Diabetes and Heart Failure

Michael R. MacDonald, MD, Golden Jubilee National Hospital, Glasgow, Scotland, United Kingdom, discussed the pathophysiological links between diabetes and heart failure (HF), treatment of diabetes to prevent HF, and treatment of diabetes in patients with HF.

The RESOLVD substudy included 663 patients with HF, 27% of whom were known to have diabetes. Of those thought to be non-diabetic, 11% had diabetes, 12% had impaired glucose tolerance, and 34% had insulin resistance [Yan RT et al. *Am J Cardiol* 2005]. The Framingham study reported a substantially increased risk of HF in patients with diabetes.

Pathophysiological Links

Numerous studies have shown that diabetes is an independent predictor of worse prognosis in patients with HF. Conversely, HF worsens the prognosis in patients with diabetes [Bertoni HG et al. *Diabetes Care* 2004]. Additionally, diabetes and HF can each lead to the other condition. Insulin resistance is common in patients with HF and is independent of HF etiology; it predicts incident HF, reduced functional capacity, more severe symptoms, and reduced survival [Doehner W. *J Am Coll Cardiol* 2008]. At the time of diabetes diagnosis, 40% of patients have macroangiopathy, 40% have albuminuria, 15% have retinopathy, 50% have hypertension, and 50% have hypertriglyceridemia [Meeuwisse-Pasterkamp SH et al. *Expert Rev Cardiovasc Ther* 2008]. Possible mechanisms for insulin resistance in HF include age, genetic factors, diet and decreased exercise, endothelial dysfunction, impaired tissue performance, oxidative stress, and humoral factors [Doehner W. *J Am Coll Cardiol* 2008]. Several studies have demonstrated evidence for a diabetic cardiomyopathy. The CHARM study reported an increased incidence of cardiovascular (CV) death or hospitalization due to HF (p=0.0009) and hospitalization due to HF (p=0.0029) in patients with diabetes versus those without diabetes [MacDonald MR et al. *Eur Heart J* 2008].

Treatment of Diabetes and HF

The CHARM study showed that increasing HbA1C is a progressive risk factor for CV death, worsening HF, and death. Results of observational studies are inconsistent, however, and no randomized trials have evaluated the effect of reducing HbA1C on HF outcomes.

A case-control study showed that metformin is the only diabetes drug that improves outcomes in patients with diabetes and HF [MacDonald MR et al. *Diabetes Care* 2010]. Sulfonylureas increase insulin release but promote fluid retention and can cause hypoglycemia. Insulin therapy is associated with a higher incidence of HF, as are thiazolidinediones.

Glucose-like peptide-1 (GLP-1) receptors are present in myocardium, and GLP-1 mimetics may have benefits in HF. They may alter substrate utilization and have beneficial effects on endothelium. GLP-1 mimetics have an inotropic effect in animals. In addition, a study in 12 HF patients showed that the GLP-1 mimetic exenatide improved ejection fraction, maximal O_2 uptake, 6-minute walk test, and quality of life.

Dr. MacDonald proposed a glycemic control strategy beginning with lifestyle interventions, followed by the addition of metformin, sulfonylurea or dipeptidyl peptidase-4 (DPP-4) inhibitor, and a DPP-4 inhibitor or an a-glucosidase inhibitor or a GLP-1 mimetic (Figure 1).

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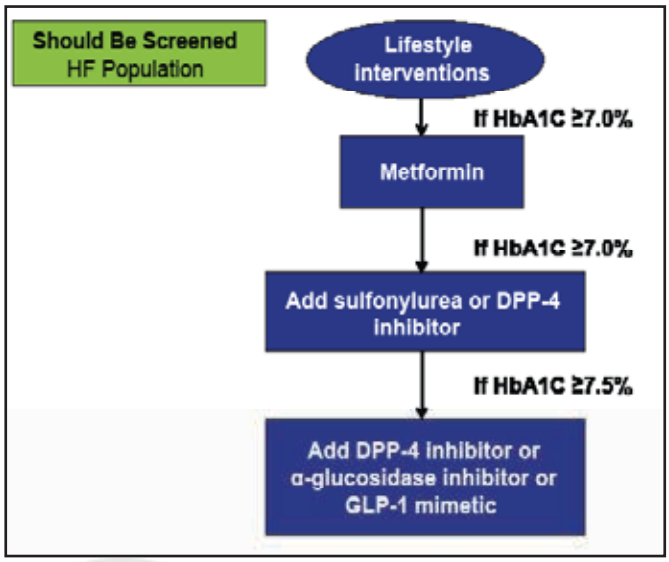
Figure 1. Glycemic Control Strategy.



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Patients with diabetes often develop HF, which places a substantial burden on healthcare resources. Diabetes appears to directly affect the myocardium, but pathophysiologic data for humans are not available. HF patients should be screened for diabetes. Prospective studies examining therapeutic strategies in patients with diabetes and acute or chronic HF are warranted.

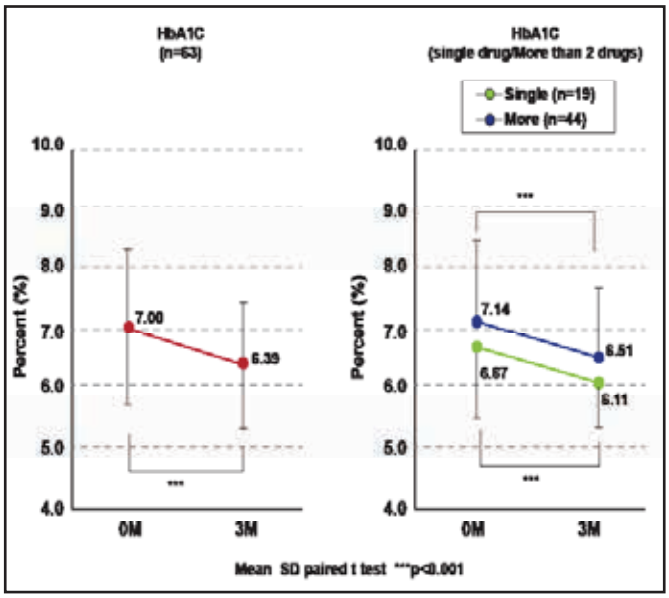
Incretins in Cardiovascular Disease

Junichi Oyama, MD, PhD, Saga University, Saga, Japan, discussed the potential benefits of incretin therapies in patients with cardiovascular disease (CVD). The 2 main incretin hormones are glucagon-like peptide-1 (GLP-1) and gastric inhibitory peptide. Glucose in the small intestine triggers release of incretins, which stimulate insulin secretion by pancreatic beta-cells; glucagon and glucose concentrations decline as insulin increases. GLP-1 also exerts beneficial effects on myocardial and endothelial function by inhibiting upregulation of reactive oxygen species and vascular cell adhesion molecule-1 mRNA in endothelial cells.

Current incretin therapies available in Japan include the GLP-1 analogues, exenatide and liraglutide, and the DPP-4 inhibitors sitagliptin, vildagliptin, alogliptin, and linagliptin. Liraglutide reduces TNF-α-induced oxidative stress and inflammation in endothelial cells and decreases mortality and infarct size in murine myocardial ischemia/reperfusion injury. In diabetes patients with stable coronary artery disease, GLP-1 infusion improved endothelial function. GLP-1 improved ejection fraction, 6-minute walk distance, maximal oxygen consumption (VO_2 max), and quality of life in heart failure patients.

The Saga-challenge Antidiabetes Observation Study for Sitagliptin [S-DOG], a nonrandomized, single-arm study, evaluated the efficacy and safety of sitagliptin in diabetes patients. The interim analysis showed that sitagliptin significantly reduced HbA1C ($p<0.001$; Figure 1), triglycerides ($p<0.01$), and blood pressure ($p<0.001$).

Figure 1. HbA1C Reductions.



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The Program of Vascular Evaluation Under Glucose Control by DPP-4 Inhibitor [PROLOGUE; UMIN000004490] study is a prospective, randomized, multicenter trial to evaluate the effects of sitagliptin versus conventional therapy on carotid artery atherosclerosis in diabetes patients. The primary endpoint is the annual change in carotid artery intima-media thickness, evaluated by ultrasonography. As of March 2012, 326 patients had been enrolled.

There is increasing evidence of the potential beneficial effects of incretin therapies on CVD beyond glycemic control. However, clinical data are insufficient, and future studies of incretin therapy for CVD are needed.

DPP-4 in Diabetic Cardiomyopathy

Dipeptidyl peptidase-4 (DPP-4) is a serine exoprotease that is expressed on the surface of many cells. DPP-4 truncates bioactive molecules, including incretin and nonincretin substrates. Among the substrates degraded by DPP-4 are stromal cell-derived factor-1 alpha (SDF-1α)