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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).