CANADIAN STROKE BEST PRACTICE RECOMMENDATIONS

Prevention of Stroke Evidence Tables

Diabetes Management

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

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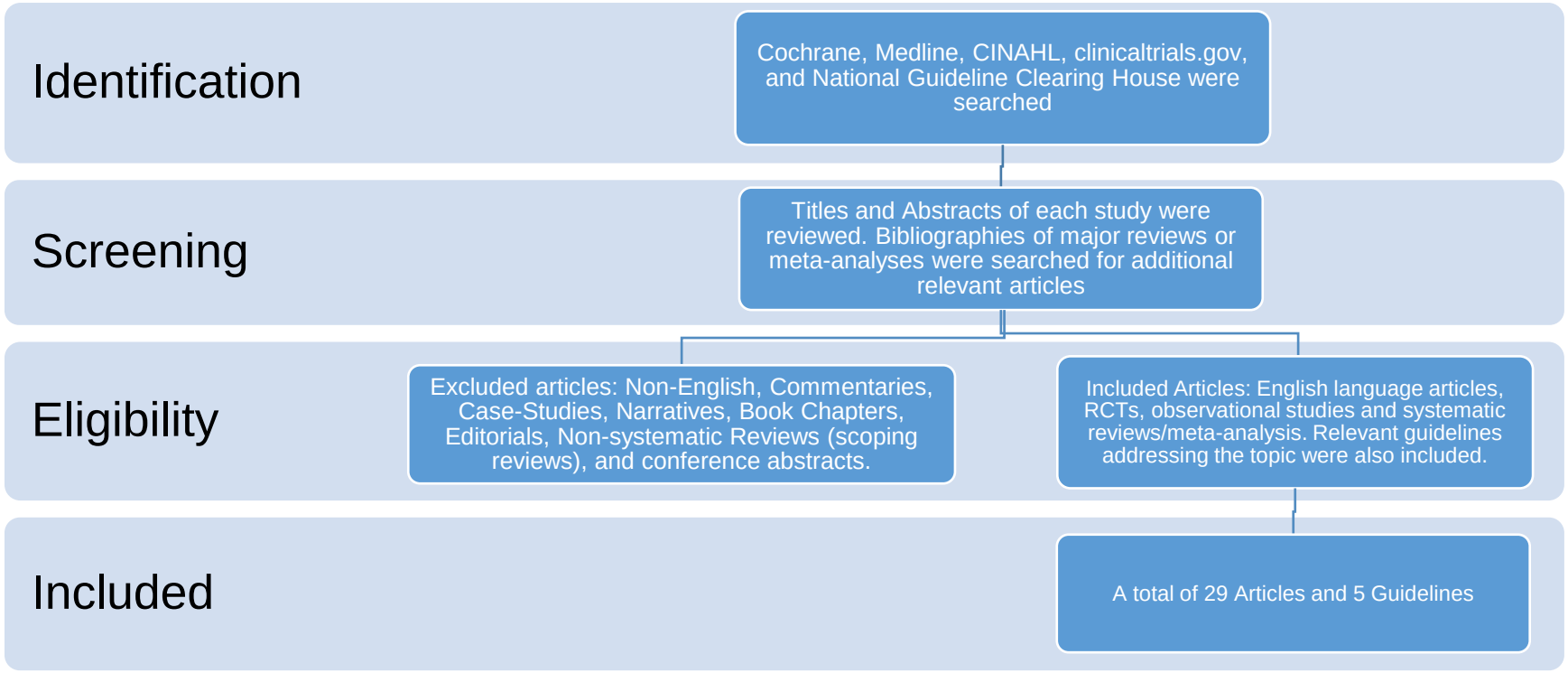
Search Strategy



Cochrane, Medline, CINAHL, clinicaltrials.gov, and National Guideline Clearing House were search using the terms (“Stroke” and Diabetes Mellitus, Type 1/ or *Diabetes Mellitus, Type 2/ or *Diabetes Mellitus). 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 29 articles and 5 guidelines were included and were separated into separate categories designed to answer specific questions.

Published Guidelines

Guideline	Recommendations
Intercollegiate Stroke Working Party. Royal College of Physicians. National Clinical guidelines for stroke. 5th Edition 2016, Edinburgh, Scotland	People with stroke or TIA should not receive pioglitazone for secondary vascular prevention.
Sharma & Gubitz 2013 **"Canadian Diabetes Association Clinical Practice Guidelines Expert Committee. Management of Stroke in Diabetes."** ***Can J Diabetes 2013*;37:S124-S125**	Patients with ischemic stroke or transient ischemic attack (TIA) should be screened for diabetes with a fasting plasma glucose, glycated hemoglobin (A1C) or 75 g oral glucose tolerance test soon after admission to hospital [Grade D, Consensus]. All patients with diabetes and ischemic stroke or TIA should receive the same treatments that are recommended for patients with ischemic stroke or TIA without diabetes since they benefit equally [Grade D, Consensus].
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.**	After a TIA or ischemic stroke, all patients should probably be screened for DM with testing of fasting plasma glucose, HbA1c, or an oral glucose tolerance test. Choice of test and timing should be guided by clinical judgment and recognition that acute illness may temporarily perturb measures of plasma glucose. In general, HbA1c may be more accurate than other screening tests in the immediate post event period (Class IIa; Level of Evidence C). (New recommendation) Use of existing guidelines from the ADA for glycemic control and cardiovascular risk factor management is recommended for patients with an ischemic stroke or TIA who also have DM or pre-DM (Class I; Level of Evidence B).

Guideline	Recommendations
Scottish Intercollegiate Guidelines Network (SIGN). "Management of diabetes. A national clinical guideline." **Edinburgh (Scotland): Scottish Intercollegiate Guidelines Network (SIGN); 2010 Mar. 170 p.**	Targets for Glycaemic Control A - A glycosylated haemoglobin (HbA1c) target of 7.0% (53 mmol/mol) among people with type 2 diabetes is reasonable to reduce risk of microvascular disease and macrovascular disease. A target of 6.5% (48 mmol/mol) may be appropriate at diagnosis. Targets should be set for individuals in order to balance benefits with harms, in particular hypoglycaemia and weight gain. Primary Prevention of Coronary Heart Disease A - Hypertension in people with diabetes should be treated aggressively with lifestyle modification and drug therapy. A - Target diastolic blood pressure in people with diabetes is ≤80 mm Hg. D - Target systolic blood pressure in people with diabetes is <130 mm Hg. A - Patients with diabetes requiring antihypertensive treatment should be commenced on: •An angiotensin converting enzyme (ACE) inhibitor (angiotensin-II receptor blocker [ARB] if ACE inhibitor intolerant), or •A calcium channel blocker, or •A thiazide diuretic A - Beta-blockers and alpha blockers should not normally be used in the initial management of blood pressure in patients with diabetes. A - Low-dose aspirin is not recommended for primary prevention of vascular disease in patients with diabetes. A - Lipid-lowering drug therapy with simvastatin 40 mg or atorvastatin 10 mg is recommended for primary prevention in patients with type 2 diabetes aged >40 years regardless of baseline cholesterol. B - Lipid-lowering drug therapy with simvastatin 40 mg should be considered for primary prevention in patients with type 1 diabetes aged >40 years.
The European Stroke Organisation (ESO) Executive Committee and the ESO Writing Committee **Guidelines for Management of Ischaemic Stroke and Transient Ischaemic Attack 2008** ***Cerebrovasc Dis 2008*;25:457–507**	Optimal Management of Vascular Risk Factors (Diabetes) Blood glucose should be checked regularly. It is recommended that diabetes should be managed with lifestyle modification and individualized pharmacological therapy (Class IV, Level C). In diabetic patients, high BP should be managed intensively (Class I, Level A) aiming for levels below 130/80 mm Hg (Class IV, Level C). Where possible, treatment should include an angiotensin-converting enzyme inhibitor or angiotensin receptor antagonist (Class I, Level A)

Evidence Tables

Pharmacological Treatment of Lipids in Persons with Diabetes for the Prevention of Stroke

Study/Type	Quality Rating	Sample Description	Method	Outcomes	Key Findings and Recommendations
i) Fibrates					
Ginsberg et al. 2010 **USA** **RCT** ***Action to Control Cardiovascular Risk in Diabetes (ACCORD) (lipid portion)***	CA: ☑ Blinding: Patient: ☒ Assessor ☒ ITT: ☑	5,518 participants, 40-79 years with type 2 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. 31% women. Median duration of DM was 8.1 years. Mean HbA1c level at baseline was 8.3%. Mean total cholesterol was 175 mg/dL. 60% were already taking a statin	All participants received 20-40 mg simvastatin daily. In addition, participants were randomized to receive 160 mg/day fenofibrate (n=2,765) or placebo (n=2,753) until study end (4-8 years).	**Primary outcome:** First occurrence of a major CVD event, including nonfatal heart attack, nonfatal stroke, or cardiovascular death **Secondary outcomes:** Total mortality	Mean duration of follow-up was 4.7 years. There was no significant reduction in the mean LDL-chol levels between groups (18.9 vs. 21.0 mg/dL) There was no significant reduction in the risk for any outcome associated with fenofibrate Fatal or non-fatal cardiovascular event: HR=0.92, 95% CI 0.79-1.08, p=0.32. Any stroke: HR=1.05, 95% CI 0.71-1.56, p=0.80 Non-fatal stroke: HR=1.17, 95% CI 0.76-1.48, p=0.48. The only significant interaction was for sex, whereby the risk of the primary outcome was reduced for men, but possibly increased for women. The study drug was discontinued in 2.4% of participants in the fenofibrate group and 1.1% of those in the placebo group because of decreased GFR. Elevations of serum creatine kinase in excess of 10x the upper limit of the normal range were similar between groups (0.4% vs. 0.3%). At end of study, 77.3% in the fenofibrate and 81.3% in the placebo group were taking their assigned medication.
Keech et al. 2005 **International** **RCT**	CA: ☑ Blinding: Patient: ☑ Assessor ☑	9,795 patients, aged 50-75 years with type 2 diabetes and an initial plasma total cholesterol of 3.0 – 6.5 mmol/L plus total	Following a 16-week run-in period, which included 4 weeks of dietary modification, and 6 weeks of placebo, and 6 weeks of fenofibrate therapy,	**Primary outcome:** Non-fatal MI or death from coronary heart disease. **Secondary outcomes:** Major cardiovascular disease	Mean LDL chol was reduced from 3.07 to 2.43 mmol/l for patients in the fibrate group and from 3.07 to 2.60 mmol/L for patients in the control group. There was a significant reduction in the risk of non-fatal MI associated with fibrate use (HR=0.76, 95%

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Fenofibrate Intervention and Event Lowering in Diabetes (FIELD) study	ITT: ☑	cholesterol to HDL ratio of ≥4.0 and a TG of 1.0-5.0 mmol/L Mean at baseline was 62 years. 63% of patients were male. 4% of patients in the placebo group and 3% in the fibrate group had experienced a previous stroke.	patients were randomized to receive either micronized fenofibrate (200 mg/day) or placebo for the study duration, planned for 5 years.	events (coronary heart disease events, total stroke, and other cardiovascular death combined), total cardiovascular disease events, coronary heart disease death, hemorrhagic and non-hemorrhagic stroke.	CI 0.62-0.94, p=0.010), but not CHD mortality (HR=1.19, 95% CI 0.90-1.57, p=0.22) or any stroke (HR=0.90, 95% CI 0.73-1.12, p=0.36). There were 61 losses to follow-up or withdrawals. The number of serious adverse drug reactions was similar between groups (0.8% vs. 0.5%).
ii) statins					
Callahan et al. 2011 **International** **RCT** ***Secondary analysis of Stroke Prevention by Aggressive Reduction in Cholesterol (SPARCL)***	CA: ☑ Blinding: Patient: ☑ Assessor ☑ ITT: ☑	4,732 individuals with previous stroke/TIA (ischemic or hemorrhagic) that occurred 1 – 6 months prior to enrolment, and with LDL between 2.6-4.9 mmoL/L and no known history of coronary heart disease. In the secondary analysis, participants were classified as having type 2 diabetes, (n=794) metabolic syndrome (MS) (n=642) and neither diabetic, nor having MS (n=3,295)	In the *SPACL* trial, participants were randomly assigned to receive either 80 mg/day atorvastatin or matching placebo for the duration of the study. Patients were assessed at 1, 3 and 6 months then every 6 months thereafter.	**Primary outcome:** Risk of fatal or non-fatal stroke events compared among study groups. **Secondary outcomes:** Stroke or TIA, major coronary event, major cardiovascular event, acute coronary event, any coronary event, revascularization procedure, or any cardiovascular event	The median duration of follow-up was 4.9 years. The risk of stroke was increased in persons with diabetes, relative to those without DM or MS (HR=1.62, 95% CI 1.33-1.98, p<0.001). The risk of major cardiovascular events was increased in persons with diabetes, relative to those without DM or MS (HR=1.66, 95% CI 1.39-1.97, p<0.001). The risk of the need for revascularization procedures was increased in persons with diabetes, relative to those without DM or MS (HR=2.39, 95% CI 1.78-3.19, p<0.001). Statin therapy was found to be equally effective in diabetics and non-diabetics.
Knop et al. 2006 **International** **RCT** ***Atorvastatin Study for the Prevention of Coronary Heart Disease Endpoints in***	CA: ☑ Blinding: Patient: ☑ Assessor ☑ ITT: ☑	2,410 patients with type 2 diabetes, 40-75 years, with LDL-chol of ≤3.6 mmol/L if recent previous MI, otherwise, ≤4.1 mmol/L and TG ≤6.8 mmol/L. Mean age at baseline was 61 years. 66% of patients were male.	Following the initiation of a NCEP Step I diet and a 6-week placebo-baseline period, patients were randomized to receive 10 mg of atorvastatin or placebo, daily for the 4-year study duration. For 252 patients in the treatment group and 253	**Primary outcome:** Clinical composite end point of cardiovascular death (including stroke), non-fatal MI and stroke **Secondary outcomes:** Time to primary outcome, non-cardiovascular death, TIA	The median duration of follow-up was 4 years. There were significant reductions in total chol, LDL chol and TGs among patients in the atorvastatin group, with increases in HDL-chol, while there were no corresponding changes in these parameters in patients in the placebo group. There were no significant changes in mean HbA1c levels in patients in either group. There was no significant reduction in risk of the

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Non-Insulin-Dependent Diabetes Mellitus (ASPEN)			in the placebo group, the study was considered "secondary prevention" patients. Of these patients, 9% & 12% (treatment & placebo, respectively) had a history of CVD.		primary outcome associated with statin use (13.7% vs. 15.0%), or the time to first primary event (HR=0.90, 95% CI 0.73-1.12, p=0.34). Treatment with statin was not associated with significant reductions in fatal or non-fatal stroke risk in either primary or secondary prevention patients. The number of adverse events was similar between groups. There were 263 cases (22%) of discontinuation of medications in the statin group and 283 (23.6%) in the placebo group.
Shepherd et al. 2006 **USA & UK** **RCT** ***Treating to New Targets Study (TNT) (diabetes subgroup)***	CA: ☑ Blinding: Patient: ☑ Assessor ☑ ITT: ☑	1,501 patients aged 35-75 years with CHD, diabetes and LDL-chol values <3.4 mmol/L. Mean age at baseline was 63 years. 73% of participants were male. The mean HbA1c value was 7.4%. Mean duration of diabetes was 8.5 years.	Following a 1-8 week washout period, patients were randomized to receive 10 or 80 mg of atorvastatin daily. Target LDL-chol levels in each group were 2.6 and 1.9 mmol/L	**Primary outcome:** Time to first occurrence of major cardiovascular event (death, MI, fatal/nonfatal stroke). **Secondary outcomes:** Any cardiovascular event, major coronary event, any coronary event, cerebrovascular event, all-cause mortality.	The duration of follow-up was 4.9 years. The changes in mean LDL chol levels from baseline to end of treatment were: 10 mg group: 2.50-2.5 mmol/L 80 mg group: 2.47-2.0 mmol/L Treatment with 80 mg statin was associated with a significant reduction in the time to major cardiovascular event (HR=0.75, 95% CI 0.58-0.97, p=0.026) and cerebrovascular event (HR=0.69, 95% CI 0.48-0.98, p=0.037). 5.4% of patients in the 10 mg group and 7.0% in the 80 mg group experienced a treatment-related adverse event. Patients in the 80 mg group experienced more cases of myalgia (3.6% vs. 2.4%)

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

Intensive Blood Glucose Control for the Prevention of Stroke

Study/Type	Quality Rating	Sample Description	Method	Outcomes	Key Findings and Recommendations
Insulin Resistance					
Kernan et al. 2016	CA: ☑	3,876 patients, ≥40 years with stroke or TIA	Patients were randomized to receive	**Primary outcome:** Fatal or non-fatal MI or fatal	Median duration of follow-up was 4.8 years.

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USA **RCT** ***Insulin Resistance After Stroke (IRIS)***	Blinding: Patient: ☑ Assessor ☑ ITT: ☑	within previous 6 months, with insulin resistance (defined as Homeostasis Model Assessment of Insulin Resistance (HOMA-IR) level>3.0). Patients with diabetes and heart failure, were excluded. Mean age was 63.5 years, 65.5% male, 87% had suffered a stroke. Mean HgA1c 5.8%	pioglitazone (target dose of 45 mg daily, n= 1,939) or placebo (n=1,937) for 5 years.	or non-fatal stroke **Secondary outcomes:** Stroke, acute coronary syndrome, composite of stroke, MI or heart failure, diabetes, death from any cause	The risk of the primary outcome was significantly lower for patients in the pioglitazone group (9.0% vs. 11.8%, HR=0.76, 95% CI 0.62-0.93, p=0.007). The risk of the development of diabetes over the study period was significantly reduced for patients in the pioglitazone group (3.8% vs. 7.7%, HR=0.48, 95% CI 0.33-0.69, p<0.001). The risk of stroke was not significantly reduced for patients in the pioglitazone group (6.5% vs. 8.0%, HR=0.82, 95% CI 0.61-1.10, p=0.19). The risk of stroke, MI or serious heart failure was not significantly reduced for patients in the pioglitazone group (10.6% vs. 12.9%, HR=0.82, 95% CI 0.65-1.05, p=0.11). The risk of all-cause mortality was not significantly reduced for patients in the pioglitazone group (7.0% vs.7.5%, HR=0.93, 95% CI 0.73-1.17, p=0.52). The frequency of adverse events including bone fracture, weight gain, edema, shortness of breath and liver enzyme abnormalities was significantly higher in the pioglitazone group. Adherence to drug regimen was lower in the pioglitazone group at exit visit (60% vs. 67%)
Type 2 Diabetes					
Marso et al. 2016a) **USA/International** **RCT** ***Liraglutide Effect and Action in Diabetes: Evaluation of Cardiovascular Outcome Results (LEADER) trial***	CA: ☑ Blinding: Patient: ☑ Assessor ☑ ITT: ☑	9,340 patients ≥50 years with type 2 DM and a glycated hemoglobin level ≥ 7.0%, with at least one cardiovascular coexisting condition (coronary heart disease, cerebrovascular disease, peripheral vascular disease, chronic kidney disease	After a 2-week run-in period, patients were randomized 1:1 to receive 1.8 mg (or the maximum tolerated dose) of liraglutide or placebo once daily as a subcutaneous injection, in addition to standard care	**Primary outcome:** Death from cardiovascular causes, nonfatal MI, or nonfatal stroke	The median duration of follow-up was 3.8 years. The risk of the primary outcome was significantly lower in the liraglutide group (13.0% vs. 14.9%, HR=0.87, 95% CI 0.78–0.97, p=0.01 for superiority). The NNT to prevent one case of the primary outcome over 3 years was 66. The risk of death from cardiovascular causes was significantly lower in the liraglutide group (4.7% vs. 6.0%, HR=0.78, 95% CI 0.66–0.93,

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		of stage ≥3, or chronic heart failure of New York Heart Association class II or III); or aged ≥60 years with at least one cardiovascular risk factor, as determined by the investigator. Mean age was 64 years, 64% were men. Mean duration of diabetes was 12.8 years. 16% of patients had sustained a previous stroke. At baseline 88% of patients were taking some form of antihyperglycemic medication (oral agents+/- insulin).			p=0.007). The risk of fatal or nonfatal stroke was not reduced significantly with liraglutide (3.7% vs. 4.3%, HR=0.86, 95% CI 0.71–1.06, p=0.16). The frequency of any adverse event was similar between groups (62.3% vs. 60.8%, p=0.12). The risk of death from cardiovascular causes was not significantly lower in the liraglutide group (4.7% vs. 6.0%, HR=0.78, 95% CI 0.66–0.93, p=0.007).
Marso et al. 2016b) ***Trial to Evaluate Cardiovascular and Other Long-term Outcomes with Semaglutide in Subjects with Type 2 Diabetes (SUSTAIN-6)*** **USA/International** **RCT**	CA: ☑ Blinding: Patient: ☑ Assessor ☑ ITT: ☑	3,297 patients ≥50 years with type 2 DM and a glycated hemoglobin level ≥ 7.0%, with established cardiovascular disease (previous cardiovascular, cerebrovascular, or peripheral vascular disease), chronic heart failure (New York Heart Association class II or III), or chronic kidney disease of ≥ stage 3 or ≥ 60 years with at least one cardiovascular risk factor. Mean age was 64.6 years, 60.7% were men. Mean duration of diabetes was 13.9 years. 11.6% of patients had sustained a previous stroke. At baseline 98.4% of	In addition to standard care (oral antihyperglycemic agents +/- insulin) patients were randomized 1:1:1:1, to receive once-weekly semaglutide (0.5 mg or 1.0 mg) or placebo, subcutaneously, for 104 weeks	**Primary outcome:** Composite of first occurrence of death from cardiovascular causes, nonfatal MI, or nonfatal stroke. **Secondary outcomes:** First occurrence of an expanded composite cardiovascular outcome (death from cardiovascular causes, nonfatal myocardial infarction, nonfatal stroke, revascularization [coronary or peripheral], and hospitalization for unstable angina or heart failure), composite outcome of death from all causes, nonfatal MI, or nonfatal stroke	The median duration of follow-up was 2.1 years. The risk of the primary outcome was significantly lower in the (combined) semaglutide group (6.6% vs. 8.9%, HR=0.74, 95% CI 0.58–0.95, p=0.02 for superiority). The risk of the expanded composite outcome was significantly lower in the (combined) semaglutide group (12.1% vs. 16.0%, HR=0.74, 95% CI 0.62–0.89, p=0.002 for superiority). The risk of death from cardiovascular causes was not significantly lower in the (combined) semaglutide group (2.7% vs. 2.8%, HR=0.98, 95% CI 0.65–1.48, p=0.92). The risk of nonfatal stroke was significantly lower in the (combined) semaglutide group (1.6% vs. 2.7%, HR=0.61, 95% CI 0.38–0.99, p=0.04). **5 mg vs. placebo** The risk of the primary outcome was not significantly lower in the semaglutide group (HR=0.77, 95% CI 0.55–1.08, p=0.13)

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		patients were taking some form of antihyperglycemic medication (oral agents+/- insulin).			The risk of nonfatal stroke was not significantly lower in the semaglutide group (HR=0.57, 95% CI 0.31–1.06 p=0.07). **10 mg vs. placebo** The risk of the primary outcome was not significantly lower in the semaglutide group (HR=0.71, 95% CI 0.49–1.02, p=0.06). The risk of nonfatal stroke was not significantly lower in the semaglutide group (HR=0.68, 95% CI 0.32–1.02, p=0.06). The frequency of any adverse event was similar between groups (0.5 mg 89.6% vs. placebo 90.8%; 10 mg 89.1% vs. placebo 89.2%). The frequencies of any adverse event leading to treatment discontinuation were (0.5 mg 11.5% vs. placebo 5.7%; 10 mg 14.5% vs. placebo 7.6%).
Zinman et al. 2015 **Canada** **RCT** ***Empagliflozin Cardiovascular Outcome Event Trial in Type 2 Diabetes Mellitus Patients (EMPA-REG OUTCOME Trial)***	CA: ☑ Blinding: Patient: ☑ Assessor ☑ ITT: ☑ (modified)	7,020 adults with type 2 DM and established cardiovascular disease, with a BMI ≤45, and an estimated glomerular filtration rate of ≥30mL/min. Participants were recruited from 42 countries (590 sites). Mean age was 63 years, 71.5% were male. Mean baseline Hgb A1c 8.08%	After a 2-week run in period, patients were randomized to receive 10 mg (n=2,345) or 25 mg (n=2,342) of empagliflozin or placebo (n=2,333) once daily for the duration of the trial. Additional agents used prior to the trial remained unchanged for the first 12 weeks and thereafter were adjusted to meet glycemic targets	**Primary outcome:** Composite of death from cardiovascular causes, nonfatal MI, or nonfatal stroke. **Secondary outcome:** Primary outcome plus hospitalization for unstable angina**.**	Median duration of follow-up was 3.1 years. The primary outcome occurred in a significantly lower percentage of patients in the empagliflozin group (10.5% vs. 12.1%: HR=0.86; 95.02% CI 0.74- 0.99; p<0.001 for noninferiority; p=0.04 for superiority, both dose levels combined). The secondary outcome occurred in 12.8% of patients in the empagliflozin group vs. 14.3% in the placebo group (HR=0.89; 95% CI, 0.78-1.01, p<0.001 for noninferiority and p=0.08 for superiority, both dose levels combined). In separate analysis of 10 mg and 25 mg vs. placebo for the primary and secondary outcomes, the hazard ratios were almost identical to the pooled result, although neither was statistically significant. Empagliflozin was associated with a significantly lower risk of death from cardiovascular causes,

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					all-cause mortality and hospitalization for heart failure. Empagliflozin was not associated with a significantly lower risk of fatal or nonfatal stroke (HR=1.18, 95% CI 0.89-1.56, p=0.26), nonfatal stroke (HR=1.24, 95% CI 0.92-1.67, p=0.16) or TIA (HR=0.85, 95% CI 0.51-1.42, p=0.54). In sub group analysis of the primary outcome, patients ≥65 years and those with Hg A1c<8.5 derived greater benefit from treatment with empagliflozin.
Marso et al. 2010 **USA** **Systematic review & meta-analysis**	NA	6 studies (4 RCTs) including the results from 27,544 persons with DM type 2, examining intensive glycemic control for the prevention of vascular events. The mean age of patients was 59 (intensive) and 62 (control) years. Patients in 2 studies included those with new-onset DM, while the duration of DM ranged from 7.7 to 11.5 years, in the remaining trials.	The agents/approaches used in the intensive groups varied widely across studies (sulphonylurea,TZD, alpha glucosidase inhibitor, and insulin), and usually involved more than one agent. In two of the older included studies, only diet was used to manage blood sugars in the control group. (no details were provided about specific regimens or doses of medications)	**Primary outcome:** All-cause mortality, non-fatal MI and stroke	Mean duration of follow-up was 5.4 years (range=2.3-11.1 years). The final mean HbA1c values were 6.6% (intensive) and 7.4% (control). There was no reduction in the risk of all-cause mortality, stroke or cardiovascular mortality associated with intensive glycemic treatment. Incident rate ratios (IRR) were: All-cause mortality: IRR=1.01, 95% CI 0.86-1.18, p=0.93 Stroke: IRR=1.02, 95% CI 0.88-1.20, p=0.76 CV mortality: IRR=1.15, 95% CI 0.81-1.63, p=0.44. Intensive treatment was associated with a reduction in the risk of non-fatal MI: IRR=0.86, 95% CI 0.77-0.97, p=0.0015.
Ray et al. 2009 **UK** **Systematic review & meta-analysis**	NA	5 RCTs including 33,040 participants with type 2 diabetes. Mean ages ranged from 53-66 years. Mean duration of diabetes ranged from <1 year to 12 years. Mean baseline Hg $A1_C$ ranged from 7.1% to 9.4%	All trials (UKPDS 33 & 34, PROactive, ADVANCE, VADT and ACCORD) compared intensive vs. standard glucose-lowering interventions, using diet, oral agents and/or insulin.	**Primary outcome:** Non-fatal MI, coronary heart disease (CHD), stroke and all-cause mortality	Mean duration of follow-up ranged from 2.9-10.1 years Intensive glucose-lowering treatment was associated with a reduced risk of non-fatal MI and CHD (OR=0.83, 95% CI 0.75-0.93 and OR=0.85, 95% CI 0.77-0.93, respectively). Intensive glucose-lowering treatment was not associated with a reduced risk of stroke or all-cause mortality (OR=0.93, 95% CI 0.81-1.06 and OR=1.02, 95% CI 0.87-1.19, respectively)

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Duckworth et al. 2009 **USA** **RCT** ***Veterans Affairs Diabetes Trial (VADT)***	CA: ☑ Blinding: Patient: ☒ Assessor ☑ ITT: ☑	1,791 military veterans with poorly controlled diabetes (Hb $A1_C$ ≥7.5%), despite maximal doses of oral agents+/- insulin. Mean duration of diabetes was 12 years Mean age was 60 years. Mean duration of diabetes was 11.5 years. Mean Hb $A1_C$ was 9.4%. Mean baseline BP was 132/76 mm Hg	Patients were randomized to receive standard (n=899) or intensive (n=892) glucose control therapy. In both study groups, patients with a BMI of ≥27 were started on two oral agents, metformin + rosiglitazone. Those with a BMI of <27were started on glimepiride plus rosiglitazone. Patients in the intensive-therapy group were started on maximal doses, and those in the standard-therapy group were started on half the maximal doses.	**Primary outcome:** First occurrence of any of the following: MI, stroke, death from CV causes, new or worsening cardiovascular causes, new/worsening CHF, **Secondary outcomes:** New/worsening angina, new TIA, intermittent claudication, death from any cause and microvascular complications	Median duration of follow-up was 5.6 years. By 3 months, median HBA1C levels were 8.4% in the standard therapy group vs. 6.9%, in the intensive group. Median Hb $A1_C$ levels were 8.4% vs. 6.9% There were no significant differences between groups in any of the primary or secondary outcomes. The primary outcome occurred in 235 patients in the intensive group vs. 264 patients in the standard therapy group (HR=0.88, 95% CI 0.74-1.05, p=0.14). There was no significant reduction in the risk of death from any cause associated with intensive therapy (102 vs. 95 deaths, HR=1.07, 95% CI 0.81-1.42, p=0.62) Intensive therapy was not associated with a significant reduction in the risk of stroke (26 vs. 36 events, HR=0.78, 95% CI 0.48-1.28) or TIA (19 vs. 13, HR=1.48, 95% CI 0.73-2.99). There were significantly more hypoglycemic events in the intensive therapy group. There were no significant differences between groups in the development of microvascular outcomes, with the exception of protection from progression to normal to microalbuminuria, associated with intensive therapy.
Gerstein et al. 2008 **USA & Canada** **RCT (factorial)** ***Action to Control Cardiovascular Risk in Diabetes (ACCORD) (glucose***	CA: ☑ Blinding: Patient: ☑ Assessor ☑ ITT: ☑	10,251 patients 40-79 years, with type 2 diabetes, HbA1c values of ≥7.5% and either a previous history of cardiovascular events or evidence of increased risk for cardiovascular events.	Patients were randomized to receive either intensive (HbA1c targets of <6.0%) or standard (HbA1c targets of 7.0- 7.9%) individualized glucose-lowering treatment strategies using multiple	**Primary outcome:** First occurrence of nonfatal MI, nonfatal stroke or death from cardiovascular causes. **Secondary outcomes:** Death from any cause	Mean duration of follow-up was 3.5 years (due to early study termination based on mortality trends suggesting increased rate of death from any cause associated with intensive therapy). Mean HbA1c values had fallen from 8.1% at baseline to 6.7% (intensive group) and 7.5% (control group) at 4 months. There was no reduction in the risk of the primary

Study/Type	Quality Rating	Sample Description	Method	Outcomes	Key Findings and Recommendations
–lowering arm)		The mean age of patients was 62.2 years. 38% of patients were female. 35% of participants had a history of previous cardiovascular events at the point of study enrolment. Median duration of DM was 10 years.	drugs including insulins and oral hypoglycemia agents		outcome associated with intensive glucose lowering (6.9% vs. 7.2%, HR=0.90, 95% CI 0.78-1.04, p=0.16). There was no increased risk of non-fatal stroke associated with intensive glucose lowering (1.3% vs. 1.2%, HR=1.06, 95% CI 0.75-1.50, p=0.74. There was an increased risk of death from any cause associated with intensive glucose lowering (HR=1.22, 95% CI 1.01-1.46, p=0.04). The incident of fatal stroke in both groups was 0.2%. Patients in the intensive group required medical assistance for hypoglycemia more frequently (10.5% vs. 3.5%), a greater proportion gained >10 kg from baseline (27.8% vs. 14.1%) and experienced any serious nonhypoglycemic adverse event (2.2% vs. 1.6%).
Patel et al. 2008 **International** **RCT (factorial)** ***Action in Diabetes and Vascular Disease: Preterax and Diamicron - MR Controlled Evaluation (ADVANCE)(glucose-lowering arm)***	CA: ☑ Blinding: Patient: ☑ Assessor ☑ ITT: ☑	11,140 patients aged ≥55 years with long standing diabetes, and a history of major or minor vascular disease. Mean age at baseline was 66 years, 42% of patients were female. 32% of participants reported a history of major macrovascular events including stroke (approximately 9%).	Patients were randomly assigned to receive either intensive glucose control (30-120 mg gliclazide + other drugs as necessary to achieve HbA_{1C} ≤6.5%) or standard glucose control for the duration of the study.	**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 median duration of follow-up was 5 years. Mean HbA1c values had fallen from 7.48% at baseline to 6.49% (intensive group) and 7.24% (control group). Intensive glucose control was associated with a reduction in the risk of major macro/microvascular events (HR=0.82, 95% CI 0.82-0.98, p=0.01). When analyzed separately, the risk was reduced for microvascular events, but not major macrovascular events. There was no significant difference between groups in the risk of death from any cause (HR=0.93, 95% CI 0.83-1.06, p=0.28). There was no reduction in the risk of fatal or nonfatal stroke or all cerebrovascular events associated with intensive intervention. Severe hypoglycaemia was significantly more frequent in the intensive treatment group (HR=1.86, 95% CI 1.42-2.40, p<0.001).

Study/Type	Quality Rating	Sample Description	Method	Outcomes	Key Findings and Recommendations
					There were 17 losses to follow-up.
Dormandy et al. 2005 **International** **RCT** ***PROspective pioglitAzone Clinical Trial In macroVascular Events (PROACTIVE)***	CA: ☑ Blinding: Patient: ☑ Assessor ☑ ITT: ☑	5,238 patients aged 35-75 years with type 2 DM, HbA1c>6.5% and evidence of extensive macrovascular disease. Mean age at baseline was 61 years. 67% of patients were male. Median time since diagnosis of DM was 8 years. 19% of patients had a history of previous stroke	Patients were assigned to treatment with pioglitazone (increasing from 15mg to 45 mg, n=2,605) or matching placebo (n=2,633) in addition to their established medication regimen (diabetic and cardiovascular) until the end of study.	**Primary outcome:** Composite of mortality, non-fatal MI, stroke, acute coronary syndrome, endovascular or surgical intervention (coronary or leg arteries), amputation above the ankle. **Secondary outcomes:** Time to the first event of death from any cause, MI and stroke, cardiovascular death and time to individual components of the primary composite	Mean duration of follow-up was 34.5 months. Median HbA1c values had fallen from 7.8% at baseline to 7.0% (intensive group) and from 7.9% to 7.6% (control group). There was no significant reduction in the risk of the primary outcome associated with pioglitazone treatment (HR=0.90, 95% CI 0.80-1.02, p=0.095) or in the risk of stroke (HR=0.81, 95% CI 0.61-1.07). There was a significant reduction in the risk of the secondary outcome (all-cause mortality, non-fatal MI and stroke) HR=0.84, 95% CI 0.72-0.98, p=0.027. Treatment compliance was in excess of 95% in both groups. Increased rates of (any) heart failure were reported more frequently in the pioglitazone group. (11% vs. 8%) Hypoglycemic symptoms were reported more frequently in patients in the pioglitazone group (28% vs. 20%).
Turner et al. 1998 **Holman et al. 2008 (Long-term follow-up)** **UK** **RCT** ***UK Prospective Diabetes Study (UKPDS) 33***	CA: ☑ Blinding: Patient: ☑ Assessor ☑ ITT: ☑	3,867 patients, aged 25-65 years, with newly-diagnosed DM II, with 2 fasting plasma glucose (FPG) levels of 6.1-15.0 mmol/L, after 3 months of dietary treatment. Mean age was 53 years, 61% male.	Patients were randomized to conventional (n=1,138) or intensive treatment (n=2,729). Patients in the conventional arm continued with diet therapy, with the aim of FPG< 15 mmol/L, without symptoms of hyperglycemia (n=1,138). Medications were added if hyperglycemia persisted. Patients in the intensive	**Primary outcome:** Any diabetes-related endpoint, including sudden death, death from hyper/hypoglycemia, fatal/non-fatal MI or stroke, angina, heart failure, renal failure, amputation, vitreous hemorrhage, retinal photocoagulation, blindness in one eye or cataract), diabetes-related deaths, all-cause mortality, microvascular complications	Median duration of follow-up was 10 years. Over the study period median Hgb A1c was significantly lower in the intensive group (7.0, 95% CI 6.2-8.2, vs. 7.9%, 95% CI 6.9-8.8, p<0.0001). The risk of any diabetes-related complication was significantly lower for patients in the intensive group (RR=0.88, 95% CI 0.79-0.99). The risks of diabetes-related deaths and all-cause mortality were not significantly lower for patients in the intensive group (RR=0.90, 95% CI 0.73-1.11 and RR=0.94, 95% CI 0.80-1.10, respectively). The risks of MI and microvascular events were

Study/Type	Quality Rating	Sample Description	Method	Outcomes	Key Findings and Recommendations
			treatment arm were given a sulphonylurea (chlorpropamide 100-500 mg, glibenclamide 2.5-20 mg, or glipizide 2.5-40 mg) or with insulin + diet therapy with the aim of maintaining FPG <6.0 mmol/L. Patients attended follow-up clinics every 3-4 months for up to 10 years		significantly reduced (RR=0.84, 95% CI 0.71-1.00 and RR=0.75, 95% CI 0.60-0.93, respectively), while the risk of stroke was not (RR=1.11, 95% CI 0.81-1.51). There were no significant differences among the intensive treatments for any of the outcomes. For example, the risk of stroke Chlorpropamide (n=619) vs. conventional treatment: RR=1.01, 95% CI 0.65-1.58 Glibenclamide (n=619) vs. conventional treatment: RR=1.98, 95% CI 0.50-2.08 Insulin (n=911) vs. conventional treatment: RR=0.86, 95% CI 0.57-1.81. The occurrence of major hypoglycemic episodes per year by treatment group was: Chlorpropamide (1.0%), glibenclamide (1.4%), insulin (1.8%), and diet (0.7%). In long-term follow-up of up to 30 years, the risks of any diabetes-related complication, diabetes-related death, death from any cause, microvascular disease and MI remained significantly reduced for patients in the intensive group; however, the risk of stroke was not significantly reduced (RR=0.91, 95% CI 0.73-0.1.13).
Type I Diabetes					
Nathan et al. 2005 **USA** **RCT** ***The Diabetes Control and Complications Trial/Epidemiology of Diabetes Interventions and Complications (DCCT/EDIC) Study Research Group***	CA: ☑ Blinding: Patient: ☒ Assessor ☑ ITT: ☑	1,441 patients with type I DM, aged 13-40 years, without a history of CVD, HTN or hypercholesterolemia, recruited from 1983-1993. Mean age was 27 years, 52% were male. Mean Hgb A1C was 9.1%	Patients were randomized to receive intensive (n=711) or conventional therapy (n=730) for an average of 6.5 years. Patients in the intensive group received ≥3 daily injections of insulin via external pump, with dose adjustment with daily glucose targets and Hgb A1c target of <6.05%. There were no glucose targets for	**Primary outcome:** Time to first event of any cardiovascular evets (nonfatal MI or stroke, CVD-related mortality, subclinical MI, angina, the need for revascularization with angioplasty or coronary-artery bypass)	Mean duration of follow-up was 17 years. Mean Hgb A1C was significantly lower at the end of 6.5 years among patients in the intensive group (7.4% vs 9.1%, p<0.01). There were 144 cardiovascular events in 83 patients at the end of follow-up. 46 events among 31 patients in the intensive group vs. 98 events among 52 patients in the conventional group. The event rates were significantly lower among the intensive group (0.38 vs. 0.80 per 100 patient-years, p= 0.007).

Study/Type	Quality Rating	Sample Description	Method	Outcomes	Key Findings and Recommendations
			patients in the conventional group, who received 1-2 daily injections of insulin		Intensive treatment was associated with a significantly reduced risk of the primary outcome (42%, 95% CI 9%-63, p=0.02). Intensive treatment was associated with a significantly reduced risk of the first occurrence of nonfatal MI, stroke, or death from cardiovascular disease (57%, 95% CI 12%-79%, p=0.02).

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

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 & meta-analysis**	NA	10 RCTs (n=21,871) examining the effects of angiotensin-converting enzyme (ACE) inhibitors and angiotensin II receptor blockers (ARBs) on cardiovascular (CV) risk in hypertensive patients with type 2 diabetes. Mean age of patients ranged from 56-64 years.	Treatment contrasts included: ACE inhibitors vs. β-blockers (n=1), ACE inhibitors vs. Ca Channel blockers (n=1), 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),	**Primary Outcome:** All-cause mortality **Secondary outcomes:** CV mortality, MI, stroke and CV events	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 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,	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)	**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).

Study/Type	Quality Rating	Sample Description	Method	Outcomes	Key Findings and Recommendations
		or already receiving treatment for elevated blood pressure. Participants in all included trials were between 40-5 and 70-82 years at baseline.	**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.		
Muramatsu et al. 2012 **Japan** **RCT** ***Nagoya Heart Study***	CA: ☑ Blinding: Patient ☒ Assessor ☑ ITT: ☑	1,150 participants aged 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%	Patients were 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.	**Primary outcome:** Composite of MI, stroke, new or worsening heart failure, coronary revascularization procedures, or sudden cardiac death **Secondary outcome:** All-cause mortality	The median duration of follow-up was 3.2 years. 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

Study/Type	Quality Rating	Sample Description	Method	Outcomes	Key Findings and Recommendations
					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 **USA** **RCT (factorial)** ***Action to Control Cardiovascular Risk in Diabetes (ACCORD) (hypertension arm)***	CA: ☑ Blinding: Patient: ☒ Assessor ☒ ITT: ☑	4,733 participants, 40-79 years with type 2 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	Patients were randomized to receive 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.	**Primary outcome:** First occurrence of a major CVD event, including nonfatal heart attack, nonfatal stroke, or cardiovascular death **Secondary outcomes:** Total mortality	Mean duration of follow-up was 4.7 years. 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***	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.	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)	**Primary outcome:** Composite of macrovascular events (death from cardiovascular causes, nonfatal MI or stroke) and microvascular events (new or worsening nephropathy)	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

Study/Type	Quality Rating	Sample Description	Method	Outcomes	Key Findings and Recommendations
and Diamicron - MR Controlled Evaluation (ADVANCE) (hypertension arm)		Mean age at baseline was 66 years. 57% of patients were male and 9% had previous stroke)	following a 6-week run-in period. After 3 months, treatment doses were doubled (4 mg/1.24 mg vs. matching placebo).	**Secondary outcomes:** Death from any cause, death from cardiovascular causes, major coronary events, fatal and nonfatal stroke	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. 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

Study/Type	Quality Rating	Sample Description	Method	Outcomes	Key Findings and Recommendations
					ramipril group (7% vs. 2%).
Turner et al. 1998 **UK** **RCT** ***United Kingdom Prospective Diabetes Study (UKPDS) 38 (hypertension portion)***	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 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.	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) 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	**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 **Secondary outcome:** Nonfatal/fatal MI, fatal/nonfatal stroke, amputation or death from peripheral vascular disease and fatal/nonfatal renal failure	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 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.

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

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