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Use of smartphone application versus written titration charts for basal insulin titration in adults with type 2 diabetes and suboptimal glycaemic control (My Dose Coach): multicentre, open-label, parallel, randomised controlled trial

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Summary

Background The majority of people with type 2 diabetes who require insulin therapy use only basal insulin in combination with other anti-diabetic agents. We tested whether using a smartphone application to titrate insulin could improve glycaemic control in people with type 2 diabetes who use basal insulin.

Methods This was a 12-week, multicentre, open-label, parallel, randomised controlled trial conducted in 36 diabetes practices in Germany. Eligible participants had type 2 diabetes, a BMI ≥25.0 kg/m^2, were on basal insulin therapy or were initiating basal insulin therapy, and had suboptimal glycaemic control (HbA1c >7.5%; 58.5 mmol/mol). Block randomisation with 1:1 allocation was performed centrally. Participants in the intervention group titrated their basal insulin dose using a smartphone application (My Dose Coach) for 12 weeks. Control group participants titrated their basal insulin dose according to a written titration chart. The primary outcome was the baseline-adjusted change in HbA1c at 12 weeks. The intention-to-treat analysis included all randomised participants.

Results Between 13 July 2021 and 21 March 2022, 251 study participants were randomly assigned (control group: n = 123; intervention group: n = 128), and 236 completed the follow-up phase (control group: n = 119; intervention group: n = 117). Regarding the HbA1c a model-based adjusted between-group difference of −0.31% (95% CI: 0.01%–0.69%; p = 0.0388) in favour of the intervention group was observed. There were 30 adverse events reported: 16 in the control group, 14 in the intervention group. Of these, 15 adverse events were serious. No event was considered to be related to the investigational device.

Interpretation Study results suggest that utilizing this digital health smartphone application for basal insulin titration may have resulted in a comparatively greater reduction in HbA1c levels among individuals with type 2 diabetes, as compared to basal insulin titration guided by a written titration schedule. No negative effect on safety outcomes was observed.

Funding Sanofi-Aventis Deutschland GmbH.

Keywords: Type 2 diabetes; Basal insulin; Insulin titration; Digital health tool; Titration app; My Dose Coach app

Introduction

Type 2 diabetes mellitus is a chronic disease characterised by persistently elevated blood glucose levels; the condition accounts for more than 90% of the 537 million cases of diabetes worldwide.[1] Of these, an estimated 80 million people with type 2 diabetes use insulin therapy[2] due to progressive failure in insulin production or function, which requires intensification of diabetes

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Trial registration: German Clinical Trials Register DRKS00024861.

Research in context

Evidence before this study

The PubMed database was screened for submissions through 6 March 2023 using the search terms 'type 2 diabetes' and 'automated insulin dosing OR smartphone app OR digital health OR device OR web OR telemonitoring OR smartphone' and 'titration' and 'randomised controlled trial OR pilot randomised controlled trial' to identify randomised controlled trials that evaluated the effect of smartphone applications or other digital health tools for basal insulin titration in people with type 2 diabetes. The search identified 20 publications. Of these, 11 studies evaluated the effect of new insulins or GLP/GIR agonists, and one study evaluated prandial insulin titration. One was a method paper and two were general titration tools for oral medications, leaving five trials that evaluated the effect of digital health tools on basal insulin titration in people with type 2 diabetes who were treated with basal insulin. One trial tested a web tool (LTHome) but did not indicate that this web tool was non-inferior to standard education. Another rather small trial tested a titration application (DiabetesPal) but did not exhibit superiority over the control group. A more complex trial in France involved up to eight visits over four months, tested a titration application compared with standard care and an interactive voice response system, and revealed superiority of the application compared with standard care but no significant effect compared with the interactive voice response system. The d_navigation device (a combination dose calculator and glucose meter) indicated superiority to standard care but also presented a significant increase in low glucose values. The AUTOMATIX trial tested a bolus calculator linked to a glucose meter in a non-inferiority trial. This device proved to be non-inferior but not superior to standard care, albeit at the cost of a significant number of low glucose values. In summary, the trials varied in interventions tested (web tools, applications, and stand-alone dose calculators), study designs, and effects on glycaemic control. Currently, there is no clear evidence that smartphone applications for basal insulin titration are effective and safe. We also identified two reviews that supported these findings. Both reviews concluded that the methodological quality of the studies was not optimal and highlighted the paucity of quality evidence for the use of such digital health tools.

Added value of this study

This randomised controlled trial demonstrates that the use of the smartphone application studied had a beneficial effect on glycaemic control compared with standard care in a healthcare system in a relatively high-income country. Concurrently, there was no significant increase in hypoglycaemia or other safety issues during the study. The usability and functionality of the application was found to be satisfactory.

Implications of all the available evidence

Approximately 80 million people worldwide with type 2 diabetes are currently estimated to require insulin treatment, most with basal insulin alone, in addition to oral medications or non-insulin injectables. Scientists, even in countries with relatively advanced healthcare systems, suggest that once basal insulin therapy is initiated, titration targets are often missed and glycaemic control remains suboptimal, thus increasing the risk of complications. Basal insulin doses are often under-titrated. New digital solutions, such as the titration applications studied herein, can provide easy-to-use and largely scalable tools to improve glycaemic outcomes effectively and safely, as an estimated 5 billion people worldwide have access to smartphones. The number of people with type 2 diabetes using insulin worldwide could double if appropriate HbA1c targets are achieved to prevent diabetes complications; consequently, such a simple digital tool can have a major impact on health status and quality of life.

management to achieve adequate glycaemic control and avoid long-term complications.[3] Most people with type 2 diabetes who are treated with insulin use basal insulin therapy in combination with non-injectable pharmacological agents. The basal insulin dose should be titrated until the individual glycaemic targets are met by adapting the insulin dose to the fasting glucose values.[3] Results of a randomised controlled trial indicate that self-titration by people with diabetes in everyday life is at least as effective in glycaemic outcomes as titration by weekly visits to a healthcare professional.[4]

However, results from clinical trials suggest that titrating basal insulin doses appears to fail in most study participants with diabetes, and a fairly significant proportion of participants experience hypoglycaemia. A longitudinal study in five European countries and the US with 40,627 people who had type 2 diabetes and were starting basal insulin treatment indicates that only 20.9% and 27.8% achieved the HbA1c target of ≤7% (≤53 mmol/L) at three and 24 months, respectively. Additionally, 8.9% of people in the study had a recorded hypoglycaemic event during the two-year observation period.[5]

A UK-based longitudinal register study offers similar results, indicating only 30% of people with elevated HbA1c levels attained glycaemic targets.[6,7]

Barriers to titration on the patient side include the following: fasting blood glucose is not measured or documented regularly, the need for titration is not recognised, the titration dose is not determined correctly, or the titration is not performed. In addition to these practical problems, cognitive (e.g., insecurity in the

autonomous adjustment of the insulin dose) or emotional problems (e.g., fear of hypoglycaemia) can also be responsible.[8–10]

Technological solutions, such as titration support system applications, can therefore provide support for people with diabetes to overcome titration barriers, as recommended in the European Association for the Study of Diabetes/American Diabetes Association consensus report for management of type 2 diabetes.[3] Evidence for a digitally supported insulin titration comes from Bergenstal et al.[11] and Franc et al.[12] Both studies have presented significant improvements in HbA1c due to digital titration support compared to a standard care group. In these studies, HbA1c was lowered by 1.0% and 1.48%, respectively, in the intervention groups, compared to 0.3% and 0.92% in the control groups, respectively. This indicates that large improvements in HbA1c can be achieved via digital health tools for insulin titration. However, in both studies, incidence of mild hypoglycaemia was rather high; in Bergenstal et al.[11] levels were significantly higher in the treatment group than in the control group.

Conversely, several studies have not demonstrated a significant improvement in HbA1c via a titration application.[13–15] These mixed findings are corroborated by two recent reviews about the use of basal insulin dosing guidance systems[16] or digital health technologies that support initiation or optimisation of insulin therapy in type 2 diabetes.[17] Both reviews have concluded that the methodological quality of the studies was not optimal and have stressed the paucity of quality evidence for the use of such digital health tools.

We therefore conducted a multicentre randomised controlled trial to evaluate the efficacy of a newly developed titration application (My Dose Coach) for basal insulin titration. My Dose Coach is based on the titration schedule agreed upon between the physician and the person with diabetes. Users are automatically reminded of the titration, and the recommended insulin dose for titration is suggested. Additionally, if the user wishes, healthcare professionals can follow patients' titration on an online platform, make an online adjustment of titration algorithms, and provide dose recommendations. A previous version of the My Dose Coach application was tested in an uncontrolled study in Mexico[18] demonstrating a substantial reduction of HbA1c values by 1.8% (19.7 mmol/mol) in people with type 2 diabetes and elevated HbA1c values (9.5% respectively. 84.4 mmol/mol).

In this multicentre randomised trial, we wanted to evaluate whether titrating the basal insulin dose with this digital health tool reduces HbA1c values as the primary outcome compared to a control group who received written titration plans from their treating physicians. Additionally, safety variables, other glycaemic outcomes, and person-reported outcomes were analysed as secondary outcome variables.

Methods

Study design

The study was designed as an open-label, multicentre, parallel, randomised controlled study with a 12-week follow-up and was conducted in 36 centres in Germany that specialise in the treatment of people with diabetes. The study design and methods are described in detail in Hermanns et al.[19] Participants in the intervention group were registered on the My Dose Coach online platform and used the application for 12 weeks. Control group participants used written information from their physician to titrate their basal insulin dose without using an application. The study was conducted in accordance with the declaration of the 18th World Medical Assembly, Helsinki, Finland, 1964 (and later versions), in accordance with the German Medical Device Law (MPG of 28 April 2020), and with DIN EN ISO 14155:2020. Ethical approval was granted by the Ethics Committee of the Medical Association of Baden-Württemberg (F-2021-016) and by the 14 competent local ethics committees. This trial is registered with the German Clinical Trial Register: DRKS00024861.

Participants

Key inclusion criteria were the diagnosis of type 2 diabetes, an indication for once-daily basal insulin therapy combined with oral antidiabetic agents or non-insulin injectables, and a last documented HbA1c >7.5% (58.5 mmol/mol) and <10.0% (85.6 mmol/mol). Key exclusion criteria were treatment with prandial insulin at baseline (meal insulin), BMI <25 kg/m^2, use of another insulin titration application, or inability to provide consent due to limited legal capacity or legal guardianship. All participants provided written informed consent.

Randomisation and masking

Study participants were randomly assigned either to the intervention group (titration of basal insulin doses via the titration application My Dose Coach) or the control group (titration of basal insulin according to a written titration scheme) at a 1:1 ratio. Computer-generated randomisation (via randomizer.org) was performed by staff at the study coordinating centre who were not involved in recruitment. The block sizes were not disclosed to trial staff in order to reduce their ability to estimate group membership based on previous randomisations. Study centres received separate sealed envelopes with the randomisation results for each participant. The envelopes were opened by the study centre staff after informed consent was provided by the participant; inclusion and exclusion criteria were verified at the first study visit. Due to the nature of the intervention, blinding of participants and study centres providing the intervention was not possible. Blinding of outcome assessors (the study participants who completed the self-report scales or the study staff who

downloaded the blood glucose results) was also not feasible.

Procedures

After obtaining participants' informed consent, their baseline data were collected (Visit 1); secondary data were collected at the final assessment (Visit 2) 12 weeks after Visit 1. During Visit 1, participants completed questionnaires regarding person-reported outcomes. Study centres documented medical data in an electronic case report file (Magana-Med, Regensburg, Germany). Data from self-monitored blood glucose measurements (SMBGs) from the two weeks prior to the baseline visit were downloaded via the DIABASS® system (Balingen, Germany) or with the practices' software and transmitted to the study coordinating site as a pseudonymised file. Due to regulatory reasons, participants' most recent HbA1c values were either taken from the medical record or determined in the central laboratory (Automated Glycohemoglobin, Analyzer HLC-723G11; Tosoh) (normal range 4.1%–6.1% [21–43 mmol/mol]) as part of a routine quarterly blood test.

After completion of the questionnaires, participants were randomly assigned to one of the two study groups (intervention or control). Both groups received their individual titration plan by their treating physician in accordance with the treatment guidelines for type 2 diabetes within a shared decision-making process.

Participants in the control group received a written titration chart to titrate their basal insulin. Participants in the intervention group were registered on the online platform by the study centre staff, and a titration algorithm was entered by the treating physician. The physician defined the starting dose of basal insulin, the individual fasting target range, the width of the respective correction range, and the corresponding dose increase of the basal insulin according to their clinical judgement of individual insulin sensitivity, multimorbidity, and hypoglycaemia risk. Based on this assessment, the physician also defined a hypoglycaemia threshold and the management of hypoglycaemic values in participants' daily routines.

Intervention group participants then downloaded the My Dose Coach application on their smartphone and were provided with instructions for using the titration application. When participants first logged in, the online platform sent a confirmation link to connect and synchronise the application with the online platform so that the titration algorithm was sent to the application and all participant entries in the application were automatically transferred to the online platform. Consequently, the physician was able to monitor the patient's therapy at any time and make any necessary adjustments, which were automatically transferred to the application, and participants received a text message informing them about the adjustments. Participants were required to perform at least one fasting blood glucose measurement per day and enter the data into the application. The application calculated the median of three consecutive fasting glucose values and recommended a basal insulin dose based on the settings stored in the online platform. Supplementary Table S1 provides additional details regarding the titration application.

After the 12-week intervention period, participants in both groups completed the same questionnaires they completed at their baseline visit. The doctor documented the participants' most recent post-randomisation HbA1c value in the medical record or took a blood sample to measure the HbA1c value in the central laboratory. All glucose data recorded since the baseline assessment were downloaded again. Intervention group participants also completed a separate questionnaire to evaluate the usability of the titration application (see Supplementary Figure S1). After completion of the follow-up visit, the titration application was uninstalled from participants' smartphones.

Outcomes

The primary outcome was the between-group difference in HbA1c changes from baseline to the 12-week follow-up visit.

Between-group differences in changes in several person-reported outcomes were used as secondary outcomes, as assessed by the German versions of the following scales: Diabetes distress was assessed by the problem areas in diabetes (PAID) questionnaire,[20] diabetes self-management by the diabetes self-management questionnaire (DSMQ),[21] diabetes empowerment by the diabetes empowerment scale (DES),[22] and self-efficacy by the general self-efficacy scale (GSE).[23] Satisfaction with insulin therapy was measured using the insulin treatment satisfaction scale (DSat).[24] The WHO-5 well-being scale (WHO-5)[25] was used to assess psychological well-being. For ease of interpretation, all scores were linearly converted to a scale between 0 and 100 in which higher values indicated higher expression in the direction of the characteristic. In the intervention group, participants also rated the functionality and usability of the application with the mobile application rating scale (MARS)[26]; items ranged from 1 (least positive) to 5 (maximum positive).

Secondary glucose outcomes were calculated from participants' glucose meter readings. Baseline values comprised glucose values measured two weeks before randomisation, and outcome values were based on all glucose values measured between randomisation and the follow-up visit. Fasting glucose values were defined as the first measured glucose value of a day between 05:00 and 10:00 am. Additionally, the mean glucose level, percentages of low and high glucose values (<70 mg/dl and >180 mg/dl, respectively), and the number of daily glucose measurements were assessed. Other secondary variables were recorded, such as the time to reach the titration target and the percentage of

HbA1c values <7.5% and <7.0% as well as the percentage of participants with an HbA1c reduction of ≥0.3% and ≥0.4%.

As safety outcomes, adverse and severe adverse events were assessed by standardised adverse events reporting forms that were completed by study centre staff. Furthermore, we evaluated the rate of critically low and high glucose measurements (<54 mg/dl and >250 mg/dl, respectively) and the occurrence of severe hypoglycaemia (assessed by the need for third-party assistance for recovery) or ketoacidosis.

Statistical analysis

Based on the studies mentioned in the Introduction, effect sizes for digital titration aids in randomised controlled trials range from −0.05 to 0.7 standard deviations.[11–15,27] Therefore, the sample size was estimated using an expected mean effect size of d = 0–375 (corresponding to a mean between-group difference in HbA1c of 0–375 with an assumed standard deviation of 1) a two-sided alpha of $\alpha = 0.05$, power of $1-\beta = 0.80$, a 1:1 randomisation, and an expected drop-out rate of 10%. This calculation resulted in a total of 251 participants needed (126 in the intervention group and 125 in the control group).

The primary statistical analysis was performed using the intention-to-treat population, which is defined as all participants who were randomised. Additionally, a sensitivity analysis using the per-protocol population was performed. Participants included in the per-protocol analysis provided baseline and follow-up data, accessed the randomly allocated intervention, and had a follow-up period longer than 41 days but no longer than 137 days. The distribution of nearly all continuous variables deviated significantly from a normal distribution; therefore, continuous variables were transformed into Van der Waerden scores using a rank normal area transformation (see Supplementary Table S2).

A random effects analysis of covariance (ANCOVA) was performed with the continuous outcome as a dependent variable, group allocation as an independent fixed factor, study centre as a random factor, and the baseline value as a covariate. A model-based adjusted difference between groups with a 95% confidence interval (CI) is reported. Model-based adjusted differences of continuous data are determined by stepwise shifting the distribution of the untransformed treatment group outcome until the highest p-values of the transformed shifted outcomes indicate equal ranks. The shifted values with p-values less than or equal to 0.05 define the lower and upper 95% confidence intervals, respectively.[28] For all glucose data or glucose data-derived outcomes, the difference between the baseline measurement and all measurements between randomisation and the follow-up assessment is the dependent variable, with the baseline values as a covariate. Glucose data as count data (the number of glucose readings in a certain glucose range per 1000 measurements) and the number of adverse as well as severe adverse events were analysed, depending on the model fit, with a mixed negative binominal regression analysis, Poisson regression analysis, or generalised Poisson regression analysis; group allocation was a fixed independent factor and study centre was a random factor adjusted for baseline values. The adjusted incidence rate ratio is provided as an estimator of the model-based adjusted between-group difference. Categorical data were analysed with mixed logistic regression models (generalised linear mixed model fit by maximum likelihood with baseline values, if appropriate) as a covariate, group allocation as a fixed independent factor, and study centre as a random factor. Adjusted odds ratios are presented for the model-based adjusted between-group difference.

Multiple imputation with the jump-to-reference approach was used to manage missing data. Missing data at the follow-up phase were imputed via a Markov chain Monte Carlo multivariate imputation algorithm with 10 estimations per missing value by using the following variables as estimators: baseline dose of basal insulin, baseline insulin unit per kilogram of body weight, pre-existing insulin therapy versus newly initiated insulin therapy, baseline BMI, and age. Sensitivity analyses were also pre-specified, particularly for relevant subgroups (e.g., existing versus new initiation of basal insulin therapy) and for the per-protocol population.[19] The statistical analysis was amended on 31.03.2022, after the German office for drugs and medical products modified their regulation regarding the approval of digital health application.

Statistical analyses were performed using IBM SPSS Statistics version 29 (IBM, Armonk, New York) and R 4.2.1 statistical packages (modules: lme, glmer, and glmTMB). A p-value of <0.05 is considered statistically significant. To account for the multiplicity of analyses, hierarchical testing was pre-specified. In Supplementary Table S3, the hierarchical order of testing is listed. Percentages of glucose values <54 mg/dl or >250 mg/dl and the total number of adverse and severe adverse events are considered to be safety variables. Therefore, the significant level for these tests remains at the α-level of 0.05 to avoid the inflation of a β-error.

Changes from the planned protocol

The statistical analysis plan was modified after recruitment of study participants started, but before the database was locked and the statistical analysis started. In addition, due to the non-normally distributed outcome variables, we report model-based adjusted values based on the shift and test technique for between-group differences for continuous variables instead of parametric or rank-based values.

Role of funding source

The funding source, Sanofi-Aventis Deutschland GmbH, had no role in data analysis, data interpretation,

or writing this report. The corresponding author had full access to all data in the study and had final responsibility for the decision to submit for publication.

Results

Between 13 July 2021 and 21 March 2022, 254 study participants were recruited in 36 study centres across Germany. From those, 123 participants were randomly allocated to the control group, and 128 were allocated to the intervention group. Three study participants were excluded prior to randomisation because they possessed non-compatible smartphones. All randomised participants were included in the intention-to-treat analysis.

After 12 weeks, 236 study participants provided outcome data (94.0%); 11 intervention group participants and four control group participants were lost to follow-up. In addition, from those allocated to the intervention group, seven could not install the application on their smartphone for various reasons and one person exceeded the follow-up period by more than 50%. In the control group, one participant exceeded the follow-up period by more than 50%, and two participants did not meet central inclusion criteria (see Fig. 1).

The descriptive variables are reported in Table 1. The majority of study participants were male and had a median age of approximately 60 years. Most of the participants (>80%) had an existing treatment with basal insulin with a median duration of one year. Glycaemic control was suboptimal, as indicated by a median HbA1c of 8.2% and 8.3% in the intervention and control groups, respectively. There was also a significant between centre difference (F [df 34,251] = 2.135, p = 0.0006) regarding the Baseline HbA1c (see Supplementary Figure S2).

In the control group, the median basal insulin dose rose from 18 insulin units (IU) (IQR 12–30 IU) at baseline to 24 (IQR 17–36 IU) at 12 weeks follow-up, whereas in the intervention group, the insulin dose rose from 18 IU (IQR 12–30 IU) to 30 IU (IQR 22–45 IU), resulting in a model-based adjusted between-group difference of 5.5 (95% CI: 2.0–9.5 IU; p = 0.0011). The respective increase of insulin units per kilogram of body weight were for the control group from 0.2 (IQR 0.1–0.3) to 0.3 (IQR 0.2–0.4) insulin units per kilogram of body weight and for the intervention group from 0.2 (IQR 0.1–0.3) to 0.4 (IQR 0.2–0.5) units per kilogram of body weight. The median follow-up period was 93.06 (±10.24) days in the control group and 91.05 (±12.07) days in the intervention group (between-group difference of 2.00 days; 95% CI: –0.87 to 4.88; p = 0.1699).

In the intervention group, the median number of days with application activities was 87 days (IQR 84 days–95.5 days) of the median 93.1 days in the follow-up period. This means that 75% of the intervention group used the application on at least 84.0 days during the follow-up period. The median number of days with logged fasting glucose values was 84 days (IQR 78.0–87 days) and the median number of days with suggested insulin doses was 82 days (IQR 74–84 days).

The median HbA1c reduction in the control group was –0.6% (IQR –0.1% to –1.4%) and –0.93% (IQR –0.4% to –1.6%) in the intervention group, resulting in a model-based adjusted between-group difference of –0.31% (95% CI: 0.01%–0.69%; p = 0.0388) in favour of the intervention group. In Fig. 2A, the distribution of the HbA1c baseline and follow-up values for both the control and intervention groups are depicted. More participants in the intervention group saw an improvement in HbA1c values than participants in the control group.

In Table 2, the results of the secondary variables are reported according to the pre-specified hierarchical testing order. The median fasting glucose was reduced by –9.0 mg/dl (9.0 mg/dl to –25.7 mg/dl) in the control group and by 18.3 mg/dl (–5.0 mg/dl to 36.8 mg/dl) in the intervention group. The model-based adjusted between-group difference was 10.5 mg/dl (96% CI: 1.5 mg/dl–19.0 mg/dl; p = 0.0263) in favour of the intervention group (see Fig. 2B). Additionally, the intervention effect was largest with higher baseline fasting glucose values.

There was no significant between-group difference regarding diabetes self-management (p = 0.2705); therefore, significance testing was eliminated for the remaining outcomes in the hierarchy.

Descriptively, between-group differences regarding hyperglycaemia-related outcomes were consistent with the primary and secondary endpoints, all of which nominally favoured the intervention group. No between-group effects were seen on any person-reported outcomes. In Supplementary Table S7 a previously unspecified analysis without adjusting for study centres effects and with the crude between group differences is provided.

Intervention group participants rated the functionality and usability of the application with a median score of 4.5 (IQR 3.7 and 4.7), and the majority rated the functionality and usability between good and very good (see Supplementary Figure S3). These results were confirmed by an ecological momentary assessment, in which we asked participants for 10 consecutive days after application initialisation and 10 days prior to the follow-up visit whether the application was used on a specific day as well as whether using the application was perceived as helpful and useful on this specific day. However, due to technical problems, the assessment was performed by only a minority of the sample. Thus, we abstained from a systematic evaluation of this assessment (see Supplementary Table S4).

In Supplementary Table S5, the per-protocol analysis is presented (see also Supplementary Table S6 with number of all available data points for this analysis). The per-protocol analysis confirmed the outcomes of the

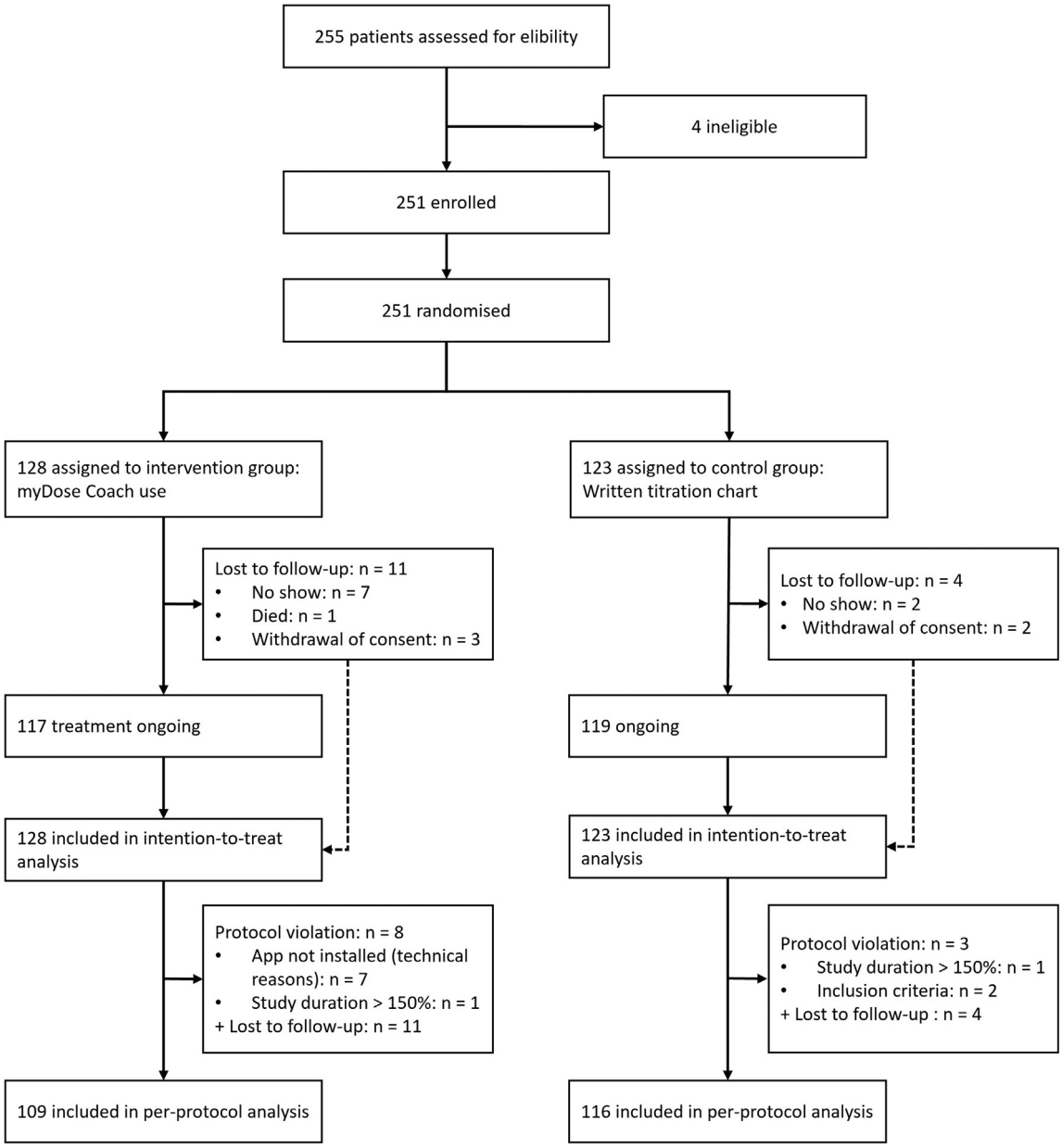

Fig. 1: Trial profile.

intention-to-treat analysis but revealed significant and more pronounced improvements in the intervention group regarding HbA1c (between-group difference: –0.46% (–0.8% to –0.1% [–5.0 mmol/mol (–8.7 mmol/mol to –1.1 mmol/mol)]; p = 0.0064) and fasting glucose values (between-group difference: –14.0 mg/dl (–23.5 mg/dl to –6.5 mg/dl; p = 0.0010)). Furthermore, all self-measured glucose values, the proportion of HbA1c values <7.5%, and the proportion of glucose values >180 mg/dl were more favourable in the intervention group.

Supplementary Figure S4 illustrates the results of a second sensitivity analysis regarding the impact of previous experience with basal insulin therapy. The effect for the intervention group on HbA1c was not moderated by previous experience with basal insulin therapy, as there was no significant interaction (p = 0.1179) in between-group allocation and previous basal insulin therapy (yes or no). The main effect for the intervention group remained significant (p = 0.0320), indicating that both people with a newly initiated basal insulin therapy and people with a pre-existing basal insulin therapy

Characteristic	Control group (n = 123)	Intervention group (n = 128)
Median age in years (±IQR)	59.5 (53.0–66.25)	60.0 (53–67)
Number of women (%)	43 (35%)	48 (37.5%)
Number of men (%)	80 (65%)	80 (62.5%)
Median BMI in kg/m^2 (IQR)	31.7 (28.7–36.6)	31.4 (27.8–35.4)
Median diabetes duration in years (IQR)	9.5 (6.0–15)	11.0 (6–16)
Median HbA1c (%) (IQR)	8.3 (7.7–9.0)	8.2 (7.8–9.1)
Median HbA1c in mmol/mol (IQR)	67.2 (60.7–74.9)	66.1 (61.7–76.0)
Median number of complications (IQR)[a]	1.0 (0–2)	1.0 (0–2)
Number with at least one complication (%)[a]	76/123 (61.8%)	76/128 (59.4%)
Number with existing BOT (%)	102 (82.9%)	99 (77.3%)
Number with newly initiated BOT (%)	21 (17.1%)	29 (22.7%)
Median duration of BOT in years (IQR)	1.0 (0.1–4)	1.0 (0.0–4)
Median basal insulin dose in IU (IQR)[b]	18 (12–30)	18 (12–30)
Median insulin units per kg in IU/kg (IQR)[b]	0.2 (0.1–0.3)	0.3 (0.1–0.3)
Mean frequency of daily glucose testing (IQR)	1.3 (0.9–2.1)	1.4 (1.1–2.3)
Mean fasting glucose in mmol/mol (IQR)	9.0 (7.6–10.1)	8.9 (7.9–10.1)

[a]Complications: retinopathy, neuropathy, nephropathy, peripheral arterial disease, diabetic foot syndrome, cardiovascular disease, or stroke. [b]For people with newly initiated basal insulin therapy, the starting dose of basal insulin was used.

Table 1: **Sample characteristics.**

improved their HbA1c values due to the intervention application.

A total of 30 adverse events were reported in 29 participants across both groups. In the intervention group, 14 adverse events were reported by 13 participants (see Table 3). Seven severe adverse events were reported in the control group, and eight severe adverse events were reported in the intervention group. Supplementary Table S8 lists all adverse and severe adverse events. There was no episode of severe hypoglycaemia or diabetic ketoacidosis reported in either group. There were three symptomatic episodes of hypoglycaemia in the intervention group, which were confirmed by a glucose reading <70 mg/dl. All affected individuals were able to self-treat their low glucose; third-party assistance was not required for recovery.

Inference statistics did not suggest a significantly higher risk exposure for either group (Table 3). Additionally, we analysed whether critically low glucose values (<54 mg/dl) or high glucose values (>250 mg/dl)

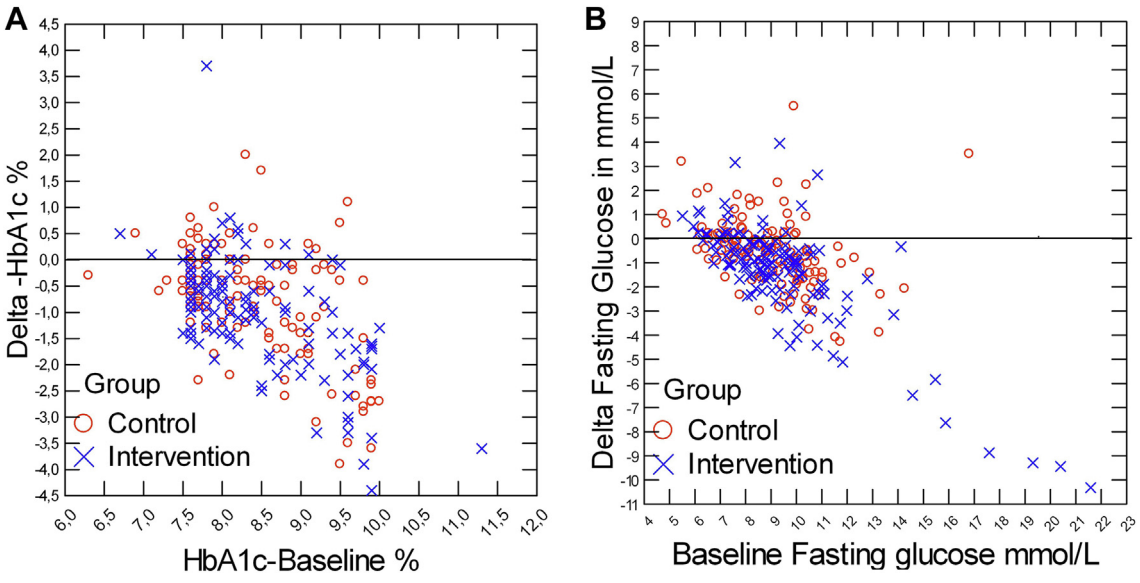

Fig. 2: Change in HbA1c (A) and fasting glucose (B) between baseline and follow-up assessments according to baseline values in the control and intervention groups. All values <0 indicate reduction in HbA1c or fasting glucose; values >0 indicate increase in these outcomes.

Variable	Control group		Intervention group		Model-based adjusted difference (95% CI)[a]	p-value
Median (IQR) or number (%)	Baseline	Follow-up	Baseline	Follow-up		
Median HbA1c (%)	8.3 (7.7–9.0)	7.4 (7.0–8.1)	8.1 (7.8–9.1)	7.3 (6.8–7.8)	−0.3 (−0.69, −0.01)	**0.0388**
Fasting glucose in mg/dl	155.7 (136.3–181.1)	147.4 (125.9–163.5)	160.0 (140.7–181.2)	138.2 (118.3–150.2)	−11.0 (−19.5. −3.5)	**0.0046**
Diabetes self-management	70.8 (62.5–79.2)	75.8 (68.8–83.3)	72.9 (62.5–81.2)	75.0 (67.2–81.7)	2.0 (−2.0, 6.0)	0.2705
Number and rate (%) of HbA1c ≤7.5%	8/123 (6.5%)	67/123 (54.5%)	4/128 (3.1%)	81/128 (63.3%)	1.6 (0.92, 2.66)[b]	0.1017
Number and rate of HbA1c reduction of >0.3%	N.A.	86/123 (69.9%)	N.A.	99/128 (77.3%)	1.47 (0.83, 2.60)[c]	0.1827
Diabetes empowerment	63.6 (45.5–78.8)	72.7 (54.5–87.9)	68.2 (45.4–81.8)	74.3 (57.5–87.9)	3.0 (−6.0, 9.1)	0.5561
Treatment satisfaction	70.0 (60.0–80.0)	78.0 (70.0–84.0)	66.0 (56.0–78.0)	78.0 (68.0–84.0)	2.0 (−2.0, 6.1)	0.3707
Days until attainment of titration target[d]	N.A.	35.5 (15.4–48.1)	N.A.	33.7 (18.3–48.3)	−0.3 (−5.3, 7.5)	0.9311
Diabetes distress	17.5 (10.0–28.7)	13.7 (6.2–25.0)	19.4 (8.7–34.7)	16.7 (6.8–30.9)	1.2 (−2.5, 4.3)	0.5596
Self-efficacy	80.0 (66.7–90.0)	83.3 (70.9–90.0)	78.3 (64.2–99.3)	81.2 (66.7–92.3)	3.3 (−1.9, 6.6)	0.2797
Number of glucose measurements per day	1.3 (0.9–2.1)	1.1 (0.9–1.5)	1.4 (1.1–2.3)	1.1 (1.0–1.6)	0.01 (−0.22, 0.46)	0.6174
WHO-5 well-being score	64.0 (48.0–76.0)	68.0 (56.0–76.0)	64.0 (41.0–72.0)	68.0 (52.0–76.0)	4.0 (−0.1, 8.1)	0.1618
Number and rate of HbA1c ≤7.0%	2/123 (1.6%)	33/123 (26.8)	1/128 (0.8%)	44/128 (34.4%)	1.4 (0.8, 2.5)[b]	0.1860
Number and rate of HbA1c reduction of >0.4%	N.A.	82/123 (66.7%)	N.A.	96/128 (75.0%)	1.5 (0.9, 2.6)[c]	0.1470
Number <70 mg/dl/1000	8.9	2.6	3.4	3.2	0.7 (0.4, 1.2)[e]	0.1720
Mean glucose in mg/dl (IQR)	166.6 (147.2–183.3)	153.1 (132.4–171.8)	162.2 (141.1–182.4)	143.5 (125.4–160.5)	−13.1 (−22.7, −4.0)	0.0051
Number >180 mg/dl/1000	325.8	314.0	238.9	187.8	0.84 (0.6, 1.1)[e]	0.1640

Data are median (IQR) or n in %. Bold indicates significant p values ($p < 0.05$). [a]Negative values favour the intervention group. If model-based adjusted differences were not odds ratios or incidence rate ratios the model-based adjusted difference is obtained by stepwise shifting the distribution of the untransformed intervention group outcome until the highest p-values of the transformed shifted outcomes values indicate equal ranks. The shifted values with p-values less than or equal to 0.05 define the lower and upper 95% confidence intervals, respectively. The model-based treatment effects shown were adjusted for the respective baseline value and study centre; they therefore do not correspond to the median differences of the raw values. [b]Baseline-adjusted odds ratio is based on a random effects logistic regression model with group allocation as a fixed factor and study centre as a random factor (control group used as reference). [c]Odds ratio based on a random effects logistic regression model with group allocation as a fixed factor and study centre as a random factor (control group used as reference). [d]If for three consecutive days, the fasting glucose was within the individual target range, the titration target was considered as meet. [e]Incidence rate ratio is based on a zero-inflated negative binominal regression analysis with group allocation as a fixed factor and study centre as a random factor (control group used as reference). According to the estimands frameword CH E9 (R1) first addendum the population refers to people with type 2 diabetes and overweight with a basal insulin therapy; the outcome variables refer to a change of the outcome variable between baseline and a 12 week follow up with no expectation of an intercurrent event and the population level summary is expressed as a model adjusted between group difference value.[29]

Table 2: **Outcomes in the intention-to-treat population.**

were more frequent in one of the two groups. These glucose excursions did not present a significant bias towards either of the two study arms (Table 3).

Discussion

The most frequent insulin regimen in type 2 diabetes is basal insulin therapy combined with oral antidiabetic agents. However, cohort studies and healthcare research studies suggest that glycaemic targets are often not met because basal insulin doses are not titrated or are insufficiently titrated to attain individual fasting glucose targets. This multicentre randomised controlled trial involved adults with overweight and type 2 diabetes who use basal insulin therapy; when these participants used a titration application, they saw significant improvements in HbA1c compared to a control group who used written titration plans. The between-group difference demonstrates a clinically relevant effect of the titration application in reducing HbA1c by 0.31% (95% CI: –0.01% to 0.69%); in the per-protocol analysis, the median HbA1c reduction was –0.45% (95% CI: –0.1% to –0.8%). More people in the intervention group than in the control group reduced their HbA1c values. The HbA1c reduction was visible across the range of baseline HbA1c values, and the same pattern was evident regarding the reduction of fasting glucose values. These findings indicate that the use of a titration application for basal insulin titration can overcome clinical inertia regarding insufficient basal insulin titration. Concurrently, there is no indication that the positive glycaemic impact of using the titration application was at the expense of an increase in adverse events or critically low or high glucose values. Additionally, the usability and functionality of the titration application was well perceived, according to the results of the MARS questionnaire.

Person-reported outcomes did not reveal a significant benefit. However, baseline scores ranged between 64% and 78% of the total scale range, indicating some degree of a ceiling effect. Therefore, a significant improvement might have been more difficult to demonstrate; the baseline PAID scores were lower than 20, which also indicates low diabetes distress.

The study was designed to closely reflect the German healthcare system; therefore, no additional visits were required between the routinely conducted quarterly visits, and insulin as well as glucose testing for all participants were fully covered by the healthcare system. Furthermore, this multicentre study was conducted in specialised diabetes practices with staff who have expertise in insulin

Variable	Control group (n = 123)	Intervention group (n = 128)	Incidence rate ratio (95% CI) and p-value
Any adverse event			
Number of participants with event (%)	16 (13.0)	13 (10.2)	
Number of events	16	14	0.84 (0.41–1.72); 0.6360[a]
Severe adverse event			
Number of participants with event (%)	7 (5.7)	7 (5.5)	
Number of events	7	8	1.11 (0.39–3.19); 0.8459[a]
Severe hypoglycaemia[b]			
Number of participants with event (%)	0 (0)	0 (0)	
Number of events	0	0	ND
Diabetic ketoacidosis			
Number of participants with event (%)	0 (0)	0 (0)	
Number of events	0	0	ND
Non-severe hypoglycemia[c]			
Number of participants with event (%)	0 (0)	3 (2.3)	
Number of events	0	3	N.A.
Additional risk marker			
Glucose values <54 mg/dl			
Number of participants with event (%)	8 (6.5)	15 (11.7)	
Number of events per 1000 measurements	1.2/1000	1.1/1000	1.0 (0.46–2.16); 0.9973[d]
Glucose values >250 mg/dl			
Number of participants with event (%)	69 (56.1)	59 (46.1)	
Number of events per 1000 measurements	50.7/1000	40.4/1000	0.92 (0.6–1.39); 0.7018[e]

[a]The p-values and incidence rate ratios (IRRs) were obtained from a zero-inflated Poisson regression model with the control group as a reference. [b]Severe hypoglycaemic events were considered to be any event which required assistance from any third party for recovery. [c]Non-severe hypoglycaemic events were symptomatic hypoglycaemic episodes or glucose readings <70 mg/dl which could be effectively treated by the affected person. [d]p-values and IRRs were obtained from a zero-inflated generalised Poisson regression model with the control group as a reference. [e]p-values and IRRs were obtained from a zero-inflated negative binominal regression model with the control group as a reference.

Table 3: **Safety outcomes during the trial period.**

titration. This may explain the relatively low baseline HbA1c numbers compared to other studies and may also explain the relatively large HbA1c improvement in the control group compared to other studies.[11–13,30]

When interpreting the results, the following limitations must be considered. First, the follow-up period was relatively short (three months) to evaluate the long-term effects of a titration application. Therefore, it is unclear whether the intervention effect persists beyond 12 weeks. Second, for regulatory reasons, blood samples to measure HbA1c in the central laboratory could only be obtained if a routine blood draw had already been scheduled. Therefore, some HbA1c values were determined in the local laboratories of the study centres rather than in the central laboratory. However, consistency was guaranteed, as the method of determining HbA1c for an individual was kept constant within this individual. Additionally, participants' self-measurements of glucose regarding fasting glucose confirm the HbA1c improvements. For the interpretation of self-measured glucose data should be considered that the median frequency of glucose measurements war 1.1, and that they resumable refers primarily to the fasting state. Significant differences in baseline HbA1c between study centres may indicate socioeconomic differences or differences in care practices that may not be fully accounted for by the study centre adjustment. The statistical analysis plan was amended after recruitment of study participants started due to regulatory issues, which might had induced a further bias. This 12-week, multicentre randomised controlled trial within the conditions of the German healthcare system demonstrates the efficacy and safety of a newly developed basal insulin titration application. The usability and functionality of this digital tool was well received by users, and the low drop-out rates and high usage rates suggest a significant reach and feasibility of use in daily life.

The estimated considerable number of overweight people worldwide who have type 2 diabetes, use insulin, and have inadequate blood glucose control[2] as well as the estimated 5.0 billion people in the world who have access to a smartphone[31] suggest that the tested application could be a valuable tool to improve blood glucose control due to its ease of use, scalability, and demonstrated efficacy and safety.

Contributors

NH contributed to study design, analysis of data, writing and editing of the manuscript.

DE contributed to study design, analysis of data, writing and editing of the manuscript.

KFG was actively involved in study management and data collection and reviewed the manuscript.

MK was actively involved in study management and data collection and reviewed the manuscript.

TR was actively involved in study management and data collection and reviewed the manuscript.

GF contributed to study design and study monitoring and reviewed the manuscript.

TH was contributed to study management and reviewed the manuscript.

BK contributed to study design, analysis of data, writing and editing of the manuscript.

Data sharing statement

Anonymised data underlying the results and analysis can be made available to researchers upon reasonable request to the corresponding author after publication. A data access agreement needs to be signed in advance.

Declaration of interests

NH reports Advisory Board member fees from Abbott Diabetes Care and Insulet as well as honoraria for lectures from Berlin Chemie AG, Becton Dickenson. Sanofi Germany and Roche Diabetes Care and Dexcom, Germany.

DE reports Advisory Board member fees from mySugr, Dexcom Germany and Roche Diabetes Care as honoraria for lectures from Berlin Chemie AG, Dexcom, Germany and Roche Diabetes Care.

KFG, MK and TR declare no conflict of interest.

GF reports Advisory Board member fees from Abbott Diabetes Care, Sanofi Germany, Dexcom as well as support for meeting attendance and travel from Novo Nordisk.

TH reports Advisory Board member fees from Abbott Diabetes Care, Sanofi Germany, Gruenenthal, Lilly Germany, Dexcom Germany and Bayer as well as honoraria for lectures from Sanofi Germany, Abbott Diabetes Care, Lilly Germany and Astra Zenecca.

BK reports Advisory Board member fees from Abbott Diabetes Care, Embecta, Roche Diabetes Care, Novo Nordisk, Berlin Chemie AG and Dexcom Germany as well as honoraria for lectures from Sanofi Germany, Novo Nordisk, Abbott Diabetes Care, Roche Diabetes Care, Berlin Chemie AG, Embecta, Dexcom and Feen. In addition he reports support for travel and fees for scientific meetings from Sanofi, Roche and Berlin Chemie as well as unpaid obligations as workshop leader and member of working groups of the German Diabetes Association.

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Appendix A. Supplementary data

Supplementary data related to this article can be found at https://doi.org/10.1016/j.lanepe.2023.100702.

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