Journal of Diabetes Science and Technology
Volume 5, Issue 6, November 2011

SYMPOSIUM

Meta-Analysis of Overnight Closed-Loop Randomized Studies in Children and Adults with Type 1 Diabetes: The Cambridge Cohort

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Abstract

Aim:

We reviewed the safety and efficacy of overnight closed-loop insulin delivery compared with conventional continuous subcutaneous insulin infusion (CSII) in two distinct age groups with type 1 diabetes mellitus (T1DM), young people aged 5 to 18 years and adults, combining data of previously published randomized studies.

Methods:

We evaluated four randomized crossover studies in 17 children and adolescents [13.4 ± 3.6 years; mean ± standard deviation (SD)] and 24 adults (37.5 ± 9.1 years) on 45 closed-loop (intervention) and 45 CSII (control) visits. Each subject attended for two overnight study visits, using either closed-loop or conventional pump therapy, in random order. In each age group, studies were designed to mimic realistic likely scenarios. In the children and adolescent studies, closed loop was used following a standard evening meal and following 40 min of moderate-intensity exercise. In the adult studies, closed loop was commenced following a 60 g carbohydrate meal or a 100 g carbohydrate meal accompanied by alcohol. The primary outcome measure was time for which plasma glucose was within target range (3.91–8.0 mmol/liter).

Results:

Overnight closed loop increased the time in target plasma glucose in both young (from 40% to 60%, $p = .002$) and adults (from 50% to 76%, $p < .001$) compared with conventional CSII. Combined analysis showed an increase from 43% to 71% with closed loop ($p < .001$). Additionally, closed loop reduced the time spent below 3.91 mmol/liter and above 8.0 mmol/liter, from 4.1% to 2.1% ($p = .01$) and 33% to 20% ($p = .03$), respectively. Glycemic variability, as measured by the SD of plasma glucose, was lower during closed loop compared with CSII (1.5 versus 2.1 mmol/liter, $p = .007$).

continued →

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Abbreviations: (CGM) continuous glucose monitoring, (CHO) carbohydrate, (CSII) continuous subcutaneous insulin infusion, (CV) coefficient of variation, (GRT) Guardian REAL-Time, (SD) standard deviation, (T1DM) type 1 diabetes mellitus

Keywords: adults, alcohol, closed loop, exercise, large meal, young

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Abstract cont.

Conclusions:

Overnight closed loop may improve glycemic control and reduce nocturnal hypoglycemia in both young people and adults with T1DM.

J Diabetes Sci Technol 2011;5(6):1352-1362

Introduction

Type 1 diabetes mellitus (T1DM) is associated with significant morbidity and decreased life expectancy.[1] Maintenance of normal glucose concentrations may significantly reduce diabetes-related complications.[2,3] However, tight control is associated with an increased risk of hypoglycemia,[4] such that episodes of and/or the fear of hypoglycemia limit the ability of patients and their families to achieve target glucose levels.[5] In addition to hyperglycemia, dynamic fluctuations in blood glucose, known as glycemic variability, may worsen outcomes.[6]

Despite advances in insulin formulations and device technology, existing insulin replacement regimens commonly fail to achieve optimal glycemic targets.[7] Self-monitoring of blood glucose is a key component of diabetes treatment, greatly enhanced by the emergence of continuous glucose monitoring (CGM), which provides information in real time on glucose values and trends, including direction and rate of change.[8] Notably, benefits gained from CGM are dependent on compliance with wearing the device, as demonstrated in the Juvenile Diabetes Research Foundation CGM study,[9] as well as the ability of the user to interpret the glucose readings correctly and make appropriate lifestyle and therapy modifications. However, this is not practical during the night while asleep, which is when more than 50% of severe hypoglycemic events in adults are reported to occur.[10] Furthermore, 75% of hypoglycemic seizures in children occur during sleep,[11] and up to 45% of children on conventional insulin therapy are likely to experience severe and prolonged nocturnal hypoglycemia.[12]

Combining insulin pumps and glucose sensors may improve diabetes control.[13] The Medtronic MiniMed Paradigm® Veo System, available in Europe, is able to suspend pump delivery during hypoglycemia using wirelessly transmitted CGM data but still requires manual entry of programmed basal rates and input of bolus doses.[14] The closed loop or artificial pancreas, which uses a computer-based algorithm to drive insulin delivery based on CGM readings, potentially offers a more convenient mode of therapy for patients with diabetes.[15,16]

We have tested a closed-loop system overnight in both young people and adults with T1DM, demonstrating improvement in glucose control and reduced nocturnal hypoglycemia.[17,18] In this article, we analyze and compare previously reported results of closed-loop studies separately[17,18] to provide a comprehensive assessment across a wide age range and under various lifestyle conditions.

Methods

Subjects

Between April 2007 and December 2009, patients were enrolled from the adult and pediatric diabetes clinics at Cambridge and Norwich, UK. Inclusion criteria were T1DM (World Health Organization criteria or confirmed C-peptide negative) and insulin pump therapy for at least 3 months. Exclusion criteria were concurrent illness or medications likely to interfere with interpretation of the study results, recurrent severe hypoglycemia unawareness, and clinically significant nephropathy, neuropathy, or retinopathy. The studies in children and adolescents (study acronyms APCam01 and APCam03) included subjects aged 5–18 years, while two studies in adults (study acronyms Angela01 and Angela02) enrolled people aged 18–65 years. Angela02 required subjects to be able to tolerate the alcohol consumed in the study, also excluding those with poorly controlled diabetes (hemoglobin A1c ≥ 10% within 3 months) or insulin resistance (total daily insulin ≥ 1.4 U/kg) and pregnant or lactating women.

The studies were conducted at the Wellcome Trust Clinical Research Facility, Addenbrooke's Hospital, Cambridge, UK. Study protocols were approved by the Cambridge Research Ethics Committee and carried out in accordance with the Declaration of Helsinki. Written informed consent was obtained from each participant. Assent was provided by those younger than 16 years of age, with consent from a parent or guardian.

Study Designs and Procedures

In the children and adolescent studies, closed loop was used following a standard evening meal (APCam01) and following 40 min of moderate-intensity exercise (APCam03). In the first adult study (Angela01), closed loop was commenced following a medium-sized meal, mimicking an evening at home. In the second adult study (Angela02), subjects consumed a large meal accompanied by alcohol, simulating an evening out.

All studies adopted a randomized crossover design where each subject completed two overnight visits 1–3 weeks apart in random order, one using closed loop (intervention) and the other using participants' usual insulin pump settings (control); see **Figure 1**. Between study visits, self-adjustment of insulin doses was permitted. Study activities and meals were matched on both visits. All meals were accompanied by an appropriate insulin bolus, calculated using subjects' usual insulin-to-carbohydrate ratios or pump bolus wizard.

One to two days prior to each study visit, a glucose sensor was inserted and calibrated. In APCam01, the Guardian REAL-Time (GRT; Medtronic MiniMed, Northridge, CA) CGM device was used during closed loop and the CGMS System Gold (Medtronic MiniMed, Northridge, CA), which does not have real-time display, was used during conventional treatment. Both were calibrated every 6 h against venous glucose. APCam03 and Angela01 studies used the 10 h and Angela02 the 1 h warm-up time FreeStyle Navigator (Abbott Diabetes Care, Alameda, CA) CGM,[19] both calibrated using finger stick capillary glucose according to manufacturer instructions. In APCam01 and Angela01, participants' insulin regimens were optimized prior to the first study visit guided by up to 5 days of CGM data.

On arrival for each study visit, patients' insulin pumps were replaced by the study pump (Deltec Cozmo, Smiths Medical, St. Paul, MN) delivering rapid-acting insulin analog aspart (Novo Nordisk, Bagsvaerd, Denmark), connecting to the established subcutaneous infusion site. A peripheral intravenous cannula was inserted for sampling of plasma glucose and plasma insulin every 15 and 30 min, respectively. Plasma glucose values were not used to adjust insulin infusion rates during visits. In Angela02, plasma ethanol values were measured every 90 to 180 min overnight.

Symptomatic hypoglycemia or CGM reading below 3.0 mmol/liter, confirmed with plasma glucose, was treated with 15–30 g quick-acting oral carbohydrate. Greater than two such episodes or single plasma glucose below 2.0 mmol/liter led to termination of the study visit.

APCam01

Subjects consumed a self-selected meal [mean 87 ± 23 g carbohydrate (CHO)] at 18:00. On the treatment visit, closed-loop insulin delivery was commenced from 20:00 until 08:00.

APCam03

A 45 g CHO snack was consumed at 16:00, followed by 40 min of treadmill exercise at 55% of peak maximal oxygen consumption at 18:00 (estimated for each subject using a ramped treadmill protocol[20] prior to the first visit), and no further meals were consumed until study end at 08:00. During the intervention visit, closed loop was commenced from 20:00 until 08:00.

Angela01

Subjects consumed a 60 g CHO meal at 19:00. During the treatment visit, closed loop was applied between 19:00 and 08:00.

Angela02

Between 20:30 and 22:00, subjects consumed a 100 g CHO meal accompanied by 9.6 ml/kg (for example, 505 ml or 6.6 U for a 70 kg subject) white wine (Chenin Blanc, South Africa, 13% alcohol volume). During the intervention visit, closed loop was commenced from 22:00 until 12:00 the following day. On the control night, subjects were permitted to set a temporary basal rate and/or reduce their meal insulin bolus according to their usual practice when drinking alcohol.

Randomization and Blinding

Subjects were randomized using computer-generated random code and sealed envelopes. Subjects were masked to plasma and sensor glucose. Investigators had access to real-time plasma glucose values in APCam03 and Angela02 for safety reasons. Plasma glucose was masked in APCam01 and Angela01.

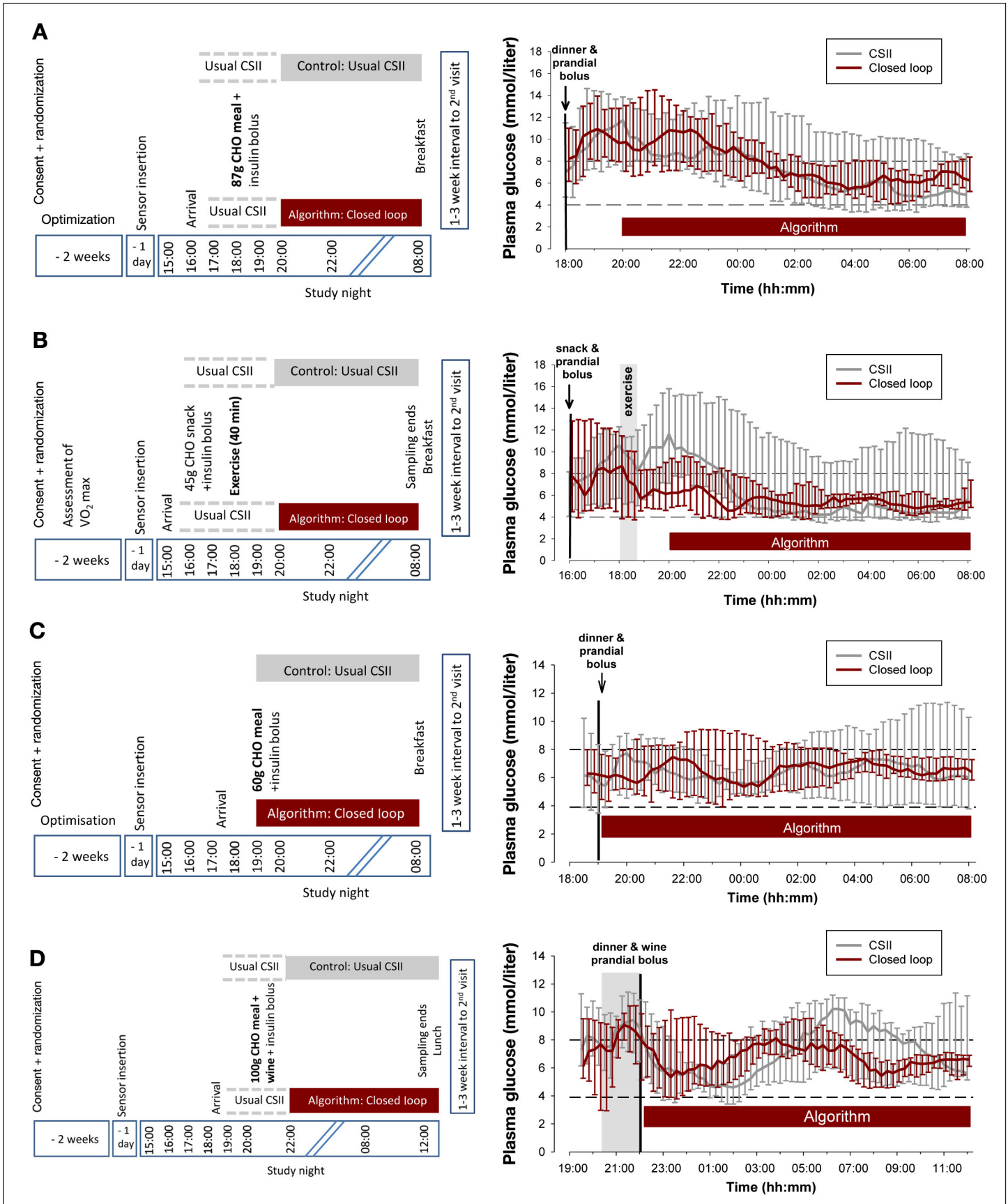

Figure 1. Study design (left panels) and overnight plasma glucose (right panels) for **(A)** APCam01, **(B)** APCam03, **(C)** Angela01, and **(D)** Angela02. Plasma glucose is represented as median and interquartile range (error bars). CHO, carbohydrate. (Right panels of **(A)** and **(B)** are reprinted from Reference 18 with permission from Elsevier.)

Closed-Loop Algorithm

Every 15 min, the sensor glucose was inputted by the research nurse into a laptop computer containing the algorithm that calculated the basal infusion rate to be adjusted manually on the insulin pump (**Figure 2**). We used algorithm version 0.00.02 to 0.01.05 in APCam01 and APCam03 and version 0.02.04 to 0.02.18 in the adult studies. The algorithm was initialized using participants' weight, total daily insulin dose, and basal insulin requirements. Information on meal CHO consumed and prandial insulin dose administered was also entered.

The model predictive control algorithm[18] used in our studies employs a compartment model of glucose kinetics[21] describing the effect of rapid-acting insulin and the CHO content of meals on sensor glucose excursions. The algorithm adapts itself to a particular subject by updating two model parameters: an endogenous glucose flux correcting for errors in model-based predictions and CHO bioavailability. Several competing models differing in the absorption of subcutaneous insulin and oral carbohydrate run in parallel.[22] A combined model forecasts plasma glucose excursions over a 2.5 h prediction horizon, aiming to achieve glucose levels between 5.8 and 7.3 mmol/liter. Safety rules limit maximum insulin infusion, suspending delivery when sensor glucose ≤ 4.3 mmol/liter or is rapidly decreasing.

Assays

Plasma glucose was measured by YSI 2300 STAT Plus analyzer (YSI, Farnborough, UK). Plasma insulin was measured by an immunochemiluminometric assay [Invitron, Monmouth, UK; intra-assay coefficient of variation (CV) 4.7%; interassay CV 7.2–8.1%]. Plasma ethanol was determined using the ethyl alcohol method (Dade Behring Inc., Atterbury, UK; intra-assay CV 2.4%; interassay CV 5.7%).

Statistical Analysis

Primary outcome measure was time in target range (3.91–8.0 mmol/liter) as measured by overnight plasma glucose concentration. Secondary outcomes included time spent below (≤3.9 mmol/liter) and above (>8.0 mmol/liter) target, glycemic variability as assessed by standard deviation (SD) of overnight glucose, the low blood glucose index assessing frequency and extent of hypoglycemia,[23] and mean insulin infusion rate and plasma insulin concentration.

The statistical methods for the individual analyses of young people and adults have been described elsewhere.[17,18] For the combined evaluation, a permutation test was used to generate a p value for each outcome as per the original analysis[18] since some subjects participated in both APCam01 and APCam03. Analyses were conducted using SAS software, Version 9.1 (SAS Institute) and SPSS, Version 15 (SPSS Inc., Chicago, IL). Kernel density of plasma glucose was estimated using the package "nonparametric kernel smoothing methods for mixed data types," Version 0.40-1, adopting a bandwidth of 0.25 mmol/liter and implemented in R, Version 2.11.1 (The R Foundation for Statistical Computing). No formal adjustment was made for multiple comparisons of pooled data.

Results

Seventeen children and adolescents and 24 adults completed 45 closed-loop (intervention) and 45 CSII (control) visits. Four subjects from APCam01 also participated in APCam03, with data from both studies included for analysis. The baseline characteristics of both groups are summarized in **Table 1**.

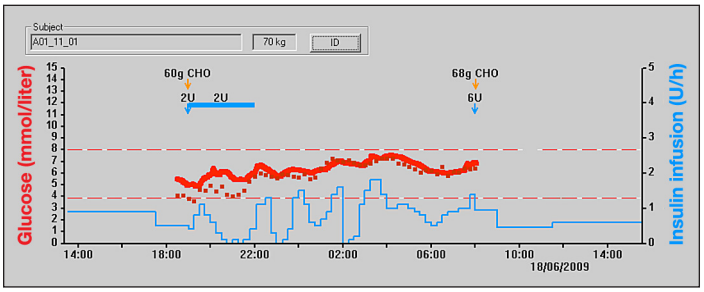

Figure 2. Sample closed-loop night as seen on the computer interface during Angela01 study. Plot shows sensor glucose (solid red curve) and insulin infusion rate (blue curve). Plasma glucose (red dots) was added later during *post hoc* analysis. On this study visit at 19:00, the subject consumed a 60 g carbohydrate evening meal accompanied by a dual wave insulin bolus delivered as 2 U immediately and 2 U over 3 h. Closed-loop insulin delivery was operational from 19:00 to 08:00.

Table 1.
Participant Characteristics[a]

	Young n = 17	Adults n = 24
Age (years)	13.4 (3.6)	37.5 (9.1)
Sex (male/female)	8/9	10/14
Body mass index (kg/m²)	21.0 (4.0)	25.7 (4.2)
Hemoglobin A1c (%)	8.5 (1.8)	7.8 (0.6)
Duration of diabetes (years)	6.2 (4.0)	20.6 (9.7)
Duration on pump (years)	1.7 (1.0)	2.4 (3.0)
Total daily insulin (U/kg/day)	0.92 (0.24)	0.73 (0.17)

[a] Values are mean (SD).

Primary Outcome

The proportion of plasma glucose in target range overnight was higher during closed loop (n = 45) compared with conventional pump therapy (n = 45) for both young (60% versus 40%, p = .002) and adults (76% versus 50%, p < .001), with an increase from 43% to 71% (p < .001) based on pooled analysis (**Table 2**). Both the time in target during closed loop and the absolute difference between interventions were higher in adults than in children and adolescents (**Figure 3**).

Secondary Outcomes

Hypoglycemia

Compared with conventional therapy, closed loop reduced the time spent below target (≤3.9 mmol/liter) in both young (4.1% to 2.1%, p = .03) and adult (6.7% to 2.8%, p = .04) subjects (**Table 3**, **Figure 4**). Pooled data showed an overall reduction from 4.1% to 2.1% (p = .01). The low blood glucose index was also decreased during closed loop in both groups and on pooled analysis (1.1 versus 1.6, p = .008).

During the children and adolescent studies, there was one episode of hypoglycemia (plasma glucose ≤ 3.0 mmol/liter) during closed loop and six during conventional pump therapy, occurring in seven subjects. The closed-loop-associated event occurred at 02:00 in APCam03 with three consecutive plasma glucose measurements of 3.0 mmol/liter. One of the hypoglycemic episodes during conventional CSII (APCam03 study) resulted in early termination of the study visit at 04:00 as plasma glucose was below 2.0 mmol/liter.

In the adult studies, there were four hypoglycemic events during closed-loop and seven during conventional pump therapy, occurring in nine participants. All the episodes during closed loop occurred before midnight and were symptomatic. Three were in the time course of action of the preceding prandial insulin dose and were not prevented by the closed-loop suspending insulin delivery. The fourth lasted 30 min with spontaneous recovery. During conventional pump therapy, three events occurred

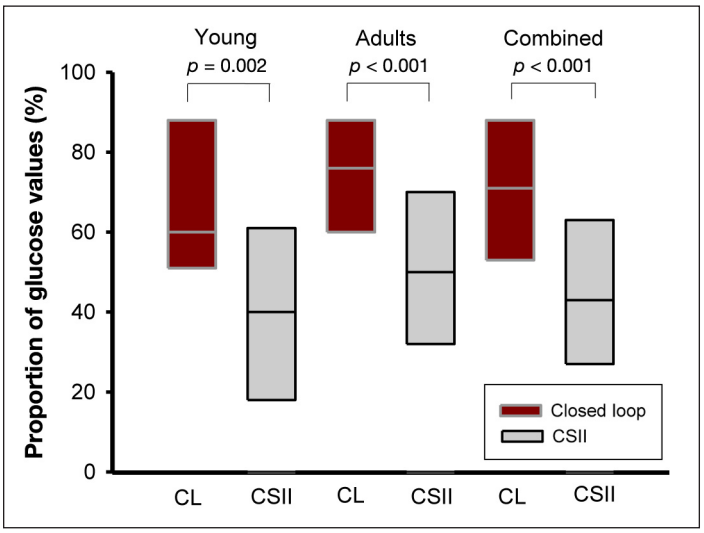

Figure 3. Comparison of plasma glucose in target range (3.91–8.0 mmol/liter) for young, adults, and combined studies. Median with interquartile range shown. CL, closed loop.

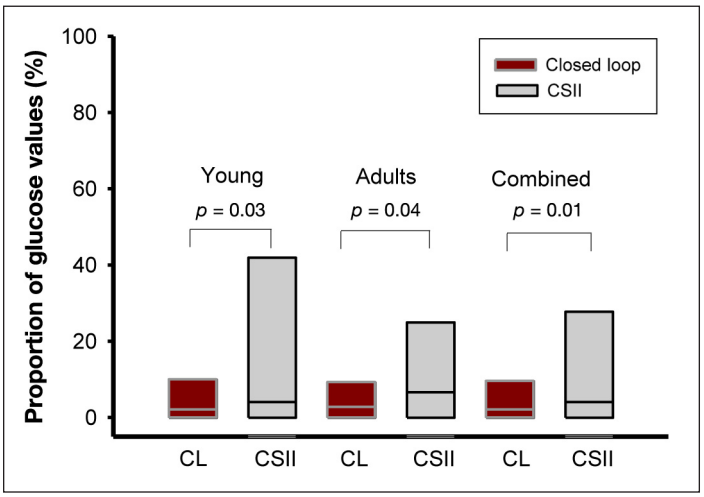

Figure 4. Comparison of plasma glucose below 3.9 mmol/liter for young, adults, and combined studies. Median with interquartile range shown. CL, closed loop.

Table 2.
Comparison of Primary Outcome in Young, Adults, and Combined Studies[a]

	Young			Adults			Combined		
	Closed loop n = 21[b]	CSII n = 21[b]	P value	Closed loop n = 24[b]	CSII n = 24[b]	P value	Closed loop n = 45[b]	CSII n = 45[b]	P value
Plasma glucose in target range 3.91–8.0 mmol/liter (%)	60 (51–88)	40 (18–61)	0.002	76 (60–88)	50 (32–70)	<0.001	71 (53–88)	43 (27–63)	<0.001

[a] Values are median (interquartile range).
[b] Number of nights per treatment.

before midnight: one was likewise in the time course of action of the prandial insulin bolus, one event occurred prior to consumption of the evening meal, and one event was 4 h after the meal. There were a further four events after midnight, one of which led to early discontinuation of that study night due to measured plasma glucose 1.9 mmol/liter.

Hyperglycemia

The proportion of glucose values above target (>8.0 mmol/liter) was lower during closed loop compared with conventional therapy nights in adults (18% versus 30%, $p = .006$), and although the difference in the young people's studies did not reach significance (25% versus 35%, $p = .13$; **Table 3**, **Figure 5**), the pooled results showed a reduction in time spent in hyperglycemia (20% versus 33%, $p = .03$). In APCam01 and APCam03, there were five glucose measurements above 16.7 mmol/liter, four of which occurred at the commencement of the study visits. One episode occurred during closed-loop and four during conventional pump therapy. In the adult studies, there were no plasma glucose values above 16.7 mmol/liter during either intervention.

Glucose Excursions and Insulin

Overnight plasma glucose profiles for each study are shown in **Figure 1**. In APCam01 (**Figure 1A**), target glycemic range was achieved from 01:00 during both closed-loop and conventional therapy and was maintained for the remainder of the night. In APCam03 (**Figure 1B**), plasma glucose remained within target for the entire duration of closed loop. In comparison during conventional pump therapy, glucose was above 8.0 mmol/liter until 22:00, and although target glycemia was maintained for the rest of the night, glucose levels tended to be lower.

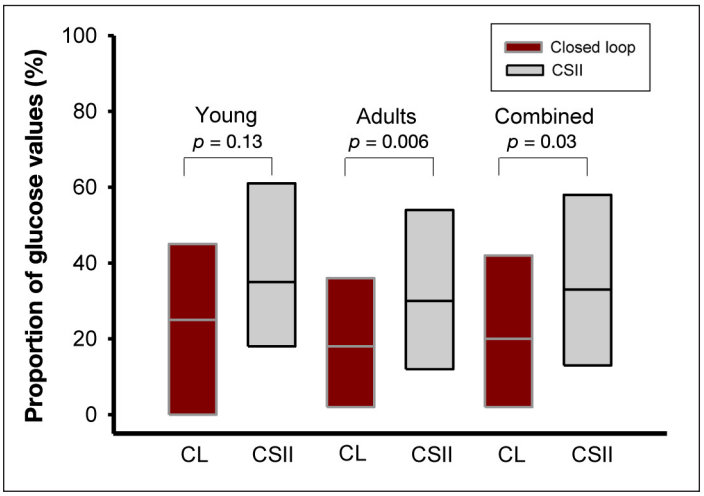

Figure 5. Comparison of plasma glucose above 8.0 mmol/liter for young, adults, and combined studies. Median with interquartile range shown. CL, closed loop.

Table 3.
Comparison of Secondary Outcomes in Young, Adults, and Combined Studies[a]

	Young			Adults			Combined		
	Closed loop $n = 21$[b]	CSII $n = 21$[b]	*P* value	Closed loop $n = 24$[b]	CSII $n = 24$[b]	*P* value	Closed loop $n = 45$[b]	CSII $n = 45$[b]	*P* value
Overnight plasma glucose (mmol/liter)	7.0 (1.8)	8.1 (3.6)	0.29	6.7 (1.1)	6.8 (1.5)	0.84	6.9 (1.5)	7.4 (2.8)	0.59
SD of plasma glucose (mmol/liter)	1.6 (1.1–2.8)	2.4 (1.7–3.2)	0.19	1.4 (1.1–1.8)	2 (1.6–2.7)	0.001	1.5 (1.1–2.1)	2.1 (1.6–2.9)	0.007
Plasma glucose ≤ 3.9 mmol/liter (%)	2.1 (0–10)	4.1 (0–42)	0.03	2.8 (0.0–9.3)	6.7 (0.0–25)	0.04	2.1 (0.0–9.6)	4.1 (0.0–27.8)	0.01
Plasma glucose ≤ 3.5 mmol/liter (%)	0 (0.0–4.1)	0 (0.0–23)	0.02	0 (0.0–4.0)	3.6 (0.0–17)	0.02	0 (0–4.1)	0 (0–18)	0.003
Plasma glucose > 8.0 mmol/liter (%)	25 (0–45)	35 (18–61)	0.13	18 (2–36)	30 (12–54)	0.006	20 (2–42)	33 (13–58)	0.03
Low blood glucose index (unitless)	1.1 (0.1–2.7)	1.6 (0.1–6.6)	0.03	1 (0.5–2.0)	1.9 (0.5–4.5)	0.01	1.1 (0.3–2.2)	1.6 (0.4–4.9)	0.008
Insulin concentration (pmol/liter)	199 (148–405)	233 (146–383)	0.23	104 (68–148)	109 (91–159)	0.14	148 (103–215)	146 (102–242)	0.40
Insulin infusion (U/h)	1 (0.6–1.4)	0.9 (0.6–1.6)	0.58	0.8 (0.6–1.0)	0.8 (0.6–1.0)	0.83	0.8 (0.6–1.2)	0.9 (0.6–1.2)	0.80

[a] Values are mean (SD) or median (interquartile range).
[b] Number of nights per treatment.

In Angela01 (**Figure 1C**), plasma glucose was maintained within target range during both closed-loop and conventional pump therapy, but the interquartile range representing glycemic variability was much smaller during closed-loop from 03:00. In Angela02 (**Figure 1D**), plasma glucose remained within target overnight on closed loop. During conventional pump therapy, plasma glucose levels were at the lower end of the target range between 01:00 and 03:00 and increased into the hyperglycemic range between 05:00 and 09:00.

The variability of plasma glucose overnight, as measured by SD, was lower during closed loop compared with conventional pump therapy (1.5 versus 2.1 mmol/liter, $p = .007$ on pooled data; **Table 3**). There was no difference in the average insulin infused or the plasma insulin concentrations measured between closed-loop and conventional therapy visits in all studies (**Table 3**).

Continuous Glucose Monitoring Accuracy

Sensor accuracy during APCam01, measured as median relative absolute difference between sensor glucose and paired plasma glucose divided by plasma glucose, was 9.2% (4.3–16.7) for GRT and 7.6% (3.8–14.1) for CGMS. Accuracy with the Freestyle Navigator CGM device was 12.7% (5.6–21.9), 8.0% (4.5–19.3), and 12.0% (6.8–17.2) in APCam03, Angela01, and Angela02, respectively.

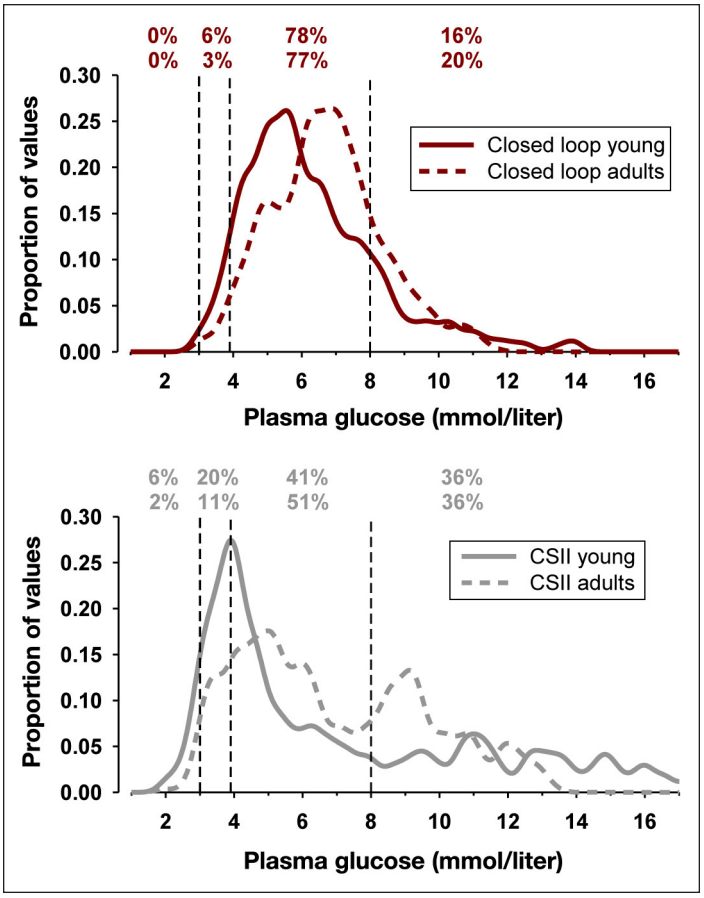

Figure 6. Distribution of plasma glucose after midnight in young and adults during closed-loop (top panel) and during conventional pump (bottom panel) therapy. Vertical dashed lines denote the threshold of significant hypoglycemia (3.0 mmol/liter) and the target glucose range (3.91 to 8.0 mmol/liter). Values at the top represent the percentage of plasma glucose values within the respective glucose ranges.

Discussion

In the present analysis of a series of studies using closed-loop insulin delivery for overnight glucose control in young people and adults with T1DM, we have demonstrated efficacy and safety superior to that achieved by conventional insulin pump therapy (**Figure 6**). Compared with CSII, closed-loop increased the time spent in target glucose range (3.91–8.0 mmol/liter) and reduced the time spent in hypoglycemia, with no difference in average overnight insulin infusion. This evaluation of pooled studies showed improvements during closed loop for all outcome measures. Glycemic control achieved with closed loop in adults tended to be better than that achieved in young people, although this difference was less pronounced after midnight. During CSII therapy, however, superior glucose control was demonstrated in adults throughout the night.

A key feature of the closed-loop system, demonstrated by our data, is its applicability in various patient populations. Insulin needs vary considerably between individuals—contributing factors include age, diabetes duration, and body weight as well as lifestyle factors such as exercise, dietary intake, and alcohol use. Our algorithm initializes individual insulin sensitivity based on body weight, total daily insulin dose, and usual basal infusion rates. It performed well in young children who tend to require lower total daily insulin per body weight, adolescents for whom the physiological demands of puberty necessitate much higher doses,[24] and adults with longer disease duration. Our algorithm also dealt effectively with exercise, alcohol consumption, and late start of closed loop.

In addition to physiological changes, behavioral factors may contribute to the poorer glycemic control seen in children and adolescents.[25] Reasons include infrequent self-testing of blood glucose, missed insulin boluses, and less structured eating patterns.[26] An important factor is the perceived fear of hypoglycemia held by both patients and caregivers, particularly during the overnight period, which may lead to excess carbohydrate consumption and/or less insulin administered with resulting hyperglycemia.[5]

Overnight closed-loop glucose control may be of particular benefit in this setting.[27]

Lifestyle differences between children and adults have a major impact on insulin demands, with the former tending to be more physically active. Exercise is associated with a significant and protracted risk of hypoglycemia in T1DM.[28] The closed-loop algorithm was able to cope with this risk and avoid significant nocturnal hypoglycemia following moderate-intensity evening exercise in APCam03. Managing fluctuations in glycemic control attributable to usual daily activities will be an essential requirement prior to employment of closed loop during daytime hours. Preliminary results of studies using our closed-loop system during the daytime as well as overnight in adolescents indicate improved efficacy compared with conventional therapy,[29] but further studies are warranted to establish daytime benefits of closed-loop insulin delivery.

As well as assessing the feasibility of our closed-loop system across a range of ages, our studies also evaluated its performance following common scenarios such as large evening meals and alcohol consumption. Postprandial glucose control remains a major challenge for patients with T1DM. Although glucose concentrations increased after the large evening meals in APCam01 (87 g carbohydrate) and to a lesser extent in Angela02 (100 g carbohydrate), overall glycemic control was maintained during closed loop with reduced occurrence of delayed hypoglycemia, as a result of the algorithm minimizing basal insulin infusion following the prandial insulin bolus.

Alcohol consumption is associated with a significant threat of delayed hypoglycemia,[30] further complicated by its effects on cognition and blunting of the counter-regulatory response.[31] Although we did not see the anticipated increased frequency of hypoglycemia during either treatment in Angela02, closed-loop performance was unaffected by moderate evening alcohol intake (9.6 ml/kg). We also assessed the impact of a later start of closed loop (22:00) on overnight glycemic control, which may not be an uncommon occurrence in adults following an evening out, showing preserved efficacy.

The closed-loop system used in our studies required manual CGM entry and alteration of pump settings every 15 min by the research nurse, which is associated with a risk of human error as well as an inherent delay in changing the pump. This approach is not feasible in clinical practice and requires development of an automated system with wireless data transmission. We have tested a prototype automated closed-loop system in eight children overnight, demonstrating safe and efficacious control.[32]

The limitations associated with interpreting pooled data from studies with variations between protocols should be taken into account. Equally, the combined analysis of a larger number of subjects provides stronger evidence of the improvement in glucose control during closed loop. When designing the studies, the differences in meal size and timing were chosen as being representative of likely common scenarios in the two age groups.

There have been several closed-loop studies[33-38] reported, none of which was randomized, and only one study had a control group for comparison. All our studies employed a randomized crossover design, thus minimizing any effect of interindividual variability on insulin sensitivity. They were designed to match real life as closely as possible in preparation for home testing of the closed loop. We used commercially available CGM and pump devices. Our algorithm considered only real-time interstitial glucose measurements based on output from a single sensor worn by participants, compared with other closed-loop studies[34,38] that used venous glucose or more than one sensor for CGM output. Importantly, the algorithm advice was always followed unlike other closed-loop studies where researchers have sometimes deviated from the algorithm, limiting the interpretation of data.[35]

In addition to the patient groups presented here, pregnant women with T1DM have unique insulin requirements, and maintenance of tight glycemic targets is essential to avoiding maternal and fetal adverse outcomes.[39] Insulin needs vary considerably with each trimester, including a progressive increase in the ratio of bolus to basal insulin doses. A feasibility study of overnight closed-loop in 10 subjects during early and late pregnancy demonstrated near-optimal glycemic control.[40]

Conclusion

Combined evaluation of our studies demonstrates that overnight closed-loop insulin delivery can improve glycemic control and reduce the risk of nocturnal hypoglycemia in both younger and older people with T1DM. Superior performance and safety of closed loop was maintained even under common challenges such as exercise, large evening meals, and drinking alcohol.

Funding:

This study was supported by the Juvenile Diabetes Research Foundation (22-2006-1113, 22-2007-1801, 22-2009-801, and 22-2009-802), Diabetes UK (BDA07/0003549), the Medical Research Council Centre for Obesity and Related Metabolic Diseases, and the National Institute for Health Research Cambridge Biomedical Research Centre.

Acknowledgments:

Smiths Medical Supplied study pumps. Abbott Diabetes care supplied Freestyle Navigator devices and sensors. Josephine Hayes provided administrative support. Jo Weston provided dietary support. Karen Whitehead and Angie Watts provided laboratory support. The Core Biochemical Assay Lab, NIHR Cambridge Biomedical Research Centre (Keith Burling) measures plasma ethanol. The Diabetes Research Network Lab Wales (Dr. Steve Luzio) measured plasma insulin. We acknowledge support by the staff at the Addenbrooke's Wellcome Trust Clinical Research Facility. We are grateful to the study volunteers and their caregivers for their continuing support and participation.

Disclosures:

Roman Hovorka has received speaker honorariums from MiniMed Medtronic, LifeScan, and Novo Nordisk; served on advisory panels for Animas and MiniMed Medtronic; received license fees from B. Braun and Becton Dickinson; and served as a consultant to Becton Dickinson, B. Braun, and Profil. Craig Kollman has served as a consultant to Medtronic International Trading Sàrl and Diabetes Technology Management. Stephanie A. Amiel has served on advisory boards for Medtronic and Johnson and Johnson and has received speaker honorariums for Medtronic, Animas, and Roche. Simon R. Heller has received speaker honorariums from Novo Nordisk, Eli Lilly, sanofi-aventis, and LifeScan and served on advisory panels for Novo Nordisk and Eli Lily. Mark L. Evans has received speaker honorariums from Eli Lilly and served on advisory panels for Medtronic, sanofi-aventis, and Cellnovo. Helen R. Murphy has received speaker honorariums from MiniMed Medtronic. Malgorzata E. Wilinska has received license fees from Becton Dickinson and has served as a consultant to Becton Dickinson. Roman Hovorka, Malgorzata E. Wilinska, and David B. Dunger report patent applications in the area of closed-loop insulin delivery.

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