Glycemic Control With Insulin Glargine Plus Insulin Glulisine Versus Premixed Insulin Analogues in Real-World Practices: A Cost-Effectiveness Study With a Randomized Pragmatic Trial Design

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ABSTRACT

Background: Cost can be an important consideration, along with safety and efficacy, in deciding the most appropriate treatment for patients with type 2 diabetes. Both basal-bolus and premixed insulin analogue regimens are widely used in clinical practice; however, limited information is available regarding cost-effectiveness.

Objective: The goal of this study was to compare glycemic control, cost-effectiveness, and quality of life effects of insulin glargine plus insulin glulisine (glargine/glulisine) versus premixed insulin analogues in real-world clinical practice.

Methods: Adults with type 2 diabetes (glycosylated hemoglobin [HbA_{1c}] ≥7.0%) at 3 US endocrinology centers were randomly assigned to receive either glargine/glulisine or premixed insulin analogues and continued treatment following the centers' usual practice. HbA_{1c}, weight, insulin dose, concomitant oral antidiabetic drug (OAD) usage, and hypoglycemia were evaluated at baseline and 3, 6, and 9 months. Medication costs, including costs for all insulin or OAD regimens, were estimated using published wholesale acquisition costs.

Results: A total of 197 patients were randomized to receive glargine/glulisine therapy (n = 106) or premixed analogue therapy (n = 91). Overall, the mean age was 56 years, the mean duration of diabetes was 13 years, with a mean HbA_{1c} of 9.25% and mean BMI of 35.8 kg/m^2 at baseline. Patients randomized to receive glargine/glulisine had a greater mean HbA_{1c} reduction from baseline (–2.3%) than patients receiving a premixed analogue regimen (–1.7%). Adjusted mean follow-up HbA_{1c} was 6.9% versus 7.5%, respectively (difference, –0.59%; $P < 0.01$). The glargine/glulisine group also used a lower mean number of OADs (0.86 vs 1.14; difference, –0.28; $P = 0.04$) but had a higher weight (240 vs 235 lb; difference, 4.55 lb; $P = 0.03$) than the premixed analogue group at follow-up. There were no significant differences in daily insulin dose and rates of hypoglycemia. Overall medication costs per 1.0% reduction in HbA_{1c} were $841 with glargine/glulisine and $1308 with premixed analogues.

Conclusions: Overall, treatment with glargine/glulisine provided greater improvement in glycemic control and may represent a more cost-effective treatment option than premixed regimens for patients with type 2 diabetes in real-world clinical practice. However, due to the pragmatic trial design, the study concluded before follow-up assessments were available for all randomized patients. (*Clin Ther*. 2011;33:841–850)

Key words: cost-effectiveness, insulin glargine, insulin glulisine, premixed insulin, type 2 diabetes.

INTRODUCTION

Along with glycemic control, the cost of medications for different diabetes treatment regimens is also an important consideration. Both basal-bolus and premixed

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insulin analogue regimens are widely used in clinical practice; however, their comparative cost-effectiveness has not been determined. In the LAPTOP (Lantus Plus Amaryl Plus Metformin Versus Premixed Insulin in Patients with Type 2 Diabetes Mellitus After Failing Oral Treatment Pathways) trial, combination treatment with insulin glargine plus the oral antidiabetic drugs (OADs) glimepiride and metformin was shown to be a safer, more effective, and more cost-effective alternative to premixed regular human/NPH insulin in patients whose type 2 diabetes was inadequately controlled with OADs.[1,2] Patients treated with insulin glargine plus OADs had a significantly greater reduction in mean glycosylated hemoglobin (HbA_{1c}) (–1.64% vs –1.31%; $P = 0.0003$) and fewer confirmed hypoglycemic episodes (4.07 vs 9.87/patient-year; $P < 0.0001$).[1] A cost analysis from this study in Germany also reported that costs per patient per year were an average of €236 (~$290 US) lower for insulin glargine plus OAD versus premixed insulin therapy.[2]

This finding was in contrast to a cost analysis based on the Initiate Insulin by Aggressive Titration and Education clinical trial,[3] which compared the safety and efficacy of initiating insulin therapy with a premixed analogue regimen (biphasic insulin aspart [BIAsp] 70/30) versus insulin glargine in addition to OADs in patients with type 2 diabetes. This study reported a greater mean HbA_{1c} reduction in the BIAsp 70/30 group (–2.79% vs –2.36%; $P < 0.01$) but a greater frequency of minor hypoglycemic episodes (3.4 vs 0.7 episodes/year; $P < 0.05$). The calculated total lifetime costs per patient treated successfully to reach HbA_{1c} <7.0% were $80,523 lower with BIAsp 70/30 than with insulin glargine.[4]

However, both of these cost analyses were based on data from randomized controlled trials that did not necessarily reflect real-world clinical practice; for example, the LAPTOP trial[1,2] did not allow use of any OAD therapy in the premixed treatment arm, and neither the LAPTOP trial nor the Initiate Insulin by Aggressive Titration and Education trial (INITIATE)[3] included use of prandial insulin with insulin glargine. Similarly, several recently published clinical trials, comparing premixed insulin with other regimens, included only basal insulin (plus oral therapy) in the comparator arm.[5–9] Predictably, this type of comparison leads to the demonstration of greater effects on fasting glucose levels with the basal insulin analogue and greater reductions in postprandial glucose levels with BID premixed insulin regimens, as seen in a systematic review by Qayyum et al.[5] This review also found that premixed analogues were associated with greater reductions in HbA_{1c} versus basal analogue therapy but an increased incidence of hypoglycemia. It is important to note that the clinical usefulness of trials comparing once-daily insulin injection (basal only) with BID injections (premixed, containing prandial insulin) has been questioned in the literature; a more relevant comparison would be between BID premixed regimens and a regimen of long-acting basal insulin plus 1 rapid-acting prandial insulin injection before the main meal.[3,6,10–13]

To the best of our knowledge, there are no published head-to-head trials from real-world clinical practice settings that compare basal plus mealtime insulin analogues with premixed analogue regimens. There is no published literature directly comparing the effects of these regimens on quality of life (QOL) or other patient-reported outcomes (PROs), although studies have reported improved QOL associated with the addition of insulin glargine to OAD therapy (versus OAD adjustment)[14] and with BID premixed insulin versus basal-bolus therapy (with NPH insulin and preprandial insulin lispro).[15]

The present study selected patients with type 2 diabetes from 3 endocrinology centers to compare the glycemic benefits, cost differences, and QOL effects associated with insulin glargine plus insulin glulisine (glargine/glulisine) versus premixed analogue therapy. This study used a pragmatic design to compare the effectiveness of glargine/glulisine with premixed analogues in a real-world clinical setting.[16,17] Pragmatic studies differ from randomized clinical trials; randomized controlled trials focus on questions comparing the efficacy of 2 agents in a highly controlled environment, whereas pragmatic studies evaluate the effectiveness of a therapeutic approach in an actual clinical setting.[16–24] In the present study, the pragmatic design allowed us to compare glycemic outcomes and PROs, as well as differences in treatment costs, between the 2 treatment arms in the clinical setting.[17,18]

PATIENTS AND METHODS

This randomized pragmatic trial was conducted from July 2005 to October 2007 at 3 US endocrinology practice centers in Baltimore, Maryland; Easton, Maryland; and Baton Rouge, Louisiana. There were 3 investigators in the study. The study included men and

women aged ≥18 years with type 2 diabetes who were experiencing inadequate glycemic control (baseline HbA_{1c} ≥7.0%) and were receiving either insulin or oral therapy. Patients included in the study must have had a BMI ≥25 kg/m^2 at baseline and been eligible for both insulin regimens. Patients taking exenatide or pramlintide before study initiation were excluded.

Approval from the local institutional review board was obtained for the original version of the study protocol and all subsequent updates. Written patient informed consent was required before treatment randomization to receive either glargine/glulisine or analogue premixed insulin. The randomization methods assigned patients to either treatment group based on whether the sum of the last 2 digits of the respective patient's Social Security number was odd or even. Because insulin glulisine had not yet been commercially released at the beginning of the study, samples were provided to patients randomized to receive glargine/glulisine. In 2006, to ensure equal access to both treatment arms, patients randomized to glargine/glulisine were provided financial assistance to cover the costs that were in excess of the copayment for insulin glulisine because of its initial formulary placement with health plans. Both these circumstances have been considered in the medication cost analysis. All premixed analogues were included for the patients randomized to the premixed group, including but not limited to 75% insulin lispro protamine suspension/25% insulin lispro and 70% insulin aspart protamine suspension/30% insulin aspart. After randomization, patients in both arms continued treatment following the center's usual practice, with no additional therapeutic protocols. Although patients were encouraged to make each requested visit, some patients not only failed to return for a specified visit but also did not return to the study site for further treatment (ie, lost to follow-up). Consequently, the adjusted mean follow-up HbA_{1c} in patients with at least 1 follow-up visit were included in the analysis (n = 128). To evaluate any potential bias among the patients who did not return to the practice site after randomization and those who completed at least 1 follow-up visit, baseline characteristics of the patients lost to follow-up in the glargine/glulisine and premixed groups were compared with those of the overall sample.

Data on HbA_{1c}, weight, and other laboratory values were collected at baseline and at 3, 6, and 9 months after randomization. Information regarding insulin dose, concomitant antidiabetic medications, and hypoglycemia was obtained directly from the patient and supplemented when necessary with extractions of medical charts at baseline and at 3, 6, and 9 months. Costs of all antidiabetic medications were obtained from the 2007 wholesale acquisition cost (WAC; First DataBank, Inc., South San Francisco, California), using the lowest strength if multiple strengths were prescribed for the same product to derive the more conservative cost estimation. Monthly cost was calculated using the adjusted daily dose multiplied by 30 days. Strips, needles, and costs for monitoring blood glucose levels were not included.

Patient-reported outcomes were assessed using the Diabetes Quality of Life (DQOL) scale,[25] EuroQoL-5D (EQ-5D),[26] and Work Productivity and Activity Impairment (WPAI) Questionnaire.[27] The DQOL is a 46-item questionnaire that assesses 4 dimensions, each measured on a 5-point Likert scale: satisfaction with treatment, impact of treatment, worries about future effects of diabetes, and worries about social and vocational issues. Higher scores indicate worse QOL (ie, greater problem frequency or dissatisfaction).[28,29] The EQ-5D consists of 5 dimensions: mobility, self-care, usual activities, pain or discomfort, and anxiety or depression. In this instrument, each dimension has 3 levels of severity, and a summary index value (standardized against population norms) can be calculated between 0 (representing death) and 1 (representing full health).[30] The WPAI contains 6 questions, including whether the patient is currently employed, how many hours missed from work because of health problems, how many hours missed from work for other reasons, how many hours actually worked, how much health problems affected productivity while working, and how much health problems affected ability to perform regular daily activities (overall impairment).[27] Higher scores are associated with greater impairment.

We used the intent-to-treat population in this analysis by including all patients with at least 1 follow-up assessment. For the statistical analysis, *t* tests were used to provide descriptive results of the comparison between treatment groups. A paired *t* test was used for differences between baseline and end-of-study outcome measures within each study group. A repeated-measures analysis, mixed-effects model was used to determine the difference in HbA_{1c}, weight, BMI, PROs adjusted for demographic characteristics, time to HbA_{1c} test, baseline HbA_{1c}, hypoglycemia, and baseline for any type of medication. Specifically, the fixed

effects of the adjustment model for HbA_{1c} were estimated as follows:

$$HbA_{1ct} = \beta_0 + \beta_1 * \text{group} + \beta_2 * \text{age} + \beta_{3-6} * \text{race} + \beta_{7-10} * \text{education} + \beta_{11} * \text{employment} + \beta_{12} * \text{diabetes duration} + \beta_{13} * \text{time to } HbA_{1ct} + \beta_{14-15} * \text{visit}_t + \beta_{16} * \text{baseline } HbA_{1c} + \beta_{17} * \text{baseline hypoglycemia} + \beta_{18} * \text{baseline oral} + \beta_{19} * \text{baseline insulin} + \beta_{20} * \text{baseline other oral} + \beta_{21} * \text{concurrent Byetta}_t + \beta_{22} * \text{number of concurrent OAD}_t + \beta_{23} * \text{sliding scale insulin}_t + \beta_{24} * \text{squared time to } HbA_{1ct},$$

$Byetta_t$ = time to Byetta; HbA_{1ct} = time to glycosylated hemoglobin testing; OAD_t = time to treatment with oral antibiabetic drugs; sliding scale $insulin_t$ = time to treatment with sliding scale insulin; squared time to HbA_{1ct} = squared time to glycosylated hemoglobin testing; $visit_t$ = time to visit.

For hypoglycemia, we used a generalized mixed-effects model with a SAS GLIMMIX procedure. All analyses were completed using SAS 9.1 (SAS Institute, Inc, Cary, North Carolina) and nested subjects within investigation sites to account for site differences in clinical practice. No additional missing data imputations were performed, because estimated group means were reported for all patients in the repeated measures analysis with mixed-effects model.

RESULTS

Baseline demographic and disease characteristics were similar among treatment groups (**Table I**). Overall, the mean age was 56 years, the mean duration of diabetes was 13 years, with a mean HbA_{1c} of 9.25% and mean BMI of 35.8 kg/m^2 at baseline. Approximately 70% of patients included in the study had used OADs during the 4 months before randomization, with no significant differences between treatment groups (**Table II**). Similarly, ~88% of patients used insulin during the 4 months before randomization, with a mean daily dose of 71 IU. There were no significant differences between treatment groups. A total of 29% of patients had chart records for hypoglycemia during the 4 months before randomization.

Overall, 197 patients were randomized to receive glargine/glulisine therapy (n = 106) or premixed analogue therapy (n = 91). Overall mean follow-up time was 183 days. The sample size by visit is shown in **Table III**. Of these patients, 1 (<1%) originally randomized to receive glargine/glulisine subsequently switched to premixed therapy, and 9 (10%) originally randomized to a premixed analogue regimen switched to glargine/glulisine therapy. In the premixed insulin group, 78% received insulin aspart 70/30 and 22% received insulin lispro 75/25. No potential bias among the patients lost to follow-up was identified, and there were no baseline differences observed for age, sex, education, ethnicity, or HbA_{1c} between these patients in the glargine/glulisine or premixed analogue groups and the total study sample. The mean age in all 3 groups was 57 years; the lost-to-follow-up glargine/glulisine group comprised 53% females versus 56% in the premixed analogue group and 54% in the total study sample. Patient race was consistent: 69%, 63%, and 67% of the patients, respectively, were white; 39%, 37%, and 38% of the patients attained an education below the college level. Baseline HbA_{1c} was slightly higher among patients in the premixed analogue group (9.5%) versus the glargine/glulisine group (9.1%) and the total sample (9.2%), but this difference was not statistically significant ($P = 0.38$).

The unadjusted HbA_{1c} values for the glargine/glulisine group for follow-up visits 2, 3, and 4 were 8.61%, 8.57%, and 8.46%, respectively. For the premixed analogue group, the unadjusted HbA_{1c} values were 8.75%, 8.48%, and 8.12%, for the same visits. The adjusted HbA_{1c} for these visits for the glargine/glulisine group was 8.5%, 7.2%, and 6.3%; for the premixed analogue group, the adjusted HbA_{1c} values were 9.1%, 7.7%, and 6.8%.

The **Figure** and **Table IV** show the adjusted mean HbA_{1c} at baseline and at the end of follow-up for each randomization group. The adjusted mean follow-up HbA_{1c} was 6.93% in the glargine/glulisine group versus 7.52% in the premixed analogue group (difference, –0.59%; 95% CI, 0.15 to 1.04; $P < 0.01$). This finding represented an improvement from the mean baseline value of 2.3% (95% CI, –2.95 to –1.65) in the glargine/glulisine group, compared with an improvement from baseline of 1.7% (95% CI, –2.20 to –1.21) in the premixed analogue group (**Table IV**). A post hoc power analysis was conducted based on the actual HbA_{1c} values of 6.9% versus 7.5% for the glargine/glulisine and

Table I. Baseline patient demographic and disease characteristics. Data are given as mean (SD) or percentage.

Characteristic	Insulin Glargine/ Insulin Glulisine (n = 106)	Premixed Insulin (n = 91)
Age, y	56.36 (12.44)	55.92 (9.87)
Female, %	52.8	56.0
Race/ethnicity, %		
White	62.26	54.95
Black	35.85	41.76
Other	1.89	3.29
Education, %		
Pre–high school	14.71	6.82
High school diploma	21.57	27.27
Attending college	31.37	40.91
College diploma	17.65	14.77
Graduate school	14.71	10.23
Current employment, %	48.54	57.95
Smoker, %	8	19
Duration of diabetes, y	13.1 (8.78)	12.9 (8.04)
BMI, kg/m^2	35.82 (7.7)	35.85 (6.5)
Weight, lb	226.12 (51.8)	228.15 (44.6)
Waist circumference, in	44.55 (6.2)	44.7 (5.6)
HbA_{1c}, %	9.33 (1.8)	9.35 (1.8)
Any hypoglycemia during previous 4 months, %	30	27
Systolic blood pressure, mm Hg	133.18 (18.1)	131.29 (15.6)
Diastolic blood pressure, mm Hg	74.88 (11.2)	74.76 (11.1)
HDL-C, mmol/L	1.20 (0.34)	1.14 (0.38)
LDL-C, mmol/L	2.61 (1.09)	2.70 (1.03)
Triglycerides, mmol/L	173.0 (132.0)	195.63 (111.8)
Daily insulin, IU	76.92 (49.4)	77.65 (48.5)

HbA_{1c} = glycosylated hemoglobin.

premixed analogue groups, respectively. Using an equal SD of 1.2, a sample of 128 patients was associated with an 80% power to detect a difference in HbA_{1c}.

The adjusted number of concomitant OADs used during follow-up was significantly lower in the glargine/glulisine group compared with the premixed analogue group: 0.86 versus 1.14 (difference, −0.28; $P = 0.04$) (**Table IV**). There were no significant differences between groups regarding daily insulin doses during follow-up (78.31 IU [mean, 3.5 injections] in the glargine/glulisine group vs 90.06 IU [mean, 2.5 injections] in the premixed analogue group; $P = 0.23$) (**Table IV**) or rates of hypoglycemia (36% of patients in the glargine/glulisine group vs 42% in the premixed analogue group; $P = 0.37$). Patients in the glargine/glulisine group had a higher adjusted weight (mean follow-up weight of 240 lb in the glargine/glulisine group vs 235 lb in the premixed analogue group; difference, 4.55 lb; $P = 0.03$; 95% CI, 0.40 to 8.71) (**Table IV**).

The cost analysis from this study indicated greater cost-effectiveness with glargine/glulisine compared with the premixed analogue regimens. Adjusted total daily costs for all concomitant OADs were $10.81 for patients treated with glargine/glulisine and $12.42 for

Table II. Oral antidiabetic drugs and insulin therapy in the 2 treatment groups during the 4 months before randomization.

Drug	Patients, %	
	Insulin Glargine/ Insulin Glulisine	Premixed Insulin
Oral antidiabetic drug		
Metformin	41.3	42.2
Sulfonylureas	32.7	36.6
Thiazolidinedione	28.8	36.6
Others	3.8	8.8
Insulin		
Basal	61.5	53.3
Prandial	36.5	33.3
Premixed	40.4	32.2
Total insulin	91.3	84.4

patients treated with premixed analogues, representing a between-group difference of –$1.61 (95% CI, –3.22 to 0.00; $P = 0.05$) (**Table IV**) and a monthly savings between-group difference of ~$48. In the analysis of PROs, nonsignificant differences between glargine/glulisine and premixed analogue regimens were found for the DQOL total score (least squares mean, 75.2 vs 74.0, respectively; $P = 0.42$) and EQ-5D index values (0.77 vs 0.79; $P = 0.54$). Cost per quality-adjusted life-years was not calculated because of minimal differences in EQ-5D utility score. On the WPAI questionnaire, nonsignificant differences between regimens were seen for the overall impairment score (26.2 vs 28.0; $P = 0.73$) and activity impairment for health

Table III. Sample size grouped according to visit.

Visit	Patients, n		
	Insulin Glargine/ Insulin Glulisine	Premixed Insulin	Total
1	106	91	197
2	64	64	128
3	42	47	89
4	25	21	46

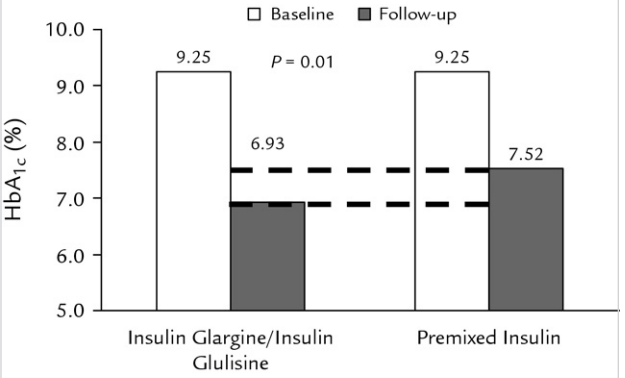

Figure. Adjusted glycosylated hemoglobin (HbA_{1c}) measurements over follow-up visits in the intent-to-treat analysis (n = 106 in the insulin glargine/insulin glulisine group; n = 91 in the premixed insulin analogue group). Mean length of follow-up was 179 days. Variables in the adjustment included education, employment, diabetes duration, time to HbA_{1c}, visit, and baseline HbA_{1c}, hypoglycemia, oral medication, insulin, and other oral medication. Specific interactions also in the adjustment included concurrent exenatide use plus number of concurrent oral antidiabetic drugs, sliding scale insulin use plus squared time to HbA_{1c}, and group plus age plus race. Difference between groups, 0.59%; 95% CI, 0.15 to 1.04; $P = 0.01$.

(56.8 vs 50.4; $P = 0.31$). However, work missed for health scores were significantly lower with glargine/glulisine versus premixed analogue regimens (–1.57 vs 0.47; $P = 0.03$).

DISCUSSION

Basal-bolus insulin therapy using glargine/glulisine provided better glycemic control at a lower medication cost relative to premixed analogue regimens in these patients with type 2 diabetes. Compared with premixed regimens, a basal-bolus regimen provides flexibility by allowing the patient and physician to adapt the insulin regimen to the patient's eating pattern. Some patients may find the administration of premixed insulin more convenient because it may require fewer daily injections (depending on the individual type of regimen selected). However, 3 injections of prandial insulin may not be needed for every patient to reach glycemic control. In patients whose disease is uncon-

Table IV. Comparison of primary outcome variables.

Parameter	Insulin Glargine/ Insulin Glulisine	Premixed Insulin	Mean Change	*P*
Adjusted mean HbA_{1c} at follow-up, %	6.93	7.52	−0.59	<0.01*
Mean change from baseline in HbA_{1c}, %	−2.3	−1.7	−0.6	NA*
Adjusted mean difference in number of concurrent OADs	0.86	1.14	−0.28	0.04*
Adjusted follow-up daily insulin units, IU	78.31	90.06	−11.75	0.23
Adjusted weight over follow-up visits, lb	240	235	4.55	0.03*
Adjusted total daily diabetes medication costs, $ (2007)	10.81	12.42	−1.61	0.05*

HbA_{1c} = glycosylated hemoglobin; NA = not applicable; OAD = oral antidiabetic drug.
*Please see Results section for corresponding 95% CI values.

trolled with basal insulin and OAD therapy, prandial insulin can be initiated in a stepwise progression by beginning with 1 injection and adding doses with other meals as necessary to reach the appropriate glycemic target.[31,32]

To the best of our knowledge, the present study is the first to compare glargine/glulisine basal-bolus therapy with premixed analogue regimens in real-world clinical practice. In this randomized pragmatic trial, glargine/glulisine resulted in greater glycemic improvements compared with premixed analogue regimens in patients with type 2 diabetes whose disease was inadequately controlled with previous treatments. The mean HbA_{1c} reduction was significantly greater in the glargine/glulisine group compared with the premixed analogue group (2.3% vs 1.7%). This difference is of clinical importance, because it exceeds the conventional 0.4% HbA_{1c} boundary used in noninferiority trials,[33–35] and because enhanced glycemic control was attained without significant differences in total insulin dose or rates of hypoglycemia. Moreover, the glargine/glulisine regimen was associated with significantly less work missed for health than premixed insulin (as measured by using the WPAI; $P = 0.03$), although there were no significant differences between glargine/glulisine and premixed analogue regimens with respect to most of the QOL measures assessed in this study. We postulate this finding could be due to the lack of difference in insulin dose and rates of hypoglycemia between the 2 groups. Moreover, the absence of a difference in hypoglycemia rates observed in the present study may explain, at least in part, the statistical similarities observed in the QOL measures. Because concerns with insulin therapy, including hypoglycemic symptoms, can negatively influence patients' attitudes regarding diabetes treatment and their perceived effect on QOL, further evaluation with larger sample sizes may help to elucidate these differences.

We believe the present study is noteworthy in that it provides insight into the use of these regimens in real-life clinical practice, more so than data derived from a controlled setting of a standard clinical trial. It may offer insights to inform real-world clinical decision making, in which diabetes treatment can be diversely different from clinical guidelines or consensus. However, a pragmatic trial design also comes with certain limitations. For example, it was challenging to maintain the preplanned patient visit schedules; hence, the study concluded before possible completion of follow-up assessments for all patients randomized to treatment. However, this action should not have compromised the validity of the study findings, as we found no evidence of selective patient attrition. Patients who completed at least 1 follow-up assessment were followed up on average for ~6 months, which is consistent with the norm reported in other clinical trials evaluating glycemic control in diabetes.[36–38] In addition, some patients dropped out of the study and, on occasion, from the practice for unknown reasons after the beginning of the study. Therefore, not all patients completed the intended 3 follow-up visits after treatment randomization. Another limitation is the use of WAC instead of actual costs of diabetes medications. However, the use of the WAC may also allow customized

applications of the findings to other practice settings in which patients are covered under different pharmacy benefit plans.

A strength of this study is the inclusion of a cost-effectiveness evaluation of basal-bolus versus premixed analogue regimens, an area lacking in the current published literature. Cost analysis is a key factor to consider both when initiating an insulin regimen and for subsequent adherence to that regimen. In this study, a basal-bolus regimen of insulin glargine plus insulin glulisine provided a cost savings of $467 per 1.0% decrease in HbA_{1c} compared with premixed analogue regimens. When costs and improvement in glycemic control were evaluated jointly, treatment costs per 1.0% reduction in HbA_{1c} during the follow-up period were estimated at $841 with glargine/glulisine and $1308 with premixed analogues, indicating a cost savings of $467 per 1.0% reduction in HbA_{1c} associated with glargine/glulisine versus a premixed analogue regimen. In a previous cost analysis of insulin therapy in a managed care organization, an approximate 10% increase in total health expenditures was reported on initiation of insulin therapy, but these costs were offset by a 40% decrease after 9 months following insulin initiation.[39] This analysis did not specify different types of insulin regimens. Another published cost analysis of diabetes therapy reported that adding a third oral agent for type 2 diabetes treatment in patients who have not achieved glycemic control with 2 oral agents was not as cost-effective as adding insulin therapy (premixed NPH/regular human insulin 70/30) to metformin.[40]

Because hypoglycemia is a significant contributor to the costs of treating diabetes,[41] a cost analysis of insulin glargine versus NPH insulin took this factor into account.[42] In this analysis from a managed care database, the lower risk of hypoglycemia associated with insulin glargine versus NPH insulin translated into 1 hypoglycemic event avoided for every 9 patients treated with insulin glargine instead of NPH insulin. The cost increase associated with treating 9 patients with insulin glargine was less than the cost of treating 1 hypoglycemic event, resulting in an overall cost savings associated with insulin glargine use.[42] In a similar analysis for patients with insulin-naive type 2 diabetes initiating therapy with insulin glargine versus premixed insulin, the lower incidence of hypoglycemia associated with insulin glargine corresponded to 1 hypoglycemic event avoided for every 15 patients treated with insulin glargine versus premixed insulin.[43] Again, the cost increase of treating 15 patients with insulin glargine versus premixed insulin ($46 per patient annually) was less than the cost of treating 1 episode of hypoglycemia, resulting in overall cost savings associated with the use of insulin glargine.

CONCLUSIONS

In a real-world clinical practice setting, treatment of type 2 diabetes with insulin glargine plus insulin glulisine provided greater improvement in glycemic control than premixed insulin regimens; this regimen may also represent a more cost-effective treatment option. Rates of hypoglycemia and total daily insulin doses were similar between treatment groups, although patients in the glargine/glulisine group required fewer concomitant OADs.

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Dr. Levin is a consultant to and Dr. Zhang is an employee of sanofi-aventis US. The authors have indicated that they have no other conflicts of interest regarding the content of this article.

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