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CLINICAL | GUIDELINES

Continuous Glucose Monitoring:

An Endocrine Society Clinical Practice Guideline



THE JOURNAL OF
CLINICAL
ENDOCRINOLOGY
& METABOLISM

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Co-Sponsoring Associations: Diabetes Technology Society and European Society of Endocrinology.

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First published in *Journal of Clinical Endocrinology & Metabolism*, October, 2011, 96 (10): 2968–2979.

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Abstract

Objective: The aim was to formulate practice guidelines for determining settings where patients are most likely to benefit from the use of continuous glucose monitoring (CGM).

Participants: The Endocrine Society appointed a Task Force of experts, a methodologist, and a medical writer.

Evidence: This evidence-based guideline was developed using the Grading of Recommendations, Assessment, Development, and Evaluation (GRADE) system to describe both the strength of recommendations and the quality of evidence.

Consensus Process: One group meeting, several conference calls, and e-mail communications enabled consensus. Committees and members of The Endocrine Society, the Diabetes Technology Society, and the European Society of Endocrinology reviewed and commented on preliminary drafts of these guidelines.

Conclusions: The Task Force evaluated three potential uses of CGM: 1) real-time CGM in adult hospital settings; 2) real-time CGM in children and adolescent outpatients; and 3) real-time CGM in adult outpatients. The Task Force used the best available data to develop evidence-based recommendations about where CGM can be beneficial in maintaining target levels of glycemia and limiting the risk of hypoglycemia. Both strength of recommendations and quality of evidence were accounted for in the guidelines.

J Clin Endocrinol Metab, October, 2011, 96 (10): 2968–2979.

Abbreviations: CGM, Continuous glucose monitoring; CIT, conventional insulin therapy; HbA_{1c}, glycosylated hemoglobin; ICU, intensive care unit; IIT, intensive insulin therapy; ISF, interstitial fluid; MDI, multiple daily injections; MICU, medical ICU; POC, point-of-care; RT-CGM, real-time CGM; SMBG, self-monitoring of blood glucose; T1DM, type 1 diabetes mellitus.

SUMMARY OF RECOMMENDATIONS

1.0. Real-time continuous glucose monitoring (RT-CGM) in adult hospital settings

1.1. We recommend against the use of RT-CGM alone for glucose management in the intensive care unit (ICU) or operating room until further studies provide sufficient evidence for its accuracy and safety in those settings (1 | ⊕○○○).

2.0. RT-CGM in children and adolescent outpatients

2.1. We recommend that RT-CGM with currently approved devices be used by children and adolescents with type 1 diabetes mellitus (T1DM) who have achieved glycosylated hemoglobin (HbA1c) levels below 7.0% because it will assist in maintaining target HbA1c levels while limiting the risk of hypoglycemia (1 | ⊕⊕⊕⊕).

2.2. We recommend RT-CGM devices be used with children and adolescents with T1DM who have HbA1c levels $\geq 7.0\%$ who are able to use these devices on a nearly daily basis (1 | ⊕⊕⊕○).

2.3. We make no recommendations for or against the use of RT-CGM by children with T1DM who are less than 8 yr of age.

2.4. We suggest that treatment guidelines be provided to patients to allow them to safely and effectively take advantage of the information provided to them by RT-CGM (2 | ⊕○○○).

2.5. We suggest the intermittent use of CGM systems designed for short-term retrospective analysis in pediatric patients with diabetes in whom clinicians worry about nocturnal hypoglycemia, dawn phenomenon, and postprandial hyperglycemia; in patients with hypoglycemic unawareness; and in patients experimenting with important changes to their diabetes regimen [such as instituting new insulin or

switching from multiple daily injections (MDI) to pump therapy] (2 | ⊕○○○).

3.0. RT-CGM in adult outpatients

3.1. We recommend that RT-CGM devices be used by adult patients with T1DM who have HbA1c levels of at least 7.0% and who have demonstrated that they can use these devices on a nearly daily basis (1 | ⊕⊕⊕⊕).

3.2. We recommend that RT-CGM devices be used by adult patients with T1DM who have HbA1c levels less than 7.0% and who have demonstrated that they can use these devices on a nearly daily basis (1 | ⊕⊕⊕⊕).

3.3. We suggest that intermittent use of CGM systems designed for short-term retrospective analysis may be of benefit in adult patients with diabetes to detect nocturnal hypoglycemia, the dawn phenomenon, and postprandial hyperglycemia, and to assist in the management of hypoglycemic unawareness and when significant changes are made to their diabetes regimen (such as instituting new insulins or switching from MDI to pump therapy) (2 | ⊕○○○).

METHOD OF DEVELOPMENT OF EVIDENCE-BASED CLINICAL PRACTICE GUIDELINES

The Clinical Guidelines Subcommittee of The Endocrine Society deemed continuous glucose monitoring (CGM) a priority area in need of practice guidelines and appointed a Task Force to formulate evidence-based recommendations. The Task Force followed the approach recommended by the Grading of Recommendations, Assessment, Development, and Evaluation (GRADE) workgroup, an international group with expertise in development and implementation of evidence-based guidelines (1). A detailed description of the grading scheme has been published elsewhere (2). The Task Force used the best available research

evidence that Task Force members identified and one commissioned systematic literature review of randomized controlled trials of CGM use (3) to inform some of the recommendations. The Task Force also used consistent language and graphical descriptions of both the strength of a recommendation and the quality of evidence. In terms of the strength of the recommendation, strong recommendations use the phrase “we recommend” and the number 1, and weak recommendations use the phrase “we suggest” and the number 2. *Cross-filled circles* indicate the quality of the evidence, such that ⊕○○○ denotes very low quality evidence; ⊕⊕○○, low quality; ⊕⊕⊕○, moderate quality; and ⊕⊕⊕⊕, high quality. The Task Force has confidence that persons who receive care according to the strong recommendations will derive, on average, more good than harm. Weak recommendations require more careful consideration of the person’s circumstances, values, and preferences to determine the best course of action. Linked to each *recommendation* is a description of the *evidence* and the *values* that panelists considered in making the recommendation. All of our recommendations are expert opinions and are evidence based. Some of these opinions are based on stronger evidence than others. For strong recommendations with GRADE 1 evidence, the Task Force has made recommendations, and for weak recommendations with GRADE 2 evidence, the Task Force has made suggestions. For recommendations in this guideline that are based on low-quality to very low-quality evidence, the reader should note that our implicit recommendation is for more research.

The task force recognizes that CGM may place educational and practical burdens on patients and their families and on diabetes care providers who must be available to support, advise, and educate them. We also recognize that there are costs associated with the use of this technology according to our recommendations and that ultimately, the routine use of this technology will depend on an evolving calculus of cost *vs.* effectiveness. We have considered the cost-benefit issues related to the use of CGM and feel that the clinical benefits justify the costs in a wide range of patients, but that these values may not be universally shared in some healthcare settings (e.g. those with resource-constrained settings, clinics unable to

provide adequate support to patients and families). Individuals or health systems may disagree with our relative valuation, and in these cases our recommendations may not apply. It may then be necessary to modify these recommendations accordingly.

INTRODUCTION

People who have diabetes mellitus face daily challenges in managing glycemic levels, as well as avoiding hypoglycemic and hyperglycemic excursions. Both severe hypoglycemia and extreme hyperglycemia have an immediate impact on mental and physical functioning. Moreover, the maintenance of glycemic control within near-normal limits has been shown to significantly decrease the development of secondary micro- and macrovascular complications to diabetes (4–6).

Capillary blood glucose measurements using portable devices have been used to assess blood glucose several times a day in an effort to provide the patient with reliable guidance for treatment (including dietary) measures to correct hypo- or hyperglycemia. However, even with frequent blood sampling for spot glucose measurements, some patients do not adequately manage their glycemic levels. It has been postulated that such patients may benefit from a system providing them with continuous real-time glucose readings. Although this argument is intuitively easy to accept, there remain a number of caveats to take into account before accepting continuous monitoring of blood glucose as a routine (or even specialized) measure to improve glycemic control in diabetes.

First, maintaining direct access to the blood on a continuous basis for an extended period has proved impractical. Hence, a number of different techniques have been evaluated, including invasive and non-invasive methods for indirectly estimating blood glucose. Second, the reliability in terms of accuracy and the precision of the various systems need proper documentation before being applied in routine care. Third, financial constraints require an ongoing evaluation of the socioeconomic consequences of these

new techniques, and therefore the eventual clinical benefits of their use need to be documented and balanced against their costs.

The glucose concentration in the interstitial fluid (ISF) has proven reasonably assessable, even for long-term monitoring in an outpatient setting, and currently the vast majority of the available technology, as well as technology under development, uses the ISF for monitoring directly or indirectly. In this context, it is of particular interest that the glucose concentration in the sc ISF has been shown to reflect the concentrations and dynamics of glucose in the brain (7). The present set of guidelines is not a technical review of available technologies. Rather, this document scrutinizes available evidence that CGM in the ISF is of clinical value in the quest to obtain and maintain near normal glycemic control in various clinical situations and subpopulations with diabetes mellitus (3).

1.0. RT-CGM IN ADULT HOSPITAL SETTINGS

Recommendation

1.1. We recommend against the use of RT-CGM alone for glucose management in the ICU or

operating room until further studies provide sufficient evidence for its accuracy and safety in those settings (1 | ⊕○○○).

1.1. Evidence

The study of van den Berghe *et al.* (8) in surgical ICU patients showing marked reduction in mortality and morbidity in those treated with intensive insulin therapy (IIT) compared with conventional insulin therapy (CIT) initiated a rapidly growing worldwide trend to aggressively treat hyperglycemia in critically ill patients. However, subsequent studies in medical ICU (MICU) patients, including those by van den Berghe *et al.* (8), as well as in surgical and MICU/surgical ICU patients, have been unable to duplicate her results (9–13). A meta-analysis before the NICE-SUGAR report, in fact, confirmed that there was no benefit to IIT (14) in the ICU population. Furthermore, these prospective, randomized controlled trials of IIT demonstrated that hypoglycemia was significantly more common in those receiving IIT than in those treated with CIT. The NICE-SUGAR study showed, in fact, an increased mortality rate in those treated with IIT (12) (Table 1). Although the reasons for this increased rate are unclear, the finding is consistent with a retrospective analysis showing that hypoglycemia was an independent risk factor for mortality (15). In one series, however, this risk was limited to patients with spontaneous hypoglycemia, but

TABLE 1. Rates of hypoglycemia in ICU patients receiving IIT vs. CIT

First author, year (Ref.)	Hypoglycemia in IIT (%)	Hypoglycemia in CIT (%)	P value	Glucose method	Whole blood source
Arabi, 2008 (9)	28.6	3.1	0.0001	Accu-Chek Inform	Artery or capillary
Brunkhorst, 2008 (10)	17.0	4.1	0.001	HemoCue	Artery or capillary
Devos, 2007 (11)	9.8	2.7	0.001	Not stated	Not stated
Grey, 2004 (78)	32.0	7.4	0.001	Not stated	Not stated
NICE-SUGAR, 2009 (12)	6.8	0.5	0.001	Blood gas analyzer	Artery (mostly)
Van den Berghe, 2001 (8)	12.7	0.76	?	ABL700	Artery
Van den Berghe, 2006 (13)	3.1	18.7	0.001	HemoCue	Capillary

iatrogenic hypoglycemia after insulin therapy was not associated with a higher mortality risk (16).

These trials used a variety of bedside point-of-care (POC) devices for testing glucose, which are listed (when specified) in Table 1. The listed devices use glucose dehydrogenase for glucose determination. Recently, the Food and Drug Administration (FDA) has warned that this method is subject to false elevation by maltose, icodextrin, galactose, and xylose, although the FDA has not proscribed their use in the hospital (17). It is unlikely, although not impossible, that patients in intensive management studies were subject to such errors. On the other hand, devices that use glucose oxidase are potentially subject to falsely lower than actual values in settings where there is high oxygen tension produced by supplemental oxygen (18). Both methods may be affected by a variety of medications. Importantly, the requirements for accuracy in a critical care setting have not yet been determined. Kost *et al.* (19) have suggested that the margins of error for blood glucose measurement should be within 15 mg/dl of the reference measurement for blood sugars less than 100 mg/dl and within 15% if above 100 mg/dl in critical care settings. It should be noted that the International Organization for Standardization (ISO) (20) suggested that the margin of error should be within 15 mg/dl for blood sugars less than 75 mg/dl. In addition to the issue of what standards should be applied, POC testing itself (rather than laboratory testing) in critically ill patients is controversial because of unresolved questions about the effects on accuracy of common conditions, *e.g.* acidosis, hypothermia, and hypotension; or medications, *e.g.* dopamine, mannitol, acetaminophen, and pressor use. These circumstances reduce tissue perfusion, which may uncouple the usual relationship between the sc and circulatory glucose. Thus, results may differ depending not only on the source of the sample—capillary, vein, or artery—but also on the concomitant cause and treatment of the patient's ICU stay. Of several studies investigating the accuracy of POC testing in the ICU, some found adequate accuracy if arterial samples were used (18, 21), whereas others generally showed marginal or clinically unacceptable accuracy with capillary samples (22–28). Despite these findings,

POC capillary samples are the most commonly used method for obtaining blood glucose measurements in the ICU. Furthermore, several studies have used capillary-derived samples to validate CGM in this setting.

With respect to ICU conditions, Kulkarni *et al.* (26) found a significant discrepancy in accuracy in those treated with IIT who had hypotension and/or were treated with a pressor as compared with those without hypotension/pressor treatment (2 SD values from the mean difference between measurements in the low range was –36.8 mg/dl). Haupt *et al.* (29) found that hypothermia can cause significant underestimation of blood glucose, and Hoedemaekers *et al.* (24) found that the ISO criteria were not met by three different meters (Accu-Chek, HemoCue, and Precision) with all readings higher than the reference standard, which can lead to potentially serious overtreatment with insulin. Most recently, Vlasselaers *et al.* (30) found significant clinical bias using both Accu-Chek and HemoCue devices as compared with standard laboratory testing and recommended caution in using such devices to regulate insulin infusion rates.

CGM may have an advantage over POC testing in that it has the potential to reduce the possibility of unknown hypoglycemic events that may occur between POC measurements. These devices use ISF rather than blood to measure glucose, but the relationship of ISF to blood in critically ill patients has been investigated only to a limited degree. Several studies of CGM have evaluated the effects of conditions that are common in the ICU, such as hypotension with or without inotrope use, hypothermia, edema, renal and hepatic failure, hyperinsulinemia, and acidosis, but these studies were small and generally not powered to assess each of those variables (Table 2) (31–37). For example, De Block *et al.* (31), in a study of 50 adult ICU patients, noted worse accuracy in patients on inotropes and better accuracy in those in acute renal failure and septic shock compared with patients on no inotropes and without these conditions. However, Holzinger *et al.* (33) found that there was no significant effect on accuracy in 27 ICU patients treated with norepinephrine for shock compared with 23 without shock, and a lack of

TABLE 2. Effects of different conditions and treatments on CGM accuracy in the ICU

First author, year (Ref.)	Condition/treatment	No. of patients	No. of paired samples	Accuracy interference
De Block, 2006 (31)	Inotropes	?	?	Yes
Goldberg, 2004 (32)	Inotrope/edema/hypotension	21	546	No
Holzinger, 2009 (33)	Inotropes	50	736	No
Monsod, 2002 (34)	Hyperinsulinemia	11	88	Yes
Pfützner, 2006 (35)	Ketosis	12	159	No
Price, 2008 (37)	Inotropes	17	371	No
Piper, 2006 (36)	Edema, hypothermia, inotropes	20	246	No

inotrope effect was noted in other studies (32, 37). CGM was not affected by mild ketosis without acidosis in a study of patients with T1DM in whom their insulin pump was temporarily stopped in a non-ICU setting (35), but the effect of keto- or lactic acidosis has not been evaluated. Other studies have noted that hypotension, hypothermia, and edema did not affect CGM accuracy (32, 36). Interestingly, hyperinsulinemia itself reduced sensor glucose compared with venous glucose readings about 20% in humans (34). These findings differ from those in a hyperinsulinemic hyperglycemic dog model in which sensor dynamics were unchanged under conditions of different insulin concentrations (38).

There have been nine studies that have evaluated the accuracy of ISF-based CGM in the ICU (23, 32, 33, 36, 37, 39–42) (Table 3); of them, only one involved use of CGM to control IIT (40). The other studies used retrospective comparisons of a reference POC value with simultaneous CGM data. Each study had a small number of patients (17 to 50, for a combined total of 256), and few data were obtained during hypoglycemia. Goldberg *et al.* (32) found that 98.7% of results were in the Clarke *et al.* (43) error grid A and B zones, although they used capillary samples as the reference method. Only four of 546 pairings found blood glucose less than 60 mg/dl. Corstjens *et al.* (23) found that 100% of the readings of MICU patients were in the A and B zones. Holzinger *et al.* (33) also found excellent clinical agreement with 98.6% in the acceptable treatment zone and none in

the life-threatening zone. In ICU patients with continuous insulin infusions, Rabiee *et al.* (41) compared the DexCom to three different methods of glucose determination—two with capillary blood from finger sticks (Accu-Chek and OneTouch) and one from serum (Hitachi 917), which was used as the “gold standard” for clinical decisions. There were 85 paired values with the Hitachi 917, and 100% of values in the A and B zones. However, when these results and the paired data with the Accu-Chek (1065 paired values compared with Dexcom) and OneTouch (232 paired values compared with Dexcom) were more closely examined, the CGM generally overestimated the actual serum glucose and missed 50% of the 30 actual hypoglycemic episodes as determined by Accu-Chek, leading the authors to conclude that it was not sufficiently safe to be used in an ICU setting. Blood glucose measurements on POC devices have been used as reference methods for CGM accuracy studies, but these devices provide readings with up to a 20% bias (or greater in some circumstances) compared to reference values. In hospitalized patients, anemia, abnormal oxygen tension, and hypotension can all degrade accuracy of these devices and make it difficult to assess the simultaneous performance of CGM. Tonyushkina *et al.* (44) and Mraz *et al.* (40), using a computer-based predictive model control algorithm in 10 post-cardiac surgery patients, found that 97% of readings were clinically acceptable (A and B zones), and there were no episodes of hypoglycemia over 24 h, whereas there were five episodes in 10 patients in the control group. In the

only study in a pediatric population, Piper *et al.* (36) found excellent clinical accuracy, with 98.8% in zones A and B in 20 patients after cardiac surgery. However, only two of 246 paired values were less than 75 mg/dl. Finally, Yamashita *et al.* (42), using an iv CGM, found 100% in zones A and B. These promising results are mitigated by other studies. Price *et al.* (37) found a poor correlation between CGM and both capillary and arterial samples when the blood sugar was less than 81 mg/dl. CGM overestimated capillary or arterial glucose by 18 mg/dl or more in 23% of readings less than 80 mg/dl, although there were only 36 comparisons in that range. Logtenberg *et al.* (39), in comparing capillary, arterial, and venous reference standards in ICU patients after cardiac surgery, found that 96.0, 92.1, and 84.6%, respectively, were within the Clarke error grid A and B zones; and 3.3, 7.4, and 14.7%, respectively, were in the D zone. Blood sugars less than 60 mg/dl were rare in their study, as well. In summary, whereas the use of CGM appears promising, it must undergo larger and rigorous testing in the ICU setting

before it can be recommended for use with IIT protocols. Finally, in the only randomized study, Mraz *et al.* (40) found that CGM provided better glycemic control without hypoglycemia in comparison with standard monitoring to manage glycemia (using an enhanced model predictive control algorithm) in an IIT protocol. This study is a harbinger of an “artificial pancreas” and represents a valuable and rapidly progressing area of research to determine whether or not the application of sophisticated model predictive controller algorithms will be sufficient to overcome the inherent inaccuracies of CGM technology.

1.1. Values and preferences

The Task Force recommends against using CGM in ICU settings where patients are likely to be unable to provide feedback about hypoglycemic symptoms. This recommendation is based on the limited available data related to accuracy and our concerns regarding potential danger in their use in guiding insulin

TABLE 3. Accuracy of ISF-based CGM systems compared with POC glucometry in ICU patients

First author, year (Ref.)	Device	Comparison	No. of patients	Site	No. of paired samples	Clarke A, B (%)	Clarke C, D, E (%)
Corstjens, 2006 (23)	CGM	Arterial ABL715/ Precision PCx	19	MICU	165	100	0
Goldberg, 2004 (32)	CGM	Capillary	21	MICU	546	98.7	1.3
Holzinger, 2009 (33)	CGM	Arterial ABL700	50	MICU	736	98.6	1.4
Logtenberg, 2009 (39)	RT-CGM	Capillary (Accu-Chek)/arterial	30	Post-op SICU	275/216	96/92.1	4.1/7.9
Mraz, 2009 (40)	CGM/eMPC	Arterial	10	SICU	24	97	3
Piper, 2006 (36)	CGM	Lab	20	Post-op ICU	246	98.8 ^a	1.2
Price, 2008 (37)	RT-CGM	Accu-Chek, capillary/arterial	17	MICU [?]	366	Not done	Not done
Rabiee, 2009 (41)	CGM	Arterial: Hitachi 917	19	SICU/ burn ICU	84	100	0
		Capillary: Accu-Chek	19		1065	99.25	0.75
		OneTouch	19		232	97.41	2.59
Yamashita, 2008 (42)	STG-22	Arterial ABL 800FLEX	50	SICU	200	100	0

SICU, Surgical ICU; eMPC, enhanced model predictive control algorithm.

^a Insulin titration grid analysis.

administration in an acute-care setting, which outweighs the possible convenience and trend awareness that the technology provides.

2.0. RT-CGM IN CHILDREN AND ADOLESCENT OUTPATIENTS

CGM use with either blinded or unblinded sensors provides clinical investigators with a powerful tool to assess new outcomes in diabetes research such as the effects of new treatments on glucose variability and exposure to biochemical hypoglycemia.

Self-monitoring of blood glucose (SMBG) is an important component of therapy for children and adolescents with T1DM for optimizing glycemic control as well as reducing the risk for hypoglycemia. However, standard methods for SMBG only provide patients with intermittent, single point-in-time snapshots of glucose levels. The readings often miss marked and sustained hyper- and hypoglycemic excursions (45), especially during the night when checking blood glucose is inconvenient (46, 47).

CGM systems have been developed that allow more complete blood glucose profiles to be obtained (48–50). However, the first generation of FDA-approved devices either provided data only for short-term retrospective analysis (the MiniMed CGMS) or were too difficult and uncomfortable to use (the GlucoWatch 2 Biographer) (51, 52). Newer RT-CGM systems provide improved accuracy and functionality and better patient tolerance (48, 53–57). Future CGM systems might contain software that can analyze inputted clinical factors and glycemic trends to predict future glucose levels (58). However, evidence is still being gathered regarding the efficacy, safety, tolerability, and subjective benefits of these devices in different populations of patients with diabetes.

Recommendation

2.1. We recommend that RT-CGM with currently approved devices be used by children and adolescents with T1DM who have achieved HbA1c levels below 7.0% because it will assist in maintaining target HbA1c levels while limiting the risk of hypoglycemia (1 | ⊕⊕⊕⊕).

2.1. Evidence

The Juvenile Diabetes Research Foundation Continuous Glucose Monitoring (JDRF CGM) (59) Study Group has demonstrated that in patients with T1DM who have achieved HbA1c levels less than 7.0%, RT-CGM use can reduce the frequency of biochemical hypoglycemia (which they defined as a blood glucose level below 70 mg/dl) and help maintain HbA1c levels less than 7.0% compared with standard blood glucose monitoring over a 6-month study period. Of the 129 enrolled subjects, 62 (or 48%) were younger than 25, and 67 (or 52%) were at least 25 yr of age. The median time per day with a glucose level of 70 mg/dl or less as measured with CGM was less in the CGM group than in the control group; however, the difference was not statistically significant. In this study, almost all the other analyses (including the time per day \leq 60 mg/dl, time per day between 71 and 180 mg/dl, and combined outcomes involving HbA1c coupled with hypoglycemia) favored the CGM group compared with the control group. Treatment effects were generally similar across age groups.

Recommendation

2.2. We recommend RT-CGM devices be used with children and adolescents with T1DM who have HbA1c levels 7.0% who are able to use these devices on a nearly daily basis (1 | ⊕⊕⊕○).

2.2. Evidence

The DirecNet GlucoWatch 2 Biographer (52), Guard Control (60), STAR-1 (55), and the JDRF randomized clinical trials [JDRF CGM RCT (61)] have all demonstrated a usage-dependent effect of lowering HbA1c in youth with T1DM. For example, the DirecNet Gluco-Watch study observed no benefit of

CGM use, primarily because few if any of the subjects used this device regularly. In the 6-month JDRF CGM RCT in patients with T1DM and HbA1c of 7.0% or greater, 83% of adults wore their CGM devices 6–7 d/wk and lowered HbA1c levels by 0.53% compared with controls. CGM was less effective in HbA1c reduction in younger patients in association with much less frequent use of the devices (61). Subjects in that study aged 8–17 yr who wore the CGM device 6–7 d/wk lowered HbA1c levels by 0.8% without increasing the frequency of low sensor glucose concentrations (62). Moreover, the improvement in glycemic control was maintained for a full 12 months in those subjects (21% of the pediatric cohort) who were able to continue the frequent use of these devices. It is also noteworthy that the incidence of severe hypoglycemia in the entire pediatric cohort was only 11.2 events per 100 patient-years over the 12 months of study. For comparison, the rate of severe hypoglycemia in intensively treated adolescents in the Diabetes Control and Complications Trial was 86 events per 100 patient years (63). Thus, CGM use may improve the safety of intensive treatment of children and adolescents with T1DM even when worn less than 6–7 d/wk.

Post hoc analyses of the JDRF CGM RCT data indicate that there are few strong predictors that can be used to identify which young patients with T1DM will use the sensor on a nearly daily basis. The only baseline characteristic other than older age that predicted near-daily CGM use was frequent daily blood glucose meter testing before entering the trial (64).

Additional data from the JDRF CGM RCT indicate that patients' perception of the inconvenience of using current CGM devices is the major obstacle to more consistent use of these systems (65).

In a randomized, controlled, multicenter European/Israeli study of both children (ages 10–17 yr) and adults with T1DM whose HbA1c levels were less than 7.5%, a *post hoc* per protocol analysis demonstrated that time spent in hypoglycemia below 63 mg/dl was reduced by 64% ($P < 0.001$) in the children (66).

Recommendation

2.3. We make no recommendations for or against the use of RT-CGM by children with T1DM who are less than 8 yr of age. More research in this field is needed.

2.3. Evidence

Randomized trials in younger age groups have been initiated, but no results have been reported yet. Limited data from nonrandomized studies indicate that these devices can be used successfully in patients less than 8 yr of age (47, 67). The quality of evidence is insufficient to support recommendations for or against its use in this patient population at this time.

Recommendation

2.4. We suggest that treatment guidelines be provided to patients to allow them to safely and effectively take advantage of the information provided to them by RT-CGM (2 | ⊕○○○).

2.4. Evidence

The DirecNet study group (68) has developed and implemented useful guidelines for initiating the use of RT-CGM. Proper training is necessary for patients and healthcare professionals to use CGM properly (69). Additional studies are needed to evaluate the effectiveness of current and future guidelines, with regard to the timing of a premeal insulin bolus, using glucose trends during exercise, and using RT-CGM when initiating pramlintide therapy.

Recommendation

2.5. We suggest the intermittent use of CGM systems designed for short-term retrospective analysis in pediatric patients with diabetes for whom clinicians worry about nocturnal hypoglycemia, dawn phenomenon, and postprandial hyperglycemia; in patients with hypoglycemic unawareness and in patients experimenting with important changes to their diabetes regimen (such as instituting new insulin or switching from MDI to pump therapy) (2 | ⊕○○○). These devices represent an alternative for patients who

cannot safely and effectively take advantage of the information provided to them by RT-CGM.

2.5. Evidence

When the MiniMed CGMS was first introduced for 3-d retrospective analysis of plasma glucose profiles, investigators quickly showed that this method of glucose monitoring revealed patterns of post-meal hyperglycemia and nocturnal hypoglycemia that were not evident during standard SMBG testing in children with T1DM (45, 47). Several small clinical trials suggested that even one or two uses of the CGMS device could lead to treatment adjustments that had long-lasting improvements in metabolic control of T1DM (70–73). The validity of these findings has been cast in doubt by the results of RT-CGM studies that indicate the need for nearly daily use of the devices to obtain and maintain lowering in HbA1c levels (61). Nevertheless, in the judgment of many diabetes care providers, retrospective analysis of short-term CGM profiles can be of benefit in individual patients in whom the causes of persistent elevations in HbA1c are unclear.

Sensor-augmented pump therapy vs. insulin pump and SMBG at onset in youth with T1D

Use of CGM in combination with insulin pump therapy during the first year of diabetes does not appear to improve metabolic control in comparison to insulin pump therapy with standard SMBG when initiated in youth with T1D at the onset of the disease.

In the ONSET Study that involved 160 youth (aged 1–16 yr) (74), no significant difference in HbA1c levels was observed after 12 months in subjects randomized to sensor-augmented pump therapy (*i.e.* pump and CGM) in comparison with the use of insulin pumps and standard blood glucose meter monitoring.

3.0. RT-CGM IN ADULT OUTPATIENTS

Recommendation

3.1. We recommend that RT-CGM devices be used by adult patients with T1DM who have HbA1c levels of at least 7.0% and who have demonstrated they can use these devices on a nearly daily basis (1 | ⊕⊕⊕⊕).

Evidence

The JDRF CGM RCT (59), the GuardControl Study (60), and O'Connell *et al.* (75) demonstrated that adults with HbA1c of at least 7.0% had a greater reduction in HbA1c with the use of RT-CGM than with intermittent SMBG. Furthermore, unlike findings with SMBG, the improvement in HbA1c with CGM is not accompanied by an increase in biochemical hypoglycemia (54, 60). The improvement in HbA1c in the CGM subjects in the 6-month JDRF trial was sustained during the 6-month observational period that followed completion of the trial (76). This ongoing benefit occurred despite reduction in office visit frequency during this observational period to levels (2.7 ± 1.2 visits over 6 months) similar to routine care. Furthermore, the incidence rate of severe hypoglycemia declined from 20.5 events per 100 patient-years during the initial 6-month randomized trial to 12.1 events per 100 patient-years during the 6-month observational follow up. In a randomized, controlled, multicenter European/Israeli study of both children (ages 10–17 yr) and adults with T1DM whose HbA1c levels were less than 7.5%, a *post hoc* per protocol analysis demonstrated that time spent in hypoglycemia below 63 mg/dl was reduced by 50% ($P = 0.02$) in the adults (66).

Recommendation

3.2. We recommend that RT-CGM devices be used by adult patients with T1DM who have HbA1c levels less than 7.0% and who have demonstrated that they can use these devices on a nearly daily basis (1 | ⊕⊕⊕⊕).

3.2. Evidence

The JDRF CGM Study Group has demonstrated that in patients with T1DM who have achieved HbA1c levels less than 7.0%, RT-CGM use can reduce the frequency of biochemical hypoglycemia (which they defined as a blood glucose level of below 70 mg/dl) and help maintain HbA1c levels less than 7.0% compared with standard blood glucose monitoring over a 6-month study period. Of the 129 enrolled subjects, 62 (or 48%) were younger than 25, and 67 (or 52%) were more than 25 yr of age. The median time per day with a glucose level of 70 mg/dl or less as measured with CGM was less in the CGM group than in the control group; however, the difference was not statistically significant. In this study, almost all the other analyses (including the time per day \leq 60 mg/dl, time per day between 71 and 180 mg/dl, and combined outcomes involving HbA1c coupled with hypoglycemia) favored the CGM group compared with the control group. Treatment effects were generally similar across age groups (59). For the CGM users who were 25 yr and older, the incidence rate of severe hypoglycemia was 21.8 events per 100 person-years during the 6-month randomized controlled trial and 7.1 events per 100 person-years during the 6 months of continued CGM use after the conclusion of the randomized clinical trial (the observational period that followed the trial). For these CGM users whose HbA1c levels were below 7.0%, these incidences were 23.6 events per 100 person-years during the 6-month randomized controlled trial and 0 per 100 patient-years during the 6 months of continued CGM use after the conclusion of the randomized clinical trial (76). This evidence of an ongoing learning curve and improvement in glycemic control over the long term points to the user dependence of CGM technology, and this may partly account for the failure of other randomized trials enrolling individuals with poorer glycemic control (55) to demonstrate a reduction in severe hypoglycemia.

Recommendation

3.3. We suggest that the intermittent use of CGM systems designed for short-term retrospective analysis may be of benefit in adult patients with diabetes to

detect nocturnal hypoglycemia, the dawn phenomenon, and postprandial hyperglycemia, and to assist in the management of hypoglycemic unawareness and when significant changes are made to their diabetes regimen (such as instituting new insulin or switching from MDI to pump therapy) (2 | \oplus ○○○). These devices represent an alternative for patients who cannot safely and effectively take advantage of the information provided to them by RT-CGM.

3.3. Evidence

The studies and conclusions discussed in recommendation 2.6 pertain to adult patients as well as pediatric patients. There is also evidence that intermittent profiles can provide additional insights in adults with type 2 diabetes mellitus regarding glucose levels and the time in target range (77).

CONCLUSIONS

CGM can be beneficial in maintaining target levels of glycemia and limiting the risk of hypoglycemia. The Task Force used best available data to make recommendations about the use of CGM in three clinical settings: 1) RT-CGM in adult hospital settings; 2) RT-CGM in children and adolescent outpatients; and 3) RT-CGM in adult outpatients. With varying degrees of strength of evidence and quality of evidence, the Task Force recommended the use of CGM in the second and third settings. The routine use of this technology will also depend in part on future determinations of its cost relative to its benefits. The Task Force recommended against using CGM in adult hospital settings at this time and can make no recommendations about the use of CGM in children less than 8 yr of age because of the paucity of data.

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Acknowledgments

The members of the Task Force thank The Endocrine Society's Clinical Guidelines Subcommittee, Clinical Affairs Core Committee, and Council for their careful, critical review of earlier versions of this manuscript and their helpful comments and suggestions. We also thank the leadership of the Diabetes Technology Society and the European Society of Endocrinology for their review and comments. Finally we thank the many members of The Endocrine Society who reviewed the draft version of this manuscript when it was posted on the Society's web site and who sent a great number of additional comments and suggestions, most of which were incorporated into the final version of the guideline.

Financial Disclosures of the Task Force

David C. Klonoff, M.D., F.A.C.P. (chair)—Financial or Business/Organizational Interests: Bayer, C8 MediSensors, Insuline, LifeScan, Medtronic Diabetes, Roche; Significant Financial Interest or Leadership Position: Diabetes Technology Society. **Bruce Buckingham, M.D.**—Financial or Business/Organizational Interests: MedTronic MiniMed, LifeScan, Novo Nordisk, JDRE, UnoMedical; Significant Financial Interest or Leadership Position: none declared. **Jens S. Christiansen, M.D., F.R.C.P.I., Dr.Med.Sci.**—Financial or Business/Organizational Interests: Novo Nordisk, Roche; Significant Financial Interest or Leadership Position: European Society of Endocrinology. **Victor M. Montori, M.D.***—Financial or Business/Organizational Interests: KER Unit (Mayo Clinic); Significant Financial Interest or Leadership Position: none declared. **William V. Tamborlane, M.D.**—Financial or Business/Organizational Interests: Medtronic Diabetes, Abbott Diabetes, Novo Nordisk, Eli Lilly, Macrogenics; Significant Financial Interest or Leadership Position: Novo Nordisk, Eli Lilly, Medtronic, Macrogenics. **Robert A. Vigersky, M.D.**—Financial or Business/Organizational Interests: Dexcom; Significant Financial Interest or Leadership Position: The Endocrine Society. **Howard Wolpert, M.D.**—Financial or Business/Organizational Interests: Insulet, Novo Nordisk, Roche; Significant Financial Interest or Leadership Position: Insulet.

*Evidence-based reviews for this guideline were prepared under contract with The Endocrine Society.

What goes into our Clinical Guidelines is a story worth telling

Developed independently by a team of experts, evidence-based, and vetted through a rigorous, multi-step peer review process, the *Continuous Glucose Monitoring* Guideline addresses:

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- Real-time CGM in Children and Adolescent Outpatients
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