Changing Fields-Diabetes Medications Invading the Cardiovascular Space

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Abstract: Cardiovascular disease (CVD) remains the leading cause of mortality in patients with type 2 diabetes, and treatment strategies that impact cardiovascular (CV) outcomes in this population is an area of growing interest. Pharmacologic agents that reduce CVD risk have been developed, and data supporting their use have grown extensively. Glucagon-like peptide 1 agonists and sodium-glucose cotransporter 2 inhibitors when added to metformin therapy provide the most CV benefit and should be considered in most patients. Data available suggest that sulfonylureas should be avoided in patients at risk for CVD and if a thiazolidinedione is utilized, pioglitazone may be preferred. When selecting an agent, the potential benefit, risk, and cost of each agent should be considered prior to initiation. The purpose of this review is to summarize the literature surrounding the CV effects of antidiabetic agents and to provide practical guidance on their use in patients with type 2 diabetes and CVD. (Curr Probl Cardiol 2021;46:100736.)

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Introduction

Cardiovascular disease (CVD) remains the leading cause of mortality and morbidity in patients with type 2 diabetes (T2DM). Over the past several years, the prevalence of T2DM has increased, and the heightened risk of adverse cardiovascular (CV) events in patients with T2DM has remained largely unchanged.[1] Therefore, developing treatment strategies to improve CV outcomes in this patient population is an area of growing interest.

Diabetes is known to cause both microvascular and CV morbidity and mortality. Research has consistently shown that strict glycemic control is associated with improvement in microvascular outcomes. However, strict glycemic control has not shown similar benefits for reducing CV morbidity and mortality.[1] Pharmacologic agents that reduce CVD risk have been developed, and data supporting their use have grown extensively. As a result of growing evidence in favor of the CV benefits of certain glucose-lowering agents, the American Diabetes Association Standards of Care in Diabetes recommends weighing CV risk factors into the selection of a glucose-lowering agent.[2] The shift in focus to not only consider the glucose-lowering capabilities, but also the CV benefits of glucose-lowering medications places CVD specialists in a position to actively participate in the creation of optimal treatment regimens for patients with T2DM and clinical atherosclerotic cardiovascular disease (ASCVD). The purpose of this article is to summarize the literature surrounding the CV effects of glucose-lowering agents and to provide practical guidance on their use in patients with T2DM and ASCVD.

Metformin

Metformin, a biguanide, is widely utilized as a first line oral agent for patients with T2DM.[2] Metformin decreases hepatic glucose production, reduces intestinal absorption of glucose, and improves insulin sensitivity by increasing peripheral glucose uptake and utilization.[3] The ability of metformin to impact glucose levels by multiple mechanisms allows metformin to effect both basal and postprandial plasma glucose levels. Metformin provides an average reduction in hemoglobin A1c between 1.0% and 1.3%.[4] Since metformin does not impact insulin secretion, the risk of hypoglycemia is relatively low when used as monotherapy. In addition to the impact on glucose regulation, metformin has a neutral effect on weight.[5]

The first trial to evaluate the impact of metformin versus diet alone on T2DM complications was the UK Prospective Diabetes Study (UKPDS 34).[6] The primary endpoint was time to first diabetes-related endpoint,

which included fatal and nonfatal myocardial infarction (MI), angina, and heart failure (HF). In the analysis, diabetes-related endpoints occurred at a rate of 29.8 events per 1000 patients years in the metformin group ($n = 342$) versus 43.3 events per 1000 patient years in the diet alone (n = 411) group (relative risk [RR] 0.68; 95% confidence interval [CI] 0.58-0.87; $P < 0.0023$). The secondary outcome of MI showed 11 events per 1000 patient years with metformin compared to 18 events per 1000 patient years in the diet alone group (RR 0.61; 95% CI 0.41-0.89; $P = 0.01$).[6] While this trial failed to show a decrease in MI, it did show the impact on diabetes related cardiovascular events, which included MI, angina, and HF. Multiple meta-analyses and systematic reviews have confirmed and discussed the cardiovascular impact of metformin, and they support the positive findings of the UKPDS 34 trial overall.[7-9] Additional information regarding the potential cardiovascular benefit of metformin will be available at the conclusion of the VA-IMPACT study.[10] This study is seeking to determine if treatment with metformin in a prediabetic population (hemoglobin A1c of 5.7%-6.5%) would reduce mortality and cardiovascular morbidity in patients with established ASCVD. This study is on schedule to be completed in 2024.[10]

The ability of metformin to provide metabolic benefit contributes to its mechanism of cardiovascular benefit, but other possible mechanisms exist. One possible benefit of metformin is its ability to reduce atherosclerosis.[11] In a study published in 2004, investigators found that common carotid intima-media thickness was significantly reduced when assessed using B-mode ultrasonography in patients receiving metformin therapy.[12] Due to its ability to improve insulin action, there could be benefits seen in endothelial function and vascular reactivity, along with a decrease in inflammation and inflammatory markers. Additionally, metformin can positively affect the number of circulating triglycerides, induce an antithrombotic effect, and decrease oxidative stress.[11-14] Last, evidence does exist that metformin may decrease infarct size after an MI and may help improve left ventricular ejection fraction.[15]

The most common adverse effects of metformin are bloating, abdominal discomfort and diarrhea. Prior to initiation, renal function via estimated glomerular filtration rate (eGFR) must be obtained and subsequently monitored every 3 to 6 months and should be monitored every 3 months for patients with an eGFR of < 45 mL/min/1.73m^2. Cardiologists should also be aware of the use of contrast dye in patients taking metformin. In patients undergoing procedures with contrast dye, holding metformin for 48 hours before and 48 hours after contrast dye will decrease the risk of any metformin-associated lactic acidosis.[2,3]

Sulfonylureas

Sulfonylureas (SUs) are insulin secretagogues that should be reserved for treatment of T2DM when other agents are unobtainable due to costs.[2] With the prevalence of new agents combined with the risk due to side effect profile of SUs, the utilization of SUs has decreased significantly.[16] SUs produce an antihyperglycemic effect by stimulating insulin release from the pancreatic beta cells, and thus should be given with meals. SUs target both fasting and prandial blood glucose, but come with a high risk of hypoglycemia and have been associated with weight gain. The average reduction in hemoglobin A1c is 0.4%-1.2%.[4] Long-term use of a SU can decrease in effectiveness as pancreatic beta-cell function decreases.[4] The University Group Diabetes Program studies showed that the first-generation SU, tobutamide, increased the risk of CV deaths.[17,18] In addition to those studies, the UKPDS 33 trial showed that SU treatment did not show a difference in macrovascular complications compared to diet alone and the UKPDS 34 trial showed an increase in diabetes-related death and all-cause mortality with the addition of SU to metformin therapy.[6,17,19] The SPREAD-DIMCAD investigators sought to determine the effects of glipizide compared to metformin on cardiovascular outcomes in patients with T2DM and coronary artery disease and concluded that metformin substantially reduced (hazard ratio [HR] 0.54; 95% CI 0.30-0.90; P= 0.026) major cardiovascular events compared to glipizide.[19,20] More recently, the Cardiovascular Outcome Study of Linagliptin Versus Glimepiride in Patients With type 2 diabetes was published that looked at the difference between addition of linagliptin versus glimepiride on cardiovascular outcomes in patients with diabetes. This trial found that linagliptin was noninferior to treatment with glimepiride for the reduction of major adverse cardiovascular events (MACE).[21] Due to the data available, SU should be avoided in patients at risk for CVD.

Thiazolidinediones

Thiazolidinediones (TZDs) first came to market after gaining U.S. Food and Drug Administration (FDA) approval in 1999.[22,23] Currently, there are 2 TZDs that are FDA approved—pioglitazone and rosiglitazone. TZDs work by improving target cell response to insulin by agonizing the proliferator-activated receptor-gamma (PPAR-gamma) receptors. This activation of PPAR-gamma receptors amplifies genes involved in glucose and lipid metabolism. TZDs also improve insulin sensitivity, but do not increase insulin secretion.[24] Due to its lack of

impact on insulin secretion, the risk of hypoglycemia is relatively low. TZDs target both fasting and postprandial blood glucose and provide an average hemoglobin A1c reduction of 0.5%-1.4%.[4] Of note, PPAR-gamma receptors are found in the collecting tubules in the kidney, and activation of PPAR-gamma receptors can lead to sodium and fluid reabsorption and retention. The package labeling for pioglitazone and rosiglitazone states that it can cause or exacerbate HF, so prescribers need to be vigilant in monitoring patients for signs and symptoms of HF and avoid use in patients with New York Heart Association (NYHA) class III or IV HF.[25,26] A meta-analysis conducted in 2007 also showed that rosiglitazone was associated with a significant risk of MI, although this finding was not found when a meta-analysis of pioglitazone was conducted.[27-29]

As with other diabetic agents, the ability to provide metabolic benefit may contribute to its mechanism of cardiovascular benefit, but other possible mechanisms may exist. One possible benefit seen in the PERISCOPE trial, was pioglitazone's ability to decrease arterial thickness.[30] It is also postulated that TZDs can decrease blood pressure, which can help in controlling CVD risk factors. TZDs are associated with a decrease in left ventricular hypertrophy and have been shown to potentially decrease inflammatory markers.[31] While these are possible benefits, it is important to consider potential hazards. Rosiglitazone is associated with increases in LDL, and both TZDs increase fluid retention, which may be harmful in patients with HF.[2,31] Cardiologists should be aware of the potential for fluid retention and be vigilant in monitoring volume status, weight, and assessing for fractures/risk of fractures, especially in elderly patients.[2,22] Due to the risks of using rosiglitazone, if a TZD is to be utilized, pioglitazone should be preferred as a result of its better side effect profile in addition to its potential cardiovascular benefits.

A. Incretin Agents

Glucagon-like peptide 1 (GLP-1) agonists and dipeptidyl peptidase-4 (DPP-4) inhibitors are 2 additional classes of antidiabetic agents with similar mechanisms targeting the incretin system. The body naturally produces GLP-1 and glucose-dependent insulinotropic polypeptide in a glucose-dependent manner.[32] Secretion of GLP-1 stimulates the pancreas to secrete insulin and decrease production of glucagon. DPP-4 is the enzyme responsible for GLP-1 inactivation.[32] DPP-4 blockade allows for endogenous levels of GLP-1 and glucose-dependent insulinotropic polypeptide to be more

abundant, which causes a reduction in glucagon levels, increased endogenous insulin secretion, and decreased gastric emptying.[32]

1. GLP-1 Agonists

Exenatide became the first GLP-1 agonist to gain approval by the FDA in 2005.[33] This class has grown to include 6 subcutaneous agents (albuglutide, dulaglutide, exenatide, liraglutide, lixisenatide, and semaglutide) and one oral agent (semaglutide). Additionally, exenatide and liraglutide are FDA approved to treat obesity through the known mechanism of slowed gastrointestinal (GI) motility and induced satiety. GLP-1 agonists provide a hemoglobin A1c reduction of 0.8%-2% and will rarely cause hypoglycemia. Based on the results from clinical trials, the ADA guidelines suggest utilizing specific GLP-1 agonists (liraglutide, semaglutide, and exenatide) as second line agents for patients with or without established ASCVD, or if weight loss is desired.[2] While the subcutaneous dosage form is often a barrier, a new oral option along with the weight-loss potential and relatively good tolerability has thrust these agents into popularity.

2. DPP-4 Inhibitors

DPP-4 inhibitors were one of the first novel classes of antidiabetic medications with sitagliptin's FDA approval in 2006. Currently, there are 4 FDA0 approved DPP-4 inhibitors (sitagliptin, saxagliptin, linagliptin, and alogliptin) in the U.S. with vildagliptin only approved in Europe, Latin America, and some countries in Asia. Additionally, dutogliptin had its investigation as an antidiabetic drug halted in phase III trials, but phase II trials are underway with dutogliptin in combination with filgrastim for patients receiving percutaneous coronary intervention post-MI.[34] DPP-4 inhibitors provide a modest hemoglobin A1c reduction (0.5%-1%), but do not cause hypoglycemia or weight gain. According to current guidelines, DPP-4 inhibitors are listed as second-line agents for patients without established ASCVD or those not at high risk for ASCVD, HF, or chronic kidney disease (CKD), in which case other agents are preferred.[2,35] There is a recommendation to avoid saxagliptin and alogliptin in patients with HF based on findings from clinical trials, although this has not been shown with other agents in the class.[36-38] Given their tolerability, minimal side effect profile, and oral dosage form, these drugs have become quite popular since coming onto the market and have increasingly replaced SUs as add-on therapy to diabetic regimens.[2,35]

3. Summary of Major CV Trials

a. GLP-1 agonists. Numerous trials have been published investigating the CV safety of GLP-1 agonists which include the EXSCEL, LEADER, SUSTAIN 6, PIONEER, ELIXA, REWIND, and HARMONY trials (Table 1).[39-45] In the EXSCEL trial, 14,752 T2DM patients were randomized to receive extended release exenatide (2 mg SQ) or placebo once weekly. The trial was designed to include 70% of patients with previous CVD and the use of open-label glucose-lowering agents was encouraged. The exenatide group showed similar outcomes to placebo regarding the primary composite MACE outcome (CV death, nonfatal MI, or nonfatal stroke). The primary outcome occurred in 11.4% of patients in the exenatide group versus 12.2% in the placebo group (HR 0.91; 95% CI 0.83-1.00; $P< 0.001$ for noninferiority, $P= 0.006$ superiority). Additionally, a subgroup analysis was performed and determined that a history of HF did not significantly affect trial outcomes, although the prevalence of HF was low in the trial.[39]

Following the EXSCEL trial, the LEADER trial evaluated 9340 T2DM patients using liraglutide (1.8 mg SQ daily) versus placebo.[40] Similar to the EXSCEL trial, most of the patients in the LEADER trial had a history of ASCVD or were aged >60 years with ASCVD risk factors. Notably, the prevalence of HF at baseline was low (18%) in the trial population. The addition of more antidiabetic agents was permitted to achieve glycemic goals. Patients receiving liraglutide had a reduction in the composite MACE outcome of CV mortality, nonfatal MI, or nonfatal stroke (13.0%) as compared to placebo (14.9%) (HR 0.87; 95% CI 0.78-0.97; $P< 0.001$ for noninferiority; $P= 0.01$ for superiority). Treatment with liraglutide resulted in a 15% reduction in all-cause mortality primarily driven by CV mortality (HR 0.85; 95% CI 0.74-0.97; $P= 0.02$). Although not significant, liraglutide numerically reduced HF hospitalization.[40] Due to the robust cardiovascular benefit in a population with established or at high risk for CVD, liraglutide is recommended as a second-line treatment option following metformin in patients with type 2 diabetes mellitus and established CVD.[2]

In the SUSTAIN-6 trial, 3297 T2DM patients were randomized to receive either semaglutide (0.25-1 mg subcutaneously [SQ] daily) or matching placebo. Similar to the EXSCEL and LEADER trials, most of the patients had a history of ASCVD or were older and had ASCVD risk factors. Furthermore, 24% had a history of HF. The primary composite 3-point MACE outcome (first occurrence of death from CV causes,

Table 1. Summary of GLP-1 agonist trials in cardiovascular disease

	REWIND – dulaglutide	EXSCEL –exenatide	LEADER –liraglutide	ELIXA – lixisenatide	SUSTAIN 6 – semaglutide	PIONEER 6 – semaglutide
Patients	• T2DM with A1C 6.5-9.5% • Age ≥ 50 with history of CVD or age ≥ 55 with risk factors** • Age ≥ 60 with ≥ 2 risk factors† • N = 9901	• T2DM with A1c 6.5%-10% • Age 18 with or without previous CV events‡ • N = 14,752	• T2DM with A1C ≥ 7.0% • Age ≥ 50 with ≥ 1 risk factors¶ • Age ≥ 60 with vascular disease risk factors¶¶ • N = 9340	• T2DM with ACS event 180 days before screening • N = 6068	• T2DM with A1c ≥ 7% • Age ≥ 50 with ≥ 1 risk factor¶ • Age ≥ 60 with ≥ 1 risk factor¶¶ • N = 3297	• T2DM • Age ≥ 50 years with CVD or CKD • Age ≥ 60 with ≥ 1 risk factor¶¶ • N = 3183
Intervention	• Dulaglutide 1.5 mg SQ weekly vs placebo • Standard of care for T2DM + CV risk factors	• Exenatide 2 mg SQ weekly vs placebo • Standard of care for T2DM	• 2 week placebo run-in • Liraglutide 1.8 mg SQ daily (or max tolerated dose) vs placebo • Standard of care for T2DM + CV risk factors	• 1 week placebo run-in • Lixisenatide 10 mcg SQ daily (max dose 20 mcg) vs placebo • Standard of care for T2DM	• 4-week semaglutide 0.25 mg SQ weekly titrated every 4 weeks to 0.5 mg SQ weekly or 1 mg SQ weekly vs placebo • Standard of care for T2DM	• Semaglutide 3 mg PO daily titrated to 7 mg PO daily at week 4 and 14 mg PO daily at week 8 depending on tolerability
Endpoints	• Primary: composite MACE* • Secondary: (1) vascular death (2) nonfatal MI (3) nonfatal stroke	• Primary: composite MACE++ • Secondary: (1) death from any cause (2) CV death or unknown causes (3) fatal or nonfatal MI (4)	• Primary: composite MACE++ • Secondary: (1) composite MACE + coronary revascularization, or CHF/UA hospitalization (2) all-cause mortality (3)	• Primary: composite MACE* + UA hospitalization • Secondary: (1) composite MACE* or CHF hospitalization, (2) composite MACE*, CHF hospitalization	• Primary: composite MACE* • Secondary: (1) expanded cardiovascular outcome¥ (2) death (3) nonfatal MI (4) nonfatal stroke (5)retinopathy	• Primary: composite MACE * • Secondary: (1) composite MACE + UA/CHF hospitalization (2) death from any cause, nonfatal MI, nonfatal stroke (3)

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Table 1. (*continued*)

	REWIND – dulaglutide	EXSCEL –exenatide	LEADER –liraglutide	ELIXA – lixisenatide	SUSTAIN 6 – semaglutide	PIONEER 6 – semaglutide
		fatal or nonfatal stroke (5) CHF hospitalization (6) ACS hospitalization	coronary revascularization (4) UA hospitalization (5) CHF hospitalization (6) microvascular event	or coronary revascularization, (3) all-cause mortality	complications (6) nephropathy	death from any cause (4)death from CV cause (5) nonfatal MI (6) nonfatal stroke (7) UA hospitalization (8) CHF hospitalization
Outcomes	Dulaglutide vs placebo • Primary: 12.0 vs 13.4%; 0.88 (0.79-0.99; $P = 0.026$) • Secondary: (1) 6.41 vs 6.99%; 0.91 (0.78-1.06) (2) 4.14 vs 4.28%; 0.96 (0.79-1.16) (3) 2.73 vs 3.53%; 0.76 (0.61-0.95)	Exenatide vs placebo • Primary: 11.4 vs 12.2%; 0.91 (0.83 – 1.00; $P< 0.001$ noninferiority $P = 0.06$ superiority) • Secondary: (1) 6.9% vs 7.9%; 0.91 (0.77-0.97) (2) 4.6% vs 5.2%; 0.88 (0.76-1.02) (3) 6.6% vs 6.7%; 0.97 (0.85-1.10) (4) 2.5% vs 2.9%; 0.85 (0.70-1.03) (5) 3.0% vs 3.1%;	Liraglutide vs placebo • Primary: 13.0 vs 14.9%; 0.87 (0.78-0.97; $P < 0.001$ noninferiority; $P = 0.01$ superiority) • Secondary: (1) 20.3% vs 22.7%; 0.88 (0.81-0.96) (2) 8.2% vs 9.6%; 0.85 (0.74-0.97) (3) 8.7% vs 9.4%; 0.91 (0.80-1.04) (4) 2.6% vs 2.7%; 0.98 (0.76-1.26) (5) 4.7% vs 5.3%; 0.87 (0.73-1.05)	Lixisenatide vs placebo • Primary: 13.4 vs 13.2%; 1.02 (0.89-1.147; $P = 0.81$) • Secondary: (1) 15.0% vs 15.5%; 0.97 (0.85-1.10) (2) 21.8% vs 21.7%; 1.00 (0.90-1.11) (3) 7.0% vs 7.4%; 0.96 (0.76-1.23)	Semaglutide vs placebo • Primary: 6.6 vs 8.9%; 0.74 (0.58-0.95; $P < 0.001$ noninferiority; $P = 0.02$ superiority) • Secondary: (1) 12.1% vs 16.0%; 0.74 (0.62-0.89) (2) 3.8% vs 3.6%; 1.05 (0.74-1.50) (3) 2.9% vs 3.9%; 0.74 (0.51-1.08) (4) 1.6% vs 2.7%; 0.61 (0.38-0.99) (5) 3.0% vs 1.8%; 1.76 (1.11-2.78)	Semaglutide vs placebo • Primary: 3.8 vs 4.8%; 0.79 (0.57-1.11; $P < 0.001$ noninferiority; $P = 0.17$ superiority) • Secondary: (1) 5.2% vs 6.3%; 0.82 (0.61-1.10) (2) 4.3% vs 5.6%; 0.77 (0.56-1.05) (3) 1.4% vs 2.8%; 0.51 (0.31-0.84) (4) 0.9% vs 1.9%; 0.49 (0.27-0.92) (5) 2.3% vs 1.9%; 1.18 (0.73-1.90)

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Table 1. (*continued*)

REWIND – dulaglutide	EXSCEL –exenatide	LEADER –liraglutide	ELIXA – lixisenatide	SUSTAIN 6 – semaglutide	PIONEER 6 – semaglutide
	0.94 (0.78-1.13) (6) 8.2% vs 7.7%; 1.05 (0.94-1.18)	(6) 7.6% vs 8.9%; 0.84 (0.73-0.97)		(6) 3.8% vs 6.1%; 0.64 (0.46 0.88)	(6) 0.8% vs 1.0%; 0.74 (0.35-1.57) (7) 0.7% vs 0.4%; 1.56 (0.60-4.01) (8)1.3% vs 1.5%; 0.86 (0.48 – 1.55)

T2DM, type 2 diabetes mellitus; A1C, hemoglobin A1C; CVD, cardiovascular disease; SQ, subcutaneous; CV, cardiovascular; MI, myocardial infarction; CHF, congestive heart failure; ACS, acute coronary syndrome; UA, unstable angina; CKD, chronic kidney disease.
*MACE= a composite of CV death, nonfatal MI, and nonfatal stroke.
**risk factors= MI, coronary, carotid, or lower extremity artery stenosis $\geq$50%, LV hypertrophy, eGFR $<$60 mL/min/1.73m^2, albuminuria.
†risk factors= tobacco use, dyslipidemia, HTN, or abdominal obesity.
‡CV events= coronary artery disease, ischemic cerebrovascular disease, or atherosclerotic peripheral arterial disease.
¶Risk factors = coronary, cerebrovascular, or peripheral vascular disease, CKD stage 3 or greater, or NYHA class II-III.
¶¶Risk factors= microalbuminuria/proteinuria, HTN with LVH, systolic or diastolic LV dysfunction, or ABI $<$ 0.9.
¥Expanded cardiovascular outcome= death from CV causes, nonfatal MI, nonfatal stroke, revascularization, hospitalization for UA, hospitalization for CHF.

nonfatal MI, or nonfatal stroke) occurred in 6.6% of patients randomized to semaglutide compared to 8.9% of patients receiving placebo (HR 0.74; 95% CI 0.58-0.95; $P < 0.001$ for noninferiority).[41] However, unlike the LEADER trial, semaglutide did not reduce all-cause mortality, CV death, or HF hospitalization.[39,41] Oral semaglutide was evaluated in the PIONEER 6 trial which randomized patients to oral semaglutide (14 mg) or matching placebo. Oral semaglutide yielded similar findings to SUSTAIN-6 when compared to placebo, proving noninferiority for the primary composite outcome of MACE (3.8% vs 4.8%; HR 0.79; 95% CI 0.57-1.11; $P < 0.001$ for noninferiority).[42]

Other GLP-1 agonists have conducted CV outcome studies worth noting. As previously mentioned, the HARMONY trial evaluated albiglutide (30-50 mg SQ) versus placebo in 9463 patients with CVD.[45] Albiglutide demonstrated a 22% reduction in MACE, however production was discontinued in 2018 due to low demand and low sales.[45] In the ELIXA trial, lixisenatide established noninferiority compared to placebo in regards to the incidence of CV death, MI, stroke, and hospitalization for angina (HR 1.02; 95% CI 0.89-1.17 $P < 0.001$ for noninferiority; $P = 0.81$ for superiority).[43] Despite establishing no excess CV harm, there were no signs of overt benefit as observed with other agents in the class. Finally, the REWIND trial concluded that MACE was reduced with dulaglitide (12.0%) compared to placebo (13.4%), but did so in a population where only 31.5% of patients had established CVD, much lower compared to previous studies.[44]

b. DPP-4 inhibitors. A number of trials have been published evaluating the CV safety of DPP-4 inhibitors, which include the EXAMINE, SAVOR-TIMI 53, TECOS, CARMELINA, and CAROLINA trials (Table 2).[36-38,46,47] EXAMINE was the first trial published and evaluated alogliptin versus placebo in 5380 T2DM patients that had recently experienced acute coronary syndrome.[46] Patients were randomized to receive alogliptin (adjusted for renal function) or placebo in addition to standard care for T2DM and CV risk factors. The alogliptin group showed similar outcomes to placebo regarding the primary composite MACE outcome (CV death, nonfatal MI, or nonfatal stroke), 11.3% versus 11.8% respectively (HR 0.96; 95% CI $\leq$1.16; $P < 0.001$ noninferiority; $P = 0.32$ superiority).[46] This study did not originally evaluate HF outcomes, so a subsequent post-hoc analysis was performed to evaluate HF outcomes, which found no difference in hospital admission for HF between alogliptin (3.1%) and placebo (2.9%) (HR 1.07; 95% CI 0.79-1.46; $P = 0.66$ superiority).[48] However, in patients with no previous history of HF, the

Table 2. Summary of DPP-IV inhibitor trials in cardiovascular disease

	EXAMINE – alogliptin	SAVOR-TIMI-53 –saxagliptin	TECOS – sitagliptin	CARMELINA – linagliptin	CAROLINA – linagliptin
Patients	• T2DM and ACS within 15-90 days prior to randomization Receiving glucose-lowering therapy • A1C 6.5%-9% (oral antidiabetic regimen) A1C 6.5-8.5% (insulin in antidiabetic regimen) N = 5380	• T2DM with A1C 6.5%-12% • Age ≥ 40 with history of CVD or age ≥ 55 (men) or 60 (women) with multiple risk factors** or vascular disease • N = 16,492	• T2DM with CVD • Age ≥ 50, A1C 6.5%-8% (on stable doses of oral antidiabetic medications or insulin), eGFR ≥30 mL/min • N = 14,671	• T2DM with A1C 6.5%-10% and high CV† and renal risk‡ • N = 6979	• T2DM with A1C 6.5%-8.5% and high CV risk¶ • A1C 6.5%-7.5% (previously treated with SU or DPP-4 inhibitor alone or in addition to metformin or alpha-glucosidase inhibitor) • N = 6033
Intervention	• Alogliptin (25 mg daily if eGFR >60 mL/min; 12.5 mg daily if GFR 30-60 mL/min; 6.25 mg daily if GFR <30 mL/min) vs placebo • Standard of care for T2DM + CV risk factors	• Saxagliptin 5 mg daily (2.5 mg daily if eGFR ≤50 mL/min) vs placebo • Standard of care for T2DM + CV risk factors	• Sitagliptin 100 mg daily (50 mg daily if eGFR ≥30 and <50 mL/min) vs placebo • Standard of care for T2DM	• Linagliptin 5 mg daily vs placebo • Standard of care for T2DM + CV risk factors	• Linagliptin 5 mg daily vs glimepiride 1 mg daily (titrated to a max dose of 4 mg) • Standard of care for T2DM
Endpoints	• Primary: composite MACE* • Secondary: (1) composite primary + UA (2) death from any cause (3) death from CV cause • Post-hoc analysis: CHF hospitalization	• Primary: composite MACE* • Secondary: (1) composite primary + hospitalization for CHF, coronary revascularization, or UA (2) death from any cause (3) death from CV cause (4) CHF hospitalization	• Primary: composite MACE* + UA hospitalization • Secondary: (1) composite MACE (2) death from any cause (3) death from CV cause (4) CHF hospitalization	• Primary: composite MACE* • Secondary: composite of sustained ESRD, death due to renal failure, sustained decrease of ≥40% in eGFR from baseline	• Primary: composite MACE* • Secondary: (1) composite MACE* + UA hospitalization, (2) CV death, (3) nonfatal MI, (4) nonfatal stroke, (5) all-cause mortality, (6) CHF hospitalization

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Table 2. (*continued*)

	EXAMINE – alogliptin	SAVOR-TIMI-53 –saxagliptin	TECOS – sitagliptin	CARMELINA – linagliptin	CAROLINA – linagliptin
Outcomes	Alogliptin vs placebo • Primary: 11.3 vs 11.8%; 0.96 (≤1.16; $P < 0.001$ for noninferiority; $P = 0.32$ superiority) • Secondary: (1) 12.7% vs 13.4%; 0.95 (≤1.14) (2) 6.5% vs 5.7%; 0.88 (0.71-1.09) (3) 4.9% vs 4.1%; 0.85 (0.66-1.10) • Post-hoc analysis: 3.1 vs 2.9%; 1.07 (0.79-1.46)	Saxagliptin vs placebo • Primary: 7.3 vs 7.2%; 1.00 (0.89-1.12; $P < 0.001$) noninferiority; $P = 0.99$ superiority) • Secondary: (1) 12.8% vs 12.4%; 1.02 (0.94-1.11) (2) 4.9% vs 4.2%; 1.11 (0.96-1.27) (3) 3.2% vs 2.9%; 1.03 (0.87-1.22) (4) 3.5% vs 2.8%; 1.27 (1.07-1.51)	Sitagliptin vs placebo • Primary:¥ 11.4 vs 11.6%; 0.98 (0.89-1.08; $P = 0.65$ superiority) • Secondary:¥ (1) 10.2% vs 10.2%; 0.99 (0.89-1.10) (2) 7.5% vs 7.3%; 1.01 (0.90-1.14) (3) 5.2% vs 5%; 1.03 (0.89-1.19) (4) 3.1% vs 3.1%; 1.00 (0.93-1.20)	Linagliptin vs placebo • Primary: 12.4% vs 12.1%; 1.02 (0.89-1.17; $P <0.001$ noninferiority; $P = 0.74$ superiority) • Secondary: 9.4% vs 8.8%; 1.04 (0.89-1.22)	Linagliptin vs glimepiride • Primary: 11.8% vs 12%; 0.98 (0.84-1.14) • Secondary: (1) 13.2% vs 13.3%; 0.99 (0.86-1.14) (2) 5.6% vs 5.6%; 1.00 (0.81-1.24) (3) 4.8% vs 4.7%; 1.01 (0.80-1.28) (4) 3.0% vs 3.5%; 0.87 (0.66-1.15) (5) 10.2% vs 11.2%; 0.91 (0.78-1.06) (6) 3.7% vs 3.1%; 1.21 (0.92-1.59)

T2DM, type 2 diabetes mellitus; ACS, acute coronary syndrome; eGFR, estimated glomerular filtration rate; CV, cardiovascular; UA, unstable angina; CHF, congestive heart failure; A1C, hemoglobin A1C; CVD, cardiovascular disease; SU, sulfonylurea; DPP-4, dipeptidyl peptidase-4.

*MACE= a composite of CV death, nonfatal MI, and nonfatal stroke.

**Risk factors= dyslipidemia, hypertension, and active smoking

†High CV risk= coronary artery disease, stroke or peripheral artery disease, and microalbuminuria or macroalbuminuria.

‡High renal risk= eGFR 45-75 mL/min/1.73m^2 and urinary albmin:creatinine ration (UACR) >200 mg/g or equivalent; eGFR 15-45 mL/min/1.73m^2 regardless of UACR.

¶High CV risk= established ASCVD; at least 2 risk factors, 1) duration of T2DM for ≥10 years, 2) systolic blood pressure >140 mmHg or receiving at least one blood pressure-lowering treatment, 3) current smoker, 4) low-density lipoprotein cholesterol ≥135 mg/dL or receiving lipid-lowering therapy; age ≥70 years; evidence of microvascular complications.

¥Reported for intention-to-treat population.

alogliptin group had significantly more hospital admissions for HF compared to the placebo group, 2.2% versus 1.3% respectively (HR 1.76; 95% CI 1.07-2.90; P= 0.03 superiority).[48]

The SAVOR-TIMI 53 trial, published shortly after EXAMINE, evaluated saxagliptin versus placebo in 16,492 T2DM patients that had a history of CVD or multiple risk factors for CVD.[47] Patients were randomized to receive saxagliptin (adjusted for renal function) or placebo in addition to other therapy for T2DM or CVD at the physician's discretion. The primary outcome of MACE (CV death, nonfatal MI, or nonfatal stroke) occurred in 7.3% of patients treated with saxagliptin versus 7.2% with placebo (HR 1.00; 95% CI 0.89-1.12;P= 0.99 superiority; P< 0.001 noninferiority). Additionally, no significant differences were observed for the secondary outcome, which was the composite primary outcome in addition to hospitalization for unstable angina, HF, or coronary revascularization. However, there was a statistically significant increase in HF hospitalization in the saxagliptin group compared to placebo, 3.5% versus 2.8% respectively (HR 1.27; 95% CI 1.07-1.51; P= 0.007 superiority).[47] Because of the results of SAVOR-TIMI 53 and the post-hoc analysis of EXAMINE, guidelines recommend to avoid saxagliptin and alogliptin in patients with HF.[3,5] For patients that have been prescribed either of these medications, guidelines recommend close monitoring for new signs and symptoms of HF.[2,35]

With the results of the EXAMINE and SAVOR-TIMI 53 trials, there was a concern that the poor HF outcomes associated with DPP-4 inhibitors may be a class effect. Therefore, the TECOS trial was a highly anticipated trial that evaluated sitagliptin versus placebo in 14,671 T2DM patients at least 50 years of age with established CVD and with a hemoglobin A1c of 6.5%-8%.[38] Patients were randomized to receive sitagliptin (adjusted for renal function) or placebo in addition to standard care. The primary composite MACE outcome of CV death, nonfatal MI, nonfatal stroke, or hospitalization for unstable angina was similar with sitagliptin and placebo, 11.4% versus 11.6%, respectively (HR 0.98; 95% CI 0.88-1.08; P< 0.001 noninferiority; P= 0.65 superiority). Unlike previous trials, there was no difference with the rate of hospitalizations for HF with sitagliptin compared to placebo, 3.1% versus 3.1%, respectively (HR 1.00; 95% CI 0.83-1.20; P= 0.98 superiority).[38]

Linagliptin was the last FDA approved DPP-4 inhibitor to have its CV data published. There are currently 2 trials that have evaluated CV safety with linagliptin, the CARMELINA trial and the CAROLINA trial.[36,37] Different from other DPP-4 studies, the CARMELINA trial evaluated 6976 T2DM patients with a hemoglobin A1c of 6.5%-10% that had high

CV and renal risk.[36] Renal risk was defined as either eGFR of 45-75 mL/min/1.73 m^2 and urinary albumin to creatinine ration higher than 200 mg/g or eGFR 15-45 mL/min/1.73 m^2 regardless of urinary albumin to creatinine ratio. Patients with high renal risk had been limited in previous studies despite this patient population carrying a high CV risk. Patients were randomized to receive linagliptin (5 mg daily) or matching placebo in addition to standard care. The primary composite MACE outcome of CV death, nonfatal MI, or nonfatal stroke was similar with linagliptin and placebo, 12.4% versus 12.1%, respectively (HR 1.02; 95% CI 0.89-1.17; $P < 0.001$ noninferiority; $P = 0.74$ superiority). Similar to the TECOS trial, linagliptin did not show any difference in hospitalization for HF compared to placebo, 6% versus 6.5%, respectively (HR 0.90; 95% CI 0.74-1.08; $P = 0.26$ superiority).[36] The CAROLINA trial was also slightly different from previous DPP-4 inhibitor CV trials as this trial sought to compare linagliptin to an active comparator, glimepiride, and included 6042 T2DM patients with a hemoglobin A1c of 6.5%-8.5% and high CVD risk.[37] Patients were randomized to receive linagliptin (5 mg daily) or glimepiride (1 mg daily titrated up to 4 mg daily). The primary composite MACE outcome of CV death, nonfatal MI, or nonfatal stroke was similar between linagliptin and glimepiride, 11.8% versus 12%, respectively (HR 0.98; 95% CI 0.84-1.14; $P < 0.001$ noninferiority; $P = 0.76$ superiority).[37]

There has been much debate regarding the true risk of DPP-4 inhibitors and HF outcomes. Multiple meta-analyses and observational studies have been published and have shown mixed results.[49-56] Nonrandomized, observational studies have suggested an increased risk of HF that is usually seen shortly after initiation of the DPP-4 inhibitor (within 30 days), similar to what was observed in SAVOR-TIMI 53.[52,53] In contrast, there are some retrospective studies that do not suggest a risk of HF, although these studies did not focus on new users, and these studies utilized comparator groups that have an inherent risk for HF.[54] One argument for the differences in HF outcomes between the large clinical trials is the disproportionate use of other antidiabetic medications. In the SAVOR-TIMI 53 trial, there were differences in the use of metformin, insulin, and TZDs (69%, 41%, and 6%, respectively) compared to what was seen in the TECOS trial (81%, 23%, and 3%, respectively).[38,47] Given metformin's beneficial effects in HF patients and insulin and TZDs negative effects, this seems to be a valid argument. However, in the recently published CARMELINA trial, there was similar usage of metformin and insulin (53% and 58%, respectively) but lower usage of TZDs (0.7%) compared to the SAVOR-TIMI 53 trial. This may have contributed to the lack of

difference in HF outcomes that was found in the CARMELINA trial.[36,47] At this time the true risk of HF remains uncertain with this drug class. Therefore, if these agents are used, it is important to monitor for signs and symptoms of HF and to discontinue therapy if HF is diagnosed or worsens.

4. Mechanism of CV Benefits

a. GLP-1 agonists. The mechanism of the demonstrated CV benefits for GLP-1 agonists is largely unknown. However, it has been hypothesized that it is multimodal and possibly not a class-wide effect given the results of the aforementioned trials.[57] GLP-1 agonists have demonstrated an improvement in traditional cardiovascular risk factors including improved hemoglobin A1c control, a reduction in LDL, weight control and blood pressure lowering. Furthermore, they likely have pleotropic effects that result in vasodilation and reduction of inflammation.[57]

As previously demonstrated, liraglutide likely has the most pronounced CV benefit of the GLP-1 agonists. Liraglutide has been shown to induce plasminogen activator inhibitor type-1 and vascular adhesion molecules. This induction has been theorized to protect against endothelial dysfunction, which is a known complication of uncontrolled diabetes. Through endothelial protection, liraglutide would prevent hypertrophy and vascular inflammation and promote vasodilation.[58] Liraglutide treatment also results in an increase in nitric oxide synthase activity, leading to pleotropic benefits.[58]

b. DPP-4 inhibitors. Similar to GLP-1 agonists, the exact mechanistic link between DPP-4 inhibitors and their CV effects are unclear, although there are a number of hypotheses.[59-62] One explanation for the negative HF outcomes seen with some DPP-4 inhibitors is the increase in insulin release. Insulin signaling causes cardiac remodeling, detrimental effects on vascular structure, and sodium retention.[63] An alternative explanation includes the potentiation of stromal cell-derived factor-1. stromal cell-derived factor-1 promotes sympathetic activation, which leads to ventricular hypertrophy and can directly suppress cardiac force and frequency.[63]

In the wake of SAVOR-TIMI 53, a study evaluated saxagliptin's effect on cardiac dysfunction in human and animal heart tissue.[61] This study showed that saxagliptin is internalized in cardiac myocytes and impairs contractility of the heart via a reduction in sarcoplasmic reticulum calcium content and diastolic calcium overload.[61] Similarly, a recent study

evaluating vildagliptin's effect on ventricular function in patients with T2DM and HF with reduced ejection fraction (HFrEF) (EF ≤40%) showed no difference in left ventricular ejection fraction reduction between vildagliptin and placebo.[64] However, there was more LV enlargement seen in the vildagliptin group, but it is unclear if this finding was due to imbalances in the groups or chance.[64] In contrast to these studies, a study evaluated sitagliptin's effects on LV function during dobutamine stress in patients with T2DM and coronary artery disease.[60] Sitagliptin was associated with improved global and regional LV performance due to a reduction in contractile dysfunction in regions of demand ischemia.[60] These differing results suggest that CV effects are drug-specific, though more studies are needed to confirm this. More information about the cardioprotective potential of DPP-4 inhibitors may be provided shortly with the ongoing evaluation of dutogliptin in addition to filgrastim in patients with recent ST-segment elevation MI with primary percutaneous coronary intervention to determine the impact on cardiac recovery.[34]

5. Safety and Monitoring

a. GLP-1 agonists. The most common side effects of GLP-1 agonists are nausea and vomiting.[33,65] However, these are typically mild and can be reduced by eating smaller portions and using slow dose titrations. GLP-1 agonists also come with a warning to use with caution in patients with a history of pancreatitis and gall bladder disease due to reports of GI adverse effects including acute cholecystitis.[33,65] Serious adverse effects include a possible risk for thyroid and pancreatic malignancy.[66] This risk was seen in animal studies, however, several meta-analyses have failed to confirm this association in humans. Due to the lack of consensus regarding these potential adverse effects, the package label recommends to avoid GLP-1 agonists if the patient has a personal or family history of medullary thyroid carcinoma or multiple endocrine neoplasia type II.[33,65] GLP-1 agonists are generally well tolerated from a CV profile when given SQ or orally. However, in several studies evaluating GLP-1 agonists as continuous intravenous (IV) infusions, tachycardia has been noted.[67] While the exact mechanism is not exactly understood, it is thought to encompass direct sino-atrial stimulation amongst other avenues.[68] Last, GLP-1 agonists rarely cause hypoglycemia. This indicates that they may be an ideal option for patients that have struggled with hypoglycemia in the past.

b. DPP-4 inhibitors. Overall, the DPP-4 inhibitors are well-tolerated and have few serious side effects. The most common side effects are usually limited to diarrhea and nausea, however more severe adverse effects such as pancreatitis and arthralgia can occur. In 2013 the FDA evaluated the risk of pancreatitis with DPP-4 inhibitors and was not able to come to any conclusions at that time.[69] Since then, meta-analyses have suggested an increased risk of pancreatitis, although it is unclear if this association is causal.[70,71] For patients with a history of pancreatitis, it may be reasonable to avoid these drugs. Amylase and lipase levels can be mildly elevated with incretin-based therapies, but the clinical correlation of those levels to actual pancreatic events remains unclear. In patients with mild GI symptoms it may be reasonable to monitor levels or even perform an abdominal ultrasound to evaluate for gallstones. In 2015 the FDA released a warning regarding DPP-4 inhibitors and the risk of arthralgias, which was confirmed in meta-analyses.[72,73] Most agents in this class are eliminated primarily via the kidney with linagliptin being the exception. Because of this, renal adjustment is required once eGFR is less than 45 mL/min/1.73 m^2 for saxagliptin and sitagliptin or CrCl <60 mL/minute for alogliptin.[74-76]

A. Sodium-glucose cotransporter 2 inhibitors

Since the approval of canagliflozin in 2013, the sodium-glucose cotransporter 2 (SGLT2) inhibitors have been the subject of much criticism and praise. In the U.S., there are currently 4 FDA-approved SGLT2 inhibitors (canagliflozin, dapagliflozin, empagliflozin, and ertugliflozin). SGLT2 inhibitors block SGLT2 receptors located in the proximal tubule of the nephron that reabsorb approximately 90% of urinary glucose. Inhibiting SGLT2 prevents the reabsorption of glucose and leads to glucosuria. The effect of SGLT2 inhibition is greater in the setting of hyperglycemia as there is typically a significant amount of glucose filtered into the urine during hyperglycemia. This mechanism provides a hemoglobin A1c reduction between 0.5% and 1% and a low risk of hypoglycemia. Additional benefits of SGLT2 inhibitors include weight loss, lowering of systolic blood pressure, and both diuresis and natriuresis.[1,77] As a result, there is much interest around using SGLT2 inhibitors for other indications, especially HF. Current guidelines recommend SGLT2 inhibitors in combination with first-line therapy in patients with established ASCVD or indicators of high ASCVD risk, CKD, or HF independent of baseline hemoglobin A1c or A1c goal.[2,35]

a. Summary of major CV trials

There have been several large clinical trials evaluating the CV safety of SGLT2 inhibitors. These trials include EMPA-REG OUTCOME, CANVAS and CANVAS-R, DECLARE-TIMI 58 and the recently completed, VERTIS CV trial (Table 3).[78-81] Further investigation into the beneficial effects of SGLT2 inhibitors in HF patients have been conducted in the DAPA-HF and CANDLE trials (Table 4).[82,83] The first trial published was the EMPA-REG OUTCOME trial that compared empagliflozin versus placebo in 7020 patients with T2DM and established CVD. Patients were randomized to receive empagliflozin (10 mg or 25 mg), or placebo.[78] Empagliflozin treatment reduced the primary composite outcome of CV death, nonfatal MI, or nonfatal stroke compared to placebo, 10.5% versus 12.1%, respectively (HR 0.85; 95% CI 0.74-0.99; $P<$ 0.001 noninferiority; $P = 0.04$ superiority). Significant reductions in all-cause mortality and CV mortality were also evident in the empagliflozin group. Hospitalization for HF was also significantly reduced in the empagliflozin group, 2.7% versus 4.1%, respectively (HR 0.65; 95% CI 0.50-0.85; $P = 0.002$). There was no difference in effect noted between the 10- and 25-mg doses.[78] Empagliflozin is currently the only SGLT2 inhibitor approved by the FDA to reduce the risk of CV death in adults with T2DM and established CVD.[84]

The CANVAS trial program was published a few years later, and it compared canagliflozin to placebo in 10,142 T2DM patients with either symptomatic CVD (if over the age of 30), or with at least 2 risk factors for CVD (if over the age of 50).[79] Patients were randomized to receive either placebo or canagliflozin (100 or 300 mg in CANVAS, and 100 mg with an optional increase to 300 mg in CANVAS-R). The primary composite outcome was identical to that of EMPA-REG OUTCOME.[78,79] The primary outcome occurred at a rate of 26.9 versus 31.5 events per 1000 patient-years (HR 0.86; 95% CI 0.75-0.97; $P < 0.001$ noninferiority; $P = 0.02$ superiority) with canagliflozin compared to placebo.[79] Similar to empagliflozin, canagliflozin also reduced HF hospitalization with rates of 5.5 versus 8.7 events per 1000 patient-years compared to placebo (HR 0.67; 95% CI 0.52-0.87; $P= 0.24$).[78,79] Contrary to EMPA-REG OUTCOME, canagliflozin did not reduce mortality (CV or all-cause) compared to placebo.[78,79] No difference in outcomes were noted between the 2 canagliflozin doses studied in the trial.[79]

DECLARE-TIMI 58, published shortly after CANVAS, evaluated the CV safety of dapagliflozin in 17,160 T2DM patients with either established CVD or multiple risk factors for CVD. Patients were randomized

Table 3. Summary of SGLT2 inhibitor trials in cardiovascular disease

	EMPA-REG OUTCOME — empagliflozin	**CANVAS/CANVAS-R — canagliflozin**	**DECLARE-TIMI 58 — dapagliflozin**	**VERTIS CV — ertugliflozin**
Patients	• T2DM ≥ 18 years old, BMI ≤ 45 and eGFR ≥ 30 mL/min/1.73 m^2 of BSA and established CVD • Not receiving glucose-lowering therapy for at least 12 weeks prior to randomization and A1C 7%-9% • Stable glucose-lowering therapy for at least 12 weeks prior to randomization and A1C 7%-10% • N = 7020	• T2DM and either 1) ≥30 years of age with history of symptomatic ASCVD or 2) ≥ 50 years of age with ≥ 2 risk factors for CVD** • eGFR ≥ 30 mL/min/1.73 m^2 of BSA • N = 10,142	• T2DM ≥40 years of age and CrCl ≥60 mL/min • Multiple risk factors for ASCVD† or established ASCVD • N = 17,160	• T2DM ≥40 years of age • Established ASCVD • Stable on glucose-lowering therapy for ≥8 weeks prior to randomization • N = 8246
Intervention	• Empagliflozin 10 mg daily vs empagliflozin 25 mg daily vs placebo • Baseline glucose-lowering therapy permitted	• CANVAS: canagliflozin 100 mg daily vs canagliflozin 300 mg daily vs placebo • CANVAS-R: canagliflozin 100 mg daily with optional increase to 300 mg daily vs placebo • Baseline glucose-lowering therapy permitted for both	• Dapagliflozin 10 mg daily vs placebo • Baseline glucose-lowering therapy permitted	• Ertugliflozin 5 mg daily vs ertugliflozin 15 mg daily vs placebo • Standard of care was held stable during first 18 weeks of study

(*continued on next page*)

Table 3. (*continued*)

	EMPA-REG OUTCOME — empagliflozin	CANVAS/CANVAS-R — canagliflozin	DECLARE-TIMI 58 — dapagliflozin	VERTIS CV — ertugliflozin
Endpoints	• Primary: composite of MACE** • Secondary: (1) composite of MACE + UA hospitalization, (2) death from any cause, (3) death from CV causes, (4) nonfatal MI excluding silent MI, (5) nonfatal stroke, (6) UA hospitalization, (7) CHF hospitalization, (8) CHF hospitalization or death from CV causes excluding fatal stroke	• Primary: composite of MACE* • Secondary: (1) death from CV causes, (2) nonfatal MI, (3) nonfatal stroke, (4) CHF hospitalization, (5) all-cause mortality,	• Primary: (1) composite of CV death or CHF hospitalization (2) MACE* • Secondary: (1) all-cause mortality, (2) CHF hospitalization, (3) MI, (4) ischemic stroke, (5) death from CV cause	• Primary: composite of MACE* • Secondary: (1) CV death, (2) nonfatal MI, (3) nonfatal stroke, (4) CHF hospitalization, (5) death from any cause
	Empagliflozin vs placebo • Primary: 10.5 vs 12.1%; 0.86 (0.74-0.99; $P < 0.001$ noninferiority; $P = 0.04$ superiority) • Secondary: (1) 12.8 vs 14.3%; 0.89 (0.78-1.01) (2) 5.7 vs 8.3%; 0.68 (0.57-0.82) (3) 3.7 vs 5.9%; 0.62 (0.49-0.77) (4) 4.5 vs 5.2%; 0.87	Canagliflozin vs placebo‡ • Primary: 26.9 vs 31.5; 0.86 (0.75-0.97; $P < 0.001$ noninferiority; $P = 0.02$ superiority) • Secondary: (1) 11.6 vs 12.8; 0.87 (0.72-1.06) (2) 9.7 vs 11.6; 0.85 (0.69-1.05) (3) 7.1 vs 8.4; 0.90 (0.71-1.15) (4) 5.5 vs 8.7; 0.67	Dapagliflozin vs placebo • Primary: (1) 4.9 vs 5.8%; 0.83 (0.73-0.95; $P = 0.005$ noninferiority) (2) 8.8 vs 9.4%; 0.93 (0.84-1.03; $P = 0.17$ noninferiority) • Secondary: (1) 6.2 vs 6.6%; 0.93 (0.82-1.04) (2) 2.5 vs 3.3%; 0.73 (0.61-0.88)	Ertugliflozin vs placebo • Primary: 11.9 vs 11.9%; 0.97 (0.85-1.11; $P < 0.001$ noninferiority) • Secondary: (1) 6.2 vs 6.7%; 0.92 (0.77-1.11) (2) 5.6 vs 5.4%; 1.0 (0.86-1.27) (3) 2.9 vs 2.8%; 1.0 (0.76-1.32) (4) 2.5 vs 3.6%; 0.70 (0.54-0.90)

(*continued on next page*)

Table 3. (*continued*)

EMPA-REG OUTCOME – empagliflozin	CANVAS/CANVAS-R – canagliflozin	DECLARE-TIMI 58 – dapagliflozin	VERTIS CV – ertugliflozin
(0.70-1.09) (5) 3.2 vs 2.6%; 1.24 (0.92-1.67) (6) 2.8 vs 2.8%; 0.99 (0.74-1.34) (7) 2.7 vs 4.1%; 0.65 (0.50-0.85) (8)5.7 vs 8.5%; 0.66 (0.55-0.79)	(0.52-0.87) (5) 17.3 vs 19.5; 0.87 (0.74-1.01)	(3) 4.6 vs 5.1%; 0.89 (0.77-1.01) (4) 2.7 vs 2.7%; 1.01 (0.84-1.21) (5) 2.9 vs 2.9%; 0.98 (0.82-1.17)	(5) 8.6 vs 9.2%; 0.93 (0.8-1.08)

T2DM, type 2 diabetes mellitus; BMI, body mass index; eGFR, estimated glomerular filtration rate; BSA, body surface area; CVD, cardiovascular disease; A1C, hemoglobin A1C; UA, unstable angina; CV, cardiovascular; MI, myocardial infarction; CHF, congestive heart failure; ASCVD, atherosclerotic cardiovascular disease; CrCl, creatinine clearance.

*MACE= a composite of CV death, nonfatal MI, and nonfatal stroke.

**Risk factors for CVD= duration of T2DM for ≥10 years; systolic blood pressure >140 mmHg recorded at screening visit, while the subject is on at least one blood pressure-lowering treatment; current daily cigarette smoker; documented microalbuminuria or macroalbuminuria; documented high-density lipoprotein cholesterol of <39 mg/dL.

†ASCVD risk factors= men age ≥55 years or women age ≥60 years with one or more traditional risk factors including hypertension, dyslipidemia (low-density lipoprotein cholesterol level >130 mg/dL or use of lipid-lowering therapies), or use of tobacco.

‡Presented as events per 1000 patient-years.

Table 4. Summary of SGLT2 inhibitor trials in heart failure

	DAPA-HF – dapagliflozin	CANDLE – canagliflozin
Patients	• ≥ 18 years old, EF ≤ 40%, and NYHA class II, III, or IV symptoms • Plasma NT-proBNP of ≥600 pg/mL (or ≥400 pg/mL if hospitalized for CHF within the previous 12 months) • N = 4744	• ≥20 years old, T2DM and NYHA class I-III symptoms • N = 233
Intervention	• Dapagliflozin 10 mg daily vs placebo • Standard heart failure device therapy and standard drug therapy was required • Baseline glucose-lowering therapy permitted	• Canagliflozin 100 mg daily or glimepiride 0.5 mg daily • Baseline glucose-lowering therapy permitted
Endpoints	• Primary: composite of hospitalization or an urgent visit for CHF, CHF hospitalization, urgent CHF visit, or CV death • Secondary: (1) CV death or CHF hospitalization, (2) CHF hospitalization and CV death, (3) worsening renal function, (5) all-cause mortality	• Primary: % change from baseline in NT-proBNP levels at 24 weeks
Outcomes	Dapagliflozin vs placebo • Primary: 16.3 vs 21.2%; 0.74 (0.65-0.85; $P < 0.001$) • Secondary: (1) 16.1 vs 20.9%; 0.75 (0.65-0.85) (2) 23.9% vs 31.3%; 0.75 (0.65-0.88) (3) 1.2 vs 1.6%; 0.71 (0.44-1.16 (4) 11.6 vs 13.9%; 0.83 (0.71-0.97)	Canagliflozin vs glimepiride • Primary: 10.4 vs 21.5%; 0.48 (-0.13-1.59; $P = 0.226$)

EF, ejection fraction; NYHA, New York Heart Association; CHF, congestive heart failure; CV, cardiovascular; T2DM, type 2 diabetes mellitus.

to receive dapagliflozin (10 mg once daily) or placebo.[80] As with the prior studies, the primary outcome was a 3-point MACE of CV death, nonfatal MI or nonfatal stroke. MACE occurred in 8.8% of patients receiving dapagliflozin compared to 9.4% of patients with placebo, satisfying noninferiority (HR 0.93; 95% CI 0.84 - 1.03; P= 0.17 superiority). An additional primary efficacy outcome of composite of CV death or HF hospitalization was evaluated in which fewer events occurred in the dapagliflozin group versus placebo, 4.9% versus 5.8%, respectively (HR 0.83; 95% CI 0.73-0.95; $P = 0.005$). This endpoint was primarily driven by HF hospitalization. There was no significant difference between groups with respect to the rate of CV death.[80]

Ertugliflozin is the most recent SGLT2 inhibitor to have its CV data published, and with it brought expectations for a class effect regarding CV benefit.[81] VERTIS-CV evaluated the CV safety of ertugliflozin in 8246 patients with T2DM and established ASCVD.[81] Patients were

randomized to receive either placebo or ertugliflozin (5 mg or 15 mg). The primary MACE outcome was identical to those of the prior studies and occurred at the same rate between groups, 11.9% versus 11.9% (HR 0.97; 95% CI 0.85-1.11 $P < 0.001$ noninferiority). A secondary endpoint of hospitalization for HF occurred less frequently in the ertugliflozin group, 2.5% vs 3.6% (HR 0.7; 95% CI 0.54-0.9; $P = 0.006$).[81] While there appears to be a class effect regarding reductions in hospitalizations for HF, reductions in MACE were only seen with empagliflozin and canagliflozin. This is an interesting finding considering VERTIS CV only included patients with established ASCVD.[81] Whether these findings are due to differences in patient populations between trials or innate differences in drug characteristics is unclear.

EMPA-REG OUTCOME, CANVAS, DECLARE-TIMI 58, and VERTIS CV had different enrollment criteria and thus major differences in the amount of patients with established ASCVD (100%, 66%, 41%, and 100% respectively).[78-81] In trials with a greater representation of "primary prevention" patients, the risk may have been too low to observe a benefit. This theory is supported by several meta-analyses of EMPA-REG OUTCOME, CANVAS, AND DECLARE-TIMI 58 in which MACE was significantly reduced overall, but the benefit was driven by patients with ASCVD compared to those without.[85,86] However, this theory is contradicted by VERTIS CV in which they enrolled only "secondary prevention" patients and saw no reduction in MACE. Similarly, in the CVD-REAL observational study, only 13% of patients had established ASCVD, and they found a significant reduction in all-cause mortality and HF hospitalization overall.[87] The reason for these conflicting findings warrants further research. On the other hand, the benefit of SGLT2 inhibitors on HF outcomes is without controversy and is further supported by a meta-analysis showing that SGLT2 inhibitors reduced the risk of HF hospitalization by 32% (HR 0.68 ; 95% CI 0.61-0.76), without regard to established ASCVD or pre-existing HF.[85]

DAPA-HF evaluated the efficacy and safety of dapagliflozin in patients with HFrEF less than or equal to 40% in patients with or without T2DM. Patients were randomized to receive either dapagliflozin (10 mg once daily) or placebo.[82] The primary composite outcome of hospitalization or an urgent visit for HF, hospitalization for HF, urgent HF visit, and CV death occurred less frequently in the dapagliflozin group compared to placebo, 16.3% versus 21.2%, respectively (HR 0.74; 95% CI 0.65-0.85; $P \leq 0.001$ superiority). Similar to previous trials, there was a reduction in hospitalization for HF with dapagliflozin compared to placebo, 9.7% versus 13.4 %, respectively (HR 0.70; 95% CI 0.59-0.83). Dapagliflozin was also

associated with improvements in HF symptoms. The effect of dapagliflozin on the primary outcome was consistent among patients with and without diabetes. However, patients in NYHA functional class III or IV had less benefit than those in class II.[82] Due to the results of the DAPA-HF trial, the FDA has recently granted approval for the use of dapagliflozin in adults with HFrEF to reduce the risk of CV death and hospitalization for HF.[88]

Like dapagliflozin, the CANDLE trial set out to evaluate the HF benefits of canagliflozin.[83] Canagliflozin was compared to glimepiride on the effect of N-terminal pro-brain natriuretic peptide (NT-proBNP) levels in Japanese patients with both T2DM and NYHA HF Class I-III over a 24-week period.[83] Patients were randomized to receive either canagliflozin (100 mg) or glimepiride (0.5 mg). The study failed to meet the predefined primary endpoint regarding the group ratio of percentage change from baseline in NT-proBNP levels at week 24 (ratio of percentage change − 0.48; 95% CI −0.13 to 1.59;*P*= 0.23 noninferiority). This finding may be due to the large proportion of patients with HF with preserved ejection fraction (HFpEF) (EF ≥50%), who may derive less clinical benefit than patients with HFrEF. On the other hand, the subgroup of patients with HFpEF receiving canagliflozin had a greater reduction in NT-proBNP and improvement in NYHA subclass compared to glimepiride.[83] The clinical impact of SGLT2 inhibitors on patients with HFpEF warrants further evaluation.

b. Mechanism of CV benefits

The exact mechanism behind the CV benefits seen with SGLT2 inhibitors remains uncertain. However, there are several proposed mechanisms to explain their CV effects, including weight loss, diuretic and natriuretic effects, blood pressure reduction, and effects on the sympathetic nervous system. Another potential mechanism for SGLT2 inhibitors is the inhibition of the sodium-hydrogen exchanger, leading to a reduction in cardiac injury, remodeling, and systolic dysfunction. Another proposed mechanism is that SGLT2 inhibitors may promote the myocardium's use of ketone bodies rather than free fatty acids and glucose, which may improve the efficiency and function of the heart.[1,32] To evaluate these mechanisms, the acute and 14-day effects of empagliflozin 10 mg on natriuresis, volume status, and neurohormonal activation were evaluated in combination with a loop diuretic in 20 patients with T2DM and stable HF. Empagliflozin augmented natriuresis and improved plasma volume.[89] Importantly, empagliflozin was not associated with electrolyte wasting, renal dysfunction, or neurohormonal activation.[89] This study

confirms that SGLT2 inhibitors may be an ideal diuretic option for the management of volume status in patients with HF and may contribute to the improved HF outcomes observed with these agents in the outcome trials discussed. Further studies are needed to better identify the exact mechanisms behind the CV benefits seen with SGLT2 inhibitors.

c. Safety and monitoring

Despite the many benefits of SLGT2 inhibitors, there are also several safety concerns worth noting. Genital mycotic infections, fractures, and euglycemic ketoacidosis are the most common side effects.[1] An increased incidence of bone fractures was reported with canagliflozin in the CANVAS trial, but not in the CANVAS-R trial. Several other meta-analyses and pooled analyses have not demonstrated an increased fracture risk, however consideration of a patient's risk of fracture may be reasonable prior to initiation.[1] Increased fracture risk has not been observed with other SGLT2 inhibitors.[78-80,82] Euglycemic ketoacidosis has been reported in patients receiving SGLT2 inhibitors, but the risk appears low.[1] One of the most debated adverse effects of SGLT2 inhibitors is lower limb amputations. An increased risk of lower limb amputations in patients receiving canagliflozin was observed in CANVAS and CANVAS-R.[79] However, patients with amputations frequently had lower limb infections, gangrene, and diabetic foot ulcers as precipitating factors.[79] On the other hand, the OBSERVE 4D study utilized data from 4 large US administrative claims databases and compared the rates of lower limb amputations in canagliflozin versus other SGLT2 inhibitors and versus non-SGLT2 inhibitor antidiabetic agents. Neither canagliflozin nor the other SGLT2 inhibitors increased amputation risk relative to non-SGLT2 inhibitors (HR 0.75; 95% CI 0.40-1.41;*P*= 0.25).[90] Nonetheless, canagliflozin has a black box warning for lower limb amputation on its FDA package labeling.[91] An increased risk for lower limb amputation was not seen in VERTIS CV (risk difference 0.1%; 95% CI −0.1 to 0.3).[81]

Last, SGLT2 inhibitors have diuretic and antihypertensive effects, which may lead to volume depletion and hypotension in some patients, although the risk appears low.[1] The FDA recommends discontinuing therapy during acute kidney injury or when eGFR is less than 30 mL/min/1.73 m^2 for dapagliflozin, 45 mL/min/1.73 m^2 for empagliflozin and less than 60 mL/min/1.73 m^2 for ertugliflozin, and renally dose adjusting when the eGFR is less than 60 mL/min/1.73 m^2 for canagliflozin.[88,91-93]

Conclusion

CVD is highly prevalent in patients with T2DM, and the literature surrounding the CV effects of antidiabetic agents continues to expand. An understanding of the CV effects of these agents can allow for optimization of patient outcomes. Careful attention should be given to the potential risks and costs of each agent prior to initiation. In general, the most robust cardiovascular benefits exist with GLP-1 agonists and SGLT2 inhibitors when added to metformin and should be strongly considered in most patients. It is becoming even more essential for cardiologists and providers of cardiovascular services to be familiar with these agents as they continue to expand from the endocrinology space and gain foothold in the cardiology realm in not only patients with diabetes but also in those without.

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