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ORIGINAL ARTICLES

Characterization of Cardiovascular Outcomes in a Type 2 Diabetes Glucose Supply and Insulin Demand Model

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Abstract

Background:

The nonsignificant reduction in macrovascular outcomes observed in Action to Control Cardiovascular Risk in Diabetes; Action in Diabetes and Vascular Disease: Preterax and Diamicron Modified Release Controlled Evaluation; and the Veterans Affairs Diabetes Trial have collectively created uncertainty with respect toward the proper extent of blood glucose reduction and also the optimal therapeutic choice to attain the reduction. In the article entitled "Glucose Supply and Insulin Demand Dynamics of Antidiabetic Agents" in this issue of *Journal of Diabetes Science and Technology*, we presented data for a pharmacokinetic/pharmacodynamic model that characterizes the effect of conventional antidiabetic therapies on the glucose supply and insulin demand dynamic. Here, it is our objective to test the hypothesis that, in conjunction with hemoglobin A1c (HbA1c), patients managed on the glucose supply side of the model would have fewer cardiovascular events versus those managed on the insulin demand side.

Methods:

To test this hypothesis, the electronic medical records of a group model health maintenance organization were queried to compile a population of patients meeting the following inclusion criteria: (1) type 2 diabetes mellitus (T2DM), (2) known date of T2DM diagnosis; (3) ICD-9 or CPT code identification and chart review confirmation of a first major cardiovascular event (myocardial infarction, coronary artery bypass graft, or angioplasty), (4) five years of continuous eligibility, and (5) on antidiabetic therapy at the beginning of the 5-year observation period. These patients were subsequently matched (1:1) to T2DM patients meeting the same criteria who had not experienced an event and were analyzed for differences in glucose control (HbA1C), the glucose supply:insulin demand dynamic (SD ratio), and categorical combinations of both parameters.

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Abbreviations: (ACCORD) Action to Control Cardiovascular Risk in Diabetes, (ADVANCE) Action in Diabetes and Vascular Disease: Preterax and Diamicron Modified Release Controlled Evaluation, (BMI) body mass index, (CE) carbohydrate exposure, (DPP-IV) dipeptidyl peptidase-4, (GNG) gluconeogenesis, (HbA1c) hemoglobin A1c, (HGU) hepatic glucose uptake, (IR) insulin resistance, (PGU) peripheral glucose uptake, (PIE) peripheral insulin exposure, (SD) glucose supply:insulin demand, (T2DM) type 2 diabetes mellitus, (TG) triglycerides, (VADT) Veterans Affairs Diabetes Trial

Keywords: cardiovascular outcomes, glucose, insulin, pharmacodynamics, pharmacokinetics

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Abstract cont.

Results:

Fifty cardiovascular event patients met inclusion criteria and were matched to controls. No difference was observed for the average HbA1c or SD ratio between patients experiencing an event and controls (7.5 ± 1.0% versus 7.3 ± 0.9%, $p = .275$, and 1.2 ± 0.3 versus 1.3 ± 0.3, $p = .205$, respectively). Likewise, for categorical representations, there were no differences in event rate at the pre-identified breakpoints (HbA1c ≥7% versus <7%; 72% versus 64%, $p = .391$, and SD ratio ≥1 versus <1; 68% versus 76%, $p = .373$, ≥1.25 versus <1.25; 42% versus 56%, $p = .161$, ≥1.5 versus <1.5; 22% versus 30%, $p = .362$, respectively). Analyzing the combined effect of glucose control and the SD dynamic, patients managed at higher glucose values and on the insulin demand side of the model (HbA1c ≥7% and SD ratio <1.25) tended to have greater cardiovascular risk than those managed at an HbA1c <7%, or HbA1c ≥7% with an SD ratio ≥1.25 (61% versus 39%; $p = .096$).

Conclusion:

Independently, more aggressive HbA1c reduction and higher SD ratio values were not independently associated with a reduction in cardiovascular outcomes. Combining the parameters, it would appear that patients managed at higher glucose values and on the insulin demand side of the model may have increased cardiovascular risk. Based on these findings, it is pertinent to conduct subsequent works to refine SD ratio estimates and apply the model to larger, long-term T2DM cardiovascular outcome trials.

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