ABSTRACT

Introduction: Ultra-rapid lispro (URLi) is a new prandial insulin lispro formulation. In the PRONTO-T2D study, URLi, in a basal-bolus regimen with glargine or degludec, was non-inferior to lispro (Humalog®) for HbA1c reduction and superior for postprandial glucose (PPG) control. We evaluated the efficacy and safety of URLi compared to lispro in younger versus older patients in PRONTO-T2D.

Methods: PRONTO-T2D was a phase 3, 26-week, double-blind, treat-to-target study in people with type 2 diabetes. In this sub-group analysis, we compared URLi to lispro on the change from baseline in HbA1c and rate of level 2 hypoglycemia (< 54 mg/dl) in patients aged < 65 (N = 406) and ≥ 65 years (N = 267).

Results: At baseline, patients < 65 versus ≥ 65 years had mean age of 54.9 versus 69.2 years and duration of diabetes 14.6 versus 19.4 years. Mean HbA1c at screening and randomization was 8.35 and 7.34%, respectively, in patients < 65 years, and 8.21 and 7.23%, respectively, in patients ≥ 65 years. At endpoint, mean HbA1c with URLi versus lispro was 6.92 versus 6.90%, respectively, in patients < 65 years and 6.89 versus 6.79%, respectively, in patients ≥ 65 years. URLi significantly reduced 1- and 2-h PPG excursions with a standardized meal test in both age groups: between-treatment differences at 1-h postmeal for younger and older patients was −9.8 and −15.1 mg/dl, respectively; and at 2-h postmeal, −18.7 and −15.1 mg/dl, respectively, all p < 0.05. Severe and nocturnal hypoglycemia were similar between groups. The relative rate (URLi/Humalog) of level 2 hypoglycemia was lower in older versus younger patients, with a significant treatment-by-age interaction observed. No differential treatment effects were noted for insulin dose, weight, and fasting and maximum glucose after the meal test.

Conclusions: URLi, in a basal-bolus regimen, resulted in endpoint HbA1c < 7% and significantly lower PPG excursions compared to lispro in both age groups, with reduced level 2 hypoglycemia in older versus younger patients.

Trial registration: ClinicalTrials.gov, NCT03214380.

Keywords: Efficacy; Elderly; Safety; Type 2 diabetes; Ultra rapid lispro; URLi
Key Summary Points

Why carry out this study?

The prevalence of type 2 diabetes among the elderly is high and is increasing.

Balancing the safety and efficacy of diabetes therapy is especially important in older adults due to comorbid medical conditions, concomitant medications, and increased risk of hypoglycemia.

Many diabetes treatment options are available, including the prandial insulin, ultra-rapid lispro (URLi).

In the PRONTO-T2D study, which evaluated the efficacy and safety of URLi versus lispro (Humalog®) in adults with type 2 diabetes, URLi was non-inferior to lispro for HbA1c reduction and showed superior PPG control with a similar safety profile to lispro.

The current study evaluated the efficacy and safety of URLi compared to lispro in patients aged < 65 versus ≥ 65 years with type 2 diabetes.

What was learned from the study?

URLi resulted in endpoint HbA1c < 7% and significantly lower postprandial glucose excursions compared to lispro in both age groups.

The incidence of severe hypoglycemia was low in both age groups.

The rate of level 2 hypoglycemia (blood glucose < 54 mg/dl) was lower with URLi in patients ≥ 65 years and higher in patients < 65 years compared to lispro.

Overall, treatment with URLi resulted in good glycemic control with an acceptable safety profile compared to lispro in patients in both age groups with type 2 diabetes.

INTRODUCTION

Type 2 diabetes mellitus is the more prevalent form of diabetes accounting for over 90% of all diabetes cases worldwide [1]. Among individuals > 65 years old in the USA, approximately 1 in 4 adults have diabetes, most of which is type 2 diabetes, and the prevalence is projected to rise with increasing life expectancy [2]. Aging is associated with increased insulin resistance and pancreatic beta-cell dysfunction, which predisposes older people to develop impaired glucose tolerance that can then progress to type 2 diabetes [3–6]. In a study evaluating the effects of age and sex on postprandial glucose (PPG) metabolism, elderly men and women were found to have higher fasting glucose and PPG levels compared to younger men and women [7].

Managing type 2 diabetes in the elderly is important because of its association with a higher risk of premature death, comorbid conditions including hypertension and cardiovascular disease, as well as cognitive impairment and increased risk for falls [8]. Many therapeutic options are available. However, treatment in the elderly requires consideration of multiple factors including comorbidities, concomitant medication, and age-related changes in drug disposition that may increase the risk of adverse events [9, 10]. The risk of hypoglycemia in particular is elevated, which is compounded by reduced nutritional intake and changes in the counter-regulatory responses to hypoglycemia [11]. Individualization of diabetes management is therefore particularly important in the elderly. Screening for diabetes complications and regular medical assessments are recommended, as findings may impact glycemic targets and diabetes treatment options [12]. Where PPG control is inadequate, researchers previously determined that rapid-acting insulin analogues are a safe and effective option [13]. However, patients must be educated about the timing of administration, the rapid onset of action of the insulin, and the risk of hypoglycemia. Studies have also shown that introducing a prandial insulin as part of a basal-bolus
regimen is more effective than a basal only regimen at managing PPG [14–17].

Ultra-rapid lispro (URLi; Lyumjev®; Eli Lilly and Company, Indiana, USA) is a new formulation of insulin lispro developed to more closely match the physiological insulin response to a meal, with the goal of improving postprandial glucose (PPG) control. In pharmacokinetic-pharmacodynamic (PK/PD) studies, URLi consistently showed an earlier onset and shorter duration of action compared with lispro (Humalog®, Eli Lilly and Company, Indiana, USA) across different populations [18]. Importantly, in patients with type 1 diabetes, PK/PD profiles were similar between young and older adults [19]. URLi was non-inferior to lispro for HbA1c reduction and showed superior PPG control and a similar safety profile to lispro in patients with type 1 and those with type 2 diabetes in the phase 3, PRONTO-T1D and PRONTO-T2D clinical trials, respectively [20, 21].

We conducted subgroup analyses on data from PRONTO-T2D to evaluate the efficacy and safety of URLi compared to lispro in patients < 65 versus ≥ 65 years old with type 2 diabetes. Pre-planned analyses compared URLi to lispro in both age groups on the change from baseline HbA1c at 26 weeks and the rate of level 2 hypoglycemia (blood glucose < 54 mg/dl).

METHODS

Study Design

PRONTO-T2D was a phase 3, double-blind, parallel-design, treat-to-target, 26-week, multicenter, multinational, randomized, controlled trial. Details of the study were reported previously [20], and a sub-group analysis from PRONTO-T2D is reported here. PRONTO-T2D was approved by local ethics review boards and conducted in accordance with Guidelines of the International Conference on Harmonization for Good Clinical Practice (Table S1 in Supplementary Material). All patients provided written informed consent. PRONTO-T2D was registered at ClinicalTrials.gov (NCT03214380).

Participants

Adults with type 2 diabetes and an HbA1c between 7.0% (53.0 mmol/mol) and 10.0% (85.8 mmol/mol) inclusive were eligible for inclusion in the trial. Eligible participants had been treated for ≥ 90 days with basal insulin in combination with one or more prandial injections of bolus insulin per day or premixed insulin at least twice daily. In addition, they may have been treated with up to three oral antihyperglycemic medications (OAMs), with stable dosing for ≥ 90 days prior to screening. Investigators at 131 study centers and 15 countries participated in the study.

Study Design and Treatment

The study included a 1-week screening period and an 8-week lead-in designed for basal insulin optimization, prior to randomization. This was followed by a 12-week active bolus titration and a 14-week maintenance phase.

Patients could continue metformin and/or a sodium–glucose cotransporter-2 inhibitor during the study. During the 8-week lead-in focusing on basal insulin optimization, patients were treated with basal insulin glargine U100 (100 U/ml) or insulin degludec U100 or U200, and three injections per day of prandial insulin lispro. They were then randomized 1:1 to blinded URLi (n = 336) or lispro (n = 337) injected 0–2 min prior to the start of each meal. Assignment to treatment groups was stratified by country, HbA1c stratum (≤ 8.0% or > 8.0% at 1 week prior to randomization), type of basal insulin, and number of pre-study prandial insulin injections (< 3 or ≥ 3/day). During the initial 12 weeks after randomization, study prandial insulin doses were adjusted in a treat-to-target manner to self-monitored blood glucose (SMBG) levels of 80 to < 110 mg/dl fasting or premeal, 90 to 130 mg/dl prebedtime, and < 140 mg/dl 1–2 h postmeal [20]. Patients then entered a 14-week maintenance period from weeks 12–26, during which basal and prandial insulin doses could be adjusted to maintain glycemic control or for safety reasons.
A 4-h standardized liquid meal test was performed at baseline (all patients on lispro) and week 26 (patients on double-blinded lispro or URLi) to assess PPG levels. The meal (Ensure Plus[^6], or a similar country option) had a nutrient composition of ~700 cal, 100 g carbohydrate, 22 g fat, and 26 g protein.

The primary end point was the change in HbA1c from baseline to 26 weeks (noninferiority margin 0.4%), with multiplicity-adjusted objectives for PPG excursions during the meal test.

Patients collected ten-point self-monitored blood glucose (SMBG) profiles prior to scheduled visits and on three non-consecutive days during the last 2 weeks of the study treatment period at the following time points: fasting (morning premeal), prior to midday/evening meals, 1- and 2-h post–morning/midday/evening meals, and at bedtime. Patients were also instructed to take a minimum of four SMBG readings daily, with additional SMBG readings as needed for diabetes management and whenever hypoglycemia was suspected. Level 2 hypoglycemia was defined as measured SMBG < 54 mg/dl. Nocturnal hypoglycemia was SMBG < 54 mg/dl occurring between bedtime and waking. Severe hypoglycemia was determined by the investigator as an episode requiring assistance of another person due to neurological impairment and was reported as a serious adverse event per protocol.

**Statistical Analyses**

The efficacy and safety of URLi and lispro were evaluated in patients aged < 65 years and in patients aged ≥ 65 years. Analyses were based on the full analysis set, which included all randomized patients who received at least one dose of study drug. Prespecified analyses comparing URLi to lispro in both age subgroups included change from baseline HbA1c at 26 weeks, the primary efficacy outcome, and level 2 hypoglycemia. Post hoc analyses were also conducted to provide complementary safety and efficacy information on the use of URLi in elderly patients. This included the proportion of patients achieving HbA1c targets, PPG excursions following a meal test at week 26, SMBG profiles, insulin dose, severe hypoglycemia, nocturnal hypoglycemia, and adverse events.

Either a mixed-effect model for repeated-measures (MMRM) or an analysis of covariance (ANCOVA), using data prior to permanent discontinuation of study insulin, was applied to efficacy data. For the hypoglycemia data, both negative binomial regression and logistic regression were performed to evaluate hypoglycemia risk by age group. The interactions of age group and treatment from the models were evaluated using a significance level of 0.1 to assess if the efficacy measures or the hypoglycemia risks were different between younger and older patients. The other safety data were analyzed using data up to the end of the study for each age group separately.

**RESULTS**

Out of 673 randomized patients, 406 (60.3%) were < 65 years old and 267 (39.7%) were ≥ 65 years old (Table 1). Average age was 54.9 years for patients < 65 years old and 69.2 for patients ≥ 65 years old. Weight and BMI were similar between age groups, while those ≥ 65 years old had a longer duration of diabetes. Treatment with oral antihyperglycemic medications (metformin and/or SGLT-2 inhibitor) during the study was somewhat higher in younger versus older patients.

**EFFICACY**

**HbA1c**

Mean HbA1c improved during the 8-week lead-in period in both age groups from ~ 8.3% at screening (67.2 mmol/mol) to ~ 7.3% (56.2 mmol/mol) at randomization (Table 1 and Fig. 1). Younger (< 65 years) and older (≥ 65 years) patients in both treatment groups showed similar reductions in HbA1c at the 26-week endpoint (Fig. 1). For younger patients, the least squares mean (LSM) difference between treatments (URLi – lispro) at week 26...
### Table 1 Demographics and clinical characteristics

|                                | Younger: Age < 65 years (N = 406) | Older: Age ≥ 65 years (N = 267) | Overall (N = 673) |
|--------------------------------|------------------------------------|---------------------------------|-------------------|
| Age (years), mean ± SD         | 54.9 ± 7.3                         | 69.2 ± 3.5                      | 60.6 ± 9.3        |
| Women/Men (%)                  | 48.3/51.7                          | 44.2/55.8                       | 46.7/53.3         |
| Race, n (%)                    |                                    |                                 |                   |
| Asian                          | 112 (27.7)                         | 52 (19.5)                       | 164 (24.4)        |
| Black or African American      | 23 (5.7)                           | 7 (2.6)                         | 30 (4.5)          |
| White                          | 257 (63.5)                         | 205 (76.8)                      | 462 (68.6)        |
| Hispanic or Latino, n (%)      | 112 (27.6)                         | 45 (16.9)                       | 157 (23.3)        |
| Weight (kg), mean ± SD         | 90.1 ± 20.4                        | 89.6 ± 20.1                     | 89.9 ± 20.2       |
| BMI (kg/m²), mean ± SD         | 32.2 ± 5.7                         | 32.3 ± 5.7                      | 32.3 ± 5.7        |
| Duration of diabetes (years),  |                                    |                                 |                   |
| mean ± SD                      | 14.6 ± 7.2                         | 19.4 ± 7.8                      | 16.5 ± 7.8        |
| Number of pre-study bolus injections, n (%) |                                    |                                 |                   |
| < 3/day                        | 101 (24.9)                         | 67 (25.1)                       | 168 (25.0)        |
| ≥ 3/day                        | 305 (75.1)                         | 200 (74.9)                      | 505 (75.0)        |
| Basal insulin during study, n (%) |                                    |                                 |                   |
| Insulin glargine               | 316 (77.8)                         | 201 (75.2)                      | 517 (76.8)        |
| Insulin degludec               | 90 (22.2)                          | 66 (24.7)                       | 156 (23.2)        |
| OAM use during study, n (%)    |                                    |                                 |                   |
| Metformin                      | 299 (73.6)                         | 176 (65.9)                      | 475 (70.6)        |
| SGLT2 inhibitor                | 78 (19.2)                          | 41 (15.4)                       | 119 (17.7)        |
| HbA1c at screening, mean ± SD  |                                    |                                 |                   |
| %                              | 8.35 ± 0.8                         | 8.21 ± 0.8                      | 8.30 ± 0.8        |
| mmol/mol                       | 67.8 ± 8.4                         | 66.2 ± 8.4                      | 67.2 ± 8.4        |
| HbA1c at randomization*, mean ± SD |                                    |                                 |                   |
| %                              | 7.34 ± 0.7                         | 7.23 ± 0.7                      | 7.30 ± 0.7        |
| mmol/mol                       | 56.7 ± 8.0                         | 55.5 ± 7.1                      | 56.2 ± 7.7        |

*After 8-week basal optimization lead-in period with basal insulin glargine U100 or degludec U100 or U200 in combination with prandial lispro. OAMs oral antihyperglycemic medications, SGLT2 sodium-glucose co-transporter-2, T2D type 2 diabetes mellitus
was 0.02% [95% CI – 0.12, 0.16], while for older patients it was 0.10% [95% CI – 0.06, 0.27]. No significant treatment-by-age difference was observed for HbA1c ($p = 0.399$). The proportion of patients achieving HbA1c < 7% at week 26 was 55.2% with URLi and 48.6% with lispro treatment in patients < 65 years old, and 63.5% with URLi and 57.6% with lispro in patients ≥ 65 years old.

**Meal Test**

Patients in both age groups who were treated with URLi showed significantly lower PPG excursions following the meal test at week 26 compared to those treated with lispro (Fig. 2). LSM difference at 1-h postmeal was – 9.8 mg/dl [– 18.2, – 1.5] for younger patients ($p = 0.022$), and – 15.1 mg/dl [– 25.3, – 4.9] for older patients ($p = 0.004$). At 2 h postmeal, LSM difference was

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Fig. 1 HbA1c time-course from screening to week 26. Data are mean at study entry and least squares mean ± standard error at all other time points. A mixed-effects model for repeated measures was used for post-baseline measures, which included treatment, visit, treatment-by-age interaction, strata (pooled country, number of bolus injections at study entry, and type of basal insulin at lead-in) as fixed factors and baseline HbA1c as a covariate. The model used an unstructured covariance structure for each patient. An analysis of covariance model was used in the analysis, which included treatment and strata (pooled country, HbA1c stratum at baseline, number of bolus injections at study entry, and type of basal insulin at lead-in) as fixed effects and baseline as a covariate.

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Fig. 2 Post prandial glucose excursions following a standardized meal test at week 26. Data are least square means ± standard error. *$p < 0.05$; **$p < 0.001$. Note: the standardized liquid meal test consisted of ~ 700 cal, 100 g carbohydrate, 22 g fat, 26 g protein. Prandial insulin dose administered during the meal test was individualized.
– 18.7 mg/dl [– 29.0, – 8.4] for younger patients \((p < 0.001)\) and – 15.1 mg/dl [– 28.4, – 1.9] for older patients \((p = 0.026)\). No significant treatment-by-age differences were observed for PPG control at 1-h \((p = 0.409)\) and 2-h postmeal \((p = 0.715)\).

Fasting glucose during the meal test was similar between URLi and lispro in both age groups. The fasting glucose LSM in patients < 65 years was 130.0 mg/dl with URLi and 124.2 mg/dl with lispro treatment \((p = 0.089)\), while in patients ≥ 65 years, LSM was 127.0 mg/dl with URLi and 127.8 mg/dl with lispro treatment \((p = 0.860)\). No significant treatment-by-age differences were observed for fasting glucose \((p = 0.186)\).

Maximum glucose during the meal test was numerically lower with URLi versus lispro treatment in patients < 65 years and significantly lower with URLi treatment in patients ≥ 65 years: LSM difference was – 6.0 mg/dl [– 16.7, 4.8] for younger patients \((p = 0.274)\) and – 16.8 mg/dl [– 30.8, – 2.7] for older patients \((p = 0.019)\). Treatment-by-age differences were not significant \((p = 0.163)\).

### SMBG

Ten-point SMBG profiles at week 26 followed a similar trend between age groups, although older patients had numerically lower fasting blood glucose and greater postprandial excursions after the morning and midday meals compared to younger patients (Fig. 3). Glucose values were significantly lower with URLi treatment compared with lispro at 1- and 2-h post-morning meal in both age groups (Fig. 3). In patients ≥ 65 years glucose values were also significantly lower with URLi treatment at 2-h post-evening meal.

Overall daily mean and daily mean premeal glucose values were not significantly different between treatments and subgroups. However, daily mean PPG values were significantly lower with URLi compared with lispro at 2-h postmeal in patients ≥ 65 years old (162.4 vs. 172.3 mg/dl; \(p = 0.035\)). Treatment-by-age differences for all other ten-point SMBG measures were not significant (all \(p > 0.1\)).

### Insulin Dose

No statistically significant differences were observed between treatments in basal, bolus, and total insulin dose (units/kg) at week 26 in both age groups (Table S2 in Supplementary Material). Mean total daily dose was ~ 1.12 units/kg in patients < 65 years, and ~ 1.12 units/kg in patients ≥ 65 years. The ratio of bolus-to-total dose was not significantly different between treatment groups or age groups at week 26: patients < 65 years, URLi, 49.8%;
lispro, 48.9%; patients ≥ 65 years, URLi, 49.7%; lispro, 48.2%. No significant treatment-by-age interaction for insulin dose or bolus/total ratio was observed (all $p > 0.1$).

**Safety**

The incidence of severe hypoglycemia was low in both age groups (Table S3 in Supplementary Material). In patients < 65 years old, none of those on URLi treatment experienced severe hypoglycemia, while four patients (2.1%) in the lispro group reported five events. In older patients, three patients (2.4%) reported four events with URLi treatment, and two patients (1.4%) reported two events with lispro treatment. While there was no between-treatment difference in level 2 hypoglycemia (< 54 mg/dl), the relative rate (i.e., URLi/lispro) was lower in patients ≥ 65 vs. < 65 years (0.78 [95% CI 0.56, 1.08] vs 1.16 [0.87, 1.54]), with a significant treatment-by-age interaction ($p = 0.071$). The rate of nocturnal hypoglycemia (< 54 mg/dl) was similar between treatments in each group and no treatment-by-age interaction for nocturnal hypoglycemia was observed.

Three deaths occurred during the study: one patient (0.2%) < 65 years old on lispro treatment (sudden death); two patients (0.7%) ≥ 65 years both on URLi treatment (acute myocardial infarction and septic shock). The incidence of SAEs, TEAEs, and discontinuations from the study because of an adverse event, was not significantly different between treatment groups and age groups (Table S4 in Supplementary Material). Injection site reactions were reported by eight patients (2.0%) < 65 years old and one patient (0.4%) ≥ 65 years old, all attributed to URLi treatment. All injection site reaction TEAEs were reported as mild or moderate severity, and one patient (< 65 years old) discontinued study treatment due to an injection site reaction (injection site edema).

Weight increased with both treatments in the younger (URLi, 1.5 kg; lispro, 1.7 kg) and older patients (URLi, 1.3 kg; lispro, 1.7 kg), with no significant differences between treatments in each age group and no significant treatment-by-age interaction observed ($p = 0.537$).

**DISCUSSION**

In this study, we compared the effects of URLi and lispro treatment between older and younger patients in the PRONTO-T2D study [20]. The results of the analyses showed similar efficacy of URLi treatment between patients aged < 65 years and those ≥ 65 years. Both age groups achieved good glycemic control, with similar reductions in HbA1c shown by URLi and lispro treatments and endpoint mean HbA1c of ~ 6.9%.

PPG control following standardized meal tests was significantly improved with URLi treatment compared with lispro in both age groups. URLi significantly reduced 1- and 2-h PPG excursions and demonstrated lower maximum glucose compared with lispro in patients < 65 and those ≥ 65 years of age. Effects of URLi and lispro treatments on 1- and 2-h PPG excursions, fasting, and maximum glucose following the meal test were similar between age groups.

Supportive of the MMTT findings, SMBG profiles, which reflect glycemic control during the participant's normal daily routine, showed significantly lower PPG levels with URLi treatment after the morning meal in both age groups. Additionally, significant improvements were observed in patients ≥ 65 years on URLi treatment at 2 h after the evening meal and for the overall mean daily 2-h postmeal timepoint. SMBG also revealed numerically lower fasting blood glucose and higher postmeal blood glucose following morning and midday meals in older versus younger patients. This may be reflective of impaired glucose tolerance with age and could be a factor in determining effective therapeutic options in the elderly. In a pooled analysis of data from six randomized studies comprising 1699 participants, the relative contribution of postprandial hyperglycemia to total glycemia was greater in older versus younger participants, while that of basal hyperglycemia was lower [22]. Insulin therapy is an effective option for individuals in whom OAMs and
other injectable agents fail to achieve optimal glycemic control or are contraindicated, such as due to comorbidities. Faster-acting insulins in particular may offer opportunities for greater improvement of PPG control due to their more rapid onset and shorter duration of action [13, 23]. Patients entering the PRONTO-T2D study on a basal plus bolus regimen, with HbA1c between 7.0 and 10.0%, had notable improvements in HbA1c following basal-bolus insulin therapy with URLi or lispro, with significantly improved postprandial glucose control demonstrated with URLi treatment in both younger and older patients.

The good glycemic control with URLi treatment in this trial, with endpoint mean HbA1c < 7% and superior PPG control, was achieved without an increased risk of hypoglycemia. Overall, the incidence of severe hypoglycemia was very low, and the rate of nocturnal hypoglycemia was also similar between treatments and across age groups. For the pre-planned analysis of clinically significant level 2 hypoglycemia (< 54 mg/dl), patients ≥ 65 years had a lower rate of level 2 hypoglycemia with URLi treatment compared with younger patients. The risk of hypoglycemia is an important consideration when treating older adults with type 2 diabetes [24]. As previously noted, reduced counter-regulatory response to hypoglycemia and failure to recognize hypoglycemia symptoms in the elderly, may result in increased risk of severe hypoglycemia and its related complications, such as injuries from falls, cognitive decline, cardiac complications, and even death [25, 26].

Strengths of this study include the double-blind design and the global nature of the study, which allowed inclusion of older patients from various geographies including North and South America, Asia, Australia, and Europe. Study limitations include the use of a liquid meal test, which allowed standardization across multiple countries in a global study but may not fully represent a typical meal. An important limitation is that individuals were excluded from participating in PRONTO-T2D if they had recent cardiovascular events, malignancies, or clinically significant renal, or hepatic impairment. However, these conditions may be more common in an ageing population and could occur simultaneously with diabetes in the real world. It is therefore important to note that the current study had a relatively healthier population and clinicians will need to continue to follow guidelines for individualizing treatment with consideration of a patient’s lifestyle, health status, and risk factors [24].

CONCLUSIONS

In conclusion, in patients with type 2 diabetes, URLi treatment in a basal-bolus regimen resulted in good glycemic control with an endpoint HbA1c < 7% and significantly improved PPG control compared to lispro in both older and younger patients. Furthermore, URLi demonstrated a lower rate of level 2 hypoglycemia in older versus younger patients.

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**Authors’ Contributions.** Q.Z. contributed to the study design, the statistical analyses, the interpretation of the research, and writing and reviewing the manuscript. F.C. contributed to the interpretation of the research, writing, and reviewing the manuscript. A.M.C. was responsible for medical oversight during the trial and contributed to the study design, the data analysis and interpretation of the research, and writing and reviewing the manuscript. All authors read the final manuscript and approved it for publication.
Disclosures. Qianyi Zhang, Farai Chigutsa, and Annette M. Chang are employees and shareholders of Eli Lilly and Company.

Compliance with Ethics Guidelines. The PRONTO-T2D study was conducted in accordance with the ethical principles of the Declaration of Helsinki and the International Conference on Harmonisation Guideline for Good Clinical Practice. The study protocol was reviewed and approved by institutional ethics committees at each study center or by a central ethics committee. All participants provided written informed consent.

Data Availability. The datasets generated and/or analyzed during the current study are available from the corresponding author on reasonable request.

Prior presentation. Parts of this study were presented in abstract form at the 80th Annual Scientific Sessions of the American Diabetes Association, 12–16 June 2020, the Annual Conference of the Association of Diabetes Care & Education Specialists, 13–16 August 2020 and at the 56th Annual Meeting of the European Association for the Study of Diabetes, 21–25 September 2020.

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REFERENCES

1. Centers for Disease Control and Prevention. National Diabetes Statistics Report, 2020 2020 [updated 8/28/2020. Available from: https://www.cdc.gov/diabetes/data/statistics-report/index.html?CDC_AA_refVal=https%3A%2F%2Fwww.cdc.gov%2Fdiabetes%2Fdata%2Fstatistics%2Fstatistics-report.html.

2. Narayan KM, Boyle JP, Geiss LS, Saaddine JB, Thompson TJ. Impact of recent increase in incidence on future diabetes burden: U.S., 2005–2050. Diabetes Care. 2006;29(9):2114–6.

3. Shou J, Chen PJ, Xiao WH. Mechanism of increased risk of insulin resistance in aging skeletal muscle. Diabetol Metab Syndr. 2020;12:14.

4. Scheen AJ. Diabetes mellitus in the elderly: insulin resistance and/or impaired insulin secretion? Diabetes Metab. 2005;31 Spec No 2:Ss27–Ss34.

5. Chang AM, Halter JB. Aging and insulin secretion. Am J Physiol Endocrinol Metab. 2003;284(1):E7-12.

6. Stumvoll M, Goldstein BJ, van Haeften TW. Type 2 diabetes: principles of pathogenesis and therapy. Lancet. 2005;365(9467):1333–46.

7. Basu R, Dalla Man C, Campioni M, Basu A, Klee G, Toffolo G, et al. Effects of age and sex on postprandial glucose metabolism: differences in glucose turnover, insulin secretion, insulin action, and hepatic insulin extraction. Diabetes. 2006;55(7):2001–14.

8. Bradley D, Hsueh W. Type 2 Diabetes in the Elderly: Challenges in a Unique Patient Population. J Geriatr Med Gerontol. 2016;2(2).

9. Kirkman MS, Briscoe VJ, Clark N, Florez H, Haas LB, Halter JB, et al. Diabetes in older adults. Diabetes Care. 2012;35(12):2650–64.

10. Kirkman MS, Briscoe VJ, Clark N, Florez H, Haas LB, Halter JB, et al. Diabetes in older adults: a consensus report. J Am Geriatr Soc. 2012;60(12):2342–56.

11. Meneilly GS, Cheung E, Tuokko H. Counterregulatory hormone responses to hypoglycemia in the elderly patient with diabetes. Diabetes. 1994;43(3):403–10.

12. Draznin B, Aroda VR, Bakris G, Benson G, Brown FM, Freeman R, et al. Older Adults: Standards of Medical Care in Diabetes-2022. Diabetes Care. 2022;45(Suppl 1):S195-s207.
13. Kant R, Chandra R, Thomas A. A Review and Update of Insulins in the Management of Elderly Patients with Diabetes. Consultant. 2010;18(7).

14. Raccah D, Bretzel RG, Owens D, Riddle M. When basal insulin therapy in type 2 diabetes mellitus is not enough—what next? Diabetes Metab Res Rev. 2007;23(4):257–64.

15. Liebl A, Prager R, Binz K, Kaiser M, Bengenstal R, Gallwitz B. Comparison of insulin analogue regimens in people with type 2 diabetes mellitus in the PREFER Study: a randomized controlled trial. Diabetes Obes Metab. 2009;11(1):45–52.

16. Rosenstock J, Ahmann AJ, Colon G, Scism-Bacon J, Jiang H, Martin S. Advancing insulin therapy in type 2 diabetes previously treated with glargine plus oral agents: prandial premixed (insulin lispro protamine suspension/lispro) versus basal/bolus (glargine/lispro) therapy. Diabetes Care. 2008;31(1):20–5.

17. Foster NC, Beck RW, Miller KM, Clements MA, Rickels MR, DiMeglio LA, et al. State of type 1 diabetes management and outcomes from the T1D Exchange in 2016–2018. Diabetes Technol Ther. 2019;21(2):66–72.

18. Leohr J, Dellva MA, Carter K, LaBell E, Linnebjerg H. Ultra Rapid Lispro (URLi) Accelerates Insulin Lispro Absorption and Insulin Action vs Humalog® Consistently Across Study Populations: A Pooled Analysis of Pharmacokinetic and Glucodynamic Data. Clin Pharmacokinet. 2021.

19. Linnebjerg H, Zhang Q, LaBell E, Dellva MA, Coulant DE, Hövelmann U, et al. Pharmacokinetics and Glucodynamics of Ultra Rapid Lispro (URLi) versus Humalog® (Lispro) in Younger Adults and Elderly Patients with Type 1 Diabetes Mellitus: A Randomised Controlled Trial. Clin Pharmacokinet. 2020;59(12):1589–99.

20. Blevins T, Zhang Q, Frias JP, Jinnouchi H, Chang AM. Randomized Double-Blind Clinical Trial Comparing Ultra Rapid Lispro With Lispro in a Basal-Bolus Regimen in Patients With Type 2 Diabetes: PRONTO-T2D. Diabetes Care. 2020;43(12):2991–8.

21. Klaff L, Cao D, Dellva MA, Tobian J, Miura J, Dahl D, et al. Ultra rapid lispro improves postprandial glucose control compared with lispro in patients with type 1 diabetes: results from the 26-week PRONTO-T1D study. Diabetes Obes Metab. 2020;22(10):1799–807.

22. Munshi MN, Pandya N, Umpierrez GE, DiGenio A, Zhou R, Riddle MC. Contributions of basal and prandial hyperglycemia to total hyperglycemia in older and younger adults with type 2 diabetes mellitus. J Am Geriatr Soc. 2013;61(4):535–41.

23. Leahy JIL, Aleppo G, Fonseca VA, Garg SK, Hirsch IB, McCall AL, et al. Optimizing Postprandial Glucose Management in Adults With Insulin-Requiring Diabetes: Report and Recommendations. J Endocr Soc. 2019;3(10):1942–57.

24. LeRoith D, Biessels GJ, Braithwaite SS, Casanueva FF, Draznin B, Halter JB, et al. Treatment of Diabetes in Older Adults: An Endocrine Society® Clinical Practice Guideline. J Clin Endocrinol Metab. 2019;104(5):1520–74.

25. Freeman J. Management of hypoglycemia in older adults with type 2 diabetes. Postgrad Med. 2019;131(4):241–50.

26. Chow L, Seaquist ER. How Significant Is Severe Hypoglycemia in Older Adults With Diabetes? Diabetes Care. 2020;43(3):512–4.