Circulation

ON MY MIND

Are We Ready to Bell The Cat?

A Call for Cardiologists to Embrace Glucose-Lowering Therapies Proven to Improve Cardiovascular Outcomes

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An old fable, "Belling the Cat," tells a story about a concerned group of mice that debate plans to nullify the threat of a menacing cat. One proposes placing a bell around its neck so that they are warned of its approach. The plan is met with applause, and the mice rejoice that their conundrum has been solved. This lasts until an old mouse asks, "That is all well, but who is to bell the cat?" All go on to make excuses why they cannot accomplish the task, and the cat continues to relentlessly hunt the mice. The moral of the fable is that it is one thing to say that something should be done but quite a different matter to actually do it.

There is a parallel between the fable and our current approach to managing cardiovascular risk in patients with type 2 diabetes mellitus (T2DM). For the first time ever, several classes of compounds initially developed for glucose lowering (oral sodium-glucose cotransporter type 2 inhibitors [SGLT2is] and injectable glucagon-like peptide-1 receptor agonists [GLP-1RAs]), have been shown to significantly improve cardiovascular outcomes, including reductions in cardiovascular mortality.[1,2] These landmark developments have been celebrated by the cardiology community as major advancements in management. However, when the time comes to actually use these agents in clinical practice, it is all too common to hear excuses for why it is too cumbersome for cardiologist to prescribe these agents.

The EMPA-REG OUTCOME ([Empagliflozin] Cardiovascular Outcome Event Trial in Type 2 Diabetes Mellitus Patients) and LEADER (Liraglutide Effect and Action in Diabetes: Evaluation of Cardiovascular Outcome Results) trials convincingly showed empagliflozin (an SGLT2i) and liraglutide (a GLP-1RA) reduced major adverse cardiac events and cardiovascular mortality in patients with T2DM and in most with established cardiovascular disease. Both compounds have received indications from the US Food and Drug Administration and European Medicines Agency for reducing cardiovascular risk in patients with T2DM and established atherosclerotic cardiovascular disease (ASCVD) independently of glucose control. However, the great majority of patients with T2DM remain on therapies that have no proven cardiovascular benefits. An analysis including 313 institutions showed that only 5.2% who met the inclusion criteria of EMPA-REG were on an SGLT2i, and 6.0% who met the inclusion criteria for LEADER were on a GLP-1RA.[3] Instead, patients with established ASCVD or at high risk of cardiovascular events were ≈3-fold more likely to be on a dipeptidyl peptidase 4 inhibitor, ≈7-fold more likely to be on a sulfonylurea, and ≈8-fold more likely to be on insulin—all therapies with no proven cardiovascular benefit.[3] This implies a paradigm in which aggressive hemoglobin A_{1c} management continues to reign supreme at the expense of therapies that improve cardiovascular mortality. Improving microvascular outcomes is important, but who is responsible for treating patients to improve their cardiovascular risk?

Cardiologists are well poised to take the lead in reducing cardiovascular risk among those with T2DM. First, the benefits of these agents have been most con-

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vincingly demonstrated in patients with established ASCVD. Second, reducing the burden of cardiovascular disease, especially cardiovascular death, is arguably the most important service we can provide to patients with T2DM. It is provocative that cardiologists continue to fight laws of diminishing returns with novel antiplatelet and cholesterol-lowering agents, yet adding empagliflozin (with a number needed to treat of 39 to prevent death) to the treatment regimen of a patient with T2DM would arguably provide the greatest benefit.

This begs the question, why have cardiologists not embraced therapies that prevent cardiovascular death? There are several key concerns typically brought up as justifications. First, cardiologists contend that it is not their place to be involved in glucose management. They may be concerned because they are unfamiliar with hemoglobin A_{1c} targets, and few have diabetes-related resources in their practices and are ill prepared to start prescribing glucose-lowering medications. They may also be unwilling to "step on the toes" of the referring clinicians (endocrinologists, primary care and family practitioners, etc). In this respect, it is critically important to decouple the use of these novel agents from the concept of lowering blood glucose and hemoglobin A_{1c}.

The hypothesis that glucose control can reduce cardiovascular mortality has been disproven in multiple clinical trials.[4] Furthermore, the mechanisms driving cardiovascular benefits of GLP-1RAs and SGLT2is are almost certainly unrelated to glucose lowering. Data emerging from recent cardiovascular outcome trials have forced us to re-examine how we think of T2DM as a disease entity. T2DM should no longer be viewed purely as a disease of glucose metabolism but rather as a complex condition in which numerous factors mediate cardiovascular risk. In this regard, we need to think of SGLT2is and GLP-1RAs as interventions that are used primarily to lower cardiovascular risk, regardless of their effects on blood glucose and hemoglobin A_{1c}. Cardiologists should not shy away from the initiation of these agents simply because they also happen to lower blood glucose, just like we would not shy away from initiating high-intensity statins in diabetic patients with established ASCVD.

The second common argument is fear of adverse events. This is certainly understandable. Our key obligation to the patients is to do no harm, and several safety signals have been brought up as potential concerns with SGLT2is and GLP-1RAs. However, in the case of SGLT2is, in large cardiovascular outcome trials of both canagliflozin and empagliflozin, adverse events were statistically more likely to occur in patients receiving placebo. Neither SGLT2is nor GLP-1RAs increased the risk of hypoglycemia compared with placebo plus standard of care, and SGLT2is were less likely than placebo to cause acute kidney injury.[1,5] The concerns about increased risk of serious urinary tract infections and hypovolemic events have remained largely theoretical and not confirmed in outcome trials. This is not to say that these agents are completely benign. SGLT2is may increase the risk of diabetic ketoacidosis; however, diabetic ketoacidosis remains a rare event in T2DM. Increased rates of amputations and fractures have also been observed with canagliflozin, but to date, this has not been seen with other agents in the class.[5] There is also a clear increase in the risk of genital fungal infections (number needed to harm, ≈20) with the use of SGLT2is. However, these are easily treatable and typically do not require discontinuation of therapy. GLP-1RAs currently are only injectable, and thus, some training would be required for cardiology practitioners to prescribe them. This, however, would not be all that different from prescribing enoxaparin. Given that cardiology is a specialty that regularly prescribes digoxin, amiodarone, and dofetilide, the balance of benefit and risk seems to be highly favorable for SGLT2is and GLP-1RAs.

Ultimately, the main goal of treating patients with T2DM is to improve their chances to live longer and feel better. The era of claiming high-quality care on the basis of a laboratory value (and one that is a poor surrogate for cardiovascular outcomes) is over. We finally have therapies that clearly improve cardiovascular mortality in patients with T2DM, yet they are not being used in the patients most likely to benefit from them. We can no longer use the excuse that it is someone else's problem. Such arguments do not hold water because reducing the risk of death and other cardiovascular complications, no matter the mechanism, is the main reason we became cardiologists. We have a moral imperative to take a greater role in managing ASCVD risk in patients with T2DM and finally bell the cat.

ARTICLE INFORMATION

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Disclosures

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