A guide for the use of LibreView digital diabetes platform in clinical practice: expert paper of the Italian Working Group for Diabetes and Technology

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Abstract

Wider access to continuous glucose monitoring systems, including flash glucose monitoring, has enabled people with diabetes to achieve lower HbA1c levels and reduce the amount of time they spend in hypoglycaemia or hyperglycaemia, and has improved their quality of life. An International Consensus Panel proposed different target glucose ranges and recommendations according different ages and situations (adults, young people and children with type 1 or type 2 diabetes, as well as elderly people who are at higher risk of hypoglycaemia, and women with diabetes during pregnancy).

In this expert opinion, we interpret the international recommendations in the context of established clinical practice for diabetes care, and propose three different step-by-step algorithms to help the healthcare professionals use the most innovative glucose metrics, including time in glucose ranges, glucose management indicator, coefficient of variation, and ambulatory glucose profile. In detail, we focus on glucose metrics as measured by the FreeStyle Libre system and as visualized on the LibreView digital diabetes platform to support appropriate interpretation of flash glucose monitoring data. This is specifically structured for healthcare professionals and general practitioners who may have a low level of confidence with diabetes technology, with the aim of optimizing diabetes management, ensuring effective use of healthcare resources and to maximise outcomes for people with diabetes.

Introduction

Continuous glucose monitoring (CGM) is an effective technology to enable people with diabetes to achieve better glucose control [1,2]. Currently, two types of CGM systems are available for personal use: real-time CGM (rtCGM) and intermittently scanned CGM, also labeled flash glucose monitoring (FGM), both of which measure glucose in the interstitial fluid (ISF) [3]. Both systems measure glucose every few minutes, and while rtCGM actively transmits data wirelessly from the sensor to a reader or smartphone app, FGM systems transmit data only when the user scans their sensor with a reader or smartphone app.

Currently, one of the most widely used glucose monitoring systems is the FreeStyle Libre FGM system (Abbott, Alameda CA), which consists of a small glucose sensor usually applied to the back of the upper arm, with a 5mm sensor filament that is inserted into the subcutaneous space and measures glucose in the ISF. The FreeStyle Libre has a 14-day wear time, during which it measures and displays on demand glucose every minute. All the data are continuously stored and available for retrospective calculation of glucose metrics at intervals of 15 minutes.

The sensors are factory calibrated, eliminating the need for users to self-calibrate using capillary-blood fingerprick tests, and are accurate, with a mean absolute relative difference (MARD) of 9.2% for adults and 9.7% for children and adolescents [4], which indicates a level of concurrence with reference blood-glucose measurements sufficient for clinical decision making. For this reason, the FreeStyle Libre system is approved for making insulin dosing decisions without the need for adjunctive fingerpick testing. The system requires that users scan their sensors to see a glucose reading and the associated trend arrow that indicates the rate of change (ROC) of glucose. The need to scan with FGM is also emphasized by the fact that if the sensor is not scanned every 8 hours, then glucose data that is collected outside of the most-recent 8 hours can be lost.

The sensor can transmit glucose values either to the LibreLink smartphone app or to a dedicated reader. Data collected by the LibreLink app are automatically uploaded to the cloud every time the phone is connected to the internet, whereas the data stored in the reader have to be uploaded following connection to an internet-connected computer. Once uploaded, all glucose data are available to view in the LibreView digital diabetes system, from where glucose management reports are automatically collated to be examined by healthcare professionals (HCPs) or by patients. Available reports include summaries of the user's percentage time in range (TIR), time below range (TBR) and time above range (TAR), as well as calculated metrics for glycemic

variability using the coefficient of variation (CV) and the overall glucose exposure using the mean sensor glucose, and the glucose management indicator (GMI). [5,6].

Use of the FGM system is associated with lowered HbA1c, in adults and in children with type 1 diabetes [7-10] and in adults with type 2 diabetes treated either with insulin [10-13] or non-insulin therapy [14,15]. A meta-analysis of 25 real-world studies indicates that HbA1c falls by a mean of -0.56% in adult users and by -0.54% for children and adolescents [7]. Use of the FGM system is also associated with less time spent in hypoglycaemia, including nocturnal hypoglycaemia, in type 1 and type 2 diabetes [16,17], improved quality of life [11, 18–20], and reduction in hospital admissions for acute diabetes events (ADEs) such as diabetic ketoacidosis (DKA) and severe hypoglycaemia [21–23]. The RELIEF study [21] showed a 56.2% and a 52.1% fall of admissions for DKA in type 1 diabetes and type 2 diabetes patients, respectively, once reimbursement for FGM was approved in France, and a 43% drop in admissions for severe hypoglycaemia was reported in Israel in the 12 months after FGM was initiated for people with T1DM [24]. The FreeStyle Libre system has been CE marked for use in pregnancy with diabetes since 2017. In a cohort of 74 participants with type 1, type 2, or gestational diabetes mellitus (GDM) from 13 sites in Europe, clinical accuracy of sensor readings versus self-monitoring blood glucose (SMBG) was demonstrated, with 88.1% and 99.8% of results within Zone A and Zones A and B of the Consensus Error Grid, respectively [25]. More recently, FGM has been demonstrated to be as effective as SMBG in lowering the HbA1c level in a cohort of 40 women with pregestational diabetes, with additional benefit in terms of TBR and glucose variability reduction. Notably, in this cohort, the number of daily FGM scans was positively associated with HbA1c reduction [26].

The majority of the outcomes data reported in the studies above was substantially generated from the first generation FreeStyle Libre sensor. More recently, the FreeStyle Libre 2 sensor has become available that includes high and low glucose alarm functionality, not previously an option for first-generation FreeStyle Libre sensors. Whether this can have additional impact on outcomes will require further studies.

In this expert opinion, we interpret the International Consensus recommendations in the context of established clinical practice for diabetes care. In doing so, we provide step-by-step algorithms to help the HCPs use the most innovative glucose metrics including time in glucose ranges, GMI, and CV, and the ambulatory glucose profile (AGP) as represented in the standardized report format. To provide relevant and practical examples, we focus on glucose metrics as measured by the

FreeStyle Libre system, and visualized with the LibreView digital diabetes platform. Ultimately, our goal is to support appropriate interpretation of FGM data in order to optimize diabetes management, ensure effective use of healthcare resources, and maximise outcomes for people with diabetes.

Application of time in glucose ranges in diabetes clinical care

As use of glucose monitoring systems becomes widespread in diabetes management, it is important to acknowledge the need to move beyond using HbA1c as the predominant marker of glucose control and to support the application of more dynamic and comprehensive measures of diabetes health. A number of metrics have been adopted for interpreting the wealth of glucose data provided by FGM (Table 1).

Time in glucose ranges indicates the proportion of each day that a person with diabetes spends with glucose readings in each of three ranges that have been defined by the international consensus group (Supplementary Table 1) [1]. TIR indicates the amount of time that glucose readings are within a defined target glucose range of 70-180 mg/dL (or 63-140 mg/dL during pregnancy). TBR refers to the amount of time spent below the target glucose range (<70 mg/dl, or <63 mg/dL during pregnancy), and TAR refers to the amount of time above the target range (>180 mg/dL, or >140 mg/dL during pregnancy). TBR and TAR can be divided into low/very low and high/very high ranges, depending on the profile of the person with diabetes. As a focus for assessing glucose control, TIR is easily understandable by people with diabetes and by their HCPs. More importantly, TIR is immediately responsive to changes in medication, diet and lifestyle that can be visualized in day-to-day diabetes management.

HbA1c is the gold-standard for understanding population-based risks for developing macrovascular and microvascular complications [27,28]; however, TIR is becoming a reference for the treatment of diabetes. With the aim to assess any relationship between TIR and long-term complications, SMBG data from the Diabetes Control and Complications Trial (DCCT) have been reanalyzed to calculate the TIR 70-180 mg/dL of participants with and without microvascular complications [29]. Study subjects who developed complications had a 10-12% (2.5-3.0 hours/day) lower TIR when compared to participants who did not develop complications. For each 10% decrease in TIR (2 hours 24 mins less each day), the risk of progression of retinopathy was increased by 64% and risk of developing microalbuminuria was increased by 40%. In a separate study that used retrospective CGM to measure glucose control in 3,262 people with type 2

diabetes, TIR was again inversely correlated with the prevalence and severity of diabetic retinopathy, so that a higher TIR was associated with less, and less severe, retinopathy [30]. Increased TIR also correlates with improved peripheral nerve function [31,32]. Most notably, analyses of blinded CGM in 2,983 people with type 2 diabetes demonstrated a relationship between TIR and carotid intimal thickness [33], and a 10-year follow up of 6,225 adult patients with type 2 diabetes has shown that TIR is correlated with the hazard ratio for all-cause mortality and for cardiovascular mortality [34].

In terms of implementing these metrics in day-to-day clinical practice, the International Consensus on Time in Range [5] has defined a series of clinical targets for TIR, TBR and TAR that can be applied to people with type 1 or type 2 diabetes. Separate recommendations have also been made for pregnant women with type 1 diabetes and for people who are at higher risk of hypoglycaemia because of age, duration of diabetes, duration of insulin therapy or impaired awareness of hypoglycaemia (IAH), irrespective of diabetes type. Because of the lack of evidence to guide CGM targets for pregnant women with type 2 diabetes or GDM, firm recommendations for TIR, TBR and TAR have not been established yet. However, recent data suggest that very strict glycemic control [35] and reduction of nocturnal hyperglycaemia may be required to normalize outcomes in pregnant women with GDM [36].

Specific targets for these groups of people with diabetes are detailed in Supplementary Table 2. The international consensus recommendations also emphasise the importance of setting individual goals for time spent within any defined glycaemic range, which is an essential part of implementing TIR, TBR and TAR in clinical practice.

Treatment algorithms to navigate LibreView digital diabetes platform

We have developed three separate algorithms that each identify a possible 6-step treatment path for different groups of people with diabetes: (1) non-fragile, non-pregnant adults with either type 1 or type 2 diabetes; (2) fragile adults with type 1 or type 2 diabetes; (3) pregnant women with type 1, type 2 or GDM. The term ‘fragile’ adults refers to the older/high-risk as reported in the consensus, i.e. people at higher risk for severe hypoglycaemia due to age, duration of diabetes, hypoglycaemia unawareness and/or people who are particularly vulnerable to adverse events associated with hypoglycaemia due to comorbid conditions like cognitive deficits, renal disease, cardiovascular disease [5]. These visual treatment algorithms are presented in Figures 1-3 and are self-explanatory when used in conjunction with the defined treatment interventions indicated in

Boxes 1-5, therefore we will not describe each treatment option in detail. However, we will clarify the general 6-step approach that is common among the three algorithms. An easy-to-use tool for reporting FGM data-informed clinical evaluation is also provided (Figure 4). With the greater use of FGM system amongst people with type 1 diabetes or type 2 diabetes, healthcare professionals and general practitioners who have low level of confidence with diabetes technology will increasingly be required to manage their patients using FGM metrics and AGP reports. We believe that the algorithms presented in this expert paper will be of benefit.

Step 1: Evaluate data sufficiency

Fundamental to accurate and meaningful interpretation of FGM data is ensuring that enough glucose data have been collected. Studies have shown that 14 consecutive days of FGM, if ≥70% of data are available, correlate satisfactorily with 3 months of glycaemic data for the assessment of mean glucose, TIR and measures of hyperglycaemia, and additional days of data do not substantially increase this correlation [37, 38]. It is worth noting that the association between the mean glucose and the laboratory-measured HbA1c is stronger when using the 14 days that immediately precede the time of the HbA1c test reading [38]. This is important in the context of Step 2, below.

Since adequate wear time can be an issue it should be discussed in the consultation. When the patient can't ensure adequate wear time, the clinician should investigate potential issues regarding sensor adhesion or adverse reactions, as well as insufficient skills or psychological distress. Provide suggestions for increasing FGM wear time, for instance providing tips to help sensor adhesion [39] or motivating the patient to increase the frequency of daily scans (e.g., before and 1-2 hours after meals, at bedtime, before, during and after exercise, and in case of symptoms of hypoglycaemia) and evaluating psychological well-being with validated tests [40, 41]. If necessary, professional psychological support may be needed and encouraged.

Similarly, while confirming the importance of the 70% data capture to use the proposed algorithm, a quick evaluation of the sensor data (not summary data) may be valuable in order to assess whether occurrences of very low (i.e. <54 mg/dL) or very high (i.e. > 250 mg/dL) glucose are evident and whether these need to discussed.

Step 2: Evaluate the glucose management indicator (GMI)

The GMI, either expressed as a % or as mmol/mol, is a measure of short-term glucose control which is intended to convey information about overall glucose exposure over the 14-day

assessment period [6]. GMI is calculated from CGM-derived mean glucose and can be compared alongside laboratory-tested HbA1c, but it is important to note that the two measures are not expected to be identical in value and are likely to differ in at least 81% of cases [6]. GMI can be used in clinical practice to evaluate the overall glucose control in the short term or when HbA1c is unavailable or unreliable. HbA1c is produced by a post-translational modification of hemoglobin when glucose reacts with the amino group on a hemoglobin molecule, forming a ketoamine. Although HbA1c formation is proportional to average blood glucose concentration, it is also influenced by a range of non-glycemic factors, such that an HbA1c test reading may be higher or lower than that predicted by average glucose alone, showing the so-called "glycation gap" [42]. These non-glycemic factors are both analytical and biological and are summarized in Supplementary Table 2, along with their influence on HbA1c accuracy.

Step 3: Identify the appropriate target glucose range and evaluate time in different glucose ranges
Each person with diabetes must have the target glucose range and time in ranges requirements that apply to his/her status. For non-fragile and fragile adults, the glucose ranges are the same, but the consensus targets differ. For fragile adults, the TIR target has been lowered from >70% to >50%, and the TBR reduced to <1%. For diabetes in pregnancy, the target glucose range must be changed from the default setting for the FreeStyle Libre system (70-180 mg/dL) to 63-140 mg/dL. This can be done in the LibreView platform.

Each of the targets for TIR, TBR and TAR and the patient's specific metrics against these targets is provided in the top part of the AGP Report that is compiled by the LibreView data platform (Figure 5). However, note that when reviewing TIR, TBR and TAR for any glucose range that is different from the default, the necessary metrics for TIR, TBR and TAR must be viewed in the 'Snapshot' report screen rather than the AGP Report screen, which always shows the default glucose ranges.

In Step 3, three alternative pathways are suggested depending on: (1) TBR and TIR are at the target levels (green pathway); (2) high TBR is a concern (red pathway); (3) low TIR is a concern (yellow pathway). Exceeding the target for TBR creates a risk of recurrent hypoglycaemia, which is associated with severe adverse events, risk of developing IAH, reduced quality of life and poor adherence with diabetes therapy [43]. Likewise, lower TIR is associated with an increased risk of microvascular and macrovascular complications of diabetes [29,30,32–34, 44]. However, this evidence has not yet been fully validated in a prospective randomized clinical trial (RCT) with TIR as the primary outcome. TAR is at a slightly lower priority for assertive management in many

patients since improvements in TIR typically come as a consequence of reduced TAR, when TBR is stably low. Following adjustments to therapy, changes in TAR should help assess the efficacy of the intervention. For women with diabetes during pregnancy, there is evidence that hyperglycaemia may be a contributing factor to adverse perinatal outcomes, such as macrosomia [45], emphasising the need to reduce TAR as much as possible.

Step 4: Evaluate the ambulatory glucose profile (AGP) and patterns of hypoglycaemia and hyperglycaemia

In patients who are not hitting their targets of TIR and/or TBR, the AGP graph (Fig. 6) helps to identify the time of occurrence (i.e. during the night, before or after meals) and the severity of any hypoglycaemic or hyperglycaemic patterns.

The AGP graph provides a visually impactful summary that allows the HCPs to identify patterns and trends in daily glucose control. The AGP graph comprises four key features: the target glucose range; the median line; the dark-blue shaded 25^{th}-75^{th} percentile band, also known as the interquartile range (IQR); the outer 5^{th}- 95^{th} percentile band, typically shaded in lighter blue. These are described in detail in Figure 6. Each of the defined features of the AGP graph tell a clear story about glucose control across each day and between different days and can be used in a systematic and straightforward way to identify trends in glucose control on which clinical decisions can be taken [46,47].

When the median line or the 25^{th} percentile falls close to or below 70 mg/dL, or the 5^{th} percentile falls close to or below 54 mg/dL regardless the value of TIR, a high priority hypoglycaemic pattern exists and an immediate action is required. Conversely, when the median line or the 75^{th} percentile rises close to or above 180 mg/dL, or the 95^{th} percentile rises close to or above 250 mg/dL, correction of hyperglycaemia is urgently required.

These thresholds for hypoglycaemia or hyperglycaemia are tighter for diabetes in pregnancy (Fig. 3) but the assessment need is the same. It is important to note that, for people who are older or more-fragile (Fig. 2), avoiding hypoglycaemia is mandatory and interventions to lower glucose should be more cautious. As indicated, patients who are meeting their recommended targets for TIR and TBR, Step 4 is not essential and their assessment can move from Step 3 to Step 5.

Step 5: Assess glucose variability within each day or among days

Measurable glucose variability is now associated with an increased risk of microvascular and macrovascular complications of diabetes [48–52]. Therefore, an essential component of any evaluation of FGM glucose metrics in a person with diabetes is the assessment of glucose variability. Glucose fluctuations within a day (intraday) and from one day to another (interday) must both be considered here. Intraday glucose variability is often associated with the specifics of treatment and can be targeted by adjusting treatment parameters as indicated. Interday variability may prompt a discussion with the patient about the causes of high or low glucose traces occurring on some days but not on others.

The parameter defined as representing glucose variability is the coefficient of variation of the 24-hour mean glucose values (CV) [53]. A threshold for CV of ≤36% is currently set as differentiating between stable and unstable glucose profile, based on the observation that the frequency of hypoglycaemic events rose significantly if this value was exceeded [54]. Thus, Step 5 indicates that any patient with CV of >36% is at a higher risk of hypoglycaemia, and that the source of excess variability should be examined by moving on to Step 6, i.e. looking at the daily glucose profiles that cover the period of the AGP in question. For patients with a CV of ≤36%, further evaluation is not mandatory. Review of daily glucose profiles is suggested irrespective of %CV value in cases where concerns may emerge during the consultation or when a deeper educational intervention is required, namely in the first period after FGM initiation. In selected individuals (e.g. pregnant women, Fig. 3) with either TIR, TBR, and CV at the target level, an enhanced management plan (Box 1) could be pursued to achieve even tighter glucose outcomes. However, this is not the first choice for fragile patients (Fig. 2). These caveats are indicated by dashed lines in each case.

Step 6: Navigate using daily glucose profiles

When glucose variability is calculated to be high (CV >36%), the aim of reviewing daily glucose printouts is to double-check when patterns of low/high glucose occur (hour of the day or day in the week). The individual daily profiles are shown either in the bottom of LibreView AGP Report, in the Daily Logs and Weekly Summary reports.

Importantly, the interpretation of daily glucose variability is facilitated if the patient has used the features of the FreeStyle Libre system to add notes on insulin doses, exercise, mealtimes and meals composition. Addressing the causes of glucose variability can mean making changes to standard treatment parameters, but for all causes of variability the value of organized diabetes education should be emphasized.

Pediatrician's point of view

FGM is widely used in children and adolescents treated either with multiple daily injections or insulin pump therapy due to its convenience and practicality [55]. Randomized controlled trials and real world data suggest that FGM improves quality of life, satisfaction for patients and care givers, self-efficacy, and frequency of glucose monitoring in a pediatric population with type 1 diabetes. HbA1c and glucose metrics are improved by using FGM compared to SMBG in some studies but not in others. However, the recent report published in the Canadian Journal of Health Technology, reviewing all data available in pediatric population with type 1 diabetes, generally suggest that the use of FGM is associated with improved clinical outcomes [56]. In general, more emphasis must be placed on education of children and adolescents with diabetes and their families when using the FreeStyle Libre system.

For some years, continuous monitoring of interstitial glucose levels has become the first choice for glucose monitoring in pediatric clinical practice, replacing traditional SMBG testing. The transition to this new way of assessing glycemic control poses new challenges for families, children and adolescents who are required to interpret all the information gathered from the FGM sensor and use it to adapt insulin and nutritional therapy. It is therefore necessary that HCPs in the pediatric diabetes team acquire the knowledge and skills to provide adequate education. This is of primary importance, as people treated in the pediatric diabetes outpatient clinic come from diverse socioeconomic, cultural and ethnic backgrounds and in most cases are newly diagnosed patients who are unfamiliar with glucose measuring.

Education on the use and interpretation of glucose results is therefore a pillar for maximizing clinical outcomes and should be provided prior to initiation of FGM and periodically during follow-up. Specifically, before starting FGM it is suggested to set appropriate expectations and discuss both with children and their families how the system works, including the possible differences in glycemic values compared to fingerprick blood glucose tests, the time-lag of sensor readings compared to fingerprick tests, and the practical interpretation of the results. After initiation and during follow-up visits, it is useful to discuss the AGP graph and the meaning of FGM-derived glucometrics, and how to use these tools to optimize insulin therapy and improve metabolic control. Notably, children and adolescents with type 1 or type 2 diabetes have the same glycaemic targets as adults [57]. Although there is evidence that it is difficult for children and adolescents with diabetes to achieve the recommended goals, except with automated insulin delivery [58], we

believe that adopting the algorithms proposed in this expert paper may help the pediatrician optimize diabetes therapy in children and adolescents using the FreeStyle Libre system..

Conclusions

In this expert opinion we have set out the core process for adhering the international recommendations [5] in the context of the LibreView digital diabetes platform. We highlighted the important use of the consensus targets for TIR, TBR, TAR and CV combined with the elements of the visual AGP format that provides insight into the dynamic changes in glucose control across a typical day. We propose treatment algorithms based on consensus targets for non-fragile, non-pregnant adults with either type 1 or type 2 diabetes, fragile adults with type 1 or type 2 diabetes, and pregnant women with diabetes. These algorithms can guide HCPs through six steps, from assessing if there is sufficient glucose data for a clinically effective diabetes review, through to deciding on potential interventions. At each step, essential checkpoints are identified along with the requirements for managing care for patients not meeting one or more of the consensus targets.

Although these algorithms are intended to clarify and consolidate the practice of using FGM glucose metrics and the associated consensus targets at the heart of diabetes care, we must emphasize the importance of individualized care and the skills of each HCP in optimizing outcomes for each person with diabetes.

Perspectives

FGM improves HbA1c and enables people with diabetes to achieve the recommended time in glucose ranges. Some cross-sectional and retrospective research has also indicated the potential of FGM to reduce the chronic complications of diabetes. More-robust prospective data are certainly needed to confirm the efficacy of increasing TIR to reduce diabetes complications. The use of FGM contributes to improve the quality of life of patients with diabetes. The FreeStyle Libre system is user-friendly, does not require self-calibration and the FreeStyle Libre 2 system provides optional alarms for hypoglycaemia and hyperglycaemia.

The LibreView platform allows health care providers and patients to be continuously connected, and it is effective for picturing and evaluating the glucose control and glucose variability.

The systematic addition of insulin data, amount of carbohydrates, duration, and type of physical activity or exercise is a comprehensible burden for patients with diabetes. However, the lack of

these data might limit the efficacy of appropriate changes to diabetes therapy, and therefore we strongly suggest adding these information at least few days before the planned visit.

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All named authors meet the International Committee of Medical Journal Editors (ICMJE) criteria for authorship for this article, take responsibility for the integrity of the work as a whole, and have given their approval for this version to be published.

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All named authors contributed to the concept and design of the manuscript and worked collaboratively to review and prepare the final manuscript.

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This article is based on previously conducted studies and does not contain any new studies with human participants or animals performed by any of the authors.

Data availability

Data sharing is not applicable to this article as no new data sets were generated during the current study.

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Table 1. Objective measures of glycaemic control derived from FGM and rtCGM systems

Metric	What does it measure?
% of sensor data captured	The proportion of possible readings captured by the rtCGM or FGM device. Provides a measure of confidence in the other data-derived outcomes.
Time in Ranges	
Time In Range (TIR)	Measures the % of time spent in the target glucose range set on the rtCGM or FGM system – defined as 70-180 mg/dL (63-140 mg/dL in pregnancy)
Time Below Range (TBR)	Measures the % of time spent below the target glucose range set on the rtCGM or FGM system – defined as below 70 mg/dL (63 mg/dL in pregnancy)
Time Above Range (TAR)	Measures the % of time spent above the target glucose range set on the rtCGM or FGM system – defined as above 180 mg/dL (140 mg/dL in pregnancy)
Mean Glucose	A measure of the average 24-hour glucose concentration calculated across all of the recorded glucose readings in a day
Glucose Management Indicator (GMI)	A measure of short-term glucose exposure that can be used in conjunction with long-term HbA1c making treatment decisions
Coefficient of Variation (CV)	A measure of variability. Expressed as %CV

Each of these measures of glucose control can be derived and reported by FGM (Flash Glucose Monitoring and rtCGM (real-time Continuous Glucose Monitoring) systems. They are all endorsed by international consensus guidance on use of CGM systems in management of diabetes [5,53].

Figure 1. Non-fragile, non-pregnant T1DM and T2DM adult patients

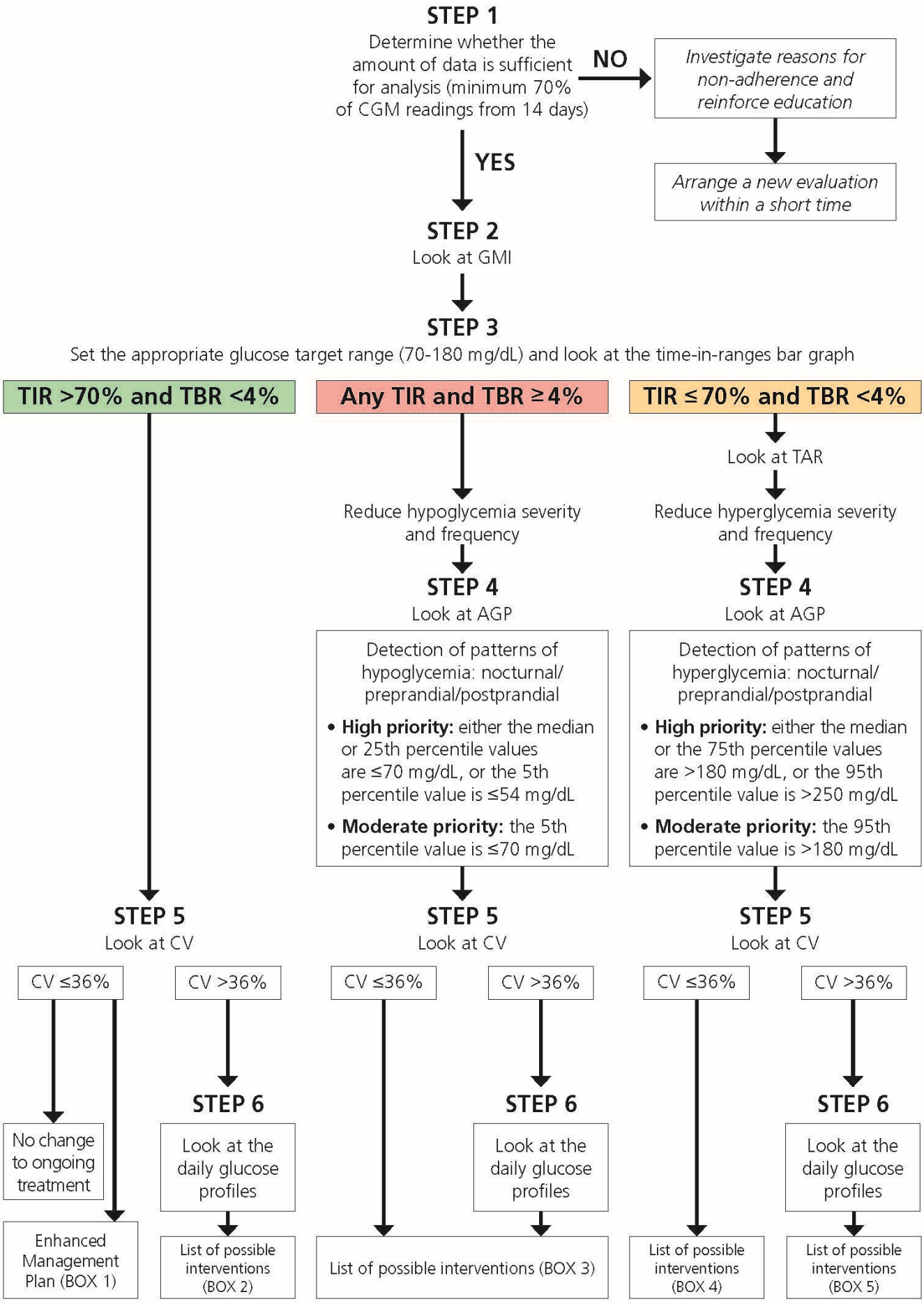


Figure 2. Fragile adult T1DM and T2DM patients

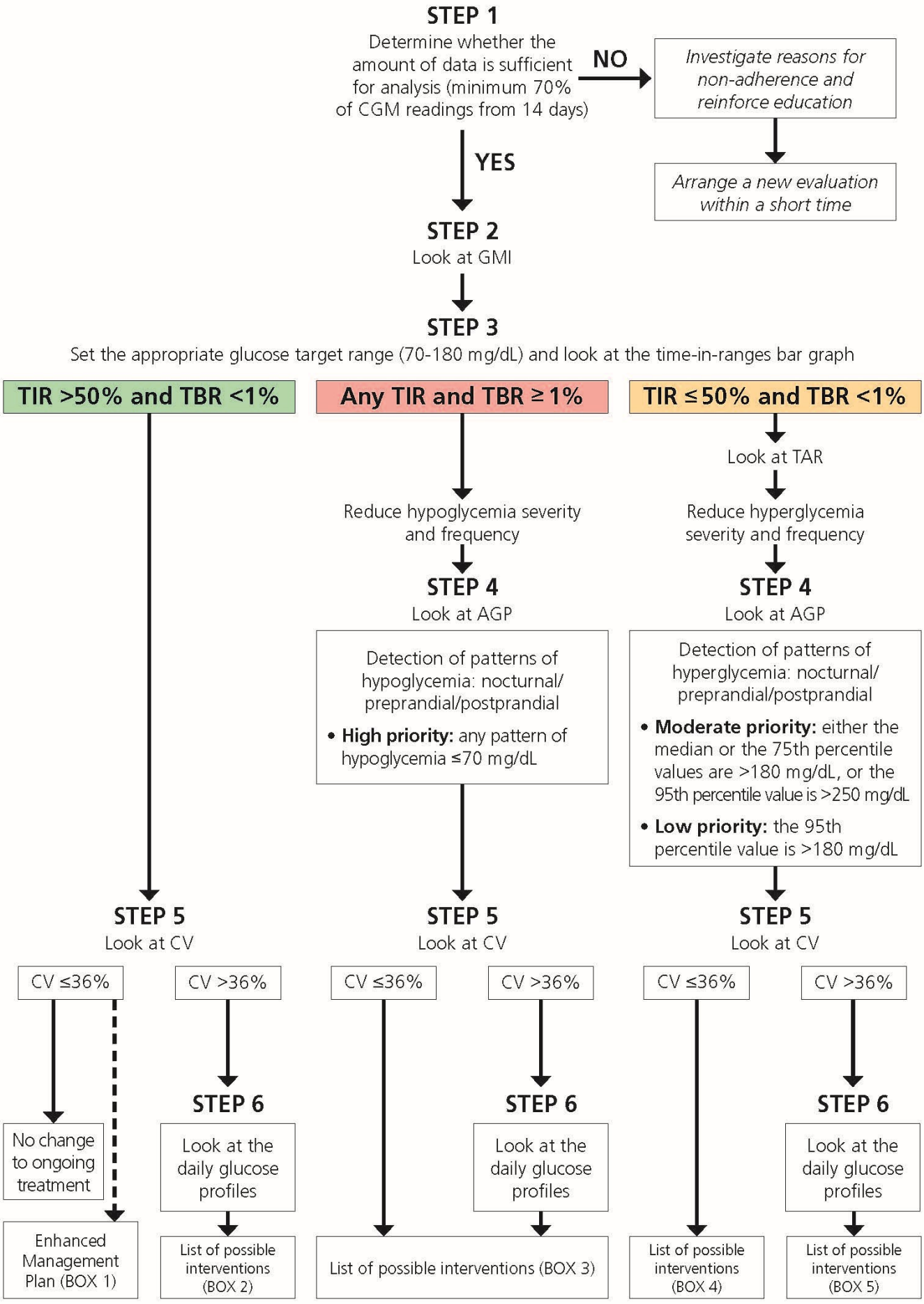
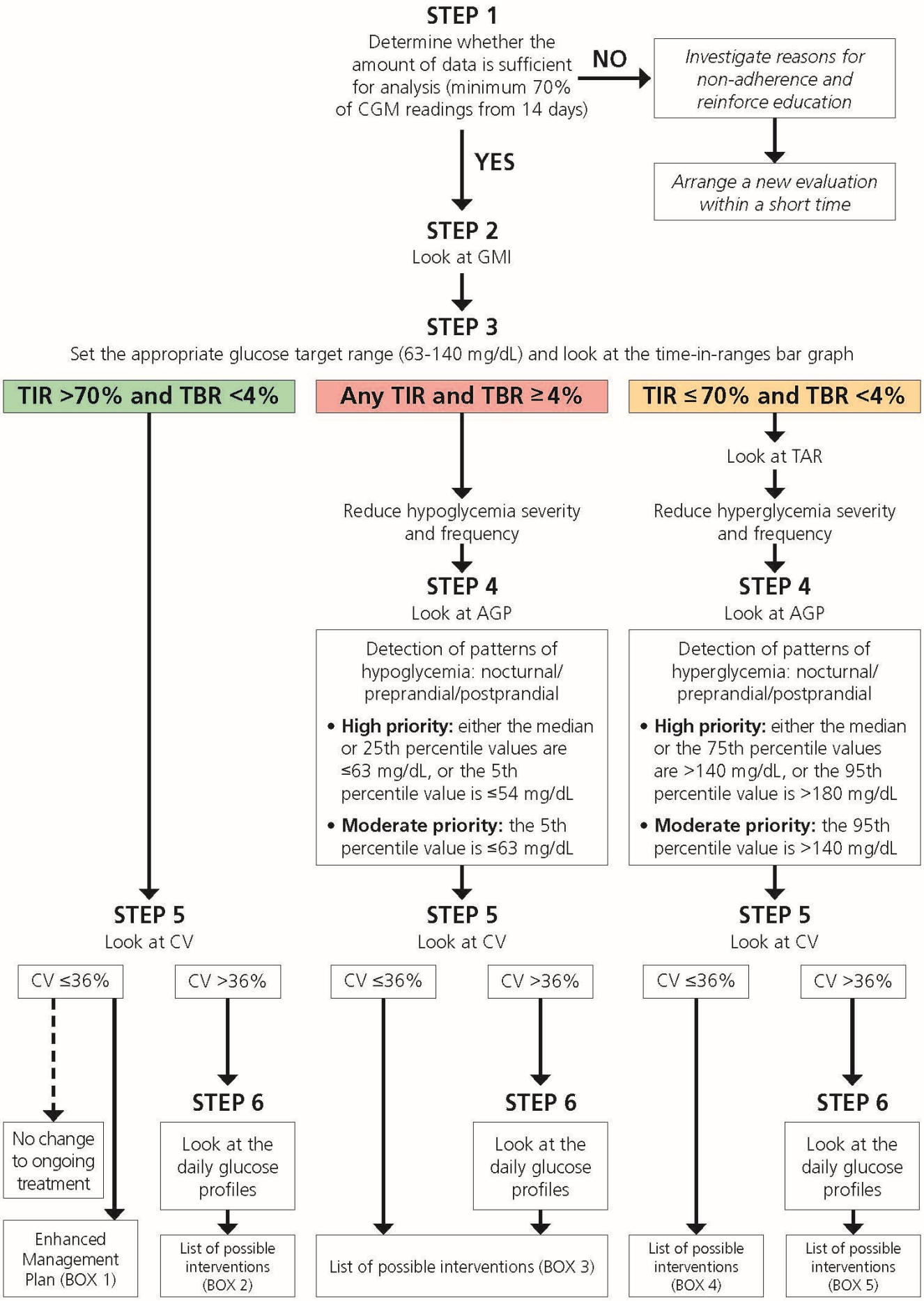


Figure 3. Pregnant T1DM, T2DM or GDM patients



Box 1. Enhanced Management Plan

- Suggest increasing the frequency of daily scans
- Suggest inserting notes on carbohydrate intake and insulin doses
- Consider aiming at more-stringent treatment targets for TIR
- Encourage patient's self-monitoring of TIR
- Encourage patient's retrospective review of FGM data
- Intensify ongoing treatment without increasing the risk of hypoglycaemia
- Discuss bolus insulin adjustments based on trend arrows
- Consider insulin bolus calculations for fat and protein

Box 2. Possible interventions for reduction of glycaemic variability

- Review the insulin injection technique
- Identify areas of lipodystrophy
- Discuss the importance of appropriate timing of bolus insulin administration
- Discuss bolus insulin adjustments based on trend arrows
- Improve management of physical activity

Box 3. Possible interventions for hypoglycaemia reduction

- Consider de-intensification of insulin therapy
- Switch to a second-generation long-acting insulin analogues [59,60]
- Reinforce the proper hypoglycaemia treatment protocol
- Suggest increasing the frequency of daily scans with FGM system
- Review carbohydrate-counting principles and insulin sensitivity factor
- Ask about prior episodes of severe hypoglycaemia and activities of daily life (physical activity, alcohol intake, etc..)
- Investigate the presence of hypoglycaemia unawareness [61]
- Consider switching to second-generation FGM system with threshold alerts
- Review the low glucose alert threshold if using second-generation FGM system
- If TBR is consistently > 4% at follow-up, consider switching to rtCGM with predictive low-glucose alerts, hybrid closed-loop or low-glucose suspend pumps [62]

Box 4. Possible interventions for hyperglycaemia reduction

- Consider intensification of insulin therapy
- Suggest increasing the frequency of daily scans with FGM system
- Review carbohydrate-counting principles
- Review hyperglycaemia correction principles with insulin sensitivity factor
- Ask about prior episodes of severe hypoglycaemia and fear of hypoglycaemia (using the FH-15 scale [63])
- Reinforce principles for diabetic ketoacidosis (DKA) prevention and early detection in patients whose time in hyperglycaemia >250 mg/dL is > 5%
- Consider adding non-insulin treatment if applicable or implement ongoing non-insulin treatment

Box 5. Possible interventions for hyperglycaemia and glycemic variability reduction

- Same as Box 3, but be more cautious with intensification of insulin therapy
- Reinforce the proper hypoglycaemia treatment protocols
- Review patient's daily habits and screen for diabetes distress

Figure 4: Tool for reporting FGM data-informed clinical evaluation

FGM REPORT TEMPLATE

Objective: to give a tool useful for patient consultation, medical peers or multidisciplinary consultation, long term monitoring.

OVERVIEW

(*1 min to fill*)

DATE OF EVALUATION ...../...../.....

PATIENT First name: _____ Last name: _____

FRAGILE ☐ Yes ☐ No

(individuals at higher risk for severe hypoglycemia due to age, duration of diabetes, duration of insulin therapy, hypoglycemia unawareness; individuals with a higher risk of complications and/or comorbid conditions; individuals requiring assisted care – Battelino T et al. *Diabetes Care* 2019; 42: 1593-1603)

PREGNANT ☐ Yes ☐ No

GLUCOSE TARGET RANGE ☐ 70-180 mg/dl ☐ 63-140 mg/dl

CGM DATA EVALUATION (last 2 weeks)

(*2-3 min to fill*)

% time sensor is active: ..... %	
Mean interstitial glucose: ..... mg/dl	
Glucose management indicator - GMI: ..... %	
Glucose variability - CV: ..... %	
Time below range (TBR): ..... %	(Level 1: ..... %; Level 2: ..... %)
Time in target range (TIR): ..... %	
Time above range (TAR): ..... %	(Level 1: ..... %; Level 2: ..... %)

Are CGM data enough for evaluation ? Yes ☐ No ☐

Are TIR and TBR in target?

☐ Yes → Skip to glucose variability assessment

☐ No → ☐ High TBR is a concern ☐ Low TIR is a concern

Predominant patterns:

☐ Nocturnal hypoglycemia	○ High	○ Moderate	○ Low	priority
☐ Pre-breakfast hypoglycemia	○ High	○ Moderate	○ Low	priority
☐ Pre-lunch hypoglycemia	○ High	○ Moderate	○ Low	priority
☐ Pre-dinner hypoglycemia	○ High	○ Moderate	○ Low	priority
☐ Morning fasting hyperglycemia	○ High	○ Moderate	○ Low	priority
☐ Pre-breakfast hyperglycemia	○ High	○ Moderate	○ Low	priority
☐ Pre-lunch hyperglycemia	○ High	○ Moderate	○ Low	priority
☐ Pre-dinner hyperglycemia	○ High	○ Moderate	○ Low	priority

Glucose variability: ☐ High (CV >36%) ☐ Low (CV ≤36%) → Skip to consultation output

Comment on daily glucose profiles: _____

CONSULTATION OUTPUT

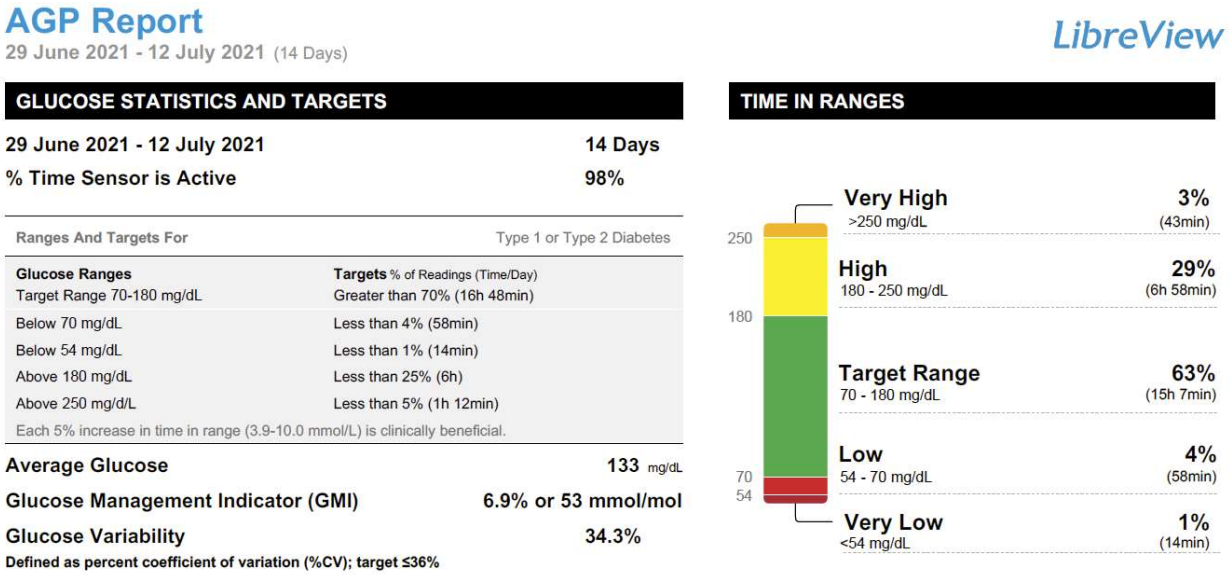
(*4-6 min to fill*)

Physician notes: _____

Patient notes: _____

Shared improvement strategies: _____

Figure 5. Time in range statistics and measures as provided in the AGP Report



AGP Report

29 June 2021 - 12 July 2021 (14 Days)

LibreView

GLUCOSE STATISTICS AND TARGETS

29 June 2021 - 12 July 2021	14 Days
% Time Sensor is Active	98%

Ranges And Targets For	Type 1 or Type 2 Diabetes
Glucose Ranges	**Targets** % of Readings (Time/Day)
Target Range 70-180 mg/dL	Greater than 70% (16h 48min)
Below 70 mg/dL	Less than 4% (58min)
Below 54 mg/dL	Less than 1% (14min)
Above 180 mg/dL	Less than 25% (6h)
Above 250 mg/d/L	Less than 5% (1h 12min)

Each 5% increase in time in range (3.9-10.0 mmol/L) is clinically beneficial.

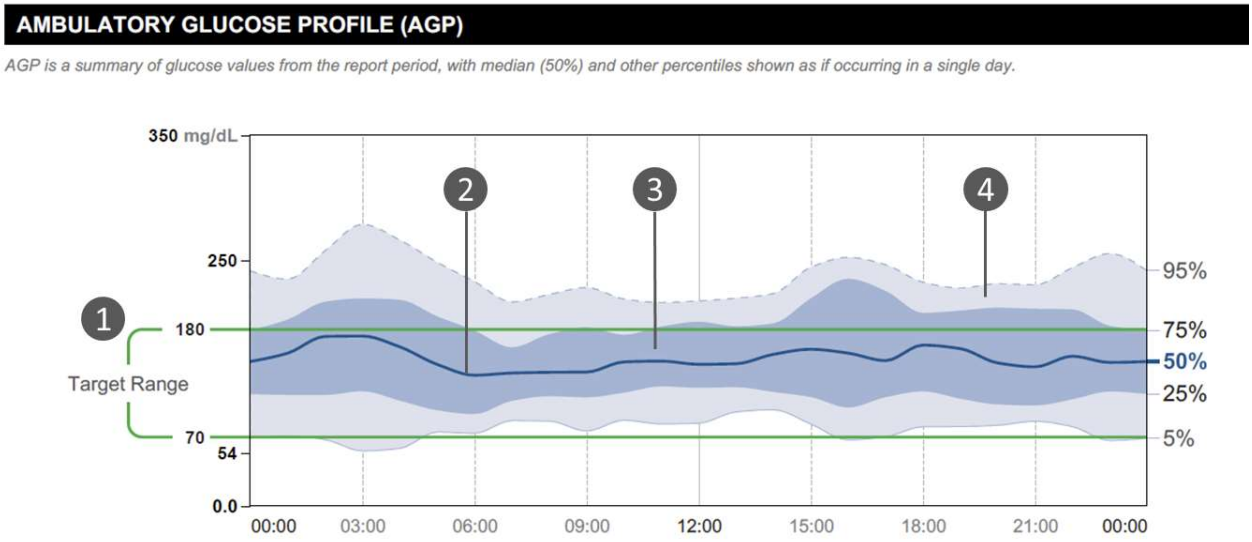
Average Glucose	133 mg/dL
Glucose Management Indicator (GMI)	6.9% or 53 mmol/mol
Glucose Variability	34.3%

Defined as percent coefficient of variation (%CV); target ≤36%

TIME IN RANGES

The AGP Report is compiled and downloaded from the LibreView diabetes data platform. The default setting is to show time in range for the target glucose range 70-180 mg/dL. For visualizing metrics for time in range 63-140 mg/dL in pregnancy, use the 'Snapshot' report.

Figure 6: The essential features of an AGP graph explained



1. **Two parallel lines** – the **Target Glucose Range**, typically 70-180 mg/dL except in pregnancy
2. **Median line** – this dark blue line shows the average glucose at each point in the day. It provides a visual trace of whether average glucose is within the target glucose range and how much oscillates during the day.
3. **Inner blue-shaded band** – this is 25th to 75th percentile band, also called the interquartile range (IQR). It shows the 50% of all glucose readings that are closest to the median line and their variability from day-to-day. This blue IQR band shows more-consistent daily trends in glucose levels and indicates how medication and mealtimes are influencing glucose control. The wider this darker-blue shaded band is, the more variable are these day-to-day readings.
4. **Outside grey-shaded band** – this is the 5th-95th percentile. This shows glucose readings that reflect 'occasional' departures from the daily average glucose. This is glucose variation that is happening on some days but not others and can indicate how behaviour and lifestyle issues are impacting on glucose control. The wider this grey band is, the more variable are these occasional readings.

Supplementary Table 1. Consensus recommendations for Time in Range, Time Below Range and Time Above Range [5]

	Time in Range (TIR)		Time Below Range (TBR)		Time Above Range (TAR)	
Diabetes group	**Target range**	**% of readings: time per day**	**Below target level**	**% of readings: time per day**	**Above target level**	**% of readings: time per day**
Type 1 / Type 2	70-180 mg/dL	>70%: >16 hrs, 48 mins	70 mg/dL	<4%: < 1 hr	>180 mg/dL	<25%: <6 hrs
			54 mg/dL	<1% < 15 mins	>250 mg/dL	<5% <1 hr, 12 mins
Older/high-risk Type 1 or Type 2*	70-180 mg/dL	>50%: >12 hrs	70 mg/dL	<1%: < 15 mins	>250 mg/dL	<10%: <2 hrs, 24 mins
Pregnancy, Type 1[§]	63-140 mg/dL	>70%: >16 hrs, 48 mins	63 mg/dL	<4%: < 1 hr	>140 mg/dL	<25%: <6 hrs
			54 mg/dL	<1%: < 15 mins		

* People with T1DM or T2DM at high-risk of hypoglycaemia because of age, duration of diabetes, duration of insulin therapy or impaired awareness of hypoglycaemia (IAH). § TIR in pregnancy are based on limited evidence. No consensus recommendations for TIR in pregnancy in T2DM or in gestational diabetes are available.

Supplementary table 2. Factors influencing HbA1c and the glycation gap

HbA1c status	Erythropoiesis	Hemolysis	Altered Hemoglobin
Falsely low (low glycators)	**Increased erythropoiesis** • Iron supplementation • Hemorrhage • Administration of erythropoietin • Pregnancy • High altitude	**Decreased erythrocyte lifespan** • Splenomegaly • Chronic liver/kidney disease • Hemolytic anemia • Hemoglobinopathies (HbS, HbC, HbD) • Antiretrovirals	• Fetal hemoglobin • Hemoglobinopathies • Methemoglobin
Falsely high (high glycators)	**Decreased erythropoiesis** • Iron deficiency • Different anemia (iron deficiency, infections, tumor)	**Increased Erythrocytes lifespan** • Splenectomy • Different anemia (iron deficiency, infections, tumor) • Hemoglobinopathies (HbH, HbF, Thalassemia)	• Fetal hemoglobin • Hemoglobinopathies • Methemoglobin

HbA1c status	Glycation	Assay-related artefacts	Individual HbA1c variations
Falsely low (low glycators)	• Ingestion of aspirin, vitamin C, vitamin E • Certain hemoglobinopathies • Increased erythrocyte pH		• Genetic and epigenetic determinants • Diet-related
Falsely high (high glycators)	• Alcoholism • Chronic renal failure • Decreased erythrocyte pH	• Asprin-iduced acetylated hemoglobin • Alcoholism (acetaldehyde) • Cigarette-associated carboxyhemoglobin • Carbamylhemoglobin (renal disease) • Hemoglobinopathies (HbS, HbC, HbD)	• Genetic and epigenetic determinants • Hyperglycation in some ethnical groups • Age • Hypertriglyceridemia • Organ Transplantation