2 month evening and night closed-loop glucose control in patients with type 1 diabetes under free-living conditions: a randomised crossover trial

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Summary

Background **An artificial pancreas (AP) that can be worn at home from dinner to waking up in the morning might be safe and efficient for first routine use in patients with type 1 diabetes. We assessed the effect on glucose control with use of an AP during the evening and night plus patient-managed sensor-augmented pump therapy (SAP) during the day, versus 24 h use of patient-managed SAP only, in free-living conditions.**

Methods **In a crossover study done in medical centres in France, Italy, and the Netherlands, patients aged 18–69 years with type 1 diabetes who used insulin pumps for continuous subcutaneous insulin infusion were randomly assigned to 2 months of AP use from dinner to waking up plus SAP use during the day versus 2 months of SAP use only under free-living conditions. Randomisation was achieved with a computer-generated allocation sequence with random block sizes of two, four, or six, masked to the investigator. Patients and investigators were not masked to the type of intervention. The AP consisted of a continuous glucose monitor (CGM) and insulin pump connected to a modified smartphone with a model predictive control algorithm. The primary endpoint was the percentage of time spent in the target glucose concentration range (3·9–10·0 mmol/L) from 2000 to 0800 h. CGM data for weeks 3–8 of the interventions were analysed on a modified intention-to-treat basis including patients who completed at least 6 weeks of each intervention period. The 2 month study period also allowed us to asses HbA_{1c} as one of the secondary outcomes. This trial is registered with ClinicalTrials.gov, number NCT02153190.**

Findings **During 2000–0800 h, the mean time spent in the target range was higher with AP than with SAP use: 66·7% versus 58·1% (paired difference 8·6% [95% CI 5·8 to 11·4], p<0·0001), through a reduction in both mean time spent in hyperglycaemia (glucose concentration >10·0 mmol/L; 31·6% *vs* 38·5%; –6·9% [–9·8% to –3·9], p<0·0001) and in hypoglycaemia (glucose concentration <3·9 mmol/L; 1·7% *vs* 3·0%; –1·6% [–2·3 to –1·0], p<0·0001). Decrease in mean HbA_{1c} during the AP period was significantly greater than during the control period (–0·3% *vs* –0·2%; paired difference –0·2 [95% CI –0·4 to –0·0], p=0·047), taking a period effect into account (p=0·0034). No serious adverse events occurred during this study, and none of the mild-to-moderate adverse events was related to the study intervention.**

Interpretation **Our results support the use of AP at home as a safe and beneficial option for patients with type 1 diabetes. The HbA_{1c} results are encouraging but preliminary.**

Funding **European Commission.**

Introduction

Over the past decades, insulin pump treatment and continuous glucose monitoring (CGM) have helped patients with type 1 diabetes to achieve and maintain near-normal glucose control, thereby diminishing the risk of long-term diabetes-related complications and reducing the mortality rate.[1,2] However, compared with less stringent glucose control, tight control can increase the risk of hypoglycaemia and requires more effort by the patient to manage their disease.[3] Patients are confronted several times a day with complex dosing decisions and can be overwhelmed by the amount of treatment options and technological information.

A closed-loop control system (artificial pancreas [AP]) is designed to automate insulin infusion so that time in the target glucose concentration range is increased while time in hypoglycaemia and hyperglycaemia and disease burden are reduced. Different approaches are being investigated, including systems with insulin infusion only and systems that combine insulin with glucagon infusion.[4,5] Current APs are composed of a CGM device, a wearable insulin pump, a glucagon pump when applicable, and a model-predictive control algorithm that is embedded in a smartphone or small tablet and wirelessly linked to the CGM device and insulin pump. Various algorithms are used to drive insulin infusion (and glucagon when applicable).[6–9] AP systems have been extensively tested for safety and efficacy in inpatient and transitional settings.[5,10–15]

Two studies have investigated night-time use of AP at home.[16,17] Night-time seems the easiest period to improve

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Research in context

Evidence before this study

We searched PubMed for articles published until Aug 31, 2015, with the terms "Diabetes Mellitus, Type 1"[Mesh] AND "(artificial AND pancreas OR [closed-loop OR (closed AND loop)])" and selected five randomised studies that were done outside of the hospital setting and investigated the use of an artificial pancreas (AP) in adults. Three of these studies had a duration of up to 7 days (Van Bon et al, 2014; Russell et al, 2014; and Leelarathna et al, 2014), two studies investigated home AP glucose control over 4–6 weeks (Nimri et al, 2014; and Thabit et al, 2014). These two long-term studies assessed overnight AP use and the results showed improved time in target glucose concentration range through reduced time in hyperglycaemia. Nimri and colleagues also showed a reduction in insulin use and the time spent in hypoglycaemia with overnight AP use compared with sensor-augmented pump therapy.

Added value of this study

To our knowledge, our trial is the first 2-month randomised controlled crossover study to investigate evening and night closed-loop control during truly free-living conditions. Evening and night closed-loop control achieved substantial improvements in the time spent in the target range and in mean glucose concentration through reductions in the amount of time spent in both hypoglycaemia and hyperglycaemia. Even though the AP was only used during the evening and night, time spent in hypoglycaemia and hyperglycaemia was also reduced over 24 h. To our knowledge, no other studies have shown an improvement in the time in the target range through reductions in both hypoglycaemia and hyperglycaemia, or a reduction of insulin use in a long-term study that includes the evening period, during which glycaemic control is more difficult to achieve.

Implications of all the available evidence

Currently, the AP field is moving from short-term transitional studies to long-term studies. Our results suggest that use of an AP at home is a safe and effective method for closed-loop insulin delivery. Continuous (24 h) AP use, and use over periods longer than 2 months, should now be prioritised for further investigation.

glucose control because changes in meals and exercise predominantly occur during the daytime.[18,19] As a next step after night-only closed-loop control, we propose extending the use of the overnight closed-loop control at home with the addition of the evening period. This increased period could maximise the time of glucose control that is possible at home because most high-risk activities—including strenuous sports and driving—are not done at home.

We therefore assessed glucose control achieved with an AP used during the evening and night and patient-managed open-loop control with use of sensor-augmented pump (SAP) therapy during the day (AP period), versus continuous SAP therapy (control period), in free-living conditions in a study of sufficient duration to assess the effect on HbA_{1c}.

Methods

See Online for appendix

Study design and participants

This trial was a multinational, randomised, crossover, open-label study in patients with type 1 diabetes treated with continuous subcutaneous insulin infusion (CSII). The study start and end dates were April 1, and Dec 15, 2014, respectively. Patients were recruited from medical centres at the University of Amsterdam (Amsterdam, Netherlands), University of Montpellier (Montpellier, France), and University of Padova (Padova, Italy). The main inclusion criteria were age 18–69 years, a diagnosis of type 1 diabetes for at least 6 months according to the American Diabetes Association criteria,[20] a BMI of less than 35 kg/m², and a concentration of HbA_{1c} of between 7·5% and 10% (58–86 mmol/mol). All patients were experienced insulin pump users and were trained in carbohydrate counting. To mitigate risk, patients with severe hypoglycaemia in the past year or ketoacidosis in the past 6 months were excluded from participation in the study. Patients were also excluded if they were pregnant or breastfeeding, used medication that substantially altered their glucose metabolism except for insulin, had uncontrolled hypertension (resting >140/90 mm Hg), or change of anthihypertensive medications in the past month, worked nightshifts or expected to be away from home for longer than 25% of the study duration, had no family member or friend nearby for assistance, had malignant disease, had an acute cardiovascular event during the previous year, had renal insufficiency (creatinine >150 μmol/L), had impairment of liver function (levels of liver enzymes more than twice the upper limit of normal), or had impaired cognitive or psychological abilities.

The study design is illustrated in the appendix. After a screening and 2-week run-in, patients used SAP—ie, insulin-pump treatment and CGM (open loop), during two 8-week sessions. In one of these sessions, patients used an AP that computed the amount of insulin to be infused during the evening and night (closed loop). The two periods were separated by a 4-week washout in which patients used the study pump with or without CGM according to their prestudy treatment. At the beginning and end of each period, HbA_{1c} was measured on International Federation of Clinical Chemistry calibrated high-performance liquid chromatography instruments.

The study was done in accordance with the Declaration of Helsinki and was approved by the institutional ethics

review board at each site. All patients provided verbal and written informed consent.

Procedures

Study personnel trained the patients to use the Accu-Chek Spirit Combo insulin pump and Aviva Combo glucose-meter (both Roche Diagnostics, Mannheim, Germany) and Dexcom G4 Platinum CGM (Dexcom, San Diego, CA, USA) in a safe and effective way during the 2-week run-in. Treatment for each patient was reviewed and optimised before and at the end of the training and thereafter on the patient's request. No patient could start the intervention if not assessed as being able to manage CGM data, including prevention of insulin stacking and modification of insulin boluses according to CGM glucose trends.

After the open-loop training, the order of the 8-week sessions was randomly assigned in a 1:1 ratio with computer-generated allocation sequence with block sizes of two, four, and six, masked to the investigator. The patients continued open-loop therapy using an insulin pump and CGM (control period) or started using the AP (AP period). During the AP period, patients used the AP from dinner to the time they woke up the next morning (closed loop) and self-managed their glucose control with insulin pump and CGM for the rest of the day (open loop). No limitations were placed on diet and normal daily activities, including exercise. Patients were advised to keep their daily patterns similar during both study periods.

The CGM alarm thresholds for hypoglycaemia and hyperglycaemia were initially set at 5·0 mmol/L and 11·1 mmol/L, respectively, but could be modified by the patients. For safety, patients were instructed to test for ketones (Freestyle Precision Xtra β-Ketone, Abbott, North Chicago, IL, USA) if the capillary glucose concentration was greater than 16·7 mmol/L and to measure capillary glucose before altering their insulin dose or hypoglycaemia and hyperglycaemia treatment. Patients were asked to check for catheter occlusion or dislodgement and pump dysfunction if they had hyperglycaemia without an obvious explanation, to calibrate their CGM twice daily, and to measure their capillary glucose concentrations at least four times a day. Patients decided their meal-time and correction boluses during open loop using the built-in bolus calculator in the glucose meter. Patients were free to adjust their insulin bolus during all periods. Device data were readout at every patient visit.

The AP consisted of the Diabetes Assistant (DiAs) developed at the University of Virginia (Charlottesville, VA, USA), with a smartphone holding the control algorithm and wireless Bluetooth connections to the CGM and insulin pump.[21] The components of the AP system are illustrated in the appendix. The DiAs system was run on a smartphone (Nexus 5, LG Group, Seoul, South Korea) with a modified Android operating system (Google, Mountain View, CA, USA).[21] The controller implemented on the DiAs was based on a modular architecture as described by Patek and colleagues[22] with a model-predictive controller[23] aiming for a fixed glucose target concentration of 6·6 mmol/L. To allow for Bluetooth communication between the DiAs and the CGM, the G4 Platinum receiver was placed in a dedicated Bluetooth-USB hub (relay box). In the event of system dysfunction and unsuccessful troubleshooting, pump basal rate insulin delivery was automatically reset within 30 min to the patient's pretrial basal rates. The DiAs was preset with the patient's basal rate pattern, carbohydrate-to-insulin ratio, and correction factor. Patients received training and a troubleshooting booklet on how to use the AP platform.

The patients interacted with the DiAs using a graphical user interface,[24] which allows real-time input like meal announcements, premeal capillary glucose concentration, or self-administered hypoglycaemia treatment, and displays CGM and insulin delivery graphs. Moreover, the interface provides hypoglycaemia and hyperglycaemia alerts. During closed loop, patients used the DiA's built-in bolus calculator to calculate meal-time boluses.

DiAs allowed for secured data streaming over the internet to a remote monitoring website with the smartphone 3G connection,[25] enabling the investigators to help patients with any technical problems. For safety reasons, data were regularly checked in real time by study staff to allow for intervention in case of any or imminent serious adverse event.

Outcomes

All outcomes were predefined in a statistical analysis plan. The primary endpoint was the percentage of time spent in the target range (3·9–10·0 mmol/L) during the evening and night. Evening and night was predefined as 2000–0800 h and would generally include the time after dinner. Secondary endpoints included percentage of time spent in the target range (3·9–10·0 mmol/L) over 24 h, early morning (0600–0700 h) blood glucose concentration, mean blood glucose, percentage of time spent below 3·9 mmol/L (hypoglycaemia) and above 10·0 mmol/L (hyperglycaemia), daily insulin use, change in HbA_{1c}, and percentage of time spent in closed-loop control (defined as the actual time spent in closed loop compared with maximum theoretical use). Mean early morning (0600–0700 h) blood glucose concentration was used as a proxy for fasting glucose. Time in tight glucose target range (4·4–7·8 mmol/L) was calculated over all given time ranges. Safety was assessed as the frequency of moderately severe (>15 min, <2·8 mmol/L) and overall (>15 min, <3·9 mmol/L) hypoglycaemic episodes, episodes of ketoacidosis, and adverse events. High and low blood glucose indexes were calculated. These are measures of the frequency and extent of low and high blood glucose readings, respectively. A higher score indicates more frequent or extensive, or both, hypoglycaemia and hyperglycaemia. The number of clinical interventions by the study team resulting in a treatment adjustment was recorded.

For assessment of patient-reported outcomes, the Diabetes Treatment Satisfaction Questionnaire (DTSQc)[26] and Hypoglycemia Fear Survey 2 (HFS2)[27] were completed by the patients at the beginning and end of both study periods. The DTSQc was completed at the end of both study periods, whereas the HFS2 was completed at the beginning and end of both study periods. The AP acceptance questionnaire[28] was completed by patients before and after the AP period only.

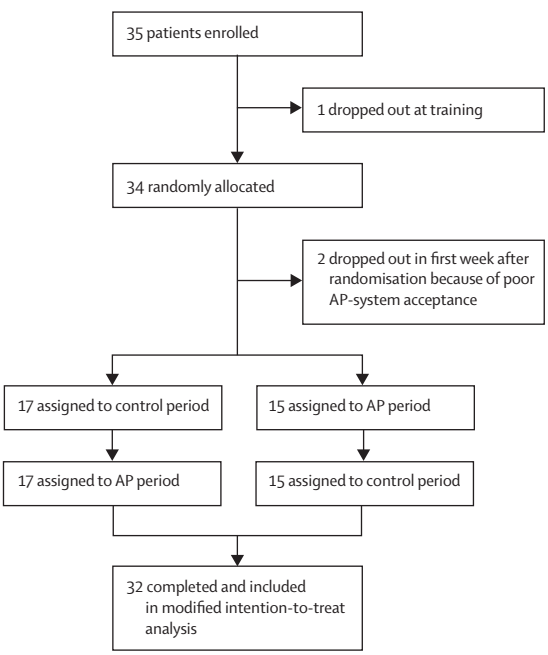

Figure 1: **Trial profile**
AP=artificial pancreas.

	Intention-to-treat population (n=32)
Age (years)	47·0 (11·2)
Sex	
Male	18 (56%)
Female	14 (44%)
BMI (kg/m²)	25·1 (3·5)
HbA_{1c} (%)	8·2 (0·6)
HbA_{1c} (mmol/mol)	65·9 (4·8)
Diabetes duration (years)	28·6 (10·8)
Insulin delivery mode, continuous subcutaneous insulin infusion	32 (100%)
Duration of continuous subcutaneous insulin infusion use (years)	12·5 (8·8)
Total daily insulin dose (U/kg)	0·6 (0·1)
Continuous glucose monitor use before start of study	3 (9%)

Data are mean (SD) or number (%).

Table 1: **Baseline characteristics of patients**

Statistical analysis

The mean time spent in the glucose target range from previous short-term studies of AP varied between 59% (SD 16%) and 84% (SD 14%).[9,10] We aimed to detect a mean difference of 10% in time spent in the target range between both intervention periods. At a power of 80% and α at 0·05, 31 patients were needed. To allow for dropouts, we aimed to include 36 patients. Because of uncertainty about the effect of study duration on power, the increase in time compared with other short-term studies was not taken into account.

As predefined in the statistical analysis plan, and based on previous experience with the DiAs platform in short-term studies, the first 2 weeks of both intervention periods were defined as learning periods and excluded from the data analysis—ie, of each 8 week AP or control period, and only data from weeks 3–8 were used in the analysis. We also did a sensitivity analysis for primary and secondary outcomes including these data. We used a modified intention-to-treat analysis, defined as completion of 6 weeks of each intervention period, thus contributing an adequate amount of data that could be analysed. All glucose indices were computed from the CGM data.

Because of the crossover design, we assessed the carryover effect.[29] If a carryover effect ($p<0·1$) was detected, the second study period was excluded from the analysis. If no carryover effect was detected, a multiway ANOVA was done including patient, treatment, and period as explanatory factors. Treatment and period effects were estimated with ANOVA when a period effect occurred ($p<0·05$). If neither carryover nor period effect occurred, normally distributed data were compared with a paired *t* test and non-normally distributed data were compared with the Wilcoxon signed-rank test. Normality of residuals was verified with the Lilliefors test. We report variables as median for non-normally distributed data and as mean for normally distributed data. 95% CI for the paired difference (Δ) for the mean and median were computed, except when a carryover effect was detected. For calculation of 95% CI for non-normally distributed data, we used the Hodges-Lehmann procedure,[30] and ANOVA if a period effect existed. All p values were two-tailed. Analyses were done with the Matlab Statistic toolbox (version 8.3).

This trial is registered with ClinicalTrials.gov, number NCT02153190.

Role of the funding source

The funders had no role in study design, data analysis, or preparation of the manuscript, and did not have access to any of the trial data. CT, JK, JP, LM, MMe, RV, and SDF had access to the raw data. The corresponding author had full access to all of the data and had final responsibility for the decision to submit for publication.

Results

Figure 1 shows the trial profile. Of 35 eligible patients who were enrolled, one patient dropped out before and

two patients dropped out after randomisation because of poor acceptance of the AP system. The remaining patients completed the study; hence, data for these 32 patients were assessed in the modified intention-to-treat analysis. Table 1 shows the baseline characteristics of the patients who completed the study. With the

	Artificial pancreas period (n=32)	Control period (n=32)	Paired difference* (n=32)	p value
Evening and night (2000–0800 h)				
Glucose concentration (mmol/L)†	9·0 (0·8)	9·3 (0·8)	−0·3 (−0·6 to −0·1)	0·0053
SD of glucose concentration† (mmol/L)†	3·1 (0·6)	3·4 (0·6)	−0·3 (−0·4 to −0·2)	<0·0001
Time spent at glucose concentration				
4·4–7·8 mmol/L†	37·7% (9·1)	31·2% (6·0)	6·5% (3·8 to 9·2)	<0·0001
3·9–10 mmol/L†	66·7% (10·1)	58·1% (9·4)	8·6% (5·8 to 11·4)	<0·0001
>10 mmol/L†	31·6% (9·9)	38·5% (9·7)	−6·9% (−9·8 to −3·9)	<0·0001
<3·9 mmol/L‡	1·7% (0·8 to 2·5)	3·0% (1·6 to 4·9)	−1·6% (−2·3 to −1·0)	<0·0001
<2·8 mmol/L‡	0·1% (0·0 to 0·2)	0·3% (0·1 to 0·6)	−0·1% (−0·3 to −0·1)	0·00014
Number of hypoglycaemic events per week				
<3·9 mmol/L†	4·3 (1·9)	5·8 (2·9)	−1·5 (−2·5 to −0·4)	0·0068
<2·8 mmol/L†	1·1 (1·1)	2·2 (1·7)	−1·1 (−1·5 to −0·7)	<0·0001
Blood glucose indices				
Low blood glucose index†	0·5 (0·2)	0·8 (0·4)	−0·3 (−0·5 to −0·20)	<0·0001
High blood glucose index†	7·1 (2·5)	8·5 (2·5)	−1·4 (−2·0 to −0·8)	<0·0001
Insulin need (IU)†	16·2 (7·0)	18·4 (8·7)	−2·3 (−3·7 to −0·8)	0·0029
Time spent in closed loop†	66·7% (17·5)	..	..	..
Early morning† (0600–0700 h)				
Glucose concentration (mmol/)†	8·0 (1·1)	8·9 (1·1)	−0·9 (−1·2 to−0·5)	<0·0001
SD of glucose concentration (mmol/L)†	2·3 (0·8)	3·1 (0·6)	−0·8 (−1·1 to−0·6)	<0·0001
Time spent at glucose concentration				
4·4–7·8 mmol/L‡	53·1% (39·7 to 68·7)	37·5% (31·8 to 40·4)	15·5% (10·9 to 25·2)	<0·0001
3·9–10 mmol/L‡	85·9% (76·5 to 92·7)	65·9% (59·3 to 71·4)	21·7% (13·1 to 24·0)	<0·0001
>10 mmol/L‡	17·0% (13·9)	33·1% (14·5)	−16·1% (−20·9 to −11·4)	<0·0001
<3·9 mmol/L‡	0·6% (0·0 to 1·5)	3·2% (1·1 to 4·9)	2·4% (−3·4 to −1·1)	0·00049
<2·8 mmol/L‡	0	0	..	..
Time spent in closed loop†	57·0% (19·3)	..	..	..
Day and night (24 h)				
Glucose concentration (mmol/L)‡	8·9 (8·6 to 9·2)	9·1 (8·8 to 9·4)	−0·2 (−0·3 to 0·0)	0·056
SD of glucose concentration (mmol/L)†	3·3 (0·5)	3·4 (0·5)	−0·2 (−0·3 to −0·1)	0·0009
Time spent at glucose concentration				
4·4–7·8 mmol/L†	36·3% (7·7)	32·6% (6·3)	3·7% (1·9 to 5·5)	0·00024
3·9–10·0 mmol/L‡	63·7% (60·4 to 70·1)	59·4% (56·7 to 64·3)	5·0% (3·0 to 6·8)	<0·0001
>10·0 mmol/L‡	33·5% (27·8 to 36·7)	36·4% (32·1 to 39·8)	−4·3% (−6·0 to −1·9)	0·00082
<3·9 mmol/L†	2·6% (1·4)	3·6% (2·0)	−1·0% (−1·5 to −0·5)	0·00022
<2·8 mmol/L‡	0·2% (0·1 to 0·4)	0·3% (0·2 to 0·7)	−0·1% (−0·2 to −0·1)	0·00029
Number of hypoglycaemic events per week				
<3·9 mmol/L†	5·7 (2·5)	6·3 (2·4)	−0·6 (−1·5 to 0·3)	0·15
<2·8 mmol/L‡	1·3 (0·7 to 2·7)	2·0 (1·1 to 3·8)	−0·8 (−1·2 to −0·4)	0·00052
Blood glucose indices				
Low blood glucose index‡	0·6 (0·4 to 0·9)	0·8 (0·6 to 1·2)	−0·2 (−0·3 to −0·1)	0·00018
High blood glucose index‡	6·9 (6·2 to 7·9)	7·8 (6·7 to 8·8)	−0·8 (−1·2 to −0·3)	0·0025
Insulin need (IU/24 h)†	36·7 (11·7)	43·2 (16·3)	−6·5 (−9·4 to −3·6)	<0·0001
Insulin need (IU/kg per 24 h)†	0·5 (0·1)	0·6 (0·1)	−0·1 (−0·1 to −0·1)	<0·0001
HbA_{1c} change (%)†	−0·3 (0·5)	−0·2 (0·4)	−0·2§ (−0·4 to −0·0)	0·047
HbA_{1c} change (mmol/mol)†	−3·5 (4·3)	−1·8 (5·0)	−2·0§ (7·8)	0·047
Time spent in closed loop‡	40·8% (30·7 to 44·7)	..	..	..

Tight glucose target range is 4·4–7·8 mmol/L. *Closed-loop minus control with 95% CI for paired difference. †Mean (SD). ‡Median (95% CI). §Treatment effect after ANOVA.

Table 2: **Primary and secondary outcomes during evening and night, morning, and 24 h (modified intention-to-treat analysis)**

exception of the evening time spent below 3·9 mmol/L, no carryover effect was detected.

Table 2 shows the results of the primary and secondary outcomes. Mean time in target glucose concentration range (primary endpoint) was higher during AP insulin delivery than during the control period between 2000 and 0800 h (66·7% *vs* 58·1%; Δ 8·6 [95% CI 5·8 to 11·4], p<0·0001; table 2). Mean glucose concentration was lower during AP insulin delivery than during the control period (9·0 mmol/L *vs* 9·3 mmol/L, p=0·0053) and median time in hypoglycaemia (<3·9 mmol/L) was reduced from 3·0% in the control period to 1·7% in the AP period (p<0·0001). Although the evening (2000–0000 h) mean glucose concentration was equal in the AP and control periods (9·4 mmol/L *vs* control 9·4 mmol/L; Δ 0 mmol/L [95% CI –0·2 to 0·3], p=0·83), median time spent in hypoglycaemia (<3·9 mmol/L) during this period was significantly reduced in the AP period compared with the control period (4·0% *vs* 1·7%; Δ 2·4% mmol/L [0·8 to 4·7], p=0·0063). Figure 2 shows the distribution of mean percentages of time in and below the target range for each individual.

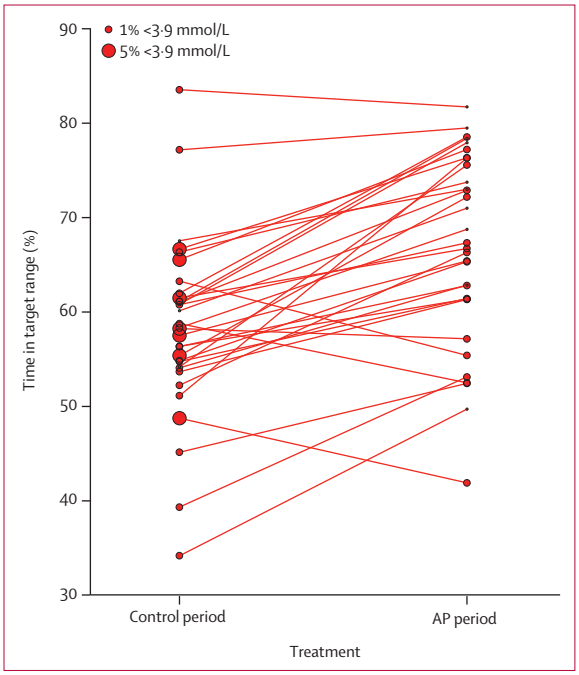

***Figure 2*: Percentage of time spent in and below target glucose concentration range for all study participants during 2000–0800 h**
Mean evening and night (2000–0800 h) percentage time in target range (3·9–10·0 mmol/L) is given for each patient for the control period, which is connected to the mean percentage time in target range for the AP period. The diameter of the circle shows percentage of time (either <1% or 5%) spent below the target range in either period. AP=artificial pancreas.

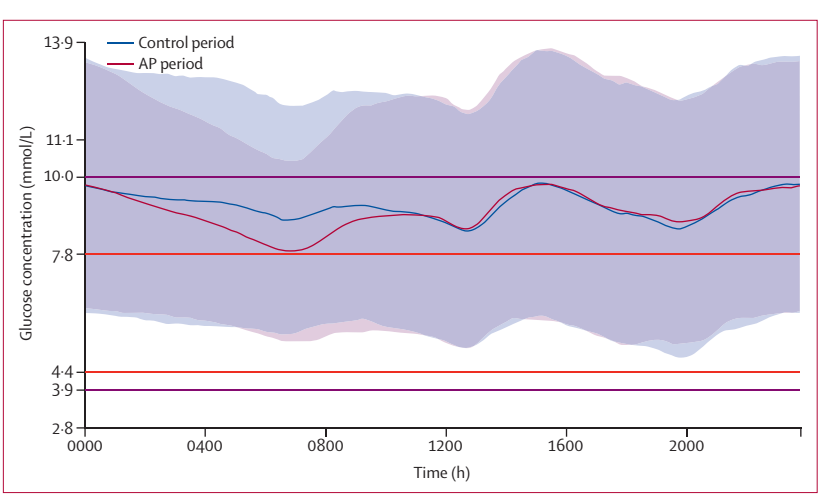

***Figure 3*: 24 h glucose control profile**
The glucose control profile of all patients analysed is shown as superimposed continuous traces of glucose monitoring during the AP and control periods. Mean blood glucose is given with 1 SD. Purple shading represents the SD for the AP period and blue shading represents the SD for the control period. 3·9–10 mmol/L represents the target glucose concentration range and 4·4–7·8 mmol/L represents the tight glucose target. AP=artificial pancreas.

Mean early morning glucose concentration was lower during the closed-loop period than during the control period (8·0 mmol/L *vs* 8·9 mmol/L; Δ 0·9 mmol/L [95% CI –1·2 to –0·5], p<0·0001; table 2). Median time in the target range was increased with the AP during this period from 65·9% to 85·9% (Δ 20%, [95% CI 13·1 to 24·0], p<0·0001).

Analysis of control over 24 h showed that median time in the target range was higher in the AP period than in the control period (63·7% *vs* 59·4%, p<0·0001; table 2), whereas mean time spent below target range (<3·9 mmol/L) was reduced from 3·6% to 2·6% (p=0·00022). Median glucose was not significantly different between the AP and control periods over 24 h. Figure 3 shows the mean glucose profile over 24 h.

Mean glucose variability during the evening and night (2000–0800 h) was reduced in the AP period compared with the control period (SD 3·1 mmol/L *vs* 3·4 mmol/L, p<0·0001), during early morning (0600–0700 h; 2·3 mmol/L *vs* 3·1 mmol/L, p<0·0001), and during 24 h (SD 3·3 mmol/L *vs* 3·4 mmol/L, p=0·0009; table 2).

Decrease in mean HbA_{1c} during the AP period was significantly greater than during the control period (–0·3% *vs* –0·2%; Δ –0·2 [95% CI –0·4 to –0·0], p=0·047; table 2). A period effect was only noted for change in HbA_{1c} (p=0·0034).

Mean insulin need was lower in the AP period than in the control period during 2000–0800 h (16·2 IU *vs* 18·4 IU, p=0·0029) and over 24 h (36·7 IU *vs* 43·2 IU, p<0·0001; table 2).

Patients spent a median of 9·8 h (40·8% [95% CI 30·7 to 44·7]) per 24 h in closed-loop control, including a mean 8·0 h (66·7% [SD 17·6]) in closed-loop control during 2000–0800 h and a mean 2·8 h (69·5% [20·4) in closed-loop control during 2000–0000 h. During 2000–0800 h, patients had their AP switched off a mean 21·0% (SD 17·5) of time because of personal preference or because of technical issues. AP was put in temporary suspend mode (eg, for taking a shower) a mean 9·7% (SD 5·0) of the time during 2000–0800 h. Sensor

problems affected AP use a mean 1·0% (SD 1·0) of the time, whereas DiAs-pump disconnections affected the system a mean 1·6% (SD 1·8) of time during 2000–0800 h. Additional information about AP functioning and use is reported in the appendix. Overall CGM accuracy, with capillary glucose concentration as a reference, expressed as mean absolute relative difference was 13·0% (3·0).

The reduction in time spent below the target range in the AP period was confirmed with a significant reduction in the number of moderately severe hypoglycaemic episodes (glucose concentration <2·8 mmol/L) per patient per week during 2000–0800 h (mean 1·1 *vs* 2·2 events, p<0·0001; table 2) and during 24 h (median 1·3 *vs* 2·0 events, p=0·00052; table 2). No serious adverse event occurred, including severe hypoglycaemic episodes as defined by the Diabetes Control and Complications Trial,[31] and there was no hospital admission for ketoacidosis. Eight adverse events occurred during the AP period and six during the control period. All adverse events were mild to moderate, and none were related to the study intervention: fever for less than 1 week (AP period, n=4; control period, n=3), upper respiratory tract infection (AP period, n=2; control period, n=1), gastrointestinal infection (AP period, n=1), otitis media with fever (control period, n=1), keratitis of the cornea (AP period, n=1), and migraine (control period, n=1). No patient needed to discontinue the study because of an adverse event. No patient needed to be contacted to prevent an imminent serious adverse event. No calls were made to check whether a patient was aware of being hypoglycaemic or to advise the patient about carbohydrate intake to end minor hypoglycaemia.

During both control and AP periods, glucose control was optimised on the initiative of the patient or study staff by changing the patient's individual setting of pump basal rate, carbohydrate-to-insulin ratio, or correction factor. This optimisation resulted in a significant difference in the number of adjustments in treatments between the AP and control periods (mean 2·7 [SD 2·7] *vs* 1·5 [2·1], respectively, Δ 1·2 95% CI 0·1 to 2·2, p=0·036) over the whole trial (weeks 1–8 of each period). This difference was not significant over the predefined evaluation period (weeks 3–8)—ie, excluding the learning period (weeks 1 and 2 of each intervention): mean 1·8 (SD 1·8) versus 1·2 (1·9) adjustments in treatment during the AP and control periods, respectively (Δ 0·6, 95% CI –0·2 to 1·4, p=0·14). The appendix provides further information about treatment adjustments.

No differences were noted in DTSQc and HFS2 between the AP and control periods (data not shown). Patients had a mean overall score of 69·1 (95% CI 63·5–4·7) of 90 points on the AP questionnaire (n=32). 23 (74%) of 31 patients who responded fully agreed or agreed with the statement "I would want to use the AP for a prolonged period of time".

Discussion

Evening and night closed-loop control resulted in significant improvements in time in mean and target glucose concentrations and a reduction in time spent in hypoglycaemia and hyperglycaemia compared with SAP. When assessed over 24 h, use of closed-loop control during the evening and night resulted in significant improvement in time in target and a reduction of percentage time spent in hypoglycaemia and hyperglycaemia. Evening and night closed-loop control significantly reduced the time spent in hypoglycaemia (glucose concentration <3·9 mmol/L) and reduced the number of episodes of glucose concentrations of less than 2·8 mmol/L over all periods. As shown in figure 2, two of four patients who had a reduction in time spent in the target range during the AP period did, however, benefit in terms of a reduction in time spent in hypoglycaemia. A slight, but significantly larger reduction of HbA_{1c} was achieved during the AP period than in the control period. To our knowledge, this is the first randomised, controlled, crossover study to investigate evening and night closed-loop control in truly free-living conditions, and the first closed-loop study with sufficient duration to make an initial assessment of the effect of AP use on HbA_{1c}.

Two previous studies investigated night-time (evening excluded) home AP glucose control versus SAP control over 4–6 weeks.[16,17] Thabit and colleagues[17] achieved improved time in the target range through reduced time in hyperglycaemia,[17] whereas Nimri and colleagues[16] were also able to reduce time in hypoglycaemia. In the study by Nimri and collegues and in our study, time in the target range was improved through a reduction in both hypoglycaemia and hyperglycaemia, effectively reducing the range of glucose control and achieving convergence to a narrow desired glucose range during the night. Of note, only our results show a significant reduction in glucose variability and in percentage time spent below 2·8 mmol/L with AP use when analysed on a modified intention-to-treat basis. Insulin dose was also reduced in the AP period compared with the control period both during 2000–0800 h and 24 h, which is similar to the findings of Nimri and colleagues,[16] but not to those of Thabit and colleagues.[17]

This study is the first in which glucose control was investigated over a prolonged period and not just overnight and included the difficult post-dinner period. Although mean glucose concentration during the evening (2000–0000 h) was not different between the closed-loop and SAP period, the use of closed-loop control significantly reduced the time spent below the target range in this period.

A strength of our study is the multicentre design, with European patients who had a broad range of eating habits and approaches to diabetes management. Furthermore, we used state-of-the-art technology, with wireless communication between the insulin pump,

CGM, and control unit, thereby enabling patients to continue their daily activities as usual. Patients were not restricted in time of meal or activities such as restaurant visits, night-time snacks, outdoor exercise, and holidays. The long duration of the study and investigation under truly free-living conditions further increase the external validity of our results.

Although patients received a thorough 2-week training on how to use the study devices, most patients had not been using CGM before the start of the trial. Therefore, full proficiency in clinical application of CGM data might not have been attained, which might have led to an overestimation of the improvement in glycaemic control seen with addition of closed-loop compared with use of SAP alone. Nonetheless, glycaemic control also improved significantly compared with baseline during the control period, including a reduction in HbA_{1c} and the time spent in hypoglycaemia, indicating that the patients did use CGM effectively.

The current system does not fully automate closed-loop insulin delivery because it requires patients to assess carbohydrate content of meals during the day, leaving room for further improvement. Furthermore, interruptions of wireless connections between devices were sometimes problematic for patients and caused the AP not to function a registered 2·6% of time. The system was in closed-loop mode a mean 66·7% (SD 17·5) of time between 2000–0800 h, and patients had their AP in temporary suspend mode for 9·7% (5·0) during this period. Although patients were advised to use the AP between 2000–0800 h, they were free to start up the system later than 2000 h if they wished to do so. Therefore, of the remaining 21·4% of time, patient's decision not to use the system for any reason cannot be separated from technical problems preventing the patient from using the device. Nonetheless, all data were analysed on a modified intention-to-treat basis. Additionally, patients scored the AP system used in this study 69·1 of 90 points and 74% indicated that they would want to use the current AP system over a prolonged period (AP acceptance questionnaire[28]), which is high acceptance for an investigational device.

The first 2 weeks of each intervention period were predefined as a learning period and excluded from data analyses. Nonetheless, a post-hoc-analysis indicated that significance of the primary and secondary outcomes (table 2) did not change at the $p<0·05$ limit after inclusion or exclusion of data from the learning period (data not shown).

Patients in the AP period received more frequent individual treatment adjustments than during the control period. The AP seems to need more adjustments before the optimum regulation is achieved; this need is perhaps related to the novelty of long-term use of the device for study staff and patients. The number of treatment adjustments was not significantly different between the AP and control evaluation periods (weeks 3–8). Additional attention might also have been attributed to the availability of remote monitoring during the AP period because remote monitoring was not available during the control period. For safety reasons, remote monitoring data were checked regularly in real time by study staff to allow for intervention in case of any or imminent serious adverse events. However, serious adverse events did not occur and no patient needed to be contacted to prevent an imminent serious adverse event. Also, no calls were made to check whether a patient was aware of being hypoglycaemic or to advise about carbohydrate intake to end a minor episode of hypoglycaemia during the control or the AP periods. In future generations of AP systems, control algorithms are likely to become self-learning with automated optimisation of algorithm parameters.

Overall, our proposed idea of individuals having at-home closed-loop control provides substantial benefits to patients with type 1 diabetes in terms of improved 24 h glucose control with reduction of both low and high glucose excursions and an acceptable burden because of device connection issues. The possible additional benefit associated with the continuous (ie, 24 h) use of an AP will have to be investigated while taking into account the practical constraints and safety of wearing the devices in the context of more stressful work and outdoor activities. Our results suggest that AP use at home is safe and beneficial for patients with type 1 diabetes and should be considered an initial option for closed-loop insulin delivery.

Contributors

All authors reviewed and provided edits and comments on manuscript drafts. JK was the main study physician responsible for the trial in Amsterdam, Netherlands, data analysis, and drafting of the original version of the manuscript. SDF was the senior engineer responsible for the trial in Padova, Italy, data analysis, and drafting of the manuscript. JP was the senior engineer responsible for the trial in Montpellier, France. CT was involved in the development of the algorithm and data analysis. MMe was involved in the algorithm implementation and data analysis. FDP did the control engineering for the control algorithm implementation on the DiAS. GL was the computer scientist responsible for the design and implementation of the remote monitoring system used during the trial. AF was the study physician in Montpellier. PM provided advice about the methods used for the statistical analyses. DB was the main study physician in Padova and was involved in the drafting of the manuscript. PK-H was the chief engineer of the DiAs smartphone-based system and user interface. BPK was involved in the development of the DiAs system. CC was the principal investigator in Padova, and was involved in the design of the protocol, data analysis, and drafting of the manuscript. JHD was the principal investigator in Amsterdam, and was involved in the design of the protocol, coordination of the study, and drafting of the manuscript. ER was the principal investigator in Montpellier, and was involved in drafting of the protocol and manuscript. LM was the principal investigator in the Pavia unit, Italy, and was involved in the development of the algorithm, data analysis, and drafting of the manuscript.

Declaration of interests

CC, CT, and LM hold patent applications related to the study control algorithms. CC has received research support from Sanofi-Aventis and Adocia. BPK holds patent applications related to the study technology and has served as an adviser to Becton, Dickinson and Company and Sanofi-Aventis, and has received research support from Animas, Becton, Dickinson and Company, Dexcom, Insulet, Roche Diagnostics, Sanofi-Aventis, and Tandem Diabetes Care, and owns stock in TypeZero Technologies. ER is a consultant or adviser for Menarini Diagnostics,

Abbott, Cellnovo, Dexcom, Eli-Lilly, Johnson & Johnson (Animas and LifeScan), Medtronic, Novo Nordisk, Roche Diagnostics, and Sanofi-Aventis, and has received research grant or material support from Abbott, Dexcom, Insulet, and Roche Diagnostics. JHD is a consultant or adviser on the speakers' bureaus for Dexcom, Johnson & Johnson (Animas and LifeScan), and Roche Diagnostics. PK-H holds patent applications related to the study technology, serves as chief technology officer of TypeZero Technologies, and has stock ownership in TypeZero Technologies. The other authors declare no competing interests.

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