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COMMENTARY

Are Type 2 Diabetes Patients Who Self-Monitor Blood Glucose Special? The Role of Confounders in the Observational ROSSO Study

Hubert Kolb, Ph.D.,[1] Stephan Martin, M.D.,[2] Volker Lodwig, Ph.D.,[3]
Lutz Heinemann, Ph.D.,[4] Werner A. Scherbaum, M.D.,[5] and Berthold Schneider, Ph.D.[6]

Abstract

Background:
In the German multicenter, retrospective cohort study (ROSSO), those patients with type 2 diabetes who performed self-monitoring of blood glucose (SMBG) had a better long-term clinical outcome. We analyzed whether confounders accounted for the lower rate of clinical events in the SMBG cohort.

Methods:
ROSSO followed 3268 persons from diagnosis of type 2 diabetes for a mean of 6.5 years. Data were retrieved from patient files of randomly contacted primary care practices.

Results:
In total, more than 60 potential confounders were documented, including nondisease-associated parameters such as patient's health insurance, marital status, habitation, and characteristics of diabetes centers. There were only modest differences for these parameters between groups with versus without SMBG, and multiple adjustments did not weaken the association of SMBG use with better outcome (odds ratio 0.65, 95% confidence interval 0.53–0.81, $p < .001$) . This was also true for subgroups of patients defined by type of antidiabetes treatment. Propensity score analysis confirmed the association of SMBG use with outcome. Using key baseline parameters, 813 matching pairs of patients were identified. The analysis again showed a better long-term outcome in the SMBG group (hazard ratio 0.67 $p = .004$).

Conclusion:
An influence of nonrecognized confounders on better outcome in the SMBG group is rendered improbable by similar results obtained with adjustments for disease-associated or disease-independent parameters, by the analysis of patient subgroups, by propensity score analysis and by performing a matched-pair analysis. The higher flexibility in pharmacological antidiabetes treatment regimens in the SMBG cohort suggests a different attitude of treating physicians and patients in association with SMBG.

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Author Affiliations: [1]Hagedorn Research Institute, Gentofte, Denmark; [2]West German Diabetes and Health Centre, Sana Clinics Gerresheim, Düsseldorf, Germany; [3]Institute for Medical Informatics and Biostatistics, Basel, Switzerland; [4]Profil Institute for Metabolic Research, Neuss, Germany; [5]Department of Endocrinology, Diabetes, and Rheumatology, University Hospital Düsseldorf, Düsseldorf, Germany; and [6]Institute for Biometry, Medical University of Hannover, Hannover, Germany

Abbreviations: (CI) confidence interval, (FBG) fasting blood glucose, (HbA1c) hemoglobin A1c, (HR) hazard ratio, (OAD) oral antidiabetes drug, (RCT) randomized controlled trial, (SMBG) self-monitoring of blood glucose

Keywords: confounder, diabetes complications, epidemiology, mortality, self-monitoring of blood glucose, type 2 diabetes

Corresponding Author: Hubert Kolb, Ph.D., Hagedorn Research Institute, DK 2820 Gentofte, Denmark; email address hubert.kolb@gmx.com

Introduction

Assessing the value of self-monitoring of blood glucose (SMBG) in type 2 diabetes has become a nightmare. At least 22 randomized controlled trials (RCTs) have been conducted on this issue (www.smwg-iwg.org). Although meta-analyses of RCTs of 6–12-months duration have come up with differences of 0.2–0.4% for mean hemoglobin A1c (HbA1c) values in favor of the group using SMBG,[1–7] no general consensus has been reached toward the value of this diagnostic procedure in this patient group, especially in patients not on insulin therapy. The probable reason is the high variability of outcomes, even between large RCTs.[8]

Two analyses have identified one major shortcoming of most trials, including all trials where the use of SMBG failed to make a difference.[8,9] It was argued that SMBG is a diagnostic procedure with no direct impact on disease course unless SMBG readings are linked to guidelines or algorithms that allow patients and the medical personnel to take appropriate steps. Hence RCTs determine not the benefit of SMBG, but the benefit of a SMBG-based intervention strategy. These strategies usually did not include empowerment of patients to self-titrate their antidiabetes medication, and quite often, therapeutic decisions by the study physician were based on HbA1c values, not taking SMBG data into account.[8]

Another aspect of RCTs is that participating patients are selected for compliance and that study physicians provide patient care at a level well above that in routine praxis. As a consequence, major improvements of metabolic control during a trial are often also seen in the control group, i.e., the study or Hawthorne effect.[10–13] The study effect is small when metabolic control of patients is already good at baseline.[14,15]

An advantage of a retrospective observational study is that it documents the unperturbed daily practice. In addition, long-term outcomes can be analyzed. A major disadvantage is the lack of randomization, i.e., patient cohorts with or without SMBG as well as treating physicians differ somewhat in characteristics, a source of confounding. ROSSO is an epidemiological study of the incidence of severe diabetes complications or death in patients with type 2 diabetes who were followed from diagnosis of diabetes for a mean of 6.5 years.[16] A 40–50% risk reduction was observed for fatal or major nonfatal events; most of the latter were cases of myocardial infarction or stroke. These observations do not prove a cause–effect relationship between use of SMBG and clinical outcome because of the lack of randomization. We used several strategies to limit the interference of confounding with the results of ROSSO. The first approach was to document a large number of disease-associated baseline parameters and also of nondisease-associated potential confounders such as location, size, and qualification of the treatment center. All differences found between SMBG, and no SMBG cohorts were included in statistical adjustments. We also tested for possible important confounders not considered in the primary analysis. These approaches included the analysis of patient subgroups defined by antidiabetes therapy or by their propensity score. Finally, a matched-pair analysis was performed. The results of these analyses are presented here; they argue against the possibility that confounders not considered in the analysis are responsible for the better clinical outcome in patients using SMBG.

Materials and Methods

Subjects and Study Design

The German ROSSO Study (retrospective study on SMBG and outcome in patients with type 2 diabetes) is a comparative, epidemiological cohort study performed in collaboration with 192 nonselected primary care practices throughout Germany. As described previously,[16] files of all patients diagnosed with type 2 diabetes between January 1, 1995, and December 31, 1999, in these practices were used as data source. Data until the end of 2003 were documented and validated by monitors visiting the practices. Persons with a diabetes diagnosis prior to the age of 45 years or with a documented follow-up of less than one year were excluded. Nine other patients were lost to follow-up at later times and were included in the analysis. The study protocol was submitted to the ethics committee of the General Medical Council of North-Rhine, Germany.

Predefined study endpoints were myocardial infarction, stroke, foot amputation, blindness (one or both eyes), or end-stage renal failure requiring hemodialysis and all-cause mortality. The composite endpoint included all of these events. Analysis of nonfatal endpoints was based on the first event occurring in a patient during the observation period. A patient was counted as using SMBG in any year based on the prescription of test strips and/or blood glucose data documented by the patient. Most patients did not discontinue SMBG once started, i.e., there were 45% of patients ever using SMBG and 39%

current users during follow-up year 6. Clinical chemistry data were from local laboratory analyses. Since HbA1c assays used by different practices were not standardized, all values were adjusted to 6.1% as upper limit of the normal range of each laboratory.

Statistical Analyses

Differences in numeric baseline data between patients with and without SMBG were assessed using Chi-square test for discontinuous and two-sided *t* tests for continuous variables.

For the matched-pair analysis, the three variables with highest differences between SMBG and no SMBG users were selected, and a fourth variable was smoking because of its strong association with general lifestyle. Patients of the SMBG cohort were stratified for the baseline characteristics of age (≤55, 55–60, >60–65, >65–70, >70 years), sex, smoker status (smoker, nonsmoker, or previous smoker), fasting blood glucose (FBG; ≤130, 130–170, >170 mg/dl) and matched with corresponding patients from the no SMBG cohort by a random computer-based procedure of SPSS. This resulted in 813 matched pairs, for which differences in incidence proportions of endpoints were analyzed with Chi-square test. The main target variable was the time from the date of diabetes diagnosis until a nonfatal or fatal endpoint (survival time). Survival analysis was performed based on Kaplan–Meier estimates. Differences in survival distribution were tested for statistical significance using the log-rank test. Estimates of hazard ratios (HRs) and associated 95% confidence intervals (CIs) were determined by means of the Cox regression procedure of SPSS. A difference of $p < .05$ was regarded as significant.

The propensity score was introduced by Rosenbaum and Rubin[17] as an aid for stratifying or matching individuals in observational studies according to covariates as possible confounders in order to remove or reduce bias. It is defined as the individual's probability of being exposed to the influence factor of interest based on the covariate values of the individual. It was used to identify the relevant individual baseline conditions for using SMBG and to stratify individuals to sets of homogenous conditions to achieve unbiased comparisons. Statistical analyses were undertaken with SPSS+ for Windows, versions 11.5, 12.0, and 13.0 (SPSS Inc., Chicago, IL).

Results

At baseline, at total of 79 items were documented for patients, the treating center, and the physician usually seeing the patient. Of these, the majority were considered as potential confounders (see **Table 1**). These included characteristics of the patient as well as of the center and the treating physician. Medication during follow-up was considered as an additional potential confounder. As no reliable information on the dose were available in the files, medication was categorized in four categories: no medication (diet only), only insulin, only oral antidiabetes drug (OAD), and insulin and OAD during follow-up until an event. For calculation of propensity score and adjustment to confounders with Cox regression analysis, the items were categorized, and it was determined by χ^2 test whether there were differences between the cohort not using SMBG and the cohort using SMBG prior to a nonfatal or fatal event. Since many items were not documented for 100% of patients, we introduced lack of data as a third category. This allowed testing for imbalances between groups for missing data. We found no significant difference in the percentage of missing data between SMBG and no SMBG groups.

Table 1.
Potential Confounders Documented for Patients and Diabetes Center

Patient characteristics
Sex, age, age at diagnosis, height, body weight, smoking (yes/no, previous), alcohol consumption (yes/no, previous), habitation (city, town, rural), health insurance (statutory, private), marital status, children, employment status, arterial hypertension, blood pressure, coronary heart disease, heart insufficiency, myocardial infarction, stroke, peripheral arterial disease, revascularization procedures and bypass surgery, cancer, depression, other chronic disease, other diabetes-related complications and surgeries (19 items), hyperlipoproteinemia, hypercholesterinemia, serum cholesterol, serum triglycerides, high-density lipoprotein cholesterol, low-density lipoprotein cholesterol, HbA1c, FBG, serum uric acid, serum creatinine, medication during follow-up (OAD, insulin + dosing, antihypertensives,[a] lipid-lowering drugs,[b] uric-acid-lowering drugs, thrombocyte aggregation inhibitors, other), diabetes education program (7 items)
Center and treating-physician characteristics
Location (city, town, rural), center size (number of newly diagnosed patients with type 2 diabetes from 1995–1999, total number of diabetes patients), qualification of treating physician (general practitioner, internist, specialization in diabetes or in endocrinology)

[a] Antihypertensive drugs comprised diuretics, beta blocker, angiotensin-converting enzyme inhibitors, angiotensin II type 1 receptor, and Ca-antagonists.
[b] Lipid-lowering drugs comprised fibrates, statins, and rare other compounds.

Table 2 describes all differences observed between groups, with a p value < .1. Baseline differences between the two cohorts were noted with regard to some demographic factors, i.e., age, sex, and habitation. Persons in the SMBG cohort were more often treated by an internist in a center located in small town/rural areas. The health insurance of patients in the SMBG group was more often nonstatutory, which requires for eligibility a salary well above average

Table 2.
Differences between SMBG and no-SMBG Groups

Baseline characteristics		SMBG		no SMBG		Two-sided p value
		Count	%	Count	%	
Qualification of treating physician	General practitioner	1031	69.9%	1348	75.2%	.001
	Internist	445	30.1%	444	24.8%	
Total		1476	100.0%	1792	100.0%	
Center location	City	732	49.6%	1030	57.5%	<.001
	Town or rural	727	49.3%	749	41.8%	
	Unknown	17	1.1%	13	0.7%	
Total		1476	100.0%	1792	100.0%	
Age	≤60 years	790	53.5%	707	39.5%	<.001
	>60 years	686	46.5%	1085	60.5%	
Total		1476	100.0%	1792	100.0%	
Sex	Male	777	52.6%	832	46.4%	<.001
	Female	699	47.4%	960	53.6%	
Total		1476	100.0%	1792	100.0%	
Patient's habitation	City	642	43.5%	913	50.9%	<.001
	Town or rural	834	56.5%	879	49.1%	
Total		1476	100.0%	1792	100.0%	
Health insurance	Public	1403	95.1%	1739	97.0%	.003
	Private	73	4.9%	53	3.0%	
Total		1476	100.0%	1792	100.0%	
Arterial hypertension [a]	No	573	38.8%	547	30.5%	<.001
	Yes	903	61.2%	1245	69.5%	
Total		1476	100.0%	1792	100.0%	
Coronary heart disease	No	1137	77.0%	1324	73.9%	.073
	Yes	304	20.6%	429	23.9%	
	Unknown	35	2.4%	39	2.2%	
Total		1476	100.0%	1792	100.0%	
Serum triglycerides	≤2 mmol/liter	449	30.4%	655	36.6%	.001
	>2 mmol/liter	371	25.1%	431	24.1%	
	Missing	656	44.4%	706	39.4%	
Total		1476	100.0%	1792	100.0%	
FBG[a]	≤8 mmol/liter	543	36.8%	999	55.7%	<.001
	>8 mmol/liter	700	47.4%	626	34.9%	
	Missing	233	15.8%	167	9.3%	
Total		1476	100.0%	1792	100.0%	
Medication during follow- up	None	66	4.5%	539	30.1%	<.001
	Only insulin	96	6.5%	6	0.3%	
	Only OAD	742	50.3%	1173	65.5%	
	Insulin + OAD	572	38.8%	74	4.1%	
Total		1476	100.0%	1792	100.0%	

[a] Blood pressure or HbA1c values were highly correlated with arterial hypertension or FBG, respectively, and therefore were not treated as independent covariates.

income level or a no-employee status. There was a higher prevalence of hypertension and coronary heart disease in the no SMBG group versus higher levels of serum triglycerides and FBG in the SMBG group. During follow-up, prescription of antidiabetes medication occurred more often in the SMBG group, with more use of insulin.

Primary endpoints were fatal (all-cause mortality) or nonfatal (myocardial infarction, stroke, foot amputation, blindness, or hemodialysis) events. In the total population, 254 (14.2%) of 1789 SMBG nonusers and 144 (9.7%) of 1479 SMBG users showed a nonfatal and/or fatal event during follow-up ($p < .001$; odds ratio 0.65, with 95% CI from 0.53 to 0.81). In the subgroup of 1912 patients who were treated during follow-up with OAD only (no treatment with insulin), 155 (13.2%) of 1170 SMBG nonusers and 68 (9.2%) of 742 SMBG users showed a nonfatal or fatal event ($p = .007$; odds ratio = 0.66, with 95% CI from 0.49 to 0.89). The unadjusted HR (i.e., the ratio of the hazard for nonfatal or fatal events between SMBG users and nonusers) was 0.62, with 95% CI from 0.50 to 0.76, in the total population and 0.65, with 95% CI from 0.49 to 0.87, in the subgroup of patients treated with OAD only. These HRs may be biased by inhomogeneities in baseline and treatment conditions between SMBG users and nonusers. To adjust for the influence of these conditions, Cox regression analysis was performed with two sets of covariates that were particularly inhomogeneous between SMBG and no SMBG. The first set was built by the disease-related variables age, sex, arterial hypertension, coronary heart disease, serum triglycerides and FBG at diagnosis, and antidiabetes treatment during follow-up (before a nonfatal event). In the second set, the nondisease-related variables qualification of treating physician, location of center, habitation, and health insurance of patient were added to the disease rated. The HRs and their 95% CI and two-sided significance probabilities achieved with these two sets of covariates by Cox regression are shown in **Table 3** together with the unadjusted HR for the total population and for patients who were treated during follow-up only with OAD. There are no remarkable differences between the adjusted and unadjusted HRs. This means that, despite the baseline differences between SMBG user and nonuser, these differences do not remarkably influence the HR.

Propensity Score Analysis

In an additional approach to evaluate the influence of confounders, we calculated the propensity score, which gives the probability that a patient with given baseline characteristics will belong to the SMBG group. It condenses all baseline covariates into one score. A significant influence on the probability to start on SMBG was found for the qualification of the physician, patient's age, health insurance type, and antidiabetes treatment during follow-up. When using the propensity score for adjusting the HR of nonfatal or fatal events between SMBG users and nonusers, essentially the same results were obtained as described in **Table 3** (adjusted HR, 0.67; 95% CI 0.25–0.85; $p = .001$). The propensity score was also used to stratify

Table 3.
Adjustments for Disease-Related and Unrelated Parameters Do Not Weaken Association between SMBG Use and Outcome

Population	Adjustment	HR	95% CI	*p* value
All patients no SMBG group: 1789 patients with 254 (13.2%) total events; SMBG group: 1479 patients with 144 (9.7%) total events[a]	None	0.616	0.502–0.756	<.001
	Disease-related parameters[b]	0.613	0.475–0.792	<.001
	Disease-related + unrelated parameters[c]	0.622	0.481–0.803	<.001
OAD-treated patients[c] no SMBG group: 1170 patients with 155 (13.2%) total events; SMBG group: 742 patients with 68 (9.2%) total events[a]	None	0.651	0.490–0.866	.003
	Disease-related parameters[b]	0.672	0.502–0.902	.008
	Disease-related + unrelated parameters[d]	0.692	0.516–0.930	.014

[a] Fatal (all-cause mortality) and nonfatal endpoints (myocardial infarction, stroke, foot amputation, blindness or hemodialysis).
[b] Disease-related parameters were age, sex, hypertension, coronary heart disease, FBG, serum triglycerides, and antidiabetes medication during follow-up.
[c] Patients treated with OAD only.
[d] Disease-unrelated baseline parameters were qualification of the treating physician (general practitioner, internist), center size (number of newly diagnosed patients with type 2 diabetes from 1995–1999), center location (city, town + rural), and patient's health insurance (statutory, private).

patients in homogenous subgroups according to baseline characteristics and treatments. The subgroups were defined by the following ranges of the propensity score: subgroup 1, range 0–0.333; subgroup 2, range 0.334–0.666; and subgroup 3, range 0.667–1. The patients of the first subgroup have low, those of the second medium, and those of the third a high probability of using SMBG. The number of SMBG users and nonusers and the number and percentage of nonfatal or fatal events within the subgroups are shown in **Table 4**. In all subgroups, the percentage of events was higher in the no SMBG group than in the SMBG group. The odds ratios for events can be considered as homogenous between subgroups (no statistically significant inhomogeneities) so that they can be pooled to a common odds ratio. The estimate of the common odds ratio is 0.68, with 95% CI from 0.52 to 0.88. This indicates a highly significant reduced risk for nonfatal or fatal events for the cohort using SMBG ($p = .003$) and is in a very good accordance with the results of the Cox regression.

Matched-Pair Analysis of Self-Monitoring of Blood Glucose Use versus Outcome in Order to Minimize Confounding

Because of the major overlap of baseline parameters between groups, it was possible to perform a matched-pair analysis. By random computer-generated lists, patients of the SMBG cohort were matched with corresponding patients of the no SMBG cohort as described in Materials in Methods. The resulting 813 matched pairs did not differ significantly for any of the potential confounders described in **Table 2** (not shown). The HR for nonfatal and fatal events was significantly lower than 1 in the SMBG cohort (HR 0.67, $p = .004$) as shown in **Table 5**. Kaplan–Meier analysis (**Figure 1**) demonstrated superior survival time (in terms of freedom from an endpoint) for patients with SMBG than for patients without SMBG over the entire observation period.

Discussion

A first approach to minimize the possible influence of confounders on outcome of ROSSO was to document at baseline from patient files more than 60 items, which included nondisease-associated parameters such as patient's health insurance and characteristics of the treating diabetes center and physician. In addition, antidiabetes medication during follow-up was considered a potential confounder.

Of the parameters documented, 13 were different between SMBG and no SMG groups at $p < .1$ and therefore were treated as potential confounders. Stepwise adjustments for potential confounders did not weaken the association between SMBG and a reduced rate of clinical endpoints within 6.5 years of follow-up. Importantly, there were no

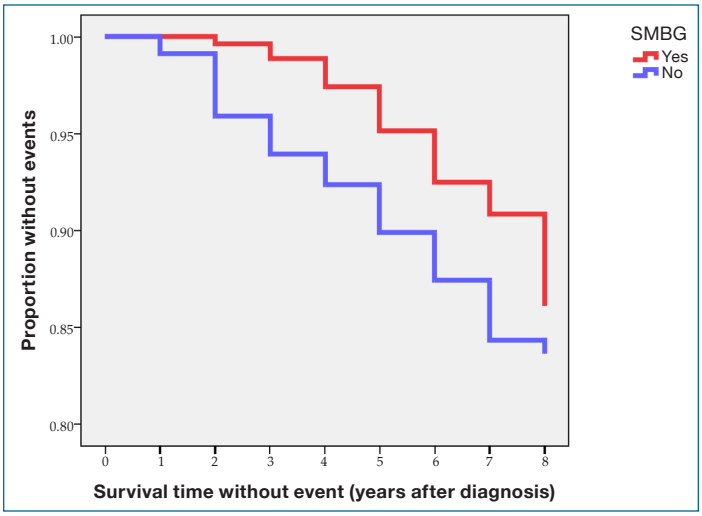

Figure 1. Kaplan–Meier survival curves for composite endpoint in matched pairs of patients with and without SMBG. Of the matched pair analysis, the SMBG cohort is shown in red and the no SMBG cohort in blue. The composite endpoint includes fatal and nonfatal endpoints. Among the 813 matched pairs, patients with SMBG showed better survival throughout the observation period. Unadjusted log-rank test: $p < .005$.

Table 4.
Analysis of Fatal and Nonfatal Events by Propensity Score

Subgroup by propensity score	No SMBG		SMBG	
	Number of patients	Events[a] (%)	Number of patients	Events[a] (%)
0 to 0.333	980	159 (16.2%)	240	31 (12.9%)
0.334 to 0.666	724	78 (10.8%)	558	43 (7.7%)
0.667 to 1	85	17 (20.0%)	681	71 (10.4%)
Total	1789	254 (14.2%)	1479	145 (9.8%)

[a] Fatal and nonfatal events combined.

Table 5.
Matched-Pair Analysis for Long-Term SMBG-Associated Outcome

Long-term outcome	No SMBG[a] n = 813	SMBG[a] n = 813	Hazard ratio	*p* value
Composite endpoint (*n*) (fatal and nonfatal[b])	113 (13.9%)	89 (10.9%)	0.667	0.004
Death (*n*) Nonfatal endpoints[b] (*n*)	33 (4.1%) 83 (10.2%)	25 (3.1%) 65 (8.0%)	0.669 0.664	0.130 0.014

[a] Matched for age class, sex, smoker status, and FBG class.
[b] Nonfatal endpoints were myocardial infarction, stroke, foot amputation, blindness, or hemodialysis.

major differences between the adjusted and unadjusted HRs. This indicates that baseline differences between the two cohorts were not related to SMBG-associated outcome.

Additional parameters not documented in ROSSO are expected to be associated with one or more of the confounders included, such as high socioeconomic status associated with a private health insurance. As described, adjusting for type of health insurance did not change results nor was this the case if only patients with statutory health insurance were analyzed (unpublished). Other undocumented parameters are the skills and knowledge of physicians that often describe SMBG compared to those that rarely recommend SMBG for noninsulin-treated diabetes. These potential confounders are expected to be associated with parameters documented, i.e., the qualification of the treating physician, the location, and the number of patients with diabetes treated in the practice. Indeed, SMBG was more often prescribed by internists than by general practitioners, but adjustment for this imbalance did not modify the outcome of ROSSO.

One reason for the robust result of ROSSO may be that almost half of the total cohort took up SMBG (45.3%) while the other half served as control. This avoids the bias that may arise if two groups compared differ widely in patient number. The latter was the case in the Fremantle Diabetes Study, the only other longitudinal observational study on the association of SMGB use with clinical outcome.[18] Here, 70.2% of 1280 patients with type 2 diabetes used SMBG already at baseline, and this percentage rose to above 80%, as judged from the 5-year longitudinal subcohort, where SMBG use rose from 75.2% to 85.5 % within two years of follow-up. In the unadjusted analysis, the all-cause mortality was significantly reduced by 24% in noninsulin-treated patients using SMBG, but this association was lost during adjustment for baseline differences between the SMBG and the much smaller control group. Similarly, multiple adjustments for different baseline parameters changed results for cardiac mortality, resulting in a higher risk in SMBG users.

An approach to assess a major influence of confounders not documented in ROSSO was to use the propensity score to stratify patients in homogenous subgroups according to baseline characteristics and treatments. Three subgroups were defined by a low, intermediate, or high probability of using SMBG. In all subgroups, the percentage of events was higher in the no SMBG group than in the SMBG group. This finding is particularly informative, because patients with a low probability of using SMBG may differ strongly from patients with a high probability of self-monitoring, for characteristics such as education, motivation, compliance, self-reliance, and overall health. However, a better outcome was associated with use of SMBG in both subgroups, i.e., clinical outcome appears to be more closely linked to the actual use of SMBG than with patient characteristics required for the use of SMBG.

A third approach was to perform a matched-pair analysis, i.e., patients of the SMBG cohort were matched with corresponding patients of the no SMBG cohort. This analysis yielded a reduced risk of severe events in the SMBG group compared to the paired no SMBG group, which was essentially identical to the risk reduction seen in the total study cohort (HR of 0.67 versus 0.62).

All approaches described earlier examined the presence of confounders that would account for the outcome of ROSSO, independent of the use of SMBG. Following our analyses, such confounders must be independent of the more than 60 baseline parameters studied. Although independent of SMBG, they should distribute in parallel with SMBG if patients are subdivided for the probability of using SMBG, and they should distribute in parallel with SMBG in the matched-pair analysis. It therefore seems justified to consider an impact of the actual use of SMBG on the course of disease.

Previous analyses of ROSSO have described a worsening of metabolic control prior to the start of SMBG and improvement thereafter.[19,20] A decrease of HbA1c values after initiation of SMBG was also noted in a longitudinal study of the Kaiser Permanente cohort.[21] Interestingly, lowering HbA1c values by a mean of 0.35% was also seen in patients without pharmacological antidiabetes medication. In ROSSO, the same trend was seen.[20] These observations suggest an impact of SMBG on a patient's coping with the disease at the level of lifestyle and general attitude or a shift of the locus of control toward the patient. Furthermore, use of SMBG was associated with more changes in antidiabetes therapy, i.e., change in OAD type or the addition of a second OAD, or use of insulin.[19,20] Metformin was prescribed more often, whereas there was no association between use of SMBG and prescriptions of antihypertensive or lipid-lowering drugs.[20]

In conclusion, the association of SMBG use with better clinical outcome is not weakened by considering more than 60 potential confounders. The association was not weakened by analyzing subgroups of patients or by propensity score analysis. Essentially, the same result was observed when analyzing 813 matched pairs derived from the SMBG and no SMBG cohort. The mechanism accounting for the outcome of ROSSO appears to be closely linked to the use of SMBG.

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