Journal of Diabetes Science and Technology
Volume 4, Issue 2, March 2010

ORIGINAL ARTICLES

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

Scott V. Monte, Pharm.D., Jerome J. Schentag, Pharm.D., Martin H. Adelman, Ph.D., and Joseph A. Paladino, Pharm.D., FCCP

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.

continued →

Author Affiliation: CPL Associates, LLC, Amherst, New York

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

Corresponding Author: Scott V. Monte, Pharm.D., CPL Associates, LLC, 3980 Sheridan Drive, Suite 501, Amherst, NY 14226; email address smonte@cplassociates.com

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.

J Diabetes Sci Technol 2010;4(2):382-390

Background

The nonsignificant reductions in macrovascular outcomes observed in Action to Control Cardiovascular Risk in Diabetes (ACCORD),[1] Action in Diabetes and Vascular Disease: Preterax and Diamicron Modified Release Controlled Evaluation (ADVANCE),[2] and Veterans Affairs Diabetes Trial (VADT)[3] have collectively created uncertainty with respect toward the extent of blood glucose reduction and also the optimal therapeutic choice to attain the reduction. The ACCORD trial demonstrated that patients randomized to intensive treatment [hemoglobin A1c (HbA1c) = 6.4%] had an increased mortality and did not have significant reductions in major cardiovascular events as compared to standard therapy (HbA1c = 7.5%), ADVANCE demonstrated that intensive therapy (HbA1c = 6.5%) yielded no statistically significant effects on major cardiovascular events or death from cardiovascular causes as compared to standard therapy (HbA1c = 7.3%), and the VADT found no significant effect of intensive glucose control (HbA1c = 6.9% versus 8.4%) on the time to first occurrence of various major cardiovascular events.

To help explain this situation, where long-term, cardiovascular outcome trials have resulted in counterintuitive outcomes, we presented data in this issue of *Journal of Diabetes Science and Technology*, for a pharmacokinetic/pharmacodynamic model that characterizes the effect of conventional antidiabetic therapies on the glucose supply [carbohydrate intake and intestinal absorption (carbohydrate exposure, CE), hepatic glucose uptake (HGU), hepatic gluconeogenesis (GNG), and insulin resistance (IR)], and insulin demand [peripheral insulin exposure (PIE) and peripheral glucose uptake (PGU)] dynamic.[4] Moreover, it is our hypothesis that the mechanism used to attain blood glucose reduction may be as important, or possibly of greater importance, than the extent of blood glucose reduction. To determine if pharmacotherapeutic strategies that favor the glucose supply or insulin demand dynamic are associated with cardiovascular benefit, we retrospectively identified patients with five years of eligibility prior to experiencing an initial event, matched them to patients not experiencing an event, and assessed the impact of the glucose supply:insulin demand (SD) ratio in conjunction with measured glucose control (HbA1c).

Methods

The supporting literature and methods used to calculate the SD ratio for each of the antidiabetic agents

included in the analysis have been described previously.[4] Briefly, the therapeutic targets of the glucose supply (CE, 1+2; HGU, 3; GNG, 4; IR, 5) and insulin demand (PGU, 6; PIE, 7) model are presented in **Figure 1**. With the respective antidiabetic therapies characterized for their impact on CE, HGU, GNG, IR, PIE, and PGU (**Table 1**), identification of their effect on the glucose supply (decrease in CE, increase in HGU, decrease in GNG, decrease in IR) and insulin demand (increase in PIE, increase in PGU) dynamic was determined according to **Equation (1)**:

$$\text{Glucose Supply (S)/Insulin Demand (D)} = \frac{1 + ((CE) + (HGU) + (GNG) + (IR))}{1 + (PIE + PGU)} \quad (1)$$

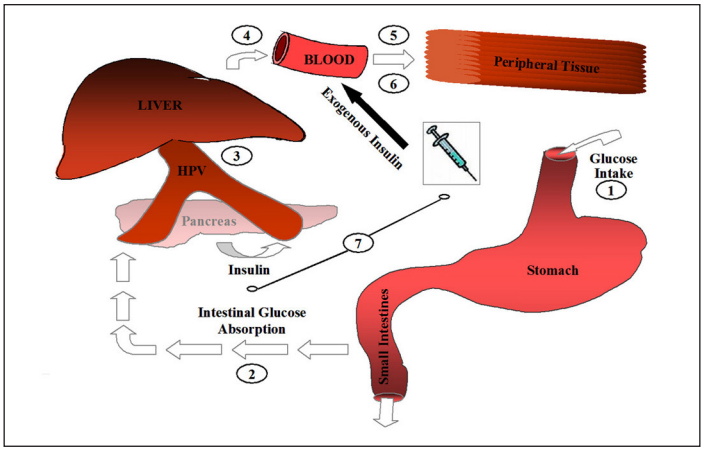

Figure 1. Glucose supply and insulin demand model. CE, 1+2; HGU, 3; GNG, 4; IR, 5; PGU, 6; PIE, 7. HPV, hepatic portal vein.

Table 1.
Glucose Supply : Insulin Demand Ratio for Antidiabetic Therapies at Maximal Therapeutic Dose

Antidiabetic agent	CE	HGU	GNG	IR	PIE	PGU	Therapeutic dose	SD ratio[a]
Miglitol	0.30	0.15	0.05	0.15	0.05	0.25	300 mg	1.25
Acarbose	0.30	0.15	0.05	0.15	0.05	0.25	300 mg	1.25
Metformin	0.15	0.40	0.35	0.38	-0.10	0.14	2000 mg	2.20
Acetohexamide	0.00	0.14	0.07	0.00	0.21	0.36	1500 mg	0.77
Chlorpropamide	0.00	0.14	0.07	0.00	0.21	0.36	500 mg	0.77
Tolazamide	0.00	0.14	0.07	0.00	0.21	0.36	1000 mg	0.77
Tolbutamide	0.00	0.14	0.07	0.00	0.21	0.36	2000 mg	0.77
Glimepiride	0.00	0.18	0.08	0.00	0.24	0.39	8 mg	0.77
Glipizide	0.00	0.18	0.08	0.00	0.24	0.39	10 mg	0.77
Glyburide	0.00	0.14	0.07	0.00	0.21	0.36	10 mg	0.77
Nateglinide	0.00	0.21	0.11	0.00	0.34	0.60	360 mg	0.69
Repaglinide	0.00	0.16	0.07	0.00	0.20	0.31	12 mg	0.81
Pioglitazone	0.00	0.40	0.21	0.35	-0.10	0.59	45 mg	1.32
Rosiglitazone	0.00	0.40	0.23	0.39	-0.10	0.70	8 mg	1.27
Troglitazone	0.00	0.40	0.22	0.35	-0.10	0.67	600 mg	1.25
Insulin aspart	0.00	0.23	0.14	0.00	0.42	0.80	0.5 U/kg	0.62
Insulin lispro	0.00	0.23	0.14	0.00	0.42	0.80	0.5 U/kg	0.62
Insulin regular	0.00	0.21	0.11	0.00	0.33	0.64	0.5 U/kg	0.67
Insulin isophane	0.00	0.23	0.10	0.00	0.28	0.40	0.5 U/kg	0.79
Insulin aspart protamine	0.00	0.23	0.10	0.00	0.28	0.40	0.5 U/kg	0.79
Insulin lispro protamine	0.00	0.23	0.10	0.00	0.28	0.40	0.5 U/kg	0.79
Insulin lente	0.00	0.23	0.10	0.00	0.28	0.40	0.5 U/kg	0.79
Insulin ultralente	0.00	0.17	0.08	0.00	0.24	0.38	0.5 U/kg	0.77
Insulin glargine	0.00	0.24	0.10	0.00	0.30	0.42	0.5 U/kg	0.78

[a] Estimates of effect for oral medications on CE, HGU, GNG, IR, PIE, and PGU were calculated for maximal therapeutic dose and linearly extrapolated for decreasing doses. Insulin, having no maximal therapeutic dose, was linearly extrapolated for increasing or decreasing dose. All combination effects on CE, HGU, GNG, IR, PIE, and PGU were considered additive.

To test the hypothesis that patients managed on the glucose supply side would have fewer cardiovascular events versus those managed on the insulin demand side, the electronic medical records of a group model health maintenance organization were queried. From the electronic medical record, de-identified health care claims, medical progress notes, and laboratory data with dates of service spanning January 1, 1997, through December 31, 2008, were reviewed 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[5,6] and chart review confirmation of a first major cardiovascular event (myocardial infarction, coronary artery bypass graft, or angioplasty); (4) five years of continuous eligibility, including medical and prescription claims, preceding the initial cardiovascular event; and (5) on antidiabetic therapy at the beginning of the 5-year observation period. From the database of 194,268 patients, an initial query identified 16,007 patients (8.2%) to have ICD-9 code 250 in their medical claims history. Of these, 15,349 (95.9%) were confirmed to have a diagnosis of T2DM and 11,751 to have a diagnosis date referenced in their medical history. Within the group of patients with T2DM and a known date of diagnosis, 1107 had an initial event, and 50 met the final inclusion parameters of five years of continuous medical and prescription claims preceding the event and presence of antidiabetic therapy at the index date. These patients were subsequently matched (1:1) to T2DM patients meeting the same criteria who had not experienced an event. Primary baseline matching criteria included age, gender, T2DM duration, body mass index (BMI), and HbA1c. Secondary matching criteria included a composite profile of blood pressure (systolic, diastolic) and cholesterol [low-density lipoprotein, high-density lipoprotein, triglycerides (TG)]. All baseline values were determined, as an average, from the first six months of the 5-year observation period. The University at Buffalo's Health Sciences Institutional Review Board previously approved the de-identified database for exempt status; informed consent was not required.

Based on the evidence presented in the aforementioned cardiovascular outcome trials in the T2DM population, it was not anticipated that average HbA1c or categorical HbA1c breakpoints would be independently associated with a reduction in cardiovascular outcomes. Similarly, because the SD ratio is a measure of the pharmacologic impact on glucose supply and insulin demand dynamics, it was not anticipated that the average SD ratio or categorical SD ratio breakpoints would be independently associated with a reduction in events. However, it was hypothesized that combing the optimal SD ratio breakpoint that minimized event rate and the American Diabetes Association-recommended HbA1c breakpoint (7%) would realize the greatest cardiovascular benefit. Therefore, in addition to evaluating the associations of mean HbA1c, categorical HbA1c (≥7% versus <7%), mean SD ratio, and categorical SD ratios (≥1, ≥1.25, ≥1.5) with cardiovascular events, we determined the optimal SD ratio breakpoint that minimized event rate, coupled the breakpoint with the recommended HbA1c threshold (7%), and analyzed the combined parameter for an association with event rate. All statistical assessments of baseline characteristics and cardiovascular outcomes were conducted with the Student's *t*-test (continuous data) or Chi-square/Fisher's exact test (categorical data).

Results

Application of the Glucose Supply and Insulin Demand Model to Cardiovascular Events

Fifty patients with an initial event and known date of occurrence were case matched with noncardiovascular event controls per aforementioned criteria. Baseline characteristics for the event and control patients are presented in **Table 2**. Age, gender, duration of T2DM, and metabolic characteristics were similar between groups, with the exception of TG that were significantly higher in the cardiovascular event cohort (288.8 ± 313.1 mg/dl versus 176.0 ± 81.8 mg/dl; $p = .017$). No significant differences in nondiabetes-related therapies were observed between groups, although more control patients tended to be on angiotensin-converting enzyme inhibitors/angiotensin receptor-blocking agents (47.6 ± 45.2% versus 32.5 ± 43.6%; $p = .090$) and also to have higher SD ratio values at baseline (1.2 ± 0.3 versus 1.1 ± 0.3; $p = .051$).

Over the course of the 5-year observation period, there was no significant difference observed for the average HbA1c between event patients and controls (7.5 ± 1.0% versus 7.3 ± 0.9%, $p = .275$, respectively). There was also no difference in event rate between the cohorts when patients were categorized at the HbA1c ≥7% breakpoint (72% versus 64%, $p = .391$, respectively). Like HbA1c, the mean SD ratio was not significantly different between the cohorts (1.2 ± 0.3 versus 1.3 ± 0.3, $p = .205$, respectively), and there was also no difference in event rate between the cohorts at the ≥1 (68% versus 76%, $p = .373$, respectively), ≥1.25 (42% versus 56%, $p = .161$, respectively), or ≥1.5 (22% versus 30%, $p = .362$) breakpoints.

As was hypothesized, more aggressive HbA1c reduction and higher SD ratio values were not independently associated with a reduction in cardiovascular events. **Figure 2** presents data for the combined impact of the recommended HbA1c breakpoint (<7%) and optimal SD ratio breakpoint (≥1.25) on cardiovascular outcomes. Identical event rates were observed for patients managed to an HbA1c <7% and SD ratio ≥1.25, HbA1c <7% and SD ratio <1.25, and HbA1c ≥7% and SD ratio ≥1.25 (44%). Compared to the remainder of the population, the only group demonstrating a trend toward greater cardiovascular event risk were those managed at higher glucose values and on the insulin demand side of the model (HbA1c ≥7% and a SD ratio <1.25; 61% versus 39%; $p = .096$).

Discussion

The overwhelming evidence that intensive blood glucose management does not confer a corresponding reduction in macrovascular events requires that we rigorously evaluate the interventions used to attain the reductions. The impact of pharmacologic intervention has been largely dismissed in the assessment of T2DM cardiovascular outcome trials.[1–3] Close inspection of therapies utilized during the trials demonstrates a focus on agents that predominantly increase PIE and peripheral glucose disposal. At baseline of the ADVANCE trial, patients in the intensive and standard groups were predominantly on sulfonylurea- (71.8% and 71.1%) and metformin- (61.0% and 60.2%) based regimens with minimal insulin utilization (1.5% and 1.4%). At the end of follow-up, sulfonylurea (92.4%) and insulin utilization (40.5%) spiked in the intensive treatment group, while in the standard group, sulfonylurea utilization decreased (58.7%) and insulin use moderately increased (24.1%).[2] Similarly, the ACCORD trial featured greater secretagogue and insulin exposure in those receiving intensive therapy versus standard therapy (86.6% and 73.8% versus 77.3% and 55.4%, respectively).[1] The VADT determined initial treatment class by BMI, metformin + rosiglitazone when ≥27 kg/m^2, glimepiride + rosiglitazone when <27 kg/m^2. Subsequently, the intensive management cohort received maximal doses, while standard therapy received one-half the maximal dose.[3] Notably, before any changes in oral medications were made, insulin was added to patients in the intensive management cohort not achieving a HbA1c <6% and only to standard-therapy patients not achieving a HbA1c <9%.

Analyzing the relationship between cardiovascular events, blood glucose reduction, and the SD ratio, it would appear that, for patients managed at higher HbA1c values (≥7%), there may be a protective cardiovascular effect if pharmacologically managed on the glucose supply side (SD ratio ≥1.25). Conversely, when the HbA1c was <7%,

Table 2.
Baseline Characteristics for Cardiovascular Event Patients and Controls

	Cardiovascular event	Controls	*p* value
Age (years)	64.6 ± 10.5	64.8 ± 11.0	.926
Gender (male)	25	25	1.00
Duration of T2DM (years)	10.6 ± 5.9	10.5 ± 3.6	.885
Weight	203.5 ± 50.5	203.1 ± 46.5	.972
BMI (kg/m^2)	32.4 ± 7.1	32.5 ± 6.4	.958
Systolic blood pressure (mmHg)	142.2 ± 14.3	145.0 ± 13.5	.308
Diastolic blood pressure (mmHg)	81.1 ± 8.6	82.4 ± 9.8	.466
Low-density lipoprotein (mg/dl)	114.2 ± 29.9	117.5 ± 23.6	.536
High-density lipoprotein (mg/dl)	43.0 ± 10.9	46.4 ± 11.3	.129
TG (mg/dl)	288.8 ± 313.1	176.0 ± 81.8	.017
Fasting plasma glucose (mg/dl)	156.7 ± 49.5	163.4 ± 51.9	.510
HbA1c (%)	7.7 ± 1.4	7.5 ± 1.19	.484
SD Ratio	1.1 ± 0.3	1.2 ± 0.3	.051
Angiotensin converting enzyme inhibitor/angiotensin receptor blocking agent (%)	32.5 ± 43.6	47.6 ± 45.2	.090
Statin (%)	29.1 ± 40.3	41.3 ± 39.5	.130

no difference in event rate was observed in patients managed at an SD ratio ≥1.25 or <1.25. These data, in context with findings of ACCORD, ADVANCE, and the VADT that demonstrated no difference with more intensive blood glucose reduction, may suggest that a more rigorous evaluation of the impact of pharmacologic intervention is warranted.

Limitations

As previously described, construction of the glucose supply and insulin demand model required multiple assumptions.[4] Most importantly, the literature used to identify the effect of each antidiabetic agent on each target was often from a small number of sources, unavailable, or conducted in patients at various stages of their disease progression. Similarly, determining the dose-response relationship for antidiabetic agents (alone and in combination with other agents) on the respective targets was often not possible because of a small literature base and the predominance of single-dose, monotherapy studies. As a consequence, the dose-response relationships were considered to be linear and synergistic between agents for the present model and may therefore have inadequately characterized the effect of the antidiabetic agents (individually and in combination) on the respective targets at the extremes of dose. Lastly, it is also likely that the glucose supply and insulin demand targets may have differing impacts on disease progression and require multiple coefficients to optimize the model.

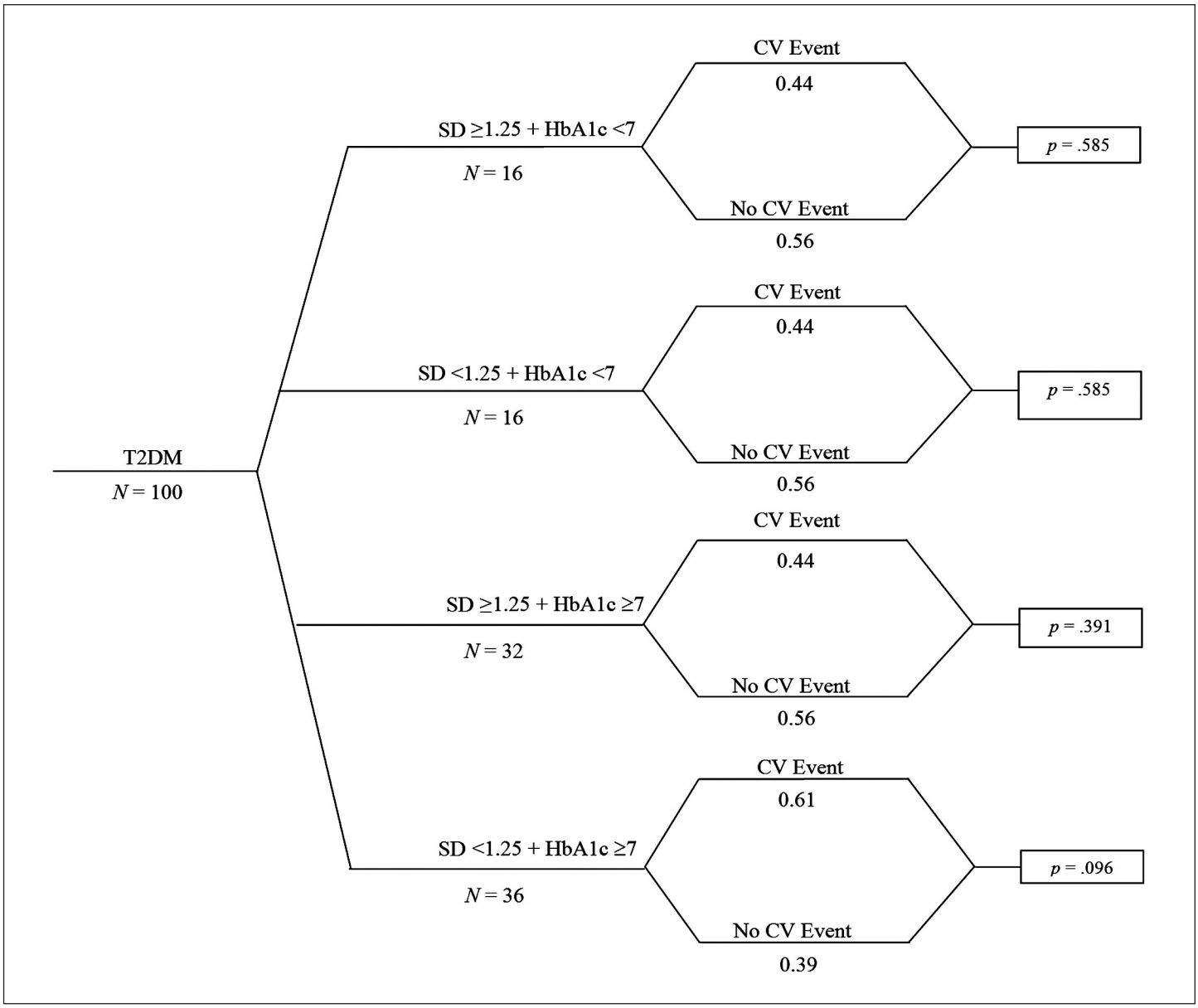

Figure 2. Combined impact of HbA1c and SD ratio on cardiovascular event. CV, cardiovascular.

All the aforementioned limitations may significantly contribute to the difficulties identifying the relationship between cardiovascular events, the extent of blood glucose reduction, and the means by which the reduction was attained. Subsequent work should strive to (1) refine SD ratio estimates; (2) integrate findings into larger, long-term T2DM cardiovascular outcome trials; (3) utilize multivariate logistic regression and/or neural network strategies to comprehensively characterize the relationship of the SD ratio and other known metabolic variables on progression to cardiovascular event; and (4) characterize SD ratios for newer antidiabetic therapies.

Glucose Supply and Insulin Demand Dynamics of Newer Antidiabetic Therapies

The integration of newer therapies (bile-acid sequestrants, dipeptidyl peptidase-4 [DPP-IV] inhibitors, incretin mimetics, and amylinomimetics) into the glucose supply and insulin demand model will require additional study to identify mechanistic actions that have been incompletely characterized. Despite the current unavailability of comprehensive mechanistic data, the available literature would suggest that bile acid sequestrants (colesevelam), incretin mimetics (exenatide), DPP-IV inhibitors (sitagliptin), and amylinomimetic (pramlintide) agents would demonstrate superior supply-side dynamics to current second-line sulfonylurea and long-acting insulin-based regimens. The available literature to characterize these therapies are presented here.

Bays and Goldberg reviewed the mechanistic glucose-lowering effects of the bile acid sequestrants (colesevelam).[7] Although there are numerous mechanisms[7–20] and contradictory evidence surrounding many of the mechanisms,[21–24] it would appear the bile acid sequestrants have the most profound effect on GNG, with more modest effects on CE (decrease), HGU (increase), IR (decrease), PGU (increase), and PIE (increase).

The incretin mimetic, exenatide, has been shown to (1) decrease total caloric intake,[25–27] (2) increase HGU,[28,29] (3) diminish hepatic glucose production,[28,29] and (4) increase PIE.[28–30] Additional studies identifying the specific effects of exenatide on GNG, IR, and PGU are needed to comprehensively characterize the glucose supply and insulin demand dynamics of exenatide. The available evidence suggests exenatide to have the most profound effects on CE (reduce), HGU (increase), GNG (decrease), and PIE (increase), with modest or negligible effects on IR and PGU.

Study is underway to characterize the mechanisms of glucose-lowering effects of the DPP-IV inhibitor, sitagliptin, in patients with T2DM (*ClinicalTrials.gov* identifier: NCT00820573). To date, DPP-IV inhibitors have been shown to (1) have no effect on total caloric intake,[25] (2) have no effect on IR,[31] and (3) increase fasting and prandial insulin secretion.[31] This evidence, in context with incretin mimetic data, would suggest that the DPP-IV inhibitors have the most profound impact on HGU (increase), GNG (decrease), and PIE (increase) with modest to negligible effects on CE, IR, and PGU.

The amylinomimetic, pramlintide: (1) increases satiety, diminishes caloric intake, and reduces weight;[32–38] (2) has no evidence for diminished intestinal absorption; (3) delays gastric emptying;[39–43] (4) decreases glucagon secretion;[44–46] (5) reduces postprandial oxidative stress;[47] (6) has no apparent effect on PGU;[48] and (7) diminishes insulin requirements.[34] It would appear pramlintide would have the most profound effect on CE (decrease), HGU (decrease), GNG (decrease), and IR (decrease), while having modest to negligible effects on PGU and PIE.

Conclusions

Alpha-glucosidase inhibitors (1.25), metformin (2.20), and thiazolidinediones (1.27–1.32) exhibit superior effects on glucose supply and insulin demand dynamics (SD ratio) versus secretagogue (0.69–0.81) and insulin-based therapies (0.62–0.79). Independently, more aggressive HbA1c reduction (<7%) and higher SD ratio values (≥1, ≥1.25, or ≥1.5) were not associated with a reduction in cardiovascular outcomes. Combining the parameters, the only group demonstrating a trend toward greater cardiovascular event risk were those managed at higher glucose values and on the insulin demand side of the model (HbA1c ≥7% and a SD ratio <1.25; 61% versus 39%; $p = .096$). Based on these findings, it is pertinent to conduct subsequent works to develop and refine SD ratio estimates and apply the model to larger, long-term T2DM cardiovascular outcome trials.

Acknowledgment:

To Steve Feuerstein for data extraction and formatting.

References:

1. Action to Control Cardiovascular Risk in Diabetes Study Group, Gerstein HC, Miller ME, Byington RP, Goff DC Jr, Bigger JT, Buse JB, Cushman WC, Genuth S, Ismail-Beigi F, Grimm RH Jr, Probstfield JL, Simons-Morton DG, Friedewald WT. Effects of intensive glucose lowering in type 2 diabetes. N Engl J Med. 2008;358(24):2545–59.
2. ADVANCE Collaborative Group, Patel A, MacMahon S, Chalmers J, Neal B, Billot L, Woodward M, Marre M, Cooper M, Glasziou P, Grobbee D, Hamet P, Harrap S, Heller S, Liu L, Mancia G, Mogensen CE, Pan C, Poulter N, Rodgers A, Williams B, Bompoint S, de Galan BE, Joshi R, Travert F. Intensive blood glucose control and vascular outcomes in patients with type 2 diabetes. N Engl J Med. 2008;358(24):2560–72.
3. Duckworth W, Abraira C, Moritz T, Reda D, Emanuele N, Reaven PD, Zieve FJ, Marks J, Davis SN, Hayward R, Warren SR, Goldman S, McCarren M, Vitek ME, Henderson WG, Huang GD, VADT Investigators. Glucose control and vascular complications in veterans with type 2 diabetes. N Engl J Med. 2009;360(2):129–39.
4. Monte SV, Schentag JJ, Adelman MH, Paladino JA. Glucose supply and insulin demand dynamics of antidiabetic agents. J Diabetes Sci Technol. 2010;4(2):365-81.
5. Newton KM, Wagner EH, Ramsey SD, McCulloch D, Evans R, Sandhu N, Davis C. The use of automated data to identify complications and comorbidities of diabetes: a validation study. J Clin Epidemiol. 1999;52(3):199–207.
6. Pladevall M, Goff DC, Nichaman MZ, Chan F, Ramsey D, Ortíz C, Labarthe DR. An assessment of the validity of ICD Code 410 to identify hospital admissions for myocardial infarction: The Corpus Christi Heart Project. Int J Epidemiol. 1996;25(5):948–52.
7. Bays HE, Goldberg RB. The 'forgotten' bile acid sequestrants: is now a good time to remember? Am J Ther. 2007;14(6):567–80.
8. Stulnig TM, Oppermann U, Steffensen KR, Schuster GU, Gustafsson JA. Liver X receptors downregulate 11beta-hydroxysteroid dehydrogenase type 1 expression and activity. Diabetes. 2002;51(8):2426–33.
9. Cao G, Liang Y, Broderick CL, Oldham BA, Beyer TP, Schmidt RJ, Zhang Y, Stayrook KR, Suen C, Otto KA, Miller AR, Dai J, Foxworthy P, Gao H, Ryan TP, Jiang XC, Burris TP, Eacho PI, Etgen GJ. Antidiabetic action of a liver x receptor agonist mediated by inhibition of hepatic gluconeogenesis. J Biol Chem. 2003;278(2):1131–6.
10. Laffitte BA, Chao LC, Li J, Walczak R, Hummasti S, Joseph SB, Castrillo A, Wilpitz DC, Mangelsdorf DJ, Collins JL, Saez E, Tontonoz P. Activation of liver X receptor improves glucose tolerance through coordinate regulation of glucose metabolism in liver and adipose tissue. Proc Natl Acad Sci U S A. 2003;100(9):5419–24.
11. Efanov AM, Sewing S, Bokvist K, Gromada J. Liver X receptor activation stimulates insulin secretion via modulation of glucose and lipid metabolism in pancreatic beta-cells. Diabetes. 2004;53 Suppl 3:S75–8.
12. Ma K, Saha PK, Chan L, Moore DD. Farnesoid X receptor is essential for normal glucose homeostasis. J Clin Invest. 2006;116(4):1102–9.
13. Mitro N, Mak PA, Vargas L, Godio C, Hampton E, Molteni V, Kreusch A, Saez E. The nuclear receptor LXR is a glucose sensor. Nature. 2007;445(7124):219–23.
14. Thomson AB, Keelan M. Feeding rats diets containing cheno- or ursodeoxycholic acid or cholestyramine modifies intestinal uptake of glucose and lipids. Digestion. 1987;38(3):160–70.
15. Feldman EB, Watt R, Feldman DS. Conjugated dihydroxy bile salt inhibition of glucose influx in rat jejunum in vitro. Am J Dig Dis. 1977;22(5):415–8.
16. Kogire M, Gomez G, Uchida T, Ishizuka J, Greeley GH Jr, Thompson JC. Chronic effect of oral cholestyramine, a bile salt sequestrant, and exogenous cholecystokinin on insulin release in rats. Pancreas. 1992;7(1):15–20.
17. Brand SJ, Morgan RG. Stimulation of pancreatic secretion and growth in the rat after feeding cholestyramine. Gastroenterology. 1982;83(4):851–9.
18. Koide M, Okabayashi Y, Otsuki M. Role of endogenous bile on basal and postprandial CCK release in humans. Dig Dis Sci. 1993;38(7):1284–90.
19. Gomez G, Upp JR Jr, Lluis F, Alexander RW, Poston GJ, Greeley GH Jr, Thompson JC. Regulation of the release of cholecystokinin by bile salts in dogs and humans. Gastroenterology. 1988;94(4):1036–46.
20. Katsuma S, Hirasawa A, Tsujimoto G. Bile acids promote glucagon-like peptide-1 secretion through TGR5 in a murine enteroendocrine cell line STC-1. Biochem Biophys Res Commun. 2005;329(1):386–90.
21. Inoue Y, Yu AM, Yim SH, Ma X, Krausz KW, Inoue J, Xiang CC, Brownstein MJ, Eggertsen G, Björkhem I, Gonzalez FJ. Regulation of bile acid biosynthesis by hepatocyte nuclear factor 4alpha. J Lipid Res. 2006;47(1):215–27.
22. De Fabiani E, Mitro N, Gilardi F, Caruso D, Galli G, Crestani M. Coordinated control of cholesterol catabolism to bile acids and of gluconeogenesis via a novel mechanism of transcription regulation linked to the fasted-to-fed cycle. J Biol Chem. 2003;278(40):39124–32.
23. Bays HE, Cohen DE. Rationale and design of a prospective clinical trial program to evaluate the glucose-lowering effects of colesevelam HCl in patients with type 2 diabetes mellitus. Curr Med Res Opin. 2007;23(7):1673–84.
24. Gustafsson BE, Angelin B, Einarsson K, Gustafsson JA. Influence of cholestyramine on synthesis of cholesterol and bile acids in germfree rats. J Lipid Res. 1978;19(8):972–7.
25. DeFronzo RA, Okerson T, Viswanathan P, Guan X, Holcombe JH, MacConell L. Effects of exenatide versus sitagliptin on postprandial glucose, insulin and glucagon secretion, gastric emptying, and caloric intake: a randomized, cross-over study. Curr Med Res Opin. 2008;24(10):2943–52.
26. Scott KA, Moran TH. The GLP-1 agonist exendin-4 reduces food intake in nonhuman primates through changes in meal size. Am J Physiol Regul Integr Comp Physiol. 2007;293(3):R983–7.
27. Edwards CM, Stanley SA, Davis R, Brynes AE, Frost GS, Seal LJ, Ghatei MA, Bloom SR. Exendin-4 reduces fasting and postprandial glucose and decreases energy intake in healthy volunteers. Am J Physiol Endocrinol Metab. 2001;281(1):E155–61.
28. Cervera A, Wajcberg E, Triplitt C, Fernandez M, Joya J, Zuo P, DeFronzo RA, Cersosimo E. Different effects of acute vs. chronic exenatide administration on the mechanism of attenuation of post-meal glucose in T2DM. American Diabetes Association 68th Scientific Sessions 2008, June 6–10, 2008, San Francisco, California.
29. Cervera A, Wajcberg E, Sriwijitkamol A, Fernandez M, Zuo P, Triplitt C, Musi N, DeFronzo RA, Cersosimo E. Mechanism of action of exenatide to reduce postprandial hyperglycemia in type 2 diabetes. Am J Physiol Endocrinol Metab. 2008;294(5):E846–52.
30. Kolterman OG, Buse JB, Fineman MS, Gaines E, Heintz S, Bicsak TA, Taylor K, Kim D, Aisporna M, Wang Y, Baron AD. Synthetic exendin-4 (exenatide) significantly reduces postprandial and fasting plasma glucose in subjects with type 2 diabetes. J Clin Endocrinol Metab. 2003;88(7):3082–9.
31. Raz I, Hanefeld M, Xu L, Caria C, Williams-Herman D, Khatami H, Sitagliptin Study 023 Group. Efficacy and safety of the dipeptidyl peptidase-4 inhibitor sitagliptin as monotherapy in patients with type 2 diabetes mellitus. Diabetologia. 2006;49(11):2564–71.

32. Chapman I, Parker B, Doran S, Feinle-Bisset C, Wishart J, Strobel S, Wang Y, Burns C, Lush C, Weyer C, Horowitz M. Effect of pramlintide on satiety and food intake in obese subjects and subjects with type 2 diabetes. Diabetologia. 2005;48(5):838–48.

33. Pullman J, Darsow T, Frias JP. Pramlintide in the management of insulin-using patients with type 2 and type 1 diabetes. Vasc Health Risk Manag. 2006;2(3):203–12.

34. Hollander P, Maggs DG, Ruggles JA, Fineman M, Shen L, Kolterman OG, Weyer C. Effect of pramlintide on weight in overweight and obese insulin-treated type 2 diabetes patients. Obes Res. 2004;12(4):661–8.

35. Hollander P, Ratner R, Fineman M, Strobel S, Shen L, Maggs D, Kolterman O, Weyer C. Addition of pramlintide to insulin therapy lowers HbA1c in conjunction with weight loss in patients with type 2 diabetes approaching glycaemic targets. Diabetes Obes Metab. 2003;5(6):408–14.

36. Hollander PA, Levy P, Fineman MS, Maggs DG, Shen LZ, Strobel SA, Weyer C, Kolterman OG. Pramlintide as an adjunct to insulin therapy improves long-term glycemic and weight control in patients with type 2 diabetes: a 1-year randomized controlled trial. Diabetes Care. 2003;26(3):784–90.

37. Ratner RE, Want LL, Fineman MS, Velte MJ, Ruggles JA, Gottlieb A, Weyer C, Kolterman OG. Adjunctive therapy with the amylin analogue pramlintide leads to a combined improvement in glycemic and weight control in insulin-treated subjects with type 2 diabetes. Diabetes Technol Ther. 2002;4(1):51–61.

38. Whitehouse F, Kruger DF, Fineman M, Shen L, Ruggles JA, Maggs DG, Weyer C, Kolterman OG. A randomized study and open-label extension evaluating the long-term efficacy of pramlintide as an adjunct to insulin therapy in type 1 diabetes. Diabetes Care. 2002;25(4):724–30.

39. Vella A, Lee JS, Camilleri M, Szarka LA, Burton DD, Zinsmeister AR, Rizza RA, Klein PD. Effects of pramlintide, an amylin analogue, on gastric emptying in type 1 and 2 diabetes mellitus. Neurogastroenterol Motil. 2002;14(2):123–31.

40. Kong MF, King P, Macdonald IA, Stubbs TA, Perkins AC, Blackshaw PE, Moyses C, Tattersall RB. Infusion of pramlintide, a human amylin analogue, delays gastric emptying in men with IDDM. Diabetologia. 1997;40(1):82–8.

41. Kong MF, Stubbs TA, King P, Macdonald IA, Lambourne JE, Blackshaw PE, Perkins AC, Tattersall RB. The effect of single doses of pramlintide on gastric emptying of two meals in men with IDDM. Diabetologia. 1998;41(5):577–83.

42. Kong MF, Macdonald IA, Tattersall RB. Gastric emptying in diabetes. Diabet Med. 1996;13(2):112–9.

43. Kellmeyer TA, Kesty NC, Wang Y, Frias JP, Fineman MS. Pharmacokinetics of an oral drug (acetaminophen) administered at various times relative to subcutaneous injection of pramlintide in subjects with type 2 diabetes. J Clin Pharmacol. 2007;47(7):798–805.

44. Fineman M, Weyer C, Maggs DG, Strobel S, Kolterman OG. The human amylin analog, pramlintide, reduces postprandial hyperglucagonemia in patients with type 2 diabetes mellitus. Horm Metab Res. 2002;34(9):504–8.

45. Fineman MS, Koda JE, Shen LZ, Strobel SA, Maggs DG, Weyer C, Kolterman OG. The human amylin analog, pramlintide, corrects postprandial hyperglucagonemia in patients with type 1 diabetes. Metabolism. 2002;51(5):636–41.

46. Nyholm B, Orskov L, Hove KY, Gravholt CH, Møller N, Alberti KG, Moyses C, Kolterman O, Schmitz O. The amylin analog pramlintide improves glycemic control and reduces postprandial glucagon concentrations in patients with type 1 diabetes mellitus. Metabolism. 1999;48(7):935–41.

47. Ceriello A, Lush CW, Darsow T, Piconi L, Corgnali M, Nanayakkara N, Frias JP, Maggs D. Pramlintide reduced markers of oxidative stress in the postprandial period in patients with type 2 diabetes. Diabetes Metab Res Rev. 2008;24(2):103–8.

48. Orskov L, Nyholm B, Yde Hove K, Gravholt CH, Møller N, Schmitz O. Effects of the amylin analogue pramlintide on hepatic glucagon responses and intermediary metabolism in type 1 diabetic subjects. Diabet Med.1999;16(10):867–74.