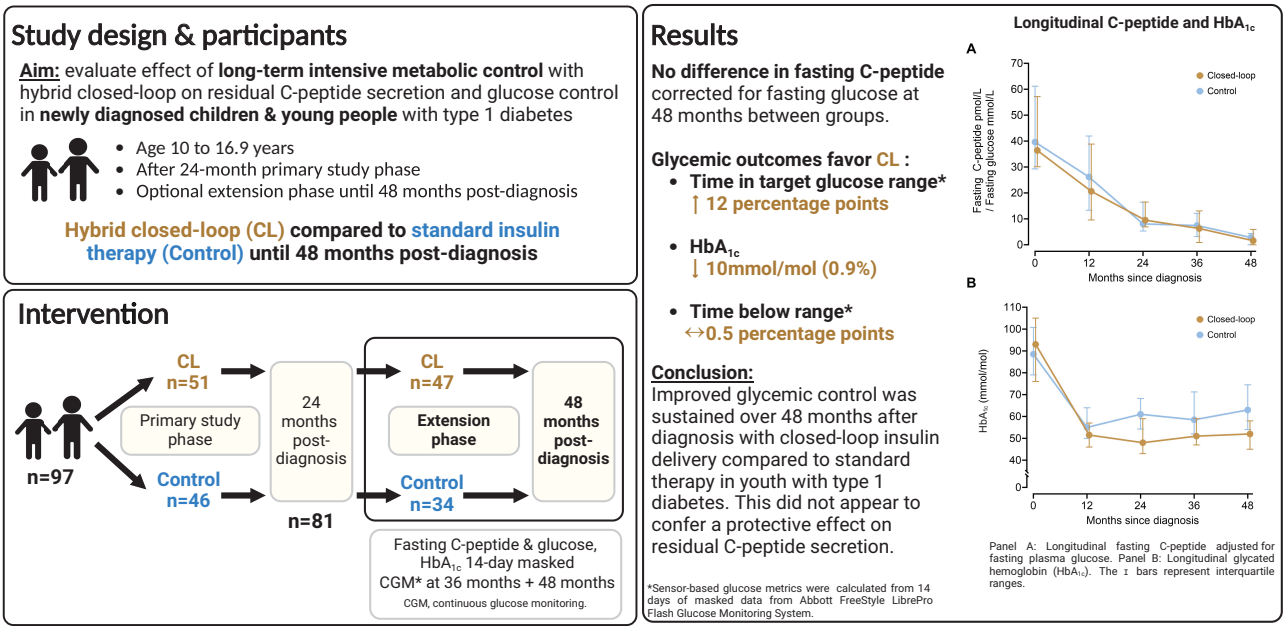
Diabetes Care
American Diabetes Association

Effect of 48 Months of Closed-Loop Insulin Delivery on Residual C-Peptide Secretion and Glycemic Control in Newly Diagnosed Youth With Type 1 Diabetes: A Randomized Trial

Julia Ware, Charlotte K. Boughton, Janet M. Allen, Malgorzata E. Wilinska, Sara Hartnell, Ajay Thankamony, Tabitha Randell, Atrayee Ghatak, Rachel E.J. Besser, Daniela Elleri, Nicola Trevelyan, Fiona M. Campbell, Judy Sibayan, Ryan Bailey, Peter Calhoun, Gareth Dunseath, and Roman Hovorka, on behalf of the CLOuD Consortium*

Diabetes Care 2024;47(8):1441–1448 | https://doi.org/10.2337/dc24-0360

Effect of 48 months of closed-loop insulin delivery on residual C-peptide secretion and glycemic control in newly diagnosed youth with type 1 diabetes



ARTICLE HIGHLIGHTS

- **Why did we undertake this study?**
  The long-term (>24 months) effect of intensive glucose control on residual C-peptide secretion is unknown.
- **What is the specific question(s) we wanted to answer?**
  We evaluated the long-term effects of intensive metabolic control using hybrid closed-loop on residual C-peptide secretion and glycemic control compared with standard therapy over 48 months from diagnosis of type 1 diabetes.
- **What did we find?**
  Significant improvements in glycemic control were sustained for 48 months from diagnosis using hybrid closed-loop compared with standard therapy, but this did not prevent β-cell decline.
- **What are the implications of our findings?**
  Hybrid closed-loop insulin delivery should be used from diagnosis of type 1 diabetes in children and young people. Other approaches are needed to slow β-cell decline.

Effect of 48 Months of Closed-Loop Insulin Delivery on Residual C-Peptide Secretion and Glycemic Control in Newly Diagnosed Youth With Type 1 Diabetes: A Randomized Trial

Julia Ware,[1,2] Charlotte K. Boughton,[1,3] Janet M. Allen,[1,2] Malgorzata E. Wilinska,[1,2] Sara Hartnell,[3] Ajay Thankamony,[2] Tabitha Randell,[4] Atrayee Ghatak,[5] Rachel E.J. Besser,[6,7] Daniela Elleri,[8] Nicola Trevelyan,[9] Fiona M. Campbell,[10] Judy Sibayan,[11] Ryan Bailey,[11] Peter Calhoun,[11] Gareth Dunseath,[12] and Roman Hovorka,[1,2] on behalf of the CLOuD Consortium*

Diabetes Care 2024;47:1441–1448 | https://doi.org/10.2337/dc24-0360

ORIGINAL ARTICLE

OBJECTIVE

We evaluated the effect of long-term intensive metabolic control with hybrid closed-loop (CL) on residual C-peptide secretion and glucose control compared with standard insulin therapy in youth with type 1 diabetes over 48 months.

RESEARCH DESIGN AND METHODS

Following the 24-month primary phase of a multicenter, randomized, parallel trial of 96 newly diagnosed youth aged 10 to 16.9 years, participants were invited to an extension phase using treatment allocated at randomization. They continued with hybrid CL using the Cambridge algorithm or standard insulin therapy (control) until 48 months after diagnosis. Analysis was by intention-to-treat.

RESULTS

At 24 months after diagnosis, 81 participants (mean ± SD age 14 ± 2 years) continued in the extension phase (47 CL, 34 control). There was no difference in fasting C-peptide corrected for fasting glucose at 48 months between groups (CL: 5 ± 9 vs. control: 6 ± 14 pmol/L per mmol/L; mean adjusted difference −2 [95% CI −7, 4; *P* = 0.54]). Central laboratory HbA_{1c} remained lower in the CL group by 0.9% (10 mmol/mol [95% CI 0.2, 1.5; 3, 17 mmol/mol); *P* = 0.009). Time in target range of 3.9 to 10.0 mmol/L was 12 percentage points (95% CI 3, 20; *P* = 0.008) higher in the CL group compared with control. There were 11 severe hypoglycemic events (6 CL, 5 control) and 7 diabetic ketoacidosis events (3 CL, 4 control) during the extension phase.

CONCLUSIONS

Improved glycemic control was sustained over 48 months after diagnosis with CL insulin delivery compared with standard therapy in youth with type 1 diabetes. This did not appear to confer a protective effect on residual C-peptide secretion.

Type 1 diabetes is a lifelong, incurable condition characterized by a deficiency of insulin caused by gradual immune-mediated destruction of pancreatic β-cells in genetically

[1]Institute of Metabolic Science-Metabolic Research Laboratories and Medical Research Council Metabolic Diseases Unit, University of Cambridge, Cambridge, U.K.
[2]Department of Paediatrics, University of Cambridge, Cambridge, U.K.
[3]Wolfson Diabetes and Endocrine Clinic, Cambridge University Hospitals National Health Service Foundation Trust, Cambridge, U.K.
[4]Department of Paediatric Diabetes and Endocrinology, Nottingham Children's Hospital, Nottingham, U.K.
[5]Department of Diabetes, Alder Hey Children's National Health Service Foundation Trust, Liverpool, U.K.
[6]Department of Paediatrics, University of Oxford, Oxford, U.K.
[7]National Institute for Health and Care Research Oxford Biomedical Research Centre, John Radcliffe Hospital, Oxford, U.K.
[8]Department of Diabetes, Royal Hospital for Sick Children, Edinburgh, U.K.
[9]Paediatric Diabetes, Southampton Children's Hospital, Southampton, U.K.
[10]Department of Paediatric Diabetes, Leeds Children's Hospital, Leeds, U.K.
[11]Jaeb Center for Health Research, Tampa, FL
[12]Diabetes Research Group, Swansea University, Swansea, U.K.

Corresponding author: Roman Hovorka, rh347@cam.ac.uk

Received 19 February 2024 and accepted 15 May 2024

Clinical trial reg. no. NCT02871089, clinicaltrials.gov

This article contains supplementary material online at https://doi.org/10.2337/figshare.25892740.

*A complete list of the CLOuD Consortium can be found in the supplementary material online.

predisposed individuals (1). More than 1 million children and young people under the age of 20 years are living with the condition worldwide (2), with incidence projected to rise from the current 13.7 per 100,000 to 17.6 per 100,000 in 2050 (3). Target glycemic control is challenging to achieve, and most children and young people with type 1 diabetes do not meet treatment guidelines for target glycated hemoglobin (HbA_{1c}) (4–6). Suboptimal glycemic control puts this population at risk for developing long-term micro- and macrovascular complications as well as premature death (7,8). Residual β-cell function is associated with improved metabolic control and a reduction in long-term microvascular complication risk (9,10). Intensive glycemic control, where hyperglycemia is minimized immediately following diagnosis of type 1 diabetes, may help to preserve residual β-cell function (11). An early exploratory study showed improved C-peptide secretion at 12 months following intensive in-hospital treatment using a treat-to-target-range algorithm with a target of 3.3 to 4.4 mmol/L for 2 weeks after diagnosis (11), but this observation has not yet been replicated (12).

Hybrid closed-loop (CL) insulin delivery is increasingly adopted clinically and has been shown to improve glycemic control in children and young people in the medium-term (13–18). The primary phase of the current study aimed to determine whether sustained intensive glycemic control using hybrid CL following diagnosis could prevent the decline in endogenous insulin secretion in youth with type 1 diabetes (19). Results showed that despite significant improvements in glycemic control with CL compared with standard therapy over 24 months, a similar decline in residual C-peptide secretion occurred in both groups (19).

Diabetes self-management is particularly challenging in the adolescent age-group due to a variety of factors, including peer group influences, importance of body image, less parental oversight, greater risk-taking, and fear of hypoglycemia, leading to higher levels of diabetes distress (20,21). What remained uncertain at the time of the primary study phase was whether hybrid CL insulin delivery would remain effective in this population in terms of improving glycemic control in the true long-term, and how this might affect any remaining β-cell function.

RESEARCH DESIGN AND METHODS

Study Design

The study adopted an open-label, multicenter, randomized, parallel design comparing hybrid CL insulin delivery and standard insulin therapy (control) over 48 months. After the initial 24-month study period (primary phase) all participants were invited to enter an extension phase of the study, where they continued with their treatment allocated at initial randomization for a further 24 months. Results from the primary study phase and a copy of the protocol are published elsewhere (19).

Participants were recruited from seven pediatric diabetes clinics in the U.K. (CLOuD Consortium members are listed in the Supplementary Material). Approval was received from Cambridge East Research Ethics Committee (16/EE/0286) and Medicines and Healthcare products Regulatory Agency. Safety aspects were overseen by an independent data safety monitoring board. The study is registered with ClinicalTrials.gov (NCT02871089).

Study Participants

All participants completing the primary study phase were invited to take part in the extension phase. For the primary study phase, the key inclusion criterion was diagnosis of type 1 diabetes within the previous 21 days. Participants were aged 10 to 16.9 years inclusive. Key exclusion criteria included concomitant disease or treatment affecting metabolic control or interpretation of HbA_{1c}. Complete inclusion and exclusion criteria for the primary study phase are listed in Supplementary Table 1. Participants aged 16 years and parents/guardians of participants <16 years opting to continue in the extension phase were asked to reconsent. Written assent was obtained from participants <16 years.

Closed-Loop System

The Cambridge model predictive control algorithm (version 0.3.71) was run in two hardware configurations, the initial FlorenceM configuration, followed by the CamAPS FX configuration. The CamAPS FX configuration superseded FlorenceM to address usability issues and improve adherence (Supplementary Fig. 1). Of the 44 participants in the CL group, 9 used the initial FlorenceM configuration during the 24 to 36-month period, the remainder used CamAPS FX. All 44 CL participants used CamAPS FX from 36 to 48 months.

In both configurations, algorithm-driven insulin delivery was adjusted automatically every 8 to 12 min, with the app-based control algorithm communicating the insulin infusion rate to the insulin pump wirelessly. The control algorithm was initialized using total daily insulin dose and body weight, and incorporated adaptive learning with regards to total daily insulin requirements, diurnal variations, meal patterns, and duration of insulin action.

Procedures

Study flowchart and visit schedules are in Supplementary Fig. 2 and Supplementary Tables 2 and 3.

During the extension phase, participants randomized to CL in the primary study phase continued CL therapy until 48 months after diagnosis, with no remote monitoring or study-related restrictions. Participants initially randomized to control continued standard insulin therapy until 48 months after diagnosis. All control group participants were commenced on multiple daily injections at diagnosis, but were free to commence insulin pump therapy and/or use flash/continuous glucose monitoring or approved CL systems at any time following randomization. Treatment adjustments were made by local diabetes clinical teams (not the research team) as clinically indicated, applying National Institute for Health and Care Excellence criteria (22) with regards to eligibility for insulin pump therapy and/or glucose monitoring use.

Study Contacts

During the extension phase participants were contacted at 3-month intervals to record adverse events, device deficiencies, and other relevant information. Two follow-up visits were conducted at 36 and 48 months after diagnosis. Fasting C-peptide and glucose samples and HbA_{1c} samples were collected following an overnight fast, and participants wore a masked glucose sensor (FreeStyle Libre Pro; Abbott Diabetes Care, Alameda, CA) for 14 days. Throughout the study, participants/guardians and/or the local diabetes clinical team were free to adjust insulin therapy, but no active treatment optimization was undertaken by the research team. Participants were able to contact a 24-h telephone help line to the local research team.

Assays

C-peptide, glucose, and HbA_{1c} were measured centrally and lipid profile was measured locally. Details are provided in the Supplementary Material.

Study Outcomes

All outcomes in the extension phase were considered secondary and were compared between treatment arms at 36 and 48 months of follow-up. Outcomes included fasting C-peptide, fasting C-peptide adjusted for fasting plasma glucose, and overall glucose control in the form of HbA_{1c}. Time in target glucose range 3.9 to 10.0 mmol/L, time in hypoglycemia <3.9 mmol/L, time in hyperglycemia >10.0 mmol/L, mean glucose, SD of glucose, and coefficient of variation of glucose were based on data from a masked glucose sensor worn for 14 days at 36 and 48 months, respectively. Additional outcomes based on sensor glucose data included time with glucose <3.0 mmol/L and >16.7 mmol/L and area above the curve <3.9 mmol/L. All sensor glucose outcomes were calculated over the whole 24-h period, whereas a subset of outcomes (time in the target range, mean sensor glucose, SD of glucose, and time <3.0 mmol/L) were also tabulated separately for daytime (0600 to 2359) and night-time (0000 to 0559). Insulin delivery metrics were additionally compared between groups.

Safety evaluation comprised the frequency of severe hypoglycemia and diabetic ketoacidosis (DKA) events as well as other adverse events or serious adverse events.

Statistical Analysis

Analyses were performed on an intention-to-treat basis, with each participant analyzed according to the treatment assigned by the initial randomization. All participants who were randomized were included in the analysis. Treatment interventions were compared using a longitudinal mixed-effects linear model adjusting for baseline value, sex, presence/absence of DKA at diagnosis, and age as fixed effects, and clinical site as a random effect. Mixed-effects regression models addressed missing data by using maximum likelihood estimation incorporating data from all randomized participants, which assumes data were missing at random. A 95% CI was reported for the difference between the interventions based on the linear mixed model. Highly skewed data were winsorized at the 10th and 90th percentiles. *P* values were two-sided and were adjusted for multiple comparisons using the adaptive Benjamini-Hochberg false discovery rate correction procedure.

A per-protocol analysis restricted to participants in the CL group who used the system at least 60% of the time during the extension phase and those in the control group who did not start insulin pump therapy was conducted.

Analyses were conducted with SAS 9.4 software (SAS Institute).

Data and Resource Availability

Deidentified data set will be made available on case-by-case basis on reasonable request for research purposes.

RESULTS

Participants

Of 97 participants initially randomized, 85 completed the primary study phase (47 CL and 38 control group). Between 31 January 2019 and 5 July 2021, 81 participants chose to enroll in the extension phase (at extension start mean ± SD age was 14 ± 2 years, 42% female [*n* = 34], HbA_{1c} 7.3 ± 1.2% [56 ± 14 mmol/mol]), of which 47 were in the CL group, and 34 in the control group. Characteristics of participants in the extension phase are shown in Table 1, while characteristics of all randomized participants in the primary study phase compared with the extension phase cohort are shown in Supplementary Table 4. There were five withdrawals during the extension phase, three in the CL group, and two in the control group. Three participants were withdrawn due to safety concerns (two CL, one control), and two participants were lost to follow-up (one CL, one control). Flow of participants is shown in Supplementary Fig. 3, and the reasons for withdrawal are shown in Supplementary Table 5.

C-Peptide Outcomes

C-peptide and glycemic outcomes for all participants in the extension phase at 36 and 48 months are shown in Table 2. In keeping with primary study phase results, there was no difference in fasting C-peptide between treatment groups at 36 or 48 months (CL 61 ± 58 pmol/L and control 69 ± 47 pmol/L at 36 months, mean adjusted difference −15 [95% CI −46, 18; *P* = 0.35]; CL 26 ± 31 pmol/L and control 29 ± 31 pmol/L at 48 months, mean adjusted difference −8 [95% CI −36, 20; *P* = 0.54]). Similarly, there was no difference in fasting C-peptide divided by fasting glucose between groups at 36 and 48 months. Overall, C-peptide levels declined in both groups over the 4-year study period (Fig. 1).

Glycemic Outcomes

The percentage time spent in target range 3.9 to 10.0 mmol/L was 12 percentage points higher (95% CI 3, 20; *P* = 0.008) in the CL group compared with control group at 48 months based on

Table 1—Characteristics of study participants at start of the extension phase (24 months after diagnosis) by treatment group

	Overall (*n* = 81)	CL (*n* = 47)	Control (*n* = 34)
Age, years	14 ± 2	14 ± 2	14 ± 2
Female sex	34 (42)	21 (45)	13 (38)
BMI percentile	62 ± 27	63 ± 27	61 ± 29
Race/ethnicity			
White	67 (83)	40 (85)	27 (79)
Black/African American	3 (4)	1 (2)	2 (6)
Asian	4 (5)	2 (4)	2 (6)
More than one race	5 (6)	4 (9)	1 (3)
Unknown/not reported	2 (2)	0 (0)	2 (6)
Presence of DKA at diagnosis	18 (22)	14 (30)	4 (12)
HbA_{1c}, at 24 months after diagnosis			
HbA_{1c}, %	7.3 ± 1.2	6.9 ± 1.0	7.9 ± 1.3
HbA_{1c}, mmol/mol	56 ± 14	52 ± 11	63 ± 14

Data are *n* (%) or mean ± SD.

Table 2—C-peptide and glycemic outcomes at 36 and 48 months

	Baseline*		36 months				48 months			
Outcomes	CL	Control	CL	Control	Mean adjusted difference (95% CI)†	*P* value†	CL	Control	Mean adjusted difference (95% CI)†	*P* value†
C-peptide outcomes										
Participants (*n*)	51	46	41	33			41	30		
Fasting C-peptide (pmol/L)†	286 ± 113	285 ± 132	61 ± 58	69 ± 47	−15 (−46, 18)	0.35	26 ± 31	29 ± 31	−8 (−36, 20)	0.54
Participants (*n*)	49	45	41	33			41	30		
Fasting C-peptide/fasting plasma glucose (pmol/L per mmol/L)‡	44 ± 23	48 ± 21	9 ± 9	11 ± 15	−3 (−9, 2)	0.26	5 ± 9	6 ± 14	−2 (−7, 4)	0.54
Glycemic outcomes										
Participants (*n*)	50	43	37	31			36	30		
Time spent at glucose level (%)										
3.9–10.0 mmol/L	74 ± 14	72 ± 13	66 ± 13	52 ± 20	15 (7, 23)	<0.001	61 ± 12	50 ± 17	12 (3, 20)	0.008
<3.9 mmol/L‡	9.1 ± 6.3	10.7 ± 7.1	13.8 ± 7.3	6.8 ± 5.5	7.0 (4.0, 10.2)	<0.001	11.7 ± 6.8	11.5 ± 8.1	0.5 (−3.7, 4.8)	0.79
<3.0 mmol/L‡	2.0 ± 2.5	2.8 ± 2.8	4.2 ± 3.6	2.1 ± 2.3	2.0 (0.6, 3.5)	0.006	4.2 ± 2.9	5.3 ± 4.8	−1.1 (−3.4, 1.2)	0.34
>10.0 mmol/L‡	15 ± 9	14 ± 10	18 ± 9	40 ± 19	−23 (−29, −16)	<0.001	26 ± 13	38 ± 20	−12 (−21, −3)	0.008
>16.7 mmol/L‡	1.0 ± 1.6	1.0 ± 1.5	2.5 ± 3.3	10.5 ± 11.3	−8.3 (−12.4, −4.4)	<0.001	3.9 ± 4.0	8.3 ± 7.7	−4.8 (−8.6, −1.2)	0.008
Mean glucose (mmol/L)	7.2 ± 1.6	7.0 ± 1.6	7.4 ± 1.6	10.0 ± 3.1	−2.5 (−3.7, −1.3)	<0.001	8.2 ± 2.2	9.3 ± 2.7	−1.4 (−2.8, 0.0)	0.06
Glucose SD (mmol/L)	2.7 ± 0.7	2.7 ± 0.8	3.4 ± 1.1	4.3 ± 1.4	−0.8 (−1.4, −0.2)	0.009	3.9 ± 1.2	4.3 ± 1.4	−0.4 (−1.1, 0.4)	0.34
CV of glucose (%)	38 ± 7	39 ± 7	46 ± 9	44 ± 10	3 (−1, 7)	0.18	47 ± 8	46 ± 9	1 (−4, 6)	0.55
Glucose area above curve <3.9 mmol/L‡	1.0 ± 0.9	1.3 ± 1.1	1.8 ± 1.2	0.8 ± 0.8	0.9 (0.4, 1.4)	<0.001	1.6 ± 1.0	1.9 ± 1.6	−0.3 (−1.0, 0.5)	0.46
HbA_{1c}										
Participants (*n*)	51	46	41	34			41	32		
HbA_{1c}, %	10.7 ± 1.8	10.5 ± 1.6	7.0 ± 0.9	7.8 ± 1.5	−0.9 (−1.4, −0.4)	0.001	7.1 ± 1.6	7.9 ± 1.4	−0.9 (−1.5, −0.2)	0.01
HbA_{1c}, mmol/mol	94 ± 20	91 ± 17	53 ± 10	62 ± 17	−10 (−15, −4)		54 ± 17	63 ± 15	−10 (−17, −3)	
Insulin metrics (units/kg/day)										
Participants (*n*)	47	44	44	34			44	33		
Total daily insulin	0.87 ± 0.33	0.82 ± 0.38	1.35 ± 0.44	1.26 ± 0.51	0.08 (−0.18, 0.34)	0.46	1.46 ± 0.72	1.31 ± 0.48	0.17 (−0.19, 0.53)	0.37
Total daily basal insulin	0.33 ± 0.12	0.36 ± 0.21	0.78 ± 0.41	0.59 ± 0.27	0.18 (−0.02, 0.38)	0.08	0.85 ± 0.57	0.64 ± 0.24	0.20 (−0.06, 0.46)	0.18
Total daily bolus insulin	0.54 ± 0.24	0.46 ± 0.28	0.57 ± 0.21	0.67 ± 0.31	−0.12 (−0.26, 0.03)	0.08	0.61 ± 0.37	0.67 ± 0.35	−0.07 (−0.29, 0.14)	0.40

Data are mean ± SD unless otherwise indicated. CV, coefficient of variation. *Baseline data were obtained 7–21 days after diagnosis of type 1 diabetes. HbA_{1c} levels are reflective of recent diagnosis, whereas glucose sensor data were obtained following the commencement of insulin therapy with multiple daily injections in all participants prior to randomization. †Based on a linear model adjusting for baseline value, gender, presence or absence of DKA at diagnosis, and age as fixed effects and clinical site as a random effect. *P* values and confidence intervals adjusted using the adaptive Benjamini-Hochberg procedure. ‡Winsorized at the 10th and 90th percentiles due to skewness prior to reporting summary statistics.

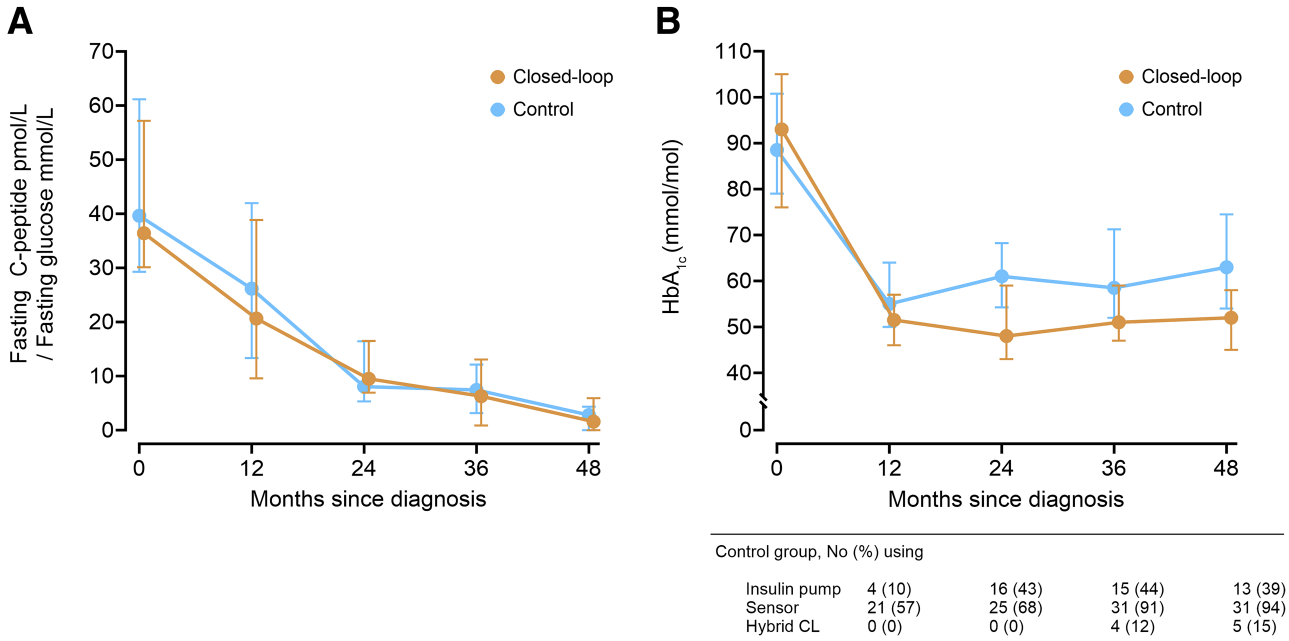


Figure 1—*A*: Longitudinal fasting C-peptide adjusted for fasting plasma glucose. *B*: Longitudinal HbA_{1c}. The numbers beneath the *x*-axis in *B* reflect the number of participants in the control group using different types of diabetes technology at each time point (sensor includes real-time and flash glucose monitoring). The I bars represent interquartile ranges.

masked Libre Pro sensor data. This was mainly due to a reduction in time in hyperglycemia >10.0 mmol/L of 12 percentage points (95% CI −21, −3; *P* = 0.008) in the CL group compared with control at 48 months. Time in range was lowest at 48 months in both groups compared with other study time points (61 ± 12% CL and 50 ± 17% control group) (Supplementary Table 6 and Supplementary Fig. 4). Time in hypoglycemia <3.9 mmol/L was not different between groups at 48 months (mean adjusted difference 0.5 percentage points [95% CI −3.7, 4.8; *P* = 0.79]), but was high in both groups at 11.7 ± 6.8% in the CL and 11.5 ± 8.1% in the control group. A post hoc comparison of time in hypoglycemia (<3.9 mmol/L) as recorded by Dexcom G6 versus Libre Pro in the CL group showed 2.9 ± 1.2% time in hypoglycemia based on Dexcom G6 versus 13.5 ± 6.2% based on Libre Pro readings (36- and 48-month data combined). Mean glucose was 1.4 mmol/L lower (95% CI 0.0, 2.8; *P* = 0.06) in the CL group compared with control at 48 months, although this difference was not statistically significant. Glucose variability as measured by the SD of glucose and coefficient of variation of glucose was similar between treatment groups. Day and night glucose control is shown in Supplementary Table 7. Longitudinal sensor glucose outcomes over 4 years are shown in Supplementary Table 6 and Supplementary Fig. 4.

Mean HbA_{1c} was 0.9 percentage points (10 mmol/mol) lower (95% CI −1.5, −0.2% [−17, −3 mmol/mol]; *P* = 0.009) in the CL group compared with the control group at 48 months. In the CL group, 59% (*n* = 24) achieved the American Diabetes Association target of HbA_{1c} <7.0% (53 mmol/mol) and 34% (*n* = 14) achieved the The International Society for Pediatric and Adolescent Diabetes (ISPAD) target of HbA_{1c} <6.5% (48 mmol/mol) at 48 months, compared with 22% (*n* = 7) and 9% (*n* = 3), respectively, in the control group. After a significant decrease following diagnosis in both groups, HbA_{1c} remained relatively stable over 4 years in the CL group, whereas it steadily increased over the first 2 years and then remained stable thereafter in the control group (Fig. 1).

Insulin Outcomes

Total daily insulin requirements were similar between treatment groups at 48 months (mean adjusted difference 0.17 units/kg/day [95% CI −0.19, 0.53; *P* = 0.37]), with a trend toward a lower proportion of insulin being given as a bolus in the CL group compared with control (Table 2). Longitudinal insulin requirements over 4 years are shown in Supplementary Table 8.

Technology Use

In the CL group, median sensor use was 97% (interquartile range 91, 99) with median 92% (82, 94) CL use from 24 to 48 months (Supplementary Table 9).

Following on from the primary study phase, where 43% of participants in the control group (*n* = 16) were using insulin pump therapy and 68% (*n* = 25) were using a glucose sensor, technology use remained high in the control group during the extension phase, with nearly all participants using a glucose sensor. At 48 months, 39% (*n* = 13) were using insulin pump therapy, 94% (*n* = 31) were using a glucose sensor, and 15% (*n* = 5) were using a hybrid CL system (Supplementary Table 10).

Per-Protocol Analysis

The differences between groups in time in target range of 3.9 to 10.0 mmol/L and HbA_{1c} at 36 and 48 months were even more marked in favor of CL in a per-protocol analysis. This analysis used data from participants in the CL group with at least 60% CL use during the extension phase and those in the control group who did not start insulin pump therapy (Supplementary Table 11).

Adverse Events

Safety-related events are summarized in Table 3. There were 11 severe hypoglycemia events, 6 events occurred in

Table 3—Safety outcomes by treatment group from 24 to 48 months

	CL (n = 47)	Control (n = 34)	P value*
Severe hypoglycemic events, *n*	6	5	
Events per participant	0.13 ± 0.40	0.15 ± 0.36	0.82
Incidence rate per 100 person-years	6.6	7.5	0.84
Participants with at least one event	5 (11)	5 (15)	0.73
DKA events, *n*	3	4	
Episodes per participant	0.06 ± 0.25	0.12 ± 0.33	0.26
Incidence rate per 100 person-years	3.3	6.0	0.27
Participants with at least one event	3 (6)	4 (12)	0.45
Serious adverse events, *n*	1	7	
Serious adverse events per participant	0.02 ± 0.15	0.21 ± 0.41	0.04
Diabetes-related serious adverse events, *n*	1	4	
Hyperglycemia with ketosis events, *n*	1	3	
Other adverse events, *n*	36	38	
Adverse events per participants	0.77 ± 1.03	1.12 ± 1.20	0.11

Data are *n* (%) or mean ± SD, unless otherwise stated. *For binary outcomes, *P* values are based on Fisher exact test. For count variables and incidence rates, *P* values are based on a Poisson regression model.

5 participants in the CL group, and 5 events occurred in 5 participants in the control group. Seven DKA events occurred, three in the CL group and four in the control group. Details of the events are in Supplementary Table 12. Eight non-treatment-related serious adverse events occurred, one in the CL group and seven in the control group. A total of 74 other adverse events (36 CL, 38 control) were reported.

Participant Contacts

A higher number of unscheduled contacts were recorded in the CL group compared with the control group. Most of these contacts (69%) were related to the study device. Different sites had high variability in their reporting of unscheduled contacts.

CONCLUSIONS

The current study shows that after diagnosis of type 1 diabetes, improvements in glycemic control with hybrid CL insulin delivery are sustained over 48 months compared with standard therapy. These sustained improvements in glycemic control do not appear to confer a protective effect on residual C-peptide secretion.

Residual C-peptide secretion, as measured by fasting C-peptide adjusted for fasting glucose, declined at a similar rate between treatment groups over 48 months. Decline appeared most rapid in the first 24 months following diagnosis, with slowing but ongoing decline evident between 24 and 48 months across treatment groups (Fig. 1). In keeping with results from the primary study phase (19), there was no difference in fasting C-peptide adjusted for fasting glucose between groups at 36 or 48 months, despite significantly lower HbA_{1c} and higher time in target glucose range in the CL group. Large observational studies have shown DKA at diagnosis is associated with higher HbA_{1c} levels and less residual β-cell function over time (23,24), and a higher number of participants in the CL group presented with DKA. However, a recent secondary analysis comparing glycemic outcomes in 51 children using CL in the primary study phase over 24 months showed no difference in C-peptide area under the curve or time in target range between those who did and did not present with DKA at diagnosis, suggesting that even if β-cell decline is faster in those with DKA at diagnosis, CL therapy appears to mitigate this effect (25). A shorter 12-month study comparing hybrid CL insulin delivery with standard care plus continuous glucose monitoring in 113 participants aged 7 to 17 years also showed a decline in residual C-peptide secretion, with no difference between groups, despite a significantly higher time in target glucose range in the CL group and similar rates of DKA at diagnosis in both groups (26). These results suggest that the level of optimized glycemic control achievable with currently available CL systems is not able to preserve endogenous insulin secretion.

The benefits in improved glycemic control in the CL group compared with control that were observed in the first 24 months (primary study phase) remained until 48 months after diagnosis. Hybrid CL insulin delivery is highly effective as a long-term therapy, with mean time in target range of 3.9 to 10.0 mmol/L 12 percentage points higher and HbA_{1c} 0.9% (10 mmol/mol) lower in the CL compared with control group at 48 months. Notably, time in target range of 3.9 to 10.0 mmol/L deteriorated in both groups over time. This is in keeping with the general epidemiological trends observed during adolescence in larger registry studies (4–6). However, use of CL continued to confer significant benefits, with a $>$10 percentage point mean difference in time in range between 24 and 48 months compared with standard therapy. This difference persisted despite an accompanying increased use of continuous glucose sensors and hybrid CL systems in the control group. These results compare well with findings of a recent meta-analysis, where pooled data from studies ranging from 3 days to 2 years in length showed an improvement in time in range of 11 percentage points with hybrid CL insulin delivery compared with standard therapy in children and adolescents with type 1 diabetes (27). Time in target range was higher at 78% in the CL group in a 12-month trial by McVean et al. (26); however, this study incorporated an intensive approach, with study contacts every 1 to 2 weeks. The present extension phase is more representative of a real-life approach with 3-monthly study contacts, in keeping with current clinical practice in the U.K. where 3-monthly clinic visits represent standard care for children and young people with type 1 diabetes.

Despite high insulin pump (39%) and glucose sensor use (94%), only 9% of participants in the control group reached the target HbA_{1c} $<$48 mmol/mol ($<$6.5%), compared with 34% in the CL group. More than half of participants in the CL group had an HbA_{1c} of $<$53 mmol/mol (7.0%) compared with one-quarter in the control group, sustained over 4 years. This is particularly significant in the adolescent age-group, where glycemic targets are less likely to be met than in younger children or adults. Large scale registry data from Europe, the U.S., Canada,

Australia, and India show a mean HbA_{1c} ranging from 63 to 77 mmol/mol (7.9–9.2%) in the adolescent age group using standard therapies (4,6). Our study outcomes highlight the long-term benefits of commencing hybrid CL at diagnosis in young people with type 1 diabetes, including mitigating some of the factors leading to the deterioration in glycemic control usually observed in this age-group. Evidence from the Epidemiology of Diabetes Interventions and Complications (EDIC) study has shown clear benefits of early intensive therapy in type 1 diabetes (7). Thus, hybrid CL insulin delivery should be considered for all youth from diagnosis of type 1 diabetes in clinical practice (28).

The time in hypoglycemia was higher than expected in both CL and control groups, with more time below range in the CL group at 36 months, although this difference was not statistically significant. We used the FreeStyle Libre Pro sensor to record glycemic data for both control and CL groups, due to its ability to record 14 days of masked glucose data. At the time the study was designed, this was the only available glucose sensor that could record this length of masked data without the need for calibration. It has been documented that 40% of the time when the FreeStyle Libre Pro Flash Glucose Monitoring System indicated values $\leq$3.3 mmol/L, actual glucose values (Yellow Spring Instrument [YSI] measurements) were between 4.5 and 8.9 mmol/L (29). Reassuringly, time in hypoglycemia ($<$3.9 mmol/L) in the CL group was 2.9 ± 1.2% based on Dexcom G6 sensor data.

Strengths of our study include the multicenter, randomized, parallel design and the 2-year extension phase duration (4 years total study duration). No exclusion criteria applied for the extension phase, and all participants in the primary study phase were invited to participate, minimizing selection bias. The study cohort is representative in ethnicity ($\sim$80% of youth with type 1 diabetes in the U.K. are White) and DKA at onset (approximately one-third present in DKA in the U.K.) (5). Clinical teams were free to optimize therapy and commence diabetes technology in the control group, including use of hybrid CL insulin delivery. Study interventions were minimal with 3-monthly contacts and annual fasting blood analysis, improving real-world generalizability of results.

Our study had certain limitations. There were more participants in the CL group compared with control (47 vs. 34) during the extension phase. This was partially due to a higher number of withdrawals in the control group during the primary study phase (6 vs. 4 in CL) and not all control participants choosing to continue in the extension phase (89% vs. 100% in CL). This lower retention observed in the control group is likely reflective of lower motivation due to not having access to CL technology via the study. However, overall retention was 78% over 48 months, high given the length of the current study. There were missing data points related to national restrictions during the coronavirus disease 2019 pandemic. We recorded a higher number of unscheduled contacts in the CL group, although these were inconsistent between sites.

In conclusion, hybrid CL insulin delivery for 48 months following diagnosis led to sustained improvements in glycemic control compared with standard therapy in young people with type 1 diabetes. These sustained improvements in glycemic control did not prevent the ongoing decline in residual C-peptide secretion.

Acknowledgments. The authors are grateful to study volunteers for their participation. They acknowledge support by the staff at the Addenbrooke's Wellcome Trust Clinical Research Facility. The authors thank the members of the Data Safety Monitoring Board and Trial Steering Committee for their oversight of the trial. The study was co-coordinated by Cambridge Clinical Trial Unit. Dexcom, Medtronic, and Abbott Diabetes Care representatives read the manuscript before submission.

No sponsor had any role in the study design, data collection, data analysis, data interpretation, or writing of the report.

Funding. This work was funded by the Leona M. and Harry B. Helmsley Charitable Trust (2016PG-T1D045 and 2016PG-T1D046), National Institute for Health Research Efficacy and Mechanism Evaluation (14/23/09) and JDRF (22-2013-266 and 2-RSC-2019-828-M-N). Additional support for the artificial pancreas work was received from National Institute for Health Research Cambridge Biomedical Research Centre and National Institute for Health Research Oxford Biomedical Research Centre. Abbott Diabetes Care supplied free glucose monitoring devices, and Dexcom supplied discounted continuous glucose monitoring devices. Medtronic supplied discounted insulin pumps, phone enclosures, continuous glucose monitoring devices, and pump consumables.

The views expressed are those of the author(s) and not necessarily those of the funders.

Duality of Interest. J.W. has received speaker honoraria from Ypsomed and Novo Nordisk. C.K.B. has received consulting fees from CamDiab and speaker honoraria from Ypsomed. M.E.W. reports patents related to closed-loop and being a consultant at CamDiab. S.H. serves as a member of Medtronic advisory board, is a director of Ask Diabetes Ltd providing training and research support in health care settings, and reports having received training honoraria from Medtronic and Sanofi and consulting fees for CamDiab. T.R. receives consultancy fees from Abbott Diabetes care and has received honoraria from Novo Nordisk for delivering educational meetings. R.E.J.B. reports receiving speaker honoraria from Eli Lilly and Springer Healthcare, reports sitting on the Novo Nordisk UK Foundation Research Selection Committee on a voluntary basis, acted as an independent advisor for Provent Bio, and received speaking honoraria from Sanofi and Medscape, which were donated to an education research fund. R.H. reports receiving speaker honoraria from Eli Lilly, Dexcom, and Novo Nordisk, receiving license and/or consultancy fees from B. Braun and Abbott Diabetes Care, patents related to closed-loop, and being director at CamDiab. No other potential conflicts of interest relevant to this article were reported.

Author Contributions. J.W., C.K.B., J.M.A., M.E.W., S.H., A.T., T.R., A.G., R.E.J.B., D.E., N.T., and F.M.C. screened and enrolled participants, provided patient care, and/or took study samples. J.W., M.E.W., R.B., P.C., and R.H. performed or supported data analysis, including the statistical analyses. J.W. and R.H. wrote the manuscript. C.K.B., J.M.A., M.E.W., T.R., A.G., R.E.J.B., D.E., N.T., F.M.C., and R.H. codesigned the study. A.T., T.R., A.G., R.E.J.B., D.E., N.T., and F.M.C. were the lead clinical investigators. J.S. supported study setup and randomization. G.D. undertook sample analysis. R.H. designed and implemented the glucose controller. All authors critically reviewed the manuscript and contributed to the interpretation of the results. R.B. and R.H. are the guarantors of this work and, as such, had full access to all the data in the study and take responsibility for the integrity of the data and the accuracy of the data analysis.

Prior Presentation. Parts of this study were presented as an abstract at the 84th Scientific Sessions of the American Diabetes Association, Orlando, FL, 21–24 June 2024.

Handling Editors. The journal editors responsible for overseeing the review of the manuscript were Cheryl A.M. Anderson and Emily K. Sims.

References

1. Todd JA. Etiology of type 1 diabetes. Immunity 2010;32:457–467

2. Patterson CC, Karuranga S, Salpea P, et al. Worldwide estimates of incidence, prevalence and mortality of type 1 diabetes in children and adolescents: results from the International Diabetes Federation Diabetes Atlas, 9th edition. Diabetes Res Clin Pract 2019;157:107842

3. Ward ZJ, Yeh JM, Reddy CL, et al. Estimating the total incidence of type 1 diabetes in children and adolescents aged 0-19 years from 1990 to 2050: a global simulation-based analysis. Lancet Diabetes Endocrinol 2022;10:848–858

4. Foster NC, Beck RW, Miller KM, et al. State of type 1 diabetes management and outcomes from the T1D Exchange in 2016-2018. Diabetes Technol Ther 2019;21:66–72
5. National Paediatric Diabetes Audit. Annual report 2020-2021: care processes and outcomes. Royal College of Paediatrics and Child Health, 2022. Accessed 19 February 2024. Available from https://www.rcpch.ac.uk/sites/default/files/2022-04/National%20NPDA%20report%202020-21%20Summary%20Report.pdf
6. Gerhardsson P, Schwandt A, Witsch M, et al. The SWEET Project 10-year benchmarking in 19 countries worldwide is associated with improved HbA1c and increased use of diabetes technology in youth with type 1 diabetes. Diabetes Technol Ther 2021;23:491–499
7. Diabetes Control and Complications Trial (DCCT)/Epidemiology of Diabetes Interventions and Complications (EDIC) Study Research Group. Intensive diabetes treatment and cardiovascular outcomes in type 1 diabetes: the DCCT/EDIC study 30-year follow-up. Diabetes Care 2016;39:686–693
8. Diabetes Control Complications Trial/Epidemiology of Diabetes Interventions Complications Study Research Group. Mortality in type 1 diabetes in the DCCT/EDIC versus the general population. Diabetes Care 2016;39:1378–1383
9. Lachin JM, McGee P, Palmer JP, DCCT/EDIC Research Group. Impact of C-peptide preservation on metabolic and clinical outcomes in the Diabetes Control and Complications Trial. Diabetes 2014;63:739–748
10. Steffes MW, Sibley S, Jackson M, Thomas W. Beta-Cell function and the development of diabetes-related complications in the diabetes control and complications trial. Diabetes Care 2003;26:832–836
11. Shah SC, Malone JI, Simpson NE. A randomized trial of intensive insulin therapy in newly diagnosed insulin-dependent diabetes mellitus. N Engl J Med 1989;320:550–554
12. Buckingham B, Beck RW, Ruedy KJ, et al.; Diabetes Research in Children Network Study Group Type 1 Diabetes TrialNet Study Group. Effectiveness of early intensive therapy on β-cell preservation in type 1 diabetes. Diabetes Care 2013;36:4030–4035
13. Ware J, Boughton CK, Allen JM, et al. Cambridge hybrid closed-loop algorithm in children and adolescents with type 1 diabetes: a multicentre 6-month randomised controlled trial. Lancet Digit Health 2022;4:e245–e255
14. Breton MD, Kanapka LG, Beck RW, et al. iDCL Trial Research Group. A randomized trial of closed-loop control in children with type 1 diabetes. N Engl J Med 2020;383:836–845
15. Brown SA, Kovatchev BP, Raghinaru D, et al.; iDCL Trial Research Group. Six-month randomized, multicenter trial of closed-loop control in type 1 diabetes. N Engl J Med 2019;381:1707–1717
16. Bergenstal RM, Nimri R, Beck RW, et al. A comparison of two hybrid closed-loop systems in adolescents and young adults with type 1 diabetes (FLAIR): a multicentre, randomised, crossover trial. Lancet 2021;397:208–219
17. Abraham MB, de Bock M, Smith GJ, et al.; Australian Juvenile Diabetes Research Fund Closed-Loop Research Group. Effect of a hybrid closed-loop system on glycemic and psychosocial outcomes in children and adolescents with type 1 diabetes: a randomized clinical trial. JAMA Pediatr 2021;175:1227–1235
18. Messer LH, Buckingham BA, Cogen F, et al. Positive impact of the bionic pancreas on diabetes control in youth 6-17 years old with type 1 diabetes: a multicenter randomized trial. Diabetes Technol Ther 2022;24:712–725
19. Boughton CK, Allen JM, Ware J, et al.; CLOuD Consortium. Closed-loop therapy and preservation of C-peptide secretion in type 1 diabetes. N Engl J Med 2022;387:882–893
20. Rankin D, Kimbell B, Hovorka R, Lawton J. Adolescents' and their parents' experiences of using a closed-loop system to manage type 1 diabetes in everyday life: qualitative study. Chronic Illn 2021;18:742–756
21. Rankin D, Kimbell B, Allen JM, et al. Adolescents' experiences of using a smartphone application hosting a closed-loop algorithm to manage type 1 diabetes in everyday life: qualitative study. J Diabetes Sci Technol 2020;15:1042–1051
22. National Institute for Health and Care Excellence. Diabetes (type 1 and type 2) in children and young people: diagnosis and management. NICE guideline NG18. Accessed 19 February 2024. Available from https://www.nice.org.uk/guidance/ng18
23. Duca LM, Wang B, Rewers M, Rewers A. Diabetic ketoacidosis at diagnosis of type 1 diabetes predicts poor long-term glycemic control. Diabetes Care 2017;40:1249–1255
24. Fredheim S, Johannesen J, Johansen A, et al.; Danish Society for Diabetes in Childhood and Adolescence. Diabetic ketoacidosis at the onset of type 1 diabetes is associated with future HbA1c levels. Diabetologia 2013;56:995–1003
25. Lakshman R, Najami M, Allen JM, et al. Diabetic ketoacidosis at onset of type 1 diabetes and glycemic outcomes with closed-loop insulin delivery. Diabetes Technol Ther 2024;26:198–202
26. McVean J, Forlenza GP, Beck RW, et al.; CLVer Study Group. Effect of tight glycemic control on pancreatic beta cell function in newly diagnosed pediatric type 1 diabetes: a randomized clinical trial. JAMA 2023;329:980–989
27. Zeng B, Gao L, Yang Q, Jia H, Sun F. Automated insulin delivery systems in children and adolescents with type 1 diabetes: a systematic review and meta-analysis of outpatient randomized controlled trials. Diabetes Care 2023;46:2300–2307
28. Ghatak A, Boughton CK, Allen JM, et al. Closed-loop from diagnosis of type 1 diabetes in children and young people. Diabetes Technol Ther 2023;25:673–674
29. Abbott Diabetes Care. FreeStyle Libre 14 Day User Manual. Flash Glucose Monitoring System. DOC39764 Rev. B 07/18; 2016