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Cardiovascular Safety Profile of Currently Available Diabetic Drugs

Komola Azimova, BS, Zinnia San Juan, MD, Debabrata Mukherjee, MD, MS, FACC

Department of Internal Medicine, Texas Tech University Health Sciences Center, Paul Foster School of Medicine, El Paso, TX

ABSTRACT

Background: Cardiovascular disease is the leading cause of morbidity and mortality among patients with diabetes, underscoring the importance of choosing drugs that do not increase cardiovascular risk and reduce the risk of cardiovascular events. Since 2008, the US Food and Drug Administration has recommended that new drugs for type 2 diabetes undergo clinical trials to demonstrate cardiovascular safety in addition to glycemic benefit. In 2012, the European Medicines Agency issued a similar recommendation.

Methods: We searched the PubMed, Cochrane CENTRAL, EMBASE, and CINAHL databases from inception through August 2013 and compiled and reviewed the existing data on the cardiovascular safety profiles of currently available diabetic drugs.

Results: While intensive glycemic control in diabetics has been consistently shown to reduce the risk of microvascular complications, the data on macrovascular risk reduction have not been as clear, and questions have been raised about possible increases in cardiovascular morbidity and mortality.

Conclusion: Careful selection of drug therapy—paying particular attention to cardiovascular safety—is important in optimizing diabetic therapy.

Address correspondence to
Debabrata Mukherjee, MD, MS, FACC
Chief, Cardiovascular Medicine
Professor and Acting Chairman
Department of Internal Medicine
Texas Tech University Health Sciences Center
Paul Foster School of Medicine
4800 Alberta Ave.
El Paso, TX 79905
Tel: (915) 215-5223
Email: debabrata.mukherjee@ttuhsc.edu

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INTRODUCTION

Patients with diabetes often present with atherosclerosis and are at an increased risk for morbidity and mortality from cardiovascular disease (CVD). The risk for stroke, heart disease, and death from heart disease in patients with diabetes is twice that of patients without diabetes.[1] While the benefit of intensive glycemic control is well established for microvascular complications, data on its effect on macrovascular complications have been disparate, with some studies showing benefit, some showing no difference, and others showing increased total and cardiovascular (CV) mortality.[2-9] Intensive glycemic control must therefore be considered in the context of multifactorial risk reduction that has been shown to reduce CV mortality and events.[10]

The drugs used in the treatment of diabetes have potential CV effects, either beneficial or harmful. In its 2008 Guidance for Industry publication, the US Food and Drug Administration (FDA) issued detailed recommendations to drug developers for demonstrating that new and existing therapies will not result in an unacceptable increase in CV risk.[11] The European Medicines Agency (EMA) issued similar guidelines in 2012 for drug developers to investigate and rule out potentially harmful drug interactions.[12]

EPIDEMIOLOGY

An estimated 1.9 million people aged 20 years or older in the United States were diagnosed with diabetes in 2010.[1] Diabetes is the seventh leading cause of mortality in the United States and a major cause of CVD and stroke. Patients with type 2 diabetes mellitus have a 3-fold increase in CV mortality and a 2-fold increase in overall mortality compared to age-matched patients without diabetes.[1,13] According to the 2007-2009 National Health Interview Survey, oral antidiabetic medications are the primary mode of treatment in more than half (58%) of adults diagnosed with diabetes, and 14% of these patients take oral medication in combination with insulin; these figures suggest a high potential for the occurrence of adverse drug effects, including CV events.

COST

The total cost of treating diabetes in the United States is estimated at $174 billion, more than twice the medical cost for people without diabetes.[1] Attention to the CV effects of drug therapy may reduce consequent CV morbidity and mortality and help reduce the total financial burden.

CURRENTLY AVAILABLE DIABETIC DRUGS

In the following sections and in the Table we review the CV safety profiles of currently available antidiabetic agents for the consideration of clinicians to help them guide and individualize patient management.

Biguanides (Metformin)

The biguanide metformin is considered a first-line agent for the treatment of type 2 diabetes mellitus because it is effective in lowering glucose, has an extensive history of use, is low in cost, has a neutral effect on weight, causes minimal hypoglycemia, and has the potential to decrease CV events.[14] The United Kingdom Prospective Diabetes Study (UKPDS), a subpopulation study that included overweight patients with diabetes, found that metformin, when initiated early in the disease, is associated with significant risk reductions of 32% for any diabetes-related endpoint (sudden death, fatal or nonfatal myocardial infarction [MI], angina, heart failure, stroke, and amputation), 42% for diabetes-related death (death from MI, stroke, peripheral vascular disease), and 36% for all-cause mortality. Metformin showed a significantly greater effect than chlorpropamide, glibenclamide, or insulin on any diabetes-related endpoint, all-cause mortality, and stroke.[15] A smaller study using metformin as an add-on to insulin confirmed as a secondary endpoint that the drug reduced the risk of macrovascular disease after a follow-up period of 4.3 years.[16] One metaanalysis suggests that the use of metformin in younger patients and for longer periods of time may correlate better with CV event reduction as compared with placebo or no therapy.[17]

Lower-quality data show benefits in other clinical CV outcomes. In a retrospective observational study involving 5,631 patients with diabetes, the incidence of congestive heart failure (CHF) was lower over a 4.7-year follow-up period in patients using metformin compared to patients on sulfonylurea treatment. Metformin treatment did not increase the risk of developing CHF regardless of dose.[18] Another study showed lower 1-year all-cause mortality, no difference in all-cause readmission, and a lower risk of readmission for heart failure in patients treated with metformin.[19] A 2-year study showed that metformin use led to significantly lower CV mortality (hazard ratio [HR] 0.79; 95% confidence interval [CI] 0.65-0.96; P=0.02) and lower rates of MI, stroke, or death (HR 0.88; 95% CI 0.79-0.99; P=0.04).[20] In patients with CHF, metformin therapy was associated with lower all-cause mortality (HR 0.69; 95% CI 0.54-0.90; P=0.006) as well as CV mortality (HR 0.80; 95% CI 0.61-1.04; P=0.10).

Metformin may also have an effect on several CV risk factors, including lipid profile and blood pressure.[21] Patients with diabetes are more likely to have hypertension and higher lipid values and are more likely to be overweight than those without diabetes.[22] Metformin decreases plasma triglyceride levels, presumably by lowering hepatic lipoprotein secretion.[23] In a study, metformin led to a 38% decrease in plasma triglycerides by lowering very low density lipoprotein (VLDL) cholesterol levels in patients with hypertriglyceridemia and glucose intolerance.[23] Another study evaluating the lipid levels of 9 patients with mild non–insulin-dependent diabetes mellitus after 3 months of metformin treatment found similar improvement in fasting plasma triglyceride and VLDL cholesterol levels along with a significant increase in high density lipoprotein (HDL) cholesterol levels.[24] The lipid-lowering effects of metformin have also been observed in a prospective randomized controlled study of nondiabetic male patients with coronary artery disease (CAD) who have undergone a coronary artery bypass graft (CABG) or angioplasty. Among these patients with normal body weight, metformin lowered the low density lipoprotein (LDL)/HDL cholesterol ratio by 10%, total cholesterol by 9%, LDL cholesterol by 12%, and apolipoprotein B by 7%. No weight change was observed in patients with normal body weight, although overweight patients did experience some weight loss (3.0 kg).[25] Overall, metformin is associated with slight weight loss ranging from 0.6 kg to 2.9 kg.[26,27]

Animal studies show that metformin may limit cardiac remodeling and reduce MI size when administered at the time of reperfusion.[28,29] Bhamra et al showed that metformin administration within 15 minutes of reperfusion reduced MI size significantly in both nondiabetic (62% $\pm$ 3.0% in the control group vs 35% $\pm$ 2.7% in the metformin group; $P<0.03$) and diabetic (60% $\pm$ 3.8% in the control group vs 43% $\pm$ 4.7% in the metformin group; $P<0.05$) rat hearts.[29] The mechanism by which metformin reduces ischemic effects may be via the induction of Akt phosphorylation at the time of reperfusion and the inhibition of the mitochondrial permeability transition pore opening that in turn reduces the oxidative stress of cardiac myocytes.[30] Other animal studies demonstrate that metformin also improves cardiac function in response to stress and provides cardioprotection against ischemia.[30-32]

Table. Cardiovascular Safety with Diabetic Drugs

Drug	Pros	Cons	Compatible with	Effect on Weight
Biguanides				
•Metformin	•Significant reduction of cardiovascular events •Reduces blood pressure •Reduces LDL levels; increases HDL levels	•Lactic acidosis (rare) •Caution indicated in older patients with CHF, renal or hepatic insufficiency	•Sulfonylureas •Meglitinides •Thiazolidinediones •DPP-4 inhibitors •GLP-1 agonists •Dopamine-2 receptor agonists •SGLT-2 inhibitors •Insulin	•Weight neutral or slight weight loss ranging from 0.6 kg to 2.9 kg
Sulfonylureas				
•Tolbutamide[a] •Chlorpropamide •Gliclazide[a] •Glipizide •Glimepiride •Glyburide •Glibenclamide[a]	•Newer-generation sulfonylureas (gliclazide and glimepiride) may have decreased CV risk	•May increase risk of CV events •May prevent protective ischemic cardiac preconditioning after MI	•Biguanides •Thiazolidinediones •DPP-4 inhibitors •GLP-1 agonists •Dopamine-2 receptor agonists •SGLT-2 inhibitors •Bile acid sequestrants •Basal insulin	•Weight gain of 2.06 kg compared to placebo when used in combination with metformin
Meglitinides				
•Repaglinide •Nateglinide	•Repaglinide associated with decrease in markers of inflammation, platelet activation, and lipid parameters	•May increase ischemic events and LVD in patients with underlying severe CAD •No effect on reducing CV outcomes •Less effective overall than metformin in delaying development of diabetes or CV outcomes	•Biguanides •Thiazolidinediones •Alpha-glucosidase inhibitors •Basal insulin	•Weight gain of 1.77 kg compared to placebo when used in combination with metformin
Thiazolidinediones				
•Pioglitazone •Rosiglitazone	•Pioglitazone associated with reduced CV risk, all-cause mortality, nonfatal MI, and stroke	•Increased CV risk with age and duration of diabetes •Increased risk of MI, CHF and mortality, and triglyceride and LDL cholesterol levels with rosiglitazone •Possible CHF exacerbation in older patients with underlying CAD	•Biguanides •Meglitinides •DPP-4 inhibitors •GLP-1 agonists •Dopamine-2 receptor agonists •SGLT-2 inhibitors •Bile acid sequestrants •Sulfonylureas •Insulin	•Weight gain of 2.08 kg compared to placebo when used in combination with metformin

Table. Continued

Drug	Pros	Cons	Compatible with	Effect on Weight
DPP-4 inhibitors				
•Alogliptin •Saxagliptin •Sitagliptin •Linagliptin •Vildagliptin[a]	•May have beneficial cardioprotective effects •Alogliptin does not increase risk of major CV events •Saxagliptin did not increase major CV events	•Hospitalization for heart failure was higher with saxagliptin in the SAVOR-TIMI 53 trial	•Biguanides •Sulfonylureas •Thiazolidinediones •Basal insulin •Inadequately studied use with GLP-1 agonists and prandial insulin	•Weight neutral •Saxagliptin associated with slight weight loss of 0.4 kg
GLP-1 agonists				
•Exenatide •Exenatide XR •Liraglutide •Albiglutide	•Modest weight loss •Antithrombotic, antiinflammatory, lipid-lowering effects •Moderate decrease in risk of CVD and CVD-related hospitalizations with exenatide	•Nausea is the most common side effect of exenatide •Reports of acute pancreatitis associated with exenatide	•Biguanides •Sulfonylureas •Thiazolidinediones •Basal insulin •Inadequately studied use with DPP-4 inhibitors and prandial insulin	•Weight loss ranging from 3 kg to 5 kg
Alpha-glucosidase inhibitors				
•Acarbose •Miglitol	•Reduction in hypertension, CV events, and development of type 2 diabetes mellitus	•Common side effects include abdominal pain, diarrhea, and flatulence	•Biguanides •Sulfonylureas •Meglitinides •Thiazolidinediones •Insulin	•Weight neutral, with possible slight weight loss of 1.0 kg
Amylin analogs				
•Pramlintide	•Reduction in CV risk factors including hsCRP, cholesterol and triglyceride levels, and body weight	•Common side effects include nausea, hypoglycemia, vomiting, headache, abdominal pain, weight loss, and fatigue	•Prandial insulin	•Weight loss of 1.5 kg
Dopamine-2 receptor agonists				
•Bromocriptine-QR	•Improves lipid profile •May reduce risk of MI, stroke, revascularization, and hospitalization for angina or CHF •May reduce risk of major CV events (MI, stroke, and CV death)	•Modest efficacy •High rates of nausea •Lack of long-term efficacy and safety data •Considerable cost	•Biguanides •Sulfonylureas •Limited data on use with thiazolidinediones and insulin	•Weight neutral

Table. Continued

Drug	Pros	Cons	Compatible with	Effect on Weight
Bile acid sequestrants				
•Colesevelam	•Lowers LDL •Long-term adherence associated with decreased risk of acute MI and stroke	•Increases triglycerides	•Biguanides •Sulfonylureas •Meglitinides •Thiazolidinediones •GLP-1 agonists •Insulin	•Weight neutral
SGLT-2 inhibitors				
•Canagliflozin •Dapagliflozin •Empagliflozin	•Reduces body weight and systolic blood pressure	•Lack of long-term efficacy and safety data •Common side effects include genital tract infections and osmotic diuresis	•Biguanides •Sulfonylureas •Thiazolidinediones •DPP-4 inhibitors •Insulin	•Weight loss ranging from 2 kg to 3 kg

[a]Not available in the United States.

CAD, coronary artery disease; CHF, congestive heart failure; CV, cardiovascular; CVD, cardiovascular disease; DPP-4, dipeptidyl peptidase 4; GLP-1, glucagon-like peptide-1; HDL, high density lipoprotein; hsCRP, high sensitivity C-reactive protein; LDL, low density lipoprotein; LVD, left ventricular dysfunction; MI, myocardial infarction; SAVOR-TIMI 53, Saxagliptin Assessment of Vascular Outcomes Recorded in Patients with Diabetes Mellitus—Thrombolysis in Myocardial Infarction study; SGLT-2, sodium-glucose cotransporter-2.

Lactic acidosis can occur with metformin use although at a much lower incidence than with its predecessor phenformin. Despite the rarity of this adverse effect, concern remains high because of the high case-fatality rate. Most cases have occurred in patients with shock or tissue hypoxia or in the presence of predisposing conditions such as renal failure, liver failure, and heart failure, that may cause lactic acidosis. When used according to current prescribing recommendations, the risk of metformin-induced lactic acidosis is close to zero.[33] A review of lactic acidosis in patients with diabetes and CHF concludes that metformin is a rare cause of lactic acidosis, and although an underlying condition can predispose patients to lactic acidosis, existing evidence suggests that metformin use is associated with improved outcomes rather than an increased risk.[34] A reevaluation of the current contraindications to metformin, citing no increased incidence of lactic acidosis despite the use of the drug in contraindicated situations, has been recommended.[35]

Sulfonylureas

The controversial effect of sulfonylureas on the CV system surfaced after the 1970s University Group Diabetes Program (UGDP) study showed that patients treated with the sulfonylurea tolbutamide experienced excess cardiac deaths compared to placebo or insulin treatments.[36] The UKPDS did not confirm the findings; that study showed no increase in fatality in patients with diabetes who were treated with sulfonylureas at the time of acute MI.[3] However, other studies have supported the initial concern from the UGDP. An observational study from the Mayo Clinic looked at early mortality in patients undergoing angioplasty for acute MI and found that treatment with sulfonylureas at the time of the MI was associated with increased fatality.[37] The Diabetes Mellitus, Insulin Glucose Infusion in Acute Myocardial Infarction (DIGAMI) study showed improved outcomes in patients treated with intravenous insulin-glucose infusions at the time of acute MI and demonstrated that the poorest outcomes were seen in patients who received sulfonylureas and no insulin-glucose infusions.[38] A Canadian retrospective population study showed an increase in the primary outcomes of all-cause mortality and fatal MI in patients treated with higher doses of first-generation sulfonylureas and glyburide but not metformin.[39] A retrospective study of US veterans showed an increase in the composite outcome of hospitalization for acute MI or stroke, or death, in patients treated with sulfonylureas compared with metformin with no difference between glyburide and glipizide.[40]

A double-blind randomized trial involving 304 patients with diabetes and CAD showed support for the use of metformin over sulfonylureas as a first-line therapy for patients with diabetes and coronary disease.[41] Patients were randomly assigned to

receive either glipizide or metformin for 3 years and were monitored for 5 years. After follow-up, 35% of glipizide users experienced the primary outcome of a composite of nonfatal CV events and death from any cause compared to 25% of metformin users. The primary outcome was less likely with metformin than with glipizide (HR 0.54; P=0.026). Mortality was also higher in the glipizide group than in the metformin group. Weight loss was more likely with metformin use, while weight gain occurred with glipizide use.

Sulfonylureas are thought to prevent the protective ischemic cardiac preconditioning that is needed as an adaptive response to reduce damage following MI.[21,42,43] They act primarily on the pancreatic β-cells to exert insulinotropic effects, although some may also bind cardiac and vascular receptors to possibly exert adverse cardiac effects.[43] The first-generation sulfonylureas, including tolbutamide, possess lower pancreatic affinity and thus are more likely to bind cardiac receptors and interfere with cardiac ischemic preconditioning.[43,44] Proposed mechanisms for adverse cardiac effects include the effect of sulfonylureas on ATP-dependent potassium channels on cardiac cells, resulting in hyperpolarization and inadequate coronary vasodilation and in a larger area of myocardial damage at the time of acute MI. Arrhythmogenic effects are also possible.

The second-generation sulfonylureas, glimepiride, glyburide (available as glibenclamide outside the United States), glipizide, and gliclazide (not available in the United States), have a lower affinity for CV tissue and may have fewer unfavorable effects, although not all data have been consistent. Glibenclamide is shown to be harmful to patients with type 2 diabetes mellitus and CAD, even when combined with metformin, and avoiding the drug is suggested in such high-risk patients.[45] A retrospective cohort study involving 11,141 patients with type 2 diabetes mellitus revealed no significant difference in overall mortality with the use of glipizide, glyburide, or glimepiride monotherapy, but the study did find a nonsignificant trend towards increased overall mortality with glyburide and glipizide vs glimepiride in patients with documented CAD.[46] A French retrospective study found decreased in-hospital mortality after acute MI in patients previously treated with sulfonylureas compared to patients treated with other oral agents, treated with insulin, and on no treatment.[47] The use of gliclazide and glimepiride was associated with a decreased risk of arrhythmia and ischemic complications, leading to better in-hospital outcomes compared to glibenclamide use. Interestingly, in older patients with a history of acute MI or percutaneous coronary intervention, no significant difference has been found between the effect of glibenclamide and gliclazide on ischemic preconditioning of the heart.[44] This finding may be attributable to several factors such as age, cohort size, degree of glycemic control, length of diabetic history, and CV risk factors.

CV mortality, nonfatal MI, and risk of mortality are increased in monotherapy with glimepiride, glibenclamide, gliclazide, and tolbutamide compared with metformin, suggesting that sulfonylureas may not be the best option for the initial management of patients with diabetes who are at risk for CV events.[48] The newer sulfonylurea gliclazide has been suggested as a better sulfonylurea agent to use for the treatment of type 2 diabetes mellitus. While previous evidence from the Action in Diabetes and Vascular Disease: Preterax and Diamicron Modified Release Controlled Evaluation (ADVANCE) trial reveals that intensive glucose control with gliclazide has no significant effect on major macrovascular events, more recent evidence shows gliclazide to be the only sulfonylurea associated with a lower risk of CV events and mortality—similar to metformin.[6,47,48] Similarly, a Danish metaanalysis of 72 randomized controlled trials involving sulfonylurea monotherapy for 24 weeks or more in patients with type 2 diabetes mellitus found that all-cause mortality; CV mortality; and a composite of MI, stroke, and CV mortality were increased in patients treated with glibenclamide, glipizide, and tolbutamide but not gliclazide or repaglinide compared to metformin.[49] These findings underscore that pancreatic cell-specific sulfonylureas, particularly gliclazide, may be beneficial in decreasing the risk of adverse CV outcomes, but sufficient evidence is still lacking that proves sulfonylurea monotherapy is a safe initial treatment option for patients with diabetes and underlying CVD.[49] In addition, higher doses of sulfonylureas have been associated with a greater risk of developing heart failure than lower doses of sulfonylureas (HR 1.38; 95% CI 1.20-1.60), as well as higher doses of metformin (adjusted HR 1.24; 95% CI 1.0-1.54).[18] Sulfonylureas have been associated with weight gain of approximately 2 kg compared to placebo when used in combination with metformin.[26,27]

Meglitinides

Meglitinides are insulin secretagogues that act on a different receptor but have a similar mode of action to sulfonylureas and exert similar but milder effects. Repaglinide and nateglinide are the 2 agents in this class that are currently available. These agents lower both glucose and hemoglobin A1c (HgA1c) levels without a significant effect on lipids. The CV safety profile of meglitinides is largely unknown.[45,50]

Although the effectiveness of repaglinide in controlling glucose levels is comparable to other antidiabetic agents, direct clinical evidence of its effect on CV outcomes and mortality is currently lacking.[51] In contrast to the findings of the Danish metaanalysis, a study comparing repaglinide with glibenclamide found that repaglinide led to increased ischemic events after 1 year of administration. However, patients on repaglinide had a baseline of more severe CAD compared to patients on glibenclamide, and adjustment for this finding reduced the relative risk.[50] Another study found that repaglinide controlled postprandial glucose excursion better than glimepiride and was associated with a significant decline in other surrogate CV markers, including markers of inflammation, platelet activation, and lipid parameters, suggesting a beneficial role in lowering CVD risk.[52] On the other hand, when compared to metformin, repaglinide was less effective in reducing similar CVD biomarkers of inflammation and endothelial dysfunction in nonobese patients with type 2 diabetes mellitus despite similar glycemic control.[53] Additionally, when used in combination with metformin, meglitinide use was associated with weight gain of approximately 1.77 kg compared to placebo.[26,27] In the Left Ventricular Dysfunction in Type 2 Diabetes Mellitus (DYDA) study, repaglinide therapy was an independent predictor of left ventricular dysfunction (LVD) after a 2-year follow-up in patients with diabetes without underlying cardiac disease at baseline; however, the exact role of repaglinide in LVD is uncertain.[54]

The Nateglinide and Valsartan in Impaired Glucose Tolerance Outcomes Research (NAVIGATOR) trial did not find nateglinide to improve CV outcomes in patients with impaired glucose tolerance and CVD or CV risk factors compared to placebo or valsartan treatment.[55,56] While valsartan at least decreased the incidence of type 2 diabetes mellitus by 14% in these patients, nateglinide had no effect on delaying the development of diabetes.

Thiazolidinediones

Thiazolidinediones (TZDs) agonize at 1 or more peroxisome-proliferator-activated receptors (PPARs) that regulate gene expression, promoting improved glucose utilization and decreased glucose production in peripheral tissue. The 2 currently available TZDs are pioglitazone and rosiglitazone.

Pioglitazone has been shown to reduce CV surrogate markers such as endothelial dysfunction, blood pressure, dyslipidemia, circulating levels of inflammatory cytokines, and prothrombotic factors.[57-59] It potently increases HDL and lowers triglycerides, apolipoprotein B, and dense LDL particles while increasing large LDL particles. The overall effect of pioglitazone on LDL is neutral in comparison to rosiglitazone, which significantly increases LDL cholesterol.[60] This difference is thought to be because of the difference in their agonist effect at the PPAR-alpha receptor.[60] Pioglitazone has also been shown to reduce carotid intima thickness and atheroma formation.[61] The PROactive study found that pioglitazone reduced the composite endpoint of all-cause mortality, nonfatal MI, and stroke in patients with type 2 diabetes mellitus who have a high risk of macrovascular events.[61] Post hoc analysis of this study supports the beneficial effect on HDL predicted by the reduction in CV events.[62]

The CV safety profile of rosiglitazone remains controversial, although its use is no longer restricted in the United States.[57] Inconsistent data associate rosiglitazone use with an increased risk of MI. Its association with CV and all-cause mortality also remains unclear.[63] Earlier studies that showed an increased risk of MI with an odds ratio of 1.43 (95% CI 1.03-1.98; P=0.03) also showed an increased risk of CV death with an odds ratio of 1.64 (95% CI 0.98-2.74; P=0.006),[64] while later evidence shows no associated increased risk of CV or all-cause mortality with rosiglitazone use.[63] A recent study supports this finding of no association between TZD use and increased CV deaths and also does not show any association with major CV events (including nonfatal MI and nonfatal CHF) among patients with diabetes compared with no TZD use.[65] However, when compared with other oral antidiabetic agents, TZD use, primarily use of rosiglitazone, was associated with an increased risk of CHF, acute MI, and mortality in older patients with diabetes.[66]

Both TZDs are known to cause dose-associated weight gain and fluid retention. TZD use is associated with weight gain of approximately 2.08 kg compared to placebo when used in combination with metformin.[26,27]

The incidence of CHF in TZD-treated patients is low, but the incidence of CHF is definitely higher in patients already treated with insulin who receive higher doses of the TZD and who have other risk factors for CHF.[27] Those who developed CHF with the use of pioglitazone in addition to insulin had underlying CAD. The studies that associated pioglitazone with increased CHF when added to insulin used higher doses of pioglitazone and included older patients with longer durations of diabetes mellitus who had preexisting microvascular and CV comorbidity. Neither TZD is recommended for older patients who may be at risk for congestive heart conditions. Both TZDs are contraindicated for patients with New York Heart Association functional class III-IV CHF.

Additionally, guidelines from the American Heart Association and the American Diabetes Association consensus statement require caution and careful clinical monitoring of patients being treated with a TZD for signs and symptoms of edema or CHF.[67]

Glucagon-Like Peptide 1 Agonists

Incretins are enteroendocrine peptides that augment insulin response in a glucose-dependent manner, regulate postprandial glucagon secretion, slow gastric emptying, and increase satiety by central mechanisms. Glucagon-like peptide 1 (GLP-1) and glucose-dependent insulinotropic polypeptide (GIP) are 2 of these incretins whose secretions are known to be impaired in type 2 diabetes mellitus; GLP-1–based therapy is meant to address this deficiency.[68] The currently available GLP-1 agonists include exenatide, exenatide extended-release, liraglutide, and albiglutide; they have been shown to provide effective HgA1c reduction of 1%-1.6%.[69-71]

In vitro studies have shown that GLP-1 agonist exendin-4 can stimulate human coronary endothelial cell proliferation and vasodilation through the nitric oxide pathway, as well as the proliferation of vasculoprotective endothelial progenitor cells. Subsequent animal studies confirm that GLP-1 analogues can improve cardiac function and morphology independent of their effect on glycemia.[72] In vitro studies also suggest that GLP-1 agonists may have antiatherosclerotic effects, and subsequent animal studies have shown consistent evidence of the delayed development of atherosclerosis and reduced plaque size following incretin-based therapies in diabetic mice.[73,74]

Original studies of exenatide efficacy showed a significant 2.8-3.1 kg weight reduction compared to placebo when used as monotherapy[75] and a 1.5-1.8 kg weight reduction when used with other oral agents or insulin.[69] Liraglutide has been shown to cause significant (4.0 $\pm$ 5.0 kg) body weight reduction in patients with type 2 diabetes mellitus and has also been shown to cause twice as much weight loss as placebo (n=27; 6.8 vs 3.3 kg; $P<0.001$) in high-risk (overweight/obese and prediabetic) patients without diabetes. Another study of overweight/obese patients without diabetes showed that liraglutide added after 5% weight loss from diet and exercise allowed significantly more patients to maintain weight loss and lose more weight compared to placebo patients.[76] The Diabetes Therapy Utilization: Researching Changes in A1C, Weight and Other Factors Through Intervention with Exenatide Once Weekly (DURATION) trials have shown significant reduction in body weight (2.5 kg [2.8-2.3 kg]) after 24 to 30 weeks of treatment with extended-release exenatide over comparators.[77]

GLP-1 agonists have also been shown to affect surrogate CV markers beneficially, including increasing left ventricular ejection fraction in the setting of cardiac insufficiency and MI and improving exercise resistance in patients with and without diabetes who have cardiac insufficiency.[78] Liraglutide treatment significantly reduced postprandial excursions of triglyceride and apolipoprotein B48 in patients with type 2 diabetes mellitus after a fat-rich meal, independently of gastric emptying.[79] In the DURATION trials, treatment with extended-release exenatide was associated with modest but significant reductions in fasting lipid levels (total cholesterol, 6.5 mg/dL; LDL cholesterol, 3.9 mg/dL; triglyceride, 6%) and blood pressure (systolic blood pressure, 2.8 mmHg; diastolic blood pressure, 0.8 mmHg). GLP-1 agonists have also been shown to directly affect the vasculature and kidneys by promoting vasodilation and inducing diuresis and natriuresis, resulting in an overall minor reduction of systolic blood pressure by 2-5 mmHg.[59] GLP-1–induced improvement of all these CV markers is postulated to improve clinical outcomes.

A retrospective database review of exenatide administration showed a significant (20%) decreased risk of CVD and CVD-related hospitalizations in patients with type 2 diabetes mellitus.[80] Overall, incretin-based therapies appear to have a beneficial effect on CV risk factors in patients with diabetes, although their long-term safety profile and the direct clinical benefit to CV outcomes remain to be determined.

Dipeptidyl Peptidase 4 Inhibitors

Dipeptidyl peptidase 4 (DPP-4) is a ubiquitous enzyme that degrades many targets such as GLP-1; the pharmacologic inhibition of DPP-4 prolongs the bioavailability of endogenous GLP-1. Currently, 4 DPP-4 inhibitors—sitagliptin, saxagliptin, linagliptin, and alogliptin—are available in the United States, and vildagliptin is available in Europe and Australia. These drugs typically cause a 0.6%-0.9% HgA1c reduction, improve postprandial glucose, are weight neutral, and are generally well tolerated.[26,27] In addition to their glucose-lowering effects, DPP-4 inhibitors may have beneficial pleiotropic effects on the CV system.[81] Some of these beneficial effects may be through GLP-1–dependent mechanisms, while others are postulated to occur through other DPP-4 targets independent of their effect on GLP-1. These targets include stromal-derived factor-1a whose prolongation leads to stimulation of endothelial progenitor cells involved in endothelial homeostasis and vascular repair. Animal studies also show a reduction in infarct size and the activation of

cardioprotective molecular pathways with DPP-4 inhibitor use.[72] These drugs are shown to prevent atherosclerosis and myocardial injury, improve endothelial dysfunction and lipid profile, lower blood pressure, and decrease arrhythmia after CABG surgery.[82] However, these studies show no significant effects of GLP-1 administration on CHF.

A metaanalysis of randomized trials found a marked reduction in risk for CV outcomes with DPP-4 inhibitor use, even when compared to metformin monotherapy, suggesting that these agents may be beneficial to high-risk patients.[59,83] Interestingly, a combination of DPP-4 inhibitor and metformin therapy did not produce any further reduction in adverse CV events. These findings suggest that DPP-4 inhibitors may be considered for patients with type 2 diabetes mellitus, who are unable to take metformin, are at a higher risk of developing CVD, or have ventricular dysfunction.

Alogliptin is not associated with increased CV risk in patients with diabetes when compared to other therapies or placebo.[84] In the recent Examination of Cardiovascular Outcomes with Alogliptin versus Standard of Care (EXAMINE) study, the effect of alogliptin vs placebo was compared in patients with type 2 diabetes mellitus who had either an acute MI or unstable angina requiring hospitalization. Among the 5,380 patients who were followed for up to 40 months, 11.3% of the patients assigned to alogliptin experienced a primary endpoint of a composite of death from CV causes, nonfatal MI, or nonfatal stroke compared to 11.8% assigned to placebo, a nonsignificant difference. These findings show that the use of alogliptin in the setting of acute coronary syndrome does not increase the risk of a major adverse cardiac event compared with placebo.[85]

Another major trial, the Saxagliptin Assessment of Vascular Outcomes Recorded in Patients with Diabetes Mellitus—Thrombolysis in Myocardial Infarction study (SAVOR-TIMI 53), looked at the effect of saxagliptin use vs placebo over a 2.1-year period on the primary endpoint of a composite of CV death, MI, or ischemic stroke in 16,492 patients with a history of type 2 diabetes mellitus or a risk for CV events.[86] The study also looked at the secondary endpoint, a composite of CV death, MI, stroke, hospitalization for unstable angina, coronary revascularization, and heart failure. No significant difference was found in the primary endpoint (7.3% of saxagliptin vs 7.2% of placebo subjects; HR 1.00; 95% CI 0.89-1.12; P=0.99) or secondary endpoint (12.8% of saxagliptin vs 12.4% of placebo subjects; HR 1.02; 95% CI 0.94-1.11; P=0.66). Hospitalization for heart failure was higher in the saxagliptin group (3.5% vs 2.8% in placebo; HR 1.27; 95% CI 1.07-1.51; P=0.007). Other major long-term prospective clinical trials involving other DPP-4 inhibitors are underway to determine the effects of DPP-4 inhibitors on CV risk in patients with type 2 diabetes mellitus who are at risk for CVD (see TECOS on sitagliptin and CAROLINA on linagliptin).[87,88] Results from these studies will hopefully further elucidate the CV safety of DPP-4 inhibitors in patients with diabetes.

Alpha-Glucosidase Inhibitors

Alpha-glucosidase inhibitors (AGIs), including acarbose and miglitol, competitively block alpha glucosidase in the proximal small bowel and prevent complex carbohydrate digestion, resulting in reduced postprandial hyperglycemia.[21] Of the 2 AGIs approved in the United States, acarbose is the more widely studied. The 2002 randomized controlled trial Study to Prevent Non-Insulin Dependent Diabetes Mellitus (STOP-NIDDM) showed a 34% relative risk reduction (RRR) of hypertension and a 49% RRR of CV events, as well as a 36% RRR of developing type 2 diabetes mellitus in patients with impaired tolerance to glucose.[89,90] The prandial antihyperglycemic action of acarbose most likely contributes to a reduction of risk of developing CVD and hypertension, as postprandial hyperglycemia is known to have harmful effects on oxidative stress and atherothrombosis.[90-92] Although the exact mechanisms are unknown, recent studies suggest that acarbose stimulates GLP-1 secretion, possibly explaining in part its positive CV effects.[93] Overall, acarbose seems to be a reasonable agent for reducing CVD risk in addition to lowering HgA1c levels in people with diabetes, but sufficient evidence is currently lacking to conclude that acarbose is superior to metformin or some sulfonylureas.[87] Acarbose must be considered second-line therapy, alone or in addition to metformin or sulfonylureas, until further data prove its long-term CV safety.

Other Agents

Pramlintide (Symlin) is an analogue of amylin, a pancreatic hormone that is cosecreted with insulin from pancreatic β-cells to regulate blood glucose levels by several mechanisms: slowing gastric emptying, preventing postprandial hyperglycemia, and suppressing food intake.[94] When used in combination with insulin therapy, pramlintide leads to modest dose-dependent reductions in HgA1c, lower cholesterol and triglyceride levels, and weight loss.[95] A post hoc analysis of a 16-week, randomized, double-blind, placebo-controlled trial of the drug involving 211 patients with type 2 diabetes mellitus revealed a significant reduction in CV risk factors including triglyceride and high sensitivity C-reactive protein levels, although no changes were observed in blood

pressure and LDL and HDL cholesterol levels.[96] Pramlintide has been associated with weight loss of approximately 1.5 kg.[26,27] Other studies confirm its neutral effect on blood pressure.[95,97] Hypoglycemia is the main concern with pramlintide use, but an insulin dose reduction at the initiation of pramlintide has mitigated the risk of hypoglycemia. Evidence showing the direct effects of pramlintide use on CV events is currently lacking.

Other minor type 2 diabetes mellitus agents that may have CV significance include quick-release bromocriptine (Bromocriptine-QR, Cycloset) and colesevelam (Welchol). Bromocriptine-QR is an FDA-approved dopamine-2 receptor agonist for type 2 diabetes mellitus treatment that has been shown to reduce plasma glucose and HgA1c levels (approximately 0.4%-0.5%), free fatty acids, and triglycerides.[98] The Cycloset Safety Trial, a 1-year randomized clinical trial involving 3,070 subjects with type 2 diabetes mellitus, showed a 39% RRR in the prespecified endpoint of time to first CV event (including MI, stroke, revascularization, and hospitalization for angina) or CHF compared to placebo.[99] Post hoc analysis showed a 52% reduction in major CV endpoints (MI, stroke, and CV death).[100]

Colesevelam is a bile acid sequestrant that was initially used as a cholesterol-lowering agent and was known to decrease the risk of CV disease and CV events by this effect. It was subsequently shown to also have glucose-lowering effects in adults with primary hyperlipidemia and diabetes, specifically an approximate 0.5% HgA1c reduction in addition to a 16% reduction in LDL cholesterol, a 7.2% reduction in total cholesterol, and a 10.3% reduction in the non-HDL fraction.[101] Additionally, several randomized controlled clinical trials have shown that colesevelam add-on therapy improves glycemic and lipid parameters in patients with type 2 diabetes mellitus that is inadequately controlled with other antidiabetic therapies, including metformin, sulfonylureas, and insulin.[102-105] When combined with other antidiabetic agents, colesevelam increases treatment efficacy by providing greater glycemic and lipid control.[102] Its dual effect on CV risk factors glycemia and lipidemia may translate to a potential for lowering long-term healthcare costs associated with diabetic and CV complications.[106] A retrospective study of insurance-claim data involving 42,549 adults with hyperlipidemia and/or type 2 diabetes mellitus showed that longer adherence to colesevelam was associated with a 43% risk reduction of acute MI and stroke.[107] The long-term effects of colesevelam on CV outcomes are largely unknown.

Canagliflozin (Invokana) is a selective sodium-glucose cotransporter-2 (SGLT-2) inhibitor that reduces renal glucose reabsorption and thereby lowers blood sugar levels. Dapagliflozin is an SGLT-2 inhibitor approved by the EMA, but its approval was denied by the FDA in 2011 because of its association with increased risk of bladder and breast cancer.[108,109] Dapagliflozin was subsequently approved by the FDA in 2014 based on additional data. Most recently, empagliflozin was approved in August 2014.

In a recent metaanalysis,[110] SGLT-2 inhibitors were compared with placebo in 45 studies and with active comparators in 13 studies and were shown to produce a 0.66% reduction in HgA1c levels. In addition, SGLT-2 inhibitors led to a reduction in body weight ranging from 2 kg to 3 kg[26,27] and a reduction in systolic blood pressure compared to other agents.[110] This metaanalysis of CV outcomes (including CV death, MI, stroke, and hospitalization for unstable angina) based on 14 clinical trials involving 6,300 subjects treated with dapagliflozin showed an odds ratio of 0.73 (95% CI 0.46-1.16) compared with the control group.[110] Dapagliflozin, when used in patients with type 2 diabetes mellitus and comorbid CVD and hypertension over a 24-week treatment period, did not adversely affect CV safety. Two major studies found no increased risk of major CV events associated with dapagliflozin use.[111,112] The HR for the primary composite endpoint (CV death, MI, stroke, and hospitalization for unstable angina) was 0.819 (95% CI 0.583-1.152), and the HR for the composite endpoint of CV death, MI, and stroke was 0.793 (95% CI 0.537-1.170). A 24-week randomized, controlled study involving 808 subjects evaluated the efficacy and safety of dapagliflozin in patients with type 2 diabetes mellitus that is inadequately controlled with insulin and/or other antidiabetic agents.[113] The findings of the study included reductions in HgA1c and body weight as well as stable insulin dosing. In a 24-week randomized trial involving 182 subjects, dapagliflozin led to a reduction of 2.08 kg (95% CI 2.84-1.31; $P<0.0001$) in total body weight in patients with type 2 diabetes mellitus inadequately controlled with metformin.[114] Based on these data, dapagliflozin received EMA approval in 2012.[115] In a pooled metaanalysis study population of 5,261 subjects on dapagliflozin vs 3,021 subjects in comparator groups, dapagliflozin use was associated with an HR of 0.819 (95% CI 0.583-1.152) for the primary composite endpoint of CV death, MI, stroke, and hospitalization for unstable angina.[116] The HR for the secondary composite endpoint (CV death, MI, stroke, hospitalization for unstable angina, unplanned coronary revascularization, and hospitalization for heart failure) was 0.734 (95% CI 0.543-0.992). Additionally, dapagliflozin improved CV risk factors by reducing glycemic levels, body weight, lipid parameters, and

blood pressure while lowering rates of cardiac events in patients with type 2 diabetes mellitus. Canagliflozin combination therapy with metformin also appears to provide greater glycemic control in patients with diabetes who experience inadequate glycemic control with metformin monotherapy.[117] A 52-week study that randomized patients already on metformin and sulfonylureas into canagliflozin or sitagliptin treatment groups showed noninferiority of canagliflozin compared to sitagliptin in the primary endpoint of HgA1c reduction and significantly greater reductions in the secondary endpoints of fasting plasma glucose, systolic blood pressure, and percentage change in body weight.[118] However, the long-term effects of these agents on CV outcomes and mortality remain undetermined. Common adverse effects of SGLT-2 treatment include genital tract infections and osmotic diuresis.

Combination Therapy

An observational study of combination therapy with metformin and sulfonylureas showed no difference in CV mortality and all-cause mortality compared to metformin and diet after adjusting for all variables, suggesting that this combination is just as safe for use as metformin alone.[119] Randomized clinical trials show improved CV markers of lipids and inflammation with the combination of metformin and pioglitazone, as well as the addition of pioglitazone to insulin therapy.[62,120] Retrospective data show that the combination of metformin and pioglitazone decreases all-cause mortality and the combined endpoint of all-cause mortality, major CV events, and cancer.[121] A randomized controlled trial is currently underway to determine the effects of combining either pioglitazone or a sulfonylurea with metformin on CV events in patients with type 2 diabetes mellitus inadequately controlled with metformin alone.[122]

Another study is currently looking into the effect of combined vildagliptin and metformin therapy on atherothrombotic markers compared to metformin monotherapy in patients with diabetes and CAD.[123]

Combination therapy involving agents with modest effects on glycemic control, such as bromocriptine-QR, colesevelam, and pramlintide, may provide added benefits for patients with type 2 diabetes mellitus in terms of weight control and CV health. All 3 of these agents when used in addition to metformin, sulfonylureas, or insulin-based therapies have shown a significant reduction in CV risk factors including LDL cholesterol, triglycerides, and free fatty acids. Bromocriptine-QR, when used in combination with other antihyperglycemic drugs, has been shown to reduce the risk of major CV complications, including acute MI and stroke, suggesting that their use may be particularly beneficial to patients at higher risk for CVD.[99,100] Colesevelam, when used in combination with other antidiabetic agents, is shown to provide additional glycemic reduction and LDL cholesterol reduction.[106] The effects of these agents on clinical CV outcomes, specifically as part of combination therapy, are not known.

CLINICAL IMPLICATIONS

Generally, metformin is the first-line agent for the treatment of type 2 diabetes mellitus and may be used in combination with other antidiabetic agents when appropriate. It is weight neutral and may improve blood pressure and lipid parameters. Data for CV benefits with metformin are encouraging, with studies showing reductions in any diabetes-related endpoint, diabetes-related death, and all-cause mortality. Metformin's benefit in cardiac remodeling and cardioprotection against ischemic events remains to be validated in human studies. Studies indicate that the greatest benefit of metformin therapy is attained when it is used in younger patients and for longer periods of time. Caution is recommended when using metformin to treat older patients and patients with CHF; the drug is contraindicated for patients with renal or hepatic insufficiency or other comorbidities that may increase the risk for lactic acidosis. Lactic acidosis is rare but remains a concern because of its high case-fatality rate. Overall, metformin is an effective first-line therapy with encouraging CV benefits for type 2 diabetes mellitus treatment.

Evidence for the safety of sulfonylurea therapy is conflicting, whether the drug is administered as monotherapy or in combination with another agent such as metformin. Some findings reveal an increased risk of CVD and mortality associated with the use of sulfonylureas. When compared to metformin therapy, sulfonylurea use has been associated with an increased risk of developing heart failure, especially at higher doses, as well as with increased fatality when used at the time of an acute MI. The second-generation sulfonylurea glibenclamide is contraindicated in patients with type 2 diabetes mellitus and CAD, and other agents in this class such as gliclazide and glimepiride may be better options, as these drugs have been associated with a decreased risk of arrhythmia and ischemic complications. Although gliclazide is associated with a lower risk of CV events and mortality compared to the first-generation sulfonylurea tolbutamide, gliclazide use compared with metformin use has been shown to increase the primary outcome of a composite of nonfatal CV events and death from any cause. Overall, sulfonylurea monotherapy may not be appropriate for patients with diabetes who are at risk for CVD, as the drug is linked with possible CHF exacerbation,

nonfatal MI, and mortality risk compared with metformin therapy.

Meglitinide therapy with repaglinide has been shown to decrease CV markers including markers of inflammation, platelet activation, and lipid parameters, albeit less effectively than metformin.

The TZD pioglitazone reduces CV surrogate markers including endothelial dysfunction, blood pressure, dyslipidemia, circulating levels of inflammatory cytokines, and prothrombotic factors, as well as carotid intima thickness and atheroma formation. It has also been shown to lower the composite of all-cause mortality, nonfatal MI, and stroke in patients with type 2 diabetes mellitus at high risk for macrovascular events. TZD use, primarily rosiglitazone, is contraindicated in patients with heart failure, as it has been shown to increase the risk of CHF and mortality, particularly in older patients with preexisting microvascular and CV comorbidity. Patients being treated with TZD agents should be carefully monitored for signs and symptoms of edema or CHF during treatment. The FDA recently removed the black box restriction for pioglitazone related to the risk of increased MI with its use.

Incretin-based therapies including GLP-1 agonists and DPP-4 inhibitors have potential positive effects on the CV system via the direct effects of GLP-1 and GIP. GLP-1 agonists induce and maintain weight loss in patients with type 2 diabetes mellitus and have a beneficial effect on surrogate CV markers, including improving left ventricular ejection fraction and exercise resistance in patients with or without diabetes who have cardiac insufficiency. Other beneficial effects include reductions in fasting lipid levels, blood pressure, and plaque size, as well as delayed atherosclerosis development. The GLP-1 analogue exenatide is associated with a significantly decreased risk of CVD and CVD-related hospitalizations in patients with type 2 diabetes mellitus. Although growing evidence supports the use of incretin-based therapies in addition to or as an alternative to metformin, their long-term effects on CVD and mortality have yet to be determined.

DPP-4 inhibitors also have beneficial CV effects, including preventing atherosclerosis and MI, improving endothelial dysfunction and lipid profile, lowering blood pressure, and decreasing the incidence of arrhythmia after CABG surgery. Some data support the reduction of CV risk in patients with diabetes on a DPP-4 inhibitor compared with patients on metformin, suggesting that DPP-4 inhibitor therapy may be an option for patients with diabetes who are unable to take metformin and are at risk of developing CVD.

Second-line therapy consisting of AGIs or other agents in combination with either metformin or insulin may provide beneficial CV effects. Acarbose has been shown to reduce the relative risk of hypertension and CV events in patients with type 2 diabetes mellitus. Other agents, including pramlintide, bromocriptine, colesevelam, and canagliflozin, when used in combination with metformin or insulin may provide greater glycemic control and improve lipid parameters in patients with diabetes. SGLT-2 inhibitors canagliflozin and dapagliflozin have been associated with reductions in other CV risk factors including total body weight, systolic blood pressure, and HgA1c levels in patients with type 2 diabetes mellitus that is inadequately controlled with metformin or insulin.

CONCLUSION

Of the 11 classes of agents discussed in this review, agents in 4 of these classes may pose potential negative CV effects until further evidence proves otherwise. Because the prevalence of CV complications and mortality is high in patients with diabetes, treatment and management of type 2 diabetes mellitus should be optimized towards reducing these risks rather than simply focusing on reducing HgA1c and glucose levels to target values. While aggressive glycemic control may be helpful in preventing CVD in young patients with diabetes, it may be detrimental in older patients with long-standing diabetes and underlying CVD.[124] Thus, treatment and management of diabetes should be adjusted on an individual basis based on age, duration of diabetes, risk for CVD, and presence of microvascular and macrovascular complications. A multifaceted disorder such as diabetes requires addressing factors beyond glucose control. Optimal care should address multifactor risk reduction, including optimal blood pressure control and correction of dyslipidemia.

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