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International Consensus on Use of Continuous Glucose Monitoring

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Title:

International Consensus on Use of Continuous Glucose Monitoring

Running Title:

CGM Consensus

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Abbreviations

AACE, American Association of Clinical Endocrinologists; ACE, American College of Endocrinology; ADA, American Diabetes Association; ADAG, A1C-Derived Average Glucose; ADRR, Average Daily Risk Range; AGP, Ambulatory Glucose Profile; ATTD, Advanced Technologies and Treatments for Diabetes Congress; AUCpp, area under the curve of postprandial blood glucose; BG, blood glucose; BGM, blood glucose meters; BMI, body mass index; CONGA, Continuous glucose monitoring, CGM; Continuous Overlapping Net Glycemic Action; CSII, continuous subcutaneous insulin infusion; CV, coefficient of variation; DCCT, The Diabetes Control and Complications Trial; DKA,

diabetic ketoacidosis; DSST**,** Digit Symbol Substitution Test; eAG, estimated Average Glucose; EDIC, Epidemiology of Diabetes Interventions and Complications; GLP-1, glucagon-like peptide-1; GRADE, glycemic risk assessment diabetes equation; GV glycemic variability; HbA1c, glycated hemoglobin; HCL, Hybrid Closed-Loop; HGI, High Glucose Index; HRR, Hourly risk range; IAH, impaired awareness of hypoglycemia; IGP, incremental glucose peak; IMT, carotid intima-media thickness; iCGM, intermittently-viewed CGM; IQR, interquartile range; ISF, interstitial fluid; ISO, International Organization for Standardization; JDRF, Juvenile Diabetes Research Foundation; LGI, Low Glucose Index; LGS, low glucose suspension; MAD, mean absolute difference; MAG, Mean Absolute Glucose Change; MAGE, mean amplitude of glucose excursions; MARD, mean absolute relative difference; MDI, multiple daily insulin injections; MODD, mean of daily differences; OAD, oral antidiabetic drug; PARD, precision absolute relative difference; RBCs, red blood cells; rtCGM, real-time continuous glucose monitoring; SAP, sensor augmented pump therapy; SD, standard deviation; SDS, Standard Deviation Score; SEG, surveillance error grid**;** SH, severe hypoglycemia; SDBG, standard deviation of blood glucose; SMBG, self-monitoring of blood glucose; T1D, type 1 diabetes; TIR, Time in Range; UKPDS, United Kingdom Prospective Diabetes Study; VGA, Variability-Grid Analysis;

(ABSTRACT)

Measurement of glycated hemoglobin (HbA1c) has been the traditional method for assessing glycemic control. However, it does not reflect intra- and inter-day glycemic excursions that may lead to acute events (such as hypoglycemia) or postprandial hyperglycemia, which have been linked to both microvascular and macrovascular complications. Continuous glucose monitoring (CGM), either from real-time use (rtCGM) or intermittently-viewed continuous glucose monitoring (iCGM), address many of the limitations inherent in HbA1c testing and SMBG. Although both provide the means to move beyond the HbA1c measurement as the sole marker of glycemic control, standardized metrics for analyzing CGM data are lacking. Moreover, clear criteria for matching people with diabetes to the most appropriate glucose monitoring methodologies, and standardised advice about how best to use the new information they provide, have yet to be established. In February 2017, the Advanced Technologies and Treatments for Diabetes (ATTD) Congress convened an international panel of physicians, researchers and individuals with diabetes who are expert in CGM technologies to address these issues. This article summarizes the ATTD consensus recommendations and represents the current understanding of how CGM results can affect outcomes.

INTRODUCTION

Glucose measurements are critical to effective diabetes management. Although measurement of glycated hemoglobin (HbA1c) has been the traditional method for assessing glycemic control, it does not reflect intra- and inter-day glycemic excursions that may lead to acute events (such as hypoglycemia) or postprandial hyperglycemia, which have been linked to both microvascular and macrovascular complications. Moreover, although self-monitoring of blood glucose (SMBG) has been shown to improve glycemic control and quality of life in both insulin-treated and non-insulin-treated diabetes when used within a structured testing regimen (1-4) [C,C,C,C], it cannot predict impending hypoglycemia or alert for hypoglycemia (5, 6) [C,C].

Real-time continuous glucose monitoring (rtCGM) and intermittently-viewed continuous glucose monitoring (iCGM) address many of the limitations inherent in HbA1c testing and SMBG. rtCGM uniformly tracks the glucose concentrations in the body's interstitial fluid (ISF), providing near real-time glucose data; iCGM uses similar methodology to show continuous glucose measurements retrospectively at the time of checking. Both rtCGM and iCGM facilitate monitoring of time spent in the target glucose range ("time in range"). However, only rtCGM can warn users if glucose is trending toward hypoglycemia or hyperglycemia. With iCGM, these trends can only be viewed after physically scanning the sensor. It is often difficult to distinguish between technologies, regarding issues such as calibrations, alarms/alerts, human factors of applying and wearing sensors and the cost, which are device-specific. As these technological details are subject to constant change the term CGM is used for all issues related to the device class unless indicated otherwise.

In February 2017, the Advanced Technologies and Treatments for Diabetes

(ATTD) Congress convened an international panel of physicians, researchers and individuals with diabetes who are expert in CGM to address these issues. The purpose of the conference was to provide guidance for clinicians, patients and researchers in utilizing, interpreting and reporting CGM data in clinical care and research. The panel was divided into subgroups to review the literature and provide evidence-based recommendations for relevant aspects of CGM utilization and reporting. Primary citations were identified for each topic, assigned a level of evidence (indicated next to the corresponding citation in the text and in the reference section) and verified by the expert panel.

This article summarizes the ATTD consensus recommendations and represents the current state of knowledge on CGM results affecting outcomes. The content represents the consensus of the panel members' comprehensive evaluation of the issues. Supporting evidence is included in the online supplemental material identified at the end of each section.

1. Limitations of HbA1c

Key Findings

- The Diabetes Control and Complications Trial (DCCT), followed by the Epidemiology of Diabetes Interventions and Complications (EDIC), demonstrated how elevated HbA1c contributes to complications in type 1 diabetes (T1D). The United Kingdom Prospective Diabetes Study (UKPDS) confirmed the importance of glycemic control as well as other components of metabolic control, namely blood pressure, on health outcomes in individuals with type 2 diabetes (T2D) (7, 8) [A,A].
- Most global organizations recommend target HbA1c levels of <7.0% (53 mmol/mol) for adults and <7.5% (58 mmol/mol) for children; although several organizations suggest an

HbA1c target of ≤6.5% for adults (9) [E] and children (10) [E]. However, all organizations agree that HbA1c targets should be individualized to each patient.

- Although HbA1c remains the reference marker for assessing glycemic control and predicting the risk of development of long-term complications, it has several limitations: 1) provides only an average of glucose levels over the previous past 2-3 months; 2) does not detect hypoglycemia or hyperglycemia on a daily basis; 3) is an unreliable measure in patients with anemia (11) [B], hemoglobinopathies (12) [B], iron deficiency (13) [B] and during pregnancy (14) [B]; 4) does not reflect rapid changes in daily glucose control. and 5) does not provide data as to how to adjust treatment regimen when HbA1c levels are elevated. In summary, although HbA1c has proved extremely valuable in patient management, is a valuable measure of population health and remains a validated indicator of glycation as a risk factor for complications, it is not as helpful for personalized diabetes management.
- The literature suggests that ethnic and racial differences exist in glycation rates (15-17) [B,C,C], which affect the accuracy of HbA1c measurements; however, a racial difference was not found in the relationship between mean glucose and fructosamine or glycated albumin levels. This suggests that the racial discordance in glycation rates is specific to the red blood cell. The effects of ethnic differences on average HbA1c cannot be entirely explained by measured differences in glycemia, differences in sociodemographic or clinical factors, or differences in access to care or quality of care (18) [E].
- An estimated HbA1c (eA1C) can be calculated if adequate rtCGM/iCGM data (70% or 10 days of the 14 days of CGM data) are available. The eA1C and laboratory measured HbA1c may differ to some degree for a given individual because there are many factors that affect an HbA1c reading, and tables that convert HbA1c to a mean glucose and vice-versa are based

on mean values for a population. Knowing how an individual's CGM-derived eA1C compares to their laboratory measured HbA1c may be helpful in safe and effect clinical management (19) [E].

Recommendations

- HbA1c should be measured with a device that is certified by the NGSP (National Glycohemoglobin Standardization Program, www.ngsp.org) or the IFCC (International Federation of Clinical Chemistry and Laboratory Medicine (www.ifcchba1c.net)
- Clinicians and patients should target an HbA1c as close to normal as possible without severe hypoglycemia (SH) or a significant amount of non-severe hypoglycemia while at the same time indicating a need to individualize glycemic targets according to patient age, duration, co-morbidities, and expected life expectancy with 'less strict' HbA1c targets for those more frail (20) [A].
- When there is a discrepancy between actual HbA1c and the estimated HbA1c based on mean glucose, other glucose measurement methods such as, fructosamine, glycated albumin, SMBG and, in particularly CGM should be used in conjunction with HbA1c measurements when assessing glycemic control and adjusting therapy.
- CGM data should be used to assess hypoglycemia and glucose variability.

Additional discussion of these recommendations and supporting evidence is presented as online supplemental material. (**APPENDIX 1**).

2. Use of glucose monitoring methodologies (SMBG and CGM) to guide management and assess outcomes in different patient populations

Key Findings

- Self-monitoring of blood glucose (SMBG) has been shown to be helpful or to correlate with effective management in insulin-treated and non-insulin-treated diabetes (1-4, 21, 22) [C,C,C,C,A,C], however, SMBG has notable limitations. First, it requires a fingerstick to obtain a blood sample. Moreover, it only provides a single "point-in-time" measurement, which provides no indication of the direction or rate of change of glucose levels. Thus, using SMBG data alone may result in inappropriate therapy decisions (such as administering correction insulin when blood glucose levels are falling). Second, obtaining glucose data via SMBG is dependent upon the patient's decision to self-monitor. Accordingly, SMBG often fails to detect nocturnal and asymptomatic hypoglycemia (5, 6) [C,C].
- iCGM provides the current glucose value plus retrospective glucose data for a specified time period upon "scanning". At the time of this writing, only one iCGM system, also known as "flash" monitoring, was available. This system utilizes two components: a glucose sensor, which is inserted the user's upper arm; and a separate touchscreen reader device. When the reader device is swiped close to the sensor, the sensor transmits both an instantaneous glucose level and an eight-hour trend graph to the reader. The only currently available iCGM device is factory calibrated, lasts up to 14 days and does not need to be calibrated by the user. However, iCGM lacks alarms for low and high glucose values, and, as with SMBG, measurements are only visualized when the user of the device chooses to make a measurement. Two studies using iCGM have demonstrated significant improvements in hypoglycemia, time in range, glycemic variability and user satisfaction (23, 24) [B,B]. The

Flash device is also available without need for scanning in a blinded mode for clinical research or retrospective glucose pattern evaluation.

- rtCGM in unblinded mode provides real-time numerical and graphical information about the current glucose level, glucose trends, and the direction/rate of change of glucose. Devices with programmable alerts/alarms that warn users of current and/or impending high or low glucose offer additional safety advantages. In Europe, a new type of implantable rtCGM system is available as an alternative for transcutaneous CGM (25) [C].
- Numerous studies have shown that use of rtCGM improves glycemic control and quality of life in both children and adults with T1D treated with either continuous subcutaneous insulin infusion (CSII) or multiple daily insulin injection (MDI) therapy, improving HbA1c, shortening the time spent in hypoglycemia and hyperglycemia and reducing moderate to severe hypoglycemia (26-37) [C,C,B,B,C,C,A,C,B,C,B]. The benefit of rtCGM was seen primarily in those patients who regularly used their devices (26, 28, 35) [C,B,B]. In a lifetime analysis, rtCGM reduced overall diabetes-related complications (38) [B]. Similar results of the cost-effectiveness of rtCGM vs SMBG were reported using a larger population base model (39).
- Using data collected from a meta-analysis of patient-level data (35) [B] sensor-augmented pump therapy was determined to be cost-effective for the treatment of T1D in the Swedish health-care system (40) [C]. Sensitivity analyses indicated further cost-effectiveness benefit of increasing the amount of rtCGM use from 5 to 7 days a week, and decreasing the use of SMBG was incrementally cost-effective at every level.
- Subsequent studies have determined that sensor-augmented pump systems with a low-glucose suspend feature (SAP+LGS) are also cost-effective relative to insulin pump therapy

alone, in the Australian (41) [C], UK (42) [[C] and French (43) [C] healthcare systems, due to improved glycemic control and reduction in hypoglycemia.

- Benefits of rtCGM use have also been reported in individuals with T2D who are managed with or without intensive insulin treatment (44-46) [B,C,C]. There are limited data regarding the benefit of rtCGM as an outcome measure for individuals with gestational diabetes (GDM) and T2D, especially in those who do not use insulin (47) [C].
- The benefit of rtCGM is directly correlated to persistence and frequency of use. A meta-analysis by Pickup et al. found that every one day increase of sensor usage per week increased the effect of continuous glucose monitoring; the effect on HbA1c is more pronounced the higher the initial HbA1c (35) [B].

Recommendations

- CGM should be considered in conjunction with HbA1c for glycemic status assessment and therapy adjustment in all T1D patients and T2D patients treated with intensive insulin therapy who are not achieving glucose targets, especially if the patient is experiencing problematic hypoglycemia.
- Structured testing regimens should be defined for patients when SMBG is prescribed.
- All patients should receive training in how to interpret and respond to their glucose data regardless of the monitoring method used. Patient education and training for CGM should utilize standardized programs with follow-up to improve adherence and facilitate appropriate use of data and diabetes therapies.

Additional discussion of these recommendations and supporting evidence is presented as online supplemental material. (**APPENDIX 2**).

3. Minimum requirements for CGM performance

Key Findings

- No internationally-accepted standard exists for CGM system performance comparable with the International Organization for Standardization (ISO) 15197 standard for SMBG, which specifies design verification procedures and the validation of performance by the intended users. However, ISO/IEEE FDIS 11073-10425 provides a normative definition of the communication between CGM devices and managers (such as cell phones, personal computers, personal health appliances, and set top boxes) in a manner that enables plug-and-play interoperability.
- In contrast to iCGM, the accuracy of current rtCGM systems is dependent on SMBG testing for calibration. Therefore, it is important to have an accurate glucose meter. Successful calibration also requires several conditions, for example, it is best performed when glucose is not changing rapidly. Importantly, users must be educated in the appropriate techniques.
- The mean absolute relative difference (MARD) is currently the most common metric used to assess the performance of CGM systems. MARD is the average of the absolute error between all CGM values and matched reference values. A small percentage indicates that the CGM readings are close to the reference glucose value; whereas, a larger MARD percentage indicates greater discrepancies between the CGM and reference glucose values.
- Comparing MARD values from different clinical studies has several limitations, thus head-to-head studies should be performed. Additional metrics, such as precision absolute relative

difference (PARD), can be used as well to obtain an additional evaluation of the CGM performance (48) [C].

- Although controversy exists regarding the exact cut point for accuracy, *in silico* testing has shown that a further lowering of mean absolute relative difference (MARD) ≤10% from reference values has little additional benefit for insulin dosing (49) [C].

Recommendations

- Only CGM systems that provide an acceptable level of sensor accuracy should be used.

Additional discussion of these recommendations and supporting evidence is presented as online supplemental material. (**APPENDIX 3**).

4. Definition and assessment of hypoglycemia in clinical studies

Key Findings

- Hypoglycemia remains a major barrier for glycemic control and a common complication of diabetes treatment, especially in T1D (50) [E].
- In adults with T1D, severe hypoglycemia (SH) is more related to duration of diabetes and socio-economic status than HbA1c (34). Similarly, in children 6-17 years old with T1D (51) [C] or adults with T2D (mostly receiving insulin or sulfonylureas (52) [B], SH was most common with the lowest and highest HbA1c levels.
- Needing assistance is the usual concise definition for severe hypoglycemia. Most children require assistance with all hypoglycemia not just severe hypoglycemia (53) [C]. Therefore, SH in children is often defined as an event associated with a seizure or loss of consciousness

or requiring emergency medical personnel or visit to the emergency department or a hospital admission. In adults, the definition of severe hypoglycemia often includes episodes associated with coma or seizure, for which the patient, perhaps being on their own, recovered spontaneously.

- The degree of hypoglycemia that causes clinical symptoms and counterregulatory response is specific to the individual and depends on the personal level of glycemic control (53) [C].
- Studies indicate that hypoglycemia for 2 or more hours impairs hormonal responses (54, 55) [C,B].
- Gradation of hypoglycemic events may be valuable. Specifically, that of a prolonged hypoglycemic event, in which the CGM levels indicate glucose levels <54 mg/dL (<3.0 mmol/L) for ≥120 minutes. While this metric is somewhat arbitrary, a study by Oz et al. found that the glycogen signal decreases with a rate of ~10% per hour in the human brain at blood glucose levels of <54 mg/dL (<3.0 mmol/L) indicating a mobilization rate commensurate with the severity of hypoglycemia (56) [B].
- The low blood glucose index (LBGI), is a metric specifically designed to calculate the risk for hypoglycemia as reflected by SMBG data (57) [B]. However, LBGI calculations based on CGM data tend to slightly underestimate risk, particularly in the low risk range (58) [C]

Recommendations

- The definition of hypoglycemia should take into consideration several parameters: the compartment of measurement (arterial, venous, and capillary blood or interstitial); the nadir level of blood glucose measured; and the duration of the event and related symptoms.

- When assessing hypoglycemia using CGM, the accuracy of the data in the lower glycemic range should be considered.
- The following classifications of hypoglycemia, based on clinical evaluation, should be used in categorizing levels of hypoglycemia:
    - Level 1: A hypoglycemia alert glucose value of <70-54 mg/dL (<3.9-3.0 mmol/L) with or without symptoms. This should be considered an alert that the individual may be at risk for developing hypoglycemia and should work to minimize the time spent in this range to reduce the risk of developing more clinically significant hypoglycemia. This need not be reported routinely in clinical studies, although this would depend on the purpose of the study. Nevertheless, most clinicians want to know how often patients are <70-54 mg/dL (<3.9-3.0 mmol/L) and would act to reduce the time spent in this range to minimize the risk of more clinically significant hypoglycemia occurring.
    - Level 2: A glucose level of <54 mg/dL (<3.0 mmol/L) with our without symptoms. This should be considered clinically significant hypoglycemia requiring immediate attention.
    - Level 3: Severe hypoglycemia. This denotes cognitive impairment requiring external assistance for recovery (59) [E] but is not defined by a specific glucose value.
- For clinical study CGM outcomes reports, hypoglycemia values <54 mg/dL (<3.0 mmol/L) should be given more weight or importance than those <70-54 mg/dL (<3.9-3.0 mmol/L).
- When assessing hypoglycemia in clinical care, other important consequences or adverse patient reported outcomes should be considered:
    - Reduced awareness of subsequent hypoglycemia.

  - Associated cardiac arrhythmia, confusion, abnormal or combative behavior.
  - Weight gain.
  - Fear of hypoglycemia.
- Hypoglycemia should be quantified in the following ways:
  - As the percentage of CGM values that are below a given threshold (<70 mg/dL [3.9 mmol/L] or < 54 mg/dL [3.0 mmol/L]) or the number of minutes or hours below these thresholds.
  - As the number of hypoglycemic events that occur over the given CGM reporting period.
- A hypoglycemic event should be defined as follows:
  - Beginning of a CGM event – readings below the threshold for at least 15 minutes is considered an event. For example, at least 15 minutes <54 mg/dL (<3.0 mmol/L) to define a clinically significant (Level 2) hypoglycemic event.
  - End of a CGM event – readings for 15 minutes at ≥70 mg/dL (≥3.9 mmol/L).
  - A second hypoglycemic event outcome of prolonged hypoglycemia is considered when CGM levels are <54 mg/dL (<3.0 mmol/L) for consecutive 120 minutes or more.
- LBGI should be reviewed when assessing hypoglycemia risk.

Additional discussion of these recommendations and supporting evidence is presented as online supplemental material. (**APPENDIX 4**).

5. Assessment of glycemic variability (GV)

Key Findings

- Numerous studies have focused on glycemic variability (GV) as an independent risk factor for diabetes complications, particularly cardiovascular disease (60-63) [C,E,C,C] and on the effects of GV on cognitive function and quality of life (64) [C].
- Acceptance of GV as a clinically valuable marker of glycemic control has greatly expanded the understanding of glycemic control beyond HbA1c alone. (65-68) [E,E,E,E].
- While the interpretation of average blood glucose is relatively straightforward, providing a direct relationship to HbA1c, GV is a reflection of a dynamic process, and its understanding and measuring are less apparent (69, 70) [E,C]. Beyond the setting of laboratory experiments, the data sources available for routine estimation of GV include episodic SMBG records and CGM traces (71) [B]. The density of the available data determines what properties of GV can be investigated.
- GV is a process characterized by the amplitude, frequency and duration of the fluctuation.
- Both the amplitude and the timing of blood glucose (BG) fluctuations contribute to the risks for hypoglycemia and hyperglycemia associated with diabetes (72) [C]. Increased glucose variability is consistently associated with mortality in the intensive care unit (73, 74) [C,B] and is a consistent predictor of hypoglycemia, both in prospective studies and within the setting of randomized clinical trials (64, 75) [C,B].
- When quantifying glucose variability from CGM data, the following physiological and statistical factors should be considered:
    - In healthy individuals, the metabolic system has a physiological equilibrium range (e.g., fasting BG) to which it returns if left undisturbed; with the progression of diabetes, this equilibrium range moves up.

- This physiological equilibrium range is relatively universal across people (hence the diagnostic criteria for pre-diabetes and diabetes). Therefore, the objective of diabetes control is to keep BG levels in the vicinity of a commonly accepted range (not the mean for a person, which is individual).
- Deviations in both directions from the range carry risks. These risks increase with the amplitude of the deviations, nonlinearly and asymmetrically into the hypoglycemic and hyperglycemic ranges.
- The timing of the deviations is of essence as it reflects system (person) dynamics and system stability. However, most of the traditional GV metrics ignore the time axis of CGM data.
- Mathematical methods (e.g., risk analysis, time series) are well developed and can be adapted to diabetes, keeping in mind the objectives of diabetes control.

- CGM data reflect the dynamics of glucose fluctuations by including all of these dimensions. A recent analysis of CGM data in comparison to blood glucose data obtained in a large study with patients with T1D showed how GV indices are related and demonstrated the impact of CGM use on GV (76) [C].
- Standard deviation (SD), coefficient of variation (CV) and mean amplitude of glucose excursions (MAGE) are widely used to quantify GV. The CV (which is the SD divided by the mean) has the advantage of being a metric relative to the mean, which makes it more descriptive of hypoglycemic excursions than the SD alone. For example, a population with a mean glucose of 150 mg/dL and an SD of 60 would have a CV of 40%.
- Stable glucose levels are defined as a CV <36%, unstable glucose levels as CV ≥36% (77) [E].

Recommendations

- GV evaluated from CGM data, should be considered among other factors of the overall clinical representation of glycemic control.
- CV should be considered the primary measure of variability; however, many clinicians may want to see SD reported as a key secondary GV measure since it is a metric with which they are familiar.
- The recommended metrics for GV should be included in summary statistics for data downloaded from CGM devices into reports.

Additional discussion of these recommendations and supporting evidence is presented as online supplemental material. (**APPENDIX 5**).

6. Time in "ranges"

- Time in range (TIR) generally refers to the time spent in an inidividual's target glucose range (usually 70-180 mg/dL [3.9-10 mmol/L, but occasionally 70-140 mg/dL [3.9-7.8 mmol/L]). TIR measurements add valuable information to assess the level of current glycemic control in addition to what is known from the HbA1c. However, clinicians, researchers and regulators now know that time in target range alone is not an adequate description of overall glycemic control. It is also necessary to quantitate the times below and above target range, using a few severity thresholds for each level. (78) [E]. Thus, time in "ranges" (TIRs) provides a more illustrative metric for clinical and research purposes.
- TIRs are useful for a research comparison of interventions and can help patients understand if the amount of clinically-significant hypoglycemia or hyperglycemia they are experiencing is

improving over time. Breaking out the time in hypoglycemia and hyperglycemia into Level 1 (monitor and take action if needed) and Level 2 (immediate action required due to the more potentially clinically significant nature of the glucose levels) can guide the urgency and degree of clinical response.

Composite Measures

- Because the function of CGM use is to monitor glucose levels with the ultimate goal of improving glycemic control, it makes clinical sense to combine TIRs data with other measures.
    - HbA1c level and time in Level 2 (Clinically significant / Immediate action required) hypoglycemia is one such combined measure.
    - Time in target range combined with time in Level 2 hypoglycemia is another such combined measure. This combined set of measures could be setup as a co-primary outcome for a clinical trial asking if one therapy is more effective than another in achieving an increased time in target range (70-180 mg/dL) while also being non-inferior for the Level 2 hypoglycemia achieved. One then needs to further define the parameters of judging non-inferior status. These examples make clinical sense, since one wants to improve glucose control (HbA1c or TIR) while also reducing or at least not increasing hypoglycemia.
    - Even broader combined measures of diabetes management such as targets for desired diabetes management are being explored (e.g., HbA1c + hypoglycemia + weight gain or HbA1c + blood pressure + low-density lipoprotein or HbA1c + blood pressure + low-density lipoprotein + aspirin use if high-risk cardiovascular disease + no tobacco use).

These composites emphasize the importance of taking a multifactorial approach to reducing diabetes complications, particularly cardiovascular disease.

Recommendations

- Times and/or percentages in target range, hypoglycemia and hyperglycemia should be assessed and reported.
- Different time in ranges (TIRs) in conjunction with a measure of GV should be reported as key diabetes control metrics in clinical studies.

7. Visualization, analysis and documentation of key CGM metrics

Key Findings

- Standardizing glucose reporting and analysis similar to an EKG output is vital to optimizing clinical decision making in diabetes. Further optimizing of such tools and expanding them into shared decision making guides is needed.
- Reporting CGM data in a standardized way, in conjunction with an HbA1c value and other clinical conditions (e.g., severe hypoglycemia, diabetic ketoacidosis) would foster a precise definition of this composite goal. Using a standardized composite goal, the medical community could establish with more confidence whether a particular insulin formulation, new technology for insulin delivery, or an innovative patient-centered approach to care was an important factor in helping individuals with diabetes reach optimal glycemic control.
- Standardized tools such as the Ambulatory Glucose Profile (AGP (79), Pattern Snapshot (Medtronic) (80), Clarity (Dexcom) (81) and others from various device makers and data management companies are now available. Use of the AGP approach was previously

endorsed by an expert panel of clinicians in a consensus conference held in 2012 (82) [E] and is recommended by this consensus group as a standard for visualization of CGM data.

- Integration of standardized metrics into electronic health records is important to maximize the clinical workflow and faciliate remote communications with patients.
- Patient responses to the current glucose level, trend arrows indicating rate of change of glucose and qualitative analysis of a graphical display of glucose versus time do not require stability of patterns. However, retrospective analysis of either CGM is dependent on stability of patterns from day to day (83) [B].
- A minimum of 14 consecutive days of data with approximately 70% of possible CGM readings over those 14 days appears to generate a report that enables optimal analysis and decision making and standard reporting and visualization of CGM data is important.

Recommendations

- 14 key metrics should be utilized to assess glycemic control and document:
    1. Mean glucose.
    2. Percentage/time in Level 2 hypoglycemic range (<54 mg/dL [3.0 mmol/L]). Urgency for action: *Clinically significant / Very low / Immediate action required.*
    3. Percentage/time in Level 1 hypoglycemic range (<70-54 mg/dL [<3.9-3.0 mmol/L]). Urgency for action: *Alert / Low / Monitor.*
    4. Percentage/time in target range: 70-180 mg/dL (3.9-10.0 mmol/L) (default); 70-140 mg/dL / 3.9-7.8 mmol/L (secondary); Individual targets closer to the physiological range can be defined, depending on age, comorbidities and/or patient adherence.

5. Percentage/time in Level 1 hyperglycemic range (>180 mg/dL [>10.0 mmol/L]). Urgency for action: *Alert / High / Monitor.*
6. Percentage/time in Level 2 hyperglycemic range (>250 mg/dL [>13.9 mmol/L]). Urgency for action: *Clinically significant / Very elevated / Immediate action.*
7. Glycemic variability, reported as CV (primary) and SD (secondary).
8. Estimated HbA1c (eA1c).
9. Data for glucose metrics (1-7) reported in 3 time blocks (sleep, wake, 24 hours) with the default times for the sleep (12:00 AM/midnight -5:59 AM) and wake (6:00AM-11:59PM) often written as midnight-6AM and 6AM to midnight.
10. Data sufficiency - minimum 2 weeks of data.
11. Data sufficiency - 70-80% of possible CGM readings over 2-week period.
12. Episodes of hypoglycemia, using a standard definition of episodes.
13. Area under the curve (AUC) (recommended for research purposes). This can be calculated from CGM analysis software and is recommended for research purposes as it is a measure the integrates to some extent the severity of a high or low glucose along with the duration of the abnormality.
14. Risk of hypoglycemia and hyperglycemia (LBGI and HBGI recommended).

- Standardized software for visualization and reporting of the 14 key CGM metrics should be considered an additional component (#15) of analysis and documentation. (Use of the AGP is recommended).
- Although severe hypoglycemia (Hypoglycemia Level 3) and diabetic ketoacidosis (Hyperglycemia Level 3) are not CGM data-based determinations, they should be reported and documented.

- For research purposes median and interquartile range (IQR) should be presented for all measurements.
- Conduct further studies to define in a variety of patient groups, including pediatrics, pregnancy, those with renal insufficiency and the elderly what is an acceptable and achievable TIR and the accompanying acceptable rates of hypoglycemia.

The key metrics for CGM analysis and reporting are presented in **Table 1**. **Figure 1** illustrates how these metrics are presented in the AGP.

CONCLUSIONS

CGM is a robust research tool, and continuous glucose data should be recognized by governing bodies as a valuable and meaningful endpoint to be used in clinical trials of new drugs and devices for diabetes treatment. The identification of hypoglycemia is as important as the measurement of time in range in clinical trials. Quantifying the duration and magnitude of glycemic excursions provides another means of assessing glucose control. The unifying theme of trials investigating the usefulness of CGM technologies is that the device must be worn on a near daily basis to optimize its benefits.

The expert panel concludes that, in clinical practice, the advanced metrics of assessing continuous glucose data presented here are appropriate as outcome parameters that complement HbA1c for a wide range of patients with diabetes and should be considered for use to help them improve glycemic control provided that appropriate educational and technical support is available.

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Table 1. **Key metrics for CGM data analysis and reporting**

CGM Metric	Measures	ATTD Consensus
1	**Mean glucose**	√ **(calculated)**
	Severe Hypoglycemia*	**Clinical Dx**: Event requiring assistance (Level 3)
	%/time In Hypoglycemic Ranges (mg/dL / mmol/L)	
2	Clinically significant / Very low / Immediate action required	**< 54 / <3.0** (Level 2)
3	Alert / Low / Monitor	**<70-54 / <3.9-3.0** (Level 1)
	%/time In Target Range (mg/dL / mmol/L)	
4	Default	**70-180 / 3.9-10.0**
	Secondary	**(70-140 / 3.9-7.8)**
	%/time In Hyperglycemic Ranges (mg/dL / mmol/L)	
5	Alert / Elevated / Monitor	**> 180 / >10** (Level 1)
6	Clinically significant / Very elevated / Immediate action required	**> 250 / > 13.9** (Level 2)
	Diabetic Ketoacidosis (DKA)	**Clinical Dx**: Ketones, acidosis, and usually hyperglycemia (Level 3)
7	**Glycemic Variability (GV)** Primary GV	**CV**
	Stable:	CV <36%,
	Unstable:	CV ≥36%
	Secondary GV	(SD)
8	**eA1c**	√ **(calculated)**
9	**3 Time Blocks: Sleep, Wake, 24 hrs.**	**12AM-6AM / 6AM-12PM / 12AM-12AM**
	Recommended Data Sufficiency	
10	Collection Period (min. # of wks)	**2**
11	% of expected CGM readings (min. %)	**70-80** (10 of 14 days)
12	**Episodes of Hypo/Hyper (minimum # minutes)** (with beginning & end of episode defined)	**15 min**
13	**Area Under the Curve (AUC)**	√ **(calculated)**
14	**Risk of Hypo & Hyper**	**LBGI / HBGI** recommended
15	**Standardized CGM visualization of data**	**AGP** recommended

* Severe hypoglycemia (Level 3) and diabetic ketoacidosis (Level 3) are not key CGM metrics, per se. However, these conditions are included in the table because they are important clinical categories that must be assessed and documented.

Title:

International Consensus on Use of Continuous Glucose Monitoring

Running Title:

CGM Consensus

Authors:

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Abbreviations

AACE, American Association of Clinical Endocrinologists; ACE, American College of Endocrinology; ADA, American Diabetes Association; ADAG, A1C-Derived Average Glucose; ADRR, Average Daily Risk Range; AGP, Ambulatory Glucose Profile; ATTD, Advanced Technologies and Treatments for Diabetes Congress; AUCpp, area under the curve of postprandial blood glucose; BG, blood glucose; BGM, blood glucose meters; BMI, body mass index; CONGA, Continuous glucose monitoring, CGM; Continuous Overlapping Net Glycemic Action; CSII, continuous subcutaneous insulin infusion; CV, coefficient of variation; DCCT, The Diabetes Control and Complications Trial; DKA,

diabetic ketoacidosis; DSST**,** Digit Symbol Substitution Test; eAG, estimated Average Glucose; EDIC, Epidemiology of Diabetes Interventions and Complications; GLP-1, glucagon-like peptide-1; GRADE, glycemic risk assessment diabetes equation; GV glycemic variability; HbA1c, glycated hemoglobin; HCL, Hybrid Closed-Loop; HGI, High Glucose Index; HRR, Hourly risk range; IAH, impaired awareness of hypoglycemia; IGP, incremental glucose peak; IMT, carotid intima-media thickness; iCGM, intermittently-viewed CGM; IQR, interquartile range; ISF, interstitial fluid; ISO, International Organization for Standardization; JDRF, Juvenile Diabetes Research Foundation; LGI, Low Glucose Index; LGS, low glucose suspension; MAD, mean absolute difference; MAG, Mean Absolute Glucose Change; MAGE, mean amplitude of glucose excursions; MARD, mean absolute relative difference; MDI, multiple daily insulin injections; MODD, mean of daily differences; OAD, oral antidiabetic drug; PARD, precision absolute relative difference; RBCs, red blood cells; rtCGM, real-time continuous glucose monitoring; SAP, sensor augmented pump therapy; SD, standard deviation; SDS, Standard Deviation Score; SEG, surveillance error grid**;** SH, severe hypoglycemia; SDBG, standard deviation of blood glucose; SMBG, self-monitoring of blood glucose; T1D, type 1 diabetes; TIR, Time in Range; UKPDS, United Kingdom Prospective Diabetes Study; VGA, Variability-Grid Analysis;

(ABSTRACT)

Measurement of glycated hemoglobin (HbA1c) has been the traditional method for assessing glycemic control. However, it does not reflect intra- and inter-day glycemic excursions that may lead to acute events (such as hypoglycemia) or postprandial hyperglycemia, which have been linked to both microvascular and macrovascular complications. Continuous glucose monitoring (CGM), either from real-time use (rtCGM) or intermittently-viewed continuous glucose monitoring (iCGM), address many of the limitations inherent in HbA1c testing and SMBG. Although both provide the means to move beyond the HbA1c measurement as the sole marker of glycemic control, standardized metrics for analyzing CGM data are lacking. Moreover, clear criteria for matching people with diabetes to the most appropriate glucose monitoring methodologies, and standardised advice about how best to use the new information they provide, have yet to be established. In February 2017, the Advanced Technologies and Treatments for Diabetes (ATTD) Congress convened an international panel of physicians, researchers and individuals with diabetes who are expert in CGM technologies to address these issues. This article summarizes the ATTD consensus recommendations and represents the current understanding of how CGM results can affect outcomes.

INTRODUCTION

Glucose measurements are critical to effective diabetes management. Although measurement of glycated hemoglobin (HbA1c) has been the traditional method for assessing glycemic control, it does not reflect intra- and inter-day glycemic excursions that may lead to acute events (such as hypoglycemia) or postprandial hyperglycemia, which have been linked to both microvascular and macrovascular complications. Moreover, although self-monitoring of blood glucose (SMBG) has been shown to improve glycemic control and quality of life in both insulin-treated and non-insulin-treated diabetes when used within a structured testing regimen (1-4) [C,C,C,C], it cannot predict impending hypoglycemia or alert for hypoglycemia (5, 6) [C,C].

Real-time continuous glucose monitoring (rtCGM) and intermittently-viewed continuous glucose monitoring (iCGM) address many of the limitations inherent in HbA1c testing and SMBG. rtCGM uniformly tracks the glucose concentrations in the body's interstitial fluid (ISF), providing near real-time glucose data; iCGM uses similar methodology to show continuous glucose measurements retrospectively at the time of checking. Both rtCGM and iCGM facilitate monitoring of time spent in the target glucose range ("time in range"). However, only rtCGM can warn users if glucose is trending toward hypoglycemia or hyperglycemia. With iCGM, these trends can only be viewed after physically scanning the sensor. It is often difficult to distinguish between technologies, regarding issues such as calibrations, alarms/alerts, human factors of applying and wearing sensors and the cost, which are device-specific. As these technological details are subject to constant change the term CGM is used for all issues related to the device class unless indicated otherwise.

In February 2017, the Advanced Technologies and Treatments for Diabetes

(ATTD) Congress convened an international panel of physicians, researchers and individuals with diabetes who are expert in CGM to address these issues. The purpose of the conference was to provide guidance for clinicians, patients and researchers in utilizing, interpreting and reporting CGM data in clinical care and research. The panel was divided into subgroups to review the literature and provide evidence-based recommendations for relevant aspects of CGM utilization and reporting. ~~. Topics included:~~

~~1. Limitations of HbA1c.~~

~~2. Selection of glucose monitoring methodologies to guide management and assess outcomes in different patient populations.~~

~~3. Minimal requirements for assessing continuous data from CGM.~~

~~4. Assessment of glycemic variability (GV).~~

~~5. Parameter(s) for assessment of hypoglycemia in clinical studies.~~

~~6. Relationship between GV and CGM use and complications.~~

~~7. Use of "time in ranges" as a diabetes outcome measure.~~

Primary citations were identified for each topic, assigned a level of evidence (indicated next to the corresponding citation in the text and in the reference section) and verified by the expert panel.

This article summarizes the ATTD consensus recommendations and represents the current state of knowledge on CGM results affecting outcomes. The content represents the consensus of the panel members' comprehensive evaluation of the issues. Supporting evidence is included in the online supplemental material identified at the end of each section.

1. Limitations of HbA1c

Key Findings

- The Diabetes Control and Complications Trial (DCCT), followed by the Epidemiology of Diabetes Interventions and Complications (EDIC), demonstrated how elevated HbA1c contributes to complications in type 1 diabetes (T1D). The United Kingdom Prospective Diabetes Study (UKPDS) confirmed the importance of glycemic control as well as other components of metabolic control, namely blood pressure, on health outcomes in individuals with type 2 diabetes (T2D) (7, 8) [A,A].
- Most global organizations recommend target HbA1c levels of <7.0% (53 mmol/mol) for adults and <7.5% (58 mmol/mol) for children; although several organizations suggest an HbA1c target of ≤6.5% for adults (9) [E] and children (10) [E]. However, all organizations agree that HbA1c targets should be individualized to each patient.
- Although HbA1c remains the reference marker for assessing glycemic control and predicting ~~provides a surrogate marker for the~~the risk of development of long-term complications, it has several limitations: 1) provides only an average of glucose levels over the previous past 2-3 months; 2) does not detect hypoglycemia or hyperglycemia on a daily basis; 3) is an unreliable measure in patients with anemia (11) [B], hemoglobinopathies (12) [B], iron deficiency (13) [B] and during pregnancy (14) [B]; 4) does not reflect rapid changes in daily glucose control. and 5) does not provide data as to how to adjust treatment regimen when HbA1c levels are elevated. In summary, although HbA1c has proved extremely valuable in patient management, is a valuable measure of population health and remains a validated indicator of glycation as a risk factor for complications, it is not as helpful for personalized diabetes management.
-

- ~~In adults with T1D, severe hypoglycemia (SH) is more related to duration of diabetes and socio-economic status than HbA1c Similarly, in children 6-17 years old with T1D or adults with T2D (mostly receiving insulin or sulfonylureas SH was most common with the lowest and highest HbA1c levels.~~
- The literature suggests that ethnic and racial differences exist in glycation rates (15-17) [B,C,C], which affect the accuracy of HbA1c measurements; however, a racial difference was not found in the relationship between mean glucose and fructosamine or glycated albumin levels. This suggests that the racial discordance in glycation rates is specific to the red blood cell. The effects of ethnic differences on average HbA1c cannot be entirely explained by measured differences in glycemia, differences in sociodemographic or clinical factors, or differences in access to care or quality of care (18) [E].
- An estimated HbA1c (eA1C) can be calculated if adequate rtCGM/iCGM data (70% or 10 days of the 14 days of CGM data) are available. The eA1C and laboratory measured HbA1c may differ to some degree for a given individual because there are many factors that affect an HbA1c reading, and tables that convert HbA1c to a mean glucose and vice-versa are based on mean values for a population. Knowing how an individual's CGM-derived eA1C compares to their laboratory measured HbA1c may be helpful in safe and effect clinical management (19) [E].

Recommendations

- HbA1c should be measured with a device that is certified by the NGSP (National Glycohemoglobin Standardization Program, www.ngsp.org) or the IFCC (International Federation of Clinical Chemistry and Laboratory Medicine (www.ifcchba1c.net)

- Clinicians and patients should target an HbA1c as close to normal as possible without severe hypoglycemia (SH) or a significant amount of non-severe hypoglycemia while at the same time indicating a need to individualize glycemic targets according to patient age, duration, co-morbidities, and expected life expectancy with 'less strict' HbA1c targets for those more frail (20) [A].
- When there is a discrepancy between actual HbA1c and the estimated HbA1c based on mean glucose, other glucose measurement methods such as, fructosamine, glycated albumin, SMBG and, in particularly CGM should be used in conjunction with HbA1c measurements when assessing glycemic control and adjusting therapy.
- CGM data should be used to assess hypoglycemia and glucose variability.

Additional discussion of these recommendations and supporting evidence is presented as online supplemental material. (**APPENDIX 1**).

2. Use of glucose monitoring methodologies (SMBG and CGM) to guide management and assess outcomes in different patient populations

Key Findings

- Self-monitoring of blood glucose (SMBG) has been shown to be helpful or to correlate with effective management in insulin-treated and non-insulin-treated diabetes (1-4, 21, 22) [C,C,C,C,A,C], however, SMBG has notable limitations. First, it requires a fingerstick to obtain a blood sample. Moreover, it only provides a single "point-in-time" measurement, which provides no indication of the direction or rate of change of glucose levels. Thus, using SMBG data alone may result in inappropriate therapy decisions (such as administering

correction insulin when blood glucose levels are falling). Second, obtaining glucose data via SMBG is dependent upon the patient's decision to self-monitor. Accordingly, SMBG often fails to detect nocturnal and asymptomatic hypoglycemia (5, 6) [C,C].

- iCGM provides the current glucose value plus retrospective glucose data for a specified time period upon "scanning". At the time of this writing, only one iCGM system, also known as "flash" monitoring, was available. This system utilizes two components: a glucose sensor, which is inserted the user's upper arm; and a separate touchscreen reader device. When the reader device is swiped close to the sensor, the sensor transmits both an instantaneous glucose level and an eight-hour trend graph to the reader. The only currently available iCGM device is factory calibrated, lasts up to 14 days and does not need to be calibrated by the user. However, iCGM lacks alarms for low and high glucose values, and, as with SMBG, measurements are only visualized when the user of the device chooses to make a measurement. Two studies using iCGM have demonstrated significant improvements in hypoglycemia, time in range, glycemic variability and user satisfaction (23, 24) [B,B]. The Flash device is also available without need for scanning in a blinded mode for clinical research or retrospective glucose pattern evaluation.
- rtCGM in unblinded mode provides real-time numerical and graphical information about the current glucose level, glucose trends, and the direction/rate of change of glucose. Devices with programmable alerts/alarms that warn users of current and/or impending high or low glucose offer additional safety advantages. In Europe, a new type of implantable rtCGM system is available as an alternative for transcutaneous CGM (25) [C].
- Numerous studies have shown that use of rtCGM improves glycemic control and quality of life in both children and adults with T1D treated with either continuous subcutaneous insulin

infusion (CSII) or multiple daily insulin injection (MDI) therapy, improving HbA1c, shortening the time spent in hypoglycemia and hyperglycemia and reducing moderate to severe hypoglycemia (26-37) [C,C,B,B,C,C,A,C,B,C,B]. The benefit of rtCGM was seen primarily in those patients who regularly used their devices (26, 28, 35) [C,B,B]. In a lifetime analysis, rtCGM reduced overall diabetes-related complications (38) [B]. Similar results of the cost-effectiveness of rtCGM vs SMBG were reported using a larger population base model (39).

- Using data collected from a meta-analysis of patient-level data (35) [B] sensor-augmented pump therapy was determined to be cost-effective for the treatment of T1D in the Swedish health-care system (40) [C]. Sensitivity analyses indicated further cost-effectiveness benefit of increasing the amount of rtCGM use from 5 to 7 days a week, and decreasing the use of SMBG was incrementally cost-effective at every level.
- Subsequent studies have determined that sensor-augmented pump systems with a low-glucose suspend feature (SAP+LGS) are also cost-effective relative to insulin pump therapy alone, in the Australian (41) [C], UK (42) [[C] and French (43) [C] healthcare systems, due to improved glycemic control and reduction in hypoglycemia.
- Benefits of rtCGM use have also been reported in individuals with T2D who are managed with or without intensive insulin treatment (44-46) [B,C,C]. There are limited data regarding the benefit of rtCGM as an outcome measure for individuals with gestational diabetes (GDM) and T2D, especially in those who do not use insulin (47) [C].
- The benefit of rtCGM is directly correlated to persistence and frequency of use. A meta-analysis by Pickup et al. found that every one day increase of sensor usage per week

increased the effect of continuous glucose monitoring; the effect on HbA1c is more pronounced the higher the initial HbA1c (35) [B].

Recommendations

- CGM should be considered in conjunction with HbA1c for glycemic status assessment and therapy adjustment in all T1D patients and T2D patients treated with intensive insulin therapy who are not achieving glucose targets, especially if the patient is experiencing problematic hypoglycemia.
- Structured testing regimens should be defined for patients when SMBG is prescribed.
- All patients should receive training in how to interpret and respond to their glucose data regardless of the monitoring method used. Patient education and training for CGM should utilize standardized programs with follow-up to improve adherence and facilitate appropriate use of data and diabetes therapies.

Additional discussion of these recommendations and supporting evidence is presented as online supplemental material. (**APPENDIX 2**).

3. Minimum requirements for CGM performance

Key Findings

- No internationally-accepted standard exists for CGM system performance comparable with the International Organization for Standardization (ISO) 15197 standard for SMBG, which specifies design verification procedures and the validation of performance by the intended users. However, ISO/IEEE FDIS 11073-10425 provides a normative definition of the

communication between CGM devices and managers (such as cell phones, personal computers, personal health appliances, and set top boxes) in a manner that enables plug-and-play interoperability.

- In contrast to iCGM, the accuracy of current rtCGM systems is dependent on SMBG testing for calibration. Therefore, it is important to have an accurate glucose meter. Successful calibration also requires several conditions, for example, it is best performed when glucose is not changing rapidly. Importantly, users must be educated in the appropriate techniques.
- The mean absolute relative difference (MARD) is currently the most common metric used to assess the performance of CGM systems. MARD is the average of the absolute error between all CGM values and matched reference values. A small percentage indicates that the CGM readings are close to the reference glucose value; whereas, a larger MARD percentage indicates greater discrepancies between the CGM and reference glucose values.
- Comparing MARD values from different clinical studies has several limitations, thus head-to-head studies should be performed. Additional metrics, such as precision absolute relative difference (PARD), can be used as well to obtain an additional evaluation of the CGM performance (48) [C].
- Although controversy exists regarding the exact cut point for accuracy, *in silico* testing has shown that a further lowering of mean absolute relative difference (MARD) ≤10% from reference values has little additional benefit for insulin dosing (49) [C].

Recommendations

- Only CGM systems that provide an acceptable level of sensor accuracy should be used.

Additional discussion of these recommendations and supporting evidence is presented as online supplemental material. (**APPENDIX 3**).

4. Definition and assessment of hypoglycemia in clinical studies

Key Findings

- Hypoglycemia remains a major barrier for glycemic control and a common complication of diabetes treatment, especially in T1D (50) [E].
- In adults with T1D, severe hypoglycemia (SH) is more related to duration of diabetes and socio-economic status than HbA1c (34). Similarly, in children 6-17 years old with T1D (51) [C] or adults with T2D (mostly receiving insulin or sulfonylureas (52) [B], SH was most common with the lowest and highest HbA1c levels.
- Needing assistance is the usual concise definition for severe hypoglycemia. Most children require assistance with all hypoglycemia not just severe hypoglycemia (53) [C]. Therefore, SH in children is often defined as an event associated with a seizure or loss of consciousness or requiring emergency medical personnel or visit to the emergency department or a hospital admission. In adults, the definition of severe hypoglycemia often includes episodes associated with coma or seizure, for which the patient, perhaps being on their own, recovered spontaneously.
- The degree of hypoglycemia that causes clinical symptoms and counterregulatory response is specific to the individual and depends on the personal level of glycemic control (53) [C].
- Studies indicate that hypoglycemia for 2 or more hours impairs hormonal responses (54, 55) [C,B].

- Gradation of hypoglycemic events may be valuable. Specifically, that of a prolonged hypoglycemic event, in which the CGM levels indicate glucose levels <54 mg/dL (<3.0 mmol/L) for ≥120 minutes. While this metric is somewhat arbitrary, a study by Oz et al. found that the glycogen signal decreases with a rate of ~10% per hour in the human brain at blood glucose levels of <54 mg/dL (<3.0 mmol/L) indicating a mobilization rate commensurate with the severity of hypoglycemia (56) [B].
- The low blood glucose index (LBGI), is a metric specifically designed to calculate the risk for hypoglycemia as reflected by SMBG data (57) [B]. However, LBGI calculations based on CGM data tend to slightly underestimate risk, particularly in the low risk range (58) [C]

Recommendations

- The definition of hypoglycemia should take into consideration several parameters: the compartment of measurement (arterial, venous, and capillary blood or interstitial); the nadir level of blood glucose measured; and the duration of the event and related symptoms.
- When assessing hypoglycemia using CGM, the accuracy of the data in the lower glycemic range should be considered.
- The following classifications of hypoglycemia, based on clinical evaluation, should be used in categorizing levels of hypoglycemia:
    - Level 1: A hypoglycemia alert glucose value of <70-54 mg/dL (<3.9-3.0 mmol/L) with or without symptoms. This should be considered an alert that the individual may be at risk for developing hypoglycemia and should work to minimize the time spent in this range to reduce the risk of developing more clinically significant hypoglycemia. This need not be reported routinely in clinical studies, although this

would depend on the purpose of the study. Nevertheless, most clinicians want to know how often patients are <70-54 mg/dL (<3.9-3.0 mmol/L) and would act to reduce the time spent in this range to minimize the risk of more clinically significant hypoglycemia occurring.

- Level 2: A glucose level of <54 mg/dL (<3.0 mmol/L) with our without symptoms. This should be considered clinically significant hypoglycemia requiring immediate attention.
- Level 3: Severe hypoglycemia. This denotes cognitive impairment requiring external assistance for recovery (59) [E] but is not defined by a specific glucose value.

- For clinical study CGM outcomes reports, hypoglycemia values <54 mg/dL (<3.0 mmol/L) should be given more weight or importance than those <70-54 mg/dL (<3.9-3.0 mmol/L).
- When assessing hypoglycemia in clinical care, other important consequences or adverse patient reported outcomes should be considered:
  - Reduced awareness of subsequent hypoglycemia.
  - Associated cardiac arrhythmia, confusion, abnormal or combative behavior.
  - Weight gain.
  - Fear of hypoglycemia.
- Hypoglycemia should be quantified in the following ways:
  - As the percentage of CGM values that are below a given threshold (<70 mg/dL [3.9 mmol/L] or < 54 mg/dL [3.0 mmol/L]) or the number of minutes or hours below these thresholds.
  - As the number of hypoglycemic events that occur over the given CGM reporting period.
- A hypoglycemic event should be defined as follows:

- Beginning of a CGM event – readings below the threshold for at least 15 minutes is considered an event. For example, at least 15 minutes <54 mg/dL (<3.0 mmol/L) to define a clinically significant (Level 2) hypoglycemic event.
- End of a CGM event – readings for 15 minutes at ≥70 mg/dL (≥3.9 mmol/L).
- A second hypoglycemic event outcome of prolonged hypoglycemia is considered when CGM levels are <54 mg/dL (<3.0 mmol/L) for consecutive 120 minutes or more.

- LBGI should be reviewed when assessing hypoglycemia risk.

Additional discussion of these recommendations and supporting evidence is presented as online supplemental material. (**APPENDIX 4**).

5. Assessment of glycemic variability (GV)

Key Findings

- Numerous studies have focused on glycemic variability (GV) as an independent risk factor for diabetes complications, particularly cardiovascular disease (60-63) [C,E,C,C] and on the effects of GV on cognitive function and quality of life (64) [C].
- Acceptance of GV as a clinically valuable marker of glycemic control has greatly expanded the understanding of glycemic control beyond HbA1c alone. (65-68) [E,E,E,E].
- While the interpretation of average blood glucose is relatively straightforward, providing a direct relationship to HbA1c, GV is a reflection of a dynamic process, and its understanding and measuring are less apparent (69, 70) [E,C]. Beyond the setting of laboratory experiments, the data sources available for routine estimation of GV include episodic SMBG records and

CGM traces (71) [B]. The density of the available data determines what properties of GV can be investigated.

- GV is a process characterized by the amplitude, frequency and duration of the fluctuation.
- Both the amplitude and the timing of blood glucose (BG) fluctuations contribute to the risks for hypoglycemia and hyperglycemia associated with diabetes (72) [C]. Increased glucose variability is consistently associated with mortality in the intensive care unit (73, 74) [C,B] and is a consistent predictor of hypoglycemia, both in prospective studies and within the setting of randomized clinical trials (64, 75) [C,B].
- When quantifying glucose variability from CGM data, the following physiological and statistical factors should be considered:
  - In healthy individuals, the metabolic system has a physiological equilibrium range (e.g., fasting BG) to which it returns if left undisturbed; with the progression of diabetes, this equilibrium range moves up.
  - This physiological equilibrium range is relatively universal across people (hence the diagnostic criteria for pre-diabetes and diabetes). Therefore, the objective of diabetes control is to keep BG levels in the vicinity of a commonly accepted range (not the mean for a person, which is individual).
  - Deviations in both directions from the range carry risks. These risks increase with the amplitude of the deviations, nonlinearly and asymmetrically into the hypoglycemic and hyperglycemic ranges.
  - The timing of the deviations is of essence as it reflects system (person) dynamics and system stability. However, most of the traditional GV metrics ignore the time axis of CGM data.

- Mathematical methods (e.g., risk analysis, time series) are well developed and can be adapted to diabetes, keeping in mind the objectives of diabetes control.

- CGM data reflect the dynamics of glucose fluctuations by including all of these dimensions. A recent analysis of CGM data in comparison to blood glucose data obtained in a large study with patients with T1D showed how GV indices are related and demonstrated the impact of CGM use on GV (76) [C].
- Standard deviation (SD), coefficient of variation (CV) and mean amplitude of glucose excursions (MAGE) are widely used to quantify GV. The CV (which is the SD divided by the mean) has the advantage of being a metric relative to the mean, which makes it more descriptive of hypoglycemic excursions than the SD alone. For example, a population with a mean glucose of 150 mg/dL and an SD of 60 would have a CV of 40%.
- Stable glucose levels are defined as a CV <36%, unstable glucose levels as CV ≥36% (77) [E].

Recommendations

- GV evaluated from CGM data, should be considered among other factors of the overall clinical representation of glycemic control.
- CV should be considered the primary measure of variability; however, many clinicians may want to see SD reported as a key secondary GV measure since it is a metric with which they are familiar.
- The recommended metrics for GV should be included in summary statistics for data downloaded from CGM devices into reports.

Additional discussion of these recommendations and supporting evidence is presented as online supplemental material. (**APPENDIX 5**).

6. Time in "ranges"

- Time in range (TIR) generally refers to the time spent in an inidividual's target glucose range (usually 70-180 mg/dL [3.9-10 mmol/L, but occasionally 70-140 mg/dL [3.9-7.8 mmol/L]). TIR measurements add valuable information to assess the level of current glycemic control in addition to what is known from the HbA1c. However, clinicians, researchers and regulators now know that time in target range alone is not an adequate description of overall glycemic control. It is also necessary to quantitate the times below and above target range, using a few severity thresholds for each level. (78) [E]. Thus, time in "ranges" (TIRs) provides a more illustrative metric for clinical and research purposes.
- TIRs are useful for a research comparison of interventions and can help patients understand if the amount of clinically-significant hypoglycemia or hyperglycemia they are experiencing is improving over time. Breaking out the time in hypoglycemia and hyperglycemia into Level 1 (monitor and take action if needed) and Level 2 (immediate action required due to the more potentially clinically significant nature of the glucose levels) can guide the urgency and degree of clinical response.

Composite Measures

- Because the function of CGM use is to monitor glucose levels with the ultimate goal of improving glycemic control, it makes clinical sense to combine TIRs data with other measures.

- HbA1c level and time in Level 2 (Clinically significant / Immediate action required) hypoglycemia is one such combined measure.
- Time in target range combined with time in Level 2 hypoglycemia is another such combined measure. This combined set of measures could be setup as a co-primary outcome for a clinical trial asking if one therapy is more effective than another in achieving an increased time in target range (70-180 mg/dL) while also being non-inferior for the Level 2 hypoglycemia achieved. One then needs to further define the parameters of judging non-inferior status. These examples make clinical sense, since one wants to improve glucose control (HbA1c or TIR) while also reducing or at least not increasing hypoglycemia.
- Even broader combined measures of diabetes management such as targets for desired diabetes management are being explored (e.g., HbA1c + hypoglycemia + weight gain or HbA1c + blood pressure + low-density lipoprotein or HbA1c + blood pressure + low-density lipoprotein + aspirin use if high-risk cardiovascular disease + no tobacco use). These composites emphasize the importance of taking a multifactorial approach to reducing diabetes complications, particularly cardiovascular disease.

Recommendations

- Times and/or percentages in target range, hypoglycemia and hyperglycemia should be assessed and reported.
- Different time in ranges (TIRs) in conjunction with a measure of GV should be reported as key diabetes control metrics in clinical studies.

7. Visualization, analysis and documentation of key CGM metrics

Key Findings

- Standardizing glucose reporting and analysis similar to an EKG output is vital to optimizing clinical decision making in diabetes. Further optimizing of such tools and expanding them into shared decision making guides is needed.
- Reporting CGM data in a standardized way, in conjunction with an HbA1c value and other clinical conditions (e.g., severe hypoglycemia, diabetic ketoacidosis) would foster a precise definition of this composite goal. Using a standardized composite goal, the medical community could establish with more confidence whether a particular insulin formulation, new technology for insulin delivery, or an innovative patient-centered approach to care was an important factor in helping individuals with diabetes reach optimal glycemic control.
- Standardized tools such as the Ambulatory Glucose Profile (AGP (79), Pattern Snapshot (Medtronic) (80), Clarity (Dexcom) (81) and others from various device makers and data management companies are now available. Use of the AGP approach was previously endorsed by an expert panel of clinicians in a consensus conference held in 2012 (82) [E] and is recommended by this consensus group as a standard for visualization of CGM data.
- Integration of standardized metrics into electronic health records is important to maximize the clinical workflow and faciliate remote communications with patients.
- Patient responses to the current glucose level, trend arrows indicating rate of change of glucose and qualitative analysis of a graphical display of glucose versus time do not require stability of patterns. However, retrospective analysis of either CGM is dependent on stability of patterns from day to day (83) [B].

- A minimum of 14 consecutive days of data with approximately 70% of possible CGM readings over those 14 days appears to generate a report that enables optimal analysis and decision making and standard reporting and visualization of CGM data is important.

Recommendations

- 14 key metrics should be utilized to assess glycemic control and document:
    1. Mean glucose.
    2. Percentage/time in Level 2 hypoglycemic range (<54 mg/dL [3.0 mmol/L]). Urgency for action: *Clinically significant / Very low / Immediate action required.*
    3. Percentage/time in Level 1 hypoglycemic range (<70-54 mg/dL [<3.9-3.0 mmol/L]). Urgency for action: *Alert / Low / Monitor.*
    4. Percentage/time in target range: 70-180 mg/dL (3.9-10.0 mmol/L) (default); 70-140 mg/dL / 3.9-7.8 mmol/L (secondary); Individual targets closer to the physiological range can be defined, depending on age, comorbidities and/or patient adherence.
    5. Percentage/time in Level 1 hyperglycemic range (>180 mg/dL [>10.0 mmol/L]). Urgency for action: *Alert / High / Monitor.*
    6. Percentage/time in Level 2 hyperglycemic range (>250 mg/dL [>13.9 mmol/L]). Urgency for action: *Clinically significant / Very elevated / Immediate action.*
    7. Glycemic variability, reported as CV (primary) and SD (secondary).
    8. Estimated HbA1c (eA1c).
    9. Data for glucose metrics (1-7) reported in 3 time blocks (sleep, wake, 24 hours) with the default times for the sleep (12:00 AM/midnight -5:59 AM) and wake (6:00AM-11:59PM) often written as midnight-6AM and 6AM to midnight.

10. Data sufficiency - minimum 2 weeks of data.

11. Data sufficiency - 70-80% of possible CGM readings over 2-week period.

12. Episodes of hypoglycemia, using a standard definition of episodes.

13. Area under the curve (AUC) (recommended for research purposes). This can be calculated from CGM analysis software and is recommended for research purposes as it is a measure the integrates to some extent the severity of a high or low glucose along with the duration of the abnormality.

14. Risk of hypoglycemia and hyperglycemia (LBGI and HBGI recommended).

- Standardized software for visualization and reporting of the 14 key CGM metrics should be considered an additional component (#15) of analysis and documentation. (Use of the AGP is recommended).
- Although severe hypoglycemia (Hypoglycemia Level 3) and diabetic ketoacidosis (Hyperglycemia Level 3) are not CGM data-based determinations, they should be reported and documented.
- For research purposes median and interquartile range (IQR) should be presented for all measurements.
- Conduct further studies to define in a variety of patient groups, including pediatrics, pregnancy, those with renal insufficiency and the elderly what is an acceptable and achievable TIR and the accompanying acceptable rates of hypoglycemia.

The key metrics for CGM analysis and reporting are presented in **Table 1**. **Figure 1** illustrates how these metrics are presented in the AGP. ~~Additional discussion of these~~

~~recommendations and supporting evidence is presented as online supplemental material. (APPENDIX 7).~~

CONCLUSIONS

CGM is a robust research tool, and continuous glucose data should be recognized by governing bodies as a valuable and meaningful endpoint to be used in clinical trials of new drugs and devices for diabetes treatment. The identification of hypoglycemia is as important as the measurement of time in range in clinical trials. Quantifying the duration and magnitude of glycemic excursions provides another means of assessing glucose control. The unifying theme of trials investigating the usefulness of CGM technologies is that the device must be worn on a near daily basis to optimize its benefits.

The expert panel concludes that, in clinical practice, the advanced metrics of assessing continuous glucose data presented here are appropriate as outcome parameters that complement HbA1c for a wide range of patients with diabetes and should be considered for use to help them improve glycemic control provided that appropriate educational and technical support is available.

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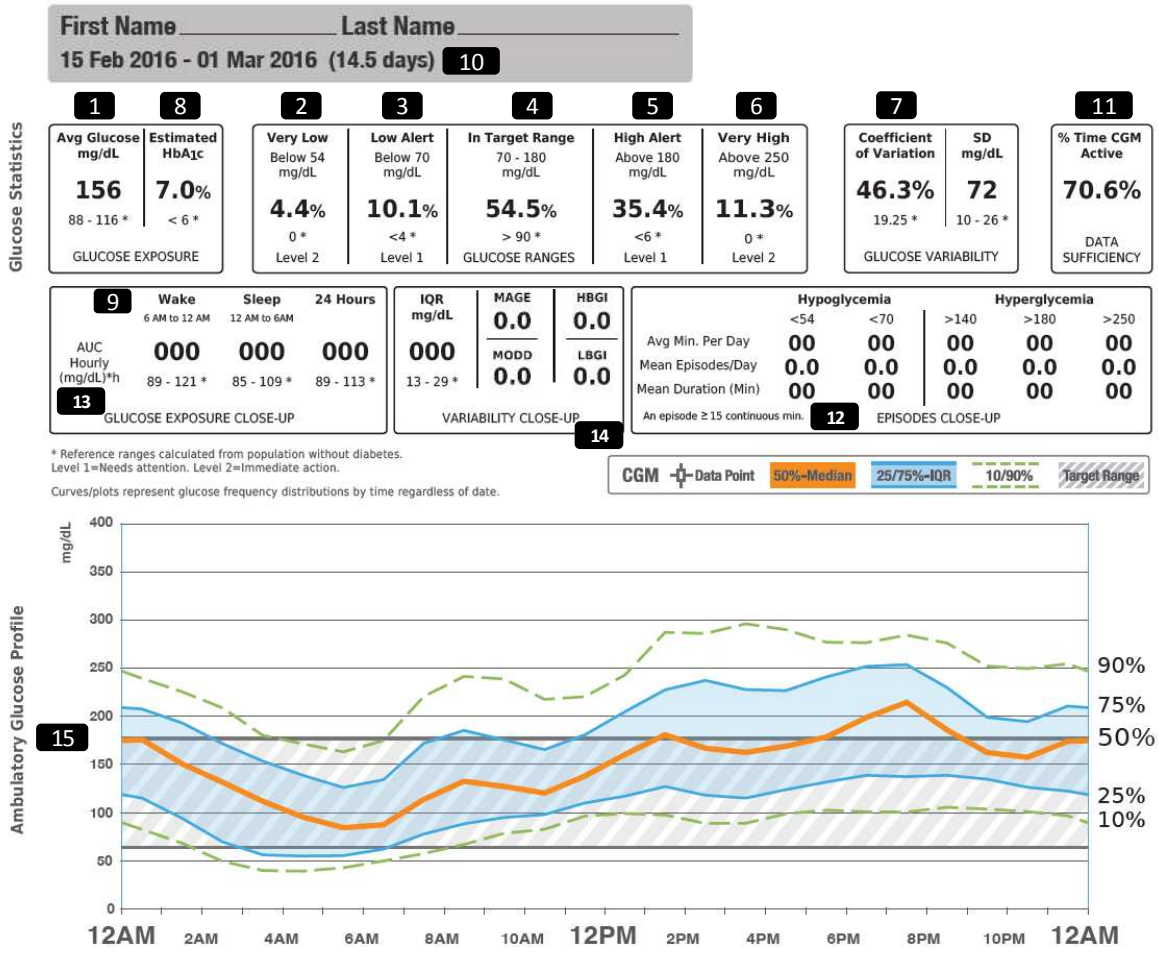
Table 1. Key metrics for CGM data analysis and reporting

CGM Metric	Measures	ATTD Consensus
1	**Mean glucose**	√ **(calculated)**
	Severe Hypoglycemia*	**Clinical Dx**: Event requiring assistance (Level 3)
	%/time In Hypoglycemic Ranges (mg/dL / mmol/L)	
2	Clinically significant / Very low / Immediate action required	**< 54 / <3.0** (Level 2)
3	Alert / Low / Monitor	**<70-54 / <3.9-3.0** (Level 1)
	%/time In Target Range (mg/dL / mmol/L)	
4	Default	**70-180 / 3.9-10.0**
	Secondary	**(70-140 / 3.9-7.8)**
	%/time In Hyperglycemic Ranges (mg/dL / mmol/L)	
5	Alert / Elevated / Monitor	**> 180 / >10** (Level 1)
6	Clinically significant / Very elevated / Immediate action required	**> 250 / > 13.9** (Level 2)
	Diabetic Ketoacidosis (DKA)	**Clinical Dx**: Ketones, acidosis, and usually hyperglycemia (Level 3)
7	**Glycemic Variability (GV)** Primary GV	**CV**
	Stable:	CV <36%,
	Unstable:	CV ≥36%
	Secondary GV	(SD)
8	**eA1c**	√ **(calculated)**
9	**3 Time Blocks: Sleep, Wake, 24 hrs.**	**12AM-6AM / 6AM-12PM / 12AM-12AM**
	Recommended Data Sufficiency	
10	Collection Period (min. # of wks)	**2**
11	% of expected CGM readings (min. %)	**70-80** (10 of 14 days)
12	**Episodes of Hypo/Hyper (minimum # minutes)** (with beginning & end of episode defined)	**15 min**
13	**Area Under the Curve (AUC)**	√ **(calculated)**
14	**Risk of Hypo & Hyper**	**LBGI / HBGI** recommended
15	**Standardized CGM visualization of data**	**AGP** recommended

* Severe hypoglycemia (Level 3) and diabetic ketoacidosis (Level 3) are not key CGM metrics, per se. However, these conditions are included in the table because they are important clinical categories that must be assessed and documented.

Figure 1. The electronic AGP report visualizes the key CGM metrics.

(1) mean glucose(2) hypoglycemia – Clinically significant / Very low / Immediate action required; (3) hypoglycemia – Alert / Low / Monitor; (4) target range; (5) hyperglycemia – Alert / Elevated / Monitor; (6) hyperglycemia - Clinically significant / Very elevated / Immediate action required; (7) glycemic variability; (8) eA1c; (9) time blocks; (10) collection period; (11) % of expected readings; (12) hypo/hyper episodes; (13) AUC; (14) hypo/hyper risk; and (15) standardized rtCGM/iCGM visualization.



APPENDIX 1. Limitations of HbA1c

What is the relationship between metabolic control and HbA1c?

To date, overall glycemic control, as measured by HbA1c, remains the established predictor of diabetes outcomes in persons with type 1 and type 2 diabetes, affecting micro- and macro-vascular complications and mortality. The Diabetes Control and Complications Trial (DCCT), followed by the Epidemiology of Diabetes Interventions and Complications (EDIC) study, demonstrated how elevated HbA1c contributes to complications in T1D (1). The United Kingdom Prospective Diabetes Study (UKPDS) confirmed the importance of glycemic control as well as other components of metabolic control, namely blood pressure, on health outcomes in people with diabetes (2).

These studies provided the empiric data that serve as the basis for HbA1c targets recommended by most global organizations. These societies, for the most part, recommend target HbA1c levels of <7% (53 mmol/mol) for adults and <7.5% (58 mmol/mol) for children, although several organizations suggest an HbA1c target of ≤6.5% for adults (AACE) (3) as well as youth (4). All groups suggest aiming for an HbA1c as close to normal as possible without severe hypoglycemia while at the same time indicating a need to individualize glycemic targets according to patient age, duration, co-morbidities, and expected life expectancy with 'less strict' HbA1c targets for those less healthy (5).

Despite advanced treatment tools, including newer pharmacologic agents (with many classes of oral hypoglycemic agents for T2D), various injectables including long- and short-acting insulin analogs) and advanced technologies (such as insulin pens, insulin pumps, and advanced insulin dosing algorithms for use with pumps or injection regimens), a minority of persons with diabetes, globally, achieve recommended HbA1c levels (6). More effective means of analyzing data from self-monitoring of blood glucose (SMBG), continuous glucose monitoring (CGM) should help provide patients and clinicians with the information needed to achieve target HbA1c levels.

How do glucose fluctuations and excursions relate to HbA1c?

An elevated HbA1c is derived from the nonenzymatic addition of increased glucose circulating in blood to amino groups of hemoglobin. HbA1c is a specific glycated hemoglobin

that results from the attachment of glucose to the N-terminal valine of the hemoglobin ß-chain (7). Normally red blood cells (RBCs) live 120 days; but they do not all lyse at the same time, so HbA1c is generally considered an 8-12 week glycemic history (8). It is important to recognize that the HbA1c represents a short-term measure of irreversible non-enzymatic glycosylation of proteins occurring throughout the body. Long-term microvascular complications in the DCCT showed the strongest correlation with nonenzymatic glycosylation of collagen and the formation of advanced glycosylation end products (AGE's), and when the DCCT mean HbA1c effect was adjusted for AGEs, the HbA1c effect was no longer significant (9). Skin collagen has a half-life of 14.8 years (10), which fits with the "metabolic memory" of EDIC, whereas the red blood cell has a half-life of about 8 weeks. There are many factors that can affect the red blood cell life-span, resulting in discrepancies between the HbA1c estimate of the mean glucose and the mean glucose by CGM. Since the CGM data provide a direct measure of mean glucose values it may be inherently more accurate in estimating the risk of long term complications than an HbA1c measurement, which can have marked differences between individuals with the same mean glucose (11-13). A common understanding has been that HbA1c testing only measures an average glucose over this time period, and that glucose fluctuations will not affect the HbA1c result. However, at least one study showed that this was not true.

Kuenen et al, as part of the HbA1c -Derived Average Glucose (ADAG) Study, showed that GV shows a significant interaction with mean blood glucose for HbA1c with T1D, but not T2D (14). This is most relevant for higher HbA1c levels. For example, with a mean blood glucose of 240 mg/dL (13.3 mmol/L), the HbA1c could be as low as 8.7% (72 mmol/mol) with low GV or as high as 9.8% (84 mmol/mol) with high GV. A direct, linear correlation between HbA1c levels and GV has been observed in studies of large groups of T1D subjects with SD as measure of GV, mainly due to the mathematical fact that the higher is the mean the larger will be the SD. It has not been seen using CV as the measure of GV. It should be noted, however, that glucose variability in the DCCT (using 7-point glucose profiles) did not play a role in the development of microvascular complications beyond the influence of the mean glucose (15).

What is the relationship of hypoglycemia to HbA1c?

HbA1c is a poor surrogate for hypoglycemic risk. For example, in adults with T1D, severe hypoglycemia is more related to duration of diabetes and socio-economic status than

HbA1c (16). Similarly, in children 6-17 years old with T1D (17) or adults with T2D (mostly receiving insulin or sulfonylureas) (18), severe hypoglycemia was most common with the lowest and highest HbA1c levels. Numerous clinical trials of new drugs and devices have shown that HbA1c levels can be lowered to target values without increasing the risk of hypoglycemia (19, 20).

These data and studies emphasize that there is no simple relationship. Nevertheless, trials where participants have been randomized to intensive or 'standard' control all show an increase in hypoglycaemia. This shows that self-management behaviours have a major influence of hypoglycaemic risk. Providing more helpful and detailed information on blood glucose fluctuations may help to reduce the risk but only if patients and their families receive support and education on how to apply this appropriately and are willing to do so; CGM technologies will not do this automatically.

What is the role of the glycation gap in interpreting HbA1c results?

An easy, accessible formula for converting a single HbA1c measurement into eAG (and vice versa) has been developed and is applicable in clinical practice, (12, 13,21). However, there is wide dispersion around the outcome of this conversion, limiting its value. In addition, some discordance between HbA1c and other measures of glycemic control may be encountered in clinical practice. The difference between the measured HbA1c (marker of intra-erythrocyte glycation) and a fructosamine-derived standardized predicted HbA1c (marker of extra cellular glycation) using the regression equation has been defined as glycation gap (22). Although treated with caution and skepticism (23), both negative and positive glycation gaps have been found to correlate with outcomes such as diabetic nephropathy, retinopathy, macrovascular complications and mortality (24-26). The hypothesis of glycation gap has also been tested using glycated albumin (27, 28).

The central question about the glycation gap, whether it really exists and what the mechanisms behind it may be, is the way by which mean blood glucose is measured and computed in its relationship with HbA1c. Unlike fructosamine and glycated albumin, which are surrogate markers, CGM provides a direct and continuous measurement of glycemia, which clearly represents a more robust approach for further testing the glycation gap hypothesis.

Which ethnic and genetic factors influence glycation?

Although the literature suggests that ethnic and racial differences exist in glycation rates (29, 30), a racial difference was not found in the relationship between mean glucose and fructosamine or glycated albumin levels, suggesting that the racial discordance in glycation rates is specific to the red blood cell. The ethnic differences between average HbA1c levels, however, cannot be entirely explained by measured differences in glycemia, differences in sociodemographic or clinical factors, or differences in access to care or quality of care (31). In June 2009, an international expert committee published a report recommending the use of an HbA1c value of ≥6.5% as a diagnostic criterion for diabetes (32).

The diagnostic cut-off was based on multi-ethnic studies which did show very consistent data for the relationship between HbA1c and microvascular disease. Furthermore, because of racial disparities in HbA1c levels, the optimal threshold for diagnosing diabetes may vary by ethnic group. For example, in the Chinese population, an HbA1c cut point of ≥6.3% may be more appropriate as a diagnostic criterion for diabetes (33). However, there is a notable concern that recommendations to interpret HbA1c results differently in racial/ethnic minority populations may actually increase health disparities (34). A recent study adds some clarity to the higher HbA1c levels in African Americans compared to Non-Hispanic Caucasians since it was designed to collect 90 continuous days of CGM data in 200 Blacks and 200 Whites with T1D and compare the relationship of mean glucose to HbA1c between these racial groups (35). On average, the HbA1c was 0.4% higher in Blacks compared to Whites with the same CGM mean glucose. This difference was less in the HbA1c range used to make the diagnosis of diabetes. Equally important, this study reinforced the fact that there is a much larger variation in the HbA1c correlation with mean glucose within races than between races.

In summary, glucose measurements are the mainstay of diabetes management, guiding insulin dosing decisions and other changes in treatment regimens. Although HbA1c testing has been used in clinical practice for over 35 years, it has clear limitations, and there are still many questions about its use that remain unanswered.

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APPENDIX 2. Selection of glucose monitoring methodologies (HbA1c, SMBG,) to guide management and assess outcomes in different patient populations

Methods for monitoring glucose

There are several ways to monitor daily glucose levels and measure overall glycemic control in patients with diabetes or prediabetes. There are no comparable data to assess which method is better in a specific scenario; therefore, our recommendations are mostly based on clinical practice guidelines.

HbA1c

HbA1c provides a surrogate marker for the development of long-term complications. However, as discussed previously, it has several limitations: 1) provides only an average of glucose levels over the previous past 2-3 months; 2) does not detect hypoglycemia or hyperglycemia on a daily basis; 3) is an unreliable measure in patients with anemia, hemoglobinopathies, and therapeutic iron intake; and 4) it does not reflect rapid changes in daily glucose control.

Self-Monitoring of Blood Glucose (SMBG)

Self-monitoring of blood glucose (SMBG) was shown to be effective in insulin-treated and non-insulin-treated diabetes. (1-4) However, as discussed previously, it has its limitations. Nevertheless, SMBG is a viable option for patients who are managed with noninsulintropic medications or lifestyle treatments and/or when cost is an issue.

*Intermittently-viewed Continuous Glucose Monitoring (iCGM***)**

iCGM provides the glucose value plus retrospective glucose data for a certain period of time upon "scanning". These systems utilize two components: a glucose sensor, which is inserted the user's upper arm; and a separate touchscreen reader device. When the reader device is swiped close to the sensor, the sensor transmits both an instantaneous glucose level and an eight-hour trend graph to the reader. This allows users to obtain individual glucose readings without the need for calibration. The biggest advantages of iCGM over is lower cost and no calibration is needed. However, iCGM lacks alarms for low and high glucose values. Although improvements

in HbA1c with T1D or T2D have not been observed, reductions in time <70 mg/dL (<3.9 mmol/L) have been reported (5, 6). These improved outcomes and user satisfaction may account for the increased use worldwide. It can also be used in a blinded mode for clinical research or retrospective glucose pattern evaluation.

Real-time Continuous Glucose Monitoring (rtCGM)

rtCGM devices (in unblinded mode) provide real-time numerical and graphical information about the current glucose level, glucose trends and the direction/velocity of changing glucose. Devices with programmable alerts/alarms that warn users of current and/or impending high or low glucose offer additional safety advantages.

Numerous studies have shown that use of real-time rtCGM improves glycemic control and quality of life in both children and adults with T1D (T1D) treated with either continuous subcutaneous insulin infusion (CSII) or multiple daily insulin injection (MDI) therapy, improving HbA1c, shortening the time spent in hypoglycemia and hyperglycemia and reducing moderate to severe hypoglycemia (SH). (7-17) However, the benefit of CGM was seen primarily in those patients who regularly used their devices. (7, 8) Benefits of rtCGM use have also been reported in individuals with T2D who are managed with or without intensive insulin treatment (18, 19). However, there are limited data regarding the use of CGM as an outcome measure for individuals with gestational diabetes (GDM) and T2D, especially in those who do not use insulin.

How does CGM influence the adherence with diabetes therapy?

CGM was found to reduce HbA1c, decrease time spent in hypoglycemia, and improve glucose variability (15). For patient education purposes, the shift from making treatment decisions based only on point measurements to using trend information is essential. The benefit of CGM is directly correlated to persistence and frequency of CGM use (at least 5 days a week or 70% of the time wear is needed for success). The effect is more pronounced the higher the initial HbA1c (15). Despite the reported benefits of CGM, the actual rates of device use have been relatively low but are increasing. In clinical studies the dropout rate remains around 50% after a year of use (20, 21). More recent data showed that only 27-38% of patients, who used a healthcare-funded sensor, adhered to treatment after 1 year of use (22, 23).

Data from the T1D Exchange registry showed a 41% CGM discontinuation rate after 1 year of use (24). The main reasons for discontinuation were related to physical discomfort, technical issues, increased burden related to sensor use, and inaccuracy of the CGM. These obstacles may be overcome with the improvement in technology and the approval of sensor reads for treatment adjustments. It should be noted that this was with older generation CGM and discontinuation rate currently likely is much lower based on recent DIAMOND studies (17, 25). Additional education and training on interpreting and applying sensor data for treatment decisions are required and may improve adherence. As shown in a 6-month observational study, with a multidisciplinary education program on sensor-augmented pump use, patients improved metabolic control with a high level of adherence and satisfaction (26). This improvement is not limited to pump users. Indeed, two randomized controlled trials have shown the benefit of rtCGM also in patients treated with multiple daily insulin injection (MDI) therapy (17, 25, 27). Also, CGM as a replacement of SMBG will result in cost savings with respect to blood glucose strips.

The use of rtCGM in 153 children and adult pump users showed an increase in the number of boluses given per day with the same overall amount of insulin (28). In addition, rtCGM facilitates usage of temporary basal rates and the bolus calculator feature of the pump (28) rtCGM users were found to rely on glucose trends and rate information when determining insulin doses to make larger changes than current recommendations suggest regardless of insulin delivery method (29, 30). In a survey including 222 subjects with T1D using rtCGM data, it was found that subjects reported use of rtCGM data to alter multiple aspects of diabetes management, including insulin dose timing, dose adjustments, and hypoglycemia prevention (30). In a recent small-scale, short-duration study, iCGM use was associated with a significant increase in delivering bolus insulin 15-20 minutes in advance of meals (31).

There are limited data regarding the use of CGM data and behavioral changes such as exercise and diet; however, a recent pilot study showed that rtCGM use promotes exercise (32). CGM may also facilitate diet adjustments. Nevertheless, the T1D exchange survey showed that use of retrospective data analysis to change the types or amount of food eaten was reported to be the least helpful feature (only 46% found this feature helpful) (24). Furthermore, the use of a rtCGM device did not facilitate retrospective data use for analysis. The T1D exchange registry

results showed that only 27% of users downloaded data from their device at least once per month, and ≤15% of users reported downloading their device at least weekly.

Two large databases, US T1D Exchange registry and European DPV-Wiss, provide strong evidence that more SMBG measurements per day are strongly associated with lower HbA1c levels across all age-groups in both insulin pump and injection users (33, 34). However, the association appeared to level-off at approximately 10 measurements per day (35). Several studies evaluated the effect of each additional glucose measurement on HbA1c. In patients with T1D, each additional glucose measurement led to a 0.2-0.3% reduction in HbA1c (34-36). In insulin-treated T2D patients, each additional glucose measurement led to a 0.16% reduction in HbA1c, while those on OAD or diet alone showed no advantage (this is a field of current debate) (36).

An iCGM device that only shows glucose level and trends on demand, when the patient needs the data and is willing to react, would be expected to decrease exhaustion related to sensor use, improve patient compliance with glucose testing, and eventually improve glycemic control. However, there are no data yet linking its use to a better HbA1c. A study of T1D subjects showed that during 6 months of use of an iCGM device, the mean number of scans were at least 15 per day compared to a mean of 6 blood glucose tests per day in the control group. (37). At the end of the study time spent in hypoglycemia (primary outcome), time spent in hyperglycemia and glucose variability were reduced in the intervention group, although there was no change in mean glucose levels and HbA1c. This is likely due to the selected study population of well controlled participants. Adherence to iCGM use was high, and user-reported treatment satisfaction was improved. In a large study of insulin-treated T2D patients, the frequency of blood glucose testing was doubled in the intervention group with a mean of 8 scans per day throughout the study (38). The time spent in hypoglycemia was somewhat reduced with no change in HbA1c. Treatment satisfaction was higher in the intervention group, and adherence to iCGM use was high. In both studies, in the intervention group SMBG was reduced to 0.1 per day for T2D and 0.5 per day.

How does CGM relate to severe hypoglycemia?

Nocturnal hypoglycemic seizures have occurred following 2.25 to 4 hours of sensor documented hypoglycemia <60 mg/dl (39). The frequency of nocturnal seizures is low, and

clinical trials generally have a low incidence of seizures, which has made it hard to demonstrate a reduction in severe hypoglycemic events (seizures) while wearing CGM unless subjects were preselected for hypoglycemia unawareness. In the first years of CGM, no reduction in SH could be shown (40); however, in T1D adults with HbA1c ≥7.0%, HbA1c was reduced without increasing frequency of SH. With improving CGM accuracy and with more thoughtful selection of patients at risk for SH, the association between CGM use and reduced hypoglycemia is much stronger. Van Beers et al. showed a reduction in occurrence of grade III (external help required) hypoglycemia in patients with impaired hypoglycemia awareness assessed using the Gold or Clarke questionnaire (41). Earlier, Ly et al had shown a reduction in grade IV (seizure or coma) hypoglycemia in patients with impaired hypoglycemia awareness using a system with LGS (42). Thus, while CGM by itself reduced grade III hypoglycemia in people with impaired hypoglycemia awareness, an automated system may be more effective in reducing grade IV hypoglycemia. At the same time, it must be acknowledged that the number of patients encountering SH in the Ly trial was low, there were 6 and 5 SHs in the 6 months prior to baseline and 6 and 0 in the control and intervention arms respectively at 6 months into the study (43). iCGM use has been shown to decrease time in hypoglycemia in both T1D and T2D patients (37, 38). While this also held true for more serious hypoglycemia with a low cut-off point, no decrease in grade III or grade IV hypoglycemia has been reported. It should be noted that current evidence does not include individuals at high risk for hypoglycemia.

How does CGM and GV relate to diabetes complications?

The Diabetes Control and Complications Trial (DCCT), which used HbA1c as a measure of glycemic control, confirmed the association between chronic hyperglycemia and the development of long-term microvascular complications of T1D (44), and established HbA1c as a surrogate marker for risk of long-term complications.

In vitro and human epidemiological studies have demonstrated that large fluctuations in glucose levels may lead to increased production of reactive oxygen species and oxidative stress processes compared with sustained hyperglycemia (45). These findings have led to interest in the role of GV as an independent risk factor for micro- or macrovascular complications in T1D. (46). However, the findings from the human studies could not be confirmed by others, and only partially by the original investigators (47, 48).

The investigation of GV as a contributor to diabetes complications, however, has itself been complicated by the use of different measures of GV and the lack of consensus as to the most important or relevant metrics in this area. Two recent meta-analyses illustrate this problem. Nalysnyk (49) conducted a systematic review of the literature and found 8 studies relating GV to complications of T1D using a variety of metrics for GV, including standard deviation of blood glucose values, 7-point capillary glucose profiles, mean amplitude of glycemic excursions (MAGE), and CGM data over a blinded 3-day wear period. Single studies showed significant associations were found between measures of GV and the prevalence of neuropathy (50, 51), nephropathy (52), carotid intima-media thickness (IMT) as an index of subclinical atherosclerosis (53), and changes in arterial blood pressures (54), although other studies did not show any significant contributions to diabetes complications attributable to GV (55, 56). A subsequent meta-analysis of GV and diabetes complications (57) focused on longer-term GV, as determined by coefficient of variation of the HbA1c levels, a much longer time horizon than CV of glucose levels. Using this metric, the authors found significant risks associated with HbA1c, SD and retinopathy, nephropathy, microalbuminuria, and cardiovascular events (58-62). However, another meta-analysis did not show a significant relationship between GV and diabetes-related complications in T1D (63). Most recently, studies utilizing CGM have demonstrated an association between glucose variability and retinopathy, microalbuminuria, and neuropathy (64, 65). However, the recent analysis based on the DCCT data showed that within-day GV (measured by SD, MAGE, M-value) does not play a clear role in development of microvascular complications beyond the influence of the mean glucose level (66).

In summary, GV may play a role in the development of microvascular and macrovascular complications in T1D. Further studies in this area, including agreement on the ideal measure of GV (short-term measures of glucose variability or longer-term measures of HbA_{1c} variability, for example) are needed. Use of CGM, which provides a more complete and representative tool for the true assessment of short-term GV, is warranted.

How does CGM relate to health care expenditure?

There are limited data on the cost-effectiveness of CGM. As part of the JDRF CGM study, which consisted of two parallel trials of CGM vs. SMBG in two cohorts, one of which enrolled subjects with baseline HbA1c $\geq$ 7.0% and the other with baseline HbA1c < 7.0%, cost-

utility analyses were conducted during the trial (20). Direct costs included the costs of the CGM technology itself, training time for subjects and staff, time devoted to diabetes care during the study, other health service utilization such as emergency department and hospital visits, as well as days missed from work or school due to diabetes, and days of work underperformance. Analyses were conducted in which the only benefit was due to improved glucose control, and sensitivity analyses were run to assess the impact of variation in the daily cost of CGM, including reductions in SMBG. During the trials, both CGM cohorts experienced increased total and direct health-care costs, albeit with increased health-related quality of life.

In a lifetime analysis, CGM reduced overall diabetes-related complications and increased life expectancy (20). When the benefit of CGM is limited to glucose lowering alone, and subsequent complication reduction, CGM is not considered cost-effective. However, when extrapolating benefits in quality of life, CGM is considered cost-effective, and if CGM use resulted in lower costs of SMBG, CGM may even be cost-saving (20). Similar results of the cost-effectiveness of CGM vs SMBG were reported using a larger population base model (67).

More recently, health economic studies have been conducted for CGM combined with continuous subcutaneous insulin infusion into sensor-augmented pump systems. Using data collected from a meta-analysis of patient-level data (15), sensor-augmented pump therapy was determined to be cost-effective for the treatment of T1D in the Swedish health-care system (68). Sensitivity analyses indicated further cost-effectiveness benefit of increasing the amount of CGM use from 5 to 7 days a week, and decreasing the use of SMBG was incrementally cost-effective at every level. Subsequent studies have determined that sensor-augmented pump systems with a low-glucose suspend feature (SAP+LGS) is also cost-effective relative to insulin pump therapy alone, in the Australian (69), UK (70), and French (71) healthcare systems, due to improved glycemic control and reduction in hypoglycemia. However, these studies were based on assumptions from a single clinical trial of SAP+LGS with very large baseline differences in hypoglycemia rates (42).

In summary, data regarding the effects of CGM in groups with very high HbA1c and suspected non-adherence are lacking; however, CGM use has been shown to decrease time spent in hypoglycemia and improve GV. Moreover, rtCGM was found to reduce HbA1c when used continuously. GV is consistently linked to mortality in the intensive care unit and is a reliable

predictor of hypoglycemia risk. Relationships between increased GV and many other outcomes, including microvascular and macrovascular outcomes are less consistent.

Limitations of CGM

A key limitation of CGM has been the lack of automation; patient intervention is needed to avoid hypoglycemia or hyperglycemia. However, automation of insulin delivery/suspension based on rtCGM data is likely to reduce diabetes burden. This can be seen with the recent approval of the first Artificial Pancreas (AP) hybrid system in the US: Medtronic 670G System (Hybrid Closed-Loop-HCL). The system provides both a low glucose suspension (LGS) and low-predictive function as well as an auto-mode option that automatically adjusts the basal insulin every six days to maintain glucose levels within target range. Importantly, the system "auto-learns" how much insulin the patient needs. Future systems (Medtronic G690) may be aggressive for insulin delivery especially after meals automatically. A recent studies demonstrated that in-home use of the system by adolescents and adults increased time in target range and reduced HbA1c, hyperglycemia and hypoglycemia compared to baseline (72, 73). Importantly, more than 85% of patients enrolled in the studies continue to use the system (Continued Access Program); one plus year data from home use of HCL in real-life shows similar outcomes. However, it is important to keep in mind that significant resources are needed for education in implementing newer technologies.

Which glucose monitoring methods are most appropriate in pre-gestational diabetic pregnant woman?

The goal for tight glycemic control during pregnancy in diabetes is to reduce neonatal and maternal complications. Numerous studies have shown a positive correlation between fetal malformations, macrosomia, preterm delivery, preeclampsia, and birth complications with the level of glucose control in all types of diabetes (74). In contrast, tight glycemic control has been inversely correlated to severe hypoglycemia in the diabetic mother (74). Severe hypoglycemia especially in early pregnancy is a major limiting factor for near-normal glucose control (74). Thus, controlling glycemia during pregnancy is an even finer balance than in non-pregnant diabetes.

HbA1c and SMBG have traditionally been used to monitor the glucose level during pregnancy. Both the glucose levels and the HbA1c are, in general, lower during diabetic pregnancy compared to non-diabetic pregnancy for several reasons. It is recommended that women measure their blood glucose pre-and postprandial, at bedtime and occasionally during the night. Postprandial monitoring is associated with better glycemic control and lower risk of preeclampsia (75). Goals have been set for optimal values, although no prospective randomized studies have clearly pointed to which glucose levels are optimal. Nevertheless, the preferred upper values have been suggested to be fasting glucose lower than 90 mg/dL (5 mmol/L), 1 hour postprandial lower than 130–140 mg/dL (7.2-7.8 mmol/L) and two-hour postprandial lower than 120 mg/dL (6.7 mmol/L) (76). However, these values are obtainable in only a minority of T1D patients, which is why the goals may be individualized and less stringent for many women to avoid hypoglycemia.

Observational studies on complications for the child of mothers with pre-gestational diabetes perform the basis for the consensus on the optimal HbA1c in the pre-pregnancy period and during pregnancy. But randomized studies are lacking. The American Diabetes Association and other associations recommend HbA1c to be as low as safely possible, optimal below 6.5% (48mmol/mol) in the pre-pregnant period (77). Further, during pregnancy in second and third trimester, HbA1c is recommended to be lower than 6% (42 mmol/mol) because these low levels decrease the risk for macrosomia. HbA1c may be useful, but it cannot be used as a primary measure, as it does not reveal short-term changes in glycemic control, postprandial glucose excursions, hypoglycemia or provide information for insulin dose adjustments (77).

Although not often used as an outcome measure in pregnancy studies, CGM has the potential to improve HbA1c, detect hypoglycemia and guide personal management of women with diabetes and their offspring. Further, CGM will clearly signal all postprandial values, and much better than SMBG. Until now few studies have been published aiming to use CGM to improve HbA1c and fetal outcome, and these show conflicting results. A UK study of 71 women including T1D and T2D randomized to the use of masked CGM was associated with a reduced HbA1c of 0.6% and reduced risk of macrosomia from week 32 to 36 (78). Another Danish study, randomizing 154 T1D and T2D pregnant women to intermittent use of real-time CGM (for 6 days in total 5 times during pregnancy) in addition to self-monitored plasma glucose seven times daily, did not improve glycemic control or pregnancy outcome in women with pregestational

diabetes (79). However, compliance was rather low in the both studies(78) (79). A systematic review found that more studies are needed to conclude if rtCGM or iCGM are superior to any other technique of glucose monitoring among pregnant women with pre-existing T1D or T2D (80). A small observational study including 12 pregnant T1D women prone to severe hypoglycemia indicated a reduction in severe hypoglycemia in early pregnancy by using rtCGM (81).

Ongoing, is the large-scale, randomized, multinational, multicenter study CONCEPTT, aiming to study 110 pre-pregnant and 214 early pregnant T1D women using rtCGM persistently versus SMBG to clarify the current discrepancy in outcomes (82). Results from that study will be published in the Summer 2017. Whether rtCGM can reduce the risk of severe hypoglycemia in pregnant women is also unclear, but that will be reported as a secondary endpoint in the CONCEPTT study (83).

Limited evidence is available for iCGM, and no studies in pregnant women have yet been published. Currently, there is no definitive evidence that favors any specific glucose monitoring method in pregnant women with pre-gestational diabetes. Thus, several daily SMBG measurements, including postprandial glucose, in conjunction with HbA1c, may be considered as today's gold standard. In theory, however, the CONCEPTT ongoing study will investigate any advantage for rtCGM.

Which glucose monitoring methods are most appropriate in patients with hypoglycemia unawareness?

A high percentage of patients with long-standing T1D develop hypoglycemia unawareness. These patients have increased risk of SH (84, 85). Frequent glucose monitoring in combination with education and/or insulin pump treatment has been shown effective for this group of patients (85).

HbA1c cannot be used as a tool to evaluate and prevent SH, as seen with the same frequency with different HbA1c levels. rtCGM may benefit patients with impaired awareness of hypoglycemia by alerting them to impending hypoglycemia. In most clinical studies, patients with recent severe hypoglycemia are excluded from participation, which also was the case in most studies on the effect of adding rtCGM or iCGM to the treatment. Excluding patients with recent episodes of SH may reduce the power to demonstrate any positive effect of CGM in

reducing SH. This may have been the case in the JDRF, ASPIRE, and Star 3 studies, where no reduction in SH could be demonstrated (7, 13, 37, 86)**.** However, one observational study investigated the effect of adding rtCGM to insulin pump treatment, in exactly the hypoglycemic-prone individuals with recent SH where all other individual therapeutic options to reduce the risk for SH have already been tried. Most patients therefore used insulin pumps, and many used the low glucose suspension (LGS) feature after adding rtCGM (23 out of 35 patients) (87). rtCGM with and without LGS though resulted in a similar four-fold decrease in severe hypoglycemia during the 12-month observation.

A subsequent study from Australia also focused on patients with hypoglycemia unawareness (42). Patients were randomized to insulin pump only or LGS for 6 months. Whereas the rate of severe hypoglycemia was unchanged in the control group, no severe hypoglycemic events were seen in the LGS group. The adjusted incidence rate of severe and moderate hypoglycemic events per 100 patient-months was 34.2 (95% CI, 22.0-53.3) for the pump-only group versus 9.5 (95% CI, 5.2-17.4) for the LGS group. No restoration of hypoglycemia awareness was noted, likely indicating the need for continuous use of the device. This study has several limitations, specifically, the significant difference between both groups was driven by two individuals with excessive hypoglycemia (reported prior to the study) and by having an atypical young population. Nevertheless, the study findings still demonstrated that the CGM and insulin pump with LGS function was superior in this SH group.

Recently, a Dutch randomized, open-label, cross-over study in patients with T1D and impaired hypoglycemic awareness according to the Gold scale was performed (41). The study included 52 patients on either insulin pump or MDI treatment. They were randomized to rtCGM or SMBG in addition to the current treatment for 4 months. A wash-out period of 3 months was then followed by the alternate treatment for 4 months. During rtCGM use, a significant reduction in time spent in hypoglycemia and the number of SH-events was observed. These results clearly support the use of rtCGM in this high-risk patient group with impaired hypoglycemia awareness, independent of CSII or MDI as therapeutic regimen for insulin substitution. No studies in patients with hypoglycemia unawareness have been published until now on iCGM, and to our knowledge, none are ongoing. But because iCGM does not have alarms for impending hypoglycemia, it may be difficult to obtain same positive results in this high-risk group.

However, in both the IMPACT and REPLACE trials (37, 38), there were significant decreases in hypoglycemia with iCGM use.

In summary, HbA1c is not representative of the risk for hypoglycemia at an individual level. CGM technologies provide a better reflection of glucose control.

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APPENDIX 3. Minimum requirements for CGM performance

What is the minimal requirement for accuracy and reliability?

No internationally-accepted standard exists for CGM system performance comparable with the International Organization for Standardization (ISO) 15197 standard for SMBG devices, which specify design verification procedures and the validation of performance by the intended users. The ISO standard is applicable to manufacturers of such systems and other organizations (e.g. regulatory authorities and conformity assessment bodies) having the responsibility for assessing the performance of these systems.

ISO/IEEE FDIS 11073-10425 provides a normative definition of the communication between CGM devices and managers (e.g., cell phones, personal computers, personal health appliances, and set top boxes) in a manner that enables plug-and-play interoperability. The performance of CGM devices measuring interstitial glucose are evaluated against blood glucose, quantifying the deviation and its clinical relevance, mostly using point and trend accuracy (defined with respect to the reference blood glucose value). CGM accuracy is dependent on SMBG test results for calibration. Therefore, it is important to have an accurate glucometer.

In the early years of CGM, the accuracy and precision were notably inferior to those of blood glucose monitoring, such that there was increased risk of error in the clinical application of CGM values. However, accuracy and precision have improved dramatically during the past 5 years. For a wide range of glucose values, iCGM and CGM data are accurate enough to use for self-adjustment of insulin dosage, detection of hypoglycemia, and evaluating response to therapy (1); however, only one rtCGM system (Dexcom G5 Mobile) is currently indicated for non-adjunctive use. Accuracy is strongly dependent on the glucose level and rate of change of glucose (2). Accuracy in the hypoglycemic range is still limited, but hopefully this will continue to improve. Use of CGM without regular use of confirmatory BGM was shown as safe and effective as using CGM with BGM in adults with well-controlled T1D at low risk for severe hypoglycemia (3).

The mean absolute relative difference (MARD) between the blood glucose values and the corresponding interstitial fluid values is currently the most common metric used to assess the performance of CGM systems. Although controversy exists regarding the exact cut point for accuracy, in silico testing has shown that a further lowering of mean absolute relative difference

(MARD) ≤10% from reference values has little additional benefit for insulin dosing.(1); however, this must be established in clinical situations, particularly in light of future closed-loop approaches.

Comparing MARD values from different clinical studies has several limitations. Additional metrics, such as precision absolute relative difference (PARD) can be used as well to obtain a better evaluation of the CGM performance. Assessing the PARD requires use of an identical CGM device as a second "reference", rather than single blood glucose measurements as reference. While this approach is not simple to use for determining accuracy, the absence of relative delays and the availability of large number of data that can be analyzed provides a complementary insight into the sensor properties (4).

A MARD of ≤10% is the minimal but not the only requirement for sensor accuracy given the limitations associated with MARD evaluation. Therefore, for research purposes and closed loop performance reporting, the grid analysis may be advantageous. A new error grid analysis was developed and named the surveillance error grid (SEG) as a tool to assess the degree of clinical risk from inaccurate SMBG systems (5). The data points of the SEG were classified in zones according to their assigned level of risk, which allowed for comparisons with the classic error grids. Automated analysis can be performed using the SEG software (6); however, the current format of SEG is not intended for CGM and would need to be adapted for continuous data.

How to use MARD properly and what are its limitations?

Due to the positively skewed distribution of the absolute relative difference, the median is always lower than the mean. Using the median instead of the mean to calculate the "MARD" is resulting in false low values. MARD is the derived from the relative difference:

$$\text{MARD} = \frac{1}{N} \times \sum_{i=1}^{N} \frac{|\hat{G}(t_i) - G(t_i)|}{G(t_i)}$$

When evaluating performance of sensors designed to suspend insulin infusion in response to actual or predicted hypoglycemia, one should focus on the %MARD for the glucose levels of greatest interest (e.g., 71–120 mg/dL [3.9 – 6.7 mmol/L and <70 mg/dL [<3.9 mmol/L]). When

approaching lower glucose values, the denominator becomes smaller, and the value becomes higher. Conversely, the difference between the reading and the reference value becomes smaller. Therefore, some studies report the mean absolute difference (MAD) for the lower end instead of the MARD, as is corresponds to smaller numbers:

$$\mathrm{MAD} = \frac{1}{\mathrm{N}} \times \sum_{\mathrm{i}=1}^{\mathrm{N}} \left| \widehat{\mathrm{G}}(\mathrm{t_i}) - \mathrm{G}(\mathrm{t_i}) \right|$$

Thus, MARD and MAD should not be confused. A MARD of ≤10% is believed to be a cut-off for making reliable treatment decisions with interstitial glucose measurements (1, 6) However, whenever using the MARD, it is essential to be aware of its limitations (7). First, the MARD depends on the number of paired measurements and is dependent on a sampling effect as well as the distribution of the values within the glucose range (8). Furthermore, MARD depends on the accuracy of the reference system (8) and is influenced by the rate of change of glucose during the study (2). Taken together, these factors limit the inter-study comparison of MARD values because experimental conditions are only comparable in head-to-head studies. Evaluating MARD with respect to the threshold of ≤10% must consider any deviation from the setup underlying the simulations originally resulting in the ≤10% MARD threshold recommendation (1). Therefore, MARD is of value for performance assessment only if the limitations are understood and the MARD is used in a meaningful way.

What is the minimal period for CGM?

Patient responses to the current glucose level, to arrows indicating rate of change of glucose, and qualitative analysis of a graphical display of glucose versus time do not require stability of patterns. Similarly, use of rtCGM for a closed-loop system does not require day-to-day stability of glucose patterns. In contrast, retrospective analysis of either real-time or masked CGM is dependent on stability of patterns from day to day (9). If glucose patterns are erratic, one may not be able to conclude anything other than the fact that the patterns are erratic. For a comprehensive and representative glucose analysis, and to base clinical decisions on CGM data, a minimum of two weeks of data should be obtained to allow determination of glucose metrics such as mean glucose level, time in range, etc. This is also true in clinical trials, where 2 weeks of data every three months is the minimal and sufficient requirement for analysis. rtCGM data

obtained from subjects with T1D and T2D showed that two weeks of data reflect a good correlation with a month of sensor use analysis (10). This two-week period should contain 70-80% of sensor data. However, patients should be encouraged to use CGM regularly regardless of the 2-week minimum for analysis.

What is the minimal period to assess variability?

The data from the JDRF randomized clinical trial was analyzed to determine the optimal sampling intervals to assess long-term glycemic control (10). Three to 30 days of rtCGM data were sampled to determine the r2 values with a full three months of rtCGM data. Data were obtained from 185 subjects who had 334 three-month intervals of rtCGM data where there were at least 12 hours of rtCGM data per day for at least 70% of the days. For three days of sampling, the r2 value ranged from 0.32 to 0.47, evaluating mean glucose, percentage of values 71–180 mg/dL (3.9-10 mmol/L), percentage of values >180mg/dL (<10 mmol/L), percentage of values <70mg/dL (<3.9), and coefficient of variation; in contrast, for 15 days of sampling, the r2 values ranged from 0.66 to 0.75. The results were similar when the analysis intervals were stratified by age group (8–14, 15–24, and >25 years), by baseline hemoglobin A1c level (<7.0% and ≥7.0% [<53 mmol/mol and ≥53 mmol/mol]), and by rtCGM device type. It was concluded that 12-15 days of CGM data every three months was needed to optimally assess overall glucose control. This analysis was made on the 15 days of data immediately before a visit. There was minimal improvement in correlations if the two-week sample was taken in the middle of the three months or was taken once per month of the 3 months. To obtain an r2 of 0.7 twelve days of data was required for assessing the mean glucose and the percentage of values within range (70-180 mg/dL [3.9-10 mmol/L]). The coefficient of variation required 15 days of data for an r2 of 0.7, and the percentage of values <70 mg/dL (<3.9 mmol/L) required 18 days of data for an r2 of 0.7.

In another study the standard deviation (SD) and coefficient of variation (CV) glucose variability measurements were calculated from 90 days of rtCGM data from pediatric participants with T1D and compared to calculated variability from several days of sensor data up to 30 days. The comparison showed that a minimum of 12-day data is required to approximate GV expressed by SD and CV (11).

Controversy exists whether it might be suitable to distinguish between Type 1 and Type 2 patients since glycemic excursions tend to be much less labile and more predictable in patients

with Type 2 diabetes (12). Another concern is whether these recommendations may be applied to blinded CGM. Blinded CGM uses retrospective calibration to obtain the best fit of the data, allowing for correction and smoothing of the dataset. Nevertheless, several current reviews recommended 14 days of sampling, to have a representative sample size (13-18). Also, in order to look for a trend by weekdays necessitates wearing the system by a multiple of seven to avoid unequal weighting of the single days. For clinical studies where CGM data is used as an outcome measure, 14 days of continuous data are generally considered the minimal requirement for determination of glucose variability and dispersion by SD and CV.

How to exclude artifacts?

As in any measurement device, the glucose values provided by CGM sensors are affected by errors. Key CGM error components include lag introduced by the blood-to-interstitium kinetics, calibration errors and random noise errors. However, not all potentially clinically relevant deviations between blood glucose and interstitial fluid (ISF) glucose are necessarily caused by an error or artifact. Several physiologic factors (such as physical activity, hypoglycemic episodes, and meals) lead to clinically relevant differences. Under certain conditions using SMBG instead of CGM even may lead to therapeutic decisions that are inappropriate or even dangerous. In the long run, these observations support shifting from blood glucose measurements ISF measurements as the primary source for therapeutic decisions (19). Interstitial glucose levels also correlate better with temporal changes in the central nervous system when compared to blood levels (20).

It is important to have real-time methods to detect when a sensor may not be performing well. Several methods have been utilized to detect sensor error: 1) internal testing for sensor current stability, if the current is highly variable this may trigger initiation of a low pass filter and subsequent time delays in the sensor reading compared to the blood glucose; 2) this may trigger a stop in the display of glucose readings, or may require a new calibration value (smart cal); 3) there can be additional internal measures of sensor stability (such electrical impedance spectroscopy); or 4) redundant sensor technology can be used such as coupling glucose oxidase methodology with a fluorescent based technology.

However, CGM sensors can be also affected by occasional, transient faults which need to be excluded prior to systematic analysis. Two common faults of are disconnection and the so-

called ‘‘compression artifact”. Disconnection consists of the loss of one or more consecutive samples caused by the interruption of communication between the sensor transmitter and the receiver. Pressure-induced sensor attenuation or dropout is caused by a mechanical pressure made on the sensor by the patient (e.g., while sleeping on the device) inducing a temporary loss of sensitivity with consequent distortion of the CGM trace. Systematic analysis revealed that the great majority of disconnections (approximately 90%) lasted less than 20 minutes. (21). Compression artifacts lasted on average 45 minutes for the duration and 24 mg/dL for the amplitude. Both disconnections and compression artifacts happened with almost equal probability during the seven days of monitoring (21). Pressure induced sensor attenuations can be detected by algorithms (22), and could be incorporated into CGM software so as not to trigger false low alarms, and have also been incorporated into closed-loop algorithms (23).

While sensor redundancy is a technically effective strategy to mitigate the impact of such sensor failures, this is limited by the additional cost and patients’ discomfort. Modeling CGM data errors and transient faults is important for the development of fault detection algorithms, which are possible both for sensor error, such as the blood-to-interstitium delay, calibration and random noise as well as for transient faults such as disconnections and compression artifacts.

How do software approaches help to analyze CGM data?

The large dataset from CGM challenges already busy clinicians or patients to rapidly review, analyze and synthesize this data for use in treatment advice and dosing adjustments. This challenge is further compounded by the lack of standard metrics and data reporting among the different manufacturers of CGM devices (e.g., Medtronic *CareLink, Dexcom CLARITY, FreeStyle Libre* software*)*. Data-mining of these large industry-collected observational databases are generating important data on real-world use and benefits (24).

Ideally, the CGM data should be interpreted together with additional accurate, objective information regarding diet, physical activity, medications (including insulin), and other factors. Some apps and patient management software (*Glooko, MySugr* and others) allow uploading of continuous data and matching with other relevant data. As use of CGM devices continues to rapidly expand, efficient incorporation and analysis of such data in real-time will become central to providing optimal patient care.

An expert panel of diabetes specialists, facilitated by the International Diabetes Center and sponsored by the Helmsley Charitable Trust, met in 2012 to discuss recommendations for standardization of analysis and presentation of glucose monitoring data, with the initial focus on data derived from CGM systems. The panel members were introduced to a universal software report, the Ambulatory Glucose Profile (AGP) (14), which has since been adapted in the commercial software.

Use of the AGP and related forms of analysis requires a certain stability and reproducibility of glucose patterns from day to day. By widening the size of the time window used for retrospective analysis to one, two, or four weeks to construct an AGP, one can take advantage of signal averaging: random noise will tend to cancel out, potentially revealing an underlying pattern. However, if the time window of observations becomes too large, then day-to-day instability and heterogeneity will blur the pattern and degrade the quality of the information obtained. AGP analysis of the JDRF-CGM data highlights significant differences in glycemic profiles between pediatric and adult age groups and between well and less well-controlled patient populations (25). The consensus panel called for further standardization of the data analysis and visualization.

In summary, no internationally accepted ISO standard exists for accuracy of CGM systems. Several factors limit the inter-study comparison of MARD values as experimental conditions are only comparable in head-to-head studies. A minimum of 14 consecutive days of data are needed to generate a report that enables optimal analysis and decision making.

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APPENDIX 4. Definition and assessment of hypoglycemia in clinical studies

How should we define hypoglycemia within the context of the method of assessment?

Hypoglycemia remains a major barrier for glycemic control and a common complication of diabetes treatment, especially in T1D. Definition of hypoglycemia is needed to evaluate the level of control of patients with diabetes and to evaluate the safety of new treatment modalities. Definition of hypoglycemia might take into consideration several parameters: the compartment of measurement (arterial, venous, and capillary blood or interstitial); the nadir level of blood glucose measured; and the duration of the event and related symptoms. The key goal is to define hypoglycemic events that are clinically meaningful, either because they are associated with a clinical issue at the time, or because they have clinically important downstream events.

For clinical use, the panel adopted a slightly modified version of the ADA recommended 3 levels of hypoglycemia report; i.e., hypoglycemia can be classified based on clinical evaluation (1):

- Level 1: A hypoglycemia alert value of <70-54 mg/dL (<3.9-3.0 mmol/L). This need not be reported routinely in clinical studies, although this would depend on the purpose of the study.
- Level 2: A glucose value of <54 mg/dL (<3.0 mmol/L) is sufficiently low to indicate clinically significant hypoglycemia.
- Level 3: Severe hypoglycemia, as defined by the ADA, denotes severe cognitive impairment requiring external assistance for recovery.

Definition of CGM-based hypoglycemia should take all of these parameters into account but need also to consider the accuracy of CGM data within the hypoglycemic range. It should be noted that CGM over short periods of time may not predict problematic hypoglycemia (2). Another point to consider is to what extent CGM readings can be viewed equivalent to arterialized plasma glucose readings in controlled research studies. CGM is generally calibrated to capillary plasma glucose measurements, whereas glucose clamp studies commonly use arterialized venous glucose. Although capillary glucose measurements are generally higher than venous measurements, they may be more equivalent to arterialized venous measures. Venous plasma glucose was found to be lower by 22.5 mg/dL (1.3 mmol/L) than capillary when below

72 mg/dL (4.0 mmol/L) (3). In older adults with T2D, interstitial glucose remains higher than venous, as the difference increases by 6 mg/dL (0.32 mmol/L) for every 18 mg/dL (1 mmol/L) drop in blood glucose (4).

In the alert range to treat to prevent hypoglycemia (<70 mg/dL [<3.9 mmol/L]), CGM values taken from closed-loop studies were found to be less accurate compared with the euglycemic range when measured by ARD (MARD, 30.6% vs. 13.9%); however, absolute difference was comparable (5). CGM accuracy in the lower glucose range (<70 mg/dL) also differs depending on the type of CGM used (6-9)

How should "time in low range" be defined?

The level of hypoglycemia that causes clinical symptoms and counterregulatory response is specific to the individual and depends on the personal level of glycemic control. (10). The relationship between the duration of hypoglycemia and ability to impair counter regulation was evaluated in several clamp studies. In individuals without diabetes, two hours at 54 mg/dL (3 mmol/L) impaired epinephrine, glucagon, pancreatic polypeptide, cortisol, and total, neurogenic and neuroglycopenic symptom responses to 50 mg/dL (2.8 mmol/L) in the next 24 hours (20-22 hours); whereas stepped reduction to 50 mg/dL (2.8 mmol/L) 24 hours earlier did not. A first event didn't lead to alteration in responses alone following the afternoon euglycaemic control. The reduction in counterregulatory responses required two episodes of hypoglycaemia on the previous day (10).

For patients with T1D, hypoglycemia of approximately 50 mg/dL (2.8 mmol/L) for two hours reduced epinephrine, pancreatic polypeptide, and symptom responses to subsequent hypoglycemia (11). Two hours at 54 mg/dL (3.0 mmol/L) on the same day before the test hypoglycemia caused further reduction in growth hormone and cortisol but no further impact on epinephrine, norepinephrine, or glucagon in the second challenge in patients with T1D with impaired responses (12). Two hours at approximately 60 mg/dL (3.3 mmol/L) reduced glucose concentration for norepinephrine release but increased glucose levels for release of other hormones. However, it had no impact on symptoms and Digit Symbol Substitution Test (DSST) but prevented deterioration in logical (immediate) memory (13).

In individuals without diabetes, symptom responses to subsequent hypoglycemia are only impaired after exposure to 52 mg/dL (2.9 mmol/L) for at least 30 minutes (14). In healthy

volunteers, two hours at 70 mg/dL (3.9 mmol/L) on two consecutive days impair epinephrine, glucagon, and MSNA, but not norepinephrine, cortisol, growth hormone, cardiovascular, or endogenous glucose production responses. Symptoms were not measured. Two hours at 60 mg/dL (3.3 mmol/L) impairs all of the above, plus norepinephrine and growth hormone (15).

At what level does hypoglycemia cause symptoms and cognitive impairment?

The counterregulatory hormones and symptoms are affected at different levels of hypoglycemia. Impaired cognitive performance was found in school children at capillary glucose levels below 54 mg/dL (3.0 mmol/L) but not in the range of 54-68 mg/dL (3-3.8 mol/l) (16). In clamp studies, 2 hours at 54 mg/dL (3.0 mmol/L) has been the most effective inducer of counterregulatory failure, but defects in responses that are probably clinically relevant have been seen with exposure to 54 mg/dL (3.0 mmol/L) for 30 minutes, but not shorter. It needs to be clarified if the adverse effects of hypoglycemia on counterregulatory hormone responses are the same if hypoglycemia occurs at night rather than the day.

What is the level of hypoglycemia that causes cardiac events?

Nocturnal hypoglycemia <63 md/dl (3.5 mmol/L) for at least 20 minutes in patients with T1D increased QTC, but actual levels of glucose were not reported (17). In another study, CGM recorded episodes of nocturnal hypoglycemia with glucose levels < 45 mg/dL (2.5 mmol/L) that were found to be associated with increased QTC (18).

In T2D patients, SH defined as glucose level <60 mg/dL with the inability of self-treatment, caused prolongation of corrected QT Interval (19). Hypoglycemia <45 mg/dL (2.5 mmol/L) was associated with a greater degree of QT prolongation, while lower levels were associated with bradycardia (20). In a clamp study including non-diabetic volunteers, hypoglycemia <44 mg/dL (2.4 mmol/L) for over two hours caused prolonged QT (21). Retrospective recording of CGM revealed a "dead-in-bed" case after several hours at 30 mg/dL (1.7 mmol/L) (22).

How many consecutive low readings constitute an event and what should be considered one event in sequential events?

In the presence of symptoms, any number of CGM readings in the hypoglycemic range will constitute a hypoglycemic event. For asymptomatic hypoglycemia in which the patient does not respond (e.g., during sleep), the duration that can be defined as hypoglycemia should be standardized. This duration or number of readings is debatable; an emerging and common definition is 15 or 20 minutes (4 or 5 readings). CGM reports every 5 minutes with at least a 5-minute delay; therefore, a hypoglycemic CGM reading implies that the patient has been hypoglycemic for at least 5 minutes and may have been hypoglycemic for up to 10 minutes beforehand. The most commonly used time period in reports is currently 15 to 20 minutes (4 or 5 CGM readings); however, this may, in fact, reflect up to 25 to 30 minutes of hypoglycemia experienced by the individual. Equally, delay in measuring the recovering glucose can over-report the duration of the hypoglycaemia by CGM. A further consideration for duration of a hypoglycemic event is whether the CGM is blinded or real time. Patients respond to real time glucose readings and trends whether symptomatic or not; thus, if a reading is 72 mg/dL (4.0 mmol/L) with a downward trend, the patient may already be hypoglycemic and will respond. Interventions to treat hypoglycemia by the patient in response to CGM readings may need to be defined and recorded as an event.

The definition of hypoglycemia used for the JDRF CGM study (23) was at least 2 readings ≤60 mg/dL (≤3.3 mmol/L) within 20 minutes. UK Hypoglycemia Study Group defined hypoglycemia as glucose level <54 mg/dL (<3.0 mmol/L) or <40 mg/dL (<2.2 mmol/L) for at least 20 minutes and the episode was completed once the glucose remained above the respective threshold value for a further 20 minutes (1). Using this definition, hypoglycemia was not associated with increased risk of SH or fear of hypoglycemia. A similar definition was used to evaluate the effect of threshold suspend on hypoglycemia defined as CGM glucose level ≤65 mg/dL for 20 minutes (24). The duration of nocturnal hypoglycemia ≤60 mg/dL (≤3.3 mmol/L) of more than 30 minutes and of two hours was reduced by the low glucose suspend system; however, no impact was reported on clinical SH in that study (25).

Hypoglycemia was defined as <70 mg/dL (<3.9 mmol/L) in a pooled analysis of two overnight closed-loop studies from the Cambridge group (5). Glucose sensor area under the curve <63 mg/dL (<3.5 mmol/L), and the number of nights with sensor glucose levels <63 mg/dL for at least 20 minutes, were used to describe hypoglycemia outcomes for the adult cohort (5). In this study, the use of overnight closed-loop did not change the time spent below the above

parameters or the time spent <70 mg/dL (<3.9 mmol/L), <63 mg/dL (<3.5 mmol/L), or <50 mg/dL (<2.8 mmol/L).

Another study of overnight closed-loop use for 6 weeks defined hypoglycemia as <60 mg/dL (<3.3 mmol/L) for more than 20 minutes. In this study closed-loop use reduced the number of hypoglycemic events at this level and also the time spent < 50 mg/dL and the area under the curve of <65 mg/dL (<3.6 mmol/L) (26). Hypoglycemia outcome measurements for overnight closed-loop use included moderately SH <50 mg/dL (2.8 mmol/L) for more than 15 minutes and overall hypoglycemia <70 mg/dL (<3.9 mmol/L) for more than 15 minutes. All nocturnal episodes were reduced by closed-loop use with reduction in moderately severe episodes only in 24 hours of evaluation; however, no clinically severe episodes in either arm of the study were reported, so clinical impact was not described (27).

In a closed-loop treatment in a pregnancy study, moderate hypoglycemia was defined as CGM glucose level ≤63 mg/dL (≤3.5 mmol/L) for 20 minutes, or longer; moderately SH was defined as CGM glucose level <50 mg/dL (<2.8 mmol/L) for more than 15 minutes (28). The study results showed no impact of closed-loop on this parameter or on clinical outcomes. Studies of day and night closed-loop use showed reduced time spent <70 mg/dL (<3.9 mmol/L) but no reports on SH (29).

Although 20 minutes has been used as the duration to define hypoglycemia in CGM data acquired during closed-loop and other studies, there is no clear evidence for that duration of hypoglycemia having clinically significant consequences. Whereas such hypoglycemia is reduced by interventions associated with reduced risk of SH, the interventions are likely to have a greater impact on duration than this defining hypoglycemia duration.

Recently, the ADA adopted the recommendations of the International Hypoglycemia Study Group for hypoglycemia classification. Glucose values <70 mg/dL (<3.9 mmol/L) were classified as alert values for treatment adjustments. A glucose concentration of <54 mg/dL (<3.0 mmol / l), detected by self-monitoring of plasma glucose, continuous glucose monitoring (for at least 20 minutes), or a laboratory measurement of plasma glucose, was sufficiently low to indicate serious, clinically significant hypoglycemia. SH was defined as severe cognitive impairment requiring assistance from another person for recovery and should allow inclusion of those episodes where there was no-one around to help and the patient recovers spontaneously from a coma or seizure with evidence consistent with hypoglycemia having occurred (1).

While CGM measures interstitial glucose levels and not blood or plasma glucose levels, ADA or International Hypoglycemia Study Group recommendations for blood or plasma glucose level hypoglycemia may not necessarily be the same (1). Indeed, data from healthy non-diabetic subjects indicated fair number of CGM values in the 60-69 mg/dL range (~1-2%) (30, 31)

The ATTD group agreed that hypoglycemia starts at <54 mg/dL (<3.0 mmol/L); however, glucose <70 mg/dL (<3.9 mmol/L) has been identified as the cutpoint at which action should be initiated to prevent hypoglycemia. This is identified as "Alert / Low".

Which expanded hypoglycemia parameters can be used?

The duration of hypoglycemia influences the counterregulatory response (32). In healthy subjects, hypoglycemic symptom scores were reduced by prolonged (30 minutes or 2 hours) but not short-duration (5 minutes) prior to hypoglycemia (14). Area under the curve (AUC) is a two-dimensional description of hypoglycemia, evaluating the depth as well as the duration of hypoglycemia. AUC was used as the primary endpoint to evaluate the threshold glucose suspend feature of the pump (24). Nocturnal hypoglycemia of AUC ≤ 65 mg/dL was found to be reduced when using the threshold suspend. Hypoglycemia can also be described by three dimensions, adding the frequency of the events to the area under the curve. No data is available yet on this parameter. In several studies, the LGI was used as a measure of the risk of SH (33). Baseline LGI (LGBI when evaluated from SMBG) was the best independent predictor of hypoglycemia outcome when switching from MDI to pump therapy (34). Several closed-loop studies have used LGI as an outcome measure (29, 35).

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APPENDIX 5. Assessment of glycemic variability (GV)

Why is GV important?

Diabetes, especially T1D, is characterized by wide swings in blood glucose levels that increase average glucose levels and often result in hypoglycemia and/or hypoglycemic events. Characterization of GV by standard metrics might be of help to optimize glucose control by reducing the frequency and the extent of both high and low glucose excursions, with the goal of maintaining optimal average glycemia without increasing the risk for hypoglycemia. Intensive lowering of average glucose levels (e.g., HbA1c) alone, without keeping GV in check, may result in increased incidence of hypoglycemia (1-4).

In the past 15 years, the ability to accurately measure GV has evolved from the inadequate method of measuring six to seven blood glucose levels per day for one or two days every few months to contemporary, daily profiles, which capture dense data sets of sensor glucose readings every five minutes. These data sets, known as time series, open new possibilities for the analysis and the optimal control of the human metabolic system in diabetes, including assessment of system dynamics, prediction of blood glucose trends and events such as impending hypoglycemia or hyperglycemia and automated closed-loop control commonly referred to as the "artificial pancreas" (AP).

An important question that should be discussed further is whether HbA1c shall remain the primary assessment of glycemic control, particularly given the increasing proliferation of technologies that allow direct assessment of average sensor glucose and glucose fluctuations (5). As discussed previously, a major limitation of the HbA1c is that is does not provide any information about the timing and magnitude of GV, nor does is provide data regarding the timing and frequency of hypoglycemia. However, from a clinical point of view, GV is of relevance with respect to acute and long-term treatment of patients with diabetes (6).

How does GV relate to outcomes?

Increased glucose variability is consistently linked to mortality in the intensive care unit (7-9) and is a consistent predictor of hypoglycemia, both in prospective studies and within the setting of randomized clinical trials (10, 11). Relationships between increased glucose variability

and many other outcomes, including microvascular and macrovascular outcomes, has not been demonstrated in a randomized controlled trial to date.

The step from epidemiology to intervention has been challenging. The HEART2D trial randomized T2D patients who had experienced a myocardial infarction to either a prandial insulin regimen or basal insulin. (12). Although designed as an intervention specifically targeting post-prandial glucose, the intervention resulted in a less than expected difference in post-prandial glucose control between treatment arms and thus little difference in glycemic variability and no difference in cardiovascular outcomes.

Which parameters can be used to measure GV?

HbA1c provides an incomplete expression of the degree of glycemia and other features of glucose control that may add to, or modify the risk of complications. For example, the risk of complications may be highly dependent on the extent of postprandial glycemic excursions (13). Subsequent studies have focused on GV as an independent risk factor for diabetes complications, particularly cardiovascular disease (14-17), and on the effects of GV on cognitive function and quality of life (18). Accepting that GV is a primary marker of glycemic control has greatly expanded the understanding of glycemic control beyond HbA1c alone. (6, 19, 20). The pros and cons of the utility of GV as a marker for the quality of diabetes management are discussed elsewhere.

How is GV measured in clinical trials with new antidiabetic drugs?

The multi-centre Fluctuation Reduction with Insulin and GLP-1 Added Together (FLAT-SUGAR) study was designed to test whether, in a T2D population with high cardiovascular risk, basal insulin with added prandial GLP-1 receptor agonist will reduce GV (and thereby cardiovascular risk markers), more effectively than insulin alone (21). The first results of the FLAT-SUGAR study confirmed that HbA1c levels can be maintained with reduced glucose variability by adding a GLP-1 receptor agonist (22). A year before the FLAT-SUGAR report, similar findings were presented by a re-analysis of data from a study of Lixisenatide - a GLP-1 receptor agonist added to basal insulin (23). A multicenter, open-label, randomized, active-controlled, parallel-group study to compare the therapeutic effect on improving postprandial glucose of either nateglinide (120 mg tid) or acarbose (50 mg tid) therapy in T2D used rtCGM to

calculate the incremental area under the curve of postprandial blood glucose (AUCpp), the incremental glucose peak (IGP), mean amplitude of glucose excursions (MAGE), and the mean of daily differences (MODD). The study results showed that both agents caused significant reductions on AUCpp and IGP (24).

In another trial comparing the efficacy and safety of once-daily insulin glargine plus gliclazide combination therapy versus twice-daily premixed insulin monotherapy, despite a significant decrease of mean HbA1c for both treatment groups, neither intervention produced a significant effect on GV, calculated as MAGE, SDBG, and MODD. In addition, the effects on rates of hypoglycemic episodes were similar between the two therapies (25). Nevertheless, does provide more information on postprandial glucose levels, GV, and hypoglycemia events when evaluating different therapeutic regimens compared with traditional SMBG (26). While the debate about the utility of GV as a marker of glycemic control and predictor of diabetes complications will undoubtedly continue and clinically meaningful reduction of HbA1c can best be achieved if combined with concurrent reduction in GV. GV is closely related to mean glucose which is closely related to HbA1c.

Which data sources can be used for the assessment of GV?

The interpretation of average blood glucose is straightforward, and an accepted laboratory marker (HbA1c) is readily available. In contrast, GV is a reflection a dynamic process, and its understanding and measuring are less apparent (27, 28). Beyond the setting of laboratory experiments, the data sources available for routine estimation of GV include episodic SMBG records and traces (29).

The density of the available data determines what properties of GV can be investigated. For example, episodic SMBG can yield information about the extent of hypoglycemia and hyperglycemic excursions based on the dispersion of the data (30, 31); whereas, yields dense data sets with data points that are regularly spaced in time (e.g. every 5 minutes) known as “time series.” This adds complexity to the data analysis, but also presents opportunities for deciphering the dynamics of glucose fluctuations (32, 33). time series can reveal details about the progression of hypoglycemia or hyperglycemia, predict impending glycemic events and enable real-time closed-loop control of glucose levels by automated algorithms (34, 35).

What is the interaction of glucose amplitude and timing?

Both the amplitude and the timing of BG fluctuations contribute to the risks for hypoglycemia and hyperglycemia associated with diabetes (5). The classic marker of the amplitude of glucose fluctuations is the MAGE, introduced in 1970 (36). This metric illustrates the concept of GV measurement that is "*devoid of time component*" (37), i.e., focusing solely on the magnitude of the minimum-to-maximum glucose span, regardless of the time it takes for BG to transition from one extreme to the next.

In contrast, studies using rtCGM assessed the temporal structure of the glucose fluctuations using multiscale entropy to evaluate their complexity (38, 39). These analyses, which focused exclusively on the timing of fluctuation, found decreased temporal complexity associated with diabetes, likely a result from the absent (in T1D) or impaired (in type 2 diabetes) pulsatile secretion of insulin (40). For most practical purposes, however, the amplitude and the timing of glucose fluctuations cannot (and should not) be separated.

The understanding that glucose fluctuations is a process characterized by the amplitude, as well as the frequency and duration of the fluctuation, unifies the interpretations of average glycemia and GV: changes in HbA1c reflect changes in glucose levels that may have small or large amplitudes, but become notable on the time scale of months; glucose variation monitored by SMBG reflects blood glucose fluctuations on the time scale of hours or days, while reflects rapid glucose transitions developing within minutes.

Which are the traditional metrics of glucose variability?

Standard deviation (SD) and coefficient of variation (CV) are widely used to quantify GV. The CV has the advantage of being a metric relative to the mean, which makes it more descriptive of hypoglycemic excursions than the SD alone. In addition to these standard statistics, various diabetes-specific metrics of GV have been introduced during the last half century, beginning with the M-Value based on a logarithmic transformation of the glucose deviation from a pre-set value (e.g., 120 mg/dL [6.7 mmol/L]) (41). Among these metrics, MAGE has been one of the most widely used (37, 42).

The validity of SD, CV and other traditional statistical metrics with data is compromised as the statistical properties of these metrics would rely on two fundamental assumptions: independence of the observations used for their computation; and symmetry of the data around

the mean. Both are violated very substantially with data; consecutive data points are not independent and the distribution of BG levels is not symmetric.

The causal relation (successive values) is more subtle, but can be handled using standard approaches to autocorrelation analysis, which, however, may prove difficult in routine assesment. Also, SD, MAGE and other variability metrics that are not adjusted for mean glucose are correlated with mean glucose. **Figure 1** shows a series of graphs that demonstrate the correlation of SD and MAGE with mean glucose from CGM data collected over 3 months and with the HbA1c collected at 3 months. In addition, there is a strong correlation of SD and MAGE, which suggest MAGE does not add much information more than just SD. Figure 1 also shows that the CV is not well correlated with the mean glucose or HbA1c. This implies that CV adds more valuable information on glycemic variability that is more independent or less influenced by the mean glucose or HbA1c value than the SD.

The Lability Index and the Mean Absolute Glucose Change (MAG) have been introduced and used in hospital settings to assess the effects of islet transplantation or increased risk for mortality in intensive care (7, 43).

Because the more comprehensive statistical assessments (e.g., Poincarré plot) would be reserved for in-depth scientific analysis of data, the consensus panel recommended that if the intent is to assess the effects independent of mean glucose, coefficient of variation (CV) may be best and preferred over SD.

How should we perform risk analysis of GV?

One common aspect of many traditional metrics of GV (including SD, M-Value, MAGE) is their bias toward hyperglycemia. This is due to a purely numerical reason: the glucose scale is highly asymmetric and the deviations towards hyperglycemia (e.g., blood glucose levels >180 mg/dL [>10 mmol/L]) occupy a much wider range and are numerically “heavier” than the deviations towards hypoglycemia (<70 mg/dL [<3.9 mmol/L]) (44). As a result, some metrics are primarily influenced by hyperglycemia and are less sensitive to hypoglycemia (45). The clinical risk associated with glycemic excursions is biased, as well. For example, a glucose rise of 1 mmol/L, from 10 to 11 mmol/L, weights substantially less in terms of clinical risk than a 18 mg/dL (1 mmol/L) blood glucose fall from 70 mg/dL [3.9 mmol/L] to 52 mg/dL [2.9 mmol/L], which is perceived as a dramatic descent into hypoglycemia. To correct this asymmetry, a

numerical transformation of the blood glucose scale was proposed, which had coefficients not derived from a particular data set, but based on the common clinical assumption that the target glucose range in diabetes was 70-180 mg/dL (3.9-10 mmol/L) (44). Because this assumption still holds, the coefficients of the glucose scale transformation remain unchanged.

Several metrics based on this risk function have been introduced: the Low Glucose Index (LGI) increases with the frequency and extent of hypoglycemic excursions and, by design, ignores hyperglycemia; the High Glucose Index (HGI) increases with the frequency and extent of hyperglycemic excursions and ignores hypoglycemia; and the Average Daily Risk Range (ADRR), which is equally sensitive to both low and high glucose excursions**. (Table 1)** It has been shown that the LGI is predictive of severe hypoglycemia (10, 46, 47), the HGI is associated with HbA1c and hyperglycemic excursions (31, 45), and the ADRR is a measure of overall GV that captures the risk of both hypoglycemia and hyperglycemia, as summarized by a recent review of studies using this metric in various settings (48).

What are the -based metrics of glucose variability?

CGM data reflect the dynamics of glucose fluctuations and therefore includes time as another dimension of GV. A more standard approach was used to GV to define the threshold for excess GV, using the percentage coefficient of variation for glucose (%CV) (49). A %CV of 36% appears to be a suitable threshold to distinguish between stable and unstable glycemia in diabetes because beyond this limit, the frequency of hypoglycemia is significantly increased, especially in insulin-treated subjects. More elaborate CGM-based metrics of GV have been introduced over 10 years ago (50, 51), and some of the existing measures, such as MAGE and LGI/HGI have been adapted for use as well. The adaptation of MAGE for CGM data followed the classic time-independent structure of this measure, and, therefore, in this case, CGM was only used as a source for amplitude assessment (52); the adaptation of the LGI and the HGI accounted for differences between SMBG and data (53).

The Mean of Daily Differences (MODD) was introduced as a measure of inter-day variability, and the Continuous Overlapping Net Glycemic Action (CONGA) was presented as a composite index of the magnitude and the timing of glucose fluctuations captured over various time periods (51). The standard deviation of the glucose rate of change was used as a marker of

the stability of the metabolic system over time, based on the premise that more erratic glucose changes are signs of system instability (50, 54).

An array of standard deviations was introduced to reflect GV contained within different clinically-relevant periods of data (55), and the clinical interpretation of various CGM-based metrics of glucose variability was discussed (56). A review of the statistical methods available for the analysis of CGM data included several graphs, such as Poincaré plot of system stability, and the Variability-Grid Analysis (VGA) used to visualize glycemic fluctuations captured by CGM (57). The VGA was also used to depict the efficacy of closed-loop control algorithms (33, 58). A recent analysis of CGM data in comparison to blood glucose data obtained in a large study with patients with T1D showed how GV indices are related and demonstrated the impact of CGM use on GV (59). There was strong correlation between time spent in hypoglycemia, and CV, LGI, and %GRADEhypoglycemia, but not with HbA1c. %GRADEhypoglycemia (glycemic risk assessment diabetes equation [GRADE]) represents percentages of GRADE scores attributable to glucose values <3.9 mmol/. A significant reduction in most GV indices was demonstrated in the intervention group at 26 weeks compared with the SMBG group. CGM reduces most GV indices compared with SMBG.

Several of the methods for computing and visualization of GV within the context of the relationship between GV and the risk for hypoglycemia have been reviewed recently, giving details on the interpretation of the VGA and of the Poincaré plot of CGM data (28).

In summary, the discussion of the utility of GV markers and the shortcomings of HbA1c as a sole “gold-standard” measure of glycemic control has been ongoing and continues to this day with opposing opinions published regularly (6, 19, 20). However, it is important to consider that HbA1c determinations are typically taken months apart, and SMBG profiles are often insufficient to allow treatment intensification without increased risk for hypoglycemia. In contrast, rtCGM-based closed-loop systems have the potential to reduce and simultaneously, average glycemia, GV, and the risk for hypoglycemia. Current technology allows for the direct observation of glucose fluctuations; thus, the assessment of glucose control in diabetes is positioned to move beyond the HbA1c assay as the sole marker of glycemic control. Glucose fluctuations are manifested at several time scales, from slow months-long changes reflected by HbA1c, to fast transitions captured by CGM data, which reflect the dynamics of glucose fluctuations on the relevant time scale (minutes-hours) that corresponds to meal dynamics and

diurnal metabolic variations, and, therefore, provide the perfect data source for understanding the two principal components of diabetes control, risk (amplitude) and time. The ability to quantify these fluctuations is critical for adjusting the management of patients with diabetes, and the effectiveness of treatment is dependent on the density of the available data, the accuracy of the data and on the methods for information retrieval and analysis.

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Figure 1. Corrleation of Glycemic Variability metrics with Mean Glucose and HbA1c

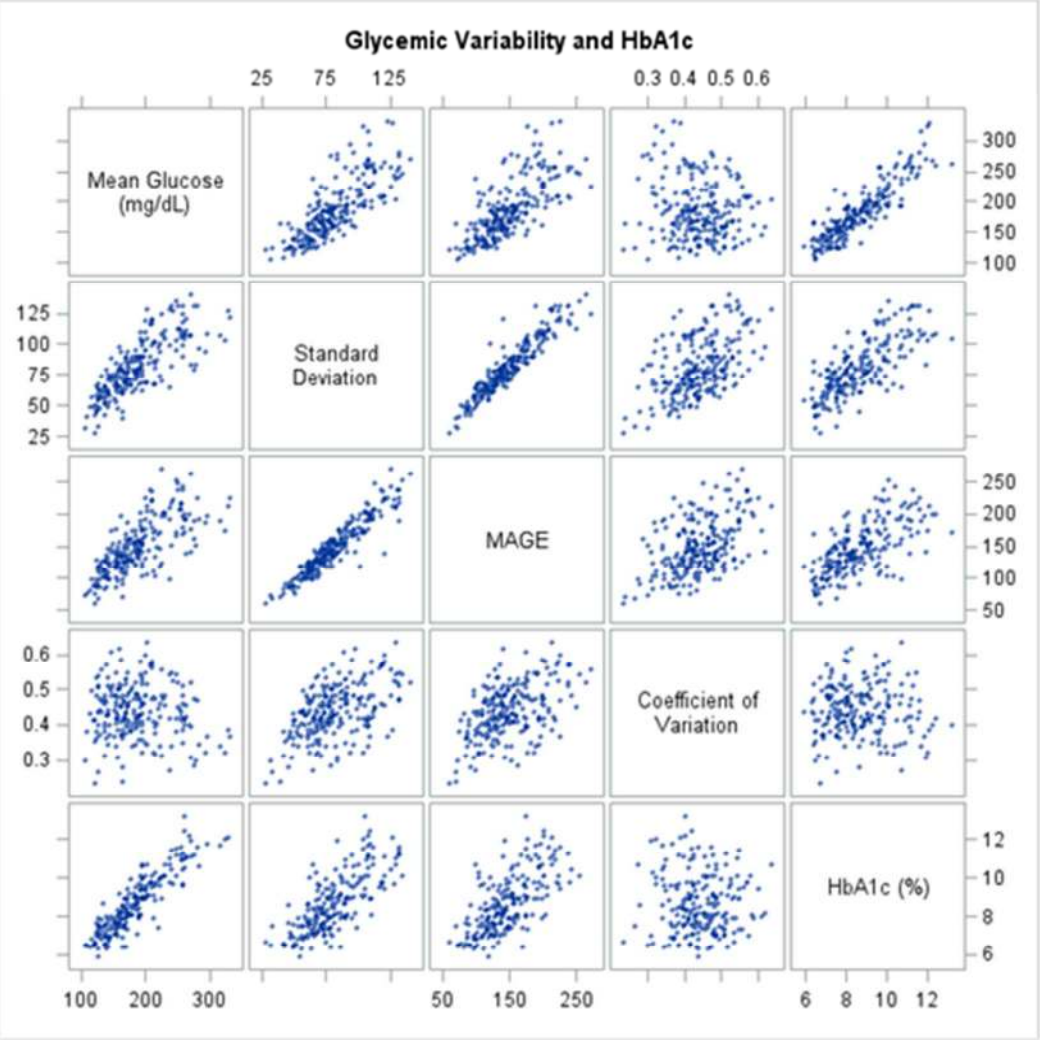

Table 1: List of traditional, risk-based and CGM-based metrics of glucose variability (modified with permission from 56)

Data source	**Temporal Resolution**	**Metric**	**Computational formula**
Episodic blood glucose determinations (e.g. self-monitoring of blood glucose (SMBG) data); adaptation to continuous glucose monitoring	Days / hours	Standard deviation (SD) and coefficient of variation (CV)	$SD = \sqrt{\frac{\sum (x_i - \bar{x})^2}{n-1}}$; $CV = \frac{SD}{Mean}$
		Mean amplitude of glucose excursions (MAGE) — the mean of glycaemic excursions from nadir to peak blood glucose (BG) level and vice versa, which exceed one SD of glucose variation(30)	$MAGE = \sum \frac{\lambda}{n}$, if $\lambda > SD$ where λ is each BG increase or decrease (absolute value) exceeding SD
		Mean absolute glucose (MAG) change — the summed absolute differences between sequential BG readings, prorated for time(38)	$MAG = \frac{\sum \lvert x_i - x_{i+1} \rvert}{\Delta T}$ where ΔT is the time between the first and the last BG measurement

(CGM) data has been done for some metrics.		Low BG index (LBGI) and high BG index (HBGI) — reflections of the risk of hypoglycaemia and hyperglycaemia, respectively, which increase gradually with the extent and the frequency of hypoglycaemic and hyperglycaemic excursions[56]	$LBGI = \frac{\sum r_l(x_i)}{n}$, where $r_l(x_i) = 22.77 \cdot f(x_i)^2$ if $f(x_i) \le 0$, and 0 otherwise; $HBGI = \frac{\sum r_h(x_i)}{n}$, where $r_h(x_i) = 22.77 \cdot f(x_i)^2$ if $f(x_i) > 0$, and 0 otherwise; $f(x_i) = (\ln(x_i)^{1.084} - 5.381)$ for BG readings $x_1,\ldots,x_n$ measured in mg/dl
		Average daily risk range (ADRR) — a risk assessment of the total daily BG variation in risk space; i.e. the sum of the peak risks of hypoglycaemia and hyperglycaemia for the day[57]	$ADRR = \frac{1}{M}\sum_{j=1}^{M}(LR^j + HR^j)$ where $LR^j = \max(r_l(x_1),\ldots r_l(x_k))$ and $HR^j = \max(r_h(x_1),\ldots,r_h(x_k))$ for BG readings $x_1,\ldots,x_k$ taken within day #j, $j=1,2\ldots,M$
Metrics specific to CGM data	Hours / minutes	SD taken over various periods of time[51]	$SD = \sqrt{\frac{\sum(x_i - \bar{x})^2}{n-1}}$
		LBGI and HBGI; typically used to visualize CGM traces in risk space, i.e. to present risk	$LBGI = \frac{\sum r_l(x_i)}{n}$, where $r_l(x_i) = 22.77 \cdot f(x_i)^2$ if $f(x_i) \le 0$, and 0 otherwise;

		instead of BG values[56]. Corrections for the LBGI and HBGI have been introduced to account for the specifics of CGM data[58]	$HBGI = \frac{\sum r_h(x_i)}{n}$, where $r_h(x_i) = 22.77 \cdot f(x_i)^2$ if $f(x_i) > 0$, and 0 otherwise; $f(x_i) = (\ln(x_i)^{1.084} - 5.381)$ for CGM readings $x_1,...,x_n$ in mg/dl
		Hourly risk range (HRR), which is similar to the ADRR, but the computation is done in hourly, not daily, increments.	$HRR = \frac{1}{M}\sum_{i=1}^{M}[LR^i + HR^i]$ where $LR^j = \max(r_l(x_1),...r_l(x_k))$ and $HR^j = \max(r_h(x_1),...,r_h(x_k))$ for CGM readings $x_1,...,x_k$ taken within hour #j, $j=1,2...,M$
		SD of the BG rate of change — a reflection of the metabolic system's ability to absorb glycaemic challenges (e.g. meals)[53]	$SD = \sqrt{\frac{\sum(R_i - \bar{R})^2}{n-1}}$ where $R_i = \frac{x(i)-x(i-1)}{\Delta t}$ is the BG rate of change at time *(i)* and $\bar{R}$ is the average BG rate of change
		Mean of daily differences (MODD) — a metric of intraday variability computed from	$\sum_{t=t1}^{tk} \frac{\lvert x(t) - x(t-24h)\rvert}{k}$

		all 24-hour intervals for which paired readings are available [47]	where k is the number of available data pairs 24-hours apart
		Continuous overlapping net glycemic action (CONGA) — a composite index of the amount of time spent in glycaemic excursions and the degree of glycaemic variation [47]	$\sqrt{\sum_{t=t1}^{tk} \frac{(D(t)-\bar{D})^2}{k-1}}$ where $D(t)$ is the difference between BG at time t and BG taken n hours earlier, and $\bar{D}$ is the average of these differences
		Area under the curve (AUC), typically used as a measure of glycaemic exposure[59]. AUC above or below clinically relevant thresholds has been reported as well	$AUC = \sum_{i=1}^{n} BG(i) \cdot \Delta t_i$ Where $BG(i)$ is the BG value (or the average of BG values) in the time window Δt_i, $I=1,2,\ldots,n$

APPENDIX 6. Time in "ranges"

To date, HbA1c has been considered the most relevant endpoint used globally to explain glycemic outcomes of a given diabetes therapy. While sentiments have existed for some time that additional outcomes "mattered" beyond HbA1c, there was not a movement until recently to standardize CGM measurement and reporting so that the information could be explained easily to patients, compared between different trials, used for regulatory discussions and possibly even included on drug labels. Recently several professional organizations and working groups have prepared statements indicating widespread agreement on the dangers of hypo- and hyperglycemia and the need to use CGM with standardized reporting in clinical trials and patient care (1-3).

Comparisons of "time in range" and "time out of range" provide useful information to patients, clinicians, and researchers. While "time in range" is self-explanatory, "time out of range" has two components: alert and severe hypoglycemia, the use of moderate hypoglycemia being between alert and serious hypoglycemia (TIR for moderate hypoglycemia: <60 mg/dL (<3.3 mmol/L) have previously also been proposed (1-3) For reasons of conformity the terms of hypoglycemia alert and serious hypoglycemia are recommended to be used analogously for CGM and SMBG threshold ranges. The consensus panel recommends using 5 thresholds or buckets (e.g., <54 mg/dL [<3.0 mmol/L]; <70 mg/dL [<3.9 mmol/L]; 70-180 mg/dL [3.9-10.0 mmol/L]; >180 mg/dL (>10 mmol/L]; >250 mg/dL [>13.9 mmol/L]) down from originally proposed 7 thresholds (<50 mg/dL [<2.8 mmol/L), <60 [<3.3 mmol/L], <70 [<3.9 mmol/L], 70-180 [3.9-10 mmol/L], >180 [>10 mmol/L], >250 [>13.9 mmol/L], >300 mg/dL [>16.7 mmol/L]) to streamline TIR ranges and make it more manageable for clinicians. These glucose ranges have emerged as important domains for assessing metabolic control and guiding diabetes treatment.

Of all the metrics the most discussion in the panel remained between defining 250 [>13.9 mmol/L] or 300 mg/dl [>16.7 mmol/L] for actionable hyperglycemia before settling on 250 mg/dl[>13.9 mmol/L]. Clearly patients spend a lot of time in hyperglycemia with current modes of therapy. In DIAMOND study the T1D patients (mean HbA1c 8.6%) spent a mean time >250 mg/dL of approximately 5 hours per day while the time >300 mg/dL was approximately 2 hours per day. In the DIAMOND for T2D patients (mean Hba1c 8.5%) the mean time > 250 mg/dL was ~2.5 hours per day while the time >300 was approximately 0.5 hours per day (1-3). In

REPLACE BG for T1D patients (mean HbA1c 7.1%) the mean time >250 mg/dL was ~2hrs/day and time >300 mg/dL ~0.5hrs/day (1-3).

Clearly, T1D is harder to control than T2D, and the hybrid closed loop is becoming the current gold standard in the US. In the regulatory trial of the 670G hybrid closed loop approximately 6% of the time was above 250 mg/dl while only 1.8% remained over 300 mg/dl (1-3). These figures were confirmed with another recent trial with a different system achieving a time > 250 mg/dL of 4.6% and > 300 mg/dL of 0.4% (1-3). As these will only improve with next generation systems and possibly improved insulins such a small percentage of 0.5-1% over 300 mg/dl may not be enough to see improvement in future trials

Although there is also controversy on the glucose threshold recommend to patients for ketone testing, the current sick day rules of ISPAD recommend ketone testing at 250mg/dL (1-3). Thus to reinforce avoiding going over 250 mg/dL will likely reduce the disastrous DKA that is still occurring.

Normal ranges have been defined in selected populations, for example in China (4), which allows for better identification of abnormalities, and could be useful to evaluating glucose target ranges in diabetic patients. While HbA1c remains a well-established parameter for assessing overall glycemic control, dividing CGM data into hypoglycemic and hyperglycemic domains provides patients and providers with a means to adjust treatment regimens to achieve optimal overall metabolic control.

A composite goal of CGM, reported in a standardized way and in conjunction with an HbA1c value, could establish with more confidence in whether a particular insulin formulation, new technology for insulin delivery, or an innovative patient-centered approach to care was an important factor in helping individuals with diabetes reach optimal glycemic control. One example to display such data is the Ambulatory Glucose Profile (AGP) (5). It is important to note that other composite targets for glycemic control are being explored. First composites of glycemic control, including HbA1c and hypoglycemia, TIR and hypoglycemia, Time out of range (time <70 mg/dl + time >180 mg/dl or time in serious hypoglycemia and hyperglycemia (time <54 mg/dl + time >250 mg/dl). It is important to agree on these definitions as we gain more data because it is no longer acceptable to just strive for good HbA1c or Time in target range without regard for hypoglycemia. In addition, there is interest in even broader composite measures of diabetes management such as targets for good diabetes management are being

explored (HbA1c + hypoglycemia + weight gain or HbA1c + low-density lipoprotein + blood pressure or HbA1c + low-density lipoprotein + blood pressure if high-risk cardiovascular disease + no tobacco use). These composites emphasize the importance of taking a multifactorial approach to reducing diabetes complications, particularly cardiovascular disease.

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