**Accuracy of Blood Glucose Meters for Self-Monitoring Affects Glucose Control and Hypoglycemia Rate in Children and Adolescents with Type 1 Diabetes**

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**Abstract**

**Aims/Hypothesis:** This study investigated the accuracy of blood glucose meters for self-monitoring and its influence on glycated hemoglobin (HbA1c) levels and the frequency of hypoglycemic coma.

**Materials and Methods:** Self-measured and simultaneously obtained laboratory blood glucose values from 9,163 patients with type 1 diabetes < 18 years of age in the German/Austrian Diabetes Prospective Documentation Initiative registry were analyzed by investigating their compliance with the International Organization for Standardization (ISO) criteria (versions 2003 and 2013) and by error grid analyses. Regression models elucidated effects on glucose control and hypoglycemia rates.

**Results:** Depending on the respective subgroup (defined by sex, age, duration of diabetes, mode of insulin therapy), 78.7–94.7% of the self-monitoring of blood glucose (SMBG) values met the old and 79.7–88.6% met the new ISO criteria. In Clarke and Parkes error grid analyses, the percentages of SMBG values in Zone A ranged between 92.8% and 94.6% (Clarke) and between 92.2% and 95.0% (Parkes). The patient group with SMBG devices measuring “far too low” (compared with the laboratory-obtained glucose levels) presented with a higher HbA1c level than those measuring “far too high,” “too high,” “identical/almost identical,” or “too low” (based on quintiles of deviation). Performing “far too high” was associated with the highest rate of hypoglycemic coma in comparison with the other deviation quintiles.

**Conclusions:** This study showed that current SMBG devices fulfilled neither the previous nor the new ISO criteria. Large deviations of the SMBG values from the “true” glucose levels resulted in higher HbA1c levels and markedly increased rates of hypoglycemic events.

**Introduction**

Self-monitoring of blood glucose (SMBG) is one of the most important pillars of today’s diabetes therapy—both for type 1 or for insulin-treated type 2. It allows patients to achieve and maintain normal blood glucose (BG) levels (e.g., by adjustment of insulin dose), therefore reducing diabetes-related complications. In the United States all SMBG devices must be approved by the Food and Drug Administration prior to market access. Within the European Union the
devices need to undergo a conformity assessment procedure by one of more than 70 “notified bodies” (generally independent commercial organizations) in order to obtain the “CE” mark (Conformité Européenne). To investigate the accuracy of SMBG devices, the standard “for the requirements for blood-glucose monitoring systems for self-testing in managing diabetes mellitus” provided by the International Organization for Standardization (ISO) is widely used. The previous standard was ISO 15197:2003, but in 2013 new, tighter criteria (ISO 15197:2013) were published, which will become mandatory after a transitional period of 3 years. ISO 15197:2003 (ISO 15197:2013) requires a proportion of ≥95% of the individual glucose measurements within ±0.837 mmol/L of the reference value at glucose concentrations <4.16 mmol/L (<5.55 mmol/L) and within ±20% (±15%) at glucose concentrations ≥4.16 mmol/L (≥5.55 mmol/L). As a novelty, the ISO 15197:2013 provides formal acceptance criteria that include testing by patients and assessment of interfering substances. Another frequently used method to specify glucose meter performance is via error grids according to Clarke et al. or Parkes et al. The error grid Zones A–E are supposed to inform the clinician about the severity of errors: the innermost Zone A hosts glucose levels within 20% of the reference method and would lead to clinically correct treatment decisions; 95% of the results in this zone are a common specification. Zone B includes differences between methods greater than 20%, but assuming without seriously adverse consequences. Zone C and E values would result in either hypoglycemia due to treatment decisions, whereas Zone D stands for dangerous results. Parkes error grids can be understood as an advancement of the Clarke error grids: Clarke grids have contiguous Zones A and D, meaning two results with almost the same amount of error could have very different clinical outcomes; the Parkes grid avoids this by using a more gradual definition of zones.

Physicians, healthcare personnel, and people with diabetes expect the numerous available SMBG devices to work properly and accurately; however, after market approval, the measurement quality is never again monitored by an independent institution. Over the last few years several publications have pointed out that not all previously approved SMBG devices conform to the current and/or planned ISO standards. Data from computer simulations have shown what enormous impact the total analytical error of BG meters can have on clinical decision-making and on glucose control.

The aim of this study was to investigate the accuracy of SMBG values in children and adolescents with type 1 diabetes by comparison with laboratory-obtained glucose levels measured in parallel and to identify possible effects on both glucose control and hypoglycemic events.

**Study Design and Methods**

**Data source**

The current study is based on the German/Austrian Diabetes software für prospektive Verlaufsbeobachtung (DPV) documentation system, a project that comprises quality assurance and scientific research. More than 200 German and Austrian pediatric diabetes centers document treatment and outcome of their diabetes patients via DPV. Locally collected longitudinal data are transferred biannually in an anonymized manner, followed by central verification and analysis. Inconsistent data are reported back to centers for correction. The DPV software documents SMBG measurements and simultaneously obtained laboratory BG values with the intention to insure accuracy of SMBG. Additionally, the various test strips prescribed for SMBG measurements are recorded.

Analysis of anonymized DPV data has ethical approval by the institutional review board of the University of Ulm, Ulm, Germany.

**Study population**

The DPV database was searched according to the following criteria: patients with type 1 diabetes, <18 years of age, parallel measurements of BG values available, and time period 2004–2012, resulting in a study sample of 9,163 patients originating from 175 centers.

**Variables**

Demographic data of our study group included age, duration of diabetes, and sex. The variables of age and duration of diabetes were categorized as 1 to <6, 6 to <12, and 12 to <18 years and 0 to <1, 1–5, and >5 years, respectively. Clinical data were SMBG values measured with the patients’ own devices, mainly by the patients themselves or occasionally by their parents or healthcare personnel, and simultaneous laboratory measurements in the same sample with the centers’ certified standard method (laboratories in Germany are bound to the guidelines of the German Federal Medical Chamber; the Austrian laboratories have to fulfill the ISO 15189 criteria). SMBG results of <1.66 mmol/L and >5.51 mmol/L were excluded from analysis. SMBG values were classified in quintiles (Q) (five equal-sized groups), according to their deviation from the laboratory-obtained glucose levels (laboratory glucose value minus SMBG value): “far too high” (Q1)/“too high” (Q2)/“identical or almost identical” (Q3)/“too low” (Q4) and “far too low” (Q5). HbA1c levels were used to assess glycemic control. In order to equalize for different laboratory methods, HbA1c data were mathematically standardized to the Diabetes Control and Complications Trial reference range (4.05–6.05% [21–43 mmol/mol]).2 Modality of insulin treatment was recorded in two categories: insulin pump therapy or injection therapy. The occurrence of (self-reported) “hypoglycemic events with coma” (hypoglycemia accompanied by loss of consciousness or seizures, according to International Society for Pediatric and Adolescent Diabetes guidelines3) was registered. The documented test strips/SMBG devices were assigned to the respective manufacturing company. For each patient, data of the most recent year of follow-up were analyzed.

**Statistical analyses**

Descriptive analysis included calculation of mean, SD, or SE for continuous variables and percentages for categorical variables. Rates of hypoglycemia with coma were estimated assuming a Poisson distribution and given as events per 100 patient-years. To study the accuracy of SMBG meters, BG values obtained with SMBG devices were compared with the centers’ laboratory results according to the old and new ISO criteria. The results are given in absolute numbers and as
percentages of SMBG results within the respective target range, including nonadjusted $P$ values for significant differences ($\chi^2$ test).

In addition, the accuracy of BG meters for self-monitoring was evaluated in Clarke or Parkes error grid analyses: the SMBG results were plotted against the laboratory-obtained BG results. The percentages of SMBG results within the error Zones A, B, and C–E were tabulated, including nonadjusted $P$ values in case of significance. Logistic regression models were used to explore the effect of potentially influencing factors on the proportions of SMBG values within acceptable limits of the ISO criteria or within error Zone A (Clarke, Parkes). The influence of insulin regimen (pump therapy vs. injection therapy) on the compliance with ISO requirements or error grid Zone A was described using odds ratios (OR).\(^1\,6\)

The association of glycemic control and the deviation of SMBG from laboratory-obtained BG values were investigated by linear regression for HbA\(_{1c}\), and by Poisson regression for hypoglycemia rate using time under risk as offset. Sex, age group, type of insulin treatment, duration of diabetes, and year of treatment were modeled as independent fixed effects, and treatment center as a random effect (covariance structure: Cholesky) in order to account for variation among diabetes centers. Adjusted means (least squared means) were calculated based on observed marginal frequencies, and $P$ values were adjusted for multiple comparisons according to the Tukey–Kramer procedure. Within the regression approach, $F$ tests were used to test for differences between groups. A $P$ value of $< 0.05$ was considered to indicate statistical significance.

All analyses were performed with SAS for Windows version 9.3 software (SAS Institute, Cary, NC).

**Results**

**Description of study cohort**

The study cohort comprised 9,163 patients with type 1 diabetes with a mean age of 12.4±3.9 years. Of the population, 48.3% ($n = 4,427$) were female. Mean duration of diabetes was 4.7±3.7 years, and 34.9% used insulin pump therapy. At least one hypoglycemic event with coma occurred in 2.0% ($n = 183$) of all patients, corresponding to a rate of 4.9 per 100 patient-years.

**Distribution of test strips for SMBG measurements**

Of the documented test strips, 66.94% were sold by the market leader for SMBG devices in Germany and Austria, followed by two manufacturers with respective market shares of 11.98% and 11.57%. One additional producer for BG meters covered 6.61% of the test strips in our cohort, whereas the remaining companies, including producers of generic products, shared the remaining 2.9%.

**Accuracy of SMBG measurements**

Comparison of SMBG values with local laboratory results according to the old and new ISO criteria showed that the required ≥ 95% of BG values within target were not met under the “real-life conditions” of our study. Table 1 presents the detailed results including subgroup analyses regarding gender, age, duration of diabetes, and mode of insulin therapy. The mode of insulin treatment was associated with the proportion of BG values within the acceptance limits for the old and new ISO criteria: patients on pump therapy had more outliers than those using injection therapy (old ISO criteria, OR = 1.302, 95% confidence interval [CI] 1.084–1.564, $P = 0.0051$; new ISO criteria, OR = 1.155, 95% CI 1.011–1.318, $P = 0.033$), whereby the distribution of the BG values was similar for both treatment modes. Based on logistic regression analysis, age, gender, duration of diabetes, or year of treatment had no significant influence on the proportion of BG values within target for both ISO standards.

The results of the accuracy analysis of the SMBG measurements using Clarke or Parkes error grids are given in Figure 1. The requirement of 95% of SMBG values within Zone A was not achieved in either error grid. Table 2 contributes detailed information about the distribution of SMBG readings in Zones A–E stratified by patient characteristics/diabetes management. Logistic regression analysis showed that again the mode of insulin treatment influenced the percentage of BG values in Zone A for both error grids: pump therapy was associated with worse results compared with injection therapy (Clarke, OR = 1.286, 95% CI 1.066–1.551, $P = 0.0089$; Parkes, OR = 1.376, 95% CI 1.148–1.650, $P = 0.0007$). Age, sex, duration of diabetes, or year of treatment was not related to the proportions of BG values in Zone A in the error grid analyses.

**Glucose control and acute complications**

Linear regression analysis revealed a significant association between the deviation of SMBG values from the laboratory-obtained glucose levels (grouped into Q) and adjusted mean HbA\(_{1c}\) levels as a marker of glycemic control: patients measuring “far too low” (Q5) (cutoff, ≥ 0.8 mmol/L) with their SMBG devices showed the highest HbA\(_{1c}\) levels (mean, 8.1% [65 mmol/mol]), differing significantly from Q1 (cutoff, −0.6 mmol/L), Q2 (cutoff, −0.1 mmol/L), Q3 (cutoff, 0.3 mmol/L), and Q4 (cutoff, 0.8 mmol/L). Those patients who measured “identical or almost identical” (Q3) or “too high” (Q2) exhibited the lowest HbA\(_{1c}\) levels (mean, 7.7% [61 mmol/mol]). Figure 2a gives adjusted group comparisons and $P$ values.

Regarding the rate of hypoglycemic events with coma, there was a significant difference between Q1 and the other groups (Q2–Q5) in terms of a higher rate for hypoglycemic coma with inaccurately high SMBG values. Figure 2b illustrates the details, including $P$ values.

**Discussion**

This large multicenter study shows that under “real life conditions” the SMBG measurements of children and adolescents fail to meet the accuracy criteria of ISO 15197:2003 and ISO 15197:2013 and also fail to meet the desired percentages of Zone A results in Clarke and Parkes error grid analyses. For ISO 15197:2003, the percentage of acceptable results ranged from 78.7% to 94.7%; for ISO 15197:2013, it ranged from 79.7% to 88.6% in the various subgroups. The Zone A error grid results ranged from a minimum of 92.2% (Parkes, subgroup with pump therapy) to a maximum of 95% (Parkes, subgroup with diabetes duration 0 to <1 years).

These results clearly lag those reported in the literature: in 2012, Tack et al.\(^1\,7\) conducted a study evaluating five commercially available BG meters in 453 adult patients with type...
1 or 2 diabetes. In this clinical setting, three SMBG devices fulfilled the ISO 15197:2003 requirements with 97.5–98.8%, whereas two BG meters missed the minimal criteria with 92.4% and 91.1%. Two meters met the ISO 15197:2013 criteria, whereas one failed narrowly; the remaining two clearly missed the target. Three devices and four devices showed a frequency of >95% of values falling into Zone A in Clarke and Parkes error grids, respectively. Similar results were found by Pflützer et al., who assessed the accuracy of six BG measurement devices, again in a clinical setting. A study carried out by Hasslacher et al. in 2013 confirmed minimal acceptable system accuracy according to ISO 15197:2003 in 19 BG systems, but only eight systems fulfilled the new ISO 15197:2013 standard.

In contrast to the well-controlled studies mentioned above, our study had “real life conditions,” with pediatric patients using their own SMBG devices. The blood samples for SMBG and laboratory-measured glucose values were

### Table 1. Self-Monitoring of Blood Glucose Measurements in Subgroups According to Patients’ Characteristics/Insulin Therapy

<table>
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<tr>
<td></td>
<td>$\Delta &lt; 0.83$ mmol/L when BG $&lt; 4.16$ mmol/L or $\Delta &lt; 0.83$ mmol/L when BG $\geq 4.16$ mmol/L</td>
<td>$\Delta &lt; 0.83$ mmol/L when BG $&lt; 4.16$ mmol/L or $\Delta &lt; 0.83$ mmol/L when BG $\geq 4.16$ mmol/L</td>
<td>$\Delta &lt; 20%$ when BG $&lt; 4.16$ mmol/L or $\Delta &lt; 20%$ when BG $\geq 4.16$ mmol/L</td>
<td>$\Delta &lt; 20%$ when BG $&lt; 4.16$ mmol/L or $\Delta &lt; 20%$ when BG $\geq 4.16$ mmol/L</td>
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<td>$\Delta &lt; 20%$ when BG $&lt; 4.16$ mmol/L or $\Delta &lt; 20%$ when BG $\geq 4.16$ mmol/L</td>
</tr>
<tr>
<td>All BG measurements</td>
<td>9,163</td>
<td>9,138 (93.6)</td>
<td>549 (86.2)</td>
<td>8,589 (94.1)</td>
</tr>
<tr>
<td>Sex</td>
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<tr>
<td>Female</td>
<td>4,427</td>
<td>4,413 (93.7)</td>
<td>223 (84.3)</td>
<td>4,190 (94.2)</td>
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<td>Male</td>
<td>4,736</td>
<td>4,725 (93.6)</td>
<td>326 (87.4)</td>
<td>4,399 (94.0)</td>
</tr>
<tr>
<td>Age (years)</td>
<td></td>
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</tr>
<tr>
<td>1 – &lt; 6</td>
<td>690</td>
<td>686 (93.1)</td>
<td>47 (78.7)</td>
<td>639 (94.2)</td>
</tr>
<tr>
<td>6 – &lt; 12</td>
<td>2,992</td>
<td>2,983 (93.0)</td>
<td>176 (83.0)</td>
<td>2,807 (93.6)</td>
</tr>
<tr>
<td>12 – &lt; 18</td>
<td>5,481</td>
<td>5,469 (94.1)</td>
<td>326 (89.0)</td>
<td>5,143 (94.4)</td>
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<tr>
<td>Diabetes duration (years)</td>
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<tr>
<td>0 – &lt; 1</td>
<td>1,399</td>
<td>1,391 (94.0)</td>
<td>55 (83.6)</td>
<td>1,336 (94.5)</td>
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<tr>
<td>1 – 5</td>
<td>4,088</td>
<td>4,081 (94.1)</td>
<td>264 (86.4)</td>
<td>3,817 (94.7)</td>
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<td>&gt; 5</td>
<td>3,676</td>
<td>3,666 (92.9)</td>
<td>230 (86.5)</td>
<td>3,436 (93.4)</td>
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<tr>
<td>Insulin therapy</td>
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<td></td>
<td></td>
<td></td>
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<tr>
<td>Pump</td>
<td>3,191</td>
<td>3,183 (92.3)</td>
<td>182 (81.9)</td>
<td>3,001 (92.9)</td>
</tr>
<tr>
<td>Injections</td>
<td>5,958</td>
<td>5,941 (94.3)</td>
<td>366 (88.3)</td>
<td>5,575 (94.7)</td>
</tr>
</tbody>
</table>


$P<0.05$, $P<0.01$, $P<0.001$.

1 or 2 diabetes. In this clinical setting, three SMBG devices fulfilled the ISO 15197:2003 requirements with 97.5–98.8%, whereas two BG meters missed the minimal criteria with 92.4% and 91.1%. Two meters met the ISO 15197:2013 criteria, whereas one failed narrowly; the remaining two clearly missed the target. Three devices and four devices showed a frequency of >95% of values falling into Zone A in Clarke and Parkes error grids, respectively. Similar results were found by Pflützer et al., who assessed the accuracy of six BG measurement devices, again in a clinical setting. A study carried out by Hasslacher et al. in 2013 confirmed minimal acceptable system accuracy according to ISO 15197:2003 in 19 BG systems, but only eight systems fulfilled the new ISO 15197:2013 standard.

In contrast to the well-controlled studies mentioned above, our study had “real life conditions,” with pediatric patients using their own SMBG devices. The blood samples for SMBG and laboratory-measured glucose values were
obtained during routine appointments in outpatient clinics or medical practices predominantly by the patients themselves or occasionally by the patient’s parents or trained healthcare personnel. In these supervised settings, possible sources known to influence glucose concentrations (e.g., unwashed hands or extensive squeezing of the finger) were very unlikely to be tolerated. No matter how old our patients were or how long their diabetes duration—factors assumed to influence the skills for BG monitoring—the results were similarly poor in those subgroups. This underlines the rather minor role that preanalytical errors might have played in our investigation.

Laboratory-measured glucose values were determined locally in concordance with the national standardization ("RiliBAEK" for Germany, ISO 15189 criteria for Austria). This implies that the SMBG measurements were not necessarily compared with the device manufacturer’s given reference method. To take the impact of a multicenter setting into account, the diabetes centers were modeled as a random effect in the regression analyses.

Lot-to-lot-variability of test strips for BG meters is certainly an issue to be discussed as a contributor to the low accuracy levels in our study. Baumstark et al. have demonstrated that the lot-to-lot difference between any two of four evaluated test strip lots per BG meter could be as high as 13%. The quality of test strips themselves is doubtless an issue: frequently there are product recalls of certain test strip lots due to noticed suboptimal results. According to the

Table 2. Distribution of Self-Monitoring of Blood Glucose Measurements Stratified by Patients’ Characteristics/Insulin Therapy in Zones A–E of Clarke and Parkes Error Grids

<table>
<thead>
<tr>
<th>Variable</th>
<th>n</th>
<th>Clarke error grid</th>
<th>Parkes error grid</th>
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<tr>
<td></td>
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<td>Zone A</td>
<td>Zone B</td>
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<tr>
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<tr>
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<td>6 – &lt; 12</td>
<td>2,983</td>
<td>93.3</td>
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<td>12 – &lt; 18</td>
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<td>94.4</td>
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<td>&gt; 5</td>
<td>3,666</td>
<td>93.3</td>
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<td>Insulin therapy</td>
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<tr>
<td>Pump (CSII)</td>
<td>3,183</td>
<td>92.8</td>
<td>6.1</td>
</tr>
<tr>
<td>Injection</td>
<td>5,941</td>
<td>94.6</td>
<td>4.5</td>
</tr>
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</table>

Data are percentages.

*P < 0.01, **P < 0.001.

BG, blood glucose; CSII, continuous subcutaneous insulin infusion.

FIG. 2. (a) Glycated hemoglobin (HbA1c) and (b) rates of hypoglycemic coma by quintiles (Q) according to the deviation of self-monitored blood glucose from laboratory-obtained blood glucose values: Q1 = SMBG far too high, Q2 = SMBG too high, Q3 = SMBG identical/almost identical, Q4 = SMBG too low, and Q5 = SMBG far too low. Estimates (±SE) are derived from multiple linear mixed models including age, sex, diabetes duration, and year of treatment, with diabetes center as a random independent variable. Analyses for HbA1c are based on 8,760 observations; those for hypoglycemic coma are based on 9,163 observations. To convert values for HbA1c in percentages into mmol/mol, subtract 2.15 and multiply by 10.929. PY, patient-years.
nature of our study, large numbers of different lots were used. Additionally—as our subjects were not given any specific training or instructions beyond standard diabetes education—there might have been some interference from lack of calibration, temperature, humidity, or poor storage of strips. All those factors are well known to affect accuracy and precision of test strips, but reflect the real life situation.

That our accuracy results were falling short of expectations might also be partly due to the “mixture” of SMBG devices: over the years 2004–2012 a broad variety of different SMBG devices was used by our patients—not just one kind of SMBG meter as in the study of “The Diabetes Research in Children Network Research Group” in 2003, although the majority of test strips documented for our study came from one manufacturer. Again, this reflects “real life” in an outpatient diabetes care setting.

Our results show that patients on pump therapy had constantly and significantly lower percentages of results within the acceptable ranges compared with patients with other forms of insulin therapy. As the bolus calculators of insulin pumps are based on SMBG values, “inaccurate” glucose values might lead to inappropriate insulin dose suggestions. Expanding our thoughts, the SMBG error would be exaggerated by any use of a second device depending on SMBG measurements for calibration, such as a continuous glucose monitoring system.

Arabadjieff and Nickols, have nicely reviewed possible factors contributing to SMBG inaccuracy; however, many of those are very unlikely to occur in children and adolescents with type 1 diabetes (e.g., oxygen therapy, additional medication like salicylates, severe anemia). Some factors leading to inaccurate blood sugar measurements become clear only over time: very recently a warning was released that a therapy with ceftriaxone may lead to incorrect low blood sugar readings. In Clarke and Parkes error grids the goal of ≥95% of Zone A results was mostly not met. For the first time we could demonstrate that deviations of SMBG measurements indeed influence HbA1c levels. The percentage of patients with self-reported hypoglycemic events with coma in our cohort was 2% (4.9±0.37 per 100 patient-years), similar to those previously found in an even larger DPV cohort and somewhat lower than the hypoglycemia rates of a study in adolescents conducted by Chase et al. Serious possible sequelae of hypoglycemic events such as permanent reduced cognition or even death emphasize the importance of our results: “far too high” SMBG values were associated with the highest rate of hypoglycemia with coma or seizures, followed by those measuring “too high” and “identical/almost identical.” This is easy to explain: incorrectly “far too high” or “too high” BG values entail overcorrection via insulin administration, resulting in hypoglycemia. Our results clearly indicate an impact of low SMBG accuracy on the rates of hypoglycemic events with coma.

In summary, this large multicenter study showed that the currently used SMBG devices fulfill neither the old nor the new ISO standard criteria. In Clarke and Parkes error grids the goal of ≥95% of Zone A results was mostly not met. For the first time we could demonstrate that deviations of SMBG values from the “true” glucose levels actually lead to a clinically relevant increase of hypoglycemic events and have a negative impact on HbA1c levels. National and international regulations for SMBG devices have to be reconsidered.

Acknowledgments

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Author Disclosure Statement

No competing financial interests exist.

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Supplementary Data

List of diabetes centers contributing data to the present analysis