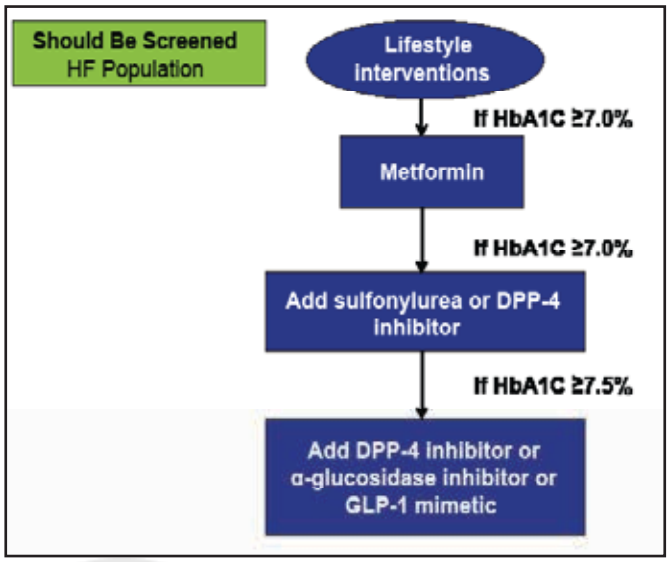
Figure 1. Glycemic Control Strategy.



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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.

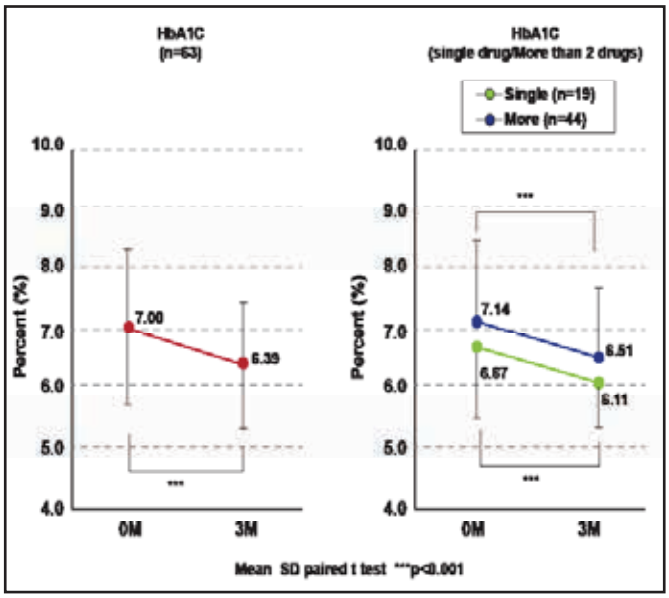
Incretins in Cardiovascular Disease

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)

and the incretins glucagon-like peptide 1 (GLP-1) and gastric inhibitory polypeptide (GIP). Yasuko Bando Kureishi, MD Nagoya University Graduate School of Medicine, Nagoya, Japan, studied the effect of DPP-4 inhibition on chronic myocardial remodeling and dysfunction associated with diabetes.

DPP-4 inhibition has been demonstrated to improve mortality and cardiac function in coronary artery disease. Zaruba et al. [*Cell Stem Cell* 2009] showed that lack of DPP-4 rescues acute myocardial injury by increasing myocardial SDF-1α levels and subsequent angiogenesis in mice.

Dr. Kureishi explored whether DPP-4 and a decline in myocardial SDF-1α are related to microangiopathy in diabetic cardiomyopathy and whether DPP-4 inhibition reverses the SDF-1α decline. The studies showed that cardiac DPP-4 localizes in the cardiac capillary vessel endothelium and that DPP-4 deficiency reverses the decline in SDF-1α levels in the diabetic heart. His experiments also showed that diabetes is associated with decreased cardiac capillary density and with increased cardiac DPP-4 activity *in situ* and *in vitro*. DPP-4 deficiency was shown to reverse the decreased capillary density induced by diabetes. Lack of DPP-4 activity also reversed impaired diastolic function in diabetic rodents, with significantly decreased left ventricular diastolic stiffness and minimum rate of ventricular pressure change (dp/dt_{min}). Dr. Kureishi also found a correlation between circulating DPP-4 activity in the human heart and the early transmitral flow velocity/early diastolic mitral valve annulus velocity ratio in patients with heart failure with preserved ejection fraction.

Dr. Kureishi concluded that cardiac DPP-4 promotes SDF-1α degradation, thereby impairing coronary angiogenesis, which contributes to the cardiac remodeling and diastolic dysfunction associated with diabetes.

Diabetic Retinopathy and Coronary Heart Disease

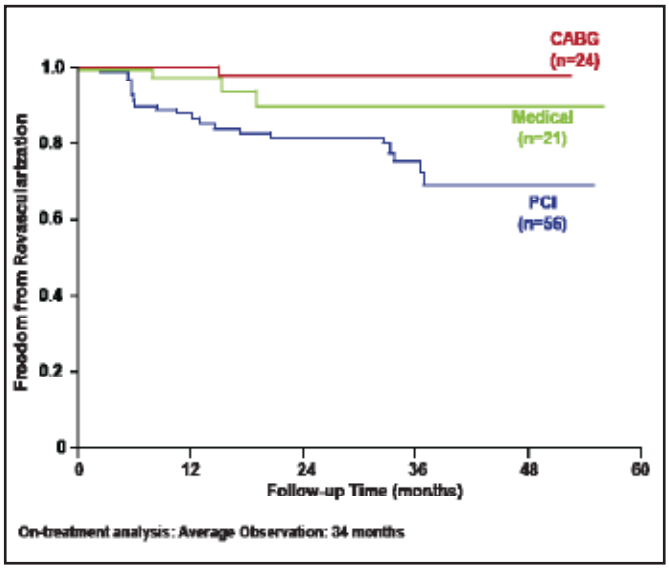
Recent evidence has shown that diabetic retinopathy (DR) is predictive of coronary artery disease (CAD) [Kramer CK et al. *Diabetes Care* 2011]. Hideo Fujita, MD, and colleagues at the University of Tokyo Hospital, Tokyo, Japan, hypothesized that proactive diagnosis can effectively detect latent CAD in patients with DR.

This cross-sectional observational study included patients with DR without a prior diagnosis of cardiovascular disease. Multiple diagnostic tests were used to screen 482 DR patients for CAD. Coronary angiography was recommended for patients who tested positive. The primary endpoints were myocardial ischemia and significant coronary artery stenosis (>50%). The cohort with CAD was followed for up to 5 years; primary endpoints were major adverse cardiovascular events (MACE) and revascularization.

A stress test was required to detect CAD in DR patients. The left main artery, proximal left anterior descending artery, and multiple vessels were frequently involved. A total of 127 patients who tested positive for CAD received coronary angiography and of these, stenosis was confirmed in 107 (27%). Among the positive group (n=107), 26 received coronary artery bypass graft (CABG), 56 received percutaneous coronary intervention (PCI), and 25 received medical therapy. Long-term follow-up and on-treatment analysis were performed in 99 (93%) of the treated patients.

Revascularization was successful in 100% of patients. There was no significant difference in MACE between the treatment groups. At 34 months, 24 CABG, 21 medical therapy, and 56 PCI patients were free from any revascularization (Figure 1). Repeat revascularization was performed in 4% of CABG and 32% of PCI patients. Myocardial infarction occurred in 2% of PCI and 0% of CABG patients. No deaths occurred.

Figure 1. Long-Term Results: Any Revascularization.



CABG=coronary artery bypass graft; PCI= percutaneous coronary intervention.
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Appropriate revascularization should be considered for DR patients. More attention should be paid to DR in terms of increased risk for CAD in the clinical setting. More extensive, well-controlled clinical studies of CAD in patients with DR are needed.