DIABETES TECHNOLOGY & THERAPEUTICS
Volume 18, Supplement 2, 2016

DOI: 10.1089/dia.2015.0345

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*ORIGINAL ARTICLE*

# Continuous Glucose Monitoring, Future Products, and Update on Worldwide Artificial Pancreas Projects

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**Abstract**

The development of accurate and easy-to-use continuous glucose monitoring (CGM) improved diabetes treatment by providing additional temporal information on glycemia and glucose trends to patient and physician. Although CGM enables users to lower their average glucose level without an increased incidence of hypoglycemia, this comes at the price of additional patient effort. Automation of insulin administration, also known as closed-loop (CL) or artificial pancreas treatment, has the promise to reduce patient effort and improve glycemic control. CGM data serve as the conditional input for insulin automation devices. The first commercial product for partial automation of insulin administration used insulin delivery shutoff at a predefined glucose level. These systems showed a reduction in hypoglycemia. Insulin-only CL devices show increased time spent in euglycemia and a reduction of hypo- and hyperglycemia. Improved glycemic control, coinciding with a minor decrease in hemoglobin A1c level, was confirmed in recent long-term home studies investigating these devices, paving the way for pivotal studies for commercialization of the artificial pancreas. Although the first results from dual-hormone CL systems are promising, because of increased cost of consumables of these systems, long-term head-to-head studies will have to prove superiority over insulin-only approaches. Now CL glucose control for daily use might finally become reality. Improved continuous glucose sensing technology, miniaturization of electrical devices, and development of algorithms were key in making this possible. Clinical adoption challenges, including device usability and reimbursement, need to be addressed. Time will tell for which patient groups CL systems will be reimbursed and whether these devices can deliver the promise that they hold.

## Introduction

Striving toward near-normal glycemia leads to an increase in episodes of severe hypoglycemia and is difficult to achieve without substantial patient and healthcare provider effort.[1] Continuous glucose monitoring (CGM) technology can aid in this quest, especially in combination with continuous subcutaneous insulin infusion (CSII). CGM allows for safe therapy intensification with hemoglobin A1c (HbA1c) reduction and can partially relieve the psychological burden of diabetes.[2,3] Nonetheless, patients still need to self-monitor glucose and take carbohydrate content of food and physical activity into account when making treatment decisions.

As shown already in 1977, advanced diabetes technology, at that time the Biostator (Ames Division, Miles Laboratories, Elkhart, IN), holds the promise to further alleviate this burden by automation of insulin administration.[4,5] At the time investigators showed that with closed-loop (CL) technology using intravenous glucose sampling and insulin and glucose administration, it was possible to achieve near-normal glucose control in patients with type 1 diabetes mellitus (T1DM). But, due to the complexity, bulkiness, and invasiveness of the procedure, the technology could not be used outside the clinical research center. The development of subcutaneous continuous glucose sensing technology allowed for less invasive glucose sensing, making at-home application of CGM technology a reality. This evolved into combined use of CSII and CGM, also known as the sensor-augmented pump (SAP), and enabled research into automation of insulin administration (artificial pancreas/CL).

## Methods and Aims

We aim to provide an overview of the development of CGM technology and its effect on diabetes treatment. We will discuss the impact of CGM on clinical outcomes and innovative approaches and will give an overview of current and ongoing artificial pancreas studies.

We performed a review of published literature on the effectiveness of CGM and CGM use in conjunction with CSII

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technology in T1DM, using the search terms ''CGM,'' ''CGMS,'' and ''continuous glucose monitor*.'' Studies on diabetes and pregnancy were excluded. Because of the maturity of the field we limited the search results to meta-analyses and systematic reviews. We performed a systematic review of published literature on the topic of CL technology, using the search terms ''artificial pancreas,'' ''closed-loop,'' ''closed loop,'' and ''diabetes,'' published in the last 5 years. Only outpatient studies with a CL intervention period of at least 4 days performed in patients with T1DM were included. Two hundred seventy-four abstracts were screened; of these, 11 met the inclusion criteria and were included in this review. We asked major CGM manufacturers to provide information about upcoming CGM products and CL technology and performed a review of clinical trial databases, financial reports, and press releases.

## CGM Technology and Directions for Future Development

Although different techniques for subcutaneous glucose measurement were introduced, currently only electrochemical transcutaneous CGM systems are available to patients.[6,7] Also, different approaches to access the glucose-containing interstitial fluid, like microdialysis and fully implantable sensors, were tested with varying success.[6,7]

Innovative approaches have brought interesting new products, like flash glucose monitoring and implantable CGM systems, to, or close to, market. Flash glucose monitoring (Abbott Diabetes Care, Alameda, CA) represents a new ''on-demand'' application of subcutaneous glucose sensing technology, effectively using CGM technology for replacement of self-monitoring of blood glucose.[8] Flash glucose monitoring could be seen as CGM on-demand, but the lack of (false-positive) alarms might actually be experienced as a benefit by some. Because of its 2-week longevity, cost per day was reduced, bringing the system within reach for out-of-pocket patient payment and within the reimbursement system in some countries such as Norway and Sweden. Also, factory calibration eliminated the need for frequent recalibration, increasing ease of use.

After failed efforts at the beginning of the century, in the coming year a CGM system using a long-term fully implantable sensor will be brought to the market, first in Europe (Eversense™; Senseonics Inc., Germantown, MD).[9,10] Implantable CGM systems can provide the patient additional ease of use because no sensor is inserted through the skin, and consequently the transmitter can be removed easily and more frequently without the need for sensor replacement. Furthermore, the hassle of weekly sensor replacement with warm-up time and the risk of damage to the inserted sensor is reduced. However, the need for implantation and removal through minor surgery imposes some discomfort on the patient and requires additional effort by the clinician. First conference presentations point toward an accuracy of around that of currently available transcutaneous CGM systems.[9] A new CGM system in development by Roche Diagnostics (Mannheim, Germany), which would be their debut in CGM manufacturing, was reported in 2013 to show an overall mean absolute relative difference of <10% but has not yet reached the market.[11]

Improvement in CGM signal filtering levels and calibration algorithms to account for random signal noise and calibration errors resulted in significant improvement of sensor performance.[12] Furthermore, reduction of biofouling and enzyme degradation might reduce signal error and improve reliability and longevity of current CGM devices.[13,14] Variability in initial sensor insertion trauma might account for between sensor variability in CGM performance.[13]

Nonetheless, through innovation in sensor technology, the overall accuracy and point precision of CGM systems have improved toward the proposed mark required for making insulin dosing decisions based on CGM data (mean absolute relative difference of <10%).[15] As of September 2015, Dexcom (San Diego, CA) has received approval for nonadjunct use of CGM in the European Union (G5™ Mobile CGM) and appears to be well underway making the same claim with the Food and Drug Administration, providing a statement of confidence in CGM reliability and accuracy by these authorities. This brings legalities in line with daily practice because patients already often use continuous glucose data as a basis for treatment decisions without confirmation of glucose values by self-monitoring of blood glucose (nonadjunct use of CGM).

Currently all CGM devices require initial calibration before displaying CGM data and (re)calibration generally at a 12-h rate during the sensor's lifetime. A further reduction of in vivo sensor-to-sensor differences in sensitivity and sensitivity degradation over the sensor lifetime of current CGM would allow for factory calibration.[16] Factory calibration of CGM eliminates an importance source of user-introduced error and increases the system's ease of use. The ability to use factory-calibrated sensors in CGM-based flash glucose monitoring might indicate that manufacturers are already capable of producing factory-calibrated CGM devices but might prefer to first focus on further improvement of accuracy while maintaining in vivo calibration.[16]

Most companies have converted their offline CGM downloads to the ''cloud,'' allowing for efficient data access by patients and clinicians. Diabetes data management platforms like Glooko® (Glooko, Palo Alto, CA) make data from devices of different manufacturers available to the patient and clinician through a universal portal or smartphone application.[17] Automated CGM data analysis and treatment advice would be a next step for CGM data platforms. Currently no universal CGM training program is available, although the ability to interpret CGM data is important to make effective use of the technology. With what we have learned so far from our patient users, it should be possible to develop such programs.[18]

Integrating CGM data in smartphone applications instead of dedicated devices, like with the Dexcom G5 Mobile, might further improve user-friendliness of CGM. Innovation in CGM technology and application of CGM data of main manufacturers are given in Table 1.

## Evidence for Clinical Relevance of CGM in T1DM

The JDRF landmark trial, performed in 2008, and its follow-up studies evaluated the benefit of CGM compared with standard glucose monitoring (self-monitoring of blood glucose) for T1DM management in two studies.[19] The study showed that in patients with HbA1c of ≥53 mmol/L (≥7.0%) and above 25 years of age, a reduction of 5.5 mmol/mol (0.5%) in HbA1c was achieved without an increase in hypoglycemia and that wear time was important in reaching this

Table 1. Innovation in Continuous Glucose Monitoring (CGM) and Application of CGM Data of the Main Manufacturers

| *Innovation or application* | *Manufacturer, device* |
|---|---|
| Innovations in CGM technology | Dexcom: G6 sensors with improved wear time (1–14 days) and interferent blocker to eliminate the impact of acetaminophen on sensor accuracy. Clinical studies are ongoing.<br>Dexcom: Development of next-generation smaller and less expensive CGM technology with Google/Alphabet. No timeline is available.<br>Medtronic: Fourth-generation sensor capable of glucose sensing over a wider area of the implanted part of the sensor with embedded diagnostics to differentiate between measurements of reliable versus nonreliable sensor data. Pivotal trials for clinical evaluation are ongoing.<br>Medtronic: Development of an integrated sensor and insulin infusion set aiming to reduce device burden of current SAP therapy. No timeline is available. |
| Regulatory/ reimbursement | Dexcom: Availability of CGM devices through pharmacies and a possible price cut with two major U.S. healthcare organizations now processing CGM as a pharmacy benefit. This allows patients to pick up Dexcom CGM devices at retail outlets just like picking up a drug prescription. With major parties like CVS and Walgreens involved, a new ground for price negotiations could be opened. This might also influence prices in markets outside the United States.<br>Dexcom: Approval of the G5 smart transmitter by the FDA and approved European CE mark. This will allow CGM data to be sent directly from the transmitter to a receiver, smartphone, or closed-loop system. iOS support is available, and support for Android devices is expected in the second half of 2016.<br>Dexcom: Insulin-dosing claim for CGM, an important step for Medicare coverage. Claim has been accepted for Europe and is expected sometime in 2016 through the FDA for the United States. |
| Data availability/ integration | Medtronic: Medtronic received FDA clearance of the MiniMed Connect for more convenient access to personal diabetes data. This keychain-sized device sends pump and CGM data to Internet-enabled devices. Expected launch is in Fall 2015.<br>Dexcom: Share of glucose data to up to five followers by mobile phone application, allowing glucose data to be shared with up to five iOS or Android followers (recently on the market).<br>Dexcom: A new ''robust'' in the cloud data platform is planned to be launched by the end of the year aiming to ''set a new standard'' for visualization of CGM data. |

Major CGM manufacturers were contacted. We thank Dexcom and Medtronic Diabetes Care for providing these data.
FDA, Food and Drug Administration; SAP, sensor-augmented pump.

reduction. The relation among wear time of CGM, baseline HbA1c, and HbA1c lowering was later confirmed by a meta-analyses of Pickup et al.[20] A Cochrane meta-analysis[21] showed that CGM technology, mostly studied in conjunction with CSII (SAP), can improve glucose control by means of a reduction in HbA1c level without increase of hypoglycemia. Whether this is true for all patient groups and whether CGM is able to reduce hypoglycemia are still debated. Only 20% of children in the JDRF landmark trial were able to maintain a high wear time, possibly explaining why so far no convincing results have been presented on effectiveness of CGM use in this group.

Although CGM can improve glycemic control and partially relieve the psychological burden of diabetes,[3] patients still need to self-monitor glucose and take carbohydrate content of food and physical activity into account when making treatment decisions. Automation of insulin administration might be able to further alleviate this burden and improve time in the target glucose range.[22]

### First Steps in Automation of Insulin Administration

The first steps in automation of insulin administration were taken with systems that automate insulin delivery shutoff at very low glucose levels based on CGM data. If the patient is unresponsive to the CGM hypoglycemia alarm, insulin delivery will remain shut off for 2 h or until the patient restarts insulin delivery. Although stopping insulin delivery might be considered only the first form of automation of insulin administration, these systems effectively represented the first approved nonadjunct use of CGM data for insulin administration decisions. From a regulatory perspective, approval of these devices was therefore also important for more advanced forms of automation of insulin administration.

Two randomized controlled trials were performed investigating low glucose suspend (LGS) (Medtronic, Northridge, CA), Bergenstal et al.[23] showed reduced incidence and duration of nonsevere hypoglycemia, whereas Ly et al.[24] showed reduced incidence and duration of nonsevere and severe hypoglycemia compared with the control arm. However, a recent report by the German Institute for Quality and Efficiency in Health Care criticized the results, concluding that presented data were not reliable because of use of events rates and a large baseline difference in prevalence of hypoglycemia in spite of randomization.[25]

Recently this ''very low glucose, insulin pump off'' feature was upgraded with basic predictive technology (predictive LGS [PLGS]) to suspend insulin infusion when the glucose

Table 2. Main Results of Artificial Pancreas Studies Ordered per Publication Date

| Reference (year) | Study setup | | | Study outcomes[a] | | | | | Conclusions |
|---|---|---|---|---|---|---|---|---|---|
| | Design | Intervention | CL period | % time below 70 mg/dL | % time above 180 mg/dL | % time 70–180 mg/dL | Mean glucose (mg/dL) | Δ HbA1c (%; mmol/mol) | |
| Kropff et al.[29] (September 2015) | Adults: daily life, 2 months, randomized crossover, $n=32$ | Intervention: DiAs, MPC, insulin-only, hybrid-CLControl: SAP | Evening–night, 2000–0800 h | 1.7 vs. 3.0 ($P<0.0001$) | 31.6 vs. 38.5 ($P<0.001$) | 66.7 vs. 58.1 ($P<0.001$) | 162.0 vs. 167.4 ($P=0.0053$) | 0.2; 3.0 ($P=0.047$) | Adults: significant improvement in evening–night glycemic control, including reduction in HbA1c |
| Thabit et al.[40] (September 2015) | Adults: daily life, 3 months, crossover, $n=32$ Children: at home, 3 months, randomized crossover, $n=24$ | Intervention: Florence, MPC, insulin-only, hybrid-CL Control: SAP | Adult: day and night Children: overnight, 0000–0800 h | Adult: 2.9 vs. 3.0 ($P=0.016$) Children: 2.2 vs. 3.5 ($P=0.7$) | Adult: 29.2 vs. 38.9 ($P<0.001$) Children: NA; % time >145 mg/dL, 37.2 vs. 60.7 ($P<0.001$) | Adult: 67.7 vs. 56.8 ($P<0.001$) Children: NA; % time 70–145 mg/dL), 59.7 vs. 34.4 ($P<0.001$) | Adult: 157 vs. 168 ($P<0.001$) Children: 146 vs. 176 ($P<0.001$) | Adult: −0.3; −4 ($P=0.002$) Children: −0.3; −4 ($P=0.17$) | First study to report on HbA1c Adults: significant improvement in glycemic control, including limited reduction in hypoglycemia over a 24-h period and reduction in HbA1c Children: significant improvement in overnight glycemic control, including trend toward reduction in HbA1c |
| Ly et al.[41] (June 2015) | Adults and adolescents: camp study, 6 days, randomized, $n=20$ | Intervention: Medtronic, PID, insulin-only, hybrid-CL Control: SAP + LGS | Day and night | 2.1 vs. 2.4 ($P=0.75$) | 28.4 vs. 24.8 ($P=0.54$) | 69.9 vs. 73.1 ($P=0.58$) | 157 vs. 147 ($P=0.27$) | — | Adults and adolescents: short-term study, no demonstration of improved glycemic control |
| Brown et al.[42] (March 2015) | Adults: bedside study, 5 days, randomized crossover, $n=10$ | Intervention: DiAs, MPC, insulin-only, hybrid-CL Control: SAP | Overnight, 2300–0700 h | 0.6 vs. 1.6 ($P$=NS) | 14.1 vs. 39.4 ($P<0.001$) | 85.4 vs. 59.1 ($P<0.001$) | 139.0 vs. 170.3 ($P<0.001$) | — | Adults: short-term study, improved glycemic control, trend toward reduction of hypoglycemia |
| Thabit et al.[43] (February 2015) | Home use, 3–4 weeks, randomized crossover Adults: $n=24$ Adolescents: $n=16$ | Intervention: Florence, MPC, insulin-only hybrid-CL Control: SAP | Overnight, 2400–0800 h | 1.9 vs. 2.9 ($P=0.014$) | NA; % time >144 mg/dL, 37.9 vs. 53.8 ($P=0.001$) | 77.4 vs. 61.8 ($P<0.001$) | 142.2 vs. 156.6 ($P<0.001$) | — | Adults and adolescents: improved glycemic control with reduction of hypoglycemia |
| Nimri et al.[44] (November 2014) | Home study, 6 weeks, randomized crossover Adults: $n=11$ Adolescents: $n=13$ | Intervention: MD-Logic, insulin-only, hybrid-CL Control: SAP | Overnight, 2300–0700 h | 2.5 vs. 5.2 ($P=0.02$) | 22.3 vs. 36.6 ($P=0.002$) | 72.9 vs. 58.7 ($P=0.001$) | 147.7 vs. 161.3 ($P=0.008$) | — | First longer-term adult and adolescent study: improved overnight mean glucose via reduction of both hypo- and hyperglycemia |
| Thabit et al.[45] (September 2014) | Adults: home study, 4 weeks, randomized crossover, $n=24$ | Intervention: Florence, MPC, insulin-only, hybrid-CL Control: SAP | Overnight, 0000–0700 h | 1.8 vs. 2.1 ($P=0.28$) | NA; % time >144 mg/dL, 44.3 vs. 57.1 ($P=0.0014$) | 73.2 vs. 61.2 ($P=0.0004$) | 147.6 vs. 162.0 ($P=0.005$) | — | Improved glycemic control |

(*continued*)

TABLE 2. (CONTINUED)

| Reference (year) | Study setup | | | Study outcomes[a] | | | | | Conclusions |
|---|---|---|---|---|---|---|---|---|---|
| | Design | Intervention | CL period | % time below 70 mg/dL | % time above 180 mg/dL | % time 70–180 mg/dL | Mean glucose (mg/dL) | Δ HbA1c (%; mmol/mol) | |
| Leelarathna et al.[32] (July 2014) | Adult: home study, 7 days, randomized crossover, $n=17$ | Intervention: Florence, MPC, insulin-only, hybrid-CL Control: SAP | Day and night | 3.7 vs. 5.0 ($P=0.34$) | 21.9 vs. 30.5 ($P=0.013$) | 75.3 vs. 62.6 ($P=0.006$) | 145.8 vs. 158.4 ($P=0.005$) | — | Adults: short-term study, improved glycemic control, trend toward reduction of hypoglycemia |
| Russell et al.[28] (June 2014) | Outpatient study, 5 days, randomized crossover Adults: $n=20$ Adolescents: $n=32$ | Intervention: bionic pancreas, dual-hormone, hybrid-CL Control: SAP | Day and night | Adults: 4.1 vs. 7.3 ($P=0.01$) Adolescents: 3.1 vs. 4.9 ($P=0.05$) | Adults: 16.5 vs. 33.8 ($P<0.001$) Adolescents: 21.0 vs. 30.6 ($P=0.01$) | Adults: 79.5 vs. 58.8 ($P<0.001$) Adolescents: 75.9 vs. 64.5 ($P<0.001$) | Adults: 133 vs. 159 ($P<0.001$) Adolescents: 142 vs. 158 ($P=0.004$) | — | Adults and adolescents: dual-hormone short-term study, significant improvement in glycemic day-and-night control, including reduction in hypoglycemia |
| Ly et al.[46] (May 2014) | Children and adolescents: diabetes camp study, 5 days, randomized camp, study, $n=20$ | Intervention: DiAs, MPC, insulin-only, hybrid-CL Control: SAP | Overnight, 0000–0700 h | Data not given ($P<0.023$) | Data not given (NS) | 92 vs. 80 ($P=0.022$) | 147 vs. 146 ($P=0.89$) | — | Short-term study: significant improvement in time spent in euglycemia and reduced time spent in hypoglycemia |
| Hovorka et al.[47] (May 2014) | Adolescents: free-living, 3 weeks, randomized cross-over, $n=16$ | Intervention: Florence, MPC, insulin-only, hybrid-CL Control: SAP | Overnight, 2300–0700 h | 1.4 vs. 0.9 ($P=0.13$) | 9.5 vs. 16.2 ($P<0.001$) | 85 vs. 69 ($P<0.001$) | 137 vs. 151 ($P<0.001$) | — | First longer-term outpatient insulin-only CL study. Improved glycemic control |

Outpatient studies with an intervention period of 4 days or longer were selected.

[a]Outcomes are given as intervention versus control, and over the time period that the closed-loop (CL) system was functioning.

DiAs, Diabetes Assistant; dual-hormone, closed-loop system that uses both insulin and glucagon infusion; HbA1c, hemoglobin A1c; hybrid-CL, mode of closed-loop operation that requires user announcement of meals or other activities to the system; insulin-only, insulin-only closed-loop system; MPC, model predictive control; NA, not available; NS, not significant; PID, proportional integral derivative; SAP, sensor-augmented pump.

level is expected to fall below 80 mg/dL within 30 min, for a maximum of 2 h or until the glucose level returns to above 70 mg/dL.[26,27] PLGS was also able to reduce the incidence and duration of hypoglycemic episodes (<70/<60 mg/dL), but with an increase in mean overnight glucose level.[26,27] Although an increase in mean glucose level does not necessarily mean worse glycemic control, in the study by Buckingham et al.[26] patients also spent a larger percentage of time in hyperglycemia, indicating that a reduction of hypoglycemia came at the price of hyperglycemia. Maahs et al.[27] showed no increase in hyperglycemia, indicating that the increase in mean glucose level observed in their study is due to a reduction of hypoglycemia only. Currently insulin pump manufacturers other than Medtronic are preparing LGS-like functionalities to be included into their pumps.

### Further Automation of insulin administration, the artificial pancreas

CL systems, also known as the ''artificial pancreas,'' are designed to automate glucose control. A CL system consist of an insulin pump (CSII), a system for real-time glucose sensing (CGM), and algorithms for safety and glucose control. Systems either communicate via wired or wireless connections or are integrated all-in-one devices.[28,29] Insulin-only and dual-hormone approaches using insulin and glucagon or amylin have been investigated.[28,30–34]

Complex algorithms are required to overcome the remaining shortcomings of CGM technology and delay in insulin action, due to both physiology and slow absorption of current ''fast-acting'' insulin. The most common algorithms are based on model predictive control, proportional integral derivative, or fuzzy logic.[35] Algorithms can be integrated or consist of separate module(s) for safety and glucose regulation.[36] Algorithm self-learning capabilities and integration of auxiliary sensors for detection of exercise might allow for individualized treatment and treatment adaption over time.[37]

Various modes of CL operation can be discriminated, ranging from fully automated insulin administration systems (full-CL) requiring virtually no user input to hybrid-CL systems requiring frequent user input, for example, for meal intake or exercise announcement.[30,38] CL systems can be used either day and night or only during a specified period of time like in nighttime-only systems. These systems use a hybrid approach, with automated insulin administration (CL) during one period (e.g., nighttime) and without automated insulin administration for the remainder of the time (e.g., daytime or for meals). After introduction of LGS and PLGS, the hypoglycemia hyperglycemic minimizer could be considered the first-generation artificial pancreas systems.[39]

The main results of available artificial pancreas studies are given in Table 2. The first results from longer-term hybrid-CL studies were recently presented.[29,40,44,45] Two studies with a duration of 2–3 months investigating evening and night, as well as day and night, artificial pancreas use showed a reduction in time in hypo- and hyperglycemia and improved mean glucose level over investigated time periods compared with SAP therapy. Both reported a modest reduction in HbA1c level (2–3 mmol/mol, 0.2–0.3%) over SAP.[40] Most of the improvement in glycemia took place during the night period.[40] This seems due to the challenging daytime circumstances with glucose perturbations due to physical activity and carbohydrate intake during meals and snacks. Consequently, depending on the user-friendliness of the first commercialized artificial pancreas systems, artificial pancreas-when-at-home could be considered as a concept for first commercial introduction of the artificial pancreas.[29] Results from these longer-term real-life studies seem to have paved the way for pivotal studies required by the Food and Drug Administration for commercial systems. Current artificial pancreas systems face clinical adoption challenges including improved wearability, connectivity between devices, and user-friendliness of interfaces. Table 3 provides an overview of currently ongoing studies, investigating longer-duration artificial pancreas use and use in specific patient groups like adolescents and children.

Fully automated CL systems incorporating glucagon administration may provide additional benefits over insulin-only systems and could be considered the third-generation and final stage of CL development.[39] However, there are now convincing data that insulin only–based systems can improve glycemic control, reduce hypo- and hypoglycemia, and improve some aspects of diabetes management burden.

A bifurcation in the artificial pancreas roadmap is therefore proposed in which both insulin-only and dual-hormone artificial pancreases are considered end-stage targets with their own pros and cons.[48] Pros of insulin-only systems might be a slight reduction in HbA1c level compared with SAP, shown so far with insulin-only CL systems (2–3 mmol/mol, 0.2–0.3%). Development of soluble pumpable glucagon, dual-chamber pumps, dual-lumen catheters, and finalization of algorithms could be considered main challenges for the dual-hormone approach, although not all might have to be solved before market introduction. In an inpatient head-to-head study, a dual-hormone artificial pancreas resulted in a significant reduction in the number of hypoglycemic events.[49] In a more recent diabetes camp study a dual-hormone artificial pancreas showed a significant reduction of time spent in hypoglycemia and a trend toward further reduction of hyperglycemia and improved time in euglycemia compared with an insulin-only approach.[50] Longer-term head-to-head studies comparing the best available insulin-only and dual-hormone AP approaches are required for a careful consideration of pros and cons of both systems. Amylin–insulin coformulation could also be considered an option for dual-hormone AP treatment but is not currently being investigated in longer-term CL systems.[34]

The added benefit of CL systems over CSII-only might increase patients' willingness for out-of-pocket payment for CGM sensors to upgrade their system with CL functionality, or even for payment by reimbursement authorities. Insulin-only systems could be seen as the natural evolution after SAP and might become available via current CSII + CGM reimbursement programs soon after market introduction. Dual-hormone approaches, because of expected increased cost for device consumables, have to prove added value over SAP and insulin-only systems to be considered for reimbursement. Table 4 provides information on possible commercialization of artificial pancreas technology in the coming years.

### Summary and Outlook

The development of accurate and easy-to-use CGM devices improved diabetes treatment by providing additional

Table 3. Planned and Ongoing Artificial Pancreas (AP) Studies Investigating Outpatient AP Use for ≥4 Days

| *Abbreviated title (registration number)* | *Responsible party* | *Status* | *Study type* | *Study design* | *Main inclusion/ exclusion criteria* | *Intervention/control* | *Period used* | *Primary outcome* | *Main secondary outcomes* | *Remarks* |
|---|---|---|---|---|---|---|---|---|---|---|
| Hybrid-CL Pivotal Trial in Type 1 Diabetes (NCT02463097) | Medtronic Diabetes | Recruiting, expected date of completion May 2016 | Pivotal, safety study, at home | Open-label, multicenter, single-arm study | T1DM, 14–75 years of age, $n=150$, HbA1c <86 mmol/mol Experienced CSII users Excluded >1 event of severe hypoglycemia <6 months, DKA <6 months | Intervention: hybrid insulin-only, MMT-670G insulin pump, with CL algorithm | 3-month day and night CL | HbA1c | Severe hypoglycemia DKA | First long-term pivotal (safety) study |
| Home testing of day and night CL with pump suspend feature (APCam11) (NCT02523131) | University of Cambridge | Not open for participants, planned study start November 2015, study completion December 2016 | Efficacy Study, Phase 2, at home | Open-label, multicenter, single-arm, randomized, parallel-group study | T1DM, >6 years of age, $n=84$, HbA1c 58–86 mmol/mol Experienced CSII users Excluded severe hypoglycemia <6 months | Intervention: hybrid insulin-only CL (FlorenceM) with insulin pump (MMT-640G) suspend feature Control: SAP, no pump suspend features | 3-month home day and night use | HbA1c | % time 70–180 mg/dL % time <70 mg/dL % time >180 mg/dL Mean glucose | MPC algorithm with Medtronic 640G insulin pump and LGS |
| CL control of glucose levels for 5 days in adults with type 1 diabetes (NCT02488616) | Institut de Recherches Cliniques de Montreal | Not yet recruiting, planned start date September 30, 2015, primary completion July 2016 | Efficacy study, free living | Open-label, randomized, three-way, crossover study | T1DM, ≥18 years of age, $n=40$, HbA1c <86 mmol/mol Excluded acute macrovascular event <6 months | Intervention 1: hybrid insulin-only CL Intervention 2: dual-hormone CL Control: SAP | 5 days at home, day and night | % time <72 mg/dL | % time 72–144 mg/dL % time 72–180 mg/dL | Comparison of SAP vs. insulin-only, multihormone CL approach |
| Algorithm to control postprandial, postexercise, and night glucose excursions in a portable CL format (NCT02160275) | Academic Medical Centre, University of Amsterdam | Study completed, October 2015 | Safety/efficacy study, free living | Open-label, randomized, crossover study | T1DM, 18–75 years of age, $n=10$, HbA1c <97 mmol/mol Excluded impaired awareness of hypoglycemia (Gold ≥4) | Intervention: dual-hormone reactive full-CL system without mealtime announcement, miniaturized prototype Control: CSII | 4 days at home, day and night | Mean glucose | % time <70 mg/dL % time 70–180 mg/dL % time >180 mg/dL | Fully integrated dual-hormone device, full-CL |
| Unified safety system (USS) Virginia CL versus SAP for hypoglycemia reduction in T1DM (NCT02302963) | University of Virginia | Recruiting, planned primary completion, June 2016 | Efficacy, home | Open-label, randomized controlled trial | T1DM, 15–65 years of age, $n=88$, HbA1c <86 mmol/mol Experienced CSII users Excluded severe hypoglycemia <6 months, DKA <12 months | Intervention: hybrid insulin-only CL, DiAs Control: SAP | 4 weeks | Low Blood Glucose Index | Not provided | Hypoglycemia reduction, adults–adolescents study |
| A multicenter study of outpatient automated blood glucose control with a bihormonal bionic pancreas (NCT02092220) | Massachusetts General Hospital, Boston University | Study completed | Efficacy, Phase 2, free living | Open-label, randomized, crossover study | T1DM, ≥18 years of age, $n=48$ Experienced CSII users Excluded severe hypoglycemia <12 months | Intervention: hybrid dual-hormone CL Control: CSII with or without CGM | 11 days | Mean glucose % time ≤70 mg/dL | % time <50 mg/dL, 70–120 mg/dL, 70–180 mg/dL, >250 mg/dL | Dual-hormone approach |

(*continued*)

TABLE 3. (CONTINUED)

| *Abbreviated title (registration number)* | *Responsible party* | *Status* | *Study type* | *Study design* | *Main inclusion/ exclusion criteria* | *Intervention/control* | *Period used* | *Primary outcome* | *Main secondary outcomes* | *Remarks* |
|---|---|---|---|---|---|---|---|---|---|---|
| Outpatient control-to-range: safety and efficacy with day-and-night In-home use (CTR3) (NCT02137512) | JDRF - Artificial Pancreas Project Consortium | Started, estimated primary completion November 2015 | Efficacy, Phase 3, at home | Open-label randomized, three-way, crossover study | T1DM, 18–69 years of age, $n=24$, HbA1c <86 mmol/mol Experienced CSII users Excluded severe hypoglycemia <12 months, DKA <12 months | Intervention: hybrid insulin-only CL, algorithm running on DiAs, 2 weeks at night, 2 weeks at evening–night, 2 weeks 24/7 Control: 2-week SAP | 2 weeks | % time ≤70 mg/dL | % time 70–180 mg/dL % time ≤60 mg/dL | Comparison of mode of CL use over three periods |
| Early feasibility study of zone-MPC and HMS with DiAs in the Outpatient Setting (NCT02463682) | William Sansum Diabetes Center | Recruiting participants, estimated primary completion October 2015 | Efficacy, outpatient | Open-label, nonrandomized, crossover study | T1DM, 21–65 years of age, $n=6$–9, HbA1c <86 mmol/mol Excluded severe hypoglycemia <12 months, DKA <12 months | Intervention: hybrid insulin-only CL, MPC, DiAS Control: SAP | 1 week | % time 70–180 mg/dL % time <70 mg/dL | % time 80–140 mg/dL | Insulin-only outpatient study |
| Zone-MPC on the DiAs platform efficacy (NCT02514785) | Stanford University | Not open for participant recruitment, estimated completion July 2016 | Efficacy, Phase 1, a hotel/ camp setting | Open-label, randomized, parallel study | T1DM, 10–19 years of age, $n=10$, CSII use >3 months Excluded severe hypoglycemia <6 months, DKA <1 month | Intervention: hybrid insulin-only, MPC, DiAs Control: SAP | 5 days and nights | % time 70–180 mg/dL | % time <70/<60/ <50 mg/dL | Insulin-only outpatient study |
| An outpatient study of automated blood glucose control with an insulin-only bionic pancreas (NCT02536950) | Stanford University | Not open for participant recruitment, estimated primary completion August 2016 | Safety, efficacy, Phase 1, home | Single-blind, nonrandomized parallel study | T1DM, 18–44 years of age, $n=16$, CSII use >6 months Excluded severe hypoglycemia <12 months, DKA <1 month | Intervention 1: hybrid insulin-only CL, fixed set point (130 mg/dL) Intervention 2: hybrid insulin-only CL "variable" set point Control: baseline blinded CGM | 14 days | Mean glucose | % time <60 mg/dL | Fixed versus variable glycemic set-point comparison |
| Reduction of nocturnal hypoglycemia and hyperglycemia in the home using predictive algorithms (NCT02438189) | In Home Closed Loop Study Group | Recruiting participants, estimated primary completion October 2015 | Safety, efficacy, Phase 2, home | Open-label, randomized, parallel study | T1DM, 15–45 years of age, $n=30$, HbA1c <86 mmol/mol Excluded DKA <3 months | Intervention: MMT-hyperglycemia minimization system + PLGS Control: SAP + PLGS | 42 nights | % time 70–180 mg/dL | % time ≤70 mg/dL % time >180 mg/dL | Next step after LGS and PLGS, introduction of hyperglycemia minimizer |

Source: ClinicalTrials.gov website (accessed October 7, 2015).

CGM, continuous glucose monitoring; CL, closed-loop; CSII, continuous subcutaneous insulin infusion; DiAs, diabetes Assistant; DKA, diabetic ketoacidosis; dual-hormone, closed-loop system that uses both insulin and glucagon; full-CL, mode of closed-loop operation that requires no user input during operation of the system; hybrid-CL, mode of closed-loop operation that requires user announcement of meals or other activities to the system; insulin-only, insulin only closed-loop system; LGS, low glucose suspend; MPC, model predictive control; PLGS, predictive low glucose suspend; SAP, sensor-augmented pump; T1DM, type 1 diabetes mellitus.

Table 4. Commercialization of Advanced Automation of Insulin Administration Systems

| *Initiative, responsible party* | *Product* | *Expected timing of a commercially available device* |
|---|---|---|
| Commercially driven | | |
| Animas | Predictive low glucose suspend or hypoglycemia-hyperglycemia minimizer with Dexcom CGM device | Unknown |
| Bigfoot Biomedical | Hybrid-CL, insulin-only, fully integrated, used for 24/7 operation. Proprietary algorithm, Asante pump body, and Dexcom CGM device | Clinical trials 2016, potential launch in late 2018 |
| Inreda Diabetic | Full-CL, dual hormone, fully integrated, used for 24/7 operation | First European CE mark study expected beginning of 2016. Approximately 2016 launch (European Union) |
| Medtronic | Hybrid-CL, insulin-only, fully integrated, MiniMed 670G, used for 24/7 operatio | U.S. launch expected April 2017, European launch April 2018 |
| Tandem | Predictive low glucose suspend or basal CL system | Potential launch in late 2017 |
| University-driven | | |
| Boston University | Hybrid-CL, dual-hormone, fully integrated, dual-chamber pump, Dexcom CGM device, used for 24/7 operation | Approximately 2018 launch (United States) |
| University of Virginia/ TypeZero Technologies | Hybrid-CL, insulin-only, connectivity-based approach (DiAs) using commercialized products (Dexcom/Roche/Tandem). Overnight and 24/7 operation | Intermediate-term studies published.[29] Clinical trials with up to 6 months in duration are planned for 2016. |
| University of Cambridge | Hybrid-CL, insulin-only, connectivity-based approach, using Abbott Navigator CGM device, algorithm on portable computer, and Abbott Florence pump. Overnight and 24/7 operation | Unknown |

CGM, continuous glucose monitoring; DiAs, Diabetes Assistant; dual-hormone, closed-loop system that uses both insulin and glucagon; full-CL, mode of closed-loop operation that requires no user input during operation of the system; hybrid-CL, mode of closed-loop operation that requires user announcement of meals or other activities to the system; insulin-only, insulin-only closed-loop system.

temporal information on glycemia and glucose trends to patient and physician. Although CGM enables users to lower their average glucose level without an increased incidence of hypoglycemia, this comes at a price—the price of additional patient effort. Automation of insulin administration has the promise to reduce the need for additional patient effort and improve glycemic control.

In the coming years CGM systems will reach an accuracy level at which further improvement translates into diminished additional clinical benefit, making other features like ease of clinical data application and factory calibration, but also use of CGM for automation of insulin administration, more important. CGM data serve as the input for insulin automation devices, and as such the development of reliable CGM technology was important in the advancement of automated insulin administration. The first commercial product using partial automation of insulin administration used insulin delivery shutoff at a predefined LGS. These systems showed a reduction in (severe) hypoglycemia compared with the most advanced treatment (SAP). Systems using additional basic predictive technology (PLGS) also showed a decrease in hypoglycemia but at the cost of a rise in mean overnight glucose level. Hybrid insulin-only CL devices were the first to show that an increased time spent in euglycemia, and a reduction of hypo- and hyperglycemia can be expected from CL technology. Improved glycemic control, with minor decreases in HbA1c levels, was confirmed in recent long-term home studies investigating these devices, paving the way for pivotal studies for commercialization of AP. Although the first results from dual-hormone CL systems are promising, because of increased cost of consumables of these systems, long-term head-to-head studies will have to prove superiority over insulin-only approaches.

After a long wait since the first experiment with the Biostator, CL glucose control for daily use seems to finally become a reality. Improved continuous glucose sensing technology, miniaturization of electrical devices, and development of algorithms were key in making this possible. University projects have provided the evidence needed for regulatory organizations to allow pivotal trials of commercial devices, while at the same time commercially driven initiatives in basic automation of insulin administration (LGS/PLGS) helped to boost confidence in the technology. Intensive collaborations among funding bodies, commercial entities, and not-for-profit organizations have been essential for the development of CL systems.

Clinical adoption challenges, including device usability and reimbursement, will need to be addressed. This includes improved connectivity between devices and improvements in algorithms and insulin to allow for a switch from hybrid-CL

to full-CL products. Time will tell for which patient groups CL systems will be reimbursed and to what extent these devices can deliver the promise they hold.

### Author Disclosure Statement

J.K. has no conflicts of interest to declare. J.H.D. is an advisory board member for Roche Diagnostics and Johnson & Johnson and has received research support from Abbott, Dexcom, Medtronic, and Senseonics.

### References


1. DCCT Research Group: Epidemiology of severe hypoglycemia in the Diabetes Control and Complications Trial. Am J Med 1991;90:450–459.
2. Hermanides J, Nørgaard K, Bruttomesso D, et al.: Sensor-augmented pump therapy lowers HbA1c in suboptimally controlled Type 1 diabetes; a randomized controlled trial. Diabet Med 2011;28:1158–1167.
3. Hommel E, Olsen B, Battelino T, et al.: Impact of continuous glucose monitoring on quality of life, treatment satisfaction, and use of medical care resources: analyses from the SWITCH study. Acta Diabetol 2014;51:845–851.
4. Albisser AM, Leibel BS, Ewart TG, et al.: Clinical control of diabetes by the artificial pancreas. Diabetes 1974;23:397–404.
5. Marliss EB, Murray FT, Stokes EF, et al.: Normalization of glycemia in diabetics during meals with insulin and glucagon delivery by the artificial pancreas. Diabetes 1977;26: 663–672.
6. Valgimigli F, Lucarelli F, Scuffi C, et al.: Evaluating the clinical accuracy of GlucoMen®Day: a novel microdialysis-based continuous glucose monitor. J Diabetes Sci Technol 2010;4:1182–1192.
7. Garg SK, Schwartz S, Edelman SV: Improved glucose excursions using an implantable real-time continuous glucose sensor in adults with type 1 diabetes. Diabetes Care 2004;27: 734–738.
8. Bailey T, Bode BW, Christiansen MP, et al.: The performance and usability of a factory-calibrated flash glucose monitoring system. Diabetes Technol Ther 2015;17:787–794.
9. Dehennis A, Mortellaro MA, Ioacara S: Multisite study of an implanted continuous glucose sensor over 90 days in patients with diabetes mellitus. J Diabetes Sci Technol 2015;9:951–956.
10. Senseonics and Rubin Medical to partner in Scandinavia to commercialize new CGM product. 2015. http://senseonics.com/uncategorized/senseonics-rubin-medical-partner-scandinavia-commercialize-cgm-product (accessed June 1, 2015).
11. Zschornack E, Schmid C, Pleus S, et al.: Evaluation of the performance of a novel system for continuous glucose monitoring. J Diabetes Sci Technol 2013;7:815–23.
12. Facchinetti A, Sparacino G, Guerra S, et al.: Real-time improvement of continuous glucose monitoring accuracy: the smart sensor concept. Diabetes Care 2013;36:793–800.
13. Klueh U, Liu Z, Feldman B, et al.: Metabolic biofouling of glucose sensors in vivo: role of tissue microhemorrhages. J Diabetes Sci Technol 2011;5:583–95.
14. Klueh U, Qiao Y, Czajkowski C, et al.: Basement membrane-based glucose sensor coatings enhance continuous glucose monitoring in vivo. J Diabetes Sci Technol 2015;9:957–965.
15. Kovatchev BP, Patek SD, Ortiz EA, et al.: Assessing sensor accuracy for non-adjunct use of continuous glucose monitoring. Diabetes Technol Ther 2014;17:1–10.
16. Hoss U, Budiman ES, Liu H, Christiansen MP: Feasibility of factory calibration for subcutaneous glucose sensors in subjects with diabetes. J Diabetes Sci Technol 2014;8:89–94.
17. Glooko Unified Platform for Diabetes Management. https://www.glooko.com/ (accessed June 1, 2015).
18. Pettus J, Price DA, Edelman SV: How patients with type 1 diabetes translate continuous glucose monitoring data into diabetes management decisions. Endocr Pract 2015;21: 613–620.
19. Ruedy KJ, Tamborlane WV: The landmark JDRF continuous glucose monitoring randomized trials: a look back at the accumulated evidence. J Cardiovasc Transl Res 2012;5: 380–387.
20. Pickup JC, Freeman SC, Sutton AJ: Glycaemic control in type 1 diabetes during real time continuous glucose monitoring compared with self monitoring of blood glucose: meta-analysis of randomised controlled trials using individual patient data. BMJ 2011;343:d3805.
21. Langendam M, Ym L, Hooft L, Jh D, Ah M, Rjpm S. Continuous glucose monitoring systems for type 1 diabetes mellitus. Cochrane Database Syst Rev 2012 Jan 18:1: CD008101.
22. Renard E, Cobelli C, Kovatchev BP: Closed loop developments to improve glucose control at home. Diabetes Res Clin Pract 2013;102:79–85.
23. Bergenstal RM, Klonoff DC, Garg SK, et al.: Threshold-based insulin-pump interruption for reduction of hypoglycemia. N Engl J Med 2013;369:224–32.
24. Ly TT, Nicholas JA, Retterath A, et al: 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;310:1240–1247.
25. Heinemann L, Hermanns N: IQWiG reanalyzes and raises questions about an article by Ly et al which concluded low glucose suspend is very beneficial. J Diabetes Sci Technol 2015 August 6 [Epub ahead of print]. doi: 10.1177/1932296815597918.
26. Buckingham BA, Cameron F, Calhoun P, et al.: Outpatient safety assessment of an in-home predictive low-glucose suspend system with type 1 diabetes subjects at elevated risk of nocturnal hypoglycemia. Diabetes Technol Ther 2013; 15:622–627.
27. Maahs DM, Calhoun P, Buckingham BA, et al.: A randomized trial of a home system to reduce nocturnal hypoglycemia in type 1 diabetes. Diabetes Care 2014;37:1885–1891.
28. Russell SJ, El-Khatib FH, Sinha M, et al.: Outpatient glycemic control with a bionic pancreas in type 1 diabetes. N Engl J Med 2014;371:313–325.
29. Kropff J, Del Favero S, Place J, et al.: 2 month evening and night closed-loop glucose control in patients with type 1 diabetes under free-living conditions: a randomised cross-over trial. Lancet Diabetes Endocrinol 2015;3:939–947.
30. Del Favero S, Place J, Kropff J, et al.: Multicenter outpatient dinner/overnight reduction of hypoglycemia and increased time of glucose in target with a wearable artificial pancreas using modular model predictive control in adults with type 1 diabetes. Diabetes Obes Metab 2015;17:468–476.
31. Kovatchev BP, Renard E, Cobelli C, et al.: Feasibility of outpatient fully integrated closed-loop control: first studies of wearable artificial pancreas. Diabetes Care 2013;36:1851–1858.
32. Leelarathna L, Dellweg S, Mader JK, et al.: Day and night home closed-loop insulin delivery in adults with type 1

diabetes: three-center randomized crossover study. Diabetes Care 2014;37:1931–1937.
33. Nimri R, Muller I, Atlas E, et al.: Night glucose control with MD-Logic artificial pancreas in home setting: a single blind, randomized crossover trial-interim analysis. Pediatr Diabetes 2014;15:91–99.
34. Weinzimer SA, Sherr JL, Cengiz E, 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;35:1994–1999.
35. Doyle FJ, Huyett LM, Lee JB, et al.: Closed-loop artificial pancreas systems: engineering the algorithms. Diabetes Care 2014;37:1191–1197.
36. Toffanin C, Messori M, Di Palma F, et al.: Artificial pancreas: model predictive control design from clinical experience. J Diabetes Sci Technol 2013;7:1470–1483.
37. Turksoy K, Paulino TML, Zaharieva DP, et al.: Classification of physical activity: information to artificial pancreas control systems in real time. J Diabetes Sci Technol 2015;9:1200–1207.
38. van Bon AC, Luijf YM, Koebrugge R, et al.: 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;16:131–136.
39. Kowalski AJ: Can we really close the loop and how soon? Accelerating the availability of an artificial pancreas: a roadmap to better diabetes outcomes. Diabetes Technol Ther 2009;11(Suppl 1):S113–S119.
40. Thabit H, Tauschmann M, Allen JM, et al.: Home use of an artificial beta cell in type 1 diabetes. N Engl J Med 2015;373:2129–2140.
41. Ly TT, Roy A, Grosman B, et al.: Day and night closed-loop control using the integrated Medtronic hybrid closed-loop system in type 1 diabetes at diabetes camp. Diabetes Care 2015;38:1205–1211.
42. Brown SA, Kovatchev BP, Breton MD, et al.: Multinight ''bedside'' closed-loop control for patients with type 1 diabetes. Diabetes Technol Ther 2015;17:203–209.
43. Thabit H, Elleri D, Leelarathna L, et al.: Unsupervised home use of an overnight closed-loop system over 3-4 weeks: a pooled analysis of randomized controlled studies in adults and adolescents with type 1 diabetes. Diabetes Obes Metab 2015;17:452–458.
44. Nimri R, Muller I, Atlas E, et al.: MD-Logic overnight control for 6 weeks of home use in patients with type 1 diabetes: randomized crossover trial. Diabetes Care 2014;37:3025–3032.
45. Thabit H, Lubina-Solomon A, Stadler M, et al.: Home use of closed-loop insulin delivery for overnight glucose control in adults with type 1 diabetes: a 4-week, multicentre, randomised crossover study. Lancet Diabetes Endocrinol 2014;2:701–709.
46. Ly TT, Breton MD, Keith-Hynes P, et al.: Overnight glucose control with an automated, unified safety system in children and adolescents with type 1 diabetes at diabetes camp. Diabetes Care 2014;37:2310–2316.
47. Hovorka R, Elleri D, Thabit H, et al.: Overnight closed-loop insulin delivery in young people with type 1 diabetes: a free-living, randomized clinical trial. Diabetes Care 2014;37:1204–1211.
48. Kowalski A: Pathway to artificial pancreas systems revisited: moving downstream. Diabetes Care 2015;38:1036–1043.
49. Castle JR, Engle JM, El Youssef J, et al.: Novel use of glucagon in a closed-loop system for prevention of hypoglycemia in type 1 diabetes. Diabetes Care 2010;33:1282–1287.
50. Haidar A, Legault L, Messier V, et al.: Comparison of dual-hormone artificial pancreas, single-hormone artificial pancreas, and conventional insulin pump therapy for glycaemic control in patients with type 1 diabetes: an open-label randomised controlled crossover trial. Lancet Diabetes Endocrinol 2015;3:17–26.

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