Replication of Mini-Sentinel Saxagliptin Study Assessing Acute Myocardial Infarction Using Electronic Medical Record Network

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OBJECTIVES

In 2009, the US Food and Drug Administration (FDA) initiated a routine prospective surveillance study using the Mini-Sentinel (M-S) program to assess potential signals of acute myocardial infarction (AMI) with use of saxagliptin, an antihyperglycemic drug of the dipeptydal-peptidase 4 (DPP-4) inhibitor class, designated for the treatment of type 2 diabetes, compared with sitagliptin, pioglitazone, second-generation sulfonylureas, and long-acting insulin. The purpose of this study was to replicate the FDA M-S analysis of saxaglitpin using real-world data from an electronic medical record network (EMR).

METHODS

This retrospective cohort study identified saxagliptin, sitagliptin, pioglitazone, second-generation sulfonylureas, and long-acting insulin using the TriNetX federated network of deidentified health data, and patient populations were identified through the platform's Dataworks-USA network. TriNetX identified 45,070 potential saxagliptin patients using RxNorm terminology occurring on or after August 1, 2009. From this cohort of all potential saxagliptin patients, we identified a sub-cohort of 28,387 saxagliptin patients who did not use saxagliptin or comparators in the previous 365 days before index, who did not have a type 1 diabetes diagnosis, and who did not have a diagnosis of primary acute myocardial infarction in the 60 days before index appear in their EMR. We also identified 4 separate cohorts of sitagliptin, pioglitazone, second-generation sulfonylureas, and long-acting insulin patients totaling to 372,998, 161,233, 953,970 and 1,264,555 patients, respectively occurring on or after August 1, 2009 and who did not use saxagliptin or comparators in the previous 365 days before index, who did not have a type 1 diabetes diagnosis, and who did not have a diagnosis of primary acute myocardial infarction in the 60 days before index appear in their EMR. For the pioglitazone cohort, patients with heart failure documented in the 365 days before index were also excluded. Users of saxagliptin and comparators were analyzed per the widely available M-S protocol and were 1:1 propensity score-matched to adjust for potential confounders. These models were run further for each pairwise comparison for patients with and without prior cardiovascular disease. Patients were followed and analyzed for outcomes of acute myocardial infarction from the first instance of treatment in the EMR from August 1, 2009, until August 31, 2014. Hazard ratios (HR) were evaluated for significance using 95% confidence intervals (CI).

Figure 1. Kaplan-Meier Survival Curve of Saxagliptin and Sitagliptin Cohort

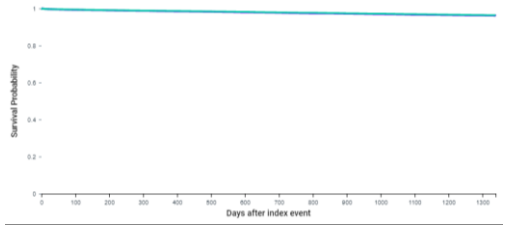

Figure 2. Kaplan-Meier Survival Curve of Saxagliptin and Pioglitazone Cohort

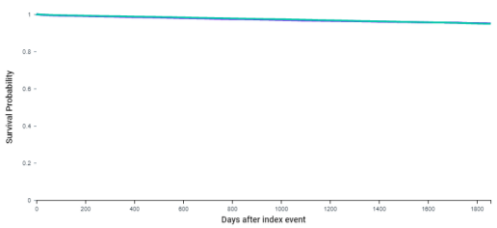

Figure 3. Kaplan-Meier Survival Curve of Saxagliptin and Second-Generation Sulfonylureas Cohort

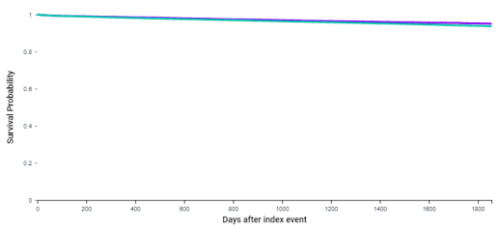

Figure 4. Kaplan-Meier Survival Curve of Saxagliptin and Long-acting Insulin Cohort

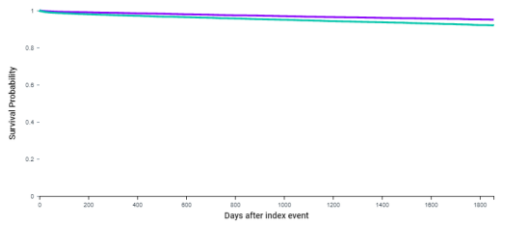

Table 1. Measures of Association for Saxagliptin and 4 Comparator Cohorts

COMPARISON	METHOD OF COVARIATE ADJUSTMENT	ALL PATIENTS	PATIENTS WITH CVD	PATIENTS WITHOUT CVD
SAXAGLIPTIN VS. SITAGLIPTIN	PSM	0.98 (0.89-1.07)	1.01 (0.92-1.10)	1.03 (0.93-1.13)
SAXAGLIPTIN VS. PIOGLITAZONE	PSM	1.07 (0.97-1.17)	1.04 (0.95-1.15)	1.06 (0.96-1.16)
SAXAGLIPTIN VS. SULFONYLUREAS	PSM	0.88 (0.80-0.9)	0.93 (0.85-1.02)	0.86 (0.79-0.94)
SAXAGLIPTIN VS. LONG-ACTING INSULIN	PSM	0.74 (0.68-0.81)	0.80 (0.73-0.88)	0.79 (0.72-0.87)

RESULTS

The adjusted HR with 95% CI was 0.98 (0.895,1.077) in the comparison with sitagliptin, 1.07 (0.971,1.174) in the comparison with pioglitazone, 0.88 (0.809,0.97) in the comparison with second-generation sulfonylureas, and 0.74 (0.683,0.817) in the comparison with long-acting insulin. The Kaplan-Meier survival curve of the saxagliptin cohort compared to the 4 comparator cohorts (Table 1) shows no difference in survival probability, indicating a negligible difference in the count of patients that had an AMI in the time window. None of the pairwise comparisons suggested an increased risk of AMI for saxagliptin users.

CONCLUSIONS

Using the M-S protocol and analysis with an electronic medical record network data source, there was no statistically significant increased risk of AMI found among saxagliptin users compared with sitagliptin, pioglitazone, second-generation sulfonylureas, and long-acting insulin. These findings were consistent with those of the FDA M-S saxagliptin study.

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Toh S, Hampp C, Reichman ME, Graham DJ, Balakrishnan S, et al. Risk for Hospitalized Heart Failure Among New Users of Saxagliptin, Sitagliptin, and Other Antihyperglycemic Drugs: A Retrospective Cohort Study. Ann Intern Med. 2016 Jun 7;164(11):705-14. doi: 10.7326/M15-2568. Epub 2016 Apr 26. Erratum in: Ann Intern Med. 2016 Aug 16;165(4):304. PMID: 27110660; PMCID: PMC5178978.