

## Understanding Heterogeneity in Response to Antidiabetes Treatment: A *Post Hoc* Analysis Using SIDES, a Subgroup Identification Algorithm

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### Abstract

#### Background:

Treatment response in patients with type 2 diabetes mellitus (T2DM) varies because of different genotypic and phenotypic characteristics. Results of clinical trials are based largely on aggregated estimates of treatment effect rather than individualized outcomes. This research assessed heterogeneity and differential treatment response using the subgroup identification based on differential effect search (SIDES) algorithm with data from a large multinational study.

#### Methods:

This was a retrospective analysis of the DURABLE trial, a randomized, open-label, two-arm, parallel study. The trial enrolled 2091 insulin-naïve T2DM patients aged 30 to 80 years. Patients received twice-daily insulin lispro mix 75/25 (LM75/25) or once-daily insulin glargine (insulin glargine). The SIDES methodology was used to find subgroups where the treatment effect was substantially different from what was observed in the full population of the clinical trial. A subgroup identification tool implementing the SIDES algorithm was used to examine data for 1092 patients (584 LM75/25 and 508 insulin glargine), achieving at-goal 12- or 24-week glycated hemoglobin A1c (A1C) ( $\leq 7.0\%$ ).

#### Results:

The overall at-goal population treatment difference (A1C reduction) was not clinically meaningful, but a clinically meaningful difference was observed (A1C reduction  $2.31\% \pm 0.06\%$  LM75/25 versus  $2.01\% \pm 0.07\%$  insulin glargine;  $p = .001$ ) in patients with a baseline fasting insulin level  $>11.4 \mu\text{IU/ml}$  and age  $\leq 56$  years.

#### Conclusion:

The observation that younger patients with higher levels of fasting insulin may benefit from a regimen that includes short-acting insulin targeting postprandial glycemia helps explain the heterogeneity in response and warrants further investigation.

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**Abbreviations:** (A1C) glycated hemoglobin A1c, (BMI) body mass index, (DURABLE) Assessing the DURABILITY of Basal versus Lispro mix 75/25 insulin Efficacy, (insulin glargine) once-daily insulin glargine, (OAM) oral antidiabetic medication, (SIDES) subgroup identification based on differential effect search, (SIT) subgroup identification tool, (SD) standard deviation, (T2DM) type 2 diabetes mellitus

**Keywords:** differential treatment response, heterogeneity, insulin, predictors of treatment effect, subgroup identification based on differential effect search, subgroup identification

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