Original Article

INSULIN LISPRO WITH CONTINUOUS SUBCUTANEOUS INSULIN INFUSION IS SAFE AND EFFECTIVE IN PATIENTS WITH TYPE 2 DIABETES: A RANDOMIZED CROSSOVER TRIAL OF INSULIN LISPRO VERSUS INSULIN ASPART

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ABSTRACT

Objective: This study provides clinical information regarding the use of insulin lispro versus insulin aspart in continuous subcutaneous insulin infusion (CSII) in adult patients with type 2 diabetes mellitus (T2D).

Methods: After a 2-week lead-in period, 122 subjects treated with CSII therapy were randomized to 32 weeks of treatment during 2 separate 16-week treatment periods (TPs) with crossover beginning with insulin lispro (n = 60) or insulin aspart (n = 62). Glycated hemoglobin A1c (HbA1c), total daily insulin dose, and weight were recorded at the end of TP1 and TP2. Adverse events (AEs) and hypoglycemic events (overall, documented symptomatic, nocturnal, or severe) were recorded throughout the TPs. Data were analyzed using statistical methods that accounted for repeated measurements.

Results: A total of 107 subjects completed the study; 7 discontinued in TP1 and 8 discontinued in TP2. Insulin lispro was noninferior to insulin aspart in endpoint (weeks 16 and 32) HbA1c over TP1 and TP2 combined. Total daily insulin dose, weight change, and incidence and rates of hypoglycemia were not statistically significantly different between treatments. One case of severe hypoglycemia and 1 of diabetic ketoacidosis was observed with insulin aspart. One case of severe infusion site abscess was noted with insulin lispro. Overall, both insulin lispro and insulin aspart were well tolerated with similar AEs reported.

Conclusion: Insulin lispro and insulin aspart performed similarly after 16 weeks of treatment, with noninferiority for HbA1c and no significant difference in parameters measured. These findings indicate that insulin lispro and insulin aspart can both be used safely and effectively in patients with T2D using CSII. (**Endocr Pract. 2015;21:247-257**)

Abbreviations:
AE = adverse event; **BG** = blood glucose; **CI** = confidence interval; **CSII** = continuous subcutaneous insulin infusion; **HbA1c** = glycated hemoglobin A1C; **LS** = least-squares; **MDI** = multiple daily injection; **OAM** = oral antihyperglycemic medication; **NIM** = noninferiority margin; **SAE** = serious adverse event; **T1D** = type 1 diabetes mellitus; **T2D** = type 2 diabetes mellitus; **TP** = treatment period; **TEAE** = treatment-emergent adverse event; **TZD** = thiazolidinedione.

INTRODUCTION

More than one-third of adults with type 2 diabetes mellitus (T2D) do not reach the American Diabetes Association goal of glycated hemoglobin A1c (HbA1c) less than 7% (1,2). The use of continuous subcutaneous insulin infusion (CSII) in T2D, although currently less common than in type 1 diabetes (T1D), allows for tight glucose control and has been shown to result in either similar or improved HbA1c values versus multiple daily injection (MDI), no reported increase in hypoglycemia, and improved patient satisfaction (3,4). As the number of patients with T2D continues to increase, so does the use of CSII in this population; therefore, it is valuable to gain more clinical information on the effects of different analog insulins in these patients.

This study compared the efficacy and safety of 2 rapid-acting analogs, insulin lispro and insulin aspart, in a T2D population already using CSII. The primary objective was

to demonstrate that CSII with lispro in patients with T2D was noninferior (noninferiority margin [NIM] 0.4%) to CSII with insulin aspart as measured by HbA1c at the end of each treatment period (TP). A 0.4% NIM was chosen for this study because it is comparable to other similar studies (5-7). The secondary objectives of the study were to compare CSII use of insulin lispro with insulin aspart with respect to total daily insulin dose (U/day and U/kg/day) at endpoints of the 2 TPs (i.e., week 16 for TP1 and week 32 for TP2), rate and frequency of hypoglycemic events, weight change, and adverse events (AEs) over each of the 2 TPs.

METHODS

Study Patients

Male or female subjects with T2D (8) who were 18 to 85 years of age at screening, treated with CSII therapy using a rapid-acting analog for at least 6 months before screening, and had an HbA1c ≤9.0% at screening were included. Subjects taking oral antihyperglycemic medications (OAMs) were required to be on a stable dose for at least 3 months prior to screening.

Subjects with more than 1 episode of severe hypoglycemia (defined as requiring third-party assistance) within 6 months before study entry, who had severe insulin resistance (required >2 U/kg/day), or who were taking or took OAMs not approved in the U.S. for use with insulin or injectable noninsulin antihyperglycemic medications within 3 months of screening were excluded from the study. Other exclusion criteria included having a history of hypoglycemia unawareness (routinely asymptomatic with a blood glucose [BG] level <45 mg/dL); having severe infection or an abscess at the infusion site(s) up to 1 year prior to screening; having a history of lipohypertrophy or lipoatrophy at the infusion site(s); or having multiple, clinically significant, pump-related occlusions, as judged by an investigator.

Study Design and Treatments Administered

This was a phase 3b, multi-center, randomized, double-blind, active comparator, 2 period (16 weeks each), 2-sequence, 32-week crossover trial comparing insulin lispro with insulin aspart in subjects with T2D using CSII. The study was registered with clinicaltrials.gov (NCT01474538) and was conducted across 12 sites in the United States in accordance with the principles of the Declaration of Helsinki (9) and the International Conference on Harmonisation Good Clinical Practices E6 Guideline (10). The protocol and informed consent form were approved by an ethical review board. Informed consent was obtained from each patient or their legal representative.

Following a screening period of up to 2 weeks, eligible subjects were randomly assigned (1:1) by an interactive voice response system to either insulin lispro or insulin aspart for 16 weeks (TP1) followed by crossover to the other treatment for an additional 16 weeks (TP2) for a total TP of 32 weeks. Subjects were stratified based on screening HbA1c value (≤8% and >8%) and thiazolidinedione (TZD) use (yes or no). Subjects in a crossover study serve as their own control, which can efficiently reduce the impact of the between-subject variability (11) and baseline characteristics to the analysis. Because HbA1c measures the previous 8 to 12 weeks of glycemic control (12) and is heavily weighted to the 4 weeks preceding the measurement (13), and because insulin lispro and insulin aspart have half-lives measured in minutes (14-16), a 16-week TP was selected to minimize the risk of carryover effect and to ensure that the endpoint measurement (32 weeks) in TP2 reflected glycemic control influenced only by the second insulin treatment. Subjects, investigators, and all other personnel involved in the conduct of the study were blinded to the individual treatment assignments for the study duration.

Clear solutions of insulin lispro (Humalog®, 100 U/mL, Eli Lilly and Company, Indianapolis, IN) and insulin aspart (NovoLog®, 100 U/mL, Novo Nordisk, A/S, Bagsværd, Denmark) were provided separately in 10-mL covered vials to mask insulin type and were used to fill the pump reservoirs. Subjects administered the insulin by CSII in 1 of 2 sequences that were each 16 weeks long. Subjects used their own insulin pump systems during the study, irrespective of brand, and continued with their existing insulin dosing regimens (basal rates, meal boluses [with/without carbohydrate counting algorithms], and correction boluses).

Subjects already using a continuous glucose monitor were permitted to continue as long as they maintained its use for the study duration. Subjects were all given the same model of BG meter, a diary to record BG measurements and hypoglycemic events for review by site personnel, and other diabetes supplies. Qualified medical staff reviewed with the subjects the need to maintain their physical activities, BG monitoring, and provided training on the BG meter and study diary entry. Signs and symptoms of hypo- and hyperglycemia and appropriate treatment were reviewed with subjects.

At randomization (week 0) and the crossover visit (week 16), subjects changed their infusion site and tubing (if using a pump with tubing) and filled a new reservoir with the investigational product under the observation of study site staff. At the last study visit (week 32), subjects changed their infusion sites and filled the new reservoirs with their poststudy insulin as designated by their investigator or physician. All other reservoir and tubing changes were done according to standard practice and the investigators' recommendations.

Subject characteristics and demographic variables were obtained at screening, and baseline hypoglycemia was captured between screening and randomization. HbA1c was collected at screening, randomization (week 0), the end of each TP (weeks 16 and 32), and, if applicable, at early termination. For HbA1c and screening laboratory tests, a central laboratory was used to maintain consistency of methods and to combine laboratory and/or diagnostic data across sites for this multicenter study.

Statistical Analysis

To demonstrate that CSII use of insulin lispro in subjects with T2D was noninferior to use of insulin aspart with regard to HbA1c with a NIM of 0.4%, 51 completers per dosing sequence (102 in total) were needed at 32 weeks. This calculation assumed no treatment difference in HbA1c between the use of insulin lispro and insulin aspart in subjects with T2D, with an SD of 1.0% (within subject) for HbA1c at endpoints (16 weeks for TP1 and 32 weeks for TP2), a 2-sided significance level of 0.05, and 80% power. Efficacy and safety analyses were conducted on the Full Analysis Set population, which included all randomized subjects receiving at least 1 dose of the study insulin.

The primary efficacy measurement was HbA1c at the endpoints of the 2 TPs and was analyzed using a mixed-effects model for repeated measures that included fixed effects (treatment, period, sequence, and TZD use [yes or no]), baseline HbA1c as a covariate, and subject as a random effect (11). To make a fair comparison between endpoints from the 2 periods, baseline HbA1c was the last value obtained at or prior to randomization. The least-squares (LS) mean difference for HbA1c between insulin lispro and insulin aspart (insulin lispro – insulin aspart) with its 95% confidence interval (CI) was reported. If the upper limit of the CI was less than the prespecified NIM of 0.4%, noninferiority was declared. As a supportive analysis, the primary efficacy variable was also analyzed on the All Completer Set population, defined as all randomized subjects who successfully completed all protocol visits, by using the same model as previously mentioned. In addition, the primary efficacy variable was also analyzed in the Full Analysis Set for TP1 only.

Total daily insulin dose, total daily insulin dose per body weight, and body weight were analyzed using similar mixed-effects model for repeated measures models as for the primary outcome HbA1c. Baseline body weight was obtained for each subject at the beginning of each TP (i.e., week 0 for TP1 and week 16 for TP2) because there could be a relatively long-lasting carryover effect of weight across TPs.

Safety measures included treatment-emergent AEs (TEAEs), serious AEs (SAEs), and hypoglycemic episodes (defined as a BG level ≤70 mg/dL, or signs and symptoms consistent with hypoglycemia). Treatment comparisons for

incidence of AEs and hypoglycemic events were analyzed using the Prescott test (17). Incidence of hypoglycemic episodes was summarized for the individual TPs. The incidence of hypoglycemic episodes (total, severe, nocturnal, and documented symptomatic) was reported by treatment for the combined periods. Specifically, severe hypoglycemia was defined as an event requiring the assistance of a third party (and verified by the investigator), nocturnal hypoglycemia was a self-reported event that occurred between bedtime and before the first meal upon waking, and documented symptomatic hypoglycemia was a BG level ≤70 mg/dL accompanied by signs and symptoms of hypoglycemia. The proportion of subjects with at least 1 hypoglycemic event was analyzed with the Prescott test (17). The rate of hypoglycemia events per 30 days was analyzed with a negative binomial regression model for repeated measurements with baseline hypoglycemia event rate included as a covariate. Repeated measurements were specified on subjects to account for the multiple-measurement nature of the crossover design.

RESULTS

Subject Disposition and Baseline Characteristics

Subject disposition is presented in Figure 1. Of the 151 subjects screened for eligibility, a total of 122 subjects were randomly assigned to insulin lispro (n = 60) or insulin aspart (n = 62) for 16 weeks (TP1) followed by treatment crossover for an additional 16 weeks (TP2). Overall, 85% of insulin lispro/insulin aspart subjects and 90% of insulin aspart/insulin lispro subjects completed the study. Subject discontinuation did not differ statistically across treatment sequence; however, twice as many subjects discontinued while in the insulin aspart treatment arm (10 [8.3%] subjects) compared to the insulin lispro treatment arm (5 [4.1%] subjects). Five (4.2%) subjects during the insulin aspart treatment arm and 1 (0.8%) subject in the insulin lispro treatment arm discontinued the study by their own decision (e.g., difficulty traveling to sites, work schedule). Because 7 subjects discontinued before TP2 (insulin aspart: 4 [6.5%] subjects; insulin lispro: 3 [5.0%] subjects), 118 subjects received at least 1 dose of insulin lispro, whereas 119 subjects had at least 1 dose of insulin aspart. There were no significant differences in demographic and baseline characteristics between the 2 treatment sequences (Table 1).

Efficacy

Noninferiority of insulin lispro to insulin aspart was demonstrated for endpoint HbA1c (Table 2), as the upper limit of the 95% CI (–0.002, 0.210) for this treatment comparison was less than 0.4%. Noninferiority of insulin lispro to insulin aspart was also demonstrated for endpoint
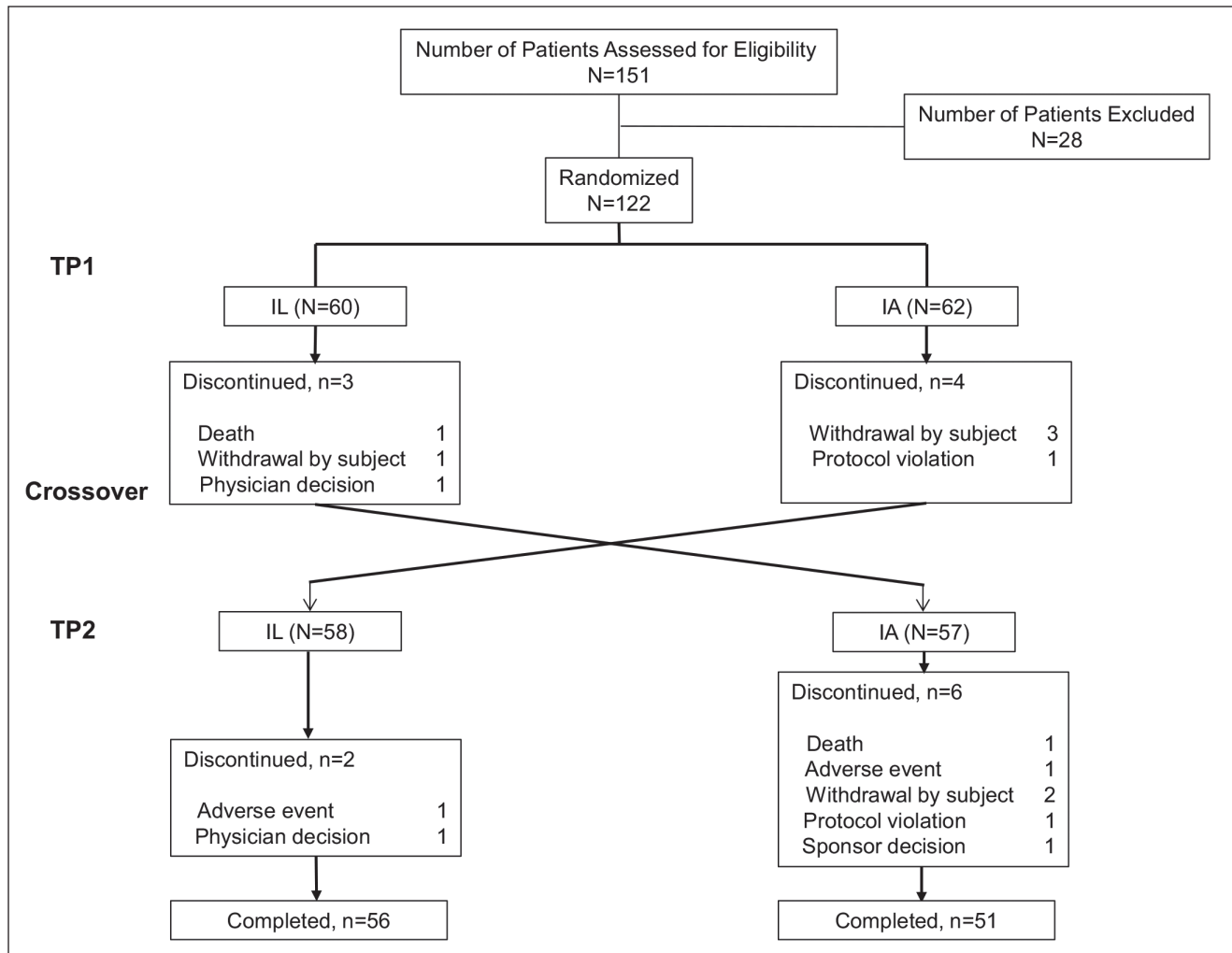
Fig. 1. Subject disposition. *IA* = insulin aspart; *IL* = insulin lispro; *TP1* = treatment period 1; *TP2* = treatment period 2.

HbA1c in the supportive analyses performed on the All Completer Set (95% CI [– 0.02, 0.19]) and TP1 in the Full Analysis Set (95% CI [–0.23, 0.18]).

The daily insulin dose between insulin lispro (80.41 units ± SE 4.78) and insulin aspart (80.69 units ± SE 4.77) was not significantly different (LS mean difference: –0.28 units; 95% CI [–2.92, 2.35]; *P* = .831). Daily insulin dose per body weight between insulin lispro (0.78 U/kg ± SE 0.04) and insulin aspart (0.78 U/kg ± SE 0.04) was not significantly different (LS mean difference: 0.00 U/kg, 95% CI [–0.02, 0.02], *P* = .966).

Weight change from baseline was similar between insulin lispro (0.31 kg ± SE 0.53) and insulin aspart (0.89 kg ± SE 0.52) with an LS mean difference of –0.58 kg (95% CI [–1.51, 0.34]) and no significant difference (*P* = .216) between treatments arms; however, numerically, subjects either gained less or lost weight from baseline to endpoint on insulin lispro in TP1 (0.20 kg [SD 3.35] for insulin lispro versus 0.82 kg [SD 2.72] for insulin aspart) and in

TP2 (–0.03 kg [SD 2.68] for insulin lispro versus 0.49 kg [SD 3.80] for insulin aspart) (Fig. 2).

Safety

Table 3 contains a summary and analysis of TEAEs for the combined TPs. There were no statistically significant differences between insulin lispro and insulin aspart treatment for TEAEs (*P* = .489). TEAEs were reported by 51.7% of subjects during insulin lispro treatment and 54.6% of subjects during insulin aspart treatment. Most TEAEs were of mild or moderate severity. No occlusions or hyperglycemia related to pump malfunction/clogging events were reported. SAE reporting was not different between insulin lispro and insulin aspart (*P* = .909). Fifteen (12.7%) subjects reported an SAE during insulin lispro treatment and 14 (11.8%) subjects reported an SAE during insulin aspart treatment. Three SAEs of interest were identified: 1 case of moderate diabetic ketoacidosis during insulin aspart treatment, 1 case of severe hypoglycemia during insulin

aspart treatment, and 1 case of severe infusion site abscess during insulin lispro treatment. The diabetic ketoacidosis and severe infusion site abscess were not considered by the investigator to be related to the study drug, but the severe hypoglycemia was. No severe hypoglycemia was observed with insulin lispro treatment. Two subject discontinuations due to an AE (1 [insulin lispro], 1 [insulin aspart]) and 2 deaths (insulin lispro: 1 [subdural hematoma],1 insulin aspart [myocardial infarction]) occurred during the study. Neither death was judged by the investigator to be related to the study drug. The overall incidence of hypoglycemia was similar between insulin lispro and insulin aspart (Fig. 3). In addition, the hypoglycemic episode rates per 30 days

were similar for insulin lispro and insulin aspart (Fig. 4 and 5).

DISCUSSION

CSII is a well-accepted insulin delivery option for patients with T1D (18), and the increasing incidence of T2D (19) may result in increased use of CSII therapy by patients with T2D who need improved glycemic control or prefer more dosing regimen flexibility (20-22). Although there is a desire to confirm safety and efficacy in the distinct T2D population, few randomized controlled trials and no blinded studies evaluating CSII in these patients have

Table 1
Subject Demographics and Baseline Characteristics[a]

Demographics[b]	IL/IA (n = 60)	IA/IL (n = 62)	Overall (n = 122)
Age (years)	58.7 ± 10.4	60.4 ± 9.7	59.6 ± 10.1
Male/female (%)	45.0/55.0	48.4/51.6	46.7/53.3
Race (%)			
American Indian or Alaska Native	1.7	0.0	0.8
Asian	0.0	3.2	1.6
Black or African American	8.3	8.1	8.2
Multiple	1.7	1.6	1.6
White	88.3	87.1	87.7
Duration of diabetes (years)	18.8 ± 9.0	19.6 ± 9.4	19.2 ± 9.2
BMI (kg/m^2)	34.4 ± 4.8	35.2 ± 4.9	34.8 ± 4.8
Daily total insulin (units)	84.7 ± 43.4	86.2 ± 33.1	85.5 ± 38.3
HbA1c (%)	7.4 ± 0.8	7.5 ± 0.9	7.4 ± 0.9
Rate of hypoglycemic events per 30 days	3.5 ± 5.8	4.4 ± 5.5	3.9 ± 5.6
Insulin entry (%)			
IA	41.7	43.5	42.6
IG	8.3	8.1	8.2
IL	50.0	48.4	49.2
Pump model (%)			
Animas®	5.0	3.2	4.1
Animas OneTouch® Ping®	5.0	9.7	7.4
Deltec Cozmo®	3.3	0.0	1.6
Medtronic MiniMed Paradigm®	83.3	83.9	83.6
OmniPod®	3.3	3.2	3.3

Abbreviations: BMI = body mass index; HbA1c = glycated hemoglobin HbA1c; IA = insulin aspart; IG = insulin glulisine; IL = insulin lispro; n1 = total number of subjects for each sequence.
[a] Values shown are mean ± SD or %.
[b] No significant differences between IL/IA and IA/IL.

HbA1c (%)	IL (n1 = 118)	IA (n1 = 119)	Between groups	
Table 2 **Endpoint HbA1c (%) by Treatment[a]**				
			Difference	**95% CI**
Endpoint[b]	7.50 ± 0.12	7.40 ± 0.12	0.10	–0.002, 0.210

Abbreviations: HbA1c = glycated hemoglobin A1c; CI = confidence interval; IA = insulin aspart; IL = insulin lispro; LS mean = least-squares mean; n1 = total number of patients for each treatment; TP = treatment period.
[a] Values shown are LS mean ± SE.
[b] The endpoint was 16 weeks for TP1 and 32 weeks for TP2.

been reported (23). In this randomized, double-blind cross-over study, we demonstrate that CSII therapy with insulin lispro is noninferior to CSII therapy with insulin aspart as measured by HbA1c at the endpoints of the 2 TPs. The upper limit of the 95% CI was less than the selected 0.4% NIM for this study (Table 2). The endpoint HbA1c values found in this study are consistent with previous studies (7.0-8.1%) with similar designs assessing CSII therapy in a T1D population (24-26). Specifically, in an adult T1D population already on CSII, Bode and colleagues (24) found no significant change in HbA1c from baseline at 16 weeks for either insulin lispro or insulin aspart. Weinzimer et al (26) similarly showed noninferiority of insulin aspart to insulin lispro with minimal changes in HbA1c over 16 weeks in pediatric patients with T1D using CSII.

Several studies comparing CSII against MDI in patients with T2D have shown that CSII offers similar or improved glycemic control (3,4,21,23,27,28) with improved patient satisfaction (3,4,22), suggesting that it may be a treatment option for patients with T2D. Insulin lispro has been investigated as a CSII therapy in patients with T2D requiring treatment intensification at study entry. In these 3 studies that compared CSII with MDI therapy, insulin lispro significantly reduced HbA1c with equivalent or improved efficacy. Herman et al observed significant improvements in HbA1c from baseline (8.4% to 6.6% for CSII and 8.1% to 6.4% for MDI) in adults (≥60 years) with HbA1c ≥7% (29). In a 2-period, 12-week crossover study comparing CSII with insulin lispro to MDI with Humalog Mix50 TID, significant reductions in HbA1c from baseline (9.0%) were seen for both regimens (final HbA1c: 7.7% for CSII and 8.6% for MDI) (30). A crossover study comparing MDI (regular human insulin and neutral protamine Hagedorn) and CSII (insulin lispro) in obese patients with an HbA1c
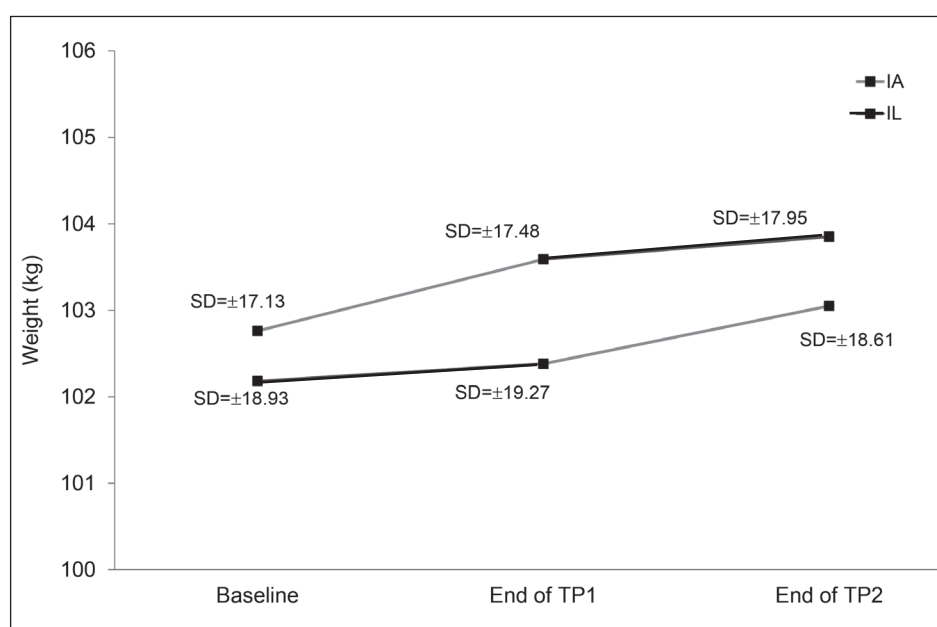
Fig. 2. Weight from baseline to the end of TP2; *IA* = insulin aspart; *IL* = insulin lispro; *kg* = kilogram; *TP1* = treatment period 1; *TP2* = treatment period 2. Values shown are mean ± SD (between-patient). At the end of TP1, subjects crossed over to the other treatment for 16 weeks.

Table 3 TEAEs ≥2% by Treatment for Combined Periods			
Preferred term	**IL (n1 = 118)**	**IA (n1 = 119)**	***P* value[a]**
Nasopharyngitis	4.2	4.2	.678
Nausea	4.2	1.7	.114
Fatigue	3.4	3.4	…
Gastroenteritis viral	2.5	0.0	.368
Sepsis	2.5	3.4	.119
Back pain	2.5	3.4	.746
Musculoskeletal pain	2.5	2.5	>.999
Depression	2.5	2.5	…
Rhinitis allergic	0.8	4.2	.246
Urinary tract infection	0.0	2.5	.368
Vitamin D deficiency	0.0	2.5	.119
Headache	0.0	2.5	.243

Abbreviations: IA = insulin aspart; IL = insulin lispro; TEAE = treatment-emergent adverse event; TP = treatment period.
[a] Missing *P* value: patients with events in the first period discontinued before receiving the other treatment and/or no patients have different event occurrence between the 2 TPs.
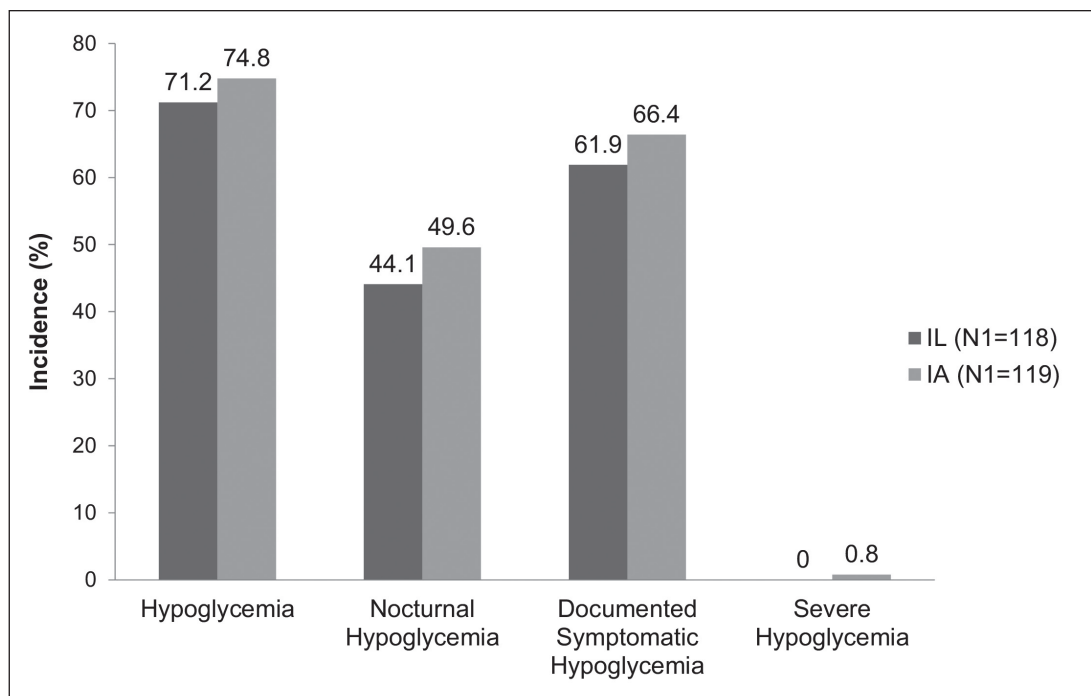
Fig. 3. Hypoglycemia episode incidence (TP1 + TP2); *IA* = insulin aspart; *IL* = insulin lispro; *TP1* = treatment period 1; *TP2* = treatment period 2. No significant difference between IL and IA.
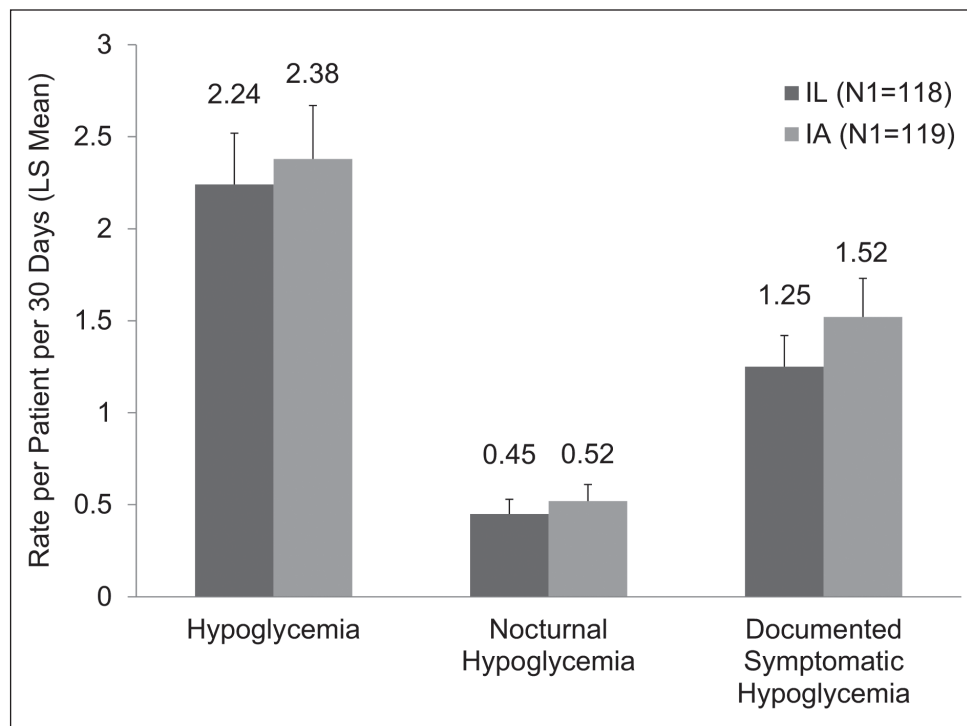
Fig. 4. Hypoglycemia episode rate per 30 days (TP1 + TP2); *IA* = insulin aspart; *IL* = insulin lispro; *LS Mean* = least-squares mean; *N1* = total number of subjects for each treatment; *TP1* = treatment period 1; *TP2* = treatment period 2. No significant difference between IL and IA.

>8.5% identified a mean reduction of 0.8% in HbA1c for CSII and a mean increase of 0.4% during treatment with MDI (31). Overall, these results suggest that insulin lispro is well tolerated and effectively reduces HbA1c in subjects requiring treatment intensification at study entry.

Whereas previous randomized controlled studies of CSII in T2D have compared CSII with MDI to show improvements in glycemic control or patient-reported outcomes (3,23), this study was designed to demonstrate the noninferiority of insulin lispro to an approved reference therapy, insulin aspart. This distinction is important when evaluating our study results, in which maintenance of glycemia or slight improvements in glycemia would demonstrate the efficacy of the insulins used in CSII rather than comparing CSII therapy to MDI, consistent with similar studies in subjects with T1D (24,25,32). Subjects had at least 6 months of previous CSII experience, which is in line with previous studies in which subjects with T1D entered the study with 3 (24,26) or 6 months (25) of CSII experience. The baseline HbA1c of 7.4% observed in this study is similar to the reported values (6.8-8.1%) for previous studies (24-26). The changes in HbA1c observed for this study are also consistent with these 3 studies in which HbA1c did not change more than 0.2%.

While the average duration of T2D of 19.2 years would suggest that many of the subjects in this trial would be likely to have low to no endogenous insulin production on the basis of near complete loss of their beta cell function (33,34), endogenous insulin cannot be ruled out as a contributor to glycemic control in this population because C-peptide levels were not measured. However, because endogenous insulin production would not be expected to change significantly over the 32-week study duration, the crossover design would control for this variable and allow comparison of the 2 insulin therapies. Additionally, the 25% of subjects taking OAMs maintained a stable dose throughout the study, allowing any changes in the glycemia to be attributed to the study insulin.

The 32-week TP with a 2-sequence crossover is an appropriate design for this study, mainly due to the rapid-acting properties of the study insulins (14-16). Because HbA1c reflects the average plasma glucose concentration over the last 8 to 12 weeks (12), the 16-week TP duration would be sufficient in that the potential residual effect from the TP1 would not carry over to the endpoint of TP2. Therefore, each TP endpoint for insulin lispro or insulin aspart only reflects the effect of its respective TP; thus, the endpoints from both TPs can be combined to make inferences about the 16-week treatment outcomes. Although the 16-week TP was appropriate for this study, longer duration studies would be helpful in characterizing longer-term CSII therapy in patients with T2D.

Using randomization as the baseline for the endpoints from both periods is appropriate if the TP2 endpoint does
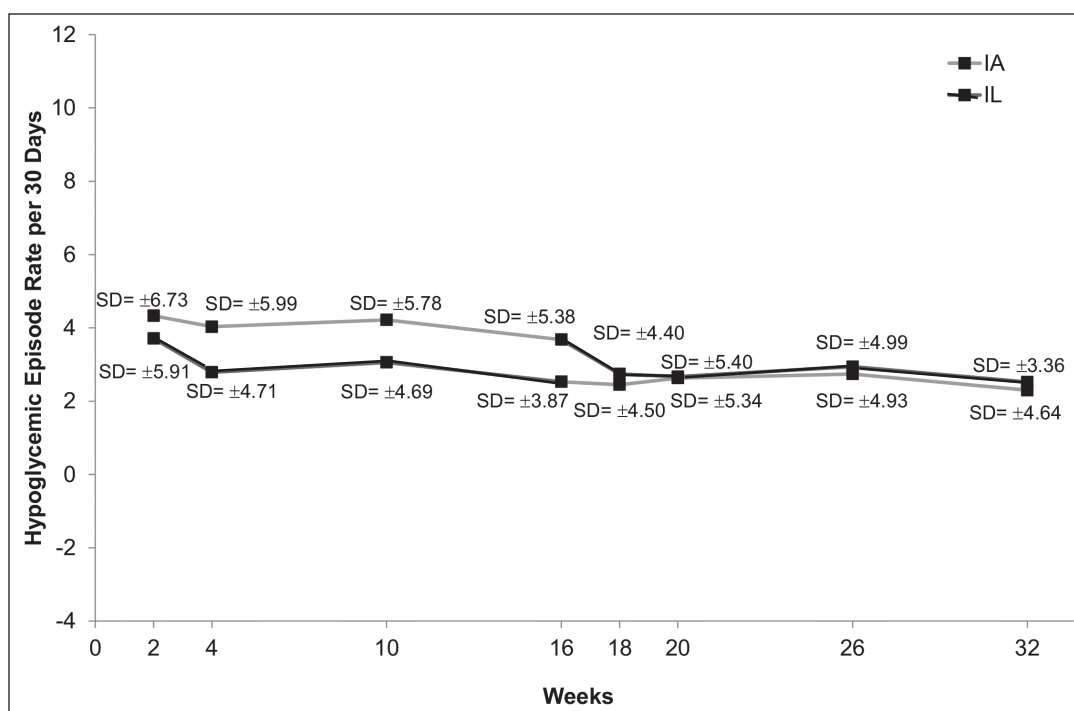
Fig. 5. Hypoglycemia episode rate per 30 days by treatment sequence; *IA* = insulin asapart; *IL* = insulin lispro; *TP1* = treatment period 1; *TP2* = treatment period 2. Values shown are mean ± SD (between-patient). At the end of TP1, subjects crossed over to the other treatment for 16 weeks.

not contain carryover effects from TP1 treatment (as in this study for the primary endpoint HbA1c). Because the study insulins have similar pharmacokinetic properties (35-37), such appropriate baseline adjustment in crossover designs allows for a fair comparison between the endpoint HbA1c values from the 2 periods and has been used in previous crossover studies in patients with T2D (38,39).

We also demonstrated that when administered by CSII, both insulins were similar with regard to total daily dose of insulin, daily dose of insulin per body weight, weight change from baseline to endpoint, incidence and rates of hypoglycemic events (all reported, severe, nocturnal, or documented symptomatic), and incidence of TEAEs. The similar effects between the insulin lispro and insulin aspart groups are consistent with previous studies comparing rapid-acting insulin analogs in T1D (24-26), although the weight-adjusted insulin dose was significantly larger in the insulin lispro group compared with the insulin aspart group in 1 study (26). The analogous effects of insulin lispro and insulin aspart are likely related to their similar pharmacokinetic and pharmacodynamic properties (40).

CONCLUSION

In this study, we demonstrated that insulin lispro is noninferior to insulin aspart with respect to HbA1c in patients with T2D who use CSII; both groups of patients had comparable dosing, weight changes, and hypoglycemic incidence and rate. These results suggest that both insulin lispro and insulin aspart are safe and effective for use in patients with T2D who use CSII therapy.

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DISCLOSURE

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REFERENCES

1. **Holman RR, Farmer AJ, Davies MJ, et al.** Three-year efficacy of complex insulin regimens in type 2 diabetes. *N Engl J Med*. 2009;361:1736-1747.

2. **American Diabetes Association.** Standards of medical care in diabetes – 2013. *Diabetes Care*. 2013;36 Supp 1: S11-S66.

3. **Raskin P, Bode BW, Marks JB, et al.** Continuous subcutaneous insulin infusion and multiple daily injection therapy are equally effective in type 2 diabetes: a randomized, parallel-group, 24-week study. *Diabetes Care*. 2003;26: 2598-2603.

4. **Gentry CK, Cross LB, Gross BN, McFarland MS, Bestermann WH.** Retrospective analysis and patient satisfaction assessment of insulin pump therapy in patients with type 2 diabetes. *South Med J*. 2011;104:24-28.

5. **Philis-Tsimikas A, Charpentier G, Clauson P, Ravn GM, Roberts VL, Thorsteinsson B.** Comparison of once-daily insulin detemir with NPH insulin added to a regimen of oral antidiabetic drugs in poorly controlled type 2 diabetes. *Clin Ther*. 2006;28:1569-1581.

6. **Chacra AR, Kipnes M, Ilga LL, et al.** Comparison of insulin lispro protamine suspension and insulin detemir in basal-bolus therapy in patients with Type 1 diabetes. *Diabet Med*. 2010:27:563-569.

7. **Fogelfield L, Dharmalingam M, Robling K, Jones C, Swanson D, Jacober S.** A randomized, treat-to-target trial comparing insulin lispro protamine suspension and insulin detemir in insulin-naïve patients with Type 2 diabetes. *Diabet Med*. 2010;27:181-188.

8. **World Health Organization.** Diabetes Mellitus. Report of a WHO Study Group. Available at: http://whqlibdoc.who.int/trs/WHO_TRS_727.pdf?ua=1. Accessed April 04, 2014.

9. **World Medical Association.** WMA Declaration of Helsinki – Ethical Principles for Medical Research Involving Human Subjects. Available at: http://www.wma.net/en/30publications/10policies/b3/. Updated October 2008. Accessed February 12, 2014.

10. **International Conference on Harmonisation.** Guideline for Good Clinical Practice E6(R1). Available at: http://www.ich.org/fileadmin/Public_Web_Site/ICH_Products/Guidelines/Efficacy/E6/E6_R1_Guideline.pdf. Last updated June 10, 1996. Accessed February 12, 2014.

11. **Grizzle JE.** The two-period change-over design and its use in clinical trials. *Biometrics*. 1965;21:467-480.

12. **Nathan DM, Turgeon H, Regan S.** Relationship between glycated haemoglobin levels and mean glucose levels over time. *Diabetologia*. 2007;50:2239-2244.

13. **Tahara Y, Shima K.** Kinetics of HbA1c, glycated albumin, and fructosamine and analysis of their weight functions against preceding plasma glucose level. *Diabetes Care*. 1995;18:440-447.

14. **Humalog [package insert].** Indianapolis, IN. Eli Lilly and Company, 2013. Available at: http://www.accessdata.fda.gov/drugsatfda_docs/label/2013/020563s115lbl.pdf. Accessed January 28, 2014.

15. **Humalog SmPC.** Available at: http://www.ema.europa.eu/docs/en_GB/document_library/EPAR_-_Product_Information/human/000088/WC500050332.pdf. Accessed January 28, 2014.

16. **NovoLog [package insert].** Bagsværd, Denmark: Novo Nordisk; 2013. Available at: http://www.accessdata.fda.gov/drugsatfda_docs/label/2013/020986s061lbl.pdf. Accessed January 28, 2014.

17. **Prescott RJ.** The comparison of success rates in cross-over trials in the presence of an order effect. *Appl Stat*. 1981;30: 9-15.

18. **Jeitler K, Horvath K, Berghold A, et al.** Continuous subcutaneous insulin infusion versus multiple daily insulin injections in patients with diabetes mellitus: systematic review and meta-analysis. *Diabetologia*. 2008;51:941-951.

19. **International Diabetes Federation.** *IDF Diabetes Atlas*. 6th ed. Brussels, Belgium: International Diabetes Federation; 2013.

20. **Edelman SV, Bode BW, Bailey TS, et al.** Insulin pump therapy in patients with type 2 diabetes safely improved glycemic control using a simple insulin dosing regimen. *Diabetes Technol Ther*. 2010;12:627-633.

21. **Frias JP, Bode BW, Bailey TS, Kipnes MS, Brunelle R, Edelman SV.** A 16-week open-label, multicenter pilot study assessing insulin pump therapy in patients with type 2 diabetes suboptimally controlled with multiple daily injections. *J Diabetes Sci Technol*. 2011;5:887-893.

22. **Rubin RR, Peyrot M, Chen X, Frias JP.** Patient-reported outcomes from a 16-week open-label, multicenter study of insulin pump therapy in patients with type 2 diabetes mellitus. *Diabetes Technol Ther*. 2010;12:901-906.

23. **Yeh HC, Brown TT, Maruthur N, et al.** Comparative effectiveness and safety of methods of insulin delivery and glucose monitoring for diabetes mellitus. *Ann Intern Med*. 2012;157:336-347.

24. **Bode B, Weinstein R, Bell D, et al.** Comparison of insulin aspart with buffered regular insulin and insulin lispro in continuous subcutaneous insulin infusion: a randomized study in type 1 diabetes. *Diabetes Care*.2002;25:439-444.

25. **Hoogma RP, Schumicki D.** Safety of insulin glulisine when given by continuous subcutaneous infusion using an external pump in patients with type 1 diabetes. *Horm Metab Res*. 2006;38:429-433.

26. **Weinzimer SA, Ternand C, Howard C, et al.** A randomized trial comparing continuous subcutaneous insulin infusion of insulin aspart versus insulin lispro in children and adolescents with type 1 diabetes. *Diabetes Care*. 2008;31: 210-215.

27. **Leinung MC, Thompson S, Luo M, Leykina L, Nardacci E.** Use of insulin pump therapy in patients with type 2 diabetes after failure of multiple daily injections. *Endocr Pract*. 2013;19:9-13.

28. **Reznik Y, Morera J, Rod A, et al.** Efficacy of continuous subcutaneous insulin infusion in type 2 diabetes mellitus: a survey on a cohort of 102 patients with prolonged follow-up. *Diabetes Technol Ther*. 2010;12:931-936.

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CSII With Insulin Lispro in T2D, *Endocr Pract.* 2015;21(No. 3) 257

29. **Herman WH, Ilag LL, Johnson SL, et al.** A clinical trial of continuous subcutaneous insulin infusion versus multiple daily injections in older adults with type 2 diabetes. *Diabetes Care* 2005;28:1568-1573.

30. **Berthe E, Lireux B, Coffin C, et al.** Effectiveness of intensive insulin therapy by multiple daily injections and continuous subcutaneous infusion: a comparison study in type 2 diabetes with conventional insulin regimen failure. *Horm Metab Res.*2007;39:224-229.

31. **Wainstein J, Metzger M, Boaz M, et al.** Insulin pump therapy vs. multiple daily injections in obese type 2 diabetic patients. *Diabet Med.*2005;22:1037-1046.

32. **van Bon AC, Bode BW, Sert-Langeron C, DeVries JH, Charpentier G.** Insulin glulisine compared to insulin aspart and to insulin lispro administered by continuous subcutaneous insulin infusion in patients with type 1 diabetes: a randomized controlled trial. *Diabetes Technol Ther.* 2011; 13:607-614.

33. **Heine RJ, Diamant M, Mbanya JC, Nathan DM.** Management of hyperglycaemia in type 2 diabetes: the end of recurrent failure? *BMJ.* 2006;333:1200-1204.

34. **Bagust A, Beale S.** Deteriorating beta-cell function in type 2 diabetes: a long-term model. *QJM.* 2003;96:281-288.

35. **Plank J, Wutte A, Brunner G, et al.** A direct comparison of insulin aspart and insulin lispro in patients with type 1 diabetes. *Diabetes Care.* 2002;25:2053-2057.

36. **Homko C, Deluzio A, Jimenez C, Kolaczynski JW, Boden G.** Comparison of insulin aspart and lispro: pharmacokinetic and metabolic effects. *Diabetes Care.* 2003;26: 2027-2031.

37. **Swan KL, Dziura JD, Steil GM, et al.** Effect of age of infusion site and type of rapid-acting analog on pharmacodynamic parameters of insulin boluses in youth with type 1 diabetes receiving insulin pump therapy. *Diabetes Care.* 2009;32:240-244.

38. **Berg JK, Shenouda SK, Heilmann CR, Gray AL, Holcombe JH.** Effects of exenatide twice daily versus sitagliptin on 24-h glucose, glucoregulatory and hormonal measures: a randomized, double-blind, crossover study. *Diabet Obes Metab.* 2011;13:982-989.

39. **Rosenstock J, Bergenstal R, Blevins T, et al.** Better glycemic control and weight loss with the novel long-acting basal insulin LY2605541 compared with insulin glargine in type 1 diabetes: a randomized, crossover study. *Diabetes Care.* 2013;36:522-528.

40. **Home PD.** The pharmacokinetics and pharmacodynamics of rapid-acting insulin analogues and their clinical consequences. *Diabetes Obes Metab.* 2012;14:780-788.