Diabetes Care
American Diabetes Association

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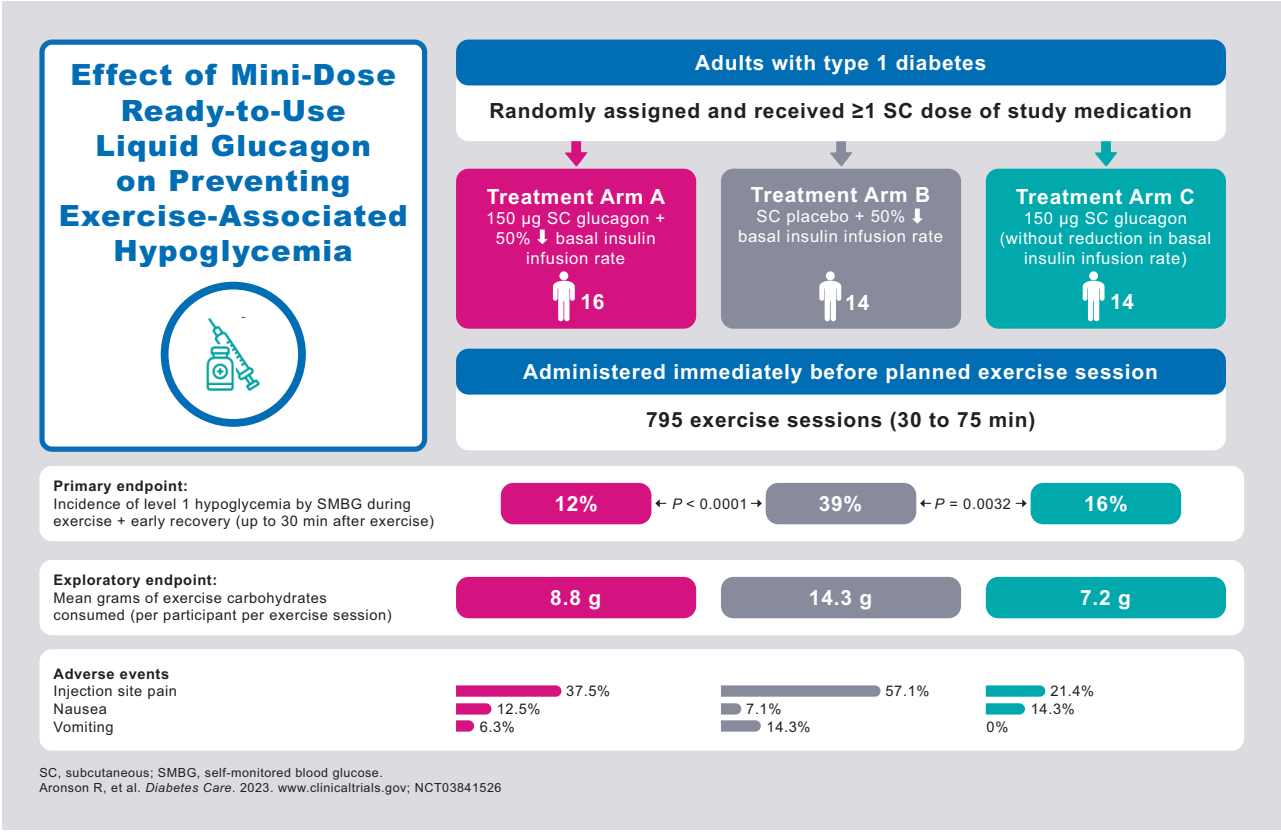
Diabetes Care 2023;46(4):765–772 | https://doi.org/10.2337/dc22-1145



ARTICLE HIGHLIGHTS

- Current strategies to mitigate exercise-associated hypoglycemia (EAH) in adults with type 1 diabetes are inconsistently effective and often cumbersome.
- Mini-dose glucagon given before aerobic exercise was hypothesized to mitigate incidence of level 1 hypoglycemia during exercise and early exercise recovery.
- Incidence was significantly lower for those who took mini-dose glucagon with or without 50% reduction in insulin basal delivery rate (basal rate reduction [BRR]) than those who did not take mini-dose glucagon but had 50% BRR.
- Mini-dose glucagon with or without BRR may be a relatively simple approach to mitigate EAH in active adults with type 1 diabetes.

Effect of Mini-Dose Ready-to-Use Liquid Glucagon on Preventing Exercise-Associated Hypoglycemia in Adults With Type 1 Diabetes

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OBJECTIVE

To determine effect of mini-dose, ready-to-use glucagon on incidence of exercise-associated hypoglycemia (EAH) in adults with type 1 diabetes.

RESEARCH DESIGN AND METHODS

Individuals initially participated in the in-clinic training phase for which they were randomly assigned to a crossover design: 150 μg glucagon (treatment arm A) or placebo (arm B) subcutaneously, immediately before exercise, plus 50% reduction in continuous subcutaneous insulin infusion (CSII) basal delivery rate. Completers were then rerandomly assigned in the 12-week outpatient investigational phase: arm A, B, or open-label C, 150 μg glucagon alone. Participants were to undertake their usual aerobic exercise at moderate to high intensity for 30 to 75 min in real-world settings. Data were analyzed for incidence of level 1 hypoglycemia based on self-monitoring blood glucose and for various secondary and exploratory end points.

RESULTS

Of 48 participants who completed the training phase, 45 continued to the outpatient phase. For all exercise sessions in the outpatient phase (n = 795), incidence of level 1 hypoglycemia was lower in both glucagon arms (A, 12% [$P < 0.0001$]; C, 16% [$P = 0.0032$]) than in the placebo arm (B, 39%). Times below range, in range, and above range from 0 to 300 min did not significantly differ among treatment arms. Consumed grams of exercise carbohydrates were lower with glucagon use than with placebo use but did not reach statistical significance ($P = 0.12$). Adverse events were similar among treatment arms.

CONCLUSIONS

Mini-dose glucagon with or without 50% reduction in CSII basal delivery rate may help to decrease EAH incidence in adults with type 1 diabetes.

Adults with type 1 diabetes should aim for at least 150 min/week of moderate- to high-intensity aerobic activity (1). But many may not achieve this goal because preparation for exercise is burdensome; insulin doses often need to be adjusted pre- and postexercise, and carbohydrate consumption may be necessary during and after exercise to mitigate the risk for exercise-associated hypoglycemia (EAH) (2–4).

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Received 10 June 2022 and accepted 30 December 2022

Clinical trial reg. no. NCT03841526, clinicaltrials.gov

This article contains supplementary material online at https://doi.org/10.2337/figshare.21801250.

Various strategies, such as carbohydrate feeding, decreasing insulin delivery (basal and/or bolus insulin), and/or suspending basal insulin delivery before exercise, have been inconsistently successful at mitigating EAH (2,3,5–10). One possible strategy is the use of a small (mini) dose of glucagon immediately before exercise to help prevent blood glucose from dropping. In one small in-clinic study, 150 μg of glucagon administered subcutaneously (SC) 5 min before fasted exercise maintained normoglycemia better than either carbohydrate feeding (40 g) or a 50% reduction in basal insulin delivery rate (basal rate reduction [BRR]) in adults on continuous subcutaneous insulin infusion (CSII) (11). In another study, 200 μg of glucagon given SC after exercise effectively raised glucose levels, indicating that glucagon works even in a setting of heightened insulin sensitivity and reduced hepatic glycogen availability (12). The purpose of this study was to investigate the efficacy and safety of mini-dose glucagon in active adults with type 1 diabetes in real-world settings.

RESEARCH DESIGN AND METHODS

The study was conducted in compliance with the International Conference on Harmonization of Technical Requirements for Registration of Pharmaceuticals for Human Use and all applicable local Good Clinical Practice regulations. Study protocol and amendments and informed consent forms were approved by an Institutional Review Board (Advarra IRB). Participants provided written informed consent before beginning the study (ClinicalTrials.gov, NCT03841526).

Study Design

The study comprised two phases: a training phase performed in a clinical research center (CRC) and then a randomized, placebo-controlled, double-blind, two-arm, parallel comparative 12-week phase, with an open-label third arm, and exercise performed in a real-world setting. Participants completed screening procedures (visit 1) and returned 1 to 2 days before their first scheduled exercise session (visit 2) for sensor placement for a continuous glucose monitor (CGM; Dexcom G5 Continuous Glucose Monitoring System; Dexcom, Inc.). Participants who had been using a sensor-augmented insulin pump discontinued sensor use for the duration of the study. Participants were unblinded to their CGM data.

Participants

Key inclusion criteria were adults aged 18 to <65 years with type 1 diabetes for ≥24 months, CSII use for ≥6 months, random C-peptide <0.6 ng/mL, history of EAH, two to three times of aerobic exercise per week, and no noninsulin therapies (e.g., metformin) for study duration. Key exclusion criteria were individuals who experienced frequent hyperglycemia with exercise as judged by one of the investigators (R.A.), one or more severe hypoglycemia episodes (required third-party assistance) within the past 12 months, use of >2 units of insulin/kg/day, glycated hemoglobin concentration >9%, kidney disease, liver disease, anemia, or hypersensitivity to glucagon or glucagon-like products or to excipients in XP-3994.

Study Drug

A 150-μg (in 30 μL) dose of ready-to-use, room-temperature, liquid-stable glucagon—XP-3994, a mini-dose of glucagon—was supplied in a 2-mL Crystal Zenith cyclic olefin polymer vial with FluroTec-coated rubber stopper. Placebo was also 30 μL and supplied in the same vial type as that for mini-dose glucagon, such that mini-dose glucagon and placebo were indistinguishable. Investigators selected 150 μg as the glucagon dose because it previously maintained glycemia in an exercise setting with no BRR in adults with type 1 diabetes (11).

CRC Phase

The main purpose of the CRC phase was to train participants on withdrawing mini-dose glucagon from a vial and giving it with a syringe and further evaluate glucagon safety in an exercise setting. Each exercise session involved 45 min of moderate- to high-intensity aerobic exercise. Participants underwent 50% BRR 5 min prior to the exercise session for the duration of the session. Participants were randomly assigned to receive mini-dose glucagon or placebo (visit 3), in a crossover design, returning after a 2- to 28-day washout for the second session (visit 4).

Real-World Phase

The primary objective of this 12-week phase was to determine whether mini-dose glucagon administered SC immediately before exercise in real-world settings prevented level 1 hypoglycemia during exercise and early exercise recovery. Participants began the real-world phase as early as 1 day after the CRC training phase. Investigators randomly assigned participants to a treatment arm (1:1:1): A, 150 μg glucagon and 50% BRR in CSII; B, placebo and 50% BRR; or C, 150 μg glucagon without BRR. Participants were instructed to continue their usual weekly exercise routine but each week to target for two to three qualified exercise sessions, each defined as a moderate- to high-intensity (achieve heart rate [HR] of ≥80% of maximum calculated HR at least once during session) aerobic exercise session lasting ≥30 but <75 min. Exercise sessions that did not meet the a priori criteria for qualified sessions, as described above, were nonqualified sessions. All exercise sessions comprised qualified and nonqualified sessions.

For each intended qualified exercise session, participants were to administer the study drug immediately beforehand. Participants in arms A or B also had a BRR. Participants were instructed to not administer study drug before an exercise session if their self-monitored blood glucose (SMBG) was outside of a predefined target range (100 to 180 mg/dL). In a supplied diary, participants also recorded time and volume of study drug, type of aerobic exercise, start and stop times of exercise, and glucose tablet and emergency kit usage during exercise. Participants chose the exercise type and setting and chose their pre-exercise meal.

Participants wore an activity monitor (Fitbit Ionic; Fitbit, LLC) as an adjunct to the diary to help to ensure criteria for a qualified exercise session were met. The monitor also recorded various activity parameters (e.g., exercise frequency and number of active minutes per week). Participants could exercise at any time of day and with any frequency, but they were instructed to administer study drug for only one exercise session per day. During sessions, participants were instructed to drink only carbohydrate-free liquids unless hypoglycemia developed. If CGM ≤70 mg/dL and SMBG confirmed the CGM result, participants were instructed to stop exercise and consume 16 g of dextrose in the form of tablets (Dex4 tablets; AMG Medical, Mont-Royal, Quebec, Canada). If SMBG remained

≤70 mg/dL at 15 min, participants were instructed to consume another 16-g serving and repeat every 15 min until SMBG >70 mg/dL. Investigators trained participants on the use of a glucagon kit (Glucagon for Injection; Eli Lilly and Company) in case treatment for severe hypoglycemia was necessary.

Participants were also instructed to record their SMBG 15 min and immediately prior to an exercise session, at 30 min of exercise, at the end of exercise, and 30 min after completing the exercise.

Participants returned to the clinic every 14 ± 3 days to download CGM and SMBG data. Participants then returned to the clinic 14 to 21 days after their last exercise session for follow-up safety and efficacy evaluations.

Safety and Tolerability

Adverse events (AEs) and treatment-emergent AEs (TEAEs) for both study phases were recorded as mild, moderate, or severe. Hypoglycemia was not considered an AE unless it required third-party assistance. Participants who received any study drug composed the safety population.

Participants' local tolerability to the study drug during the CRC phase was assessed by using a modified Draize scale (13). Injection sites were examined for erythema and edema 10 ± 5 and 60 ± 5 min after each exercise session. Erythema and edema scores each ranged from 0 to 4; 0 indicated no erythema or edema and 4 indicated severe erythema (beet redness to slight eschar formation) or severe edema (raised >1 mm and beyond exposure area). Participants self-reported type and duration of injection site discomfort. Type was classified as pain; itching; tingling, twitching, or numbness; irritation; or none. Duration was categorized by five time periods (<1 min, 1 to 2 min, 3 to 5 min, 6 to 9 min, and >10 min) and recorded as specific total duration.

Efficacy Determined via Patient-Reported Outcomes

Participants assessed their beliefs regarding exercise and hypoglycemia through three survey instruments—Barriers to Physical Activity in Diabetes Type 1 (BAPAD-1) (14), Hypoglycemia Fear Survey II (HFS-II) (15), and Hypoglycemia Confidence Scale (HCS) (16)—at the first CRC exercise session (visit 3) and then at 14 to 21 days after the last exercise session in the real-world phase (follow-up visit).

Statistical Analysis

Sample size was derived by using 80% power for detecting a difference in mean incidence of level 1 hypoglycemia associated with exercise session at the 0.05 significance level based on a one-way ANOVA. With an estimated effect size of 0.262 (26.2% difference in incidence of level 1 hypoglycemia between treatment and placebo; variance of means, 59 mg/dL; common SD, 15 mg/dL), 42 participants (14 per treatment arm) in the real-world phase were required. Accounting for 15% attrition, 48 participants were randomly assigned.

Primary End Point

The primary end point was incidence rate of level 1 hypoglycemia (SMBG ≤70 mg/dL) during the real-world phase. Hypoglycemia events were those that occurred during an exercise session or within 30 ± 2 min afterward. The analyzed data set comprised all exercise sessions (qualified and nonqualified) for which participants dosed themselves with treatment A, B, or C. Incidence rate was calculated by dividing the number of level 1 hypoglycemia events by the number of all exercise sessions. Inferential analysis of incidence rates among treatment arms was performed with a two-sided ANCOVA model with treatment as main effect, sex as factor, and age and weight as covariates. If analysis yielded $P < 0.05$, then multiple comparisons were performed by using least-squares mean contrast. If model residuals failed normality assumptions and log transformation could not resolve, nonparametric Wilcoxon methods were used. Post hoc analysis of incidence rate of level 2 hypoglycemia (SMBG <54 mg/dL) was also performed. The analyzed data set comprised all evaluable exercise sessions for which participants dosed themselves with treatment A, B, or C before starting an exercise session (i.e., dosing time was before exercise starting time).

Secondary End Points

Treatment differences for time below range—cumulative and proportional (%) minutes from 0 to 300 min when CGM ≤70 or <54 mg/dL—were evaluated with an ANCOVA model and with treatment as main effect, sex as factor, and age and weight as covariates. Any instance of CGM ≤70 or <54 mg/dL during an exercise session was also analyzed as cumulative area over the curve ($AOC_{0–300\ min}$ [min·mg/dL]; estimated with trapezoidal rule). If model assumptions were violated, the Kruskal-Wallis nonparametric test was used instead.

Patient-reported outcome data collected at the CRC phase (visit 3) were compared among treatment arms with ANOVA; data collected at the real-world phase were likewise compared. When analyses yielded $P < 0.05$, post hoc analyses were performed to identify which pairs of treatment arms significantly differed. Changes from baseline values were analyzed with an ANCOVA model and with treatment arm in the real-world phase as main effect, sex and treatment sequence in the CRC phase as factors, and age, body weight, and baseline values as covariates.

Exploratory End Points

Treatment differences for time above range—cumulative and proportional (percentage) minutes from 0 to 300 min when CGM >180 or >250 mg/dL—were evaluated with an ANCOVA model if model assumptions were upheld or with Kruskal-Wallis test if assumptions were violated and with treatment as main effect, sex as factor, and age and weight as covariates. Any instance of CGM >180 or >250 mg/dL during an exercise session was also analyzed as cumulative $AOC_{0–300\ min}$. Grams of carbohydrates consumed as glucose tablets per participant per exercise session were compared among treatment arms with ANOVA. Frequency of nocturnal hypoglycemia were compared among treatment arms with a Fisher exact test. For CGM data collected between 0000 h and 0600 h after an exercise session the day before, a nocturnal level 1 or level 2 hypoglycemia event was any instance when CGM ≤70 or <54 mg/dL was immediately preceded by CGM >70 or >54 mg/dL, respectively.

Data and Resource Availability

The data sets generated during and/or analyzed in the current study are available from the corresponding author upon reasonable request.

RESULTS

Participants

Seventy-five patients were screened, and 48 who met eligibility criteria were then randomly assigned to a training phase treatment sequence (24 participants each) (Supplementary Fig. 1). Forty-five (93.8%) participants completed the CRC phase and were then randomly assigned to a treatment arm for the real-world phase (Table 1). One participant who was randomly assigned to treatment arm B withdrew before they received any study drug or completed any exercise sessions. Two participants who were randomly assigned to treatment arm C withdrew after at least one dose of the study drug and at least one exercise session.

Forty-two (93.3%) participants completed the real-world phase, which comprised all (16 of 16) participants in treatment arm A, 93.3% (14 of 15) in arm B, and 85.7% (12 of 14) in arm C. No significant differences were noted for number of qualified exercise sessions per participant per treatment arm (A, 4.6 [mean] vs. B and C, 10.4; $P = 0.0944$) nor for cumulative minutes of qualified exercise sessions per participant per treatment arm (A, 554 ± 278 min [mean ± SD]; B, 798 ± 430 min; C, 687 ± 468 min; $P = 0.24$).

Primary End Point

A priori analysis of all 795 exercise sessions—315 qualified sessions and 480 nonqualified sessions—revealed incidence of level 1 hypoglycemia was significantly lower for treatment arm A (150 μg glucagon plus 50% BRR, 12%) than that for treatment arm B (placebo plus 50% BRR, 39%; $P < 0.0001$) (Table 2 and Fig. 1). Incidence for open-label treatment arm C (150 μg glucagon without BRR, 16%) was also significantly lower than that for treatment arm B ($P = 0.0032$). Incidence between treatment arms A and C did not significantly differ ($P = 0.21$). A similar pattern was seen in a post hoc analysis for the 315 qualified exercise sessions. A post hoc analysis for level 2 hypoglycemia among all exercise sessions also showed a significantly lower incidence for treatment arm A (1.8%) than for arm B (12.7%), but not for arm C (6.3%).

Secondary End Points

Among qualified, nonqualified, and all exercise sessions, time below range—cumulative and proportional minutes from 0 to 300 min when CGM ≤70 or <54 mg/dL—did not significantly differ among treatment arms (Supplementary Table 1). Likewise, instance of CGM ≤70 or <54 mg/dL during an exercise session analyzed as $AOC_{0–300\ min}$ did not significantly differ.

Patient-reported outcomes via BAPAD-1, HFS-II, and HCS did not significantly differ among treatment arms at the CRC phase (visit 3) nor at the follow-up visit at the end of the real-world phase.

Exploratory End Points

Among qualified, nonqualified, and all exercise sessions, time above range—cumulative and proportional minutes from 0 to 300 min and cumulative $AOC_{0–300min}$ for CGM >180 or >250 mg/dL—did not significantly differ among treatment arms. Number of participants who experienced any nocturnal level 1 hypoglycemia event and number of events per participant were similar among treatment arms (Supplementary Table 2). Median numbers of nocturnal level 1 and level 2 hypoglycemic events were not significantly different among treatment arms (A, 0.0 and 0.0; B, 3.5 and 1.0; C, 2.0 and 0.5, respectively). Grams of carbohydrates consumed as glucose tablets per participant per any exercise session were higher in the placebo arm B than in arms A and C, but the differences among arms did not reach statistical significance (A, 8.8; B, 14.3; C, 7.2; $P = 0.12$). Data collected from the wearable activity monitor, including HR, daily steps, calories burned, distance

Table 1—Demographic and baseline characteristics by treatment arm for adults with type 1 diabetes who participated in the CRC phase of the study and then also in the 12-week real-world phase of the study ($N = 44$)

	Real-world phase		
Participant characteristic	Treatment arm A ($N = 16$)	Treatment arm B ($N = 14$)	Treatment arm C ($N = 14$)
Age, years, mean (SD)	35.8 (9.0)	37.6 (11.8)	40.1 (13.6)
Sex, *n* (%)			
Male	9 (56.3)	7 (50)	6 (42.9)
Female	7 (43.8)	7 (50)	8 (57.1)
Ethnicity, *n* (%)			
Hispanic or Latino	1 (6.3)	0	1 (7.1)
Not Hispanic nor Latino	15 (93.8)	14 (100)	13 (92.9)
Race, *n* (%)			
American Indian or Alaska Native	0	0	0
Asian	3 (18.8)	1 (7.1)	1 (7.1)
Black	1 (6.3)	0	0
White	11 (68.8)	12 (85.7)	13 (92.9)
Native Hawaiian or another Pacific Islander	0	0	0
Other	1 (6.3)	1 (7.1)	0
Weight, kg, mean (SD)	80.1 (19.6)	80.9 (16.3)	79.9 (14.9)
Height, cm, mean (SD)	170.9 (12.7)	174.4 (8.7)	168.0 (8.1)
BMI, kg/m^2	27.2 (4.5)	26.5 (4.6)	28.3 (4.6)

Treatment arm A, mini-dose glucagon with 50% BRR. Treatment arm B, placebo with 50% BRR. Treatment arm C, mini-dose glucagon without BRR.

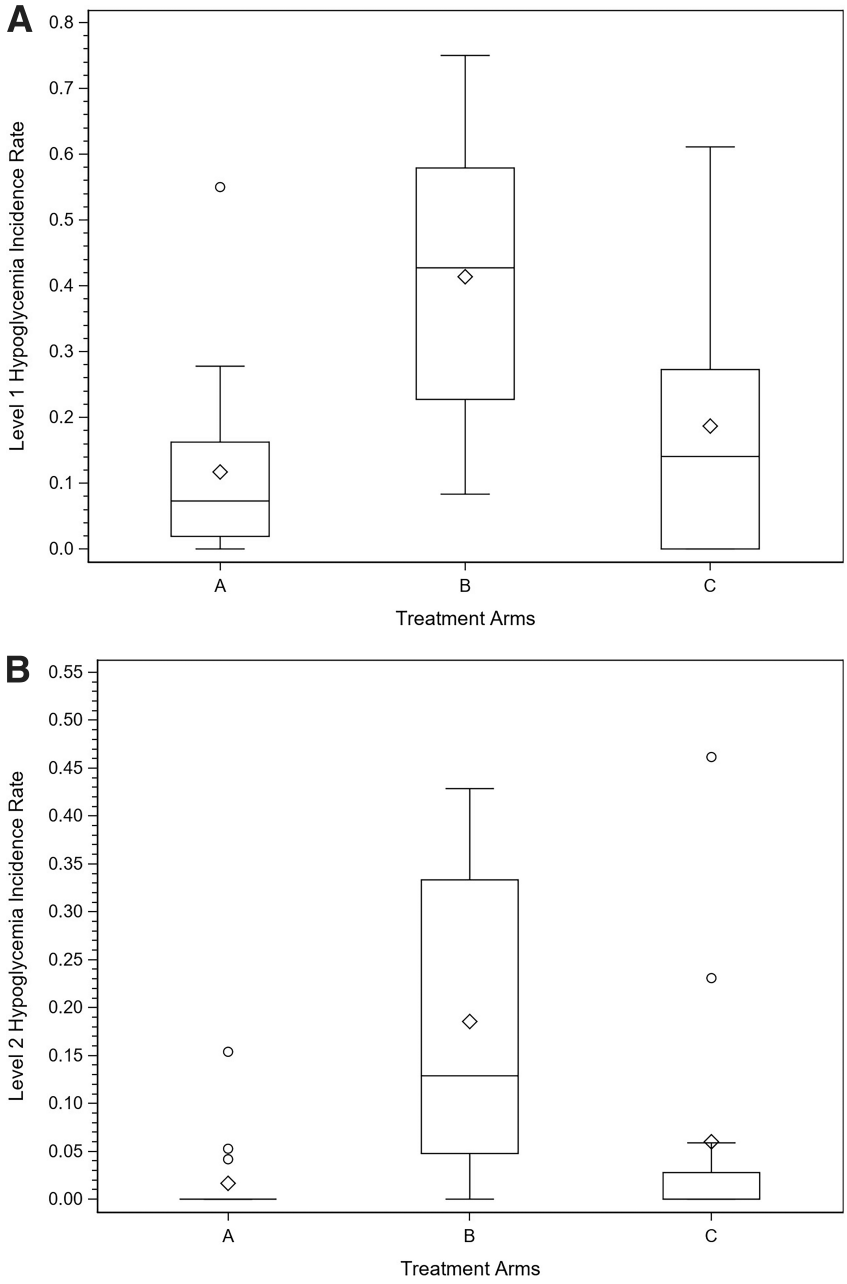

Figure 1—*A*: Box-and-whisker plot of the incidence rate of level 1 hypoglycemia (SMBG ≤70 mg/dL) among adults with type 1 diabetes for all exercise sessions and treatment arms (A [*n* = 16], B [*n* = 14], or C [*n* = 14]). *B*: Box-and-whisker plot of the incidence rate of level 2 hypoglycemia (SMBG <54 mg/dL) among adults with type 1 diabetes who met post hoc analysis criteria (A [*n* = 15], B [*n* = 14], or C [*n* = 13]). For each box, the horizontal line represents the median value and lower and upper boundaries represent 25th and 75th percentiles, respectively. Whiskers represent the extreme values that are not outliers. The circles indicate outliers. The diamond within each box represents the mean value. Incidence rate was determined by dividing the number of hypoglycemic events by the number of exercise sessions. Treatment arm A, mini-dose glucagon with 50% BRR. Treatment arm B, placebo with 50% BRR. Treatment arm C, mini-dose glucagon without BRR.

covered, floors climbed, and active minutes, did not significantly differ among treatment arms (Supplementary Table 3).

Safety and Tolerability

CRC Phase

Forty-one (85.4%) of 48 participants experienced one or more TEAEs (Table 3). Twenty of 46 (43.5%) experienced a treatment-related TEAE with mini-dose glucagon, and 27 of 47 (57.4%) experienced a TEAE with placebo. At 10 and 60 min after each exercise session, edema was not seen (score, 0) for participants in arm A, and very slight edema/barely perceptible edema (score, 1) or well-defined edema (score, 2) was seen for one participant each in arm B. No safety concerns prevented participants from proceeding with the real-world phase.

Real-World Phase

Thirty-eight of 44 (86.4%) participants experienced one or more TEAEs. Nine of 16 (56.3%) participants in treatment arm A, 9 of 14 (64.3%) in arm B, and 8 of 14 (57.1%) in arm C experienced TEAEs related to the study drug (Table 3). Nine (20.5%) participants experienced one or more moderately severe TEAEs; these TEAEs were limited to participants in arms A and B. No serious AEs or deaths occurred, and no participants discontinued treatment during the real-world phase due to TEAEs.

CONCLUSIONS

The study found the incidence rate of level 1 hypoglycemia associated with prolonged moderate- to high-intensity exercise in real-world settings was significantly lower—69% lower—after pre-exercise SC administration of 150 μg XP-3994, a ready-to-use, room-temperature liquid-stable glucagon, versus placebo (50% BRR alone) in adults with type 1 diabetes. Even without any concurrent BRR, incidence rate of hypoglycemia was 59% lower among those who used pre-exercise glucagon.

Current guidelines for mitigating EAH in adults with type 1 diabetes include consuming carbohydrates immediately before and/or during exercise, with or without 50% to 80% BRR initiated up to 90 min before exercise, lasting until the exercise stops (2). Yet, not all studies have confirmed the guidelines' reliability. In one study, glucose concentrations did not significantly differ between those for participants with 50% BRR before exercise and those for participants with 100% BRR before exercise (8). In another study, 50% BRR started 60 min before exercise did not prevent EAH (17). In the DIABRASPORT study (10), frequency of hypoglycemia events after 80% BRR before moderate exercise or after 100% BRR and intense exercise was similar to the frequency during rest, whereas more events occurred after 50% BRR and moderate exercise or after 80% BRR and intense exercise. Yet, other studies show 50% to 80% BRR started 90 min pre-exercise decreased the risk for EAH better than 100% BRR at exercise onset

Table 2—Statistics generated by treatment arm through a priori analysis of the primary end point of level 1 hypoglycemia (SMBG ≤70 mg/dL and through post hoc analysis of level 2 hypoglycemia (SMBG <54 mg/dL) associated with exercise for adults with type 1 diabetes in the 12-week real-world phase of the study

Statistics	Treatment arm A (*N* = 16)	Treatment arm B (*N* = 14)	Treatment arm C (*N* = 14)	Overall (*N* = 44)	*P* value
Level 1 hypoglycemia					
Mean incidence, %	12	39	16	24	Overall, 0.0002*; A vs. B, <0.0001; C vs. B, 0.0032; A vs. C, 0.2072
Mean number completed any exercise session per participant	15.7	21.6	17.4	18.1	0.1337†
Level 2 hypoglycemia					
Mean incidence, % (95% CI)	1.8 (0.05, 3.5)	12.7 (8.9, 16.5)	6.3 (3.2, 9.4)	7.4 (5.6, 9.3)	ND‡
Mean number completed exercise sessions per participant§	14.9	20.9	18.2	17.9	ND

Treatment arm A, mini-dose glucagon with 50% BRR. Treatment arm B, placebo with 50% BRR. Treatment arm C, mini-dose glucagon without BRR. ND, not determined. **P* value for comparison of incidence of level 1 hypoglycemia among treatment arms. †*P* value for comparison of number of exercise sessions per participant among treatment arms. ‡Inferential analysis to compare any two treatment arms was not performed; rather, 95% CIs were calculated and presented. §Overall, *N* = 42; *n* = 15 for treatment arm A, *n* = 14 for treatment arm B, and *n* = 13 for treatment arm C. For participants' exercise sessions to be included in the data set for analysis, dosing time occurred before exercise start time.

(7), and 50% BRR alone decreased blood glucose by more than did carbohydrate consumption and 50% BRR (9). The current study revealed that 50% BRR plus mini-dose glucagon decreased the incidence of level 1 hypoglycemia by 69% compared with 50% BRR alone. Therefore, by using glucagon before exercise, adults with diabetes may have EAH less often. Earlier reductions pre-exercise or greater reductions during exercise in the CSII basal delivery rate may equally mitigate EAH risk, but these reductions are difficult to do in real-world settings because exercise may be unplanned or preplanning BRR may not be practical (4).

Although incidence of hypoglycemia decreased during exercise or early exercise recovery after mini-dose glucagon with or without BRR, time below range for level 1 or level 2 hypoglycemia did not significantly differ among treatment arms. This finding may indicate that when EAH does occur, mini-dose glucagon may not mitigate the duration for EAH. Therefore, adults with type 1 diabetes should still be prepared to manage EAH through increased glucose monitoring, further basal or bolus insulin reduction, and carbohydrate consumption.

The clinical importance of mini-dose glucagon may be challenged because carbohydrate consumption could also increase glucose levels, thus mitigating EAH. However, extra caloric intake may be undesirable for some adults with type 1 diabetes and for those who also use exercise for weight management or maintenance. Recreationally active people and some athletes with type 1 diabetes have a low-carbohydrate diet for various reasons (18); therefore, consuming carbohydrates for preventing EAH is often undesirable. In the current study, participants who received placebo consumed more glucose tablets during exercise than those who received mini-dose glucagon. Therefore, EAH may be effectively mitigated with adjunct glucagon and with less carbohydrate consumption. Furthermore, carbohydrates consumed as glucose tablets per participant per exercise session was decreased by 38% or 50% with mini-dose glucagon ± 50% BRR, respectively, versus placebo.

Postexercise hyperglycemia may also be concerning for adults with type 1 diabetes, especially after prolonged aggressive BRRs, after excessive carbohydrate consumption, or possibly after glucagon for exercise. In a preliminary study (11), only one participant had postexercise glucose ≥250 mg/dL after 150 μg of glucagon versus five participants after glucose tablets. In the current study, time >180 or >250 mg/dL—time above range—did not differ among treatment arms; therefore, mini-dose glucagon effectively mitigated EAH without inadvertently causing hyperglycemia.

Each participant wore a real-time CGM and an activity monitor; parameters including daily steps, calories burned, and distance covered did not significantly differ among treatment arms. Although an effective adjunct therapy for preventing EAH may encourage patients to engage in more frequent or intense exercise, exercise frequency and intensity did not differ among treatment arms. However, the study was not designed to detect significant differences in exercise parameters. Also, the study included specific directions for exercise duration and intensity and for BRR that may have prevented a difference from emerging.

The safety profile for 150 μg of glucagon mirrored that for 1 mg of similar glucagon (19) and other glucagon formulations (20,21). Common TEAEs included injection site pain, nausea, and vomiting. Use of mini-dose glucagon did not adversely affect patient-reported outcomes; changes in BAPAD-1, HFS-II, and HCS scores did not significantly differ among treatment arms, but scores generally improved (more likely to exercise, less fear of hypoglycemia, and more confidence to manage hypoglycemia) in all arms.

A study strength is the real-world setting, with participants allowed to perform assorted aerobic exercises at various times of day, of various durations and intensities (qualified and nonqualified exercise sessions), and in various fed or unfed states, which overall supports the generalizability of the study findings. Having CGM data and measures of exercise performance from the activity

Table 3—Summary of TEAEs by preferred term reported by ≥2 or 5% participants in the safety population for the CRC phase and the 12-week real-world phase of the study

	CRC phase			Real-world phase			
TEAE data	Treatment arm A (*N* = 46)	Treatment arm B (placebo) (*N* = 47)	Overall (*N* = 48)	Treatment arm A (*N* = 16)	Treatment arm B (placebo) (*N* = 14)	Treatment arm C (*N* = 14)	Overall (*N* = 44)
Total number of TEAEs	34	42	76	51	47	43	141
Number (%) of participants with at least one TEAE	27 (58.7)	30 (63.8)	41 (85.4)	14 (87.5)	12 (85.7)	12 (85.7)	38 (86.4)
Preferred term, number of participants (%)							
Injection site pain	15 (32.6)	18 (38.3)	26 (54.2)	6 (37.5)	8 (57.1)	3 (21.4)	17 (38.6)
Injection site reaction	0	3 (6.4)	3 (6.3)	0	1 (7.1)	0	1 (2.3)
Injection site discomfort	4 (8.7)	1 (2.1)	5 (10.4)	1 (6.3)	1 (7.1)	1 (7.1)	3 (6.8)
Injection site irritation	1 (2.2)	3 (6.4)	4 (8.3)	0	0	1 (7.1)	1 (2.3)
Nausea	2 (4.3)	1 (2.1)	3 (6.3)	2 (12.5)	1 (7.1)	2 (14.3)	5 (11.4)
Vomiting	1 (2.2)	0	1 (2.1)	1 (6.3)	2 (14.3)	0	3 (6.8)
Gastroenteritis, viral	NR	NR	NR	1 (6.3)	1 (7.1)	1 (7.1)	3 (6.8)
Nasopharyngitis	0	2 (4.3)	2 (4.2)	0	1 (7.1)	2 (14.3)	3 (6.8)
Upper respiratory tract infection	1 (2.2)	2 (4.3)	3 (6.3)	1 (6.3)	2 (14.3)	0	3 (6.8)
Fall*	NR	NR	NR	0	2 (14.3)	1 (7.1)	3 (6.8)
Hyperglycemia	NR	NR	NR	0	2 (14.3)	2 (14.3)	4 (9.1)
Dizziness†	4 (8.7)	1 (2.1)	4 (8.3)	1 (6.3)	0	1 (7.1)	2 (4.5)

Treatment arm A, mini-dose glucagon with 50% BRR. Treatment arm B, placebo with 50% BRR. Treatment arm C, mini-dose glucagon without BRR. NR, none reported. *Fall is coded with the Medical Dictionary for Regulatory Activities (MedDRA) system organ class injury, poisoning, and procedural complications. †Dizziness is coded with the MedDRA system organ class nervous system disorders.

monitor further adds credibility to the study.

One study limitation is that participants were generally fit and regular exercisers, so the findings may not apply to less fit people with diabetes. Second, participants used CSII; therefore, findings may not be extrapolated to those who use other insulin delivery modes. Further research is needed to evaluate use of mini-dose glucagon in these populations, especially because those who use multiple daily insulin injections are generally unable to change their basal insulin dosing around exercise. Third, because participants were unblinded to their CGM data, participants may have, based on their CGM data, exercised more or less often or for longer or shorter duration. Participants may have also consumed more or less glucose tablets more or less often. Lastly, participants in treatment arm A (mean, 4.6/participant; mini-dose glucagon plus 50% BRR) performed fewer qualified exercise sessions and for less time than those in treatment arms B (placebo plus 50% BRR; 10.4/participant) and C (mini-dose glucagon alone; 10.4/participant) over the 12-week real-world phase.

In conclusion, results of the current study indicated ready-to-use, room-temperature liquid-stable mini-dose glucagon with or without 50% BRR, compared with 50% BRR alone, before moderate- to high-intensity aerobic exercise effectively decreased incidence rate of level 1 hypoglycemia in adults with type 1 diabetes. Mini-dose glucagon with or without BRR before exercise may be a simple, viable approach to prevent EAH in active adults with type 1 diabetes and on CSII.

Acknowledgments. The authors thank Ahn Nguyen for help with study design and data acquisition, Matthew Krecic for editorial assistance in the development of this manuscript, Nicole C. Close for statistical plan development and statistical analyses, James G. Moore for post hoc statistical support and review of the manuscript, and Robbie Huang for post hoc statistical support (all are or were employees of Xeris Pharmaceuticals, Inc.).

Funding. This study was funded by Xeris Pharmaceuticals, Inc.

Duality of Interest. R.A. has received advisory fees from Sanofi, Novo Nordisk, Boehringer Ingelheim, Eli Lilly and Company, HTL-STREFA, Gilead Sciences, Merck, and Xeris Pharmaceuticals, Inc. and research funding from Novo Nordisk, AstraZeneca, Eli Lilly and Company, Zealand Pharma, Xeris Pharmaceuticals, Inc., Medpace, Kowa Pharmaceuticals, Insulet, Dexcom, and

Bayer. M.C.R. has served in an advisory role for Xeris Pharmaceuticals, Inc., Zealand Pharma, Zucara Therapeutics, and Supersapiens; has received compensation as a speaker at scientific sessions, workshops, or both sponsored by Novo Nordisk, Eli Lilly and Company, Sanofi, Insulet, and Medtronic Diabetes; has received in-kind research support from Dexcom; and owns stock and shares with Supersapiens and Zucara Therapeutics. V.C. and M.K.J. are employees of Xeris Pharmaceuticals, Inc. No other potential conflicts of interest relevant to this article were reported.

Author Contributions. All authors were involved in conducting the trial and drafting the manuscript and reviewed, edited, and approved the manuscript for submission. V.C. is the guarantor of this work and, as such, had full access to all of the data in the study and takes responsibility for the integrity of the data and the accuracy of the data analysis.

Prior Presentation. This work was presented in part in abstract form at the 80th Scientific Sessions of the American Diabetes Association, 12–16 June 2020.

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