Randomized Comparison of Pramlintide or Mealtime Insulin Added to Basal Insulin Treatment for Patients With Type 2 Diabetes

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OBJECTIVE — To compare the efficacy and safety of adding mealtime pramlintide or rapid-acting insulin analogs (RAIAs) to basal insulin for patients with inadequately controlled type 2 diabetes.

RESEARCH DESIGN AND METHODS — In a 24-week open-label, multicenter study, 113 patients were randomly assigned 1:1 to addition of mealtime pramlintide (120 μg) or a titrated RAIA to basal insulin and prior oral antihyperglycemic drugs (OADs). At screening, patients were insulin naive or had been receiving <50 units/day basal insulin for <6 months. The basal insulin dosage was titrated from day 1, seeking fasting plasma glucose (FPG) ≥70–<100 mg/dl. Pramlintide and an RAIA were initiated on day 1 and week 4, respectively. The proportion of patients achieving A1C ≤7.0% without weight gain or severe hypoglycemia at week 24 was the primary end point.

RESULTS — More pramlintide- than RAIA-treated patients achieved the primary end point (30 vs. 11%, $P = 0.018$) with a similar dose of basal insulin. Pramlintide and an RAIA yielded similar mean ± SEM values for FPG and A1C at 24 weeks (122 ± 7 vs. 123 ± 5 mg/dl and 7.2 ± 0.2 vs. 7.0 ± 0.1%, respectively) and similar least squares mean reductions from baseline to end point (−31 ± 6 vs. −34 ± 6 mg/dl and −1.1 ± 0.2 vs. −1.3 ± 0.2%, respectively). RAIAs but not pramlintide caused weight gain (+4.7 ± 0.7 vs. +0.0 ± 0.7 kg, $P < 0.0001$). Fewer patients reported mild to moderate hypoglycemia with pramlintide than with the RAIA (55 vs. 82%), but more patients reported nausea (21 vs. 0%). No severe hypoglycemia occurred in either group.

CONCLUSIONS — In patients taking basal insulin and OADs, premeal fixed-dose pramlintide improved glycemic control as effectively as titrated RAIAs. The pramlintide regimen sometimes caused nausea but no weight gain and less hypoglycemia.

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Adding basal insulin therapy to oral agents improves glycemic control for many patients with type 2 diabetes, but up to 50% of patients continue to have A1C values >7% (1–5). Persistent after-meal hyperglycemia is generally observed in such patients (6). The usual next step in treatment is addition of mealtime insulin injections, but this approach increases risks of weight gain and hypoglycemia (4,6).

Previous studies have shown that defects in addition to insulin deficiency contribute to after-meal hyperglycemia. Both insulin and amylin are secreted by β-cells, and, in individuals with abnormal β-cell function, glucose- and mixed meal–stimulated secretion of both hormones is delayed and reduced (7–9). Insulin deficiency impairs suppression of hepatic glucose production and enhancement of glucose uptake by tissues that normally limit postmeal hyperglycemia. Amylin deficiency accelerates gastric emptying, increases glucagon secretion, and alters satiety mechanisms (10,11).

Pramlintide, an injectable synthetic analog of amylin, slows gastric emptying, attenuates postprandial glucagon secretion, enhances satiety, and reduces food intake (12–14). Pramlintide is approved as adjunctive treatment for patients with diabetes who use mealtime insulin with or without oral antihyperglycemic drugs (OADs) and have not achieved desired glucose control. Recently, a 16-week, double-blind, placebo-controlled study of patients with type 2 diabetes showed that pramlintide reduces A1C and weight without increasing insulin-induced hypoglycemia when added to basal insulin ± OADs without mealtime insulin (15).

Pramlintide may offer an additional therapeutic option for mealtime use by patients with type 2 diabetes already using basal insulin. Rapid-acting insulin analogs (RAIAs) and pramlintide have different mechanisms of action and different patterns of desired and unwanted effects. Although both can limit after-meal hyperglycemia, RAIAs often cause weight gain and hypoglycemia (6), whereas pramlintide is associated with weight loss and nausea (15,16). This study was designed to compare the efficacy and side effects of pramlintide versus RAIAs when added to basal insulin to intensify treatment of type 2 diabetes.

RESEARCH DESIGN AND METHODS

— Patients enrolled were aged 18–75 years, had a clinical diagnosis of type 2 diabetes, and had A1C >7% and ≤10% with or without use of any combination of metformin, thiazolidinedione, or sulfonylurea OADs. Study participants were pramlintide naive and either insulin naive or had used <50 units/day of basal insulin for <6 months. Inclusion criteria included BMI ≥25 and ≤50 kg/m^2. Female patients were neither pregnant nor lactating and were postmenopausal or using birth control. Candidates were excluded if they adhered poorly to diabetes manage-

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ment recommendations, had recurrent severe hypoglycemia within the last 6 months, or had a history of hypoglycemia unawareness. Patients with gastroparesis or those who required medications to alter gastric motility were excluded, as were patients using exenatide or sitagliptin, any antiobesity agents, systemic glucocorticoid agents, or investigational medications. Patients with eating disorders, a history of bariatric surgery, or plans to lose weight were excluded, as were patients with any significant medical conditions or advanced diabetes complications.

Ethical considerations

The study protocol was approved by applicable institutional review boards and conducted in accordance with the Declaration of Helsinki. All patients provided written informed consent before study initiation.

Study design and interventions

This was a randomized, open-label, parallel-group, multicenter 24-week study conducted at 29 centers throughout the U.S. between April 2007 and May 2008 (a complete list of the participating investigators can be found in the APPENDIX). After the screening visit, eligible patients visited the study center on day 1 (baseline) and at weeks 4, 8, 12, 18, and 24. Scheduled telephone visits to review self-monitored glucose measurements and direct insulin adjustment occurred between visits. Random assignment 1:1 to pramlintide (Amylin Pharmaceuticals, San Diego, CA) or to an RAIA (insulin lispro, insulin aspart, or insulin glulisine) occurred at baseline and was centrally generated and stratified according to A1C screening values (≤9.0% or >9.0%) and insulin use (insulin naive or receiving basal insulin at screening).

All patients received insulin glargine or detemir throughout the study, once or twice daily. Basal insulin was titrated at the investigator's direction weekly or twice weekly to achieve a fasting plasma glucose (FPG) concentration of ≥70–<100 mg/dl, as in the Treat-To-Target Study (1). Study medication (pramlintide or an RAIA) was self-administered subcutaneously before major meals. Patients in the pramlintide treatment group received 120 μg s.c. before major meals beginning on day 1 because a prior study demonstrated no increased risk of hypoglycemia when fixed-dose pramlintide was added to basal insulin (15). Dose reduction to 60 μg pramlintide per meal was permitted for patients with persistent clinically significant nausea. Patients randomly assigned to an RAIA received only titrated basal insulin therapy for 4 weeks to avoid the hypoglycemia risk associated with titrating basal insulin and an RAIA simultaneously. After 4 weeks, RAIA-randomized patients started RAIA therapy with 5 units of lispro, aspart, or glulisine before each meal. Mealtime insulin doses were adjusted with investigator guidance by 1–2 units every 3–7 days with the aim of maintaining glucose concentrations at ≥70 and <100 mg/dl before the subsequent meal or (for the dinnertime dose) at bedtime. Patients self-monitored blood glucose daily according to individualized advice from site investigators. A seven-point glucose profile consisting of measurements taken 15 min before and 1.5–2 h after the start of each of the three meals and at bedtime was completed during the week before each visit. At each visit, weight, body circumference, and vital signs were measured and blood glucose values were reviewed. Participants were counseled on adjustment of basal and mealtime insulin dosage (RAIA group) at each visit. A1C was measured at all study visits, and FPG was measured at screening, baseline, and weeks 4, 12, and 24. No specific lifestyle modification was advised; patients were asked to maintain usual diet and exercise patterns.

Study end points

The primary end point was the proportion of patients achieving the following prespecified criteria at week 24: *1*) A1C ≤7.0%, *2*) no weight gain from baseline, and *3*) no severe hypoglycemia. Severe hypoglycemia was defined as an event requiring assistance of another individual and/or administration of glucagon injection or intravenous glucose. Secondary end points included the individual components of the composite end point, insulin dose, A1C, change in A1C, proportion of patients reaching A1C ≤6.5%, FPG, postprandial glucose increments, changes in weight, changes in waist circumference, and adverse events including the incidence, severity, and time courses of hypoglycemia and nausea.

Statistical analyses

A sample size of 45 patients per group was predicted to provide 90% power to detect a 27% difference in the proportion of patients achieving the primary end point ($\alpha = 0.05$). Analyses were performed on patients within the intent-to-treat (ITT) population including all randomly assigned patients receiving at least one dose of study medication. Missing individual data were imputed from the last scheduled visit (last observation carried forward). Insulin dose was analyzed in the ITT observed population. Measured values for insulin dose, A1C, FPG, and glucose increments are presented as arithmetic mean ± SEM.

Fisher's exact test was used to compare the proportion of patients achieving the primary end point. The Cochran-Mantel-Haenszel test that controlled for A1C at screening was used as a confirmatory test. Intergroup comparisons of continuous changes from baseline were assessed with ANOVA models including treatment group, A1C at screening (≤9.0% or >9.0%), insulin treatment before screening, and baseline value (for parameters other than A1C). Data were reported as least squares mean change ± SEM.

RESULTS

Patient disposition, baseline demographics, and therapies

Of 113 patients randomly assigned, 48 (84%) pramlintide-treated and 50 (89%) RAIA-treated patients completed the study (Table 1). One patient in the pramlintide group withdrew consent before injecting study medication, resulting in an ITT population of 56 patients per treatment group. Baseline characteristics were well matched between groups (Table 1). Before the study, 46% of patients used insulin and 91% of patients used at least one OAD.

Basal insulin dosage increased steadily throughout the study, resulting in similar mean doses at week 24: 52 ± 4 units/day (0.48 ± 0.04 unit · kg^{-1} · day^{-1}) for pramlintide-treated patients and 57 ± 4 units/day (0.52 ± 0.04 units · kg^{-1} · day^{-1}) for patients in the RAIA arm (Fig. 1*A*). After 24 weeks, RAIA-treated patients administered a mean daily dose of 37 ± 3 units (0.34 ± 0.03 unit · kg^{-1} · day^{-1}) of insulin lispro, aspart, or glulisine. Numbers of patients initiating therapy with insulin lispro, aspart, or glulisine were 16 (29%), 31 (55%), and 9 (16%), respectively. To achieve glycemic results similar to those of the pramlintide group, patients in the RAIA group used an average of 80% more insulin (basal + rapid-acting) at week 24 (94 vs. 52 units, respectively).

Forty-six participants (82%) continued to take 120 μg pramlintide before

Table 1—*Patient disposition and demographic and clinical characteristics at baseline*

	Pramlintide	RAIA
Disposition		
Randomized	57	56
Withdrew before treatment	1	0
Completed	48	50
Withdrew between treatment and week 24	8	6
Reason for withdrawal		
Withdrawal of consent	4	2
Adverse event	2	0
Investigator decision	1	0
Protocol violation	0	0
Lost to follow-up	2	4
Baseline demographics		
ITT population	56	56
Sex (male/female)	34/22	37/19
Race (Caucasian/other)	48/8	43/13
Age (years)	55 ± 11	54 ± 10
Weight (kg)	108 ± 22	103 ± 18
BMI (kg/m^2)	36 ± 6	36 ± 6
Diabetes duration (years)	10 ± 7	9 ± 6
A1C (%)	8.2 ± 0.8	8.3 ± 0.8
FPG (mg/dl)	155 ± 40	164 ± 50
OAD use at randomization	50	52
Average number of oral medications per patient	1.9	1.7
Sulfonylurea	34	29
Metformin	36	38
Thiazolidinediones	16	15
Combined drug formulations	5	2
Insulin use before randomization	27	24
Daily basal insulin dose at baseline (units/day)	20 ± 10	24 ± 12
Type of basal insulin initiated after randomization		
Insulin glargine q.d.	37	45
Insulin glargine b.i.d.	1	0
Insulin detemir q.d.	18	11
Insulin detemir b.i.d.	0	0

Data are *n* or means ± SD.

meals throughout the study. Two participants reduced the dosage to 60 μg because of nausea.

Primary end point

The primary composite end point comprised several highly desirable goals assessed after 24 weeks of treatment: A1C ≤7.0%, no weight gain from baseline, and no severe hypoglycemia (Table 2). Significantly more pramlintide-treated than RAIA-treated patients achieved this end point (30 vs. 11%, $P = 0.018$). Among the components of the composite, only the percentage of patients without weight gain at week 24 differed significantly between pramlintide- and RAIA-treated patients (59 vs. 16%, $P < 0.0001$). No significant differences in the frequency of achieving A1C ≤7.0% or in the incidence of severe hypoglycemia were observed between groups.

Secondary end points

A1C. Mean A1C at 24 weeks was 7.2 ± 0.2% with addition of pramlintide and 7.0 ± 0.1% with addition of an RAIA (Fig. 1*B*). The least squares mean reduction of A1C from baseline was −1.1 ± 0.2 for pramlintide and −1.3 ± 0.2 for RAIA ($P = 0.46$ between groups). A1C ≤6.5% at 24 weeks was achieved by 16 of 56 (29%) of patients treated with pramlintide and by 19 of 56 (34%) of patients treated with an RAIA ($P = 0.68$ between groups). A1C values were stable after week 12 (Fig. 1*B*).

Weight and waist circumference. A significant between-group difference in weight was observed throughout the study (Fig. 1*C*). At week 24, mean weights were 106 ± 3 kg (pramlintide) versus 109 ± 3 kg (RAIA). Least squares mean changes in weight from baseline were +0.0 ± 0.7 kg (pramlintide) versus +4.7 ± 0.7 kg (RAIA) ($P < 0.0001$).

Differences in waist measurements were consistent with weight differences. Waist circumferences at week 24 were 115 ± 2 and 120 ± 2 cm for the pramlintide and RAIA groups, respectively. Least squares mean changes in waist circumference from baseline were −0.6 ± 0.9 and +2.2 ± 0.9 cm, respectively ($P = 0.016$).

FPG. Similar basal insulin titration in both treatment arms resulted in similar mean FPG concentrations at week 24: 122 ± 7 mg/dl (pramlintide) and 123 ± 5 mg/day (RAIA) (Fig. 1*D*). The least squares mean change of FPG from baseline was −31 ± 6 mg/dl (pramlintide) and −34 ± 6 mg/dl (RAIA) ($P = 0.65$). An FPG concentration <100 mg/dl was achieved at week 24 by 17 of 56 (30%) of pramlintide-treated and 15 of 56 (27%) of RAIA-treated patients ($P = 0.83$).

Postprandial glucose increments. Postprandial glucose increments were similar between treatment groups at week 24 (Fig. 2*A*). No significant difference in the least squares mean change in postprandial increment from baseline to week 24 was found between treatment groups (−17 ± 5 mg/dl [pramlintide] vs. −27 ± 5 mg/dl [RAIA], $P = 0.17$).

Adverse events. The most common adverse events were hypoglycemia and nausea (Fig. 2*B*). Although no episodes of severe hypoglycemia were observed, mild or moderate hypoglycemia occurred more frequently than nausea in both treatment groups and was observed in more patients treated with RAIAs (82%) than with pramlintide (55%). Hypoglycemic events occurred more frequently in the pramlintide treatment group in the first 4 weeks but were more common in the RAIA treatment group from 18 to 24 weeks (Fig. 2*C*). Nausea was reported only in the pramlintide group (12 of 56 [21%]), most often early in treatment (10 of 56 patients in the first 4 weeks), and declined over time (Fig. 2*D*). Two patients (4%) withdrew from pramlintide therapy and the study because of nausea.

Eight serious adverse events were reported in six patients during the study: one patient in the pramlintide group (coronary artery disease) and five patients in the RAIA group (coronary artery disease, congestive heart failure, ischemic cerebral infarction, syncope, noncardiac chest pain, cellulitis, and biliary dyskinesia).

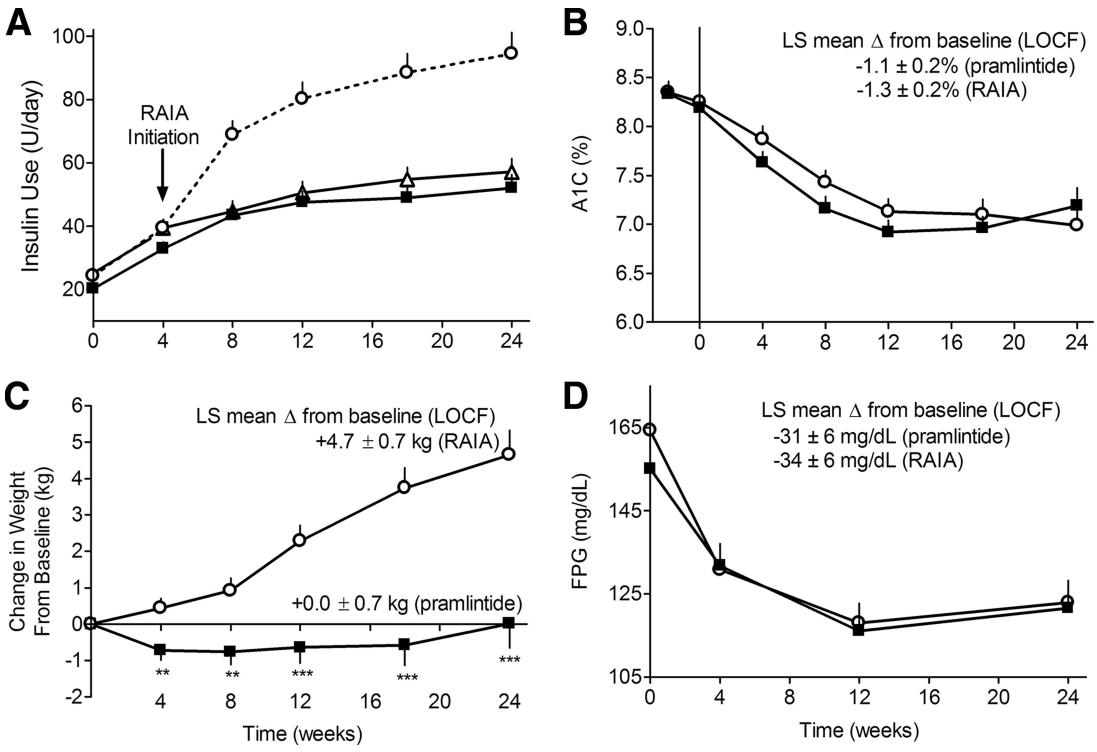

Figure 1—A: *Mean changes in insulin dosage over the course of the trial. Solid squares, unbroken line = basal insulin in the pramlintide group. Open triangles, unbroken line = basal insulin in the RAIA group. Open circles, broken line = total insulin (basal plus mealtime) in the RAIA group.* B: *Mean A1C at each visit. Solid squares = pramlintide; open circles = RAIA.* C: *Least squares mean weight changes over time with the last observation carried forward. Solid squares = pramlintide; open circles = RAIA.* ***P < 0.001; **P < 0.01. D: *Mean fasting plasma glucose over time. Solid squares = pramlintide; open circles = RAIA. LOCF, last observation carried forward; LS, least squares.*

CONCLUSIONS — This head-to-head comparison demonstrated that premeal pramlintide and RAIA have similar glycemic effects when either agent is added to titrated basal insulin with or without an OAD. On average, pramlintide reduced A1C from 8.2 to 7.2%, and an RAIA reduced A1C from 8.3 to 7.0% after 24 weeks of treatment. Reductions in A1C, FPG, and postmeal glycemic increments were not statistically different between treatment groups. However, changes in body weight accompanying improved glycemic control differed between treatments. By the most conservative assessment (the between-treatment difference of change from baseline in all patients receiving study medication, last observation carried forward), RAIA treatment contributed to a 4.7 kg (10.3 lb) gain compared with pramlintide treatment over 24 weeks. With similar glycemic effects and no severe hypoglycemic events with either treatment, the composite primary end point favored pramlintide over an RAIA because of the difference in weight gain.

Other clinical differences between these therapies are related to unwanted effects. The incidence of hypoglycemia was greater with an RAIA plus basal insulin than with pramlintide plus basal insulin (82 vs. 55%). Nausea occurred more frequently with pramlintide, and two patients (4%) withdrew from the study. However, as in other clinical studies, reports of nausea associated with pramlintide declined steadily during continued treatment.

This study builds on findings of a 16-week study that compared administration of pramlintide versus placebo during titration of basal insulin with continuation of an OAD, in which glycemic control improved more with pramlintide than with placebo and no severe hypoglycemia was reported (15). Weight declined a mean of 1.6 kg with pramlintide but increased 0.7 kg with placebo. The larger absolute body weight difference between groups in this study is probably due to RAIA-associated weight gain.

The potential clinical importance of weight gain associated with treatment for hyperglycemia has been studied for many years and remains controversial. An unfavorable relationship between adiposity and a variety of medical outcomes, including cardiovascular disease, is well established (17,18). Recently, an obser-

Table 2—*Primary end point*

	Pramlintide	RAIA	Fisher's exact test *P* value
n	56	56	
Patients achieving composite end point*	17 (30)	6 (11)	0.018
Individual end points			
Patients achieving A1C ≤7.0% at week 24	27 (48)	34 (61)	0.25
Patients with no weight gain at week 24	33 (59)	9 (16)	<0.0001
Incidence of severe hypoglycemia	0 (0)	0 (0)	NS

Data are *n* (%). *Composite end point: A1C ≤7.0% at week 24 with no weight gain and no severe hypoglycemia. NS, not significant.

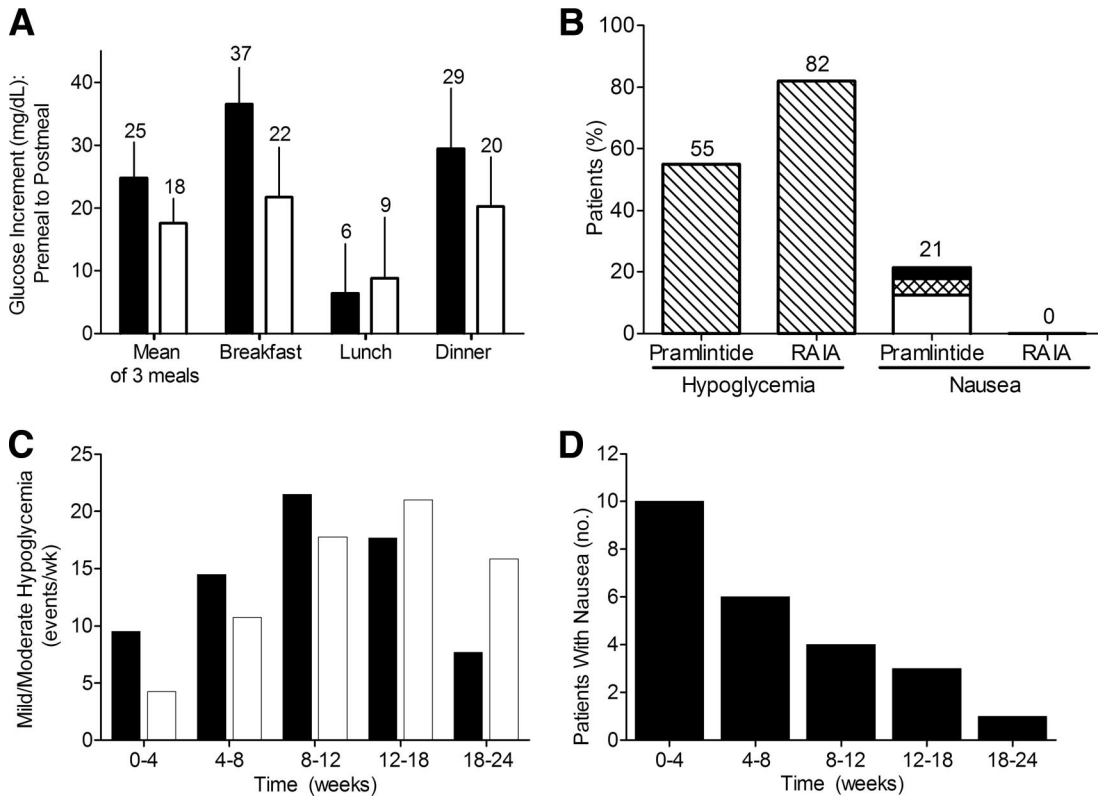

Figure 2—A: *Postprandial glucose increments from before to after meals at 24 weeks. Black bars = pramlintide; white bars = RAIA.* B: *Incidence and severity of hypoglycemia and nausea in patients treated with pramlintide or RAIA in addition to basal insulin. White bar = mild; striped bar = mild or moderate; cross-hatched bar = moderate; black bar = severe.* C: *The rate of hypoglycemia (events/week) over the course of the study with RAIA and pramlintide treatment. Black bars = pramlintide; white bars = RAIA.* D: *Number of patients reporting nausea over time during treatment with pramlintide.*

vational study of ~4,900 patients with type 2 diabetes showed a 13% increase in risk for fatal or nonfatal coronary heart disease with each 1-unit increase of BMI over ~6 years (19). Furthermore, evidence suggests that intended weight reduction reduces cardiovascular risk factors (20) and mortality (21). However, direct evidence that weight gain associated with insulin treatment is harmful is lacking. Notably, at the end of 10 years of randomized treatment, the U.K. Prospective Diabetes Study (UKPDS) showed a marginally significant reduction of myocardial infarction (16%, $P = 0.052$) with insulin or sulfonylurea treatment compared with dietary treatment, despite greater weight gain. Follow-up after cessation of randomized treatment showed persistence of the difference over time, and the advantage of insulin or sulfonylurea became statistically significant with more events (15%, $P < 0.01$) (22,23). Other findings indirectly suggest that avoiding weight gain and hypoglycemia while improving glycemic control may provide cardiovascular benefit. In a study embedded in the UKPDS, treatment of obese patients with metformin, which is not associated with weight gain or hypoglycemia, reduced the incidences of myocardial infarction and all-cause mortality (23). Similar trends were shown in another study with acarbose, an antihyperglycemic agent that also does not cause weight gain or hypoglycemia (24). In contrast, the Action to Control Cardiovascular Risk in Diabetes (ACCORD) trial, which compared intensive versus standard glycemic control strategies associated with weight gain and hypoglycemia, was stopped early because of higher all-cause mortality in the intensive arm, despite a 1.1% lower A1C in this group (25). Potential underlying mechanisms include the doubled occurrence of weight gain >10 kg with intensive treatment, the threefold increase of severe hypoglycemia, or both.

This study had several limitations. It was a small study, powered to address the composite primary outcome but not separate clinical outcomes, and the open-label design allows the possibility of unintended bias. The 4-week delay in initiating an RAIA to avoid insulin-induced hypoglycemia from simultaneous initiation of basal and rapid-acting insulin was also a limitation. Because of the difference in the timing of RAIA initiation, the potential for weight gain in the RAIA group may be underestimated at week 24, but glycemic outcomes at week 24 did not seem to be affected, as insulin doses, A1C, and FPG in both treatment groups stabilized after 12 weeks, well before the study's end. The incidence of nausea accompanying initiation of pramlintide (~20%) was confirmed as a leading drawback of starting treatment at 120 μg. Both nausea associated with pramlintide and hypoglycemia/weight gain associated with an RAIA might have been mitigated by more gradual titration. The small imbalance in use of detemir as the basal insulin (18 with pramlintide and 11 with an RAIA) is of uncertain significance. Differences in overall costs between the pramlintide and RAIA regimens might exist but are not addressed in this study of efficacy and safety.

Overall, these findings support the role of mealtime pramlintide as a potential alternative to RAIAs for patients using basal insulin treatment with or without OADs who are not achieving glycemic goals. Longer-term studies to evaluate cardiovascular and microvascular outcomes of controlling after-meal hyper-

glycemia without weight gain and hypoglycemia would be helpful to inform clinical treatment decisions for patients with type 2 diabetes.

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APPENDIX

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