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A Multicenter Trial of a Tubeless, On-Body Automated Insulin Delivery System With Customizable Glycemic Targets in Child and Adult Participants With Type 1 Diabetes: A Review and Q&A With Trial Investigators

INTRODUCTION

Advances in technology have revolutionized management of type 1 diabetes (T1D); however, many patients remain unable to meet or maintain glycemic targets.¹⁻⁵ Technological advancements, such as automated insulin delivery (AID) systems, have been developed to help patients meet these targets. These systems utilize a glucose sensor and a unique algorithm to appropriately dispense insulin to the patient via a subcutaneous insulin delivery system. The use of these systems has been shown to lead to improved glycemic control and reduced hypoglycemia exposure.⁶⁻⁹

In January 2022, the FDA cleared a novel AID system for use by individuals with T1D who are 6 years of age and older.¹⁰ The Omnipod® 5 Automated Insulin Delivery System (Insulet Corporation) is a tubeless, on-body AID system with customizable glycemic targets.¹¹ FDA clearance was based on the results of a single-arm, multicenter, prospective study wherein the effectiveness and safety of the Omnipod® 5 System were assessed and which showed that both child and adult participants had a significant reduction in glycated hemoglobin A_{1c} (HbA_{1c}), regardless of baseline glycemic control, as well as improvements in time spent in target glucose range ($P < .0001$ for both), with a very low occurrence of hypoglycemia.^{2,9}

Apart from the Omnipod® 5 System, the AID systems that are currently commercially available in the United States use tethered pumps that connect to the infusion site cannula through tubing. To accommodate the tubing, users must place the pump on their person in a location such as a pocket or belt.^{9,12} The device typically needs to be disconnected during activities such as swimming or bathing; therefore, no insulin can be delivered to the user during these times.^{9,13} The algorithm in these systems is hosted within the pump itself.¹³

The Omnipod® 5 System has a unique configuration utilizing a tubeless insulin pump (Pod), which is a small (3.9 x 5.2 x 1.45 cm) adhesive patch pump worn on the body.¹¹ The cannula is

Omnipod® 5 Automated Insulin Delivery System

The Omnipod 5 Automated Insulin Delivery System is indicated for use by individuals with Type 1 diabetes mellitus in persons 6 years of age and older. The Omnipod 5 System is intended for single patient, home use and requires a prescription. The Omnipod 5 System is compatible with the following U-100 insulins: NovoLog®, Humalog®, and Admelog®.

automatically deployed directly under the Pod, creating an infusion site without external tubing. The Pod is waterproof (IP28) and is worn continuously for up to 72 hours. All user interactions are conducted wirelessly through a mobile app on a compatible smartphone or free Insulet-provided controller; smartphone users must also download the Dexcom G6 app.^{9,11} The algorithm itself is located on the Pod, and the glucose sensor (Dexcom G6, Dexcom Inc) communicates directly with the Pod through Bluetooth wireless technology.^{9,11,14} Important alerts are communicated and boluses are delivered via the controller or smartphone; the user's device should always be kept nearby.¹¹

This is a review article that presents the study results that were reported in a 2021 publication by Brown et al.⁹

STUDY METHODS

A total of 241 patients were enrolled in the clinical trial (NCT04196140)¹⁵ across 17 sites in the United States between December 19, 2019, and February 28, 2020.⁹ Study participants were enrolled into 2 cohorts: a cohort consisting of 112 children (range: 6-13.9 years) and a cohort consisting of 128 adolescents/adults (range: 14-70 years).⁹ Key inclusion criteria were age (range: 6-70 years), T1D diagnosis for at least 6 months, and a point-of-care HbA_{1c} of less than 10%. Key exclusion criteria were a history of severe hypoglycemia or diabetic ketoacidosis (DKA) for at least 6 months and use of non-insulin anti-diabetic medication other than metformin.^{9,15} Both child and adult cohorts underwent a 2-week standard therapy phase of their usual insulin regimen to gather glucose sensor data which would then be compared with their time using the Omnipod® 5 Automated Insulin Delivery System.⁹ Glucose sensors were worn by all participants during the standard therapy phase. If a glucose sensor was not already part of a participant's typical routine, it was worn in blinded mode during the standard therapy phase.⁹

The standard therapy phase was followed by a 3-month study period (with 9 follow-up visits) using the Omnipod® 5 System. Study participants, or their parents, were trained on all aspects of the Omnipod® 5 System, which included the on-body Pod that houses the embedded AID algorithm as well as an on-body interoperable

glucose sensor (Dexcom G6, Dexcom Inc), and the Omnipod® 5 mobile application, which was loaded on a locked-down Android phone. The mobile application was used to set and help maintain glucose targets; however, because the glucose sensor communicated directly with the algorithm on the Pod, once AID was initiated, the user did not need to be near their phone for automation to continue.⁹

After the initial set-up, participants could start the automated mode, during which time the Pod is enabled to administer microboluses of insulin at 5-minute intervals based on user-selected glucose targets. Microboluses are determined by the user's glycemic values (current and projected). Adjustment of insulin delivery is continuous and based on an adaptive basal rate. The basal rate was governed by the participant's total daily insulin delivered, which is tracked and updated with each Pod change.⁹

Participants could select their own glucose target (range: 110-150 mg/dL; programmable in 10-mg/dL increments to vary by time of day), and they were able to calculate mealtime and correction boluses through the SmartBolus Calculator, a component of the mobile application. These boluses were based on participant-defined insulin-to-carbohydrate ratios, correction factors, and glucose targets, and were then administered through the Pod. Participants also had access to the system's Activity feature (formerly "HypoProtect"), which could be utilized during exercise and other times when less insulin may be needed. In Activity, the system is set at a higher glucose target (ie, 150 mg/dL) and insulin delivery is restricted.⁹

HbA_{1c} was recorded at baseline and at the final study visit. Primary effectiveness outcomes were changes in HbA_{1c} and the percent of time in the target glucose range (70-180 mg/dL) during the 3-month study phase compared with the 2-week standard therapy phase.^{9,15} Primary safety outcomes were the incidence rates of severe hypoglycemia and DKA.⁹

Secondary outcomes included the percent of time patients were outside of the target glucose range (ie, < 70 mg/dL or > 180 mg/dL) as well as the percent of time patients spent in prespecified target glucose ranges (< 54 mg/dL, ≥ 250 mg/dL, ≥ 300 mg/dL). Investigators also reviewed additional glycemic measures (mean, standard deviation [SD], and coefficient of variation of sensor glucose); clinical measures

Omnipod® 5 Automated Insulin Delivery System (continued)

The Omnipod 5 ACE Pump (Pod) is intended for the subcutaneous delivery of insulin, at set and variable rates, for the management of diabetes mellitus in persons requiring insulin. The Omnipod 5 ACE Pump is able to reliably and securely communicate with compatible, digitally connected devices, including automated insulin dosing software, to receive, execute, and confirm commands from these devices. SmartAdjust™ technology is intended for use with compatible integrated continuous glucose monitors (iCGM) and alternate controller enabled (ACE) pumps to automatically increase, decrease, and pause delivery of insulin based on current and predicted glucose values.

(total daily dose of insulin, total daily basal or bolus insulin delivery, and body-mass index [BMI]); and system-specific measures (percent of study time spent in automated mode; number and type of device deficiencies observed).⁹

Assessments were conducted in a modified intention-to-treat (ITT) data set of participants undergoing the AID phase. Effectiveness and safety data from both cohorts were analyzed separately, with results reported as either means with SDs or medians with interquartile ranges (IQRs). For effectiveness outcomes, the investigators set the power for this study at 90%. One-sided tests were considered significant at a level of 2.5%, although the cutoff was 1.25% for the 2 primary effectiveness outcomes. A mean difference and SD of the difference in HbA_{1c} of 0.5% and 0.8%, respectively, was assumed in the sample size estimation, as well as a mean difference and SD of 10% and 15% for time in range (TIR). All *P* values were considered significant at a 2-sided level of .05. Paired *t* tests or Wilcoxon signed-rank tests were used to evaluate effectiveness outcomes in groups of less than 10 participants, or in instances where Shapiro-Wilk tests of normality were significant (*P* < .05).⁹

For safety outcomes, incidence rates of severe hypoglycemia and DKA were compared with published rates.^{3,4,9}

STUDY RESULTS

Study results data are discussed here in terms of mean values (±SD) unless otherwise indicated. Of the 241 participants enrolled in the study, 240 participants entered the ITT automated insulin delivery system analysis, and these data were analyzed to determine study outcomes. It should be noted that 98% of the study population (*n* = 235; 111 children, 124 adults) completed the main study. Age was determined at the date of informed consent. The mean age of child participants was 10.3 years (±2.2 years; range: 6.0-13.9 years). Note that 1 participant's birthday fell immediately after the informed consent date, so despite rounding up to 14 years, the participant was still included in the child cohort and considered to be 13.9 years. Most of these participants were living with diabetes for 4.7 years (±2.6 years). The mean age of adult participants was 36.9 years

(±13.9 years; range: 14.5-69.8 years), with 17.9 years (±11.6 years) of diabetes duration. The majority of patients in both cohorts reported current or prior continuous glucose monitoring use (children, 96.4% [*n* = 108]; adults, 98.4% [*n* = 126]) and insulin pump use (children, 89.3% [*n* = 100]; adults, 89.8% [*n* = 115]). At baseline, 11.6% (*n* = 13) of children and 18.0% (*n* = 23) of adults were using multiple daily injections as their standard therapy method.⁹

Efficacy

After the 3-month study period, a significant reduction in mean HbA_{1c} was noted in both cohorts, independent of baseline glycemic control. Children had an approximately 0.71% (±0.63%) reduction in mean HbA_{1c} from 7.67% (±0.95%) to 6.99% (±0.63%) while adults saw a 0.38% (±0.54%) reduction from 7.16% (±0.86%) to 6.78% (±0.68%) (*P* < .0001 for all) (Figure 1).⁹ It should be noted that the changes and *P* values were calculated only for those who had HbA_{1c} values available at both baseline (112 children, 128 adults) and end of study (108 children, 124 adults).⁹

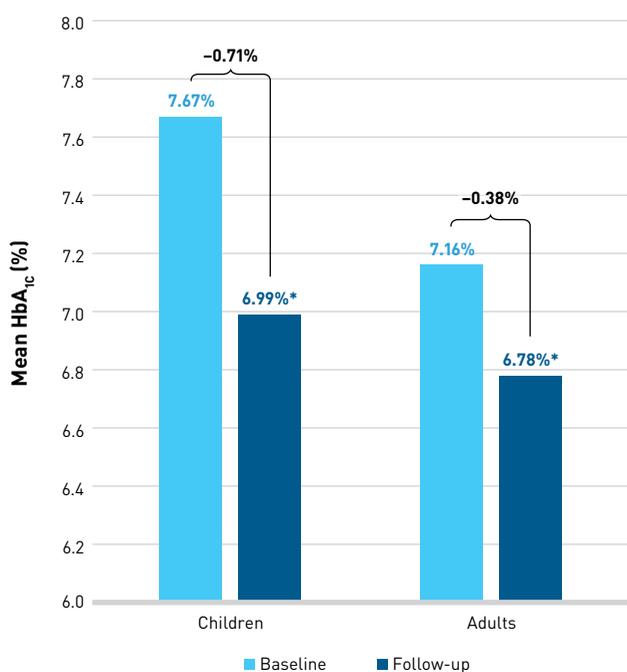
Compared with standard therapy, while using the Omnipod® 5 System, participants in both cohorts had significantly improved percentage of TIR (Figure 2).^{2,9} Children experienced an increase of about 15.6% in mean TIR, from 52.5% (±15.6%) to 68.0% (±8.1%), while adults had an increase of about 9.3% in mean TIR, from 64.7% (±16.6%) to 73.9% (±11.0%) (*P* < .0001 for all). In both adults and children, percentage of TIR improved in days 1 to 3 (to 73.5% and 62.6%, respectively); in children, percentage of TIR continued to rise in days 4 to 6 (to 68.0%).⁹

Additional glycemic benefits were demonstrated in secondary outcomes for both cohorts.⁹ For adult patients, median time in hypoglycemia < 70 mg/dL (IQR) decreased from 2.00% (0.63%-4.06%) to 1.09% (0.46%-1.75%) (*P* < .0001). For children, median time for this measure remained low, from 1.38% (0.42%-2.67%) to 1.48% (0.65%-2.23%) (*P* = .8153).⁹ Nocturnal TIR (from midnight to 6 AM) also increased by 22.9% in children, from 55.3% (±19.0%) to 78.1% (±10.8%), and 13.8% in adults, from 64.3% (±19.5%) to 78.1% (±13.9%) (*P* < .0001 for all),⁹ suggesting greater amounts of glycemic control and dampening of the risk for nocturnal hypoglycemia.

Omnipod® 5 Automated Insulin Delivery System (continued)

The Omnipod 5 SmartBolus Calculator is intended to calculate a suggested bolus dose based on user-entered carbohydrates, most recent sensor glucose value (or blood glucose reading if using fingerstick), rate of change of the sensor glucose (if applicable), insulin on board (IOB), and programmable correction factor, insulin to carbohydrate ratio, and target glucose value.

Figure 1. Change in Mean HbA_{1c} After 3 Months of Automated Insulin Delivery Compared With Baseline in Children and Adults^{1,9,a-d}



*The improvements of Omnipod® 5 vs ST (baseline) were statistically significant ($P < .0001$).⁹

HbA_{1c}, glycated hemoglobin A_{1c}; IQR, interquartile range; SD, standard deviation.

^aAn HbA_{1c} goal of <7% is appropriate for many children and nonpregnant adults.¹

^bResults are shown before (baseline) and after (follow-up) the 3-month automated insulin delivery phase for only for those participants who had HbA_{1c} values available at both time points (baseline, 112 children and 128 adults; follow-up, 108 children and 124 adults).⁹

^cImprovement was seen in both age groups regardless of baseline glycemic control and was significant ($P < .0001$). Results are discussed in terms of mean values (\pm SD) unless otherwise indicated. Children experienced a reduction in mean HbA_{1c} of 0.71% (\pm 0.63%), from 7.67% (\pm 0.95%) to 6.99% (\pm 0.63%); adults experienced a 0.38% (\pm 0.54%) reduction in mean HbA_{1c} from 7.16% (\pm 0.86%) to 6.78% (\pm 0.68%).⁹

^dThe automated delivery mode was used throughout the total study time by both cohorts (children: median, 96.4% [IQR: 93.8%-97.9%]; adults: median, 96.7% [IQR: 93.4%-98.0%]).⁹

The automated delivery mode was used throughout the total study time by both cohorts (children: median, 96.4% [IQR: 93.8%-97.9%]; adults: median, 96.7% [IQR: 93.4%-98.0%]), with 110 mg/dL being the most commonly selected set point. TIR was 68.4% (\pm 9.1%) for children and 75.6% (\pm 9.9%) for adults at the self-selected glucose target of 110 mg/dL, but glycemic improvements were noted in both cohorts at all customizable self-selected glucose targets.⁹

Though a slight BMI increase was noted in children, from 18.6 kg/m² (\pm 3.2 kg/m²) to 19.2 kg/m² (\pm 3.6 kg/m²) ($P < .0001$ by paired *t* tests), the z-score for BMI (0.4 ± 0.8) remained unchanged from baseline to follow-up, suggesting that the increase was due to normal growth. There was no noted BMI change in the adult cohort. A significant increase in total daily insulin requirements (units/kg) was noted in children, from 0.85 (\pm 0.24) to 0.92 (\pm 0.25) ($P < .0001$), while a marginal but nonsignificant decrease was seen in adults, from 0.61 (\pm 0.22) to 0.59 (\pm 0.21) ($P = .02$).⁹

Safety

Adverse events (AEs) reported during the study were rates of hyperglycemia associated with ketosis,⁹ as well as serious AEs, such as severe hypoglycemia—defined as requiring assistance due to altered consciousness—and DKA.^{1,9,16} In addition to examining participant medication use and device issues, participants were asked about AEs during study visits; surveillance was not conducted outside of those visits.⁹ In comparison to the rates reported in the T1D Exchange Registry, a low incidence rate of hypoglycemia was noted during the trial, with 4.8 (per 100 person-years) severe hypoglycemic events occurring, and likewise only 1.2 (per 100 person-years) DKA events occurring.^{3,4,9}

In the 3-month clinical study, 3 cases of severe hypoglycemia and 1 case of DKA were reported in children and adults/adolescents during Omnipod® 5 System use. These cases were not related to AID malfunction.⁹

Limitations

Limitations of the study include a single-arm design, lack of a control group, not accounting for some improvements or effects potentially

Omnipod® 5 Automated Insulin Delivery System

Warning: SmartAdjust technology should NOT be used by anyone under the age of 6 years old. SmartAdjust technology should also NOT be used in people who require less than 6 units of insulin per day as the safety of the technology has not been evaluated in this population.

due to study-related participation alone, and unequal durations of the experimental and standard therapy phases. The study authors noted that most study participants exhibited high levels of glycemic control and were versed in the use of diabetes technology, such as insulin pumps and glucose sensors, thus generalizability of the study results may be limited.⁹ Nonetheless, the authors shared that as benefits were noted in this well-controlled study population, results are promising for a real-world population.

A software anomaly occurred and led to an approximately 3-month study pause. However, participants were able to continue the study and use the device in manual mode to deliver insulin boluses or use another insulin regimen. The investigators noted that the pause in continuous automation use may have led to an underestimation of effectiveness, as the pause allowed, for some participants, as few as 28 days of continuous system use before final testing of HbA_{1c}, a long-term measure. No AEs occurred as a result of the anomaly.⁹

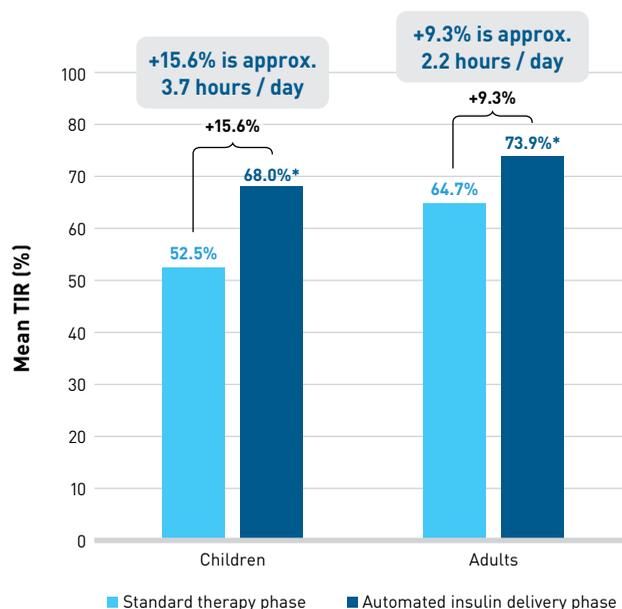
Strengths

Strengths of the study include the broad range of participant ages (range: 6-70 years) and baseline HbA_{1c} (range: 5.2%-10.3%). Furthermore, the study did not require prestudy sensor use and enrolled both those who used a pump and those with multiple daily injections. The authors noted a high rate of device acceptance across both adult and child participants, and this was further evidenced by 95% choosing to enroll in the extension phase of the trial. Study authors also observed that the Omnipod® 5 System's ability to report data remotely through cloud-based transmission may help to decrease patient burden of use seen in manual data uploads inherent in some diabetes management technology.⁹

CONCLUSIONS

The use of the Omnipod® 5 System was found to be safe and showed significant improvements in HbA_{1c} and time spent in the target glucose range with minimal episodes of hypoglycemia for both adults and children during the 3-month study period. An HbA_{1c} goal of less than

Figure 2. Automated Insulin Delivery vs Standard Therapy: Change in Percentage of Time Spent in Target Glucose Range for Children and Adults^{2,9,a-d}



*The improvements of Omnipod® 5 vs ST (baseline) were statistically significant ($P < .0001$).⁹

IQR, interquartile range; ST, standard therapy; TIR, time in range.

^aTarget glucose range: 70-180 mg/dL.⁹

^bThe automated delivery mode was used throughout the total study time by both cohorts (children: median, 96.4% [IQR: 93.8%-97.9%]; adults: median, 96.7% [IQR: 93.4%-98.0%]), with 110 mg/dL being the most commonly selected set point.⁹

^cResults are discussed in terms of mean values (\pm SD) unless otherwise indicated. Children and adults had significantly improved percentage of mean TIR while using automated insulin delivery compared with standard therapy ($P < .0001$ for both). Children experienced an increase of about 15.6% (\pm 11.5%) in mean TIR from 52.5% (\pm 15.6%) to 68.0% (\pm 8.1%), which is an improvement of approximately 3.7 hours per day. Adults experienced an increase of about 9.3% in mean TIR from 64.7% (\pm 16.6%) to 73.9% (\pm 11.0%), an improvement of approximately 2.2 hours per day.⁹

^dDuring the automated insulin delivery phase, 82% of children and 69% of adults met established clinical targets for TIR (children, > 60%; adults, > 70%).^{2,3}

Omnipod® 5 Automated Insulin Delivery System (continued)

The Omnipod 5 System is NOT recommended for people who are unable to monitor glucose as recommended by their healthcare provider, are unable to maintain contact with their healthcare provider, are unable to use the Omnipod 5 System according to instructions, are taking hydroxyurea as it could lead to falsely elevated CGM values and result in over-delivery of insulin that can lead to severe hypoglycemia, and do NOT have adequate hearing and/or vision to allow recognition of all functions of the Omnipod 5 System, including alerts, alarms, and reminders.

7% was achieved by 53% of children (mean HbA_{1c}, 6.99%) and 66% of adults (mean HbA_{1c}, 6.78%), respectively, which are consistent with recommended HbA_{1c} goals for both age groups.^{1,9} Children saw an improvement of 3.7 hours per day in the target glucose range, while adults showed an improvement of 2.2 hours per day at the self-selected glucose target of 110 mg/dL.⁹

In both cohorts, improvements in glycemic measures were seen mostly overnight and were determined to be due to clinically meaningful reductions in hyperglycemia.⁹

A total of 93% of child participants and 95% of adult participants achieved the international consensus recommendation of spending less than 4% of their time in hypoglycemia below 70 mg/dL. Overall, median time (IQR) below 70 mg/dL was 1.48% (0.65%-2.23%) for children and 1.09% (0.46%-1.75%) for adults.^{1,2,9}

There was approximately 1 device deficiency per person-month of system use. Deficiencies mostly concerned the Pod, with a malfunction relating to the hazard alarm used to alert study users that the Pod needed to be replaced; according to the authors, this type of issue would have had a negligible effect on the results of the study.⁹ •

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SUMMARY

This *AJMC*[®] Clinical Brief provides key information regarding a study by Brown et al published in *Diabetes Care* in July 2021 (doi:10.2337/dci21-0172). The authors of the publication are Sue A. Brown, MD; Gregory P. Forlenza, MD; Bruce W. Bode, MD; Jordan E. Pinsker, MD; Carol J. Levy, MD; Amy B. Criego, MD; David W. Hansen, MD, MPH; Irl B. Hirsch, MD; Anders L. Carlson, MD; Richard M. Bergenstal, MD; Jennifer L. Sherr, MD, PhD; Sanjeev N. Mehta, MD, MPH; Lori M. Laffel, MD, MPH; Viral N. Shah, MD; Anuj Bhargava, MD; Ruth S. Weinstock, MD, PhD; Sarah A. MacLeish, DO; Daniel J. DeSalvo, MD; Thomas C. Jones, MD; Grazia Aleppo, MD; Trang T. Ly, MBBS, PhD; and Bruce A. Buckingham, MD; for the Omnipod[®] 5 Research Group. Please consult the full publication for complete study information and author affiliations.

Omnipod[®] 5 Automated Insulin Delivery System (continued)

Device components including the Pod, CGM transmitter, and CGM sensor must be removed before Magnetic Resonance Imaging (MRI), Computed Tomography (CT) scan, or diathermy treatment. In addition, the Controller and smartphone should be placed outside of the procedure room. Exposure to MRI, CT, or diathermy treatment can damage the components. Visit www.omnipod.com/safety for additional important safety information.

Expert Q&A on a Tubeless, Automated Insulin Delivery System With Customizable Glycemic Targets

An editor from *The American Journal of Managed Care*® (AJMC®) spoke with **Amy B. Criego, MD, MS**, and **Bruce W. Bode, MD**, about advances in technology for the treatment of type 1 diabetes (T1D). Criego and Bode are coauthors of “Multicenter trial of a tubeless, on-body automated insulin delivery system with customizable glycemic targets in pediatric and adult participants with type 1 diabetes,” published in *Diabetes Care* in July 2021. This publication, by Sue A. Brown, MD, et al, presented the results of the first 3-month outpatient pivotal single-arm, multicenter, prospective clinical study of the Omnipod® 5 Automated Insulin Delivery System (Insulet Corporation; Acton, MA), the first and only tubeless automated insulin delivery (AID) system in the United States. Criego is the department chair of pediatric endocrinology and medical director of the International Diabetes Center at the Park Nicollet Clinic in St Louis Park, Minnesota, and Bode is a diabetes specialist with Atlanta Diabetes Associates and clinical associate professor in the Department of Medicine at Emory University in Atlanta, Georgia.

AJMC®: How have the algorithms and technology of AID systems played a key role in T1D management?

Criego: The key with AID is connectivity with a reliable continuous glucose monitor [CGM] for the algorithm to work

properly. When the connected pump and CGM devices were introduced, they initially sought to suspend insulin to prevent hypoglycemia. With AID for hyperglycemia, the newer devices improve time in range (TIR) by not only decreasing the time below range but also decreasing the time spent above range. That stable communication between a reliable sensor and algorithm-containing pump is the key to today’s AID devices.

Bode: AID systems began with Medtronic’s MiniMed 670G. Then came Tandem’s Control-IQ. Now there’s the Omnipod® 5 System. All these systems make decisions every 5 minutes based on data received from the CGM. The MiniMed 670G had a glucose target of only 120 mg/dL with correction only down to 150 mg/dL, whereas the Control-IQ treats to a range of 112.5 mg/dL to 160 mg/dL, with a range of 110 mg/dL to 120 mg/dL in Sleep Activity. With the Omnipod® 5 System, the user can choose between 5 glucose targets starting at 110 mg/dL and adjust in 10 mg/dL increments up to 150 mg/dL, with up to 8 different segments per day. During exercise, there is the Activity [feature], which I’ll touch on later. Among the participants using Omnipod® 5 in the trial, rates of hypoglycemia were low, and episodes of severe hypoglycemia, or even [diabetic] ketoacidosis [DKA], were rare. With the use of AID, patients can get their glucose levels near normal without experiencing a high incidence of hypoglycemia.

Omnipod® 5 Automated Insulin Delivery System (*continued*)

The Omnipod 5 Automated Insulin Delivery System is indicated for use by individuals with Type 1 diabetes mellitus in persons 6 years of age and older. The Omnipod 5 System is intended for single patient, home use and requires a prescription. The Omnipod 5 System is compatible with the following U-100 insulins: NovoLog®, Humalog®, and Admelog®.

AJMC®: Where do these AID systems fit into the guidelines from the American Diabetes Association on the management of T1D?

Criego: In children, the primary focus has been avoidance of hypoglycemia. However, children were spending too much time in hyperglycemia, which can cause future complications. Now, studies are indicating a relationship between time in target glucose range and glycated hemoglobin A_{1c} (HbA_{1c}). Focusing on TIR allows us to improve glycemic management by making changes at a faster cadence than providers [could]. AID also can adjust for miscalculations when dosing decisions or dose timing may not be ideal. Most studies will ask: Is there an improvement in HbA_{1c} with the use of an automated device? Absolutely, there is. The TIR improves and so does the HbA_{1c}. These devices show promise for diabetes management in our pediatric population by not only improving TIR but also by decreasing the day-to-day burden and distress associated with T1D management.

Bode: The American Diabetes Association guidelines include both insulin pumps and CGMs for anyone with T1D who can safely manage the device(s) and for those with type 2 diabetes and other forms of diabetes who are on multiple daily injections. The messaging has indicated that pumps have been of benefit for a while—since the MiniMed 670G in 2016. Pumps decrease hypoglycemia, allow for rapid-acting insulin covering both basal and bolus, [and] allow patients to count carbs, use correction doses, and look at insulin on board. Having a CGM that communicates with an insulin pump and makes insulin delivery decisions every 5 minutes not only prevents hypoglycemia substantially but also decreases time in hyperglycemia.

AJMC®: How do tubeless AID systems impact the autonomy of patients and their caregivers?

Criego: For caregivers, a tubeless system is very nice for 3 reasons. First, not having to worry about tubing gives the caregiver options for placement on the child's body. Second, caregivers do not have to worry about the pump being disconnected for long periods of time. This impacts younger children, older children, and adolescents. There are many young athletes who don't like to have their tubed pump connected during competitions or practices. However, disconnecting the pump can lead to prolonged disconnections and hyperglycemia. A tubeless system offers the opportunity to still receive insulin delivery and insulin modulation during athletics. Users will continue to have on-body automation even when they don't have the controller or app close by. Third, the ability to administer insulin doses from the controller device is beneficial during the daytime with active children and beneficial overnight when sleep may be disrupted if a tubed/connected pump for insulin delivery needs to be found.

Bode: Omnipod® 5's tubeless system benefits patients of all ages. [For example], children often tear off tubes, whereas older adults with diabetes may struggle to fill up tubing or manually inject insulin. In my experience, patients who don't like to work with the tubes have been using Omnipod® [devices] for a long time.

AJMC®: How may the tubeless AID impact complications associated with T1D?

Criego: Regarding complications, in the short term we focus [mainly] on severe hypoglycemia and DKA. AID systems

Omnipod® 5 Automated Insulin Delivery System (*continued*)

The **Omnipod 5 ACE Pump (Pod)** is intended for the subcutaneous delivery of insulin, at set and variable rates, for the management of diabetes mellitus in persons requiring insulin. The Omnipod 5 ACE Pump is able to reliably and securely communicate with compatible, digitally connected devices, including automated insulin dosing software, to receive, execute, and confirm commands from these devices. SmartAdjust™ technology is intended for use with compatible integrated continuous glucose monitors (iCGM) and alternate controller enabled (ACE) pumps to automatically increase, decrease, and pause delivery of insulin based on current and predicted glucose values.

can help with the prevention of severe hypoglycemia by decreasing or completely stopping insulin delivery proactively. Available systems reduce the time below range and the time in the very low range, which reduces short-term risk for severe hypoglycemia. Long-term complications are known to be associated with hypoglycemia and hyperglycemia. In the study by Brown et al, there were 3.7 more hours each day spent in the target glucose range (70-180 mg/dL) using the Omnipod® 5 System vs standard therapy for the pediatric population. Cumulatively, that's getting close to 2 months out of a year. If a person receives a diagnosis with T1D at age 6, [for example,] by age 26, that's close to 3.5 more years over that 20-year duration that an individual will have spent with their glucose in range; this will decrease long-term complications.

Bode: Study results indicated that patients with diabetes, aged 50 years to 70 years, who used the Omnipod® 5 System remained in the target glycemic range for, on average, 79% of the time. Spending 70% or more of one's time in range—with HbA_{1c} less than 7%—can markedly decrease long-term outcomes for complications such as retinopathy, nephropathy, and peripheral neuropathy, as well as cardiovascular disease.

AJMC®: Placing the pump on the bodies of kids can be a struggle. Might the use of a tubeless system ameliorate this?

Criego: The tubeless system greatly increases the reliability of the insertion because there are fewer steps. The patient [or their caregiver] adheres the Pod to the body and taps the controller or compatible smartphone to automatically insert the cannula to deliver insulin. There is no difference in the angle of insertion, which can be a problem with some of the tubed pumps. It's also nice for use in children because they

“The tubeless system greatly increases the reliability of the insertion because there are fewer steps.”

—Amy B. Criego, MD, MS

can't see the needle. Most of the children in the study were already wearing a CGM. The feeling of the insertion and the wearing of the Omnipod® 5 device are both very similar to the insertion experience with the CGM. In the study, the children who came over from injection therapy transitioned easily to the tubeless system. In my opinion, it's a win for the children and for the parents to manage the child's diabetes without worrying about the tubing, which may lead to a site being more easily dislodged with activity.

AJMC®: Were there aspects of the clinical trial design and results that stood out to you?

Criego: The personalized glucose targets were shown to give caregivers comfort with their children and the target glycemic ranges. Many parents started their child at a higher range, then subsequently gained confidence in the device to keep their child in range. That was a big win. The time below range improved no matter what the glucose target was. There wasn't any decrease in that improvement if the target was 110 mg/dL

Omnipod® 5 Automated Insulin Delivery System (continued)

The **Omnipod 5 SmartBolus Calculator** is intended to calculate a suggested bolus dose based on user-entered carbohydrates, most recent sensor glucose value (or blood glucose reading if using fingerstick), rate of change of the sensor glucose (if applicable), insulin on board (IOB), and programmable correction factor, insulin to carbohydrate ratio, and target glucose value.

vs 140 mg/dL, which was nice to see. I wasn't surprised by the findings; I knew time below range was going to be improved from what we were doing with standard therapy.

Bode: Regarding design, the Omnipod® 5 study was similar to the study that the Medtronic 670G system had to do to get FDA clearance. The Omnipod® 5 study investigators enrolled both adults and children. The trial began with a 2-week standard therapy phase to establish baselines, continued with AID for 3 months, and extended up to another 12 months or longer. Investigators examined change in HbA_{1c} and TIR between 70 mg/dL and 180 mg/dL as well as time below 70 mg/dL, below 54 mg/dL, above 180 mg/dL, and above 250 mg/dL. They studied 2 primary safety outcomes: DKA and severe hypoglycemia.

Regarding exciting results, there were several. First, TIR improved dramatically: from 64.7% to 73.9% in adolescents and adults. The HbA_{1c} for adolescents and adults also went from 7.16% to 6.78%. Use of the Omnipod® 5 System demonstrated a statistically significant improvement for both outcomes (both $P < .0001$). For children, mean baseline time in glucose range above 180 mg/dL was 45.3%; this fell to 30.2% at the end of the study. Those patients also saw a decrease in HbA_{1c} from 7.67% to 6.99%. Fifty-three percent of the children in the study had an HbA_{1c} under 7%, which is very difficult for children [to maintain]. Only 23% of the children who entered the trial had an HbA_{1c} below 7% at baseline.

AJMC®: Regarding safety, were the adverse event rates that were seen expected?

Criego: Yes. They were typical for any sort of pump therapy. There were some skin reactions to the adhesives. These were

addressed with skin preparation before insertion. There was some hyperglycemia, which can happen when a cannula gets dislodged. The adverse events were consistent with real-life use and were minimal. The majority of study participants have continued to use the delivery system; there was nothing that made anyone want to stop using it. In my opinion, that speaks volumes.

Bode: Severe hypoglycemia and DKA were the major safety end points. Out of the 128 adults in this study, 2 experienced severe hypoglycemia. That [translates to] an average of 6 adults per 100 per year. According to the T1D Exchange Registry, normally, 25 adults per 100 will have severe hypoglycemia in a year. Also, no adults experienced DKA. Normally, about 11 adults per 100 per year will have DKA. One child had severe hypoglycemia and 1 child had DKA. Both incidents were much lower than average; per 100 person-years, 25 children normally have severe hypoglycemia and 10.8 will have DKA, according to the T1D Exchange Registry.

AJMC®: The Omnipod® 5 System allows users to set customizable glucose targets. What is the impact of that feature on the management of T1D in children and adults?

Criego: The personalization of the glucose targets was key. With the other systems, users have a set glucose target. Study participants really valued the ability to have a different target during the day or the night, up to 8 targets. Another unique feature is the bolus delivery calculations that are adjusted for trending arrows. That's especially nice for children, who tend to have more glucose variability and more frequent eating than their adult counterparts.

Omnipod® 5 Automated Insulin Delivery System (*continued*)

Warning: SmartAdjust technology should NOT be used by anyone under the age of 6 years old. SmartAdjust technology should also NOT be used in people who require less than 6 units of insulin per day as the safety of the technology has not been evaluated in this population.

Bode: Most participants chose glucose targets between 110 mg/dL and 120 mg/dL. Some chose 130 mg/dL and 150 mg/dL for exercise. Patients shared with us that they loved this feature. A female patient in the study, aged 24 years, who is continuing to use the Omnipod® 5 System, told me, “It’s the best thing ever.” She’s doing very well with the Pod. She uses a glucose target of 120 mg/dL because she’s able to get under 7% HbA_{1c} with that target very easily: she’s at 6.2%. She’s at goal and has no hypoglycemia. Before using the Omnipod® 5 System, she experienced a lot of hypoglycemia. The customizable targets allow patients to select a range that is safe for them and provides more individualized diabetes management.

AJMC®: Another feature of the Omnipod® 5 System is “Activity,” which was referred to as “HypoProtect” in the pivotal studies. This can be utilized in times of reduced insulin needs. Who would be best suited to use this feature?

Criego: Our study population includes quite a few athletes. They practice all types of athletics—from soccer to cross country to hockey—and different kinds of exercise, from intermittent exercise to more continual cardiovascular exercise. Activity helps patients avoid the hypoglycemia that can occur for some of them both during an athletic event and, for some, after the event, when they settle down after that big adrenaline surge. It’s also nice for children at daycare and for events that can come up spontaneously.

Bode: When a patient wants to limit insulin delivery during instances when they typically go low, such as exercise, Activity sets the glucose target at 150 mg/dL and automatically restricts insulin delivery.

“The customizable targets allow patients to select a range that is safe for them and provides more individualized diabetes management.”

—Bruce W. Bode, MD

AJMC®: Is there any impact on the overnight period, when glycemic levels in children can fluctuate?

Criego: Participants have chosen different glucose targets for nighttime. Some children went on overnight visits at friends’ houses and the parents used overnight targets as an extra safety feature.

AJMC®: The Omnipod® 5 System is cleared for use in patients with type 1 diabetes who are aged at least 6 years. In your opinion, what aspects enable the system’s use in this population?

Criego: Many of our younger patients have chosen the tubeless system because they are mobile and active. And the adolescents may not want to deal with the tubing; they ask,

Omnipod® 5 Automated Insulin Delivery System (continued)

The Omnipod 5 System is NOT recommended for people who are unable to monitor glucose as recommended by their healthcare provider, are unable to maintain contact with their healthcare provider, are unable to use the Omnipod 5 System according to instructions, are taking hydroxyurea as it could lead to falsely elevated CGM values and result in over-delivery of insulin that can lead to severe hypoglycemia, and do NOT have adequate hearing and/or vision to allow recognition of all functions of the Omnipod 5 System, including alerts, alarms, and reminders. Device components including the Pod, CGM transmitter, and CGM sensor must be removed before Magnetic Resonance Imaging (MRI), Computed Tomography (CT) scan, or diathermy treatment. In addition, the Controller and smartphone should be placed outside of the procedure room. Exposure to MRI, CT, or diathermy treatment can damage the components. Visit www.omnipod.com/safety for additional important safety information.

“Where will I put it in my clothing?” “Where am I going to carry it?” The Omnipod® 5 System alleviates those concerns with an on-body experience for automation and a remote device or app for bolus delivery.

Bode: In my opinion, it is going to be very successful because it's so simple. The patient fills up the Pod with rapid-acting insulin; places the Pod on their arm, back, flank, or leg; and taps the controller or compatible smartphone to automatically insert the cannula to deliver insulin. The Omnipod® 5 System then adjusts insulin every 5 minutes, accounting for not only the current glucose sensor reading but also the rate of change whether the sensor is going up or down. The Omnipod® 5 System adapts with every Pod change. Up to every 3 days, the patient will fill another Pod with rapid-acting insulin and will continue to manage boluses for food.

AJMC®: What are the implications of the availability of the Omnipod® 5 System through the pharmacy benefit? How does this impact how you prescribe them?

Criego: We hope that patients will continue to be able to obtain their Omnipod® 5 System through pharmacy channels. [For example], the copay for the Omnipod DASH® System may be lower for some patients when the device is obtained through pharmacy channels. They're not locked into the typical 4-year insurance contract and warranty seen with tubed devices. This has been a nice change from traditional channels for pump therapy. Patients can go through pharmacy channels for continuous glucose monitoring, too. Going through pharmacy channels eases access for patients and their families and creates much less paperwork for providers. Less paperwork

for providers means the end user will have the product in hand to manage their diabetes sooner.

Bode: As a provider, it is much easier to go through the pharmacy benefit. For patients on Medicare, for example, going through Medicare's durable medical equipment [DME] coverage takes more time. If the device doesn't arrive to the patient on time, they may have to go back to injections and even come off the sensor [while they are waiting]. It's a disaster. Coming from pharmacy makes it easier. If a Pod falls out and the patient doesn't have it, they can get one from the pharmacy.

Regarding prescribing, it's much easier for me. DME always requires multiple forms and sometimes requires follow-up information. The process can be slow and frustrating. Going through pharmacy is much better. From a managed care perspective, in my opinion, it's incredible.

AJMC®: The Omnipod® 5 System will be offered at a price parity with Omnipod DASH®. What does this mean for managed care?

Bode: The Omnipod® 5 System will be priced at the same level as the Omnipod DASH® System. This system contains a Pod with an embedded algorithm, communicates with the Dexcom G6, and is fully operable with a compatible personal phone, but at no price increase to payers.

AJMC®: What do each of you take away from these results?

Criego: The increased TIR and the reductions in HbA_{1c} across all age groups speak for themselves. There will be some long-term data forthcoming. It's hard to believe that we were in the

Omnipod DASH® Insulin Management System Important Safety Information

The Omnipod DASH® Insulin Management System is intended for subcutaneous delivery of insulin at set and variable rates for the management of diabetes mellitus in persons requiring insulin. Additionally, the Omnipod DASH® System is interoperable with a compatible blood glucose meter to receive and display blood glucose measurements. The Omnipod DASH® System has been tested and found to be safe for use with the following U-100 insulin: NovoLog®, Humalog®, Apidra®, Fiasp®, Lyumjev®, or Admelog®. Refer to the Omnipod DASH® Insulin Management System User Guide at omnipod.com for complete safety information including indications, contraindications, warnings, cautions, and instructions.

pre-pivotal study that started in December 2019. I feel like this is already in my clinical practice because these patients have been using the Pod for so long now as study participants that it almost seems like it is already available. I can't wait for the rest of the providers and patients to have the opportunity to try this if they want to. We talk about it a lot. I work with 4 other pediatric endocrinologists, so they're fully aware of the results that have been published. The sustainability of those results is going to be interesting to watch now that we have patients who have been in this study for so long. Again, the

usability and continued use of the research device with no one wanting to opt out at our site speaks to the point that not only do we see it as successful, but that patients are continuing to want to use it, and so they're seeing the benefits at home, too.

Bode: What's amazing to me is that almost no one dropped out of the study, even at the end. Participants liked it so much that they just continued. Ninety-two percent of the adult participants and 99% of the children continued to use it. It's phenomenal that [it is] that successful. •

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