In a recent randomized trial, the diabetes drug saxagliptin (Onglyza; a dipeptidyl peptidase (DPP)-4 inhibitor) was associated with a modest but statistically significant increase in hospital admissions for heart failure (NEJM JW Gen Med Oct 1 2013 and N Engl J Med 369:1317). Now, industry-supported researchers have examined the cardiovascular safety of another DPP-4 inhibitor, sitagliptin (Januvia), in nearly 15,000 type 2 diabetic patients with established cardiovascular disease and glycosylated hemoglobin (HbA\textsubscript{1c}) levels of 6.5% to 8.0% while taking one or two glucose-lowering agents. Patients were randomized to add either sitagliptin or placebo to their diabetes regimens, and treating clinicians were encouraged to adjust regimens to achieve individually appropriate HbA\textsubscript{1c} targets.

During a median follow-up of 3 years, HbA\textsubscript{1c} levels averaged 0.3% lower with sitagliptin than with placebo. The primary composite outcome (cardiovascular-related death, nonfatal myocardial infarction or stroke, or hospitalization for unstable angina) occurred in 11.4% and 11.6% of patients in the two groups, respectively; sitagliptin was statistically noninferior, but not superior, to placebo. Rates of hospitalization for heart failure were 3.1% in both groups. Although this study did not focus on microvascular outcomes, incidences of diabetic eye conditions, neuropathy, microalbuminuria, and renal failure were similar in the two groups.

Comment

The sponsoring company already had announced in April 2015 that this trial achieved its primary goal — demonstrating that sitagliptin is safe from the cardiovascular perspective. However, showing that a diabetes drug is not worse than placebo with respect to cardiovascular outcomes is not sufficient to support its use. The ultimate goal is to improve important clinical outcomes, and this trial showed no lower incidence of either macrovascular or microvascular outcomes with sitagliptin. Therefore, the role of this drug — which costs about US$5,000 annually for patients who must pay out of pocket — in treating patients with type 2 diabetes remains unclear.
Allan S. Brett, MD Reviewing Green JB et al., *N Engl J Med* 2015 Jun 8;