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ORIGINAL RESEARCH

Real-World Glycemic Lowering Effectiveness of Linagliptin Among Adults with Type 2 Diabetes by Age, Renal Function, and Race

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ABSTRACT

Introduction: To assess real-world effectiveness of linagliptin in persons with type 2 diabetes mellitus (T2DM) across a range of ages and renal function. Effectiveness was assessed in different races, with a focus on African Americans (AA).
Methods: This was a non-interventional retrospective cohort study using data in the Optum clinical database from adults with T2DM initiating linagliptin. Date of the first linagliptin prescription was the index date. Outcomes included change in glycated hemoglobin (HbA1c) and the percentage of persons achieving an HbA1c < 7% (53 mmol/mol) during the 60–180 days following linagliptin initiation. Analyses of age by renal function were conducted. Multivariate regression analysis was performed to assess change in HbA1c, controlling for an a priori list of covariates.
Results: Overall, 11,001 persons were included. Mean pre-index HbA1c value was 8.2% (66 mmol/mol), with higher levels in younger versus older persons and AAs versus other race groups. Persons initiating linagliptin had an average HbA1c reduction of 0.51% (5.6 mmol/mol). Without adjusting for age, renal function, race, and pre-index HbA1c, greater reductions in HbA1c were observed in younger versus older persons, persons with higher versus lower estimated glomerular filtration rate (eGFR), and AAs versus white or Asians. After multivariate analysis, variables significantly associated with a greater HbA1c reduction included higher pre-index HbA1c and older age.
Conclusions: These results support the HbA1c-lowering effectiveness of linagliptin across age, race, and renal function categories among a large real-world population of adults with T2DM.

Keywords: Effectiveness; Glycated hemoglobin; Linagliptin; Renal function; Type 2 diabetes mellitus

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Key Summary Points

Why carry out the study?

Information on efficacy of dipeptidyl peptidase-4 (DPP-4) inhibitor use is largely from clinical trials.

Few data evaluate the effects of age, renal function, and race on glycated hemoglobin (HbA1c) effectiveness.

What was learned from the study?

This real-world–evidence study shows that a single dose of linagliptin is effective across age, renal function, and race.

The findings support the use of linagliptin in older persons with type 2 diabetes who have concomitant renal compromise in a real-world setting.

INTRODUCTION

Diabetes and associated renal disease increase with age and diabetes duration, especially in African Americans (AA) [1]. Diabetes mellitus disease duration is associated with more complex treatment regimens for glycemic control and renal and cardiovascular comorbidities with concomitant polypharmacy. Several glucose-lowering agents are contraindicated in chronic kidney disease and must be discontinued, and other medications require dose adjustment [2, 3]. Use of medications that do not require dose adjustment mitigates treatment complexity.

Dipeptidyl peptidase-4 (DPP-4) inhibitors reduce glycated hemoglobin (HbA1c) in adults with type 2 diabetes mellitus (T2DM) [4–6]. Of four DPP-4 inhibitors approved for use in the US, only linagliptin requires no dose adjustment with moderate to severe renal impairment [7].

Although there are many randomized controlled clinical trial data on linagliptin [8–10], data comparing linagliptin's glycemic effectiveness in a large real-world cohort of persons with T2DM across predefined ranges of age and renal function are limited. The current study sought to determine whether linagliptin has similar glycemic effectiveness across these variables. The objective was to evaluate change in HbA1c and percentage of persons achieving an HbA1c $< 7.0\%$ (53 mmol/mol).

METHODS

Study Design

This retrospective cohort study used data from persons in the Optum clinical electronic health records (EHR) database between July 1, 2011, and March 31, 2017 (see Fig. S1 in the electronic supplementary material). The EHR database consists of data from $>$ 60 million persons across the USA and Puerto Rico (see Table S1 for participant flow and Table S2 for comorbid conditions in the electronic supplementary material).

Persons were included if they had $\geq$ 1 written prescription for linagliptin or single-tablet combination linagliptin/metformin between January 1, 2012, and September 30, 2016. The pre-index (for consistency with other instances) period was a period of 180 days (6 months) before the date of the first prescription for linagliptin. The post-index period was 6 months after the first linagliptin prescription. Study population included adults $\geq$ 40 years old. To be considered for these analyses, they needed at least one diagnosis code for type 2 diabetes and had to have at least one HbA1c value in the 6 months before the linagliptin prescription. In addition, they had to have at least 1 HbA1c value 60–180 days after the linagliptin prescription (the post-index period). Persons were excluded if another DPP-4 inhibitor or other glucose-lowering medication was prescribed in the pre-index period or if a new glucose-lowering medication besides linagliptin was prescribed on the index date. Persons could be on stable doses of any approved glucose-lowering medications and combinations of such

medications in the pre-index period. Persons with malignancy or transplants were excluded.

Outcome Measures

The primary outcome variable, change in HbA1c, was calculated by subtracting a person's last pre-index HbA1c from the person's last post-index HbA1c. HbA1c goal was defined as any post-index HbA1c value of < 7% (53 mmol/mol).

Covariates

Demographic variables were age, age categories, sex, race, ethnicity, and US geographic region. Pre-index glucose-lowering medications were identified based on written prescription, medication administration, and medication history records in the EHR (180 days). Persons were categorized into renal function groups based on pre-index estimated glomerular filtration rate (eGFR, ml/min/1.73 m^2) [11].

Statistical Analyses

All study variables, including pre-index and outcome measures, were analyzed descriptively. Continuous measures were compared using *t* tests; categorical measures were compared using chi-square tests. *P* values were not adjusted for multiple comparisons. The change in outcome measures was reported for the overall study population and in the African American cohort in predefined subgroups of persons, including age categories (40–54, 55–64, 65–74, ≥ 75 years), eGFR (< 30, 30–44, 45–59, 60–89, ≥ 90 ml/min/1.73 m^2), and race.

Multivariable modeling assessed the change in HbA1c in the overall sample and in the African American cohort, controlling for an a priori list of covariates. Final adjustments only included variables that affected differences in the unadjusted analyses: age, eGFR, race, and pre-index HbA1c.

Table 1 Baseline characteristics

Characteristic	Value[a]
Mean age (SD), years	64 (11)
Sex	
Women	5603 (51)
Race	
African American	1455 (13.2)
White	8645 (78.6)
Asian	241 (2.2)
Other	660 (6.0)
Ethnicity	
Hispanic	927 (8.4)
Non-Hispanic	9550 (86.8)
Unknown	524 (4.8)
Baseline HbA1c, mmol/mol; mean(SD)/ %; mean (SD)	66 (18)/8.2 (1.6)
Baseline eGFR, ml/min/1.73 m^2; mean (SD)	68.7 (26.8)
Baseline glucose-lowering therapy[b]	
Metformin monotherapy	1993 (18.1)
Sulfonylurea monotherapy	1022 (9.3)
Any use of metformin	5454 (49.6)
Any use of sulfonylureas	3882 (35.3)
Any use of insulin	2816 (25.6)
Other medications	2559 (23.3)
No glucose-lowering medications	2440 (22.2)

eGFR estimated glomerular filtration rate, *HbA1c* glycated hemoglobin, *SD* standard deviation

[a] Values are *n* (%) unless otherwise indicated

[b] Used in > 3% of persons

Baseline = pre-index value

RESULTS

Study Population

Overall, 11,001 persons with T2DM met all inclusion and exclusion criteria and had both

Table 2 Change in HbA1c by demographic and clinical characteristics: overall population

	n	Baseline HbA1c		Unadjusted change in HbA1c		Adjusted LS mean change in HbA1c[a]		% of persons reaching HbA1c 7% (53 mmol/mol)
		mmol/mol mean(SD)	% (SD)	mmol/mol (SD)	% (SD)	mmol/mol	% (SD)	
All	11,001	66 (17.7)	8.17 (1.62)	− 5.6 (16.0)	− 0.51 (1.46)			35.7
Age, years								
40–54	2325	70 (20.2)	8.62 (1.85)	− 7.1 (18.0)	− 0.65 (1.65)	− 3.3	− 0.30	30.3
55–64	3332	67 (18.3)	8.30 (1.67)	− 6.4 (16.8)	− 0.59 (1.54)	− 4.5	− 0.41	35.6
65–74	3077	64 (15.8)	7.96 (1.45)	− 4.7 (14.9)	− 0.43 (1.36)	− 4.5	− 0.41	37.9
≥ 75	2267	62 (14.8)	7.80 (1.35)	− 3.9 (13.2)	− 0.36 (1.21)	− 4.6	− 0.42	38.6
P value[b]		< 0.001		< 0.001		≤ 0.004		< 0.001
eGFR, ml/min/1.73 m^2								
< 30	679	60 (16.4)	7.64 (1.50)	− 2.4 (16.0)	− 0.22 (1.46)	− 3.8	− 0.35	46.7
30–44	1646	63 (16.7)	7.87 (1.53)	− 3.6 (14.6)	− 0.33 (1.34)	− 3.8	− 0.35	38.9
45–59	1727	64 (16.9)	7.98 (1.55)	− 5.1 (15.5)	− 0.47 (1.42)	− 4.8	− 0.44	40.2
60–89	3256	66 (17.1)	8.18 (1.56)	− 6.0 (15.7)	− 0.55 (1.44)	− 4.8	− 0.44	35.7

Table 2 continued

	n	Baseline HbA1c		Unadjusted change in HbA1c		Adjusted LS mean change in HbA1c[a]		% of persons reaching HbA1c 7% (53 mmol/mol)
		mmol/mol mean(SD)	% (SD)	mmol/mol (SD)	% (SD)	mmol/mol	% (SD)	
≥ 90	2603	70 (19.0)	8.57 (1.74)	− 7.7 (17.3)	− 0.70 (1.58)	− 4.7	− 0.43	30.1
P value		< 0.001		< 0.001		0.010		< 0.001
Race								
African American	1455	68 (21.0)	8.42 (1.92)	− 7.4 (18.7)	− 0.68 (1.71)	− 4.8	− 0.44	36.2
White	8645	65 (16.9)	8.12 (1.55)	− 5.2 (15.5)	− 0.48 (1.42)	− 4.4	− 0.40	35.8
Asian	241	64 (17.1)	8.05 (1.56)	− 4.5 (13.8)	− 0.41 (1.26)	− 3.3	− 0.30	35.7
Other	660	67 (18.6)	8.3 (1.7)	− 5.6 (16.0)	− 0.51 (1.46)	− 4.5	− 0.41	33.8
P value		< 0.001		0.001		0.34		0.741

ANOVA analysis of variance, *eGFR* estimated glomerular filtration rate, *HbA1c* glycated hemoglobin, *LS* least squares, *SD* standard deviation

[a] Adjusted for age, race, renal function, and pre-index HbA1c

[b] ANOVA

Table 3 Change in HbA1c by demographic and clinical characteristics: African American cohort

	n	Baseline HbA1c		Unadjusted change in HbA1c		Adjusted LS mean change in HbA1c[a]		% of persons reaching HbA1c < 7% (53 mmol/mol)
		mmol/mol (SD)	% (SD)	mmol/mol (SD)	%	mmol/mol	%	
All	1455	68 (21.0)	8.42 (1.92)	− 7.4 (18.7)	− 0.68 (1.71)	− 7.3	− 0.67	36.2
Age, years								
40–54	346	74 (23.2)	8.87 (2.13)	− 8.5 (20.0)	− 0.78 (1.83)	− 6.3	− 0.58	32.4
55–64	478	70 (21.6)	8.55 (1.98)	− 8.1 (20.0)	− 0.74 (1.83)	− 7.9	− 0.72	35.4
65–74	384	66 (19.7)	8.22 (1.80)	− 7.0 (18.5)	− 0.64 (1.69)	− 9.1	− 0.83	39.8
≥ 75	247	63 (16.1)	7.88 (1.47)	− 5.4 (13.7)	− 0.49 (1.25)	− 9.8	− 0.90	37.6
P value[b]		< 0.001		0.183		0.054		0.189
eGFR, ml/min/1.73 m^2								
< 30	97	61 (19.0)	7.74 (1.74)	− 7.3 (16.5)	− 0.67 (1.51)	− 11.5	− 1.05	59.8
30–44	217	64 (19.3)	8.05 (1.77)	− 4.3 (17.7)	− 0.39 (1.62)	− 6.9	− 0.63	35.0
45–59	230	65 (19.9)	8.14 (1.82)	− 4.7 (17.2)	− 0.42 (1.57)	− 6.3	− 0.58	39.6
60–89	395	69 (21.4)	8.46 (1.96)	− 9.0 (19.6)	− 0.82 (1.79)	− 9.4	− 0.86	38.7

Table 3 continued

	n	Baseline HbA1c		Unadjusted change in HbA1c		Adjusted LS mean change in HbA1c[a]		% of persons reaching HbA1c < 7% (53 mmol/mol)
		mmol/mol (SD)	% (SD)	mmol/mol (SD)	%	mmol/mol	%	
≥ 90	395	74 (21.8)	8.90 (1.99)	− 9.6 (19.3)	− 0.88 (1.77)	− 8.4	− 0.77	28.4
P value		< 0.001		< 0.001		0.020		< 0.001

ANOVA analysis of variance, *eGFR* estimated glomerular filtration rate, *HbA1c* glycated hemoglobin, *LS* least squares, *SD* standard deviation

[a] Adjusted for age, renal function, and pre-index HbA1c

[b] ANOVA

pre-index (baseline) and post-index HbA1c values available. Characteristics of the study cohort are shown in Table 1 and Table S2 in the electronic supplementary material. Background glucose-lowering medication use is summarized in Table 1. About 22% were on no other medications, about 50% on metformin alone or in combination, and about 25% on insulin alone or in combination. There were smaller numbers of persons on various combinations of background medications including three medications ($n = 1153$, 10%) or four or more medications ($n = 330$, 3.0%).

Adjusted and Unadjusted HbA1c Changes: Persons Reaching HbA1c Goal

In the overall population, the unadjusted analysis demonstrated a greater change in HbA1c in younger versus older persons ($P < 0.001$) and those with higher versus lower eGFR ($P < 0.001$) (Table 2). Pre-index HbA1c was higher in younger versus older persons and those with higher versus lower eGFR. African Americans had a greater change in HbA1c versus whites or Asians ($P < 0.001$). In the African American cohort, the unadjusted analyses also demonstrated a greater change in HbA1c in younger versus older persons ($P < 0.001$) and those with higher versus lower eGFR ($P < 0.001$) (Table 3).

The adjusted analyses diminished some of the differences in the unadjusted analyses (*P* values reported). Overall, 36% of all persons achieved an HbA1c goal of < 7% (53 mmol/mol) in the post-index period. The proportion of persons reaching this goal was different across age categories, with fewer younger than older persons reaching goal, and across renal function categories, with fewer persons with higher eGFR reaching goal. The proportion of persons reaching goal was not significantly different across race categories. In the African American cohort, decreases in HbA1c were observed across all age and renal function categories, but small sample size limited statistical comparisons. Changes in HbA1c cross-tabulated by age and renal function are

shown in Table S3 in the electronic supplementary material.

DISCUSSION

This study demonstrates the glycemic effectiveness of linagliptin in adults with T2DM across a range of ages, renal function, and race in a real-world practice setting. These observations expand on previous clinical trial results in smaller groups of persons with renal impairment [6, 8, 12, 13], older age [8, 9, 14], and African American race [10, 15]. HbA1c reductions were different across age and renal function. Such differences are common in real-world studies. Change in HbA1c is often a function of baseline HbA1c (greater reduction with high baseline values). Because of pre-index HbA1c differences across groups, it was important to adjust for this variable. Unadjusted differences across age and renal function categories were attenuated in the adjusted analyses. Importantly, resultant reductions in HbA1c were roughly comparable across all age and renal function categories for the whole group and the African American cohort.

These data add to the observations from other trials of the glycemic efficacy of linagliptin in a broad range of populations characterized by age, declining renal function, and African American race. In addition, linagliptin use in large randomized trials does not increase the risk for renal or cardiovascular disease [16–18]. The main limitation of this study is whether the results are generalizable, especially in some cohorts that are not fully represented.

CONCLUSIONS

The findings in the current study support the use of linagliptin in older persons with T2DM who have concomitant renal compromise in a real-world setting.

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Data Availability. The datasets during and/or analyzed during the current study are available from the corresponding author on reasonable request.

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