Shifting Paradigm of Type 2 Diabetes: From Neutrality to Benefit on Cardiovascular Outcomes

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In this Issue...

Since 2008 all new medicines for managing type 2 diabetes have had to demonstrate cardiovascular safety. Now recent data are showing that, in patients with type 2 diabetes who are at high risk for CVD events, some agents may also provide cardioprotective *benefit*.

Which agents are likely to provide the best outcomes in which patients? Does the evidence indicate a class effect among the SGLT-2 inhibitors? The GLP-1 receptor agonists? How strong is the association between DPP-4 inhibitors and CHF? How have the indications for metformin changed? Do these findings indicate a potential paradigm shift in managing type 2 diabetes?

In this issue, to help answer these questions, Dr. Nestoras Mathioudakis from the Johns Hopkins School of Medicine reviews the recent evidence describing the effects of antihyper-glycemic medications on macrovascular events.

LEARNING OBJECTIVES

- Identify antihyperglycemic medications that have been shown to reduce composite cardiovascular disease risk (death from cardiovascular causes, nonfatal myocardial infarction, and nonfatal stroke) in patients with type 2 diabetes at high risk for CVD.
- Discuss the association between DPP-4 inhibitors and congestive heart failure.
- Describe expected clinical outcomes when using metformin in patients with previous historical contraindications or precautions (congestive heart failure, chronic kidney disease, and chronic liver disease).

GUEST AUTHOR OF THE MONTH

Commentary & Reviews

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Guest Faculty Disclosure

Dr. Mathioudakis has disclosed that he has received consulting fees from GlucoMe and honoraria as a faculty lecturer for PriMed CME.

Unlabeled/Unapproved uses

Dr. Mathioudakis has indicated that there will be no references to unlabeled or unapproved uses of drugs or products.

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IN THIS ISSUE

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COMMENTARY

Cardiovascular disease (CVD) remains the leading cause of death for patients with type 2 diabetes.[1] Compared to their nondiabetes counterparts, patients with diabetes have a two- to fourfold increased risk of CVD in their lifetimes, with 60% ultimately dying from CVD-related causes.[2] However, while the link between hyperglycemia and CVD has been firmly established, it is less clear — in contrast to the strong evidence that glycemic control reduces risk of microvascular complications (eyes, kidney, and nerves) — whether improving glycemic control actually results in reductions in CVD risk in patients with type 2 diabetes.

Since 2008, when the FDA began requiring demonstration of CV safety of glucose-lowering medications,[2] 18 studies have been initiated on the CV safety of newer antidiabetic drugs.[2] As a result, for the first time in decades, antidiabetic agents are finally beginning to demonstrate an impact not only on glycemic control and microvascular outcomes, but also on macrovascular outcomes (ie, CVD risk). Clinicians now find themselves in the midst of a shifting paradigm in the management of type 2 diabetes, in which antihyperglycemic medications can be selected to prevent both micro- and macrovascular complications.

Of those 18 clinical trials, half have been completed and half are ongoing. At this point, based on the nine completed trials of DPP-4 inhibitors, SGLT-2 inhibitors, GLP-1 receptor agonists, and basal insulin, sufficient evidence has accumulated to suggest a CVD benefit for the SGLT-2 inhibitors empagliflozin and canagliflozin and the GLP-1 RAs liraglutide and semaglutide.

In this newsletter, we review the landmark studies for empagliflozin (Zinman et al), canagliflozin (Neal et al), and liraglutide (Marso et al), all published in the *New England Journal of Medicine*. All three of these studies were conducted in patients at high risk for CVD events, and each suggested a beneficial effect compared to placebo on composite outcomes of major adverse cardiovascular events. In addition, although the (reviewed) study by Pfeffer and colleagues, using the GLP-1 RA lixisenatide in patients with recent acute coronary syndrome (ACS), showed no benefit of lixisenatide following ACS, it was reassuring that this incretin medication was neutral with respect to CVD outcomes, particularly heart failure hospitalizations.

To help clarify the conflicting information regarding heart failure and DPP-4 inhibitors, we

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review a 2017 comprehensive meta-analysis by Elgendy and colleagues on the cardiovascular safety of DPP-4 inhibitors. These findings show that the association between DPP-4 inhibitors is weak and is mainly driven by the results from a large clinical trial of saxagliptin.

Metformin is the cornerstone agent to reduce CVD events in type 2 diabetes, as it reduces insulin resistance and has favorable effects on lipid profile.[3] Decades of experience with metformin support its role in reducing coronary artery calcium, risk of myocardial infarction, and all-cause mortality.[3] The (reviewed) findings of a recent systematic review by Crowley et al on clinical outcomes of metformin use specifically in patients with CHF and CKD (two conditions that have historically been considered contraindications or precautions to use of this medication) confirmed that metformin reduces all-cause mortality in these patient populations, as well as reducing readmission in patients with underlying CHF.

Given the wealth of cardiovascular outcomes data that has emerged over the last few years, I am beginning to change my treatment paradigm for type 2 diabetes. Metformin remains my first-line therapy. However, newer agents like GLP-1 RAs and SGLT-2 inhibitors, which have proven efficacy in CVD risk reduction, are now replacing agents like DPP-4 inhibitors and sulfonylureas as second-line agents. Liraglutide, semaglutide, empagliflozin, and canagliflozin have been shown to decrease the primary composite outcome of CV death, nonfatal myocardial infarction, and nonfatal stroke compared with placebo in patients with CVD or at high risk for CVD. It is worth mentioning that a large clinical trial of once-weekly exenatide failed to show any cardiovascular benefit in patients with type 2 diabetes with and without previous CVD.[4] Thus, while at least two GLP-1 RAs have been shown to confer cardioprotection, this is not uniformly a class effect.

For my patients with type 2 diabetes who already have established CVD or multiple CVD risk factors, these agents are particularly appealing. In the third-line category now are insulin, DPP-4 inhibitors, and sulfonylureas. DPP-4 inhibitors are overall neutral with respect to CVD outcomes; however, the slight incidence of heart failure admissions with saxagliptin (and the trend toward increased risk for alogliptin), makes these agents less appealing for patients with CVD or CHF. Although cheap and effective, sulfonylureas are least attractive in patients with underlying CVD, given their associated weight gain, hypoglycemia risk, and increased risk of CVD events and mortality in several studies.[5] Finally, since thiazolidenediones (TZDs) are associated with fluid retention (and thus increased risk of heart failure), they are probably best avoided in diabetic patients with ischemic heart failure. However, it is worth noting that TZDs may offer CV benefit in patients with CVD and a previous MI in the absence of heart failure (PROactive Study)[6] as well as following recent stroke/transient ischemic attack (IRIS Study, 2016).[7]

We find ourselves at an exciting time in the development of pharmaceutical agents for type 2 diabetes. Over the next three to four years, additional trials evaluating CVD outcomes will be completed for the SGLT-2 inhibitors dapagliflozin and ertugliflozin, the DPP-4 inhibitor linagliptin, and the TZD pioglitazone.[2] Having cardiovascular outcomes information about multiple drugs within a given class will allow us to draw stronger inferences about the cardiovascular effects of the entire drug class. While recent statistics suggest that overall mortality rates for diabetic patients are on the decline in the United States,[8] significant efforts are still needed to reduce the excess mortality burden conferred by this chronic disease. Now that we finally have some pharmacologic options on the table for CVD risk reduction, hopefully we can begin to narrow the mortality gap between our diabetic and nondiabetic patients.

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Cardioprotective Effects of the SGLT-2 Inhibitor Empagliflozin

Zinman B, Wanner C, Lachin JM, et al; EMPA-REG OUTCOME Investigators. Empagliflozin, cardiovascular outcomes, and mortality in type 2 diabetes. *N Engl J Med* 2015 Nov 26;373(22):2117-28.

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The landmark EMPA-REG study, published in the *New England Journal of Medicine* in 2015, reported that in patients with type 2 diabetes at high risk for cardiovascular events, treatment with the SGLT-2 inhibitor empagliflozin resulted in significant reductions in cardiovascular morbidity and mortality compared to placebo.

This study enrolled approximately 7000 patients, followed for 3.1 years. The primary outcome was a composite of death from cardiovascular causes, nonfatal myocardial infarction, or nonfatal stroke. Hospitalization for unstable angina was an additional secondary outcome. The investigators defined cardiovascular disease as the presence of one or more of the following: prior myocardial infarction, multivessel coronary artery disease (CAD) on angiography, single-vessel CAD with at least 50% luminal narrowing, unstable angina with evidence of CAD, history of stroke, and occlusive PAD. Patients otherwise received standard therapy for cardiovascular disease risk reduction.

The study demonstrated a 14% reduction in the primary outcome with empagliflozin (hazard ratio 0.86; 95% CI 0.74-0.99). This effect was largely driven by a reduction in death from CVD causes (38% relative risk reduction). There were no significant between-group differences in rates of MI or stroke. There were lower rates of hospitalization for heart failure (35% relative risk reduction) and death from any cause (32% relative risk reduction) in the empagliflozin arm compared to placebo. However, there were no significant differences in the key secondary outcome of unstable angina ($P = .08$).

Interestingly, although there is a clear dose response of empagliflozin with respect to glycemic control (ie, greater response to 25 mg dose compared to 10 mg dose), in this study, no differences were observed for cardiovascular outcomes between the 10 mg and 25 mg empagliflozin groups. At 12 weeks, the mean difference in A1c between empagliflozin and placebo was – 0.54% (95% CI – 0.58 to – 0.49) in the 10 mg group and – 0.60% (95% CI – 0.64 to – 0.55) in the 25 mg group. A higher proportion of patients in the placebo arm ultimately required additional glucose-lowering medications, including insulin and sulfonylureas.

The authors postulate that the mechanisms behind cardiac benefits are likely multifactorial, involving changes in arterial stiffness, cardiac function, cardiac oxygen demand, cardiorenal effects, control of hyperglycemia, weight, visceral adiposity, and blood pressure. Given the very early separation in the Kaplan-Meier curves for the outcomes between placebo and empagliflozin arms (three months), it is likely that the glucose-lowering effect plays less of a role in the cardioprotection than other properties of this drug, such as blood pressure control and weight loss. At 28 weeks, the difference between empagliflozin and placebo for weight and systolic blood pressure was – 2 kg and – 4 mmHg, respectively. Notably, there was compensatory increase in heart rate with blood pressure reductions. With respect to lipids,

empagliflozin resulted in increases of about 2 mg/dL to 4 mg/dL in LDL and ~ 2 mg/dL increases in HDL. Since these lipid particles have competing effects on atherosclerosis, it is difficult to draw inferences about their net effects on CVD risk.

This study was one of the first large clinical trials to show a direct effect of a glucose-lowering medication on CVD outcomes in a high-risk population. Although there is some debate about whether it is appropriate to use composite cardiovascular endpoints, this study supports the use of empagliflozin in patients with type 2 diabetes who have underlying cardiovascular disease and require a modest glucose-lowering medication. In December 2016, empagliflozin became the first antidiabetic agent to receive FDA approval for the indication of reduction in risk of cardiovascular death in adults with type 2 diabetes and established cardiovascular disease.

Cardiovascular Effects of the SGLT-2 Inhibitor Canagliflozin

Neal B, Perkovic V, Mahaffey KW, et al; for the CANVAS Program Collaborative Group. Canagliflozin and cardiovascular and renal events in type 2 diabetes. *N Engl J Med* 2017;377:644-57.

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Following the EMPA-REG trial, which demonstrated favorable cardiovascular effects of empagliflozin, the results of the CANVAS trials were published in the *New England Journal of Medicine* in August, 2017, showing very similar effects of the SGLT-2 inhibitor canagliflozin. This study integrated data from two large clinical trials, including 10,142 participants with type 2 diabetes and high cardiovascular risk. The first CANVAS trial began in 2009 before canagliflozin had received approval by FDA. Because drug approval in 2013 required unmasking of interim data from this trial, a second trial (CANVAS-R), which started in 2014, was designed to evaluate both renal and cardiovascular safety. Results from both trials were combined to maximize statistical power for evaluation of cardiorenal safety and efficacy. Participants either had established CVD or two or more risk factors for CVD: diabetes for 10 or more years, systolic blood pressure > 140 mmHg, smoking, albuminuria, or HDL < 39 mg/dl. Therefore, this study included a lower-risk population of patients than EMPA-REG.

Participants were randomized to receive canagliflozin or placebo and were followed for a mean of 3.6 years. As in the EMPA-REG study, the primary outcome was a composite of death from cardiovascular causes, nonfatal myocardial infarction, or nonfatal stroke. Similarly to empagliflozin, canagliflozin showed a 14% lower risk of the primary endpoint than placebo (hazard ratio 0.86, 95% CI 0.75-0.97). Again, like empagliflozin, canagliflozin showed a benefit using a composite primary cardiovascular endpoint, but the individual components (death from CVD, nonfatal MI, and nonfatal stroke) showed nonsignificant trends toward benefit.

Generally, the findings from the CANVAS trials were aligned with those from the EMPA-REG trial, suggesting a class effect of SGLT-2 inhibitors. One difference was highlighted by the authors of this study, however: in the EMPA-REG trial, the hazard ratio for nonfatal stroke was nonsignificantly increased in the empagliflozin arm (1.24; 95% CI 0.92-1.67), while in the CANVAS trials, the risk was nonsignificantly decreased (hazard ratio 0.90; 95% CI 0.71-1.15). Since there was not a statistically significant difference in the effect of either empagliflozin or canagliflozin on stroke risk, it is difficult to say whether the differences in the effect sizes are related to actual differences between the drugs or to the trial characteristics themselves.

Besides the known side effects of SGLT-2 inhibitors (urinary and genital infections), there was an unexpected finding of increased amputation rates with canagliflozin. The hazard ratio for lower extremity amputations (toes, feet, or legs) was 97% higher with canagliflozin than with placebo (HR 1.97; 95% CI, 1.41-2.75). This absolute risk was disproportionately higher in patients with a history of amputation or peripheral vascular disease. In May 2017, the FDA issued an alert requiring an update in the product label for canagliflozin advising clinicians to consider risk factors for amputations prior to starting this medication, counsel

patients on the importance of preventive foot care, and discontinue treatment if any signs of lower extremity ulceration or infection appear.

CV Outcomes with the GLP-1 Agonist Liraglutide in Type 2 Diabetes

Marso SP, Daniels GH, Brown-Frandsen K, et al; LEADER Steering Committee; LEADER Trial Investigators. Liraglutide and Cardiovascular Outcomes in Type 2 Diabetes. *N Engl J Med* 2016;375:311-22.

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The LEADER trial was a large randomized controlled trial originally designed to evaluate the cardiovascular safety of the GLP-1 receptor agonist (GLP-1 RA) liraglutide. GLP-1 RAs are associated with weight loss and slight blood pressure lowering. However, they are also associated with an increased pulse rate. This trial sought to determine whether once-daily GLP-1 RA liraglutide was safe from a cardiovascular standpoint. The results of the study, published in the *New England Journal of Medicine* in July 2016, showed that liraglutide not only had a safe cardiovascular profile, it also conferred cardiovascular benefit compared to placebo.

In this study, 9,340 participants with high risk for cardiovascular disease were randomized to receive liraglutide or placebo and followed for a median of 3.8 years. The primary endpoint was a composite of cardiovascular death, nonfatal myocardial infarction, or nonfatal stroke. Treatment with liraglutide resulted in a 13% reduction in the primary composite cardiovascular endpoint (hazard ratio 0.87; 95% CI 0.78-0.97; P = .01 for superiority). There was a 22% lower odds of death from cardiovascular disease with liraglutide (hazard ratio 0.78; 95% CI 0.66-0.93) and 15% lower all-cause mortality (hazard ratio 0.85; 95% CI 0.74-0.97). As with the SGLT-2 inhibitors (reviewed herein), there was no significant difference in the rates of individual endpoints of nonfatal myocardial infarction or nonfatal stroke, although there was a trend toward benefit with each. Hospitalizations for heart failure were also nonsignificantly lower in the liraglutide group.

Gastrointestinal (GI) effects have been the most common side effects observed with GLP-1 receptor agonists. In this study, frequencies of GI side effects with liraglutide were relatively low, with nausea occurring in only 1.6%, vomiting in 0.7%, and abdominal discomfort in 0.2% of participants. Despite the interest in the potential association between GLP-1 RAs and pancreatitis, there were no differences in frequencies of pancreatitis between the groups (0.4% in liraglutide vs 0.5% in placebo; P = .44). However, although absolute rates were very low, there was a trend toward higher rates of pancreatic cancer with liraglutide than with placebo (0.3% vs 0.1%, P = .06).

The main difference in this trial compared to the SGLT-2 inhibitor studies is the time to benefit. With SGLT-2 inhibitors, the time to benefit is very early (three to six months). In this study, the Kaplan-Meier curves for the primary endpoint between placebo and liraglutide begin to diverge around 12 months. The authors postulate that these differences in time to cardiovascular effect are due to modification of atherosclerotic vascular disease with the GLP-1 RAs, whereas with SGLT-2 inhibitors the effects are most likely related to hemodynamic changes. Unlike empagliflozin, which showed varying direction of effect with respect to individual cardiovascular endpoints (ie, lower CVD death, higher silent myocardial infarction, higher fatal and nonfatal stroke), liraglutide showed that the direction of effect for each individual component was in the favorable direction, even though only the composite endpoint was significant. This pattern of cardiovascular benefit was also observed with canagliflozin.

In addition to liraglutide, the GLP-1 RA semaglutide was recently shown (SUSTAIN-6 trial)[1] to be superior to placebo in the primary composite cardiovascular endpoint (HR 0.74; 95% CI 0.58-0.95). Unlike the LEADER trial (liraglutide) and EMPA-REG trial (empagliflozin), the reduction in the primary composite endpoint was not driven by decrease in cardiovascular death but rather by reduction in nonfatal stroke (HR 0.61; 95% CI, 0.38-0.99).

The results of these two studies effectively added a second drug class to the antidiabetes armamentarium for cardiovascular disease prevention. Indeed, based on these findings, the US FDA approved a new indication for liraglutide in August 2017 as a medication to reduce the risk of major adverse cardiovascular events, heart attack, stroke, and cardiovascular death in adults with type 2 diabetes and established cardiovascular disease.[2] Although not FDA- approved as of this writing, in October 2017, once-weekly semaglutide received a positive 16-0 vote from the FDA's Endocrinologic and Metabolic Drugs Advisory Committee as a medication to improve glycemic control in adults with type 2 diabetes.[3]

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Lixisenatide in Diabetic Patients with Acute Coronary Syndrome

Pfeffer MA, Claggett B, Diaz R, et al; ELIXA Investigators. Lixisenatide in patients with type 2 diabetes and acute coronary syndrome. *N Engl J Med.* 2015 Dec 3;373(23):2247-57.

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Lixisenatide is a once-daily GLP-1 RA administered in a 10- or 20-mg dose. This study by Pfeffer et al, published in the New England Journal of Medicine in December 2015, sought to evaluate whether lixisenatide improves clinical outcomes compared to placebo in patients with type 2 diabetes who had a recent acute coronary syndrome. The study was prompted by research from animal models and early studies in humans suggesting that GLP-1 receptor agonists might improve cardiovascular outcomes.

The study enrolled 6,068 adult patients 30 years or older with type 2 diabetes who had had an acute coronary event within 180 days before screening. Participants were randomized to receive lixisenatide or placebo. The starting dose of lixisenatide was 10 mcg per day for the first two weeks, then increased if needed to 20 mcg per day per the study investigators. The primary endpoint was a composite of death from cardiovascular causes, nonfatal myocardial infarction, nonfatal stroke, or hospitalization for unstable angina. Participants were followed for a median of 25 months.

The study found no difference in cardiovascular outcomes in this very high-risk patient population: 13.4% and 13.2% of participants in the lixisenatide and placebo arms had the primary outcome (hazard ratio 1.02, 95% CI, 0.89-1.17). There were also no significant differences in the secondary outcome of heart failure hospitalizations (hazard ratio 0.96; 95% CI 0.75-1.23) or death (0.94; 95% CI 0.78-1.13).

As expected, gastrointestinal side effects were the most common adverse event leading to discontinuation of the drug (4.9% in lixisenatide group and 1.2% in placebo group). There were no significant differences in rates of pancreatitis or pancreatic cancer.

What are the implications of this study? This study found a neutral effect of heart failure hospitalizations with this GLP-1 RA in patients both with and without prior heart failure history. Although the study did not demonstrate superiority of lixisenatide over placebo in

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patients with a recent acute coronary syndrome, the neutral influence of the drug suggests that it presents a safe option to use in this patient population. These findings are particularly reassuring in light of the concern that DPP-4 inhibitors (another incretin drug class) have been implicated in increased rates of heart failure hospitalizations.[1]

References:

1. Elgendy IY, Mahmoud AN, Barakat AF, et al. Cardiovascular Safety of Dipeptidyl-Peptidase IV Inhibitors: A Meta-Analysis of Placebo-Controlled Randomized Trials. *Am J Cardiovasc Drugs* 2017;17:143-55.

Cardiovascular Safety of DPP-4 Inhibitors

Elgendy IY, Mahmoud AN, Barakat AF, et al. Cardiovascular safety of dipeptidyl-peptidase iv inhibitors: A meta-analysis of placebo-controlled randomized trials. *Am J Cardiovasc Drugs* 2017;17:143-55.

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Clinical studies have revealed conflicting findings regarding the cardiovascular safety of dipeptidyl-peptidase-4 (DPP-4) inhibitors. The largest randomized controlled trial (RCT) designed to evaluate the cardiovascular safety of DPP-4 inhibitors found that saxagliptin was associated with a 27% increased risk for heart failure hospitalizations compared to placebo.[1] However, two other large RCTs using the DPP-4 inhibitors alogliptin[2] and sitagliptin[3] found no significant increase in the risk of heart failure compared to placebo. Despite the lack of statistically significant increased risk with alogliptin, numerically more participants receiving alogliptin were readmitted for heart failure than placebo (3.9% vs 3.3%), with a hazard ratio of 1.07 (0.79-1.46; *P* = .657).

On the basis of this information, the US FDA issued a safety communication on April 5, 2016 warning clinicians about the potential increased risk of heart failure with the DPP-4 inhibitors saxagliptin and alogliptin. The FDA advised discontinuation of medications containing saxagliptin or alogliptin in patients who develop heart failure and monitoring for and educating patients on the signs and symptoms of heart failure.

This study, by Elgendy et al, sought to systematically evaluate the cardiovascular safety of DPP-4 inhibitors. Unlike previous meta-analyses, which included data from observational studies, this meta-analysis included only RCTs that reported cardiovascular outcomes of DPP-4 inhibitors compared to placebo. To avoid potential confounding, studies that compared DPP-4 inhibitors to another active antidiabetes drug were also excluded.

A total of 90 RCTs with 66,730 patients were included in this comprehensive meta-analysis. The study found a nonsignificant trend for increased risk of heart failure (odds ratio 1.11; 95% CI, 0.99-1.25) at a mean follow-up of 108 weeks with DPP-4 inhibitors compared to placebo. There were no significant differences in all-cause mortality, cardiovascular mortality, myocardial infarction, and ischemic stroke between DPP-4 and placebo groups. A sensitivity analysis of the three large RCTs of DPP-4 inhibitors suggested that the SAVOR-TIMI trial (the large RCT of saxagliptin) was largely driving the finding of increase heart failure risk. The reasons for the unexpected increase in heart failure with saxagliptin are not entirely clear, but one potential explanation offered by the authors of this study was the relatively large proportion (13%) of participants with baseline heart failure in that study. Generally, clinical trials of antidiabetic medications have included much lower numbers of heart failure patients.

The authors of this study noted that in a large multicenter cohort of approximately 1.5 million diabetic patients, DPP-4 inhibitors were not linked to heart failure compared to other oral antidiabetic drugs. The totality of these data suggests that if there is any increased risk of heart failure, the evidence is very weak and is limited to saxagliptin and possibly alogliptin.

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Since the mechanism underlying the association between heart failure and DPP-4 inhibitors is not completely understood and there was a potential safety signal observed with two drugs in this class, there are two approaches to management of diabetic patients with underlying heart failure. The first would be to avoid DPP-4 inhibitors altogether on the basis of this weak safety signal. The second would be to use sitagliptin, which has not been shown to increase the risk of heart failure compared to placebo (hazard ratio 1.0; 95% CI 0.83-1.20).[3] We tend to use the latter approach, which is in line with the most recent FDA safety communication.

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Revisiting Historical Contraindications or Precautions for Metformin

Crowley MJ, Diamantidis CJ, McDuffie JR, et al. Clinical Outcomes of metformin use in populations with chronic kidney disease, congestive heart failure, or chronic liver disease: A systematic review. *Ann Intern Med.* 2017;166:191-200.

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Metformin is the first-line drug for type 2 diabetes mellitus in the United States. It was initially approved for use in 1994 and achieved first-line status because of its neutral effect on weight and hypoglycemia, as well as evidence suggesting lower overall mortality with this medication. Upon its initial approval, the FDA applied a black box warning about the risk of lactic acidosis with metformin. The rationale for this was that phenformin, a related biguanide that was withdrawn from the market in 1978, was associated with higher rates of lactic acidosis. The initial warning cautioned against the use of metformin in conditions that could promote lactate accumulation or impair excretion of the drug, such as chronic kidney disease (CKD), congestive heart failure (CHF), and chronic liver disease (CLD).

Over the subsequent decades, it became clear that this concern was mainly theoretical, as evidence did not point to a clear association between metformin use and lactic acidosis in these clinical conditions. Accordingly, in 2006, the FDA removed CHF as a contraindication to metformin use, but maintained acute or unstable CHF as a precaution. More recently, in April 2016, the FDA again revised its warning about metformin in CKD, moving away from a creatinine-based definition of renal impairment to one based on estimated glomerular filtration rate (eGFR; under the revision, metformin may be continued for GFR ≥ 30 ml/min/1.73 m^2). This change meant that more patients would be eligible to receive metformin.

To allow clinicians to better understand its safety and efficacy in patients who had one or more historical contraindications or precautions to metformin use, Crowley and colleagues performed an outcomes data meta-analysis. Inclusion criteria were RCTs and observational studies (prospective and retrospective) of at least one month's duration of adults with type 2 diabetes and precaution or contraindication to metformin use. Studies must have included one arm with metformin and one without and reported all-cause mortality and major adverse cardiovascular events. The meta-analysis included observational studies of patients with CKD (n = 6), CHF (n = 11), and CLD (n = 3).

In patients with moderate to severe CKD, metformin was associated with a 22% reduction in all-cause mortality (hazard ratio 0.78; 95% CI, 0.63-0.96). Similarly, in patients with CHF, metformin was associated with a 22% reduction in all-cause mortality (hazard ratio 0.78; 95% CI 0.71-0.87), a 13% reduction in CHF readmission (hazard ratio 0.87; 95% CI 0.78-0.97), and no difference in cardiovascular mortality (hazard ratio 0.77; 95% CI 0.53-1.12). Given the small number of studies using metformin in CLD, the authors were not able to do a meta-analysis for this condition. However, they noted that one low risk of bias study found that metformin use was associated with longer survival, regardless of severity of CLD.

This important study not only provides reassurance to clinicians about the safety of metformin use in patients with CKD and CHF, it also suggests that the drug may provide benefits with respect to overall mortality. Unlike previous reviews, this analysis focused specifically on diabetes populations that had historical contraindications or precautions to metformin use. Although they included observational studies, in some ways, this allowed the authors to reach conclusions about outcomes that require long-term follow-up, such as mortality. The findings were consistent with a previous analysis showing reduced mortality with metformin use in CHF.[1] Therefore, metformin should remain a first-line medication in diabetes and should be continued in patients with CHF.

References:

1. Eurich DT, Weir DL, Majumdar SR, et al. Comparative safety and effectiveness of metformin in patients with diabetes mellitus and heart failure: systematic review of observational studies involving 34,000 patients. *Circ Heart Fail*. 2013; 6:395-402.

KEY TAKEAWAYS

- The SGLT-2 inhibitors empagliflozin and canagliflozin have been shown to reduce composite major adverse cardiovascular events in patients with type 2 diabetes at elevated risk of CVD.
- The GLP-1 receptor agonists liraglutide and semaglutide have been shown to reduce composite major adverse cardiovascular events in patients with type 2 diabetes at elevated risk of CVD. This benefit should not be considered a class effect.
- The DPP-4 inhibitors saxagliptin and alogliptin may increase the risk of heart failure hospitalizations. This caution should not be considered a class effect.
- Metformin is associated with reduced heart failure hospitalizations in patients with underlying CHF as well as reduced all-cause mortality.

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