Nonglycemic Outcomes of Antidiabetic Medications

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IN BRIEF The number of medications used to treat diabetes has increased dramatically in the past 15 years. With so many options that have shown significant A1C improvement, it is important to consider side effects, precautions, and additional benefits these agents may offer. This article is a review of some of the most compelling literature available on the nonglycemic benefits of sulfonylureas, thiazolidinediones, biguanides, glucagon-like peptide 1 receptor agonists, dipeptidyl peptidase 4 inhibitors, and sodium–glucose cotransporter 2 inhibitors. Other classes of antihyperglycemic agents, such as dopamine agonists, meglitinides, and amylin agonists, are not discussed in this article.

Sulfonylureas have been commercially available globally since the 1950s. Chlorpropamide, tolbutamide, and tolazamide were some of the first agents in the class and are commonly referred to as first-generation sulfonylureas. It was not until the 1980s that higher-potency second-generation sulfonylureas such as glipizide, glyburide, and glimepiride were approved by the U.S. Food and Drug Administration (FDA).

Thiazolidinediones (TZDs) are a class of medications that were widely used in the treatment of type 2 diabetes, but because of their side-effect profile, have lost popularity in recent years. FDA-approved agents in this class include pioglitazone and rosiglitazone.

In 1995, the FDA approved the biguanide metformin. Although attempts have been made to develop other biguanides, metformin remains the only FDA-approved agent in this class and is the first-line agent for the treatment of type 2 diabetes.

The dipeptidyl peptidase 4 (DPP-4) inhibitor class was first introduced when sitagliptin received FDA approval in 2006. Subsequently, saxagliptin, linagliptin, and alogliptin have received FDA approval.

Glucagon-like peptide 1 (GLP-1) receptor agonists were introduced to the U.S. market around the same time as DPP-4 inhibitors. The first FDA-approved agent in this class of antihyperglycemic medications was exenatide in 2005, followed by liraglutide, albiglutide, dulaglutide, lixisenatide, and semaglutide.

The newest class of antihyperglycemic medications are called sodium–glucose cotransporter 2 (SGLT2) inhibitors. Canagliflozin was the first to receive FDA approval in 2013. Not long after that, dapagliflozin and empagliflozin also entered the U.S. market. Ertugliflozin was approved at the end of 2017, and sotagliflozin, a dual SGLT2/SGLT1 inhibitor, is under FDA review.

All of these agents have proven effective in reducing blood glucose and A1C, but many of them have additional pleiotropic effects that should be considered when formulating a patient-specific treatment regimen.

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Sulfonylureas

Cardiovascular Effects

Two of the earliest studies assessing the cardiovascular (CV) safety of sulfonylureas were the University Group Diabetes Program (UGDP) and the U.K. Prospective Diabetes Study (UKPDS), and these studies had conflicting results. In the UGDP, which recruited patients from 1961 to 1965, CV mortality between placebo and sulfonylurea was significant enough to warrant discontinuation of tolbutamide use in the study because tolbutamide and diet appeared to be less effective than diet alone or than insulin and diet with regard to CV mortality (1). The UKPDS, conducted between 1977 and 1991, had a 10-year follow-up that demonstrated a lower absolute risk for death from any cause (30.3 vs. 33.1 events/1,000 patient-years) and myocardial infarction (MI) (19.6 vs. 21.1 events/1,000 patient-years) in the sulfonylurea plus insulin group versus the metformin group (2). Given the substantial time between these two major studies, the patients recruited may represent different CV risk categories.

As more selective second-generation sulfonylureas were developed, theories emerged on the potential mechanisms of cardiac toxicity. Animal study data have shown that gliclazide has a higher affinity and selectivity for pancreatic β-cells (3). From these data, we can hypothesize that sulfonylureas with higher pancreatic β-cell selectivity may result in less cardiac toxicity; however, no large-scale randomized controlled trials (RCTs) have been developed to test this theory.

In a 2013 meta-analysis, a significant increase in CV mortality (1.27, 95% CI 1.18–1.34) and CV composite endpoints (1.10, 95% CI 1.04–1.16) was found. However, when assessing only RCTs, no significant difference was found with either of those endpoints. This meta-analysis included trials with first-generation sulfonylureas. Although the evidence was not significant, it does show a trend toward worsening CV outcomes (4). In 2016, another meta-analysis was performed that excluded first-generation sulfonylureas. Researchers in this analysis found no significant increase in risk of all-cause CV mortality, MI, or stroke (5).

Further studies are needed to clarify the effects of sulfonylureas on CV outcomes. Given that these agents are falling out of favor with the development of more efficacious and safer agents, a trial of the magnitude of the UGDP or UKPDS is not likely.

Microvascular Effects

In addition to their macrovascular effects, sulfonylureas have been studied for potential microvascular benefits. In the 10-year follow-up of the UKPDS, the absolute risk for microvascular disease in the sulfonylurea plus insulin group versus the metformin group was 11.0 versus 12.4 events/1,000 patient-years (2).

The limited nonglycemic benefits, gradual loss of efficacy for glycemic control, associated weight gain, and hypoglycemia risk of sulfonylureas means that their use in treating diabetes may quickly fall out of favor in a market now saturated with strong competitors.

Thiazolidinediones

Cardiovascular Effects

In 2005, the PROactive (PROspective pioglitAzone Clinical Trial In macroVascular Events) trial, a prospective RCT involving 5,238 patients with type 2 diabetes treated with pioglitazone or placebo, was completed. Although it did not meet its primary endpoint with regard to mortality and CV events, pioglitazone users saw a reduction in a composite endpoint of all-cause mortality, nonfatal MI, and stroke (hazard ratio [HR] 0.84, 95% CI 0.72–0.98, $P = 0.027$, number needed to treat [NNT] = 48). This study did see an increase in the rate of heart failure in the treatment arm compared to placebo (11 vs. 8%, number needed to harm [NNH] = 33), but overall mortality and CV events tended to decline in the pioglitazone group with heart failure (6). The use of TZDs is contraindicated in patients with established heart failure.

In 2007, a meta-analysis was conducted to evaluate the effect of rosiglitazone on CV morbidity and mortality (7). Rosiglitazone was associated with a significantly higher risk of MI (odds ratio [OR] 1.43, 95% CI 1.03–1.98, $P = 0.03$) and a statistically nonsignificant increase in the risk of death due to CV causes (OR 1.64, 95% CI 0.98–2.74, $P = 0.06$) (7). These findings, along with the results of the ACCORD (Action to Control Cardiovascular Risk in Diabetes) trial (8), prompted the FDA in 2008 to draft guidance on the need for CV outcome data for medications used to treat diabetes. These negative findings associated with rosiglitazone have left a negative stigma associated with all TZD drugs.

The IRIS (Insulin Resistance Intervention After Stroke) trial demonstrated that patients with prediabetes and a recent history of ischemic stroke or transient ischemic attack (TIA) had a significantly lower risk of recurrent stroke and CV events when they were treated with pioglitazone compared to placebo (9 vs. 11.8%, $P = 0.007$, NNT = 36) (9).

The TOSCA.IT (Thiazolidinediones or Sulfonylureas and Cardiovascular Accidents Intervention Trial) was a multicenter, randomized, pragmatic clinical trial that randomly assigned patients ($n = 3,028$) enrolled in the study to receive as add-on therapy to metformin either pioglitazone or a sulfonylurea (glibenclamide, glimepiride, or gliclazide). This study found no difference in the composite endpoint of death and nonfatal CV event between patients treated with pioglitazone and those treated with a sulfonylurea (HR 0.96, 95% CI 0.74–1.26, $P = 0.79$) (10).

TZDs, specifically pioglitazone, may provide the greatest CV benefit to

patients with prediabetes and a recent history of ischemic stroke or TIA.

Biguanides

Cardiovascular Effects

It has been suggested that metformin may reduce CV risk to a greater extent than can be attributed to a reduction in glucose. In 2010, a meta-analysis was published of 35 clinical trials, including >18,000 patients. A significant benefit in CV events was seen compared to placebo (OR 0.94, 95% CI 0.82–1.07, $P = 0.031$), but not compared to active comparator (OR 1.03, 95% CI, 0.72–1.77, $P = 0.89$) (11). A smaller recent meta-analysis revisiting the topic of CV benefits with metformin included 13 trials with >4,000 patients with type 2 diabetes taking metformin or a comparator. In this case, metformin showed no significant effect on risk of CV death, MI, or stroke (12). Metformin has proven CV benefit in poorly controlled or obese patients with diabetes, but there is not enough evidence to conclude that these benefits are due to something more than improved glycemic control and weight loss.

Weight Effects

In 2002, the Diabetes Prevention Program research trial published results demonstrating weight loss in patients receiving metformin compared to placebo (weight reduced 2.06 ± 5.65% vs. 0.02 ± 5.52%) (13). Ten years later, the follow-up Diabetes Prevention Program Outcome Study confirmed that weight loss remained significantly greater in the metformin group than in the placebo group (2.0 vs. 0.2%, $P<0.001$) (13).

Metformin-associated weight loss has been extensively studied. Researchers are exploring this side effect in more specific demographics such as elderly, obese, and nondiabetic patients. There is a clear, well-documented, and accepted weight loss benefit associated with the use of metformin.

Cholesterol Effects

In addition to weight loss, some patients may also experience a beneficial effect on their cholesterol levels, specifically a reduction in LDL cholesterol. In a 2015 meta-analysis of the KORA (Cooperative Health Research in the Region of Augsburg) cohort studies, researchers wanted to investigate the pleiotropic effects of metformin through the identification of metabolite variations in treatment groups (14). This analysis pulled data for >7,000 patients with a diagnosis of type 2 diabetes. Researchers found that metformin use was associated with a significant reduction in LDL cholesterol of –13.14 mg/dL (95% CI –22.88 to –3.40, $P = 0.008$) and in total cholesterol of –19.16 mg/dL (95% CI –29.77 to –8.55, $P = 0.0004$). Metformin's effect on HDL cholesterol and triglycerides was not significant (14). A 2016 RCT of metformin in nondiabetic post-MI patients had similar results (15).

Cancer Effects

Another metabolite assessed in the KORA studies meta-analysis was one linked to two genes responsible for DNA repair. This association may play a part in the protective effect metformin has for various cancers. For example, a 2014 meta-analysis found a significant reduction in cancer incidence in metformin users when adjusted for BMI (relative risk [RR] 0.82, 95% CI 0.70–0.96), but that difference was no longer significant when limiting the analysis to prospective trials or RCTs. There was also a significant reduction in cancer mortality (RR 0.66, 95% CI 0.54–0.81), and this remained significant when adjusted for BMI. The same analysis looked into the effect of metformin on specific subtypes of cancers. Only two achieved a statistically significant reduction: liver cancer (RR 0.47, 95% CI 0.28–0.79) and lung cancer (RR 0.82, 95% CI 0.67–0.99). Breast, colon, and pancreatic cancers trended toward a protective effect but fell just short of statistical significance (16). A 2011 nested case-control study included 482 patients and had similar results to this meta-analysis. Patients were classified as having gastrointestinal, pancreatic, lung, or other cancers. Exposure to metformin was associated with reduced incidence of cancer (OR 0.46, 95% CI 0.25–0.85, $P = 0.014$) (17).

Further studies have looked into the specific subsets of cancer to uncover stronger evidence for the use of metformin. One such study found that diabetic patients with stage ≥2 human epidermal growth factor receptor 2–positive breast cancer who were trea-ted with metformin had a median survival of 42.4 months compared to patients not treated with metformin, who had a median survival of 37.4 months. Even metformin users with diabetes had a longer survival duration than people without diabetes who did not use metformin ($P = 0.007$) (18). A retrospective cohort study performed in 2011 looked into protective effects of metformin use in 595 patients with colorectal cancer (CRC). It was concluded that the estimated 3-year CRC-specific survival rates were 92.4 and 90.8% ($P = 0.042$) and estimated 3-year overall survival was 89.6 and 87.9% ($P = 0.018$) for metformin and nonmetformin cohorts, respectively (19). The data seem to suggest that metformin may indeed play a role in delaying the progression of certain subtypes of cancers, possibly due to its ability to regulate DNA repair enzymes.

DPP-4 Inhibitors

Cardiovascular Effects

As with various other classes of drugs in the diabetes treatment sphere, companies that manufacture DPP-4 inhibitors have been conducting CV outcomes trials (CVOTs). Experts have concluded that, as a class, DPP-4 inhibitors likely do not increase or decrease the risk of CV events compared to placebo (20). A large population cohort study evaluated major adverse CV events (MACE) for patients on metformin who were also

taking either a DPP-4 inhibitor or a sulfonylurea. MACE was a composite of MI and hospitalizations for stroke, heart failure, and hypoglycemia. DPP-4 inhibitor users had a lower risk of a MACE endpoint than sulfonylurea users (HR 0.68, [95% CI 0.55–0.83], NNT = 138). Further analysis showed that DPP-4 inhibitors significantly reduced the risk of stroke, but not MI or hospitalization for heart failure (21). In another large population cohort study, the incidence of the combination of MI and ischemic stroke in DPP-4 inhibitor users compared to nonusers was 37.89 versus 47.54/1,000 person-years; of MI was 12.70 versus 16.18/1,000 person-years; and of ischemic stroke was 26.37 versus 32.46/1,000 person-years, respectively (22).

Saxagliptin was compared to placebo in an RCT in which 16,492 patients were followed for 2 years for MACE outcomes (CV death, MI, or ischemic stroke). The study found no difference between the saxagliptin group and the placebo group for the primary MACE outcome (HR 1.00, CI 0.89–1.12). The saxagliptin group had a higher risk of hospitalization for heart failure (HR 1.27, 95% CI 1.07–1.51, P = 0.007, NNH = 142), and a subsequent analysis showed that an estimated glomerular filtration rate <60 mL/min and a history of heart failure were the greatest risk factors (23,24).

Alogliptin was compared to placebo in an RCT of 5,380 patients with recent MI or unstable angina who were followed for up to 40 months. For the primary MACE composite endpoint of CV death, nonfatal MI, or nonfatal stroke, there was no significant difference between alogliptin and placebo (HR 0.96 ± 1.16, P = 0.32). Heart failure hospitalizations were not assessed (25). Other studies have confirmed these results (26,27).

A retrospective analysis of data from 17,000 patients over 5 years who took vildagliptin or placebo or any non-vildagliptin comparator assessed MACE (MI, stroke, or CV death) as its primary composite outcome along with heart failure events. Vildagliptin did not show any significant difference in MACE outcomes (RR 0.82 [95% CI 0.61–1.11]) or in heart failure events (RR 1.08 [95% CI 0.68–1.70]) (28). Vildagliptin is not currently approved by the FDA, but it is used in other countries such as Japan, India, and across Europe.

Sitagliptin was compared to placebo in a 14,671-patient RCT. The trial's primary outcome was the same MACE composite endpoint as was used in trials of other drugs in this class. No significant difference between sitagliptin and placebo was found (11.4 vs. 11.6%, respectively). There also was no difference in heart failure hospitalizations (3.1% for both groups) (29).

Linagliptin shows no significant difference in MACE (CV death, nonfatal MI, nonfatal stroke, and hospitalization for unstable angina) (HR 1.09, 95% CI 0.68–1.75) (30). Linagliptin was evaluated for its CV and renal safety compared to placebo as add-on therapy in the CARMELINA (Cardiovascular and Renal Microvascular Outcome Study With Linagliptin in Patients With Type 2 Diabetes Mellitus) trial, which was completed in January 2018 (NCT01897532) but does not have published results.

DPP-4 inhibitors can be used safely in patients in various states of CV health because they pose no greater risk for such CV outcomes than placebo. Although study results have only detected a significant heart failure hospitalization risk increase with saxagliptin, the FDA has taken a conservative approach to such a serious adverse event and applied the warning to all agents in the class.

Renal Effects

DPP-4 inhibitors have been found to provide some renoprotective effects, and, given that nephropathy is a common complication of diabetes, these agents could be beneficial in patients suffering from or at higher risk of developing these types of complications. This effect is observed across all agents in the class as demonstrated by a 2016 retrospective observational cohort study that found the urine albumin-creatinine ratio 1 year before DPP-4 inhibitor initiation had increased on average 39 mg/g, yet decreased 45 mg/g 1 year after initiation of a DPP-4 inhibitor (P <0.05) (31). A crossover trial using sitagliptin and alogliptin as alternating therapies without a washout period suggested that switching to alogliptin (higher DPP-4 affinity than sitagliptin) may result in an additional reduction in urinary albumin. However, because of the short duration of this trial, it is unclear which agent was responsible for the reductions (32). What is clear is that DPP-4 inhibitors are not only safe to use in renally impaired patients, but also may improve or preserve renal function over time. Studies performed on individual agents within the class are discussed below.

Each DPP-4 inhibitor has been assessed individually for renal benefits, and those data can be found in the following studies: saxagliptin (33,34), vidagliptin (35,36), sitagliptin (37–40), and linagliptin (41–44). All of these studies demonstrate the efficacy of DPP-4 inhibitors in patients with normal to severe renal impairment.

In all cases, DPP-4 inhibitors result in greater reductions in A1C compared to placebo. It is also clear that these agents are safe to use across the spectrum of renal dysfunction without concern for significantly increased adverse events, which cannot be said of many other classes of antihyperglycemic drugs. In addition to their renal safety, they may provide some degree of protection and slow the progression of renal disease, as evidenced by a reduction in micro- and macroalbuminuria. Groups most likely to see a strong response to these agents include elderly patients not taking a renin-angiotensin-aldosterone system inhibitor and those with preexisting albuminuria. Reductions in

urine albumin can be expected in most cases, but beyond that, no other outcomes have been shown to be significantly different from placebo or active comparator.

GLP-1 Receptor Agonists

Cardiovascular Effects

All GLP-1 receptor agonist CVOTs have been in patients with type 2 diabetes at high risk of CV disease and have assessed MACE as their primary outcome compared to placebo.

Liraglutide was the first FDA-approved GLP-1 receptor agonist to demonstrate a CV benefit in the LEADER (Liraglutide Effect and Action in Diabetes: Evaluation of Cardiovascular Outcome Results) program. Compared to placebo, patients randomized to liraglutide therapy had fewer events of the composite 3-point MACE (death from CV causes, nonfatal MI, or nonfatal stroke) (13 vs. 14.9%, $P = 0.01$ for superiority, NNT = 53). Fewer patients treated with liraglutide died from CV causes compared to those taking placebo (4.7 vs. 6%, $P = 0.007$, NNT = 77) (45). A post hoc analysis of the MI events in the LEADER trial showed a nonsignificant trend toward less CV death due to MI events in patients taking liraglutide versus placebo (4.7 vs. 6.7%, $P = 0.28$) (46).

CV benefit was not observed with lixisenatide in ELIXA (Evaluation of Lixisenatide in Acute Coronary Syndrome), as it was found to be noninferior for a 4-point MACE composite endpoint (CV death, MI, stroke, or hospitalization for unstable angina) (13.4 vs. 13.2%, $P < 0.001$ for noninferiority). There was not a higher rate of serious adverse events, severe hypoglycemia, or allergic reactions in the lixisenatide group compared to placebo (47).

Semaglutide is a once-weekly GLP-1 receptor agonist that was evaluated in the SUSTAIN-6 (Trial to Evaluate Cardiovascular and Other Long-Term Outcomes with Semaglutide in Subjects with Type 2 Diabetes) trial. Semaglutide was observed to be superior compared to placebo for the 3-point MACE (CV death, nonfatal MI, or nonfatal stroke) (6.6 vs. 8.9%, $P < 0.001$ for noninferiority, NNT = 44). Rates of nonfatal stroke were also lower among patients who were treated with semaglutide compared to placebo (1.6 vs. 2.7%, $P = 0.04$ for noninferiority, NNT = 91). There was a significantly higher incidence of retinopathy complications associated with the use of semaglutide compared to placebo (3.0 vs. 1.8%, $P = 0.02$, NNH = 84) (48), but a difference in retinopathy incidence was not observed in the SUSTAIN-7 (Efficacy and Safety of Semaglutide Versus Dulaglutide as Add-On to Metformin in Subjects With Type 2 Diabetes) trial when semaglutide was compared to dulaglutide (49). Semaglutide was approved by the FDA in December 2017.

The EXSCEL (Exenatide Study of Cardiovascular Event Lowering) trial, which evaluated once-weekly extended-release exenatide, demonstrated CV safety but no difference for the 3-point MACE (death from CV causes, nonfatal MI, or nonfatal stroke) (11.4 vs. 12.2%, $P < 0.001$ for noninferiority) (50).

Two other GLP-1 receptor agonists are currently undergoing evaluation for CV safety (albiglutide [NCT02465515] and dulaglutide [NCT01394952]). Until these studies are completed, liraglutide and semaglutide are the only agents in the class with evidence of CV benefit. Table 1 provides a comparison of all published CVOTs.

Hospitalization for Heart Failure Effects

Congestive heart failure (CHF) risk and hospitalization for heart failure are CV outcomes of particular interest with incretin therapies such as GLP-1 receptor agonists and DPP-4 inhibitors. A secondary analysis of the SAVOR-TIMI 53 (Saxagliptin Assessment of Vascular Outcomes Recorded in Patients with Diabetes Mellitus–Thrombolysis in Myocardial Infarction) trial revealed a possible increased risk of CHF associated with saxagliptin. This concern prompted investigators to conduct a cohort study using the U.K. Clinical Practice Research Datalink to determine whether there was an increased risk of CHF associated with either DPP-4 inhibitors or GLP-1 receptor agonists. In this cohort, 0.9% of patients treated with a GLP-1 receptor agonist were hospitalized for heart failure compared to 0.7% of control subjects, thus indicating no increased risk for heart failure (51). A multicenter observational study had similar results (52). These results are consistent with the findings in randomized placebo-controlled studies in which no significant reductions in hospitalizations for heart failure were observed for liraglutide (45), semaglutide (48), once-weekly exenatide (50), or lixisenatide (47). GLP-1 receptor agonists do not appear to increase or reduce the risk of hospitalizations for heart failure.

Renal Effects

The LEADER program evaluated liraglutide for microvascular outcomes (composite endpoint of renal and retinal events) compared to placebo and found a significantly lower rate of nephropathy events among those treated with liraglutide (5.7 vs. 7.2%, $P = 0.003$, NNT = 67) (45). When the composite renal outcomes (a composite of new-onset persistent macroalbuminuria, persistent doubling of the serum creatinine level, end-stage renal disease, or death due to renal disease) of patients in the LEADER program were evaluated further, the reduction in new-onset persistent macroalbuminuria was the most significant driver of the positive renal composite outcomes among patients treated with liraglutide compared to those treated with placebo (3.4 vs. 4.6%, $P = 0.004$, NNT = 83) (53). Currently, liraglutide is the only GLP-1 receptor agonist on the market to demonstrate renal protective effects in a randomized controlled environment.

TABLE 1. Summary of Completed CVOTs

	ELIXA (47)	EXSCEL (50)	SUSTAIN-6* (48)	LEADER (45)	CANVAS Program (58)	EMPA-REG (57)	TECOS (29)	SAVOR-TIMI (23)	EXAMINE (25)
n	6,068	14,752	3,297	9,340	10,142	7,020	14,735	16,492	5,380
Established CV disease, %	100	73.1	83.0	81.3	65.6	99	NR	78	100
Median trial duration, years	2.1	3.2	2.1	3.8	3.6	3.1	3.0	2.1	1.5
Primary outcome	4-point MACE	3-point MACE	3-point MACE	3-point MACE	3-point MACE	3-point MACE	4-point MACE	3-point MACE	3-point MACE
A1C reduction, %	–0.27	–0.53	–0.7 and –1.0	–0.40	–0.58	–0.24 and –0.36	–0.29	NR	–0.36
Primary MACE endpoint, HR	1.02 (0.89–1.17) *P* = 0.81	0.91 (0.83–1.00) *P* = 0.06	**0.74 (0.58–0.95) *P* = 0.02 NNT = 44**	**0.87 (0.78–0.97) *P* = 0.01 NNT = 53**	**0.86 (0.75–0.97) *P* = 0.02 NNT = 223**	**0.86 (0.74–0.99) *P* = 0.04 NNT = 62**	0.98 (0.89–1.08) *P* = 0.65	1.00 (0.89–1.12) *P* = 0.99	0.96 (≤1.16) *P* = 0.32
CV death, HR	0.98 (0.78–1.22) *P* = 0.85	0.88 (0.73–1.05) *P* = 0.63	0.98 (0.65–1.48) *P* = 0.92	**0.78 (0.66–0.93) *P* = 0.007 NNT = 77**	0.87 (0.72–1.06) *P* = NR	**0.62 (0.49–0.77) *P* <0.001 NNT = 45**	1.03 (0.89–1.19) *P* = 0.71	1.03 (0.87–1.22) *P* = 0.72	0.79 (0.60–1.04) *P* = 0.10
Nonfatal MI, HR	1.03 (0.87–1.22) *P* = NR	0.95 (0.84–1.09) *P* = 0.63	0.74 (0.51–1.08) *P* = 0.12	0.88 (0.75–1.03) *P* = 0.11	0.85 (0.69–1.05) *P* = NR	0.87 (0.70–1.09) *P* = 0.22	0.95† (0.81–1.11) *P* = 0.49	NR	1.08 (0.88–1.33) *P* = 0.47
Nonfatal stroke, HR	1.12 (0.79–1.58) *P* = NR	0.86 (0.70–1.07) *P* = 0.63	**0.61 (0.38–0.99) *P* = 0.04 NNT = 91**	0.89 (0.72–1.11) *P* = 0.30	0.90 (0.71–1.15) *P* = NR	1.24 (0.92–1.67) *P* = 0.16	0.97† (0.79–1.19) *P* = 0.76	NR	0.91 (0.55–1.50) *P* = 0.71
All-cause mortality, HR	0.94 (0.78–1.13) *P* = 0.50	**0.86 (0.77–0.97) *P* = NR NNT = 100**	1.05 (0.741.50) *P* = 0.79	**0.85 (0.74–0.97) *P* = 0.02 NNT = 71**	0.87 (0.74–1.01) *P* = 0.24	**0.68 (0.57–0.82) *P* <0.001 NNT = 38**	1.01 (0.90–1.14) *P* = 0.88	1.11 (0.96–1.27) *P* = 0.15	0.88 (0.71–1.09) *P* = 0.23

*HR reported as HR (95% CI). *Noninferiority margin set to 1.8, therefore not meeting the post-marketing requirement of a noninferiority margin of <1.3. †Includes fatal and nonfatal events. Bold text signifies statistically significant values. NR, not reported.*

Weight Effects

Weight loss is a known potential side effect of GLP-1 receptor agonist therapy. A meta-analysis evaluating the efficacy of GLP-1 receptor agonists (liraglutide or exenatide) in reducing weight among obese or overweight patients with or without type 2 diabetes determined that, over a minimum treatment duration of 20 weeks, a mean weight reduction of –2.9 kg was observed (95% CI –3.6 to –2.2 kg, 21 trials, 6,411 participants). Of the 21 trials used to perform the random effects meta-analysis, three studies evaluated the effect of a GLP-1 receptor agonist in patients without diabetes (mean weight reduction –3.2 kg, 95% CI –4.3 to –2.1), and the remaining 18 studies were conducted in patients with diabetes (mean weight reduction –2.8 kg, 95% CI –3.4 to –2.3) (54). Another meta-analysis comparing twice-daily exenatide or liraglutide to placebo, insulin, or TZDs had similar results (55). Liraglutide also has weight loss effects in obese or overweight individuals with prediabetes (56).

The pronounced effects on weight loss and waist circumference reduction with liraglutide subsequently led to its study as a weight loss agent at higher doses. The resulting robust clinical data associated with liraglutide's efficacy in weight reduction at a 3.0-mg dose led to the subsequent approval of its indication for weight loss at this dose. Although other GLP-1 receptor agonists have also shown weight loss effects, liraglutide is the agent with the greatest amount of evidence supporting its use as an adjunctive therapy for weight loss in patients with or without diabetes.

SGLT2 Inhibitors

Cardiovascular Effects

All CVOTs that have been conducted with SGLT2 inhibitors versus placebo have been in patients with type 2 diabetes at high risk of CV disease and assessed MACE as the primary outcome. All SGLT2 inhibitors can increase the risk of genital infections.

In the EMPA-REG OUTCOME (BI 10773 [Empagliflozin] Cardiovascular Outcome Event Trial in Type 2 Diabetes Mellitus Patients) trial of empagliflozin (n = 7,020) the MACE outcome (CV death, nonfatal MI, and nonfatal stroke) occurred in 10.5% of patients in the intervention arm and 12.1% of patients in the placebo arm (HR 0.86, 95% CI, 0.74–0.99, P <0.001 for noninferiority and P = 0.04 for superiority, NNT = 62). Patients treated with empagliflozin had significantly lower rates of CV death compared to patients in the placebo arm (3.7 vs. 5.9%, relative risk reduction [RRR] = 38%, NNT = 45) (57).

In the CANVAS (Canagliflozin Cardiovascular Assessment Study) Program for canagliflozin (n = 10,142), the MACE outcome (CV death, nonfatal MI, and nonfatal stroke), occurred in fewer patients in the canagliflozin arm compared to the placebo arm (26.9 vs. 31.5 participants with an event/1,000 patient-years; HR 0.86, 95% CI 0.75–0.97, P <0.001 for noninferiority and P = 0.02 for superiority, NNT = 223). Unlike empagliflozin, no differences were found for CV death. There was a higher risk for the amputation of the toes, midfoot, or leg (below and above the knee) with canagliflozin compared to placebo (NNH = 346) (58). The increased risk of amputation observed in the CANVAS Program led the FDA to require all canagliflozin drug labels to be updated with a boxed warning describing this risk. Phase 3 clinical trials with ertugliflozin have shown signals of increased risk of lower-limb amputations; however, at this time, there is no boxed warning for this agent. The other agents in this class also do not carry this boxed warning on their label.

The CV safety of dapagliflozin is being evaluated in the DECLARE-TIMI58 program (NCT01730534). Registry data covering all hospitalizations and all outpatient hospital visits in Denmark, Norway, and Sweden (CVD-REAL Nordic Study), compared new users of dapagliflozin to new users of DPP-4 inhibitors. The analysis showed that dapagliflozin was associated with a lower risk of MACE (nonfatal MI, nonfatal stroke, and CV death) compared to DPP-4 inhibitors (HR 0.79, 95% CI 0.67–0.94) (59).

The CVD-REAL Nordic study, as a whole, compared new users of SGLT2 inhibitors and new users of all other glucose-lowering medications. The majority of patients in the SGLT2 inhibitor arm were taking dapagliflozin (94%), followed by empagliflozin (5%) and canagliflozin (1%). Compared to other glucose-lowering drugs, SGLT2 inhibitors were associated with a decreased risk of CV mortality (HR 0.53, 95% CI 0.40–0.71) and MACE (HR 0.78, 95% CI 0.69–0.87). These findings are consistent with other CVOTs, suggesting that the CV benefits may be a class effect (60). See Table 1 for a comparison of all published CVOTs.

Hospitalizations for Heart Failure

When assessing CV outcomes of antihyperglycemic medications, hospitalizations due to heart failure may also be assessed depending on the study. In the CANVAS Program, canagliflozin was observed to have a lower incidence of hospitalizations due to heart failure compared to placebo (5.5 v. 8.7 participants/1,000 patient-years, NNT = 314) (58). The reduction in hospitalizations due to heart failure was also observed in the EMPA-REG OUTCOME study in patients treated with empagliflozin compared to those taking placebo (2.7 vs. 4.1%, NNT = 71) (57).

When heart failure outcomes were evaluated in all patients and subgroups, including patients with and without baseline heart failure, investigators observed that a lower percentage of patients experienced a composite outcome of heart failure or CV death in the empagliflozin group compared to those treated with placebo (5.7 vs. 8.5%, NNT = 35 over 3 years). Empagliflozin provided a consistent benefit

in patients with or without heart failure at baseline (61).

A large multinational analysis was conducted to determine whether this reduction in hospitalizations due to heart failure is a class effect of the SGLT2 inhibitors (62). The CVD-REAL study evaluated heart failure hospitalizations and death in patients who initiated an SGLT2 inhibitor compared to those who initiated another oral glucose-lowering drug. Use of an SGLT2 inhibitor was associated with lower rates of hospitalizations for heart failure, death, and a composite of hospitalizations for heart failure or death (62).

Renal Effects

One of the prespecified objectives of the EMPA-REG OUTCOME trial was to assess the effect of empagliflozin on renal outcomes. Incident or worsening nephropathy occurred in fewer patients randomized to receive empagliflozin (12.7 vs.18.8%, RRR = 39%, NNT = 16). There was less worsening of renal function and fewer renal replacement therapies were initiated compared to placebo. There were no differences in adverse event profiles between patients with renal impairment and the overall trial population (63).

Renal outcomes associated with canagliflozin were evaluated in the CANVAS Program, in which researchers observed that the progression of albuminuria occurred less frequently in the canagliflozin arm than with placebo (89.4 vs. 128.7 participants with an event/1,000 patient-years, NNT = 28). The composite renal outcome was also lower in patients randomized to the canagliflozin arm compared to placebo (5.5 vs. 9/1,000 patient-years, NNT = 287) (58).

Weight Effects

SGLT2 inhibitors as a class may also allow some patients to lose a modest amount of weight, as calories are lost through the excretion of excess glucose in patients' urine. The effects of dapagliflozin on weight loss has been observed in multiple studies (64–67). In a 24-week study of patients with type 2 diabetes, patients randomized to receive dapagliflozin experienced a mean weight loss of 2.08 kg compared to those taking placebo (65). Weight loss has ranged in studies from ~2 to 4 kg and appears to be sustained for at least 2 years (64,66,67).

Canagliflozin's effects on weight loss have also been evaluated in RCTs (68–70). In a 52-week study comparing canagliflozin to glimepiride, a subgroup of patients were evaluated for changes in body weight. Investigators observed average differences in body weight of –6.4 and –6.2 kg at 52 weeks for the 100- and 300-mg doses of canagliflozin, respectively, compared to patients taking glimepiride, who experienced a slight increase in weight (68). Other studies comparing canagliflozin to DPP-4 inhibitors and insulin have shown weight reduction ranging from 2 to 3 kg (69,70).

Empagliflozin has also been shown to have a mean weight loss effect when compared to placebo as add-on therapy to pioglitazone with or without metformin at two different doses (–1.62 and –1.47 kg with 10- and 25-mg doses of empagliflozin, respectively, versus +0.34 kg in those taking placebo (71).

Conclusion

Given the increasing number of pharmacologic options for the treatment of diabetes, choosing an appropriate option for a given patient can be challenging. Considering the pleotropic benefits of certain drug classes may help health care providers make decisions among drug therapy choices.

CV benefit has been demonstrated with some SGLT2 inhibitors (canagliflozin and empagliflozin), pioglitazone, and some GLP-1 receptor agonists (liraglutide and semaglutide), with a mortality benefit seen with empagliflozin and liraglutide. Reducing hospitalizations due to heart failure has only been demonstrated within the SGLT2 inhibitor class, with canagliflozin and empagliflozin being the only two agents with data from RCTs, but observational study data suggest that this may be a class effect.

The DPP-4 inhibitors have all been extensively studied with regard to renal disease, and the available published literature suggests that all agents in this class have shown some degree of urine albumin reduction. Liraglutide is the only GLP-1 receptor agonist to demonstrate a lower rate of nephropathy, driven primarily by a reduction in new-onset persistent macroalbuminuria, in an RCT. Within the SGLT2 inhibitor class, canagliflozin reduced the progression of albuminuria, and empagliflozin was shown to have a lower rate of incident or worsening nephropathy compared to placebo.

Obesity is a significant risk factor associated with the development of type 2 diabetes. Therefore, many patients who have type 2 diabetes are overweight or obese. Some classes of antidiabetic medications are known to cause weight gain, but some newer agents have been shown to promote weight loss. Metformin, SGLT2 inhibitors, and GLP-1 receptor agonists have all shown weight loss effects.

Of all available antidiabetic agents, metformin is the only agent that has shown the potential to help delay the progression of certain subtypes of cancers, possibly due to its regulation DNA repair enzymes.

As evidence regarding the nonglycemic benefits of antidiabetic medications has begun to accumulate, professional organizations have taken notice, and treatment guidelines have been updated accordingly. The American Association of Clinical Endocrinologists now provides tiered recommendations for pharmacologic interventions in its clinical practice guidelines in which metformin, GLP-1 receptor agonists, and SGLT2 inhibitors are recommended ahead of other classes of medications. The American Diabetes Association (ADA) has also updated its practice guidelines to recommend that candidates for dual therapy take atherosclerotic CV disease status into consideration and consider adding

agents proven to reduce CV events and CV mortality. Additionally, the ADA guidelines will now be updated periodically throughout each year instead of just annually to ensure that guidelines available online take new evidence into consideration for clinical practice decisions as early as possible.

When selecting a pharmacologic intervention, it is imperative that the therapy regimen be personalized for each patient. The benefits of therapy should always be weighed against the potential risks depending on each patient's health status and medical history. Health care providers should use all available evidence to make an informed therapeutic recommendation to each patient, providing the risks and benefits of each option and a sound medical rationale. The pleotropic benefits of certain agents should be taken into consideration when formulating a patient-specific pharmacologic treatment algorithm.

Duality of Interest

C.M. is a fellow for Becton Dickinson and Company. D.S. is an employee at Becton Dickinson and Company. D.P. is a part of the speaker's bureau for Astra Zeneca, Boehringer Ingelheim, Merck, Mannkind, Novo Nordisk, and Sanofi and is a consultant for Eli Lilly, Merck, Novo Nordisk, and Sanofi. J.G. is a part of the speakers bureaus of Novo Nordisk and Sanofi and is a consultant for Becton Dickinson and Company. No other potential conflicts of interest relevant to this article were reported.

Author Contributions

All of the authors researched data, contributed to discussion, and wrote, reviewed, and edited the manuscript. C.M. is the guarantor of this work and, as such, had full access to all the study reports included in this report and takes responsibility for the integrity and accuracy of this analysis.

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