






BRIEF REPORT

No more hypoglycaemia on days with physical activity and unrestricted diet when using a closed-loop system for 12 weeks: A post hoc secondary analysis of the multicentre, randomized controlled Diabeloop WP7 trial

Sylvia Franc MD^{1,2,3}  | Pierre-Yves Benhamou MD⁴  | Sophie Borot MD⁵ |
Lucy Chaillous MD⁶ | Brigitte Delemer MD⁷ | Maeva Doron PhD⁸ |
Bruno Guerci MD⁹ | H el ene Hanaire MD¹⁰  | Erik Huneker PhD¹¹ |
Nathalie Jeandidier MD¹² | Coralie Amadou MD^{1,13} | Eric Renard MD¹⁴  |
Yves Reznik MD¹⁵  | Pauline Schaepelynck MD¹⁶ | Chantal Simon MD¹⁷ |
Charles Thivolet MD¹⁸ | Claire Thomas PhD³ | Patrick Hannaert PhD¹⁹  |
Guillaume Charpentier MD^{2,3}

¹Department of Diabetes, Sud-Francilien Hospital, Corbeil-Essonnes, France

²Centre d'Etude et de Recherche pour l'Intensification du Traitement du Diab ete (CERITD), Evry, France

³Laboratoire de Biologie de l'Exercice pour la Performance et la Sant e, Universit e Evry Val d'Essonne, Institut de Recherches Biom edicales des Arm ees, Universit e Paris Saclay, Evry, France

⁴Department of Diabetology, University Hospital Grenoble Alpes, Grenoble, France

⁵Department of Endocrinology, Metabolism, Diabetes and Nutrition, Centre Hospitalier Universitaire Jean Minjoz, Besan on, France

⁶CHU de Nantes - Hospital Laennec, Saint-Herblain, France

⁷Department of Endocrinology, Diabetes and Nutrition, Reims University Hospital, Reims, France

⁸Universit e Grenoble Alpes, Commissariat   l'Energie Atomique, Laboratoire d' lectronique et de technologie de l'information, D epartement micro Technologies pour la Biologie et la Sant e, Grenoble, France

⁹Endocrinology-Diabetes Care Unit, University of Lorraine, Vandoeuvre L es Nancy, France

¹⁰Department of Diabetology, Metabolic Diseases and Nutrition, CHU Toulouse, University of Toulouse, Toulouse, France

¹¹Diabeloop S.A., Paris, France

¹²Department of Endocrinology, Diabetes and Nutrition, CHRU of Strasbourg (UDS), Strasbourg, France

¹³University Paris-Saclay, Orsay, France

¹⁴Department of Endocrinology, Diabetes and Nutrition, Montpellier University Hospital, and Institute of Functional Genomics, CNRS, INSERM, University of Montpellier, Montpellier, France

¹⁵Department of Endocrinology, University of Caen C te de Nacre Regional Hospital Center, Caen, France

¹⁶Department of Nutrition-Endocrinology-Metabolic Disorders, Marseille University Hospital, Sainte Marguerite Hospital, Marseille, France

¹⁷Department of Endocrinology, Diabetes and Nutrition, Centre Hospitalier Lyon Sud, Lyon, France

¹⁸Center for Diabetes, Lyon University Hospital, Lyon, France

¹⁹School of Medicine and Pharmacy of Poitiers, Isch mie Reperfusion en Transplantation d'Organes M canismes et Innovations Th rapeutiques, Institut National de la Sant e et de la Recherche M dicale, Unit  Mixte de Recherche 1082, Poitiers, France

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Correspondence

Sylvia Franc, MD, Department of Diabetes, Sud-Francilien Hospital, 40 Avenue Serge Dassault, 91100 Corbeil-Essonnes, France. Email: sylvia.franc@chsf.fr

Funding information

Diabeloop SA; French Innovation Fund

Abstract

A post hoc analysis of the Diabeloop WP7 multicentre, randomized controlled trial was performed to investigate the efficacy of the Diabeloop Generation-1 (DBLG1) closed-loop system in controlling the hypoglycaemia induced by physical activity (PA) in real-life conditions. Glycaemic outcomes were compared between days with and without PA in 56 patients with type 1 diabetes (T1D) using DBLG1 for 12 weeks. After the patient announces a PA, DBLG1 reduces insulin delivery and, if necessary, calculates the amount of preventive carbohydrates (CHO). Daily time spent in the interstitial glucose range less than 70 mg/dL was not significantly different between days with and without PA ($2.0\% \pm 1.5\%$ vs. $2.2\% \pm 1.1\%$), regardless of the intensity or duration of the PA. Preventive CHO intake recommended by the system was significantly higher in days with PA (41.1 ± 35.5 vs. 21.8 ± 28.5 g/day; $P < .0001$), and insulin delivery was significantly lower (31.5 ± 10.5 vs. 34.0 ± 10.5 U/day; $P < .0001$). The time spent in hyperglycaemia and the glycaemic variation coefficient increased significantly on days with PA. In real-life conditions, the use of DBLG1 avoids PA-induced hypoglycaemia. Insulin adjustments and preventive CHO recommendation may explain this therapeutic benefit.

KEYWORDS

artificial pancreas, closed-loop system, continuous glucose monitoring, glycaemic control, hypoglycaemia, insulin pump therapy, physical activity, physical intervention, randomized controlled trial, type 1 diabetes

1 | INTRODUCTION

The ideal goal of insulin therapy for type 1 diabetes (T1D) is to normalize blood glucose levels, without increasing exposure to hypoglycaemia. A meta-analysis of 27 randomized controlled trials (RCTs) by Weisman et al.¹ showed that closed-loop (CL) artificial pancreas systems allow staying within the glycaemic target for a significantly longer time compared with conventional pump therapy (continuous subcutaneous insulin infusion with blinded continuous glucose monitoring [CGM] or unblinded sensor-augmented pump [SAP] therapy). However, CL systems often do not protect against sudden drops in blood glucose caused by moderate intensity physical exercise (PE).²⁻⁴

In 12 patients under glycaemic control with a Medtronic-derived CL system, Patel et al.⁵ showed that a simple method to prevent hypoglycaemia was to eat a snack just before and in the middle of the PE period (see also de Bock et al.⁶). Turksoy et al.⁷ reported that consuming an appropriate amount of carbohydrates (CHO) combined with predictive hypoglycaemia alarms can prevent most hypoglycaemic events.

The Diabeloop Generation-1 (DBLG1) CL system is a hybrid, single-hormone CL device, which has a self-learning algorithm that regulates insulin delivery as a function of CGM, CHO intake and PA lasting more than 15 minutes.^{8,9} We have previously shown that DBLG1 completely suppressed exercise-induced hypoglycaemia in 14 free-living patients consuming unrestricted diets for 3 days.⁹

Regular physical activity (PA) is beneficial for patients with T1D because it improves well-being and fitness, reduces cardiovascular risk and helps with reaching target lipid profile and glycaemic goals.^{10,11} A previous 12-week randomized study in 63 free-living patients eating an unrestricted diet (Diabeloop WP7 trial) showed that DBLG1 improves glucose control compared with SAP systems.⁸ Unlike SAP systems, DBLG1 records PA data in its internal memory. Therefore, the Diabeloop WP7 database was accessed to compare hypoglycaemia on days with and without PA.

2 | METHODS

2.1 | Study design

Post hoc analysis of the Diabeloop WP7 study, a 12-week, multicentre, open-label, randomized, controlled, crossover trial of DBLG1 in 68 patients with T1D under real-life conditions⁸ (ClinicalTrials.gov NCT02987556), was performed. The trial involved 12 French centres, from March 2017 until August 2018. A full description of the study is presented in Benhamou et al.⁸ Briefly, participants were adult patients with T1D and an HbA1c of 10% or less, who were treated with wearable insulin pump therapy. Patients were randomly assigned (1:1) to receive DBLG1-driven insulin therapy or sensor-assisted pump therapy over 12 weeks, followed by an 8-week washout period and the subsequent crossover intervention. Only the CL crossover period was analysed.

Similar to other studies in real-life conditions, participants were free to decide the characteristics of their PA. They were only asked to announce the duration and intensity (mild, moderate, intense) of each PA session, 60 minutes before starting it.⁸ We have previously shown¹² that the patient's self-assessment of PA intensity is reliable. Thus, patients who perform PA at 50% of VO_2 max self-rate it as moderate and those performing PA at 75% of VO_2 max self-rate it as intense. When the patient declares a PA at least 2 hours before its onset, and if the glycaemic forecast is lower than 160 mg/dL (at the beginning of PA), a preventive CHO intake is requested depending on (a) the intensity of the PA and (b) the deviation from the glycaemic target.

2.2 | The Diabeloop system

A Cellnovo (or Kaleido) insulin patch pump is managed by the Diabeloop application installed on an android smartphone, and is connected to a Dexcom G5 Mobile CGM system using Bluetooth Low Energy technology (for technical details, see^{8,9,13,14}).

DBLG1 comprises the announcement of PA and the software calculation of a preventive CHO intake. The latter is calibrated according to the duration and intensity of the PA to be performed.^{8,9} The CGM provides one glycaemia value every 5 minutes to the system. The self-learning algorithm rapidly optimizes insulin delivery during hypoglycaemic or hyperglycaemic challenges (in approximately 7 hours; it takes approximately 7 days to perform long-term optimization).

2.3 | Outcome measures

The Diabeloop database was accessed to extract the following data (recorded during the DBLG1 periods): (a) days with or without recorded PA, (b) PA duration and intensity, (c) time between the announcement and the start of the PA (notifications made at the beginning or after the session were considered "without announcement"), (d) daily time (24 hours) and overnight time spent in the interstitial glucose range less than 70 mg/dL (time below range [TBR]), (e) preventive CHO intake recommended by DBLG1, (f) preventive CHO intake estimated and recorded by the patient, (g) insulin delivery, (h) mean CGM and variation coefficient. Cut-points for each glycaemic range were those used in the Diabeloop WP7 RCT⁸ and defined in the consensus report of outcome measures for artificial pancreas clinical trials.¹⁵

2.3.1 | Primary outcome measure

The primary outcome was the difference in TBR between days with and without PA.

2.3.2 | Secondary outcome measures

Secondary outcomes included the following comparisons between days with and without PA: TBR as a function of the intensity, duration and

delay of PA announcement, preventive CHO, insulin delivery, mean glycaemia estimated from interstitial glucose and variation coefficient, time spent in the normoglycaemic range (TIR 70-180 mg/dL) and in the hyperglycaemic range of more than 180 mg/dL (time above range [TAR]).

2.4 | Statistical analysis

Data are presented as mean \pm standard deviation (SD). Statistical comparisons of the primary outcome (TBR between days with and without PA) were made using two methods: (a) a mixed model for repeated measures, with corrections for baseline HbA1c and centre, and (b) an ordinal logistic model with multinomial distribution (1% TBR classes, cumulative logit link function), with corrections for baseline HbA1c and Centre. For preventive CHOs (system-recommended and patient-declared), statistical comparisons were made with the Wilcoxon test (days with vs. days without PA) or with the Kruskal-Wallis test (PA intensity, duration and delay of announcement). Other statistical comparisons were made with the above mixed model.

3 | RESULTS

3.1 | Participants

Sixty-three patients completed both CL 12-week treatment periods and were included in the study.⁸ Their mean age was 48.2 ± 13.4 years, 62% were female and they had a medium-high education level. Mean diabetes duration was 28 ± 13.6 years; mean HbA1c level was $7.6\% \pm 0.9\%$ (59.4 ± 9.8 mmol/mol).

3.2 | Registered PA events

The Diabeloop database registered 1256 PA events. Seven patients did not record any PA, and were excluded from the analysis. The remaining 56 participants recorded 19.9 ± 24.1 PA events/patient. There were 938 days with at least one PA event announced and 4260 days with no announced PA. Patients announced in advance 71.4% of their PA sessions. One PA session was announced the day before (21.6 hours) and the remaining sessions were announced with an average upstream time of 79.4 ± 82.8 minutes (min-max 1-596 minutes; median 59 minutes) (Table S1 and Figure S1). The duration of PA was 82.3 ± 58.3 minutes (min-max 8-480 minutes; median 60 minutes) (Table S2 and Figure S2), with intensity, "mild" (40%), "moderate" (41%) or "intense" (19%), respectively.

3.3 | Primary outcome

According to the mixed model for repeated measures, TBR was not significantly different between days with or without PA announced to the software ($2.0\% \pm 1.5\%$ vs. $2.2\% \pm 1.1\%$, respectively; $P = .282$)

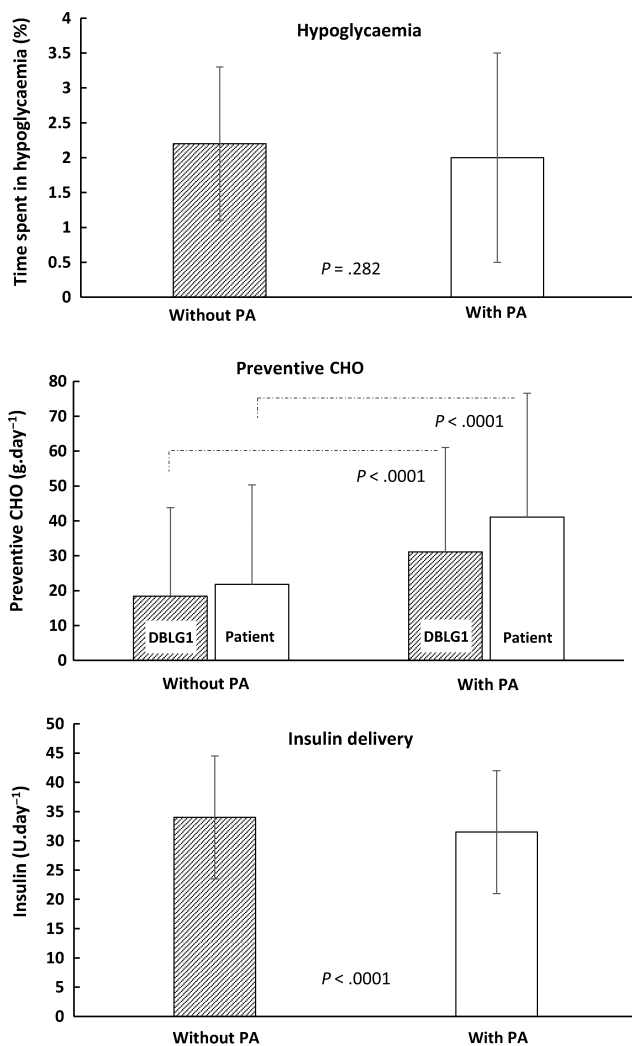


FIGURE 1 Time spent in hypoglycaemia during days with or without physical activity, and associated changes in carbohydrate (CHO) intake and insulin delivery. (Top) Time spent in hypoglycaemia (interstitial glucose <70 mg/dL). (Middle) Preventive CHO intake. “DBLG1” indicates preventive CHO intake recommended by the system. “Patient” indicates preventive CHO intake recorded by the patient. (Bottom) Insulin delivery

(Figure 1, top panel). One patient spent 1 day with TBR = 0% and most patients were in the TBR range of >0% to 4% range. Statistical analysis with the ordinal logistic model (with 1% TBR classes) confirmed that there was no more TBR with PA than without PA (Figure S3). In fact, the TBR was significantly lower with PA than without PA ($P = .0065$).

3.4 | Secondary outcomes

TBR was not significantly influenced by: (a) PA intensity (TBR = 1.6% ± 1.8% [$N = 36$] for mild, 2.0% ± 1.4% for moderate [$N = 50$] and 2.2% ± 1.7% [$N = 34$] for intense; $P = .209$; N indicates the number of patients) or (b) PA duration (TBR = 1.9% [$N = 13$] for <30 minutes, 2.1% [$N = 46$] for 30–60 minutes, 1.9% [$N = 44$] for 60–90 minutes,

2.0% [$N = 52$] for >90 minutes; $P = .953$). The time elapsed between the announcement and the onset of PA did not significantly influence the TBR (1.7% ± 0.3%, 2.3% ± 0.3%, 2.2% ± 0.3% and 2.3% ± 0.3% for announcement at 60 or more minutes before PA, 30–60 minutes before PA, <30 minutes before PA and at the start of PA, respectively; $P = .285$). Overnight TBR was not significantly different after days with or without PA (1.2% ± 0.2% vs. 1.6% ± 0.2%, respectively; $P = .507$).

Preventive CHO intake was significantly higher with PA than without PA (Figure 1, middle panel). This was the case for the preventive CHO recommended by DBLG1 (31.1 ± 29.9 vs. 18.4 ± 25.4 g/day, $P < .0001$), as well as for the preventive CHO recorded by the patient (41.1 ± 35.5 vs. 21.8 ± 28.5 g/day, $P < .0001$) (Figure 1, middle panel). Recorded CHO intake increased with increasing PA duration (e.g. 49.4 ± 38.3 vs. 37.8 ± 30.3 g/day for >90- and <30-minute periods, respectively; $P < .001$). The mean delay between the intake and the PA onset was 36.4 ± 57.0 minutes (min-max 1–1295 minutes; median 59 minutes). The same patient who announced a PA session the day before (21.6 hours) announced the intake at the same time.

Total insulin delivery was significantly lower on days with PA (31.5 ± 10.5 U/day) compared with days without PA (34.0 ± 10.5 U/day; $P < .0001$) (Figure 1, bottom panel). Similar results were obtained with basal insulin (10.5 ± 0.5 U/day vs. 11.1 ± 0.5 U/day on days with and without PA, respectively; $P < .001$), and for bolus insulin (21.0 ± 1.0 U/day vs. 23.0 ± 1.0 U/day; $P < .001$). The HbA1c covariate had a positive and significant effect on basal, bolus and total insulin doses (2.7 ± 5.9, 4.9 ± 8.7 and 7.5 ± 13.4, respectively; $P < .001$ for each variable; Centre had no effect).

Figure S4 shows the median sensor IQRs of CGM levels: mean value was slightly, but significantly higher with PA (158.6 ± 12.0 mg/dL) than without PA (156.3 ± 12.0 mg/dL; $P = .044$). The average CGM coefficient of variation was higher with PA (32.0% ± 3.7%) than without PA (30.9% ± 3.7%; $P = .019$).

An increase in the daily time spent in TAR was observed with PA (28.7% ± 9.3%) versus without PA (26.8% ± 8.6%, $P = .017$). A very small, but significant decrease was found in the daily time spent in TIR with PA (69.1% ± 8.2%) compared with TIR without PA (70.9% ± 8.2%, $P = .017$).

4 | DISCUSSION

No more hypoglycaemia was found on days with PA compared with days without PA when using DBLG1 for 12 weeks, regardless of the duration or intensity of the PA. This finding was accompanied by an increase in preventive CHO intake and a reduction in insulin delivery. A small but significant increase in hyperglycaemic time was found in days with PA.

Various approaches have been used to prevent or manage hypoglycaemia, and help people with T1D to engage in safe and regular PA.^{2–4} These include education concerning the timing and type of PA.^{2,4} The PEAK group¹¹ issued a consensus statement on glucose targets, insulin dose adjustments and nutritional issues. The American

TABLE 1 Prevention of physical activity (PA)-induced hypoglycaemia with closed-loop (CL) systems combined with dietary interventions

System	Reference	N	Time frame	Dietary intervention	Result
Medtronic PID-IFB	5	12	105 min	CHO supplement (15-30 g)	No decrease in glucose levels
Medtronic 670G	6	8	4 d	CHO supplement ^a	No exercise-induced hypoglycaemia
Multivariable HEA	7	6	3 d	CHO supplement (14 ± 7.8 g)	Most hypoglycaemic events were avoided
DBLG1	9	13	3 d	Unrestricted (CHO = 12-17 g) ^b	No exercise-induced hypoglycaemia
DBLG1	This study	63	12 wk	Unrestricted (CHO ~30 g)	No more hypoglycaemia on days with PA

Abbreviations: CHO, carbohydrates; DBLG1, Diabeloop first-generation CL system; HEA, hypoglycaemia early alarm; N, number of patients; PID-IFB, proportional-integral-derivative with insulin feedback.

^aCalculated for each participant.

^bValue obtained from the Diabeloop SP6 database (not reported in Hanaire et al.⁷).

Diabetes Association recommends that adults with T1D engage in at least 150 minutes of moderate to vigorous aerobic activity per week.¹⁶ This objective was partially achieved in our study, where patients underwent PA sessions (mostly mild to moderate) of an average duration of 136.5 minutes per week.

Current guidelines recommend limiting PA-induced hypoglycaemia by reducing or suppressing insulin delivery. In patients using insulin pumps, manually reducing the subcutaneous insulin infusion within 60-90 minutes before starting PA lowers “insulin on board” and reduces the occurrence of hypoglycaemia.^{11,17,18} This seems difficult to achieve in real-life conditions¹⁹ because it implies anticipating PA sessions at least 1 hour before the start of exercise (only a small benefit was observed with insulin administration adjustments made 5 minutes before²⁰). Moreover, marked reductions in blood glucose are not prevented simply by reducing insulin delivery.⁵ In such a case, a CHO supplement⁵⁻⁷ or an unrestricted diet⁹ prevents exercise-induced hypoglycaemia. The control of PA-induced hypoglycaemia by DBLG1 was associated with a calibrated increase in preventive CHO intake (mean value = 20 g) and a small but significant reduction of insulin delivery (−2.5 units).

The participants in our study consumed a preventive CHO of around 30% more than that recommended by DBLG1, and this may have contributed to the increase in hyperglycaemic time on days with PA versus days without PA (28 minutes). Activation of counter-regulatory mechanisms during intense anaerobic or aerobic PA may also have played a role in the observed hyperglycaemia.^{21,22}

The present post hoc analysis of the Diabeloop WP7 trial clearly confirms and extends previous studies^{5-7,9} that have shown that PA-induced hypoglycaemia can be avoided by adding CHO supplements or an unrestricted diet (Table 1). Dual-hormone systems (insulin and glucagon) can prevent PA-hypoglycaemia,³ but increase the cost and complexity of insulin pump devices.

4.1 | Study limitations

The study limitations were similar to those of other real-life studies. In particular, participants were free to decide the characteristics of their PA, and only the duration and intensity (mild, moderate, intense) of

each PA session were documented in the Diabeloop database. Participants did not sufficiently observe the CHO intake recommended by DBLG1. Preventive CHO may favour weight gain. We were unable to compare the performance of DBLG1 with that of standard care, because only DBLG1 recorded upcoming PA announcements (duration and intensity of PA). The post hoc nature of this analysis precluded the assessment of statistical power. Physiological factors that may contribute to glycaemic control during PA were not studied (e.g. counter-regulations involving the autonomic nervous system and/or glucagon).²³ Besides TIR (CGM 70-180 mg/dL), TBR (CGM <70 mg/dL) and TAR (CGM >180 mg/dL), other glycaemic excursions were not analysed. The algorithm of the CL system does not distinguish PA performed in the postprandial versus the post-absorptive state.

In conclusion, when using DBLG1 in real-life conditions, there is no more hypoglycaemia on days with PA compared with days without PA. This absence of supplementary hypoglycaemia was independent of the PA intensity and duration or the delay in notification. Small but significant increases in hyperglycaemic time and glycaemic variability were found on days with PA. Future studies should take this concern into account, in order to improve the algorithms of CL systems comprising the announcement of PA.

ACKNOWLEDGEMENTS

The authors acknowledge Ricardo P. Garay (Craven, Villemoisson-sur-Orge, France) for editorial support. Diabeloop S.A. (Paris, France) provided the CL artificial pancreas. This study was funded by the French Innovation Fund and Diabeloop S.A. CERITD designed and conducted the study. Parts of the results were presented at the ATTD 2020 meeting (February 2020, Madrid), and at the virtual congress of the Francophone Diabetes Society in September 2020.

CONFLICT OF INTEREST

SF declares congress invitations from Sanofi, Eli Lilly, MSD, Novo Nordisk, Roche, Abbott and Boehringer; she has received speaker honoraria from Lilly and Novo Nordisk, and served on advisory board panels for Novo Nordisk, Diabeloop, Roche, Sanofi, Janssen and Lifescan. She also owns shares in Diabeloop SA. PYB has received speaker honoraria from Abbott, Roche, Eli Lilly, Novo Nordisk and Sanofi, and has served on advisory board panels for Abbott,

Diabeloop, Roche, Medtronic, Dexcom, Insulet, Lifescan, Eli Lilly, Novo Nordisk and Sanofi. SB has received personal compensation for board participation and speaking fees from Abbott, Eli Lilly, Novo Nordisk, Medtronic and Sanofi Aventis. LC has received personal compensation for board participation and speaking fees from Eli Lilly, Lifescan, Novo Nordisk, Roche Diagnostics, Medtronic and Sanofi Aventis. BD has received personal compensation for board participation and speaking fees from Eli Lilly, Novo Nordisk, Sanofi Aventis, MSD and Astra Zeneca. MD is employed by Univ. Grenoble Alpes, CEA LETI, F-38000 Grenoble. BG participated as an advisory panel/board member of Sanofi, Eli Lilly, NovoNordisk, Novartis, GSK, MSD, Boehringer Ingelheim, AstraZeneca, Abbott, Medtronic and Roche Diagnostics; he also participated as a clinical investigator for Sanofi, Eli Lilly, NovoNordisk, GSK, BMS, AstraZeneca, Medtronic, Abbott, Roche Diagnostics, MSD, Novartis, Janssen and Boehringer Ingelheim, and received research support from Medtronic, Vitalaire, Sanofi, Eli Lilly and Novo Nordisk. HH has received personal compensation for board participation and speaking fees from Abbott, Dexcom, Eli Lilly, Lifescan, Novo Nordisk, Roche Diagnostics, Medtronic, Sanofi Aventis and BD. EH is an employee of Diabeloop S.A. NJ received personal compensation for board participation and speaking fees from Eli Lilly, Novo Nordisk, Sanofi Aventis and Roche. CA has received congress invitations from Eli Lilly and AstraZeneca, and has received speaker honoraria from Diabeloop. ER is a consultant/advisor for Abbott, Air Liquide SI, Bastide Médical, Beckton-Dickinson, Cellnovo, Dexcom, Eli-Lilly, Hillo, Insulet, Johnson & Johnson (Animas, LifeScan), Medirio, Medtronic, Novo-Nordisk, Roche Diagnostics and Sanofi-Aventis, and has received research grant/material support from Abbott, Dexcom, Insulet, Roche Diagnostics and Tandem Diabetes Care. YR has received personal compensation for board participation and speaking fees from Novo Nordisk, Sanofi, Eli Lilly, Medtronic, Takeda, Abbott and Roche. PS has received speaking fees from Sanofi, Abbott and Lilly, and for participation on the boards of Novo-Nordisk and Sanofi. C. Thivolet received personal compensation for board participation and speaking fees from Medtronic, Insulet, Sanofi, Lilly, Novo-Nordisk and Abbott. CS, C. Thomas and PH have no conflicts of interest to declare. GC is CMO of Diabeloop SA, owns shares in Diabeloop SA, is employed by CERITD and received personal compensation for board participation, research funding and speaking fees from Astra-Zeneca, Boehringer, Eli Lilly, Johnson & Johnson, MSD, Novo-Nordisk, Sanofi-Aventis and Voluntas.

AUTHOR CONTRIBUTIONS

SF, PYB, SB, LC, BD, BG, HH, NJ, CA, ER, YR, PS, ChT and GC designed the study. SF and GC wrote the protocol and liaised with regulatory authorities. SF, PYB, SB, LC, BD, BG, HH, NJ, CA, ER, YR, PS, ChT and GC were involved with patient enrolment and follow-up. SF, PYB, SB, LC, BG, HH, NJ, CA, ER, YR, PS, CS, ChT, CIT, PH and GC interpreted data. MD engineered the algorithm. SF wrote the manuscript. All the authors revised the manuscript. SF and PH revised and edited the final version of the manuscript, which was accepted by all authors.

PEER REVIEW

The peer review history for this article is available at <https://publons.com/publon/10.1111/dom.14442>.

DATA AVAILABILITY STATEMENT

Data will be available upon request to SF.

ORCID

Sylvia Franc  <https://orcid.org/0000-0001-5123-7743>

Pierre-Yves Benhamou  <https://orcid.org/0000-0003-4378-0468>

Hélène Hanaire  <https://orcid.org/0000-0002-8794-8990>

Eric Renard  <https://orcid.org/0000-0002-3407-7263>

Yves Reznik  <https://orcid.org/0000-0002-6267-8058>

Patrick Hannaert  <https://orcid.org/0000-0003-4995-3913>

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SUPPORTING INFORMATION

Additional supporting information may be found online in the Supporting Information section at the end of this article.

How to cite this article: Franc S, Benhamou P-Y, Borot S, et al. No more hypoglycaemia on days with physical activity and unrestricted diet when using a closed-loop system for 12 weeks: A post hoc secondary analysis of the multicentre, randomized controlled Diabeloop WP7 trial. *Diabetes Obes Metab*. 2021;23(9):2170-2176. <https://doi.org/10.1111/dom.14442>