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The Use of Decomposition Methods in Real-World Treatment Benefits Evaluation for Patients with Type 2 Diabetes Initiating Different Injectable Therapies: Findings from the INITIATOR Study

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ABSTRACT

Background: Determining characteristics of patients likely to benefit from a particular treatment could help physicians set personalized targets. **Objectives:** To use decomposition methodology on real-world data to identify the relative contributions of treatment effects and patients' baseline characteristics. **Methods:** Decomposition analyses were performed on data from the Initiation of New Injectable Treatment Introduced after Antidiabetic Therapy with Oral-only Regimens (INITIATOR) study, a real-world study of patients with type 2 diabetes started on insulin glargine (GLA) or liraglutide (LIRA). These analyses investigated relative contributions of differences in baseline characteristics and treatment effects to observed differences in 1-year outcomes for reduction in glycated hemoglobin A_{1c} (HbA_{1c}) and treatment persistence. **Results:** The greater HbA_{1c} reduction seen with GLA compared with LIRA (−1.39% vs. −0.74%) was primarily due to differences in baseline characteristics (HbA_{1c} and endocrinologist as prescribing physician; $P < 0.050$). Patients with baseline HbA_{1c} of 9.0% or more or evidence of diagnosis codes related to mental illness achieved greater HbA_{1c} reductions with GLA, whereas patients with baseline polypharmacy (6–10 classes) or hypoglycemia achieved greater reductions with LIRA. Decomposition analyses also showed that the higher persistence seen with GLA (65% vs. 49%) was mainly caused by differences in treatment effects ($P < 0.001$). Patients 65 years and older, those with HbA_{1c} of 9.0% or more, those taking three oral antidiabetes drugs, and those with polypharmacy of more than 10 classes had higher persistence with GLA; patients 18 to 39 years and those with HbA_{1c} of 7.0% to less than 8.0% had higher persistence with LIRA. **Conclusions:** Although decomposition does not demonstrate causal relationships, this method could be useful for examining the source of differences in outcomes between treatments in a real-world setting and could help physicians identify patients likely to respond to a particular treatment.

Keywords: choice, decomposition analysis, insulin glargine, liraglutide, personalized medicine, real-world, type 2 diabetes.

Introduction

Recently published guidelines on the management of type 2 diabetes (T2D) recommend that physicians set targets for glycemic control that are personalized to each individual patient. The target level of glycated hemoglobin A_{1c} (HbA_{1c}) should be practical and achievable for each patient, taking into account factors such as medical history and personal circumstances [1–3].

The choice of HbA_{1c} target is made easier if the physician knows that a patient is likely to benefit from a particular drug therapy. Comparative effectiveness research based on observational data helps to identify effective treatments, and a key component of comparative effectiveness research is to take into account the heterogeneity of the treatment response (i.e., why certain patients respond better than others when given the same treatment) [4]. Various regression methods are commonly used in observational studies to estimate the average treatment response (e.g., change in HbA_{1c}) while adjusting for imbalance in baseline characteristics (e.g., age, sex, and comorbid conditions) between the treated and untreated groups or between two treatment groups. This is most commonly done by using the treatment response as the dependent variable and including treatment (e.g., treatment 1 or 2) and the other covariates (i.e., baseline characteristics) as independent variables. The resulting regression coefficient (i.e., beta) for the treatment term then provides an estimate of the adjusted overall treatment effect

Conflicts of interest: W. Wei is an employee of Sanofi US. L. Brekke and E. Buysman are employees of Optum, under contract with Sanofi US. M. Grabner and X. Ke are employees of HealthCore, Inc., under contract with Sanofi US, for the conduct of this study. L. Xie and O. Baser are employees of STATinMED Research, under contract with Sanofi US.

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(i.e., difference between the two treatments). These regression methods have well-known limitations including possible bias from unmeasured confounders and model mis-specification, but are widely used.

Standard regression methods can be expanded to estimate heterogeneity of the treatment response by including interactions between the treatment variable and the other covariates that may affect the response. The regression coefficient of a particular treatment-covariate interaction is then an estimate of the effect of the covariate on treatment response. Although a valid approach, the many interaction terms used in this method may be difficult to interpret. The impact of the interaction terms on a specific population is often particularly difficult to understand from the model results without further analysis. These issues can make exploring heterogeneity of response through interactions challenging.

"Decomposition" is an alternative regression method for comparing two groups that, in our context, can be used for estimating the heterogeneity of treatment response while avoiding the use of treatment interaction terms. It also directly gives estimates of the average effect of each covariate on the treatment response within the study population, which is useful for interpretation. This methodology is often called the Blinder-Oaxaca decomposition, named after the developers of the technique as originally applied to wage discrimination [5,6]. Decomposition can be applied both to continuous and categorical outcomes and to linear and nonlinear regression models [5–9]. In decomposition, instead of the interaction terms a stratified regression is performed; that is, separate regressions are estimated for treatment 1 and treatment 2 groups. In both models, the dependent variable is again the response variable (e.g., change in HbA_{1c}) and both regressions have the same set of independent covariates that may affect the response. But there are no "treatment" terms in the regressions because the regressions are all either on the treatment 1 subpopulation or on the treatment 2 subpopulation.

The information that would be contained in the interaction terms of a single regression model is still present in the decomposition models but it is now contained in the differences in the regression coefficients between the two models—the treatment 1 model versus the treatment 2 model. To make that information explicit, the decomposition method rearranges the regression equations to separate out two components of the difference in response between the treatment 1 and treatment 2 groups: a component coming from differences in baseline characteristics (often called the "explained" part in the decomposition literature because it is explained by observed differences in the baseline characteristics) and a component coming from differences in the regression coefficients (often called the "unexplained" part in the decomposition literature because it is not explained by observed differences in the baseline characteristics). In our context, in which one regression is on treatment 1 subjects and the other is on treatment 2 subjects, the unexplained part is the treatment effect that would come from the interactions with treatment in the more standard single regression approach but evaluated using the mean covariates from just one of the populations (e.g., population 2) [10]. In particular, if the treatment effects vanish in the standard regression method (i.e., there are no differences between the treatment coefficients), then the unexplained part will also vanish. Thus, the terms "unexplained part" and "treatment effects" are used interchangeably in this article. As a regression-based method, however, the decomposition method has the same possibility of biases from mis-specification and unmeasured confounders as other regression techniques and thus one must be similarly cautious in the interpretation of the treatment effects coming from the models —they indicate relationships in the current data and thus warrant further investigation but they may or may not correspond to true causal relationships. The method relies on the treatment 1 regression results giving an accurate description when applied to the treatment 2 population and vice versa. This may be particularly problematic if the covariate distributions in the two populations do not have a similar range of values, in which case more extrapolation is required. Additional details about the decomposition method are given in the Methods section.

An opportunity to apply decomposition analysis to real-world data from the field of diabetes care recently arose: the 26-week, randomized controlled Liraglutide Effect and Action in Diabetes 5 (LEAD-5) trial indicated that when added to metformin and sulfonylurea, treatment with liraglutide (LIRA; a once-daily glucagon-like peptide 1 receptor agonist) resulted in significant improvements in glycemic control and body weight compared with insulin glargine (GLA) [11]. LIRA reduced HbA_{1c} significantly compared with GLA (1.33% vs. 1.09%; $P = 0.0015$) and was also associated with greater weight loss (treatment difference −3.43 kg; $P < 0.0001$) as well as with higher frequency of gastro-intestinal adverse events. The Initiation of New Injectable Treatment Introduced after Antidiabetic Therapy with Oral-only Regimens (INITIATOR) study was designed and conducted to see whether this finding from the LEAD-5 study translated into the real-world setting. This large, observational, longitudinal study assessed the characteristics and 1-year outcomes of patients with T2D started on injectable therapy with either GLA (administered via prefilled disposable pen) or LIRA [12,13].

The objective of this present analysis was to use decomposition methodology on real-world data from the INITIATOR study to identify the relative contributions of treatment effects and patients' baseline characteristics to observed differences in response to the two treatments. Response was assessed in two ways: change in HbA_{1c} and treatment persistence.

Methods

Study Design and Patients

Commercial health care claims data linked to laboratory results were extracted from two large, independent administrative claims databases associated with Optum™ and HealthCore® in the United States. Data from these two databases include medical claims, pharmacy claims, and laboratory results; both databases have been used in hundreds of peer-reviewed publications across multiple therapeutic areas. Data were obtained for all patients with T2D 18 years and older, previously on oral antidiabetes drugs (OADs) only, with a baseline HbA_{1c} of 7.0% or more, and who initiated (using a 6-month washout period) either GLA (administered via prefilled disposable pen) or LIRA between April 1, 2010, and March 31, 2012. The administrative claims and laboratory results were complemented by information from medical charts; patients were excluded if a medical chart was not available. The index date was defined as the earliest prescription fill date. T2D was defined as having one or more inpatient/emergency department medical claim or two or more ambulatory medical claims (≥30 days apart) with a primary or secondary *International Classification of Diseases, Ninth Revision, Clinical Modification* code for T2D (250.x0 or 250.x2) [14].

In addition, patients included in the study were required to have one or more pharmacy claim for an OAD during the baseline period and to have had continuous health care coverage during the 6 months before (baseline) and the 12 months after initiation (follow-up) (Fig. 1).

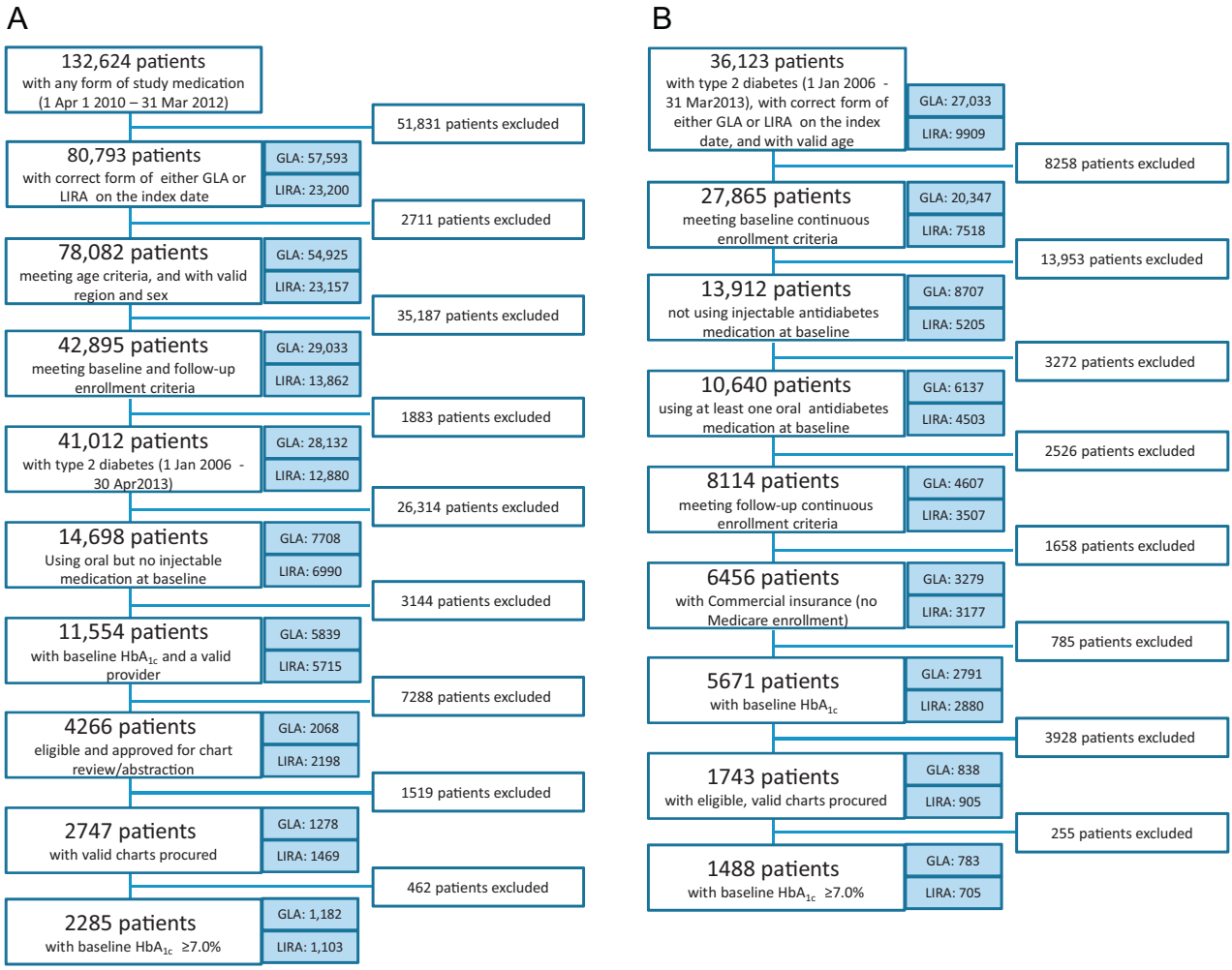


Fig. 1 – Attrition diagrams for the patients from the (A) Optum and (B) HealthCore databases. GLA, glargine; HbA_{1c}, glycated hemoglobin A_{1c}; LIRA, liraglutide.

Outcome Measures

Change in HbA_{1c} between baseline and follow-up was calculated for all patients with available results. The HbA_{1c} measurement closest to the index date (but not later than 15 days after the index date) was chosen as the baseline value; the follow-up value was chosen as the measurement closest to the index date plus 359 days (1-year follow-up) and within the range of index date plus 269 days through index date plus 449 days (90 days before and after the end of 1-year follow-up). Treatment persistence was defined as the percentage of patients remaining on therapy without discontinuation for the duration of the 1-year follow-up period. Study medication was considered to have been discontinued if a prescription was not refilled within the expected time of medication coverage (the 90th percentile of time between the first and second prescriptions among patients with more than one prescription, stratified by the metric quantity supplied and irrespective of postindex eligibility). Patients who restarted their index medication after discontinuing during the follow-up period were considered nonpersistent [12,13,15].

Statistical Analyses

Baseline variables were compared between GLA and LIRA cohorts using Student t tests or χ^2 tests, depending on the distribution of the measure.

To model the outcomes for the decomposition analyses, regressions adjusted by baseline covariates were run separately on each of the two cohorts (linear regression for HbA_{1c} reduction and logistic regression for treatment persistence). Then, the following equation was used, where subscript 1 denotes the GLA cohort and subscript 2 denotes the LIRA cohort:

$$\overline{Y}_1-\overline{Y}_2=\left(\overline{F\left[\sum X_1\,\beta_1\right]}-\overline{F\left[\sum X_2\,\beta_1\right]}\right)+\left(\overline{F\left[\sum X_2\,\beta_1\right]}-\overline{F\left[\sum X_2\,\beta_2\right]}\right),$$

where $\overline{Y}_1$ and $\overline{Y}_2$ are average predicted values, $\Sigma X_i\beta_j$ denotes the sum of covariates from population $i\,(X_i)$ times beta coefficients from regression of population $j\,(\beta_j)$, and $F[Z]$ is a nonlinear function that depends on the type of model being used. For change in HbA_{1c}, where ordinary least-squares regression was used, $F[Z] = Z$. For persistence, where logistic regression was used, $F[Z]$ was the inverse logistic function. The bar over the $\Sigma X_i\beta_j$ terms denotes the average over population i.

The equation describes how the differences in outcomes between the two groups ($\overline{Y}_1 - \overline{Y}_2$) are accounted for by explained factors (caused by differences in baseline characteristics):

$$\left(\overline{F\left[\sum X_1\,\beta_1\right]}-\overline{F\left[\sum X_2\,\beta_1\right]}\right),$$

and by unexplained factors (caused by differences in treatment effects):

$$\left(\overline{F\left[\sum X_2\,\beta_1\right]} - \overline{F\left[\sum X_2\,\beta_2\right]}\right).$$

Thus, the explained part is the change in average predicted values when the covariate values are changed from observed population 1 values to observed population 2 values but the regression coefficients (betas) are held fixed (with values from the population 1 regression). The unexplained part is the change in average predicted values when the covariate values are held fixed (with values from population 2) but the regression coefficients are changed from the values from the population 1 regression to the values from the population 2 regression. The unexplained part is thus the treatment effect as applied to population 2. The "overall" explained and unexplained parts can be further broken down into individual terms because of particular covariates. These are called "detailed" explained and unexplained decompositions. For linear regression the detailed decompositions are the individual terms from the $\Sigma X_i\beta_j$ sums corresponding to each particular covariate, that is, $\beta_1(\bar{x}_1 - \bar{x}_2)$ for explained decomposition and $\bar{x}_2(\beta_1 - \beta_2)$ for unexplained decomposition. For the logistic regression, the detailed decompositions were estimated using the method given by Yun [16].

The baseline variables included as independent variables in the regressions were age, sex, US region, HbA_{1c}, body mass index, OAD class count, Quan-modified Charlson comorbidity index score, specialty of index prescribing physician, any diabetes-related inpatient hospitalization, any diabetes-related emergency department visit, number of ambulatory visits, hypertension, hyperlipidemia, neuropathy, retinopathy, mental illness, polypharmacy as the number of therapeutic classes of medications prescribed (0–5, 6–10, or 10+), any hypoglycemia event, and a flag for notes in the medical chart of improving weight control as the reason for initiating index therapy.

Data were analyzed using SAS 9.3 software (SAS Institute, Inc., Cary, NC) [17]. The oaxaca package for the STATA software system (StataCorp LP, College Station, TX) [18] was used to run all decomposition modeling and analyses (oaxaca was originally written by Jann [7], updated version August 2011). (See Ref. [7] and oaxaca documentation for details about how to run the package.)

Results

Demographic and Clinical Characteristics of the INITIATOR Patient Population

A total of 3773 patients with T2D were included in this analysis (Fig. 1). Overall, women comprised 43.9% of the patient population, mean age was 52.5 years, and the mean number of OADs filled at baseline was 2. The number of patients in the final sample who had complete data for follow-up HbA_{1c} and all covariates that were included in the analysis of follow-up HbA_{1c} was 2166 (57.4%).

The two groups showed some differences in baseline characteristics (Table 1). Patients in the GLA prefilled disposable-pen group had a higher mean burden of comorbidity (as shown by the Quan-modified Charlson comorbidity index score), higher mean HbA_{1c}, and lower mean body weight; in addition, a greater proportion of this group was male. Patients in the LIRA group had a higher mean body weight and were more likely to have "improve weight control" recorded by their physician as a reason for treatment initiation (17.8% in the LIRA group compared with 3.5% in the GLA group) ($P < 0.001$).

HbA_{1c}: Main Findings and Decomposition

The final sample with complete information on all covariates of interest had 2166 patients for the decomposition analysis of the "HbA_{1c} changes" outcome. There was a significantly greater 1-year reduction in HbA_{1c} in patients in the GLA prefilled disposable-pen group (−1.39%) compared with patients in the LIRA group (−0.74%). Overall, the decomposition analysis revealed that the difference between the two groups (−0.65%) was largely due to the differences in baseline population characteristics (the explained part: −0.73%; $P < 0.001$). This was offset by a small and nonsignificant effect caused by differences in treatment effects (the unexplained part: 0.09%) (Table 2).

Detailed decomposition analysis of the explained part of the HbA_{1c} change identified the following significant baseline factors:

1. Baseline HbA_{1c} of 7.0% to less than 8.0%: This accounted for a difference of −0.191 ($P = 0.001$), which is 26.2% of the explained difference and 29.6% of the total difference between the two groups. This difference in change in HbA_{1c} is driven by the higher proportion of baseline HbA_{1c} of 7.0% to less than 8.0% in the LIRA group (37.2%) compared with the GLA group (15.5%). Higher proportions of baseline HbA_{1c} of 7.0% to less than 8.0% are associated with smaller reductions in HbA_{1c}.
2. Baseline HbA_{1c} of 8.0% to less than 9.0%: This accounted for a difference of −0.037 ($P = 0.003$), which is 5.1% of the explained difference and 5.8% of the total difference between the two groups. This difference in change in HbA_{1c} is driven by the higher proportion of baseline HbA_{1c} of 8.0% to less than 9.0% in the LIRA group (29.8%) compared with the GLA group (20.7%). Higher proportions of baseline HbA_{1c} of 8.0% to less than 9.0% are associated with smaller reductions in HbA_{1c}.
3. Baseline HbA_{1c} of 9.0% or more: This accounted for a difference of −0.398 ($P = 0.001$), which is 54.5% of the explained difference and 61.7% of the total difference between the two groups. This difference in change in HbA_{1c} is driven by the lower proportion of baseline HbA_{1c} of 9.0% or more in the LIRA group (33.0%) compared with the GLA group (63.8%). Higher proportions of baseline HbA_{1c} of 9.0% or more are associated with larger HbA_{1c} reductions. On the basis of the decomposition analyses of different baseline HbA_{1c} groups, the results showed that lower levels of baseline HbA_{1c} are associated with smaller reductions in HbA_{1c}.
4. Having an endocrinologist as the index prescribing physician (as opposed to a primary care physician or a health care professional from another specialty): This accounted for a difference of 0.028 ($P = 0.014$), which is −3.9% of the explained difference and −4.4% of the total difference between the two groups (the negative sign indicates that this contributed toward making the total difference between groups smaller rather than larger). This difference in change in HbA_{1c} is driven by the higher proportion of endocrinologists in the LIRA group (26.9%) compared with the GLA group (18.4%). Higher proportions of endocrinologists are associated with greater reductions in HbA_{1c}.
5. Detailed decomposition analysis of the (overall nonsignificant) unexplained part of the HbA_{1c} change (the part of the change attributed to differences in treatment effects rather than to differences in baseline characteristics) showed that patients with baseline HbA_{1c} of 9.0% or more or who had diagnosis codes of mental illness achieved greater 1-year reductions in HbA_{1c} when taking GLA than when taking LIRA. In contrast, patients with baseline polypharmacy of 6 to 10 classes or any hypogylcemia achieved greater 1-year reductions in HbA_{1c} when taking LIRA than when taking GLA (Fig. 2).

Table 1 – Baseline demographic and clinical characteristics of patients in the INITIATOR study (N = 3773).

Characteristic	GLA (n = 1965)	LIRA (n = 1808)	P value
Age (y), mean ± SD	53.0 ± 8.80	51.9 ± 8.76	<0.0001
Sex, n (%)*			
Male	1143 (58.2)	975 (53.9)	0.0087
Female	822 (41.8)	833 (46.1)	0.0087
Duration of disease (y), mean ± SD	7.33 ± 7.60	6.57 ± 5.52	0.1011
Health plan type, n (%)*			
HMO	327 (16.6)	265 (14.7)	0.0941
POS	976 (49.7)	890 (49.2)	0.7854
PPO	517 (26.3)	495 (27.4)	0.4595
Other	145 (7.4)	158 (8.7)	0.1247
Body weight (kg), mean ± SD	101.0 ± 23.3	110.9 ± 24.1	<0.0001
HbA_{1c} (%), mean ± SD	9.97 ± 1.94	8.76 ± 1.52	<0.0001
Prescribing physician, n (%)*			
Endocrinologist	367 (18.7)	454 (25.1)	<0.0001
Primary care physician	1367 (69.6)	1157 (64.0)	0.0003
OADs, n (%)*			
Metformin	1559 (79.3)	1506 (83.3)	0.0019
DPP-4 inhibitors	762 (38.8)	723 (40.0)	0.4471
Meglitinides	57 (2.9)	51 (2.8)	0.8830
Sulfonylureas	1211 (61.6)	954 (52.8)	<0.0001
Thiazolidinediones	613 (31.2)	589 (32.6)	0.3629
Alpha-glucosidase inhibitors	16 (0.8)	8 (0.4)	0.1513
Number of OADs per patient, mean ± SD	2.15 ± 0.90	2.12 ± 0.91	0.3474
Comorbidities, n (%)*			
Myocardial infarction	43 (2.2)	22 (1.2)	0.0220
Congestive heart failure	68 (3.5)	40 (2.2)	0.0216
Renal disease	117 (6.0)	64 (3.5)	0.0005
Hypoglycemia	46 (2.3)	32 (1.8)	0.2181
Neuropathy	158 (8.0)	118 (6.5)	0.0744
Nephropathy	74 (3.8)	67 (3.7)	0.9225
Retinopathy	152 (7.7)	100 (5.5)	0.0067
Obesity†	1119 (71.2)	1248 (86.8)	<0.0001
Quan-modified CCI, mean ± SD	0.86 ± 1.48	0.63 ± 1.17	<0.0001
Weight control as the reason for initiating index therapy, n (%)*	68 (3.5)	322 (17.8)	<0.0001
Total diabetes-related costs ($), mean ± SD per patient	3260 ± 11,894	2084 ± 4513	<0.0001

BMI, body mass index; CCI, Charlson comorbidity index; DPP-4, dipeptidyl peptidase 4; GLA, glargine; HbA_{1c}, glycated hemoglobin A_{1c}; HMO, health maintenance organization; LIRA, liraglutide; POS, point of service; PPO, preferred provider organization; OADs, oral antidiabetes drugs.
* Dichotomous or categorical variables were compared using χ^2 tests (continuous variables were compared using Student *t* tests).
† Obesity is defined as BMI ≥ 30 kg/m^2 in the subset of patients with BMI available (n = 1572 for GLA and n = 1438 for LIRA).

Treatment Persistence: Main Findings and Decomposition

The final sample with complete information on all covariates of interest consisted of 3010 patients for the decomposition analysis of the treatment persistence outcome. Treatment persistence at 1 year was found to be significantly higher in the GLA group (64.8%) compared with the LIRA group (48.7%). Overall decomposition analysis showed that the difference between the two groups (16.1%) was largely due to differences in treatment effects (the unexplained part: 17.9%; $P < 0.001$). This was offset by a small and nonsignificant effect caused by differences in baseline characteristics (the explained part: −1.8%) (Table 3).

Detailed decomposition analysis of the explained part of the difference in persistence between the two groups identified one significant baseline factor: diabetes-related inpatient

Table 2 – HbA_{1c} changes: Results of overall decomposition analysis at 1 y (N = 2166).

	GLA (n = 1107)	LIRA (n = 1059)	Difference (GLA – LIRA)	Explained difference (attributed to differences in baseline characteristics)	Unexplained difference (attributed to differences in treatment effects)
Mean HbA_{1c} change (%)	−1.387	−0.742	−0.645	−0.730	0.085
P value	<0.001	<0.001	<0.001	<0.001	0.434

GLA, glargine; HbA_{1c}, glycated hemoglobin A_{1c}; LIRA, liraglutide.

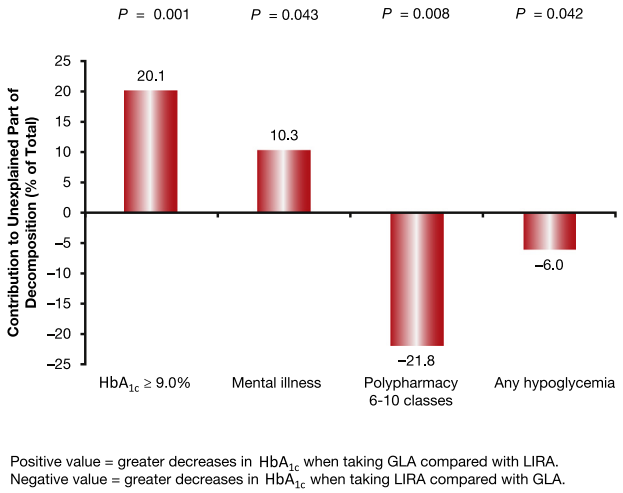


Fig. 2 – Contribution of treatment effects to reductions in HbA_{1c}. Other baseline factors adjusted in the decomposition analysis were age, sex, region, other HbA_{1c} categories, body mass index, other OAD count categories, Charlson comorbidity index, comorbid conditions, prescriber of index drug, health care resource utilization, polypharmacy, hypoglycemia, and use of index drug for body weight control. GLA, glargine; HbA_{1c}, glycated hemoglobin A_{1c}; LIRA, liraglutide; OAD, oral antidiabetes drug.

hospitalization accounted for a difference of −0.007% of the persistence rate ($P = 0.018$), which is −4.06% of the total difference between the groups.

Detailed decomposition analysis of the unexplained part of the difference in persistence showed that patients who were older (aged ≥65 years), and those with baseline HbA_{1c} of 9.0% or more, an OAD class count of 3, or with polypharmacy of more than 10 classes, had a higher rate of persistence with GLA compared with similar patients taking LIRA. Patients who were younger (aged 18–39 years), and those with baseline HbA_{1c} of 7.0% to less than 8.0%, had a higher rate of persistence with LIRA than with GLA (Fig. 3).

Discussion

The application of decomposition analysis to real-world data from the INITIATOR study suggested that differences in patients' baseline characteristics contributed most to the observed 1-year difference in effects on HbA_{1c} between the GLA and LIRA groups. Differences in treatment effects, however, appeared to contribute most to the observed difference in 1-year persistence between the two groups.

If verified by additional research, both these main findings could have potential implications for the future management of patients with T2D in terms of the personalized selection of treatment for individual patients. For HbA_{1c} control, patients with a high baseline HbA_{1c} and patients with evidence of diagnosis codes related to mental illness might benefit more from taking GLA to achieve greater 1-year reductions compared with taking LIRA. In contrast, patients with polypharmacy (6–10 classes) or with any baseline hypoglycemia might benefit more from taking LIRA to achieve greater 1-year reductions in HbA_{1c} rather than taking GLA.

For improving treatment persistence, care for patients 65 years or older, those with a high baseline HbA_{1c}, those taking three different classes of OADs, and those with polypharmacy (>10 classes) might be personalized to achieve a higher 1-year rate of treatment persistence by recommending GLA. Patients aged 18 to 39 years and those with baseline HbA_{1c} of 7.0% to less than 8.0% might be personalized to achieve a higher 1-year rate of persistence by taking LIRA.

This study suggests that decomposition can usefully be applied to real-world data in the clinical setting to examine the source of differences in outcomes between two pharmaceutical treatments. Blinder-Oaxaca decomposition is an established method for investigating differences between groups. A review of published articles reveals that it has been used, among others, to identify factors that contribute to the gap in nutrition between poor and nonpoor children in India [19], the poorer health status of women compared with men [20], sex differences in disability in older adults [21], inequalities in health between indigenous and nonindigenous populations in India [22], and different uptake rates for cervical screening with Papanicolaou test in Canada and the United States [23].

Decomposition has also been used to investigate factors contributing to economic inequalities in visual impairment [24] and eye care utilization [25] in Iran, infant mortality in Iran [26], differences in the prevalence and severity of chronic health conditions in Spain [27], differences in health care use among Mexican immigrants in California [28], racial disparities in access to preventive dental care in South Africa [29], differences in the costs of health care for gastroesophageal reflux disease among patients with chronic obstructive pulmonary disease [30], and racial disparities in access to weight-related counseling during preventive health care visits in the United States [31]. Decomposition has also been previously suggested for use in comparing pharmaceutical treatments, although it is not yet widely used [10,32]. One particular advantage of this method is that it quantifies the proportion that each covariate contributes to the differences in the observed outcomes. This representation of the results may improve decision making in personalized selection of treatment and help patients realize greater treatment effectiveness on the basis of their individual conditions.

Limitations of the present study include the fact that it is retrospective and observational. This means that the analyses may be subject to selection bias and confounding, and that it is difficult to establish the causality of drug effects on the observed outcomes. The data used in the analyses were obtained from a managed care population of patients with T2D and required the availability of complete data for the analysis; this may not necessarily be representative of patients with T2D overall, so caution is needed before extrapolating the findings to a wider population. When comparing the baseline demographic characteristics of the population with data for follow-up HbA_{1c} and all covariates that were included in the follow-up HbA_{1c} analysis with those of patients who were not included in the analysis, some differences were observed. Even though these differences reach statistical significance, one could argue about the clinical relevance of the differences (see Appendix Table 1 in Supplemental Materials found at http://dx.doi.org/10.1016/j.jval.2017.05.019).

Decomposition, being a regression-based method, can suffer bias from unmeasured confounders and mis-specification of the model. The exact decomposition is also not unique, depending on the choice of reference group and the choice of method for detailed decomposition in the nonlinear model case. Different choices may, in some cases, slightly alter one's interpretation of the results. The decomposition method uses the same information as is present in a single regression including interactions of treatment with all other covariates. The exact same beta coefficients can in fact be calculated using either the two stratified models or the single interacting model. In that sense the two methods are equivalent. There can be some differences in

Table 3 – Treatment persistence: Results of overall decomposition analysis at 1 y (N = 3010).

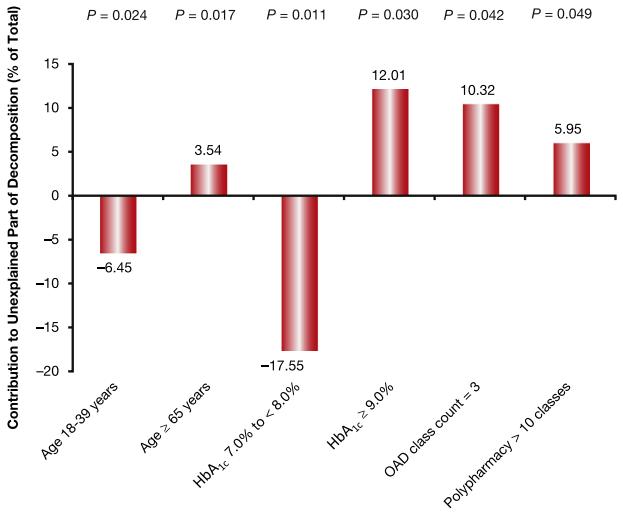
	GLA (n = 1572)	LIRA (n = 1438)	Difference (GLA − LIRA)	Explained difference (attributed to differences in baseline characteristics)	Unexplained difference (attributed to differences in treatment effects)
Mean persistence (%)	64.8	48.7	16.1	−1.8	17.9
P value	<0.001	<0.001	<0.001	0.215	<0.001

GLA, glargine; LIRA, liraglutide.

standard errors calculated with standard statistical packages in the two methods but because the coefficients themselves match for any sample, bootstrapping techniques, for example, applied to both models appear guaranteed to produce identical standard errors. Given this equivalence, the stratification in decomposition itself does not appear to mitigate multicollinearity concerns arising from the many interaction terms in the interacting single model, although there are some contradictory statements in the literature [10,32]. Either method requires sufficient sample size and covariate variation within cohorts to accurately estimate all the required terms in both cohorts. There must also be sufficient covariate distribution overlap with good model fit so that the beta coefficients from one cohort can be used to accurately represent the outcome based on the covariate distributions of the other cohort.

Also, we used a specific empirical method for calculating persistence, and it is unknown whether other methods would have different results. The expected time of medication coverage is defined in our article as the 90th percentile of time between the first and second prescriptions among patients with more than one prescription, stratified by the metric quantity supplied and irrespective of postindex eligibility. This percentile of time was then used to determine whether a given patient was considered persistent or not. Sensitivity analyses were conducted using the 75th and the 95th percentiles to calculate the expected time of medication coverage, but were analyzed only descriptively because results were consistent using the three different percentiles in the descriptive analysis. The baseline characteristics of patients included in the cohort with data for all covariates included in the follow-up persistence analysis are compared with those of patients not included in this sample in Appendix Table 2 in Supplemental Materials found at http://dx.doi.org/10.1016/j.jval.2017.05.019.

Finally, pharmacy claims data were used to estimate the level of persistence with therapy. These data show that prescriptions have been filled, but not that the therapies were actually taken as prescribed; this remains a potential source of error. Another source is the reliance on health care claims data, which are always potentially subject to coding errors on data entry. Our study, however, linked the claims data to medical charts, allowing for a much richer description of patient characteristics (e.g., body mass index). This study is also one of the first to apply multivariable decomposition analysis to pharmaceutical treatments in a real-world setting; therefore, potential inherent flaws to this approach remain to be determined. Possible future applications for decomposition analysis to pharmaceutical treatments could include validation using various types of data for different diseases and treatments of interest.



Positive value = greater increases in persistence when taking GLA compared with LIRA.
Negative value = greater increases in persistence when taking LIRA compared with GLA.

Fig. 3 – Contribution of treatment effects to persistence. Other baseline factors adjusted in the decomposition analysis were other age categories, sex, region, other HbA_{1c} categories, body mass index, other OAD count categories, Charlson comorbidity index, comorbid conditions, prescriber of index drug, health care resource utilization, polypharmacy, hypoglycemia, use of index drug for body weight control, and patient-paid amount for index therapy. GLA, glargine; HbA_{1c}, glycated hemoglobin A_{1c}; LIRA, liraglutide; OAD, oral antidiabetes drug.

Conclusions

This study suggests that decomposition analysis could be a useful tool for examining the source of differences in outcomes between two pharmaceutical treatments in a real-world setting. Differences in baseline characteristics (the explained component) between the two treatment groups contributed most to differences in HbA_{1c} outcomes at 1 year, whereas differences in treatment effects (the unexplained component) contributed most to differences in treatment persistence.

If the validity of decomposition results is confirmed in future studies, detailed decomposition of the unexplained differences in outcomes between two drug therapies could serve as a solid evidence base for practicing personalized medicine, helping physicians identify patients who may be more likely to respond to a particular treatment.

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Supplemental Materials

Supplemental material accompanying this article can be found in the online version as a hyperlink at http://dx.doi.org/10.1016/j.jval.2017.05.019 or, if a hard copy of article, at www.valueinhealthjournal.com/issues (select volume, issue, and article).

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