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BRIEF REPORT

Changes in Basal and Bolus Insulin Requirements with Tirzepatide as an Adjunctive Therapy in Adults with Type 1 Diabetes Using Tandem Control-IQ

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ABSTRACT

***Introduction*:** This study was aimed at investigating changes in insulin requirements and glycemic outcomes in adults with type 1 diabetes (T1D) using Control IQ (Tandem Diabetes) automated insulin delivery system (AID) over 8 months of tirzepatide treatment.

***Methods*:** In this single-center, observational study, we collected demographic, A1c, weight, sensor glucose, and insulin dose data for adults with T1D who were using AID and initiated tirzepatide adjunct therapy for clinical indications ($n=11$, median age 37, 64% female and mean body mass index of 39.6 kg/m^2). Data were compared from baseline and over 8 months.

***Results*:** Within 2 months of tirzepatide treatment, there were significant reductions in total daily insulin [median (IQR) 73.9 (47.6–95.8) to 51.7 (46.7–66.8) units/day, $p<0.001$], basal insulin [47 (28.2–51.8) to 32.4 (25.5–46.3) units/day, $p<0.001$], and bolus insulin [31.4 (19.9–38.3) to 17.9 (14.9–22.2) units/day, $p<0.001$] requirements. Insulin dose reduction from 2 to 8 months was modest. The frequency of user-initiated boluses did not differ throughout the study. Despite reductions in total insulin requirement, time in range (70–180 mg/dl) increased by 7%, A1c reduced by 0.5%, weight reduced by 9%, without increase in time below 70 mg/dl.

***Conclusions*:** This pilot study provides clinical guidance on insulin titration for adults with T1D who may initiate tirzepatide therapy. Based on the findings of this study, we recommend reducing 25% of total daily insulin dose at tirzepatide initiation in adults with T1D using AID with baseline A1c of less than 7.5%. Higher doses of tirzepatide were associated with greater weight loss, however, the reduction in insulin requirement was minimal.

Prior Publication: This analysis used the data from a previous manuscript aimed at evaluating safety and efficacy of tirzepatide in type 1 diabetes, which was published in the Journal of Diabetes Science and Technology [2].

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Key Summary Points
Why carry out this study?
Tirzepatide use in type 1 diabetes and its effect on insulin titration is unknown.
We investigated the changes in insulin doses after tirzepatide initiation over 8 months in adults with type 1 diabetes using an automated insulin delivery system.
What was learned from the study?
Tirzepatide treatment reduced total daily insulin dose by 30% within 2 months and sustained for 8 months.
Both basal insulin and bolus insulin doses were reduced significantly 31% and 43% within 2 months while basal/total insulin ratio increased from 56% to 63% and sustained over time.
In adults with type 1 diabetes, reduction in basal and bolus doses may be required within a month of tirzepatide treatment.

INTRODUCTION

Tirzepatide is a once-weekly dual agonist to glucose-dependent insulinotropic polypeptide (GIP) and glucagon-like peptide-1 (GLP-1) receptors which is currently FDA-approved for the treatment of type 2 diabetes and obesity [1]. A few recent studies showed significant reduction in weight and A1c without increase in risk for hypoglycemia in adults with type 1 diabetes (T1D) [2, 3]. Though mechanisms of GLP-1 receptor agonists' (GLP-1RA) or dual agonist, tirzepatide for weight loss is not evaluated in T1D, it is expected that weight loss mechanism would be similar to that of T2D and obesity without diabetes [4].

The automated insulin delivery system (AID) is the standard of care in managing T1D [5] and has been shown to improve glycemic outcomes compared to multiple daily injections (MDI) and insulin pump (continuous subcutaneous insulin infusion, CSII) use alone [6, 7]. As AID systems dynamically modulate insulin delivery in response to glucose levels, it is of clinical interest to understand how GLP-1RA use impacts glycemic outcomes and insulin delivery in individuals with T1D using AID. The Tandem t:slim X2 with Control-IQ technology (referred here as Control-IQ) is an AID system that dynamically changes basal insulin delivery every 5 min in response to predicted glucose levels [8]. It additionally delivers automatic correction boluses of insulin (60% of calculated correction dose) up to once per hour when the system predicts glucose levels > 180 mg/dl [8].

In this research, we used our previously published feasibility data [2] of tirzepatide adjunctive therapy in adults with T1D to explore the changes in insulin doses (both basal and bolus) and its relationship with change in body weight in adults using Control-IQ technology, to help establish clinical expectations for the use of tirzepatide with AID systems in adults with T1D.

METHODS

In this retrospective study, we collected electronic health records (EHR) data of adults with T1D who were using Control IQ, and were prescribed tirzepatide between June 17, 2022, and September 16, 2022. Continuous glucose monitoring (CGM) and insulin pump data were collected (from the Tandem t:connect database) every month starting from the first prescription of tirzepatide until 8 months or drug discontinuation by the patients. Three months of CGM data prior to the first tirzepatide dose were collected as the baseline CGM. CGM data was used to generate ambulatory glucose profile (AGP), a 24-h glucose course. The lowest dose of 2.5 mg tirzepatide was the initiation dose for all patients and the dosages were up titrated and adjusted by the physicians based on individual patients' glycemic and/or weight loss goal and

adverse events of the treatment. This study was approved by the Colorado Multiple Institutional Review Board under the exempt category due to retrospective nature of the study.

Statistical Analysis

Changes in insulin doses, body weight, and glycemia were analyzed for changes over an 8-month period of tirzepatide use and compared to baseline. Continuous variables are reported as median (interquartile range (IQR)). Categorical variables are reported as numbers and percentages. Wilcoxon signed-rank test was used to compare variables at the baseline with values in time intervals at 0–2, 2–3, 3–6, and 6–8 months. All analyses were performed using IBM's SPSS v29.0 and GraphPad Prism v10.0. p values < 0.05 were considered significant.

RESULTS

Eleven adults [median age 37 years, diabetes duration 24 years, seven female patients (64%)] using Control-IQ who received tirzepatide as an adjunct therapy were included in this analysis. Baseline characteristics of participants are presented in Table 1. Median (IQR) body mass index (BMI) was 39.6 (35.6–40.7) kg/m^2.

There was significant reduction in total daily insulin dose from median of 73.9 (IQR; 47.6–95.8) units/day at the baseline to 51.7 (46.7–66.8) units/day in 0–2 month, with minor subsequent reductions: 46.2 (40.9–74.2) units/day in 2–3 month, 45.3 (34.2–73.3) units/day in 3–6 month, and 41.8 (32.0–66.4) units/day in 6–8 months ($p < 0.01$ for all compared with baseline) (Fig. 1). Both basal insulin and bolus insulin dose were reduced within the first 2 months and sustained over 8 months (Figs. 1 and 2).

When bolus insulin dose is analyzed by user-initiated boluses vs automated correction boluses, both were significantly decreased in the first 2 months and sustained in the following months (Fig. 1). The number of automated correction bolus counts reduced similarly; however, the number of user-initiated bolus counts did not differ at any time points (p = ns for all timepoints), even though the amount of insulin in those boluses did (Fig. 1). Figure 2 indicates that the largest reduction in bolus insulin was observed in the first 2 months of tirzepatide initiation (43%), and sustained in months 2–8, culminating in a 49.7% decrease from baseline ($p = 0.001$). Changes in insulin doses at various timepoints are provided in Supplementary

Table 1 Baseline characteristics of the participants

	Median (interquartile range), $n = 11$
Age (years), median (min–max)	37 (34–49)
Sex (female), n (%)	7 (63.6)
Race/ethnicity (non-Hispanic White), n (%)	10 (90.9)
Diabetes duration (years), median (min–max)	24 (15–35)
A1c (%)	7.0 (6.7–7.4)
Weight (kg)	114.3 (94.8–129.3)
Body mass index (kg/m^2)	39.6 (35.6–40.7)
Total daily insulin dose (IU/day)	63.7 (43.2–114)
Total daily insulin dose per kilogram (IU/day/kg)	0.58 (0.46–1.00)

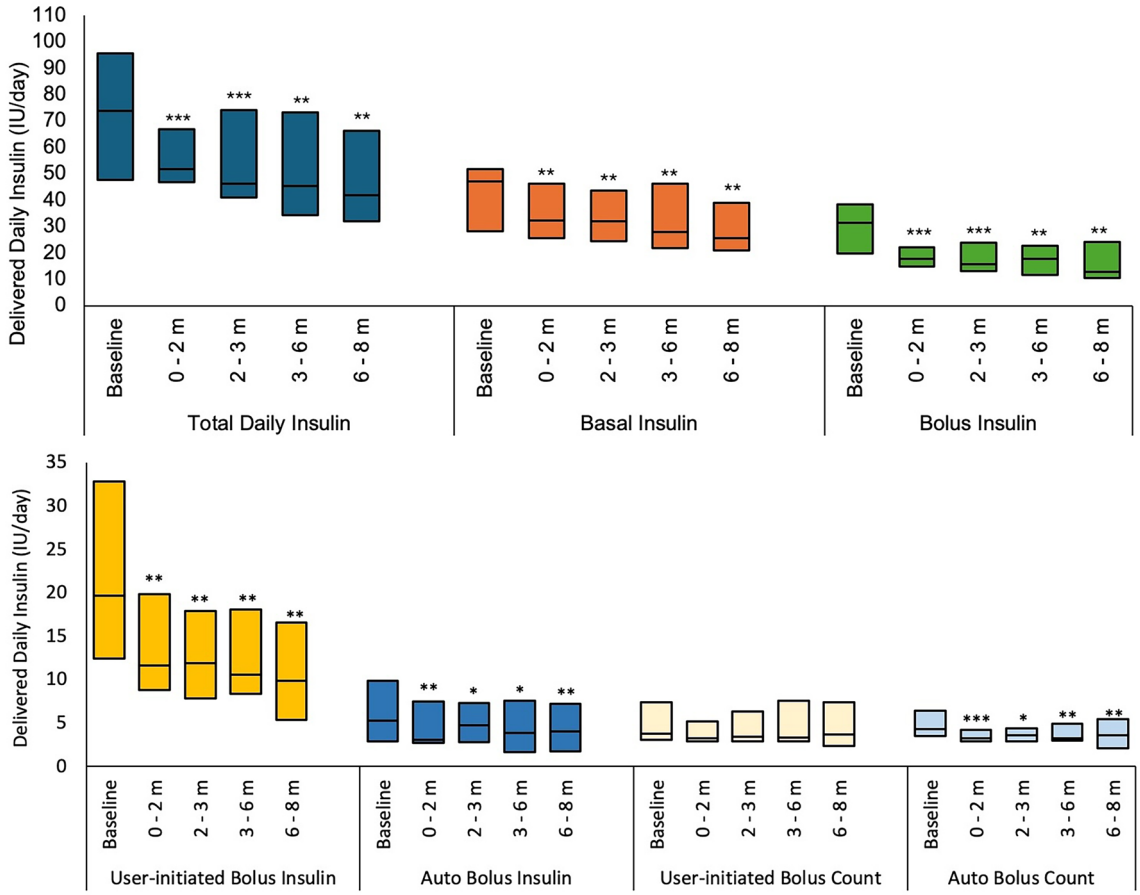

Fig. 1 Delivered daily insulin doses and bolus counts at baseline, 0–2, 2–3, 3–6, 6–8 months. All timepoints were compared to baseline. $^{*}p < 0.05$, $^{**}p < 0.01$, $^{***}p < 0.001$. Of 11 participants, two were on 2.5 mg tirzepatide, four were on 5.0 mg tirzepatide, and five were on 7.5 mg tirzepatide at 3 months. At 6 months, two were on 5.0 mg tirzepatide, three were on 7.5 mg, three were on 10.0 mg, one was on 12.5 mg, and two were on 15.0 mg tirzepatide. At 8 months, two, one, three, three, and two patients were on 5.0, 7.5, 10.0, 12.5, and 15.0 mg tirzepatide, respectively

Table S1. Due to the overall decrease of bolus insulin, the ratio of basal insulin/total daily dose increased from 53.7 (52.2–60.6%) at baseline to 59.8 (53.5–70.9%) at 0–2 months ($p = 0.022$), 61.0 (51.8–71.2%) at 2–3 months ($p = 0.047$), 62.9 (54.3–68.2%) at 3-6 months ($p = 0.008$), and 63.1 (52.9–65.5%) at 6–8 months ($p = 0.017$).

Carbohydrate entry into the pump decreased throughout the 8 months post tirzepatide, with average carbohydrate consumption declining from (mean ± SD) 120 ± 67 g per day to 70 ± 37 g/day at 0–2 months, 81 ± 64 g/day at 2–3 months, 66 ± 89 g/day at 3–6 months, and 45 ± 103 g/day at 6–8 months.

Total body weight and BMI ($n = 9$) reduced significantly from 114.3 (94.8–129.3) kg at baseline to 105.7 (95.2–110.2) kg at 6 months ($p = 0.015$) and from 39.6 (37.1–40.6) kg/m^2 to 36.3 (33.4–38.5) kg/m^2 ($p = 0.015$), respectively. Total daily insulin dose calculated by units/kg ($n = 8$) also decreased from baseline 0.53 (0.44–0.83) units/day/kg to 0.40 (0.32–0.58) units/day/kg at 6 months ($p = 0.017$).

An increase in time in range (70–180 mg/dl) (TIR) was observed in the first 2 months and sustained in the following months; median increases from the baseline were 12.9% in 0–2 months, 13.8% in 2–3 months, 15.8% in

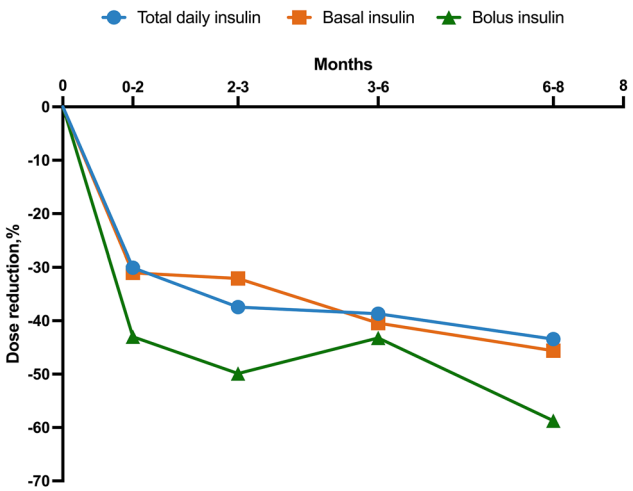

Fig. 2 Percent dose reduction for median total daily insulin (*blue solid line*), basal insulin (*orange line*), bolus insulin (*green line*) after tirzepatide treatment at 0–2, 2–3, 3–6, and 6–8-month time intervals

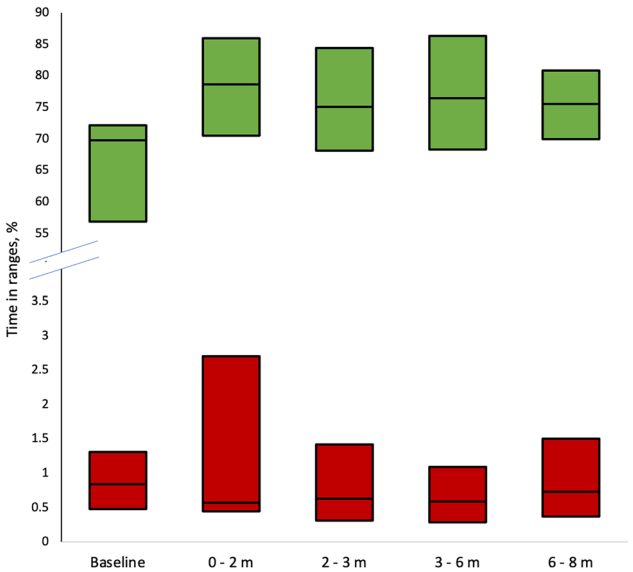

Fig. 3 Time in range (70–180 mg/dl) (*green*) and time below range (< 70 mg/dl) (*red*) at baseline, 0–2, 2–3, 3–6, 6–8 months. All timepoints were compared to baseline. Median and quartile values are shown with *boxes*. One person is missing at the last two timepoints. $^{*}p < 0.05$, $^{**}p < 0.01$, $^{***}p < 0.001$

3–6 months, and 15.3% in 6–8 months ($p < 0.02$ for all) (Fig. 3). A1c reduced from 7.0 (6.7–7.4) % to 6.3 (5.8–7.2) % ($p = 0.063$) after tirzepatide treatment. Time below range (< 70 mg/dl) (TBR) did not differ between baseline and time intervals (0.8% at baseline vs. 0.6% at 0–2 months, 0.6% at 2–3 months, 0.6% at 3–6 months, and 0.7% at 6–8 months, $p =$ ns for all) (Fig. 3). Ambulatory glucose profile also showed improvement throughout the day, more pronounced during daytime (Fig. 4a). Post-prandial glucose course was also lower after tirzepatide treatment (Fig. 4b).

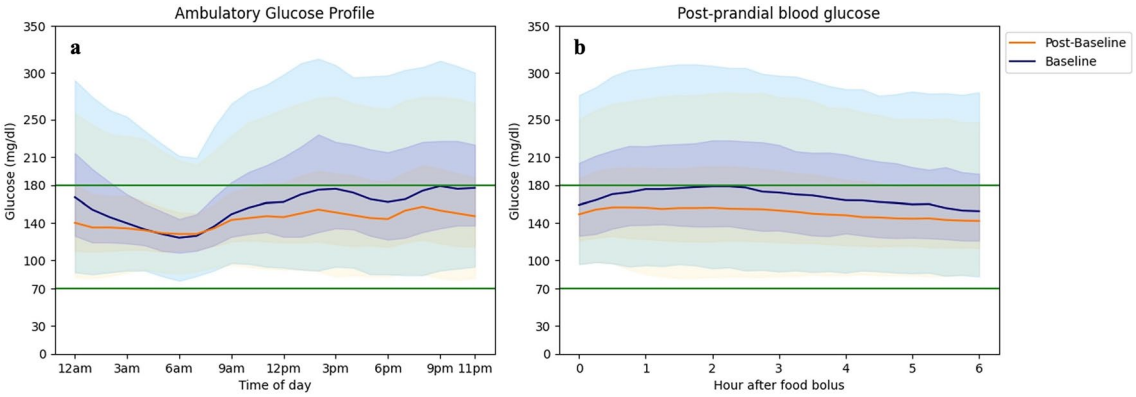

Fig. 4 Ambulatory glucose profiles at the baseline (*dark blue solid line*) and after tirzepatide treatment (post-baseline) (*orange solid line*). **a** 24-h glucose course. **b** Glucose course following user-initiated boluses via carbohydrate entry to the pump

DISCUSSION

Our study showed a 30% reduction in total insulin dose within 2 months of tirzepatide treatment in adults with T1D. Both basal and bolus insulin requirements were reduced, however, bolus insulin requirement was reduced relatively more than basal insulin leading to an increased basal/total daily insulin ratio. Besides dose and weight reductions, total daily insulin units/kg also decreased by 25% at 6 months, which may indicate an increase in insulin sensitivity.

Our study provides guidance on insulin dose adjustment when tirzepatide therapy is initiated in adults with T1D. We recommend reducing basal and bolus doses by 20–30% in line with weight loss within the first month of tirzepatide initiation (with 2.5 mg/week starting dose). In the following months, an additional 5–10% reduction compared to baseline may be needed. These reductions can be achieved through different approaches among people using AID, MDI, or CSII. The Control-IQ AID system is a basal-dependent system, which dynamically modulates the basal rates set by the users based on predicted sensor glucose levels, which means direct basal adjustments can help with the insulin reduction needed with tirzepatide. Higher correction factor (which will reduce the insulin delivery for automated boluses) and higher carbohydrate–insulin ratio (which will reduce user-initiated meal insulin boluses) adjustments would be needed to prevent hypoglycemia, especially after meals. Finally, the patient's weight and total daily insulin settings can be manually adjusted and should be updated to achieve better glycemic management with tirzepatide treatment. Other AID systems such as Omnipod 5, Medtronic 780 G, iLet, and CamAPS FX are basal-independent systems and these systems do not use user-set basal rates for automated insulin delivery [9–11]. We suggest adjusting the modifiable settings (carbohydrate–insulin ratio, correction factor, active insulin time or target glucose, and so on) depending on the functionality of the AID systems with intention to reduce insulin delivery by 20–30% during tirzepatide initiation. Multiple daily injection users may be more vulnerable for hypoglycemia than AID users due to lack of basal automation and may require more frequent evaluations and updates in their insulin doses. In these patients, 15% basal reduction and 20–25% bolus reduction in the first months can be implemented with monitoring nighttime and postprandial glucose for fine-tuning the basal and bolus doses, respectively. For non-AID pumps, basal rates can be reduced for all hours, while considering diurnal rhythm and changing basal insulin needs throughout the day [10].

Moreover, insulin reduction may depend on baseline A1c. For example, people with T1D

with higher A1c (A1c > 8%) may not require 20–30% reduction in insulin dose while someone with A1c close to 7% indicating more optimal insulin use may require close to 30% reduction in insulin dose. The baseline A1c of our cohort was 7.0% and therefore, we assume that for people with higher A1c (> 8%), up to 15% reduction in total insulin dose should be reasonable starting strategy. Patients with higher A1c (> 9%) probably may not need any dose reduction, especially during the first month of adjunct treatment with GLP-1RA. In this regard, further studies with larger cohorts are needed to provide evidence for insulin titration in patients with higher A1c and suboptimal glycemic management.

This study is the first to report on tirzepatide use in people with T1D using an AID system, Tandem Control-IQ. This study provides early insight into the insulin- and weight-specific patterns of people with T1D initiating tirzepatide while using an AID system and provides some clinical principles to consider. Limitations include small sample size, retrospective study design without controls, data collection from EHR, and variable tirzepatide dose titrations. Actual Control-IQ technology settings were not analyzed in this analysis, so it is possible that the insulin reduction seen in this study were due to both the user/healthcare provider changing user-modifiable insulin parameters, but also due to the Control-IQ technology automation which modulates insulin delivery as needed to maintain glucose levels in range. Moreover, our findings are only applicable with tirzepatide therapy. The various GLP-1RA such as semaglutide and dulaglutide are different in many ways, such as dose initiation, dose titration, and weight loss efficacy over time and therefore, insulin titration strategies may be different with different GLP-1RA therapies. Future studies with larger sample sizes can provide more precise insulin titration for tirzepatide use in T1D, with additional insight into AID contributions for safe insulin titration. Changes in insulin sensitivity should also be analyzed with larger cohorts.

CONCLUSIONS

In conclusion, up to 30% reduction in total insulin dose were observed within the first 2 months of tirzepatide treatment in adults with T1D and obesity with baseline A1c of 7.0% using Control-IQ. Decreased insulin units/kg may suggest a potential increase in insulin sensitivity. Tirzepatide may take the glycemic improvement of AID a step further and future studies are needed to evaluate the insulin dose titration with tirzepatide treatment in T1D.

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Author Contributions. Viral N. Shah (V.N.S), Kagan E. Karakus (K.E.K), and Halis K. Akturk (H.K.A) were involved in the conception, design, and conduct of the study and the analysis and interpretation of the results. Matthew P. Klein helped with data collection. K.E.K. wrote the first draft of the manuscript, and all authors edited, reviewed, and approved the final version of the manuscript. V.N.S. is the guarantor of this work and, as such, had full access to all the data in the study and takes responsibility for the integrity of the data and the accuracy of the data analysis. V.N.S was employed at Barbara Davis Center for Diabetes when this work was carried out. V.N.S is currently affiliated with Indiana University School of Medicine.

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Data Availability. The datasets generated during and/or analyzed during the current study

are available from the corresponding author on reasonable request.

Declarations

Conflict of interest. The author declared the following potential conflicts of interest with respect to the research, authorship, and/or publication of this article: Halis K. Akturk received research support through University of Colorado from Dexcom, Tandem Diabetes, Senseonics, Medtronic, Eli Lilly, REMD Biotherapeutics, IM Therapeutics, and IAFMS and received honoraria through University of Colorado from Senseonics and Mannkind for advisory board attendance. Viral N. Shah received research support from Novo Nordisk, Insulet, and Tandem Diabetes Care and received honoraria from Dexcom, Embecta, Insulet, Ascensia Diabetes Care, Tandem Diabetes Care, Genomelink and LumosFit for consulting or speaking arrangements. Kagan E. Karakus and Matthew P. Klien do not report any conflicts of interest.

Ethical Approval. This study was approved by the Colorado Multiple Institutional Review Board under the exempt category due to the retrospective nature of the study.

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