Lessons and Perspectives on Heart Failure Management From Considerations Based on the CHART-2 Study

Naoki Sato, MD, PhD

The incidence of ischemic heart failure (IHF) is increasing part because of improved outcomes of myocardial infarction, even in elderly patients, through the progression in both coronary intervention techniques and transportation systems. Approximately 30–40% of patients with hospitalized and chronic HF have an ischemic etiology. Therefore, it is important to improve the outcome of patients with IHF. On the other hand, the number of cases of diabetes mellitus (DM) is reportedly about 9 million in Japan, which has an effect on the incidence of associated complications, including chronic kidney disease (CKD). From these viewpoints, the results reported by Miura et al in this issue of the Journal, based on the large database from the CHART-2 study, are important. They conclude that DM was a prognostic factor in IHF and furthermore, that CKD exacerbated its poor outcome, suggesting that management for IHF should include preventive and ameliorative therapies of DM or CKD.

In 1972, Rubler et al reported a new type of cardiomyopathy-associated diabetic glomerulosclerosis, a so-called diabetic cardiomyopathy. Their report triggered much clinical research into the relationship between DM and HF and the focus is again on this relationship. Because the proportion of DM cases among patients hospitalized with HF is so high (≈30–40%), it is assumed that DM is related to the pathophysiological conditions of HF. The relationship between DM and HF is bidirectional; that is, DM accelerates coronary artery disease, renal insufficiency, and cardiac metabolism and...
then causes cardiac dysfunction, especially in IHF. In HF, even if non-ischemic, insulin resistance develops, with increased risk of progression to new DM. This vicious cycle between DM and HF should be considered in the clinical setting. In diabetic patients, cardiac function should be routinely examined and in IHF patients, blood glucose levels should be checked periodically. The metabolic abnormalities in DM affect cardiac function via many factors, including metabolic ones such as mitochondrial dysfunction, increased concentrations of free fatty acids, and epicardial adipose tissue (Figure 1). In acute HF, blood glucose concentrations at presentation are prognostic for 30-day mortality. Taken together, appropriate therapies targeting the critical challenge of preventing worsening HF with DM, although hypoglycemia is realized as a limiting factor in beneficial glycemic control, should be addressed.

The results from the CHART-2 study also suggest the clinical significance of CKD in IHF. It is well known that CKD is an independent risk factor for HF and exacerbates the progression of cardiac dysfunction as well as atherosclerosis (Figure 1). Furthermore, anemia, a strong prognostic marker in HF, is commonly concomitant with CKD. Actually the management of cardiorenal-anemia syndrome is very difficult because it is not easy to detect the therapeutic window for both organs’ protection. To solve this issue, new biomarkers and devices to measure volume balance should be developed and also new pharmacological approaches to restoring metabolic abnormalities will be needed. At the present time, beneficial effects of metformin, which might activate adenosine monophosphate-activated protein kinase and regulate the free fatty acid uptake in the mitochondria, have been reported, but any other beneficial effects of antidiabetic agents have not been proved yet. From these considerations based on the report by Miura et al, a novel pharmacological treatment for metabolic dysfunction in HF with DM and/or CKD should be challenged (Figure 2). Finally, it should be kept in mind that primary prevention of DM, CKD, and HF is also important. Even in this field, pharmacologic metabolic modification might need to be taken into account. Such metabolic treatments for HF with DM and/or CKD could be important as the future direction for developing novel therapies for HF.

Disclosures
The author reports no conflict of interest regarding this manuscript.

References