The number of diabetic patients is increasing at an alarming rate and, according to the World Health Organisation, is estimated to reach 300 million worldwide by the year 2025. Coronary heart disease is the leading cause of death in these patients. Diabetic patients are 2 to 3 times more likely to develop coronary heart disease, and they experience worse clinical outcomes after coronary artery angioplasty, cardiac bypass surgery, acute myocardial infarction, and the onset of cardiac failure. Clearly, new treatment strategies that are specifically directed to improving clinical outcomes in diabetic patients with coronary heart disease and in those patients who develop cardiac failure need to be developed.

GLP-1 Therapy
Beyond Glucose Control

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The opinions expressed in this article are not necessarily those of the editors or of the American Heart Association.

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before surgery) reduced inotrope requirements and improved glycemic control, although it did not improve LV ejection fraction, in both diabetic and nondiabetic patients. The mechanism through which GLP-1 improved LV contractile function in these different settings is unclear, although it may in part be because of increased myocardial glucose uptake.

Findings from our laboratory suggest that GLP-1(7-36) therapy is capable of limiting acute myocardial ischemia-reperfusion injury, as evidenced by a reduction in myocardial infarct size in both the isolated and in situ rat heart when GLP-1(7-36), coadministered with a DPP-IV inhibitor, was given to the heart before a period of sustained ischemia followed by reperfusion. In addition, we have also observed, in an isolated rat heart model, that GLP-1(7-36) is protective against myocardial ischemia-reperfusion injury when given either as a preconditioning mimetic or at reperfusion. The mechanism underlying this cardioprotective effect is independent of any effect on glucose and has been linked to GLP-1 receptor activation and recruitment of intracellular signaling pathways involving Akt, Erk1/2, p70S6K, and AMPK as well as the downstream phosphorylation and inhibition of the proapoptotic protein BAD. A prior study in the porcine heart failed to demonstrate a reduction in infarct size with GLP-1(7-36), although the drug was administered in the absence of a DPP-IV inhibitor in that study, which may explain the lack of cardioprotection.

Interestingly, recent studies suggest that GLP-1(9-36), the metabolite that is generated by DPP-IV, is also capable of increasing myocardial glucose uptake, improving LV contractile function in a canine model of pacing-induced dilated cardiomyopathy, improving posts ischemic myocardial injury and LV contractile function, and inducing vasorelaxation through a mechanism that involves nitric oxide and cGMP. The situation is further complicated by the recent report that some of the beneficial cardiovascular effects of GLP-1(7-36) have been shown to be present in mice lacking the GLP-1 receptor. These findings suggest that there may be a currently unidentified GLP-1 receptor or that GLP-1(7-36) and its metabolite GLP-1(9-36) may be capable of exerting non-receptor-dependent effects on the cardiovascular system.

In this issue of Circulation: Heart Failure, a new study by Shannon’s research group has demonstrated beneficial cardiovascular effects with chronic GLP-1(7-36) therapy (comprising 3 months of subcutaneous injection) in a rat model of progressive, hypertensive-related heart failure, in terms of preserved LV systolic function, less cardiac apoptosis, increased myocardial glucose uptake, and most importantly, improved survival (from 44% to 72%). This is the first study to examine the effect of chronic GLP-1 therapy on survival in a clinically relevant heart failure experimental model, and the findings suggest that this therapeutic strategy may improve clinical outcomes in patients with cardiac failure. To ascertain whether the cardioprotective effects of GLP-1 are maintained with chronic therapy in this particular heart failure model, it would have been interesting to determine whether the myocardium was more resistant to myocardial infarction. In addition, whether this therapeutic strategy confers the same beneficial effects in the diabetic failing myocardium remains to be determined.

The use of GLP-1 as a clinical therapy, however, is hampered by the need to administer it as an infusion, because it is rapidly broken down in plasma by DPP-IV. Therefore, as a therapeutic antidiabetic strategy, synthetic analogues of GLP-1 (such as exenatide and liraglutide) that are resistant to the degradative actions of DPP-IV have been developed. In addition, pharmacological inhibitors of DPP-IV that are capable of augmenting endogenous levels of GLP-1, such as sitagliptin and vildagliptin, are in clinical use. Another innovative, experimental, alternative approach to chronic administration of GLP-1 is to use adeno viral gene therapy, an approach that has been demonstrated to successfully treat hyperglycemia in a diabetic mouse model for up to 2 months.

Whether the beneficial cardiovascular effects observed with GLP-1 can be reproduced by these newer antidiabetic therapies needs to be investigated. It is important to appreciate that these 2 pharmacological approaches may have differing cardiovascular effects, depending on the extent to which the drug therapy potentiates either endogenous levels of GLP-1(7-36) or its metabolite GLP-1(9-36). Initial studies suggest that the GLP-1 analogue exendin-4 is capable of reducing myocardial infarct size when administered to perfused rat hearts at the onset of myocardial reperfusion. Therefore, the ability of the newer antidiabetic agents such as GLP-1 to confer cardioprotection, independent of their effect on glucose levels, allows for the possibility of developing an antidiabetic therapy that not only combats hyperglycemia in diabetic patients but is also able to improve cardiovascular outcomes in diabetic and nondiabetic patients. Interestingly, the results of initial clinical studies examining chronic GLP-1 therapy seem to suggest that both nondiabetic and diabetic patients may benefit from its salutatory cardiovascular effects.

Clearly, further experimental and clinical studies are needed to determine whether synthetic GLP-1 analogues and DPP-IV inhibitors are able to reproduce the beneficial effects of GLP-1 therapy in terms of protection from acute myocardial ischemia-reperfusion therapy and the consequences of cardiac failure.

Disclosures
None.

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