



TITLE: **Continuous Glucose Monitoring Devices in
Diabetes Mellitus:**

- **CGMS System**
- **GlucoWatch Biographer**

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CONTINUOUS GLUCOSE MONITORING DEVICES IN DIABETES MELLITUS

INTRODUCTION

The California Technology Assessment Forum is requested to review the scientific evidence for the use of continuous blood glucose monitoring devices in patients with diabetes mellitus. These devices are intended for use as an adjunct to, and not a replacement for, fingerstick self-monitored blood glucose.

BACKGROUND

Diabetes mellitus

Diabetes has been classified into type 1 diabetes mellitus, characterized by lack of insulin production, and type 2 diabetes, characterized by insulin resistance. An estimated 17 million people in the United States are known to have diabetes mellitus, of whom 1.4 million have type 1 diabetes. Current management guidelines recommend target pre-prandial (pre meal) blood glucose values of 90 to 130 mg per deciliter, peak post-prandial (after meal) blood glucose values <180 mg per deciliter, and hemoglobin A1c (HbA1c) levels of $\leq 7.0\%$ (American Diabetes Association 2003).

Chronically uncontrolled hyperglycemia leads to a wide range of adverse health outcomes including retinopathy, nephropathy, neuropathy, and cardiovascular disease. These complications result in significant morbidity and mortality for patients with diabetes. Strategies to prevent or reduce the occurrence of secondary diabetic complications have been intensively studied.

Intensive management of glucose levels

Two large randomized controlled trials have demonstrated that intensive management of blood glucose levels reduces the rate of diabetic complications compared with conventional management. However, intensive management was also associated with a 3-fold increase in the rates of severe hypoglycemic events. Intensive management of diabetes mellitus consists of three or more daily injections of insulin, use of an insulin pump, or use of oral agents to achieve normoglycemia.

BACKGROUND, continued

The Diabetes Control and Complications Trial (DCCT)

The Diabetes Control and Complications Trial randomized 1441 patients with insulin-treated diabetes to either intensive management or conventional therapy (1993). The primary endpoint was diabetic retinopathy. Secondary outcomes included renal, neurologic, cardiovascular, and neuropsychological outcomes and adverse effects associated with the treatment regimens.

Patients in the DCCT had a mean age of 27 years and were followed for an average of 6.5 years. At baseline the median HbA1c level was 8.9%. In the intensive treatment arm, HbA1c dropped to median of about 7% while patient in the usual care group maintained a median HbA1c of 9%.

Patients without retinopathy at baseline who received intensive glucose management had a 76% (95% CI: 62-85%) reduction in retinopathy compared to patients randomized to usual care. Among participants with retinopathy at baseline who were randomized to intensive therapy, there was a 54% (95% CI: 39-66%) reduction in progression of retinopathy. Furthermore, intensive therapy significantly reduced the risk of microalbuminuria (39%), albuminuria (54%), and clinical neuropathy (60%). The incidence of major cardiovascular and peripheral vascular events was low as expected in this young cohort (0.5 events per 100 person-years vs. 0.8 events, RR 0.59, 95% CI 0.32-1.10). Mortality was not reduced by intensive therapy with a trend towards more deaths in the intensively treated group (7 deaths among those randomized to intensive therapy vs. 4 deaths in the usual care group).

Intensive therapy was associated with more than a three-fold increased risk of severe hypoglycemia defined as an episode with symptoms consistent with hypoglycemia in which the patient required the assistance of another person and was associated with a blood glucose level < 50 mg/dl or prompt recovery after therapy for hypoglycemia. The rate of severe hypoglycemia was 62 episodes per 100 person-years in the intensive therapy group versus 19 episodes per 100 person-years in the usual care group. During 5 years of follow-up, 60% of patients in the intensive therapy group experienced at least 1 severe hypoglycemic event and 36% experienced 3 or more. Severe hypoglycemic events can be fatal.

BACKGROUND, continued

The United Kingdom Prospective Diabetes Study (UKPDS).

The United Kingdom Prospective Diabetes Study (UKPDS) enrolled 3,867 patients with a new diagnosis of type 2 diabetes who had persistent elevation of fasting blood glucose (between 110 and 270 mg/dL) after 3 months of dietary treatment (1998). The study compared intensive glycemic management with medications (goal fasting blood glucose < 108 mg/dL) to conventional management: diet therapy alone until fasting blood glucose levels were greater than 270 mg/dL. The primary outcome was the incidence of any diabetes-related endpoint (sudden death, death from hyperglycemia or hypoglycemia, myocardial infarction, angina, heart failure, stroke, peripheral vascular disease, renal failure, amputation, retinopathy, blindness or cataract extraction). Secondary outcomes included diabetes-related death and all-cause mortality.

Patients in the UKPDS had a mean age of 53 years and were followed for a median of 10 years. At baseline the median HbA1c level was 7.1%. In the intensive treatment arm, HbA1c was maintained at about 7% during follow-up while patients in the usual care group maintained a median HbA1c of 7.9%.

Patients in the intensive management group had a 12% lower risk of any diabetes-related endpoint (95% CI: 1-21%) compared to patients randomized to conventional management.. The intensive management group also had a non-significant 10% reduction in diabetes-related death (p=0.34) and a non-significant 6% reduction in all-cause mortality (p=0.44). The most significant factor was a reduction in microvascular endpoints with a 25% reduction (95% CI: 7-40%).

As in the DCCT, there was a significant two- to three-fold increased risk of severe hypoglycemic events. The rate of severe hypoglycemia was 1.8 episodes per 100 person-years in the intensive therapy group treated with insulin, 1.2 episodes per 100 person-years in the intensive therapy group treated with oral therapy, versus 0.7 episodes per 100 person-years in the usual care group.

BACKGROUND, continued

The United Kingdom Prospective Diabetes Study (UKPDS), continued Post-hoc observational analyses in both the DCCT and UKPDS suggest that there is a continuous reduction in microvascular and macrovascular complications of diabetes: for every 1% lowering of HbA1c from greater than 10% down to 6%, there is a corresponding reduction in complications of between 12-43%. There was no clear threshold below which benefits stopped accruing. Observational studies including patients with and without diabetes suggest that this relationship continues for HbA1c levels below 5% (Khaw *et al.* 2001). Although observational studies cannot demonstrate a cause-effect relationship, they can estimate the potential dose effect.

Hypoglycemia

Severe hypoglycemic episodes were the major adverse events associated with intensive therapy in both the DCCT and the UKPDS. Untreated severe hypoglycemic episodes may result in coma, seizures, and even death. Furthermore, avoidance of hypoglycemia in children may be of particular importance because of the potential sensitivity of the developing neurological system. The authors of one study examining neuropsychiatric function of children with diabetes suggest that children with recurrent hypoglycemia may accumulate long term deficits in verbal knowledge, even if the brain is not permanently damaged (Northam *et al.* 2001).

Blood glucose monitoring

Currently, many outpatients with both type 1 and type 2 diabetes mellitus monitor their blood glucose levels one or more times each day, using fingerstick blood sampling and analysis with reagent strips and a portable glucose meter device. Test results are used to adjust insulin dosing, assess the response to exercise and meals, and prevent hypoglycemia. Performance of 4 or more self-monitored blood glucose (SMBG) tests per day is particularly important in type 1 diabetics receiving intensive insulin therapy. This is because the primary drawback of such intensive therapy is a several-fold increase in the occurrence of severe hypoglycemia (Group 1998). However, the finger pricks necessary to obtain the blood samples are painful and often inconvenient (Bantle *et al.* 1997).

BACKGROUND, continued

Blood glucose monitoring, continued

Perhaps for this reason, the long-term compliance with such monitoring has been poor (Fischer 1995). A 1993 study showed that 20% of patients with type 1 diabetes never tested their own blood glucose, and only 15% tested it at least 3 times a day (Harris *et al.* 1993). Furthermore, the precision of patients' fingerstick SMBG is weak, sometimes leading to wrong or even dangerous therapeutic decisions. Conventional SMBG recordings, even if performed multiple times per day, often may not sufficiently reflect an individual's true diurnal blood glucose profile (see discussion of Bolinder *et al.*, 1997 below).

Continuous Glucose Monitoring Technologies

Recently, significant progress has been directed toward the development of minimally invasive or non-invasive continuous glucose monitoring approaches (Mastrototaro 1999), although all of the current technologies require regular fingerstick blood glucose monitoring as well for calibration of the devices and because the values are not available in real time. Several technologies have been studied: 1) subcutaneous interstitial fluid sampling by microdialysis or open-tissue microperfusion; 2) implantable subcutaneous glucose sensors; 3) transdermal glucose monitoring systems; and 4) optical glucose sensors (Heinemann *et al.* 1998). With regard to the first two of these technologies, the interstitial fluid of non-glucose producing tissues has been studied extensively as a site for continuous glucose monitoring. Because of easy access, the subcutaneous tissue has been preferred (Fischer 1995). A host of studies have shown that the interstitial fluid glucose concentration is practically identical to that in the blood (Bolinder *et al.* 1992; Bolinder *et al.* 1993), both under steady state conditions and after a meal or glucose load. For example, Bantle and colleagues (Bantle *et al.* 1997) reported a direct comparison of plasma glucose, fingerstick capillary blood glucose and dermal interstitial fluid glucose measurements in 17 subjects with type 1 diabetes during a 5-hour pre- and postprandial period when plasma glucose was changing rapidly. Results showed that dermal interstitial fluid glucose was highly correlated with plasma glucose ($r = 0.95$, $p < .0001$).

BACKGROUND, continued

Continuous Glucose Monitoring Technologies, continued

The mean absolute and percent differences between dermal interstitial fluid glucose and plasma glucose were 21 mg/dL and 10.6%, respectively. Capillary blood glucose values were not better correlated with plasma glucose values than were the dermal interstitial fluid glucose values (Bantle *et al.* 1997). Other studies have shown that the mean tissue glucose level correlates significantly ($r = 0.56$, $p < .01$) with the diabetic patient's HbA1c value (Bolinder *et al.* 1997). Thus, investigators have concluded that dermal interstitial fluid glucose can be used to estimate plasma glucose.

1. Subcutaneous Interstitial Fluid Sampling/Microdialysis Techniques

Direct monitoring of blood glucose concentrations by means of double- or single-lumen cannulas, either with or without microdialysis devices, has been useful in research. For example, Bolinder *et al.* (Bolinder *et al.* 1997) used a microdialysis technique for continuous monitoring of adipose tissue glucose in 24 type 1 diabetic outpatients during a 3-day study period. The hourly microdialysis glucose profiles were compared with those obtained by fingerstick SMBG performed 7 times a day. Results showed that in 7 (29%) patients, the SMBG profiles showed highly inaccurate results (>5 -6 major inconsistencies) as compared to the continuous microdialysis glucose recordings and in 13 (54%) patients the SMBG results were moderately inaccurate (3-4 major inconsistencies). In only 4 patients (17%) did SMBG provide a valid reflection (0-2 inconsistencies) of the diurnal glucose profile. The inaccuracy of the SMBG data was due more often to the fact that wide glucose swings remained unrecognized, rather than to erroneous testing techniques ($p < .05$), and it was more evident during the night ($p < .05$). The investigators concluded that in many type 1 diabetic patients, the true diurnal variability in glucose levels is too great to be accurately reflected even by frequent (7 x daily) SMBG. However, clotting problems have prevented the application of continuous microdialysis measurements in subcutaneous tissue over intervals longer than approximately 24 hours (Fischer 1996).

BACKGROUND, continued

Continuous Glucose Monitoring Technologies, continued

2. Implantable Subcutaneous Glucose Sensors

Researchers have also developed electroenzymatic glucose sensors intended for in vivo implantation (Johnson *et al.* 1992; Fischer 1995). In these sensors, glucose oxidase catalyzes the reaction of glucose and oxygen to form hydrogen peroxide and gluconic acid; the amount of reaction is directly proportional to the prevailing glucose concentration.

The sensor measures electrochemically either the amount of oxygen consumed or the amount of hydrogen peroxide formed by the enzymatic reaction. In tests of electroenzymatic glucose sensors implanted in the subcutaneous tissue of normal human subjects, there has been excellent correlation between subcutaneous glucose concentrations measured by the sensor and capillary fingerstick blood glucose levels measured by a commercial analyzer (Johnson *et al.* 1992). Sensors implanted in the subcutaneous tissue of the abdomen have functioned safely and accurately in monitoring blood glucose levels continuously for 72 hours. Typically, following injection of a local anesthetic, the portion of the sensor containing the electrodes is aseptically inserted into the subcutaneous tissue with an 18- gauge hypodermic needle. Sensor signals reflect the actual tissue glucose concentration, but must sometimes be calibrated against the plasma glucose level (Ishikawa *et al.* 1998). Published studies indicate that sensors are accurate for monitoring subcutaneous tissue glucose concentrations ranging from approximately 40 mg/dL to approximately 400 mg/dL (Johnson *et al.* 1992; Ishikawa *et al.* 1998; Bode *et al.* 1999). In 6 non-diabetic individuals, the average error of the sensor (difference between the glucose values obtained by the sensor and those obtained by capillary fingerstick) ranged between 6.8 mg/dL and 12.0 mg/dL over 3 separate 24-hour implantation periods. Study subjects did not report pain or discomfort during the test periods or following removal of the sensors, and no infections or irritation were documented.

BACKGROUND, continued

Continuous Glucose Monitoring Technologies, continued

The **Continuous Glucose Monitoring System (CGMS)**, MiniMed, Inc.) is comprised of a disposable subcutaneous glucose sensing device connected by a cable to a pager-sized glucose monitor. The system measures the subcutaneous tissue glucose level every 10 seconds and stores an average value every 5 minutes, for a total of 288 measurements each day. ***CGMS does not provide glucose information directly to the patient.*** A communication device enables the data stored in the monitor to be downloaded and retrieved on a personal computer at the end of the 72-hour monitoring period. Review of the data is intended to help the clinician and patient to identify periods of glucose highs and lows. This information may be used to suggest specific changes in the timing and dosing of insulin infusion (by pump) or injection (by syringe), dietary modifications, and changes in the timing and frequency of SMBG measurements (Bode *et al.* 1999). It may be particularly useful in the care of patients who are difficult to control due to rapidly fluctuating glucose levels. It is not a substitute for SMBG.

3. Transdermal Glucose Monitoring Systems

In 1995, Tamada *et al* (1995) reported that a glucose flux obtained transdermally through the use of a low-level electric current showed a quantitative relationship to plasma glucose. While glucose transport correlated well with blood glucose in a linear manner, the sensitivity (i.e., the amount to glucose extracted compare with the blood glucose) varied among individuals and between skin sites. Calibration with the blood glucose was found to compensate for this variability.

The **GlucoWatch Automatic Glucose Biographer** (Cygnus, Inc., Redwood City, CA) is based upon this transdermal method of obtaining subcutaneous glucose samples. It combines reverse iontophoresis (described below) with an electrochemical sensor to make frequent glucose measurements, up to once every 20 minutes for up to 12 hours. These data provide information on glucose patterns and trends (Garg *et al.* 1999; Tamada *et al.* 1999). The GlucoWatch biographer uses a constant, low-level electrical current conducted through the skin between an anode and cathode (a process known as reverse iontophoresis) to extract glucose through the skin and uses an electrochemical-enzymatic sensor to measure the amount of glucose in the extracted sample.

BACKGROUND, continued

Continuous Glucose Monitoring Technologies, continued

Glucose extraction and detection are achieved using 2 hydrogel pads placed against the skin and an electrode assembly in contact with the hydrogel pads and the biographer electronics. A single fingerstick blood glucose measurement obtained 3 hours after application of the GlucoWatch is required for initial calibration of the biographer. The entire process of glucose determination requires about 20 minutes, yielding a maximum of 3 glucose measurements per hour. Thus, the GlucoWatch biographer values lag behind the corresponding blood glucose values by about 20 minutes. Because it requires 20 minutes to determine the average glucose, this procedure creates a “moving average” type of measurement that is conceptually somewhat different from the “single point in time” blood glucose values obtained with current SMBG devices. A schematic diagram of the sensor operation of the GlucoWatch biographer is found in Garg *et al* (Garg *et al.* 1999) and a photograph and full description of the device is found in Tamada *et al* (1999). The GlucoWatch G2 Biographer determines glucose levels every 10 minutes and stores up to 6 glucose measurements per hour. However, all of the clinical studies published at the time of this review have used the first generation GlucoWatch Biographer.

In contrast to the CGMS device, the GlucoWatch biographer allows the user to define alarm settings for high and low glucose readings in order to detect unsuspected hyper- or hypoglycemic episodes. The manufacturer recommends that these values be confirmed with SMBG as there are false alarms, particularly with low blood glucose readings.

4. Optical Glucose Sensors

Optical glucose sensors, which estimate subcutaneous glucose levels by light absorption measurements, are currently under development. They rely upon the fact that variation of blood glucose levels changes the light scattering properties of skin tissue (Heinemann *et al.* 1998). However, clinical trial data are not yet available, so the technology will not be further discussed here.

BACKGROUND, continued

The Role of Continuous Glucose Monitoring

Continuous glucose monitoring can be used both for warning about hypoglycemia and for conducting general intensified metabolic “checkups” under outpatient conditions (Fischer 1995). The potential advantage of continuous glucose monitoring is that it allows the identification of the general patterns and trends of glucose levels in a given patient in a manner not currently available with periodic blood glucose monitoring. Measuring blood glucose values every 5 to 10 minutes gives a much more complete picture of blood glucose patterns than even the 7 checks a day used in the DCCT. Knowledge of these patterns and excursions may enable the clinician and patient to make appropriate changes in diabetes management (Bode *et al.* 1999). Ideally, this will result in improved glycemic control (lower HbA1c) with fewer hypoglycemic episodes and a lower incidence of micro- and macrovascular diabetes complications. One concern is that tighter control will increase the frequency of severe hypoglycemic episodes as documented in the DCCT and UKPDS.

TECHNOLOGY ASSESSMENT (TA)

TA Criterion 1: The technology must have final approval from the appropriate government regulatory bodies.

The Continuous Glucose Monitoring System (CGMS, MiniMed, Inc., Sylmar, CA) received FDA 510k approval on June 15, 1999. The MiniMed system was approved for use based on experience in type 1 diabetics. This device is intended to continuously record interstitial glucose levels in persons with diabetes mellitus. This information is intended to supplement, not replace blood glucose information obtained by using standard home glucose monitoring devices. In addition, in its approval letter the FDA notes: “The system is intended for prescription use only, will not allow readings to be made available directly to patients in real time, provides readings that will be available for review by physicians only after the entire recording interval (suggested as 72 hours), is currently intended for occasional rather than everyday use, is to be used only as a supplement to, and not a replacement for, standard invasive measurement, is not intended to change patient management based on the numbers generated, but to guide future management of the patient based on response to trends noticed.



TA Criterion 1: The technology must have final approval from the appropriate government regulatory bodies, (continued)

That is, these trends or patterns may be used to suggest when to take fingerstick glucose measurements to better manage the patient”. As a condition of approval, the FDA required the manufacturer to conduct post-marketing studies to assess its safety and effectiveness in persons with type 2 diabetes, children with diabetes, gestational onset of diabetes, diabetics with concomitant disease states, long- and short-term duration diabetics, non-Caucasian diabetics.

The GlucoWatch Automatic Glucose Biographer (Cygnus, Inc., Redwood City, CA) received FDA approval on March 22, 2001. A supplement was approved to extend the approval to a second generation model, the GlucoWatch G2 biographer on March 21, 2002. according to the FDA, the device is intended for use in detecting trends and tracking patterns in glucose levels in children and adults with diabetes. This information is intended to supplement, not replace blood glucose information obtained using standard home glucose monitoring devices. In addition, the system is intended for use in the detection and assessment of episodes of hyperglycemia and hypoglycemia, facilitating both acute and long-term therapy adjustments, which may minimize these excursions. Interpretation of Biographer results should be based on the trends and patterns seen with several sequential readings over time.

TA Criterion 1 is met.

TA Criterion 2: The scientific evidence must permit conclusions concerning the effectiveness of the technology regarding health outcomes.

Almost all studies limited participation to type 1 diabetics or type 2 diabetics who were receiving therapy with insulin. Outcomes assessed in the various clinical trials summarized below include: accuracy and precision of continuous glucose monitoring results compared to plasma or capillary (fingerstick) blood glucose measurements and adverse effects, such as pain, irritation, or infection at sensor insertion or application sites. Ideally, trials would report data on important clinical outcomes such as retinopathy, renal function, neuropathy, heart attacks and strokes.

TA Criterion 2: The scientific evidence must permit conclusions concerning the effectiveness of the technology regarding health outcomes, (continued)

However, long-term control of hyperglycemia (HbA1c levels), avoidance of hypoglycemic episodes, and quality of life are adequate surrogate markers given the findings from the DCCT and the UKPDS. Change in the incidence of hypoglycemia is particularly important as one study (Desouza *et al.* 2003) has documented a statistically significant increase in the frequency of ischemia during hypoglycemia compared with normoglycemia ($p < 0.01$). Ischemic heart disease is the leading cause of death in patients with diabetes.

1. Implantable Subcutaneous Glucose Sensors (CGMS)

At least 12 case-series have been published assessing the accuracy of the CGMS device compared to conventional measures of blood glucose including SMBG, traditional laboratory measures of blood glucose, and HbA1c. Many of these studies reported on adverse events and the incidence of hypoglycemic events detected by the device. Seven studies reported adjusting insulin regimens based on the CGMS results and followed the patients for several months to assess the effects of the adjustments on glycemic control. Three of these studies had controls: a pilot study that randomized 11 patients (Chase *et al.* 2001), a larger randomized trial of 75 patients (Chico *et al.* 2003), and one cross-over study of 27 patients (Ludvigsson *et al.* 2003). All 3 studies with controls enrolled only patients with type 1 diabetes.

Level of Evidence: 2, 5

2. Transdermal Glucose Monitoring System (GlucoWatch biographer)

The GlucoWatch biographer literature is more difficult to assess. The majority of the published literature shares co-authors and most of the studies are reported in at least 3 publications (Garg *et al.* 1999; Tamada *et al.* 2000a; Tierney *et al.* 2000b; Pitzer *et al.* 2001; Tierney *et al.* 2001; Eastman *et al.* 2002; Potts *et al.* 2002). For example, the paper by Tierney *et al.* (2000b) summarizes 6 studies which appear to include all of the participants in the earlier reports of Garg and Tamada (Garg *et al.* 1999; Tamada *et al.* 1999).

TA Criterion 2: The scientific evidence must permit conclusions concerning the effectiveness of the technology regarding health outcomes, (continued)

Level of Evidence: 2, 5

2. Transdermal Glucose Monitoring System (GlucoWatch biographer), continued

The report of Pitzer *et al* (Pitzer *et al.* 2001) summarizes 4 of the same 6 studies with the same number of participants in the 4 studies, but more data points for 3 of the studies and half the data points in the 4th. All of these studies are case series that assess the accuracy of the device when used in a controlled clinical setting or at home. The summary of the studies reported below may include some duplication because of the overlapping evidence. None of the above studies included controls.

One randomized, controlled trial (n=40) has been published comparing outcomes in patients using the GlucoWatch Biographer to outcomes in patients using only intermittent capillary (fingerstick) blood glucose monitoring (Chase *et al.* 2003).

Level of Evidence: 2, 5

TA Criterion 2 is met.

TA Criterion 3: The technology must improve the net health outcomes.

1. Implantable Subcutaneous Glucose Sensors (CGMS)

Accuracy

Ishikawa *et al* (1998) reported results of the initial clinical evaluation of a subcutaneously implanted, microsensor-based amperometric glucose-monitoring system. Flexible wire microsensors were subcutaneously implanted for up to 3 days in 10 non-diabetic and 10 insulin-dependent-diabetic volunteers. All subjects ate standard meal tests and underwent intravenous glucose-tolerance tests.

TA Criterion 3: The technology must improve the net health outcomes (continued)

1. Implantable Subcutaneous Glucose Sensors (CGMS)

Accuracy, continued

Sensor readings were compared to hourly plasma glucose measurements. The sensor signals were continuously recorded, and the glucose concentration estimates were derived after initially calibrating the sensor using a single blood sample (one-point calibration). Regression analysis revealed that the sensor estimated glucose concentrations were linearly related to the plasma glucose concentrations ($R^2 = 0.75$) over a wide glucose concentration range (33-466 mg/dL). The mean difference between the estimated and actual glucose concentration was -2.2 ± 3.8 mg/dL. Overall, 95% of sensor readings were considered to be clinically accurate or acceptable predictions of the plasma glucose. In addition, the sensors responded promptly to acute changes in blood glucose. The sensing “rise time” was fast enough to track the sudden increase in glucose concentration during the intravenous glucose tolerance test. The sensing “delay time,” defined as the time that elapsed between the intravenous glucose bolus and the time at which the sensor detected its maximal value, was 10.4 ± 2.3 minutes.

Mastrototaro (1999) summarized results of a multicenter clinical study of the Continuous Glucose Monitoring System (CGMS) conducted by MiniMed, Inc. in support of their FDA PMA application. The study was designed to compare the accuracy of CGMS glucose trends compared to periodic glucose measurements obtained from a blood glucose meter. The study also assessed the length of useful device life, changes in performance over the device’s life, and differences in performance following sensor insertion by the clinician versus the patient. Overall, 62 outpatients were enrolled at 4 clinical centers. Patients wore 5-10 glucose sensors for periods of up to 20 days, and tested their blood glucose approximately 11 times each day using a standard reference capillary blood glucose meter. The data collected and stored in the CGMS were compared to the values stored in the memory of the reference meter. The comparison involved more than 7,500 paired data points collected from more than 1,100 total days of sensor use. The accuracy of the CGMS was measured by comparing the average glucose difference between the CGMS and the reference meter.

TA Criterion 3: The technology must improve the net health outcomes (continued)

1. Implantable Subcutaneous Glucose Sensors (CGMS)

Accuracy, continued

On average, the CGMS reported glucose values 5.4 mg/dL less than the reference meter. There was a median daily correlation between the CGMS and the blood glucose of 0.92, suggesting the utility of the CGMS as a trending device. The 62 patients wore an average of 7 sensors consecutively for 18 days. The median functional half-life of the sensor was 69 hours. Sensor performance did not differ significantly between those inserted by the clinician and those inserted by the patient..

Gross *et al* examined the performance of the CGMS among 135 patients with diabetes during home use (Gross *et al.* 2000a). Patients had glucose sensor implantation in the clinic and wore the device at home for 3 or more days. The blood glucose values obtained by the CGMS were then compared to those obtained by routine SMBG. The correlation in values was very high ($r=0.91$) and the mean absolute difference in glucose values was $18.0 \pm 19.8\%$. Overall, 96.2% of sensor readings were considered to be clinically accurate or acceptable predictions of the plasma glucose. The authors concluded that the CGMS performed reliably and accurately under routine outpatient conditions.

Gross and Ter Veer (2000) reported the results of a postmarketing surveillance study requested by the FDA as a condition for approval. 238 patients from 13 clinical sites wore 278 devices for a total of 961 days. There were 4,015 paired sensor and SMBG values using the patients' home meter. The patients were 35.6 years old and 57% were female. Most were type 1 diabetics (83%) with an average HbA1c of 7.9%. There was excellent agreement between the paired readings with a correlation coefficient of 0.91 and a median absolute difference of 12.6%. No significant differences in CGMS performance were noted in subgroups based on age (adult vs. pediatric), ethnicity (Caucasian vs. non-Caucasian), chronic illness, or duration of diabetes. Minimal differences were noted between type 1 ($r=0.91$) and type 2 ($r=0.88$) diabetics. Pregnant women showed a lower correlation ($r=0.84$) than nonpregnant women (0.90). These differences are unlikely to be clinically important.

TA Criterion 3: The technology must improve the net health outcomes (continued)

1. Implantable Subcutaneous Glucose Sensors (CGMS)

Accuracy, continued

The authors conclude that CGMS can be used with confidence in a wide range of patient populations to supplement SMBG.

Salardi *et al* (2002) studied whether CGMS 1) was sufficiently representative of the overall metabolic control as assessed by HbA1c; 2) could be used to identify a particular blood glucose threshold value affecting hemoglobin glycation; and 3) was able to show any relationship between particular glycemic profiles and HbA1c levels. Of 44 pediatric patients with type 1 diabetes who wore CGMS devices, 28 subjects were selected for the study. Criteria for inclusion were high levels of HbA1c (> or =8%) for more than 1 year or a history of frequent hypoglycemic episodes and a complete CGMS registration for 72 h. Age of the subjects ranged from 5.7 to 24.8 years, the mean duration of disease was 7.63 +/- 4.75 years, and the mean HbA1c value was 8.7 +/- 1.3%. The glucose profiles showed a high frequency of prolonged hyperglycemic periods (80% of subjects) and a low frequency of postmeal glycemic peaks (29% of subjects). Postlunch values were significantly correlated with HbA1c levels, but the correlation disappeared when controlling for glucose area values. Glucose area values significantly correlated with HbA1c levels both when considered as a whole (40-400 mg/dl; $r = 0.53$, $P = 0.002$) and when considered fractionated (40-150, 40-200, 40-250, 40-300 mg/dl), apart from the 40-90 mg/dl partial area. Three-day glucose profiles are representative of the overall glucose control, because glucose area values correlate with HbA1c levels. The only glucose threshold below which there seems to be no correlation with HbA1c is 90 mg/dl. Only glucose area, and not postprandial glucose values, are directly and independently correlated with HbA1c. The authors conclude that to improve metabolic control, it is necessary to lower the whole mean 24-h glycemia and not just the postprandial glucose values.

TA Criterion 3: The technology must improve the net health outcomes (continued)

1. Implantable Subcutaneous Glucose Sensors (CGMS)

Accuracy, continued

Investigators around the world continue to perform small studies evaluating the accuracy of the CGMS device compared to capillary or plasma glucose levels. At least 5 more studies including a total of only 103 patients were published in 2002-2003 ((McGowan *et al.* 2002; Metzger *et al.* 2002; Monsod *et al.* 2002; Djakoure-Platonoff *et al.* 2003; Guerci *et al.* 2003). All confirmed good accuracy and fair precision for the device. However, the consistent message was that CGMS cannot be used as a replacement for glucose meters because it does not satisfy the standard performance requirements for glucometers. There were particular concerns that nocturnal glycemic measurements tended to be spuriously low (McGowan *et al.* 2002) and that nocturnal hypoglycemia should be confirmed independently before therapeutic decisions were made.

Glycemic control

There are four uncontrolled case series that report on the effects of CGMS on glycemic control. Additionally, there are three randomized studies: two using a parallel design and one using a cross-over design. In these studies, patients and their doctors review the glucose profile obtained from the CGMS to adjust their insulin regimens and are followed over time to assess the effects of the changes on glycemic control, usually measured by HbA1c.

Bode and colleagues (Bode *et al.* 1999) conducted a 10-week uncontrolled pilot study to determine if use of continuous glucose monitoring by the Continuous Glucose Monitoring System (CGMS) could improve glycemic control. The investigators enrolled a total of 9 study subjects with uncontrolled type 1 diabetes mellitus (HbA1c > 8.5%) despite intensive insulin therapy (insulin infusion pump or multiple daily injections). Following a baseline measurement of HbA1c, study subjects wore a continuous glucose monitor for a one-week period. Subjects also performed routine fingerstick SMBG for comparison. At the end of the first week, subjects returned to the clinician to have appropriate adjustments made to his or her diabetes management.

TA Criterion 3: The technology must improve the net health outcomes (continued)

Glycemic control, continued

The clinician first made therapeutic recommendations based on the subject's fingerstick glucose results. Then, after downloading the data from the continuous subcutaneous monitor and creating glucose profiles, the clinician recommended further changes in diet, insulin dosing and SMBG schedules. The subject then returned home to implement these adjustments for one week. At the beginning of the next week, this cycle was repeated, with one week of sensor wear, followed by data download and data review, refinement of subject's regimen and one further week of implementation. No further therapy adjustments were made, but HbA1c was repeated 8-12 weeks after the baseline measurement. The glucose monitors performed with good reliability and accuracy during the pilot study. Agreement between the continuous sensor subcutaneous glucose readings and the intermittent fingerstick glucose readings was quite high, with a median correlation of 0.92 and a mean absolute difference in values of 19.1%. Initial review of intermittent fingerstick glucose data failed to provide adequate information on which to base therapeutic adjustments in 8 of 9 patients. However, following CGMS download, all 9 patients showed clear trends in their glucose profiles that resulted in changes to their diabetes regimen. Of more import, subsequent mean HbA1c values decreased from 9.9% (SD 1.1%) at baseline to 8.8% (SD 1.0%) at 5 weeks ($p=.0006$), without a change in total daily insulin requirement ($p=N.S.$). At 10 weeks, without further changes to therapy, HbA1c was 8.6% (SD 1.2%), still significantly reduced from baseline ($p=.019$). Thus, unlike the intermittent fingerstick SMBG results, the continuous glucose profiles enabled the clinician to identify glucose patterns and excursions that helped direct changes in therapy, resulting in improved glycemic control.

While the authors concluded that additional studies are needed to validate their findings, the pilot study of these 9 patients showed the potential for continuous glucose monitoring to provide valuable information enabling therapy adjustments that could dramatically improve patients' glycemic control. As the study investigators acknowledge, results of an uncontrolled study like this must be interpreted with caution due to the lack of a randomized control group, the selection of patients with elevated HbA1c levels, and the potential influence of a Hawthorne effect.

TA Criterion 3: The technology must improve the net health outcomes (continued)

Glycemic control, continued

That is, patients' enrollment in a clinical study, expectation of increased scrutiny from clinicians, and the very act of wearing a device that the subjects knew would provide an unalterable continuous record of their subcutaneous glucose level, could have led by itself to increased patient compliance with their diabetes regimen and thus to improved glucose control (Bode *et al.* 1999).

Kaufman *et al* (2001) conducted a study to determine whether the CGMS could be used to make clinical decisions and whether it has an impact on glycemic control in pediatric type 1 diabetic subjects. Pediatric subjects were recruited if they had HbA1c >8.0% with management problems (n = 35) or episodes of severe or nocturnal hypoglycemia or hypoglycemia unawareness associated with HbA1c < or =8.0% (n = 12). A total of 47 patients with a mean HbA1c value of 8.6 +/- 1.6% (mean age 11.8 +/- 4.6 years, youngest 2.7 years, and diabetes duration 5.5 +/- 3.5 years) on three to four insulin injections/day (n = 24) or insulin pump therapy (n = 23) were followed with the CGMS for a mean of 69.5 +/- 28 h. Comparisons were made between the number of high (>150 mg/dl) and low (<70 mg/dl) glucose patterns discerned with the sensor or the logbook, and HbA1c levels were evaluated. In patients on injection therapy, 30 high or low glucose patterns were discerned with the logbook records and 120 patterns with the CGMS. Specific alterations of the diabetes regimen were made. An overall significant change in HbA1c, from 3 months before wearing the sensor to 6 months after (p=0.04), was found in the subjects. Post hoc analysis showed a significant change in HbA1c from 8.6 +/- 1.5% at baseline to 8.4 +/- 1.3% at 3 months (p=0.03). The authors concluded that CGMS could be used by pediatric patients to detect abnormal patterns of glycemia and that the information obtained could be used to alter the diabetes regimen and impact glycemic outcome. The absolute change in HbA1c was modest (0.2%) compared to that reported in the study of Bode *et al* (91.3% reduction). This may reflect the fact that patients in this study have a lower initial HbA1c level compared to that of Bode (8.6% vs. 9.9%).

TA Criterion 3: The technology must improve the net health outcomes (continued)

Glycemic control, continued

Salardi *et al* (2002). studied whether knowledge of the CGMS profile affected glycemic control over 6 months. Of 44 pediatric patients with type 1 diabetes who wore CGMS devices, 28 subjects with high levels of HbA1c (> or =8%) for more than 1 year or a history of frequent hypoglycemic episodes and a complete CGMS registration for 72 h were selected for follow-up. On average the patients were 14.8 years old and had baseline HbA1c levels of 8.7%. HbA1c levels were significantly decreased at 3 months (0.4%, $p=0.05$) and 6 months (0.4%, $p=0.03$) after use of CGMS. The authors conclude that using the information obtained with the CGMS may decrease HbA1c levels. In this study as well, the reduction in HbA1c was a modest 0.4% which could be due to a combination of regression to the mean as the subjects were picked partly due to elevated HbA1c levels and the Hawthorne effect.

Schiaffini *et al* (2002) designed a study primarily to evaluate whether CGMS would help to minimize the hypoglycemic risk in children with type 1 diabetes mellitus (see details in section on hypoglycemia below). Eighteen patients completed the 6-week study. At the beginning and end of the study, fructosamine, glycosylated hemoglobin (HbA1c), median glycemia, number and duration of hypoglycemic events and insulin requirement were measured. At the 6-week point, the fructosamine level was reduced (330 +/- 30 vs. 349 +/- 24 micro mol/l; $p < 0.05$) even though the total insulin dose was unchanged. Furthermore, there was a significant reduction in hypoglycemic events (2.5 vs. 3.9, $p < 0.05$). HbA1c was decreased minimally (7.5 vs. 7.6, p NS), although the length of follow-up is too short to expect to see a change in HbA1c. The authors conclude that CGMS is a useful device for modifying insulin therapy in order to reduce hypoglycemic events while improving overall glycemic control.

Chase *et al.* (2001) conducted a pilot study to determine whether the use of continuous subcutaneous glucose monitoring would help in detecting unrecognized nocturnal hypoglycemia and in lowering HbA1c levels (without increasing the risk for severe hypoglycemia) in children with type 1 diabetes.

TA Criterion 3: The technology must improve the net health outcomes (continued)

Glycemic control, continued

Eleven children with type 1 diabetes and HbA1c values consistently >8.0% were randomized either to the CGMS group or to the control group. The CGMS group used 6 3-day sensors within a 30-day period. Both groups self-monitored their blood glucose levels a minimum of 4 times daily. HbA1c levels were measured at the start, at 1-month, and after 3 months of study. The 5 children using the CGMS had 17 asymptomatic episodes (85%) of glucose levels below 60 mg/dL (3.25 mmol/L) and 3 symptomatic episodes (15%) during the night in the study month. The 6 control children had 4 symptomatic nocturnal low episodes during the month. After the 30-day period of wearing the CGMS, the 5 children had a significantly lower mean HbA1c level compared with their initial level (mean +/- standard error of the mean [SEM] decrease = .36% +/- .07%). The mean decrease in HbA1c level for the control was .2% +/- .2%. After 3 months, 4 of the 5 children who used the CGMS continued to have lower HbA1c values in comparison to their initial values (mean +/- SEM decrease = 1.04% +/- .43%). Three of the 6 control participants also had lower HbA1c values at 3 months (mean +/- SEM decrease for the group = .62% +/- .44%). No severe hypoglycemic events occurred in either the CGMS or the control groups. The authors conclude that in this pilot trial, continuous subcutaneous glucose monitoring was helpful in detecting asymptomatic nocturnal hypoglycemia as well as in lowering HbA1c values without increasing the risk for severe hypoglycemia in children with type 1 diabetes. This pilot study provides good data for designing a larger study, which could definitively answer the question of whether CGMS can lower HbA1c without increasing hypoglycemic episodes.

A second randomized clinical trial, by Chico *et al* (2003) evaluated whether CGMS was useful for investigating the incidence of unrecognized hypoglycemia in type 1 and type 2 diabetic patients and for improving metabolic control in type 1 diabetic patients. The investigators randomized 75 type 1 diabetics to a CGMS group (n=40) or a control group (n=35) using intensive capillary glucose measurements alone. Patients in the control group had insulin therapy modified based on at least 8 fingerstick glucose measurements per day for 3 days. 70 diabetic subjects (40 type 1 and 30 type 2 subjects) were monitored using the CGMS. The number of unrecognized hypoglycemic events was recorded.

TA Criterion 3: The technology must improve the net health outcomes (continued)

Glycemic control, continued

HbA1c levels were measured before the monitoring period and 3 months later. The CGMS detected unrecognized hypoglycemia in 62.5% of the type 1 diabetic patients and in 46.6% of the type 2 diabetic patients. They found that 73.7% of all events occurred at night. HbA1c concentrations decreased significantly in both the group of type 1 diabetic subjects monitored with the CGMS (from 8.3 +/- 1.6 to 7.5 +/- 1.2%, $P < 0.01$) and the control group (from 8.0 +/- 1.4 to 7.5 +/- 0.8%, $P < 0.01$). The greatest reduction was observed in the subgroup of patients who started continuous subcutaneous insulin infusion therapy, both in the CGMS-monitored and control groups (from 9.4 +/- 2 to 7.2 +/- 1.4% and from 8.1 +/- 1.8 to 7.1 +/- 0.6%, respectively). The authors conclude that CGMS was useful for detecting unrecognized hypoglycemia in type 1 and type 2 diabetic subjects; however, it is not better than standard capillary glucose measurements for improving metabolic control of type 1 diabetic subjects, regardless of the therapeutic regimen.

Several problems with this study limit its usefulness. The authors de-emphasized the randomized controlled trial in favor of the observational component of the study. They give few details about randomization, allocation concealment and follow-up. The differences between the CGMS and control group, including the imbalance in numbers, are unexplained. Furthermore, they do not compare the two groups directly. They perform examine the changes in HbA1c within each group, but do not give any figures comparing the changes between groups. Ideally, the authors would perform a t-test comparing the change in HbA1c level in the CGMS group (0.8% reduction) to that in the control group (0.5% reduction). The authors conclude that the use of CGMS was no better than SMBG, but offer no analyses to back that up.

Ludvigsson *et al* (2003) used CGMS in a randomized crossover study including 27 diabetic patients aged 12.5 +/- 3.3 (mean; standard deviation; range: 5-19) years. All patients were treated with intensive insulin therapy, 14 with multiple injections, and 13 with pumps. The patients were randomized into an open or blind study arm. Both arms wore the CGMS sensor for 3 days every 2 weeks.

TA Criterion 3: The technology must improve the net health outcomes (continued)

Glycemic control, continued

CGMS profiles were used in the open study arm to adjust insulin therapy at follow-up visits every 6 weeks. Both the patients and the diabetes team were masked to the CGMS profiles in the blinded arm, and insulin therapy adjustments were based solely on 7-point BG profiles performed by the patients. At 3 months the 2 study arms were crossed over. Despite initial problems with a device new to both patients and the diabetes team, HbA1c decreased significantly in the open arm (from 7.70% to 7.31%) but not in the blind arm (7.75% to 7.65%). At the end of 12 weeks the between group difference was significant ($p=0.011$), but the absolute difference was modest. A total of 26/27 patients experienced daytime low subcutaneous glucose (<3.0 mmol/L; .8 episodes/day; duration 58 +/- 29 minutes; 5.5% of total time), and 27/27 patients had at least 1 nocturnal episode of low subcutaneous glucose (.4 episodes/night; duration 132 +/- 81 minutes; 10.1% of total time). The authors concluded that the use of CGMS facilitated an improved treatment, and patients received new insight, increased motivation and improved metabolic control. A cross-over design is not ideal for investigating CGMS as significant carry-over effects would be expected in the group randomized to the open CGMS group. Changes in insulin regimen, diet, and exercise pattern made on the basis of the CGMS profile would remain in place after the cross-over to the “blind” study arm.

Hypoglycemic events

Boland *et al* (2001) studied 56 children with type 1 diabetes (age 2-18 years) who wore the CGMS for 3 days. Patients entered four fingerstick blood samples into the monitor for calibration and kept records of food intake, exercise, and hypoglycemic symptoms. Data were downloaded, and glycemic patterns were identified. Despite satisfactory HbA1c levels (7.7 +/- 1.4%) and premeal glucose levels near the target range, the CGMS revealed profound postprandial hyperglycemia. Almost 90% of the peak postprandial glucose levels after every meal were >180 mg/dl (above target), and almost 50% were >300 mg/dl. Additionally, the CGMS revealed frequent and prolonged asymptomatic hypoglycemia (glucose <60 mg/dl) in almost 70% of the children.

TA Criterion 3: The technology must improve the net health outcomes (continued)

Hypoglycemic events, continued

The authors conclude that despite excellent HbA1c levels and target preprandial glucose levels, children often experience nocturnal hypoglycemia and postprandial hyperglycemia that are not evident with routine monitoring. They suggest that repeated use of the CGMS may provide a means to optimize basal and bolus insulin replacement in patients with type 1 diabetes.

Salardi *et al* (2002) studied 28 subjects with high levels of HbA1c ($>$ or $=8\%$) for more than 1 year or a history of frequent hypoglycemic episodes and a complete CGMS registration for 72 h. Age of the subjects ranged from 5.7 to 24.8 years, the mean duration of disease was 7.63 ± 4.75 years, and the mean HbA1c value was $8.7 \pm 1.3\%$. The glucose profiles showed a high frequency of prolonged hyperglycemic periods (80% of subjects) and a low frequency of postmeal glyceemic peaks (29% of subjects). The authors conclude that to improve metabolic control, it is necessary to lower the whole mean 24-h glycemia and not just the postprandial glucose values.

Schiaffini *et al* (2002) designed a study to evaluate whether CGMS is sufficiently sensitive to detect asymptomatic hypoglycemia, and to determine if its periodic application would help to minimize the hypoglycemic risk in children with type 1 diabetes mellitus. Twenty-seven children (age range 6-13.1 years) were enrolled in the study. The sensor was inserted subcutaneously in each patient and the standard four or five registrations of capillary glycemia per day were performed. Eighteen patients continued in the study and the glucose sensor was again inserted after a 6-week interval. At the beginning and end of the study, fructosamine, HbA1c, median glycemia, number and duration of hypoglycemic events and insulin requirement were evaluated. A significantly higher number of asymptomatic hypoglycemic events were revealed by CGMS in comparison with the standard system (3.6 ± 2.3 vs. 0.7 ± 0.9 ; $p < 0.0001$). In patients who continued in the study, insulin therapy adjustments reduced the incidence of hypoglycemic events (2.5 ± 1.7 vs. 3.9 ± 2.2 ; $p < 0.05$).



TA Criterion 3: The technology must improve the net health outcomes (continued)

Hypoglycemic events, continued

They conclude that CGMS is a useful device not only for detecting unrecognized hypoglycemia, but also for modifying insulin therapy in order to reduce hypoglycemic events. The system appears to be useful in avoiding long exposure to hypoglycemia while maintaining or improving overall glycemic control.

Zavalkoff *et al* (Zavalkoff *et al.* 2002) used the CGMS to evaluate how well the customary intermittent SMBG correlates with integrated values during the surrounding time periods in ambulatory patients with type 1 diabetes. Eighteen young patients with type 1 diabetes were monitored with CGMS for up to 72 h, during which they continued to perform the four standard SMBG tests (preprandial and bedtime). Correlations were examined between each of the four standard SMBG tests and the mean CGMS values from defined periods that preceded and followed. They also tested how well a low bedtime SMBG predicted nocturnal hypoglycemia. Strong correlations were found between 1) SMBG at breakfast and the mean CGMS value for the preceding 8 h ($r = 0.7514$), 2) SMBG at dinner and the CGMS from lunch to dinner ($r = 0.7538$), 3) SMBG at bedtime and the CGMS from dinner to bedtime ($r = 0.8145$), and 4) SMBG at bedtime and the CGMS from bedtime to breakfast ($r = 0.6463$). The remaining correlations were weak and not statistically significant. These correlations were independent of insulin-delivery method: virtually identical results were obtained when data from patients on conventional versus intensive regimes were analyzed separately. A bedtime SMBG <7 mmol/l did not predict nocturnal hypoglycemia (defined as at least one CGMS value <3). The authors conclude that breakfast and dinnertime SMBG values are good indicators of integrated glucose values in the time period preceding them, while the bedtime test correlates well with the integrated values both preceding and following it.

Amin *et al* (2003) determined hypoglycemia prevalence in prepubertal children on thrice (TID) and twice (BID) daily insulin regimens using the CGMS. Twenty-eight children aged <12 years (median 9.8, range 6.9-11.8) wore the sensor for three consecutive days and nights. Hypoglycemia was defined as glucose <60 mg/dl for >15 min.

TA Criterion 3: The technology must improve the net health outcomes (continued)

Hypoglycemic events, continued

Data are expressed as the percentage of time period spent hypoglycemic. Hypoglycemia prevalence was 10.1% (mean 2.6 h. per subject-day). Hypoglycemia was more common at night compared with daytime (18.81 vs. 4.4%, $P < 0.001$); 78 and 43% of subjects showed hypoglycemia on at least one night and two or more nights, respectively. Nocturnal episodes were prolonged (median 3.3 h) and asymptomatic (91% of episodes). Prevalence was greater between 0400 and 0730 h than between 2200 and 0400 h (25.5 vs. 15.4%, $P < 0.001$). On a TID compared with a BID regimen, nocturnal hypoglycemia prevalence was reduced, particularly between 0400-0730 h (22.9 vs. 27.4%, $P = 0.005$), whereas hypoglycemia the following morning (0730-1200 h) was greater (7.8 vs. 2.8%, $P < 0.001$). Nocturnal hypoglycemia risk was associated with decreasing age (by a factor of 0.6 for a year less in age), increased insulin dose (by 1.6 for an increase of 0.1 units/kg/day), insulin regimen (by 0.2 on a BID compared with a TID regimen), and increased weight standard deviation score (SDS) (by 2.7 for a one SDS rise). The authors conclude that standard insulin regimens result in high prevalence and large intraindividual variation in hypoglycemia, particularly at night. Independent risk factors for nocturnal hypoglycemia were younger age, greater daily insulin dose, insulin regimen, and increasing weight.

Yogev *et al* (2002) examined the efficacy of the CGMS for treatment adjustment in patients with diabetic pregnancy treated with insulin. The study sample consisted of eight women with diabetic pregnancy, six with pre-pregnancy Type 1 diabetes mellitus and two with gestational diabetes (GDM), all being treated with multiple daily insulin injections. Gestational age ranged from 24 to 32 weeks. Data derived from the CGMS for 72 h were compared with fingerstick glucose measurements (six to eight times a day), and treatment was adjusted on the basis of the findings. Two to four weeks later, the patients were re-evaluated with CGMS. In the first part of the study, an average of 744 +/- 33 glucose measurements was recorded for each patient with CGMS. The mean total time of hyperglycemia (glucose level > 7.7 mmol/l) undetected by the fingerstick method was 152 +/- 33 min/day. Nocturnal hypoglycemic events (glucose level < 2.7 mmol/l) were recorded in seven patients.

TA Criterion 3: The technology must improve the net health outcomes (continued)

Hypoglycemic events, continued

Based on the additional information obtained by continuous monitoring, the insulin regimen was changed in all patients. CGMS re-evaluation after treatment adjustment showed a reduction in undetected hyperglycemia to 89 +/- 17 min/day and in nocturnal hypoglycemic events, which were recorded in only one patient. The authors conclude that continuous glucose monitoring may diagnose high blood glucose levels and nocturnal hypoglycemic events that are unrecognized by intermittent blood glucose monitoring and could serve as a useful tool for the long-term management of diabetic pregnancies. A large prospective study is needed to determine the clinical implications of this new monitoring technique.

Chico *et al* (2003) evaluated whether CGMS was useful for investigating the incidence of unrecognized hypoglycemia in type 1 and type 2 diabetic patients and for improving metabolic control in type 1 diabetic patients. 70 diabetic subjects (40 type 1 and 30 type 2 subjects) were monitored using the CGMS. The number of unrecognized hypoglycemic events was recorded. The CGMS detected unrecognized hypoglycemia in 62.5% of the type 1 diabetic patients and in 46.6% of the type 2 diabetic patients. They found that 73.7% of all events occurred at night. The authors conclude that CGMS was useful for detecting unrecognized hypoglycemia in type 1 and type 2 diabetic subjects.

In the randomized cross-over trial, by Ludvigsson *et al* (2003) 27 diabetic patients wore the CGMS sensor for 3 days every 2 weeks. CGMS profiles were used in the open study arm to adjust insulin therapy at follow-up visits every 6 weeks. Both the patients and the diabetes team were masked to the CGMS profiles in the blinded arm, and insulin therapy adjustments were based solely on 7-point BG profiles performed by the patients. At 3 months the 2 study arms were crossed over. A total of 26/27 patients experienced daytime low subcutaneous glucose (<3.0 mmol/L; .8 episodes/day; duration 58 +/- 29 minutes; 5.5% of total time), and 27/27 patients had at least 1 nocturnal episode of low subcutaneous glucose (.4 episodes/night; duration 132 +/- 81 minutes; 10.1% of total time). Two patients experienced severe hypoglycemia: one during the blind arm, one during the open arm. The authors report that there were no differences in hypoglycemic events registered on the CGMS between the two arms, but no data were presented.

TA Criterion 3: The technology must improve the net health outcomes (continued)

Adverse Effects

Ishikawa *et al* (1998) reported results of the initial clinical evaluation of a subcutaneously implanted, microsensor-based amperometric glucose-monitoring system in 10 non-diabetic and 10 insulin-dependent-diabetic volunteers.. There were no significant adverse events during the study. Among the 20 study subjects, only 1 reported pain during the sensor insertion and none reported discomfort associated with wearing the sensors. There were no problems with bleeding, hyperemia or cellulitis. However, multiple problems caused by corrosion and broken electrical contacts had to be overcome. In fact, because of these problems, the system was only functional during 32% of the testing periods.

Mastrototaro *et al* (1999) performed a total of 380 abdominal insertion site inspections on the 62 patients. Of these, 324 (85%) were reported as normal. The remainder (15%) found redness, discomfort, bleeding or bruising at the insertion site and in some cases the development of small papules. The abnormalities were rated as mild or moderate in severity, and all patients recovered without further incident when the sensors were removed .

Boland *et al* (2001) reported that in 2 of the 56 children in the study, the first sensor had to be replaced during the initial visit because it failed to meet performance parameters. The system was well tolerated by all subjects and there was no evidence of infection or inflammation at the insertion site.

Amin *et al* (2003) found that the sensor became dislodged or disconnected within 24 hours of insertion in 6/34 (18%) of study subjects. They also report that the system was well tolerated by subjects without evidence of inflammation at the sensor insertion site. Both Gureci (Guerci *et al.* 2003) and Yogev (Yogev *et al.* 2003) also reported no irritation or infection at the insertion site in their studies.

TA Criterion 3: The technology must improve the net health outcomes (continued)

Adverse Effects, continued

Chico *et al* (2003) evaluated the CGMS in 70 diabetic subjects (40 type 1 and 30 type 2 subjects). No skin lesions were observed (irritation, allergy, infection), although 8 subjects felt discomfort during the monitoring period. In 6 subjects, the sensor had to be replaced immediately after insertion due to an “error” message.

2. Transdermal Glucose Monitoring System (GlucoWatch biographer)

Accuracy

Garg *et al* (1999) compared measurement of glucose obtained via iontophoretic extraction with the GlucoWatch Automatic Glucose Biographer with capillary blood glucose values in both a controlled clinical setting and a home environment. In the outpatient clinic setting, 28 young adults with type 1 diabetes used 76 GlucoWatch biographers (some wore 2 at once to test precision, some wore them on multiple days). In the home setting, 12 subjects used 28 GlucoWatch biographers. All subjects also determined capillary blood glucose values once or twice each hour. Results showed close tracking of the biographer and fingerstick blood glucose values over the 12 hours of operation. Comparisons showed that the GlucoWatch glucose values correlated well to capillary blood glucose values in both the clinic setting ($r=0.90$, 1,554 paired data points) and the home setting ($r=0.85$, 204 paired data points). The GlucoWatch performed well in both hypoglycemic and hyperglycemic ranges. For the 36 subjects who wore two GlucoWatch biographers simultaneously, the correlation between the two biographers was excellent ($r=0.94$); results showed a mean difference of only 0.5 ± 19.3 mg/dL. More than 96% of GlucoWatch biographer glucose values determined in the clinic or home setting were in the clinically acceptable range of accuracy.

Overall, 7.3% of biographer readings could not be used due to technical problems (e.g., excessive skin sweating or temperature changes) in the clinic setting and 19.7% of points were unusable in the home environment. The authors concluded that glucose measurements correlated well between the two methods and that the GlucoWatch measurements had high precision.

TA Criterion 3: The technology must improve the net health outcomes (continued)

2. Transdermal Glucose Monitoring System (GlucoWatch biographer)

Accuracy, continued

In another uncontrolled, multicenter trial, Tamada *et al* (1999) studied the GlucoWatch among 92 subjects with type 1 or type 2 diabetes requiring treatment with insulin. Participants wore a total of 155 biographers (1-2 each) during the 15-hour session and performed 2 fingersticks per hour for comparative blood glucose measurements. Diet and insulin were manipulated to produce a broad range of blood glucose levels during the study period. Results showed close tracking of blood glucose over a range of 40-400 mg/dL for up to 12 hours after a single point calibration. The GlucoWatch biographer readings lagged behind serial blood glucose values by a mean of 18 minutes. An analysis of 2,167 data pairs showed a linear relationship ($r=0.88$) between biographer and fingerstick glucose measurements. The mean absolute error between the 2 measurements was 15.6% and the mean error $-1 + 33$ mg/dL. Overall, 96.8% of the data fell in the clinically acceptable range of accuracy. Among the 31 subjects who wore 2 devices simultaneously, there was a high degree of precision (agreement between the independent biographer measurements) ($r=0.93$). About 1 measurement every 3 hours was unusable due to technical factors (e.g., glucose values outside the 40-400 mg/dL range). The authors concluded that there was close agreement between GlucoWatch biographer readings and fingerstick blood glucose measurements, and that the automatic frequent, and noninvasive measurements obtained with the GlucoWatch could provide more information about glucose levels than the current standard of care.

A summary of the accuracy statistics from 6 studies in a mix of home and clinic environments was published by Tierney *et al* (2000b). The studies included a total of 520 biographer uses with 14,509 paired data points. The mean absolute value of the relative difference ranged from 17% to 21% and the linear correlation ranged from 0.80 to 0.85. 94 to 98% of the biographer readings were in the clinically acceptable A+B region of the Clarke Error Grid. In the home environment, the mean difference between the GlucoWatch biographer and serial fingerstick blood glucose measurements was 0.26 mmol/L ($r=0.80$).

TA Criterion 3: The technology must improve the net health outcomes (continued)

2. Transdermal Glucose Monitoring System (GlucoWatch biographer)

Accuracy, continued

Biographer precision as measured by the coefficient of variation was approximately 10%. A slightly positive bias was observed for biographer readings at low glucose levels.

The question that remains with all of these trials is whether the detailed information on glucose patterns and trends actually led to changes in therapeutic regimen and to improved blood glucose control (lower HbA1c) or fewer episodes of hypoglycemia. Only one study of the GlucoWatch biographer has addressed this question.

Glycemic control

The literature search found no published case-series assessing the effect of using the GlucoWatch biographer on long term glycemic control. There was one controlled clinical trial: Chase *et al* (2003) randomized 40 children with type 1 diabetes who had poor glucose control (HbA1c>8%) to diabetes management with or without the biographer. Conventional glucose monitoring was performed 4 times per day in both groups. Those randomized to the GlucoWatch biographer were asked to wear the device three times per week for three months. Both groups were followed for an additional 6 months. During the 3 month active phase, HbA1c levels declined from 8.9% to 8.4% in the group randomized to wear the GlucoWatch biographer and rose from 8.6% to 9.0% in the control group ($p<0.05$ GlucoWatch biographer vs. control). At the end of the 6-month follow-up period, the differences between the groups were no longer significant (HbA1c 8.4% in GlucoWatch biographer group vs. 8.6% in control group). Interestingly, insulin dosage was changed more frequently in the control group, suggesting that the effects of the GlucoWatch biographer were due to other factors.

TA Criterion 3: The technology must improve the net health outcomes (continued)

Hypoglycemic events

Pitzer *et al* (2001) summarized the data on hypoglycemic events from 4 clinical studies involving 1091 uses of the GlucoWatch biographer which generated 14,487 paired (biographer and SMBG) readings. An ROC curve analysis was done to evaluate different cutoffs for the hypoglycemic alarm. In all 4 studies the optimal results were obtained using 5.6 mmol/l (101 mg/dL) as the threshold. This yielded a sensitivity of 75-89% and a specificity of 10-17%. In the home environment the sensitivity was 75% and the specificity was 90%. Thus, a biographer set to emit an alarm below a glucose level of 101 mg/dL would miss 25% of the hypoglycemic events and 10% of the alarms would be false positives. There were no data on whether use of the biographer increased or decreased the frequency of hypoglycemic episodes.

In the RCT of Chase *et al* (2003), hypoglycemia was defined as a blood glucose measurement ≤ 70 mg/dL. Hypoglycemia was detected more frequently in the biographer group (approx. 2.7 events per 100 person-hours) compared with the control group (approximately 1.6 events per 100 person-hours, $p < 0.005$). Detection was more common at night and the GlucoWatch biographer group detected nocturnal hypoglycemia more frequently even on nights when they did not wear the device. There were no severe hypoglycemic events in either group during the study period. Again, no data were presented on the effect of biographer use on the frequency or total time patients were hypoglycemic.

Adverse Effects

Garg *et al* (1999) reported that during the first 3 hours of GlucoWatch operation, all subjects noted local skin irritation, itching and tingling that usually subsided by the end of that period. Skin irritation was again assessed immediately after removal of the GlucoWatch in the clinic or approximately 12 hours after its removal at home. Mild skin erythema and edema were observed in all subjects. Follow-up at 72 hours revealed no further skin reactions or infections.

TA Criterion 3: The technology must improve the net health outcomes (continued)

Adverse Effects, continued

Similarly, in the study of Tamada *et al* (1999), after removal of the biographers, mild skin irritation was noted at the site of iontophoresis, but in all cases the irritation resolved within 3-7 days. The series of studies reported by Tierney *et al* found that most patients (83%) using the biographer showed no edema or erythema, 1.2% reported having strong edema and 0.1% reported intense erythema (Tierney *et al.* 2000b). Another study reported that 67% of patients observed mild erythema at the applications site (Eastman *et al.* 2002). While 74% of these reactions resolved within 24 hours, 7% were still present after 48 hours.

In the RCT of Chase *et al* (2003), one patient dropped out of the study because of a mild skin reaction. Major complaints of the participants included difficulty calibrating the device, difficulty hearing the hypoglycemic alarm, and the frequency of alarms at night when blood glucose was not low (1.5 alarms for each low glucose detected).

By report from the manufacturer, the G2 Biographer has a lower incidence of skin reactions, but no clinical studies using this device have been published at the time of this review.

TA Criterion 3 is not met.



CALIFORNIA TECHNOLOGY ASSESSMENT FORUMSM

TA Criterion 4: The technology must improve the net health outcomes.

The established alternative to continuous glucose monitoring devices is self-monitoring of blood glucose (SMBG), measurement of capillary blood glucose levels one or more times each day using fingerstick blood sampling and analysis with reagent strips and a portable glucose meter device. Currently, this remains the standard method of self-monitoring for persons with diabetes mellitus, although a less-invasive method of monitoring would be desirable. SMBG is associated with improved glycemic control, particularly in patients with type 1 diabetes (Schiffrin *et al.* 1982; Yeo *et al.* 1985; Lam *et al.* 1986; Anderson *et al.* 1997; Evans *et al.* 1999).

1. Implantable Subcutaneous Glucose Sensors (CGMS)

Three randomized controlled trials have been published: two with parallel design (Chase *et al.* 2001; Chico *et al.* 2003) and one with a crossover design (Ludvigsson *et al.* 2003). All 3 compared the addition of periodic CMGS to usual self-monitoring with fingerstick blood sampling in patients with type 1 diabetes who were attempting to achieve tight control with intensive therapy.

As described above, the study of Chase *et al.* randomized 11 children with type 1 diabetes. Those in the CGMS group used 6 3-day sensors over 1 month. Both groups monitored their blood glucose levels with fingersticks at least 4 times daily. During the 1-month period where the sensors were used, the CGMS group changed insulin dosage more frequently than the control group (11.5 vs. 5.2 changes per participant, $p=0.001$). At the end of 3 months of follow-up, HbA1c levels had decreased from 9.86% to 8.82% in the 5 children randomized to CGMS compared to a drop from 9.02% to 8.4% in the 6 children in the placebo group. No p -value was given for the comparison in the change in glycemic control. Symptomatic hypoglycemic events were similar in the two groups and there were no severe hypoglycemic events. There were no significant differences between the two groups on two quality of life measures: the Fear of Hypoglycemia or the DCCT Quality of Life questionnaires.

TA Criterion 4: The technology must improve the net health outcomes, (continued)

1. Implantable Subcutaneous Glucose Sensors (CGMS), continued

The study was too small to have sufficient power to detect a difference between the 2 groups in terms of glycemic control and both too small and too short to detect any difference in severe or symptomatic hypoglycemic events. The large drop in HbA1c level in the CGMS group may reflect regression to the mean given the much higher baseline HbA1c level in the CGMS group (9.9%) compared with the control group (9.0%). Alternatively, clinicians treating patients with HbA1c levels close to 10% are more likely to be aggressive in intensifying the treatment regimen than clinicians treating patients with HbA1c levels close to 9%. Finally, the HbA1c level in the CGMS group was still higher than that of the control group at the end of the study period.

The controlled trial of Chico *et al* (2003) randomized 75 patients with type 1 diabetes to CGMS (n=40) or control (n=35). Patients in the control group had insulin therapy modified based on at least 8 fingerstick glucose measurements per day for 3 days. In the CGMS group, HbA1c levels dropped from 8.3% to 7.5% (p<0.01). In the control group, HbA1c levels dropped from 8.0% to 7.5% (p<0.01). No between group comparisons were presented in terms of the differences in glycemic control (reduction in HbA1c of 0.8% vs. 0.5%) or in the number of symptomatic or severe hypoglycemic events. The authors conclude that management based on frequent fingersticks and more intensive clinic follow-up is as effective as management based on CGMS data. The methodologic reporting of the study was grossly inadequate. There was no description of the method of randomization or allocation concealment. There was minimal description of recruitment, follow-up, and retention, and the key analysis (between group comparison) was not reported.

Finally, Ludvigsson *et al* (2003) used CGMS in a randomized crossover study of 27 pediatric patients treated with intensive insulin therapy. Both groups wore the CGMS sensor for 3 days every 2 weeks. CGMS profiles were used in the open study arm to adjust insulin therapy at follow-up visits every 6 weeks. Both the patients and the diabetes team were masked to the CGMS profiles in the blinded arm, and insulin therapy adjustments were based solely on 7-point BG profiles performed by the patients.

TA Criterion 4: The technology must improve the net health outcomes, (continued)

1. Implantable Subcutaneous Glucose Sensors (CGMS), continued

HbA1c decreased significantly in the open arm (from 7.70% to 7.31%) but not in the blind arm (7.75% to 7.65%). At the end of 12 weeks the between group difference was significant ($p=0.011$), but the absolute difference was modest. The authors report that there were no differences in hypoglycemic events registered between the two arms on the CGMS, but no data were presented. A cross-over design is not ideal for investigating CGMS as significant carry-over effects would be expected in the group randomized to the open CGMS group. Changes in insulin regimen, diet, and exercise pattern made on the basis of the CGMS profile would remain in place after the cross-over to the “blind” study arm. Again this study is relatively small and of brief duration, though innovative in design as both arms wore the CGMS device which reduces effects from partial unblinding and provides access to CGMS data in both groups.

2. Transdermal Glucose Monitoring System (GlucoWatch biographer)

Only one controlled clinical trial of the GlucoWatch biographer has been published. Chase *et al* (2003) randomized 40 children with type 1 diabetes who had poor glucose control ($HbA1c > 8\%$) to diabetes management with or without the biographer. Conventional glucose monitoring was performed 4 times per day in both groups. Those randomized to the GlucoWatch biographer were asked to wear the device three times per week for three months. During the 3 month active phase, HbA1c levels declined from 8.9% to 8.4% in the group randomized to wear the GlucoWatch biographer and rose from 8.6% to 9.0% in the control group ($p < 0.05$ GlucoWatch biographer vs. control). At the end of the 6-month follow-up period, the differences between the groups were no longer significant (HbA1c 8.4% in GlucoWatch biographer group vs. 8.6% in control group). Interestingly, insulin dosage was changed more frequently in the control group, suggesting that the effects of the GlucoWatch biographer were due to other factors. There were no severe hypoglycemic events in either group during the study period. Unfortunately, no data were presented on the effect of biographer use on the frequency or total time patients were hypoglycemic. One patient dropped out of the study because of a mild skin reaction.



TA Criterion 4: The technology must improve the net health outcomes, (continued)

2. Transdermal Glucose Monitoring System (GlucoWatch biographer), continued

Major complaints of the participants included difficulty calibrating the device, difficulty hearing the hypoglycemic alarm, and the frequency of alarms at night when blood glucose was not low (1.5 alarms for each low glucose detected).

TA Criterion 4 is not met.

TA Criterion 5: The improvement must be attainable outside the investigational settings.

Most of the published studies derive from academic institutions and thus do not allow evaluation of continuous glucose monitoring under conditions of usual medical practice. However, the study of Gross *et al* (2000) reported on the accuracy of the CGMS device in 238 patients treated in the community. Results reported in that study were comparable to data obtained using the CGMS device in an academic setting. However, studies have not yet unequivocally demonstrated the efficacy of this procedure in improving glycemic control in the investigational setting. Whether continuous glucose monitoring will be effective in improving glycemic control when performed in the community setting under conditions of usual medical practice remains to be demonstrated.

TA Criterion 5 is not met.



OPINIONS OF OTHERS

Blue Cross Blue Shield Association (BCBSA)

The BCBSA TEC Medical Advisory Panel reviewed this topic in June 2002 and determined that based on the scientific evidence, the use of intermittent or continuous interstitial fluid glucose monitoring in patients with diabetes mellitus did not meet BCBSA Technology Evaluation Center (TEC) criteria.

Centers for Medicare and Medicaid Services (CMS)

The June 25, 2003 CMS Summary Report of the Durable Medical Equipment (DME) Public Meeting indicates that a request was made to establish a code for the GlucoWatch G2 Automatic Glucose Biographer. It was determined that these items are not covered.

National Heritage Insurance Company, the CMS carrier for Northern California provides coverage for continuous glucose monitoring when specific requirements are met.

The CMS MCAC has not reviewed this topic.

American Association of Clinical Endocrinologists (California Chapter)

The American Association of Clinical Endocrinologists has been asked to provide a position/consensus statement and participation at the meeting.

American Diabetes Association

The American Diabetes Association has been asked to provide a position/opinion statement and participation at the meeting.

CONCLUSION

Development of a noninvasive or minimally invasive and automatic approach to monitoring of blood glucose has the potential to produce significant improvements in the quality of life for persons with diabetes mellitus. Indeed, continuous glucose monitoring technologies hold promise for improving the care of patients with both type 1 and type 2 diabetes. Automated continuous monitoring of subcutaneous tissue glucose is now possible using both an implantable subcutaneous glucose sensor (the Continuous Glucose Monitoring System manufactured by MiniMed, Inc.) and using a transdermal system (the GlucoWatch Automatic Glucose Biographer manufactured by Cygnus, Inc.). Both devices have received FDA approval. Notably, neither device reduces the need for patients to monitor themselves with regular fingerstick glucose measurements.

There are many publications available concerning implantable electroenzymatic glucose sensors implanted in the subcutaneous tissue of non-diabetic and diabetic subjects. These uncontrolled clinical trials have demonstrated excellent correlations between subcutaneous glucose concentrations measured by the sensor and plasma or capillary fingerstick blood glucose levels. The sensors appeared to be accurate for subcutaneous tissue glucose concentrations ranging from approximately 40 to 400 mg/dL, although the devices appear to underestimate glucose levels as they fall below 70 mg/dL. Most of the data use the CGMS device. Similar data exist for the accuracy of the transdermal GlucoWatch biographer. Again accuracy decreases at the low end of glucose concentrations. Clinical decisions regarding changes in insulin dosage and timing, exercise, and meal composition should be made only on the basis of the patterns of glycemia revealed by these devices. Individual readings from either device need to be verified by fingerstick glucose measurements before any clinical intervention is implemented.

Four uncontrolled trials assessed changes in glycemic control using the CGMS device in a total of 104 patients followed from 1.5 to 6 months. All reported decreases in HbA1c levels ranging from 0.1% to 1.3%. Results of uncontrolled studies like these must be interpreted with caution due to the lack of a randomized control group, the selection of patients with elevated HbA1c levels, and the potential influence of a Hawthorne effect. Three randomized, controlled clinical trials have been published with promising results.

CONCLUSION, continued

The studies randomized 113 patients with type 1 diabetes to management with CGMS or fingerstick glucose monitoring (up to 8 per day). In all three studies there was a reduction of 0.3-0.4% in HbA1c level for the CGMS group compared to the control group. Only one of the three studies reported statistics comparing the results between groups randomized to CGMS or control monitoring. In that study, there was a statistically significant improvement in glycemic control in the CGMS group compared to the control ($p=0.011$). No increase in hypoglycemic episodes was reported in any of the studies, though the reporting was not complete. No skin lesions (irritation, allergy, infection) were reported in these studies, although reporting was again incomplete. Eight subjects felt some discomfort during the monitoring period. In 6 subjects, the sensor had to be replaced immediately after insertion due to an “error” message.

Nevertheless, all three of the clinical trials had significant flaws. The study of Chase *et al.* (2001) only randomized 11 children and there were large differences in important baseline characteristics, such as HbA1c levels, that could explain the findings. Furthermore, no between group analyses were presented. The largest study (Chico *et al.* 2003) presented almost no methodological details, making it impossible to assess the quality of the study. Again, no between group analyses were presented. Finally the study of Ludvigsson *et al.* (2003) used a cross-over design which is a poor design for studying this device given the likelihood of a large carry-over effect that would not be eliminated by a washout period. The overall results of the studies of CGMS designed to assess clinical outcomes are promising, but inadequate to clearly demonstrate benefit. Furthermore, the small numbers of study subjects and short follow-up times do not allow for an adequate assessment of the risk for hypoglycemia.

For the GlucoWatch biographer, no uncontrolled studies of glycemic control were identified. Only one controlled clinical trial of the GlucoWatch biographer has been published. Chase *et al.* (2003) randomized 40 children with type 1 diabetes who had poor glucose control ($HbA1c > 8\%$) to diabetes management with or without the biographer. During the 3 month active phase, HbA1c levels declined from 8.9% to 8.4% in the group randomized to wear the GlucoWatch biographer and rose from 8.6% to 9.0% in the control group ($p < 0.05$ GlucoWatch biographer vs. control).

CONCLUSION, continued

At the end of the 6-month follow-up period, the differences between the groups was no longer significant (HbA1c 8.4% in GlucoWatch biographer group vs. 8.6% in control group). There were no severe hypoglycemic events in either group during the study period. Unfortunately, no data were presented on the effect of biographer use on the frequency or total time patients were hypoglycemic. One patient dropped out of the study because of a mild skin reaction. Major complaints of the participants included difficulty calibrating the device, difficulty hearing the hypoglycemic alarm, and the frequency of alarms at night when blood glucose was not low (1.5 alarms for each low glucose detected). Prior studies have documented frequent skin reactions with the device. The manufacturer has attempted to address this with the release of a second-generation device, the GlucoWatch G2 biographer. No clinical studies using this device were identified in the published literature.

Whether the information about glucose patterns and trends lead to detection of impending hypo- and hyperglycemia and to early treatment of these frequent occurrences in diabetes remains to be demonstrated. Further study of continuous glucose monitoring techniques is needed, especially to assess their impact on efficacy and safety of insulin dosing. Ideally, these promising technologies would be further evaluated in larger and longer randomized, controlled trials comparing them to outcomes obtained using existing self-monitoring of blood glucose. The essential outcomes are change in HbA1c levels, frequency of hypoglycemic events, adverse events, and quality of life. Studies of adequate power to detect changes in microvascular or macrovascular outcomes would need to be equivalent in size and scope to the DCCT and are unlikely to be performed.

Currently, TA criteria 3-5 are not met.



RECOMMENDATION

It is recommended that the CGMS system and Glucowatch Biographer do not meet California Technology Assessment Forum criteria for safety and efficacy.

October 8, 2003

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