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BRIEF REPORT

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Efficacy of two telemonitoring systems to improve glycaemic control during basal insulin initiation in patients with type 2 diabetes: The TeleDiab-2 randomized controlled trial

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Abstract

TeleDiab-2 was a 13-month randomized controlled trial evaluating the efficacy and safety of two telemonitoring systems to optimize basal insulin (BI) initiation in subjects with inadequately controlled type 2 diabetes (HbA1c, 7.5%-10%). A total of 191 participants (mean age 58.7 years, mean HbA1c 8.9%) were randomized into three groups: group 1(G1, standard care, n = 63), group 2 (G2, interactive voice response system, n = 64) and group 3 (G3, Diabeo-BI app software, n = 64). The two telemonitoring systems proposed daily adjustments of BI doses, in order to facilitate the achievement of fasting blood glucose (FBG) values targeted at ~100 mg/dL. At 4 months follow-up, HbA1c reduction was significantly higher in the telemonitoring groups (G2: −1.44% and G3: −1.48% vs. G1: −0.92%; $P < 0.002$). Moreover, target

FBG was reached by twice as many patients in the telemonitoring groups as in the control group, and insulin doses were also titrated to higher levels. No severe hypoglycaemia was observed in the telemonitoring groups and mild hypoglycaemia frequency was similar in all groups. In conclusion, both telemonitoring systems improved glycaemic control to a similar extent, without increasing hypoglycaemic episodes.

KEYWORDS
basal insulin, glycaemic control, insulin therapy, randomized trial, type 2 diabetes

1 | INTRODUCTION

Following the initiation of a basal insulin (BI) therapy in patients with type 2 diabetes (T2D) treated with oral hypoglycaemic agents and/or glucagon-like peptide-1 agonists, a significant proportion of them do not reach glycaemic targets.[1] One year after BI initiation, only 25% of US patients with T2D were at the target level for HbA1c (<7.0%),[2] and 35% of insulin-treated French patients had HbA1c > 8.0%.[3] Among other reasons, insulin titration is hampered by the increased risk of hypoglycaemia from targeting fasting blood glucose (FBG) at ~100 mg/dL, in order to achieve HbA1c < 7% (see Section 1 in the File S1).[4]

A previous study (TeleDiab-1) showed that a new telemedicine device, Diabeo app software, enables patients with type 1 diabetes (T1D) to adjust insulin doses and improve their glycaemic control.[5] This positive result pushed us to investigate if a Diabeo app (adapted to BI initiation, Diabeo-BI) could help subjects with T2D to reach glycaemic targets during BI initiation and titration. A simpler system, limited to automatic titration of BI doses via an interactive voice response system (IVRS), was used as a comparative telemonitoring system.

2 | METHODS

2.1 | Study design and treatment

TeleDiab-2 was a randomized, controlled, open-label 13-month trial, conducted in subjects with inadequately controlled T2D from 18 French hospitals between December 2008 and January 2012. The participants had inadequate glycaemic control (HbA1c between 7.5% and 10%) with oral antidiabetics at the maximum tolerated dose (metformin ± sulfonylureas ± dipeptidyl peptidase-4 inhibitors) and required addition of BI. Details of oral antidiabetic treatments at baseline are presented in the File S1 (Table S1 in File S1). Other inclusion criteria were diabetes duration >3 years and body mass index (BMI) < 40 kg/m^2 (for additional information see Section 2 in the File S1).

After giving informed consent, the participants were randomized using a predefined block size (with stratification by centre[4]) into group 1 (G1, control group), group 2 (G2, IVRS group) and group 3 (G3, Diabeo-BI app software) (see Section 3 in the File S1). BI doses were gradually adjusted based on capillary blood glucose (BG) levels. Details of the algorithms used for the adjustment of BI doses with IVRS and Diabeo-BI are presented in the File S1 (Section 4; see also Reference 5). The study lasted 4 months, with a 9-month extension period (Figure 1). During the extension period, IVRS was discontinued in the G2 arm and G2 patients were mixed with those from the G1 arm (Diabeo-BI was continued in the G3 arm). Patients in G2 and G3 had telephone consultations every 2 weeks during the initial 4-month period, and all patients had face-to-face visits at 4 and 13 months (Figure 1).

2.2 | Effectiveness and safety assessments

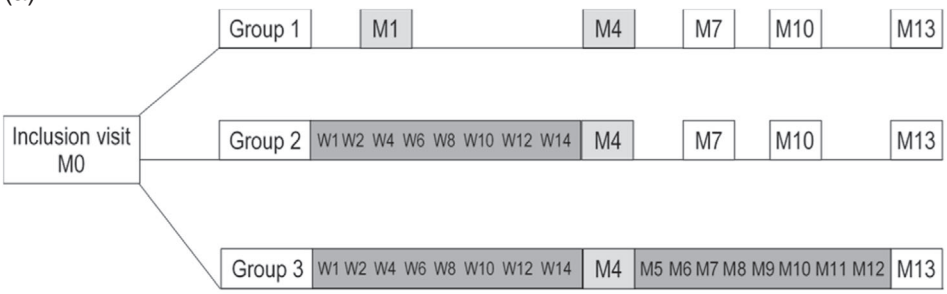
The primary effectiveness outcome was the decrease in HbA1c levels at month 4 (M4). For secondary outcomes, the three groups were compared with respect to: (a) the percentage of patients reaching HbA1c < 7.0%, (b) the percentage of patients reaching FBG between 73 and 108 mg/dL (average value of the last 4 days, measured by a glucometer), (c) FBG values (average of the last 4 days before evaluation), (d) pre- and postprandial BG (8-point profiles), (e) changes in insulin doses, and (f) quality of life (QOL), using the Diabetes Health Profile QOL scale as well as items from the Diabetes QOL satisfaction dimension).[6,7]

Safety assessments included the frequency of mild or severe symptomatic hypoglycaemic episodes (the latter being defined as requiring the intervention of a third party) and changes in body weight.

2.3 | Ethics

The study was approved by the ethical committee [Comité de Protection des Personnes (CPP); Committee for People Protection) of Ile de France VI. All procedures were conducted in accordance with the Declaration of Helsinki and Good Clinical Practice guidelines and in accordance with French privacy law (Informatique et Libertés) when processing personal healthcare data (Act of January 6, 1978, amended by Law No. 2004-801 of August 6, 2004). The trial was registered with ClinicalTrials.gov identification number: NCT00937703.

(a)



(b)

	M0-M4	M4-M13 Extension
Group 1 (G1)	Standard care Face-to- face visit at M4 (~30 min) and optional visit at M1	Standard care
Group 2 (G2)	IVRS + short telephone consultations (~5 min) + Face-to-face visit of ~30 min at M4	Standard care
Group 3 (G3)	Diabeo-BI + short telephone consultations (~5 min) + Face-to-face visit of ~30 min at M4	Diabeo-BI + short telephone consultations

FIGURE 1 Overall study design A, and details of telephone consultations and visits, B. M1: optional face-to-face visit (control group, G1). M4 and M13: face-to-face visits for all patients. From W1 to W4: weekly phone consultations (for patients in the G2 and G3 groups). From W6 to W14: bimonthly phone consultations (for patients in the G2 and G3 groups). From M5 to M12: monthly phone consultations (for patients in the G3 group). IVRS, interactive voice response system

2.4 | Statistics

A sample population of 180 participants was estimated to detect a 0.7% ± 1.2% HbA1c mean difference between investigational and control groups. Quantitative variables were analysed by using one-way analyses of covariance. For qualitative variables, groups were compared by using logistic regression analysis. Data are presented as mean ± SD (or SEM) as appropriate.

3 | RESULTS

In total, 189 participants entered the study (intention-to-treat population) and were included in the full analysis set (Figure S1 in File S1). All participants were on double or triple oral therapy (Table S1 in File S1), and their baseline demographic and clinical characteristics were similar in all three groups (mean age of participants: 58.7 years, *diabetes* duration: 13.1 years, BMI: 29.7 kg/m^2 and HbA1c: 8.9%) (Tables S2 and S3 in File S1). Patients initiated insulin therapy with detemir at bedtime (except four patients on glargine) at an average dose of 10.5 ± 2.9 U/day.

3.1 | Effectiveness and safety outcomes at month 4 (M4)

A total of 174 participants were followed at M4, with 171 having HbA1c data available (Figure S1 in File S1).

3.1.1 | Primary outcome

HbA1c levels decreased significantly more in patients from the investigational arms (G2: 7.42% ± 0.91% and G3: 7.47% ± 0.90%) than in the control arm (G1: 7.96% ± 0.88%, $P < 0.002$) (Figure 2A). HbA1c decreases from baseline were also significantly higher in G2 (−1.44%) and G3 (−1.48%) arms compared with the control arm, G1 (−0.92%, $P < 0.002$) (Figure 2A).

3.1.2 | Secondary outcomes

At M4, most secondary criteria were in favour of the telemonitoring arms. The glycaemic control target (HbA1c < 7.0%) was achieved in twice as many patients (G2: 32.8% and G3: 29.8%) as in the control arm (G1: 12.5%, $P < 0.02$) (Figure 2B). FBG targeted at 73 to 108 mg/dL was also achieved in twice as many patients (G2: 82.5% and G3: 82.7%) as in the control arm (G1: 41.8%, $P < 0.001$). FBG (average of the last four days) was significantly lower (G2: 115 ± 26 mg/dL and G3: 112 ± 25 mg/dL) compared with the control arm (G1: 132 ± 24 mg/dL, $P < 0.002$). Pre- and postprandial BG (8-point profiles) were also significantly lower in G2 and G3 compared with G1 (Figure S2 in File S1). BI was uptitrated to higher doses in the investigational arms (G2: 0.49 ± 0.34 U/kg/day and G3: 0.54 ± 0.32 U/kg/day) than in the control arm (G1: 0.40 ± 0.24 U/kg/day) (differences between G3 and G1 reached statistical significance, $P \leq 0.02$, Figure 2C). Finally, no statistically significant differences between groups were found concerning patients' satisfaction.

3.1.3 | Safety outcomes

Mild hypoglycaemic episodes were rare (0.3 ± 0.7 per patient during the week before M4), with no significant differences between the three arms. No severe hypoglycaemia was reported. A significant body weight gain was observed at M4 in G2 (+2.4 ± 3.5 kg vs. 0.9 ± 2.5 kg in G1, $P = 0.01$), but not in G3 (+1.2 ± 2.8 kg).

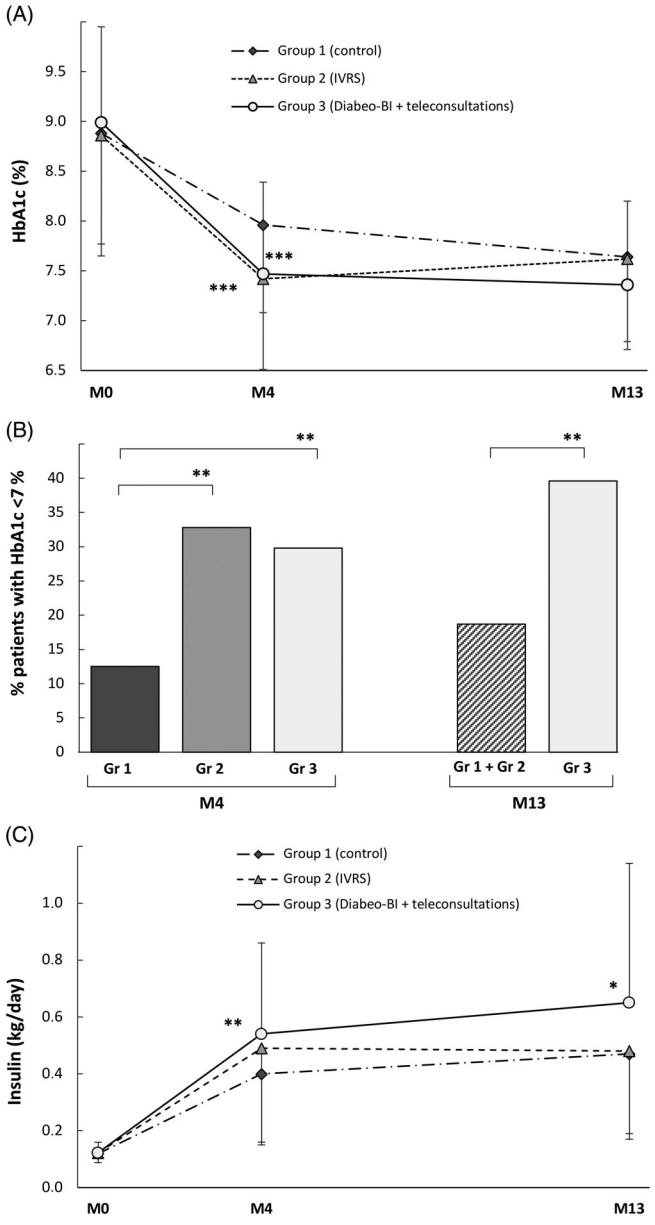


FIGURE 2 A, Changes from baseline in HbA1c levels at M4 and M13. HbA1c levels decreased more in patients from the G2 and G3 arms compared with the control arm, G1 (−0.53% and −0.51%, respectively; ***P < 0.002). B, Percentage of patients achieving target for glycaemic control (HbA1c <7.0%) at M4 and M13. At M4, the number of patients at target was significantly higher in the G2 and G3 arms as compared to the control arm (**P < 0.02). Control arm: G1: dark grey, G2: light grey and G3: pale cream. At M13, glycaemic control target was achieved in twice as many patients of G3 as in those of the control arm G1+G2 (P = 0.023). IVRS, interactive voice response system

3.2 | Extension period

After M4, 98.1% (52/53) of patients from G3 wished to continue with Diabeo-BI (Figure S1 in File S1). In the G2 arm, IVRS was discontinued and G2 patients continued with a standard follow-up, as in the control arm (G1), with face-to-face visits every 3 months and no telemedicine. In all, 158 patients completed the extension phase (Figure S1 in File S1).

At M13, G2 and G1 had similar values of HbA1c and insulin doses (Figure 2). HbA1c levels were lower in G3 compared with the control arm (G1 + G2) but the difference was not statistically significant. Conversely, the glycaemic control target (HbA1c < 7.0%) was achieved in twice as many G3 patients (30.2%) than in those from the control arm (13.8%, P = 0.023) (Figure S2 in File S1). BI was uptitrated to 0.47 ± 0.28 U/kg/day in G1 and 0.48 ± 0.31 U/kg/day in G2 (Figure 2C). In G3, BI was uptitrated up to 0.65 ± 0.49 U/kg/day (P = 0.05 vs. G1). A second BI was added to 5% of patients, and a short-acting analogue to 10% of patients (Table S3 in File S1).

Mild hypoglycaemic episodes were rare (0.2 ± 0.5, 0.3 ± 0.7 and 0.4 ± 1.0 per patient the week before the M13 visit in G1, G2 and G3, respectively), with no differences between the three groups (Section 5 in the File S1). Severe hypoglycaemia occurred in one patient from G1 and in one patient from G2 (twice), but not in any G3 patients. Weight gain between baseline and M13 was not significantly different between groups (G1: +1.9 ± 5.5 kg, G2: +3.8 ± 4.4 kg, G3: 2.8 ± 4.8 kg).

4 | DISCUSSION

Diabeo-BI and IVRS both improved insulin titration and glycemic control compared with the control group at M4. Thus, the number of responders (patients reaching target HbA1c and FBG values) was twice as high as in the control arm. This improved glycaemic control was associated with a significant increase in the uptitrated BI doses, without increasing the incidence of hypoglycaemia. Finally, most of the therapeutic benefits obtained with Diabeo-BI were maintained during the extension phase of 9 months.

TeleDiab-2 was conducted with patients from 18 French hospitals, who were followed through face-to-face consultations at M0, M4 and M13 (during the initial 4-month period, patients from G2 and G3 had telephone consultations every 2 weeks). Therefore, patients using Diabeo-BI or IVRS calculated daily insulin doses by themselves, with a considerable gain in autonomy. To our knowledge, TeleDiab-2 is the first long-term (>1 year) randomized, controlled study evaluating the impact of a "basal calculator" (Diabeo-BI app software) uploaded to a smartphone to initiate BI therapy in T2D patients, without prior dose validation by a healthcare provider (HCP). Indeed, many of the current, web-based self-management systems for insulin titration require dose-validation by HCPs. This is the case for the PREDICTIVE 303 algorithm,[8,9] the LTHome system[10] and TeLiPro.[11] Studies with the Diabetes Pal smartphone[12] and the MyStar DoseCoach glucometer[13] included patients already treated with insulin and failed to show superiority in terms of HbA1c reduction. The Welldoc system[14] has shown some metabolic efficacy in subjects with particularly unbalanced T2D, but it does not propose automatic adjustment of insulin doses. Finally, a recent study[15] showed an additional HbA1c reduction (−0.7%) by using an algorithmic insulin titration guidance (d-Nav device) with HCP support

compared with HCP support alone (a value close to the −0.5% of additional HbA1c reduction reported here).

Considering the widespread use of smartphones, the Diabeo-BI app could increasingly be used in the future. Although no cost analysis has been performed, Diabeo-BI app has a strong potential for health resource optimization and cost savings (Diabeo-BI is now compatible with Bluetooth BG Meters, allowing direct automated BG upload). Otherwise, a simple IVRS would be of practical value for less autonomous patients (e.g. elderly subjects).

Our study had several limitations. BI adjustment was coupled with some coaching functions, mainly during the extension phase, designed to encourage patients to persist with their diet or physical activity, and which could probably contribute to G3 improvements.[16] Moreover, the time spent in face-to-face or remote consultations was not assessed.

In conclusion, Diabeo-BI and IVRS telemonitoring systems both improved insulin titration and glycaemic control in patients with T2D, without increasing the risk of hypoglycaemia.

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CERITD developed the smartphone algorithms in collaboration with Voluntis. CERITD is a non-profit clinical translational research centre located next to Corbeil Hospital (Evry, France).

Voluntis provided the software for diabetes treatment. Orange (Paris, France) provided the smartphone, telephone lines and IVRS system.

CONFLICT OF INTEREST

S.F., A.D., C.R. and G.C. are employees of CERITD. G.O. is an employee of Voluntis. The other authors declare that they have no competing interests. CERITD funded the study. Novo Nordisk provided an unrestricted grant.

AUTHOR CONTRIBUTIONS

S.F., G.C., M.J. and P.Y.B. contributed to the conception and design of the study. M.J., A.D., C.F., P.Y.B., M.R., B.B., E.B., P.S., B.G., D.D., S.B., A.P., G.O., K.M. and Y.R. contributed to the acquisition, analysis and interpretation of data. S.F. wrote the manuscript, and P.Y.B., M.J., A.P., C.R. and G.C. contributed to a critical revision of the manuscript. All authors approved the final version of the manuscript. CERITD was fully involved in the study design and coordination. Novo Nordisk was not involved in study coordination, monitoring visits or data management.

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REFERENCES

1. Raccah D, Chou E, Colagiuri S, et al. A global study of the unmet need for glycemic control and predictor factors among patients with type 2 diabetes mellitus who have achieved optimal fasting plasma glucose control on basal insulin. *Diabetes Metab Res Rev*. 2017;33:e2858.
2. Baser O, Tangirala K, Wei W, Xie L. Real-world outcomes of initiating insulin glargine-based treatment versus premixed analog insulins among US patients with type 2 diabetes failing oral antidiabetic drugs. *Clinicoecon Outcomes Res*. 2013;3:497-505.
3. Bouée S, Avignon A, Halimi S. Diabète de type 2: pratiques d'intensification thérapeutique chez les médecins généralistes en France en 2008–2009. *Bulletin Epidémiologique Hebdomadaire*. 2010;42–43:436-440.
4. Yki-Järvinen H, Kauppinen-Mäkelin R, Tiikkainen M, et al. Insulin glargine or NPH combined with metformin in type 2 diabetes: the LANMET study. *Diabetologia*. 2006;49:442-451.
5. Charpentier G, Benhamou P-Y, Dardari D, et al. The Diabeo software enabling individualized insulin dose adjustments combined with telemedicine support improves HbA1c in poorly controlled type 1 diabetic patients: a 6-month, randomized, open-label, parallel-group, multicenter trial (TeleDiab-1 study). *Diabetes Care*. 2011;34:533-539.
6. Meadows K, Steen N, McColl E, et al. The Diabetes Health Profile (DHP): a new instrument for assessing the psychosocial profile of insulin requiring patients--development and psychometric evaluation. *Qual Life Res*. 1996;5:242-254.
7. The DCCT Research Group. Reliability and validity of a diabetes quality-of-life measure for the diabetes control and complications trial (DCCT). *Diabetes Care*. 1988;11:725-732.
8. Hsu WC, Lau KHK, Huang R, et al. Utilization of a cloud-based Diabetes Management Program for insulin initiation and titration enables collaborative decision making between healthcare providers and patients. *Diabetes Technol Ther*. 2016;18:59-67.
9. Meneghini L, Koenen C, Weng W, Selam JL. The usage of a simplified self-titration dosing guideline (303 algorithm) for insulin detemir in patients with type 2 diabetes–results of the randomized, controlled PREDICTIVE 303 study. *Diabetes Obes Metab*. 2007;9:902-913.
10. Bajaj HS, Venn K, Ye C, Aronson R. Randomized trial of long-acting insulin glargine titration web tool (LTHome) versus enhanced usual therapy of glargine titration (INNOVATE trial). *Diabetes Technol Ther*. 2016;18:610-615.
11. Kempf K, Altpeter B, Berger J, et al. Efficacy of the telemedical lifestyle intervention program TeLiPro in advanced stages of type 2 diabetes: a randomized controlled trial. *Diabetes Care*. 2017;40:863-871.
12. Bee YM, Batcagan-Abueg APM, Chei C-L, et al. A smartphone application to deliver a treat-to-target insulin titration algorithm in insulin-naive patients with type 2 diabetes: a pilot randomized controlled trial. *Diabetes Care*. 2016;39:e174-e176.
13. Edelman S, Bain S, Hasslacher C, et al. Device-supported versus routine titration of insulin glargine 300 U/mL (Gla-300) in T2DM: efficacy and safety. *Diabetologia*. 2017;60:S307. https://doi.org./10.1007/s00125-017-4350-z.
14. Quinn CC, Shardell MD, Terrin ML, Barr EA, Ballew SH, Gruber-Baldini AL. Cluster-randomized trial of a mobile phone personalized behavioral intervention for blood glucose control. *Diabetes Care*. 2011;34:1934-1942.
15. Bergenstal RM, Johnson M, Passi R, et al. Automated insulin dosing guidance to optimise insulin management in patients with type 2 diabetes: a multicentre, randomised, controlled trial. *Lancet*. 2019;393:1138-1148.

16. Swinnen SGHA, DeVries JH. Contact frequency determines outcome of basal insulin initiation trials in type 2 diabetes. *Diabetologia*. 2009; 52:2324-2327.

SUPPORTING INFORMATION

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

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