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.

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Time in Range: State of the Evidence Overview

The current gold standard for diabetes management, defined by 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.

The growing body of evidence, collected for this State of the Evidence, continues to demonstrate that CGM and the metrics it provides (TIR, TBR, and TAR) have added value in clinical, research, and regulatory settings far beyond A1C. Expert consensus recommendations of population-specific TIR, TBR, and TAR goals advocate for the use of these metrics as a complement to A1C (Danne et al. 2017; Battelino et al. 2019).

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 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., 2022). 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).

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). In fact, there is mounting evidence of the association between TIR and the risk of microvascular and macrovascular complications, independent of A1C. 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). 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 new 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). 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. 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). 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). 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, including hospitalizations and emergency room visits (Shi & Hellmund 2020). 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 in humans.

Time in Range: State of the Evidence Bibliography

(References in each section are primarily ordered alphabetically)

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Contents

Validation of CGM Metrics

Peer-Reviewed Publications

a. 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 the metric of TIR or dTIR is not only a helpful diabetes management tool independent of HbA1c but may also be an equally good risk indicator for acute and chronic diabetes complications.

b. 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.

c. 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.

d. 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.

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. 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.

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. 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%.

g. 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 Research and Clinical Practice*. 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.

h. 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.

i. 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.

j. 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. doi:10.1111/dom.14906
- 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.

k. 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.

l. 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.

m. 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.

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. 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.

Published Abstracts/Other

a. Kjolhede EA, Natman J, Ekelund J, Salo S, Nielsen NF, Eliasson B, Eeg-Olofsson K.Association between A1C and time in range in adults with type 1 diabetes using sensor-based glucose monitoring: A Swedish National Diabetes Register population-based study. Presented at the European Association for the Study of Diabetes 2022.

   ● This study with real-world data showed a clear association between A1C and TIR in adults with T1D, suggesting that TIR may be a relevant complement to A1C in everyday practice. Further studies are needed to evaluate if TIR is also associated with risk of complications and costs.

b. 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.

c. Layne JE, Bergenstal RM, Barleen NA, Dixon RF, Zisser H. Long-Term A1C Outcomes with and without Intermittent CGM Use in Adults with T2D Participating in the Onduo Program [Abstract 597-P]. *Diabetes*. 2021; 70(Supplement 1).

   ● The Onduo Virtual Diabetes Clinic (VDC) combines a mobile app, remote lifestyle coaching, and telehealth. This retrospective analysis of A1C outcomes in adults with T2D assessed change in A1C with and without RT-CGM use in VDC patients after 1 year.
   ● Results indicate significantly greater improvement in A1C in the RT-CGM cohort compared to no CGM including a 16% increase in participants meeting the ADA treatment target. Improvements achieved at 6 months were sustained at 1 year.
   ● Those with an A1C > 9.0% had a 2.8% reduction from baseline for the RT-CGM group compared to a 1.8% reduction from baseline for the SMBG group.
   ● After 1 year, those on RT-CGM were more likely to meet ADA and HEDIS treatment targets of A1C < 7.0% and < 8.0% respectively. Significant increases in the proportion of participants meeting these targets was observed at 1 year in the RT-CGM cohort.

- Overall, the study found participation in the Onduo Virtual Care Program, which provided access to a Dexcom G6, was associated with significant reduction in A1C at 1 year compared to baseline.

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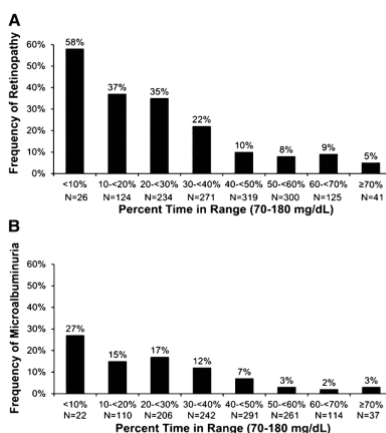
Figure 1—Frequency of development of microvascular complication according to level of TIR (70–180 mg/dL) computed from quarterly seven-point blood glucose testing. A: Retinopathy. B: Microalbuminuria.

b. 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.

c. 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.

d. 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.

e. 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).

f. 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.

g. 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.

h. 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.
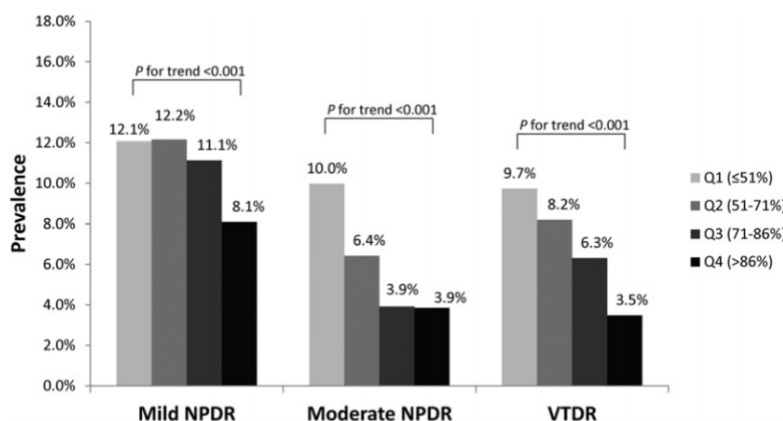

Figure 1—Prevalence of DR by severity, as a function of TIR quartile.

i. [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–e581.2022;107(2): e570–e581.2022;107(2): e570–e581.2022;107(2): e570–e581.2022;107(2): e570–e581.2022;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.

j. [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.

k. [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.

l. [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.

m. 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.

n. 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.

o. 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.

p. 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. 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.
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, 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.

d. 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.

e. 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.

f. 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.

Published Abstracts/Other

a. Hagelqvist PG, Andersen A, Maytham K, Andreasen CR, Engberg S, Lindhardt T, Forman JL, Pedersen-Bjergaard U, Knop FK, Vilsbøll T. Glycaemia and cardiac arrhythmias in people with type 1 diabetes: a prospective observational study. Short oral presentation presented at the European Association for the Study of Diabetes Annual Meeting on 5 October 2023.

- This prospective observational study used continuous glucose monitoring and implantable loop recorders to investigate potential associations between hypoglycaemia, hyperglycaemia and glycaemic variability in 30 adults with type 1 diabetes.
- During daytime, the subject-specific hourly incidence of arrhythmias tended to increase with increasing time spent in hypoglycaemia compared to euglycaemia. Daytime hyperglycaemia was associated with increased risk of arrhythmias compared to euglycaemia. No association was found between nighttime hypoglycaemia or nighttime hyperglycaemia and risk of arrhythmias. A daytime increase in glucose above the subject-specific mean showed an increased risk of arrhythmias (IRR 1.10 [95% CI 1.03 - 1.17] per 1 mmol/l increase).
- Acute hypoglycaemia and hyperglycaemia during daytime may contribute to an increased risk of arrhythmias in individuals with type 1 diabetes. Since no similar link was found during nighttime, this may indicate diurnal differences in arrhythmogenic susceptibility.

GMI and A1C

Peer-Reviewed Publications

a. 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. *JAMA*. 2017;317(4):371-378.

- Randomized clinical trial of 158 adults with type 1 diabetes.

- Continuous glucose monitoring resulted in better glycemic control compared with usual care.

b. 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. *Annals of Internal Medicine*. 2017 Sept 19;167(6):365.
   - Randomized clinical trial of 158 adults with type 2 diabetes.
   - 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.

c. 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.

d. 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.

e. 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.

f. 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.

g. 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. *JAMA*. 2017;317(4):379-387.
- Randomized clinical trial of 161 adults with type 1 diabetes.
- Glycemic control was improved during continuous glucose monitoring compared with conventional treatment.

h. 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.

i. 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.

j. 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.

Accuracy of CGM

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. Battelino T, Danne T, Edelman S, Choudhary P, Renard E, Westerback J, Mukherjee B, Picard P, Pilorget V, Bergenstal R. Comparison of second-generation basal insulin analogues glargine 300u/ml and degludec 100u/ml using continuous glucose monitoring in people with T1D: InRange Randomized Controlled Trial. [ATTD Abstract A-4]. 2022.
   - 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.
   - The aim of this study was to propose and analyze approaches to model the influence of exercise on basal insulin uptake, using the example of insulin degludec (Deg-100).
   - Multicenter, randomized, active-controlled, parallel-group, 12-week open-label study comparing efficacy of Gla-300 and Ideg-100 using 20-day-CGM profiles (>10 days evaluable) at Week 12. Inclusion: adults with T1D treated with multiple daily injections, using BI analogues once daily and rapid-acting insulin analogues for >1 year; A1C <7 and <10% at screening; not requiring CGM for routine care during study.
   - Using clinically relevant CGM metrics, the InRange study showed that Gla-300 is non-inferior to IDeg-100 in people with T1D, with similar hypoglycemia and safety profiles.

c. Beck R, Raghinaru D, Peter Calhoun, Bergenstal 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.

d. 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.

e. 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 iscCGM 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. [add in chart here]

f. 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.

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.
- A1C was strongly correlated with mean glucose value, time in range between 70-180 mg/dL, and percentage of glucose values above 13.9mmol/L (250mg/dL)
- These associations suggest that CGM-derived metrics may help guide diabetes therapy efforts in a manner independent of A1C.

h. 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 assessed 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.

i. 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.

j. 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.

k. 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.

l. 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.

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.

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. 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.
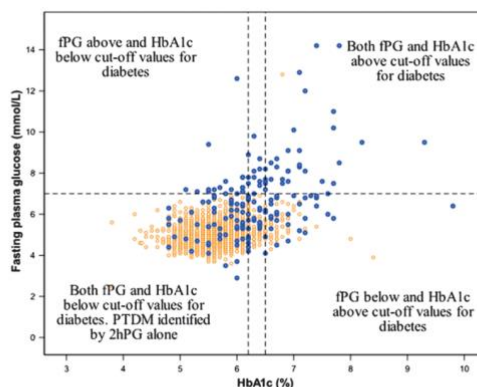
FIGURE 2. The relationship between HbA1c threshold values of 6.2% (44.3 mmol/mol) and 6.5% (47.5 mmol/mol) and posttransplant diabetes mellitus (PTDM) (repeatedly elevated measurements of fPG that did not normalize during the first 10 weeks after renal transplantation or fPG≥7.0 mmol/L (≥126 mg/dL) and 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.

e. 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.

f. 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, 20 23. 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.

g. 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.

h. 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.

i. 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.

j. 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.

k. 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.

l. 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.

m. 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.

n. 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.

o. 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.

p. 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.

q. 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.

r. 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.

Published Abstracts/Other

a. 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
   i. 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.
   ii. Based on glycemic data from 33 Black and 85 white youth with type 1 diabetes, investigators found that non-Hispanic black youth had higher HbA1c even after adjusting for TIR.
b. Totomirova T and Arnaudova M. Should we continue using HbA1c for Treatment adjustment in patients with type 2 diabetes? [Abstract 623-P]. *Diabetes* 2021; 70(Supplement 1).
   - This study compared the results derived from non-real time CGM and HbA1c to discover which one could be more useful for drug prescription decisions in people with type 2 diabetes.
   - The study included 85 people with type 2 diabetes receiving different treatment regimens (31 on oral therapy, 33 treated with premixed insulin, and 21 on multiple insulin injections). Individuals performed non-real time CGM by using iPro for seven days and HbA1c was measured at the end of this period.
   - CGM was more precise than HbA1c in defining patients with good control. HbA1c correlated badly with overall blood glucose excursion (r1 = -0.096, r = 0.200, r3 = 0.377). No difference was between studied groups in regard to CGM percentage of time spent within the limits, above and below the limits, as well as to AUC above upper limit.
   - They concluded that CGM was more precise than HbA1c in diabetes control assessment and thus in treatment adjustment.

Limitations of TIR and CGM

Peer-Reviewed Publications

a. 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.

Published 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.
b. Kompala T, Wong JC, Neinstein AB. Diabetes providers value CGM data despite challenges in data review process [Abstract 636-P]. *Diabetes* 2021; 70(Supplement 1).
   - This survey study examined the ways that diabetes care providers interact with patient CGM data as well as how they present data to their patients.

- Of the 182 respondents, all of whom prescribed CGM, 75% were at academic medical centers, 66% were endocrinologists, and 70% practiced in urban settings. Nearly 70% reported CGM use in a majority of their patients with type 1 diabetes. Over 50% of respondents reported usage rates of CGM under 10% in people with type 2 diabetes.
- Most providers included CGM data in the electronic health record but only 41% had an efficient process for data capture. 81% reported that their CGM data review was valued by patients but only half (55%) reported having adequate time or an efficient process to do so. Even so, 90% of providers directly involved patients in data review.
- While there was uniform support for CGM among providers, problems relating to inadequate time and inefficient data review processes remain. Findings recommend improvements in data access and integration, supportive clinical infrastructure, and decreased administrative burden to obtain CGM.

Other outcomes

Peer-Reviewed Publications

a. 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 Technology & Therapeutics*. Published online October 13, 2023. doi:10.1089/dia.2023.0380
    - This study evaluated the relationship between TIR and TITR measured by CGM from 9 studies with 912 participants with type 1 diabetes and 2 studies with 184 participants with type 2 diabetes.
    - The correlation between TIR and TITR was 0.94 and nonlinear. The TIR-TITR relationship varied according to CV and TBR, such that the higher the CV or higher the amount of TBR the greater was TITR for a given TIR.

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.
- 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. 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. doi:10.1007/s13300-023-01429-x
- 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.

e. 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.

f. 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, $p < 0.05$).

g. 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.

h. 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.

i. 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.

j. 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.

k. 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.

l. 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.

Published 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.

Economics

Peer-Reviewed Publications

- [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$_{1c}$.
- [Heinemann](#) L, Freckmann G. CGM versus FGM; or, continuous glucose monitoring is not flash glucose monitoring. *Journal of Diabetes Science and Technology*. 2015;9(5):947–950.
  - This commentary piece seeks to compare CGMs and FGMs and highlight some of the advantages and disadvantages of each.
  - One of the advantages to the FGM is the lower cost and they also point out that CGMs have primarily been used by well-informed patients whereas the FGM has been used by patients who are just beginning to pay closer attention to their glycemic control.
- [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.
- [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.

- 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.

- 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.

- 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.
- 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.
- 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.

- Clinical and economic impact of professional CGM use in patients with type 2 diabetes. Patients who used professional CGMs saw an improvement in their A1C.
- Large healthcare claims and lab dataset from the US to determine the patients that were prescribed professional CGMs.
- Economic benefits for patients who used professional CGMs more than once within a year of who used it during a change in diabetes therapy. Thus, this suggests that professional CGM use may help decrease rising trends in healthcare costs for people with type 2 diabetes, while also improving clinical outcomes.

Published 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. Jendle J, Eeg-Olofsson K, Svensson A, Franzen S. Cost effectiveness of the FreeStyle Libre System vs. self-monitoring of blood glucose in people with type 2 diabetes on insulin treatment not reaching glycemic goals in Sweden [abstract 135-LB]. *Diabetes*. 2021; 70(Supplement 1).
- This study assessed the cost effectiveness of the FreeStyle Libre system versus SMBG in people with type 2 diabetes treated with insulin, who were not reaching their glycemic goals.

- Data included baseline patients' characteristics and A1C information, which all came from the recent real-world study using the Swedish National Diabetes Registry combined with hypoglycemia rates from the REPLACE trial. Analyses were performed in 2 different populations: one with an A1C greater than or equal to 8-9% (64-75 mmol/mol) and another group with an A1C greater than or equal to 9-12% (75-108 mmol/mol).
- Libre was associated with improvement in clinical outcomes. This system seemed to be a cost-effective disease management option compared to SMBG, based on a willingness-to-pay threshold of $34,113 per QALY gained. See table below.

d. Norman G, Paudel ML, Bancroft T, Lynch PM. Real-time continuous glucose monitor (RTCGM) use associated with decreased diabetes medical costs for patients with type 2 diabetes [abstract 66-LB]. *Diabetes* 2021 June;70 (supplement 1).
- This study assessed the impact of rtCGM on diabetes-related medical costs for patients with T2D. Costs were evaluated 12 months prior to CGM (pre-index period) and 6 months after prescription of CGM (post-index period).
- Change in cost was evaluated as PPPM, or per-person per-month, and 571 patients with T2D were evaluated.
- Data showed that after initiating rtCGM use, cost PPPM decreased by an average of $424. This was driven, in part, by reduction in diabetes-related inpatient medical costs. Inpatient hospital stays were also reduced.
- Conclusion is that use of rtCGM is associated with decreased diabetes-related medical costs in people with type 2 diabetes, so increased access to CGM among patients with type 2 diabetes could help reduce cost of diabetes-related care.

e. Webinar presented by IQVIA-A Movement in Diabetes: Using Time-in-Range. 2020.
- (Same data as #46) - Aitken M, Villa P, Lamotte M, Tewary V, Ramos M. Advancing Glycemic Management in People with Diabetes. IQVIA Institute for Human Data Science. 2019.
- 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.

Glucose (glycemic) Variability

Peer-Reviewed Publications

a. Berget C. Innovating today for a better tomorrow: How Omnipod 5 Automated Insulin Delivery System is changing diabetes care. Presentation at the Advanced Technologies & Treatments for Diabetes Conference. February 2023.
   - This dataset is the first preview of how Omnipod 5 is being used across a variety of age groups and other demographics throughout the customer base (n=31,691).
   - For those using the system's most aggressive target of 110 md/dL (n=17,339), average TIR was 71% and TBR was 1%. Time in range decreased from early childhood through adolescence to early adulthood, with time in range then hitting a minimum and increasing up to and through old age.
   - Tubeless insulin pump users experienced significantly lower mean HbA1c (7.6% [95% CI, 7.5-7.6]) compared to those using MDI (7.8% [95% CI, 7.7-7.8]). Further analysis suggested those in the pump group had a higher percentage of TIR (52% [48-56] vs 48% [45-52]; P=0.151) than their counterparts using MDI injections.

b. Brownlee M, Hirsch IB. Glycemic variability: A hemoglobin A1c–independent risk factor for diabetic complications. *JAMA*. 2006;295(14):1707–8.
   - This is an editorial piece that focuses on glycemic variability.
   - This paper highlights the strong relationship between A1C and diabetic complications, explaining that this is the basis of the ADA's current recommended treatment goal of A1C being below 7%. They do point out, however, that only about a third of patients achieve that goal.

c. 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.

d. 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.

e. den Braber N, Vollenbroek-Hutten M, Westerik K, Bakker S, Navis G, van Beijnum BJ, Laverman G. Glucose regulation beyond A1C in type 1 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.

f. 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.

g. 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$^{3.9-10}$) 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.

h. 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.

i. 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.

j. 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.

k. Jun JE, Lee SE, Lee YB, Ahn JY, Kim G, Hur KY, et al. Continuous glucose monitoring defined glucose variability is associated with cardiovascular autonomic neuropathy in type 1 diabetes. *Diabetes Metabolism Research and Reviews*. 2019; 35(2): e3092.
   - This study examined the association between glycemic variability and cardiovascular autonomic neuropathy (CAN) in type 1 diabetes independent of mean glucose.
   - Participants included 80 adults with type 1 diabetes who underwent 3-day CGM and autonomic function tests within 3 months.
   - The study found that CGM-defined GV was associated with CAN independent of mean glucose in adults with type 1 diabetes. Among internationally standardized CGM parameters, those describing the degree of level 2 hypoglycemia were the most significant contributors to this association.

l. 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.

m. 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.

n. 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.

o. 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.

p. Riddle MC, Gerstein HC, Cefalu WT. Maturation of CGM and glycemic measurements beyond HbA1c—A turning point in research and clinical decisions. *Diabetes Care*. 2017 Dec 1;40(12):1611.

- Reviews clinical evidence regarding CGM use as well as its current limitations. It summarizes one study and two consensus reports as well as several related studies and narratives that examine CGM and hypoglycemia.
- CGM provides huge potential value, but to harvest this potential, terms surrounding CGM must be standardized and hypoglycemia should be refined to include three main categories: severe events requiring assistance, clinically important events with values lower than 54 mg/dL (3.0 mmol/L), and events with values between 54 and 70 mg/dL (3.0 and 3.9 mmol/L)
- The paper highlights CGM limitations and lingering questions that the consensus papers and study do not address. It also discusses new research possibilities CGMs offer, such as measuring glycemic variability and using CGM as an outcome measure in clinical trials. Lastly, it notes the continued need for support from a physician or an experienced provider for optimal CGM use.

q. 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."

r. 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.

s. Tang Y, Shah H, Bueno Junior CR, Sun X, Mitri J, Sambataro M, Sambado L, Gerstein HC, Fonseca V, Doria A, Pop-Busui R. Intensive risk factor management and cardiovascular autonomic neuropathy in type 2 diabetes: The ACCORD Trial. *Diabetes Care*. 2021 Jan;44(1): 164-173

- This study tested the effect of intensively treating traditional risk factors for cardiovascular autonomic neuropathy such as hyperglycemia, hypertension, and dyslipidemia, for adults with type 2 diabetes and high cardiovascular risk.
- The data resulted in intensive glucose treatment reducing CAN risk by 16% compared to standard treatment and intensive blood pressure intervention decreasing CAN risk by 25%, specifically in older populations.
- The final conclusion demonstrated a positive effect for intensive glycemic therapy and intensive blood pressure control on cardiovascular autonomic neuropathy in type 2 diabetes.

t. Tylee TS, Trence DL. Glycemic variability: looking beyond the A1C. *Diabetes Spectrum*. 2012;25(3):149–53.
   - Glucose variability could be used as an independent risk factor for diabetes complications. With the use of CGMs, more data points can be collected and used to calculate mean amplitude of glucose excursions (MAGE), which is a measure of within-day glucose variability.
   - Glycemic variability may also affect psychosocial outcomes, as a study found that patients with type 1 diabetes found high glucose values (> 180 mg/dl) to be associated with negative mood ratings, including tension, anhedonia, and decreased arousal, although no association was seen with between-day glucose variability. And another study found that patients with type 2 diabetes found that negative mood (depression, anxiety) and cognitive symptoms (difficulty concentrating, slowed thinking) were associated with a change in blood glucose after a meal, suggesting that within-day glucose variability can negatively affect an individual's mood and psychological well-being.
   - Limitation of A1C: A1C reflects average glucose level but not variability
   - The paper also discusses and summarizes DCCT data

u. 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.

v. 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.

w. 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.

x. van der Linden J, Welsh JB, Hirsch IB, Garg SK. Real-time continuous glucose monitoring during the Coronavirus Disease 2019 pandemic and its impact on time in range. *Diabetes Technol Ther*. 2021;23(S1):S1-S7. doi:10.1089/dia.2020.0649

- Participants include 65,067 U.S. Dexcom G6 users
- This study compares Time in Range data during the early pandemic period (April 20 – June 14, 2020) to Time in Range data in the eight weeks prior to lockdown (January 6 –

March 1, 2020). The study included data from users in all fifty states, as well as Washington DC, Puerto Rico, the US Virgin Islands, and Guam.

- TIR improved by +29 minutes/day from 59% in the pre-pandemic period to 61% in the early pandemic period (p<0.001). This was driven by improvements in hyperglycemia; the proportion of participants achieving the goal of <5% of glucose values >250 mg/dl increased by 4% to 38% during the early pandemic period.
- Users in economically wealthier zip codes had higher pre- and intra-pandemic TIR values and greater relative improvements in TIR.
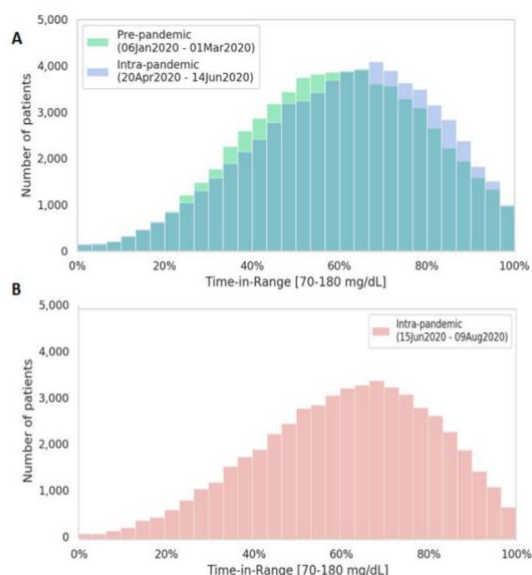
Figure 1. Distribution of 65,067 individuals according to time-in-range values during pre-pandemic (green) and intra-pandemic (blue) intervals (**A**). **B**, distribution of time-in-range values from a more recent intra-pandemic interval.

Published Abstracts/Other

a. Beck S, Kelly C, Njeru N, Gorelick J, Bowers J, Price D. Nonadjunctive Continuous Glucose Monitoring to Control Hypoglycemia (COACH) [abstract 69-LB]. *Diabetes*. 2021; 70 (Supplement 1).
    - The Continuous Monitoring and Control of Hypoglycemia (COACH) Study assessed nonadjunctive use of the Dexcom CGM system (G5) in diabetes management. This analysis of the COACH study assessed the frequency of clinically severe hypoglycemic events and DKA events with use of CGM. The post-approval 12-month observational study included 519 adults with insulin-requiring diabetes who have not used a CGM. Participants used SMBG for 6 months and a CGM for 6 months and were asked monthly about any hypoglycemia and DKA events.

- Compared to the SMBG phase, the frequency of moderate and severe hypoglycemic events was significantly (p=0.0051) lower (62% decrease) during the CGM phase. The mean number of hypoglycemic events for the SMBG and CGM phases was 0.081 and 0.031, respectively. DKA frequency was also lower with 2 participants experiencing DKA in the SMBG phase and no participants experiencing DKA in the CGM phase. This indicates that compared to SMBG, CGM use is effective in reducing rates of severe hypoglycemia and DKA.

b. Bergenstal R, Kehlet Watt S, Matos ASA, Lingvay I, Mader JK, Nishida T, Rosenstock J. CGM outcomes and hypoglycaemia duration with once-weekly insulin icodec versus once-daily insulin glargine u100 in insulin-naïve type 2 diabetes: ONWARDS 1 exploratory analysis. Short oral presentation presented at the European Association for the Study of Diabetes Annual Meeting on 3 October 2023.

- ONWARDS 1, a phase 3a study, assessed time in range, time below range, time above range, and hypoglycemia in insulin-naïve individuals with T2D randomized to once-weekly icodec (n=492) or once-daily glargine U100 (n=492) via CGM.
- TIR and TAR at weeks 22-26, 48-52, and 74-78 was significantly improved with icodec vs glargine U100, with no significant difference in TBR <54 mg/dL and a similar duration of hypoglycaemia <70 mg/dL between arms.

c. Dowd R, Derdzinski M, Puhr S, Welsh J. Time-in-range is impacted more by high threshold alerts than by screen view frequency for users of a real-time CGM system [abstract 601-P]. *Diabetes*. 2021; 70(Supplement 1).

- This real-world cohort study analyzes the correlation between TIR, hyperglycemia alert use, and screen view frequency to assess the use of rt-CGM and hyperglycemia alerts for improving TIR.
- Data from 19,376 patients in the US who use Dexcom G6 CGM was analyzed. Data from users with greater than 70% device utilization and validated alert settings were included.
- Compared to non-use, consistent use of the hyperglycemia alert was associated with a ~5.5% higher TIR. Screen view frequency was weakly associated with increased TIR, "likely because the trend screen must be accessed to silence the alert." Hyperglycemia alerts may motivate effective treatment decisions and lowering the hyperglycemia alert threshold may help patients improve their TIR.

d. Galindo R, Davis G, Idrees T, Urrutia M, et al. Performance evaluation of Dexcom G6 continuous glucose monitoring and capillary blood glucose after hospital discharge in patients with diabetes [abstract 613-P]. *Diabetes*. 2021; 70(Supplement 1).

- This study compared glycemic outcomes between capillary blood glucose (CBG) and CGM (Dexcom G6) after hospital discharge.

- A blinded CGM was inserted in 82 patients with DM and patients were asked to perform CBG testing 3 to 4 times/day and return both the CGM and the CBG logs after 10 days of discharge. Only 42 of the 82 patients returned their CBG logs.
- The researchers showed that detection of daily and nocturnal hypoglycemia were significantly higher in the CGM group vs. CBG logs. See table below.
- This study demonstrated that CGM provides a significantly better assessment of glycemic control after hospital discharge. However, further prospective study is needed to determine the efficacy of rtCGM in preventing hypoglycemic events after discharge.

e. Lu J, Chen D, Xu W, Yang D, Liu Z, Lin B. Relationship between CGM-derived metrics and risk factors for hypoglycemia among patients with type 2 diabetes with TIR more than 70%. Short oral presentation presented at the European Association for the Study of Diabetes on 21 September 2022.

- This study explored the risk factors associated with hypoglycemia by using CGM in type 2 diabetes patients with TIR.
- Of 111 subjects, 53 patients experienced 278 events with a glucose level<3.9mmol/l and 63 events with a glucose level<3.0mmol/L. The highest incidence of hypoglycemia occurred from 10pm to 6am.
- The incidence of hypoglycemia is high in type 2 diabetes patients with TIR>70%. MBG and GV including MAGE, MODD, CV, LBGI and LAGE are the significant and independent risk factors for hypoglycemia. Low MBG and large glucose excursions may possibly develop hypoglycemia. To achieve good glycemic control without inducing hypoglycemia, maintaining glucose in a euglycemic range and minimizing glucose excursions are of great importance.

f. Perez-Nieves M, Hankosky E, Fan L, Gelsey F, Ebay E, Sims T, et al. Continuous glucose monitoring utilization and associated metrics in people with diabetes on insulin therapy in the U.S. [abstract 73-LB]. *Diabetes*. 2021; 70(Supplement 1).

- This study aimed to describe real-world CGM use and CGM-derived glucometrics in people with diabetes treated with insulin.
- Using Glooko's cloud-based data storage, health data for adults with T1D and T2D using insulin therapy and CGM was analyzed and linked with Decision Resources Group Real-World Evidence repository (Jan 1, 2015 - Jul 30, 2019).
- As seen in the table below, level 2 hypoglycemia and CV were within the international consensus guideline recommendations, but TIR was below the recommended 70%, potentially due to time spent in level 2 hyperglycemia. The study concluded that there is unmet clinical need for people with diabetes to meet guideline recommended targets and technological and therapy advancements may help address this need.

g. 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.

CGM Utility in Clinical Practice

Peer-Reviewed Publications

a. 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 of 1076 patients with type 1 diabetes assess frequency of self-monitored blood glucose (SMBG) testing and motives for testing.
   - 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
b. 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.
c. 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.

d. 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.

Published Abstracts/Other

a. Resnik Y, Carvalho M, Fendri S, Prevost G, Chaillous L, Riveline JP, Hanaire H, Dubois S, Pasche H, Houeto P, Renard E. Should people with type 2 diabetes treated by multiple daily injections with home healthcare daily support be switched to a hybrid closed-loop system? The Close AP+ study. Short oral presentation presented at the European Association for the Study of Diabetes Annual Meeting on 5 October 2023.

- This study evaluated the efficacy and safety of a hybrid closed loop (HCL) system with tailored home healthcare (HHC) services in non-autonomous people with T2D who need at-home nursing care for their insulin treatment.
- 30 participants (mean age 69.5±8.6 yrs) on an MDI regimen requiring assistance from a family nurse were given Dexcom G6 sensors for continuous glucose monitoring and randomized to either switch to the Tandem t:slim X2 insulin pump with Control-IQ technology HCL system, or were assigned to stay on MDI. Primary endpoint was the change in time in target glucose range (TIR, 70-180 mg/dL).
- Over the 12 week study, TIR changed from 34.4±21.2% vs. 38.9±23.2% at baseline to 63.0±9.4 % vs. 36.6±21.9 %, on HCL vs. MDI, respectively, with a mean difference of +30.3% (p<0.001). Time above target glucose range (>180mg/dl) decreased by 28.4±21.8% on HCL while increasing by 2.2±14.4% on MDI (p<0.001).
- At study end, most patients felt that HCL was in the best interest for their health (89%) and quality of life (100%). These results show HCL combined with tailored HHC services significantly improves glucose control with no safety issue in PwT2D previously under MDI regimen.

Guidelines related to CGM/TIR

Peer-Reviewed Publications

a. 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.

b. 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.

c. 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…"

d. 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.

e. 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.

f. 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%

g. 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.

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. 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.

Professional CGM and/or Type 2 Diabetes

Peer-Reviewed Publications

a. 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.
b. 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.

c. 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.

d. 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.

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. doi:10.3389/fpubh.2022.1005513
- A total of 499 people without diabetes were followed-up for 5 years. Time in range metrics were measured at the start and medical records were checked over the period of study.
- 22 subjects developed type 2 diabetes. Multivariate analysis revealed 'time above range' to be significantly associated with a greater risk (OR = 1.06, CI 1.01-1.11) of developing diabetes (AUC = 0.94, Brier = 0.035).
- Time above range provides additional information to that offered by glycated hemoglobin to identify patients at a higher risk of developing type 2 diabetes in a population-based study.

f. Price DA, Deng Q, Kipnes M, Beck S. Episodic real-time CGM use in adults with type 1 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

g. 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.

h. 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).

i. Sofizadeh S, Pehrsson A, Ólafsdóttir AF, Lind M. Evaluation of Reference Metrics for Continuous Glucose Monitoring in Persons Without Diabetes and Prediabetes. *J Diabetes Sci Technol*. 2022;16(2):373-382. doi:10.1177/1932296820965599

- This study sought to identify the glucose profiles of people without diabetes, in order to develop a standard for comparison in clinical practice and clinical trials of glucose-lowering products.
- Investigators evaluated CGM metrics from 60 participants without diabetes or prediabetes who passed an oral glucose tolerance test and wore Dexcom G4 Platinum for 14 days.
- People without prediabetes or diabetes show a non-negligible % time in hypoglycemia (median 1.6% and mean 3.2%). Glycemic variability was significantly greater during daytime compared with nighttime.

Published Abstracts/Other

a. Carlson A, Daniel T, Desantis A, Jabbour S, Karslioglu-French, et al. Meta-analysis of two real-world chart review studies to determine the effectiveness of FreeStyle Libre Flash Glucose Monitoring System on HbA1c in adults with type 2 diabetes managed with basal insulin [abstract 71-LB]. *Diabetes*. 2021; 70(Supplement 1).
   - This meta-analysis of two retrospective chart review studies evaluated the effectiveness of the FreeStyle Libre Flash Glucose Monitor on A1C in people with T2D in a real-world setting.
   - Each study population included adults who had been on basal insulin for at least 1 year, had been using the FreeStyle Libre for at least 3 months, and who had an A1C between 8 and 12%. The Meta-analysis included 191 records from individuals with T2D on basal insulin from 14 medical centers in Canada and the US. A1C results were recorded between 90 and 194 days from the beginning of FreeStyle Libre use.
   - Mean change in A1C after at least 3 months of FreeStyle Libre use was significantly reduced by 1.1 ± 0.14% (p<0.0001). Due to differences in initial A1C between centers, there was moderate to high heterogeneity between the centers. There were no significant A1C differences based on age group, sex, BMI or duration of insulin use.
   - People with T2D on basal insulin therapy who use FreeStyle Libre for 3 to 6 months significantly reduced A1C.

b. Grace T, Salyer J. Real-time CGM coverage eligibility should include type 2 diabetes patients treated with less-intensive therapy [abstract 600-P]. *Diabetes.* 2021; 70(Supplement 1).
   - This 6 month, prospective interventional study assessed the clinical effects of Dexcom G6, an rtCGM, in 38 patients with T2D who were treated with only basal insulin or a non-insulin therapy.
   - Use of rtCGM led to significant reductions in mean A1C at both 3 months (-2.8%, p<0.001) and 6 months (-3.0%, p<0.001) from a baseline of 10.1%.
   - 6 months of use of rtCGM also led to an increase in TIR from 57% to 72% (p<0.001) and a decrease in TAR from 43% to 28% (p<0.001).

- Findings from this study suggest that rtCGM use in T2D adults with less-intensive regimens confers significant glycemic benefits and refutes the current requirements for rtCGM eligibility.

c. Lever CS, Williman JA, Boucsein A, Watson A, Sampson RS, Sergel-Stringer OT, Keesing C, Wheeler BJ, de Bock MI, Paul RG. Randomized controlled trial of real time continuous glucose monitoring in people with type 2 diabetes on insulin (the 2GO-CGM study). Short oral presentation presented at the European Association for the Study of Diabetes Annual Meeting on 5 October 2023.

- This randomized controlled trial assessed the effect of initiating real-time CGM (rtCGM) on glycaemia in a high-risk, predominantly indigenous population of adults with T2D on insulin.
- 67 participants were randomized to rtCGM or SMBG, with both arms supported by prescribing diabetes nurse specialists who adjusted insulin according to an insulin titration algorithm at weeks two and eight. The primary objective was to compare the percentage of time in range between the groups during the last 14 days of the trial.
- Mean TIR increased from 37 ± 25% to 52 ± 24% in the rtCGM group but did not change in the SMBG group. The baseline-adjusted between-group difference at the end of the trial was 9.8% (95%CI -1.6 to 21; p = 0.090).

d. Vigersky RA, Im G, Smith MB, MacLeod J. InPen smart insulin pen plus continuous glucose monitoring (CGM) identifies missed correction opportunities: impact on glycaemia and potential for actionable markers. Short oral presentation presented at the European Association for the Study of Diabetes Annual Meeting on 3 October 2023.

- In this retrospective cohort study, investigators analyzed sensor glucose data from 5,153 individuals who had recently started using the InPen Smart Insulin Pen, and identified missed correction opportunities (defined as instances of elevated sensor glucose levels for which the InPen's recommended dose was no less than the user's correction threshold).
- Participants averaged 5.31±4.10 hours of missed correction opportunity per day. The
- durations of the missed correction opportunities per day showed strong negative correlation with TIR (r=-0.85, p<0.0001) and TAR (r=0.86, p<0.0001), but no strong correlation against TBR (r=-0.21, p<0.0001).
- These findings inform future product development to support users in knowing when and by how much to correct SG based on active insulin dose data and limiting non-actionable SG alerts.

Continuous Personal CGM and/or Type 1 Diabetes

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. 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.

c. 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.

d. 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.

e. 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.

f. 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.

g. 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.

h. 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

i. 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.

j. Lin T, Manfredo JA, Illesca N, et al. Improving continuous glucose monitoring uptake in underserved youth with type 1 diabetes: The IMPACT study. *Diabetes Technol Ther*. 2023;25(1):13-19. doi:10.1089/dia.2022.0347
    - This study sought to investigate if trying a CGM for a temporary trial period increased the uptake of personal CGM in minority and low-income youth with T1D.
    - 26 participants, 15 of whom were CGM naive. Participants had follow ups at 5 and 10 days to examine CGM data and desire to continue CGM. Additional followup 3-6 months in to assess recorded CGM use and A1C.
    - After trial CGM use, 85% of participants reported wanting personal CGM, and at 3–6 months follow-up 76% had obtained one and 43% were using a personal CGM. There were no improvements in A1C or time in range, but participants reported an increase in the perceived benefits of CGM usage
    - Study shows that placing a sample CGM at the point of care can improve uptake of personal CGM and may help mitigate disparities in CGM use in minority and underserved youth.

k. 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

l. 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 to those who have type 1 diabetes.

CGM and TIR in Specific Settings/Populations

Pregnancy

Peer-Reviewed Publications

a. 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%.

b. 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.

c. 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.

d. 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.

e. 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.

f. 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-a nhydroglucitol, 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. TIR and 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, TIR, and TAR.

g. 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 TIR 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 TIR of >70% and a TAR of <25% from as early as possible during pregnancy.

h. Sanusi AA, Xue Y, McIlwraith C, et al. Association of continuous glucose monitoring metrics with pregnancy outcomes in patients with preexisting diabetes. *Diabetes Care*. Published online October 2, 2023. doi:10.2337/dc23-0636
   - This retrospective cohort study evaluated association between 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 TBR, were associated with neonatal morbidity. For each 5 percentage-point increase in TIR (65-140 mg/dL), there was 28% reduced odds of

neonatal morbidity. The statistically optimal TIR was found to be 66-71%, supporting the American Diabetes Association's recommendation of 70% time between 65-140 mg/dL in pregnancy.

i. 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 TIR, A1C, and GMI in pregnant women with type 1.
- GMI levels were calculated using a regression analysis, and linear models were used to compare TIR, A2C, and GMI by each trimester.
- Results showed a significant negative correlation between TIR and A1C: each 10% increase in TIR was associated with a 0.3% reduction in A1C. The correlation between TIR 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 TIR 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.

j. 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 TIR as assessed on CGM used by pregnant individuals with type 1 diabetes.
- Higher TIR is associated with lower preeclampsia and lower gestational age. This association is seen early in gestation, when each 5-unit increase in TIR is associated with ~50% reduction in the odds of these complications.

k. 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 TIR target attainment despite their increase throughout gestation. At their peak, targets were only achieved by 44% of women for TIR, 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).

Published Abstracts/Other

a. 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.

Hospital Setting

Peer-Reviewed Publications

a. 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.

b. 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.

c. 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.

Published Abstracts/Other

d. Davis G, Migdal A, Urrutia M, Zamudio-Coronado K, Perez-Guzman M, Albury B, et al. Comparison of Dexcom G6 continuous glucose monitoring and point-of-care blood glucose testing in hospitalized patients with diabetes [abstract 619-P]. *Diabetes*. 2021; 70(Supplement 1).

- This study compared performance of CGM (Dexcom G6) vs. point-of-care BG testing in a non-ICU setting.
- The study used blinded G6 data, 91 subjects per group (CGM and BGM) with a median hospital stay of 8 days to compare inpatient glycemic control metrics.
- The authors calculated the MARD of G6 in this study population to be 12.5%.
- The study concluded that rtCGM detects more hypoglycemia than POC BGM, but more prospective study is needed to determine benefits of rtCGM to improve inpatient diabetes care and reduce hypo and hyperglycemia in patients.

e. Murray-Bachmann R, Ziskovich K, Sarbanes M, Leung TM, Myers A, Murthi S, Poretsky L. Reliability of the FreeStyle Libre Continuous Monitoring System in the inpatient setting: Implications for the COVID-19 surge [Abstract 631-P]. *Diabetes*. 2020; 70(Supplement 1).

- This prospective cohort study examined the correlation of the capillary blood glucose obtained by the PCOT device (Accuchek Inform II) with the hospital laboratory serum glucose values and with FreeStyle Libre continuous glucose monitor readings (FDA-waived CGM restrictions for inpatient use during the COVID-19 pandemic).
- The study included 52 adult patients with diabetes (96% had T2D) who were recruited from non-critical hospital units. CGM sensors were placed on patients' arms, POCT and serum glucose measures were taken as ordered.

- On average, for each unit increase in Libre-recorded glucose level, there was a 0.92 increase in Accuchek glucose level and a 1.05 unit increase in serum glucose level.
- The findings indicate "excellent correlation" between the standard POCT and FreeStyle Libre CGM as well as between serum glucose and CGM. The advantages of CGM over blood glucose testing (reduced patient discomfort and reduced staff exposure to patients during the pandemic) support consideration by hospitals to replace PCOT with CGM use.

f. Spanakis E. Efficacy and safety of real-time continuous glucose monitoring guiding insulin administration in the hospital: A randomized clinical trial. Presentation at the 58th European Association for the Study of Diabetes Conference (EASD). September 2022.
- Rt-CGM resulted in a similar improvement in glycemic control and TIR compared with POC standard of care. Rt-CGM was effective in guiding insulin therapy.
- Rt-CGM resulted in a 40-69% reduction of TBR and hypoglycemic events (although not severe).
- Among subjects who experienced hypoglycemia, there was a statistically significant reduction in recurrent hypoglycemic events and TBR.

TIR Review Articles Bibliography

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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.
c. 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
d. 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
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.
f. 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.
g. Beyond A1C Writing Group. Need for regulatory change to incorporate beyond A1C glycemic metrics. *Diabetes Care*. 2018;41(6):e92–4.
h. 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.

i.   Brownlee M, Hirsch IB. Glycemic variability: A hemoglobin A1c–independent risk factor for diabetic complications. *JAMA*. 2006;295(14):1707–8.

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k.   Carlson AL, Criego AB, Martens TW, Bergenstal RM. HbA1c: The glucose management indicator, time in range, and standardization of continuous glucose monitoring reports in clinical practice. *Endocrinology and Metabolism Clinics of North America*. 2019; 49(1): 95-107.

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q.   Hirsch IB. Glycemic variability: it's not just about A1C anymore! *Diabetes Technol Ther.* 2005;7(5):780-783.

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