Closed-Loop Insulin Delivery Versus Sensor-Augmented Pump Therapy in Older Adults With Type 1 Diabetes (ORACL): A Randomized, Crossover Trial

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OBJECTIVE

To assess the efficacy and safety of closed-loop insulin delivery compared with sensor-augmented pump therapy among older adults with type 1 diabetes.

RESEARCH DESIGN AND METHODS

This open-label, randomized (1:1), crossover trial compared 4 months of closed-loop versus sensor-augmented pump therapy. Eligible adults were aged ≥60 years, with type 1 diabetes (duration ≥10 years), using an insulin pump. The primary outcome was continuous glucose monitoring (CGM) time in range (TIR; 3.9–10.0 mmol/L).

RESULTS

There were 30 participants (mean age 67 [SD 5] years), with median type 1 diabetes duration of 38 years (interquartile range [IQR] 20–47), randomized ($n = 15$ to each sequence); all completed the trial. The mean TIR was 75.2% (SD 6.3) during the closed-loop stage and 69.0% (9.1) during the sensor-augmented pump stage (difference of 6.2 percentage points [95% CI 4.4 to 8.0]; $P < 0.0001$). All prespecified CGM metrics favored closed loop over the sensor-augmented pump; benefits were greatest overnight. Closed loop reduced CGM time <3.9 mmol/L during 24 h/day by 0.5 percentage points (95% CI 0.3 to 1.1; $P = 0.0005$) and overnight by 0.8 percentage points (0.4 to 1.1; $P < 0.0001$) compared with sensor-augmented pump. There was no significant difference in HbA_{1c} between closed-loop versus sensor-augmented pump stages (7.3% [IQR, 7.1–7.5] (56 mmol/mol [54–59]) vs. 7.5% [7.1–7.9] (59 mmol/mol [54–62]), respectively; $P = 0.13$). Three severe hypoglycemia events occurred during the closed-loop stage and two occurred during the sensor-augmented pump stage; no hypoglycemic events required hospitalization. One episode of diabetic ketoacidosis occurred during the sensor-augmented pump stage; no serious adverse events occurred during the closed-loop stage.

CONCLUSIONS

Closed-loop therapy is an effective treatment option for older adults with long-duration type 1 diabetes, and no safety issues were identified. These older adults had higher TIR accompanied by less time below range during closed loop than during sensor-augmented pump therapy. Of particular clinical importance, closed loop reduced the time spent in hypoglycemic range overnight.

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Older adults with type 1 diabetes are at greater risk of severe hypoglycemia and its sequelae than younger people with type 1 diabetes (1). For older adults, there can be additional clinical challenges to maintaining healthy glucose levels (2). These challenges may include diverse factors such as medical comorbidities, cognitive impairment, reduced dexterity and frailty. Moreover, with manual determination of insulin dosing, high levels of hypoglycemia are seen among older adults with long-duration type 1 diabetes (3).

Sensor-augmented pump therapy, integrating real-time continuous glucose monitoring (CGM) with manually dosed continuous subcutaneous insulin infusion via pump, reduces hypoglycemia without compromising HbA_{1c}; many modern systems incorporate threshold-based and predictive insulin suspension (4–6). Closed-loop systems, which automatically deliver subcutaneous insulin via pump with glucose-responsive dosing, can safely improve glycemia for individuals with type 1 diabetes (7–10). While previous randomized trials have demonstrated glucose benefits of closed-loop over sensor-augmented pump therapy among children and/or a broad age range of adults with type 1 diabetes, none have specifically targeted older adults. Recently, a single-arm study of 15 older adults with type 1 diabetes showed more favorable glucose metrics during 4 weeks of using closed-loop therapy compared with a preceding period using sensor-augmented pump therapy (11). However, it cannot be assumed that the safety and efficacy outcomes from randomized closed-loop trials involving younger individuals will be matched in older adults.

International consensus recommends relatively conservative CGM-based clinical targets in advanced age, independent of frailty and functional status (12). Consensus recommendations suggest a less stringent time in range (TIR) target of >50% for older adults with diabetes, compared with >70% for younger adults, while focusing on hypoglycemia avoidance (target <1% time with glucose <3.9 mmol/L). There is now randomized trial evidence from the Wireless Innovations for Seniors with Diabetes Mellitus (WISDM) study that for older adults with type 1 diabetes, use of real-time CGM reduces hypoglycemia while improving TIR (13). However, information to date regarding the potential usefulness of sensor-augmented pump and closed-loop technology specifically in older adults with type 1 diabetes is primarily from retrospective, pilot, and real-world studies, and randomized trial evidence is lacking (11,14–16). In the OldeR Adult Closed Loop (ORACL) trial, we aimed to address this issue by comparing safety and efficacy of closed-loop insulin delivery versus sensor-augmented pump therapy among older adults with type 1 diabetes. We hypothesized that closed-loop insulin delivery would be safe and improve CGM metrics among older adults with long-duration type 1 diabetes.

RESEARCH DESIGN AND METHODS

Study Design

We conducted an open-label, two-center, two-stage randomized, crossover trial comparing 4 months of closed-loop versus sensor-augmented pump therapy in older adults with type 1 diabetes (trial number ACTRN12619000515190; ANZCTR.org.au). The trial was conducted at two tertiary Australian hospitals affiliated with the University of Melbourne—St Vincent's Hospital Melbourne and The Royal Melbourne Hospital. The protocol was approved by a central Human Research Ethics Committee, and written informed consent was obtained from participants prior to study entry. Participants were recruited from local hospital clinics, private endocrinology practices, and the general community. The safety of trial participants was overseen by an independent clinical trial monitor.

This trial consisted of collection of baseline measures (first visit), run-in period (3–6 weeks), prerandomization measures (2 weeks), randomization, then two 4-month stages undertaken in random order (Supplementary Fig. 1). As a carryover effect was not anticipated for CGM metrics, a crossover design was chosen to enable paired analyses; this allowed a smaller sample size than a parallel-group design. The closed-loop intervention was a commercial MiniMed 670G system (Medtronic, Northridge, CA). The closed-loop platform comprised a glucose sensor (Guardian Sensor3) and transmitter (Guardian Link3) for real-time CGM, an insulin pump (MiniMed 670G) with insulin delivery consumables, and an insulin delivery control algorithm. The comparator was sensor-augmented pump therapy using the same MiniMed 670G system exclusively in its "manual mode," with CGM alerts and optional low-glucose suspend (without either automated delivery or predictive low-glucose suspend activated). By prohibiting predictive low-glucose suspend, there was no algorithm determining any aspect of the insulin dosing during the comparator stage. Participants continued to use their usual insulin preparation throughout the trial.

At baseline, participants underwent clinical assessment with testing for frailty (assessed by the FRAIL [fatigue, resistance, aerobic capacity, illnesses and loss of weight] scale, Mini Nutritional Assessment, Sarcopenia SARC-F [strength, assistance walking, rise from a chair, climb stairs, and falls], Walking Speed, Grip Strength and Physical Activity [17–22]), functional ability (assessed by Katz Activities of Daily Living and Lawton-Brody Instrumental Activities of Daily Living [23,24]), cognitive functioning (assessed by Montreal Cognitive Assessment [MoCA] version 8.1, Mini-Mental State Examination, National Adult Reading Test, Trail Making Test A and B, Symbol Digit Modalities Test, and grooved pegboard [25–29]), hypoglycemia awareness (assessed by Gold and Clarke scores), and psychosocial well-being (assessed by Hypoglycemia Fear Survey, Problem Areas in Diabetes short form [PAID-5], Geriatric Depression Scale: Short Form, DAWN [Diabetes Attitudes, Wishes and Needs] Impact of Diabetes Profile, INSPIRE, and user friendliness of current pump).

MoCA testing was administered by certified users. Fasting venous samples were collected for C-peptide, glucose, and HbA_{1c}, which were measured in a central laboratory. The C-peptide assay limit of detection was 3 pmol/L.

The run-in period involved provision of standardized sensor-augmented pump therapy (as described above), together with multidisciplinary education from diabetes nurse educators, dietitians, and endocrinologists experienced in type 1 diabetes clinical care. Sensor-augmented pump settings were clinically individualized based on study clinician assessment. After completion of the run-in, sensor glucose data were collected for 2 weeks during sensor-augmented pump therapy prior to randomization. Clinical review visits, with device upload and review of

pump settings, occurred during the first month of each stage and at the midpoint of each stage. Due to restrictions related to coronavirus disease 2019 (COVID-19) precautions, some visits after randomization were conducted remotely (via videoconference or telephone) and/or as home visits.

Participants

Individuals aged ≥60 years were eligible if they had type 1 diabetes for ≥10 years, were using an insulin pump with rapid-acting analog insulin, and had HbA_{1c} ≤10.5% (≤91 mmol/mol). Participants could be independent or be receiving caregiver assistance for their diabetes management. Exclusion criteria included non-type 1 diabetes, clinical diagnosis of moderate or severe dementia, and any physical or psychological condition or the use of any medication likely to compromise the ability to meet protocol requirements or the interpretation of the trial results. Full eligibility criteria are available in Supplementary Table 1.

Randomization

Eligible participants were randomly assigned (1:1) to one of two sequences: continuation of sensor-augmented pump therapy for 4 months, followed by closed loop therapy for 4 months, or the opposite sequence (i.e., closed loop, followed by crossover to sensor-augmented pump therapy). Randomization sequence was generated using permuted block design, stratified by trial site. Randomization occurred at the completion of run-in and after collection of baseline and prerandomization data; allocation was concealed from participants and site investigators until that time.

Outcomes

The primary outcome was CGM TIR during closed-loop versus sensor-augmented pump stages. Secondary CGM-based outcomes, each examined for the overall (24 h/day), overnight (0000–0559 h), and daytime (0600–2359 h) periods, were the proportion of time CGM was within ranges 3.9–10.0 mmol/L (excluding the primary outcome) and 3.9–7.8 mmol/L, the proportion of time CGM was above target (above thresholds of 10.0, 13.9, and 16.7 mmol/L); the proportion of time CGM was below target (below thresholds of 3.9, 3.3, and 3.0 mmol/L), mean sensor glucose, and sensor glucose SD and coefficient of variation (CV). These CGM metrics were selected with reference to consensus CGM-based recommendations for clinical trials (30,31). To reflect the effect of the technology after a 1-month settling-in period, the CGM outcomes were compared during the final 3 months of each trial stage. Glucose outcomes were calculated over the whole 3-month period, separately for each stage. Samples for HbA_{1c} measurement in a central laboratory were collected at the end of each stage.

Nonglucose secondary outcomes examined clinical, cognitive, and psychosocial parameters (Table 2 and Supplementary Table 2). Safety outcomes were serious adverse events, device-related adverse events, and severe hypoglycemia events, defined as hypoglycemia requiring the assistance of another person to actively administer carbohydrate, glucagon, or take other corrective actions to resolve.

Statistical Analysis

Assuming the primary outcome has an SD of 13% (consistent with our local CGM data for adults using insulin pumps), and conservative correlation between stages of 0.5, at least 24 participants were required to detect a minimum absolute difference between stages of 8 percentage points with 80% power and 5% significance level. To allow for a 20% dropout rate, we planned to enroll 30 participants.

The primary outcome was analyzed by a mixed effects linear regression model using restricted maximum likelihood estimation with unstructured covariance. Participants were entered as random intercepts, while intervention and period were entered as fixed effects. The model fit was estimated by visual inspection of the residuals. Results are presented as mean differences with 95% CI (adjusted for period effect).

Continuous secondary outcomes were analyzed in the same manner. When the model fit was insufficient, the period-adjusted sign test, as described by Senn (32), was used, and results are presented as median differences with 95% CI. While conditional negative binomial regression was planned for count outcomes, due to the small number of events these were transformed into binary outcomes and analyzed using conditional logistic regression. Results of secondary outcomes were not adjusted for multiple comparisons. A sensitivity analysis without adjustment for period effect was performed for all outcomes.

All analyses were by intention-to-treat principle. Missing data were handled by a maximum likelihood approach within the model estimation when mixed effects linear regression was performed. For nonparametric analyses, simple missing data imputation was performed (replacement by the median value of the stage). All *P* values are two-tailed, and *P* values of <0.05 were deemed to indicate statistical significance. Analyses were performed using Stata 16.1 statistical software (StataCorp LLC). The statistical analysis plan was uploaded to ANZCTR.org.au prior to trial completion.

RESULTS

From 4 April 2019 to 16 April 2020, 30 participants (19 women and 11 men; mean age 67 [SD 5] years), with a median type 1 diabetes duration of 38 years (interquartile range [IQR] 20–47]) were enrolled and randomized. There were 15 participants randomly assigned to the closed-loop regimen, followed by crossover to sensor-augmented pump, and 15 participants were randomly assigned to the opposite sequence. Two individuals enrolled and then withdrew consent before randomization (neither was using CGM at enrollment, and each decided they did not wish to continue wearing glucose sensors).

The trial profile is shown in Supplementary Fig. 2. All 30 randomized participants completed the trial; their baseline characteristics are provided in Table 1. None of the participants were frail or malnourished, although six were prefrail and four were at risk for malnutrition. All screened negative for depression. Overall, the normative cognitive results show the participants scored higher than older adult population average levels. As assessed using MoCA, 24 participants (80%) had normal cognitive function, and six (20%) had mild cognitive impairment; none met criteria for dementia.

A comparison of trial stages showed all prespecified CGM metrics were more

favorable during closed loop than sensor-augmented pump (Table 2). The primary outcome, TIR measured by CGM, was significantly higher in the closed-loop stage (75.2% [SD 6.3]) than in the sensor-augmented pump stage (69.0% [9.1]; difference of 6.2 percentage points [95% CI 4.4 to 8.0]; $P < 0.0001$), a difference that amounted to 90 min/day. The time with CGM >10.0 mmol/L was 5.4 percentage points lower (95% CI 3.5 to 7.3) in the closed loop stage than in the sensor-augmented pump stage ($P < 0.0001$), a difference that amounted to 78 min/day. The time below each hypoglycemia threshold (3.9, 3.3, and 3.0 mmol/L) was lower during closed loop than sensor-augmented pump; the time <3.9 and <3.0 mmol/L amounted to 7 and 2 min/day, respectively, less with closed loop than sensor-augmented pump. The differences in CGM metrics between stages were most pronounced overnight (Fig. 1).

Glucose variability, as measured by sensor glucose SD and CV, was significantly lower during the closed-loop stage than during the sensor-augmented pump stage (Table 2). The improvements in CGM metrics during closed loop were achieved with no overall change in insulin dose delivered, though with greater within-day variability in dosing during closed loop than sensor-augmented pump (Supplementary Fig. 3). HbA_{1c} was not significantly different between closed-loop versus sensor-augmented pump stages (7.3% [IQR, 7.1–7.5] (56 mmol/mol [54–59]) vs. 7.5% [7.1–7.9] (59 mmol/mol [54–62]), respectively; $P = 0.13$). There were no significant differences between stages for any clinical outcomes, for psychosocial well-being or cognitive functioning (Table 2 and Supplementary Table 2). Participants were positive about using closed-loop therapy before starting (INSPIRE results at baseline 78.0% [SD 11.6]), and remained positive about the impact of closed-loop delivery on living with diabetes at the end of the closed-loop stage (68.2% [11.9]), although the degree of positivity was more before than after using closed loop (difference of 9.8 percentage points [95% CI 5.4 to 14.3], $P < 0.0001$).

The CGM metrics overnight (0000–0559 h) and daytime (0600–2359 h) all

Table 1—Participant characteristics

	Analysis group ($N = 30$)
Age, years	
Mean (SD)	67 (5)
Median (IQR)	68 (64–71)
Range	60–75
Sex	
Women	19 (63)
Men	11 (37)
BMI, kg/m^2	27.6 (26.4–31.0)
Duration of type 1 diabetes, years	38 (20–47)
Insulin total daily dose, units/kg body weight	0.55 (0.41–0.66)
Insulin – proportion basal insulin, %	46 (41–54)
CGM use at study entry	12 (40)*
CGM use ever	26 (87)†
HbA_{1c} at baseline, %, mean (SD)	7.6 (0.9)
HbA_{1c} at baseline, mmol/mol, mean (SD)	59 (9)
HbA_{1c} at randomization, %, mean (SD)	7.5 (0.6)
HbA_{1c} at randomization, mmol/mol, mean (SD)	58 (7)
C-peptide (measured fasting, in the absence of hypoglycemia)	
C-peptide level, pmol/L	7 (3–21)
C-peptide detectable (≥3 pmol/L)	23 (77)
Severe hypoglycemia‡ (events in the past 12 months)	
0 events	21 (70)
1 event	5 (17)
≥2 events	4 (13)
Impaired awareness of hypoglycemia	
Gold score ≥4	10 (33)
Clarke score ≥4	9 (30)
Montreal Cognitive Assessment (MoCA)	
MoCA score	27 (26–28)
Normal cognitive function (MoCA score ≥26)	24 (80)
Mild cognitive impairment (MoCA score 18–25)	6 (20)
Mini Mental State Examination score	30 (29–30)
Verbal IQ	
National Adult Reading Test score	37 (32–44)
National Adult Reading Test ≥1.5 SD below normative data	0 (0)
Executive functioning	
Trail Making Task B, s	85.5 (60.6–110.3)
Trail Making Task B ≥1.5 SD below normative data	3 (10)
Psychomotor speed	
Symbol Digit Modalities Test (*n* correct)	41 (34–46)
Symbol Digit Modalities Test ≥1.5 SD below normative data	0 (0)
Trail Making Task A, s	29.5 (24.8–40.5)
Trail Making Task A ≥1.5 SD below normative data	2 (7)
Grooved pegboard (dominant), s	82 (75–100)
Pegboard (dominant) ≥1.5 SD below normative data	5 (17)
Grooved pegboard (nondominant), s	102 (80–117)
Pegboard (nondominant) ≥1.5 SD below normative data	3 (10)
FRAIL scale categories	
Nonfrail	24 (80)
Prefrail	6 (20)
Frail	0 (0)

Continued on p. 385

Table 1—Continued

	Analysis group (N = 30)
Mini Nutritional Assessment	
Normal nutritional status	26 (87)
At risk for malnutrition	4 (13)
Malnourished	0 (0)
Sarcopenia: SARC-F	0 (0)
Walking speed—normal (>0.8 m/s)	30 (100)
Grip strength—normal (≥27 kg for men; ≥16 kg for women)	29 (97)
Activities of daily living	
Katz Activities of Daily Living score	6 (6–6)
Lawton-Brody Activities of Daily Living score	8 (8–8)
Caregiver assistance required for diabetes management	1 (3)
Physical activity—relative to others own age	
More active	19 (63)
About as active	9 (30)
Less active	2 (7)
Hypoglycemia Fear Survey II short form	
Behavior subscale	3.5 (2–5)
Worry subscale	5 (3–10)
Possible diabetes-related emotional distress (PAID-5 score ≥8)	6 (20)
Depression (Geriatric Depression Scale: short form score >5)	0 (0)
DAWN Impact of Diabetes Profile composite raw score	4.5 (4.3–4.9)
Inadequate sleep quality (Pittsburgh Sleep Quality Index score >5)	14 (47)

Presented are baseline data collected at the first visit (other than the HbA_{1c} at randomization). Data are *n* (%), median (IQR), or mean (SD) where indicated. DAWN, Diabetes Attitudes, Wishes and Needs; PAID, Problem Areas in Diabetes; SARC-F, strength, assistance walking, rise from a chair, climb stairs, and falls. *Among the 12 participants using CGM at study entry, 9 were using real-time CGM, and 3 were using intermittently scanned CGM. †Among the 26 participants who had ever used CGM, 23 had used real-time CGM. ‡Severe hypoglycemia event defined as hypoglycemia needing assistance from another person for recovery.

favored closed loop over sensor-augmented pump (Table 3). Mean TIR overnight was 86.9% (SD 6.9) during closed-loop therapy (overnight difference 10.1 percentage points [95% CI 6.9 to 13.4]; $P < 0.0001$). Overnight, there was a significantly lower proportion of time that CGM was below each of the hypoglycemia thresholds (3.9, 3.3, and 3.0 mmol/L) with closed-loop than sensor-augmented pump therapy. Mean sensor glucose and glucose variability were significantly lower during overnight and daytime periods in the closed loop stage than in the sensor-augmented pump stage.

Safety outcomes are tabulated in Supplementary Table 3. No serious adverse events occurred during the closed loop stage. Two serious adverse events occurred during the sensor-augmented pump stage: an episode of diabetic ketoacidosis presumed due to insulin delivery line occlusion, and a vitreous hemorrhage unrelated to the trial. Five severe hypoglycemia events occurred among five different trial participants: three were during the closed-loop stage, and two were during the sensor-augmented pump stage. None required hospitalization or involved hypoglycemia-related seizures or loss of consciousness, and one event in each stage involved altered consciousness (events detailed in the footnote of Supplementary Table 3).

There were high levels of adherence to the protocol. Closed-loop and sensor-augmented pump stages had similar duration (123 days [IQR 122–124] and 123 days [121–125], respectively), high sensor use (at 97.2% [94.2–98.3] and 96.3% [93.5–97.8], respectively), and most days with ≥70% CGM valid readings (at 121 days [116–124] and 119 days [111–122], respectively). During the closed-loop stage, automated basal insulin delivery was operational for 93.3% (IQR 88.2–96.1) of the total time and 98.5% (95.0–99.1) of the time when sensor glucose data were available. During the sensor-augmented pump stage, closed loop was not operational.

Examining the individual participant results, even with relatively favorable CGM metrics during comparator sensor-augmented pump stage, we found there were still improvements during closed-loop delivery for most participants for TIR, time above range, and time below range (Supplementary Fig. 4). We examined the proportion of participants meeting the recommended CGM-based targets for older adults (12). There was almost complete achievement of the >50% TIR target and the <50% time >10.0 mmol/L target during both stages (30 participants [100%] during closed loop vs. 29 participants [97%] during sensor-augmented pump for both targets; $P > 0.99$). However, there were more participants during the closed loop than the sensor-augmented pump stage who met the hypoglycemia target of <1% time <3.9 mmol/L (13 participants [43%] vs. 7 participants [23%], respectively; $P = 0.031$) and the target of <10% time >13.9 mmol/L (29 participants [97%] vs. 22 participants [73%], respectively; $P = 0.016$). More participants met all four CGM-based target recommendations for older adults during closed-loop than sensor-augmented pump therapy (13 participants [43%] vs. 3 participants [10%], respectively; $P = 0.0020$). Looking at the practical application of this technology by examining CGM metrics by trial month, we found the CGM effects of therapy were sustained in this trial for 4 months (Supplementary Fig. 5).

CONCLUSIONS

To our knowledge, this is the first randomized, crossover clinical trial exclusively involving older adults with long-duration type 1 diabetes. We showed that closed-loop insulin delivery provided significantly better glucose control than did sensor-augmented pump therapy. The TIR increase was equivalent to an extra 90 min/day in the closed-loop stage compared with the sensor-augmented pump stage, a difference considered clinically significant (12). In addition to increasing TIR, closed loop reduced both hypoglycemia and hyperglycemia, consistent with trials

Table 2—Primary and secondary outcomes

	Closed-loop stage (n = 30)	Sensor-augmented pump stage (n = 30)	Difference	P value
Glucose and insulin outcomes				
Proportion of time at glucose concentration				
3.9–10.0 mmol/L, %*	75.2 (6.3)	69.0 (9.1)	6.2 (4.4 to 8.0)	<0.0001
3.9–7.8 mmol/L, %	48.2 (6.1)	42.8 (9.1)	5.4 (3.6 to 7.2)	<0.0001
>10.0 mmol/L, %	23.6 (6.6)	29.0 (9.8)	−5.4 (−7.3 to −3.5)	<0.0001
>13.9 mmol/L, %	3.9 (2.2–5.9)	4.9 (3.1–10.6)	−1.2 (−2.9 to −0.9)	0.0022
>16.7 mmol/L, %	0.66 (0.38–1.32)	0.87 (0.69–3.54)	−0.62 (−1.01 to −0.29)	<0.0001
<3.9 mmol/L, %	1.21 (0.60–1.68)	1.69 (1.00–2.54)	−0.47 (−1.05 to −0.25)	0.0005
<3.3 mmol/L, %	0.37 (0.12–0.49)	0.41 (0.20–0.78)	−0.19 (−0.36 to −0.06)	0.025
<3.0 mmol/L, %	0.13 (0.03–0.24)	0.16 (0.10–0.38)	−0.11 (−0.16 to −0.05)	0.0078
Mean glucose concentration, mmol/L	8.4 (8.0–8.8)	8.7 (7.9–9.2)	−0.2 (−0.5 to −0.1)	0.035
SD of glucose concentration, mmol/L	2.6 (2.4–2.9)	2.9 (2.8–3.5)	−0.4 (−0.5 to −0.2)	<0.0001
CV of glucose concentration, %	31.3 (29.9–33.9)	35.3 (32.9–36.1)	−3.4 (−4.5 to −1.7)	<0.0001
HbA_{1c}, %	7.3 (7.1–7.5)	7.5 (7.1–7.9)	−0.2 (−0.3 to 0)	0.13
HbA_{1c}, mmol/mol	56 (54–59)	59 (54–62)	−2 (−3 to 0)	0.11
Insulin total daily dose, units	38.3 (30.1–60.9)	38.2 (31.2–59.2)	−0.5 (−1.8 to 0.3)	0.26
Psychosocial well-being outcomes				
Gold score	3 (2–4)	3 (2–4)	0 (0 to 0)	0.48
Clarke score	2 (1–4)	2 (1–4)	0 (−1 to 0)	0.43
Hypoglycemia Fear Survey				
Total scale	7.5 (4–10)	7.5 (5–10)	−1 (−3 to 1)	0.72
Worry subscale	4.5 (2–7)	4.5 (3–7)	0 (−1 to 0)	0.14
Behavior subscale	2 (1–4)	2 (1–4)	0.0 (−2 to 0)	0.087
Diabetes distress (PAID-5)	4.3 (2.9)	4.6 (3.2)	−0.3 (−1.1 to 0.5)	0.46
Geriatric Depression Scale	1 (0–2)	1 (0–2)	0 (0 to 0)	>0.99
Impact of diabetes on quality of life (DIDP raw score)	4.5 (4.3–4.8)	4.7 (4.4–5.0)	0.0 (−0.2 to 0.0)	0.46
Perceived sleep quality (PSQI score)	5 (3–8)	5.5 (3–7)	0 (−1 to 1)	0.79

Results presented as mean (SD) or median (interquartile range); analyses using period-adjusted mixed effect linear regression or period-adjusted sign test, respectively. Differences presented as mean or median difference (95% CI). DIDP, Diabetes Attitudes, Wishes and Needs (DAWN) Impact of Diabetes Profile; PAID, Problem Areas in Diabetes; PSQI, Pittsburgh Sleep Quality Index. *Primary outcome. Sensor glucose and insulin outcomes are for the final 3 months of each stage.

involving younger individuals with type 1 diabetes using closed loop (9,10).

Closed-loop insulin delivery had its greatest benefit overnight, improving the proportion of time spent within, above, and below CGM target range. Of particular clinical importance among this older cohort was the fourfold reduction in the time overnight spent below all hypoglycemia thresholds examined in our study (3.9, 3.3, and 3.0 mmol/L) with closed loop. These findings are not unexpected, with almost all insulin delivered overnight being basal insulin, dosing of which is automated with this closed-loop system, and the overnight period being mostly free of the challenges faced during the daytime relating to food, exercise, and other activities impacting glucose levels. Similar beneficial patterns from closed loop overnight have been seen in younger cohorts (9,10,33,34). HbA_{1c} was not significantly different between the stages when adjusting for period effect (primary analysis), although a statistically significant small HbA_{1c} improvement of 0.2% with closed loop was seen in a sensitivity analysis (without adjustment for period effect); therefore, trial participation may have improved HbA_{1c}. The lack of HbA_{1c} difference with the closed-loop intervention is perhaps not surprising, since the group's HbA_{1c} levels at baseline did not have much room for improvement. While HbA_{1c} measurement is independent of the pump-CGM system, and there is extensive evidence relating levels to long-term risk of diabetes-related complications, this trial focused on examining shorter-term intervention effects. In this regard, CGM has been shown to be a better tool than HbA_{1c} to capture an individual's average glucose and glucose trends (notwithstanding the additional information CGM provides regarding hypoglycemia) (35).

No major safety issues were identified in the trial. No hypoglycemic events required emergency clinical care, and no device-related serious adverse events occurred during the closed-loop intervention. While the rates of severe hypoglycemia during CGM wear were higher than have been reported in some other trials, we note that participants in the present trial had high levels of severe hypoglycemia prior to enrolment; they also had very long-duration type 1 diabetes, and one-third had impaired awareness of hypoglycemia, both of which increase severe hypoglycemia risk (36, 37). We defined severe hypoglycemia events using the American Diabetes Association classification, as recommended for closed-loop trial reporting (30,38). However, varying definitions limit event rate comparison. None of the severe hypoglycemia events during this trial met the T1D Exchange severe hypoglycemia definition of hypoglycemia resulting in seizure or loss of consciousness (36). When comparing with WISDM, which reported one severe hypoglycemia event among 103 older adults randomized to CGM for 6 months, we note that one event in each stage of the present trial met the WISDM

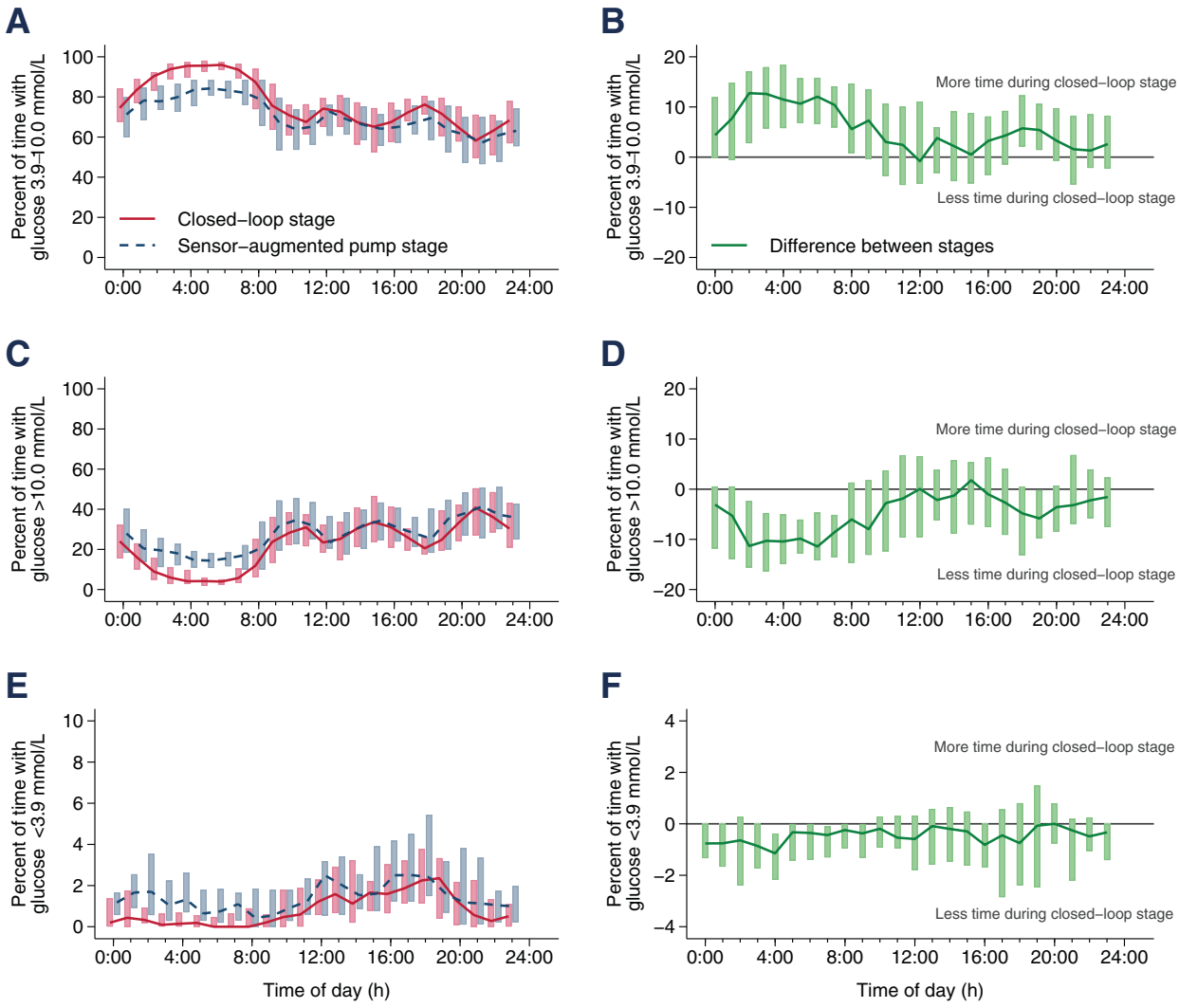

Figure 1—Proportion of time spent in CGM ranges. The proportion of time spent with CGM 3.9–10.0 mmol/L by trial stage (*A*) and paired within participants (*B*). The proportion of time spent with CGM >10.0 mmol/L by trial stage (*C*) and paired within participants (*D*). The proportion of time spent with CGM <3.9 mmol/L by trial stage (*E*) and paired within participants (*F*). The lines indicate the median, and the shaded boxes indicate IQR. Glucose outcomes are for the final 3 months of each stage.

severe hypoglycemia definition requiring altered consciousness (13). Moreover, the number of severe hypoglycemia events reported in the 12 months prior to enrollment in WISDM was approximately half the number reported in the present trial, where the event definition did not require altered consciousness. Greater consistency in trial reporting of severe hypoglycemia would facilitate interpretation of comparisons between studies.

We are mindful that the study was conducted during the time the COVID-19 pandemic has affected Australia (39). No participants contracted COVID-19 during the study. It is not possible to evaluate whether the pandemic had an impact on the findings; however, with the randomization and crossover design, we believe the indirect effects of COVID-19 were evenly distributed. The run-in period with multidisciplinary education was unaffected, because these visits were undertaken face-to-face prior to local impact from COVID-19. However, review visits after randomization were affected, with many being conducted remotely. Therefore, although the pandemic impacted everyday life and diabetes management during the trial period, we do not believe it had any systematic impact on the reported results.

With CGM wear >95% throughout the trial, and closed loop operational for 98% of CGM wear during the intervention stage, our results show it is possible to maintain high levels of use of this technology in a controlled trial environment among engaged participants. These engagement levels are in line with research that has shown more consistent use of CGM and MiniMed 670G by individuals aged ≥50 years compared with younger cohorts over a 1-year period (16). Further clinical and real-world studies are required to determine the effectiveness of closed loop in adults aged ≥60 years who spend less time wearing CGM than seen in this trial.

The detailed description of participants' clinical, cognitive, frailty, and functional status allows contextualization of our results to clinical practice (i.e., older adults who are cognitively healthy, not frail, and are using insulin pumps). This information also enables

Table 3—Overnight (0000–0559 h) and daytime (0600–2359 h) sensor glucose outcomes

	Closed-loop stage (n = 30)	Sensor-augmented pump stage (n = 30)	Difference	P value
Overnight period (0000–0559 h)				
Proportion of time at glucose concentration				
3.9–10.0 mmol/L, %	86.9 (6.9)	76.8 (11.3)	10.1 (6.9 to 13.4)	<0.0001
3.9–7.8 mmol/L, %	63.2 (10.0)	49.9 (12.1)	13.3 (10.5 to 16.1)	<0.0001
>10.0 mmol/L, %	11.3 (7.0–15.1)	18.0 (13.1–24.4)	−9.5 (−12.6 to −4.6)	<0.0001
>13.9 mmol/L, %	0.81 (0.37–1.96)	1.74 (1.00–4.29)	−1.09 (−2.34 to −0.52)	0.0025
>16.7 mmol/L, %	0.16 (0.00–0.37)	0.22 (0.05–0.74)	−0.10 (−0.39 to 0.00)	0.050
<3.9 mmol/L, %	0.38 (0.15–0.88)	1.33 (0.82–2.49)	−0.83 (−1.05 to −0.44)	<0.0001
<3.3 mmol/L, %	0.08 (0.00–0.29)	0.35 (0.15–0.62)	−0.14 (−0.41 to −0.03)	0.0008
<3.0 mmol/L, %	0.03 (0.00–0.13)	0.13 (0.06–0.32)	−0.09 (−0.25 to 0.00)	0.018
Mean glucose concentration, mmol/L	7.6 (0.6)	8.1 (0.9)	−0.5 (−0.7 to −0.3)	<0.0001
SD of glucose concentration, mmol/L	2.0 (0.4)	2.5 (0.4)	−0.5 (−0.7 to −0.4)	<0.0001
CV of glucose concentration, %	25.6 (23.6–29.3)	31.7 (28.9–33.8)	−5.3 (−7.7 to −3.2)	0.0025
Daytime period (0600–2359 h)				
Proportion of time at glucose concentration				
3.9–10.0 mmol/L, %	71.2 (7.2)	66.3 (9.6)	4.9 (3.2 to 6.5)	<0.0001
3.9–7.8 mmol/L, %	43.1 (6.9)	40.4 (9.5)	2.8 (0.8 to 4.7)	0.0055
>10.0 mmol/L, %	27.4 (7.6)	31.6 (10.6)	−4.2 (−5.9 to −2.4)	<0.0001
>13.9 mmol/L, %	4.9 (2.9–7.5)	5.6 (3.8–12.2)	−1.5 (−3.3 to −0.9)	0.0022
>16.7 mmol/L, %	0.80 (0.41–1.65)	1.13 (0.88–4.63)	−0.82 (−1.57 to −0.35)	<0.0001
<3.9 mmol/L, %	1.32 (0.66–1.90)	1.54 (1.00–2.69)	−0.43 (−1.22 to −0.08)	0.066
<3.3 mmol/L, %	0.40 (0.14–0.51)	0.31 (0.21–0.94)	−0.13 (−0.35 to −0.05)	0.025
<3.0 mmol/L, %	0.16 (0.04–0.28)	0.14 (0.07–0.44)	−0.06 (−0.18 to −0.03)	0.025
Mean glucose concentration, mmol/L	8.7 (0.6)	8.9 (0.9)	−0.2 (−0.4 to −0.1)	0.0076
SD of glucose concentration, mmol/L	2.8 (0.4)	3.1 (0.4)	−0.4 (−0.4 to −0.3)	<0.0001
CV of glucose concentration, %	31.8 (30.6–33.6)	35.0 (32.8–36.5)	−3.3 (−4.3 to −1.6)	<0.0001

Results are presented as mean (SD) or median (interquartile range); analyses using period-adjusted mixed effect linear regression or period-adjusted sign test, respectively. Differences presented as mean or median difference (95% CI). Glucose outcomes are for the final 3 months of each stage.

our findings to be related to clinical guidelines that risk-stratify individuals to determine glucose targets and overall diabetes management strategies, such as recent Diabetes UK guidelines (2). These treatment guidelines emphasize a risk-stratification approach for older adults, primarily based on the functional status of the individual. Following the approach taken by Chaytor et al. (40), we considered results ≥1.5 SD below the mean of demographically corrected normative data to indicate impaired test performance. Based on these cognitive results, and in the absence of frailty, we consider the 29 trial participants who were independent with diabetes self-management to be in the lowest risk category of the Diabetes UK management guidelines. Further evidence is needed regarding the effectiveness of individualized, risk-stratified CGM targets and advanced diabetes technology (including closed-loop therapy) in older adults across the spectrum of frailty and functional categories. Of clinical relevance, participants' cognitive and functional status did not deteriorate during the trial with the more intensive closed-loop therapy intervention, although longer-term effects will need further study.

At an individual level, closed-loop insulin delivery resulted in an additional 10 participants (33%) achieving all four CGM target recommendations for older adults (>50% TIR, <50% time >10.0 mmol/L, <10% time >13.9 mmol/L, and <1% time <3.9 mmol/L) (12). We note that if targeting TIR >70% (i.e., the consensus target recommended for younger adults without comorbidities), together with the stringent hypoglycemia target of <1% time <3.9 mmol/L, then nine participants met both targets during the closed-loop stage compared with only one during sensor-augmented pump therapy. The group's median TIR during the closed-loop stage was >70%, without any adverse clinical events relating to dysglycemia. Moreover, our results indicate that closed-loop therapy achieved high TIR, while avoiding trade-off increases in time above or below target. Even during the comparator stage, this group's median TIR was 69%, and 80% of participants had TIR >60%, evidence of older adults without frailty safely achieving TIR levels far above the minimum target of >50% recommended by Battelino et al. (12) for older adults. These trial results support individualization of glucose targets for older adults, including giving consideration to tighter targets in the absence of frailty. Consideration of a higher TIR target (even up to the >70% target recommended for the general adult population) therefore warrants exploration for older robust, and possibly even prefrail, individuals with type 1 diabetes who are in relatively good health. Furthermore, consideration of whether a combination of CGM targets is met may provide more clinically valuable results than individual targets. Determining the optimal

components of a global CGM-based composite metric and a related scoring system relevant to clinical care remains under investigation (41).

Evidence for glucose management in older adults with type 1 diabetes demonstrates successive incremental improvements as technology has progressed, including clinically important reductions of hypoglycemia. Baseline results from the WISDM study of older adults (with similar clinical characteristics to the present trial group), who were using insulin pumps or multiple daily injections and monitoring glucose only with finger-prick testing, show the group were spending at least 1 h/day in hypoglycemia range (42). Real-time CGM intervention in WISDM almost halved hypoglycemia time down to 2.7% and increased TIR to 63% (13). In the current study, after participants received multidisciplinary education and were established on sensor-augmented pump therapy during run-in, we previously reported their median TIR was 71% and time <3.9 mmol/L was 2.0% prerandomization (43). Subsequently, during the trial's closed-loop intervention, even with the relatively favorable CGM metrics during the sensor-augmented pump comparator stage, there were significant, sustained benefits seen with the closed-loop intervention.

Our randomized trial showed 75% TIR with closed-loop insulin delivery, an improvement of 6 percentage points over sensor-augmented pump when accounting for period effect. This is lower than a single-arm study in older adults that reported 80% TIR during 4 weeks of closed loop, an increase of 10 percentage points over the preceding sensor-augmented pump period (11); however, without randomization or crossover, those results may partly reflect the short intervention and a period effect (noting a period effect was observed in most of the glucose outcomes in the present trial). Moreover, Bisio et al. (11) did not report participants' cognitive or functional status to facilitate clinical characterization of the group. Randomized trials of younger adults have shown TIR ~11 percentage points higher with closed loop than sensor-augmented pump; however, we note TIR during closed loop in these previous trials was similar to our study, whereas TIR during sensor-augmented pump was in many cases much lower (<60%), which may reflect the different groups studied (9,33,34).

A key strength of our study is the investigation of older adults with type 1 diabetes, a group among whom little was previously known about closed-loop effects. The comprehensive assessments that characterized the participants enable the results to be contextualized in relation to participants' functional status. Other strengths include the randomized crossover design, strong comparator, and 100% trial retention of all randomized participants.

There are factors that impact the generalizability of our findings: individuals with moderate or severe dementia were excluded, and although six participants (20%) had cognitive impairment on MoCA testing, none met criteria for mild dementia. Furthermore, none of the trial participants were frail as assessed by the FRAIL scale; however, six (20%) were prefrail, indicating a possible future vulnerability to frailty.

Other limitations include the trial size and that the duration of intervention may not have been sufficient to detect differences in non-CGM outcomes. We acknowledge that the intervention was a first-generation closed-loop system. Subsequent generation systems with features such as allowing tighter glycemia, better user interface, fewer alarms, fewer (if any) blood glucose calibrations, and greater persistence in closed loop may result in better glucose control and psychosocial well-being among older adults, and warrant investigation. With the period effect observed, further research is warranted to investigate whether closed loop impacts long-term sensor-augmented pump therapy and whether intermittent use of closed loop affects subsequent sensor-augmented pump therapy.

In conclusion, older age is not a barrier to closed-loop therapy, and closed loop has important clinical benefits. Closed-loop insulin delivery safely improved all CGM outcomes compared with sensor-augmented pump therapy among older adults with long-duration type 1 diabetes and no frailty. Closed loop increased TIR and reduced time below range, particularly overnight. Further research is needed to examine the effects and safety of closed loop among people with frailty or major cognitive impairment and among individuals with less favorable preexisting glycemia.

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Author Contributions. S.A.M. led the study and wrote the report. S.A.M., S.T., G.M.W., M.H.L., D.N.O., N.A.O., V.S., P.G.C., and R.J.M. co-designed the study. S.A.M., S.F., M.H.L., A.M.A., P.G.C., and R.J.M. were responsible for screening and enrollment of participants, arranging informed consent, and for providing medical care. S.V., S.F., and C.A.G. contributed to refining the protocol. S.V. and V.S. contributed to the data analysis. All authors critically reviewed the report and made the decision to submit for publication. S.A.M., S.V., and V.S. are the guarantors of this work and, as such, had full access to all data in the study

and take responsibility for the integrity of the data and the accuracy of the data analysis.

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