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Cardiovascular Protection in the Treatment of Type 2 Diabetes: A Review of Clinical Trial Results Across Drug Classes

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ABSTRACT

Patients with type 2 diabetes (T2DM) have a significantly higher risk of developing cardiovascular disease (CVD)—namely myocardial infarction, heart failure, and stroke. Despite clear advances in the prevention and treatment of CVD, the impact of T2DM on CVD outcome remains high and continues to escalate. Available evidence indicates that the risk of macrovascular complications increases with the severity of hyperglycemia, thus suggesting that the relation between metabolic disturbances and vascular damage is approximately linear. Although current antidiabetic drugs are highly effective for the management of hyperglycemia, most T2DM patients remain exposed to a substantial and concrete risk of CVD. Over the last decade many glucose-lowering agents have been tested for their safety and efficacy in T2DM with CVD. Noteworthy, most of these studies failed to show a significant benefit in terms of CV morbidity and mortality, despite intensive glycemic control. The recent trials Empagliflozin Cardiovascular Outcome Event Trial in Type 2 Diabetes Mellitus Patients−Removing Excess Glucose (EMPA-REG OUTCOME); Trial to Evaluate Cardiovascular and Other Long-term Outcomes with Semaglutide in Subjects with Type 2 Diabetes (SUSTAIN-6); Liraglutide Effect and Action in Diabetes: Evaluation of Cardiovascular Outcome Results (LEADER); and Insulin Resistance Intervention After Stroke (IRIS) have shed some light on this important clinical issue, thus showing a convincing effect of empagliflozin, liraglutide, and pioglitazone on CVD outcomes. Here we provide a critical and updated overview of the main glucose-lowering agents and their risk/benefit ratio for the prevention of CVD in patients with T2DM.

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GLUCOSE-LOWERING STRATEGIES AND CARDIOVASCULAR DISEASE

Epidemiologic studies have outlined a strong association between type 2 diabetes mellitus (T2DM) and cardiovascular disease (CVD).[1,2] It is well established that patients with T2DM are exposed to a significantly higher risk to develop myocardial infarction (MI) and stroke than matched subjects without T2DM.[2] Diabetic patients hospitalized for unstable angina or non-Q-wave MI display a significantly higher 2-year morbidity and mortality as compared with

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nondiabetic subjects.[3] In the seminal study by Haffner et al,[4] the 7-year risk of MI was as high in diabetic patients without prior MI as it was in nondiabetic patients with prior MI, thus establishing diabetes as a "CV disease risk equivalent." The increased prevalence of CVD in the setting of T2DM can be largely attributed to the heavy atherosclerotic burden and adverse plaque phenotype, as well as the inability to compensate for these alterations.[5,6]

Despite clear advances in the prevention and treatment of CVD, the impact of T2DM on CVD outcome remains significant and continues to escalate as the obesity epidemic takes its toll.[7] Even though the CVD burden has been reduced over the last decade, this is only partially true in the diabetic patient. Data accumulated over the last 10 years strongly suggest that the risk of macrovascular complications increases with the severity of abnormality of blood glucose, indicating that the relation between metabolic disturbances and vascular damage is approximately linear.[8,9] In the large, prospective Norfolk study, the relationship between glycated hemoglobin (HbA_{1c}), CVD, and total mortality was indeed linear, even among patients without T2DM; of note, 72% of the events occurred in persons with HbA_{1c} concentrations between 5% and 6.9%.[10] In other words, CVD may already be detectable in patients with HbA_{1c} values below the diagnostic threshold for diabetes, whereas in patients with overt T2DM the relative risk of CVD has been shown to increase by approximately 16% for every percentage point increase in HbA_{1c}.[10]

Given this background, one can certainly postulate that—similar to hypertension and hypercholesterolemia—approaches aiming at reducing the hyperglycemic burden should result in a clear-cut reduction of vascular events in the diabetic population. However, the relation between glucose-lowering approaches and CVD is much more complex than is the case with other cardiovascular (CV) risk factors. Indeed, the success of glucose-lowering strategies in terms of CV outcome cannot be easily predicted from changes in surrogate endpoints (such as plasma glucose levels or HbA_{1c}).[6] Although HbA_{1c} is a reliable marker of glycemic control, it may explain less than 25% of the risk of developing diabetic microvascular complications.[11] This may be partially explained by the notion that HbA_{1c} does not correlate with glycemic variability when adjusted for mean blood glucose, and tailoring glucose-lowering strategies only on the level of HbA_{1c} may leave diabetic patients exposed to a substantial burden of glycemic peaks and nadirs.[12] Despite the increasing number of individuals affected by T2DM, few definitive CV outcome trials of licensed therapies have been performed.[13-15] In the present review we critically discuss the effects of different glucose-lowering medications on CVD outcomes (**Table 1**) in patients with T2DM.

METFORMIN

Metformin—a biguanide that reduces hepatic glucose production while improving insulin sensitivity—is still considered the first-line drug for the treatment of T2DM patients.[16] This is mostly due to the fact that metformin is overall well tolerated, effectively lowers HbA_{1c} levels by 1% to 2%, has a favorable impact on body weight, does not increase the risk of hypoglycemia when given in monotherapy, and last but not least, is highly cost-effective.[16] Of note, metformin is one of the few drugs showing a significant reduction of macrovascular events and diabetes-related mortality. Cardiovascular benefits of metformin mostly derive from the UK Prospective Diabetes Study (UKPDS) trial, the results of which were published in 1998.[17] In this trial 3867 patients with newly diagnosed T2DM were randomized to intensive treatment with sulfonylureas or with insulin, versus conventional therapy.[17] A subgroup of UKPDS patients who were overweight (>120% ideal body weight) were randomized either to intensive therapy with metformin (n = 342) or conventional dietary measures (n = 411).[17] In this group of patients, treatment with metformin was associated with a 32% reduction of any diabetes-related endpoint ($P = .002$), 42% reduction in diabetes-related death ($P = .017$), and 36% reduction in mortality ($P = .011$). Most interestingly from a CV perspective, patients receiving metformin displayed a 39% reduction in the risk of nonfatal MI ($P = .01$).[17] Despite the small number of patients enrolled, the protective effects of metformin were still observed in the 10-year posttrial monitoring of patients who survived to the end of the UKPDS trial.[18] Although HbA_{1c} levels were no longer different between intensive and conventional arms, metformin-related risk reductions persisted for any diabetes-related endpoint, MI (33%, $P = .005$), and mortality (27%, $P = .002$).[18] Although UKPDS provides some evidence—albeit with limited statistical power compared with other CV outcome trials—that metformin may represent a cardioprotective agent, not many randomized trials have been performed to confirm the CV benefits of the drug.[19] After the publication of the UKPDS, only 1 randomized, placebo-controlled trial was performed.[20] In this relatively small trial, 390 patients treated with insulin were randomized to either metformin or placebo. The primary endpoint was an aggregate of microvascular and macrovascular morbidity and mortality, whereas the secondary endpoint was defined by microvascular and macrovascular morbidity and mortality, as separate aggregate scores. After 4.3 years, metformin was not associated with an improvement in the primary endpoint (hazard ratio [HR] 0.92, $P = .33$), but there was a reduction in the secondary endpoint of macrovascular events (HR 0.61, $P = .02$). Moreover, metformin improved body weight and glycemic control and reduced the requirement of insulin.[20] These overall positive findings prompted the investigators to conclude that metformin treatment should be continued after the introduction of insulin in any patient with T2DM, unless contraindicated.

The remaining evidence, and perhaps the largest body of data, comes from observational studies showing that metformin use, either as monotherapy or in combination with another oral agent, has been associated with reduced CV events, CV deaths, and total mortality.[21-24] Despite the fact

Table 1 Properties and Cardiovascular Effects of Noninsulin Glucose-Lowering Drugs for the Treatment of Type 2 Diabetes

Drug Class	CV Effects	Clinical Use in Patients with CVD
Biguanides	• Few randomized, but many observational studies available • Reduces risk of MI by 39%, diabetes-related endpoint by 32%, diabetes-related death by 42%, mortality by 36% (UKPDS) • Safety concerns on the association with sulfonylureas	• First choice in T2DM patients with and without atherosclerotic vascular disease • Precautions should be taken in patients with ACS, HF, CKD (stages IV and V) • Not indicated in the presence of acidosis or dehydration
Sulfonylureas	• Several observational studies available • Reduction of microvascular complications (UKPDS) • Increased CV mortality (UGDP trial) • Impairment of ischemic preconditioning (?)	• Combination therapy in T2DM patients with and without CVD (if HbA_{1c} target not achieved after ~3 mo of monotherapy with metformin) • Precautions should be taken in patients with multiple comorbidities, ACS, HF, and advanced CKD (stages IV and V)
Thiazolidinediones	• Reduce risk of MI and stroke (PROActive and IRIS trials with pioglitazone) • Improve diabetic dyslipidemia • Increase HF hospitalization	• Combination therapy in T2DM patients with and without CVD and/or CKD (up to stage V, eGFR <15 mL/min/1.73 m^2) • Precautions should be taken in patients with ACS • Contraindicated in patients with or at risk of HF
Glucagon-like peptide-1 receptor agonists	• Significant reduction of composite CV endpoints in LEADER and SUSTAIN-6 trials • No significant effects on CV mortality, nonfatal MI, and hospitalization for HF with liraglutide and semaglutide • Reduced risk of nonfatal stroke with semaglutide	• Combination therapy in T2DM patients with and without CVD (including HF and ACS) • Limited data in patients with advanced CKD (stages IV and V) • Exenatide is eliminated by renal mechanisms and should not be given in patients with severe ESRD • Liraglutide is not eliminated by renal or hepatic mechanisms, but it should be used with caution since there are only limited data in patients with renal or hepatic impairment
Dipeptidyl peptidase-4 inhibitors	• Well tolerated • No reduction of CV endpoints (SAVOR-TIMI 53, EXAMINE, TECOS) • Increased risk of HF with saxagliptin and alogliptin (?)	• Combination therapy in T2DM patients with and without CVD • Although sitagliptin seems to be safe, the use of alogliptin and saxagliptin in patients with pre-existing HF is still debated • Indicated in patients with CKD (any stage)
Sodium glucose cotransporter 2 inhibitors	• In the EMPA-REG OUTCOME trial, empagliflozin reduced CV death, HF hospitalization, and total mortality by 38%, 35%, and 32%, respectively • No direct effect on the rates of MI or stroke with empagliflozin • Reduction of systolic and diastolic BP	• Combination therapy in T2DM patients with and without CVD (paucity of data on SGLT2 in primary prevention) • Evidence of benefit in patients with HF • No evidence of benefit in ACS

ACS = acute coronary syndrome; BP = blood pressure; CKD = chronic kidney disease; CVD = cardiovascular disease; eGFR = estimated glomerular filtration rate; EMPA-REG OUTCOME = Empagliflozin Cardiovascular Outcome Event Trial in Type 2 Diabetes Mellitus Patients—Removing Excess Glucose; ESRD = end-stage renal disease; EXAMINE = Examination of Cardiovascular Outcomes with Alogliptin versus Standard of Care; HF = heart failure; IRIS = Insulin Resistance Intervention After Stroke; LEADER = Liraglutide Effect and Action in Diabetes: Evaluation of Cardiovascular Outcome Results; MACE = major adverse cardiovascular events; MI = myocardial infarction; PROActive = Prospective Pioglitazone Clinical Trial in Macrovascular Events; SAVOR-TIMI 53 = Saxagliptin Assessment of Vascular Outcomes Recorded in Patients with Diabetes Mellitus—Thrombolysis in Myocardial Infarction; SGLT2 = sodium glucose cotransporter 2; SUSTAIN-6 = Trial to Evaluate Cardiovascular and Other Long-term Outcomes with Semaglutide in Subjects with Type 2 Diabetes; T2DM = type 2 diabetes mellitus; TECOS = Trial Evaluating Cardiovascular Outcomes with Sitagliptin; UGDP = University Group Diabetes Program; UKPDS = UK Prospective Diabetes Study.

that these cohort studies all demonstrated CV benefits of metformin, they were flawed by important biases arising from the lack of group matching for all variables that could affect the outcome. Importantly, 2 recent meta-analyses of randomized, controlled trials evaluating the effectiveness of metformin in T2DM patients failed to show its ability to modify clinically relevant outcomes.[25] A more careful reading of the UKPDS results shows a higher death rate in patients given metformin plus sulfonylurea as compared with those given sulfonylurea alone (HR 1.60; 95% confidence interval [CI], 1.02-2.52). Although the UKPDS investigators attributed this result to the play of chance (likely due to the small sample size), there remain concerns about the safety of metformin in this setting. Indeed, the meta-analyses of Boussageon et al[25] and Lamanna et al[26] confirmed an increase of CV risk when metformin was added to sulfonylureas. Further randomized studies able to reproduce the findings of the UKPDS study are needed to

increase confidence of cardiologists regarding the clear-cut cardioprotective effects of metformin.

SULFONYLUREAS

Sulfonylureas stimulate insulin secretion from pancreatic β-cells by binding to the sulfonylurea receptor 1, which is part of the $K_{ir}6.2$ adenosine triphosphate−sensitive potassium channel. As monotherapy, sulfonylureas are effective glucose-lowering drugs, leading to reductions in fasting plasma glucose by 36-72 mg/dL and HbA_{1c} by 1%-2%.[27] However, they are associated with a significant risk of moderate hypoglycemia, reported in 20%-40%, and severe hypoglycemia—requiring third-party assistance—in 1%-7% of patients, depending on the population, the definition of hypoglycemia, and the type and pharmacokinetics of the sulfonylurea.[27] Furthermore, there are concerns about the CV safety of sulfonylureas. In 1970 the University Group Diabetes Program (UGDP) trial reported an increased risk of CV death associated with the use of tolbutamide compared with placebo or insulin.[28,29] Because the $K_{ir}6.2$ adenosine triphosphate−sensitive potassium channel is also expressed in smooth muscle cells and cardiomyocytes, several authors have postulated that the increased CV mortality reported by UGDP could be the result of an impaired vasodilatory response during acute myocardial ischemia. The sulfonylurea glimepiride was found to impair ischemic preconditioning in T2DM patients with coronary artery disease, as compared with insulin.[30] However, in contrast to glimepiride, tolbutamide has only a low affinity for cardiac sulfonylurea receptors, and interference with ischemic preconditioning seems unlikely to account for the excess mortality reported by the UGDP.[28] Moreover, subsequent studies failed to establish a definite link between sulfonylurea treatment before acute MI and in-hospital mortality. After the UGDP concerns, several randomized trials with sulfonylureas have been performed. The A Diabetes Outcome Prevention Trial (ADOPT), which compared metformin, rosiglitazone, and glyburide therapy with respect to glycemic control, did not report any difference among the 4 treatment groups as far as CV outcomes were concerned.[31] However, these findings should be interpreted with caution because the trial was not designed to test the CV safety of glyburide. In the UKPDS; Action in Diabetes and Vascular Disease: Preterax and Diamicron MR Controlled Evaluation (ADVANCE); and Action to Control Cardiovascular Risk in Diabetes (ACCORD) trials, in which sulfonylureas were highly represented in the intensive glucose-lowering arms, no increased CV risk was reported by the investigators.[13,14,32,33] In contrast, a number of observational studies support the notion that sulfonylureas may increase CV risk, especially when compared with metformin therapy.[34,35] The ongoing Cardiovascular Outcome Trial of Linagliptin Versus Glimepiride in Type 2 Diabetes (CAROLINA) trial, which compares linagliptin with glimepiride in T2DM patients, might help to clarify and define the CV safety of these drugs.[36]

THIAZOLIDINEDIONES

The glucose-lowering effect of thiazolidinediones is due to their ability to activate the peroxisome proliferator−activated receptor (PPAR)-γ, thus fostering insulin sensitivity in skeletal muscle, liver, and adipose tissue.[37] Thiazolidinediones include troglitazone, pioglitazone, and rosiglitazone. Troglitazone was withdrawn because of hepatotoxicity, whereas safety concerns about rosiglitazone and pioglitazone were raised owing to increased CV risk (MI and heart failure [HF]) and risk of bladder cancer and bone fractures, respectively.[37,38] As glucose-lowering agents, thiazolidinediones are well tolerated and are not associated with any risk of hypoglycemia.[27] They have also been shown to be associated with more durable glycemic control when compared with sulfonylureas and metformin.[16] An important undesirable effect of this class of drugs is fluid retention due to renal sodium reabsorption, reported in 4%-6% of patients receiving thiazolidinediones.[37]

A number of observational studies that have compared rosiglitazone with other oral antidiabetic medications have shown an increased risk of mortality and HF.[39,40] A nationwide retrospective cohort study including 227,571 Medicare beneficiaries aged 65 years or older showed that, when compared with prescription of pioglitazone, prescription of rosiglitazone was associated with an increased risk of stroke, HF, and all-cause mortality.[40] The meta-analysis by Nissen and Wolski[41] showed that rosiglitazone was associated with a significant increase in the risk of MI and with an increase in the risk of CV death, with borderline significance. Several other meta-analyses confirmed adverse CV effects associated with rosiglitazone.[42,43] This evidence led to the withdrawal of rosiglitazone in Europe and restricted its use in the United States. On the basis of such safety concerns, the Rosiglitazone Evaluated for Cardiac Outcomes and Regulation of Glycaemia in Diabetes (RECORD) trial was specifically designed to test the CV safety of rosiglitazone as compared with placebo. The study confirmed an increased risk of HF (HR 2.10; 95% CI, 1.35-3.27), whereas data on MI risk remained not conclusive (HR 1.14; 95% CI, 0.80-1.63).[44] After the publication of the RECORD trial, the US Food and Drug Administration lifted some of the restrictions, stating that rosiglitazone was not associated with increased MI risk.[32]

In contrast to rosiglitazone, the CV effects of pioglitazone seem to be more promising. The Prospective Pioglitazone Clinical Trial In Macrovascular Events (PROactive) study which was designed to investigate whether pioglitazone reduces macrovascular morbidity and mortality in 5238 high-risk T2DM patients followed for 34.5 months, showed that the drug was not effective in reducing the composite primary endpoint of all-cause mortality, nonfatal MI, stroke, and limb amputation (HR 0.90; 95% CI, 0.80-1.02; $P = .095$), whereas it significantly reduced the secondary endpoint of all-cause mortality, nonfatal MI, and stroke (0.84; 95% CI, 0.72-0.98; $P = .027$).[45] However, pioglitazone significantly increased hospitalization for HF

Table 2 Recent Randomized, Controlled Trials with Noninsulin Glucose-Lowering Drugs Showing Improvement of Cardiovascular Outcomes

Variable	IRIS[46]	LEADER[47]	SUSTAIN-6[48]	EMPA-REG OUTCOME[49]
No. of patients	3876	9340	3297	7020
Population	Patients with recent history of ischemic stroke or TIA, with insulin resistance but without T2DM	T2DM patients with CVD or high CV risk	T2DM patients with CVD or high CV risk	T2DM patients with CVD
Intervention	Pioglitazone vs placebo	Liraglutide vs placebo	Semaglutide vs placebo	Empagliflozin vs placebo
Median follow-up (y)	4.8	3.8	2.1	3.1
Mean age (y)	63	64	64	63
Mean HbA_{1c} (%)	5.8	8.7	8.7	8.1
Mean BMI (kg/m^2)	29.9	32.5	32.8	30.5
CKD (%)	NR	25	70	26
Prior HF (%)	0	14	21-24	10
Definition of primary outcome	Fatal or nonfatal stroke or MI	CV death, nonfatal MI, or nonfatal stroke	CV death, nonfatal MI, or nonfatal stroke	CV death, nonfatal MI, or nonfatal stroke
HR for primary outcome (95% CI)	0.76 (0.62-0.93), $P = .007$	0.87 (0.78-0.97), $P < .001$ for noninferiority; $P = .01$ for superiority	0.74 (0.58-0.95), $P < .001$ for noninferiority; $P = .02$ for superiority	0.86 (0.74-0.99), $P = .04$ for superiority
Hospitalization for HF, HR (95% CI) unless otherwise noted	3.8% vs 3.7%, $P = .80$	0.87 (0.73-1.05), $P = .14$	1.11 (0.77-1.61), $P = .57$	0.65 (0.50-0.85), $P = .002$
CV mortality, HR (95% CI)	NA	0.78 (0.66-0.93), $P = .007$	0.98 (0.65-1.48), $P = .92$	0.62 (0.49-0.77), $P < .001$
All-cause mortality, HR (95% CI)	0.93 (0.73-1.17), $P = .52$	0.85 (0.74-0.97), $P = .02$	1.05 (0.74-1.50), $P = .79$	0.68 (0.57-0.82), $P < .001$
Comments	Although pioglitazone significantly reduced the rate of stroke and MI, no between-group differences in all-cause mortality were observed. Pioglitazone was also associated with a greater frequency of weight gain, edema, and bone fractures requiring surgery or hospitalization.	Survival curves for 3-point MACE started to separate after 12-18 mo from randomization, whereas no effects were seen for HF-related outcomes. These findings suggest that liraglutide may reduce CV events mostly via an antiatherosclerotic mechanism.	Decreased CV risk with semaglutide was mostly driven by a significant (39%) reduction in the rate of nonfatal stroke and a nonsignificant (26%) decrease in nonfatal MI, with no significant difference in the rate of CV death. The beneficial effect of semaglutide on CV outcomes may relate to modification of the progression of atherosclerosis.	Benefits of empagliflozin were seen already after 3 mo. This suggests that hemodynamic factors (ie, BP reduction, osmotic diuresis) may be significantly involved. However, utilization of β-hydroxybutyrate instead of fatty acids might also contribute to improve myocardial efficiency thus preventing HF. The exact mechanisms underlying empagliflozin-related benefits remain to be elucidated.

Table 2 Continued

Variable	IRIS[46]	LEADER[47]	SUSTAIN-6[48]	EMPA-REG OUTCOME[49]
Adverse events	As compared with placebo, pioglitazone was associated with a greater frequency of weight gain (52.2% vs 33.7%, $P < .001$), edema (35.6% vs 24.9%, $P < .001$), and bone fracture requiring surgery or hospitalization (5.1% vs 3.2%, $P = .003$).	Risk of any adverse event was increased with liraglutide as compared with placebo (9.5% vs 7.3%, $P < .001$). The most common adverse events were gastrointestinal symptoms and events (nausea, abdominal pain, vomiting, diarrhea, acute gallstone disease, acute cholecystitis) and injection-site reaction.	Rates of retinopathy complications (vitreous hemorrhage, blindness, or conditions requiring treatment with an intravitreal agent or photocoagulation) were significantly higher with semaglutide as compared with placebo (HR 1.76; 95% CI, 1.11-2.78; $P = .02$).	Among patients receiving empagliflozin, there was an increased rate of genital infections as compared with placebo (6.5% vs 1.8%, $P < .001$). No increase in other adverse events was reported.

BMI = body mass index; BP = blood pressure; CI = confidence interval; CKD = chronic kidney disease; CVD = cardiovascular disease; EMPA-REG OUTCOME = Empagliflozin Cardiovascular Outcome Event Trial in Type 2 Diabetes Mellitus Patients—Removing Excess Glucose; HbA_{1c} = glycated hemoglobin; HF = heart failure; HR = hazard ratio; IRIS = Insulin Resistance Intervention After Stroke; LEADER = Liraglutide Effect and Action in Diabetes: Evaluation of Cardiovascular Outcome Results; MACE = major adverse cardiovascular events; MI = myocardial infarction; NA = not applicable; NR = not reported; SUSTAIN-6 = Trial to Evaluate Cardiovascular and Other Long-term Outcomes with Semaglutide in Subjects with Type 2 Diabetes; T2DM = type 2 diabetes mellitus; TIA = transient ischemic attack.

(6% vs 4%) but not HF-related mortality. Very recently the Insulin Resistance Intervention After Stroke (IRIS) trial, conducted in patients without diabetes who had insulin resistance along with a recent history of ischemic stroke or TIA, showed that the risk of stroke or MI was lower among patients who received pioglitazone than among those who received placebo (**Table 2**).[46] However, pioglitazone did not reduce mortality. The beneficial effects of pioglitazone were mostly driven by nonglycemic effects, given the negligible difference in HbA_{1c} levels between pioglitazone and placebo. In this trial pioglitazone was also associated with a lower risk of diabetes but with higher risks of weight gain, edema, and fracture.[46] Taken together, evidence so far available discourages the use of thiazolidinediones (especially rosiglitazone) as first-choice glucose-lowering drugs for the management of T2DM patients. More recently, dual PPAR-$\alpha\gamma$ agonists have been tested in randomized clinical trials; however, these drugs failed to show a favorable CV profile, as reported in the Effect of Aleglitazar on Cardiovascular Outcomes After Acute Coronary Syndrome in Patients With Type 2 Diabetes Mellitus (AleCardio) trial.[50]

DIPEPTIDYL PEPTIDASE-4 INHIBITORS

Dipeptidyl peptidase-4 (DPP-4) inhibitors block the degradation of glucagon-like peptide-1 (GLP-1), gastric inhibitory peptide, and a variety of other peptides, including brain natriuretic peptide.[51] Therefore, these drugs raise GLP-1/gastric inhibitory peptide levels, thus leading to insulin secretion from β-cells and decreased secretion of glucagon from pancreatic α-cells.[32] Inhibitors of DPP-4 are effective in reducing HbA_{1c}, do not lead to hypoglycemia, and are not associated with weight gain.[16] Several meta-analyses of retrospective studies have shown that DPP-4 inhibitors (individually and as a class) are associated with reductions in CV events.[52] However, the studies examined were not specifically designed to appraise the effect of DPP-4 inhibitors on CVD.[32] Three randomized trials—Saxagliptin Assessment of Vascular Outcomes Recorded in Patients with Diabetes Mellitus—Thrombolysis in Myocardial Infarction (SAVOR-TIMI 53); Examination of Cardiovascular Outcomes with Alogliptin versus Standard of Care (EXAMINE); and Trial Evaluating Cardiovascular Outcomes with Sitagliptin (TECOS)—were conducted over the last few years to systematically investigate the CV safety and efficacy of DPP-4 inhibitors in patients with T2DM (**Table 3**).[53-56] In the SAVOR-TIMI 53 trial, which randomized 16,492 high-risk T2DM patients to receive saxagliptin or placebo, more patients in the saxagliptin group than in the placebo group were hospitalized for HF (3.5% vs. 2.8%; HR 1.27; 95% CI, 1.07-1.51; $P = .007$).[53] However, these findings were not paralleled by a concomitant increase in HF-related deaths in patients taking saxagliptin (44 and 40 cases in saxagliptin and placebo, respectively). Subjects at greatest risk of HF hospitalization had previous HF, an estimated glomerular filtration rate

Table 3 Design and Outcomes of SAVOR-TIMI 53, EXAMINE, and TECOS Trials

Variable	SAVOR-TIMI 53[53]	EXAMINE[54]	TECOS[55]
No. of patients	16,492	5380	14,671
Population	T2DM patients with CVD or high CV risk	T2DM with an acute MI or UA requiring hospitalization within the previous 15-90 d	T2DM patients with CVD or high CV risk
Intervention	Saxagliptin vs placebo	Alogliptin vs placebo	Sitagliptin vs placebo
Mean age (y)	65	61	65
Diabetes duration (y)	10	7	11.6
Established CVD (%)	78	100	74
Mean HbA_{1c} (%)	8 ± 1.4	8 ± 1.1	7.2 ± 0.5
Mean BMI (kg/m^2)	31	28.7	30.2
Prior HF (%)	12.8	28	18
Median follow-up (y)	2.1	1.5	3.0
Hypoglycemia			
Intervention	15.3	6.7	2.0*
Placebo	13.4	6.5	1.7*
Definition of primary outcome	CV death, nonfatal MI, nonfatal ischemic stroke	CV death, nonfatal MI, nonfatal stroke	CV death, nonfatal MI, nonfatal stroke, or UA hospitalization
HR for primary outcome (95% CI)	1.00 (0.89-1.12)	0.96 (≤1.16)	0.98 (0.88-1.09)
Definition of secondary outcome	CV death, MI, stroke, hospitalization for UA, HF, or coronary revascularization	Primary outcome + urgent revascularization due to UA within 24 hours after hospital admission	CV death, nonfatal MI, or nonfatal stroke
HR for secondary outcome (95% CI)	1.02 (0.94-1.11)	0.95 (≤1.14)	0.99 (0.84-1.11)
Hospitalization for HF, HR (95% CI)	1.27 (1.07-1.51)	1.19 (0.89-1.59)	1.00 (0.83-1.20)
CV mortality, HR (95% CI)	1.03 (0.87-1.22)	0.85 (0.66-1.10)	1.02 (0.90-1.15)
All-cause mortality, HR (95% CI)	1.11 (0.96-1.27)	0.88 (0.71-1.09)	1.01 (0.90-1.14)
Comments	Subjects at greatest risk of HF hospitalization had previous HF, an eGFR ≤60 mL/min/1.73 m^2, or elevated baseline levels of NT-proBNP	Post hoc analyses showed that alogliptin increased HF incidence in patients who had signs of HF at the time of randomization (HR 1.76; 95% CI, 1.07-2.90)	A recent post hoc analysis confirmed that sitagliptin does not increase HF hospitalization even after adjustment for pre-existing HF
Adverse events	The rate of any hypoglycemic event (minor and major) was significantly increased with saxagliptin as compared with placebo (15.3% vs 13.4%, $P < .001$)	Incidences of hypoglycemia, cancer, pancreatitis, and initiation of dialysis were similar with alogliptin and placebo	There was no significant difference between sitagliptin and placebo with respect to the overall incidence of infections, cancer, site-reported renal failure, or severe hypoglycemia

BMI = body mass index; CI = confidence interval; CKD = chronic kidney disease; CVD = cardiovascular disease; eGFR = estimated glomerular filtration rate; EXAMINE = Examination of Cardiovascular Outcomes with Alogliptin versus Standard of Care; HbA_{1c} = glycated hemoglobin; HF = heart failure; HR = hazard ratio; MI = myocardial infarction; NT-proBNP = N-terminal pro B-type natriuretic peptide; SAVOR-TIMI 53 = Saxagliptin Assessment of Vascular Outcomes Recorded in Patients with Diabetes Mellitus—Thrombolysis in Myocardial Infarction; T2DM = type 2 diabetes mellitus; TECOS = Trial Evaluating Cardiovascular Outcomes with Sitagliptin; UA = unstable angina.

*These values refer to severe hypoglycemia only.

≤60 mL/min/1.73 m^2, or elevated baseline levels of N-terminal pro B-type natriuretic peptide. By contrast in the EXAMINE trial, which randomized 5380 T2DM patients with an acute coronary syndrome to receive alogliptin or placebo, the incidence of HF was comparable among the treatment arms (3.1% and 2.9%, respectively).[54] However, post hoc analyses showed that alogliptin increased HF incidence in patients who had signs of HF at the time of randomization (HR 1.76; 95% CI, 1.07-2.90).[57] Hence, data from SAVOR-TIMI 53 and EXAMINE confirmed that

DPP-4 inhibitors may increase HF hospitalization in patients with pre-existing HF and high brain natriuretic peptide (BNP) levels at baseline (**Table 3**). A recent meta-analysis including SAVOR-TIMI 53 and EXAMINE trials has confirmed a 25% increase in HF hospitalizations related to DPP-4 inhibitors.[58] In contrast, the TECOS trial, which was launched to assess noninferiority as well as long-term CV safety of adding sitagliptin to usual care in 14,671 patients with T2DM and CVD, showed similar outcome rates for HF hospitalization in the 2 groups (HR 1.00; 95% CI, 0.83-1.20; $P = .98$).[55] Sitagliptin did not increase HF hospitalization even after adjustment for pre-existing HF, as shown by McGuire et al in a very recent TECOS substudy.[59] These encouraging data suggest that increased HF risk is not a class effect of DPP-4 inhibitors. Further evidence is needed to draw solid conclusions on the safety of saxagliptin and alogliptin in people with T2DM and CVD. The ongoing Cardiovascular Outcome Trial of Linagliptin Versus Glimepiride in Type 2 Diabetes (CAROLINA) trial has been designed to examine the effect of linagliptin on CV outcomes with an active comparator (glimepiride) rather than placebo.

GLP-1 RECEPTOR AGONISTS

Glucagon-like peptide-1 receptor agonists (GLP-1 RAs) have the ability to mimic endogenous GLP-1, resulting in a glucose-dependent increase in insulin secretion and an inhibition of glucagon secretion.[60] Glucagon-like peptide-1 RAs are generally well tolerated; the most common adverse effect is nausea, which is usually transient (4-8 weeks).[16] The risk of hypoglycemia in patients receiving GLP-1 RAs is low, unless they are combined with insulin or sulfonylureas.[27,61] Moreover, the reduction of HbA_{1c} levels with these drugs is long-lasting, and this is mostly due to a durable effect on the pancreatic β-cell to enhance insulin secretion.[62]

The receptor for GLP-1 is abundantly expressed in the vascular endothelium, smooth muscle cells, and cardiomyocytes, suggesting that these drugs may act on the entire CV system.[63] A series of experimental studies in animal models has shown that GLP-1 RAs may improve insulin sensitivity, left ventricular (LV) remodeling, and cardiac contractility in models of chronic HF and MI.[64] In human subjects, GLP-1 RAs have shown a consistent and favorable impact on several CV risk factors, such as body weight, blood pressure, endothelial function, and low-density lipoprotein cholesterol.[65] In several small studies conducted in patients with HF (with and without diabetes), chronic infusion of GLP-1 significantly improved LV ejection fraction (LVEF), VO_2 max, 6-minute walk distance, and Minnesota Living with Heart Failure quality-of-life score. Importantly, GLP-1-related benefits were seen in both diabetic and nondiabetic patients, and no episodes of hypoglycemia or gastrointestinal side effects were observed.[66] Infusion with GLP-1 also significantly increased LVEF and infarct-zone-related wall motion in patients with MI.[67] A placebo-controlled, randomized study showed that infusion of exenatide—started before reperfusion in ST-elevation myocardial infarction patients undergoing percutaneous coronary intervention—significantly reduced ischemia and myocardial salvage index (quantitated by cardiac magnetic resonance imaging) after 3 months.[68]

Long-term randomized, controlled studies were recently completed to examine whether GLP-1 RAs affect CV outcome in high-risk individuals. The Evaluation of Lixisenatide in Acute Coronary Syndrome (ELIXA) trial investigated the effects of lixisenatide versus placebo in 6068 diabetic patients with a recent acute coronary syndrome. The primary endpoint of CV death, MI, stroke, or hospitalization for unstable angina occurred in 13.4% of patients in the lixisenatide group and in 13.2% in the placebo group (HR 1.02; 95% CI, 0.89-1.17), thus showing noninferiority of lixisenatide to placebo. However, the study did not show superiority as far as CV outcome is concerned.[69] In the Liraglutide Effect and Action in Diabetes: Evaluation of Cardiovascular Outcome Results (LEADER) trial, T2DM patients at high CV risk were randomly assigned to receive liraglutide or placebo. After a median follow-up of 3.8 years, liraglutide significantly reduced the occurrence of the 3-point major adverse CV events by 13%, CV death by 22%, and all-cause mortality by 15%, without significant effects on nonfatal MI, nonfatal stroke, and hospitalization for HF (**Table 2**).[47] Cardiovascular benefits of liraglutide were observed quite early as compared with classic glycemic control trials in patients with T1DM and T2DM (ie, Diabetes Control and Complications Trial [DCCT], UKPDS), in which the reduction of CV events took many more years to emerge.[6] Moreover, the benefits of liraglutide were seen despite the fact that CV risk factors were significantly controlled by guideline-based medical treatment. In LEADER, cumulative event curves for 3-point major adverse CV events started to separate after 12-18 months from randomization, whereas no effects were seen for HF-related outcomes. These findings suggest that liraglutide may reduce CV events mostly via an antiatherosclerotic mechanism.[70] Along the same line, the very recent Trial to Evaluate Cardiovascular and Other Long-term Outcomes with Semaglutide in Subjects with Type 2 Diabetes (SUSTAIN-6) trial showed that semaglutide significantly reduced the primary composite endpoint of CV death, nonfatal MI, or nonfatal stroke (HR 0.74; 95% CI, 0.58-0.95; $P < .001$ for noninferiority).[48] These beneficial effects were mostly driven by a significant (39%) reduction in the rate of nonfatal stroke and a nonsignificant (26%) decrease in nonfatal MI, with no significant difference in the rate of CV death. Moreover, treatment with semaglutide increased retinopathy complications (HR 1.76; 95% CI, 1.11-2.78; $P = .02$).[48] Further studies are needed to demonstrate the mechanism whereby GLP-1 RAs improve CV outcomes in T2DM. A definitive answer concerning the CV impact of GLP-1 RAs as well as putative class effects awaits the completion of the trials Exenatide Study of Cardiovascular Event Lowering (EXSCEL; exenatide) and Researching CV

Events with a Weekly Incretin in Diabetes (REWIND; dulaglutide).

SODIUM GLUCOSE COTRANSPORTER 2 INHIBITORS

Sodium glucose cotransporter 2 (SGLT2) inhibitors are the newest class of oral agents approved for the treatment of T2DM. Their mechanism of action is inhibition of SGLT2, a low-affinity, high-capacity sodium-glucose cotransporter located in the proximal tubule.[71] Inhibition of SGLT2 leads to the elimination of 60-80 g glucose per day; however, this value is highly dependent on renal function and the hyperglycemic burden.[72] The effect of SGLT2 inhibitors on glucose elimination is proportional to glycemic levels, being modest or even negligible in conditions of mild hyperglycemia. This "self-limiting" action explains the low risk of hypoglycemia associated with this class of drugs, except when used in combination with insulin or sulfonylureas.[32] Sodium glucose cotransporter 2 inhibitor–induced glycosuria promotes a mild diuresis and calorie loss, thus leading to modest reductions in body weight.[71] All SGLT2 inhibitors have also shown a significant reduction in systolic and diastolic blood pressure, with the greatest reductions observed for systolic blood pressure.[73] Emerging evidence indicates that SGLT2 inhibitors have the ability to confer cardioprotection in high-risk T2DM patients. The recent Empagliflozin Cardiovascular Outcome Event Trial in Type 2 Diabetes Mellitus Patients–Removing Excess Glucose (EMPA-REG OUTCOME) trial was the first study to show unequivocal CV benefits of an SGLT2 inhibitor (**Table 2**).[49] The publication of this study has brought great enthusiasm

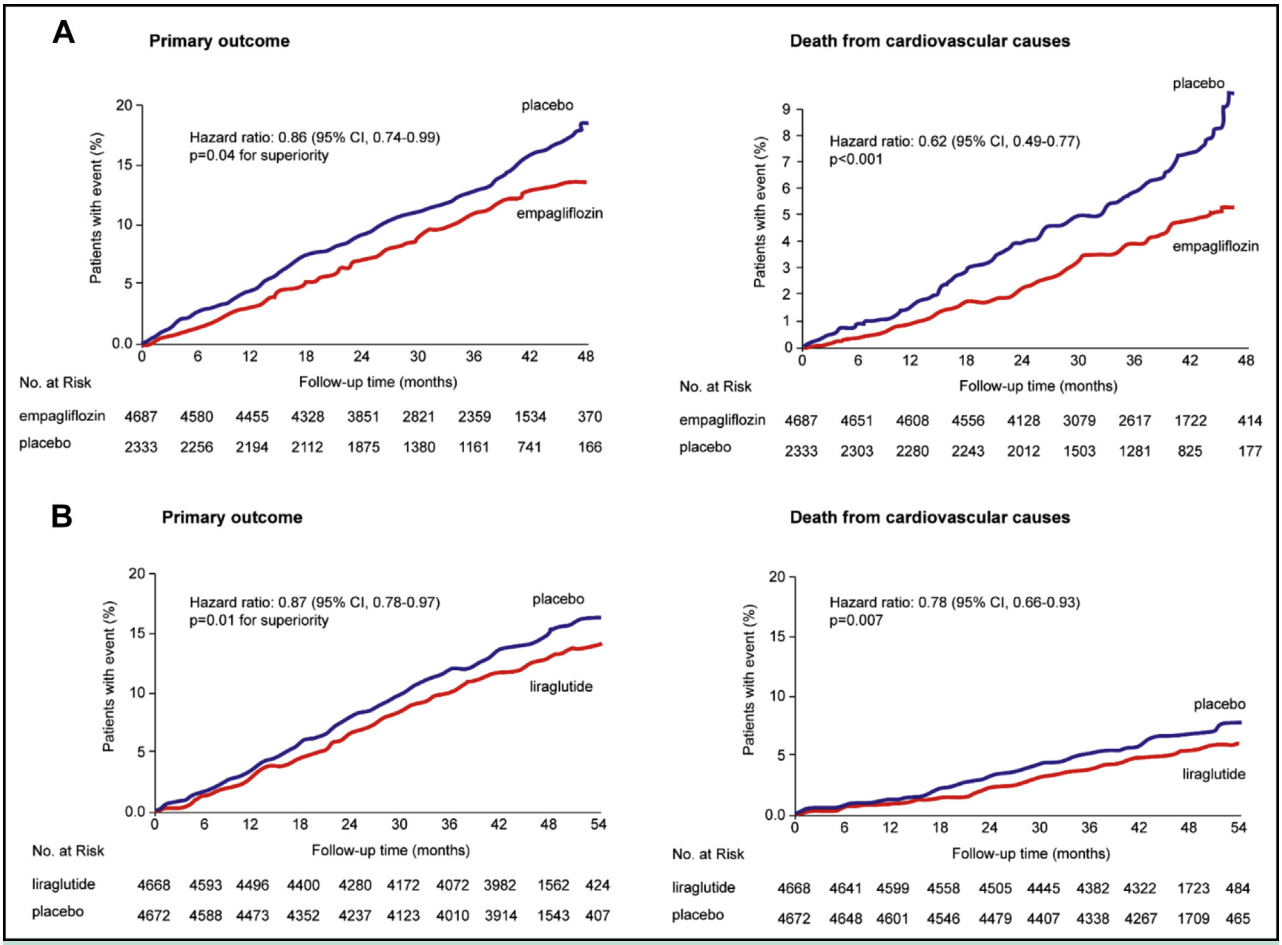

Figure Cumulative incidence of the primary outcome and cardiovascular death in the Empagliflozin Cardiovascular Outcome Event Trial in Type 2 Diabetes Mellitus Patients–Removing Excess Glucose (EMPA-REG OUTCOME)[49] (**A**) and Liraglutide Effect and Action in Diabetes: Evaluation of Cardiovascular Outcome Results (LEADER)[47] (**B**) trials. Treatment with empagliflozin in EMPA-REG OUTCOME led to an early and unusual divarication of the curves already after 3-6 months, whereas in LEADER survival curves for 3-point major adverse cardiovascular events and cardiovascular death started to separate later, after 12-18 months from randomization. Reproduced from Zinman B, et al. Empagliflozin, cardiovascular outcomes, and mortality in type 2 diabetes. *N Engl J Med*. 2015;373:2117-2128. Copyright © 2015 Massachusetts Medical Society. Reprinted with permission from Massachusetts Medical Society; and from Marso SP, et al. Liraglutide and cardiovascular outcomes in type 2 diabetes. *N Engl J Med*. 2016;375:311-322. Copyright © 2016 Massachusetts Medical Society. Reprinted with permission from Massachusetts Medical Society.

among cardiologists and diabetologists because—for decades—no randomized clinical trials in diabetes have demonstrated such a significant impact on CV and total mortality. In EMPA-REG OUTCOME, 7020 T2DM patients at high CV risk were randomized to receive 10 mg or 25 mg of empagliflozin or placebo once daily. After a median observation time of 3.1 years, empagliflozin (pooled 10 mg and 25 mg doses) significantly reduced the primary composite outcome of CV death, nonfatal MI, or nonfatal stroke (HR 0.86; 95% CI, 0.74-0.99; $P = .04$ for superiority; **Figure**).[49] Although empagliflozin did not show a direct effect on the rates of MI or stroke, death from CV causes, hospitalization for HF, and death from any cause were reduced by 38%, 35%, and 32%, respectively. A subgroup analysis of the EMPA-REG OUTCOME data confirmed that empagliflozin reduces HF hospitalization and CV death, with a consistent benefit in patients with and without baseline HF.[74] As compared with the recent LEADER trial, in which the effects of liraglutide were seen after 12 months, benefits of empagliflozin emerged much earlier, suggesting that hemodynamic factors may be significantly involved (**Figure**, **Table 2**).[75] This hypothesis is supported by the effects of empagliflozin on blood pressure and by the fact that risk of MI and stroke was not affected, whereas major differences were observed for HF. The reduction in blood pressure cannot entirely explain the rapid CV effects of empagliflozin because previous trials with blood pressure−lowering drugs took much longer to show reductions in CV outcomes.[6] Undoubtedly, volume depletion plays a major role in the reductions of HF hospitalizations, and this was also demonstrated by a 4% increase in hematocrit. Cardiac utilization of β-hydroxybutyrate in place of fatty acids might also contribute to transduce oxygen consumption into work efficiency at the mitochondrial level.[76] Although further studies are needed to explain the improvement of CV outcomes with empagliflozin, the benefits of this drug on CV outcomes is indisputable, at least as far as HF and CV mortality are concerned. A very recent meta-analysis including 81 trials with a total of 37,195 patients and mean follow-up of 89 weeks showed that SGLT2 inhibitors were associated with a lower risk of all-cause mortality (odds ratio [OR] 0.72; 95% CI, 0.59-0.86; $P < .001$), CV mortality (OR 0.67; 95% CI, 0.53-0.84; $P = .001$), and HF (OR 0.67; 95% CI, 0.51-0.87; $P = .003$), but a similar risk of MI (OR 0.89; 95% CI, 0.74-1.09; $P = .29$) and stroke/transient ischemic attack (OR 1.09; 95% CI, 0.87-1.37; $P = .47$) as compared with placebo. The reduction in all-cause mortality was noticed with empagliflozin but not with other SGLT2 inhibitors.[77] A potential harm was observed with dapagliflozin on CV mortality (OR 2.15; 95% CI, 0.92-5.04; $P = .08$).[77]

CONCLUSIONS

The management of CVD in patients with T2DM is a fast-growing field. Over the last few years several trials have proven CVD safety of different antidiabetic drugs, whereas other studies—namely EMPA-REG OUTCOME, LEADER, SUSTAIN-6, and IRIS—have shown a benefit of empagliflozin, liraglutide, semaglutide, and pioglitazone on CV outcomes. Although these data are very promising, there remain important aspects that require clarification. These include (1) the exact mechanisms by which these drugs may have yielded rapid CV benefits as compared with other classes of antidiabetic drugs; (2) which patients may benefit more from these drugs (ie, patients with HF, kidney disease, etc); and (3) whether these drugs are equally effective in T2DM patients without CVD (primary prevention). Ongoing and future studies will help to clarify these important issues.

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