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EDITORIAL COMMENT

The Prognostic Efficacy of DPP-4 Inhibitors in Asian HFpEF

Do They Still Have a Chance?*

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Accumulating evidence has suggested the close pathologic interactions between diabetes and heart failure. Indeed, numerous previous studies constantly indicated a substantially increased risk of heart failure in diabetic patients,[1] as well as higher risk of the development and progression of diabetes in those with heart failure.[2] Moreover, the complication of diabetes in patients with heart failure has also been established to associate with poorer outcomes, increased mortality, and worse quality of life, compared with those without diabetes.[3] Because diabetes is frequently accompanied by other atherogenic risk factors, such as smoking habits, dyslipidemia, and hypertension, the link between heart failure and diabetes has been conventionally considered to be through the context of coronary artery disease (CAD), the decreased left ventricular systolic and diastolic dysfunction induced by transient and permanent severe ischemia for the heart. On the contrary, the direct pathologic interaction of diabetes with the development and progression of heart failure, irrespective of the presence and the absence of major CAD and valvular disease, has led to the terminology of diabetic cardiomyopathy.[4] The hyperglycemia and hyperinsulinemia in combination with activation of renin-angiotensin-aldosterone system-induced left ventricular hypertrophy, diastolic dysfunction, and heart failure with preserved ejection fraction (HFpEF) rather than that with reduced ejection fraction (HFrEF) are the predominant pathophysiologic features of diabetic cardiomyopathy. Indeed, diabetes has been a particularly emerging issue in patients with HFpEF, as more than 40% of patients with HFpEF have been reported to concomitantly have diabetes.[5] Although the treatment of HFpEF, which was shown to improve outcomes, has long been lacking, a sodium-glucose cotransporter-2 (SGLT2) inhibitor, empagliflozin, was first shown to reduce the risk of the composite of cardiovascular death and heart failure hospitalization in patients with HFpEF (Empagliflozin outcome trial in patients with chronic heart failure with preserved ejection fraction [EMPEROR-Preserved] study).[6] Nevertheless, the medication specifically beneficial for HFpEF patients with diabetes is yet to be established, as a subanalysis from EMPEROR-Preserved showed no difference in prognostic impact of empagliflozin in patients with and without diabetes,[7] indicating no specific merit of empagliflozin for diabetic patients with HFpEF, although it was primarily presented as an antihyperglycemic medication.

On the other hand, while substantial beneficial effects of SGLT2 inhibitors and glucagon-like peptide-1 (GLP-1) receptor agonists reduce the risk of all-cause and cardiovascular mortalities in diabetic patients,[8] the positive prognostic effect of dipeptidyl peptidase-4 (DPP-4) inhibitors has been rarely demonstrated.[9,10] Moreover, in contrast to SGLT2 inhibitors having become an important medication to treat HFrEF and HFpEF irrespective of complicating diabetes, previous randomized trials and observational studies of DPP-4 inhibitors have raised a serious concern of increasing the risk of heart failure.[11,12]

In this issue of *JACC: Asia*, a retrospective observational study of a multicenter registry of Japanese patients with heart failure by Enzan et al[13] aimed to evaluate whether DPP-4 inhibitors have any prognostic impact in patients with heart failure, when they were divided in accordance with left ventricular

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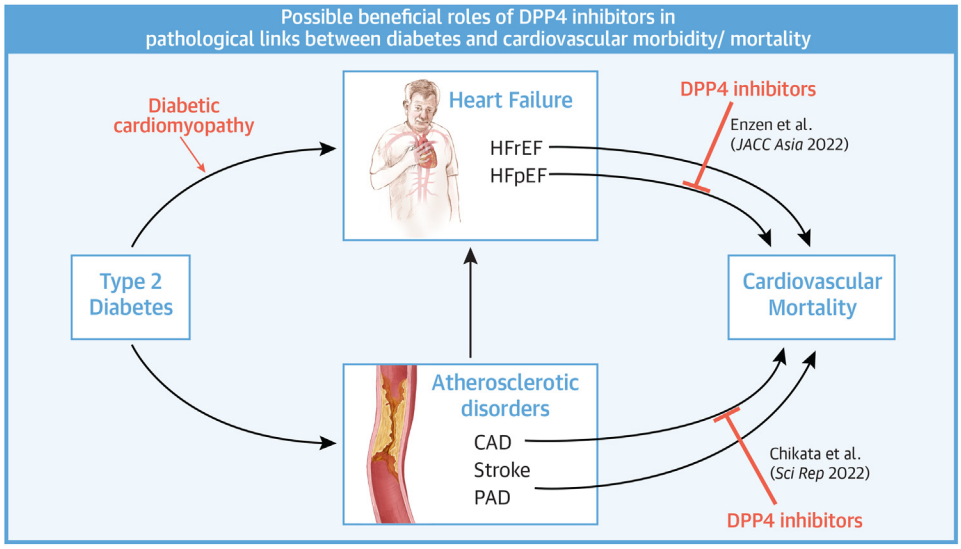
FIGURE 1 Pathologic Links Between Diabetes and Cardiovascular Morbidity/Mortality



Pathologic links from type 2 diabetes to cardiovascular mortality through 2 major pathways, heart failure and atherosclerotic disorders. Dipeptidyl peptidase-4 (DPP-4) inhibitors have been indicated to improve outcomes of Asian (Japanese) diabetic patients with heart failure with preserved ejection fraction (HFpEF)[13] and those after percutaneous coronary intervention (PCI).[14] CAD = coronary artery disease; HFrEF = heart failure with reduced ejection fraction; PAD = peripheral arterial disease.

ejection fraction (<40%, 40%-50%, and ≥50%, HFrEF, heart failure with mid-range or mildly-reduced ejection fraction, and HFpEF, respectively). Multivariate cox proportional hazard analysis showed that taking DPP-4 inhibitors was significantly associated with decreased risk of primary endpoint, the composite of cardiovascular death or heart failure hospitalization, only in patients with HFpEF, but not in other types of heart failure, heart failure with mid-range or mildly-reduced ejection fraction, and HFrEF. Furthermore, the cubic spline analysis showed a positive correlation between the prognostic benefit of DPP-4 inhibitors and left ventricular ejection fraction, when it was between approximately 40% and 55%. Indeed, the author's group previously showed that DPP-4 inhibitor, teneligliptin, inhibits cardiac hypertrophy, which is inextricably involved in diastolic dysfunction, by suppressing the nicotinamide adenine dinucleotide phosphate oxidase 4-histone deacetylase 4 axis,[14] which might be a possible explanation of the findings in the present study. In contrast to previous interventional and observational studies that indicated that DPP-4 inhibitors had at least no benefit for patients with diabetes or even worse for those with both of diabetes and heart failure, the present study first demonstrated a significant favorable effect of DPP-4 inhibitors in Japanese diabetic patients with HFpEF providing new insights regarding the prognostic benefit of DPP-4 inhibitors as a possible option in the treatment of HFpEF.

Moreover, we also recently reported a beneficial prognostic impact of DPP-4 inhibitors, which significantly improved outcomes in Japanese diabetic patients with CAD.[15] In that study, use of DPP-4 inhibitors was significantly associated with reduced risk of cardiovascular events including mortality in patients with diabetes who underwent percutaneous coronary intervention, in which insulin-like growth factor-1, one of the substrates of catalytic degradation of DPP-4, may play a part. Of interest, we have found that favorable prognostic impact of DPP-4 inhibitors was further enhanced in individuals who are not overweight (body mass index [BMI] ≤25 kg/m^2) compared with those who are overweight (BMI >25 kg/m^2).

We might need to consider any racial/ethnic differences, including those of genetic backgrounds, in the pathophysiology of diabetes and the responses for antidiabetic medications, DPP-4 inhibitors in particular. For diabetic patients in Europe and the United States, insulin resistance accompanied by obesity are the predominant pathophysiologic conditions, whereas impaired insulin secretion is the major issue for type 2 diabetes in Asians.[16] With respect to

response for DPP-4 inhibitors, the greater glucose-lowering efficacy in Asians compared with non-Asians was described.[17] Although the exact reasons are yet to be elucidated, at least in part, the better response for DPP-4 inhibitors in Asians may be explained by less obesity leading to lower baseline DPP-4 activity, hence this class of antidiabetic agent can be more effective. Indeed, our previous study demonstrated that the prognostic benefit of DPP-4 inhibitors was significantly enhanced in individuals without high BMI ($\leq$25 kg/m^2).[15]

Taking the findings in the present study including Japanese patients with diabetes and heart failure and our previous study including those with diabetes and CAD together, DPP-4 inhibitors, which have not been shown to be associated with better outcomes of diabetic patients based on previous large-scale randomized trials mainly involving patients with a BMI of around 30, may still have a chance to be effective in the Asian diabetic population whose treatment is complicated by CAD and/or HFpEF (**Figure 1**).

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