Beneficial Prognostic Effects of Statins in Heart Failure With Preserved Ejection Fraction (HFpEF) Patients

— HFpEF as a Manifestation of Systemic Disease —

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Epidemiologic studies indicate that almost half of heart failure (HF) patients have preserved ejection fraction and that this proportion has increased over time.^{1,2} Patients with HF with preserved ejection fraction (HFpEF) have better prognosis and are more likely to die from non-cardiovascular causes than those with HF with reduced ejection fraction (HFrEF).³ Also, standard phar-

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macological treatments for HFrEF including angiotensin-converting enzyme inhibitors, angiotensin receptor blockers, spironolactone and β -blocker have failed to improve the prognosis of HFpEF.⁴ Thus, patients with HFpEF have

Figure. Recent hypothesis on the development of heart failure with preserved ejection fraction (HFpEF) and effects of statins. Statins may improve the prognosis of HFpEF through the anti-inflammatory effects. NO-cGMP-PKG, nitric oxide-cyclic guanosine monophosphate-protein kinase G.

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different clinical features from those with HFpEF, associated with the different pathophysiology of HF. The pathophysiology of HFpEF remains incompletely defined, but traditionally it has been attributed to hypertensive left ventricular (LV) remodeling. Recent studies suggested that the systemic inflammation associated with aging, and comorbidities such as obesity, hypertension, diabetes mellitus, and renal insufficiency, are involved in the pathogenesis of HFpEF.^{4,5} Although inflammatory biomarkers, such as soluble interleukin-1 receptor-like 1, C-reactive protein, and growth differentiation factor-15, are elevated in both types of HF,^{6,7} the extent of inflammation is higher in HFpEF than in HFrEF,⁶ suggesting that systemic inflammation plays a more important role in HFpEF than in HFrEF. Systemic inflammation in HFpEF may accelerate myocardial remodeling and dysfunction through coronary microvascular endothelial dysfunction,⁸ with subsequent myocardial infiltration of activated leukocytes and interstitial fibrosis without cardiomyocyte death.^{8,9} These conditions also cause oxidative stress that inhibits the nitric oxide-cyclic guanosine monophosphate-protein kinase G signaling pathway, resulting in cardiomyocyte hypertrophy and enhanced myofiber stiffness.¹⁰ Thus, unlike HFrEF, in which remodeling is driven by cardiomyocyte cell death due to ischemia, infection, or toxicity, the central pathophysiology of HFpEF involves myocardial remodeling with limited cardiomyocyte cell damage and systemic endothelial dysfunction associated with systemic inflammation.⁵ Thus, statins with anti-inflammatory effects could improve the prognosis of HFpEF (**Figure**).

The prognostic impact of statins in patients with HF is controversial. A large-scale landmark trial, CORONA, failed to demonstrate the prognostic benefits of statins in HF patients.¹¹ Given, however, the subjects were limited to HFrEF patients, the prognostic impact of statins on HFpEF remains to be elucidated.¹¹ In this issue of the Journal, Marume et al report that the use of statins is associated with reduced all-cause mortality in HFpEF patients, regardless of serum cholesterol level in the JASPER Study.¹² Although previous studies have already demonstrated that the use of statins is associated with improved all-cause mortality in HFpEF patients,^{13,14} this study examined whether the use of statins is associated with better prognosis in HFpEF patients, particularly in those without coronary artery disease (CAD). Nochioka et al also reported in their Chart-2 Study that the use of statins was associated with better prognosis of HFpEF, regardless of the presence or absence of CAD.¹³ In the JASPER Study, the statin use was also associated with reduced all-cause mortality and hospitalization due to worsening of HF, but was not associated with cardiovascular death. In animal models, statins improve endothelial redox balance and restore nitric oxide bioavailability independently of low-density lipoprotein,¹⁵ attenuate oxidative stress, prevent progression of cardiac hypertrophy and extra-cellular remodeling, and subsequently ameliorate LV function.^{16,17} These findings support the positive outcomes associated with statins in HFpEF patients. In HFpEF patients, microvascular endothelial dysfunction develops not only in coronary arteries but also in systemic arteries, leading to initiation and worsening of HFpEF through myocardial diastolic dysfunction and end-organ dysfunction (**Figure**). Thus, HFpEF could be regarded as a manifestation of “systemic disease”, and thus statins could improve the prognosis of HFpEF through improvement of systemic endothelial and end-organ func-

tions. As noted here, several experimental studies have indicated the beneficial effects of statins. The mechanism of the possible beneficial prognostic effects of statins, however, remains to be elucidated, which was also the case in the Marume et al study.¹² Thus, further studies are needed to confirm the beneficial prognostic effects of statins in HFpEF patients.

Disclosures

The author declares no conflicts of interest.

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