Nutrition, Metabolism and Cardiovascular Diseases

Real-world outcomes with different technology modalities in type 1 diabetes

--Manuscript Draft--

Manuscript Number:	NMCD-D-20-01216R1
Article Type:	Research Paper
Keywords:	Type 1 diabetes; continuous glucose monitoring; sensor-augmented pump, hybrid closed-loop systems
Corresponding Author:	Pilar I Beato-Víbora Badajoz University Hospital Badajoz, SPAIN
First Author:	Pilar I Beato-Víbora, PhD
Order of Authors:	Pilar I Beato-Víbora, PhD
	Fabiola Gallego-Gamero, MD
	Ana Ambrojo-López, MD
Abstract:	Background and Aims Several treatment modalities are available for type 1 diabetes (T1D), including continuous glucose monitoring (CGM) and flash glucose monitoring (FGM) with MDI, sensor-augmented pumps with predictive low-glucose suspend function (SAP-PLGS) and hybrid closed-loop systems (HCL). The aim of the study was to evaluate the real-world benefits obtained with these treatment modalities. Methods and Results A cross-sectional study was performed, selecting 4 groups of T1D subjects, regarding their treatment modalities, paired by age, sex and diabetes duration. A comparison was performed, concerning time in different glucose ranges in 2-week sensor downloads. Estimated HbA1c, glycaemic variability measures and sensor use were also compared. 302 T1D people were included (age: 39 ± 12 years, 47% male, diabetes duration: 21 ± 10 years, estimated HbA1c: 7.28 ± 0.84% (56 ± 9 mmol/mol), baseline HbA1c: 7.4 ± 1.0% (57 ± 11 mmol/mol), length of use of the device 8 [3-21] months). Group 1 (CGM+MDI) and 2 (FGM+MDI) showed no differences in time in different glucose ranges. Group 4 (HCL) showed a higher time 70-180 mg/dl and a lower time in hypoglycaemia than group 3 (SAP-PLGS). Group 1 and 2 showed lower time 70-180 mg/dl, higher time in hyperglycaemia and higher glycaemic variability measures than group 3. Group 4 was superior to groups 1 and 2 in all the outcomes. Conclusion Real-life achievements in glycaemic control and glycaemic variability are described. HCL offer the maximum benefit in terms of time in range and hypoglycaemia protection, compared to CGM+MDI, FGM+MDI and SAP-PLGS.

Title

Real-world outcomes with different technology modalities in type 1 diabetes

Running title: Glycaemic control and glycaemic variability with different diabetes technologies.

Authors

Beato-Víbora Pilar Isabel, Gallego-Gamero Fabiola, Ambrojo-López Ana.

Endocrinology and Nutrition Department. Badajoz University Hospital. Badajoz. Spain

Corresponding author

Beato-Víbora Pilar I.

email address: pilar.beato@salud-juntaex.es

phone number: 0034659267272

Manuscript word count: 3173

Abstract word count: 248

Abstract

Background and Aims. Several treatment modalities are available for type 1 diabetes (T1D), including continuous glucose monitoring (CGM) and flash glucose monitoring (FGM) with MDI, sensor-augmented pumps with predictive low-glucose suspend function (SAP-PLGS) and hybrid closed-loop systems (HCL). The aim of the study was to evaluate the real-world benefits obtained with these treatment modalities.

Methods and Results. A cross-sectional study was performed, selecting 4 groups of T1D subjects, regarding their treatment modalities, paired by age, sex and diabetes duration. A comparison was performed, concerning time in different glucose ranges in 2-week sensor downloads. Estimated HbA1c, glycaemic variability measures and sensor use were also compared.

302 T1D people were included (age: 39 ± 12 years, 47% male, diabetes duration: 21 ± 10 years, estimated HbA1c: 7.28 ± 0.84% (56 ± 9 mmol/mol), baseline HbA1c: 7.4 ± 1.0% (57 ± 11 mmol/mol), length of use of the device 8 [3-21] months). Group 1 (CGM+MDI) and 2 (FGM+MDI) showed no differences in time in different glucose ranges. Group 4 (HCL) showed a higher time 70-180 mg/dl and a lower time in hypoglycaemia than group 3 (SAP-PLGS). Group 1 and 2 showed lower time 70-180 mg/dl, higher time in hyperglycaemia and higher glycaemic variability measures than group 3. Group 4 was superior to groups 1 and 2 in all the outcomes.

Conclusion. Real-life achievements in glycaemic control and glycaemic variability are described. HCL offer the maximum benefit in terms of time in range and hypoglycaemia protection, compared to CGM+MDI, FGM+MDI and SAP-PLGS.

Keywords: type 1 diabetes; continuous glucose monitoring; sensor-augmented pump, hybrid closed-loop systems.

Introduction

In the past decades, the use of technology to improve glycaemic control in people with type 1 diabetes (T1D) has become standard practice. Continuous glucose monitoring (CGM) and Flash Glucose Monitoring (FGM) have been shown to improve glycaemic control and reduce the frequency of hypoglycemia as stand-alone systems in patients on multiple daily insulin injections (MDI) [1-5].

Sensor-augmented pumps have evolved from no automation to different levels of automation, including suspension “on low” and suspension “before low”. Sensor-augmented pumps with predictive low glucose suspend function (SAP-PLGS) allow the system to stop insulin infusion when a low sensor glucose level is predicted. These systems have been shown to reduce HbA1c and the frequency of hypoglycaemia events in randomised control trials and in real-world clinical practice [6-8].

In hybrid closed-loop systems (HCL), the insulin infusion is controlled by an algorithm, which adjusts the insulin infusion every five minutes, according to the sensor glucose values. A significant improvement in the time in range 70-180 mg/dl has been demonstrated, in comparison with conventional treatment [9-11].

Clinicians have to consider several aspects when deciding which treatment modality is more suitable for each individual. The benefit in relation to glycaemic control, hypoglycaemia frequency and glycaemic variability has to been analysed in conjunction with the technology burden imposed on the patient and the cost of the device for the health care system.

Longitudinal studies comparing different treatment modalities, including combinations of MDI and pumps with or without CGM have shown similar reductions in HbA1c and hypoglycaemia with both CGM + MDI and sensor-augmented-pumps after 1 year and 3 years of follow-up [12, 13].

The study aimed to evaluate the outcomes in glycaemic control and glycaemic variability that are achieved with each diabetes technology option in real-life clinical practice.

Material and Methods

A cross-sectional design study was performed including all the T1D individuals using CGM or FGM who were being followed at the Endocrinology Department in Badajoz University Hospital (Badajoz, Spain). Four different treatment modalities were identified and four groups, according to these treatment modalities, were defined: group 1 (CGM + MDI), group 2 (FGM + MDI), group 3 (SAP-PLGS) and group 4 (HCL). From each treatment strategy, paired groups were selected, according to age, gender and diabetes duration, with a ratio from 1:1 to 1:1.2 for groups 1, 2 and 3 and a ratio of 1:2.2 for group 4.

The study period was defined between January 2019 and March 2020. The most recent download for each patient, in this period, was selected. A 2 week-download period was considered for the analysis of sensor data.

The variables analysed included estimated HbA1c, mean sensor glucose, time in range 70-180 mg/dl, time in hypoglycaemia < 54 mg/dl and < 70 mg/dl and time in hyperglycaemia > 180 mg/dl and > 250 mg/dl. Glycaemic variability measures were extracted from the download reports or calculated by the EasyGV® software [14], including standard deviation (SD), coefficient of variation (CV) and Mean Amplitude of Glycaemic Excursions (MAGE). Sensor use was recorded for each patient. The length of use of the device and the HbA1c before the initiation of the device were recorded. The number of visits per year was 4, on average, for all the groups. Data from women during pregnancy were not included in the analysis. Hypoglycaemia awareness could not be evaluated in all the patients, and it was not included in the analysis. All the subjects had received the same structured diabetes education, including training in carbohydrate counting.

All the subjects included in the study had given written consent for the use of their glucose monitoring and pump data for research purposes. The protocol was approved by the local Ethics Committee and was conducted according to the principles of the Declaration of Helsinki.

Data analysis was performed using SPSS statistics software v22. Results are presented as mean ± standard deviation values or median [interquartile range]. A paired Student's t-test was used for the analysis of differences. For unpaired samples, the independent samples t-test was used. For non-parametric variables, a Wilcoxon signed-rank test or a Mann-Whitney test were applied. Comparisons between proportions were analysed by a

chi-squared test. For multiple group comparisons, a one-way ANOVA test was used. Correlation analysis was performed using the Pearson method. A p-value < 0.05 was considered statistically significant.

Results

An initial cohort of 457 patients was considered. Patients without any sensor download in the study period were excluded (n = 22). A group of 302 subjects was selected from the initial cohort, producing four groups according to technology modality, paired by age, sex and diabetes duration.

In group 1 (CGM + MDI), The CGM devices used were Dexcom G5® and Dexcom G6® (91%, n = 86), and Eversense XL® (9%, n = 8). In group 2 (FGM + MDI), all the subjects used FreeStyle Libre® version 1. All subjects in group 3 (SAP-PLGS) were using the MiniMed 640G® pump with Guardian Sensor 3® and all had the PLGS function activated. All subjects in group 4 (HCL) were using the MiniMed 670G® system with Guardian Sensor 3®. Forty percent (n = 121) of the individuals were pump users (group 3 and 4) and 60% (n = 181) were on MDI (groups 1 and 2).

No differences in age, diabetes duration or sex were found between groups 1, 2, 3 and 4 (Table 1). Patient characteristics were as follows: age 39 ± 12, 47% (n = 141) males, diabetes duration: 21 ± 10 years, HbA1c: 7.28 ± 0.84% (56 ± 9 mmol/ml), mean glucose: 162 ± 24 mg/dl, SD: 58 ± 14 mg/dl, CV: 36 ± 6%, time in range 70-180: 63 ± 14%, time < 70 mg/dl: 3.5 ± 3.9%, time < 54 mg/dl: 0.8 ± 1.5%, time > 180 mg/dl: 34 ± 15% time > 250

mg/dl: 10 ± 10% %. Sensor use was 89 ± 13%, and 84% (n = 255) of the subjects had a sensor use ≥ 80%. Time in auto-mode in group 4 was 84 ± 23%.

The main indication for the initiation of the device was "poor glycaemic control (HbA1c > 7%)" in 60% (n = 182) in the whole cohort (63% in group 1, 60% in group 2, 49% in group 3, 77% in group 4, p = 0.37 between groups).

HbA1c before the start of the use of the device was 7.4 ± 1.0% (57 ± 11 mmol/mol) in the whole cohort (group 1: 7.5 ± 1.1% (58 ± 12 mmol/mol), group 2: 7.6 ± 1.2% (60 ± 13 mmol/mol), group 3: 7.0 ± 0.7% (53 ± 8 mmol/mol), group 4: 7.6 ± 0.8% (60 ± 9 mmol/mol), $p < 0.05$ for group 3 compared to groups 1, 2 and 4; $p > 0.005$ for comparisons between groups 1, 2 and 4).

The length of use of the device was 8 [3-21] months for the whole cohort (group 1: 10 [3-19] months, group 2: 3 [1-6] months, group 3: 32 [20-44] months, group 4: 6 [4-9] months, $p < 0.001$ for all the groups).

The outcomes in glycaemic control and glycaemic variability in the four groups are shown in Table 2. Group 1 (CGM + MDI) and group 2 (FGM + MDI) did not show any significant difference between them regarding time in range 70-180 mg/dl, time in hypoglycaemia range (< 74 mg/dl, < 54 mg/dl), time in hyperglycaemia range (> 180 mg/dl, > 250 mg/dl) or any glycaemic variability measure. Sensor use was also similar between groups.

When comparing group 3 (SAP-PLGS) to group 4 (HCL), time in range 70-180 mg/dl was higher and time in hypoglycaemia (< 74 mg/dl, < 54 mg/dl) was lower in group 4. Time in hyperglycaemia range (> 180 mg/dl, > 250 mg/dl) and glycaemic variability measures were not significantly different between groups. Sensor use was significantly higher in group 4 compared to group 3.

Group 1 (CGM + MDI) and group 2 (FGM + MDI) showed a lower time in range 70-180 mg/dl and higher time in hyperglycaemia (> 180 mg/dl, > 250 mg/dl) than group 3 (SAP-PLGS). Also, higher glycaemic variability measures were found in groups 1 and 2 compared to group 3. No differences in time in hypoglycaemia were seen and sensor use was higher in the MDI groups.

When comparing group 1 (CGM + MDI) and group 2 (FGM + MDI) to group 4 (HCL), all comparisons were favourable to group 4, including time in range 70-180 mg/dl, time in hypo- and hyperglycaemia ranges and all the glycaemic variability measures (SD, CV and MAGE). Nevertheless, sensor use was higher in the MDI groups compared to HCL.

The differences in time in range 70-180 mg/dl, time < 70 mg/dl and time > 180 mg/dl are represented in Figure 1.

A significant but small correlation was found between the length of the use of the device and the time in range 70-180 mg/dl in the whole cohort (Pearson coefficient r = 0.171, p = 0.003).

Discussion

Different treatment options for T1D people are available. CGM or FGM with MDI, sensor-augmented pumps with predictive low glucose suspend function and hybrid closed-loop systems are four widely used choices.

When deciding to use any of these options, many aspects have to be taken into consideration, including expected improvement in glycaemic control, technology burden on the patients, patient preferences and cost. Data obtained from real-world populations offer additional information that could guide clinical decisions, as no data from randomised control trials comparing all those technology choices are available.

In our study, we evaluated the outcomes in a relatively well-controlled T1D population, with stable diabetes and good adherence to the sensors and paired by some of the main demographic characteristics, and the outcomes when using the four different options were compared.

HCL showed the greatest benefit in time in range 70-180 mg/dl. No differences were seen between CGM or FGM when used as stand-alone devices in any of the glucose ranges. Interestingly, HCL were superior to SAP-PLGS in time in hypoglycaemia but not in time in hyperglycaemia. Inversely, SAP-PLGS were superior to MDI combinations in time in range 70-180 mg/dl and time in hyperglycaemia, but not in time in hypoglycaemia ranges.

Glycaemic variability measures showed a greater benefit in pump users (group 3 and 4, HCL and SAP-PLGS) than in MDI users (groups 1 and 2).

According to the international consensus guidelines [15], the HCL group was the only one reaching the target of > 70% in time in range 70-180 mg/dl. Similarly, the SAP-PLGS and the HCL groups were the ones that reached the 36% target in CV that is considered stable diabetes [16].

Sensor use was 88% in patients on HCL and 84% in patients on SAP-PLGS. We could hypothesise that the advantage of the insulin automation is perceived by the patient and he/she tends to use the sensor as continuously as possible. Nevertheless, in both cases the use was > 80%, as generally recommended, and therefore a major independent impact on glycaemic control should not be expected.

In our patients, we did not find any significant difference in the time spent in hypoglycaemia ranges between patients using CGM, with low alarms, and patients using FGM, without low alarms. We could hypothesise that in our general population of T1D subjects, with no specific issues regarding hypoglycaemia awareness, the information provided by FGM, including glucose levels and trends, could have been sufficient to control hypoglycaemia. CGM has shown superiority over FGM without alarms specifically in subjects with impaired awareness of hypoglycaemia or high hypoglycaemia risk, as reported by Reddy *et al*. [17]. Additionally, in a randomised control trial, real-time alerts have shown superiority over FGM without alerts, regarding hypoglycaemia frequency, in physically active subjects [18].

The Gold, Diamond and HypoDE studies first showed the benefit provided by CGM + MDI in a general population of T1D subjects and specifically in subjects with impaired

awareness of hypoglycaemia [1-3]. The Impact study also showed the improvement in glycaemic control provided by FGM in T1D subjects on MDI, data that have been confirmed in real-world analyses [4,5]. Abraham *et al*. found higher hypoglycaemia protection in patients using SAP-PLGS compared to sensor-augmented pump therapy alone [4]. More recently, the 670G® pivotal study showed a 72.2% of time 70-180 mg/dl in adolescents and adults [9-10].

Soupal *et al*. reported longitudinal real-world data comparing the use of CGM + MDI with CGM as a part of a sensor-augmented pump, concluding that MDI regimens are an equivalent but a lower-cost alternative to sensor-augmented pumps [12, 13]. However, no FGM or HCL were included in these analyses.

Recently, a systematic review and network meta-analysis has found a low certainty of evidence coming from randomised clinical trials regarding time in range achieved with multiple technologies in T1D [19], and also showed that the efficacy of closed-loop systems appeared better than all other approaches, including CGM+MDI, FGM+MDI and low glucose suspend systems. Additionally, Dovc *et al*. have summarised the current evidence from randomised controlled trials regarding the outcomes of each diabetes technology choice. They have showed a 60% average time in range with MDI + CGM, a slightly superior time in range with SAP-PLGS and a > 70% time in range with closed-loop systems [20].

In the future, it will become necessary to evaluate the differences in glycaemic outcomes when FreeStyle Libre® version 2 is widely available and when more advanced hybrid closed-loop systems reach the market [21, 22].

The clinical implication of our study is that, in clinical practice, the most complex diabetes technology options offer the highest time in range 70-180 mg/dl and the highest hypoglycaemia protection. T1D subjects on MDI, using glucose monitoring, CGM or FGM, achieve a nearly 60% of time in range 70-180 mg/dl. SAP-PLGS allow a nearly 70% time in range 70-180 mg/dl, with similar hypoglycaemia frequency. To reach a > 70% of time 70-180 mg/dl and a greater reduction in hypoglycaemia, automation of insulin infusion is required. When choosing a diabetes technology option, T1D patients and healthcare professionals have to balance the benefits, in terms of glycaemic control, on one side, and the burden on the people with T1D and the economic cost imposed on the healthcare system, on the other side.

Our study has limitations. The main limitation is that, although the subjects were paired by some relevant demographic characteristics, i.e. age, diabetes duration and sex, several other variables could affect the outcomes. The groups were not paired according to baseline glycaemic control, and the group using SAP-PLGS had a lower baseline HbA1c than the rest of the groups. Also, the length of the use of the device was different between groups. This difference in the length of use of the device is mainly explained by the different chronology of the introduction of each diabetes technology option in the market and its inclusion in the local reimbursement.

The strengths of our study are a large number of subjects included in each group of treatment and the representation of the most common treatment strategies in current clinical practice. To the best of our knowledge, no previous comparisons including patients using HCL have been reported.

In conclusion, our study shows the different glycaemic control and glycaemic variability outcomes achieved with four diabetes technology combinations in real-world practice in T1D people. The most complex diabetes technology options, with the highest automation of insulin infusion, allow the highest time in range and hypoglycaemia protection.

References

1. Lind M, Polonsky W, Hirsch IB, Heise T, Bolinder J, Dahlqvist S, Schwarz E, Ólafsdóttir AF, Frid A, Wedel H, Ahlén E, Nyström T, Hellman J. 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 Jan 24;317(4):379-387. https://doi: 10.1001/jama.2016.19976. Erratum in: JAMA. 2017 May 9;317(18):1912.

2. Beck RW, Riddlesworth T, Ruedy K, Ahmann A, Bergenstal R, Haller S, Kollman C, Kruger D, McGill JB, Polonsky W, Toschi E, Wolpert H, Price D; 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 Jan 24;317(4):371-378. https://doi: 10.1001/jama.2016.19975.

3. Heinemann L, Freckmann G, Ehrmann D, Faber-Heinemann G, Guerra S, Waldenmaier D, Hermanns N. Real-time continuous glucose monitoring in adults with type 1 diabetes and impaired hypoglycaemia awareness or severe hypoglycaemia treated with multiple daily insulin injections (HypoDE): a multicentre, randomised controlled trial. Lancet. 2018 Apr 7;391(10128):1367-1377. https://doi: 10.1016/S0140-6736(18)30297-6. Epub 2018 Feb 16.

4. Bolinder J, Antuna R, Geelhoed-Duijvestijn P, Kröger J, Weitgasser R. Novel glucose-sensing technology and hypoglycaemia in type 1 diabetes: a multicentre, non-masked, randomised controlled trial. Lancet. 2016 Nov 5;388(10057):2254-2263. https://doi: 10.1016/S0140-6736(16)31535-5. Epub 2016 Sep 12.

5. Gomez-Peralta F, Dunn T, Landuyt K, Xu Y, Merino-Torres JF. Flash glucose monitoring reduces glycemic variability and hypoglycemia: real-world data from Spain. BMJ Open Diabetes Res Care. 2020 Mar;8(1):e001052. https://doi: 10.1136/bmjdrc-2019-001052.

6. Abraham MB, Nicholas JA, Smith GJ, Fairchild JM, King BR, Ambler GR, Cameron FJ, Davis EA, Jones TW; PLGM Study Group. Reduction in Hypoglycemia With the Predictive Low-Glucose Management System: A Long-term Randomized Controlled Trial in Adolescents With Type 1 Diabetes. Diabetes Care. 2018 Feb;41(2):303-310. https://doi: 10.2337/dc17-1604. Epub 2017 Nov 30.

7. Beato-Víbora PI, Gil-Poch E, Galán-Bueno L, Lázaro-Martín L, Arroyo-Díez FJ. The Incremental Benefits of the Predictive Low-Glucose Suspend Function Compared to the Low-Glucose Suspend Function as Automation Against Hypoglycemia in Sensor-Augmented Pump Therapy. J Diabetes Sci Technol. 2018 Nov;12(6):1241-1243. https://doi: 10.1177/1932296818791536. Epub 2018 Jul 30.

8. Beato-Víbora PI, Quirós-López C, Lázaro-Martín L, Martín-Frías M, Barrio-Castellanos R, Gil-Poch E, Arroyo-Díez FJ, Giménez-Álvarez M. Impact of Sensor-Augmented Pump Therapy with Predictive Low-Glucose Suspend Function on Glycemic Control and Patient Satisfaction in Adults and Children with Type 1 Diabetes. Diabetes Technol Ther. 2018 Nov;20(11):738-743. https://doi: 10.1089/dia.2018.0199. Epub 2018 Sep 25.

9. Garg SK, Weinzimer SA, Tamborlane WV, Buckingham BA, Bode BW, Bailey TS, Brazg RL, Ilany J, Slover RH, Anderson SM, Bergenstal RM, Grosman B, Roy A, Cordero TL, Shin J, Lee SW, Kaufman FR. Glucose Outcomes with the In-Home Use of a Hybrid Closed-Loop Insulin Delivery System in Adolescents and Adults with Type 1 Diabetes. Diabetes Technol Ther. 2017 Mar;19(3):155-163. https://doi: 10.1089/dia.2016.0421. Epub 2017 Jan 30.

10. Bergenstal RM, Garg S, Weinzimer SA, Buckingham BA, Bode BW, Tamborlane WV, Kaufman FR. Safety of a Hybrid Closed-Loop Insulin Delivery System in Patients With Type 1 Diabetes. JAMA. 2016 Oct 4;316(13):1407-1408. https://doi: 10.1001/jama.2016.11708.

11. Beato-Víbora PI, Gallego-Gamero F, Lázaro-Martín L, Romero-Pérez MDM, Arroyo-Díez FJ. Prospective Analysis of the Impact of Commercialized Hybrid Closed-Loop System on Glycemic Control, Glycemic Variability, and Patient-Related Outcomes in

Children and Adults: A Focus on Superiority Over Predictive Low-Glucose Suspend Technology. Diabetes Technol Ther. 2020 Aug 28. https://doi: 10.1089/dia.2019.0400. Epub ahead of print.

12. Šoupal J, Petruželková L, Flekač M, Pelcl T, Matoulek M, Daňková M, Škrha J, Svačina Š, Prázný M. Comparison of Different Treatment Modalities for Type 1 Diabetes, Including Sensor-Augmented Insulin Regimens, in 52 Weeks of Follow-Up: A COMISAIR Study. Diabetes Technol Ther. 2016 Sep;18(9):532-8. https://doi: 10.1089/dia.2016.0171. Epub 2016 Aug 2.

13. Šoupal J, Petruželková L, Grunberger G, Hásková A, Flekač M, Matoulek M, Mikeš O, Pelcl T, Škrha J Jr, Horová E, Škrha J, Parkin CG, Svačina Š, Prázný M. Glycemic Outcomes in Adults With T1D Are Impacted More by Continuous Glucose Monitoring Than by Insulin Delivery Method: 3 Years of Follow-Up From the COMISAIR Study. Diabetes Care. 2020 Jan;43(1):37-43. https://doi: 10.2337/dc19-0888. Epub 2019 Sep 17.

14. Hill NR, Oliver NS, Choudhary P, Levy JC, Hindmarsh P, Matthews DR. Normal reference range for mean tissue glucose and glycemic variability derived from continuous glucose monitoring for subjects without diabetes in different ethnic groups. Diabetes Technol Ther. 2011 Sep;13(9):921-8. https://doi: 10.1089/dia.2010.0247. Epub 2011 Jun 29.

15. Battelino T, Danne T, Bergenstal RM, Amiel SA, Beck R, Biester T, Bosi E, Buckingham BA, Cefalu WT, Close KL, Cobelli C, Dassau E, DeVries JH, Donaghue KC, Dovc K, Doyle FJ 3rd, Garg S, Grunberger G, Heller S, Heinemann L, Hirsch IB, Hovorka R, Jia W,

Kordonouri O, Kovatchev B, Kowalski A, Laffel L, Levine B, Mayorov A, Mathieu C, Murphy HR, Nimri R, Nørgaard K, Parkin CG, Renard E, Rodbard D, Saboo B, Schatz D, Stoner K, Urakami T, Weinzimer SA, Phillip M. Clinical Targets for Continuous Glucose Monitoring Data Interpretation: Recommendations From the International Consensus on Time in Range. Diabetes Care. 2019 Aug;42(8):1593-1603. https://doi: 10.2337/dci19-0028. Epub 2019 Jun 8.

16. Danne T, Nimri R, Battelino T, Bergenstal RM, Close KL, DeVries JH, Garg S, Heinemann L, Hirsch I, Amiel SA, Beck R, Bosi E, Buckingham B, Cobelli C, Dassau E, Doyle FJ 3rd, Heller S, Hovorka R, Jia W, Jones T, Kordonouri O, Kovatchev B, Kowalski A, Laffel L, Maahs D, Murphy HR, Nørgaard K, Parkin CG, Renard E, Saboo B, Scharf M, Tamborlane WV, Weinzimer SA, Phillip M. International Consensus on Use of Continuous Glucose Monitoring. Diabetes Care. 2017 Dec;40(12):1631-1640. https://doi: 10.2337/dc17-1600.

17. Reddy M, Jugnee N, Anantharaja S, Oliver N. Switching from Flash Glucose Monitoring to Continuous Glucose Monitoring on Hypoglycemia in Adults with Type 1 Diabetes at High Hypoglycemia Risk: The Extension Phase of the I HART CGM Study. Diabetes Technol Ther. 2018 Nov;20(11):751-757. https://doi: 10.1089/dia.2018.0252.

18. Hásková A, Radovnická L, Petruželková L, Parkin CG, Grunberger G, Horová E, Navrátilová V, Kádě O, Matoulek M, Prázný M, Šoupal J. Real-time CGM Is Superior to Flash Glucose Monitoring for Glucose Control in Type 1 Diabetes: The CORRIDA Randomized Controlled Trial. Diabetes Care. 2020 Nov;43(11):2744-2750. https://doi:10.2337/dc20-0112.

19. 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 Aug;43(8):1967-1975. https://doi: 10.2337/dc19-1785.

20. Dovc K, Battelino T. Time in range centered diabetes care. Clin Pediatr Endocrinol. 2021;30(1):1-10. https: doi: 10.1297/cpe.30.1.

21. Lee MH, Vogrin S, Paldus B, Jones HM, Obeyesekere V, Sims C, Wyatt SA, Ward GM, McAuley SA, MacIsaac RJ, Krishnamurthy B, Sundararajan V, Jenkins AJ, O'Neal DN. Glucose Control in Adults with Type 1 Diabetes Using a Medtronic Prototype Enhanced-Hybrid Closed-Loop System: A Feasibility Study. Diabetes Technol Ther. 2019 Sep;21(9):499-506. https://doi: 10.1089/dia.2019.0120. Epub 2019 Jul 2.

22. Carlson, AL. et al. Safety And Glycemic Outcomes Of The MiniMed™ AHCL System in Subjects With T1D. 80th International Conference of the American Diabetes Association, June 12-16, 2020, Chicago/Virtual.

The authors received no funding from an external source.

The authors declare no conflict of interest.

Table 1. Comparison between treatment groups.

	All	Group 1 CGM + MDI	Group 2 FGM + MDI	Group 3 SAP-PLGS	Group 4 HCL	p value
n	302	94	87	78	43	
Age (years)	39 ± 12	40 ± 12	40 ± 13	39 ± 11	38 ± 11	0.738
Diabetes duration (years)	21 ± 10	22 ± 10	19 ± 12	22 ± 10	21 ± 9	0.220
Sex (male) n (%)	47 (141)	48 (51)	45 (52)	31 (40)	17 (40)	0.261

CGM: continuous glucose monitoring, FGM: flash glucose monitoring, SAP-PLGS: sensor-augmented pump with predictive low glucose suspend function. HCL: hybrid closed-loop system, MDI: multiple daily insulin injections.

Table 2. Glycaemic control and glycaemic variability outcomes in the four different treatment modalities.

	Group 1 **CGM + MDI**	**Group 2** **FGM + MDI**	*p value* *Group 1 vs 2*	**Group 3** **SAP-PLGS**	**Group 4** **HCL**	*p value* *Group 3 vs 4*	*p value* *Group 1 and 2 vs 3*	*p value* *Group 1 and 2 vs 4*
n	94	87		78	43			
Estimated HbA1c (%) (mmol/mol)	7.48 ± 0.97 58 ± 11	7.42 ± 0.91 58 ± 10	0.654	7.04 ± 0.67 53 ± 8	7.0 ± 0.42 53 ± 4	0.700	**≤0.003**	**≤0.001**
Mean glucose (mg/dl)	168 ± 28	166 ± 26	0.664	155 ± 19	154 ± 12	0.676	**≤0.002**	**<0.001**
Time 70-180 mg/dl (%)	59 ± 15	58 ± 14	0.798	67 ± 11	71 ± 10	**0.030**	**<0.001**	**<0.001**
Time < 70 mg/dl (%)	3.6 ± 4.6	4.4 ± 4.1	0.070	3.3 ± 3.6	1.9 ± 1.6	**0.013**	NS	**≤0.016**
Time < 54 mg/dl (%)	0.9 ± 2.2	0.7 ± 1.0	0.792	0.9 ± 1.4	0.5 ± 0.6	**0.012**	NS	**≤0.048**
Time > 180 mg/dl (%)	38 ± 16	37 ± 16	0.914	30 ± 13	27 ± 9	0.161	**≤0.001**	**<0.001**
Time > 250 mg/dl (%)	13 ± 12	12 ± 10	0.932	7 ± 6	6 ± 5	0.450	**<0.001**	**<0.001**
SD (mg/dl)	62 ± 14	63 ± 15	0.720	53 ± 10	51 ± 12	0.299	**<0.001**	**<0.001**
CV (%)	37 ± 6	38 ± 6	0.414	34 ± 5	33 ± 6	0.171	**≤0.003**	**≤0.001**
MAGE (mg/dl)	139 ± 32	150 ± 37	0.061	126 ± 24	123 ± 27	0.217	**≤0.015**	**≤0.004**
Sensor use (%)	95 ± 7	89 ± 16	0.637	84 ± 11	88 ± 14	**<0.001**	**<0.001**	**≤0.003**

CGM: continuous glucose monitoring, FGM: flash glucose monitoring, SAP-PLGS: sensor-augmented pump with predictive low glucose suspend function. HCL: hybrid closed-loop system, MDI: multiple daily insulin injections, SD: standard deviation, CV: coefficient of variation, MAGE: mean amplitude of glycaemic excursions.

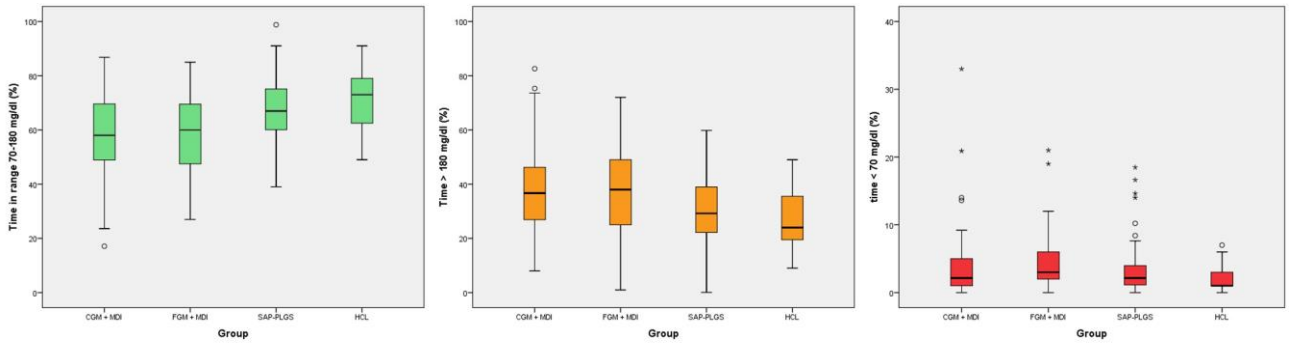

Figure 1. Time in range 70-180 mg/dl (left), time < 70 mg/dl (middle), time > 180 mg/dl (right) in the four different therapy modalities. Time in range 70-180 mg/dl: all $p < 0.05$. Time < 70 mg/dl: all $p < 0.05$, except CGM + MDI vs SAP-PLGG ($p = 0.909$) and FGM + MDI vs SAP-PLGS ($p = 0.052$). Time > 180 mg/dl: all $p \leq 0.01$ except SAP-PLGS vs HCL ($p = 0.161$). CGM: continuous glucose monitoring, FGM: flash glucose monitoring, SAP-PLGS: sensor-augmented pump with predictive low glucose suspend function. HCL: hybrid closed-loop system.