


Efficacy of a Hybrid Closed-Loop Solution in Patients With Excessive Time in Hypoglycaemia: A Post Hoc Analysis of Trials With DBLGI System

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Abstract

Background: Automated insulin delivery is an efficient treatment for patients with type 1 diabetes. Little is known on its impact on patients with excessive time in hypoglycaemia.

Methods: We performed a post hoc analysis of three randomized control trials that used the DBLGI (Diabeloop Generation I) hybrid closed-loop solution. Patients whose time below 70 mg/dL during baseline, open-loop phase exceeded 5% were selected. The outcomes were the differences between the closed-loop and the open-loop phases in time in various ranges and Glycemia Risk Index (GRI).

Results: We identified 45 patients exhibiting $\geq 5\%$ of time below 70 mg/dL during the open-loop phase. Under closed-loop, the time in hypoglycaemia (54 to <70 mg/dL) dropped from 7.9% (SD 2.4) to 3.2% (SD 1.6) (difference -4.7% [-5.3 ; -4.1], $P < 10^{-4}$). The time below 54 mg/dL decreased from 1.9% (SD 1.3) to 0.8% (SD 0.7) (difference -0.9% [-1.4 ; -0.8], $P < 10^{-4}$). The time in range (TIR 70–180 mg/dL) improved from 63.3 (SD 9.5) to 68.2% (SD 8.2) (difference 5.1% [2.9 ; 7.0], $P < 10^{-4}$). The GRI improved from 51.2 (SD 12.4) to 38.0 (SD 10.9) (difference 13.2 [10.4 ; 16.0], $P < 10^{-4}$).

Conclusion: DBLGI decreased time in hypoglycaemia by more than 50% even in patients with excessive time in hypoglycaemia at baseline, while also improving both TIR and GRI, under real-life conditions. The improvement in GRI (13.2%) exceeded that of the improvement in TIR (5.1%) indicating that in this data set, GRI was more sensitive than TIR to the improvement in glycaemia achieved with closed-loop. These results support the safety and efficacy of this treatment.

Keywords

artificial pancreas, closed-loop, hypoglycaemia, type 1 diabetes

Introduction

Automated insulin delivery has recently emerged as the most-efficient treatment for patients with type 1 diabetes (T1D). Several pivotal trials have allowed various hybrid closed-loop solutions to be cleared by regulatory authorities.^{1–5} These studies aimed at describing the time in range (TIR; 70–180 mg/dL) as the main efficacy outcome, and the incidence of acute metabolic events as the safety criterium. In most if all of these studies, patients with a past history of severe hypoglycaemia or with hypoglycaemia unawareness have been excluded and, if not, the average baseline of time

below range (0 to <70 mg/dL) was below the threshold of 5% that was proposed in the international consensus on continuous glucose monitoring (CGM) data.^{6,7} So far, very few trials targeted patients at risk for hypoglycaemia.⁸ Whether closed-loop insulin delivery is also efficient and safe among patients with excessive time in hypoglycaemia is the question that we addressed in the following study, that contributes to the knowledge in this field. Time in a target range of 70 to 180 mg/dl has been proposed as a CGM metric that is linked to the quality of glycaemic control.⁹ The Glycemia Risk Index (GRI) is a new composite metric that has been demonstrated

to correlate with opinions of clinicians as to the quality of glycaemia. Compared to TIR, the GRI has been shown to correlate more closely with the opinions of clinicians as to the quality of CGM control.¹⁰ It is not known whether either metric is linked to improved time in the hypoglycemic range (below 70 mg/dL) with the use of closed-loop control compared to open-loop control in patients with T1D whose baseline frequency of time in hypoglycaemia range exceeds 5%. In this post hoc study, we assessed the impact of using the DBLG1 closed-loop solution on the time in hypoglycemia among patients with excessive time in hypoglycemia at baseline, and we looked at the evolution of TIR and GRI in this population.

Methods

Objective

The main objective of this study was to assess the impact of using the DBLG1 (Diabeloop Generation 1) hybrid closed-loop system on the time in hypoglycemic range (0 to <70 mg/dL) among T1D patients selected with more than 5% (\geq) in hypoglycemic range during baseline, open-loop evaluation. The secondary objectives were to describe the evolution of the different glucose metrics, including TIR and GRI, under closed loop.

Participants

This study compiled data obtained from three randomized controlled trials and declared on ClinicalTrials.gov as NCT02987556 (WP7 trial),³ NCT04190277 (WP8 DBLUS trial), and NCT03671915 (WP9 DBL4K trial).¹¹ Briefly, WP7 was a crossover trial performed among adult patients during two periods of 12 weeks each, only patients of second arm who used the Kaleido pump were selected ($n = 30$); WP9 crossover trial had involved children aged 6 to 12 year old who used the Kaleido pump for 6 weeks ($n = 17$); in these crossover trials, the open-loop data came from the crossover period in open-loop; WP8 was a parallel group trial including adolescents and adult patients who used the

Dana-i pump ($n = 142$), where we used the 14-day run-in period performed with the trial pump and CGM as the baseline, open-loop control period. Of note, regarding the risk for hypoglycaemia, all three trials had excluded patients with hypoglycaemia unawareness (Gold score >4) and with a recent history of severe hypoglycaemia.^{3,11} Among all these patients, we selected those whose time below optimal range (0 to <70 mg/dL) during baseline, open-loop phase exceeded 5% (\geq). We based this criterion upon the international consensus that recommends a time <4% below 70 mg/dL (≥ 54 to <70, low glucose) and a time <1% below 54 mg/dL (<54, very low glucose) in non-high-risk patients.⁷

Insulin Delivery DBLG1 System

DBLG1 is a hybrid, closed-loop insulin delivery system combining a Dexcom G6[®] continuous glucose monitoring device, an insulin pump (Kaleido[®] or Dana-i[®]) and the DBLG1 software into a dedicated controller handset. Briefly, algorithm is a machine learning system, allowing customization through 10 different settings in order to respond to the diversity of existing T1D metabolic profiles [details in reference # 3].

Study design. In a post hoc analysis, we looked at the glucose metrics among all patients who had gone through the WP7 trial (arm 2), the WP8 trial, and the WP9 trial, and we selected the population of patients whose baseline, open-loop data showed an average time below optimal range (0 to <70 mg/dL) exceeding 5% (\geq). Among this population, we then looked at the time in optimal range (70-180 mg/dL) and the time below range (0 to <70 mg/dL) during the whole period using the DBLG1 closed-loop system. The main outcome was the difference in time below range between the closed-loop and the open-loop phases. We also looked at the GRI, which is a recently introduced CGM metric that was validated by clinician ratings.¹⁰ Briefly, GRI was built with a data set of 14-day CGM tracings from 225 insulin-treated adults with diabetes. These tracings were ranked by 330 highly experienced clinicians worldwide from best to worst

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Table 1. Baseline Characteristics of Participants.

Characteristics	WP7 (n = 30)		WP8 (n = 142)		WP9 (n = 17)	
	≥5% LG	<5% LG	≥5% LG	<5% LG	≥5% LG	<5% LG
% Time in Low Glucose (0 to <70 mg/dL)						
Number of patients	9	21	28	114	8	9
Gender: female (n)	3 (33.33)	9 (42.86)	18 (64.29)	73 (64.04)	4 (50.0)	5 (55.56)
Age (years)	46.78 (10.15)	48.19 (12.23)	35.71 (16.7)	36.23 (16.45)	7.88 (0.99)	8.44 (2.07)
Duration of diabetes (years)	25.56 (13.57)	26.05 (12.75)	23.07 (11.94)	20.66 (13.43)	5.25 (1.58)	5.89 (2.37)
HbA1c (%)	6.88 (0.75)	7.76 (0.75)	7.53 (0.89)	8.07 (1.08)	6.92 (0.47)	7.42 (0.38)
Total daily insulin (U/d)	36.25 (12.22)	36.84 (9.16)	40.57 (14.18)	44.12 (16.05)	21.31 (3.51)	24.08 (6.8)

Data are given as n (%) or mean (SD). LG: low glucose

glycemic control. A model was built to predict the clinician ranking based on seven standard metrics in an Ambulatory Glucose Profile (AGP): very low-glucose and low-glucose hypoglycaemia; very high-glucose and high-glucose hyperglycaemia; TIR; mean glucose; and coefficient of variation.¹⁰ The GRI can present as a single score expressing both the effects of hypoglycaemia and hyperglycaemia on a 0 to 100 scale of percentiles, with 0 the best and 100 the worst. The GRI can be expressed either as a population mean (similar to how the TIR can be expressed) or else as a distribution of the quality of a population's individual patients' glycaemia in five quintiles from A (the best) to E (the worst).

Statistical analysis. A paired *t*-test was performed to compare the time below range, the TIR and the GRI in our selected population between the closed-loop and the open-loop phases. In order to take into account any size effect in the observed differences between closed-loop and open-loop outcomes, we performed the Cohen's *d* test with Hedges and Olkin's correction (a *d* test lower than 0.2, lower than 0.5 and higher than 0.8 suggests a minor, moderate and high effect, respectively). All results were reported in intention to treat (i.e., whether the closed-loop function was on, off, or dysfunctioning). In this article, we defined time in low glucose as (54 to <70 mg/dL), and time in very low glucose as (<54 mg/dL).

Results

Population

The total number of patients exhibiting ≥5% of time in low glucose during the open-loop phase of their respective trials was 45, including 9 among 30 adult patients in the WP7 trial, 28 among 142 patients in the WP8 trial (among which 7 were between 14 and 17 year old) and 8 among 17 children in the WP9 trial. Table 1 summarizes demographic data (age, gender, duration of diabetes, baseline HbA1c, and mean total daily insulin dosage) of both categories of patients (those exhibiting ≥5% or <5% of time in low glucose). There was a trend to a lower HbA1c and a lower insulin requirement in

the population with excessive time in low glucose. The median duration under closed-loop therapy for the whole population was 37 days [36.4, 51.2], as opposed to median time under open-loop treatment which was 17 days [24.3, 38.9].

Main outcome. Among patients in WP7 trial, the time in low glucose dropped from 8.3% in open-loop phase to 3.3% in closed-loop period (difference -5.9% [-6.8; -3.1]). In patients from WP8 trial, the time in low glucose dropped from 7.9 to 3.1% (difference -4.9% [-5.6; -4.0]). In children from WP9 trial, the time in low glucose was decreased from 7.4% to 3.5% (difference -4.0% [-5.3; -2.7]). Thus overall, while using the closed-loop device, the whole population experienced a reduction in time in low glucose that dropped from 7.9% (SD 2.4) to 3.2% (SD 1.6) (difference -4.7% [-5.3; -4.1], $P < 10^{-4}$). As summarized in Table 2, the time in very low glucose (<54 mg/dL) was also reduced from 1.9% (SD 1.3) in open-loop to 0.8% (SD 0.7) in closed-loop (difference -0.9% [-1.4; -0.8], $P < 10^{-4}$). Individual data showing that time in low glucose ranged from 5.1 to 15.6% are provided in appendix (Supplemental Table S1). The glucose metrics for the population with baseline time in low glucose under 5% (<) are provided in Supplemental Table S2.

Secondary Outcomes

Meanwhile, the time in optimal range (TIR 70-180 mg/dL) in the selected population has been raised from 65.4% to 72.0% in WP7 trial, from 62.5% to 67.4% in WP8 trial, and from 63.6% to 66.8% in WP9 trial. The overall population increased its TIR from 63.3% (SD 9.5) to 68.2% (SD 8.2) (difference 5.1% [2.9; 7.0], $P < 10^{-4}$). All these results are summarized in Table 2 and individual results are illustrated in Figure 1.

We looked at the number of patients who reached the targets from the International CGM consensus,⁷ that is, a TIR 70 to 180 mg/dL above 70% (>) combined with a time below 70 mg/dL under 4% (<) and a time below 54 mg/dL under 1% (<). Overall this number increased from 0 in open-loop to 13 patients in closed-loop. The number of patients that

Table 2. 24-h Glucose Control During OL and CL Periods in Patients Exhibiting $\geq 5\%$ of Time in Low Glucose.

WP7 (n = 9)		WP8 (n = 28)		WP9 (n = 8)		Total (n = 45)	
OL	CL	OL	CL	OL	CL	OL	CL
Diff CL-OL		Diff CL-OL		Diff CL-OL		Diff CL-OL	
P value		P value		P value		P value	
size effect		size effect		size effect		size effect	
Time in low glucose (54 to <70 mg/dL) (%)							
8.3 \pm 2.3	3.3 \pm 1.6	7.9 \pm 2.5	3.1 \pm 1.7	7.4 \pm 2.1	3.5 \pm 1.7	7.9 \pm 2.4	3.2 \pm 1.6
-5.9 [-6.8, -3.1]		-4.9 [-5.6, -4.0]		-4.0 [-5.3, -2.7]		-4.7 [-5.3, -4.1]	
0.0003		<10 ⁻⁴		0.0002		<10 ⁻⁴	
2.1		2.1		1.7		2.2	
Time in very low glucose (<54 mg/dL) (%)							
2.1 \pm 1.1	0.8 \pm 0.5	1.9 \pm 1.5	0.7 \pm 0.8	1.6 \pm 0.9	0.9 \pm 0.6	1.9 \pm 1.3	0.8 \pm 0.7
-1.3 [-2.1, -0.5]		-0.9 [-1.6, -0.8]		-0.6 [-1.1, -0.3]		-0.9 [-1.4, -0.8]	
0.0044		<10 ⁻⁴		0.0047		<10 ⁻⁴	
1.3		0.9		0.8		1.0	
Time in range (70-180 mg/dL) (%)							
65.4 \pm 9.4	72.0 \pm 10.6	62.5 \pm 10.3	67.4 \pm 8.2	63.6 \pm 6.8	66.8 \pm 3.8	63.3 \pm 9.5	68.2 \pm 8.2
6 [2.4, 10.7]		4.7 [1.8, 8.0]		0.2 [-0.7, 7.1]		5.1 [2.9, 7.0]	
0.0066		0.0028		0.0944		<10 ⁻⁴	
0.5		0.5		0.5		0.5	
Time in high glucose (>180 mg/dL) (%)							
26.3 \pm 10.1	24.7 \pm 10.8	29.6 \pm 10.6	29.5 \pm 7.9	29 \pm 7.7	29.8 \pm 3.6	28.8 \pm 9.9	28.6 \pm 8.1
0.4 [-5.8, 2.7]		-0.3 [-3.2, 3]		0.5 [-4.2, 5.7]		-0.2 [-2.4, 1.9]	
0.417		0.955		0.773		0.827	
0.1		0.0		0.1		0.0	
Time in very high glucose (>250 mg/dL) (%)							
7.7 \pm 5	6.3 \pm 4.8	9.7 \pm 5.9	8.5 \pm 4.6	10.5 \pm 5.2	8.4 \pm 3.1	9.4 \pm 5.6	8 \pm 4.4
-1.2 [-3.6, 0.9]		-0.7 [-3, 0.7]		-2.7 [-5.2, 1.1]		-1.1 [-2.6, -0.1]	
0.196		0.204		0.161		0.035	
0.2		0.2		0.4		0.3	
Glycemia Risk Index							
48.8 \pm 10.9	33.7 \pm 12.5	52.0 \pm 13.9	38.8 \pm 11.4	50.8 \pm 9.0	39.9 \pm 6.7	51.2 \pm 12.4	38.0 \pm 12.9
-15.3 [-21.0, -9.1]		-12.6 [-17.3, -9.2]		-11.0 [-15.4, -6.5]		-13.1 [-16.0, -10.4]	
0.0003		<10 ⁻⁴		0.0007		<10 ⁻⁴	
1.1		1.0		1.1		1.1	

Data are given as mean (SD). Differences are shown as median [95% CI]. Paired t-test and Cohen's *d* test are provided. Abbreviation: OL, open loop; CL, closed loop; CI, confidence interval.

reached a TIR 70 to 180 mg/dL above 70% (>) combined with a time below 70 mg/dL under 4% (<), a time below 54 mg/dL under 1% (<) and a Glucose Management Indicator under 7% (<) was 0 in open-loop and 11 in closed-loop.

We also looked at the GRI, which is a recently introduced composite metric integrating the hypoglycaemia and hyperglycaemia components of ambulatory glucose profile into a single index that was validated by clinician rankings.¹⁰ Data provided in Table 2 and Supplemental Figure S1 showed an improvement of this index when patients moved from to open-loop to closed-loop therapy.

Thus, the mean GRI for our combined population from three studies improved from 51.2 (\pm 12.4) on open-loop control to 38.0 (\pm 10.9) on closed-loop control, for a difference of 13.2. The distribution of GRI scores (A, B, C, D, E) for the

whole population (n = 45) was 0, 10, 26, 8, and 1 for open-loop control and 3, 22, 19, 1, and 0 for closed-loop control. Figure 2 illustrates that this improvement was mostly linked with the hypoglycaemia component.

Discussion

This post hoc analysis of three randomized trials using the DBLG1 hybrid closed-loop solution focused on patients that presented with excessive time in hypoglycaemia when treated with their baseline, usual open-loop treatment. We selected all patients staying more than 5% in hypoglycaemia, this threshold being proposed by the International Consensus on CGM data^{6,7} and meaning more than 72 minutes per day below the 70 mg/dL level. Our study showed that the time

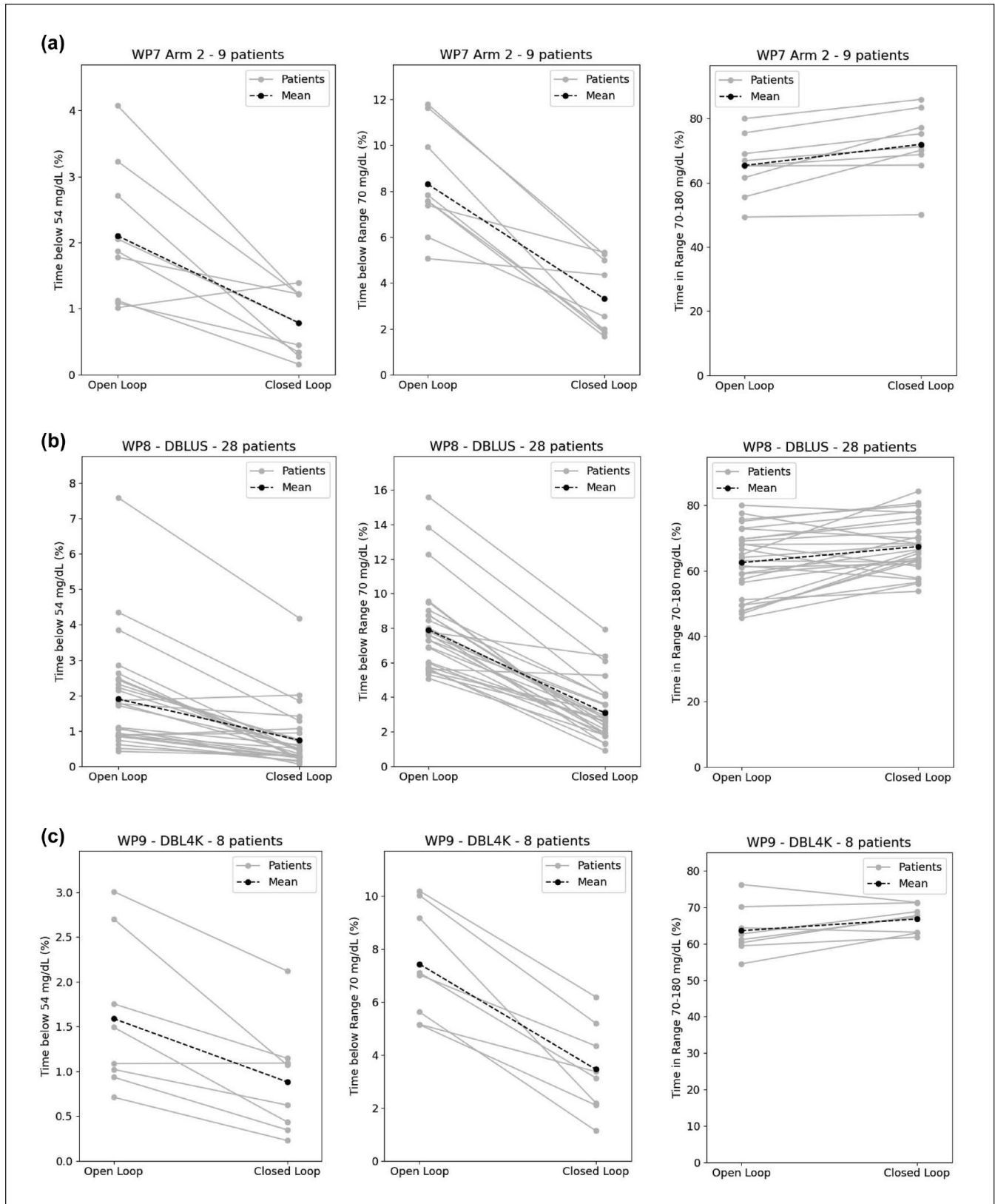


Figure I. Individual trajectories from open-loop to closed-loop for time below 54 mg/dL, time below 70 mg/dL and time in range 70 to 180 mg/dL for (a) WP7 trial (9 patients), (b) WP8 trial (28 patients), and (c) WP9 trial (8 patients). The black line represents the mean.

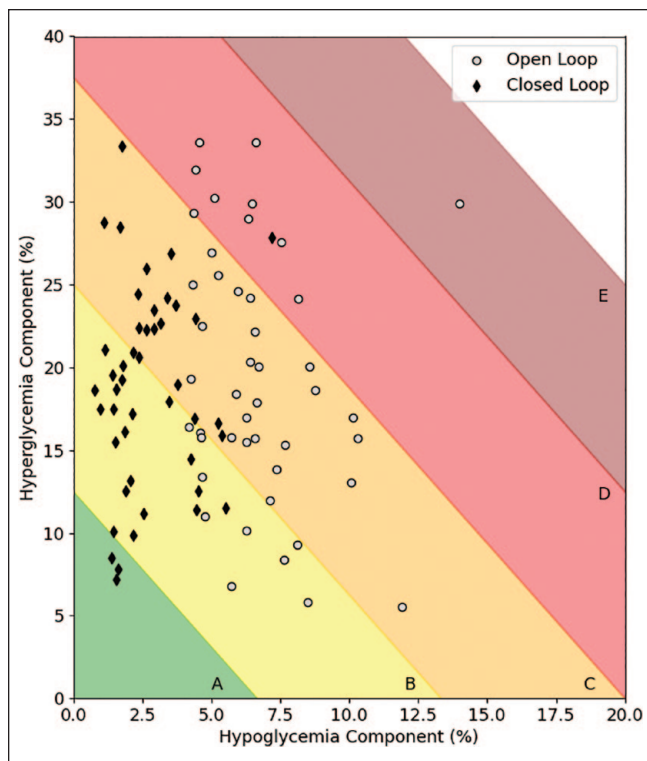


Figure 2. Evolution of individual Glycemia Risk Index from open-loop to closed-loop. See reference 10 for a description of this index.

spent in low glucose (54 to <70 mg/dL) was reduced by 59% (from 114 to 46 minutes per day, i.e., 68 minutes reduction). Similarly, the time spent in very low glucose (<54 mg/dL) was also reduced by 59% (from 27 to 11 minutes, i.e., 16 minutes reduction). On the contrary, the time in optimal range (70-180 mg/dL) increased by 7.8% (15.2-16.4 hours per day, 71 minutes increase).

The GRI also improved after switching from open-loop control to closed-loop control. The difference in improvement in the two metrics, which are both on a 100-point scale, was 5.1% for the TIR and 13.2 percentile points for the GRI. The GRI thus showed greater sensitivity to improvement in control for this intervention. The reason for greater sensitivity of the GRI is related to the derivation of the GRI which accounts for time spent in both hypoglycaemia and hyperglycaemia with increased weighting to hypoglycaemia over hyperglycaemia and greater weighting to extreme hypoglycaemia over less-extreme hypoglycaemia. The TIR, on the contrary, treats all times outside of target range as equally significant, be they times in hypoglycaemia or hyperglycaemia or be they severe or not severe outliers. In this population transitioning to closed-loop intervention, where there was a goal of minimizing hypoglycaemia, the GRI, compared to TIR, showed a greater dynamic range to differences in the amount of time spent in hypoglycaemia. The original

article presenting GRI featured a population of insulin users equally using different types of regimens (multiple daily injections in T1D, open-loop in T1D, closed-loop in T1D, and multiple daily injections in T2D).¹⁰ The improvement in both metrics of control in our study argues both for the safety and efficacy of the closed-loop system in this particular population.

Hypoglycaemia has been associated with an increased risk of cardiovascular events and all-cause mortality in insulin-treated patients with T1D or T2D.¹² Hypoglycaemia is also responsible for substantial healthcare costs and can have profound negative effects on quality of life.^{13,14} Reimbursement criteria for new technological devices in diabetes should not only put emphasis on HbA1c and TIR but also consider patients with optimal A1c level but excessive time in hypoglycaemia. It is possible that GRI will become a widely used metric for expressing the quality of glycaemia if future studies, like this one demonstrate a high dynamic range associated with a favorable outcome, and especially if future outcomes studies link better glycaemia, as represented by the GRI, with a decreased frequency of adverse diabetic vascular outcomes. Indeed, our study population had fair baseline A1c, ranging from 6.9% to 7.5%, and one can speculate that the expectations of these patients from a closed-loop solution were more related with a relief from the burden of hypoglycaemia. It is established that hypoglycaemia is the main barrier to tight glucose control.¹⁵ Improvements in fear of hypoglycaemia and diabetes distress have been documented with the use of closed-loop.¹⁶ A recent trial reported that patients with low baseline A1c improved mostly by reducing hypoglycaemia and concluded that there were no reason to exclude individuals with T1D from automated insulin delivery based on their HbA1c.¹⁷

To the best of our knowledge, most controlled studies using closed-loop insulin delivery have not involved patients with excessive time in hypoglycaemia so far. In the pivotal trials of all five commercially available closed-loop solutions, the median cumulated time below 70 mg/dL and below 54 mg/dL never exceeded 5%.¹⁻⁵ One study had focused on 29 patients with HbA1c <7.5%, excluding those with hypoglycaemia unawareness and reported that time below 70 mg/dL was reduced from 5.3% to 2.9% and time below 54 mg/dL fell from 1.0% to 0.3%, while time in optimal range increased from 65.6% to 76.2%.⁸ The strength and originality of our study were to focus only on patients exceeding 5% time in hypoglycaemia. Its weaknesses are its post hoc design, the small sample, and possible selection bias. Actually, very positive outcomes have been recently reported with a specifically designed and customizable closed-loop solution in patients presenting with hypoglycaemia unawareness and a history of severe hypoglycemic episodes.^{18,19}

In conclusion, our study supports the use of closed-loop treatment also in T1D patients experiencing excessive time in hypoglycaemia and brings arguments for the efficacy and safety of this treatment in this population.

Abbreviations

DBLG1, diabeloop generation 1; GRI, Glycemia Risk Index; TIR, time in range; CGM, continuous glucose monitoring; T1D, type 1 diabetes; AGP, ambulatory glucose profile.

Author Contributions

PYB: study design, patient enrolment and follow-up, data interpretation, and manuscript writing. AA, YT, SP, and SM: study design, data interpretation, and statistical analysis. SF, DK, and JB: patient enrolment and follow-up, data interpretation, and manuscript editing. GC: study design, protocol writing, relation with regulation authorities, patient follow-up, data interpretation, and manuscript editing. PYB is the guarantor of this work and, as such, had full access to all of the data in the study and take responsibility for the integrity of the data and the accuracy of the data analysis.

Declaration of Conflicting Interests

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Ethics Approval and Informed Consent

The study was conducted in accordance with the Helsinki Declaration and in accordance with the French law concerning personal healthcare.

Trial Registration

This study was registered under ClinicalTrials.gov NCT02987556, NCT04190277, and NCT03671915.

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Supplemental Material

Supplemental material for this article is available online.

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