New antihyperglycemic medications with cardiovascular protection for patients with diabetes: What do surgeons need to know?

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Although diabetes mellitus has long been known to significantly increase the risk of cardiovascular disease (CVD),¹ traditional anti-hyperglycemic medications have failed to improve cardiovascular (CV) outcomes.²⁻⁴ However, in the past 4 years, major breakthroughs have been made in this field. Two new classes of antihyperglycemia medications, sodium-glucose cotransporter-2 inhibitors (SGLT2is) and glucagon-like peptide-1 receptor agonists (GLP-1RAs), have recently been shown to improve not only glycemic control but also CV outcomes in patients with type 2 diabetes mellitus (T2DM). Because the proportion of patients with T2DM undergoing coronary artery bypass grafting (CABG) and other surgeries is rapidly increasing,⁵ surgeons will begin to encounter these medications with greater frequency. Here we review the essential information that surgeons need to be aware of as they participate in the team-based care of patients with T2DM and CVD.

EVIDENCE OF CV BENEFITS WITH SGLT2is

SGLT2is inhibit glucose reabsorption and increase glucose excretion in the kidney, thus leading to so-called sweet pee and improved glycemic control.⁶ Three CV outcomes trials with SGLT2is have been published to date (Table 1),⁷⁻¹³ and all have shown CV benefits. In the Empagliflozin Cardiovascular Outcome Event Trial in Type 2 Diabetes Mellitus Patients trial, 7020 patients with T2DM and known CVD were randomized to empagliflozin or placebo.⁷ After a median of 3.1 years, the primary end point of 3-point major adverse cardiovascular events (MACE) (ie, CV death, myocardial infarction [MI], or stroke) was significantly reduced with empagliflozin treatment (hazard ratio [HR], 0.86; 95% confidence interval [CI], 0.74-0.99; $P < .04$). This was largely driven by a reduction in CV death (HR, 0.62; 95% CI, 0.49-0.77; $P < .001$). Of note, significant reductions in all-cause mortality (32%) and heart failure (HF) (35%) were also observed.

Central Message

SGLT2 inhibitors and GLP-1 receptor agonists have recently been shown to improve CV outcomes in patients with diabetes. Here we review what surgeons need to know about these medications.

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Canagliflozin was evaluated in the Canagliflozin Cardiovascular Assessment Study (CANVAS) program, which consisted of 2 sister trials (CANVAS and CANVAS-Renal) in primary and secondary prevention patients with T2DM.⁸ Over a median follow-up of 3.6 years, 3-point MACE was significantly reduced with canagliflozin (HR, 0.86; 95% CI, 0.75-0.97; $P = .02$). Other exploratory outcomes indicated a potential benefit for death from HF (HR, 0.78; 95% CI, 0.67-0.91) and for a composite outcome of progression of renal disease (HR, 0.60; 95% CI, 0.47-0.77). An approximately 2-fold increase in the risk for lower-leg amputations was observed with canagliflozin (HR, 1.97; 95% CI, 1.41-2.75).

The final SGLT2i with published CV outcomes data is dapagliflozin, which was evaluated in the Dapagliflozin Effect on Cardiovascular Events–Thrombolysis in Myocardial Infarction 58 trial.⁹ This trial differed from the others in that it enrolled a “healthier” population (approximately 60% were primary prevention patients, and all had an estimated creatinine clearance ≥ 60 mL/min), and it evaluated coprimary end points of 3-point MACE and a composite of CV death or hospitalization for HF. The reduction in CV death or hospitalization for HF events was significant (HR, 0.83; 95% CI, 0.73-0.95; $P = .005$), but the reduction in 3-point MACE was not

TABLE 1. Summary results of published sodium-glucose cotransporter-2 inhibitor (SGLT2i) and glucagon-like peptide-1 receptor agonist (GLP-1RA) diabetes cardiovascular (CV) disease outcomes trials to date

Drug	SGLT2i			GLP-1RA			
	Empagliflozin	Canagliflozin	Dapagliflozin	Liraglutide	Semaglutide	Lixisenatide	Exenatide
Trial	Empagliflozin Cardiovascular Outcome Event Trial in Type 2 Diabetes Mellitus Patients ⁷	Canagliflozin Cardiovascular Assessment Study ⁸	Dapagliflozin Effect on Cardiovascular Events—Thrombolysis in Myocardial Infarction 58 ⁹	Liraglutide Effect and Action in Diabetes: Evaluation of Cardiovascular Outcome Results ¹⁰	Trial to Evaluate Cardiovascular and Other Long-term Outcomes with Semaglutide in Subjects with Type 2 Diabetes ¹¹	Evaluation of Lixisenatide in Acute Coronary Syndrome ¹²	Exenatide Study of Cardiovascular Event Lowering ¹³
N	7020	10,142	17,160	9340	3297	6068	14,752
Median age (y)	63	63	64	64	65	60	62
Baseline HbA1c (%)	8.1	8.2	8.3	8.7	8.7	7.6-7.7	8.0
Proportion of secondary prevention patients (%)	100	72	41	81	72	100	73
Median follow-up (y)	3.1	2.4	4.2	3.8	2.1	2.1	3.2
MACE*	0.86 (0.74-0.99)	0.86 (0.75-0.97)	0.93 (0.84-1.03)	0.87 (0.78-0.97)	0.74 (0.58-0.95)	1.02 (0.89-1.17)	0.91 (0.83-1.00)
CV death	0.62 (0.49-0.77)	0.87 (0.72-1.06)	0.98 (0.82-1.17)	0.78 (0.66-0.93)	0.98 (0.65-1.48)	0.98 (0.78-1.22)	0.88 (0.76-1.02)
MI	0.87 (0.70-1.09)	0.89 (0.73-1.09)	0.89 (0.77-1.01)	0.86 (0.73-1.00)	0.74 (0.51-1.08)	1.03 (0.87-1.22)	0.97 (0.85-1.10)
Stroke	1.18 (0.89-1.56)	0.87 (0.69-1.09)	1.01 (0.84-1.21)	0.86 (0.71-1.06)	0.61 (0.38-0.99)	1.12 (0.79-1.58)	0.85 (0.70-1.03)
HF hospitalization	0.65 (0.50-0.85)	0.67 (0.52-0.87)	0.73 (0.61-0.88)	0.87 (0.73-1.05)	1.11 (0.77-1.61)	0.96 (0.75-1.23)	0.94 (0.78-1.18)

Values for estimates are presented as hazard ratio (95% confidence interval). *SGLT2i*, Sodium-glucose cotransporter-2 inhibitors; *GLP-1RA*, glucagon-like peptide-1 receptor agonists; *HbA1c*, glycated hemoglobin; *MACE*, major adverse cardiovascular event; *MI*, myocardial infarction; *HF*, heart failure. *Three-point MACE was defined as a composite of CV death, MI, or stroke. This was the primary end point in all of the above trials except for Evaluation of Lixisenatide in Acute Coronary Syndrome,¹² which used 4-point MACE, which was a composite of CV death, MI, stroke, or hospitalization for unstable angina. Dapagliflozin Effect on Cardiovascular Events—Thrombolysis in Myocardial Infarction 58⁹ also had another primary end point, time to CV death or hospitalization for HF.

(HR, 0.93; 95% CI, 0.84-1.03; $P = .17$). The reduction in CV death or hospitalization for HF events reflected a lower rate of hospitalization for HF (27%) but not a lower rate of CV death. The secondary outcome of progression of renal disease was also reduced with dapagliflozin (HR, 0.53; 95% CI, 0.43-0.66).

Overall, SGLT2is likely have a class effect with regard to improved CV outcomes, and these benefits appears to be greater for HF and renal events than for atherosclerotic end points such as MI and stroke.¹⁴ The mechanism(s) by which SGLT2is impart CV outcomes is not clear,¹⁵ but natriuresis and renoprotective effects may explain, at least in part, the reduction in hospitalization for HF and the benefits in renal outcomes.¹⁴ Improvement in glycemic control is unlikely to account for the decrease in macrovascular complications.^{16,17}

EVIDENCE OF CV PROTECTION WITH GLP-1RAs

GLP-1RAs are incretin hormone mimetics that lower postprandial glucose concentrations by augmenting insulin secretion and suppressing glucagon release.¹⁸ To date, 5 CV outcomes trials have been published with these agents

(Table 1), with varying results. Evaluation of Lixisenatide in Acute Coronary Syndrome was the only trial to investigate the effect of a GLP-1RA in patients with acute coronary syndrome within the previous 6 months, and it showed that lixisenatide had no significant effect on CV outcomes.¹² In contrast, the Liraglutide Effect and Action in Diabetes: Evaluation of Cardiovascular Outcome Results trial showed that liraglutide reduced risk of 3-point MACE by 13% in patients with T2DM patients, mostly with established CVD (HR, 0.87; 95% CI, 0.78-0.97; $P = .01$).¹⁰ Significant reductions in CV death (22%) and all-cause death (15%) were also observed, although no benefit for HF was observed. Similarly, semaglutide led to a 26% risk reduction for 3-point MACE among mostly secondary prevention patients in Trial to Evaluate Cardiovascular and Other Long-term Outcomes with Semaglutide in Subjects with Type 2 Diabetes.¹¹ Semaglutide was associated with a significant reduction in stroke (39%) and a nonsignificant reduction in MI (26%), but essentially no reduction in CV death.

In the Exenatide Study of Cardiovascular Event Lowering trial, once-weekly exenatide was studied in a

mostly secondary prevention population, and while the reduction in 3-point MACE did not reach statistical significance (HR, 0.9; 95% CI, 0.83-1.0; $P = .06$), the reduction in the secondary exploratory outcome of all-cause mortality did (HR, 0.86; 95% CI, 0.77-0.97).¹³ Finally, the Harmony Outcomes Trial examined the CV effects of albiglutide, a therapy that the manufacturer withdrew from the market in the midst of the trial for economic reasons.¹⁹ Among secondary prevention patients with T2DM, albiglutide led to a 22% reduction of 3-point MACE (HR, 0.78; 95% CI, 0.68-0.90; $P = .0006$), which was largely driven by a 25% reduction in MI. Again, there was no significant effect on HF events.

As opposed to SGLT2is, GLP-1RAs appear to have a greater effect on atherosclerotic disease rather than on incidence of HF. There is also likely a class effect of GLP-1RAs,²⁰ although the benefits appear greater with some drugs (eg, liraglutide, semaglutide, and albiglutide) than with others (eg, lixisenatide and exenatide). Whether there are real differences within the class remains uncertain.¹⁹ The mechanism(s) by which GLP-1RAs affect CV outcomes may be related to antiatherogenic pathways, including pathways that affect inflammation, cardiac output, ischemic conditioning, and endothelial function.²¹

PRACTICAL CONSIDERATIONS IN THE USE OF SGLT2is AND GLP-1RAs

Although current use of these therapies is quite low,²² the frequency with which providers will encounter SGLT2i and GLP-1RA medications will undoubtedly increase in the coming years. The patients who will be prescribed these therapies will be adults with T2DM (usually with glycated hemoglobin >7% and already receiving metformin therapy) and established atherosclerotic CVD,²³ although there is increasing evidence (such as from the Dapagliflozin Effect on Cardiovascular Events–Thrombolysis in Myocardial Infarction 58 trial) that these medications may also be beneficial in a high-risk primary prevention population.⁹ The decision regarding whether to initiate an SGLT2i versus a GLP-1RA may be based on several factors, including the specific type of CV benefit sought, possible contraindications or cautions, patient preference, and cost.

In patients for whom there is a particular concern for the development or progression of HF or renal disease, an SGLT2i may be the most appropriate option. On the other hand, if the primary concern is the development of new or worsening atherosclerotic CVD, and if weight loss is also desired, then a GLP-1RA might be chosen.²³ The most important issue is to get eligible patients on at least 1 type of antihyperglycemic medication with CV benefit, whereas the addition of both concurrently may be considered,^{23,24} the potential CV effects of dual therapy have not been specifically studied.

In terms of contraindications and cautions with SGLT2i therapy, canagliflozin specifically should be avoided in patients with history of peripheral arterial disease, amputation, neuropathy, or diabetic foot ulcers.²³ There is no evidence from the trial data or from postmarketing pharmacovigilance studies that the other SGLT2i medications, empagliflozin or dapagliflozin, lead to increased amputation risk.²⁵ Further, canagliflozin should not be used in patients with a history of osteoporosis, as an increased risk of fracture was observed in the CANVAS trials.⁸ SGLT2i therapy in general should be avoided in patients with a history of recurrent genital candidiasis, because the trials from all 3 SGLT2i therapies report a significantly increased risk of genital infections.²³ Indeed, the Food and Drug Administration issued a warning about the increased risk of necrotizing fasciitis of the perineum, or Fournier's gangrene, seen in patients receiving SGLT2i therapy.²⁶ In addition, SGLT2is should not be used in patients with a history of diabetic ketoacidosis (DKA) because the therapy may increase this risk (described further below).²³ Finally, SGLT2i therapy is currently not recommended for individuals with severe chronic kidney disease and estimated glomerular filtration rate < 45 mL/min/1.73 m²,²³ although this may change because several trials are underway to specifically test the efficacy of SGLT2i therapy in this population. The Canagliflozin and Renal Endpoints in Diabetes with Established Nephropathy Clinical Evaluation trial, which tested canagliflozin in patients with estimated glomerular filtration rate ≥ 30 mL/min/1.73 m², was stopped prematurely due to overwhelming benefits on the primary composite outcome of end-stage renal disease, doubling of serum creatinine, and renal or CV death,²⁷ which supports the idea that SGLT2i therapy may in fact be beneficial in this high-risk population.

In regard to GLP-1RAs, these therapies should be used with caution in patients with severe renal impairment and/or end-stage renal disease, although further studies in this high-risk group are ongoing.²³ Postmarketing case reports have raised concern about GLP-1RAs leading to acute pancreatitis, and although this was not seen in the clinical trials, it is reasonable to be cautious about using these agents in patients with a history of pancreatitis.^{16,23} Because medullary thyroid cancer and multiple endocrine neoplasia syndrome type 2 have been reported in patients taking GLP-1RA agents, although admittedly in low numbers, these medications should not be used in patients with a personal or family history of either of these cancers.^{20,23} Shorter-acting GLP-1RAs delay gastric emptying, so these should be used in caution in patients with prior gastric surgery.²³ Finally, semaglutide has been associated with diabetic retinopathy complications, likely due to a rapid decrease in glucose levels, so it should be used cautiously in patients with retinopathy.¹⁷

Both SGLT2is and GLP-1RAs can lead to hypoglycemia, especially in patients receiving insulin or insulin secretagogues (such as sulfonylureas); a lower dose of insulin or sulfonylureas may be necessary when these medications are initiated.²³

With regard to patient preferences, these are likely to be related to potential side effects as well as to the route of administration. SGLT2i therapy is generally well tolerated and has the advantage of being administered orally. GLP-1RA therapy, on the other hand, commonly leads to nausea and vomiting, a side effect that can limit tolerance to these medications.²⁸ These symptoms are often transient with the long-acting GLP-1RAs and can be mitigated by dose escalation and reduction of meal size.²⁹ GLP-1RAs are also only currently available in injectable form, and although once-weekly injections are available, these formulations more commonly lead to injection site reactions. These injection site reactions generally resolve over time but can be bothersome to patients. An oral form of semaglutide has been developed, but it has not yet come to market.

SPECIFIC IMPLICATIONS FOR SURGEONS

A few points regarding SGLT2i and GLP-1RA therapy are particularly important for surgeons to be aware of. A post hoc analysis of the Empagliflozin Cardiovascular Outcome Event Trial in Type 2 Diabetes Mellitus Patients trial showed that patients with a self-reported history of CABG received the same CV benefits from empagliflozin as those without a history of CABG.³⁰ A similar analysis of the Liraglutide Effect and Action in Diabetes: Evaluation of Cardiovascular Outcome Results trial indicated that patients with a history of CABG also received similar benefits from liraglutide as those without CABG.³¹ These studies suggest that SGLT2is and GLP-1RAs may be important components of secondary preventive care in the CABG population.

SGLT2is and GLP-1RAs have generally not been studied in the acute MI population, with the exception of lixisenatide, which did not show improvement on CV outcomes.¹⁵ That being said, it is likely safe to initiate these medications before discharge in patients who have been admitted for a CV event, such as acute coronary syndrome requiring CABG.²³ Enlisting the guidance of a cardiologist, endocrinologist, and/or pharmacist to determine whether these therapies are appropriate for patients hospitalized for cardiac surgery would be very reasonable. Certain populations of patients who might be cared for by surgeons require caution when using these medications. Specifically, SGLT2i therapy should be used with caution in patients with peripheral arterial disease, especially if they have had a prior amputation.²³ In addition, patients with prior gastric surgery may not tolerate GLP-1RA therapy.

Drug-drug interactions with SGLT2i and GLP-1RA therapies do not appear to be a significant clinical issue for

medications that are commonly used in surgical patients.^{32,33} However, it is important to note that both classes of medications can lead to hypoglycemia, especially when coadministered with other antihyperglycemia medications. In addition, SGLT2is cause an osmotic diuresis and intravascular volume contraction, so it is important to closely monitor renal function and use caution when treating with SGLT2is in conjunction with other therapies that may lead to acute renal failure, such as diuretics or nonsteroidal anti-inflammatory drugs.

The timing of initiation of SGLT2is or GLP-1RAs with relation to surgery in general, and CABG specifically, has not been studied. Therefore, it is unknown whether these medications could safely be started preoperatively to achieve glycemic control. However, given that these medications can be associated with hypoglycemia, especially when used in conjunction with other antihyperglycemia agents, use of these medications around the time of surgery should be approached with caution. SGLT2is, in particular, may pose perioperative risks due to euglycemic DKA. Traditional DKA can present postoperatively, and is characterized by hyperglycemia, anion-gap acidosis, and elevated plasma and urine ketones.³⁴ However, with SGLT2is, euglycemic DKA has been reported in which patients have normal or only moderately elevated glucose levels. The mechanism by which SGLT2is may lead to this disorder is unknown. Although the rates of euglycemic DKA have been very low in SGLT2i clinical trials, the Food and Drug Administration Adverse Event Reporting System has identified 73 cases of DKA related to SGLT2i therapy, and this is likely an underestimate.³⁵ The only reported cases of euglycemic DKA in patients with T2DM have occurred after surgery, similar to traditional DKA.³⁴

The risk of euglycemic DKA warrants vigilance because the diagnosis can often be missed. Patients may present with nonspecific symptoms such as nausea, vomiting, shortness of breath, abdominal pain, or confusion, so the index of suspicion for this disorder should be high for patients on SGLT2i therapy.^{34,35} Whether the risk of euglycemic DKA warrants holding SGLT2is preoperatively is unknown.

CONCLUSIONS

This is an incredibly exciting time in the landscape of diabetes and CV risk management. Since the first positive trials with SGLT2i and GLP-1RA therapies were published in 2015-2016, 5 more have been reported, and at least another 10 will be published in the coming 4 years. With this rapid evolution, increasing numbers of patients will be initiated on these therapies, and surgeons will need to be aware both of the potential benefits of these medications as well as potential risks. As we move closer to the goal of team-based care, in which multiple providers work together to take care of complex, high-risk patients, the surgeon's

role in preventing CVD among patients with T2DM will be critical.

Conflict of Interest Statement

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