ABSTRACT

Title
Comparison of Risk of Hospitalization for Hypersensitivity (Including Severe Cutaneous) Reactions between Patients with Type 2 Diabetes Initiating Saxagliptin and Those Initiating Other Oral Anti-Diabetic Treatments.

Keywords
Saxagliptin, diabetes mellitus, pharmacoepidemiology, hypersensitivity, DPP4.

Rationale and background
The risk of severe hypersensitivity reactions associated with saxagliptin use among patients with type 2 diabetes mellitus (DM) in real-world settings is unknown.

Research question and objectives
Research Question: What is the risk of hospitalizations for severe hypersensitivity and severe cutaneous reactions, defined as anaphylaxis, angioedema, generalized urticaria, Stevens-Johnson syndrome (SJS), toxic epidermal necrolysis (TEN), and other severe skin reactions, among patients with type 2 DM who are new initiators of saxagliptin compared to those who are new initiators of other oral anti-diabetic (OAD) treatments?

Primary Objective: To compare the incidence of hospitalization for any severe hypersensitivity reaction (i.e., anaphylaxis, angioedema, generalized urticaria, SJS, TEN, and other severe skin reactions, such as acute generalized exanthematous pustulosis and drug rash with eosinophilia/systemic symptoms) between patients with type 2 DM who are new initiators of saxagliptin and those who are new initiators of OADs in classes other than dipeptidyl peptidase IV (DPP-4) inhibitors.

Secondary Objective 1: To compare baseline patient characteristics between type 2 DM patients who are new initiators of saxagliptin and those who are new initiators of OADs in classes other than DPP-4 inhibitors, and to identify important prognostic variables that should be balanced between the study groups and included in the propensity score used for the primary analysis.

Secondary Objective 2: To compare the incidence of hospitalizations for hypersensitivity reactions, both individually and combined based on mechanism of action (Group 1: anaphylaxis, angioedema, and urticaria; Group 2: SJS, TEN, and other severe skin reactions), between patients with type 2 DM who are new initiators of saxagliptin and those who are new initiators of OADs in classes other than DPP-4 inhibitors.

Secondary Objective 3: To compare the incidence of hospitalizations and/or emergency department (ED) visits for any severe hypersensitivity reaction between patients with type 2 DM who are new initiators of saxagliptin and those who are new initiators of OADs in classes other than DPP-4 inhibitors.

Secondary Objective 4: To examine risk factors for severe hypersensitivity reactions observed at higher risk among saxagliptin initiators, if any.

Study design
This was a prospectively-designed database cohort study of hypersensitivity reactions among new initiators of saxagliptin compared to those who are new initiators of OADs in classes other than DPP-4 inhibitors.

Setting
This study used data from US Medicare, the HealthCore Integrated Research Database℠ (HIRD℠), theClinical Practice Research Datalink (CPRD, previously named the General Practice Research Database [GPRD]), and The

Health Improvement Network (THIN). This report represents the results of the final analysis for the study and includes data from the respective data sources from between 2009 and 2014.

Subjects and study size, including dropouts

Patients were eligible for inclusion if they were: 1) 18 years of age or older, 2) newly prescribed saxagliptin (with or without other OADs) or OAD in a class other than DPP-4 inhibitors (with or without other OADs), and 3) enrolled in the respective data source for at least 180 days prior to the (apparently) new prescription of saxagliptin or other OAD in a class other than DPP-4 inhibitors. Follow-up began on the date a patient was first prescribed or dispensed saxagliptin or an OAD in a different class, which represented the index date. Follow-up continued until the earliest of the following: study outcome, the end of study data, or discontinuation of saxagliptin or the index comparator OAD (i.e., no further prescription or drug claim within 30 days after the last prescription's days' supply).

Variables, data sources, and statistical analyses

The primary outcome was hospitalizations for a hypersensitivity reaction, determined based on diagnosis codes within each data source. The positive predictive value (PPV) of hypersensitivity diagnosis coding algorithms was evaluated within each data source via medical record adjudication by experts in hypersensitivity and skin reactions. We sought to develop coding algorithms for hypersensitivity reactions with at least 80% PPV compared to confirmed events by medical record review.

Within each data source (US Medicare, HealthCore Integrated Research Database℠, Clinical Practice Research Datalink, The Health Improvement Network), descriptive statistics compared baseline characteristics between initiators of saxagliptin and comparator OADs in classes other than DPP-4 inhibitors. Propensity scores (PS) were developed within each data source using logistic regression, incorporating measured potential predictors of saxagliptin therapy as independent variables and comparison group status (saxagliptin group vs. comparator group) as the outcome. Incidence rates (IRs) of hypersensitivity reactions were determined in each cohort. Cox proportional hazards regression was used to determine adjusted hazard ratios (HRs) with 95% confidence intervals (CIs) of hypersensitivity reactions among saxagliptin initiators versus other OAD uses, adjusting for propensity score, prior OAD therapy, quarter of observation, and geographic region.

Results

Across all four data sources, diagnosis coding algorithms to identify hospitalizations for severe hypersensitivity reactions with a PPV of at least 80% were unable to be developed due to the lack of specificity of the diagnosis codes and the low incidence of events. Therefore, electronically-identified diagnoses were classified as events if confirmed by medical record review, and we conservatively classified patients with electronically-identified diagnoses, but who did not have medical records available for outcome confirmation, as having events. Patients who were adjudicated as not having had a diagnosis after medical record review were classified as not having had events, and their follow-up time was censored at the hypersensitivity reaction diagnosis date. There were no associations between saxagliptin initiation and hospitalizations for severe hypersensitivity reactions within US Medicare (fully adjusted HR, 0.80 [95% CI, 0.62-1.02]), within the HIRD℠ (fully adjusted HR, 0.48 [95% CI, 0.17-1.38]), and within CPRD (PS only-adjusted HR, 1.80 [95% CI, 0.31-10.28]). There were no identified hospitalizations for severe hypersensitivity reactions within THIN. A meta-analysis across the four data sources was unable to be conducted due to the low number of hospitalized hypersensitivity reaction events.