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Editorial Board Member of *World Journal of Diabetes*, Fernando Cordido, MD, PhD, Professor, Department of Medicine, University A Coruña, A Coruña 15006, Spain

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RESPONSIBLE EDITORS FOR THIS ISSUE

Prevention of macrovascular complications in patients with type 2 diabetes mellitus: Review of cardiovascular safety and efficacy of newer diabetes medications

Ravi Kant, Kashif M Munir, Arshpreet Kaur, Vipin Verma

ORCID number: Ravi Kant (0000-0002-9599-8082); Kashif M Munir (0000-0002-1075-1284); Arshpreet Kaur (0000-0002-7266-9358); Vipin Verma (0000-0001-5370-3146).

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Ravi Kant, Division of Endocrinology, Diabetes and Nutrition, Medical University of South Carolina/Anmed Campus, Anderson, SC 29621, United States

Kashif M Munir, Division of Endocrinology, Diabetes and Nutrition, University of Maryland School of Medicine, Baltimore, MD 21201, United States

Arshpreet Kaur, Division of Endocrinology, Diabetes and Nutrition, Sinai Hospital, Baltimore, MD 21215, United States

Vipin Verma, Department of Medicine, Medical University of South Carolina/Anmed Campus, Anderson, SC 29621, United States

Corresponding author: Ravi Kant, MD, Affiliate Associate Professor, Division of Endocrinology, Diabetes and Nutrition, Medical University of South Carolina/Anmed Campus, 2000 E Greenville St., Suite # 3100, Anderson, SC 29621, United States. kant.ravi.md@gmail.com
Telephone: +1-864-5124160
Fax: +1-864-5124165

Abstract

Lack of conclusive beneficial effects of strict glycemic control on macrovascular complications has been very frustrating for clinicians involved in care of patients with diabetes mellitus (DM). Highly publicized controversy surrounding cardiovascular (CV) safety of rosiglitazone resulted in major changes in United States Food and Drug Administration policy in 2008 regarding approval process of new antidiabetic medications, which has resulted in revolutionary data from several large CV outcome trials over the last few years. All drugs in glucagon-like peptide-1 receptor agonist (GLP-1 RA) and sodium-glucose cotransporter-2 (SGLT-2) inhibitor classes have shown to be CV safe with heterogeneous results on CV efficacy. Given twofold higher CV disease mortality in patients with DM than without DM, GLP-1 RAs and SGLT-2-inhibitors are important additions to clinician's armamentarium and should be second line-therapy particularly in patients with T2DM and established atherosclerotic CV disease or high risks for CV disease. Abundance of data and heterogeneity in CV outcome trials results can make it difficult for clinicians, particularly primary care physicians, to stay updated with all the recent evidence. The scope of this comprehensive review will focus on all major CV outcome studies evaluating CV safety and efficacy of GLP-1 RAs and SGLT-2 inhibitors.

Key words: Newer antidiabetic medications; Glucagon-like peptide-1 receptor agonist; Sodium-glucose cotransporter-2 inhibitors; Type 2 diabetes mellitus; Macrovascular complications; Cardiovascular outcome trials; Major cardiovascular events; Heart failure; Prevention of heart disease

Core tip: Multiple cardiovascular (CV) outcome trials performed mainly to meet regulatory requirements by United States Food and Drug Administration have provided very important findings on CV safety and efficacy of newer anti-diabetic drugs. All drugs in glucagon-like peptide-1 receptor agonist (GLP-1 RA) and sodium-glucose cotransporter-2 (SGLT-2)-inhibitor classes have shown to be CV safe with heterogeneous results on CV efficacy. Abundance of data and heterogeneity in CV outcome trials results can make it difficult for clinicians to stay updated with all the recent evidence. The scope of this comprehensive review will focus on all major CV outcome studies evaluating CV safety and efficacy of GLP-1 RAs and SGLT-2 inhibitors.

INTRODUCTION

Type 2 diabetes mellitus (T2DM) is associated with long-term complications, which can be broadly classified as macrovascular and microvascular complications. The UK Prospective Diabetes Study (UKPDS) provided much needed information on glycemic goals for T2DM management and demonstrated that strict glycemic control significantly reduces microvascular complications, but failed to show beneficial effects on macrovascular complications[1]. A 10-year post-trial follow up of UKPDS subjects showed a 15% reduction in risk for myocardial infarction (MI) in the intensive therapy group, despite loss of glycemic differences after the first year of conclusion of the UKPDS trial[2]. This ongoing benefit is now widely known as a "legacy effect" of early strict glycemic control. Interestingly, the Action to Control Cardiovascular Risk in Diabetes (ACCORD) study around the same time showed an unexplained increase in mortality with intensive glycemic control in older patients with long standing T2DM with no significant reduction of major cardiovascular (CV) events[3].

Lack of conclusive beneficial effects of strict glycemic control on macrovascular outcomes has been very frustrating for clinicians involved in care of patients with diabetes mellitus (DM). Due to conflicting results and uncertainty on beneficial effects of glucose lowering therapies on major CV events, there has been growing interest in determining how glucose-lowering pharmacotherapies impact risk for major CV events. Sulfonylureas and rosiglitazone have shown association with an increased risk of adverse CV events and mortality[4,5]. Nissen *et al*[5] showed 43% increased risk of MI with rosiglitazone treatment, which led to highly publicized controversy surrounding CV safety of rosiglitazone. This resulted in major changes in United States Food and Drug Administration (US FDA) policy in 2008 regarding approval process of new antidiabetic medications. Improved glycemic control alone is no longer sufficient and US FDA has requested CV outcome data from randomized, controlled trials for approval of new drugs for treatment of DM[6].

Changes in FDA approval policy for new antidiabetes drugs has resulted in revolutionary data from several large CV outcome trials over the last few years[7]. The primary composite endpoint for majority of CV outcome trials has been major adverse cardiovascular events (MACE), a composite of death from CV causes, nonfatal MI, or nonfatal stroke. Abundance of data and heterogeneity in CV outcome trials results can make it difficult for clinicians, particularly primary care physicians, to stay updated with all the recent evidence. The scope of this review will focus on all major CV outcome studies evaluating CV safety and efficacy of glucagon-like peptide-1 receptor agonists (GLP-1 RA) and sodium-glucose cotransporter-2 (SGLT-2) inhibitors.

GLP-1 RA

Intestinal L-cells secrete GLP-1, a potent incretin hormone, in response to nutrient ingestion[8]. Synthetic GLP-1 RA drugs are beneficial for patients with T2DM through their multiple mechanisms of action such as increasing glucose stimulated pancreatic insulin secretion, inducing expansion of insulin secreting pancreatic beta-cell mass, decreasing gastric emptying, inhibiting glucagon and gastric acid secretion and promoting satiety through GLP-1 effects on the central nervous system[8]. GLP-1 RA's have gained popularity over the last decade due to their beneficial effects on metabolic endpoints aside from the reduction of blood glucose such as promoting weight loss, helping patients with portion control, favorable effects on blood pressure and cholesterol, and accumulated data over the last few years showing their CV safety and efficacy. There are currently five FDA approved GLP-1 agonists available for clinicians to help manage diabetes of their patients. These medications include exenatide (Daily injection approved in 2005 and once weekly injection approved in 2012), liraglutide (approved in 2010), dulaglutide (approved in 2014), lixisenatide (approved in 2016), and semaglutide (approved in 2017). Albiglutide was approved in 2014 for management of T2DM but was taken off market in May, 2018 due to limited prescribing of the drug. Therefore, we will not review details of albiglutide CV outcome trial (Harmony Outcomes) in this review article.

GLP-1 RA CV OUTCOME STUDIES

Lixisenatide in patients with type 2 diabetes and acute coronary syndrome (ELIXA) was the first CV outcome trial of GLP-1 RA's[9]. Addition of lixisenatide to usual care did not significantly decrease the rate of major adverse cardiovascular events (MACE). ELIXA enrolled 6068 patients with T2DM who had a MI or who had been hospitalized for unstable angina within the previous 180 d. The median follow-up was only 25 mo. Patients were randomized to receive lixisenatide or placebo in addition to locally determined standards of care. Lixisenatide showed noninferiority to placebo in terms of MACE primary composite end point of CV death, MI, stroke, or hospitalization for unstable angina [13.4% *vs* 13.2% events; hazard ratio (HR), 1.02; 95% confidence interval (CI): 0.89 to 1.17; $P < 0.001$] but did not show superiority (P = 0.81). There was no significant decrease in the rate of hospitalization for heart failure or the rate of death. Failure to detect a benefit from lixisenatide for the primary MACE end point could have been due to enrollment of high risk patients with recent coronary artery disease and short duration of follow up.

Liraglutide and Cardiovascular Outcomes in Type 2 Diabetes (LEADER) studied the CV effects of liraglutide and not only showed noninferiority, but superiority to placebo for MACE (composite of CV death, nonfatal MI, or nonfatal stroke), CV death and all-cause mortality[10]. A total of 9340 patients with T2DM and high CV risks were followed for 3.8 years. Patients who received liraglutide had 13% relative risk reduction in the primary endpoint of MACE compared with placebo (13.0% *vs* 14.9% events; HR, 0.87; 95%CI: 0.78 to 0.97; $P < 0.001$ for noninferiority; P = 0.01). Beneficial effects of liraglutide on reducing MACE was primarily due to significant reduction in CV death (4.7% in liraglutide group *vs* 6.0% in placebo; HR, 0.78; 95%CI: 0.66 to 0.93; P = 0.007). Liraglutide also showed significant reduction in all-cause mortality (hazard ratio, 0.85; 95%CI: 0.74 to 0.97; P = 0.02). It's important to note that CV death and all cause death benefits were apparent after 12-15 mo and 18 mo of liraglutide treatment, respectively. More patients in the placebo arm required insulin and other oral anti-diabetes drugs such as sulfonylureas, to intensify their glycemic control. Unfavorable CV effects of other anti-diabetic drugs may have altered statistics in liraglutide's favor.

Semaglutide and Cardiovascular Outcomes in Patients with Type 2 Diabetes (SUSTAIN-6) confirmed the noninferiority of semaglutide to placebo for the primary MACE endpoint, a composite of CV death, nonfatal MI, or nonfatal stroke (6.6% *vs* 8.9% events; HR, 0.74; 95%CI: 0.58 to 0.95; $P < 0.001$ for noninferiority) and nonfatal stroke (1.6% *vs* 2.7% events, HR, 0.61; 95%CI: 0.38 to 0.99; P = 0.04)[11]. Unlike liraglutide, semaglutide treated patients lower risk of primary composite outcome (MACE) was predominantly driven by a significant decrease in the rate of nonfatal stroke and a nonsignificant decrease in nonfatal MI (HR ratio, 0.74; 95%CI: 0.51 to 1.08; P = 0.12). Rates of CV death were similar in semaglutide and control group. Notably, diabetic retinopathy complications occurred at significantly higher rate in semaglutide treated patients (HR, 1.76; 95%CI: 1.11 to 2.78; P = 0.02).

The fourth trial, Effects of Once-Weekly Exenatide on Cardiovascular Outcomes in Type 2 Diabetes (EXSCEL) was different than previous CV outcome trials of GLP-1

agonists as it was performed in a usual-care setting among patients with T2DM at a wide range of CV risk[12]. Unlike previous CV outcome trials studying GLP-1 RAs, where patients with high risks for CV disease were enrolled, 26.9% of subjects in EXSCEL trial did not have previous CV disease at randomization. After a median follow up of 3.2 years, once weekly exenatide was non-inferior to placebo for MACE (composite of CV death, nonfatal MI, or nonfatal stroke) but failed to show superiority (11.4% *vs* 12.2% events, HR, 0.91; 95%CI: 0.83 to 1.00; *P* < 0.001 for noninferiority and *P* = 0.06 for superiority). Even though there was 14% lower rate of death from any cause in the exenatide group compared to placebo (HR, 0.86; 95%CI: 0.77 to 0.97); this difference was not considered to be statistically significant on the basis of the hierarchical testing plan. A large proportion, 43%, of exenatide treated subjects prematurely discontinued the trial regimen, which authors speculated to be due to complexity of first generation exenatide injection device used in the trial and lack of run in period. Even with these limitations and a quarter of the study population without history of CV disease, treatment with exenatide almost reached statistical significance for primary endpoint MACE, and it's encouraging that direction of CV outcomes was consistent with beneficial effects seen in previous trials.

CV outcome trial (REWIND) for dulaglutide, has been completed but results are not published yet. However, the manufacturer of dulaglutide announced in a press release that patients who were treated with dulaglutide in REWIND trial had significantly reduced CV outcomes compared with placebo, meeting the primary trial endpoint[13].

Meta-analysis of 4 major CV outcome trials of GLP-1 RAs, ELIXA (lixisenatide), LEADER (liraglutide), SUSTAIN 6 (semaglutide), and EXSCEL (extended-release exenatide) provided further valuable information regarding CV safety and efficacy of the GLP-1 RA drug class[14]. A total of 33457 participants were included from four CV outcome trials in the meta-analysis. GLP-1 RAs as a class showed robust CV safety and efficacy. Patients treated with GLP-1 RAs demonstrated 10% reduced risk of MACE, a composite of CV death, nonfatal MI, or nonfatal stroke, (HR, 0.90, 95%CI: 0.82–0.99; *P* = 0.033), a 13% risk reduction in CV mortality (HR, 0.87; 95%CI: 0.79–0.96; *P* = 0.007), and a 12% relative risk reduction in all-cause mortality (HR, 0.88, 95%CI: 0.81–0.95; *P* = 0.002), compared to those treated with placebo.

GLP1 RA CV OUTCOME STUDIES DISCUSSION

Even though the statistical results differ in all four major CV outcome trials for GLP-1 RAs, the overall trend and magnitude of results were similar towards CV efficacy except in the ELIXA trial (Table 1). Liraglutide and semaglutide significantly reduced risk for primary endpoint of MACE (a composite of CV death, nonfatal MI, or nonfatal stroke). CV deaths and all-cause mortality risks were significantly lower with liraglutide use and semaglutide decreased risk for nonfatal stroke by 39% after 2 years of treatment. Lixisenatide and once weekly exenatide failed to show CV efficacy. Once weekly exenatide, however, decreased MACE by 9% and all-cause mortality risk by 14% after 3.2 years of treatment but just failed to reach statistical significance. Notably, CV benefits of GLP-1 RAs were shown even with patients receiving standard of care management for CV risk management including anti-platelet medications and treatment for hypertension and hyperlipidemia.

Differences in CV outcomes could be explained by differences in study population mainly in terms of CV disease risk, duration of follow up and adherence to trial drug. ELIXA had neutral results for CV efficacy, but this was the only trial that only enrolled subjects with recent MI or hospitalization for unstable angina[9]. It can be argued that patients already had too far advanced atherosclerotic disease to benefit from drug. On the other hand, EXSCEL is the only trial that included patients with diverse CV risks (approximately 27% of patients without known CV disease), which makes its results more applicable to a broad range of patients with T2DM seen in usual clinical practice[12]. However, including lower risk subjects also makes it more likely to not accrue sufficient adverse CV events in a timely manner to reach statistical significance. The other two trials recruited patients with T2DM who were at high risk for CV events and it can be argued that it may have helped to show superior CV safety with relatively short duration of follow up. It cannot be disputed that drug specific differences in GLP-1 RA class (structural similarities to human GLP-1, and short acting *vs* longer acting GLP-1 RAs) may also have contributed to variable CV efficacy outcome. However, there is robust evidence for CV safety of all GLP-1 RAs and it stands to reason that GLP-1 RA drug class has favorable effects on MACE (CV death, nonfatal MI and nonfatal stroke).

Table 1 Summary of cardiovascular outcome trials of glucagon-like peptide-1 receptor agonists

Drug	ELIXA	LEADER	SUSTAIN-6	EXSCEL
	Lixisenatide	**Liraglutide**	**Semaglutide**	**Exenatide**
Study design and salient features	Enrolled 6068 patients with T2DM and recent coronary event within 180 d; Median DM duration 9.2 yr; Median follow up 25 mo	Enrolled 9340 patients with T2DM and with high CV risks; Median DM duration 12.8 yr; Median follow up 3.8 yr	Enrolled 3297 patients with T2DM and established CV disease or with high CV risks; Median DM duration 13.2 yr and 14.1 yr in low dose and high dose treatment group, respectively; Median follow up 104 wk	Enrolled 14752 patients with T2DM at a wide range of CV risk; Approximately 27% of patients without known CV disease; Median DM duration 12 yr; Median follow up 3.2 yr; 43% subjects prematurely discontinued exenatide
Primary endpoint/MACE	No significant difference in MACE-4	13% reduction in MACE	26% reduction in MACE	9% reduction in MACE[1]
Secondary Outcomes	No significant difference in death from CV causes; No significant differences in rate of hospitalization for heart failure	22% reduction in death from CV causes[2]; 15% reduction in all-cause mortality[2]	39% reduction in nonfatal stroke; 26% reduction in nonfatal myocardial infarction[3]; No significant difference in CV death or all-cause mortality	14% reduction in all-cause mortality[4]; No significant differences in death from CV causes

[1]Nonsignificant reduction (hazard ratio, 0.91; 95% confidence Interval, 0.83 to 1.00; $P < 0.001$ for noninferiority and $P = 0.06$ for superiority);
[2]Cardiovascular death and all-cause mortality benefits were apparent after 12-15 mo and 18 mo of liraglutide treatment, respectively;
[3]Nonsignificant reduction (hazard ratio, 0.74; 95% confidence interval, 0.51-1.08; $P = 0.12$);
[4]This difference was not considered to be statistically significant on the basis of the hierarchical testing plan. T2DM: Type 2 diabetes mellitus; DM: Diabetes mellitus; CV: Cardiovascular; MACE: Major adverse cardiovascular events, a composite of death from cardiovascular causes, non-fatal myocardial infarction, or nonfatal stroke; MACE-4: MACE endpoint as above and hospitalization for unstable angina.

SGLT-2-INHIBITORS

SGLT-2 proteins are expressed in the proximal convoluted tubule of the kidneys and are responsible for approximately 90% of renal glucose reabsorption[15,16]. SGLT-2 inhibitors are FDA approved drugs for treatment of patients with T2DM that work through a unique mechanism of reducing renal threshold for glucose reabsorption, resulting in increased glycosuria and decreased blood glucose. There are currently four drugs in SGLT-2-inhibitor class approved by US FDA; Canagliflozin (approved in 2013), Dapagliflozin (approved in 2014), Empagliflozin (approved in 2014) and Ertugliflozin (approved in 2017). SGLT-2-inhibitor drugs are only approved for estimated glomerular filtration rate (GFR) > 45. Several recent large-scale clinical trials have provided exciting data on CV safety and efficacy of empagliflozin, canagliflozin and dapagliflozin. A clinical trial looking at the CV safety of Ertugliflozin is currently ongoing and is expected to be completed in September, 2019.

SGLT-2-INHIBITORS CV OUTCOME STUDIES

Empagliflozin, Cardiovascular Outcomes, and Mortality in Type 2 Diabetes (EMPA-REG OUTCOME) studied CV safety and efficacy of empagliflozin in 7028 patients with T2DM and established CV disease[17]. Patients were randomized in a 1:1:1 fashion to receive either empagliflozin 10 mg, empagliflozin 25 mg, or placebo. Pooled empagliflozin was superior to placebo for primary composite outcome of MACE (a composite of CV death, nonfatal MI, or nonfatal stroke). Results were similar for two doses of empagliflozin vs placebo for the primary endpoint. Pooled empagliflozin group showed 14% reduced relative risk for MACE (10.5% *vs* 12.1% events; HR, 0.86; 95%CI: 0.74 to 0.99; $P < 0.001$ for noninferiority; $P = 0.04$ for superiority), 38% relative risk reduction for CV deaths (3.7% *vs* 5.9%, $P < 0.001$), 35% relative risk reduction for CHF hospitalization (2.7% *vs* 4.1%, $P = 0.002$) and 32% relative risk reduction for all-cause mortality (5.7% *vs* 8.3%, $P < 0.001$). Heart failure hospitalization risk reduction results were similar in patients with and without CHF at baseline. Patients with established chronic kidney disease had numerically higher event rates for all outcomes than in patients with estimated GFR > 60 mL/min in both treatment and placebo groups.

The Canagliflozin Cardiovascular Assessment Study (CANVAS) comprised of two identical trials studying non-inferiority and superiority of canagliflozin compared with placebo on MACE (a composite of CV death, nonfatal MI, or nonfatal stroke); CV death and death from any cause[18]. A total of 9,734 patients with T2DM and either established CV disease (age 30 years or above) or high risk of CV disease (age 50 years

or above with 2 or more risk factors) completed the trial with a mean follow up of 188.2 wk. Results showed a significant decrease in primary endpoint of MACE in canagliflozin treated individuals compared with placebo (26.9 *vs* 31.5 participants with an event per 1000 patient-years; HR, 0.86; 95%CI: 0.75 to 0.97; *P* < 0.001 for noninferiority; *P* = 0.02 for superiority). Patients treated with canagliflozin had significantly lower rates of hospitalization for heart failure (HR 0.67; 95%CI: 0.52–0.87). No significant difference was found in the two groups for outcomes of death from any cause and death from CV causes. There was a higher risk of amputation of toes, feet or legs (primarily at level of toe and metatarsal) with canagliflozin *vs* placebo (6.3 *vs* 3.4 participants with amputation per 1000 patient-years; HR, 1.97; 95%CI: 1.41 to 2.75). Of note, canagliflozin treated group showed 27% reduction in progression of albuminuria and 40% reduction in adverse renal outcome (a composite of sustained 40% reduction in the estimated GFR, the need for renal-replacement therapy, or death from renal causes). However, based on pre-specified hypothesis testing sequence, the renal outcomes were not considered statistically significant.

The Dapagliflozin Effect on Cardio-vascular Events–Thrombolysis in Myocardial Infarction 58 (DECLARE-TIMI 58) was a randomized, double-blind, placebo controlled, phase 3 trial that evaluated the non-inferiority of dapagliflozin on MACE (a composite of CV death, nonfatal MI, or nonfatal stroke) and a composite of CV death or hospitalization for heart failure, in patients with T2DM (40 years or older) and established atherosclerotic CV disease or multiple risk factors for atherosclerotic CV disease[19]. A total of 13198 out of 17160 randomized participants completed the trial with a median follow up of 4.2 years. This trial included the highest proportion of patients (more than 10000 patients), without established atherosclerotic CV disease compared to previous CV outcome trials. Individuals with a creatinine clearance < 60 mL per minute were excluded from trial. Results showed that dapagliflozin was noninferior to placebo for MACE but failed to show superiority (8.8% *vs* 9.4% events; HR, 0.93; 95%CI: 0.84 to 1.03; *P* = 0.17). A significantly lower rate of hospitalization for heart failure was noted in the dapagliflozin group (HR, 0.73; 95%CI: 0.61 to 0.88); there was no difference in the rate of CV death in the two groups (HR, 0.98; 95%CI: 0.82 to 1.17). Diabetic ketoacidosis was more common in the dapagliflozin group than in the placebo group (0.3% *vs* 0.1%; hazard ratio, 2.18; 95%CI: 1.10 to 4.30; *P* = 0.02). There was no difference in the rates of amputations in the two groups.

Zelniker *et al*[20] performed a meta-analysis of all major CV outcome trials of SGLT-2-Inhibitors in patients with T2DM. A total of 34322 patients were included from 3 major trials; 60.2% of patients had established CV disease and rest had multiple risks factors for CV disease. As a group, SGLT-2-inhibitors demonstrated 11% reduction in MACE, a composite of CV death, nonfatal MI, or nonfatal stroke (HR, 0.89; 95%CI: 0.83-0.96; *P* = 0.0014) but benefit was not seen in patients without established atherosclerotic CV disease. There was 23% relative risk reduction of CV death or hospitalization for heart failure in SGLT-2-inhibitors treated patients compared to placebo (HR, 0.77; 95%CI: 0.71-0.84; *P* < 0.0001), with favorable effects seen regardless of presence or absence of atherosclerotic CV disease or heart failure. Though beyond the scope this review article, it is important to mention that SGLT-2-inhibitors significantly reduced (45%) progression of renal disease irrespective of baseline atherosclerotic CV disease. Patients with worse renal function had greater benefit in terms of hospitalization for heart failure.

SGLT-2-INHIBITORS CV OUTCOME STUDIES DISCUSSION

Empagliflozin and canagliflozin both showed a 14% risk reduction in MACE (a composite of CV death, nonfatal MI, or nonfatal stroke) but dapagliflozin neither decreased nor increased the risk for MACE in patients with T2DM, compared to placebo (Table 2). Empagliflozin also showed robust risk reduction for CV death (38%), hospitalization for HF (35%) and all-cause mortality (32%) in patients with T2DM and established atherosclerotic CV disease after a median follow up of 3.1 year. Canagliflozin and dapagliflozin treatment resulted in a significantly lower rate of hospitalization for heart failure (33% relative risk reduction for canagliflozin and 27% for dapagliflozin) but failed to significantly decrease death from CV causes or death from any cause[18,19]. As a group, SGLT-2-inhibitors have shown more robust and consistent effect on prevention of hospitalization for heart failure in patients with T2DM with or without history of heart failure or atherosclerotic CV disease[20]. Beneficial effects on major adverse CV events was not only moderate, but also limited to patients with established CV disease.

Heterogeneity of CV efficacy outcomes for various SGLT-2-inhibitors may be

Table 2 Summary of cardiovascular outcome trials of sodium-glucose cotransporter-2-inhibitors

Drug	EMPA-REG outcome Empagliflozin	CANVAS Canagliflozin	DECLARE-TIMI 58 Dapagliflozin
Study Design and salient features	Enrolled 7028 patients with T2DM and established CV disease; 100% subjects with established CV disease; DM duration: 57% > 10 yr and 25.1% 5-10 yr; Median follow up 3.1 yr	Enrolled 9734 patients with T2DM and either established CV disease or high risk of CV disease; 65.6% subjects with established CV disease; Mean DM duration 13.5 yr; Mean follow up 188.2 wk	Enrolled 17160 patients with T2DM and with variable CV risks; 40.5% subjects with established CV disease; Median DM duration 11 yr; Median follow up of 4.2 yr
Primary endpoint/MACE	14% reduction in MACE in pooled empagliflozin group	14% reduction in MACE	No significant difference in MACE
Secondary Outcomes	35% reduction in hospitalization for heart failure[1]; 38% reduction in death from CV causes; 32% reduction in all-cause mortality	33% reduction in hospitalization for heart failure; No significant difference in death from CV causes; No significant difference in all-cause mortality	27% reduction in hospitalization for heart failure; No significant difference in death from CV causes; No significant difference in all-cause mortality

[1]Heart failure hospitalization risk reduction results were similar in patients with and without CHF at baseline. T2DM: Type 2 diabetes mellitus; DM: Diabetes mellitus; CV: Cardiovascular; MACE: Major adverse cardiovascular events, a composite of death from cardiovascular causes, non-fatal myocardial infarction, or nonfatal stroke.

explained by differences in individual drugs, but cannot be definitively stated due to lack of head to head randomized controlled trials. However, differences in CV outcomes of SGLT-2-inhibitor drugs can be explained, at least in part, due to differences in study design and patient populations studied. EMPA-REG OUTCOME only included patients with established CV disease but 65.6% patients enrolled in CANVAS program, and only 40.5% patients in DECLARE-TIMI 58 had established CV disease[17-19]. Since reduction of MACE with SGLT-2-inhibitors was only seen in patients with established atherosclerotic CV disease, a lower proportion of this patient population in DECLARE-TIMI 58 may have resulted in failure to show superiority for the primary composite MACE endpoint. Also, DECLARE-TIMI 58 trial excluded patients with creatinine clearance < 60 mL per minute, but other two trials had a higher proportion of patients with renal insufficiency (eGFR < 60 mL/min per 1.73 m^2); 25.9% in EMPA-REG OUTCOME and 20.1% in CANVAS. A lower proportion of individuals with renal insufficiency and established atherosclerotic CV disease may have been responsible for lower mortality rates in the placebo group in DECLARE-TIMI 58 compared to EMPA-REG OUTCOME. It cannot be assessed how much of these differences in patient population affected the final CV outcome, but these observations underscore the fact that clinicians should be cautious in generalizing results of these CV outcome trials to patients with diverse CV risk factors. However, the above reviewed CV outcome trials have confirmed CV safety of SGLT-2-inhibitors. Overall, the evidence is strong for beneficial effects of SGLT-2-inhibitors on reducing hospitalization for heart failure, and moderate reduction of major adverse CV events has only been clearly demonstrated in individuals with T2DM and established atherosclerotic CV disease.

CONCLUSION

Multiple CV outcome trials performed mainly to meet regulatory requirements by US FDA have provided very important findings on CV safety and efficacy of newer anti-diabetic drugs. All drugs in GLP-1 RA and SGLT-2-inhibitor classes have shown to be CV safe with heterogeneous results on CV efficacy. However, the overall trend and magnitude of CV outcomes is similar within the drug classes. GLP-1 RAs have beneficial effects on MACE (a composite of CV death, nonfatal MI and nonfatal stroke). SGLT-2-inhibitors have stronger and consistent evidence for prevention of hospitalization for heart failure than on atherosclerotic MACE, where beneficial outcome was only seen in patients with T2DM and established atherosclerotic CV disease. Given twofold higher CV disease mortality in patients with DM than without DM[21], GLP-1 RAs and SGLT-2-inhibitors are important additions to clinician's armamentarium and should be second line-therapy particularly in patients with T2DM and established atherosclerotic CV disease or high risks for CV disease. In fact, the recent consensus statement from the ADA and EASD confirms this point and suggests GLP-1 RA's and SGLT-2 inhibitors after metformin in high CV-risk individuals[22].

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