

Improvement in Glycemic Excursions With a Transcutaneous, Real-Time Continuous Glucose Sensor

A randomized controlled trial

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OBJECTIVE — Hypoglycemia and wide glucose excursions continue to be major obstacles to achieving target HbA_{1c} values and the associated reductions in long-term complications (and economic costs) in people with insulin-treated diabetes. In this study we evaluated the accuracy, safety, and clinical effectiveness of a continuous glucose-sensing device.

RESEARCH DESIGN AND METHODS — A total of 91 insulin-requiring patients with type 1 ($n = 75$) and type 2 ($n = 16$) diabetes were enrolled in this multicenter randomized study. Subjects wore a transcutaneous, 3-day, continuous glucose-sensing system for three consecutive 72-h periods. Subjects were randomly assigned (1:1 ratio) to either a control group (continuous glucose data not provided) or a display group (continuous glucose data not provided during period 1 but displayed during periods 2 and 3). During periods 2 and 3, patients in the display group had real-time access to sensor glucose values, could review glucose trends over the preceding 1, 3, and 9 h, and were provided with high (≥ 200 mg/dl) and low (≤ 80 mg/dl) alerts and a low (≤ 55 mg/dl) alarm. Sensors were inserted by patients, and both groups used (or wore) the system during daily activities. Device accuracy was assessed by comparing continuous glucose values to paired self-monitoring of blood glucose (SMBG) meter readings. Clinical effectiveness was evaluated by analyzing between-group (control vs. display, periods 2 and 3) and within-group (display, period 1 vs. period 3) differences in time spent in high, low, and target (81–140 mg/dl) glucose zones.

RESULTS — When prospective, real-time sensor values were compared with SMBG values, 95.4% of 6,767 paired glucose values fell within Clarke error grid A and B zones. Pearson's correlation coefficient was 0.88, and mean and median absolute relative differences were 21.2 and 15.9%, respectively. No systematic bias was detected at any of the prespecified glucose levels (50, 80, 100, 150, and 200 mg/dl). When compared with control subjects, the display group spent 21% less time as hypoglycemic (< 55 mg/dl), 23% less time as hyperglycemic (≥ 240 mg/dl), and 26% more time in the target (81–140 mg/dl) glucose range ($P < 0.001$ for each comparison). Nocturnal (10:00 P.M. to 6:00 A.M.) hypoglycemia, as assessed at two thresholds, was also reduced by 38% (< 55 mg/dl; $P < 0.001$) and 33% (55–80 mg/dl; $P < 0.001$) in the display group compared with control subjects.

CONCLUSIONS — We conclude that real-time continuous glucose monitoring for periods up to 72 h is accurate and safe in insulin-requiring subjects with type 1 and type 2 diabetes. This

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Abbreviations: ARD, absolute relative difference; DCCT, Diabetes Control and Complications Trial; SMBG, self-monitoring of blood glucose.

A table elsewhere in this issue shows conventional and Système International (SI) units and conversion factors for many substances.

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study demonstrates that availability of real-time, continuously measured glucose levels can significantly improve glycemic excursions by reducing exposure to hyperglycemia without increasing the risk of hypoglycemia, which may reduce long-term diabetes complications and their associated economic costs.

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Intensive insulin therapy delays and prevents the progression of microvascular disease in patients with type 1 and type 2 diabetes (1,2). In the Diabetes Control and Complications Trial (DCCT), for example, intensive insulin therapy significantly reduced retinopathy (47–76%), microalbuminuria (39%), albuminuria (54%), and neuropathy (60%). Furthermore, the DCCT Epidemiology of Diabetes Interventions and Complications (EDIC) study established the fact that early control of diabetes over 6.5 years will allow for continued protection against both microvascular (3) and macrovascular (4) complications 18 years after the DCCT was completed despite mean HbA_{1c} (A1C) values of 8.0 and 8.2% for those patients assigned to receive intensive treatment and conventional treatment, respectively. Further analysis of DCCT data suggests that A1C values may not reflect all the improvements seen in the intensively treated group, and the authors went on to suggest that glucose excursions may play a role in the development of diabetes complications (5). It has also been suggested that glycemic control may be more appropriately expressed in terms of glucose variability in conjunction with A1C, rather than by A1C alone (6).

Hypoglycemia is the main limiting factor in the glycemic management of insulin-treated diabetic subjects (7). In the DCCT, for instance, attempts to achieve near-normal glucose levels resulted in a 3.3-fold increase in the rate of severe hypoglycemia. Frequent self-monitoring of blood glucose (SMBG) is an integral part of intensive diabetes management that

has been shown to improve glycemic control (8). Patients, however, dislike frequent SMBG because of its associated pain, inconvenience, and invasive nature. More recent availability of continuous glucose sensors has given patients the ability to view real-time glucose values, review trend graphs of recent glucose values, and receive alarms/alerts for impending hypo- or hyperglycemia. Clinical studies of continuous glucose monitoring systems have, in some instances, shown improvements in glycemic control (9). For example, a recent study demonstrated reduced glucose excursions when real-time continuous glucose values from a long-term implantable sensor were available to patients with type 1 diabetes (10).

In this study, we evaluated the safety and efficacy of a short-term (72-h) real-time continuous glucose sensor (STS System; DexCom, San Diego, CA) in a randomized, controlled fashion. The clinical effectiveness of this system was evaluated in patients who were provided real-time glucose values, trend information, and alerts/alarms (the display group), compared with patients who were blinded to this information for the duration of the study (the control group).

RESEARCH DESIGN AND METHODS

Ninety-one adult subjects with either type 1 or type 2 diabetes requiring insulin therapy were enrolled in this multicenter study. Subjects were randomly assigned (1:1 ratio) to either a control group ($n = 44$; continuous glucose data were not provided during any of the three periods) or a display group ($n = 47$; continuous glucose data were not provided during period 1 but were displayed during periods 2 and 3). Seventy-five subjects had type 1 diabetes and 16 subjects had type 2 diabetes with a mean \pm SD age and duration of diabetes of 44 ± 13 and 21 ± 12 years, respectively. Fifty-three subjects (58%) were male, and 85 subjects (93%) were Caucasian. Fifty-one (56%) subjects used continuous subcutaneous insulin infusions (control = 24, display = 27), and 40 (44%) used multiple daily injection therapy (control = 20, display = 20); the method of insulin delivery was not significantly different between groups ($P = 0.78$). A1C values were 7.6 ± 1.1 and $8.0 \pm 1.5\%$ for the control and display groups, respectively. There were no demographic differences between groups ($P < 0.05$).

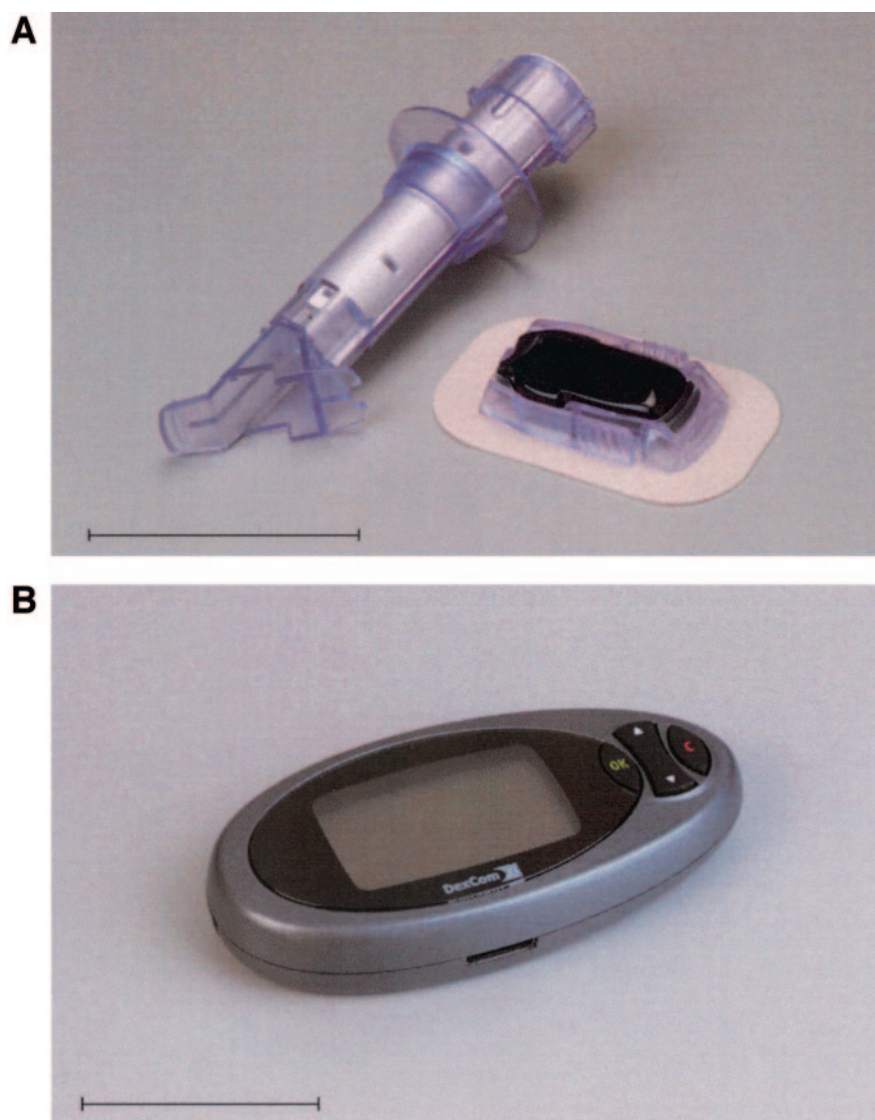


Figure 1—A: DexCom STS sensor, applicator, and transmitter. Scale line, 5 cm. B: DexCom STS receiver (wireless). Scale line, 5 cm.

Sensor and transmitter

The STS sensor consists of an applicator, sensor probe, and transmitter housing (Fig. 1A). The applicator is a single-use disposable unit that houses the introducer needle and the sensor probe contained within it. The transmitter housing was adhered to the patient's abdomen, and the needle (containing the sensor probe) was then inserted into the subcutaneous tissue of the abdomen. The needle was retracted, and the applicator was removed, leaving the sensor probe within the subcutaneous tissue. After the transmitter was installed, an averaged glucose signal was wirelessly sent to the receiver via low-powered radio frequency at 5-min intervals.

Receiver

The STS receiver is an externally worn pager-sized device (Fig. 1B). For the purposes of this study, the receiver used uploaded SMBG meter values for calibration (i.e., to convert the glucose signal measured by the sensor into a user-viewable glucose concentration). Two hours after the sensor was first inserted, two SMBG values were uploaded for calibration. Thereafter, patients were instructed to upload one SMBG value every 12 h (morning and evening). Once calibrated, the receiver displayed a glucose value that was updated at 5-min intervals. The receiver also displayed glucose trend graphs of the preceding 1, 3, or 9 h and generated high and low glucose alerts and alarms. In

this study, the high glucose alert was set at 200 mg/dl, and the low glucose alert was set at 80 mg/dl. A hypoglycemia alarm was triggered at glucose levels ≤ 55 mg/dl.

In addition to logging continuous sensor values, the receiver stored uploaded SMBG meter values. These data were then downloaded to a computer that was also used to set the STS receivers, in accordance with the study protocol, to a “blinded” configuration (continuous glucose values, trend graphs, and alerts/alarms not provided) or an “unblinded” configuration (continuous glucose values, trend graphs, and alerts/alarms provided).

Study design

This was a prospective, randomized, controlled study conducted at four clinical research sites in the U.S. The study population included patients ≥ 18 years old with type 1 or type 2 diabetes requiring insulin therapy. A computer-generated block randomization scheme was used to assign patients (1:1) to either the control or display group. Patients with type 1 and type 2 diabetes were randomized separately to maintain a balanced ratio across both cohorts. All patients were instructed to use SMBG values (not continuous sensor values) to guide major therapeutic decisions related to diabetes management (e.g., insulin dosing). Each patient was assigned two SMBG meters: one meter was used for STS System calibration; the other was used for all other fingersticks (i.e., those used for comparative or confirmatory purposes). The study protocol was approved by all participating institution review boards, and all subjects provided written informed consent before study participation. Patients in both groups inserted sensors themselves and wore the sensor (one per insertion period) at home or at work during daily activities. Patients recorded insulin dosing, other medications, meal times, and activities in a study diary. All subjects participated in three consecutive 72-h insertion periods.

Insertion period 1 (study days 1–3)

All patients underwent sensor insertion on the morning of study day 1. During the first insertion period, all receivers assigned to both control and display groups were blinded. To allow for comparison of STS System glucose measurements to SMBG values in a controlled setting, patients randomly assigned to the control group underwent two 12-h in-clinic days (during hours 0–12 and 48–60). Display

group patients did not participate in any in-clinic days. During home use, both groups followed the same schedule of approximately eight SMBG fingersticks daily: two were uploaded to the receiver for calibration, and approximately six were performed with a separate comparative meter.

During both 12-h in-clinic days, control group patients were closely monitored by clinical staff. Meals and insulin levels were adjusted to obtain a full range of glucose values. Patients took a fingerstick with their assigned comparative SMBG meter at 20-min intervals. This frequency, however, was doubled when glucose levels were >239 or <81 mg/dl to gain additional information on sensor performance at high and low glucose levels. A subgroup of 14 control patients also had blood drawn at 20-min intervals (concurrent with SMBG measurements) both to allow for comparison of sensor performance to a laboratory standard (Yellow Springs Instrument) and to enable determination of the variance ratio required for Deming regression analysis.

Insertion period 2 (study days 4–6)

On the morning of study day 4, all patients returned to the clinic; the first sensor was removed, and the second sensor was inserted. Study staff members were asked to review diabetes management with patients in both cohorts. Receivers for patients in the display group were then unblinded (control group receivers remained blinded for the entire study). Control group patients were instructed to take two fingersticks daily for calibration and six fingersticks daily for comparative purposes, as they did during home use of insertion period 1. Patients in the display group also took two fingersticks daily for system calibration. During insertion period 2, however, display group patients were also asked to confirm alerts (≤ 80 or ≥ 200 mg/dl) and alarms (≤ 55 mg/dl) using their comparative SMBG meter. Approximately eight daily fingersticks were anticipated for display group patients for purposes of calibration, comparison, and confirmation of alerts/alarms.

Insertion period 3 (study days 7–10)

On the morning of study day 7, patients returned to the clinic for removal of the second sensor and insertion of the final sensor. The control group remained blinded and the display group remained unblinded during insertion period 3. The SMBG fingerstick schedule was the same

as that of insertion period 2. All patients returned to the clinic on the morning of study day 10 for removal of the final sensor. Patients were contacted by telephone 6–10 days later to identify any potential issues after removal of the final sensor.

End points

The primary efficacy end point was sensor bias (compared with SMBG measurements) during home use. To satisfy this end point, sensor bias had to be <15 mg/dl at 50 and 80 mg/dl and $<15\%$ at 100, 150, and 200 mg/dl. Secondary assessments of sensor accuracy included the Clarke error grid, Pearson's correlation coefficient, and mean/median absolute relative difference (ARD) analyses. Clinical effectiveness was evaluated by within-group (display group, period 1 vs. period 3) and between-group (control vs. display groups, periods 2 and 3) comparisons of time spent within several hypo-, hyper-, and euglycemic ranges. A retrospective evaluation of the hypoglycemia warning system was also performed. Safety was assessed in terms of the incidence of adverse device effects.

Statistical analysis

In general, the statistical comparison of continuous variables was conducted using the *t* test or Wilcoxon's rank-sum test, as appropriate. For the comparison of categorical variables, the Mantel-Haenszel χ^2 test or the Kruskal-Wallis test was used for ordinal variables, and Pearson's χ^2 test (for $2 \times C$ tables) or Fisher's exact test (for 2×2 tables) was used for nominal variables. ANCOVA was used to model certain continuous efficacy variables with selected covariates. All treatment group comparisons were conducted at the $\alpha = 0.05$ level of significance using two-tailed tests, unless otherwise stated.

The prespecified primary efficacy end point was bias of paired sensor and SMBG values during home use as compared using Deming regression. The Deming method takes into account the error in the comparative meter measurements by using a variance ratio between the sensor and the SMBG meter (11). The variance ratio used to calculate the bias results was 1.63 (sensor) to 1 (meter). These data were evaluated prospectively (using the receiver values as displayed to or blinded from the study subjects in real time).

RESULTS— A total of 3,650 paired glucose values from the sensor and the SMBG meter in the home setting were

compared using Deming regression. The calculated bias in milligrams per deciliter (90% CIs) was 3.8 (3.0–4.7), 7.8 (7.2–8.4), 10.4 (9.9–10.9), 17.0 (16.5–17.5), and 23.5 (22.8–24.3) at the levels of 50, 80, 100, 150, and 200 mg/dl, respectively. Based on these results, the null hypothesis (bias >15 mg/dl at 50 and 80 mg/dl, or >15% at 100, 150, and 200 mg/dl) was rejected, indicating that sensor glucose values were within prespecified accuracy limits compared with SMBG glucose values.

More than 95% of 6,767 paired sensor-SMBG data points collected during in-clinic days (95.3%) and during home use (95.5%) were in Clarke (12) error grid regions A or B (clinically accurate or acceptable). These results were consistent over a wide range of glucose values obtained in both settings (Fig. 2A and B). Additional accuracy metrics included a Pearson correlation coefficient of 0.88, a mean ARD of 21.2%, and a median ARD of 15.9%.

Clinical effectiveness

The randomized design of this study allowed for analyses involving the clinical utility of real-time availability of continuous glucose values. One analysis compared the proportion of time spent in low, mid, and high glucose ranges, both for 24 h (all day) and during nighttime hours (10:00 P.M. to 6:00 A.M.), between randomization groups (control vs. display, during periods 2 and 3), as well as within the display group (blinded during period 1 vs. unblinded during period 3). The results of the between-group comparison are presented in Fig. 3A and B. There was no difference in the average number of fingersticks between the groups (control group = 7.0/day, display group = 6.6/day; $P = 0.38$).

The within-group comparison showed that display group patients, once unblinded, reduced the time spent at low glucose values (<55 mg/dl) by 9% (0.94 vs. 0.86 h; $P = 0.015$) and high glucose levels (>240 mg/dl) by 15% (6.78 vs. 5.79 h; $P < 0.0001$) and increased their time spent in the target glucose range (81–140 mg/dl) by 16% (5.77 vs. 6.69 h; $P < 0.0001$) (ex. in Fig. 4).

A retrospective evaluation of the hypoglycemia warning system was also performed. When unblinded, it provided three means of warning to the user: 1) glucose trend graph dropping to <100 mg/dl with a rate of fall >1 mg · dl⁻¹ · min⁻¹, 2) a low alert for glucose ≤80 mg/

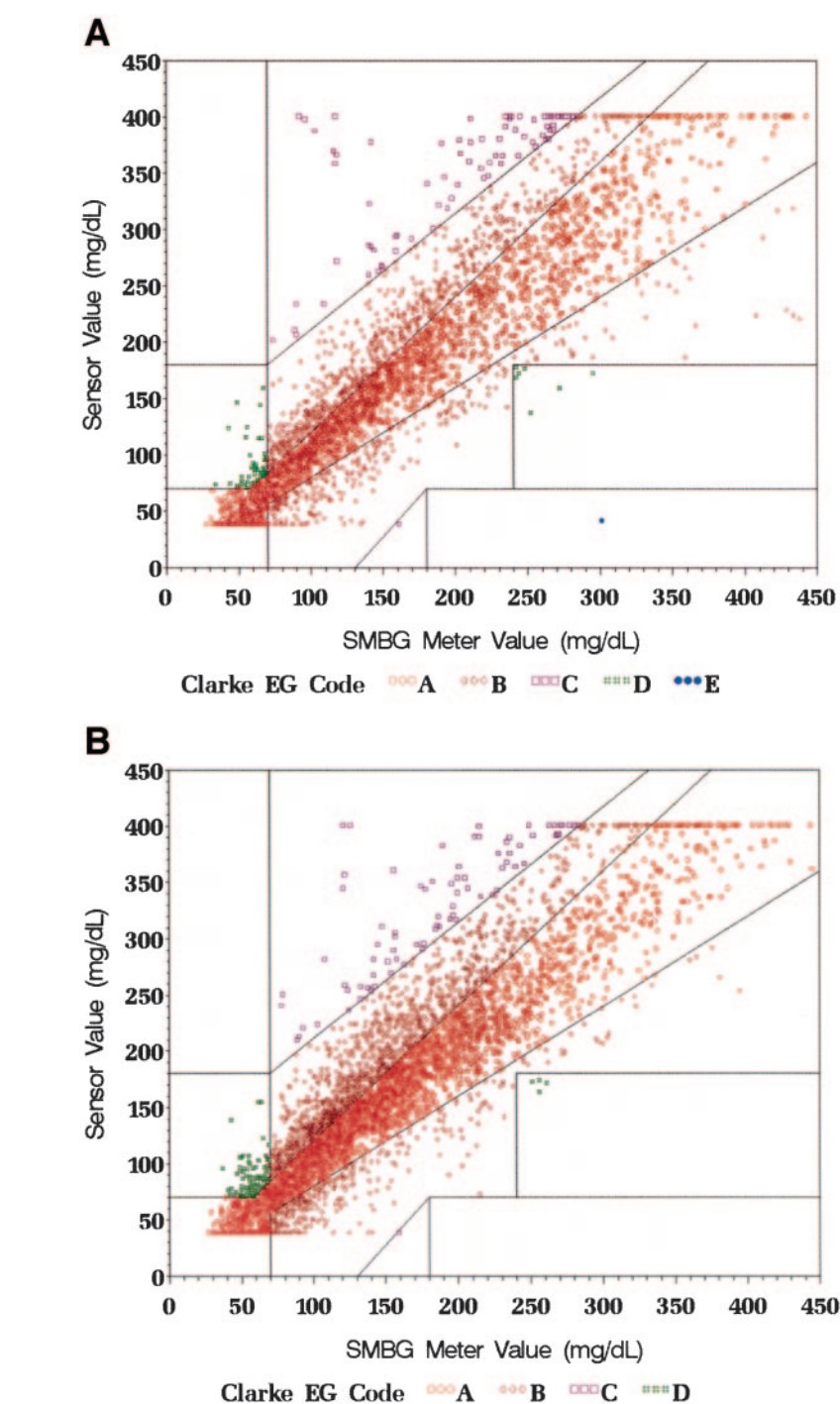


Figure 2—A: In-clinic Clarke error grid. In-clinic data obtained from the control group during the two 12-h in-clinic sessions of insertion period 1 (hours 0–12 and 48–60), total of 2,846 matched pairs (95.3% in regions A + B). Clarke error grid region A, clinically accurate (deviate from reference by <20%); region B, errors would lead to benign or no treatment; region C, errors would result in overcorrecting acceptable blood glucose levels; region D, errors represent dangerous failures to detect and treat; region E, erroneous treatment zone (treatment decisions opposite of what is required). B: Home use Clarke error grid. Home use includes data from both the control group (insertion periods 2 and 3) and the display group (insertion periods 1, 2, and 3), a total of 3,921 matched pairs (95.5% in regions A + B).

dl, and 3) a low alarm for glucose ≤55 mg/dl. During insertion periods 2 and 3 (combined) the control group experi-

enced a total of 197 hypoglycemic events (SMBG ≤55 mg/dl). If the STS System had been unblinded, 188 (95%) of these

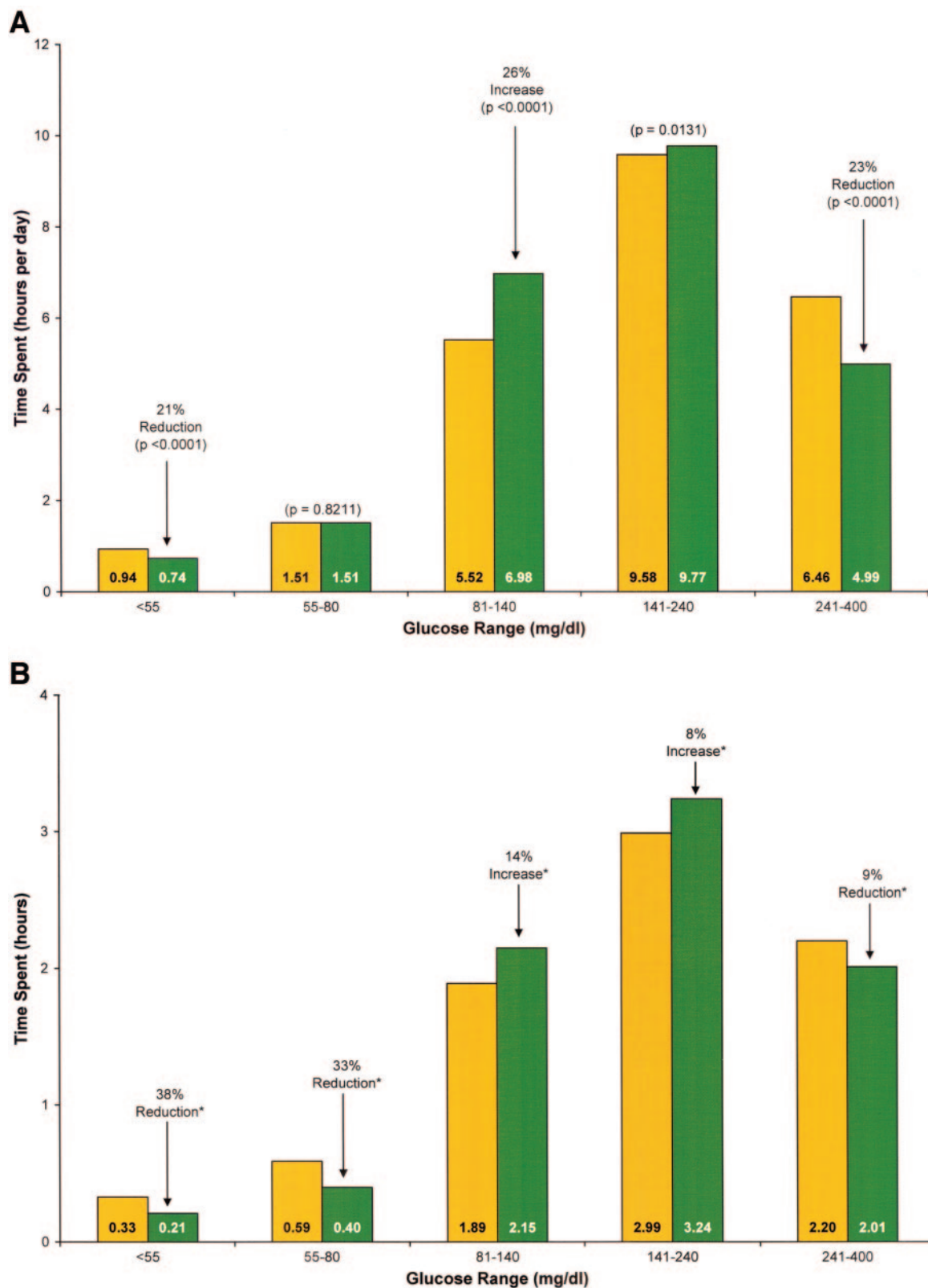


Figure 3—A: Time spent (hours per day) in glucose ranges: control group versus display group (periods 2 and 3). The control group (yellow bars) was blinded to sensor data (and alerts/alarms) whereas the display group (green bars) was unblinded and was provided with high and low alerts/alarms. Patients randomly assigned to the display group spent 26% more time in the target glucose range (80–140 mg/dl) compared with the control group ($P < 0.0001$). The display group also spent 21% less time in the hypoglycemic range (<55 mg/dl) and 23% less time in the hyperglycemic range (>240 mg/dl) compared with the control group ($P < 0.0001$ for both comparisons). B: Nighttime hours (10:00 P.M. to 6:00 A.M.) spent in various glucose ranges: control group versus display group (periods 2 and 3). Control group (blinded) (yellow bars) and display group (unblinded) (green bars). Patients in the display group spent significantly less time in hypoglycemic and hyperglycemic ranges ($P < 0.0001$), with more time spent in the target range ($P < 0.0001$). * $P < 0.0001$.

Period 1:
Median Glucose (min, max)
 = 200 mg/dl (42, 350)
Mean Glucose \pm Stdev
 = 200 \pm 69 mg/dl

Period 2:
Median Glucose (min, max)
 = 176 mg/dl (54, 334)
Mean Glucose \pm Stdev
 = 178 \pm 57 mg/dl

Period 3:
Median Glucose (min, max)
 = 148 mg/dl (60, 264)
Mean Glucose \pm Stdev
 = 150 \pm 42

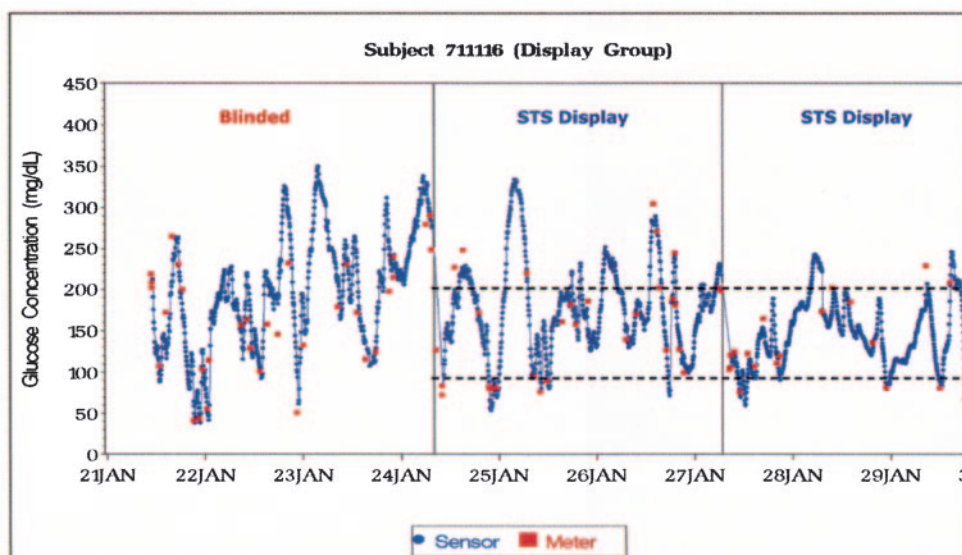


Figure 4—Glycemic pattern versus time for subject 71116. Once unblinded to sensor data, this subject's median glucose value was reduced. This improvement was observed within just 6 days of unblinded device use (during insertion periods 2 and 3) and without a prescribed regimen intended to modify therapy based on STS System values, alerts, or alarm.

events would have been preceded by at least one of the above warnings, and patients would have received (on average) 2.5 warnings before each event with a mean \pm SD lead-time (from warning to event) of 47 \pm 51 min.

Safety evaluation

Twenty-one adverse device effects were reported in 16 patients (17.5%). The events consisted of blister ($n = 1$), bullae around the site ($n = 1$), edema ($n = 2$), and erythema ($n = 17$). All were mild, required no treatment, and resolved within 7 days. There were no hypoglycemia events requiring assistance in the display group, but three such events (in two subjects) occurred in the control group.

CONCLUSIONS— This is the first randomized, controlled, multicenter study using the STS System. We report that patients, when given unblinded access to continuous glucose readings and alerts/alarms, were more effectively able to manage both hypo- and hyperglycemic episodes. This is evidenced by the fact that the display group spent, on average, 21% less time hypoglycemic (<55 mg/dl), 23% less time hyperglycemic (>240 mg/dl), and 26% more time in the target glycemic range (81–140 mg/dl) compared with control subjects. The in-group analysis of display group patients showed that they reduced the time spent in the hypoglycemic range by 9%, reduced the time spent hyperglycemic by 15%, and increased the time spent in the target gly-

cemic range by 16%. These results indicate that real-time access to continuous glucose measurements, coupled with alerts/alarms for high and low glucose values, significantly reduced glycemic variability. Also noteworthy is the fact that these improvements were observed within just 6 days of unblinded device use (during insertion periods 2 and 3) and without a prescribed regimen intended to modify therapy based on STS System values, alerts, or alarms. Device insertion, wear, and use appeared safe over three consecutive 3-day periods.

The ability to warn patients of impending hypoglycemia is another potential benefit of continuous glucose monitoring. The retrospective analysis of the hypoglycemia warning system of the device indicates that 95% of the occurrences of glucose \leq 55 mg/dl (by SMBG) experienced by the control group during insertion periods 2 and 3 would have been detected; and patients would have been warned, on average, 2.5 times before the hypoglycemic event during the preceding 47 min. Nocturnal hypoglycemic excursions place patients with insulin-treated diabetes at significant risk of acute complications. In this study, unblinded access to continuous glucose values reduced the duration of nocturnal hypoglycemia (<80 mg/dl) by 33% and decreased the time spent profoundly hypoglycemic (<55 mg/dl) by 38%.

Improvements in glucose excursions could potentially be explained by the frequency of follow-up during this 10-day

study, but both the control and display groups met with study personnel an equal number of times and received similar diabetes management education, which suggests that these differences are more likely explained by the patients' real-time access to continuous glucose values and the presence of associated low and high glucose alerts/alarms. Real-time continuous glucose readings improved the time spent in target glucose ranges while concurrently reducing the risk of hypoglycemia, which may improve patient outcomes; changes in A1C levels, however, were not evaluated because this was a 10-day study. Nevertheless, with evidence of reduced exposure to hyperglycemia along with reduced risk of hypoglycemia, HMOs are likely to reimburse use of continuous glucose sensors.

With current practice standards becoming more aggressive in their attempts to lower A1C values, hypoglycemia will increasingly become the limiting factor in the achievement of euglycemia. The availability of continuous glucose data to patients with low and high glucose alerts may impact quality of life, health care outcomes, and cost (13).

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References

1. The Diabetes Control and Complications Trial Research Group: The effect of intensive treatment of diabetes on the development and progression of long-term complications in insulin-dependent diabetes mellitus. *N Engl J Med* 329:977–986, 1993
2. UK Prospective Diabetes Study (UKPDS) Group: Intensive blood glucose control with sulphonylureas or insulin compared with conventional treatment and risk of complications in patients with type 2 diabetes (UKPDS 33). *Lancet* 352:854–865, 1998
3. The Epidemiology of Diabetes Interventions and Complications (EDIC) Study: sustained effect of intensive treatment of type 1 diabetes mellitus on development and progression of diabetic nephropathy. *JAMA* 290:2159–2167, 2003
4. Nathan DM: Effect of intensive diabetes management on cardiovascular events in type 1 diabetes. In *Proceedings of the 65th Annual Scientific Sessions of the American Diabetes Association, San Diego, CA, 10–14 June 2005*. Alexandria, VA, American Diabetes Association, 2005
5. The Diabetes Control and Complications Trial Research Group: The relationship of glycemic exposure (HbA_{1c}) to the risk of development and progression of retinopathy in the Diabetes Control and Complications Trial. *Diabetes* 44:968–983, 1995
6. Hirsch IB, Brownlee M: Should minimal blood glucose variability become the gold standard of glycemic control? *J Diabetes Complications* 19:178–181, 2005
7. Cryer PE, Davis SN, Shamoon H: Hypoglycemia in diabetes. *Diabetes Care* 26:1902–1912, 2003
8. Murata GH, Shah JH, Hoffman RM, Wendel CS, Adam KD, Solvas PA, Bokhari SU, Duckworth WC: Intensified blood glucose monitoring improves glycemic control in stable, insulin-treated veterans with type 2 diabetes: the Diabetes Outcomes in Veterans Study (DOVES). *Diabetes Care* 26:1759–1763, 2003
9. Klonoff DC: Continuous glucose monitoring: roadmap for 21st century diabetes therapy. *Diabetes Care* 28:1231–1239, 2005
10. Garg SK, Schwartz S, Edelman SV: Improved glucose excursions using an implantable real-time continuous glucose sensor in adults with type 1 diabetes. *Diabetes Care* 27:734–738, 2004
11. Deming WE: *Statistical Adjustment of Data*. New York, Dover, 1964
12. Clarke WL, Cox D, Gonder-Frederick LA, Carter W, Pohl SL: Evaluating clinical accuracy of systems for self-monitoring of blood glucose. *Diabetes Care* 10:622–628, 1987
13. Nordfeldt S, Jonsson D: Short-term effects of severe hypoglycaemia in children and adolescents with type 1 diabetes: a cost-of-illness study. *Acta Paediatr* 90:137–142, 2001