Clinical Trials

Association of Antidiabetic Medications Targeting the Glucagon-Like Peptide 1 Pathway and Heart Failure Events in Patients With Diabetes

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ABSTRACT

Background: Glucagon-like peptide-1 (GLP-1) agonists and dipeptidyl peptidase 4 (DPP-4) inhibitors (GLP-1 agents) may be protective in heart failure (HF). We set out to determine whether GLP-1 agent use is associated with HF risk in diabetics.

Methods and Results: In this retrospective cohort study of members of a large health system, we identified >19,000 adult diabetics from January 1, 2000, to July 1, 2012. GLP-1 agent users were matched 1:2 to control subjects with the use of propensity matching based on age, race, sex, coronary disease, HF, diabetes duration, and number of antidiabetic medications. The association of GLP-1 agents with time to HF hospitalization was tested with multivariable Cox regression. All-cause hospitalization and mortality were secondary end points. We identified 1,426 users of GLP-1 agents and 2,798 control subjects. Both were similar except for angiotensin-converting enzyme inhibitors/angiotensin receptor blocker use, number of antidiabetic medications, and age. There were 199 hospitalizations, of which 128 were for HF, and 114 deaths. GLP-1 agents were associated with reduced risk of HF hospitalization (adjusted hazard ratio [aHR] 0.51, 95% confidence interval [CI] 0.34−0.77; $P = .002$), all-cause hospitalization (aHR 0.54, 95% CI 0.38−0.74; $P = .001$), and death (aHR 0.31, 95% CI 0.18−0.53; $P = .001$).

Conclusions: GLP-1 agents may reduce the risk of HF events in diabetics. (*J Cardiac Fail 2015;21:2−8*)

Key Words: GLP-1 agonist, DPP-4 inhibitor, heart failure, outcomes.

Heart failure (HF) continues to be an enormous public health problem in the US, with a prevalence of 5.7 million individuals affected, an incidence of >500,000 new cases annually[1] and an estimated 5-year mortality rate of 50%.[2] Insulin resistance and diabetes mellitus (DM) have long been recognized as important risk factors for the development of HF. Data from the Framingham Heart Study indicate that men and women with DM are 4−5 times more likely to develop HF, even after controlling for other risk factors such as coronary artery disease (CAD) and valvular heart disease.[3] Even early manifestations of insulin resistance, such as the metabolic syndrome, have been associated with increased risk of incident HF.[4,5] Additionally, DM worsens functional capacity and clinical outcomes in patients with established HF.[6−8] With this important association in mind, attention has been given to examining the cardiovascular (CV) effects of antidiabetic medications on outcomes in patients with HF.

Agents that target the GLP-1 pathway, including GLP-1 agonists and dipeptidyl-peptidase-4 (DPP-4) inhibitors, have recently received much attention. GLP-1 is an incretin hormone that leads to a rapid rise in circulating insulin

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levels after nutrient intake, and it is quickly inactivated in circulating blood by the enzyme DPP-4.[9] Studies in animal models and small human trials have shown that these agents appear to have favorable CV effects relevant to HF, including improved hemodynamics and exercise capacity.[10–13] However, the actual clinical relevance to HF patients remains largely unknown.

Recently completed randomized controlled trials have shown that DPP-4 inhibitors saxagliptin and alogliptin do not have a significant impact on major adverse cardiac events related to atherosclerotic CV disease.[14,15] However, the trials did not primarily address the effect of these agents on heart failure outcomes in diabetics. To inquire into this knowledge gap, we performed a retrospective propensity-matched analysis to determine whether exposure to agents affecting the GLP-1 pathway (GLP-1 agonists and DPP-4 inhibitors, collectively referred to herein as "GLP-1 agents") is associated with time to 1st hospitalization for HF in patients with DM.

Methods

Study Population

We performed a retrospective cohort study of subjects receiving care through the Henry Ford Health System, a vertically integrated health system serving the primary and specialty health care needs of individuals in southeast Michigan. The system includes several hospitals, a multispecialty physician group of ~1,000 physicians, and an affiliated health maintenance organization (HMO). The system maintains a central repository of administrative data, which we queried for this study. For the subset of patients enrolled in the HMO, data included insurance claims information, as well as enrollment and disenrollment dates. The study population was limited to individuals who were continuously enrolled in the HMO for ≥1 year before the DM diagnosis and who received care through system physicians. Therefore, we had information available for health care visits and prescription fills both within and outside the health system. Using electronic data sources, we identified patients ≥18 years of age with a primary diagnosis of DM, an oral antidiabetic drug fill, and no earlier diagnosis of HF from January 1, 2000, to July 1, 2012. Patients were followed until the 1st of the following events: HF hospitalization, death, disenrollment from the health plan, or the end of follow-up on July 1, 2012. The study was approved by the Institutional Review Board at Henry Ford Hospital.

Data Sources

Data for this study were obtained from electronic administrative databases maintained by the health system and from vital records from the Michigan Department of Community Health. The administrative data captured claims (ie, coded diagnoses, procedures, and prescription fills) occurring both within and outside the health system. A master patient index contained demographic data (ie, date of birth, sex, and race). Laboratory results were available for tests performed within the health system. The Michigan State Division of Vital Records and Health Statistics was queried with the patient social security numbers to identify deaths.

Statistical Analysis

We identified patients with a diagnosis of DM with an oral medication fill and without an earlier diagnosis of HF from January 1, 2000, to July 1, 2012. Those initiating treatment with a GLP-1 agent were matched 1:2 with control subjects by means of propensity score matching. Logistic regression was used to predict the use of a GLP-1 agent and then generate a propensity score. This regression model was adjusted for age, sex, race, DM duration, number of antidiabetic drugs, and CAD. Patients prescribed and not prescribed a GLP-1 agent were assigned in a 1:2 match where the propensity scores were matched to 0.001. Chi-square tests for categoric responses and Student t test for continuous variables were used to compare the groups on the propensity matching variables, duration of diabetes, number of antidiabetic drugs, beta-blocker use, angiotensin-converting enzyme inhibitor (ACEi)/angiotensin receptor blocker (ARB) use, ejection fraction, myocardial infarction (MI), hypertension, kidney disease, peripheral arterial disease, stroke, and chronic obstructive pulmonary disease.

Time to 1st hospitalization for HF was the primary end point for this study. Hospitalization for HF was the 1st inpatient admission with a primary discharge diagnosis of HF during the period of observation. A primary hospital discharge diagnosis of HF has been shown by our group and others to be a highly specific claim signature for HF (specificity 95%–100%).[16,17] Secondary end points included all-cause hospitalization and all-cause mortality. Secondary end points were also analyzed based on GLP-1 agonist or DPP-4 inhibitor use.

Multivariable Cox proportional hazards regression was used to model the association of treatment with a GLP-1 agent with time to first hospitalization for HF and other outcomes. Each model included the propensity score, number of antidiabetic drugs, duration of diabetes, baseline beta-blocker use, and ACEi/ARB use.

Results

We identified >19,000 patients with a diagnosis of DM with an oral medication fill and without a previous diagnosis of HF between January 1, 2000 and July 1, 2012. A total of 1,426 new users of GLP-1 agents and 2,798 propensity score–matched (for age, race, sex, duration of diabetes, and number of antidiabetic medications) control subjects were identified. The groups were well matched overall, although there were statistically significant differences in age, number of antidiabetic drugs taken, and ACEi/ARB use. Patients in the GLP-1 group were slightly younger (GLP-1 group 60 ± 11.4 years vs control group 61.2 ± 12.4 years; $P = .003$) and took fewer concomitant antidiabetic drugs compared with control subjects (GLP-1 group 1.35 ± 0.87 medications vs control group 1.53 ± 0.60 medications; $P = .001$). Hypertension was the most common comorbidity, and there were similar prevalences of other comorbid conditions between groups. Patients in both groups had a very low rate of established CV disease, including CAD, earlier MI, stroke, and peripheral arterial disease. Use of beta-blockers was similar between the groups, whereas the control group showed greater ACEi/ARB use (GLP-1 group 62.1% vs control group 66.7%; $P = .003$; Table 1). Regarding concurrent antidiabetic drugs, approximately half of the patients in each group were treated with