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REVIEW

Glucose-Lowering Therapies for Cardiovascular Risk Reduction in Type 2 Diabetes Mellitus: State-of-the-Art Review

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Abstract

Type 2 diabetes mellitus (T2DM) is a major cardiovascular (CV) risk factor. Although antihyperglycemic therapies have typically focused on glycemic control, a paradigm shift for the treatment of T2DM has occurred, with an increased focus on CV risk reduction. Clinicians should base their clinical decisions on the beneficial effects of specific glucose-lowering agents on CV outcomes, while avoiding those therapeutic strategies with potential detrimental effects. Importantly, the presence of comorbidities (eg, established cardiovascular diseases, hypertension, obesity) should also guide the clinical decision toward therapies proven to reduce CV outcomes in that specific population. In this state-of-the-art review resulting from a comprehensive literature search (Pubmed, Google Scholar), we summarize the evidence related to the CV outcomes trials reported in the past several decades. Finally, we propose a therapeutic plan for patients with T2DM, suggesting the use of specific glucose-lowering agents based on the characteristics and presence of comorbidities of the individual patient.

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Improved glycemic control is associated with reduced risk for microvascular complications in patients with diabetes.[1,2] However, glycemic control has failed to consistently reduce the risk for macrovascular complications and overall mortality, indicating either that lowering plasma glucose levels in itself does not prevent cardiovascular (CV) disease (CVD) or that the mechanism by which plasma glucose level is lowered is more important.[1] Some antihyperglycemic therapies also have been reported to increase CVD risk.[3] As a result, the US Food and Drug Administration (FDA) requires CV outcomes trials (CVOTs) for new therapies to determine CV safety in patients with type 2 diabetes mellitus (T2DM).

In this article, we review the effects of antihyperglycemic therapies on the development and progression of CVD (Table 1) and discuss how, despite similar glucose-lowering effects, different therapies may result in different CV effects. We conducted an electronic literature search of PubMed and Google Scholar limited to articles published in English between January 1, 1960, and May 1, 2018. The following key words and their combination were searched: *diabetes*, *cardiovascular outcomes*, *cardiovascular outcome trials*, *heart failure*, *cardiovascular death*, *lifestyle interventions*, *weight loss*, *glucose-lowering agents*, *antihyperglycemic agents*, *hypoglycemia*, *metformin*, *sulfonylurea*, *tolbutamide*, *thiazolidinediones*, *DPP-4 inhibitors*, *SGLT-2 inhibitors*, *GLP-1 receptor agonists*, *PPAR*, *troglitazone*, *tesaglitazar*, *pioglitazone*, *rosiglitazone*, *sitagliptin*, *alogliptin*, *linagliptin*, *saxagliptin*, *empagliflozin*, *canagliflozin*, *dapagliflozin*, *ertugliflozin*, *liraglutide*, *exenatide*, *lixisenatide*, *albiglutide*, *dulaglutide*, *semaglutide*, *insulin*, *glargine*, and *degludec*; 112 articles were considered appropriate for the objective of this state-of-the-art review.

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LIFESTYLE

Lifestyle intervention is a cardinal point for the prevention and management of T2DM, as highlighted by the reduction in incident diabetes in patients receiving lifestyle interventions.[21-26] Once T2DM is diagnosed, the effect of lifestyle intervention, particularly on CV outcomes, is less established.

ARTICLE HIGHLIGHTS

- Diabetes is a major risk factor for cardiovascular diseases.
- Antihyperglycemic agents, despite similar glucose-lowering effects, present different cardiovascular safety and efficacy profiles.
- Two sodium-glucose cotransporter 2 inhibitors, empagliflozin and canagliflozin, and 2 glucagon-like peptide 1 receptor agonists, liraglutide and semaglutide, have reduced cardiovascular events compared with placebo.
- Glucose-lowering agents should be tailored to the individual patient's comorbidities, and when possible, those that have documented cardiovascular benefit should be preferred.

The Look AHEAD (Action for Health in Diabetes) study randomized 5145 obese patients with T2DM, with and without prior CVD, to intensive weight-loss lifestyle intervention (caloric restriction and physical activity) or standard of care with diabetes education, with the goal of reducing body weight and improving long-term CV outcomes. Although weight and waist circumference losses and glucose control were significantly improved in the intensive treatment group compared with the standard of care group, the CV event rate reduction did not reach statistical significance after nearly 10 years of follow-up.[9] This result is possibly due to a lower than anticipated rate of CV events that rendered the study underpowered. A post hoc analysis of the Look AHEAD study revealed that larger weight loss led to lower incidence of CVD.[27,28] A significant 21% relative risk reduction (16.9 vs 14.3 events per 1000 person-years) for the primary end point (composite of the first occurrence of death from CV causes, nonfatal acute myocardial infarction, stroke, or admission to hospital for angina) and a significant 24% relative risk reduction (25.3 vs 21.2 events per 1000 person-years) for the secondary end point (primary end point in addition to death from any cause, myocardial infarction, stroke, or hospitalization for angina; death from any cause, myocardial infarction, stroke, hospitalization for angina, coronary artery bypass grafting, percutaneous coronary intervention, hospitalization for heart failure [HF], or peripheral vascular disease) in those patients who lost more than 10% of their body weight at the end of the study compared with those who maintained a stable body weight or increased weight over time. When compared with the control group receiving diabetes education but without intensive lifestyle intervention, more than 10% weight loss was still associated with significant reductions of the primary and secondary end points by 20% (16.8 vs 14.5 events per 1000 person-years) and 21% (24.6 vs 21.3 events per 1000 person-years), respectively,[28] thus highlighting the beneficial effects of weight loss, independent of the strategy used.

Finally, the results of the Look AHEAD study suggest that CV risk reduction can be achieved with weight loss—targeted interventions when the degree of weight loss exceeds 10%. However, because the Look AHEAD study did not meet the primary end point, the following analyses should be interpreted with caution.

METFORMIN

The biguanide metformin is recommended by both the American Diabetes Association[29] and the American Association of Clinical Endocrinologists[30] as the first-line oral agent for the management of T2DM. This recommendation is primarily due to its significant efficacy in lowering glycated hemoglobin (HbA_{1c}) (1.0%-1.5%),[31] negligible risk of hypoglycemia, and favorable effects on body weight and cost-effectiveness.[32,33]

Metformin is not without adverse effects, and its use is limited in selected patient populations. Gastrointestinal upset, notably diarrhea, is a common adverse effect of metformin and occurs in up to a third of patients. Although extended-release formulations have improved its tolerability, gastrointestinal upset can still occur. Additionally, the concern over the risk of lactic acidosis associated with its predecessors, phenformin and buformin,[34] does not seem to be associated with metformin.[35] However, the risk may persist in patients with severe renal dysfunction, moderate-severe hepatic dysfunction and those with acute congestive HF.

Although there is no prospective, randomized controlled clinical trial evaluating the CV effects of metformin, available data suggest

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TABLE 1. Effects of Glucose-Lowering Therapies on Major Cardiovascular Outcomes in Randomized Controlled Trials[a,b]

Reference, year	Intervention	Follow-up	No. of patients	Key inclusion criteria	Primary outcome	Primary outcome results	Key secondary findings
University Group Diabetes Program,[4] 1975	Insulin titrated to normal glucose levels, fixed-dosed insulin, placebo, or tolbutamide	8.5 y	823	Non–insulin-dependent diabetes mellitus	CV hospitalization Angina pectoris	Only crude event rates available: CV hospitalization: 5.2% (placebo) vs 5.8% (tolbutamide) vs 1.6% (insulin standard) vs 3.2% (insulin variable) Angina pectoris: 11.1% (placebo) vs 15.8% (tolbutamide) vs 8.6% (insulin standard) vs 10.2% (insulin variable)	NA
Dormandy et al (PROactive),[5] 2005	Pioglitazone target dose of 45 mg daily vs placebo	34.5 mo	5238	Established coronary or peripheral arterial disease	Composite of: • ACM • Nonfatal MI • Stroke • ACS • Revascularization • Above-ankle amputation	NS	16% decrease in secondary end point of ACM, nonfatal MI, and stroke (P=.027)
Home et al (RECORD),[6] 2009	Rosiglitazone target dose of 8 mg daily vs placebo	5.5 y	4447	Body mass index >25 kg/m^2	CV hospitalization or CV death	Met criteria for noninferiority; NS for superiority	Increased risk of HF hospitalizations in patients treated with rosiglitazone compared with placebo (2.7% vs 1.3%, P=.001)
ORIGIN Trial Investigators,[7] 2012	Insulin glargine titrated to a fasting plasma glucose level of ≤95 mg/dL or standard of care	6.2 y	12,537	Established CVD Type 2 diabetes mellitus, impaired glucose tolerance, impaired fasting glucose	Co-primary outcomes: • Nonfatal MI • Nonfatal stroke • CV death Plus • Revascularization • HF hospitalization	Met criteria for noninferiority; NS for superiority	20% decrease in new cases of diabetes in the insulin glargine group (P=.05)
White et al (EXAMINE),[8] 2013	Alogliptin 6.25-25 mg daily based on estimated glomerular filtration rate or placebo	40 mo	5380	Recent ACS (15-90 d)	Composite of: • CV death • Nonfatal MI • Nonfatal stroke	Met criteria for noninferiority; NS for superiority	No difference between groups in adverse effect profile

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TABLE 1. Continued

Reference, year	Intervention	Follow-up	No. of patients	Key inclusion criteria	Primary outcome	Primary outcome results	Key secondary findings
Look AHEAD Research Group,[9] 2013	Lifestyle intervention (caloric restriction and moderate-intensity exercise) vs diabetes support and education	9.6 y	5145	Body mass index >25 kg/m^2	Composite of: • CV death • Nonfatal MI • Nonfatal stroke • Hospitalization for angina	NS	Weight loss at 1 year: 8.6% vs 0.7% (P<0.05) Weight loss at study end: 6% vs. 3.5% (*P*<.05)
Scirica et al (SAVOR-TIMI 53),[10] 2013	Saxagliptin 2.5-5 mg daily or placebo	2.1 y	16,492	Established CVD or at least 2 CV risk factors	Composite of: • CV death • MI • Stroke	Met criteria for noninferiority; NS for superiority	27% increase in HF hospitalization (*P*=.007)
Zinman et al (EMPA-REG OUTCOME),[11] (2015)	Empagliflozin 10 mg or 25 mg once daily vs placebo	3.1 y	7020	Established CVD	Composite of: • CV death • Nonfatal MI • Nonfatal stroke	Met criteria for noninferiority and superiority 14% RRR, 1.6% ARR, NNT=62	32% decrease in ACM (*P*<.001) 38% decrease in CV death (*P*<.001) 35% decrease in HF hospitalizations (*P*=.002)
Pfeffer et al (ELIXA),[12] 2015	Lixisenatide target dose of 20 μg daily or placebo	2.1 y	6068	ACS within prior 180 d	Composite of: • CV death • MI • Stroke • Unstable angina	Met criteria for noninferiority; NS for superiority	No difference between groups in adverse effect profile
Green et al (TECOS),[13] 2015	Sitagliptin 50-100 mg daily based on estimated glomerular filtration rate or placebo	3 y	14,671	Established CVD	Composite of: • CV death • Nonfatal MI • Nonfatal stroke • Hospitalization for unstable angina	Met criteria for noninferiority; NS for superiority	No difference between groups in adverse effect profile
Kernan et al (IRIS),[14] 2016	Pioglitazone target dose of 45 mg daily vs placebo	4.8 y	3876	Recent cerebrovascular accident and HOMA-IR >3.0	Fatal or nonfatal stroke or MI	24% RRR, 2.8% ARR, NNT=36	Increased frequency of >4.5 kg weight gain, edema, and bone fracture but no increase in HF

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TABLE 1. Continued

Reference, year	Intervention	Follow-up	No. of patients	Key inclusion criteria	Primary outcome	Primary outcome results	Key secondary findings
Margulies et al (FIGHT),[15] 2016	Liraglutide target dose of 1.8 mg daily or placebo	6 mo	300	HF with EF ≤40% Recent HF hospitalization or daily oral furosemide dose ≥40 mg Type 2 diabetes mellitus: 59%	Global rank score using hierarchical testing across 3 tiers: • Time to death • Time to HF rehospitalization • Time-average % change in NT-proBNP	NS	Frequency of hypoglycemia was lower in the liraglutide group ($P<.001$) Trend toward increase in time to death or rehospitalization for HF in patients with T2DM treated with liraglutide (30% increase, $P=.07$)
Marso et al (LEADER),[16] 2016	Liraglutide target dose of 1.8 mg daily or placebo	3.8 y	9340	Established CVD or at least 1 CV risk factor	Composite of: • CV death • Nonfatal MI • Nonfatal stroke	13% RRR, 1.9% ARR, NNT=53	15% decrease in ACM ($P=.02$) 22% decrease in CV death ($P=.007$) No difference in HF hospitalization
Marso et al (SUSTAIN-6),[17] 2016	Semaglutide 0.5 mg, 1 mg once weekly or placebo	2.1 y	3297	Established CVD or CKD with at least one CV risk factor	Composite of: • CV death • Nonfatal MI • Nonfatal stroke	Met criteria for noninferiority and superiority 26% RRR, 2.3% ARR, NNT=43	26% decrease in nonfatal stroke ($P=.04$) No difference in ACM, CV death, or HF hospitalizations
Neal et al (CANVAS),[18] 2017	Canagliflozin 100 mg or 300 mg daily vs placebo	3.6 y	10,142	Established CVD or age >50 y and 2 CV risk factors	Composite of: • CV death • Nonfatal MI • Nonfatal stroke	Met criteria for noninferiority and superiority 14% RRR[c]	33% decrease in HF hospitalizations (95% CI, 0.52-0.87) Increase in risk of lower limb amputation (6.3 vs 3.4 participants per 1000 patient-years, $P<.001$)
Marso et al (DEVOTE),[19] 2017	Insulin degludec or glargine titrated to a fasting plasma glucose level of 71-90 mg/dL or 90-126 mg/dL if high risk for hypoglycemia	2 y	7637	Established CV or renal disease or age ≥60 y and at least 1 CV risk factor	Composite of: • CV death • Nonfatal MI • Nonfatal stroke	Met criteria for noninferiority; NS for superiority	Frequency of hypoglycemia was lower in the insulin degludec group ($P<.001$)

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TABLE 1. Continued

Reference, year	Intervention	Follow-up	No. of patients	Key inclusion criteria	Primary outcome	Primary outcome results	Key secondary findings
Holman et al (EXSCEL),[20] 2017	Exenatide 2 mg once weekly or placebo	3.2 y	14,752	Type 2 diabetes with or without CVD	Composite of: • CV death • Nonfatal MI • Nonfatal stroke	Met criteria for noninferiority; NS for superiority	No difference between groups in adverse effect profile

[a]ACM = all-cause mortality; ACS = acute coronary syndrome; ARR = absolute risk reduction; CANVAS = Canagliflozin Cardiovascular Assessment Study; CANVAS-R = Study of the Effects of Canagliflozin on Renal Endpoints in Adult Participants With Type 2 Diabetes Mellitus; CKD = chronic kidney disease; CV = cardiovascular; CVD = CV death; DEVOTE = Trial Comparing Cardiovascular Safety of Insulin Degludec Versus Insulin Glargine in Patients With Type 2 Diabetes at High Risk of Cardiovascular Events; ELIXA = Evaluation of Lixisenatide in Acute Coronary Syndrome; EMPA-REG OUTCOME = Empagliflozin Cardiovascular Outcome Event Trial in Type 2 Diabetes Mellitus Patients—Removing Excess Glucose; EXAMINE = Alogliptin After Acute Coronary Syndrome in Patients With Type 2 Diabetes; EXSCEL = Exenatide Study of Cardiovascular Event Lowering; FIGHT = Functional Impact of GLP-1 for Heart Failure Treatment; HF = heart failure; HOMA-IR = homeostasis model assessment of insulin resistance; IRIS = Insulin Resistance Intervention After Stroke; LEADER = Liraglutide Effect and Action in Diabetes: Evaluation of Cardiovascular Outcome Results; Look AHEAD = Action for Health in Diabetes; MI = myocardial infarction; NA = not available; NNT = number needed to treat; NS = not significant; NTproBNP = N-terminal pro-B-type natriuretic peptide; ORIGIN = Outcome Reduction With Initial Glargine Intervention; PROactive = Prospective Pioglitazone Clinical Trial in Macrovascular Events; RECORD = Rosiglitazone Evaluated for Cardiovascular Outcomes and Regulation of Glycaemia in Diabetes; RRR = relative risk reduction; SAVOR-TIMI 53 = Saxagliptin Assessment of Vascular Outcomes Recorded in Patients with Diabetes Mellitus—Thrombolysis in Myocardial Infarction 53; SUSTAIN-6 = Trial to Evaluate Cardiovascular and Other Long-term Outcomes With Semaglutide in Subjects With Type 2 Diabetes; TECOS = Trial Evaluating Cardiovascular Outcomes with Sitagliptin.

[b]SI conversion factors: To convert glucose values to mmol/L, multiply by 0.0555.

[c]Because of different treatment allocation ratio and different follow-up time in CANVAS and CANVAS-R, ARR and NNT could not be calculated.

that metformin has favorable CV effects in patients with T2DM. In the UK Prospective Diabetes Study in which patients were randomized to "conventional" vs intensive glycemic control, metformin decreased myocardial infarction risk by 39%, diabetes-related deaths by 32%, and all-cause mortality by 36% in a subgroup of overweight and obese patients with T2DM.[36] Such results, although promising, only resulted from a small number of events (98 [29.8 events per 1000 patient-years] vs 160 [43.3 events per 1000 patient-years] for the metformin added group and the conventional treatment group, respectively). The benefits of metformin have been suggested in meta-analyses of all clinical trials.[37-40]

Given that metformin is currently considered the standard of care, most patients enrolled in CVOTs received metformin at baseline. Because of the low cost of metformin and generally favorable adverse effect profile, it seems likely that metformin will remain preferred as initial therapy.

SULFONYLUREA

Sulfonylureas improve glycemic control by stimulating pancreatic beta-cell production of insulin.[41] First-generation therapies in this class, including chlorpropamide and tolbutamide, were very long-acting, resulting in a high risk of hypoglycemia.[42,43] Second-generation therapies, such as glipizide, have a shorter half-life and lower risk of hypoglycemia. Sulfonylureas can also cause considerable weight gain,[44] making them less preferred in patients who are overweight or obese. Because of their low cost and ability to significantly lower HbA_{1c} levels by as much as 2%, current guidelines recommend sulfonylureas as second-line agents for use in combination with metformin in selected patients without established CVD.[29]

The earliest data regarding the CV safety of sulfonylureas comes from the University Group Diabetes Program, which randomized 823 patients to standard-dosed ultralente insulin (10-16 U/d), variable-dosed ultralente insulin, placebo, or tolbutamide.[4] One year into the study, phenformin and an appropriate placebo was added. Cardiovascular-related mortality was 2.5-fold higher in the tolbutamide group[45] compared with diet alone, which led

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the investigators to discontinue the tolbutamide arm of the study. Given the similarities in chemical structure and mechanism of action of all sulfonylureas, the FDA added a special warning on the increased risk of CV mortality to all drugs in the sulfonylurea class.

The 10-year posttrial monitoring of the UK Prospective Diabetes Study, however, found a significant reduction in the risk for myocardial infarction and mortality from any cause in the intensive therapy group receiving sulfonylurea-insulin compared with conventional therapy, suggesting that although perhaps not an optimal strategy, glucose lowering with sulfonylurea-insulin combination is still effective.[39] However, the combination of sulfonylurea and metformin has been associated with an increased risk of diabetes-related and all-cause mortality and myocardial infarction compared with metformin alone.[46] Subsequent meta-analyses in recent years using randomized clinical trial data or observational data have also found conflicting results.[47,48] The ongoing CAROLINA (Cardiovascular Outcome Trial of Linagliptin Versus Glimepiride in Type 2 Diabetes) study, which is comparing the CV safety of linagliptin to glimepiride, may offer additional insight on the CV safety of sulfonylureas.[49]

Considering that sulfonylureas present a very high risk of hypoglycemia and induce weight gain, both major risk factors for CVD, and the FDA label suggests the potential increased risk for CV mortality, they should be considered a last-line option compared with the other glucose-lowering strategies. This is true in patients without established CVD but is particularly important for those with established CVD, who are already at high risk for development of future cardiac events.

THIAZOLIDINEDIONE

The peroxisome proliferator—activated receptor (PPAR) is a nuclear membrane-bound, ligand-activated transcription factor that activates or inhibits a portfolio of genes and thus possesses diverse biological actions.[50,51] Furthermore, the biology of PPAR agonism and related physiologic effects can differ across species (ie, mouse vs human) and across receptor subtypes (α, γ, δ).[50]

Troglitazone was associated with potentially fatal hepatotoxicity; tesaglitazar, a dual PPAR-α and PPAR-γ agonist, was associated with renal impairment; rosiglitazone increases low-density lipoprotein cholesterol (LDL-C) but has a neutral effect on triglycerides; pioglitazone has a neutral effect on LDL-C and reduces triglycerides.[52] Pioglitazone partially activates the PPAR-α in addition to PPAR-γ, which may explain its favorable lipid profile effects, although aleglitazar, a dual PPAR-α and PPAR-γ agonist, increases LDL-C. Thus, the clinical effects of pharmacological PPAR agonists must be evaluated on an individual basis.

Cardiovascular outcomes have been evaluated for the PPAR-γ agonists rosiglitazone, pioglitazone, aleglitazar, and muraglitazar. The development of the dual PPAR-α and PPAR-γ agonists muraglitazar and aleglitazar were halted because of a significantly increased risk of major CV events.[53,54] Pioglitazone appears to have neutral or antiatherogenic effects, whereas rosiglitazone may increase the risk of CVD, consistent with their differential effects on intermediate end points such as LDL-C. All PPAR-γ agonists have been associated with an increase in the risk of HF.[55] Peroxisome proliferator—activated receptor γ agonists increase fluid retention by inhibiting sodium reabsorption and enhancing vascular permeability, which can be problematic in patients with HF.[3] Consequently, PPAR-γ agonists are contraindicated in patients with symptomatic HF.[3]

In the Prospective Pioglitazone Clinical Trial in Macrovascular Events (PROactive) study, patients with T2DM and established CVD were randomized to either pioglitazone or placebo.[5] The primary end point was time to all-cause mortality, nonfatal myocardial infarction, stroke, acute coronary syndrome, endovascular or surgical intervention on the coronary or leg arteries, or amputation above the ankle. Among 5238 randomized patients, there was no significant difference between pioglitazone and placebo with respect to the primary end point. The main secondary end point of all-cause mortality, nonfatal myocardial infarction, and stroke was, however, significantly lower in the pioglitazone arm, but the number of patients with new-onset HF was greater in the pioglitazone arm than in the placebo group. The mechanism by which pioglitazone increases HF appears to

be related to increased sodium and water retention[56] and not due to a negative effect on the heart.[57]

The antiatherosclerotic effects of pioglitazone in patients with prior ischemic stroke or transient ischemic attack but without diabetes were studied in the more recent Insulin Resistance Intervention After Stroke (IRIS) trial.[14] Patients with insulin resistance, defined as homeostasis model of assessment of insulin resistance value greater than 3.0, but without T2DM were eligible. Patients with HF were excluded. During a median 4.8 years of follow-up, the primary outcome of stroke or myocardial infarction was significantly lower in the pioglitazone arm compared with placebo. In an additional analysis of the IRIS study, pioglitazone was also associated with a reduction in acute coronary syndrome.[58] The IRIS study further supports the beneficial CV effects of pioglitazone, except for HF.[59,60]

The Rosiglitazone Evaluated for Cardiovascular Outcomes and Regulation of Glycaemia in Diabetes (RECORD) trial was a randomized, open-label, active-control trial designed to assess the noninferior CV safety of rosiglitazone against metformin or a sulfonylurea.[6] The primary end point and noninferiority margin were set as the composite of CV death and CV hospitalization and 1.20 for the hazard ratio, respectively. Patients with HF or a major CV event within the previous 3 months were excluded.

During a mean 5.5 years of follow-up for 4447 patients, the primary end point did not significantly differ between rosiglitazone and control, and therefore, rosiglitazone met the primary end point of noninferiority. The risk of myocardial infarction was numerically higher in the rosiglitazone arm, whereas the risk of stroke was numerically lower in the rosiglitazone arm. Rosiglitazone did, however, double the risk of HF.

An increased risk of myocardial infarction with rosiglitazone therapy has also been observed in several meta-analyses,[59-62] including one that excluded short-term studies and studies that did not prespecify the analysis of CV outcomes.[63] The relative risk of myocardial infarction in meta-analyses has been estimated at 1.40, whereas the randomized RECORD trial demonstrated a smaller effect size (relative risk, 1.14), which is similar to the expected effect size based on rosiglitazone's effect on LDL-C.[64] Although a causal role for rosiglitazone with respect to CVD remains debatable,[65] rosiglitazone should be utilized as a last-line glucose-lowering PPAR agonist or, considering the broad choice of antihyperglycemic therapies, avoided in patients with or at risk for CVD.

DIPEPTIDYL PEPTIDASE 4 INHIBITORS

Incretins were discovered after investigators noticed that the administration of intravenous glucose exerted a lower insulin secretion response compared with the oral administration, which led to the theory that the gastrointestinal tract exerted control over insulin secretion.[66-68] Briefly, glucagon-like peptide 1 (GLP-1) produced by the L cells in the gut stimulates the secretion of insulin from the pancreatic beta cells in response to a carbohydrate-rich meal, slows gastric emptying inducing satiety, and reduces the endogenous production of glucagon during fasting states, therefore improving postprandial as well as fasting glycemia.[69-72] The half-life of GLP-1 is extremely short as it is cleaved by the dipeptidyl peptidase 4 (DPP-4).[72,73] The activity of DPP-4 is increased in obese individuals and those with diabetes, therefore reducing the availability of GLP-1.[72,74,75] Treatment with DPP-4 inhibitors improves glycemic control by restoring the physiologic levels of GLP-1.

Currently, 4 DPP-4 inhibitors are clinically available for the treatment of T2DM as an adjunct to diet and exercise based on their efficacy in reducing HbA_{1c}: alogliptin, saxagliptin, sitagliptin, and linagliptin. The DPP-4 inhibitors induce a modest reduction in HbA_{1c} of 0.5% to 0.8%, with an extremely low risk of hypoglycemia.

Although a number of preclinical studies suggested that DPP-4 inhibitors may exert beneficial CV effects, DPP-4 inhibitors do not represent an effective therapeutic strategy for CV risk reduction in patients with T2DM[76] and, in some circumstances, may even be harmful. To date, the results of 3 CVOTs have been published to establish CV safety and efficacy of alogliptin, saxagliptin, and sitagliptin. The CVOTs for linagliptin are ongoing. The CARMELINA (Cardiovascular and Renal Microvascular Outcome Study

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With Linagliptin in Patients With Type 2 Diabetes Mellitus) trial will compare the CV effects of linagliptin with placebo, while the CAROLINA study will compare the CV effects of linagliptin with glimepiride.[49]

The EXAMINE (Alogliptin After Acute Coronary Syndrome in Patients With Type 2 Diabetes) trial[8] was a double-blind noninferiority trial that randomized 5380 patients with T2DM and recent (15-90 days) acute coronary syndrome (myocardial infarction or unstable angina requiring hospitalization) to alogliptin or placebo in addition to standard of care for up to 40 months. Alogliptin significantly reduced HbA_{1c} levels by 0.36% compared with placebo without significant changes in body weight. Alogliptin met the primary end point for noninferiority compared with placebo (composite of death from CV causes, nonfatal myocardial infarction, or nonfatal stroke) but was not superior to placebo.[77] A post hoc analysis showed a nonsignificant 19% relative risk increase (0.9% absolute risk increase) of time to first event of hospitalization for HF but without affecting HF-related outcomes (ie, CV death and hospital admission for HF). The prescribing information now includes a warning for increased HF risk in the alogliptin label, "particularly in patient with established heart or kidney disease."

The CV safety of saxagliptin has been tested in the double-blind noninferiority to placebo trial SAVOR-TIMI 53 (Saxagliptin Assessment of Vascular Outcomes Recorded in Patients With Diabetes Mellitus—Thrombolysis in Myocardial Infarction 53)[10] on a slightly different study population compared with EXAMINE. In SAVOR-TIMI 53, more than 16,000 patients with T2DM and high risk for CV events were randomized to saxagliptin or placebo for up to 2.9 years, with a median follow-up of 2.1 years. Saxagliptin was noninferior to placebo. The primary end point (CV death, nonfatal myocardial infarction, or nonfatal ischemic stroke) occurred at a similar rate in the saxagliptin and the placebo groups. However, a significant 27% relative risk increase for HF hospitalizations was found in the saxagliptin group (3.5% and 2.8% of patients in the saxagliptin and placebo groups, respectively), which occurred as early as 6 months from randomization until the end of the study, particularly in patients with prior HF or chronic kidney disease.[78] Based on these results, similar to alogliptin, saxagliptin prescribing information includes a warning to reflect increased HF risk.

The TECOS (Trial Evaluating Cardiovascular Outcomes With Sitagliptin) study[13] assessed CV safety of sitagliptin in 14,671 patients with established CVD in a double-blind placebo-controlled fashion. Sitagliptin reduced HbA_{1c} by 0.29% and was found to be noninferior for both the composite primary (CV death, nonfatal myocardial infarction, nonfatal stroke, or hospitalization for unstable angina) and the secondary end points (first confirmed event of CV death, nonfatal myocardial infarction, or nonfatal stroke). Sitagliptin did not increase the risk of HF compared with placebo.[79]

SODIUM-GLUCOSE COTRANSPORTER 2 INHIBITORS

Sodium-glucose cotransporters (SGLTs) are membrane proteins involved in the transport of glucose, vitamins, amino acids, and ions found in the brush border of the gut epithelium, in the proximal renal tubules, and in the heart.[80-82] The most studied SGLTs are SGLT-1 and SGLT-2, located in the proximal kidney tubule where they mediate glucose reabsorption at the glomerulus level.[81] Sodium-glucose cotransporter 1 is also highly expressed in the gut, where it facilitates glucose absorption, and was recently found also in the heart, although its cardiac role is still unclear.

Sodium-glucose cotransporter 2 inhibitors (and SGLT-1 to a smaller extent) reduce the glucose renal threshold and increase glucose excretion in the urine by 60 to 100 g/d, therefore acting through an insulin-independent manner. Sodium-glucose cotransporter 2 inhibitors also significantly improve blood pressure,[83,84] body weight, body composition,[85] as well as other CV risk factors.[86] Conversely, they do increase LDL-C levels slightly, but this increase does not appear to be clinically important. Sodium-glucose cotransporter 2 inhibitors are associated with a low risk of hypoglycemia compared with other glucose-lowering agents (eg, sulfonylurea).[87] To date, 4 SGLT-2 inhibitors (empagliflozin, canagliflozin, dapagliflozin, and ertugliflozin) are

clinically available and can reduce HbA_{1c} levels by 0.5% to 1.0%.

Although the CVOTs for empagliflozin and canagliflozin have been completed and the results published, the CVOTs for dapagliflozin (Multicenter Trial to Evaluate the Effect of Dapagliflozin on the Incidence of Cardiovascular Events—Thrombolysis in Myocardial Infarction 58 [DECLARE-TIMI 58])[88] and ertugliflozin (Cardiovascular Outcomes Following Ertugliflozin Treatment in Type 2 Diabetes Mellitus Participants With Vascular Disease [VERTIS CV]) are still ongoing. The DECLARE-TIMI 58 study will help address the question of whether SGLT-2 inhibitors can be effective in primary prevention for CVD, as tested in a subgroup of the canagliflozin CVOT. In the meantime, although not resulting from a randomized, controlled trial, a recent real-world observational analysis reported a 39% relative risk reduction of HF hospitalization in patients with diabetes who initiated treatment with SGLT-2 inhibitors compared with other glucose-lowering agents, as well as a 51% relative risk reduction in all-cause mortality.[89]

The CV safety and efficacy of empagliflozin was evaluated in the double-blind placebo-controlled EMPA-REG OUTCOME trial (Empagliflozin Cardiovascular Outcome Event Trial in Type 2 Diabetes Mellitus Patients—Removing Excess Glucose)[11] in which 7020 patients with history of long-standing T2DM and established CVD were randomized to receive empagliflozin, 10 mg or 25 mg, or placebo for 4 years. After 12 weeks from treatment initiation, the investigators were encouraged to adjust concomitant glucose-lowering therapy to achieve glycemic control. At study end, empagliflozin reduced HbA_{1c} by 0.3% compared with placebo. Empagliflozin significantly reduced the incidence of the primary end point (composite of death from CV causes, nonfatal myocardial infarction excluding silent myocardial infarction, or nonfatal stroke) vs placebo, with a 14% relative risk reduction (43.9 vs 37.4 events per 1000 person-years). These effects were driven by a 38% relative risk reduction of death from CV causes (20.2 vs 12.4 events per 1000 person-years) and a 32% relative risk reduction of death from any cause (28.6 vs 19.4 events per 1000 person-years). Moreover, empagliflozin decreased the risk of hospitalization for HF by 35% (14.5 vs 9.4 events per 1000 person-years), and this effect occurred in patients with and without established HF at study enrollment and with different baseline risk of HF.[90]

Overall, empagliflozin was safe and effective from CV standpoints. Although a nonsignificant increase in stroke was reported in the EMPA-REG OUTCOME trial,[11] a subsequent analysis of the study suggested that empagliflozin did not increase the risk of cerebrovascular events.[91] Empagliflozin was associated with an increase in genitourinary infections, largely related to increased genital yeast infections.[11] Despite concerns related to potential diabetic ketoacidosis[92] and bone fractures[93] seen previously in patients treated with SGLT-2 inhibitors, no increase in these end points were seen in the EMPA-REG OUTCOME trial.

Empagliflozin became the first glucose-lowering drug proven to reduce CV mortality in an appropriately designed clinical trial. As such, the prescribing information now includes the beneficial effects in reducing CV death. The CV effects seen despite minor improvements in HbA_{1c} suggested that such results were unrelated to the glucose-lowering effects of empagliflozin. The CV benefits appeared very early in the trial, supporting a glucose-lowering–independent mechanism. However, HF events and HF-related characteristics (eg, left ventricular ejection fraction) were not well described, and ongoing trials with empagliflozin and other SGLT-2 inhibitors in HF are currently open to enrollment.[94] Moreover, clinical trials in patients without diabetes are also ongoing.[94]

The CV safety and efficacy of canagliflozin were tested in the CANVAS Program[18] that included the results of 2 trials: the CANVAS (Canagliflozin Cardiovascular Assessment Study) and the CANVAS-R (Study of the Effects of Canagliflozin on Renal Endpoints in Adult Participants With Type 2 Diabetes Mellitus). The CANVAS Program enrolled 10,142 patients with T2DM (HbA_{1c} >7.0% and <10.5%) who were 30 years or older with a history of symptomatic atherosclerotic CVD or 50 years or older with at least 2 CVD risk factors to canagliflozin, 100 mg or 300 mg, or placebo in the CANVAS study

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and to canagliflozin, 100 mg, and optional increase to 300 mg after 13 weeks of treatment or placebo in the CANVAS-R trial, therefore testing the effects of canagliflozin in both primary and secondary prevention for CVD. This protocol contrasts that of the EMPA-REG OUTCOME trial, in which empagliflozin was only tested in patients with established CVD. Patients randomized to canagliflozin had a significant reduction in HbA_{1c} at the end of the trial of about 0.6% compared with placebo. Canagliflozin was found to be superior to placebo in regard to the composite primary end point (death from CV causes, nonfatal myocardial infarction, or nonfatal stroke) with a 14% relative risk reduction compared with placebo (31.5 vs 26.9 events per 1000 person-years). Canagliflozin did not significantly reduce any of the individual outcomes measured in the composite or death from any cause. A 33% relative risk reduction of HF hospitalization was seen in patients treated with canagliflozin (8.7 vs 5.5 events per 1000 person-years). Importantly, the composite end point for CV death and hospitalizations for HF was significantly lower in patients treated with canagliflozin compared with placebo by 22% (20.3 vs 16.3 events per 1000 person-years).[95] Because the CANVAS Program was designed using a sequential hypothesis plan, and because CV death and all-cause mortality were not significantly reduced, the HF hospitalization finding should be interpreted with caution.

Although total serious adverse events reported with canagliflozin were significantly lower compared with placebo, patients randomized to canagliflozin experienced an increased risk of lower limb amputation (6.3 vs 3.4 participants per 1000 patient-years), with the majority being the toe and the metatarsal. The risk of amputation was higher in patients with prior amputation. The prescribing information for canagliflozin includes an increased risk of amputation. A significant increase in fractures was also reported in patients treated with canagliflozin, but when the CANVAS and CANVAS-R studies were analyzed separately, fractures were increased in the CANVAS trial but not in the CANVAS-R study. The differences reported in the 2 studies are not clear and require further investigation. A significant increase in genitourinary infection was seen with canagliflozin,[18] mostly due to an increase in genital yeast infections in men. Although diabetic ketoacidosis was also increased, it occurred at an extremely low rate and did not reach statistical significance.

Importantly, the beneficial effects of canagliflozin, as well as adverse effects (eg, amputations), were present both in patients with established CVD at baseline and in those with risk factors, suggesting that the CV effects of canagliflozin are consistent in both primary and secondary prevention.[96] The beneficial CV effects of canagliflozin cannot be explained by the improvements in glycemic control, particularly because the effects were found within weeks of trial initiation. The hospitalizations for HF seen in the CANVAS study have not been well characterized, and clinical trials with canagliflozin in patients with HF are ongoing.

GLP-1 RECEPTOR AGONISTS

Like the DPP-4 inhibitors reviewed previously, GLP-1 receptor agonists (RAs) also augment the incretin system to improve glycemic control.[72] In addition to increasing postprandial insulin secretion, GLP-1RAs also reduce glucagon secretion, contributing to improved fasting glycemia. Moreover, GLP-1 is highly involved in the food intake—satiety process, and increased GLP-1 is associated with slowing gastric emptying and direct effects on the central nervous system, which promotes satiety. Such effects result in sustained weight loss, to the extent that one of the GLP-1RAs, liraglutide, is clinically available for the treatment of obesity at a higher dose (3.0 mg/d).[97] When excessive, however, the beneficial effects on satiety can lead to intolerance by inducing nausea and vomiting. Importantly, GLP-1 receptors are not only located on the beta cell of the pancreas but also in the heart and vasculature.[69]

Glucagon-like peptide 1 RAs induce a variable reduction of HbA_{1c} between 0.5% and 1.5%. Similar to DPP-4 inhibitors, GLP-1RAs present very low risk for hypoglycemia given that their effects are glucose dependent. Glucagon-like peptide 1 RAs also improve body composition and have a modest effect on blood pressure. Six GLP-1RAs are clinically available: liraglutide, exenatide, lixisenatide,

TABLE 2. Summary of Guidelines-Recommended Use of Sodium-Glucose Cotransporter 2 Inhibitors and Glucagon-Like Peptide 1 Receptor Agonists for Reducing Cardiovascular Risk

Guideline	Recommendations	Evidence grade
Canadian Diabetes Association clinical practice guidelines,[109] 2016	• Empagliflozin should be considered in patients with diabetes and established CVD • Liraglutide should be considered in patients ≥50 y with diabetes and established CVD	Grade 1, level 1A Grade 1, level 1A (if <50 y, Grade D)
European Guidelines on CVD prevention in clinical practice,[110] 2016	• SGLT-2 inhibitors should be considered in patients with diabetes and established CVD	Class IIa, level B
European Society of Cardiology position paper on noninsulin antidiabetic pharmacotherapy in patients with CVD,[111] 2018	• Antidiabetic pharmacotherapy should be selected according to effects on cardiovascular risk in patients with diabetes and established CVD • Empagliflozin and liraglutide may be considered preferred treatment choices	Not provided
ACC Expert Consensus Decision Pathway for optimization of heart failure treatment,[112] 2018	• Consider SGLT-2 inhibitors in patients with heart failure and diabetes and follow current ADA Standards of Care	Intermediate
ADA Standards of Medical Care in Diabetes,[29] 2018	• Empagliflozin or liraglutide should be considered in diabetic patients with established CVD receiving lifestyle management and metformin • Canagliflozin may also be considered in diabetic patients with established CVD receiving lifestyle management and metformin	Grade A Grade C
ACE/AACE comprehensive type 2 diabetes management algorithm,[30] 2018	• GLP-1 receptor agonists and SGLT-2 inhibitors are recommended as preferred add-on agents to lifestyle management and metformin	Not provided

AACE = American Association of Clinical Endocrinologists; ACC = American College of Cardiology; ACE = American College of Endocrinology; ADA = American Diabetes Association; CVD = cardiovascular disease; GLP = glucagon-like peptide; SGLT = sodium-glucose cotransporter.

albiglutide, dulaglutide, and semaglutide. Although CVOT results have been reported for liraglutide, exenatide, lixisenatide, and semaglutide, the CVOTs for albiglutide and dulaglutide are still ongoing. Importantly, although semaglutide has shown highly promising CV effects in the SUSTAIN-6 (Trial to Evaluate Cardiovascular and Other Long-term Outcomes With Semaglutide in Subjects With Type 2 Diabetes) study, a postmarketing CVOT is also ongoing.

Both liraglutide and semaglutide have shown a beneficial CV profile,[16,17] whereas lixisenatide and exenatide have a neutral CV profile.[12,20] Of note, exenatide was found to have favorable effects on selected secondary end points (eg, death from any cause).[20] However, dedicated trials in patients with HF with reduced ejection fraction have reported controversial results when a GLP-1RA strategy was implemented.[15]

Lixisenatide is a once-daily GLP-1RA, and its CV safety and efficacy was tested in the ELIXA study (Evaluation of Lixisenatide in Acute Coronary Syndrome), a double-blind randomized placebo-controlled study.[12] A total of 6068 diabetic patients 30 years or older were randomized to lixisenatide once-daily subcutaneous injections or volume-matched placebo within 180 days from an acute coronary syndrome and were followed up for a median of 25 months. Patients began

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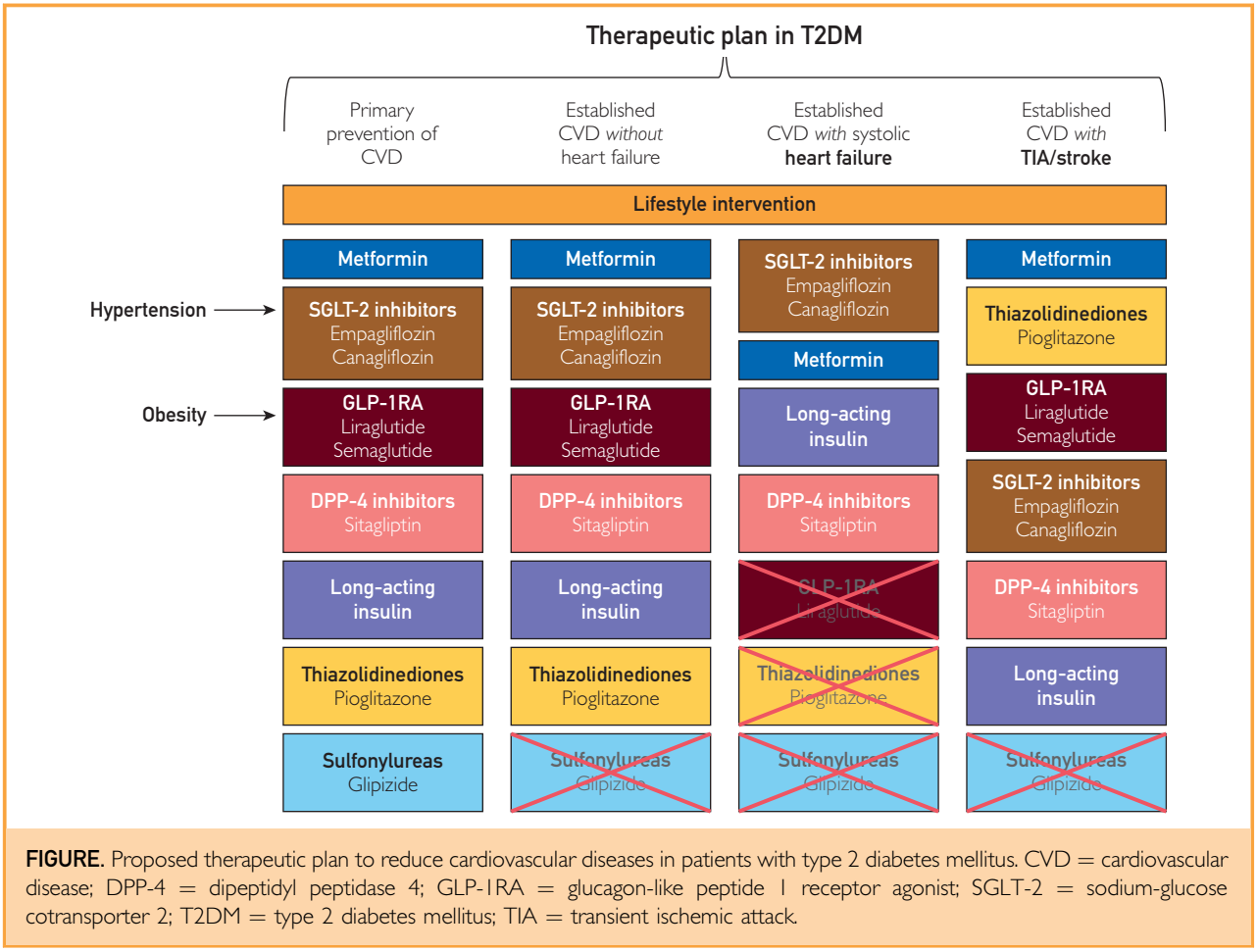

FIGURE. Proposed therapeutic plan to reduce cardiovascular diseases in patients with type 2 diabetes mellitus. CVD = cardiovascular disease; DPP-4 = dipeptidyl peptidase 4; GLP-1RA = glucagon-like peptide 1 receptor agonist; SGLT-2 = sodium-glucose cotransporter 2; T2DM = type 2 diabetes mellitus; TIA = transient ischemic attack.

treatment with lixisenatide, 10 μg, or volume-matched placebo for 2 weeks, and then, at the discretion of the investigator, the dose was increased up to 20 μg. Before randomization, patients underwent a 1-week run-in period of unblinded placebo to learn how to self-administer the subcutaneous daily injections. Lixisenatide reduced HbA_{1c} levels by 0.27% and was noninferior to placebo in respect to the primary composite CV outcome (CV death, myocardial infarction, stroke, or hospitalization for unstable angina). Lixisenatide presented a good overall safety profile—serious gastrointestinal-related adverse events were not increased compared with placebo.

The Liraglutide Effect and Action in Diabetes: Evaluation of Cardiovascular Outcome Results (LEADER) study tested the CV safety of liraglutide compared with placebo in 9340 patients with diabetes 50 years or older with an established CVD or 60 years or older if presenting with at least one or more CVD risk factors.[16] After a median follow-up of 3.8 years, liraglutide induced a significant HbA_{1c} reduction (0.40%) and met the primary end point for noninferiority compared with placebo. Importantly, liraglutide also showed a statistically significant 13% relative risk reduction for the composite primary end point (death from CV causes, nonfatal myocardial infarction, or nonfatal stroke) (39 vs 34 events per 1000 person-year), a 22% relative risk reduction for CV death (16 vs 12 events per 1000 person-year), and a 15% relative risk reduction for death for any cause (25 vs 21 events per 1000 person-year). The individual CV end points (ie, nonfatal myocardial infarction, nonfatal stroke) were not significantly

reduced, although myocardial infarction, which was not included in the primary composite end point, was significantly reduced by liraglutide. Heart failure—related hospitalizations were not different between the liraglutide and placebo groups. Based on the impressive CV benefits reported in the LEADER study, liraglutide, similar to empagliflozin, received a change in the label to include the reduction in CV events. Although the beneficial CV effects of liraglutide in the LEADER trial were remarkable, they were less pronounced than those reported with empagliflozin in the EMPA-REG OUTCOME trial. We could speculate that such a difference can be partly explained by the fact that in the EMPA-REG OUTCOME trial more patients had an established CVD, whereas in the LEADER study, a proportion of patients were only at high risk for CVD, therefore accounting for a smaller number of events.

The most common adverse effects reported with liraglutide were gastrointestinal. In addition, liraglutide was associated with greater risk of acute gallstone disease and injection-site reactions. There are also some safety concerns with liraglutide in patients with HF. Although the LEADER study found a nonsignificant 13% relative risk reduction in hospitalization for HF with liraglutide, in the Functional Impact of GLP-1 for Heart Failure Treatment (FIGHT) study, patients with and without diabetes and with advanced HF and reduced ejection fraction, liraglutide was associated with a trend toward harm in patients randomized to liraglutide, and this trend appeared to be more evident in patients with diabetes.[15] It has been hypothesized that in patients with more advanced HF already presenting with a catabolic state associated with greater reduction of lean mass, liraglutide, by promoting weight loss, may also favor lean mass loss.[98] The FIGHT trial, however, did not assess body composition to test this hypothesis. Moreover, liraglutide induces an increase in heart rate by 3 to 8 beats/min, which is associated with poor clinical outcomes in HF with reduced ejection fraction.[99] In fact, therapeutics reducing heart rate reduce HF hospitalizations, at least in patients with HF and reduced ejection fraction.[100] Additional studies are warranted to further explore potential mechanisms to explain the associated harm with liraglutide in patients with HF.

The CV safety of semaglutide was tested in the preapproval SUSTAIN-6 study[17] comparing semaglutide with placebo. SUSTAIN-6 enrolled only 3297 patients with diabetes aged 50 years or older with established CVD, chronic HF, or chronic kidney disease or 60 years of age and at least one CV risk factor. Patients underwent a dose-escalation protocol, starting with subcutaneous injection of 0.25 mg/d for 4 weeks and then escalated to 0.5 mg to reach the maintenance dose (0.5 mg or 1.0 mg) of semaglutide throughout the duration of the study.

After a median of 2.1 years, semaglutide induced a reduction in HbA_{1c} of 1.1% with 0.5 mg and 1.4% with 1.0 mg compared with placebo. In regard to the primary composite CV end point (death from CV causes, nonfatal myocardial, or nonfatal stroke), semaglutide reduced the incidence of the primary end point for safety, showing noninferiority compared with placebo. Semaglutide was also superior to placebo, showing a 26% relative risk reduction for the primary composite CV end point (44.4 vs 32.4 events per 1000 person-year). The reduction in individual CV end points was only statistically significant for stroke and revascularization, with a 39% relative risk reduction (13.1 vs 8.0 events per 1000 person-year) and 35% relative risk reduction (38.5 vs 25.0 events per 1000 person-year), respectively, favoring semaglutide over placebo. Contrary to liraglutide, semaglutide did not reduce CV-related death.[17] Semaglutide increased the risk for retinopathy complications.[17]

Exenatide is a once-weekly GLP-1RA whose CV safety was tested in the Exenatide Study of Cardiovascular Event Lowering (EXSCEL).[20] The EXSCEL trial enrolled 14,752 patients with T2DM with established CVD or with CV risk factors. After a median of 3.2 years of follow-up, exenatide improved glycemic control, resulting in a significant reduction in HbA_{1c} of 0.53% compared with placebo. With respect to the CV composite end point that included death from CV causes, nonfatal myocardial infarction, or nonfatal stroke, exenatide was noninferior to placebo, therefore meeting the primary end point of

noninferiority. Exenatide did not result in a statistically significant reduction for the composite primary end point. However, there was a favorable trend with exenatide compared with placebo. Although the primary end point for superiority was not met, for hypothesis-generating purposes, exenatide was associated with a 14% relative risk reduction for death from any cause (23 vs 20 events per 1000 person-years). There were no major concerns in terms of non-CV safety profile for exenatide except for thyroid papillary carcinomas, which were more likely to occur in the exenatide-treated patients; however, the overall number of events (10 for exenatide vs 4 for placebo) was low.

Of note, the EXSCEL trial had an interesting study design that required interruption of treatment in patients who experienced 2 or more severe hypoglycemic events, severe kidney dysfunction or received renal replacement therapy, or had an increased calcitonin level. This study design led to premature interruption of treatment in a number of patients, which might have influenced the overall trial results. However, in the per-protocol sensitivity analysis, the results for the primary end point were not different compared with the intention-to-treat analysis.

INSULIN

Historically, the effects of insulin on CV outcomes have been controversial.[101] On one hand, insulin reduces blood glucose levels, which may reduce CV outcomes in the long term.[102,103] Yet, insulin leads to weight gain, an independent risk factor for CVD.[104] The effects of basal insulin on CV outcomes were prospectively studied in the Outcome Reduction With Initial Glargine Intervention (ORIGIN) trial.[7] Patients with high CV risk and impaired glucose metabolism or T2DM were randomized to either insulin glargine or standard of care. The prespecified co-primary outcomes were the composite of death from CV causes, nonfatal myocardial infarction, or nonfatal stroke and the composite of death from CV causes, nonfatal myocardial infarction, nonfatal stroke, any revascularization, or hospitalization for HF. Patients in the insulin glargine arm were treated to a target fasting blood glucose level of less than or equal to 95 mg/dL (to convert to mmol/L, multiply by 0.0555). After a median follow-up of 6.2 years, there was no significant difference between the 2 arms with respect to either co-primary end point or all-cause mortality. These results suggest that the net effects of exogenous basal insulin on CV outcomes were neutral. However, the CV benefits of glucose lowering were not truly tested in this population, which had well-controlled glucose levels before randomization. Importantly, an additional post hoc analysis of the ORIGIN study also found no association between insulin glargine and an increased risk of new-onset HF.[105]

The DEVOTE (Trial Comparing Cardiovascular Safety of Insulin Degludec Versus Insulin Glargine in Patients With Type 2 Diabetes at High Risk of Cardiovascular Events) study randomized 7637 patients with T2DM to receive either insulin degludec, an ultralong-acting basal insulin, or insulin glargine.[19] There was no significant difference in CV death, nonfatal myocardial infarction, or nonfatal stroke between the degludec and glargine arms; however, patients randomized to degludec experienced a significantly lower risk of severe hypoglycemia, which is an important CV risk factor.[106] However, although glargine seems to have neutral effects on HF incidence,[105] the effects of degludec on HF are unknown.

DISCUSSION

Despite the existence of several different classes of drugs for the treatment of T2DM, only 2 of them have shown beneficial CV effects: 2 GLP1RAs, liraglutide and semaglutide, and 2 SGLT-2 inhibitors, empagliflozin and canagliflozin. Taken together, the data obtained by the CVOTs published so far should guide diabetes-treating clinicians to pick the most appropriate antihyperglycemic drug not just to improve glycemic control to reduce long-term microvascular complications but also to reduce CV risk in patients with diabetes. Interestingly, the shift in diabetes treatment has resulted in increased interest of diabetologists to targeting CV outcomes and of cardiologists to treat diabetes to reduce CV risk.[107] Importantly, drug therapy selection should be individualized and tailored to patient characteristics, risk factors, and goals, as

recently suggested by the American Diabetes Association guidelines.[29]

In addition to selecting antihyperglycemic therapy based on the presence or absence of established CVD,[29] we propose that additional CV-related considerations be taken into account. For example, in patients with HF, liraglutide has been found to be either neutral or detrimental, whereas both empagliflozin and canagliflozin exert beneficial effects by reducing HF-related hospitalizations. Conversely, in patients without HF but with current genitourinary infections and/or obesity, the use of liraglutide and semaglutide over SGLT-2 inhibitors should be preferred. As others have proposed[108] and more recent guidelines have hinted at[29,30,109-112] (Table 2), we also suggest an alternative therapeutic algorithm, which in addition to the efficacy on glycemic control also includes efficacy on CV outcomes and potential adverse effects in addition to the hypoglycemic risks encountered with the different drugs (Figure).

CONCLUSION

The treatment of diabetes has evolved over time, and to date, the priority should be given to those drugs with beneficial CV effects in the setting of a more comprehensive, yet individualized, approach.

Abbreviations and Acronyms: **CANVAS** = Canagliflozin Cardiovascular Assessment Study; **CANVAS-R** = Study of the Effects of Canagliflozin on Renal Endpoints in Adult Participants With Type 2 Diabetes Mellitus; **CV** = cardiovascular; **CVD** = CV disease; **CVOT** = CV outcomes trial; **DPP-4** = dipeptidyl peptidase 4; **EMPA-REG OUTCOME** = Empagliflozin Cardiovascular Outcome Event Trial in Type 2 Diabetes Mellitus Patients—Removing Excess Glucose; **EXSCEL** = Exenatide Study of Cardiovascular Event Lowering; **FDA** = Food and Drug Administration; **GLP-1** = glucagon-like peptide 1; **HbA_{1c}** = glycated hemoglobin; **HF** = heart failure; **IRIS** = Insulin Resistance Intervention After Stroke; **LDL-C** = low-density lipoprotein cholesterol; **LEADER** = Liraglutide Effect and Action in Diabetes: Evaluation of Cardiovascular Outcome Results Look; **AHEAD** = Action for Health in Diabetes; **PPAR** = peroxisome proliferator–activated receptor; **RA** = receptor agonist; **SGLT** = sodium-glucose cotransporter; **SUSTAIN-6** = Trial to Evaluate Cardiovascular and Other Long-term Outcomes With Semaglutide in Subjects With Type 2 Diabetes; **T2DM** = type 2 diabetes mellitus

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