From The Medical Letter on Drugs and Therapeutics

Cardiovascular Benefits of SGLT2 Inhibitors and GLP-1 Receptor Agonists in Type 2 Diabetes

Since 2008, because of safety concerns, the FDA has mandated long-term cardiovascular outcomes trials be conducted for all new drugs for type 2 diabetes.[1] Reductions in the incidence of macrovascular complications in these trials with some sodium-glucose co-transporter 2 (SGLT2) inhibitors and glucagon-like peptide 1 (GLP-1) receptor agonists in patients at risk for cardiovascular disease (see **Table**) have led to new recommendations.[2-4]

Metformin (Glucophage, and others) is the drug of choice for initial treatment of type 2 diabetes.[5] For patients who do not achieve their A1C goal with metformin, the choice of an additional drug varies with the comorbidities of the patient. For those with atherosclerotic cardiovascular disease (ASCVD), an SGLT2 inhibitor or a GLP-1 receptor agonist with proven cardiovascular benefits is now preferred.[3] The SGLT2 inhibitors empagliflozin (Jardiance) and canagliflozin (Invokana) and the GLP-1 receptor agonist liraglutide (Victoza) are the only drugs to date with an FDA-approved indication for cardiovascular risk reduction in patients with type 2 diabetes and established cardiovascular disease.[6]

SGLT2 inhibitors can cause genital mycotic and urinary tract infections, acute kidney injury, volume depletion, hypotension, and ketoacidosis. An increased risk of fractures and of lower limb amputation, primarily at the level of the toe or metatarsal, have been reported with canagliflozin.[7]

GLP-1 receptor agonists can cause injection-site reactions, nausea, vomiting, diarrhea, renal impairment, and acute renal failure, and they might increase the risk of pancreatitis and cholangiocarcinoma.[8] Thyroid C-cell carcinoma has been reported in animals and thyroid C-cell hyperplasia in humans; these drugs are contraindicated for use in patients with a personal or family history of medullary thyroid carcinoma and in those with multiple endocrine neoplasia type 2.[9] Semaglutide (Ozempic) has been associated with a significant increase in diabetic retinopathy complications.[10,11]

The American College of Cardiology preferentially recommends use of liraglutide, particularly for patients with osteoporosis, prior amputations, severe peripheral artery disease, peripheral neuropathy, or active lower extremity soft tissue ulcers or infections, or empagliflozin, especially for those at high risk for heart failure.[2]

Recent retrospective analyses have suggested that use of any SGLT2 inhibitor may reduce the risk of cardiovascular events[12] and hospitalization for heart failure.[13] In one meta-analysis that included 236 trials, SGLT2 inhibitors and GLP-1 receptor agonists were both associated with lower cardiovascular and all-cause mortality in patients with type 2 diabetes.[14]

In patients with type 2 diabetes and atherosclerotic cardiovascular disease (ASCVD) who have not achieved their A1C goal with metformin, addition of the SGLT2 inhibitor empagliflozin (Jardiance) or the GLP-1 receptor agonist liraglutide (Victoza) is recommended to improve cardiovascular outcomes. Results to date suggest that all SGLT2 inhibitors may reduce the risk of hospitalization for heart failure.

Table. Cardiovascular Outcomes With SGLT2 Inhibitors and GLP-1 Receptor Agonists[a]

Study	Cardiovascular (CV) Endpoints	Results (in Addition to Standard Treatment)	FDA-Approved CV Indications
SGLT2 Inhibitors			
Metformin is available in fixed-dose combinations with canagliflozin, dapagliflozin, and empagliflozin as Invokamet and Invokamet XR, Xigduo XR, and Synjardy, respectively			
Canagliflozin-Invokana (Janssen)			
CANVAS and CANVAS-R (*N Engl J Med*. 2017;377:644) 126.1 weeks (n = 10 142; high CV risk)	Major adverse CV events (MACE)	Canagliflozin 26.9 events per 1000 patient-years[b]	Reduce risk of MACE in patients with established cardiovascular disease (CVD)
		Placebo 31.5 events per 1000 patient-years	
	Hospitalization for heart failure (HF)	Canagliflozin 5.5 events per 1000 patient-years (*Circulation*. 2018;138:458)[b]	
		Placebo 8.7 events per 1000 patient-years	
Dapagliflozin-Farxiga (AstraZeneca)			
DECLARE-TIMI58 (*N Engl J Med*. 2019;380:347) 4.2 years (n = 17 160; with or at risk for atherosclerotic CVD [ASCVD])	MACE	Dapagliflozin 8.8% (met prespecified criteria for noninferiority)	Not approved
		Placebo 9.4%	
	Composite of CV death or hospitalization for HF	Dapagliflozin 4.9% (no difference in CV death; significant difference in hospitalization for HF)	
		Placebo 5.8%	
Empagliflozin-Jardiance (Boehringer Ingelheim/Lilly)			
EMPA-REG OUTCOME (*N Engl J Med*. 2015;373:2117) 3.1 years (n = 7020; high CV risk)	MACE	Empagliflozin 10.5%[b]	Reduce risk of CV death in patients with established CVD
		Placebo 12.1%	
	Hospitalization for HF	Empagliflozin 2.7%[b]	
		Placebo 4.1%	
	CV death	Empagliflozin 3.7%[b]	
		Placebo 5.9%	

(continued)

Table. Cardiovascular Outcomes With SGLT2 Inhibitors and GLP-1 Receptor Agonists[a] (continued)

Study	Cardiovascular (CV) Endpoints	Results (in Addition to Standard Treatment)	FDA-Approved CV Indications
GLP-1 Receptor Agonists			
Dulaglutide-Trulicity (Lilly)			
REWIND >5 years (n = 9901; with or without CVD)	MACE	Dulaglutide (results not published to date; according to the manufacturer, they were statistically significant)	Not approved
		Placebo (results not published to date)	
Exenatide ER-Bydureon (BMS/AstraZeneca)			
EXSCEL (*N Engl J Med*. 2017;377:1228) 3.2 years (n = 14 752; with or without CVD)	MACE	Exenatide ER 11.4%	Not approved
		Placebo 12.2%	
	Hospitalization for HF	Exenatide ER 3.0%	
		Placebo 3.1%	
Liraglutide-Victoza (Novo Nordisk)			
LEADER (*N Engl J Med*. 2016;375:311) 3.8 years (n = 9340; high CV risk)	MACE	Liraglutide 13.0%[b]	Reduce risk of MACE in patients with established CVD
		Placebo 14.9%	
	CV death	Liraglutide 4.7%[b]	
		Placebo 6.0%	
	Hospitalization for HF	Liraglutide 4.7%	
		Placebo 5.3%	
Lixisenatide-Adlyxin (Sanofi)			
ELIXA (*N Engl J Med*. 2015;373:2247) 25 months (n = 6068; recent acute coronary syndrome)	CV death, myocardial infarction, stroke, or hospitalization for unstable angina	Lixisenatide 13.4% (met prespecified criteria for noninferiority)	Not approved
		Placebo 13.2%	
	Hospitalization for HF	Lixisenatide 4.0%	
		Placebo 4.2%	
Semaglutide-Ozempic (Novo Nordisk)			
SUSTAIN-6 (*N Engl J Med*. 2016;375:1834) 2.1 years (n = 3297; high CV risk)	MACE	Semaglutide 6.6%[b]	Not approved
		Placebo 8.9%	
	Nonfatal stroke	Semaglutide 1.6%[b]	
		Placebo 2.7%	

[a] In patients with type 2 diabetes. Trials are ongoing for dapagliflozin in patients with chronic kidney disease (DAPA-CKD) or HF (DAPA-HF), empagliflozin in patients with or without CVD (EMPRISE), with HF with reduced ejection fraction (EMPEROR-Reduced) or with preserved ejection fraction (EMPEROR-Preserved), and ertugliflozin in patients with established ASCVD (VERTIS-CV).

[b] Statistically significant vs placebo.

ARTICLE INFORMATION

Once a month, *The Medical Letter* provides a previously published article to *JAMA* to be republished.

Previous Publication: This article was published in *The Medical Letter on Drugs and Therapeutics*. February 25, 2019;61(1566):26-28. The Table was modified from the original to fit within this space. It is reprinted here with permission from ©The Medical Letter Inc.

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