

Cardiovascular outcomes of antidiabetic drugs



Ranjit Kumar Nath¹, Neeraj Pandit², Ajay Raj², B.N. Pandit³, Vinod Kumar⁴, Rajeev Bhardwaj⁴,
Ajay Pratap Singh⁴, Ashok Thakur⁴

¹Professor and Head, ²Professor, ³Associate Professor, ⁴Senior Resident, Department of Cardiology, Dr Ram Manohar Lohia Hospital and Atal Bihari Vajpayee Institute of Medical Sciences, New Delhi, India

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ABSTRACT

Type 2 Diabetes Mellitus (T2DM) is associated with a high risk of atherosclerotic cardiovascular disease (ASCVD). Intensive blood glucose reduction with antidiabetic drugs significantly reduce microvascular complications but there is no strong evidence of reduction in cardiovascular (CV) events. In 2008, the US Food and Drug Administration (FDA) issued guidance to demonstrate cardiovascular safety of newer antidiabetic drugs in addition to reduction in blood glucose level. After which a number of CVOTs were conducted involving newer antidiabetic drugs. The newer drugs (e.g. GLP-1 RAs, SGLT2 inhibitors and DPP 4 inhibitors) might have potential effects on body weight, lipid parameters and blood pressure, as well as endothelial dysfunctions, inflammatory markers and oxidative stress. The current review summarizes the results of the main trials focused on the cardiovascular outcomes of traditional as well as newer antidiabetic drugs.

Key words: Antidiabetic drugs; Cardiovascular outcomes; DPP 4 inhibitors; SGLT2 inhibitors; GLP-1 receptor agonist

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INTRODUCTION

Worldwide about 463 million adults (20-79 years) are living with diabetes and will rise to 700 million by 2045, a 51% increase.¹ In India, about 77 million people are having diabetes which are expected to increase to 134 million by 2045.² Cardiovascular diseases (CVD) are the most common cause of death in diabetes.¹ The risk of CV diseases almost doubles in individuals with diabetes compared to those without diabetes.³

Diabetic patients have impaired myocardial metabolism of glucose and have greater reliance on fatty acids and ketone bodies as energy substrates. Free fatty acid breakdown is a less efficient way of myocardial energy production as it requires about 10% more oxygen to produce the same amount of ATP produced by glucose breakdown. These alterations in energy metabolism are responsible

for the oxygen supply demand mismatch and increases susceptibility of the diabetic heart to myocardial ischemia.⁴ Effective blood sugar control may improve myocardial energy metabolism and thereby decrease cardiovascular risk.

However, United Kingdom Prospective Diabetes Study (UKPDS), demonstrated that intensive blood-glucose control with either sulphonylurea or insulin significantly reduced the risk of microvascular complications, but not macrovascular disease, in patients with type 2 diabetes.⁵ Two large trials, ACCORD (Action to Control CV Risk in Diabetes)⁶ and ADVANCE (Action in Diabetes and Vascular Disease: PreterAx and DiamicroN Controlled Evaluation),⁷ also demonstrated no significant effects on cardiovascular outcomes for intensive glucose reduction compared to standard therapy. Similarly, VADT (Veterans Affairs Diabetes Trial) found no difference in major CV events or death between intensive and standard treatment

Address for Correspondence:

Dr. Vinod Kumar, M.D., Senior Resident, Department of Cardiology, Dr. Ram Manohar Lohia Hospital and ABVIMS, New Delhi, India.
Mobile: +91-9414375066, **E-mail:** drvinodpoonia@gmail.com

Table 1: Summary of trials of intensive glucose reduction therapy vs less intensive therapy

Trials (year)	Intervention	No of patients	% with CV disease	Median follow-up (years)	Major CV events (HR) (95% CI)	Hospitalisation for HF (95% CI)
UKPDS (1998)	Intensive therapy vs less intensive therapy	3867	none	10.7 years	0.80 (0.62–1.04)	0.55 (0.19–1.60)
ACCORD (2008)	Intensive therapy vs less intensivetherapy	10,251	35	3.5 years	0.90 (0.78–1.04)	1.18 (0.93–1.49)
ADVANCE (2008)	Intensive therapy vs less intensive therapy	11,140	32	5.0 years	0.94 (0.84–1.06)	0.95 (0.79–1.14)
VADT (2009)	Intensive therapy vs less intensive therapy	1791	40	5.6 years	0.90 (0.70–1.16)	0.92 (0.68–1.25)

groups.⁸ Major diabetes trials of intensive glucose reduction are summarized in Table 1.

So the data have shown that intensive blood glucose reduction with traditional hypoglycemic drugs significantly reduce the microvascular complications but there is no strong evidence of reduction in CV events. Weight gain and hypoglycemia associated with antidiabetic drugs are two important risk factors for adverse CV outcomes. Because of increased risk of HF and MI with the use of some antidiabetic drugs (e.g. Thiazolidinediones), FDA in 2008, issued guidance to demonstrate CV safety of all newer hypoglycemic agents prior to seeking approval, following which a number of CVOTs were conducted using the primary endpoint of 3-point MACE (CV death, non-fatal MI, non-fatal stroke) or 4-point MACE (the 3-point MACE plus hospitalization for unstable angina).⁹

The purpose of this review is to describe the cardiovascular outcomes of traditional antidiabetic drugs, as well as the newer drugs like dipeptidyl peptidase-4 (DPP-4) inhibitors, glucagon-like peptide-1 (GLP-1) receptor agonists, and sodium-glucose cotransporter 2 (SGLT-2) inhibitors.

INSULIN

There is no CVOT with insulin therapy to demonstrate CV safety, but insulin being part of the intensive control arm of the UKPDS, ACCORD, ADVANCE and VADT trials, did not to show increased risk for major CV events compared to standard therapy. Furthermore, a meta-analysis of the ACCORD, ADVANCE, UKPDS and VADT trials including 27,049 patients, showed a 9% reduction of major CV events (CV death, non-fatal MI or non-fatal stroke) with the intensive therapy compared with less-intensive glucose control (HR 0.91) primarily because of a 15% reduced risk of MI (HR 0.85). Although there was no significant effect on all cause and CV mortality and HF hospitalization.¹⁰

Two recent trials, ORIGIN (Outcome Reduction with an Initial Glargine Intervention)¹¹ and DEVOTE (Trial Comparing CV Safety of Insulin Degludec versus Insulin Glargine in Patients with Type 2 Diabetes at High Risk of CV Events)¹² also demonstrated the CV safety of two

basal insulins glargine and degludec. In the ORIGIN trial, 12537 patients at high CV risk were randomized to once daily injection of insulin glargine vs standard care. There was no significant difference in composite of CV death, MI and stroke (HR 1.02) or a 5-point MACE including HF hospitalization and revascularization for CVD (HR 0.90) between two groups.¹¹ Similarly, DEVOTE study evaluated 7637 patient with type 2 diabetes at high CV risk and found that insulin degludec was noninferior to glargine with respect to the incidence of major CV events (8.5% vs 9.3%).¹² Insulin may cause sodium and fluid retention due to anti-natriuretic effect in the distal tubule but whether this can increase risk or worsen heart failure is unknown.

SULFONYLUREAS

They act primarily on the pancreatic b-cells to increase insulin secretion and possibly bind cardiac and vascular receptors to exert adverse cardiac effects. The first-generation sulfonylureas have lower pancreatic affinity and thus more likely to bind cardiac receptors. They may prevent ischemic preconditioning that is an adaptive response to reduce myocardial damage following MI.¹³ In addition, they have been associated with weight gain, fluid retention, and hypoglycemia, which are all known CV risk factors. In the UKPDS, there was no increased mortality in the sulfonylurea-treated subjects but retrospective studies have demonstrated that all-cause mortality and CV events were significantly increased in patients treated with initial monotherapy with SU compared with metformin.¹⁴

The second-generation sulfonylureas have lower affinity for CV tissues and is associated with lower risk of hypoglycemia and less weight gain. Thus may have fewer adverse CV effects, although all data have not been consistent. Glimepiride however may be safer in patients with CVD, since it has no detrimental effects on ischemic preconditioning.¹⁵ In older patients with a history of acute MI or PCI, no significant difference has been found between glibenclamide and gliclazide on ischemic preconditioning of the heart.¹⁶ A Danish nationwide study demonstrated that monotherapy with the most SUs, including glimepiride, glibenclamide, glipizide, and tolbutamide, seems to be associated with

increased mortality and cardiovascular risk compared with metformin. Gliclazide and repaglinide appear to be associated with a lower risk than other SUs.¹⁷ Sufficient evidence is still lacking that proves sulfonylurea monotherapy is a safe initial treatment option for patients with diabetes and underlying CVD. In addition, higher doses of sulfonylureas have been associated with a greater risk of developing heart failure than lower doses of sulfonylureas as well as higher doses of metformin.¹³

MEGLITINIDES

They are insulin secretagogues which act on different pancreatic β cell receptors but have a similar mode of action to sulfonylureas. They lower blood glucose by stimulating insulin secretion by regulating ATP-dependent potassium channels in pancreatic β -cells. They have a rapid onset of action and a short half-life. Two agents repaglinide and nateglinide are currently available. Direct clinical evidence of their effect on CV outcomes and mortality is currently lacking. The Nateglinide and Valsartan in Impaired Glucose Tolerance Outcomes Research (NAVIGATOR) study demonstrated no beneficial effect of nateglinide in stopping the progression from prediabetes to diabetes compared with placebo and there was no effect on CV outcomes in people with impaired glucose tolerance with high CV risk.¹⁸

BIGUANIDES (METFORMIN)

Metformin acts by decreasing hepatic gluconeogenesis, increasing insulin sensitivity and peripheral glucose utilization mainly in liver and skeletal muscle. It has beneficial effects on lipid metabolism, neutral effect on body weight, minimal hypoglycemia, and potential to decrease CV events.

The UKPDS, subanalysis that included 342 overweight patients treated with metformin after failure of diet alone found that metformin is associated with significant risk reductions of 32% for any diabetes related endpoint (sudden death, MI, heart failure, stroke, and amputation), 42% for diabetes-related death (death from MI, stroke and PVD) and 36% for all-cause mortality.⁵ A recent, very large meta-analysis including more than 1 million patients from 40 studies demonstrated that treatment with metformin was associated with reduced risk of CV death (HR 0.81) and all-cause mortality (HR 0.67).¹⁹ Metformin have also been shown to lower all-cause mortality and composite CV endpoints compared with glipizide.²⁰ CV benefits of metformin may become evident after a period of several years, as illustrated in meta-analysis of randomised trials which are not evident in short term trials. Metformin

treatment may did not increase the risk of developing HF regardless of dose.²¹

ALPHA-GLUCOSIDASE INHIBITORS

Alpha-glucosidase inhibitors includes acarbose and miglitol. They competitively block alpha glucosidase in the proximal small bowel and prevent complex carbohydrate digestion, resulting in reduced postprandial hyperglycemia. The postprandial anti-hyperglycemic action likely contributes to CV risk reduction, as postprandial hyperglycemia is known to have adverse CV effects. Recent studies suggest that acarbose stimulates GLP-1 secretion, possibly explaining in part its positive CV effects. The STOP-NIDDM (Study to Prevent Non-Insulin-Dependent Diabetes Mellitus) trial showed a 34% relative risk reduction of hypertension and a 49% RRR of CV events, as well as a 36% RRR of developing type 2 DM in patients with impaired tolerance to glucose.²² However, ACE (Acarbose Cardiovascular Evaluation) trial in 6522 Chinese patients with CAD and impaired glucose tolerance found no effect of acarbose on a 5-point composite MACE of CV death, non-fatal MI, non-fatal stroke, hospitalization for unstable angina and hospitalization for HF.²³ Therefore, acarbose may be considered second-line therapy, alone or in addition to metformin or sulfonylureas, until further data prove its long-term CV safety.

THIAZOLIDINEDIONES

Thiazolidinediones are peroxisome proliferator-activated receptor-gamma (PPAR γ) agonists that regulate gene expression and improved insulin sensitivity. They lower blood glucose by improved glucose utilization in peripheral tissues and decreased glucose production. They have potential beneficial effects on lipids profile, BP, inflammatory bio markers, endothelial function and fibrinolysis. Two agents in this class, rosiglitazone and pioglitazone were approved by FDA in 1999.

PROACTIVE (PROspective pioglitAzone clinical trial in macrovascular events) study demonstrated benefits of pioglitazone in reducing primary endpoints of MI (HR 0.83), stroke (HR 0.81), and coronary revascularization (HR 0.88) in 5238 patients with T2DM with evidence of macrovascular disease. Significant reduction was also noted in the secondary composite endpoint of all-cause mortality, non-fatal MI, and stroke (HR 0.84). Although risk of HF was higher with pioglitazone than placebo, but it was not associated with increased mortality.²⁴ Similarly, TOSCAIT (Thiazolidinediones Or Sulfonylureas Cardiovascular Accidents Intervention Trial) trial in 3,028 type 2 diabetes patients found no significant difference in primary

outcomes of all-cause death, non-fatal MI, urgent coronary revascularization, or non-fatal stroke between pioglitazone versus sulfonylurea, used as add-on therapy to metformin.²⁵ Rosiglitazone was withdrawn from the European market in September 2010 because of associated CV risks. However, RECORD (Rosiglitazone Evaluated for CV Outcomes in Oral Agent Combination Therapy for Type 2 Diabetes) trial did not find significant difference in CV death (HR 0.84), MI (HR 1.14) and stroke (HR 0.72) with rosiglitazone compared to metformin and sulphonylurea. Although, there was a significant increase in the rate of heart failure with rosiglitazone (HR 2.10).²⁶ Incidence of CHF in TZD-treated patients is low but the risk increases in patients treated with insulin and higher doses of the TZD and in older patients with pre-existing CV comorbidity.²⁷ TZDs are contraindicated in patients with NYHA class III-IV HF.²⁷

Glucagon-Like Peptide receptor 1 Agonists (GLP-1RAs)

Glucagon-like peptide-1 (GLP-1) is an incretin hormone which is released from the gut in response to meal. GLP-1RAs activate the endogenous GLP-1 receptor and exert effects similar to the GLP-1 hormone. They stimulate insulin release, inhibits glucagon secretion and delay gastric emptying. They have low risk of hypoglycaemia, causes weight loss and reduce BP. They may improve endothelial function, reduce infarct size, improve LV function in MI and ischemic pre-conditioning.²⁸ Major CVOTs of GLP-1RAs are summarized in Table 2.

The first CVOT among the GLP-1 RAs was ELIXA (evaluation of lixisenatide in ACS) trial which demonstrated non-inferiority of lixisenatide compared to placebo for the primary composite outcomes of CV death, stroke, nonfatal MI, or unstable angina (13.4% vs. 13.2%, HR 1.02) in 6068 patients of T2DM with history of ACS within previous 180 days. Hospitalization for HF was not increased.²⁹ The larger EXSCEL (Effects of Once-Weekly Exenatide on CV Outcomes in Type 2 Diabetes) trial involving 14,752 patients also showed borderline beneficial effects with

exenatide. The primary composite outcome occurred in 11.4% of patients in the exenatide group compared with 12.2% in the placebo group.³⁰ However, LEADER (Liraglutide Effect and Action in Diabetes: Evaluation of CV Outcome Results) and SUSTAIN-6 (Trial to Evaluate CV and Other Long-term Outcomes with Semaglutide in Subjects with Type 2 Diabetes) were able to demonstrate CVD event reduction with GLP-1RA. LEADER trial showed significant reduction in the primary composite outcome of CV death, MI and stroke (13% vs. 14.9%; HR, 0.87) and hospitalisation for HF (HR 0.87) with liraglutide in 9,340 patients with T2DM with CVD or high CV risk.³¹ SUSTAIN-6 trial demonstrated similar reduction in the primary composite CV outcome of CV death, nonfatal MI, or nonfatal stroke with semaglutide compared to placebo (6.6% vs 8.9%) but no significant effect on HF admissions.³² Harmony outcomes trial also demonstrated significant reduction in the primary composite CV end point with albiglutide compared to placebo (7% vs 9%) in patients with T2DM and established CV disease.³³ Similarly, REWIND (Dulaglutide and CV outcomes in type 2 diabetes) trial demonstrated superiority of dulaglutide compared with placebo (HR 0.88).³⁴ PIONEER 6 (Peptide Innovation for Early Diabetes Treatment) was the most recent CVOT published in 2019 included 3183 patients. Although this trial did not show significant CV benefit but CV deaths were reduced and no significant effect on HF hospitalization with oral semaglutide was noted.³⁵

CV benefits of GLP1 analogues may not be a class effect. Liraglutide, subcutaneous semaglutide, albiglutide and dulaglutide have shown significant reductions in composite CV outcomes, whereas lixisenatide, weekly exenatide and oral semaglutide have shown non-inferiority but failed to show superiority over placebo.

Dipeptidyl Peptidase 4 (DPP-4) Inhibitors

DPP-4 is an enzyme that degrades GLP-1 and prolongs the bioavailability of endogenous GLP-1. They are

Table 2: Summary CVOTs of GLP-1RA

Trials (Drug)	Publication year	No of patients	% with CV disease	Median follow-up (years)	Primary composite CV outcome (HR(95%CI))	CV death HR (95% CI)	HF hospitalisation HR (95% CI)
ELIXA (Lixisenatide)	2016	6068	100	2.1	1.02 (0.89- 1.17)	0.98 (0.78-1.22)	0.96 (0.75–1.23)
EXSCEL (Exenatide)	2017	14752	73.1	3.2	0.91 (0.83-1.00)	0.88 (0.76–1.02)	0.94 (0.78–1.13)
LEADER (Liraglutide)	2016	9340	81	3.8	0.87 (0.78-0.97)	0.78 (0.66–0.93)	0.87 (0.73–1.05)
SUSTAIN-6 (Semaglutide)	2016	3297	60	2.1	0.74 (0.58-0.95)	0.98 (0.65–1.48)	1.11 (0.77–1.61)
REWIND (Dulaglutide)	2019	9901	31.5	5.4	0.88 (0.79- 0.99)	0.91 (0.78–1.06)	0.93 (0.77-1.12)
HARMONY OUTCOME (albiglutide)	2018	9463	100	1.6	0.78 (0.68-0.90)	0.93 (0.73–1.19)	-
PIONEER 6 (Oral Semaglutide)	2019	3183	84.7	1.3	0.79 (0.57- 1.11)	0.51 (0.31–0.84)	0.86 (0.48–1.55)

weight neutral and have minimal hypoglycaemia risk. In addition, they may have beneficial pleiotropic effects on the CV system. Currently available 4 DPP-4 inhibitors are sitagliptin, saxagliptin, linagliptin, alogliptin, vildagliptin and teneligliptin. In addition, oncedaily DPP4 inhibitors are omarigliptin and trelagliptin. Major CVOTs of DPP-4 inhibitors are summarized in Table 3.

SAVOR-TIMI 53 (Saxagliptin Assessment of Vascular Outcomes Recorded in Patients with Diabetes Mellitus – Thrombolysis in Myocardial Infarction 53) was the first CV outcome study for DPP-4 inhibitors which found no significant difference in the primary end point of a composite of CV death, MI, or ischemic stroke (7.3% vs 7.2%) but it showed an unexpected 27% increased risk of HF hospitalizations (3.5% vs. 2.8%) with saxagliptin compared to placebo.³⁶ Similarly, EXAMINE (Examination of CV Outcomes With Alogliptin Versus Standard of Care) study found no significant difference in the primary endpoint of a composite of CV death, MI, or ischemic stroke with alogliptin compared to placebo (11.3% vs 11.8%) in patients with type 2 DM who had acute MI or unstable angina requiring hospitalization. Post-hoc analysis suggested increased HF hospitalizations (2.2% vs. 1.3%) in patients without history of HF (HR 1.76) but no increase in those with pre-existing HF (HR 1.0)³⁷. TECOS (Trial Evaluating CV Outcomes with Sitagliptin) trial also demonstrated noninferiority of sitagliptin compared to placebo for the primary composite CV outcome (HR 0.98). Rates of HF hospitalization also did not differ between the two groups (HR 1.0).³⁸

CARMELINA (Cardiovascular and Renal Microvascular Outcome Study with Linagliptin in Patients with Type 2 DM) trial demonstrated the noninferiority of linagliptin compared to placebo with respect to cardiovascular and renal events.³⁹ Linagliptin was also found noninferior to the glimepiride on prevention of MACE (11.8% vs

12.0% respectively) in CAROLINA (CV Outcome Study of Linagliptin vs Glimepiride in Type 2 Diabetes) trial.⁴⁰

There is no CV outcome trial for vildagliptin, equivalent to those for the other DPP-4 inhibitors. However, in VIVID (Vildagliptin in Ventricular Dysfunction Diabetes) trial, patients taking vildagliptin had a nonsignificant increase in rates of any CV event (27.3 vs 24.6%) and death from cardiovascular causes (5.5 vs 3.2%) compared to placebo. After 1 year, LVEF declined by 4.95% in the vildagliptin group and 4.33% in the placebo group.⁴¹ Early trials with teneligliptin have reported no CV adverse effects but significant QTc prolongation with higher doses (160 mg) of teneligliptin was observed.⁴² CV safety of Omarigliptin, was evaluated in a randomized, doubleblind study (OMNEON) including 4202 patients with T2DM and established CVD. In this study, there was no increase in the risk of MACE or HF with omarigliptin at 54 Weeks.⁴³

Thus, CVOTs demonstrated no major CV risks or benefit of DPP-4inhibitors. However, increased risk of HF hospitalizations was a concern with these drugs. SAVOR-TIMI 53 trial showed significant increase in risk for HF hospitalization with saxagliptin (3.5% versus 2.8%; HR 1.27), while EXAMINE trial showed non-significant increase in HF hospitalization with alogliptin (3.9% vs 3.3%, HR 1.19). Although there was no increase in risk of HF hospitalization with sitagliptin in TECOS trial [HR 1.00] and linagliptin in CARMELINA (HR 0.90).VIVID did not find any significant decline in LVEF in vildagliptin arm, compared to placebo over 1 year, suggesting no adverse effect on HF. Omarigliptin CV outcome trial also did not find increase in risk of HF hospitalization (HR 0.60).Therefore, DPP-4 inhibitors may be considered for patients with type 2 DM with high CV risk, who are unable to take metformin.

SGLT-2 (Sodiumglucose Cotransporter 2) Inhibitors

SGLT2inhibitors reduce renal glucose reabsorption in the proximal tubule, and lower blood glucose through

Table 3: Summary of CVOT of DPP4 inhibitors

Trials	Publication year	No of patients	% with CV disease	Median followup (years)	Primary composite CV outcome (HR (95% CI))	CV death HR (95% CI)	HF hospitalisation HR (95% CI)
SAVORTIMI 53 (Saxagliptin)	2013	16492	78.4	2.1	1.00 (0.89–1.12)	1.03 (0.87–1.22)	1.27 (1.07–1.51)
EXAMINE (Alogliptin)	2013	5400	100	1.5	0.96 (≤ 1.16)	0.85 (0.66–1.10)	1.07 (0.79–1.46)
TECOS (Sitagliptin)	2013	14671	100	2.8	0.98 (0.89–1.08)	1.03 (0.89–1.19)	1.00 (0.83–1.20)
CARMELINA (Linagliptin)	2019	6980	57	4.5	1.02 (0.89–1.17)	0.96(0.81–1.14)	0.90 (0.74–1.08)
CAROLINA (Linagliptin)	2019	6042	34.5	6.3	0.98 (0.84–1.14)	1.00 (0.81–1.24)	1.21 (0.92–1.59)
OMNEON (Omarigliptin)	2017	4202	-	1.5	1.00 (0.77-1.29)	1.06 (0.66- 1.68)	0.60(0.35- 1.05)

Table 4: Summary of CVOT of SGLT 2 inhibitors

Trials (Drug)	Publication year	No of patients	% with CV disease	Median followup (years)	Primary composite CV outcome (HR) (95% CI)	CV death HR (95% CI)	HF hospitalisation HR (95% CI)
EMPA REG (Empagliflozine)	2015	7020	99	3.1	0.86 (0.74–0.99)	0.62 (0.49–0.77)	0.65 (0.50–0.85)
CANVAS (Canagliflozine)	2017	10142	65	2.4	0.88 (0.75–1.03)	0.87 (0.72–1.06)	0.67 (0.52–0.87)
DECLARE TIMI 58 (Dapagliflozine)	2018	17276	41	6	0.93 (0.84–1.03)	0.98 (0.82–1.17)	0.73 (0.61–0.88)
CREDENCE (Canagliflozine)	2019	4401	50.5	2.6	0.80 (0.67–0.95) ¹	0.78 (0.61–1.00)	0.61 (0.47–0.80)
DAPA HF (Dapagliflozin)	2019	4744	55.5	1.5	0.74 (0.65–0.85) ²	0.82 (0.69–0.98)	0.70 (0.59 to 0.83)

1: Secondary outcome (CV death, myocardial infarction, or stroke)

2: Primary composite endpoint (Worsening heart failure or death from CV causes)

glucosuria. Glycosuria and natriuresis causes osmotic diuresis which may contribute to hemodynamic benefits through reduced blood pressure and decreased intravascular volume, similar to diuretic therapy. Canagliflozin was the first SGLT2 inhibitor to be approved by the FDA in 2013. Subsequently dapagliflozin and empagliflozin were approved in 2014 and most recently ertugliflozin in December 2017. Major CVOTs of SGLT-2 inhibitors are summarized in Table 4.

EMPA-REG outcome (Empagliflozin CV Outcome Event Trial in Type 2 DM) trial demonstrated a 14% reduction in primary composite outcome of CV death, MI, and stroke with empagliflozin compared to placebo (10.5% vs 12.1%) in 7020 patients with known CVD. There was also 28% lower incidence of CV mortality (3.7% vs. 5.9%), 32% lower all-cause mortality (5.7% vs. 8.3%) and 35% lower HF hospitalization (2.7% vs. 4.1%) with empagliflozin.⁴⁴ This was a major paradigm shift from the previous antidiabetic drugs that either had no effect or increased risk of HF hospitalization. CANVAS (Canagliflozin Cardiovascular Assessment Study) program, comprising two sister trials, was designed to assess the CV safety and efficacy of canagliflozin in 10,142 patients with type 2 DM and high CV risk. Canagliflozin significantly reduced the 3-point MACE and HF hospitalization but had no significant effect on CV death or all-cause mortality.⁴⁵ Similarly, CREDENCE (Canagliflozin and Renal Endpoints in Diabetes with Established Nephropathy Clinical Evaluation) trial demonstrated significant reduction in CV death, MI, or stroke (HR 0.80) and HF hospitalization (HR 0.61) with canagliflozin in patients with type 2 DM and CKD.⁴⁶ However, sub analysis of DECLARE-TIMI 58 (Dapagliflozin Effect on Cardiovascular Events) trial showed no significant reduction in the combined MACE outcome (8.8% vs. 9.4%) but did show a significant reduction in HF hospitalization rate (2.5% vs. 3.3%) with dapagliflozin.⁴⁷ Recently, a systematic review and meta-

analysis including data from above-mentioned 3 trials involving 34,322 patients (60.2% of whom had ASCVD) demonstrated 11% reduction in MACE (HR 0.89) with SGLT2 inhibitors, with benefit noted only in patients with ASCVD. SGLT2 inhibitors were also associated with 23% reduction in the risk of HF hospitalization or CV death and a 45% reduction in the risk of progression of renal disease (HR 0.55), with similar benefits noted in those with or without ASCVD.⁴⁸ Trial to assess cardiovascular outcomes of ertugliflozin in patients with T2DM and established vascular disease is currently undergoing and expected to be completed in 2021 (NCT01986881).

There is no head on comparison trial but available evidences suggest that SGLT-2 inhibitors are superior to the other antidiabetic drugs in terms of reducing CV and all-cause mortality, hospitalisation for HF and progression of renal disease regardless of existing ASCVD or CKD in patients with T2DM. A systematic review and network meta-analysis suggests that empagliflozin is superior to both canagliflozin and dapagliflozin in reducing all-cause and CV mortality but have similar effects on HF Hospitalisation.⁴⁹

CONCLUSION

Although CV outcome trials have been conducted with the newer antidiabetic drugs, but vast evidence from experience with metformin use supports the long-term CV benefits associated with this agent. The CV effects of sulfonylureas remain controversial, although an increased risk of hypoglycaemia may increase CV risk. Acarbose may decrease CV risk by decreasing postprandial hyperglycemia as shown in the Stop-NIDDM study, but a 5-point MACE was not reduced by acarbose in the ACE study. Although pioglitazone increases the risk of heart failure but the TOSCA IT study found a similar occurrence of MACE when it was compared with sulfonylurea therapy.

Basal insulin glargine and degludec as well as DPP-4 inhibitors have neutral effects on CV outcome although HF hospitalization is a concern with DPP4 inhibitors particularly with saxagliptin and alogliptin. SGLT-2i and GLP-1RAs both lowered the risk of MACE, hospitalisation for HF, and renal events. Empagliflozin is superior to other SGLT-2 inhibitors for all-cause and CV mortality reduction. According to the recent ADA (American Diabetes Association)/ EASD (European Association for the Study of Diabetes) consensus report 2018, newer hypoglycemic agents, mainly SGLT-2i and GLP-1RAs should be used before the use of metformin for CV risk reduction in patients with or without ASCVD.⁵⁰ Future data should provide additional insights into the efficacy and safety of these drugs.

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Author's Contribution:

RKN-Conceptualized and designed the article, literature search, prepared first draft of the manuscript; **NP**-Review of the study, critical revision of the manuscript, proof reading; **AR**-Interpretation, critical revision of the manuscript; **BNP**-Critical revision of the manuscript, proof reading; **VK**-Conceptualized and designed the article, literature search, prepared the major part of manuscript; **RB**-Literature search and referencing.

Work attributed to:

Department of Cardiology, Dr Ram Manohar Lohia Hospital and ABVIMS, New Delhi, India.

Orcid ID:

Dr.(Prof.) Ranjit Kumar Nath - <https://orcid.org/0000-0002-8258-0445>

Dr. Vinod Kumar - <https://orcid.org/0000-0002-1001-2684>

Dr. Ajay Pratap Singh - <https://orcid.org/0000-0003-3127-6539>

Dr. Ashok Kumar Thakur - <https://orcid.org/0000-0001-6502-5717>

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