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REVIEW ARTICLE

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Time in range—A new gold standard in type 2 diabetes research?

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[Correction added on 14 March 2025, after first online publication: The corresponding author has been updated to Elif I. Ekinci in this version.]

Abstract

Glycated haemoglobin (HbA1c) is currently the gold standard outcome measure for type 2 diabetes trials. Time in range is a continuous glucose monitoring (CGM) metric defined as the proportion of time in euglycemia (3.9–10.0 mmol/L) and may be valuable not only in type 1 diabetes clinical trials but also as an endpoint in type 2 diabetes trials. This narrative review aimed to assess the relative merits of time in range versus HbA1c as outcome measures for type 2 diabetes studies. It reviews the strengths and limitations of time in range as an outcome measure and evaluates studies in type 2 diabetes that have used time in range as a primary or secondary outcome measure. A literature search was conducted on PubMed and MEDLINE databases using key terms "time in range" AND "diabetes" OR "type 2 diabetes mellitus". Further evidence was obtained from relevant references of retrieved articles. Literature search identified 247 papers, of which 110 were included in this review. These included a broad range of articles, including 45 randomized trials using time in range as an outcome measure in patients with type 2 diabetes, as well as papers validating time in range. Time in range provides valuable and clinically relevant information and should be used as an important endpoint in type 2 diabetes in clinical trial settings, in conjunction with HbA1c.

KEYWORDS
consensus recommendations, continuous glucose monitoring, diabetes mellitus, HbA1c, time in range(s), type 2

1 | INTRODUCTION

Glycated haemoglobin (HbA1c) has long been considered the gold standard for assessing long-term glycaemia in people with type 2 diabetes. Continuous glucose monitoring (CGM) devices have become widely used, not just for people living with type 1 diabetes but also for those with type 2 diabetes.[1] CGM measures glucose levels in the interstitial fluid every 1–15 min, and an average glucose is recorded every 5–15 min for 24 h a day continuously. CGM enables better visualization and understanding of glucose levels by people with diabetes. Time in range (TIR) is a CGM metric which, by consensus, represents the percentage of time that glucose readings are within the desired range of 3.9–10.0 mmol/L (70–180 mg/dL). This metric has been increasingly used as an outcome measure to assess diabetes management both in clinical practice and clinical trials, especially in those trials involving people with type 1 diabetes.[2]

The use of CGM in type 2 diabetes research is increasing. It is a useful tool to not only improve glycaemic management but also to more accurately assess the impact of interventions on diabetes management. Batelino et al.[3] have made consensus recommendations on the use of CGM for clinical trials to assess the impact of an intervention; therefore, an increasing number of trials are using TIR as an outcome measure.

HbA1c has been the gold standard assessment of diabetes management for 29 years, since the publication of the Diabetes Control and Complications Trial (DCCT) which showed that an elevated HbA1c was associated with an increased risk of development and progression of microvascular complications.[4] HbA1c is measured based on the non-enzymatic glycation of haemoglobin, from which blood glucose levels over the normal ~120-day life span of the red blood cell can be inferred.

HbA1c is an indirect measure of glycaemic exposure and may not accurately reflect glycaemia in people with haemoglobinopathies, anaemia, kidney failure and even some ethnic groups, due to differences in the propensity of haemoglobin to glycosylation (Table S1 appendix). Some studies have shown HbA1c measurements are higher in US African Americans and Hispanic populations than in Caucasians.[5] These differences can make HbA1c a less reliable marker of glycaemia in certain populations. Therefore, management decisions in those with type 2 diabetes may be better served by CGM measures, including TIR.

Time in range (TIR) provides insight into short-term glycaemic management in the clinical setting by providing real-time feedback on glucose patterns. In research settings, TIR can be a valuable marker of the effectiveness of the trial intervention. There are other CGM metrics available, which will be discussed briefly later in this review; however, TIR is the most validated one so far. In this narrative review, we explore the strengths and limitations of TIR as an outcome measure with a review of trials in type 2 diabetes that have used TIR as either a primary or secondary outcome. We propose that TIR should be used routinely as an important outcome measure in type 2 diabetes trials in conjunction with HbA1c. Diabetes in pregnancy is beyond the scope of this review.

2 | METHODS

We conducted a literature search on the PubMed and MEDLINE databases using medical subject heading (MeSH) terms "time in range" AND "diabetes" OR "type 2 diabetes mellitus" OR "diabetes mellitus" OR "glycemic control" OR "glycated haemoglobin" OR "diabetes treatment" OR "glucose-lowering drugs" OR "diabetes complications" OR "microvascular complications" OR "macrovascular complications". Retrieved articles were filtered to remove duplicates and irrelevant results. The reference lists of the selected articles were also searched for any relevant papers. Relevant papers on TIR, HbA1c and CGM in type 2 diabetes published since year 2000 were included. The search was limited to humans, and the English language.

3 | RESULTS

A total of 1260 potentially relevant articles were identified. After screening for relevance, 110 articles were included in this review (Figure 1). A Medline search using the MeSH terms "time in range" AND "diabetes mellitus, type 2" yielded 247 results, including 45 randomized controlled trials involving individuals with Type 2 diabetes, where TIR was considered either a primary or secondary outcome (Table 1). Of these, 11 studies featured CGM as the intervention. Specifically, 21 studies used TIR as a primary outcome, 19 as a secondary outcome and 5 as a co-primary outcome. Studies that used TIR as the primary outcome, without including HbA1c as an outcome, had durations ranging from 13 days to 3 months, with a median duration of 51.5 days. All studies that included HbA1c as a primary or secondary outcome were greater than 3 months duration, with a median duration of 58 weeks duration. The trials were conducted across a diverse set of countries, including the United States, United Kingdom, Japan, Korea, China, Australia, Canada, Singapore and several European nations. The most commonly used CGM devices were the FreeStyle Libre Pro by Abbott, employed in 13 studies, Medtronic products in 10 studies, followed by the Dexcom G6 in 8 studies, and the Dexcom G4 in 2 studies. Additionally, 3 studies derived TIR from self-monitoring of blood glucose through fingerpricking.

4 | DISCUSSION

4.1 | Definitions of TIR and other CGM metrics

The International Consensus on Time in Range (ICTR) defines targets for TIR, time above range (TAR) and time below range (TBR) for people with type 1 and type 2 diabetes.[51] They recommend assessing all the metrics together as 'TIR' in clinical and research settings as it is more illustrative overall. They recommend >70% of time spent within target ranges (around 16 h 48 min per day) for both type 1 and type 2 diabetes.[52,53] TBR is split into two levels: Level 1 (3.0–3.9 mmol/L, 54–69 mg/dL) signals risk of hypoglycaemia, and Level 2 (<3.0 mmol/L, <54 mg/dL) is clinically significant, requiring immediate attention, with a target of <1% of the day. TAR is also split into two levels: Level 1 (>10 mmol/L, >180 mg/dL) and Level 2 (>13.9 mmol/L, >250 mg/dL).

TIR targets for specific subgroups, such as the elderly or other high-risk individuals, have also been defined by the ICTR. A TIR target of >50% per day (12 h) for individuals over 60 years or those at high risk is recommended.[3] However, this target is based on consensus opinion considering the higher rates of hypoglycaemia and hypoglycaemia unawareness in older adults and is not well validated.[54] A 2021 review involving 15 expert endocrinologists worldwide proposed individualized TIR targets for various subgroups[55] (Figure 2). They endorsed the ICTR recommendation of >70% TIR at 3.9–10 mmol/L for individuals with type 1 and type 2 diabetes; however, for highly motivated, newly diagnosed patients without comorbidities, a stricter target of >80% TIR at 3.9–8.9 mmol/L may be considered.

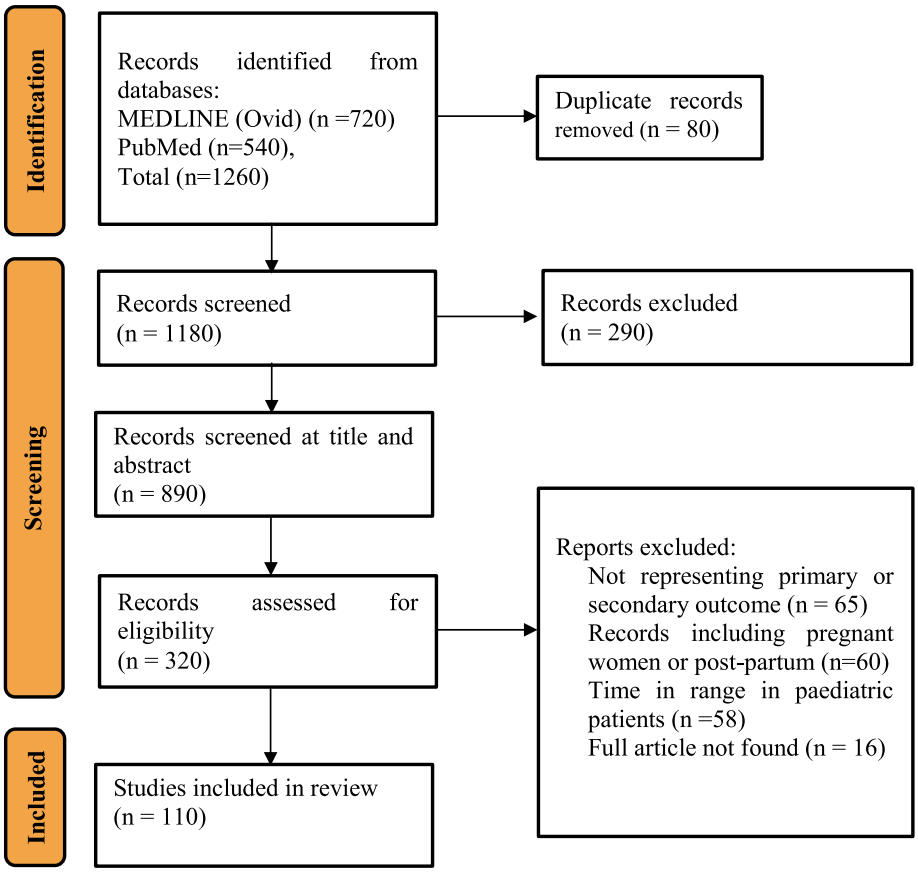

FIGURE 1 PRISMA (Preferred Reporting Items for Systematic Reviews and Meta-Analyses) flowchart for narrative review.

For adolescents with type 1 diabetes, the target was >80% TIR at 3.9–10 mmol/L, due to the propensity for greater glycaemic variability. Although difficult to achieve, dedicated education and support on carbohydrate counting, meal planning, exercise management and use of insulin pumps may help to achieve this. Additionally, for those with macrovascular complications, a more relaxed target (>70% TIR at 4.4–10 mmol/L) was recommended to mitigate the heightened risk with hypoglycemia.[56] An even looser target (>70% TIR at 5.0–10 mmol/L) was suggested for patients with renal or hepatic disease. Individualized TIR targets are crucial, even in clinical trials, to minimize hypoglycaemia. A more streamlined consensus on subgroup-specific targets by the ICTR would be beneficial.

A correlation analysis conducted by Montaser et al. on 75,563 CGM profiles from studies involving both type 1 and type 2 diabetes identified two key clusters of CGM metrics: exposure to hyperglycaemia and risk of hypoglycemia.[57] Together, these clusters account for 90% of the variance in CGM data. Hyperglycaemia is associated with TIR and the Glycemia Management Index (GMI), while hypoglycaemia correlates with TBR and the Coefficient of Variation (CV).

GMI, previously known as the estimated HbA1c, is calculated from mean glucose levels using formulas validated in multiple studies.[58,59] CV%, which reflects glycaemic variability (GV), is calculated by dividing the standard deviation (SD) of sensor glucose (SG) values by the mean SG value over the same observation period x100, and a threshold of 36% has been shown to differentiate between stable and unstable glycemia.[60] CV has been shown to be relatively sensitive and predictive of hypoglycaemia.[60,61] The strengths and limitations of these measures are discussed later in this review. While the primary focus in this manuscript is on T2D, the rationale for emphasizing TIR has similar implications for T1D, given the comparable TIR targets and associated diabetes complication outcomes.

4.2 | Strengths of TIR as an outcome measure

In comparison to HbA1c, TIR is not affected by ethnicity, hemoglobinopathies or anaemia, making it a more reliable outcome measure of glycaemia in populations that often get excluded in studies using HbA1c as a primary outcome measure. Some trials in people with Type 2 diabetes have shown discrepancies in the significance of outcomes between HbA1c and TIR, as outlined below[19,48] and shown TIR can be a valuable marker of the effectiveness of a trial, thus justifying the need for both outcome measures even further. Furthermore, consensus recommendations have been made on the optimal duration of CGM wear being 14 consecutive days with at least 70% wear for accurate interpretation of CGM metrics; however, this has not been well validated.[3] This measure of CGM accuracy was based on a study involving 257 people with type 1 diabetes who wore a CGM over 3 months that found that the incremental sampling of CGM data correlation to the full 3 months of CGM data improved with the number of days of data collected; however, there was a plateau at about 14 days with an R^2 value of 0.84–0.86 for metrics including TIR, mean

TABLE 1 Studies involving time in range as an outcome measure in people with type 2 diabetes.

Author, year	Country	Population, sample size, type of study	Time in range as primary, secondary or co-primary outcome	HbA1c included as outcome	Intervention	Device used	Length of study	Findings
Lind et al.[6] (2024)	US	$N = 76$, insulin-treated type 2 diabetes, single-centre, parallel, open-label, randomized controlled trial	Primary	Yes	Continuous glucose monitoring (CGM) versus blood glucose monitoring (BGM)	Dexcom G6	12 months	Compared with BGM, CGM usage was associated with significantly greater improvements in time in range (TIR) (between-group difference 15.2%, 95% CI 4.6; 25.9), HbA1c (−0.9%, −1.4; −0.3, total daily insulin dose (−10.6 units/day, −19.9; −1.3), weight (−3.3 kg, −5.5; −1.1), and BMI (−1.1 kg/m2, −1.8; −0.3) and greater self-rated diabetes-related health, well-being, satisfaction, and health behaviour.
Li et al.[7] (2024)	Australia	$N = 46$, Type 2 diabetes, randomized case-crossover clinical trial	Primary	No	Equil patch—Medtronic MMT-712 insulin pump versus Medtronic MMT-712—Equil patch insulin pump)	Medtronic IPro2	13 days	There was no significant difference in parameters of daily GV and postprandial glucose excursions between the Equil patch insulin pump treatment and the Medtronic insulin pump treatment. Similarly, there was no between-treatment difference in TIR, TBR, and TAR, as well as the incidence of hypoglycaemia.
Vernstrøm et al.[8] (2024)	England	$N = 120$, Type 2 diabetes, two parallel designs, placebo-controlled, randomized clinical trial	Secondary	Yes	Effect of empagliflozin, semaglutide, and their combination on vascular function.	FreeStyle Libre Pro	32 weeks	The carotid-femoral pulse wave velocity did not change significantly in any of the groups compared with placebo. Twenty-four-hour systolic BP was reduced by 10 mmHg (95% CI 6–14), $p < 0.001$ in the combination group, significantly superior to both placebo and monotherapy ($p < 0.05$). Combination treatment increased glycaemic TIR from 72% at baseline to 91% at week 32, $p < 0.00$, without increasing time below range (TBR). All active treatment groups significantly lowered HbA1c compared with baseline, with the most pronounced reductions seen in the semaglutide and the combination group.
Selvin et al.[9] (2024)	US	$N = 172$, Type 2 diabetes, N/A	Primary	No	Dexcom G4 and Abbott Libre Pro CGM sensors	Dexcom G4	3 months	At baseline (up to 2 weeks of CGM), mean glucose for both the Abbott and Dexcom sensors was approximately 150 mg/dL (8.3 mmol/L) and TIR (70–180 mg/dL [3.9–10.0 mmol/L]) was just below 80%.
Chen et al.[10] (2024)	China	$N = 42$, Type 2 diabetes, prospective, randomized, controlled trial	Co-primary	No	Low-to-Moderate-Intensity Continuous Training (LMICT) versus Moderate-Intensity Interval Training (MIIT) versus Reduced-Exertion High-Intensity Training (REHIT)	GS1	28 days	Compared with the control group, the MIIT group showed significant improvements in mean glucose (MG), glucose standard deviation (SD), time above range (TAR), and TIR. In the MIIT group, TIR values increased significantly over time ($F = 8.947$, $p = 0.001$).

(Continues)

TABLE 1 (Continued)

Author, year	Country	Population, sample size, type of study	Time in range as primary, secondary or co-primary outcome	HbA1c included as outcome	Intervention	Device used	Length of study	Findings
Ji et al.[11] (2024)	China	$N = 868$, Type 2 diabetes, randomized, double-blind and double-dummy trial	Secondary	Yes	Once-weekly subcutaneous semaglutide 0.5 and 1.0 mg	N/A	30 weeks	Overall, reductions in HbA1c from baseline to EOT were significantly greater with OW s.c. semaglutide 0.5 or 1.0 mg compared with sitagliptin across baseline subgroups ($p < 0.05$). The proportion of dTIR of seven-point Self-monitoring of blood glucose (SMBG) measurements at EOT was greater for participants treated with OW s.c. semaglutide (0.5 or 1.0 mg) versus sitagliptin ($p < 0.005$).
Haluzik et al.[12] (2024)	Finland	$N = 2420$, Type 2 diabetes, post hoc analysis	Primary	No	Fixed-ratio combination of insulin glargine 100 U/mL plus lixisenatide (iGlarLixi)	SMBG (Derived TIR)	30 weeks	Numerically greater improvements in least square (LS) means dTIR were seen from baseline to EOT with iGlarLixi (25.7%) versus iGlar (15.8%), Lixi (11.7%) or GLP-1 RA (16.2%). At EOT, the mean (SD) dTBR was 0.71% ± 3.4%, 0.61% ± 3.2%, 0.08% ± 1.0% and 0.0% ± 0.0% for iGlarLixi, iGlar, Lixi and GLP-1 RA, respectively.
Borel et al.[13] (2024)	France	$N = 20$. Type 2 diabetes, randomized, controlled, crossover, open-label, multicentre trial	Primary	No	CGM combined with continuous subcutaneous insulin infusion (CSII)	Dexcom G6	12 weeks	TIR increased to 76.0% (interquartile range 69.0–84.0) during the closed-loop condition vs. 61.0% (interquartile range 55.0–70.0) during the CSII + CGM condition; mean difference was 15.0 percentage points (interquartile range 8.0–22.0; $p < 0.001$).
Cordiner et al.[14] (2024)	Scotland	$N = 30$, Type 2 diabetes, open-label, randomized crossover study	Secondary	No	Low-dose sulfonylureas plus a dipeptidyl peptidase 4 (DPP4) inhibitor.	FreeStyle Libre Pro	8 weeks	SU combination with DPP4i showed additive effect on glucose lowering: mean glucose area under the curve (mean 95% CI) (mmol/L) was control 11.5 (10.7–12.3), DPP4i 10.2 (9.4–11.1), SU 9.7 (8.9–10.5), SUDPP4i 8.7 (7.9–9.5) ($p < 0.001$). Only treatments involving SU increased TIR between 3 and 10 mmol/L (%) versus control: control 67.4 (56.6–78.2), DPP4i 64.5 (45.6–83.74), SU 71.83 (52.59–71.25), SUDPP4i 68.4 (66.16–85.83) ($p < 0.001$ SU and SUDPP4i vs. control).
Kawaguchi et al.[15] (2024)	Japan	N = 36, Type 2 diabetes, randomized, non-blinded, parallel-group comparison study	Primary	Yes	Fixed-ratio combinations of Insulin glargine U100/ lixisenatide and insulin degludec/liraglutide	FreeStyle Libre Pro	18 weeks	The TIR and TBR level 1 showed no significant differences between the two groups. HbA1c was 7.0 ± 0.9 in the IGlarLixi group and 7.2 ± 0.6 in the IDegLira group ($p = 0.394$) with no significant difference.

TABLE 1 (Continued)

Author, year	Country	Population, sample size, type of study	Time in range as primary, secondary or co-primary outcome	HbA1c included as outcome	Intervention	Device used	Length of study	Findings
Idrees et al.[16] (2024)	UK	$N = 100$, Type 2 diabetes, randomized controlled trial	Primary	No	rt-CGM in adjusting insulin therapy in long-term care facilities (LTCF).	Dexcom G6	60 days	There were no differences in TIR (53.38% ± 30.16% vs. 48.81% ± 28.03%, $p = 0.40$), mean daily mean CGM glucose (184.10 ± 43.4 mg/dL vs. 190.0 ± 45.82 mg/dL, $p = 0.71$) or the percentage of TBR<70 mg/dL (0.83% ± 2.59% vs. 1.18% ± 3.54%, $p = 0.51$) or TBR <54 mg/dL (0.23% ± 0.85% vs. 0.56% ± 2.24%, $p = 0.88$) between rt-CGM and POC groups
Peng et al.[17] (2024)	China	$N = 200$, Type 2 diabetes, prospective, single-centre, randomized, controlled, open trial	Co-primary	Yes	Nursing education project	FreeStyle Libre Pro	6 months	Concerning standardized insulin self-injection, the intervention group was superior to the control group, and the difference between the 2 groups was statistically significant ($p < 0.05$). The HbA1c levels ($p = 0.000$), TIR ($p = 0.005$) and adipose hyperplasia incidence rate 6 months after discharge ($p = 0.000$) all improved in the intervention group compared to the control group.
Philis-Tsimikas et al.[18] (2024)	US, Europe, Latin America	$N = 1569$, Type 2 diabetes, post hoc analysis	Primary	No	Insulin degludec/liraglutide fixed-ratio combination (IDegLira) versus insulin glargine 100 units/mL (glargine U100)	SMBG (Derived TIR)	104 weeks	ETDs for change from baseline to EOT in dTIR were significantly greater with IDegLira versus glargine U100 in DUAL V (4.18%, $p = 0.027$) and DUAL VIII (5.17%, $p = 0.001$).
Karakasis et al.[19] (2023)	Greece, Serbia, Italy	$N = 3962$, Type 2 diabetes, systematic review and meta-analysis	Secondary	Yes	Once-weekly insulin basal analogues	N/A	16 weeks	Once-weekly insulin demonstrated a significantly greater TIR compared with once-daily insulin analogues (MD 3.54%, 95% CI 1.56, 5.53; $p = 0.005$) and a greater HbA1c reduction however there was no statistically significant difference. (mean difference reduction - 0.13%, 95% confidence interval [CI] -0.23, −0.03; $p = 0.08$). Once-weekly insulins had an association with higher odds of level 1 hypoglycaemia but were safer in terms of level 2 or 3 nocturnal hypoglycaemic events (OR 0.74, 95% CI 0.56, 0.97; $p = 0.03$).
Kitazawa et al.[20] (2023)	Japan	$N = 168$, Type 2 diabetes, randomized unblinded trial	Primary	Yes	Lifestyle intervention programme via a smartphone app	isCGM	12 weeks	After 12 weeks, TIR of blood glucose at 70–140 mg/dL significantly improved in the App group compared with the C group (−2.6 min/day vs. +31.5 min/day, $p = 0.03$). Changes in TAR did not differ, whereas TBR (blood glucose <70 mg/dL; +23.5 min/day vs. −8.9 min/day, $p = 0.02$) improved in the App group.
Tanaka et al.[21] (2023)	Japan	$N = 30$, Type 2 diabetes, open-label randomized crossover comparative study	Secondary	No	Hospitalized patients received either mitiglinide/voglibose or glimepiride	Medtronic IPro2	16 days	The reactive hyperaemia index was 1.670 ± 0.369 during treatment with mitiglinide/voglibose and 1.716 ± 0.492 during treatment with glimepiride, with no significant difference between the two. MAGE was significantly lower in

(Continues)

TABLE 1 (Continued)

Author, year	Country	Population, sample size, type of study	Time in range as primary, secondary or co-primary outcome	HbA1c included as outcome	Intervention	Device used	Length of study	Findings
								the mitiglinide/voglibose group (47.6 ± 18.5 mg/dL) than in the glimepiride group (100.6 ± 32.2 mg/dL). The use of mitiglinide/voglibose was associated with a significantly higher TIR (TIR; 70–180 mg/dL) (93.6% ± 12.3%) compared with glimepiride (83.31% ± 13.03%).
Zang et al.[22] (2023)	China	$N = 73$, Type 2 diabetes, randomized, double-blinded, and placebo-controlled trial	Co-primary	Yes	Intravenous infusion of Umbilical Cord Derived Mesenchymal Stem Cells	Medtronic IPro2	48 weeks	TIR and HbA1c were both significantly improved in UC-MSCs and placebo groups after 48 weeks of therapy compared with baseline.
Frias et al.[23] (2023)	England	$N = 92$, Type 2 diabetes, multicentre, randomized, double-blind, parallel-group, active-controlled, phase 2 trial	Secondary	Yes	Once-weekly subcutaneous semaglutide with cagrilintide (CagriSema), semaglutide or cagrilintide	Dexcom G6	32 weeks	The mean change in HbA1c from baseline to week 32 (CagriSema: −2·2%[SE 0·15]; semaglutide: −1·8%[0·16]; cagrilintide: −0·9% [0·15]) was greater with CagriSema versus cagrilintide (estimated treatment difference −1·3% [95% CI −1·7 to −0·8]; $p < 0·0001$), but not versus semaglutide (−0·4% [−0·8 to 0·0]; $p = 0·075$). At week 32, TIR (3·9–10·0 mmol/L [70–180 mg/dL]) measured by CGM was 88·9% with CagriSema, 76·2% with semaglutide, and 71·7% with cagrilintide - Changes from baseline in TIR and TITR were analysed post hoc, and were both significantly greater with CagriSema versus cagrilintide, but not versus semaglutide
Kudo et al.[24] (2023)	Japan	$N = 36$, Type 2 diabetes, multicentre, randomized, two-arm, open-label, parallel-group comparison study.	Secondary	Yes	Dapagliflozin in patients on basal insulin supported oral therapy (BOT)	Medtronic IPro2	12 weeks	In the dapagliflozin add- on group, mean glucose (183–156 mg/dL, $p = 0.001$), maximum glucose (300–253, $p < 0.01$), and SD glucose (57–45, $p < 0.05$) decreased. TIR increased ($p < 0.05$), while time above the range decreased in the dapagliflozin add- on group but not in the no add- on group.
Guo et al.[25] (2023)	China	$N = 878$, Type 2 diabetes, Post hoc analysis	Primary	No	Insulin glargine and lixisenatide (iGlarLixi), Insulin glargine100units/mL (iGlar) or lixisenatide (Lixi)	SMBG (Derived TIR)	30 weeks	The changes from baseline to EOT in TIR with GlarLixi were greater versus iGlar (ETD1: 11.45% [95%CI, 7.66% to 15.24%]) or Lixi (ETD2: 20.54% [95%CI, 15.74% to 25.33%]) in LixiLan-O-AP, and versus iGlar (ETD:1 6.59% [95% CI,12.09% to 21.08%]) inLixiLan-L-CN. iGlarLixi (from 8.4% to 6.3%) achieved a significantly greater HbA1c reduction than iGlar (from 8.3% to 6.8%) or Lixi (from 8.3% to 7.3%).
Lee et al.[26] (2023)	Korea	$N = 89$, Type 2 diabetes on metformin, double-blind,	Secondary	Yes	Anagliptin 100 mg BID or sitagliptin 100 mg QD	N/A	12 weeks	The decrease from baseline in MAGE at 12 weeks after DPP-4 inhibitor treatment was significantly greater in the anagliptin BID group (−30.4 ± 25.6 mg/dL ($p < 0.001$)) than in

TABLE 1 (Continued)

Author, year	Country	Population, sample size, type of study	Time in range as primary, secondary or co-primary outcome	HbA1c included as outcome	Intervention	Device used	Length of study	Findings
		multicentre, active-controlled, randomized study						the sitagliptin QD group (−9.5 ± 38.0 mg/dL ($p = 0.215$)) ($p < 0.05$). The TIR after dinner increased by 33.0% ± 22.0% ($p < 0.001$) in the anagliptin group and by 14.6% ± 28.2% ($p = 0.014$) in the sitagliptin group, with a statistically significant difference ($p = 0.009$). No statistically significant differences were observed between the groups in the changes in HbA1c
Aronson et al.[27] (2023)	Canada	$N = 116$, Type 2 diabetes, multisite, open-label, randomized controlled trial	Primary	Yes	isCGM device plus diabetes self-management education (isCGM + DSME) or DSME alone	FreeStyle Libre Pro	16 weeks	At 16 weeks of follow-up, the isCGM and DSME arm had a significantly greater mean TIR by 9.9% (2.4 hours) (95% CI, −17.3% to −2.5%; $p < 0.01$), significantly less TAR by 8.1% (1.9 h) (95% CI, 0.5% to 15.7%; $p = 0.037$), and a greater reduction in mean HbA1c by 0.3% (3 mmol/mol) (95% CI, 0% to 0.7%; $p = 0.048$) versus the DSME arm.
Ajjan et al.[28] (2023)	UK	$N = 141$, Type 2 diabetes on insulin and/or a sulphonylurea, phase 2 parallel-group open-label, randomized controlled trial	Primary	Yes	SMBG with intermittently scanned continuous glucose monitoring (isCGM)	FreeStyle Libre Pro	3 months	isCGM was associated with increased TIR by 17 min/day (95% credible interval − 105 to +153 min/day), with 59% probability of benefit. Users of isCGM showed lower hypoglycaemic exposure (<3.9 mmol/L) at days 76–90 (−80 min/day; 95% CI −118, −43), also evident at days 16–30 (−28 min/day; 95% CI −92, 2). Compared with baseline, HbA1c showed similar reductions of 7 mmol/mol at 3 months in both study arms.
Meng et al.[29] (2023)	China	$N = 33$, Type 2 diabetes, open-label, randomized, parallel-controlled, clinical trial	Secondary	Yes	Premixed insulin (Ins), premixed insulin combined with metformin (Ins + Met) or mulberry twig alkaloids(Ins + SZ-A)	Medtronic IPro2	12 weeks	The CGM indicators of the three groups during the lead-in period all showed significant improvements compared to the screening period ($p < 0.05$). Compared with those in the lead-in period, all of the CGM indicators improved in the Ins + Met and Ins + SZ-A groups after 12 weeks of treatment ($p < 0.05$). HbA1c and FBG in the three groups were significantly improved after 12 weeks of treatment ($p < 0.05$).
Chao et al.[30] (2023)	US	$N = 77$, Type 1 and Type 2 diabetes, single-arm, prospective, interventional study	Secondary	Yes	Non-adjunctive CGM use in adults with diabetes using intensive insulin therapy (IIT).	Dexcom G6	28 weeks	Mean HbA1c decreased by 1.3, 1.0 and 1.0 percentage points for participants with T1D, T2D or age ≥65, respectively ($p < 0.001$ for each). CGM-based metrics including TIR also improved significantly.
Takuma et al.[31] (2023)	Japan	$N = 340$, Type 2 diabetes, prospective, randomized, open-	Secondary	Yes	Dapagliflozin versus sitagliptin	FreeStyle Libre Pro	24 weeks	Sitagliptin was significantly superior in achieving HbA1c level <7.0% in the lower body mass index (BMI) group (71.1% vs. 43.6%; $p < 0.05$), with no significant differences in other subgroups. Dapagliflozin was superior to sitagliptin in

(Continues)

TABLE 1 (Continued)

Author, year	Country	Population, sample size, type of study	Time in range as primary, secondary or co-primary outcome	HbA1c included as outcome	Intervention	Device used	Length of study	Findings
		label, parallel-group study						achieving TIR > 70% in the higher BMI group (85.7% vs. 52.9%; $p < 0.01$).
Spanakis et al.[32] (2022)	US	$N = 185$, Type 1 and Type 2 diabetes, multicentre, noninferiority open-label randomized study	Primary	No	CGM on inpatient insulin adjustment	Dexcom G6	N/A	There were no significant differences in TIR (54.51% ± 27.72 vs. 48.64% ± 24.25; $p = 0.14$), mean daily glucose (183.2 ± 40 vs. 186.8 ± 39 mg/dL; $p = 0.36$) or percent of patients with CGM values <70 mg/dL (36% vs. 39%; $p = 0.68$) or <54 mg/dL (14 vs. 24%; $p = 0.12$) between the CGM-guided and POC groups
Bajaj et al.[33] (2022)	Canada	$N = 104$, Type 2 diabetes, open-label, treat-to-target, multicentre randomized controlled trial	Primary	Yes	Fixed-ratio combination of insulin glargine and lixisenatide (iGlarLixi) versus insulin glargine U100 (iGlar) and gliclazide	N/A	12 weeks	Co-primary outcomes of average TIRs within 24- and 12-h (6 am to 6 pm) periods at the end of trial were 70.5% ± 16.8% and 72.9% ± 17.6% for iGlarLixi, whereas these TIRs were 65.6% ± 21.6% and 67.3% ± 20.7% for the iGlar + gliclazide regimen, respectively, with no significant differences between groups ($p = 0.35$ for 24-h TIR and $p = 0.14$ for 12-h TIR). Self-reported hypoglycaemic events throughout the trial period and CGM-reported hypoglycaemia (<4 and <3 mmol/L) were similar between randomized treatments.
Cheng et al.[34] (2022)	Singapore	$N = 28$, Type 2 diabetes, single-centre, open-label randomized controlled trial	Secondary	Yes	Roux-en-Y gastric bypass (RYGB) versus best medical treatment	N/A	12 months	At 12 months, 50% of RYGB subjects achieved diabetes remission; 83% stopped all glucose-lowering medications. By year 5, 42% were in remission. None attained diabetes remission in the medical group. Percentage declines in fasting plasma glucose, HbA1c and BMI were significantly greater in the RYGB arm (all $p < 0.05$).
Kawaguchi et al.[35] (2022)	Japan	$N = 24$, Type 2 diabetes, randomized, open-label, crossover-controlled trial	Primary	No	Insulin degludec/insulin aspart (IDegAsp) and insulin degludec/liraglutide (IDegLira)	FreeStyle Libre Pro	15 days	The TIR was significantly higher in IDegLira than in IDegAsp. Postprandial glucose levels 90 and 120 min after breakfast and 60, 90, and 120 min after lunch were significantly lower for IDegLira than for IDegAsp.
Yan et al.[36] (2022)	China	$N = 172$, Type 2 diabetes, prospective, randomized controlled trial	Primary	Yes	Real-time and retrospective flash glucose monitoring (FGM)	FreeStyle Libre Pro	3 months	TIR (3.9 ∼ 10.0 mmol/L, TIR) increased significantly after 3 months in the real-time FGM group (6.5%) compared with the retrospective FGM group (−1.1%) ($p = 0.014$). HbA1c decreased in both groups (both $p < 0.01$). Real-time FGMs increased daily exercise time compared with the retrospective group ($p = 0.002$). HbA1c decreased in both groups (both $p < 0.01$).
Kawaguchi et al.[37] (2021)	Japan	$N = 40$, Type 2 diabetes, randomized,	Primary	No	Multiple daily injections and insulin glargine U100 and lixisenatide (iGlarLixi)	FreeStyle Libre Pro	13 days	The TIR did not significantly differ between the groups. However, the TBR level 1 was lower in the iGlarLixi + insulin glulisine group ($p = 0.047$).

TABLE 1 (Continued)

Author, year	Country	Population, sample size, type of study	Time in range as primary, secondary or co-primary outcome	HbA1c included as outcome	Intervention	Device used	Length of study	Findings
		open-label, parallel-group, controlled trial			combination (iGlarLixi + insulin glulisine			
Bae et al.[38] (2021)	Korea	$N = 65$, Type 2 diabetes, randomized, multicentre, double-blinded, parallel-group, placebo-controlled trial	Co-primary	Yes	Teneligliptin	Medtronic IPro2	12 weeks	After 12 weeks, a significant reduction (by 0.84%) in HbA1c levels was observed in the teneligliptin group compared to that in the placebo group (by 0.08%), with a between-group least squares mean difference of −0.76% (95% confidence interval [CI], −1.08 to −0.44). (TIR70–180) at week 12 was 82.0% ± 16.0% in the teneligliptin group, and placebo-adjusted change in TIR70–180 from baseline was 13.3% (95% CI, 6.0 to 20.6).
Bergenstal et al.[39] (2021)	US	$N = 114$, Type 2 diabetes, randomized controlled trial	Secondary	Yes	Blood glucoe monitoring testing (BGM) versus real-time CGM (CGM)	Dexcom G4	16 weeks	A1c means decreased from 8.19 to 7.07 (1.12% difference) with CGM ($n = 59$) and 7.85 to 7.03 (0.82% difference) with BGM ($n = 55$) ($p < 0.001$). BGM and CGM groups showed significant improvements in TIR and glucose variability—with no significant difference between the two groups.
Bajaj et al.[40] (2021)	Canada, Czech Republic, Germany, Italy, and the U.S	$N = 154$, Type 2 diabetes, multicentre, open-label, randomized, active-controlled, parallel-group, treat-to-target phase 2 trial	Primary	Yes	Switching to icodec versus once-daily insulin glargine 100 units/mL (IGlar U100)	Dexcom G6	16 weeks	Estimated mean TIR during weeks 15 and 16 was 72.9% (icodec LD; $n = 54$), 66.0% (icodec NLD; $n = 50$), and 65.0% (IGlar U100; $n = 50$), with a statistically significant difference favouring icodec LD versus IGlar U100 (7.9%-points [95% CI 1.8–13.9]). Mean HbA1c reduced from 7.9% (62.8 mmol/mol) at baseline to 7.1% (54.4 mmol/mol icodec LD) and 7.4% (57.6 mmol/mol icodec NLD and IGlar U100); incidences and rates of AEs and hypoglycaemic episodes were comparable.
Wang et al.[41] (2021)	China	$N = 81$, Type 2 diabetes, randomized, double-blind, active comparator-controlled clinical trial	Secondary	Yes	Chiglitazar or sitagliptin	N/A	24 weeks	After treatment for 24 weeks, the data showed a similar reduction in HbA1c between chiglitazar and sitagliptin. The 24-h mean blo-od glucose (MBG), SD and mean amplitude of glycemic excursion (MAGE) were significantly decreased, and the TIR was increased after chiglitazar and sitagliptin therapy.
Holzer et al.[42] (2021)	Germany	$N = 6$, Type 2 diabetes, randomized crossover study	Co-primary	No	Resistance exercise with whole-body electromyostimulation (WB-EMS) versus resistance exercise without electromyostimulation (RES) versus cycling endurance exercise (END).	FreeStyle Libre Pro	4 days	Postprandially increased glucose levels decreased in all cases. Time to baseline (initial value prior to meal intake) was quite similar for WB-EMS, RES and END. Neither glucose area under the curve (AUC), nor TIR from the start of the experiment to its end (8 h later) differed significantly.

(Continues)

TABLE 1 (Continued)

Author, year	Country	Population, sample size, type of study	Time in range as primary, secondary or co-primary outcome	HbA1c included as outcome	Intervention	Device used	Length of study	Findings
Pan et al.[43] (2021)	China	$N = 138$, Type 2 diabetes, double-blinded, randomized, controlled clinical trial	Secondary	Yes	Jinlida granules with versus without metformin	Medtronic IPro2	16 weeks	Compared with the pre-test, fasting plasma glucose, 2 h postprandial plasma glucose, HbA1c, and traditional Chinese medicine symptom score all decreased in the four groups at the end of the test, and the combination treatment group showed the most significant decrease. TIR of the Jinlida and metformin groups improved after intervention compared with the baseline (Jinlida group: 78.68 ± 26.15 versus 55.47 ± 33.29; metformin group: 87.29 ± 12.21 vs. 75.44 ± 25.42; $p < 0.01$).
Goldenberg et al.[44] (2021)	United States, Canada, Poland, South Africa and Slovakia	$N = 498$, Type 2 diabetes, randomized, crossover, open-label, multicentre, active-controlled trial	Primary	Yes	Insulin degludec U100 (degludec) versus insulin glargine U100 (glargine U100)	FreeStyle Libre Pro	18 weeks	Noninferiority and superiority were confirmed for degludec versus glargine U100 for the primary endpoint, with a mean TIR of 72.1% for degludec versus 70.7% for glargine U100 (estimated treatment difference [ETD] 1.43% [95% confidence interval (CI): 0.12, 2.74; $p = 0.03$] or 20.6 min/d). Mean HbA1c values were numerically similar for degludec (54.1 mmol/mol [7.1%]) and glargine U100 (54.8 mmol/mol [7.2%]) but the treatment difference reached statistical significance (ETD −0.06% [95% CI: −0.11, −0.01]).
Lingvay et al.[45] (2021)	Croatia, Germany, Hungary, Poland, Slovakia, Spain, and the U.S	$N = 205$, type 2 diabetes, phase 2, randomized, open-label, treat-to-target trial	Primary	Yes	Efficacy and safety of Insulin icodec different once-weekly titration algorithms.	Dexcom G6	16 weeks	TIR improved from baseline (means: A, 57.0%; B, 55.2%; C, 51.0%; IGlar U100, 55.3%) to weeks 15 and 16 (estimated mean: A, 76.6%; B, 83.0%; C, 80.9%; IGlar U100, 75.9%). TIR was greater for titration B than for IGlar U100 (estimated treatment difference 7.08%-points; 95% CI 2.12 to 12.04; $p = 0.005$). The ETD for HbA_{1c} was 0.02%-points (95% CI −0.20 to 0.24) for titration A versus IGlar U100, −0.20%-points (95% CI −0.42 to 0.02) for titration B versus IGlar U100, and − 0.36%-points (95% CI −0.58 to −0.14%) for titration C versus IGlar U100
Breyton et al.[46] (2021)	France	$N = 8$, Type 2 diabetes, randomized crossover pilot study	Secondary	No	Slowly Digestible Starch (SDS)	Medtronic IPro2	2 weeks	Glycaemic variability was significantly lower during High-SDS diet compared to Low-SDS diet for MAGE (Mean Amplitude of Glycaemic Excursions, $p < 0.01$), SD ($p < 0.05$), and CV (Coefficient of Variation, $p < 0.01$). The TIR [140e180 mg/ dL [was significantly higher during High-SDS diet ($p < 0.0001$) whereas TIRs 180 mg/dL were significantly lower during High-SDS diet.
Gao et al.[47] (2020)	N/A		Secondary	Yes	Acarbose (ACA) versus Metformin (MET)	N/A	12 weeks	Compared with baseline, several GV indices (SD, mean amplitude of glycaemic excursions [MAGE]) and blood glucose

TABLE 1 (Continued)

Author, year	Country	Population, sample size, type of study	Time in range as primary, secondary or co-primary outcome	HbA1c included as outcome	Intervention	Device used	Length of study	Findings
		$N = 124$, Type 2 diabetes, open-label randomized trial						control indices (mean glucose [MG], TIR and HbA1c) were both significantly improved in INS + ACA and INS + MET after 12-week therapy.
Vianna et al.[48] (2019)	Croatia, Germany, Hungary, Poland, Slovakia, Spain	$N = 97$, Type 2 diabetes, prospective, randomized, open-label (blinded to the observer), active-controlled, single-centre, parallel design study	Secondary	Yes	10 mg dapagliflozin or 120 mg gliclazide MR	Medtronic IPro2	12 weeks	Reduction in GV, as measured by the mean amplitude of glycaemic excursions, was superior in the dapagliflozin group versus the gliclazide MR group (−0.9 mmol/L [95% CI −1.5, −0.4] vs. −0.2 mmol/L [95% CI −0.6, 0.3]; $p = 0.030$ [ITT]). Dapagliflozin has demonstrated a tendency to increase TIR to a greater extent than gliclazide MR, with fewer episodes of hypoglycaemia. The change in baseline HbA1c for Dapagliflozin group −1.1%(−1.3,-0.9) and Gliclazide MR group −1.3% (−1.4,-1.1) ($p = 0.358$).
Sheyda Sofizadeh et al.[49] (2019)	Sweden	$N = 124$, Type 2 diabetes, double-blind, placebo-controlled trial with a parallel-group design	Primary	Yes	Liraglutide vs. Placebo	Dexcom G4	24 weeks	Mean time in target range was higher in the liraglutide group than in the placebo group: 430 versus 244 min/24 h ($p < 0.001$) and 960 versus 695 min/24 h ($p < 0.001$) for the two glycaemic ranges considered, 4–7 mmol/L and 4–10 mmol/L, respectively. HbA1c was also significantly lower in the liraglutide group. Mean time in hypoglycaemia was similar for participants receiving liraglutide and those receiving placebo after 24 weeks of treatment.
Sampaio et al.[50] (2012)	Brazil	$N = 20$, Type 2 diabetes, open, randomized (1:1), controlled, parallel, trials	Secondary	No	Insulin glargine (iGlar) associated with regular insulin (iReg) versus uses continuous insulin intravenous delivery followed by NPH insulin and iReg (St. Care) post Myocardial infarction	Medtronic IPro2	84 hours	Mean glycemia was 141 ± 39 mg/dL for St. Care and 132 ± 42 mg/dL for iGlar by CBG or 138 ± 35 mg/dL for St. Care and 129 ± 34 mg/dL for iGlar by CGMS. Percentage of TIR (80–180 mg/dL) by CGMS was 73 ± 18% for iGlar and 77 ± 11% for St. Care. No severe hypoglycaemia (≤40 mg/dL) was detected by CBG, but CGMS indicated 11 (St. Care) and seven (iGlar) excursions in four subjects from each group, mostly in sulfonylurea users (six of eight patients).

Abbreviations: CI, confidence interval; dTIR, derived time in range; EOT, end of treatment; FGM, flash glucose monitoring; SMBG, self-monitored blood glucose; T1D, type 1 diabetes; T2D, type 2 diabetes.

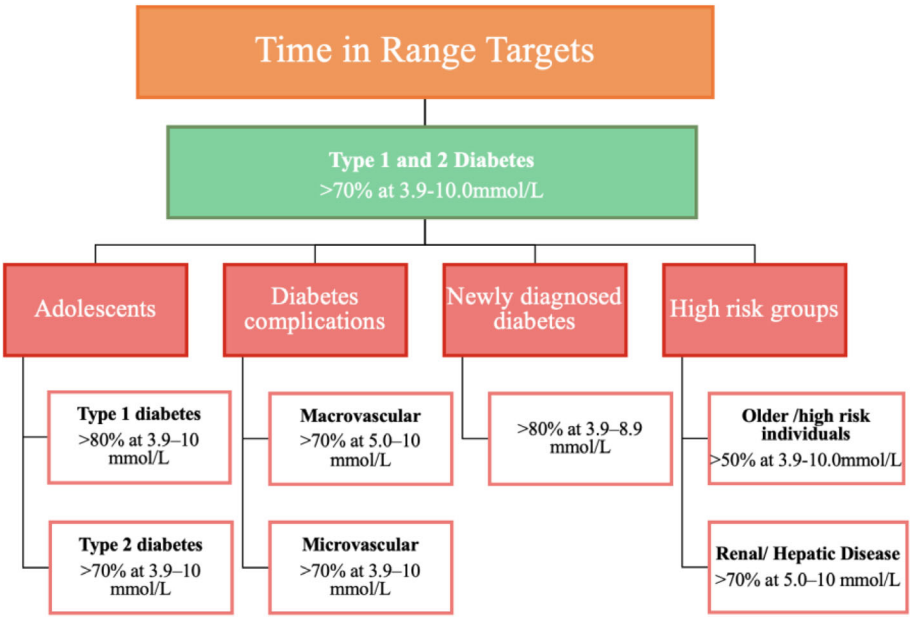

FIGURE 2 Time in range targets for various subgroups. Adapted from Kalra et al.[55]

TABLE 2 Correlation between time in range (3.9–10 mmol/L, 70–180 mg/dL) and HbA1c in 2 meta-analysis of randomized controlled trials.

Authors	Study size (n), study type	Population	Study Aim(s)	Findings	Correlation coefficient (r) between time in range and HbA1c
Beck et al.	545, Retrospective analysis of data from 4 RCTs	Type 1 diabetes = all studies	To better understand the metrics of time in range and hyperglycaemia and their relationship to HbA1c	TIR of 70% corresponded with A1C of 7%, TIR of 50% corresponded with A1c of 8% Every 10% increase in TIR = 0.5% (5.5 mmol/mol) A1C reduction[68, 69]	r = −0.67
Vigersky et al.	1440, Retrospective analysis of data from 18 RCTs	Type 1 diabetes = 15 studies Type 2 diabetes = 4 studies	To understand the relationship between time in range and HbA1c	TIR of 70% corresponded with A1C of 6.7% Every 10% increase in TIR = 0.8% (8.7 mmol/mol) A1C reduction	r = −0.84

Abbreviations: RCT, randomized controlled trial; TIR, time in range.

blood glucose and level 1 hyperglycaemia.[62] A subsequent study by Xing et al. provided similar findings.[63] The aforementioned determinants defining a minimum valid CGM dataset have been used in clinical trials.[64] However, a recent analysis of people with type 2 diabetes who were not using insulin found that a CGM wear duration of 7–10 days might be sufficient to accurately estimate TIR.[65] They utilized CGM data from a randomized trial to compute TIR by sequentially adding daily CGM data until the cumulative TIR values for the glucose ranges of 3.9–7.8 mmol/L (70–140 mg/dL) and 3.9-10 mmol/L (70–180 mg/dL) stabilized to ±2% of the final values. They found that ranges of 3.9-10 mmol/L stabilized within 7 ± 3 days and ranges 70–140 mg/dL stabilized within 10 ± 3 days.[65] The duration of wear may be even lower in type 2 diabetes and is a further advantage of TIR use in clinical trials to obtain results in a shorter timeframe.[63,65] Recent studies have shown significant improvements in the accuracy of CGM systems. Newer CGM models demonstrate enhanced performance compared to previous generations, with reduced mean absolute relative difference (MARD) and improved reliability.[66] A novel subcutaneous glucose sensor exhibited consistent accuracy over 10 days of wear, with an overall MARD of 9.6% and minimal risk associated with glucose discrepancies.[67] Advanced calibration algorithms have also contributed to accuracy improvements.

The following are 3 major supportive factors for TIR as an outcome measure for type 2 diabetes trials:

4.2.1 | Correlation of TIR and HbA1c

The use of TIR has been validated in several studies as it correlates well with HbA1c (Table 2). Beck et al. performed a cross-sectional longitudinal analysis of datasets from four clinical trials that assessed the effectiveness of CGM in 545 participants with type 1 diabetes. All participants had a HbA1c measured at baseline and 6 months. They found that a TIR of 70% reflected an average HbA1c of 7% (53 mmol/mol) with a moderate correlation ($r = -0.67$) using Spearman partial correlation analysis.[70] A 10% increase in TIR correlated with a 0.5% reduction in HbA1c. Importantly, they demonstrated that a given TIR corresponded to a wide range of possible HbA1c levels, further highlighting the limitations of HbA1c and the need for TIR to be incorporated into standard practice as a direct measure of glycaemia. In comparison, a correlation analysis from 18 randomized controlled trials that reported paired HbA1c and %TIR metrics in people with type 1 and type 2 diabetes ($n = 1137$) found a strong correlation ($r = -0.84$) between HbA1c and TIR using linear regression analysis and Pearson's correlation coefficient.[71] The authors reported that every absolute 10% change in TIR was associated with a 0.8% (9 mmol/mol) change in HbA1C. The differences in these values between both studies were attributed to the differences in the number of studies analysed, the population characteristics and methods of blood glucose measurements. Beck et al.[70] analysed 4 randomized trials using CGM in people with type 1 diabetes, whereas Vigersky et al[71] analysed 18 randomized trials with data over a 10-year time period with CGM and self-monitoring blood glucose in both type 1 and type 2 diabetes. It could be argued that Vigersky et al[71] have a more robust dataset representative of a wider population of people with diabetes. However, the majority of the population in both studies was Caucasian, and since the relationship of mean blood glucose to HbA1c differs by ethnicity, it may not apply to the non-Caucasian population. Neither study specified whether people with kidney disease were included, which could lead to falsely lower HbA1c levels.[72] Additional prospective studies are required in this area. These two correlation analyses were carried out in a population with Type 1 diabetes.

4.2.2 | Association between TIR and diabetes complications

Reduced TIR is associated with increased risk of microvascular complications. A retrospective analysis by Beck et al. involving 1440 participants from the DCCT estimated TIR based on seven daily blood glucose measurements every three months for a year.[73] Participants with a TIR <30% had a significantly higher incidence of retinopathy compared to those with TIR ≥50% (38% vs. 8%). Each 10% reduction in TIR was associated with a 64% increased risk of retinopathy. Additionally, 27% of those with a TIR <10% developed microalbuminuria, compared to 3% of those with a TIR ≥70%. While this study highlights an association between TIR and microvascular complications, the data were based on limited seven-point finger-prick measurements, which may not fully capture long-term TIR trends.

A study of 3262 people with type 2 diabetes found that reduced TIR was linked to increased diabetic retinopathy severity, but when adjusted for HbA1c, no significant difference was observed.[74] However, reduced TIR remained significantly associated with the degree of microalbuminuria, even after adjusting for HbA1c. Unlike the previous study that estimated TIR from blood glucose measurements, this study used real-time CGM for 3 days. Shah et al.'s 7-year longitudinal analysis confirmed the association between TIR and incident diabetic retinopathy.[75] As outlined in a recent systematic review by Yapanis et al., other studies have also demonstrated higher TIR was associated with reduced risk of albuminuria, retinopathy, cardiovascular disease mortality, all-cause mortality and abnormal carotid intima-media thickness.[76–79] The association between TIR and both microvascular and macrovascular complications is becoming increasingly established and has led to increasing recognition as an important outcome measure in diabetes research, which has been well summarized in a commentary by Beck.[80]

4.2.3 | Benefits of other CGM metrics reported along with TIR

TIR correlates poorly with metrics related to hypoglycaemia risk such as TBR and CV. The international consensus statement by Battelino et al.[64] recommends that all CGM data should be included in the final analysis. Reporting TIR along with metrics of hypoglycaemia, including Level 1 and Level 2 TBR, can be valuable especially in trials involving populations at risk of hypoglycaemia or interventions that directly reduce glucose such as sulfonylureas therapy, exercise or insulin.

A United Kingdom database of 8655 patients with diabetes reported that 7.3% of people with type 2 diabetes on insulin therapy had at least one episode of severe hypoglycaemia—a comparable figure to people with Type 1 diabetes (7.1%).[81] An IQVIA publication on a CORE diabetes model simulated clinical outcomes and costs for people with diabetes and demonstrated that an improvement in TIR to >80% and a reduction in hypoglycaemic events by up to 40% can lead to a reduction in costs of $6.7–9.7 billion over 10 years in USA.[82] Type 2 diabetes is more prevalent than type 1 diabetes, and including these metrics as part of clinical trials will allow for easier detection of hypoglycaemia and overall improvement in healthcare costs.

There is no consensus on a clinically meaningful TBR measure, which likely depends on an individual's frailty and comorbidities. ICTR guidelines suggest targets of <4% time in hypoglycaemia (<3.9 mmol/L; 70 mg/dL) and <1% time in severe hypoglycaemia (<3.0 mmol/L; 54 mg/dL). An observational CGM study in people with type 2 diabetes found that 49.1% had at least one hypoglycaemic episode, with 75% being asymptomatic, which would have been missed using HbA1c alone.[83] The 4-T trial comparing different insulin regimens in people with type 2 diabetes did a subgroup analysis of the frequency of low-glucose events using CGM with that of self-reported hypoglycaemic events and found CGM-detected hypoglycaemia was several folds higher than self-reported hypoglycaemia and highlighted the under-reporting and potential hypoglycaemia unawareness in T2D trials.[84] Further observational studies have

shown CGM metrics including TBR and CV are more predictive of hypoglycaemia compared to HbA1c alone, which does not capture GV well.[85,86] A large observational study showed hypoglycaemia was common at all levels of HbA1c but patients with HbA1c <6% or ≥9% appeared to be at highest risk for severe hypoglycaemia.[87] Hypoglycaemia can be associated with unfavourable health outcomes including a higher risk of falls, fractures, cardiovascular events and mortality.[87] A recent cross-sectional study in patients with type 2 diabetes has shown patients on insulin and sulfonylureas, with a HbA1c <7%, had a significantly higher TAR and TBR compared with those not treated with those agents.[86] This provides a further advantage in using TIR as an outcome measure, especially for these hypoglycaemia-inducing agents, given other CGM metrics including TBR are always to be reported along with it.

5 | LIMITATIONS OF TIR AS AN OUTCOME MEASURE

TIR as a clinical trial metric does have some limitations. TIR strongly inversely correlates with hyperglycaemia ($R = -0.886$); however, it does not represent hypoglycaemia.[57] Therefore, TIR as a clinical trial outcome metric should provide a robust assessment of chronic complication risk, but not of hypoglycaemia.

To address this limitation, Klonoff et al.[88] have proposed a Glycaemic Risk Index (GRI) which represents a composite score weighting very high and very low glucose levels that may be used as a clinical trial outcome to assess the risk for chronic complications due to exposure to elevated glucose levels and also the risk for hypoglycaemia. 330 expert diabetologists from six continents were invited to rank a dataset of 14-day CGM tracings from 225 adults with diabetes using metrics including TBR and TAR to develop this equation. The association of GRI with DKA risk has yet to be defined.

However, even a construct such as GRI cannot detail all of the insights provided by the multiple metrics included in the standardized CGM report required to guide clinical decisions. For example, the ambulatory glucose profile (AGP) will provide unique insights regarding patterns of glycaemia according to the time of day, which are essential to clinical decision-making. Other metrics, including CV, GMI, TAR and TBR, provide complementary information that can be used to guide further management; however, these are less validated as outcome measures so far. Ultimately, however, even a review of all of the summary metrics included in a standardized report may not be sufficient, and it may be necessary to assess glycaemic patterns on individual days while accounting for the circumstances under which they occur in order to implement fully informed clinical decisions.

An additional advantage of HbA1c as an outcome measure is that it has been internationally standardized, including the measurement, reference system and reporting according to the International Federation of Clinical Chemistry and Laboratory Medicine (IFCC) standards.[89] In contrast, studies have shown there are discrepancies in glycaemic metrics derived from different CGM models,[90,91] and there is no standardization available as yet, making this a further limitation.

HbA1c as an outcome measure requires a single blood sample that can be readily obtained and is inexpensive to process. In contrast, TIR as an outcome measure incurs a significant cost. A cost-effectiveness trial in 2018 has shown CGM devices can cost $15.20 USD/day.[92] This financial burden is especially pronounced in countries with limited research funding, where the allocation of resources toward advanced technologies may not be feasible. Additionally, smaller-scale trials or studies conducted by independent researchers often face significant challenges in securing the necessary funding to incorporate CGM into their protocols. These economic barriers not only limit the widespread adoption of TIR as a standard outcome measure but also contribute to disparities in diabetes research and care, potentially excluding underfunded regions and populations from advancements based on this metric. However, the cost-effectiveness of CGM has been demonstrated in trials, with a threshold of $100,000 per quality-adjusted life year (QALY) in type 1 diabetes.[92] In insulin-treated type 2 diabetes, CGM offers clinical benefits and favourable economic outcomes, with a UK study reporting an incremental cost-effectiveness ratio of £3684/QALY.[93,94] Studies specifically looking at the cost-effectiveness of CGM over HbA1c for clinical trials are yet to be established. Over time, we can hope that advancements in technology and increased accessibility will drive down the cost of CGM, making its valuable metrics more widely available for research and clinical practice.

Additional limitations include CGM devices which may not be readily accessible, where sensors and the processing of data is not standardized, and where the generation of a meaningful dataset may take 2 weeks. CGM devices vary in their accuracy particularly on Day 1 post insertion due to local injury at the insertion site, which can induce an inflammatory reaction that reduces local glucose bioavailability.[95] The consistent use of a single CGM device with standardized insertion procedures in both control and intervention groups will address these issues.

Finally, while there are increasing data, there are no long-term prospective randomized controlled trials that have validated the association between TIR and diabetes macrovascular or microvascular complications. Given the very close relationship of TIR and HbA1c, it is unlikely that a study such as UKPDS will be repeated with TIR incorporated as an outcome measure. It is more likely that post-marketing observational analyses using information from the very large platforms to which CGM devices are uploaded will provide confirmatory evidence of the relationship of TIR with chronic complication development.

6 | INTERPRETING TIR CHANGES IN CLINICAL TRIALS

6.1 | International consensus statement on interpretation of clinically meaningful TIR changes

A recent international consensus statement by Batellino et al. provides recommendations on the use of CGM and its metrics in clinical

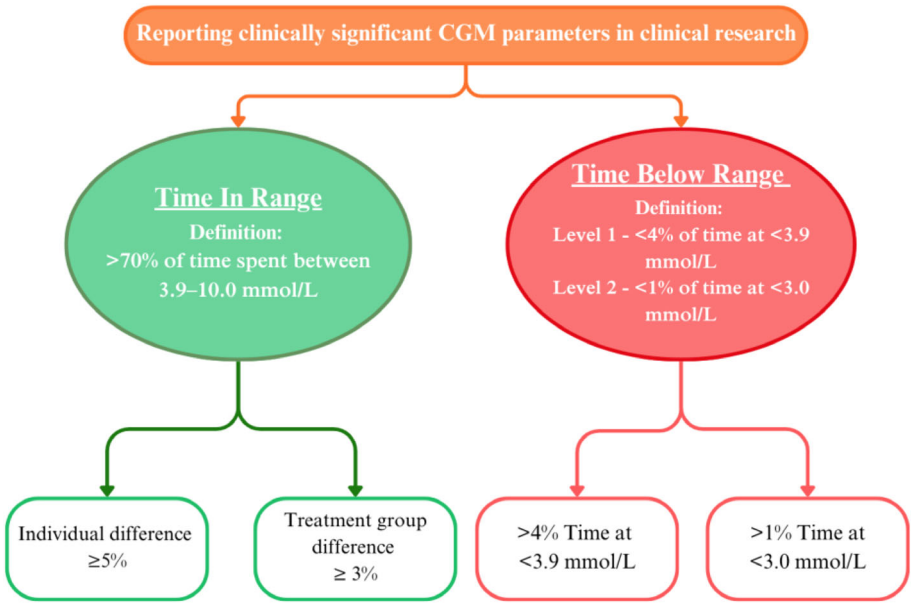

FIGURE 3 Reporting of clinically significant time in range and time below range outcomes in clinical trials – recommendations from the International Consensus of Time in Range (ICTR). Individual difference = ≥5% change in time in range in an individual participant in a study or clinical trial is considered clinically significant. Treatment group difference = ≥3% difference in the time in range between two groups in a clinical trial or study is considered clinically significant.

trials for type 1 and type 2 diabetes.[3] They encourage the use of TIR as an outcome measure given it is instantly sensitive to dietary, lifestyle and pharmacological modifications that can be seen in a clinical trial environment as well as the association with diabetes complications as outlined above. Battelino et al.[3] have also made recommendations on the interpretation of clinically meaningful TIR targets and changes in TIR following an intervention (Figure 3). 'A difference of ≥5% (absolute percentage points) in TIR is considered clinically meaningful for an individual participant in a clinical study'.[3] They based this conclusion on the DCCT trial retrospective analysis of 7-point blood glucose monitoring study outlined above, that related the change of percentage TIR to a clinically meaningful HbA1c and diabetes complications.[73] They found that the difference in mean TIR between those who developed retinopathy and microalbuminuria and those who did not was 10–12%, corresponding to an HbA1c difference of 1.0–1.4%. Although TIR differences of 5% were not analysed, it is plausible that the international consensus panel chose it as a more conservative measure. In clinical trials, a HbA1c improvement of ≥0.5% with a therapeutic intervention is considered to be clinically significant according to the ADA and NICE guidelines[96,97] and therefore the correlation of HbA1c and TIR found by Vigersky et al.,[71] ≥0.4%–0.5% would correspond to a change in TIR of ~5%. In terms of study populations, a between-group difference of ≥3% is considered clinically significant, and studies can be adequately powered to detect this. This was based on consensus opinion from the expert panel of the ICTR.

6.2 | Trials looking at TIR as an outcome measure in Type 2 diabetes

Table 1 summarizes recent meta-analyses and randomized trials using TIR as a primary or secondary outcome. A systematic review and meta-analysis by Karakasis et al.[19] of nine randomized trials comparing once-weekly versus once-daily insulin analogues found that once-weekly insulin significantly increased TIR (MD 3.54%, 95% CI 1.56, 5.53; $p = 0.005$), meeting ICTR's clinically meaningful threshold (>3%). However, HbA1c reductions (MD 0.13%, 95% CI 0.23, 0.03; $p = 0.08$) were neither statistically nor clinically significant.[19] The once-weekly insulins were associated with higher odds of level 1 hypoglycaemia, an important consideration to make when prescribing this insulin for a higher hypoglycaemia risk population.

A randomized trial comparing dapagliflozin and gliclazide MR in 135 participants with uncontrolled type 2 diabetes found that dapagliflozin increased TIR by 24.9%, compared to 17.4% in the gliclazide group—a clinically significant 7.5% difference based on ICTR recommendations.[48] However, HbA1c showed no significant change from baseline in either group. While TBR was not compared due to most values being zero, incident hypoglycaemic episodes were significantly higher in the gliclazide group (25.0% vs. 2.2%, $p = 0.001$). The incidence of hypoglycaemia was defined as either at least 15 continuous minutes of CGM readings ≤3.9 mmol/L or participant-reported hypoglycaemia, which were symptomatic episodes reported at each study visit or additionally measured glucose ≤3.9 mmol/L.

Both studies were greater than 3 months in duration, making HbA1c valid to use. The two studies above highlight the ability of TIR as a metric of glycaemic quality to provide a level of precision when assessing exposure to hyperglycaemia above that of HbA1c in addition to the wealth of information provided by other CGM metrics relating to hypoglycaemia, GV and patterns across the diurnal cycle.

Several trials using TIR as a primary outcome have shown alignment with HbA1c outcomes. A randomized trial of liraglutide in 124 participants with type 2 diabetes on multiple daily insulin injections (MDI) found a significantly higher TIR in the liraglutide group (66.6% vs. 48.3%, $p < 0.001$) and a corresponding HbA1c reduction (57.8 vs. 68.7 mmol/L, $p < 0.001$). Time in hypoglycaemia (<3.9 mmol/

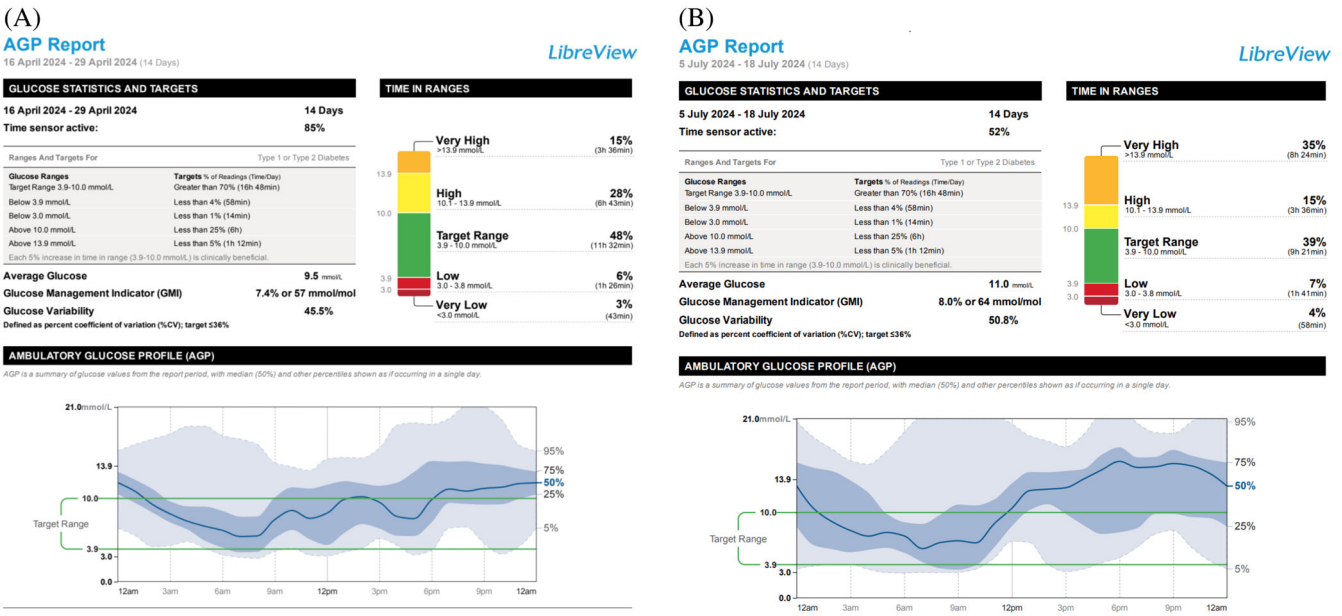

FIGURE 4 (A) An ambulatory glucose profile on LibreView CGM demonstrating major glycaemic fluctuations with a reasonable HbA1c. (B) An ambulatory glucose profile on LibreView CGM demonstrating major glycaemic fluctuations with a reasonable HbA1c.

L) was similar between the groups.[49] Another study by Kawaguchi et al. on 36 patients with type 2 diabetes compared insulin degludec/liraglutide and insulin glargine/lixisenatide, used TIR as a primary outcome measure and found no significant differences between groups in TIR or HbA1c.[15] The SWITCH PRO trial by Goldenberg et al. comparing insulin glargine to insulin degludec in patients with type 2 diabetes and ≥1 hypoglycaemia risk factor reported a slightly higher TIR for degludec (72.1% vs. 70.7% for glargine), with a small but statistically significant HbA1c difference (7.1% vs. 7.2%).[44] They also found degludec had a lower nocturnal TBR compared with glargine and significantly lower nocturnal hypoglycaemic episodes. This demonstrates how TIR can provide complementary insights to HbA1c by providing the TBR metric.

Recent trials have used TIR as the primary outcome without reporting HbA1c differences. A crossover randomized trial with 24 patients with type 2 diabetes compared the efficacy of insulin degludec/aspart (IDegAsp) and insulin degludec/liraglutide (IDegLira) in managing postprandial glucose.[35] The study found a higher TIR in the IDegLira group (86.3% vs. 76.3%, $p = 0.009$) and lower postprandial glucose levels at breakfast and lunch, with no significant differences in TBR. The use of CGM allowed for a detailed comparison of postprandial glucose and TIR, offering valuable insights beyond HbA1c. The increasing use of TIR provides additional, clinically significant data on interventions.

6.3 | What are the other alternatives to TIR?

GMI and TIR can provide complementary insights into glycaemic patterns. Discordance between TIR and GMI should prompt further exploration of the GV and TBR values. For example, Figure 4A shows the ambulatory glucose profile of a case with a reasonable GMI of 7.4% but below target TIR of 48%. Further evaluation of supporting CGM metrics reveals significant GV of 45.5%, including both high (15%) and low (3%) glucose excursions. Unlike HbA1c, GMI is unaffected by hemoglobinopathies or anaemia, and studies in type 1 diabetes have shown good alignment with lab-measured HbA1c, as long as no major events have influenced blood glucose levels.[62] However, other studies have shown it is identical to Hba1c only 19% of time.[98] A prospective study looking at GMI in 144 adults with obstructive sleep apnoea and type 2 diabetes not using insulin found only a moderate correlation between HbA1c and GMI ($r = 0.68–0.71$), with 36%–43% of participants having a ≥0.5 percentage point difference between the metrics.[9] This difference needs to be considered to avoid hypoglycaemia, as GMI has not yet been fully validated as an outcome measure or linked to long-term complications.

Another alternative to TIR is a newer metric named time in tight glucose range (TITR), which is defined as a glucose level between 3.9 and 7.8 mmol/L (70–140 mg/dL) with a target recommendation of >50% of time per day. This range was based on studies in people without diabetes that have shown they spend 96% of their time between 3.9 and 7.8 mmol/L; therefore, it is suggested this would be a more accurate measure of euglycemia.[99] This new range is yet to be incorporated into consensus recommendations; however, some studies have shown its correlation with TIR,[100,101] and HbA1c.[102] A retrospective study of 13 461 individuals with type 1 diabetes using the Medtronic 780G insulin pump reported TITR targets of ~45%, ~50% and ~55%, correlating with GMI estimates of <7.0%, <6.8% and <6.5%, respectively, making >50% a reasonable target.[102] TITR has been associated with diabetes-related complications. A recent cross-sectional analysis of 1067 individuals with type 1 diabetes found that each 10% increase in TITR was linked to a lower risk of microvascular

complications (OR 0.762; 95% CI 0.679–0.855; $p < 0.001$) and stroke, even after adjusting for HbA1c[103] This highlights TITR's potential as a valuable marker for long-term diabetes outcomes, though its limitations align with those of TIR, as outlined above.

Glycaemic Risk Index (GRI) is another more recent composite metric that can be considered an outcome measure. A benefit of GRI is that it gives more importance to the risk of hypoglycaemia compared to the risk of hyperglycaemia, which is an important component TIR lacks. A recent cohort study by Wang et al. in 1204 adults with type 2 diabetes without diabetic retinopathy found that for each 1 standard deviation increase in GRI, there was a 20% increase in retinopathy.[104] Further randomized trials and longer-term studies are required to validate GRI with other microvascular and macrovascular diabetes complications to consider it as a primary outcome measure.

The final outcome measure to consider is glycaemic variability (GV), which reflects the degree of glucose fluctuation and is measured by %CV. A recent analysis of CGM data from 2559 patients with type 2 diabetes revealed a strong inverse correlation between TIR and estimated HbA1c (eHbA1c) ($r = -0.908$). However, this relationship was influenced by glycaemic variability (GV). Specifically, in patients with unstable glucose levels (CV >36%), TIR exhibited high variability, suggesting that GV may mediate the relationship between TIR and eHbA1c.[105] This highlights the potential importance of considering GV in clinical assessments. GV has been strongly associated with the risk of hypoglycaemia, particularly during insulin therapy,[106] and is linked to an increased risk of adverse cardiovascular outcomes, primarily due to hypoglycemia.[107] While GV is a useful marker for hypoglycaemia and can be considered alongside TIR for a comprehensive view of overall glycaemic management, it does not effectively capture hyperglycaemia on its own. Additionally, GV has not yet been definitively associated with long-term diabetes complications, warranting further studies.

7 | CONCLUSIONS

We propose that TIR should be considered a primary research outcome for trials in people with type 2 diabetes where CGM is available. Given that the international consensus defines TIR targets similarly for both T1D and T2D, most arguments presented in this manuscript broadly apply to both conditions. TIR offers key advantages: it captures short-term glycaemic fluctuations, remains reliable in those with hemoglobinopathies or anaemia, supports personalized glycaemic assessment and correlates with HbA1c. Other CGM glycaemic metrics generated simultaneously at no extra cost or effort provide important insights which HbA1c does not. Leading global endocrinology and diabetes associations back its use as a validated outcome measure. As technology advances with less intrusive, more accurate, and less expensive devices, TIR on CGM is poised to become the gold standard for glycaemic assessment, driving better clinical outcomes. However, additional randomized trials are essential to establish its association with diabetes complications and form guidelines for its use in type 2 diabetes research. Other metrics still need validation before they can be widely adopted in diabetes studies.

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CONFLICT OF INTEREST STATEMENT

The authors declare that they have no conflict of interests.

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DATA AVAILABILITY STATEMENT

Data sharing not applicable to this article as no datasets were generated or analysed during the current study.

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SUPPORTING INFORMATION

Additional supporting information can be found online in the Supporting Information section at the end of this article.

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