Patients with CVD and Diabetes: what to Choose and How to Start?

Sodium-glucose cotransporter 2 inhibitors and glucagon-like peptide 1 receptor agonists have been approved for improving glycemic control in adults with type 2 diabetes mellitus, with many agents demonstrating significant positive effects in multiple CV outcomes trials.

The unexpected benefits appear to be largely consistent across class of medication, but only certain agents have been approved for CV indications.

In a systematic review and meta-analysis, investigators evaluated data from eight trials, including 42,920 patients enrolled in GLP-1 receptor agonist trials and 34,322 patients in SGLT2 inhibitor trials.**(Ref:1)** Both drug

classes led to similar reductions in MACE: GLP-1 receptor agonists reducing risk by 12% ($p < 0.001$), and SGLT2 inhibitors by 11% ($p = 0.001$). The benefit was limited to patients with established ASCVD; in this setting, reduction in risk for MACE was about 14% for each drug class.

There were differences: SGLT2 inhibitors had a more marked effect on

preventing hospitalization for HF and progression of kidney disease. Indeed, the Food and Drug Administration has approved canagliflozin to treat diabetic kidney disease (DKD) and reduce the risk of hospitalization for HF in patients with T2DM and DKD.

Given that T2DM is a major risk factor for morbidity and mortality from CV disease, these agents are considered

major advances. While the overall benefits of agents within each class are similar, specific effects differ, and the unique side effect profile of each class might influence drug choice.

Yet the bigger issue, it seems, is considering these agents as a whole.

Take patients with HF as an example. In a large outpatient registry in the United States, 27% of adults with T2DM had a

diagnosis of HF, a little more than half of which was HF with a preserved ejection fraction. Although some decisions regarding the use of a T2DM medication in patients with HF appeared consistent with evidence (less use of thiazolidinediones, like Glutazones), other choices appeared contrary to evidence (less use of metformin and SGLT2 inhibitors).

These associations may represent residual safety concerns about using metformin in patients with HF, despite more recent evidence that it is safe and may be beneficial. As for the newer agents, there may be a hesitancy to use novel medications in complicated patients.

It may be time to reconsider that: SGLT2 inhibitors have cardioprotective and

renoprotective effects, as demonstrated in major trials. In one recent review, the authors called the substantial and consistent risk reduction in HF hospitalization as "the most impressive finding seen" across four trials of SGLT2 inhibitors: DECLARE-TIMI 58, DAPA-HF, EMPEROR-Preserved, and EMPEROR-Reduced.**(Ref:2)**

Subsequently, the SGLT2 inhibitor dapagliflozin became the first to receive an expanded indication in the United States to treat HF with reduced ejection fraction in adults with or without T2DM (**Table**)

New Agents for T2DM and Specific CV Indications

	CV Indication
GLP-1 Receptor Agonists	
Dulaglutide	To reduce MACE risk in adults with/without CVD
Liraglutide	To reduce MACE risk in adults with CVD
Semaglutide	To reduce MACE risk in adults with CVD
Albiglutide, Exenatide, Lixisenatide	—
SGLT2 Inhibitors	
Canagliflozin	To reduce MACE in adults with CVD
Dapagliflozin	To treat HFrEF in adults with/without T2DM
Empagliflozin	To reduce risk of CV death in adults with CVD
Ertugliflozin	—

Decision Pathway

In 2018, Laurence Sperling, MD, and colleagues published an ACC expert consensus decision pathway covering novel therapies for CV risk reduction in patients with T2DM and ASCVD. **(Ref:3)** Now they have updated the document, based on recent studies. **(Ref:4)**

Actually rather than just being antihyperglycemics, both drug classes are "more anti-atherosclerotic agents." While GLP-1 receptor agonists and SGLT2 inhibitors reduce atherosclerotic MACE to a similar degree in patients with established ASCVD, there are differences between the drug classes, which may impact choice of therapy. Time to benefit is quick in both, but

SGLT2 inhibitors show a faster divergence of event curves, with a slightly greater delay in benefits with the GLP-1 receptor agonists.

In the systematic review and meta-analysis noted above, for example, both classes reduced the risk of myocardial infarction and CV death, but only GLP-1 receptor agonists reduced the risk of stroke. SGLT2 inhibitors

reduced hospitalization for HF by 31% ($p < 0.001$), whereas GLP-1 receptor agonists did not have a significant effect (hazard ratio [HR]: 0.93; $p = 0.20$). Both GLP-1 receptor agonists and SGLT2 inhibitors reduced the risk of progression of kidney disease, including macroalbuminuria (both $p < 0.001$), but only SGLT2 inhibitors reduced the risk of worsening estimated glomerular

filtration rate, end-stage kidney disease, or renal death (HR: 0.55; p <0.001).

Both classes lead to modest and relatively similar reductions of hemoglobin A1c; therefore, they appear to exert their beneficial CV effects independent of glucose control through their individual pleiotropic properties.

As the updated decision pathway published in *JACC* puts it, "Previously, CV specialists focused on risk factor optimization in patients with diabetes. Medications used for glycemic control were not adjusted by CV specialists, in part because they were not expected to demonstrate direct CV benefit. However, the recent development of SGLT2 inhibitors and GLP-1 receptor

agonists has, for the first time, demonstrated that specific treatments developed for glucose lowering can directly improve CV outcomes." **(Ref:4)**

Dr. Sperling suggests that cardiologists become champions of these new drugs and agents of change by incorporating them into their clinical practices and, more broadly, using them throughout their health systems. These are not

glucose-lowering agents. The benefits for each of these classes appear to go above and beyond their impact on hemoglobin A1c. It is an area of rapid evolution, it is an area we need to become engaged with and not just sit on the guidelines with knowledge alone. These agents will one day be care measures for cardiologists, much as statins are today.

Take-home Messages:

- Glucagon-like peptide 1 (GLP-1) receptor agonists and sodium-glucose cotransporter-2 (SGLT2) inhibitors are two new classes of antihyperglycemic agents that also significantly reduce risk for cardiovascular (CV) disease.

- Both have a similar significant impact on major adverse cardiac events (MACE), but SGLT2 inhibitors have a more marked effect on preventing hospitalization for heart failure (HF) and progression of kidney disease.
- The American College of Cardiology (ACC) is updating the clinical use of these novel therapies

for cardiovascular risk reduction in patients with type 2 diabetes mellitus (T2DM) and atherosclerotic cardiovascular disease (ASCVD). These agents should be considered anti-atherosclerotic agents that cardiologists should be using in appropriate patients.

References:

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3. **Das SR, Everett BM, Birtcher KK, et al.** 2018 ACC Expert Consensus Decision Pathway on Novel Therapies for Cardiovascular Risk Reduction in Patients with Type 2 Diabetes and Atherosclerotic Cardiovascular Disease: A Report of the American College of Cardiology Task Force on Expert Consensus Decision Pathways. *J Am Coll*

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