

# Short-Term Outcomes for Veterans Receiving Basal Insulin, Metformin, and a Sulfonylurea Who Are Started on a Third Noninsulin Agent Versus Prandial Insulin

Andrew D. Santeusanio<sup>1</sup> and Monica M. Bowen<sup>2</sup>

## ABSTRACT

**Aims.** Despite numerous recent advances in the management of patients with type 2 diabetes, there remains a paucity of data to guide sequential treatment intensification.

**Methods.** This was a single-center, retrospective cohort study of patients receiving metformin, basal insulin, and a sulfonylurea who were started on a third noninsulin agent or prandial insulin. The primary outcome for this study was change in A1C at 6 months after treatment intensification. Secondary outcomes included change in weight at 6 months, change in A1C at 1 year, percentage of patients achieving an A1C <7.5% at 1 year, documented episodes of hypoglycemia, and time to progression to prandial insulin.

**Results.** A total of 62 patients were identified for inclusion in the study: 28 receiving prandial insulin and 34 treated with a noninsulin agent. There was no significant difference in A1C change between the two treatment arms at either 6 months (−0.53 vs. −0.84%,  $P = 0.31$ ) or 1 year (−0.67 vs. −0.86%,  $P = 0.61$ ) after intervention. Patients receiving noninsulin agents gained significantly less weight at 6 months (−2.09 vs. 1.99 kg,  $P < 0.01$ ) and experienced fewer annual episodes of hypoglycemia (1.0 vs. 2.6,  $P = 0.01$ ). Among patients treated with noninsulin agents, those receiving a glucagon-like peptide 1 receptor agonist were more likely to have an A1C <7.5% at 1 year than patients receiving a dipeptidyl peptidase 4 inhibitor (50 vs. 13%,  $P = 0.05$ ).

**Conclusion.** These results highlight that, in select patients, noninsulin therapies can be added to a backbone of metformin, basal insulin, and a sulfonylurea with similar A1C reductions but improved metabolic parameters relative to intensive insulin therapy.

Diabetes remains one of the most prevalent chronic disease states in the United States. In 2012, 29.1 million adults and children, or roughly 9.3% of the population, were estimated to have diabetes, with another 1.5 million new cases diagnosed annually (1). More than 90% of patients newly diagnosed with diabetes are classified as having type 2 diabetes and are characterized as displaying primarily insulin resistance rather than an absolute insulin deficiency. Metabolic parameters are of particular concern in these patients

because more than 80% of individuals with type 2 diabetes are overweight, placing them at an increased risk for cardiovascular disease and other diabetes-related morbidity and mortality (2). This result may be exacerbated by the additional weight gain frequently observed with a number of the traditional antihyperglycemic medications and particularly progression to intensive insulin therapy. In the UK Prospective Diabetes Study (UKPDS), patients receiving intensive insulin therapy gained in excess of 5 kg during the 10-year follow-

<sup>1</sup>Department of Pharmacy, Mount Sinai Hospital, New York, NY

<sup>2</sup>Department of Pharmacy, Lebanon VA Medical Center, Lebanon, PA

Corresponding author: Andrew D. Santeusanio, [andrew.santeusanio@mountsinai.org](mailto:andrew.santeusanio@mountsinai.org)

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up period, which was >3 kg more than conventionally treated patients (3). Another study by Holman et al. (4) of patients with type 2 diabetes found that patients treated with prandial insulin averaged 5.7 kg of weight gain compared with 1.9 kg for individuals receiving only basal insulin therapy. Given these data demonstrating the potential deleterious effects of multiple daily insulin injections on patients' metabolic profile, when and how to intensify insulin therapy remains an ongoing debate among providers caring for patients with type 2 diabetes.

Compliance with insulin treatment is another potential barrier for patients considering initiating chronic intensive insulin. Intensive insulin therapy can require as many as four injections per day, in addition to regular self-monitoring of blood glucose. This places an increased medication burden on patients and their caregivers who are responsible for adhering to the prescribed insulin regimen. Other patients may decline to take their insulin for reasons not associated with injection frequency. Fear of weight gain and hypoglycemia has also been shown to contribute to poor compliance with insulin regimens. One study conducted in 341 women with type 1 diabetes found that 31% intentionally under-dosed insulin to manipulate their weight, resulting in poorer glycemic control, more diabetes-related hospitalizations, and an increased incidence of microvascular complications (5). In the Diabetes Control and Complications Trial, 29 patients experienced severe hypoglycemia during the first year of the study. In these patients, long-term follow-up revealed more frequent under-dosing of insulin and 2.2 kg more weight gain on average than in patients who did not experience severe hypoglycemia (6). Weight gain and poor glycemic control can in turn further insulin resistance and accelerate the physiological processes underlying type 2 diabetes. As a result, patients

on chronic insulin therapy may find themselves in a vicious cycle of weight gain, increased insulin requirements, and further weight gain.

Consensus recommendations for the initial management of type 2 diabetes consist of metformin in addition to lifestyle modifications. Beyond first-line therapy, the American Diabetes Association's position statement recommends individualizing therapy based on patient-specific preferences and comorbidities (7). Prandial insulin is generally recommended when combination therapy with two oral agents and basal insulin fails, but in some patients, the addition of a third noninsulin agent such as a glucagon-like peptide 1 (GLP-1) agonist or dipeptidyl peptidase 4 (DPP-4) inhibitor in place of prandial insulin has been associated with less weight gain, decreased incidence of hypoglycemia, and ultimately better outcomes than intensive insulin therapy (8). To help guide future treatment decision-making, this study was undertaken to gain insight into the risks and benefits of starting prandial insulin versus adding additional noninsulin therapies in patients whose diabetes remained uncontrolled on basal insulin, metformin, and a sulfonylurea.

### Materials and Methods

This was a retrospective cohort study, approved by the Pharmacy Performance Excellence Council, of patients with type 2 diabetes chronically followed at the Lebanon Veterans Affairs (VA) Medical Center. All patients were managed under the care of a primary care physician, endocrinologist, or independent pharmacotherapy specialist with a scope of practice in diabetes management. Patients were identified via the Computerized Patient Record System database if they had a prescription for immediate-release metformin, basal insulin, and a sulfonylurea as well as either prandial insulin or a GLP-1 receptor agonist or DPP-4 inhibitor filled between 1 January 2012 and

31 December 2012. Specific medications evaluated in the database query included the following: immediate-release metformin, insulin glargine, insulin detemir, glimepiride, glipizide, glyburide, insulin lispro, insulin aspart, exenatide, liraglutide, sitagliptin, and linagliptin, based on the VA National Formulary and local restrictions. The thiazolidinedione medications were not included in the review because of the significant weight gain associated with these agents as well as post-marketing safety concerns.

Patients were included in the study if they had prandial insulin, a GLP-1 agonist, or a DPP-4 inhibitor added to their medication regimen during the study period and tried this medication for at least 2 months. For the purposes of this study, prandial insulin therapy was defined as a rapid-acting insulin analog administered at least twice per day with meals. The decision of when to discontinue sulfonylurea therapy after intensive insulin initiation was made at the discretion of the treating provider. Patients were excluded if they had a thyroid-stimulating hormone (TSH) level <0.5 or >5.0 mIU/L, did not have baseline or follow-up A1C or weight measurements available, or passed away or entered hospice care during the course of the review period. This scenario resulted in a study population of 62 patients who were included in the final data analysis.

All subjects determined to be eligible for the study were evaluated in two groups based on whether they received a third noninsulin agent or prandial insulin at the time of treatment intensification. Patients were then assessed from the time of medication intervention until 31 December 2013 or until medication discontinuation if this occurred prior to the conclusion of the review period. Retrospective chart review through the Computerized Patient Record System database was used to gather all baseline demographic as well as outcomes data. Because of the retrospective nature of the study,

the investigators did not have routine access to refill records, and all subjects with active medication prescriptions were assumed to be compliant with therapy. The primary outcome for this study was the change in A1C from the time of intervention to 6 months post-intervention. Secondary outcomes included change in A1C at 1 year post-intervention; percentage of patients with A1C <7.5% at 1 year post-intervention; patient-reported blood glucose readings <70 mg/dL, as documented in progress notes; and change in weight from the time of intervention to 6 months post-intervention. In patients who initially received a third noninsulin agent, time until eventual progression to prandial insulin and indication for any medication changes were also documented and assessed. Patients who discontinued the intervention medication before 1 year of follow-up or did not have 1-year A1C results were subsequently excluded from the 1-year A1C data analysis. The entire patient cohort was included in analysis of all other primary and secondary outcomes.

All data were collected and analyzed in accordance with local ethics guidelines. Student *t* tests were performed on all continuous variables, and nominal data were assessed by means of the  $\chi^2$  test at  $\alpha = 0.05$  for significance. Additional subgroup analysis was conducted to assess differences in primary and secondary outcomes based on the identity of the fourth noninsulin agent added to baseline therapy.

**Results**

Sixty-two patients were identified for inclusion: 28 receiving prandial insulin and 34 receiving a third noninsulin agent. Baseline characteristics were similar between patients treated with prandial insulin and those receiving a third noninsulin agent; however, patients receiving noninsulin agents had a higher mean BMI and were more likely to be followed by an endocrinologist (Table 1). At the time of intervention, all patients were receiving one of two

**TABLE 1. Baseline Characteristics**

	Prandial Insulin (n = 28)	Noninsulin Agent (n = 34)	P
Age, years	64.1 ± 5.5	62.6 ± 6.2	NS
Male sex, n (%)	28 (100)	32 (94)	NS
Race, n (%)			NS
White/European	25 (89)	31 (91)	
African American	3 (11)	2 (6)	
Native American	0 (0)	1 (3)	
Managing prescriber, n (%)			0.01
Pharmacist	5 (18)	8 (23)	
Endocrinologist	14 (50)	25 (74)	
Primary Care	9 (32)	1 (3)	
Duration of diabetes, years	11.0 ± 7.0	12.9 ± 5.8	NS
Serum creatinine, mg/dL	1.0 ± 0.3	1.0 ± 0.3	NS
A1C, %	8.9 ± 1.1	9.1 ± 1.2	NS
BMI, kg/m <sup>2</sup>	33.8 ± 6.1	37.1 ± 6.3	0.04
Basal insulin dose, units/kg	0.4 ± 0.3	0.4 ± 0.3	NS
History of atherosclerotic disease, n (%)*	10 (36)	8 (24)	NS

*Data are expressed as mean ± SD unless otherwise noted. \*Defined as coronary artery disease, cerebrovascular disease, or peripheral vascular disease.*

initial treatment regimens. Twenty-seven patients were treated with a combination of metformin/glipizide/insulin glargine, and 35 were receiving metformin/glyburide/insulin glargine. These initial regimens were also similarly distributed between the separate intervention arms.

**Prandial Insulin Versus Noninsulin Therapy (Table 2)**

Patients receiving additional therapy with a noninsulin agent demonstrated

a greater reduction in A1C than patients treated with prandial insulin at both 6 months (−0.84 vs. −0.53%, *P* = 0.31) and 1 year (−0.86 vs. −0.67%, *P* = 0.61) post-intervention, although these differences did not reach statistical significance at either time point. Patients treated with a noninsulin agent also demonstrated a net 4-kg weight loss at 6 months and reported less hypoglycemia when compared with the intensive insulin treatment

**TABLE 2. Addition of Noninsulin Agent Versus Prandial Insulin**

Outcomes at 6 Months	Prandial Insulin (n = 28)	Noninsulin Agent (n = 34)	P
Change in A1C, %	−0.53 ± 1.19	−0.84 ± 1.19	0.31
Weight change, kg	1.99 ± 2.45	−2.09 ± 4.22	<0.01
Outcomes at 1 Year	Prandial Insulin (n = 23)	Noninsulin Agent (n = 25)	P
Change in A1C, %	−0.67 ± 1.2	−0.86 ± 1.3	0.61
Patients with A1C <7.5%, n (%)	7 (30)	7 (28)	0.85
Documented hypoglycemic episodes, n/patient-year	2.6	1.0	0.01

*Data are expressed as mean ± SD unless otherwise noted.*

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**TABLE 3. DPP-4 Inhibitor Versus GLP-1 Receptor Agonist as Third Noninsulin Agent**

Outcomes at 6 Months	DPP-4 Inhibitor (n = 22)	GLP-1 Agonist (n = 12)	P
Change in A1C, %	-0.85 ± 1.0	-0.83 ± 1.4	0.95
Weight change, kg	-0.95 ± 3.54	-4.13 ± 4.49	0.06
Outcomes at 1 Year	DPP-4 Inhibitor (n = 15)	GLP-1 Agonist (n = 10)	P
Change in A1C, %	-0.81 ± 1.1	-0.93 ± 1.5	0.84
Patients with A1C <7.5%, n (%)*	2 (13)	5 (50)	0.05
Documented hypoglycemic episodes, n/patient-year	1.0	0.9	0.83
Outcomes at Study Conclusion	DPP-4 Inhibitor (n = 22)	GLP-1 Agonist (n = 12)	P
Patients progressing to prandial insulin, n (%)	10 (45)	2 (17)	0.10
Median time to progression to prandial insulin, months	9	10	—
Reason for medication discontinuation, n			
Side effects	1	0	
Lack of compliance	0	1	
Lack of efficacy	9	1	

Data are expressed as mean ± SD unless otherwise noted. \*Baseline A1C, %: DPP-4 inhibitor 9.2 ± 1.2 vs. GLP-1 receptor agonist 8.9 ± 1.0 (P = 0.55).

arm, both of which were statistically significant. There was no difference in the proportion of patients achieving an A1C level <7.5% at 1 year (28 vs. 30%, P = 0.85).

**GLP-1 Receptor Agonists Versus DPP-4 Inhibitors in Noninsulin-Treated Patients (Table 3)**

Among the noninsulin therapies, A1C lowering was similar between the GLP-1 receptor agonists and DPP-4 inhibitors at both 6 months (-0.83 vs. -0.85%, P = 0.95) and 1 year (-0.93 vs. -0.81%, P = 0.84). Patients in the GLP-1 receptor agonist treatment arm experienced greater weight loss than the DPP-4 inhibitor-treated patients (-4.13 vs. -0.95 kg, P = 0.06) and were more likely to achieve an A1C level <7.5% at 1 year (50 vs. 13%, P = 0.05). The incidence of hypoglycemia was similar between the two treatment modalities (GLP-1 receptor agonist = 0.9/patient-year vs. DPP-4 inhibitor = 1.1/patient-year); however, the DPP-4 inhibitor treatment arm did demonstrate a higher proportion of patients

progressing to prandial insulin than the GLP-1 receptor agonist-treated patients. The primary reason for progression to prandial insulin in both treatment groups was a lack of therapeutic efficacy. Additionally, one patient in the DPP-4 inhibitor treatment group was forced to discontinue therapy because of recurrent upper respiratory tract infections, and one patient treated with a GLP-1 receptor agonist was unable to tolerate a twice-daily exenatide dosing schedule because of severe nausea.

**Discussion**

A number of previous randomized controlled trials have evaluated the addition of insulin versus noninsulin therapies to a baseline regimen of metformin plus a sulfonylurea. A comprehensive managed care review from July 2000 to March 2009 found that the addition of insulin therapy to a backbone of two oral antidiabetic drugs resulted in greater A1C lowering and reduced annual health care costs when compared to the addition of a third oral agent or a GLP-1 receptor agonist (9). A retrospective cohort re-

view from four Australian centers also assessed outcomes after intensification of therapy in patients receiving basal insulin and found that intensive insulin therapy was associated with greater A1C reductions than noninsulin therapy but more significant weight gain (10). However, to our knowledge, this study is the first to assess the treatment outcomes of insulin intensification with prandial insulin compared to the addition of a third noninsulin agent in patients already receiving basal insulin in combination with two oral agents. We believe this is an important question to address for patients because prandial insulin initiation is generally associated with a more significant injection burden, greater weight gain, and more frequent hypoglycemia than daily basal insulin alone or alternative noninsulin therapies. In the landmark trial by Holman et al. (11), prandial insulin intensification was associated with further hypoglycemia and weight gain compared to biphasic or basal insulin treatment with no additional reduction in A1C. An assessment of treatment satisfaction from

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this trial also reported that prandial insulin therapy was associated with lower scores on the Insulin Treatment Satisfaction Questionnaire compared to the biphasic or basal treatment arms (12).

Another recently published, randomized controlled trial compared the addition of once-weekly exenatide plus pioglitazone or intensive insulin therapy to a backbone of metformin plus a sulfonylurea and reported greater A1C reductions in the exenatide/pioglitazone-treated patients with fewer episodes of hypoglycemia and significantly less weight gain (13). Trials such as these demonstrate the potential efficacy and safety of noninsulin therapies in certain patient populations with type 2 diabetes refractory to first-line treatment. The diversity of these studies also highlights the importance of patient selection and the need to individualize treatment when attempting to modify or intensify diabetes therapies (8).

The results of our study found that veteran patients receiving metformin, a sulfonylurea, and basal insulin treated with an additional non-prandial insulin modality (GLP-1 receptor agonist or DPP-4 inhibitor) demonstrated equivalent A1C lowering but with less weight gain and fewer episodes of hypoglycemia than patients treated with prandial insulin. Despite its superior A1C-lowering potential, the failure of prandial insulin to outperform the noninsulin therapies may be partially attributable to the increased simplicity and reduced injection burden with the noninsulin modalities. At the time of the study, linagliptin and liraglutide were the VA-preferred DPP-4 inhibitor and GLP-1 receptor agonist, respectively. These medications are both dosed once daily compared to a prandial insulin regimen, which typically consists of three mealtime injections that must be dosed in conjunction with food. Patients treated with prandial insulin in this study also experienced more significant weight gain and

more frequent hypoglycemic episodes than noninsulin-treated patients, both of which have previously been identified as risk factors for intentional dosage manipulation or altered dietary intake to avoid hypoglycemia and weight gain (5,6). This result underscores the importance of shared decision-making when considering insulin initiation or intensification to ensure that patients understand the potential risks and benefits of therapy and agree to actively participate in the management of their insulin regimen. Alternatively, patients who have reservations or potential barriers to compliance with a prescribed insulin regimen may benefit from simplification of their regimen and would be more suitable candidates for noninsulin therapies.

In patients for whom a non-prandial insulin treatment modality is preferred, the results of this study support that greater weight loss can be obtained with a GLP-1 receptor agonist relative to a DPP-4 inhibitor, with similar reductions in A1C. The GLP-1 receptor agonist treatment arm was also associated with a greater proportion of patients who achieved an A1C level <7.5% at 1 year despite a similar baseline A1C (9.2 vs. 8.9%,  $P = 0.55$ ) and subsequently lead to less progression to prandial insulin. Of note, nearly 50% of patients receiving a DPP-4 inhibitor progressed to prandial insulin within 1 year of initiation of therapy, with a median time to progression of 9 months. These results should also be interpreted in the context of the recently published LEADER (Liraglutide Effect and Action in Diabetes: Evaluation of Cardiovascular Outcome Results) trial (14), which demonstrated the potential for liraglutide to reduce cardiovascular mortality among high-risk patients with type 2 diabetes and further support the notion that GLP-1 receptor agonists may be the preferred class of incretin mimetics in obese patients at high risk for cardiovascular disease. Cost and ease of administration should still be considered before initi-

ating a GLP-1 receptor agonist because these agents are expensive and require routine injection. Some patients may have difficulty tolerating immediate-release exenatide in particular because of the dose-limiting adverse effect of nausea; liraglutide or a long-acting GLP-1 receptor agonist should be preferred in these patients.

Several limitations to this study must be considered when attempting to extrapolate the results. This work was a small, nonrandomized study of predominantly male veteran patients. Caution should be used when applying these data to other non-veteran patient populations including women. The retrospective nature of this study limited the ability to actively assess compliance; subsequently, provider documentation was relied on to evaluate prescribing changes, incidence of hypoglycemia, and adherence to medication therapy. Sodium-glucose cotransporter 2 inhibitors and the thiazolidinediones were not included because of the timing of the review period, and, subsequently, their impact on outcomes could not be assessed. Patients receiving prandial insulin generally require more rigorous blood glucose monitoring than patients taking a GLP-1 receptor agonist or DPP-4 inhibitor, making them more likely to have a documented hypoglycemic event in their medical chart. Additionally, the decision of when to discontinue sulfonylurea therapy after intensive insulin initiation was made at the discretion of the treating provider; subsequently, 14 patients in the prandial insulin treatment arm remained on sulfonylurea therapy for the duration of the study. Finally, GLP-1 receptor agonists and DPP-4 inhibitors were more likely to be prescribed by endocrinologists and pharmacotherapy specialists than prandial insulin (97 vs. 68%) and were generally initiated in patients with a higher baseline BMI (37.1 vs. 33.8 kg/m<sup>2</sup>). As a result, confounding variables related to these two differences in the baseline patient populations, such as medical literacy and additional life-

style modifications, cannot be entirely excluded.

### Conclusion

In certain patients with type 2 diabetes already receiving therapy with metformin, a sulfonylurea, and basal insulin, the addition of a non-prandial insulin therapy (GLP-1 receptor agonist or DPP-4 inhibitor) may be associated with similar A1C lowering at 6 months and 1 year, less hypoglycemia, and less weight gain when compared with starting prandial insulin. It is reasonable to consider a trial of a GLP-1 receptor agonist or DPP-4 inhibitor in these patients before initiating prandial insulin, especially if compliance with intensive insulin therapy is a concern. All patients should be assessed before initiating prandial insulin to identify and address potential barriers to compliance. In patients for whom a noninsulin therapy is preferred, treatment with a GLP-1 receptor agonist may be associated with greater weight loss and decreased progression to prandial insulin than treatment with a DPP-4 inhibitor.

### Duality of Interest

No potential conflicts of interest relevant to this article were reported.

### Author Contributions

A.D.S. collected data and wrote the manuscript. M.M.B. designed the study and edited the manuscript. A.D.S. is the guarantor of this work and, as such, had full access to all the data in the study and takes responsibility for the integrity of the data and the accuracy of the data analysis.

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