Individualizing Time-in-Range Goals in Management of Diabetes Mellitus and Role of Insulin: Clinical Insights From a Multinational Panel

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ABSTRACT

Diabetes mellitus is a global health concern associated with significant morbidity and mortality. Inadequate control of diabetes leads to chronic complications and higher mortality rates, which emphasizes the importance of achieving glycemic targets. Although glycated hemoglobin (HbA$_{1c}$) is the gold standard for measuring glycemic control, it has several

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limitations. Therefore, in recent years, along with the emergence of continuous glucose monitoring (CGM) technology, glycemic control modalities have moved beyond HbA_{1c}. They encompass modern glucometrics, such as glycemic variability (GV) and time-in-range (TIR). The key advantage of these newer metrics over HbA_{1c} is that they allow personalized diabetes management with person-centric glycemic control. Basal insulin analogues, especially second-generation basal insulins with properties such as longer duration of action and low risk of hypoglycemia, have demonstrated clinical benefits by reducing GV and improving TIR. Therefore, for more effective and accurate diabetes management, the development of an integrated approach with second-generation basal insulin and glucometrics involving GV and TIR is the need of the hour. With this objective, a multinational group of endocrinologists and diabetologists reviewed the existing recommendations on TIR, provided their clinical insights into the individualization of TIR targets, and elucidated on the role of the second-generation basal insulin analogues in addressing TIR.

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Key Summary Points

Although glycated hemoglobin (HbA$_{1c}$) is the gold standard for measuring glycemic control, it has several limitations. Glycemic control modalities have moved beyond HbA$_{1c}$ and encompass modern glucometrics, such as glycemic variability (GV) and time-in-range (TIR).

The key advantage of these newer metrics over HbA$_{1c}$ is that they allow personalized diabetes management with person-centric glycemic control.

Basal insulin analogues, especially second-generation basal insulins with properties such as longer duration of action and low risk of hypoglycemia, have demonstrated clinical benefits by reducing GV and improving TIR.

A multinational group of endocrinologists and diabetologists provided their clinical insights for guiding clinicians on the initiation of insulin therapy in people with diabetes, with emphasis on the role of the second-generation basal insulin analogues.

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DIGITAL FEATURES

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INTRODUCTION

Optimal management of diabetes necessitates frequent and precise measurement of blood glucose levels [1]. Landmark trials in diabetes, including UKPDS (UK Prospective Diabetes Study) and DCCT (Diabetes Control and Complications Trial), demonstrated that glycated hemoglobin (HbA$_{1c}$) is linked to vascular complications [2, 3]. Thereafter, HbA$_{1c}$ was widely accepted as a biomarker of glycemia and emerged as the benchmark for diabetes management. Despite its importance as an indicator for the development for diabetes-related complications, many studies have also revealed the limitations of this biomarker of glycemia [4]. Apart from inaccurate test results in the presence of several medical conditions, HbA$_{1c}$ neither provides any information on glucose dynamics nor captures glucose fluctuations [4].

Self-monitoring of blood glucose (SMBG) serves as the primary technique to evaluate and manage glycemic control [5]. Self-monitoring of blood glucose provides immediate blood glucose values through intermittent finger-stick measurements [5]. The glucose values derived from SMBG are useful in monitoring the glycemic effects of antidiabetic medications, food, and exercise [4]. However, the use of SMBG is limited as a result of physical discomfort, inconvenience, inaccuracy of results in a few instances, and errors in capillary blood glucose readings and data recording [5]. Secondly, the most important drawback of capillary blood glucose readings is the limited amount of information retrieved on the basis of measurements at few specific time points per day (such as before meals and at bedtime) compared to 5–10-min sampling by a continuous glucose sensor [6].

Clinical observations have revealed that glucose profiles can greatly differ even in individuals with well-controlled diabetes. While some people with diabetes have small or moderate glucose excursions with rare hypoglycemia events, others have significantly large glucose fluctuations with frequent episodes of hypoglycemia. Such fluctuations in glucose levels over time within the same day, or between different days at the same time points, are reflected as GV. GV is one of the major components of dysglycemia in people with diabetes [4]. Accumulating evidence indicates that apart from chronic hyperglycemia, the chronic complications of diabetes also result from hypoglycemia and GV [1]. Besides, GV is also a major determinant of hypoglycemia, which gives another reason to target GV for intervention [7, 8]. However, GV is not accurately reflected by both widely used tools for monitoring glycemia, namely HbA_{1c} and SMBG [5, 9]. Therefore, apart from reducing the glycemic burden, as recorded by HbA_{1c}, minimizing GV is an appropriate treatment goal and the need of the hour [10].

A reliable measurement of GV is provided by continuous glucose monitoring (CGM), which allows for 24-h real-time measurement of glucose levels [10], and it can be performed in real time or intermittently. Intermittently viewed monitoring (I-CGM) shows continuous glucose numbers retrospectively. This method of monitoring is an intermediate between a CGM system and a normal blood glucose meter. Unlike I-CGM, real-time CGM (RT-CGM) offers real-time measurement of glucose trends, direction, and the rate of glycemic change. It must be noted that CGM provides results based on measurements of the interstitial fluid and not of blood monitoring; therefore, "real-time" may be a misnomer and delays are a part of this process as well [11]. The development of CGM technology has permitted the creation of new metrics for monitoring glucose, such as GV and the percentage of time spent in target glucose range—called TIR (time-in-range). These metrics provide clinical insights into short-term glycemic control. CGM also provides key inputs to allow algorithm-based insulin delivery [9].

As a result of the limitations of HbA_{1c} in monitoring short-term glycemic changes and the emergence of new metrics for monitoring glucose, the term "beyond HbA_{1c}" has emerged in the field of diabetes research over the past few years. The field of "beyond HbA_{1c}" includes glucometrics, such as TIR, GV, and the percentage of time in hyperglycemia and hypoglycemia, and person-reported outcomes, i.e., quality-of-life (QoL) assessments. With the increasing accuracy of CGM, blood glucose monitoring in people with diabetes is entering a new era [9].

Even though there is evidence favoring early initiation of insulin therapy in individuals with poorly controlled diabetes by oral antidiabetic drugs (OADs), the optimal use of insulin therapy is delayed by several physician- and person-related barriers. The second-generation basal insulin analogues glargine 300 U/mL (Gla-300) and insulin degludec evidently provide more therapeutic benefits, have lower risk of hypoglycemia, and also possess longer action profiles (> 24 h) compared to first-generation insulin analogues [12]. As compared to first-generation insulin analogues, second-generation analogues offer lower GV and comparable TIR [13]. Further, emerging evidence indicates that these second-generation basal insulin analogues help overcome barriers associated with early insulin use and effectively address parameters involved in moving "beyond HbA_{1c}" [12].

With this background, an effort was undertaken to develop clinical evidence-based expert opinions and views for delineating appropriate basal insulin strategies for the treatment of diabetes, based on modern glucose metrics such as GV and TIR. This document summarizes the background evidence-based discussion and key opinions and views of multinational experts on basal insulin strategies for better accuracy in diabetes management.

METHODS

A group of multinational clinical experts comprising diabetologists and endocrinologists from 15 countries, namely India, Nepal, Indonesia, Ghana, UAE, Bangladesh, Egypt,

Malaysia, Philippines, Nigeria, Sri Lanka, Qatar, Maldives, South Africa, and Singapore, met virtually on 31 May 2020. The expert panel thoroughly reviewed available literature evidence and discussed the importance of TIR and basal insulin strategies in diabetes management, with emphasis on the role of second-generation basal insulin analogues. The clinical insights into TIR provided were based on the review of the Advanced Technologies and Treatments for Diabetes (ATTD) international consensus on the use of CGM 2017 and TIR 2019. Additionally, a review of published literature comparing the TIR profiles of the basal insulins was conducted on the basis of databases searches from PubMed and Google Scholar using the terms "time in range" in combination with "glargine," "degludec," and "detemir." Further, a gray literature search was performed using the same search terms. Articles published in journals resulting from these searches in the last 5 years and relevant references cited in those articles were examined. Only the relevant articles published in English were included.

On the basis of key opinions, review of scientific evidence, and clinical judgment, the panel provided their clinical insights into individualizing TIR and basal insulin strategies in diabetes management, which are summarized in this article. This article is based on previously conducted studies and does not contain any studies with human participants or animals performed by any of the authors.

EMERGING GLUCOSE METRICS AND MEASURES: IMPACT ON DIABETES OUTCOMES

Moving "Beyond HbA$_{1c}$": Need of the Hour

Measurement of HbA$_{1c}$ is considered the gold standard method for assessing chronic glycemic control in people with diabetes. However, the measurement of HbA$_{1c}$ has its limitations, including its inability to measure acute glucose fluctuations. Further HbA$_{1c}$ is an unreliable measure in patients with anemia, iron deficiency, hemoglobinopathies, and during

pregnancy; moreover, it does not provide information about hypoglycemia and on how to adjust the treatment regimen when HbA$_{1c}$ levels are elevated. Therefore, although HbA$_{1c}$ is a valuable indicator of glycation, as well as an indicator of population health and diabetic complications, some limitations do exist for this parameter as well [14].

Lack of Reliability of HbA$_{1c}$ in Estimating Prevailing Glycemia: Concept of Glycation Gap

Absolute dependence on HbA$_{1c}$ for assessment of glycemic control in diabetes may lead to an error in clinical assessment and management owing to either under- or overestimation of prevailing glycemia. The deviation of HbA$_{1c}$ from serum fructosamine-predicted HbA$_{1c}$ is defined as the glycation gap (GGap), and depicts an individually consistent difference between other measures of mean glycemia and HbA$_{1c}$ [15]. A glycation gap is found in around 40% of people with diabetes and is associated with diabetes-related complications and mortality [15]. Individuals with a positive GGap may receive uptitration of glycemia treatment, putting them at undue risk for hypoglycemia. However, individuals with a negative GGap may be falsely reassured with a measured HbA$_{1c}$ level that is lower than actual glycemic status. This does not result in appropriate therapy intensification to improve glycemia, putting such individuals at risk for diabetes-related complications [15]. Therefore, for therapeutic purposes, using HbA$_{1c}$ levels alone is not completely reliable for evaluating glycemic status [15].

SMBG: Limitations in Filling Glycation Gap

Although SMBG has gained broad application with the widespread availability of glucometers, this traditional method only measures single glucose values at time points determined by the user. Therefore, SMBG only provides a snapshot of the whole glucose picture—ignoring rapid glycemic changes occurring between SMBG

measurements [4]. It does not provide any indication of the rate or direction of glucose level changes [14]. As a result, even frequent SMBG does not adequately reflect the GV or GGap in people with diabetes, since it provides only serial, single time-point measurements in 24-h glucose dynamics [5].

Continuous Glucose Monitoring

The field of daily management of diabetes with glucose concentration monitoring was revolutionized with the introduction of minimally invasive needle CGM sensors in 1999 [16]. CGM sensors measure interstitial glucose concentrations. A transmitter is linked to the sensor, which sends signals to an insulin pump or handheld receiver or smartphone supported with an appropriate application. CGM is commonly used in two ways: real-time CGM by patients and retrospective CGM by clinicians [17].

CGM sensors provide almost continuous glucose measurement, delivering readings every 5 min. Additionally, the use of CGM reveals hypo- and hyperglycemic events that are not detected by SMBG. This system improves glycemic control and reduces GV [18, 19]. Besides the real-time availability of glucose concentration, CGM also provides users with visual/acoustic hypoglycemic alerts, which help mitigate or avoid hypoglycemia [16].

Unlike SMBG, which measures glucose levels in the blood, CGM measures glucose changes in interstitial fluid (ISF). There are differences between blood glucose and ISF glucose: while blood transfers glucose to all parts of the body, ISF transfers glucose to cells. Further, ISF glucose is measured continuously every few minutes, while SMBG is performed a few times every day [20].

Compared to HbA_{1c}, CGM is a more direct and integrated method for estimating mean glucose levels [21]. This method helps in mean glucose calculations through a better reflection of glycemic peaks and troughs along with providing high-density data, thereby addressing the GGap for individual patients. Therefore, CGM potentially complements HbA_{1c} for estimating glycemic control [15].

Systematic analyses of CGM data enable visualization of glucose changes over time and also help identify factors responsible for such changes, thereby providing indications for optimizing diabetes therapy [20]. However, implantation of the CGM system is associated with some inconvenience and discomfort, as well as requiring higher levels of medical intervention [22]. The advantages and disadvantages of the CGM system are summarized in Table 1.

Improved Glycemic Outcomes with CGM: Clinical Evidence

In Type 1 Diabetes Mellitus: Although conventional intensive insulin therapy leads to good glycemic control, it is associated with the risk of hypoglycemia [29]. In an open-label, randomized crossover trial (Glycaemic control & Optimisation of Life quality in type 1 Diabetes [GOLD] study) conducted among adults with type 1 diabetes mellitus (T1DM), it was observed that intensive insulin therapy with multiple daily insulin injections (MDI) was more effective using CGM as compared to conventional treatment (HbA_{1c}, 7.92% vs. 8.35%) [18]. The GOLD 3 study assessed the effects of CGM on nocturnal and daytime hypoglycemia in people with T1DM treated with MDI. The time with nocturnal glucose levels below 70 mg/dL decreased by 48%, while glucose levels below 54 mg/dL reduced by 65% with CGM. Time with daytime glucose levels below 70 mg/dL reduced by 40% and below 54 mg/dL by 54%. The study concluded that CGM reduced both nocturnal and daytime hypoglycemia in people with T1DM treated with MDI and improved hypoglycemia-related confidence, thereby improving the QoL [29].

In Type 2 Diabetes Mellitus: In people with type 2 diabetes mellitus (T2DM) using insulin, CGM is a monitoring tool and influences the choice of insulin regimen. This method can be used to motivate patients to choose earlier insulin treatments, in case of oral antidiabetic drug failure, and for selecting the most appropriate insulin regimen [30].

Table 1 Advantages and limitations of CGM

Advantages [22, 23]	Limitations
Detailed assessment of glycemic control	*Safety issues:* Site reactions; rashes due to adhesives; falling off, pulling off, sweating (all significantly improved with recent modifications); losing receiver or transmitter; various transmission issues at night; sensors malfunctioning, and silencing of alarms if the smartphone is in silent or vibration mode [24].
Provides comprehensive glucose data	*Technical issues:* Adjustment of initial calibration and regular daily recalibrations required for some of the currently available devices; episodic differences in the performance of the sensor in the same individual; sensors can be used for only varying lengths of time, with implantable sensors lasting the longest [24].
	Sensor accuracy issues: In extreme glucose ranges, such as <60 mg/dL or >200 mg/dL, observed during prolonged aerobic exercise, sensor accuracy may be compromised. This disadvantage continues to be a challenge and calls for patient awareness [25].
Alerts for hypoglycemia and hyperglycemia	*Privacy and data concerns*: There are risks to the privacy of data of patients and their ownership and ability to control how their information is collected, stored, and used [26]. However, privacy and patient-data-related concerns are associated with cloud data storage and the risk for hacks, and not technically with the sensor per se.
No missed recordings	*User/patient-related issues:* Burden of wearing a device continuously; a skin puncture is done each time for insertion of the glucose sensor into the subcutaneous part of skin tissue; complex and difficult to personalize the user interface [24]. However, the user interface, displays, user-friendliness, data management, and data analysis software have significantly improved over time [27].
	Impact of sleep positions: "Compression lows"—Specific sleep positions might result in aberrant glucose readings, such as a sudden decrease in reported glucose values, presumably due to decreased local blood flow caused by tissue compression. In some cases, aberrant CGM readings display elevated values [28].

CGM may be useful in predicting hypoglycemia in high-risk populations such as elderly people using insulin. Klimontov and Myakina used blinded CGM in 83 insulin-treated elderly inpatients (65–80 years old) to assess the risk of nocturnal hypoglycemia. The study observed nocturnal hypoglycemia in 39% of the 24-h CGM recordings [31].

A prospective randomized trial by Ehrhardt et al. comparing SMBG and RT-CGM demonstrated a significant improvement in HbA$_{1c}$ following RT-CGM in people with T2DM not taking prandial insulin. While the mean decline in HbA$_{1c}$ at 12 weeks was $0.5 \pm 0.8\%$ in the SMBG group, it was $1.0 \pm 1.1\%$ in the RT-CGM group ($p = 0.006$) [32]. In the study by Zick et al., 72 h of CGM was used in people with T2DM on MDI. It was reported that CGM detected 56.9% of individuals with hypoglycemia, compared to 26.4% detected by conventional SMBG. Moreover, in people with T2DM treated with a variety of insulin regimens, CGM revealed a more comprehensive picture of hypoglycemia, even during a period of stable therapy [33]. As per a study by Pazos-Couselo et al., significantly higher percentages of hyperglycemic ($p = 0.047$) and hypoglycemic episodes ($p = 0.016$) were detected by CGM compared to SMBG. Further CGM detected nocturnal hypoglycemia in 33% of participants. It was also observed that 19% of participants who reportedly had no hypoglycemia by SMBG measurements had hypoglycemia when assessed using CGM measurements [34].

Optimal utilization of CGM may also help in motivating or avoiding diabetes burnout in people with T2DM. Evidence indicates that improved lifestyle and behavior changes, i.e., reduced diabetes burnout associated with RT-CGM use, result in reduced HbA_{1c} levels in these people [35].

RECENT TECHNIQUES FOR MEASURING BLOOD GLUCOSE FLUCTUATIONS: TIME-IN-RANGE AND GLYCEMIC VARIABILITY

GV refers to fluctuations in blood glucose levels. Fluctuations in blood glucose levels can lead to intraday and interday variations, which can increase both the risk of hypoglycemia and glycemic excursions to the hyperglycemic range [36]. For people using CGM, TIR is defined as the time spent in the target glucose range (70–180 mg/dL) while aiming at reducing the time spent in hypoglycemia. TIR serves as an outcome measure for glycemic control in clinical trials, for complementing other components such as HbA_{1c} and blood glucose levels [37].

GV and Its Implications in Diabetes Mellitus

Several studies have elucidated the relationship between GV and hypoglycemia. Hypoglycemia is more common in individuals with increased GV [36]. A pooled analysis of six randomized controlled trials (RCTs) conducted among people with T2DM treated with 24 weeks of Gla-100 or comparators demonstrated that all measures of GV were significantly associated with poor glycemic control and the development of hypoglycemia during the trial [38]. Moreover, intraday GV is associated with a higher risk of nocturnal and overall hypoglycemia, and a decrease in GV is strongly correlated with a reduction in both hyperglycemic and hypoglycemic episodes [36].

Studies have highlighted the key role played by GV in T1DM as well. Besides reinforcing the relationship between GV and the risk of hypoglycemia, these studies have also shown a link between GV and the development of cardiovascular autonomic dysfunction in adults with T1DM. Further the increased inflammation as a result of GV could lead to endothelial damage and vascular complications in adults with T1DM [39].

Analysis of data from the double-blind Trial Comparing Cardiovascular Safety of Insulin Degludec versus Insulin Glargine (Gla-100) in Patients with Type 2 Diabetes at High Risk of Cardiovascular Events (DEVOTE) evaluated the link between GV and the occurrence of severe hypoglycemia and subsequent mortality. An increased risk of severe hypoglycemia (hazard ratio [HR] 4.11, 95% confidence interval [CI] 3.15, 5.35) and all-cause mortality (HR 1.58, 95% CI 1.23, 2.03) was observed in individuals with interday fasting GV [40]. People experiencing severe hypoglycemia have a greater than twofold higher risk of cardiovascular death and all-cause mortality [41].

GV also has implications for diabetic complications. It is associated with markers of cardiovascular and endothelial damage. High GV is associated with cognitive impairment in people with T2DM [36]. GV has also been associated with the prediction of mortality: a higher risk of mortality is observed in individuals with higher visit-to-visit GV [36]. Besides, it has been observed that GV has implications for patients' QoL and psychological well-being. In insulin-treated people, high GV is associated with poor QoL, as well as increased length of hospital stay. When diabetes treatment is associated with the perception of reduced GV, there is a simultaneous improvement in QoL parameters, such as treatment satisfaction, work productivity, and absenteeism [36].

To avoid hypoglycemia, providing treatment that can control blood glucose levels and at the same time minimize interday and intraday GV is important. Mori et al. conducted a study to assess the actual state of interday GV and identify factors affecting GV in diabetic outpatients on insulin therapy. Interday GV was seen in 93% of outpatients, and 62% of patients showed inconsistent interday GV. Interday variability was associated with the following factors: gender (higher in women compared to

men, $p = 0.04$), diabetes type (higher in people with T1DM compared to those with T2DM, $p < 0.001$), dose of insulin (mean of the daily differences [MODD] correlated positively with total insulin dose, bolus insulin dose, and basal insulin but not with bolus dose to basal dose ratio; $p = 0.001$, 0.016, 0.001, and 0.361, respectively), and treatment regimen (MODD value highest in individuals treated with basal and bolus insulin and lowest in those treated with mixed preparations). The study indicated that treatment and instructions based on individuals' characteristics, interday GV, and lifestyle are important for people receiving insulin therapy [42].

Connecting the Dots: Time-in-Range and Impact on Diabetes Outcomes

Advancements in CGM technology have provided access to alternative indices and new metrics of glucose control. Among these metrics, TIR has emerged as a preferred measure among individuals with diabetes. Also, emerging evidence indicates that TIR can predict long-term complications of diabetes and pregnancy outcomes. However, in the case of physicians who are mostly familiar with HbA$_{1c}$ and blood glucose measurements, it might be difficult to understand and explain TIR goals to patients, position TIR in comparison to other glucose metrics, and interpret TIR [43]. The Advanced Technologies & Treatments for Diabetes (ATTD) international consensus on the use of CGM 2017 standardized the use of CGM to promote therapy adjustments in people with both type 1 and type 2 diabetes mellitus, especially those with frequent hypoglycemia. Before the 2017 consensus, different studies used different time-in-target ranges, and hence one study could not be compared with another. To overcome such variations and discrepancies, the ATTD consensus categorized hypoglycemia into three levels:

(i) Level 1 (54 to < 70 mg/dL)
(ii) Level 2 (< 54 mg/dL)
(iii) Level 3 (severe hypoglycemia causing cognitive impairment, not defined by definite glucose value)

Hyperglycemia was also categorized into three levels:

(i) Level 1 (alert level, > 180 mg/dL to ≤ 250 mg/dL)
(ii) Level 2 (clinically significant, > 250 mg/dL)
(iii) Level 3 (clinical diagnosis: hyperosmolar hyperglycemic or state ketoacidosis)

Categorization of the time spent in the three levels of hypoglycemia and hyperglycemia allows a more accurate assessment of severity and facilitates initiation of the most appropriate response [14, 37].

On the basis of the categorization of hypo- and hyperglycemia into different levels based on glucose values, the ATTD consensus panel defined TIR as the time spent in an individual's target glucose range of 70–180 mg/dL (3.9–10 mmol/L) [14]. The TIR metric includes three CGM measurements: percentage of readings and time per day above target glucose range (TAR), within target glucose range (TIR), and time below target glucose range (TBR). As per the recent ATTD international consensus on TIR (2019), most people with T1DM and T2DM should aim to spend more than 70% of time per day (approx. > 17 h) in TIR (70–180 mg/dL), with TBR (< 70 mg/dL) less than 4% and TAR (> 180 mg/dL) being less than 25% of time per day (Fig. 1) [44].

Petersson et al. evaluated the relationship between time-in-target range (TIT) and HbA$_{1c}$ through CGM in children and adolescents with T1DM. While TIR was defined as 70–180 mg/dL, TIT was defined as 70–140 mg/dL. Over 60 days, the mean TIR was 60.8% (± 13.1%), while the mean TIT was 40.9% (± standard deviation [SD], 12.2%). Moreover, a significant nonlinear relation was observed between TIT and HbA$_{1c}$ during the study period. The study concluded that in addition to HbA$_{1c}$, time spent in TIT could be a useful metric to assess glycemic control [45].

Beck et al. conducted analyses utilizing datasets from four randomized trials including 545 adults with type 1 diabetes who had central laboratory measurements of HbA$_{1c}$ at baseline and 6 months. TIR (70–180 mg/dL [3.9–10.0 mmol/L]) of 70% and 50% corresponded with HbA$_{1c}$ values of approximately 7% and 8%,

Type 1# and
Type 2 diabetes

*For patients aged <25 years, if 7.5% HbA$_{1c}$ is desired,
then time-in–range should be set around 60%.
*Includes percentage of values >250 mg/dL.
**Includes percentage of values <54 mg/dL.

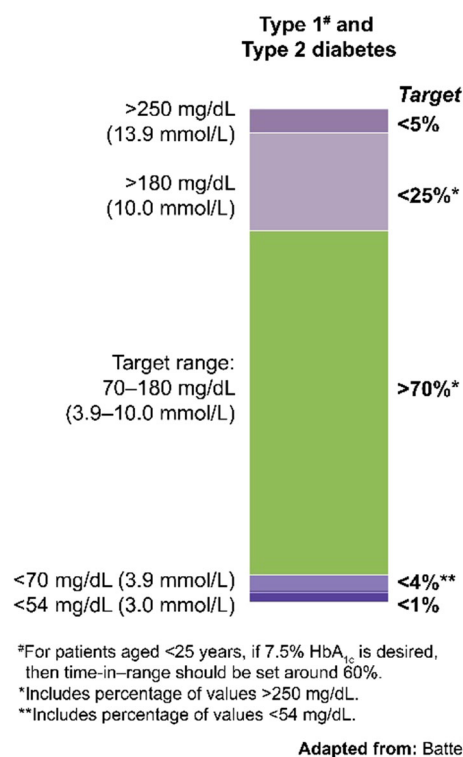Adapted from: Battelino et al., 2019.

Fig. 1 Continuous glucose monitoring-based time-in-range targets for patients with diabetes [44]

respectively. An increase in TIR of 10% (2.4 h per day) corresponded to a decrease in HbA$_{1c}$ of approximately 0.6%, establishing an inverse relationship between the two [46].

Vigersky and McMahon also analyzed the relationship between TIR and HbA$_{1c}$ across multiple studies ($n = 1137$), including people with T2DM. The study revealed that for target HbA$_{1c}$ of $\leq 7\%$ and $\leq 6.5\%$, the %TIR targets should be approximately 65% and 70%, respectively. The study reported that for achieving a target decrease in HbA$_{1c}$ of 0.8% (9 mmol/mol), there was a 10% change in %TIR [47].

Apart from measuring glycemic control in patients, TIR may also be used as an appropriate clinical endpoint in diabetes research [48]. For example, TIR serves as a valid clinical outcome for evaluating the risk of vascular complications of diabetes. Evidence suggests that TIR is inversely correlated with the risk of developing vascular complications in people with diabetes [48]. On the basis of the above discussion

points, the expert panel put forward recommendations for TIR management based on population type and the phase of life. The recommendations are captured herein and summarized in Fig. 2.

TIR Recommendations for Different Populations and Life Phases

- TIR is a useful metric in OAD inadequacy in adults, as OAD inadequacy is usually seen within 5 years in two-thirds of cases.
- In T1DM, the lower cutoff may be 80 mg/dL to prevent hypoglycemia.
- Adults with T2DM without complications deserve tight control: $> 80\%$ in 70–160 mg/dL, as this group is mostly on metformin and the risk of hypoglycemia is low; hence, 70 mg/dL is the acceptable lower limit and TAR $< 15\%$, TBR $< 5\%$.
- The definition of TIR needs to be individualized particularly in organ dysfunction, pregnancy, and the elderly.
- TIR recommendations based on the four phases of life can be adolescents T1DM/T2DM (10–18 years), adults (> 18 years), pregnancy, and elderly.
- **For adolescents:** A target range of 70–180 mg/dL is acceptable in T1DM and T2DM. Setting the lower limit to a value above 70 mg/dL will suspend insulin too early, which is not recommended. Higher TIR is recommended for T1DM, as they are more prone to GV due to reduced endogenous insulin.

  (i) In T1DM: $> 80\%$ TIR in a target blood glucose of 70–180 mg/dL; $< 15\%$ TAR and $< 5\%$ TBR
  (ii) In T2DM: $> 70\%$ TIR in a target blood glucose of 70–180 mg/dL; $< 25\%$ TAR and $< 5\%$ TBR

- For adults: As most people with diabetes fall into this category, it is better to strive for tighter control in adults. Hence, two recommendations can be considered for TIR in adults and individualized as needed:

  (i) Same as ATTD consensus recommendations for T1DM and T2DM: $> 70\%$ TIR in a
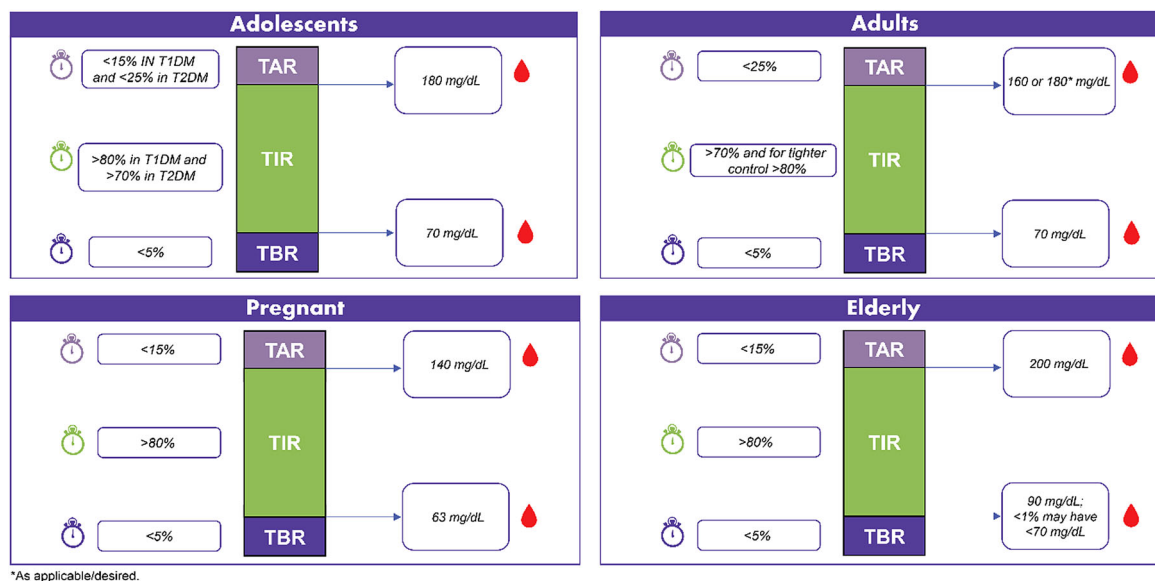
Fig. 2 Panel recommendations for TIR based on age group

target blood glucose of 70–180 mg/dL; < 25% TAR and < 5% TBR, or

(ii) Tighter control: > 80% TIR in a target blood glucose of 70–160 mg/dL; < 15% TAR and < 5% TBR. Tighter control is recommended in people who are highly motivated, newly diagnosed, have a long-life expectancy, and do not have co-morbidities.

- **For pregnancy:** Considering the target range similar to ATTD consensus recommendations, the time spent in the target range should be increased by 10%, as it has the potential to lead to better outcomes: > 80% TIR in a target blood glucose of 63–140 mg/dL; < 15% TAR and < 5% TBR.
- **For elderly:** Targets need to be relaxed with more time spent in the relaxed range, as this group is more susceptible to hypoglycemia; > 80% TIR in a target blood glucose of 90–200 mg/dL; < 15% TAR, < 5% TBR (< 90 mg/dL) < 1% (< 70 mg/dL).
- 80–90% children aged < 10 years have hypoglycemia unawareness. Thus, the lower limit of TIR should be relaxed.
- CGM reading differences with increase in temperature should be taken in account both during physiological (e.g., during summer) and pathological (medication intake

such as antipyretic, e.g., acetaminophen) conditions.
- The variation between CGM and SMBG is most evident during times when blood glucose levels are rapidly changing.

Relationship Between Time-in-Range and Microvascular Outcomes

A strong association between HbA$_{1c}$ levels and the risk of diabetes-associated chronic vascular complications was first established in the landmark DCCT trial [2]. Using the dataset of the DCCT trial, Beck et al. evaluated the association between TIR and development and/or progression of microalbuminuria, and diabetic retinopathy. For every 10 percentage-point decrease in TIR, the hazard rate for the development of microalbuminuria was increased by 40% (95% CI 25–56), while a 64% (95% CI 51–78) increase in retinopathy progression was observed (Fig. 3). This indicates a strong association between TIR and the risk of microvascular complications [48]. Another study investigated the association between diabetic retinopathy and TIR assessed by CGM in people with T2DM. Persons with more advanced diabetic retinopathy had significantly lower TIR and higher
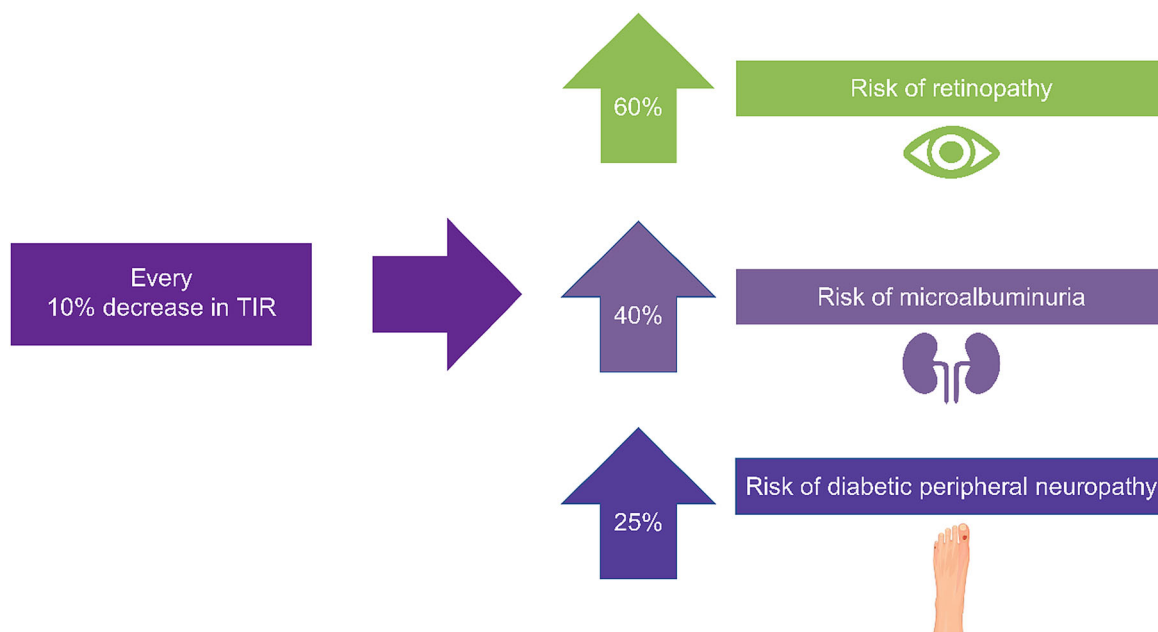
Fig. 3 Impact of TIR on microvascular outcomes [46]

measures of GV. Moreover, with increasing TIR, the prevalence of diabetic retinopathy decreased, based on severity. TIR was negatively associated with diabetic retinopathy; people with T2DM with vision-threatening retinopathy had the lowest TIR [49].

Another common microvascular complication is diabetic peripheral neuropathy (DPN). In a study on the association between TIR and DPN, Mayeda et al. demonstrated that DPN prevalence was 43% and 74% among participants who were within the target range > 70% and < 70% of the time, respectively. For every 10% decrease in TIR, there was a 25% increase in the risk of DPN. However, there was no significant association between HbA_{1c} and DPN symptoms. Therefore, the study concluded that the prevalence of DPN is inversely correlated with TIR [50].

Effect of Time-in-Range on Macrovascular Outcomes

Carotid intima-media thickness (CIMT) serves as a biomarker of subclinical atherosclerosis and can be used to predict incident cardiovascular events. A recent study investigated the use of TIR, measured by CGM and CIMT, as a surrogate marker of cardiovascular disease. It was observed that people with T2DM and abnormal CIMT had significantly lower TIR compared to those with normal CIMT ($p < 0.001$). These findings suggest a link between TIR and macrovascular disease [51].

Daily Life Measures Based on Time-in-Range

An online survey was conducted to understand patients' perspectives regarding the success of diabetes therapies, factors having the greatest impact on their daily lives, and the drivers of diabetes and mindset improvement. The study revealed TIR as the most common factor that had a great impact on daily life across all three study groups (people with T1DM [T1], people with T2DM on insulin therapy [T2I], and people with T2DM not on insulin therapy [T2NI]). Further, 36% of T2I respondents, 54% of T1 respondents, and 22% of T2NI respondents reported TIR as the key factor for a positive mindset [52].

Individualizing TIR Goals for Improving Outcomes

In patients undergoing cardiac surgery, poor perioperative control of blood glucose levels is associated with poor outcomes. Various glycemic targets have been prescribed to reduce wound infection and overall mortality rates. A prospective study by Omar et al. evaluated glucose control in patients with or without diabetes, after cardiac surgery. The glycemic target of the patients was 6.0–8.1 mmol/L, as determined by TIR. The patients with > 80% TIR had better outcomes in terms of wound infection ($p = 0.05$), length of hospital and intensive care unit (ICU) stay ($p = 0.03$ and $p = 0.04$, respectively), and length of ventilation ($p = 0.03$) as compared to those with < 80% TIR [53].

Randomized trial data confirm that CGM leads to improvement in both neonatal health outcomes and maternal glucose control. The common target throughout pregnancy is to increase TIR while reducing TAR and TBR. During the second and third trimesters, 5% lower TIR and 5% higher TAR is associated with an increased risk of neonatal hypoglycemia, large-for-gestational age infants, and neonatal ICU admission. Therefore, a TIR of > 70% (16 h, 48 min) and a TAR of < 25% (6 h) should be aimed for optimal neonatal outcomes as early as possible during pregnancy [54].

The proposed clinical insights for TIR management in the presence of complications are presented herein and in Fig. 4.

Clinical Insights on TIR Recommendations for Different Complications

- CGM should be considered in pregnancy, renal failure, discordance between HbA$_{1c}$, and clinical features/SMBG.
- TIR is an "additional" measure (along with other glycemic parameters), mainly if more accessible parameters are inconclusive.
- There is a need for more longitudinal studies (cross-sectional) to establish TIR as a surrogate marker of complications.

- **For individuals at high risk of hypoglycemia (renal/hepatic disease):** A relaxed target range with a high lower limit is recommended; > 70% TIR in a target blood glucose of 90–180 mg/dL; < 25% TAR and < 5% TBR.
- **With micro-/macrovascular complications:**
  (i) **Microvascular:** Same as adults; > 70% TIR in a target blood glucose of 70–180 mg/dL; < 25% TAR and < 5% TBR or > 80% TIR in a target blood glucose of 70–160 mg/dL; < 15% TAR and < 5% TBR.
  (ii) **Macrovascular:** Same target as microvascular complications or relaxed as following ≥ 70% TIR in a target blood glucose of 80–180 mg/dL; < 25% TAR and < 5% TBR. While stringent control has shown microvascular benefits, people with macrovascular complications may be at a higher risk of hypoglycemia, and hence relaxed targets are recommended.
- **With concomitant acute infections:**
  (i) **Non-hospitalized:** ≥ 75% TIR in a target blood glucose of 80–180 mg/dL; < 20% TAR and < 5% TBR.
  (ii) **Hospitalized:** > 80% TIR in a target blood glucose of 140–180 mg/dL; < 15% TAR and < 5% TBR. The cutoffs are kept in this range, assuming that use of antipyretics such as acetaminophen in acute infections can have an effect on CGM readings, giving a false higher value.
- Those with fever taking antipyretics and on CGM should undergo cross-check with finger stick method.
- In patients with sepsis in ICU: TAR (> 180 mg/dL) should be minimized to < 5% and the lower limit of 70 mg/dL should be pushed to 80 mg/dL to minimize mortality.
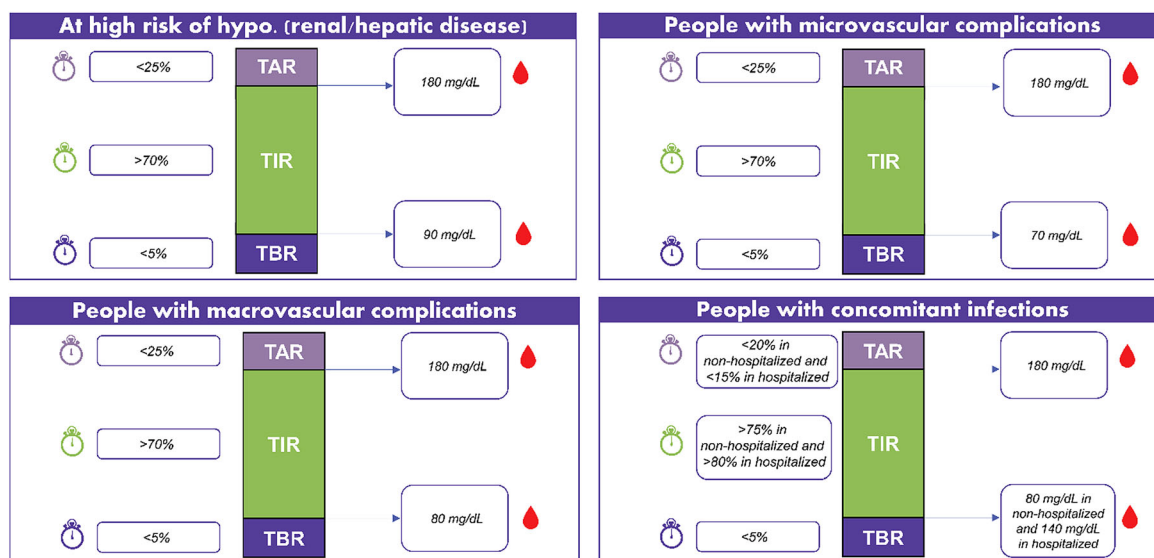
Fig. 4 Panel recommendations for TIR based on complications profile

BASAL INSULIN STRATEGIES FOR TIME-IN-RANGE AND GV: EMERGING POSITION OF SECOND-GENERATION BASAL INSULINS

Management of GV as the Stepping-Stone in Diabetes Management

As intraday and interday GV are risk factors in people with diabetes [55], several factors have been proposed to help reduce GV in such individuals who are on insulin treatment, such as [55-60]:

- Timely insulinization
- Choice of insulin
- Initiation dose
- Proper timing of injection of prandial insulin (for regular or rapid-acting analogue)
- Systematic and adequate titration
- Prompt intensification (using prandial insulin) when indicated
- Stepwise intensification
- Simple regimen
- Dosing flexibility

Role of Basal Insulin Analogues in Controlling GV in People with Diabetes

Different basal insulin analogues with varied time–action profiles have been developed over the years. These include first-generation basal insulin analogues, viz. Gla-100 and insulin detemir, second-generation basal insulin analogues, viz. Gla-300 and insulin degludec. Understanding the differences between first- and second-generation basal insulin analogues helps healthcare providers in making the most appropriate treatment decisions according to individual needs of people with diabetes [58].

Advantages of Second-Generation Over First-Generation Basal Insulin Analogues

Both first-generation and second-generation basal insulin analogues have similar efficacy in terms of reducing HbA_{1c}. However, compared to first-generation analogues, newer analogues have longer and more stable pharmacokinetics (PK) and pharmacodynamics (PD) profiles. Second-generation basal insulin analogues are associated with low variability, with predictable and stable glycemic control beyond 24 h, thus, providing clinically meaningful benefits compared to first-generation basal

insulin analogues, including longer duration of action (> 24-h coverage), reduced GV due to a more stable PK profile, and better injection time flexibility [12]. Furthermore, the second-generation basal insulin analogues have a lower risk of all-day hypoglycemia and nocturnal hypoglycemia compared to first-generation basal insulin analogues [12]. These analogues are associated with a greater improvement in treatment satisfaction, patient-related outcomes, and QoL [61, 62]. Taken together, second-generation basal insulin analogues provide new treatment options to physicians for achieving target glycemic levels [12].

Improved Control Over Glucose Variability: Comparing First-Generation and Second-Generation Basal Insulin Analogues in T1DM and T2DM

A study by Yu evaluated the real-world benefits of Gla-300 in lowering nocturnal fluctuations in blood glucose levels and nocturnal hypoglycemia in people with T2DM. The mean nocturnal glucose level achieved during the Gla-300 (121 ± 31.23 mg/dL) treatment phase was similar to that achieved during the Gla-100 (126.1 ± 35.11 mg/dL) treatment phase. Variability in mean nocturnal glucose levels (SD and CV) and the mean amplitude of glucose excursions between nights were lower during the Gla-300 treatment period compared to the Gla-100 treatment period. The study concluded that Gla-300 is comparable to Gla-100 in providing tight glycemic control. Besides, it was observed that Gla-300 had a greater potential to reduce the frequency of nocturnal hypoglycemia vs. Gla-100 [63].

A two-period crossover study compared glucose control with Gla-300 and Gla-100 in people with T1DM. Both Gla-300 and Gla-100 had a comparable percentage of time within the target glucose range. For Gla-300, a significantly lower increase in CGM-based glucose measurement was observed during the last 4 h of the 24-h injection interval as compared to Gla-100 (least-squares mean difference -14.7 mg/dL [95% CI -26.9 to -2.5]; $p = 0.0192$). Irrespective of morning or evening injection, mean

24-h glucose curves for the Gla-300 group were smoother than for the Gla-100 group—indicating lower glycemic excursions. Compared to Gla-100, the nocturnal hypoglycemia rate was lower with Gla-300 (4.0 vs. 9.0 events per participant-year: rate ratio 0.45 [95% CI 0.24–0.82]) [13].

An open-label, multicenter, prospective, observational study by Yamamoto et al. enrolled 21 participants with T1DM to investigate the differences in GV between Gla-100 and IDeg using CGM. The results showed that the mean amplitude of glycemic excursions was significantly reduced with degludec ($p = 0.028$), as was the area under the curve for daily blood glucose level < 70 mg/dL ($p = 0.046$). The authors concluded that degludec confers reduced hypoglycemia and daily blood glucose variability in participants with T1DM as compared to Gla-100 [64].

Another study by Iga et al. involving 20 patients with T1DM reported that fasting interstitial GV on the CGM curves was significantly less with IDeg than Gla-100 (25.9 ± 22.0 vs. 43.8 ± 30.1 mg/dL, $p = 0.04$). The authors concluded that while the hypoglycemic episodes were similar with both IDeg and Gla-100, treatment with IDeg was associated with lower GV [65].

Second-Generation Basal Insulins: Gla-300 vs. Insulin Degludec

Studies have compared the safety and efficacy of the second-generation basal insulin analogues Gla-300 and insulin degludec in adults with T1DM or T2DM. A study comparing the PK/PD profiles of Gla-300 vs. IDeg-100 demonstrated an evenly distributed PK profile and better steady-state PD profile with Gla-300 (20% lower within-day variability) in people with T1DM, with a once-daily dosing regimen of 0.4 U/kg/day [66]. However, an earlier study reported IDeg-200 to have lower intraday variability (37% lower) and interday variability (ca. four times lower) compared to Gla-300 [67]. The BRIGHT study was the first head-to-head clinical trial evaluating the efficacy and safety of two second-generation basal insulin analogues

(Gla-300 and IDed-100) in insulin-naïve adults with T2DM inadequately controlled with OADs (± GLP-1RA). Both insulins provided similar glycemic control, with relatively low and comparable hypoglycemia incidence and rates during the overall study period. However, during the titration period, hypoglycemia was lower with Gla-300 as compared to IDeg [68]. Another head-to-head trial, the Trial Comparing the Efficacy and Safety of Insulin Degludec 200 units/mL and Insulin Glargine 300 units/mL in Subjects with Type 2 Diabetes Mellitus Inadequately Treated with Basal Insulin and Oral Antidiabetic Drugs (CONCLUDE), reported that incidence of overall symptomatic hypoglycemia was not significantly different between Gla-300 and IDeg-200 during the maintenance period in individuals with T2DM. Since the study could not meet its primary endpoint, the secondary endpoints were considered exploratory and not conclusive [69]. A small-scale study used CGM for comparing the safety and efficacy of Gla-300 and insulin degludec. The mean percentage of TIR was similar with both insulin types ($p = 0.848$), but the percentage of time in hypoglycemia was significantly lower with Gla-300 as compared to insulin degludec ($p = 0.002$). The percentage of time spent with nocturnal or severe hypoglycemia was also significantly lower with Gla-300 than with insulin degludec (1.1 ± 2.4 vs. 4.2 ± 5.8 and 0.04 ± 0.18 and 1.8 ± 3.0, respectively). The study showed that during insulin degludec treatment, the mean percentage of time with hypoglycemia, especially nocturnal hypoglycemia, significantly correlated negatively with albumin level, possibly as a result of the reversible binding of insulin degludec to albumin [70]. Another study by Yamabe et al. showed that although both these insulins were comparable in terms of efficacy, nocturnal hypoglycemia was significantly lower with Gla-300 compared to insulin degludec ($p = 0.021$). The study indicated that although both these long-acting insulin analogues are comparable in terms of efficacy, Gla-300 has lesser risk of nocturnal hypoglycemia than insulin degludec [71].

Although the use of CGM allows better assessment of glycemic control taking TIR into consideration, large-scale studies based on CGM to compare the safety and efficacy of Gla-300 and IDeg are lacking. The InRange is an ongoing multicenter phase IV study that will collect CGM data over 20 days in adults with T1DM receiving either Gla-300 or IDeg-100. Although the study is aimed at showing the noninferiority of Gla-300 to IDeg-100 in terms of glycemic control and TIR, upon completion, it is also expected to provide valuable insights into the utility of CGM in clinical practice [72].

With this background, the experts delineated recommendations for the management of TIR in different patient populations. The use of second-generation basal insulins was emphasized by the expert members. The clinical insights regarding the choice of treatment modality for TIR management are summarized below.

Clinical Insights on TIR Recommendations, Based on Modality of Treatment

- Second-generation basal insulin scores better than insulin regimens in terms of increased duration of action, lesser GV, improved quality of life, reduction of diabetes distress, better adherence, prevention of cognitive dysfunction, and long-term complications.
- In practice, second-generation basal insulin brings down blood glucose with lower hypoglycemia compared to first-generation insulin for equivalent glucose levels.
- TIR recommendations remain the same regardless of the modality of treatment. The treatment should be directed at achieving TIR. This can be achieved with basal insulins, especially second-generation basal insulins.
- TIR targets remain the same regardless of whether the patient was on insulin or OADs (taking into consideration specific population, age group, and associated complications).

CONCLUSION AND FUTURE PERSPECTIVES

On the basis of clinical evidence, the expert panel suggests the use of CGM-based glucose metrics, such as TIR and GV, in addition to HbA_{1c} for effective diabetes management and decreasing the risk of both micro- and macrovascular complications. In this review, the panel individualized TIR for specific populations and complications in the context of diabetes. As personalized diabetes management moves from theory to practice, it is hoped that these recommendations can help practitioners effectively refine patient care models. Finally, person-centric glycemic control with CGM and second-generation basal insulin analogues is an option for more effective and accurate diabetes management, along with improved adherence and QoL measures.

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