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Integrating cardioprotective glucose-lowering medications into clinical practice

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Patients with type 2 diabetes suffer from both microvascular and macrovascular complications. Optimal glycemic control is well known to reduce the microvascular complications of retinopathy, nephropathy, and neuropathy. However, despite having multiple classes of antidiabetes medications, we have not been able to favorably affect the cardiovascular (CV) complications of diabetes, which cause considerable morbidity and premature CV mortality in patients with diabetes. The recent publication of the EMPA-REG Outcome and the LEADER studies demonstrating favorable CV outcomes with empagliflozin and liraglutide have led to a decision by the Food and Drug Administration to approve an additional indication (besides glucose lowering) – to reduce the risk of myocardial infarction, stroke, and CV death with liraglutide, and to reduce the risk of CV death with empagliflozin in adult patients with type 2 diabetes mellitus and established CV disease. This represents a paradigm shift in diabetes management and will have a major impact on diabetes treatment algorithms. ***Cardiovasc Endocrinol Metab*** **7:24–27**

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Introduction

Nearly 100 years ago, the discovery of insulin marked the dawn of a new era in the treatment of diabetes. Twenty years ago, the UKPDS documented the benefits of intensive glucose control on microvascular complications in patients with type 2 diabetes mellitus (T2DM) [1]. However, until recently, despite the availability of a dozen classes of agents to treat diabetes, no diabetes medication has shown proven benefits on cardiovascular disease (CVD), which is a major cause of morbidity and mortality in T2DM [1]. Some medications such as the glitazones and saxagliptin (a DPP-4 inhibitor) increase the risk of hospitalization for heart failure (HF) [1]. In the Action to Control Cardiovascular Risk in Diabetes study, tight glycemic control increased cardiovascular (CV) and all-cause mortality [2]. The recent publication of the EMPA-REG OUTCOME study in 2015 documenting a significant reduction in CV and all-cause mortality, and hospitalization for HF with an SGLT2 inhibitor (empagliflozin) truly represents a landmark in the field of diabetes treatment [3]. This was followed in 2016 by the LEADER study, which reported a significant reduction in CV mortality with a GLP-1 agonist (liraglutide) [4]. Subsequently, in 2017, the CANVAS and the SUSTAIN-6 studies showed potential CV benefits with canagliflozin (an SGLT2 inhibitor) and semaglutide (a GLP-1 agonist) [5,6]. Recently, the FDA approved new indications for empagliflozin to reduce the risk of CV death and for liraglutide to reduce the risk of major adverse CV events and CV death in adult patients with T2DM and established CV disease (*https://www.fda.gov/newsevents/newsroom/pressannouncements/ucm531517.htm*, *http://press.novonordisk-us.com/2017-08-25-Victoza-R-liraglutide-is-approved-in-the-US-as-the-only-type-2-diabetes-treatment-indicated-to-reduce-the-risk-of-three-major-adverse-cardiovascular-events*). In the previous articles, the authors have discussed the various CV outcome trials and the potential mechanisms of the CV benefits of SGLT2-inhibitors and GLP-1 agonists. In this article, we focus on integrating these cardioprotective medications into clinical practice.

Current treatment guidelines for pharmacologic treatment of type 2 diabetes

The major clinical practice guidelines (ADA/EASD, AACE) suggest starting with metformin as the first antidiabetic agent in patients with T2DM, provided that there are no unacceptable side-effects (gastrointestinal) or contraindications [estimated glomerular filtration rate (eGFR) <45 ml/min or congestive heart failure (CHF)] [7,8]. In patients who do not reach therapeutic goals, there is a wide choice of second-line agents to add to metformin. These include the addition of a sulfonylurea, DPP-4 inhibitor, GLP-1 agonist, SGLT2-inhibitor, acarbose, pioglitazone, or basal insulin. The choice of the second agent is made on the basis of considerations of efficacy, hypoglycemia risk, weight gain potential, other side-effects, cost, and patient preference. Further, in patients with suboptimal glycemic control at presentation, there is an option to use dual-drug or even triple-drug combination. Patients with gross symptoms and acute medical/surgical conditions require insulin therapy.

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With the publication of the EMPA-REG OUTCOME and the LEADER studies, the ADA/EASD guidelines were updated in January 2017 to include the potential CV benefit of empagliflozin and liraglutide in patients with patients with T2DM and CVD [7].

Integrating cardioprotective glucose-lowering medications into clinical practice

On the basis of the EMPA-REG OUTCOME and LEADER studies and the endorsement by the ADA/EASD/AACE guidelines, it is not unreasonable for clinicians to automatically consider/prescribe these agents in all T2DM patients who do not achieve optimal glucose control with metformin monotherapy. Some clinicians may even consider empagliflozin/liraglutide as initial monotherapy or in combination with metformin as initial combination therapy in all patients. However, it is important to note that the EMPA-REG OUTCOME study was carried out in patients with established CVD and an eGFR of more than 30 ml/min/1.73 m^2 of body-surface area (Modification of Diet in Renal Disease criteria). About 11% of patients had NYHA CHF class 1–2 on the basis of clinical criteria [3]. In the LEADER study [4], ~80% of patients had established CVD (and were >50 years old) and ~20% were more than 60 years old and had at least one CV risk factor, as determined by the investigator (microalbuminuria/proteinuria, hypertension and left ventricular (LV) hypertrophy, LV systolic/diastolic dysfunction, or an ankle–brachial index <0.9) (4). Notably, ~14% of patients had NYHA CHF class 2/3 and ~2.5% had eGFR in the 15–30 ml/min range. Thus, one cannot extrapolate the findings of the EMPA-REG OUTCOME/LEADER study and start all T2DM patients on empagliflozin, especially those without established CVD, those with NYHA CHF class 3–4, or those with an eGFR less than 30 ml/min.

It is also important to note that in the EMPA-REG OUTCOME study, empagliflozin did not have any beneficial effects on traditional atherothrombotic events: myocardial infarction (MI) and stroke. In fact, there were marginally more strokes with empagliflozin. The beneficial CVD effects were primarily driven by a 38% reduction in CV death. In addition, hospitalizations for CHF were also significantly reduced by 35%. This suggests an improvement in myocardial function, independent of atherosclerosis and perhaps related to either hemodynamic changes (blood pressure, diuretic effect, arterial stiffness, etc.) [9], or improvements in myocardial fuel energetics [10,11]. With liraglutide in the LEADER study, similar to the EMPA-REG study, the CV benefit was driven primarily by a significant 22% reduction in CV death, along with nonsignificant ~12% decreases in MI and stroke. However, with liraglutide, there was no reduction in hospitalizations for CHF, suggesting perhaps that the benefit of CV death was driven by a decrease (albeit nonsignificant) in traditional atherosclerotic events: MI and stroke. Thus, the FDA gave the additional CV indication for liraglutide to reduce the risk of MI, stroke, and CV death and for empagliflozin to reduce the risk of CV death in adult patients with T2DM and established CVD.

In addition to liraglutide and empagliflozin, two other T2DM drugs have shown beneficial CV effects: semaglutide (a GLP-1 agonist in the SUSTAIN-6 study) and canagliflozin (an SGLT2-inhibitor in the CANVAS Program) [5,6]. However, the semaglutide study was designed as a noninferiority study only and hence its CV superiority benefit is nominal as the study was not powered for this outcome. It is noteworthy that the CV benefit of semaglutide was driven by a 39% reduction in stroke. There was, however, a concomitant 76% increase in retinopathy. In the case of canagliflozin, because of the unblinding of the interim CV outcome results in the original CANVAS study to the regulatory authorities, a second separate study (CANVAS-R) was initiated. Thus, the sequential hypothesis testing plan for the CANVAS Program included testing first for noninferiority in major adverse CV events with a 1.3 margin [on the basis of the integrated database of CANVAS and CANVAS-R ($\alpha = 5\%$)]. This objective was achieved. The next objective was to test the superiority of canagliflozin in all-cause mortality (on the basis of the integrated CANVAS/CANVAS-R database), but with the removal of all study time and mortality events accrued before 20 November 2012 ($\alpha = 5\%$). This objective did not achieve statistical significance. Hence, the main conclusion from the CANVAS program is CV safety. However, given that the effects of canagliflozin on CV mortality and CHF hospitalization were generally similar to empagliflozin, there is reason to believe that this is a class effect. It is noteworthy that in the CANVAS Program, there were unexpectedly more events of lower-limb amputations with canagliflozin, which resulted in the FDA placing a warning for this on the prescribing label (*https://www.fda.gov/Drugs/DrugSafety/ucm557507.htm*).

Type 2 diabetes mellitus patients with pre-existing cardiovascular disease

On the basis of the results of the EMPA-REG OUTCOME and the LEADER studies and the recent FDA approval, there is a strong rationale for clinicians to prescribe liraglutide to reduce the risk of MI, stroke, and CV death and empagliflozin to reduce the risk of CV death in adult patients with T2DM and established CV disease, provided that there are no contraindications. However, in patients with CKD and CHF, currently, the evidence is not clear. In the LEADER study, a subgroup analysis suggested that liraglutide did not have CV benefits in those with CHF, whereas in the EMPA-REG study, a subgroup analysis was not carried out. For CKD, a subgroup analysis in the LEADER study suggests that liraglutide led to CV benefits only in those with eGFR 30–60 ml/min, whereas empagliflozin led to CV benefits

in those with eGFR 60–90 ml/min. Thus, until the results of ongoing studies in CHF/CKD patients are published, it may be prudent to use liraglutide or empagliflozin only in those with NYHA CHF class 1/2 and those with eGFR more than 30 ml/min. It is noteworthy that, with empagliflozin, when the eGFR is low, the filtered load of glucose is proportionately reduced and there is less glucosuria and less glucose lowering with the drug. However, unlike HbA1c reductions, systolic blood pressure and weight reductions with empagliflozin are generally maintained in patients with CKD [12].

Type 2 diabetes mellitus patients at high risk for cardiovascular events (without established cardiovascular disease)

Compared with T2DM patients with established CV disease, the use of empagliflozin and liraglutide in patients who do not have established CV disease is not clear. One might argue that the LEADER study included ~20% of patients who had no established CV disease. However, in these patients, the subgroup analysis clearly showed that they did not have any CV benefit. For empagliflozin, on the basis of its putative mechanism of action (beneficial hemodynamic/metabolic effects), one could make a case for using empagliflozin in T2DM patients without established CV disease. It is noteworthy that, in the CANVAS program, ~40 of patients did not have established CVD at baseline. In these patients, a subgroup analysis showed that, similar to liraglutide in the LEADER study, canagliflozin did not have any CVD benefit in those without CVD at baseline. Thus, the decision to use empagliflozin, canagliflozin, or liraglutide in T2DM patients without established CV disease, but at high CVD risk, should be an individual decision made on the basis of other factors including the risk–benefit ratio and cost-effectiveness.

Type 2 diabetes mellitus patients with pre-existing cardiovascular disease and congestive heart failure

In T2DM patients who have established CV disease and CHF greater than NYHA class 1/2, at present, one cannot recommend the use of liraglutide or empagliflozin. As already mentioned, the subgroup analysis with liraglutide suggested that the CV benefits only occurred in those without CHF. Also, hospitalizations for CHF were not significantly reduced with liraglutide in the LEADER study. In another trial of recently hospitalized patients with established CHF and reduced LV ejection fraction, liraglutide did not lead to greater posthospitalization clinical stability after 6 months, despite previous studies indicating that GLP-1 therapy might ameliorate mechanisms of myocardial insulin resistance reported in patients with severe cardiomyopathies [13]. In this study, the point estimates consistently suggested a higher risk of CHF-related events with liraglutide that were higher in magnitude in patients with diabetes than in the overall study population. The authors specifically suggested the need for caution and close monitoring when considering liraglutide/other GLP-1 agonists for weight loss or diabetes management in patients with HF and reduced LV ejection fraction. For empagliflozin, on the basis of the significant reduction in hospitalization for CHF in the EMPA-REG study and also the beneficial hemodynamic effects, one could consider the use of empagliflozin in those with T2DM, established CVD, and NYHA class 1/2. Empagliflozin use in those with class 3/4 CHF is currently being studied (*https://clinicaltrials.gov/ct2/show/NCT03057977?term=empagliflozin&cond=Heart+Failure&cntry1=NA%3AUS&rank=4*).

Conclusion

We now have a dozen classes of medications to improve glycemic control in T2DM. However, glycemic control *per se* does not reduce the excess CV morbidity/mortality that afflicts most T2DM patients. In this context, it is encouraging that two diabetes medications, liraglutide and empagliflozin, have shown CV benefits in large randomized trials and have been assigned an additional indication by the FDA (besides glucose lowering) – to reduce the risk of MI, stroke, and CV death with liraglutide, and to reduce the risk of CV death with empagliflozin in adult patients with T2DM and established CV disease. In these patients, if there are no contraindications, and on the basis of individual considerations and cost issues, liraglutide and empagliflozin should be the drugs of choice for step-up treatment after metformin failure and perhaps even as initial combination therapy with metformin or as monotherapy in treatment-naive patients. In selected patients, on the basis of the risk/benefit ratio, one may also consider combining both liraglutide and empagliflozin (with or without metformin) as an off-label indication. This combination would combine the potential antiatherosclerotic effects of liraglutide (reduction of MI/stroke/CV death) with the potential hemodynamic/myocardial metabolic benefits of empagliflozin (reduction of hospitalization for CHF and CV death).

In those with advanced CHF or CKD, the studies are ongoing and in these patients, the risks/benefits will need to be determined on an individual basis. Currently, it is not clear whether the CV benefits observed with liraglutide and empagliflozin are class effects of GLP-1 agonists/SGLT2-inhibitors or compound-specific effects. There is reason to believe that the CV effects may be class effects on the basis of the positive CV effects observed in the semaglutide and canagliflozin studies, although the main conclusion from these studies is CV safety. In the age of precision medicine in the future, we need to look for predictive biomarkers that may help us personalize treatment for our patients when we use different DM medications. We also need to explore the potential renal benefits of the SGLT2 inhibitors and GLP-1 agonists.

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Conflicts of interest

Sunder Mudaliar is consultant to Astra-Zeneca and also serves on their Speaker's Bureau. He has received Research support from Janssen Pharmaceuticals paid to the Veterans Medical Foundation.

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