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Authors
Nguyen, Kevin T
Xu, Nicole Y
Buckingham, Bruce A
et al.

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Improving the Patient Experience With Longer Wear Infusion Sets Symposium Report

Kevin T. Nguyen, BA[1], Nicole Y. Xu, BA[1], Bruce A. Buckingham, MD[2], Sarnath Chattaraj, PhD, MS[3], Ohad Cohen, MD[4], Lutz Heinemann, PhD[5], John Pickup, MA, BM, DPhil, DSc, FRCPath[6], Jannet Svensson, MD, PhD[7], Robert A. Vigersky, MD[3], Jenise C. Wong, MD, PhD[8], and Ralph Ziegler, MD[9]

Abstract

Continuous subcutaneous insulin infusion (CSII) therapy is becoming increasingly popular. CSII provides convenient insulin delivery, precise dosing, easy adjustments for physical activity, stress, or illness, and integration with continuous glucose monitors in hybrid or other closed-loop systems. However, even as insulin pump hardware and software have advanced, technology for insulin infusion sets (IISs) has stayed relatively stagnant over time and is often referred to as the "Achilles heel" of CSII. To discuss barriers to insulin pump therapy and present information about advancements in, and results from clinical trials of extended wear IISs, Diabetes Technology Society virtually hosted the "Improving the Patient Experience with Longer Wear Infusion Sets Symposium" on December 1, 2021. The symposium featured experts in the field of IISs, including representatives from Steno Diabetes Center Copenhagen, University of California San Francisco, Stanford University, Medtronic Diabetes, and Science Consulting in Diabetes. The webinar's seven speakers covered (1) advancements in insulin pump therapy, (2) efficacy of longer wear infusion sets, and (3) innovations to reduce plastics and insulin waste.

Keywords

diabetes, infusion set, insulin, insulin pump, longer wear, waste

Introduction

The use of insulin pumps by people with diabetes (PwD) is increasing, as technology improves and data accumulates indicating the benefits of constant but adjustable basal insulin infusion and convenient accurate insulin bolus delivery. Data from the Type 1 Diabetes (T1D) Exchange clinic registry comparing an initial cohort from 2010 to 2012 to a later cohort from 2016 to 2018 demonstrated that the percentage of people with T1D using insulin pumps increased across all age groups from 57% to 63%.[1]

Continuous subcutaneous insulin infusion (CSII) from a pump depends on the reliable administration of insulin into the subcutaneous space via an insulin infusion set (IIS). An IIS typically sits on the skin and is affixed to the body with an adhesive patch. A steel or Teflon cannula at the end of the IIS is implanted in the subcutaneous tissue, allowing insulin infusion into the subcutaneous tissue. However, even as hardware for delivery and software for dosing and monitoring delivery have been advancing, technology for IISs has stayed relatively stagnant and IISs have been referred to as the "Achilles heel" of subcutaneous insulin infusion.[2]

IISs continue to be associated with variety of complications. The incidence of such complications increases with extended wear time beyond the indicated time on the label. Nevertheless, many PwD prefer to use their IISs and insertion sites longer than the manufacturer-recommended duration to minimize pain with insertion procedures and reduce costs.[3]

IIS reactions can include occlusion, kinking, and insertion site reactions, such as irritation, infections, lipohypertrophy,

[1]Diabetes Technology Society, Burlingame, CA, USA
[2]Stanford University, Stanford, CA, USA
[3]Medtronic Diabetes, Northridge, CA, USA
[4]Medtronic Diabetes EMEA, Tolochenaz, Switzerland
[5]Science Consulting in Diabetes GmbH, Kaarst, Germany
[6]Faculty of Life Sciences & Medicine, King's College London, London, UK
[7]Steno Diabetes Center Copenhagen, Herlev, Denmark
[8]University of California, San Francisco, San Francisco, CA, USA
[9]Diabetes Clinic for Children and Adolescents, Muenster, Germany

Corresponding Author:
Kevin T. Nguyen, BA, Diabetes Technology Society, 845 Malcolm Road Suite 5, Burlingame, CA 94010, USA.
Email: kevin.nguyen9217@gmail.com

and variable insulin absorption, all of which could interfere with metabolic control.[4] Because of problems associated with prolonged IIS wear, until this year, all U.S. Food and Drug Administration (FDA)-cleared IISs have been indicated for a maximal usage time of two to three days. In July 2021, Unomedical ConvaTec/Medtronic received FDA clearance for the first IIS that can be worn up to seven days.[5] No other IIS product is FDA-cleared for this duration. Other companies currently working to develop extended wear infusion sets (EWISs) include ConvaTec[6] and Capillary Biomedical.[7]

EWISs will make it possible to use an IIS for a longer period of time without changing the set. If good glycemic control can be maintained with the same IIS for more than three days, then this could improve the quality of life of insulin pump users. Additional outcomes of EWIS usage will be reduction of insulin waste, plastic waste, and adverse events.

On December 1, 2021, Diabetes Technology Society presented a webinar entitled "Improving the Patient Experience with Longer Wear Infusion Sets Symposium." This three-part report summarizes the main topics of the webinar and (1) characterizes advancements in insulin pump therapy, (2) efficacy of longer wear infusion sets, and (3) innovations to reduce insulin and plastic waste.

Section 1: Advancements in Insulin Pump Therapy

Jannet Svensson, MD, PhD

Chief Physician in Pediatrics, Department of Pediatrics and Adolescent Medicine, Steno Diabetes Center Copenhagen, Herlev, Denmark

Key Points

- Issues with wearability and unmet expectations are two major barriers for patients on insulin pump therapy.
- Healthcare professionals need to educate their patients about both the benefits and challenges when using insulin pumps to ensure that expectations are realistic.
- When it comes to overcoming barriers to insulin pump therapy, proper training may be more important than the access to equipment.

Jenise C. Wong, MD, PhD

Associate Professor of Pediatrics, University of California San Francisco, San Francisco, California, USA

Key Points

- Insulin pumps can improve patient experience and quality of life.
- Pumps may have psychological effects which can negatively impact the patient experience.
- Patient experience with pumps can be improved with education, proper support, and innovations in design which reduce burden.

Sarnath Chattaraj, PhD, MS

Senior Research Director, Medtronic Diabetes, Northridge, California, USA

Key Points

- Continuous inflammation induced by insulin instability is an important target for lengthening the duration of infusion set wear
- Novel approaches have been developed for IISs that mitigate insulin aggregation and preservative loss, as well as those that improve adhesive performance
- Extended wear technology is currently being advanced to other devices to reduce user burden for people living with diabetes

Overcoming Barriers to Insulin Pump Therapy

Various reasons for dissatisfaction with current IISs limit their popularity among PwD. These reasons include issues with wearability, such as allergic reactions to the adhesives used to secure the devices and other comfort issues.[8,9] Inflammation, skin irritation, or local infections can occur at the insertion site if IISs are worn longer than recommended. Additionally, smaller children with diabetes have fewer skin sites available to rotate their IISs, increasing risk of skin irritation. Active PwD playing contact sports may fear damaging the equipment or the equipment may harm the body when hit during sport. PwD and their caregivers may also worry about malfunction, such as occlusions and kinking of the catheter which interrupt the flow of insulin, or unexplained hypoglycemia, which can occur if insulin is erroneously delivered.

PwD may also be frustrated if CSII therapy does not perform to their expectations. Many PwD who begin CSII therapy expect the processes to be more automated than they are, requiring little input from the user.[10,11] However, refilling insulin, priming IIS tubes, monitoring glucose, counting carbohydrates, and correcting bolus doses, among other things, can be time consuming. Additionally, the timing of IIS replacement every third day may be inconvenient. If the target glucose is not reached, then the troubleshooting of CSII can be complex. Knowing whether the insulin is injected or the IIS is malfunctioning is not always obvious and patients who do not have the ability to troubleshoot the pump may feel anxious about using IISs.[12,13] Furthermore, the amount of equipment one needs to bring on vacation may be

overwhelming. The current IISs are not suitable for extended wear and must be replaced every two to three days.

Improving the Patient Experience With Insulin Pump Therapy

Many PwD turn to their healthcare professionals (HCPs) to educate and train them to properly use and troubleshoot their IISs, which puts HCPs in a unique position to impact the patient experience with CSII therapy. During initial visits, HCPs should discuss both the advantages and disadvantages of pumps and IISs to set clear expectations. HCPs can also offer trials and samples, allowing their patients to try multiple types of IISs before committing to CSII therapy. HCPs should also address behavioral health; if pumps cause or contribute to diabetes distress, burnout, and/or anxiety, HCPs can make sure their patients receive the proper support.[14] This can be through open communication and frequent check-ins with the healthcare team, but also through connecting patients with peers, support groups, or online communities where patients can learn what others have experienced as well.

Innovations in insulin pump and IIS design will also contribute positively to the patient experience. Improvements in the reliability and durability of IIS to allow for longer wear are currently being researched, developed, and manufactured. Anticipated advances to reduce the size of devices and minimize user work through automatic data capture and a reduced need for data review will further improve the patient experience.

Insulin Stability and Longer Wear Infusion Sets

From the time insulin is produced by a manufacturer until the time the insulin is administered to a patient via an IIS, the insulin has been subjected to conditions of temperature and physical agitation that may not be ideal for insulin stability.[15] Additionally, in vitro insulin lispro and insulin aspart stability testing has demonstrated that less than 50% of the preservative content remained in the insulin reaching the catheter when pumped with the traditional IISs. Preservatives play a crucial role in insulin stability by preventing insulin aggregation and subsequently, local inflammation.[16] Dynamic light scattering has shown greater formation of insulin aggregates with infused insulin containing reduced preservative concentrations compared to normal preservative concentrations. Furthermore, an in-vitro macrophage cell culture study has observed an increased amount of associated cytokine production from insulin containing reduced preservative concentrations compared to normal concentrations.[17] Additionally, preservative loss and insulin aggregation contribute to decreased IIS wear duration, increased rate of occlusions (with cannula occlusion by insulin aggregates being the main cause for site loss), and IIS failure.

From their research, Medtronic Diabetes has identified and applied mitigations for insulin aggregation to develop the Medtronic Extended Infusion Set (MEIS).[18] Compared to standard IISs, the MEIS features a new proprietary H-Cap connector[17,19] that improves insulin stability and infusion set site performance, a new IIS tubing[17,19] that improves preservative retention and insulin stability, and a new adhesive patch[20] that improves adherence to skin for longer durations while also retaining wear comfort and easy removal. These advancements in IIS components have allowed the MEIS to extend device wear duration to seven days by mitigating some of the fundamental insulin stability challenges facing standard IISs.

The MEIS is now CE marked and FDA cleared. Additionally, the MEIS has been approved for cross labeling for 7-day use along with insulins such as insulin aspart.[21] Labels on both the MEIS and insulin will go hand-in-hand to allow PwD to wear an IIS for up to seven days.[22] MEIS is currently available on the European market and will soon be available in the United States (US). Medtronic has completed feasibility assessments of the MEIS with ultra-rapid acting insulins and is now beginning formal clinical studies to achieve expanded labeling on more ultra-rapid acting insulins. In the future, Medtronic will be able to apply the mitigations and platform technology developed for MEIS to enable extended wear on IISs with angled cannulas and more value-oriented IISs with reusable inserters.

Section 2: Efficacy of Longer Wear Infusion Sets

Ohad Cohen, MD
Director of Medical Affairs, Medtronic Diabetes EMEA, Tolochenaz, Switzerland

Key Points

- There is an unmet need for longer insulin infusion set wear duration in pump users
- Today we are sharing some of the key exploratory pump system outcomes of the pivotal trial with Medtronic Extended Infusion Set.
- The results of the trial demonstrate that the device met the safety endpoints of the study in the hybrid closed loop system.

Bruce Buckingham, MD
Stanford University, Stanford, California, USA

Key Points

- The MEIS U.S. pivotal trial assessed two criteria for unexplained hyperglycemia and demonstrated a low rate of infusion set failure for both definitions of unexplained hyperglycemia.

- Compared to other studies on 7-day infusion set wear, a greater percentage of users were able to wear the MEIS until scheduled removal.
- Based on all EWIS study results, no new safety issues were identified with 7-day MEIS use in seven days compared to studies for 3-day standard sets in three days.

Comparison of Efficacy and Performance of 2- to 3-Day Sets vs. Extended Infusion Sets on Comfort and Duration of Wear

To assess the efficacy of the MEIS featuring the new H-Cap connectors, extended wear tubing, and improved adhesive patches, Medtronic conducted a pivotal study of 259 participants and 3041 IISs across 15 investigational sites. Participants first wore a standard, 2- to 3-day IIS for two weeks to establish a baseline, and then wore MEIS for 174 hours or until set failure for 12 consecutive weeks. The goal of the study was to determine the rate of IIS failure due to unexplained hyperglycemia, which was a major risk factor preventing extended wear for standard sets. IIS failure due to unexplained hyperglycemia was defined by one of two criteria.

Criteria 1 (used in the MEIS Pivotal Study)

- A blood glucose meter (MBG) reading greater than 250 mg/dL (more than 3 hours postmeal) and failure of a correction dose to lower the BGM reading by at least 50 mg/dL within 60 minutes.
- One additional bolus correction was allowed after the initial bolus to lower the MBG by at least 50 mg/dL within 90 minutes after the second correction.
    - This second correction bolus was used to overcome partial occlusion that may have been resolved by the time the second correction bolus was administered.

Criteria 2 (used in previous studies of other EWISs)

- A fingerstick blood glucose that does not decrease by at least 50 mg/dL within 1 hour of a correction bolus for a fingerstick glucose greater than 250 mg/dL
- OR the presence of serum ketones greater than 0.6 mmol/L with a glucose greater than 250 mg/dL

Results from the U.S. Pivotal study using both criteria for unexplained hyperglycemia demonstrated very low rates of unexplained hyperglycemia, even when compared to the rate of unexplained hyperglycemia in standard 3-day sets at day three.

In studies that defined the first criteria, both insulin lispro and insulin aspart were examined and IIS failure rate due to unexplained hyperglycemia was determined. There were two episodes of unexplained hyperglycemia in the insulin lispro group for a 0.13% incidence and an upper limit of confidence interval of 0.51% failure. There were six such episodes in the insulin aspart group for a 0.41% incidence and an upper limit of confidence interval of 1.00% failure. Both the insulin lispro and insulin aspart groups met the prespecified threshold of 20% for the upper limit of confidence interval.

When the presence of serum ketones was defined in studies for the second criteria, the rate of IIS failures due to unexplained hyperglycemia remained low. There were 37 events, which was a 1.2% incidence of glucose being above 250 mg/dL and blood ketones being greater than 0.6 mmol/L. By both criteria, there was less than a 1.5% incidence of unexplained hyperglycemia with seven days of infusion set wear.

Results from the study comparing a 3-day standard infusion set to the 7-day MEIS demonstrated that the EWIS had a better survival rate compared to the standard 2- to 3-day set on day one, a better survival rate at day three (the MEIS had a 15%-18% better survival rate than standard IISs at day three), and an equivalent survival rate of the EWIS on day seven compared to a 3-day set on day seven.[23-25]

When comparing reasons for failure between the MEIS pivotal study and data from previously conducted studies on other standard 3-day sets, the MEIS demonstrated fewer accidental removals, adhesive issues, leakage issues, removals due to site discomfort, mechanical failures, unexplained hyperglycemia, presence of serum ketones, presence of infusion site infections, kinked cannulas, and occlusions.[6,23,26,27] In all, 77.8% of patients wearing the MEIS removed the IIS on the scheduled date (after 168 hours) compared to only 48% of patients wearing other ISs.

Pivotal Data of Extended Insulin Infusion Technology

The pivotal study also demonstrated other favorable patient outcomes compared to use of the standard 3-day sets, including an overall reduction in HbA1c, especially for those with higher HbA1c at baseline for both the insulin lispro and insulin aspart groups. Time in Range (TIR) was maintained through the seven days across all age groups and actually improved by 2.8%. Patients on MEIS spent more TIR than patients using standard IIS. Finally, the total daily dose (TDD) was not altered across the 7-day wear time; no change in insulin dosage was needed to maintain target glycemic control.

In addition to the reduced HbA1c and increased TIR, the MEIS met several other safety endpoints. No new safety issues were identified using this 7-day system compared to studies for 3-day systems. There were no Serious Adverse Events, no Serious Adverse Device Effects and Unanticipated Adverse Device Effects, no Severe Hypoglycemia. Severe Hyperglycemia was equivalent to the 3-day infusion sets at

less than 3%. There were no instances of diabetic ketoacidosis and the rate of skin infections was less than 1%, a lower rate than was seen in a number of previous IIS studies. Additionally, all subjects recovered from infections without sequelae. Although lipohypertrophy, a complication of both multiple daily injections (MDI) and CSII therapy related to the anabolic effects of insulin (44% to 53% prevalence), is a cause for concern, no lipohypertrophy-related issues were reported during the pivotal study, and future studies have been designed to specifically examine risk for lipohypertrophy when using the MEIS.

At the end of the pivotal study, patient satisfaction with the MEIS was surveyed and compared to satisfaction scores obtained for standard set use at the beginning of the study. Categories of satisfaction included ease of insertion, comfort of wear, duration of wear, time required to change, and the convenience of use. Patient responses revealed a statistical improvement in mean satisfaction scores at end of study compared to baseline. Additionally, the percentage of users who expressed extreme satisfaction with their infusion sets also increased in every category, meaning that patients who were already happy with the 3-day set were even more satisfied when they switched to the MEIS.

Section 3: Innovations to Reduce Plastic and Insulin Waste

Robert Vigersky, MD

Chief Medical Officer, Medtronic Diabetes, Washington, District of Columbia, USA

Key Points

- Insulin wastage while changing infusion sets and reservoirs occurs in three ways: (1) during routine reservoir change with the infusion set, (2) during priming of the tubing, and (3) during early reservoir change if the infusion set fails.
- If an infusion set is changed every seven days instead of every three days, the amount of wastage based on a total daily dose of insulin of 35, 46, or 62 units per day is reduced from 8000 to 9000 units to 3500 to 6000 units per year depending on the length of the tubing.
- The cost savings accrued by using an extended wear infusion set is $881 to $1677 per year.

Lutz Heinemann, PhD

Science Consulting in Diabetes GmbH, Kaarst, Germany

Key Points

- Diabetes sustainability and waste management is a complex topic. The Green Diabetes Declaration is the first declaration or initiative linking medical devices for any disease with the environment and the disease example is diabetes, which affects more people and requires more measurements and more decisions on a daily basis than any other disease. Changes have to be made at all levels: patients, hospitals, practices, and storage.
- Manufacturers are starting to implement sustainability and waste management strategies, but more needs to be done. These topics should be central to all considerations about the design and packaging of new medical devices.
- The use of a 7-day infusion set reduces the amount of plastic waste by 55% to 63% compared to a 3-day set or single use syringes, resulting in a more environmentally sustainable option for insulin therapy.

Cost Savings of Reduced Insulin Waste With Longer Wear Sets

Advancements to extend IIS wear duration not only demonstrated improved patient outcomes, they can also represent potential, significant savings in the cost of insulin per year. Because of the nature of IIS technology, a substantial amount of insulin wastage is associated with set change. There are three areas where insulin is lost during a reservoir change or IIS change. The first is reservoir change waste, which involves unusable insulin (which is about 41.3 units)[28] that remains in the reservoir after it is replaced. This means that each time a reservoir is exchanged on its scheduled change date, 41.3 units of insulin are lost. The second is infusion set change waste, which consists of different amounts of insulin that are used for priming and filling the IIS tubing. The amount of insulin lost depends on whether a person with diabetes is using a standard IIS or an EWIS, as well as the length of the tubing. The range of infusion set change waste is 17.4 to 25.1 units each time an IIS is replaced.[28] The third is residual reservoir waste, which involves the insulin remaining in the reservoir when the IIS fails within one day of a scheduled set change. In other words, although the insulin in the reservoir is not completely used, the reservoir must be removed early with less than one day of insulin remaining. The amount of insulin lost depends on the patient's TDD and can range from 289 to 512 units per year for a 2- to 3-day set, or 72.8 to 258 units per year for a 7-day set.[28]

Differences in device lifetimes between the standard IIS and EWISs also contribute to differential insulin wastage. A standard set without failures will last 72 hours before it must be removed and replaced. However, additional set changes are required whenever set failures shorten the IIS lifetime. The average standard set lifetime is 65.95 hours, meaning PwD will need 132.8 sets for a full year. On the other hand, an EWIS without failures will last 168 hours, but has an average lifetime of 151.6 hours, meaning PwD will need 57.8 sets per year.

Taking each factor/source of insulin waste into consideration, the average cost of wasted insulin per year can be modeled. Regardless of whether the 23-inch tubing or the 46-inch tubing is used, the EWIS contributes to less insulin wasted and therefore a lower annual cost of insulin for PwD. Taking the market cost of insulin to be $338.44/1000 units, the calculated annual savings range from $881 to $1677 depending on the TDD.[28] This estimate does not factor into account any additional cost savings from minimizing adverse events or by reducing plastic wastage. Future studies have been developed to assess the actual cost-effectiveness of saved insulin and the number of quality-adjusted life years gained by using the MEIS.

The Green Initiative to Reduce Plastic and Insulin Waste

The use of EWISs also leads to ecological savings in the form of reduced plastic waste, which will help alleviate a very serious but complex issue of sustainability in medical devices. By 2030, annual plastic emissions are predicted to reach up to 53 million metric tons per year.[29,30]

On July 21, 2021, Diabetes Technology Society convened the Green Diabetes Summit (GDS), a milestone event to discuss for the first time in an international forum how diabetes affects the environment.[31] The GDS assembled healthcare professionals, representatives from patient organizations, waste management experts, government agencies, and device manufacturers from the U.S. and six European countries. The purposes of the GDS were (1) to provide background on the complexity of diabetes device sustainability and waste management from a variety of perspectives, and (2) to determine the feasibility and role of a coalition of stakeholders to address issues in sustainability and waste management that no single stakeholder can resolve on their own. The GDS determined that there is a need to form coalitions and now is the time to stop environmentally damaging processes caused by the production and disposal of diabetes devices, and the resulting "Green Declaration" put forward a set of twelve programmatic goals to which all stakeholders can aspire.[32]

The question remains how to move forward. The European Strategy for Plastics in a Circular Economy was adopted in January 2018 to reduce greenhouse gas emissions and dependence on imported fossil fuels. By 2030, all plastics on the European market must be reusable or recyclable in a cost-effective manner.[33] It is not a secret that the medical device industry generates a lot of plastic waste each year. While each medical device requires its own solutions to improving sustainability, there are common design considerations that manufacturers should apply. For example, manufacturers should strive for bio-based, recyclable, or reusable materials, smaller products with minimal packaging, ecologically friendly manufacturing processes, reduced long-distance transportation and volume, and fewer single-use devices.

The MEIS is one potential solution to the issue of medical device sustainability. As insulin pump and IIS use continues to increase, the single-use nature and frequent replacements of standard 2- to 3-day IISs contributes to a significant amount of annual plastic and insulin waste. A Medtronic study compared two single-use syringes and six commercial, serter-incorporated IISs with various tubing lengths and determined the average amount (kg/year) of disposed plastic at the end of each product service life. The study results found that when EWISs were used in place of standard IISs, 1,820 kg/year of plastic waste per 1000 users was saved. The introduction of 7-day IISs is estimated to reduce annual plastic waste by between 55% to 63% relative to usage of existing single-use syringes and 2- to 3-day IISs, representing a significant reduction in diabetes-associated plastic waste for both the product itself and its packaging.

Changes must be made at all levels. Manufacturers are beginning to react to increased pressure from patients and government for medical device sustainability regulations, but more actions are needed. The topics of sustainability and waste management should be central to all considerations for product design, including product packaging. We will all have to move out of our comfort zones, and we should start this change today.

Conclusion

Insulin pump therapy is effective, but it requires overcoming technological and psychological barriers. One barrier that has bothered many patients is poor performance of IISs and the need to change them as frequently as every two to three days. Recent product design by Medtronic has led to development of the EWIS system, which has received both FDA clearance and a CE Mark for seven days of use. Data from investigational and pivotal trial have demonstrated that this new IIS is associated with less hypoglycemia and fewer site complications compared to traditional 3-day IIS systems. The use of extended wear IIS systems compared to traditional 2- to 3-day systems is expected to result in three significant positive outcomes. We expect to see: first, an improvement in patient experience with insulin pump therapy due to increased reliability and durability of IISs; second, considerably less wasted insulin, due to fewer necessary site changes; and third, considerably less plastic being used, due to fewer IIS systems being discarded. Thus, the use of EWIS devices for IIS wearers will provide psychological, economic, and environmental benefits.

Abbreviations

CE, Conformitè Europëenne; CSII, continuous subcutaneous insulin infusion; EWIS, extended wear infusion set; FDA, United States Food and Drug Administration; GDS, Green Diabetes Summit; HbA1c, hemoglobin A1c; HCP, healthcare professional; IIS, insulin infusion set; MBG, blood glucose meter; MDI, multiple daily injections; MEIS, Medtronic Extended Infusion Set; PwD, people

with diabetes; TDD, total daily dose; T1D, type 1 diabetes; TIR, time in range; US, United States.

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ORCID iDs

Kevin T. Nguyen https://orcid.org/0000-0001-9102-6537
Nicole Y. Xu https://orcid.org/0000-0001-9353-8819
Bruce A. Buckingham https://orcid.org/0000-0003-4581-4887
Sarnath Chattaraj https://orcid.org/0000-0003-0409-0886
Ohad Cohen https://orcid.org/0000-0003-4337-1795
Lutz Heinemann https://orcid.org/0000-0003-2493-1304
John Pickup https://orcid.org/0000-0002-4373-3269
Jannet Svensson https://orcid.org/0000-0002-9365-0728
Robert A. Vigersky https://orcid.org/0000-0002-3546-3385
Jenise C. Wong https://orcid.org/0000-0003-0573-6650
Ralph Ziegler https://orcid.org/0000-0002-2373-3720

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