COMMENTARY

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Should We Be Combining GLP-1 Receptor Agonists and SGLT2 Inhibitors in Treating Diabetes?

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Both glucagon-like peptide-1 (GLP-1) receptor agonists and sodium-glucose cotransporter 2 (SGLT2) inhibitors are effective antihyperglycemic drugs that have been shown to reduce the risk of macrovascular events in large-scale outcomes trials in patients with type 2 diabetes.[1-4] Certain members of both drug classes carry a Food and Drug Administration–approved label for a reduction in the risk of cardiovascular death or of major adverse cardiovascular events. However, the long-term use of these 2 types of drugs prevents different types of cardiovascular harm.[5] On the one hand, GLP-1 receptor agonists reduce the risk of atherosclerotic ischemic events and have little effect on heart failure.[1,2] On the other hand, SGLT2 inhibitors decrease the risk of heart failure leading to death or hospitalization, but have little effect on the occurrence of myocardial infarction and stroke.[3,4]

MECHANISMS UNDERLYING THE DISTINCTIVE CARDIOVASCULAR BENEFITS OF GLP-1 RECEPTOR AGONISTS AND SGLT2 INHIBITORS

How might GLP-1 receptor agonists prevent atherosclerotic ischemic events? GLP-1 receptor signaling appears to inhibit the formation, diminish the size, modify the composition, and promote the stability of atheromatous plaques.[6,7] In experimental models, GLP-1 receptor agonists reduce macrophage infiltration, decrease the size of necrotic cores, promote thicker fibrous caps, and minimize smooth muscle proliferation. Although similar effects can theoretically be produced by dipeptidyl peptidase-4 inhibitors, drugs that inhibit the breakdown of endogenous GLP-1 also potentiate the actions of stromal cell–derived factor-1, which functions as a proinflammatory chemokine that augments the macrophage response in atheroma and activates matrix metalloproteinases, thereby contributing to plaque instability.[8,9] Mutual neutralization of positive and negative influences on plaque formation and stability could explain why dipeptidyl peptidase-4 inhibitors have not reduced the risk of myocardial infarction and stroke in large-scale clinical trials.[10,11]

How do SGLT2 inhibitors lower the risk of new-onset heart failure? By inhibiting sodium reabsorption in the proximal renal tubule (where most such reabsorption takes place), SGLT2 inhibitors cause a decrease in plasma volume, which accounts for the striking hemoconcentration seen during treatment with these drugs.[3,4] In addition, in patients with a reduced ejection fraction, SGLT2 inhibitors might interfere with the deleterious effects of an overactive sodium-hydrogen exchanger in the diabetic heart.[12] Increased expression of sodium-hydrogen exchanger-1 has been postulated to impair cardiac contractility and accelerate the loss of cardiomyocytes that contributes to the evolution of cardiomyopathy. Furthermore, SGLT2 inhibitors can ameliorate both the inflammation of epicardial fat and cardiac fibrosis.[12,13] Both mechanisms have been implicated in the impairment of ventricular distensibility that characterizes the majority of patients with chronic heart failure and a preserved ejection fraction.[14]

COULD CONCURRENT TREATMENT WITH GLP-1 RECEPTOR AGONISTS AND SGLT2 INHIBITORS PRODUCE SYNERGISTIC EFFECTS ON CARDIOVASCULAR RISK?

If GLP-1 receptor agonists and SGLT2 inhibitors were given together, would they act synergistically to reduce

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cardiovascular risk or would concurrent administration detract from the benefits that are seen when each is given individually in large-scale clinical trials? Both types of agents exert important natriuretic actions by virtue of their inhibition of the sodium-hydrogen exchanger-3 in the proximal renal tubule.[15] Both types of drugs also improve nitric oxide–dependent endothelial function.[16] These 2 mechanisms (if potentiated by concurrent use) could lead to an enhanced effect to lower blood pressure, a benefit that might be further augmented by a shared action of both classes of drugs to reduce body weight. Additionally, both types of agents reduce urinary protein excretion and slow the rate of decline in glomerular filtration rate.[17,18] The latter effect might be related to an action of both classes of drugs to enhance the delivery of sodium to distal segments of the nephron, and thus (by promoting tubuloglomerular feedback) ameliorate glomerular hyperfiltration.[15,18]

Additional synergies might result from an ability of SGLT2 inhibitors to antagonize several actions of GLP-1 receptor agonists on the heart, which might be deleterious in some patients. GLP-1 receptor agonists have been reported to worsen the clinical course of patients with established heart failure, whether or not they have glucose intolerance. In one placebo-controlled trial,[19] the use of liraglutide was accompanied by a higher risk of hospitalization for heart failure and worsening of renal function. In a second placebo-controlled trial,[20] treatment with liraglutide led to an increase in heart rate and a heightened risk of serious adverse cardiovascular events.

What can account for these worrisome observations? In some patients with heart failure, the inflammation of epicardial fat could act in a paracrine manner to cause fibrosis in the underlying myocardium.[21] Although both GLP-1 receptor agonists and SGLT2 inhibitors have been reported to reduce the quantity of epicardial fat in experimental models,[13,22] GLP-1 receptor agonists may promote adipose tissue inflammation, whereas SGLT2 inhibitors appear to alleviate it.[23] Therefore, concurrent treatment with both drugs might neutralize a potential adverse effect of GLP-1 receptor agonists on adipocyte biology, which could underlie the detrimental responses seen in clinical trials of these drugs in patients with heart failure.

Furthermore, GLP-1 receptor agonists increase intracellular cyclic adenosine monophosphate in cardiomyocytes, an effect that may contribute to the increases in heart rate seen when liraglutide is given to patients with heart failure and to patients with diabetes without heart failure.[24] Drug-induced increases in cyclic adenosine monophosphate in the myocardium have been shown to accelerate the progression of heart failure and increase the risk of cardiovascular death.[25] An excess of cyclic adenosine monophosphate in certain cardiomyocyte microdomains increases intracellular calcium and causes calcium overload, thereby triggering cardiomyocyte necrosis.[25] Potentially, cyclic adenosine monophosphate can cause such an injury because of its action to stimulate the activity of sodium-hydrogen exchanger-1; experimentally, inhibition of sodium-hydrogen exchanger-1 may counter the deleterious effects of agents that increase cyclic adenosine monophosphate in the heart.[26-28] Therefore, it is noteworthy that SGLT2 inhibitors inhibit sodium-hydrogen exchanger-1 in cardiomyocytes, which can lead to a reduction in intracellular calcium and its cardiotoxic actions.[12] Therefore, theoretically, SGLT2 inhibition could attenuate a direct adverse effect of GLP-1 receptor agonists on the failing heart.

CONCLUSIONS

Several lines of evidence provide a strong basis for the combined use of GLP-1 receptor agonists and SGLT2 inhibitors in the treatment of type 2 diabetes. Investigators[5,16] have already argued for using these 2 classes of drugs in combination on the basis of their complementary benefits in large-scale clinical trials. SGLT2 inhibitors and GLP-1receptor agonists not only improve the control of blood glucose, blood pressure, and body weight, but also might act together to minimize the evolution and progression of diabetic nephropathy. Additionally, they reduce the risk of different types of clinically important adverse cardiovascular events, raising the possibility that combined therapy might produce more comprehensive benefits than when either type of drug is given alone. Simultaneous therapy with both classes might also neutralize several potentially deleterious actions of glucagon-like peptide-1 receptor agonists on the myocardium and on epicardial fat, which may underlie the risks of treatment with these drugs in patients with established heart failure.

Despite these intriguing possibilities, no clinical trials have evaluated the long-term effects of combined use of the 2 drugs in patients with type 2 diabetes who are at meaningful cardiovascular risk. Given the commercial availability of these drugs and the fact that individual members of both classes have a Food and Drug Administration–approved indication to reduce cardiovascular risk, should we not know more about what happens when both classes of drugs are used together?

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