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Glycometabolic outcomes in adult type 1 diabetic patients switching to closed-loop systems

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ABSTRACT

Objective: This study aimed to evaluate glycometabolic outcomes in AID technology-naïve T1D patients after switching to Hybrid Closed Loop (HCL) and Advanced Hybrid Closed Loop (AHCL) systems.
Research design and methods: This was a 12-month, prospective, observational, two-center study on 54 type 1 diabetes (T1D) patients aged 19–65 years managed with multiple daily injections (MDI) or Continuous Subcutaneous Insulin Infusion (CSII) in open-loop to evaluate the superiority in terms of effectiveness and safety of Automated Insulin Delivery (AID) systems.
Results: HbA1c levels significantly improved at the end of the study. Time spent with glucose levels in target range ($TIR_{70\text{-}180\ mg/dL,\ 3.9\text{-}10\ mmol/L}$) increased from 50.5 ± 15.6% at baseline to 73.6 ± 8.0% at 12 months ($p < 0.001$); time spent above range ($TAR_{180\text{-}250\ mg/dL,\ 10\text{-}13.9\ mmol/L}$ and $TAR_{\geq 250\ mg/dL,\ 13.9\ mmol/L}$) decreased from 30.6 ± 9.0% and 14.2 ± 10.2 at baseline to 19.3 ± 5.3% and 4.8 ± 3.3% at 12 months ($p < 0.001$ for both), respectively; time spent below range ($TBR_{54\text{-}69\ mg/dL,\ 3\text{-}3.8\ mmol/L}$ and $TBR_{<54\ mg/dL,\ 3.0\ mmol/L}$) decreased from 3.5 ± 2.6% and 1.2 ± 1.4% at baseline to 1.9 ± 1.5% and 0.4 ± 0.7% at the end of the study ($p < 0.001$ for both); coefficient of variation (CV) decreased from 35.9 ± 7.8% at baseline to 33.0 ± 5.3% ($p < 0.05$). Satisfaction with the new technology was scored as high.
Conclusion: AID-naïve T1D patients switching to HCL/AHCL systems have significantly and safely improved their glycometabolic outcomes with their high satisfaction with the new type of treatment.

1. Introduction

The achievement of glycemic control goals in type 1 diabetes mellitus (T1D) is inextricably linked to a significant reduction in the onset and progression of microvascular complications, such as diabetic retinopathy, nephropathy, and neuropathy [1–2]. Although to a lesser extent, similar advantages seem to be registered in the long term also on macrovascular complications [3–4].

Although the widespread marketing of fast and slow insulin analogs and the pharmacological evolution of these molecules has made it possible to optimize "basal-bolus" insulin therapy, effectively reducing the hypoglycemic risk and glycemic variability, glycemic targets are often not reached. In fact, in the United States, fewer than 30% of T1D patients reach glycemic targets [only 21% of adults achieve ADA goals <7.0% (53 mmol/mol) and only 37% achieve values <7.5% (58.5 mmol/mol)] [5]. Similarly, in Italy, about 70% of patients with T1D have a glycated hemoglobin (HbA1c) ≥7% (53 mmol/mol) and 35% have values above 8.0% (64 mmol/mol) [6].

Multi-injection insulin therapy and its intensification when the therapeutic goals are not reached also leads to an increased risk of hypoglycemia. This often becomes one of the main obstacles to achieving the glycemic targets [7] because, while reducing the quality of life of patients [8], in its most serious forms it can even be the cause of permanent damage to the central nervous system and even death [9–10].

In recent years, the improvement in the performance of glycemic sensors measured in terms of mean absolute relative deviations (MARD) has allowed a complete integration of these with insulin pumps. Therefore, integrated systems implemented with algorithms with predictive low glucose suspend (PLGS) function were first marketed, which demonstrated the ability to reduce the hypoglycemic risk without

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worsening glycemic control [11–12]. More recently, devices with automated insulin delivery, also known as a closed loop or "artificial pancreas", in which the basal insulin delivery is entirely controlled by the algorithm itself to keep the patient in the time in range (TIR) for as long as possible (glycemia 70–180 mg/dl, 3.9–10 mmol/l), while minimizing hypoglycemic events, have been commercialized. These systems are also known as hybrid closed loop (HCL). Randomized control trials (RCTs) such as the real-world ones have documented an improvement in glycemic control (in terms of TIR and HbA1c) and a significant reduction in the time below range (TBR) (glycemia < 70 mg/dl, 3.9 mmol/l) with HCL systems [13,14]. The further evolution of HCL technology has led to the development of advanced hybrid closed loop (AHCL) systems capable of also delivering correction insulin microboluses to control any glycemic rises even more efficiently. The AHCL systems have been shown to consistently obtain TIRs on average higher than 70% [15–18], which represents the reference target of the current national and international guidelines [19,20]. In the presence of proven effectiveness and safety of AID systems, they could become the "gold standard" of insulin therapy in T1D in the near future. National and international guidelines [19,20] already state that these systems should be offered to all patients with T1D who are able to use them safely (alone or with a caregiver). However, real-world studies have the limitation of not having baseline patient data, which limits the clinical applicability of the results, while RCTs on these systems often have patient samples with initial values of HbA1c and other glico-metabolic parameters that are generally better than those found in the general T1D population and with low percentages of patients switching from previous MDI therapy. Indeed, this type of clinical studies is usually conducted on "overly" selected patients.

Based on these premises, the present study aimed to evaluate, in a real-world context, the improvements in glycometabolic outcomes in adult patients with T1D and a sub-optimal glycemic control and/or at high risk of hypoglycemia switching them from open-loop insulin therapies to HCL and AHCL. Particularly, the primary study endpoints were the efficacy outcomes derived by the data from the CGM download, while secondary endpoints where the safety outcomes.

2. Patients and methods

2.1. Ethic approval

The study was conducted in two Sicilian diabetes centers according to the Declaration of Helsinki principles. The protocol was approved by the ethics committee of the respective hospitals. Informed consent to use the clinical and biochemical data was obtained from each participant.

2.2. Study protocol

From December 2018 to April 2022, we consecutively enrolled patients switched from insulin therapy that did not include an HCL/AHCL system to AID technology. The HCL and AHCL systems used in this protocol were the Medtronic Minimed™ 670G and the Medtronic Minimed™ 780G. Initially, the study envisaged the use of the Medtronic Minimed™ 670G HCL system, but the marketing shortly after of the AHCL 780G system, which effectively replaced the previous model, resulted in a mixed series of users of the two technologies. By most international guidelines and by the Italian guidelines [19–21], the eligibility criteria for switching to integrated AID system were the occurrence of one or more of the following conditions, despite optimized therapy:

- Patients with poor diabetes control (HbA1c > 7.5%, 58 mmol/mol) and/or significant glycemic variability [coefficient of variation (CV) > 36%]
- Patients with problematic hypoglycemia (frequent symptomatic hypoglycemia, hypoglycemia unawareness, previous episodes of severe hypoglycemia in the last 12 months)
- To improve the quality of life (QoL) (e.g., patients who practiced physical activity frequently and/or with fear of hypoglycemia, even with HbA1c values at target).

2.3. Inclusion and exclusion criteria

Inclusion criteria: The 12-month study was conducted in adult (≥18 years of age) patients with T1D, a disease duration of at least 36 months, on insulin therapy since diagnosis, AID technology-naïve [in therapy with multiple daily injections or an insulin pump (CSII) in "open-loop" (with or without hypoglycemia prevention algorithms such as LGS/PLGS systems), with or without rt-CGM or is-CGM devices].

Exclusion criteria: patients already treated with AID systems, contextual pregnancy, presence of severe medical conditions (significant cardiac and/or pulmonary disease, stage III or higher chronic renal failure, established neoplasms, steroid therapy for any condition, etc.).

2.4. Training

All patients were provided with four instruction sessions of approximately 2 h each before switching to the AID system. In these learning sessions, all the components of the Medtronic Minimed™ 670G (patients recruited between December 2018 and August 2020) and Medtronic Minimed™ 780G (patients enrolled between September 2020 and April 2022) system were explained. These consisted of a) the insulin pump, b) the glucose sensor (Guardian™3 Sensor/Guardian™4 Sensor), c) the transmitter (Guardian™ Link 3 Transmitter for 670G and Guardian™ Link 4 Transmitter for 780G), and d) the dedicated blood glucose meter (Ascensia Contour Next® 2.4 for 670G, Roche Accu-Chek Guide Link ® for the 780G). The "bolus wizard" and when to make special boluses with the device in manual mode were explained.

Separate sessions were dedicated to the use of the glycemic sensor (skin insertion, calibration if indicated, interpretation of trend arrows), the use of the device in automatic mode, and the proper management of the physical activity.

All patients were educated/re-educated on carbohydrate counting (by a dietitian), insulin-to-carbohydrate ratio (I/CHO), sensitivity factor (FSI), glycemic goals, and active insulin. All patients shared data relating to the glycemic sensor and insulin pump (CareLink™ System software for healthcare professionals) with the care team.

2.5. Application of the closed loop systems

After the "training" phase, the insulin pump was applied, and the basal insulin administration was programmed and maintained in manual mode for 2 weeks ("run-in" period, with the LGS/PLGS functions active). All the patients then accessed the clinical centers about 15 days after the application of the insulin pump. After verifying the correct use of the device and performing a data download from the Carelink™ platform, a TIR higher than at least 50% was required for the subsequent switch to automatic mode (Auto Mode). In Auto Mode the active insulin time was set on average between 2 and 3 h, and for the 780G system the glycemic target was usually set at 100 mg/dl.

We activated a special messaging tool and telephone contacts to solve any need remotely. All patients were asked to promptly report any serious adverse events, such as severe hypoglycemia (defined by the need for third-party assistance) or diabetic ketoacidosis (DKA) requiring hospitalization. In case of significant hyperglycemia with positive ketonemia, they were urged to contact the care team as soon as possible.

Subsequent face-to-face visits were instead scheduled after approximately 6 and 12 months since the beginning of the therapy in Auto-Mode. At each visit, the anthropometric [(weight, body mass index (BMI)] and clinical parameters (blood pressure, heart rate) were

recorded, a blood sample was taken for the glycated hemoglobin measurement and the pump-sensor data was downloaded from the Carelink™ platform for the last 30 days. If necessary, the pump parameters were changed (I/CHO ratio, active insulin time, and glycemic target for the 780G). Where necessary, patients underwent another dietary consultation.

2.6. Study endpoints

At the baseline visit, we recorded the demographic, anthropometric, and clinical data of the patients, took a blood sample for HbA_{1c} measurement, and downloaded the data relating to the glycemic sensors (rt-CGM/is-CGM) for those patients who already used them.

Glycemic variability was assessed by the coefficient of variation (CV, the ratio of the standard deviation to the mean glucose value).

Efficacy outcomes, which were the primary study endpoints, were the data from the CGM download [parameter changes from baseline where applicable: Mean glucose (mg/dL), CV (%), $TIR_{70\text{-}180\ mg/dL,\ 3.9\text{-}10\ mmol/L}$, hereinafter referred to as $TIR_{70\text{-}180}$ (%), time above range $(TAR)_{180\text{-}250\ mg/dL,\ 10\text{-}13.9\ mmol/L}$, hereinafter referred to as $(TAR)_{180\text{-}250}$ (%), $TAR_{\geq 250\ mg/dL,\ 13.9\ mmol/L}$, hereinafter referred to as $TAR_{>250}$ (%), glucose management index (GMI) (%)] and changes in HbA_{1c} from baseline.

Safety outcomes, which were the secondary study endpoints, were CGM data related to hypoglycemia risk (end-of-study analysis of $TBR_{54\text{-}69\ mg/dL,\ 3\text{-}3.8\ mmol/L}$, hereinafter referred to as $TBR_{54\text{-}70}$, $TBR_{<54\ mg/dL,\ 3\ mmol/L}$, hereinafter referred to as $TBR_{<54}$, and changes from baseline where applicable) and 12-month recording of any severe hypoglycemia episodes and any episodes of DKA. System compliance was evaluated in terms of the use of the glycemic sensor (%) and permanence in auto-mode (%) (at the end of the study).

2.7. QoL and patient satisfaction assessment questionnaire

Since no questionnaire specifically assessing QoL using closed-loop systems has so far been validated, QoL and perception of the goodness of therapy were evaluated using four of the items of a validated CSII-QoL scale [22], suitably modified to be adapted to AID systems. The four multiple-choice questions (MCQs) were administered to all participants at the end of the study. The MCQs created using the Google Forms tool and made available online are as follows: [1] Overall, the automatic pump has improved my quality of life compared to previous therapy (pens or manual pump); [2] I completely trust the automatic insulin pump; [3] I would recommend my current therapy to a person with a similar form of diabetes; [4] I would never go back to any therapy other than the automatic insulin pump. The possible answers were: “Strongly agree”, “Agree”, “Neither agree nor disagree”, “Disagree”, and “Strongly disagree”.

2.8. Statistical analysis

Data are shown as mean ± standard deviation (SD). The distribution of values was evaluated using the Shapiro-Wilk test. In order to describe the magnitude of the increase (or of the decrease) of each endpoint parameter compared to baseline, the effect size was calculated using the mean or median (for normally or non-normally distributed variables, respectively) and the 95% CI of the absolute difference between the values after the end of the treatment and those at the enrolment for each specific endpoint considered. The assessment of the before-after analysis was done using the One-way analysis of variance (ANOVA), or the Kruskal-Wallis test, for normally and non-normally distributed variables, respectively. Sub-analysis of the study endpoints was performed using the two-way ANOVA. The Student *t*-test for paired samples or the Wilcoxon test for normally or non-normally distributed variables, respectively, were employed to calculate the difference between selected parameters (i.e., weight and BMI) at the beginning and the end of the study. Finally, differences in the percentages of patients in terms of TIR, TAR, and TBR were calculated using the Chi-squared test. Statistical analysis was performed using MedCalc Software Ltd. (Ostend, Belgium), version 19.6–64 bit. A p-value of <0.05 was considered statically significant.

3. Results

3.1. General and metabolic parameters of the patient cohort at the time of study enrolment

A total of 54 patients with T1DM were enrolled. Of these, 51 completed the study, while 2 patients returned to MDI due to refusal to continue insulin pump therapy, and 1 patient was lost to follow-up and, after a few months, hospitalized for DKA. Therefore, the latter was prescribed a previously used stand-alone CSII system and was followed up in another hospital. These 3 patients were not included in the follow-up data analysis.

There were no episodes of severe hypoglycemia requiring third party assistance during the study. Patients recruited up to September 2020 started therapy with the HCL system (Medtronic Minimed™ 670G, n = 22), while patients enrolled later started an AHCL system (Medtronic Minimed™ 780G, n = 32). At baseline, approximately 30% of patients were on MDI therapy, with the remaining 70% already on insulin pump therapy (CSII alone, SAP-therapy, or PLGS systems).

The general and metabolic parameters of the enrolled cohort are reported in Table 2.

The mean age of the included patients was 38 years (range 18–65 years) with approximately 20 years of disease duration. At enrolment, HbA1c demonstrated poor glycemic control (HbA1c = 8.3%, 67 mmol/mol); in line with the data detected by the glycemic sensors (GMI = 8.1%) and glycemic variability at the upper limit of normality (35.9%). Thirty-eight of 54 patients were on glycemic sensor monitoring (rt-CGM or is-CGM) at baseline, representing 70.4% of the entire sample (baseline distribution of rt-CGM and is-CGM users was 84% and 16%,

Table 1
General characteristics and metabolic parameters of the study cohort: all subjects, MDI group, and CSII group.

General parameters	All patients	MDI group	CSII group	*p*-value
N	54	16	38	–
Age (years)	38.2 ± 14.5	31.1 ± 10.3	41.2 ± 15.0	**0.017**
Male/Female	29/25	9/7	20/18	–
Duration of the disease (years)	21.0 ± 12.7	14.4 ± 10.1	23.8 ± 12.7	**0.011**
Weight (Kg)	74.6 ± 14.8	72.2 ± 15.8	75.6 ± 14.4	0.441
BMI (Kg/m^2)	26.5 ± 5.1	25.0 ± 5.4	27.2 ± 4.8	0.155
Metabolic parameters	**All subjects**	**MDI group**	**CSII group**	***p* value**
HbA1c (%) [mmol/mol]	8.3 ± 1.4 [67.2]	9.1 ± 1.5 [75.9]	7.9 ± 1.2 [62.8]	**0.003**
Mean glucose (mg/dl) [mmol/l]*	198.6 ± 38.8 [11.0 ± 2.2]	232.9 ± 34.7 [12.9 ± 1.9]	186.4 ± 32.7 [10.4 ± 1.8]	**0.001**
GMI (%)*	8.1 ± 0.9	8.9 ± 0.8	7.8 ± 0.8	**0.001**
CV (%)*	35.9 ± 7.8	33.1 ± 11.8	37.0 ± 5.7	0.182
$TIR_{70\text{-}180}$ (%)*	50.4 ± 15.6	40.0 ± 10.5	54.2 ± 15.5	**0.012**
$TAR_{180\text{-}250}$ (%)*	30.6 ± 9.0	34.8 ± 8.3	29.1 ± 8.9	0.084
$TAR_{>250}$ (%)*	14.2 ± 10.2	19.5 ± 10.1	12.3 ± 9.7	0.055
$TBR_{54\text{-}69}$ (%)*	3.5 ± 2.6	4.5 ± 3.1	3.2 ± 2.3	0.170
$TBR_{<54}$ (%)*	1.2 ± 1.3	1.2 ± 1.5	1.1 ± 1.3	0.910

Abbreviations. BMI, body mass index; rt-CGM, real-time Continuous glucose monitoring; is-CGM, intermittently scanning Continuous glucose monitoring, CSII, Continuous subcutaneous insulin infusion; CV, Coefficient of variation; GMI, Glucose management index; F, female; FGM, Flash glucose monitoring; MDI, Multiple daily injections; TAR, Time above range; TBR, Time below range; TIR, Time in rage. *Parameters of patients already on CGM/FGM systems. Values are mean ± standard deviation.

Table 2
Sub-analysis of the effects of hybrid closed loop (HCL) and advanced hybrid closed loop (AHCL).

	HCL			AHCL		
	Time 0	**Time 6**	**Time 12**	**Time 0**	**Time 6**	**Time 12**
HbA1c (%) [mmol/mol]	8.8 ± 1.5 [72.7] (n = 22)	7.5 ± 0.8* [58.5] (n = 22)	7.3 ± 0.6*,† [56.3] (n = 22)	8.0 ± 1.2 [63.9] (n = 32)	7.0 ± 0.4* [53.0] (n = 29)	6.9 ± 0.4* [51.9] (n = 29)
Mean Glucose (mg/dl) [mmol/l]	216.0 ± 35.6 [12.0 ± 2.0] (n = 12)	155.0 ± 11.9* [8.6 ± 0.7] (n = 22)	152.4 ± 9.2* [8.5 ± 0.5] (n = 22)	190.6 ± 38.2 [10.6 ± 2.1] (n = 26)	148.7 ± 11.3* [8.2 ± 0.6] (n = 29)	147.4 ± 12.9* [8.2 ± 0.7] (n = 29)
GMI (%)	8.5 ± 0.8 (n = 12)	7.0 ± 0.4* (n = 22)	6.9 ± 0.3* (n = 22)	7.9 ± 0.9 (n = 26)	6.9 ± 0.3* (n = 29)	6.8 ± 0.3* (n = 29)
CV (%)	35.9 ± 8.4 (n = 12)	34.0 ± 6.9† (n = 22)	32.8 ± 5.6 (n = 22)	36.0 ± 7.7 (n = 26)	32.0 ± 4.3* (n = 29)	33.1 ± 5.2 (n = 29)
TIR_{70-180} (%)	44.3 ± 14.4 (n = 12)	69.8 ± 10.7* (n = 22)	72.1 ± 6.7* (n = 22)	53.3 ± 15.5 (n = 26)	75.0 ± 7.9* (n = 29)	74.8 ± 8.7* (n = 29)
$TAR_{180-250}$ (%)	34.2 ± 11.1 (n = 12)	21.3 ± 5.8* (n = 22)	20.4 ± 4.5* (n = 22)	28.9 ± 7.5 (n = 26)	18.5 ± 4.6* (n = 29)	18.5 ± 5.8* (n = 29)
$TAR_{>250}$ (%)	16.8 ± 10.0 (n = 12)	6.0 ± 5.1* (n = 22)	5.0 ± 3.1* (n = 22)	13.0 ± 10.3 (n = 26)	4.4 ± 3.2* (n = 29)	4.6 ± 3.4* (n = 29)
TBR_{54-69} (%)	3.6 ± 3.4 (n = 12)	2.1 ± 1.7 (n = 22)	2.0 ± 1.7 (n = 22)	3.5 ± 2.2 (n = 26)	1.8 ± 1.5* (n = 29)	1.8 ± 1.4* (n = 29)
$TBR_{<54}$ (%)	1.2 ± 1.7 (n = 12)	0.8 ± 1.1 (n = 22)	0.5 ± 0.8 (n = 22)	1.2 ± 1.2 (n = 26)	0.3 ± 0.5* (n = 29)	0.3 ± 0.5* (n = 29)

Abbreviations. CV, Coefficient of variation; GMI, Glucose management index; TAR, Time above range; TBR, Time below range; TIR, Time in rage. *p < 0.05 (1-way ANOVA) vs. Time 0; †p < 0.05 vs. AHCL (same follow-up times). Values are mean ± standard deviation.

respectively). All baseline parameters derived from the rtCGM/isCGM systems relating to hyperglycemic risk (TIR_{70-180}, $TAR_{180-250}$, $TAR_{>250}$) were outside the reference "targets". Notably, at enrolment, patients in the MDI group had higher HbA1c, glucose, GMI, and lower TIR_{70-180}, than those in the CSII group. They were also younger, with shorter disease duration than the CSII group (Table 2).

3.2. Comparison to baseline

Laboratory-measured **HbA1c** decreased from 8.3 (67 mmol/mol) ± 1.4% at baseline to 7.2 (55 mmol/mol) ± 0.6% at 6 months and 7.0 (53 mmol/mol) ± 0.5 at 12 months (p < 0.001). The treatment effect was −0.9% [95% CI −1.2, −0.7] from baseline at 6 months and −1.0% [95% CI −1.6, −0.7] at 12 months (Fig. 1, **panel A**), thus supporting the efficacy of the treatment.

Similarly, **mean glucose value** decreased from 198.6 ± 38.8 mg/dl (11 ± 2.1 mmol/L) at baseline to 151.4 ± 11.9 mg/dl (8.4 ± 0.7 mmol/L) at 6 months and 149.6 ± 11.6 mg/dl (8.3 ± 0.6 mmol/L) at 12 months (p < 0.001). The treatment effect was −39.5 mg/dl [95% CI −59.1, −27.0] from baseline at 6 months and −41.5 mg/dl [95% CI −67.0, −26.6] at 12 months (Fig. 1, **panel B**).

GMI decreased as well from 8.1 ± 0.9% at baseline to 7.0 ± 0.4% at 6 months and to 6.9 ± 0.3 at 12 months (p < 0.001). The treatment effect was −1.1% [95% CI −1.4, −0.8] from baseline at 6 months and −1.2% [95% CI −1.5, −0.9] at 12 months (Fig. 1, **panel C**).

CV decreased from 35.9 ± 7.8% at baseline to 32.8 ± 5.6% at 6 months and 33.0 ± 5.3 at 12 months (p = 0.038). The treatment effect was: −4.0% [95% CI −7.7, −0.0] from baseline at 6 months and −5.2% [95% CI −8.5, −0.7] at 12 months (Fig. 1, **panel D**).

TIR_{70-180} increased from 50.5 ± 15.6% at baseline to 72.8 ± 9.5% at 6 months and 73.6 ± 8.0% at 12 months (p < 0.001). The treatment effect was 23.5% [95% CI 18.1, 28.8] from baseline at 6 months and 24.4% [95% CI 17.3, 33.3]) at 12 months. Starting from extremely low baseline values (only 10.5% of patients had a TIR_{70-180} > 70% at baseline), 66.7% of participants achieved a TIR_{70-180} > 70%, as recommended by international guidelines at both 6 and 12 months (Fig. 2). Compared to enrolment, the percentage of patients achieving a TIR>70% was 6.4 times higher with AID technology.

$TAR_{180-250}$ and **$TAR_{>250}$** decreased from 30.6 ± 9.0% and 14.2 ± 10.2 at baseline to 19.7 ± 5.3% and 5.1 ± 4.2% at 6 months and 19.3 ± 5.3% and 4.8 ± 3.3% at 12 months (p < 0.001 for both). The treatment effect was −11.8% [95% CI −14.9, −8.6] from baseline at 6 months and −12.4% [95% CI −15.4, −9.3] at 12 months for $TAR_{180-250}$, and −8.5% [95% CI −11.7, −5.4] at 6 months and −6.0% [95% CI −10.7, −2.7] for $TAR_{>250}$. 86.3% and 52.9% of participants achieved a $TAR_{180-250}$ < 25% and a $TAR_{>250}$ < 5%, respectively (from baseline values of 28.9% and 10.5%), as recommended by international guidelines (Fig. 2).

Supporting the safety of the treatment, **TBR_{54-69}** and **$TBR_{<54}$** decreased from 3.5 ± 2.6% and 1.2 ± 1.4 at baseline to 1.9 ± 1.6% and 0.5 ± 0.9% at 6 months, and 1.9 ± 1.5% and 0.4 ± 0.7% at 12 months (p < 0.001 for both). The treatment effect was (absolute value) −2.1% [95% CI −3.1, −1.1] and (percentage value) −50.0% [95% CI –66.7, −21.5] from baseline at 6 months (absolute value) and −1.0% [95% CI −3.0, −0.6] and (percentage value) −33.3% [95% CI –66.7, −7.3] at 12 months for TBR_{54-69}, (absolute value); −1.8% [95% CI −2.5, −1.1] and (percentage value) –100.0% [95% CI –100.0, −100.0] at 6 months, and (absolute value) −1.7% [95% CI −2.4, −1.1] and (percentage value) –100.0% [95% CI –100.0, −89.1] for $TBR_{<54}$. 92.2% and 72.5% of participants achieved a TBR_{54-69} < 4% and a $TBR_{<54}$ < 1%, respectively, as recommended by international guidelines) (Fig. 2).

3.3. HCL vs. AHCL sub-analysis

Laboratory-measured **HbA1c** decreased significantly from baseline at 6 months and 12 months in both closed-loop systems, indicating their efficacy. In the HCL group, the treatment effect was −1.3% [95% CI −3.8, −0.3] from baseline at 6 months and −1.4% [95% CI −4.1, 0.3] at 12 months. HbA1c also decreased in the AHCL group with a treatment effect of −0.9% [95% CI −7.9, 0.3] from baseline ad 6 months and −0.8% [95% CI −7.9, 0.3] at 12 months, respectively. However, after 12 months, the HbA1c levels achieved by the AHCL group were significantly lower than those of the HCL group (Table 3).

GMI (%) decreased significantly from baseline at 6 months and 12 months in both closed-loop systems. In the HCL group, the treatment effect was −1.8% [95% CI −2.8, 0.2] from baseline at 6 months and −1.7% [95% CI −2.6, 0.0] 12 months. GMI also decreased in the AHCL group. The treatment effect was −0.7% [95% CI −2.4, −0.0] and −0.7% [95% CI −2.6, −0.0], respectively, at 6 and at 12 months (Table 1).

Mean glucose level decreased significantly at the end of the study in both HCL and AHCL groups. The treatment effect was −68.5 mg/dl [95% CI −110.5, 6.4] in the HCL group and −31.0 mg/dl [95% CI −110.9, 0.7] in the AHCL group, while the **glucose variability**, as indicated by the **CV** decreased significantly from baseline only at 6 months in the AHCL group (Table 2). The treatment effect was −6.0% [95% CI −18.0, 29.3] in the HCL group and −4.5% [95% CI −16.8, 12.2] in the AHCL group.

TIR_{70-180} significantly increased at 6 months and 12 months in both HCL (the treatment effect was 30.5% [95% CI −6.4, 57.4] and 33.5%

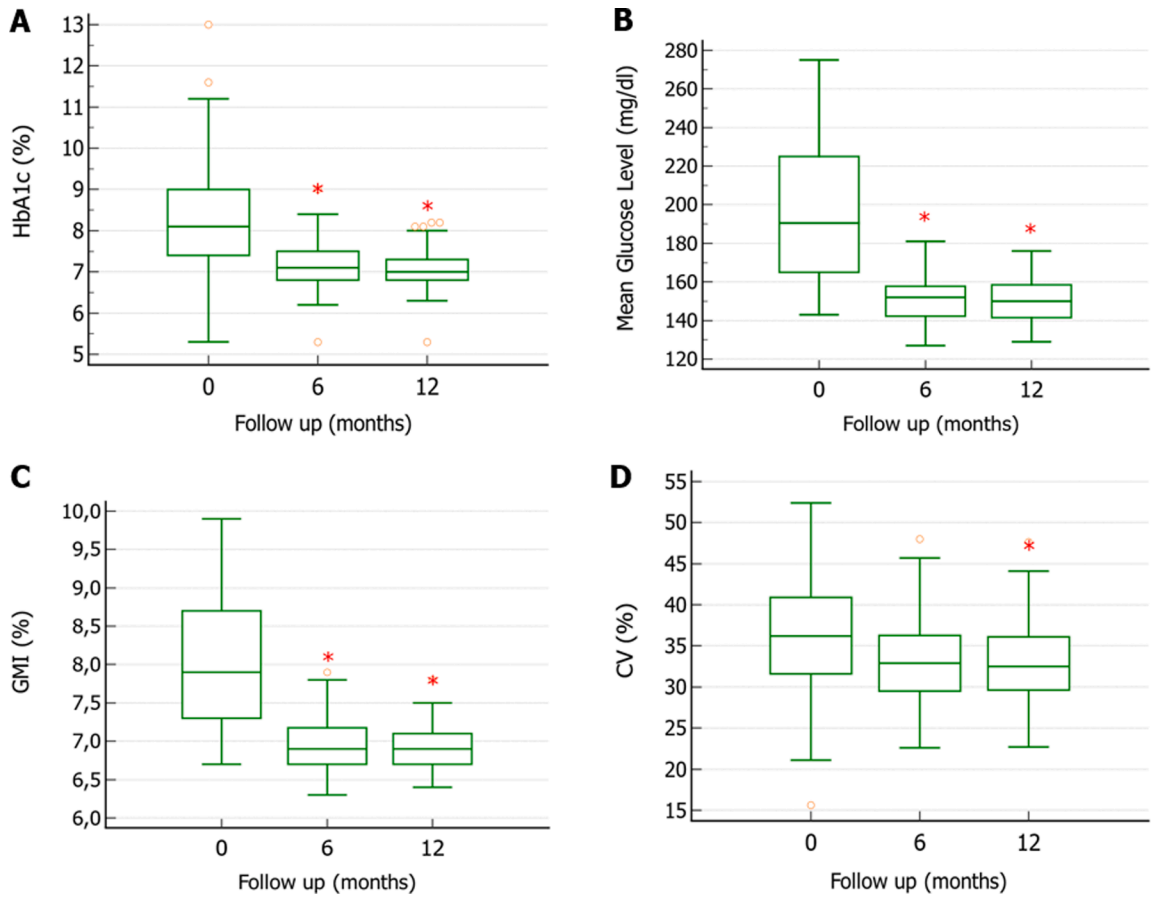

Fig. 1. Effects of the "Closed Loop" systems on metabolic parameters in patients with type 1 diabetes mellitus. The use of the HCL and AHCL systems results in a significantly improved HbA1c at the 6th and 12th month of observation (**Panel A**), significantly reduced mean glucose levels at the 6th and 12th month of observation (**Panel B**), significantly reduced GMI at the 6th and 12th month of observation (**Panel C**), and significantly improved CV starting from the 12th month of observation (**Panel D**) compared to baseline insulin therapy. ***Abbreviations.*** CV, Coefficient of variation; GMI, Glucose management index. *p < 0.05 vs. Time 0.

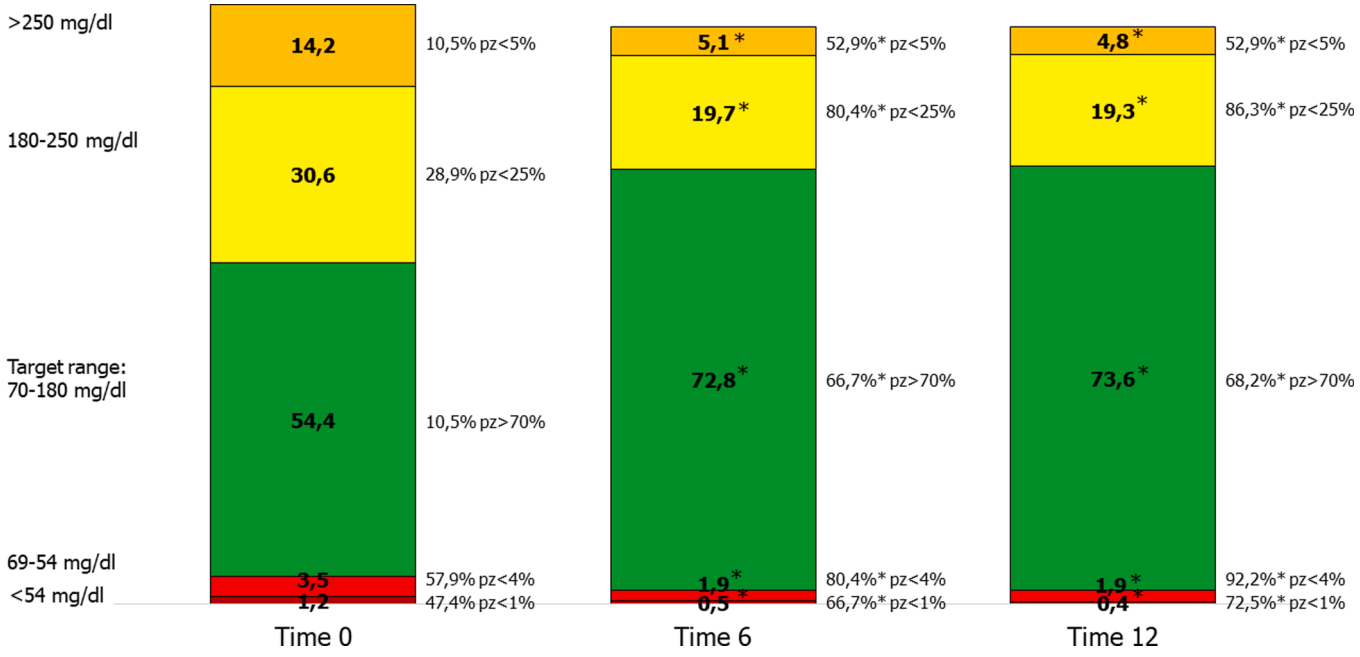

Fig. 2. Effects of the "Closed Loop" systems on TIR, TAR and TBR. The use of HCL and AHCL significantly increased the $TIR_{70\text{-}180}$ at the 6th and 12th month of observation, significantly reduced the $TAR_{180\text{-}250}$, and the $TAR_{>250}$ and $TBR_{54\text{-}69}$ and $TBR_{<54}$ at the 6th and 12th month of observation compared to non-closed-loop insulin therapy. *p < 0.05 (Chi-squared test) vs. Time 0.

Table 3
Sub-analysis of the changes at 6 and at 12 months, according to the use of multiple daily injections (MDI) or continuous subcutaneous insulin infusion (CSII) before the switch to the closed loop system.

	Time 6mean (95% CI)			**Time 12**mean (95% CI)		
	MDI	**CSII**	***p* value**	**MDI**	**CSII**	***p* value**
HbA1c (%)	−2.7 (−4.4 to −1.0)	−1.0 (−1.4 to −0.5)	**0.001**	−2.9 (−4.6 to −1.2)	−1.1 (−1.6 to −0.6)	**0.006**
Mean glucose (mg/dl) [mmol/l]	−79.7 [−4.4] (−103.4 to −56.0) [−5.7 to −3.1]	−36.9 [−2.0] (−49.3 to −24.4) [−2.7 to −1.3]	**0.001**	−78.3 [−4.3] (−105.1 to −51.5) [−5.8 to −2.8]	−40.0 [−2.2] (−53.3 to −26.7) [−2.9 to −1.5]	**0.006**
GMI (%)	−1.9 (−2.5 to −1.4)	−0.9 (−1.1 to −0.6)	**0.001**	−1.9 (−2.5 to −1.3)	−1.0 (−1.3 to −0.7)	**0.005**
CV (%)	1.8 (−9.5 to 13.1)	−5.9 (−8.7 to −3.1)	**0.041**	−0.4 (−11.2 to 11.9)	−4.9 (−8.0 to −1.9)	0.176
TIR_{70-180} (%)	32.8 (23.7 to 41.9)	20.4 (14.1 to 26.6)	**0.039**	32.2 (23.7 to 40.7)	21.8 (15.2 to 28.4)	0.091
$TAR_{180-250}$ (%)	−16.4 (−23.0 to −9.9)	−10.2 (−15.8 to −6.6)	0.078	−15.6 (−21.7 to −9.4)	−11.3 (−15.0 to −7.6)	0.229
$TAR_{>250}$ (%)	−13.0 (−21.3 to −4.7)	−7.0 (−10.3 to −3.7)	0.093	−13.3 (−21.5 to −5.1)	−8.2 (−12.2 to −4.3)	0.188
TBR_{54-69} (%)	−3.5 (−5.8 to −1.2)	−1.6 (−2.8 to −0.4)	0.100	−3.5 (−5.9 to −1.1)	−1.7 (−2.8 to −0.5)	0.092
$TBR_{<54}$ (%)	−2.0 (−5.2 to 1.2)	−1.7 (−2.4 to −1.0)	0.745	−2.3 (−4.6 to 0.1)	−1.6 (−2.3 to −0.9)	0.414

Abbreviations. CI, confidence interval; CV, Coefficient of variation; GMI, Glucose management index; TAR, time above range; TBR, Time below range; TIR, Time in rage. *p* calculated using the Student' *t* test or the Mann-Whitney *U* test, for normally or non-normally distributed variables, respectively. Values are mean and 95% of the confidence interval.

[95% CI 2.7, 55.8]) and the AHCL (the treatment effect was 20.0% [95% CI −4.6, 47.9] and 30.3% [95% CI −0.9, 212.7]) groups. 59.1% and 72.4% of participants achieved a $TIR_{70-180} > 70\%$, as recommended by international guidelines, respectively, in HCL and AHCL groups (Fig. 3).

$TAR_{180-250}$ and **$TAR_{>250}$** significantly decreased from baseline at 12 months in both the HCL (the treatment effect was −16.5% [95% CI −33.3, 6.0] and −10.0% [95% CI −32.3, −0.1]) and the AHCL group (the treatment effect from baseline −10.5% [95% CI −27.7, 0.2] and −4.0% [95% CI −28.3, 1.6]). 86.4% and 86.2% of participants achieved a $TAR_{180-250} < 25\%$, while a $TAR_{>250} < 5\%$ was obtained by 50.0% and 55.1%, as recommended by international guidelines, respectively, in the HCL and AHCL group (Fig. 3).

TBR_{54-69} and **$TBR_{<54}$** significantly decreased from baseline at 12 months in the HCL group (the treatment effect in respect of basal values (absolute value) −2.5% [95% CI −7.0, −1.0], (percentage value) −58.3% [95% CI −100.0, 50.0] and (absolute value) −3.0% [95% CI −3.0, 0.0], (percentage value) –100.0% [95% CI −100.0, 0.0]), and in the AHCL group (treatment effect in respect of basal values (absolute value) −1.0% [95% CI −6.4, −1.4], (percentage value) −33.3% [95% CI −100.0, 135.0] and (absolute value) −1.0% [95% CI −4.5, 0.0] (percentage value) −100.0% [95% CI −100.0, 0.0]). 90.9% and 93.1% of participants achieved a $TBR_{54-69} < 4\%$ and a $TBR_{<54} < 1\%$ was achieved by 68.2% and 75.9%, as recommended by international guidelines, respectively, in HCL and AHCL groups (Fig. 3).

Overall, after 12 months, the HbA1c levels achieved by the AHCL group were significantly lower than those of the HCL group and the percentage of patients reaching the target in terms of TIR was significantly higher (72.4% vs. 59.1%) (Fig. 3); we found no other differences relative to all other parameters analyzed.

3.4. *Weight* and BMI

Body weight (74.2 ± 14.4 kg vs. 74.6 ± 14.8 kg, p = 0.855) and BMI (26.5 ± 5.1 Kg/m^2 vs. 26.1 ± 6.1 Kg/m^2, p = 0.918) did not change significantly at the end of the study compared to baseline values.

3.5. Compliance with therapy

At the end of the study (12 months), participants in the HCL and AHCL groups used the sensor for a mean of 87.5 ± 9.0% and 84.7 ± 16.6% (p = 0.419) of the time, respectively, with overall use of 87.5 ± 13.8% of the time. Furthermore, HCL and AHCL participants spent an average of 86.8 ± 13.7% and 86.2 ± 18.1% (p = 0.901) in Auto Mode, corresponding to 86.5 ± 16.2% in the overall cohort.

3.6. MDI vs. CSII sub-analysis

A sub-analysis of the 6- and 12-months changes from baseline by MDI or CSII use before switching to closed loop system showed a higher degree of improvement in patients with a more unfavorable initial glycometabolic setting (i.e. the MDI group) (see Table 2). Notably, the improvement in HbA1c, blood glucose, GMI, CV, and TIR_{70-180} achieved after 6 months was higher in the MDI group then in the CSII group. At 12 months, the improvement in HbA1c, mean blood glucose, and GMI remained significantly higher in the MDI group than in the CSII group (Table 3).

3.7. Evaluation of patient satisfaction

A subjective improvement in QoL was perceived by patients after switching to closed-loop systems. As a result, the vast majority of participants (up to 97.5%) agreed or strongly agreed with the statement "Overall, the automatic pump has improved my quality of life compared to previous therapy (pens or manual pump)", while the rest neither agreed nor disagreed. None of the participants disagreed or strongly disagreed with the statement (**Supplementary Fig. 1**).

The participants showed satisfaction with the therapy. In fact, approximately 75% of the patients stated that they completely trusted the automatic system, 97.5% would recommend it to a person with a similar form of diabetes, and finally, approximately 95% would never return to previous therapy (**Supplementary Fig. 2**).

4. Discussion

This 1-year prospective, two-center observational study extensively evaluated glycometabolic outcomes in AID technology-naïve adult T1D patients after switching to insulin pump therapy with HCL (Medtronic Minimed™ 670G) or AHCL (Medtronic Minimed™ 780G). In our cohort, approximately 30% of the patients came from a previous MDI therapy (±use of rt-CGM or is-CGM), while the remaining 70% had already been treated with CSII (±use of rt-CGM or is-CGM) but in "open-loop" with or without hypoglycemia prevention algorithms (PLGS Systems). Our data support the efficacy of the treatment. In fact, at the end of the study (12 months), a mean HbA1c of 7.0% (53 mmol/mol) was achieved, closely in line with GMI values (6.9%), with a median reduction from baseline

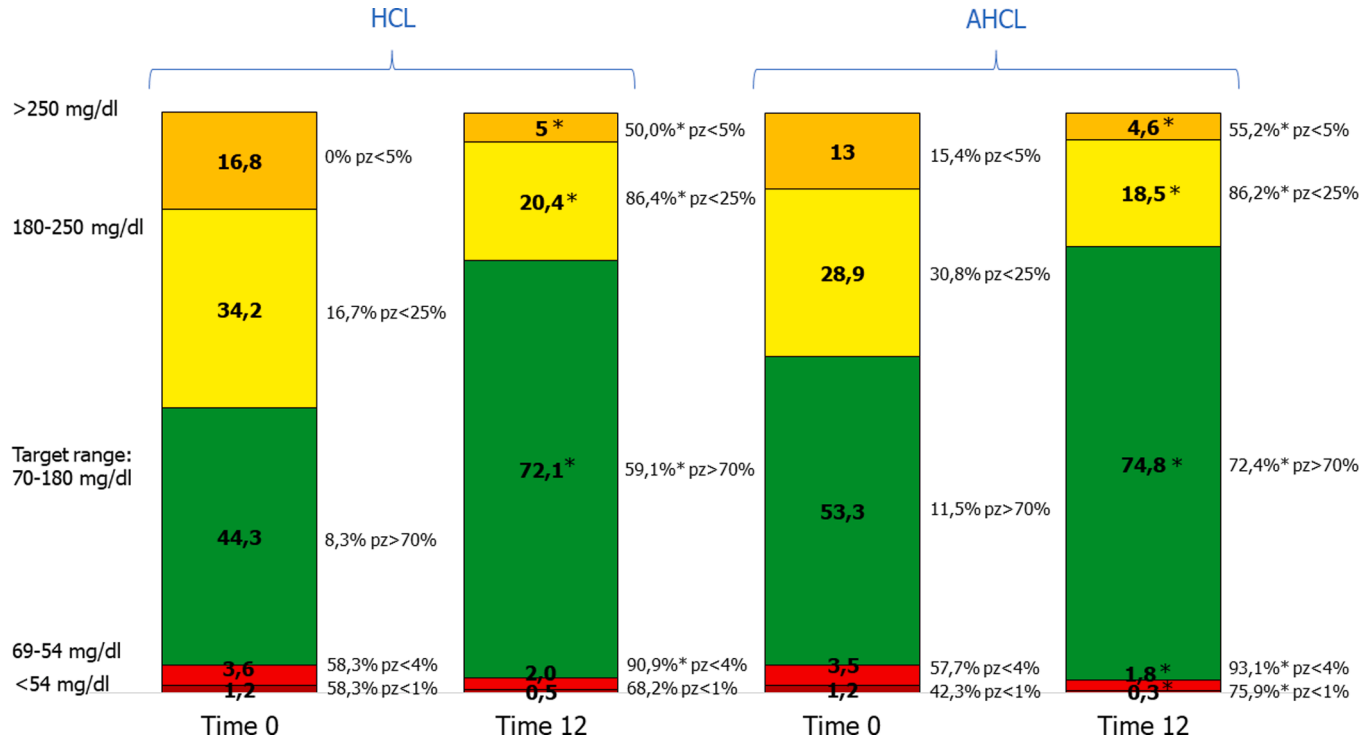

Fig. 3. Effects of hybrid closed loop (HCL) and advanced hybrid closed loop (AHCL) systems on TIR, TAR and TBR. The use of HCL and AHCL significantly increased the $TIR_{70\text{-}180}$ at the 6th and 12th month of observation, significantly reduced the $TAR_{180\text{-}250}$, and the $TAR_{>250}$ and $TBR_{54\text{-}69}$ and $TBR_{<54}$ at the 6th and 12th month of observation compared to baseline insulin therapy. *$p < 0.05$ (Chi-squared test) vs. Time 0.

of 1.0% for HbA1c and 1.2% for GMI; it is also noteworthy that the average $TIR_{70\text{-}180}$ obtained at the end of the study was 73.5%, with an absolute increase compared to the baseline of as much as 20.5%, which represents a very relevant data. The improvement in glycemic control was obtained without worsening, indeed improving, the parameters relating to the risk of hypoglycemia (already low at baseline), with an average reduction of $TBR_{54\text{-}69}$, $TBR_{<54}$, and CV by 1.0%, 1.7%, and 5.2% at the end of the study, respectively. Furthermore, about 67% of the patients obtained a $TIR_{70\text{-}180} > 70\%$ and 92% a $TBR_{54\text{-}69} < 4\%$, cut-offs currently recommended by all national (Italian) and international guidelines [19–21].

HbA1c was significantly lower in patients using an AHCL system than in those using an HCL algorithm, as the percentage of patients meeting the TIR target was significantly higher. Indeed, in the AHCL cohort, we documented a mean HbA1c of 6.9% (52 mmol/mol) compared to a mean of 7.3% (56 mmol/mol) in the HCL group. Probably due to the smallness of the subpopulations studied, we found no significant differences in TIR between HCL and AHCL systems. In their pivotal study, Carlson and colleagues [23] found an improvement in TIR from 68.8% to 74.5% after 3 months of the use of the 780G system use, similar to what found in the present study, but our average value at baseline was much lower. Other studies have demonstrated that the AHCL system provides an additional improvement in TIR and HbA1c [24,25] compared to the HCL algorithm in line with the results of the multinational FLAIR crossover RCT [26]. In our study, although the majority of the patients who used the AHCL system optimized their parameters (glycemic target: 100 mg/dl, active insulin time: 2 h), allowing for the achievement of better glycometabolic control [17,18,27], probably if we had used these parameters in all patients, we would have obtained even higher TIRs as, demonstrated by other studies [18,27].

Patients who previously practiced MDI therapy and who showed significantly worse baseline parameters than those already treated with CSII achieved significantly greater improvements in glycemic parameters compared to the latter At the end of the study, these patients achieved values similar to the group that already practiced CSII (but in "open-loop"), demonstrating the fact that the worse the baseline glycemic control, the more consistent the advantages of the "closed-loop" switch will be. Our results confirm and extend those of a recent meta-analysis [28] comparing multiple insulin therapies with time in range, showing that HCL systems perform better than other therapeutic strategies. In any case, the MDI group obtained a mean TIR of >70% and a mean TAR < 25%, confirming the results of a 12-week study that evaluated the glycemic outcomes in 34 children and adolescents with T1DM who switched from MDI therapy to Minimed 780G [29]. Our results in terms of $TIR_{70\text{-}180}$ and HbA1c obtained at the end of the study are in line with those shown by other studies (both RCTs and "Real-World"), concerning HCL [13,30–32] and AHCL [17,18,29,32] systems. However, it is interesting to note that we obtained these results by studying a cohort of T1D patients with baseline glycemic values on average worse than in many other previously published RCTs [24,27,33,34] in which more selected patients were recruited. A significant percentage of patients also came from multi-injection therapy and many of them were naive to glycemic sensors. The latter have also achieved great gains in terms of improved metabolic outcomes after switching to AID systems.

No episodes of severe hypoglycemia and no episodes of DKA were detected during the study. The safety of these systems has already been documented by some reviews analyzing national registries and/or by randomized trials, observational studies, retrospective studies, and case reports [35,36].

Weight and BMI after 12 months did not change significantly from baseline, as already confirmed by the literature [37]. This suggests that the improvement in glycemic control is independent of a change in body weight or BMI.

An important contribution to obtaining good glycometabolic control at the end of the study is closely linked to patient adherence to the correct use of the system. This was evaluated through the percentage of use of the sensor and the time spent in "Auto Mode" at the end of the study (87.5% and 86.5%, respectively). Real-life studies have reported a

higher discontinuation rate for HCL systems, usually due to "alarm fatigue", than clinical trials [38]. However, the "retention" in our study was extremely high, as nearly all patients had completed the 12-month follow-up. This was probably due to the protocol design, educational programs, and also the use of AHCL systems which showed a lower rate of therapy discontinuation. Indeed, only three patients dropped out of the study: two of them (both in the HCL group) returned to MDI therapy and the other patient lost to follow-up and was then hospitalized for DKA for probable improper use of the device. Comprehensive training plays a key role in achieving long-term success with new technologies. For this reason, our educational scheme was managed with a protocol that included several training sessions (see the "training" section).

QoL and patient satisfaction with the AID system were assessed through a specific 4-item MCQ questionnaire, modified for AID systems. The advantages/disadvantages ratio evaluated by the patients was unanimously in favor of the use of the new technology. Indeed, over 95% of patients in the study reported that the AID system improved overall QoL. Furthermore, 75% of the patients stated that they completely trust the automatic system, 97.5% would recommend it to a person with a similar form of diabetes and, finally, about 95% would never go back to the therapy previously practiced.

This study has many relevant strengths. First, our series faithfully reflects what happens in daily clinical practice. Indeed, patients with a broad age range (18–65 years) were consecutively recruited from a real-life cohort with multiple types of therapies, ranging from those with no technology (MDI + self-monitoring of blood glucose) to those that were already treated with pump systems also with PLGS algorithm. Furthermore, the prospective design and duration of the study follow-up (12 months) were adequate to detect not only the glycometabolic benefits described but also their long term duration; even longer follow-up (of several years) could be very informative about the "durability" of AID systems. However, some limitations should be noted. First, only two centers participated in patient recruitment and the sample size is small and, for this reason, the sub-analyses have a low statistical weight. Furthermore, our population consists of a relatively young cohort (mean age 38 years) for making a strong statement on the applicability to an older age group of people with T1D. In addition, only one manufacturer's system was evaluated but different technologies (HCL and AHCL systems) were used, which make the treatment of patients heterogeneous. However, this last aspect could also be seen as a strength, as it allowed us to evaluate the differences between the two technologies.

5. Conclusion

The switch to therapy with AID systems in patients coming from multiple types of insulin treatments has made it possible to obtain a significant improvement in all glycemic parameters (HbA1c, $TIR_{70\text{-}180}$, $TAR_{180\text{-}250}$, $TAR_{>25}$, GMI, average glycemia), with a simultaneous reduction of hypoglycemia risk parameters ($TBR_{54\text{-}69}$, $TBR_{<54}$, CV). The "durability" of these advantages was significant (12 months), allowing us to hypothesize that the benefits of this technology do not diminish over time. Evaluation of the QoL and patient satisfaction revealed high scores in all areas explored. Almost all of the study participants declared that they would never go back to their previous therapy, confirming their high satisfaction with the AID therapy. Our study shows that these technologies should be offered to all patients with T1D, regardless of baseline glycemic control, and especially to those who have poor glycemic control even without experience with technological systems at baseline. In conclusion, our study confirms that the new AID systems represent nowadays the "gold standard" in the treatment of T1D.

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Attestation and data sharing statement

Data will be made available to the editors of the journal for review or query upon request.

Declaration of Competing Interest

The authors declare that they have no known competing financial interests or personal relationships that could have appeared to influence the work reported in this paper.

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None.

Author's contributions

G.P. conceived the study; G.P. extracted the data from the clinical charts and elaborated the dataset; R.C. analyzed the data and created the figures; R.C. and G.P. wrote the draft; R.C., A.E.C., R.A.C., C.F. and S.L.V. reviewed the article; S.L.V. and A.E.C. supervised the study; G.P. and S. L.V. are the project managers. All authors approved the final version of the article.

Appendix A. Supplementary data

Supplementary data to this article can be found online at https://doi.org/10.1016/j.diabres.2023.110907.

References

[1] Diabetes Control and Complications Trial Research Group; Nathan DM, Genuth S, Lachin J, Cleary P, Crofford O, Davis M, et al. The effect of intensive treatment of diabetes on the development and progression of long-term complications in insulin-dependent diabetes mellitus. N Engl J Med. 1993 Sep 30;329(14):977-86. doi: 10.1056/NEJM199309303291401. PMID: 8366922.

[2] Diabetes Control and Complications Trial/Epidemiology of Diabetes Interventions and Complications Research Group; Lachin JM, Genuth S, Cleary P, Davis MD, Nathan DM. Retinopathy and nephropathy in patients with type 1 diabetes four years after a trial of intensive therapy. N Engl J Med. 2000 Feb 10;342(6):381-9. doi: 10.1056/NEJM200002103420603. Erratum in: N Engl J Med 2000 May 4;342 (18):1376. PMID: 10666428; PMCID: PMC2630213.

[3] Selvin E, Marinopoulos S, Berkenblit G, Rami T, Brancati FL, Powe NR, et al. Meta-analysis: glycosylated hemoglobin and cardiovascular disease in diabetes mellitus. Ann Intern Med 2004 Sep 21;141(6):421–31. https://doi.org/10.7326/0003-4819-141-6-200409210-00007. PMID: 15381515.

[4] Stettler C, Allemann S, Jüni P, Cull CA, Holman RR, Egger M, et al. Glycemic control and macrovascular disease in types 1 and 2 diabetes mellitus: Meta-analysis of randomized trials. Am Heart J 2006 Jul;152(1):27–38. https://doi.org/10.1016/j.ahj.2005.09.015. PMID: 16824829.

[5] Foster NC, Beck RW, Miller KM, Clements MA, Rickels MR, DiMeglio LA, et al. State of Type 1 Diabetes Management and Outcomes from the T1D Exchange in 2016-2018. Diabetes Technol Ther. 2019 Feb;21(2):66-72. doi: 10.1089/dia.2018.0384. Epub 2019 Jan 18. Erratum in: Diabetes Technol Ther. 2019 Apr;21(4):230. PMID: 30657336; PMCID: PMC7061293.

[6] Diabete tipo 1. Annali Associazione Medici Diabetologi (AMD) 2020. https://aemmedi.it/nuovi-annali-amd-2020/.

[7] Cryer PE. Hypoglycemia: still the limiting factor in the glycemic management of diabetes. Endocr Pract 2008 Sep;14(6):750–6. https://doi.org/10.4158/EP.14.6.750. PMID: 18996798.

[8] Johnson SR, Cooper MN, Davis EA, Jones TW. Hypoglycaemia, fear of hypoglycaemia and quality of life in children with Type 1 diabetes and their parents. Diabet Med 2013 Sep;30(9):1126–31. https://doi.org/10.1111/dme.12247. Epub 2013 Jun 28 PMID: 23808967.

[9] Feltbower RG, Bodansky HJ, Patterson CC, Parslow RC, Stephenson CR, Reynolds C, et al. Acute complications and drug misuse are important causes of death for children and young adults with type 1 diabetes: results from the Yorkshire Register of diabetes in children and young adults. Diabetes Care 2008 May;31(5):922–6. https://doi.org/10.2337/dc07-2029. Epub 2008 Feb 19 PMID: 18285550.

[10] Skrivarhaug T, Bangstad HJ, Stene LC, Sandvik L, Hanssen KF, Joner G. Long-term mortality in a nationwide cohort of childhood-onset type 1 diabetic patients in Norway. Diabetologia 2006 Feb;49(2):298–305. https://doi.org/10.1007/s00125-005-0082-6. Epub 2005 Dec 20 PMID: 16365724.

[11] Abraham MB, Nicholas JA, Smith GJ, Fairchild JM, King BR, Ambler GR, et al. 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. doi: 10.2337/dc17-1604. Epub 2017 Nov 30. PMID: 29191844.

[12] Forlenza GP, Li Z, Buckingham BA, Pinsker JE, Cengiz E, Wadwa RP, et al. Predictive Low-Glucose Suspend Reduces Hypoglycemia in Adults, Adolescents, and Children With Type 1 Diabetes in an At-Home Randomized Crossover Study:

Results of the PROLOG Trial. Diabetes Care 2018 Oct;41(10):2155–61. https://doi.org/10.2337/dc18-0771. Epub 2018 Aug 8 PMID: 30089663.
[13] Faulds ER, Zappe J, Dungan KM. Real-world implications of hybrid close loop (HCL) insulin delivery system. Endocr Pract. 2019 May;25(5):477-484. doi: 10.4158/EP-2018-0515. Epub 2019 Mar 13. PMID: 30865545; PMCID: PMC6832708.
[14] Garg SK, Grunberger G, Weinstock R, Lawson ML, Hirsch IB, DiMeglio LA, et al. Improved Glycemia with Hybrid Closed-Loop Versus Continuous Subcutaneous Insulin Infusion Therapy: Results from a Randomized Controlled Trial. Diabetes Technol Ther 2023 Jan;25(1):1–12.
[15] Breton MD, Kovatchev BP. One Year Real-World Use of the Control-IQ Advanced Hybrid Closed-Loop Technology. Diabetes Technol Ther. 2021 Sep;23(9):601-608. doi: 10.1089/dia.2021.0097. Epub 2021 Apr 21. PMID: 33784196; PMCID: PMC8501470.
[16] Pinsker JE, Müller L, Constantin A, Leas S, Manning M, McElwee Malloy M, et al. Real-World Patient-Reported Outcomes and Glycemic Results with Initiation of Control-IQ Technology. Diabetes Technol Ther. 2021 Feb;23(2):120-127. doi: 10.1089/dia.2020.0388. Epub 2020 Sep 10. PMID: 32846114; PMCID: PMC7868573.
[17] Silva JD, Lepore G, Battelino T, Arrieta A, Castañeda J, Grossman B, et al. Real-World Performance of the MiniMed™ 780G System: First Report of Outcomes from 4120 Users. Diabetes Technol Ther 2022 Feb;24(2):113–9. https://doi.org/10.1089/dia.2021.0203. PMID: 34524003; PMCID: PMC8817690.
[18] Arrieta A, Battelino T, Scaramuzza AE, Da Silva J, Castañeda J, Cordero TL, et al. Comparison of MiniMed 780G system.
[19] ElSayed NA, Aleppo G, Aroda VR, Bannuru RR, Brown FM, Bruemmer D, et al., on behalf of the American Diabetes Association. 7. Diabetes Technology: Standards of Care in Diabetes-2023. Diabetes Care. 2023 Jan 1;46(Suppl 1):S111-S127. doi: 10.2337/dc23-S007. PMID: 36507635; PMCID: PMC9810474.
[20] Linee Guida AMD-SID-SIEDP. La terapia del diabete tipo 1. Sistema Nazionale delle Linee Guida Dell'Istituto Superiore di Sanità. Roma 16–03-2022.. https://snlg.iss.it/wp-content/uploads/2022/04/LG_La-terapia-del-diabete-di-tipo-1_rev.pdf.
[21] Grunberger G, Sherr J, Allende M, Blevins T, Bode B, Handelsman Y, et al. American association of clinical endocrinology clinical practice guideline: the use of advanced technology in the management of persons with diabetes mellitus. Endocr Pract 2021 Jun;27(6):505–37. https://doi.org/10.1016/j.eprac.2021.04.008. PMID: 34116789.
[22] Sakane N, Murata T, Tone A, Kato K, Kimura M, Kawashima S, et al. Development and Validation of the Continuous Subcutaneous Insulin Infusion-Related Quality-of-Life (CSII-QOL) Scale. Diabetes Technol Ther 2020 Mar;22(3):216–21. https://doi.org/10.1089/dia.2019.0216. PMID: 31638420.
[23] Carlson AL, Bode BW, Brazg RL, Christiansen MP, Garg SK, Kaiserman K, et al. 97-LB: Safety and Glycemic Outcomes of the MiniMed Advanced Hybrid Closed-Loop (AHCL) System in Subjects with T1D. Diabetes 1 June 2020; 69 (Supplement_1): 97–LB. https://doi.org/10.2337/db20-97-LB.
[24] Lepore G, Rossini A, Bellante R, Corsi A, Scaranna C, Dodesini AR, et al. Switching to the Minimed™ 780G system achieves clinical targets for CGM in adults with type 1 diabetes regardless of previous insulin strategy and baseline glucose control. Acta Diabetol 2022 Oct;59(10):1309–15. https://doi.org/10.1007/s00592-022-01937-5. Epub 2022 Jul 20 PMID: 35857108.
[25] Tornese G, Buzzurro F, Carletti C, Faleschini E, Barbi E. Six-Month Effectiveness of Advanced vs. Standard Hybrid Closed-Loop System in Children and Adolescents With Type 1 Diabetes Mellitus. Front Endocrinol (Lausanne). 2021 Nov 9;12:766314. doi: 10.3389/fendo.2021.766314. PMID: 34858339; PMCID: PMC8630740.
[26] Bergenstal RM, Nimri R, Beck RW, Criego A, Laffel L, Schatz D, et al. FLAIR Study Group. A comparison of two hybrid closed-loop systems in adolescents and young adults with type 1 diabetes (FLAIR): a multicentre, randomised, crossover trial. Lancet. 2021 Jan 16;397(10270):208-219. doi: 10.1016/S0140-6736(20)32514-9. PMID: 33453783; PMCID: PMC9194961.
[27] Beato-Víbora PI, Gallego-Gamero F, Ambrojo-López A, Gil-Poch E, Martín-Romo I, Arroyo-Díez FJ. Rapid Improvement in Time in Range After the Implementation of an Advanced Hybrid Closed-Loop System in Adolescents and Adults with Type 1 Diabetes. Diabetes Technol Ther 2021 Sep;23(9):609–15. https://doi.org/10.1089/dia.2021.0037. Epub 2021 Apr 20 PMID: 33784187.
[28] 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):1967–75. https://doi.org/10.2337/dc19-1785. PMID: 32669412.
[29] Petrovski G, Al Khalaf F, Campbell J, Day E, Almajaly D, Hussain K, et al. Glycemic outcomes of Advanced Hybrid Closed Loop system in children and adolescents with Type 1 Diabetes, previously treated with Multiple Daily Injections (MiniMed 780G system in T1D individuals, previously treated with MDI). BMC Endocr Disord 2022 Mar 29;22(1):80. https://doi.org/10.1186/s12902-022-00996-7. PMID: 35351095; PMCID: PMC8962027.
[30] Petrovski G, Al Khalaf F, Campbell J, Umer F, Almajaly D, Hamdan M, et al. One-year experience of hybrid closed-loop system in children and adolescents with type 1 diabetes previously treated with multiple daily injections: drivers to successful outcomes. Acta Diabetol. 2021 Feb;58(2):207-213. doi: 10.1007/s00592-020-01607-4. Epub 2020 Oct 12. PMID: 33044604; PMCID: PMC7548407.
[31] Garg SK, Weinzimer SA, Tamborlane WV, Buckingham BA, Bode BW, Bailey TS, et al. 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. doi: 10.1089/dia.2016.0421. Epub 2017 Jan 30. PMID: 28134564; PMCID: PMC5359676.
[32] Carlson AL, Sherr JL, Shulman DI, Garg SK, Pop-Busui R, Bode BW, et al. Safety and Glycemic Outcomes During the MiniMed™ Advanced Hybrid Closed-Loop System Pivotal Trial in Adolescents and Adults with Type 1 Diabetes. Diabetes Technol Ther. 2022 Mar;24(3):178-189. doi: 10.1089/dia.2021.0319. Epub 2021 Nov 16. PMID: 34694909; PMCID: PMC8971997.
[33] Matejko B, Juza A, Kieć-Wilk B, Cyranka K, Krzyżowska S, Chen X, et al. Transitioning of People With Type 1 Diabetes From Multiple Daily Injections and Self-Monitoring of Blood Glucose Directly to MiniMed 780G Advanced Hybrid Closed-Loop System: A Two-Center, Randomized. Controlled Study Diabetes Care 2022 Nov 1;45(11):2628–35. https://doi.org/10.2337/dc22-0470. PMID: 35972259; PMCID: PMC9862281.
[34] Pintaudi B, Gironi I, Nicosia R, Meneghini E, Disoteo O, Mion E, et al. Minimed Medtronic 780G optimizes glucose control in patients with type 1 diabetes mellitus. Nutr Metab Cardiovasc Dis 2022 Jul;32(7):1719–24. https://doi.org/10.1016/j.numecd.2022.03.031. Epub 2022 Apr 13 PMID: 35599092.
[35] Mameli C, Smylie GM, Galati A, Rapone B, Cardona-Hernandez R, Zuccotti G, et al. Safety, metabolic and psychological outcomes of Medtronic MiniMed 670G in children, adolescents and young adults: a systematic review. Eur J Pediatr. 2023 May;182(5):1949-1963. doi: 10.1007/s00431-023-04833-4. Epub 2023 Feb 21. PMID: 36809498; PMCID: PMC9942055.
[36] Madsen KP, Olsen KR, Rytter K, Willaing I, Pedersen-Bjergaard U, Schmidt S, et al. Effects of initiating insulin pump therapy in the real world: A nationwide, register-based study of adults with type 1 diabetes. Diabetes Res Clin Pract 2023 Feb;196:110225. https://doi.org/10.1016/j.diabres.2022.110225. Epub 2022 Dec 17 PMID: 36535513.
[37] Seget S, Jarosz-Chobot P, Ochab A, Polanska J, Rusak E, Witoszek P, et al. Body mass index, basal insulin and glycemic control in children with type 1 diabetes treated with the advanced hybrid closed loop system remain stable - 1-year prospective, observational, two-center study. Front Endocrinol (Lausanne) 2022 Oct;11(13):1036808. https://doi.org/10.3389/fendo.2022.1036808. PMID: 36303875; PMCID: PMC9592809.
[38] Messer LH, Berget C, Vigers T, Pyle L, Geno C, Wadwa RP, 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 Mar;21(2):319-327. doi: 10.1111/pedi.12971. Epub 2020 Jan 3. PMID: 31885123; PMCID: PMC7204392.