CANADIAN STROKE BEST PRACTICE RECOMMENDATIONS

Secondary Prevention of Stroke

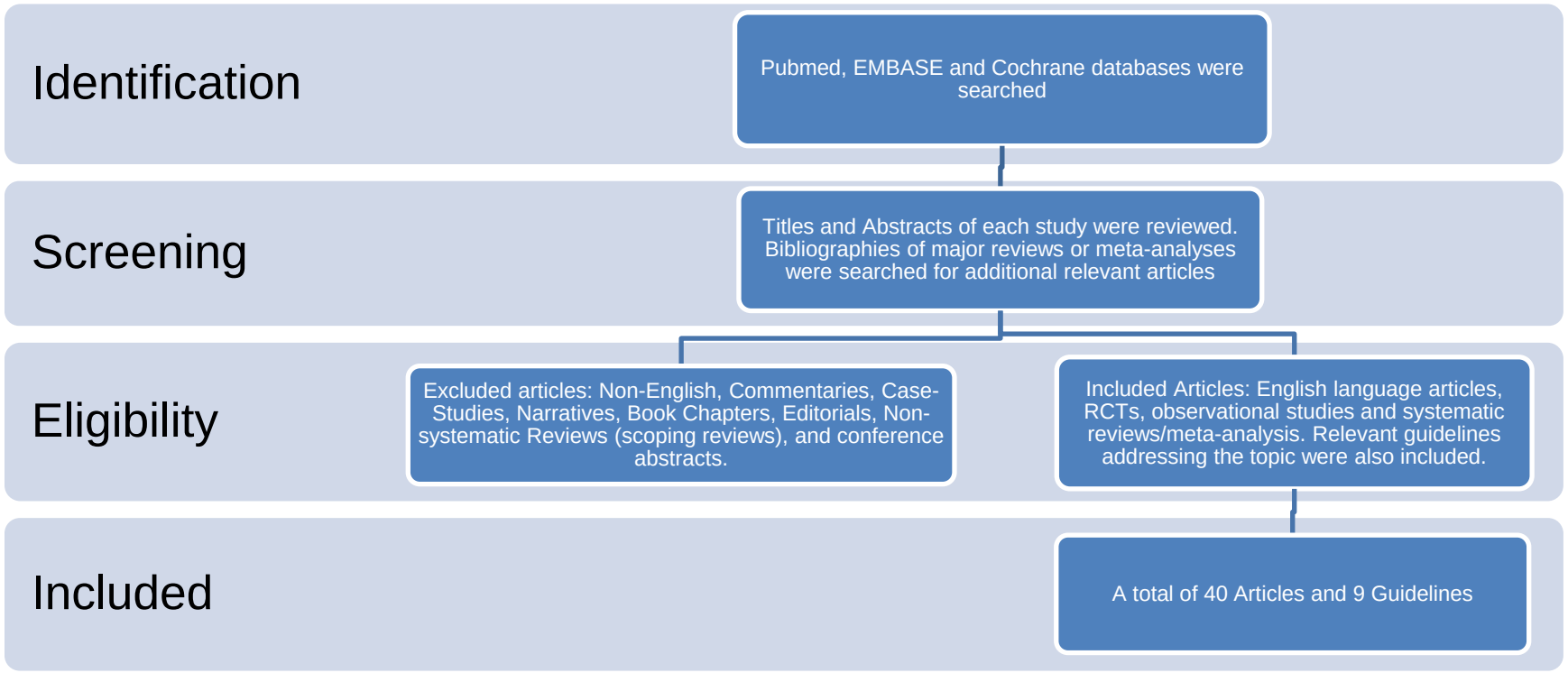
Seventh Edition, 2020

Evidence Table: *Blood Pressure and Stroke Prevention*

Gladstone D, Poppe A (Writing Group Chairs)
on Behalf of the Canadian Stroke Best Practice Recommendations
Secondary Prevention of Stroke Writing Group and in collaboration with the Canadian Stroke Consortium

Table of Contents

Search Strategy



Pubmed, EMBASE and the Cochrane Central Register of Controlled Trials databases were search using the terms (“stroke” and “hypertension” or “secondary prevention” or “blood pressure”). Titles and abstract of each article were reviewed for relevance. Bibliographies were reviewed to find additional relevant articles. Articles were excluded if they were: non-English, commentaries, case-studies, narrative, book chapters, editorials, non-systematic review, or conference abstracts. Additional searches for relevant best practice guidelines were completed and included in a separate section of the review. A total of 40 articles and 9 guidelines were included and were separated into separate categories designed to answer specific questions.

Published Guidelines

Guideline	Recommendations
Rabi DM, McBrien KA, Sapir-Pichhadze R, et al. **Hypertension Canada's 2020 Comprehensive Guidelines for the Prevention, Diagnosis, Risk Assessment, and Treatment of Hypertension in Adults and Children.** ***Canadian Journal of Cardiology* 2020; 36: 596-624.** **(selected)**	*Hypertension and Stroke XI.* Treatment of hypertension in association with stroke Recommendations A. BP management in acute ischemic stroke (onset to 72 hours) 1. For guidelines on BP management in acute ischemic stroke, refer to the current Canadian Stroke Best Practices recommendations (www.strokebestpractices.ca/recommendations). B. BP management after acute ischemic stroke 1. Strong consideration should be given to the initiation of antihypertensive therapy after the acute phase of a stroke or transient ischemic attack (Grade A). 2. After the acute phase of a stroke, BP-lowering treatment is recommended to a target of consistently < 140/90 mm Hg (Grade C). 3. Treatment with an ACE inhibitor and thiazide/thiazidelike diuretic combination is preferred (Grade A). 4. For patients with stroke, the use of an ACE inhibitor with an ARB is not recommended (Grade B). C. BP management in hemorrhagic stroke (onset to 72 hours) 1. For guidelines on BP management in acute hemorrhagic stroke, refer to the current Canadian Stroke Best Practices recommendations
Risk reduction of cognitive decline and dementia: WHO guidelines. Geneva: World Health Organization; 2019. Licence: CC BY-NC-SA 3.0 IGO	Management of hypertension should be offered to adults with hypertension according to existing WHO guidelines. Quality of evidence: low to high (for different interventions) Strength of the recommendation: strong Management of hypertension may be offered to adults with hypertension to reduce the risk of cognitive decline and/or dementia. Quality of evidence: very low (in relation to dementia outcomes) Strength of the recommendation: conditional
Williams B, Mancia G, Spiering W, Agabiti Rosei E, Azizi M, Burnier M, Clement DL, Coca A, de Simone G, Dominiczak A, Kahan T. **2018 ESC/ESH Guidelines for the management of arterial hypertension.** ***Eur Heart J*. 2018;39(33):3021-3104** **(selected)**	*Therapeutic strategies in hypertensive patients with acute stroke and cerebrovascular disease* In patients with acute intracerebral haemorrhage: • Immediate BP lowering is not recommended for patients with SBP <220 mmHg. Class III; Level A • In patients with SBP >_220 mmHg, careful acute BP lowering with i.v. therapy to <180 mmHg should be considered. Class IIa; Level B In acute ischaemic stroke, routine BP lowering with antihypertensive therapy is not recommended, with the exceptions: Class III; Level A • In patients with acute ischaemic stroke who are eligible for i.v. thrombolysis, BP should be carefully lowered and maintained at <180/105 mmHg for at least the first 24 h after thrombolysis. Class IIa; Level B • In patients with markedly elevated BP who do not receive fibrinolysis, drug therapy may be considered, based on clinical judgement, to reduce BP by 15% during the first 24 h after the stroke onset. Class IIb; Level C In hypertensive patients with an acute cerebrovascular event, antihypertensive treatment is recommended: • Immediately for TIA. Class I; Level A • After several days in ischaemic stroke. Class I; Level A In all hypertensive patients with ischaemic stroke or TIA, an SBP target range of 120–130 mmHg should be considered. Class IIa; Level B The recommended antihypertensive drug treatment strategy for stroke prevention is a RAS blocker plus a CCB or a thiazide like diuretic. Class I; Level A.

Guideline	Recommendations
Whelton PK, Carey RM, Aronow WS, Casey DE Jr, Collins KJ, Dennison Himmelfarb C, DePalma SM, Gidding S, Jamerson KA, Jones DW, MacLaughlin EJ, Muntner P, Ovbiagele B, Smith SC Jr, Spencer CC, Stafford RS, Taler SJ, Thomas RJ, Williams KA Sr, Williamson JD, Wright JT Jr. **2017 ACC/AHA/AAPA/ABC/ACPM/AGS/APhA/ ASH/ASPC/ NMA/PCNA guideline for the prevention, detection, evaluation, and management of high blood pressure in adults: executive summary: a report of the American College of Cardiology/American Heart Association Task Force on Clinical Practice Guidelines.** ***Hypertension.* 2018;71:1269–1324.** **(selected)**	*Recommendations for Treatment of Hypertension for Secondary Stroke Prevention* 1. Adults with previously treated hypertension who experience a stroke or transient ischemic attack (TIA) should be restarted on antihypertensive treatment after the first few days of the index event to reduce the risk of recurrent stroke and other vascular events. COE 1; LOE A 2. For adults who experience a stroke or TIA, treatment with a thiazide diuretic, ACE inhibitor, or ARB, or combination treatment consisting of a thiazide diuretic plus ACE inhibitor, is useful. COE 1; LOE A 3. Adults not previously treated for hypertension who experience a stroke or TIA and have an established BP of 140/90 mm Hg or higher should be prescribed antihypertensive treatment a few days after the index event to reduce the risk of recurrent stroke and other vascular events. COE 1; LOE B-R 4. For adults who experience a stroke or TIA, selection of specific drugs should be individualized on the basis of patient comorbidities and agent pharmacological class. COE 1; LOE B-NR 5. For adults who experience a stroke or TIA, a BP goal of less than 130/80 mm Hg may be reasonable. COE IIb LOE B-R 6. For adults with a lacunar stroke, a target SBP goal of less than 130 mm Hg may be reasonable. COE IIb LOE B-R
Nerenberg KA, Zarnke KB, Leung AA, Dasgupta K, Butalia S, McBrien K, Harris KC, Nakhla M, Cloutier L, Gelfer M, Lamarre-Cliche M. **Hypertension Canada's 2018 Guidelines for Diagnosis, Risk Assessment, Prevention, and Treatment of Hypertension in Adults and Children.** ***Can J Cardiol* 2018 May 1;34(5):506-25.**	**BP management after acute ischemic stroke** 1. Strong consideration should be given to the initiation of antihypertensive therapy after the acute phase of a stroke or transient ischemic attack (Grade A). 2. After the acute phase of a stroke, BP-lowering treatment is recommended to a target of consistently < 140/90 mm Hg (Grade C). 3. Treatment with an ACE inhibitor and thiazide/ thiazide-like diuretic combination is preferred (Grade B). 4. For patients with stroke, the combination of an ACE inhibitor and ARB is not recommended (Grade B).
Clinical Guidelines for Stroke Management 2017. Melbourne (Australia): National Stroke Foundation. Section 4 Secondary Prevention	**Strong Recommendation** • All stroke and TIA patients, with a clinic blood pressure of >140/90mmHg should have long term blood pressure lowering therapy initiated or intensified. • Blood pressure lowering therapy should be initiated or intensified before discharge for those with stroke or TIA, or soon after TIA if the patient is not admitted.

Guideline	Recommendations
	• Any of the following drug classes are acceptable as blood pressure lowering therapy; angiotensin-converting-enzyme inhibitor, angiotensin II receptor antagonists, calcium channel blocker, thiazide diuretics. Beta-blockers should not be used as first-line agents unless the patient has ischaemic heart disease. **Weak Recommendation** • In patients with a systolic blood pressure of 120-140mmHg who are not on treatment, initiation of antihypertensive treatment is reasonable, with best evidence for dual (ACEI/diuretic) therapy. • The ideal long-term blood pressure target is not well established. A target of <130mmHg systolic may achieve greater benefit than a target of 140mmHg systolic, especially in patients with stroke due to small vessel disease, provided there are no adverse effects from excessive blood pressure lowering.
Leung AA, Daskalopoulou SS, Dasgupta K, McBrien K, Butalia S, Zarnke KB, et al. for Hypertension Canada, **Hypertension Canada's 2017 Guidelines for Diagnosis, Risk Assessment, Prevention, and Treatment of Hypertension in Adults. *Canadian*** ***Journal of Cardiology* 2017 May;33(5):557-576** **(selected)**	1. Antihypertensive therapy should be prescribed for average DBP measurements of ≥100 mmHg (Grade A) or average SBP measurements of ≥160 mmHg (Grade A) in patients without macrovascular target organ damage or other cardiovascular risk factors. 2. Antihypertensive therapy should be strongly considered for average DPB readings ≥90 mmHg (Grade A) or for average SBP readings ≥140 mmHg (Grade B for 140-160 mmHg; Grade A for >160 mmHg; revised guideline) in the presence of macrovascular target organ damage or other independent cardiovascular risk factors.
Intercollegiate Stroke Working Party. Royal College of Physicians. National Clinical guidelines for stroke. 5th Edition 2016, Edinburgh, Scotland	A- People with stroke or TIA should have their blood pressure checked, and treatment should be initiated and/or increased as tolerated to consistently achieve a clinic systolic blood pressure below 130 mmHg, except for people with severe bilateral carotid artery stenosis, for whom a systolic blood pressure target of 140–150 mmHg is appropriate. B- For people with stroke or TIA aged 55 or over, or of African or Caribbean origin at any age, antihypertensive treatment should be initiated with a long-acting dihydropyridine calcium channel blocker or a thiazide-like diuretic. If target blood pressure is not achieved, an angiotensin converting enzyme inhibitor or angiotensin II receptor blocker should be added. C- For people with stroke or TIA not of African or Caribbean origin and younger than 55 years, antihypertensive treatment should be initiated with an angiotensin converting enzyme inhibitor or an angiotensin II receptor blocker. D- Blood pressure-lowering treatment for people with stroke or TIA should be initiated prior to the transfer of care out of hospital or at 2 weeks, whichever is the soonest, or at the first clinic visit for people not admitted. E- Blood pressure-lowering treatment for people with stroke or TIA should be monitored frequently and increased to achieve target blood pressure as quickly as tolerated and safe in primary care. People whose blood pressure remains above target despite treatment should be checked for medication adherence before being referred for a specialist opinion.

Guideline	Recommendations
Kernan WN, Ovbiagele B, Black HR, Bravata DM, Chimowitz MI, Ezekowitz MD, Fang MC, Fisher M, Furie KL, Heck DV, Johnston SC, Kasner SE, Kittner SJ, Mitchell PH, Rich MW, Richardson D, Schwamm LH, Wilson JA. **Guidelines for the prevention of stroke in patients with stroke and transient ischemic attack: a guideline for healthcare professionals from the American heart association/American stroke association.** ***Stroke 2014*;45:2160-2236.**	• Initiation of BP therapy is indicated for previously untreated patients with ischemic stroke or TIA who, after the first several days, have an established BP ≥140 mm Hg systolic or ≥90 mm Hg diastolic (Class I; Level of Evidence B). Initiation of therapy for patients with BP <140 mm Hg systolic and <90 mm Hg diastolic is of uncertain benefit (Class IIb; Level of Evidence C). • Clarification of parameters for initiating BP therapy Resumption of BP therapy is indicated for previously treated patients with known hypertension for both prevention of recurrent stroke and prevention of other vascular events in those who have had an ischemic stroke or TIA and are beyond the first several days (Class I; Level of Evidence A). • Clarification of parameters for resuming BP therapy Goals for target BP level or reduction from pretreatment baseline are uncertain and should be individualized, but it is reasonable to achieve a systolic pressure <140 mm Hg and a diastolic pressure <90 mm Hg (Class IIa; Level of Evidence B). For patients with a recent lacunar stroke, it might be reasonable to target a systolic BP of <130 mm Hg (Class IIb; Level of Evidence B). • Several lifestyle modifications have been associated with BP reductions and are a reasonable part of a comprehensive antihypertensive therapy (Class IIa; Level of Evidence C). These modifications include salt restriction; weight loss; the consumption of a diet rich in fruits, vegetables, and low-fat dairy products; regular aerobic physical activity; and limited alcohol consumption. • The optimal drug regimen to achieve the recommended level of reductions is uncertain because direct comparisons between regimens are limited. The available data indicate that diuretics or the combination of diuretics and an angiotensin-converting enzyme inhibitor is useful (Class I; Level of Evidence A). • The choice of specific drugs and targets should be individualized on the basis of pharmacological properties, mechanism of action, and consideration of specific patient characteristics for which specific agents are probably indicated (eg, extracranial cerebrovascular occlusive disease, renal impairment, cardiac disease, and DM) (Class IIa; Level of Evidence B).
Meschia JF, Bushnell C, Boden-Albala B, Braun LT, Bravata DM, Chaturvedi S, et al; on behalf of the American Heart Association Stroke Council, Council on Cardiovascular and Stroke Nursing, Council on Clinical Cardiology, Council on Functional Genomics and Translational Biology, and Council on Hypertension. **Guidelines for the primary prevention of stroke: a statement for healthcare**	1. Regular BP screening and appropriate treatment of patients with hypertension, including lifestyle modification and pharmacological therapy, are recommended (Class I; Level of Evidence A). 2. Annual screening for high BP and health-promoting lifestyle modification are recommended for patients with prehypertension (SBP of 120 to 139 mmHg or DBP of 80 to 89 mmHg) (Class I; Level of Evidence A). 3. Patients who have hypertension should be treated with antihypertensive drugs to a target BP of <140/90 mmHg (Class I; Level of Evidence A). 4. Successful reduction of BP is more important in reducing stroke risk than the choice of a specific agent, and treatment should be individualized on the basis of other patient characteristics and medication tolerance (Class I; Level of Evidence A). 5. Self-measured BP monitoring is recommended to improve BP control. (Class I; Level of Evidence A).

Guideline	Recommendations
professionals from the American Heart Association/American Stroke Association. ***Stroke.* 2014;45:3754–3832. (selected)**	
James PA, Oparil S, Carter BL, et al. **2014 evidence-based guideline for the management of high blood pressure in adults: report from the panel members appointed to the Eighth Joint National Committee (JNC 8).** ***JAMA* 2014; 311: 507-20 (selected)**	Recommendation 1 In the general population aged 60 years, initiate pharmacologic treatment to lower blood pressure (BP) at systolic blood pressure (SBP) ≥150 mm Hg or diastolic blood pressure (DBP) ≥90 mm Hg and treat to a goal SBP <150 mm Hg and goal DBP <90 mm Hg. (Strong Recommendation –Grade A) Recommendation 2 In the general population <60 years, initiate pharmacologic treatment to lower BP at DBP ≥90mm Hg and treat to a goal DBP <90mmHg. (For ages 30-59 years, Strong Recommendation – Grade A; For ages 18-29 years, Expert Opinion – Grade E) Recommendation 3 In the general population <60 years, initiate pharmacologic treatment to lower BP at SBP ≥140 mm Hg and treat to a goal SBP <140 mm Hg. (Expert Opinion – Grade E) Recommendation 4 In the population aged ≥18 years with chronic kidney disease (CKD), initiate pharmacologic treatment to lower BP at SBP ≥140mmHg or DBP ≥90 mmHg and treat to goal SBP<140mm Hg and goal DBP<90mmHg. (Expert Opinion – Grade E) Recommendation 5 In the population aged ≥18years with diabetes, initiate pharmacologic treatment to lower BP at SBP≥140mmHg or DBP ≥90 mm Hg and treat to a goal SBP <140 mm Hg and goal DBP <90 mm Hg. (Expert Opinion – Grade E)

Evidence Tables

Association between Hypertension and Stroke Risk

Study/Type	Quality Rating	Sample Description	Method	Outcomes	Key Findings and Recommendations
Yano et al. 2018 **USA** **Prospective study**	NA	4,851 participants included in the CARDIA study, aged 18 to 30 years who had not experienced any CVD events before age 40 years, who were recruited from 4 US field centers. The mean age when follow-up began was 35.7 years, 45% were men.	Blood pressures were recorded at baseline and at years 2, 5, 7, 10, 15, 20, 25 and 30. Using the highest BP measured from the first examination to the examination closest to, but not after, age 40 years, each participant was categorized as having normal BP at all examinations, elevated BP (SBP 120-129 mm Hg; DBP >80 mm Hg at 1 or more examinations); stage 1 HTN (SBP 130-139 mm Hg; or DBP 80-89 mm Hg at 1 or more examinations) or stage 2 HTN (≥140mmHg, DBP≥ 90 mm Hg, or taking antihypertensive medication at 1 or more examinations). The association between future CVD events and HTN was examined.	CVD events: fatal and nonfatal coronary heart disease (CHD), heart failure, stroke, TIA, or intervention for peripheral artery disease (PAD).	2,574 persons had normal BP, 455 had elevated BP, 1,194 had stage 1 HTN and 638 had stage 2 HTN. During a median follow-up of 18.8 years, there were 228 CVD events (CHD, 109; stroke, 63; heart failure, 48; peripheral artery disease, 8 and 319 all-cause deaths. CVD event incidence rates for normal BP, elevated BP, stage 1 HTN and stage 2 HTN were 1.37 (95% CI, 1.07-1.75), 2.74 (95% CI, 1.78-4.20), 3.15 (95% CI, 2.47-4.02), and 8.04 (95% CI, 6.45-10.03) per 1000 person-years, respectively. In the fully adjusted model (including age when follow-up time started, race, sex, educational level, study site, BMI, smoking status, physical activity, total cholesterol, high-density lipoprotein cholesterol, and fasting glucose), the risk of any CVD event was significantly higher among those with elevated, stage 1 and stage 2 HTN, compared with normal BP (HR=1.67, 95% CI 1.01-2.77, HR=1.75, 95% CI 1.22-2.53 and HR= 3.49, 95% CI 2.42-5.05, respectively). The risk of all-cause mortality was significantly higher among those with stage 2 HTN compared with normal BP (adj HR= 2.19, 95% CI 1.61-2.99)
O'Donnell et al. 2016 **Canada (International)**	NA	Participants were recruited from 32 countries from 2007-2015. Cases were 13,447	All key vascular risk factors (hypertension, DM, smoking, waist-to-hip ratio, diet, physical activity, alcohol intake, psychosocial factors,	The odds of all stroke, ischemic stroke and intracerebral hemorrhagic stroke (ICH) and population attributable risk (PAR)	Self-reported hypertension was associated with an increased risk of stroke. All stroke: OR=2.56, 99% CI 2.33-2.80; PAR 34.4%, 99% CI 32.0-36.9% Ischemic stroke: OR=2.34, 99% CI 2.10-2.60; PAR 32.0%, 99% CI 29.1-35.1%

Study/Type	Quality Rating	Sample Description	Method	Outcomes	Key Findings and Recommendations
INTERSTROKE Phase 2 **Case-control study**		persons admitted to hospital within 5 days of first acute stroke and 72 hours of admission to hospital (77% ischemic stroke, 23% ICH). Mean age was 62.2 years. 40.4% of cases were women. 13,472 controls were matched for age and sex and were recruited from the community or hospitals (in-patient or outpatient, unrelated to treatment for stroke or TIA)	cardiac causes and ApoB:ApoA1) were collected using questionnaires, physical examinations and blood and urine samples. Hypertension was defined as self-reported or blood pressure ≥140/90 mm Hg		Hemorrhagic stroke: OR=3.71, 99% CI 3.09-4.31; PAR 42.8%, 99% CI 38.9-46.8% Self-reported hypertension or blood pressure >140/90 mm Hg was associated with an increased risk of stroke. All stroke: OR=2.98, 99% CI 2.72-3.28; PAR 47.9%, 99% CI 45.1-50.6% Ischemic stroke: OR=2.78, 99% CI 2.50-3.10; PAR 45.7%, 99% CI 42.4-49.0% Hemorrhagic stroke: OR=4.09, 99% CI 3.51-4.77; PAR 56.4%, 99% CI 52.0-60.6%
O'Donnell et al. 2010 **Canada (International)** **INTERSTROKE Phase 1** **Case-control study**	NA	Participants were recruited from 22 countries from 2007-2010. Cases were 3,000 persons admitted to hospital within 5 days of acute stroke (78% ischemic stroke, 22% ICH). Mean age was 61 years. 37% women 3,000 controls were matched for age and sex and were recruited from the community or hospitals (in-patient or outpatient, unrelated to treatment for stroke or TIA)	All key vascular risk factors (hypertension, DM, smoking, waist-to-hip ratio, BMI, physical activity, alcohol intake, psychological stress, depression, diet) were collected using questionnaires, physical examinations and blood and urine samples. Hypertension was defined as self-reported or blood pressure ≥160/90 mm Hg	The odds of all stroke, ischemic stroke and hemorrhagic stroke Results were adjusted for age, sex, and region	Self-reported hypertension was associated with an increased risk of stroke. All stroke: OR=2.64, 99% CI 2.26-3.08 Ischemic stroke: OR=2.37, 99% CI 2.00-2.79 Hemorrhagic stroke: OR=3.8, 99% CI 2.96-4.78 Self-reported hypertension or blood pressure >160/90 mm Hg was associated with an increased risk of stroke. All stroke: OR=3.89, 99% CI 3.33-4.54 Ischemic stroke: OR=3.14, 99% CI 2.67-3.71 Hemorrhagic stroke: OR=9.18, 99% CI 6.80-12.39 The risk for all stroke given a history of HTN was highest in developing countries.

Study/Type	Quality Rating	Sample Description	Method	Outcomes	Key Findings and Recommendations
Rapsomaniki et al. 2014 **UK** **Observational study**	NA	1,258,006 patients, from the CALIBER database, aged ≥30 years, selected from 225 primary care practices (1997-2010) with no previous history of CVD.	Relationships between hypertension and 12 cardiovascular diseases were explored. Hypertension was defined as ≥140/90 mm Hg. Isolated systolic HTN was defined as ≥140 mm Hg with DBP<90 mm Hg and isolated diastolic HTN as SBP<140 mm Hg and DPB≥90 mm Hg	12 CVD (stable angina, unstable angina, MI, CHD mortality, heart failure, cardiac arrest/sudden cardiac death, TIA, ischemic stroke, SAH, ICH, PAD, AAA and total CVD).	There were 83,098 first cardiovascular events during a median follow-up of 5.2 years. HTN was recorded in 545,816 patients. For each increase of 20/10 mm Hg, the risks were significantly increased for: TIA: HR (SBP)=1.15, 95% CI 1.11-1.19, HR (DBP)=1.15, 95% CI 1.10-1.19 Ischemic stroke: HR (SBP)=1.35, 95% CI 1.28-1.42, HR (DBP)=1.30, 95% CI 1.23-1.38 SAH: HR (SBP)=1.43, 95% CI 1.25-1.63, HR (DBP)=1.42, 95% CI 1.25-1.60 ICH: HR (SBP)=1.44, 95% CI 1.32-1.58, HR (DBP)=1.50, 95% CI 1.37-1.64 For each 20/10 mm Hg, the risks of TIA, ischemic stroke and ICH increased across age cohorts (30-59 yrs, 60-79 yrs and ≥80 yrs), with the highest risks noted in the youngest patients. Compared with persons with SBP <115 mm Hg, the pattern of risk of TIA, ischemic stroke, SAH and ICH increased with increasing BP among patients aged 30-59 yrs. The effects were not as pronounced for patients aged 60-79 yrs and there were no significant increased risks for patients ≥80 yrs. The patterns were similar for DBP <75 mm Hg, across all age groups. The lifetime risk of ischemic stroke (from index age of 30 years) in persons with HTN was 7.6% (95% CI 7.3%-7.8%) compared with 6.5% (95% CI 6.2%-6.9%) for persons without HTN.
Bestehorn et al. 2008 **Germany**	NA	47,394 patients under the care of 2,482 general physicians, diagnosed with hypertension	Physicians documented: age, sex and measured current BP, the presence/absence of risk factors including pre-treated hypertension,	**Primary outcome:** Risk of first stroke within 10 years using the Framingham Stroke Risk (low, medium and high risks are defined as <10%, 10-20%, and >20%).	The most prevalent stroke risk factors were a positive family history of cardiovascular disease (46.1%), diabetes mellitus (36.1%), coronary artery disease (34.4%), and left ventricular hypertrophy (33.3%).

Study/Type	Quality Rating	Sample Description	Method	Outcomes	Key Findings and Recommendations
Observational study			diabetes mellitus, smoking, atrial fibrillation, left ventricular hypertrophy, coronary artery disease, positive family history and use of current antihypertensive medication.		The mean SBP/DBP was 147/86 mmHg, even though 73.5% of the total cohort was receiving combination therapy for HTN. The mean 10-year risk of stroke was 26% in the total cohort (0–19% in 50.6% of patients, 20–49% in 32.7%, and ≥50% in 16.7%)
Du et al. 2000 **UK/USA** **Case-control study**	NA	Patients with first-ever stroke were identified from a community-based stroke register. Cases were <80 years, and registered with a participating practitioner (n=267). Two controls/case from the same practice register were included, matched for age and sex (n=534).	Risk factors were identified through chart review and included HTN (SBP>160 mmHg and/or a DBP> 95 mmHg) on at least two occasions within any three-month period or use of HTN medication. Additional risk factors included history of angina, TIA, MI, atrial fibrillation, diabetes, renal failure, obesity, smoking, family history of stroke and ETOH intake.	**Primary outcome:** Risk of stroke in subjects with ≥1 multiple risk factors	157 (58.8%) of the cases and 212 (39.7%) of the controls were defined as hypertensive. The risk of stroke was higher among subjects who were hypertensive (adjusted OR=2.45, 95% CI 1.62 to 3.71, p< 0.001). The risk of stroke remained elevated in patients whose HTN was moderately well-controlled (adjusted OR=3.10, 95% CI 1.94 to 4.96) and was no longer significantly elevated among patients who were well-controlled (adjusted OR=1.49, 95% CI 0.8 to 2.49). In hypertensive subjects who were current smokers, the risk of stroke was increased (adjusted OR=6.1, 95% CI 2.7 to 13.7) compared with non-smokers without hypertension. In hypertensive subjects with diabetes, the risk of stroke was increased (adjusted OR=4.22, 95% CI 2.13 to 8.37). In subjects with hypertension + 1, 2 and 3 other risk factor the risk of stroke was increased significantly (adjusted ORs=4.51, 95% CI 2.60 to 7.83; 4.96, 95% CI 2.68 to 9.17 and 9.58, 95% CI 4.74 to 19.34, respectively).

Pharmacological Treatment of Hypertension for Primary and Secondary Prevention of Stroke

Study/Type	Quality Rating	Sample Description	Method	Outcomes	Key Findings and Recommendations
Systematic reviews & meta-analyses					
Zonneveld et al. 2018 **The Netherlands** **Cochrane review**	5 trials were considered to be of high methodological quality	11 RCTs, representing data from 38,742 adult participants who had experienced an ischemic or intracerebral hemorrhagic stroke (excluding SAH)	Trials evaluated blood pressure-lowering drugs (BPLDs) started at least 48 hours after stroke or TIA. 8 trials compared BPLDs vs. placebo or no treatment (35,110 participants), and 3 compared intensive vs. standard blood-pressure lowering regimens (n=3,632).	**Primary outcome:** Recurrent stroke **Secondary outcomes:** Major vascular event (i.e., composite of cardiovascular death, nonfatal stroke, and nonfatal myocardial infarction),	Median duration of follow-up duration was reported in 6 studies, and ranged from 12 to 47 months. The risk of recurrent stroke was reduced significantly with BPLDs, when compared with placebo or no treatment (RR=0.81, 95% CI 0.70-0.93). Based on results from 8 trials of moderate-quality. The effect was most pronounced (i.e. significant) for persons with baseline SBP>140 mm Hg. ACE inhibitors and diuretics were the most effect antihypertensive agents. The risk of a major vascular event was not reduced significantly with BPLDs (RR=0.9, 95% CI (0.78-1.04). Based on the results from 4 high-quality trials. Intensive blood pressure-lowering vs. standard did not reduce the risks of recurrent stroke, time to recurrent stroke, risk of major vascular event, myocardial infarction, or all-cause mortality.
Bangalore et al. 2017 **USA**	One trial was classified as low risk of bias, fulfilling all criteria (sequence generation of allocation; CA and blinding). All other trials had ≥1 component rated as having an unclear risk of bias	17 RCTs published between 1994 and 2015 including data from 55,163 participants, with/without previous stroke, with/without diabetes, with/without kidney disease, and/or with/without hypertension. Trials included those aged ≥40 years, and those aged ≥70 years.	Trials comparing different goal SBP targets (<150, <140, <130 and <120 mm Hg) against a reference standard of <160 mm Hg.	**Primary outcomes:** Stroke, MI, death, cardiovascular death, heart failure **Safety outcomes:** Serious adverse events	Mean duration of follow-up was 3.7 years (204,103 patient-years). **Stroke:** The risk of stroke was decreased in a comparison of target SBP <120 vs. <160 mm Hg (RR=0.54, 95% CI 0.29-1.00). There were no significant reductions in risk for any of the other pairings (<150 vs. <160 mm Hg; <140 vs. <160 mm Hg; <130 vs. <160 mm Hg). Compared with a target SBP of <120 mm Hg, the risk of stroke was significantly increased with SBP <140 mm Hg (RR=1.72, 95% CI 1.42-2.58), <150 mm Hg (RR=1.97, 95% CI 1.26-3.08) and <160 mm Hg (RR=3.27, 95% CI 1.78-6.00). SBP targets of <120 and <130 mmHg were deemed best for stroke prevention.

Study/Type	Quality Rating	Sample Description	Method	Outcomes	Key Findings and Recommendations
					MI: The risk of MI was decreased in a comparison of target SBP <120 vs. <160 mm Hg (RR=0.68, 95% CI 0.47-1.00). There were no significant reductions in risk for any of the other pairings (<150 vs. <160 mm Hg; <140 vs. <160 mm Hg; <130 vs. <160 mm Hg). **All other primary outcomes:** There were no significant reductions in the risks of death, cardiovascular death, or heart failure when comparing any of the BP targets. **Safety:** The risks of serious adverse events were significantly increased with SBP targets of <120 vs <150 mm Hg (RR= 1.83, 95% CI, 1.05-3.20) and <120 vs <140 mm Hg (RR= 2.12; 95% CI, 1.46-3.08). BP targets of <140 mm Hg and <150 mm Hg were the safest targets for the outcome of serious adverse effects. An SBP target of <130 mm Hg had optimal balance between efficacy and safety.
Katsanos et al. 2017 **Greece**	The risks of attrition and detection bias were considered unclear in many trials. The risks of performance and detection bias were considered high in 2 studies. The risks of reporting bias and selection	14 RCTs including 42,736 participants with a history of stroke. Mean age at baseline ranged from 59 to 71.8 years.	Trials compared antihypertensive agents vs. placebo (n=11), more intensive vs. less intensive BP control (n=2) and comparison of antihypertensive agents (n=1).	**Primary outcomes:** Recurrent stroke, ischemic stroke, ICH, disabling or fatal stroke, MI, all-cause mortality, cardiovascular mortality	The mean duration of follow-up ranged from 12-60 months. The risks of recurrent stroke, disabling or fatal stroke and cardiovascular death were all significantly reduced with antihypertensive treatment compared with placebo (RR=0.73, 95% CI 0.62–0.87, p <0.001 [results from 11 studies included], RR=0.71, 95% CI 0.59–0.85, <0.001 [results of 7 studies included], and RR=0.85, 95% CI 0.75–0.96, p=0.01 [results of 8 studies included], respectively. The risks of ischemic stroke, hemorrhagic stroke, MI or death from any cause were not reduced significantly. In subgroup analysis, lower SBP was associated with lower frequency of recurrent stroke (<130 vs.

Study/Type	Quality Rating	Sample Description	Method	Outcomes	Key Findings and Recommendations
	bias were considered low.				130-140 vs. ≥140 mm Hg; 8.3% vs. 9.2% vs. 11.7%, p=0.048) and cardiovascular death (0.8% vs. 3.3% vs. 5.5%, p=0.49). In meta-regression analysis, increasingly lower SBP was linearly associated with significant reductions in recurrent stroke, MI, death from any cause and cardiovascular death. Increasingly lower DBP was linearly associated with significant reductions in the risk of recurrent stroke and cardiovascular death.
Ettehad et al. 2016 **UK**	Ten studies were judged to be of unclear risk of bias and 113 were deemed to be at low risk of bias.	123 studies with 613,815 participants with a minimum of 1,000 patient-years of follow-up	Trials compared blood pressure lowering drug vs. placebo (n=71); different blood pressure lowering drugs (n=31); more intensive vs. less intensive treatment (n=9), active treatment vs. placebo + comparison of active drugs (n=7) and more intensive vs. less intensive treatment + comparison of active drugs (n=5).	**Primary outcomes:** Major cardiovascular events, coronary heart disease, stroke, heart failure, renal failure, all-cause mortality	Every 10 mm Hg reduction in SBP significantly reduced the risk of major cardiovascular disease events (RR= 0·80, 95% CI 0·77–0·83), coronary heart disease (RR=0·83, 95% CI 0·78–0·88), stroke (RR=0·73, 95% CI 0·68–0·77), heart failure (RR=0·72, 95% CI 0·67–0·78) and all-cause mortality (RR=0.87, 95%CI 0·84–0·91). The reduction in the risk of major cardiovascular events was proportional to the magnitude of the blood pressure reduction achieved. The risk of stroke was reduced with antihypertensive treatment across different strata of baseline BP (mm Hg), (p for interaction=0.38) <130: RR=0.65, 95% CI 0.27-1.57 130-139: RR=0.73, 95% CI 0.62-0.85 140-149: RR=0.78, 95% CI 0.70-0.87 150-159: RR=0.65, 95% CI 0.54-0.78 ≥160: RR=0.70, 95% CI 0.64-0.78 The risk of stroke was reduced significantly per each 10 mm Hg decrease in SBP with antihypertensive treatment in persons with and without existing cardiovascular disease (RR=0·74, 95% CI 0.67-0.81 and RR=0·75, 95% CI 0.63-0.89, respectively). The most effective antihypertensive agents for the reduction in stroke risk were angiotensin receptor

Study/Type	Quality Rating	Sample Description	Method	Outcomes	Key Findings and Recommendations
					blockers and calcium channel blockers. Beta-blockers were inferior to other classes of antihypertensives.
Xie et al. 2016 **Australia**	7 trials had Jadad scores <3 and 7 had Jadad scores ≥3	19 RCTs including 44,989 participants, with hypertension, at high risk of cardiovascular or renal disease, or both. 5 trials only included persons with diabetes and 6, with chronic kidney disease. One trial included children. The mean baseline SBP ranged from 123-172 mm Hg and mean DBP ranged from 76-105 mm Hg. Overall, mean BP was 159/92 mm Hg.	Trials compared more intensive vs less intensive blood pressure-lowering treatment, with at least 6 months' follow-up. The BP targets varied among trials.	**Primary outcomes:** Major cardiovascular events, (MI, stroke, heart failure, or cardiovascular death), separately and combined; nonvascular and all-cause mortality; end-stage kidney disease; and adverse events.	Mean duration of follow-up was 3.8 years. The mean follow-up BP levels were 133/76 mm Hg in the more intensive treatment group and 140/81 mm Hg in the less intensive group. Across all trials, the weighted mean follow-up difference in BP groups was 6·8/3·5 mm Hg. Intensive BP treatment significantly reduced the risk of major CV events (HR=0·86, 95% CI 0·78–0·96, p=0·0050). Based on the results from 14 trials. Intensive BP treatment significantly reduced the risk of stroke (HR=0·78, 95% CI 0·67–0·90, p=0·001). Based on the results from 14 trials. Intensive BP treatment did not significantly reduce the risks of heart failure, end-stage kidney disease, cardiovascular or non-cardiovascular death, or all-cause mortality. There were no differences in major vascular events between groups, based on subgroup analysis defined according to a broad range of baseline characteristics. Absolute benefits were proportional to absolute risk. The risk of severe hypotension was significantly higher in the more intensive group (0.3% vs. 0.1%, RR=2·68, 95% CI 1·21–5·89, p=0·015). The risks of dizziness or adverse events leading to discontinuation of treatment) were not significantly increased in the more intensive group.
Lee et al. 2012 **International**	NA	11 RCTs representing data from 42,572 participants (794 with previous stroke) who	Comparisons of treatment of tight BP control (SBP <130 mmHg) vs. usual control	**Primary outcome:** Stroke risk and achieved level of different SBP (intensive vs. usual).	Follow-up duration ranged from 2.6 to 5.3 years. The final mean SBPs, were 126.5mmHg in the intensive treatment arms and 132.6mmHg in the

Study/Type	Quality Rating	Sample Description	Method	Outcomes	Key Findings and Recommendations
		were at high risk for CVD.	(SBP 130 to 139 mmHg) on subsequent stroke risk. Treatment contrasts included i) active treatment with nisoldipine or enalapril, candesartan, ramipril, perindopril, verapamil- or atenolol-based therapy, trandolapril, fosinopril or amlodipine, vs. placebo or ii) non-specific antihypertensive drug vs. standard treatment	**Secondary outcomes:** Major vascular event (i.e., composite of cardiovascular death, nonfatal stroke, and nonfatal myocardial infarction), major coronary events, total death, vascular death	conventional arms. The (mean SBP reduction was 6.1mmHg). Tight SBP target was associated with a lower future stroke risk (RR= 0.80; 95% CI, 0.70 to 0.92, p < 0.01), a lower risk of major vascular events (RR= 0.91, 95% CI 0.86 to 0.96; p < 0.001), a lower risk of major coronary events (RR= 0.91, 95% CI 0.85 to 0.98, p< 0.01, but was not associated with a significantly lower risk of total death (RR= 0.95, 95% CI 0.89 to 1.01, p = 0.08). The risk of hypotension or any adverse event was higher in patients in active treatment groups (RR=3.43, 95% CI 2.46 to 4.79, p<0.001 and RR=1.18, 95% CI 1.11 to 1.25, p <0.001, respectively). In subgroup analyses, patients with diabetes, those without a history of CVD, and younger than 65 years, experienced the greatest stroke risk reduction.
Musini 2009 **Canada** **Cochrane review**	NA	15 RCTs (n=24,055 subjects ≥ 60 years) with moderate to severe hypertension (SBP≥ 140 mmHg and/or a DBP≥ 90 mmHg)	Comparisons of anti-hypertensive drug therapies including: ACE inhibitors, ARBs, β-blockers, combined α and β-blockers, calcium-channel blockers, diuretics, α-adrenergic blockers, central sympatholytics, direct vasodilators or peripheral adrenergic antagonists vs. placebo or no treatment. Minimum duration of therapy was 1 year. 12/15 trials instituted a stepped care approach to	**Primary outcome:** Deaths from all causes **Secondary outcomes:** Fatal MI or rapid cardiac death, fatal strokes, fatal/non-fatal MI, fatal/non-fatal stroke	Follow-up ranged from 1-6 years. Losses to follow-up ranged from <5% to 25% (n=12) or were not reported. Total mortality was lower in patients in the treatment group (1,215 vs. 1,299). RR= 0.90, 95% CI 0.84 to 0.97, p=0.006. Results from 12 trials included. Cardiovascular morality was lower in patients in the treatment group (493 vs. 613). RR=0.77, 95% CI 0.68 to 0.86, p<0.0001. Results from 10 trials included. Cerebrovascular mortality was lower in patients in the treatment group (136 vs. 194). RR= 0.66, 95% CI 0.53 to 0.82, p=0.0002. Results from 10 trials included.

Study/Type	Quality Rating	Sample Description	Method	Outcomes	Key Findings and Recommendations
			treatment. In over 70% of trials a thiazide diuretic was the first line drug in the treatment group.		Deaths due to coronary heart disease (CHD) were lower in patients in the treatment groups (296 vs. 346). RR=0.77, 95% CI 0.65 to 0.90, p<0.0001. Results from 9 trials included. There were fewer cases of cardiovascular mortality and morbidity among patients in the treatment groups (1,276 vs. 1,709). RR=0.72, 95% CI 0.68 to 0.77, p<0.0001. Results from 13 trials included. Withdrawals due to adverse events were greater among patients in the treatment group (372 vs. 215). RR= 1.71, 95% CI 1.45 to 2.00, p<0.0001. Results from 3 trials included.
Law et al. 2009 **UK** **Systematic review & meta-analysis**	NA	147 RCTs (n=464,000) that included participants with no history of CVD, but a history of HTN (n=27), a history of coronary heart disease, without selection based on blood pressure (CHD)(n=74) and a history of stroke in which participants were treated for HTN according to targets (n=13). The mean age at study entry ranged from 57-64 years.	108 trials compared blood pressure lowering medications vs. placebo (n=92) or usual care (n=16) and 46 trials compared different types of blood pressure medications.	CHD events and stroke	The mean duration of study follow-up ranged from 1.7-4.5 years. There were 22,115 incident stroke events. A blood pressure treatment-associated reduction of 10 mm Hg systolic and 5 mm Hg diastolic was associated with a reduced risk of stroke (RR=0.59, 95% CI 0.52-0.67) The risk of stroke was significantly reduced in trials that included persons with no prior history of stroke, a history of CHD, and a history of stroke. The risk of stroke associated with individual types of medications was significantly reduced: Thiazides: RR=0.62, 95% CI 0.53-0.72 β-blockers: RR=0.83, 95% CI 0.70-0.99 ACE inhibitors: RR=0.78, 95% CI 0.66-0.92 ARBs: no studies Calcium channel blockers: RR=0.66, 95% CI 0.58-0.75 Overall: RR=0.73, 95% CI 0.66-0.80 The risk of stroke in drug comparison trials was:

Study/Type	Quality Rating	Sample Description	Method	Outcomes	Key Findings and Recommendations
					Thiazide vs. any other: RR=0.94, 95% CI 0.82-1.09 β-blockers vs. any other: RR=**1.18, 95% CI 1.03-1.36** ACE inhibitors vs. any other: RR=1.06, 95% CI 0.94-1.20 ARB vs. any other: RR=0.90, 95% CI 0.71-1.13 Calcium channel blockers vs. any other: **RR=0.91, 95% CI 0.84-0.98** The reduction in the risk of stroke was significant, regardless of baseline diastolic BP (6 categories ranging from 70-74 to ≥95 mm Hg) or systolic BP (7 categories ranging from 110-119 to ≥170 mm Hg).
Clinical trials including participants (portion or whole sample) who had sustained a previous stroke or TIA					
Kitagawa et al. 2019 **Japan** **RCT** ***The Recurrent Stroke Prevention Clinical Outcome (RESPECT) Study***	CA: ☑ Blinding: Patient: ☒ Assessor ☑ ITT: ☑	1,280 patients (2,000 planned) aged 50-85 years with a history of stroke within the previous 30 days to 3 years with a SBP of 130 to 180 mm Hg or DBP of 80 to 110 mm Hg, on a regimen of 0 to 3 antihypertensive medications. Mean age was 67.3 years, 69% were men. 85% of strokes were ischemic, 15% ICH. The median time from qualifying stroke to randomization was 4.6 months	Patients were randomized 1:1 to a standard treatment group with a target of <140/90mm Hg (n = 640) or an intensive treatment group with a target of <120/80 mm Hg (n =640). The study was planned to continue until the number of recurrent strokes in each group reached 244. An updated systematic review was also performed using the results of the present trial in addition to the SPS3 trial, PAST-BP and PODCAST trials (all described below)	**Primary outcome:** Recurrent stroke **Secondary outcomes:** Ischemic stroke, ICH, SAH, MI, major vascular event, all-cause mortality, composite of all-cause mortality, nonfatal stroke, and nonfatal MI	The trial was stopped early due to difficulties with recruitment and lack of funding. Mean duration of follow-up was 3.9 years. At 1 year of follow-up, the achieved BP was 132.0/77.5 mm Hg in the standard target group and 123.7/72.8 mm Hg in the intensive target group (mean SBP difference=8.3mm Hg) There were 52 strokes (2.26% per year) in the standard group and 39 (1.65% per year) in the intensive group. The risk of recurrent stroke was not reduced significantly with intensive BP treatment (HR=0.73, 95% CI 0.49-1.11, p=0.15). There were no significant differences between groups for an of the secondary outcomes except a lower recurrence of ICH in the intensive group (0.04% per year vs. 0.46% per year; HR=0.09, 95% CI 0.01-0.70, p=0.02). In the updated meta-analysis, the risk of recurrent stroke was reduced significantly with intensive

Study/Type	Quality Rating	Sample Description	Method	Outcomes	Key Findings and Recommendations
					therapy (HR=0.78, 95% CI 0.64-0.96, p=0.02, NNT=67).
Bath et al. 2017 **UK** **RCT** ***Prevention of Decline in Cognition after Stroke Trial' (PODCAST)***	CA: ☑ Blinding: Patient ☒ Assessor☑ ITT: ☑	83 participants recruited from 19 sites (600 planned), functionally independent, who had suffered an ischemic or ICH in the previous 3-7 months, aged ≥70 years with t-MMSE > 16 or age > 60 years and t-MMSE 17 to 20 and SBP 125 to 170 mmHg and total chol of 3 to 8 mmol/l. Mean age was 73 years, 77% were men, median time from stroke onset to randomisation was 4.5 months.	Patients were randomized to an intensive blood pressure lowering program (target SBP< 125 mmHg, n=41) or a moderate blood pressure lowering using guideline standards (target SBP<140 mmHg, n=42), for at least 6 months. In the subset of patients with ischemic stroke, patients were also randomized to receive intensive lipid lowering treatment (target LDL chol <2.0 mmol/L, n=39) or guidelines standard treatment target LDL<3.0 mmol/L, n=38)	**Primary outcome:** Cognition, assessed annually up to 8 years using Addenbrooke's Cognitive Examination-R (ACE-R) **Secondary cognitive outcomes:** Stroop test, Trail-Making Tests A and B, category fluency (animal naming); MMSE, Telephone Interview for Cognition Scale-Modified (TICS-M), premorbid cognitive function assessed in an informant interview using the IQCODE and dementia (DSM IV)	Median duration of follow-up was 24 months. Mean baseline SBP and DBP was 147.1 and 82.1 mm Hg. Mean total chol was 4.0 mmol/L. The mean SBP and DBP was reduced significantly more in the intensive BP group (mean difference –10.6 and -5.5 mmHg, p<0.01, respectively). Mean baseline ACE-R scores were 85.7 (intensive BP) and 86.5 (guideline BP). At follow-up, mean ACE-R scores were 80.8 (intensive BP) and 84.4 (guideline BP). The mean difference between groups was not significant (-3.6, 95% CI -9.7, 2.4, p=0.24). There were no significant differences between groups for any of the secondary cognitive outcomes between BP groups. Mean total, LDL and non-HDL cholesterol levels were significantly lower in the intensive lipid-lowering group. At follow-up, mean ACE-R scores were 86.5 (intensive lipid reduction + BP lowering) and 78.2 (guideline lipid reduction + BP lowering). The mean difference between groups was not significant (4.4, 95% CI -2.1, 10.9, p=0.18). The intensive lipid group had significantly higher cognition scores, assessed using the Trail Making (time-sec), category fluency (animal naming) the Stroop (3 accuracy and interference accuracy). Mean mRS was significantly lower, and EQ-VAS was significantly higher in the intensive lipid group.

Study/Type	Quality Rating	Sample Description	Method	Outcomes	Key Findings and Recommendations
					The number of serious adverse events did not differ between groups. The incidence of dementia and death did not differ significantly between groups.
Mant et al. 2016 **UK** **RCT** ***Prevention After Stroke-Blood Pressure (PAST-BP)***	CA: ☑ Blinding: Patient ☒ Assessor☑ ITT: ☑	529 patients recruited from the offices of 99 primary care physicians, from 2009-2011 with a history of stroke and SBP ≥125 mm Hg. Patients were excluded if they were already taking ≥3 antihypertensive agents, they had a greater than 20 mm Hg postural change in SBP on standing, or were being treated to a 130 mm Hg SBP target. Mean age was 72 years, 59% were male, 44% had stroke as index event, 53% were TIA. Patients were taking an average of 1 antihypertensive agent at baseline.	Patients were randomized to an intensive arm with a target SBP <130 mm Hg or a target reduction of 10 mm Hg if their baseline BP was 125-140 mm Hg (n=266) or, to a standard arm with a target SBP of < 140 mm Hg (n=263). Physicians treated patients with agents/doses at their discretion, but were provided with evidence-based guidelines.	**Primary outcome:** Change in SBP from baseline to one year **Secondary outcomes:** DBP at 6 and 12 months, SBP at 6 months, and proportion achieving target BP at 12 months, major cardiovascular events (composite of fatal and non-fatal stroke, MI, fatal coronary heart disease, or other cardiovascular death), emergency hospital admissions, and deaths	There were significantly more patient withdrawals by 12 months in the intensive arm (52 vs. 32, p=0.02). Mean baseline SBP in the intensive arm was 143.5 mm Hg and 127.4 mm Hg at one year. Mean baseline SBP in the standard care arm was 142.2 mm Hg and 129.4 mm Hg at one year. The adjusted one-year difference between groups was -2.94 mm Hg (95% CI -5.68 to -0.21). The proportions of patients who achieved a target SBP of < 140 mm Hg were similar in the two arms (82% vs. 82%, p=0.59). There was one major cardiovascular event in the intensive arm (nonfatal MI) vs. 5 in the standard care arm (3 strokes, 1non-fatal MI and 1 one cardiovascular death) (HR= 0.19, 95% CI 0.02 to 1.87; p=0.16)
Benavente et al. 2013 **USA & Canada** **RCT** ***Secondary Prevention of Small Subcortical Strokes (SPS3) Trial (blood***	CA: ☑ Blinding: Patient ☒ Assessor ☒ ITT: ☑	3,020 participants, mean age of 63 years, who were normotensive or hypertensive and had sustained a confirmed lacunar stroke within the previous 180 days. Participants with disabling stroke, or previous ICH or cortical stroke, were excluded.	At least 2 weeks following the event, patients were randomized (1:1) to a SBP target of 130-149 mm Hg or <130 mm Hg. Patients were followed every 1 or 3 months to ensure that blood pressure remained within target range.	**Primary outcome:** Recurrent stroke and disabling stroke (mRS score of ≥3-5) **Secondary outcomes:** MI, major vascular event and death	Mean duration of follow-up was 3.7 years. At one year, the mean SBPs were 138 mm Hg (higher target group) and 127 mm Hg (lower target group). There were (non-significantly) fewer strokes in the lower target group (2.25% vs. 2.77% per patient year, HR=0.81, 95% CI 0.64-1.03, p=0.08). There were (non-significantly) fewer disabling strokes in the lower target group (0.72 vs. 0.89%

Study/Type	Quality Rating	Sample Description	Method	Outcomes	Key Findings and Recommendations
pressure component)			Adjustments to medications were made, as appropriate.		per person years, HR=0.81, 95% CI 0.53-1.23, p=0.32). There were (non-significantly) fewer MIs, major vascular events and vascular deaths in the lower target group. In subgroup analysis examining age, sex, history of diabetes, race, region of residence or baseline SBP), no significant interactions were reported. There were no differences between groups in the number of adverse events reported, or adverse events related to blood pressure management.
Beckett et al. 2008 **UK** **RCT** ***The Hypertension in the Very Elderly Trial (HYVET) Study***	CA: ☑ Blinding: Patient: ☑ Assessor ☑ ITT: ☑ (primary analysis)	3,845 patients >80 years of age with persistent hypertension (defined as a sustained systolic blood pressure of 160 mm Hg). 7% of patients had experienced a previous stroke	Patients were randomized to receive 1.5 mg of the diuretic indapamide (sustained release) (n=1,933) or placebo (n=1,912). The ACE inhibitor perindopril (2 or 4 mg), or placebo, was added if necessary, to achieve the target blood pressure of 150/80 mm Hg. Target systolic blood pressure was <150 mm Hg, and target diastolic blood pressure was < 80 mm Hg.	**Primary outcome:** Fatal or nonfatal stroke at the end of follow-up (2 years) **Secondary outcomes:** Death from any cause, death from cardiovascular causes, death from cardiac causes, and death from stroke	The median duration of follow up was 1.8 years. 12.4% of patients in the active treatment group experienced a fatal or nonfatal stroke at the end of follow-up compared with 17.7% of patients in the placebo group (unadjusted HR=0.70, 95% CI 0.49 to 1.01, p=0.06). Fewer patients in the active treatment group experienced death from stroke (6.5% vs. 10.7%, unadjusted HR= 0.61, 95% CI 0.38 to 0.99, p=0.046) or death from any cause (47.2% vs. 59.6%, unadjusted HR= 0.79, 95% CI 0.65 to 0.95, p=0.02). Fewer patients in the active treatment group experienced any cardiovascular event (33.7% vs. 50.6%, unadjusted HR= 0.66, 95% CI 0.53 to 0.82, <0.001). The number of serious adverse events reported was lower among patients in the active treatment group (358 vs. 448, p = 0.001). Only five of these events (three in the placebo group and two in the active-treatment group) were deemed to be possibly related to the trial medication.

Study/Type	Quality Rating	Sample Description	Method	Outcomes	Key Findings and Recommendations
Beckett et al. 2012 **UK** **RCT** ***HYVET* Study Group (1-year open-label extension)**	CA: ☑ Blinding: Patient: ☒ Assessor ☑ ITT: ☑ (primary analysis)	To be eligible for entry into the extension portion of the trial, participants only needed to be on double blind treatment at the time of their final visit. 924 patients (92%) in the active treatment group and 788 patients (90%) in the control group continued to receive treatment.	All patients received active treatment for 1 year as per the original study protocol. (indapamide SR 1.5 mg alone (step 1), indapamide SR plus perindopril 2 mg (step 2), and finally indapamide SR plus perindopril 4 mg (step 3).	Same as original protocol	There were no significant between-group differences in the incidence of fatal/nonfatal stroke (9 vs. 4, HR= 1.92, 95% CI 0.59 to 6.22, p=0.28), heart failure (2 vs. 9, HR= 0.28, 95% CI 0.03 to 2.73, p=0.28), or all cardiovascular events (12 vs. 13, HR= 0.78, 95% CI 0.36 to 1.72, p=0.55). The risk of all-cause mortality and cardiovascular mortality was lower in patients previously receiving active treatment (17 vs. 30, HR= 0.48, 95% CI 0.26 to 0.87, p= 0.02 and 2 vs. 9, HR= 0.19, 95% CI 0.04 to 0.87, p=0.03, respectively).
Beckett et al. 2014 **UK** **RCT** ***HYVET* Study Group (subgroup and per protocol analyses)**	As above	Per original study ITT analysis (n=3845), per protocol analysis (n=3822)	Subgroups included age (80-84.9 years and ≥85 years), sex, history of CVD, baseline SBP (160-169, 170-179, ≥180 mm Hg)	Total mortality, cardiovascular mortality, stroke, heart failure and cardiovascular events	For the outcome of stroke, there was a trend towards reduced risk associated with active treatment across all subgroups. For the outcome of total mortality, the risk was significantly reduced for women, younger patients (80-84.9 yrs) and those without a history of CVD taking active treatment, with trends towards reduced risk for the remaining subgroups. The median follow-up for per protocol patients was 1.7 years. In per protocol analysis, there was a significant reduction in the risk of fatal/non-fatal stroke and stroke mortality associated with active treatment (HR=0.63, 95% CI 0.44-0.92, p<0.016 and HR=0.55, 95% CI 0.33-0.92, p<0.021, respectively).
Yusuf et al. 2008 **International** **RCT (factorial)** ***Ongoing Telmisartan Alone and in Combination***	CA: ☑ Blinding: Patient ☑ Assessor ☑ ITT: ☑	25,620 patients with coronary, peripheral, or cerebrovascular disease or diabetes with end-organ damage who could not tolerate ACE inhibitors. Mean age was 66 years, 216% were	Patients were randomized to receive either an ACE-inhibitor (ramipril 10 mg/day, n=8,576), an ARB (telmisartan 80 mg/day, n=8,542) or a combination of both drugs (n=8,502).	**Primary outcome:** Death from cardiovascular causes, MI, stroke or hospitalization for heart failure **Secondary outcomes:** Composite outcome of death from cardiovascular causes,	Median follow-up period was 56 months. Death from cardiovascular causes was similar among groups (ramipril: 16.5%, telmisartan 16.7% and combination therapy 16.3%). Death from MI or stroke was similar across groups (ramipril: 4.7%, telmisartan 4.3% and combination therapy 4.4%).

Study/Type	Quality Rating	Sample Description	Method	Outcomes	Key Findings and Recommendations
with Ramipril Global Endpoint Trial (ONTARGET)		women. 21% had previous stroke or TIA		myocardial infarction, or stroke and new onset of heart failure, diabetes mellitus, atrial fibrillation, dementia or cognitive decline, nephropathy, and revascularization procedures.	Death from any cause was similar across groups (ramipril: 11.8%, telmisartan 11.6% and combination therapy 12.5%). Occurrence of stroke was similar among groups (ramipril: 14.1%, telmisartan 13.9% and combination therapy 14.1%). The use of telmisartan was associated with a higher incidence of hypotensive symptoms (p<0.001) than treatment with ramipril. Combination therapy was associated with increased risk of hypotensive symptoms (p<0.001), syncope (p=0.03) and renal dysfunction (p<0.001) when compared to ramipril.
Yusuf et al. 2008, Foulquier et al. 2014 **International** **RCT** ***Telmisartan Randomised AssessmeNt Study in ACE iNtolerant subjects with cardiovascular Disease (TRANSCEND)***	CA: ☑ Blinding: Patient ☑ Assessor ☑ ITT: ☑	5,926 high-risk patients who were intolerant to ACE-inhibitors (same design as ONTARGET). Mean age was 67 years, 43% were female, 22% had prior stroke/TIA	Following a 3-week run-in period (week 1-placebo daily, 2 weeks 80 mg telmisartan), patients were randomized to receive either telmisartan (80mg/day, n=2,954) or placebo (n=2,972). All patients received treatment for hypertension with proven therapies, as required	**Primary outcome:** Composite of cardiovascular death, MI, stroke or hospitalization for heart failure **Secondary outcomes:** Composite of cardiovascular death, MI or stroke Additional outcomes: new heart failure, development of DM, AF, dementia nephropathy and revascularization.	**Main Results** Median follow-up was 56 months. Mean blood pressure was significantly lower among patients in the telmisartan group throughout the trial. Non-significantly fewer patients in the telmisartan group experienced the primary outcome (15.7% vs. 17.0%, HR=0.92, 95% CI 0.81-1.05, p=0.216). There was no difference between groups in the risk of the individual components of the primary outcome. After adjusting for multiple comparisons, Non-significantly fewer patients in the telmisartan group experienced the composite outcome of cardiovascular death or stroke (13.0% vs. 14.8%, HR=0.87, 95% CI 0.76-1.00, p=0.068). No differences between groups were noted based on subgroup analysis (history of CVD, DM, blood pressure, age, sex, HOPE score or statin use) **Post hoc analysis (Foulquier et al. 2014)**

Study/Type	Quality Rating	Sample Description	Method	Outcomes	Key Findings and Recommendations
					Analysis of patients who were hypertensive (≥140/90 mm Hg, n=5098) at the start of run in compared with those who were normotensive (n=828). Patients who were hypertensive were significantly older, with higher BMIs, higher pulse pressures and rates and a higher percentage had experienced a previous stroke or TIA. There was no significant difference in the risk of any of the outcomes between groups (p for interaction all>0.05). Among patients with hypertension, the risks of the primary and secondary outcomes and MI were significantly lower for patients taking telmisartan, treated after 6 months (vs. ≤6 months).
Yusuf et al. 2008 **International** **RCT (factorial)** ***Prevention Regimen For Effectively Avoiding Second Strokes (PRoFESS)***	CA: ☑ Blinding: Patient ☑ Assessor ☑ ITT: ☑	20,332 patients >50 years who had suffered an ischemic stroke within 120 days	Patients were randomly assigned to an active treatment group (80 mg/day telmisartan, n=10,146) or placebo (n=10,186). All patients received open-label treatment for hypertension as necessary at the discretion of the investigators	**Primary outcome:** Recurrent stroke by end of follow-up **Secondary outcomes:** Major cardiovascular events (death from cardiovascular causes, myocardial infarction, recurrent stroke, or worsening or new heart failure) and new-onset diabetes.	Median follow-up was 2.5 years. The median interval from stroke to randomization was 15 days. A non-significantly fewer number of patients in the active therapy group experienced recurrent stroke (8.7% vs. 9.2%, HR=0.95, 95% CI 0.86 to 1.04, p= 0.23). A non-significantly fewer number of patients in the active therapy group experienced death from cardiovascular causes, recurrent stroke, myocardial infarction, or new or worsening heart failure (13.5% vs. 14.4%, HR=0.94, 95% CI 0.87 to 1.01, = 0.11). There were more cases of adverse events leading to discontinuation of the study drug in the active therapy group (14.3% vs. 11.1%, p<0.001). A non-significantly fewer number of patients in the active therapy group developed new-onset

Study/Type	Quality Rating	Sample Description	Method	Outcomes	Key Findings and Recommendations
					diabetes (1.2% vs. 1.5%, HR=0.82, 95% CI 0.65 to 1.04, p= 0.10). No significant differences were reported for any subgroup analysis. Post hoc analyses suggested the impact of telmisartan may be time-dependent, with greater benefits apparent after > 6 months of treatment. A total of 125 patients (0.6%) were lost to follow up. (51 in the active therapy group and 74 in the placebo group).
Jamerson et al. 2008 **International** **RCT** ***Avoiding Cardiovascular Events Through Combination Therapy in Patients Living With Systolic Hypertension (ACCOMPLISH)***	CA: ☑ Blinding: Patient ☑ Assessor ☑ ITT: ☑	11,506 patients with hypertension, and at high risk for cardiovascular events. Mean age was 68 years, 60% were men. 13% had a previous stroke	Patients were randomized to receive either 20 mg benazepril + 5 mg amlodipine once daily (n=5,744) or 20 mg benazepril + 12.5 mg hydrochlorothiazide (HCTZ) (n=5,762). Benazepril was increased to 40 mg after one month in both groups. Investigators could increase amlodipine to 10 mg or HCTZ to 25 mg to meet target blood pressure of <140/90 mmHg (130/80 mmHg for patients with diabetes or kidney disease). The addition of other antihypertensive agents was permitted if they were not of the same class as the study drugs.	**Primary outcome:** Time to the first event (composite of cardiovascular event and death from cardiovascular causes). **Secondary outcomes:** Individual components of primary outcome	Mean follow-up was approximately 36 months in both groups. The trial was terminated early. Blood pressure control (defined as< 140/90 mm Hg), was achieved by 75.4% of patients in the benazepril–amlodipine group and 72.4% in the benazepril–HCTZ group. There were fewer events in the benazepril–amlodipine group compared with the benazepril–HCTZ group (552 vs. 679, RRR=20%, HR= 0.80, 95% CI, 0.72 to 0.90, p<0.001). There was no significant difference in death from cardiovascular causes between groups (HR=0.80 (0.62 to 1.03, p=0.08) or fatal/nonfatal stroke (HR=0.84, 95% CI 0.65 to 1.08, p=0.17). There were significantly fewer fatal/nonfatal myocardial infarctions in the group receiving benazepril-amlodipine (HR = 0.78, 95% CI 0.62 to 0.99, p=0.04). There were reports of 23 drug-related serious adverse events in the benazepril-amlodipine group and 21 in the benazepril–HCTZ group.
Schrader et al. 2005	CA: ☑	1,352 individuals with hypertension and a	Participants were randomized to receive	**Primary outcome:** Mortality and number of	Mean follow-up was 2.5 years.

Study/Type	Quality Rating	Sample Description	Method	Outcomes	Key Findings and Recommendations
Germany/Austria **RCT** ***Morbidity and Mortality After Stroke (MOSES*)**	Blinding: Patient: ☑ Assessor ☑ ITT: ☑	history of TIA, ischemic stroke or cerebral hemorrhage	either nitrendipine (10 mg, n=671) or eprosartan (600 mg, n=681) daily. Target blood pressures were 140/90 mmHg. Additional therapy with diuretics, β-blockers or α-blockers was permitted as necessary to reach target pressure.	cardiovascular and cerebrovascular events (composite index) **Secondary outcomes:** Single components of the combined primary end point.	Fewer total events occurred in the eprosartan group (206 vs. 255, Incidence Density Ratio= 0.79, 95% CI, 0.66 to 0.96, p=0.014). Fewer fatal/nonfatal strokes occurred in the eprosartan group (102 vs. 134, Incidence Density Ratio= 0.75, 95% CI 0.58 0.97, p=0.026). There was no difference in the risk of mortality between groups (57 vs. 52, HR= 1.07, 95% CI 0.73 1.56, p= 0.725). Frequency of adverse events was similar in both groups.
Lithell et al. 2003 **International** **RCT** ***Study on Cognition and Prognosis in the Elderly (SCOPE)* study**	CA: ☑ Blinding: Patient: ☑ Assessor ☑ ITT: ☑ (primary analysis)	4,964 patients aged 70–89 years, with treated or untreated SBP of 160–179 mmHg, and/or DBP 90–99 mmHg, and a Mini Mental State Examination (MMSE) test score > 24. Mean age was 76 years, 64.5% were women. 3.9% had a previous stroke.	Patients were randomized to receive 8-16 mg candesartan (n=2,477) or placebo (n=2,460) daily, with open-label active antihypertensive therapy added as needed. The recommendation was to start with HCT 12.5 mg once daily. Other drugs, except ACE-I and ARBs could be added later. (active antihypertensive therapy was used in 84% of control group patients). Patients were treated for 3-5 years.	**Primary outcome:** Cardiovascular mortality, stroke and MI at end of follow-up (composite outcome) **Secondary outcomes:** Cardiovascular death, non-fatal and fatal stroke and myocardial infarction, cognitive function measured by the MMSE and dementia.	The mean follow-up was 3.7 years. Blood pressures fell significantly in patients in both groups. The primary outcome occurred in 242 patients in the candesartan group and in 268 patients in the control group. The associated risk reduction was 10.9%, 95% CI -6.0% to 25.1%, p= 0.19). Non-fatal stroke occurred in 68 patients in the candesartan group and in 93 patients in the control group. The associated risk reduction was 27.8%, 95% CI, 1.3 to 47.2, p= 0.04). All stroke occurred in 89 patients in the candesartan group and in 115 patients in the control group. The associated risk reduction was 23.6%, 95% CI -0.7% to 42.1%, p= 0.056). There were no differences between the treatment groups in the proportions of patients who had a significant cognitive decline or developed dementia. In both treatment groups the most common adverse events were dizziness/vertigo (21%),

Study/Type	Quality Rating	Sample Description	Method	Outcomes	Key Findings and Recommendations
					accident/injury (18.4%), back pain (19.2%) and bronchitis (16.0%). 8 patients were lost to follow-up.
Dahlof et al. 2002 **Sweden/ International** **RCT** ***Losartan Intervention For Endpoint reduction in hypertension (LIFE)* study**	CA: ☑ Blinding: Patient: ☑ Assessor ☑ ITT: ☑	9,193 patients aged 55-80 years with essential hypertension and left ventricular hypertrophy. Mean age was 67 years, 54% were women. 8% had a history of cerebrovascular disease	Patients were randomized to receive either a losartan-based (n=4,605) or atenolol-based (n=4,588) antihypertensive regimen for 4 years.	**Primary outcome:** Cardiovascular mortality, stroke and MI at end of follow-up (composite outcome) **Secondary outcomes:** Total mortality, new onset diabetes	The mean duration of follow-up was 4.8 years. Blood pressures were reduced substantially in both groups. Fewer patients in the losartan group experienced the composite endpoint (11% vs. 13%, adjusted HR=0.87, 95% CI 0.77 to 0.98, p=0.021). Fewer patients in the losartan group experienced a fatal or nonfatal stroke (5% vs. 7%, adjusted HR=0.75, 95% CI 0.63 to 0.89, p<0.001) or new onset of diabetes (6% vs. 8%, adjusted HR=0.75, 95% CI 0.63 to 0.88, p<0.001).
***Antihypertensive & Lipid Lowering Treatment to Prevent Heart Attack Trial (ALLHAT)* Collaborative Research Group 2002, Cushman et al. 2012 (long-term follow-up)** **USA/Canada** **RCT**	CA: ☑ Blinding: Patient: ☑ Assessor ☑ ITT: ☑	33,357 hypertensive patients > 55 years with at least one other coronary CHD risk factor. The mean age at baseline was 67 years, 47% were women. 23% had a history of stroke or MI.	Patients were randomized to receive chlorthalidone, 12.5 to 25 mg/d (n = 15,255), amlodipine, 2.5 to 10 mg/d (n = 9,048), or lisinopril, 10 to 40 mg/d (n = 9,054) for approximately 4 to 8 years.	**Primary outcome:** Combined fatal CHD or nonfatal myocardial infarction **Secondary outcomes:** All-cause mortality, stroke, combined CHD (primary outcome, coronary revascularization, or angina with hospitalization), and combined CVD (combined CHD, stroke, treated angina without hospitalization, heart failure and peripheral arterial disease).	The mean follow-up was 4.9 years. The 6-year rate/100 person for the primary outcome was similar across treatment groups (11.5 vs. 11.3 vs. 11.4). The 6-year rate/100 person for the risk of stroke was 5.6 (chlorthalidone), 5.4 (amlodipine) and 6.5 (lisinopril). Compared with chlorthalidone, the risk of stroke was higher with lisinopril (RR=1.15, 95% CI 1.02 to 1.30, p=0.02). The 6-year rate/100 person for the risk of heart failure was 7.7 (chlorthalidone), 10.2 (amlodipine) and 8.7 lisinopril). Compared with chlorthalidone, the risk of heart failure was higher with amlodipine (RR=1.38, 95% CI 1.25 to 1.52, p<0.01) and lisinopril (RR=1.19, 95% CI 1.07 to 1.31, p<0.01). **Long-term follow-up** The results from 21,623 participants were included.

Study/Type	Quality Rating	Sample Description	Method	Outcomes	Key Findings and Recommendations
					The mean duration of follow-up was 8.8 years. The 10-year rate/100 person for all-cause mortality was similar across treatment groups: 33.6 (chlorthalidone), 33.2 (amlodipine) and 32.8 (lisinopril). The risk of stroke mortality associated with amlodipine was not significantly higher compared with chlorthalidone (reference) HR=1.01, 95% CI 0.84-1.20 The risk of stroke mortality was significantly higher in the lisinopril group (vs. chlorthalidone) HR=1.20, 95% CI 1.01-1.41. There was no difference between groups for the combined outcome of fatal/nonfatal hospitalized stroke. When comparing in-trial and post-trial events, there were no significant between groups (amlodipine vs. diuretic and lisinopril vs. diuretic) in terms of all-cause mortality or mortality attributable to stroke.
Reisin et al. 2014 **Subgroup analysis of ALLHAT**	NA	33,252 patients with baseline BMI recorded	Randomized patients were classified post hoc by BMI as normal weight (BMI<25, n=6,625), overweight (BMI≥25 to <30, n=12,613) and obese (≥30, n=14,014)	**Primary outcome:** Combined fatal CHD or nonfatal myocardial infarction **Secondary outcomes:** All-cause mortality, stroke, combined CHD (primary outcome, coronary revascularization, or angina with hospitalization), and combined CVD (combined CHD, stroke, treated angina without hospitalization, heart failure and peripheral arterial disease).	By year 5, 66.1%, 66.5% and 65.1% who were normal weight, overweight and obese were well-controlled (BP<140/90 mm Hg) There were no significant interactions (treatment group x BMI group). The best BP control was achieved with chlorthalidone and lisinopril, the poorest. For the treatment contrast of amlodipine vs. chlorthalidone, the risk of stroke was not significantly reduced, regardless of BMI group Normal weight: HR=0.97, 95% CI 0.74-1.25 Overweight: HR=0.89, 95% CI 0.72-1.09 Obese: HR=0.95, 95% CI 0.78-1.16

Study/Type	Quality Rating	Sample Description	Method	Outcomes	Key Findings and Recommendations
					For the treatment contrast of lisinopril vs. chlorthalidone, the risk of stroke was not significantly reduced, regardless of BMI group Normal weight: HR=1.14, 95% CI 0.89-1.46 Overweight: HR=1.15, 95% CI 0.95-1.39 Obese: HR=1.15, 95% CI 0.95-1.39
***Perindopril Protection Against Recurrent Stroke Study (PROGRESS)* Collaborative Group 2001** **Australia** **RCT**	CA: ☑ Blinding: Patient ☑ Assessor ☑ ITT: ☑	6,105 patients with a history of stroke (ischemic or hemorrhagic) or TIA within the previous 5 years. No blood pressure entry criteria	Patients who adhered to, and tolerated, the run-in treatment were randomly assigned to continued active therapy (n=3,051) or matching placebo (n=3,054). Patients in the active treatment group received a flexible regimen based on perindopril (4 mg daily) with the addition of indapamide (2.5 mg daily) in patients for whom the responsible physician judged there to be no specific indication for or contraindication to treatment with a diuretic.	**Primary outcome:** Fatal/nonfatal stroke **Secondary outcomes:** Fatal or disabling stroke, total vascular events (vascular death, non-fatal MI, non-fatal stroke), death due to any vascular cause Participants were seen 5 times during the first year and then bi-annually up to 4 years.	4-year outcome data was available for all but 3 patients. Mean duration of follow-up was 3.9 years. 22% of patients had discontinued medication by end of study follow-up. Significantly fewer patients in the active treatment group had: a stroke at the end of follow-up (10% vs. 14%, RRR=28%, 95% CI 17%-38 %, p< 0.0001); or suffered a major vascular event (15% vs. 20%, RRR=26%, 95% CI 16% to 34%). There was no significant difference in mortality between groups (10.0% vs. 10.4%, RRR=4%, 95% CI -12% to 18%). Patients treated with combination therapy had fewer strokes compared with patients who received double placebo (8.4% vs. 14.4%, RRR=43%, 95% CI 30% to 54%). The occurrence of stroke in patients treated with single therapy was not significantly different compared with patients who received placebo (12.3% vs. 12.9%). Patients who were both normotensive and hypertensive at baseline had significant reductions in the risk of stroke.
Perry et al. 2000 **Additional analysis from *Systolic Hypertension in the Elderly***	CA: ☑ Blinding: Patient ☑ Assessor ☑ ITT: ☑	4,736 persons aged ≥60 years with systolic blood pressures from 160-219 mm Hg. Mean age was 71.6 years, 43.2% were men. 1.4% had a previous stroke	Subjects were randomized to receive 12.5 mg/d of chlorthalidone. If required to maintain target BP, additional treatment could be added including	**Primary outcome:** Occurrence, type and subtype of stroke	The average follow-up was 4.5 years. The incidence of all stroke was lower in patients receiving active treatment (103 vs. 159, adjusted risk ratio=0.63, 95% CI 0.49 to 0.81)

Study/Type	Quality Rating	Sample Description	Method	Outcomes	Key Findings and Recommendations
Program (SHEP) **trial** **USA** **RCT**			25 mg of chlorthalidone, 25 mg/d of atenolol or 0.05 mg/d of reserpine (n = 2,365) or placebo (n = 2,371).		The incidences of ischemic stroke and hemorrhagic were lower in patients receiving active treatment (85 vs.132, adjusted risk ratio=0.63; 95% CI 0.48 to 0.82 and 9 vs. 19 adjusted RR=0.46, 95% CI 0.21 to 1.0, respectively). There was no difference in stroke recurrence between groups (12 vs. 17, p=0.34). Subjects who met pre-specified BP targets were at lower risk for development of stroke.
Hansson et al. 1998 **International** **RCT** ***Hypertension Optimal Treatment (HOT)***	CA: ☑ Blinding: Patient: ☑ Assessor ☑ ITT: ☒	18,790 patients, aged 50 to 80 years with diastolic blood pressure between 100 mm Hg and 115 mm Hg. A small number of participants (~1.2%) had experienced a previous stroke	Patients were randomly allocated to 1 of 3 target groups based on diastolic BP; ≤ 90 m Hg (n=6264), ≤ 85 mm Hg (n=6264) or ≤ 80 mm Hg (n=6262). All patients received a 5-step treatment regimen beginning with felodipine 5 mg/day followed by the addition of ACE inhibitors or β-blockers, increased felodipine, increased ACE-inhibitors or β-blockers and, finally, a diuretic. Additional steps were added, as required to achieve target BP. All patients were then randomized to receive 75 mg of ASA/day (n=9399) or matching placebo (n=9391).	**Primary outcome:** Major cardiovascular events (fatal and nonfatal MI, strokes and all other cardiovascular deaths) **Secondary outcomes:** Individual components of primary outcome	There were no differences among groups for the outcomes of major cardiovascular events (232 vs. 234 vs. 217, p=0.5), major cardiovascular events, including silent myocardial infarction (274 vs. 276 vs. 263, p=0.66), all stroke (94 vs.111 vs. 89, p=0.74) or total mortality (188 vs. 194 vs. 207, p=0.32). In 1,501 patients with diabetes mellitus at baseline, the risk of major CV events was doubled for patients in the ≤90 mm Hg group compared with ≤80 mg Hg (RR=2.06, 95% CI 1.24 to 3.44). In 3,080 patients with pre-existing ischemic heart disease, the lowest targeted BP group was associated with the fewest stroke events (p=0.046). There was a 43% reduction of strokes in ≤80 mm Hg target group compared with ≤90 mm Hg target group. Treatment with ASA significantly reduced major cardiovascular events by 15% (p=0.03) and all MI by 36% (p=0.002). There were 7 fatal bleeds in the ASA group and 8 in the placebo group. There were more nonfatal major bleeds in the ASA group (129 vs.70, p<0.001).

Study/Type	Quality Rating	Sample Description	Method	Outcomes	Key Findings and Recommendations
					491 (2.6%) patients were lost to follow-up.
Clinical trials including participants at high risk of cardiovascular disease with no history of previous stroke					
White et al. 2019 **USA** **RCT** ***Intensive Versus Standard Ambulatory Blood Pressure Lowering to Prevent Functional Decline In the Elderly (INFINITY)***	CA: ☑ Blinding: Patient: ☒ Assessor ☑ ITT: ☑	199 persons ≥75 years, with systolic HTN based on clinic and ambulatory blood pressure measurements, (or SBP 150 to 170 mm Hg if taking ≥1 antihypertensive drugs, or >170 mm Hg if taking 0 to 1 antihypertensive drug at screening) and with visible white matter hyperintensity lesions on MRI (typically ≥0.5% lesion volume). Persons with a history of stroke were excluded. Mean age was 85 years, 54% were women.	Patients were randomized to receive intensive treatment (24-hour SBP target ≤130 mmHg), or to standard treatment (≤145 mmHg),	**Primary outcomes:** Gait speed, 4-step ascent/decent, sit to stand, supine to sit, unipedal balance, functional reach, accrual of white matter hyperintensity lesions **Secondary outcomes:** Change in cognitive function (executive function, processing time) **Safety outcomes:** Mortality, major nonfatal cardiovascular events Outcomes were assessed at 18 and 36 months	The mean 24-hour SBP was 127.7 mmHg in the intensive treatment group and 144.0 mmHg in the standard treatment group (mean difference of 16.3 mmHg). There were no differences between groups in mean changes from baseline and 18 or 36 months in any of the mobility measures. There were no differences between groups in changes from baseline and 36 months in any of the assessments of cognitive function except for the California Computerized Assessment Package Sequential Reaction Time (-23.2 vs. 32.6 msec), favouring the intensive group. The percentage increase in white matter hyperintensity was significantly less in the intensive group (0.29% vs. 0.5%, p=0.03). The risk of a serious cardiovascular event was significantly lower in the intensive group (HR=0.24, 95% CI, 0.08–0.68; P<0.01). The most common event was arrhythmia. There was a single stroke in the intensive group and 2 in the standard group.
Lonn et al. 2016 **Canada** **RCT** ***Heart Outcomes Prevention Evaluation-3 (HOPE-3) (blood-pressure lowering arm)***	CA: ☑ Blinding: Patient: ☑ Assessor ☑ ITT: ☑	12,705 men ≥55 and women ≥65 years with at least one cardiovascular risk factor (women ≥60 years with at least 2 risk factors were also eligible), but without known cardiovascular (CV) disease. Persons with an absolute indication for, or contraindication to any of the study medications	2 x 2 factorial design (blood pressure and statin arms). During a 4-week run in period participants took both active study medications. Those who were compliant with treatment and did not suffer adverse events were randomized to receive 16 mg/day candesartan +12.5 mg	**Primary outcomes:** i) Composite of death from CVD, or nonfatal MI or nonfatal stroke ii) i) + resuscitated cardiac arrest, heart failure or revascularization **Secondary outcomes:** primary outcome ii) + angina + evidence of ischemia, fatal or nonfatal stroke	Mean baseline blood pressure was similar between groups (combination therapy vs. placebo) SBP: 138.2 vs. 137.9 mm Hg DBP: 82.0 vs. 81.8 mm Hg The median duration of follow-up was 5.6 years. The mean decrease in SBP over the trials was 10.0 mm Hg (combination therapy) and 4.0 mm Hg (placebo). The corresponding mean decreases for DBP were 5.7 and 2.7 mm Hg.

Study/Type	Quality Rating	Sample Description	Method	Outcomes	Key Findings and Recommendations
		were excluded. Participants were recruited from 228 centers in 21 countries. Mean age was 65.7 years, 46% were male, 47% of participants had 2 CV risk factors, 24% had ≥3.	hydrochlorothiazide (HCTZ) or placebo for the duration of the trial. All participants received individualized lifestyle advice.	**Additional outcomes:** Death from any cause, components of the primary and secondary outcomes, new onset diabetes, hospitalizations	The risk of the first primary outcome was non-significantly lower in the combination therapy group (4.1% vs. 4.4%, HR=0.93, 95% CI 0.79-1.10, p=0.40). The risk of the second primary outcome was non-significantly lower in the combination therapy group (4.9% vs. 5.2%, HR=0.95, 95% CI 0.81-1.11, p=0.51) The risk of the secondary outcome was non-significantly lower in the combination therapy group (5.3% vs. 5.7%, HR=0.92, 95% CI 0.79-1.06, p=0.26). The risk of fatal of nonfatal stroke was non-significantly lower in the combination therapy group (1.2% vs. 1.5%, HR=0.80, 95% CI 0.59-1.08). The risk of any of the additional outcomes was non-significantly lower in the combination therapy group. In subgroup analysis, based on baseline BP, participants in the highest tertile (SBP>143.5 mm Hg) had a significantly lower risk of the first and second primary outcomes (HR=0.73, 95% CI 0.56-0.94 and HR=0.76, 95% CI 0.60-0.96). At 5 years, 75.0% of patients in the combination therapy group were taking their prescribed medication compared with 75.7% in the placebo group.
Wright et al. 2015 **USA** **RCT**	CA: ☑ Blinding: Patient ☒ Assessor☒ ITT: ☑	9,250 participants aged ≥ 50 years with SBP ≥130-180 mm Hg and at least one additional CVD risk factor were recruited from 102 clinical sites. Patients with diabetes or	Patients were randomized to an intensive BP arm with a goal of SBP <120 mm Hg using 2-drug therapy, if required (n=4,678) vs. a standard arm with a goal	**Primary outcomes:** First occurrence of: MI, acute coronary syndrome, heart failure or cardiovascular death **Secondary outcomes:**	Study was terminated early after a median follow-up of 3.26 years. Over the study period, the mean SBP of patients in the intensive group was lower (121.5 vs. 134.6 mm Hg)

Study/Type	Quality Rating	Sample Description	Method	Outcomes	Key Findings and Recommendations
Systolic Blood Pressure Intervention Trial (SPRINT)		previous stroke were excluded. Mean age for patients in both groups was 67.9 years, 36% were female. Mean Framingham 10-year risk score was 20.1%. <10% of patients in both groups were not taking any antihypertensive agents	of SBP <140 mm Hg (n=4,683) for up to 6 years. Participants were seen monthly for the first 3 months and every 3 months thereafter, with adjustments to medications, as required. Lifestyle modification was encouraged as part of the management strategy	Individual components of the primary outcome	The primary outcome occurred in 562 patients. The risk was significantly lower for patients in the intensive group (1.65%/yr vs. 2.19%/yr, HR=0.75, 95% CI 0.64-0.89, p<0.001). No significant interactions were noted in subgroup analyses of presence of chronic kidney disease, age, sex, race, previous CVD or baseline SBP. The risks of cardiovascular death or death from any cause were significantly reduced in the intensive therapy group (HR=0.57, 95% CI 0.38-0.85, p=0.005 and HR=0.73, 95% CI 0.60-0.90, p=0.003, respectively). The numbers needed to treat to prevent: Primary composite outcome was 61; Death from any cause was 90 and Death from cardiovascular cause was 172. The risk of stroke was not significantly reduced in the intensive therapy group (1.3%/yr vs. 1.5%/yr, HR=0.89, 95% CI 0.63-1.25, p=0.50). The risks of serious adverse events including episodes of hypotension, syncope, electrolyte abnormality, and acute renal failure were all significantly higher in the intensive group. The risk of serum sodium and potassium abnormalities and orthostatic hypotension were significantly increased in the intensive group.

Intensive Treatment of Hypertension in Persons with Diabetes for the Prevention of Stroke

Study/Type	Quality Rating	Sample Description	Method	Outcomes	Key Findings and Recommendations
Hao et al. 2014 **China** **Systematic review &**	NA	10 RCTs (n=21,871) examining the effects of angiotensin-converting enzyme (ACE) inhibitors and angiotensin II	Treatment contrasts included: ACE inhibitors vs. β-blockers (n=1), ACE inhibitors vs. Ca Channel blockers (n=1),	**Primary Outcome:** All-cause mortality **Secondary outcomes:** CV mortality, MI, stroke and	Mean duration of follow-up ranged from 2.5->9 years. Treatment with ACE/ARBs was not associated with a significant reduction in the risk of all-cause

Study/Type	Quality Rating	Sample Description	Method	Outcomes	Key Findings and Recommendations
meta-analysis		receptor blockers (ARBs) on cardiovascular (CV) risk in hypertensive patients with type 2 diabetes. Mean age of patients ranged from 56-64 years.	ARB vs. placebo (n=1), ACE inhibitor vs. other drugs (n=1), Angiotensin 2 receptor blocker vs. placebo (n=2), ACE inhibitor vs. placebo (n=2), Angiotensin 2 receptor blocker vs. Ca channel blocker(n=2),	CV events	mortality (HR=0.91, 95% CI 0.83-1.00, p=0.062). Treatment with ACE/ARBs, was not associated with a significant reduction in the risk of stroke (HR=0.99, 95% CI 0.85-1.15, p=0.86). Results from 8 trials included.
Arguedas et al. 2013 **Costa Rico & Canada** **Cochrane review**	NA	5 RCTs (n=7,314) examining trials comparing 'lower' BP targets (any target <130/85mmHg) with 'standard' BP targets (<140 - 160/90 – 100 mmHg) in people with diabetes. Participants were adults with type II DM and elevated blood pressure, or already receiving treatment for elevated blood pressure. Participants in all included trials were between 40-5 and 70-82 years at baseline.	Treatment contrasts of the included studies: **ACCORD-BP**: intensive group (SBP <120 mm Hg) vs. standard group (SBP<140 mm Hg) **ABCD-H & ABCD-2V**: intensive group (DBP <75 mm Hg) vs. moderate group (DBP 80-89 mm Hg) **ABCD-N**: intensive group (DBP of 10 mm Hg below baseline) vs. standard group (DBP 80-89 mm Hg). **HOT** subgroup: DBP ≤90 mm Hg vs. ≤85 mm Hg vs. ≤80 mm Hg Hypertensive agents used included Calcium channel blockers, ACE inhibitors and ARBs. In some cases, no specific drug regimen was described.	**Primary outcome:** All-cause mortality, adverse events **Secondary outcomes:** Systolic and diastolic BPs achieved, number of antihypertensive agents required.	In the single trial aimed at reductions in SBP (ACCORD) intensive BP control was not associated with reductions in total mortality (RR= 1.05, 95% CI 0.84-1.30) but was associated with reduction in the risk of stroke (RR=0.58, 95% CI 0.39 to 0.88, p= 0.009). In the 4 trials aimed at reductions in DBP, intensive BP control was not associated with reductions in total mortality (RR= 0.73, 95% CI 0.53-1.01, p=0.054) or stroke (RR= 0.67, 95% CI 0.42-1.05, p=0.077).
Muramatsu et al.	CA: ☑	1,150 participants aged	Patients were	**Primary outcome:**	The median duration of follow-up was 3.2 years.

Study/Type	Quality Rating	Sample Description	Method	Outcomes	Key Findings and Recommendations
2012 **Japan** **RCT** ***Nagoya Heart Study***	Blinding: Patient ☒ Assessor ☑ ITT: ☑	30-75 years with HTN (BP≥140/90 mm Hg) and diabetes or impaired glucose tolerance. Mean age was 63 years, 34% were female. 57% of patients were already taking antihypertensive agents at start of the study. Baseline BP was 145/82 mm Hg. Mean baseline hg $A1_C$ was 7.0%	randomized to a valsartan (n=575) or the amlodipine (n=575) treatment group. Starting doses were 80 mg valsartan or 5 mg amlodipine once daily. During follow-up, target blood pressure was ≤130/80 mmHg. Physicians could increase the respective doses to a maximum of 160 mg or 10 mg daily after 4 weeks, and add additional agents, if needed. Blood glucose control was performed according to the Japan Diabetes Society treatment guidelines.	Composite of MI, stroke, new or worsening heart failure, coronary revascularization procedures, or sudden cardiac death **Secondary outcome:** All-cause mortality	The mean BPs did not differ significantly between groups throughout the study period. (131/73 vs. 132/74 mm Hg). The primary outcome occurred in 54 patients in the valsartan group vs. 56 patients in the amlodipine group (HR=0.97, 95% CI 0.66-1.40, p=0.85). The incidences of ischemic and hemorrhagic stroke were similar between groups (1.7% vs. 1.9%, HR=0.90, 95% CI 0.38-2.12, p=0.81 and 0.3% vs. 0.7%, HR=0.50, 95% CI 0.09-2.74, p=0.43, respectively). The incidences of cardiovascular death and all-cause mortality were similar between groups (0.7% vs. 0.7%, HR=1.00, 95% CI 0.25-3.99, p=0.99 and 3.8% vs. 2.8%, HR=1.37, 95% CI 0.72-2.61, p=0.34). There were 106 adverse events reported for 94 patients in the valsartan group and 112 events in 94 patients in the amlodipine group. There were no serious adverse events reported.
Redon et al. 2012 **Additional subgroup analysis from *ONTARGET*** **RCT**	CA: ☑ Blinding: Patient ☑ Assessor ☑ ITT: ☑	25,620 patients with coronary, peripheral, or cerebrovascular disease or diabetes with end-organ damage who could not tolerate ACE inhibitors. 9,603 (37.5%) of the total sample were patients with type 2 DM	Patients were randomized to receive either an ACE-inhibitor (ramipril 10 mg/day, n=8,576), an ARB (telmisartan 80 mg/day, n=8,542) or a combination of both drugs (n=8,502). Comparisons between diabetic and non-diabetic patients	**Primary outcome:** Death from cardiovascular causes, MI, stroke or hospitalization for heart failure	The primary outcome occurred more frequently in diabetic patients (20.2% vs. 14.2%, HR=1.48; 95% CI 1.38 to 1.57). The risks for components of the primary outcome were higher in diabetics: CV death (HR=1.56, 95% CI 1.42 to 1.71), MI (HR= 1.30, 95% CI 1.17 to 1.46), stroke (HR= 1.39, 95% CI 1.23 to 1.56) and hospitalization for CHF (HR= 2.06, 95% CI 1.82 to 2.32).
Cushman et al. 2010	CA: ☑	4,733 participants, 40-79 years with type 2	Patients were randomized to receive	**Primary outcome:** First occurrence of a major	Mean duration of follow-up was 4.7 years.

Study/Type	Quality Rating	Sample Description	Method	Outcomes	Key Findings and Recommendations
USA **RCT (factorial)** ***Action to Control Cardiovascular Risk in Diabetes (ACCORD) (hypertension arm)***	Blinding: Patient: ☒ Assessor ☒ ITT: ☑	diabetes mellitus with an HbA1c level of 7.5%-9.0%, if on more drugs or 7.5%-11%, if on fewer drugs. Mean age of all participants at baseline was 62 years. 48% of patients were women. Median duration of DM was 8.1 years. Mean systolic BP was 139 mm Hg and mean diastolic BP was77 mm Hg	either intensive therapy (target = SBP <120mm Hg; n=2,362) or standard therapy (target SBP = 140mm Hg; n=2,371) using treatment strategies in current clinical practice.	CVD event, including nonfatal heart attack, nonfatal stroke, or cardiovascular death **Secondary outcomes:** Total mortality	After the first year, the average systolic BP was 119.3 mmHg in the intensive therapy vs. 133.5 mmHg in the standard group. Diastolic blood pressure was 64.4 mmHg in the intensive vs. 70.5 in the standard group. There was no significant reduction in the risk for the primary outcome associated with intensive HTN treatment (HR=0.88, 95% CI 0.73-1.06, p=0.20). There were significant reductions in the risk of any and non-fatal stroke associated with intensive HTN treatment (HR=0.59, 95% CI 0.39-0.89, p=0.01 and HR=0.63, 95% CI 0.41-0.96, p=0.03, respectively). Serious adverse events, attributed to therapy occurred more often in patients in the intensive group (3.3% vs. 1.3%, p<0.001).
Patel et al. 2007 **International** **RCT (factorial)** ***Action in Diabetes and Vascular Disease: Preterax and Diamicron - MR Controlled Evaluation (ADVANCE) (hypertension arm)***	CA: ☑ Blinding: Patient: ☑ Assessor ☑ ITT: ☑	11,140 patients with long-standing type 2 diabetes, aged ≥55 years with a history of major cardiovascular disease or at least one additional risk factor. Mean age at baseline was 66 years. 57% of patients were male and 9% had previous stroke)	Patients were randomized to receive either a fixed combination of perindopril (2 mg) and indapamide (0.625 mg) (n=5,569) or matching placebo (n=5,571) following a 6-week run-in period. After 3 months, treatment doses were doubled (4 mg/1.24 mg vs. matching placebo).	**Primary outcome:** Composite of macrovascular events (death from cardiovascular causes, nonfatal MI or stroke) and microvascular events (new or worsening nephropathy) **Secondary outcomes:** Death from any cause, death from cardiovascular causes, major coronary events, fatal and nonfatal stroke	The mean duration of follow-up was 4.3 years. At the end of follow-up, 73% and 74% of patients were adherent to study medication (active vs. placebo). The mean reductions in systolic and diastolic blood pressures in patents in the active study groups were 5.6 and 2.2 mm Hg, respectively. Active treatment was associated with reduction in the risk of combined micro/macrovascular events, (15.5% vs. 16.8%, RRR=9%, 95% CI 0%-17%) all deaths (7.3% vs. 8.5%, RRR=14%, 95% CI 2%-25%) and cardiovascular death (3.8% vs. 4.6%, RRR=18%, 95% CI 2%-32%). Active treatment was not associated with reduction in the risk of total cerebrovascular events, (5.1% vs. 5.4%, RRR=6%, 95% CI -10%-20%) or major cerebrovascular events (3.9% vs.

Study/Type	Quality Rating	Sample Description	Method	Outcomes	Key Findings and Recommendations
					3.9%, RRR=2%, 95% CI -18%-19%). 73% and 74% of patients, respectively in the active treatment and placebo groups were adherent to the assigned treatment. Serious suspected adverse drug reactions were reported in 0.8% of patients in the active treatment group compared with 0.6% of patients in the placebo group.
Heart Outcomes Prevention Evaluation (HOPE) Study **Investigators 2000** **International** **RCT**	CA: ☑ Blinding: Patient: ☑ Assessor ☑ ITT: ☑	3,577 people with diabetes, ≥ 55 years who had a previous cardiovascular event or at least one other cardiovascular risk factor, no clinical proteinuria, heart failure, or low ejection fraction.	Patients were randomized to receive 10 mg ramipril and 400 IU vitamin E (n=1,808) or placebo (n=1,769), daily for the study duration. The planned follow-up period was 5 years.	**Primary outcome:** Cardiovascular mortality, stroke and MI at end of follow-up (composite outcome) **Secondary outcomes:** Total mortality, overt nephropathy	The median duration of follow-up was 4.5 years. The study was stopped 6 months early. Fewer patients in the ramipril group experienced the composite endpoint (15.5% vs. 19.8%, RRR= 25%, 95% CI 12% to 36%, p=0.0004) or fatal or non-fatal stroke (4.2% vs. 6.1%, RRR= 33%, 95% CI 10% to 50%, p=0.0074). Mortality was lower among patients in the ramipril group (10.8% vs. 14.0%, RRR=24%, 95% CI 8% to 37%, p=0.004). Fewer patients in the ramipril group developed overt nephropathy (15.1% vs. 17.6%, RRR=16%, 95% CI 1% to 29%, p=0.036). Cough was one of the most frequently cited reason for stopping study medications. Its frequency was higher among patients in the ramipril group (7% vs. 2%).
Turner et al. 1998 **UK** **RCT** ***United Kingdom Prospective Diabetes Study (UKPDS) 38***	CA: ☑ Blinding: Patient: ☒ Assessor ☑ ITT: ☑	1,148 hypertensive patients aged 25-65 years with newly diagnosed type II diabetes and HTN (SBP≥160 mm Hg and DBP≥90 mm Hg, if untreated or ≥150 mm Hg and ≥85 mm Hg, if	Patients were randomly assigned to tight control vs. less tight control of blood pressure groups. Tight control patients received either captopril 25– 50 mg twice daily (n=400) or atenolol 50 – 100 mg/day (n=358)	**Primary outcome:** Time to occurrence of a first clinical end point related to diabetes (including death, fatal/nonfatal MI, heart failure, stroke), death related to diabetes and all-cause mortality	Median duration of follow-up was 8.4 years. Mean blood pressures (baseline and during study) were: Tight control group: 159/94 vs. 144/82 mm Hg Less tight control group: 160/94 vs. 154/87 mm Hg. There was a reduced risk of developing any end

Study/Type	Quality Rating	Sample Description	Method	Outcomes	Key Findings and Recommendations
(hypertension portion)		treated). Mean age at baseline was 56 years. 55% of patients were male. 36% of patients were receiving treatment for HTN at the start of study.	to achieve a BP of <150/<85 mmHg. Additional agents were added if target blood pressures were not achieved. Less tight control patients (n=390) were treated to achieve a target BP of <180/<105 without the use of an ACE-inhibitor or β-blocker	**Secondary outcome:** Nonfatal/fatal MI, fatal/nonfatal stroke, amputation or death from peripheral vascular disease and fatal/nonfatal renal failure	point related to diabetes associated with tight blood pressure control (RR=0.78, 95% CI 0.62-0.92, p=0.0042) including any stroke (RR=0.56, 95% CI 0.35-0.89, p=0.013). When analyzed individually, there was no significant risk reduction associated with tight control for the outcomes of fatal stroke (RR=0.42, 95% CI 0.13-1.33) or nonfatal stroke (RR=1.05, 95% CI 0.54-2.06). At the end of study, vital status was known for 96% of participants.

Abbreviations

ARR: absolute risk reduction	CA: concealed allocation	CI: confidence interval
HR: hazard ratio	ITT: intention-to-treat	NNTB: number needed to benefit
NNTH: number needed to harm	OR: odds ratio	RR: relative risk
RRR: relative risk reduction		

Reference List

Effects of ramipril on cardiovascular and microvascular outcomes in people with diabetes mellitus: results of the HOPE study and MICRO-HOPE substudy. Heart Outcomes Prevention Evaluation Study Investigators. *Lancet* 2000;355:253-59.

Efficacy of nitric oxide, with or without continuing antihypertensive treatment, for management of high blood pressure in acute stroke (ENOS): a partial-factorial randomised controlled trial. *Lancet* (London, England). 2015;385(9968):617-28.

Major outcomes in high-risk hypertensive patients randomized to angiotensin-converting enzyme inhibitor or calcium channel blocker vs diuretic: The Antihypertensive and Lipid-Lowering Treatment to Prevent Heart Attack Trial (ALLHAT). *JAMA* 2002;288:2981-97.

The ONTARGET Investigators. Telmisartan, ramipril, or both in patients at high risk for vascular events. *N Engl J Med*. 2008;358:1547–1559.

Tight blood pressure control and risk of macrovascular and microvascular complications in type 2 diabetes: UKPDS 38. UK Prospective Diabetes Study Group. *BMJ* 1998;317:703-13.

Arguedas JA, Leiva V, Wright JM. Blood pressure targets for hypertension in people with diabetes mellitus. *Cochrane Database Syst Rev* 2013;10:CD008277.

Bangalore S, Toklu B, Gianos E, Schwartzbard A, Weintraub H, Ogedegbe G, Messerli FH. Optimal systolic blood pressure target after SPRINT: insights from a network meta-analysis of randomized trials. *Am J Med*. 2017 Jun 1;130(6):707-19. **NEW**

Bath PM, Scutt P, Blackburn DJ, Ankolekar S, Krishnan K, Ballard C, et al. Intensive versus guideline blood pressure and lipid lowering in patients with previous stroke: Main results from the Pilot 'Prevention of Decline in Cognition after Stroke Trial' (PODCAST) Randomised Controlled Trial. *PLoS ONE* 2017 Jan 17;12(1):e0164608. **NEW**

Beckett NS, Peters R, Fletcher AE, et al. Treatment of hypertension in patients 80 years of age or older. *N Engl J Med* 2008;358:1887-98.

Beckett NS, Peters R, Tuomilehto J, et al. Immediate and late benefits of treating very elderly people with hypertension: Results from active treatment extension to Hypertension in the Very Elderly. A randomised controlled trial. *BMJ* 2012;344:d7541.

Beckett N, Peters R, Leonetti G, Duggan J, Fagard R, Thijs L et al. Subgroup and per-protocol analyses from the Hypertension in the Very Elderly Trial. *J Hypertens 2014*; 32(7):1478-1487.

Benavente OR, Coffey CS, Conwit R, Hart RG, McClure LA, Pearce LA, Pergola PE, Szychowski JM: Blood-pressure targets in patients with recent lacunar stroke: the SPS3 randomised trial. *Lancet* 2013;382:507-515.

Bestehorn K, Wahle K, Kirch W. Stroke risk screening of adults with hypertension: prospective cross-sectional study in primary care. *Clin Drug Investig* 2008;28:281-89.

Cushman WC, Evans GW, Byington RP, et al. Effects of intensive blood-pressure control in type 2 diabetes mellitus. *N Engl J Med* 2010;362:1575-85.

Cushman WC, Davis BR, Pressel SL, et al. Mortality and morbidity during and after the Antihypertensive and Lipid-Lowering Treatment to Prevent Heart Attack Trial. *J Clin Hypertens (Greenwich)* 2012;14:20-31.

Dahlof B, Devereux RB, Kjeldsen SE, et al. Cardiovascular morbidity and mortality in the Losartan Intervention for Endpoint reduction in hypertension study (LIFE): a randomised trial against atenolol. *Lancet* 2002;359:995-1003.

Du X, McNamee R, Cruickshank K. Stroke risk from multiple risk factors combined with hypertension: a primary care based case-control study in a defined population of northwest England. *Ann Epidemiol* 2000;10:380-88.

Ettehad D, Emdin CA, Kiran A, Anderson SG, Callender T, Emberson J, et al. Blood pressure lowering for prevention of cardiovascular disease and death: a systematic review and meta-analysis. *Lancet.* 2016;387:957– 967. **NEW**

Foulquier S, Bohm M, Schmieder R, Sleight P, Teo K, Yusuf S et al. Impact of telmisartan on cardiovascular outcome in hypertensive patients at high risk: a Telmisartan Randomised AssessmeNt Study in ACE iNtolerant subjects with cardiovascular Disease subanalysis. *J Hypertens 2014*; 32(6):1334-1341.

Hansson L, Zanchetti A, Carruthers SG, et al. Effects of intensive blood-pressure lowering and low-dose aspirin in patients with hypertension: principal results of the Hypertension Optimal Treatment (HOT) randomised trial. HOT Study Group. *Lancet* 1998;351:1755-62.

Hao G, Wang Z, Guo R et al. Effects of ACEI/ARB in hypertensive patients with type 2 diabetes mellitus: a meta-analysis of randomized controlled studies. *BMC Cardiovasc Disord* 2014;14:148.

Jamerson K, Weber MA, Bakris GL, et al. Benazepril plus amlodipine or hydrochlorothiazide for hypertension in high-risk patients. *N Engl J Med* 2008;359:2417-28.

Katsanos AH, Filippatou A, Manios E, et al. Blood Pressure Reduction and Secondary Stroke Prevention: A Systematic Review and Metaregression Analysis of Randomized Clinical Trials. *Hypertension* 2017; 69: 171-9. **NEW**

Kitagawa K, Yamamoto Y, Arima H, Maeda T, Sunami N, Kanzawa T, et al. Effect of Standard vs Intensive Blood Pressure Control on the Risk of Recurrent Stroke: A Randomized Clinical Trial and Meta-analysis. *JAMA Neurol*. 2019 Jul 29;76(11):1309-1318. **NEW**

Law MR, Morris JK, Wald NJ. Use of blood pressure lowering drugs in the prevention of cardiovascular disease: meta-analysis of 147 randomised trials in the context of expectations from prospective epidemiological studies. *BMJ* 2009;338:b1665.

Lee M, Saver JL, Hong KS, et al. Does achieving an intensive versus usual blood pressure level prevent stroke? *Ann Neurol* 2012;71:133-40.

Lithell H, Hansson L, Skoog I, et al. The Study on Cognition and Prognosis in the Elderly (SCOPE): principal results of a randomized double-blind intervention trial. *J Hypertens* 2003;21:875-86.

Lonn EM, Bosch J, López-Jaramillo P, Zhu J, Liu L, Pais P, Diaz R, Xavier D, Sliwa K, Dans A, Avezum A. Blood-pressure lowering in intermediate-risk persons without cardiovascular disease. *NEJM 2016*;374(21):2009-20. **NEW**

Mant J, McManus RJ, Roalfe A, et al. Different systolic blood pressure targets for people with history of stroke or transient ischaemic attack: PAST-BP (Prevention After Stroke--Blood Pressure) randomised controlled trial. *BMJ* (Clinical research ed). 2016;352:i708. **NEW**

Muramatsu T, Matsushita K, Yamashita K et al. Comparison between valsartan and amlodipine regarding cardiovascular morbidity and mortality in hypertensive patients with glucose intolerance: NAGOYA HEART Study. *Hypertension* 2012;59(3):580-586.

Musini VM, Tejani AM, Bassett K, et al. Pharmacotherapy for hypertension in the elderly. *Cochrane Database Syst Rev* 2009; Issue 4. Art. No.CD000028.

O'Donnell MJ, Chin SL, Rangarajan S, et al. Global and regional effects of potentially modifiable risk factors associated with acute stroke in 32 countries (INTERSTROKE): a case-control study. *Lancet* 2016;388(10046):761-775.

O'Donnell MJ, Xavier D, Liu L, et al. Risk factors for ischaemic and intracerebral haemorrhagic stroke in 22 countries (the INTERSTROKE study): a case-control study. *Lancet* 2010;376:112-23.

Patel A, MacMahon S, Chalmers J, et al. Intensive blood glucose control and vascular outcomes in patients with type 2 diabetes. *N Engl J Med* 2008;358:2560-72.

Perry HM, Jr., Davis BR, Price TR, et al. Effect of treating isolated systolic hypertension on the risk of developing various types and subtypes of stroke: the Systolic Hypertension in the Elderly Program (SHEP). *JAMA* 2000;284:465-71.

PROGRESS Collaborative Group Randomised trial of a perindopril-based blood-pressure-lowering regimen among 6,105 individuals with previous stroke or transient ischaemic attack. *Lancet* 2001;358:1033-41.

Rapsomaniki E, Timmis A, George J, Pujades-Rodriguez M, Shah AD, Denaxas S et al. Blood pressure and incidence of twelve cardiovascular diseases: lifetime risks, healthy life-years lost, and age-specific associations in 1.25 million people. *Lancet 2014*; 383(9932):1899-1911.

Redon J, Mancia G, Sleight P, et al. Safety and efficacy of low blood pressures among patients with diabetes: subgroup analyses from the ONTARGET (ONgoing Telmisartan Alone and in combination with Ramipril Global Endpoint Trial). *J Am Coll Cardiol* 2012;59:74-83.

Reisin E, Graves JW, Yamal JM, Barzilay JI, Pressel SL, Einhorn PT et al. Blood pressure control and cardiovascular outcomes in normal-weight, overweight, and obese hypertensive patients treated with three different antihypertensives in ALLHAT. *J Hypertens 2014*; 32(7):1503-1513.

Schrader J, Luders S, Kulschewski A, et al. Morbidity and Mortality After Stroke, Eprosartan Compared with Nitrendipine for Secondary Prevention: principal results of a prospective randomized controlled study (MOSES). *Stroke* 2005;36:1218-26.

White WB, Wakefield DB, Moscufo N, Guttmann CRG, Kaplan RF, Bohannon RW, Fellows D, Wolfson L. Effects of Intensive Versus Standard Ambulatory Blood Pressure Control on Cerebrovascular Outcomes in Older People (INFINITY). *Circulation* 2019. 2019 Nov 12;140(20):1626-1635. **NEW**

Wright JT, Jr., Williamson JD, Whelton PK et al. A Randomized Trial of Intensive versus Standard Blood-Pressure Control. *N Engl J Med* 2015;373(22):2103-2116.

Xie X, Atkins E, Lv J, Bennett A, Neal B, Ninomiya T, et al. Effects of intensive blood pressure lowering on cardiovascular and renal outcomes: updated systematic review and meta-analysis. *Lancet.* 2016;387:435– 443. **NEW**

Yano Y, Reis JP, Colangelo LA, et al. Association of Blood Pressure Classification in Young Adults Using the 2017 American College of Cardiology/American Heart Association Blood Pressure Guideline With Cardiovascular Events Later in Life. *JAMA*. 2018; 320: 1774-82. **NEW**

Yusuf S, Diener HC, Sacco RL, et al. Telmisartan to prevent recurrent stroke and cardiovascular events. *N Engl J Med* 2008;359:1225-37.

Yusuf S, Teo KK, Pogue J, et al. Telmisartan, ramipril, or both in patients at high risk for vascular events. *N Engl J Med* 2008;358:1547-59.

Yusuf S, Teo K, Anderson C, Pogue J, Dyal L, Copland I et al. Effects of the angiotensin-receptor blocker telmisartan on cardiovascular events in high-risk patients intolerant to angiotensin-converting enzyme inhibitors: a randomised controlled trial. *Lancet* 2008; 372(9644):1174-1183.

Yusuf S, Lonn E, Pais P, Bosch J, Lopez-Jaramillo P, Zhu J, et al. Blood-Pressure and Cholesterol Lowering in Persons without Cardiovascular Disease. *N Engl J Med. 2016*;374(21):2032-43.

Zonneveld TP, Richard E, VergouwenMDI, Nederkoorn PJ, de Haan RJ, Roos YBWEM, Kruyt ND. Blood pressure-lowering treatment for preventing recurrent stroke, major vascular events, and dementia in patients with a history of stroke or transient ischaemic attack. *Cochrane Database of Systematic Reviews* 2018, Issue 7. Art. No.: CD007858. DOI: 10.1002/14651858.CD007858.pub2. **NEW**