Effect of Automated Bolus Calculation on Glucose Variability and Quality of Life in Patients With Type 1 Diabetes on CSII Treatment

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ABSTRACT

Purpose: Automated bolus calculation may benefit patients with poorly controlled type 1 diabetes who are relatively new to continuous subcutaneous insulin infusion (CSII). This study investigated the effect of automated bolus calculation on glucose variability, glucose control, and diabetes-related quality of life in patients with reasonably well-controlled type 1 diabetes, accustomed to treatment with CSII for several years.

Methods: This open-label, single-center study included 32 patients (mean age, 45.9 [15.1] years; 34% male; disease duration, 27.3 [12.9] years; glycosylated hemoglobin [HbA1c] level, 64.6 [12.5] mmol/mol [8.1% (1.1%)]; CSII treatment, 9.0 [7.8] years) who were randomly assigned to receive 4 months’ treatment with a bolus calculator (n = 14) or continuation of standard care without a bolus calculator (n = 18). All participants received dietary counseling on carbohydrate counting. Primary outcome was glucose variability, as assessed by the SD of 7-point glucose profiles. Secondary outcomes included HbA1c, rate of (severe) hypoglycemia, and diabetes-related quality of life.

Findings: After 4 months of follow-up, glucose variability had improved in the bolus calculator group compared with the control group (change, –0.8 [0.9] vs 0.1 [0.9] mmol/L; P = 0.030). Mean glucose levels did not change in either group (0.4 [1.1] vs 0.3 [0.9] mmol/L; P = 0.95). There were also no differences in change in hypoglycemia rate (–0.6 [1.6] vs –0.4 [1.6] event per patient per week; P = 0.67), HbA1c value (–0.5 [6.6] vs –4.9 [10.6] mmol/mol; P = 0.21), or diabetes-related quality of life between the bolus calculator group and the control group.

Implications: Use of a bolus calculator modestly improved glucose variability in this relatively small group of patients with longstanding type 1 diabetes on CSII but did not affect other parameters of glycemic control or diabetes-related quality of life. (Clin Ther. 2018;40:862–871) © 2018 The Authors. Published by Elsevier HS Journals, Inc.

Key words: continuous subcutaneous insulin infusion, bolus calculator, insulin therapy, glucose variability, type 1 diabetes.

INTRODUCTION

Various large-scale clinical trials have shown the importance of near-normalization of glucose control to reduce the risks of microvascular complications in individuals with diabetes.1,2 Intensive insulin therapy is paramount to achieving such good glycemic control in patients with type 1 diabetes and in those with prolonged type 2 diabetes approaching the insulin-deficient state.

Optimal insulin therapy requires patients to estimate the amount of prandial insulin before each meal according to several factors, including current glucose level, anticipated carbohydrate intake, insulin-to-carbohydrate ratio (ICR), estimated insulin sensitivity, target blood glucose level, and anticipated physical activity.3 Adjustment of the insulin dose to carbo-
hydrate intake has shown improvement in glycemic control, treatment satisfaction, and patient’s well-being. Previous studies, however, have shown that more than one half of the patients estimate their prandial insulin dose incorrectly, many because they fear injecting too much insulin and causing hypoglycemia. Patients with poor numeracy skills have higher glycosylated hemoglobin (HbA1c) levels compared with patients with good numeracy skills.

Automatic bolus calculators have emerged to aid in insulin bolus estimation, taking into account individualized ICR and insulin sensitivity factor (ISF), as well as the effect of previously administered insulin (ie, insulin on board). In daily practice, however, such bolus calculators are used by a minority of adult patients receiving CSII. There is still uncertainty about the benefit of automated bolus calculation. Some studies have shown improvements in glycemic control and quality of life in poorly controlled patients treated with CSII or multiple daily injections (MDIs), but others have not. In most studies, however, extensive education on carbohydrate counting accompanied the initiation of the bolus calculator, which was not routinely provided in the control situation. In addition, many participants in studies involving CSII were new to this form of treatment, and most studies excluded participants with (relatively) good glucose control.

The objective of the present study was to investigate whether a bolus calculator could still benefit patients with stable CSII treatment, for whom improvement of already moderate to good glycemic control is not the primary aim of treatment. We hypothesized that in such cases, the use of bolus calculation would decrease glucose variability, reduce the hypoglycemic burden, and, consequently, improve diabetes-related quality of life without deteriorating glucose control. To test this hypothesis, we conducted a randomized controlled open-label trial in patients with diabetes treated by CSII, in which both groups received (repeated) dietary counseling at the start.

**PATIENTS AND METHODS**

**Study Design**

This 16-week, randomized controlled, single-center, open-label study was performed at the Radboud University Medical Center in Nijmegen, the Netherlands, between February 2014 and May 2016. The study was approved by the local institutional review board and performed according to the principles of the Declaration of Helsinki. All participants provided written informed consent.

**Study Population**

Patients with type 1 diabetes treated with CSII were recruited from the outpatient clinic. People were eligible for participation in the study when they met the following criteria: treatment with CSII for at least 6 months, age between 18 and 60 years, HbA1c value <86 mmol/mol (10%), disease duration >2 years, and a total daily insulin dose <1 U/kg. Key exclusion criteria were current use of a bolus calculator, inability or unwillingness to perform frequent blood glucose measurements, pregnancy or intention to become pregnant, prednisone treatment, a recent cardiovascular event, or the presence of severe microvascular complications. Although we initially invited patients with long-duration type 2 diabetes to participate, only 2 patients were enrolled, both of whom were randomized to the bolus calculation group. Because of the low numbers and this imbalance, we decided to exclude these patients from analysis.

**Study Procedure**

At the screening visit, participants completed various diabetes-related quality of life questionnaires (Confidence in Diabetes Self-Care scale, Hypoglycemia Fear Survey, Problem Areas in Diabetes questionnaire), and HbA1c levels were measured. All participants received dietary advice from a dietitian concerning carbohydrate counting and insulin bolus calculation; the knowledge thus acquired was tested by examination. When participants failed this test, they were scheduled for a second visit by a dietitian. Subsequently, participants were randomized to either the bolus calculator group or the control group. For random allocation concealment, we used opaque, sealed envelopes and blocks of 4 subjects.

The second visit occurred 2 weeks later. Participants collected 7-point blood glucose profiles for 5 days before the visit and kept a diary about their carbohydrate intake during these days. Participants randomized to the bolus calculator group were consulted by a diabetes educator to receive information about use of the bolus calculator. ICR and ISF were calculated based on the insulin total daily dose (TDD), and ratios were programmed into the bolus calculator. The ICR was calculated by using the 500 rule (ICR = 500 divided by TDD) and ISF by using the 100 rule.
Corporation (Kobe, Hyōgo Prefecture, Japan). Target blood glucose levels were determined individually, and insulin on board time was set at 4 hours for each participant. All participants were advised to maintain their current lifestyle with respect to diet and physical exercise during the study period. After 2 months, participants again collected 7-point blood glucose profiles for 5 days, and adjustments to pump settings were performed if necessary.

Final assessment took place after 4 months at the outpatient clinic. Participants again collected 7-point blood glucose profiles for 5 days and completed a diary about carbohydrate intake. Blood samples were collected to determine HbA1c levels, and diabetes-related quality of life was reassessed with the aforementioned questionnaires.

**Study Outcomes**

The primary end point of this study was the change in glucose variability, calculated from the 7-point glucose profiles. Secondary end points were changes in HbA1c, low blood glucose index (LBGI), high blood glucose index (HBGI), the total amount of insulin used, incidence of (severe) hypoglycemia, diabetes-related quality of life, and presence of impaired awareness of hypoglycemia.

**Measurements**

For blood glucose measurements, patients used their own glucose meters. Patients continued using their current insulin pump, and they started using the bolus calculator that was provided by this pump. Hypoglycemia was defined as a self-measured glucose level <3.0 mmol/L and severe hypoglycemia as those events requiring assistance from another person for recovery. HbA1c levels were measured by using the Tosoh G8 HPLC-analyzer, distributed by Sysmex Corporation (Kobe, Hyōgo Prefecture, Japan).

Diabetes-related quality of life was assessed by use of questionnaires. The Hypoglycemia Fear Survey is divided into 2 sub-questionnaires; fear that is manifested in certain behavior (15 items) and in certain worries (13 items). The behavior subscale has good reliability (Cronbach’s α = 0.92). It has a cutoff score of 20, with higher scores indicating more fear of hypoglycemia. The Confidence in Diabetes Self-Care scale asks patients to indicate their level of confidence regarding daily activities related to their diabetes (20 items). Scores range from 0 to 100, with higher scores reflecting more confidence in diabetes self-care. This test has a high internal consistency in Dutch patients (Cronbach’s α = 0.86) and high test–retest reliability (Spearman’s ρ = 0.85; P < 0.0001). The Problem Areas in Diabetes questionnaire consists of 20 items with possible diabetes-related problems, for which patients need to rate how much of a problem these items are at that moment in their lives. Scores range from 0 to 100. Higher scores indicate more diabetes-related distress, and a score ≥40 is related to severe diabetes-related distress. Internal consistency (Cronbach’s α = 0.93–0.95) and test–retest reliability (Pearson’s correlation = 0.83) are high.

We also assessed the status of awareness of hypoglycemia, using the Dutch-modified translation of the Clarke questionnaire that was validated with hypoglycemic glucose clamps.

**Calculations and Statistical Analysis**

Glucose variability was defined by the SD of 7-point blood glucose profiles over 5 consecutive days. The ICR, reflecting the amount of carbohydrates that can be processed by 1 unit of insulin, was calculated by dividing the amount of carbohydrates ingested by the amount of insulin injected at that time. The ISF, reflecting the blood glucose level response (in millimoles per liter) to 1 unit of insulin injected, was calculated by dividing the fall in blood glucose level by the amount of insulin used. The LBGI and HBGI were calculated by using the EasyGV version 9.0.R2 (available free for noncommercial use at www.easygv.co.uk) to assess the risks of hypoglycemia and hyperglycemia, respectively.

We calculated that for the detection of a 20% decrease in glucose variability at a 2-sided significance level of 0.05 with a power of 80%, the total number of subjects needed would be 14 per group. To account for dropouts, we thus aimed to enroll a total of 30 subjects.

Data were analyzed by using IBM SPSS statistics version 22 (IBM SPSS Statistics, IBM Corporation, Armonk, New York). A total of 187 people were screened for participation in this study, 48 of whom were potentially eligible. Fourteen subjects were excluded or withdrew consent before randomization. Hence, the analysis included 32 participants: 14 randomized to the bolus calculator group and 18 to
the control group. We performed an intention-to-treat analysis on the remaining 32 patients. Missing data were imputed by using inference methods. Student’s independent 2-sample t tests were used to compare the 2 study groups and paired-samples t tests for the calculation of within-groups changes over time. Two-way ANOVA analyses were used to compare the mean differences in blood glucose level and SDs between the groups. Pearson’s $\chi^2$ analyses were used for categorical variables. A $P$ value $<0.05$ was considered statistically significant.

RESULTS
All patients randomized to treatment completed the study (Figure 1). Baseline characteristics of the study participants are presented in Table I. Groups were comparable with regard to age, sex, disease duration, HbA1c level, and history of microvascular complications.

Changes in Glycemic Parameters
The 7-point glucose profiles averaged over 5 days are shown in Figure 2. There were no differences between mean glucose levels at baseline and end of the study for either the bolus calculator group (8.3 [1.2] vs 8.7 [1.4] mmol/L; difference, 0.4 mmol/L [95% CI, −0.4 to 1.1]; $P = 0.58$) or the control group (8.2 [1.4] vs 8.6 [1.5] mmol/L; difference, 0.3 mmol/L [95% CI, −0.2 to 0.9]; $P = 0.07$) at any time point or between the groups (difference, 0.03 mmol/L [95% CI, −0.8 to 0.9]; $P = 0.95$). Glucose variability, as assessed by the SD of these profiles, declined significantly in the bolus calculator group over time but did not change in the
control group (Figure 3). This change in glucose variability in the bolus calculator group was significantly different from that in the control group (–0.8 [0.9] vs 0.1 [0.9] mmol/L; difference, –0.9 mmol/L [95% CI, –1.7 to –0.1]; \( P = 0.030 \)).

HbA1c fell slightly in both the bolus calculator group and the control group, but neither effect nor the difference between groups reached statistical significance (–0.5 [6.6] vs –4.9 [10.6] mmol/mol; difference, 4.3 mmol/mol [95% CI, –2.5 to 11.2]; \( P = 0.21 \)). LBGI and HBGI also did not change (neither in the bolus calculator group nor in the control group). LBGI did not differ between groups (–1.3 [4.8] vs 0.3 [5.2]; difference, –1.6 [95% CI, –5.4 to 2.2] for the bolus calculator group vs control group, respectively; \( P = 0.39 \)). HBGI also did not differ between groups (1.3 [5.3] vs 0.1 [3.7]; difference, 1.3 [95% CI, –2.1 to 4.6] for the bolus calculator group vs the control group; \( P = 0.45 \)) (Table II).

### Hypoglycemia Rates

Frequency of biochemical hypoglycemia decreased numerically in the bolus calculator group with 0.6 event per week (95% CI, –0.5 to 1.2; \( P = 0.39 \)), but neither finding reached statistical significance. One patient in each group experienced a severe hypoglycemic event. However, the event in the bolus calculator group occurred directly after randomization before the patient had started to use the bolus calculator.

### Diabetes-related Quality of Life

Neither fear of hypoglycemia nor diabetes-related problems or confidence in diabetes self-care changed during follow-up in the bolus calculator group or in the control group; there were no differences between the groups (Table III). The average score on the modified Clarke questionnaire changed with –0.2 (95% CI, –0.3 to 0.8; \( P = 0.39 \)) in the bolus calculator group and with –0.1 (95% CI, –0.3 to 0.5; \( P = 0.72 \)) in the control group. None of the patients in either group changed from normal awareness to impaired awareness of hypoglycemia or vice versa during the study period.

### Subgroup Analysis

Subgroup analyses were performed for the primary outcome based on age (≤50 vs >50 years), sex, duration of CSII therapy (≤6 vs >6 years), and

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**Table I. Baseline characteristics.** Unless otherwise indicated, data are mean (SD) or median (quartile 1, quartile 3).

<table>
<thead>
<tr>
<th>Characteristic</th>
<th>Bolus Calculator (n = 14)</th>
<th>Control Group (n = 18)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Male</td>
<td>6 (43%)</td>
<td>5 (28%)</td>
</tr>
<tr>
<td>Age, y</td>
<td>48 (15)</td>
<td>45 (15)</td>
</tr>
<tr>
<td>Weight, kg</td>
<td>81.7 (12.3)</td>
<td>76.6 (13.7)</td>
</tr>
<tr>
<td>Height, cm</td>
<td>172.4 (9.5)</td>
<td>173.1 (8.8)</td>
</tr>
<tr>
<td>Body mass index, kg/m²</td>
<td>27.6 (4.5)</td>
<td>25.6 (4.7)</td>
</tr>
<tr>
<td>Disease duration, y</td>
<td>28 (14)</td>
<td>27 (12)</td>
</tr>
<tr>
<td>Duration insulin pump therapy, y</td>
<td>7 (3, 13)</td>
<td>6 (2, 16)</td>
</tr>
<tr>
<td>Total insulin dose, IU</td>
<td>40 (13)</td>
<td>41 (23)</td>
</tr>
<tr>
<td>Basal/bolus insulin ratio</td>
<td>61/39</td>
<td>58/42</td>
</tr>
<tr>
<td>HbA1c, mmol/mol</td>
<td>65 (11)</td>
<td>64 (14)</td>
</tr>
<tr>
<td>HbA1c, %</td>
<td>8.1 (1.0)</td>
<td>8.0 (1.3)</td>
</tr>
<tr>
<td>History of microvascular complications</td>
<td>6 (43%)</td>
<td>6 (33%)</td>
</tr>
<tr>
<td>Retinopathy</td>
<td>4 (29%)</td>
<td>5 (28%)</td>
</tr>
<tr>
<td>Neuropathy</td>
<td>3 (21%)</td>
<td>3 (17%)</td>
</tr>
<tr>
<td>Nephropathy</td>
<td>2 (14%)</td>
<td>3 (17%)</td>
</tr>
<tr>
<td>History of peripheral vascular disease</td>
<td>1 (7%)</td>
<td>2 (11%)</td>
</tr>
<tr>
<td>History of cardiovascular events</td>
<td>0</td>
<td>0</td>
</tr>
</tbody>
</table>

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**Clinical Therapeutics**
HbA1c level (≤64 vs >64 mmol/mol). The decline in glucose variability overall seemed to be mainly driven by the subgroup of patients aged >50 years, in whom use of the bolus calculator reduced glucose variability by 1.1 mmol/L (95% CI, –2.5 to 0.3) versus an increase of 0.8 mmol/L (95% CI, –0.04 to 1.6) in those randomized to the control group (difference, –1.9 mmol/L [95% CI, –3.2 to –0.5]; P = 0.019). There was no change in glucose variability based on differences in sex, duration of CSII therapy, or HbA1c levels.

DISCUSSION

The main finding of the present study is that short-term use of a bolus calculator in patients with type 1 diabetes on CSII for several years had a modest beneficial effect on glucose variability but did not change overall glucose control, incidence of hypoglycemia, or diabetes-related quality of life. We also found a negligible effect of the bolus calculator on the prevalence of impaired awareness of hypoglycemia.

Our study is in agreement with several previous studies showing no or minimal effects of the use of a bolus calculator on glucose control. One study in children and adolescents with type 1 diabetes on CSII found a borderline decrease (P = 0.056) in glucose variability after 1 year of bolus calculator use but observed no change in HbA1c levels.19 Similarly, Gross et al17 found no differences in average deviation of postprandial glucose levels from target in patients receiving CSII using a bolus calculator. Another study also showed no improvement in glucose control in patients treated with MDI and a bolus calculator.12 We found no differences in frequency of hypoglycemia after the start of using a bolus calculator, again in line with results of other studies.16,17,19

In contrast, other studies have reported an improvement in glucose control after use of a bolus calculator in patients with CSII. Yamada et al16 showed a drop in HbA1c level in patients with type 1 diabetes who were started on a bolus calculator. They included patients new to CSII therapy and use of a bolus calculator. The differences in design may partially explain the differences; although the study by Yamada et al included new patients, our patients were on CSII for almost 10 years. Garg et al18 found improved glucose control in patients using insulin
guidance software (experimental group) because of significantly more glucose values within the target range (3.89–8.33 mmol/L). However, patients in the experimental group also performed a significantly higher number of self-monitoring of blood glucose (SMBG) tests.

We found no improvement in diabetes-related quality of life after use of a bolus calculator, which is in agreement with several other studies that examined diabetes-related quality of life. The exception is 2 studies showing improvement in treatment satisfaction, but not in other areas, among patients treated with MDI. It is plausible that quality of life in our participants was already at such a high level that further improvement could not be achieved. Indeed, baseline scores of the Problem Areas in Diabetes questionnaire in our participants reflect very little diabetes-related distress. Alternatively, although many patients report that the bolus calculator is easy to use and preferred over self-calculations to determine insulin doses, the associated need for self-measurement and check for carbohydrate content may diminish enthusiasm for the device.

In our study, subgroup analyses showed consistent results in change in glucose variability. Further research is needed to determine if elderly patients (aged > 50 years) benefit more from use of a bolus calculator compared with younger patients.

There are a number of potential explanations for the limited benefits of introducing automated bolus calculation in our study. First, patients in our study had a mean disease duration of 27 years, and they were treated with CSII for almost 10 years on average. Given this long duration, patients may already be familiar with the principles of carbohydrate counting and estimating required insulin doses. It is also possible that they felt less comfortable with and were therefore less likely to rely on advice from the bolus

### Table II. Low blood glucose index (LBGI) and high blood glucose index (HBGI).

<table>
<thead>
<tr>
<th>Variable</th>
<th>Bolus Calculator Group</th>
<th>Risk*</th>
<th>Control Group</th>
<th>Risk*</th>
<th>P</th>
</tr>
</thead>
<tbody>
<tr>
<td>LBGI</td>
<td>Baseline</td>
<td>7.3 (3.9)</td>
<td>High</td>
<td>7.5 (5.0)</td>
<td>High</td>
</tr>
<tr>
<td></td>
<td>End of study</td>
<td>6.0 (3.3)</td>
<td>High</td>
<td>8.1 (5.5)</td>
<td>High</td>
</tr>
<tr>
<td>HBGI</td>
<td>Baseline</td>
<td>10.2 (4.7)</td>
<td>Moderate</td>
<td>9.6 (3.9)</td>
<td>Low</td>
</tr>
<tr>
<td></td>
<td>End of study</td>
<td>11.5 (4.3)</td>
<td>Moderate</td>
<td>10.7 (4.5)</td>
<td>Moderate</td>
</tr>
</tbody>
</table>

*Risk of hypoglycemia/hyperglycemia; data are shown as mean (SD). Calculation of risk scores for LBGI: index ≤1.1 reflects a minimal risk; index > 1.1 to ≤2.5 reflects a low risk; index > 2.5 to ≤5.0 reflects a moderate risk; and index > 5.0 reflects a high risk of hypoglycemia. Calculation of risk scores for HBGI: index < 5.0 reflects a minimal risk; index > 5.0 to ≤2.5 reflects a low risk; index > 2.5 to ≤5.0 reflects a moderate risk; and index > 5.0 reflects a high risk of hyperglycemia.

### Table III. Secondary outcome measurements: quality of life. Values are given as mean (SD).

<table>
<thead>
<tr>
<th>Variable</th>
<th>Bolus Calculator Group</th>
<th>Control Group</th>
<th>P</th>
</tr>
</thead>
<tbody>
<tr>
<td>CIDS</td>
<td>Baseline</td>
<td>86 (6)</td>
<td>87 (6)</td>
</tr>
<tr>
<td></td>
<td>End of study</td>
<td>85 (7)</td>
<td>87 (7)</td>
</tr>
<tr>
<td>PAID</td>
<td>Baseline</td>
<td>20 (20)</td>
<td>22 (15)</td>
</tr>
<tr>
<td></td>
<td>End of study</td>
<td>19 (17)</td>
<td>23 (17)</td>
</tr>
<tr>
<td>HFS</td>
<td>Baseline</td>
<td>16 (9)</td>
<td>14 (8)</td>
</tr>
<tr>
<td></td>
<td>End of study</td>
<td>15 (8)</td>
<td>16 (10)</td>
</tr>
</tbody>
</table>

CIDS = Confidence in Diabetes Self-Care scale (scores range from 0–100, with higher scores reflecting more confidence); HFS = Hypoglycemia Fear Survey (scores range from 0–52, with higher scores reflecting more fear of hypoglycemia); PAID = Problem Areas in Diabetes questionnaire (scores range from 0–100, with higher scores reflecting more diabetes-related distress).
calculator than on their own estimations. We did not specifically select patients experiencing extreme glucose excursions and excluded patients with very high HbA1c levels but not those with optimal glycemic control (HbA1c levels <53 mmol/mol [7%]). This approach not only explained why patients in our study were moderately controlled but also made it harder to show added benefit of an intervention aimed at improving glycemic management. Therefore, although not supported by our subgroup analysis, we cannot exclude a potential beneficial effect of automated bolus calculation in patients with poor glucose control or those recently starting insulin pump therapy.

Our study has limitations. The study was randomized and controlled but not blinded. However, a completely blinded trial would require a complicated design that would in itself jeopardize generalization. Although based on a power calculation, the number of study subjects was relatively small and from 1 center only, which limits generalizability. Glucose data were collected from SMBG tests, which may provide less information than continuous glucose monitoring (CGM). However, current reimbursement restrictions limit widespread implementation of CGM in clinical practice, and thus most patients need to rely on SMBG. The use of SMBG therefore better approaches real-world practice in most patients compared with CGM. Another limitation is the relative short duration of the study. However, although the durability of the effects of automated bolus calculation remains to be determined, 4 months was sufficient to detect differences in the primary outcome. In addition, most other studies examining bolus calculators were of similarly short duration.11,12,17 Strengths of this study are the randomized controlled design and the homogeneity of the study population. Furthermore, our control group received equally intensive dietary education on carbohydrate counting; thus, any differences between the groups could be solely attributed to the bolus calculator per se.

CONCLUSIONS
Among patients with longstanding diabetes and moderate glucose control on CSII, additional use of a bolus calculator had limited beneficial effects on glucose variability but did not affect other glycemic end points or diabetes-related quality of life. As such, we believe that automated bolus calculation fits in a tailor-made personalized treatment strategy for individuals with sufficient motivation for its use rather than being implemented according to a one-size-fits-all approach.

CONFLICTS OF INTEREST
The authors have indicated that they have no conflicts of interest regarding the content of this article. The sponsor had no involvement in the study design; in the collection, analysis, and interpretation of the data; writing of the manuscript; and the decision to submit the manuscript for publication.

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Author’s contributions: S.P.v.d.H., L.J.Z., C.J.T. and B.E.d.G. designed the study. S.P.v.d.H. and L.J.Z. collected the data for the study. L.A.v.M. analyzed the data and wrote the first version of the manuscript. E.B. contributed to analysis and interpretation of the psychologic data. All authors discussed the results and implications and commented on the manuscript at all stages.

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