New Horizons in Reducing Cardiovascular Risk in T2DM

In 2015, diabetes was the seventh leading cause of death, with almost 60% of patients dying of cardiovascular (CV) events and complications. In fact, a majority of hospitalizations associated with diabetes are also related to CV issues.[1-3] Even small increases in blood glucose level or hemoglobin A1c (HbA1c) above the normal range (>7.0%) can increase CV risk.[4,5] Conversely, maintenance of near normal blood glucose levels have been associated with reduced CV and microvascular complications associated with T2DM.[6] As a result, all updated guidelines recommend early intensification of antihyperglycemic therapy to maintain HbA1c levels <7.0% to the extent feasible in a patient with T2DM.[7,8] Additionally, in 2008, the Food and Drug Administration recommended that antihyperglycemic agents should be evaluated for meaningful reduction of adverse CV outcomes in conjunction with glucose lowering.[9] Furthermore, two new classes of antihyperglycemic agents, glucagon-like peptide-1 receptor agonists (GLP-1 RAs) and sodium-glucose co-transporter 2 (SGLT2) inhibitors, have shown promise in improving CV outcomes in T2DM. Despite guidelines and the availability of such efficacious antihyperglycemic agents, glycemic control remains suboptimal among patients with T2DM, thereby indicating an unmet need to overcome patient-reported barriers.[10,11]

This ECHO summarizes data from key studies that underscore the CV protective nature of GLP-1 RAs in T2DM. Also addressed is the critical importance of selecting antiglycemic agents that not only improve glycemic control, but additionally limit poor outcomes of T2DM-associated micro- and macrovascular disease. Lastly, practical guidance is offered to ensure patient-centered approaches to improve adherence to therapy, particularly in light of the availability of an oral formulation of GLP-1 RA.

Key CV Outcomes Studies in T2DM

SGLT2 Inhibitors (Table 1)

SGLT2 inhibitors are known to decrease renal glucose reabsorption and increase urinary glucose excretion, leading to reduced plasma glucose level and body weight without the risk of hypoglycemia.[12] Currently, empagliflozin, canagliflozin, dapagliflozin, and ertugliflozin have been approved as adjunct therapy in T2DM. In the EMPA-REG OUTCOME trial, empagliflozin treatment demonstrated significant risk reduction in 3-point MACE (CV death, nonfatal myocardial infarction [MI], and nonfatal stroke) (HR 0.86, 95% CI 0.74–0.99, p = 0.04) compared to placebo. There was also a significant reduction in

hospitalizations for heart failure (HF) among empagliflozin-treated patients.[13] Similarly, the CANVAS study reported a significant reduction in the relative risk of the primary CV endpoint by 14% (HR 0.86, 95% CI 0.75–0.97, p = 0.02 for superiority) and reduction in hospitalization for HF with canagliflozin.[14] Dapagliflozin, however, did not demonstrate significant risk reduction of MACE or CV death but led to decreased hospitalizations for HF in the DECLARE-TIMI trial.[15] The VERTIS-CV trial is currently investigating the CV safety of ertugliflozin among patients with T2DM.[16]

Table 1 summarizes the CV outcomes of approved SGLT2 inhibitors in T2DM.

Clinical Trial (Agent)	Hazard Ratio and Confidence Interval vs Placebo
EMPA-REG (Empagliflozin)	**HR 0.86 (CI: 0.74-0.99); P=0.04 for Superiority**
CANVAS Program (Canagliflozin)	**HR 0.86 (CI: 0.75-0.97); P=0.02 for Superiority**
DECLARE-TIMI (Dapagliflozin)	**HR 0.93 (CI: 0.84-1.03); P=0.17 for Superiority (NS)***
VERTIS-CV (Ertugliflozin)	**Ongoing, data are preliminary**

Table 1. SGLT2 Inhibitors: Reduction in Composite Endpoint for Cardiovascular Disease (CVD) Risk.
Abbreviations: NS - not significant. * Dapagliflozin reported HR 0.83 (CI: 0.73-0.95) for CV death/hospitalization for HF (P=0.005). (These data do not represent head-to-head studies; the differences in the results of the various trials may be due to different inclusion/exclusion criteria).

GLP-1 Receptor Agonists (Table 2)

GLP-1 RAs stimulate glucose-dependent insulin secretion and reduce glucagon secretion, gastric emptying, and appetite, which ultimately lead to glycemic control. These agents are also associated with improvements in lipids, reductions in blood pressure and bodyweight, and a low risk of hypoglycemia.[17] Table 2 shows the summary of key clinical trial results related to CV outcomes with GLP-1 RAs in T2DM (not head-to head trials). The ELIXA[18] (lixisenatide), LEADER[19] (liraglutide), SUSTAIN 6[20] (semaglutide), HARMONY[21] (albiglutide), REWIND[22] (dulaglutide), and EXSCEL[23] (extended-release exenatide) trials have clarified the CV safety of GLP-1 RAs. Specifically, liraglutide and semaglutide have been shown to reduce CV events in patients with T2DM who are at high CV risk.[19,20] In the SUSTAIN-6 trial, semaglutide treatment resulted in significantly lowered rate of CV death, nonfatal MI, or nonfatal stroke among patients with T2DM who were at high CV risk.[20] Similarly, in the LEADER trial, liraglutide lowered the rate of the first occurrence of death from CV causes, nonfatal MI, or nonfatal stroke among patients with T2DM and a high CV risk.[19] However, dulaglutide, lixisenatide, and once-weekly exenatide did not show superiority in CV outcomes as compared with placebo.[18,22,23] Importantly, the GLP-1 RA class of drugs was associated with a significant 10% relative risk reduction in three-point MACE.[24]

Although GLP-1 RAs are effective treatments for T2DM, these agents are administered as subcutaneous injections, which is considered a major barrier for widespread use among patients with T2DM.[25] To overcome this, an oral formulation of semaglutide has been developed and investigated in the treatment of T2DM. In the PIONEER trials, oral semaglutide has resulted in a significant reduction in HbA1c[26] and has recently demonstrated non-inferiority in the number of adverse CV events as compared with placebo.[27] Close evaluation of PIONEER 6 (Table 2) demonstrates that based on hazard ratio (HR) vs. placebo for a composite CV endpoint, oral semaglutide appears as effective in reducing CV risk as injectable GLP-1RAs. Based on these results, oral semaglutide has now been approved and ongoing trials are further studying its efficacy in T2DM.[28-30]

Clinical Trial (Agent)	Hazard Ratio and Confidence Interval vs Placebo
LEADER (Liraglutide)	**HR 0.87 (CI: 0.78-0.97); P=0.01 for Superiority**
HARMONY (Albiglutide)	**HR 0.78 (CI: 0.68-0.90); P=0.0001 for Superiority**
REWIND (Dulaglutide)	**HR 0.88 (CI: 0.79-0.99); P=026 for Superiority (NS)**
SUSTAIN-6 (Semaglutide)	**HR 0.74 (CI: 0.58-0.95); P<0.001 for Superiority**
PIONEER 4 (Semaglutide, oral)	**Comparative HbA1c lowering trial; suggestive for ↓CVD outcomes but not powered for this endpoint.**
PIONEER 6 (Semaglutide, oral)	**HR 0.79 (CI: 0.57-1.11); P<0.01 for Superiority**

Table 2. GLP-1 Receptor Agonists: Reduction in Composite Endpoint for Cardiovascular Disease (CVD) Risk. (These data do not represent head-to-head studies; the differences in the results of the various trials may be due to different inclusion/exclusion criteria).

Patient-Centered Approaches to Overcome Barriers in Treatment Intensification

Recent data have indicated that only 50% of patients with T2DM achieve individualized glycemic targets.[10,11] Thus, many patients with T2DM continue to be at risk for developing CV complications that not only adversely impact mental health, employment, absenteeism, work productivity, but also lead to increased healthcare costs. While most patients with T2DM require therapy intensification when HbA1c goals are not met with metformin, the most recent guidelines suggest adding a second or third oral anti-diabetic drug. The guidelines recommend the addition of GLP-1 RAs for patients that would benefit from CV health effects (for instance, those with obesity and high risk of CV events).[7,8] Recent evidence, however, has shown that add-on therapies are not optimally prescribed in current clinical practice.[31] In a retrospective healthcare claims study, only 38% of patients with T2DM were prescribed add-on therapy and 57.5% remained on metformin monotherapy. Real-world data indicate that patients often discontinue GLP-1 RAs even when these agents have been prescribed for their T2DM treatment regimen. For instance, multivariate regression analysis showed that only 29% of patients were adherent

to GLP-1 RA treatment.[32] Although cost is one of the barriers for lack of persistence to GLP-1 RAs, another major contributing factor is their route of administration.[25,33] Experts, therefore, recommend a patient-centered approach for treatment intensification in T2DM. They suggest starting with adjunct GLP-1 RAs among T2DM patients at high risk for CV events and also reducing delays in starting GLP-RAs among patients that are not at goal. For patients with T2DM who display an aversion to injectable agents or who prefer an oral agent, an oral agent if suitable and available is appropriate along with education and counseling concerning potential impacts of polypharmacy and dosing at mealtimes.

Conclusion

CV complications are precipitated by uncontrolled hyperglycemia among patients with T2DM. These complications form the primary basis of increased morbidity and mortality in T2DM. GLP-1 RAs have shown considerable efficacy in reducing CV events among patients with T2DM, with liraglutide and semaglutide being associated with improved outcomes among T2DM patients with a high CV risk profile. In spite of these advantages, GLP-1 RAs are underused in current clinical practice, possibly due to their subcutaneous route of administration. An oral formulation of semaglutide has recently been approved by the FDA; its judicious use in patients with T2DM, perhaps especially in the primary care setting, may lead to both improved patient adherence with their antiglycemic therapy as well as reduced CV risk.[29]

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