COMMENT ON UDELL ET AL.

Saxagliptin and Cardiovascular Outcomes in Patients With Type 2 Diabetes and Moderate or Severe Renal Impairment: Observations From the SAVOR-TIMI 53 Trial. Diabetes Care 2015;38:696–705

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We read the analysis of the Saxagliptin Assessment of Vascular Outcomes Recorded in Patients with Diabetes Mellitus–Thrombolysis in Myocardial Infarction 53 (SAVOR-TIMI 53) trial by Udell et al. (1) with interest. The important finding is the increased risk of hospitalization for heart failure with increasing severity of nephropathy. This highlights yet another association between macrovascular and microvascular complications in diabetes. The initial data by the same group reported a 27% higher incidence of hospitalization for heart failure among patients treated with saxagliptin as compared with placebo (2). The authors have not been able to provide a watertight explanation for this phenomenon. While the SAVOR-TIMI 53 trial conducted extensive clinical and laboratory assessment of its participants and identified risk factors for heart failure in both cohorts, cardiac autonomic function determination has not been reported to be part of the study design.

It is well known that cardiovascular disease is more frequent in patients with diabetes. Even if asymptomatic, its prognosis is the same as that of clinically apparent disease. Cardiovascular autonomic neuropathy (CAN) is associated with increased mortality in diabetes. CAN can cause left ventricular dysfunction through alteration in myocardial blood flow and sympathetic denervation and changes in myocardial neurotransmitters, including catecholamines and neurotransmitters of the neuropeptidergic system (3).

The presence of nephropathy is associated with not only increased prevalence of CAN but also early onset and increased severity of CAN (4). Moreover, severity of autonomic dysfunction increases with severity of nephropathy (5). As CAN often develops in parallel with diabetic nephropathy, it may act as a confounder in the association between the diabetic nephropathy and increased risk of cardiovascular mortality (6). In the SAVOR-TIMI 53 trial, a similar confounding effect may explain the relationship of increased severity of nephropathy and heart failure.

Recently, a study evaluated normoalbuminuric patients with type 1 diabetes with and without CAN (6). In patients with CAN, left ventricular function was decreased in both diastole and systole, and CAN was independently associated with increased risk of subclinical left ventricular dysfunction.

Saxagliptin acts through the incretin pathway, which has a close link with the autonomic nervous system. The incretin effect has been found to be attenuated in the presence of autonomic neuropathy (7). It is possible that preexisting CAN may have modified the response to saxagliptin and contributed to the increased risk of hospitalization noted by Udell et al. (1).

The evaluation and quantification of CAN are fairly standardized and are recommended as a means of cardiovascular risk stratification by American Diabetes Association. It would be beneficial, therefore, to include CAN evaluation when designing cardiovascular outcome trials in diabetes. CAN may emerge as a significant predictor of cardiovascular outcomes trials and as a tool to help decide appropriate choice of glucose-lowering therapy in future. This hypothesis, however, needs to be studied in greater detail.

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