Six Months of Hybrid Closed-Loop Versus Manual Insulin Delivery With Fingerprick Blood Glucose Monitoring in Adults With Type 1 Diabetes: A Randomized, Controlled Trial

Diabetes Care 2020;43:3024–3033 | https://doi.org/10.2337/dc20-1447

*Sybil A. McAuley,[1,2] Melissa H. Lee,[1,2] Barbora Paldus,[1,2] Sara Vogrin,[1] Martin I. de Bock,[3,4,5,6] Mary B. Abraham,[3,4,5] Leon A. Bach,[7,8] Morton G. Burt,[9,10] Neale D. Cohen,[11] Peter G. Colman,[12] Elizabeth A. Davis,[3,4,5] Christel Hendrieckx,[13,14] D. Jane Holmes-Walker,[15,16] Joey Kaye,[17] Anthony C. Keech,[18] Kavita Kumareswaran,[7,11] Richard J. MacIsaac,[1,2] Roland W. McCallum,[19] Catriona M. Sims,[1] Jane Speight,[13,14] Stephen N. Stranks,[9,10] Vijaya Sundararajan,[20] Steven Trawley,[1,14,21] Glenn M. Ward,[1,2] Alicia J. Jenkins,[1,2,17] Timothy W. Jones,[3,4,5] and David N. O'Neal,[1,2] for the Australian JDRF Closed-Loop Research Group**

OBJECTIVE

To investigate glycemic and psychosocial outcomes with hybrid closed-loop (HCL) versus user-determined insulin dosing with multiple daily injections (MDI) or insulin pump (i.e., standard therapy for most adults with type 1 diabetes).

RESEARCH DESIGN AND METHODS

Adults with type 1 diabetes using MDI or insulin pump without continuous glucose monitoring (CGM) were randomized to 26 weeks of HCL (Medtronic 670G) or continuation of current therapy. The primary outcome was masked CGM time in range (TIR; 70–180 mg/dL) during the final 3 weeks.

RESULTS

Participants were randomized to HCL ($n = 61$) or control ($n = 59$). Baseline mean (SD) age was 44.2 (11.7) years, HbA_{1c} was 7.4% (0.9%) (57 [10] mmol/mol), 53% were women, and 51% used MDI. HCL TIR increased from (baseline) 55% (13%) to (26 weeks) 70% (10%) with the control group unchanged: (baseline) 55% (12%) and (26 weeks) 55% (13%) (difference 15% [95% CI 11, 19]; $P < 0.0001$). For HCL, HbA_{1c} was lower (median [95% CI] difference −0.4% [−0.6, −0.2]; −4 mmol/mol [−7, −2]; $P < 0.0001$) and diabetes-specific positive well-being was higher (difference 1.2 [95% CI 0.4, 1.9]; $P < 0.0048$) without a deterioration in diabetes distress, perceived sleep quality, or cognition. Seventeen (9 device-related) versus 13 serious adverse events occurred in the HCL and control groups, respectively.

CONCLUSIONS

In adults with type 1 diabetes, 26 weeks of HCL improved TIR, HbA_{1c}, and their sense of satisfaction from managing their diabetes compared with those continuing with user-determined insulin dosing and self-monitoring of blood glucose. For most people living with type 1 diabetes globally, this trial demonstrates that HCL is feasible, acceptable, and advantageous.

[1]*Department of Medicine, University of Melbourne, Melbourne, Victoria, Australia*
[2]*Department of Endocrinology and Diabetes, St Vincent's Hospital Melbourne, Fitzroy, Victoria, Australia*
[3]*Department of Endocrinology and Diabetes, Perth Children's Hospital, Nedlands, Western Australia, Australia*
[4]*Telethon Kids Institute, University of Western Australia, Nedlands, Western Australia, Australia*
[5]*School of Paediatrics and Child Health, University of Western Australia, Nedlands, Western Australia, Australia*
[6]*Department of Paediatrics and Child Health, University of Otago, Wellington, New Zealand*
[7]*Department of Endocrinology and Diabetes, The Alfred, Melbourne, Victoria, Australia*
[8]*Department of Medicine (Alfred Medical Research and Education Precinct), Monash University, Melbourne, Victoria, Australia*
[9]*Southern Adelaide Diabetes and Endocrine Services, Flinders Medical Centre, Bedford Park, South Australia, Australia*
[10]*College of Medicine and Public Health, Flinders University, Bedford Park, South Australia, Australia*
[11]*Baker Heart and Diabetes Institute, Melbourne, Victoria, Australia*
[12]*Department of Diabetes and Endocrinology, Royal Melbourne Hospital, Parkville, Victoria, Australia*
[13]*School of Psychology, Deakin University, Geelong, Victoria, Australia*
[14]*Australian Centre for Behavioural Research in Diabetes, North Melbourne, Victoria, Australia*
[15]*Department of Diabetes and Endocrinology, Westmead Hospital, Westmead, New South Wales, Australia*
[16]*Sydney Medical School, University of Sydney, Camperdown, New South Wales, Australia*

Despite recent significant therapeutic advances for type 1 diabetes, only modest improvements in glycemia, health, and quality of life have been achieved (1,2). Together with glucose monitoring, intensive insulin therapy via multiple daily injections (MDI) or continuous subcutaneous insulin infusion (pump) is a core strategy of current type 1 diabetes management. However, maintaining optimal glycemia with manual determination of insulin dosing remains challenging, and recommended targets are met by a minority of people with type 1 diabetes (3,4). Closed-loop (CL) systems with automated insulin delivery help address these challenges. Hybrid CL (HCL) systems involve automated basal delivery and a user-initiated component for (meal or high glucose correction) boluses (5). Meta-analyses of early CL trials suggest improved glycemia compared with manual insulin dose determination (6,7). CL research has greatly increased recently (8). Randomized trials have shown glucose benefits with HCL over sensor-augmented pump therapy for 3 and 6 months in outpatient settings (9,10). However, most previous HCL studies have incorporated sensor-augmented pumps as the comparator (6,7,9,10) and are of limited relevance to the majority of people with type 1 diabetes globally. Continuous glucose monitoring (CGM) uptake has been relatively low worldwide, being highest in the U.S., where ~29% of adults with type 1 diabetes were CGM users in 2018 (2), and lower in other countries with limited reimbursement by national authorities or health insurance companies. For example, the Australasian Diabetes Data Network reported in 2019 that only 13% of adults used CGM (11). Consequently, most adults with type 1 diabetes managed with MDI or pump undertake home self-monitoring of blood glucose (SMBG).

Furthermore, studies to date have focused almost exclusively on metabolic outcomes in spite of recognition that psychological and cognitive factors are important in their own right and can also influence glycemia, with associations between increasing diabetes-specific distress and dysglycemia (12). In keeping, some studies have shown that use of diabetes technologies (including short-term use of HCL) is associated with reductions in diabetes distress (13,14). Among adults with type 1 diabetes, inadequate sleep quality has been associated with increased fear of hypoglycemia, greater nocturnal glycemic variation, and reduced insulin sensitivity (15,16), with experimentally induced sleep deprivation producing a prolonged state of cognitive impairment and hypoglycemic symptoms post-recovery (17). Therefore, HCL systems will be of greatest benefit if, in addition to improving glycemia, they also substantially reduce the psychological and cognitive burden of living with type 1 diabetes. Messer et al. (18) have conducted human-factors research in youth using Medtronic 670G. Corresponding research involving adults is lacking, with longer-term intervention trials needed focusing on both glycemia and holistic outcomes such as psychosocial well-being, sleep quality, and cognitive function.

The first commercial HCL device is the MiniMed 670G system, available since 2017 after U.S. Food and Drug Administration approval based upon the findings from an uncontrolled, pivotal study (19). Randomized, controlled trial evidence has not yet been published. Therefore, we performed a randomized, controlled trial comparing HCL with the MiniMed 670G system versus usual care (manually determined insulin delivery by MDI or pump without real-time CGM) over 26 weeks. We examined glucose outcomes, psychosocial outcomes, cognition, and subjective sleep quality.

RESEARCH DESIGN AND METHODS

Study Design

We conducted an open-label, randomized, controlled, parallel-group clinical trial (Australian New Zealand Clinical Trials Registry ACTRN12617000520336) at seven tertiary hospitals in Australia comparing 26 weeks of HCL therapy with continuing standard diabetes care (without real-time CGM). The trial protocol (20) was approved by a central Human Research Ethics Committee (St Vincent's Hospital Melbourne), and governance was provided at each participating center. An independent Data Safety and Monitoring Board (DSMB) provided trial oversight.

The trial involved 16 study visits, including run-in and intervention periods. The run-in period was at least 5 weeks, with duration dependent on participants' individual preexisting carbohydrate counting and diabetes self-management knowledge determining their training requirements. During run-in, individualized education was provided by diabetes nurse educators and dietitians regarding diabetes self-management (including carbohydrate counting and use of an insulin bolus dose calculator). Participants using MDI were given an Accu-Chek Aviva Expert meter (Roche Diagnostics, Mannheim, Germany) with in-built bolus dose calculator and education regarding its use. Participants using pumps used the pump's bolus calculator. After education, participants undertook 3 weeks of baseline masked CGM, with a further 1–2 weeks if data were not available for ≥70% of the time. After run-in, participants were randomly assigned to use an HCL system (HCL group) or to continue their current diabetes therapy (control group) for a 26-week period.

The HCL group was trained in the use of the MiniMed 670G system (Medtronic, Northridge, CA) consisting of a glucose sensor (Enlite 3) and transmitter (GST3c MiniLink), coupled with an insulin pump

[17]Department of Endocrinology and Diabetes, Sir Charles Gairdner Hospital, Nedlands, Western Australia, Australia
[18]NHMRC Clinical Trials Centre, University of Sydney, Camperdown, New South Wales, Australia
[19]Department of Diabetes and Endocrinology, Royal Hobart Hospital, Hobart, Tasmania, Australia
[20]Department of Public Health, La Trobe University, Melbourne, Victoria, Australia
[21]The Cairnmillar Institute, Hawthorn East, Victoria, Australia

Corresponding author: David N. O'Neal, dno@unimelb.edu.au

Received 12 June 2020 and accepted 16 September 2020

Clinical trial reg. no. ACTRN12617000520336, www.anzctr.org.au

This article contains supplementary material online at https://doi.org/10.2337/figshare.13014374.

*A complete list of the members of the Australian JDRF Closed-Loop Research Group can be found in the supplementary material online.

incorporating a modified proportional integral derivative algorithm with insulin feedback (21). Target glucose is 120 mg/dL, with an optional increased temporary target of 150 mg/dL. Either insulin aspart or insulin lispro were used. Insulin boluses to manage meal-related insulin requirements and correction of elevated glucose levels were initiated by the participant, who entered an estimate of the amount of carbohydrate to be consumed into the pump and checked their capillary blood glucose level; an individualized insulin bolus was then advised by the pump, with delivery initiated by the participant. Control participants continued using their own personal insulin delivery device for 26 weeks, in conjunction with a bolus dose calculator (integrated within either their insulin pump or the glucose meter provided during run-in) to assist with meal-related dose estimation. All participants wore masked CGM (Guardian Sensor 3; Medtronic) to collect study outcome measurements at three time points: baseline prerandomization (for 3 weeks), mid-study (for 2 weeks), and study end (for 3 weeks). For participants randomized to HCL, the masked-CGM sensor was worn in addition to the 670G system's real-time CGM. Medtronic processed deidentified masked-CGM recordings using internal proprietary software and provided the raw data set to the research team for analysis. After completion of the final participant, Medtronic provided the de-identified CSV files of HCL pump downloads from randomization to study end to the research team for analysis.

Adverse events were collected throughout the trial. Reportable adverse events included serious adverse events, severe hypoglycemia (defined as hypoglycemia requiring assistance from another person to administer carbohydrate or glucagon or take other corrective actions), ketoacidosis, and adverse events occurring in association with a trial device.

Participants

Inclusion criteria were: aged between 25 and 75 years; a clinical diagnosis of type 1 diabetes for at least 1 year; HbA_{1c} level $\leq$10.5% ($\leq$91 mmol/mol); and MDI or insulin pump use. Purposive sampling ensured at least 40% of participants were on MDI or insulin pump. Exclusion criteria were: current real-time CGM use and use of any noninsulin glucose-lowering agent within the preceding 3 months. Complete eligibility criteria are provided in Supplementary Table 1.

Randomization

Randomization of participants to HCL or control post–run-in was via a central electronic database, with 1:1 computer-generated group allocation using minimization with three stratification variables: proportion of time in glucose range 70–180 mg/dL prerandomization ($\leq$50% or $>$50%); insulin delivery modality at enrollment (MDI or pump); and trial site. Clinical site investigators were responsible for trial implementation and medical care during the trial. Group allocation generation was designed by an investigator without trial involvement at the clinical sites. Allocation was masked to the trial statistical team and to all investigators undertaking data and laboratory analyses.

Outcomes

The primary outcome was the percentage of time that the masked CGM glucose measurements, at 23–26 weeks post-randomization, were in the target range of 70–180 mg/dL, termed time in range (TIR). Secondary glucose outcomes included: the proportion of time that glucose was above and below thresholds outside the target range, mean glucose, glucose SD, coefficient of variation (CV), and HbA_{1c}. Glucose metrics were calculated separately for overall (0000–2359 h), daytime (0600–2359 h), and nighttime (0000–0559 h). HbA_{1c} measurement used laboratory Bio-Rad D-100 analyzers certified by the NGSP as having traceability to the DCCT. These glucose outcomes are consistent with those recommended by current consensus guidelines (22,23). Intermediate-term glycemia (over $\sim$2 weeks) was measured by serum 1,5-anhydroglucitol (GlycoMark, Inc., New York, NY).

Nonglucose-related secondary outcomes included: clinical measures (change in total daily dose of insulin and basal/bolus proportions, change in insulin-to-carbohydrate ratio, and change in body weight); psychosocial measures (diabetes treatment satisfaction [Diabetes Treatment Satisfaction Questionnaires (DTSQs)], diabetes distress [Problem Area in Diabetes scale (PAID)], diabetes-specific positive well-being [four-item subscale of the W-BQ28], and diabetes-specific quality of life [DAWN2 Impact of Diabetes Profile (DIDP)]); cognitive functioning (Prospective and Retrospective Memory Questionnaire [PRMQ]), and subjective sleep quality (Pittsburgh Sleep Quality Index [PSQI]) (see published protocol [20]). Safety outcomes were frequency of severe hypoglycemia, diabetic ketoacidosis, adverse events related to the trial device, and any other untoward medical occurrence. Health economic outcomes, electrocardiograph profiles, and biomarkers of novel vascular risk factors will be reported separately.

Statistical Analysis

A sample size of 120 randomized in a 1:1 ratio (HCL/control) provides 80% power with a type I error rate (two-sided) of 5% to reject the null hypothesis of no between-group difference in the proportion of TIR, assuming that the proportion of TIR with intervention would be at least 5% higher than in the control group, with a common SD of 9%, allowing for a dropout rate of 10%.

Data from all randomized participants were analyzed on an intention-to-treat basis. Missing data were replaced under a "missing at random" assumption and were multiply imputed using a multivariate normal regression imputation method, with imputations performed separately for each treatment arm. Sensitivity analyses of the primary outcome included changing the missing data replacement assumption to "missing completely at random" and to "missing not at random" as well as to the per-protocol population. The primary and main secondary outcomes are presented in this study. In addition, a prespecified subgroup analysis was undertaken according to baseline insulin delivery modality. Other secondary outcomes were analyzed separately after these main analyses were performed. Analyses of data for key outcomes were validated by an independent biostatistician.

To test for the effect of treatment allocation on outcomes, an ANCOVA was conducted, adjusting for treatment arm and baseline percentage time in target range. Where ANCOVA assumptions were violated, a rank-sum test was performed. Safety outcomes were analyzed as counts of events for each treatment group and the proportion of participants experiencing at least one event in each treatment group. The statistical analysis plan was published prior to the completion of the study visits (24). All *P* values are two-tailed. Analyses were performed with

STATA version 15.1, R version 3.5.2, and R Studio version 1.2.5033.

Role of the Funding Sources
JDRF Australia provided input into the trial design. The funders of the trial had no role in data collection, data analysis, data interpretation, or writing of the report. The corresponding author had full access to all of the data in the trial and had final responsibility for the decision to submit for publication.

RESULTS

Trial participants ($n = 150$) were recruited between 26 April 2017 and 24 January 2019. Between 28 June 2017 and 2 May 2019, a total of 120 participants were randomized to the HCL group ($n = 61$) or the control group ($n = 59$). Sixty-four (53%) of the participants were women. Participants' ages ranged from 25 to 70 years, their duration of diabetes from 1 to 59 years, and their HbA_{1c} at enrollment from 5.7 to 10.4% (39–90 mmol/mol). Insulin pumps were being used by 59 participants (49%). The baseline characteristics of the HCL and control groups were balanced (Table 1). In total, 110 randomized participants completed the trial (Supplementary Fig. 1). Missing data for each of the outcomes are presented in Supplementary Table 2.

In the primary analysis of the entire trial population (Table 2), the mean (SD) percent TIR increased for those assigned to HCL from 55% (13%) at baseline to 70% (10%) at study end and remained unchanged in control participants, with 55% (12%) at baseline and 55% (13%) at study end (difference 15% [95% CI 11, 19]; $P < 0.0001$). There was no effect of sex on primary outcome. In the complete case population analysis ($n = 100$), using a missing-completely-at-random assumption, the between-arm difference in TIR at study end was 15% (14, 16) ($P < 0.0001$). Sensitivity analyses of the primary outcome showed similar results: the difference between arms after adjustment for stratification variables was 14.5% (10.7, 18.2), and with missing data imputed under a missing-not-at-random assumption, the differences were 16.9% (12.8, 21.0) and 12.7% (8.7, 16.8) for −1 SD and 1 SD, respectively.

The treatment effect was evident at 3 months (Supplementary Table 3). All secondary glucose outcomes at 26 weeks favored the intervention group, with less time in each of the low and high glucose ranges, lower mean glucose, lower glucose SD and CV, lower HbA_{1c}, and higher 1,5-anhydroglucitol levels compared with standard therapy (Table 2 and Fig. 1).

Total daily insulin dose did not change between randomization and study end in either group, and there was no between-arm difference at study end. There was a larger mean (SD) decrease in proportional basal insulin use with HCL (HCL −5.4% [16.9%] vs. control 1.9% [8.2%]; $P = 0.0034$) and a larger increase in proportional bolus insulin use by study end (HCL 5.0% [17.0%] vs. control −1.6% [8.1%]; $P = 0.0067$). Body weight did not change between randomization and study end for either group. There was no between-arm difference in change in body weight at study end ($P = 0.77$).

Psychosocial, cognitive, and sleep quality outcomes are presented in Table 2. At 26 weeks, compared with the control group, HCL participants had better diabetes-specific positive well-being (four-item subscale of W-BQ28: 1.2 [0.4, 1.9]; $P = 0.0048$) and better diabetes-specific quality of life (DIDP: −0.3 [−0.6, 0.0]; $P = 0.023$). Diabetes treatment satisfaction, diabetes distress, prospective or retrospective cognitive functioning, and subjective sleep quality did not differ at study end.

The total number of study visits (in-person, e-mail, and phone) for HCL participants was greater than for the control group (median [interquartile range (IQR)] 31 [23, 38] vs. 19 [15, 24] visits; $P < 0.001$) as was time spent with HCL participants for study activities, education,

Table 1—Participant baseline characteristics

	HCL group ($n = 61$)	Control group ($n = 59$)
Age, years	43.7 (11.7)	44.7 (11.8)
Sex		
Women	33 (54)	31 (53)
Men	28 (46)	28 (47)
Socioeconomic status of area of residence in upper 50th percentile	48 (79)	52 (88)
BMI, kg/m^2	26.8 (5.3)	26.0 (4.0)
Diabetes duration, years	24.0 (12.0)	24.1 (12.5)
Insulin delivery modality		
Pump	31 (51)	28 (47)
MDI	30 (49)	31 (53)
Insulin TDD/weight (units/kg)	0.51 (0.41, 0.63)	0.54 (0.45, 0.66)
HbA_{1c} at enrollment		
%	7.8 (1.1)	7.7 (0.9)
mmol/mol	62 (12)	61 (10)
HbA_{1c} at randomization		
%	7.4 (0.9)	7.5 (0.8)
mmol/mol	57 (10)	58 (9)
C-peptide, pmol/mL	0.01 (0, 0.03)	0 (0, 0.01)
Carbohydrate counting	51 (84)	51 (86)
Microvascular complications: history	19 (31)	15 (25)
Macrovascular complications: history	4 (7)	6 (10)
Diabetic ketoacidosis: history of any event during the preceding 12 months	2 (3)	2 (3)
Severe hypoglycemia: history of any event during the preceding 12 months	8 (13)	6 (10)
Severe hypoglycemia: number of reported events during the preceding 12 months*	1.5 (1, 5)	2 (1, 4)
Hypoglycemia awareness (Gold score)	3 (2, 4)	2 (2, 4)
Severe diabetes distress (PAID score ≥40)	15 (25)	12 (20)
Inadequate sleep quality (PSQI >5)	34 (55)	31 (52)

Continuous data are presented as mean (SD) or median (IQR). Categorical data are presented as frequency (%). TDD, total daily dose. *Within subgroup of participants who experienced any severe hypoglycemia event.

Table 2—Primary and secondary glucose and clinical and psychosocial outcomes

	Baseline prerandomization		Study end			
	HCL group (n = 61)	Control group (n = 59)	HCL group (n = 61)	Control group (n = 59)	Difference HCL − control	P value
Percentage of time glucose 70–180 mg/dL*	55.2 (13.4)	54.5 (11.8)	69.9 (9.5)	54.7 (12.7)	14.8 (11.0, 18.5)	<0.0001
Percentage of time glucose 70–140 mg/dL*	34.5 (11.1)	33.1 (11.9)	44.1 (8.5)	33.6 (12.0)	9.7 (6.3, 13.2)	<0.0001
Percentage of time glucose <70 mg/dL†	4.6 (2.0, 7.6)	4.0 (2.3, 6.3)	1.8 (1.1, 3.4)	3.8 (2.9, 5.2)	−2.0 (−2.5, −1.3)	<0.0001
Percentage of time glucose <59 mg/dL†	1.8 (0.9, 3.4)	1.7 (0.8, 2.9)	0.6 (0.3, 1.3)	1.4 (1.0, 2.3)	−0.8 (−1.1, −0.6)	<0.0001
Percentage of time glucose <54 mg/dL†	0.8 (0.3, 1.9)	0.9 (0.4, 1.6)	0.2 (0.1, 0.8)	0.9 (0.4, 1.5)	−0.6 (−0.8, −0.3)	<0.0001
Percentage of time glucose <50 mg/dL†	0.5 (0.1, 1.5)	0.6 (0.3, 1.1)	0.1 (0.1, 0.5)	0.6 (0.2, 1.3)	−0.4 (−0.6, −0.2)	<0.0001
Percentage of time glucose >180 mg/dL*	39.2 (15.4)	40.7 (13.7)	27.6 (9.5)	40.3 (14.4)	−12.0 (−16.1, −7.9)	<0.0001
Percentage of time glucose >200 mg/dL†	11.6 (6.3, 20.3)	11.9 (8.9, 20.5)	5.7 (3.5, 8.3)	13.3 (9.8, 17.7)	−7.5 (−5.6, −9.4)	<0.0001
Percentage of time glucose >250 mg/dL†	3.7 (1.9, 7.4)	3.9 (1.7, 7.7)	1.3 (0.5, 2.8)	4.3 (2.8, 6.8)	−2.9 (−2.1, −3.5)	<0.0001
Mean glucose, mg/dL*	169 (27)	173 (25)	157 (14)	171 (23)	−13 (−20, −7)	0.00014
Glucose SD*	67 (13)	68 (13)	54 (11)	67 (13)	−13 (−16, −7)	<0.0001
Glucose CV*	39.7 (6.0)	39.4 (5.0)	34.7 (4.5)	39.3 (5.4)	−4.7 (−6.5, −2.9)	<0.0001
Fasting capillary blood glucose*	167 (76)	166 (72)	155 (54)	171 (76)	−18 (−29, −7)	0.0017
HbA_{1c}, %*	7.4 (0.9)	7.5 (0.8)	7.0 (0.6)	7.4 (0.8)	−0.4 (−0.6, −0.2)	<0.0001
HbA_{1c}, mmol/mol*	57 (10)	58 (9)	53 (7)	57 (9)	−4 (−7, −2)	<0.0001
1,5-Anhydroglucitol, μg/mL†	3.4 (2.2, 4.6)	3.0 (1.7, 5.4)	4.9 (3.4, 6.8)	3.3 (1.8, 5.2)	1.6 (0.7, 2.3)	0.00046
Insulin TDD, units†	38 (32, 52)	40 (31, 51)	38 (31, 46)	42 (34, 49)	—	—
Change in insulin TDD, units†	—	—	−1.2 (−5.8, 3.1)	−0.5 (−4.8, 2.9)	−0.6 (−2.9, 2.5)	0.64
Insulin TDD/weight, units/kg†	0.51 (0.41, 0.63)	0.54 (0.45, 0.66)	0.50 (0.43, 0.57)	0.54 (0.48, 0.60)	—	—
Change in insulin TDD /weight, units/kg†	—	—	−0.01 (−0.10, 0.03)	−0.02 (−0.10, 0.04)	−0.01 (−0.04, 0.03)	0.85
Basal insulin proportion, %*	51 (13)	50 (13)	46 (14)	52 (12)	—	—
Change in basal insulin proportion, %*	—	—	−5.4 (16.9)	1.9 (8.2)	−6.7 (−11.1, −2.3)	0.0034
ICR†	9.8 (7.3, 13.5)	9.7 (7.3, 12)	9.1 (6.8, 11.9)	8.7 (7.6, 10.5)	—	—
Change in ICR†	..	..	−1.2 (−2.4, 0.0)	0.0 (−0.8, 0.0)	−0.8 (−1.4, −0.1)	0.0078
Body weight, kg†	79.4 (66.7, 89.3)	74.4 (65.8, 86.0)	81.3 (68.4, 91.7)	74.3 (69.0, 83.6)	—	—
Change in body weight, kg†	—	—	0.6 (−1.9, 2.1)	0.7 (−0.7, 1.5)	−0.1 (−1.1, 0.9)	0.77
Diabetes treatment satisfaction: DTSQs*	26.0 (5.1)	26.1 (5.1)	28.2 (5.9)	27.3 (5.1)	1.0 (−0.8, 2.7)	0.29
Diabetes distress: PAID‡	20.0 (12.5, 38.8)	17.5 (11.9, 34.4)	16.7 (10.2, 27.4)	21.2 (9.5, 36.2)	−17 (−33, 3)	0.10
Impact of diabetes on quality of life: DIDP*	4.7 (0.8)	4.7 (0.7)	4.5 (0.9)	4.8 (0.7)	−0.3 (−0.6, 0.0)	0.023
Diabetes-specific positive well-being: four-item subscale of W-BQ28*	6.5 (2.4)	6.9 (2.4)	7.8 (2.4)	6.8 (2.6)	1.2 (0.4, 1.9)	0.0048
Prospective memory: PRMQ Prospective†	17 (13, 22)	17 (14, 22)	17 (14, 20)	18 (15, 24)	−1.0 (−3.0, 0.0)	0.11
Retrospective memory: PRMQ Retrospective†	14 (11, 18)	13 (11, 17)	15 (11, 18)	15 (12, 17.5)	0.0 (−2.0, 2.0)	0.87
Perceived sleep quality: PSQI*	6.4 (3.2)	6.1 (3.2)	6.5 (3.1)	5.8 (3.0)	0.5 (−0.5, 1.5)	0.34

ICR, insulin-to-carbohydrate ratio; TDD, total daily dose. *Results presented as mean (SD) or mean difference (95% CI); analysis using ANCOVA with adjustment for baseline value. †Results presented as median (IQR) or median difference (95% CI); analysis using rank-sum test. ‡Results presented as median (IQR) or percentage difference (95% CI); analysis using ANCOVA with adjustment for baseline value with outcome log-transformed. Glucose levels are presented in milligrams per deciliter.

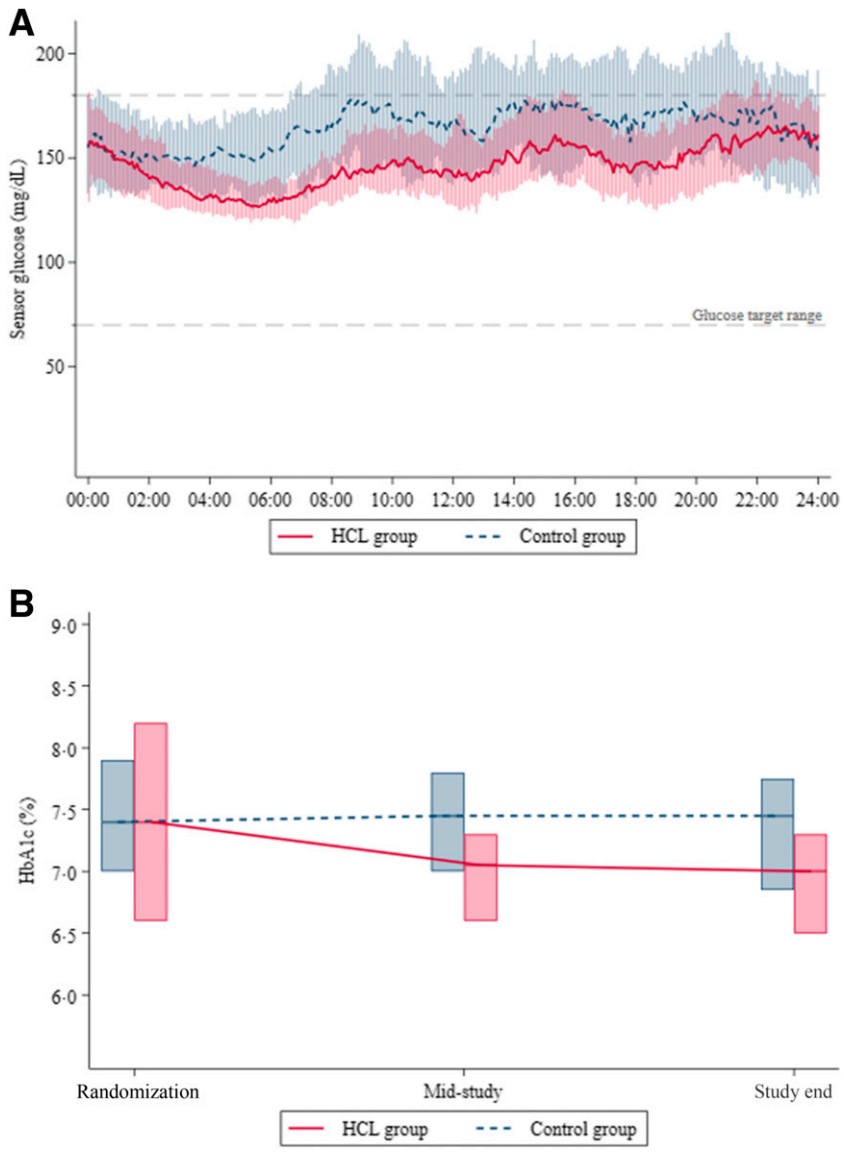

Figure 1—Glucose levels with HCL vs. control. *A* shows sensor glucose during the final 3 weeks of the trial. Lines denote median values, and shaded regions represent IQRs. Participants randomized to HCL therapy are shown by a red solid line; participants randomized to control (continuation of usual diabetes therapy) are shown by a blue dashed line. *B* shows HbA_{1c}. Boxes represent HbA_{1c} level at randomization, mid-study, and study end among participants assigned either HCL therapy (red) or control (blue). The lines represent the medians, and the bottom and top of each box represent the 25th and 75th percentiles.

and review of pump settings compared with control participants (27 [21, 32] vs. 14 [11, 19] hours; $P < 0.001$).

Compared with those already using pumps, participants using MDI at baseline required twice as long to achieve initial HCL activation (median [IQR] 28 [17, 35] days vs. 14 [9, 20] days, respectively). In the prespecified subgroup analyses by baseline insulin delivery modality (MDI or pump), both subgroups independently each had similar, significant glucose benefits from HCL (Fig. 2).

In the prespecified CGM analysis with daytime and night analyzed separately, the effect of HCL was evident for both periods with higher TIR, less time in hyperglycemia and hypoglycemia, and lower mean glucose, glucose SD, and CV. A slightly larger effect of HCL was seen at night than daytime for these parameters, other than mean glucose (Supplementary Fig. 2).

Analysis of CGM and insulin delivery data downloaded from the study pumps indicate that TIR increased to 70% post-randomization, which persisted until study end (Supplementary Fig. 4), and median (IQR) percent time CGM use was 84% (77, 89) with percent CGM time in HCL of 89% (84, 93). Supplementary Table 4 summarizes the CGM data pre- and post-HCL activation, showing that the increase in TIR occurred shortly following HCL activation. Overall, the median (IQR) percent time CGM use from first HCL activation to study end was 91% (84, 94), and percent CGM time in HCL was 94% (89, 97). For those assigned to HCL, the median number of calibrations per day was 3.5 (3, 4).

Safety outcomes were monitored by the DSMB; no trial intervention was undertaken. The number of serious adverse events after randomization by assigned group was 17 and 13 in the HCL and control groups, respectively (Table 3). The number of severe hypoglycemia events was eight and seven in the HCL and control groups, respectively. Overall, nine adverse events related to the trial device: four were episodes of severe hypoglycemia (two relating to the CL algorithm; one after a prandial bolus dose; and one overnight during open-loop insulin delivery with low-glucose suspend setting on); one was diabetic ketoacidosis; two were ketosis secondary to presumed insulin delivery line failure; one was ketosis after multiple pump suspensions; and one related to insulin infusion set dislodgement.

CONCLUSIONS

In this report of the first randomized, controlled trial with the MiniMed 670G, we found that 26 weeks of HCL improved CGM TIR by 15 percentage points compared with manual insulin dosing and SMBG for adults with type 1 diabetes. The comparator represents the current standard of resource provision for the majority of people with type 1 diabetes globally (25). The 15% difference in TIR translates to 3.6 additional hours per day within the healthy glucose range for HCL users compared with the control group. This TIR difference was achieved by reductions in time above and below predefined high and low glucose thresholds, respectively, with HCL improving all CGM parameters after the 26-week intervention. These improvements in CGM parameters were significant when analyzed over the entire 24 h, as well as during daytime and nighttime separately.

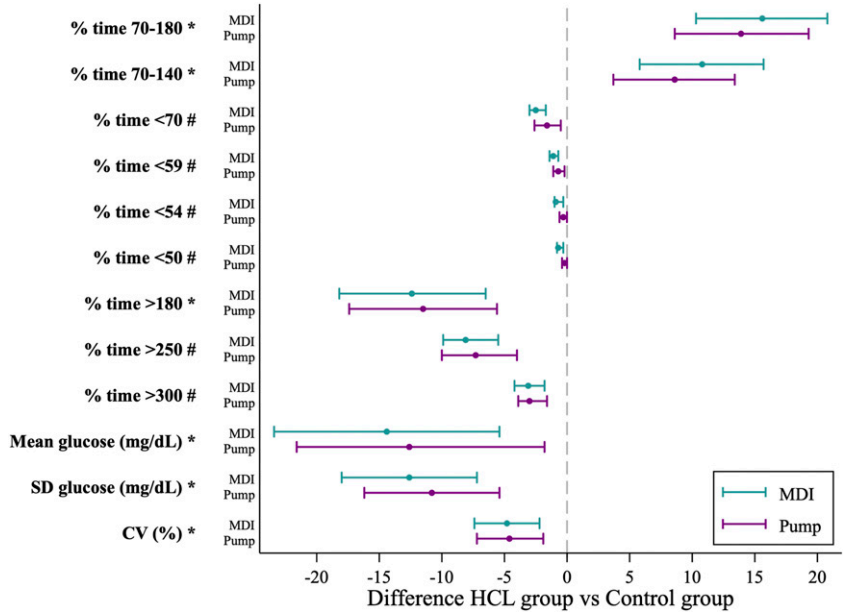

Figure 2—Subgroup analysis by baseline insulin delivery. Forest plot of differences in sensor glucose metrics at study end between participants assigned to HCL intervention vs. control, presented by insulin delivery at enrollment (MDI, aqua; pump, purple). Percent time glucose mg/dL. *Lines represent mean difference with adjustment for baseline values (95% CI). #Lines represent median difference (95% CI).

Analysis of downloaded pump data revealed that CGM use, HCL activation, and the TIR were durable. This contrasts with retrospective audits of U.S. clinic data in which significant discontinuation rates were observed (26–28). Differences in outcomes between our study and the aforementioned audits may relate to participant selection, the intensive education (including training on responding to alarms), level of health care professional and technical support, unrestricted access to consumables, and improvements in sensor configuration following the initial rollout of the technology.

The modest reduction in HbA_{1c} of 0.4% (4 mmol/mol) at 26 weeks reflected the observed reduction in both hyper- and hypoglycemia, as well as near-target average prerandomization HbA_{1c}. The improvement (increase) in 1,5-anhydroglucitol levels likely reflects diminished hyperglycemia, as the circulating levels of this naturally occurring metabolically inert polyol are lost via the urine with hyperglycemia. Importantly, differences in all measures of glycemia (CGM, 1,5-anydroglucitol, and HbA_{1c}), which vary in location (interstitial fluid, serum, and hemoglobin, respectively) and time frame, are concordant and favor the HCL versus control group.

Table 3—Safety outcomes: serious adverse events during randomized period

	HCL group (n = 61)	Control group (n = 59)
Any serious adverse event		
Number of events	17	13
Number of participants (%)	13 (21)	9 (15)
Number of events per 100 person-years	56	44
Severe hypoglycemia		
Number of events*	8	7
Number of events related to study device	4	—
Number of participants (%)	6 (10)	3 (5)
Diabetic ketoacidosis		
Number of events*	1	2
Number of events related to study device	1	—
Number of participants (%)	1 (2)	2 (3)
Any other untoward medical occurrence		
Number of events*	8	4
Number of events related to study device	4	—
Number of participants (%)	7 (11)	4 (7)

*Including number of events related to study device.

The TIR of 70% observed with HCL insulin delivery in this study was similar to the 72% TIR reported by the MiniMed 670G safety study (19), as well as that reported in 6-month studies by Kovatchev et al. (9) (with 64% TIR using a Roche Accu-Chek Spirit insulin pump or a Dexcom G4 or G5 sensor with inControl AP software) and Brown et al. (10) (with 71% TIR using a system comprising a Tandem Diabetes t:slim X2 insulin pump, a Dexcom G6 sensor, and the Control-IQ algorithm). The relatively greater improvement in overnight glycemia was also consistent with results of shorter-duration studies with various systems reported in two meta-analyses (6,7). This suggests that it is the conceptual approach of automated insulin delivery that has the major impact on glycemia rather than any specific algorithm or platform.

The control group in this trial reflects current resource provision for glucose management for the majority of adults living with type 1 diabetes. In Australia, where the trial was conducted, SMBG is the only subsidized monitoring option (regardless of mode of insulin delivery, with exception of specific groups [e.g., <21 years of age and pregnancy, which were exclusions in the present trial]). TIR improvement with HCL was independent of MDI or insulin pump use by participants at enrollment. The equivalent outcomes observed in each of these subgroups supports the benefit of HCL regardless of prior exposure to insulin pump therapy. Provision of detailed education during run-in regarding carbohydrate counting and diabetes self-management and the tools to facilitate prandial insulin dose calculation to all participants ensured that study outcomes were not influenced by differences in the ability to self-manage prandial insulin dosing. Our findings highlight that, with guidance and support, adults with type 1 diabetes who had less pretrial exposure to diabetes technologies experienced similar glycemic benefits with HCL to those who had previously used insulin pumps, which refutes

prior assumptions made by clinicians as well as experiences of participants in a shorter trial, some of whom expressed that HCL could be "too big a step" (29,30).

Notably, even in a sample with near-target baseline HbA_{1c}, the improvement in glycemia occurred with an increase in diabetes-specific positive well-being. Participants allocated HCL felt more positive about their diabetes and experienced a greater sense of satisfaction from managing the condition compared with those allocated to continue with MDI or insulin pump. The absence of an increase in diabetes treatment satisfaction or a reduction in diabetes distress in our trial may be explained by the counterbalancing of potential benefits with the burden of adding new technology to diabetes self-management and/or trial protocol requirements (26). This is consistent with some experiences reported in qualitative studies of HCL (30). While it is noteworthy that no deterioration in self-reported sleep quality was detected in the participants using HCL, this contrasts with the improved nighttime glycemic metrics observed in that group. It is possible that, as with the diabetes burden and treatment satisfaction measures, subjective sleep benefits were masked by sleep disruption from HCL therapy (31). The absence of any detectable increase in self-perceived memory failures among those managing HCL is encouraging, as these have been previously linked to forgetting medication among adults with type 1 diabetes (32). It is possible that longer studies, resulting in greater familiarity with HCL technology, could still result in improvements in the nonglycemic parameters discussed above.

Study strengths include a protocol with the control group reflecting current clinical practice, a holistic assessment of outcomes, and the robust implementation in clinical centers by health professionals engaged in the day-to-day clinical care of adults with type 1 diabetes. Protocol implementation was standardized across all seven sites. In this near-clinical setting, the trial withdrawal rate (8% postrandomization) was within the expected level. The primary outcome, measured with identical masked-CGM systems for both the intervention and control groups, ensured that collection of outcome data did not influence the participants' own responses to their glucose levels. CGM outcome measurements in the intervention group also did not impact the CL algorithm controlling insulin delivery, as a second independent sensor was in place (in addition to the sensor of the HCL system). Nonglucose secondary outcomes that are highly relevant to the health and lives of people with type 1 diabetes were robustly examined. Finally, the use of a commercially available HCL system enables rapid translation of study results into clinical practice.

There were limitations to the trial. As all study sites were tertiary diabetes centers, our study outcomes may not generalize to implementation of the technology by health care professionals with less type 1 diabetes technology experience or who are based outside specialized multidisciplinary team centers. Control group participants were not using real-time CGM, which can improve TIR and reduce hypoglycemia (33–35). However, it should be recognized that the most significant incremental health care cost relates to CGM provision and pump rather than incorporation of the algorithm itself into an insulin delivery system. This protocol included a single HCL system; the patient-reported outcomes reflect the users' experiences with this specific system. Outcomes are determined not only by device characteristics, but also by engagement and empowerment of the person using the device. While the implementation of the protocol was standardized, the impact of variation in the participants' type 1 diabetes education was not investigated formally.

A recent meta-analysis concluded that CL systems ranked best out of type 1 diabetes management technologies for TIR (36). However, we recognize that many people with type 1 diabetes may choose modes of insulin delivery (e.g., smart pens) and glucose monitoring (e.g., flash glucose monitoring) for reasons unrelated to glycemic management, such as ease of use, comfort, intrusiveness, and financial considerations (37). There is a need for CL technology, including the user interface, to evolve further to address these needs. Subsequent refinements to the Medtronic HCL platform have included broadened glucose and insulin delivery parameters permitting CL persistence with fewer alarms, automated correction boluses for hyperglycemia, lower glucose targets, and nonadjunctive use of sensor glucose (38), in addition to improvements in sensor performance. The ultimate CL goal is a system optimized to interface seamlessly with the user's needs while minimizing both the physical and psychological burden on the person with diabetes. There remains an ongoing requirement to evaluate future CL enhancements over longer periods and to include a range of holistic outcomes. Moreover, there is also a need for research to ensure that the model of care supporting implementation of this important technology uses resources effectively and enables people with type 1 diabetes to use these devices to their full potential so as to maximize human health.

Acknowledgments. The authors thank the study volunteers for participation. The authors also thank the trial nurses, diabetes educators, and dietitians at the clinical sites for the support; lead site trial nurse Sue-Anne Wyatt (St Vincent's Hospital Melbourne, Fitzroy, Victoria, Australia); DSMB members John Santamaria (St Vincent's Hospital Melbourne), Chris Cowell (Westmead Children's Hospital, Westmead, New South Wales, Austrlia), Val Gebski (NHMRC Clinical Trials Centre, University of Sydney, Camperdown, New South Wales, Australia), and Danny Liew (School of Public Health and Preventive Medicine, Monash University, Melbourne, Victoria, Australia); and central support by trial monitors Helen Pater and Sarah Mulray (NHMRC Clinical Trials Centre), 1,5-anhydroglucitol assays by Dr. Andrzej Januszewski (NHMRC Clinical Trials Centre), and database assistance by Dr. Adrienne Kirby (NHMRC Clinical Trials Centre).

Funding. This trial was funded by JDRF Australian Type 1 Diabetes Clinical Research Network (3-SRA-2016-351-M-B), a special initiative of the Australian Research Council, and the National Health and Medical Research Council of Australia (APP1099379). In-kind support was provided by Medtronic (HCL systems, masked CGM devices, and technical expertise with device issues) and Roche Diabetes Care (blood glucose meters for participants using MDI). S.A.M. is supported by a JDRF Research Award (5-ECR-2017-371-A-N). J.S. and C.H. are supported by core funding to the Australian Centre for Behavioural Research in Diabetes provided by the collaboration between Diabetes Victoria and Deakin University. A.J.J. is supported by a National Health and Medical Research Council Fellowship and is a Sydney Medical School Foundation Fellow. R.J.M. received research grants from the Rebecca L. Cooper Medical Research Foundation, St Vincent's Foundation, JDRF, Diabetes Australia Research Trust/Program, and the National Health and Medical Research Council of Australia. A.J.J. received research support from the National Health and Medical Research Council of Australia, JDRF Australia, and JDRF International.

JDRF Australia provided input into the trial design. The funders of the trial had no role in data collection, data analysis, data interpretation, or writing of the report.

Duality of Interest. S.A.M. reports support for research from Medtronic and speaker honoraria from Roche. M.H.L. reports speaker honoraria

from Medtronic. B.P. reports speaker honoraria fees from Medtronic. L.A.B. reports grant funding from AstraZeneca. N.D.C. reports personal fees from Medtronic and Abbott Laboratories and grant funds from Ypsomed Group. J.K. reports speaker fees from Novo Nordisk and AstraZeneca and advisory board fees from Abbott Diabetes Care. R.J.M. reports research grants from Novo Nordisk, Servier, Medtronic, and Grey Innovation; received honoraria for lectures from Eli Lilly and Company, Novo Nordisk, Sanofi, AstraZeneca, Merck Sharp & Dohme, Norvartis, and Boehringer Ingelheim; received travel support from Novo Nordisk, Sanofi, and Boehringer Ingelheim; is on the advisory boards for Novo Nordisk, Sanofi, Boehringer Ingelheim and Lilly Diabetes Alliance, and AstraZeneca; and has been a principal investigator for industry-sponsored clinical trials run by Novo Nordisk, Bayer, Janssen-Cilag, and AbbVie Inc. J.S. has served on advisory boards for Medtronic, Roche Diabetes Care, and Sanofi Diabetes; her research group (Australian Centre for Behavioural Research in Diabetes) has received honoraria for this advisory board participation and has also received unrestricted educational grants and/or in-kind support from Abbott Diabetes Care, AstraZeneca, Medtronic, Roche Diabetes Care, and Sanofi Diabetes; has received sponsorship to attend educational meetings from Medtronic, Roche Diabetes Care, and Sanofi Diabetes; and has received consultancy income or speaker fees from Abbott Diabetes Care, AstraZeneca, Medtronic, Novo Nordisk, Roche Diabetes Care, and Sanofi Diabetes. S.T. reports nonfinancial support from Abbott Diabetes Care. A.J.J. has received research support from Medtronic, Sanofi, Abbott Laboratories, and Mylan and has served on advisory boards for Medtronic, Sanofi, and Abbott Diabetes Care. D.N.O. has served on advisory boards for Abbott Laboratories, Medtronic, Merck Sharp & Dohme, Novo Nordisk, Roche, and Sanofi; received research support from Medtronic, Novo Nordisk, Roche, Eli Lilly and Company, and Sanofi; and received travel support from Novo Nordisk and Merck Sharp & Dohme. No other potential conflicts of interest were reported.

Author Contributions. D.N.O. led the study. S.A.M., M.I.d.B., E.A.D., A.C.K., J.S., V.S., S.T., A.J.J., T.W.J., and D.N.O. codesigned the study. L.A.B., M.G.B., N.D.C., P.G.C., D.J.H.-W., J.K., R.J.M., S.N.S., and G.M.W. contributed to refining the protocol. S.A.M., M.H.L., B.P., L.A.B., M.G.B., N.D.C., P.G.C., D.J.H.-W., J.K., R.J.M., R.W.M., S.N.S., G.M.W., and D.N.O. were responsible for participant screening and enrollment and informed consent and providing medical care. S.A.M. wrote the first draft of the report with input from D.N.O. S.V. and V.S. contributed to data analysis. S.A.M., S.V., C.H., J.S., V.S., S.T., A.J.J., and D.N.O. contributed to interpretation of the results. All authors critically reviewed the report. D.N.O. is the guarantor of this work and, as such, had full access to all of the data in the study and takes responsibility for the integrity of the data and the accuracy of the data analysis.

Prior Presentation. This work was presented at the 80th Scientific Sessions of the American Diabetes Association, 12–16 June 2020.

References

1. Nathan DM; DCCT/EDIC Research Group. The Diabetes Control and Complications Trial/Epidemiology of Diabetes Interventions and Complications study at 30 years: overview. Diabetes Care 2014;37:9–16
2. 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
3. Beck RW, Tamborlane WV, Bergenstal RM, Miller KM, DuBose SN, Hall CA; T1D Exchange Clinic Network. The T1D Exchange clinic registry. J Clin Endocrinol Metab 2012;97:4383–4389
4. McKnight JA, Wild SH, Lamb MJ, et al. Glycaemic control of type 1 diabetes in clinical practice early in the 21st century: an international comparison. Diabet Med 2015;32:1036–1050
5. Thabit H, Hovorka R. Coming of age: the artificial pancreas for type 1 diabetes. Diabetologia 2016;59:1795–1805
6. Weisman A, Bai JW, Cardinez M, Kramer CK, Perkins BA. Effect of artificial pancreas systems on glycaemic control in patients with type 1 diabetes: a systematic review and meta-analysis of outpatient randomised controlled trials. Lancet Diabetes Endocrinol 2017;5:501–512
7. Bekiari E, Kitsios K, Thabit H, et al. Artificial pancreas treatment for outpatients with type 1 diabetes: systematic review and meta-analysis. BMJ 2018;361:k1310
8. Boughton CK, Hovorka R. Automated insulin delivery in adults. Endocrinol Metab Clin North Am 2020;49:167–178
9. Kovatchev B, Anderson SM, Raghinaru D, et al.; iDCL Study Group. Randomized controlled trial of mobile closed-loop control [published correction appears in Diabetes Care 2020;43:1366]. Diabetes Care 2020;43:607–615
10. 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
11. Australasian Diabetes Data Network. Research, 2019. Accessed 12 June 2020. Available from https://www.addn.org.au/research
12. Hessler DM, Fisher L, Polonsky WH, et al. Diabetes distress is linked with worsening diabetes management over time in adults with type 1 diabetes. Diabet Med 2017;34:1228–1234
13. Sharifi A, De Bock MI, Jayawardene D, et al. Glycemia, treatment satisfaction, cognition, and sleep quality in adults and adolescents with type 1 diabetes when using a closed-loop system overnight versus sensor-augmented pump with low-glucose suspend function: a randomized crossover study. Diabetes Technol Ther 2016;18:772–783
14. Polonsky WH, Hessler D, Ruedy KJ, Beck RW; DIAMOND Study Group. The impact of continuous glucose monitoring on markers of quality of life in adults with type 1 diabetes: further findings from the DIAMOND randomized clinical trial. Diabetes Care 2017;40:736–741
15. Martyn-Nemeth P, Phillips SA, Mihailescu D, et al. Poor sleep quality is associated with nocturnal glycaemic variability and fear of hypoglycaemia in adults with type 1 diabetes. J Adv Nurs 2018;74:2373–2380
16. Rusu A, Bala C, Ciobanu D, Cerghizan A, Roman G. Sleep quality and sleep duration, but not circadian parameters are associated with decreased insulin sensitivity in type 1 diabetes. Chronobiol Int 2019;36:1148–1155
17. Inkster BE, Zammitt NN, Ritchie SJ, Deary IJ, Morrison I, Frier BM. Effects of sleep deprivation on hypoglycemia-induced cognitive impairment and recovery in adults with type 1 diabetes. Diabetes Care 2016;39:750–756
18. Messer LH, Berget C, Vigers T, et al. Real world hybrid closed-loop discontinuation: predictors and perceptions of youth discontinuing the 670G system in the first 6 months. Pediatr Diabetes 2020;21:319–327
19. Bergenstal RM, Garg S, Weinzimer SA, et al. Safety of a hybrid closed-loop insulin delivery system in patients with type 1 diabetes. JAMA 2016;316:1407–1408
20. McAuley SA, de Bock MI, Sundararajan V, et al. Effect of 6 months of hybrid closed-loop insulin delivery in adults with type 1 diabetes: a randomised controlled trial protocol. BMJ Open 2018;8:e020274
21. Steil GM, Palerm CC, Kurtz N, et al. The effect of insulin feedback on closed loop glucose control. J Clin Endocrinol Metab 2011;96:1402–1408
22. Maahs DM, Buckingham BA, Castle JR, et al. Outcome measures for artificial pancreas clinical trials: a consensus report. Diabetes Care 2016;39:1175–1179
23. International Hypoglycaemia Study Group. Glucose concentrations of less than 3.0 mmol/L (54 mg/dL) should be reported in clinical trials: a joint position statement of the American Diabetes Association and the European Association for the Study of Diabetes. Diabetes Care 2017;40:155–157
24. Australian New Zealand Clinical Trials Registry. Adult Hybrid Closed Loop Study (HCL Adult) Statistical Analysis Plan, 2019. Accessed 13 April 2020. Available from https://www.anzctr.org.au/Steps11and12/372617-(Uploaded-28-10-2019-11-59-34)-Study-related%20document.pdf
25. Graham C. Continuous glucose monitoring and global reimbursement: an update. Diabetes Technol Ther 2017;19:S60–S66
26. Berget C, Messer LH, Vigers T, et al. Six months of hybrid closed loop in the real-world: an evaluation of children and young adults using the 670G system. Pediatr Diabetes 2020;21:310–318
27. Lal RA, Basina M, Maahs DM, Hood K, Buckingham B, Wilson DM. One year clinical experience of the first commercial hybrid closed-loop system. Diabetes Care 2019;42:2190–2196
28. Akturk HK, Giordano D, Champakanath A, Brackett S, Garg S, Snell-Bergeon J. Long-term real-life glycaemic outcomes with a hybrid closed-loop system compared with sensor-augmented pump therapy in patients with type 1 diabetes. Diabetes Obes Metab 2020;22:583–589
29. Lawton J, Kimbell B, Rankin D, et al.; CLOuD Consortium. Health professionals' views about who would benefit from using a closed-loop system: a qualitative study. Diabet Med 2020;37:1030–1037
30. Hendrieckx C, Poole LA, Sharifi A, et al. "It is definitely a game changer": a qualitative study

of experiences with in-home overnight closed-loop technology among adults with type 1 diabetes. Diabetes Technol Ther 2017;19:410–416
31. Farrington C. Psychosocial impacts of hybrid closed-loop systems in the management of diabetes: a review. Diabet Med 2018;35:436–449
32. Trawley S, Baptista S, Pouwer F, Speight J. Prospective memory slips are associated with forgetting to take glucose-lowering therapies among adults with diabetes: results from the second Diabetes MILES - Australia (MILES-2) survey. Diabet Med 2019;36:569–577
33. Battelino T, Conget I, Olsen B, et al.; SWITCH Study Group. The use and efficacy of continuous glucose monitoring in type 1 diabetes treated with insulin pump therapy: a randomised controlled trial. Diabetologia 2012;55:3155–3162
34. Beck RW, Riddlesworth T, Ruedy K, et al.; DIAMOND Study Group. Effect of continuous glucose monitoring on glycemic control in adults with type 1 diabetes using insulin injections: the DIAMOND randomized clinical trial. JAMA 2017;317:371–378
35. Lind M, Polonsky W, Hirsch IB, et al. Continuous glucose monitoring vs conventional therapy for glycemic control in adults with type 1 diabetes treated with multiple daily insulin injections: the GOLD randomized clinical trial. JAMA 2017;317:379–387
36. Pease A, Lo C, Earnest A, Kiriakova V, Liew D, Zoungas S. Time in range for multiple technologies in type 1 diabetes: a systematic review and network meta-analysis. Diabetes Care 2020;43:1967–1975
37. Tanenbaum ML, Hanes SJ, Miller KM, Naranjo D, Bensen R, Hood KK. Diabetes device use in adults with type 1 diabetes: barriers to uptake and potential intervention targets. Diabetes Care 2017;40:181–187
38. Lee MH, Vogrin S, Paldus B, et al. Glucose control in adults with type 1 diabetes using a medtronic prototype enhanced-hybrid closed-loop system: a feasibility study. Diabetes Technol Ther 2019;21:499–506