Do Dipeptidyl Peptidase-4 Inhibitors Increase the Risk of Heart Failure?*

Deepak L. Bhatt, MD, MPH, † Matthew A. Cavender, MD, MPH †

An association between diabetes and the risk of heart failure has been seen in observational studies. The mechanism is undefined, and it remains unclear whether dipeptidyl peptidase (DPP)-4 this association is related to concomitant medical problems associated with diabetes (e.g., ischemic heart disease, renal dysfunction, hypertension) or the direct effect of poorly controlled blood glucose. Current American Diabetes Association guidelines recommend that commonly used anti-hyperglycemic agents (e.g., thiazolidinedione agents) should be used with caution in patients with heart failure (1,2).

In this issue of JACC Heart Failure, Weir et al. (3) report on their finding that the dipeptidyl peptidase inhibitor sitagliptin is associated with hospitalization for heart failure in patients recently diagnosed with heart failure. The authors carefully performed this analysis in a cohort of patients identified in a large insurance claims database who had type 2 diabetes (taking metformin or a sulfonylurea) and newly diagnosed heart failure. Within this cohort, they identified all cases with the primary outcome of interest and matched them with up to 10 similar controls. They then performed a nested case-control study to determine the odds of a variety of endpoints in patients with diabetes and newly diagnosed heart failure taking sitagliptin versus those not taking sitagliptin.

The authors found no overall association between sitagliptin and the composite endpoints of all-cause death or hospital admission and death or heart failure admission. In addition, they found no association between the individual endpoints of all-cause death or hospital admission. However, they did find a statistically significant association between sitagliptin and heart failure admission that was present even after adjusting for potential confounders (adjusted odds ratio: 1.84; 95% confidence interval [CI]: 1.16 to 2.92; p = 0.01).

The finding that sitagliptin is associated with hospitalization due to heart failure adds to the known associations of other diabetes medications with heart failure. For example, fluid retention may occur in patients treated with thiazolidinedione medications. Findings recently reported have described a possible increase in the risk of heart failure with various antihyperglycemic agents (including other DPP-IV inhibitors). The AleCardio (Effect of Aleglitazar on Cardiovascular Outcomes After Acute Coronary Syndrome in Patients With Type 2 Diabetes Mellitus) trial randomized 7,226 patients with diabetes and recent acute coronary syndrome to aleglitazar (a dual peroxisome proliferator-activated receptor-α/γ agonist) or placebo (4). The trial was stopped early by the data

* Editorials published in JACC: Heart Failure reflect the views of the authors and do not necessarily represent the views of JACC: Heart Failure or the American College of Cardiology.

From the (TIMI) Thrombolysis in Myocardial Infarction Study Group, Brigham and Women’s Hospital Heart & Vascular Center, Boston, Massachusetts; and the (Harvard Medical School, Boston, Massachusetts. Dr. Bhatt is a member of the Advisory Board for Elsevier Practice Update Cardiology, Medscape Cardiology, and Regado Biosciences; is on the Board of Directors of the Boston VA Research Institute and Society of Cardiovascular Patient Care; is Chair of the American Heart Association Get With The Guidelines Steering Committee; is on the Data Monitoring Committees of Duke Clinical Research Institute, Harvard Clinical Research Institute, Mayo Clinic and the Population Health Research Institute; has received honoraria from the American College of Cardiology (Editor, Clinical Trials, CardioSource), Belvoir Publications (Editor in Chief, Harvard Heart Letter), Duke Clinical Research Institute (clinical trial steering committees), Harvard Clinical Research Institute (clinical trial steering committee), HMP Communications (Editor in Chief, Journal of Invasive Cardiology), Population Health Research Institute (clinical trial steering committee), Slack Publications (Chief Medical Editor, Cardiology Today’s Intervention), WebMD (CME steering committees); Clinical Cardiology (Deputy Editor), Journal of the American College of Cardiology (Section Editor, Pharmacology); has received research grants from Amarin, AstraZeneca, Bristol-Myers Squibb, Eisai, Ethicon, Medtronic, Roche, Sanofi Aventis, and The Medicines Company; has unfunded research with FlowCo, PLx Pharma, and Takeda; and is the co-Principal Investigator of the SAVOR-TIMI 53 trial, which was funded by AstraZeneca and Bristol-Myers Squibb. Dr. Cavender was a co-investigator in the SAVOR-TIMI 53 trial, which was funded by AstraZeneca and Bristol-Myers Squibb.
safety monitoring committee in part because of a numeric, although not statistically significant, excess in the incidence of hospitalization for heart failure with alogliptan (n = 122, 3.4%) when compared with placebo (n = 100, 2.8%; hazard ratio [HR]: 1.22; 95% CI: 0.94 to 1.59). The EXAMINE (Cardiovascular Outcomes Study of Alogliptin in Patients With Type 2 Diabetes and Acute Coronary Syndrome) trial, which randomized 5,380 patients with type 2 diabetes and recent acute coronary syndrome to usual medical care or usual medical care plus the DPP-4 inhibitor alogliptin, did not find a statistically significant increase in the composite of cardiovascular death or hospitalization for heart failure (HR: 0.98; 95% CI: 0.82 to 1.21) (5). However, when examining hospitalization for heart failure within this composite endpoint, there was a numeric excess that did not achieve statistical significance (3.9% vs. 3.3%; HR: 1.19; 95% CI: 0.90 to 1.58) but was of similar relative magnitude as that seen in the AleCardio trial (6).

These findings are particularly relevant given the results of the SAVOR-TIMI 53 (Saxagliptin Assessment of Vascular Outcomes Recorded in Patients with Diabetes Mellitus–Thrombolysis In Myocardial Infarction 53) trial. This double-blind, placebo-controlled trial randomized 16,492 patients with type 2 diabetes who were at high risk for cardiovascular events (including 12.8% who had a history of heart failure) to usual diabetes care plus saxagliptin or usual diabetes care plus placebo (7). After a median follow-up of 2.1 years, there were no differences in the risk of cardiovascular death, myocardial infarction, or stroke. However, there was an excess of hospitalization for heart failure in the patients treated with saxagliptin that reached statistical significance (3.5% vs. 2.8%; HR: 1.27; 95% CI: 1.07 to 1.51).

The results of these clinical trials have refocused attention on the relationships among diabetes, the medications used to treat diabetes, and heart failure. As such, the association described in the current analysis, which is of considerable interest given the findings of recent clinical trials, must be considered with the possibility that other studies, which may not have found an association before this period of increased attention, were not pursued because of the perceived lack of scientific interest. Likewise, one must also bear in mind the possibility of type I error when considering both the results of recent randomized clinical trials and the present paper in which multiple endpoints are analyzed.

Before recent studies, there was little evidence, either clinical or basic science, to suggest DPP-4 inhibition would increase the risk of heart failure. In contrast, basic science data largely suggested that DPP-4 inhibition should improve cardiovascular events, including ventricular function (8). The VIVIDD (Vildagliptin in Ventricular Dysfunction Diabetes) trial randomized 254 patients with type 2 diabetes and New York Heart Association functional class I to III heart failure to vildagliptin or placebo. There was no difference in left ventricular function after 1 year; however, patients treated with vildagliptin did have an increase in left ventricular end-diastolic volume, providing some suggestion that patients treated with DPP-IV inhibition could be at increased risk for heart failure.

The findings by Weir et al. (3) are derived from a nested case-control study. As such, selection of controls is important. Despite the use of incident density sampling to match cases and controls on the basis of age and sex, which is a valid and epidemiologically sound approach, important differences in the populations can remain, and it does not rule out the potential for confounding. For example, there was a 4.8% absolute higher rate of ischemic heart disease and a 9.5% absolute higher rate of history of diabetes complications in the patients treated with sitagliptin when compared with patients who were not treated with sitagliptin. Furthermore, these observations are from an insurance claims database that lacks granularity on many important clinical variables that are important in understanding outcomes and adjusting for potential confounding (including severity of heart failure and left ventricular dysfunction).

Also, the relative effect of sitagliptin on the odds of heart failure admission was moderate, and this association was based on a small number of events. Of the 824 admissions to the hospital for heart failure during follow-up, the patient had been taking sitagliptin over the prior 90 days in only 25 cases. This would be considered very few events in a clinical trial. Furthermore, the observations were derived from a large insurance claims database in which there is significant potential for misclassification bias. This is of importance for this particular analysis given the impact that a change in only a few events could have on the overall association that was seen.

With these considerations in mind, the present findings are important and do add to a small but growing body of evidence that suggests DPP-4 inhibitors as a class of drugs, and possibly diabetes drugs in general, may increase the risk of heart failure. This increase in absolute risk, if present at all, appears to be small. Thus far, this association does not seem to increase significantly the risk of mortality given the neutral effects on mortality seen in the present analysis and the randomized clinical trials. Moving forward, basic science and epidemiological studies
are needed to explore these potential associations and identify mechanisms through which antihyperglycemic agents might cause heart failure (Figure 1). The findings of this analysis, as well as other recent studies, highlight the need for well-designed trials that rigorously assess for heart failure in patients with diabetes. The ongoing TECOS (Trial Evaluating Cardiovascular Outcomes with Sitagliptin) has randomized approximately 14,000 patients with type 2 diabetes to sitagliptin or placebo, and may help establish whether the class of DPP-4 inhibitors does indeed cause heart failure. Further subgroup and biomarker analyses from recently completed trials may also add insight. In the meantime, diabetic patients at risk for heart failure hospitalization (e.g., those with pre-existing heart failure) who are started on DPP-4 inhibitors, and perhaps diabetes medications in general, should be followed closely as outpatients for symptoms and signs of heart failure.

**REPRINT REQUESTS AND CORRESPONDENCE:** Dr. Deepak L. Bhatt, Brigham and Women’s Hospital Heart & Vascular Center, 75 Francis Street, Boston, Massachusetts 02115. E-mail: DLBHATTMD@post.harvard.edu.

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**KEY WORDS** diabetes, heart failure, hospitalization, mortality, sitagliptin