ABSTRACT

Title
Comparison of Risk of Hospitalization for Acute Kidney Injury between Patients with Type 2 Diabetes Initiating Saxagliptin and Those Initiating Other Oral Anti-Diabetic Treatments.

Keywords
Saxagliptin, diabetes mellitus, pharmacoepidemiology, acute kidney injury, DPP4 inhibitor.

Rationale and background
The risk of acute kidney injury (AKI) 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 AKI 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 1: To compare the incidence of hospitalizations for AKI 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 examine risk factors for AKI outcomes noted at higher risk among saxagliptin initiators, if any.

Study design
This was a prospectively-designed database cohort study of hospitalizations for AKI 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℠), the Clinical 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 that 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). Approved v2.0 930095376 2.0 NIR PASS Study Report D1680R00013 Final Analysis Report BMS-477118 Saxagliptin

Variables, data sources, and statistical analyses

The primary outcome was hospitalizations for AKI, as determined by an inpatient diagnosis of AKI *plus* at least one of the following recorded within 7 days prior to the hospital admission: a) an emergency department visit with a recorded diagnosis code for AKI, b) an outpatient visit with a recorded diagnosis code for AKI, or c) a claim for a serum creatinine or serum chemistry panel that includes a creatinine (within the US data sources) or an available serum creatinine test result (within the UK data sources). Hospitalizations for AKI were confirmed by medical record review by nephrologist adjudicators. Diagnosis coding algorithms that identified hospitalization for AKI with _80% positive predictive value (PPV) were determined.

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 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 of outcomes were determined in each cohort. Cox proportional hazards regression was used to determine hazard ratios (HRs) with 95% confidence intervals (CIs) of AKI in saxagliptin initiators versus other OAD uses, adjusting for propensity score, prior OAD therapy, quarter of observation, and geographic region.

Results

Within the two US data sources, we were able to identify a refined electronic algorithm to identify hospitalizations with a PPV greater than 80%. Within both of these data sources, we found no significant associations in incidence or risk of hospitalizations for AKI among saxagliptin initiators, as demonstrated by fully adjusted hazard ratios of 0.99 (95% CI, 0.88-1.11) within US Medicare and 0.88 (95% CI, 0.29-2.74) within the HIRD℠. The same was true in a meta-analysis of the results of the two US data sources (fully adjusted HR, 0.99 [95% CI, 0.88-1.11]). Within the two UK data sources, we were unable to identify a diagnosis coding algorithm with _80% PPV due to the absence of validated events among saxagliptin initiators, so a sensitivity algorithm was used in analyses. Within both CPRD and THIN, hazard ratios for the risk of hospitalizations for AKI were unable to be calculated, and there were no differences in the incidence rates of hospitalizations for AKI between saxagliptin initiators and initiators of other OADs.