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Structured self-monitoring of blood glucose is associated with more appropriate therapeutic interventions than unstructured self-monitoring: A novel analysis of data from the PRISMA trial

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ABSTRACT

Aims: To investigate the relationship between single therapeutic interventions and indicators of glycemic control in the PRISMA trial, a large study comparing the effects of intensive structured SMBG (ISM) vs. active control (AC) in non-insulin-treated type 2 diabetes (T2D).
Methods: Information was collected at four time points, corresponding to months 3, 6, 9, and 12 and visits 2, 3, 4, and 5, respectively. Data on therapeutic interventions, HbA_{1c} levels and the number of hypoglycemic episodes at each visit were analyzed.
Results: Intensification of drug therapy occurred in 20.3% vs. 15.6%, and no change in 71.8% vs. 78.7% of visits for the ISM and AC groups, respectively. On the other hand, de-intensification and redistribution of drugs and/or drug dose occurred in a similar proportion of visits. Intensification of drug therapy in both groups was associated with significant reductions in HbA_{1c} vs. the previous visit, while de-intensification of therapy led to a significant increase in HbA_{1c} in the AC group only. **Conclusions.** Our data strongly support that structured SMBG has clinical value in reducing HbA_{1c} in non-insulin-treated T2D and suggest that this clinical benefit may be mediated by more appropriate and timely changes in drug therapy.

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[1] A complete list of the PRISMA Study Group Investigators can be found in the Supplementary Data online of Bosi E et al. Diab Care 2013; 36(1): 2887.
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1. Introduction

With the overall goal of achieving and maintaining glycemic control, self-monitoring of blood glucose (SMBG) has been proposed as a useful tool. The utility of SMBG is well established in type 1 diabetes and in insulin-treated type 2 diabetes (T2D), and is recommended in current guidelines [1]. Data on the benefits of SMBG in non-insulin-treated T2D have been debated for years [2–7], although a recent meta-analysis suggested that SMBG may be associated with slightly better short-term glycemic control [8,9]. Currently, most scientific societies consider routine SMBG in T2D patients not treated with insulin of limited additional clinical impact, unless it is incorporated as a structured tool in glucose management [10].

Structured SMBG, in which the timing and frequency of testing are planned to obtain information regarding glucose control, was initially reported to be associated with earlier and more frequent changes in diabetes medications in patients with non-insulin-treated T2D with inadequate glycemic control [6]. Following this report, the Prospective Randomized Trial on Intensive SMBG Management Added Value in Non-insulin-Treated T2DM Patients (PRISMA) trial randomized > 1,000 patients with T2D treated with oral agents and/or diet to either an intensive structured monitoring (ISM) or discretionary, unstructured SMBG (active control [AC]) and assessed changes in HbA_{1c} from baseline in either group [11]. The reduction in HbA1c at 12 months was significantly larger with ISM (-0.39%) compared to AC (-0.27%) with a between-group difference of −0.12% (95% CI, −0.210 to −0.024; p = 0.013) [12]. This decrease in HbA_{1c} is of interest also considering that the enrolled patients were relatively well-controlled at baseline, with a median HbA_{1c} of 7.3%. A subsequent analysis of data from the PRISMA trial found that structured SMBG was not associated with worsening of quality of life [13]. Indeed, based on the diabetes-specific quality of life and locus of control questionnaires, there was no significant difference in the quality-of-life domains between the ISM and AC groups.

A meta-analysis of 8 randomized controlled trials (RCTs) comparing structured with unstructured SMBG reported that only the former is associated with significant reductions in HbA_{1c} (-0.2% [−0.3 to − 0.1], p = 0.003) [9]. Moreover, the benefits are greater when SMBG data are used to adjust the prescription of diabetes medications (-0.3% [–0.4 to 0.1], data from 3 RCTs). The efficacy of structured SMBG was further highlighted by the recent SMBG study in 231 patients with non-insulin-treated T2D, reporting improvements in all measures of glycemic variability with structured monitoring [14].

While the benefits of structured SMBG appear to be evident also in patients with T2D who are not on insulin therapy, the reasons underlying this benefit remain elusive. In this analysis, we have investigated the relationship between single therapeutic interventions and indicators of glycemic control in the PRISMA trial. Specifically, we examined if therapeutic changes in the ISM and AC groups, i.e. with or without structured SMBG use respectively, were associated with different changes in HbA_{1C} and occurrence of hypoglycemia.

2. Research design and methods

2.1. *PRISMA study*

PRISMA (Clinical Trial Registration Number: NCT00643474) was a 12-month, prospective, multicenter, open-label, parallel-group, controlled clinical trial, in which patients were randomized to ISM (n = 501) or AC (n = 523) at 39 diabetes centers in Italy. Patients recruitment started in April 2008 and was completed in May 2010. The study design and results have been described in detail elsewhere [11,12]. Briefly, patients with non-insulin-treated T2D, aged 35–75 years, with disease duration of 1–10 years and HbA1c 7.0–9.0%, were eligible. Major exclusion criteria were insulin treatment for > 7 days, previous use of structured SMBG, impending complications of diabetes, limited life expectancy, planned or actual pregnancy, and breastfeeding.

Patients in the ISM group performed 4-point capillary glucose measurements before breakfast and lunch, 2 h after lunch, and 5 h after lunch but before dinner (postabsorptive) on 3 days per week throughout the study. Patients in the AC group were also required to complete a 3-day, 4-point profile in the week before visits at months 6 and 12 to obtain sufficient SMBG data for comparison with the ISM group. However, these data were not available for consideration by the study investigators for glycemic evaluation or adjustment of medications.

At each follow-up visit at months 3, 6, 9, and 12, diabetes medications were prescribed aiming at an HbA1c target < 7.0% in both groups. In the ISM group, SMBG data were transferred wireless from the patient's glucometer to a personal computer through the Accu-Chek Smart-Pix system device reader (Roche Diabetes Care GmbH, Mannheim, Germany) and analyzed by an *ad hoc* software providing easy-to-read summary statistics and therapeutic suggestions.

2.2. *Present analysis*

The PRISMA database was enriched with information on therapeutic interventions as listed in the clinical reporting forms. Information was collected at four time points, corresponding to months 3, 6, 9, and 12 and visits 2, 3, 4, and 5, respectively. All therapeutic interventions were classified into 4 types irrespective of the drug used: i) no change in drug therapy; ii) intensification of drug therapy (i.e. drug adjunct and/or dose increment); iii) de-intensification of drug therapy (i.e. drug discontinuation and/or dose reduction); iv) redistribution of drugs and/or dose (i.e. any other type of drug therapy change). The reasons for drug changes were not taken into consideration as they were numerous and highly heterogenous and thus could not be categorized. Data on HbA_{1c} levels and the number of hypoglycemic episodes at each visit were analyzed. Each HbA_{1c} value at the planned visit was assumed to reflect the therapeutic change of the prior visit; accordingly, all visits where a different than the prescribed therapy was found (likely reflecting inter-visit therapeutic changes) were excluded.

2.3. Statistical analysis

The relationship between the type of therapeutic adjustments and changes in HbA_{1c} was investigated by means of a mixed linear model with "*HbA_{1c} changes from the prior visit*" as model response variable (dependent variable) and with "*visit*", "*stratification factor*", "*randomized group*", "*therapeutic adjustment made at prior visit*" and "*randomized group*"-by-"*therapeutic adjustment made at prior visit*" interaction as model fixed effects (independent variables). The variance–covariance matrix of the mixed model, which takes into account the correlation across repeated measures, was parameterized using the unstructured form. The statistical model conceived in this way is also able to estimate the effects of the so-called time-dependent covariates (for example: *the type of therapeutic adjustment*), i.e. dynamic covariates that can change value or status over time within the same patient. Maximum likelihood estimates of the model parameters were obtained with the Mixed procedure of SAS software. Results are reported as least-square means estimates with standard errors.

3. Results

Nine hundred seventy-four patients (478 in the ISM group and 496 in the AC group) and a total of 3563 visits were included in this analysis. Demographics and baseline characteristics of the included subjects are shown in Table 1. The proportion of therapeutic changes, including intensification of drug therapy, de-intensification of drug therapy, and redistribution of drugs and/or dose, at each visit in the two groups was significantly greater at visits 2–4 in the ISM compared to AC group (visit 2: $p = 0.0144$; visit 3: $p = 0.0068$; visit 4: $p = 0.0068$) (Fig. 1). The four types of therapeutic interventions at each visit and in the two groups are shown in Supplementary Table 1. Overall, intensification of drug therapy occurred in 20.3% vs 15.6%, and no change in 71.8% vs 78.7% of visits for the ISM and AC groups, respectively. On the other hand, de-intensification and redistribution of drugs and/or drug dose occurred in a similar proportion of visits in the ISM and AC groups.

In the whole study population, median entry HbA1c levels were 7.00%, 7.26%, 6.95%, and 7.50% when no change, intensification, de-intensification, and redistribution of drug therapy occurred, respectively.

Intensification of drug therapy in both groups was associated with significant reductions in HbA_{1c} vs. the previous visit, while de-intensification of therapy lead to a significant increase in HbA_{1c} in the AC group only (Fig. 2).

The incidence of hypoglycemia per visit, adjusted for stratification factor and incidence at the previous visit, was rather low (data not shown). A significantly higher incidence of hypoglycemia in the ISM compared to the AC group (4.3 vs. 1.7 events per visit every 100 patients, $p < 0.001$) was found in association with no change in drug therapy but not with other types of therapeutic intervention.

4. Discussion

The present analysis extends the previously reported results of the PRISMA study [12], showing that modification of diabetes therapy occurred more frequently in the ISM than the AC group. This suggests a link between availability of information from structured SMBG data and a 'proactive' attitude to manage patients with T2D. Importantly, while intensification of drug therapy led to a reduction in HbA_{1c} in both the ISM and AC groups, intensification of therapy occurred in a greater proportion of patients in the ISM group. Furthermore, de-intensification of drug therapy led to an increase in HbA_{1c} in the AC but not in the ISM group. Both the more frequent intensification of therapy in the ISM group with the associated HbA_{1c} reduction and the increase in HbA_{1c} in the AC group when therapy was made less intensive could explain the greater reduction in HbA_{1c} observed in the ISM compared to the AC group at the end of the study.

In interpreting this data, the possibility that patients using ISM may have made more effective lifestyle changes as a consequence of their awareness of SMBG data cannot be excluded. Indeed, continuous use of structured SMBG, as in the PRISMA trial, may potentially generate greater awareness of the disease and lead to a healthier lifestyle [12,13]. However, a decrease in HbA_{1c} levels associated with therapy intensification was also seen in the AC group, in which structured SMBG was not performed and thus SMBG-driven lifestyle changes could not occur. Moreover, HbA_{1c} levels were not reduced in those ISM patients who did not undergo changes in drug therapy (Fig. 2). Altogether, these data strongly suggest that greater glucose control in the ISM patients can be explained by structured SMBG-driven intensification of drug therapy rather than other factors.

De-intensification of drug therapy led to a significant increase in HbA_{1c} in the AC but not the ISM group. Importantly, in the ISM group, structured SMBG data were available and a treatment algorithm prompted sulphonylureas/glinides discontinuation or dose reduction in case of negative difference between post- and pre-prandial SMBG values or occurrence of hypoglycemia (either documented or self-reported). This suggests that the investigators were assisted by the algorithm when they de-intensified drug therapy in the ISM group; by contrast, without the support of structured SMBG data, de-intensification of drug therapy may have been less appropriate in the AC group. However, de-intensification of drug therapy occurred only in<5% of visits in both groups, and further studies are needed to clarify whether our findings may be relevant to clinical practice.

Overall, the incidence of hypoglycemia per visit was rather low and clinically insignificant. While a slightly higher incidence of non-severe events with ISM than AC has already been reported [12], our analysis shows that hypoglycemia was not associated with drug therapy intensification or other therapeutic changes and may represent the likely consequence of increased detection of low BG events due to more frequent SMBG testing.

Of note, GLP-1 RA and DPP-4 inhibitors including exenatide, liraglutide, sitagliptin, vildagliptin, and saxagliptin, were only licensed in Italy sometime after the study start and were not included in the diabetes medication algorithm. As a result, it cannot be excluded that, if investigators were provided with additional new-generation drugs with high efficacy [15], low hypoglycemia risk, lower frequency of

Table 1 – Demographics and baseline characteristics of included patients.

	ISM (n = 478)	AC (n = 496)	Total (n = 974)	P-value
Age (years)				
Mean ± SD (n)	60.99 ± 8.1 (473)	61.26 ± 8.79 (492)	61.13 ± 8.45 (965)	0.6275
Median (25th – 75th)	61.47 (55.64–67.43)	62.07 (55.13–68.38)	61.7 (55.25–67.96)	
Min - Max	31.4–75.61	32.36–78.08	31.4–78.08	
Disease Duration (years)				
Mean ± SD (n)	6.06 ± 3.39 (329)	6.05 ± 3.57 (336)	6.05 ± 3.48 (665)	0.9766
Median (25th – 75th)	5.88 (3.54–8.8)	5.87 (3.02–8.59)	5.88 (3.25–8.65)	
Min - Max	0.34–20.73	0.55–21.63	0.34–21.63	
BMI (kg/m^2)				
Mean ± SD (n)	30.56 ± 5.17 (461)	30.6 ± 5.37 (483)	30.58 ± 5.27 (944)	0.9001
Median (25th – 75th)	29.7 (27.04–33.5)	29.6 (27–34)	29.63 (27–33.8)	
Min - Max	18.07–53.85	16.3–57	16.3–57	
Weight				
Mean ± SD (n)	84.36 ± 15.9 (461)	84.02 ± 16.83 (483)	84.19 ± 16.37 (944)	0.7468
Median (25th – 75th)	82 (74–94)	82 (73.3–92.3)	82 (73.5–93.35)	
Min - Max	45–162	44–175	44–175	
Height				
Mean ± SD (n)	166.14 ± 9.31 (461)	165.47 ± 9.71 (483)	165.8 ± 9.52 (944)	0.2836
Median (25th – 75th)	167 (160–172)	165 (158–172)	166 (159–172)	
Min - Max	141–200	140–194	140–200	
Basal HbA_{1c} (%)				
Mean ± SD (n)	7.39 ± 0.75 (472)	7.33 ± 0.69 (483)	7.36 ± 0.72 (955)	0.1960
Median (25th – 75th)	7.3 (6.9–7.8)	7.3 (6.9–7.7)	7.3 (6.9–7.8)	
Min - Max	4.5–10	5.2–10	4.5–10	
Stratification				
Diet only	20 (4.2%)	35 (7.1%)	55 (5.7%)	0.0513
Diet + Drugs	458 (95.8%)	460 (92.9%)	918 (94.3%)	
Gender				
Male	293 (61.3%)	296 (59.7%)	589 (60.5%)	0.6053
Female	185 (38.7%)	200 (40.3%)	385 (39.5%)	
School attended				
1	146 (30.5%)	141 (28.4%)	287 (29.5%)	0.8315
2	182 (38.1%)	204 (41.1%)	386 (39.6%)	
3	108 (22.6%)	111 (22.4%)	219 (22.5%)	
4	30 (6.3%)	31 (6.3%)	61 (6.3%)	
5	3 (0.6%)	1 (0.2%)	4 (0.4%)	
ND	9 (1.9%)	8 (1.6%)	17 (1.7%)	

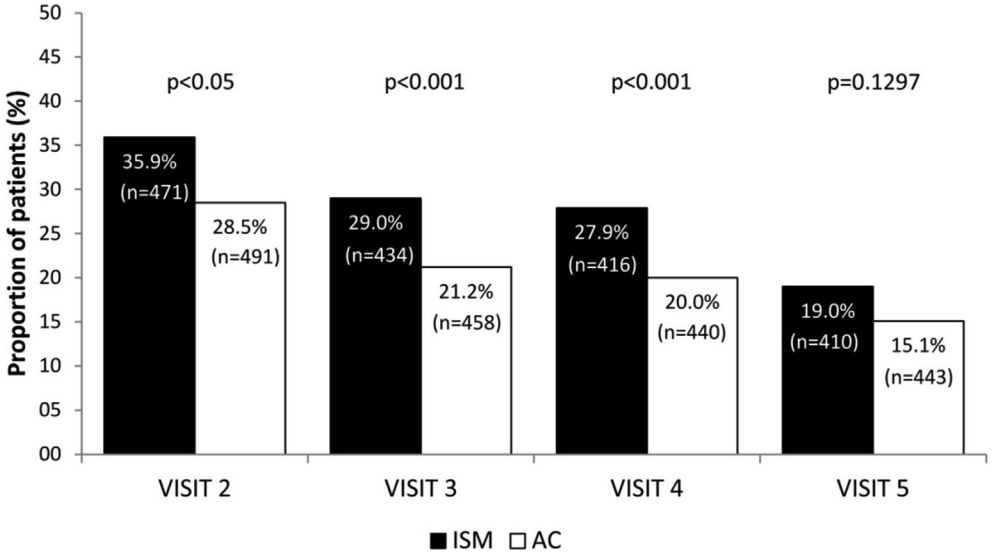

Fig. 1 – Proportion of patients with at least one therapy change in the ISM and AC groups.

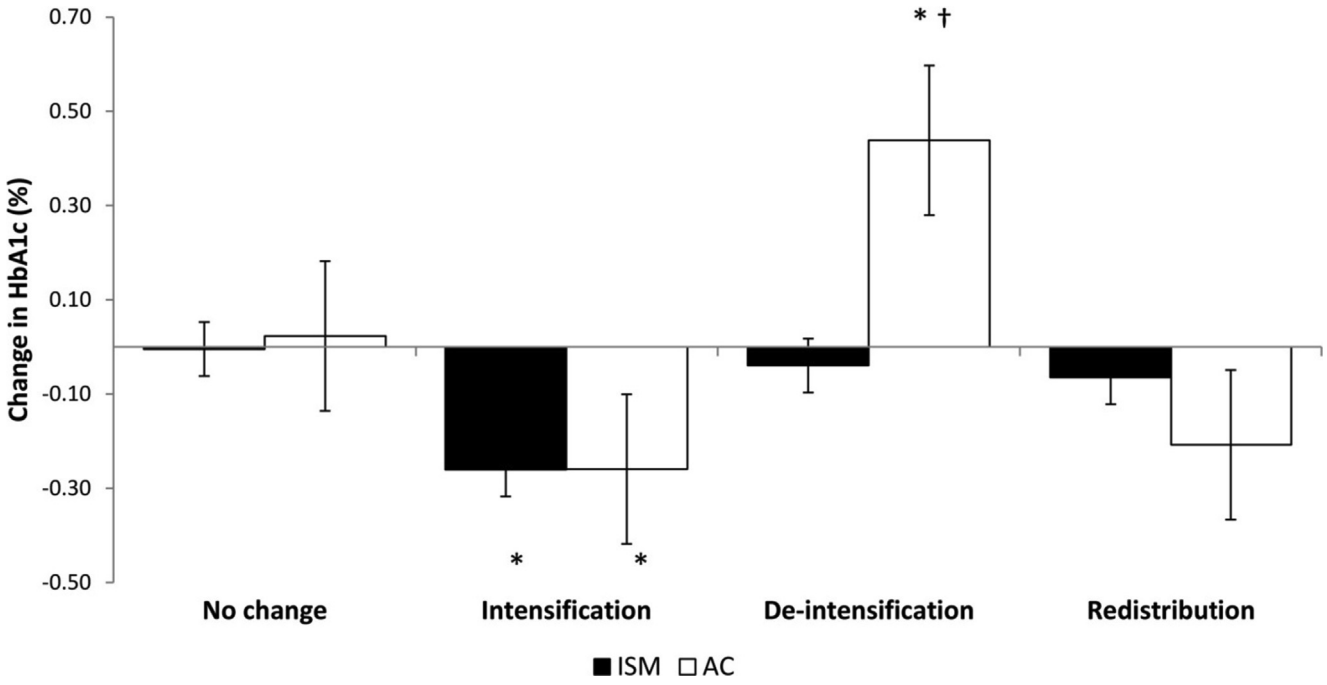

Fig. 2 – Change in HbA_{1c} vs. baseline according to therapeutic intervention in the ISM and AC groups. * $p < 0.05$ vs baseline; † $p < 0.05$ vs ISM.

administration [16,17], and/or cardiovascular/renal benefits [18–20], this could affect their attitude to review patients' therapy and, in turn, short-term glycemic outcomes.

Moreover, different patient characteristics or different SMBG testing schemes may lead to different results. As an example, in the STeP study, Polonsky et al. enrolled patients with a mean HbA_{1c} at baseline of 8.9% and adopted a 7-point SMBG profile on 3 days per week, which was associated with HbA_{1c} decreases of −1.3% and −0.8% in the intervention and control groups, respectively [6]. Since the extent of HbA_{1c} lowering depends upon baseline values, it is not known if different results in terms of the relationship between drug changes and metabolic outcomes would be obtained with a T2D population with high HbA_{1c} at baseline. A detailed analysis of the therapeutic changes from the SteP study is not available at present.

As only subjects aged 35 to 75 years were enrolled in the PRISMA trial, the applicability of our findings to older men or women is unknown. Indeed, the inclusion of frail elderly patients in whom avoidance of hypoglycemia is crucial and less stringent glycemic targets are generally recommended could potentially result in different therapeutic choices and outcomes in either the ISM or AC groups.

In recent years, the advent of continuous glucose monitoring (CGM) technology has revolutionized the approach to diabetes care, with ever-growing evidence supporting its efficacy also in T2D patients on less intensive insulin regimens [21] or non-insulin-based therapies [22]. However, conventional blood glucose self-monitoring still remains the most widely used and reimbursed method to monitor glucose levels in this setting of patients.

Current guidelines for the management of hyperglycemia in T2D recommend drugs with proven cardiovascular and/or renal benefits to be initiated in patients with certain comorbidities (i.e. atherosclerotic cardiovascular disease, chronic kidney disease, heart failure) or indicators of high cardiovascular risk, irrespectively of their HbA1c levels [23]. Nevertheless, structured SMBG (together with an updated, SMBG-informed, diabetes medication algorithm) may still have a role when inadequate glycemic control is an issue in non-insulin-treated T2D patients with prevailing fasting or post-prandial hyperglycemia, or in sulphonylureas and/or glinides treated subjects which are at higher risk of hypoglycemia.

5. Conclusions

Our data strongly support the hypothesis that structured SMBG has clinical value in reducing HbA_{1c} in non-insulin-treated T2D patients and suggest that this benefit is, at least in part, mediated by more appropriate and timely changes of drug therapy based on a personalized analysis of glucose profiles. Therefore, availability of structured SMBG data may allow physicians to intensify the pharmacological therapy at an earlier stage and without incurring in increased risk of hypoglycemia, overcoming therapeutic inertia.

6. Ethics approval and consent to participate

The PRISMA trial was approved by the Ethics Committee of each site and complies with the Helsinki Declaration. All patients provided written informed consent before enrollment.

Author contributions

S.D.M. and C. P. retrieved data from patients' medical records. Er.B. conducted an independent statistical analysis of the data. S.D.M. and F.G prepared the first draft of the manuscript.

All authors participated in reviewing and interpreting the data. All authors revised the manuscript and gave final approval to submit the article for publication.

Declaration of Competing Interest

The authors declare that they have no known competing financial interests or personal relationships that could have appeared to influence the work reported in this paper.

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Data availability statement

The data that support the findings of this study are available from the corresponding author upon reasonable request.

Appendix A. Supplementary data

Supplementary data to this article can be found online at https://doi.org/10.1016/j.ultsonch.2019.104640.

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