Diabetes Care Publish Ahead of Print, published online April 1, 2008

Adjust To Target In Type 2 Diabetes: Comparison Of A Simple Algorithm To Carbohydrate Counting For Adjustment Of Mealtime Insulin Glulisine

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Clinical Trial Registry No. NCT00135057

Received for publication 06 November 2007 and accepted in revised form 13 March 2008.

ABSTRACT

Objective: Carbohydrate counting is an effective approach to mealtime insulin adjustment in type 1 diabetes, but has not been rigorously assessed in type 2 diabetes.

Research and Design Methods: This 24-week, multicenter, randomized, controlled study compared two algorithms for adjusting mealtime (glulisine) insulin along with a standard algorithm for adjusting background (glargine) insulin in 273 intent-to-treat patients with type 2 diabetes. Glulisine and glargine were adjusted weekly in both groups based on previous week's self monitored blood glucose (SMBG) results. The Simple Algorithm group was provided set doses of glulisine to take before each meal. The Carbohydrate Counting group was provided an insulin to carbohydrate ratio to use for each meal and adjusted their glulisine dose based on amount of carbohydrate consumed.

Results: A1C levels at week 24 were 6.70% (Simple Algorithm) and 6.54% (Carb Count). The respective mean A1C changes from baseline to 24 weeks were –1.46% and –1.59% (P=.24). A1C <7.0% was achieved by 73.2% (Simple Algorithm) and 69.2% (Carb Count) (P=.70); respective values for A1C <6.5% were 44.3% and 49.5% (P=.28). The total daily dose of insulin was lower and there was a trend toward less weight gain in Carb Count patients. Severe hypoglycemia rates were low and equal in the two groups.

Conclusions: Weekly basal:bolus insulin adjustments based on premeal and bedtime glucose patterns resulted in significant reductions in A1C. Having two effective approaches to delivering and adjusting rapid-acting mealtime insulin may increase physicians' and patients' willingness to advance therapy to a basal:bolus insulin regimen.

Glycosylated hemoglobin (A1C) and postprandial glucose (PPG) have been related to risk for long-term complications in diabetes (1, 2, 3). Insulin therapy is often needed to achieve target A1C and PPG in type 2 diabetes (4). While many insulin regimens are available, this study examined the use of a physiologic regimen that includes a long-acting insulin to provide a basal insulin level for the entire day and a rapid-acting insulin for bolus administration at mealtimes (5,6).

Establishing the optimal mealtime insulin dose in basal:bolus therapy may be difficult because it often involves calculations that consider multiple factors such as current blood glucose (BG), target BG, insulin-to-carbohydrate (I:C) ratios, total carbohydrate content of meals, and activity levels (7). Insulin delivery based on carbohydrate counting is the "gold standard" for improving glycemic control in type 1 diabetes (8, 9), but is difficult for some patients (10, 11). Neither large, randomized studies of intensive basal:bolus analog insulin therapy in patients with type 2 diabetes nor studies evaluating the efficacy of carbohydrate counting in type 2 diabetes have been conducted. This 24-week study compared an I:C ratio to a simple pattern control–based algorithm for adjusting the dose of prandial insulin glulisine.

RESEARCH DESIGN AND METHODS

Design. *Study Design.* —This multicenter, controlled, open, randomized, parallel-group study included 2 weeks of screening followed by 24 weeks of treatment. Randomization (1:1) was balanced by metformin administration, baseline number of insulin injections, injection with pen versus syringe and vial, and study center. The study complied with the International Council on Harmonization E6 guideline of May 1996, and with the ethical principles of the Declaration of Helsinki. Institutional review boards approved the protocol and study documents. All patients provided informed written consent.

Patients. — Participants were 18–70 years old, had type 2 diabetes for ≥6 months, with A1C of 7–10% at screening, and had taken ≥2 insulin injections/day (36% on 2 injections, 64% on more than 2 injections) ± metformin (one-third were on metformin), for ≥3 months before study entry. Upon entry into study, 37% were using glargine and at least one injection of a rapid-acting insulin analog, 36% were using a pre-mixed insulin and the remainder were on a mix of various other regimens.

Reasons for exclusion were treatment with oral antidiabetic drugs (except metformin) within 3 months before study entry; women planning pregnancy, pregnant, or lactating; serum creatinine ≥1.5 mg/dL in men (≥1.4 mg/dL in women) taking metformin and >3.0 mg/dL for any subject; clinically significant renal disease (other than proteinuria); hepatic disease; New York Heart Association class III–IV heart failure; or any disease or condition that might interfere with study completion.

Treatments: Targets were fasting BG (FBG) <95 mg/dL, preprandial (before lunch and dinner) BG <100 mg/dL, and bedtime BG <130 mg/dL.

Insulin Glargine Dosing. — The initial insulin glargine dose was calculated as 50% of the pre-randomization total daily insulin dose. Subsequently, dosing was titrated weekly according to the mean of the last 3 days of fasting SMBG (Table 1). A dose increase could be split into ≥2 increments over the week.

Insulin Glulisine Dosing. — The remaining 50% of the total daily insulin dose was used for mealtime insulin glulisine which was split to cover 3 meals – 50% for the largest (most carbohydrate), 33%, middle-sized, and 17%,

the smallest meal. Glulisine dose adjustment for both groups was based on pre-lunch/dinner and bedtime (these 3 time-points are referred to as mealtime) BG patterns from the previous week as shown in Table 1. Simple Algorithm patients premeal doses were set weekly, based on the algorithm in Table 1. Study staff taught the Carb Count group about carbohydrate counting and how to use an I:C ratio. The I:C ratios for each meal were determined based on the algorithm in Table 1. An I:C ratio allows patients to adjust their insulin based on the amount of carbohydrate they choose to eat at a meal.

Additional Antidiabetic Medications. — Patients taking metformin at randomization continued using it at the same dose. No other insulin or oral antidiabetic agents were permitted.

Dietary and Lifestyle Recommendations. — Educational materials were specially designed for this study based on the International Diabetes Center *Type 2 Diabetes BASICS* client book (12). The materials for the Simple Algorithm group omitted all references to carbohydrate intake except in the context of treating hypoglycemia and having carbohydrate if consuming alcohol.

Patient Diaries and Study Visits: ***Diaries.—*** All patients recorded SMBG before meals and at bedtime; insulin doses; food and estimated carbohydrate intake per meal (Carb Count group); information related to hypoglycemia; activity level; and a 7-point BG profile at weeks 0, 12, 18, and 24.

Visits.—Study visits occurred at screening, baseline, weeks 2, 6, 12, 18, and 24 (endpoint). Evaluations included physical examinations, vital signs, electrocardiogram, A1C, hematology and chemistry laboratory tests, and diary review. Adverse events (AEs), hypoglycemic episodes, and concomitant medications were recorded. There was weekly contact either by a study visit or a phone call to review diaries and adjust insulin doses.

Efficacy and Safety Variables: ***Efficacy.*** — The primary endpoint was the change from baseline to week 24 in A1C. Secondary variables were change in A1C from baseline to individual study time points; changes from baseline to week 24 in FPG, preprandial and postprandial BG, 7-point BG profile, average basal, bolus, and total insulin doses; lipids; percentages of patients achieving A1C <7.0% and <6.5% at week 24; and weight gain.

Safety. — All AEs were recorded. Clinical chemistry, hematology values, and physical examinations, including weight and vital signs, were documented.

Hypoglycemia. — Severe hypoglycemia was defined as requiring assistance and involved either SMBG <36 mg/dL or treatment with oral carbohydrates, intravenous glucose or glucagon, with a prompt response to that therapy. Symptomatic hypoglycemia was also documented.

Data Analysis: ***Populations.*** — The safety population included patients who took ≥1 dose of study medication and had any follow-up information. The intent-to-treat (ITT) population included patients evaluated for safety who had baseline and an on-therapy observation for ≥1 efficacy variable, but excluded patients who never received treatment or who were treated but had no postbaseline efficacy assessments.

Sample Size.— The noninferiority hypothesis was to be tested; a study with 86 evaluable subjects per treatment arm would have 90% power to detect treatment differences of 0.5%. The standard deviation of $\sigma = 1.0$ used in the power computations corresponds to the 95% upper confidence limit of the standard deviation of the A1C change from a previous insulin glulisine trial.

Statistical Methodology. —A mixed-model repeated-measures analysis including covariates baseline A1C, number of daily injections before the study (2 or >2), metformin use at randomization, injection method (pen or vial), and study site provided

adjusted estimates and changes from baseline by visit for weeks 2, 6, 12, 18, and 24 for A1C, FPG, 7-point BG profile, basal and bolus insulin doses, lipids, weight, and BMI. Percentages of patients achieving A1C <7.0% and <6.5% were analyzed by logistic regression that included treatment arm, baseline A1C, and other randomization factors. A Poisson regression model, incorporating overdispersion, analyzed the rate of hypoglycemia; a logistic regression model analyzed hypoglycemia incidence.

RESULTS

Patients – Of 281 patients randomized, 273 comprised the ITT population (Table 2) (136 Simple Algorithm, 137 Carb Count; Figure 1). Forty ITT patients (12 Simple Algorithm, 28 Carb Count) discontinued treatment.

Primary Efficacy Analysis. The primary efficacy analysis employed ANCOVA to compare change from baseline in A1C at Week 24 after adjusting for baseline A1C. Non-inferiority of the Simple Algorithm compared with Carb Counting was established because the mean A1C improved in both treatment arms to a similar degree (Simple Algorithm: 1.46% decrease; Carb Count: 1.59% decrease), and the 95% confidence bounds on the mean difference were well within the non-inferiority margin of 0.5% specified in the study protocol (Week 24: Carb Count – Simple Algo = -0.13%) with 95% CB: (-0.35%, 0.09%).

Secondary Efficacy Analyses. A1C levels at week 24 were 6.70% (Simple Algorithm) and 6.54% (Carb Count) (Figure 2A); at each time point, changes from baseline were statistically significant with both treatments (*P*<.0001). By 12 weeks both groups had achieved an average A1C of <7.0%. At endpoint, 73.0% (Simple Algorithm) and 69.2% (Carb Count) patients had A1C <7.0% (*P*=.70); respective values for A1C <6.5% were 44.3% and 49.5% (*P*=.28).

By week 24, both arms had significantly improved FPG adjusted means from baseline (Simple Algorithm, 112.0 mg/dL; Carb Count, 101.8 mg/dL; *P*<.0001 for both). The change from baseline was -40.4 mg/dL in Simple Algorithm patients and -50.6 mg/dL in Carb Count patients (*P*=.059) (Figure 2B). By 12 weeks the average FPG was 108 mg/dL (Simple Algorithm) and 112 mg/dL (Carb Count). Blood glucose values at each visit declined in both arms, and the within-group change from baseline was statistically significant over all daily time points and study visits (Figure 2C).

Changes in Insulin Doses. — At baseline, the mean insulin glulisine, glargine, and total insulin doses were 53.9, 53.9, and 107.8 units (Simple Algorithm), and 50.5, 50.5, and 100.9 units (Carb Count). At week 24, the adjusted mean insulin glulisine (*P*=.0011), glargine (*P*<.0001), and total insulin doses (*P*=.0002) were significantly higher in Simple Algorithm than in Carb Count patients (108.7, 102.5, and 207.4 units vs. 88.9, 86.4, and 175.5 units, respectively). At 24 weeks, the total insulin dose was 1.9 units/kg (Simple Algorithm) and 1.7 (Carb Count group). **(see online Table 3)**

Lipids. —Adjusted mean total cholesterol decreased slightly in both groups from baseline to week 24. A significant decrease was observed only for week 12 among Carb Count patients from 175.0 to 168.5 mg/dL (–8.35 mg/dL; *P*<.01). Neither HDL- nor LDL-cholesterol changed significantly from baseline to week 24 in either group; no between-group differences were observed at week 12 or 24. Triglycerides decreased significantly from baseline to week 12 in both the Carb Count (144.0 to 128.5 mg/dL) and Simple Algorithm (164.7 to 148.3 mg/dL) groups (-18.27 mg/dL, P<0.0001 and -15.14 mg/dL, P< 0.004, respectively). There was also a significant reduction in triglycerides from baseline to week 24 in the Carb Count (144.0 to 133.0 mg/dL) group but not the Simple Algorithm (164.7 to 153.4

mg/dL) group (-13.19 mg/dL, P=0.008 and -8.19 mg/dL P=0.170, respectively).

Weight and BMI. — Both groups gained weight at 24 weeks: Simple Algorithm, 3.6 kg (3.4%); Carb Count, 2.4 kg (2.3%) , (*P*=.06 for the between-group difference at week 24). BMI showed a small but significant increase at 24 weeks: Simple Algorithm, 1.28 kg/m^2: Carb Count, 0.83 kg/m^2 (both *P*<.0001 versus baseline; *P*=.037 between groups).

Safey: *Adverse Events.* —The population used to determine adverse events and hypoglycemia came from the safety population. Overall, 102 (73.9%) Simple Algorithm and 98 (70.5%) Carb Count patients reported ≥1 treatment-emergent AE. In both groups, the most common were upper respiratory tract infection (17.4%, Simple Algorithm; 10.8%, Carb Count), nasopharyngitis (8.7% versus 5.8%), sinusitis (8.0% versus 6.5%), and influenza (5.1% versus 6.5%). Of 42 serious AEs, 41 were nonfatal: 22 (15.9%), Simple Algorithm and 19 (13.7%), Carb Count. One death, due to myocardial infarction, occurred in the Carb Count group. AEs led 6 (4.3%) patients in the Carb Count group and 3 (2.2%) in the Simple Algorithm group to discontinue treatment.

Hypoglycemia. —The Simple Algorithm had 53 episodes of severe hypoglycemia in 19 patients and Carb Count group had 37 episodes in 19 patients, leading to estimates of, 0.89 and 0.67 events/patient-year for the two groups (*P*=.58). SMBG < 70 mg/dL with symptoms was not statistically significant between the two groups (*P*=.08). However, SMBG < 50 mg/dL with symptoms was slightly but statistically significantly more common in the Carb Count group than the Simple Algorithm group (8.0 vs 4.9 events/patient-year, *P*=0.02).

Clinical and Laboratory Examinations. — Changes from baseline were minor and not clinically significant.

CONCLUSIONS

This is one of the few randomized controlled trials evaluating basal:bolus analog insulin therapy in obese patients with type 2 diabetes and one of the first studies evaluating the use of carbohydrate counting in patients with type 2 diabetes. Using a simple algorithm to adjust mealtime insulin glulisine each week based on SMBG patterns was as effective as adjusting mealtime insulin using I:C ratios. Both approaches yielded a reduction of about 1.5% in A1C with no significant differences in mean A1C change from baseline or in the percent of patients achieving A1C goals of <6.5% (13) or <7.0% (14). Both regimens were well tolerated. The risk for severe hypoglycemia was low and not significantly different between groups.

Other studies (15, 16), have shown that patients well-controlled on insulin often have a basal:bolus insulin ratio close to 50%:50%. At week 24, after multiple weekly titrations of insulin based on SMBG patterns, both the Simple Algorithm and the Carb Count groups had basal:bolus insulin ratios of approximately 49%:51%. In addition, at the end of the study, the bolus insulin dose was split between breakfast, lunch and dinner, approximately, 27%, 35%, and 38% in the Simple Algorithm group, and 25%, 34%, and 41% in the Carb Count group. At week 24, both groups required large total daily insulin doses (Simple Algorithm, 1.9 U/kg and Carb Count, 1.7 U/kg). The lower total insulin doses for Carb Count patients may reflect the more matching of insulin doses to carbohydrate intake at each meal, as opposed to the set meal doses of those in the Simple Algorithm group.

A recent study comparing three approaches to starting a single type of analog insulin in patients with type 2 diabetes (basal, biphasic premixed, prandial) concluded that while each regimen improved glucose control, most patients were likely to need more than one type of insulin to achieve target glucose

levels (17). The percent of patients who achieved the study's target A1C <6.5% was 8.1% basal, 17.0% biphasic and 23.9% prandial. Although one cannot directly compare insulin regimens from different study populations, it seems that our study population would be more difficult to control since patients had a longer duration of diabetes and were more obese than subjects in the Holman et al. trial. In the study reported here, however, patients with type 2 diabetes using basal:bolus therapy achieved an A1C <6.5% almost half the time: 44.3% Simple Algorithm and 49.5% Carb Count.

While basal:bolus insulin therapy can improve glycemic control in type 1 (6,18) and type 2 (19, 20) diabetes, the most effective use of SMBG for adjusting the basal:bolus insulins has not been clearly established (21-24). Some feel that postprandial monitoring is critical to establishing good glycemic control, while others are not convinced that postprandial testing is essential (2). In the present study, we showed that patients with type 2 diabetes utilizing fasting and mealtime SMBG testing alone to monitor and adjust their rapid-acting and long-acting insulin analogs achieved excellent glucose control as measured by A1c with minimal severe hypoglycemia.

The key elements of successful insulin therapy are to optimize glycemic control while minimizing hypoglycemia. Patients can learn to adjust mealtime insulin by either using a simple algorithm or learning to use I:C ratios. I:C ratios allow flexibility in food choices and enables relatively precise matching of mealtime insulin needs but can seem complex and may be difficult for some patients to implement (10, 11). We have shown that a standard mealtime insulin glulisine dose adjusted weekly on the basis of preprandial BG patterns can achieve the same goals as a regimen that adjusts mealtime insulin based on I:C ratios. It may be that our Simple Algorithm patients either consumed fairly consistent amounts of carbohydrates, thus minimizing needed changes in insulin dosing, or learned to modify their carbohydrate intake based on SMBG measurements.

Having two effective approaches to deliver and adjust rapid-acting mealtime insulin — a simple algorithm and I:C ratio — may increase patients' and clinicians' willingness to undertake basal:bolus insulin therapy, a step that is often needed to achieve optimal glucose control in type 2 diabetes.

ACKNOWLEDGMENTS

The authors acknowledge David M. Kendall, MD and Poul Strange, MD, PhD for their contributions to the protocol design, Michael Miller, PhD for statistical analysis, Elizabeth Lee, MD for overall study management, all of the study site investigators, Kelli Bradbury, ARNP-C, Gary Graf, ARNP-C, and all the study coordinators and Mary Ann Carr for her expert manuscript preparation assistance. Editorial support provided through the sanofi-aventis US Group.

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Table 1. Insulin Glargine and Insulin Glulisine Dose Adjustment Based on Pattern of Mealtime BG Values for the Past Week

Insulin Glargine Adjustments – Both Groups		
Mean of Last 3-Day Fasting SMBG, mg/dL	**Adjustment**	
>180	Increase 8 U	
140–180	Increase 6 U	
120–139	Increase 4 U	
95–119	Increase 2 U	
70–94	No change	
<70	Decrease by the same number of units as insulin glulisine increase that titration week, or up to 10% of total insulin glargine dose	
Insulin Glulisine Adjustments		
Simple Algorithm Group		
Mealtime Dose, U	**Pattern of Mealtime BG Values Below Target***	**Pattern of Mealtime BG Values Above Target†**
≤10	Decrease by 1 U	Increase by 1 U
>11–19	Decrease by 2 U	Increase by 2 U
≥20	Decrease by 3 U	Increase by 3 U
Carbohydrate Counting (Insulin to Carb Ratio) Group‡		
Mealtime Dose	**Pattern of Mealtime BG Values Below Target***	**Pattern of Mealtime BG Values Above Target†**
1U/20 g	**Decrease to 1U/25 g**	**Increase to 1U/15 g**
1U/15 g	**Decrease to 1U/20 g**	**Increase to 1U/10 g**
1U/10 g	**Decrease to 1U/15 g**	**Increase to 2U/15 g**
2U/15 g	**Decrease to 1U/10 g**	**Increase to 3U/15 g**
3U/15 g§	**Decrease to 2U/15 g**	**Increase to 4U/15 g**

U = units

* If > ½ of the mealtime BG values for the week were below target.

† If > ½ of the mealtime BG values for the week were above target.

‡ Each patient in the Carb Count group was also given a schedule for a mealtime insulin glulisine correction dose to add a few units if high, or subtract a few units if low.

§ Increase mealtime insulin as needed following this pattern.

Table 2. Demographic and Clinical Characteristics and Prior Insulin Treatment in the ITT Population

Characteristic	Statistic	Simple Algorithm (N=136)	Carb Count (N=137)	*P*-value
Age (years)	Mean (SD)	55.1 (8.8)	55.0 (9.5)	.8026
	Range	29 - 70	28 - 71	
Sex	N (%) Male	53 (39.0)	67 (48.9)	.2468
	N (%) Female	83 (61.0)	70 (51.1)	
Race	N (%) White	111 (81.6)	109 (79.6)	.2776
	N (%) Black	15 (11.0)	15 (10.9)	
	N (%) Asian/Oriental	2 (1.5)	0 (0.0)	
	N (%) Multiracial	0 (0.0)	1 (0.7)	
	N (%) Other	8 (5.9)	12 (8.8)	
Height (cm)	Mean (SD)	169 (10.6)	170 (9.8)	.4560
	Range	146 - 198	150 - 193	
Weight (kg)	Mean (SD)	107 (24.2)	103 (21.7)	.1217
	Range	61 - 187	52 - 171	
BMI (kg/cm^2)	Mean (SD)	37.7 (8.1)	35.6 (7.2)	.0416
	Range	21 - 63	17 - 60	
A1C (%)	Mean (SD)	8.1 (0.9)	8.3 (0.9)	.0825
	Range	7 - 10	6 - 11	
FPG (mg/dL)	Mean (SD)	162 (58.2)	163 (54.2)	.8112
	Range	49 - 306	52 - 341	
Age at Onset (year)	Mean (SD)	42.8 (10.6)	42.4 (9.6)	.8594
	Range	13 - 66	14 - 63	
Diabetes Duration (years)	Mean (SD)	12.9 (7.7)	13.0 (7.8)	.9055
	Range	0 - 40	0 - 36	
Has subject used a pen for insulin administration?	N (%) No	66 (48.5)	62 (45.3)	.7788
	N (%) Yes	69 (50.7)	75 (54.7)	
Number of Injections at randomization	N (%) 2 per day	43 (31.6)	57 (41.6)	.0211
	N (%) more than 2 per day	93 (68.4)	80 (58.4)	
Metformin used at randomization	N (%) No	90 (66.2)	89 (65.0)	.5793
	N (%) Yes	46 (33.8)	48 (35.0)	

SD = standard deviation

Figure 1. **Disposition of patients. ITT = intent to treat; AEs = adverse events.**

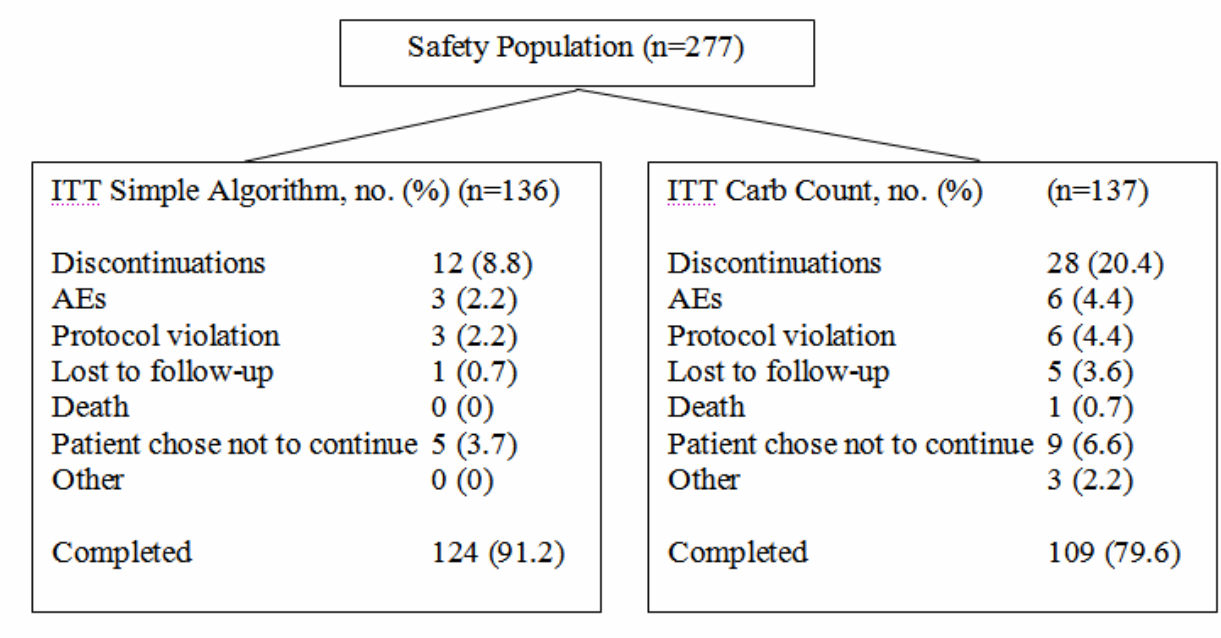

Figure 2. A, A1C: Change from baseline in Simple Algorithm and Carb Count groups at weeks 2, 6, 12, 18, and 24 (ITT population). B, FPG: Change from baseline in Simple Algorithm and Carb Count groups at weeks 2, 6, 12, 18, and 24 (ITT population). C, Glucose Profiles from 7 point SMBG testing at baseline and week 24 in Simple Algorithm and Carb Count groups (ITT population).