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Real-world Glycemic Control by Age, Race, and Renal Function Among Patients with Type 2 Diabetes Mellitus Treated with Linagliptin

Final Study Report

Date 04 February 2018

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Executive Summary

Background

Dipeptidyl peptidase-4 (DPP-4) inhibitors are indicated to improve glycemic control in adults with type 2 diabetes mellitus (T2DM), a patient population with a wide range of renal function capacity. While overall efficacy of linagliptin, an approved DPP-4 inhibitor, for lowering glycosylated hemoglobin (HbA1c) is well established, potential differences between patient subgroups (e.g., age, level of renal function, and race/ethnicity) are not well understood. In contrast to most other DPP-4 inhibitors, linagliptin does not require dose adjustment with declining renal function. This affords simplicity for chronic management of HbA1c.

Data from clinical studies demonstrate that the expected reduction in HbA1c with linagliptin should be similar irrespective of age, but direct comparisons across age groups have not been conducted. Current literature indicate that decline in renal function is associated with reduced glycemic control, hypertension, albuminuria and dyslipidemia. Furthermore, there is some evidence to suggest that the decline in renal function varies by demographic factors such as age and race. Additionally, linagliptin may offer a better therapeutic option for African Americans who tend to experience a more rapid decline in renal function compared to non-Hispanic Caucasians. However, there is limited evidence about the real world effectiveness and safety of linagliptin across age, renal function levels, and race among adults with T2DM.

Objective

The aim of this study was to describe real world glycemic-lowering effectiveness across a range of ages and renal function among adults with T2DM who are initiated on linagliptin. In addition, effectiveness by race with a focus on African American individuals was examined.

Methods

This was a non-interventional, retrospective cohort study using existing data from patients in the Optum Clinical Database which contains electronic health record data from providers across the United States (U.S.). Adult patients with T2DM initiating linagliptin were identified during an identification period starting on 01 January 2012 and ending on 30 September 2016. The date of the first written prescription for linagliptin during the identification period was designated as the index date. Baseline characteristics were evaluated during the 180-day period prior to the index date (pre-index period) and on the index date. Outcomes were assessed during the 180-day period following the index date (follow-up period).

Across the range of age, race and renal function categories, outcomes that were evaluated included change in HbA1c and percentage of patients achieving an HbA1c goal of < 7.0% during the 60 to 180 days after initiation of linagliptin. These measures were also evaluated among the subgroup of African American patients. Analyses of age by renal function were performed. A multivariable linear regression model was conducted as a secondary analysis to assess change in HbA1c, controlling for an *a priori* list of covariates.

Results

Among the overall sample (N = 11,001) mean (standard deviation (SD)) age was 64.3 (11.4) years and 50.9% were female. The proportion of patients in each age category was 21.1% for age 40 to 54 years, 30.3% for age 55 to 64 years, 28.0% for age 65 to 74 years, and 20.6% for age 75 years or older. The majority of patients (78.6%) were White, 13.2% were African American, 2.2% were Asian, and 6.0% were unknown/other. Most of the patients resided in the South (45.0%) or Midwest (37.0%).

The most common pre-index antihyperglycemic medication regimens were no evidence of pre-index antihyperglycemic medication (22.2%), metformin only (18.1%), metformin plus sulfonylurea (14.0%), and sulfonylurea only (9.3%). There were 5,454 (49.6%) patients with a pre-index regimen containing metformin, 3,882 (35.3%) patients with a pre-index regimen containing sulfonylurea, and 2,816 (25.6%) of patients with a pre-index regimen containing insulin. Mean (SD) pre-index HbA1c was 8.17% (1.62). A total of 5,701 (51.8%) patients had a pre-index HbA1c < 8% and 8,371 (76.1%) patients had a pre-index HbA1c < 9%. Among patients with a pre-index eGFR value, mean (SD) pre-index eGFR was 68.7 (26.8) ml/min/1.73 m^2.

Pre-index HbA1c varied across age categories (p<0.001) with younger patients having higher pre-index HbA1c values compared with older patients. Mean (95% CI) pre-index HbA1c values were 8.62% (8.55% to 8.70%) for patients 40 to 54 years, 8.30% (8.24% to 8.35%) for patients 55 to 64 years, 7.96% (7.91% to 8.01%) for patients 65 to 74 years, and 7.80% (7.75% to 7.86%) for patients 75 years and older.

Pre-index HbA1c varied across renal function categories (p<0.001). Patients with eGFR ≥ 90 ml/min/1.73 m^2 had the highest pre-index HbA1c (mean 8.57%, 95% CI 8.51% to 8.64%), followed by patients with eGFR 60 to 89 ml/min/1.73 m^2 (mean 8.18%, 95% CI 8.13% to 8.23%), patients with eGFR 45 to 59 ml/min/1.73 m^2 (mean 7.98%, 95% CI 7.91% to 8.05%), 30 to 44 ml/min/1.73 m^2(mean 7.87%, 95% CI 7.79% to 7.94%), and patients with eGFR < 30 ml/min/1.73 m^2 (mean 7.64%, 95% CI 7.53% to 7.75%).

Pre-index HbA1c was higher among African American patients (mean 8.42%, 95% CI 8.33% to 8.52%) compared with White (mean 8.12%, 95% CI 8.09% to 8.15%) or Asian (mean 8.05%, 95% CI 7.85% to 8.25%) patients (p<0.001).

Patients initiating linagliptin had an average reduction in HbA1c of 0.51% between 60 and 180 days after starting therapy. Across pre-defined age categories, change in HbA1c ranged from -0.65% in the 40 to 54 years age group to -0.36% in the 75 years and older age group. For the pre-defined renal function categories, change in HbA1c ranged from -0.70% for patients with eGFR ≥ 90 ml/min/1.73 m^2 to -0.22% for patients with eGFR < 30 ml/min/1.73 m^2. Change in HbA1c by race ranged from -0.68% for African American individuals to -0.41% for Asian individuals. Without adjusting for age, renal function, race, and pre-index HbA1c, there appeared to be greater reductions in HbA1c for younger patients compared with older patients, for patients with higher eGFR compared with patients with lower eGFR, and for individuals of African American race compared with individuals of White/Caucasian or Asian race.

Overall, 35.7% of patients reached the goal HbA1c (< 7%) during 60 to 180 days after the index date. The proportion of patients reaching the goal HbA1c (< 7%) was significantly different across age categories (p<0.001) with a lower proportion of patients age 40 to 54 years reaching goal (30.3%) compared with

35.6% of patients age 55 to 64 years, 37.9% of patients age 65 to 74 years, and 38.6% of patients 75 years or older.

In the multivariable model, variables that were significantly associated with a greater reduction in HbA1c were higher pre-index HbA1c value, older age groups compared with patients 40 to 54 years of age, anemia, other lower respiratory disease, other nutritional, endocrine and metabolic disorders, and male gender. Variables that were significantly associated with less of a reduction in HbA1c were Hispanic ethnicity, patients with eGFR 30 to 44 ml/min/1.73 m^2 compared with eGFR 60 to 89 ml/min/1.73m^2, diseases of the heart, and mood disorders. There were no significant differences in change in HbA1c with race, Charlson comorbidity index, geographic region, or eGFR < 30 ml/min/1.73 m^2, 45 to 59 ml/min/1.73m^2, or ≥ 90 ml/min/1.73m^2 compared with eGFR 60 to 89 ml/min/1.73m^2.

After adjusting for all of the covariates in the model, the mean adjusted change in HbA1c was -0.31 for patients 40 to 54 years of age, -0.42 for patients 55 to 64 years of age, -0.44 for patients 65 to 74 years of age, and -0.45 for patients 75 years of age and older. The mean adjusted change in HbA1c was significantly different for patients 40 to 54 years of age compared with patients 55 to 64 years of age (p=0.001), compared with patients 65 to 74 years of age (p<0.001), and compared with patients 75 years of age and older (p<0.001).

Among the subgroup of individuals with African American race, unadjusted change in HbA1c ranged from a high of -0.78% in the 40 to 54 years age group to a low of -0.49% in the 75 years and older age group. Across pre-defined renal function categories, unadjusted change in HbA1c ranged from a high of -0.88% for patients with eGFR ≥ 90 ml/min/1.73 m^2 to a low of -0.39% for patients with eGFR 30 to 44 ml/min/1.73 m^2. The proportion of African Americans reaching HbA1c goal was 36.2%, which was comparable to the overall sample. Within the African American subgroup, the proportion of patients reaching HbA1c goal was not significantly different across age categories. Although there appeared to be differences across the renal function categories, sample sizes for some of the renal function categories were too small to evaluate in the African American subgroup.

Conclusion

Across a large, real-world sample of patients with T2DM in the U.S., reduction in HbA1c averaged 0.51% between 60 and 180 days after starting linagliptin therapy. After adjusting for demographics and clinical characteristics including pre-index HbA1c, race, and pre-index renal function, the mean change in HbA1c was -0.31 for patients 40 to 54 years of age, -0.42 for patients 55 to 64 years of age, -0.44 for patients 65 to 74 years of age, and -0.45 for patients 75 years of age and older. Overall, these results provide support for the HbA1c lowering effectiveness of linagliptin across age, race, and renal function categories among a large, real-world sample of adult patients with T2DM.