CANADIAN STROKE BEST PRACTICE RECOMMENDATIONS

Prevention of Stroke Evidence Tables

Blood Pressure Management

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on Behalf of the Canadian Stroke Best Practice Recommendations
PREVENTION of STROKE Writing Group

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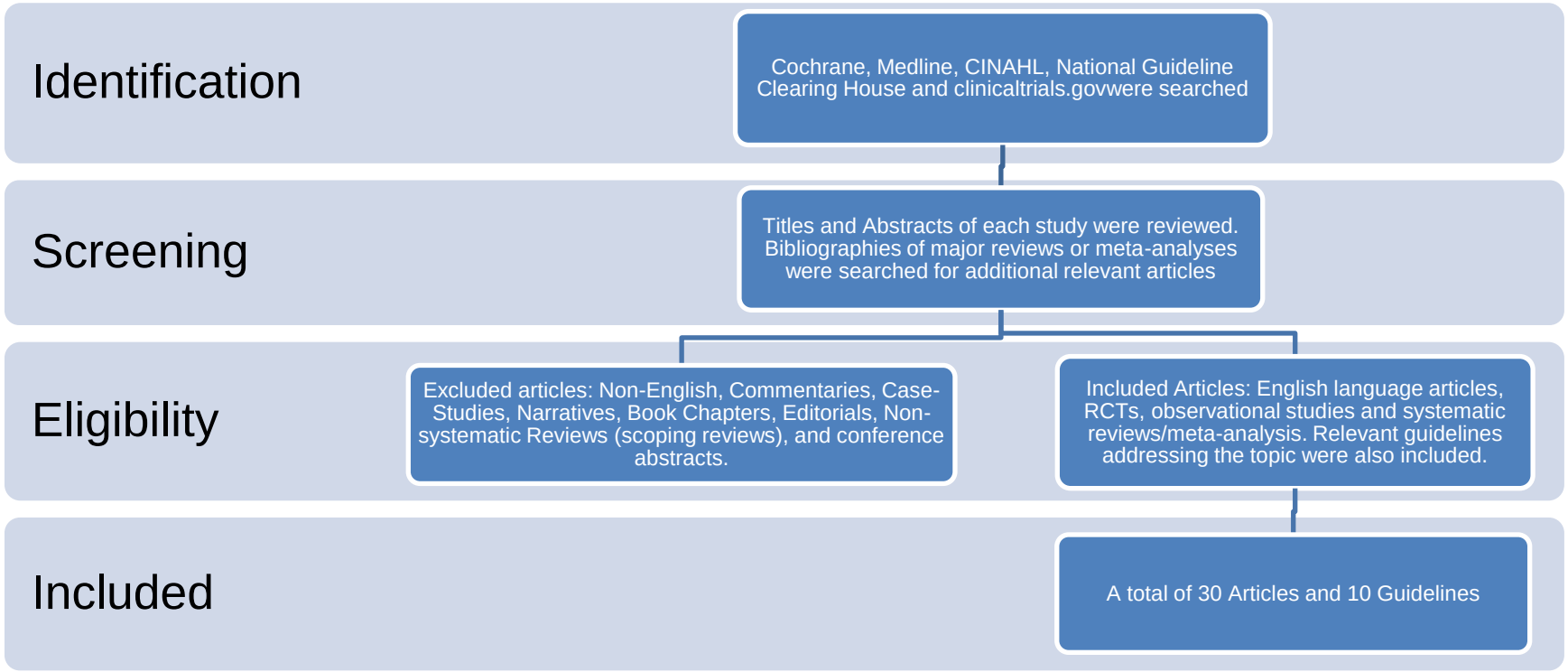
Search Strategy



Cochrane, Medline, CINAHL, National Guideline Clearing House and clinicaltrials.gov 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 30 articles and 10 guidelines were included and were separated into separate categories designed to answer specific questions.

Published Guidelines

Guideline	Recommendations
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), doi: 10.1016/j.cjca.2017.03.005. **(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.
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**	• 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).

Guideline	Recommendations
stroke association. ***Stroke 2014*;45:2160-2236.**	• 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).
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)
National Clinical Guideline Centre. Hypertension. Clinical management of primary hypertension in adults. London (UK): National Institute for Health and Clinical Excellence (NICE); 2011	Monitoring Treatment and Blood Pressure Targets Use clinic blood pressure measurements to monitor the response to antihypertensive treatment with lifestyle modifications or drugs. [new 2011] Aim for a target clinic blood pressure below 140/90 mmHg in people aged under 80 years with treated hypertension. [new 2011] Aim for a target clinic blood pressure below 150/90 mmHg in people aged 80 years and over, with treated hypertension. [new

Guideline	Recommendations
	2011] For people identified as having a 'white-coat effect'*, consider ABPM or HBPM as an adjunct to clinic blood pressure measurements to monitor the response to antihypertensive treatment with lifestyle modification or drugs. [new 2011] When using ABPM or HBPM to monitor the response to treatment (for example, in people identified as having a 'white-coat effect'* and people who choose to monitor their blood pressure at home), aim for a target average blood pressure during the person's usual waking hours of: •Below 135/85 mmHg for people aged under 80 years •Below 145/85 mmHg for people aged 80 years and over [new 2011]
National Stroke Foundation. Clinical Guidelines for Stroke Management 2010. Melbourne, Australia	• All stroke and TIA patients, whether normotensive or hypertensive, should receive blood pressure lowering therapy, unless contraindicated by symptomatic hypotension. (Grade A) • New blood pressure lowering therapy should commence before discharge for those with stroke or TIA, or soon after TIA if the patient is not admitted. (Grade B)
New Zealand Clinical Guidelines for Stroke Management 2010, Stroke Foundation of New Zealand, Auckland.	• All patients after stroke or TIA, whether normotensive or hypertensive, should receive blood pressure lowering therapy for secondary prevention, unless contraindicated by symptomatic hypotension (Grade A) • New blood pressure lowering therapy should commence prior to discharge for those with minor stroke or TIA or soon after TIA if the patient is not admitted (Nazir et al, 2004; Nazir et al, 2005). (Grade B) • Cautious introduction of BP lowering medication may be required in older people with frailty due to risk of complications such as symptomatic hypotension
"National Clinical Guidelines and Recommendations for the Care of People with Stroke and transient Ischemic Attack" March 2010 **(Irish Heart Foundation: Council for Stroke)**	• It is recommended that blood pressure be checked regularly. Blood pressure lowering is recommended after the acute phase, including if tolerated in patients with normal blood pressure. • Antihypertensive therapy can be safely commenced, or resumed if discontinued, 7 - 14 days following stroke. • Blood pressure should be checked. It is recommended that high blood pressure should be managed with lifestyle modification and individualised pharmacological therapy. • There is evidence that modest reductions in blood pressure significantly reduce risk of recurrent stroke. This is the case even in subjects who were within normotensive limits at time of presentation. Recommended blood pressure treatment goals are systolic blood pressure <135/85 mmHg for non-diabetic subjects and <130/80 for diabetic subjects. • For prehypertensive (120-139/80-90 mmHg) with congestive heart failure, history of coronary heart disease, diabetes, or chronic renal failure cautious introduction of antihypertensive medication is also recommended and may reduce risk of recurrence. • Care needs to be taken in subjects with known severe bilateral carotid stenosis especially with symptoms of haemodynamic ischaemia, and blood pressure in this group should not typically be actively reduced below 140/90 mmHg.
"Management of patients with stroke or TIA: assessment, investigation, immediate management and secondary prevention. A national clinical guideline" December 2008	Patients with **ischaemic stroke or TIA** • All patients with a previous stroke or TIA should be considered for treatment with an Ace inhibitor (for example, perindopril) and thiazide (for example, indapamide) regardless of blood pressure, unless contraindicated. (Grade A) • Patients with hypertension should be treated to <140/85 mm hg (<130/80 mm Hg for patients with diabetes). (Grade D) Patients with primary **intracerebral haemorrhage** • Lowering blood pressure (non-acutely) following ICH using a combination therapy of Ace inhibitor and thiazide diuretic should be considered to prevent further vascular events. (Grade A)
The European Stroke Organisation (ESO) Executive Committee and the	**Blood Pressure** • It is recommended that BP be checked regularly. BP lowering is recommended after the acute phase, including in patients

Guideline	Recommendations
ESO Writing Committee **Guidelines for Management of Ischaemic Stroke and Transient Ischaemic Attack 2008** ***Cerebrovasc Dis* 2008;25:457–507**	with normal BP (Class I, Level A) • BP should be checked regularly. It is recommended that high BP should be managed with lifestyle modification and individualized pharmacological therapy (Class I, Level A) aiming at normal levels of 120/80 mm Hg (Class IV, GCP). For prehypertensive (120–139/80–90 mm Hg) with congestive heart failure, MI, diabetes, or chronic renal failure antihypertensive medication is indicated (Class 1, Level A).

Evidence Tables

Association between Hypertension and Stroke Risk

Study/Type	Quality Rating	Sample Description	Method	Outcomes	Key Findings and Recommendations
O'Donnell et al. 2016 **Canada (International)** **INTERSTROKE Phase 2** **Case-control study**	NA	Participants were recruited from 32 countries from 2007-2015. Cases were 13,447 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)	All key vascular risk factors (hypertension, DM, smoking, waist-to-hip ratio, diet, physical activity, alcohol intake, psychosocial factors, 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	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% 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	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	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

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		matched for age and sex and were recruited from the community or hospitals (in-patient or outpatient, unrelated to treatment for stroke or TIA)	pressure ≥160/90 mm Hg		highest in developing countries.
Rapsomanki 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	NA	47,394 patients under the care of 2,482 general	Physicians documented: age, sex and measured	**Primary outcome:** Risk of first stroke within 10	The most prevalent stroke risk factors were a positive family history of cardiovascular disease

Study/Type	Quality Rating	Sample Description	Method	Outcomes	Key Findings and Recommendations
Germany **Observational study**		physicians, diagnosed with hypertension	current BP, the presence/absence of risk factors including pre-treated hypertension, diabetes mellitus, smoking, atrial fibrillation, left ventricular hypertrophy, coronary artery disease, positive family history and use of current antihypertensive medication.	years using the Framingham Stroke Risk (low, medium and high risks are defined as <10%, 10-20%, and >20%).	(46.1%), diabetes mellitus (36.1%), coronary artery disease (34.4%), and left ventricular hypertrophy (33.3%). 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					
Lee et al. 2012 **International** **Systematic review & Meta-analysis**	NA	11 RCTs representing data from 42,572 participants (794 with previous stroke) who were at high risk for CVD.	Comparisons of treatment of tight BP control (SBP <130 mmHg) vs. usual control (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	**Primary outcome:** Stroke risk and achieved level of different SBP (intensive vs. usual). **Secondary outcomes:** Major vascular event (i.e., composite of cardiovascular death, nonfatal stroke, and nonfatal myocardial infarction), major coronary events, total death, vascular death	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 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	**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

Study/Type	Quality Rating	Sample Description	Method	Outcomes	Key Findings and Recommendations
			therapy was 1 year. 12/15 trials instituted a stepped care approach to treatment. In over 70% of trials a thiazide diuretic was the first line drug in the treatment group.		the treatment group (136 vs. 194). RR= 0.66, 95% CI 0.53 to 0.82, p=0.0002. Results from 10 trials included. 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: Thiazide vs. any other: RR=0.94, 95% CI 0.82-1.09

Study/Type	Quality Rating	Sample Description	Method	Outcomes	Key Findings and Recommendations
					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					
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 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.	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 hydrochlorothiazide (HCTZ) or placebo for the duration of the trial. All participants received individualized lifestyle advice.	**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 **Additional outcomes:** Death from any cause, components of the primary and secondary outcomes, new onset diabetes, hospitalizations	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. 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

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					(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 sub group 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.
Yusef et al. 2016 **Canada** **RCT** ***Heart Outcomes Prevention Evaluation-3 (HOPE-3) (statin + blood pressure lowering arms)***	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 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.	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 hydrochlorothiazide (HCTZ) or placebo and to 10 mg/day rosuvastatin or placebo for the duration of the trial. The outcomes of [participants assigned to active combination therapy (n=3,180) were compared with those who received dual placebo (n=3,168)	**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 **Additional outcomes:** Death from any cause, components of the primary and secondary outcomes, new onset diabetes, hospitalizations	The median duration of follow-up was 5.6 years. Mean baseline blood pressure was similar between groups (combination therapy vs. dual placebo) SBP: 138.2 vs. 137.9 mm Hg DBP: 81.9 vs. 81.8 mm Hg Over the course of the trial mean SBP and DBP were 6.2 and 3.2 mm Hg lower, respectively in the combination therapy group. The risk of the first primary outcome was significantly lower in the combination therapy group (3.6% vs. 5.0%, HR=0.72, 95% CI 0.57-0.90, p=0.005). NNT=72 The risk of the second primary outcome was significantly lower in the combination therapy group (4.6% vs. 6.5%, HR=0.71, 95% CI 0.57-0.87, p=0.003). NNT=63 The risk of the secondary outcome was significantly lower in the combination therapy group (4.8% vs. 6.2%, HR=0.77, 95% CI 0.66-0.89, p<0.001). The risk of fatal or nonfatal stroke was significantly lower in the combination therapy group (1.0% vs.

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					1.7%, HR=0.56, 95% CI 0.36-0.87). The risk of hospitalization for CV causes was significantly lower in the combination therapy group (4.4% vs. 6.0%, HR=0.73, 95% CI 0.59-0.91, p=0.005). The results did not vary significantly in subgroup analyses based on baseline CV risk, lipid level, C-reactive protein level, blood pressure, and race or ethnic group At the end of the trial, 74.6% of patients in the combination therapy group were taking their prescribed medication compared with 71.8% in the placebo/placebo group.
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 2009-2011with 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)
Wright et al. 2015 **USA**	CA: ☑ Blinding: Patient ☒ Assessor☒	9,250 participants aged ≥ 50 years with SBP ≥130-180 mm Hg and at least one additional CVD risk factor were recruited	Patients were randomized to an intensive BP arm with a goal of SBP <120 mm Hg using 2-drug therapy, if	**Primary outcomes:** First occurrence of: MI, acute coronary syndrome, heart failure or cardiovascular death	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

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RCT ***Systolic Blood Pressure Intervention Trial (SPRINT)***	ITT: ☑	from 102 clinical sites. Patients with diabetes or 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	required (n=4,678) vs. a standard arm with a goal 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	**Secondary outcomes:** Individual components of the primary outcome	Hg) 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 sub group 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.
Benavente et al. 2013 **USA & Canada** **RCT** ***Secondary Prevention of Small Subcortical Strokes (SPS3)***	CA: ☑ Blinding: Patient ☒ Assessor ☒ ITT: ☑	3020 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. Adjustments	**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

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Trial (blood pressure component)			to medications were made, as appropriate.		strokes in the lower target group (0.72 vs. 0.89% 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.
Cushman et al. 2010 **International** **RCT** ***Action to Control Cardiovascular Risk in Diabetes (ACCORD)***	CA: ☑ Blinding: Patient ☒ Assessor ☒ ITT: ☑	4,733 participants with type 2 diabetes with a SBP between 130 and 180 mm Hg	Patients were randomly assigned to intensive BP therapy, targeting a systolic pressure of <120 mm Hg (n=2,362), or standard therapy, targeting a systolic pressure of <140 mm Hg (n=2,371). Non-fixed treatment strategies, using approaches and medications in clinical practice were used to achieve target BPs. For participants in the intensive therapy group, visits to assess blood pressure were scheduled once a month for 4 months and every 2 months thereafter; for participants in the standard-therapy group, visits were scheduled at months 1 and 4 and every 4 months thereafter.	**Primary outcome:** Composite including nonfatal myocardial infarction, nonfatal stroke, or death from cardiovascular causes.	The mean follow-up was 4.7 years. The mean number of medications after the first year was higher in the intensive group (3.4 vs. 2.1). After 1 year, the mean systolic blood pressure was 119.3 mm Hg in the intensive therapy group and 133.5 mm Hg in the standard-therapy group. The corresponding mean diastolic blood pressures were 64.4 and 70.5 mm Hg. The primary outcome occurred in intensive-therapy 208 patients (1.87%/yr.) and 237 standard therapy patients (2.09/yr). There was no difference between groups (HR= 0.88, 95% CI 0.73 to 1.06, p= 0.20). There were significantly fewer fatal and nonfatal strokes in patients in the intensive therapy group (36 vs. 62, HR= 0.59, 95% CI 0.39 to 0.89, p<0.01 and 34 vs. 55, HR=0.63, 95% CI 0.41 to 0.96, p=0.03, respectively). There were no significant differences between groups for the outcomes of death from any cause, death from cardiovascular cause, major coronary disease event, fatal or nonfatal heart failure or nonfatal myocardial infarction

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					Patients in the intensive-therapy group had significantly higher rates of serious adverse events (hypotension, syncope) attributed to antihypertensive treatment, as well as higher rates of hypokalemia and elevations in serum creatinine level.
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.
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).

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Beckett et al. 2014 **UK** **RCT** ***HYVET* Study Group (sub group and per protocol analyses)**	As above	Per original study ITT analysis (n=3845), per protocol analysis (n=3822)	Sub groups included age (80-84.9 yrs 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 sub groups. 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).
Yusef et al. 2008 **International** **RCT (factorial)** ***Ongoing Telmisartan Alone and in Combination with Ramipril Global Endpoint Trial (ONTARGET)***	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.	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, myocardial infarction, or stroke and new onset of heart failure, diabetes mellitus, atrial fibrillation, dementia or cognitive decline, nephropathy, and revascularization procedures.	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%). 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.

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Yusef et al. 2008 **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.	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)
Foulquier et al. 2014 **Post-hoc analysis of TRANSCEND**	NA	As above	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)	As above	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).
Yusef et al. 2008 **International** **RCT (factorial)** ***Prevention Regimen For Effectively***	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	**Primary outcome:** Recurrent stroke by end of follow-up **Secondary outcomes:** Major cardiovascular events (death from cardiovascular causes, myocardial infarction, recurrent stroke, or	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).

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Avoiding Second Strokes (PRoFESS)			necessary at the discretion of the investigators	worsening or new heart failure) and new-onset diabetes.	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 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 sub group 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).
Jameson 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	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	**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).

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			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.		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 **Germany/Austria** **RCT** ***Morbidity and Mortality After Stroke (MOSES*)**	CA: ☑ Blinding: Patient: ☑ Assessor ☑ ITT: ☑	1,352 individuals with hypertension and a history of TIA, ischemic stroke or cerebral hemorrhage	Participants were randomized to receive 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.	**Primary outcome:** Mortality and number of cardiovascular and cerebrovascular events (composite index) **Secondary outcomes:** Single components of the combined primary end point.	Mean follow-up was 2.5 years. 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	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).

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					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%), 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.	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** **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% of the sample were female.	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 = 9054) 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).

Study/Type	Quality Rating	Sample Description	Method	Outcomes	Key Findings and Recommendations
Cushman et al. 2012 **USA** **Long-term follow-up of *ALLHAT* participants**	NA	The results from 21,623 participants from the ALLHAT study were included	Continued surveillance for 8-13 years following study end.	**Primary outcomes:** Mortality, including all-cause mortality, CV mortality and mortality from CHD, stroke, heart failure and other CVD. **Secondary outcomes:** Fatal/nonfatal hospitalized events (including stroke).	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 **Sub group 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 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

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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 Program (SHEP)*** **trial** **USA** **RCT**	CA: ☑ Blinding: Patient ☑ Assessor ☑ ITT: ☑	4,736 persons aged ≥60 years with systolic blood pressures from 160-219 mm Hg.	Subjects were randomized to receive 12.5 mg/d of chlorthalidone. If required to maintain target BP, additional treatment could be added including 25 mg of chlorthalidone, 25 mg/d of atenolol or 0.05 mg/d of reserpine (n = 2,365) or placebo (n = 2,371).	**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) 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

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					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). 491 (2.6%) patients were lost to follow-up.

CA: concealed allocation; ITT: intention-to-treat

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