Current Advances of Artificial Pancreas Systems: A Comprehensive Review of the Clinical Evidence

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Since Banting and Best isolated insulin in the 1920s, dramatic progress has been made in the treatment of type 1 diabetes mellitus (T1DM). However, dose titration and timely injection to maintain optimal glycemic control are often challenging for T1DM patients and their families because they require frequent blood glucose checks. In recent years, technological advances in insulin pumps and continuous glucose monitoring systems have created paradigm shifts in T1DM care that are being extended to develop artificial pancreas systems (APSs). Numerous studies that demonstrate the superiority of glycemic control offered by APSs over those offered by conventional treatment are still being published, and rapid commercialization and use in actual practice have already begun. Given this rapid development, keeping up with the latest knowledge in an organized way is confusing for both patients and medical staff. Herein, we explore the history, clinical evidence, and current state of APSs, focusing on various development groups and the commercialization status. We also discuss APS development in groups outside the usual T1DM patients and the administration of adjunct agents, such as amylin analogues, in APSs.

Keywords: Blood glucose self-monitoring; Diabetes mellitus, type 1; Hypoglycemia; Insulin infusion systems; Pancreas, artificial; Wearable electronic devices

INTRODUCTION

Type 1 diabetes mellitus (T1DM), an insulin-dependent disease, is increasing in many countries, and it is known that serious complications and disease-related mortality are higher in T1DM than in type 2 diabetes mellitus (T2DM) [1,2]. In addition, the lifelong, intensive insulin treatment needed by T1DM patients creates many physical, psychological, and economic burdens [3]. Several treatments have been tried as alternatives to insulin, but many limitations remain. Immune modulation treatments such as teplizumab are being studied, but they remain prophylactic rather than curative [4]. Pancreatic transplantation is also performed, but it is not widely practiced because of the risks inherent in using immunosuppressive drugs and surgery [5]. Drugs other than insulin currently used in T2DM are also being studied for their applicability in T1DM, but they remain adjunctive [6]. Therefore, the best treatment to date for T1DM is proper blood glucose monitoring and appropriate insulin administration.

According to the results of one study, only 17% of children and 21% of adults with T1DM achieve their target glycemic levels, which is quite poor [7]. Moreover, severe hypoglycemia occurs frequently, with an annual incidence of 4.0% to 8.3%, depending on the degree of glycemic control [8]. Due to the complexity and difficulty of management, it is well-established that structured insulin dosing training is important for maintaining glycemic control and quality of life. However, the reality is that the process is neither easy nor comfortable [9].
When insulin pumps and continuous subcutaneous insulin infusion (CSII) were introduced in the 1970s, it became possible to reduce the number of injections to one every 3 or 4 days, replacing the need for manual multiple daily insulin injections (MDI) [10]. In a large retrospective study, CSII was reported to be more effective for glycemic control and hypoglycemia than MDI, but many randomized controlled trials (RCTs) did not show improvement [11-13]. Because CSII still requires manual insulin dose determination, difficulties for patients are inevitable. Therefore, an artificial pancreas system (APS), a closed-loop system that automatically administers an appropriate insulin dose according to the blood glucose level as mediated by the natural healthy pancreas, has been the goal for T1DM patients for many years. Recently, several APSs have been developed and validated very rapidly by various groups, and they are already being used in actual clinical practice. This review will focus on the clinical evidence for APSs and their application from various development groups in actual practice.

**BASIC CONCEPT AND HISTORY OF THE ARTIFICIAL PANCREAS SYSTEMS**

A workable closed-loop system must contain a real-time blood glucose monitor, a device for injecting insulin, and an algorithm to link them. In other words, it requires a continuous glucose monitoring system (CGM), a CSII or insulin pump, and autonomous control algorithms. The concept of an APS has been around for a long time; however, the opportunity for substantial development requires advances in CGMs [14]. Although many non-invasive blood glucose monitoring devices have been developed, the CGM currently used is operated by attaching a sensor to the subcutaneous tissue and detecting glucose in the interstitial fluid at 1- to 5-minute interval. Before mobile devices such as smartphones were developed, the CGM was linked to an insulin pump. Sensor augmented pumps (SAPs), which link an insulin pump to a CGM and display glucose data, were developed in the late 2000s and produced a marked improvement in glycemic control compared with MDI or an insulin pump alone (Figs. 1 and 2) [15]. Later, an SAP with a low glucose suspension (LGS) function (LGS SAP), which stops insulin infusion in cases of hypoglycemia, and an SAP with a predictive low glucose suspension (PLGS) function (PLGS SAP), which stops infusions before hypoglycemia occurs by predicting it, was sequentially developed and verified clinically (Figs. 2 and 3) [16-18]. Up to that point, the insulin dose still had to be manually determined and as such, these were not closed-loop systems.

The first closed-loop system was developed quite early in the 2000s and operated using a personal computer (PC)-based control algorithm (Fig. 1) [19-22]. From the early to the mid-2010s, it was developed into a portable form using a control algorithm installed on a smartphone or the pump itself [23,24]. The closed-loop system for insulin began as an overnight closed-loop (OCL) system for use during the fasting period at night, when the control algorithm application was relatively simple [21,25-27]. Subsequently, it was developed for use both in fasting and non-fasting periods, with major improvements in glycemic control (Fig. 1) [22-27].
in the day and at night, but the automatic control worked only for the basal rate, not for meal bolus insulin, which is complex to calculate; this was called a hybrid closed-loop system (HCL) (Figs. 2 and 3) [28-30]. The HCL has been commercialized and

Fig. 2. Timeline of landmark studies of the artificial pancreas system. NEJM, New England Journal of Medicine; RCT, randomized control trial; SAP, sensor augmented pump; D Care, Diabetes Care; PLGS, predictive low glucose suspension; BMJ, British Medical Journal; PGCS, portable glucose control system; OCL, overnight closed-loop; T1DM, type 1 diabetes mellitus; HCL, hybrid closed-loop; T2DM, type 2 diabetes mellitus; JAMA, Journal of American Medical Association; Lancet D&E, Lancet Diabetes Endocrinol; Lancet Digit H, Lancet Digital Health; DBLG1, Diabeloop Generation 1; D Technol, Diabetes Technology & Therapeutics; IRCM, Institut de Recherches Cliniques de Montreal; DOM, Diabetes Obesity and Metabolism; AP, artificial pancreas. Subgroups of the same study.

Fig. 3. Key features of sensor augmented pump and artificial pancreas systems. CGM, continuous glucose monitoring system; LGS, low glucose suspension; PLGS, predictive low glucose suspension; TIR, time in range; TBR, time below range.

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used in practice since the late 2010s (Fig. 1). Concurrently, a dual-hormone closed-loop system, dispensing glucagon as well as insulin, was developed in the late 2000s [31-33]. Although several short-term studies have revealed the superiori-
ty of the dual-hormone closed-loop system over the single-
hormone closed-loop system in terms of hypoglycemia, it has not yet been used in practice [34-36]. Most recently, advanced HCL (single-hormone) was developed and commercialized with an additional auto-correction bolus feature, which frequently corrects blood glucose levels exceeding the target, and showed superior glycemic control compared to the previous HCL (Figs. 1-3) [37,38]. However, advanced HCL is still not a full closed-loop system (FCL) because a meal announcement is required.

Since 2013, patients and caregivers who are unsatisfied with the development rate of commercial APSs have developed do-it-yourself (DIY) APSs using open source platforms [39]. Furthermore, to overcome the limitations of insulin-based APSs, other peptide hormones such as amylin analogues and glucose-like peptide 1 (GLP-1) receptor (GLP-1R) agonists have been investigated, and intraperitoneal (IP) insulin delivery systems have been in development [40-42]. Furthermore, several APS studies have been conducted in patients with T2DM and pregnant T1DM (Fig. 2) [43,44].

**MAJOR GROUPS**

A number of APSs have been developed and clinically validated; however, most of them were performed by only a few large groups (Fig. 4). Since various people and institutions were involved in the development and verification of APS, it is difficult to fully attribute the development groups. Therefore, in this article, we used the company names of APSs only if they were commercialized. Otherwise, we utilized the main institution name. For the insulin-only closed-loop system, the main groups comprise the companies CamDiab (Cambridge, UK), DreaMed (Petah Tikva, Israel), Medtronic (Minneapolis, MN, USA), and TypeZero Technology (Charlottesville, VA, USA) [24,25,28,45]. For convenience, we will call them the CamDiab, DreaMed, Medtronic, and TypeZero groups, respectively, in this article. CamDiab is an APS company that was mainly developed by colleagues at Cambridge University. CamDiab group developed a control algorithm, which was commercialized in 2020 as CamAPS FX, which runs as a mobile application. Colleagues at Jesse Z and Sara Lea Shafer Institute for Endocrinology and Diabetes (Israel) mainly conducted clinical trials and founded the DreaMed company. The DreaMed group developed the MD-Logic APS algorithm, which was commercialized in 2015 as GlucoSitter, and it developed a decision support software called Advisor Pro for insulin dosing in 2018. The Medtronic group developed its own HCL control algorithm, which became the Minimed 670G system, in 2016, and additionally adopted several algorithmic features of the MD-Logic algorithm from the DreaMed group for an advanced HCL that became Minimed 780G in 2020 [24,38]. TypeZero Technologies was founded by colleagues at Virginia University. The TypeZero group first developed the DiAs closed-loop platform, and developed it into the inControl algorithm that has since been used in the Tandem Control-IQ system [46]. Some other groups have entered this arena since the late 2010s. The Diabeloop group of France developed the Diabeloop Generation 1 (DBLG1) system, which was smartphone-based and received the Conformité Européenne (CE) mark in 2018, and subsequently made Diabeloop for highly unstable diabetes (DBLHU system) to treat brittle diabetes [47,48]. The Insulet group (United States) developed an HCL control algorithm called Omnipod 5, a later version of the Horizon system that worked with the Omnipod patch insulin pump and has not yet been commercialized [49].

Regarding the dual-hormone closed-loop systems, Beta Bionics company (Irvine, CA, USA), Inreda Diabetic company (Goor, the Netherlands), Institut de Recherches Cliniques de Montreal (IRCM, Montreal, QC, Canada), and Oregon Health and Science University (Portland, OR, USA) are the major groups [50-53]. We will refer to them as the Beta Bionics, Inreda, IRCM, and Oregon groups, respectively. The development and validation of APS from the Beta Bionics group were mainly conducted by Boston University and Harvard Medical School. They initially used two separate pumps for insulin and glucagon and then developed a dual-chamber pump called Bi-hormonal iLet, which they are preparing for commercialization [51,54]. The Inreda group, primarily led by Amsterdam University, also initially used two pumps from other companies for insulin and glucagon, respectively, but it has since developed and is using its own algorithm-embedded dual-chamber pump called the Inreda Artificial Pancreas [50,55]. It received the CE mark in 2020 and is preparing for commercialization. The IRCM and Oregon groups also independently developed their own control algorithms with two separate pump systems, but they have not yet commercialized them.
CONTROL ALGORITHMS

Currently, the main control algorithms used for closed loops are proportional, integral, and derivative control (PID) algorithms, model predictive control (MPC) algorithms, and fuzzy logic algorithms [56], all of which are widely used in other control applications, such as autonomous vehicles (Fig. 5). As a simple explanation of the PID concept, “proportional” can be understood to correspond to the present because it detects how far away the glucose level is from the target right now; “integral” corresponds to the past to see the area deviating from the target in the previous trajectory, and “derivative” corresponds to the future, predicting the future direction of changes in the glucose level [57]. It requires only a sensor glucose variable to
operate, which makes it simple and easy to implement. MPC algorithms predict changes in the dependent variable after a specific time by adjusting the independent variables. In an APS, an MPC models the glucose level as the dependent variable and adjusts independent variables such as body mass index, carbohydrate intake, and insulin-on-board. This modeling is performed with updated information every few minutes. Generally, MPC shows better performance than PID, but it is more complex and challenging to operate [56]. Fuzzy logic algorithms produce correctness as a matter of degree instead of as a yes or no result [20]. In an APS, fuzzy logic operates through supervised learning based on expert opinions to establish a specific decision. In addition to these options, several modified algorithms have also been used. For example, the proportional and derivative (PD) algorithm is a PID algorithm without the integral feature, and the fading memory PD algorithm uses weighting to privilege more current data [33].

For their insulin-only closed-loop systems, the Medtronic group used a PID algorithm, the CamDiab, Diabeloop, Insulet, and TypeZero groups used MPC algorithms, and the DreaMed group adopted a fuzzy logic algorithm. Most DIY APSs are based on MPC algorithms. For their dual-hormone closed-loop systems, the Inreda group used a PID algorithm for both insulin and glucagon, and the Oregon group used a fading memory PD algorithm. Both the Beta Bionics and IRCM groups adopted an MPC algorithm for insulin, but for glucagon, the Beta Bionics group used a PD algorithm, and the IRCM group used heuristic logical rules (Fig. 4).

**CLINICAL EVIDENCE FOR PRE-STAGE ARTIFICIAL PANCREAS SYSTEMS**

As a pre-stage for APSs, the first SAP that linked a CGM and an insulin pump was developed by the Medtronic group in 2006 (Table 1). Although it had no control algorithm, it still represented a big technological advance as it could control the glucose level while monitoring it in real-time. In 2010, during a study of 485 T1DM patients, the SAP decreased glycosylated hemoglobin (HbA1c) by 0.6% more than MDI for 1 year [15]. However, SAP still could not improve severe hypoglycemia [15,58] and so the group developed an SAP with an LGS function that automatically stops insulin infusion in the event of...
hypoglycemia and commercialized it as the Minimed 530G and later 630G (Medtronic). In 2013, the Medtronic group performed a study of 95 patients with hypoglycemia unawareness and found that hypoglycemic events were 3.6-fold fewer with LGS SAP than with CSII [59]. Another study in the same year compared the LGS SAP with the SAP alone in 247 patients and found that nocturnal hypoglycemic events were reduced by 31.8% with LGS SAP [16]. Next, instead of stopping the infusion upon hypoglycemia, the Medtronic group developed the PLGS SAP, commercialized as the Minimed 640G, to stop the infusion rate by predicting hypoglycemia 30 min in advance. After demonstrating superiority in preventing nocturnal hypoglycemia [17,18], the PLGS SAP was shown to decrease hypoglycemia, compared with the performance of SAP and CSII, in all-day and long-term studies in 2017 to 2019 [60-62]. In 2018, another PLGS SAP made by Tandem and named the Basal IQ algorithm was introduced, which showed a significant reduction in time below range (TBR) < 70 mg/dL compared with that of SAP [63].

CLINICAL EVIDENCE FOR SINGLE-HORMONE CLOSED-LOOP SYSTEMS

For the devices mentioned above, the insulin dose had to be set by the user. Therefore, the next step was a closed-loop system that automatically determined the insulin dose using a control algorithm. Research has been in progress for a long time, but its use in actual practice has been slowed by safety issues. First, an OCL was developed to automatically determine the infusion rate during the night, which is much simpler to calculate than the dynamic requirements of postprandial blood glucose control (Supplementary Table 1). In 2010 to 2011, the CamDiab group published small clinical studies of its OCL in hospitalized children and adults with T1DM and reported improve-

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Table 1. Clinical evidence of sensor augmented pumps in type 1 diabetes mellitus

| Year | Group | CGM | Pump | System | Design | No. | Age, yr | Setting | Duration | Intervention | Control | Outcome (intervention vs. control) |
|------|-------|-----|------|--------|--------|-----|--------|---------|----------|-------------|---------|----------------------------------|
| 2010 | Medtronic | Medtronic | Medtronic | Minimed | Minimed | 485 | 7–70 | Home | 12 months | SAP | MDI | HbA1c 7.5% vs. 8.1%, P < 0.05, Severe hypoglycemia: 13.3% vs. 13.5/100 person years, P = 0.30 |
| 2013 | Medtronic | Medtronic | Medtronic | Minimed 530G | Minimed 530G | 95 | 4–50 | Home | 6 months | LGS SAP | CSII | Severe to moderate hypoglycemic events: 9.5 vs. 34.2/100 patient-months |
| 2013 | Medtronic | Medtronic | Medtronic | Minimed 530G | Minimed 530G | 247 | 16–70 | Home | 3 months | LGS SAP | SAP | Nocturnal hypoglycemic events: 1.5 vs. 2.2/patient-week |
| 2014 | Medtronic | Medtronic | Medtronic | Prototype of 640G | Prototype of 640G | 45 | 14–45 | Home | 42 days | PLGS SAP | SAP | ON hypoglycemia (≤60 mg/dL) events: 21% vs. 33%, P < 0.01 |
| 2015 | Medtronic | Medtronic | Medtronic | Prototype of 640G | Prototype of 640G | 81 | 4–14 | Home | 3 weeks | PLGS SAP | SAP | ON TBR < 70: 4.6% vs. 10.1%, P < 0.01 (11–14 years), ON TBR < 70: 3.1% vs. 6.2%, P < 0.01 (4–10 years) |
| 2017 | Medtronic | Medtronic | Medtronic | Minimed 640G | Minimed 640G | 100 | 8–18 | Home | 14 days | PLGS SAP | SAP | Hypoglycemic event (<65 mg/dL): 4.4 vs. 7.4, P < 0.01 |
| 2018 | Medtronic | Medtronic | Medtronic | Minimed 640G | Minimed 640G | 154 | 8–20 | Home | 6 months | PLGS SAP | SAP | TBR < 65: 1.5% vs. 2.6%, P < 0.01, TBR < 54: 0.6% vs. 1.2%, P < 0.01 |
| 2018 | Tandem | Dexcom G5 | t:slim X2 | Basal IQ | Minimed 640G | 103 | 6–72 | Home | 6 weeks | PLGS SAP | SAP | TIR 70–180: 65% vs. 63%, P < 0.01, TBR < 70: 2.6% vs. 3.2%, P < 0.01, < 54: 0.4% vs. 0.5%, P < 0.01 |
| 2019 | Medtronic | Guardian | Sensor 3 | Minimed 640G | Minimed 640G | 153 | 24–75 | Home | 6 months | PLGS SAP | CSII | TIR 70–180: 59.5% vs. 57.8%, P = 0.047, TBR < 70: 4.0% vs. 8.4%, P < 0.01, < 54: 0.9% vs. 3.6%, P < 0.01 |

The unit of TIR and TBR target is mg/dL.
CGM, continuous glucose monitoring system; RCT, randomized control trial; SAP, sensor augmented pump; MDI, multiple daily insulin injection; HbA1c, glycosylated hemoglobin; LGS, low glucose suspension; CSII, continuous subcutaneous insulin infusion; PLGS, predictive low glucose suspension; ON, overnight; TBR, time below range; TIR, time in range.

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ments in overnight time in range (TIR) 70 to 144 mg/dL and TBR <70 mg/dL compared with CSII [21,22]. In 2012, the Medtronic and DreaMed groups also showed improvements in overnight TIRs compared with those of the CSII and SAP, respectively, in small studies of inpatients though both studies had single arm designs [64,65]. Subsequently, the research expanded to non-hospital environments. In 2013, the DreaMed group compared OCL and SAP for 1 day in a diabetes camp for 56 adolescents with T1DM, the largest number at that time. During the night, hypoglycemic events of <63 mg/dL decreased (7 vs. 22, \( P=0.003 \)), and mean overnight glucose levels were also kept lower (126.4 mg/dL vs. 140.4 mg/dL) [15]. Subsequently, the TypeZero group showed an improvement in the overnight TIR with OCL compared with SAP in a diabetes camp for 20 adolescents in a per-protocol study [66].

Since 2014, home-based OCL studies have been conducted in earnest, with the DreaMed group showing improvements over SAP in overnight TIR and TBR in a 6-week study of 24 adolescents and adults [67]. In the same year, the CamDiab group conducted home-based OCL studies for adolescents and adults for 3 and 4 weeks, respectively, and showed overnight TIR improvements compared with SAP [26,68]. In the following year, a 12-week home-based study, the longest study at that time, was conducted by the same group and showed improvements in overnight TIR compared with SAP in 25 children and adolescents (59.7% vs. 34.4%, \( P<0.001 \)) [28]. In the same year, the TypeZero group also showed TIR improvements by using a control algorithm that covered dinner time in addition to overnight, in a 2-month home-based study of 32 adults (8:00 PM–8:00 AM TIR 70 to 180 mg/dL; 66.7% vs. 58.1%, \( P<0.001 \)) [27]. In 2017, the DreaMed group performed an OCL study on 75 T1DM patients [69].

Next, OCL developed into HCL, which controls the basal rate both overnight and during the day (Table 2). First, the TypeZero and CamDiab groups conducted separate HCL studies in inpatient settings in 2013 [23,29] and short-term supervised outpatient settings in 2014, and reported heterogeneous TIR and TBR results [70,71]. In 2015, the Medtronic group conducted an HCL study and compared it with LGS SAP for 6 days at a diabetes camp. Although they failed to show a difference in TIR, it was the first clinical use of an algorithm-integrated pump [30]. In the same year, the CamDiab group demonstrated a TIR improvement for HCL over SAP in a home-based study of 33 adults for 12 weeks (67.7% vs. 56.8%, \( P<0.001 \)) [28]. In 2016, HCL studies were expanded to younger ages, with the CamDiab and TypeZero groups demonstrating TIR or TBR improvement in children and adolescents in home-based and diabetes camp settings, respectively [72-74].

At that point, HCLs began to be commercialized. In 2016, the Medtronic group conducted a pivotal single arm trial for 3 months with 124 adult and adolescent patients and showed improvement in HbA1c and TIR compared with CSII (HbA1c, 7.4% to 6.9%; TIR, 66.7% to 72.5%) [24]. Based on that study, the Minimed 670G (Medtronic) was approved by the U.S. Food and Drug Administration (FDA) as the first commercialized HCL in the world. After that, a single arm study of the Minimed 670G was conducted in 7 to 13-year-old children for 3 months. It showed an improvement over SAP in TIR and TBR, and its indication was expanded to children aged 7 years and older [75]. In 2020, because the previous Minimed 670G studies were single arm, a 6-month RCT was conducted among 120 adult T1DM patients, and it reported improvements in TIR and TBR compared with MDI and CSII [76].

In 2017, the CamDiab group demonstrated TIR improvements with HCL over SAP, even among well-controlled T1DM patients in the home setting [77]. In the following year, it performed the then-largest RCT of HCL (86 patients for 12 weeks) among adults and children older than 6 years, reporting improvements in TIR (65% vs. 54%, \( P<0.001 \)) [78], after which the group further verified HCL safety in children aged 1 to 6 years [79]. Resultantly, CamAPS FX, a mobile APS application from the CamDiab group, received the CE mark and was commercialized in 2020 for T1DM patients 1-year-old or older.

After performing mid- to long-term single arm studies in 2016 to 2017 [80,81], the TypeZero group conducted the largest HCL study to date in 2019 of 168 adolescents and adults for 6 months using a Tandem pump called t:slim X2, and the results showed TIR (71% vs. 59%, \( P<0.001 \)) and TBR (1.58% vs. 2.25%, \( P<0.001 \)) improvements compared with SAP [45], and subsequently, the Tandem Control-IQ system received FDA approval. In an extension study, the HCL group was again divided into the HCL and PLGS SAP groups, and the HCL group still showed superior TIR (67.6% vs. 60.4%, \( P<0.001 \)) [82]. In 2020, the study was expanded to 101 children aged 6 to 13 years, and their TIR improved compared with the SAP group for 16 weeks (67% vs. 55%, \( P<0.001 \)) [83], which allowed the Tandem Control-IQ to gain approval for use in children aged 6 years and older. Control-IQ is also called advanced HCL because it has the feature of an automatic correction bolus, which automatically delivers 60% of the calculated correction factor
### Table 2. Clinical evidence of hybrid closed-loop system (single-hormone) in type 1 diabetes mellitus patients

| Year | Group   | CGM   | Pump       | System       | Design      | No. | Age yr | Setting    | Duration | Intervention | Control | Outcome (intervention vs. control) |
|------|---------|-------|------------|--------------|-------------|-----|--------|------------|----------|--------------|---------|-----------------------------------|
| 2013 | TypeZero | DexCom | Omnipod    | DiAs         | Single-arm  | 20  | 21-65  | Hotel      | 42 hours | HCL          | SAP     | ON TIR 70–180: 72% vs. 80%, P=0.22 |
| 2013 | CamDiab | DexCom | Animas 2020| NA           | RCT, crossover | 12  | 12-18  | Inpatient  | 36 hours | HCL          | CSII    | TIR 70–180: 84.6% vs. 65.4%, P=0.02 |
| 2014 | CamDiab | FreeStyle | Dana R   | Florence system | RCT, crossover | 17  | ≥18    | Supervised outpatient | 8 days | HCL          | SAP     | TIR 70–180: 74.5% vs. 53.8%, P=0.34; <63: 2.3% vs. 2.2%, P=0.66 |
| 2014 | TypeZero | DexCom | Omnipod    | DiAs         | RCT, crossover | 6   | 21–44  | Supervised outpatient | 42 hours | HCL          | SAP     | TIR 70–180: 74% vs. 49% |
| 2014 | TypeZero | DexCom | T-slim     | DiAs         | RCT, crossover | 18  | 21–65  | Supervised outpatient | 40 hours | HCL          | SAP     | TIR 70–180: 74.5% vs. 50% |
| 2014 | Diabeloop | DexCom | NA         | Diabeloop algorithm | Single arm | 12  | ≥18    | Inpatient  | 5 hours  (postprandial) | HCL          | SAP      | TIR 70–180: 84.5% vs. 69.2% |
| 2015 | Medtronic | Medtronic 4S | Minimed pump | PID-IFB algorithm | RCT, parallel | 21  | 14–40  | Diabetes Camp | 6 days    | HCL          | LGS SAP | TIR 70–180: 66.9% vs. 73.1% |
| 2015 | CamDiab | FreeStyle Navigator | Dana R | Florence system | RCT, crossover | 33  | ≥18    | Home       | 12 weeks | HCL          | SAP     | TIR 70–180: 67.7% vs. 56.8%, P=0.01 |
| 2016 | CamDiab | FreeStyle Navigator II | Dana R | Florence system | RCT, crossover | 12  | 10–18  | Home       | 7 days    | HCL          | SAP     | TIR 70–180: 72% vs. 53%, P<0.01 |
| 2016 | TypeZero | Diabeloop | Platinum | Accu-Chek Spirit Combo | DiAs         | 30  | 5–9    | Diabetes Camp | 3 days    | HCL          | SAP     | TIR 70–180: 56.0% vs. 59.7% |
| 2016 | TypeZero | Diabeloop | Platinum | Roche Accu-Chek pump | RCT, parallel | 33  | Mean 17.9 | Diabetes Camp | 5 days    | HCL          | SAP     | TIR 70–180: 78.6% vs. 65.4% |
| 2016 | Medtronic | Guardian Sensor 3 | Minimed 670G | Minimed 670G | Single arm | 124  | 14–75  | Home       | 3 months  | HCL          | CSII    | TIR 70–180: 72.5% vs. 66.7%, P<0.01 |
| 2016 | TypeZero | Diabeloop | Platinum | Roche Accu-Chek pump | RCT, crossover | 30  | 18–66  | Home       | 2 weeks   | HCL          | SAP     | TIR 70–180: 78.3% vs. 65%, P<0.01 |
| 2016 | TypeZero | Diabeloop | Platinum | Roche Accu-Chek pump | RCT, crossover | 14  | Median 45 | Home       | 6 months  | HCL          | SAP     | TIR 70–180: 77% vs. 66%, P<0.01 |
| 2016 | CamDiab | FreeStyle Navigator II | Dana R | Florence system | RCT, crossover | 29  | ≥18    | Home       | 4 weeks    | HCL          | CSII    | TIR 70–180: 76.2% vs. 65.6%, P<0.01 |
| 2018 | CamDiab | Medtronic | Dielux | Modified 640G | RCT, parallel | 86  | ≥18    | Home       | 12 weeks  | HCL          | SAP     | TIR 70–180: 65% vs. 54%, P=0.01 |
| 2018 | Diabeloop | DexCom G5 | Cellnovo pump | DBLG1 | Single arm | 8   | ≥18    | Home       | 3 weeks    | HCL          | NA      | TIR 70–180: 70.2% vs. 70.2%, P=0.01 |

(Continued to the next page)
### Table 2. Continued

| Year | Group | CGM | Pump | System | Design       | No.  | Age yr | Setting | Duration | Intervention | Control | Outcome (intervention vs. control) |
|------|-------|-----|------|--------|--------------|------|--------|---------|----------|--------------|---------|-----------------------------------|
| 2019 | Medtronic | Guardian Sensor 3 | Medtronic | 670G | Single arm | 105  | 7–13   | Home   | 3 months | HCL | SAP | TIR 70–180: 65.0% vs. 56.2%, P<0.01; TBR <70: 30% vs. 47%, P<0.01; <54: 0.8% vs. 1.3%, P<0.01 |
| 2019 | CamDiab | Medtronic Enlite 3 | Medtronic | 670G | Modified 640G | Florence M system | RCT, crossover | 24  | 1–7   | Home | 3 weeks | HCL (diluted) | HCL (standard) | TIR 70–180: 72% vs. 70%, P=0.16 (diluted vs. standard insulin); TBR <70: 4.5% vs. 4.7%, P=0.47 (diluted vs. standard insulin) |
| 2019 | Diabetes | Medtronic Enlite 3 | Medtronic | 670G | MD-Logic Paradigm VeoTM | MD-Logic | RCT, crossover | 48  | ≥12   | Home | 60 hours | Prototype of AHCL | SAP | TIR 70–180: 66.6% vs. 59.9%, P<0.01; TBR <70: 2.3% vs. 1.5%, P=0.37, <54: 0.2% vs. 0%, P=0.25 |
| 2019 | TypeZero | Dexcom G6 | Cellnovo t:slim X2 | Control-IQ | RCT, parallel | 168  | 14–72 | Home | 6 months | HCL | SAP | TIR 70–180: 71% vs. 59%, P<0.01; TBR <70: 1.58% vs. 2.25%, P<0.01; <54: 0.29% vs. 0.33%, P=0.02 |
| 2019 | Diabeloop | Dexcom G6 | Cellnovo Generation 1 | DBLG1 | RCT, crossover | 63   | ≥18   | Home | 12 weeks | HCL | SAP | TIR 70–180: 68.5% vs. 59.4%, P<0.01; TBR <70: 0.8 vs. 2.0%, P<0.01; <50: 0.2% vs. 0.7%, P<0.01 |
| 2020 | TypeZero | Dexcom G6 | Cellnovo t:slim X2 | Control-IQ | RCT, parallel | 109  | 14–72 | Home | 3 months | HCL | PLGS SAP | TIR 70–180: 67% vs. 57%, P<0.01; TBR <70: 1.48% vs. 0.35%, P=0.02 |
| 2020 | Diabeloop | Dexcom G6 | Cellnovo Generation 1 | DBLG1 | RCT, crossover | 101  | 6–13  | Home | 16 weeks | HCL | SAP | TIR 70–180: 67% vs. 55%, P<0.01; TBR <70: 1.6% vs. 1.8%, P=NA; <54: 0.2% vs. 0.3%, P=NA |
| 2020 | Medtronic | Guardian Sensor 3 | Minimed 670G | Minimed 670G | RCT, parallel | 120  | 25–75 | Home | 6 months | HCL | MDI or CSII | TIR 70–180: 69.9% vs. 54.7%, P<0.01; TBR <70: 1.8% vs. 3.8%, P<0.01; <50: 0.2% vs. 0.9%, P<0.01 |
| 2020 | Diabeloop | Dexcom G5 | Cellnovo Generation 1 | DBLG1 | RCT, crossover | 38   | ≥18   | Inpatient | 72 hours | HCL | SAP | TIR 70–180: 80.5% vs. 54.3%, P<0.01; TBR <70: 80.2% vs. 64.2%, P<0.01 (exercise) |
| 2020 | Insulet | Dexcom G4 | Omnipod | Omnipod 5 algorithm | Single arm | 36   | 6–65  | Hotel/rental home | 4 days | HCL | SAP, CSII, or MDI | TIR 70–180: 73.7% vs. 68.0%, P<0.08 (adult) |
| 2020 | Medtronic | Guardian Sensor 3 | Minimed 780G | Minimed 780G | RCT, crossover | 60   | 7–80  | Home | 4 weeks | AHCL | PLGS SAP | TIR 70–180: 70.4% vs. 57.9%, P<0.01 |
| 2021 | Insulet | Dexcom G6 | Omnipod | Omnipod 5 algorithm | Single arm | 36   | ≥6   | Home | 2 weeks | HCL | SAP, MDI, or CSII | TIR 70–180: 76% vs. 74%, TBR <70: 2.1% vs. 1.7%, P<0.01; <54: 0.46% vs. 0.40%, P<0.01 (non-inferior) |
| 2021 | Diabeloop | Dexcom G6 | Kaleido pump | DBLH | RCT, 2 of 1 crossover | 5   | ≥22   | Home (Brittle) | 8 weeks | HCL | PLGS SAP | TIR 70–180: 73.3% vs. 43.5%, P<0.01; TBR <70: 0.9% vs. 3.7%, P<0.01; <54: 0.2% vs. 1.3%, P<0.01 |
| 2021 | Diabeloop | Dexcom G6 | Kaleido pump | DBLG1 | Single arm | 25   | ≥22   | Home | 6 months | HCL | SAP | TIR 70–180: 69.7% vs. 53%, P<0.01; TBR <70: 1.3% vs. 2.4%, P<0.03; <54: 0.24% vs. 0.32%, P=0.42 |

The unit of TIR and TBR target is mg/dL.
CGM, continuous glucose monitoring system; HCL, hybrid closed-loop system; SAP, sensor augmented pump; ON, overnight; TIR, time in range; NA, not available; RCT, randomized control trial; CSII, continuous subcutaneous insulin infusion; TBR, time below range; LGS, low glucose suspension; AHCL, advanced hybrid closed-loop; PLGS, predictive low glucose suspension; MDI, multiple daily insulin injection.

Overnight closed-loop system is used for children and adolescent group in the same study.
up to once an hour when the predicted glucose value in 30 minutes is above 180 mg/dL.

In 2019 the DreaMed group, which had been quiet after the OCL era, conducted a short-term clinical study of an all-day HCL and added an automated bolus correction function using the MD-Logic algorithm [84]. Subsequently, the Medtronic group developed an advanced HCL using its own PID algorithm and some of the features of the DreaMed group [38]. With the combined control algorithms, if the sensor glucose rises, the automated correction function operates up to every 5 minutes to reach the target (100 to 120 mg/dL). Most recently, in 2021, the advanced HCL of the Medtronic group was compared with the PLGS SAP in 60 adults and children aged 6 years and older for 4 weeks, resulting in improved TIR and TBR (TIR, 70.4% vs.57.9%, P<0.001; TBR, 2.1% vs. 2.5%, P<0.032) [37]. In addition, Medtronic's advanced HCL was compared with HCL (Minimed 670G) in 113 adolescents and adults for 3 months and showed superiority in daytime (6:00 AM to midnight) time above range >180 mg/dL (34% vs. 37%, P<0.0001) and all-day TIR (67% vs. 63%, P<0.0001) and non-inferiority in all-day TBR <54 mg/dL [38]. However, in contrast to expectations, greater effects were seen from 5:00 AM to 10:00 AM than in the rest of the time, which implies that the glycemic improvements shown in this study were not mainly due to postprandial glucose control. Although this feature might correct the postprandial glucose not controlled by the usual bolus infusion to some extent, it is still insufficient, and an advanced HCL requires carbohydrate counting. In 2020, it was commercialized as Minimed 780G (Medtronic), received CE mark approval and at the time of writing, is awaiting FDA approval.

Other groups have conducted HCL studies. After performing several non-RCT pilot studies [85,86], the Diabeloop group of France conducted a home-based 12-week RCT of its own HCL algorithm, called DBLG1, in 2019 among 63 adult T1DM patients, showing TIR improvement compared with SAP (68.5% vs. 59.4%, P<0.001) [47]. The following year, it conducted a short-term study of inpatient adult T1DM patients during meals and exercise environments and demonstrated TIR improvement compared with SAP [87]. The group performed another study in 2021 targeting brittle diabetes using the DBLG1 algorithm; five highly unstable adult T1DM patients were studied for 8 weeks in two 4-week crossover studies [48]. Although the control group showed a poor TIR of 43.5%, even using the PLGS SAP, this HCL improved the TIR to as much as 73.3%. This group also published a real-world single arm study of a pre-launch commercialized DBLG1 system in 2021 [88]. After receiving the CE mark in 2018, the group is currently preparing to launch a commercial HCL product that will work with various insulin pumps.

Separately, the Insulet group conducted APS studies using an Omnipod tubeless patch pump. Previously, HCL studies from another group had used the Omnipod pump (Insulet) [23,89], but the Insulet group began research using its own control algorithm in the late 2010s. After completing small safety and feasibility studies in 2018 to 2019 [90,91], the group performed several single arm studies of pump-embedded control algorithms called Horizon and Omnipod 5 and compared them with standard treatment using SAP, CSII, or MDI. Following a hotel and rental home-based study in 2020 [92], the group conducted home-based research for 2 weeks in 2021 among 36 child and adult T1DM patients and reported TIR improvements (75.1% vs. 65.6%, P<0.05 in the adult group) [49].

As explained above, single-hormone APS developed from OCL systems to day-and-night HCL systems, and testing has proceeded from small short-term hospital-based studies to large long-term home-based studies. At the same time, the control groups evolved from CSII to SAP, PLGS, and even older HCL systems. In recent years, studies conducted for 3 to 6 months with more than 100 patients have been published, changing the standard of APS research. Furthermore, commercialized APSs are now used in actual practice, quickly following the announcement of clinical studies.

REAL-WORLD EXPERIENCE AND USABILITY OF COMMERCIALIZED SINGLE-HORMONE CLOSED-LOOP SYSTEMS

In the present day, since several HCLs have been commercialized, there have been studies based in real-world experience. First, for Minimed 670G, a 3-month retrospective study of 3,141 children and adults revealed improvements in TIR of 7.3% (66.0% to 73.3%, P<0.001) and TBR of 0.6% (2.1 to 2.7%, P<0.001) [93]. Another retrospective study of 127 adults showed improvements in TIR of 11% (59.5% to 70.1%, P<0.001) and TBR of 1% (3.2% to 2.2%, P<0.05) after 6 months of follow-up [94]. Another study conducted in 92 children for 6 months revealed a 6% TIR reduction (50.7% to 56.9%, P=0.007) with no change in TBR [95]. Over all, the above real-world studies showed similar glycemic improvements to those which were observed in previous controlled trials.

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However, auto-mode usage was as low as 51.2% to 80.8% in the above real-world studies compared to 87.2% in the previous pivotal trial, with an especially low rate in the study of children (51.2%) [24,93-95]. Moreover, a 1-year prospective study of 84 children and adults revealed that the number of participants who stopped using auto-mode was 33% (46%, if analyzed with those who provided data), and patients who used auto-mode more than 70% were only 32% [96]. The main reasons for this were frequent alarm and sensor calibration issues.

On the other hand, in another 1-year prospective cohort study of 30 children, the auto-mode was used in 85.6% of cases, and TIR was improved by as much as 26.5% (46.9% to 73.4%, \( P \leq 0.01 \)), far better than previous observational studies [97]. The difference between this and other studies was that the specific selection and initiation protocols were used, and structured education was provided with follow-up. Therefore, to successfully use this HCL in real-world practice, it seems that the user’s motivation and intensive education are crucial.

In addition, although there has been no real-world study of the Minimed 780G to date, auto-mode usage was 14% higher than 670G in the landmark RCT (83% vs. 69%, \( P < 0.0001 \)) [38]. This is thought to be due to the kick-out process in Minimed 670G, which stopped the auto-mode when sensor glucose levels were higher than the target for a certain time (>300 mg/dL for 1 hour or >250 mg/dL for 3 hours), and the auto-bolus correction of the Minimed 780G can encourage the patient to stay longer in auto-mode. Therefore, it is expected that auto-mode usage can be improved in real-world practice when using the Minimed 780G.

In the case of Control-IQ, there was a 1-year retrospective study of 9,451 child and adult patients who mostly used Basal IQ (PLGS SAP) in the past and changed to use Control-IQ (HCL) [98]. In this study, TIR was improved by 10% (63.6% to 73.6%, \( P < 0.001 \)), and TBR was kept as low as around 1%, so glycemic improvements seen in the RCTs were substantiated in the real-world study. In addition, the time spent in auto-mode was 95%, which is much higher than that in the Minimed 670G studies. Similarly, in a prospective cohort of 191 child patients, TIR was improved by 9% (57% to 66%, \( P < 0.001 \)) and TBR was reduced by 0.4% (2.2% to 1.8%, \( P = 0.01 \)) at 6-month follow-up [99]. Auto-mode usage was as high as 86.4%, and the number of patients who stopped using the device was only 3.5%, showing good usability even for children. This might be due to the feature of Control-IQ, which has no kick-out process for hyperglycemia, does not require calibration, and to some extent, has auto-correction bolus function. In addition, since most participants in those studies previously used Tandem insulin pumps, it seems that familiarity with the devices might have contributed to the results.

For CamAPS FX, because it was recently approved by CE, there have been few published real-world studies, despite many ongoing cohort studies. Auto-mode usage was as high as 95% in an RCT that used commercialized CamAPS FX [100]. This can be partly attributed to the features of CamAPS FX, which uses Dexcom G6, a factory-calibrated CGM.

**CLINICAL EVIDENCE FOR DUAL-HORMONE CLOSED-LOOP SYSTEMS**

Patients with T1DM often have impairments in counter-regulatory response to hypoglycemia as well as insulin secretion [101]. Single-hormone closed-loop systems can reduce hypoglycemia by suspending insulin administration or by decreasing the basal insulin rate. However, because of the time gap between the onset of insulin action and the rise in blood glucose, single-hormone APS users remain at high risk of developing hypoglycemia after meals, especially if they exercise [102]. Therefore, dual-hormone APSs have been designed to deliver small boluses of glucagon when hypoglycemia is predicted, in addition to suspending insulin delivery.

The first dual-hormone system began to develop early (Table 3). Since 2010, the Beta Bionics, Inreda, IRCM, and Oregon groups have conducted short-term (up to 28 hours) studies comparing CSII or single HCL in 10 to 15 hospitalized adult T1DM patients [32,33,55,103,104]. Some of these studies showed improvements in TIR and TBR, but others did not. In 2014, the Beta Bionics group conducted a study in hotel (adult) and diabetes camp (youth) environments for 5 days among 52 (20 adults, 32 adolescents) T1DM patients, the largest number of subjects to date in a dual-hormone study [51]. Unlike previous studies, the control algorithm in the Beta Bionics study was run on a smartphone rather than a PC. Compared with CSII, TIR 70 to 180 mg/dL was improved by approximately 30% in adults, reaching 79.5% (adult) with the dual-hormone HCL, which was remarkable compared with the TIR 70 to 180 mg/dL of about 70% reported in insulin-only HCL studies during the same period. However, that study compared a dual-hormone HCL with CSII and still did not significantly reduce hypoglycemia in children or adolescents. In 2015, the IRCM group published two 3-arm studies that compared dual-hor-
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Table 3. Clinical evidence of dual-hormone-closed-loop system in type 1 diabetes mellitus

| Year | Design | Group | Intervention | Control | Duration | Setting | Age, yr | Intervention type | TIR 72–180 | TIR 70–180 | TBR <70 |
|------|--------|-------|-------------|---------|----------|---------|--------|------------------|------------|------------|-------|
| 2010 [35] | RCT, crossover | Medtronic | Dual HCL | NA | 18–45 | Inpatient | ≥18 | D-Tron+pumps | 90% vs. 84% | 88% vs. 71% | <0.01 |
| 2011 [36] | RCT, crossover | Medtronic | Dual HCL | NA | 18–45 | Inpatient | ≥18 | D-Tron+pumps | 90% vs. 84% | 88% vs. 71% | <0.01 |

The unit of TIR and TBR target is mg/dL. COM, continuous glucose monitoring; HCL, hybrid closed-loop systems; NA, not available; TIR, time in range; TBR, time below range; RCT, randomized control trial; CSII, continuous subcutaneous insulin infusion; IRCM, Institut de Recherches Cliniques de Montreal; ON, overnight; SAP, sensor-augmented pump; PLGS, predictive low glucose suspension; FCL, full-closed-loop system.
mone HCL with both CSII and insulin-only HCL [34,52]. One was a short-term study of 24 hours in 30 inpatient adolescents and adults and showed an improving but statistically insignificant trend in TIR and TBR compared with single-hormone HCL [52]. On the other hand, the study of 33 children and adolescents conducted during 3 nights at a diabetes camp showed that with the dual-hormone HCL, TBR improved compared with a single-hormone HCL (0% vs. 3.1%) [34]. Therefore, it was suggested that dual-hormone HCL would be helpful in groups particularly vulnerable to hypoglycemia, such as children, but not in all groups. In 2016, the Beta Bionics group performed an additional 5-day pediatric study (ages 6 to 11) at a diabetes camp, and both TIR and TBR were improved compared with CSII [105]. In the same year, the Oregon and IRCM groups showed better hypoglycemia control with dual-hormone HCL than with SAP and single-hormone HCL, respectively, in short-term studies of exercising patients [106,107].

Up to that point, studies have been conducted in hospitals, hotels, and camps, with participants in so-called outpatient studies spending their nights at a hotel [51]. In 2016, the Inreda group performed the first truly home-based dual-hormone study for a short period and reported significantly improved TIR compared with CSII [108]. Notably, unlike the previous studies by other groups that used two pumps for insulin and glucagon, the Inreda group used one dual-chamber pump called the Inreda Artificial Pancreas (Inreda Diabetic). The IRCM group performed home-based dual-hormone studies in 2016 to 2017, with SAP or single-hormone HCL as the control condition, and succeeded in showing improvements only in comparison with SAP, not with single-hormone HCL [109,110]. In 2017, the Beta Bionics group conducted a home-based study in 43 adults for up to 11 days and reported considerable improvements in TIR and TBR compared with CSII or SAP [111].

Next, the Oregon group performed outpatient dual-hormone studies with single-hormone HCL as the control, focusing on efficacy during exercise. In 2018, the dual-hormone system in 20 exercising T1DM patients across 4 days showed improvement in TBR 70 mg/dL compared with single-hormone HCL (1.3% vs. 2.8%, \( P < 0.001 \)) [53]. In 2020, the group also showed the efficacy of dual-hormone HCL with a stable liquid glucagon formulation in an exercising outpatient setting [36]. In 2021, the Inreda group conducted a two-week home-based study, the longest of the dual-hormone studies so far, and showed an improvement in TIR and TBR compared with CSII or SAP [50]. Remarkably, all the other dual-hormone systems were HCL systems, but in this study, the bolus dose was determined without requiring the user to enter the carbohydrate amount, so it can be regarded as an FCL. In the most recent study at the time of writing, the Beta Bionics group reported a small (7 days with 10 patients) study comparing a dual-hormone HCL using a dual-chamber pump (iLet, Beta Bionics) and dasiglucagon [54] with a single-hormone HCL. Although that study did not report statistical differences, the dual-hormone HCL showed higher TIR and TBR values than the single-hormone HCL.

Dual-hormone APS studies have thus grown larger and longer over time, and studies using CSII or SAP as the control have provided comparisons with single-hormone HCL systems. The development of dual-chamber pumps (Inreda and Beta Bionics groups), rather than separate pumps, is also a remarkable change. In addition, as shown in the Inreda group study, FCL is nearly a reality. According to the clinical evidence to date, dual-hormone APs produce superior TIR and TBR to those with CSII or SAP. However, compared with single-hormone HCL systems, APs have shown improvements only in groups vulnerable to hypoglycemia, such as exercising patients or children. However, most studies have compared dual-hormone HCL with its own single-hormone HCL in relatively small samples, and they generally showed superior TIR of 80s% versus 70s%, compared with the single-hormone group's HCL studies. More accurate results could be obtained by conducting dual-hormone studies on a larger scale and comparing those systems with single-hormone HCL systems from single-hormone groups. Due to the limitations of using two pumps or two chambers and glucagon instability, no large-scale or long-term dual-hormone study has yet been conducted in contrast to single-hormone HCL systems. Although the Inreda APS received the CE mark [50], no product has yet been commercialized. The glucagon pump needs to be replaced daily, and the infusion set needs to be exchanged every 24 hours because the current glucagon formulations are unstable in the infusion sets after 24 hours. These problems might be solved by using a novel glucagon analog that is currently under development.

Additionally, the side effects of glucagon may be an important issue. Although none of the available data seemed to report serious adverse events to date, glucagon can cause side effects such as nausea and vomiting, and erythema at the glucagon infusion site. Glucagon also has potential pleiotropic effects on cardiac contractility, renal function, and the central nervous system [112]. Therefore, patients should be monitored for potential side effects of glucagon on the cardiovascular sys-
tem, renal system, liver, and lipoprotein levels in long-term trials [112]. Other possible safety concerns, such as potential hepatic glycogen depletion and impaired glucagon response, have been raised regarding the use of glucagon in APS. However, in a human study of 11 adults with T1DM, hepatic glycogen stores and the response to glucagon were maintained after repeated doses of glucagon [113]. Given the lack of evidence regarding the long-term safety of glucagon in APS, additional data from large, long-term follow-up studies are necessary to address these concerns.

**ADVERSE EVENTS OF CLOSED-LOOP SYSTEMS**

So far, we have focused on the effects of APS, but adverse events should not be overlooked. The main adverse events in the previous major clinical trials are presented in Supplementary Table 2. For single-hormone HCL studies, although each study presented a different form, TBR <54 or <50 mg/dL were significantly improved in HCL compared to CSII (Florence system, TBR <50 mg/dL, 0.3% vs. 1.0%, \(P<0.01\); Minimed 670G, TBR <54 mg/dL, 0.2% vs. 0.9%, \(P<0.01\)) [24,77]. When compared with SAP, some studies of single-hormone HCL showed improvements (Control-IQ, TBR <54 mg/dL, 0.29% vs. 0.35%, \(P=0.02\); DBLG1, TBR <50 mg/dL, 0.2% vs. 0.7%, \(P<0.01\)) [45,47], and some did not show any difference (Florence system, TBR <50 mg/dL, 0.3% vs. 0.5%, \(P=0.11\); DBLG1, TBR <54 mg/dL, 0.24% vs. 0.32%, \(P=0.42\)) [78,88]. When it comes to advanced HCL, TBR <54 mg/dL was superior to PLGS SAP (Minimed 780G vs. 640G, TBR <54 mg/dL, 0.4% vs. 0.5%, \(P=0.03\)) and was non-inferior to HCL (Minimed 780G vs. 670G, TBR <54 mg/dL, 0.46% vs. 0.50%, \(P<0.01\) [non-inferior test]) [37,38]. For dual-hormone closed-loop systems, despite presenting only TBR of <60 mg/dL rather than <54 mg/dL, they all showed significant improvements even when compared to SAP (Beta bionics, TBR <60 mg/dL, 0.6% vs. 1.9%, \(P<0.01\); Inreda, TBR <60 mg/dL, 0% vs. 0.5%, \(P<0.01\)) [50,111].

For severe hypoglycemia, which requires assistance from another person, most clinical studies showed no events in either the closed-loop system group or the control group. There were a few cases where it was slightly higher in the closed-loop or advanced closed-loop group, although no statistical comparison was presented (Minimed 670G vs. MDI or CSII, 8 events vs. 7 events; DBLG1 vs. SAP, 5 events vs. 3 events; 780G vs. 670G, 1 events vs. 0 events); however, most events were not related to the control algorithm [38,47,76]. Diabetic ketoacidosis also did not occur in either group in most studies, and even if it occurred, most of the cases were caused by other reasons (e.g., infusion set error) rather than automated insulin delivery function [37,45,76,78]. Therefore, based on these results, it can be said that the current APS is safe in terms of adverse events.

**CLINICAL EVIDENCE IN OTHER PATIENT GROUPS**

**Type 2 diabetes mellitus**

Most APS studies have been conducted in patients with T1DM who are insulin-dependent. However, T2DM patients can also become insulin-dependent as the disease progresses. Therefore, APS could be of great help to these patients. T2DM studies have been conducted mainly by the CamDiab group, though all were short-term and conducted among hospitalized patients (Table 4). The first HCL study in T2DM patients was performed in 2014 in 12 insulin-naive patients and reported improvement in TIR 70 to 180 mg/dL with HCL compared with glucose-lowering medication (40% vs. 24%, \(P=0.016\)) [114]. In 2017, a study was conducted in T2DM patients on insulin treatment for 3 days, resulting in TIR 100 to 180 mg/dL improvements compared with conventional insulin treatment (59.8% vs. 38.1%, \(P=0.004\)) [115]. In the following year, a larger study (136 patients, mean 8 days) produced substantial TIR improvements (65.8% vs. 41.5%, \(P<0.001\)) [43]. Moreover, a subgroup analysis showed that dialysis patients had even more remarkable improvement in TIR 100 to 180 mg/dL (69.0% vs. 31.5%, \(P<0.001\)) [116]. The IRCM group, which has mainly studied dual-hormone APS, announced a T2DM patient study of a single-hormone HCL in 2019 [117]. This was a small pilot study of 15 patients using MDI, and TIR 70 to 180 mg/dL on plasma glucose (PG), but not on sensor glucose, which is an APS study standard, was improved by the HCL. In the CamDiab studies, TIR improved by approximately 20% compared with conventional treatment, and the TIR in the HCL group was somewhat lower than in T1DM studies, which seems to be because TIR 100 to 180 mg/dL was used in T2DM studies instead of TIR 70 to 180 mg/dL. T2DM APS studies have not yet been conducted in outpatient settings, have been limited to short-term studies, and have not yet been compared with SAP.

**Pregnant type 1 diabetes mellitus patients**

Pregnant T1DM patients have different blood glucose targets
| Year   | Group         | CGM          | Pump         | Design       | No. | Age, yr | Setting | Duration | Intervention         | Control          | Outcome (intervention vs. control)                                                                 |
|--------|---------------|--------------|--------------|--------------|-----|---------|---------|----------|-----------------------|------------------|----------------------------------------------------------------------------------------------------|
|        |                |              |              |              |     |         |         |          |                        |                  | TIR (mg/dL)                                                                                         |
|        |                |              |              |              |     |         |         |          | TBR (mg/dL)            |                  |                                                                                                   |
| T2DM   |                |              |              |              |     |         |         |          |                        |                  |                                                                                                   |
| 2014   | CamDiab       | Freestyle    | Animas 2020  | RCT,         | 12  | ≥18     | Inpatient | 1 day    | HCL                   | OAD (insulin     | TIR 70–180: 40% vs. 24%, *p* = 0.02 TBR <70: 0% vs. 0%, *p* = 1.000 |                               |
|        |                | Navigator     |              | crossover    |     |         |         |          | naive                 |                  |                                                                                                   |
| 2017   | CamDiab       | Freestyle    | Dana R       | RCT,         | 40  | ≥18     | Inpatient | 3 days   | HCL                   | Conventional     | TIR 100–180: 59.8% vs. 38.1%, *p* < 0.01 TBR <63: 0% vs. 0.0%, *p* = 0.35 |                               |
|        |                | Navigator II  |              | parallel     |     |         |         |          | insulin therapy       |                  |                                                                                                   |
| 2018   | CamDiab       | Freestyle    | Dana R       | RCT,         | 136 | ≥18     | Inpatient | Up to 15 days | HCL                   | Conventional     | TIR 100–180: 65.8% vs. 41.5%, *p* < 0.01 TBR <70: 0.5% vs. 0.0%, *p* = 0.13 |                               |
|        |                | Navigator II  |              | parallel     |     |         |         |          | insulin therapy       |                  |                                                                                                   |
| 2019   | CamDiab       | Freestyle    | Dana R       | RCT,         | 17  | ≥18     | Inpatient | Up to 15 days | HCL                   | Conventional     | TIR 100–180: 69.0% vs. 31.5%, *p* < 0.01 TBR <54: 0.0% vs. 0.0%, *p* = 0.82 |                               |
|        |                | Navigator II  |              | parallel     |     |         |         |          | insulin therapy       |                  |                                                                                                   |
| 2019   | IRCM          | Dexcom G4    | Accu-Chek   | RCT,         | 15  | ≥18     | Inpatient | 1 day    | HCL                   | MDI               | TIR 72–180: 92% vs. 85%, *p* < 0.05 (plasma); 90% vs. 84%, *p* = 0.11 (sensor) TBR <72: 0% vs. 0%, *p* = 0.22 (plasma); 0% vs. 0%, *p* = 0.45 (sensor) |                               |
|        |                | Platinum      | Combo        | crossover    |     |         |         |          |                        |                  |                                                                                                   |

Pregnant T1DM

| Year   | Group         | CGM          | Pump         | Design       | No. | Setting | Duration | Intervention | Control          | Outcome (intervention vs. control)                                                                 |
|--------|---------------|--------------|--------------|--------------|-----|---------|----------|--------------|------------------|----------------------------------------------------------------------------------------------------|
|        |                |              |              |              |     |         |          |              |                  | TIR (mg/dL)                                                                                         |
|        |                |              |              |              |     |         |          |              | TBR (mg/dL)            |                                                                                                   |
| 2011   | CamDiab       | Freestyle    | Deltec       | Single arm   | 10  | NA      | Inpatient | 2 days      | OCL (early       | OCL (late         | TIR 63–140: 84% vs. 100%, *p* = 0.09 TBR <63: 0% vs. 0%, *p* = 0.13 |                               |
|        |                | Navigator     | Cosmo        |              |     |         |         |              | pregnancy)      | pregnancy)       |                                                                                                   |
| 2011   | CamDiab       | Freestyle    | Animas 2020  | RCT,         | 12  | NA      | Inpatient | 2 days      | HCL              | CSII              | TIR 63–140: 81% vs. 81%, *p* = 0.75 TBR <45: 0.0% vs. 0.3%, *p* = 0.04 |                               |
|        |                | Navigator     |              | parallel     |     |         |         |              |                  |                                                                                                   |
| 2016   | CamDiab       | Freestyle    | Dana R       | RCT,         | 16  | NA      | Home     | 4 weeks     | OCL              | SAP               | ON TIR 63–140: 74.7% vs. 59.6%, *p* < 0.01 ON TBR <63: 1.3% vs. 1.9%, *p* = 0.28 |                               |
|        |                | Navigator II  |              | crossover    |     |         |         |              |                  |                                                                                                   |
| 2018   | CamDiab       | Freestyle    | Dana R       | RCT,         | 16  | NA      | Home     | 4 weeks     | HCL              | SAP               | TIR 63–140: 62.3% vs. 60.1%, *p* = 0.47 TBR <63: 1.6% vs. 2.7%, *p* = 0.04 |                               |
|        |                | Navigator II  |              | crossover    |     |         |         |              |                  |                                                                                                   |

The unit of TIR and TBR target is mg/dL.

T2DM, type 2 diabetes mellitus; T1DM, type 1 diabetes mellitus; CGM, continuous glucose monitoring system; RCT, randomized control trial; HCL, hybrid closed-loop system; OAD, oral antidiabetic drug; TIR, time in range; TBR, time below range; HD, hemodialysis; MDI, multiple daily insulin injection; NA, not available; OCL, overnight closed-loop system; SAP, sensor augmented pump; ON, overnight.
than the general T1DM population, and insulin resistance increases as pregnancy progresses, so the insulin requirement also changes during pregnancy [118]. Glycemic control during pregnancy is crucial because it has a considerable influence on both fetal and maternal outcomes. A large-scale study in pregnant T1DM patients found that CGM improved maternal and fetal outcomes [119]. Few APS studies have been conducted in pregnant subjects, mostly performed by the CamDiab group (Table 4). In 2011, after a safety study of OCL [120], HCL was compared with CSII for 2 days in 12 pregnant T1DM patients in a hospital, resulting in TBR <45 mg/dL improvement (0.0% vs. 0.3%, \( P=0.04 \)) but no change in TIR 63 to 140 mg/dL [121]. In 2016, the HCL was compared with SAP for 4 weeks in 16 outpatients, and overnight TIR 63 to 140 mg/dL was remarkably improved (74.7% vs. 59.6%, \( P=0.002 \)) [44]. In 2018, a similar study design was used to assess similar subjects all-day, and TIR did not differ, but TBR <63 mg/dL was improved (1.6% vs. 2.7%, \( P=0.04 \)) [122]. To date, although evidence is lacking for all-day TIR, HCL has been shown to improve all-day TBR and overnight TIR. Based on this evidence, CamAPS FX was approved by CE in 2020 for use in pregnant T1DM patients. However, obstetric and neonatal outcomes have not been examined or compared with conventional treatments and more evidence is needed to inform on the suitability of the approach in such cases.

**DO-IT-YOURSELF CLOSED-LOOP SYSTEMS**

Advances in technology such as closed-loop APSs have allowed patients with T1DM to have better glycemic control and improved quality of life. However, some T1DM patients and their caregivers were unsatisfied with the current pace of commercial APS development and thus began the #WeAreNot-Waiting movement on social media in 2013 [39]. Initially, this DIY movement included only a few users who were developing and sharing programs to manage their CGM and insulin pumps independently. Since then, several open source platforms have been developed to allow T1DM patients to build artificial pancreas technology without regulatory approval, and the number of DIY closed-loop users has been growing steadily alongside several thousands of patients using commercial closed-loop systems [123]. A DIY closed-loop system uses a processor capable of receiving CGM data and open source control algorithms to control the rate of insulin delivery through a compatible insulin pump [123].

The three main DIY closed-loop software systems in use are OpenAPS, Loop, and AndroidAPS [39]. None of them had received regulatory approval because they had not undergone clinical trials, and all studies to date have been retrospective (Supplementary Table 3) [124-132]. One randomized clinical trial using AndroidAPS and the DANA-I pump is currently ongoing (ACTRN1262000034932) [133]. In addition, Tidepool, a non-profit software organization sponsored by Juvenile Diabetes Research Foundation and the Helmsley Charitable Trust, is developing an APS application based on the Loop DIY algorithm to receive FDA approval [39]. Although these DIY closed-loop systems have not yet been approved, they have the benefits of rapid development cycles and flexibility in terms of customization (such as individualized target glucose ranges) [125]. Observational studies conducted via online surveys and sentiment analyses of Twitter data suggest that DIY closed-loop systems have beneficial effects on glycemic control and users’ quality of life [126]. For example, in an online survey, 56% of DIY closed-loop users reported a large improvement in sleep quality [134]. A study conducted in Italy reported a significant decrease in HbA1c (from 7.17% to 6.61%, \( P<0.05 \)) after implementation of the OpenAPS in 30 patients with T1DM [135]. Data from T1DM patients in Korea using OpenAPS also showed a significant decrease in HbA1c (6.8% to 6.3%, \( P<0.001 \)) and an increase in percent TIR (70.1% to 83.3%, \( P<0.001 \)) [136]. However, these data have sample size and methodological limitations. Given the lack of regulatory approval and insufficient data regarding safety, the use of DIY closed-loop systems is considered risky. When a problem occurs in a DIY system, it can be difficult to solve. Moreover, when medical accidents occur, the subject of responsibility is unclear, and legal and ethical problems can arise [137].

In May 2020, Diabetes UK released a position statement about unapproved DIY closed-loop systems recommending that T1DM patients who wish to use such systems are aware that their choice is at their own risk [138]. DIY closed-loop systems cannot be ignored, but there is a paucity of research on their safety and efficacy. Therefore, patients using DIY closed-loop systems should continue to receive care from healthcare professionals.

**OTHER POTENTIAL ADJUNCTIVE HORMONES AND HORMONE-LIKE PEPTIDES**

Researchers are looking for ways to address the challenges that
result from the pharmacokinetics of insulin in APSs. To mimic the function of the pancreas more perfectly and reduce the time of postprandial hyperglycemia, researchers have been investigating other peptide hormones and hormone-like peptides.

Amylin analogues
Amylin is a peptide hormone that is co-secreted with insulin and is produced by pancreatic β-cells. It regulates postprandial glucagon secretion and hepatic glucose production, delays gastric emptying, and promotes satiety [139,140]. Patients with T1DM often have a deficiency in this peptide because of the destruction of β-cells [141]. In light of this, several studies have investigated the efficacy of co-administration of synthetic amylin (pramlintide) in closed-loop systems (Supplementary Table 4) [142,143]. These trials suggest that co-administration of pramlintide with insulin reduces the magnitude of postprandial increments in PG by delaying the time to peak postprandial PG compared with the treatment with insulin alone or insulin plus placebo [40,142-144]. In a study conducted by Weinzimer et al. [142], pramlintide administration delayed the time to peak blood glucose (2.5 hours vs. 1.5 hours, P<0.0001) compared with a closed-loop system alone. Another trial compared the post-meal incremental PG area under the curve (AUC) from a single dose of pramlintide (60 μg) with that of a control group (without pramlintide). Insulin with pramlintide reduced the post-meal incremental PG AUC (P=0.0002) [143]. In a randomized, single-blind, 24-hour, crossover inpatient study, mean 24-hour glucose measured by CGM was lower upon co-administration of pramlintide versus placebo (153 mg/dL vs. 174.6 mg/dL, P=0.012) [144]. In a randomized crossover trial comparing a rapid insulin alone APS with a rapid insulin and pramlintide system, the rapid insulin and pramlintide system increased TIR from 74% to 84% (P=0.0014) [40]. These studies were small and conducted under controlled conditions in the hospital. The most common adverse effects of pramlintide are gastrointestinal symptoms, such as nausea and vomiting, which occur in 9.5% to 59% of patients [145]. To determine whether chronic administration of pramlintide could improve glycemic control in patients with T1DM, longer studies with dose titration should be conducted under the conditions of daily life.

GLP-1 receptor agonist
GLP-1 is released mostly by intestinal L-cells, with small quantities secreted by pancreas [146]. GLP-1Rs are expressed not only in the gastrointestinal tract, but also in other tissues and organs, including the vascular smooth muscle, brain, heart, kidney, and lung [146]. Following several trials in T2DM patients, a GLP-1R agonist has been approved for diabetes management, and it also demonstrated cardiovascular benefits [147]. Therefore, GLP-1R agonists are under investigation as potential adjunctive therapies for closed-loop APSs [148].

An RCT with a crossover design suggested the efficacy of an adjuvant GLP-1 agonist (liraglutide) and insulin in patients with T1DM using a closed-loop system (Supplementary Table 4). In the study of Ilkowitz et al. [41], the mean blood glucose levels and postprandial blood glucose levels were lower in the liraglutide arm (liraglutide vs. insulin monotherapy, 144.6 mg/dL vs. 159.7 mg/dL, P=0.0002). In a head-to-head study comparing a GLP-1 agonist (exenatide) and pramlintide in T1DM patients using a closed-loop system, the GLP-1 agonist showed a postprandial glucose-lowering effect superior to that of pramlintide (TIR 70 to 180 mg/dL, 77% vs. 62%) [148]. These studies support the idea that the adjunctive use of a GLP-1 agonist could closely mimic the physiological state of the pancreas. However, it is important to note that both studies were performed for fewer than 2 days with only 10 to 15 participants. Further research in large samples is required to investigate the long-term use of a GLP-1 agonist in a closed-loop system.

Intraperitoneal delivery of insulin
To achieve suitable glycemic levels, IP insulin delivery is considered a viable alternative to the conventional route for insulin delivery [149]. IP insulin delivery systems are generally composed of a catheter inserted into the peritoneal cavity and an insulin infusion pump. Insulin is infused from an externally placed or implanted pump into the abdominal wall. Some researchers have suggested that IP insulin delivery has physiological advantages that result from faster pharmacokinetics and pharmacodynamics, which provide a better insulin/glucagon balance [150,151]. Other researchers have reported that IP insulin delivery might reduce the frequency of hypoglycemic events (Supplementary Table 4) [152,153]. Renard et al. [154] demonstrated the feasibility of a closed-loop IP insulin pump in a hospital setting. Recently, Dassau et al. [42] conducted a pilot study comparing an implantable IP insulin pump to subcutaneous insulin injection from an APS. In that study, the IP route provided better glucose control than subcutaneous insulin delivery. However, implantable IP insulin pumps are avail-
able in only a few European countries, and further studies are required to address safety issues such as infections or hematomas at the implant site.

LIMITATIONS AND FUTURE DIRECTIONS

Since the basic experiments in the 2000s, numerous APSs have been developed, clinically validated, commercialized, and used in actual practice for T1DM patients. Despite recent radical advances in APS technology, a genuinely FCL that effectively accomplishes glycemic control in every situation without meal or exercise announcements has not yet been demonstrated. Several early studies attempted automatic control of postprandial glucose without the need to enter carbohydrate contents, but most of them were non-comparative feasibility studies conducted for short periods in hospital settings [19,20,155-157]. Although FCL in early studies offers better glycemic control than open-loop systems [155], some studies showed that they were worse than HCL with meal announcements [19]. These shortcomings result from the inherent limitations of closed-loop systems. In healthy human bodies, blood glucose is detected, and insulin is directly secreted into the blood vessels by the pancreas. In contrast, in a closed-loop system, a CGM detects glucose in interstitial fluid, not blood, and insulin is injected into subcutaneous tissues instead of blood vessels, which incurs time lags. For this reason, controlling glucose without the help of manual bolus control remains difficult in situations where blood glucose changes rapidly, such as after meals or during exercise. In addition, as shown by real-world evidence, improving compliance is an important issue because of the difficulty in wearing current systems [158].

Several possibilities for solving these problems have been suggested and attempted. To solve the time lag during insulin infusion, it might be possible to develop and apply faster-acting insulin. APS studies using faster-acting insulin (e.g., Fiasp) are in progress and at the time of writing, CamAPS FX has been approved to use Fiasp [100,159]. In addition, it could be possible for an APS system to accurately predict the blood glucose response automatically by having the patient take a picture of their meal using an artificially intelligent camera instead of manually counting the carbohydrates [160]. As seen in the Inreda group study, advances in a dual-hormone closed-loop system that can actively improve hypoglycemia might also lead to an FCL [50]. To that end, the instability of glucagon and the inconvenience of multiple insertion sites must be corrected. Building an all-in-one wearable APS system that combines CGM, a patch pump, and the control algorithm into one device to improve user comfort is another development direction. Because APS has only been evaluated in short-term hospital-based studies in T2DM patients, and no study has considered pregnant T2DM or gestational diabetes patients [43,117], APS development for those populations, who require intensive insulin treatment, is a task for future researchers. In addition, APS studies might also be needed in situations in which blood glucose goes rapidly out of control, such as during steroid treatments, transplantation, or chemotherapy.

SUPPLEMENTARY MATERIALS

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CONFLICTS OF INTEREST

No potential conflict of interest relevant to this article was reported.

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REFERENCES

1. DiMeglio LA, Evans-Molina C, Oram RA. Type 1 diabetes.
Lancet 2018;391:2449-62.
2. Chae HW, Seo GH, Song K, Choi HS, Suh J, Kwon A, et al. Incidence and prevalence of type 1 diabetes mellitus among Korean children and adolescents between 2007 and 2017: an epidemiologic study based on a national database. Diabetes Metab J 2020;44:866-74.
3. SEARCH for Diabetes in Youth Study Group, Liese AD, D’Agostino RB Jr, Hamman RF, Kilgo PD, Lawrence JM, et al. The burden of diabetes mellitus among US youth: prevalence estimates from the SEARCH for Diabetes in Youth Study. Pediatrics 2006;118:1510-8.
4. Dayan CM, Korah M, Tatovic D, Bundy BN, Herold KC. Changing the landscape for type 1 diabetes: the first step to prevention. Lancet 2019;394:1286-96.
5. Dean PG, Kukla A, Stegall MD, Kudva YC. Pancreas transplantation. BMJ 2017;357:j1321.
6. Cai X, Lin C, Yang W, Nie L, Ji L. Non-insulin antidiabetes treatment in type 1 diabetes mellitus: a systematic review and meta-analysis. Diabetes Metab J 2021;45:312-25.
7. Foster NC, Beck RW, Miller KM, Clements MA, Rickels MR, DiMeglio LA, et al. State of type 1 diabetes management and outcomes from the T1D exchange in 2016-2018. Diabetes Technol Ther 2019;21:66-72.
8. Pettus JH, Zhou FL, Shepherd L, Preblick R, Hunt PR, Paranjpe S, et al. Incidences of severe hypoglycemia and diabetic ketoacidosis and prevalence of microvascular complications stratified by age and glycemic control in U.S. adult patients with type 1 diabetes: a real-world study. Diabetes Care 2019;42:2220-7.
9. Hopkins D, Lawrence I, Mansell P, Thompson G, Amiel S, Campbell M, et al. Improved biomedical and psychological outcomes 1 year after structured education in flexible insulin therapy for people with type 1 diabetes: the U.K. DAFNE experience. Diabetes Care 2012;35:1638-42.
10. Pickup JC. Insulin-pump therapy for type 1 diabetes mellitus. N Engl J Med 2012;366:1616-24.
11. Karges B, Schwandt A, Heidtmann B, Kordonouri O, Binder E, Schierloh U, et al. Association of insulin pump therapy vs insulin injection therapy with severe hypoglycemia, ketoacidosis, and glycemic control among children, adolescents, and young adults with type 1 diabetes. JAMA 2017;318:1358-66.
12. Blair JC, McKay A, Ridyard C, Thornborough K, Bedson E, Peak M, et al. Continuous subcutaneous insulin infusion versus multiple daily injection regimens in children and young people at diagnosis of type 1 diabetes: pragmatic randomized controlled trial and economic evaluation. BMJ 2019;365:l1226.
13. Yeh HC, Brown TT, Maruthur N, Ranasinghe P, Berger Z, Suh YD, et al. Comparative effectiveness and safety of methods of insulin delivery and glucose monitoring for diabetes mellitus: a systematic review and meta-analysis. Ann Intern Med 2012;157:336-47.
14. Cappon G, Vettoretti M, Sparacino G, Facchinetti A. Continuous glucose monitoring sensors for diabetes management: a review of technologies and applications. Diabetes Metab J 2019;43:383-97.
15. Bergenstal RM, Tamborlane WV, Ahmann A, Buse JB, Dailey G, Davis SN, et al. Effectiveness of sensor-augmented insulin-pump therapy in type 1 diabetes. N Engl J Med 2010;363:311-20.
16. Bergenstal RM, Klonoff DC, Garg SK, Bode BW, Meredith M, Slover RH, et al. Threshold-based insulin-pump interruption for reduction of hypoglycemia. N Engl J Med 2013;369:224-32.
17. Maahs DM, Calhoum P, Buckingham BA, Chase HP, Hramiak I, Lum J, et al. A randomized trial of a home system to reduce nocturnal hypoglycemia in type 1 diabetes. Diabetes Care 2014;37:1885-91.
18. Buckingham BA, Raghinaru D, Cameron F, Bequette BW, Chase HP, Maahs DM, et al. Predictive low-glucose insulin suspension reduces duration of nocturnal hypoglycemia in children without increasing ketosis. Diabetes Care 2015;38:1197-204.
19. Weinzimer SA, Steil GM, Swan KL, Dziura J, Kurtz N, Tamborlane WV. Fully automated closed-loop insulin delivery versus semiautomated hybrid control in pediatric patients with type 1 diabetes using an artificial pancreas. Diabetes Care 2008;31:934-9.
20. Atlas E, Nimri R, Miller S, Grunberg EA, Phillip M. MD-logic artificial pancreas system: a pilot study in adults with type 1 diabetes. Diabetes Care 2010;33:1072-6.
21. Hovorka R, Allen JM, Elleri D, Chassin LJ, Harris J, Xing D, et al. Manual closed-loop insulin delivery in children and adolescents with type 1 diabetes: a phase 2 randomised crossover trial. Lancet 2010;375:743-51.
22. Hovorka R, Kumareswaran K, Harris J, Allen JM, Elleri D, Xing D, et al. Overnight closed loop insulin delivery (artificial pancreas) in adults with type 1 diabetes: crossover randomised controlled studies. BMJ 2011;342:d1855.
23. Kovatchev BP, Renard E, Cobelli C, Zisser HC, Keith-Hynes P,
Anderson SM, et al. Feasibility of outpatient fully integrated closed-loop control: first studies of wearable artificial pancreas. Diabetes Care 2013;36:1851-8.

24. Bergenstal RM, Garg S, Weinzimer SA, Buckingham BA, Bode BW, Tamborlane WV, et al. Safety of a hybrid closed-loop insulin delivery system in patients with type 1 diabetes. JAMA 2016;316:1407-8.

25. Phillip M, Battelino T, Atlas E, Kordonouri O, Bratina N, Miller S, et al. Nocturnal glucose control with an artificial pancreas at a diabetes camp. N Engl J Med 2013;368:824-33.

26. Thabit H, Lubina-Solomon A, Stadler M, Leelarathna L, Walkinshaw E, Pernet A, 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;2:701-9.

27. Kropff J, Del Favero S, Place J, Toffanin C, Visentin R, Monaro M, et al. 2 Month evening and night closed-loop glucose control in patients with type 1 diabetes under free-living conditions: a randomised crossover trial. Lancet Diabetes Endocrinol 2015;3:939-47.

28. Thabit H, Tauschmann M, Allen JM, Leelarathna L, Hartnell S, Wilinska ME, et al. Home use of an artificial beta cell in type 1 diabetes. N Engl J Med 2015;373:2129-40.

29. Elleri D, Allen JM, Katikaneni R, Cantwell M, Ramchandani N, Hepburn S, et al. A bihormonal closed-loop artificial pancreas for type 1 diabetes camp. Diabetes Care 2015;38:1205-11.

30. Ly TT, Roy A, Grosman B, Shin J, Campbell A, Monirabbasi S, Leelarathna L, Caldwell K, et al. Closed-loop basal insulin delivery over 36 hours in adolescents with type 1 diabetes: randomized clinical trial. Diabetes Care 2013;36:838-44.

31. El-Khatib FH, Jiang J, Damiano ER. A feasibility study of bihormonal closed-loop blood glucose control using dual subcutaneous infusion of insulin and glucagon in ambulatory diabetic swine. J Diabetes Sci Technol 2009;3:789-803.

32. El-Khatib FH, Russell SJ, Nathan DM, Sutherlin RG, Damiano ER. A bihormonal closed-loop artificial pancreas for type 1 diabetes. Sci Transl Med 2010;2:27ra27.

33. Castle JR, Engle JM, El Youssef J, Massoud RG, Yuen KC, Kagan R, et al. Novel use of glucagon in a closed-loop system for prevention of hypoglycemia in type 1 diabetes. Diabetes Care 2010;33:1282-7.

34. Haidar A, Legault L, Matteau-Pelletier L, Messier V, Dallaire M, Ladouceur M, et al. Outpatient overnight glucose control with dual-hormone artificial pancreas, single-hormone artificial pancreas, or conventional insulin pump therapy in children and adolescents with type 1 diabetes: an open-label, randomised controlled trial. Lancet Diabetes Endocrinol 2015;3:595-604.

35. Dovc K, Macedoni M, Bratina N, Lepej D, Nimri R, Atlas E, et al. Closed-loop glucose control in young people with type 1 diabetes during and after unannounced physical activity: a randomised controlled crossover trial. Diabetologia 2017;60:2157-67.

36. Wilson LM, Jacobs PG, Ramsey KL, Resalat N, Reddy R, Bramigan D, et al. Dual-hormone closed-loop system using a liquid stable glucagon formulation versus insulin-only closed-loop system compared with a predictive low glucose suspend system: an open-label, outpatient, single-center, crossover, randomized controlled trial. Diabetes Care 2020;43:2721-9.

37. Collyns OJ, Meier RA, Betts ZL, Chan DS, Frampton C, Frewen CM, et al. Improved glycemic outcomes with Medtronic MiniMed Advanced Hybrid Closed-Loop Delivery: results from a randomized crossover trial comparing automated insulin delivery with predictive low glucose suspend in people with type 1 diabetes. Diabetes Care 2021;44:969-75.

38. Bergenstal RM, Nimri R, Beck RW, Criego A, Laffel L, Schatz D, et al. A comparison of two hybrid closed-loop systems in adolescents and young adults with type 1 diabetes (FLAIR): a multicentre, randomised, crossover trial. Lancet 2021;397:208-19.

39. Wilmot EG, Danne T. DIY artificial pancreas systems: the clinician perspective. Lancet Diabetes Endocrinol 2020;8:183-5.

40. Haidar A, Tsoukas MA, Bernier-Twardy S, Yale JF, Rutkowski J, Bossy A, et al. A novel dual-hormone insulin-and-pramlintide artificial pancreas for type 1 diabetes: a randomized controlled crossover trial. Diabetes Care 2020;43:597-606.

41. Ilkowitz JT, Katikaneni R, Cantwell M, Ramchandani N, Hepburn RA. Adjuvant liraglutide and insulin versus insulin monotherapy in the closed-loop system in type 1 diabetes: a randomized open-labeled crossover design trial. J Diabetes Sci Technol 2016;10:1108-14.
noncritical care. N Engl J Med 2018;379:547-56.
44. Stewart ZA, Wilinska ME, Hartnell S, Temple RC, Rayman G, Stanley KP, et al. Closed-loop insulin delivery during pregnancy in women with type 1 diabetes. N Engl J Med 2016;375:644-54.
45. Brown SA, Kovatchev BP, Raghinaru D, Lum JW, Buckingham BA, Kudva YC, et al. Six-month randomized, multicenter trial of closed-loop control in type 1 diabetes. N Engl J Med 2019;381:1707-17.
46. Brown S, Raghinaru D, Emory E, Kovatchev B. First look at control-IQ: a new-generation automated insulin delivery system. Diabetes Care 2018;41:2634-36.
47. Benhamou PY, Franc S, Reznik Y, Thivolet C, Schaeplényck P, Renard E, et al. Closed-loop insulin delivery in adults with type 1 diabetes in real-life conditions: a 12-week multicentre, open-label randomised controlled crossover trial. Lancet Digit Health 2019;1:e17-25.
48. Benhamou PY, Lablanche S, Vambergue A, Doron M, Franc S, Charpentier G. Patients with highly unstable type 1 diabetes eligible for islet transplantation can be managed with a closed-loop insulin delivery system: a series of N-of-1 randomized controlled trials. Diabetes Obes Metab 2021;23:186-94.
49. Forlenza GP, Buckingham BA, Brown SA, Bode BW, Levy CJ, Criego AB, et al. First outpatient evaluation of a tubeless automated insulin delivery system with customizable glucose targets in children and adults with type 1 diabetes. Diabetes Technol Ther 2021;23:410-24.
50. Blauw H, Onvlee AJ, Klaassen M, van Bon AC, DeVries JH. Fully closed loop glucose control with a bihormonal artificial pancreas in adults with type 1 diabetes: an outpatient, randomized, crossover trial. Diabetes Care 2021;44:836-8.
51. Russell SJ, El-Khatib FH, Sinha M, Magyar KL, McKeon K, Goergen LG, et al. Outpatient glycemic control with a bionic pancreas in type 1 diabetes. N Engl J Med 2014;371:313-25.
52. Haidar A, Legault L, Messier V, Mitre TM, Leroux C, Rabasa-Lhoret R. Comparison of dual-hormone artificial pancreas, single-hormone artificial pancreas, and conventional insulin pump therapy for glycemic control in patients with type 1 diabetes: an open-label randomised controlled crossover trial. Lancet Diabetes Endocrinol 2015;3:17-26.
53. Castle JR, El Youssef J, Wilson LM, Reddy R, Resalat N, Brangan D, et al. Randomized outpatient trial of single- and dual-hormone closed-loop systems that adapt to exercise using wearable sensors. Diabetes Care 2018;41:1471-7.
54. Castellanos LE, Balliro CA, Sherwood JS, Jafri R, Hillard MA, Greaux E, et al. Performance of the insulin-only iLet bionic pancreas and the bihormonal iLet using dasiglucagon in adults with type 1 diabetes in a home-use setting. Diabetes Care 2021;44:e118-20.
55. Van Bon AC, Jonker LD, Koebrugge R, Koops R, Hoekstra JB, DeVries JH. Feasibility of a bihormonal closed-loop system to control postexercise and postprandial glucose excursions. J Diabetes Sci Technol 2012;6:1114-22.
56. Lal RA, Ekhlaspour L, Hood K, Buckingham B. Realizing a closed-loop (artificial pancreas) system for the treatment of type 1 diabetes. Endocr Rev 2019;40:1521-46.
57. Unbehauen H. Control systems, robotics automation: system analysis control: classical approaches II. Oxford: Eolss Publisher; 2009. Chapter 4, PID control; p58-79.
58. Slover RH, Welsh JB, Criego A, Weinziermer SA, Willi SM, Wood MA, et al. Effectiveness of sensor-augmented pump therapy in children and adolescents with type 1 diabetes in the STAR 3 study. Pediatr Diabetes 2012;13:6-11.
59. Ly TT, Nicholas JA, Retterath A, Lim EM, Davis EA, Jones TW. Effect of sensor-augmented insulin pump therapy and automated insulin suspension vs standard insulin pump therapy on hypoglycemia in patients with type 1 diabetes: a randomized clinical trial. JAMA 2013;310:1240-7.
60. Battelino T, Nimri R, Dove K, Phillip M, Bratina N. Prevention of hypoglycemia with predictive low glucose insulin suspension in children with type 1 diabetes: a randomized controlled trial. Diabetes Care 2017;40:764-70.
61. Abraham MB, Nicholas JA, Smith GJ, Fairchild JM, King BR, Ambler GR, et al. Reduction in hypoglycemia with the predictive low-glucose management system: a long-term randomized controlled trial in adolescents with type 1 diabetes. Diabetes Care 2018;41:303-10.
62. Bosi E, Choudhary P, de Valk HW, Lablanche S, Castaneda J, de Portu S, et al. Efficacy and safety of suspend-before-low insulin pump technology in hypoglycaemia-prone adults with type 1 diabetes (SMILE): an open-label randomised controlled trial. Lancet Diabetes Endocrinol 2019;7:462-72.
63. Forlenza GP, Li Z, Buckingham BA, Pinsker JE, Cengiz E, Wadwa RP, et al. Predictive low-glucose suspend reduces hypoglycemia in adults, adolescents, and children with type 1 diabetes in an at-home randomized crossover study: results of the PROLOG trial. Diabetes Care 2018;41:2155-61.
64. O’Grady MJ, Retterath AJ, Keenan DB, Kurtz N, Cantwell M, Spital G, et al. The use of an automated, portable glucose control system for overnight glucose control in adolescents and adults with type 1 diabetes. Diabetes Care 2019;42:929-37.
young adults with type 1 diabetes. Diabetes Care 2012;35:2182-7.

65. Nimri R, Atlas E, Ajzensztejn M, Miller S, Oron T, Phillip M. Feasibility study of automated overnight closed-loop glucose control under MD-logic artificial pancreas in patients with type 1 diabetes: the DREAM Project. Diabetes Technol Ther 2012;14:728-35.

66. Ly TT, Breton MD, Keith-Hynes P, De Salvo D, Clinton P, Benassi K, 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;37:2310-6.

67. Nimri R, Muller I, Atlas E, Miller S, Fogel A, Bratina N, et al. MD-logic overnight control for 6 weeks of home use in patients with type 1 diabetes: randomized crossover trial. Diabetes Care 2014;37:3025-32.

68. Hovorka R, Elleri D, Thabit H, Allen JM, Leelarathna L, El-Khairi R, et al. Overnight closed-loop insulin delivery in young people with type 1 diabetes: a free-living, randomized clinical trial. Diabetes Care 2014;37:1204-11.

69. Nimri R, Bratina N, Kordonouri O, Avbelj Stefanja M, Fath M, Biester T, et al. MD-Logic overnight type 1 diabetes control in home settings: a multicentre, multinational, single blind randomized trial. Diabetes Obes Metab 2017;19:553-61.

70. Kovatchev BP, Renard E, Cobelli C, Zisser HC, Keith-Hynes P, Anderson SM, et al. Safety of outpatient closed-loop control: first randomized crossover trials of a wearable artificial pancreas. Diabetes Care 2014;37:1789-96.

71. Leelarathna L, Dellwe S, Mader JK, Allen JM, Benesch C, Doll W, et al. Day and night home closed-loop insulin delivery in adults with type 1 diabetes: three-center randomized crossover study. Diabetes Care 2014;37:1931-7.

72. Tauschmann M, Allen JM, Wilinska ME, Thabit H, Acerrini CL, Dunger DB, et al. Home use of day-and-night hybrid closed-loop insulin delivery in suboptimally controlled adolescents with type 1 diabetes: a 3-week, free-living, randomized crossover trial. Diabetes Care 2016;39:2019-25.

73. Tauschmann M, Allen JM, Wilinska ME, Thabit H, Acerrini CL, Dunger DB, 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;39:1180-5.

74. Ly TT, Buckingham BA, DeSalvo DJ, Shanmughan S, Sattin-Smith M, DeBoer MD, et al. Day-and-night closed-loop control using the unified safety system in adolescents with type 1 diabetes at camp. Diabetes Care 2016;39:e106-7.

75. Forlenza GP, Pinhas-Hamiel O, Liljenquist DR, Shulman DI, Bailey TS, Bode BW, et al. Safety evaluation of the MiniMed 670G system in children 7-13 years of age with type 1 diabetes. Diabetes Technol Ther 2019;21:11-9.

76. Mcauley SA, Lee MH, Paldus B, Vogrinn S, de Bock MI, Abraham MB, et al. Six months of hybrid closed-loop versus manual insulin delivery with fingerprick blood glucose monitoring in adults with type 1 diabetes: a randomized, controlled trial. Diabetes Care 2020;43:3024-33.

77. Bally L, Thabit H, Kojzar H, Mader JK, Qerimi-Hyseni J, Hartnell S, et al. Day-and-night glycaemic control with closed-loop insulin delivery versus conventional insulin pump therapy in free-living adults with well controlled type 1 diabetes: an open-label, randomised, crossover study. Lancet Diabetes Endocrinol 2017;5:261-70.

78. Tauschmann M, Thabit H, Bally L, Allen JM, Hartnell S, Wilinska ME, et al. Closed-loop insulin delivery in suboptimally controlled type 1 diabetes: a multicentre, 12-week randomised trial. Lancet 2018;392:1321-9.

79. Tauschmann M, Allen JM, Nagl K, Fritsch M, Yong J, Metcalfe E, et al. Home use of day-and-night hybrid closed-loop insulin delivery in very young children: a multicenter, 3-week, randomized trial. Diabetes Care 2019;42:594-600.

80. Anderson SM, Raghinaru D, Pinsker JE, Boscari F, Renard E, Buckingham BA, et al. Multinational home use of closed-loop control is safe and effective. Diabetes Care 2016;39:1143-50.

81. Kovatchev B, Cheng P, Anderson SM, Pinsker JE, Boscari F, Buckingham BA, 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.

82. Brown SA, Beck RW, Raghinaru D, Buckingham BA, Laffel LM, Wadwa RP, et al. Glycemic outcomes of use of CLC versus PLGS in type 1 diabetes: a randomized controlled trial. Diabetes Care 2020;43:1822-8.

83. Breton MD, Kanapka LG, Beck RW, Ekhlaspour L, Forlenza GP, Cengiz E, et al. A randomized trial of closed-loop control in children with type 1 diabetes. N Engl J Med 2020;383:836-45.

84. Biester T, Nij R, Remus K, Farfel A, Muller I, Biester S, et al. DREAM5: an open-label, randomized, cross-over study to evaluate the safety and efficacy of day and night closed-loop control by comparing the MD-Logic automated insulin delivery system to sensor augmented pump therapy in patients with type 1 diabetes at home. Diabetes Obes Metab 2019;21:822-8.

85. Quemerais MA, Doron M, Dutrech F, Melki V, Franc S, An-
tonakios M, et al. Preliminary evaluation of a new semi-closed-loop insulin therapy system over the prandial period in adult patients with type 1 diabetes: the WP6.0 Diabeloop study. J Diabetes Sci Technol 2014;8:1177-84.

86. Benhamou PY, Huneker E, Franc S, Doron M, Charpentier G; Diabeloop Consortium. Customization of home closed-loop insulin delivery in adult patients with type 1 diabetes, assisted with structured remote monitoring: the pilot WP7 Diabeloop study. Acta Diabetol 2018;55:549-56.

87. Hanaire H, Franc S, Borot S, Penfornis A, Benhamou PY, Schaepernck P, et al. Efficacy of the Diabeloop closed-loop system to improve glycaemic control in patients with type 1 diabetes exposed to gastronomic dinners or to sustained physical exercise. Diabetes Obes Metab 2020;22:324-34.

88. Amadou C, Franc S, Benhamou PY, Lablanche S, Huneker E, Charpentier G, et al. Diabeloop DBLG1 closed-loop system enables patients with type 1 diabetes to significantly improve their glycemic control in real-life situations without serious adverse events: 6-month follow-up. Diabetes Care 2021;44:844-6.

89. Del Favero S, Bruttomesso D, Di Palma F, Lanzola G, Visentin R, Filippi A, et al. First use of model predictive control in outpatient wearable artificial pancreas. Diabetes Care 2014;37:1212-5.

90. Buckingham BA, Christiansen MP, Forlenza GP, Wadwa RP, Peyser TA, Lee JB, et al. Performance of the Omnipod personalized model predictive control algorithm with meal bolus challenges in adults with type 1 diabetes. Diabetes Technol Ther 2018:20:585-95.

91. Forlenza GP, Buckingham BA, Christiansen MP, Wadwa RP, Peyser TA, Lee JB, et al. Performance of Omnipod personalized model predictive control algorithm with moderate intensity exercise in adults with type 1 diabetes. Diabetes Technol Ther 2019;21:265-72.

92. Sherr JL, Buckingham BA, Forlenza GP, Galderisi A, Ekhlaspour L, Wadwa RP, et al. Safety and performance of the Omnipod hybrid closed-loop system in adults, adolescents, and children with type 1 diabetes over 5 days under free-living conditions. Diabetes Technol Ther 2020;22:174-84.

93. Stone MP, Agrawal P, Chen X, Liu M, Shin J, Cordero TL, et al. Retrospective analysis of 3-month real-world glucose data after the MiniMed 670G system commercial launch. Diabetes Technol Ther 2018;20:689-92.

94. Akturk HK, Giordano D, Champakanath A, Brackett S, Garg S, Snell-Bergeon J. Long-term real-life glycaemic outcomes with a hybrid closed-loop system compared with sensor-augmented pump therapy in patients with type 1 diabetes. Diabetes Obes Metab 2020;22:583-9.

95. Berget C, Messer LH, Vigers T, Frohnnert BI, Pyle L, Wadwa RP, et al. Six months of hybrid closed loop in the real-world: an evaluation of children and young adults using the 670G system. Pediatr Diabetes 2020;21:310-8.

96. Lal RA, Basina M, Maahs DM, Hood K, Buckingham B, Wilson DM. One year clinical experience of the first commercial hybrid closed-loop system. Diabetes Care 2019;42:2190-6.

97. Petrovski G, Al Khalaf F, Campbell J, Umer F, Almajaly D, Hamdan M, et al. One-year experience of hybrid closed-loop system in children and adolescents with type 1 diabetes previously treated with multiple daily injections: drivers to successful outcomes. Acta Diabetol 2021;58:207-13.

98. Breton MD, Kovatchev BP. One year real-world use of the control-IQ advanced hybrid closed-loop technology. Diabetes Technol Ther 2021;23:601-8.

99. Messer LH, Berget C, Pyle L, Vigers T, Cobry E, Driscoll KA, et al. Real-world use of a new hybrid closed loop improves glycemic control in youth with type 1 diabetes. Diabetes Technol Ther 2021 Jun 21 [Epub]. https://doi.org/10.1089/dia.2021.0165.

100. Boughton CK, Hartnell S, Thabit H, Poettler T, Herzig D, Wilinska ME, et al. Hybrid closed-loop glucose control with faster insulin aspart compared with standard insulin aspart in adults with type 1 diabetes: a double-blind, multicentre, multinational, randomized, crossover study. Diabetes Obes Metab 2021;23:1389-96.

101. Taborsky GJ Jr, Mundinger TO. Minireview: the role of the autonomic nervous system in mediating the glucagon response to hypoglycemia. Endocrinology 2012;153:1055-62.

102. Sylow L, Kleinert M, Richter EA, Jensen TE. Exercise-stimulated glucose uptake: regulation and implications for glycemic control. Nat Rev Endocrinol 2017;13:133-48.

103. Haidar A, Legault L, Dallaire M, Alkhateeb A, Coriati A, Messier V, et al. Glucose-responsive insulin and glucagon delivery (dual-hormone artificial pancreas) in adults with type 1 diabetes: a randomized crossover controlled trial. CMAJ 2013;185:297-305.

104. van Bon AC, Luijff YM, Koeburger R, Koops R, Hoekstra JB, DeVries JH. Feasibility of a portable bihormonal closed-loop system to control glucose excursions at home under free-living conditions for 48 hours. Diabetes Technol Ther 2014;16:131-6.

105. Russell SJ, Hillard MA, Balliro C, Magyar KL, Selagamsetty R,
Sinha M, 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;4:233-43.

106. Jacobs PG, El Youssef J, Reddy R, Resalat N, Branigan D, Condon J, et al. Randomized trial of a dual-hormone artificial pancreas with dosing adjustment during exercise compared with no adjustment and sensor-augmented pump therapy. Diabetes Obes Metab 2016;18:1110-9.

107. Taleb N, Emami A, Suppere C, Messier V, Legault L, Ladouceur M, et al. Efficacy of single-hormone and dual-hormone artificial pancreases during continuous and interval exercise in adult patients with type 1 diabetes: randomised controlled crossover trial. Diabetologia 2016;59:2561-71.

108. Blauw H, van Bon AC, Koops R, DeVries JH; on behalf of the PCDIAB consortium. Performance and safety of an integrated bif hormonal artificial pancreas for fully automated glucose control at home. Diabetes Obes Metab 2016;18:671-7.

109. Haidar A, Rabasa-Lhoret R, Legault L, Lovblom LE, Rakheja R, Messier V, et al. Single- and dual-hormone artificial pancreas for overnight glucose control in type 1 diabetes. J Clin Endocrinol Metab 2016;101:214-23.

110. Haidar A, Messier V, Legault L, Ladouceur M, Rabasa-Lhoret R. Outpatient 60-hour day-and-night glucose control with dual-hormone artificial pancreas, single-hormone artificial pancreas, or sensor-augmented pump therapy in adults with type 1 diabetes: an open-label, randomised, crossover, controlled trial. Diabetes Obes Metab 2017;19:713-20.

111. El-Khatib FH, Balliro C, Hillard MA, Magyar KL, Ekhlaspour L, Sinha M, et al. Home use of a bif hormonal bionic pancreas versus insulin pump therapy in adults with type 1 diabetes: a multicentre randomized crossover trial. Lancet 2017;389:369-80.

112. Taleb N, Haidar A, Messier V, Gingras V, Legault L, Rabasa-Lhoret R. Glucagon in artificial pancreas systems: potential benefits and safety profile of future chronic use. Diabetes Obes Metab 2017;19:13-23.

113. Castle JR, El Youssef J, Bakhtiani PA, Cai Y, Stobbe JM, Branigan D, et al. Effect of repeated glucagon doses on hepatic glycogen in type 1 diabetes: implications for a bif hormonal closed-loop system. Diabetes Care 2015;38:2115-9.

114. Kumareswaran K, Thabit H, Leelarathna L, Caldwell K, Elleri D, Allen JM, et al. Feasibility of closed-loop insulin delivery in type 2 diabetes: a randomized controlled study. Diabetes Care 2014;37:1198-203.

115. Thabit H, Hartnell S, Allen JM, Lake A, Wilinska ME, Ruan Y, et al. Closed-loop insulin delivery in inpatients with type 2 diabetes: a randomised, parallel-group trial. Lancet Diabetes Endocrinol 2017;5:117-24.

116. Bally L, Gubler P, Thabit H, Hartnell S, Ruan Y, Wilinska ME, et al. Fully closed-loop insulin delivery improves glucose control of inpatients with type 2 diabetes receiving hemodialysis. Kidney Int 2019;96:593-6.

117. Taleb N, Carpentier AC, Messier V, Ladouceur M, Haidar A, Rabasa-Lhoret R. Efficacy of artificial pancreas use in patients with type 2 diabetes using intensive insulin therapy: a randomized crossover pilot trial. Diabetes Care 2019;42:e107-9.

118. Marcinkevage JA, Narayan KM. Gestational diabetes mellitus: taking it to heart. Prim Care Diabetes 2011;5:81-8.

119. Feig DS, Donovan LE, Corcory R, Murphy KE, Amiel SA, Hunt KE, et al. Continuous glucose monitoring in pregnant women with type 1 diabetes (CONCEPTT): a multicentre international randomised controlled trial. Lancet 2017;390:2347-59.

120. Murphy HR, Elleri D, Allen JM, Harris J, Simmons D, Raymond G, et al. Closed-loop insulin delivery during pregnancy complicated by type 1 diabetes. Diabetes Care 2011;34:406-11.

121. Murphy HR, Kumareswaran K, Elleri D, Allen JM, Caldwell K, Biagioni M, et al. Safety and efficacy of 24-h closed-loop insulin delivery in well-controlled pregnant women with type 1 diabetes: a randomized crossover case series. Diabetes Care 2011;34:2527-9.

122. Stewart ZA, Wilinska ME, Hartnell S, O’Neil LK, Rayman G, Scott EM, et al. Day-and-night closed-loop insulin delivery in a broad population of pregnant women with type 1 diabetes: a randomized controlled crossover trial. Diabetes Care 2018;41:1391-9.

123. Ahmed SH, Ewins DL, Bridges J, Timmis A, Payne N, Mooney C, et al. Do-it-yourself (DIY) artificial pancreas systems for type 1 diabetes: perspectives of two adult users, parent of a child and healthcare professionals. Adv Ther 2020;37:3929-41.

124. Lewis D, Leibrand S; #OpenAPS Community. Real-world use of open source artificial pancreas systems. J Diabetes Sci Technol 2016;10:1411.

125. Lee JM, Newman MW, Gebremariam A, Choi P, Lewis D, Nordgren W, et al. Real-world use and self-reported health outcomes of a patient-designed do-it-yourself mobile technology system for diabetes: lessons for mobile health. Diabetes Technol Ther 2017;19:209-19.

126. Litchman ML, Lewis D, Kelly LA, Gee PM. Twitter analysis of #OpenAPS DIY artificial pancreas technology use suggests
improved A1C and quality of life. J Diabetes Sci Technol 2019; 13:164-70.
127. Hng TM, Burren D. Appearance of do-it-yourself closed-loop systems to manage type 1 diabetes. Intern Med J 2018;48: 1400-4.
128. Holstein A, Bolli B. Normoglycaemic control with a selfmade fully closed-loop insulin delivery system during emergency surgery: an extemporaneous stress test. Acta Diabetol 2019; 56:807-9.
129. Marshall DC, Holloway M, Korer M, Woodman J, Brackenridge A, Hussain S. Do-it-yourself artificial pancreas systems in type 1 diabetes: perspectives of two adult users, a caregiver and three physicians. Diabetes Ther 2019;10:1553-64.
130. Melmer A, Zuger T, Lewis DM, Leibrand S, Stettler C, Laimer M. Glycaemic control in individuals with type 1 diabetes using an open source artificial pancreas system (OpenAPS). Diabetes Obes Metab 2019;21:2333-7.
131. Braune K, O’Donnell S, Cleal B, Lewis D, Tappe A, Willaing I, et al. Real-world use of do-it-yourself artificial pancreas systems in children and adolescents with type 1 diabetes: online survey and analysis of self-reported clinical outcomes. JMIR Mhealth Uhealth 2019;7:e14087.
132. Braune K, May A, Thurm U. Safe and successful completion of a half marathon by an adult with type 1 diabetes using a personalized open source artificial pancreas system. J Diabetes Sci Technol 2020;14:1137-8.
133. Burnside M, Lewis D, Crocket H, Wilson R, Williman J, Jefferies C, et al. CREATE (Community deRivEd AutomaTEd insulin delivery) trial. Randomised parallel arm open label clinical trial comparing automated insulin delivery using a mobile controller (AnyDANA-loop) with an open-source algorithm with sensor augmented pump therapy in type 1 diabetes. J Diabetes Metab Disord 2020;19:1-15.
134. Lewis D. History and perspective on DIY closed looping. J Diabetes Sci Technol 2019;13:790-3.
135. Provenzano V, Guastamacchia E, Brancato D, Cappiello G, Maioli A, Mancini R, et al. Closing the loop with OpenAPS in people with type 1 diabetes: experience from Italy. Diabetes 2018;67(Suppl 1):993.
136. Choi SB, Hong ES, Noh YH. Open artificial pancreas system reduced hypoglycemia and improved glycemic control in patients with type 1 diabetes. Diabetes 2018;67(Suppl 1):964.
137. Jennings P, Hussain S. Do-it-yourself artificial pancreas systems: a review of the emerging evidence and insights for healthcare professionals. J Diabetes Sci Technol 2020;14:868-77.
138. Dowling L, Wilmot EG, Choudhary P. Do-it-yourself closed-loop systems for people living with type 1 diabetes. Diabet Med 2020;37:1977-80.
139. Lutz TA. The role of amylin in the control of energy homeostasis. Am J Physiol Regul Integr Comp Physiol 2010;298: R1475-84.
140. Schmitz O, Brock B, Runbye J. Amylin agonists: a novel approach in the treatment of diabetes. Diabetes 2004;53 Suppl 3:S233-8.
141. Hieronymus L, Griffin S. Role of amylin in type 1 and type 2 diabetes. Diabetes Educ 2015;41(1 Suppl):47S-56S.
142. Weinzimer SA, Sherr JL, Cengiz E, Kim G, Ruiz JL, Carria L, et al. Effect of pramlintide on prandial glycemic excursions during closed-loop control in adolescents and young adults with type 1 diabetes. Diabetes Care 2012;35:1994-9.
143. Sherr JL, Patel NS, Michaud CI, Palau-Collazo MM, Van Name MA, Tamborlane WV, et al. Mitigating meal-related glycemic excursions in an insulin-sparing manner during closed-loop insulin delivery: the beneficial effects of adjunctive pramlintide and liraglutide. Diabetes Care 2016;39:1127-34.
144. Riddle MC, Nahra R, Han J, Castle J, Hanavan K, Hompesch M, et al. Control of postprandial hyperglycemia in type 1 diabetes by 24-hour fixed-dose coadministration of pramlintide and regular human insulin: a randomized, two-way crossover study. Diabetes Care 2018;41:2346-52.
145. Taylor JR, Campbell KM. Diabetes drug update: how 4 new options stack up. J Fam Pract 2007;56:207-15.
146. Cho YM, Fujita Y, Kieffer TJ. Glucagon-like peptide-1: glucose homeostasis and beyond. Annu Rev Physiol 2014;76:535-59.
147. Boyle JG, Livingstone R, Petrie JR. Cardiovascular benefits of GLP-1 agonists in type 2 diabetes: a comparative review. Clin Sci (Lond) 2018;132:1699-709.
148. Renukuntla VS, Ramchandani N, Trast J, Cantwell M, Heptulla RA. Role of glucagon-like peptide-1 analogue versus amylin as an adjuvant therapy in type 1 diabetes in a closed loop setting with ePID algorithm. J Diabetes Sci Technol 2014;8:1011-7.
149. Renard E. Insulin delivery route for the artificial pancreas: subcutaneous, intraperitoneal, or intravenous? Pros and cons. J Diabetes Sci Technol 2008;2:735-8.
150. van Dijk PR, Groenier KH, DeVries JH, Gans RO, Kleefstra N, Bilo HJ, et al. Continuous intraperitoneal insulin infusion versus subcutaneous insulin therapy in the treatment of type 1
Update on artificial pancreas systems

diabetes: effects on glycemic variability. Diabetes Technol Ther 2015;17:379-84.

151. Logtenberg SJ, Kleefstra N, Houweling ST, Groenier KH, Gans RO, van Ballegooie E, et al. Improved glycemic control with intraperitoneal versus subcutaneous insulin in type 1 diabetes: a randomized controlled trial. Diabetes Care 2009;32:1372-7.

152. Liebl A, Hoogma R, Renard E, Geelhoed-Duijvestijn PH, Klein E, Diglas J, et al. A reduction in severe hypoglycaemia in type 1 diabetes in a randomized crossover study of continuous intraperitoneal compared with subcutaneous insulin infusion. Diabetes Obes Metab 2009;11:1001-8.

153. Jeandidier N, Selam JL, Renard E, Guerci B, Lassman-Vague V, Rocher L, et al. Decreased severe hypoglycemia frequency during intraperitoneal insulin infusion using programmable implantable pumps. Evadiac Study Group. Diabetes Care 1996;19:780.

154. Renard E, Place J, Cantwell M, Chevassus H, Palerm CC. Closed-loop insulin delivery using a subcutaneous glucose sensor and intraperitoneal insulin delivery: feasibility study testing a new model for the artificial pancreas. Diabetes Care 2010;33:121-7.

155. Steil GM, Rebrin K, Darwin C, Hariri F, Saad MF. Feasibility of automating insulin delivery for the treatment of type 1 diabetes. Diabetes 2006;55:44-50.

156. Dassau E, Zisser H, Harvey RA, Percival MW, Grosman B, Bevier W, et al. Clinical evaluation of a personalized artificial pancreas. Diabetes Care 2013;36:801-9.

157. Turksoy K, Bayrak ES, Quinn L, Littlejohn E, Cinar A. Multi-variable adaptive closed-loop control of an artificial pancreas without meal and activity announcement. Diabetes Technol Ther 2013;15:386-400.

158. Horowitz ME, Kaye WA, Pepper GM, Reynolds KE, Patel SR, Knudson KC, et al. An analysis of Medtronic MiniMed 670G insulin pump use in clinical practice and the impact on glycemic control, quality of life, and compliance. Diabetes Res Clin Pract 2021;177:108876.

159. Grosman B, Wu D, Parikh N, Roy A, Voskanyan G, Kurtz N, et al. Fast-acting insulin aspart (Fiasp(R)) improves glycemic outcomes when used with MiniMedTM 670G hybrid closed-loop system in simulated trials compared to NovoLog(R). Comput Methods Programs Biomed 2021;205:106087.

160. Alfonsi JE, Choi EE, Arshad T, Sammad SS, Pais V, Nguyen C, et al. Carbohydrate counting App using image recognition for youth with type 1 diabetes: pilot randomized control trial. JMIR Mhealth Uhealth 2020;8:e22074.
**Supplementary Table 1.** Clinical evidence of overnight closed-loop system (single-hormone) in type 1 diabetes mellitus

| Year  | Group         | CGM            | Pump        | System         | Design          | No. | Age, yr | Setting   | Duration | Intervention | Control     | Outcome (intervention vs. control)                                                                 |
|-------|---------------|----------------|-------------|----------------|-----------------|-----|---------|-----------|----------|--------------|-------------|-------------------------------------------------------------------------------------------------------------------|
| 2010  | CamDiab       | Freestyle      | DeTeck      | Navigator      | RCT, crossover  | 19  | 5–18    | Hospital  | 1 night  | OCL          | CSII        | ON TIR 70–145: 60% vs. 40%, \(P<0.01\) ON TBR ≤70: 2.1% vs. 4.1%, \(P=0.03\) |
|       |               | Navigator      | Cozmo       | RCT, crossover |                 |     |         |           |          |              |             |                                                                                                                   |
| 2011  | CamDiab       | FreeStyle      | Deltec      | Navigator      | RCT, crossover  | 24  | 18–65   | Hospital  | 1 night  | OCL          | CSII        | ON TIR 70–145: 22% better in OCL, \(P<0.01\) ON TBR ≤70: 3% better OCL, \(P=0.04\) |
|       |               | Navigator      | Cozmo       | RCT, crossover |                 |     |         |           |          |              |             |                                                                                                                   |
| 2012  | Medtronic     | Medtronic      | Paradigm    | Enlite         | RCT, crossover  |     | 12–25   | Hospital  | 2 nights | OCL          | CSII        | ON TIR 70–145: 84.5% vs. 46.7%, \(P<0.01\)                                                                 |
|       |               | Medtronic      | Veo         | Medtronic      | Single arm PGCS |     |         |           |          |              |             |                                                                                                                   |
| 2012  | DreaMed       | Medtronic      | Medtronic   | Enlite         | RCT, crossover  | 56  | 10–18   | Diabetes  | 2 nights | OCL          | SAP         | ON TIR 63–140: 92% vs. 73%, \(P=0.03\) ON TBR <63: 0% vs. 0%, \(P=NA\) |
|       |               | Medtronic      | Veo         | Medtronic      | Single arm PGCS |     |         | Hospital  |          |              |             |                                                                                                                   |
| 2013  | DreaMed       | Medtronic      | Medtronic   | Enlite         | RCT, crossover  |     | 10–18   | Diabetes  | 2 nights | OCL          | SAP         | ON TIR 70–145: 22% better in OCL, \(P<0.01\) ON TBR ≤70: 3% better OCL, \(P=0.04\) |
|       |               | Medtronic      | Veo         | Medtronic      | Single arm PGCS |     |         | Hospital  |          |              |             |                                                                                                                   |
| 2014  | TypeZero      | Dexcom G4t:sim | DiAs        | RCT, crossover | RCT, crossover  | 20  | 10–35   | Diabetes  | 5–6 nights | OCL          | SAP         | ON TIR 70–145: 84.5% vs. 46.7%, \(P<0.01\) ON TBR ≤70: 3% better OCL, \(P=0.04\) |
|       |               | G4t:sim        | DiAs        | RCT, crossover |                 |     |         | Hospital  |          |              |             |                                                                                                                   |
| 2014  | DreaMed       | Medtronic      | Medtronic   | Enlite         | RCT, crossover  | 24  | 12–43   | Home     | 6 weeks   | OCL          | SAP         | ON TIR 70–145: 84.5% vs. 46.7%, \(P<0.01\) ON TBR <63: 0% vs. 0%, \(P=NA\) |
|       |               | Medtronic      | Veo         | Medtronic      | Single arm PGCS |     |         | Home     |          |              |             |                                                                                                                   |
| 2014  | CamDiab       | FreeStyle      | Dana R      | Navigator      | RCT, crossover  | 16  | 12–18   | Home     | 3 weeks   | OCL          | SAP         | ON TIR 70–145: 64% vs. 47%, \(P=0.01\) ON TBR <54: 0.1% vs. 0.0%, \(P=0.07\) |
|       |               | Navigator      |             | RCT, crossover |                 |     |         | Hospital  |          |              |             |                                                                                                                   |
| 2014  | CamDiab       | FreeStyle      | Dana R      | Navigator      | RCT, crossover  | 24  | ≥18     | Home     | 4 weeks   | OCL          | SAP         | ON TIR 70–145: 52.6% vs. 39.1%, \(P<0.01\) ON TBR <50: 0.2% vs. 0.2%, \(P=0.63\) |
|       |               | Navigator      |             | RCT, crossover |                 |     |         | Hospital  |          |              |             |                                                                                                                   |
| 2015  | CamDiab       | FreeStyle      | Dana R      | Navigator      | RCT, crossover  | 25  | 6–18    | Home     | 12 weeks  | OCL          | SAP         | ON TIR 70–145: 59.7% vs. 34.4%, \(P<0.01\) ON TBR <50: 0.3% vs. 0.6%, \(P=0.31\) |
|       |               | Navigator      |             | RCT, crossover |                 |     |         | Hospital  |          |              |             |                                                                                                                   |
| 2015  | TypeZero      | Dexcom G4Acc-Check | DiAs    | RCT, crossover | RCT, crossover  | 32  | 18–69   | Home     | 2 months  | OCL +dinner | SAP         | 8PM–8AM TIR 70–180: 66.7% vs. 58.1%, \(P<0.01\) 8PM–8AM TBR <50: 0.1% vs. 0.3%, \(P<0.01\) |
|       |               | G4Acc-Check    | DiAs       | RCT, crossover |                 |     |         | Home     |          |              |             |                                                                                                                   |
| 2017  | DreaMed       | Medtronic      | Medtronic   | Enlite         | RCT, crossover  | 75  | 15–65   | Home     | 4 nights  | OCL          | SAP         | ON TIR 90–140: 75% vs. 50%, \(P<0.01\) ON TBR <70: 2.07% vs. 2.6%, \(P<0.01\) |
|       |               | Medtronic      | Veo         | Medtronic      | Single arm PGCS |     |         | Home     |          |              |             |                                                                                                                   |

The unit of TIR and TBR target is mg/dL.

CGM, continuous glucose monitoring system; NA, not available; RCT, randomized control trial; OCL, overnight closed-loop system; CSII, continuous subcutaneous insulin infusion; ON, overnight; TIR, time in range; TBR, time below range; SAP, sensor augmented pump.

*Hybrid closed-loop system is used for adult group in the same study.*
**Supplementary Table 2.** Adverse events of closed-loop systems in major clinical trials

| Study | Comparison | Age, yr | No. | TBR <54 mg/dL | Severe hypoglycemia (events) | Diabetic ketoacidosis (events) |
|-------|------------|---------|-----|---------------|-----------------------------|-------------------------------|
| **Control-IQ, TypeZero group** | | | | | | |
| Brown et al. (2019) [45] | HCL vs. SAP | 14–72 | 168 | 0.29% vs. 0.35%, *P*=0.02 | 0 vs. 0, *P*=NA | 1 vs. 0, *P*=NA |
| Brown et al. (2020) [82] | HCL vs. PLGS SAP | 14–72 | 109 | 0.20% vs. 0.22%, *P*=NA | 0 vs. 0, *P*=NA | 0 vs. 0, *P*=NA |
| Breton et al. (2020) [83] | HCL vs. SAP | 6–13 | 101 | 0.2% vs. 0.3%, *P*=NA | 0 vs. 0, *P*=NA | 0 vs. 0, *P*=NA |
| **Florence (pre-stage of CamAPS FX), CamDiab group** | | | | | | |
| Bally et al. (2017) [77] | HCL vs. CSII | ≥18 | 29 | 0.3% vs. 1.0%, *P*<0.01 | 0 vs. 0, *P*=NA | 0 vs. 0, *P*=NA |
| Tauschmann et al. (2018) [78] | HCL vs. SAP | ≥6 | 86 | 0.3% vs. 0.5%, *P*=0.11 | 0 vs. 0, *P*=NA | 1 vs. 0, *P*=NA |
| **Minimed 670G, Medtronic group** | | | | | | |
| Bergenstal et al. (2016) [24] | HCL vs. CSII (single arm) | 14–75 | 124 | 0.6% vs. 1.0%, *P*=NA | 0 vs. 0, *P*=NA | 0 vs. 0, *P*=NA |
| McAuley et al. (2020) [76] | HCL vs. MDI or CSII | 25–75 | 120 | 0.2% vs. 0.9%, *P*<0.01 | 8 vs. 7, *P*=NA | 1 vs. 2, *P*=NA |
| **Minimed 780G, Medtronic group** | | | | | | |
| Collyns et al. (2021) [37] | AHCL vs. PLGS SAP | 7–80 | 60 | 0.4% vs. 0.5%, *P*=0.03 | 0 vs. 0, *P*=NA | 0 vs. 1, *P*=NA |
| Bergenstal et al. (2021) [38] | AHCL vs. HCL | 14–29 | 113 | 0.46% vs. 0.50%, *P*<0.01 | 1 vs. 0, *P*=NA | 0 vs. 0, *P*=NA |
| **DBLG1, Diabeloop group** | | | | | | |
| Benhamou et al. (2019) [47] | HCL vs. SAP | ≥18 | 63 | 0.2% vs. 0.7%, *P*<0.01 | 5 vs. 3, *P*=NA | 0 vs. 0, *P*=NA |
| Amadou et al. (2021) [88] | HCL vs. SAP (single arm) | ≥22 | 25 | 0.24% vs. 0.32%, *P*=0.42 | 0 vs. 0, *P*=NA | NA |
| **Beta Bionics group** | | | | | | |
| El-Khatib et al. (2017) [111] | Dual HCL vs. CSII or SAP | ≥18 | 43 | 0.6% vs. 1.9%, *P*<0.01 | 0 vs. 1, *P*=NA | NA |
| Castellanos et al. (2021) [54] | Dual HCL vs. HCL | ≥18 | 10 | 0.2% vs. 0.6%, *P*=NA | 0 vs. 0, *P*=NA | 0 vs. 0, *P*=NA |
| **Inreda group** | | | | | | |
| Blauw et al. (2021) [50] | Dual FCL vs. HCL | ≥18 | 23 | 0% vs. 0.5%, *P*<0.01 | 0 vs. 0, *P*=NA | 0 vs. 0, *P*=NA |

TBR, time below range; HCL, hybrid closed-loop system; SAP, sensor augmented pump; NA, not available; PLGS, predictive low glucose suspension; CSII, continuous subcutaneous insulin infusion; MDI, multiple daily insulin injection; AHCL, advanced hybrid closed-loop; FCL, full closed-loop system.

* TBR <50 mg/dL was presented as outcome, instead of TBR <54 mg/dL.
* *P* value of non-inferiority test.
* TBR <60 mg/dL was presented as outcome, instead of TBR <54 mg/dL.
### Supplementary Table 3. Clinical evidence of DIY closed-loop system in type 1 diabetes mellitus

| Year | Country | System          | Design                        | No. | Participants | Setting  | Duration | Intervention | Control | Outcome (intervention vs. control) |
|------|---------|-----------------|-------------------------------|-----|--------------|----------|----------|--------------|---------|----------------------------------|
| 2016 | USA     | Open-APS        | Cross-sectional, online survey| 18  | Adult        | Home     | Online survey | DIY APS      | Before DIY APS                  | TIR 80–180: 81% vs. 58%, P = NA; HbA1c: 7.1% to 6.2%, P = NA Sleep quality improvement: 56% |
| 2017 | USA     | Night-scout     | Cross-sectional, online survey| 1,157 | Child to Adult | Home     | Online survey | Nightscout     | Non-Night-scout       | HbA1c: 6.8% vs. 7.6% (adult); 7.1% vs. 8.1% (13–17 years); 6.9% vs. 7.8% (6–12 years); 7.2% vs. 8.0% (0–5 years), P = NA |
| 2018 | Australia | DIY (Various)   | Cross-sectional, online survey| 68  | ≥ 10 years   | Home     | Online survey | DIY APS    | CSII or MDI       | More time in target glucose range (100%), better sleep (7%), less frequent hypoglycemia (74%), improved HbA1c (68%) |
| 2019 | USA     | Open-APS        | Qualitative netnography analysis| 328 | NA           | NA       | 2 years | DIY APS      | NA       | Users reported a reduction in diabetes related burden or distress Range of HbA1c: 4.9%–6.8% |
| 2019 | Germany | Open-APS        | Case report                   | 1   | Adult        | Hospital (acute cholecystectomy) | 4 days | DIY APS      | NA       | TIR: 99% (preoperative and perioperative period) |
| 2019 | UK      | Open-APS        | Case report                   | 3   | Adult, Child (11 months) | Home     | Up to 1 year | DIY APS    | Before DIY APS | Achieved TIR: 80%–90% (2 adults) HbA1c: 6.1% vs. 7.4% (in 6 months) |
| 2019 | Switzerland, USA | Open-APS | Retrospective record analysis | 34 | Adult | Home | Mean 8 months | DIY APS | SAP | Estimated HbA1c: 6.2% vs. 6.6%, P < 0.01 Mean glucose: 133 mg/dL vs. 144 mg/dL, P < 0.01 |
| 2019 | Various | DIY (Various)   | Cross-sectional, online survey| 209 | 3–20 years | Home     | Online survey | DIY APS    | Before DIY APS     | TIR 70–180: 80.7% vs. 64.2%, P < 0.01 HbA1c: 6.27% vs. 6.91%, P < 0.01 |
| 2020 | Germany | Open-APS        | Case report                   | 1   | Adult        | Exercise (Half marathon) | 2 days | DIY APS      | NA       | TIR 70–180: 100% (during Half Marathon race), 95.8% (race day and the following day) |

The unit of TIR and TBR target is mg/dL.
DIY, do-it-yourself; APS, artificial pancreas system; TIR, time in range; NA, not available; HbA1c, glycosylated hemoglobin; CSII, continuous subcutaneous insulin infusion; MDI, multiple daily insulin injection; SAP, sensor augmented pump.
Supplement Table 4. Clinical evidence of amylin analogues, GLP-1 receptor agonist, and intraperitoneal insulin delivery in artificial pancreas system

| Year          | Group          | CGM       | Pump                   | Design            | No. | Age, yr | Setting | Duration | Intervention                  | Control    | Outcome (intervention vs. control)                                                                 |
|---------------|----------------|-----------|------------------------|-------------------|-----|---------|---------|----------|--------------------------------|------------|---------------------------------------------------------------------------------------------|
| Amylin analogue |                |           |                        |                   |     |         |         |          |                                 |            |                                                                                             |
| 2012 [142]    | Yale University | Medtronic | Sof-sensors            | Paradigm 715      | 8   | 15–18   | Inpatient | 24 hours | HCL+ pramlintide                   | HCL        | Time to peak BG: 2.5 hours vs. 1.5 hours, P<0.01 Magnitude of glycemic excursion: 88 mg/dL vs. 113 mg/dL, P<0.01 |
| 2016 [143]    | Yale University | Medtronic | Sof-sensors            | Paradigm 715      | 10  | 15–18   | Inpatient | 24 hours | HCL+ pramlintide                   | HCL        | Time to peak BG: 2.6 hours vs. 1.6 hours, P<0.01 Reduction incremental BG AUC (P<0.01)        |
| 2018 [144]    | Oregon         | Dexcom G4 | Platinum               | Paradigm Revel    | 34  | 18–70   | Inpatient | 24 hours | SAP (Insulin+ pramlintide)        | SAP (insulin+ placebo) | TIR 70–180: 61.5% vs. 50.2%, P=0.046 TBR <70: 7.4% vs. 3.7%, P=0.47                      |
| 2020 [40]     | IRCM           | Dexcom G5 | MiniMed Paradigm Veo or 630G | RCT, crossover | 28  | >18     | Inpatient | 24 hours | Dual HCL (insulin+ pramlintide)    | HCL        | TIR 70–180: 84% vs. 74%, P<0.01 TBR <70: 0.0% vs. 1.2%, P=0.43                             |
| GLP-1 receptor agonist |                |           |                        |                   |     |         |         |          |                                 |            |                                                                                             |
| 2014 [148]    | Albert Einstein | Medtronic | Sof-sensors            | Paradigm 715      | 10  | 18–30   | Inpatient | 27 hours | HCL+ exenatide                    | HCL, HCL+ pramlintide | TIR 80–180: 77% vs. 61%, P=0.03 TIR 80–180: 62% vs. 61%, P=0.83 (HCL+exenatide vs. HCL) TIR 80–180: 59% vs. 61%, P=0.03 (HCL+pramlintide vs. HCL) |
| 2016 [41]     | Albert Einstein | Medtronic | Enlite                 | Medtronic Paradigm | 15  | 18–40   | Inpatient | 2 days   | HCL+ liraglutide                  | HCL        | Mean BG: 144.6 mg/dL vs. 159.7 mg/dL, P<0.01 2-hour postprandial BG: better in liraglutide arm, P<0.05 |
| 2016 [143]    | Yale University | Medtronic | Enlite                 | Paradigm 715      | 10  | 15–18   | Inpatient | 24 hours | HCL+ liraglutide                  | HCL        | Reductions in BG excursions (P=0.05) Incremental BG AUC (P<0.01)                          |
| Intraperitoneal |                |           |                        |                   |     |         |         |          |                                 |            |                                                                                             |
| 2010 [154]    | Montpellier University | Medtronic | MMT-2007D              | RCT, crossover    | 8   | 18–70   | Inpatient | 48 hours | IP HCL                            | IP pump    | TIR 80–120: 39.1% vs. 27.7%, P=0.05 TBR <60: 1.6% vs. 0.6%, P=0.69                        |
| 2017 [42]     | UC Santa Barbara | Dexcom | Seven Plus             | Rosche DiaPort system | 10  | 18–65   | Inpatient | 24 hours | IP FCL                            | SC FCL     | TIR 70–180: 65.7% vs. 43.9%, P<0.01 TBR <70: 2.5% vs. 4.1%, P=0.42                     |

The unit of TIR and TBR target is mg/dL.
GLP-1, glucagon-like peptide 1; CGM, continuous glucose monitoring system; HCL, hybrid closed-loop system; BG, blood glucose; AUC, area under curve; RCT, randomized control trial; SAP, sensor augmented pump; TIR, time in range; TBR, time below range; IRCM, Institut de Recherches Cliniques de Montreal; IP, intraperitoneal; FCL, full closed-loop system; SC, subcutaneous.