# 1 ABSTRACT

**Title**

Comparison of Risk of Major Cardiovascular Events Between Patients with Type 2 Diabetes Initiating Saxagliptin and Those Initiating Other Oral Anti-Diabetic Treatments.

**Keywords**

Saxagliptin, diabetes mellitus, pharmacoepidemiology, myocardial infarction, stroke.

**Rationale and background**

The risk of major adverse cardiovascular events (MACE), defined as a composite of nonfatal myocardial infarction, nonfatal stroke, or death from cardiovascular causes, 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 MACE for patients with type 2 DM who are new initiators of saxagliptin compared to those who are new initiators of oral anti-diabetic drugs (OAD) in classes other than dipeptidyl peptidase IV (DPP-4) inhibitors?

**Primary Objective**: To compare the incidence of MACE among 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 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 DPP4 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 a composite of nonfatal myocardial infarction, nonfatal stroke, or death from cardiovascular causes plus coronary and carotid revascularization procedures

among 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 all-cause mortality among 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 cardiovascular outcomes noted at higher risk among saxagliptin initiators, if any.

**Study design**

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

**Setting**

This study uses data from US Medicare, the HealthCore Integrated Research DatabaseSM (HIRDSM), the Clinical Practice Research Datalink (CPRD, previously named the General Practice Research Database [GPRD]), and The Health Improvement Network (THIN). This report represents the second interim analysis for the study and includes data from the respective data sources from between 2009 and 2012.

**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 endpoint, 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 and data sources**

The primary outcome was MACE, defined in two ways: 1) a composite of nonfatal acute myocardial infarction (AMI) hospitalization, nonfatal acute stroke hospitalization, or death from cardiovascular causes that include deaths due to AMI, acute stroke, congestive heart failure, dysrhythmia, sudden death, or coronary revascularization, or 2) a composite of nonfatal AMI hospitalization, nonfatal acute stroke hospitalization, or death from cardiovascular causes that include deaths due to AMI, acute stroke, congestive heart failure, dysrhythmia, sudden death, coronary revascularization, or deep venous thrombosis/pulmonary embolism.

Within each data source, 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 adjusted hazard ratios (HRs) with 95% confidence intervals (CIs) of MACE in saxagliptin initiators versus other OAD uses, adjusting for propensity score.

**Results**

Within the US Medicare, there was a decrease in incidence rates of medical record-confirmed MACE events between saxagliptin and other OAD initiators (9.0 [95% CI, 7.6-10.5] versus 11.4 [95% CI, 11.0-12.0] events per 1,000 person-years, respectively; fully adjusted HR, 0.80 [95% CI, 0.67-0.96]). Within the HIRDSM, there were no differences in incidence rates of medical record-confirmed MACE events between saxagliptin and other OAD initiators (1.8 [95% CI, 0.6-3.8] versus 2.1 [95% CI, 1.6-2.8] events per 1,000 person-years, respectively; fully adjusted HR, 0.96 [95% CI, 0.39-2.35]). Within CPRD, there were no differences in incidence rates of medical record-confirmed MACE events between saxagliptin and other OAD initiators (6.1 [95% CI, 2.2-13.3] versus 6.3 [95% CI, 4.7-8.3] events per 1,000 person-years, respectively; fully adjusted HR, 0.95 [95% CI, 0.38-2.37]). Within THIN excluding CPRD, there were no differences in incidence rates of medical record-confirmed MACE events between saxagliptin and other OAD initiators (8.8 [95% CI, 1.8-25.7] versus 6.4 [95% CI, 3.6-10.5] events per 1,000 person-years, respectively; fully adjusted HR, 1.39 [95% CI, 0.35-5.50]). Additionally, there were no significant differences with the use of the initial electronic or refined algorithms or with the inclusion of death due to deep venous thrombosis or pulmonary embolism.