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EDITORIAL COMMENT

Cardiovascular Benefits of GLP-1 Receptor Agonism

Is Inflammation a Key?*

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We stand on the threshold of an exciting area when at long last we have novel antidiabetic therapies proven to reduce cardiovascular events. Recent large-scale trials have finally established the beneficial effects of 2 classes of such medications: SGLT2 inhibitors (1,2) and GLP-1 receptor agonists (3–5). The recent advances have enormous clinical consequences, given the worldwide spread of the diabetes epidemic, the intolerable toll of consequent cardiovascular complications, and the increasing recognition that cardiovascular specialists must contribute directly to the management of diabetes in our patients.

From a translational perspective, these recent victories of clinical science raise some important mechanistic questions, not only to understand how these benefits occur, but also to gain insight to inform further advances in the quest to control the cardiovascular complications of diabetes. In this regard, a key question surrounds the quandary of glucose control versus other effects of these agents that may confer the cardiovascular benefit. Is the glucose-lowering property of these agents contributing to the reduction of events? Probably not, since insulin and other glucose-lowering drugs mainly reduce microvascular complications but have not proven to contribute to a reduction of macrovascular events in patients with type 2 diabetes—at least not within the timeframe of the studies conducted with these agents. What then might account for the clinical benefits that have accrued in recent trials with antidiabetic drugs?

To understand better the potential mechanisms of SGLT2 inhibitors or GLP-1 receptor agonists on cardiovascular events in subjects with diabetes, a more detailed analysis of the Kaplan-Meier curves in EMPA-REG OUTCOME (Empagliflozin, Cardiovascular Outcomes, and Mortality in Type 2 Diabetes) (2) and the CANVAS (CANagliflozin cardioVascular Assessment Study) program (1) (SGLT2 inhibitors versus placebo) or in LEADER (Liraglutide and Cardiovascular Outcomes in Type 2 Diabetes) (4), SUSTAIN-6 (Semaglutide and Cardiovascular Outcomes in Patients with Type 2 Diabetes) (3), and HARMONY (Albiglutide and Cardiovascular Outcomes in Patients With Type 2 Diabetes and Cardiovascular Disease) (5) (GLP-1 receptor agonists versus placebo) may provide further insight: SGLT2 inhibitors significantly

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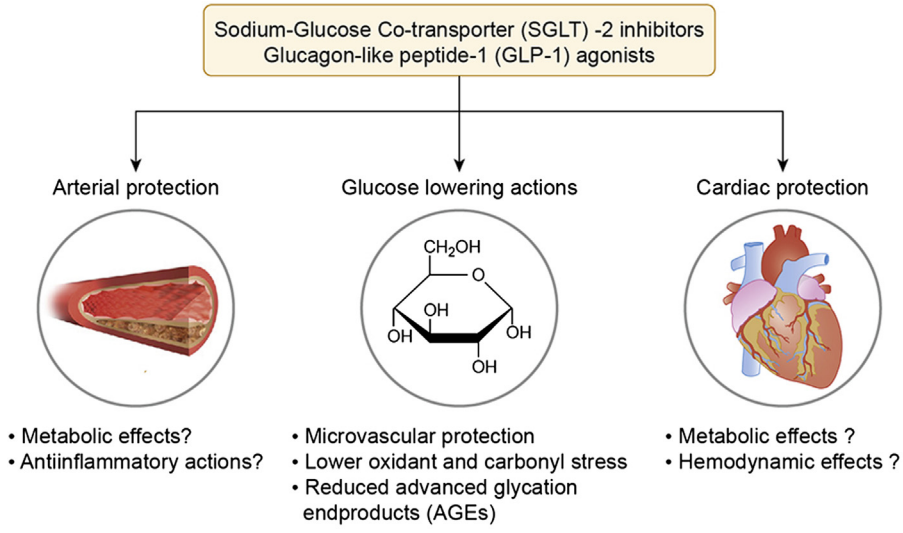
FIGURE 1 Potential Mechanisms Through Which SGLT-2 Inhibitors and GLP-1 Agonists Exhibit Beneficial Cardiovascular Effects



GLP-1 = glucagon-like peptide-1; SGLT = sodium-glucose co-transporter.

reduced major adverse cardiovascular events with a very early separation of the curves after the first few months. This early benefit together with the reduction of heart failure hospitalization suggests that the reduction in cardiovascular events by the agents derives mainly from an effect on heart failure-related events. In contrast, the separation of the Kaplan-Meier curves in LEADER, SUSTAIN-6, and HARMONY only started to occur after 12 to 18 months—resembling the effects seen in statin trials—rendering it likely that these effects link to arteriosclerosis-driven events. The observations that liraglutide reduced coronary revascularization and that albiglutide lowered the incidence of nonfatal myocardial infarction, 2 outcomes clearly related to atherosclerotic vascular disease, support this notion.

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By what mechanisms could GLP-1 receptor agonists such as liraglutide or semaglutide influence vascular disease? Rakipovski et al. (6) addressed this key question in an elegant experimental approach employing atherosclerosis-prone mice (lacking apolipoprotein E or the low density lipoprotein receptor). These mice underwent treatment with liraglutide or semaglutide at different concentrations (6). In this issue of *JACC: Basic to Translational Science*, they demonstrate that either agent significantly reduced aortic plaque areas, independent of effects on cholesterol levels and—at least partially—independent of changes in body weight. In addition, they report that these GLP-1 receptor agonists decrease the expression of genes in the aorta in multiple atherosclerotic pathways associated with inflammation. Decades of basic and clinical biomarker studies, and now a large clinical trial, have established the contribution of inflammation to atherosclerosis (7) and that anti-inflammatory agents can improve cardiovascular outcomes (8). Therefore, the GLP-1 agonists studied in these experiments influence mechanisms deemed central to atherosclerosis and its clinical complications.

The strengths of this study include the use of two different types of experimental atherosclerosis-mice, the use of 2 different GLP-1 receptor agonists that have demonstrated decreased cardiovascular events, and the unbiased approach to seek changes in arterial gene expression. Because vascular cells do not express GLP-1 receptors, the effects seen most likely link to indirect actions of GLP-1 receptor agonists on other tissues. For example, activation of GLP-1 receptors in the gut may reinforce the barrier function of the intestinal epithelium, thus leading to a reduced inflammation. Such a proposed mechanism seems particularly intriguing, because mediators elaborated by the intestinal microbiome associate with the development of vascular disease both experimentally and in patients (reviewed by Tang and Hazen [9] and Villanueva-Millan et al. [10]). Moreover, GLP-1 receptor-mediated effects on

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hepatic lipid content, as seen in the study by Rakipovski et al. (6), may also contribute to the anti-inflammatory and antiatherosclerotic properties of these agents (**Figure 1**). This study characterized mRNA expression, but not corresponding protein in tissues, and does not provide data on circulating inflammatory markers such as tumor necrosis factor-α and interleukin-6.

The results of this study beg the question of how well the results of experiments in hypercholesterolemic mice apply to humans, particularly those who receive standard of care medication such as statins, agents that can themselves exert anti-inflammatory actions? Exploration of such questions will require further translational research, for example, biomarkers studies to bolster the clinical significance of the experimental findings. Despite these limitations and unresolved issues, this study helps to unravel a strand of the mystery of the likely multiple mechanisms of benefit of GLP-1 receptor agonists. In drug development, findings from basic science studies often lead to the development of new therapeutic concepts. In the field of GLP-1 receptor agonists, we observe the contrary: the drugs were initially developed to lower blood glucose, and the gratifying and long-sought findings of improved cardiovascular outcomes that emerged from recent clinical trials now inspire us to turn back to the laboratory to set up experimental studies to gain further insight how these agents reduce cardiovascular events. The potential "pleiotropic" effects of the SGLT-2 antagonists presents a parallel challenge. We now need to consider these classes of agents as not merely targeting glucose, but rather as drugs that can improve cardiovascular outcomes. We must look beneath their "sugar coating" and seek effects beyond glycemic control, such as anti-inflammatory and other actions that can contribute to their cardiovascular benefits.

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