Individually Adaptive Artificial Pancreas Improves Glucose Control in Subjects with Type 1 Diabetes. A One-Month Free-living Conditions Trial.

Running title: **Adaptive AP: clinical results**

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Keywords: Closed-loop, Blood-glucose control, Run-to-Run, Clinical trial, Outpatient, Model predictive control

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ABSTRACT (243 words)

BACKGROUND

To evaluate the efficacy of a run-to-run adaptive wearable artificial pancreas (R2R-AP) after one month of closed-loop glucose control in subjects with Type 1 diabetes (T1D) under free-living conditions.

METHODS

Eighteen adults, who previously completed a one-month closed-loop study with a non-adaptive AP (NA-AP), volunteered for an additional one-month extension study in which the AP was equipped with an adaptive model predictive control algorithm (R2R-AP). Continuous Glucose Monitoring (CGM) data were analyzed on an intention-to-treat basis by comparing the last week of R2R-AP vs. the last week of NA-AP. The primary endpoint was the time in target range (3.9-10mmol/l).

RESULTS

Time in target range was increased over 24 hours by the R2R-AP vs. the NA-AP: mean 66.90% (SD: 13.34) vs. 61.82% (11.12), p=0.09. The increase was significant during the night: 74.01% (14.61) vs. 64.31% (15.71), p=0.03, and at wake-up time: median 92.43% (25^{th}; 75^{th} percentiles: 78.22; 99.53) vs. 84.54% (57.14; 88.52), p=0.02. Time above target (>10 mmol/l) was decreased during the whole day: 30.98% (13.22) vs. 36.17% (11.53), p=0.10. The decrease was significant during the night 24.23% (15.03) vs. 34.49% (16.25), p=0.03, and at wake-up time: 7.57% (0.00; 14.29) vs. 14.29% (8.25; 42.86), p=0.05. Time spent below target (<3.9 mmol/l) was low and similar with the two treatments.

CONCLUSIONS

The R2R-AP, by capturing intra- and inter-day variability of a T1D subject, further improves glucose control over NA-AP in subjects with T1D in a one-month trial under free living conditions.

Contemporary outpatient artificial pancreas (AP) studies in free-living conditions have moved from days to months duration (1-2). People with type 1 diabetes (T1D) exhibit an intra- and inter-day variability in their glycemic status, e.g. insulin sensitivity, which can occur during both day and night. Thus, insulin infusion needs to be continually adjusted and an adaptive strategy able to capture this variability becomes a key AP algorithmic component in long-term studies. A classic adaptive approach in the control literature is the run-to-run (R2R) strategy, which evaluates a predefined selection of performance metrics in the previous run (day k) to determine the proper update to impose in the next day (day k+1). In the diabetes area, R2R has been used for daily adaptation of basal insulin (3), meal boluses, and for adapting a cost function residing in a control algorithm (4). Recently, a R2R update of basal insulin therapy based on continuous glucose monitoring (CGM) measurements (5) and a R2R closed-loop strategy (6) have been tested in silico with the UVA/Padova simulator (7).

Encouraged by the positive in silico results, we proposed the T1D subjects enrolled in a recent one-month closed-loop clinical trial (8) to extend their closed-loop treatment with an additional month by using a R2R adaptive AP (R2R-AP) 24 hours/day again under free-living conditions, i.e. with no clinical supervision and no protocol constraints. Data from the last week of R2R-AP vs. the last week of non-adaptive AP (NA-AP) were compared, with time in target range (3.9-10 mmol/l) as primary endpoint.

RESEARCH DESIGN AND METHODS

Study design and participants

In 2014, a multinational randomized crossover open-label study in patients with T1D was completed on a population of 32 patients. The aim was to investigate the use of a NA-AP during evening and night at home versus SAP therapy (9). After the completion of this study, 20 of the 32 patients from medical centers at the universities of Amsterdam (the Netherlands), Montpellier (France), and Padova (Italy) consented to participate in a one-month single-arm extension study with the aim to investigate the use of NA-AP 24 hours per day in free-living conditions (8). Of these 20 patients, 18 were enrolled in the present second extension study. The potential participants were provided with

an information letter and a consent form, which were specific to the extension study. This trial was registered with ClinicalTrials.gov, number NCT02153190, was performed in accordance with the Declaration of Helsinki, and approved by the institutional ethics review board at each site.

AP platform

The AP system used in this extension study was the same as used in the preceding studies (8-9). The AP was composed of a Dexcom G4 Platinum CGM (Dexcom, San Diego, CA, USA), an Accu-Check Spirit Combo insulin pump (Roche Diagnostics, Mannheim, Germany) and the Diabetes Assistant (DiAs) (10) developed at the University of Virginia (Charlottesville, VA, USA) on which the R2R-AP algorithm was implemented. The DiAs consists of an Android (Google Inc., Mountain View, CA, USA) Nexus 5 (LG Group, Seoul, South Korea) smartphone equipped with communication, control and user interface software connected to the CGM and the insulin pump via Bluetooth. The DiAs was preset with the patient's basal rate pattern, carbohydrate-to-insulin ratio (CR), and correction factor. In case of system dysfunction and unsuccessful troubleshooting, the control algorithm was automatically deactivated after 30 minutes and the pump basal rate was reset to the patient's pre-study basal rate. The patients interacted with the DiAs graphical user interface (11), which allows real-time inputs like meal announcements, pre-meal capillary glucose level or self-administered hypoglycemia treatment. The DiAs interface displays CGM and insulin delivery graphs, and provides hypo- and hyperglycemia alerts through a traffic lights representation. DiAs also allows for secured data streaming over the internet to a remote monitoring website (12) through the smart-phone 3G connection. This permitted real-time monitoring and remote assistance of the patients as needed.

Adaptive control algorithm

The control algorithm implemented on DiAs was based on the modular architecture described in (13). The core of the controller was the model predictive control (MPC) described in (14), which adjusts the nominal basal insulin delivery (patient's basal profile) and the meal boluses in real-time based on the past CGM data and an estimate of the patient's glycemic status. The basal profile and the CR pattern, entered by the patient during the initialization phase, may be inadequate due to the

intra- and inter-day variability of each patient. This will force the MPC to perform large adjustments, hampering its effectiveness. To address patient intra- and inter-day variability, we introduced the R2R-AP, i.e. the MPC enriched with a R2R strategy devoted to the daily automatic adaptation of the patient's nocturnal basal insulin and CR pattern. The goal is to optimize the tuning of these parameters and to adapt them to the slow inter-day variability. Based on the blood glucose control observed in the previous run (day k) the R2R algorithm modifies these parameters and updates the controller for the next day (day k+1). Since the major concern is to avoid hypoglycemia, the R2R updating law is primarily designed to minimize the percentage of time spent below 3.9 mmol/L and parameters are modified accordingly. Once this primary goal is achieved, a secondary updating law is designed to reduce the percentage of time spent above 10 mmol/L and to bring the average Blood Glucose (BG) to the desired target. Of note, each CR in the pattern is updated separately. The algorithm can handle cases when there are more than the three main CR intervals (breakfast, lunch and dinner) to accommodate real-life needs. Daytime basal profile is not updated. No restrictions are applied to the patient's usual habits. If, during a particular interval, any of the R2R-algorithm assumptions is violated the associated parameter is not updated for that day. For instance if a meal is consumed during night time, the nocturnal basal is not updated for that day. A detailed description of the R2R-AP algorithm can be found in (6), with in silico results achieved with the UVA/Padova simulator in (7). The R2R algorithm is implemented on the DiAs.

Procedures

Each patient received a refreshment training on the AP platform at the clinical research center of approximately 2 hours . The study personnel checked that each patient was proficient in the study device use, including the insulin pump and the CGM. After the training, the Bluetooth connections were established, the R2R-AP was initiated and turned in closed-loop mode. The study procedures were then identical to those of the previous 4 week study extension (8). There were no limitations on diet and normal daily activities, including exercise.

The CGM glucose alarm thresholds for hypo- and hyperglycemia were initially set at 5.0 and 11.1 mmol/l, but could be modified by the patients. For safety, patients were instructed to test for ketones

(Freestyle Precision Xtra β-Ketone, Abbott, North Chicago, Illinois, US) if capillary glucose was >16.7 mmol/l and to perform a capillary glucose before making clinical decisions concerning insulin dosing or hypo- and hyperglycemia treatment. Patients were requested to check for catheter occlusion/dislodgement and pump dysfunction in case of hyperglycemia without obvious explanation, to calibrate their CGM twice daily and to perform at least four capillary glucose measurements per day. Patients were free to adjust their meal bolus. Device data were read-out at the end of the study.

Outcome metrics

R2R-AP vs NA-AP

The main aim of this study was to show the benefits of R2R-AP with respect to NA-AP after one month of system use. To this purpose, we evaluated glucose control during the last week of both one-month interventions (R2R-AP and NA-AP) using standard outcome measures (15). Since, as was concluded from our in silico analyses, 3 weeks is the minimum time of use before benefits of the daily adjustments performed by the R2R-AP can be expected (6).

The primary endpoint was the percentage of time spent in target range (3.9-10 mmol/l, time-in-target) during the last week of the study. Secondary endpoints included the percentage of time in tight target (3.9-7.8 mmol/l, time-in-tight-target), mean blood glucose, standard deviation (SD) of blood glucose, percentage of time below 3.9 mmol/l (time-in-hypo), below 3.3 mmol/l, above 10 mmol/l mmol/l (time-in-hyper), above 13.9 mmol/l, and total daily insulin use, all evaluated over the same weeks. Primary and secondary endpoints were evaluated per 24 hours, during nighttime (0:00-8:00), day-time (8:00-0:00), and wake-up time (7:00-8:00) as a proxy for fasting glucose.

R2R-AP: Safety

Safety was assessed by the frequency of moderately severe (>15 minutes, <2.8 mmol/l) and overall (>15 minutes, <3.9 mmol/l) hypoglycemic episodes, and adverse events.

R2R-AP: Technical Performance

As a proxy of the technical performance of R2R-AP system, we evaluated the percentage of time in closed-loop. For the technical performance of the R2R module, we evaluated the number of successful daily updates operated by R2R-AP compared to the theoretical maximum number of updates expressed as a percentage.

R2R-AP: Trends in Time of Glucose Metrics

Glucose control metrics are expected to gradually improve over time, as the R2R modules gradually adapts daily CRs and nocturnal basal insulin infusion based on previous day performance. Therefore, we assessed the trend per day over time of the following metrics: time-in-target, time-in-tight-target, time-in-hypo, time-in-hyper, and mean glucose using methodology described below.

Statistical methods

Data analysis was based on a modified intention-to-treat principle. Only patients who completed at least three weeks of R2R-AP use over 24 hours were considered for analysis. All glucose indices have been computed from CGM data.

The outcome indices are reported as median (25^{th}, 75^{th} percentiles) for non-normally distributed data and as mean (SD) otherwise.

R2R-AP vs NA-AP

In order to evaluate the statistical significance of the difference of each index, a paired-sample t-test was used for normally distributed data. Otherwise, if at least one distribution was non-normal, the nonparametric Wilcoxon signed rank test was used. Moreover, a paired difference (Δ) (with its confidence interval) for each pair was computed. For calculation of 95% CI for non-normally distributed data, we used the Hodges- Lehmann procedure (16).

R2R-AP: Trends in Time of Glucose Metrics

The trend in time of each glucose control metric was evaluated as follows: for each patient, a model describing a linear in time variation of the metric under consideration was fitted by least-squares.

The trend in time is the slope of the fitted line. To verify that the median of the trends was significantly different from zero in the population, a single-tail Wilcoxon signed rank test was performed.

All analyses were performed with the Matlab Statistic toolbox (version 9.1).

Role of the funding source

Neither the European Commission, which supported the study, nor Dexcom Inc. or Roche Diabetes Care AG, which provided research material support, had any influence on trial design, analysis or preparation of the manuscript, nor had access to any of the trial data. C. T., J. K., J. P., L. M., M. M., R. V., S. D. F. had access to the raw data. The corresponding author had full access to all of the data and the final responsibility to submit for publication.

RESULTS

Eighteen T1D subjects participated in the study and all of them completed the 4-week study period. The baseline characteristics of the subjects are reported in Table 1.

R2R-AP vs NA-AP

The primary and secondary outcomes are shown in Table 2. Figure 1 shows the daily median glucose trends achieved over the last week, surrounded by colored shadows representing the 25th and the 75th percentiles. The R2R-AP improvements become more pronounced over the night, while the profiles converge again during the morning, are graphically similar during the day and start to diverge over the evening.

<u>24 hour Glucose</u>

Overall, a trend towards improved control was observed with R2R-AP with respect to NA-AP: time-in-target increased Δ=5.78% (p=0.099) and so does time-in-tight-target Δ=6.67% (p=0.0508). Time-in-hyper (>10 mmol/l) tended to be reduced by Δ=5.97% (p=0.10), whereas the differences on the other outcomes were negligible and not significant.

<u>Nighttime Glucose</u>

Time-in-target was increased by 11.70% (p=0.034). Trends towards increased time-in -tight target, Δ=10.70% (p=0.065), and decreased mean glucose, Δ=-0.76 mmol/l (p=0.08) were also observed. Time-in-hyper was reduced by 12.50% (p=0.0266) and this reduction was not accompanied by an increased risk of hypoglycemia. Indeed, neither time-in-hypoglycemia (<3.9 mmol/l) nor the number of hypoglycemic events increased.

Wake-up Glucose

Mean glucose at wakeup time was decreased by 1.28 mmol/l (p=0.0199), time-in-tight-target was increased by 23.97% (p=0.0027), the median time in target range was increased (92.43% vs. 84.54%, p=0.0249) and the median time above target was almost halved (7.57% vs. 14.29%, p=0.0468). Time-in-hypoglycemia was 0.00 (0.00, 0.00) with both treatments.

Daytime Glucose

Comparison between R2R-AP and NA-AP showed neither material nor statistically significant differences. Nevertheless, R2R-AP was not inferior to NA-AP and equally safe.

Insulin

No significant changes were found in insulin delivery between R2R-AP and NA-AP in all the considered daily subintervals. In the 24-hour time period, a nearly significant increase in the percentage of total insulin delivered as basal, Δ=4.08% p=0.0518, was seen.

R2R-AP: Safety

As for the NA-AP (8), the R2R-AP proved to be safe: no difference was found in low BG index (LBGI) and high BG index (HBGI) (17), no serious adverse events occurred, including no severe hypoglycemic episodes as defined by DCCT (18), and no hospitalization for ketoacidosis was seen.

R2R-AP: Technical Performance

The technical performance was evaluated on 15 patients since 3 patients experienced problems during the saving of this information. During the last week of the study, R2R-AP was active 86.55% (81.39, 92.62) of time, similarly to NA-AP system, 90.76% (81.09, 93.99), p=0.93. Nocturnal basal

was successfully updated by the R2R-AP 62% of the times. In contrast, only 23% of diurnal CR updates were successfully completed by R2R-AP. Non-successful updates were classified based on the cause that prevented the update, and results are displayed in Figure 2: left panel for nocturnal basal and right panel for diurnal CR.

R2R-AP: Trend in time of Glucose Metrics

Figures 3-7 describe the daily variation in nocturnal glucose control metrics. Positive trends were observed for time-in-target (Figure 3, p=0.0447) and time-in-tight-target (Figure 4, p=0.0693), negative trends for mean glucose (Figure 7, p=0.0753) and time-in-hyper (Figure 5, p=0.0447), whereas a zero trend was identified for time-in-hypo (Figure 6, p=0.2412). The same analysis was performed on diurnal outcomes. However, no significant trends were observed (data not shown).

DISCUSSION

This study was, to the best of our knowledge, the first attempt to test in vivo an in silico designed adaptive automated insulin delivery strategy aimed to deal with T1D subject intra- and inter-day variability. R2R-AP significantly improved the time-in-target during the night (00:00-08:00) compared to NA-AP without significant increase of time-in-hypo, which was very small in both periods. The improved nocturnal glucose control resulted in a significant reduction of the mean glucose at wakeup time (07:00-08:00), which was accompanied by a significant increase of time-in-target and time-in-tight-target, and a significant reduction of the risk of hyperglycemia without increasing the risk of hypoglycemia. These results support the notion that a R2R-AP is safe and effective.

Collected data show that R2R-AP and NA-AP performed similarly during the day (08:00-00:00). This could be related to the limited number of successfully updates in daily CR patterns. In fact, the CR update mechanism was designed under the assumption that a meal bolus was followed by at least 3 hours of closed-loop control without other perturbations such as snacks or correction boluses, so that the control performance achieved in that period was a good indicator of CR efficacy. For safety reasons, a conservative policy was in place, preventing the update if a perturbation occurred in the 3 hours post-prandial period. When tested in free-living conditions (no protocol restriction was present), a number of unexpected events was faced by R2R-AP impeding the update to happen. In

35% of the cases, other meals/snacks occurred within less than 3 hours from another meal preventing both CRs to be updated. Moreover, the patient modified 26% of meal boluses suggested by the closed-loop algorithm, in some cases in view of impending physical exercise. In all these cases, the conservative R2R strategy in place did not execute the adaptation.

During the night (00:00-08:00), the manual user interventions were practically absent (2%), and the presence of meals was limited to 8%. Therefore, the nocturnal basal insulin was successfully updated by R2R-AP the 62% of the times, resulting in a substantially improved nocturnal glucose control.

The limited number of participants and the consequent reduced number daily updates of the CR is one of the limitations of this study. Other limitations include the non-randomized design and the risk of a selection bias because the use of NA-AP and R2R-AP systems was only proposed to subjects previously enrolled in another AP study.

CONCLUSION

This report compares for the first time the glucose control performance achieved by a R2R-AP vs a NA-AP designed to cope with the patients' intra- and inter-day variability. The performance of the two AP algorithms has been assessed by considering the same group of patients (n=18) in two one-month single-arm clinical studies in free-living conditions. R2R-AP significantly improved the glucose control performance during the night and maintained equivalent control performance during the day, where the R2R algorithm did not have a sufficient number of updates in view of many failed adaptation attempts. Despite the acknowledged limitations, this clinical study clearly shows the potential advantages of an adaptive AP based on a R2R strategy designed to improve glucose control and to further increase the quality of life of subjects affected by type 1 diabetes.

Future work will include longer testing of a less conservative version of the R2R update strategy that will likely increase the rate of successfully updates in presence of external disturbances and unexpected events.

Acknowledgments

We thank patients and their family members for their continued dedication during the extension study. We thank Dexcom Inc. and Roche Diabetes Care AG for providing research material support. This study was funded by European Commission, Framework Program 7 (FP7-ICT-2009-4 grant number 247138).

Author Disclosure Statement

C. C., C. T. and L. M. hold patent applications related to the study control algorithms; C. C. has received research support from Sanofi-Aventis and Adocia. B. P. K. holds patent applications related to the study technology and has served as an advisor to Becton, Dickinson, and Company (BD) and Sanofi-Aventis and has received research support from Animas Inc., BD, Dexcom, Insulet, Roche Diagnostics, Sanofi-Aventis, and Tandem Diabetes Care; stock ownership: TypeZero Technologies. E. R. is consultant/advisor for Menarini Diagnostics, Abbott, Cellnovo, Dexcom, Eli-Lilly, Johnson & Johnson (Animas, LifeScan), Medtronic, Novo-Nordisk, Roche Diagnostics and Sanofi-Aventis and has received research grant/material support from Abbott, Dexcom, Insulet and Roche Diagnostics. J. H. D. is a consultant/advisor on the speakers' bureau for Dexcom, Johnson & Johnson (Animas, LifeScan) and Roche Diagnostics. P. K. H. holds patent applications related to the study technology, serves as CTO of TypeZero Technologies and has stock ownership in TypeZero Technologies. No other potential conflicts of interest relevant to this article are reported.

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Figures

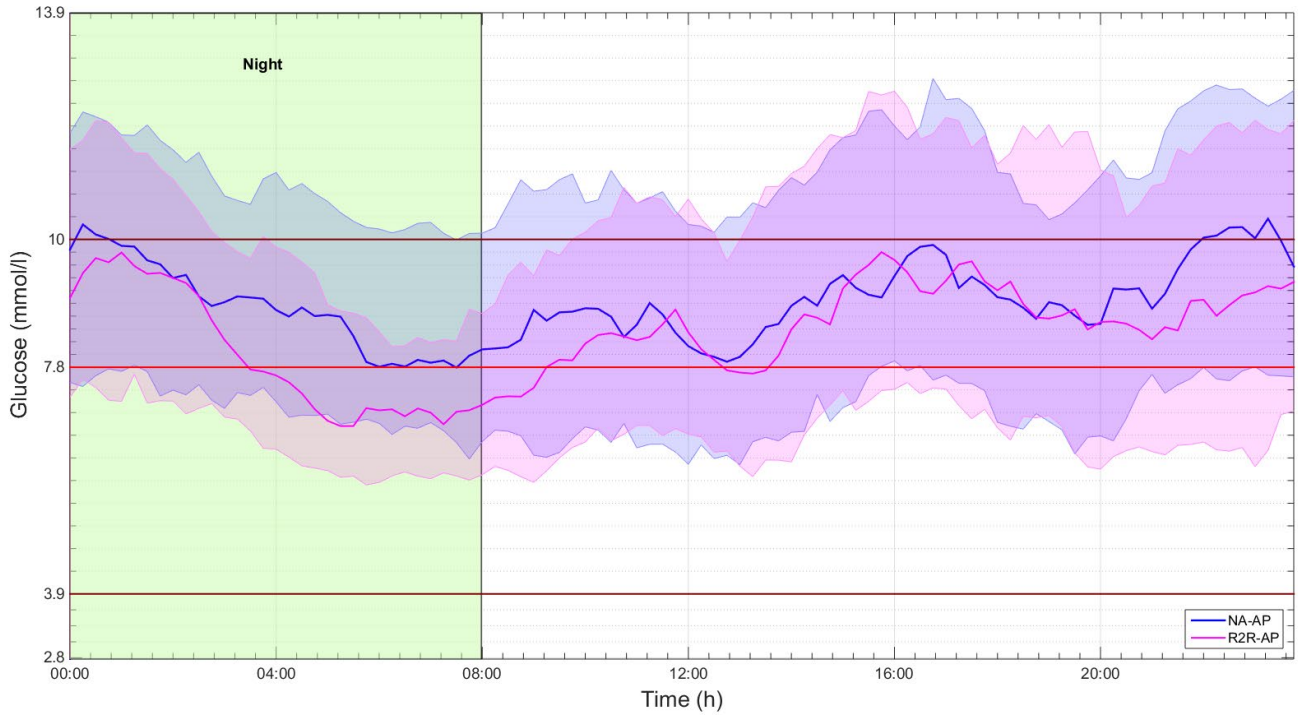


Figure 1. Glucose profile over 24 hours for non-adaptive artificial pancreas (NA-AP) and adaptive run-to-run artificial pancreas (R2R-AP). Trends are shown in terms of median (central solid line) and 25^{th} – 75^{th} percentiles (shadowed regions).

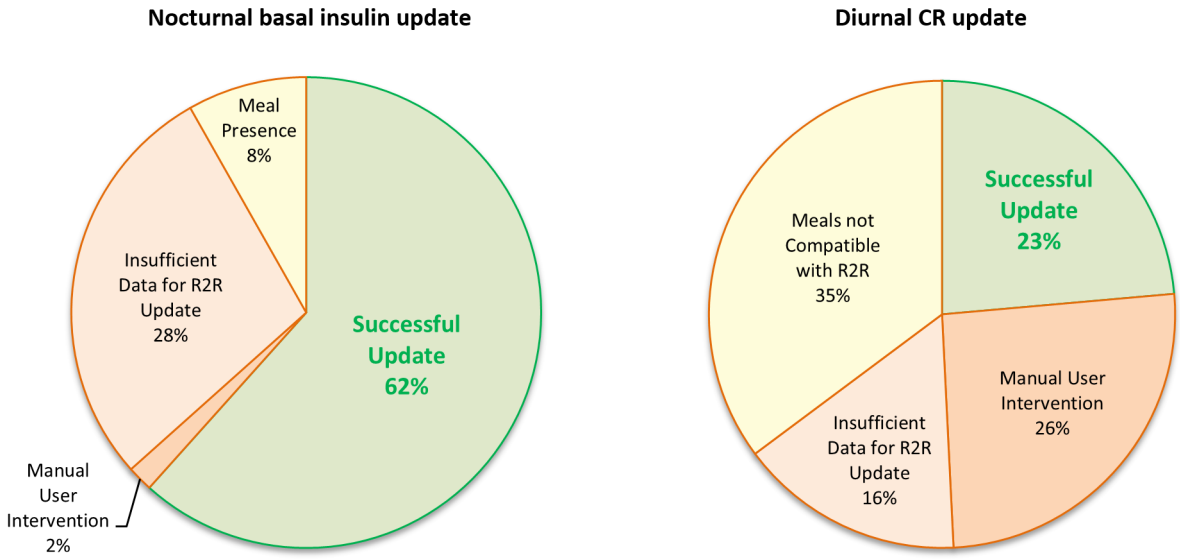
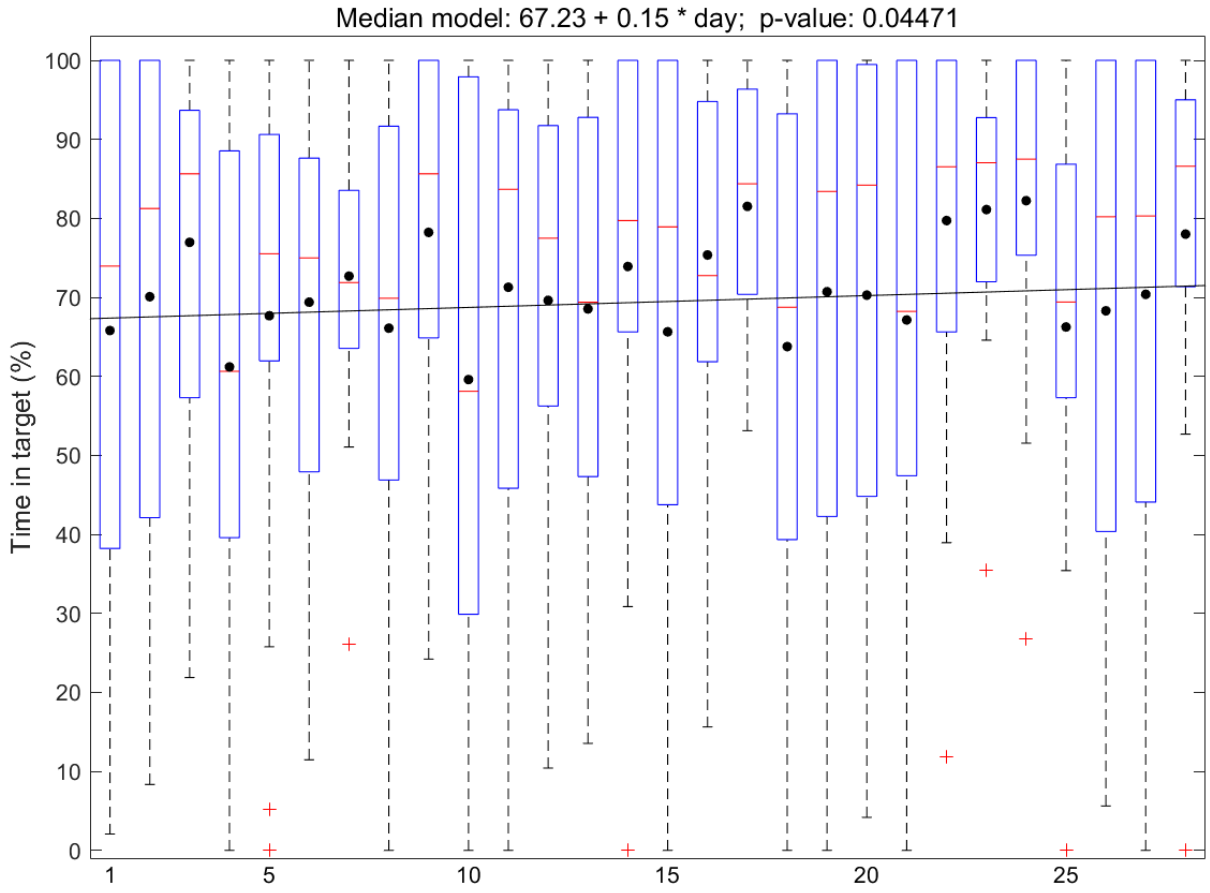
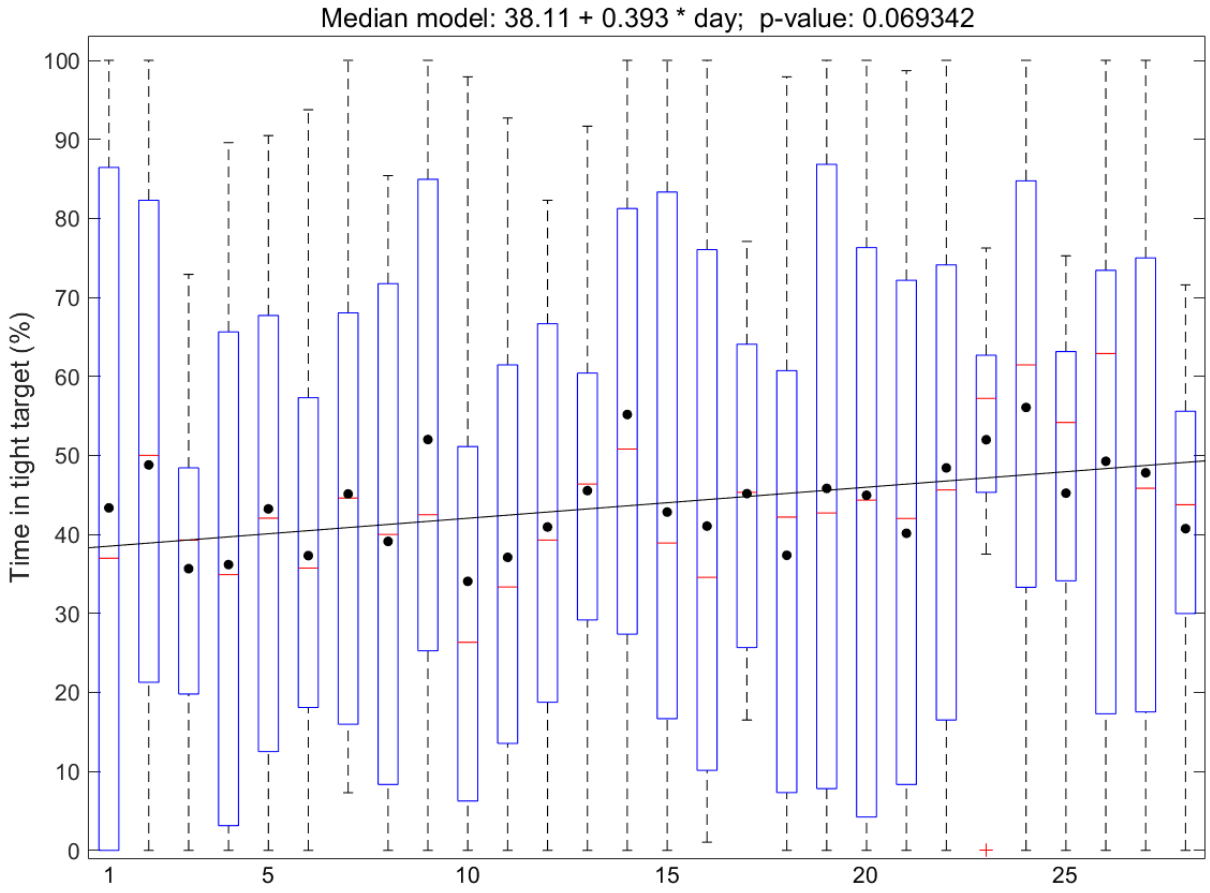


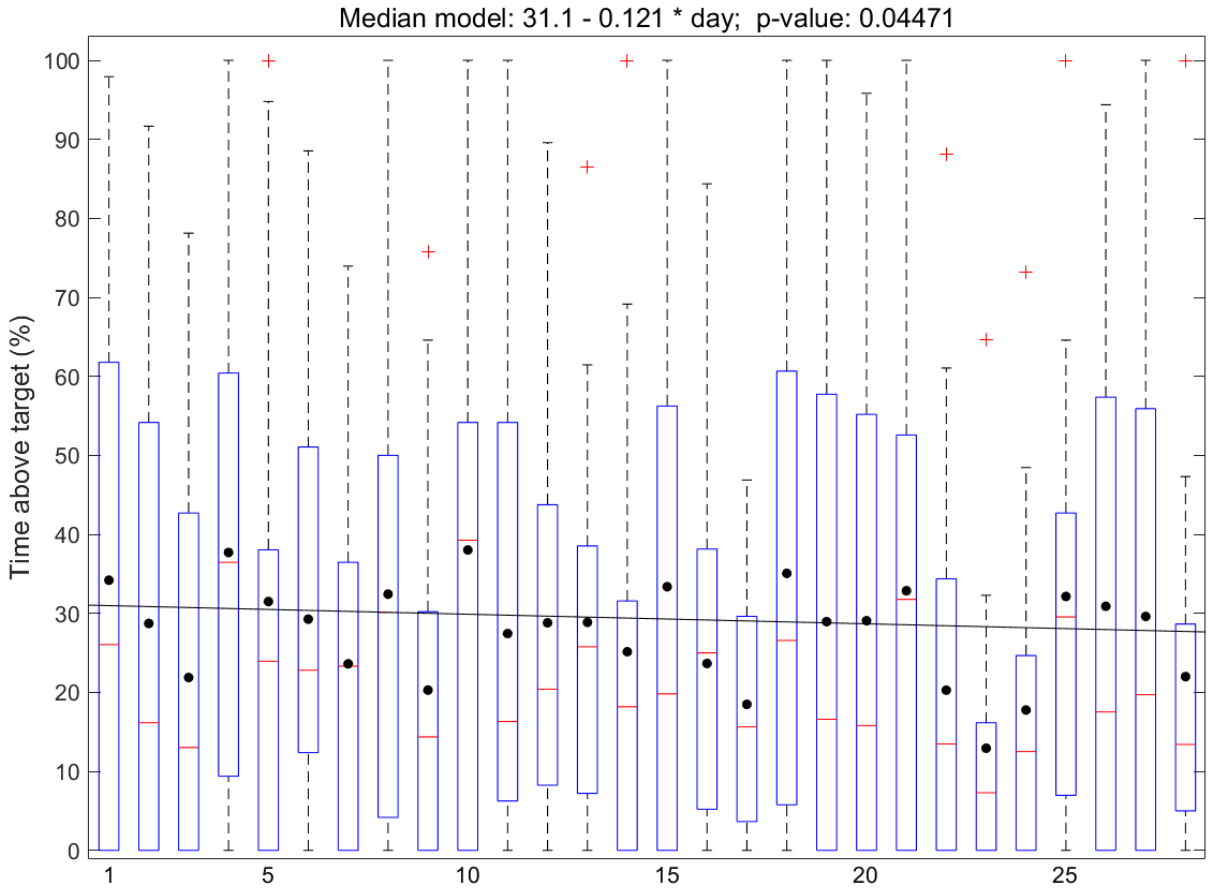
Figure 2. Left panel. Every day, the R2R strategy tries to update the nocturnal basal insulin pattern. The update is applied only in case of nominal patient behaviors (no meals during the nighttime, glucose controlled in closed-loop mode and no temporary basal insulin modifications). The nocturnal R2R states are the following. **Successful update**: successful update of the current nocturnal basal value. **Manual user intervention**: update aborted because of manual interventions on insulin delivery rate. **Insufficient data for R2R update**: update aborted because data do not allow the evaluation of the performance indices for various reasons (not enough time spent in closed-loop, insufficient data, system failures, etc.). **Meal presence**: update aborted because of nocturnal meal. **Right panel.** The CR pattern is divided in several intervals and, three hours after each interval, R2R tries to perform an update to be considered in the subsequent day. The diurnal R2R states are the following. **Successful update**: successful update of the current CR value. **Manual user intervention**: update aborted because of manual interventions on insulin delivery. **Insufficient data for R2R update**: update aborted because data do not allow the evaluation of the performance indices of the considered CR interval for various reasons (not enough time spent in closed-loop, insufficient data, system failures, etc.). **Meals not compatible with R2R**: update aborted because of multiple meals in the considered CR interval or because of previous meals interfering with the evaluation of the performance indices associated to the current meal.



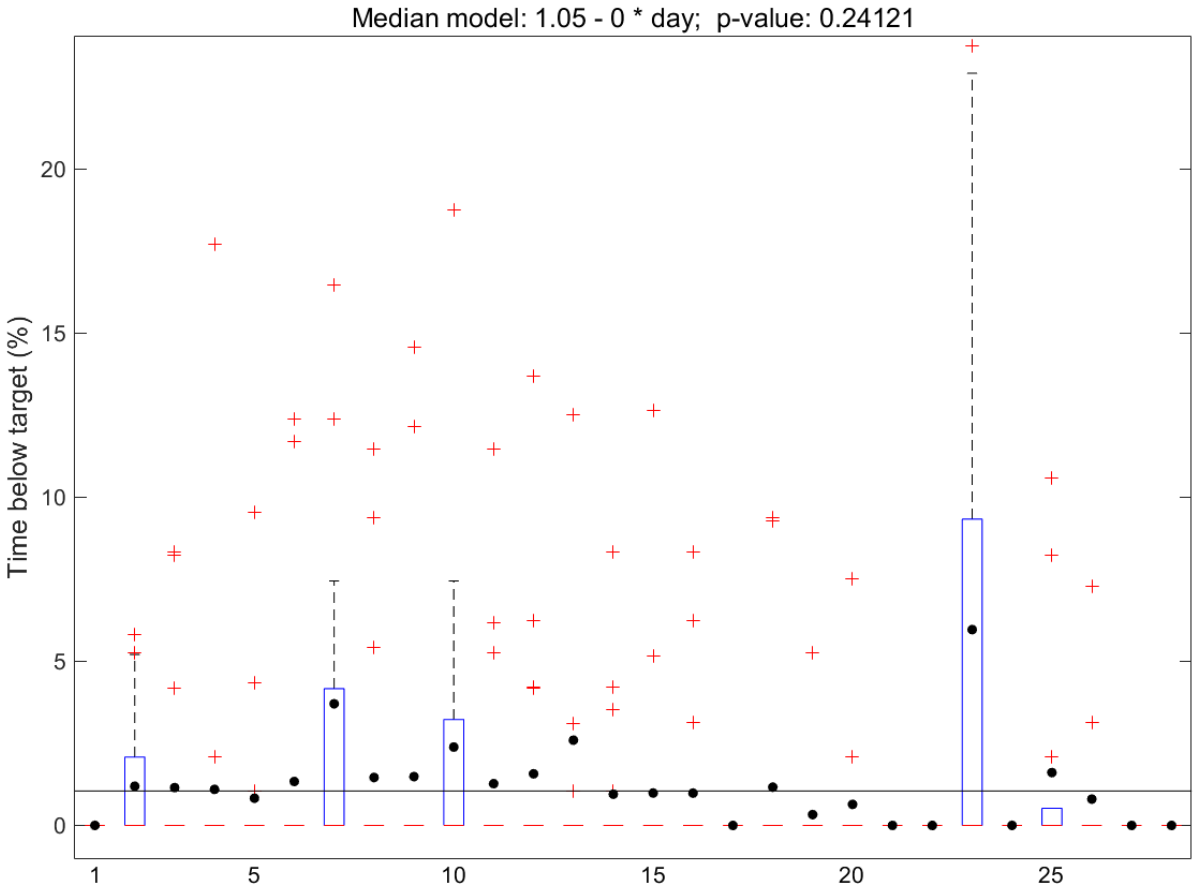
Figures 3. For each day, a boxplot of the nightly outcome metrics of the 18 individuals is shown. The red line represents the median and the box goes from 25th to 75th percentiles (lower and upper quartiles) including 50% of the data. The red crosses are the outliers and the whiskers mark the data in 1.5 interquartile range (IQR) respect to lower and upper quartile. Within each box, the average value is also shown as a filled dot. A linear model was computed for each of the 18 patients for each outcome metric: the 18 linear models were then averaged (median, black solid line) to identify a trend. To assess statistical significance of each metric trend, a single-tail Wilcoxon signed rank test was performed on the 18 individual linear models slopes.



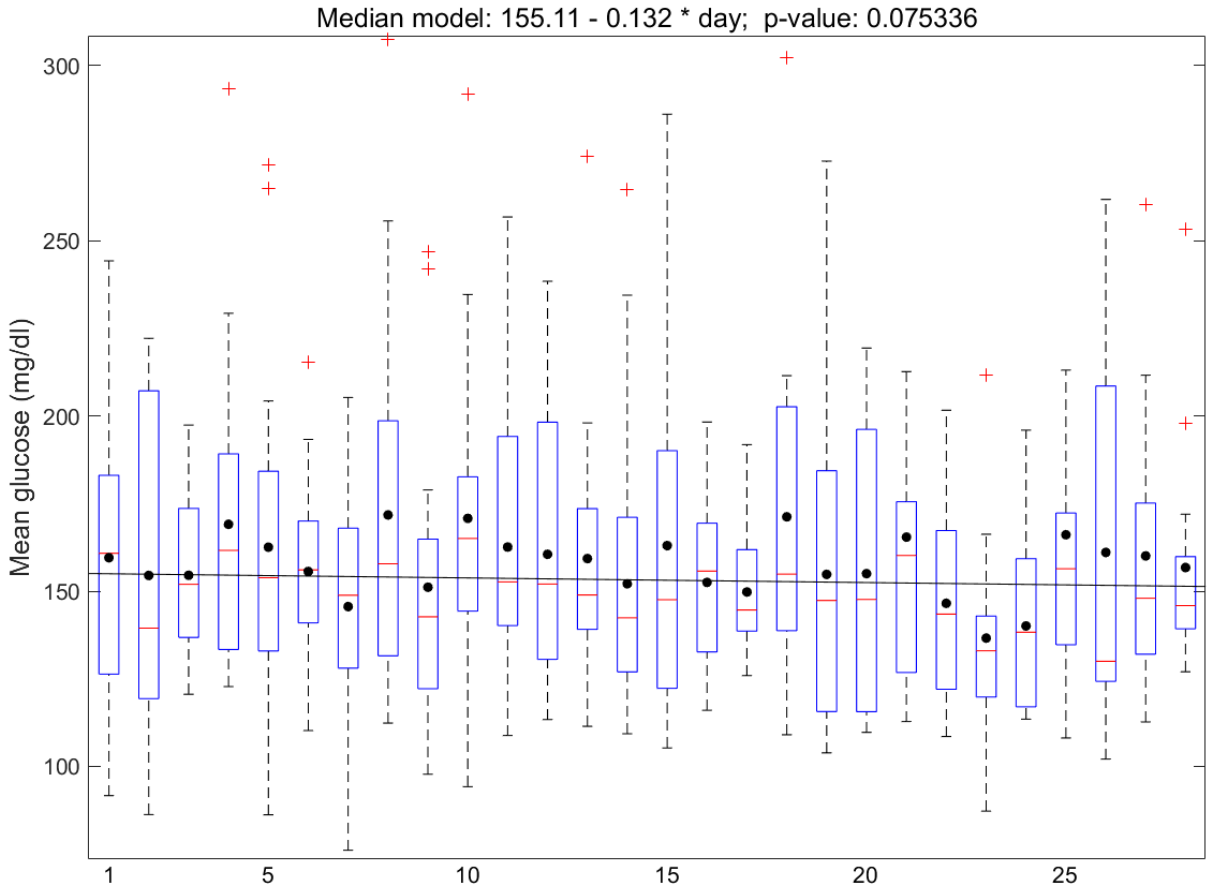
Figures 4. For each day, a boxplot of the nightly outcome metrics of the 18 individuals is shown. The red line represents the median and the box goes from 25th to 75th percentiles (lower and upper quartiles) including 50% of the data. The red crosses are the outliers and the whiskers mark the data in 1.5 interquartile range (IQR) respect to lower and upper quartile. Within each box, the average value is also shown as a filled dot. A linear model was computed for each of the 18 patients for each outcome metric: the 18 linear models were then averaged (median, black solid line) to identify a trend. To assess statistical significance of each metric trend, a single-tail Wilcoxon signed rank test was performed on the 18 individual linear models slopes.



Figures 5. For each day, a boxplot of the nightly outcome metrics of the 18 individuals is shown. The red line represents the median and the box goes from 25th to 75th percentiles (lower and upper quartiles) including 50% of the data. The red crosses are the outliers and the whiskers mark the data in 1.5 interquartile range (IQR) respect to lower and upper quartile. Within each box, the average value is also shown as a filled dot. A linear model was computed for each of the 18 patients for each outcome metric: the 18 linear models were then averaged (median, black solid line) to identify a trend. To assess statistical significance of each metric trend, a single-tail Wilcoxon signed rank test was performed on the 18 individual linear models slopes.



Figures 6. For each day, a boxplot of the nightly outcome metrics of the 18 individuals is shown. The red line represents the median and the box goes from 25th to 75th percentiles (lower and upper quartiles) including 50% of the data. The red crosses are the outliers and the whiskers mark the data in 1.5 interquartile range (IQR) respect to lower and upper quartile. Within each box, the average value is also shown as a filled dot. A linear model was computed for each of the 18 patients for each outcome metric: the 18 linear models were then averaged (median, black solid line) to identify a trend. To assess statistical significance of each metric trend, a single-tail Wilcoxon signed rank test was performed on the 18 individual linear models slopes.



Figures 7. For each day, a boxplot of the nightly outcome metrics of the 18 individuals is shown. The red line represents the median and the box goes from 25th to 75th percentiles (lower and upper quartiles) including 50% of the data. The red crosses are the outliers and the whiskers mark the data in 1.5 interquartile range (IQR) respect to lower and upper quartile. Within each box, the average value is also shown as a filled dot. A linear model was computed for each of the 18 patients for each outcome metric: the 18 linear models were then averaged (median, black solid line) to identify a trend. To assess statistical significance of each metric trend, a single-tail Wilcoxon signed rank test was performed on the 18 individual linear models slopes.

Contributors

All authors reviewed and provided edits and comments on manuscript drafts. In addition, authors had the following responsibilities: M. M.: development of the algorithm, data analysis and drafting of the manuscript; J. K.: main study physician responsible for the trial in Amsterdam; S. D. F.: senior engineer responsible for the trial in Padova and assisting the trial in Amsterdam, data analysis, drafted the manuscript; J. P.: senior engineer responsible for the trial in Montpellier; R. V.: engineer providing technical support during the trial in Padova; R.C.: engineer providing technical support during the trial in Padova and assisting the trial in Amsterdam; C. T.: development of the algorithm and data analysis; F. D. P.: control engineering responsible for control algorithm implementation on the DiAs; G. L.: computer scientist responsible for the design and implementation of the remote monitoring system used during the trial.; A. F.: main study physician responsible for the trial in Montpellier; F.B. and S.G. clinician providing medical support to the patients during the trial in Padova; A. A.: coordinating physician for the performance of the trial in Padova; P. K. H.: chief engineer of the DiAs smartphone-based system and user interface; B. P. K.: principal investigator at UVA, development of the DiAs system; D. B.: main study physician in Padova, drafting of manuscript; L. M.: principal investigator of Pavia Unit, algorithm development, data analysis and drafting of the manuscript; J. H. D.: principal investigator in Amsterdam, design of the protocol and drafting of the manuscript. E. R.: principal investigator of Montpellier, drafting of the protocol and manuscript; C. C.: principal investigator in Padova, design of the protocol, data analysis, drafting of the manuscript.

Table 1. Baseline characteristics of T1D subjects.

Caption: Baseline characteristics of the 18 T1D subjects that completed the extension experiments and that were included in the data analysis.

Variable	Study population (n=18)
Age (years) (SD)	46.44 (11.21)
Sex	
Male (n) (%)	7 (38.89)
Female (n) (%)	11 (61.11)
Body mass index (BMI) (kg/m^2) (SD)	24.83 (3.69)
HbA1c (%) (SD)	8.2 (0.7)
Diabetes duration (years) (SD)	29.22 (12.44)
Insulin delivery mode, CSII (n) (%)	18 (100)
Duration of CSII use (years) (SD)	10.34 (5.37)
Total Daily Insulin dose (U/kg) (SD)	0.53 (0.11)
For categorical variables n (%) is presented. For continuous variables mean (SD) is presented. CSII: continuous subcutaneous insulin infusion	

Table 2. Primary and secondary outcomes.

Caption: Primary and secondary outcomes evaluated on the last week of the study**.**

	24-hour R2R-AP (n=18)	24-hour NA-AP (n=18)	Paired difference (with CI) (n=18)	p value
Day and Night (24h)				
Mean glucose, mmol/l[+]	9.03 (1.23)	9.23 (0.89)	-0.20 (-0.78, 0.38)	0.48
SD of glucose, mmol/l[+]	3.20 (0.91)	3.03 (0.51)	0.16 (-0.26, 0.59)	0.43
CV of glucose mmol/l[+]	0.35 (0.06)	0.33 (0.05)	0.02 (-0.01, 0.05)	0.17
Time spent at glucose concentration. %				
3.9-7.8 mmol/l[+]	43.40 (12.16)	37.32 (9.70)	6.08 (-0.03, 12.19)	0.051
3.9-10 mmol/l[+]	66.90 (13.34)	61.82 (11.12)	5.08 (-1.07, 11.23)	0.099
>16.7 mmol/l[$]	1.50 (0.33, 4.61)	1.36 (1.02, 2.97)	-0.54 (-1.09, 4.41)	0.65
>13.9 mmol/l[$]	7.13 (2.89, 10.69)	6.83 (4.78, 11.24)	0.76 (-3.51, 4.43)	0.88
>10 mmol/l[+]	30.98 (13.22)	36.17 (11.53)	-5.19 (-11.53, 1.15)	0.10
<3.9 mmol/l[+]	2.12 (1.33)	2.01 (1.69)	0.11 (-0.69, 0.91)	0.78
<3.3 mmol/l[+]	0.77 (0.51)	0.78 (0.74)	-0.01 (-0.35, 0.33)	0.96
<2.8 mmol/l[$]	0.16 (0.04, 0.37)	0.14 (0.00, 0.44)	0.06 (-0.24, 0.17)	0.62
No. of hypoglycemic events per week				
<3.9 mmol/l[$]	4.12 (3.09, 7.15)	3.70 (1.10, 6.26)	-0.48 (-2.09, 1.46)	0.53
<2.8 mmol/l[$]	1.07 (1.01, 2.09)	1.02 (0.00, 2.03)	0.52 (-0.56, 1.08)	0.52
Blood glucose indices				
LBGI[+]	0.54 (0.27)	0.52 (0.34)	0.02 (-0.12, 0.17)	0.74
HBGI[$]	6.67 (5.10, 7.86)	7.24 (6.02, 8.92)	-0.41 (-2.17, 1.66)	0.65
Insulin need, IU/24h[+]	39.01 (14.75)	40.12 (15.36)	-1.11 (-4.93, 2.71)	0.55
% per basal insulin[+]	50.12 (15.59)	45.35 (12.47)	4.77 (-0.04, 9.58)	0.052
% per bolus insulin[+]	49.88 (15.59)	54.65 (12.47)	-4.77 (-9.58, 0.04)	0.052
Time in closed-loop over 24 hours, %[$]	86.55 (81.39, 92.62)	90.76 (81.09, 93.99)	0.10 (-10.81, 6.89)	0.93

Night (00:00-08:00)				
Mean glucose, mmol/l[+]	8.54 (1.21)	9.12 (1.23)	-0.58 (-1.25, 0.08)	0.08
SD of glucose, mmol/l[+]	2.68 (0.85)	2.66 (0.56)	0.02 (-0.40, 0.43)	0.93
CV of glucose mmol/l[+]	0.31 (0.07)	0.29 (0.05)	0.02 (-0.01, 0.05)	0.27
Time spent at glucose concentration. %				
3.9-7.8 mmol/l[+]	49.54 (15.50)	40.16 (17.76)	9.38 (-0.66, 19.43)	0.065
3.9-10 mmol/l[+]	74.01 (14.61)	64.31 (15.71)	9.70 (0.82, 18.58)	**0.034**
>16.7 mmol/l[$]	0.10 (0.00, 3.58)	0.72 (0.00, 1.49)	0.00 (-0.75, 3.37)	0.50
>13.9 mmol/l[$]	4.05 (0.00, 10.52)	4.83 (1.07, 9.72)	-1.30 (-4.45, 3.48)	0.46
>10 mmol/l[+]	24.23 (15.03)	34.49 (16.25)	-10.26 (-19.18, -1.34)	**0.027**
<3.9 mmol/l[$]	1.11 (0.00, 2.31)	0.03 (0.00, 2.23)	0.00 (-0.29, 0.92)	0.33
<3.3 mmol/l[$]	0.12 (0.00, 1.19)	0.00 (0.00, 1.19)	0.00 (-0.40, 0.29)	1.00
<2.8 mmol/l[$]	0.00 (0.00, 0.06)	0.00 (0.00, 0.42)	0.00 (-0.46, 0.04)	0.38
No. of hypoglycemic events per week				
<3.9 mmol/l[$]	1.00 (0.00, 2.00)	0.00 (0.00, 1.00)	0.50 (0.00,1.50)	0.13
<2.8 mmol/l[$]	0.00 (0.00, 0.00)	0.00 (0.00, 1.00)	0.00 (-0.50, 0.00)	0.30
Blood glucose indices				
LBGI[$]	0.36 (0.10, 0.66)	0.18 (0.03, 0.58)	0.03 (-0.12, 0.26)	0.29
HBGI[+]	5.80 (3.51)	7.16 (3.38)	-1.36 (-3.24, 0.53)	0.15
Insulin need, IU/24h[$]	8.31 (5.11, 10.20)	7.79 (4.99, 9.80)	-0.06 (-1.50, 2.00)	0.98
% per basal insulin[+]	74.38 (17.07)	71.99 (19.47)	2.38 (-3.03, 7.80)	0.37
% per bolus insulin[+]	25.62 (17.07)	28.01 (19.47)	-2.38 (-7.80, 3.03)	0.37
Time in closed-loop over 24 hours, %[$]	86.73 (82.08, 93.48)	92.20 (78.68, 97.85)	-1.19 (-15.43, 8.36)	0.85

Wake up (07:00-08:00)				
Mean glucose, mmol/l[+]	7.40 (1.16)	8.52 (1.74)	-1.11 (-2.03, -0.20)	**0.02**
SD of glucose, mmol/l[$]	1.47 (1.02, 2.49)	1.89 (1.60, 2.54)	-0.42 (-1.12, 0.58)	0.42
CV of glucose mmol/l[$]	0.22 (0.16, 0.33)	0.24 (0.19, 0.27)	0.00 (-0.10, 0.08)	0.81
Time spent at glucose concentration. %				
3.9-7.8 mmol/l[+]	70.84 (20.15)	49.27 (22.03)	21.58 (8.62, 34.53)	**0.003**
3.9-10 mmol/l[$]	92.43 (78.22, 99.53)	84.54 (57.14, 88.52)	11.30 (1.99,24.57)	**0.025**
>16.7 mmol/l[$]	0.00 (0.00, 0.00)	0.00 (0.00, 0.00)	0.00 (0.00, 1.96)	0.75
>13.9 mmol/l[$]	0.00 (0.00, 0.00)	0.00 (0.00, 9.24)	0.00 (-7.14, 1.56)	0.43
>10 mmol/l[$]	7.57 (0.00, 14.29)	14.29 (8.25, 42.86)	-9.50 (-24.75, -0.04)	**0.047**
<3.9 mmol/l[$]	0.00 (0.00, 0.00)	0.00 (0.00, 0.00)	0.00 (0.00, 2.30)	1.00
<3.3 mmol/l[$]	0.00 (0.00, 0.00)	0.00 (0.00, 0.00)	0.00 (0.00, 0.00)	1.00
<2.8 mmol/l[$]	0.00 (0.00, 0.00)	0.00 (0.00, 0.00)	0.00 (0.00, 0.00)	1.00
No. of hypoglycemic events per week				
<3.9 mmol/l[$]	0.00 (0.00, 0.00)	0.00 (0.00, 0.00)	0.00 (0.00, 0.49)	1.00
<2.8 mmol/l[$]	0.00 (0.00, 0.00)	0.00 (0.00, 0.00)	0.00 (0.00, 0.00)	1.00
Blood glucose indices				
LBGI[$]	0.23 (0.03, 1.07)	0.10 (0.01, 0.71)	0.05 (-0.22, 0.57)	0.27
HBGI[$]	2.12 (1.10, 3.81)	4.33 (2.96, 7.87)	-2.10 (-5.68, 0.12)	0.058
Insulin need, IU/24h[$]	1.28 (0.51, 2.33)	1.24 (0.47, 2.10)	0.12 (-0.43, 0.64)	0.62
% of basal insulin[$]	60.46 (14.44, 100.00)	60.68 (19.29, 100.00)	0.39 (-7.05, 15.65)	0.56
% of bolus insulin[$]	39.54 (0.00, 85.56)	39.32 (0.00, 80.71)	-0.39 (-16.20, 6.81)	0.56
Time in closed-loop over 24 hours, %[$]	85.71 (73.63, 94.58)	85.71 (75.48, 91.85)	0 (-14.76, 7.38)	0.63

Day (08:00-00:00)				
Median glucose, mmol/l[$]	8.85 (8.40, 9.78)	8.98 (8.68, 10.08)	-0.03 (-0.76, 0.71)	0.81
SD of glucose, mmol/l[+]	3.31 (0.98)	3.13 (0.56)	0.17 (-0.30, 0.64)	0.45
CV of glucose mmol/l[+]	0.35 (0.05)	0.34 (0.05)	0.01 (-0.02, 0.04)	0.39
Time spent at glucose concentration. %				
3.9-7.8 mmol/l[+]	40.31 (13.64)	35.99 (9.35)	4.32 (-1.64, 10.27)	0.14
3.9-10 mmol/l[$]	61.97 (58.67, 78.27)	61.97 (49.86, 68.94)	2.43 (-4.79, 10.44)	0.53
>16.7 mmol/l[$]	1.92 (0.00, 4.76)	1.43 (0.68, 4.35)	0.52 (-1.02, 3.39)	0.37
>13.9 mmol/l[+]	11.10 (11.36)	9.23 (7.08)	1.87 (-3.88, 7.62)	0.50
>10 mmol/l[+]	34.49 (15.32)	36.93 (11.65)	-2.44 (-9.69, 4.81)	0.49
<3.9 mmol/l[+]	2.30 (1.36)	2.43 (2.01)	-0.12 (-1.00, 0.75)	0.77
<3.3 mmol/l[+]	0.87 (0.66)	0.91 (0.91)	-0.04 (-0.53, 0.45)	0.87
<2.8 mmol/l[$]	0.23 (0.03, 0.35)	0.02 (0.00, 0.34)	0.05 (-0.24, 0.22)	0.83
No. of hypoglycemic events per week				
<3.9 mmol/l[+]	4.06 (3.13)	4.28 (3.28)	-0.22 (-2.24, 1.80)	0.82
<2.8 mmol/l[$]	1.04 (0.00, 2.04)	0.00 (0.00, 2.02)	0.52 (-0.51, 1.07)	0.49
Blood glucose indices				
LBGI[+]	0.58 (0.27)	0.59 (0.36)	-0.01 (-0.16, 0.15)	0.91
HBGI[$]	7.23 (4.86, 9.23)	6.89 (6.31, 10.55)	-0.21 (-2.25, 2.42)	0.95
Insulin need, IU/24h[+]	29.10 (10.82)	30.71 (11.74)	-1.60 (-4.33, 1.12)	0.23
% per basal insulin[+]	41.60 (17.41)	37.21 (15.08)	4.39 (-1.66, 10.44)	0.14
% per bolus insulin[+]	58.40 (17.41)	62.79 (15.08)	-4.39 (-10.44, 1.66)	0.14
Time in closed-loop over 24 hours, %[$]	87.83 (78.93, 92.96)	90.40 (80.53, 93.11)	-0.74 (-7.97, 6.06)	0.98

[+]Mean or [$]median is given as appropriate. *95% confidence interval (CI) of paired difference is given. R2R-AP: adaptive artificial pancreas. NA-AP: non-adaptive artificial pancreas.