

# The DURAbility of Basal versus Lispro mix 75/25 insulin Efficacy (DURABLE) Trial

## Comparing the durability of lispro mix 75/25 and glargine

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**OBJECTIVE**—This study compared the durability of glycemic control of twice-daily insulin lispro mix 75/25 (LM75/25: 75% insulin lispro protamine suspension/25% lispro) and once-daily insulin glargine, added to oral antihyperglycemic drugs in type 2 diabetes patients.

**RESEARCH DESIGN AND METHODS**—During the initiation phase, patients were randomized to LM75/25 or glargine. After 6 months, patients with A1C  $\leq 7.0\%$  advanced to the maintenance phase for  $\leq 24$  months. The primary objective was the between-group comparison of duration of maintaining the A1C goal.

**RESULTS**—Of 900 patients receiving LM75/25 and 918 patients receiving glargine who completed initiation, 473 and 419, respectively, had A1C  $\leq 7.0\%$  and continued into maintenance. Baseline characteristics except age were similar in this group. Median time of maintaining the A1C goal was 16.8 months for LM75/25 (95% CI 14.0–19.7) and 14.4 months for glargine (95% CI 13.4–16.8;  $P = 0.040$ ). A1C goal was maintained in 202 LM75/25-treated patients (43%) and in 147 glargine-treated patients (35%;  $P = 0.006$ ). No differences were observed in overall, nocturnal, or severe hypoglycemia. LM75/25 patients had higher total daily insulin dose ( $0.45 \pm 0.21$  vs.  $0.37 \pm 0.21$  units/kg/day) and more weight gain ( $5.4 \pm 5.8$  vs.  $3.7 \pm 5.6$  kg) from baseline. Patients taking LM75/25 and glargine with lower baseline A1C levels were more likely to maintain the A1C goal ( $P = 0.043$  and  $P < 0.001$ , respectively).

**CONCLUSIONS**—A modestly longer durability of glycemic control was achieved with LM75/25 compared with glargine. Patients with lower baseline A1C levels were more likely to maintain the goal, supporting the concept of earlier insulin initiation.

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When patients with type 2 diabetes are unable to maintain glycemic control using oral antihyperglycemic drugs (OADs), insulin is an accepted next step (1,2). In short-term studies comparing starter insulins, greater A1C reduction was demonstrated with twice-daily premixed insulin analogs compared with once-daily insulin glargine (LANTUS insulin glargine [recombinant

DNA origin], sanofi-aventis) (3,4). Although valuable, these studies did not address the duration that adequate A1C control can be maintained with starter insulin. The Treating to Target in Type 2 Diabetes Trial (4-T) evaluated the 1- and 3-year safety and efficacy of various starter insulins (5,6). However, this trial required a second insulin formulation for persistent hyperglycemia. Therefore, data

specific to long-term efficacy of a single therapy are lacking.

The current study examined the efficacy, safety, and durability of twice-daily lispro mix 75/25 (LM75/25; Humalog Mix75/25: 75% insulin lispro protamine suspension, 25% lispro, Eli Lilly and Company) compared with once-daily glargine with OADs (7). The study's 6-month initiation phase demonstrated a slightly lower end point A1C with LM75/25, with more overall hypoglycemia but less nocturnal hypoglycemia, compared with glargine (8). At 6 months, patients with A1C  $> 7.0\%$  could enroll in an intensification substudy (9). Patients with A1C  $\leq 7.0\%$  continued into a 24-month maintenance phase evaluating how long each insulin regimen could maintain the A1C goal, which was the primary objective of the DURAbility of Basal versus Lispro mix 75/25 insulin Efficacy (DURABLE) trial. These results offer the first evaluation of durability for these two insulin initiation regimens.

## RESEARCH DESIGN AND METHODS

### Study design

The DURABLE trial (7) was a 30-month, randomized, multicenter, multinational, open-label, two-arm, parallel study conducted at 242 centers in 11 countries between 2005 and 2009. The trial enrolled 2091 insulin-naïve patients with type 2 diabetes, aged 30–80 years, A1C  $> 7.0\%$ , and taking two or more OADs (metformin, sulfonylurea, pioglitazone, or rosiglitazone) for  $\geq 90$  days. Exclusion criteria included a history of long-term insulin use, severe hypoglycemia, and significant concomitant disease (7). Eligible patients were randomized, by country, to LM75/25 or glargine, stratified within the country by sulfonylurea and thiazolidinedione use.

All patients had a 6-month initiation phase to attain A1C  $\leq 7.0\%$  (10). At 6 months, patients with A1C  $\leq 7.0\%$  were monitored for up to an additional 24 months (maintenance phase) to evaluate how long

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the A1C goal ( $A1C \leq 7.0\%$  or  $A1C > 7.0\%$  but increased  $< 0.4\%$  from last  $A1C \leq 7.0\%$ ) could be maintained (Fig. 1). Because rescue therapy was not offered in maintenance, patients discontinued if A1C increased to  $> 7.5\%$ . The trial was conducted in accordance with International Conference on Harmonization guidelines and the Declaration of Helsinki (11). A1C, measured every 3 months, and 1,5-anhydroglucitol were evaluated centrally (Covance Laboratories). Homeostasis model assessment was used to assess insulin resistance (HOMA-IR) and  $\beta$ -cell function (HOMA-B) (12).

### Study medications and treatments

The LM75/25 starting dose was 10 units twice daily, and the glargine starting dose

was 10 units once daily (7,10,13), both added to prestudy OADs. Insulin was adjusted to achieve  $A1C \leq 6.5\%$  using regimen-specific insulin-titration algorithms (7,10,14) based on self-monitored plasma glucose (SMPG) review. During the 6-month initiation phase, dose adjustments were reviewed by an external data monitoring committee; this was not continued during maintenance because patients had an  $A1C \leq 7.0\%$  (7). Doses were assessed and adjusted  $\leq 3$  months according to patients' twice-daily SMPG values.

Plasma glucose  $\leq 70$  mg/dL (3.9 mmol/L) or symptoms defined hypoglycemia. Hypoglycemia occurring after bedtime and before morning meal/insulin dose was "nocturnal." Hypoglycemia

requiring assistance with oral carbohydrate, intravenous glucose, or glucagon was "severe" (15). Serious adverse events (SAEs) were life-threatening or resulted in hospitalization, persistent or significant disability, or death.

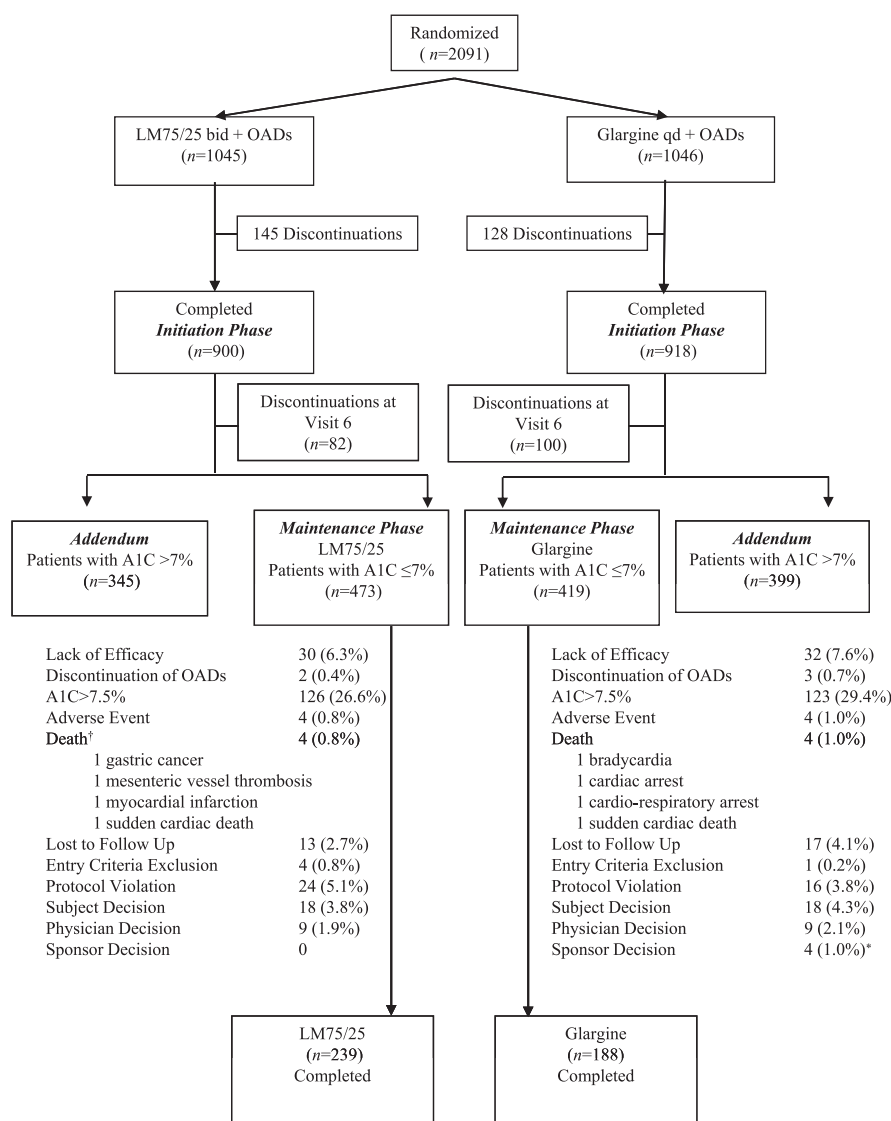
### Outcome measures

The primary efficacy measure was duration from the time participants first achieved an  $A1C \leq 7.0\%$  to when they were no longer at the A1C goal. Secondary measures included A1C change from baseline (randomization), A1C by visit, 7-point SMPG profile, 1,5-anhydroglucitol, weight change, total daily insulin dose, and hypoglycemia rate, and incidence.

### Statistical methods

The sample size was based on time to failure of A1C control. With 1,000 patients/arm and assuming a 10% dropout rate, approximately 900 patients/arm would reach 6 months, where it was estimated 30% of glargine-treated patients and 45% of LM75/25-treated patients would achieve  $A1C \leq 7.0\%$  (3,4,14,16,17) and continue into maintenance. At maintenance phase completion, with this sample, considering dropouts and required discontinuations ( $A1C > 7.5\%$ ), it would be possible to detect a between-group difference, for example, of 76 vs. 65% maintaining control with LM75/25 versus glargine (11% between-group difference) with approximately 84% power and a two-sided  $\alpha$  of 0.05, or alternatively, 78 vs. 63%, respectively, with a 15% between-group difference with 95% power.

All analyses were performed on the intent-to-treat population. The time of maintaining glycemic control was compared between groups with a stratified log-rank test. Strata included country and thiazolidinedione and sulfonylurea use. The time to first achieving control was the starting point (3 or 6 months after randomization). A Cox regression model to analyze time to failure was implemented as supportive analysis, which included the mentioned stratification variables and OADs, gender, diabetes duration, HOMA-B, HOMA-IR, baseline A1C, and country. SAEs and other categorical variables were compared with the Fisher exact test. End point A1C and hypoglycemia rates were compared using ANOVA, with treatment and stratification variables in the model. Hypoglycemia incidence was compared using the Cochran-Mantel-Haenszel statistic stratified by country,



**Figure 1**—Flow diagram of patients' disposition. bid, twice daily; qd, once daily. \*P = 0.048 between-group difference. †One further death related to pancreatic carcinoma occurred in the LM75/25 group after study discontinuation.

thiazolidinedione, and sulfonylurea use. Results are presented as number and percentage or mean  $\pm$  SD. Values of  $P < 0.05$  were considered statistically significant.

## RESULTS

### Patient disposition and baseline characteristics

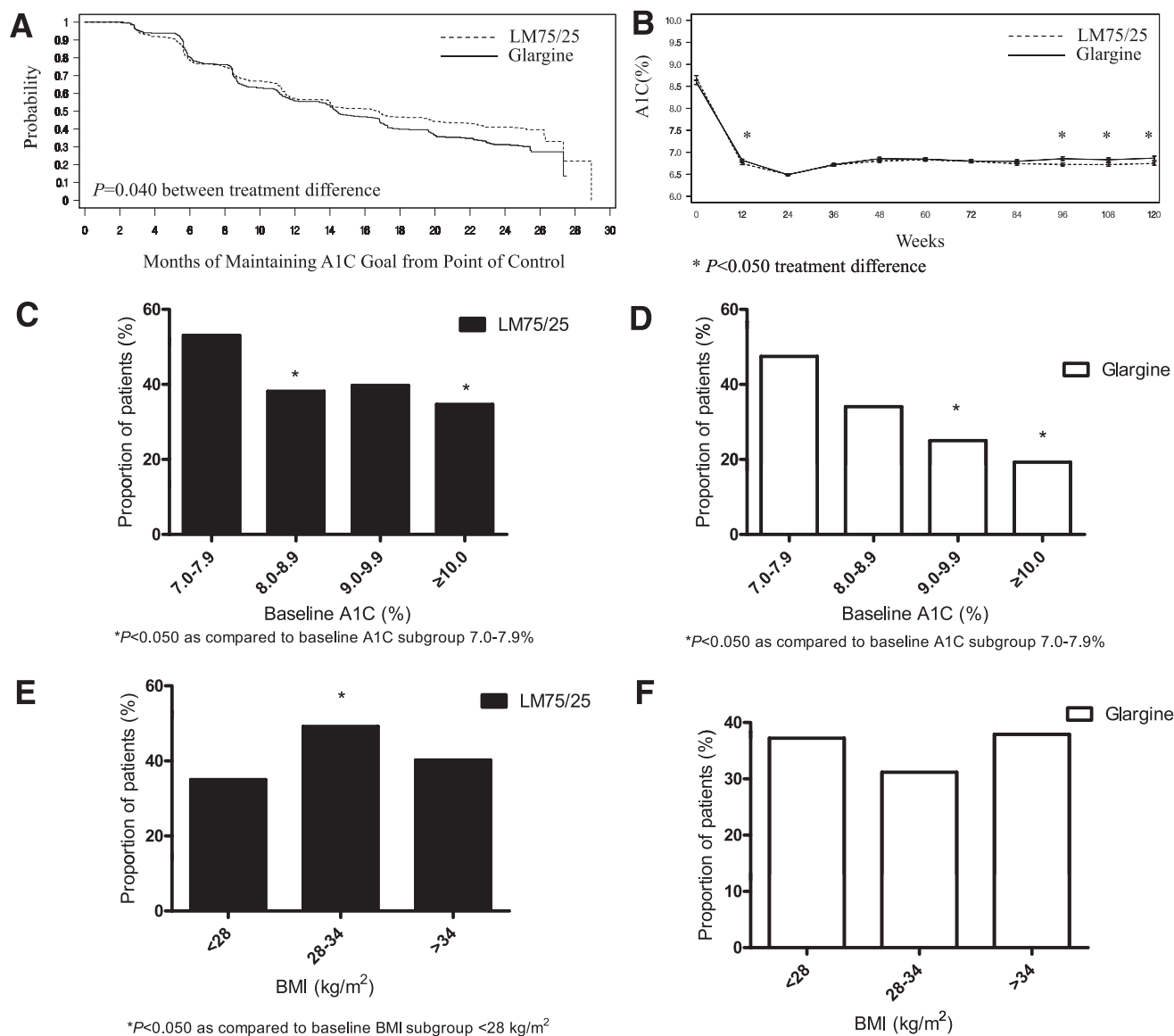
In the initiation phase, 2,091 patients were randomized, with 1,045 to LM75/25 and

1,046 to glargine. Of 900 LM75/25-treated patients and 918 glargine-treated patients who completed the initiation phase, 473 (53%) and 419 (46%), respectively, achieved  $A1C \leq 7.0\%$  and continued into the maintenance phase (Fig. 1). In this group, 73% were non-Hispanic whites, 5% were of African descent, 9% were Asian, 10% were Hispanic, and 2% were of other racial or ethnic origin. Other than age (LM75/25:  $59 \pm 9$  years vs. glargine  $57 \pm 9$  years,  $P = 0.039$ ), baseline characteristics

at randomization were similar: men, 480 (54%); BMI,  $31.9 \pm 5.7$  kg/m<sup>2</sup>; diabetes duration,  $9.5 \pm 6.0$  years; A1C,  $8.7 \pm 1.1\%$ ; and fasting plasma glucose (FPG),  $189 \pm 49$  mg/dL. Sulfonylurea use was predominant (LM75/25, 89%; glargine, 87%), with sulfonylurea/metformin as the most common combination.

### Glycemic control

The median time of maintaining the A1C goal was 16.8 months (95% CI 14.0–19.7)



**Figure 2**—A: Time to failure of regimen to maintain A1C goal in patients receiving insulin lispro mix 75/25 (LM75/25) and glargine. B: A1C by visit. C: Percentage of patients maintaining the A1C goal at the end point within the LM75/25 treatment group by baseline A1C subgroup. D: Percentage of patients maintaining the A1C goal at the end point within the glargine treatment group by baseline A1C subgroup. The between-group comparison showed a significantly higher percentage of LM75/25-treated patients with a baseline A1C  $> 10.0\%$  maintained the A1C goal at the end point compared with glargine-treated patients with a baseline A1C  $> 10.0\%$  at the end point ( $P = 0.044$ ). E: Percentage of patients maintaining A1C goal at end point within the LM75/25 treatment group by baseline BMI subgroup. F: Percentage of patients maintaining the A1C goal at the end point within the glargine treatment group by baseline BMI subgroup (between-group comparison showed significantly higher percentage of LM75/25-treated patients with baseline BMI 28–34 kg/m<sup>2</sup> maintained A1C goal at end point compared with glargine-treated patients with baseline BMI 28–34 kg/m<sup>2</sup> at end point,  $P < 0.001$ ).

for LM75/25 and 14.4 months (95% CI 13.4–16.8) for glargine ( $P = 0.040$ ; Fig. 2A). After adjusting for baseline A1C, gender, thiazolidinedione, sulfonylurea use, HOMA-B, HOMA-IR, diabetes duration, and country, LM75/25-treated patients were more likely than glargine-treated patients to maintain the A1C goal longer, with a hazard ratio of losing glycemic control of 0.78 (95% CI 0.66–0.93;  $P = 0.010$ ). Diabetes duration, baseline A1C, and country had significant effects on time of maintaining the A1C goal (Table 1). The time to initial attainment of A1C  $\leq 7.0\%$  was not different (LM75/25:  $3.7 \pm 1.3$  months vs. glargine:  $3.8 \pm 1.4$  months,  $P = 0.173$ ).

The A1C goal was maintained for 202 patients (43%) receiving LM75/25 and for 147 patients (35%) receiving glargine ( $P = 0.006$ ); Fig. 2B illustrates A1C by visit. At the end point, A1C reduction was greater in LM75/25-treated patients ( $-1.6 \pm 1.2\%$ ) versus glargine ( $-1.4 \pm 1.2\%$ ,  $P = 0.017$ ) and was lower with LM75/25 ( $7.1 \pm 0.8\%$ ) than with glargine ( $7.2 \pm 0.8\%$ ,  $P = 0.017$ ).

Compared with baseline, both therapies lowered SMPG values at all times ( $P < 0.001$ ; Supplementary Fig. 1A). For LM75/25-treated patients, the end point FPG was higher ( $P < 0.001$ ), whereas pre-lunch ( $P = 0.031$ ) and dinner 2-h postprandial ( $P < 0.001$ ) glucose levels were

lower compared with glargine-treated patients.

At the end point, 1,5-anhydroglucitol was significantly higher for LM75/25-treated patients ( $5.8 \pm 5.2 \mu\text{g/dL}$ ) compared with glargine-treated patients ( $4.8 \pm 5.3 \mu\text{g/dL}$ ;  $P = 0.004$ ).

### Weight gain and insulin dose

During the entire study, LM75/25-treated patients gained more weight than glargine-treated patients ( $5.4 \pm 5.8$  vs.  $3.7 \pm 5.6$  kg;  $P < 0.001$ ), but weight gain during maintenance was similar ( $1.6 \pm 4.7$  vs.  $1.8 \pm 4.5$  kg;  $P = 0.599$ ). At 6 months, total daily insulin was  $0.43 \pm 0.19$  units/kg/day for LM75/25 and  $0.36 \pm 0.19$  units/kg/day for glargine ( $P < 0.001$ ). At 30 months, total daily insulin was  $0.45 \pm 0.21$  units/kg/day for LM75/25 vs.  $0.37 \pm 0.21$  units/kg/day for glargine ( $P < 0.001$ ).

### Safety

There was no difference between groups in overall, nocturnal, or severe hypoglycemia (Table 2).

There was no difference in SAE incidence between groups (LM75/25: 13.1%, glargine: 14.1%,  $P = 0.696$ ). The incidence of SAEs related to the cardiovascular system (LM75/25: 5.9%, glargine: 7.2%;  $P = 0.497$ ), and cancer (LM75/25: 1.9%, glargine: 0.7%;  $P = 0.152$ ) were similar between groups. In each group, there

were four adverse events that led to discontinuation ( $P = 1.000$ ; Fig. 1) and four deaths ( $P = 1.000$ ; Fig. 1). In addition, an SAE in a LM75/25-treated patient led to death after discontinuation.

### Within-group comparisons of baseline and end point characteristics

Compared with LM75/25-treated patients unable to maintain goal, patients receiving LM75/25 who maintained goal had lower baseline A1C levels (Table 3). Glargine-treated patients who maintained the goal had lower baseline A1C, postprandial glucose and mean plasma glucose, shorter diabetes duration, and higher 1,5-anhydroglucitol compared with those who did not maintain the goal (Table 3). Within-group comparisons at the end point are presented in Table 3.

For LM75/25, patients with a baseline A1C of 8.0–8.9 and  $\geq 10.0\%$  were less likely to maintain the goal at the end point than the subgroup with a baseline A1C of 7.0–7.9% (Fig. 2C). For glargine, patients with an A1C of 9.0–9.9 and  $\geq 10.0\%$  were less likely to maintain the goal versus patients with a baseline A1C 7.0–7.9% (Fig. 2D). Baseline BMI subgroup analyses are presented in Fig. 2E and F.

**CONCLUSIONS**—The 30-month DURABLE study offers the first long-term comparison of starter insulin durability, evaluating LM75/25 and glargine added to OADs, in a large, multinational population of type 2 diabetic patients. LM75/25 therapy resulted in a modestly longer durability of glycemic control, with no difference in hypoglycemia and more weight gain compared with glargine. A moderately higher percentage of patients randomized to LM75/25 (43%) maintained the protocol-specified definition of A1C goal compared with patients randomized to glargine (35%).

These findings support previous shorter studies demonstrating varying degrees of improved glycemic control with analog mixtures compared with glargine (3,4,8). The modest between-group difference observed is somewhat surprising, given previous results (3,4). Although speculative, this may be related to the trial length. At later visits, there was some between-group separation in time maintaining goal and A1C by visit; this may have separated further with longer follow-up. This could be related to the predominance of concomitant sulfonylurea

**Table 1—Analysis of duration of maintaining A1C goal with the Cox regression model**

Parameter	Estimate	SE	P	HR	95% CI
Treatment (LM75/25 vs. glargine)	−0.25	0.09	0.010	0.78	(0.66–0.93)
Thiazolidinedione use (yes vs. no)	−0.22	0.12	0.061	0.81	(0.64–1.01)
Sulfonylurea use (yes vs. no)	0.25	0.17	0.140	1.29	(0.92–1.80)
Sex (male vs. female)	0.01	0.09	0.880	1.01	(0.85–1.21)
Duration of diabetes (years)	0.02	0.01	0.020	1.02	(1.00–1.03)
HOMA-B	0.00	0.00	0.103	1.00	(1.00–1.00)
HOMA-IR	−0.00	0.01	0.760	1.00	(0.97–1.02)
Baseline A1C (%)	0.28	0.04	<0.001	1.32	(1.22–1.43)
Country vs. United States					
Argentina	0.07	0.15	0.640	1.10	(0.81–1.42)
Australia	0.22	0.25	0.370	1.25	(0.77–2.04)
Brazil	0.15	0.22	0.500	1.17	(0.75–1.81)
Canada	0.23	0.19	0.220	1.26	(0.87–1.81)
Spain	−0.58	0.22	0.010	0.56	(0.36–0.87)
Greece	0.39	0.28	0.160	1.48	(0.86–2.54)
Hungary	−0.05	0.23	0.840	0.95	(0.61–1.50)
India	0.39	0.16	0.020	1.48	(1.07–2.04)
The Netherlands	−0.21	0.32	0.502	0.81	(0.44–1.50)
Romania	−0.02	0.27	0.940	0.98	(0.58–1.66)

HR, hazard ratio of losing glycemic control.

Table 2—Incidence and rate of hypoglycemia

Variable	LM75/25	Glargine	P
Hypoglycemia* incidence, n (%)			
Overall	235 (49.9)	188 (45.3)	0.370
Documented symptomatic (PG $\leq$ 70 mg/dL [3.9 mmol/L])	173 (36.7)	128 (30.8)	0.128
Documented asymptomatic (PG $\leq$ 70 mg/dL [3.9 mmol/L])	108 (22.9)	102 (24.6)	0.375
Nocturnal	136 (28.9)	126 (30.4)	0.397
Severe†	20 (4.2)	12 (2.9)	0.391
Hypoglycemia* rate (episodes/pt/year)			
Overall			
Median (interquartile range)	0.0 (0.0–22.8)	0.0 (0.0–19.0)	
Mean $\pm$ SD	18.6 $\pm$ 35.5	16.4 $\pm$ 34.8	0.581
Documented symptomatic (PG $\leq$ 70 mg/dL [3.9 mmol/L])			
Median (interquartile range)	0.0 (0.0–8.9)	0.0 (0.0–4.7)	
Mean $\pm$ SD	10.0 $\pm$ 24.5	8.2 $\pm$ 24.8	0.354
Documented asymptomatic (PG $\leq$ 70 mg/dL [3.9 mmol/L])			
Median (interquartile range)	0.0 (0.0–0.0)	0.0 (0.0–0.0)	
Mean	5.9 $\pm$ 19.4	6.7 $\pm$ 19.5	0.415
Nocturnal			
Median (interquartile range)	0.0 (0.0–4.3)	0.0 (0.0–4.7)	
Mean	5.9 $\pm$ 16.0	7.7 $\pm$ 19.4	0.065
Severe†			
Median (interquartile range)	0.0 (0.0–0.0)	0.0 (0.0–0.0)	
Mean	0.03 $\pm$ 0.21	0.07 $\pm$ 1.03	0.268

PG, plasma glucose; pt, patient. \*Hypoglycemia was recorded any time a patient experienced symptoms of hypoglycemia or had a self-monitored plasma glucose  $\leq$ 70 mg/dL (3.9 mmol/L), and event was deemed severe if it required assistance; for all nonsevere hypoglycemia, values were calculated at end point (using last observation carried forward) for the period between the previous office visit and end point office visit. †For severe hypoglycemia, incidence and rate were calculated over the entire study duration due to the rare occurrence of severe hypoglycemia.

use within DURABLE (88% overall) in contrast to previous studies, which may have helped to partially compensate for meal-related insulin secretory deficits within the glargine arm. Additionally, because somewhat fewer glargine patients advanced into maintenance (473 LM75/25 vs. 419 glargine), there were actually fewer patients to fail, and this may have attenuated the between-group difference.

Although basal insulin is often recommended as a starter insulin (1,2), premixed analog insulin may be appropriate in some situations (18). When baseline characteristics predictive of success are compared between treatment groups, for glargine, patients with lower postprandial glucose and mean plasma glucose, shorter diabetes duration, and higher 1,5-anhydroglucitol were more likely to maintain the goal at the end point. These baseline characteristics did not differ among patients receiving LM75/25 who did or did not maintain the goal. This suggests that patients with greater first- and second-phase insulin secretory capacity are more likely to maintain glycemic targets when basal insulin is added to OADs. Conversely, this may not be as requisite for maintenance of targets

with the addition of LM75/25 where the rapid-acting analog component can further compensate for meal-related insulin secretory deficits. Baseline characteristics and measures such as 1,5-anhydroglucitol (19) and postprandial glucose may be useful for guiding treatment decisions when initiating insulin.

Patients in both treatment groups who maintained the goal had lower baseline A1C. Additionally, for both, the lowest baseline A1C subgroup (A1C 7.0–7.9%) had a numerically higher percentage of patients who maintained the goal at the end point compared with the baseline A1C subgroups  $\geq$ 8.0%; this difference reached statistical significance in two of three within-group comparisons for each regimen. This highlights the potential importance of early insulin use in an effort to maintain A1C goals.

However, with very modest insulin titration over the last 2 years of the study and no allowed rescue therapy, both regimens demonstrated a relatively short duration of control. This corroborates the 4-T study, where by 3 years, 67.7% of patients receiving premix and 81.6% receiving a basal analog required a second insulin (6). Both studies illustrate the progressive nature of type 2 diabetes,

necessitating diligence for monitoring and insulin adjustment as well as appropriate therapy advancement.

This study was designed to evaluate starter insulin durability. Although this design provided valuable clinical information, including expected time to maintain the A1C goal once achieved, the design may have introduced a lead-time bias based on starting dose imbalances, allowing more LM75/25-treated patients to achieve the goal by 6 months. However, the lack of difference in average time to attain A1C  $\leq$ 7.0% between groups is reassuring. Only patients who achieved A1C  $\leq$ 7.0% continued into maintenance. At 6 months, more patients receiving LM75/25 had an A1C  $\leq$ 7.0%, leading to a 7% difference in patients continuing into maintenance (LM75/25: 473/900 [53%] vs. glargine: 419/918 [46%]). Although this is somewhat disproportionate, the design mandated that patients achieve control by 6 months to continue in the maintenance phase, otherwise they could participate in an insulin intensification substudy (9). The number starting maintenance was different, but this would not necessarily lead to a greater percentage maintaining the goal at the end point. And, as was discussed, this may have actually

Table 3—Patient demographics, baseline and end point characteristics for LM75/25 and glargine-treated patients who did and did not maintain A1C goal\*

	LM75/25			Glargine		
	Maintained goal	Did not maintain goal	P	Maintained goal	Did not maintain goal	P
Baseline demographics and characteristics†						
Age (years)	59.5 ± 9.2	58.1 ± 9.1	0.353	57.5 ± 8.2	57.4 ± 9.9	0.905
Male	111 (55.0)	134 (49.4)	0.308	81 (55.1)	154 (56.6)	0.331
Race/ethnicity			0.311			0.199
Caucasian	158 (78.2)	189 (69.7)		118 (80.3)	188 (69.1)	
African descent	11 (5.4)	13 (4.8)		6 (4.1)	17 (6.3)	
Asian	10 (5.0)	28 (10.3)		7 (4.8)	34 (12.5)	
Hispanic	21 (10.4)	31 (11.4)		13 (8.8)	28 (10.3)	
Other	2 (1.0)	10 (3.7)		3 (2.0)	5 (1.8)	
Weight (kg)	89.7 ± 19.2	87.8 ± 18.9	0.794	92.2 ± 20.5	89.7 ± 19.9	0.762
BMI (kg/m <sup>2</sup> )	31.6 ± 5.6	31.7 ± 5.8	0.266	32.5 ± 6.0	31.8 ± 5.6	0.993
Duration of diabetes (years)	9.4 ± 6.2	9.9 ± 6.4	0.708	8.4 ± 4.9	9.7 ± 6.1	0.036
A1C (%)	8.5 ± 1.1	8.8 ± 1.2	0.043	8.3 ± 0.9	8.8 ± 1.1	<0.001
HOMA-B	39.5 ± 112.2	33.7 ± 35.9	0.423	31.7 ± 25.2	31.2 ± 33.4	0.923
HOMA-IR	4.5 ± 3.6	4.6 ± 3.4	0.714	4.6 ± 4.4	4.2 ± 3.7	0.416
FPG (mg/dL)	184.7 ± 46.8	188.9 ± 49.2	0.466	188.5 ± 49.1	192.2 ± 48.8	0.283
PPG (mg/dL)	224.0 ± 52.5	231.7 ± 54.3	0.516	219.3 ± 51.2	233.5 ± 54.9	0.010
MPG (mg/dL)	201.4 ± 48.4	208.0 ± 49.1	0.425	200.6 ± 48.1	210.4 ± 50.6	0.035
1,5-Anhydroglucitol (μg/dL)	5.9 ± 4.2	5.7 ± 4.6	0.553	6.3 ± 4.6	5.4 ± 4.2	0.004
Thiazolidinedione use	91 (45.0)	94 (34.7)	0.193	74 (50.3)	101 (37.1)	0.117
Sulfonylurea use	173 (85.6)	249 (91.9)	0.464	121 (82.3)	245 (90.1)	0.544
End point characteristics†						
A1C (%)	6.5 ± 0.5	7.5 ± 0.7	<0.001	6.5 ± 0.5	7.6 ± 0.7	<0.001
Insulin dose (units/kg/day)	0.42 ± 0.20	0.48 ± 0.22	0.011	0.35 ± 0.20	0.37 ± 0.21	0.274
Weight change (kg)	5.2 ± 6.9	5.5 ± 5.0	0.350	2.5 ± 6.4	4.3 ± 5.1	<0.001
Overall hypoglycemia rate (epi/pt/year)	21.7 ± 39.7	16.3 ± 31.9	0.022	21.7 ± 41.8	13.7 ± 30.2	0.011
Nocturnal hypoglycemia rate (epi/pt/year)	6.4 ± 13.7	5.4 ± 17.5	0.123	8.6 ± 19.5	7.2 ± 19.3	0.426

epi, episode; MPG, mean plasma glucose; PPG, postprandial glucose; pt, patient. \*Goal was defined as A1C ≤7.0% or A1C >7.0% but with an increase <0.4% from last A1C ≤7.0%. †Continuous data are presented as mean ± SD; categorical data are presented as number (%).

attenuated between-group differences (i.e., conservative bias). More frequent A1C measurements and visits may have added clarity about the exact duration of control and helped facilitate continued insulin titration, but over 30 months, this could have been burdensome and affected discontinuation.

Therapy with LM75/25 demonstrated a modestly greater duration of control, with no difference in hypoglycemia and more weight gain. Patients with lower baseline A1C values were more likely to maintain the A1C goal with either regimen, which supports earlier initiation of insulin. In addition, patients with higher baseline postprandial glucose and lower 1,5-anhydroglucitol were less likely to maintain the goal with basal insulin added to OADs compared with LM75/25. This has not been previously demonstrated and suggests the potential utility of such measures when initiating therapy. Further

prospective study evaluating utility of measures for tailoring therapy is needed.

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