.7% (95% CI: 7.9%–9.5%) for the high SBP group, and 14.1% (95% CI: 13.0%–15.2%) for the very high SBP group. Compared with pts in the high-normal SBP group, the risk of 1° outcome was higher for pts in the very low-normal SBP group AHR: 1.29 (95% CI: 1.07–1.56), in the high SBP group AHR: 1.23 (95% CI: 1.07–1.41), and in the very high SBP group AHR: 2.08 (95% CI: 1.83–2.37).	Relevant 2° endpoint: Compared with pts in the high-normal SBP group, the risk of 2º outcome was higher for pts in the very low-normal SBP group AHR: 1.31 (95% CI: 1.13–1.52), in the low-normal SBP group AHR: 1.16 (95% CI: 1.03–1.31), in the high SBP group AHR: 1.24 (95% CI: 1.11–1.39), and in the very high SBP group AHR: 1.94 (95% CI: 1.74–2.16). Summary: Among pts with recent noncardioembolic ischemic stroke, SBP levels during follow-up in the very low-normal (<120 mm Hg), high (140–≤150 mm Hg), or very high (≥150 mm Hg) range were associated with increased risk of recurrent stroke.
Ovbiagele B, et al., 2013 (221) 22244715	Aim: To assess association of maintaining low-normal vs. high-normal SBP levels with risk of recurrent stroke. Study type: Post hoc analysis of a multicenter trial involving 3,680 pts with recent noncardioembolic ischemic stroke followed up for 2 y	Inclusion criteria: Pts with an ischemic stroke <120 d before randomization Categories: ● Based on mean in-trial SBP value was low-normal (<120 mm Hg), high-normal (120 to <140 mm Hg), or high (>140 mm Hg). ● 1° outcome was stroke	1° outcome: First recurrence of stroke of any type Key findings: Rate of recurrent stroke was 9.1% in the low-normal group, 6.7% in the high-normal group, and 10% in the high group. Difference in recurrent stroke rate between low-normal and high-normal groups was more prominent within the first 6 mo (low-normal, 4.5%; high-normal, 2.5%; high, 3.4%) vs. after 6 mo (low-normal, 4.6%; high-normal, 4.2%; high, 6.6%). Over study period, compared with the high-normal group, risk of the 1° outcome trended higher in the low-normal group AHR: 1.47 (95% CI: 0.94–2.29; p=0.09) and was higher in the high group AHR: 1.39 (95% CI: 1.08–1.79; p=0.01).	Summary: Results support a possible pattern of increased risk of recurrent stroke in pts with low-normal SBP levels, especially within the first 6 mo after first stroke. However, this study likely was not sufficiently powered to detect more than a strong statistical trend underlying this relationship.

Lin MP, et al., 2015 (222) 25765723	Aim: To assess link between SBP and mortality after stroke. Study type: Analyses of nationally representative survey data (NHANES) Study Size: 455 pts	Inclusion criteria: Adults ≥20 y with self-reported stroke. Categories: Baseline SBP was as low to normal (<120 mm Hg), normal (120–140 mm Hg), and high (≥140 mm Hg).	1° outcomes: All-cause and vascular mortality Key findings: 2 y after assessment, the low to normal SBP group tended to have the highest cumulative all-cause mortality (11.5%), compared with mortality rates of 8.5% and 7.5% in the normal and high SBP groups, respectively. Similar patterns were seen with vascular mortality. After adjusting for covariates, compared with the high SBP group, the low to normal group had higher all-cause mortality AHR: 1.96 (95% CI: 1.13–3.39; p=0.017) and trended toward higher vascular mortality AHR: 2.08 (95% CI: 0.93–4.6; p=0.075). Compared with the normal BP group, the risk of all-cause and vascular mortality trended higher in low to normal BP group but did not achieve statistical significance.	Summary: After stroke, compared with SBP in the high range, low to normal SBP may be associated with poorer mortality outcomes. Study limited by self-reported nature and retrospective design.
Kim J, et al., 2014 (223) 24509123	Aim: To investigate the association between BP and vascular events up to 10 y after stroke. Study type: Analysis of population based study (North East Melbourne Stroke Incidence Study (NEMESIS)	Inclusion criteria: 5-y survivors of stroke Categories: Stratification by quartiles of SBP Follow-up: Annually by telephone at 6, 8, and 9 y and face-to-face interview at 7 and 10 y after stroke.	1° outcomes: Composite of all-cause death or nonfatal vascular event (stroke or AMI); and all-cause death alone. Key findings: In 5-y survivors of stroke, compared to a SBP of 131–141 mm Hg, SBP of 120 mm Hg or less was associated with a 61% greater risk of stroke, acute MI and death (HR: 1.61; 95% CI: 1.08–2.41; p=0.019). Compared to the reference category of SBP 131–141 mm Hg, there were no differences in outcome in the pts with SBP 121–130 mm Hg (p=0.491) or 142–210 mm Hg (p=0.313). Findings were not modified after adjusting for antihypertensive drug prescriptions.	Summary: There appears to be a greater risk of poor outcome in long-term survivors of stroke with low SBP. This is further evidence that low SBP may result in poor prognosis.
Wang WT, et al., 2016 (224) 27082571	Aim: To investigate the relative effects of BP-lowering therapies [ACEI, ARB, BB, CCBs, diuretics, and	Inclusion criteria: • RCTs comparing the effects of any of the 6 most commonly used BP-lowering drug classes [ACEI, ARB, alpha-blocker, BB, diuretics, and CCB] vs. placebo	1° outcome: Recurrent stroke 2° outcome: CHD, and MACCE Key findings: • Compared with placebo, ACEI plus diuretic	• Virtually all BP-lowering medication classes reduced vascular events including recurrent stroke. • The higher the average BP reduction between the treatment vs. control groups the larger the risk reduction in recurrent stroke events and MACCE.

	combinations of 3 drugs] in pts with a prior stroke history Study size: 15 RCTs composed of 39,329 participants previous stroke	or comparing 1 type of antihypertensive agent with another type on pts who have suffered from stroke or TIA s • RCTs reporting outcomes of interest with a follow-up of more than a month.	reduced recurrent stroke (OR: 0.54; 95% CI: 0.33–0.90). • ACEI plus diuretic had a higher probability of being at the best ranking position (31%). Compared with regimens not including diuretics, diuretics-based treatments resulted in a significantly larger reduction in BP (12.0 mm Hg; 95% CI: 7.0–16.9), ● Treatment regimens including diuretics had a RR of 0.619 (95% CI: 0.515–0.743) for recurrent stroke, which was significantly lower than treatments that did not include diuretics (RR = 0.882; 95% CI: 0.800–0.973) with a p value for interaction of 0.0008. ● None of the between-drug comparisons showed significant differences in effect on outcomes	• Diuretic-based treatments lowered the risk of recurrent stroke more than treatments that did not include diuretics. • There were no significant differences in effect on 2º stroke reduction between the various individual antihypertensive medication classes.
Katsanos AH, et al., 2017 (225) 27802419	Aim: To assess the association of BP reduction with recurrent stroke and CV events using available RCT data on 2º stroke prevention Study size: 14 studies with 42,736 pts	Inclusion criteria: RCTs of antihypertensives for 2º stroke prevention pts that reported achieved BP values during the follow-up period. Exclusion criteria: Observational studies, case series, case reports, RCTs in non-IS/TIA population, and studies not reporting data on finally achieved BP values	1° outcome: Recurrent stroke 2° outcome: MI, death from any cause, and risk of CV death Key findings: ● SBP reduction linearly associated with lower risk of recurrent stroke (regression slope, 0.02; 95% CI: 0.01–0.04; p=0.049), MI (regression slope, 0.022; 95% CI: 0.002–0.041; p=0.024), death from any cause (regression slope, 0.02; 95% CI: 0.01–0.03; p=0.001), and CV death (regression slope, 0.05; 95% CI: 0.03–0.07; p<0.001). ● No relation was observed between the degree of SBP reduction and the risk of disabling or fatal stroke (regression slope, 0.001; 95% CI: −0.024–0.022; p=0.944). ● Relation of SBP reduction with ischemic or hemorrhagic stroke was not assessed due to the small number of studies with available data (<10).	Summary: BP reduction is linearly associated with the magnitude of risk reduction in recurrent cerebrovascular and CV events, but optimal BP target not evaluated.

Data Supplement 45. RCTs and Meta-analysis Comparing PAD (Section 9.5)

Study Acronym; Author; Year Published	Aim of Study; Study Type; Study Size (N)	Patient Population	Study Intervention (# patients) / Study Comparator (# patients)	Endpoint Results (Absolute Event Rates, P value; OR or RR; & 95% CI)	Relevant 2° Endpoint (if any); Study Limitations; Adverse Events
HOPE Östergren J, et al., 2004 (226) 14683738	Aim: To assess the impact of ramipril compared to placebo on the prevention of major CV events in PAD pts in the HOPE study. Study type: Multicenter, double-blind RCT Size: 9,541 randomized in HOPE (1,725 randomized who had baseline PAD, defined by ABI with pulse detection by either Doppler or palpation)	Inclusion criteria: • ≥55 y • Existing CVD (CAD, stroke, PAD) or DM with an additional CVD risk factor (smoking, HTN, hypercholesterolemia, low HDL, microalbuminuria) Exclusion criteria: • Received ACEI or vitamin E or had uncontrolled HTN • HF or LV dysfunction *All eligible pts had 7- to 10-d run-in period, received 2.5 mg ramipril daily; those who tolerated were then assigned placebo for 10–14 d and then were randomized to1 of intervention arms or control	Intervention: Ramipril (10 mg/d): 4,645 randomized Intervention: Placebo: 4,652 randomized	1° endpoint: • Combined CV death, nonfatal MI, nonfatal stroke • In pts with history of symptomatic PAD, comparing ramipril to placebo: RR: 0.75; 95% CI: 0.61–0.92 • In pts with no history of symptomatic PAD, but severe subclinical disease defined as ABI <0.6, comparing ramipril to placebo: RR: 0.77; 95% CI: 0.55–1.09 • In pts with no history of symptomatic PAD, but moderate subclinical disease defined as ABI 0.6–0.9, comparing ramipril to placebo: RR: 0.72; 95% CI: 0.56–0.92 1° Safety endpoint: N/A Summary: Ramipril prevented clinical events in pts with clinical evidence of PAD as well as in those without PAD. The relative benefit was similar in pts classified by levels of ABI, even though event rates were higher in pts with subclinical and clinical ABI.	Relevant 2° endpoint: • Individual components of composite endpoint, all-cause mortality, hospitalizations for HF, DM complications • In pts with history of symptomatic PAD, comparing ramipril to placebo: for MI, RR: 0.75 (95% CI: 0.58–0.98); for stroke, RR: 0.72 (95% CI: 0.50–1.05); for CVD mortality, RR: 0.75 (95% CI: 0.56–0.99); for total mortality, RR: 0.85 (95% CI: 0.68–1.07); for DM complications, RR: 0.87 (95% CI: 0.74–1.09); for HF, RR: 0.81 (95% CI: 0.53–1.24) • In pts with no history of symptomatic PAD, but severe subclinical disease defined as ABI <0.6, comparing ramipril to placebo: for MI, RR: 0.73 (95% CI: 0.48–1.11); for stroke, RR: 0.99 (95% CI: 0.52–1.89); for CVD mortality, RR: 0.76 (95% CI: 0.46–1.25); for total mortality, RR: 0.81 (95% CI: 0.55–1.19); for DM, RR: 0.83 (95% CI: 0.50–1.39); for HF, RR: 0.66 (95% CI: 0.34–1.28) • In pts with no history of symptomatic PAD, but moderate subclinical disease defined as ABI 0.6–0.9, comparing ramipril to placebo: for MI, RR: 0.81 (95% CI: 0.60–1.09); for stroke, RR: 0.44 (95% CI: 0.26–0.77); for CVD mortality, RR: 0.62 (95% CI: 0.42–0.90); for total mortality, RR: 0.58 (95% CI: 0.42–0.79); for diabetic complications, RR: 0.80 (95% CI: 0.53–1.21); for HF, RR: 0.69 (95% CI: 0.38–1.23)

					Study limitations and adverse events: ABI not measured by Doppler gold standard
Overlack A, et al., 1994 (227) 8059778	Aim: To determine the effect of perindopril compared to placebo on various clinical outcomes in pt subgroups. Study type: Multicenter, double-blinded RCT (3 wk placebo run-in period, 6 wk double-blind phase) Size: 490 (54 with PAD)	Inclusion criteria: • Mild newly diagnosed essential HTN in addition to 1 concomitant diseases or therapies: hyperlipidemia, DM-2, IHD, cardiac arrhythmias, PAD, nephropathy with proteinuria, COPD, or degenerative join disease with NSAIDs • 40–75 y *Antihypertensive treatment was stopped 1 wk prior to randomization, required DBP 95–104 mm Hg Exclusion criteria: N/A	Intervention: Perindopril (4 mg/d): 253 randomized Comparator: Placebo: 237 randomized	1° endpoint: • ABI measured by Doppler • In pts with baseline PAD, there was no difference in post-treatment Doppler Index between perindopril (0.75) vs. placebo (0.75); p>0.05 1° Safety endpoint: Spontaneously reported side effects: 5.5% of pts in perindopril, 3.8% of pts in placebo Summary: In pts with PAD, Doppler index at baseline was not different between the 2 groups and remained unchanged during treatment. Pain-free and maximal walking distances increased from baseline but there were no significant between group differences.	Relevant 2° endpoint: • Pain-free walking distance (m), maximal walking distance • In pts with baseline PAD, there was no difference in change in pain-free walking distance (m) between perindopril (+11 m) vs. placebo (+11 m); p>0.05 • In pts with baseline PAD, there was no difference in change in maximal walking distance between perindopril (pre-trial: 318 m (SD: 45), post-trial: 323 m (SD: 43) vs. placebo (pre-trial: 333 m (SD: 43), post-trial: 369 m (SD: 46) Study limitations and adverse events: Short follow-up, unable to assess hard clinical outcomes
Schweizer J, et al., 1998 (228) 9581724	Aim: To determine whether treatment with high dose verapamil prevents restenosis in pts with PAD at high risk for reoccurrence after successful PTCA. Study type: Double-blind RCT (6 mo duration)	Inclusion criteria: • PAD (based on arterial angiography and color-coded duplex ultrasound) present for >6 mo • Primary success of PTCA treatment (≥30% reduction of initial lumen constriction) • Stable angina pectoris, mild HTN and at least1	Intervention: Verapamil (240 mg/twice/d): 49 randomized Comparator: Placebo: 49 randomized	1° endpoint: • Percentage of diameter stenosis • At 6 wk, mean % diameter stenosis in verapamil group was 46.8 (SD: 14.1) vs. placebo was 55.5 (SD: 10.0) • At 6 mo, mean % diameter stenosis in verapamil group was 48.0 (SD: 11.5) vs.	Relevant 2° endpoint: • Intima/media thickness was 1.2 mm (SD: 0.31) in verapamil vs. 1.9 mm (SD: 0.47), p<0.001 • Septal thickness was 10.2 mm (SD: 1.1) in verapamil vs. 11.9 mm (SD: 2.3), p<0.001 • Crurobrachial ratio dorsalis pedis was 0.76 (SD: 0.10) in verapamil vs. placebo was 0.72 (SD: 0.08)

	Size: 98 pts	additional risk factor: DM, hyperlipoproteinemia, total or subtotal vascular occlusion of dilated segmented, eccentric stenosis, residual stenosis of at least 30%, or stenosis localized in the distal superficial femoral artery Exclusion criteria: • History of pelvic stenosis • Previous adjuvant therapy with calcium antagonists or beta-adrenergic blocking agents • Age >75 y • Prior revascularization of same area • 1st, 2nd, or 3rd AV block, sinoatrial block, diseases of supporting or connective tissues, moderate arterial HTN with SBP >170 mm Hg and DBP >95 mm Hg • Pts requiring stent for large anatomic segments or elastic stenosis		placebo was 69.6 (SD: 12.2), p<0.01 1° Safety endpoint: N/A Summary: In pts with PAD at increased risk for restenosis, the administration of high dose verapamil prevented recurrent stenosis for 6 mo after successful peripheral angioplasty and was well tolerated.	• Crurobrachial ratio tibial artery was 0.76 (SD: 0.09) in verapamil vs. placebo was 0.70 (SD: 0.10) • Arterial pressure was 134/87 mm Hg (SD: 5.2/4.2) in verapamil vs. placebo was 165/97 mm Hg (6.5/4.4), p<0.001 • Total vessel diameter was 8.3 mm (SD: 0.3) in verapamil vs. 7.5 mm (SD: 0.3), p<0.001 Study limitations and adverse events: Short follow-up, unable to assess hard clinical outcomes
NORMA Espinola-Klein C, et al., 2011 (229) 21646599	Aim: Evaluate the effects of treatment with the endothelium-dependent vasodilating beta 1-selective blocker nebivolol, as compared with the nonvasodilating beta 1-selective blocker metoprolol, on clinical parameters of PAD and endothelial function, and to compare the	Inclusion criteria: • Stable intermittent claudication for ≥6 mo and an ABI of <0.9 • Stage 1 arterial HTN (SBP: 140–159 mm Hg, DBP: 90–99 mm Hg untreated, or treated stage 1 arterial HTN) • SBP at time of enrollment 100–160 mm Hg	Intervention arms: • Nebivolol (5 mg/d): 65 randomized • Metoprolol (95 mg/d): 63 randomized	1° endpoint: • Change in ABI measured by Doppler • In nebivolol: initial ABI 0.62 (SD: 0.16), post-treatment ABI 0.68 (SD: 0.20), p-value for change: 0.002 • In metoprolol: initial ABI 0.63 (SD: 0.17), post-treatment ABI 0.67 (SD:	Relevant 2° endpoint: • Change in absolute claudication distance were 32.7 m in nebivolol (p-value 0.03) vs. 39.7 m in metoprolol (p-value 0.01), but no difference between 2 groups (p-value 0.54) • Changes in SBP were -5.2 mm Hg in nebivolol (p=0.001) and -3.9 mm Hg in metoprolol (p=0.01), no difference between groups

	tolerability of both drugs in pts with PAD Study type: Double-blinded RCT (48 wk) Size: 128	• DBP at time of enrollment <100 mm Hg Exclusion criteria: • Premenopausal women • Critical limb ischemia with rest pain, leg ulcer, gangrene, severe angina pectoris that limits exercise capacity, severe HF that limits exercise capacity, hyperthyroidism, poorly controlled DM (HbA1c>10%) • Contraindications for BBs • Acute MI within 6 mo before screening • Previous treatment with nebivolol or carvedilol *Concomitant treatment with calcium antagonists, ACEIs, angiotensin II type 1 receptor antagonists, aspirin, clopidogrel, statins, estrogens was permitted if no change in dosage had been made in the previous 3 mo before screening		0.21), p-value for change: 0.04 • Comparing ABI change in nebivolol to metoprolol: 0.02 (p=0.69). 1st safety endpoint: N/A Summary: BB therapy was well tolerated in pts with intermittent claudication and HTN during a treatment period of 1 y. In the direct comparison, there was no significant difference between nebivolol and metoprolol.	• No change in flow-mediated dilatation in either group (p=0.16) Study limitations and adverse events: • Absence of placebo group • 21 total adverse events, 10 in nebivolol, 11 in metoprolol (adverse events: bradycardia, tachycardia, blurred vision, worsening HTN, edema, worsening claudication, blurred vision, erectile dysfunction, edema, vertigo, temporary dysesthesia of the hands, dyspnea, skin irritation, headache, moderate diarrhea)
INVEST Bavry AA, et al., 2010 (230) 19996066	Aim: To examine the effect of average treated BP on adverse outcomes in PAD pts with CAD and to compare 2 antihypertensive medications Study type: Post hoc analysis of international	Inclusion criteria: • ≥50 y • HTN, clinically stable CAD • Pt reported PAD Exclusion criteria: Contraindications to the treatment groups	Interventions: ● Calcium antagonist-based strategy: verapamil with or without trandolapril ● BB-based strategy: atenolol with or without hydrochlorothiazide *2º medications only given to achieve BP of	1° endpoint: • Composite outcome: all-cause death, nonfatal MI, nonfatal stroke • No statistically significant difference in composite 1° outcome OR: 0.90 (95% CI: 0.76, 1.07) comparing calcium antagonist based group to BB based group in fully adjusted model	Relevant 2° endpoint: N/A • This trial also notes the J-shaped relationship between BP achieved and clinical outcomes • Risk of 1° outcome was reduced most when SBP was treated to 130–140 mm Hg and DBP 60–90, as opposed to <130/80 as 2005 guidelines suggest in PAD pts Study limitations and adverse events:

	randomized, blinded-endpoint trial (48 wk) Size: 22,576 in total trial (2,699 with PAD in this analysis)		<140/90 mm Hg in all participants except for those with renal impairment or DM, BP<130/85 mm Hg	• Kaplan–Meier curve for 1° outcome shows slightly lower cumulative incidence in calcium antagonist group (log rank p=0.26) 1st safety endpoint: N/A Summary: Among PAD pts, the incidence of the 1° outcome was not significantly different between treatment groups.	• PAD was not uniformly measured or adjudicated (only based on pt report) • Asymptomatic PAD was not captured
VALUE Zanchetti A, et al., 2006 (231) 17053536	Aim: To examine the effect of valsartan vs. amlodipine on cardiac morbidity and mortality in hypertensive pts at high CV risk Study type: Prespecified additional analyses of international randomized, double-blind, parallel-group trial Size: 15,245 in total trial (2,114 with PAD)	Inclusion criteria: • ≥50 y • HTN (untreated: 160–210/<115 mm Hg, treated: <210/<115 mm Hg) • High risk for cardiac events (male sex, verified DM, current smoking, high cholesterol, LV hypertrophy by ECG, proteinuria on dipstick, serum creatinine 150–265 micromol/L, coronary disease diagnosis, cerebrovascular disease diagnosis, or PAD diagnosis) Exclusion criteria: • Renal artery stenosis • Pregnancy • AMI, coronary angioplasty or CABG in last 3 mo • Severe hepatic disease • Severe chronic renal failure	Interventions: • Valsartan: 7,649 total • Amlodipine: 7,596 total *No PAD-specific numbers available	1° endpoint: • Composite of sudden cardiac death, fatal MI, death during/after percutaneous coronary intervention or CABG, HF requiring hospitalization, nonfatal MI, or emergency procedure to prevent MI • There was no significant difference in the 1° outcome by treatment group among all pts and by PAD status. Among pts with PAD, the 1° outcome occurred in 13.4% of valsartan vs. 13.6% of amlodipine pts. Among pts without PAD, the corresponding % were 10.1% and 9.9%. 1st safety endpoint: --- Summary: The effects of treatments on occurrence of the 1° outcome did not different by PAD status.	Relevant 2° endpoint: N/A Study limitations and adverse events: • Limited subgroup analyses, only 1° outcome reported • High-risk population limits generalizability

		• Congestive HF requiring ACEI therapy • Pts on monotherapy with 3 blockers for both CAD and HTN			
Piller LB, et al., 2014 (232) 25002161	Aim: To compare, by randomized treatment groups (amlodipine, lisinopril, chlorthalidone) hospitalized or revascularized PAD rates and subsequent morbidity and mortality. Study type: Post-hoc analysis of prospective, randomized, double-blinded active-control trial (ALLHAT study—amlodipine, lisinopril compared to chlorthalidone control arm) Size: 33,357 pts	Inclusion criteria: • BP of 140–180/90–110 for untreated, 160/100 for treated pts • Age ≥55 y • Have at least1 CV risk factor (risk factors: old myocardial injury or stroke, history of coronary revascularization procedure, other documented atherosclerotic CVD PAD, history of intermittent claudication, peripheral artery revascularization or peripheral artery angioplasty, DM-2, current cigarette smoking, HDL <0.90 mmol/L, LVH, major ST depression, T-wave inversion) Exclusion criteria: • Canadian pts for whom outcome measures could not be assessed (n=533)	Intervention arms: • Amlodipine: 8,898 randomized • Lisinopril: 8,904 randomized Comparator: Chlorthalidone: 15,002 randomized *Goal BP was <140/90 in each randomized group (achieved using study drug but adding open-label agents at physician discretion when necessary)	1° endpoint: • PAD requiring hospitalization or outpatient revascularization procedure • 830 cases of PAD over 8.8 y follow-up; no significant difference between treatment groups after adjustment • HR comparing amlodipine to chlorthalidone: 0.86 (95% CI: 0.72, 1.03) after full adjustment, p-value: 0.099 • HR comparing lisinopril to chlorthalidone: 0.98 (95% CI: 0.83, 1.17) after full adjustment, p-value: 0.847 • Kaplan Meier: Y-to-PAD was longer amlodipine vs. chlorthalidone (no difference between lisinopril and chlorthalidone) 1° Safety endpoint: N/A	Relevant 2° endpoint: • Post-PAD morbidity and mortality • Comparing amlodipine to chlorthalidone, no difference in post-PAD morbidity or mortality: MI, HR: 0.82 (95% CI: 0.48, 1.40); Stroke, HR: 0.86 (95% CI: 0.41, 1.79); Cardiac Revascularization, HR: 1.39 (95% CI: 0.81, 2.39); HF, HR 1.32 (95% CI: 0.79, 2.18); Total Mortality, HR: 0.92 (95% CI: 0.74, 1.15) • Comparing lisinopril to chlorthalidone, no difference in post-PAD morbidity or mortality: MI, HR: 0.74 (95% CI: 0.44, 1.25); Stroke, HR: 0.94 (95% CI: 0.48, 1.86); Cardiac Revascularization, HR: 1.25 (95% CI: 0.73, 2.13); HF, HR: 1.08 (95% CI: 0.65, 1.80); Total Mortality, HR: 0.95 (95% CI: 0.77, 1.18) Study limitations and adverse events: • PAD not specifically collected at baseline, thus cannot detect actual incidence (however, randomization presumably resulted in equal number of baseline PAD cases in each group) • Asymptomatic PAD likely missed (definition used in this study based on hospitalization, likely only capturing very severe cases)
Thompson AM, et al., 2011 (113) 21364140	Aim: To evaluate the effect of antihypertensive treatment on 2º prevention of CVD events and all-cause mortality among pts	Inclusion criteria: RCTs of antihypertensive treatment among pts with BP <140/90 mm Hg for the prevention of CVD events.	Interventions: Any antihypertensive agent compared with placebo or no treatment.	Results: Compared with controls, pts receiving antihypertensive medications had a pooled RR of 0.77 (95% CI: 0.61, 0.77) for stroke: 0.80 (95% CI: 0.69,	Study limitations and adverse events: • PAD not specifically collected at baseline, thus cannot detect actual incidence (however, randomization presumably resulted in equal number of baseline PAD cases in each group)

	without clinically defined HTN. Study type: Meta-analysis including 25 RCTs Size: 64,162 pts without HTN.	Exclusion criteria: CVD events were not reported by HTN status that included participants with and without HTN; study population did not include persons with BP in the normal or prehypertensive ranges; study population did not include persons with preexisting CVD or CVD equivalents, such as DM; antihypertensive medication was not a part of the intervention; treatment allocation was not random; measure of variance not reported; participants were <18 y; there were differences between intervention and control groups other than antihypertensive treatment. Preexisting CVD included PAD.		0.93) for MI: 0.71 (95% CI: 0.65, 0.77) for CHF: 0.85 (95% CI: 0.80, 0.90) for composite CVD events: 0.83 (95% CI: 0.69, 0.99) for CVD mortality and 0.87 (95% CI: 0.80, 0.95) for all-cause mortality from random effect models. Results did not differ according to trial characteristics or subgroups defined by clinical history, although no specific PAD subgroup was defined. Summary: Among pts with clinical history of CVD, including PAD, but without HTN, antihypertensive treatment was associated with reduced risk of stroke, CHF, composite CVD events and all-cause mortality.	• Asymptomatic PAD likely missed (definition used in this study based on hospitalization, likely only capturing very severe cases)

Data Supplement 46. RCTs and Meta-analyses Comparing BP Targets in DM (Section 9.6)

Study Acronym; Author; Year Published	Aim of Study; Study Type; Study Size (N)	Patient Population	Study Intervention (# pts) / Study Comparator (# pts)	Endpoint Results (Absolute Event Rates, P value; OR or RR; & 95% CI)	Relevant 2° Endpoint (if any); Study Limitations; Adverse Events; Summary
ADVANCE Kaplan NM, et al., 2007 (233) 17765962	Aim: To assess the effects of an ACEI perindopril and a diuretic indapamide combination on serious vascular events in pts with	DM-2 pts 30–55 y. Inclusion criteria: At least 1 of the following: history of major CVD, (stroke, MI, admission for TIA, UA, coronary	• Fixed combination of perindopril and indapamide compared with perindopril and placebo.	1° endpoints: Composite of CV death, nonfatal MI, nonfatal stroke, new or worsening nephropathy, or retinopathy. Results: After 4.3 y follow-up, pts assigned to active therapy had a reduction of SBP of 5.6 mm Hg. RR of major macro- or micro-	Summary: • This large RCT provides evidence that routine administration of fixed combination ACEI and thiazide-type diuretic therapy reduces risk of major CV events in those with at least 1 risk factor.

	DM irrespective of initial BP levels or the use of other BP-lowering drugs. Study type: RCT Size: 11,140 pts, 4.3 y follow-up	revascularization, or amputation for PVD) or at least 1 other risk factor (history of microvascular disease, microalbuminuria, proliferative diabetic retinopathy, retinal photocoagulation therapy, macular edema, blindness, cigarette smoking, high cholesterol, low HDL cholesterol, diagnosis of DM at least 10 y before enrollment or ≥65 y at entry Exclusion criteria: HbA1c target ≤6.5% or indication for insulin.		vascular events decreased by 9% (HR: 0.91; (95% CI: 0.83, 1.00), p<0.04). Death from CVD decreased by 18%; RR: 0.82 (95% CI: 0.68, 0.98) and death from any cause decreased by 14%; RR: 0.86 (95% CI: 0.75, 0.98). The effects of study treatment did not differ by initial BP or concomitant use of other treatments at baseline. The pts had at least 1 CV risk factor.	• The ADVANCE trial included DM pts both with and without HTN. In this RCT, pts were randomized to active treatment or placebo rather than to a different BP goal, so that it is impossible to determine whether the benefit was due to the treatment of HTN *per se*.
ACCORD Cushman WC, et al., 2010 (234) 20228401	Aim: To assess whether therapy targeting normal SBP (<120 mm Hg) reduces major CV events in DM-2 at high risk for CV events. Study type: RCT Size: 4,733 pts, 4.7 y follow-up	Inclusion criteria: DM-2 with HgbA1c ≥7.5%; ≥40 y with CVD or ≥55 y with anatomical evidence of atherosclerosis, albuminuria, LVH, or ≥2 additional risk factors for CVD. Exclusion criteria: BMI ≥45, serum creatinine >1.5, and other serious illness.	• Pts were randomly assigned to intensive therapy SBP <120 mm Hg or standard therapy SBP <140 mm Hg.	1° outcomes: Nonfatal MI, nonfatal stroke, or CV death. Results: Mean SBP in the intensive therapy group was 119.3 mm Hg and in the standard therapy group was 133.5 mm Hg. The annual 1° outcome 1.87% in the intensive therapy group and 2.09% in the standard therapy group HR: 0.88; 95% CI: 0.073–1.06; p=0.20. The annual rates of death from any cause were 1.28% and 1.19% in the 2 groups, respectively (HR: 0.59; 95% CI: 0.39–0.89; p=0.01). Serious adverse events attributed to antihypertensive treatment occurred in 3.3% of the intensive therapy group and 1.3% of the standard therapy group (p<0.001).	Limitations: This trial had an open label design. The rate of adverse events in the standard therapy group was less than expected. Pts younger than 40 y or older than 79 y were not included. Summary: In pts with DM-2 and high risk for CV events, targeting SBP of <120 as compared with <140 mm Hg did not reduce the rate of composite outcome of fatal and nonfatal major CV events and was associated with greater risk for adverse events.

Margolis KL et al., 2014 (235) 24595629	Aim: To compare effects of combinations of standard and intensive treatment of glycemia and BP in the ACCORD trial. Study type: RCT Size: 4,733 pts, 4.7 y follow-up	Inclusion criteria: Type 2 DM with HgbA1c ≥7.5%; ≥40 y with CVD or ≥55 y with anatomical evidence of atherosclerosis, albuminuria, LVH, or at least 2 additional risk factors for CVD. Exclusion criteria: BMI ≥45, serum creatinine >1.5, and other serious illness.	• Pts were randomly assigned to intensive therapy SBP<120 mm Hg or standard therapy SBP<140 mm Hg.	1° outcomes: Nonfatal MI, nonfatal stroke, or CV death. Results: In the BP trial, risk of the 1° outcome was lower in the groups intensively treated for glycemia HR: 0.67 (95% CI: 0.50, 0.91), BP HR: 0.74 (95% CI: 0.55, 1.00), or both HR: 0.71 (95% CI: 0.52, 0.96) compared with combined standard BP and glycemia treatment. For 2º outcomes, MI was significantly reduced by intensive glycemia treatment and stroke by intensive BP treatment; most other HRs were neutral or favored intensive treatment groups.	Limitations: 2° analysis; results analyzed across individual cells of a factorial design with shorter follow-up than originally intended reducing power to detect meaningful differences and interactions; results may not apply to younger, healthier diabetics. Conclusions: Either intensive BP or glycemia control reduced major CVD compared with combined standard treatment, but the combination was no better than the individual intensive interventions.
Soliman EZ et al., 2015 (236) 26459421	Aim: To compare effects of combinations of standard and intensive control of BP on the risk of LVH in the ACCORD trial. Study type: RCT Size: 4,331 pts, 4.7 y follow-up	Inclusion criteria: DM-2 with HgbA1c ≥7.5%; ≥40 y with CVD or ≥55 y with anatomical evidence of atherosclerosis, albuminuria, LVH, or at least 2 additional risk factors for CVD. Exclusion criteria: BMI ≥45, serum creatinine >1.5, and other serious illness.	• Pts were randomly assigned to intensive therapy SBP<120 mm Hg or standard therapy SBP<140 mm Hg.	1° outcomes: Nonfatal MI, nonfatal stroke, or CV death. Results: The outcome measures were electrocardiographic LVH defined by Cornell voltage (binary variable) and mean Cornell index (continuous variable). The baseline prevalence of LVH (5.3% vs. 5.4%; p=0.91) and the mean Cornell index (1,456 vs. 1,470 μV; p=0.45) were similar in the intensive (n=2,154) and standard (n=2,177) BP-lowering arms, respectively. However, after median follow-up of 4.4 y, intensive, compared with standard, BP lowering was associated with a 39% lower risk of LVH (OR: 0.61; 95% CI: 0.43–0.88; p=0.008) and a significantly lower adjusted mean Cornell index (1,352 vs. 1,447 μV; p<0.001). The lower risk of LVH associated with intensive BP lowering during follow-up was because of more regression of baseline LVH and lower rate of developing new LVH, compared with standard BP lowering. No interactions by age, sex, or race were observed.	Limitations: 2º analysis; open-label design; LVH defined by EKG and not by echo or cardiac MRI; results may not apply to younger, healthier diabetics. Conclusions: Targeting a SBP of <120 mm Hg when compared with <140 mm Hg in pts with HTN and DM produces a greater reduction in LVH

Xie X, et al., 2015 (21) 26559744	Aim: To assess the efficacy and safety of intensive BP lowering strategies. Study type: Systematic review and meta-analysis Size: 19 trials with 44,989 pts; 3.8 y of follow-up.	Inclusion criteria: RCTs with different BP targets or different BP changes between more vs. less intense therapy with at least 6 mo follow-up. Exclusion criteria: Trials that did not assess a different target or relevant outcome.	• 5 RCTs (6,960 pts) enrolled only pts with DM and 6 trials (2,809 pts) specifically recruited pts with CKD.	1° outcomes: Major CV events, defined as MI, stroke, HF or CV death, separately and combined; nonvascular and all-cause mortality; ESKD; and adverse events; new onset microalbuminuria/macroalbuminuria or change from micro- to macroalbuminuria and retinopathy in pts with DM. Results: Pts in the more intensive BP-lowering treatment group had mean BP 133/76 mm Hg compared with 140/81 mm Hg in the less intensive group. Intensive BP-lowering treatment achieved RR reductions for major CV events: 14% (95% CI: 4–22), MI: 13% (95% CI: 0–24), stroke: 22% (95% CI: 10–32), albuminuria: 10% (95% CI: 3–16), and retinopathy progression: 19% (95% CI: 0–34). However, more intensive treatment had no clear effects on HF: RR: 15% (95% CI: -11–34), CV death: 9% (-11–26), total mortality: 9% (95% CI: -3–19), or ESKD: 10% (95% CI: -6–23). The reduction in major CV events was consistent across pt groups, and additional BP lowering had a clear benefit even in pts with SBP <140 mm Hg. The absolute benefits were greatest in trials in which all enrolled pts had vascular disease, renal disease, or DM. Serious adverse events associated with BP lowering were only reported by 6 trials and had an event rate of 1%–2% per y in intensive BP lowering group pts, compared with 0.9% in the less intensive treatment group (RR: 1.35; 95% CI: 0.93–1.97). Severe hypotension was more frequent in the more intensive treatment regimen (RR: 2.68; 95% CI: 1.21–5.89; p=0·015), but the absolute excess was small (0.3% vs. 0.1% per pt-y for the duration of follow-up).	Study limitations: Only 6,960 pts with DM were included in the total study size of 44,989 pts. Conclusions: The absolute CV benefits were greatest in trials in which all enrolled pts had vascular disease, renal disease or DM. However, only 6,960 of the 44,989 pts had DM and no sub-analysis for DM was provided; however, the outcome benefits were qualitatively most striking for pts with DM, CKD and/or vascular disease.

ACCOMPLISH Weber MA, et al., 2010 (237) 20620720	Aim: To determine which combination therapy in pts with HTN and DM most effectively decreases CV events. Study type: RCT Size: 2,842 pts with DM from the ACCOMPLISH study of 6,946 pts; 30 mo follow-up	Inclusion criteria: HTN and DM with high risk for CV events. Exclusion criteria: BMI >45; serum Cr >1.5; other serious illness	• Pts were randomly assigned to benazepril plus amlodipine or benazepril plus hydrochlorothiazide. BPs were 145/79 at baseline.	1° outcomes: Composite of death from CV causes, nonfatal MI, nonfatal stroke, hospitalization for angina, resuscitation after sudden cardiac arrest, and coronary revascularization. Results: The mean achieved BP was 131.5/72.6 and 132.7/73.7 in the B + A and B + H groups, respectively, during the 30 mo of follow-up. There were 8.8% and 11% 1° events, respectively (HR: 0.79; 95% CI: 0.684–0.92; p=0.003). In the pts with DM there were clear coronary benefits with B + A, including both acute clinical events (p=0.013 and revascularizations (p=0.024). There were no unexpected adverse events.	Summary: In pts with DM and HTN, combining an ACEI with a CCB, compared with hydrochlorothiazide, was superior in reducing CV events.
ASCOT Ostergren J, et al., 2008 (238) 18854748	Aim: To compare the effects of an amlodipine-based regimen vs. and atenolol-based regimen on CV outcomes in pts with DM Study type: RCT (BP lowering arm of ASCOT) Size: 5,137 pts with DM, minimum 4 y follow-up	Inclusion criteria: Pts 40–65 y with HTN (>160/100 mm Hg) or treated HTN and DM plus 2 additional CV risk factors: PAD, previous stroke or TIA, male sex, ≥55 y, microalbuminuria, smoking, total cholesterol to HDL ratio ≥6, or family history of CHD.	• Pts were randomly assigned to an amlodipine-based regimen with addition of perindopril as required or an atenolol-based regimen with addition of a thiazide as required and therapy titrated as required to achieve target BP of 130/80 mm Hg.	1° outcomes: Fatal CHD and nonfatal MI. Results: BPs were 136/75 (amlodipine and 137/76 (atenolol) at the end of study. There was a 3/1.9 mm Hg lower BP in pts on amlodipine. The amlodipine-based regimen reduced CV events and procedures compared to the atenolol-based regimen (HR 0.86; 0.76-0.98; p=0.026). Fatal and nonfatal strokes were reduced by 25% (p=0.017), PAD by 48% (p=0.004) and noncoronary vascularization procedures by 57% (p=0.001).	Summary: In the large DM subgroup of the BP-lowering arm of ASCOT, the benefits of an amlodipine-based treatment compared with an atenolol-based treatment on the incidence of total CV events and procedures was significant.
SHEP Kostis JB, et al., 2005 (239) 15619390	Aim: To assess the long-term mortality rate of pts with DM pts in the SHEP trial randomly assigned to stepped care with chlorthalidone or placebo.	Inclusion criteria: Isolated systolic HTN (SBP 160–219 mm Hg) with DBP <90 mm Hg. Exclusion criteria: Pts with insulin–dependent DM and those who	• Pts were randomly assigned to chlorthalidone or placebo. If BP remained above goal, atenolol or placebo was added.	1° outcomes: CV mortality rate Results: BP was 11.1/3.4 mm Hg lower in the active treatment group at the end of the study. Diuretic treatment in pts with DM was strongly associated with long-term CV mortality rate (AHR: 0.668 (95% CI: 0.526,	Summary: Chlorthalidone-based treatment improved long-term outcomes in pts with DM.

	Study type: RCT Size: 4,732 pts; follow-up 14.3 y	required diuretic therapy.		0.848) and total mortality rate: 0.805 (95% CI: 0.680, 0.952).	
ROADMAP Menne J, et al., 2012 (240) 22418908	Aim: To assess whether olmesartan compared to placebo delays the onset of albuminuria in pts with DM and HTN. Study type: RCT Size: 4,020 pts; follow-up 3.2 y	Inclusion criteria: Pts with HTN defined as BP ≥130/80 mm Hg and at least 1 CV risk factor.	• Pts were randomly assigned to olmesartan or placebo. Additional antihypertensive therapy except for ACEs and ARBs to lower BP.	1° outcome: Time to onset of microalbuminuria. Results: Average BP was 126.3/74.7 and 129.5/76.6, respectively (significant not stated). Olmesartan delayed the onset of microalbuminuria by 25% (0.75; 95% CI: 0.61–0.92; p=0.007). CV events were comparable in the 2 groups.	Summary: Pts with better BP reduction are less likely to develop microalbuminuria. Treatment with an ARB delayed the onset of microalbuminuria independently of baseline BP and degree of BP reduction.
ABCD Estacio RO, et al., 1998 (241) 9486993	Aim: To compare the effects of "intensive" compared with "moderate" BP treatment on 24-h creatinine clearance (GFR) in pts with DM and HTN. Study type: RCT – open label Size: 472 pts; follow-up 5 y	Inclusion criteria: Pts with HTN defined as DBP ≥90 mm Hg and DM-2	• Pts were randomly assigned to "intensive" treatment (DBP<75 mm Hg and "moderate" treatment (DBP 80–89 mm Hg) with a combination of nisoldipine and enalapril as the initial antihypertensive medication.	1° outcome: Change in 24-h creatinine clearance. Results: • The mean BP achieved was 132/78 in the intensive group and 138/86 in the moderate control group. During the 5-y follow-up period, there was no difference in GFR between the groups. After the first y of antihypertensive treatment, GFR stabilized in both the intensive and moderate groups with normal albumin excretion or microalbuminuria. In contrast, pts with overt albuminuria demonstrated steady decline in GFR whether on intensive or moderate therapy. Neither was there a significant difference in the progression from normal to micro- or micro-to overt albuminuria. • Intensive therapy demonstrated a lower overall incidence of deaths, 5.5% vs. 10.7%; p=0.037 (2° endpoint).	Limitations: Open-label design; the definition of DM was 2 fasting blood glucose measurements >140 mg/dL as opposed to >126 today; serious side effects were not reported. Risk of bias due to a greater proportion of pts with established CVD at baseline assigned to the standard BP target. Summary: BP control of 138/86 or 132/78 with either nisoldipine or enalapril as the initial antihypertensive agent appeared to stabilize renal function in HTN pts with type 2 DM without overt albuminuria over a 5-y period. For the ABCD trials, only ABDC (H) included strictly pts with HTN and DM. The quality of evidence is low due to imprecision and risk of bias.
Hypertension Optimal Treatment (HOT trial)	Aim: To assess the optimum target DBP	Inclusion criteria: Pts with HTN defined as	• Pts were randomly assigned to 1 of 3 DBP target	1° outcomes: Major CV events, MI, stroke, CV mortality and total mortality.	Limitations: Open-label design; the definition of DM-2 fasting blood glucose measurements >140 mg/dL

Hansson L, et al., 1998 (242) 9635947	in the treatment of HTN. Study type: RCT Size: 1,501 pts in the DM subgroup; follow-up 3.8 y	DBP 100–115 mm Hg and DM.	groups: ≤90, ≤85, or ≤80 mm Hg.	Results: In the group randomized to ≤80 mm Hg, the risk of major CV events was halved in comparison to the target ≤90. CV mortality was lower in the ≤80 group compared to the other groups.	as opposed to >126 today; serious side effects were not reported; potential bias due to subgroup analysis. Summary: In pts with DM and HTN, intensive lowering of BP was associated with a low rate of CV events. The quality of evidence is low to very low due to imprecision and risk of bias.
UKPDS 1998 (243) 9732337	Aim: To determine whether tight control of BP prevents macrovascular and microvascular complications in pts with DM-2. Study type: RCT Size: 1,148 hypertensive pts with type 2 DM Follow-up: 8.4 y	Inclusion criteria: Fasting plasma glucose concentration >6 mmol/l in 2 mornings. Exclusion criteria: Ketonuria >3 mmol/l; history of MI in the previous y; current angina or HF; >1 major vascular episode; serum creatinine concentration >175 µmol/l; retinopathy requiring laser treatment; malignant HTN; an uncorrected endocrine abnormality; an occupation that would preclude insulin treatment; a severe concurrent illness; inadequate understanding or unwillingness to enter the study.	• Pts were randomized to tight BP control (target BP<150/85 mm Hg) or less tight BP control (target <180/105 mm Hg),	1° outcomes: 1) First clinical endpoint related to DM (sudden death, death from hyperglycemia or hypoglycemia, fatal or nonfatal MI, angina, HF, stroke, renal failure, amputation, vitreous hemorrhage, retinal photocoagulation, blindness in 1 eye or cataract extraction). 2) Death related to DM. 3) Death from all causes. Results: BP in the tight BP control group was 144/82 compared with the group assigned less tight control (154/87), p<0.0001. Reductions in risk in the group assigned tight BP control compared with those of the less tight control group were 24% (95% CI: 8%–38%; p=0.0046) in DM related endpoints; 32% in deaths related to DM (95% CI: 6%–51%; p<0.019; 44% in strokes (95% CI: 11%–65%; p<0.013; and 37% (95% CI: 11%–36%; p<0.0092 in microvascular endpoints, predominantly due to risk of retinal photocoagulation.	Limitations: DBP targets were high (85 mm Hg in the tight control group and 105 mm Hg in the less tight control group) and similar to the cutoffs for the no treatment groups in trials comparing treatment with no treatment. UKPDS evaluated lowering both SBP and DBP so it is impossible to separate the outcomes effects of DBP. Therefore, the evidence is of low quality. Summary: Tight BP control in pts with HTN and DM-2 achieved a clinically important reduction in the risk of death related to DM, complications related to DM, progression of DM retinopathy and deterioration of visual acuity, but the quality of evidence is low.
Arguedas JA, et al., 2013 (244) 24170669	Aim: To determine if "lower" BP targets (any target <130/85	Inclusion criteria: RCTs in which individuals were	• Pts with HTN and DM were randomly assigned to the	1° outcomes: Total mortality, total serious adverse events, MI, stroke, CHF, and ESRD.	Conclusions: Evidence from RCTs does not support BP targets lower

	mm Hg) are associated with reduction in mortality and morbidity compared to "standard" BP targets (<140–160/90–100 mm Hg) in pts with DM. Study type: Meta-analysis of RCTs. Size: 5 RCTs recruiting a total of 7,314 ps. Mean follow-up: 4.5 y	randomized to a "lower" compared with a "standard" BP target. Exclusion criteria: Studies that did not meet the inclusion criteria. Excluded studies were UKPDS 1998, HTN in Diabetes Study IV 1996, SANDS 2008, Lewis 1999 and the Steno-2 study.	intensive or standard BP control group.	Results: Only 1 trial (ACCORD) compared outcomes associated with 'lower' (<120 mm Hg) or 'standard' (<140 mm Hg) SBP targets in 4734 pts. Despite achieving a significantly lower BP (119.3/64.4 mm Hg vs. 133.5/70.5 mm Hg, p<0.0001), and using more antihypertensive medications, the only significant benefit in the group assigned to 'lower' SBP was a reduction in the incidence of stroke: RR: 0.58; (95% CI: 0.39–0.88; p=0.009), absolute risk reduction 1.1%. The effect of SBP targets on mortality was compatible with both a reduction and increase in risk: RR: 1.05 (95% CI: 0.84, 1.30), low quality evidence. Trying to achieve the 'lower' SBP target was associated with a significant increase in the number of other serious adverse events: RR: 2.58, (95% CI: 1.70–3.91; p<0.00001, absolute risk increase 2.0%. 4 trials (ABCD-H, ABCD-N, ABCD-2V, and a subgroup of HTN Optimal Treatment) specifically compared clinical outcomes associated with 'lower' vs. 'standard' targets for DBP in pts with DM. The total number of pts included in the DBP target analysis was 2580. Pts assigned to 'lower' DBP had a significantly lower achieved BP: 128/76 mm Hg vs. 135/83 mm Hg; p<0.0001. There was a trend towards reduction in total mortality in the group assigned to the 'lower' DBP target: RR: 0.73 (95% CI: 0.53–1.01), mainly due to a trend to lower non-CV mortality. There was no difference in stroke: RR: 0.67, (95% CI: 0.42–1.05), in MI: RR: 0.95 (95% CI: 0.64–1.40) or in CHF: RR: 1.06 (95% CI: 0.58–1.92), low-quality evidence. End-stage renal failure and total serious adverse events were not reported in any of the trials. A sensitivity analysis of trials comparing DBP targets <80 mm Hg (as suggested in clinical guidelines)	than standard targets in pts with HTN and DM.

				vs. <90 mm Hg showed similar results. There was a high risk of selection bias for every outcome analyzed in favor of the 'lower' target in the trials included for the analysis of DBP targets.	
Palmer SC, et al., 2015 (245) 26009228	Aim: To investigate the benefits and harms of BP-lowering drugs in adults with DM Study type: Network meta-analysis of RCTs. Size: 157 studies in 43,256 pts mostly with DM and CKD. Mean follow-up: 4.5 y	Inclusion criteria: Pts ≥18 y with DM and CKD and were treated in clinical trials that compared any orally administered antihypertensive agent alone or in combination with a 2nd antihypertensive agent or combination, placebo, or control. Exclusion criteria: Pts who underwent kidney transplantation or dialysis.	N/A	1° outcomes: All-cause mortality and ESKD (need for dialysis or transplantation). Results: No drug regimen was more effective than placebo for reducing all-cause mortality. However, compared with placebo, ESRD was significantly less likely after dual treatment with an ARB and an ACEI: OR: 0.62 (95% CI: 0.43–0.90) and after ARB monotherapy: OR: 0.77 (95% CI: 0.65–0.92). No regimen significantly increased hyperkalemia or acute kidney injury, although combined ACEI and ARB treatment had the lowest rank among all interventions because of borderline increases in estimated risks of these harms; OR: 2.69 (95% CI: 0.97–7.47) for hyperkalemia; OR: 2.69 (95% CI: 0.98–7.38) for acute kidney injury.	Limitations: Effects of BP treatment on CV events and related mortality were uncertain. Data for the outcome of ESKD were restricted largely to pts with macroalbuminuria. Acute kidney injury was poorly defined with low quality of evidence. Conclusions: No BP-lowering strategy prolonged survival in adults with DM and CKD. ACEIs and ARBs, alone or in combination, were the most effective strategies against ESKD. Any benefits of combined ACEI and ARB treatment need to be balanced against potential harms of hyperkalemia and acute kidney injury.
Turnbull F, et al., 2005 (246) 15983291	Aim: To determine the benefits associated with different treatment regimens in pts with and without DM and whether there are important differences in the effects of different BP-lowering regimens in these 2 pt groups. Study type: Meta-analysis of RCTs.	Inclusion criteria: Randomization of pts between a BP-lowering agent and a control (placebo or less intensive BP-lowering regimen) or randomization of pts between regimens based on different classes of BP-lowering drugs. Exclusion criteria: Studies not meeting the above criteria.	N/A	1° outcomes: Nonfatal stroke or death from cerebrovascular disease; nonfatal MI or death from CAD; HF causing death or requiring hospitalization; total CV events; total CV deaths; and total mortality. Results: Total major CV events were reduced to a comparable extent in individuals with and without DM by regimens based on ACEIs, calcium antagonists, ARBs and diuretics/ BBs ($p<0.19$ for all). There was limited evidence that lower BP goals produced larger reductions in total major CV events in pts with vs. without DM ($p<0.03$).	Limitations: No analysis of renal outcomes, risk of new DM or progression of existing DM; combined comparison of persons taking diuretics and BB s; some studies selected pts on the basis of the presence or absence of DM. Summary: Effects of BP-lowering agents on major CV events were broadly comparable for pts with and without DM.

	Size: 27 RCTs including 158,709 pts (33,395 with DM and 125,314 without DM). Follow-up: Minimum 1,000 pt-y				
ALLHAT Whelton PK, et al., 2005 (247) 15983290	Aim: To determine the optimal first step antihypertensive drug therapy in DM-2 or impaired fasting blood glucose levels and specifically whether treatment with a CCB or ACEI decreases clinical complications compared to treatment with a thiazide type diuretic. Study type: RCT Size: 31,512 pts stratified into type 2 DM (13,101), IFG (1,399) and normoglycemia (17,012)	Inclusion criteria: Pts ≥55 y with HTN and at least 1 other risk factor for CHD. Exclusion criteria: No history of DM or no fasting glucose measurement or nonfasting glucose level ≥110 mg/dL.	• Pts were randomly assigned to double-blind first-step treatment with chlorthalidone 12.525 mg/d, amlodipine 2.5–10 mg/d or Lisinopril 10–40 mg/d.	1° outcomes: Fatal CHD and nonfatal MI Results: There was no significant difference in RR (RR) for the 1° outcome in DM or NG pts assigned to amlodipine or lisinopril vs. chlorthalidone or in IFG pts assigned to lisinopril vs. chlorthalidone RR: 1.73 (95% CI: 1.10, 2.72). A significantly higher RR was noted for the 1° outcome in IFG pts assigned to amlodipine vs. chlorthalidone. Stroke was more common in NG pts assigned to lisinopril vs. chlorthalidone RR: 1.31 (95% CI: 1.10, 1.57). HF was more common in DM and NG pts assigned to amlodipine RR: 1.39 (95% CI: 1.22, 1.59) and 1.30 (95% CI: 1.12, 1.51), respectively or lisinopril: 1.15 (95% CI: 1.00–1.32) and 1.19 (95% CI: 1.02, 1.39), respectively vs. chlorthalidone.	Limitations: Microalbuminuria was not measured. Summary: Our results provide no evidence of superiority for treatment with CCBs or ACEIs compared with a thiazide-type diuretic during first-step antihypertensive therapy in DM, IFG, or NG.

Data Supplement 47. Nonrandomized Trials, Observational Studies, and/or Registries in DM (Section 9.6)

Study Acronym; Author; Year Published	Study Type/Design; Study Size (N)	Patient Population	Primary Endpoint and Results (include P value; OR or RR; & 95% CI)	Summary/Conclusion Comment(s)

ADVANCE Hata J, et al., 2013 (248) 23926207	Aim: To assess the effects of visit-to-visit SBP variability and maximum SBP on the risks of macrovascular or microvascular outcomes by using data from the ADVANCE trial. Study type: Observational analysis Size: 8,811 pts	Inclusion criteria: Pts had not experienced major macro- or microvascular events during first 2 y of the ADVANCE trial Exclusion criteria: None	1° endpoint: Composite of CV death, nonfatal MI, nonfatal stroke, new or worsening nephropathy, or retinopathy. Results: Major macro- and micro-vascular events were associated with SBP variability even after adjustment for mean SBP and other confounding factors. For the highest 10% variability, HR: 1.54 (95% CI: 0.99, 2.39) for macrovascular events; for microvascular events, HR: 1.84 (95% CI: 1.19, 2.84).	Summary: Visit-to-visit SBP variability and maximum SBP are independent risk factors for macro- and micro-vascular events.
ADVANCE-ON Zoungas S, et al., 2014 (249) 25234206	Aim: To determine whether the mortality benefit that had been observed among pts originally assigned to BP-lowering therapy were still evident at the end of 6-y follow-up Study type: Observational analysis Size: 8,494 pts	Inclusion criteria: Pts with DM who participated in post-trial follow-up for 6 y Exclusion criteria: See above	1° endpoint: Death from any cause and major macrovascular complications (a composite of nonfatal MI, nonfatal stroke, or death from any CV cause. Results: The reductions in the risk of death from any cause and of death from CV causes that had been observed in the group receiving active BP-lowering treatment during the ADVANCE trial were attenuated but significant at the end of the post-trial follow-up. HRs were 0.95 (95% CI: 0.84–0.99; p=0.03) and 0.88 (95% CI: 0.77–0.99; p=0.04), respectively.	Summary: Benefits were attenuated but still present at the end of 6 y.
ROADMAP Mene J, et al., 2014 (250) 24772521	Aim: To determine whether the ROADMAP olmesartan medoxomil treatment resulted in a potential long-term micro- and macro-vascular benefit. Study type: Observational analysis Size: 1,758 pts; 3.3 y follow-up	Inclusion criteria: See above Exclusion criteria: See above	1° endpoint: See above Results: The original ROADMAP study showed a 23% reduction in microalbuminuria despite good and comparable BP control in both groups. Pts who developed microalbuminuria had a higher incidence of cardio- and cerebrovascular events: OR: 1.77 (95% CI: 1.03–3.03; p=0.039) compared to those in whom this was not the case. DM retinopathy and HF requiring hospitalization also were reduced.	Summary: renal artery stenosis blockade might cause a sustained reduction in micro- and macro-vascular events.
Edmin C, et al., 2015 (251)	Aim: Determine associations between BP-lowering	Inclusion criteria: All RCTs of BP-lowering treatment in	• BP-lowering drug vs. placebo: 26 RCTs	Limitations: Reliability of this meta-analysis is limited by the scarcity of large trials with

25668264	treatment and presence of vascular disease in DM-2 Study type: Large meta-analysis of 40 high quality RCTs (1/1966–10/2014) judged low risk of bias Size: 100,354 pts with DM; all trials >1,000 pt-y of follow-up BP-lowering drug vs. placebo: 26 RCTs • More intensive vs. less intensive BP lowering: 7 RCTs • BP-lowering vs. another drug: 17 RCTs	which entire trial population had DM-2 or in which the results of a DM subgroup were obtained. Studies were included regardless of the presence or absence of defined HTN. Exclusion criteria: Trials conducted predominantly in pts with type 1 DM were excluded.	• More intensive vs. less intensive BP lowering: 7 RCTs • BP-lowering vs. another drug: 17 RCTs Results: Baseline BP: A 10-mm Hg SBP reduction was associated with a significantly lower risk of all-cause mortality RR: 0.87 (95% CI: 0.78–0.96), CVD events RR: 0.89 (95% CI: 0.80–0.98), and stroke events RR: 0.73 (95% CI: 0.64–0.83). The associations for HF and renal failure were not significant. For microvascular events, a 10-mm reduction in SBP was associated with a lower risk of retinopathy RR: 0.87 (95% CI: 0.76–0.99) and albuminuria RR: 0.83 (95% CI: 0.79–0.87). Stratified by initial SBP: Trials stratified by SBP >140 to <140 mm Hg showed significant interactions for all-cause mortality RR: 0.73 (95% CI: 0.64–0.84) vs. 1.07 (95% CI: 0.92–1.26), CVD RR: 0.74 (95% CI: 0.65–0.85) vs. RR: 0.96 (95% CI: 0.88–1.05), CHD RR: 0.73 (95% CI: 0.61–0.87) vs. RR: 0.97 (95% CI: 0.86–1.10), HF RR: 0.75 (95% CI: 0.59–0.94) vs. RR: 0.97 (95% CI: 0.79–1.19) and albuminuria RR: 0.71 (95% CI: 0.63–0.79) vs. RR: 0.86 (95% CI: 0.81–0.99). Stratified by achieved SBP: Trials stratified by SBP achieved in the treatment group ≥130 or <130 mm Hg and the associations of a 10-mm Hg SBP reduction compared between the strata showed significant interactions for all-cause mortality RR: 0.75 (95% CI: 0.65–0.86) vs. RR: 1.06 (95% CI: 0.90–1.265), CVD RR: 0.74 (95% CI: 0.64–0.85) vs. RR: 0.96 (95% CI: 0.88–1.05), CHD RR: 0.70 (95% CI: 0.58–0.83) vs. RR: 0.97 (95% CI: 0.85–1.10), HF	achieved SBP levels in the 120–130 mm Hg range. The relatively short follow-up of included trails may have prevented associations of BP-lowering treatment with vascular outcomes from being observed, particularly for outcomes such as HF and renal failure, which are often a consequence of MI or albuminuria, respectively. Summary: • This large meta-analysis of 40 RCTs provides evidence that BP lowering is associated with lower risks of outcomes in pts with initial mean SBP ≥140 mm Hg compared with those <140 mm Hg with the exception of stroke, albuminuria and retinopathy. When trials were stratified by achieved SBP treatment was associated with lower risks only in the <130 mm Hg stratum for stroke and albuminuria. • This meta-analysis shows that although BP lowering was not associated with a lower risk of CVD or CHD events at a baseline SBP <140 mm Hg, it does observe lower risks of stroke, retinopathy and progression of albuminuria. • This study provides evidence that for individuals at high risk for these outcomes (history of cerebrovascular disease or mild nonproliferative retinopathy), commencement of therapy below an initial SBP of 140 mm Hg and treatment to SBP <130 may be indicated.

			RR: 0.75 (95% CI: 0.59–0.95) vs. RR: 1.00 (95% CI: 0.81–1.23) and albuminuria RR: 0.71 (95% CI: 0.64–0.79) vs. RR: 0.86 (95% CI: 0.81–0.90) with higher risk in the ≥130 mm Hg group. Stratified by class of medications: Few differences were observed in the association between BP-lowering treatment and outcomes for regimens based on different classes of medications, except HF, in which diuretics were associated with lower RR: 0.83 (95% CI: 0.72–0.95) than all other classes. This was driven largely by the results of ALLHAT.	
Cheng J, et al., 2014 (252) 24687000	Aim: To separately evaluate the effects of ACEIs and ARBs on all-cause mortality, CV deaths, and major CV events in pts with DM Study type: Meta-analysis of 35 high quality RCTs (1966–2012) Size: 56,444 pts with DM; all trials had follow-up of at least 12 mo	Inclusion criteria: RCTs including post hoc analyses and subgroups for DM with median follow-up of at least 12 mo. Comparisons with placebo, no treatment or other antihypertensive drugs, including ACEIs and ARBs. Exclusion criteria: Cross-over trials	• ACEIs significantly reduced the risk of all-cause mortality by 13% (RR: 0.87; 95% CI: 0.78–0.98), CV deaths by 17% (RR: 0.83; 95% CI: 0.70–0.99), and major CV events by 14% (RR: 0.86; 95% CI: 0.77–0.95), including MI by 21% (RR: 0.79; 95% CI: 0.65–0.95) and HF by 19% (RR: 0.81; 95% CI: 0.71–0.93). Treatment with ARBs did not significantly affect all-cause mortality (RR: 0.94 (95% CI: 0.82–1.08), CV death rate (RR: 1.21 (95% CI: 0.81–1.80) and major CV events (RR: 0.94; 95% CI: 0.85–1.01) with the exception of HF (RR: 0.70; 95% CI: 0.59–0.82).	Summary: • RCTs comparing ACEs vs. active drugs/placebo/no treatment: 26 RCTs (12 active drugs, 11 placebo) • RCTs comparing ARBs vs. active drugs/placebo/no treatment: 13 RCTs (3 active drugs, 10 placebo) • This meta-analysis provides evidence that ACEIs reduce all-cause mortality, CV mortality, and major CV events in pts with DM, whereas ARBs had no benefits on these outcomes.
Arguedas JA, et al., 2013 (244) 24170669	Aim: To determine if "lower" BP targets (any target <130/85 mm Hg) are associated with reduction in mortality and morbidity compared to "standard" BP targets (<140–160/90–100 mm Hg) in pts with DM. Study type: Meta-analysis of RCTs.	Inclusion criteria: RCTs in which individuals were randomized to a "lower" compared with a "standard" BP target. Exclusion criteria: Studies that did not meet the inclusion criteria. Excluded studies were UKPDS 1998, HTN in Diabetes Study IV	1° outcomes: Total mortality, total serious adverse events, MI, stroke, CHF, and ESRD. Results: Only 1 trial (ACCORD) compared outcomes associated with 'lower' (<120 mm Hg) or 'standard' (<140 mm Hg) SBP targets in 4734 pts. Despite achieving a significantly lower BP (119.3/64.4 mm Hg vs. 133.5/70.5 mm Hg, p<0.0001), and using more antihypertensive medications, the only significant benefit in the group assigned to 'lower' SBP was a reduction in the incidence	Conclusions: Evidence from RCTs does not support BP targets lower than standard targets in pts with HTN and DM.

	Size: 5 RCTs recruiting a total of 7,314 ps. Mean follow-up: 4.5 y	1996, SANDS 2008, Lewis 1999 and the Steno-2 study.	of stroke: RR: 0.58 (95% CI: 0.39–0.88; p=0.009), absolute risk reduction 1.1%. The effect of SBP targets on mortality was compatible with both a reduction and increase in risk: RR: 1.05 (95% CI: 0.84–1.30), low-quality evidence. Trying to achieve the 'lower' SBP target was associated with a significant increase in the number of other serious adverse events: RR: 2.58 (95% CI: 1.70–3.91; p<0.00001), absolute risk increase 2.0%. 4 trials (ABCD-H, ABCD-N, ABCD-2V, and a subgroup of HOT) specifically compared clinical outcomes associated with 'lower' vs. 'standard' targets for DBP in pts with DM. The total number of pts included in the DBP target analysis was 2580. Pts assigned to 'lower' DBP had a significantly lower achieved BP: 128/76 mm Hg vs. 135/83 mm Hg, p<0.0001. There was a trend towards reduction in total mortality in the group assigned to the 'lower' DBP target: RR: 0.73 (95% CI: 0.53–1.01), mainly due to a trend to lower non- CV mortality. There was no difference in stroke: RR: 0.67 (95% CI: 0.42–1.05), in MI: RR: 0.95 (95% CI: 0.64–1.40) or in CHF: RR: 1.06 (95% CI: 0.58–1.92), low quality evidence. End-stage renal failure and total serious adverse events were not reported in any of the trials. A sensitivity analysis of trials comparing DBP targets <80 mm Hg (as suggested in clinical guidelines) vs. <90 mm Hg showed similar results. There was a high risk of selection bias for every outcome analyzed in favor of the 'lower' target in the trials included for the analysis of DBP targets.	
Cushman WC, et al., 2010 (234) 20228401	Aim: To assess whether therapy targeting normal SBP (<120 mm Hg) reduces major	Inclusion criteria: Type 2 DM with HgbA1c ≥7.5%; ≥40 y with CVD or ≥55 y with anatomical evidence of	Pts were randomly assigned to intensive therapy SBP<120 mm Hg or standard therapy SBP<140 mm Hg.	Limitations: This trial had an open label design. The rate of adverse events in the standard therapy group was less than

	CV events in type 2 DM at high risk for CV events. Study type: RCT Size: 4,733 pts, 4.7 y follow-up	atherosclerosis, albuminuria, LVH, or at least 2 additional risk factors for CVD. Exclusion criteria: BMI ≥45, serum creatinine >1.5, and other serious illness.	1° outcomes: Nonfatal MI, nonfatal stroke, or CV death. Results: Mean SBP in the intensive therapy group was 119.3 mm Hg and in the standard therapy group was 133.5 mm Hg. The annual 1° outcome 1.87% in the intensive therapy group and 2.09% in the standard therapy group HR: 0.88 (95% CI: 0.073–1.06; p=0.20). The annual rates of death from any cause were 1.28% and 1.19% in the 2 groups, respectively (HR: 0.59; 95% CI: 0.39–0.89; p=0.01). Serious adverse events attributed to antihypertensive treatment occurred in 3.3% of the intensive therapy group and 1.3% of the standard therapy group (p<0.001).	expected. Pts younger than 40 y or older than 79 y were not included. Summary: In pts with type 2 DM and high risk for CV events, targeting SBP of <120 as compared with <140 mm Hg did not reduce the rate of composite outcome of fatal and nonfatal major CV events and was associated with greater risk for adverse events.
Hartley L, et al., 2014 (253) 25436436	Aim: To determine the effectiveness of transcendental meditation for the 1° prevention of CVD Study type: Literature review of RCTs Size: 4 trials with a total of 430 pts	Inclusion criteria: ≥3 mo duration, healthy adults or adults at high risk of CVD, comparison of no or minimal intervention. Exclusion criteria: Multi-factorial interviews	1° outcomes: Clinical CVD events and major CVD risk factors Results: No conclusions of the effectiveness of transcendental meditation for the 1° prevention of CVD	Limitations: Limited evidence Summary: No conclusions as to the effectiveness of transcendental meditation for the 1° prevention of CVD. There was considerable heterogeneity between trials and the included studies were small, short-term, and at overall serious risk of bias.
Schmieder RE, et al., 2007 (254) 17416265	Study type: Topic review	Inclusion criteria: N/A Exclusion criteria: N/A	1° outcomes: N/A Results: N/A	Limitations: N/A Summary: N/A
Lv, et al., 2013 (127) 23798459	Aim: To assess the renal and CV effects of intensive BP lowering in people with CKD Study type: Systematic review Size: 9,287 pts with CKD and 1,264 kidney failure events	Inclusion criteria: • Randomized trials of pts with CKD assigned to different target BP that reported kidney failure and CV events. • 11 trials on 9,287 pts with CKD and 1,264 kidney failure events (doubling of serum creatinine, 50% decline in GFR or ESKD) • Included AASK, REIN-2,	Results: Compared with standard regimens, more intensive BP lowering reduced risk of composite endpoint HR: 0.82 (95% CI: 0.68–0.98) and ESKD HR: 0.79 (95% CI: 0.67–0.93). Effect was modified by proteinuria (p=0.006) and markers of trial quality. Intensive BP lowering reduced the risk of kidney failure HR: 0.73 (95% CI: 0.62–0.86) but not in pts without proteinuria at baseline HR: 1.12 (95% CI: 0.67–1.87). No clear effect on CV events or death.	Limitations: All trials used open label, in 2 pts were blinded, substantial variability in design quality. There was substantial variability in BP targets by MAP, SBP and DBP or only DBP. Most trials did not include pts with diabetic kidney disease Summary: • Renal outcomes: 7 trials (N=5308) recorded a total of 1,264 kidney failure events. A -7.7 mm Hg difference in SBP and a -4.9 mm Hg

		MDRD, Wuhl (children), Toto, Schrier plus 5 trials with CKD subgroups, also included the late nonrandomized follow-up studies for AASK and MDRD • BP targets varied substantially between trials. 2 trials targeted mean BP <92 mm Hg for the intensive treatment arm, and 107 mm Hg in the standard treatment arm. 1 trial aimed for BP <130/80 mm Hg vs. a DBP of 90 mm Hg, 1 study targeted <120/80 mm Hg vs. 135–140/85–90 mm Hg, and 4 studies had DBP <75–80 mm Hg vs. from 80–90 mm Hg. A trial involving pediatric pts targeted a 24-h mean BP <the 50th percentile, compared with the 50th to 95th percentiles in the control group. 2 trials had more liberal targets for intensive treatment (<140–150 mm Hg SBP, 85 mm Hg DBP)		difference in DBP seen between treatment arms. Overall, a more intensive regimen reduced risk of composite kidney failure events by 17% (HR: 0.82; 95% CI: 0.68, 0.98), reduced the risk of ESKD alone by 18% (pooled HR for composite outcomes: 0.79; 95% CI: 0.67, 0.93). • Intensive BP lowering had no effect on kidney failure in pts who did not have proteinuria (3 trials involving 1,218 pts (HR: 1.12; 95% CI: 0.67–1.87), but it did reduce the risk of progressive kidney failure by 27% (5 trials involving 1,703 pts (HR: 0.73; 95% CI: 0.62–0.86) in pts who did have proteinuria at baseline. • CV outcomes: major CV events reported in 5 trials (472 CV events in 5,308 pts with CKD). Intensive BP lowering did not reduce risk of CV events in pts with CKD, but the CIs remained wide (RR: 1.09 (95% CI: 0.83, 1.42). 6 trials reported stroke outcomes (197 events in 5,411 pts), 5 trials reported MI (138 events in 4,317 pts), and 5 trials reported HF (118 events in 5,308 pts). They saw no clear effect of intensive treatment on any of these vascular outcomes. • Death: 10 trials involving 6,788 pts reported 846 deaths. There was no clear effect of intensive BP lowering on risk of all-cause death (RR: 0.94 (95% CI: 0.84, 1.05) or CV death (RR: 1.20 (95% CI: 0.82, 1.75).

Data Supplement 48. Atrial Fibrillation (Section 9.8)

Study Acronym; Author; Year Published	Aim of Study	Study Type	Study Size (N)	Patient Population	Study Intervention (# patients) / Study Comparator (# patients)	Endpoints	P Value; OR, HR, or RR; & 95% CI	Study Limitations & Adverse Events
Jibrini, et al., 2008 (255) 18223352	Aim: To assess the effectiveness of ACEIs and ARBs in the prevention of AF, and to identify those clinical entities in which RAAS inhibition would most likely benefit the pts.	Study type: Meta-analysis	• 11 published studies; 55, 989 pts (26,973 pts in intervention, 29,016pts in comparator)	Inclusion criteria: Studies of RAAS blockade in CHF, MI, electrical cardioversion, and HTN) with incidence of AF noted during follow-up. Exclusion criteria: Studies without the measurement of AF or use of RAAS blockade.	Intervention: RAAS blockade Intervention: Placebo, amlodipine, BB or thiazide diuretic	1° endpoint (efficacy) and results: AF occurrence or reoccurrence.	Treatment with RAAS blockers reduced RR of AF in pts with HTN by 23% (p<0.001), by 11% in pts after MI (p<0.05), by 51% after electrical cardioversion (p<0.001), by 32% in pts with HF (p<0.001) and by 19% overall (p<0.001).	• Not a comprehensive analysis of all antihypertensive. Adverse events not catalogued in meta-analysis.
Zhao et al., 2015 (256) 26668582	Aim: To investigate the effectiveness and safety of ACEIs or angiotensin II receptor blockers (ARBs) on preventing AF in essential hypertensive pts. Study type: Meta-analysis	Intervention: RAAS blockade, n=20,491 Comparator: BB/calcium antagonist, n=22,401	Inclusion criteria: RCTs on the effects of ACEI/ ARBs on essential hypertensive pts. Exclusion criteria: Non-RCTs, subjects who were not treated with ACEI or ARB, and trials not	1° endpoint: AF occurrence or reoccurrence.	• ACEI/ARBs reduced the incidence of AF recurrence compared to calcium antagonists (RR: 0.48; 95% CI: 0.40–0.58; p<0.00001) or b-blockers (RR: 0.39; 95% CI: 0.20–0.74; p=0.005). ACEI/ARBs may reduce the incidence of AF recurrence and CHF, with fewer serious adverse effects, but did not prevent new onset of AF.	N/A	• Doxazosin was associated with a higher incidence (2%) of AF/AFL prior to having the drug discontinued by the trial. Excluding doxazosin, there was no relationship between treatment drug and AF/AFL incidence.	• 2° analysis of RCT.

	Size: 10 studies, n=42,892		mentioning of AF prevention.					

Data Supplement 49. Valvular Heart Disease (Section 9.9)

Study Acronym; Author; Year Published	Aim of Study; Study Type; Study Size (N)	Study Intervention (# patients) / Study Comparator (# patients)	Patient Population	Endpoints	P Value; OR, HR, or RR; & 95% CI	Study Limitations & Adverse Events
Healey et al., 2005 (257) 15936615	Aim: Systematic review of all RCT evaluating the benefit of trials of ACEI and ARBs in prevention of AF Study type: Meta-analysis Size: 11 studies included with 56,308 pts	Intervention: n=27,089 RAAS blockade Comparators: n=29,220 placebo or active control antihypertensive	Inclusion criteria: Studies of RAAS blockade in CHF, MI, electrical cardioversion, and HTN) with incidence of AF noted during follow-up Exclusion criteria: Studies without the measurement of AF or use of RAAS blockade.	1° endpoint: AF occurrence or reoccurrence	• ACEIs and ARBs reduced RR of AF by 28% (p=0.0002), greatest in pts with HF [RR reduction: 44%; p=0.007). No significant reduction in AF in pts with HTN (RR reduction: 12%; p=0.4), but 1 trial found a significant 29% reduction in pts with LVH. Following cardioversion there was a large effect (48% RR reduction; 95% CI: 21%–65%).	• ACEIs and ARBs appear to be effective in prevention of AF probably limited to pts with systolic LV dysfunction or HTN LVH
Jibrini et al., 2008 (255) 18223352	Aim: To assess the effectiveness of ACEIs and ARBs in the prevention of AF, and to identify those clinical entities in which RAAS inhibition would most likely benefit the pts. Study type: Meta-analysis	Intervention: n=26,973 RAAS blockade Comparators: n=29,016 placebo, amlodipine, BB or thiazide diuretic	Inclusion criteria: Studies of RAAS blockade in CHF, MI, electrical cardioversion, and HTN) with incidence of AF noted during follow-up Exclusion criteria: Studies without the measurement of AF or use of RAAS blockade.	1° endpoint: AF occurrence or reoccurrence.	• Treatment with RAAS blockers reduced RR of AF in pts with HTN by 23% (p<0.001), by 11% in pts after MI (p<0.05), by 51% after electrical cardioversion (p<0.001), by 32% in pts with HF (p<0.001) and by 19% overall (p<0.001).	N/A

	Size: 11 studies, 55,989 pts					
Zhao et al., 2015 (256) 26668582	Aim: To investigate the effectiveness and safety of ACEIs or angiotensin II receptor blockers (ARBs) on preventing AF in essential hypertensive pts. Study type: Meta-analysis Size: 10 studies, n=42,892	Intervention: RAAS blockade, n=20,491 Comparator: BB/calcium antagonist, n=22,401	Inclusion criteria: RCTs on the effects of ACEI/ ARBs on essential hypertensive pts. Exclusion criteria: Non-RCTs, subjects who were not treated with ACEI or ARB, and trials not mentioning of AF prevention.	1° endpoint: AF occurrence or reoccurrence.	• ACEI/ARBs reduced the incidence of AF recurrence compared to calcium antagonists (RR: 0.48; 95% CI: 0.40–0.58; p<0.00001) or b-blockers (RR: 0.39; 95% CI: 0.20–0.74; p=0.005). ACEI/ARBs may reduce the incidence of AF recurrence and CHF, with fewer serious adverse effects, but did not prevent new onset of AF.	N/A
Hansson et al., 1999 (258) 10030325	Aim: CAPP Trial was designed to compare the effects of ACE inhibition and conventional therapy on CV morbidity and mortality in pts with HTN. Study type: RCT Size: 10,985	Intervention: Captopril, n=5,592 Comparator: 5,493 pts were allocated to diuretics or BBs	Inclusion criteria: Pts aged 25–66 y with a measured DBP of ≥100 mm Hg on 2 occasions were included. Exclusion criteria: 2º HTN, serum creatinine concentration of more than 150 micromol/L, and disorders that required treatment with BB.	1° endpoint: Fatal and nonfatal MI and stroke, and other CV deaths. 2° endpoint: New or deteriorated IHD and CHF, AF, DM, TIA s, and death from all causes.	• Captopril and conventional treatment did not differ in rates of all cardiac events—fatal and nonfatal MI, other CV deaths and sudden deaths, IHD, CHF, or AF (0·94; p=0·30).	N/A
Hansson et al., 1999 (259) 10577635	Aim: STOPH-2 aimed to compare the effects of conventional and newer antihypertensive drugs on CV mortality and morbidity in elderly pts.	Intervention: n=2205 pts treated with ACEI Comparator: n=2,213 pts treated with BB or diuretic combination or n=2,196 pts treated with CCB	Inclusion criteria: HTN with BP ≥ 180 mm Hg systolic, aged 70–84 y Exclusion criteria: Outside of the age range (n=14)	1° endpoint: CV death 2° endpoint: CV events, DM and AF	• Old and new antihypertensive drugs were similar in prevention of CV mortality or major events. Decrease in BP was of major importance for the prevention of CV events. No difference in AF frequency was found (5.3% with ACEI, 4.1% with CCB and 5.2% with older drugs).	N/A

	Study type: RCT Size: 6,614					
Wachtell et al., 2005 (260) 15734615	Aim: LIFE trial aimed to determine whether angiotensin II receptor blockade is better than beta-blockade in preventing new-onset AF. Study type: RCT Size: 9,193	Intervention: n=4,298 treated with losartan Comparator: n=4,182 treated with atenolol	Inclusion criteria: Hypertensive pts with LVH by echo Exclusion criteria: Prior AF history in 342 pts	1° endpoint: new onset of AF 2° endpoint: None	• New-onset AF occurred in 150 pts randomized to losartan vs. 221 to atenolol (6.8 vs.10.1 per 1,000 person-y; RR: 0.67; 95% CI: 0.55–0.83; p<0.001) despite similar BP reduction. Pts receiving losartan tended to stay in sinus rhythm longer (p=0.057) than those receiving atenolol.	N/A
Haywood et al., 2009 (261) 19926008	Aim: To investigate incidence of development of AF/AFL in pts enrolled in this comparative trial of antihypertensives (ALLHAT). Study type: RCT Size: 81,474	Intervention: n=42,418 on diuretics Comparator: n=39,056	Inclusion criteria: Essential HTN with BP >140/90 without medications, >180 systolic if on medications Exclusion criteria: Not meeting inclusion criteria	1° endpoint: ECG evidence of AF/AFL on follow-up of HTN and dyslipidemia	• AF/AFL occurred in 641 pts on follow-up. Incidence did not differ by class of antihypertensive, other than increased frequency in the doxazosin group by 33% vs. chlorthalidone group (p=0.05 after risk adjustment).	• Doxazosin group was limited by higher cardiac event rates and early termination of this portion of the trial.
Julius et al., 2004 Julius, 2004 610} 15207952	Aim: The Valsartan Antihypertensive Long-term Use Evaluation (VALUE) trial: does valsartan reduce cardiac morbidity and mortality more than amlodipine for the same degree of BP reduction in in hypertensive pts at high CV risk.	Intervention: n=7,649 on valsartan Comparator: n=7,596 on amlodipine	Inclusion criteria: Hypertensive pts, ≥50 y with DM, current smoking, high total cholesterol, LVH by ECG, proteinuria on dipstick and CKD (not end-stage) Exclusion criteria: ESRD, renal artery stenosis, pregnancy, AMI, PTCA or CABG within the past 3 mo, clinically	1° endpoint: Cardiac mortality, morbidity, HF, stroke, all-cause death, new onset DM Safety endpoint: Hypotension, syncope 2° endpoint: AF	• AF occurred in 2.4% with valsartan and 2.0% with amlodipine; p=0.1197.	N/A

	Study type: RCT Size: 15,245		relevant valvular disease, cerebrovascular accident in the past 3 mo, severe hepatic disease, severe chronic renal failure, CHF requiring ACEI therapy and pts on monotherapy with blockers for both CAD and HTN.			

Data Supplement 50. RCTs and Meta-analysis Comparing Valvular Heart Disease (Section 9.9)

Study Acronym; Author; Year Published	Aim of Study; Study Type; Study Size (N)	Study Intervention (# patients)/Study Comparator (# patients)	Patient Population	Endpoints	P Value; OR, HR, or RR; & 95% CI	Study Limitations & Adverse Events
SCOPE-AS Chockalingam A, et al., 2004 (262) 15077102	Aim: To determine the clinical tolerance and efficacy of the ACEI enalapril in the setting of symptomatic severe AS. Study type: RCT Size: 56 pts	Intervention: Enalapril 2.5 mg BID increasing to 10 mg BID (37 pts) Comparator: Placebo (19 pts)	Inclusion criteria: Severe aortic stenosis (aortic valve area <0.75 cm^2, mean aortic gradient >50 mm Hg, or aortic valve Doppler jet >4.5 m/s) and symptomatic NYHA class III or IV dyspnea or angina Exclusion criteria: Persistent hypotension (SBP <90 or mean BP <60), severe mitral stenosis (mitral valve orifice <1.0 cm^2), known intolerance for ACEI, and renal dysfunction (serum creatinine >2.5 mg/dL).	1° endpoint: Improvements in Borg dyspnea index and 6-min walk distance at 1 mo Safety endpoint: Development of hypotension 2° endpoint: Minor ACEI intolerance, cough, presyncope, improvement in NYHA class, and echo parameters	• Pts who tolerated enalapril (n=34) had significant improvement in NYHA class, Borg index (5.4 ± 1.2 vs. 5.6 ± 1.7; p=0.03), and 6-min walk distance (402 ± 150 vs. 376 ± 174; p=0.003) compared with control pts.	• Treatment with enalapril resulted in hypotension in 3 of 5 pts with LV dysfunction and congestive HF had hypotension.

SEAS Rieck ÅE Hypertension, 2012 (263) 22647889	Aim: To determine the impact of HTN on LV structure and outcome during progression of aortic valve stenosis Study type: RCT observational substudy of SEAS trial Size: 1616 pts	Intervention: 1,340 pts with HTN Comparator: 276 pts without HTN	Inclusion criteria: Pts 45- 85 y who had asymptomatic, mild-to-moderate aortic valve stenosis, as assessed on echo, with a peak aortic-jet velocity of 2.5–4 m per second, were eligible for the study.	1° endpoint: Echo LV mass; MACE; mortality	• HTN predicted 51% higher incidence of abnormal LV geometry at final study visit independent of other confounders (p<0.01). • HTN was associated with a 56% higher rate of ischemic CV events and a 2-fold increased mortality (both p<0.01).	• No specific randomized intervention for HTN.
Eleid MF, et al., 2013 (264) 23956211	Aim: To evaluate the hemodynamic effects of vasodilator therapy in pts with LGSAS Study type: Nitroprusside infusion Size: 24	Intervention: Infusion of IV sodium nitroprusside to reduce BP and arterial afterload (18 pts with hypertensive LGSAS) Comparator: Baseline hemodynamics (6 pts with low EF LGSAS)	Inclusion criteria: Symptomatic pts with HTN (aortic SBP >140 mm Hg) and low-gradient (mean gradient <40 mm Hg) severe aortic stenosis (aortic valve area <1 cm (2)) with preserved EF (EF >50%). Exclusion criteria: Moderate or severe concomitant valvular heart disease (e.g., aortic, mitral or tricuspid regurgitation), reduced left ventricular EF (>50%), age <18 y, and complex CHD.	1° endpoint: Nitroprusside reduced mean PA pressure (25±10 mm Hg) and LV end-DBP (11±5 mm Hg; p<0.001 for both compared with baseline). 2° endpoint: Aortic valve area (0.86±0.11 to 1.02±0.16 cm (2); p=0.001) and mean gradient (27±5 to 29±6 mm Hg; p=0.02) increased with nitroprusside.	• Treatment of HTN with vasodilator therapy results in a lowering of the total LV afterload, with a decrease in LV filling pressures and PA pressures.	• No translation to clinical or ambulatory vasodilator use.
RIAS Trial Bull S, et al., 2015 (265) 25796267	Aim: To determine if ACEIs improve outcomes in AS. Study type: RCT Size: 100	Intervention: Ramipril ramped up from 2.5 to 5 to 10 mg for 1 y (50 pts) Comparator: Placebo (50 pts)	Inclusion criteria: Pts >18 y with moderate or severe aortic stenosis (valve area <1.5 cm^2, or peak velocity >3.0 m/s [peak valve gradient >36 mm Hg]), 2 who were asymptomatic as judged by pt-reported symptoms,	1° endpoint: Adverse events; laboratory abnormalities; change in LVM from baseline to 12 mo measured by CMR. 2° endpoint: Change in LV EF and function by CMR and echo, change in	• Reduction in LVM in the ramipril group vs. placebo group (mean change -3.9 vs. +4.5 g, respectively; p=0.0057); preserved tissue Doppler systolic velocity compared with placebo (+0.0 vs. -0.5 cm/s;	• A larger clinical outcome trial to confirm these findings and explore their clinical relevance is required.

			and who did not have indications for valve replacement surgery. Exclusion criteria: Any other significant (>mild) VHD, excess hypo- or HTN (BP <100/40 or >200/110 mm Hg). Intolerance of ACEIs or ARBs or their prescription over the previous 3 mo	BNP); and change in distance walked on exercise tolerance testing.	p=0.04); trend to less progression of the aortic stenosis (valve area 0.0 cm^2 vs. -0.2 cm^2 in the placebo arm; p=0.067).	
Scognamiglio R, et al., 1994 (266) 8058074	Aim: To assess whether vasodilator therapy reduces or delays the need for valve replacement Study type: RCT Size: 143	Intervention: Nifedipine 20 mg Q12 H (69 pts) Comparator: Digoxin 0.25 mg daily (74 pts)	Inclusion criteria: Asymptomatic pts with isolated, chronic, severe aortic regurgitation and normal LV systolic function Exclusion criteria: Worsening aortic regurgitation within 6 mo, DBP above 90 mm Hg, CAD, aortic valve gradient ≥ 20 mm Hg, other valvular or CHD, poor quality echo or an LV EF <50%.	1° endpoint: Frequency of valve replacement	• At 6 y, a 34% of the digoxin group had undergone valve replacement, but only 15% of the nifedipine group (p<0.001)	• No placebo group, and digoxin is a poor comparator due to toxicity which is now recognized.
Evangelista A, et al., 2005 (267) 16192479	Aim: To identify the possible beneficial effects of vasodilator therapy on LV function and the need for aortic-valve replacement. Study type: RCT Size: 95 pts	Intervention: Nifedipine 20 mg Q12 H or enalpril 20 mg daily (32 pts nifedipine, 32 pts enalapril) Comparator: Placebo (31 pts)	Inclusion criteria: Consecutive pts with asymptomatic, chronic, severe aortic regurgitation and normal LV function Exclusion criteria: LVEF <50%, AF, CAD or other nonaortic VHD	1° endpoint: Frequency of valve replacement	• Rate of aortic-valve replacement was similar among the groups: 39% in the control group, 50% in the enalapril group, and 41% in the nifedipine group (p=0.62).	N/A

Scognamiglio R, et al., 1994 (266) 8058074	Aim: To assess whether vasodilator therapy delays need for valve replacement in pts with asymptomatic severe AR. Study type: RCT Size: 143 pts	Intervention: 69 pts received nifedipine Comparator: 74 pts received digoxin	Inclusion criteria: Severe aortic regurgitation without symptoms Exclusion criteria: DBP >90, recent worsening of aortic regurgitation, mixed aortic stenosis / aortic regurgitation or any additional valve disease, LVEF <50.	1° endpoint: Worsening symptoms, LVEF decline to <50% or both, requiring valve replacement surgery	• 15% met criteria for valve replacement with nifedipine, but 34% did with digoxin (p<0.001)	• No placebo control.
Evangelista A, et al., 2005 (14) 16192479	Aim: To assess whether vasodilator therapy delays need for valve replacement in pts with asymptomatic severe AR. Study type: RCT Size: 95 pts	Intervention: 32 pts received enalapril; 32 pts received nifedipine Comparators: 31 pts received placebo	Inclusion criteria: Severe aortic regurgitation without symptoms Exclusion criteria: Not listed.	1° endpoint: Worsening symptoms, LVEF decline to <50% or both, requiring valve replacement surgery	• 41% met criteria for valve replacement with nifedipine, 50% did with enalapril, and 39% in the control group (p=0.62)	• BP of 145/75 average between the 3 groups, indicate lack of severity. Post-Rx BP is not reported.

Data Supplement 51. RCTs Comparing Race/Ethnicity (Section 10.1)

Study Acronym; Author; Year Published	Aim of Study; Study Type; Study Size (N)	Patient Population	Study Intervention (# patients) / Study Comparator (# patients)	Endpoint Results (Absolute Event Rates, P value; OR or RR; & 95% CI)	Relevant 2° Endpoint (if any); Study Limitations; Adverse Events; Summary
Leenen F, et al., 2006 (268) 16864749	Study type: RCT comparison of an alpha blocker, ACEI, or CCB, each compared to a thiazide-type diuretic. This is post hoc comparison between	• >50 y • Lisinopril (n=9,054); Amlodipine (9,048) • African American 15,085 (35.5%) • White 11,580 (47.0%)	• Amlodipine vs. Lisinopril	• No significant difference in 1° outcome (nonfatal MI and fatal CHD) or other prespecified outcomes: • CHD, 1° outcome plus revascularization and hospitalized	• In African Americans, Lisinopril less effective than amlodipine for BP reduction (mean follow-up BP 2.7/1.6 mm Hg higher with Lisinopril) and in reducing strokes (RR:1.51; 95% CI: 1.22–1.86) and

	CCB vs. ACEI incl in race subgroup. Size: 42,418			angina, composite CVD, HF, ESRD, except strokes	combined CVD (RR: 1.13; 95% CI:1.02–1.24; p=0.025)
Wright JT et al. 2008 (269) 18227370	Study type: Race subgroup comparison of RCT comparison of an ACEI or CCB compared to a thiazide-type diuretic on nonfatal or fatal CHD in pts with metabolic syndrome	• >50 y • African American n=12,818 • Non-African American n=24,473	• Chlorthalidone vs. Amlodipine, or Lisinopril	• No difference in 1° outcome (nonfatal MI and fatal CHD). Other prespecified outcomes: • CHD, 1° outcome plus revascularization and hospitalized angina, composite CVD, stroke, HF, ESRD	• In African Americans with metabolic/cardiometabolic syndrome: Amlodipine similar for chlorthalidone for all outcomes but inferior for HF (HR: 1.50; 95% CI: 1.18–1.90) and combined CVD (HR: 1.14; 95% CI: 1.00–1.29). Lisinopril less effective for SBP reduction by 4 mm Hg; combined CHD (HR: 1.19 (95% CI: 1.01, 1.40); combined CVD (HR: 1.24; 95% CI: 1.09–1.40); stroke (HR: 1.37; 95% CI: 1.07–1.76); HF (HR: 1.49; 95% CI: 1.17–1.90); and ESRD (HR: 1.70; 95% CI: 1.13–2.55)
Wright JT, et al., 2009 (270) 19433694	Study type: Race subgroup comparison of RCT comparison of an alpha blocker vs. a thiazide-type diuretic Size: 9,061	• >50 y • (35.5% African American)	• Chlorthalidone vs. Doxazosin	• No difference in 1° outcome (nonfatal MI and fatal CHD). Other prespecified outcomes: CHD, 1° outcome plus revascularization and hospitalized angina, composite CVD, stroke, HF, ESRD	• In African Americans: combined CVD (HR: 1.28; 95% CI: 1.16–1.42); HF (HR: 1.84; 95% CI: 1.51–2.24); stroke HR (CI): 1.10–1.73)
SPRINT Wright JT Jr, et al., 2015 (114) 26551272	Aim: To test the effectiveness of a goal SBP<120 mm Hg vs. a goal SBP<140 mm Hg for the prevention of CVD in pts with SBP≥130 mm Hg at baseline. Study type: RCT	Inclusion criteria: SBP≥130 mm Hg, with upper limit varying as number of pre-trial BP-lowering meds increased. age ≥50 y Presence of at least 1 of the following: • Clinical or subclinical CVD • CKD stage 3 or greater • Age≥75 y	Intervention: Intensive BP-lowering treatment to goal SBP<120 mm Hg Comparison: • Standard BP-lowering treatment to goal SBP<140 mm Hg • Net treatment difference ~3 drugs (2.8) on average vs. 2 drugs (1.8) on average	1° endpoint: CVD (MI, ACS, stroke, HF, CVD death) HR: 0.75 (0.64–0.89) Other endpoints: • Total deaths: 0.73 (0.60–0.90) • 1° or death: 0.78 (0.67–0.90) • Components of 1° composite mostly consistent in direction other than ACS – no difference. CKD outcomes:	Summary: • More intensive SBP lowering to a goal of <120 mm Hg with achieved mean of ~121 mm Hg resulted in less CVD and lower total mortality over 3.26 y in comparison with a goal SBP<140 mm Hg and achieved SBP of ~135 mm Hg. • There were small increases in some expected SAEs. Perhaps unexpected, a sizable

	Size: 9361 participants followed median of 3.26 y	• Framingham General CVD risk≥15% in 10 y Exclusion criteria: Major ones included DM, history of stroke, ESRD (eGFR <20)	• During the trial, mean SBP was 121.5 vs. 134.6.	• 1° in CKD pts: reduction in GFR of ≥50% or ESRD 0.89 (0.42–1.87) • Incident albuminuria: 0.72 (0.48–1.07) • In pts without CKD: reduction in GFR ≥30% and to <60 • 3.49 (2.44–5.10) • Incident albuminuria: 0.81 (0.63–1.04) Adverse events: • SAEs: 1.04; p=0.25 • Significant absolute increases seen in intensive group for hypotension (1%), syncope (0.6%), electrolyte abnormality (0.8%), acute kidney injury/acute renal failure (1.6%) over the study period. • 1.7% fewer pts had orthostatic hypotension in intensive group; p=0.01.	increase in reduced eGFR in the non-CKD group and AKI/ARF overall was observed in the intensive group. While of uncertain etiology and significance, there is speculation this could be an acute hemodynamic effect, especially given the findings regarding albuminuria. Limitations: Few participants were untreated at baseline ~9%, so SPRINT provides little if any insight at present regarding BP-lowering medication initiation for untreated people with SBP 130–139.
VA Coop 1967 (262) 4862069	Study type: RCT to examine effect of treatment of severe HTN Size: 143	• 54% African American • DBP 115–129 mm Hg	• HCTZ, Reserpine, Hydralazine vs. placebo	• CVD or stroke events, Grade 3 or 4 retinopathy, doubling of creatinine or BUN. Study terminated early for 27 events vs. 2 events (placebo vs. active)	N/A
VA Coop 1970 (271) 4914579	Study type: RCT to examine effect of treatment of mild to moderately severe HTN Size: 380	• 42% African American • DBP 90–115 mm Hg	• HCTZ, Reserpine, Hydralazine vs. placebo	• CVD or stroke events, Grade 3 or 4 retinopathy, doubling of creatinine or BUN	

HTN Detection and Follow-up Program (HDFP) 1979 6480895 (272)	Study type: RCT; comparison of stepped care at academic centers vs. usual care provided by community Size: 10,950 pts	• 44% African American • 30–69 y	• Chlorthalidone, Reserpine, Hydralazine, Guanethidine vs. referral to community care	• 23% decrease in mortality in African Americans on Stepped Care	N/A
LIFE Dahlof B, et al. 2002 11937178 (14)	Study type: RCT comparison of an ARB compared to a BB on CVD	• 55–80 y (mean 66.9 y) • African American 533 (6) • White 8,503 (92) • Asian 43 (0.5) • Hispanic 100 (1) • Other 14 (0.2)	• Losartan vs. Atenolol	• Interaction of race and treatment on CVD events (p=0.005) CVD increased 55% in African Americans in the Losartan group	N/A
VALUE Julius S, et al. 2006 (265) 16864741 (273)	Study type: RCT comparison of an ARB vs. a CCB on CVD	• >50 y (mean 67.3 y) • African American 658 (4.3) • White 13,643 (89.1) • Asian 535 (3.5) • Other 474 (3.1)	• Valsartan vs. Amlodipine	• CVD increased ~20% (NS) in African Americans in Valsartan group	N/A
AASK Norris K, et al. 2006 17059993 (174)	Study type: RCT comparison of 2 BP targets and 3 drug regimens on renal outcomes Size: 1,094 pts	• 18–70 y; African Americans; • eGFR: 25–65 mL/min/1.73 m^2	• MAP of <92 mm Hg compared to MAP 102–107 mm Hg and an ACEI or CCB each compared to a BB	• No difference between BP targets. ACEI > BB > CCB	N/A
ALLHAT 2002 (274) 12479763	Study type: RCT comparison of an alpha blocker, ACEI, or CCB, each compared to a thiazide-type diuretic Size: 42,418	• >50 y • African American 15,085 (35.5) • White 19,977 (47.0) • Hispanics 5,299 (12.5)	• Chlorthalidone vs. Doxazosin, Amlodipine, or Lisinopril	• No difference in 1° outcome (nonfatal MI and fatal CHD)	• Chlorthalidone (and amlodipine was superior in reducing BP by 4/1 mm Hg and CVD events (stroke and CVD) vs. lisinopril in African Americans
INVEST Pepine CJ, et al., 2003 (275)	Study type: RCT comparison of CCB plus an ACEI	• ≥ 50 y with HTN and CHD • 36% Hispanic	• Verapamil/trandolapril vs. Atenolol/ HCTZ	•No difference in 1° outcome (nonfatal MI, nonfatal stroke, all-cause mortality). Mean SBP	N/A

14657064	compared to a BB plus a thiazide diuretic Size: 22,576	• 13% African American • 49% White		reduction Hispanics vs. non-Hispanic pts (-21.3 vs. -17.4 mm Hg; p<0.001)	
Wright JT, et al., 2005 (276) 15811979	Study type: Race subgroup comparison of RCT comparison of an alpha blocker, ACEI, or CCB compared to a thiazide-type diuretic	• >50 y • African American, n=11,792 • Non-African American, n=21,565	• Chlorthalidone vs. Amlodipine, or Lisinopril	• No difference in 1° outcome (nonfatal MI and fatal CHD). Other prespecified outcomes: CHD, 1° outcome plus revascularization and hospitalized angina, composite CVD, stroke, HF, ESRD	• In African Americans: Amlodipine similar to chlorthalidone for all outcomes but inferior for HF (HR: 1.37; 95% CI: 1.24–1.51). Lisinopril less effective for SBP reduction by 4 mm Hg, stroke (HR: 1.40; 95% CI: 1.17–1.68), combined CVD (HR: 1.19; 95% CI: 1.09–1.30), HF (HR: 1.30; 95% CI: 1.10–1.54).

Data Supplement 52. RCTs Comparing Women With Hypertension (Section 10.2.1)

Study Acronym; Author; Year Published	Aim of Study; Study Type; Study Size (N)	Patient Population	Study Intervention (# patients) / Study Comparator (# patients)	Endpoint Results (Absolute Event Rates, P value; OR or RR; & 95% CI)	Relevant 2° Endpoint (if any); Study Limitations; Adverse Events; Summary
Turnbull F, et al., 2008 (277) 18852183	Aim: Assess sex differences in response to BP treatment Study type: Meta-analysis of 31 RCTs Size: 103,268 men, 87,349 women	Mean ages: • Women: 63.0 y • Men: 61.7 y	Intervention: N/A Comparator: N/A	1° endpoint: Nonfatal stroke or death from cerebrovascular disease (ICD 430–438); (ii) nonfatal MI or deaths from CHD, excluding SCD (ICD 410–414); (iii) HF causing death or requiring hospitalization (ICD 428); (iv) total major CV events (stroke, CHD events, HF, other CV death); (v) total CV deaths (ICD 396–459); and (vi) total mortality Safety endpoint: N/A	Summary: Achieved BP reductions were comparable for men and women in every comparison made. For the 1° outcome of total major CV events there was no evidence that men and women obtained different levels of protection from BP-lowering or that regimens based on ACEIs, calcium antagonists, ARBs, or diuretics/BBs were more effective in1 sex than the other (all p-homogeneity >0.08).
Wing L, et al., 2003 (278) 12584366	Aim: Comparison of ACE vs. Diuretic on incident CVD	Inclusion criteria: Pts 65–84 y	Intervention: ACE Comparator: Diuretic	Endpoint: All CV events or death from any cause Safety endpoint: N/A	Summary: Among male subjects, HR: 0.83 (95% CI: 0.71–0.97; p=0.02); among female subjects, HR: 1.00 (95% CI: 0.83–1.21; p=0.98); the p value for

	Study type: Practice-based RCT open label treatment, blinded event Size: 6,083 pts	Exclusion criteria: Life-threatening illness, contraindication to an ACEI or diuretic, a plasma creatinine concentration of more than 2.5 mg per deciliter (221 micromol per liter), malignant hypertension, or dementia	Note: Clinicians chose which ACE or diuretic		the interaction between sex and treatment-group assignment was 0.15.
Fletcher A, et al., 1988 (279) 2907053	Aim: Monitoring event rates in pts assigned to treatment by clinicians Study type: Observational Size: 2,607	Inclusion criteria: Age >18 y Exclusion criteria: N/A	Intervention: N/A	1° endpoint: Total mortality incident "IHD" Safety endpoint: N/A	Summary: BBs reduced mortality in men but not women (p<0.01)
Forette F, et al., 2002 (280) 12374512	Aim: Legacy follow-up for dementia prevention Study type: RCT with legacy follow-up Size: 2,902 in the legacy follow-up	Inclusion criteria: Age ≥60 y Exclusion criteria: HTN 2° to a disorder that needed specific medical or surgical treatment; congestive HF; dissecting aortic aneurysm; serum creatinine concentration at presentation of 180 micromol/l or more; stroke or MI in the y before the study; dementia; substance abuse; any disorder prohibiting a sitting or standing position; any severe concomitant or non-CVD	Intervention: Nitrendipine + HCTZ Comparator: Placebo	1° endpoint: Incidence of dementia 2° endpoint: Cognitive decline measured by MMSE Safety endpoint: N/A • Cases Active: 21 • Cases Placebo; 43 • Rate 3.3 vs. 7.4 cases/1,000 pt y 0.38 (95% CI: 0.23–0.64; p<0.001) • MMSE: No impact	• Study discontinued early for CVD benefit so a legacy follow-up with both groups (off protocol) yielded a follow-up of 3.7 y SBP was 149 mm Hg in treatment vs. 156 mm Hg in control arm Summary dementia: • Compared with the controls, long-term antihypertensive therapy reduced the risk of dementia by 55%, from 7.4–3.3 cases per 1,000 pt-y (43 vs. 21 cases; p<0.001). After adjustment for sex, age, education, and entry BP, the relative HR associated with the use of nitrendipine was 0.38 (95% CI: 0.23, 0.64), p<0.001. • Lack of impact on MMSE not surprising given low sensitivity to change and large sample size

Data Supplement 53. RCTs Comparing Pregnancy (Section 10.2.2)

Study Acronym (if applicable) Author Year	Study Type/Design*; Study Size (N)	Patient Population	Primary Endpoint and Results (include P value; OR or RR; & 95% CI)	Summary/Conclusion Comment(s)
Pucci M, et al., 2015 (281) 25612630	Study type: Review of published reports of fetotoxicity of ACE/ARB antihypertensives in the first trimester of pregnancy. Usually case/control design. Size: N/A	Inclusion criteria: Pregnant women receiving ACE/ARB in the 1st trimester of pregnancy only and comparable controls Exclusion criteria: Use of ACE/ARB later in pregnancy	1° endpoint: Adverse outcomes of pregnancy Results: Adverse events are higher in pregnancies of women who receive ACE/ARB in the first trimester of pregnancy but results are not independent of known confounders	• Fetotoxicity in the first trimester of pregnancy cannot be definitely attributed to ACE/ARB treatment; data are inconclusive. •Other known causes of fetotoxicity may be responsible for increased risk in the first trimester (HTN, obesity, undiagnosed DM, other anti-hypertensives)
Moretti ME, et al., 2012 22203847 (282)	Study type: Case control comparing pts exposed to ACE/ARB in the first trimester to healthy controls and those on other anti-hypertensives Size: 388 total pts (equally divided)	Inclusion criteria: Mothers calling into the Mother Risk Program re: medication toxicity during pregnancy Exclusion criteria: Non-English speaking	1° endpoint: Malformations and adverse fetal outcomes Results: No difference among groups but study under-powered	• Supportive of above review
Ferrer RL, et al., 2000 (283) 11094241	Study type: Meta-analysis Size: 46 observational studies and randomized control trials	Inclusion criteria: Pre-specified quality entrance criteria Exclusion criteria: N/A	1° endpoint: Adverse pregnancy outcomes Results: • Maternal HTN increases risk for 1) perinatal mortality (OR: 3.4:1) and 2) placental abruption (2.1:1) • ACEIs are associated with fetopathy (fetal renal failure)	• HTN by itself is associated with adverse perinatal outcomes • ACEIs independently are responsible for some outcomes

*Quality assessment analysis may need to be applied on a case-by-case basis for controversial studies (by ERC chairs).

Data Supplement 54. RCT for Older Persons (Section 10.3.1)

Study Acronym; Author; Year Published	Aim of Study; Study Type; Study Size (N)	Patient Population	Study Intervention (# patients) / Study Comparator (# patients)	Endpoint Results (Absolute Event Rates, P value; OR or RR; & 95% CI)	Relevant 2° Endpoint (if any); Study Limitations; Adverse Events; Summary
SPRINT Senior Williamson JD, et al., 2016 (190) 27195814	Aim: Intensive SBP goal <120 mm Hg) vs. standard (SBP goal <140) Study type: RCT Size: 2,636; 30% met criteria for being classified as ambulatory frail Mean follow-up:3.1 y	Inclusion criteria: Men and women age 75+; mean age 79.8 y; 38% women; 17% black, 74% Caucasian Exclusion criteria: Nursing home residents; prevalent DM, stroke, Class III/IV HF, dementia	Intervention: Medications and dietary advice to achieve SBP of <120 mm Hg Comparator: Medications and dietary advice to achieve SBP of <140 mm Hg • Achieved SBP: Intensive=123.4 mm Hg Standard=134.8 mm Hg	1° endpoint: Composite CVD outcome (AMI, non-MI ACS, stroke, HF, CVD death. Results: • 102 events in the intensive treatment group vs. 148 events in the standard treatment group; HR: 0.66; 95% CI: 0.51–0.85 and all-cause mortality (73 deaths vs. 107 deaths, respectively; HR: 0.67; 95% CI: 0.49–0.91. No difference in falls, orthostatic hypotension, or overall SAEs. • NNT for 1° outcome=27 and NNT for all-cause mortality=41	Limitations: Does not apply to nursing home pts or those with dementia or advance Conclusions: Intensive SBP is safe and effective for lowering CVD events and total mortality in adults ≥75 y

Data Supplement 55. RCTs Comparing Hypertensive Crises and Emergencies (Section 11.2)

Study Acronym; Author; Year Published	Aim of Study; Study Type; Study Size (N)	Patient Population	Study Intervention (# patients) / Study Comparator (# patients)	Endpoint Results (Absolute Event Rates, P value; OR or RR; & 95% CI)	Relevant 2° Endpoint (if any); Study Limitations; Adverse Events; Summary
CLUE Peacock WF, et al., 2011 (284) 21707983	Aim: Compare safety and efficacy of IV nicardipine vs. labetalol in the management of acute HTN. Study type: RCT	Inclusion criteria: SBP ≥180 mm Hg on 2 consecutive occasions 10 min apart in the ED.	• 110 pts randomized to nicardipine; 116 to labetalol. End-organ damage preceded randomization in 63%% with no difference between the groups. The target BP range (TR; at the discretion of the	Results: Within 39 min, nicardipine pts reached TR than labetalol pts (91.7 vs. 82.5%; p=0.039). Of 6 BP measurements taken 5 min apart, nicardipine pts had a higher rate of 5 and 6 SBP measures in the TR than labetalol pts (47.3 vs. 32.8%;	Limitations: Study unblinded; large number of pts without end-organ damage (which usually defines a hypertensive emergency); physicians ordered fewer dose titrations of labetalol than nicardipine; thus, lack of BP decline might have been due to insufficient dosing by physicians hesitant to administer successively increasing doses of labetalol as recommended by the FDA.

	Size: 226 pts		treating physician) was defined as SBP ± 20 mm Hg. ● Dosing titrations were those recommended by the FDA.	p=0.026). Rescue medications did not differ between the nicardipine and labetalol groups. Nicardipine pts were more likely in the TR than labetalol pts (OR: 2.73; 95% CI: 1.1–6.7; p=0.028).	Conclusions: Pts treated with nicardipine are more likely to reach the physician-specified TR than those treated with labetalol. In this study (2014), initial SBP was not a predictor of the ability to achieve the pre-specified TR in 30 min. Subgroup analysis demonstrated the similar results for sub-populations with end-organ damage (n=141) and renal dysfunction (n=104).
Liu-DeRyke X, et al., 2013 (285) 23760911	Aim: Compare ability of IV nicardipine and labetalol to lower BP in acute hemorrhagic or ischemic stroke. Study type: RCT (pseudo-randomization) Size: 54 pts	Inclusion criteria: Pts with acute hemorrhagic or ischemic stroke who were at or exceeded AHA guidelines BP recommendations. Exclusion criteria: Traumatic brain injury; intracranial neoplasm, received antihypertensive medication within previous 24 h, brain stem herniation, immediate brain death, acute MI, or bradycardia <50 bpm.	● 28 pts randomized to labetalol and 26 to nicardipine. Goal BP defined using the latest consensus recommendations.	Results: All pts receiving nicardipine achieved BP goal Compared with 61% in the labetalol group (p<0.001). 89% of the nicardipine group achieved goal within 60 min vs. 25% in the labetalol group (p<0.001). The nicardipine group had better maintenance of BP, greater percent of time spent within goal and less BP variability compared with the labetalol group (p<0.001). Less rescue medication had to be given to the nicardipine than the labetalol group (p<0.001).	Limitations: Very small; pseudo-randomization. Conclusions: In acutely hypertensive stroke pts, a superior BP-lowering response was achieved with nicardipine over labetalol. Despite this, there was no significant difference in clinical outcomes.
CATIS He J, et al., 2014 (202) 24240777	Aim: Evaluate whether immediate BP reduction in pts with acute ischemic stroke would reduce death and major disability in 14 d or hospital discharge. Study type: RCT Size: 4,071 pts	Inclusion criteria: Pts had nonthrombolysed ischemic stroke within 48 h of onset and elevated SBP. Baseline SBP was 166.7 mm Hg in the antihypertensive treatment group and 165.6 mm Hg in the control group.	● This was a Chinese multicenter, single-blinded, blinded endpoints RCT conducted in 26 hospitals in China. 2,038 pts were randomized to receive antihypertensive treatment and 2,033 were randomized to the control group. The trial was designed to test a BP	Results: In the antihypertensive treatment group, SBP was reduced from 166.7 to 144.7 mm Hg (-12.7%) within 24 h and in the control group from 165.6 to 152.9 mm Hg (-7.2%) (absolute difference -9.1 mm Hg; 95% CI: -10.2– -8.1; p<0.001). Mean SBP was 137.3 mm Hg in the antihypertensive treatment	Limitations: Study excluded pts with BP ≥220/120 mm Hg, so the results do not apply to such pts. Pts treated acutely with thrombolytic therapy were excluded. Trial performed exclusively in Chinese pts. Conclusions: Among pts with acute ischemic stroke, BP reduction with antihypertensive medications, compared to absence of antihypertensive medications, did not reduce the likelihood of death and major disability at 14 d or hospital discharge.

			reduction strategy rather than the efficacy of specific antihypertensive drugs. Pts in the control group discontinued their home BP medications. 1° outcome: Combination of death and major disability at 14 d or hospital discharge.	group and 146.5 mm Hg in the control group at the 7th d of randomization (absolute difference -9.3 mm Hg; 95% CI: -10.1– -8.4; p<0.001). The 1° outcome did not differ between treatment groups (OR: 1.00; 95% CI: 0.88–1.14) at 14 d or hospital discharge. The 2º outcome of death and major disability at 3 mo post-treatment follow-up did not differ between the groups.	
INTERAC-2 Anderson CS, et al., 2013 (191) 23713578	Study type: RCT Size: 2,839 pts	•To compare the management strategy of targeting SBP<140 mm Hg within 1 h with the current guideline strategy of targeting SBP to <180 mm Hg with the use of agents of the physicians' choosing.	• This was an international, multicenter, prospective randomized open-treatment, blinded endpoint trial. The pts had onset of spontaneous ICH within 6 h of enrollment. 1° outcome: Death or major disability, defined as a score of 3-6 on the modified Rankin scale, at 90 d.	Results: 719 of 1,382 pts receiving intensive treatment as compared to 785 of 1,412 pts receiving guideline-recommended treatment had a 1° outcome event [OR with intensive treatment: 0.87; 95% CI: 0.75–1.01; p=0.06). Ordinal analysis showed significantly lower modified Rankin scores with intensive treatment (OR for greater disability: 0.87; 95% CI: 0.77–1.00; p=0.04). Mortality was 11.9% in the group receiving intensive treatment and 12.0% in the group receiving guideline-recommended treatment. Nonfatal serious events were not significantly different between the groups.	Limitations: No major limitations. Conclusions: In pts with ICH, intensive lowering of BP resulted in a borderline significant reduction in the rate of death or severe disability at 90 d. An ordinal analysis of modified Rankin scores indicated improved functional outcomes with intensive lowering of BP. Intensive BP reduction was shown to be safe and to result in significantly better health-related quality of life.

PRONTO Peacock WF, et al., 2014 (286) 24655702	Study type: RCT Size: 104 pts	• To determine the efficacy and safety of clevidipine vs. standard-of-care (SOC) iv antihypertensive therapy in hypertensive acute HF.	• This was a randomized, open-label, active control study of clevidipine vs. standard-of-care in ED pts with acute HF with SBP ≥160 mm Hg. 1° outcome: Co-1° endpoints were median time to and % attaining a SBP within a prespecified TR at 30 min.	Results: More clevidipine pts reached target BP reduction (71%) than did those receiving standard-of-care (37%) and clevidipine was faster to target (p=0.0006). Serious adverse events were similar between clevidipine and standard-of-care.	Limitations: Small study, open-label design. Conclusions: In hypertensive acute HF, clevidipine safely and rapidly reduced BP and improved dyspnea more effectively that standard-of-care.
Farias S, et al., 2014 13849948 (287)	Aim: To determine if achievement of target BP is less likely in pts with higher initial BP using a post hoc analysis in a pt subset from CLUE Study type: RCT Post-hoc Analysis Size: 223 pts	Inclusion criteria: SBP ≥180 mm Hg on 2 consecutive occasions 10 min apart in the ED. Exclusion criteria: Contraindication to giving either a BB or CCB or clinical scenarios in which a compelling agent was indicated.	• This was a post hoc analysis of CLUE, an RCT, in which pts were dichotomized using the median presenting SBP as the partition point. Individuals above and below the median were evaluated as to the proportion achieving the 1° outcome. 1° outcome: Achievement of target SBP range within 30 min.	Results: Early achievement of target SBP was independent of presenting SBP.	Limitations: 2º analysis of the 1° CLUE study; SBP control only evaluated for the first 30 min posttreatment; no inclusion of critically ill pts; 80% of enrolled subjects were African-American. Conclusions: Presenting SBP does not appear to affect the ultimate ability to reduce BP for pts with marked, acute HTN in the ED when treated with either IV nicardipine or IV labetalol.

Data Supplement 56. RCTs Assessing Impact of Hypertension Therapy on Dementia Incidence (Section 11.3)

Study Acronym; Author; Year Published	Aim of Study; Study Type; Study Size (N)	Patient Population	Study Intervention (# patients) / Study Comparator (# patients)	Endpoint Results (Absolute Event Rates, P value; OR or RR; & 95% CI)	Relevant 2° Endpoint (if any); Study Limitations; Adverse Events; Summary
SHEP Applegate WB, et al., 1994 (288) 7944835	Aim: Compare loss of instrumental activities of daily living by SBP	Inclusion criteria: 60–80 y (mean 71.6 y)	Intervention: Chlorthalidone + Atenolol or reserpine	1° endpoint: Loss of dementia-related functions (instrumental activities of daily living)	Relevant 2° endpoint: Incidence of surrogate markers for dementia

	treatment vs. placebo Study type: RCT Size: 4,736 Duration: 5 y	Exclusion criteria: History and/or signs of major CVDs (e.g., previous MI, coronary artery surgery, major arrhythmias, conduction defect, recent stroke, carotid artery disease, ≥2 TIAs and signs or symptoms in a single neurological distribution); other major diseases (e.g., cancer, alcoholic liver disease, established renal dysfunction) with competing risk factors for the 1° endpoint; stroke; presence of medical management problems (e.g., insulin dependent DM, history of dementia, evidence of alcohol abuse); bradycardia; people maintained on BBs, diuretics, other antihypertensive drugs, anticoagulants.	Comparator: Placebo SBP Treatment/Placebo difference: -12 mm Hg Achieved mean SPB: 143 mm Hg in treatment group vs. 155 mm Hg in placebo group	Cases • Active: 37 • Placebo: 44 • p=0.84 (0.54,1.31) • No cognitive function instrument included in trial	Summary: Nonsignificant 16% lower incidence of incident instrumental activity of daily living disability. However, assignment to the placebo group and the resulting occurrence of CV events independently predicted missed assessments. However, when 20%–30% and 40%–80% of the subjects who missed the assessment were assumed to be cognitively/functionally impaired, assignment to active treatment reduced the risk of these outcomes. Thus, in the SHEP study, the cognitive and functional evaluations were biased toward the null effect by differential dropout. This might have obscured the appraisal of a protective effect of treatment on the cognitive and functional decline of older hypertensive adults
Syst-Eur Forette F, et al., 1998 (289) 9802273	Aim: Incident dementia Study type: RCT Size: 2,418 pts Duration: 2 y	Inclusion criteria: ≥60 y Exclusion criteria: HTN 2° to a disorder that needed specific medical or surgical treatment; congestive HF; dissecting aortic aneurysm; serum creatinine concentration at presentation of 180 micromoles/l or more; stroke or MI in the y before the study; dementia; substance abuse; any disorder prohibiting a sitting or standing position; any severe concomitant or non-CVD	Intervention: Nitrendipine ± enalapril ± HCTZ Comparator: Placebo SBP treatment/placebo difference: -8.3 mm Hg Achieved SBP in 152 mm Hg treatment arm; 160 mm Hg placebo arm	Endpoint: Dementia (defined by MMSE) Cases: • Active: 11 • Placebo: 21 • (3.8 vs. 7.7 per 1,000 pt-y) • p=0.05	Summary: Trial stopped early for positive effect on CVD outcomes.

Syst-Eur (legacy follow-up) Forette F, et al., 2002 (280) 12374512	Aim: Legacy follow-up for dementia prevention Study type: RCT with legacy follow-up Size: 2,902 pts Duration: 3.7 y	Inclusion criteria: ≥60 y Exclusion criteria: HTN 2°ary to a disorder that needed specific medical or surgical treatment; congestive HF; dissecting aortic aneurysm; serum creatinine concentration at presentation of 180 micromoles/l or more; stroke or MI in the y before the study; dementia; substance abuse; any disorder prohibiting a sitting or standing position; any severe concomitant or non-CVD	Intervention: Open label follow-up of Syst-Eur pts originally assigned to Nitrendipine ± enalapril ± HCTZ vs. placebo SBP Treatment/Placebo difference: -7.0 mm Hg Achieved SBP in 149 mm Hg treatment arm 156 mm Hg placebo arm	1° endpoint: Incidence of dementia Endpoint 2: Cognitive decline measured by MMSE Safety endpoint: N/A • Cases active: 21 • Cases placebo; 43 • Rate 3.3 vs. 7.4 cases/1,000 pt-y • 0.38 (95% CI: 0.23–0.64; p<0.001)	• This legacy follow-up with both groups (off protocol) yielded a follow-up of 3.7 y SBP was 149 mm Hg in treatment vs. 156 mm Hg in control arm Summary dementia: • Compared with the controls, long-term antihypertensive therapy reduced the risk of dementia by 55%, from 7.4–3.3 cases per 1,000 pt-y (43 vs. 21 cases; p<0.001). After adjustment for sex, age, education, and entry BP, the RH rate associated with the use of nitrendipine was 0.38; 95% CI: 0.23–0.64; p<0.001. • Lack of impact on MMSE not surprising given low sensitivity to change and large sample size
SCOPE Lithell H, et al., 2003 (290) 12714861	Aim: Incident dementia (cognitive decline as 2º outcome) Study type: RCT Size: 4,964 Duration: 3.7 y	Inclusion criteria: 70–89 y (mean 76 y) Exclusion criteria: Prevalent dementia; 2º HTN, SBP >180 mm Hg, orthostatic hypotension, need for antihypertensive treatment other than hydrochlorothiazide during run-in; stroke or MI within 6 mo; decompensated HF; serum creatinine>180 micromole/l (men) or>140 micromole/l (women);	Intervention: Candesartan ± HCTZ Comparator: Placebo ± Rx for community based SPB standard SBP Treatment/Placebo difference: -3.2 mm Hg	Endpoint: • Incident dementia • Also decline in MMSE Dementia Cases: • Active: 62 • Placebo: 57 • p=1.08 (0.75–1.56) • Cognitive decline slower in treatment group	Summary: • Mean follow-up 3.7 y. Treatment group SBP=144 mm Hg and placebo 147 mm Hg; thus, relatively minimal differences in achieved SBP between arms • There were no significant differences between the treatment groups in either dementia or cognitive decline.
PROGRESS Tzourio C, et al., 2003 (291) 12742805	AIM: Dementia with or without recurrent stroke Study type: RCT Size: 6,105 pts	Inclusion criteria: Prior stroke or TIA, any adult age	Intervention: Perindopril ± indapamide Comparator: Placebo	Endpoint: Dementia alone or with recurrent stroke Dementia cases: Only stroke-related dementia reduction of 34% (95% CI: 3–55), p=0.03.	Summary: Dementia alone was not affected in this trial. Only dementia associated with incident cerebrovascular accident

	Duration: 3.9 y		SBP Treatment/Placebo difference: -9.4 mm Hg • Achieved SBP in 138 mm Hg treatment arm 147 mm Hg placebo arm		
Hypertension in the Very Elderly Trial cognitive function assessment (HYVET-Cog) Peters R, et al., 2008 (292) 18614402	Aim: Incident dementia 2º aim Study type: RCT Size: 3,336 Duration: 2.2 y	Inclusion criteria: ≥80 y Exclusion criteria: Prevalent dementia	Intervention: Indapamide ± Perindopril Comparator: Placebo SBP treatment/placebo difference: - 15 mm Hg • Target SBP 150 mm Hg • Achieved SPB in treatment arm=146 mm Hg	1° endpoint: Incident dementia Events: • Treatment=126 • Placebo=137 • 14% reduction not significant HR: 0.86 (95% CI: 0.67–1.09)	Summary: Stopped early due to benefit in 1° outcome.

Data Supplement 57. RCTs for Patients Undergoing Surgical Procedures (Section 11.5)

Study Acronym; Author; Year Published	Aim of Study; Study Type; Study Size (N)	Patient Population	Study Intervention (# patients) / Study Comparator (# patients)	Endpoint Results (Absolute Event Rates, P value; OR or RR; & 95% CI)	Relevant 2° Endpoint (if any); Study Limitations; Adverse Events; Summary
POISE Study Group, et al., 2008 (293) 16875901	Aim: Definitively establish the effects of BB therapy in pts undergoing noncardiac surgery	Inclusion criteria: Pts undergoing noncardiac surgery with, or at risk for ASVD	Intervention: extended release metoprolol succinate Comparator: Placebo	1° endpoint: Composite of CV death, NF MI, NF cardiac arrest Results: Fewer pts taking metoprolol than placebo reached the 1° endpoint, HR: 0.84; 95% CI 0.70–0.99; p=0.0399.	Limitations: No data for pts <45 y, no data for pts undergoing cardiac surgery Conclusions: This study highlights combined benefits and

	Study type: RCT Size: 8,351			However more in metoprolol group had death HR: 1.33; 1.03–1.74; p=0.0317 and more had stroke HR: 2.17; 1.26–3.74; p=0.0053.	risk of BB regimen in noncardiac surgery and importance of pt physician discussion in deciding upon its use.

Data Supplement 58. Observational and Nonrandomized Studies for Patients Undergoing Surgical Procedures (Section 11.5)

Study Acronym; Author; Year Published	Study Type/Design; Study Size (N)	Patient Population	Primary Endpoint and Results (P value; OR or RR; & 95% CI)	Summary/Conclusion Comment(s)
Howell SJ, et al., 2004 (294) 15013960	Study type: A systematic review and meta-analysis Size: 30 observational studies	Inclusion criteria: Available crude OR for association between HTN and periop CV complications along with variance Exclusion criteria: N/A. Studies defining HTN solely on admission BP	1° endpoint: Periop CV complications Results: Pts with SBP >180 or DBP >110 mm Hg more prone to periop ischemia, arrhythmias, and CV lability OR: 1.35 (1.17–1.56).	• Pts with SBP >180 or DBP >110 mm Hg more prone to periop ischemia, arrhythmias, and CV lability OR: 1.35 (1.17–1.56). But there was no evidence that deferring surgery in such pts reduces periop risk • Conclude that planned surgery should not be deferred on basis of single admission BP. History of target organ damage more important than preop BP in predicting complications
Hart GR and Anderson RJ, 1981 (295) 6114720	Study type: Literature review Size: 72 pts BB s, 148 pts Clonidine	Inclusion criteria: Symptoms on cessation of BBs or clonidine Exclusion criteria: CP Bypass, carotid endarterectomy	1° endpoint: CV symptoms or events after abrupt cessation of BBs or clonidine Results: Symptoms of anxiety, chest pain with tachycardia, HTN, myocardial ischemia; less frequently MI may occur on abrupt withdrawal of BB or Clonidine	• Summary of case reports. CV events such as tachycardia, HTN, angina, myocardial ischemia or infarction can occur after abrupt withdrawal of BB or Clonidine. No information on incidence.
Shammash JB, et al., 2001 (296) 11136500	Study type: Prospective observational study Size: 140 pts	Inclusion criteria: Review of 140 pts undergoing vascular surgery at university hospitals Exclusion criteria: N/A	1° endpoint: In-hospital mortality Results: 50% mortality in 8 pts with BB discontinued vs. 1.5% mortality in pts with BB continued. OR: 65.0; p=0.001	• Discontinuing BB immediately after vascular surgery may increase the risk of postoperative CV morbidity and mortality

Lindenauer PK, et al., 2005 (297) 16049209	Study type: Retrospective cohort Size: 122,338 pts	Inclusion criteria: Age >18 y, major noncardiac surgery Exclusion criteria: contraindication to BB therapy	1° endpoint: In-hospital mortality Results: On BB therapy, mortality in low risk (RCRI =0) OR: 1.43 (1.29–1.58) to high risk (RCRI) OR 4 or higher OR 0.57 (0.42–0.76)	• Periop BB therapy is associated with a reduced risk of in-hospital death among high-risk, but not low-risk pts undergoing major noncardiac surgery.
Wallace AW, et al., 2010 (298) 20864832	Study type: Retrospective study Size: 38,779 operations	Inclusion criteria: All surgical pts at SF VAMC Exclusion criteria: N/A	1° endpoint: 30-d and 1-y mortality Results: Addition of BB therapy associated with reduction in 30-d OR: 0.52 (0.33–83; p=0.006) and 1-y OR: 0.64 (0.51–0.79; p<0.0001) mortality	• Periop BB therapy based upon periop Cardiac Risk Reduction protocol is associated with a reduction in 30-d and 1-y mortality. Periop withdrawal of BB is associated with increased mortality
Andersson C, et al 2014 (299) 24247428	Study type: Retrospective cohort study Size: 28,263 pts	Inclusion criteria: Pts with IHD undergoing noncardiac surgery Exclusion criteria: N/A	1° endpoint: 30-d risk of MACE and all-cause mortality Results: Among pts with HF BB Rx HR: 0.78 (0.67–90) for MACE and all-cause mortality 0.80 (0.70-0.92) all-cause mortality; and with recent Hx MI HR: 0.60 (0.42–0.86) MACE, 0.80 (0.53–1.21) all-cause mortality	• Among pts with IHD undergoing noncardiac surgery, use of BB associated with lower risk of 30 d MACE and mortality only among those with HF or recent MI
Hoeks SE, et al., 2007 (300) 16935011	Study type: Prospective survey Size: 771 pts	Inclusion criteria: Pts 18 y and older undergoing peripheral vascular surgery Exclusion criteria: N/A	1° endpoint: 1-y mortality Results: 1 y BB use had lower mortality c/w non-BB users (HR: 0.4; 95% CI: 0.2–0.7); BB withdrawal had increased mortality c/w nonusers (HR: 2.7; 95% CI: 1.2–5.9)	• Periop BB use was independently associated with lower risk of 1-y mortality while periop withdrawal was associated with higher risk of 1 y mortality
Barrett TW, et al 2007 (301) 17702038	Study type: Retrospective cohort study Size: 3,062 pts	Inclusion criteria: Pts undergoing vascular surgery Exclusion criteria: N/A	1° endpoint: Long-term mortality, median follow-up 2.7 y Results: Use of BB over study period c/w no BB reduced mortality (HR: 0.84; 95% CI: 0.73–0.96; p=0.0106)	• The use of propensity-adjusted BB c/w use reduced long-term mortality by 16%
London MJ, et al. 2013 (302) 23613075	Study type: Retrospective cohort analysis Size: 136,745 pts	Inclusion criteria: Pts undergoing major noncardiac surgery	1° endpoint: All-cause 30-d mortality and cardiac morbidity (cardiac arrest, or non-Q wave MI	• BB therapy was associated with lower rates of 30-d all-cause mortality in pts with ≥2 Revised Cardiac Index Factors

		Exclusion criteria: N/A	Results: BB exposure lower 30-d mortality in pts with 2 or more RCIF (RR: 0.63; 95% CI: 0.50–0.80; p<.001)	
Turan A, et al. 2012 (303) 22253266	Study type: Matched observational study Size: 79,228 pts	Inclusion criteria: Pts with noncardiac surgery Exclusion criteria: N/A	1° endpoint: Intraoperative and post-operative upper airway complications, in-hospital complications, and 30-d mortality Results: ACEI usage was not associated with either 30-d mortality (OR: 0.93; 95% CI: 0.73–1.19; p=0.22	• No association found between use of ACEIs and intraoperative or postoperative upper airway complications, in-hospital complications, or 30-d mortality
Rosenman DJ, et al 2008 (304) 18698608	Study type: Review of observational and randomized studies Size: 434 pts	Inclusion criteria: Adult pts, most >18 y, nonemergent surgery, using ACEI or ARA chronically Exclusion criteria: N/A	1° endpoint: Hypotension requiring vasopressors at or shortly after induction of anesthesia Results: Pts receiving preoperative ACEI or ARA more likely to develop hypotension requiring vasopressors. RR: 1.51; 95% CI: 1.14–2.01	• Pts receiving immediate preoperative ACEI or ARA were more likely to develop hypotension requiring vasopressors at or shortly after induction of anesthesia. Sufficient data were not present to assess other outcomes.
Roshanov P.S., et al. 2017 (305) 27775997	Study type: International prospective cohort Size: 14,687 pts	Inclusion criteria: Pts at least 44 y undergoing noncardiac surgery requiring overnight hospital admission Exclusion criteria: N/A	1° endpoint: 30-d all-cause death, stroke, or myocardial injury Results: ACEI/ARB users who withheld ACEI/ARB in the 24 H before surgery were less likely to suffer death, MI or stroke 0.82; 95% CI: 0.70–0.96; p=0.01	• Withholding ACEI/ARB before major noncardiac surgery was associated with a lower risk of death and postoperative vascular events.

Data Supplement 59. RCTs of Adherence and Compliance with Fixed Dose Combinations Regimens (Section 12.1.1)

Study Acronym; Author; Year Published	Aim of Study; Study Type; Study Size (N)	Patient Population	Study Intervention (# patients) / Study Comparator (# patients)	Endpoint Results (Absolute Event Rates, P value; OR or RR; & 95% CI)	Relevant 2° Endpoint (if any); Study Limitations; Adverse Events

COMFORT Matsumura K, et al., 2012 (306) 22447014	Aim: Evaluate whether a combination pill of antihypertensive drugs improves medication adherence in hypertensive pts vs. use of single agents. Study type: Multicenter, open, RCT at 29 sites in Japan. Adherence assessed by pill count. Size: 207 pts	Inclusion criteria: • ≥20 y agent with HTN • Could be treated with an ARB and diuretic Exclusion criteria: • Extremely high BP (≥200 mm Hg SBP or ≥120 mm Hg DBP) • Serious renal or liver dysfunction • Taking >4 tablets, excluding study drugs	Intervention: Combination tablet of (Losartan 50 mg/HCTZ 12.5 mg; n=103) Comparator: ARB and a thiazide diuretic as separate agents (n=104)	1° endpoint: Adherence rates as assessed by pill count 98% in both groups (p=0.89) over entire study period (0–6 mo). Safety endpoint: No differences in serious adverse events (1% vs. 1%; p=0.99) or mild adverse events (6% vs. 10%; p-0.31)	2° endpoint: No significant difference in mean SBP and DBP (0.3 and 0.1 mm Hg respectively; p=0.84/0.96). Study limitations: • Adherence rate very high for both groups and likely does not represent real-world rates. • Short duration (6 mo) and thus does not provide much information on medication persistence (continuation of drug therapy long-term) • Possible selection bias with 2 run-in phases • Different healthcare system (Japan) with medications provided through public medical insurance

Data Supplement 60. Nonrandomized Trials, Observational Studies, and/or Registries of Antihypertensive Medication Adherence Strategies (Section 12.1.1)

Study Acronym; Author; Year Published	Study Type/Design; Study Size (N)	Patient Population	Primary Endpoint and Results (include P value; OR or RR; & 95% CI)	Summary/Conclusion Comment(s)
Schroeder K, et al., 2004 (307) 15078641	Study type: Systematic review of RCTs. Size: 38 studies testing 58 different interventions containing data on 15,519 pts; 9 studies assessed simplification of dosing regimen	Inclusion criteria: • Database search for all RCTs, all languages, in Cochrane Controlled Trials Register, MEDLINE, EMBASE, and CINAHL (all y through 2002) • Population of interest were pts with essential HTN in primary care, outpatient, or community setting • Interventions aimed to increase adherence to BP-lowering medication • Reported outcome was adherence	1° endpoints: Adherence as assessed by pill counts, self-report, or electronic monitoring system Results: • 9 studies assessed simplification of dosing regimen, 7 of which compared adherence associated with frequency of administration (twice daily vs. once daily [n=6] or 3 times daily vs. twice daily [n=1]). • All studies examining effect of dosing frequency demonstrated improved adherence (range: 8%, 19.6% improvement; p<0.01 for all).	• Adherence to antihypertensive medication was significantly improved with once daily vs. multiple daily dosing regimens. Most studies used an electronic monitoring system. Limitations in the systematic review include heterogeneity in pts, interventions, and outcomes, and the majority of studies were of low quality. In addition, different definitions of adherence in the RCTs make it difficult to examine the precise relationship of adherence to BP control.

		• RCT where pt care in intervention group(s) compared to either no intervention or usual care	• Only 1 of the 7 studies demonstrated improved BP control (change in SBP 6 mm Hg; p<0.01). However, different medications used for comparison (once daily amlodipine 5 mg vs. diltiazem SR 60 mg twice daily).	
Iskedjian M, et al., 2002 (308) 11911560	Study type: Meta-analysis Size: 8 studies involving a total of 11,485 observations (1,830 for once daily dosing, 4,405 for twice daily dosing, 4,147 for >twice daily dosing, 9,655 for maximum daily dose).	Inclusion criteria: • Database search of MEDLINE, EMBASE, and International Pharmaceutical Abstracts (1980–1998) • 1° studies that compared adherence rates between different dosing regimens • Prospective trials (e.g., RCTs, cohort studies), retrospective studies, database analyses • Any published study using an instrument to measure adherence, but must have used some measurement tool in each comparison group. • Adherence rates to solid, oral dosage form for treatment of HTN of at least 10 wk duration	1° endpoints: Medication adherence rates compared between once daily and maximum daily dose, once daily and twice daily, twice daily and >twice daily Results: • Average adherence rates with once daily dosing were greater compared to maximum daily dose regimens (91.4% [SD=2.2%] vs. 83.2% [SD=3.5%]; z=4.46; p<0001.) • Average adherence rates with once daily dosing were greater compared to twice daily dosing regimens (92.7% [SD=2.3%] vs. 87.1% [SD=2.9%]; z=2.22; p=0.026.) • There was no difference in adherence rates between regimens dosed twice daily or greater than twice daily (90.8% [SD=4.7%] vs. 86.3% [SD=6.7%]; z=1.82; p=0.069).	• Antihypertensive regimens dosed once daily were associated with significantly improved adherence compared to twice daily or maximum daily dose regimens.
Claxton AJ, et al., 2001 (309) 11558866	Study type: Systematic review Size: 76 studies	Inclusion criteria: • Database search of MEDLINE, Psychinfo, HealthStar, Health & Psychological Instruments, and Cochrane library 1986–2000 • Compliance rates assessed using electronic monitoring device • Data pooled to calculate mean compliance with once daily, twice daily, 3 times daily, and 4 times daily dosing regimens	1° endpoints: Mean compliance rates by prescribed dose regimen Results: • 26 studies evaluated CVD; 17 HTN only. • For all studies, mean dose-taking compliance defined as number of appropriate doses taken during each d was 79% for once daily, 69% for twice daily, 65% for 3 times daily and 51% for 4 times daily dosing (p≤0.001 for once daily vs. 3 times daily, once daily vs. 4 times daily, and twice daily vs. 4 times daily; no statistically significant between once daily vs. twice daily or twice daily vs. 3 times daily dosing).	• Medication compliance as measured by electronic monitoring devices were improved with less frequent dosing. Once-daily dosing was associated with the greatest rate of compliance. Limitations of this analysis include heterogeneity of studies and disease states studied.

			• For 14 studies that assessed ability to take doses within prescribed time frame, once daily regimens were associated with better dose-time compliance (74% ± 31%) compared to twice daily (58% ± 23%) or 3 times daily (46% ± 8%); formal statistical analysis not conducted due to too few studies.	
Sherrill B, et al., 2011 (310) 22142349	Study type: Meta-analysis to compare health resource use cost, adherence, and persistence between groups of pts taking antihypertensives as SPCs vs. free-equivalent components. Size: 15 retrospective database studies in HTN	Inclusion criteria: • Database search of PubMed, EMBASE, The Cochrane Library, and EconLit (no limit on publication dates) • English-language publications • Clinical trial or observational study (e.g., database or registry) that compared SPC with free-equivalent components • Data on compliance, adherence, persistence, and/or health care costs and/or resource use (unadjusted cost analyses)	1° endpoints: Health care costs, adherence, persistence Results: • All-cause total costs were estimated to be lower with SPC vs. free-equivalent components free-equivalent components by $2,039 (95% CI: $1030, $3047) in 2009 dollars and HTN/CV-related costs were lower by $709 (95% CI: $117, $1,032), 2009 dollars. • Adherence as measured by MPR was greater for SPC vs. free-equivalent components (total inverse variance 13.31; 95% CI: 8.26–18.35). • Persistence to therapy was greater with SPC than free-equivalent components (risk ratio: 2.13; 95% CI: 1.11–4.09)	• Medication adherence and persistence was significantly greater with SPC than free-equivalent components. Costs were also significantly lower with SPC than with free-equivalent components. However, cost data should be interpreted with caution considering unadjusted costs were used in this meta-analysis. In addition, heterogeneity was present in analyses of each outcome. This meta-analysis did not include the observational study by Yang et al. as that study used an adjusted analysis methodology.
Yang W, et al., 2010 (311) 20629600	Study type: Observational analysis using multivariate regression-adjusted analysis to compare compliance/persistence, health care resources, and cost associated with SPC or FC antihypertensives over 6 mo study period both nationally and at the state level. Size: 579,581 pts (382,476 SPC and 197,375 FC) identified in MarketScan Database (2006–2008)	Inclusion criteria: • Pts in MarketScan Database • Diagnosis of HTN based on ICD-9 codes 401.xx and 405.xx • Pts initiated on any of the following SPC treatments or the same FC: ARB + CCB, ARB + HCTZ, ACEI + HCTZ • For SPC cohort, at least 1 prescription filled in observational window • For FC cohort, pts filled individual components separately within 15 d of each other and with 15 d overlap of supply • ≥18 y	Endpoints: • 1° outcome: Compliance and persistence with the index therapy (SPC or FC) measured by MPR within 6 mo of index date • 2° outcomes: Healthcare resource utilization (number of all-cause hospitalizations, number ER visits, number CV hospitalizations, and CV-related ER visits) and health care costs (all cause medical costs, all-prescription drug costs, CV-related medical service costs, and HTN prescription-related drug costs) Results: • Compliance nationally as assessed by MPR was improved in pts taking SPC vs. FC antihypertensives (difference=11.6%; 95% CI: 11.4%–11.7%).	• This large observational study found that medication compliance/persistence to antihypertensives was improved with SPC compared to FC using an adjusted multivariate regression model. All-cause medical costs were also decreased with the used of SPC antihypertensives, although prescription costs were greater.

		• Continuous eligibility in database for 6 mo after index date • Valid 3-digit zip code in database	• Treatment discontinuation rates were lower with SPC vs. FC antihypertensives (40.7% vs. 59.3%; 95% CI: 0.46–0.48). • There were fewer all-cause hospitalizations and ER visits in SPC vs. FC pts IRR: 0.77 (95% CI: 0.75–0.79) and IRR: 0.87 (95% CI: 0.86, 0.89), respectively. • All-cause medical costs were reduced with SPC vs. FC (-$208; 95% CI: -$302– -$114), but antihypertensive prescription costs were greater ($53; 95% CI: $51–$55).	
Gupta, et al., 2010 (312) 20026768	Study type: Meta-analysis to assess compliance, adherence, persistence, BP control, and safety with FDC antihypertensives compared to their free components Size: 15 studies (n=32,331) with ≥1 evaluated outcome; 3 cohort studies and 2 trials of compliance (n=17,999); 3 cohort studies on persistence (n=12,653); 5 trials of adverse drug effects of FDCs (n=1,775); 9 trials of BP change (n=1,671)	Inclusion criteria: • Database search of PubMed (1966–February 2008), Web of Science (1970 to April 2008), and the Cochrane Controlled Trial (1800–April 2008). • Clinical trials or cohort studies included if published in English and compared an FDC of hypertensive agents with free-drug combination of its components. • Extractable data reported including compliance (or adherence), persistence, BP-lowering effects, adverse effects	1° endpoint: • Compliance (or adherence) and persistence to therapy • BP-lowering efficacy • Adverse effects Results: • Use of FDC therapy was associated with a 21% increase in compliance, both in the cohort studies (n=5) and clinical trials (OR: 1.21; 95% CI: 1.00–1.47) and (OR: 1.21; 95% CI: 1.03–1.43). There was a 50% increase in persistence with therapy, but this was not statistically significant (OR: 1.54: 95% CI: 0.95–2.49). Analysis of all 6 retrospective cohort studies indicated that FDC therapy was associated with a 29% increase in compliance and persistence to therapy (OR: 1.29; 95% CI: 1.11–1.50). No sign of heterogeneity of publication bias. • FDC therapy was associated with a nonsignificant reduction in SBP (-4.1 mm Hg; 95% CI: -9.8–1.5 mm Hg; p=0.15) and DBP (-3.1 mm Hg; 95% CI: -7.1–0.9 mm Hg; p=0.13) compared to free-drug combinations. Strong evidence of heterogeneity but no evidence of publication bias. • FDC therapy was associated with a 20% nonsignificant decrease in adverse effects (OR:	• Use of FDC therapy is associated with significant improvements in compliance and persistence to antihypertensive therapy and possible improvement in BP control and decreased risk of adverse effects.

			0.80; 95% CI: 0.58, 1.11) compared to free-drug combinations.	
Bangalore S, et al., 2007 (313) 17679131	Study type: Meta-analysis to assess if compliance is improved with FDC therapy compared to free-drug regimens in chronic diseases including HTN, HIV, tuberculosis, and DM Size: 9 studies total (n=20,242), 4 of which were in hypertensive populations (n=17,175)	Inclusion criteria: • Database search of MEDLINE (1966–2005) • Studies included if published in English and compared an FDC with free-drug combination of its components and reported medication compliance (adherence) or persistence	1° endpoint: Compliance, considered as either adherence or persistence to medication therapy Results: • Use of FDC therapy was associated with a 26% decreased risk of noncompliance vs. free-drug combinations (pooled RR: 0.74 (95% CI: 0.69, 0.80), p<0.0001) in all diseases states. There was no evidence of heterogeneity. • In hypertensive pts, FDC was associated with 24% decreased risk of noncompliance (pooled RR: 0.76 (95% CI: 0.71, 0.81), p<0.0001) compared to free-drug regimen. There was no evidence of publication bias. • Marked heterogeneity in how compliance was measured among studies	• Use of FDC combination therapy in hypertensive pts was associated with a 24% decreased risk of noncompliance compared to use of free-drug regimens.
Kumagai N, et al., 2013 (314) 23072348	Study type: Prospective, multicenter, observational study of pts converted from free-drug combinations of an ARB and amlodipine to the same product as a FDC. Size: 196 pts	Inclusion criteria: • Outpatients with essential HTN • Self-measured home BP • Prescribed FDC of an ARB (8 mg candesartan, 80 mg valsartan, or 40 mg telmisartan) and 5 mg) and 5 mg amlodipine • Pts divided into 2 groups: Group 1 received an ARB and amlodipine in the morning as free drug combinations and Group 2 took ARB in the morning and amlodipine in the evening. After 1 mo, both groups converted to once daily FDC product. Exclusion criteria: • Severe renal of liver dysfunction • Severe HF • Prescription of time-specific packs	Endpoints: • Adherence to antihypertensive therapy as measured by self-reporting • Self-monitored BP measurements and clinical BP measurements before and after switch to FDC antihypertensive therapy. • Drug costs Results: • Self-monitoring BP measurements taken during early morning was lower with FDC compared to free-drug combinations (-5 mm Hg SBP, -2 mm Hg DBP; p<0.01 for both) • Average clinic BP was lower with FDC compared to free-drug combination (-5 mm Hg SBP, -2 mm Hg SBP; p<-0.01). • Self-reported adherence was improved with FDC vs. free-combination agents (~99% vs. 95% p<0.01). SBP was significantly lower in the group with improved adherence (~7.5 mm Hg)	• Use of FDC with an ARB and amlodipine was associated with improved adherence, lower BP, and decreased health care costs compared to free-drug combination therapy. Limitations to this study include the observational design, low numbers of pts, use of self-reported adherence, short follow-up period, non-U.S. country with a different health care system (Japan), and very high baseline rate of adherence (~95%) as well post-switch to FDC (~99%), which is not what is seen in usual practice.

			compared to the group without improved drug adherence (~4 mm Hg; p<0.05). • Healthcare costs were decreased by 31% per pt from 17,075 yen ($216.93 USD; Aug. 2012) to 11,815 yen ($150.10 USD; Aug. 2012) over the 3 mo period.	
Mazzaglia G, et al., 2009 (315) 19805653	Study type: Retrospective cohort Size: 18,046 pts	Inclusion criteria: Newly diagnosed and treated hypertensive pts ≥35 y initially free of CVD identified from Italian general pt registry. Exclusion criteria: CHD, cerebrovascular disorders, congestive HF who had been hospitalized for CABG or coronary angioplasty, those recovered in a cardiology ward before index diagnosis, incident CV event in the 180 d after index diagnosis, pts receiving nitrates	1° endpoint: Describe adherence to antihypertensive therapy and its associate with concurrent drug use, comorbidities, and CV risk factors. Adherence was estimated by calculating the proportion of days which pt had pills available during the follow-up. Results: At baseline (6 mo after index diagnosis), adherence rates were high (≥80% proportion of days covered) in 8.1% of pts, intermediate (40-79% proportion of d covered) in 4.5%, and low (≤40% proportion of d covered) in 51%. Multiple drug treatment (1.62; 95% CI: 1.43–1.83), dyslipidemia (1.52; 95% CI: 1.24–1.87), DM (1.40; 95% CI: 1.15–1.71), obesity (1.50; 95% CI: 1.26–1.78) and antihypertensive combination therapy (1.29; 95% CI: 1.15–1.45) were associated with high adherence to treatment (p<0.001).	• High adherence was associated with a 38% decreased risk of CV events compared with low adherence. Combination therapy associated with 29% improved adherence compared to monotherapy.
Jackson KC, et al., 2008 (316) 18803997	Study type: Retrospective cohort study Size: 908 pts	Inclusion criteria: • ≥18 y and diagnosis of HTN • Benefit-eligible for pharmacy claims • Antihypertensive naive (no prescription fill for antihypertensive drug ≥110 d prior to index date) • Received 1 of 3 regimens: 1.) 2 pill regimen with valsartan + amlodipine, 2.) 2-pill regimen with valsartan/HCTZ in FDC + amlodipine, 3.) 3-pill regimen with valsartan + HCTZ + amlodipine as free-drug components	1° endpoint: Adherence as measured by MPR Results: 224 pts received valsartan + amlodipine, 619 received valsartan/HCTZ + amlodipine, and 65 received valsartan + HCTZ + amlodipine. MPR ratios were 75.4% with valsartan + amlodipine, 73.1% with valsartan/HCTZ + amlodipine, and 60.5% with valsartan + HCTZ + amlodipine (p=0.005). Older age was associated with improved MPR (75.2% for those ≥64 y. vs. 69.6% for 18 to <36 y; p=0.023).	• An inverse relationship existed between the number of pills and adjusted MPR, with lower adherence noted in 3-pill regimens vs. 2-pill regimens.

		Exclusion criteria: Pts who received <2 prescription fills, did not continuously have prescriptions refilled for each medication, or switched from1 medication to another without a time overlap		
Dickson M, et al., 2008 (317) 18303937	Study type: Retrospective cohort study Size: 5,704 pts	Inclusion criteria: • 65–100 y on index date • Received at least 2 prescriptions for study drugs (amlodipine/benazepril FDC n=2336] or DHP-CCB and ACEI as separate agents [n=3368] between 1997–2001 • Continuously eligible for Medicaid for 12 mo following index date Exclusion criteria: • >180 d of hospitalization • <30 d of study drug supply • Any nursing home claims during the12 mo follow-up period	1° endpoint: Determine rates of compliance (MPR) and total costs of care (defined as sum of payments for Medicaid claims for ambulatory care, hospital claims, prescription drug claims, and Medicare ross claims) in pts treated with FDC amlodipine/benazepril vs. a DHP-CCB and ACEI prescribed as free-combination agents. Results: MPR was significantly higher for pts receiving FDC compared with free-combination therapy (63.5% vs. 49%; p<0.05). Average total cost of care (2002 value) was $3,179 with FDC compared to $5,236 with free-combination agents (p<0.0001). Multivariate regression analysis indicated an increase of 0.5% for each 1-unit increase in MPR, and for each comorbidity there was a 10.4% increase. Total cost of care for FDC group was 12.5% lower than free-combination group (p<0.003)	• FDC combination therapy with amlodipine/benazepril was associated with better compliance than a DHP-CCB and ACEI as free-combination agents. FDC was also associated with lower total costs of care.

Data Supplement 61. RCTs and Meta-analysis on Strategies to Promote Lifestyle Modification (Section 12.1.2)

Study Acronym; Author; Year Published	Aim of Study; Study Type; Study Size (N)	Patient Population	Study Intervention (# patients) / Study Comparator (# patients)	Endpoint Results (Absolute Event Rates, P value; OR or RR; & 95% CI)	Relevant 2° Endpoint; Study Limitations; Adverse Events Summary
Artinian NT, et al., 2010 (318) 20625115	Aim: To provide evidence-based recommendations on implementing PA and dietary interventions among adults,	Inclusion criteria: Included studies were limited to adult pts ≥18 y; English language; randomized controlled or quasi-experimental designs	Cognitive-behavioral strategies for promoting behavior change including Goal Setting, Self-Monitoring, Frequent and Prolonged Contact, Feedback and Reinforcement, Self-Efficacy Enhancement, Incentives, Modeling, Problem Solving, Relapse Prevention, Motivational	• Variable, too numerous to summarize here.	• Variable, too numerous to summarize here.

	including adults of racial/ethnic minority and/or socioeconomically disadvantaged populations. Study type: Literature review, evidence synthesis and recommendations using ACC/AHA evidence grading. Size: 70 studies, including 65 RCTs published from 1997–2007.	or meta-analyses; focused on the effects of diet or PA interventions on weight, BP, PA level, aerobic and resistance exercise, fitness, or consumption of calories, fruits, vegetables, fiber, total fat, saturated fat, cholesterol or salt Exclusion criteria: Feeding trials, observational studies of specific nutrients, and observational studies of aerobic capacity were excluded. Given the varying goals and outcomes of the different identified intervention studies, when possible we used a common measure of effect size to quantify and compare the success of each intervention.	Interviewing; also Intervention Processes or Delivery Strategies, including Targeting Single Behaviors Versus Multiple Behaviors, Print- or Media-Only Delivery Strategies, Group, Individual, Technology, and Multicomponent-Based Delivery Strategies, Group-Based Interventions, Individual-Focused Interventions, Computer/Technology-Based Interventions, and Multicomponent Intervention Delivery Strategies; also, Special Considerations for Interventions With Minority and Socioeconomically Disadvantaged Populations, including Setting in Which Healthcare Is Delivered, Peer/Lay Led Versus Professionally Led, Cultural Sensitivity, Literacy Level Sensitivity, Barriers to Behavior Change, and Acculturation. In addition, Fostering Initiation and Maintenance of Behavior Change. Comparator: Usual care or other comparison group		
Eckel RH, et al., 2013 (319) 24239922	Document: Guideline	Inclusion criteria: N/A Exclusion criteria: N/A	Comparator: Usual care or other comparison group	N/A	N/A

Data Supplement 62. RCTs, Meta-analyses, and Systematic Reviews on the Effect of Structured, Team-based Care Interventions for Hypertension Control (Section 12.2)

Study Acronym; Author; Year Published	Aim of Study; Study Type; Study Size (N)	Patient Population	Study Intervention (# patients) / Study Comparator (# patients)	Endpoint Results (Absolute Event Rates, P value; OR or RR; & 95% CI)	Relevant 2° Endpoint (if any); Study Limitations; Adverse Events Summary

Brownstein JN, et al., 2007 (320) 17478270	Aim: Examine the effectiveness of community health workers in supporting the care of pts with HTN Study type: Systematic review Size: 14 studies, including 8 RCTs	Inclusion criteria: Studies examining the effects of an intervention involving community health workers on the care of pts with HTN Exclusion criteria: Studies that focused exclusively on outcomes among community health workers and those involving peers who merely led support groups	Intervention: Community health workers as HTN care team members. Community health workers were broadly defined as health workers who were trained as part of an intervention, had no formal paraprofessional designation, and had relationship with the community being served. The community health workers, predominantly women, were recruited from the community, and resembled the pts in race/ethnicity and socioeconomic background. Roles included: (1) providing health education and information to pts and families; (2) ensuring that pts received services necessary for BP control; (3) providing direct services, including measuring and monitoring BP; (4) providing social support to the pts and their family members; and (5) serving as mediators between pts and the healthcare and social service systems. Comparator: Usual care or other comparison group	1° endpoint: Differences between groups in BP control groups favored community health worker groups over control and ranged from 4%–46% over 6–24 mo, across 7 RCTs; though 1 RCT showed no difference between groups. Safety endpoint: N/A	2° endpoints: • Appointment keeping: significant improvements ranging from 19%–39% (relative changes) over 12–24 mo in community health worker intervention • Adherence to medications: Range of findings included significant improvement in community health worker intervention group compared with control, between-group differences ranged from 8%–14%; 26% greater compliance among pts receiving intense community health worker interventions; and 17% significant improvement in adherence to medication with counseling by community health workers. Limitations: High level of heterogeneity of the populations, settings, interventions, and outcomes Summary: Including community health workers as part of the HTN care team resulted in significant improvements BP control, appointment keeping, and adherence to antihypertensive medications, primarily among low income, urban African Americans.

Carter BL, et al., 2009 (321) 19858431	Aim: Determine potency of interventions for BP involving nurses and pharmacists Study type: Meta-analysis Size: 37 RCTs of team-based HTN care involving nurse or pharmacist intervention	Inclusion criteria: RCT of team-based HTN care involving nurse or pharmacist intervention Exclusion criteria: Absence of above	Intervention: Team-based HTN care involving nurse or pharmacist intervention in nearly all studies involving nurses or pharmacists in clinics, consistent and dedicated case management activities were provided that were distinct from traditional nursing or pharmacist duties. However, pharmacists in community pharmacies usually had to incorporate the intervention with traditional medication dispensing functions. Comparator: Usual care	1° endpoint: OR (95% CI) for controlled BP were nurses: 1.69 (1.48, 1.93); pharmacists within primary care clinics: 2.17 (1.75, 2.68); and community pharmacists: 2.89 (1.83, 4.55). Mean (SD) reductions in SBP were: nurse intervention, 5.84 (8.05) mm Hg; pharmacists in clinics, 7.76 (7.81) mm Hg; and community pharmacists, 9.31 (5.00) mm Hg. There were no significant differences between nurse and pharmacist effects (p≥0.19). 1° Safety endpoint: N/A	• Stepwise regression was used to compare studies that included a given intervention strategy with studies that did not. Several individual components of the interventions were associated with significant reductions in mean SBP including pharmacist recommended medication to physician (-27.21 mm Hg; p=0.002), counseling about lifestyle modification (-12.63 mm Hg; p=0.03), pharmacist performed the intervention (-11.70 mm Hg; p=0.03), use of a treatment algorithm (-8.46 mm Hg; p<0.001), completion of a drug profile and/or medication history (-8.28 mm Hg; p=0.001),and the overall intervention potency score assigned by the study reviewers (p<0.001). The factors associated with a reduction in DBP were: referral was made to a specialist (-19.61 mm Hg; p=0.04), providing pt education about BP medications (-17.60 mm Hg; p=0.003), completion of a drug profile and/or medication history (-7.27 mm Hg; p=0.006), pharmacist performed the intervention (-4.03 mm Hg; p=0.04), or nurse performed the intervention (-3.94 mm Hg; p=0.04). Summary: Interventions involving pharmacists or nurses were associated with significantly improved BP control.
Clark CE, et al., 2010 (322) 20732968	Aim: Review trials of nurse led interventions for HTN in primary care to clarify the evidence base, establish whether nurse prescribing is an important intervention	Inclusion criteria: RCT of nursing intervention for HTN Exclusion criteria: Absence of above	Intervention: Interventions were categorized as nurse support delivered by either telephone, community monitoring or nurse led clinics. These were held in either primary care or 2º care. 1 study used alternate	1° endpoint: • Compared with usual care, Interventions that included a stepped treatment algorithm showed greater reductions in SBP (weighted MD -8.2 mm Hg (95% CI: -11.5– -4.9);	Summary: Nurse led interventions that included a stepped treatment algorithm or nurse led prescribing showed significantly greater reductions of SBP and DBP than usual care. Telephone monitoring was associated with higher achievement of study targets for BP. Community monitoring showed lower

	Study type: Meta-analysis Size: 32 RCTs of nursing intervention for HTN		sessions with nurses at home and in general practice. 14 studies included a stepped treatment algorithm and 9 included nurse prescribing in the protocol. Comparator: Usual care	• Nurse prescribing showed greater reductions SBP, −8.9 mm Hg, (95% CI: −12.5– -5.3), and DBP, −4.0 mm Hg, (95% CI: −5.3– -2.7); • Telephone monitoring showed higher achievement of BP targets (RR: 1.24; 95% CI: 1.08–1.43); • Community monitoring showed greater reductions in (weighted MD) SBP, −4.8 mm Hg, (95% CI: -7.0– -2.7), and DBP, −3.5 mm Hg, (95% CI: −4.5– -2.5). Safety endpoint: N/A	outcome SBP, greater reductions in SBP and DBP, and, although pooling of data was not possible, greater achievement of study BP targets.
Proia KK, et al., 2014 (323) 24933494	Aim: Examine current evidence on the effectiveness of team-based care in improving BP outcomes (update of prior systematic review) Study type: Systematic review Size: 52 studies of team-based primary care for pts with 1° HTN	Inclusion criteria: Study of team-based care; conducted in a high-income economy; reported at least 1 BP outcome of interest; included a comparison group or had an interrupted time-series design with at least 2 measurements before and after the intervention; targeted populations with 1° HTN or populations with comorbid conditions such as DM as long as the 1° focus of the intervention was BP control; and did not	Intervention: Team-based care was defined as adding new staff or changing the roles of existing staff to work with a PCP for HTN care. Team members who collaborated with pts and PCPs were predominantly nurses (28 studies); pharmacists (15 studies); both nurses and pharmacists (5 studies); or community health workers, integrated care managers, or behavioral interventionists (4 studies). Key roles included HTN medication management, active pt follow-up, and adherence and self-management support. Interventions were usually	1° endpoint: • Proportion with controlled BP: Absolute percentage point (pct pt) change in pts with controlled BP from 33 studies comparing team-based care to usual care: median effect estimate was 12 pct pts (IQI=3.2–20.8 pct pts). Most individual effect estimates in the favorable direction were significant (p<0.05). • Reduction in SBP (44 studies): The median reduction in SBP was 5.4 mm Hg (IQI=2.0–7.2 mm Hg). Most individual effect estimates were significant (p<0.05). • Reduction in DBP: The overall median reduction in	2° endpoints: Compared with pts in usual care, the proportion of pts receiving team-based care with "high" medication adherence (defined as taking medications as prescribed >80% of the time) increased by a median of 16.3 pct pts (9 studies). Stratified analyses for BP outcomes: • Team member role in medication management: Larger improvements in BP outcomes than overall estimates were demonstrated when team members could make changes to medications independent of the PCP or team members could provide medication recommendations and make changes with the PCP's approval as compared to team members providing only adherence support and information on medication and HTN.

		Exclusion criteria: Inclusion of populations with 2º HTN (e.g., pregnancy) or with a history of CVD (e.g., MI)	implemented across multiple settings in the healthcare system and in the community, where they were implemented in pharmacies and through home outreach visits. Comparator: Usual care	DBP was 1.8 mm Hg (IQI=0.7–3.2 mm Hg) from 38 studies. Safety endpoint: No harm to pts was identified from team-based care interventions in the included studies or the broader literature.	•Number of team members added: Adding ≥2 members demonstrated larger improvements in the proportion of pts with controlled BP and reduction in DBP compared to adding only 1; median reductions in SBP were similar regardless of team size. • Improvement in the proportion of pts with controlled BP was similar for studies from both healthcare and community settings. Limitations: Included studies reported significant differences in pt demographics between intervention and comparison groups at baseline, possible contamination within intervention and comparison groups, and issues related to inadequate description of populations and implemented interventions. Summary: There is strong evidence that team-based care is effective in improving BP outcomes, especially when pharmacists and nurses are part of the team.
Santschi V, et al., 2014 (324) 24721801	Aim: Assess effect of pharmacists interventions on BP and determine potential determinants of heterogeneity Study type: Meta-analysis Size: 39 RCTs were included with 14,224 pts	Inclusion criteria: RCT of pharmacist intervention delivered by a pharmacist alone or in collaboration with other healthcare professionals Exclusion criteria: Absence of above	Intervention: Pharmacist intervention delivered by a pharmacist alone or in collaboration with other healthcare professionals. Pharmacist interventions mainly included pt education, feedback to physician, and medication management. Comparator: Usual care	1º endpoint: Pharmacist interventions were associated with a large reduction in systolic and DBP of -7.6 mm Hg (95% CI: -9.0– -6.3 mm Hg) and -3.9 mm Hg (95% CI: -5– -2.8 mm Hg), respectively Safety endpoint: N/A	Summary: Pharmacist interventions, alone or in collaboration with other healthcare professionals, improved BP management

Shaw RJ, et al., 2014 (325) 25023250	Aim: Determine whether nurse-managed protocols are effective for outpatient management of pts with DM, HTN, and hyperlipidemia (HTN RCT outcomes only included here) Study type: Meta-analysis Size: 12 RCTs, with 10,362 pts, of nurse-managed protocols for outpatient management of HTN	Inclusion criteria: RCT of nurse-managed protocols for outpatient management of HTN Exclusion criteria: Absence of above	Intervention: Involvement of a registered nurse or a licensed practical nurse functioning beyond the usual scope of practice, such as adjusting medications and conducting interventions based on a written protocol. All studies used a nurse who titrated medications by following a protocol. Comparator: Usual care	1° endpoint: • SBP and DBP decreased by 3.68 mm Hg (95% CI: 1.05–6.31 mm Hg) and 1.56 mm Hg (95% CI: 0.36–2.76 mm Hg), respectively, with high variability (I^2>70%) • Nurse-managed protocols were more likely to achieve target BP than control protocols (OR: 1.41; 95% CI: 0.98–2.02), though difference was not significant and treatment effects were highly variable (Q 35.20; I^2=74%). Safety endpoint: N/A	• Included studies of low/good quality as well as moderate/fair, and high quality • Descriptions of interventions and protocols were limited Summary: Nurse-managed protocols for HTN care were associated with a mean decrease in SBP and DBP but not increase in HTN control.
Carter BL, et al., 2015 (326) 25805647	Aim: Evaluate if a physician/pharmacist collaborative model would be implemented as determined by improved BP control and whether long-term BP control could be sustained Study type: Cluster RCT Size: 32 primary care offices from 15 states enrolled 625 pts with uncontrolled HTN; 54% from racial/ethnic minority groups and 50% with DM or CKD	Inclusion criteria: Offices were required to have an onsite clinical pharmacist must have practiced in the office. Pts were eligible if they were English or Spanish speaking, ≥18 y with uncontrolled BP as measured by the SC on the baseline visit. Exclusion criteria: Absence of above	Intervention: Pharmacist conducted medical record review and a structured interview with the subject, including 1) a medication history; 2) an assessment of knowledge of BP medications, dosages and timing, and potential side effects; and 3) other barriers to BP control (e.g., side effects and nonadherence). The model recommended a telephone call at 2 wk, structured face-to-face visits at baseline, 1, 2, 4, 6, and 8 mo and additional visits if BP remained uncontrolled. The pharmacist created a care plan with recommendations for the physician to adjust	1° endpoint: BP control at 9 mo was 43% in intervention offices compared with 34% in control group (adjusted OR: 1.57 (95% CI: 0.99, 2.50), p=0.059). Safety endpoint: N/A	2° endpoints: • The adjusted difference in mean SBP/DBP between the intervention and control groups for all pts at 9 mo was −6.1/−2.9 mm Hg (p=0.002 / p=0.005, respectively), and it was −6.4/−2.9 mm Hg (p=0.009 / p=0.044, respectively) in pts from racial or ethnic minorities. • BP control and mean BP were significantly improved in pts from racial minorities in intervention offices at 18 and 24 mo (p=0.048 and p<0.001) compared with the control group. Summary: Although the results of the 1° outcome (BP control) were negative, the key 2º endpoint (mean BP) was significantly improved in the intervention group. Thus, the findings for 2º endpoints suggest that team-based care using clinical pharmacists significantly

			therapy based on the JNC-7, and the BP goals were <140/90 mm Hg for uncomplicated HTN or <130/80 mm Hg for pts with DM or CKD. The pharmacists did not follow algorithms or protocols other than JNC-7. Physicians were free to accept or to reject any recommendation or to modify the plan. Recommendations to pts focused on medication education, improving adherence, and strategies to implement lifestyle modifications. Comparator: Pharmacists in control offices were instructed to avoid intervention for study pts with HTN, but they could provide usual care curbside consultations if physicians specifically asked questions.		reduced BP in subjects from racial minority groups.

Data Supplement 63. Electronic Health Records and Patient Registries (Section 12.3.1)

Study Acronym Author Year Published	Aim of Study; Study Type; Study Size (N)	Patient Population	Study Intervention (# patients) / Study Comparator (# patients)	Endpoint Results (Absolute Event Rates, P value; OR or RR; & 95% CI)	Relevant 2° Endpoint (if any); Study Limitations; Adverse Events Summary
Bardach NS, et al., 2013 (327) 24026600	Aim: To assess the effect of P4P incentives on quality in EHR-enabled small practices in the	• Participating clinics (n=42 for each group) had similar baseline characteristics, with	• A city program provided all participating clinics with the same EHR software with decision support	• Intervention clinics had greater adjusted absolute improvement in rates of appropriate antithrombotic prescription (12.0% vs.	• Although the effect of the intervention was lower than the 10% improvement that we estimated a priori, the absolute risk reduction for BP control among pts with DM was 7.8% (NNT, 13). This

	context of an established QI initiative. Study type and size: A cluster-randomized trial of small (<10 clinicians) primary care clinics in New York City from April 2009 through March 2010.	a mean of 4,592 (median, 2,500) pts at the intervention group clinics and 3,042 (median, 2,000) at the control group clinics.	and pt registry functionalities and QI specialists offering technical assistance. • Incentivized clinics were paid for each pt whose care met the performance criteria, but they received higher payments for pts with comorbidities, who had Medicaid insurance, or who were uninsured (maximum payments: $200/pt; $100,000/clinic). Quality reports were given quarterly to both the intervention and control groups.	6.1%, difference: 6.0% (95% CI: 2.2%, 9.7%), p=0.001 for interaction term), BP control (no comorbidities: 9.7% vs. 4.3%, difference: 5.5% (95% CI: 1.6%, 9.3%), p=0.01 for interaction term; with DM: 9.0% vs. 1.2%, difference: 7.8% (95% CI: 3.2%, 12.4%), p=0.007 for interaction term; with DM or ischemic vascular disease: 9.5% vs. 1.7%, difference: 7.8% (95% CI: 3.0%, 12.6%), p=0.01 for interaction term), and in smoking cessation interventions (12.4% vs. 7.7%, difference: 4.7% (95% CI: -0.3%, 9.6%), p=0.02 for interaction term). Intervention clinics performed better on all measures for Medicaid and uninsured pts except cholesterol control, but no differences were statistically significant.	suggests that, for every 13 pts seeing incentivized clinicians, 1 more pt would achieve BP control. The 7.8% absolute change in BP control for pts with DM represents a 46% relative increase in BP control among intervention pts compared with the baseline of 16.8%. Further research is needed to determine whether this effect of the P4P intervention on BP control increases or decreases over time. However, this NNT to achieve BP control through incentives, taken together with the large relative increase in percentage of pts with BP control and the potential effect of BP control on risk of ischemic vascular events, suggests a reasonable opportunity to reduce morbidity and mortality through P4P as structured in this study. Limitations: Some clinics exited the program after randomization, with more control clinics leaving than intervention clinics. Additionally, this intervention occurred in the setting of a voluntary QI program. This may reflect a high level of intrinsic motivation to improve among practices in the study, as demonstrated by engagement with the QI specialists
Banerjee D, et al., 2012 (328) 22031453	Study type: 3-y, cross-sectional sample using pt EHRs.	• 251,590 pts ≥18 y. Underlying HTN was defined as 2 or more abnormal BP readings ≥140/90 mm Hg and/or pharmaceutical treatment. Appropriate HTN diagnosis was defined by the reporting of ICD-9 codes (401.0–	• To identify prevalent and incident HTN cases in a large outpatient healthcare system, examine the diagnosis rates of prevalent and incident HTN, and identify clinical and demographic factors	• The prevalence of HTN was 28.7%, and the diagnosis rate was 62.9%. The incidence of HTN was 13.3%, with a diagnosis rate of 19.9%. Predictors of diagnosis for prevalent HTN included older age, Asian, African American, higher BMI, and increased number	• Outpatient EHR diagnosis rates are suboptimal, yet EHR diagnosis of HTN is strongly associated with treatment. Targeted efforts to improve diagnosis should be a priority.

		401.9). Factors associated with HTN diagnosis were assessed through multivariate analyses of pt clinical and demographic characteristics.	associated with appropriate HTN diagnosis.	of ABP readings. Predictors for incident HTN diagnosis were similar. In pts with 2 or more abnormal BP readings, HTN diagnosis was associated with significantly higher medication treatment rates (92.6% vs. 15.8%; p<0.0001).	
Jaffe MG, et al., 2013 (329) 23989679	Aim: Study the effect of a multipronged, system-based, QI approach on HTN control. Study type: Observational Size: All pts with HTN in the KPNC system were included	Inclusion criteria: 350,000 pts in the KPNC system with HTN in 2001, increasing to 650,000 in 2009 Eligibility: • ≥2 HTN diagnoses coded in primary care visits in the prior 2 y • ≥1 primary care HTN diagnoses and 1 or more hospitalizations with a 1° or 2° HTN diagnosis in the prior 2 y • ≥1 primary care HTN diagnoses and 1 or more filled prescriptions for HTN medication within the prior 6 mo, or • ≥1 primary care HTN diagnoses and 1 or more stroke-related hospitalizations or a history of coronary disease, HF, or DM	Intervention: KPNC HTN Program includes: HTN registry, HTN control monitoring and feedback system, evidence-based practice guidelines, medical assistant BP recheck program, and promotion of single polypill formulation (lisinopril-hydrochlorothiazide) Comparator: Insured pts in California from 2006–2009 who were included in the HEDIS commercial measurement by California health insurance plans participating in the NCQA quality measure reporting process. A 2º comparison group was included to obtain the reported national mean NCQA HEDIS commercial rates of	1° endpoint: • HTN control rates in KPNC pts with HTN improved from 43.6% (95% CI: 39.4%, 48.6%) in 2001 to 80.4% (95% CI: 75.6%, 84.4%) by the end of the study period (p<0.001 for trend). • By comparison, national mean NCQA HEDIS commercial measurement HTN control increased from 55.4%–64.1%. • California mean NCQA HEDIS commercial rates of HTN control were similar to those reported nationally from 2006–2009 (63.4%–69.4%). 1° Safety endpoint: N/A	• A system-based approach to HTN control that includes performance measurement and QI strategies led to a significant improvement in HTN control (80%, compared to 44% baseline control) in a large population of pts in a managed care health plan.

			HTN control from 2001–2009 from health plans that participated in the NCQA HEDIS quality measure reporting process.		
Rakotz MK, et al., 2014 (330) 25024244	Aim: The goal of this study was to develop a technology-based strategy to identify pts with undiagnosed HTN in 23 primary care practices and integrate this innovation into a continuous QI initiative in a large, integrated health system.	• Of the 139,666 active adult primary care pts in these 23 practices, 47,822 already had a diagnosis of HTN, white-coat HTN, pre-HTN, or elevated BP. The 3 screening algorithms for undiagnosed HTN were applied to the remaining pts' EHRs. There were 1,586 pts who met the criteria of 1 or more of the algorithms and were therefore considered at risk for undiagnosed HTN.	• In phase 1, we reviewed EHRs using algorithms designed to identify pts at risk for undiagnosed HTN. We then invited each at-risk pt to complete an automated office BP protocol. In phase 2, we instituted a QI process that included regular physician feedback and office-based computer alerts to evaluate at-risk pts not screened in phase 1. Study pts were observed for 24 additional mo to determine rates of diagnostic resolution. After phase 1, we established a continuous QI initiative to further evaluate pts who remained at risk for undiagnosed HTN. In this 24-mo follow-up phase (phase 2), all primary care physicians received monthly lists of their pts who continued to be at risk for undiagnosed HTN.	• Of the 1,033 at-risk pts who remained active during phase 2, 740 (72%) were classified by the end of the follow-up period: 361 had HTN diagnosed, 290 had either white coat HTN, pre-HTN, or elevated BP diagnosed, and 89 had normal BP. By the end of the follow-up period, 293 pts (28%) had not been classified and remained at risk for undiagnosed HTN.	• Although we used multiple algorithms to identify pts with elevated BP readings, it is unlikely that we identified all pts with undiagnosed HTN.

			These pts were contacted by staff via telephone or letter to arrange a follow-up appointment. These pts remained on the physicians' lists until an automated office BP evaluation was completed or an ICD-9 diagnosis was entered into the chart that indicated the pt's at-risk status had been resolved. In addition, when an at-risk pt arrived for an office visit for any reason, a best practice advisory was prominently displayed on that pt's EHR screen to notify the medical assistant and physician that an automated office BP measurement was needed.		
Borden WB, et al., 2014 (331) 25447261	Aim: The purpose of this study was to examine the effect of the 2014 expert panel BP management recommendations on pts managed in U.S. ambulatory CV practices.	• Using the National CV Data Registry PINNACLE Registry, we assessed the proportion of 1,185,253 pts who met the 2003 and 2014 panel recommendations, highlighting the populations of pts for whom the BP goals changed.	N/A	• Of 1,185,253 pts in the study cohort, 706,859 (59.6%) achieved the 2003 JNC-7 goals. Using the 2014 recommendations, 880,378 (74.3%) pts were at goal. Among the 173,519 (14.6%) for whom goal achievement changed, 40,323 (23.2%) had a prior stroke or TIA, and 112,174 (64.6%) had CAD. In addition, the average Framingham risk score in	• Among U.S. ambulatory cardiology pts with HTN, nearly 1 in 7 who did not meet JNC-7 recommendations would now meet the 2014 treatment goals.

				this group was 8.5 ± 3.2%, and the 10-y atherosclerotic CVD risk score was 28.0 ± 19.5%.	

Data Supplement 64. RCTs, Meta-analyses, and Systematic Reviews on the Effect of Telehealth Interventions to Improve Hypertension Control (Section 12.3.2)

Study Acronym; Author; Year Published	Aim of Study; Study Type; Study Size (N)	Patient Population	Study Intervention (# patients) / Study Comparator (# patients)	Endpoint Results (Absolute Event Rates, P value; OR or RR; & 95% CI)	Relevant 2° Endpoint (if any); Study Limitations; Adverse Events Summary
Burke LE, et al., 2015 (332) 26271892	Aim: Review of the Scientific Literature on mHealth Tools Related to CVD Prevention Study type: Systematic review Size: 69 studies of the use of mobile technologies to reduce CVD risk behaviors	Inclusion criteria Studies of electronic and mobile technology tools in CV prevention; published from 2004–2014 in English language; enrolling adults except for smoking cessation, for which adolescents were also included; conducted in the U.S. and in developed countries. Exclusion criteria: Absence of above.	Intervention: Mobile technologies to reduce CVD risk behaviors– varied across studies Comparator: Varied across studies.	1° endpoint: Varied across studies. 1° Safety endpoint: N/A	Summary: mHealth or mobile technologies have the potential to transform the delivery of health-related messages and ongoing interventions targeting behavior change. Moreover, the use of monitoring devices (e.g., Bluetooth-enabled BP monitors and blood glucose monitors) permits the sharing of important pt self-management parameters with healthcare providers in real time and the delivery of feedback and guidance to pts when they need it. Furthermore, using mHealth tools for monitoring provides the clinician data that far exceed what can be measured in the brief clinical encounter and reflect the status of physiological or behavioral measures in the person's natural setting.
Liu S, et al., 2013 (333) 23618507	Aim: Assess the efficacy of e-counselling in reducing BP	Inclusion criteria: 1) Trials that investigated the effect of Internet-based lifestyle interventions on SBP and DBP, 2) trials that included	Intervention: Internet-based intervention as preventive e-counselling or advice using Web sites or e-mails to modify exercise or diet as a	1° endpoint: MD in BP reduction (Internet-based – usual care): SBP: -3.8 mm Hg (95% CI: -5.63– -2.06), I^2=61	• Behavior change techniques that were used in more than 50% of the successful internet-based interventions included the following: providing information on consequences of behavior in general

	Study type: Systematic review, meta-analysis Size: 13 RCTs or case-control studies	supplemental components such as mobile text messages, telephone, or in-person support, 3) intervention duration of at least 8 wk, and 4) SBP and DBP reported as 1° or 2° outcome, measured at a clinic or office. Exclusion criteria: Absence of above.	means of improving BP control. These Internet-based interventions were primarily self-guided, and access was gained via desktop computer, laptop, tablet, or smart phone. The duration of each intervention had to be at least 8 wk in order to achieve clinically meaningful outcomes, including the pt's ability to learn and adhere to complex new behaviors, and to allow for sufficient time to demonstrate a stable reduction in BP. The majority (9/13) of interventions had supplemental components that were not internet-based, such as text messages, in-person visits, and live support and 10/13 targeted both exercise and diet behaviors. Comparator: Usual care with no internet-based strategy.	DBP: -2.1 mm Hg (95% CI: -3.51– -0.65), I^2=57 Influence of intervention attributes: Intervention duration: Long-term (≥6 mo) intervention: SBP -5.8 mm Hg (95% CI: -4.3– -4.1) Short-term (<6 mo) intervention: SBP -3.47 mm Hg (95% CI: -5.2– -1.7) DBP mean reduction: results not reported, not statistically significant. # of behavior change techniques: ≥5 behavior change techniques: SBP -5.92 mm Hg (95% CI: -7.43– -4.42) / DBP -2.45 mm Hg (95% CI: -3.50– -1.41) <5 behavior change techniques: SBP -2.69 mm Hg (95% CI: -4.61– -0.78) / DBP -0.02 mm Hg (95% CI: -1.20–1.17) 1° Safety endpoint: N/A	(86%), incorporating feedback on performance (86%), prompting self-monitoring of behaviors (71%), and giving instructions on how to perform the targeted behavior change (71%). Summary: Internet-based interventions reduced SBP and DBP significantly compared to usual care. Internet-based interventions had greater effect on BP lowering if they were 1) long-term (≥ 6 mo) in duration, and 2) used >5 behavior change techniques.
Omboni S, et al., 2013 (334) 23299557	Aim: Review data from RCTs on the effectiveness of HBPT vs. usual care with respect to improvement of BP control, healthcare resources utilization and costs,	Inclusion criteria: • English language • Published up to Feb. 2012 • RCT testing HBPT vs. usual care.	Intervention: HBPT had to be based on the use of an electronic automated BP monitor storing values obtained at the pt's home and transferring them to a remote computer	1° endpoint: Compared to usual care, HBPT improved: • Office SBP by 4.71 mm Hg (95% CI: 6.18–3.24; p<0.001); I^2=52.2%; p=0.003 • Office DBP by 2.45 mm Hg (95% CI: 3.33–1.57; p<0.001); I^2=40.4%; p=0.048	Limitations: • HBPT intervention features (telemonitoring systems and self-monitoring programs) as well as inclusion criteria and demographic and clinical characteristics of the comparative groups varied across

	pt's quality of life and adverse events. Study type: Meta-analysis Size: 23 unique RCTs with 7037 pts (though not all studies reported on all outcomes of interest)	Exclusion criteria: Absence of above	through a telephone line (wired or wireless), a modem or an Internet connection. At least 1 self BP measurement had to be available for each pt in the intervention group. Comparator: Usual care	● Office BP Control (<140/90 mm Hg nondiabetic pts and <130/80 mm Hg diabetic pts): RR: 1.16 (95% CI: 1.04–1.29; p<0.001); I^2=69%; p<0.001 2° endpoint: Compared to usual care, HBPT improved: ● Greater prescription of antihypertensive medications: weighted MD 0.40 (95% CI: 0.17–0.62; p<0.001); I^2=84.2%; p<0.001 ● Lower number of office visits: weighted MD -0.18 (95% CI: -0.37–0.00); I^2=32.7%; p=0.146 ● Quality of life physical component of SF-12 or SF-36 questionnaire: weighted MD 2.78 (95% CI: 1.15–4.41); I^2=0.0%; p=0.853 ● There was no difference between HBPT and usual care in: ● Therapeutic adherence [92% HBPT vs. 90% usual care; between-group difference +1.30% (95% CI: -2.31–4.90; p=0.481), I^2=0.00%; p=0.888) ● Quality of life mental component of SF-12 or SF-36 questionnaire: weighted MD -0.11 (95% CI: -1.65–1.43); I^2=0.0%; p=0.984 Cost: ● Healthcare costs were significantly higher in the	studies and contributed to the high heterogeneity of the studies ● Most studies were powered to test differences in BP lowering, not 2º outcomes Summary: HBPT yielded greater SBP and DBP reductions and a larger proportion of pts achieving BP control than usual care. HBPT vs. usual care resulted in greater prescription of antihypertensive medications and fewer office visits but no difference in therapeutic adherence. Healthcare costs were higher with HBPT than usual care, but when HBPT-related costs were excluded, medical costs were similar between groups. Use of HBPT vs. usual care improved quality of life physical component but not mental. Authors note that the amount of office BP reduction attributable to HBPT was in line with that observed in RCTs of antihypertensive drugs compared with placebo. The estimate was also larger than that usually related to HBP self-monitoring, which speaks in favor of a possible added value of the teletransmission approach.

				HBPT group vs. usual care: weighted MD 662.92 (95% CI: 540.81–785.04) euros per pt; I^2=99.6%; p<0.001, but costs were similar when only medical costs (excluding HBPT-related costs) were considered (-12.4; 95% CI: -930.52–906.23) euros; p=0.767. Safety endpoint: No difference was observed in the risk of adverse events (RR: 1.22; 95% CI: 0.86–1.71; p=0.111)	
Verberk W, et al., 2011 (335) 21527847	Aim: Examine the usefulness of telecare for HTN management Study type: Meta-analysis Size: 9 RCTs with 2,501 pts	Inclusion criteria: 1) Published in the English language, 2) pts were diagnosed as hypertensive and performed BP self-measurement at home, 3) RCTs that compared telecare of BP with usual care, 4) data were transmitted to healthcare providers by telephone, modem, Internet, or mail, and 5) either change in BP or the number of pts that reached their target BP was an outcome and was provided in the study. Date restrictions not reported. Exclusion criteria: Absence of above	Intervention: Telecare for HTN management (treatment and/or coaching). Telecare involved a data transmission process to collect data on a pt's health status to allow remote HTN management. Procedures varied in length and frequency of contact and method of delivery (i.e., often telephone or cell phone with or without internet/computer; with or without behavioral counseling by nurse or pharmacist), often as an adjunct to "usual care" clinical visits. Comparator: Usual care	1° endpoint: Difference in BP Reduction (Telecare-Usual care): ● SBP 5.2 ± 1.5 mm Hg (95% CI: 2.31–8.07) ● DBP 2.1 ± 0.8 mm Hg (95% CI: 0.52–3.69) Safety endpoint: N/A	Limitations: Telecare intervention methods varied greatly across studies Summary: Telecare led to a greater decrease in SBP and DBP compared with usual care. Telecare seems a valuable tool to support HTN management.

Agarwal R, et al., 2011 (27) 21115879	Aim: Quantify both the magnitude and mechanisms of benefit (including effect on therapeutic inertia) of home BP monitoring on BP reduction. Therapeutic inertia was defined as no change in medications combined with uncontrolled BP. Study type: Systematic review and meta-analysis Size: 37 RCTs with 9,446 pts. Trial settings included community (n=5), dialysis unit (n=2), general practices (n=18), hospitals and general practice (n=1), and hospital-based outpatient units (n=11).	Inclusion criteria: Studies that randomized pts to control or home BP monitoring group Exclusion criteria: Absence of above	Intervention: Home BP monitoring as an adjunct to usual care for HTN Comparator: Usual care with BP monitoring in clinic	1° endpoint: Compared with usual care alone, home-based BP monitoring: ●Reduced SBP: -2.63 mm Hg (95% CI: -4.24 – -1.02) and ● Reduced DBP: -1.68 mm Hg (95% CI: -2.58– -0.79) ● Greater reduction in SBP by HBPM interventions was seen with added telemonitoring (effect size -3.20; 95% CI: -4.66– -1.73) vs. home BP monitoring (effect size -1.26; 95% CI: -2.20– -0.31; p=0.029). This finding is relevant to telemonitoring	2° endpoints: ● More frequent reductions in antihypertensive medication (presumably due to identification of white coat HTN): RR: 2.02 (95% CI: 1.32–3.11) ● Lowered therapeutic inertia (i.e., unchanged medication despite elevated BP: RR for unchanged medication 0.82 (95% CI: 0.68–0.99) Limitations: Different inclusion and exclusion criteria, different BP measurement techniques, drug titration protocols, pt populations, and duration of follow-up across studies likely introduced significant heterogeneity in effect size. Summary: Home BP monitoring leads to a small but significant reduction in SBP and DBP. Greater reduction in SBP is seen when HBPM is accompanied by specific programs to titrate antihypertensive drugs. 1 such strategy is telemonitoring, in which BP readings obtained at home are relayed to the provider who can then take appropriate action, thus reducing therapeutic inertia.

Data Supplement 65. RCTs and Observational Studies that Report on the Effect of Performance Measures and on Hypertension Control (Section 12.4.1)

Study Acronym; Author; Year Published	Aim of Study; Study Type; Study Size (N)	Patient Population	Study Intervention (# patients) / Study Comparator (# patients)	Endpoint Results (Absolute Event Rates, P value; OR or RR; & 95% CI)	Relevant 2° Endpoint (if any); Study Limitations; Adverse Events

Svetkey LP, et al., 2009 (336) 19920081	Aim: Study the effect of physician intervention and/or pt intervention vs. usual care, to assess the impact of education, monitoring, and feedback protocol to help improve HTN control Study type: Nested 2×2 RCT Size: 8 primary care practices, 32 physicians, 574 pts	Inclusion criteria: Practices: matched pairs (intervention vs. usual care) by specialty (internal medicine vs. family physician) and by pt socioeconomic mix. All physicians were invited to participate. Pt eligibility: ≥25 y, hypertensive by billing code. Pt exclusion: Self-reported CKD, CVD event within past 6 mo, pregnant, breastfeeding, or planning a pregnancy.	Physician Intervention: 18 mo of online training, self-monitoring, quarterly feedback reports. Pt Intervention: 20 weekly group sessions for 6 mo, followed by 12 monthly telephone counseling contacts, focused on weight loss, DASH dietary patter, exercise, and reduce sodium intake. Comparator: Usual care	1° endpoint: Pt intervention + physician intervention group had greatest BP lowering at 6 mo (-9.7 mm Hg ± 12.7), but at 18 mo there was no significant difference between groups. 1° Safety endpoint: N/A	• This trial suggests that pt level monitoring and feedback, in combination with physician level monitoring and feedback, provides additional 6 mo BP control above and beyond usual care. The impact of the intervention diminished after the weekly pt group sessions ended and monthly telephone calls began instead.
Jaffe MG, et al., 2013 (329) 23989679	Aim: Study the effect of a multipronged, system-based, QI approach on HTN control. Study type: Observational Size: All pts with HTN in the KPNC system were included	Inclusion criteria: 350,000 pts in the KPNC system with HTN in 2001, increasing to 650,000 in 2009 Eligibility: • ≥2 HTN diagnoses coded in primary care visits in the prior 2 y • ≥1 primary care HTN diagnoses and 1 or more hospitalizations with a 1° or 2° HTN diagnosis in the prior 2 y • ≥1 primary care HTN diagnoses and 1 or more filled prescriptions for HTN medication within the prior 6 mo, or	Intervention: KPNC HTN Program includes: HTN registry, HTN control monitoring and feedback system, evidence-based practice guidelines, medical assistant BP recheck program, and promotion of single polypill formulation (lisinopril-hydrochlorothiazide) Comparator: Insured pts in California from 2006–2009 who were included in the HEDIS commercial measurement by California health insurance plans participating in the NCQA quality measure reporting process. A 2º comparison group was included to obtain the reported national mean NCQA HEDIS commercial rates of HTN control from 2001–	1° endpoint: • HTN control rates in KPNC pts with HTN improved from 43.6% (95% CI: 39.4%–48.6%) in 2001 to 80.4% (95% CI: 75.6%–84.4%) by the end of the study period ($p<0.001$ for trend). • By comparison, national mean NCQA HEDIS commercial measurement HTN control increased from 55.4%–64.1%. • California mean NCQA HEDIS commercial rates of HTN control were similar to those reported nationally from 2006–2009 (63.4%–69.4%).	• A system-based approach to HTN control that includes performance measurement and QI strategies led to a significant improvement in HTN control (80%, compared to 44% baseline control) in a large population of pts in a managed care health plan.

		• ≥1 primary care HTN diagnoses and 1 or more stroke-related hospitalizations or a history of coronary disease, HF, or DM	2009 from health plans that participated in the NCQA HEDIS quality measure reporting process.	1° Safety endpoint: N/A	
Lusignan Sd, et al., 2013 (337) 23536132	Aim: Study the effect of an audit-based education intervention to guidelines/prompts, vs. usual care, to help improve BP control in pts with CKD Study type: Cluster RCT Size: 93 general practices (30 audit-based education intervention, 32 Guidelines/prompts, and 31 usual care)	Inclusion criteria: All pts with CKD in the participating practices	Intervention: Audit-based education vs. guidelines/prompts Comparator: Usual care	1° endpoint: SBP was significantly lower in the audit-based education group (-2.41 mm Hg; 95% CI: 0.59–4.29). There was no significant change in BP in the other 2 groups. 1° Safety endpoint: No reports of harm.	• This trial suggests that an intervention that includes specific performance and feedback reports improves BP control in pts with CKD, compared to usual care. To the contrary, the use of practice guidelines and prompts did not improve BP control compared to usual care.

Data Supplement 66. RCTs, Meta-analyses, and Systematic Reviews on Quality Improvement Strategies on Hypertension Treatment Outcomes (Section 12.4.2)

Study Acronym; Author; Year Published	Aim of Study; Study Type; Study Size (N)	Patient Population	Study Intervention (# patients) / Study Comparator (# patients)	Endpoint Results (Absolute Event Rates, P value; OR or RR; & 95% CI)	Relevant 2° Endpoint (if any); Study Limitations; Adverse Events Summary
Walsh JM, et al., 2006 (338) 16799359	Aim: Assess the effectiveness of QI strategies in lowering BP Study type: Systematic review	Inclusion criteria: Trials, controlled before–after studies, and interrupted time series evaluating QI interventions targeting HTN control and reporting BP outcomes.	Intervention: QI interventions targeting some component of provider behavior or organizational change to improve HTN control Comparator: Contemporaneous	• The majority of articles described interventions consisting of more than 1 strategy with the median number of QI strategies per comparison =3. Results are organized below by type of QI strategy. • Variety of strategies used	Limitations: Studies varied by design, population, sample size, setting, and methodological quality. Definition of each QI strategy varied across studies. Few studies assessed a single QI strategy; because most studies included more than 1 QI strategy, it could not be discerned which individual QI strategies had the

	Size: 44 articles reporting 57 comparisons	Exclusion criteria: Articles focusing only on 2º HTN or specialized subpopulations (e.g., HTN in pts with alcoholism)	observation of cohorts differing primarily with respect to exposure to the QI intervention	SBP/DBP, median reduction: 4.5 mm Hg (IQR: 1.5–11.0)/ 2.1 mm Hg (IQR: -0.2–5.0) SBP/DBP control: 16% (IQR: 10.3–32.2)/ 6% (IQR: 1.5–17.5) • Provider reminders SBP/DBP, median reduction: 1.2 mm Hg (IQR: 1.0–1.9)/ 0.3 mm Hg (IQR: -0.2–1.7) DBP control: 5% (IQR: 2.0–7.0) • Facilitated relay of clinical data SBP/DBP, median reduction: 8.0 mm Hg (IQR: 2.5–12.3)/ 1.8 mm Hg (IQR: -0.1–4.5) SBP/DBP control: 25% (IQR: 17.0–34.2)/ 2% (IQR: 1.6–5.0) • Audit and feedback SBP/DBP, median reduction: 1.5 mm Hg (IQR: 1.2–1.7)/ 0.6 mm Hg (IQR: 0.4–1.0) SBP/DBP control: -3.5% (IQR: -5.7–1.4)/ 2.0% (IQR: 1.7–4.3) • Provider education SBP/DBP, median reduction: 3.3 mm Hg (IQR: 1.2–5.4)/ 0.6 mm Hg (IQR: -0.7v3.4) SBP/DBP control: 11% (IQR: 1.4–13.1)/ 4% (IQR: 1.7–11.3) • Pt education SBP/DBP, median reduction: 8.1 mm Hg (IQR: 3.3–11.8)/ 3.8 mm Hg (IQR: 0.6–6.7) SBP/DBP control: 19% (IQR: 11.4–33.2)/ 17% (IQR: 11.4–24.5) • Promotion of self–management	greatest effects or whether certain combinations of individual QI strategies were more “potent” than others. Summary: QI strategies are associated with improved HTN control. QI strategies improved SBP and the proportion of pts achieving SBP control and had a more modest effect on DBP and the proportion of pts achieving DBP control. Team change (i.e., a focus on HTN by someone in addition to the pt’s physician) had the largest effect on both SBP and DBP. All of the strategies assessed may be beneficial in terms of clinically meaningful reductions in BP under some circumstances and in varying combinations.

				SBP/DBP, median reduction: 3.3 mm Hg (IQR: 2.6–10.1)/ 2.8 mm Hg (IQR: 0.4–6.7) SBP/DBP control: 13%/ 9% (IQR: 5.3–11.4) • Pt reminders SBP/DBP, median reduction: 3.3 mm Hg (IQR: 2.3–4.5)/ 0.4 mm Hg (IQR: -2.4–5.0) DBP control: 2% (IQR: 1.1–9.4) • Team change SBP/DBP, median reduction: 9.7 mm Hg (IQR: 4.2–14.0) (p<0.05)/ 4.2 mm Hg (IQR: 0.2–6.8) (p<0.05) SBP/DBP control: 22% (IQR: 9.0–33.8)/ 17% (IQR: 5.7–24.5) • Financial incentives SBP/DBP, median reduction: -13.3 mm Hg/ 0.0 mm Hg (IQR: -2.0–2.5) DBP control: 4% (IQR: -1.1–9.4) Safety endpoint: N/A	
Carter BL, et al., 2009 (321) 19858431	Aim: Determine potency of interventions for BP involving nurses and pharmacists Study type: Meta-analysis Size: 37 RCTs of team-based HTN care involving nurse or	Inclusion criteria: RCT of team-based HTN care involving nurse or pharmacist intervention Exclusion criteria: Absence of above	Intervention: Team-based HTN care involving nurse or pharmacist intervention In nearly all studies involving nurses or pharmacists in clinics, consistent and dedicated case management activities were provided that were distinct from traditional nursing or	1° endpoint: • OR (95% CI) for controlled BP were: nurses: 1.69 (1.48, 1.93); pharmacists within primary care clinics: 2.17 (1.75, 2.68); and community pharmacists: 2.89 (1.83, 4.55). • Mean (SD) reductions in SBP were: nurse intervention: 5.84 (8.05) mm Hg; pharmacists in clinics: 7.76(7.81) mm Hg; and	• Stepwise regression was used to compare studies that included a given intervention strategy with studies that did not. Several individual components of the interventions were associated with significant reductions in mean SBP including pharmacist recommended medication to physician (-27.21 mm Hg; p=0.002), counseling about lifestyle modification (-12.63 mm Hg; p=0.03), pharmacist performed the intervention (-11.70 mm Hg; p=0.03), use of a treatment

	pharmacist intervention		pharmacist duties. However, pharmacists in community pharmacies usually had to incorporate the intervention with traditional medication dispensing functions. Comparator: Usual care	community pharmacists: 9.31 (5.00) mm Hg. • There were no significant differences between nurse and pharmacist effects (p≥0.19). Safety endpoint: N/A	algorithm (-8.46 mm Hg; p<0.001), completion of a drug profile and/or medication history (-8.28 mm Hg; p=0.001), and the overall intervention potency score assigned by the study reviewers (p<0.001). The factors associated with a reduction in DBP were: referral was made to a specialist (−19.61 mm Hg; p=0.04), providing pt education about BP medications (-17.60 mm Hg; p=0.003), completion of a drug profile and/or medication history (-7.27 mm Hg; p=0.006), pharmacist performed the intervention (-4.03 mm Hg; p=0.04), or nurse performed the intervention (-3.94 mm Hg; p=0.04). Summary: Interventions involving pharmacists or nurses were associated with significantly improved BP control.
Agarwal R, et al., 2011 (27) 21115879	Aim: Quantify both the magnitude and mechanisms of benefit (including effect on therapeutic inertia) of home BP monitoring on BP reduction. Therapeutic inertia was defined as no change in medications combined with uncontrolled BP. Study type: Systematic Review and Meta-analysis	Inclusion criteria: Studies that randomized pts to control or home BP monitoring group Exclusion criteria: Absence of above	Intervention: Home BP monitoring as an adjunct to usual care for HTN Comparator: Usual care with BP monitoring in clinic	1° endpoint: Compared with usual care alone, home-based BP monitoring: • Reduced SBP: -2.63 mm Hg (95% CI: -4.24– -1.02) and • Reduced DBP: -1.68 mm Hg (95% CI: -2.58– -0.79) • Greater reduction in SBP by home BP monitoring interventions was seen with added telemonitoring effect size: -3.20 (95% CI: -4.66– -1.73) vs. home BP monitoring effect size: -1.26; 95% CI: -2.20– -0.31; p=0.029. Safety endpoint: N/A	2° endpoints: • More frequent reductions in antihypertensive medication (presumably due to identification of white coat HTN): RR: 2.02; 95% CI: 1.32–3.11 • Lowered therapeutic inertia (i.e., unchanged medication despite elevated BP: RR for unchanged medication 0.82 (95% CI: 0.68–0.99) Limitations: Different inclusion and exclusion criteria, different BP measurement techniques, drug titration protocols, pt populations, and duration of follow-up across studies likely introduced significant heterogeneity in effect size.

	Size: 37 RCTs with 9446 pts. Trial settings included community (n=5), dialysis unit (n=2), general practices (n=18), hospitals and general practice (n=1), and hospital-based outpatient units (n=11).				Summary: ● Home BP monitoring leads to small but significant reduction in SBP and DBP. Greater reduction in SBP is seen accompanied by specific programs to titrate antihypertensive drugs. One such strategy is telemonitoring, in which BP readings obtained at home are relayed to the provider who can then take appropriate action.
Anchala R, et al., 2012 (339) 23071713	Aim: Evaluate the role of decision support systems in prevention of CVD among pts Study type: Systematic review and meta-analysis Size: 10 studies with 5 studies reporting effect on BP (BP results only reported here)	Inclusion criteria: 1) Cross-sectional, case control, cohort, and RCTs, 2) Studies conducted among adult pts ≥18, 3) studies on prevention of CV disorders (MI, stroke, CHD, peripheral vascular disorders and HF) and management of HTN, 4) studies on interventions including: decision support systems, clinical decision supports systems, computerized decision support systems, clinical decision making tools and medical decision making Exclusion criteria: Absence of above	Intervention: Decision support systems, clinical decision supports systems, computerized decision support systems, clinical decision making tools and medical decision making in the management of HTN Comparator: Usual care	1° endpoint: ● Reduction in SBP (5 studies): 2.32 mm Hg (95% CI: -3.96– -0.69) ● Reduction in DBP (2 studies): 0.42 mm Hg (95% CI: -2.30–1.47) Safety endpoint: N/A	Limitations: ● Small number of studies of varied quality. ● Interventions varied across studies. Summary: Clinical decision support resulted in modest reduction of SBP and no significant reduction of DBP.
Proia KK, et al., 2014 (323) 24933494	Aim: Examine current evidence on the effectiveness of team-based care in improving BP outcomes (update of	Inclusion criteria: Study of team-based care; conducted in a high-income economy; reported at least 1 BP outcome of interest; included a comparison group or had	Intervention: Team-based care was defined as adding new staff or changing the roles of existing staff to work with a PCP for HTN care. Team members who	1° endpoint: ● Proportion with controlled BP: Absolute percentage point (pct pt) change in pts with controlled BP from 33 studies comparing team-based care to usual care: median effect	2° endpoints: Compared with pts in usual care, the proportion of pts receiving team-based care with "high" medication adherence (defined as taking medications as prescribed >80% of the time) increased by a median of 16.3 pct pts (9 studies).

	prior systematic review) Study type: Systematic review Size: 52 studies of team-based primary care for pts with 1° HTN	an interrupted time-series design with at least 2 measurements before and after the intervention; targeted populations with 1° HTN or populations with comorbid conditions such as DM as long as the primary focus of the intervention was BP control; and did not Exclusion criteria: Inclusion of populations with 2º HTN (e.g., pregnancy) or with a history of CVD (e.g., MI)	collaborated with pts and PCPs were predominantly nurses (28 studies); pharmacists (15 studies); both nurses and pharmacists (5 studies); or community health workers, integrated care managers, or behavioral interventionists (4 studies). Key roles included HTN medication management, active pt follow-up, and adherence and self-management support. Interventions were usually implemented across multiple settings in the healthcare system and in the community, where they were implemented in pharmacies and through home outreach visits. Comparator: Usual care	estimate was 12 pct pts (IQI=3.2–20.8 pct pts). Most individual effect estimates in the favorable direction were significant ($p<0.05$). • Reduction in SBP (44 studies): The median reduction in SBP was 5.4 mm Hg (IQI=2.0–7.2 mm Hg). Most individual effect estimates were significant ($p<0.05$). • Reduction in DBP: The overall median reduction in DBP was 1.8 mm Hg (IQI=0.7–3.2 mm Hg) from 38 studies. Safety endpoint: No harm to pts was identified from team-based care interventions in the included studies or the broader literature.	Stratified analyses for BP outcomes: • Team member role in medication management: Larger improvements in BP outcomes than overall estimates were demonstrated when team members could make changes to medications independent of the PCP or team members could provide medication recommendations and make changes with the PCP's approval as compared to team members providing only adherence support and information on medication and HTN. • Number of team members added: Adding ≥2 members demonstrated larger improvements in the proportion of pts with controlled BP and reduction in DBP compared to adding only 1; median reductions in SBP were similar regardless of team size. • Improvement in the proportion of pts with controlled BP was similar for studies from both healthcare and community settings. Limitations: Included studies reported significant differences in pt demographics between intervention and comparison groups at baseline, possible contamination within intervention and comparison groups, and issues related to inadequate description of populations and implemented interventions. Summary: There is strong evidence that team-based care is effective in

					improving BP outcomes, especially when pharmacists and nurses are part of the team.

Data Supplement 67. Nonrandomized Trials, Observational Studies, and/or Registries of Effect of Quality Improvement Strategies on Hypertension Treatment Outcomes (Section 12.4.2)

Study Acronym; Author; Year Published	Study Type/Design; Study Size (N)	Patient Population	Primary Endpoint and Results (include P value; OR or RR; & 95% CI)	Summary/Conclusion Comment(s)
Thomas KL, et al., 2014 (340) 25351480	Study type: Community-based HTN QI program [multifaceted BP control program using a web-based health portal (Heart360), community health coaches, and PA guidance] to improve HTN control in a diverse community setting Design: Pre-post study without a concurrent control Size: 1756 pts with HTN from 8 clinics: • Median age, 60 y • Female, 65.6% • African American, 76.1%	Inclusion criteria: Individuals from pt sites >18 y with a previous billing diagnosis of HTN (ICD-9 code 401.X) or a previous clinical diagnosis of HTN in the medical record. Exclusion criteria: Did not reside in Durham County or had a neurocognitive disorder that prevented enrollment	1° endpoint: 1) Difference in SBP and DBP from enrollment (BP obtained in the clinic at enrollment) to the last BP as measured in clinic within 6 mo after enrollment, 2) proportion of pts that achieved BP <140/90 mm Hg by last clinic visit within 6 mo, and 3) proportion of pts with BP <140/90 mm Hg or drop in SBP ≥10 mm Hg by last visit relative to their enrollment BP. Results: • Mean change in BP: -4.7 mm Hg (SD ± 21.4) / -2.8 mm Hg (SD ± 11.8) after 6 mo • BP control (<140/90 mm Hg) rate: Increased from 51% at baseline to 63% at 6 mo • Proportion with BP<140/90 or ≥10 mm Hg decrease in SBP at 6 mo was 69% • Among those who were in tiers 1 (BP=140/90–159/99 mm Hg) and 2 (BP≥159/99 mm Hg) at enrollment (n=889), BP change was -8.8 mm Hg (SD ± 15.8) / -5.0 mm Hg (SD ± 10.0) and -23.7 mm Hg (SD ± 26.5) / -10.1 mm Hg (SD ± 14.1), respectively.	Summary: A multicomponent-tiered HTN program that included team-based care with PAs and community health coaches was associated with improved BP control in a diverse community-based population. Though the web-based approach presented technical challenges for some pts, there was a direct association between higher use of Heart360 and larger recorded BP declines as entered into Heart360. This provides some indirect evidence that those pts who were more engaged with their BP self-monitoring achieved better BP control.
Jaffe MG, et al., 2013 (329) 23989679	Study type: Quasi-experimental evaluation of multi-faceted QI program that included 1) Health system-wide HTN registry, 2) HTN control rates (with provider audit and feedback), 3)	Inclusion criteria: Pts identified with HTN within an integrated health care delivery system (KPNC) from 2001–2009	1° endpoint: BP control using NCQA HEDIS measures Results: BP control increased from 44%–80% from 2001–2009 with the KPNC QI program compared to 55.4% to 64.1% for the national mean and 63.4% to	Summary: Implementation of a large-scale HTN program was associated with a significant increase in HTN control compared with state and national control rates.

	evidence-based practice HTN guideline, 4) medical assistant visits for follow-up measurements with no pt copayment for these follow-up visits, and 5) promotion of single-pill combination therapy. Design: Contemporaneous control group external to healthcare system Size: Kaiser HTN registry increased from 349,937 pts in 2001 to 652,763 in 2009.	Exclusion criteria: None stated	69.4% for the Ca mean from 2006 to 2009 NCQA HEDIS commercial measurement comparison groups.	

Data Supplement 68. RCTs Comparing Financial Incentives (Section 12.5)

Study Acronym; Author; Year Published	Aim of Study; Study Type; Study Size (N)	Patient Population	Study Intervention (# patients) / Study Comparator (# patients)	Endpoint Results (Absolute Event Rates, P value; OR or RR; & 95% CI)	Relevant 2° Endpoint (if any); Study Limitations; Adverse Events Summary
Peterson LA, et al., 2013 (341) 24026599 Hysong, SJ, et al., 2012 (342) 23145846	Aim: To test the effect of explicit financial incentives to reward guideline recommended HTN care. Study type: Cluster randomized trial of 12 VA Outpatient clinics with 5 performance periods and a 12-mo washout Size: 83 PCPs and 42 nonphysician	• Study population was providers, not pts: a minimum of 5 fulltime PCPs from 12 hospital-based primary care clinics in 5 A Networks. Then, the clinics were randomized to 1 of 4 study groups, 1) physician level (individual) incentives, 2) practice-level incentives, 3) physician-level plus practice-level (combined) incentives, and 4) no incentives (control).	Interventions: Education, Financial Incentives, Audit and Feedback; Intervention group pts received up to 5 incentive payments in their paychecks ~every 4 mo and were notified each time a payment was posted. Comparator: 4 different groups,1 paid incentives at the practice level,1 paid incentives at the physician level, 1 paid	1° endpoint: In unadjusted analyses, the percentage of pts either with controlled HTN or receiving an appropriate response increased for each incentive group between baseline and final performance period, 75% to 84% in the individual group, 80% to 85% in the practice group, and 79% to88% in the combined group. Performance did not change in control group, 86%. The adjusted estimated ab-solute change over the study of the pts meeting the combined BP or	Summary: • Mean (SD) total payments over the study were $4,270 ($459), $2672 ($153), and $1,648 ($248) for the combined, individual, and practice-level interventions, respectively. Change in BP control or appropriate response to uncontrolled BP compared with the control group was significantly greater only in the individual incentives group. Change in guideline-recommended medication use was not significant compared with the control group. The effect of the incentive was not sustained after a washout.

	personnel (e.g., nurses, pharmacists). Main Outcomes and Measures: Among a random sample, number of pts achieving guideline-recommended BP thresholds or receiving an appropriate response to uncontrolled BP, number of pts prescribed guideline-recommended medications, and number who developed hypotension.		for both levels and the 4th paid no incentives. (19–20 physicians in each group)	appropriate response measure was 8.84% (95% CI: 4.20%–11.80%) for the individual group, 3.70% (95% CI: 0.24%, 7.68%) for the practice group, 5.54% (95% CI: 1.92%–9.52%) for the combined group, and 0.47% (95% CI: −3.12%–4.04%) for the control group. The adjusted estimated absolute difference over the study in the change between the proportion of the physician's pts achieving BP control or receiving an appropriate response for the individual incentive group and the controls was 8.36% (95% CI: 2.40%–13.00%; p=0.005). 1° Safety endpoint: N/A	• Financial incentives may constitute an insufficiently strong intervention to influence goal commitment when providers attribute performance to external forces beyond their control.
Karunaratne K, et al., 2013 (343) 23658247	Aim: The aim of this study was to evaluate the effectiveness of renal indicators outlined in P4P on the management of HTN in primary care. To estimate the cost implications of the resulting changes in prescribing patterns of antihypertensive medication following introduction of such indicators. Study type: Prospective cohort study using a large primary care database.	Inclusion criteria: A total of 10,040 pts had confirmed stage 3–5 CKD in the 2 y pre-QOF and formed the study cohort. Exclusion criteria: None	Intervention: The implementation of national estimated GFR reporting and the inclusion of renal-specific indicators in a primary care P4P system since April 2006 has promoted identification and better management of risk factors related to CKD. In the UK, the P4P framework is known as the QOF. Comparator: N/A	• Mean age of the cohort at the start of the study period was 64.8 y, 55% were female. In those pts with stage 3–5 CKD 83.9% were hypertensive, defined by a pre-P4P BP of >140/85 or currently taking antihypertensive medication. The proportion of pts with CKD 3–5 attaining the BP target of 145/80 increased from 41.5% in the pre-QOF period to 50.0% in the post-QOF period. This increase was even more marked for those with HTN in the pre-QOF period (28.8%–45.1%). In the hypertensive pts, mean BP fell from 146/79 mm Hg to 140/76 in the first 2 y post-P4P [p<0.01, analysis of variance].	Summary: Population BP control has improved since the introduction of P4P renal indicators, and this improvement has been sustained. This was associated with a significant increase in the use of antihypertensive medication, resulting in increased prescription cost. Longer-term follow-up will establish whether or not this translates to improved outcomes in terms of progression of CKD, CVD and pt mortality.

	This cohort was taken from a database collated as part of a clinical decision support system used to assist the management of CKD in primary care. Size: 90,250 pts on general practitioner registers with a valid serum creatinine estimation in the 6-y study period. A total of 10 040 pts had confirmed stage 3–5 CKD in the 2 y pre-QOF and formed the study cohort.			BP reduction was sustained in the last 2 y of the study, 139/75 ($p<0.01$, analysis of variance). The proportion of hypertensive pts taking ACEIs or angiotensin blockers increased, this was also sustained in the third time period. An increase in the prescribing of diuretics, CCBs and BBs was also observed. The additional cost of increased prescribing was calculated to be euro 25.00 per hypertensive pt based on GP prescription data.	
Serumaga B, et al., 2011 (344) 21266440	Aim: The aim of this study was to evaluate the effectiveness of renal indicators outlined in P4P on the management of HTN in primary care. To estimate the cost implications of the resulting changes in prescribing patterns of antihypertensive medication following introduction of such indicators. Study type: Interrupted time series study	Inclusion criteria: Pts with HTN diagnosed between Jan. 2000–Aug. 2007. Exclusion criteria: None	Intervention: The UK P4P incentive (the Quality and Outcomes Framework), which was implemented in April 2004 and included specific targets for general practitioners to show high quality care for pts with HTN (and other diseases). Comparator: None	• After accounting for secular trends, no changes in BP monitoring: level change: 0.85 (95% CI: −3.04–4.74), p=0.669 and trend change: −0.01, (95% CI: −0.24–0.21), p=0.615, control: −1.19 (95% CI: -2.06–1.09), p=0.109 and −0.01 (95% CI: −0.06–0.03), p=0.569, or treatment intensity; 0.67: (95% CI: −1.27–2.81), p=0.412 and 0.02 (95% CI: −0.23–0.19, p=0.706 were attributable to P4P. P4P had no effect on the cumulative incidence of stroke, MI, renal failure, HF, or all-cause mortality in both treatments experienced and newly treated subgroups.	Summary: Good quality of care for HTN was stable or improving before P4P was introduced. P4P had no discernible effects on processes of care or on HTN related clinical outcomes. Generous financial incentives, as designed in the UK P4P policy, may not be sufficient to improve quality of care and outcomes for HTN and other common chronic conditions.

	Size: 470,725 pts with HTN diagnosed between Jan 2000–Aug 2007.				
Bardach NS, et al., 2013 (327) 24026600	Aim: To assess the effect of P4P incentives on quality in EHR-enabled small practices in the context of an established QI initiative. Study Type & Size: A cluster-randomized trial of small (<10 clinicians) primary care clinics in New York City from April 2009–March 2010.	• Participating clinics (n=42 for each group) had similar baseline characteristics, with a mean of 4,592 (median, 2,500) pts at the intervention group clinics and 3,042 (median, 2,000) at the control group clinics.	• A city program provided all participating clinics with the same EHR software with decision support and pt registry functionalities and QI specialists offering technical assistance. • Incentivized clinics were paid for each pt whose care met the performance criteria, but they received higher payments for pts with comorbidities, who had Medicaid insurance, or who were uninsured (maximum payments: $200/pt; 100,000/clinic). Quality reports were given quarterly to both the intervention and control groups.	• Intervention clinics had greater adjusted absolute improvement in rates of appropriate antithrombotic prescription 12.0% vs. 6.1%, difference: 6.0% (95% CI: 2.2%–9.7%; p=0.001 for interaction term), BP control (no comorbidities): 9.7% vs. 4.3%, difference: 5.5% (95% CI: 1.6%–9.3%; p=0.01 for interaction term); with DM: 9.0% vs. 1.2%, difference: 7.8% (95% CI: 3.2%–12.4%; p=0.007 for interaction term); with DM or ischemic vascular disease: 9.5% vs. 1.7%, difference: 7.8% (95% CI: 3.0%–2.6%; p=0.01 for interaction term), and in smoking cessation interventions (12.4% vs. 7.7%), difference: 4.7% (95% CI: −0.3%–9.6%; p=0.02 for interaction term). Intervention clinics performed better on all measures for Medicaid and uninsured pts except cholesterol control, but no differences were statistically significant.	Summary: In our study, although the effect of the intervention was lower than the 10% improvement that we estimated a priori, the absolute risk reduction for BP control among pts with DM was 7.8% (NNT, 13). This suggests that, for every 13 pts seeing incentivized clinicians, 1 more pt would achieve BP control. The 7.8% absolute change in BP control for pts with DM represents a 46% relative increase in BP control among intervention pts compared with the baseline of 16.8%. Further research is needed to determine whether this effect of the P4P intervention on BP control increases or decreases over time. However, this NNT to achieve BP control through incentives, taken together with the large relative increase in percentage of pts with BP control and the potential effect of BP control on risk of ischemic vascular events, suggests a reasonable opportunity to reduce morbidity and mortality through P4P as structured in this study. Limitations: Some clinics exited the program after randomization, with more control clinics leaving than intervention clinics. Additionally, this intervention occurred in the setting of a voluntary QI program. This may reflect a high level of intrinsic

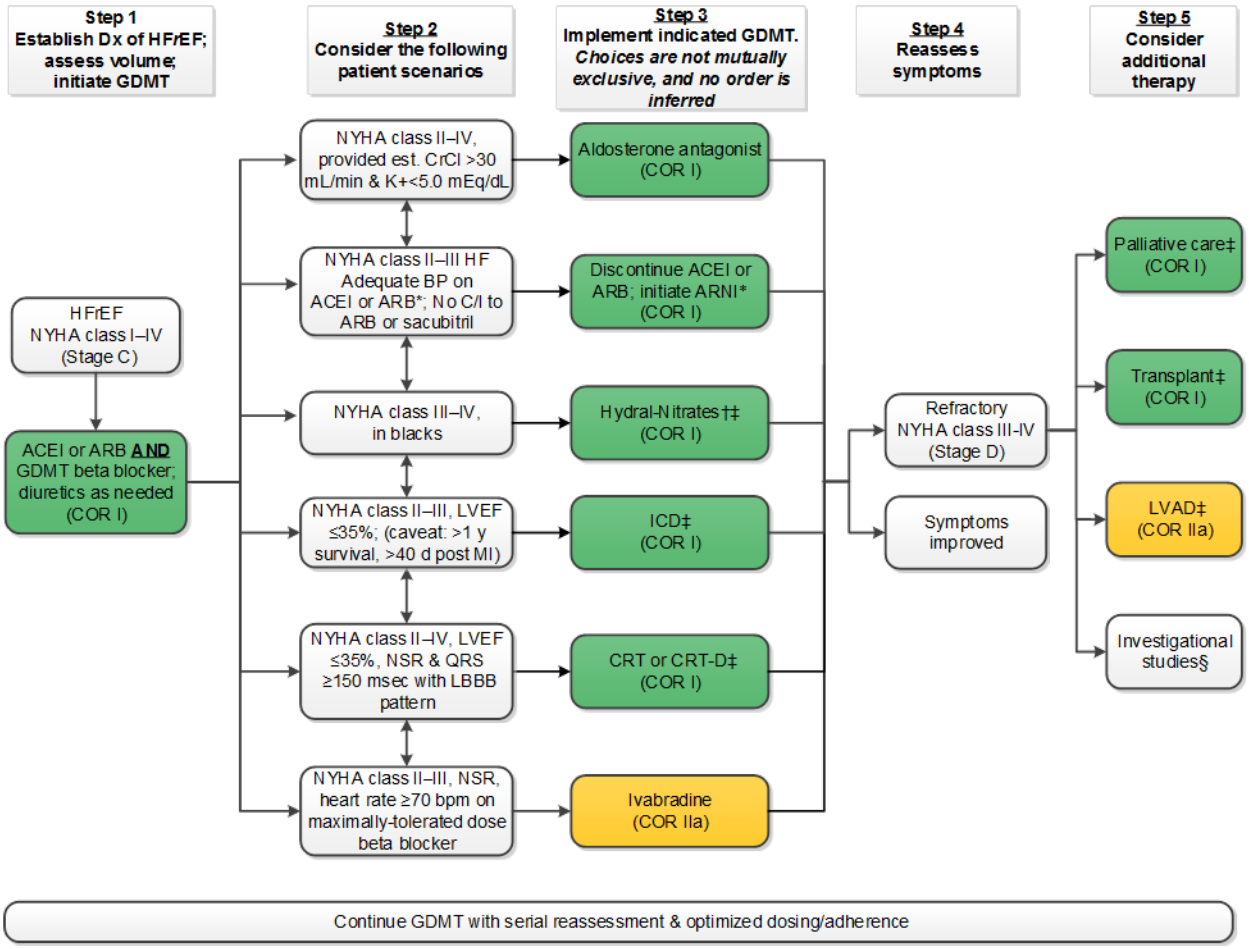
					motivation to improve among practices in the study, as demonstrated by engagement with the QI specialists
Maimaris W, et al., 2013 (345) 23935461	Aim: To assess strategies for influencing HTN care including procurement of essential medications, the existence of simple national guidelines for HTN management, introduction of financial incentives for health care practitioners to diagnose or treat HTN, and enhanced health insurance coverage. Study type: Systematic review examining the effect of national or regional health system arrangements on HTN care and control	Study selection criteria based on: 1) HTN awareness. Defined as pts with clinically measured hypertensives who have been diagnosed by a health care professional as hypertensive. 2) HTN treatment. Defined as the use of at least 1 antihypertensive medication in a pt with known HTN. 3) Antihypertensive medication adherence. Defined as consistently taking the antihypertensive medication regimen as prescribed by the health care provider. 4) HTN control: defined as the achievement of BP<140/90 mm Hg (or other explicitly defined threshold) in individuals being treated for HTN, or, alternatively, measured by the mean BP amongst individuals with HTN.	• The screening process is described using an adapted PRISMA flowchart. 5,514 articles were screened by title and abstract for inclusion. The full text of 122 of the 5,514 articles was obtained and assessed for eligibility. 53 studies met eligibility criteria for this review. 51 of the included studies were quantitative and 2 were qualitative. Of the 51 quantitative studies, 1 was an RCT; 12 were cohort studies, 2 of which were retrospective; 3 were case-control studies; 32 were cross-sectional studies; and 3 were ecological studies. 42 of the 53 studies (79%) were carried out in countries classified by the World Bank as high-income countries, 36 of which were in the U.S. 6 studies were carried out in upper middle-income countries, 3 in lower middle-income	• Health insurance status: 15 cross-sectional studies reported comparisons of HTN outcomes in insured and uninsured pts. 8 of these 15 studies reported that insurance was associated with improved HTN treatment, control or medication adherence. The 7 other cross-sectional studies that compared HTN outcomes in insured pts and uninsured pts, reported no significant negative or positive associations between insurance status and HTN outcome. • Medication costs or medication co-payments: All 6 of these studies reported significant associations between reduced co-payments or costs and improved HTN control or medication adherence. • Co-payments for medical care: 14 quantitative studies measured the association of medication co-payments or costs with HTN control or treatment adherence, 9 of which were set in the U.S., and 1 in each of Cameroon, China, Finland, Israel, and Brazil. 2 of the 14 studies had a low risk of bias. 7 of the 14 studies were cohort studies, 1 was a case-control study, and 6 were cross-sectional studies. All 7 cohort	• Although lacking longitudinal studies, we found a large positive association between having a routine physician or place of care for HTN management and treatment, awareness, control, and adherence to antihypertensive treatment, again in the U.S. publication and reporting bias noted by authors.

			countries, and 1 in a low-income country.	studies reported associations between increased medication costs or co-payments and reductions in HTN control or reduced adherence to antihypertensive medication, although for 1 of these 7 cohort studies, the association between increased copayments and reduced medication adherence was only found for low medication co-payments, and at high co-payment levels medication adherence was actually found to increase (OR for medication adherence vs. baseline of 1 for $0 co-payments was 0.72 for $1–$9 co-payments (p=0.05), 1.02 for $10–$29 co-payments (p=0.05), and 1.32 for co-payments . $30 (p=0.05) • Physician remuneration models: 2 studies evaluated the association of physician remuneration models with HTN control or treatment adherence, 1 an ecological study set in Canada, and 1 a U.S. cross-sectional study. Neither study had a low risk of bias. The U.S. study reported improved rates of HTN control amongst pts treated under a capitation model compared to fee-for service pts (adjusted OR for HTN control: 1.82 (95% CI: 1.02–3.27) for capitation vs. fee-for-service pts). The Canadian study reported highest rates of HTN	

				treatment and control among practices using a capitation model, compared to fee-for-service and salary model. HTN awareness levels were highest in practices with a fixed salary remuneration model.	

Additional Data Supplement Tables and Figures

Data Supplement A. Treatment of HF*r*EF Stages C and D



Colors correspond to COR in Table 1. For all medical therapies dosing should be optimized and serial assessment exercised.

*See text for important treatment directions.

†Hydral-Nitrates Green Box- The combination of ISDN/HYD with ARNI has not been robustly tested. BP response should be carefully followed.

‡See 2013 HF guideline.

§Participation in investigational studies is also appropriate for stage C, NYHA class II and III HF.

ACEI indicates angiotensin-converting enzyme inhibitor; ARB, angiotensin receptor blocker; ARNI, angiotensin receptor-neprilysin inhibitor; BP, blood pressure; bpm, beats per minute; C/I, contraindication; CRT-D, cardiac resynchronization therapy-device; COR, class of recommendation; Dx, diagnosis; GDMT, guideline-directed management and therapy; HF*r*EF, heart failure with reduced ejection fraction; ICD, implantable cardioverter-defibrillator; ISDN/HYD, isosorbide dinitrate hydral-nitrates; LBBB, left bundle-branch block; LVEF, left ventricular

ejection fraction; LVAD, left ventricular assist device; NSR, normal sinus rhythm; and NYHA, New York Heart Association.

Data Supplement B. Medication Adherence Assessment Scales

Hill-Bone Compliance Scale (346)

How often do you:

1. Forget to take your high BP medicine?
2. Decide NOT to take your high BP medicine?
3. Eat salty foods
4. Shake salt on your food before you eat it?
5. Eat fast food?
6. Make the next appointment before you leave the doctor's office?
7. Miss scheduled appointments?
8. Forget to get prescriptions filled?
9. Run out of high BP pills?
10. Skip your high BP medicine before you go to the doctor?
11. Miss taking your high BP pills when you feel better?
12. Miss taking your high BP pills when you feel sick?
13. Take someone else's high BP pills?
14. Miss taking your high BP pills when you are careless?

Response:

1. All of the Time
2. Most of the Time
3. Some of the Time
4. None of the Time

Medication taking subscale: Items 1,2, 8,9,10,11,12,13,14.
Reducing sodium intake subscale: Items 3,4,5.
Appointment keeping subscale: Items 6,7.

BP indicates blood pressure.

Data Supplement C. Categories Defining Normal BP, Elevated BP, and Stages 1, 2, and 3 Hypertension

		SBP (mm Hg) →				
		<120	120–129	130–139	140–159	160+
↓ DBP (mm Hg)	<80	Normal	Elevated	Stage 1	Stage 2	Stage 2
	80–89	Stage 1	Stage 1	Stage 1	Stage 2	Stage 2
	90–99	Stage 2	Stage 2	Stage 2	Stage 2	Stage 2
	100+	Stage 2	Stage 2	Stage 2	Stage 2	Stage 2

Stages 1, 2, and 3 refer to the stage of hypertension.

BP indicates blood pressure; DBP, diastolic blood pressure; and SBP, systolic blood pressure.

Data Supplement D. Fixed-Dose Combination Antihypertensive Drugs

Class	Drug	Dosage Strengths (mg/mg)	Daily Frequency*
2-drug combinations			
ACE Inhibitors + Thiazide	Benazepril/Hydrochlorothiazide	10/12.5, 20/12.5, 20/25	1
	Captopril/Hydrochlorothiazide	25/15, 50/15, 25/25, 50/25	2
	Enalapril/Hydrochlorothiazide	5/12.5, 10/25	1 or 2
	Fosinopril/Hydrochlorothiazide	10/12.5, 20/12.5	1
	Lisinopril/Hydrochlorothiazide	10/12.5, 20/12.5, 20/25	1
	Moexipril/Hydrochlorothiazide	7.5/12.5, 15/12.5, 15/25	1 or 2
	Quinapril/Hydrochlorothiazide	10/12.5, 20/12.5, 20/25	1 or 2
ARBs + Thiazide	Azilsartan/Chlorthalidone	40/12.5, 40/25	1
	Candesartan/Hydrochlorothiazide	16/12.5, 32/12.5, 32/25	1
	Eprosartan/Hydrochlorothiazide	600/12.5, 600/25	1
	Irbesartan/Hydrochlorothiazide	150/12.5, 300/12.5, 300/25	1
	Losartan/Hydrochlorothiazide	50/12.5, 100/12.5, 100/25	1 or 2
	Olmesartan/Hydrochlorothiazide	20/12.5, 40/12.5, 40/25	1
	Telmisartan/Hydrochlorothiazide	40/12.5, 80/12.5, 80/25	1
	Valsartan/Hydrochlorothiazide	80/12.5, 160/12.5, 320/12.5, 160/25, 320/25	1
CCB – dihydropyridine + ACEIs	Amlodipine/Benazepril	2.5/10, 5/10, 5/20, 10/20, 5/40, 10/40	1
	Enalapril/Felodipine	5/5	1
	Perindopril/Amlodipine	3.5/2.5, 7/5, 14/10	1
CCB – dihydropyridine + ARB	Amlodipine/Olmesartan	5/20, 10/20, 4/40	1
	Amlodipine/Valsartan	5/160, 10/160, 5/320, 10/320	1
	Telmisartan/Amlodipine	40/5, 80/5, 40/10, 80/10	1
CCB – nondihydropyridine + ACEIs	Trandolapril/Verapamil	2/180, 1/250, 2/240, 4/240	1
Beta blocker + Thiazide	Atenolol/Chlorthalidone	50/25, 100/25	1
	Bisoprolol/Hydrochlorothiazide	2.5/6.25, 5/6.25, 10/6.25	1
	Metoprolol succinate/Hydrochlorothiazide	25/12.5, 50/12.5, 100/12.5	1
	Metoprolol tartrate/ Hydrochlorothiazide	50/25, 100/25, 100/50	1 or 2
	Nadolol/Bendroflumethiazide	40/5, 80/5	1
	Propranolol/Hydrochlorothiazide	40/25, 80/25	1 or 2
Direct renin inhibitor + CCB – dihydropyridine	Aliskiren/amlodipine	150/5, 150/10, 300/5, 300/10	1
Direct renin inhibitor + Thiazide	Aliskiren/ Hydrochlorothiazide	150/12.5, 150/25, 300/12.5, 300/25	1
Direct renin inhibitor + CCB – dihydropyridine	Aliskiren/Amlodipine	150/5, 150/10, 300/5, 300/10	1
Direct renin inhibitor + Thiazide	Aliskiren/Hydrochlorothiazide	150/12.5, 150/25, 300/12.5, 300/25	1
Central acting agent + Thiazide	Clonidine/Chlorthalidone	0.1/15, 0.2/15, 0.3/15	1 or 2
	Methyldopa/Hydrochlorothiazide	250/15, 250/25	2
Diuretic- potassium sparing + Thiazide	Amiloride/Hydrochlorothiazide	5/50	1
	Triamterene/Hydrochlorothiazide	37.5/25, 75/50	1
Diuretic- aldosterone antagonist + Thiazide	Spironolactone/ Hydrochlorothiazide	25/25	1 or 2
3-drug combinations			
ARB + CCB – dihydropyridine + Thiazide	Amlodipine/Valsartan/ Hydrochlorothiazide	5/160/12.5, 10/160/12.5, 5/160/25, 10/160/25, 10/320/25	1
	Olmesartan/Amlodipine/ Hydrochlorothiazide	20/5/12.5, 40/5/12.5, 40/5/25, 40/10/12.5, 40/10/25	1
Direct renin inhibitor + CCB – dihydropyridine + Thiazide	Aliskiren/Amlodipine/Hydrochlorothiazide	150/5/12.5, 300/5/12.5, 300/5/25, 300/10/12.5, 300/10/25	1

*Dosages may vary from those listed in the FDA approved labeling http://dailymed.nlm.nih.gov/dailymed/index.cfm).

ACE indicates angiotensin-converting enzyme; ARB, angiotensin-receptor blocker; and CCB, calcium channel blocker.

From Chobanian et al. JNC 7. (347)

Data Supplement E. Examples of Hypertension Quality Improvement Strategies

Quality Improvement Strategy	Examples
Audit and feedback on performance	• Feedback of performance to individual providers • Benchmarking – provision of outcomes data from top performers for comparison with provider's own data • Performance measures, quality indicators and reports • Use of registries to track BP control status at system and provider levels
Provider education	• In person, online, or other education to improve BP measurement and management skills • Training to improve communication, cultural competency, and ability to inspire and support lifestyle modification
Patient education	• Intensive education strategies promoting hypertension self-management • Cultural and linguistic tailoring of materials to increase acceptability
Promotion of self-management	• Reduce barriers for patients to receive and adhere to medications and to implement lifestyle modification
Patient reminder systems (for follow-up appointments, BP checks, and self-management)	• Postcards, calls, texts, or emails to patients • Telehealth-delivered reminders
System change	• Standardization of BP measurement using an automated device and standardized protocol • Screening to identify all patients eligible for hypertension management • Systematic follow-up of patients for the initiation and intensification of antihypertensive therapy • Decision support to providers to guide protocol-based treatment decisions • Physician or other clinical champion designated to lead hypertension care improvement initiatives • Hypertension specialist available for consult • Partner with community resources to support BP management

BP indicates blood pressure.

Adapted with permission from Walsh et al. (348).

Data Supplement F. Barriers and Improvement Strategies in Antihypertensive Medication Adherence (349-353)

Barriers	Improvement Strategies
Patient Level	
• Multiple comorbid conditions requiring complex medication regimens • Convenience factors (e.g., dosing frequency) • Health beliefs • Behavioral factors • Lack of involvement in the treatment decision–making process • Issues with treatment of asymptomatic diseases (e.g., treatment side effects) • Resource constraints • Suboptimal health literacy	• Educate patients about hypertension, consequences of hypertension, and possible adverse effects of medications • Collaborate with patient to establish goals of therapy and plan of care • Maintain contact with patients; consider telehealth approaches (Section 12.3.2). • Integrate pill-taking into daily routine activities of daily living with adherence support tools such as reminders, pillboxes, packaging, or other aids • Use motivation interventions to support medication adherence and lifestyle modification efforts • Use medication adherence scales to facilitate identification of barriers and facilitators to and behaviors associated with adequate adherence • Address health literacy o Teach-back method o Empower patients to ask questions o Use visual, interactive education o Health literacy universal precautions tool kit o Provide medication list/pictorial medication schedule
Provider and Health System Levels	
• Prescription of complex drug regimens • Inadequate communication with patient about regimen, adverse effects, treatment goals • Inadequate communication among multiple providers • Office visit time limitations • Limited access to care, pharmacies, prescription refills	• Assess for nonadherence and explore barriers to medication adherence • Use a multifactorial approach to optimize adherence • Participate in training to enhance communication skills and increase cultural competence • Use a multifactorial approach to optimize adherence • Reduce complexity of medication regimen • Utilize agents that are dosed once daily over those which require multiple daily doses • Utilize fixed-dose combination agents when available and simplify drug regimens • Consider overall side effect profile and preferentially use agents that are well tolerated • Use low-cost and generic antihypertensives from drug classes where RCTs have demonstrated a reduction in cardiovascular events when appropriate (354) • Use team-based care approaches (Section 12.2) • Use health information technology-based approaches (Section 12.3)

RCTs indicate randomized controlled trials.

Data Supplement G. Examples of Strategies to Promote Lifestyle Modification Interventions in Patients With Hypertension (318, 319, 355-361)

	Lifestyle Modification Intervention	References
Tobacco Cessation	• Ask all adults about tobacco use • Advise them to stop using tobacco • Provide behavioral interventions • Consider pharmacotherapy for tobacco cessation	(361, 362)
Weight Loss	• Offer or refer obese adults to intensive cognitive and behavioral interventions aimed at to improve weight status and other risk factors for important health outcomes.	(355, 356)
Sodium Reduction	• Offer or refer to behavioral counselling aimed at reduced intake of dietary sodium • Encourage use of food labels to choose lower sodium products	
Alcohol	• Screen adults ≥18 y of age for alcohol misuse and provide persons engaged in risky or hazardous drinking with behavioral counseling interventions to reduce alcohol misuse.	(357, 358)
Physical Activity and Diet	• Use medium- to high-intensity behavioral counseling interventions to improve intermediate health outcomes; addressing barriers, such as lack of access to affordable healthier foods, transportation barriers and poor local safety.	(359, 360)

Data Supplement H. Responsibilities and Roles of the Hypertension Team

Hypertension Team Responsibilities	
• Communication and care coordination among various team members, the patient and family members or other support persons. • Effective use of evidence-based diagnosis and management guidelines • Regular, structured follow-up mechanisms and reminder systems to monitor patient progress • Engage patients in their care by shared decision making • Medication adherence support and appropriate education about hypertension medication • Medication addition and titration using evidence-based treatment algorithms • Use of evidence-based tools and resources designed to maximize self-management (including health behavior change, lifestyle modification, etc.) • Follow a single, personalized plan of care based upon patient characteristics and needs	
Individual Hypertension Team Members	**Roles (examples)**
Primary Care Physician, Physician Assistant, Advanced Practice Nurse	Routine and complex hypertension care, managing primary care issues.
Cardiologist	Routine and complex hypertension care, especially for patient with cardiac disease or high risk for major cardiovascular events.
Nephrologist, Endocrinologist, Hypertension Specialist	Management of complex hypertension care, especially due to secondary causes, and/or resistant hypertension.
Nurse (including in-office, home care, internal and external population health personnel)	Accurate assessment of BP, medication reconciliation, patient education, self-management, lifestyle modification and adherence.
Clinical Pharmacist	Comprehensive medication management, which involves identification and documentation of medication-related problems, initiating, modifying, and discontinuing medication to address identified problems, and educating patients on their medication regimen.
Dietician	Ongoing patient-centered counseling to assess dietary habits and preferences, set and monitor goals for healthy lifestyle
Social Worker	Assess for psychosocial, cultural and financial barriers, find solutions to overcome these barriers.
Community Health Providers	Assess for psychosocial, cultural and financial barriers, identify and promote acceptable community-based resources to overcome these barriers.

BP indicates blood pressure.

Data Supplement I. Examples of Telehealth Strategies and Technologies to Promote Effective Hypertension Management

Telehealth strategies
• Automated BP data capture and transmission of the patient's self-measured BP • Self-management support including education, reminders, and feedback that is automated or delivered by a healthcare professional • Medication titration and follow-up monitoring protocols/algorithm • Prescription refill reminders • Medication adherence assessments • Self-monitoring of lifestyle behaviors • Integration of behavior change techniques, including in person or e-counseling • Case/care/population health management
Commonly used telehealth technologies
• Wired "land line" telephone • Wireless smart phone applications • Internet-based website via computers and handheld devices • Text messaging • E-mail messaging • Social networking and social media websites/applications • Wireless BP measurement devices • Electronic pill dispensers/counters

BP indicates blood pressure.

Data Supplement J. Publicly Available Performance Measures Used to Assess Hypertension Care Quality Services (363-367)

Quality Measure	Source	Description	Additional information
Controlling High BP PQRS Measure #236; NQF #0018	NCQA	Percentage of patients 18–85 y of age who had a diagnosis of hypertension and whose BP was adequately controlled (<140/90 mm Hg during the measurement period)	Used in the CMS, PQRS, MSSP, Medicare Advantage "Stars" ratings; component of Commercial Health Plan HEDIS quality measure set
Comprehensive Diabetes Care: BP Control (<140/90 mm Hg) NQF #0061	NCQA	The percentage of patients 18–75 y of age with DM (type 1 and type 2) whose most recent BP level taken during the measurement y is <140/90 mm Hg	Used for: • Accreditation • Decision-making by businesses about health plan purchasing • Decision-making by consumers about health plan/provider choice • External oversight/Medicaid • External oversight/Medicare • External oversight/State government program • Internal quality improvement • Public reporting
Adult Kidney Disease: BP Management PQRS #122	PCPI, RPA	Percentage of patient visits for those patients ≥18 y of age with a diagnosis of CKD (stage 3, 4, or 5, not receiving renal replacement therapy) with a BP<140/90 mm Hg OR ≥140/90 mm Hg with a documented plan of care	Used in PQRS
Percentage of patients ≥18 y of age with BP documented in the medical record (every 2 y if <120/80 mm Hg, every y if 120–139/80–89 mm Hg)	ICSI	This measure is used to assess the percentage of patients age 18 y of age and older with BP documented in the medical record (every 2 y if <120/80 mm Hg, every y if 120–139/80–89 mm Hg)	Used for internal quality improvement
Controlling High BP for People with Serious Mental Illness NQF #2602	NCQA	The percentage of patients 18–85 y of age with serious mental illness who had a diagnosis of hypertension and whose BP was adequately controlled during the measurement	Current Use: • Accreditation • Decision-making by businesses about health plan purchasing • Decision-making by consumers about health plan/provider choice • External oversight/Medicaid • External oversight/state government program \internal quality improvement
Diabetes Care for People with Serious Mental Illness: BP Control (<140/90 mm Hg) NQF #2606	NCQA	The percentage of patients 18–75 y of age with a serious mental illness and DM (type 1 and type 2) whose most recent BP reading during the measurement year is <140/90 mm Hg	Current Use: • Accreditation • Decision-making by businesses about health plan purchasing • Decision-making by consumers about health plan/provider choice • External oversight/Medicaid

Quality Measure	Source	Description	Additional information
			• External oversight/state government program • Internal quality improvement
Hypertension diagnosis and treatment: percentage of adult patients ≥18 y of age diagnosed with hypertension who are not at goal for hypertension and have received counseling on diet and physical activity in the past 12 mo	ICSI	Used to assess the percentage adult patients ≥ 18 y of age diagnosed with hypertension who are not at goal for hypertension and have received counseling on diet and physical activity in the past 12 mo	Used for Internal Quality Improvement
Ambulatory care sensitive conditions: age-standardized acute care hospitalization rate for conditions where appropriate ambulatory care prevents or reduces the need for admission to the hospital per 100,000 population <75 y of age	CIHI	Used to assess the age-standardized acute care hospitalization rate for conditions where appropriate ambulatory care prevents or reduces the need for admission to the hospital per 100,000 population <75 y of age	Used for: • Monitoring health state(s) • National health policymaking • National reporting • State/Provincial health policymaking
Hypertension: the relative resource use by members with hypertension during the measurement y	NCQA	Used to assess the relative resource use by members with hypertension by reporting total standard cost and service frequency for all services for which the organization has paid or expects to pay during the measurement y	Used for: • Accreditation • External oversight/Medicaid • External oversight/Medicare • External oversight/State government program • Monitoring and planning • Public reporting

BP indicates blood pressure; CIHI, Canadian Institute for Health Information; CKD, chronic kidney disease; CMS, Centers for Medicare and Medicaid Services; DM, diabetes mellitus; HEDIS, healthcare Effectiveness Data and Information Set; ICSI, Institute for Clinical Systems Improvement; MSSP, Medicare Shared Savings Program; NCQA, National Committee for Quality Assurance; NQF, National Quality Forum; OR, odds ratio; PCPI, Physician Consortium for Performance Improvement; and PQRS, Physician Quality Reporting System; and RPA, Renal Physicians Association.

Data Supplement K. Online Quality Improvement Resources for Treatment and Control of Hypertension

American College of Cardiology/American Heart Association/Centers for Disease Control Science Advisory for the Effective Approach to High Blood Pressure Control[i]

http://content.onlinejacc.org/article.aspx?articleid=1778408

American Medical Association Measure, Act and Partner (M.A.P.) to help patients control blood pressure and ultimately prevent heart disease

http://www.ama-assn.org/ama/pub/about-ama/strategic-focus/improving-health-outcomes/improving-blood-pressure-control.page

United States Health and Human Services (HHS)/Centers for Disease Control (CDC) Million Hearts Campaign Evidence-based Treatment Protocols for Improving Blood Pressure Control

http://millionhearts.hhs.gov/resources/protocols.html

Department of Defense/Veterans' Affairs

http://www.healthquality.va.gov/guidelines/CD/htn/

Kaiser Permanente Hypertension Management programs to improve blood pressure control

http://kpcmi.org/how-we-work/hypertension-control/

Institute for Clinical Systems Improvement (ICSI) Hypertension Diagnosis and Treatment Guidelines

https://www.icsi.org/guidelines__more/catalog_guidelines_and_more/catalog_guidelines/catalog_cardiovascular_guidelines/hypertension/

New York Health and Hospitals Corporation (HHC) Hypertension Collaborative Care Pathway

http://millionhearts.hhs.gov/Docs/NYC_HHC_Hypertension_Protocol.pdf

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