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Integrated personalized diabetes management improves glycemic control in patients with insulin-treated type 2 diabetes: Results of the PDM-ProValue study program

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ABSTRACT

Aims: Globally, many patients with insulin-treated type-2 diabetes are suboptimally controlled. The PDM-ProValue study program evaluated whether integrated personalized diabetes management (iPDM) has the potential to improve clinical outcomes.

Methods: 101 practices with 907 patients participated in the 12-month, prospective, controlled, cluster-randomized study program. HbA1c levels, therapy changes, frequency of hypoglycemic episodes, patient reported outcomes, and physician satisfaction were assessed.

Results: iPDM led to a greater reduction in HbA1c after 12 months vs. usual care (−0.5%, $p < 0.0001$ vs. −0.3%, $p < 0.0001$), (Diff. 0.2%, $p = 0.0324$). Most of the HbA1c reduction occurred after 3 months and remained stable thereafter. The percentage of patients with therapy adjustments was higher in the iPDM group at all visits ($p < 0.01$ at week 3, month 3, month 6). Patient adherence at month 12 was higher in the iPDM group compared to

Abbreviations: AEs, adverse events; BG, blood glucose; CNL, control; DSP, diabetes specialist practitioner; DT-PSQ, Diabetes Treatment-Physician Satisfaction Questionnaire; DTSQc, Diabetes Treatment Satisfaction Questionnaire (change); DTSQs, Diabetes Treatment Satisfaction Questionnaire (status); GCP, Good Clinical Practice; GEE, Generalized Estimating Equations; GKV, Gesetzliche Krankenversicherung; GP, general practitioner; HbA1c, glycosylated hemoglobin; iPDM, integrated personalized diabetes management; PDM, personalized diabetes management; PRO, patient-reported outcomes; PwD, patients with diabetes; SD, standard deviation; SMBG, self-monitoring of blood glucose

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Digital tools
Clinical inertia

baseline (Odds ratio = 2.39; p = 0.0003); also, patient treatment satisfaction (DTSQc: 12.2 vs. 10.4, δ = 1.78, p = 0.004; DTSQs: 31.0 vs. 30.0, δ = 0.924, p = 0.02), and physician satisfaction was higher in the intervention group.

Conclusions: iPDM improved the use of diagnostic data leading to better glycemic control, more timely treatment adjustments (indicating reduced clinical inertia), and increased patient adherence and treatment satisfaction among patients and physicians.

1. Introduction

Around the world, many persons with type 2 diabetes treated with insulin currently do not achieve their treatment goals despite considerable advances in clinical diagnostics and therapeutic options such as glucose monitoring techniques and insulin delivery [1,2]. Suboptimal blood glucose (BG) control is associated with more frequent long-term complications and hospitalizations, higher healthcare costs and elevated mortality rates [3–6].

An important driver of suboptimal glycemic control is clinical inertia: clinicians, for instance, often do not initiate or intensify antidiabetic therapy as recommended in guidelines for persons with type 2 diabetes [7–9], and persons with diabetes (PwD) often have difficulties implementing therapeutic recommendations in their everyday life. In this regard, many PwD are not able to interpret and act adequately upon their self-measured BG (SMBG) data [10,11]. Appropriate use of SMBG data, however, supports therapy optimization and promotes desired behavioral changes, leading to improved clinical outcomes in PwD [12–15]. The daily burden of diabetes self-management, which leads to treatment fatigue for many PwD must also be considered [16]. Such factors can negatively affect patients' motivation as well as their ability and willingness to adhere to prescribed regimens [17].

Use of diabetes data management software has been shown to convey significant benefits through time and cost savings for the diabetes team, combined with relevant improvements in glycemic control [18–20]. Moreover, communication between the physician and the patient within a trusting, collaborative relationship is known to improve clinical outcomes [21–23].

The American Diabetes Association and the European Association for the Study of Diabetes recommend a patient-centered and personalized approach for the treatment of PwD with T2D [24]. Instead of a "one-size-fits-all" approach, personalization is necessary, balancing the benefits of optimizing glycemic control with its potential risks including hypoglycemia or preexisting conditions. For diabetes treatment to be effective, the patient's attitude, age, diabetes duration, diabetes medical history (e.g. known diabetes complications) and comorbidities, and estimated life expectancy, as well as required resources and support systems should be taken into account. To meet these demands, the clinical team must select the adequate diagnostic and therapeutic approach and support the PwD in an appropriate way.

By combining the above-mentioned aspects, the integrated personalized diabetes management (iPDM) approach combines structured SMBG, use of diabetes data management software, collaborative patient-physician communication, and support of therapeutic decision-making in an iterative, 6-step, structured intervention process [25,26]. While the effectiveness of individual essential components of the iPDM concept has been demonstrated [12–15,18–23], the combination of these components in an integrated, structured process has never been studied in patients with insulin-treated type 2 diabetes in a large scale randomized controlled study program.

The aim of the PDM-ProValue study program was to investigate whether taking care of patients with insulin-treated T2D according to the iPDM concept improves glycemic control, patient-reported outcomes (PRO), physician treatment satisfaction, and intensifies therapy adjustments in a close-to-real-world outpatient setting.

2. Subjects, materials and methods

The prospective PDM-ProValue study program consists of two parallel, controlled, cluster-randomized, multi-center clinical trials with an identical study design to assess insulin-treated PwD in general practitioner (GP) practices and diabetes specialist practitioner (DSP) practices across Germany. Details of the study methods have been published previously [27]. The study program was performed according to the Good Clinical Practice (GCP) standard and was approved by the Ethics Committees of the Medical Association Baden-Württemberg and Saxony (Ethik-Kommission der Landesärztekammer Baden-Württemberg bzw. Sachsen) and The Federal Institute for Drugs and Medical Devices (Bundesinstitut für Arzneimittel und Medizinprodukte, BfArM). Trials were registered with ClinicalTrials.gov NCT02268929 (PDM-ProValueGP), NCT02156349 (PDM-ProValueDSP).

2.1. Subjects

Study practices were selected based on their ability to meet the requirements of the study program including number of PwD treated, equipment, and staff. GP and DSP practices were randomly assigned (by means of centralized permuted-block randomization) to the intervention group (iPDM) or the control group (CNL), the latter continued to provide treatment according to their customary medical routine (usual care).

Patient inclusion criteria were: diagnosis of T2D; age ≥18 years; HbA1c ≥ 7.5% (58 mmol/mol) measured during the last 6 weeks prior to study inclusion; subcutaneous insulin therapy for ≥6 months; insured by a statutory health insurance fund (Gesetzliche Krankenversicherung (GKV); willing and able to follow the study procedures; and signed informed consent. Exclusion criteria were: type 1 diabetes; treatment with an insulin pump; experience with use of diabetes data management systems/software; other diseases, disorders or therapies that could impair patient ability to adhere to the study protocol and/or lead to erroneous laboratory measurements; pregnancy, breast-feeding or plan to become pregnant during study participation; and dependency relationship (e.g., colleague or family member) with a representative of the study sponsor or an investigator.

2.2. *iPDM process*

Physicians in the iPDM group received training based on a structured curriculum during four one-hour sessions that included video instruction programs and roleplay exercises. Patients in the iPDM group followed the structured iPDM process (Fig. 1) involving six recurring steps:

(1) Structured assessment and patient education

At the beginning of the process, the medical team assessed the diabetes-related health status and skills of the patient and instructed him/her in the performance of correct BG measurements.

(2) Structured and therapy-adapted SMBG

At baseline, the patients were advised to execute 3-day, 7-point glucose profiles in the first 3 weeks after enrollment independent of the current HbA1c level. The agreement on the SMBG testing regime was documented and provided to the PwD as a printout. At subsequent visits, physicians recommended structured SMBG according to individualized, therapy-adapted testing regimens based on current antidiabetic therapy and HbA1c level (≥7.5% [≥58 mmol/mol] or <7.5% [<58 mmol/mol]). Such regimens included defined (mostly) daily SMBG and event-related measurements as well as periodic utilization of HbA1c-dependent 7-point glucose profiles in the last 4 weeks before the next scheduled visit. Three 7-point glucose profiles at 3 consecutive days were recommended for patients with HbA1c ≥ 7.5%; only a 1-day, 7-point profile was recommended for patients with HbA1c < 7.5%. If the current antidiabetic treatment was found to be inadequate (indicated by HbA1c ≥ 7.5% [≥58 mmol/mol]), the physician was requested – if identified as necessary - to adjust the SMBG regimen. Measured BG values were stored in the BG meter. In addition, the patient was invited to enter his/her measured 7-point BG profile values manually in a paper documentation sheet. Study participants using a SMBG system that was compatible with the data management system had the option to use their current meter throughout the study. All other study participants were provided a suitable SMBG system (Accu-Chek® Aviva, Accu-Chek® Aviva Nano or Accu-Chek® Mobile with an infrared interface [Roche Diabetes Care GmbH]).

(3) Structured documentation

At the next (scheduled) visit, SMBG data were uploaded from the meter data storage (via the Accu-Chek® Smart Pix device reader) for subsequent documentation and structured analysis. SMBG values were systematically processed electronically using the Accu-Chek® Smart Pix Software. This approach enabled systematic evaluation and visualization of SMBG data. The evaluation was presented as an electronic report with selectable elements, including graphics, tables

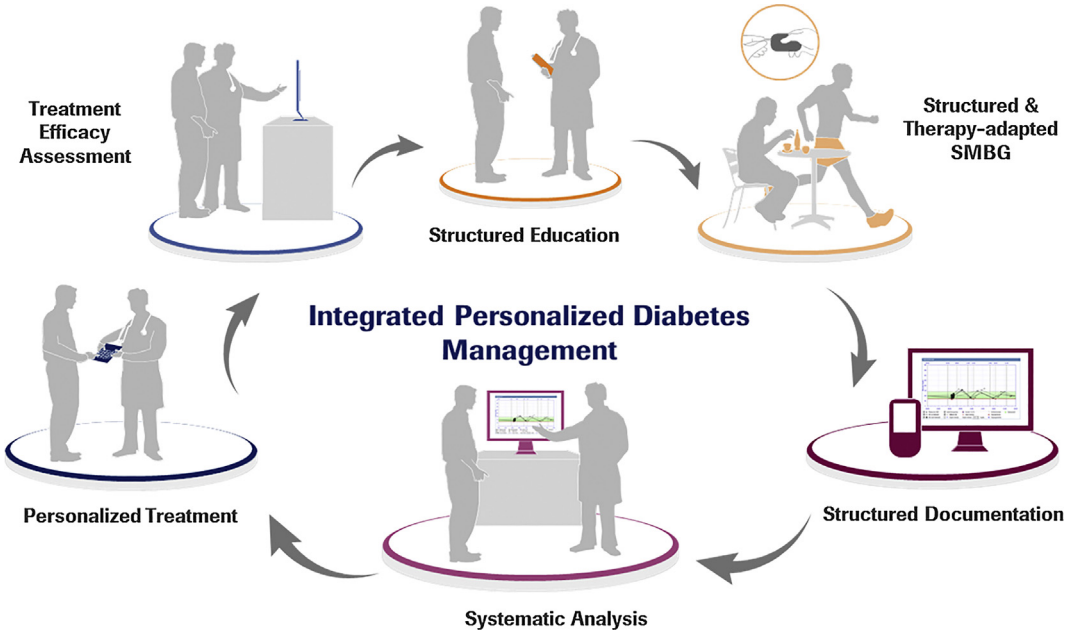


Fig. 1 – The 6 steps of the integrated personalized diabetes management process (iPDM cycle).

and statistics [27]. Based on the reviewed BG data the software also provided indications for problematic glycemic conditions such as hypo- and hyperglycemia as well as pronounced BG variations.

(4) Systematic analysis

During the visit, the patient and the physician collaboratively reviewed the BG data in a structured manner: After a first overview of all collected data, processed BG values were analyzed in detail (e.g. daily curve, weekly curve, special events) and abnormal glycemic patterns and glycemic risks were identified. In addition, patient adherence regarding the agreed-upon SMBG regimen was evaluated with a newly developed adherence tool (using a diabetes data management software).

(5) Personalized treatment

Based on the results of the systematic analysis of the measured BG values, PwD and physicians discussed whether, and if so, how, the diabetes therapy should be adapted. In a joint decision, both parties agreed upon treatment adaptions such as therapy changes, an adjusted SMBG measurement scheme or other measures like diabetes counselling. If the SMBG testing regime was changed the new regime was documented and provided to the PwD as a printout.

(6) Treatment effectiveness assessment

During the next visit, PwD and physicians analyzed measured BG values as described above and assessed whether previous measures had been sufficient to achieve the jointly agreed-upon therapy objectives or if therapy had to be further adjusted. By doing so, a new iPDM cycle was started. Iterative repetition of the iPDM process aimed at initiating a learning process for the PwD. In addition, the PwD was empowered to utilize exemplary strategies in analyzing diabetes therapy and problem-solving processes.

2.3. *Procedures*

Study participants in both groups were provided with medical care under the regular conditions in Germany. PwD in the intervention group were treated according to the structured iPDM process as described above. The medical teams in each iPDM practice were trained in the iPDM process according to a written curriculum, which describes the recurring intervention steps and PwD-centered communication. Throughout the 12-month study period, six visits were scheduled as follows: baseline, week 3 and months 3, 6, 9 and 12.

At the baseline visit, investigators confirmed patient eligibility, described the study in detail (relevant to both study arms) and obtained written informed consent. Patient medical history and socio-demographic information as well as current diabetes therapy were documented and SMBG data were uploaded to the Accu-Chek® SmartPix system. Physical examinations were conducted and blood samples were collected to check the laboratory parameters HbA1c, lipid profile, microalbuminuria, high-sensitivity C-reactive protein (hs-CRP), and serum creatinine as well as to exclude pregnancy (in premenopausal women only). PRO questionnaires regarding patient's diabetes treatment satisfaction and self-efficacy were administered. PwD were trained in correct SMBG testing and were provided with instructions as to their prescribed BG testing regimens.

At all subsequent visits uploaded SMBG data were analyzed for the iPDM group with a focus on glycemic patterns and glycemic disorders that were presented in the report using a "risk traffic light" system (red, yellow, green) to indicate problematic areas. Based on these analyses, physicians recommended changes in therapy and SMBG regimens as needed and collaborated with PwD in confirming or adjusting future therapy objectives. HbA1c levels and lipid profiles were again assessed at months 3, 6, 9 and 12. Other laboratory measurements were repeated at months 6 and 12. Administration of PRO questionnaires was repeated at months 6 and 12. A newly developed questionnaire to assess treatment satisfaction from the physician's point of view was administered at baseline and month 12. Furthermore, the physicians' perception of their patients' adherence to the recommended therapy was requested at month 12. Induced measures such as referrals and trainings, incidental therapy complications, especially hypoglycemia, long-term diabetes complications and other adverse events (AEs), including the seriousness, intensity, causality and outcome of AEs were documented at all visits.

2.4. *Outcomes*

The primary endpoint variable was improvement in glycemic control for PwD in the iPDM group vs. CNL group as assessed by the between-group change in HbA1c from baseline to month 12. Secondary endpoint variables included assessment of the percentage of PwD achieving an HbA1c reduction >0.5% (>6 mmol/mol), diabetes therapy adjustments, changes in SMBG testing frequency, and various PROs.

2.5. *Measures*

Laboratory measurements. Measurement of HbA1c, lipid profiles and pregnancy tests (premenopausal patients) was performed at baseline (month 0), months 3, 6, 9, and 12. Measurement of microalbuminuria, hs-CRP and creatinine was performed at baseline, months 6 and 12. All measurements were performed by a central laboratory (Bioscientia, Ingelheim, Germany).

Diabetes therapy adjustments: Changes in diabetes therapy (insulin and oral/non-insulin antidiabetic medications) were documented at all visits.

Adherence: Change of PwD adherence at month 12 vs. baseline was assessed and documented by the study physicians. Physicians were asked to rate each patient's compliance, comparing post-study adherence to observed adherence during the first three months of the study.

Patient treatment satisfaction: Patient satisfaction was assessed at baseline and months 6 and 12. Furthermore, changes in satisfaction were assessed at month 12 using the Diabetes Treatment Satisfaction Questionnaires for status (DTSQs) and for change (DTSQc) [28,29].

Physician satisfaction: The Diabetes Treatment-Physician Satisfaction Questionnaire (DT-PSQ) instrument was used to assess the physicians' perception of their satisfaction with patient treatment regarding the diabetes therapy used, effect of therapy, expense and benefit of therapy, quality of analysis and discussion of SMBG data, benefit of SMBG values, effectiveness of physician-patient discussions, and recent change in quality of the analyses and discussions of SMBG values assessed at month 12 [30].

2.6. *Statistical analysis*

A sample size of 474 PwD treated in GP practices and 548 PwD treated in DSP practices were planned for recruitment. The analyses of change in HbA1c and other study endpoints (e.g. self-management behaviors) were performed for the modified intent-to-treat (mITT) population. The mITT population is defined as all participants with assessments at baseline and at least one of the visits 3–6 of age, sex, HbA1c (laboratory measurement), recommended diabetes therapy type and at least one complete and non-contradictory follow-up information concerning HbA1c (date and value). The statistical analysis plan has been described previously [27].

The difference in change from baseline HbA1c at 12 months (Δ HbA1c month 0 to month 12) between the PwD in the iPDM and CNL groups was analyzed by means of Generalized Estimating Equations (GEE; population-averaged model) to consider the dependency of the PwD within a cluster [31]. Baseline HbA1c, gender, age and level of outpatient care were considered as covariates in the GEE model [31]. Covariate-adjusted GEE methods were also applied to secondary endpoints.

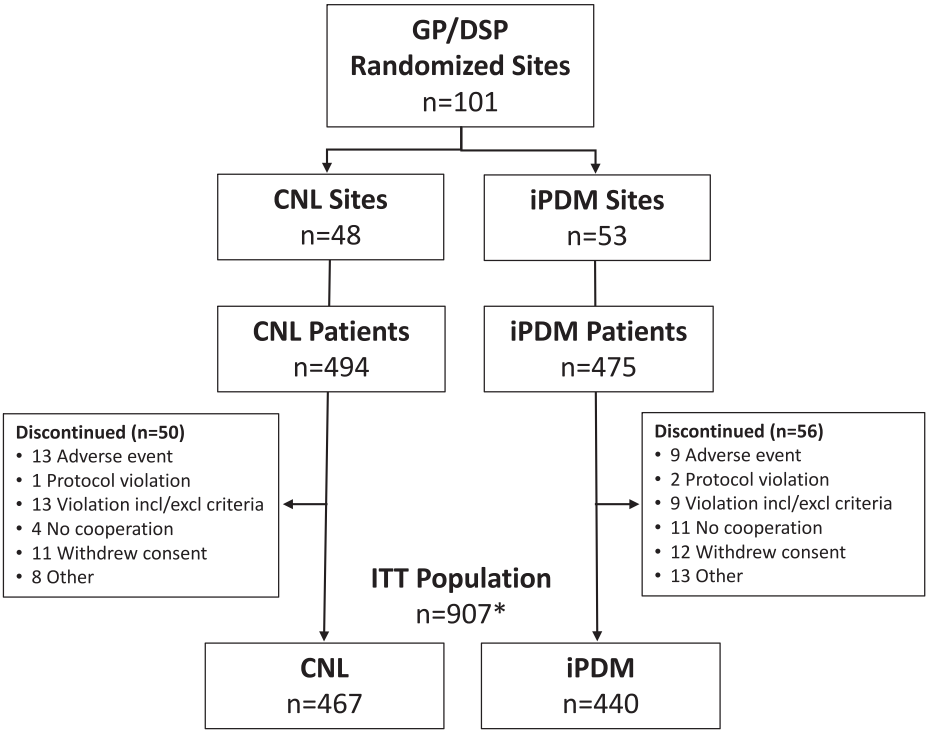
As stated above, the PDM-ProValue study program was conducted in two separate study cohorts (GP and DSP). Due to the high similarity in patient characteristics, study design and study results of the GP and DSP study, it was decided to pool the data into one data set for analysis; results from the pooled-data analysis are presented here. Details of study outcomes of the two study cohorts are provided in the supplementary materials (See Supplemental Materials PDM ProValue.doc).

3. Role of the funding source

The funder of the study (Roche Diabetes Care Deutschland GmbH) participated in study design, data collection, data analysis, data interpretation, and writing of this report. The corresponding author had full access to all the data in the study and had final responsibility for the decision to submit for publication.

4. Results

A total of 101 GP and DSP practices were recruited and randomized to the iPDM (n = 53) and CNL (n = 48) study arms (Fig. 2). Of the 969 PwD enrolled, 907 met the mITT criteria (iPDM n = 440; CNL n = 467) (Table 1). No protocol-related AE or serious AE (SAE) were reported.



*Includes 44 patients who were discontinued but met the ITT criteria (CNL n=23, iPDM n=21).

Fig. 2 – PwD disposition.

4.1. *Glycemic control*

After 12 months, improvement in glycemic control (HbA1c reduction) was greater in the iPDM group (−0.5% [−6 mmol/mol], $p < 0.0001$) compared to the CNL group (−0.3% [−4 mmol/mol], $p < 0.0001$); with a between-group difference of 0.2% (2 mmol/mol), $p = 0.0324$) (Fig. 3).

Significant pre/post reductions (within-group changes) were already observed after 3 months (−0.5% [5 mmol/mol] vs. −0.3% [3 mmol/mol], $p = 0.0054$) and remained almost constant subsequently (Table 2).

A higher percentage of patients in the iPDM group achieved reductions in HbA1c > 0.5% (6 mmol/mol) from baseline after 3, 6, 9 and 12 months vs. those in the CNL group (Fig. 4). Odds ratios (OR), a measure of the relative chance to achieve an HbA1c reduction >0.5%, were significant ($p < 0.05$) at months 3, 6 and 9 but not at month 12.

In both study groups, HbA1c reductions were most prominent in patients with baseline HbA1c values ≥9.0%. However, the between-group difference (−0.4%) of such patients was clinically but not statistically significant based on p-value analysis using GEE and LS means. (Fig. 5).

Linear regression showed that the HbA1c reduction effect increased in relation to baseline HbA1c values in both groups, an effect in favor of the iPDM group was observed at all baseline HbA1c levels.

Table 1 – Socio-demographic and disease characteristics of the mITT population at Baseline.

	iPDM n = 440	CNL n = 467
Male, n (%)	266 (60.5%)	261 (55.9%)
Age (years), mean (SD)	64.5 (10.9)	64.9 (10.0)
Current smoker, n (%)	66 (15.0%)	63 (13.5%)
BMI (kg/sqm), mean (SD)	33.8 (6.1)	34.0 (6.1)
Highest education, n (%)		
Lower secondary education	134 (30.5%)	159 (34.0%)
Higher secondary education	56 (12.7%)	52 (11.1%)
Apprenticeship	147 (33.4%)	153 (32.8%)
Tertiary/High school/Technical	71 (16.1%)	60 (12.8%)
University	26 (6.0%)	27 (5.7%)
Patients with concomitant disease, n (%)	415 (94.3%)	449 (96.1%)
Hypertension	391 (88.9%)	424 (90.8%)
Dyslipidemia	343 (78.0%)	348 (74.5%)
Atrial fibrillation	28 (6.4%)	42 (9.0%)
Patients with Diabetes complications, n (%)	317 (72%)	329 (70.4%)
pAD	69 (15.7%)	48 (10.3%)
CHD	121 (27.5%)	115 (24.6%)
MI	45 (10.2%)	46 (9.9%)
Stroke	27 (6.1%)	26 (5.6%)
Diabetic nephropathy	141 (32.0%)	105 (22.5%)
Diabetic retinopathy/maculopathy	68 (15.5%)	68 (14.6%)
Diabetic neuropathy	198 (45.0%)	207 (44.3%)
Diabetic foot syndrome	62 (14.1%)	80 (17.1%)
Living status, n (%)		
Living alone	102 (23.2%)	135 (28.9%)
With partner only	266 (60.5%)	246 (52.7%)
With partner and others	59 (13.4%)	64 (13.7%)
Time since diagnosis (years), mean (SD)	14.4 (8.7)	14.3 (7.8)
Baseline HbA1c (%), mean (SD)	8.5 (1.1)	8.4 (1.0)
Baseline HbA1c (mmol/mol), mean (SD)	69 (12)	68 (11)
Diabetes regimen, n (%)		
Basal supported oral therapy	126 (28.6%)	133 (28.5%)
Supplementary insulin therapy	12 (2.7%)	15 (3.2%)
Conventional therapy	33 (7.5%)	31 (6.6%)
Intensified conventional therapy	269 (61.1%)	288 (61.7%)
SMBG frequency per week, mean (SD)	20.3 (10.9)	21.4 (11.2)
Time since start of insulin (years), mean (SD)	7.1 (6.6)	7.3 (6.5)
Symptomatic hypoglycemic events in last 3 months, mean (SD)	0.9 (2.6)	0.8 (2.3)
Symptomatic hypoglycemic events requiring carbohydrates in last 3 months, mean (SD)	0.8 (2.5)	0.8 (2.2)
Support required regarding diabetes (%)	61 (13.9%)	54 (11.6%)
Partner, n (%)	44 (10.0%)	27 (5.7%)
Other family member, n (%)	10 (2.3%)	22 (4.7%)

pAD, peripheral artery disease; CHD, coronary heart disease; MI, myocardial infarction, SD: standard deviation.

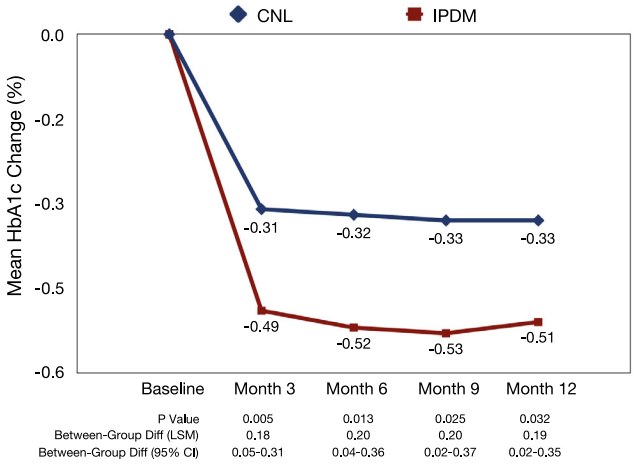


Fig. 3 – Change in HbA1c from baseline during the study. CNL: Control, iPDM: integrated personalized diabetes management.

4.2. *Hypoglycemia*

No significant differences between the PwD in the iPDM group and the CNL group, were observed when calculating the incidence rate ratio of hypoglycemic episodes (defined as BG levels <70 mg/dL [3.9 mmol/L]): ranging from 1.17 (week 3) to 1.06 (month 12) (Table 3).

4.3. *Diabetes therapy adjustments*

A higher percentage of PwD in the iPDM group vs. those in the CNL group received recommendations to adjust their insulin therapy throughout the study (Fig. 6). Changes in prescription of oral antidiabetic medications were negligible in both groups.

PwD in the iPDM group vs. the CNL group experienced more behavioral/lifestyle recommendations for diabetes training (22.3% vs. 14.1%; OR = 1.8; p = 0.045), physical activity/exercise (40.4% vs. 20.3%; OR = 2.4; p = 0.0063) and nutrition counseling (37.0% vs. 23.3%; OR = 2.2; p = 0.013).

4.4. *Adherence*

As stated by physicians, PwD in the iPDM group vs. those in the CNL group demonstrated better adherence to their predetermined treatment regimen after 12 months compared with the first 3 months and the time period before study start (Table 3).

4.5. *PwD and physician satisfaction*

Already at baseline, DTSQs scores showed high treatment satisfaction of PwD in both groups on a scale of 0–36 (0 = very dissatisfied, 36 = very satisfied) (Table 3). After 12 months, the iPDM group showed a greater improvement in treatment satisfaction (as measured by DTSQC scores and similarly, the mean DTSQs was higher in the iPDM group compared to CNL group.

Physician satisfaction was markedly higher in the iPDM group compared to the CNL group. The total score (general assessment of the current diabetes therapy) and all scores of the DT-PSQ questionnaire (effect of diabetes therapy, effort and benefit of diabetes therapy, assessment of the quality of the analysis and discussion of BG values, benefit of using BG data, and effectiveness of the discussion with patient) showed differences between CNL and iPDM at month 12 (Table 3).

4.6. *Changes in blood pressure and lipid levels*

No significant changes in blood pressure, total cholesterol, HDL-cholesterol, LDL-cholesterol or triglyceride levels were observed in either study group.

4.7. *Adverse events*

A total of 746 PwD (379 CNL, 367 iPDM) reported an adverse event during the study period; 106 CNL and 99 iPDM PwD reported a serious adverse event. Three AEs (2 CNL, 1 iPDM) were reported as possibly related to medical product; 18 events (10 CNL, 8 iPDM) were reported as related or possibly related to medical procedure. These events were non-serious symptomatic hypoglycemia.

5. Discussion

This study program showed that an integrative, personalized process which includes (1) structured assessment, (2) structured SMBG, (3) use of data management software to systematically document, process and visualize SMBG data, (4) systematic analytics and change of therapy and (5) collaborative communication, in the clinically challenging group of PwD with insulin-treated T2D improves glycemic control. A significant and rapid HbA1c reduction of 0.5% was observed in the iPDM group at the 3-month follow-up. This improved level of glycemic control remained nearly constant for the remaining study period. Although the HbA1c reduction in the iPDM group did not achieve a difference of $\geq$ 0.4% compared to CNL as specified in the protocol (27), the considerable HbA1c reduction observed in the CNL group could be explained by a study effect among CNL physicians and subsequently their patients. The reduction in HbA1c observed in iPDM patients with baseline HbA1c $\geq$ 9.0% (−1.3%) compared with control patients (−0.9%) is also notable, account for approximately 24% of the study population. It is noteworthy that the improvement in HbA1c was not at the expense of an increase in hypoglycemia risk; BG values < 70 mg/dl as well as severe hypoglycemic events did not increase. Since avoidance of hypoglycemia is an important therapeutic goal for the considered PwD collective, this finding is of clinical relevance.

The results observed in our study are in line with the findings reported in the Cochrane Review about personalized care planning [32]. The review, which included nine studies concerning diabetes, found a combined mean HbA1c difference between intervention and control of −0.2% (95% confidence interval (CI) −0.4% to −0.1%).

Table 2 – Between- and within-group changes in HbA1c from baseline at study visits.

Visit	Study Arm	n	Baseline HbA1c	Visit HbA1c	Within group change		Between group change	
			Mean ± SD % (mmol/mol)	Mean ± SD % (mmol/mol)	LSM, % (mmol/mol)	p value	LSM, % (mmol/mol)	p value
Baseline	CNL	467	8.4 ± 1.0 (68 ± 11)					
	iPDM	440	8.5 ± 1.1 (69 ± 12)					
Month 3	CNL	456	8.4 ± 1.0 (68 ± 11)	8.1 ± 1.1 (64 ± 12)	0.3 (4)	<0.0001		
	iPDM	427	8.5 ± 1.1 (69 ± 11.6)	7.9 ± 1.0 (63 ± 11)	0.5 (5)	<0.0001	0.184 (2)	0.0054
Month 6	CNL	444	8.4 ± 1.0 (68 ± 11)	8.0 ± 1.1 (64 ± 12)	0.3 (3.5)	<0.0001		
	iPDM	412	8.5 ± 1.1 (69 ± 12)	7.9 ± 1.1 (62 ± 12)	0.5 (6)	<0.0001	0.201 (2)	0.0134
Month 9	CNL	444	8.4 ± 1.0 (68 ± 11)	8.0 ± 1.2 (64 ± 13)	0.3 (4)	<0.0001		
	iPDM	421	8.5 ± 1.1 (69 ± 12)	7.9 ± 1.0 (63 ± 11)	0.5 (6)	<0.0001	0.197 (2)	0.0254
Month 12	CNL	440	8.3 ± 1.0 (68 ± 1)	8.0 ± 1.1 (64 ± 12)	0.3 (4)	<0.0001		
	iPDM	413	8.5 ± 1.1 (69 ± 12)	7.9 ± 1.1 (63 ± 12)	0.5 (6)	<0.0001	0.185 (2)	0.0324

LSM, Least Squares Mean.

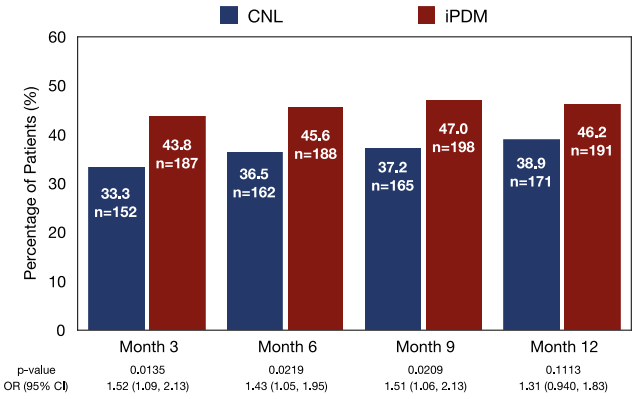


Fig. 4 – Percentage of PwD who achieved >0.5% HbA1c reductions from baseline.

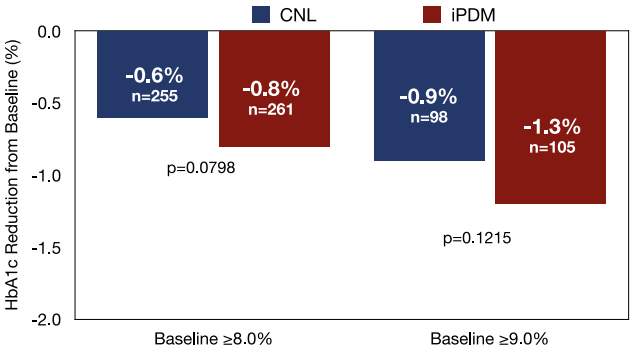


Fig. 5 – Change in HbA1c with higher baseline levels.

Nevertheless, despite the similar between-group difference in HbA1c of 0.2% at study end, our results demonstrate that the iPDM intervention confers significant clinical benefits. It resulted an early and clinically significant improvement in glycemic control, a higher proportion of patients achieving >0.5% HbA1c reductions and greater magnitude of glycemic improvement among patients with ≥9.0% HbA1c at baseline. It is well known that these outcomes are associated with reductions in microvascular/macrovascular complications [33–35] and costs [36,37]. Thus, the early and stable achievement of improved HbA1c seen in the iPDM group will most probablylead to significant reductions in micro- and macrovascular risk in the coming years.

Numerous clinical studies with different diabetes drugs have reported a positive relationship between baseline HbA1c, magnitude of HbA1c change and the treatment effect following pharmacologic intervention [38–40], a similar improvement in glycemic control was observed in this study with iPDM, i.e. a behavioral intervention based on a structured diagnostic process induced an improvement like antidiabetic drugs.

A reason for such a reduction in HbA1c with iPDM is most probably that more patients adjusted their insulin therapy more often. A large number of patients in the iPDM group received an adjustment in insulin therapy during the early part of the study (between week 3 and the 3-month follow-up) when HbA1c reductions were most pronounced; 52% of patients in the iPDM group were requested to adjust their insulin therapy compared to 33% of the patients in the CNL group ($p = 0.005$). This difference in insulin adjustments between groups remained constant during the entire study duration. Patients in the iPDM group also received more non-pharmacological recommendations such as participation in diabetes education, dietary counseling, or instructions and encouragement for more physical activity. In general, therapy adjustments were agreed upon in both groups but to a greater extent in the iPDM group. Subsequently, physicians rated the adherence of patients in the iPDM group higher, which is an indication of a higher feeling of involvement and active participation in the therapy process. In essence, the iPDM process resulted in more focused and timely therapy changes and greater patient adherence to their therapy, i.e. reduces clinical inertia.

Comparison of scores in the diabetes treatment satisfaction questionnaire (DTSQc) and the corresponding physician satisfaction scale (DT-PSQ) demonstrated that patients as well as physicians were significantly more satisfied with this new process than with the traditional approach. Treatment satisfaction is a key contributor to optimal clinical outcomes [41,23], and clinicians play a major role in promoting treatment satisfaction through good communication with their patients [21]. In addition, physicians believed that the iPDM process has beneficial effects with regard to the overall assessment and effects of diabetes therapy, and they rated the ratio between efforts and benefits as good. Furthermore, physicians stated that the iPDM process enabled them to gain an overview of BG values more quickly and that they could discuss these values with patients and make the appropriate adjustments more easily. This led to the overall assessment that physicians rated the discussion of BG values as more effective in the iPDM vs. CNL groups.

A key strength of the PDM-ProValue study program was its multicenter, cluster design of the study program with a large number of study centers, a study duration of one year and a broad range of measuring points (also in the CNL group). Thus, the study provides a detailed insight into patient and physician behavior, generating data which allow a detailed assessment of the iPDM process, including the process of patient-physician interaction, and other outcome variables allowing assessment of effectiveness / economic aspects of the iPDM intervention (these results will be published separately). This highly intensive and standardized data gathering in all study sites (iPDM and CNL centers) assured the availability of a broad range of high quality data; however, this approach also induced a high engagement of the participating CNL physicians, leading to the marked improvements observed also in the CNL group (e.g., study effect).

A second strength is that the iPDM approach was based on common clinical routine and supplemented by integrated digital tools to optimize the care process by supporting therapy decisions and monitoring therapy outcomes. The main focus was directed towards restructuring and improvement of the therapeutic process, which is more structured than usual care and more personalized as postulated by the guidelines for the treatment of patients with T2D. A final strength of the study was use of the easy-to-use and well-established components of the iPDM cycle. The iPDM approach does not require

Table 3 – Hypoglycemic events (measured BG values <70 mg/dl), PwD and physician satisfaction scores, and patient adherence as reported by physicians.

Visit	Study Arm	n	Mean ± SD	Visit LSM (95% CI)	Between-group difference LSM (95% CI)	p-value
Hypoglycemic events (BG levels < 70 mg/dl [<3.9 mmol/L])						
Week 3	CNL	451	1.1 ± 3.2			
	iPDM	425	1.2 ± 2.9		1.2 (0.8, 1.7)	0.4238
Month 3	CNL	467	1.0 ± 2.4			
	iPDM	439	1.1 ± 2.2		1.1 (0.8, 1.5)	0.4118
Month 6	CNL	467	0.9 ± 2.3			
	iPDM	440	1.0 ± 2.0		1.1 (0.8, 1.5)	0.4890
Month 9	CNL	467	0.9 ± 2.2			
	iPDM	440	1.0 ± 1.8		1.1 (0.8, 1.4)	0.6705
Month 12	CNL	467	0.9 ± 2.1			
	iPDM	440	1.0 ± 1.8		1.1 (0.8, 1.4)	0.6927
Percentage of PwD with better adherence than before study start[*]						
Visit	CNL (%)		iPDM (%)		Odds ratio	p-value
Month 12	26.5		46.6		2.3	0.0015
Percentage of PwD with better adherence than during first 3 months of study[*]						
Visit	CNL (%)		iPDM (%)		Odds ratio	p-value
Month 12	36.7		55.3		2.4	0.0003
DTSQs						
Baseline	CNL	443	29.6 ± 6.3			
	iPDM	419	29.4 ± 6.2			
Month 6	CNL	399	30.1 ± 5.9	30.2 (29.6, 30.8)		
	iPDM	368	30.5 ± 5.6	30.5 (29.9, 31.0)	0.31 (−0.52, 1.1)	0.466
Month 12	CNL	399	30.0 ± 6.1	30.1 (29.5, 30.6)		
	iPDM	370	30.9 ± 5.5	31.0 (30.4, 31.6)	0.92 (0.13, 1.7)	0.0127
DTSQc						
Month 12	CNL	401		10.4 (9.6, 11.3)		
	iPDM	370		12.2 (11.4, 13.1)	1.8 (0.59, 3.0)	0.0035
DT-PSQ						
General assessment of diabetes therapy						
Baseline	CNL	467	43.2 ± 8.7			
	iPDM	440	39.9 ± 10.2			
Month 12	CNL	441	47.4 ± 10.1	4.9 (3.2, 6.5)		
	iPDM	414	50.9 ± 10.3	9.7 (8.1, 11.4)	4.9 (2.5, 7.2)	<0.0001
Effect of diabetes therapy						
Baseline	CNL	441	26.3 ± 6.1			
	iPDM	414	24.3 ± 7.0			
Month 12	CNL	441	29.1 ± 6.6	3.3 (2.2, 4.4)		
	iPDM	414	31.7 ± 6.6	6.7 (5.7, 7.7)	3.4 (1.9, 4.9)	<0.0001
Expense and benefit of diabetes therapy						
Baseline	CNL	441	16.9 ± 3.2			
	iPDM	414	15.7 ± 3.8			
Month 12	CNL	441	18.2 ± 3.8	1.6 (1.0, 2.3)		
	iPDM	414	19.2 ± 4.1	3.0 (2.4, 3.6)	1.4 (0.5, 2.3)	0.0027
Assessment of the quality of the analysis and discussion of blood glucose values						
Baseline	CNL	441	31.9 ± 9.1			
	iPDM	414	28.7 ± 10.0			
Month 12	CNL	441	35.0 ± 9.9	3.7 (1.5, 6.0)		
	iPDM	414	42.5 ± 6.9	12.4 (11.0, 13.8)	8.7 (6.1, 11.3)	<0.0001
Benefit of blood glucose values						
Baseline	CNL	441	22.5 ± 6.8			
	iPDM	414	20.3 ± 7.5			
Month 12	CNL	441	24.8 ± 7.30	2.7 (1.0, 4.4)		
	iPDM	414	30.5 ± 4.56	9.3 (8.4, 10.2)	6.6 (4.7, 8.5)	<0.0001

Table 3 – continued

Effectiveness of the discussion						
Baseline	CNL	467	9.5 ± 2.6			
	iPDM	440	8.4 ± 2.8			
Month 12	CNL	441	10.2 ± 2.9	1.0 (0.4, 1.6)		
	iPDM	414	12.1 ± 2.6	3.1 (2.6, 3.4)	2.1 (1.3, 2.9)	<0.0001

LSM, Least Squares Mean; higher score = higher satisfaction; CI, confidence interval; SD, standard deviation; IRR, incidence rate ratio; BG-blood glucose; n, number of patients contributing to summary statistics; PwD, patients with diabetes; DTSQs, Diabetes Treatment Satisfaction Questionnaire (status); DTSQc, Diabetes Treatment Satisfaction Questionnaire (change); DT-PSQ, Diabetes Treatment-Physician Satisfaction Questionnaire.

* much better or better versus no change, worse or much worse.

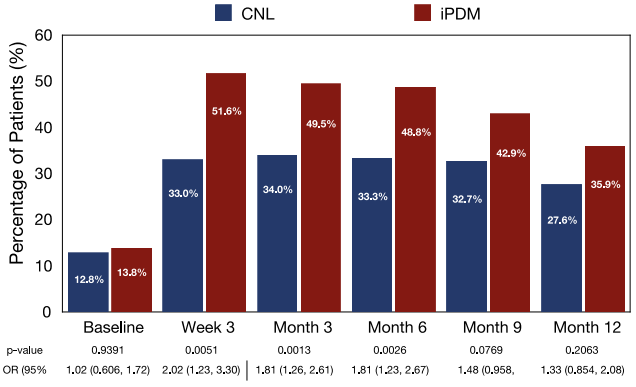


Fig. 6 – Percentage of PwD in the iPDM group or the CNL group that had a change in insulin therapy during their study participation. Odds ratio adjusted for study, gender, age and considering center as cluster.

physicians to learn and manipulate new technologies; the basic tools and methods of iPDM are already available worldwide. Although this may change as more advanced digital technologies are introduced, physicians who are using current technologies will be able to build upon their experience and expertise, and the observed effect may be even more pronounced.

A limitation of the study program is that only the frequency of recommended therapeutic adjustments could be documented; it is not known whether these changes were realized and clinically appropriate. The physicians' estimation of adherence is also somewhat questionable due to the study effect, and should be considered a limitation. Additionally, we were unable to accurately capture data regarding physicians' additional interaction time associated with the intervention.

iPDM physicians appear to have been encouraged to make more and earlier therapy adaptations, resulting in improved glycemic control and helping to overcome clinical inertia. In addition, the physician satisfaction questionnaire showed significantly improved ratings for the iPDM group regarding quality of analysis and discussion of BG values, and for the effectiveness of discussions with patients. The significant improvement in diabetes treatment satisfaction with the iPDM process among patients and their increased adherence as reported by physicians support this conclusion. In this regard, patients are more activated and better integrated in the therapy process when participating in iPDM.

Taken together, these findings suggest that the comprehensive analysis of patients' glycemic status and therapy effects facilitated by the iPDM process inspired greater confidence among physicians in adjusting treatment. Collaboration with patients in their decision-making allowed them to identify and recommend therapy options that met the clinical needs and/or individual lifestyle circumstances of each patient.

Given in the increasing prevalence of T2D and its associated costs, there is a clear need to develop new strategies and (digital) solutions for better treatment of this large patient group. A personalized, integrated approach has the potential to support the implementation of the ADA/EASD guidelines in everyday diabetes care and to strengthen patient empowerment. The PDM-ProValue study program demonstrated that iPDM is an effective, practical measure to meet this challenge, providing a framework for identifying patient knowledge/training deficits, collecting and analyzing BG data, guiding therapy and encouraging patient adherence due to patient-physician collaboration. The introduction of a digitally supported process is feasible across health care systems with varying types of diagnostic tools – from SMBG only to CGM and advanced insulin delivery technologies, so that low-cost approaches may especially benefit from iPDM. In the future, the effectiveness of newly developed digital tools and combinations (e.g., integrating telemedicine and coaching, or systems with dedicated patient interfaces) should be studied with a similar study design.

The results of the PDM-ProValue study program demonstrate that use of an integrated, structured and personalized approach in the evaluation of diagnostic data and therapeutic decision-making provides tangible benefits for patients with insulin-treated T2D and their physicians. iPDM represents an easy-to-implement approach with an integrated software solution. This low-cost approach was found to improve clinical outcomes in patients with T2D, a continuously growing population. For the diabetes team, iPDM improves the quality and effectiveness of their communication with such patients. iPDM has the potential to streamline the delivery of patient care and to optimize clinical workflows on several levels. It is compatible with novel diagnostic tools, e.g. continuous glucose monitoring, and can be implemented in a broad range of health care systems to overcome clinical inertia.

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