COMMENTARY

In-Home Closed Loop Control for Artificial Pancreas: Patient and Provider Perspective

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THE ARTIFICIAL PANCREAS aims to improve glucose control while reducing the burden of diabetes management. Components of closed loop systems include continuous glucose monitors (CGMs) and continuous subcutaneous insulin infusion systems, available clinically for many years, with more recent research development of algorithms to automate insulin dosing. Suspension of insulin infusion at a hypoglycemia threshold was the initial step¹ and the Medtronic 530G remains the only commercially available system in the United States in 2016. The second step, predicted low glucose suspension systems, which shut off insulin delivery in advance of hypoglycemia, that are available internationally.

The next steps in development of automated insulin delivery are increasingly sophisticated algorithms ranging from hybrid systems requiring premeal boluses for food to fully automated closed loop systems. In a parallel pathway, multihormonal systems are being developed. Multiple trials testing the feasibility and the safety of different closed loop systems including hybrid or full-automated systems have been published.² In addition to the increasing complexity of the artificial pancreas AP systems, the length of AP research studies has steadily increased. Similarly, the level of medical supervision has evolved from hospital to camp/hotel and finally home use.^{3–5} The publication of the 3-month study in *JAMA*⁶ earlier this year resulted in FDA approval of the Medtronic 670G hybrid closed loop system on September 28, 2016. Per the Medtronic website, the 670G will be available commercially in spring of 2017.⁷

In this issue of *Diabetes Technology & Therapeutics*, Kovatchev et al.⁸ present a multicenter, multicountry, 6-month trial in adults with type 1 diabetes (T1D) in free-living conditions using the wireless portable Diabetes Assistant (DiAs) developed by the University of Virginia. The trial resulted in a significant reduction in hypoglycemia (4.1% vs. 1.3%; $P < 0.001$) and 77% of time was spent in range with rare occasions of hyperglycemia (24% of time >10 mmol/L, 4% > 13.9 mmol/L during day time and 21% of time >10 mmol/L and 1% > 13.9 mmol/L during night time). Of note, and as might be expected with an earlier technology, the median use of closed loop mode was 118 h/week (70.2% of time). The analysis showed that the reduction in HbA1c to

6.9% and hypoglycemia to 0.9% was restricted to the subjects who used the closed loop system more than 70% of time. The reduction in both HbA1c and hypoglycemia was correlated with system use (Spearman's r [95% CI]: 0.55 [0.004–0.83] and 0.4 [–0.21–0.77]). As AP systems evolve from research use in small groups with intensive oversight to use in larger clinical populations with less supervision and support, the usability of the AP systems will need to improve for widespread adoption.⁹

As mentioned by the authors, this phase 2 study was not designed to measure the effect of glycemic control. Therefore, there was no control arm. Although 100% of participants reported the system as beneficial overnight, some subjects reported feeling hassled by the burden of the system, and this was more prominent in participants who used the system less. The inclusion of patient reports of usability and satisfaction are essential elements of studies on AP systems and will provide a sense of how successful these technologies will be for translation from research to clinical practice.^{10–12} Data on human factors and psychosocial elements of AP are needed elements to include in all pivotal trials of these systems—in addition to glucose metrics¹³—to evaluate the effectiveness of AP systems.

The improvements in glycemia in this trial are very similar to the 670G hybrid closed loop system by Medtronic,⁶ in which HbA1c changed from 7.4% (standard deviation [SD] 0.9) to 6.9% (SD 0.6), and the percentage of time with hypoglycemia decreased from 1.0% (SD 1.1) to 0.6% (SD 0.6). In contrast, as might be expected with a system being used in a pivotal trial, the median use of the 670G system was 87.2%. However, one should be cautious when comparing short-term studies that may have different study objectives in small and potentially heterogeneous patient populations.¹⁴ It is important to note that DiAs proved to be wearable and safe to use during an extended phase of the trial.

With the development of more accurate CGMs and complex algorithms in recent years, various modes of closed loop systems are in development as reviewed by Kropff.² In addition to the first FDA-approved hybrid closed loop system (Minimed 670G System), other systems are undergoing clinical testing by industry and academia. These include fully automated closed loop systems that require no user

input, including meal and exercise announcements. It also should be noted that there is a small community of people with T1D who use homemade systems to automate insulin delivery.¹⁵

Dual hormone systems are being developed in parallel to automated insulin delivery systems.¹⁶ Blauw reported that subjects spent significantly more time in euglycemia (median interquartile range: [84.7 (82.2–87.8)% for their bihormonal artificial pancreas vs. 68.5 (57.9–83.6)% for the control]) with no significant change in hypoglycemia.¹⁷ In another recent publication, subjects spent more time in target range during both single (median: 76% [65%, 91%]) and dual hormone therapies (median: 81% [68%, 93%]) than during conventional therapy (median: 47% [36%, 71%]) with no significant difference between single or dual hormone therapy ($P=0.50$).¹⁸

Not every group has tested the efficacy and safety of its systems in the pediatric population. Minimed 670G, DiAs, FlorenceM, MD-Logic, and bionic pancreas were tested in children and adolescents.^{5,19–22} The first longer term closed loop study (6 weeks of home use) was done by Nimri et al., in which the MD-Logic system significantly decreased hypoglycemia and increased time spent in target range.²¹ Thabit also tested the Florence system over night for 3 weeks in adolescents,^{3,5} and the subjects spent more time in range and decreased mean glucose during closed loop study. The bionic pancreas team at Boston University and Massachusetts General Hospital published a trial in young children in camp settings.²³ Children between 6 and 11 years old in the bionic pancreas arm had a lower CGM measured glucose level (7.6 mmol/L [SD 0.6] vs. 9.3 mmol/L [1.7]; $P=0.00037$) and spent less time with hypoglycemia (1.2% [SD 1.1] vs. 2.8% [1.2]; $P<0.0001$). More studies are needed in younger—as well as elderly—populations to address differences in patient behaviors, insulin sensitivity, and other factors.

The advent of clinical use of automated insulin delivery systems will raise many questions. Will this technology change the patient's and provider's perspective? Will all patients want a fully automated artificial pancreas 24 h a day? Considerations of psychosocial and human factors include the burden of carrying multiple devices and engagement with the technology. Individuals will vary in their needs and desires from these systems given the diversity of people with T1D.

Research has demonstrated the efficacy of individual AP systems and AP systems as a class. However, we should be cognizant of the general characteristics of the patient populations who participate in these trials (low HbA1c, early adopters of diabetes technology, etc). With this assumption of selection bias in initial study participants who have access to these studies, we should consider whether and how we aim to extend these results to the general population with T1D? Postmarketing studies will be important to document system use by patients, quality of life, and glycemic control, and how to improve clinical translation.

The role of an endocrinologist in dissemination of AP systems also needs to be considered. It is likely that an interdisciplinary approach will be needed to train patients, as with current diabetes technology initiation. But with the new AP technology, the diabetes management team will also require education as these systems have been in use in relatively few research centers. An additional question is how

will the diabetes team provide on-going assistance to patients once they initiate an artificial pancreas system? Familiarity with these systems and best practice will need to be developed. Technology to share data may provide more efficient communication in between visits as the functionality of these systems improves. This has been seen with the evolution of current pump and CGM technologies. These advances may also facilitate the connection between patient and provider. Additional concerns will be how educational and socioeconomic barriers might limit the uptake of these systems to the broadest population possible. Continued refinement of cost-benefit analyses, quality of life, and glucose metrics¹³ is to be expected as our understanding of the clinical application of these systems increases. As more closed loop systems gain FDA approval, the landscape of research and clinical care in diabetes will evolve with new and perhaps unanticipated questions to address.

Author Disclosure Statement

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References

1. Bergenstal RM, Klonoff DC, Garg SK, et al.: Threshold-based insulin-pump interruption for reduction of hypoglycemia. *N Engl J Med* 2013;369:224–232.
2. Kropff J, DeVries JH: Continuous glucose monitoring, future products, and update on worldwide artificial pancreas projects. *Diabetes Technol Ther* 2016;18 Suppl 2:S253–S263.
3. Hovorka R, Elleri D, Thabit H, et al.: Overnight closed-loop insulin delivery in young people with type 1 diabetes: a free-living, randomized clinical trial. *Diabetes Care* 2014; 37:1204–1211.
4. Thabit H, Lubina-Solomon A, Stadler M, et al.: Home use of closed-loop insulin delivery for overnight glucose control in adults with type 1 diabetes: a 4-week, multicentre, randomised crossover study. *Lancet Diabetes Endocrinol* 2014;2:701–709.
5. Thabit H, Elleri D, Leelarathna L, et al.: Unsupervised home use of an overnight closed-loop system over 3–4 weeks: a pooled analysis of randomized controlled studies in adults and adolescents with type 1 diabetes. *Diabetes Obes Metab* 2015;17:452–458.
6. Bergenstal RM, Garg S, Weinzier SA, et al.: Safety of a hybrid closed-loop insulin delivery system in patients with type 1 diabetes. *JAMA* 2016;316:1407–1408.
7. Tilleskjor S. Breaking news: FDA approves the MiniMed 670G System, World's First Hybrid Closed Loop System 2016. www.medtronicdiabetes.com/blog/introducing-the-minimed-670g-system (accessed November 29, 2016).
8. Kovatchev B, Cheng P, Anderson SM, et al.: Feasibility of long-term closed-loop control: a multicenter 6-month trial of 24/7 automated insulin delivery. *Diabetes Technol Ther* 2017;19:18–24.
9. Forlenza GP, Sankaranarayanan S, Maahs DM: Refining the closed loop in the data age: research-to-practice transitions in diabetes technology. *Diabetes Technol Ther* 2015; 17:304–306.
10. Barnard KD, Hood KK, Weissberg-Benchell J, et al.: Psychosocial assessment of artificial pancreas (AP): com-

- mentary and review of existing measures and their applicability in AP research. *Diabetes Technol Ther* 2015;17:295–300.
11. Liberman A, Buckingham B: Diabetes technology and the human factor. *Diabetes Technol Ther* 2016;18 Suppl 1: S101–S111.
 12. Naranjo D, Tanenbaum ML, Iturralde E, et al.: Diabetes technology: uptake, outcomes, barriers, and the intersection with distress. *J Diabetes Sci Technol* 2016;10:852–858.
 13. Maahs DM, Buckingham BA, Castle JR, et al.: Outcome measures for artificial pancreas clinical trials: a consensus report. *Diabetes Care* 2016;39:1175–1179.
 14. Russell SJ, Beck RW: Design considerations for artificial pancreas pivotal studies. *Diabetes Care* 2016;39:1161–1167.
 15. Lewis D: What is #OpenAPS? 2016. <https://OpenAPS.org> (accessed November 29, 2016).
 16. Kowalski A: Pathway to artificial pancreas systems revisited: moving downstream. *Diabetes Care* 2015;38:1036–1043.
 17. Blauw H, van Bon AC, Koops R, et al.: Performance and safety of an integrated bihormonal artificial pancreas for fully automated glucose control at home. *Diabetes Obes Metab* 2016;18:671–677.
 18. Haidar A, Rabasa-Lhoret R, Legault L, et al.: Single- and dual-hormone artificial pancreas for overnight glucose control in type 1 diabetes. *J Clin Endocrinol Metab* 2016; 101:214–223.
 19. Russell SJ, El-Khatib FH, Sinha M, et al.: Outpatient glycemic control with a bionic pancreas in type 1 diabetes. *N Engl J Med* 2014;371:313–325.
 20. Ly TT, Breton MD, Keith-Hynes P, et al.: Overnight glucose control with an automated, unified safety system in children and adolescents with type 1 diabetes at diabetes camp. *Diabetes Care* 2014;37:2310–2316.
 21. Nimri R, Muller I, Atlas E, et al.: MD-Logic overnight control for 6 weeks of home use in patients with type 1 diabetes: randomized crossover trial. *Diabetes Care* 2014;37: 3025–3032.
 22. Del Favero S, Boscari F, Messori M, et al.: Randomized summer camp crossover trial in 5- to 9-year-old children: outpatient wearable artificial pancreas is feasible and safe. *Diabetes Care* 2016;39:1180–1185.
 23. Russell SJ, Hillard MA, Balliro C, et al.: Day and night glycaemic control with a bionic pancreas versus conventional insulin pump therapy in preadolescent children with type 1 diabetes: a randomised crossover trial. *Lancet Diabetes Endocrinol* 2016;4:233–243.

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