Canadian Stroke Best Practices

CANADIAN STROKE BEST PRACTICE RECOMMENDATIONS

Secondary Prevention of Stroke

Seventh Edition, 2020

Evidence Table: *Diabetes Management*

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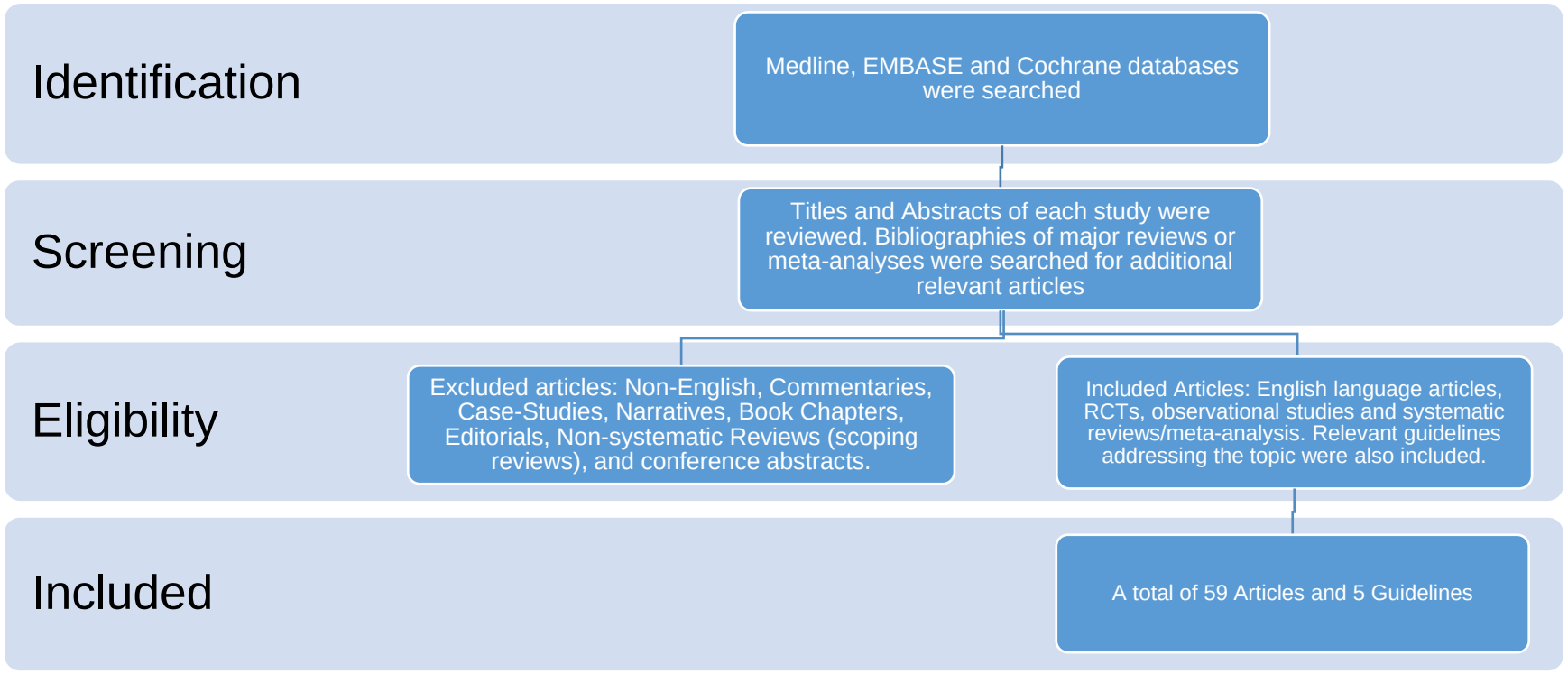
Search Strategy



Pubmed, EMBASE and the Cochrane Central Register of Controlled Trials databases 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 59 articles and 5 guidelines were included and were separated into separate categories designed to answer specific questions.

Published Guidelines

Guideline	Recommendations
Risk reduction of cognitive decline and dementia: WHO guidelines. Geneva: World Health Organization; 2019. Licence: CC BY-NC-SA 3.0 IGO	The management of diabetes in the form of medications and/or lifestyle interventions should be offered to adults with diabetes according to existing WHO guidelines. Quality of evidence: very low to moderate (for different interventions) Strength of the recommendation: strong The management of diabetes may be offered to adults with diabetes to reduce the risk of cognitive decline and/or dementia. Quality of evidence: very low Strength of the recommendation: conditional
Arnett DK, Blumenthal RS, Albert MA, Buroker AB, Goldberger ZD, Hahn EJ, Himmelfarb CD, Khera A, Lloyd-Jones D, McEvoy JW, Michos ED, Miedema MD, Muñoz D, Smith SC Jr, Virani SS, Williams KA Sr, Yeboah J, Ziaeian B. **2019 ACC/AHA guideline on the primary prevention of cardiovascular disease: a report of the American College of Cardiology/American Heart Association Task Force on Clinical Practice Guidelines.** ***Circulation*. 2019;140:e596–e646** **(selected)**	For adults with T2DM, it is reasonable to initiate metformin as first-line therapy along with lifestyle therapies at the time of diagnosis to improve glycemic control and reduce ASCVD risk. COE IIa; LOE B-R. For adults with T2DM and additional ASCVD risk factors who require glucose lowering therapy despite initial lifestyle modifications and metformin, it may be reasonable to initiate a sodium-glucose cotransporter 2 (SGLT-2) inhibitor or a glucagon-like peptide-1 receptor (GLP-1R) agonist to improve glycemic control and reduce CVD risk. COE IIb; LOE B-R. In adults 40 to 75 years of age with diabetes, regardless of estimated 10-year ASCVD risk, moderate-intensity statin therapy is indicated. COE I; LOE A. In adults with diabetes mellitus who have multiple ASCVD risk factors, it is reasonable to prescribe high-intensity statin therapy with the aim to reduce LDL-C levels by 50% or more. COE IIa; LOE B-R
Tobe SW, Stone JA, Anderson T, et al. Canadian Cardiovascular Harmonized National Guidelines Endeavour (C-CHANGE) guideline for the prevention and management of cardiovascular disease in primary care: 2018 update. ***CMAJ* 2018; 190: E1192-e206** **(selected)**	In addition to guideline statements already included in Diabetes Canada 2018 Clinical Practice Guidelines for the Prevention and Management of Diabetes in Canada (below) Statin therapy should be used to reduce CV risk in adults with type 1 or type 2 diabetes with any of the following features: • Clinical CVD • Age ≥ 40 yr • Age < 40 yr and 1 of the following: • Diabetes duration > 15 yr and age > 30 yr • Microvascular complications • Warrants therapy based on the presence of other CV risk factors according to the 2016 CCS Guideline for the Diagnosis and Treatment of Dyslipidemia. In adults with type 2 diabetes with clinical CVD in whom glycemic targets are not achieved with existing antihyperglycemic

Guideline	Recommendations
	medication, an antihyperglycemic agent with demonstrated CV outcome benefit (empagliflozin, liraglutide, canagliflozin) should be added to reduce the risk of major CV events. • An SGLT2 inhibitor with demonstrated reduction in hospital admissions for heart failure may be added to reduce the risk of admission for heart failure. ACE inhibitor or ARB, at doses that have demonstrated vascular protection, should be used to reduce CV risk in adults with type 1 or type 2 diabetes with any of the following: • Clinical CVD • Age ≥ 55 yr with an additional CV risk factor or end organ damage (albuminuria, retinopathy, left ventricular hypertrophy) • Microvascular complications
Diabetes Canada Clinical Practice Guidelines Expert Committee. Diabetes Canada 2018 Clinical Practice Guidelines for the Prevention and Management of Diabetes in Canada. ***Can J Diabetes*. 2018;42(Suppl 1): S1-S325** **(selected)**	Cardiovascular protection in people with diabetes 1. All individuals with diabetes should follow a comprehensive, multifaceted approach to reduce CV risk, including: a. A1C ≤7.0% implemented early in the course of diabetes [Grade C, Level 3] b. Systolic BP of <130 mmHg [Grade C, Level 3] and diastolic BP of <80 mmHg [Grade B, Level 1] c. Additional vascular-protective medications in the majority of adults with diabetes (see recommendations below) [Grade A, Level 1 for those with type 2 diabetes age >40 years with albuminuria; Grade D, Consensus for those with type 1 diabetes] d. Achievement and maintenance of healthy weight goals [Grade D, Consensus] e. Healthy eating (see Nutrition Therapy chapter, p. S64 for specific dietary recommendations) f. Regular physical activity [Grade D, Consensus] g. Smoking cessation [Grade C, Level 3]. 2. Statin therapy should be used to reduce CV risk in adults with type 1 or type 2 diabetes with any of the following features: a. Clinical CVD [Grade A, Level 1 (79)] b. Age ≥40 years [Grade A, Level 1 (79,80), for type 2 diabetes; Grade D, Consensus for type 1 diabetes] c. Age >40 and one of the following i) Diabetes duration >15 years and age >30 years [Grade D, Consensus] ii. Microvascular complications [Grade D, Consensus] iii. Warrants therapy based on the presence of other CV risk factors according to the 2016 Canadian Cardiovascular Society Guidelines for the Diagnosis and Treatment of Dyslipidemia (81) [Grade D, Consensus]. 3. For individuals not at LDL-C goal despite statin therapy, a combination of statin therapy with second-line agents may be used to achieve the goal and the agent used should be selected based upon the size of the existing gap to LDL-C goal [Grade D, Consensus]. Generally, ezetimibe should be considered [Grade D, Consensus]. In people with diabetes who also have concomitant clinical CVD, ezetimibe or evolocumab may be used to further reduce major adverse cardiac events [Grade A, Level 1 (82) for ezetimibe, Grade A, Level 1 (85) for evolocumab], and they should also be considered in those with concomitant familial hypercholesterolemia [Grade D, Consensus for ezetimibe and PCSK9 inhibitor]. 8. In adults with type 2 diabetes with clinical CVD in whom glycemic targets are not achieved with existing antihyperglycemic medication(s) and with an eGFR > 30mL/min/1.73 m^2, an antihyperglycemic agent with demonstrated CV outcome benefit should be added to reduce the risk of major CV events [Grade A, Level 1A (47) for empagliflozin; Grade A,

Guideline	Recommendations
	Level 1A for liraglutide (45); Grade C, Level 2 for canagliflozin (48).
American Diabetes Association. **8. Pharmacologic approaches to glycemic treatment: standards of medical care in diabetes—2018.** ***Diabetes Care* 2018; 41 (suppl 1): S73–85** **(selected)**	Metformin, if not contraindicated and if tolerated, is the preferred initial pharmacologic agent for the treatment of type 2 diabetes. A Long-term use of metformin may be associated with biochemical vitamin $B1_2$ deficiency, and periodic measurement of vitamin B_{12} levels should be considered in metformin-treated patients, especially in those with anemia or peripheral neuropathy. B Consider initiating dual therapy in patients with newly diagnosed type 2 diabetes who have A1C ≥9% (75 mmol/mol). E In patients without atherosclerotic cardiovascular disease, if monotherapy or dual therapy does not achieve or maintain the A1C goal over 3 months, add an additional antihyperglycemic agent based on drug-specific and patient factors. A A patient-centered approach should be used to guide the choice of pharmacologic agents. Considerations include efficacy, hypoglycemia risk, history of atherosclerotic cardiovascular disease, impact on weight, potential side effects, renal effects, delivery method (oral versus subcutaneous), cost, and patient preferences. E In patients with type 2 diabetes and established atherosclerotic cardiovascular disease, antihyperglycemic therapy should begin with lifestyle management and metformin and subsequently incorporate an agent proven to reduce major adverse cardiovascular events and cardiovascular mortality (currently empagliflozin and liraglutide), after considering drug-specific and patient factors. A In patients with type 2 diabetes and established atherosclerotic cardiovascular disease, after lifestyle management and metformin, the antihyperglycemic agent canagliflozin may be considered to reduce major adverse cardiovascular events, based on drug-specific and patient factors. C
Clinical Guidelines for Stroke Management 2017. Melbourne (Australia): National Stroke Foundation. Section 4 Secondary Prevention	**Practice point** Patients with glucose intolerance or diabetes should be managed in line with Diabetes Australia Best Practice Guidelines.
Piepoli MF, Hoes AW, Agewall S, et al. **2016 European Guidelines on cardiovascular disease prevention in clinical practice: the Sixth Joint Task Force of the European Society of Cardiology and Other Societies on Cardiovascular Disease**	Metformin is recommended as a first-line therapy, if tolerated and not contra-indicated, following evaluation of renal function. Class I; Level B In patients with type 2 DM and CVD, the use of an SGLT2 inhibitor should be considered early in the course of the disease to reduce CV and total mortality. Class IIa; Level B. Lipid lowering agents (principally statins) are recommended to reduce CV risk in all patients with type 2 or type 1 DM above the age of 40 years. Class I; Level A. BP targets in type 2 DM are generally recommended to be <140/85 mmHg, but a lower target of <130/80 mmHg is

Guideline	Recommendations
Prevention in Clinical Practice (constituted by representatives of 10 societies and by invited experts) Developed with the special contribution of the European Association for Cardiovascular Prevention & Rehabilitation (EACPR). ***Eur Heart J* 2016; 37: 2315–81. (selected)**	recommended in selected patients (e.g. younger patients at elevated risk for specific complications) for additional gains on stroke, retinopathy and albuminuria risk. Renin-angiotensin-aldosterone system blocker is recommended in the treatment of hypertension in DM, particularly in the presence of proteinuria or micro- albuminuria. Recommended BP target in patients with type 1 DM is <130/80 mmHg. Class I; Leve B
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 M & Gubitz G **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**	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
and transient ischemic attack: A guideline for healthcare professionals from the American Heart Association/American Stroke Association. ***Stroke 2014*;45:2160-2236.**	
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**	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)

Guideline	Recommendations
***Cerebrovasc Dis 2008*;25:457–507**	

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.

Study/Type	Quality Rating	Sample Description	Method	Outcomes	Key Findings and Recommendations
Keech et al. 2005 **International** **RCT *Fenofibrate Intervention and Event Lowering in Diabetes (FIELD) study***	CA: ☑ Blinding: Patient: ☑ Assessor ☑ ITT: ☑	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 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.	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, patients were randomized to receive either micronized fenofibrate (200 mg/day) or placebo for the study duration, planned for 5 years.	**Primary outcome:** Non-fatal MI or death from coronary heart disease. **Secondary outcomes:** Major cardiovascular disease 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.	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% 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**	CA: ☑ Blinding:	2,410 patients with type 2 diabetes, 40-75 years, with LDL-chol of ≤3.6	Following the initiation of a NCEP Step I diet and a 6-week placebo-baseline	**Primary outcome:** Clinical composite end point of cardiovascular death	The median duration of follow-up was 4 years.

Study/Type	Quality Rating	Sample Description	Method	Outcomes	Key Findings and Recommendations
RCT ***Atorvastatin Study for the Prevention of Coronary Heart Disease Endpoints in Non-Insulin-Dependent Diabetes Mellitus (ASPEN)***	Patient: ☑ Assessor ☑ ITT: ☑	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.	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 in the placebo group, the study was considered "secondary prevention" patients. Of these patients, 9% & 12% (treatment & placebo, respectively) had a history of CVD.	(including stroke), non-fatal MI and stroke **Secondary outcomes:** Time to primary outcome, non-cardiovascular death, TIA	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 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

Study/Type	Quality Rating	Sample Description	Method	Outcomes	Key Findings and Recommendations
					treatment-related adverse event. Patients in the 80 mg group experienced more cases of myalgia (3.6% vs. 2.4%).
iii) Evolocumab					
Sabatine et al. 2017 **USA/International** **RCT** ***Further Cardiovascular Outcomes Research with PCSK9 Inhibition in Subjects with Elevated Risk (FOURIER) Trial*** **Pre-specified sub group analysis**	CA: ☑ Blinding: Patient: ☑ Assessor ☑ ITT: ☑	27,564 patients from 49 countries, aged 40-85 years, with established atherosclerotic cardiovascular disease and a fasting LDL cholesterol level of ≥1.8 mmol/L, or HDL chol level of ≥2.6 mmol/L, who were also receiving ≥20 mg/day of a statin. Mean age was 63 years, 24.6% of the patients were women. 81.1% of the patients had a history of MI, 19.4% had a previous nonhemorrhagic stroke. Median baseline LDL level was 2.4 mmol/L	Patients were randomized 1:1 to receive evolocumab (either 140 mg every 2 weeks or 420 mg every month, by subcutaneous injection, according to patient preference) or placebo, for the duration of the trial.	**Primary outcome:** Composite of cardiovascular death, MI, stroke, hospitalization for unstable angina, or coronary revascularization. **Secondary outcome:** Composite of cardiovascular death, myocardial infarction, or stroke.	Median duration of follow-up was 2.2 years. **Overall results** At 48 weeks, the mean absolute reduction associated with evolocumab was 1.45 mmol/L (95% CI,1.43 to 1.47). The median reduction was 0.78 mmol/L. The risk of the primary outcome was significantly lower for patients in the evolocumab group (9.8% vs. 11.3%, HR=0.85, 95% CI 0.79‑0.92, p<0.001). The risk of the secondary outcome was significantly lower for patients in the evolocumab group 5.9% vs. 7.4%, HR=0.80, 95% CI 0.73‑0.88, p<0.001). The risk of any stroke was significantly lower for patients in the evolocumab group (1.5% vs. 1.9%, HR=0.79, 95% CI 0.66‑0.95, p<0.01). The risk of ischemic stroke or TIA was significantly lower for patients in the evolocumab group (1.7% vs. 2.1%, HR=0.77, 95% CI 0.65‑0.92, p=0.003). There was no significant reduction in the risk of cardiovascular death (1.8% vs. 1.7%, HR= 1.05, 95% CI 0.88‑1.25, p=0.62). **Diabetes subgroup** 11,031 patients (40%) had diabetes. The 3 -year risk of the primary outcome was significantly higher in persons with vs.

Study/Type	Quality Rating	Sample Description	Method	Outcomes	Key Findings and Recommendations
					without diabetes (17.1% vs. 13.0%, HR= 1·26, 95% CI 1·13–1·40, p<0·0001). The risk of the primary outcome was significantly lower for patients in the evolocumab group (HR=0.83, 95% CI 0.75-0.93, p=0.0008). The absolute risk reductions in the primary endpoint with evolocumab in patients with diabetes was 2·7% (95% CI 0·7–4·8) over 3 years; NNT 37 (95% CI 21–137) vs. 1.6% (95% CI 0.1-3.2%); NNT 62 (95% CI 32-1226) in persons without diabetes. The risk of the secondary outcome was significantly lower for patients in the evolocumab group (HR=0.82, 95% CI 0.72-0.93, p=0.0021). Among persons without diabetes or those with prediabetes at baseline, evolocumab did not increase the risk of new-onset diabetes

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, Spence et al. 2019 **USA** **RCT** ***Insulin Resistance After Stroke (IRIS)***	CA: ☑ Blinding: Patient: ☑ Assessor ☑ ITT: ☑	3,876 patients, ≥40 years with stroke or TIA 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%	Patients were randomized to receive pioglitazone (target dose of 45 mg daily, n= 1,939) or placebo (n=1,937) for 5 years.	**Primary outcome:** Fatal or non-fatal MI or fatal or non-fatal stroke **Secondary outcomes:** Stroke, acute coronary syndrome, composite of stroke, MI or heart failure, diabetes, death from any cause	Median duration of follow-up was 4.8 years. 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%). **Prediabetic subgroup (Spence et al. 2019)** 1,454 participants with prediabetes, as defined by the American Diabetes Association (HbA1c 5.7% to 6.4% or a fasting plasma glucose 5.5-6.9 mmol/L) and adherence ≥80%.

Study/Type	Quality Rating	Sample Description	Method	Outcomes	Key Findings and Recommendations
					Pioglitazone significantly reduced the risks of: stroke or MI (HR=0.57; 95% CI, 0.39-0.84; p=.004). stroke (HR= 0.64; 95% CI, 0.42-0.99; p= .04), stroke/MI/hospitalization for heart failure (HR= 0.61; 95% CI, 0.42-0.88; p= .008), and new-onset diabetes (HR= 0.18; 95% CI, 0.10-0.33; p < .001).
Management of Type 2 Diabetes- Systematic review and meta-analyses					
Zelniker et al. 2019 **USA**	Risk of bias was assessed as low in all trials	8 RCTs including 77,242 patients, 42 920 (55.6%) in GLP1-RA trials (ELIXA, LEADER, SUSTAIN-6, EXSCEL and HARMONY), and 34,322 (44.4%) in SGLT2i trials (EMPA-REG, CANVAS, DECLARE-TIMI-58). Mean age ranged from 60.3-64.6 years, percentage of women ranged from 28%-40%).	Trials compared the potential benefit of GLP1-RA and SGLT2i vs. placebo in patients with and without established atherosclerotic cardiovascular disease (ASCVD)	**Primary outcomes:** Composite of MI, stroke, and cardiovascular death (MACE); hospitalization for heart failure; and progression of kidney disease	Median duration of follow-up ranged from 1.6-4.2 years. 56,473 patients (73.1%) had established ASCVD (range 41% to 100%). 8,213 of 77,242 patients (10.6%) experienced a MACE event (4,871 patients in the GLP1-RA trials and 3,342 patients in the SGLT2i trials). 84.7% occurred in the group with established ASCVD. Both drug classes reduced MACE by a similar magnitude; however, the effect was only significant in persons with established ASCVD (HR=0.87, 95% CI0.82-0.92 vs. HR=1.03, 95% CI 0.87-1.23). 4,274 patients experienced an MI, 2,237 experienced a stroke and 3,132 experienced cardiovascular death. GLP1-RA reduced the risk of stroke significantly (HR= 0.86; 95% CI, 0.77–0.97), whereas SGLT2i had no effect (HR= 0.97; 95% CI, 0.86–1.10). Both drug classes significantly reduced the risk of cardiovascular death (GLP1-RA: HR= 0.88; 95% CI, 0.80–0.96; P=0.004; SGLT2i: HR=0.84; 95% CI, 0.75–0.94; P=0.002).
Lee et al. 2017 **USA**	One trial had high risks of selection bias and reporting	3 RCTs (IRIS, J-SPIRIT, PROactive) that included a total of 4,980 persons with a previous stroke who had	Trials compared pioglitazone vs. placebo	**Primary outcome:** Recurrent stroke **Secondary outcome:** All major vascular events	Pioglitazone was associated with significant reduction in the risk of recurrent stroke (HR=0.68; 95% CI, 0.50–0.92; P=0.01) and the secondary outcome (HR=0.75; 95% CI, 0.64–0.87; P=0.0001).

Study/Type	Quality Rating	Sample Description	Method	Outcomes	Key Findings and Recommendations
	bias, another trial was open label (nonblinded)	diabetes, newly diagnosed diabetes or insulin resistance. Mean ages were 63.5, 68.5 and 62.3 years. 35%, 24% and 39% of participants were women.		**Safety outcomes:** All-cause mortality, heart failure	Pioglitazone was not associated with significant increases in the risks of all-cause mortality or heart failure (HR= 0.94; 95% CI, 0.79–1.12; P=0.48 and HR= 1.21; 95% CI, 0.81–1.80; P=0.54, respectively).
Seidu et al. 2016 **UK**	16 RCTs had Jadad scores ≥3	19 RCTs that included persons with type 2 diabetes of any duration. Mean age at baseline ranged from 52 to 69 years. Mean duration of diabetes ranged from 0 to 11.7 years.	Trials compared intensive glycemic control alone or as part of a multifactorial intervention vs. a control group (standard care, placebo or less-intensive treatment). Most studies compared standard treatment with intensive glycemic control only. Four trials examined multifactorial interventions including behavior modification	**Primary outcomes:** Non-fatal MI, non-fatal stroke, cardiovascular disease (CV) mortality and all-cause mortality	Median duration of follow-up ranged from 0 to 12 years. The risk of non-fatal stroke was not significantly reduced with intensive glycemic treatment (RR=0.96, 95% CI 0.86- 1.07). Results from 14 trials included (n= 78, 568) The risks of CVD mortality and all-cause mortality were not significantly reduced with intensive glycemic treatment (RR=1.00, 95% CI 0.90- 1.10 and RR=1.00, 95% CI 0.94-1.06, respectively). The results from 18 trials were included (n= 83, 938 and n= 84,266) The risk of non-fatal MI was significantly reduced with intensive glycemic treatment (RR=90, 95% CI 0.83- 0.96). Results from 16 trials were included (n = 79, 595). The results of a meta-regression suggested that "*intensive glucose-lowering and multifactorial interventions are predicted to have the desired beneficial effect of reducing CVD mortality in populations where the incidence rate is greater than about 6.3 CVD deaths per 1000 person-years or an average 10–year CVD risk of 6.3%.*"
Marso et al. 2010 **USA**	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	The agents/approaches used in the intensive groups varied widely across studies (sulphonylurea,TZD, alpha glucosidase inhibitor, and insulin),	**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

Study/Type	Quality Rating	Sample Description	Method	Outcomes	Key Findings and Recommendations
		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.	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)		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**	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)
Management of Type 2 Diabetes-Clinical Trials using Glucagon-like peptide 1 (GLP-1) receptor agonist					
Malhotra et al. 2020 **USA** **Systematic review & meta-analysis**	Risk of bias was assessed as low in all trials	8 RCTs, including 56,251 patients (ELIXA, EXSECL, FIGHT, HARMONY, LEADER, PIONEER-6, SUSTAIN-6 and REWIND)	Trials compared the outcomes of patients with Type 2 DM treated with GLP-1R agonists vs. placebo.	**Primary outcomes:** Nonfatal or fatal strokes **Secondary outcomes:** All-cause or cardiovascular mortality, MI and major adverse cardiovascular events (MACE)	The odds of all strokes and fatal strokes were significantly reduced with GLP-1R agonists (OR=0.84, 95% CI 0.76–0.94, p=0.002 and OR=0.84, 95% CI 0.75–0.93, p=0.001, respectively). GLP-1R agonists significantly reduced MACE by 13% (OR=0.87; 95% CI 0.81–0.94, p=0.0003), cardiovascular mortality by 12% (OR= 0.88; 95% CI 0.81–0.95; p=0.002) and all-cause mortality by 12% (OR= 0.88; 95% CI 0.82–0.95, p=0.0007). Among patients with prior history of MI or nonfatal strokes, GLP-1R agonists were associated with significantly reduced odds of recurrent MACE (5 RCTs; OR= 0.86; 95% CI

Study/Type	Quality Rating	Sample Description	Method	Outcomes	Key Findings and Recommendations
					0.80–0.92; p<0.0001).
Barkas et al. 2019 **Greece** **Systematic review & meta-analysis**		5 RCTs (ELIXA, LEADER, SUSTAIN, EXSCEL and HARMONY) including 42,358 participants. Mean age ranged from 60.3 to 64.6 years. Percent male ranged from 60.7% to 69.3%.	Trials compared glucagon-like peptide 1 receptor (GLP-1R) agonists vs. placebo	**Primary outcome:** Stroke	Duration of the intervention ranged from 2.1 to 3.8 years. The risk of total stroke was significantly lower with GLP-1R (RR=0.87, 95% CI 0.78–0.98, p = 0.021) and nonfatal stroke (RR=0.88, 95% CI 0.78–0.99, p = 0.035), with no significant reduction in the risk of fatal stroke (RR=0.84, 95% CI 0.60–1.17, p = 0.29, 4 trials)
Bellastella et al. 2019 **Italy** **Systematic review & meta-analysis**	All trials assessed as being of low risk of bias	7 RCTs ELIXA (2015), LEADER (2016), SUSTAIN-6 (2016), EXSCEL (2017), HARMONY (2018), REWIND (2019) and PIONEER-6 (2019). Mean age ranged from 60 to 66.2 years. Median duration of follow-up ranged from 1.3 to 5.4 years.	Participants were randomized to receive a GLP-1 receptor antagonist (Lixisenatide, Liraglutide, Semaglutide, Exenatide, Albiglutide, Dulaglutide) or placebo	**Primary outcome:** Nonfatal stroke **Secondary outcomes:** Fatal and total stroke	The risks of nonfatal and total stroke were significantly lower in the treatment group (HR=0.85, 95% CI, 0.76–0.94, p=0.002 and HR= 0.84, 95% CI 0.76–0.93, p=0.001, respectively). The risk of fatal stroke was not reduced significantly in the treatment group (HR= 0.81, 95% CI 0.62–1.08, p=0.150).
Gerstein et al. 2019 **Canada/International** **RCT** ***Researching Cardiovascular Events with a Weekly Incretin in Diabetes (REWIND)***	CA: ☑ Blinding: Patient: ☑ Assessor ☑ ITT: ☑	9,901 persons ≥50 years with type 2 diabetes and $HbA1_c$ ≤9·5%, and a BMI ≥23, who had either a previous cardiovascular event or cardiovascular risk factors. Mean age was 66.2 years, 53% were men. Baseline $HbA1_c$ was 7.3%. 20% had a previous cardiovascular event, 31.5% reported previous cardiovascular disease.	Participants were randomly assigned (1:1) to either weekly subcutaneous injection of dulaglutide (1·5 mg) or placebo	**Primary outcome:** First occurrence of the composite endpoint of non-fatal MI, non-fatal stroke, or death from cardiovascular causes **Secondary outcomes:** Microvascular events (diabetic retinopathy, renal disease), hospital admission for unstable angina; each component of the primary composite cardiovascular outcome; death; and heart failure requiring either hospital admission or an urgent visit requiring therapy	Median duration of follow-up was 5.4 years. The primary outcome occurred less frequently in the dulaglutide group (12·0% [2·4 per 100 person-years] vs. 13·4% [2·7 per 100 person-years]; HR= 0·88, 95% CI 0·79–0·99; p=0·026). There was a significantly lower risk of nonfatal stroke), and of microvascular events (renal only). There were no interactions noted for the primary outcome (age, duration of diabetes, history of cardiovascular disease), baseline $HbA1_c$ or BMI. Dulaglutide did not significantly reduce the risks of all-cause mortality, heart failure, revascularisation, or hospital admissions. The numbers of serious adverse events did not differ significantly between groups; however,

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					gastrointestinal adverse events were more common in the dulaglutide group (47·4% vs. 34·1%, p<0·0001).
Husain et al. 2019 **Canada/International** **RCT** ***Peptide Innovation for Early Diabetes Treatment (PIONEER) 6***	CA: ☑ Blinding: Patient: ☑ Assessor ☑ ITT: ☑	3,183 patients ≥50 years with established cardiovascular disease (e.g. previous MI or stroke) or chronic kidney disease (85%), or ≥ 60 years with cardiovascular risk factors only (15%). Mean age was 66 years, 31.6% were women. Mean glycated hemoglobin was 8.2%.	In addition to standard care, patients were randomly assigned (1:1) to receive once-daily oral semaglutide (target dose, 14 mg) or placebo for the duration of the trial (accrual of 122 events)	**Primary outcome:** Incidence of a major adverse cardiovascular event (death from cardiovascular causes, nonfatal MI, or nonfatal stroke). **Secondary outcomes:** Components of the primary outcome	The median duration of the trial was 15.9 months. The primary outcome occurred in 3.8% of patients in the oral semaglutide group and 4.8% of patients in the placebo group (HR=0.79, 95% CI 0.57 to 1.11; p<0.001, for noninferiority). The occurrences of death from any cause, and death from cardiovascular causes were significantly reduced with oral semaglutide, while those of nonfatal stroke, and nonfatal MI were not. Gastrointestinal adverse events were more common in the oral semaglutide group (6.8% vs. 1.6% in the placebo group)
Hernandez et al. 2018 **UK/International** **RCT** ***A Long Term, Randomised, Double Blind, Placebo-controlled Study to Determine the Effect of Albiglutide, When Added to Standard Blood Glucose Lowering Therapies, on Major Cardiovascular Events in Patients with Type 2 Diabetes Mellitus (HARMONY)***	CA: ☑ Blinding: Patient: ☑ Assessor ☑ ITT: ☑	9,463 participants ≥40 years with type 2 diabetes and cardiovascular disease. Mean age was 64.1 years, 31% were women. The mean duration of diabetes was 14.1 years. 17.5% had previous stroke. Mean glycated hemoglobin concentration was 8·7%.	Participants were randomized to receive a subcutaneous injection of albiglutide (30–50 mg, based on glycemic response and tolerability) or of a matched volume of placebo once a week, in addition to standard care. Additional glucose-lowering medications could be adjusted or added.	**Primary outcome:** Cardiovascular death, MI or stroke **Secondary outcomes:** the primary composite, with the addition of urgent revascularisation for unstable angina, the individual components of the primary endpoint, and the composite of cardiovascular death or hospital admission because of heart failure	Median duration of follow-up was 1.6 years. The risk of the primary composite outcome was significantly lower in the albiglutide group (7% vs. 9%; HR= 0·78, 95% CI 0·68–0·90, <0·0001 for non-inferiority, p=0·0006 for superiority. There was no difference in the risk of fatal or nonfatal stroke between groups (2% vs. 2%; HR= 0·86, 95% CI 0·66–1·14, p=0·300 for non-superiority, while the risk of MI was significantly lower in the albiglutide group (4% vs. 5% HR=0·75, 95% CI 0·61–0·90, p for non-inferiority =0·003). The risk of hypoglycemia was significantly higher in the albiglutide group (RR=0·56, 95% CI 0·36–0·87)
Holman et al. 2017	CA: ☑	14,752 patients with type 2 diabetes,	Participants were randomized 1:1 to	**Primary outcome:** Composite of death from	Median duration of follow-up was 3.2 years.

Study/Type	Quality Rating	Sample Description	Method	Outcomes	Key Findings and Recommendations
UK ***RCT*** ***Exenatide Study of Cardiovascular Event Lowering (EXSCEL) Study***	Blinding: Patient: ☑ Assessor ☑ ITT: ☑	managed on a current diabetes regimen, with or without previous cardiovascular disease. Median age was 62 years. 38% were women. Median duration of diabetes was 12.0 years. Median glycated hemoglobin level was 8.0%. 73% had a history of CVD.	receive 2 mg extended release exenatide or matching placebo once weekly for the duration of the trial.	cardiovascular causes, nonfatal MI, or nonfatal stroke. **Secondary outcomes:** Death from any cause, death from cardiovascular causes, and the first occurrence of nonfatal or fatal MI nonfatal or fatal stroke, hospitalization for acute coronary syndrome, and hospitalization for heart failure	The occurrence of the primary outcome was 11.4% in the exenatide group and 12.2% in the placebo group (HR= 0.91, 95% CI 0.83−1.00, p<0.001 for noninferiority, p=0.06 for superiority). The occurrence of fatal or nonfatal stroke was 2.5% in the exenatide group and 2.9% in the placebo group (HR= 0.85, 95% CI 0.70−1.03, p<0.095). The incidence of serious adverse events did not differ significantly between groups (16.8% vs. 16.6%).
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 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	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, 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).

Study/Type	Quality Rating	Sample Description	Method	Outcomes	Key Findings and Recommendations
		medication (oral agents+/- insulin).			
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 patients were taking some form of antihyperglycemic medication (oral agents+/- insulin).	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) 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

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					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%).
Management of Type 2 Diabetes-Clinical Trials using Sodium–glucose cotransporter 2 (SGLT-2) inhibitor					
Cannon et al. 2020 **USA** **RCT** ***Evaluation of Ertugliflozin Efficacy and Safety Cardiovascular Outcomes Trial (VERTIS CV)***	CA: ☑ Blinding: Patient: ☑ Assessor ☑ ITT: ☑	8,246 patients ≥40 years with type 2 diabetes and atherosclerotic cardiovascular disease. Mean age was 64.4 years, 70% were men. Mean $HgbA1_C$ was 8.0%, 21% had a previous stroke.	Patients were randomized 1:1:1 to receive 5 or 15 mg of ertugliflozin or placebo once daily in addition to standard care. Data from the 2 active treatment groups were combined for analysis. Noninferiority analysis was performed, of the primary outcome with the noninferiority margin set at 1.3. Tests of superiority were then performed on the secondary outcome.	**Primary outcome:** Major adverse cardiovascular events (a composite of death from cardiovascular causes, nonfatal MI or nonfatal stroke). **Secondary outcome:** A composite of death from cardiovascular causes or hospitalization for heart failure.	Mean duration of follow-up was 3.5 years. The primary outcome occurred in 11.9% of patients in the ertugliflozin group and 11.9% of patients in the control group (HR=0.97; 95% CI 0.85 to 1.11; p<0.001 for noninferiority). The secondary outcome occurred in 8.1% of patients in the ertugliflozin group and 9.1% of patients in the control group (HR=0.88; 95% CI 0.75 to 1.03; p=0.11 for superiority). Fatal or nonfatal stroke occurred in 3.4% of patients in the ertugliflozin group and 3.2% of patients in the control group (HR=1.06; 95% CI 0.82 to 1.37). Nonfatal stroke occurred in 2.9% of patients in the ertugliflozin group and 2.8% of patients in the control group (HR=1.00; 95% CI 0.76 to 1.32). Serious adverse events occurred in 34.9% of patients in the 5 mg group, in 34.1% in the 15 mg ertugliflozin group and in 36.1% in the placebo group.
Zelniker et al. 2018 **USA** **Systematic review & meta-analysis**	The risk of bias was assessed as low in all 3 trials	3 RCTs comparing sodium-glucose cotransporter-2 inhibitors (SGLT-2) vs. placebo (EMPA-REG OUTCOME, CANVAS Program, and DECLARE-TIMI 58), including the results of	Trials compared Empagliflozin, Canagliflozin and Dapagliflozin vs. placebo	**Primary outcomes:** Major adverse cardiovascular event (MACE) including MI, stroke, and cardiovascular death, the composite of cardiovascular death or hospitalization for heart failure, their individual	The proportion of patients with established atherosclerotic cardiovascular disease (CVD) was 40.6% (DECLARE), 65.6% (CANVAS) and 100% (EMPA-REG). Mean of 60.2%. In total, 3,342 (9·7%) of 3,4322 patients had a MACE. Of those events, 2,588 (77·4%) occurred in the group with established atherosclerotic cardiovascular disease. Overall, SGLT2 reduced

Study/Type	Quality Rating	Sample Description	Method	Outcomes	Key Findings and Recommendations
		34,322 participants. All trials are described below. The mean age was 63·5 years, 35·1% were women. 60·2% of patients were known to have atherosclerotic cardiovascular disease and 13 672 (39·8%) had multiple risk factors but without known atherosclerotic cardiovascular disease.		components, and a standardized composite of renal outcomes including worsening eGFR, end-stage renal disease, or renal death	the risk of a major adverse cardiac event by 11% (HR=0·89, 95% CI 0·83–0·96, p=0·0014). However, the benefit was only seen in persons with established atherosclerotic CVD (HR=0·86, 95% CI 0·80–0·93 vs. persons with multiple risk factors; HR=1·00, 95% CI 0·87–1·16, p for interaction=0·0501). Overall, SGLT2 significantly reduced the risk for the composite of cardiovascular death or hospitalization for heart failure by 23% (HR= 0·77 [95% CI 0·71–0·84, p<0·0001). The risk in persons with established atherosclerotic cardiovascular disease was reduced significantly in the SGLT-2 group (HR= 0·76, 95% CI 0·69–0·84). The risk reduction among persons in the SGLT-2 group in persons with multiple risk factors was 16% (HR=0·84, 95% CI 0·69–1·01). Other outcomes for which SGLT2 decreased the risk in patients with established atherosclerotic cardiovascular disease and in those with multiple risk factors included all-cause death, and the composite of worsening of renal function, end-stage renal disease, or renal death. The overall risk of ischemic stroke was not reduced significantly in the SGLT2 group (HR=0.97, 95% CI 0.86-1.10), nor was the risk reduced significantly in persons with established atherosclerotic CVD, or in those with multiple risk factors. The risks of amputations and diabetic ketoacidosis were significantly higher in the SGLT-2 group.
Perkovic et al. 2019, Mahaffey et al. 2019 **USA/International** **RCT** ***Canagliflozin and***	CA: ☑ Blinding: Patient: ☑ Assessor ☑ ITT: ☑	4,401persons ≥30 years with a clinical diagnosis of type 2 diabetes, a HgbA1$_c$ of 6.5%–12.0% and chronic kidney disease, with an estimated GFR 30 to	Participants were randomized (1:1) to receive 100 mg oral canagliflozin or placebo daily for the duration of the trial.	**Primary outcome:** A composite of end stage kidney disease, doubling of the serum creatinine level, or renal or cardiovascular death	Median duration of follow-up was 2.62 years. The trial was stopped prematurely due to efficacy. The event rate of the primary outcome was significantly lower in the canagliflozin group (43.2 vs. 61.2 per 1000 patient-years; HR= 0.70; 95% CI 0.59 to 0.82; p=0.00001). There were no

Study/Type	Quality Rating	Sample Description	Method	Outcomes	Key Findings and Recommendations
Renal Events in Diabetes with Established Nephropathy Clinical Evaluation (CREDENCE) trial		<90 mL/min/1.73 m^2 and albuminuria >300 to 5000 mg/g. All the patients were required to be on a stable dose of an ACE or ARB for at least 4 weeks before randomization. Mean age was 63 years, 33.9% were women. 50% had existing cardiovascular disease.		**Secondary outcomes:** A composite of cardiovascular death or hospitalization for heart failure; a composite of cardiovascular death, MI or stroke **Safety outcomes:** Fractures, pancreatitis, ketoacidosis, and renal-cell carcinoma	interactions reported for the primary outcome, based on estimated baseline GFR The event rate for cardiovascular death was 19.0 per 1000 patient-years for the canagliflozin group vs. 24.4 per 1000 patient-years for the placebo group (HR=0.78, 95% CI 0.61–1.00, p=0.05). The event rate for the secondary outcome of cardiovascular death, MI or stroke was significantly lower in the canagliflozin group (38.7 vs. 48.7 per 1000 patient-years; HR= 0.80; 95% CI 0.67 to 0.95; p=0.01). P values were not reported for adverse events, but the frequencies of adverse events appear similar between groups. **Primary vs. Secondary prevention (Mahaffey et al. 2019)** 2,181 (49.6%) participants had no history of cardiovascular disease and were classified as the primary prevention cohort. The risk of the primary outcome was reduced significantly in the primary prevention cohort who were taking canagliflozin (10.2% vs. 14.5%; HR= 0.69, 95% CI 0.54–0.88). 2,222 (45.4%) participants had a history of cardiovascular disease (coronary, cerebrovascular, or peripheral vascular disease) and were classified as the secondary prevention cohort. The risk of the primary outcome was reduced significantly in the secondary prevention cohort who were taking canagliflozin (12% vs. 16.4%; HR= 0.70, 95% CI 0.56–0.88). The risk of nonfatal stroke was not reduced significantly in either the total sample the primary

Study/Type	Quality Rating	Sample Description	Method	Outcomes	Key Findings and Recommendations
					prevention cohort or the secondary prevention cohort.
Wiviott et al. 2019 **USA/International** **RCT** ***The Dapagliflozin Effect on Cardiovascular Events–Thrombolysis in Myocardial Infarction 58 (DECLARE–TIMI 58)***	CA: ☑ Blinding: Patient: ☑ Assessor ☑ ITT: ☑	17,160 participants ≥40 years with type 2 diabetes and with multiple risk factors for atherosclerotic CVD or established atherosclerotic CVD (defined as clinically evident ischemic heart disease, ischemic cerebrovascular disease, or peripheral artery disease). Mean age was 64 years, 37.5% were women. 40.6% of participants had an established history of atherosclerotic CVD. The mean glycated hemoglobin level was 8.3 and the median duration of diabetes was 11.0 years.	Participants were randomized 1:1 to receive 10 mg of dapagliflozin daily or matching placebo for the duration of the trial. The use of other glucose-lowering agents was at the discretion of the treating physician.	**Primary outcomes:** Major adverse cardiovascular events (MACE), including cardiovascular death, MI or ischemic stroke, and a composite of cardiovascular death or hospitalization for heart failure. **Secondary outcomes:** A renal composite (≥40% decrease in estimated glomerular filtration rate to <60 ml per minute per 1.73 m^2 of body-surface area, new end-stage renal disease, or death from renal or cardiovascular causes) and death from any cause.	Median duration of follow-up was 4.2 years. The risk of CVD death or hospitalization for heart failure was reduced significantly in the dapagliflozin group (4.9% vs. 5.8%, HR=0.83, 95% CI 0.73−0.95, p=0.005). The risk of hospitalization for heart failure was reduced significantly in the dapagliflozin group (2.5% vs.3.3%, HR=0.73, 95% CI 0.61−0.88). The risk of the secondary outcome was reduced significantly in the dapagliflozin group (4.3% vs.5.6%, HR=0.76, 95% CI 0.67−0.87). The overall risk of MACE was not reduced significantly in the dapagliflozin group, nor were some individual components including death from any cause, MI, ischemic stroke, death from CVD, or death from non-CVD. Diabetic ketoacidosis, genital infections and serious adverse events leading to the discontinuation of medication were significantly higher in the dapagliflozin group.
Neal et al. 2017, Zhou et al. 2019 **Australia** **RCT** ***The Canagliflozin Cardiovascular Assessment Study (CANVAS)***	CA: ☑ Blinding: Patient: ☑ Assessor ☑ ITT: ☑	10,142 participants recruited from 2 sister trials (CANVAS and CANVAS-renal) with type 2 diabetes and high cardiovascular risk. Mean age was 63.3 years, 35.8% were women. Mean duration of diabetes was 13.5 years. 65.6% had a history of cardiovascular disease at baseline.	Participants were randomized to receive canagliflozin (100 or 300 mg) or matching placebo, daily for the duration of the trial.	**Primary outcome:** Composite of death from cardiovascular causes, nonfatal MI, or nonfatal stroke. **Secondary outcomes:** Death from any cause, death from cardiovascular causes, progression of albuminuria, and the composite of death from cardiovascular causes and hospitalization for heart failure	The mean and median duration of follow-up was 188.2 weeks, and 126.1 weeks, respectively. 29% of persons discontinued their medication prematurely. Significantly fewer persons in the canagliflozin group experienced the primary outcome (26.9 vs. 31.5 events per 1,000-persons years; HR= 0.86, 95% CI 0.75–0.97, p< <0.001 for noninferiority and p=0.02 for superiority). The risk of fatal or nonfatal stroke was not significantly reduced with canagliflozin (11.2 vs. 12.6 events per 1,000-persons years; HR= 0.87, 95% CI 0.69–1.09).

Study/Type	Quality Rating	Sample Description	Method	Outcomes	Key Findings and Recommendations
					The risk of death from cardiovascular causes or hospitalization for heart failure was significantly lower in the canagliflozin group (16.3 vs. 20.8 events per 1,000-persons years; HR= 0.78, 95% CI 0.67–0.91). The rate of serious adverse events was significantly lower in the canagliflozin group (104.3 vs.120 events per 1,000-persons years, p=0.04), although there were significantly more fractures and amputations associated with canagliflozin. **Subgroup of persons with previous stroke or TIA (2019).** 1,958 (19%) participants had a history of prior stroke or TIA at baseline. There were 309 stroke/TIA events (123 with prior stroke or TIA vs.186 without). There was no significant reduction in the risk of combined stroke events in the canagliflozin group (HR=0.87, 95% CI 0.69- 1.09), nor were there significant reductions in the risks of fatal or nonfatal stroke, stroke of undetermined etiology, or TIA. There was a significant reduction in the risk of hemorrhagic stroke (n=30, HR=0.43, 95% CI 0.20- 0.89) in the canagliflozin group.
Zinman et al. 2015 **Canada** **RCT** ***Empagliflozin Cardiovascular Outcome Event Trial in Type 2 Diabetes Mellitus Patients (EMPA-REG***	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	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	**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,

Study/Type	Quality Rating	Sample Description	Method	Outcomes	Key Findings and Recommendations
OUTCOME Trial)		baseline Hgb A1c 8.08%	12 weeks and thereafter were adjusted to meet glycemic targets		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, 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.
Management of Type 2 Diabetes-Clinical Trials using Dipeptidyl peptidase (DPP)-4 inhibitor					
Rosenstock et al. 2019 **USA/International** ***The Cardiovascular and Renal Microvascular Outcome Study with Linagliptin (CARMELIN)***	CA: ☑ Blinding: Patient: ☑ Assessor ☑ ITT: ☑	6,979 adults with type 2 diabetes, HbA1c values of 6.5% to 10.0% inclusive, and at high CV and renal risk. Mean age was 65.9 years, 63% were men. 96.8% of patients were taking ≥1 glucose-lowering medication.	Patients were randomized 1:1 to receive linagliptin, 5 mg once daily, or placebo added to usual care for the duration of the trial. Other glucose-lowering medications or insulin could be added based on clinical need and local clinical guidelines.	**Primary outcome:** Time to first occurrence of the composite of CV death, nonfatal MI, or nonfatal stroke (3-point MACE). **Secondary outcomes:** Time to first occurrence of adjudicated death due to renal failure, ESRD, or sustained 40% or higher decrease in eGFR from baseline	Median duration of follow-up was 2.2 years. Linagliptin was non-inferior to placebo (using an upper limit of the confidence interval of less than 1.3) for the risk of the primary outcome (12.4% vs.12.1%, HR=1.02; 5% CI, 0.89-1.17, p<0.001). Linagliptin was not superior to placebo for a variety of cardiovascular and non-cardiovascular events including all-cause death, cardiovascular death, fatal or nonfatal MI, fatal or nonfatal stroke and 4-point MACE (including hospitalization for unstable angina). The kidney outcome occurred in 9.4% and 8.8% in persons taking linagliptin and placebo, respectively (HR=1.04; 95% CI, 0.89-1.22; p=

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					0.62), which did not meet the threshold for superiority. The occurrence of adverse events was similar between groups (77.2% vs. 78.1%)
Barkas et al. 2017 **Greece** **Systematic review & meta-analysis**	NA	19 small RCTs (n=9,278) and 3 large, multicentre RCTs (n=36,395) including persons with diabetes. Mean age ranged from 51-74 years. Percentage of men ranged from 39-71%.	Trials compared dipeptidyl peptidase (DPP)-4 inhibitors vs. placebo with treatment duration ≥12 weeks.	**Primary outcome:** Stroke	The duration of the intervention ranged from 12 weeks to 3 years. The results for the 19 small and 3 large trials are only reported separately. The odds of stroke were not reduced significantly in either the small or large trials (OR=0.64, 95% 0.34-1.21; p = 0.170 and OR=1.00, 95% CI: 0.85–1.17; p = 0.958, respectively).
Green et al. 2015 **USA** ***Trial Evaluating Cardiovascular Outcomes with Sitagliptin (TECOS) Study***	CA: ☑ Blinding: Patient: ☑ Assessor ☑ ITT: ☑	14,671 patients ≥50 years with type 2 diabetes and established cardiovascular disease, with a glycated hemoglobin level of 6.5 to 8.0% when treated with stable doses of one or two oral antihyperglycemic agents. Mean age was 65.5 years, 69% were men. Mean duration of diabetes was 11.6 years.	Patients were randomized 1:1 to receive either 100 mg sitagliptin daily (or 50 mg daily if the baseline eGFR was ≥30 and <50 ml per minute per 1.73 m^2) or matching placebo for the duration of the study, in addition to usual care.	**Primary outcome:** First confirmed event of cardiovascular death, nonfatal MI, nonfatal stroke, or hospitalization for unstable angina. **Secondary outcome:** First confirmed event of cardiovascular death, nonfatal MI, or nonfatal stroke	Median duration of follow-up was 3.0 years. 27% of participants discontinued study medications prematurely. There was no significant difference between groups in the risk of the primary outcome (11.4% vs.11.6%; HR=0.98, 95% CI 0.89–1.10). There was no significant difference between groups in the risk of the secondary outcome (10.2% vs.10.2%; HR=0.99, 95% CI 0.89–1.10). There were no significant differences between groups in the individual components of the primary outcome, or hospitalization for heart failure.
Scirica et al. 2013 **USA** **RCT** ***Saxagliptin Assessment of Vascular Outcomes Recorded in Patients with Diabetes***	CA: ☑ Blinding: Patient: ☑ Assessor ☑ ITT: ☑	16,492 patients with a history of documented type 2 diabetes mellitus, a glycated hemoglobin level of 6.5% to 12.0%, and either a history of established cardiovascular disease or multiple risk factors for vascular disease.	Patients were randomized 1:1 to receive 5 mg saxagliptin daily (or 2.5 mg daily in patients with an estimated GFR of ≤50 ml per minute) or matching placebo for the duration of the trial, in addition to additional treatment	**Primary outcome:** Composite of cardiovascular death, nonfatal MI or nonfatal ischemic stroke. **Secondary outcome:** primary composite end point plus hospitalization for heart failure, coronary revascularization, or	Median duration of follow-up was 2.1 years. 18.4% of persons in the saxagliptin and 20.8% of persons in the placebo group discontinued their medication prematurely. Glycated hemoglobin levels were significantly lower in the saxagliptin group at 1 year (7.6% vs. 7.9%), at 2 years (7.5% vs. 7.8%), and at the end of the treatment period (7.7% vs. 7.9%, p<0.001).

Study/Type	Quality Rating	Sample Description	Method	Outcomes	Key Findings and Recommendations
***Mellitus (SAVOR)–Thrombolysis in Myocardial Infarction* (TIMI) 53**		Mean age was 65 years, 67% were men. Median duration of diabetes was 10 years.	provided at discretion of the treating physician.	unstable angina.	There were no significant differences between groups in the risks of the primary or secondary outcomes (7.3% vs. 7.2%, HR= 1.00, 95% CI 0.89–1.12, p=0.99 for superiority and 12.8% vs. 12.4%, HR= 1.02, 95% CI 0.94–1.11, p=0.66 for superiority, respectively). The risk of hospitalization due to heart failure was significantly higher in the saxagliptin group (3.5% vs. 2.8%; HR=1.27, 95% CI 1.07–1.51, p=0.007). The risk of adverse events was similar between groups with the exception of significantly more episodes of hypoglycemia in the saxagliptin group.
Management of Type 2 Diabetes-Clinical Trials using Pioglitazone					
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

Study/Type	Quality Rating	Sample Description	Method	Outcomes	Key Findings and Recommendations
					pioglitazone group (28% vs. 20%).
Management of Type 2 Diabetes-Clinical Trials (intensive vs. standard care)					
Duckworth et al. 2009, Hayward et al. 2015, Reaven et al. 2019 **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 for the duration of the trial. 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 HgbA1C levels were 8.4% in the standard therapy group vs. 6.9%, in the intensive group. 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. **Hayward et al. 2015 (long-term follow-up)** 1,391 patients were available for follow-up. Median duration of follow-up was 9.8 years. The difference in median HgbA1c between

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					groups had decreased to 0.2% to 0.3%. The risk of the primary outcome was significantly lower in the he intensive-therapy group (HR=0.83; 95% CI 0.70 to 0.99, p=0.04). The absolute reduction in risk of major cardiovascular events was 8.6 per 1,000 person-years. Intensive therapy did not significantly reduce the risks of cardiovascular mortality (HR=0.88; 95% CI, 0.64 to 1.20; P=0.42), or total mortality (HR=1.05; 95% CI, 0.89 to 1.25; P=0.54). **Reaven et al. 2019 (15-yr follow-up)** 1,391 patients were available for follow-up. Median duration of follow-up was 13.6 yrs. Median HgbA1c was 8.0% in both groups. The risk of the primary outcome was not significantly lower in the intensive-therapy group (HR=0.91; 95% CI, 0.78 to 1.06; P=0.23). Intensive therapy did not significantly reduce the risks of cardiovascular mortality (HR=0.94; 95% CI, 0.73 to 1.20), or total mortality (HR=1.02; 95% CI, 0.88 to 1.18). The risk of non-fatal stroke was not significantly reduced in the intensive therapy group (13.3 vs. 13.6 per 1,000-person years).
Gerstein et al. 2008 **USA & Canada** **RCT (factorial)** ***Action to Control Cardiovascular Risk in Diabetes (ACCORD) (glucose –lowering arm)***	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 drugs including insulins	**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 outcome associated with intensive glucose

Study/Type	Quality Rating	Sample Description	Method	Outcomes	Key Findings and Recommendations
		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.	and oral hypoglycemia agents		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.
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 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	**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 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-

Study/Type	Quality Rating	Sample Description	Method	Outcomes	Key Findings and Recommendations
					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).
Management of 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 patients in the conventional group, who received 1-2 daily injections of insulin	**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). 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).

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	NA	5 RCTs (n=7,314)	Treatment contrasts of	**Primary outcome:**	In the single trial aimed at reductions in SBP

Study/Type	Quality Rating	Sample Description	Method	Outcomes	Key Findings and Recommendations
Costa Rico & Canada **Cochrane review**		examining trials comparing 'lower' BP targets (any target <130/85mmHg) with 'standard' BP targets (<140 - 160/90 – 100 mmHg) in people with diabetes. Participants were adults with type II DM and elevated blood pressure, or already receiving treatment for elevated blood pressure. Participants in all included trials were between 40-5 and 70-82 years at baseline.	the included studies: **ACCORD-BP**: intensive group (SBP <120 mm Hg) vs. standard group (SBP<140 mm Hg) **ABCD-H & ABCD-2V**: intensive group (DBP <75 mm Hg) vs. moderate group (DBP 80-89 mm Hg) **ABCD-N**: intensive group (DBP of 10 mm Hg below baseline) vs. standard group (DBP 80-89 mm Hg). **HOT** subgroup: DBP ≤90 mm Hg vs. ≤85 mm Hg vs. ≤80 mm Hg Hypertensive agents used included Calcium channel blockers, ACE inhibitors and ARBs. In some cases, no specific drug regimen was described.	All-cause mortality, adverse events **Secondary outcomes:** Systolic and diastolic BPs achieved, number of antihypertensive agents required.	(ACCORD) intensive BP control was not associated with reductions in total mortality (RR= 1.05, 95% CI 0.84-1.30) but was associated with reduction in the risk of stroke (RR=0.58, 95% CI 0.39 to 0.88, p= 0.009). In the 4 trials aimed at reductions in DBP, intensive BP control was not associated with reductions in total mortality (RR= 0.73, 95% CI 0.53-1.01, p=0.054) or stroke (RR= 0.67, 95% CI 0.42-1.05, p=0.077).
Muramatsu et al. 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	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	**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

Study/Type	Quality Rating	Sample Description	Method	Outcomes	Key Findings and Recommendations
		baseline hg $A1_C$ was 7.0%	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.		stroke were similar between groups (1.7% vs. 1.9%, HR=0.90, 95% CI 0.38-2.12, p=0.81 and 0.3% vs. 0.7%, HR=0.50, 95% CI 0.09-2.74, p=0.43, respectively). The incidences of cardiovascular death and all-cause mortality were similar between groups (0.7% vs. 0.7%, HR=1.00, 95% CI 0.25-3.99, p=0.99 and 3.8% vs. 2.8%, HR=1.37, 95% CI 0.72-2.61, p=0.34). There were 106 adverse events reported for 94 patients in the valsartan group and 112 events in 94 patients in the amlodipine group. There were no serious adverse events reported.
Redon et al. 2012 **Additional subgroup analysis from *ONTARGET*** **RCT**	CA: ☑ Blinding: Patient ☑ Assessor ☑ ITT: ☑	25,620 patients with coronary, peripheral, or cerebrovascular disease or diabetes with end-organ damage who could not tolerate ACE inhibitors. 9,603 (37.5%) of the total sample were patients with type 2 DM	Patients were randomized to receive either an ACE-inhibitor (ramipril 10 mg/day, n=8,576), an ARB (telmisartan 80 mg/day, n=8,542) or a combination of both drugs (n=8,502). Comparisons between diabetic and non-diabetic patients	**Primary outcome:** Death from cardiovascular causes, MI, stroke or hospitalization for heart failure	The primary outcome occurred more frequently in diabetic patients (20.2% vs. 14.2%, HR=1.48; 95% CI 1.38 to 1.57). The risks for components of the primary outcome were higher in diabetics: CV death (HR=1.56, 95% CI 1.42 to 1.71), MI (HR= 1.30, 95% CI 1.17 to 1.46), stroke (HR= 1.39, 95% CI 1.23 to 1.56) and hospitalization for CHF (HR= 2.06, 95% CI 1.82 to 2.32).
Cushman et al. 2010 **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	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

Study/Type	Quality Rating	Sample Description	Method	Outcomes	Key Findings and Recommendations
		systolic BP was 139 mm Hg and mean diastolic BP was77 mm Hg			any and non-fatal stroke associated with intensive HTN treatment (HR=0.59, 95% CI 0.39-0.89, p=0.01 and HR=0.63, 95% CI 0.41-0.96, p=0.03, respectively). Serious adverse events, attributed to therapy occurred more often in patients in the intensive group (3.3% vs. 1.3%, p<0.001).
Patel et al. 2007 **International** **RCT (factorial)** ***Action in Diabetes and Vascular Disease: Preterax and Diamicron - MR Controlled Evaluation (ADVANCE) (hypertension arm)***	CA: ☑ Blinding: Patient: ☑ Assessor ☑ ITT: ☑	11,140 patients with long-standing type 2 diabetes, aged ≥55 years with a history of major cardiovascular disease or at least one additional risk factor. Mean age at baseline was 66 years. 57% of patients were male and 9% had previous stroke)	Patients were randomized to receive either a fixed combination of perindopril (2 mg) and indapamide (0.625 mg) (n=5,569) or matching placebo (n=5,571) following a 6-week run-in period. After 3 months, treatment doses were doubled (4 mg/1.24 mg vs. matching placebo).	**Primary outcome:** Composite of macrovascular events (death from cardiovascular causes, nonfatal MI or stroke) and microvascular events (new or worsening nephropathy) **Secondary outcomes:** Death from any cause, death from cardiovascular causes, major coronary events, fatal and nonfatal stroke	The mean duration of follow-up was 4.3 years. At the end of follow-up, 73% and 74% of patients were adherent to study medication (active vs. placebo). The mean reductions in systolic and diastolic blood pressures in patents in the active study groups were 5.6 and 2.2 mm Hg, respectively. Active treatment was associated with reduction in the risk of combined micro/macrovascular events, (15.5% vs. 16.8%, RRR=9%, 95% CI 0%-17%) all deaths (7.3% vs. 8.5%, RRR=14%, 95% CI 2%-25%) and cardiovascular death (3.8% vs. 4.6%, RRR=18%, 95% CI 2%-32%). Active treatment was not associated with reduction in the risk of total cerebrovascular events, (5.1% vs. 5.4%, RRR=6%, 95% CI -10%-20%) or major cerebrovascular events (3.9% vs. 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)	CA: ☑ Blinding:	3,577 people with diabetes, ≥ 55 years who had a previous	Patients were randomized to receive 10 mg ramipril and 400 IU	**Primary outcome:** Cardiovascular mortality, stroke and MI at end of	The median duration of follow-up was 4.5 years. The study was stopped 6 months early.

Study/Type	Quality Rating	Sample Description	Method	Outcomes	Key Findings and Recommendations
Study Investigators 2000 **International** **RCT**	Patient: ☑ Assessor ☑ ITT: ☑	cardiovascular event or at least one other cardiovascular risk factor, no clinical proteinuria, heart failure, or low ejection fraction.	vitamin E (n=1,808) or placebo (n=1,769), daily for the study duration. The planned follow-up period was 5 years.	follow-up (composite outcome) **Secondary outcomes:** Total mortality, overt nephropathy	Fewer patients in the ramipril group experienced the composite endpoint (15.5% vs. 19.8%, RRR= 25%, 95% CI 12% to 36%, p=0.0004) or fatal or non-fatal stroke (4.2% vs. 6.1%, RRR= 33%, 95% CI 10% to 50%, p=0.0074). Mortality was lower among patients in the ramipril group (10.8% vs. 14.0%, RRR=24%, 95% CI 8% to 37%, p=0.004). Fewer patients in the ramipril group developed overt nephropathy (15.1% vs. 17.6%, RRR=16%, 95% CI 1% to 29%, p=0.036). Cough was one of the most frequently cited reason for stopping study medications. Its frequency was higher among patients in the ramipril group (7% vs. 2%).
Turner et al. 1998 **UK** **RCT** ***United Kingdom Prospective Diabetes Study (UKPDS) 38 (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.

Antiplatelets in Persons with Diabetes for the Prevention of Stroke

Study/Type	Quality Rating	Sample Description	Method	Outcomes	Key Findings and Recommendations
Bhatt et al. 2016 **USA** **RCT** ***Prevention of Cardiovascular Events in Patients with Prior Heart Attack Using Ticagrelor Compared to Placebo on a Background of Aspirin – Thrombolysis in Myocardial Infarction 54***	CA: ☑ Blinding: Patient: ☑ Assessor ☑ ITT: ☑	21,162 patients with a history of MI 1-3 years prior and at least 1 additional atherothrombotic risk factor (age ≥65 years, DM type 2, requiring medication, second prior spontaneous MI, chronic renal dysfunction, or multivessel coronary artery disease). Mean age was ~65 years, 75% were men. 1.6% had previous stroke.	Patients were randomized to ticagrelor (90 or 60 mg twice daily) or placebo for the duration of the trial. All patients were also taking aspirin daily. The outcomes of persons with (n=6,806) and without diabetes (n=14,355), were compared.	**Primary Outcome:** Composite of cardiovascular death, MI, or stroke within 3 years of randomization **Safety outcomes:** Major and minor bleeding events	Median duration of follow-up was 33 months. The risks of all cardiovascular outcomes were higher in patients with diabetes. The risk of the primary outcome in patients with diabetes was significantly lower in the ticagrelor group (doses combined, 10.1% vs 11.6%, HR= 0.84, 95% CI 0.72 – 0.99; ARR 1.5%; p=0.03), as was the risk in non-diabetic patients (6.7% vs. 7.8%, HR=0.84 (95% CI 0.74 – 0.96; ARR 1.1%; p=0.01). P for interaction =0.99 The risk of coronary death in patients with diabetes was significantly lower in the ticagrelor group (2.3% vs. 3.4%, HR=0.66, 95% CI 0.48 – 0.91, ARR 1.1%; p=0.01), but was not significantly reduced in non-diabetic patients

Study/Type	Quality Rating	Sample Description	Method	Outcomes	Key Findings and Recommendations
(PEGASUS-TIMI 54) **Subgroup analysis**					(1.5% vs. 1.4%, HR= 0.88, 95% CI 0.65 – 1.19; ARR 0.1%; p=0.39). Ticagrelor significantly reduced cardiovascular death by 22% in patients with diabetes (HR=: 0.78; 95% CI: 0.61 to 0.99; p=0.0495). Among patients with diabetes, the risk of stroke was significantly reduced in the ticagrelor group (1.8% vs. 2.5%, HR=0.69, 95% CI 0.49–0.99, p 0.0447). The risks of major and major or minor bleeding were significantly increased among diabetic patients in the ticagrelor group (HR= 2.56, 95% CI 1.52–4.33, p=0.0004 and HR=2.91, 95% CI 1.84–4.59, p<0.0001, respectively).

Low Carbohydrate Diets

Study/Type	Quality Rating	Sample Description	Method	Outcomes	Key Findings and Recommendations
McKenzie et al. 2017 **USA** **Non-randomized trial**	NA	262 persons with type 2 diabetes, aged 21-65 years. Mean age was 54 years, 67% were women.	Participants received individualized nutritional recommendations at a Virta Clinic necessary to sustain nutritional ketosis by titrating carbohydrate and protein intake to the patient's individual tolerance. Typical CHO intake was <30 g/day. Participants were encouraged to monitor and maintain serum beta-hydroxybutyrate (BOHB)	**Primary Outcome:** Diabetes status at 11 weeks (defined as HbA1c ≥6.5% or HbA1c level <6.5% but taking at least one hypoglycemic medication **Secondary outcomes:** Body weight, changes in medication, blood pressure, fasting glucose, total cholesterol, low-density lipoprotein cholesterol, high-density lipoprotein	238 participants were retained at 11-week follow-up. Among completers, the mean HbA1c had decreased from 7.6% at baseline to 6.1% at follow-up (mean difference=-1.1, p<0.001). Mean fasting glucose decreased from 163-129 mg/dL (mean difference =33, p<0.001). Mean BMI had decreased from 40.7 to 37.7 (p<0.001). Mean systolic and diastolic blood pressures had decreased significantly (132-125 mm Hg, p<0.001 and 82-78 mm Hg, p<0.001).

Study/Type	Quality Rating	Sample Description	Method	Outcomes	Key Findings and Recommendations
			levels ≥0.5 mmol·L^{-1}	cholesterol, triglycerides, C-reactive protein	All other secondary outcomes improved significantly from baseline to follow-up, except for HDL-chol which remained unchanged. Of the initial 262 subjects, 42.7% experienced a decrease in their medications while 8.0% eliminated their medications. 5.0% of participants were prescribed a new class or increased dose of medication, while 33.6% had no change in their medications. 10.7% were taking no hypoglycemic medications at entry into the study or at follow-up.
Tay et al. 2015, 2018 **Australia** **RCT**	CA: ☑ Blinding: Patient: ☒ Assessor ☑ ITT: ☒	115 adults with BMI 26-45 and with type 2 diabetes (HbA1c≥7%), taking medication, were recruited by public advertisement. Mean age was 58 years, 42% were women. Mean duration of diabetes was 8 years.	Participants were randomized to consume either a hypocaloric low carbohydrate (LC) diet (50 g/d, 14% of energy) or an energy-matched high carbohydrate (HC) diet (53% of energy as carbohydrate), combined with supervised aerobic and resistance exercise (60 min; 3 d/wk), for 52 weeks. Both diet plans were individualized and matched for energy with moderate (30%) restriction to facilitate weight loss (500–1000-kcal/d deficit; 1,357–2,143-kcal/d energy prescription)	**Primary outcome:** Change in HbA1c at 52 weeks **Secondary outcomes:** Changes in glycemic variability (GV), fasting blood glucose, diabetes medication, weight, blood lipids, and blood pressure.	68% of participants completed the study. At the end of the trial there was no significant difference between groups in mean change in HbA1c (-1% vs. -1%, MD=0.1, 95% CI -0.3 to 0.5, p=0.65), or mean BMI (-3.2 vs. -3.5, MD=0.3, 95% CI -0.6 to 1.2, p=0.31). Mean weight reduction in the LC group was 9.8 kg of baseline vs. -10.1 kg in the HC group. Compared with the HC diet, the LC diet produced at least a 2-fold greater mean decreases in GV indexes. Mean fasting glucose, mean maximum and minimum glucose levels fell in both groups, although there were no significant differences between groups. Mean systolic and diastolic blood pressures decreased in both groups but the differences between groups were not significant. Mean HDL increased significantly more in the LC group (0.1 vs, 0.06 mmol/L, p=0.002), while mean triglyceride fell significantly more in the LC group (-0.4 vs. -0.01, p=0.001). A significantly higher proportion of persons in the LC group decreased their antiglycemic medications by ≥20% (30% vs. 12%, p=0.001).

Study/Type	Quality Rating	Sample Description	Method	Outcomes	Key Findings and Recommendations
					2018 (2-year outcomes) 61 participants completed the study. Persons in both groups had lost weight, with no significant differences between groups (LC -6.8 kg vs. HC -6.6 kg). 69% of persons maintained a weight loss of ≥5%, and 34% achieved ≥10%. HbA1c reductions were similar in both groups (LC -0.6% vs. HC -0.9%, p=0.52). Mean blood pressure and fasting glucose levels were similar between groups. The LC group maintained greater improvements in lipid profile and diurnal blood glucose stability. A significantly higher proportion of persons in the LC group decreased their antiglycemic medications by ≥20% (38% vs. 16%, p=0.04).
Bueno et al. 2013 **Brazil** **Systematic review & meta-analysis**	4 trials were rated as high quality, the remainder, low quality.	13 RCTs (n= 1,577) including participants ≥ 18 years with a mean BMI ≥ 27·5. 7 trials included persons with type 2 diabetes or cardiovascular risk factors. Mean ages ranged from 39.8 to 60 years. 16 to 100% of participants were women.	Trials compared a low-fat diet (LFD), characterized by restricted-energy diet, with < 30 % of energy from fat or to a very-low-carbohydrate ketogenic diet (VLCKD), with ≤ 50 g carbohydrates/d or ≤10% of daily energy from carbohydrates. Minimum follow-up period was ≥12 months.	**Primary outcome:** Weight loss **Secondary outcomes:** Serum lipids, blood glucose indices	Persons in the VLCKD group achieved significantly greater weight loss (WMD= –0·91 kg, 95% CI –1·65 to–0·17, p=0.02). Persons in the VLCKD group achieved significantly greater reductions in TGs (WMD= –0·18 mmol/L, 95% CI -0·27 to –0·08, p<0.0002), significantly greater increases in HDL chol (WMD= 0·09, 95% CI 0·06 to 0·12, p<0.0001) and significantly greater reductions in LDL chol (WMD=0·12, 95% CI 0·04 to 0·20, p=0.002). Fasting blood glucose was non-significantly lower in the VLCKD group (WMD= -0·08 mmol/L, 95 % CI -0·18, 0·02, p=0.11, n=8 trials, 770 persons). HbA1c levels were non-significantly lower in the VLCKD group (-0·24%, 95 % CI -0·5, 0·06), p=0.12, n=4 trials, 319 persons)

Abbreviations

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

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