Comparative Effectiveness of Basal-Bolus *Versus* Premix Analog Insulin on Glycemic Variability and Patient-Centered Outcomes during Insulin Intensification in Type 1 and Type 2 Diabetes: A Randomized, Controlled, Crossover Trial

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Context: In patients with diabetes, intraday glucose variability might predict health outcomes independently from glycosylated hemoglobin (HbA_{1c}).

Objective: Our objective was to evaluate patient satisfaction (PS), quality of life (QoL), glycemic control, and variability during insulin intensification to HbA_{1c} below 7.0%.

Patients, Design, and Setting: Eighty-two type 1 and 306 insulin-treated type 2 diabetes patients (47% male; age 54 ± 11 yr; HbA_{1c} = 7.8 ± 0.7%) participated in this multicenter, randomized, crossover trial at 52 U.S. centers.

Interventions: Interventions included insulin glargine plus premeal glulisine (n = 192) *vs.* twice-daily premix 75/25 or 70/30 analog insulin (n = 196) for 12 wk and crossed to the alternate arm for 12 wk.

Main Outcome Measures: Main outcome measures included PS and QoL questionnaires, 3-d continuous glucose monitoring (CGM), and HbA_{1c} every 4–8 wk.

Results: Mean ± SE HbA_{1c} change was −0.39 ± 0.09% for glargine-glulisine and −0.05 ± 0.09% for premix ($P < 0.0001$). The PS net benefit scale (0–100) improved from 51.1 to 60.5 ± 1.2 for glargine-glulisine and worsened to 45.4 ± 1.2 for premix ($P < 0.0001$). The PS regimen acceptance scale was comparable ($P = 0.33$). Overall QoL favored glargine-glulisine ($P < 0.001$), as did perceived health ($P < 0.0001$), symptom distress ($P < 0.0001$), general health perceptions ($P < 0.01$), and psychosocial ($P < 0.02$). CGM daily glucose mean, daily glucose SD (glycemic variability), and percent time over 140 mg/dl were lower for glargine-glulisine by 13.1 ± 2.7 mg/dl, 5.9 ± 1.4 mg/dl, and 7.3 ± 1.6%, respectively (all $P < 0.0001$), with no difference in CGM percent time below 70 mg/dl ($P = 0.09$). Symptomatic hypoglycemia rates were comparable. HbA_{1c}, mean CGM daily glucose, and glycemic variability were independent predictors of PS net benefit.

Conclusions: Patient satisfaction was impacted more positively by improved QoL, reduced glucose variability, and better glycemic control with a basal-bolus regimen than negatively by the burden of additional injections, thereby facilitating insulin intensification and the ability to achieve HbA_{1c} below 7.0%. **(*J Clin Endocrinol Metab* 97: 3504–3514, 2012)**

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Abbreviations: BMI, Body mass index; CGM, continuous glucose monitoring; HbA_{1c}, glycosylated hemoglobin; QoL, quality of life; SMBG, self-monitoring of blood glucose.

Maintaining glycosylated hemoglobin (HbA_{1c}) less than 7.0% in persons with either type 1 or type 2 diabetes has been shown to reduce microvascular and some macrovascular complications (1, 2). Current treatment guidelines recommend maintaining HbA_{1c} below 7.0% (3) or no more than 6.5% (4) for most patients with diabetes. If target levels are not met, diet, exercise, and diabetes medications are adjusted accordingly.

HbA_{1c} represents average glucose for the previous 2–3 months, but similar HbA_{1c} levels can be achieved with a wide range of fasting, preprandial, and postprandial glucose levels. For type 1 and insulin-treated type 2 diabetes patients failing to achieve target goals, insulin can be increased and the number of injections and types of insulin varied. Insulin titration algorithms based upon self-monitored fasting, preprandial and/or postprandial glucose levels, and the occurrence of hypoglycemia are tools for adjusting insulin. However, dose escalation is often hampered by fluctuating glucose excursions, fear of hypoglycemia, and the associated symptoms of hypo- and hyperglycemia. Such excursions are not fully reflected in the typical daily measures of self-monitored blood glucose, mean daily glucose, or HbA_{1c}, making clinical management even more difficult. However, such excursions can be detected using continuous glucose monitoring (CGM) and summarized using glycemic variability indices (5–7). One study concluded that glycemic variability is one of the components of glycemic disorders in patients with diabetes and that the use of CGM will need to be increased to promote better assessment and management of glycemic variability in both type 1 and type 2 diabetes (8). Another study found that a CGM system had a positive effect on the self-management of diabetes by lowering glycemic variability (9).

A recent review concluded that ambulatory 24-h glucose should be considered in addition to HbA_{1c} and fasting glucose when evaluating the comparative effectiveness of therapeutic regimens (10). In addition, there is evidence that glycemic variability might be an independent risk factor for longer-term vascular complications (11–13). However, other studies have found that HbA_{1c} and mean blood glucose show stronger associations with cardiovascular disease risk factors than do postprandial glycemia or glucose variability in persons with diabetes (14). Although results demonstrating that glycemic variability as a cause of longer-term diabetes complications are inconclusive, it has been shown to be related to shorter-term outcomes such as behavioral changes in children (15) and hypoglycemia (16). One small sample of 36 patients studied at one point in time found that although levels of high glucose were associated with poorer mood ratings, glycemic variability was not found to be an independent predictor (17).

Patient-centered outcomes such as regimen burden, convenience, and adverse side effects also impact therapeutic effectiveness in achieving target HbA_{1c} by limiting the ability to intensify therapy. We demonstrated previously that reduced HbA_{1c} is associated with quality-of-life (QoL) and health economic benefits (18); however, evidence as to whether glycemic variability is associated with QoL and patient satisfaction, both of which might impact insulin intensification, is lacking. To draw a valid causal inference between the effects of glycemic variability and patient-centered outcomes such as satisfaction and QoL, which might impact the ability to intensify therapy, requires a longitudinal, crossover clinical trial design randomizing patients to regimens that produce systematic differences in glycemic variability. In this way, variables that might confound the effects of the hypothesized association are minimized. Because basal-bolus insulin regimens more closely mimic the physiological requirements for insulin, such regimens could potentially result in a smoother, less variable 24-h glucose profile at the same level of HbA_{1c} compared with conventional insulin regimens.

The primary objective of this study was to determine whether less variable glucose profiles might positively impact patient acceptance and QoL, thus offsetting the burden of additional injections, reducing hypoglycemia with increasing doses, and increasing the probability of reaching target HbA_{1c}. To investigate this hypothesis, we evaluated patient satisfaction, QoL, HbA_{1c}, and glycemic variability in type 1 and insulin-treated type 2 diabetes patients randomized to either a basal-bolus regimen of insulin glargine plus premeal insulin glulisine or to premix analog insulin during a 6-month, multicenter, randomized, crossover clinical trial.

Materials and Methods

Design overview

This comparative effectiveness trial included a screening visit, 3-wk lead-in period, and two 12-wk treatment (crossover) phases. During lead-in, patients remained on their preexisting insulin regimen and, if applicable, oral antihyperglycemic agents. Subjects received training on the Medtronic CGMS System Gold (blinded CGM), electronic hand-held personal digital assistant (e-diary), and self-monitoring of blood glucose (SMBG), including recording glucose, insulin doses, and symptoms of hypo- or hyperglycemia. They transmitted e-diary data daily to the central server (Phase V Technologies, Wellesley Hills, MA) using the personal digital assistant's wireless acoustic modem and a land-line telephone handset.

Setting and participants

Six hundred eighty individuals with either type 1 or insulin-treated type 2 diabetes for at least 6 months were screened at 58 centers in the United States. Inclusion criteria were age 21–70 yr; stable on premix 75/25 or 70/30 insulin, neutral protamine Hagedorn, or insulin glargine with short-acting insulin, consisting of two injections daily, with or without concomitant oral medications (metformin, thiazolidinedione, and/or α-glucosidase inhibitor) for 3 months before screening; baseline HbA_{1c}

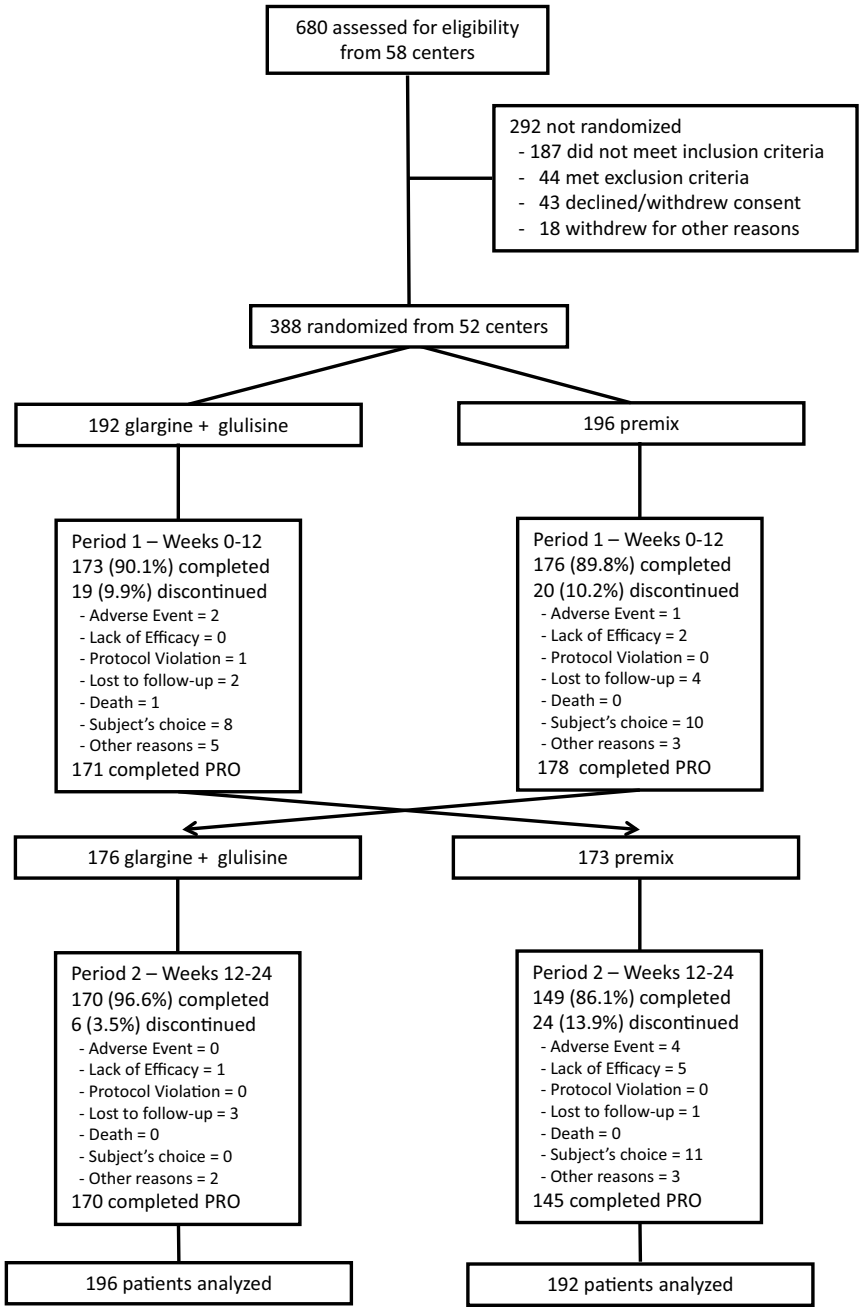

FIG. 1. CONSORT (Consolidated Standards of Reporting Trials) flow diagram for multicenter, randomized crossover clinical trial of glargine-glulisine *vs.* premix insulin therapy. PRO, Patient-reported outcomes.

7.0% or higher and no higher than 9.0%; employed, unpaid work, or active lifestyle; and able to read English at the sixth-grade level. Exclusion criteria included significant cardiac disease, cancer, or laboratory abnormalities; insulin pump or concomitant oral diabetes medications not listed above; and inability to complete a 72-h CGM session after three attempts during the lead-in period before randomization. The protocol was approved by the institutional review board at each center, and informed consent was obtained from all subjects.

Randomization and interventions

As outlined in Fig. 1, 192 persons were randomized initially to insulin glargine (rDNA origin) injection (Lantus) once-daily plus insulin glulisine (rDNA origin) injection (Apidra) before meals, and 196 persons to premix analog insulin (Humalog Mix 75/25 or Novolog Mix 70/30) twice daily. At the end of the initial 12-wk treatment (period 1), all patients crossed over to the alternate treatment arm for an additional 12 wk (period 2). Insulin doses were adjusted weekly by the clinical site according to a prespecified insulin intensification algorithm to achieve target fasting [<110 mg/dl (6.1 mmol/liter)], bedtime [<130 mg/dl (7.2 mmol/liter)], and premeal [<110 mg/dl (6.1 mmol/liter)] glucose levels until HbA_{1c} was below 7.0% (for details, see Supplemental Appendix 1, published on The Endocrine Society's Journals Online web site at http://jcem.endojournals.org). Patients also adjusted doses according to diet and exercise requirements; however, there was no specific algorithm for carbohydrate counting or other dietary recommendations. To facilitate intensification, e-dairy data were analyzed on a central server in real time to provide algorithm-based descriptive statistics and insulin-dosing criteria. Results were available to clinical sites using a Web-based remote monitoring system to review daily four-point glucose readings, insulin dosages, hypoglycemia, other symptoms, and adverse events. Each week, the clinic staff telephoned the patient to provide insulin-dosing recommendations.

Outcomes and follow-up

HbA_{1c} was measured at wk 0 (baseline), 4, 8, 12, 16, 20, and 24. Fasting plasma glucose was measured at wk 0, 4, 12, 16, and 24 and lipids at wk 0, 12, and 24. Hypoglycemic events, adverse events, standard clinical chemistry and hematology, physical examinations, vital signs, and weight were measured at baseline and follow-up clinic visits. At wk −3, 0, 8, 12, 20, and 24, and at early withdrawal, patient-reported outcomes questionnaires were completed at the clinic and sent to the survey center (Phase V Technologies). Questionnaires consisted of validated generic and diabetes-specific modules of treatment satisfaction, QoL, and barriers to insulin adherence (19, 20) (see Supplemental Appendix 2 for listing of scales and subscales). These measures have been used by the authors previously and found to be responsive to the effects of therapeutic interventions (21–23) and the impact of side effects of medication (24), symptoms of diabetes (25–27), changes in HbA_{1c} (18, 28–30), diabetes-related treatment satisfaction, and diabetes-related weight changes (31). All scales were coded such that higher scores reflected more favorable responses.

Blinded CGM for 72 consecutive hours was conducted before baseline (wk −2 to −1), the end of period 1 (wk 10–12), and the end of period 2 (wk 22–24). If the initial CGM session was not

adequate, it was repeated a second or third time as required. CGM measures included mean daily sensor glucose (average of 288 values across days within a session), glycemic variability as measured by the intra-day glucose SD (sensor glucose SD within a calendar day averaged across days within a session), and percent time sensor glucose was below 70 mg/dl (3.9 mmol/liter) or above 140 mg/dl (7.8 mmol/liter). For the e-diary blood glucose data, the glucose value from the meter was considered the gold standard.

Statistical analysis

The net benefit patient satisfaction scale and the QoL factor score were the prespecified co-primary endpoints sharing α of 0.05 and each required to achieve statistical significance at $\alpha = 0.031$ using a modified Bonferroni adjustment for correlated endpoints. Treatment effects were analyzed for each QoL and treatment satisfaction scale using a linear mixed model. Weeks 8, 12, 20, and 24 were the repeated-measures dependent variables; wk 0 and 12 (baseline for periods 1 and 2, respectively) were used as covariates. Period and sequence were fixed effects. Other effects and covariates (age, gender, center, type of diabetes, and race) were evaluated. Laboratory and CGM data were analyzed using similar models. Rates of hypoglycemia were analyzed using negative binomial models. All other variables were secondary endpoints for which *P* values report nominal significance. Linear mixed models and logistic regression were used to examine relationships between treatment, HbA_{1c}, CGM glycemic control and variability, satisfaction, and QoL. Data are given as means ± SE unless specified otherwise.

Results

Study accrual, withdrawals, and baseline characteristics

Study accrual (82 type 1 and 306 type 2 diabetes patients), allocation, and reasons for withdrawal are detailed in Fig. 1. Withdrawal was similar between groups for period 1; however, during period 2, four times as many patients in the premix arm withdrew compared with the glargine-glulisine arm ($P < 0.001$). Baseline demographics and clinical characteristics did not differ between initial treatment allocations (Table 1).

HbA_{1c}, fasting plasma glucose, target goals, weight, hypoglycemia, and adverse events

Baseline-adjusted HbA_{1c} and fasting plasma glucose at the ends of periods 1 and 2 and combined across both periods adjusting for covariates were significantly lower

TABLE 1. Demographic and clinical characteristics of study groups at randomization

	Glargine-glulisine to premix (n = 192)	Premix to glargine-glulisine (n = 196)
Type 1 diabetes	39 (20.3)	43 (21.9)
Type 2 diabetes	153 (79.7)	153 (78.1)
Male	91 (47.4)	93 (47.4)
Married[a]	125 (66.5)	116 (59.8)
Caucasian	150 (78.1)	151 (77.0)
Occupation[b]		
Paid employment	108 (57.8)	116 (61.4)
Retired/student/unemployed	79 (42.2)	73 (38.6)
Highest education completed[b]		
Less than high school diploma	16 (8.5)	17 (8.8)
High school diploma	52 (27.7)	45 (23.3)
Some college/associates degree	62 (33.0)	76 (39.2)
College degree or higher	58 (30.9)	56 (28.9)
Family income (2010 U.S. dollars)[b]		
Less than $45,000	80 (43.8)	90 (47.4)
$45,000–89,999	63 (34.4)	68 (35.8)
$90,000 or higher	40 (21.8)	32 (16.9)
Age (yr)	53.7 ± 10.7 (22–76)	53.4 ± 11.5 (23–76)
Duration of diabetes (yr)	15.5 ± 9.3 (1.5–45.5)	16.6 ± 9.7 (0.7–53.7)
BMI (kg/m^2)	34.7 ± 7.9 (18.1–60.2)	33.9 ± 7.7 (17.9–64.1)
HbA_{1c} (%)	7.8 ± 0.7 (6.2–10.0)	7.8 ± 0.7 (6.2–9.8)
Fasting plasma glucose (mg/dl)	165 ± 64 (44–374)	161 ± 64 (31–438)
Current diabetes therapy		
Long- and rapid-acting insulin (not premix)		
Type 1 diabetes	28 (71.8)	37 (86.0)
Type 2 diabetes	92 (60.1)	77 (50.3)
Insulin and oral hypoglycemic agents		
Type 2 diabetes	80 (52.3)	72 (47.1)

Demographic and previous medication data are presented as n (percent). Clinical data are presented as mean ± SD, with ranges in *parentheses*.

[a] Four subjects in glargine-glulisine and two subjects in premix did not report marital status.

[b] The difference between total n in the group and the sum of n for the variable is due to subjects failing to report demographic characteristics.

TABLE 2. Analysis of differences in mean changes of HbA_{1c} (percent) and fasting plasma glucose (milligrams per deciliter)

Periods and measure	Glargine-glulisine				Premix			
	n	LSM[a]	SE	95% CI	n	LSM[a]	SE	95% CI
Period 1 change in HbA_{1c}	191	−0.52	0.10	(−0.71–−0.33)	196	−0.20	0.10	(−0.39–−0.01)
Period 2 change in HbA_{1c}	176	−0.25	0.10	(−0.44–−0.06)	172	0.10	0.10	(−0.09–0.29)
Overall change in HbA_{1c}	367	−0.39	0.09	(−0.57–−0.21)	368	−0.05	0.09	(−0.23–0.12)
Period 1 change in FPG	191	−31.0	8.8	(−48.2–−13.9)	196	−6.2	8.9	(−23.6–11.1)
Period 2 change in FPG	176	−23.5	9.0	(−41.1–−5.8)	172	−11.5	8.9	(−29.0–6.0)
Overall change in FPG	367	−27.3	8.3	(−43.6–−10.9)	368	−8.8	8.3	(−25.2–7.5)

Least-squares means (LSM), SE, 95% confidence interval (CI), and *P* values are calculated from a linear mixed model adjusted for period, sequence, age, sex, race, diabetes type, center, and baseline HbA_{1c} or glucose. The multivariate dependent variable was the last observation carried forward changes in response during periods 1 and 2. FPG, Fasting plasma glucose (milligrams per deciliter).

[a] LSM treatment effects, glargine-glulisine *vs.* premix, $P < 0.0001$.

for glargine-glulisine *vs.* premix (Table 2). Period, type of diabetes (both $P < 0.001$), and race ($P = 0.025$) effects were statistically significant covariates, whereas sequence ($P = 0.79$), sex ($P = 0.41$), center ($P = 0.12$), and age ($P = 0.67$) effects were not. The percentage of patients reaching target HbA_{1c} below 7.0% at the end of period 1 was greater for glargine-glulisine, 53.1% (n = 102 of 192), *vs.* premix, 29.1% (57 of 196) ($P < 0.001$). After crossing from premix to glargine-glulisine, at the end of period 2, the percentage reaching target HbA_{1c} was still significantly higher for glargine-glulisine, 56.8% (100 of 176), *vs.* 45.1% (78 of 173) for premix ($P = 0.028$), as well as for both periods combined, 54.8% (201 of 367) *vs.* 36.4% (134 of 368) ($P < 0.001$). During period 1, weight increased by mean (SE) 2.3 (0.4) kg for glargine-glulisine and by 0.9 (0.3) kg for premix and during period 2 by 1.1 kg (0.3) for glargine-glulisine and by 1.2 (0.4) kg for premix. The frequency and severity of hypoglycemia (Table 3) and nonhypoglycemic adverse events were comparable for the two insulin regimens.

Patient-reported outcomes

As shown in Table 4, baseline overall satisfaction of 61.3 indicated that patients were moderately satisfied with their lead-in insulin treatment (0 for greatest dissatisfaction to 100 for highest satisfaction). The co-primary net benefit satisfaction scale improved for glargine-glulisine compared with worsening with premix. All net benefit subscales (advocacy, preference, perceived efficacy and general satisfaction) demonstrated a significantly greater improvement for glargine-glulisine compared with premix. There was a more positive treatment impact on net benefit for glargine-glulisine *vs.* premix in type 1 compared with type 2 diabetes ($P < 0.0001$). The four net benefit subscales also showed greater improvement for type 1 compared with type 2 diabetes (all $P < 0.0001$). The

TABLE 3. Analysis of differences in mean changes of hypoglycemia

Symptomatic hypoglycemia	Glargine-glulisine			Premix			Glargine-glulisine *vs.* premix	
	n	% of patients	Number of events	n	% of patients	Number of events	*P* value	IRR[a] (95% CI)
Period 1								
<70 mg/dl	124	64.6	1328	130	66.3	1280	0.76	0.94 (0.61–1.43)
<50 mg/dl	88	45.8	446	86	43.9	442	0.59	1.12 (0.74–1.68)
<36 mg/dl	32	16.7	64	27	13.8	64	0.37	1.29 (0.74–2.27)
Severe[b]	22	11.5	102	24	12.2	65	0.79	0.92 (0.50–1.71)
Serious[c]	5	2.6	5	3	1.5	3	0.45	1.74 (0.41–7.39)
Period 2								
<70 mg/dl	111	63.1	1191	112	64.7	1149	0.69	0.91 (0.59–1.43)
<50 mg/dl	81	46.0	343	83	48.0	290	0.71	0.92 (0.60–1.41)
<36 mg/dl	26	14.8	46	29	16.8	45	0.48	0.81 (0.45–1.46)
Severe[b]	21	11.9	59	19	11.0	72	0.83	1.07 (0.55–2.08)
Serious[c]	2	1.1	3	1	0.6	1	0.58	2.00 (0.18–22.7)

[a] Glargine-glulisine/premix.

[b] Events requiring assistance and either SMBG below 36 mg/dl or prompt response to countermeasures.

[c] Hypoglycemia with coma/loss of consciousness or seizure/convulsion.

TABLE 4. Treatment satisfaction and quality of life measures: Treatment effects mixed model (combining Periods 1 and 2)

Scale and subscales	Baseline wk 0/12 covariate	Mean ± SE		Mean treatment difference (95% CI)	Treatment main-effect *P* value
		Glargine-glulisine	Premix		
Treatment satisfaction scales					
Net benefit[a]					
Total (n = 388)	51.1	60.5 ± 1.2	45.4 ± 1.2	15.1 (11.7–18.4)	<0.0001[b]
Type 1 diabetes (n = 82)	44.8	56.2 ± 2.6	28.5 ± 2.6	27.7 (20.2–35.3)	<0.0001[b]
Type 2 diabetes (n = 306)	52.6	61.3 ± 1.3	49.7 ± 1.3	11.6 (8.0–15.2)	<0.0001[b]
Advocacy	61.3	68.5 ± 1.4	51.4 ± 1.4	17.1 (13.2–21.0)	<0.0001[b]
Preference	37.8	49.8 ± 1.2	36.9 ± 1.3	12.8 (9.4–16.3)	<0.0001[b]
Efficacy/effectiveness	50.2	61.4 ± 1.1	46.1 ± 1.1	15.3 (12.1–18.4)	<0.0001[b]
General satisfaction	55.5	62.7 ± 1.4	47.6 ± 1.4	15.1 (11.3–18.8)	<0.0001[b]
Regimen acceptance[a]					
Total (n = 388)	66.4	67.3 ± 0.5	66.5 ± 0.5	0.7 (−0.8–2.2)	0.333
Type 1 diabetes (n = 82)	63.5	64.6 ± 1.3	60.6 ± 1.3	4.0 (0.3–7.6)	0.033[b]
Type 2 diabetes (n = 306)	67.1	67.9 ± 0.6	68.0 ± 0.6	−0.1 (−1.7–1.6)	0.928
Burden	65.0	65.7 ± 0.6	68.0 ± 0.6	−2.2 (−4.0–−0.5)	0.013[c]
Convenience	59.7	59.6 ± 0.7	63.5 ± 0.7	−3.9 (−5.9–−2.0)	<0.001[c]
Flexibility	58.2	61.7 ± 0.8	55.9 ± 0.9	5.8 (3.5–8.2)	<0.0001[b]
Hassle	65.6	67.7 ± 0.7	66.0 ± 0.7	1.7 (−0.3–3.7)	0.094
Social	71.6	72.7 ± 0.7	71.3 ± 0.7	1.3 (−0.6–3.3)	0.186
Pain	76.3	72.8 ± 0.7	78.2 ± 0.7	−5.4 (−7.5–−3.4)	<0.0001[c]
Side effects	68.4	67.9 ± 0.7	64.2 ± 0.7	3.7 (1.8–5.6)	<0.001[b]
Interference	66.4	69.7 ± 0.8	65.6 ± 0.8	4.1 (1.9–6.3)	<0.001[b]
Overall satisfaction	61.3	65.5 ± 0.7	59.0 ± 0.70	6.4 (4.5–8.4)	<0.0001[b]
Overall QoL summary measures					
Overall QoL factor score[a]	0.00	0.07 ± 0.03	−0.06 ± 0.03	0.13 (0.06–0.20)	<0.001[b]
Psychosocial (item-wise)	441.2	445.7 ± 2.0	439.0 ± 2.0	6.7 (1.1–12.2)	0.018[b]
Psychosocial (composite)	438.4	442.1 ± 2.0	436.2 ± 2.0	5.9 (0.2–11.5)	0.041[b]
Perceived health (1–10)	6.48	6.66 ± 0.07	6.26 ± 0.07	0.39 (0.20–0.59)	<0.0001[b]
Health limitations and life interference					
Physical activity	8.11	8.13 ± 0.12	8.23 ± 0.12	−0.09 (−0.41–0.23)	0.565
Diabetes symptom interference	4.87	4.87 ± 0.04	4.82 ± 0.04	0.05 (−0.05–0.16)	0.338
Other symptom interference	4.65	4.71 ± 0.04	4.59 ± 0.04	0.11 (0.01–0.23)	0.040[b]
General health perceptions					
General perceived health	423.2	427.3 ± 2.5	417.7 ± 2.5	9.5 (2.5–16.6)	0.008[b]
General health status	420.2	423.5 ± 3.3	413.3 ± 3.4	10.3 (1.0–19.6)	0.031[b]
Sleep	477.2	478.0 ± 3.3	476.01 ± 3.3	1.9 (−7.3–11.2)	0.686
Vitality	371.4	378.9 ± 3.3	363.7 ± 3.3	15.1 (5.8–24.4)	0.001[b]
Mental health					
Psychological distress	483.2	487.1 ± 2.3	481.9 ± 2.3	5.2 (−1.2–11.6)	0.111
Anxiety	474.1	476.9 ± 2.7	473.5 ± 2.7	3.4 (−4.2–11.0)	0.385
Behavioral/emotional control	491.2	496.5 ± 2.5	490.3 ± 2.6	6.2 (−0.9–13.3)	0.086
Depression	482.7	485.9 ± 2.8	481.3 ± 2.8	4.7 (−3.0–12.4)	0.234
Psychological well-being	392.4	397.4 ± 2.6	392.4 ± 2.6	5.0 (−2.1–12.1)	0.168
Emotional ties	407.8	404.3 ± 5.6	407.2 ± 5.7	−2.9 (−18.3–12.5)	0.710
General positive affect	390.6	396.7 ± 2.6	390.5 ± 2.6	6.1 (−1.0–13.3)	0.094
Life satisfaction	415.6	421.2 ± 3.2	416.4 ± 3.2	4.8 (−4.1–13.7)	0.286
Overall mental health	449.2	453.6 ± 2.1	448.2 ± 2.1	5.4 (−0.6–11.3)	0.077
Composite cognitive	4.0	4.0 ± 0.02	4.0 ± 0.02	0.02 (−0.04–0.07)	0.494
Mental acuity	4.3	4.3 ± 0.02	4.3 ± 0.02	0.04 (−0.03–0.10)	0.249
Disorientation and detachment	4.6	4.6 ± 0.03	4.5 ± 0.03	0.04 (−0.02–0.10)	0.168
Cognitive performance	3.0	3.0 ± 0.03	3.0 ± 0.03	−0.02 (−0.10–0.05)	0.568
Symptom distress	542.7	546.5 ± 1.7	537.1 ± 1.7	9.4 (4.8–14.1)	<0.0001[b]

Data are means ± SE or mean [95% confidence interval (CI)] and are reported for the total sample (n = 388) unless specified otherwise. A higher score indicates a better outcome.

[a] Co-primary endpoints.

[b] Significant difference in favor of glargine-glulisine.

[c] Significant difference in favor of premix.

TABLE 5. CGM results by treatment

CGM sensor glucose measure	Baseline wk 0/12 covariate	Mean ± SE		Treatment difference (95% CI)	Treatment-effect *P* value
		Glargine-glulisine	Premix		
Daily mean (mg/dl)	164.2	147.8 ± 1.8	160.4 ± 1.9	−13.1 ± 2.7 (−18.4–−7.8)	<0.0001
Daily SD (mg/dl)	47.2	42.6 ± 0.8	48.5 ± 0.9	−5.9 ± 1.4 (−8.6–−3.2)	<0.0001
% time >140 mg/dl	57.2	46.1 ± 1.1	53.7 ± 1.1	−7.3 ± 1.6 (−10.4–−4.2)	<0.0001
% time <70 mg/dl	6.4	7.8 ± 0.5	6.7 ± 0.5	1.1 ± 0.7 (−0.2–2.5)	0.094

CI, Confidence interval.

regimen acceptance satisfaction scale was comparable, indicating similar perceived burden and convenience, although individual subscales favored one treatment over the other. However, type 1 patients demonstrated a significantly more favorable regimen acceptance score while on glargine-glulisine. Among 24-wk completers, more patients chose glargine-glulisine (69%) over premix (31%) ($P < 0.0001$) as the one that provided better glucose control, and this preference was greater for patients with type 1 diabetes (84 *vs.* 16%) ($P < 0.0001$). Individuals who withdrew early had lower net benefit scores compared with completers [42.6 (2.6) *vs.* 54.1 (0.9), $P < 0.0001$]. However, this effect was due primarily to premix dropouts *vs.* completers [27.3 (3.7) *vs.* 47.4 (1.2)] compared with the glargine-glulisine dropouts *vs.* completers [58.0 (3.7) *vs.* 60.8 (1.2)]. The QoL factor score improved for glargine-glulisine *vs.* worsening for premix (Table 4). QoL scales generally showed significant improvement for glargine-glulisine *vs.* a worsening for premix. The overall mental health composite scale trended toward improvement for glargine-glulisine *vs.* worsening for premix. Type of diabetes was not a significant treatment-effect modifier of the QoL factor score.

CGM, SMBG, and insulin titration

During CGM, the mean daily sensor glucose, intra-day sensor glucose SD, and percent time sensor glucose was above 140 mg/dl (7.8 mmol/liter) all decreased significantly more for glargine-glulisine compared with premix ($P < 0.0001$) (Table 5). CGM percent time below 70 mg/dl (3.9 mmol/liter) (hypoglycemia) was not statistically significantly different between glargine-glulisine and premix. Consistent with the sensor glucose SD results, the four-point SMBG profiles indicated more variation before meals and bedtime for premix compared with glargine-glulisine. The total daily insulin dose during months 1–3 increased by 31.3% for patients starting on glargine-glulisine and by 16.0% for those starting on premix (Table 6). During months 4–6, insulin dose increased by 14.3% for those switching to glargine-glulisine and by 12.4% for those switching to premix.

Associations between HbA_{1c}, CGM parameters, treatment satisfaction, and QoL

Each 10-point increase in net benefit during treatment increased the likelihood of reaching target HbA1c below 7.0% by 10% [odds ratio = 1.10 (95% confidence interval = 1.02–1.18, $P = 0.014$)] after adjusting for baseline HbA_{1c} ($P < 0.0001$), baseline net benefit ($P = 0.004$), and type of diabetes ($P = 0.013$). Age, gender, and duration of diabetes were not significant predictors. Change in HbA_{1c}, CGM sensor glucose, and CGM sensor glucose SD were all independent predictors of the net benefit scale. For each percent unit decrease in HbA_{1c}, patient satisfaction improved by (mean ± SE) 4.7 ± 1.2 units ($P < 0.0001$); for each 10 mg/dl (0.6 mmol/liter) decrease in mean sensor

TABLE 6. SMBG and monthly daily insulin dose

4-Point interval	12-wk mean 4-point SMBG (mg/dl)		wk of study	Monthly daily insulin dose (units)	
	Glargine-glulisine SMBG	Premix SMBG		Total daily dose (glargine and glulisine)	Total daily premix dose
Period 1 (wk 1–12)					
Before breakfast	146.1 ± 0.9	163.3 ± 1.0	1–4	98.7 (47.0 ± 2.2 & 51.7 ± 2.6)	100.6 ± 7.7
Before lunch	144.9 ± 1.1	140.8 ± 1.2	5–8	117.6 (55.5 ± 2.5 & 62.1 ± 3.0)	108.6 ± 4.8
Before dinner	152.9 ± 1.1	184.2 ± 1.2	9–12	129.6 (60.9 ± 2.8 & 68.7 ± 3.5)	116.7 ± 5.3
Bedtime	170.0 ± 1.2	174.9 ± 1.3			
Period 2 (wk 13–24)					
Before breakfast	149.4 ± 1.0	160.6 ± 1.1	13–16	113.7 (53.7 ± 2.6 & 60.0 ± 3.1)	131.6 ± 6.4
Before lunch	142.7 ± 1.1	133.4 ± 1.3	17–20	125.0 (59.0 ± 2.8 & 66.0 ± 3.5)	141.4 ± 7.0
Before dinner	155.6 ± 1.3	177.6 ± 1.5	21–24	130.0 (61.1 ± 3.0 & 68.9 ± 3.7)	147.9 ± 7.7
Bedtime	174.3 ± 1.4	167.4 ± 1.5			

glucose, patient satisfaction increased by 1.1 ± 0.3 units ($P < 0.0001$); and for each 10 mg/dl (0.6 mmol/liter) decrease in sensor glucose SD, satisfaction increased by 1.5 ± 0.6 units ($P < 0.013$). Age, sex, and body mass index (BMI) were not statistically significant predictors. The predictive model of the perceived health scale indicated improvement with decreased CGM sensor glucose, sensor glucose SD, and percent time above 140 mg/dl (7.8 mmol/liter) (all $P < 0.05$). Predictive models of sensor glucose SD indicated a decrease of 2.3 ± 1.1 mg/dl (0.13 ± 0.06 mmol/liter) for glargine-glulisine *vs.* premix ($P = 0.037$), increase of 10.6 ± 1.7 mg/dl (0.59 ± 0.09 mmol/liter) for type 1 *vs.* type 2 diabetes, decrease of 3.4 ± 0.8 mg/dl (0.19 ± 0.04 mmol/liter) per 10 kg/m^2 increase in BMI, decrease of 2.4 ± 0.6 mg/dl (0.13 ± 0.03 mmol/liter) per 10-yr increase in age, and increase of 7.8 ± 0.7 mg/dl (0.43 ± 0.04 mmol/liter) with each percent unit increase in HbA_{1c} (all $P < 0.0001$). Sex was not a significant predictor of sensor glucose SD.

Discussion

The importance of intensive glucose control for preventing diabetes-related complications is well established (1, 2, 32). However, individuals with type 1 and type 2 diabetes frequently fail to achieve HbA_{1c} goals of less than 7.0% or no more than 6.5% recommended by professional organizations (3, 4). This failure often arises from reluctance by patients or physicians to increase insulin dose due to fear of hypoglycemia. For patients with type 2 diabetes poorly controlled on diet and oral agents, insulin treatment is often delayed because of the perceived burden of injections and glucose self-monitoring, weight gain, and risk of hypoglycemia. For those patients already on insulin, similar concerns also impede insulin intensification.

Target glycemia measures such as HbA_{1c} and fasting plasma glucose often fail to distinguish between highly fluctuating glucose profiles and those that are more stable. Although the impact of postprandial glycemic excursions has been investigated in relation to longer-term complications, oxidative stress, and microvascular pathology (11–13), the greatest impact of reduced glycemic variability might be to facilitate patient acceptance, allowing greater insulin intensification.

When evaluating the comparative effectiveness of insulin regimens, glycemic variability, satisfaction, and QoL might provide additional evidence of therapeutic benefit. To date, there have been no quantitative studies demonstrating an association between decreased glycemic variability, improved patient satisfaction and QoL, and higher probability of reaching goal HbA_{1c}. In healthy adults, normal physiological insulin secretion prevents widely varying glucose fluctuations. However, for the diabetes patient, defects in insulin secretion cause both chronic sustained hyperglycemia and acute daily fluctuations in glucose levels corresponding to meals, exercise, and diabetes medications. The prevalence of high and low excursions might not be reflected in either standard four-point glucose profiles or HbA_{1c} but can be quantified using 24-h ambulatory glucose monitoring.

Insulin intensification algorithms facilitate achieving target HbA_{1c} by dose adjustments according to SMBG (33, 34). Patient-centered outcomes such as tolerability, burden, convenience, and QoL are key factors that influence the ability to adhere to insulin adjustments. For patients injecting insulin once or twice daily, basal-bolus insulin regimens might also be postponed because of the perceived burden of additional injections and glucose self-monitoring (35). However, such regimens might confer benefits associated with a more physiological nondiabetic intra-day glucose profile that could potentially offset regimen burden.

By optimizing the clinician's ability to follow the algorithm, insulin dose increases could be maximized according to daily fasting and premeal glucose levels in a standardized fashion across centers. Insulin doses increased each month; however, in the glargine-glulisine arm, the increase during the first period was approximately twice as high as in the premix group, the dropout rate during the second period was four times lower, and patient satisfaction and QoL outcomes were significantly higher. Rates of hypoglycemia were comparable. The lowering of HbA_{1c} was significantly greater for glargine-glulisine *vs.* premix by 0.33%. However, this difference alone did not account for the improvement in satisfaction or QoL outcomes. Rather, both CGM sensor glucose mean and SD were independent predictors.

Our results indicate that for insulin-using patients treated with two daily injections of insulin and moderately satisfied with their current therapy, there is opportunity to improve acceptance of insulin treatment while increasing the probability of reaching HbA_{1c} goals using a basal-bolus regimen. As expected, the impact was greater for patients with type 1 diabetes because it is much more difficult to control glycemic excursions in this population. Studies have suggested that ease of use, convenience, social comfort, and flexibility of the treatment process are important issues to both type 1 and type 2 diabetic patients for insulin administration (36, 37). While on glargine-glulisine, patients reported substantial and stable improvement in satisfaction ratings in contrast to no change or worsening for those on premix. Our findings documented that fewer patients withdrew from the glargine-

glulisine regimen as insulin was intensified, and patients had a 50% higher probability of achieving target HbA_{1c} below 7.0%. They also had improved health perceptions, QoL, and satisfaction when on the glargine-glulisine regimen. These results are consistent with previous studies showing higher satisfaction in patients on insulin pumps, which also more closely mimic the body's insulin requirements (38, 39).

During a period of carefully monitored insulin titration, maximum effectiveness of glycemic control, treatment satisfaction, and QoL outcomes can be achieved using a basal-bolus regimen such as insulin glargine plus glulisine compared with a simpler regimen using premix analog insulin. One of the major concerns that creates barriers to adoption of insulin and intensification is the perception that patients will fail to adhere to a more complex insulin regimen. However, we have demonstrated that overall regimen acceptance was comparable between the two treatment arms. This finding supports the general recommendation that multiple injections using a basal-bolus insulin regimen can be used by patients and that improved health outcomes appear to offset the impact of increased burden associated with the insulin regimen.

Limitations of this study included the open-label design and the relatively short duration of each treatment period. Although the gold standard for clinical trials is to use a double-blind design, insulin-treated diabetes requiring daily insulin adjustments by the patient must be open label to ensure patient safety. In addition, to adequately evaluate treatment satisfaction and QoL, the number of injections must reflect the actual regimen without the bias of additional saline injections required for blinding. The 3-month duration of each period was chosen to achieve a steady-state measure of HbA_{1c}; however, this limited the endpoints to shorter-term patient-centered outcomes.

The CGM measures indicated decreased intra-day mean glucose, glycemic variability, and excursions above 140 mg/dl (7.8 mmol/liter), which were associated with improvements in patient satisfaction and perceived health independent of concurrent lowering of daily glucose and HbA_{1c}. As such, this study provides important and significant evidence that glycemic variability mediates improvements in patient-centered outcomes and should be considered when evaluating the comparative effectiveness of insulin regimens. The barriers to diabetes management are multifactorial, but our comparative effectiveness crossover trial supports the hypothesis that glycemic variability plays an important role in patient satisfaction with insulin therapy. Increased communication between clinicians and patients concerning these patient-centered factors, especially in individuals failing to intensify or maintain their insulin regimen, might better inform the clinical decision process when weighing the risks and benefits of alternative methods of delivering intensive insulin regimens.

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