Time in Range State of the Evidence

A collection of peer-reviewed articles and published abstracts demonstrating the impact of the novel diabetes metric Time in Range.

By The diaTribe Foundation &
The Time in Range Coalition

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Time in Range: State of the Evidence Overview

The current gold standard metric for diabetes management, hemoglobin A1c (A1C), is useful for estimating average blood glucose levels and predicting future complications but does not provide people with diabetes sufficient information to best manage their condition day to day. Nor does it provide healthcare professionals the specific information needed for medication adjustments. The diaTribe Foundation and the Time in Range Coalition believe that time in range (TIR), including time below range (TBR) and time above range (TAR), as measured by a continuous glucose monitor (CGM), should be used in addition to A1C to inform individual and population-level diabetes care and management as well as regulatory decision making.

CGM and the metrics it provides (TIR, TBR, and TAR) have added value in clinical, research, and regulatory settings far beyond A1C as demonstrated in this growing body of evidence.Expert consensus recommendations and clinical practice guidelines advocate for the use of these metrics as a complement to A1C in both patient care and clinical research (Agiostratidou et al., 2017; American Diabetes Association, 2021; Battelino et al., 2019; Battelino et al., 2023; Danne et al., 2017; Grunberger et al., 2021; Mohan et al., 2023; Spanakis et al., 2023).

Continuous glucose monitoring is shown to be superior to self-monitoring blood glucose (SMBG) in helping people with diabetes monitor and improve their glycemic control, specifically in improving their TIR, reducing TAR and glucose variability, and lowering their risk of hypoglycemia (Bolinder et al., 2016; Petrie et al., 2017; Beck et al., 2017; Lind et al., 2017; Dunn et al., 2018; Hood et al., 2020; Thabit et al., 2020; Maiorino et al., 2020; Lee et al., 2021; Kieu et al., 2023; Beck et al., 2022; Ajjan et al., 2023; Jancev et al., 2024; Lind et al., 2024; Uhl et al., 2024; Ferreira et al., 2024; Kim et al., 2024; Lever et al., 2024; Reed et al., 2024). Further, emerging evidence directly ties CGM use to lower risk of developing diabetic retinopathy and proliferative diabetic retinopathy, even after adjusting for A1C (Liu et al., 2024). Unlike SMBG, which requires people with diabetes to collect at least seven fingersticks a day to effectively calculate their TIR, continuous glucose monitoring automatically measures glucose levels every one to five minutes. Data shows people with diabetes using SMBG do not test as regularly as advised, further reducing the data points available to guide management adjustments without CGM (Hansen et al., 2009).

There are many confounding factors known to undermine the accuracy of A1C which do not affect TIR, making it a more consistent indicator of glycemia (Nayak et al., 2019; Shepard et al., 2015). For example, A1C has been shown to frequently overestimate glycemia in African

American individuals, increasing the risk of premature diagnoses and overtreatment (Herman et al., 2007; Bergenstal et al., 2017; Karter et al., 2023; Wolffenbuttel et al., 2013). Conversely, evidence suggests A1C underestimates glycemia in patients with kidney disease (Kim et al., 2015; Li et al., 2014; Ng et al., 2010; Peacock et al., 2008; Sharif et al., 2010; Speeckaert et al., 2014; Galindo et al., 2024). Specifically, use of CGM in patients with diabetes and end-stage kidney disease identified significant undiagnosed hyperglycemia not captured by A1C (Kaminski et al., 2024). Other factors found to impact the accuracy of A1C include use of certain medications (Mitchell et al. 2018), anemia (Misra et al., 2018), age (Dubowitz et al., 2014), and other various commonly co-occuring conditions.

Additionally, research shows that A1C and TIR have a strong, negative correlation, indicating that TIR may predict risk of long-term complication in parallel to A1C. (Vigersky & McMahon, 2019; Beck et al., 2019; Rodbard, 2020; Eliasson et al., 2024; Vandenbempt et al., 2024). In fact, there is mounting evidence of the association between TIR and the risk of microvascular and macrovascular complications, in some cases independent of A1C (Beck, 2023; Guo et al., 2020). In a cross-sectional study of patients with type 2 diabetes, TIR was significantly associated with the prevalence and severity of diabetic retinopathy (DR) even after adjusting for clinical risk factors, including A1C (Lu et al. 2018). Subsequent studies have reaffirmed the association between TIR and DR in type 2 diabetes (Raj et al., 2022; Sheng et al., 2023; Yoo et al., 2020; Lu, Home, & Zhou 2020; Pratama et al., 2024). Analysis of the Diabetes Control and Complications Trial longitudinal data similarly showed TIR was strongly associated with the risk of DR and development of microalbuminuria in type 1 diabetes—in fact, for each 10-percentage point reduction in TIR, the risk of DR progression increased 64 percent and risk of adverse microalbuminuria outcome increased 40 percent (Beck et al. 2019). Similarly, a more recent study found that every 5 percent decrease in TIR increased odds of incident diabetic retinopathy by 18% (Shah et al., 2024). Strong associations have also been identified between TIR and diabetic peripheral neuropathy (Li et al. 2020; Mayeda et al. 2020; Yoo et al. 2020). In patients with type 2 diabetes and moderate-to-severe chronic kidney disease, lower TIR and higher glucose management indicator (GMI) were associated with symptoms of diabetes peripheral neuropathy (DPN). In contrast, the study found no significant association between A1C and DPN symptoms (Mayeda et al. 2020). In a cross-sectional study of individuals with type 2 diabetes, there was an association between greater TIR and reduced cardiovascular autonomic neuropathy (CAN) independent of A1C and glucose variability (Guo et al. 2020). The same study found no difference in A1C among different stages of CAN.

Further, increased TIR has been cross-sectionally associated with a lower risk of abnormal carotid intima-media thickness, a marker for cardiovascular disease (Lu, Home, & Zhou 2020; Lu et al. 2020). A longitudinal study showed that an increase in TIR was significantly associated with a decrease in albuminuria among type 1 patients with a history of albuminuria, over a year-long period (Ranjan et al. 2020). A strong correlation has also been found between lower TIR and increased risk of all-cause and cardiovascular disease-related morality (Lu et al. 2020). In addition to risk indicated by TIR, acute daytime TAR and TBR are associated with increased risk of cardiac arrhythmias (Hagelqvist et al., 2023). This growing evidence demonstrating time in range is predictive of numerous micro- and macrovascular complications underscores the metric's relevance in both diabetes management and clinical research.

The use of CGM and TIR has also been correlated to improved psychosocial outcomes. Across types of diabetes, CGM initiation is tied to reduced diabetes distress and fear of hypoglycemia (Gilbert et al., 2021). Type 1 patients using CGM report positive psychosocial outcomes including lower levels of stress and improved sleep (Burckhardt et al. 2018; Nana et al. 2019; Volčanšek Š et al. 2019; Pinsker et al. 2021). This is especially true for children with type 1 and their parents, in particular, who report reduced fear of hypoglycemia using remote monitoring (Burckhardt et al. 2018). In a dQ&A survey of 3,461 people with diabetes, most people with type 1 ranked TIR, of all the outcomes used to assess diabetes therapies, as having the biggest impact on daily life (Runge et al. 2018). Spending more time in range and less time in severe hyperglycemia has also been shown to improve mood (Polonsky & Fortmann 2020; Ehrmann et al., 2021). In contrast, lower time in range is associated with lower quality of life, worse diabetes-related stress, and lower satisfaction with treatment (Díaz-Soto, 2024). In type 2 diabetes, a qualitative study showed CGM use not only supported measurable changes in diet, physical activity, and medication adherence, but also enhanced individuals' feelings of self-efficacy, control, and motivation around their diabetes management (Clark et al., 2024). These findings reveal the importance of using TIR when exploring the psychosocial and behavioral impact of diabetes and assessing the safety and efficacy of therapies and devices used in diabetes management.

Beyond improving quality of life outcomes, CGM and TIR may also provide substantial cost savings (Shi & Hellmund 2020; Roze et al. 2021; Jendle et al., 2021; Norman et al., 2022; Jiao et al., 2022). Both intermittently- scanned and real-time CGM have been associated with reduced hospitalizations and emergency department visits among individuals with both type 1 and type 2 diabetes, reducing costly utilization (Shi & Hellmund, 2020; Reaven et al., 2023; Triki et al., 2021). Intermittently-scanned CGM (isCGM) is estimated to save roughly 50% in

average costs associated with severe hypoglycemia in both type 1 and type 2 patients compared to SMBG, (Shi & Hellmund 2020). Similarly, a study in the United States found average per-patient-per-month diabetes-related medical costs decreased-$424 (95% confidence interval [CI] -$816 to -$31, P= 0.035) among patients with type 2 diabetes after initiating rtCGM (Norman et al., 2022). TIR derived from CGM appears to be a useful indicator of cost-saving improvements in management, as well. A report released by the IQVIA Institute for Human Data Science reported that improvements in TIR and reducing hypoglycemic events by up to 40% in type 1 patients were estimated to reduce the risk of developing diabetes-related complications, and that reduction would lead to an estimated $6.7–$9.7 billion decline in costs over a 10-year period. Moreover, improving TIR from 58% to 70% was estimated to yield a $2.1–$4.2 billion cost reduction. Further increasing TIR to 80% resulted in an estimated additional $1.9–$2.7 billion in savings, for a total cumulative $4–$6.9 billion cost reduction (Aitken et al. 2019). Further research is needed to document the cost-effectiveness of TIR.

The evidence generated to date supports the use of TIR as a clinically meaningful endpoint and the inclusion of TIR in product labeling to aid patients and their healthcare providers in making clinical decisions and choosing individual treatment regimens. In 2023, both the US Food and Drug Administration (FDA) as well as the European Medicines Agency (EMA) published guidance and updated standards for diabetes medication clinical trials. Both publications have been long-awaited and indicate important recognition of the value of TIR and the perspectives of patient-advocate voices like the Time In Range Coalition and the diaTribe Foundation. While we celebrate these steps forward, there is still a tremendous amount of work to be done. We hope that this State of the Evidence will continue to serve as an important educational resource on the science of TIR for patients, clinicians, policymakers, and regulators as we continue our advocacy for improved care and treatment for individuals living with diabetes.

Methodology

Bibliographic databases were searched from 2017 to present to review recent findings in support of the use of TIR in daily diabetes management and as an outcome measure in clinical trials. The following MeSH terms were used; (blood glucose monitoring/methods and time in range or time below range or time above range) or (glucose analysis and time in range or time below range or time above range). Historical search of reference lists of relevant randomized clinical trials, scientific congresses and systematic and narrative reviews were also undertaken. We restricted our search to articles written in English and conducted in humans.

This document is not intended to be a systematic review, but rather a compilation of the most impactful and high-quality research on TIR.

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Validation of CGM Metrics

Peer-Reviewed Publications

a. Advani A. Positioning time in range in diabetes management. *Diabetologia*. 2020;1–11.
    - This review discusses the role of time in range in clinical diabetes care and as an endpoint in clinical trials, given the emerging correlation to complications.

b. Aernouts C, Beldé SPW, Lambrechts J, et al. Metabolic dysfunction-associated steatotic liver disease is associated with worse time in ranges in type 1 diabetes. *Diabetes Obes Metab*. 2024;26(9):3781-3790. doi:10.1111/dom.15723
    - This cross-sectional study investigated the relationship between CGM metrics and metabolic dysfunction-associated steatotic liver disease (MASLD) in type 1 diabetes.
    - Among 302 participants, MASLD was present in 17% of cases. In those with MASLD, time in range (TIR) (P = .038) and time below range (TBR) (P = .032) were lower and time above range (TAR) was higher (P = .006), whereas HbA1c did not reach significance (P = .068).
    - Multivariable logistic regression analysis showed that TIR, TAR, TBR and GMI were associated with MASLD independently from metabolic syndrome components.

c. Agiostratidou G, Anhalt H, Ball D, et al. Standardizing Clinically Meaningful Outcome Measures Beyond HbA1c for Type 1 Diabetes: A Consensus Report of the American Association of Clinical Endocrinologists, the American Association of Diabetes Educators, the American Diabetes Association, the Endocrine Society, JDRF International, The Leona M. and Harry B. Helmsley Charitable Trust, the Pediatric Endocrine Society, and the T1D Exchange. *Diabetes Care*. 2017;40(12):1622-1630. doi:10.2337/dc17-1624
    - In this consensus report, the the American Association of Clinical Endocrinologists, the American Association of Diabetes Educators, the American Diabetes Association, the Endocrine Society, JDRF International, The Leona M. and Harry B. Helmsley Charitable Trust, the Pediatric Endocrine Society, and the T1D Exchange define and recommend the use of clinically meaningful outcome beyond HbA1c (including hypoglycemia, hyperglycemia, time in range, diabetic ketoacidosis, and patient-reported outcomes) in the research, development, and evaluation of type 1 diabetes therapies.

d. Beck RW. The Association of Time in Range and Diabetic Complications: The Evidence Is Strong. *Diabetes Technol Ther*. 2023;25(6):375-377. doi:10.1089/dia.2023.0141

- This review article summarizes existing evidence on the association between CGM-measured time in range and diabetes-related complications. Further, the author concludes that because both TIR and A1C are reflective of hyperglycemia and are highly correlated, and because many studies have now shown the association between TIR and complications, TIR should be considered a clinical relevant metric for patient care and clinically meaningful endpoint for clinical trials.

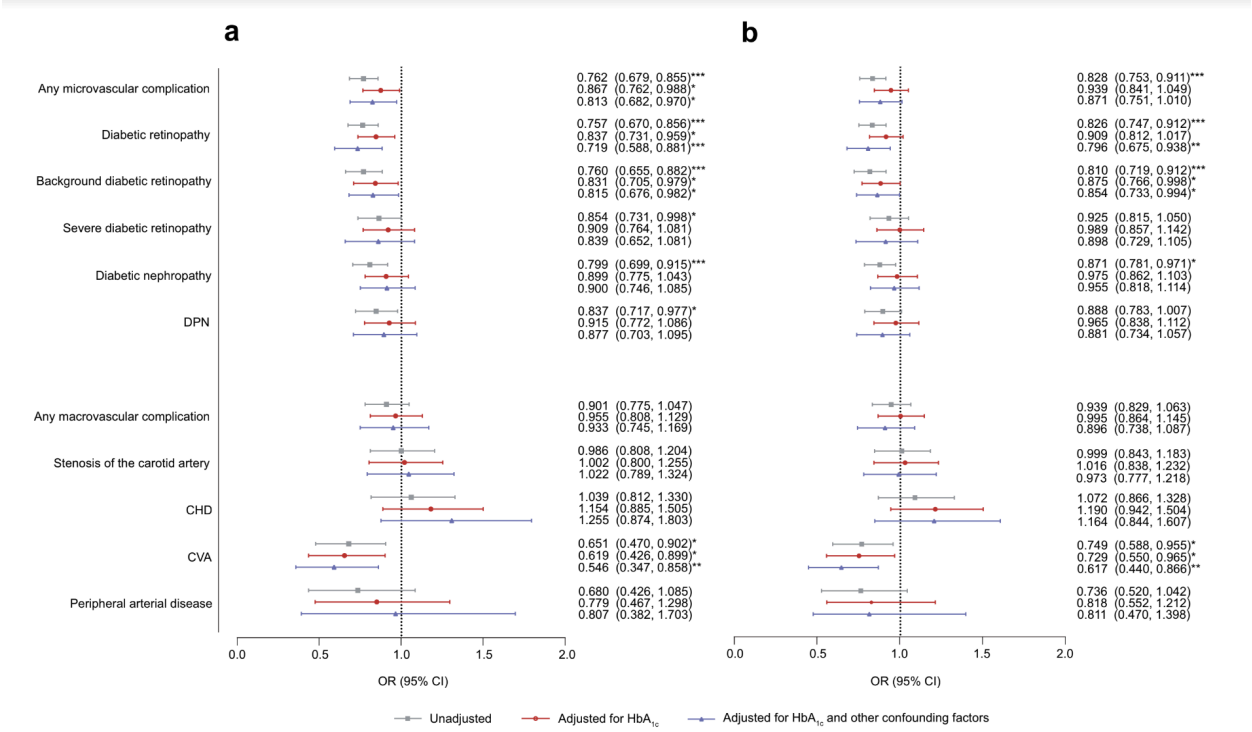
e. Bellido V, Pinés-Corrales P, Villar-Taibo R, Ampudia-Blasco F. Time-in-range for monitoring glucose control: is it time for a change? *Diabetes Research and Clinical Practice*. 2021;177.
   - This review article explores recent evidence supporting the use of time in range in diabetes management, including the metric's link to long-term diabetes complications and the need for individualized targets for specific groups such as older or high-risk individuals, pregnant women.

f. Bergenstal RM, Hachmann-Nielsen E, Kvist K, Peters AL, Tarp JM, Buse JB. Increased derived time in range is associated with reduced risk of major adverse cardiovascular events, severe hypoglycemia, and microvascular events in type 2 diabetes: A post hoc analysis of DEVOTE. *Diabetes Technol Ther*. 2023;25(6):378-383. doi:10.1089/dia.2022.0447
   - This post hoc analysis investigated the association between TIR, derived from 8-point glucose profiles (derived TIR [dTIR]) at 12 months, and time to cardiovascular or severe hypoglycemic episodes in 7637 people with type 2 diabetes in the DEVOTE trial, most of whom were at high risk for cardiovascular events.
   - At 12 months, dTIR was significantly negatively associated with time to first major adverse cardiovascular event ($P = 0.0087$), severe hypoglycemic episode ($P < 0.0001$), or microvascular event ($P = 0.024$).
   - These findings support the recommendation of striving for TIR >70% as a primary target and validate the clinical value of a secondary target of >50%. Additionally, they suggest

g. De Meulemeester J, Charleer S, Visser MM, De Block C, Mathieu C, Gillard P. The association of chronic complications with time in tight range and time in range in people with type 1 diabetes: a retrospective cross-sectional real-world study. *Diabetologia*. Published online May 24, 2024. doi:10.1007/s00125-024-06171-y
   - This retrospective cross-sectional study evaluated the association of chronic complications with time in tight range (TITR: 70–140 mg/dL or 3.9–7.8 mmol/l)

and time in range (TIR: 70–180 mg/dL or 3.9–10.0 mmol/l) in people with type 1 diabetes.

- Among 808 adults with type 1 diabetes, the prevalence of any microvascular complication, diabetic retinopathy, diabetic nephropathy and a cerebrovascular accident decreased with increasing TITR/TIR quartiles.
- After adjustment for HbA1c, TITR was found to be an independent risk factor for any microvascular complication, diabetic retinopathy, background diabetic retinopathy, and cerebrovascular accident
- A 10% increase in TITR or TIR was associated with 23.8 and 17.2% lower incidences, respectively, of any microvascular complication and 34.9 and 25.1% lower incidences, respectively, of cerebrovascular accident.



h. Lu J, Home PD, Zhou J. Comparison of Multiple Cut Points for Time in Range in Relation to Risk of Abnormal Carotid Intima-Media Thickness and Diabetic Retinopathy. *Diabetes Care*. 2020;43(8):e99-e101.

- This cross-sectional study of Chinese hospitalized patients looked at the relationship between TIR and diabetic retinopathy (DR) and carotid intima-media thickness (CIMT).

- Participants included patients with type 2 diabetes and there were 2,893 people included in the analysis. Each participant had only 3-day masked subcutaneous glucose monitoring by a CGM.
- TIRs with the upper limit from 140–150 to 200 mg/dL were all significantly associated with abnormal CIMT and DR.

i. Rodbard D. Metrics to evaluate quality of glycemic control: Comparison of time in target, hypoglycemic, and hyperglycemic ranges with "risk indices". *Diabetes Technol Ther*. 2018;20(5):325-334. doi:10.1089/dia.2017.0416
   - This study aimed to cross-validate metrics for quality of glycemic control, hypoglycemia, and hyperglycemia.
   - Simple readily understandable criteria such as %TIR, %Hypoglycemia, and %Hyperglycemia are highly correlated with and appear to be as informative as “risk indices.”

j. Sheng X, Li T, Hu Y, Xiong CS, Hu L. Correlation between blood glucose indexes generated by the flash glucose monitoring system and diabetic vascular complications. *Diabetes Metab Syndr Obes*. 2023;16:2447-2456. doi:10.2147/DMSO.S418224
   - In this retrospective study, 545 adult patients with type 2 diabetes wore a flash CGM for 7–14 days while hospitalized. Patients were followed for one year after using the flash CGM and reexamined for occurrence of complications including diabetic nephropathy, diabetic retinopathy, diabetic peripheral neuropathy, and carotid atherosclerotic lesions
   - TIR was negatively correlated with HbA1C, CV, SDBG, and amplitude of glycemic excursion (MV)
   - TIR in the diabetic microvascular complication group was significantly lower than that in the non-microvascular complication group, and the difference was statistically significant.
   - TIR <40% was identified as a risk factor for diabetic nephropathy, diabetic peripheral neuropathy, and diabetic retinopathy.
   - The mean TAR in the diabetic nephropathy group was significantly higher than that in the non-diabetic nephropathy group.
   - TAR, CV, SD, MAGE, and HbA1C in the diabetic retinopathy group were significantly higher than those in the non- diabetic retinopathy group.
   - TAR, ABG, CV, SD, MAGE, and HbA1C in the diabetic peripheral neuropathy group were significantly higher than those in the non-diabetic peripheral neuropathy group.

k. Xie P, Deng B, Zhang X, et al. Time in range in relation to amputation and all-cause mortality in hospitalised patients with diabetic foot ulcers. *Diabetes Metab Res Rev*. 2022;38(2):e3498. doi:10.1002/dmrr.3498
    - This retrospective analysis assessed the association of TIR (calculated from seven-point blood glucose profiles) with amputation and all-cause mortality in 303 hospitalized patients with diabetic foot ulcers.
    - Findings show that TIR is inversely associated with amputation and all-cause mortality of hospitalized patients with diabetic foot ulcers, even after controlling for 15 confounding variables.

l. Yapanis M, James S, Craig ME, O'Neal D, Ekinci EI. Complications of diabetes and metrics of glycemic management derived from continuous glucose monitoring. *J Clin Endocrinol Metab*. 2022;107(6):e2221-e2236.
    - This review article synthesizes evidence from 34 studies of microvascular and macrovascular complications in 20,852 people with type 1 and type 2 diabetes. The evidence reviewed showed that glycemic variability and low time in range (TIR) showed associations with all studied microvascular and macrovascular complications of diabetes. Notably, higher TIR was associated with reduced risk of albuminuria, retinopathy, cardiovascular disease mortality, all-cause mortality, and abnormal carotid intima-media thickness. Peripheral neuropathy was predominantly associated with standard deviation of blood glucose levels and mean amplitude of glycemic excursions.

m. Yoo JH, Choi MS, Ahn J, Park SW, Kim Y, Hur KY, et al. Association between continuous glucose monitoring-derived time in range, other core metrics, and albuminuria in type 2 diabetes. *Diabetes Technol Ther*. 2020;22(10):768-776. doi:10.1089/dia.2019.0499
    - This cross-sectional study investigated the association between TIR, hyperglycemia, hypoglycemia metrics, and albuminuria.
    - A total of 866 subjects with type 2 diabetes who underwent 3 or 6 days of CGM and had urinary albumin-to-creatinine ratio (ACR) measurements were retrospectively reviewed.
    - TIR and hyperglycemia metrics are strongly associated with albuminuria in type 2 diabetes.

n. Yoo JH, Kim JH. Time in range from continuous glucose monitoring: a novel metric for glycemic control. *Diabetes & Metabolism Journal*. 2020;44(6):828-839.
    - This review article provides information about the core CGM-derived metrics and provides information on the relationships between these metrics.

TIR and A1C

Peer-Reviewed Publications

a. Al Hayek A, Alzahrani WM, Sobki SH, Al-Saeed AH, Al Dawish M. Comparison of point-of-care and laboratory glycated hemoglobin A1c and its relationship to time-in-range and glucose variability: A real-world study. *Cureus*. 2023;15(1).
    - The study performed a comparison of point-of-care testing for HbA1c vs the standard lab method (Lab HbA1c) and their relationship to TIR and glucose variability (GV) among people with diabetes presented to the outpatient diabetes clinics.
    - This single-center cross-sectional study was carried out on people with diabetes at and above 14 years of age. 97 people total were included.
    - The mean values of Lab-HbA1c and POCT HbA1c were 8.82% and 8.52%, respectively. TIR, TBR, and TAR were 33.47 min (47.78%), 5.44min (8.41%) and 28.8 min (43.81%), respectively.
    - The findings show that TIR and GV can be used as endpoints and valuable parameters for diabetes management.
b. Beck RW, Bergenstal RM, Cheng P, Kollman C, Carlson AL, Johnson ML, et al. The relationships between time in range, hyperglycemia metrics, and HbA1c. *J Diabetes Sci Technol*. 2019;13(4):614-626.
    - Correlations among CGM metrics (TIR 70-180, time >180 mg/dL, time >250 mg/dL, mean glucose, area under the curve above 180 mg/dL, high blood glucose index, and TIR 70-140 mg/dL) were typically 0.90 or greater. Correlations of each metric with A1C were lower (absolute values 0.66-0.71 at baseline and 0.73-0.78 at month 6)
    - Analyses were conducted using datasets from four randomized trials encompassing 545 adults (92% white) with type 1 diabetes (T1D). CGM metrics were calculated and compared with each other and A1C
    - In T1D, CGM measures reflecting hyperglycemia (including TIR and mean glucose) are highly correlated with each other but only moderately correlated with A1C. For a given TIR or change in TIR there is a wide range of possible corresponding A1C values.
c. Bosoni P, Calcaterra V, Tibollo V, Malovini A, Zuccotti G, Mameli C, et al. Exploring the Inter-subject variability in the relationship between glucose monitoring metrics and glycated hemoglobin for pediatric patients with type 1 diabetes. *Journal of Pediatric Endocrinology and Metabolism*. 2021; 34(5): 619-625.

- 27 children and adolescents with type 1 diabetes under multiple daily injection insulin-therapy participated in the study. All participants used Abbott's FreeStyle Libre for eight months.
- Time in range and time in target range show a negative relationship with A1C while time above range and time severely above range show a positive relationship.
- This study confirms the relationship between CGM metrics and A1C in pediatrics and highlights the importance of an individualized interpretation of CGM data.

d. Eliasson B, Allansson Kjölhede E, Salö S, Fabrin Nielsen N, Eeg-Olofsson K. Associations Between HbA1c and Glucose Time in Range Using Continuous Glucose Monitoring in Type 1 Diabetes: Cross-Sectional Population-Based Study. *Diabetes Ther.* Published online April 10, 2024. doi:10.1007/s13300-024-01572-z
   - This cross-sectional study explored the relationship between HbA1c and CGM-derived metrics among 27,980 adults with type 1 diabetes in the Swedish National Diabetes Registry.
   - The overall association between HbA1c and TIR was – 0.71 (Pearson's r), with R2 0.51 in crude linear regression and 0.57 in an adjusted model.
   - The correlation between HbA1c and CGM-derived measures of variability were found to be weaker (fully adjusted R2 values were 0.458 between HbA1c and SD; 0.175 between HbA1c and CV; and 0.101 between HbA1c and TBR)

e. Goldenberg RM, Aroda VR, Billings LK, et al. Correlation between time in range and HbA1c in people with type 2 diabetes on basal insulin: Post hoc analysis of the SWITCH PRO study. *Diabetes Ther*. 2023;14(5):915-924. doi:10.1007/s13300-023-01389-2
   - The randomized controlled stage IV SWITCH PRO study analyzed the relationship between TIR derived from CGM and A1C in 419 participants with type 2 diabetes at risk for hypoglycemia following treatment intensification with either insulin degludec or or insulin glargine U100.
   - A moderate inverse linear correlation was observed between TIR and HbA1c at baseline (rs -0.54), becoming stronger following treatment intensification during maintenance periods. Changes in TIR and HbA1c from baseline to end of the first maintenance period were also linearly inversely correlated in the full cohort (rs -0.40) and the subgroup with baseline HbA1c ≥ 7.5% (rs -0.43). This was less apparent in the subgroup with baseline HbA1c < 7.5% (rs -0.17) (p-interaction = 0.07)

- This is one of the first large interventional clinical studies to use TIR as the primary outcome, and supports TIR as a valid clinical indicator of glycemic control

f. Hallström S, Hirsch IB, Ekelund M, et al. Characteristics of continuous glucose monitoring metrics in persons with type 1 and type 2 diabetes treated with multiple daily insulin injections. *Diabetes Technol Ther*. 2021;23(6):425-433. doi:10.1089/dia.2020.0577
   - This study aims to assess differences in levels of hypoglycemia, mean glucose, and TIR in people with type 1 and type 2 diabetes treated with MDI.
   - This study used data from two multicenter randomized control trials (GOLD and MDI-Liraglutide) where 161 people with type 1 diabetes and 124 people with type 2 diabetes treated with MDI were monitored with masked CGM. Researchers compared conventionally-used CGM metrics including mean glucose, the SD of mean glucose, coefficient of variation (CV), mean amplitude of glycemic excursions (MAGE), TIR, TAR, and TBR.
   - While they had similar mean glucose levels, people with type 1 diabetes compared to people with type 2 diabetes treated with multiple daily injections spent considerably more time in hypoglycemia (5.1% vs 1.0%) and have higher glucose variability (CV of 41% vs 28% and SD of 4.4 mmol/l (79 mg/dL) vs 3.0 mmol/l (54 mg/dL)).
   - Participants with type 1 diabetes had higher A1C levels at the same TIR level compared to participants with type 2 diabetes. People with type 1 also spent less TIR than people with type 2 diabetes. Differences found between people with type 1 and type 2 diabetes treated with MDI need to be incorporated into clinical care, trial design, and in CGM guidelines.

g. Hirsch IB, Welsh JB, Calhoun P, Puhr S, Walker TC, Price DA. Associations between HbA1c and continuous glucose monitoring-derived glycaemic variables. *Diabet Med*. 2019; 36(12): 1637-1642.
   - This study examined the association between A1C levels and CGM-derived metrics such as mean glucose value, time in range between 70-180 mg/dL, and time below 70mg/dL.
   - HbA1c was strongly correlated with mean glucose value (r=0.80), time spent with glucose values in the 3.9-10.0 mmol/l range (time in range; r=-0.75) and percentage of glucose values >13.9 mmol/l (r=0.72), but was weakly correlated with the percentage of glucose values <3.9 mmol/l (r=-0.39) or <3.0 mmol/l (r=-0.21).

- These associations suggest that CGM-derived metrics may help guide diabetes therapy efforts in a manner independent of A1C.

h. Lu J, Ma X, Zhang L, Mo Y, Lu W, Zhu W, et al. Glycemic variability modifies the relationship between time in range and hemoglobin A1c estimated from continuous glucose monitoring: A preliminary study. *Diabetes Res Clin Pract.* 2020;161:108032.
   - This study sought to investigate the relationship between A1C and TIR and understand how glycemic variability plays a role.
   - Data from the CGMs of 2559 patients with type 2 diabetes were analyzed.
   - They found that there was a strong correlation between TIR and A1C and that glycemic variability significantly mediates this relationship. Thus, glycemic variability should be taken into account when determining individualized TIR targets.

i. Rodbard D. Continuous glucose monitoring metrics (mean glucose, time above range and time in range) are superior to glycated haemoglobin for assessment of therapeutic efficacy. *Diabetes Obes Metab*. 2023;25(2):596-601.
   - Authors of this study analyzed correlations among CGM metrics from studies of 545 people with T1D, 5,910 people with T2D and 98 people with T1D during pregnancy and the postpartum period.
   - CGM metrics % TAR AND % TIR show much higher correlations with mean glucose than with HbA1c and provide sensitive indicators of efficacy.
   - Mean glucose from CGM may be the best glycemic metric and shows consistently higher correlations with % TAR than with % TIR.

j. Rodbard D. Glucose time in range, time above range, and time below range depend on mean or median glucose or HbA1c, glucose coefficient of variation, and shape of the glucose distribution. *Diabetes Technology & Therapeutics*. 2020;22(7):492-500.
   - This paper examined the expected relationship between TIR, TAR, TBR with percent A1C and percent of coefficient variation (CV).
   - Both percent TIR and percent TAR are approximately linearly related to mean and median glucose (or percent HbA1c). Percent TAR provides linearity over a wider range than percent TIR. Risk of hypoglycemia (percent TBR) is critically dependent on both glycemic variability (percent CV) and mean or median glucose. These relationships support the use of percent TIR, percent TAR, and percent TBR as metrics of quality of glycemic control for clinical, research, and regulatory purposes.

k. Sakai T, Aoyama K, Inazumi K, Kikuchi R, Sato Y, Tada A et al. Time in range correlates glycated albumin measured immediately after 2 weeks of continuous glucose monitoring. *Journal of Diabetes Complications*. 2021; 35(8):107962.

- Glycated albumin (GA) was measured at the conclusion of 2-week CGM in 71 diabetes outpatients. The correlation between GA and indices such as TIR obtained from CGM were statistically analyzed.
- TIR and TAR were significantly correlated with GA. Upon performing multiple regression analysis, TIR, TAR, and BMI indicated a significant regression coefficient with respect to GA.

l. Selvin E Wang D, Rooney MR, et al. The associations of mean glucose and time in range from continuous glucose monitoring with HbA1c in adults with type 2 diabetes. *Diabetes Technology & Therapeutics*. 2023;25(1):86-90. doi:10.1089/dia.2022.0178
   - Secondary analysis of 186 adults with type 2 diabetes wearing both Abbott Libre Pro and Dexcom G4 CGM. The study sought to examine the association between A1C and TIR in this group.
   - There were strong correlations between CGM mean glucose and A1C, but large differences in CGM mean glucose and TIR at any given A1C value. Mean glucose and HbA1c were strongly correlated in T2D patients not taking insulin but discordance is evident at the individual level.

m. Shah VN, Akturk HK, Vigers T, Pyle L, Oliver N, Klonoff DC. Relationship between daytime versus nighttime continuous glucose monitoring metrics with A1C in adults with type 1 diabetes. *Diabetes Technol Ther*. 2023;25(1):62-68. doi:10.1089/dia.2022.0365
   - Study aimed to evaluate the influence of daytime versus nighttime CGM-based metrics on A1C in adults with type 1 diabetes.
   - CGM data from 407 adults in two studies were included. The association between daytime and nighttime mean glucose, TIR, TAR, and TITR were examined within five specific A1C ranges.
   - Mean glucose increased with higher A1C, however there was no statistical difference in mean glucose between daytime versus nighttime within the five A1C groups (ranges). Differences between five A1C groups' daytime versus nighttime mean glucose, TIR, TITR, and TAR were also not statistically significant.

n. Valenzano M, Cibrario Bertolotti I, Valenzano A, Grassi G. Time in range–A1c hemoglobin relationship in continuous glucose monitoring of type 1 diabetes: a real-world study. *BMJ Open.* 2021;9:e001045. doi: 10.1136/bmjdrc-2019-001045
   - Also referred to as the REALISM-T1D study, this observational study aims to assess the relationship between A1C and TIR, and other CGM metrics, using real-world data. With this study, researchers aim to facilitate the adoption of CGM metrics in clinical practice.

- 70 adults with type 1 diabetes wore either a flash glucose monitor (FGM) or real-time monitor (rtCGM) for one year. Follow-up visits were performed after 90, 180, and 365 days where A1C and TIR data was assessed. The study was otherwise observational.
- Results align with those of previous interventional trials and demonstrate a strong linear correlation between A1C and TIR. The study found statistically significant differences in the regression intercept of FGM and rtCGM sensor data, indicating a need for tailored models for different monitoring systems

o. Vandenbempt M, Matheussen H, Charleer S, Rochtus A, Casteels K. The Relationship Between Glycated Hemoglobin and Time in Range in a Pediatric Population. *Diabetes Technol Ther*. Published online January 4, 2024. doi:10.1089/dia.2023.0482

- This cohort study looked at the correlation between HbA1c and TIR (70–180 mg/dL) at 2, 4, and 12 weeks (TIR_{2w}, $TIR_{4w,}$ and TIR_{12w}) before consultation in 168 youth (ages 0–18) with type 1 diabetes.
- Results showed strong linear correlations between HbA1c and TIR2w (R = -0.571), HbA1c and TIR4w (R = -0.603), and between HbA1c and TIR12w (R = -0.624).
- A 10% change in TIR12w led to an estimated 0.33% change in HbA1c. In contrast, a 1% change in HbA1c represented an estimated 11.88% change in TIR12w.
- It is important to note that individuals with conditions known to affect the accuracy of HbA1c (glucose-6-phosphate dehydrogenase deficiency, hemoglobinopathies such as thalassemia and sickle cell disease) were excluded from this study.

p. Vigersky RA, McMahon C. The relationship of hemoglobin A1C to time-in-range in patients with diabetes. *Diabetes Technology & Therapeutics*. 2019;21(2):81–5.

- 18 articles that paired HbA1C and percent TIR data were evaluated by linear regression analysis and Pearson's correlation coefficient. There was an excellent correlation between the two metrics. This good correlation may permit the transition to percent TIR as the preferred metric for determining the outcome of clinical studies predicting the risk of diabetes complications and assessing an individual patient's glycemic control.

Abstracts/Other

a. Norman GJ, Paudel ML, Bancroft T, Lynch PM. A Retrospective Analysis of the Association between HbA1c and Continuous Glucose Monitor Use for U.S. Patients with Type 2 Diabetes [Abstract 77-LB]. *Diabetes*. 2021; 70(Supplement 1).
    - This retrospective observational study assessed the impact of CGM use on glycemia in T2D patients in a real world setting, both on intensive and less intensive treatments.
    - In an analysis of A1C reduction from baseline after 6 months, those using SMBG (n=81,575) had 0.09% reduction in A1C from baseline, those on any CGM (n=1,406) had a 0.46% reduction from baseline and those on rtCGM (n=148) had a 0.72% reduction from baseline. The reduction effects were more pronounced for those on rtCGM and those who were non-intensively treated (NIT).
    - 12% of individuals using SMBG, 25.2% of individuals using any CGM, and 39.2% of individuals using rtCGM achieved an A1C reduction $\geq$ 1%. Reductions in A1C were highest in individuals on non-intensive treatments and using rtCGM.
    - The study concluded that use of CGM in real world settings leads to improved glycemic control in people with T2D and that CGM access should be expanded for a broader T2D population.

TIR and Microvascular Disease

Peer-Reviewed Publications

a. Beck RW, Bergenstal RM, Riddlesworth TD, Kollman C, Li Z, Brown AS, et al. Validation of time in range as an outcome measure for diabetes clinical trials. *Diabetes Care*. 2019;42(3):400–5.
    - This cohort study demonstrated the association of TIR (70-180 mg/dL) with the development or progression of retinopathy and microalbuminuria using lab blood glucose measurements collected 7 times per day from the Diabetes Control and Complications Trial (DCCT).
    - The 7 fingerstick samples were collected during a single day every 3 months and retinopathy progression was assessed every 6 months and urinary microalbuminuria development every 12 months

- TIR is strongly associated with the risk of microvascular complications. With the advances in CGM technology, the metric should be an accepted endpoint for clinical trials.

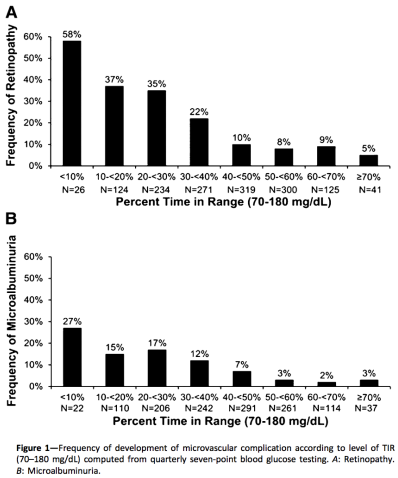


Figure 1—Frequency of development of microvascular complication according to level of TIR (70–180 mg/dL) computed from quarterly seven-point blood glucose testing. *A*: Retinopathy. *B*: Microalbuminuria.

b. El Malahi A, Van Elsen M, Charleer S, Dirinck E, et al. Relationship between Time in Range, glycemic variability, HbA1c, and Complications in Adults with T1D. *Journal of Clinical Endocrinology & Metabolism*. 2022;107(2): e570–e581.
   - 515 people with type 1 diabetes using sensor-augmented pump therapy were followed for 24 months. Baseline A1C and CGM-derived metrics (TIR [70-180 mg/dL], CV, and SD) obtained from the first 2 weeks of rt-CGM.
   - Lower TIR was associated with the presence of composite microvascular complications and with hospitalization for hypoglycemia or ketoacidosis. TIR, SD, and CV were not associated with macrovascular complications.

c. Feng Z, Guo Q, Wang W, Yuan Y, Jin X, Zhou J, et al. Time in range, especially overnight time in range, is associated with sudomotor dysfunction in patients with type 1 diabetes. *Diabetol Metab Syndr*. 2021; 13:119.
   - This study explores the relationship between TIR (including overnight TIR) and sudomotor function. Sudomotor dysfunction is a common feature of diabetic autonomic neuropathy that typically manifests first as anhidrosis (lack of sweating) of the extremities.
   - 95 people with type 1 participated in the investigation. TIR including night time TIR was evaluated with a CGM. Logistic regressions were used to examine the association of TIR and overnight TIR with sudomotor function.

- TIR is negatively correlated with sudomotor dysfunction in type 1 independent of A1C. Additionally, decreased nocturnal TIR is more closely related to the impaired function of sudomotor nerves in sweat glands.

d. Guo QY, Lu B, Guo ZH, Feng ZQ, Yuan YY, Jin XG, et al. Continuous glucose monitoring defined time in range is associated with sudomotor dysfunction in type 2 diabetes. *World Journal of Diabetes*. 2020 Nov 15; 11(11):489-500.
   - This cross-sectional study explored the relationship between TIR and sudomotor function detected by SUDOSCAN.
   - Participants included 466 inpatients with type 2 diabetes. All subjects underwent 3-day CGM and SUDOSCAN.
   - This study found that tight glycemic control, as assessed by TIR, is important for sudomotor dysfunction in people with type 2 diabetes.

e. Hirsch IB, Sherr JL, Hood KK. Connecting the dots: Validation of time in range metrics with microvascular outcomes. *Diabetes Care*. 2019;42(3):345–8.
   - This paper argues that TIR should be accepted as a primary outcome for future clinical investigations in addition to A1C. TIR is a valid endpoint and it is especially important since it informs providers and patients where their efforts should be focused to help individualize the patient's care.
   - Lower TIR has been associated with microvascular complications.

f. Guo Q, Zang P, Xu S, Song W, Zhang Z, Liu C, et al. Time in Range, as a Novel Metric of Glycemic Control, Is Reversely Associated with Presence of Diabetic Cardiovascular Autonomic Neuropathy Independent of HbA1c in Chinese Type 2 Diabetes. *Journal of Diabetes Research*. 2020.
   - This cross-sectional study demonstrated the relationship between TIR using CGMs and cardiovascular autonomic neuropathy (CAN).
   - Participants included 349 individuals with type 2 diabetes. More specifically, there were 228 diabetic individuals without cardiovascular autonomic neuropathy (without confirmed CAN) including absent CAN (n = 83 cases) and early CAN (n = 145 cases) and 121 diabetic individuals complicated with cardiovascular autonomic neuropathy (CAN) including definite CAN (n = 109 cases) and severe CAN (n = 12 cases). All patients underwent 3-day CGM.
   - They concluded that in Chinese patients, TIR is associated with the presence of CAN independent of HbA1c and GV metrics.

g. Kim MY, Kim G, Park JY, et al. The association between continuous glucose monitoring-derived metrics and cardiovascular autonomic neuropathy in outpatients with type 2 diabetes. *Diabetes Technol Ther*. 2021;23(6):434-442. doi:10.1089/dia.2020.0599

- This study investigated associations between CGM metrics and cardiovascular autonomic neuropathy (CAN) in 284 patients with type 2 diabetes.
- The odds ratio of presence of CAN was 0.876 [95% confidence interval (CI): 0.79–0.98] per 10% increase in the TIR 70–180 mg/dL, after adjusting for age, sex, diabetes duration, any medications, and glycemic variability.
- A 10% increase in the TIR was significantly inversely associated with the severity of CAN (OR: 0.89, 95% CI: 0.81–0.98).
- Among the metrics of hyperglycemia, each 10% increase in a time above range (TAR) >180 mg/dL was also independently correlated with the presence of CAN (OR: 1.141, 97.5% CI:1.01–1.29) and the severity of CAN (OR: 1.13, 97.5% CI: 1.01–1.26).

h. Kuroda N, Kusunoki Y, Osugi K, Ohigashi M, Azuma D, Ikeda H, et al. Relationships between time in range, glycemic variability including hypoglycemia and types of diabetes therapy in Japanese patients with type 2 diabetes mellitus: Hyogo Diabetes Hypoglycemia Cognition Complications study. *Journal of Diabetes Investigation*. Feb 2021; 12:244-253.
   - This cohort study investigated the relationships between TIR, glycemic variability and patient characteristics in patients with type 2 diabetes mellitus.
   - Participants included 281 outpatients with type 2 diabetes.
   - The results of this study suggest that disease duration, diabetic peripheral neuropathy, and urinary albumin excretion are associated with TIR deterioration. In addition, low HbA1c levels and the use of antidiabetic drugs like sulfonylureas potentially associated with severe hypoglycemia might worsen the time below range in the elderly.

i. Li F, Zhang Y, Li H, et al. TIR generated by continuous glucose monitoring is associated with peripheral nerve function in type 2 diabetes. *Diabetes Res Clin Pract*. 2020;166:108289. doi:10.1016/j.diabres.2020.108289
   - The goal of this study was to explore the association between the Time in Range and nerve conduction study parameters in people with type 2 diabetes.
   - 740 patients with type 2 diabetes participated in the study, who were all divided based on TIR (low: ≤53%; medium: 54-76%; high: ≥77%).
   - Higher TIR tertiles were independently associated with better peripheral nerve function. CGM-derived TIR may be a promising approach to screen patients for further assessment of possible diabetic peripheral neuropathy.

j. Liu TYA, Shpigel J, Khan F, et al. Use of Diabetes Technologies and Retinopathy in Adults With Type 1 Diabetes. *JAMA Netw Open*. 2024;7(3):e240728. doi:10.1001/jamanetworkopen.2024.0728

- This retrospective cohort study assessed the relationship between use of CGM, insulin pump, or both, and diabetic retinopathy and proliferative diabetic retinopathy in 550 adults with type 1 diabetes over 8 years.
- Participants were 24.5% Black/African American, 4.9% Hispanic, and 68.4% White. Most patients (72.0%) had private or commercial insurance and 54.7% were employed. Patients were equally distributed across the Area Deprivation Index scores by quintile.
- After adjusting for age, sex, race and ethnicity, diabetes duration, microvascular and macrovascular complications, insurance type, and mean HbA1c, results showed that CGM was associated with lower odds of diabetic retinopathy (OR, 0.52; 95% CI, 0.32-0.84; P = .008) and proliferative diabetic retinopathy (OR, 0.42; 95% CI, 0.23-0.75; P = .004), compared with no CGM use.
- Authors concluded CGM use was associated with lower odds of developing diabetic retinopathy and proliferative diabetic retinopathy, even after adjusting for HbA1c, suggesting CGM may be useful for monitoring and mitigating risk of these complications.

k. Lu J, Ma X, Zhou J, Zhang L, Mo Y, Ying L, et al. Association of time in range, as assessed by continuous glucose monitoring, with diabetic retinopathy in type 2 diabetes. *Diabetes Care*. 2018;41(11):2370–6.
   - This cross-sectional study included 3,262 patients with type 2 diabetes.
   - Demonstrated association between TIR and diabetic retinopathy and that TIR was also associated with the severity of diabetic retinopathy, even after adjusting for clinical risk factors such as HbA1C.
   - Some of the drawbacks of A1C include inability to reflect individual patterns of glycemic control. TIR alone is not an adequate description of glycemic control, but it can provide a more individualized approach.

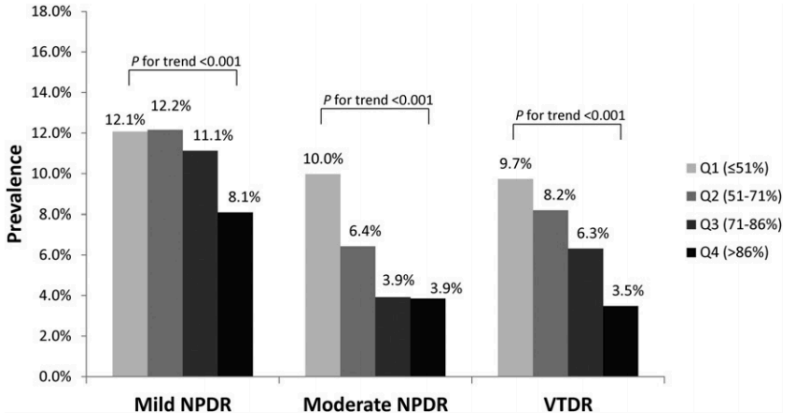


Figure 1—Prevalence of DR by severity, as a function of TIR quartile.

l. Mayeda L, Katz R, Ahmad I, et al. Glucose time in range and peripheral neuropathy in type 2 diabetes mellitus and chronic kidney disease. *BMJ Open Diabetes Res Care*. 2020;8(1):e000991. doi:10.1136/bmjdrc-2019-000991
   - In this cross-sectional study, participants included 105 people with type 2 diabetes treated with insulin or sulfonylurea, 81 people with CKD, and 24 matched control participants.
   - Each participant wore a CGM for 2 6-day periods.
   - Researchers hypothesized that compared with hemoglobin A1c, CGM may better capture risk of diabetes complications in patients with chronic kidney disease (CKD), including diabetic peripheral neuropathy (DPN).
   - Lower TIR and higher GMI were significantly associated with DPN symptoms. In contrast, HbA1c was not found to be associated with peripheral neuropathy.

m. Pratama KG, Angelia M, Amelia YS, Sukmadi N. Time in Range: Unveiling the Correlation with Diabetic Retinopathy in Type 2 Diabetes: A Systematic Review and Meta-Analysis. *Clinical Diabetology*. 2024;13(3):132-139. doi:10.5603/cd.99931
   - This systematic review and meta-analysis investigated the relationship between time in range (TIR) and diabetic retinopathy (DR) in type 2 diabetes.
   - Meta-analysis of five studies indicated lower TIR and higher standard deviation, mean amplitude of glucose excursions, and coefficient of variation (all glucose variability metrics) were significantly associated with DR in T2D patients.

n. Ranjan AG, Rosenlund SV, Hansen TW, Rossing P, Andersen S, Nørgaard K. Improved time in range over 1 year is associated with reduced albuminuria in individuals with sensor-augmented insulin pump–treated type 1 diabetes. *Diabetes Care*. 2020 Sep 3;dc200909.

- This longitudinal study investigated the association between TIR and albuminuria in persons treated with sensor-augmented insulin pumps.
- Participants included 55 patients with type 1 diabetes with a history of albuminuria and on stable renin-angiotensin-aldosterone system (RAAS) inhibition.
- Treatment-induced increase in percent TIR was significantly associated with decrease in albuminuria in type 1 diabetes.

o. Raj R, Mishra R, Jha N, Joshi V, Correa R, Kern P. Time in range, as measured by CGM, as a predictor of microvascular complications in type 2 diabetes: a systematic review. *BMJ Open Diabetes Res Care*. 2022.

- The authors conducted a systematic review to examine the association between TIR and microvascular complications of diabetes.
- 11 studies with a total of 13,987 patients were included.
- A 10% increase in TIR was associated with a reduction in albuminuria, severity of retinopathy, and prevalence of peripheral and autonomic neuropathy. In addition, an association was observed between urinary albumin to creatinine ratio but not with estimated glomerular filtration rate.

p. Sebastian-Valles F, Martínez-Alfonso J, Arranz Martin JA, et al. Time above range and no coefficient of variation is associated with diabetic retinopathy in individuals with type 1 diabetes and glycated hemoglobin within target. *Acta Diabetol*. Published online August 6, 2024. doi:10.1007/s00592-024-02347-5

- This cross-sectional study investigated the association between glucose metrics and diabetic retinopathy in people with type 1 diabetes (T1D) using flash continuous glucose monitoring (FGM).
- Among 1070 participants, 24.8% presented some form of retinopathy. In the analysis involving the entire sample of subjects, Time Above Range (TAR)>250 mg/dL (OR=1.07, p=0.025) was associated with diabetic retinopathy (as were male gender, duration of diabetes, history of ischemic stroke). No association was observed between the coefficient of variation and diabetic retinopathy (p=0.934).
- In patients with A1C<7%, the highest quartile of TAR>250 was independently linked to diabetic retinopathy (OR=8.32, p=0.040), in addition to smoking (OR=2.90, p=0.031), duration of diabetes (OR=1.09, p<0.001), and hypertension (OR=2.35, p=0.040).
- Importantly, TAR>250 mg/dL was found to be a modifiable factor associated with diabetic retinopathy, even among those maintaining recommended A1C

levels – highlighting the importance of using multiple glucose metrics to tailor management strategies.

q. Shah VN, Kanapka LG, Akturk HK, et al. Time in Range Is Associated with Incident Diabetic Retinopathy in Adults with Type 1 Diabetes: A Longitudinal Study. *Diabetes Technology & Therapeutics*. 2024;26(4):246-251. doi:10.1089/dia.2023.0486
   - This retrospective longitudinal study analyzed 7 years of CGM data from 902 adults with type 1 diabetes without a diagnosis of diabetic retinopathy (DR) and 71 adults with new incident diagnosis of diabetic retinopathy but normal eye examinations in the past.
   - Adjusting for age, diabetes duration, and CGM type, each 5% decrease in time in target range 70-180 mg/dL (TIR), 5% decrease in time in tight target range 70-140 mg/dL (TITR), and 5% increase in time above 180 mg/dL (TAR) were associated with 18%, 28%, and 20% increase in odds of incident DR, respectively.
   - TIR was negatively associated with development of diabetic retinopathy. Time in tight target range (TTIR 70-140 mg/dL) and time above range (TAR>180 mg/dL) were also associated with diabetic retinopathy
   - This is the first longitudinal study to demonstrate association between CGM metrics and diabetic retinopathy.

r. Sheng X, Xiong GH, Yu PF, Liu JP. The correlation between time in range and diabetic microvascular complications utilizing information management platform. *International Journal of Endocrinology*. 2020 Dec 15; vol. 2020: 1-7.
   - This study explored the relationship between TIR and A1C through the information big data management platform. The association between TIR and diabetic microvascular complications was also investigated.
   - 1,895 males and 1,513 females with diabetes were included, with an average age of 59.74 ± 13.40 years old and an average course of disease of 8.28 ± 7.11 years.
   - This study found that TIR may serve as a reference index for short-term blood glucose control, strongly reflecting the clinical blood glucose regulation and predicting the risk of diabetic microvascular complications.
   - Decreased TIR was shown to be a risk factor for microvascular complications including nephropathy, peripheral nephropathy, and retinopathy.

s. Varghese JS, Ho J, Anjana RM, Pradeepa R, Patel S, Jebarani S, Baskar V, Narayan V, Mohan V. Profiles of Intraday Glucose in Type 2 Diabetes and Their Association with Complications: An Analysis of Continuous Glucose Monitoring Data. *Diabetes Technology & Therapeutics*. 2021; 23(8).

- 5,901 adult type 2 diabetes patients (ages 18-80) were assessed using two weeks of CGM data, collected between 2015 and 2019.
- The researchers hypothesized that profiles associated with departure from recommendations would be associated with higher prevalent complications.
- There were three derived profiles of glycemic patterns integrating eight AGP characteristics. Each patient was assigned to a profile based on the highest probability of membership derived from NMF. The three profiles included: Profile 1 ("TIR Profile"), Profile 2 ("Hypo"), and Profile 3 ("Hyper").
- "Hypo" and "Hyper" profiles had higher prevalent odds of all complications compared with "TIR profile" after adjusting for HbA1c, age at onset of diabetes, duration of diabetes, and sex.

TABLE 3. ADJUSTED ODDS RATIO OF PREVALENT COMPLICATIONS WITH PROFILE MEMBERSHIP (N=5901)

	TIR profile	*Hypo profile*	*Hyper profile*
Retinopathy-related complications			
NPDR	1.00	1.44 (1.20, 1.73)	1.33 (1.11, 1.58)
PDR	1.00	2.84 (1.65, 4.88)	1.39 (0.78, 2.45)
NPDR or PDR	1.00	1.49 (1.24, 1.79)	1.33 (1.12, 1.58)
Nephropathy-related complications			
Microalbuminuria or macroalbuminuria	1.00	1.29 (1.11, 1.49)	1.31 (1.14, 1.51)
Macroalbuminuria	1.00	1.58 (1.25, 1.98)	1.37 (1.10, 1.71)
Diabetic kidney disease	1.00	1.65 (1.18, 2.31)	1.88 (1.37, 2.58)

Associations were adjusted for HbA1c (%), age at onset of diabetes (years), duration of diabetes till CGM initiation (years), and sex. CGM, continuous glucose monitoring.

- The "hyper profile" and "hypo profile" represented poorer control of intraday glucose, with the mean daily glucose, MAGE, and GMI being highest in "Hyper profile," while percentage of those with coefficient of variation greater than 36% was higher in "hypo profile."
- The odds of prevalent retinopathy (both NPDR and PDR) and nephropathy were higher among both "hypo" and "hyper profiles" relative to "TIR profile," with the "Hypo profile" having the highest odds of PDR.

t. Yang J, Yang X, Zhao D, Wang X, Wei W, Yuan H. Association of time in range, as assessed by continuous glucose monitoring, with painful diabetes polyneuropathy. *Journal of Diabetes Investigation*. 2021;12: 828-836.
   - A cross-sectional study of 364 individuals with diabetes peripheral neuropathy were enrolled.
   - Diabetes peripheral neuropathy (DPN) was diagnosed according to the following criteria: 1) more than one typical symptom; 2) abnormal Toronto Clinical Scoring System (TCSS); and/or 3) abnormal nerve conduction test (NCT).
   - Participants were assessed with a sensor-based flash glucose monitoring system and were also asked to evaluate their pain during the 2 weeks of

monitoring. The severity of pain was rated using an 11-step numerical rating scale (NRS) including on a scale of 1-10, with higher scores indicating more severe pain. Multiple linear regression analysis was used to estimate the association between TIR and the NRS score.

- TIR was negatively correlated with NRS ($r = -0.506$, $P < 0.001$), TCSS score ($r = -0.388$, $P < 0.001$) and abnormal NCT ($r = -0.245$, $P < 0.001$). TIR was also negatively correlated with female sex, age, diabetes mellitus duration, FPG, HbA1c and drinking ($P < 0.05$).
- The levels of TIR were significantly decreased in diabetes patients with PDN. Additionally, TIR was significantly negatively correlated with the NRS score.

TIR and Macrovascular Disease

Peer-Reviewed Publications

a. Hagelqvist PG, Andersen A, Maytham K, et al. Glycaemia and cardiac arrhythmias in people with type 1 diabetes: A prospective observational study. *Diabetes Obes Metab*. 2023;25(8):2300-2309. doi:10.1111/dom.15108
    - This prospective observational study used continuous glucose monitoring and implantable loop recorders to investigate potential associations between hypoglycaemia, hyperglycaemia and glycaemic variability in 31 adults with type 1 diabetes.
    - During daytime, a trend of increased risk of arrhythmias was observed when comparing time spent in hypoglycaemia with euglycaemia (IRR 1.08 [95% CI: 0.99-1.18] per 5 minutes).
    - Both the occurrence and time spent in hyperglycaemia during the daytime were associated with an increased risk of arrhythmias compared with euglycaemia (IRR 2.03 [95% CI: 1.21-3.40] and IRR 1.07 [95% CI: 1.02-1.13] per 5 minutes, respectively).
    - Night-time hypoglycaemia and hyperglycaemia were not associated with the risk of arrhythmias.
    - Increased glycaemic variability was not associated with an increased risk of arrhythmias during daytime, whereas a reduced risk was observed during night-time.
    - The authors conclude acute hypoglycaemia and hyperglycaemia during daytime may increase the risk of arrhythmias in individuals with type 1 diabetes, but no

such associations were found during night-time, indicating diurnal differences in arrhythmia susceptibility.

b. Li J, Li Y, Ma W, Liu Y, Yin X, Xie C, et al. Association of Time in Range levels with Lower Extremity Arterial Disease in patients with type 2 diabetes. *Diabetes Metab Syndr*. 2020 Sep 28;14(6):2081-2085.
    - This cross-sectional study evaluated 336 patients with type 2 diabetes, including 179 patients with Lower Extremity Arterial Disease (LEAD) and 157 patients without it.
    - TIR is significantly and independently associated with diabetic lower artery extremity disease in type 2 diabetes. TIR was significantly lower in patients with LEAD than in those without. The prevalence of LEAD by severity decreased with ascending quartiles of TIR.
c. Lu J, Ma X, Shen Y, Wu Q, Wang R, Zhang L, et al. Time in range is associated with carotid intima-media thickness in type 2 diabetes. *Diabetes Technology & Therapeutics*. 2020;22(2):72–8.
    - The goal of this cross-sectional study was to look at the association between TIR obtained from a CGM and carotid intima-media thickness (CIMT) as a marker for cardiovascular disease.
    - Participants included 2215 patients with type 2 diabetes.
    - Compared with patients with normal CIMT, those with abnormal CIMT had significantly lower TIR. In the fully adjusted model that controlled for the traditional risk factor of CVD, each 10% increase in TIR was associated with a 6.4% lower risk of CIMT.
    - When dividing the data by sex, TIR was significantly associated with CIMT in males and not in females.
d. Lu J, Wang C, Shen Y, Chen L, Zhang L, Cai J, et al. Time in Range in Relation to All-Cause and Cardiovascular Mortality in Patients With Type 2 Diabetes: A Prospective Cohort Study. *Diabetes Care*. 2021 Feb; 44(2): 549-555.
    - This prospective cohort study evaluated 6,225 patients with type 2 diabetes between January 2005 and December 2015. Participants wore CGM for three days and were all fed the same diet. Mean follow-up time was 6.9 years.
    - A strong correlation was found between lower TIR during the study period and increased risk of all-cause and CVD-related morality. Every 10% decrease in TIR was associated with a 5% increase in CVD-related mortality and 8% increase in all-cause mortality. For all subgroups except women, the association between TIR and all-cause mortality held consistent.

e. Wei Y, Liu C, Liu Y, et al. The association between time in the glucose target range and normal ankle-brachial index: a cross-sectional analysis. *Cardiovascular Diabetology*. December 2022.
   - The purpose of this study was to explore the relationship between TIR and abnormal ankle-brachial index (ABI) in type 2 diabetes.
   - The overall prevalence of abnormal ABI was 20.2% (low 4.9% and high 15.3%). TIR was lower in patients with abnormal ABI values (P = 0.009). The prevalence of abnormal ABI decreased with increasing quartiles of TIR (P = 0.026). Abnormal ABI was negatively correlated with TIR and positively correlated with hypertension, age, diabetes duration, UREA, Scr, ACR, TAR, MBG, and M values (P < 0.05). The logistic regression revealed a significant association between TIR and abnormal ABI, while HbA1C and blood glucose variability measures had no explicit correlation with abnormal ABI. Additionally, there was a significant difference in LDL between the low and high ABI groups (P = 0.009), and in Scr between normal and low groups (P = 0.007). And there were significant differences in TIR (P = 0.003), age (P = 0.023), UREA (P = 0.006), ACR (P = 0.004), TAR (P = 0.015), and MBG (P = 0.014) between normal and high ABI groups, and in diabetes duration between both normal and low (P = 0.023) and normal and high (P = 0.006) groups.
   - In people with type 2 diabetes, abnormal ABI is associated with lower TIR, and the correlation is stronger than that with HbA1C. Therefore, the role of TIR should be emphasized in the evaluation of lower limb vascular diseases.

Limitations of A1C

Peer-Reviewed Publications

a. Beck R, Connor C, Mullen D, Wesley D, Bergenstal R. The fallacy of average: how using HbA1c alone to assess glycemic control can be misleading. *Diabetes Care*. 2017;40(8):994-999.
   - This study utilized a statistical analysis, plotting a mean glucose measured with continuous glucose monitoring (CGM) versus central laboratory-measured HbA1c in 387 participants in three randomized trials.
   - The study showed that HbA1c may underestimate or overestimate mean glucose. Estimating glycemic control from HbA1c alone is in essence applying a population average to an individual, which can be misleading.

- A patient's CGM glucose profile has considerable value for optimizing their diabetes management

b. Bergenstal RM, Gal RL, Connor CG, Gubitosi-Klug R, Kruger D, Olson BA, et al. Racial differences in the relationship of glucose concentrations and hemoglobin A1c levels. *Ann Intern Med*. 2017; 167(2):95-102.
   - This prospective, 12-week observational study aimed to determine whether a racial difference exists in the relationship of mean glucose and A1C.
   - 104 black persons and 104 white persons aged 8 years or older who had had type 1 diabetes for at least 2 years and had an A1C level of 6.0% to 12.0% were included.
   - For a given A1C level, the mean glucose concentration was significantly lower in black persons than in white persons, which was reflected in mean HbA1c values in black persons being 0.4 percentage points higher than those in white persons for a given mean glucose concentration.
   - One of the limitations was that there were too few participants with A1C levels less than 6.5% to generalize the results to such individuals.
   - On average, A1C levels overestimate the mean glucose concentration in black persons compared with white persons, possibly owing to racial differences in the glycation of hemoglobin. However, because race only partially explains the observed A1C differences between black persons and white persons, future research should focus on identifying and modifying barriers impeding improved glycemic control in black persons with diabetes.

c. Cembrowski G, Mei J, Guérin R, Cervinski MA, McCudden C. Derivation of real metrics of long term patient and analytical variation of three hemoglobin A1c assays demonstrates both borderline and highly acceptable analytical performance. *Journal of Laboratory and Precision Medicine*. 2020;5:26.
   - This study sought to compare the precision of different HbA1c assays.
   - Low imprecision HbA1c assays are able to better indicate patient glycemia than higher imprecision HbA1c
   - Both the Sebia and Roche provide superior information.
   - Information made available by CGMs show that HbA1cs are not sufficiently accurate.

d. Christakis NJ, Gioe M, Gomez R, et al. Determination of glucose-independent racial disparity in HbA1c for youth with type 1 diabetes in the era of continuous glucose monitoring. *J Diabetes Sci Technol*. Published online September 12, 2023. doi:10.1177/19322968231199113

- This study sought to clarify the relationship between HbA1c and glucose data from continuous glucose monitoring (CGM) in non-Hispanic Black versus non-Hispanic white individuals
- Participants were 33 non-Hispanic Black and 85 non-Hispanic white youth with type 1 diabetes.
- Black patients were found to have higher unadjusted levels of HbA1c, mean blood glucose, standard deviation, and GMI as well as lower TIR and percent sensor use (PSU)
- In conclusion, non-Hispanic Black youth with T1D have clinically relevant higher average HbA1c at any given level of mean blood glucose or time in range than white patients, which may pose an additional risk for diabetes complications development.

e. Dubowitz N, Xue W, Long Q, et al. Aging is associated with increased HbA1c levels, independently of glucose levels and insulin resistance, and also with decreased HbA1c diagnostic specificity. *Diabet Med*. 2014;31(8):927-935. doi:10.1111/dme.12459
   - This cross-sectional study analyzed whether A1C is confounded by age differences, what explains age differences, and whether these differences impact diagnostic accuracy using A1C.
   - Looking at two large datasets of adults without known diabetes, both glucose intolerance and HbA1c levels increased with age. In multivariate analyses of subjects with normal glucose tolerance, the relationship between age and HbA1c remained significant (P<0.001) after adjustment for covariates including race, BMI, waist circumference, sagittal abdominal diameter, triglyceride/HDL ratio, and fasting and 2-h plasma glucose and other glucose levels, as assessed by an oral glucose tolerance test.
   - In both datasets, the HbA1c of an 80-year-old individual with normal glucose tolerance would be 3.82 mmol/mol (0.35%) greater than that of a 30-year-old with normal glucose tolerance, a difference that is clinically significant.
   - The specificity of A1C- based diagnostic criteria for prediabetes decreased substantially with increasing age. Screening with HbA1c will tend to over diagnose diabetes and prediabetes in older patients, meaning guiding management based only on HbA1c levels might increase hypoglycaemia risk in older patients.

f. Eide IA, Halden TAS, Hartmann A, Åsberg A, Dahle DO, Reisæter AV, et al. Limitations of hemoglobin A1c for the diagnosis of posttransplant diabetes mellitus. *Transplantation*. 2015;99(3)-629-635.

- The goal of this study was to assess the sensitivity of applying the A1C criterion alone or in combination with a single measurement of fasting plasma glucose (fPG) of 7.0 mmol/L or higher (≥126 mg/dL) at 10 weeks after transplantation as screening tests for the diagnosis of post transplantation diabetes mellitus.
- From 1999 to 2011, measurements of fPG, A1C, and oral glucose tolerance test (OGTT) were performed in 1,619 nondiabetic renal transplant recipients.
- They concluded that the proposed diagnostic A1C criterion failed to detect most cases of PTDM. Thus, they propose that the A1C threshold value be lowered for renal transplant recipients.

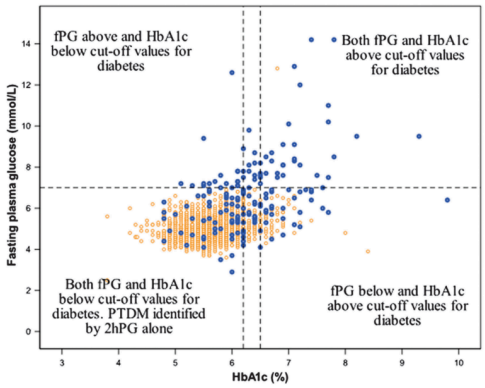


FIGURE 2. The relationship between HbA1c threshold values of 6.2% (44.3 mmol/mol) and 6.5% (47.5 mmol/mol) and posttransplant diabetes mellitus (PTDM) (repeatedly elevated measurements of fPG that did not normalize during the first 10 weeks after renal transplantation or fPG≥7.0 mmol/L (≥126 mg/dL) and 2hPG ≥11.1 mmol/L (≥200 mg/dL) during an OGTT at 10 weeks after transplantation). Shown is the distribution of fasting plasma glucose (fPG) concentrations in relation to HbA1c levels. Horizontal line: The diagnostic threshold value for fPG of 7.0 mmol/L (≥126 mg/dL). Vertical lines: The proposed diagnostic HbA1c threshold values of 6.5% (47.5 mmol/mol) and the alternative threshold value of 6.2% (44.3 mmol/mol). HbA1c, fPG, and OGTT were measured 10 weeks after renal transplantation. Right hand side of the vertical lines: Observations of patients who were identified as diabetic by HbA1c. Observations of PTDM (*blue*), non-PTDM (*orange*). HbA1c, glycosylated hemoglobin; OGTT, oral glucose tolerance test.

g. Galindo RJ, Moazzami B, Tuttle KR, Bergenstal RM, Peng L, Umpierrez GE. Continuous Glucose Monitoring Metrics and Hemoglobin A1c Relationship in Patients with Type 2 Diabetes Treated by Hemodialysis. *Diabetes Technol Ther*. Published online June 14, 2024. doi:10.1089/dia.2024.0145
    - This prospective observational study assessed the relationship between CGM metrics and A1C in patients with type 2 diabetes and end-stage kidney disease (ESKD) treated by hemodialysis.
    - 59 participants used a Dexcom G6 PRo for 10 days (mean age 57.7 ± 9.3 years, 58% were female, 86% were non-Hispanic Black).
    - GMI had a strong negative correlation with TIR 70–180 mg/dL (r = -0.96). The correlation between GMI and HbA1c (r = 0.68) was moderate. Up to 29% of participants had a discordance between HbA1c and GMI of <0.5%, with 49% having a discordance of >1%.
    - Results confirm previous findings that A1C underestimates average glucose in patients with type 2 diabetes and ESKD.

h. Herman WH, Ma Y, Uwaifo G, Haffner S, Kahn SE, Horton ES, et al. Differences in race and ethnicity among patients with impaired glucose tolerance in the Diabetes Prevention Program. *Diabetes Care*. 2007 Oct 30;30(10): 2453-57.
    - This paper sought to examine racial and ethnic differences in A1C in individuals with impaired glucose tolerance (IGT).
    - 3,819 individuals aged ≥25 years with IGT who were found to be eligible to participate in the Diabetes Prevention Program were studied. A1C was compared among five racial and ethnic groups before and after adjustment for factors that differed among groups or might affect glycemia.
    - The study found that A1C levels are higher among U.S. racial and ethnic minority groups with IGT after adjustment for factors likely to affect glycemia.
i. Kaminski CY, Galindo RJ, Navarrete JE, et al. Assessment of Glycemic Control by Continuous Glucose Monitoring, Hemoglobin A1c, Fructosamine, and Glycated Albumin in Patients With End-Stage Kidney Disease and Burnt-Out Diabetes. *Diabetes Care*. 2024;47(2):267-271. doi:10.2337/dc23-1276
    - Patients with diabetes and end-stage kidney disease (ESKD) may experience "burnt-out diabetes," defined as having an HbA1c value <6.5% without antidiabetic therapy for >6 months.
    - This pilot prospective study sought to assess glycemic control by continuous glucose monitoring (Dexcom G6 CGM) metrics and glycemic markers in ESKD patients on hemodialysis with burnt-out diabetes.
    - Participants were 40 patients with ESKD, 20 with burnt-out diabetes and 20 without a history of diabetes.
    - Participants with burnt-out diabetes had higher CGM-measured daily glucose levels, lower percent time in the range 70-180 mg/dL, higher percent time above range (>250 mg/dL), and longer duration of hyperglycemia >180 mg/dL (hours/day) compared with patients without diabetes (all $P < 0.01$). HbA1c and fructosamine levels were similar between groups, but patients with burnt-out diabetes had higher levels of glycated albumin than did patients without diabetes.
    - The use of CGM demonstrated that patients with burnt-out diabetes have significant undiagnosed hyperglycemia. CGM and glycated albumin provide better assessment of glycemic control than do values of HbA1c and fructosamine in patients with ESKD.
j. Karter AJ, Parker MM, Moffet HH, Gilliam LK. Racial and Ethnic Differences in the Association Between Mean Glucose and Hemoglobin A1c. *Diabetes Technology & Therapeutics*. Published online October 12, 2023. doi:10.1089/dia.2023.0153

- This retrospective study evaluated racial/ethnic differences in the association between mean glucose (based on continuous glucose monitor (CGM) data) and A1C among 1788 patients with diabetes from Kaiser Permanente Northern California (KPNC) who used CGM devices during 2016 to 2021.
- Mean A1C was 0.33 (95% confidence interval: 0.23–0.44; P < 0.0001) percentage points higher among African American patients relative to white patients for a given mean glucose.
- A1C results for Asians, Latinos, and multiethnic patients were not significantly different from those of white patients. Variance for the association between mean glucose and A1C was substantially greater within groups than between racial/ethnic groups (65% vs. 9%, respectively).
- These findings suggest A1C results may overestimate glycemia for African American patients and could lead to premature diabetes diagnoses, overtreatment, or invalid assessments of health disparities.

k. Kim IY, Kim MJ, Lee DW, Lee SB, Rhee H, Song SH, et al. Glycated albumin is a more accurate glycaemic indicator than hemoglobin A1c in diabetic patients with pre-dialysis chronic kidney disease. *Nephrology*. 2015;20(10).
   - This paper aimed to test glycated albumin (GA) assays on patients with diabetes and pre-dialysis CKD.
   - 146 patients with diabetes were included in the study.
   - They found that the glucose/A1C and GA/A1C ratios were significantly higher in the CKD group than those in the non-CKD group and the glucose/GA did not vary significantly between the two groups.
   - They concluded that A1C significantly underestimated glycemic control, whereas GA more accurately reflected glycemic control in diabetic patients with pre-dialysis CKD.

l. Li Q, Ju Y, Jin T, Pang B, Deng J, Du T, et al. Haemoglobin A1c measurement in patients with chronic kidney disease. *Clinical Biochemistry*. 2014;47(6):481-484.
   - This paper investigated the interference of carbamylated hemoglobin to hemoglobin A1C measurements in patients with CKD.
   - 152 patients with CKD were included in the study.
   - They found that despite the increase in blood urea concentration from stage 3 to stage 5, there was no corresponding increase in A1C values.

m. Lundholm MD, Emanuele MA, Ashraf A, and Nadeem S. Applications and pitfalls of hemoglobin A1C and alternative methods of glycemic monitoring. *Journal of Diabetes and its Complications*. 2020;34(8): 107585.

- This paper focused on the limitations of alternative markers and continuous glucose monitors.
- Gathered papers from PubMed and the Cochrane Library that covered the limitations of A1C, fructosamine, glycated albumin, 1,5-anhydroglucitol, skin autofluorescence, and continuous glucose monitoring
- Conclusions
    - A1C reflects three months of glycemic control and is not an ideal marker in all patient populations
    - Fructosamine and glycated albumin reflect mean blood glucose over three weeks.
    - 1,5-Anhydroglucitol can measure hyperglycemic excursions in days to weeks.
    - Continuous glucose monitors provide immediate feedback for timely intervention to reduce glycemic excursions and can assess glycemic variability. With the CGM, they also highlighted some of the barriers including inexperience, cost, discomfort, and medication interference.
- The larger conclusion was that the main limitations for all these alternative methods are a lack of standardization for clinically useful cut-offs or guidelines, and a lack of long-term data on their association with complications, particularly in varied patient populations.

n. Misra A, Bloomgarden ZT. Discordance between HbA1c and glycemia. *Journal of Diabetes*. 2018;10(12):908-910.
    - This retrospective study on persons with type 2 diabetes looked at the relationship between HbA1c and fasting blood glucose
    - Significant discordance was found between HbA1c and fasting blood glucose in 23% of patients
    - Reliance on HbA1c for diagnosis of prediabetes and diabetes may sometimes be erroneous
    - It would be ideal to combine HbA1c levels with multiple blood glucose measurements, as provided by continuous glucose monitoring
    - Anemia is a relevant cause for discordance as countries such as China and India who have a high number of people with diabetes also have a high prevalence of anemia. Concurrent measurements of iron, hemoglobin, and HbA1c are critical in these populations.
o. Mitchell K, Mukhopadhyay B. Drug-induced falsely low A1C: Report of a case series from a diabetes clinic. *Clinical Diabetes*. 2018;36(1):80-84.

- This retrospective case review showed that A1c levels may be inaccurately low for a significant number of diabetes patients who used sulfasalazine and dapsone.
- Sulfasalazine is the most common cause of anomalous A1c results.
- Larger studies are needed to determine if A1c is reliable in the majority of people taking sulfasalazine.

p. Nayak A, Singh B, Dunmore S. Potential clinical error arising from use of HbA1c in diabetes: Effects of the glycation gap. *Endocrine Reviews*. May 2019; 40(4): 988-999.
- The glycation gap (GGap) and the hemoglobin glycation index (HGI) show a consistent difference between HbA1c and other measures of mean glycemia. GGAP and HGI may be important for caregivers and providers to understand the impact of the validity of HbA1c measurements.
- Despite standardization of assays, discrepancy between HbA1c and other assessments of glycemia may affect accurate interpretation of glycemic control and its management.
- HbA1c alone may not always be reliable for diagnostic purposes, with studies showing a low sensitivity of HbA1c for diagnosis, leading to missed diagnoses and inaccurate diagnoses.
- The incorporation of GGap/HGI during assessment of glycemia control would help to ascertain how far HbA1c diverges from alternative estimates of glycemia to avoid misinterpretation of glycemic control and to avoid inappropriate therapeutic management.
- The measurement of GGap and HGI are important to diabetes clinicians and their patients in individualization of therapy and the avoidance of harm arising from consequent inappropriate assessment of glycemia and use of therapies.

q. Ng JM, Cooke M, Bhandari S, Atkin SL, and Kilpatrick ES. The effect of iron and erythropoietin treatment on the A1C of patients with diabetes and chronic kidney disease. *Diabetes Care*. 2010;33(11):2310-13.
- This paper aims to examine the effect of intravenous iron and erythropoietin-stimulating agents (ESAs) on glycemic control, A1C, and chronic kidney disease (CKD).
- This was a prospective study of patients with type 2 diabetes and CKD stage IIIB or IV undergoing intravenous iron (group A) and/or ESA (group B).
- Both iron and ESA cause a significant fall in A1C values without a change to glycemic control in patients with diabetes and CKD. At the present time, regular capillary glucose measurements and the concurrent use of CGM remain the best alternative measurements of glycemic control in this patient group.

r. Peacock TP, Shihabi ZK, Bleyer AJ, Dolbare EL, Byers JR, Knovich MA, et al. Comparison of glycated albumin and hemoglobin A1C levels in diabetic subjects on hemodialysis. *Kidney International*. 2008;73(9):1062-1068.
    - This study is researching the claim that glycated albumin is thought to more accurately reflect glycemic control in diabetic hemodialysis patients than hemoglobin A1C because of shortened red cell survival.
    - Blood samples were collected from 307 patients with diabetes – 258 of whom were on hemodialysis and 49 were without overt renal disease.
    - They found that in the patients with renal disease, the mean serum glucose and glycated albumin concentrations were significantly higher while A1C was lower. Their results show that in diabetic hemodialysis patients, A1C levels significantly underestimate glycemic control while the glycated albumin levels are more reflective.
s. Selvin E, Rawlings AM, Bergenstal RM, Coresh J, and Brancati FL. No racial differences in the association of glycated hemoglobin with kidney disease and cardiovascular outcomes. *Diabetes Care*. 2013 Oct 36; 36(10): 2995-3001.
    - This prospective cohort analysis compared the associations of diabetes diagnostic categories for A1C and fasting glucose with clinical outcomes in black and white persons.
    - 2,484 black and 8,593 white participants without diabetes or cardiovascular disease were studied and tested for race interactions.
    - With respect to long-term outcomes, the findings support a similar interpretation of A1C in blacks and whites for diagnosis and treatment of diabetes. A1C is a risk factor for vascular outcomes and mortality in both black and white adults.
t. Sharif A and Baboolal K. Diagnostic application of the A1C assay in renal disease. *JASN*. 2010;21(3)-383-385.
    - This paper highlights DCCT and UKPDS as pivotal studies that showed the link between A1C and diabetes-related complications.
    - The researchers note that renal impairment can affect the legitimacy of the A1C assay through altered erythropoiesis but also through direct interactions with glycated hemoglobin analyses.
    - The researchers also spoke about factors that could artificially decrease the A1C assay in hemodialysis patients including shortened blood cell survival, red blood cell transfusion and erythropoietin treatment.
u. Shepard JG, Airee A, Dake AW, McFarland MS, and Vora A. Limitations of A1c interpretation. *Southern Medical Journal*. 2015;108(12):724-729.

- This is a review article on the methods for measuring A1C and how different conditions can affect the clinical utility of the test.
- Some of the conditions mentioned include those that impair erythrocyte production or alter the normal process of glycation. Patient age and ethnicity have also been shown to skew A1C results.

v. Shipman KE, Jawad M, Sullivan KM, Ford C, and Gama R. Effect of chronic kidney disease on A1C in individuals being screened for diabetes. *Primary Care Diabetes*. 2015;9(2):142-146.
   - This paper studied the prevalence of CKD and its association with A1C as a diagnostic test for type 2 diabetes.
   - 949 participants with type 2 diabetes and CKD were included in the study.
   - They found that severe CKD, that is stage 4 or greater, is rare in primary care patients that were being screened for type 2 diabetes. They also discovered that although A1C is higher in patients with CKD stage 3 compared to those with eGFR greater than or equal to 60, this was due to effects other than the presence of CKD.

w. Speeckaert M, Biesenn WV, Delanghe J, Slingerland R, Wiecek A, Heaf J, et al. Are there better alternatives than haemoglobin A1c to estimate glycaemic control in the chronic kidney disease population? *Nephrology Dialysis Transplantation*. 2014;29(12):2167-2177.
   - This consensus review paper from the European Renal Association-European Dialysis and Transplant Association presents the current knowledge and evidence of the use of alternative glycaemic markers (glycated albumin, fructosamine, 1,5-anhydroglucitol and continuous glucose monitoring [CGM]) in light of the differing association between glycaemic control and morbidity/mortality observed in patients with renal insufficiency. CGM was the only marker evaluated without known biases in this population, though at time of publication, A1c remained the most widely accessible and therefore the reference standard.

x. Venkatraman S, Echouffo-Tcheugui JB, Selvin E, Fang M. Trends and disparities in glycemic control and severe hyperglycemia among us adults with diabetes using insulin, 1988-2020. *JAMA Netw Open.*2022;5(12):e2247656.
   - This cross-sectional study investigated if glycemic control has improved among US adults with diabetes using insulin over the past 30 years.
   - The study population included non-pregnant US adults aged 20 or older with diabetes and using insulin. The data sets compared were from 1988-1994 and 2017-2020.

- The overall percentage of participants with an A1C of less than 7% remained constant between the two periods. The researchers found that Mexican Americans were less likely than non-Hispanic White adults to achieve the A1C target and these disparities increased over time.
- The study concluded that glycemic control has stagnated over the past three decades while racial disparities have increased among insulin-using US adults.

y. Wolffenbuttel BHR, Herman WH, Gross JL, Dharmalingam M, Jiang HH, and Hardin DS. Ethnic differences in glycemic markers in patients with type 2 diabetes. *Diabetes Care*. 2013; 36(10): 2931-36.
   - The aim of this study was to assess the relationships between A1C and the mean SMBG across different ethnic groups with type 2 diabetes and to assess whether estimated average glucose (AG) is an accurate measure of glycemia in different ethnic groups.
   - 1,879 participants with type 2 diabetes in the DURABLE trial who were 30 to 80 years of age from 11 countries were included.
   - For a given degree of glycemia, A1C levels vary among different ethnic groups. Ethnicity needs to be taken into account when using A1C to assess glycemic control or to set glycemic targets. Estimated AG is not a reliable marker for mean glycemia and therefore is of limited clinical value.

z. Wright LA, Hirsch IB. Metrics beyond hemoglobin A1C in diabetes management: Time in range, hypoglycemia, and other parameters. *Diabetes Technol Ther*. 2017; 19(S2): S16-S26
   - This review article discusses clinical instances in which A1C should not be used, and synthesizes scenarios in which alternative biomarkers may be falsely high or falsely low. Further, the authors highlight the potential for continuous glucose monitoring to inform individualized management.

Benefits of CGM Data Review

Peer-Reviewed Publications

a. Akturk HK, Dowd R, Shankar K, Derdzinski M. Real-World Evidence and Glycemic Improvement Using Dexcom G6 Features. *Diabetes Technol Ther.* 2021;23(S1):S21-S26. doi:10.1089/dia.2020.0654
   - This study reports patterns in real-world use of discretionary features of the Dexcom G6 CGM system, including: the “High Glucose” threshold alert (adjustable), the “Low Glucose’’threshold alert (adjustable), the “Urgent Low

Soon" alert, the Share feature for remote monitoring, the Dexcom CLARITY suite of analytic tools and reports, and a voice-enabled feature for announcing the current glucose value and trend.
- Engagement with these features was calculated for 35,993 users over a 6-month observation period.
- Individuals who used more of the alert and notification features had more favorable glycemic outcomes, including time in range (TIR), than those who used fewer.
- More extensive engagement with CLARITY notifications was associated with higher TIR.

b. Maines E, Pertile R, Cauvin V, Soffiati M, Franceschi R. Glucose metrics improvement in youths with type 1 diabetes using the Ambulatory Glucose Profile report: A real-world study. *Diabetes Res Clin Pract*. 2024;212:111720. doi:10.1016/j.diabres.2024.111720
   - This real-world study analyzed differences in TIR between youth who received structured counseling on interpreting their AGP report and used it regularly versus those who did not.
   - At 12 months, those who trained and using their AGP report had a higher percent sensor usage and higher TIR, as well as lower time above range and A1C.
   - Systematic use of the AGP software was feasible and showed improved metabolic control in youths with T1D. This may be related to increased sensor usage and more informed decisions.

c. Polonsky WH, Soriano EC, Fortmann AL. The Role of Retrospective Data Review in the Personal Use of Real-Time Continuous Glucose Monitoring: Perceived Impact on Quality of Life and Health Outcomes. *Diabetes Technol Ther.* 2022;24(7):492-501. doi:10.1089/dia.2021.0526
   - This cross-sectional study found that receiving a weekly summary of one's CGM data may contribute to health benefits.
   - 398 adults with T1D or insulin-using T2D (ages 21–75 years, nearly half T1D and half T2D) who were current users of the Dexcom G5 or G6 RT-CGM systems, had downloaded the Dexcom CLARITY app, and had chosen to receive the weekly CLARITY email summary of their glucose data were surveyed. Additionally, 7 participants completed semi-structured interviews.
   - The majority reported that receiving and viewing the report contributed to improved hypoglycemic confidence (75.9%) and overall well-being (50.0%), reduced diabetes distress (59.3%–74.1%), and helped to improve A1C (73.1%)

and reduce problems with hypoglycemia (61.8%) and chronic hyperglycemia (73.1%).
- There was broad agreement among respondents (80%–90%) that the weekly report helped them feel better (e.g.,''helps me to feel more in control of diabetes,'' ''helps me to stay motivated'') and do better (e.g., ''encourages me to stick with my diabetes care'', ''helps me to acknowledge problems, and make positive changes''), with similar findings for the T1D and T2D groups.

Abstracts/Other

a. van der Linden J, Puhr S, Welsh J, Walker T. Frequent engagement with retrospective real-time CGM is associated with improved glycemic control [abstract 622-P]. *Diabetes*. 2021; 70(Supplement 1).
   - This study evaluated the association between Dexcom's CLARITY mobile diabetes management app and glycemic metrics.
   - Data came from a sample of 25,000 US-based users who had transitioned from the Dexcom G5 to the Dexcom G6 CGM in September 2020. Users were organized into groups based on how often they used CLARITY - never, at least once, or every day in September 2021. Utilization was then calculated as the number of sensor glucose values over the number of total possible sensor glucose values for days with greater than or equal to 1 glucose value.
   - CLARITY engagement was associated with lower mean glucose and higher TIR, mainly attributable to less hyperglycemia.

GMI, Mean Glucose, and A1C

Peer-Reviewed Publications

a. Bergenstal RM, Beck RW, Close KL, Grunberger G, Sacks DB, Kowalski A, et al. Glucose management indicator (GMI): a new term for estimating A1C from continuous glucose monitoring. *Diabetes Care*. 2018;41(11):2275–80.
   - Estimated A1C (eA1C) is a measure converting the mean glucose from CGM or self-monitored blood glucose readings, using a formula derived from glucose readings from a population of individuals, into an estimate of a simultaneously measured laboratory A1C. Many patients and clinicians find the eA1C to be a helpful educational tool, but others are often confused or even frustrated if the eA1C and laboratory-measured A1C do not agree.

- This led the authors to work toward a multipart solution to facilitate the retention of such a metric, which includes renaming the eA1C the glucose management indicator (GMI) and generating a new formula for converting CGM-derived mean glucose to GMI based on recent clinical trials using the most accurate CGM systems available. This solution also required ensuring a smooth transition from the old eA1C to the new GMI is providing new CGM analyses and explanations to further understand how to interpret GMI and use it most effectively in clinical practice.

b. Fabris C, Heinemann L, Beck RW, Cobelli C, Kovatchev B. Estimation of hemoglobin A1c from continuous glucose monitoring data in individuals with type 1 diabetes: Is time in range all we need? *Diabetes Technology and Therapeutics*. 2020;22(7):501-508.
   - This study aims to bridge the gap between A1C and TIR by introducing TIR-driven estimated A1C (eA1C). This study used data from Protocol 1 (training data set - 125 individuals w/ T1D) and Protocol 3 (testing data set - 168 individuals) of the International Diabetes Closed-Loop Trial.
   - Mean absolute differences between HbA1c and eA1c 3- and 6-month post calibration were 0.25% and 0.24%; Pearson's correlation coefficients were 0.93 and 0.93; percentages of eA1c within 10% from reference HbA1c were 97.6% and 96.3%, respectively
   - Using a model individualized with one A1C measurement, TIR provides an accurate approximation of A1C for at least 6 months, reflecting blood glucose fluctuations and nonglycemic biological factors. Thus, eA1C is an intermediate metric that mathematically adjusts a CGM-based assessment of glycemic control to individual glycation rates.

c. Grimsmann JM, von Sengbusch S, Freff M, Ermer U, Placzek K, Danne T, et al. Glucose management indicator based on sensor data and laboratory HbA1c in People with type 1 diabetes from the DPV database: Differences by sensor type. *Diabetes Care*. 2020 Jul 20;dc200259.
   - This study analyzed 132,361 CGM days from a total of 1,973 individuals with type 1 diabetes for ≥1 year from the German/ Austrian/Swiss/Luxembourgian Prospective Diabetes Follow-up Registry. The study revealed discrepancies between CGM-derived GMI and laboratory A1C. They also found that these discrepancies differed between intermittent scanning CGM and real time CGM
   - CGMs are typically more accurate in the euglycemic range rather than the hypoglycemic or hyperglycemic range. Different modes of calibration also lead to different sensitivities, and it is necessary to adjust the GMI formula to each sensor type.

d. Juvenile Diabetes Research Foundation Continuous Glucose Monitoring Study Group. Hemoglobin A1c and mean glucose in patients with type 1 diabetes: analysis of data from the Juvenile Diabetes Research Foundation continuous glucose monitoring randomized trial. *Diabetes Care*. 2011;34(3):540–4.
    - This study aimed to determine the relationship between mean sensor glucose concentrations and A1C values in individuals with type 1 diabetes from the Juvenile Diabetes Research Foundation continuous glucose monitoring randomized trial.
    - Sensor data was collected at least 4 days/week for 3 months before a central laboratory–measured A1C was performed for 252 subjects aged 8–74 years, the majority of whom had stable A1C values.
    - The authors determined that there is substantial individual variability between the measured versus calculated mean glucose concentrations.
e. Perlman JE, Gooley TA, McNulty B, Meyers J, Hirsch IB. HbA1c and glucose management indicator discordance: A real-world analysis. *Diabetes Technol Ther*. 2021;23(4):253-258. doi:10.1089/dia.2020.0501
    - This retrospective study calculated HbA1c-GMI discordance and assessed for any impact of comorbidities.
    - Data was collected from 641 patients with type 1 diabetes between 2012 – 2019. Most patients had diabetes for greater than 20 years. The mean duration of CGM wear was 24.5 ± 8 days.
    - Only 11% of patients had HbA1c-GMI discordance <0.1%, but 50% and 22% had differences ≥0.5% and ≥1%. There was increased discordance with advanced chronic kidney disease.

CGM Accuracy, Metrics, and General Benefits

Peer-Reviewed Publications

a. Aleppo G, Ruedy KJ, Riddlesworth TD, Kruger DF, Peters AL, Hirsch I, Bergenstal RM, Toschi E, Ahmann AJ, Shah VN, Rickels MR, Bode BW, Philis-Tsimikas A, Pop-Busui R, Rodriguez H, Eyth E, Bhargava A, Kollman C, Beck RW; REPLACE-BG Study Group. REPLACE-BG: A randomized trial comparing continuous glucose monitoring with and without routine blood glucose monitoring in adults with well-controlled type 1 diabetes. *Diabetes Care*. 2017; 40(4): 538-545.

- This randomized clinical trial sought to assess if using CGM without adjunctive BGM measurements would be as safe and effective as using CGM with BGM measurements.
- Participants were over 18 years of age, used an insulin pump, and had an A1C of less than or equal to 9.0%.
- The primary outcome of the 26-week trial was time in range. The TIR of those on CGM only remained at 63% for both baseline and at 26 weeks. The TIR of those on CGM+BGM remained at 65% for both baseline and at 26 weeks.
- Results indicated that use of CGM without confirmatory use of BGM is safe and effective.

b. Beck R, Raghinaru D; Calhoun P; Bergenstal R. The relationship between percent time <70 mg/dL and Percent Time <54 mg/dL measured by continuous glucose monitoring. *Diabetes Technology & Therapeutics*. February 2023. 25(3).
   - Datasets with Dexcom CGM data from 9 type 1 diabetes randomized trials were pooled to evaluate the relationship between CGM-measured T<70 and T<54.
   - For blinded data, the T<54 : T<70 ratio varied from 19% when the amount of T<70 was <1% to 44% when the amount of T<70 was ≥7% whereas for unblinded data the ratio varied from 15% to 42%, respectively. When T<70 was 4%, the predicted T<54 was 1.18%, 0.94%, and 0.91% for the blinded, unblinded, and AID data, respectively (P<0.001 comparing blinded versus unblinded and AID).
   - The T<54 : T<70 ratio increases with greater T<70, and the ratio generally is higher with blinded than unblinded CGM data, with the latter appearing to be similar to AID system data. The finding of greater T<54 for a given T<70 with blinded CGM data is presumed to be due to an action being taken by the unblinded CGM user and/or by the AID system to minimize hypoglycemia which will have the effect of reducing the amount of T<54.

c. Camerlingo N, Vettoretti M, Facchinetti A, Sparacino G, Mader JK, Choudhary P, Del Favero S. An analytical approach to determine the optimal duration of continuous glucose monitoring data required to reliably estimate time in hypoglycemia. *Scientific Reports*. 2020; 10(1):18180.
   - TBR is estimated from data recorded by CGM sensors, but the duration of CGM recording guaranteeing a reliable indicator is under debate in the literature. This study framed this as a random variable estimation problem and studied the convergence of the estimator, deriving a formula that links the TBR estimation error variance with the CGM recording length.

- This formula was tested on 148 individuals with type 1 diabetes. The formula demonstrated to predict the uncertainty of the TBR estimate in a single patient, using patient-specific parameters and on the population level without the need of parameters individualization. The approach can be applied to TIR and TAR and adopted by clinicians.
- Article emphasized the differences between cohorts in clinical trials and individuals.

d. Hermanns N, Ehrmann D, Heinemann L, Freckmann G, Waldenmaier D, Calhoun P. Real-time continuous glucose monitoring can predict severe hypoglycemia in people with type 1 diabetes: Combined analysis of the HypoDE and DIAMOND trials. *Diabetes Technology and Therapeutics*. 2022.
   - Combining the DIAMOND and HypoDE trials, the study analyzed hypoglycemia parameters from masked CGM over 14 days during baseline from open CGM over 14 days after randomization. Receiver operating characteristics (ROC) curves were used to evaluate the screening performance of these measures to predict future severe hypoglycemia. Data from 288 individuals with type 1 diabetes were analyzed.
   - Results showed that CGM-derived hypoglycemic parameters have a good screening performance to significantly predict future clinical hypoglycemia.

e. Marak MC, Calhoun P, Damiano ER, Russell SJ, Ruedy KJ, Beck RW. Testing the real-world accuracy of the Dexcom G6 Pro CGM during the Insulin-Only Bionic Pancreas Pivotal Trial. *Diabetes Technol Ther*. Published online October 3, 2023. doi:10.1089/dia.2023.0287
   - The Insulin-Only Bionic Pancreas Trial offered a unique opportunity to assess CGM accuracy in real-world settings over the first 48-60 hours of wear, without sampling biases that may occur in accuracy studies using unblinded sensors.
   - 53 study participants with type 1 diabetes wore a blinded Dexcom G6 Pro sensor and used a blood glucose meter to regularly measure glucose levels. BGM measurements were paired with the closest CGM reading within 5 minutes, resulting in 1073 CGM-BGM measurement pairs.
   - In general, CGM values tended to be slightly higher than BGM values across the range of glucose values. The overall mean bias was +4 mg/dL, with a bias of +6 mg/dL in the first 12 h, +6 mg/dL in 12–24 h, and +3 mg/dL after 24 h. The CGM was most accurate when the rate of change of glucose levels was low. The mean absolute relative difference (MARD) was 11.0% over a median period of 50 h (range 47–79 h). The MARD was 13.6% in the first 12 h, 10.5% in hours 12–24, and 10.1% after the first 24 h.

- Investigators found similar accuracy results as were previously measured in a lab setting. CGM accuracy at home was high, with a MARD of 11.0% when compared with BGM measurements over a median period of 50 h, suggesting the Dexcom G6 offers a high degree of accuracy on the first day and beyond.

Benefits of Sensor Use in both T1D and T2D

a. Beck SE, Kelly C, Price DA; COACH Study Group. Non-adjunctive continuous glucose monitoring for control of hypoglycaemia (COACH): Results of a post-approval observational study. *Diabet Med*. 2022;39(2):e14739. doi:10.1111/dme.14739
   - This 12-month observational study is the first study powered to evaluate the impact of non-adjunctive real-time continuous glucose monitoring (RT-CGM) use on the rate of debilitating moderate or severe hypoglycemic events.
   - 519 adults with insulin-requiring diabetes (33.5% T2D) who were new to RT-CGM participated in a 6-month control phase phase where insulin dosing decisions were based on self monitoring of blood glucose (SMBG) values, followed by a 6-month phase where decisions were based on RT-CGM data (i.e. non-adjunctive RT-CGM use).
   - The mean per-patient frequency of hypoglycaemic events decreased by 63% from 0.08 (0.016) during the SMBG phase to 0.03 (0.010) during the RT-CGM phase (p = 0.005).
   - HbA1c decreased during the RT-CGM phase both for participants with type 1 diabetes (T1D) and T2D and there was a trend towards larger reductions among individuals with higher baseline HbA1c.
   - Results demonstrate that among adults with insulin-requiring diabetes, non-adjunctive use of RT-CGM data is safe, resulting in significantly fewer debilitating hypoglycemic events than management using SMBG.
b. Di Molfetta S, Caruso I, Cignarelli A, et al. Professional continuous glucose monitoring in patients with diabetes mellitus: A systematic review and meta-analysis. *Diabetes Obes Metab*. 2023;25(5):1301-1310. doi:10.1111/dom.14981
   - This study aimed to evaluate the effect on glucose control of professional CGM-based care as compared with standard care in the management of people with type 1 and type 2 diabetes.
   - The use of professional-CGM was associated with greater A1C reduction from baseline (-0.28%, 95% CI -0.36% to -0.21%, I2 = 0%) than usual care, irrespective of type of diabetes, length of follow up, frequency of CGM use and duration of CGM recording. In some studies professional-CGM showed a

beneficial effect on change in TIR from baseline (5.59%, 95% CI 0.12 to 11.06) and a neutral effect on change in time below range from baseline (-0.11%, 95% CI -1.76% to 1.55%).
    - In people with type 1 and type 2 diabetes, professional-CGM-driven care is superior to usual care in improving glucose control without increasing hypoglycemia.

c. Dunn TC, Xu Y, Hayter G, Ajjan RA. Real-world flash glucose monitoring patterns and associations between self-monitoring frequency and glycaemic measures: A European analysis of over 60 million glucose tests. *Diabetes Res Clin Pract*. 2018; 137: 37-46.
    - This study analyzed vast amounts of flash CGM data (over 60 million glucose readings) across the world to determine the characteristics of glucose monitoring at the world population level.
    - The study examined glucose parameters such as estimated A1C and time in, above, and below range identified as 70-180mg/dL. Each individual was sorted and ranked based on scan frequency.
    - The study found that A1C gradually but significantly decreased from 8.0% to 6.7% as the number of scans per day increased from 4.4 to 48.1 scans. Users performed an average of 16.3 scans per day. Time in range increased from 12.0 hours to 16.8 hours per day across the same trend. Additionally, time below 70mg/dL decreased by 15% and time above 150mg/dL decreased from 10.4 to 5.7 hours per day.
    - The study concluded that increases in scans of flash CGM was linked to improved glycemic markers such as increased TIR and reduced TAR and TBR.

d. Hansen MV, Pedersen-Bjergaard U, Heller SR, et al. Frequency and motives of blood glucose self-monitoring in type 1 diabetes. *Diabetes Res Clin Pract*. 2009;85(2):183-188. doi:10.1016/j.diabres.2009.04.022
    - This cross-sectional multicentre survey assessed the frequency of self-monitored blood glucose (SMBG) testing and motives for testing among 1076 patients with type 1 diabetes
    - SMBG was performed daily by 39% of the patients and less than weekly by 24%
    - 67% reported to perform routine testing, while the remaining 33% only tested when hypo- or hyperglycaemia was suspected
    - Lower HbA1c was associated with more frequent testing

e. Maiorino MI, Signoriello S, Maio A, Chiodini P, Bellastella G, Scappaticcio L, et al. Effects of continuous glucose monitoring on metrics of glycemic control in diabetes: A

systematic review with meta-analysis of randomized controlled trials. *Diabetes Care*. 2020;43(5):1146–56.

- This paper conducted a systematic review and meta-analysis of 15 randomized controlled trials (RCTs) including 2,461 comparing CGM with usual care for parameters of glycemic control in both type 1 and type 2 diabetes.
- Compared with the usual care (overall data), CGM was associated with modest reduction in HbA1c and lower time above range, time below range, and glucose variability, with heterogeneity between studies. The increase in TIR was significant and robust independent of diabetes type, method of insulin delivery, and reason for CGM use.

f. Karter AJ, Parker MM, Moffet HH, Gilliam LK, Dlott R. Association of real-time continuous glucose monitoring with glycemic control and acute metabolic events among patients with insulin-treated diabetes. *JAMA*. 2021; 325(22): 2273-2284.

- This study assesses the association between CGM use and outcomes such as A1C, hospitalization due to hypoglycemia, and hospitalization due to hyperglycemia.
- This study included participants with type 1 and type 2 diabetes; 5,673 people with type 1 and 36,080 people with type 2, all of whom are treated with insulin. None of the participants had any prior experience with CGM use
- Study found that use of rtCGM was associated with a 0.40% decrease in A1C, a statistically significant mark. Rates of hospitalization for hypoglycemia also decreased significantly by 2.73%. There was no significant difference in hospitalization due to hyperglycemia.

g. Reaven PD, Newell M, Rivas S, Zhou X, Norman GJ, Zhou JJ. Initiation of Continuous Glucose Monitoring Is Linked to Improved Glycemic Control and Fewer Clinical Events in Type 1 and Type 2 Diabetes in the Veterans Health Administration. *Diabetes Care*. 2023;46(4):854-863. doi:10.2337/dc22-2189

- This large retrospective observational cohort study sought to determine whether CGM initiation improves glycemic management and reduces risk of hospital admission.
- Declines in HbA1c were significantly greater in CGM users with T1D (20.26%; 95% CI 20.33, 20.19%) and T2D (20.35%; 95% CI 20.40, 20.31%) than in nonusers at 12 months.
- Percentages of patients with A1C <8 and <9% after 12 months were also significantly greater among CGM users.

- In T1D, CGM initiation was associated with significantly reduced risk of hypoglycemia (hazard ratio [HR] 0.69; 95% CI 0.48, 0.98) and all-cause hospitalization (HR 0.75; 95% CI 0.63, 0.90).
- In T2D, there was a reduction in risk of hyperglycemia (HR 0.87; 95% CI 0.77, 0.99) and all-cause hospitalization (HR 0.89; 95% CI 0.83, 0.97) among CGM users.

Limitations of TIR and CGM

Peer-Reviewed Publications

a. Freckmann G, Pleus S, Schauer S, Link M, Jendrike N, Waldenmaier D, et al. Choice of continuous glucose monitoring systems may affect metrics: Clinically relevant differences in times in ranges. *Exp Clin Endocrinol Diabetes*. 2021 Jan 28. doi: 10.1055/a-1347-2550.
    - This interventional, non-randomized study aimed to determine whether the type of CGM used can influence health metrics and clinical decision-making. More specifically, researchers used an isCGM and an rtCGM system to compare CGM metrics.
    - To assess differences in CGM measurements, 24 participants with type 1 diabetes wore both a FreeStyle Libre (System A) and a Dexcom G5 (System B) sensor for 7 days. The study included induced postprandial excursions on two study days. Researchers compared mean glucose, coefficient of variation (CV), GMI, TIR, TAR, and TBR measurements between the two CGM systems. CGM metrics were also compared with SMBG measurements.
    - The two CGM systems showed, on average, very similar results for time spent in range and for CV. However, individual TIR and CV differed in the subjects. These differences would not lead to different clinical decisions based on recommendations in the ADA Standards of Care. Measures or TBR and TAR differed substantially between the two CGM systems and would lead to different clinical decisions.
b. Kompala T, Wong J, Neinstein A. Diabetes Specialists Value Continuous Glucose Monitoring Despite Challenges in Prescribing and Data Review Process. J Diabetes Sci Technol. 2023;17(5):1265-1273. doi:10.1177/19322968221088267
    - This study sought to assess diabetes clinicians' behavior related to CGM and CGM-derived data utilization. The analysis includes survey responses from 182

providers, of whom most worked at academic centers (73.2 %), were endocrinologists (70.6%), and practiced in urban settings (70.7%).

- 69.4% of providers reported CGM use in the majority of their patients with type 1 diabetes. In contrast, just half of the providers reported CGM use in 10% to 50% of their patients with type 2 diabetes. No difference was found in rates of CGM use based on providers' years of experience, patient volume, practice setting, or clinic type.
- All respondents believed CGM improved quality of life and could optimize diabetes control and most reported that their patients were interested in CGM.
- Nearly all providers reviewed CGM data each visit (97.7%) and actively involved patients in the data interpretation (98.8%).
- 56.1% of clinicians agreed they had an efficient process to obtain and review CGM data during a typical scheduled in-clinic visit, 68.9% endorsed having adequate software and computer resources to visualize the CGM data, but only 45.1% endorsed adequate time to obtain and interpret the CGM data. Still, 98.7% agreed it was worth the effort to have CGM data to discuss with the patient.
- Top reported facilitators of CGM use were the providers' view of CGM as a beneficial tool for diabetes care and patients' desire to use CGM.
- Frequently reported barriers related to challenges in insurance coverage, burdensome prescription process, and prohibitive cost. Respondents also described the challenges in accessing CGM data and limited time and support for training patients and CGM review.

Abstracts/Other

a. Bergenstal R, Hachmann-Nielsen E, Tarp J, Kvist K, Buse J. Real world continuous glucose monitoring data on time-in-range from a U.S. population, 2015-2019 [Abstract 65-LB]. *Diabetes* 2021; 70(Supplement 1).
    - This real-world study aimed to analyze the proportion of people with ≥70% TIR and the proportion with ≥70% TIR and <1% time <54 mg/dL in an adult population.
    - Data were collected from 2015 to 2019 from the Cornerstone4Care (C4C) database, a patient support program for people with T1D and T2D on any treatment type. CGM traces were divided into 14-day periods according to the AGP-reporting system. Only profiles with data aligned with these standards were included.

- In total, 484 individuals uploaded CGM-data to the database (4727 AGPs); 242 had T1D and 74 had T2D, the rest were unknown. Average TIR based on mean profiles was 63%, 68%, and 64% for T1D, T2D, and all, respectively.
- Less than half of the population achieved ≥70% TIR and about 30% of that group also had <1% time <54 mg/dL. The study concluded that there's an opportunity to improve attainment of TIR goals and support the use of CGM data in optimizing diabetes care.

Individualized Target Ranges

Peer-Reviewed Publications

a. Akturk HK, Battelino T, Castañeda J, Arrieta A, van den Heuvel T, Cohen O. Future of Time-in-Range Goals in the Era of Advanced Hybrid Closed-Loop Automated Insulin Delivery Systems. *Diabetes Technol Ther*. 2024;26(S3):102-106. doi:10.1089/dia.2023.0432
    - This review article delves into the current status of time in tight range (TITR; 70–140 mg/dL) as an emerging marker and explores how advanced hybrid closed-loop systems may offer a promising avenue for achieving this higher level of glycemic control.
b. Bahillo-Curieses P, Fernández Velasco P, Pérez-López P, Vidueira Martínez AM, Nieto de la Marca M de la O, Díaz-Soto G. Utility of time in tight range (TITR) in evaluating metabolic control in pediatric and adult patients with type 1 diabetes in treatment with advanced hybrid closed-loop systems. *Endocrine*. Published online May 30, 2024. doi:10.1007/s12020-024-03881-6
    - This prospective observational study analyzed the relationship between time in tight range (TITR; 70–140 mg/dL) and other metrics among 117 adult and pediatric participants with type 1 diabetes initiating use of the Medtronic MiniMed 780G system.
    - HbA1c, TIR, TITR, GMI, TBR, and TAR all showed significant improvements after AHCL initiation. CV also improved, while time between 140–180 mg/dl remained unchanged.
    - TITR > 50% was achieved by 76.3% of patients.
    - Authors conclude that TITR may be best suited to indicate improvements in metabolic control following AHCL initiation given that greatest improvement was seen in this metric

c. Beck RW. Is It Time to Replace Time-in-Range with Time-in-Tight-Range? Maybe Not. *Diabetes Technol Ther.* 2024;26(3):147-150. doi:10.1089/dia.2023.0602
    - This editorial review article discusses what existing evidence suggests as the usefulness of a lower 70–140 mg/dL glucose target. Beck suggests that DCCT and Swedish registry data only demonstrate a causal relationship between complications and glucose concentrations substantially above 180 mg/dL, and suggests that TITR may not be a valuable metric unless it is proven that glucose concentrations between 140 and 180 mg/dL have a meaningful effect on the risk of complications. Based on existing evidence on the relationship between TIR and TITR, the author asserts that TIR is more appropriate for patient care than TITR except when treatment goals are near normoglycemia (such as when targeting T2D remission) or when a person's TIR approaches 90% or higher.
d. Beck RW, Raghinaru D, Calhoun P, Bergenstal RM. A Comparison of Continuous Glucose Monitoring-Measured Time-in-Range 70-180 mg/dL Versus Time-in-Tight-Range 70-140 mg/dL. *Diabetes Technol Ther*. 2024;26(3):151-155. doi:10.1089/dia.2023.0380
    - This study analyzed CGM data collected using blinded or unblinded Dexcom sensors from 9 studies with 912 participants with T1D and 2 studies with 184 participants with T2D.
    - Researchers found the overall correlation between TIR and TITR was 0.94, meaning that TIR and TITR are highly correlated, although the relationship is nonlinear.
    - TITR was higher for a given TIR for T2D compared with T1D, though after adjusting for the differences in CV or TBR, the differences were minimized.
    - The TIR-TITR relationship was nonlinear, with a higher ratio of TITR:TIR observed as TIR increase—ranging from 0.42 when TIR was 20% to 0.66 when TIR was 80%.
    - The TIR-TITR relationship varied according to CV and TBR, such that the higher the CV or amount of TBR, the greater was TITR for a given TIR.
e. Castañeda J, Arrieta A, van den Heuvel T, Battelino T, Cohen O. Time in Tight Glucose Range in Type 1 Diabetes: Predictive Factors and Achievable Targets in Real-World Users of the MiniMed 780G System. *Diabetes Care*. 2024;47(5):790-797. doi:10.2337/dc23-1581
    - This retrospective observational study examined time spent in the 70–140 mg/dL (TITR) range, as well as its predictors and relationship to time in range 70–180 mg/dL (TIR) among real-world users of the Medtronic MiniMed 780G system.

- 13,461 users showed an average TITR of 48.9% in those age ≤15 years and 48.8% in those >15 years old. The groups had an average TIR of 71.2% and 73.9%, respectively.
- Consistent use of a glucose target (GT) of 100 mg/dL and active insulin time (AIT) of 2 h were the most relevant factors predicting higher TITR ($P < 0.0001$). The relative impact of these settings on TITR was 60% and 86% greater than that on TIR, respectively.
- TITRs of ~45%, ~50%, and ~55% (56.4% and 58.0%) were best associated with glucose management indicators <7.0%, <6.8%, and <6.5%, respectively.
- TITRs of >45%, >50%, and >55% were achieved in 91%, 74%, and 55% of those age ≤15 years and 93%, 81%, and 57% of older group users, respectively, at optimal settings.
- The authors conclude that 1) mean TIR and mean TITR is high in MiniMed 780G users, 2) consistent use of optimal GT/AIT improves TITR , 3) the impact of these settings on TITR is larger than on TIR, and 4) a TITR target >50% should be considered as a treatment goal.

f. Dovc K and Battelino T. Time in range centered diabetes care. *Clinical Pediatric Endocrinology*. 2021 Jan; 30(1):1-10.
   - This article reviews the current evidence behind CGM use and appropriate time in range targets.

g. Dunn TC, Ajjan RA, Bergenstal RM, Xu Y. Is It Time to Move Beyond TIR to TITR? Real-World Data from Over 20,000 *iabetes Technol Ther.*Users of Continuous Glucose Monitoring in Patients with Type 1 and Type 2 Diabetes. D 2024;26(3):203-210. doi:10.1089/dia.2023.0565
   - This study evaluated the relationship between average glucose (AG), time in range 70–180 mg/dL (TIR), and time in tight range 70–140 mg/dL (TITR).
   - A retrospective analysis was conducted of real-world de-identified data from 22,006 FreeStyle Libre CGM users with type 1 (T1D) or type 2 diabetes (T2D).
   - T2D subgroups, regardless of treatment type, displayed the highest TIR and TITR values, associated with lowest glycemic variability (measured as glucose coefficient of variation [CV] of 23–30%). The T1D group showed the lowest TIR and TITR, associated with the highest CVs (36-38%).
   - Overall, higher CV was associated with lower TIR and TITR for AG values below 180 and 140 mg/dL, respectively, with the reverse holding true for AG values above these thresholds.

- The authors conclude that TITR, rather than TIR, may be preferable to employ once AG falls below 140 mg/dL and near-normal glucose levels are required clinically.

h. Kalra S, Shaikh S, Priya G, Baruah MP, Verma A, Das AK, et al. Individualizing time-in-range goals in management of diabetes mellitus and role of insulin: Clinical insights from a multinational panel. *Diabetes Therapy*. 2020 Dec 26; 12:465-485.
   - A multinational group of endocrinologists and diabetologists reviewed the existing recommendations on TIR, provided their clinical insights into the individualization of TIR targets, and clarified the role of second-generation basal insulin analogues in addressing TIR.
   - 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 A1C for effective diabetes management and decreasing the risk of both micro- and macrovascular complications. In addition, 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.

i. Passanisi S, Piona C, Salzano G, et al. Aiming for the Best Glycemic Control Beyond Time in Range: Time in Tight Range as a New Continuous Glucose Monitoring Metric in Children and Adolescents with Type 1 Diabetes Using Different Treatment Modalities. *Diabetes Technol Ther*. 2024;26(3):161-166. doi:10.1089/dia.2023.0373
   - This real-world cross-sectional study evaluated time in tight range (TITR) 70–140 mg/dL (3.9–7.8 mmol/L), its correlation with standard continuous glucose monitoring (CGM) metrics, and the clinical variables that possibly have a substantial impact on its value.
   - Among 854 children and adolescents with type 1 diabetes using different treatment strategies, average TITR was 36.4% ±12.8%.
   - A time in range (TIR) cut-off value of 71.9% identified subjects achieving a TITR ≥50% (area under curve 0.98; 95% confidence interval 0.97–0.99, $P < 0.001$), and a strong positive correlation between these two metrics was observed ($r = 0.95$, $P < 0.001$). A 1% increase in TIR was associated with 1.84 increased likelihood of achieving TITR ≥50%.
   - Use of a hybrid-closed loop system ($B = 7.78$; $P < 0.001$),, disease duration ($B = -0.26$, $P = 0.006$), coefficient of variation ($B = -0.30$, $P = 0.004$), and glycated hemoglobin ($B = -8.82$; $P < 0.001$) emerged as significant predictors of TITR levels.

j. Tanenbaum ML, Pang E, Tam R, et al. "We're taught green is good": Perspectives on time in range and time in tight range from youth with type 1 diabetes, and parents of youth with type 1 diabetes. *Diabet Med*. Published online August 8, 2024:e15423. doi:10.1111/dme.15423
    - This qualitative study assessed pediatric and parent CGM user experiences with TIR metrics and reactions to TITR as a potential new target.
    - Semi-structured interviews and focus groups with thirty participants showed individuals had varying levels of understanding of TIR. Some developed personally preferred glucose ranges. Parents often aimed to surpass 70% TIR. Many described feelings of stress and disappointment when they did not meet a TIR goal.
    - Concerns about TITR included increased stress and burden; risk of hypoglycaemia; and family conflict. Some participants said TITR would not change their daily lives; others said it would improve their diabetes management. Families requested care team support and a clear scientific rationale for TITR.
k. Xu Y, Dunn TC, Bergenstal RM, Cheng A, Dabiri Y, Ajjan RA. Time in Range, Time in Tight Range, and Average Glucose Relationships Are Modulated by Glycemic Variability: Identification of a Glucose Distribution Model Connecting Glycemic Parameters Using Real-World Data. *Diabetes Technol Ther*. Published online February 26, 2024. doi:10.1089/dia.2023.0564
    - This real-world study analyzed data from 29,164 individuals with type 1 diabetes (T1D), type 2 diabetes (T2D) and gestational diabetes (GDM) using FreeStyle Libre flash continuous glucose monitoring (FCGM) to investigate whether glycemic variability (assessed as glucose coefficient of variation [CV]) affects the relationship between average glucose (AG) and time in range (TIR)/time in tight range (TITR).
    - At an AG of 150 mg/dL, the low CV tertile had an average TIR of 80% ± 5.6% while the high CV tertile had a TIR of 62% ± 6.8%. At an AG of 130 mg/dL the low CV tertile had a average TITR of 65% ± 7.5% and high CV tertile had a TITR of 49% ± 7.0%.
    - In contrast, higher CV was associated with increased TIR and TITR at AG levels outside the upper limit of these ranges (>140 mg/dL and >180 mg/dL).
    - Results glycemic variability can significantly influence the relationship between AG and TIR with opposing effects according to AG level

Patient/User Reported Outcomes

Peer-Reviewed Publications

a. Aslani S, Jensen CW, Olsson AO, Thomsen SS, Cichosz SL. Time in range is associated with less hypoglycemia fear and higher diabetes technology acceptance in adults with well-controlled T1D. *Journal of Diabetes and its Complications*. 2023;37(2):108388.
    - The goal of this report was to investigate the association between TIR and scores from the Hypoglycemia Fear Survey (HFS)/Diabetes Technology Questionnaire (DTQ).
    - 171 people with diabetes were included in the analysis. Association between TIR and HFS/DTQ scores was investigated based on data from a 26-week clinical-trial (REPLACE-BG).4 The surveys were analyzed from the 26-week follow-up.
    - The weak association between TIR and HFS/DTQ scores indicate that a higher TIR is associated with less hypoglycemic fear and better technology acceptance.
b. Burckhardt M-A, Roberts A, Smith GJ, Abraham MB, Davis EA, Jones TW. The use of continuous glucose monitoring with remote monitoring improves psychosocial measures in parents of children with type 1 diabetes: a randomized crossover trial. *Diabetes Care*. 2018;41(12):2641–3.
    - Participants included children aged 2-12 years old with type 1 diabetes. The parents of the children were also studied.
    - The study included two 3-month periods using conventional blood glucose monitoring, which acted as the control, and the Dexcom G5 Mobile CGM with remote monitoring.f
    - The first to do so, this study looked at the effects of CGMs with remote monitoring on psychosocial outcomes in children with type 1 diabetes. This remote capability was part of the Dexcom G5 Mobile system.
    - They found that there was improved quality of life, family stress was reduced, parental sleep improved, and the use of this remote monitoring reduced parental fear of hypoglycemia.
c. Charleer S, De Block C, Nobels F, Radermecker RB, Lowyck I, Mullens A, et al. Sustained impact of real-time continuous glucose monitoring in adults with type 1 diabetes on insulin pump therapy: Results after the 24-Month RESCUE study. *Diabetes Care*. 2020 Oct; dc201531.
    - This prospective, observational, cohort study evaluated the impact of nationwide reimbursement of rtCGM on 441 adults with type 1 diabetes on

insulin pumps. Forty-two percent had impaired awareness of hypoglycemia (IAH). This is the largest and longest prospective real-world cohort study to assess outcomes after initiation of rtCGM reimbursement.

- Over 24 months, the use of rtCGM led to sustained improvements in hypoglycemia-related glucose control, lower HbA1c, lower fear of hypoglycemia, less acute hypoglycemia-related events, and fewer diabetes-related days off from work, particularly in those with IAH. On the other hand, reaching targets for TIR and hyperglycemia proved to be more difficult, with barely 30% achieving the recommended levels.

d. Clark T, Polonsky W, Soriano E. The Potential Impact of CGM Use on Diabetes-Related Attitudes and Behaviors in Adults with T2D: A Qualitative Investigation of the Patient Experience. *Diabetes Technol Ther.* Published online March 25, 2024. doi:10.1089/dia.2023.0612
   - This qualitative study sought to explore the attitudinal and behavioral changes underlying glycemic benefits of CGM use among adults with type 2 diabetes.
   - In-depth, semi-structured interviews of 34 participants revealed 6 primary themes: 1) Making the Invisible Visible, highlighting the newfound awareness of T2D in daily life; 2) Effective Decision Making, emphasizing the use of realtime glucose data for immediate and long-term choices; 3) Enhanced Self-Efficacy, describing a renewed sense of control and motivation; 4) Diabetes-Related Diet Modifications; 5) Changes in Physical Activity; and 6) Changes in Medication Taking.
   - These findings highlight CGM's potential to bring about meaningful attitudinal and behavioral changes which likely contributed to the significant glycemic benefits observed over the study period.

e. Díaz-Soto G, Pérez-López P, Férnandez-Velasco P, et al. Quality of life, diabetes-related stress and treatment satisfaction are correlated with glycemia risk index (GRI), time in range and hypoglycemia/hyperglycemia components in type 1 diabetes. *Endocrine*. Published online May 24, 2024. doi:10.1007/s12020-024-03846-9
   - This cross-sectional study investigated the relationship between CGM metrics and diabetes quality of life (DQoL), diabetes-related stress (DDS), perception of hypoglycemia (Clarke Test), visual analogic scale (VAS) and diabetes knowledge (DKQ2) in 92 adults with type 1 diabetes under under intensive insulin treatment and flash glucose monitoring.
   - Lower TIR and higher glycemia risk index (GRI) were associated with worse quality of life, diabetes-related stress and satisfaction with treatment.

f. Ehrmann D, Priesterroth L, Schmitt A, Kulzer B, Hermanns N. Associations of Time in Range and Other Continuous Glucose Monitoring-Derived Metrics With Well-Being and Patient-Reported Outcomes: Overview and Trends. *Diabetes Spectr*. 2021;34(2):149-155. doi:10.2337/ds20-0096
    - This narrative review summarizes current evidence on the association between CGM metrics and patient reported outcomes (PROs), finding preliminary evidence that suggests higher TIR is associated with better mood or less anger and negative affect and that TBR is associated with fear of hypoglycemia.
    - However, further research is needed focusing on a more precise timing between the assessments of glucose and PROs, possibly using ecological momentary assessment for a more real-time measurement of PROs

g. Evans EI, Pincus KJ, Seung H, Rochester-Eyeguokan CD. Health Literacy of Patients using Continuous Glucose Monitoring. *J Am Pharm Assoc (2003)*. Published online April 23, 2024:102109. doi:10.1016/j.japh.2024.102109
    - This study surveyed 82 participants with type 1 or type 2 diabetes who use CGMs. Health literacy was assessed using the Health Literacy/Subjective Numeracy Scale (HLS/SNS), and CGM comfort and understanding wer assessed using an investigator-developed survey.
    - Participants with higher HLS/SNS scores reported higher levels of CGM understanding and comfort. A1c <8% was also associated with higher levels of CGM comfort and understanding,
    - 51% reported no or inadequate training prior to CGM initiation, suggesting baselines literacy assessment and literacy-sensitive CGM training could help optimize benefits of CGM use.

h. Gilbert TR, Noar A, Blalock O, Polonsky WH. Change in Hemoglobin A1c and Quality of Life with Real-Time Continuous Glucose Monitoring Use by People with Insulin-Treated Diabetes in the Landmark Study. *Diabetes Technol Ther*. 2021;23(S1):S35-S39. doi:10.1089/dia.2020.0666
    - This real-world prospective study utilized A1C data and validated psychosocial questionnaires to examine changes in glycemia and quality of life during the first few months of CGM use.
    - Participants were 248 adults ages 25–65 with T1D or T2D who were on intensive insulin therapy and had never used a CGM before.
    - Mean A1C fell significantly from 8.2% at baseline to 7.1% at the end of the study ($P<0.001$)
    - Significant reductions in diabetes distress and hypoglycemic concerns were observed ($P < 0.001$).

i. Lawton J, Blackburn M, Allen J, et al. Patients' and caregivers' experiences of using continuous glucose monitoring to support diabetes self-management: qualitative study. *BMC Endocr Disord*. 2018;18(1):12. doi:10.1186/s12902-018-0239-1
   - This qualitative study conducted in-depth interviews with 24 adults, adolescents and parents using CGM for type 1 diabetes to explore user experience.
   - Participants found CGM an empowering tool because they could access blood glucose data effortlessly, and predictive information aided short-term lifestyle planning and enabled individuals to take action to prevent hypoglycaemia and hyperglycaemia. Having access to continuous data allowed participants to develop a better understanding of how insulin, activity and food impacted on blood glucose and motivated individuals to make changes and break cycles of over-treating.
   - Participants described historical CGM data as providing better, more nuanced information (compared to SMBG) to inform changes to background insulin doses and mealtime ratios. However, while participants expressed confidence making immediate adjustments to address impending hypoglycaemia and hypoglycaemia, most described needing and expecting health professionals to interpret historical CGM data and determine changes to background insulin doses and mealtime ratios.
   - In sum, CGM can be an empowering and motivational tool to fine-tune and optimize blood glucose control. However, individuals may benefit from psycho-social education, training and/or technological support to make optimal use of CGM data and use alarms appropriately.

j. Marigliano M, Pertile R, Mozzillo E, et al. Satisfaction with continuous glucose monitoring is positively correlated with time in range in children with type 1 diabetes. *Diabetes Res Clin Pract*. 2023;204:110895. doi:10.1016/j.diabres.2023.110895
   - This cross-sectional study of 210 children and adolescents with type 1 diabetes assessed the relationship between glucose control and CGM satisfaction as measured through a questionnaire
   - CGM satisfaction (CGM-SAT) scores were not associated with age, gender, annual HbA1c, % of time with an active sensor, time above range (TAR), time below range (TBR), and coefficient of variation (CV). However, CGM satisfaction was positively correlated with time in range (TIR, $p < 0.05$) and negatively correlated with glycemia risk index (GRI, $p < 0.05$).

k. Nana M, Moore S, Ang E, Lee Z, Bondugulapati L. Flash glucose monitoring: Impact on markers of glycaemic control and patient-reported outcomes in individuals with type 1

diabetes mellitus in the real-world setting. *Diabetes Research and Clinical Practice*. 2019;157:107893.

- Retrospective observational study that included patients ages >18 with type 1 diabetes who were prescribed a FreeStyle Libre FGM. This included 90 people.
- In conducting this study, the aim was to assess glycemic parameters and patient-reported outcomes in patients using Flash glucose monitoring (FGM). The results show that FGM was associated with significant improvements in A1C and they found that patients had positive experiences with the FGM.

l. Polonsky WH, Fortmann AL. The influence of time in range on daily mood in adults with type 1 diabetes, *Journal of Diabetes and Its Complications*. 2020;34(12):107746.

- This study investigated the impact of TIR on mood in 219 adults with type 1 diabetes who used CGM over a two-week period.
- Greater daily percent TIR and less time in "severe" hyperglycemia were both significantly associated with higher ratings on all positive mood elements and lower ratings on most negative mood elements. When entered together as predictors, percent TIR but not percent TAR emerged as an independent predictor of many of the positive and negative mood variables. Neither daily changes in time spent in hypoglycemia nor glycemic variability were significantly related to reported mood.
- Future research utilizing blinded CGM data may be useful to further examine the cognitive and physiological-associated pathways.

m. Runge AS, Kennedy L, Brown AS, Dove AE, Levine BJ, Koontz SP, et al. Does time-in-range matter? Perspectives from people with diabetes on the success of current therapies and the drivers of improved outcomes. *Clinical Diabetes*. 2018;36(2):112–9.

- Advocates for updated metrics that include TIR rather than solely A1C. Patients feel significant stress regarding their glycemic control and that incorporating TIR can be a helpful way to reduce this stress.
- Surveyed 3461 (92% white) members of the dQ&A patient panel through online survey which assessed "patient perceptions of the success of current diabetes drugs and devices across six categories."
- Notably, those with type 1 diabetes felt that the TIR metric had a greater impact on their daily life over A1C, yet people with T2D scored these metrics about the same.

n. Volčanšek Š, Lunder M, Janež A. Acceptability of continuous glucose monitoring in elderly diabetes patients using multiple daily insulin injections. *Diabetes Technol Ther*. 2019; 21(10): 566-574.

- This study analyzed the impact of CGMs on patient-reported outcome measures (PROMs) in elderly people with diabetes on multiple daily injections (MDI) and well-controlled diabetes. 25 MDI-treated people with diabetes over the age of 65 were instructed to use a CGM and PROMs were measured by questionnaires. CGM-recorded glycemic control metrics (TIR, TBR, CV) were compared during blinded CGM and real-time CGM.
- Satisfaction with CGM use among participants was high. 95% of participants expressed improved sense of security with CGM use, 68% reported improved sleep quality, and 82% were willing to use a CGM device after finishing the study protocol. CGM introduction did not lead to additional diabetes distress. There were significant improvements in TIR, time in hypoglycemia, and reduced glycemic variability.
- The study concluded that introduction of CGM in elderly people with well-controlled diabetes on MDI resulted in high satisfaction without introducing additional diabetes distress. CGM use also led to improved glucose control.

Abstracts/Other

a. Sainz N, Sommi A, Asamoa E, Shoger E, Wood R, Alexander C. Perceived benefits of TIR varies between patient CGM users vs HCPs. Short oral presentation presented at the European Association for the Study of Diabetes on 21 September 2022.
    - This study aimed to compare the perceived benefits of using TIR among CGM users and HCPs.
    - 67% of PWD perceived TIR as simple and intuitive for them to understand, whereas 56% of HCPs reported that TIR is simple and intuitive for patients to understand. 70% of HCPs identified TIR as a metric that informs treatment decisions to manage glucose, compared to 54% of PWD. Additionally, 68% of HCPs identified TIR as a better indicator of overall glycemic control than A1C, compared to 53% of PWD. 67% of HCPs reported that TIR provides information needed to individualize care, whereas 46% of PWD reported that TIR provides their healthcare team with the information needed to individualize care.
    - This study highlights differences in perceived TIR benefits between HCPs and PWD who use CGM. When considering the benefits of TIR, PWD value the simplicity and clarity of TIR whereas HCPs value the information and management help that TIR provides.

b. Sommi A, Sainz N, Asamoa E, Shoger E, Wood R, Alexander C. Resources used by HCPs to educate PWD about TIR. Short oral presentation presented at the European Association for the Study of Diabetes on 20 September 2022.
    - The study aimed to assess the resources used by different types of HCPs when they educate patients about TIR.
    - There was significant variation in resources used among DCESs, Endos, and PCPs. In response to an open-ended question about resources HCPs use to educate patients about TIR, DEs were more likely to use CGM reports than PCPs (57% vs 31%). When discussing CGM data, DEs and Endos were more likely to use a computer printout than PCPs (Endo 78%, DE 70% vs PCP 28%) while PCPs preferred to provide a verbal summary (PCP 52% vs Endo 27%, DE 29%). DEs were most likely to recommend CGM for all patients (DE 57% vs. Endo 34% vs. PCP 15%), and more likely than Endos to discuss TIR with patients not using CGM (56% vs. 34%).
    - This data highlights the differences in TIR use among HCPs. DEs relied more heavily on TIR and CGm reports while PCPs more often relied on verbal instructions. Among non-CGM users, a large discrepancy exists between DEs and Endos regarding TIR discussions.

Utility in Clinical Practice

Peer-Reviewed Publications

a. Bellido V, Aguilera E, Cardona-Hernandez R, et al. Expert recommendations for using time-in-range and other continuous glucose monitoring metrics to achieve patient-centered glycemic control in people with diabetes. *J Diabetes Sci Technol*. 2023;17(5):1326-1336. doi:10.1177/19322968221088601
    - This review article provides practical insights to quick interpretation of patient-centered metrics based on continuous glucose monitoring data, and shows visual examples of common clinical situations with practical recommendations for their management.
b. Brown S, Basu A, Kovatchev B. Beyond HbA1c: Using continuous glucose monitoring metrics to enhance interpretation of treatment effect and improve clinical decision-making. *Diabetic Medicine*. 2019;36(6): 679-687.
    - This review presents several clinical scenarios of glycaemic outcomes from CGM data that can be analyzed to describe glycaemic variability and related risks of

hyperglycaemia and hypoglycaemia in order to support relevant interpretation of complex CGM data streams.

c. De Block C, Cheng AYY, Christensen TB, Patted URH, Ginovker A. Healthcare professionals' knowledge of and attitudes towards the use of time in range in diabetes management: Online survey across seven countries. *Diabetes Ther*. 2023;14(8):1399-1413.
    - This study utilized an online survey in seven countries to investigate knowledge of and attitudes towards use of TIR among healthcare professionals, as well as benefits and barriers to its use in clinical practice.
    - Participants are 741 specialists, 671 general practitioners, and 307 allied professionals (diabetes nurse specialists, diabetes educators, nurses, NPs, and PAs).
    - 90% agreed TIR is likely/somewhat likely to become the standard of diabetes management.
    - Perceived benefits of TIR included helping to optimize medication regimen, providing HCPs the knowledge and insights to make informed clinical decisions, and empowering people with diabetes with information to successfully manage their diabetes.
    - Barriers to wider adoption included limited CGM access and lack of HCP training and education.
    - Most participants considered integration of TIR into clinical guidelines, recognition of TIR by regulators as a primary clinical endpoint, and recognition of TIR by payers as a parameter for diabetes treatment evaluation as necessary to facilitate increased use of TIR.
d. Johnson M, Martens T, Criego A, Carlson A, Simonson G, Bergenstal R. Utilizing the ambulatory glucose profile to standardize and implement continuous glucose monitoring in clinical practice. *Diabetes Technology & Therapeutics*. 2019;21(2).
    - The authors present an updated AGP report featuring the core CGM metrics and a visualization of glucose patterns that need clinical attention
    - The AGP report displays the CGM metrics agreed upon by numerous CGM consensus reports which inform clinicians and patients if additional glucose management changes are needed.
e. Ribeiro RT, Andrade R, Nascimento do Ó D, Lopes AF, Raposo JF. Impact of blinded retrospective continuous glucose monitoring on clinical decision making and glycemic control in persons with type 2 diabetes on insulin therapy. *Nutr Metab Cardiovasc Dis*. 2021;31(4):1267-1275. doi:10.1016/j.numecd.2020.12.024

- This study evaluated the effect of blinded retrospective CGM on clinical decision-making and glycemic control.
- Participants included 102 patients with insulin-treated type 2 diabetes, less than 66 years old and A1C>7.5%. Individuals conducted a 7-day blinded rCGM (iPro2) every 4 months for 1 year.
- The findings revealed that blinded rCGM significantly improved clinical outcomes, effective shared decision-making, and satisfaction with treatment. Lower A1C was achieved at 4 months with the rCGM-based intervention. A significant increase in TIR was observed, with no difference in exposure time to hypoglycemia.

f. Sheng T, Offringa R, Kerr D, et al. Diabetes healthcare professionals use multiple continuous glucose monitoring data indicators to assess glucose management. *J Diabetes Sci Technol*. 2019;14(2):271-276. doi:10.1177/1932296819873641
   - The researchers asked HCPs to assess de-identified CGM datasets (each spanning seven days) and rank order each day by relative glycemic management (from “best” to “worst”). They also asked HCPs to endorse features of CGM data that were important in making such assessments.
   - 91% of HCPs endorsed hypoglycemia and 88% of HCPs endorsed glycemic variance to be important. Educators more frequently endorsed time in range and daily lows and highs.

Abstracts/Other

a. Hunt M, Duncan R, Payne D, et al. 23-OR: Streamlining Diabetes Device Integration into the Electronic Health Record. *Diabetes*. 2024;73(Supplement_1):23-OR. doi:10.2337/db24-23-OR
   a. This study reports an example of successful integration of CGMs, pumps, smart pens, and meters into the Electronic Health Record (EHR).
   b. A skilled integration team and targeted role-specific education allowed for successful integration of diabetes device data into the EHR. Within 6 months, over 200 patients connected devices to the EHR. Majority of the devices were CGMs (60%) followed by pumps. 70% of the devices were syncing remotely.
   c. The efficiency for data retrieval and storage made data from people with diabetes accessible and actionable, thereby reducing retrieval and documentation burden for HCPs.

b. Seav SM, Yeh Lee M, Ongwela L, et al. 38-OR: Implementation of an EHR-Integrated Hospital-Wide CGM Protocol for Insulin Dosing. *Diabetes*. 2024;73(Supplement_1):38-OR. doi:10.2337/db24-38-OR
    a. This study explored the feasibility and acceptability of a standardized electronic health record (EHR)-integrated hospital-wide protocol for personal CGM use and CGM-based insulin dosing, implemented at Stanford Health Care.
    b. 135 patients used a personal CGM under the protocol in 185 inpatient encounters (Patients were 26% non-English speakers, 26% type 1 diabetes. Automated insulin delivery used in 23% of encounters, multiple brands and generations of CGMs were used).
    c. Of 1506 CGM validations, 87.7% met the requisite accuracy criteria ("%20/20") for CGM-based insulin dosing, and 99.3% fell within Clarke zones A or B.
    d. Based on surveys, a majority of nurses found glucose management under the protocol effective (74%), easy to use (67%), and efficient (63%); 80% of nurses preferred inpatient CGM to FSBG. A majority of patients liked glucose management under the CGM protocol (63%), reported positive interaction with nursing staff about CGM use (63%), and felt the number of interruptions related to diabetes management was reasonable (63%).
    e. This inpatient CGM protocol received favorable feedback from both nurses and patients, and is the first to offer guidance tailored individually according to CGM type.

Economics

Peer-Reviewed Publications

a. Charleer S, De Block C, Van Huffel L, Broos B, Fieuws S, Nobels F, et al. Quality of life and glucose control after 1 year of nationwide reimbursement of intermittently scanned continuous glucose monitoring in adults living with type 1 diabetes (FUTURE): A prospective observational real-world cohort study. *Diabetes Care*. 2019;dc191610.
    - A 12-month prospective observational multicenter real-world study in Belgium to investigate impact of isCGM on quality of life and glycemic control.
    - Participants included 1,913 adults with type 1 diabetes.
    - Nationwide unrestricted reimbursement of isCGM in people with type 1 diabetes treated in specialist diabetes centers results in higher treatment satisfaction,

less severe hypoglycemia, and less work absenteeism, while maintaining quality of life and HbA_{1c}.

b. Huang ES, O'Grady M, Basu A, Winn A, John P, Lee J, et al. The cost-effectiveness of continuous glucose monitoring in type 1 diabetes. *Diabetes Care*. 2010 June;33(6):1269-74.
    - This paper explored the cost-effectiveness of CGM versus standard glucose monitoring in type 1 diabetes patients.
    - The research was conducted in populations in which CGM has produced a significant glycemic benefit.
    - They found that CGM patients experienced an immediate quality-of-life benefit and improved glucose control. Long-term projections indicate that CGM is cost-effective among type 1 diabetic patients at the $100,000/QALY threshold, although considerable uncertainty surrounds these estimates. Additionally, CGM was projected to reduce the lifetime probability of microvascular complications.

c. Isitt J, Roze S, Sharland H, et al. Cost effectiveness of real-time continuous glucose monitoring system versus self-monitoring of blood glucose in people with type 2 diabetes on insulin therapy in the UK. *Diabetes Therapy*. October 2022.
    - This study aimed to conduct a cost effective analysis of rt-CGM versus SMBG based on a retrospective cohort study in insulin-treated people with type 2 diabetes adapted to the UK.
    - Long-term costs and clinical outcomes were estimated using the CORE Diabetes Model, with clinical input data sourced from a retrospective cohort study.
    - rt-CGM was associated with increased quality-adjusted life expectancy of 0.731 quality-adjusted life years (QALYs) and increased mean total lifetime costs of Great British pounds (GBP) 2694, and an incremental cost-effectiveness ratio of GBP 3684 per QALY compared with SMBG. Key drivers of outcomes included HbA1c reduction and reduced fingerstick testing QoL benefit.
    - rt-CGM was associated with improved clinical outcomes and is highly likely to be cost effective versus SMBG in people with T2D on insulin therapy in the UK.

d. Jendle J, Eeg-Olofsson K, Svensson AM, Franzen S, Lamotte M, Levrat-Guillen F. Cost-Effectiveness of the FreeStyle Libre® System Versus Blood Glucose Self-Monitoring in Individuals with Type 2 Diabetes on Insulin Treatment in Sweden. *Diabetes Ther*. 2021;12(12):3137-3152. doi:10.1007/s13300-021-01172-1
    - This study assessed the cost effectiveness of using the FreeStyle Libre Flash Continuous Glucose Monitoring (CGM) System compared to SMBG in individuals with type 2 diabetes (T2D) treated with insulin from a Swedish societal perspective.

- Analysis was conducted using the IQVIA Core Diabetes model v9.5, with data from a real-world study using Swedish National Diabetes Register data. Two cohorts of individuals with T2D were considered based on baseline HbA1c: 8–9% [64–75 mmol/mol] and 9–12% [75–108 mmol/mol]).
- Individuals with T2D who had a baseline HbA1c of 8–9% (64–75 mmol/mol) and 9–12% (75–108 mmol/mol) and used FSL gained 0.50 and 0.57 quality-adjusted life-years (QALYs), respectively, at an incremental cost of SEK 109,957 and SEK 82,170 compared to SMBG, generating an incremental cost-utility ratio of SEK 219,127 and SEK 144,412 per QALY gained.
- Assuming a willingness-to-pay threshold of SEK 300,000 per QALY gained, CGM use was considered cost-effective compared to SMBG for the majority of the individuals in both the lower and higher HbA1c cohorts. The key driver identified was the additional quality-of-life benefit from CGM use.

e. Jiao Y, Lin R, Hua X, et al. A systematic review: Cost-effectiveness of continuous glucose monitoring compared to self-monitoring of blood glucose in type 1 diabetes. *Endocrinol Diabetes Metab*. 2022;5(6):e369. doi:10.1002/edm2.369
   - This systematic review synthesized evidence from 19 studies about CGM cost-effectiveness for type 1 diabetes.
   - The estimated lifetime incremental cost-effectiveness ratio range was $18,734–$99,941 and the quality-adjusted life year gain range was 0.76–2.99.
   - Most studies (n = 17) concluded that CGM is a cost-effective tool. Cost-effectiveness is driven by reducing short- and long-term complications. Use in patients with suboptimal management or at risk of severe hypoglycaemia is most cost-effective.

f. Ni K, Tampe CA, Sol K, Richardson DB, Pereira RI. Effect of CGM Access Expansion on Uptake Among Patients on Medicaid With Diabetes. *Diabetes Care*. 2023;46(2):391-398. doi:10.2337/dc22-1287
   - This retrospective cohort study assessed CGM uptake and adherence, as well as pre- and post-CGM HbA1c among 3,036 adults with diabetes enrolled in a U.S. Medicaid program that fully subsidized CGM.
   - CGM were very well received by both individuals with type 1 diabetes and individuals with type 2 diabetes with similar high fill adherence levels. No significant difference in CGM uptake outcomes were noted among racial/ethnic groups.
   - CGM use was associated with improved HbA1c among those with type 2 diabetes (21.2% [13.1 mmol/mol]; P < 0.001)

- Results suggest that previously documented racial/ethnic disparities to CGM uptake and adherence among adults with diabetes can largely be overcome by subsidies. Further, CGM use led to significant HbA1c improvements among those with type 2 diabetes, demonstrating that increased access to CGM coverage may help to reduce disparities in diabetes technology use and clinical goal attainment.

g. Norman GJ, Paudel ML, Parkin CG, Bancroft T, Lynch PM. Association Between Real-Time Continuous Glucose Monitor Use and Diabetes-Related Medical Costs for Patients with Type 2 Diabetes. *Diabetes Technol Ther*. 2022;24(7):520-524. doi:10.1089/dia.2021.0525
   - This study sought to understand the association between rtCGM use in individuals with T2D and diabetes-related health care resource utilization costs.
   - Retrospective analysis of administrative claims data from 571 individuals with T2D (90% insulin treated) found that average per-patient-per-month (PPPM) diabetes-related medical costs decreased -$424 (95% confidence interval [CI] -$816 to -$31, P= 0.035) after initiating rtCGM.
   - These reductions were driven, in part, by reductions in diabetes-related inpatient medical costs: -$358 (95% CI -$706 to -$10, P= 0.044). Inpatient hospital admissions were reduced on average -0.006 PPPM (P = 0.057) and total hospital days were reduced an average of -0.042 PPPM (P = 0.139).
   - These findings provide real-world evidence that rtCGM use was associated with diabetes-related health care resource utilization cost reductions in patients with T2D.

h. Pathak S, Kearin K, Kahkoska AR, et al. Impact of expanding access to continuous glucose monitoring systems among insulin users with type 1 or type 2 diabetes. *Diabetes Technol Ther*. 2023;25(3):169-177. doi:10.1089/dia.2022.0418
   - This retrospective study analyzed data from pharmacy and medical claims from 2016 to 2020 to estimate the prevalence of CGM use among people with type 1 diabetes and type 2 diabetes who use insulin.
   - The study aimed to see if a CGM coverage policy change in 2018 increased its utilization.
   - Researchers found that the policy resulted in an immediate 9.5% increase in CGM use among people with T1D and a 2.8% increase among people with T2D. From 2016 to 2020, people with T1D went from 18.8% to 58.2% CGM utilization, and people with T2D went from 1.2% utilization to 14.9%

- The study concluded that CGM utilization increased significantly following its inclusion in the pharmacy benefit of insurance coverage. Overall use remained higher among people with T1D.

i. Puckrein GA, Hirsch IB, Parkin CG, Taylor BT, Norman GJ, Xu L, Marrero DG. Assessment of glucose monitoring adherence in medicare beneficiaries with insulin-treated diabetes. *Diabetes Technol Ther*. 2023 Jan;25(1):31-38.
   - This retrospective analysis used 12 months of data from the Centers for Medicare & Medicaid Services to analyze potential associations between race/ethnicity and adherence to prescribed glucose monitoring.
   - Additionally, researchers measured how adherence impacted diabetes-related inpatient hospitalizations and associated costs among participants using insulin.
   - Researchers found the percentage of White (3.65%) rtCGM adherent beneficiaries was significantly larger than Black (1.58%) and Hispanic (1.28%) beneficiaries. Hospitalizations and costs were also higher for Black and Hispanic participants.
   - The study concluded that Race/Ethnicity is associated with increased hospitalizations and costs and that people of color were less likely to use rtCGM despite Medicare coverage.
j. Roze S, Isitt JJ, Smith-Palmer J, Lynch P. Evaluation of the long-term cost effectiveness of the Dexcom G6 Continuous Glucose Monitor versus self-monitoring of blood glucose in people with type 1 diabetes in Canada. *ClinicoEconomics and Outcomes Research*. 2021; 13: 717-725.
   - This health economic analysis was performed to determine the long-term cost-effectiveness of the Dexcom G6 RT-CGM system versus SMBG in adults with T1D in Canada. The analysis was performed using the IQVIA Core Diabetes Model. Patients with a mean baseline A1C of 8.6% were assumed to have an A1C reduction of 1.0% with CGM versus 0.4% reduction with SMBG. RT-CGM was also associated with a quality of life (QoL) benefit owing to reduced incidence of hypoglycemia, reduced fear of hypoglycemia (FoH) and elimination of fingerstick testing. Direct medical costs were sourced from published literature, and inflated to 2019 Canadian dollars (CAD).
   - Dexcom G6 RT-CGM was projected to improve mean quality-adjusted life expectancy by 2.09 QALYs relative SMBG but mean total lifetime costs were CAD 35,353 higher with RT-CGM resulting in an incremental cost-effectiveness ratio (ICER) of CAD 16,931 per QALY gained. Sensitivity analyses revealed that assumptions relating to the QoL benefit associated with reduced FoH and the

elimination of fingersticks with RT-CGM as well as SMBG usage and change in A1C were the key drivers of cost-effectiveness.
    - The study found that for adults with T1D in Canada, RT-CGM is associated with improved glycemic control and QoL benefits due to reduced FoH and elimination of fingerstick testing and over a lifetime is cost-effective relative to SMBG.

k. Shi L, Hellmund R. Cost comparison of flash continuous glucose monitoring with self-monitoring of blood glucose in adults with type 1 or type 2 diabetes using intensive insulin—from a US private payer perspective, *US Endocrinology*. 2020;16(1):24–30
    - The goal of this study was to assess the costs associated with the flash CGM system as a replacement for routine self-monitoring or blood glucose (SBGM) in patients with type 1 and type 2 diabetes.
    - Annual cost of using the FreeStyle Libre 14-day system for people with type 1 and type 2 diabetes was 61% and 63% lower, respectively, compared to testing with fingersticks on a per patient per year basis (PPPY). The data compared list prices and was modeled using the American Diabetes Association guidelines for testing, which are 6-10 or more times per day for people using intensive insulin therapy.
    - Using the FreeStyle Libre 14-day system is estimated to save roughly 50% in average costs associated with severe hypoglycemia (low blood sugar) in both type 1 and type 2 patients compared to SMBG, including from hospitalizations and emergency room visits.
    - They concluded that for US private payers that use intensive insulin, the flash CGM system was more cost effective when compared to SBGM.

l. Sierra JA, Shah M, Gill MS, Flores Z, Chawla H, Kaufman FR, et al. Clinical and economic benefits of professional CGM among people with type 2 diabetes in the United States: analysis of claims and lab data. *Journal of Medical Economics*. 2018;21(3):225–30.
    - This study assessed the clinical and economic impact of professional CGM use in patients with type 2 diabetes in a large dataset of U.S. healthcare claims and lab results.
    - Patients who utilized professional CGM saw an improvement in A1C.
    - There was no statistically significant difference in growth of total annual costs for people who used professional CGM compared to those who did not ($1,270, p = .08). Patients using professional CGM more than once per year had a –$3,376 difference in the growth of total costs (p = .05). Patients who used professional CGM while changing their diabetes treatment regimen also had a difference of –$3,327 in growth of total costs (p = .0023).

- Results indicate significant clinical benefit from professional CGM use, and economic benefits for those who utilized professional CGM more than once per year or when changing therapies.

m. Triki N, Yekutiel N, Levi L, Azuri J. The effects of continuous glucose monitoring system on patient outcomes and associated costs in a real-world setting. *Diabetic Medicine*. 2021 Jan 12;38(5):e14518.
   - This real-world cohort study evaluated the effects of CGM on glucose levels and overall healthcare costs.
   - Participants included 527 people with type 1 diabetes over a year-long period. Researchers compared their medical records pre-CGM use and post-CGM use, and collected data related to glucose control, medical services, and related costs.
   - The study found that CGM can improve blood glucose control, decrease emergency room visit rates (30%–19%), and reduce hospitalization rates (22%–12%) with the highest decrease among the high-adherence group. It also decreases hospitalization duration. However, as CGM adherence increases, so does the cost per patient, which may place an added burden on healthcare systems.

Abstracts/Other

a. Aitken M, Villa P, Lamotte M, Tewary V, Ramos M. Advancing glycemic management in people with diabetes. IQVIA Institute for Human Data Science. 2019.
   - This report concluded that, improvements in TIR and reducing hypoglycemic events by up to 40% in people with Type 1 diabetes were estimated to reduce the risk of developing diabetes-related complications, such as myocardial infarction, end-stage renal disease, severe vision loss and amputation, resulting in a conservative reduction of $6.7–9.7 billion in costs over a 10-year period, based on the relationship between TIR and HbA1c.
   - Notably, this study used the IQVIA Core Diabetes Model and converted A1C values to TIR in order to extrapolate this data.
   - This report concluded that, improvements in TIR and reducing hypoglycemic events by up to 40% in people with Type 1 diabetes were estimated to reduce the risk of developing diabetes-related complications, such as myocardial infarction, end-stage renal disease, severe vision loss and amputation, resulting in a conservative reduction of $6.7–9.7 billion in costs over a 10-year period, based on the relationship between TIR and HbA1c.

- Notably, this study used the IQVIA Core Diabetes Model and converted A1C values to TIR in order to extrapolate this data.

b. Aitken M, Villa P, Tewary V, Anderson A. *Innovation in Diabetes Care Technology: Key Issues Impacting Access and Optimal Use*. IQVIA Institute for Human Data Science; 2020.
   - This report highlights the value of advanced technology such as connected care in terms of improved health outcomes, lower overall cost, and higher quality of life.

c. Alshannaq H, Norman GJ, Lynch PM. 141-LB: Cost-Effectiveness of Real-Time Continuous Glucose Monitoring (rt-CGM) vs. Intermittent-Scanning Continuous Glucose Monitoring (is-CGM) from a U.S. Payer Perspective in Patients with Type 2 Diabetes on Multiple Daily Injections of Insulin (PwT2D on MDI). *Diabetes*. 2023;72(Supplement_1):141-LB. doi:10.2337/db23-141-LB
   - This cost-effectiveness analysis suggests that rt-CGM is cost-saving and cost-effective vs is-CGM in PwT2D on MDI in the United States.
   - Using data from the DIAMOND and REPLACE randomized controlled trials, investigators conducted lifetime projections of disease outcomes and costs from a US payer perspective using the IQVIA Core Diabetes Model v9.5+.
   - The model, based on Medicare pricing and 80% reimbursement, projects rt-CGM users to have higher quality-adjusted life years (QALYs) than isCGM users by 0.454 with cost savings of -$1,355, and an incremental cost-effectiveness ratio of -$2,983/QALY.

d. Garg SK, Hirsch IB, Repetto E, et al. 1927-LB: Impact of Continuous Glucose Monitoring Use on Hospitalizations in People with Type 2 Diabetes—Real-World Analysis. *Diabetes*. 2024;73(Supplement_1):1927-LB. doi:10.2337/db24-1927-LB
   - This retrospective analysis investigated the real-world impact of CGM on hospitalizations in a large population of 74,264 people with type 2 diabetes treated with non-insulin (NIT; n=25,788), basal insulin (BIT; n=25,292), and prandial insulin therapy (PIT; n=23,184).
   - All-cause hospitalizations (ACH), acute diabetes-related hospitalizations (ADH), and acute diabetes-related emergency room visits (ADER) were significantly reduced in the first 6 months in all three groups, and the reductions were sustained during 6-12 months in all groups, as well.
   - Results show use of CGM in a real-world setting was associated with significant reductions in all-cause hospitalizations, acute diabetes-related hospitalizations and ER visits across different therapeutic regimes in people with type 2 diabetes.

e. Webinar presented by IQVIA-A Movement in Diabetes: Using Time-in-Range. IQVIA Institute for Human Data Science. 2020.
    - Using the IQVIA Core Diabetes Model, improvements in TIR and reducing hypoglycemic events by up to 40% in people with Type 1 diabetes were estimated to reduce the risk of developing diabetes-related complications, such as myocardial infarction, end-stage renal disease, severe vision loss and amputation, resulting in a conservative reduction of $6.7–9.7 billion in costs over a 10-year period, based on the relationship between TIR and HbA1c.
    - Further cost reductions may be possible due to reductions in hypoglycemia for people with type 2 diabetes.
    - Improving TIR from 58% to 70% yielded $2.1–4.2 billion cost reduction. Improving TIR further to 80% yielded an additional $1.9–2.7 billion, resulting in a total of $4.0–6.9 billion cost reduction.

f. Zeng A, Beltran A, Bell T, Wood R. 1053-P: Enhancing Accessibility—Assessing the Impact of Expanded CGM Coverage on CGM Adoption. *Diabetes*. 2024;73(Supplement_1):1053-P. doi:10.2337/db24-1053-P
    - In April 2023, the Center for Medicare and Medicaid Services (CMS) expanded continuous glucose monitoring (CGM) coverage to people with diabetes (PWD) on Medicare and basal insulin only. This study examines the impact of these guidelines on CGM accessibility.
    - A dQ&A survey of 177 non-CGM-using PWD on Medicare and basal insulin only, 270 primary care physicians (PCPs), and 187 endocrinologists assessed awareness of expanded coverage, impact on prescribing behavior, and CGM use from May to October 2023.
    - Awareness of the new guidelines was high among endocrinologists (78%), but only 31% of PWD (31%) and 44% PCPs were aware.
    - Among those aware, 76% of endocrinologists and 64% of PCPs reported increasing the number CGM prescriptions written due to the guideline change. Since April 2023, CGM usage has increased significantly among PWD on Medicare and basal insulin only ($p<.05$), rising from 15% in March 2023 to 24% in September 2023. (By contrast, CGM usage was stagnant around 15% from Sep. 2022 to Mar. 2023.)

Glycemic Variability

Peer-Reviewed Publications

a. Hawks ZW, Beck ED, Jung L, et al. Dynamic associations between glucose and ecological momentary cognition in Type 1 Diabetes. *NPJ Digit Med*. 2024;7(1):59. Published 2024 Mar 18. doi:10.1038/s41746-024-01036-5
    - This study is the first to examine moment-to-moment dynamic associations between glucose and cognition in naturalistic environments using continuous glucose monitoring (CGM) and ecological momentary assessment (EMA).
    - Analysis was based on longitudinal CGM glucose and EMA cognition time series from 200 adults with type 1 diabetes. Cognitive tasks measured processing speed (digital symbol matching [DSM]) and sustained attention (gradual onset continuous performance test [GCPT])
    - Results show large glucose fluctuations were associated with slower and less accurate DSM performance, and this pattern remained consistent across all reaction time cutoffs. Group estimates of cognitive vulnerability to glucose fluctuations were not significant for GCPT, suggesting that processing speed (DSM) may be more vulnerable to glucose fluctuations than sustained attention (GCPT).
    - Meaningful individual differences in reaction time at a given glucose fluctuation suggest that glucose fluctuations affect cognitive slowing for some individuals to a greater extent than others. However, these individual differences were not observed for cognitive accuracy.
    - For processing speed, (1) older age, (2) greater CGM time in hypoglycemia, (3) greater number of lifetime severe hypoglycemic events, (4) presence of microvascular complication(s), (5) greater CGM glucose variability, (6) greater self-reported tiredness/fatigue, and (7) larger neck circumference predicted greater cognitive vulnerability to glucose fluctuations.
b. Hirsch IB. Glycemic variability: it's not just about A1C anymore! *Diabetes Technol Ther.* 2005;7(5):780-783.
    - This review article highlights growing evidence that glycemic variability is a significant risk factor for microvascular complications, and highlights the clinical value of using glycemic variability measures such as standard deviation in diabetes management.

c. Nevo-Shenker M, Shalitin S. The Impact of Hypo- and Hyperglycemia on Cognition and Brain Development in Young Children with Type 1 Diabetes. *Horm Res Paediatr.* 2021;94(3-4):115-123. doi:10.1159/000517352
    - This review article summarizes the existing data on the impact of glycemic extremes on brain structure and cognitive function in youth with type 1 diabetes and the use of new diabetes technologies that may reduce these complications.
d. Salsa-Castelo M, Neves C, Neves JS, Carvalho D. Association of glycemic variability and time in range with lipid profile in type 1 diabetes. *Endocrine*. 2024;83(1):69-76. doi:10.1007/s12020-023-03464-x
    - This retrospective observational cohort study sought to analyze the association between glycemic control and lipid profile in patients with type 1 diabetes, focusing on glycemic variability and time in range obtained from continuous glucose monitoring (CGM).
    - In the cross-sectional analysis, higher HbA1c, higher glucose management indicator (GMI), higher time above range (TAR) and lower time in range (TIR) were associated with higher triglyceride levels.
    - In the longitudinal analysis, an increase in time below range (TBR) was associated with a decrease of HDL cholesterol.
    - In both analyses, an increase in the coefficient of variability (CV) was associated with a significant decrease of HDL cholesterol. HbA1c was not associated with total cholesterol or LDL cholesterol.
e. Tylee TS, Trence DL. Glycemic variability: looking beyond the A1C. *Diabetes Spectrum*. 2012;25(3):149–53.
    - This review article summarizes the conflicting existing evidence on the relationship between glycemic variability and complications in both type 1 and type 2 diabetes, and highlights that this important element of glycemic exposure is not captured by A1C.
    - The review also notes that beyond complications, glycemic variability may also affect psychosocial outcomes, citing studies which have connected within-day variability and glucose levels >180 mg/dL to mood and psychological well-being

Guidelines for CGM/TIR

a. American Diabetes Association. Standards of Medical Care in Diabetes – 2021. *Diabetes Care*. 2021 Jan 1; 44 (Supplement 1): S6.

- The 2021 ADA Standards of Care had some notable revisions that relate to TIR and CGM in the Glycemic Targets section (Section 6).
- The "A1C" subsection has been expanded to include TIR and other measures.
- The subsection formerly titled "A1C Goals" which recommended an A1C goal of <7% has been renamed to "Glycemic Goals" and now also includes a TIR goal of >70% and a time below range goal of <4%.
- The subsection formerly titled "A1C Testing," which recommended A1C testing 2-4 times per year, was retitled to "Glycemic Assessment" and recommends that people "assess glycemic status (A1C or other glycemic measurement)" 2-4 times per year.
- The 2021 Standards of Care no longer differentiates CGM-related recommendations by type of diabetes and instead, endorses CGM for everyone using rapid-acting insulin. The ADA also changed terminology from "blinded CGM" to "professional CGM" which may help encourage greater use of CGM.

b. American Diabetes Association Professional Practice Committee. Standards of Care in Diabetes—2024. *Diabetes Care*. 2024;47(Supplement 1):S1-S321.
   - The 2024 ADA Standards of Care included notable revisions related to continuous glucose monitoring (CGM) and time in range (TIR).
   - Section 6 ("Glycemic Goals and Hypoglycemia Prevention") was updated with recent data on the limitations of A1C and an outline of CGM metrics and recommended glycemic goals.
   - The following key recommendations were added or updated in Section 7 ("Diabetes Technology"):
     1. Recommendation 7.1 was added to state that people with diabetes should be offered any type of diabetes device (including CGM)
     2. Recommendation 7.2 was added to emphasize the need to start CGM early in type 1 diabetes, even at diagnosis, to promote early achievement of glycemic goals
     3. Recommendation 7.3 was added to emphasize that health care professionals should acquire sufficient knowledge for the use and application of diabetes technology for people with diabetes.
     4. Recommendation 7.15 was updated to reflect the benefits of intermittently scanned CGM in less intensively treated people with type 2 diabetes.
     5. Recommendation 7.33 was added to emphasize continuation of personal CGM use in hospitalized individuals with diabetes when clinically appropriate in a hybrid fashion and under an institutional protocol.

- Text on CGM systems was updated to include the benefits of CGM use in type 2 diabetes for those using nonintensive insulin therapy and/or not using insulin therapy, reflect CGMs now integrated with automated insulin delivery systems and/or approved for use in pregnancy, and to include suggestions to streamline the approach to CGM interpretation to modify therapeutic approaches.

c. Battelino T, Moshe P, Alexander C, Amiel S, Arreaza-Rubin G, et al. Continuous glucose monitoring and metrics for clinical trials: an international consensus statement. *Lancet Diabetes & Endocrinology*. January 2023. 11(1): 42-57.
   - The purpose of this consensus statement is to recommend the ways CGM data might be used in prospective clinical studies, either as a specified study endpoint or as supportive complementary glucose metrics, to provide clinical information that can be considered by investigators, regulators, companies, clinicians, and individuals with diabetes who are stakeholders in trial outcomes.
   - Authors of the consensus statement provide recommendations on how to optimize CGM-derived glucose data collection in clinical studies, including the specific glucose metrics and specific glucose metrics that should be evaluated.

d. Battelino T, Danne T, Bergenstal RM, Amiel SA, Beck R, Biester T, et al. Clinical targets for continuous glucose monitoring data interpretation: recommendations from the international consensus on time in range. *Diabetes Care*. 2019;42(8):1593–603.
   - Successful use of CGM technology in routine clinical practice remains relatively low. This may be due in part to the lack of clear and agreed-upon glycemic targets that both diabetes teams and people with diabetes can work toward.
   - Presents a list of 10 standardized CGM metrics for clinical care (2019), estimates of A1C for a given TIR (table 5), as well as guidance on targets for assessment of glycemic control for adults with type 1 or type 2 diabetes, older/high-risk individuals, and pregnant individuals.
   - Concludes that TIR (within target range, below range, and above range) are useful clinical targets and outcome measurements that complement A1C and should be used for day-to-day treatment decision-making.

e. Danne T, Nimri R, Battelino T, Bergenstal RM, Close KL, DeVries JH, et al. International consensus on use of continuous glucose monitoring. *Diabetes Care*. 2017;40(12):1631–40.
   - This article summarizes the 2017 Advanced Technologies & Treatments for Diabetes (ATTD) consensus recommendations and represents the current state of knowledge on CGM results affecting outcomes.
   - Discussed the “key findings” and “recommendations” regarding the limitations of A1C, the use of SMBG and CGMs to manage and assess outcomes in different

populations, the minimum requirements for CGM performance, the definition and assessment of hypoglycemia in clinical studies, assessing glycemic variability, TIR, and documenting CGM metrics.
    - It would be beneficial to establish criteria to match people with appropriate CGM monitors and establish definitions for hypoglycemia, glycemic variability, and TIR.
    - Conclusion: "The advanced metrics of assessing continuous glucose data presented here are appropriate as outcome parameters that complement HbA1c for a wide range of patients with diabetes and should be considered for use to help them improve glycemic control…"
f. Deeb A, Muammar T, Alsaffar H, Sedaghat S, Al Hassani N, Odeh R, Alkhayyat H, Al Sinani A, Attia N, Adhami S, Elbarbary N. Use of ambulatory glucose monitoring and analysis of ambulatory glucose profile in clinical practice for diabetes management; a position statement of the Arab Society of Paediatric Endocrinology and Diabetes. *Diabetes Res Clin Pract*. 2021; 173:108671
    - This position statement by the Arab Society of Paediatric Endocrinology recommends the use of isCGM for patients in the Middle East and North Africa.
g. Grunberger G, Sherr J, Allende M, et al. American Association of Clinical Endocrinology Clinical Practice Guideline: The use of advanced technology in the management of persons with diabetes mellitus. *Endocr Pract*. 2021;27(6):505-537. doi:10.1016/j.eprac.2021.04.008
    - The 40-page guideline was developed from a literature search of nearly 2,500 articles published between 2012 and February 2021.
    - The AACE recommends that certain targets be considered to individualize insulin therapy in CGM systems so that every person is getting the care that they need.
    - The following are the priority metrics for clinical decision-making in the use of diabetes technology: All persons with diabetes--Number of days of active CGM use: 14 days preferred; Percentage of data available from active CGM use: >70% of data from 14 days; Mean glucose: individualized to targets; GMI: individualized to targets; Glycemic variability, %CV: <36
    - The guideline recommends starting with Time in Range and time below range for assessment of glycemic control and focusing on reducing time below range. In both people with type 1 and type 2: %TIR 70 to 180 mg/dL: >70%; %TBR <70 mg/dL: <4%; %TBR <54 mg/dL: <1%; %TAR >180 mg/dL: <25%; %TAR >250 mg/dL: <5%.

- For older people or those at high risk for type 1 or type 2: %TIR 70 to 180 mg/dL: >50%; %TBR <70 mg/dL: <1%; %TBR <54 mg/dL: ~0%; %TAR >250 mg/dL: <10%
- In pregnant people with T1D: %TIR 63 to 140 mg/dL: >70%; %TBR <63 mg/dL: <4%; %TBR <54 mg/dL: <1%; %TAR >140 mg/dL: <25%

h. Mohan V, Joshi S, Mithal A, Kesavadev J, Unnikrishnan AG, Saboo B, et al. Expert consensus recommendations on time in range for monitoring glucose levels in people with diabetes: An Indian perspective. *Diabetes Therapy*. 2023;1–13.
   - A consensus meeting was held in India in 2021 with experts in the field of diabetes care in order to develop consensus recommendations for TIR thresholds for different patient profiles in India. Their expert recommendations are reported here.
   - The aim of this paper is to aid clinicians across India to routinely use CGM and CGM data reports for optimizing individualized diabetes care, by implementing clinical targets for TIR.

i. Petrie JR, Peters AL, Bergenstal RM, Holl RW, Fleming GA, Heinemann L. Improving the clinical value and utility of CGM systems: Issues and recommendations. *Diabetes Care*. 2017 Dec 1;40(12):1614.
   - Outlines recommendations for improving the regulatory use and clinical use of CGMs to "best ensure effective and appropriate use of CGM as the technology continues to develop." These recommendations are grouped within 5 "themes," and are tailored to all involved stakeholders (regulatory agencies, manufacturing companies, researchers, research funding bodies, patient groups, and consumers of CGM tech).
   - They collected evidence from 6 clinical studies on T1D and 4 clinical studies on T2D that supports the benefits of using CGMs, and also noted common design limitations (specifically highlighting a need for greater standardization within the studies)
   - The CGM limitations discussed in this paper can be grouped into technical issues, user issues, safety issues, and costs.

j. Spanakis EK, Cook CB, Kulasa K, et al. A consensus statement for continuous glucose monitoring metrics for inpatient clinical trials. *J Diabetes Sci Technol*. Published online August 17, 2023. doi:10.1177/19322968231191104
   - This consensus statement establishes metrics for research in the use of continuous glucose monitors (CGMs) in a hospital setting.
   - Panelists defined terms related to 10 dimensions of measurements related to the use of CGMs including (1) hospital hypoglycemia, (2) hospital hyperglycemia,

(3) hospital time in range, (4) hospital glycemic variability, (5) hospital glycemia risk index, (6) accuracy of CGM devices and reference methods for CGMs in the hospital, (7) meaningful time blocks for hospital glycemic goals, (8) hospital CGM data sufficiency, (9) using CGM data for insulin dosing, and (10) miscellaneous factors.

CGM and Type 1 Diabetes

Peer-Reviewed Publications

a. Al Hayek A, Robert A, Dawish M. Effectiveness of the Freestyle Libre 2 flash glucose monitoring system on diabetes-self-management practices and glycemic parameters among patients with type 1 diabetes using insulin pump. *Diabetes & Metabolic Syndrome*. 2021:15(5):102265.
    - This prospective study was performed among 47 patients with T1D (13-21 years) who self-tested their glucose levels with finger-pricks and BGM. Data related to the glycemic profile, i.e., mean TIR, mean TAR, mean TBR, mean glucose level, A1C, total daily dose of insulin, frequency of glucose monitoring and DSM responses were collected at baseline and 12 weeks.
b. Beck RW, Riddlesworth T, Ruedy K, Ahmann A, Bergenstal R, Haller S, et al. Effect of Continuous Glucose Monitoring on Glycemic Control in Adults With Type 1 Diabetes Using Insulin Injections: The DIAMOND Randomized Clinical Trial. *JAMA*. 2017;317(4):371-378.
    - This randomized clinical trial examined whether use of continuous glucose monitoring (CGM) improves A1c in a population of 158 adults with type 1 diabetes treated with multiple daily injections
    - Mean HbA1c reduction from baseline was 1.1% at 12 weeks and 1.0% at 24 weeks in the CGM group and 0.5% and 0.4%, respectively, in the control group ($P < .001$)
    - Median duration of hypoglycemia at less than <70 mg/dL was 43 minuntes per day (inter-quartile range [IQR], 27–69) in the CGM group vs 80 min/day (IQR, 36–111) in the control group ($P = .002$).
    - Continuous glucose monitoring resulted in better glycemic control compared with usual care.
c. Bolinder J, Antuna R, Geelhoed-Duijvestijn P, Kroger J, Weitgasser R. Novel glucose-sensing technology and hypoglycaemia in type 1 diabetes: a multicentre, non-masked, randomised controlled trial. *The Lancet*. 2016;388(10057):2254-2263.

- This study aimed to assess whether a factory-calibrated, sensor-based, flash CGM compared with SMBG reduced exposure to hypoglycemia in patients with type 1 diabetes.
- Participants included 241 adult patients with well controlled type 1 diabetes from 23 European diabetes centers.
- Flash CGM reduced the time adults with well controlled type 1 diabetes spent in hypoglycemia.
- Mean time in hypoglycemia changed from 3·38 h/day at baseline to 2·03 h/day at 6 months in the intervention group, and from 3·44 h/day to 3·27 h/day in the control group.

d. Brett McQueen R, Perez-Nieves M, Todd Alonso G, et al. Association between continuous glucose monitoring metrics and clinical outcomes in adults with type 1 diabetes in a real-world setting. *Diabetes Res Clin Pract*. 2024;212:111690. doi:10.1016/j.diabres.2024.111690
   - This retrospective, longitudinal cohort study analyzed the relationships between TIR, CV, HbA1c, and hypoglycemia among 542 adults with type 1 diabetes in a real-world setting.
   - For every 10% increase in TIR, HbA1c was significantly reduced by 0.34 % (4 mmol/mol) at the same visit and 0.20 % (2 mmol/mol) at the subsequent visit. There was a significant reduction in the frequency of hypoglycemic events when comparing CV levels < 30 % to CV levels ≥ 40.1 %, and a reduction in the frequency of hypoglycemic events for all other CV levels < 40 % compared with CV ≥ 40.1 %, although these reached statistical significance only for Level 2 events.
   - Results confirmed the inverse relationship between TIR and HbA1c seen in prior randomized controlled trials, but suggested the magnitude of the relationship in a real-world setting may be smaller than that observed in controlled trials.

e. Calhoun P, Price D, Beck RW. Glycemic Improvement using continuous glucose monitoring by baseline time in range: Subgroup analyses from the DIAMOND type 1 diabetes study. *Diabetes Technology and Therapeutics*. 2020;(ja).
   - This study evaluated the impact of rtCGM or SMBG on TIR on 153 people with type 1 diabetes (rtCGM, n=101; SMBG, n=52).
   - Compared with SMBG, use of rtCGM increased mean TIR by an additional 16 min/day for participants with a baseline TIR <40%, 77 min/day for baseline TIR <50%, 88min/day for baseline TIR <60%. Participants in the rtCGM group also

reduced their mean glucose and time spent in hyperglycemic and hypoglycemic ranges significantly more than participants in the SMBG group.

f. Campbell FM, Murphy NP, Stewart C, Biester T, Kordonouri O. Outcomes of using flash glucose monitoring technology by children and young people with type 1 diabetes in a single arm study. *Pediatric Diabetes*. 2018;19(7):1294-1301.
   - This study evaluated the use of flash CGM in children and teenagers with type 1 diabetes.
   - Participants included 76 children and teenagers with type 1 diabetes. Mean age was 10.3 ± 4.0 years and type 1 diabetes duration was 5.4 ± 3.7 years.
   - Flash CGM significantly improved TIR, reduced time in hyperglycemia, and lowered A1C. Time in hypoglycemia was unaffected.

g. Dicembrini I, Cosentino C, Monami M, Mannucci E, Pala L. Effects of real-time continuous glucose monitoring in type 1 diabetes: a meta-analysis of randomized controlled trials. *Acta Diabetol*. 2021; 58(4): 401-410.
   - This meta-analysis aimed to assess the effects of CGM and FGM on glycemic control in people with type 1 diabetes. The analysis includes randomized clinical trials comparing CGM or FGM with SMBG, with a duration of at least 12 weeks, identified in Medline or clinicaltrials.gov. The primary endpoint was A1C and secondary endpoints include severe hypoglycemia, TIR, health-related quality of life, and treatment satisfaction. Separate analyses were performed for trials comparing CGM with SMBG, and those comparing CGM + CSII and SMBG + MDI and CGM-regulated insulin infusion system (CRIS) and CSII + SMBG.
   - CGM was associated with a lower A1C and risk of severe hypoglycemia at endpoint than SMBG. FGM showed a significant reduction in the incidence of mild hypoglycemia and increased treatment satisfaction; there were no significant changes in A1C. CGM + CSII in comparison with SMBG + MDI was associated with a significant reduction in A1C.

h. Fagherazzi G, Aguayo GA, Zhang L, et al. Heterogeneity of glycaemic phenotypes in type 1 diabetes. *Diabetologia*. Published online May 23, 2024. doi:10.1007/s00125-024-06179-4
   - This study analyzed glycemic data, including CGM metrics, to uncover glycemic phenotype heterogeneity in type 1 diabetes.
   - Analysis was done using the Discriminative Dimensionality Reduction with Trees (DDRTree) algorithm and clustering analysis methods. Data included A1C, time in range (TIR), time below range (TBR), CV, Gold score and glycemia risk index (GRI) from 618 participants with type 1 diabetes.

- Seven glycemic phenotypes were identified. Notably, findings highlighted significant associations between these glycemic phenotypes and various socioeconomic factors, cardiovascular risk markers, diabetes treatment, and history of diabetes-related complications.
- Findings pave the way for clinicians and researchers to better understand the complexity of type 1 diabetes glycemic phenotypes, which may be used to design future precision diabetes interventions.

i. Fuhri Snethlage CM, McDonald TJ, Oram RD, et al. Residual β-Cell Function Is Associated With Longer Time in Range in Individuals With Type 1 Diabetes. *Diabetes Care*. Published online August 3, 2023:dc230776. doi:10.2337/dc23-0776
   - This cross-sectional study investigated the associations between residual β-cell function and metrics of continuous glucose monitoring (CGM) in 489 individuals with type 1 diabetes.
   - A higher urinary C-peptide-to-creatinine ratio (UCPCR) correlated with higher TIR ($r = 0.330$, $P < 0.05$), lower TBR ($r = -0.237$, $P < 0.05$), lower TAR ($r = -0.302$, $P < 0.05$), and lower glucose CV ($r = -0.356$, $P < 0.05$). Glucagon/glucose ratios correlated with longer TIR ($r = 0.234$, $P < 0.05$).
   - Significantly longer TIR, shorter TBR and TAR, and lower CV were observed in individuals with greater UCPCR-assessed β-cell function. Therefore, better CGM-derived metrics in individuals with preserved β-cell function may be a contributor to a lower risk of developing long-term complications

j. Gubitosi-Klug RA, Braffett BH, Bebu I, et al. Continuous glucose monitoring in adults with type 1 diabetes with 35 years duration from the DCCT/EDIC study. *Diabetes Care*. 2022;45(3):659-665. doi:10.2337/dc21-0629
   - CGM-derived metrics were compared for daytime and nighttime periods using blinded CGM for a minimum of 6.5 days (average 11.9 days) and correlated with A1C levels, routine use of diabetes devices, and other characteristics in 765 participants.
   - In adults with long-standing type 1 diabetes, short-term blinded CGM profiles revealed frequent clinically significant hypoglycemia (<54 mg/dL) during the night and more time in hyperglycemia during the day. The small subset of participants using routine CGM and insulin pumps had fewer hypoglycemic and hyperglycemic excursions and lower HbA1c levels. Thus, strategies to lower meal-stimulated hyperglycemia during the day and prevent hypoglycemia at night are relevant clinical goals in older patients with type 1 diabetes.

k. Hansen KW, Bibby BM. The frequency of intermittently scanned glucose and diurnal variation of glycemic metrics. *J Diabetes Sci Technol*. 2022 Nov;16(6):1461-1465.

- The purpose of this study is to understand the relation between the frequency of isCGM scanning and diurnal variation of TIR and TBR.
- Study included isCGM data (60 days) from 163 persons with type 1 diabetes. Used to calculate mean TIR and median TBR for 15-minute periods and presented for daytime and nighttime. The values for tertiles of scanning frequency were compared.
- The 1st tertile (n = 53) scanned <10 times; the 2nd tertile (n = 56) 10-13 times, and the 3rd tertile (n = 54) >13 per 24 hours. TIR increased significantly from the 1st to the 3rd scan tertile both during the day and the night. In contrast, TBR was not significantly associated with scan tertiles during daytime or nighttime. In one model, a 50% increase in 24-hour scanning frequency was associated with a 7.8 percentage point increase in TIR.
- Increased scanning frequency was associated with a higher TIR both during daytime and nighttime with no change in TBR.

l. Hood KK, DiMeglio LA, Riddle MC. Putting continuous glucose monitoring to work for people with type 1 diabetes. *Diabetes Care*. 2020 Jan 1;43(1):19.
   - This paper summarizes the following 6 CGM-related studies:
     - 3 reports describing CGM experiences in diverse populations: Miller et al., DPV registry in Germany and Australia, and Prahalad et al. (testing 41 individuals). Found a mean A1C of 7.8% and mean TIR (70-180) of 45%
     - Dovc et al. (randomized study w/ 20 young adults). Showed how CGM can provide ways to measure experimental glycemic outcomes
     - 2 articles reporting long-term study results comparing CGM to SMBG (Soupal et al. and Oliver et al.)
   - General conclusions: “CGM can safely and effectively be used for people with type 1 diabetes in a variety of clinical and novel research settings.” CGMs should be accessible and used more widely.
   - Limitations: Access to constant glycemic data can be associated with burden and burnout, and the cost-to-benefit ratios for different clinical populations and for key clinically relevant outcomes remain to be directly defined.

m. The ISCHIA Study Group. Prevention of hypoglycemia by intermittent-scanning continuous glucose monitoring device combined with structured education in patients with diabetes mellitus: A randomized, crossover trial. *Diabetes Research and Clinical Practice*. November 13 2022.
   - The investigators conducted a randomized-crossover trial to compare the intermittent-scanning CGM device with structured education (intervention) to SMBG (control) in the reduction of time below range.

- This trial involved 104 adults with type 1 diabetes mellitus using multiple daily injections. Participants were randomly allocated to either sequence Intervention/Control or sequence Control/Intervention. During the Intervention period which lasted 84 days, participants used the first-generation FreeStyle Libre and received structured education on how to prevent hypoglycemia based on the trend arrow and by frequent sensor scanning (≥10 times a day). Confirmatory SMBG was conducted before dosing insulin. The Control period lasted 84 days. The primary endpoint was the decrease in the time below range (TBR; <70 mg/dL).
- The time below range was significantly reduced in the Intervention arm compared to the Control arm (2.42 ± 1.68 h/day [10.1 %±7.0 %] vs 3.10 ± 2.28 h/day [12.9 %±9.5 %], *P* = 0.012). The ratio of high-risk participants with low blood glucose index >5 was significantly reduced (8.6 % vs 23.7 %, *P* < 0.001).
- The use of isCGM combined with structured education significantly reduced the time below range in patients with T1DM.

n. Kim JY, Jin SM, Andrade SB, Chen B, Kim JH. Real-World Continuous Glucose Monitoring Data from a Population with Type 1 Diabetes in South Korea: Nationwide Single-System Analysis. *Diabetes Technol Ther*. 2024;26(6):394-402. doi:10.1089/dia.2023.0513
    - This study assessed real-world glycemic outcomes among Dexcom G6 users in South Korea, a unique study setting given that reimbursement for CGM devices and a nationwide education program for T1D (including repeated systematic education and training in insulin dose adjustment, carbohydrate counting,and CGM data interpretation) began almost simultaneously.
    - Among 2288 users, those with higher CGM utilization had higher TIR (67.8% vs. 52.7%), and lower TBR <70 mg/dL (2.3% vs. 4.7%) and TAR >180 mg/dL (30.0% vs. 42.6%) than those with low CGM utilization (P < 0.001 for all). Notably, only users with >70% interday utilization were included.
    - Users whose data were shared with others had higher TIR than those who did not (63.3% vs. 60.8%, P = 0.001).
    - Comparing the real-world outcomes from this national sample to that of other countries supports previous findings that CGM is more effective when paired with education.
o. Laffel LM, Kanapka LG, Beck RW, Bergamo K, Clements MA, Criego A, et al. Effect of continuous glucose monitoring on glycemic control in adolescents and young adults with type 1 diabetes: a randomized clinical trial. *JAMA*. 2020;323(23):2388–96.

- Randomized clinical trial with 153 participants, ages 14-24 that had type 1 and screening hemoglobin A1C of 7.5% to 10.9%.
- Duration of the study: 26 weeks from January 2018 to May 2019 at 14 endocrinology practices in the US.
- In this randomized clinical trial, adolescents and young adults with type 1 diabetes were studied to determine the effects of CGM use on glycemic control.
- The results show a small but statistically significant improvement in glycemic control over the course of the study. Compared to standard blood glucose monitoring, patients using CGM had significantly lower A1C levels.
- The CGM group reported significantly higher glucose monitoring satisfaction at 26 weeks than the BGM group. No statistically significant between-group differences were observed for problem areas in diabetes, hypoglycemia confidence, or sleep quality.

p. Lee K, Gunasinghe S, Chapman A, Findlow L, Hyland J, et al. Real-world outcomes of a glucose sensor use in type 1 diabetes--findings from a large UK centre. *Biosensors*. 2021; 11(11):457.
   - This study aimed to measure the impact of flash-CGM and real-time-CGM use on glycaemic outcomes in adults with type 1 diabetes under routine clinical care.
   - 23% of flash-CGM users and 32% of rtCGM users achieved a TIR of greater than 70%. For TBR, 70% of rt-CGM users and 58% of fCGM users met international recommendations of less than 4%.

q. Lind M, Polonsky W, Hirsch IB, Heise T, Bolinder J, Dahlqvist S, et al. Continuous glucose monitoring vs conventional therapy for glycemic control in adults with type 1 diabetes treated with multiple daily insulin injections: The GOLD Randomized Clinical Trial . *JAMA*. 2017;317(4):379-387.
   - This randomized clinical trial assessed whether continuous glucose monitoring improves glycemic control in adults with type 1 diabetes treated with multiple daily insulin injections
   - Among 161 adults with type 1 diabetes, glycemic control was improved during continuous glucose monitoring compared with conventional treatment (hemoglobin [HbA1c] of 7.92% vs 8.35% [63 vs 68 mmol/mol]). The mean difference in HbA1c was 0.43% (4.7 mmol/mol).

r. Nørgaard K, Ranjan AG, Laugesen C, et al. Glucose monitoring metrics in individuals with type 1 diabetes using different treatment modalities: A real-world observational study. *Diabetes Care*. Published online August 23, 2023. doi:10.2337/dc23-1137

- This cross-sectional study investigated the association between continuous glucose monitoring (CGM)-derived glycemic metrics and different insulin treatment modalities using real-world data.
- Subjects were 3,184 CGM users, of which 1,622 used multiple daily injections (MDI), 503 used insulin pumps with unintegrated CGM (SUP), 354 used sensor-augmented pumps with low glucose management (SAP), and 561 used automated insulin delivery (AID).
- Proportion of participants achieving recommended TIR >70%, TAR <25%, and TBR <4% was significantly higher among those using SAP and AID than among those using MDI without CGM alarm features.

s. Reutrakul S, Irsheed GA, Park M, et al. Association between sleep variability and time in range of glucose levels in patients with type 1 diabetes: Cross-sectional study. *Sleep Health*. Published online September 12, 2023;S2352-7218(23)00140-7. doi:10.1016/j.sleh.2023.07.007
   - Investigators assessed associations between sleep patterns and glycemic parameters gathered through blinded CGM in 76 adult participants.
   - After adjusting for age, sex, insulin delivery mode/CGM use, and ethnicity, each hour increase in sleep variability (represented by standard deviation of mid-sleep time) was associated with 9.64% less time in range.

t. Šoupal J, Petruželková L, Grunberger G, Hásková A, Flekač M, Matoulek M, Mikeš O, Pelcl T, Škrha J Jr, Horová E, Škrha J, Parkin CG, Svačina Š, Prázný M. Glycemic outcomes in adults with T1D are impacted more by continuous glucose monitoring than by insulin delivery method: 3 years of follow-up from the COMISAIR study. *Diabetes Care*. 2020; 43(1): 37-43.
   - This study assessed the impact of four different treatment strategies in adults with T1D: rtCGM with multiple daily insulin injections, rtCGM with subcutaneous insulin infusion, SMBG with multiple daily injections, and SMBG with subcutaneous insulin infusion
   - The study included 94 participants, all with T1D, examining A1C, percent time in range between 70-180mg/dL, time below range (less than 70mg/dL), and incidence of hypoglycemia over a 3 year period
   - After 3 years, both groups using rtCGM had significantly lower A1C than SMBG groups (7.0% and 6.9% for each CGM group compared to 7.7% and 8.0% in SMBG groups). TIR was also significantly higher in CGM groups (48.7-69% for CGM + MDI, 50.9%-72.3% for CGM + CSII). Significant reductions in TBR occurred only in the rtCGM + MDI group.

- The study was able to conclude that rtCGM is superior to SMBG in reducing A1C, hypoglycemia, and other endpoints in people with T1D regardless of insulin delivery method.

u. Thabit H, Prabhu JN, Mubita W, Fullwood C, Azmi S, Urwin A, et al. Use of Factory-Calibrated Real-time Continuous Glucose Monitoring Improves Time in Target and HbA1c in a Multiethnic Cohort of Adolescents and Young Adults With Type 1 Diabetes: The MILLENNIAL Study. *Diabetes Care*. 2020 Jul 28;dc200736.
   - This paper studied using Dexcom CGMs on young adults with T1D, the age group that typically has the highest A1C, to improve glycemic control. In this randomized studied, they found that TIR was significantly higher during CGM compared with self-monitoring of blood glucose

v. Urakami T, Yoshida K, Kuwabara R, Mine Y, et al. Frequent scanning using flash glucose monitoring contributes to better glycemic control in children and adolescents with type 1 diabetes. *Journal of Diabetes Investigation*. 2022. 13(1):185-190.
   - The study examined the impact of scanning frequency with flash glucose monitoring on glycemic control in children and adolescents with type 1 diabetes.
   - The findings showed that patients with a higher scanning frequency had better glycemic control, with greater TIRs and lower HbA1c levels, compared to those with a lower scanning frequency.

w. Visser MM, Charleer S, Fieuws S, et al. Comparing real-time and intermittently scanned continuous glucose monitoring in adults with type 1 diabetes (ALERTT1): a 6-month, prospective, multicentre, randomised controlled trial. *Lancet*. 2021;397(10291):2275-2283. doi:10.1016/S0140-6736(21)00789-3
   - This prospective randomized controlled trial assessed the difference in time in range and A1C between those on intermittently scanned continuous glucose monitoring (isCGM) and real time continuous glucose monitoring (rtCGM).
   - 254 participants were randomly assigned to either rtCGM (n=127) or isCGM (n=127). All participants were adults who were previously already using isCGM.
   - After 6 months, time in range was significantly higher for rtCGM (59.6%) than isCGM (51.9%). A1C levels were also lower for rtCGM (7.1%) than isCGM (7.4%). It was also found that those on rtCGM experienced less events of hypoglycemia (n=3 vs n=13)
   - These results indicate a significant improvement in time in range 6 months after someone with type 1 diabetes switched from isCGM to rtCGM. Healthcare providers should consider rtCGM over isCGM for those who have type 1 diabetes.

x. Visser MM, Charleer S, Fieuws S, De Block C, Hilbrands R, Van Huffel L, et al. Effect of switching from intermittently scanned to real-time continuous glucose monitoring in adults with type 1 diabetes: 24-month results from the randomised ALERTT1 trial. *The Lancet Diabetes & Endocrinology*. 2023;11(2):96–108.
    - 119 participants were assigned to the is-rtCGM group of whom 112 (94%) completed the 24-month trial, and 123 participants were assigned to the rt-rtCGM group of whom 117 (95%) completed the 24-month trial. TIR increased from 51·8% (95% CI 49·1-54·5) at start of rtCGM (month 6) to 63·5% (60·7-66·3) at month 12 in the is-rtCGM group, and remained stable up to month 24 (change 11·7 percentage points [pp] [9·4-14·0; p<0·0001). In the rt-rtCGM group, TIR increased from 52·5% (95% CI 49·8-55·1) at start of rtCGM (month 0) to 63·0% (60·3-65·8) at month 12, also remaining stable up to month 24 (change 10·5 pp [8·2-12·8]; p<0·0001). HbA1c decreased from 7·4% (57 mmol/mol; month 6) to 6·9% (52 mmol/mol) at month 24 (change -0·54 pp [95% CI -0·64 to -0·44]; -5 mmol/mol [95% CI -6 to -4]; p<0·0001) in the is-rtCGM group, and from 7·4% (57 mmol/mol; month 0) to 7·0% (53 mmol/mol) at month 24 (change -0·43 pp [95% CI -0·53 to -0·33]; -4 mmol/mol [95% CI -5 to -3]; p<0·0001) in the rt-rtCGM group. The change in HFS-worry score was -2·67 (month 24 vs month 6; p=0·0008) in the is-rtCGM group and -5·17 points (month 24 vs month 0; p<0·0001) in the rt-rtCGM group. Time in clinically significant hypoglycaemia was unchanged in both groups after month 12. Severe hypoglycaemia decreased from 31·0 to 3·3 per 100 patient-years after switching to rtCGM.
    - Glycemic control and hypoglycemia worry improved significantly up to 24 months after switching from isCGM without alerts to rtCGM with alerts, supporting the use of rtCGM in the case of adults with type 1 diabetes

Abstracts/Other

a. Liggins R, Calhoun P, Peers S, Riddell MC, Beck RW. 1777-LB: Time Below Range Is Correlated with Level 2 (L2) Hypoglycemia Event Rates in Type 1 Diabetes—Results from DCLP3, DIAMOND, and WISDM Trials. *Diabetes*. 2024;73(Supplement_1):1777-LB. doi:10.2337/db24-1777-LB
    a. This study looked at the relationship between CGM time below range (TBR; T<70 and T<54 mg/dL), and individual symptomatic hypoglycemic events (glucose <54 mg/dL for ≥15 min).

b. Using CGM data from three trials that measured glucose over a 6-month period, there was a strong correlation between hypoglycemic event rates and T<70 or T<54 (R = 0.91-0.93 for CGM and SMBG users). Participants not meeting hypoglycemic clinical targets had frequent level 2 hypoglycemic events.

CGM and Type 2 Diabetes

Peer-Reviewed Publications

a. Ajjan RA, Battelino T, Cos X, et al. Continuous glucose monitoring for the routine care of type 2 diabetes mellitus. *Nat Rev Endocrinol*. Published online April 8, 2024:1-15. doi:10.1038/s41574-024-00973-1
    - This article reviews existing evidence on the glycemic effects of CGM in T2DM, as well as the effect of CGM on quality of life, treatment satisfaction, and behavioral changes, and provides expert perspective on the use of CGM in the heterogeneous population of individuals with T2DM.
    - Further, the authors identify the outstanding gaps in evidence that need to be addressed to best inform clinical decisions in primary care management of T2D.
    - Most broadly, the review concludes that CGM sensors are beneficial in people with T2DM on non-insulin therapies when applied intermittently (at least every 3 months) as standard of care.
b. Ajjan RA, Heller SR, Everett CC, et al. Multicenter Randomized Trial of Intermittently Scanned Continuous Glucose Monitoring Versus Self-Monitoring of Blood Glucose in Individuals With Type 2 Diabetes and Recent-Onset Acute Myocardial Infarction: Results of the LIBERATES Trial. *Diabetes Care*. 2023;46(2):441-449. doi:10.2337/dc22-1219
    - This multicenter randomized controlled trial compared self-monitoring of blood glucose (SMBG) with intermittently-scanned/flash continuous glucose monitoring (isCGM) in 141 individuals with type 2 diabetes (T2D) and recent myocardial infarction (MI), who were treated with insulin and/or sulphonylurea before hospital admission.
    - isCGM was associated with a 17 min/day increase in TIR (95% confidence interval -105 to +153 min/day), with 59% probability of benefit. isCGM users also had lower TBR than the SMBG group.

- Compared with SMBG, isCGM in T2D individuals with MI marginally increases TIR and significantly reduces hypoglycemic exposure while equally improving HbA1c.

c. Aleppo G, Beck RW, Bailey R, et al. The Effect of Discontinuing Continuous Glucose Monitoring in Adults With Type 2 Diabetes Treated With Basal Insulin. *Diabetes Care*. 2021;44(12):2729-2737. doi:10.2337/dc21-1304
   - This study found that among adults with type 2 diabetes treated with basal insulin who had been using real-time CGM, discontinuing CGM resulted in a loss of about one-half
     of the initial gain in TIR that had been achieved during CGM use.
   - 110 participants across multiple centers were randomized to either real-time CGM or blood glucose monitoring (BGM) for 8 months, after which half of the CGM group continued using CGM and half went back to using BGM.
   - In the group that discontinued CGM, mean TIR improved from 38% before initiating CGM to 62% after 8 months of CGM, then decreased to 50% after discontinuing CGM. Little difference in TIR was found between 8 and 14 months in the group that continued CGM use throughout.
   - The adjusted treatment group difference in mean TIR between those who discontinued CGM versus those who continued use was 26% at 14 weeks (95% CI 216% to 4%, P = 0.20).

d. Aleppo G, Hirsch IB, Parkin CG, et al. Coverage for continuous glucose monitoring for individuals with type 2 diabetes treated with nonintensive therapies: An evidence-based approach to policymaking. *Diabetes Technol Ther*. 2023;10.1089/dia.2023.0268. doi:10.1089/dia.2023.0268
   - This review article reports key findings from recent randomized, observational, and retrospective studies investigating use of CGM in T2D individuals treated with basal insulin only and/or noninsulin therapies and presents an evidence-based rationale for expanding access to CGM within this population.

e. Aronson R, Brown RE, Chu L, et al. IMpact of flash glucose Monitoring in pEople with type 2 Diabetes Inadequately controlled with non-insulin Antihyperglycaemic ThErapy (IMMEDIATE): A randomized controlled trial. *Diabetes Obes Metab*. 2023;25(4):1024-1031. doi:10.1111/dom.14949
   - This multisite randomized controlled trial assessed efficacy of and user satisfaction with intermittently scanned CGM (isCGM) in adults using non-insulin therapies for management of type 2 diabetes.
   - 116 participants with baseline A1C ≥7.5% (58 mmol/mol) were randomized to either isCGM plus diabetes self-management education (DSME) or DSME alone.

- At 16 week follow-up, the isCGM + DSME group had significantly 9.9% higher TIR, (95% CI, 17.3% to 2.5%; P < .01), 8.1% significantly less TAR (95% CI, 0.5% to 15.7%; P = .037), and a 0.3% greater reduction in mean A1C (95% CI, 0% to 0.7%; P = .048) compared to those assigned DSME alone.
- There were no significant differences in TBR or hypoglycemic events between the two groups. Glucose monitoring satisfaction was higher among the isCGM group.

f. Beck RW, Riddlesworth T, Ruedy K, Ahmann A, Bergenstal R, Haller S, et al. Continuous glucose monitoring versus usual care in patients with type 2 diabetes receiving multiple daily insulin injections: A randomized trial. *Annals of Internal Medicine*. 2017 Sept 19;167(6):365.
   - This randomized clinical trial examined the effectiveness of CGM in adults with type 2 diabetes receiving multiple daily injections of insulin.
   - Among 158 adults with type 2 diabetes from 25 endocrinology practices in North America, mean HbA1c levels decreased to 7.7% in the CGM group and 8.0% in the control group at 24 weeks (adjusted difference in mean change, −0.3% [95% CI, −0.5% to 0.0%]; P = 0.022).
   - A high percentage of adults who received multiple daily insulin injections for type 2 diabetes used CGM on a daily or near-daily basis for 24 weeks and had improved glycemic control.

g. Carlson AL, Daniel TD, DeSantis A, et al. Flash glucose monitoring in type 2 diabetes managed with basal insulin in the USA: a retrospective real-world chart review study and meta-analysis. *BMJ Open Diabetes Res Care*. 2022;10(1):e002590. doi:10.1136/bmjdrc-2021-002590
   - This real-world observational review study in the USA and meta-analysis of a larger USA and Canada cohort assessed the impact of flash glucose monitoring (fCGM) use on HbA1C in adults with type 2 diabetes managed with basal insulin.
   - Medical record analysis (n=100) from 8 USA study sites showed significant HbA1c decrease of 1.4%±1.3% after fCGM device use, p<0.0001 (mean±SD). Similarly, meta-analysis of medical records from USA and Canada sites (n=191) showed HbA1c significantly decreased by 1.1%±0.14% (mean±SE), with moderate to high heterogeneity between sites explained by differences in baseline HbA1c between sites.
   - These findings suggest that the use of CGM in type 2 diabetes treated with basal insulin has the potential to be a valuable tool to support the improvement of glucose control.

h. Cichosz SL, Kronborg T, Laugesen E, et al. From Stability to Variability: Classification of Healthy Individuals, Prediabetes, and Type 2 Diabetes using Glycemic Variability Indices from Continuous Glucose Monitoring Data. *Diabetes Technol Ther*. Published online August 8, 2024. doi:10.1089/dia.2024.0226
    - This study analyzed data from five studies that collected at least two days of CGM data from participants to investigate the continuum of glucose control from normoglycemia to dysglycemia in development of type 2 diabetes.
    - Participants were 282 individuals without diabetes, 133 with prediabetes, and 432 with type 2 diabetes. Statistically significant differences ($p<0.01$) were noted in mean glucose, Time Below Range, Time Above 140 mg/dl, Mobility, Multiscale Complexity Index and Glycemic Risk Index when transitioning from health to prediabetes.
    - Findings suggest CGM metrics may be useful in detecting and classifying the gradual deterioration of glucose homeostasis and increased glycemic variability indicative of the progression to type 2 diabetes.
i. den Braber N, Vollenbroek-Hutten M, Westerik K, Bakker S, Navis G, van Beijnum BJ, Laverman G. Glucose regulation beyond A1C in type 2 diabetes treated with insulin: real world evidence from the DIALECT-2 cohort. *Diabetes Care*. July 2021;44(8):1-7.
    - 79 participants were split into three different groups based on A1c: low, intermediate, and high (≤53, 54-62, and ≥63) or (≤7, 7.1-7.8, and ≥7.9%). FreeStyle Libre sensors were used to measure blood glucose time in range (TIR), time below range (TBR), time above range (TAR), glucose variability parameters, day and night duration, and frequency of TBR and TAR.
    - CGMs were used for a median of 10 days/patient. TIR was not different for low and intermediate A1C categories (76.8% [68.3-88.2] vs. 76& [72.5-80/1]). Meanwhile in the lower category, TBR was higher and TAR was lower (7.7% [2.4-19.1] vs. 0.7% [0.3-6.1] and 8.2% [5.7-17.6] vs. 20.4% [11.6-27.0]. People in the highest A1c category had lower TIR (52.7% [40.9-67.3]) and higher TAR (44.1% [27.8-57]), than the other A1c categories, but did not have less TBR during the night. All participants had more and longer (88 [45-195.5] vs. 53.4 [34.4-82.8] minutes) TBR episodes during the night than during the day.
    - A high A1c did not reduce the occurrence of nocturnal hypoglycemia, and low A1c was not associated with the highest TIR. Optimal personalization of glycemic control requires the use of newer tools, including CGM-derived parameters.
j. Ferreira ROM, Trevisan T, Pasqualotto E, et al. Continuous Glucose Monitoring Systems in Noninsulin-Treated People with Type 2 Diabetes: A Systematic Review and

Meta-Analysis of Randomized Controlled Trials. *Diabetes Technol Ther*. 2024;26(4):252-262. doi:10.1089/dia.2023.0390

- This systematic review and meta-analysis assessed the efficacy of CGM in managing glucose levels in non insulin-treated people with type 2 diabetes, using data from six randomized controlled trials (n=407).
- Among people with type 2 diabetes not on insulin, CGM use increased time in range (weighted mean difference 8.63%, 95% CI 4.54–12.71) and improved treatment satisfaction (standard mean difference 0.79, 95% CI 0.54–1.05) compared to self monitoring of blood glucose (SMBG)).
- Compared with SMBG, CGM also significantly reduced A1C, time in level 2 hypoglycemia, glucose time >180 mg/dL and the standard deviation of glucose variation

k. Gao X, Li H, Yu Y, et al. The relationship between time in range and dusk phenomenon in outpatients with type 2 diabetes mellitus. *Diabetes, Metabolic Syndrome and Obesity*. May 25 2023; 16.

- The dusk phenomenon refers to a spontaneous and transient pre-dinner hyperglycemia that affects glucose fluctuation and glycemic control, and the increasing use of continuous glucose monitoring (CGM) has facilitated its diagnosis. This study looked at the frequency of the dusk phenomenon and its relationship with the TIR in patients with type 2 diabetes.
- This study involved 102 patients with T2DM who underwent CGM for 14 days. CGM-derived metrics and clinical characteristics were evaluated.
- The percentage of clinical dusk phenomenon (CLDP) was 11.76% (10.34% in men, 13.64% in women). Compared with the non-CLDP group, the CLDP group tended to be younger and have a lower percentage of TIR (%$TIR^{3.9\text{-}10}$) and higher percentage of time above range (%$TAR^{>10}$ and %$TAR^{>13.9}$) ($P \leq 0.05$). Adjusted for confounding factors, the binary logistic regression analysis showed a negative association of CLDP with %TIR (odds ratio < 1, $P < 0.05$).
- The CLDP was frequently present in patients with T2DM. The TIR was significantly correlated with the CLDP and could serve as an independent negative predictor.

l. Grace T, Salyer J. Use of Real-Time Continuous Glucose Monitoring Improves Glycemic Control and Other Clinical Outcomes in Type 2 Diabetes Patients Treated with Less Intensive Therapy. *Diabetes Technol Ther*. 2022;24(1):26-31. doi:10.1089/dia.2021.0212

- This 6-month, prospective, interventional, single-arm study assessed the clinical effects of use rtCGM in patients with T2D treated with basal insulin only or non-insulin therapy.
- After 6 months, the group of 38 participants showed reduced HbA1c (-3.0% ± 1.3%, P< 0.001) and average glucose (-23.6 ± 38.8, P< 0.001) with rtCGM use. %TIR increased 15.2 ± 22.3, P < 0.001, with all patients maintaining %TBR targets (<4% at 70 mg/dL, <1% at <54 mg/dL). No changes in glycemic variability were observed. The greatest improvements in %TIR and %TAR were seen in patients treated with ≤1 medication.

m. Jancev M, Vissers TACM, Visseren FLJ, et al. Continuous glucose monitoring in adults with type 2 diabetes: a systematic review and meta-analysis. *Diabetologia*. 2024;67(5):798-810. doi:10.1007/s00125-024-06107-6
   - This systematic review and meta-analysis compiled 12 randomized controlled trials published before May 2023 to assess the effect of CGM on glycaemic control in adults with type 2 diabetes
   - Among the cumulative 1248 participants, CGM use (rtCGM or isCGM) led to a mean difference (MD) in HbA1c of −3.43 mmol/mol (−0.31%) compared to SMBG, with comparable effect among users of insulin and other oral agents
   - CGM was also associated with an increase in TIR (+6.36%) and a decrease in TBR (−0.66%), TAR (−5.86%) and glycaemic variability (−1.47%)
   - Based on these findings, the authors conclude CGM is associated with improvements in glycaemic control compared with SMBG in adults with type 2 diabetes.

n. Lever CS, Williman JA, Boucsein A, et al. Real time continuous glucose monitoring in high-risk people with insulin-requiring type 2 diabetes: A randomised controlled trial. *Diabet Med*. 2024;41(8):e15348. doi:10.1111/dme.15348
   - This randomized controlled trial (the 2GO-CGM study) investigated the impact of real-time CGM on glycemia in a predominantly indigenous population of adults with insulin-requiring type 2 diabetes in New Zealand (≥0.2units/kg/day of insulin and elevated A1C ≥64 mmol/mol (8.0%)).
   - Following a 2-week blinded CGM run-in phase, participants were randomized to rtCGM or control (self-monitoring blood glucose [SMBG] + blinded CGM).
   - Mean TIR increased from in the rtCGM group but did not change in the SMBG group. Baseline-adjusted between-group difference in TIR was 10.4% [95% CI −0.9 to 21.7; P=0.070].
   - Despite the improvement in glycemia in the CGM group, there was no between-group difference in mean total daily insulin dosage.

- The trial concluded that real-time CGM improved glycemia in a high-risk population with insulin-treated T2D and elevated HbA1c.

o. Lind N, Christensen MB, Hansen DL, Nørgaard K. Comparing Continuous Glucose Monitoring and Blood Glucose Monitoring in Adults With Inadequately Controlled, Insulin-Treated Type 2 Diabetes (Steno2tech Study): A 12-Month, Single-Center, Randomized Controlled Trial. *Diabetes Care*. Published online March 15, 2024:dc232194. doi:10.2337/dc23-2194
   - This single-center randomized controlled trial sought to compare the effects of CGM versus SMBG over one year in 76 adults with insulin-treated type 2 diabetes and HbA1c ≥ 7.5% (58 mmol/mol .
   - The primary outcome in this study was TIR, assessed at baseline and after 6 and 12 months by blinded CGM. CGM usage was found to be associated with significantly greater improvements in TIR (between-group difference 15.2%, 95% CI 4.6;25.9)
   - CGM use was also associated with significantly greater improvements in A1C and total daily insulin dose as well as with greater self-rated diabetes-related health, well-being, satisfaction, and health behavior.

p. Liu L, Ke W, Xu L, et al. Evaluating the role of time in range as a glycemic target during short-term intensive insulin therapy in patients with newly diagnosed type 2 diabetes. *J Diabetes*. 2023;15(2):133-144. doi:10.1111/1753-0407.13355
   - This study aimed to investigate the role of time in range during short-term intensive insulin therapy (SIIT) as a novel glycemic target by predicting clinical outcomes.
   - The findings advocate time in range among people in diabetes remission above 65% as a novel glycemic target during SIIT for clinical decision-making.

q. Lu J, Ying Z, Wang P, Fu M, Han C, Zhang M. Effects of continuous glucose monitoring on glycaemic control in type 2 diabetes: A systematic review and network meta-analysis of randomized controlled trials. *Diabetes Obes Metab*. Published online October 12, 2023. doi:10.1111/dom.15328
   - This study assessed the efficacy of CGM v. SMBG in maintaining glycemic control in 1425 individuals with type 2 diabetes from 11 studies.
   - Traditional meta-analysis revealed that CGM exhibited a significantly decreased time above range and time below range and a significantly increased time in range compared with SMBG.

r. Martens T, Beck RW, Bailey R, Ruedy KJ, Calhoun P, Peters AL, et al. Effect of continuous glucose monitoring on glycemic control in patients with type 2 diabetes

treated with basal insulin: A randomized clinical trial. *JAMA*. 2021; 325(22): 2262–2272.

- This study assessed whether use of CGM was associated with improvements in A1C for adults with type 2 diabetes treated with basal insulin, without prandial insulin.
- The study included 175 adults with type 2 diabetes, monitoring changes in A1C over 8 months.
- Results showed a statistically significant 1.1% decrease in A1C over the 8 month period in the CGM group; this is compared to a 0.6% decrease in the BGM group.
- This study also compared time in range between each group, showing a 59% TIR for the CGM group compared to 43% in the BGM group, a statistically significant difference.

s. Mayberry LS, Guy C, Hendrickson CD, McCoy AB, Elasy T. Rates and Correlates of Uptake of Continuous Glucose Monitors Among Adults with Type 2 Diabetes in Primary Care and Endocrinology Settings. *J Gen Intern Med*. 2023;38(11):2546-2552. doi:10.1007/s11606-023-08222-3

- This retrospective cohort study sought to determine prevalence and correlates of CGM use among adults with type 2 diabetes in real-world settings, and to examine rates of new CGM prescriptions across clinic types and medication regimens.
- Participants were 30,585 adults with type 2 diabetes and primary care or endocrinology visit at Vanderbilt University Medical Center large academic medical center, during 2021.
- 13% of participants had used a CGM. CGM users were more likely to be younger, to have private health insurance, and to receive endocrinology care compared to non-users. CGM users had higher A1C values on average, and 72% had an intensive insulin regimen while 12% were not taking insulin.
- From 2020 to 2021, monthly rates of CGM prescriptions to new users grew 36% overall, but 125% in primary care.

t. Nemlekar PM, Hannah KL, Norman GJ. Association Between Change in A1C and Use of Professional Continuous Glucose Monitoring in Adults With Type 2 Diabetes on Noninsulin Therapies: A Real-World Evidence Study. *Clin Diabetes*. 2023;41(3):359-366. doi:10.2337/cd22-0080

- This retrospective observational analysis examined the association between change in A1C and professional continuous glucose monitoring (p-CGM) use in adult patients with type 2 diabetes who were not using insulin. p-CGM refers to

devices provided to patients for short-term use, with data typically blinded to the user and transmitted to thieir healthcare provider.
- The study included data from 15,481 adults age 30 or older with an A1C between 7.8–10.5% who had no prior personal or p-CGM use.
- Those who used p-CGM showed a greater average decrease in A1C from baseline to the end of follow-up, regardless of whether they started insulin during the follow-up period.

u. Ni K, Tampe CA, Sol K, Cervantes L, Pereira RI. Continuous Glucose Monitor: Reclaiming Type 2 Diabetes Self-efficacy and Mitigating Disparities. *J Endocr Soc*. 2024;8(8):bvae125. doi:10.1210/jendso/bvae125
   - This qualitative study investigated the CGM usage experience in the primary care setting across a US Medicaid population with type 2 diabetes at federally qualified health centers.
   - 28 participants (21% non-Hispanic White, 57% Hispanic, 18% non-Hispanic Black; 68% English-speaking (68%), 32% Spanish-speaking; 53% reported 9 or fewer years of formal education) completed semi-structured phone interviews.
   - Six major themes identified include: initial expectations and overcoming initiation barriers, convenience and ease promote daily use, increased knowledge leads to improved self-management, collaboration with provider and clinical team, improved self-reported outcomes, and barriers and burdens are generally tolerated.
   - CGM use was experienced as easy to understand and use and was overwhelmingly well-received by participants with T2DM from diverse backgrounds. Participants viewed the CGM as a tool for diabetes self-efficacy and became self-advocates for their diabetes care. Personalized clinic and family support helped mitigate access barriers.
   - Expanded CGM access for socially marginalized patients with type 2 diabetes can enhance diabetes self-management to help mitigate diabetes outcome disparities.

v. Ogawa W, Hirota Y, Osonoi T, Tosaki T, Kato Y, et al. Effect of the FreeStyle Libre flash glucose monitoring system on glycemic control in individuals with type 2 diabetes treated with basal-bolus insulin therapy: An open label, prospective, multicenter trial in Japan. *Journal of Diabetes Investig*. 2021; 12(1):82-90.
   - This was a 90-day single-arm study that enrolled 94 adults with type 2 diabetes on insulin.

- Time spent in hypoglycemia (<70mg/dL) was low at baseline (0.51 ± 0.93 h/day) and did not significantly decrease at study end (0.47 ± 0.63 h/dY). Time in range, time in hyperglycemia and estimated A1C all improved versus baseline (by +1.7 ± 3.0 h/day, -1.6 ± .4 h/day and -0.4 ± 0.8%, respectively, P<0.0001 in each). The mean treatment satisfaction score increased by 11.8 ± 5.3 (P<0.0001).
- Use of FreeStyle Libre by Japanese type 2 diabetes patients treated with basal-bolus insulin therapy showed a low baseline of hypoglycemia, and enabled improved glycemic control and treatment satisfaction.

w. Price DA, Deng Q, Kipnes M, Beck S. Episodic real-time CGM use in adults with type 2 diabetes: Results of a pilot randomized controlled trial. *Diabetes Ther*. 2021;12(7):2089-2099. doi:10.1007/s13300-021-01086-y
   - This study explored whether adults with type 2 and elevated A1C who were using non-insulin antihyperglycemics could benefit from use of rtCGM
   - 70 people were enrolled in this study, and data from 68 were used. The study enrolled people who used two or more non-insulin therapies and had A1c values of 7.8-10.5%. One group used unblinded rtCGM and the control group used a CMBG and wore a blinded rtCGM.
   - 34.1% of the rtCGM group vs. 17.4% of the SMBG group reached the A1C goal of less than 7.5% at week 12. Mean TIR at week 8 increased for the rtCGM group (56.3 vs. 63.1) while it decreased for the SMBG group (68.4 vs. 55.1).
   - rtCGM use resulted in short-term glycemic benefits

x. Reed J, Dong T, Eaton E, et al. Continuous glucose monitoring for glycaemic control and cardiovascular risk reduction in patients with type 2 diabetes not on insulin therapy: A clinical trial. *Diabetes Obes Metab*. 2024;26(7):2881-2889. doi:10.1111/dom.15608
   - This two-phase crossover study (1 phase with blinded CGM, a second with unblinded CGM) evaluated the impact of CGM on glycemic control and cardiometabolic risk in people with type 2 diabetes (T2D) at high cardiovascular risk who were not on insulin therapy.
   - Among 47 participants, CGM use was associated with a reduction in average glucose (184.0 to 147.2 mg/dl, p < .001), an increase in time in range (57.8 to 82.8%, p < .001) and a trend towards lower glucose variability (26.2 to 23.8%). There were significant reductions in HbA1c, BMI, triglycerides, blood pressure, total cholesterol, diabetes distress and 10-year predicted risk for atherosclerotic cardiovascular disease (p < .05 for all) and an increase in prescriptions for sodium-glucose cotransporter 2 inhibitors (36.2 to 83.0%)

and glucagon-like peptide-1 receptor agonists (42.5 to 87.2%, p < .001 for both).
- Results indicate CGM can be a safe and effective tool to improve diabetes management in patients at high risk for adverse cardiovascular outcomes.

y. Simonson GD, Bergenstal RM, Johnson ML, Davidson JL, Martens TW. Effect of professional CGM (pCGM) on glucose management in type 2 diabetes patients in primary care. *Journal of Diabetes Science and Technology*. 2021 Mar 10;15(3): 539-545.
- This study assessed the effect of professional CGM in primary care on glucose management in a MD and RN/Certified Diabetes Care and Education Specialist (CDCES) Care Model.
- For two weeks, 68 individuals (average age: 61.6 years, average duration of diabetes: 15 years, mean A1C: 8.8%,) who had type 2 diabetes wore pCGM. Shared-decision making was also used to modify lifestyle and medications.
- Using a pCGM in primary care, with an MD or RN/CDCES Care Model, was found to be effective at lowering A1C and increasing TIR without necessarily requiring additional medications. Time in hyperglycemia also improved along with more hypoglycemia in the subset of 37 participants who wore a second pCGM. Glycemic improvement was due to lifestyle counseling (68% of participants) and intensification of therapy (65% of participants).

z. Tanaka K, Okada Y, Uemura F, Tanaka Y. Associations between time in range and insulin secretory capacity in Japanese patients with type 2 diabetes. *Sci Rep*. 2024;14(1):12910. doi:10.1038/s41598-024-63678-5
- This retrospective study investigated the relationship between TIR and insulin secretory capacity in type 2 diabetes (T2D).
- Participants were 330 individuals with T2D admitted for diabetes education who underwent intermittently scanned continuous glucose monitoring (isCGM) and had their fasting serum C-peptide immunoreactivity (S-CPR) measured within 5 days of admission.
- S-CPR index (S-CPR [ng/mL]/fasting plasma glucose [mg/dL]× 100) correlated significantly with TIR, which was confirmed by multivariate analysis including A1C. S-CPR index values of ≥ 1.88 correlated significantly with TIR> 70%.
- Results suggest the S-CPR index might be a potentially useful biomarker insulin secretory capacity, in association with TIR.

aa. Uhl S, Choure A, Rouse B, Loblack A, Reaven P. Effectiveness of Continuous Glucose Monitoring on Metrics of Glycemic Control in Type 2 Diabetes Mellitus: A Systematic

Review and Meta-analysis of Randomized Controlled Trials. *J Clin Endocrinol Metab*. 2024;109(4):1119-1131. doi:10.1210/clinem/dgad652

- This systematic review and meta-analysis synthesized fourteen randomized control trials, including a cumulative 825 patients using rt-CGM and 822 in using FGM
- The pooled mean difference for all studies showed a statistically significant decrease in A1C in patients using CGM compared with SMBG
- Pooled analysis of 4 RCTs using rt-CGM indicated a statistically significant increase in TIR associated with use of rt-CGM compared with SMBG
- Moderate certainty of evidence indicated that use of CGM had a modest but statistically significant reduction in A1C levels of about 0.32%, with little difference between rt-CGM and FGM (0.34% and 0.33% change in A1C, respectively)

bb. Wright EE, Kerr MSD, Reyes IJ, Nabutovsky Y, Miller E. Use of Flash Continuous Glucose Monitoring Is Associated With A1C Reduction in People With Type 2 Diabetes Treated With Basal Insulin or Noninsulin Therapy. *Diabetes Spectr*. 2021;34(2):184-189. doi:10.2337/ds20-0069

- This retrospective, observational study assessed changes in A1C after initiation of flash CGM in 1,034 adults with type 2 diabetes and baseline A1C ≥8%.
- Results show prescription of flash CGM was associated with significant reductions in A1C in patients with type 2 diabetes treated with either basal insulin or noninsulin therapy.

cc. Wright EE, Roberts GJ, Chuang JS, Nabutovsky Y, Virdi N, Miller E. Initiating GLP-1 Therapy in Combination with FreeStyle Libre Provides Greater Benefit Compared with GLP-1 Therapy Alone. *Diabetes Technol Ther*. Published online May 31, 2024. doi:10.1089/dia.2024.0015

- This real-world observational study compared changes in A1C between people acquiring GLP-1 with the Freestyle Libre CGM (GLP-1+FSL) versus GLP-1 without CGM (GLP-1).
- 24,724 participants were identified from the Optum electronic health records database, and included adults with type 2 diabetes (T2D) and A1C≥8%. GLP-1+FSL subjects acquired their first CGM within 30 days of GLP-1 acquisition (GLP-1+FSL, n = 478).
- Comparing the GLP-1+FSL group to an unmatched cohort of all other GLP-1 users as well as a cohort of GLP-1-users matched 1:5 on baseline insulin therapy, age, sex, baseline HbA1c, and GLP-1 type, A1C reduction was greater among those using CGM. (-2.43% vs. -1.73% in the unmatched cohort,

difference 0.70%, P < 0.001 and -2.43% vs. -2.06% in the matched cohort, difference 0.37%, P < 0.001).

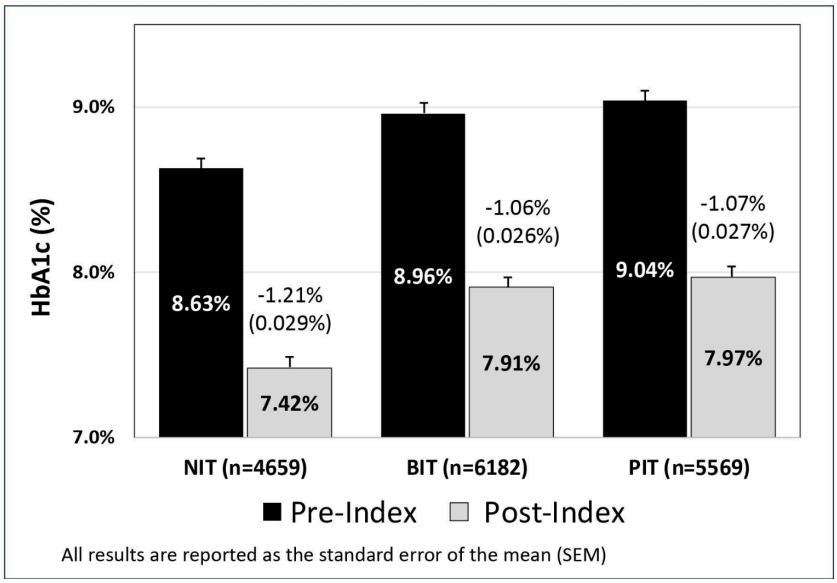
- GLP-1+FSL vs. GLP-1 treatment was associated with greater A1C reduction in the intensive insulin (-2.32% vs. -1.50%), nonintensive insulin (-2.50% vs. -1.74%), and noninsulin group (-2.46% vs. -1.78%), as well as in patients using semaglutide (-2.73% vs. -1.92%) and dulaglutide (-2.45% vs. -1.71%) GLP-1 RA, all P < 0.001.
- These results suggest that initiating CGM alongside GLP-1 provides additional glycemic benefit for adults with suboptimally controlled T2D compared to GLP-1 alone.

Abstracts/Other

a. Galindo Rj, Sree Burugapalli B, Brandner L, Bindal A. 1926-LB: Use of Continuous Glucose Monitoring and Health Care Resource Utilization in Patients with Diabetes Treated with Sulfonylureas/Meglitinides. *Diabetes*. 2024;73(Supplement_1):1926-LB. doi:10.2337/db24-1926-LB
   - This retrospective cohort study investigated the relationship between CGM use and acute diabetes events (ADE), all-cause hospitalizations (ACH), and emergency department (ED) visits among people with type 2 diabetes (T2D), treated with sulfonylurea (SU) or meglitinide therapy in the United States.
   - Using Inovalon Insights claims data, two subgroups were analyzed: <65 group (n = 2,976) and ≥65 group (n = 1,895). For both subgroups, ADE, acute hyperglycemic events, ACH, and ED visit rates were significantly lower during CGM use period, compared to pre-CGM use.
   - Compared to pre-CGM use, patients on CGM with type 2 diabetes treated with SU/meglitinides had lower healthcare utilization
b. Garg SK, Hirsch IB, Repetto E, et al. 355-OR: Glycemic Outcomes with CGM Use in Patients with Type 2 Diabetes—Real-World Analysis. *Diabetes*. 2024;73(Supplement_1):355-OR. doi:10.2337/db24-355-OR
   - This large real-world study analyzed claims data from 16,410 million patients with type 2 diabetes (T2D), including sub-groups using non-insulin therapies (NIT), basal insulin (BIT), and prandial insulin (PIT). Two periods were observed: the pre-index period, 360 days prior to patients' first CGM claim and post-index period, 360 days after to the first CGM claim.

- At 12 months, CGM use was associated with significant improvements in A1C in both non-insulin and insulin-treated patients with T2D.

Figure. HbA1c Change from Baseline during the Post-Index Period



CGM/TIR in Specific Settings and Populations

Pregnancy

Peer-Reviewed Publications

a. Baretić M, Lekšić G, Ivanišević M. Ambulatory Glucose Profile Changes During Pregnancy in Women With Type 1 Diabetes Using Intermittently Scanned Continuous Glucose Monitoring Empowered by Personalized Education. *Diabetes Spectr.* 2023;36(4):373-378. doi:10.2337/ds22-0094
   - This retrospective cohort study evaluated the effect of intermittently scanned continuous glucose monitoring (isCGM) empowered by education on glucose dynamics and to predict third trimester time in pregnancy target range (63–140 mg/dL or 3.5–7.8 mmol/L [TIRp]).
   - Analysis included data from 38 pregnant individuals with type 1 diabetes who used a first-generation Free-Style Libre isCGM system for at least 3 months before conception and had sensor data captured >70% of the time the system was used. Patients received personalized education on diabetes and on

minimizing hypoglycemia and hyperglycemia using CGM trend arrows and frequent sensor scanning.
    - Using isCGM empowered by personalized education improved glycemic parameters of glucose regulation (TIRp, glucose management indicator, and mean glucose), hyperglycemia (time above range), glucose variability (SD and coefficient of variation [%CV]), and scanning frequency, but did not improve parameters of hypoglycemia (time below range and a number of low glucose events).
    - Logistic regression analysis showed that the first trimester %CV and scanning frequency contributed to the third trimester TIRp (P <0.01, adjusted R2 0.40).

b. Benhalima K, Beunen K, Van Wilder N, et al. Comparing advanced hybrid closed loop therapy and standard insulin therapy in pregnant women with type 1 diabetes (CRISTAL): a parallel-group, open-label, randomised controlled trial. *Lancet Diabetes Endocrinol*. 2024;12(6):390-403. doi:10.1016/S2213-8587(24)00089-5.
    - This multi-center, double-arm, parallel-group, open-label, randomized controlled trial investigated whether the MiniMed 780G can improve glycemic control with less hypoglycaemia in pregnant women with type 1 diabetes.
    - 95 pregnant women aged 18–45 years with type 1 diabetes who received care from secondary and tertiary care specialist endocrinology centers at 12 hospitals were randomly assigned (1:1) to advanced hybrid closed-loop (AHCL) therapy (MiniMed 780G) or standard insulin therapy (standard of care) at a median of 10.1 weeks of gestation.
    - In pregnant women starting with tighter glycaemic control, AHCL therapy did not significantly improve overall time in target range but improved overnight time in target range, reduced time below range, and improved treatment satisfaction.

c. Bitar G, Cornthwaite JA, Sadek S, et al. Continuous glucose monitoring and time in range: Association with adverse outcomes among people with type 2 or gestational diabetes mellitus. *Am J Perinatol*. Published online March 1, 2023. doi:10.1055/s-0043-1764208
    - In this retrospective cohort study, investigators compared maternal and neonatal outcomes when glucose was within a range of 70-140 mg/dL >70% of the time versus ≤ 70%. Subjects were 141 pregnant people with type 2 or gestational diabetes.
    - Compared with those with TIR > 70%, the primary composite outcome (capturing large for gestational age, NICU admission, need for intravenous glucose, respiratory support, or neonatal death) occurred more frequently in neonates of individuals TIR ≤70% (71.4 vs. 37.8%, aOR: 4.8, 95% CI: 1.6, 15.7).

- Individuals with TIR ≤70% were more likely to have hypertensive disorders (42.9 vs. 16.2%, OR: 3.9, 95% CI: 1.3, 13.0), preterm delivery (54 vs. 27%, OR: 3.1, 95% CI: 1.1, 9.1) , and cesarean delivery (96.4 vs. 51.4%, OR: 4.6, 95% CI: 2.2, 15.1) compared with those with TIR >70%.

d. Carlson AL, Beck RW, Li Z, et al. Glucose levels measured with continuous glucose monitoring in uncomplicated pregnancies. *BMJ Open Diabetes Res Care*. 2024;12(3):e003989. doi:10.1136/bmjdrc-2023-003989
   - This observational, non-intervention study sought to describe the CGM-derived patterns of glycemia observed throughout uncomplicated pregnancy in a large cohort of individuals participating in the Glucose Levels Across Maternity (GLAM) Study.
   - Analysis included 413 pregnant individuals who had uncomplicated pregnancies (defined as A1c <5.7% (<39mmol/mol) in early pregnancy, and no large-for-gestational-age birth, hypertensive disorders of pregnancy, or gestational diabetes mellitus [ie, abnormal oral glucose tolerance test]) and wore a Dexcom G6 continuous glucose monitor for a median of 123 days.
   - Mean glucose levels and time 63–120 mg/dL (3.5–6.7mmol/L) remained nearly stable throughout pregnancy and values above 140 mg/dL (7.8mmol/L) were rare. Mean glucose levels in pregnancy trend higher as BMI increases into the overweight/obesity range.
   - These findings may inform treatment targets for pregnant individuals.

e. Feig DS, Donovan LE, Corcoy R, Murphy KE, Amiel SA, Hunt KF, et al. Continuous glucose monitoring in pregnant women with type 1 diabetes (CONCEPTT): A multicentre international randomised controlled trial. *Lancet*. 2017; 390(10110): 2347-2359. doi:10.1016/S0140-6736(17)32400-5
   - The aim of this multicentre, open-label, randomized controlled trial was to examine the effectiveness of CGM use on maternal glucose control and obstetric and neonatal health outcomes.
   - Study participants were 325 women 18-40 years old on intensive insulin therapy who had type 1 diabetes for over a year. There were two parallel trials for participants who were either pregnant (≤13 weeks and 6 days' gestation) or planning pregnancy. Participants were randomly assigned to either CGM, in addition to capillary glucose monitoring, or capillary glucose monitoring alone. The primary outcome was change in A1C from randomization to 34 weeks' gestation in pregnant women and to 24 weeks or conception in women planning pregnancy. Secondary outcomes included obstetric and neonatal health outcomes, assessed with all available data without imputation.

- On average, pregnant women using CGM had a small decrease in A1C, an increase in TIR, and a decrease in TBR than the control group. Neonatal outcomes were significantly improved including lower incidence of large for gestational age, fewer neonatal intensive care admissions lasting more than 24 hours, fewer incidences of neonatal hypoglycemia, and 1-day shorter length of hospital stay. There was no apparent benefit in women planning pregnancy.
- The study concluded that the use of CGM during pregnancy in people with type 1 diabetes is associated with improved neonatal outcomes, which are likely attributed to reduced maternal hypoglycemia. CGM should be offered to all pregnant women with type 1 diabetes using intensive insulin therapy. This study is the first to indicate potential for improvements in non-glycaemic health outcomes from CGM use.

f. Fishel Bartal M, Ashby Cornthwaite JA, Ghafir D, et al. Time in range and pregnancy outcomes in people with diabetes using continuous glucose monitoring. *Am J Perinatol*. 2023;40(5):461-466. doi:10.1055/a-1904-9279
   - This retrospective study compared outcomes between pregnant people with time in range greater than 70%, as recommended by the international consensus on continuous glucose monitoring, and those with TIR ≤ 70%.
   - Among 65 patients with pregestational diabetes who used CGM, 50% reached the recommended time in range using CGM. Time in range >70% was associated with reduced rate of some neonatal complications, including NICU admission, requiring IV glucose, and longer hospital stay. At the same time, time in range ≤70% was associated with increased risk for adverse maternal outcomes such as hypertensive disorders.

g. Gao V, Snell-Bergeon JK, Malecha E, Johnson CA, Polsky S. Clinical Effectiveness of Continuous Glucose Monitoring in Pregnancies Affected by Type 1 Diabetes. *Diabetes Technol Ther.* Published online March 25, 2024. doi:10.1089/dia.2023.0548
   - This real-world retrospective study assessed the clinical effectiveness, assessed through maternal glucose control and gestational health outcomes, of CGM use compared with self-monitoring of blood glucose (SMBG) in pregnancies associated with type 1 diabetes.
   - Investigators identified 160 type 1 diabetes pregnancies managed with CGM therapy (n = 109) or SMBG (n = 51) over a 6.5-year period (2014–2020). CGM use was defined as ≥60% wear in the second and third trimesters of pregnancy.
   - The CGM group had more participants meeting trimester-specific hemoglobin A1C (HbA1c) goals throughout pregnancy and postpartum, and fewer participants never meeting HbA1c goals in any trimester than the SMBG group.

- There were no significant differences in neonatal outcomes between groups, other than for macrosomia (12.8% CGM vs. 29.4% SMBG, P = 0.01). Infants of CGM users required a neonatal intensive care unit admission less often (52.9% CGM vs. 68.3% SMBG, P = 0.0989).
- The study concluded that CGM use was associated with improved maternal glucose levels in a diverse real-world cohort.

h. Liang X, Fu Y, Lu S, et al. Continuous glucose monitoring-derived glycemic metrics and adverse pregnancy outcomes among women with gestational diabetes: a prospective cohort story. *The Lancet*. Published online June 12, 2023.
   - Investigators aimed to explore the relationship between CGM-derived metrics during pregnancy and pregnancy outcomes among women with gestational diabetes mellitus.
   - Participants included 1,302 pregnant women with GDM at a mean gestational age of 26 weeks. The primary outcome was any adverse pregnancy outcome, defined as having at least one of the outcomes: preterm birth, large-for-gestational-age (LGA) birth, fetal distress, premature rupture of membranes, and neonatal intensive care unit (NICU) admission.
   - Per 1-SD difference in time above range (TAR), glucose area under the curve (AUC), nighttime mean blood glucose (MBG), daytime MBG, and daily MBG was associated with higher risk of any adverse pregnancy outcome, with odds ratio: 1.22 (95% CI 1.08–1.36), 1.22 (95% CI 1.09–1.37), 1.18 (95% CI 1.05–1.32), 1.21 (95% CI 1.07–1.35), and 1.22 (95% CI 1.09–1.37), respectively. Time in range, TAR, AUC, nighttime MBG, daytime MBG, daily MBG, and mean amplitude of glucose excursions were positively associated, while time blow range was inversely associated with the risk of LGA. Additionally, higher value for TAR was associated with higher risk of NICU admission. We further summarized the potential thresholds of TAR (2.5%) and daily MBG (4.8 mmol/L) to distinguish individuals with and without any adverse pregnancy outcome.

i. Ling P, Yang D, Wang C, et al. Basal Hyperglycemia Contributes More Than Fifty Percent to Time in Range in Pregnant Women with Type 1 Diabetes. *J Clin Endocrinol Metab*. Published online April 30, 2024. doi:10.1210/clinem/dgae291
   - This observational study evaluated the relative contribution of basal hyperglycemia (BHG) and postprandial hyperglycemia (PHG) to the time in pregnancy target range (3.5–7.9 mmol/L [TIRp]) categories and adverse pregnancy outcomes in pregnant women with type 1 diabetes (T1D).
   - The analysis included 112 pregnancies with T1DM from the CARNATION study who wore continuous glucose monitoring (CGM) devices during pregnancy.

- For participants who experienced time in range 3.5–7.9 mmol/L (TIR) of
    1. **<60%**: BHG accounted for 74.9% (36.8, 100), PHG accounted for 25.1% (0, 63.2) (P < .001)
    2. **60%–78%:** BHG accounted for 69.2% (13.4, 100), PHG accounted for 0.8% (0, 86.6) (P < .001)
    3. **≥78%:** BHG accounted for 66.5% (10.0, 100) PHG accounted for 33.5% (0, 90.0) (P < .001)
- Participants with higher BHG contribution rates tended to have more adverse pregnancy outcomes.
- Investigators concluded that optimization of insulin regimens targeting the lowering of BHG is important for pregnant women with T1DM who do not reach the glycemic target of TIR (3.5-7.8 mmol/L)

j. Majewska A, Stanirowski PJ, Tatur J, et al. Flash glucose monitoring in gestational diabetes mellitus (FLAMINGO): a randomised controlled trial. *Acta Diabetol*. 2023;60(9):1171-1177. doi:10.1007/s00592-023-02091-2
    - This unblinded randomized controlled trial assessed the efficacy of flash glucose monitoring (FGM) in gestational diabetes mellitus (GDM).
    - 100 women were randomized to FGM or self-monitoring of blood glucose (SMBG) after being diagnosed with GDM between 24 and 28 weeks of gestation.
    - There was no significant difference in mean glycaemia between the groups. Compared to the SMBG control, the FGM group significantly reduced their fasting (p=0.027) and postprandial glycaemia (p=0.034) during the first 4 weeks following GDM diagnosis, with no significant difference in progression to insulin therapy (OR 1.09, 95% CI 0.47–2.57).
    - Incidence of fetal macrosomia was significantly higher in SMBG as compared to FGM group (OR 5.63, 95% CI 1.16–27.22).
    - Results indicate FGM has an impact on glycaemic control, dietary habits and incidence of fetal macrosomia in patients with GDM.

k. McLean A, Barr E, Tabuai G, Murphy HR, Maple-Brown L. Continuous Glucose Monitoring Metrics in High-Risk Pregnant Women with Type 2 Diabetes. *Diabetes Technol Ther*. 2023;25(12):836-844. doi:10.1089/dia.2023.0300
    - This prospective observational pilot study looked at the association between continuous glucose monitoring metrics (using a pregnancy-specific target glucose range of 3.5–7.8 mmol/L or 63–140 mg/dL [TIRp]) and neonatal hypoglycemia and large for gestational age infants in 41 women with preexisting type 2 diabetes (T2D) in Australia.

- The participants, of whom 73% of women identified as Aboriginal or Torres Strait Islander, wore flash (intermittently-scanned) continuous glucose monitors (CGM) for at least 2 weeks. On average, the women used CGM for 15 weeks and scanned 4.4 times per day.
- For the subgroup with sensor use >50% (n = 29), mean TIRp increased by 9%, TAR reduced by 12%, average glucose reduced by 1 mmol/L, and TBR increased by 3%
- Those with neonatal hypoglycemia had lower TIRp, higher TAR, higher average glucose, and higher median GMI in early pregnancy than those without neonatal hypoglycemia. In late pregnancy, all metrics (except TBR) were significantly different between the groups, including hyperglycemia (lower TIRp, higher TAR, average glucose, and GMI) and glucose variability metrics (higher SD, IQR, and CV).
- Those with LGA had lower TIRp, higher TAR, and higher average glucose in early pregnancy compared with those without LGA.
- Each 1% increase TIRp was associated with a 4%–5% reduction in risk of neonatal complications
- In this high-risk group of women with T2D, CGM metrics only improved during pregnancy in those with greater sensor use and were associated with LGA in early pregnancy and neonatal hypoglycemia throughout.

l. McLean A, Sinha A, Barr E, Maple-Brown L. Feasibility and Acceptability of Intermittently Scanned Continuous Glucose Monitoring for Women with Type 2 Diabetes in Pregnancy. *J Diabetes Sci Technol*. 2023;17(1):256-258. doi:10.1177/19322968221124956

- This prospective pilot study assessed the feasibility and acceptability of intermittently-scanned continuous glucose monitoring (iscCGM) in pregnancy among women with pre-existing type 2 diabetes (T2D).
- Most participants found iscCGM was worthwhile and easy to use. 47 (94%) would recommend iscCGM to others. Self-reported frequency of glucose testing four times per day increased from 36% to 68% (P = .001), compared with prior finger-stick measurements.
- Feasibility assessment revealed that nearly all eligible women agreed to participate and were able to use the technology. Ethnicity and remoteness were not necessarily barriers to use. However, in this real-world setting, late referrals (23%), discontinuation (21%), and variability of use meant that few patients used iscCGM for the entire pregnancy

m. Meek CL, Stewart ZA, Feig DS, et al. Metabolomic insights into maternal and neonatal complications in pregnancies affected by type 1 diabetes. *Diabetologia*. 2023;66(11):2101-2116. doi:10.1007/s00125-023-05989-2
    - This study assessed the association between metabolomic patterns associated with risk factors (maternal hyperglycaemia, diet, BMI, weight gain) and perinatal complications (pre-eclampsia, large for gestational age [LGA], neonatal hypoglycaemia, hyperinsulinism) among 174 subjects in the Continuous Glucose Monitoring in Women with Type 1 Diabetes in Pregnancy Trial (CONCEPTT).
    - Maternal continuous glucose monitoring time-above-range (but not BMI or excessive gestational weight gain) was associated with increased triacylglycerols in maternal blood and increased carnitines in cord blood, indicators that were subsequently associated with LGA, neonatal hypoglycaemia and offspring hyperinsulinism
    - The study's findings underscore that altered lipid metabolism is a key pathophysiological feature of type 1 diabetes pregnancy, and reinforce the need for new strategies for optimizing maternal diet and insulin dosing from the first trimester to improve pregnancy outcomes in type 1 diabetes.
n. Meek CL, Tundidor D, Feig DS, Yamamoto JM, Scott EM, Ma DD, et al. Novel biochemical markers of glycemia to predict pregnancy outcomes in women with type 1 diabetes. *Diabetes Care*. 2021 Jan; dc202360.
    - This study aimed to assess the predictive performance of A1C, CGM metrics, and alternative biochemical markers of glycemia (such as (glycated CD59, 1,5-anhydroglucitol, fructosamine, glycated albumin) at ~12, 24, and 34 weeks' gestation to predict obstetric and neonatal outcomes.
    - Participants included 157 pregnant women with type 1 diabetes from the CONCEPTT trial.
    - A1C, CGM metrics, and alternative laboratory markers were all significantly associated with obstetric and neonatal outcomes at 24 weeks' gestation. More outcomes were associated with CGM metrics during the first trimester and with laboratory markers during the third trimester. Time in pregnancy target range of 63–140 mg/dL or 3.5–7.8 mmol/L (TIRp) and time above range (TAR) were the most consistently predictive CGM metrics. A1C was also a consistent predictor of suboptimal pregnancy outcomes. Some alternative laboratory markers showed promise, but overall, they had lower predictive ability than A1C.
    - A1C is still an important biomarker for obstetric and neonatal outcomes in type 1 diabetes pregnancy. Alternative biochemical markers of glycemia and other

CGM metrics did not substantially increase the prediction of pregnancy outcomes compared with A1C, TIRp, and TAR.

o. Murphy HR. Continuous glucose monitoring targets in type 1 diabetes pregnancy: every 5% time in range matters. *Diabetologia*. 2019 Jun 3; 62:1123–1128.
   - This paper summarizes key findings from an observational cohort study of 186 pregnancies with T1D by Kristensen et al. and the CONCEPTT trial which included 108 pregnancies with T1D.
   - A 5% lower time in pregnancy target range (63–140 mg/dL [TIRp]) and 5% higher TAR during the second and third trimesters is associated with increased risk of large for gestational age infants, neonatal hypoglycaemia and neonatal intensive care unit admissions. For optimal neonatal outcomes, women and clinicians should aim for a TIRp of >70% and a TAR of <25% from as early as possible during pregnancy.

p. Murphy HR. Roadmap to the Effective Use of Continuous Glucose Monitoring in Pregnancy. *Diabetes Spectrum*. 2023;36(4):315-319. doi:10.2337/dsi23-0004
   - This review article discusses the existing evidence on the use of CGM for management of diabetes in pregnancy, identifies gaps for future research, and highlights existing management goals (70% time in range for pregnancy [TIRp; 63–140 mg/dL]) and the evidence supporting these goals—including that every 5% increase in TIRp reduces the risk of pregnancy complications.

q. Polsky S, Valent AM, Isganaitis E, et al. Performance of the Dexcom G7 Continuous Glucose Monitoring System in Pregnant Women with Diabetes. *Diabetes Technol Ther*. 2024;26(5):307-312. doi:10.1089/dia.2023.0516
   - This prospective observational study evaluated the safety and accuracy of the Dexcom G7 continuous glucose monitor (CGM) system during pregnancy.
   - CGM values from 105 women with type 1 (n = 59), type 2 (n = 21), or gestational diabetes (n = 25) were compared to arterialized venous glucose values from the YSI comparator instrument during 6-hour clinic sessions at different time points throughout the sensors' 10-day wear period.
   - 83.2% of CGM values in the 70–180 mg/dL range were within 15% of comparator values.
   - Of CGM values in the 40–400 mg/dL range, the %20/20 agreement rate (values within 20% or 20 mg/dL of comparator values) was 92.5%. Of values in the 63–140 mg/dL range, the %20/20 agreement rate was 92.3%.
   - The %20/20 agreement rates on days 1, 4 and 7, and 10 were 78.6%, 96.3%, and 97.3%, respectively. The sensors' 10-day survival rate was 90.3%.

- There were no serious adverse events. Results suggest the G7 system is accurate and safe during pregnancies complicated by diabetes and does not require confirmatory fingerstick testing.

r. Sanusi AA, Xue Y, McIlwraith C, et al. Association of Continuous Glucose Monitoring Metrics With Pregnancy Outcomes in Patients With Preexisting Diabetes. *Diabetes Care*. 2024;47(1):89-96. doi:10.2337/dc23-0636
   - This retrospective cohort study evaluated association between continuous glucose monitoring (CGM) metrics and perinatal outcomes in an effort to identify evidence-based TIR targets to reduce morbidity.
   - Subjects were 117 patients with type 1 or type 2 diabetes who used real-time CGM.
   - All CGM metrics, except time below range (TBR), were associated with neonatal morbidity. For each 5 percentage-point increase in time in pregnancy target range (defined in this study as 65-140 mg/dL [TIRp]), there was 28% reduced odds of neonatal morbidity. The statistically optimal TIRp was found to be 66-71%, supporting the American Diabetes Association's recommendation of 70% time between 65-140 mg/dL in pregnancy.
   - 5% increases in GV were associated with a 35% increase in the odds of the composite neonatal outcome. Higher GV was uniquely associated with increased risks for preeclampsia and preterm birth at <37 weeks' gestational age.

s. Shah VN, Snell-Bergeon JK, Demmitt JK, et al. Relationships between TIR, HbA1c and the glucose management indicator in pregnancies complicated by type 1 diabetes. *Diabetes Technol Ther.* 2021;23(12):783-790. doi:10.1089/dia.2021.0093
   - CGM data from 27 women with type 1 diabetes was collected throughout pregnancy and used to evaluate the relationship between time in pregnancy target range (63-140 mg/dL [TIRp]), A1C, and glucose management indicator (GMI) in pregnant women with type 1 diabetes.
   - GMI levels were calculated using a regression analysis, and linear models were used to compare TIR, A1C, and GMI by each trimester.
   - Results showed a significant negative correlation between TIRp and A1C: each 10% increase in TIRp was associated with a 0.3% reduction in A1C. The correlation between TIRp and A1C was stronger (r=-0.8) during the second and third trimesters than during the first trimester (r=-0.4). There was a good correlation between TIRp and GMI during each trimester (r=0.9 for each trimester). The relationship between GMI and A1C, especially during the second (r=0.8) and third trimesters (r=0.8) was strong.

t. Sobhani NC, Goemans SL, Nguyen A, Richley M, Gabby L, Han CS, et al. Perinatal outcomes and time-in-range on continuous glucose monitoring for type 1 diabetes. *American Journal of Obstetrics & Gynecology*. 2023;228(1):S73–4.
    - Objective of the study was to examine the association between perinatal outcomes and time in pregnancy target range (defined in this study as 70-140 mg/dL [TIRp]) as assessed on CGM used by pregnant individuals with type 1 diabetes.
    - Higher TIRp is associated with lower preeclampsia and lower gestational age. This association is seen early in gestation, when each 5-unit increase in TIRp is associated with ~50% reduction in the odds of these complications.
u. Sobhani NC, Goemans S, Nguyen A, et al. Continuous glucose monitoring in pregnancies with type 1 diabetes: small increases in time-in-range improve maternal and perinatal outcomes. *Am J Obstet Gynecol*. Published online January 17, 2024. doi:10.1016/j.ajog.2024.01.010
    - This multicenter retrospective cohort study examined the association between CGM-derived time in pregnancy target range (defined in this study as 70–140 mg/dL [TIRp]) and perinatal outcomes among 91 pregnant individuals with type 1 diabetes.
    - Higher TIRp was found to be associated with lower risk of preeclampsia and large for gestational age (LGA) infants. More specifically, every 5-unit increase in TIRp at 12 weeks was associated with 45% reduced risk of preeclampsia (adjusted risk ratio, 0.55; 95% CI, 0.30–0.99) and 46% reduced risk of LGA (adjusted risk ratio, 0.54; 95% CI, 0.29–0.99).
v. Søholm JC, Nørgaard SK, Nørgaard K, et al. Mean Glucose and Gestational Weight Gain as Predictors of Large-for-Gestational-Age Infants in Pregnant Women with Type 1 Diabetes Using Continuous Glucose Monitoring. *Diabetes Technol Ther*. Published online April 22, 2024. doi:10.1089/dia.2023.0583
    - This cohort study compared glycemic metrics during pregnancy between women with type 1 diabetes (T1D) delivering large-for-gestational-age (LGA) and appropriate-for-gestational-age (AGA) infants in order to identify predictors of LGA infants.
    - Participants were 111 women with type 1 diabetes using intermittently-scanned continuous glucose monitoring (isCGM) from conception through delivery.
    - Mean glucose decreased during pregnancy in both groups, with women delivering LGA infants having a 0.4 mmol/L higher mean glucose from 11–33 weeks (P = 0.01) compared with women delivering AGA infants.

- Mean time in range for pregnancy (TIRp, 63–140 mg/dL) >70% was obtained from 34 weeks in women delivering LGA infants and from 22–33 weeks in women delivering AGA infants.
- Independent predictors for delivering LGA infants were mean glucose throughout pregnancy and gestational weight gain.

w. Szmuilowicz ED, Barbour L, Brown FM, et al. Continuous Glucose Monitoring Metrics for Pregnancies Complicated by Diabetes: Critical Appraisal of Current Evidence. *J Diabetes Sci Technol*. Published online April 12, 2024. doi:10.1177/19322968241239341
   - This review examines existing evidence on factors contributing to high rates of adverse pregnancy outcomes in women with type 1 and type 2 diabetes in pregnancy despite use of CGM.

x. Tundidor D, Meek CL, Yamamoto J, et al. Continuous Glucose Monitoring Time-in-Range and HbA1c Targets in Pregnant Women with Type 1 Diabetes. *Diabetes Technol Ther*. 2021;23(10):710-714. doi:10.1089/dia.2021.0073
   - This sub-analysis examined attainment of pregnancy glucose targets, and associations with pregnancy outcomes in 221 individuals participating in the multi-center CONCEPTT randomized controlled trial. Notably, the study only analyzed 6-day CGM readings.
   - Investigators found that trial participants had a low rate of time pregnancy target range (63–140 mg/dL [TIRp]) target attainment despite their increase throughout gestation. At their peak, targets were only achieved by 44% of women for TIRp, 46.4% for TAR, and 63.1% for TBR at 34 weeks in the RT-CGM group.
   - Attainment of CGM and NICE HbA1c targets increased throughout gestation and all targets (both NICE/ADA HbA1c and CGM) were more likely to be achieved by RT-CGM users (compared to those assigned blinded CGM).

y. Wang S, Xin H, Li L, Li P. Time in range measurements for hyperglycemia management during pregnancy. *Clin Chim Acta*. 2022;531:56-61. doi:10.1016/j.cca.2022.03.017
   - This review article synthesizes research on the ties between time in range (and especially time above range) and pregnancy outcomes, as well as the use of continuous glucose monitoring to evaluate and manage glycemia in pregnancy.

Abstracts/Other

a. Jones D, Thomson L, Kusinski LC, Beardsall K, Meek CL. 66-OR: Using Continuous Glucose Monitoring to Identify Neonatal Hypoglycemia following Gestational

Diabetes—The DiGest Newborn Study. *Diabetes*. 2024;73(Supplement_1):66-OR. doi:10.2337/db24-66-OR

- This study assessed the efficacy of current perinatal guidelines to identify neonatal hypoglycemia (NH) using CGM in neonates of mothers with gestational diabetes in the DiGest trial.
- Among 13 mother-infant dyads, neonates wore CGM for mean 3.9 days with mean percent time below range (TBR) 2.8%, and a mean glucose 91.8 mg/dL (5.1 mmol/L).
- CGM identified periods of suspected NH which were not detected clinically with standard monitoring and were identified after the first 24 hours of life, outside of typical monitoring periods. CGM was well tolerated by mothers and neonates, suggesting CGM may offer novel opportunities to improve the identification of NH following gestational diabetes.

b. Zheng J. Continuous glucose monitoring-derived glycaemic metrics and adverse pregnancy outcomes among women with gestational diabetes. Short oral presentation presented at the European Association for the Study of Diabetes Annual Meeting on 4 October 2023.
   - This study assessed associations between CGM metrics and pregnancy outcomes (preterm birth, small- or large-for-gestational-age (SGA or LGA) birth, fetal distress, premature rupture of membranes and primary cesarean delivery) among 1302 pregnant women with gestational diabetes
   - Difference in time above range (TAR), glucose area under the curve (AUC), and nighttime and daytime mean blood glucose (MBG) were associated with higher risk of any adverse pregnancy outcome. TIR, TAR, AUC, nighttime and daytime MBG and mean amplitude of glucose excursions were positively associated, while time below range were inversely associated with risk of LGA.

Older Adults

Peer-Reviewed Publications

a. Bao S, Bailey R, Calhoun P, Beck RW. Effectiveness of Continuous Glucose Monitoring in Older Adults with Type 2 Diabetes Treated with Basal Insulin. *Diabetes Technol Ther*. 2022;24(5):299-306. doi:10.1089/dia.2021.0494
   - This study examined safety and efficacy of real-time continuous glucose monitoring (CGM) in adults 65 years old and older with type 2 diabetes (T2D) using basal without bolus insulin.

- Utilizing data from the MOBILE randomized controlled trial, investigators found adults ≥65 using CGM had a greater reduction in HbA1c (adjusted mean difference= -0.65%, 95% confidence interval [CI], -1.49 to 0.19) and greater time in range (mean adjusted treatment group difference, 19%; 95% CI, 4 to 35, p=0.01) compared to those using blood glucose monitoring (BGM).
- The observed benefit to A1C and TIR with CGM use among adults ≥65 was found to be at least as great as the benefit observed in adults younger than 65.
- Adults using CGM spent less time with glucose >180, 250, and 300 mg/dL than those using BGM, though the treatment effect was similar between those ≥65 and those <65 years old.

b. Miller K, Kanapka L, Ahmann A, Aleppo G, Ang L, Pratley R, et al. Benefit of continuous glucose monitoring in reducing hypoglycemia is sustained through 12 months of use among older adults with type 1 diabetes. *Diabetes Technology and Therapeutics*. 2022. 24(6): 424-434.
   - This study evaluated glycemic outcomes in the Wireless Innovation for Seniors with Diabetes Mellitus (WISDM) randomized clinical trial (RCT) participants. WISDM RCT was a 26-week RCT comparing CGM with BGM in 203 adults aged 60 and above with type 1 diabetes.
   - Among people who used CGM throughout the entire study, the median time time <70 mg/dL decreased from 5.0% at baseline to 2.6% at 26 weeks and remained stable with a median of 2.8% at 52 weeks. Participants spent more time in range 70-180 mg/dL (mean 56% vs. 64%; p< 0.001) and had lower A1C (mean 7.6% vs. 7.4%, p = 0.01) from baseline to 52 weeks. Among people who initiated a CGM after using a BGM, median time <70 mg/dL decreased from 3.9% to 1.9% (p<0.001), TIR increased from 56% to 60% (p=0.006) and A1C decreased from 7.5% to 7.3% (p=0.025).
   - CGM use reduces hypoglycemia without increasing hyperglycemia in older adults with type 1 diabetes.

c. O'Neal DN, Cohen O, Vogrin S, Vigersky RA, Jenkins AJ; Australian JDRF Closed-Loop Research Group. An assessment of clinical continuous glucose monitoring targets for older and high-risk people living with type 1 diabetes. *Diabetes Technol Ther*. 2023;25(2):108-115. doi:10.1089/dia.2022.0350
   - The aim of this study was to assess relationships between CGM metrics TIR, TBR, TAR, and coefficient of variation (CV) in relation to currently recommended clinical CGM targets for older people

- Post hoc analysis using the JDRF Australia Adult Hybrid Closed Loop trial database examined correlations in 120 adults with type 1 diabetes of 3 weeks masked CGM (Guardian Sensor 3)
- Correlations between baseline TIR and TAR were strong, weak for TBR and glucose CV, while moderate between CV and TBR ($r = 0.726$; $P < 0.0001$).
- Changes in TIR were not associated with changes in TBR, so the study recommended that for older AID users, while TBR targets should be prioritized to reduce hypoglycemia-related risk, TBR should be addressed independently of TIR.

Abstracts/Other

a. Slyne C, Roberts K, Conery CD, et al. 145-OR: Assessing the Current State of Diabetes Care in Long-Term Facilities Using Continuous Glucose Monitoring. *Diabetes*. 2024;73(Supplement_1):145-OR. doi:10.2337/db24-145-OR
    a. This cross-sectional study assessed the current state of glycemia in long term care facility residents with multiple comorbidities.
    b. Masked CGM data was collected from 65 residents (mean age 65) across 8 facilities who had diabetes and were on any oral or injectable hypoglycemic medications. 14% were on sulfonylurea medications and 68% were on insulin.
    c. 26% of the cohort had >1% time spent in hypoglycemia. 54% of the cohort spent >10% time >250mg/dL, 37% spent >25% time >250 mg/dL, and 14% spending >90% time >250 mg/dL. Only 44% of the cohort had >50% TIR (70-180 mg/dL). The latest A1C was <7% in 45% of the cohort, 7-8% in 27%, 8.1-9% in 12%, and >9% in 16%.
    d. Fingerstick reading frequency was 2 or fewer times/day in 74% of the cohort, 3 times/day in 13%, and 4 or more times/day in 13%.
    e. Results demonstrate a high burden of both hypoglycemia and hyperglycemia among this multi-morbid cohort of residents with diabetes living in long-term care facilities, despite fair control of A1C. More consistent use of CGM could help identify glycemic excursions to improve therapeutic decision-making.

Hospitalization & Post-Operation

Peer-Reviewed Publications

a. Ang L, Lin YK, Schroeder LF, et al. Feasibility and Performance of Continuous Glucose Monitoring to Guide Computerized Insulin Infusion Therapy in Cardiovascular Intensive

Care Unit. *J Diabetes Sci Technol*. 2024;18(3):562-569. doi:10.1177/19322968241241005

- This pilot study evaluated the feasibility of real-time continuous glucose monitoring (CGM) for titrating continuous intravenous insulin infusion (CII) to manage hyperglycemia in postoperative individuals in the cardiovascular intensive care unit.
- Based on 864 paired point of care blood glucose (POC-BG) and CGM values, mean and median absolute relative difference between POC-BG and CGM values were 13.2% and 9.8%, respectively
- Responses from nurses reported CGMs being very or quite convenient (93%) and it was favored over POC-BG testing (93%). Majority of patients (93%) reported their care process using CGM as being good or very good.

b. Davis GM, Spanakis EK, Migdal AL, et al. Accuracy of Dexcom G6 Continuous Glucose Monitoring in Non-Critically Ill Hospitalized Patients With Diabetes. *Diabetes Care*. 2021;44(7):1641-1646. doi:10.2337/dc20-2856
   - This study sought to assess the accuracy of Dexcom G6 continuous glucose monitoring through retrospective matched-pair analysis with capillary point-of-care (POC) glucose data from three inpatient CGM studies.
   - 218 participants (96% with type 2 diabetes, with a mean age of 60.6 ± 12 years) were included in the analysis.
   - The overall mean absolute relative difference (MARD) was 12.8%, and median absolute relative difference (ARD) was 10.1%.
   - The proportion of CGM values within 15, 20, and 30% or 15, 20, and 30 mg/dL of POC reference values for blood glucose >100 mg/dL or≤ 100 mg/dL, respectively, were 68.7, 81.7, and 93.8%.
   - MARD and median ARD were higher in the case of hypoglycemia (<70 mg/dL) and severe anemia (hemoglobin <7 g/dL).
   - Results indicate that CGM technology is a reliable tool for hospital use and may help improve glucose monitoring in non–critically ill hospitalized patients with diabetes.

c. Davis GM, Hughes MS, Brown SA, et al. Automated insulin delivery with remote real-time continuous glucose monitoring for hospitalized patients with diabetes: A multicenter, single-arm, feasibility trial. *Diabetes Technol Ther*. 2023;10.1089/dia.2023.0304. doi:10.1089/dia.2023.0304
   - This multicenter pilot trial tested feasibility, safety, and effectiveness of Omnipod AID 5 System in 22 hospitalized patients with insulin-requiring diabetes.

- Of the 16 patients with adequate CGM data for analysis, overall was 68% ± 16%, with 0.17% ± 0.3% time <70 mg/dL and 0.06% ± 0.2% time <54 mg/dL.
- Sensor mean glucose was 167 ± 21 mg/dL. There were no DKA or severe hypoglycemic events. All participants reported satisfaction with the system at study end.

d. Murray-Bachmann R, Leung TM, Myers AK, et al. Reliability of continuous glucose monitoring system in the inpatient setting. *J Clin Transl Endocrinol*. 2021;25:100262. Published 2021 Jul 7. doi:10.1016/j.jcte.2021.100262
   - This prospective cohort study sought to examine the relationships between glucose reading obtained by Freestyle Libre continuous glucose monitoring (CGM) and capillary blood glucose results obtained by an AccuChek inpatient glucose meter (POCT), as well as between CGM reading and serum glucose levels obtained in a hospital laboratory.
   - The regression analysis showed a negative bias between Libre and AccuChek, with Libre glucose readings on average being lower than those of AccuChek. Mean absolute relative difference (MARD) between Libre and AccuChek was 15.6%.
   - Regression analysis showed a negative bias between Libre and serum glucose. MARD between Libre and serum glucose was 13.2%.
   - Findings indicate acceptable agreement between the standard POCT and the CGMS as well as between serum glucose and the CGM values.

e. Omar AS, Salama A, Allam M, Elgohary Y, Mohammed S, Tuli AK, et al. Association of time in blood glucose range with outcomes following cardiac surgery. *BMC Anesthesiology*. 2015 Jan 26; 15(14).
   - This prospective descriptive study aimed to assess glucose control, as determined by TIR, in patients after cardiac surgery with glycemic targets of 6.0 to 8.1 mmol/L, and to determine factors related to poor control.
   - Participants included 227 consecutive patients, 100 with and 127 without diabetes, after cardiac surgery. Patients were divided into two groups, those who maintained >80% and <80% TIR. Outcome variables were compared in people with diabetes and people without diabetes.
   - After cardiac surgery, patients with >80% TIR, whether or not they had diabetes, had better outcomes than those with <80% TIR, as determined by wound infection, lengths of ventilation, and ICU stay. Additionally, they were not subject to frequent hypoglycemic events.
   - Preoperatively high A1C is likely a good predictor of poor glycemic control.

f. Spanakis EK, Urrutia A, Galindo RJ, et al. Continuous Glucose Monitoring-Guided Insulin Administration in Hospitalized Patients With Diabetes: A Randomized Clinical Trial. *Diabetes Care*. 2022;45(10):2369-2375. doi:10.2337/dc22-0716
    - This randomized trial assessed the safety and efficacy of continuous glucose monitoring (CGM) in adjusting inpatient insulin therapy.
    - Participants were 185 general medicine and surgery patients with type 1 and type 2 diabetes treated with a basal-bolus insulin regimen. Primary endpoints were differences in time in range (TIR; 70–180 mg/dL) and hypoglycemia (<70 mg/dL and <54 mg/dL).
    - All subjects underwent point-of-care (POC) capillary glucose testing before meals and bedtime. Patients in the standard of care (POC group) wore a blinded Dexcom G6 CGM with insulin dose adjusted based on POC results, while in the CGM group, insulin adjustment was based on daily CGM profile.
    - 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.
    - Among patients with one or more hypoglycemic events, the CGM group experienced a significant reduction in hypoglycemia reoccurrence (1.80 ± 1.54 vs. 2.94 ± 2.76 events/patient; P = 0.03), lower percentage of time below range <70 mg/dL (1.89% ± 3.27 vs. 5.47% ± 8.49; P = 0.02), and lower incidence rate ratio <70 mg/dL (0.53 [95% CI 0.31–0.92]) and <54 mg/dL (0.37 [95% CI 0.17–0.83]) than the POC group.
    - Results suggest real-time CGM is safe and effective in guiding inpatient insulin therapy, resulting in similar glycemic control and a significant reduction in recurrent hypoglycemic events compared with POC-guided adjustment.

g. Sugimoto T, Saji N, Omura T, et al. Cross-sectional association of continuous glucose monitoring-derived metrics with cerebral small vessel disease in older adults with type 2 diabetes. *Diabetes Obes Metab*. 2024;26(8):3318-3327. doi:10.1111/dom.15659
    - This cross-sectional study examined associations between CGM-derived metrics and cerebral small vessel disease (SVD) among 80 adults with type 2 diabetes aged ≥70 years.
    - Higher hyperglycemic metrics, including mean sensor glucose, TAR >180 mg/dl, and TAR >250 mg/dl were associated with a higher total SVD score.
    - In contrast, a higher TIR (per 10% increase) was associated with a lower total SVD score (odds ratio 0.73, 95% confidence interval 0.56-0.95).

- Other glucose metrics, including A1C, were not associated with total cerebral SVD scores.

h. Veríssimo D, Vinhais J, Ivo C, et al. Continuous glucose monitoring vs. capillary blood glucose in hospitalized type 2 diabetes patients. *Cureus*. 2023;15(8):e43832. doi:10.7759/cureus.43832
   - In this retrospective cohort study, investigators assessed time in range using CGM as compared to capillary blood glucose monitoring among 60 hospitalized patients with type 2 diabetes on intensive insulin therapy.
   - CGM users had a higher number of readings per day (six vs. four, $p < 0.001$), in-range readings
   - (53.5% vs. 35%, $p = 0.027$), fewer above-range readings (25.5% vs. 56.5%, $p = 0.003$), particularly above 250 mg/dL (5% vs. 27.5%, $p = 0.001$), with no difference in the percentage of hypoglycemia occurrence (1% vs. 0%, $p = 0.107$). Lower mean glucose (161.9 mg/dL vs. 206.5 mg/dL, $p < 0.001$) was also observed in this group.

i. Voglová Hagerf B, Protus M, Nemetova L, et al. Accuracy and Feasibility of Real-time Continuous Glucose Monitoring in Critically Ill Patients After Abdominal Surgery and Solid Organ Transplantation. *Diabetes Care*. 2024;47(6):956-963. doi:10.2337/dc23-1663
   - This prospective study assessed the feasibility and accuracy of the Dexcom G6 CGM in ICU patients after major abdominal surgeries.
   - Based on 1,546 sensor glucose values from 61 patients paired to arterial blood glucose (ABL) values, MARD was 9.4%, relative bias was 1.4%, and 92.8% of values fell in zone A, 6.1% fell in zone B, and 1.2% fell in zone C of the surveillance error grid. For comparison, bedside glucose meter MARD compared with ABL was 5.8%.
   - Median time in range was 78%, with minimum (<1%) time spent in hypoglycemia. A comparison between nonblinded versus blinded sensors showed a slightly higher average glycemia in the blinded group and no clinically significant difference in times in designated time ranges.
   - Results show clinically applicable accuracy and reliability of Dexcom G6 CGM in postoperative ICU patients, an additional calibration protocol may be beneficial, and the infraclavicular region is a feasible alternative sensor placement site.

j. Wang Y, Li S, Lu J, et al. Threshold of hyperglycaemia associated with mortality in critically ill patients: a multicentre, prospective, observational study using continuous

glucose monitoring. *Diabetologia*. 2024;67(7):1295-1303. doi:10.1007/s00125-024-06136-1

- This multicenter, prospective observational cohort study, known as the The INDIGO-ICU (INDices of contInuous Glucose monitoring and adverse Outcomes in Intensive Care Units) study, used CGM to investigate the threshold of hyperglycemia related to mortality risk in critically ill patients.
- Among 293 critically ill participants, time above ranges (TAR) with an upper threshold of 190 mg/dl (10.5 mmol/l) or higher were significantly associated with risk of in-hospital mortality, with hazards increasing incrementally for every additional 10% TAR.
- This study may help to inform optimal time in range targets for critically ill inpatients. Future randomized controlled trials should be conducted to determine if targeting a sensor glucose level <190 mg/dL reduces the risk of mortality in critically ill patients.

k. Wang Y, Lu J, Wang M, et al. Real-time continuous glucose monitoring-guided glucose management in inpatients with diabetes receiving short-term continuous subcutaneous insulin infusion: a randomized clinical trial. *The Lancet Regional Health – Western Pacific*. 2024;48. doi:10.1016/j.lanwpc.2024.101067

- This single-center randomized, parallel controlled trial evaluated effectiveness of CGM in inpatients with type 1 and type 2 diabetes being treated with short-term continuous subcutaneous insulin infusion (CSII).
- 475 participants were randomized to real-time CGM or POC glucose testing plus blinded CGM. The mean time above range above 10 mmol/L (180 mg/dL) was significantly lower in the rtCGM group than in the POC group (28.3 ± 15.8% vs. 36.6 ± 19.0%, P < 0.001), whereas there was no significant between-group difference in the time below range <3.9 mmol/L (P = 0.11).
- The time to reach target glucose was significantly shorter in the rtCGM group than in the POC group (2.0 [1.0–4.0] days vs. 4.0 [2.0–5.0] days, P < 0.001).
- Findings show use of CGM resulted in better glucose control than POC testing among inpatients with diabetes receiving short-term continuous insulin without increasing hypoglycemia.

Abstracts/Other

a. Flint Kl, O'Connor M, Sabean A, et al. 40-OR: The Association of Continuous Glucose Monitoring Metrics with Hospital-Related Clinical Outcomes. *Diabetes*. 2024;73(Supplement_1):40-OR. doi:10.2337/db24-40-OR

a. This prospective observational study examined the association between CGM metrics and hospital-related clinical outcomes in the non-intensive care inpatient setting.
b. In this cohort of 326 adults (78% type 2 diabetes, 12% type 1 diabetes, 10% other), multivariable regression analyses demonstrated a significant association between 30-day ED visits and increased %TAR (p = 0.01) and borderline association of 30-day readmissions and %TBR (p = 0.06).
c. These findings suggest CGM, and CGM hyperglycemia data in particular, could help identify patients that may benefit from increased support after hospital discharge.

Primary Care

Peer-Reviewed Publications

h. Kieu A, King J, Govender RD, Östlundh L. The Benefits of Utilizing Continuous Glucose Monitoring of Diabetes Mellitus in Primary Care: A Systematic Review. J *Diabetes Sci Technol.* 2023;17(3):762-774. doi:10.1177/19322968211070855
    - This systematic review assessed whether continuous glucose monitoring use was associated with improved glycemic control, decreased rates of hypoglycemia, and improved staff/physician satisfaction in primary care.
    - Analysis suggests with moderate certainty of evidence that CGM/is-CGM may be more effective at lowering HbA1c than usual care by a WMD of −0.43% (12 mg/dL, 5 mmol/mol) in the four randomized controlled trials identified.
    - Among 40006 participants from 10 studies of CGM use in patients with diabetes (type 1, type 2, and gestational) under the care of a primary care provider, CGM appeared to be effective at reducing hypoglycemic events, and patient and staff satisfaction with CGM was high.

Abstracts/Other

a. Milosavljevic J, Mathias Pm, Schechter C, Agarwal S. 360-OR: Defining New Targets for Interventions to Increase Continuous Glucose Monitoring (CGM) Use in Primary Care. *Diabetes*. 2024;73(Supplement_1):360-OR. doi:10.2337/db24-360-OR
    a. CGM adoption remains limited in primary care settings, where the majority of people with diabetes receive health care. This study examined health record data from a large safety net hospital in the Bronx, NY to identify factors contributing to CGM prescriptions in primary care.

b. Out of 40,791 people with type 2 diabetes, 10.1% were prescribed CGM.
c. CGM was 40% less likely to be prescribed for Spanish vs. English-speaking patients, 15% less likely with public insurance, and 25% less likely with diabetes complications.
d. Conversely, CGM was 30% more likely to be prescribed with each additional A1C percentage point and 6% more likely with each additional prescriber year of experience. CGM prescriptions increased in a dose-response manner with treatment intensification.
e. Findings suggest targets for interventions to increase use of CGM in primary care could include Spanish language support services; aid for better prior authorization procedures for public insurance; and increased education of CGM benefits for providers with less years of experience.

Remote Monitoring

Peer-Reviewed Publications

a. Prahalad P, Scheinker D, Desai M, et al. Equitable implementation of a precision digital health program for glucose management in individuals with newly diagnosed type 1 diabetes. *Nat Med*. 2024;30(7):2067-2075. doi:10.1038/s41591-024-02975-y
    - This prospective study assess the impact of a systematic and equitable digital-health-team-based care program implementing tighter glucose targets (HbA1c < 7%), early technology use (continuous glucose monitoring starts <1 month after diagnosis) and remote patient monitoring on glycemia in young people with newly diagnosed T1D enrolled in the Teamwork, Targets, Technology, and Tight Control Study.
    - At 12 months after diabetes diagnosis, young people in this study had a mean HbA1c of 6.58% and mean GMI of 7.11%. An HbA1c <7% was reached by 64% of participants by A1c and 57% by GMI. Participants had a mean TIR of 68% with minimal hypoglycemia. Young people in 4T Study 1 had a lower HbA1c at 6 months after diagnosis. We achieved these outcomes while providing equitable access to CGM and remote patient monitoring.

Other Indications

Peer-Reviewed Publications

a. Bomholt T, Kofod D, Norgaard K, et al. Can the use of continuous glucose monitoring improve glycemic control in patients with type 1 and 2 diabetes receiving dialysis? *Nephrology*. July 2023; 147(2):91-96.
    - This review highlights the potential for continuous glucose monitoring (CGM) to circumvent the pitfalls of HbA1c in dialysis patients and provide detailed information on glycemia. Guidelines recommend a minimum of 50% time spent in the target range (3.9–10.0 mmol/L) and less than 1% below range (<3.9 mmol/L) for patients receiving dialysis but additional long-term data on CGM use and metric targets are needed in the dialysis population.
b. Hoppe JE, Sjoberg J, Hong G, et al. Remote endpoints for clinical trials in cystic fibrosis: Report from the U.S. CF foundation remote endpoints task force. *J Cyst Fibros*. Published online February 29, 2024. doi:10.1016/j.jcf.2024.02.011
    - This review article describes the findings of the Remote Endpoint Task Force, convened by the Cystic Fibrosis Foundation to better understand the current and future use of remote endpoints for clinical research. The authors highlight the potential for remote endpoint collection through continuous glucose monitoring to provide a better understanding of dysglycemia compared to an in-clinic oral glucose tolerance test, as well as the potential for all types of remote endpoints to encourage more diverse participation in clinical trials while minimizing participant burden. The authors conclude that Incorporation of remote assessments into clinical trials as exploratory endpoints is a logical next step but that the digital divide and participant characteristics associated with access must be considered to avoid inadvertently exacerbating disparities in access to clinical trial participation.

CGM for Screening and Diagnosis

Peer-Reviewed Publications

a. Di Filippo D, Henry A, Bell C, et al. A new continuous glucose monitor for the diagnosis of gestational diabetes mellitus: a pilot study. *BMC Pregnancy Childbirth*. 2023;23(1):186. Published 2023 Mar 18. doi:10.1186/s12884-023-05496-7

- This pilot study sought to assess the acceptability of CGM as a diagnostic test for gestational diabetes (GDM), as well as the association between its results with oral glucose tolerance test (OGTT) results and risk factors and sonographic features of GDM.
- Women considered CGM significantly more acceptable than OGTT (81% versus 27% rating 5/5, p<0.001).
- CGM triangulation analysis suggests OGTT screening may result in both false positives and negatives. Further research including larger cohorts of patients, and additional triangulation elements is needed to explore CGM potential for GDM diagnosis.

b. Durnwald C, Beck RW, Li Z, et al. Continuous Glucose Monitoring Profiles in Pregnancies With and Without Gestational Diabetes Mellitus. *Diabetes Care*. Published online May 3, 2024. doi:10.2337/dc23-2149
   - This multicenter prospective observational study examined whether continuous glucose monitoring (CGM)-derived glycemic patterns can characterize pregnancies with gestational diabetes mellitus (GDM) as diagnosed by standard oral glucose tolerance test at 24-28 weeks' gestation compared with those without GDM.
   - 768 pregnant individuals participating in the Glucose Levels Across Maternity (GLAM) Study wore blinded Dexcom G6 CGMs from before 17 weeks gestation through birth.
   - Participants who went on to be diagnosed with GDM (n = 58 [8%]) had higher mean glucose (109 ± 13 vs. 100 ± 8 mg/dL [6.0 ± 0.7 vs. 5.6 ± 0.4 mmol/L], P < 0.001), greater glucose SD (23 ± 4 vs. 19 ± 3 mg/dL [1.3 ± 0.2 vs. 1.1 ± 0.2 mmol/L], P < 0.001), less time in range 63–120 mg/dL (3.5–6.7 mmol/L) (70% ± 17% vs. 84% ± 8%, P < 0.001), greater percent time >120 mg/dL (>6.7 mmol/L) (median 23% vs. 12%, P < 0.001), and greater percent time >140 mg/dL (>7.8 mmol/L) (median 7.4% vs. 2.7%, P < 0.001) than those without GDM throughout gestation prior to OGTT.
   - Median percent time >120 mg/dL (>6.7 mmol/L) and time >140 mg/dL (>7.8 mmol/L) were higher as early as 13–14 weeks of gestation (32% vs. 14%, P < 0.001, and 5.2% vs. 2.0%, P < 0.001, respectively) and persisted during the entire study period prior to OGTT.
   - Results demonstrate that pregnant individuals who develop GDM have higher CGM-measured glucose levels and more hyperglycemia prior to OGTT at 24–34 weeks' gestation (compared with those who do not develop GDM).

c. Haynes A, Alexandra Tully, Grant J. Smith, et al. Early Dysglycemia Is Detectable Using Continuous Glucose Monitoring in Very Young Children at Risk of Type 1 Diabetes. *Diabetes Care*. Published online July 30, 2024:dc240540. doi:10.2337/dc24-0540
    - This cross-sectional analysis assessed whether CGM can detect early dysglycemia in very young children with presymptomatic type 1 diabetes (T1D) and predict risk of progression to clinical onset. Participants were children being longitudinally observed in the Australian Environmental Determinants of Islet Autoimmunity (ENDIA) study from birth to age 10 years.
    - 31 ENDIA children with persistent multiple islet autoimmunity (PM Ab+) and 24 age-matched controls underwent CGM assessment alongside standard clinical monitoring.
    - PM Ab+ children had higher median glucose standard deviation and coefficient of variation. Percentage of time >7.8 mmol/L was also greater in PM Ab+ children. Mean sensor glucose level did not differ significantly between groups.
    - The study concluded that CGM is feasible and well tolerated in very young children, and CGM metrics indicate type 1 diabetes progression in children under 10 as has been found in older participants.
d. Li Z, Beck R, Durnwald C, et al. Continuous Glucose Monitoring Prediction of Gestational Diabetes Mellitus and Perinatal Complications. *Diabetes Technol Ther*. Published online July 23, 2024. doi:10.1089/dia.2024.0080
    - This prospective observational study assessed the performance of CGM metrics to predict development of gestational diabetes mellitus (GDM) and perinatal complications.
    - CGM data were collected from 760 pregnant women from enrollment through the remainder of gestation. GDM was diagnosed using the oral glucose tolerance test (OGTT) at 24–34 weeks of gestation.
    - CGM-measured hyperglycemic metrics such as time >140 mg/dL predicted GDM with high AUROCs as early as 13–14 weeks of gestation. These metrics were also similar statistically to the OGTT at 24–34 weeks in predicting large-for-gestational-age births and hypertensive disorders of pregnancy, although sensitivity was low for both.
    - CGM could potentially be used as an early screening tool for elevated hyperglycemia during gestation, which could be used in addition to or instead of the OGTT.
e. Marco A, Pazos-Couselo M, Moreno-Fernandez J, et al. Time above range for predicting the development of type 2 diabetes. *Front Public Health*. 2022;10:1005513. Published 2022 Dec 8. doi:10.3389/fpubh.2022.1005513

- This study investigated the prognostic value of time in range metrics, as measured by continuous glucose monitoring (CGM), with respect to development of type 2 diabetes among a subsample of the A Estrada Glycation and Inflammation Study (AEGIS)
  prospective population-based study.
- 499 individuals without diabetes wore CGM for 7 days and were followed for 5 years. 22 participants developed type 2 diabetes.
- Time in range (TIR) was defined as the percentage of time in the glucose range of 70–140 mg/dL (3.9–7.8 mmol/L), time below range (TBR) as the percentage of time <70 mg/dL (<3.9 mmol/L), and time above range (TAR) as the percentage of time >140 mg/dL (>7.8 mmol/L)
- After adjusting for age, gender, family history of diabetes, body mass index and glycated hemoglobin concentration, multivariate analysis revealed TAR was significantly associated with a greater risk (OR = 1.06, CI 1.01–1.11) of developing type 2 diabetes (AUC = 0.94).

f. Shilo S, Keshet A, Rossman H, et al. Continuous glucose monitoring and intrapersonal variability in fasting glucose. *Nat Med*. 2024;30(5):1424-1431. doi:10.1038/s41591-024-02908-9

- Given the role plasma fasting glucose (FG) plays in the diagnosis of prediabetes and diabetes globally, this study investigated intraperson FG variability among nondiabetic adults aged 40–70 using CGM.
- FG was measured during 59,565 morning windows of 8,315 individuals (7.16 ± 3.17 days per participant). Mean FG was 96.2 ± 12.87 mg/dL, rising by 0.234 mg/dL per year with age. Intraperson, day-to-day variability expressed as FG standard deviation was 7.52 ± 4.31 mg/dL.
- Among 5,328 individuals who would have been considered to have normal FG based on the first FG measurement, 40% and 3% would have been reclassified as having glucose in the prediabetes and diabetes ranges, respectively, based on sequential measurements throughout the study.
- These findings suggest relying on one or two FG values for ruling out prediabetes or diabetes may lead to misdiagnosis, as there is considerable variability in FG levels from the same person.

g. Wilson DM, Pietropaolo SL, Acevedo-Calado M, et al. CGM Metrics Identify Dysglycemic States in Participants From the TrialNet Pathway to Prevention Study. *Diabetes Care*. 2023;46(3):526-534. doi:10.2337/dc22-1297

- This study found that CGM could aid in the identification of individuals, including those with a normal oral glucose tolerance test (OGTT) who are likely to rapidly progress to clinical stage 3 type 1 diabetes.
- Participants were 105 individuals in the TrialNet Pathway to Prevention study who had a first- or second-degree relative with type 1 diabetes. Three subgroups were identified: individuals with (1) stage 2 type 1 diabetes (n = 42) with two or more diabetes-related autoantibodies and abnormal OGTT; (2) stage 1 type 1 diabetes (n = 53) with two or more diabetes-related autoantibodies and normal OGTT; and (3) negative test for all diabetes-related autoantibodies and normal OGTT (n = 10).
- Based on data from 7-day CGM assessments and OGTTs conducted at 6-month intervals, investigators found that spending ≥5% time with glucose levels ≥140 mg/dL (P = 0.01), ≥8% time with glucose levels ≥140 mg/dL (P = 0.02), ≥5% time with glucose levels ≥160 mg/dL (P = 0.0001), and ≥8% time with glucose levels ≥160 mg/dL (P = 0.02) were all associated with progression to stage 3 disease.
- Stage 2 participants and those who progressed to stage 3 also exhibited higher mean daytime glucose values; spent more time with glucose values over 120, 140, and 160 mg/dL; and had greater variability.

Abstracts/Other

a. Calhoun P, Spanbauer C, Steck A, et al. 74-OR: ADA Presidents' Select Abstract: CGM Metrics from Five Studies Identify Participants at High Risk of Imminent Type 1 Diabetes (T1D) Development. *Diabetes*. 2024;73(Supplement_1):74-OR. doi:10.2337/db24-74-OR
    a. This study assessed whether CGM metrics can accurately identify imminent stage 3 T1D diagnosis in those with islet autoantibody (IAb) positivity.
    b. Data was collected from participants in five studies who had at least 1 positive IAb type. A CGM and baseline factor model and a baseline-only model were compared. Median follow-up time was 2.6 years (IQR: 1.5 to 3.6 years).
    c. The CGM model found % time >140 mg/dL (TA140), area under the curve 140 mg/dL (AUC140), glucose SD, sex, first degree relative, IA2A, and GADA status were more predictive of T1D progression compared to the baseline-only model (C-statistic: 0.76 vs. 0.62).
    d. Finding suggest CGM metrics can help predict T1D progression and classify participant's risk of impending T1D diagnosis. CGM can be used to better

monitor the risk of T1D progression and define eligibility for potential prevention trials.

TIR as an Outcome Measure

Peer-Reviewed Publications

a. Aleppo G, Gal RL, Raghinaru D, et al. Comprehensive telehealth model to support diabetes self-management. *JAMA Netw Open*. 2023;6(10):e2336876. doi:10.1001/jamanetworkopen.2023.36876
    - This prospective, single-arm cohort VDiSC study assessed clinical benefits associated with remote, telehealth diabetes education among 234 participants with type 1 and type 2 diabetes who either not using CGM at baseline or were using CGM but had either TIR <60% or time <54 mg/dL was more than 1%.
    - Participants completed three remote video training sessions with a CDCES over the course of the study as well as interim check-ins via video and phone calls, texts, and emails. Topics depended on participants' previous familiarity with CGM, but included: CGM initiation (including sensor insertion, alerts and alarms, uploading data, and visualizing data), use of data-visualization tools and CGM data to make self-management changes in insulin dosing, meals, and exercise, individualizing CGM use, and troubleshooting concerns or issues.
    - The CDCES was authorized to make insulin dose adjustments within a range of up to 20% for basal insulin and up to 30% for insulin boluses, with a study endocrinologist available for consultation as needed. The CDCES also had access to a decision-support app platform that generates algorithm-based recommendations for insulin dosing.
    - Over 6 months, mean TIR increased 11% among participants with type 1 diabetes, and 18% among participants with type 2 diabetes.
    - Additionally, mean time <70 mg/dL decreased by 0.8% and time <54 mg/dL decreased by 0.3% in T1D participants over 6 months.
b. Battelino T, Danne T, Edelman SV, et al. Continuous glucose monitoring-based time-in-range using insulin glargine 300 units/ml versus insulin degludec 100 units/ml in type 1 diabetes: The head-to-head randomized controlled InRange trial. *Diabetes Obes Metab*. 2023;25(2):545-555. doi:10.1111/dom.14898]

- InRange was the first large randomized controlled trial to use continuous blood glucose monitoring (CGM) time-in-range (TIR) as a primary efficacy endpoint to compare second-generation basal insulin analogues, insulin glargine 300 U/mL (Gla-300) and insulin degludec 100 U/mL (IDeg-100) in adults with T1D.
- This 12-week, multicentre, randomized, active-controlled, parallel-group, open-label study compared TIR and variability between Gla-300 and IDeg-100 using blinded 20-day CGM profiles.
- Participants were343 adults with T1D treated with multiple daily injections, using basal insulin once daily and rapid-acting insulin analogues for at least 1 year, with an HbA1c of 7%–10% at screening.
- Non-inferiority was shown on the primary endpoint (percentage TIR ≥ 70 to ≤ 180 mg/dl) as well as the main secondary endpoint (glucose total coefficient of variation)
- Gla-300 was found to be non-inferior to IDeg-100 in people with T1D, with comparable hypoglycaemia and safety profiles.

c. Beyond A1C Writing Group. Need for regulatory change to incorporate beyond A1C glycemic metrics. *Diabetes Care*. 2018;41(6):e92–4.
   - This article reports the outcomes of a 2017 meeting of key stakeholders. The participants agreed that current A1C-focused regulatory decisions do not accurately reflect the recent advances in diabetes technology and cannot capture the daily reality of living with diabetes. To this end, the authors assert that regulatory bodies should acknowledge therapies that improve time in range, glycemic variability, and quality of life.

d. Eckstein ML, Weilguni B, Tauschmann M, et al. Time in range for closed-loop systems versus standard of care during physical exercise in people with type 1 diabetes: A systematic review and meta-analysis. *J Clin Med*. 2021;10(11):2445. doi:10.3390/jcm10112445
   - This systematic review and meta-analysis compared time in range (TIR) (70-180 mg/dL or 3.9-10.0 mmol/L) outcomes between fully closed-loop systems (CLS) and standard of care (including hybrid systems) during physical exercise in people with type 1 diabetes (T1D).
   - Analysis of 6 randomized controlled trials involving 153 participants with T1D of all age groups showed that CLS moderately improved TIR in comparison to standard of care during physical exercise in people with T1D, with a particularly pronounced effect among children and adolescents.

e. Ekhlaspour L, Town M, Raghinaru D, Lum J, Brown S, Buckingham B. Glycemic outcomes in baseline hemoglobin A1C subgroups in the International Diabetes Closed-Loop Trial. *Diabetes Technology and Therapeutics*. 2022.
   - In a 6-month RCT, 112 participants were randomly assigned to closed-loop control after obtaining 2 weeks of baseline CGM data.
   - All A1C subgroups showed an improvement in TIR due to reduction of both hyperglycemia and hypoglycemia. Using a closed-loop system significantly improves time in range 70-180 mg/dL in people with type 1 diabetes.

f. Giorgino F, Battelino T, Bergenstal RM, et al. The Role of Ultra-Rapid-Acting Insulin Analogs in Diabetes: An Expert Consensus. *J Diabetes Sci Technol*. Published online November 8, 2023:19322968231204584. doi:10.1177/19322968231204584
   - This expert consensus report reviews the evidence on ultra-rapid-acting insulin analogs (URAA) and defines populations for whom URAA may be beneficial. Further, the report provides practical recommendations to guide health care professionals on how to best use URAA.
   - URAA have been shown to provide sustained glycemic control, with significantly lower postprandial glucose excursions. When used in insulin pumps, URAA improved overall time in range.

g. Moser O, Muller A, Aberer F, et al. Comparison of insulin glargine 300 U/mL and insulin degludec 100 U/mL around spontaneous exercise sessions in adults with type 1 diabetes: A randomized cross-over trial (ULTRAFLEXI-1 Study). *Diabetes Technology & Therapeutic*s. March 2023; 25(3):161-168.
   - A randomized trial was performed and in each of the four 2-weeks-periods, participants attended six spontaneous 60 min moderate-intensity evening cycle ergometer exercise sessions. The basal insulin administered on the exercise days were IGlar U300 100% or 75% of the regular dose or IDeg U100 100% or 75%, respectively (morning injection). The primary outcome was the TBR<70 during the 24 hour post-exercise periods of the six spontaneous exercise sessions in the four trial arms and was analyzed in hierarchical order using the repeated measures linear mixed model.
   - 25 people with type 1 diabetes were enrolled (14 males) with a mean age of 41.4 ± 11.9 years and an HbA1c of 7.5% ± 0.8% (59 ± 9 mmol/mol). The mean ± standard error of mean TBR<70 during the 24 h periods following the exercise sessions was 2.71% ± 0.51% for IGlar U300 (100%) and 4.37% ± 0.69% for IDeg U100 (100%) (P = 0.023) as well as 2.28% ± 0.53% for IGlar U300 and 2.55% ± 0.58% for IDeg U100 when using a 75% dose on exercise days (P =

0.720). Time in glucose range70-180 was the highest in the IDeg U100 (100%) group.
    - TBR<70 within the first 24 h after spontaneous exercise sessions was significantly lower when receiving IGlar U300 compared to IDeg U100 when a regular basal dose was administered.

h. Patel PM, Abaniel RM, Dogra N, Lo CB, Frazzitta MA, Virdi NS. Trends in time in range–related publications and clinical trials: A bibliometric review. *Diabetes Spectr*. 2023;(ds220085).
    - This review describes the marked increase in the number of trials, publications, and abstracts reporting time in range (TIR), and highlights the increasing significance and acceptance of TIR as an outcome measure in diabetes management.

i. Pease A, Lo C, Earnest A, Kiriakova V, Liew D, Zoungas S. Time in range for multiple technologies in type 1 diabetes: A systematic review and network meta-analysis. *Diabetes Care*. 2020;43(8):1967-1975. doi:10.2337/dc19-1785
    - The researchers compared and ranked technologies for time in glycemic ranges.
    - Closed-loop systems led to greater percent time in range than any other management strategy. Mean percent time in range was 17.85 longer than with usual care of multiple daily injections with capillary glucose testing. Closed-loop systems ranked best for percent time in range or above range, and ranked highly for time below range.
    - The efficacy of closed-loop systems appeared better than all the other approaches.

j. Pinsker JE, Müller L, Constantin A, Leas S, Manning M, McElwee Malloy M, Singh H, Habif S. Real-world patient-reported outcomes and glycemic results with initiation of control-IQ technology. *Diabetes Technology & Therapeutics*. 2021; 23(2): 120-7.
    - Study examining the effect of the t:slim X2 insulin pump with Control-IQ technology on real-world outcomes and glycemic control. This is an advanced hybrid closed-loop system that was approved in the US in early 2020.
    - 1435 participants over the age of 14, all with T1D completed a questionnaire at two different time points, the first after 3 weeks and the second at 7 weeks.
    - TIR average was 78.2% at the first time point and 79.2% at the second time point. Participants reported high satisfaction at time point 2, citing sensor accuracy, improved diabetes control, reduction in extreme glucose levels, and improved sleep quality as the reasoning for this satisfaction. Participants also reported improved quality of life, ease of use, and ease of connectivity to CGM as valuable features.

k. Pulkkinen MA, Varimo TJ, Hakonen ET, et al. MiniMed 780G™ in 2- to 6-Year-Old Children: Safety and Clinical Outcomes After the First 12 Weeks. *Diabetes Technol Ther*. 2023;25(2):100-107. doi:10.1089/dia.2022.0313
    - The impact of the advanced hybrid closed-loop (AHCL) system on glycemic outcome in 2- to 6-year-old children with type 1 diabetes and the diabetes distress of caregivers were evaluated.
    - No events of diabetic ketoacidosis or severe hypoglycemia occurred. Between 0 and 12 weeks, HbA1c mean sensor glucose value, and time above range (TAR) decreased and time in range (TIR) increased significantly, whereas no significant change in time below range (TBR) was observed.
    - MiniMed 780G™ AHCL is a safe system and 12-week use was associated with improvements in glycemic control in 2- to 6-year-old children with type 1 diabetes. In addition, AHCL is associated with a reduction in parental diabetes distress after 12-week use.
l. Renard E, Joubert M, Villard O, et al. Safety and efficacy of sustained automated insulin delivery compared with sensor and pump therapy in adults with type 1 diabetes at high risk for hypoglycemia: A randomized controlled trial. *Diabetes Care*. Published online September 20, 2023:dc230685. doi:10.2337/dc23-0685
    - This study assess the safety and efficacy of automated insulin delivery (AID) in 72 adults with type 1 diabetes at high risk for hypoglycemia.
    - Compared with using a sensor and pump (S&P), AID resulted in significant reduction of TBR by -3.7% (95% CI -4.8, -2.6), P < 0.001; an 8.6% increase in TIR (95% CI 5.2-12.1), P < 0.001; and a -5.3% decrease in TAR (95% CI -87.7, -1.8), P = 0.004.
m. Reznik Y, Carvalho M, Fendri S, et al. Should people with type 2 diabetes treated by multiple daily insulin injections with home health care support be switched to hybrid closed-loop? The CLOSE AP+ randomized controlled trial. *Diabetes Obes Metab.* 2024;26(2):622-630. doi:10.1111/dom.15351
    - This multi-center randomized controlled trial assessed the feasibility, safety, and efficacy of automated insulin delivery (AID) assisted by home health care (HHC) services in people with type 2 diabetes unable to manage multiple daily insulin injections (MDI) at home on their own.
    - 30 adults with type 2 diabetes using MDI and requiring nursing support were randomized to continue MDI or initiate AID and followed over 12 weeks. The primary outcome was the percentage time in the target glucose range of 70-180 mg/dl (TIR).

- Compared with MDI, AID resulted in a significant increase in TIR by 27.4% [95% CI (15.0-39.8); p < .001], a decrease in time above range by 27.7% and an unchanged time below range of <1%.
- A between-group difference in HbA1c was 1.3% favoring AID. Neither severe hypoglycaemia nor ketoacidosis occurred in either group. Patient and caregiver satisfaction with AID was high.

n. Rosenstock J, Bain SC, Gowda A, et al. Weekly Icodec versus Daily Glargine U100 in Type 2 Diabetes without Previous Insulin. *N Engl J Med*. 2023;389(4):297-308. doi:10.1056/NEJMoa2303208
   - This 78-week phase 3a randomized trial assessed the use of once-weekly insulin icodec for diabetes management in insulin-naive adults with type 2 diabetes.
   - The primary endpoint was the change in the glycated hemoglobin level from baseline to week 52; the confirmatory secondary endpoint was the percentage of time spent in the glycemic range of 70 to 180 mg per deciliter (3.9 to 10.0 mmol per liter)(TIR) in weeks 48 to 52.
   - Among 984 participants, the mean reduction in the glycated hemoglobin level at 52 weeks was greater for those using icodec than for those using glargine U100.
   - The percentage TIR was significantly higher with icodec than with glargine U100 (71.9% vs. 66.9%. The estimated between-group difference (4.27 percentage points [95% CI, 1.92 to 6.62]; P<0.001) confirmed superiority.
   - Results show glycemic control was significantly better with once-weekly insulin icodec than with once-daily insulin glargine U100, with similarly low rates of hypoglycemia in both groups.

o. Wadwa RP, Reed ZW, Buckingham BA, et al. Trial of hybrid closed-loop control in young children with type 1 diabetes. *N Engl J Med*. 2023;388(11):991-1001. doi:10.1056/NEJMoa2210834
   - In this 13-week, multicenter trial, they randomly assigned children who were 2-6 years of age who had type 1 diabetes to receive treatment with a closed-loop system of insulin delivery or standard care that included either an insulin pump or MID of insulin plus a CGM.
   - A total of 102 children underwent randomization (68 to closed-loop group and 34 to the standard-care group). HbA1c levels at baseline ranged from 5.2 to 11.5%. The mean percentage of time that the glucose level was within the target range increased from 56.7±18.0% at baseline to 69.3±11.1% during the 13-week follow-up period in the closed-loop group and from 54.9±14.7% to 55.9±12.6% in the standard-care group (mean adjusted difference, 12.4

percentage points [equivalent to approximately 3 hours per day]; 95% confidence interval, 9.5 to 15.3; P<0.001).

- At the conclusion of the study, 31% of participants on Control-IQ achieved a TIR >70% and a TBR<4% at 13 weeks compared to 13% at baseline. In the standard care arm, only 6% of participants met this goal at 13 weeks compared to 12% at baseline.
- Glucose levels were in the target range for a greater percentage of time with a closed-loop system than with standard care.

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3. Agiostratidou G, Anhalt H, Ball D, et al. Standardizing Clinically Meaningful Outcome Measures Beyond HbA1c for Type 1 Diabetes: A Consensus Report of the American Association of Clinical Endocrinologists, the American Association of Diabetes Educators, the American Diabetes Association, the Endocrine Society, JDRF International, The Leona M. and Harry B. Helmsley Charitable Trust, the Pediatric Endocrine Society, and the T1D Exchange. *Diabetes Care*. 2017;40(12):1622-1630. doi:10.2337/dc17-1624

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