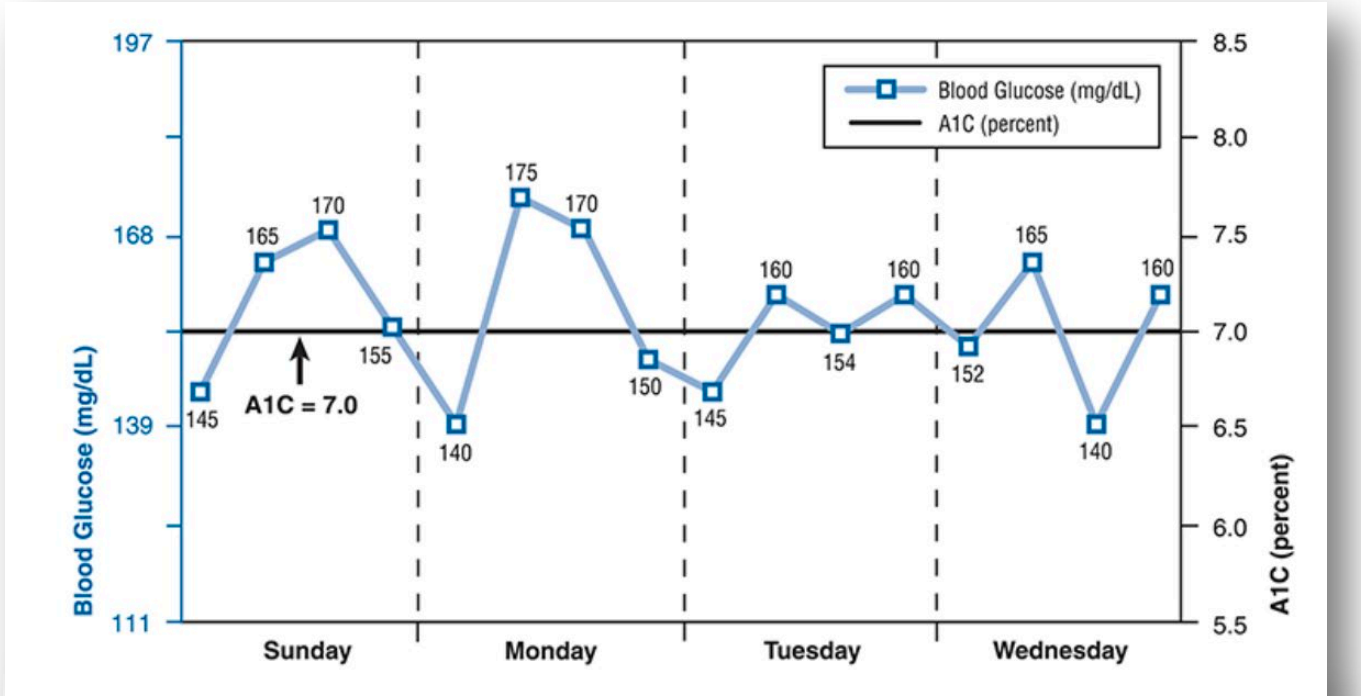
Continuous Glucose Monitoring (CGM)

Assessing Glycemic Control: Hemoglobin A1C

- Hemoglobin A1C (A1C) indirectly measures average blood glucose levels over a 3-month period
- Has advantages over fasting plasma glucose or oral glucose tolerance tests, providing a longer-term average of glucose levels
- Widely used and accepted metric of glycemic control with strong predictive value for diabetic complications



Blood glucose (mg/dL) measurements were taken four times per day (fasting or pre-breakfast, pre-lunch, pre-dinner, and bedtime).

The straight black line shows an A1C measurement of 7.0 percent. The blue line shows an example of how blood glucose test results might look from self-monitoring four times a day over a 4-day period.

ADA. *Diabetes Care*. 2019 Jan;42(Suppl 1):S61-S70.

Image: https://www.niddk.nih.gov/health-information/diabetes/overview/tests-diagnosis/a1c-test#diagnose
Accessed January 9, 2020.

Monitoring Glycemic Control: Hemoglobin A1C

- A1C targets to prevent microvascular complications are based on prior outcomes trials in both type 1 diabetes (T1D) and type 2 diabetes (T2D)
- Long-term follow-up showed the importance of **early, tight glucose control (A1C <7%) results in fewer microvascular complications** (diabetic kidney disease, neuropathy, and retinopathy) in T1D and T2D

DCCT:

- Investigated the correlation between A1C and microvascular complications in patients with T1D
- **Results:** tighter glycemic control can reduce the development and progression of microvascular complications by up to 76%

UKPDS:

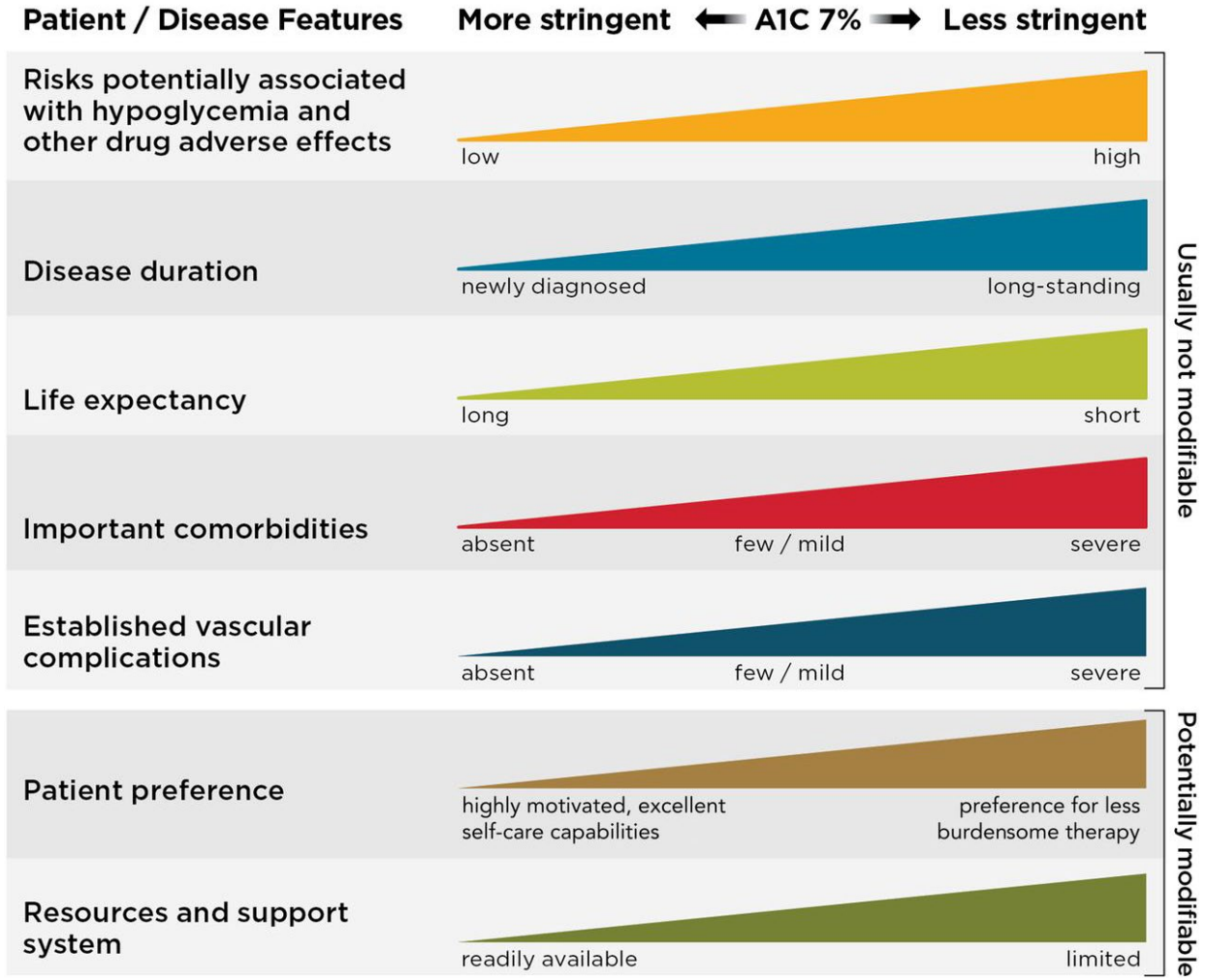
- Investigated effect of tight glycemic control on microvascular and macrovascular complications in patients withT2D
- **Results:** tight glycemic control reduced the risk of microvascular complications, but not of macrovascular disease

ADA. *Diabetes Care*. 2019 Jan;42(Suppl 1):S61-S70.

Legend: A1C, hemoglobin A1C; DCCT, Diabetes Control and Complications Trial; UKPDS, United Kingdom Prospective Diabetes Study.

Individualizing Glycemic Control According to A1C Targets

- This figure represents a broad framework to guide clinical decisions for patients with T1D and T2D
- ADA recommends glycemic targets be individualized based on key patient/disease features
- Life expectancy and burden of disease are important variables in determining stringency of glycemic control targets



Legend: A1C, hemoglobin A1C; ADA, American Diabetes Association; T1D, type 1 diabetes; T2D, type 2 diabetes.

•ADA. *Diabetes Care*. 2019 Jan;42(Suppl 1):S61-S70.

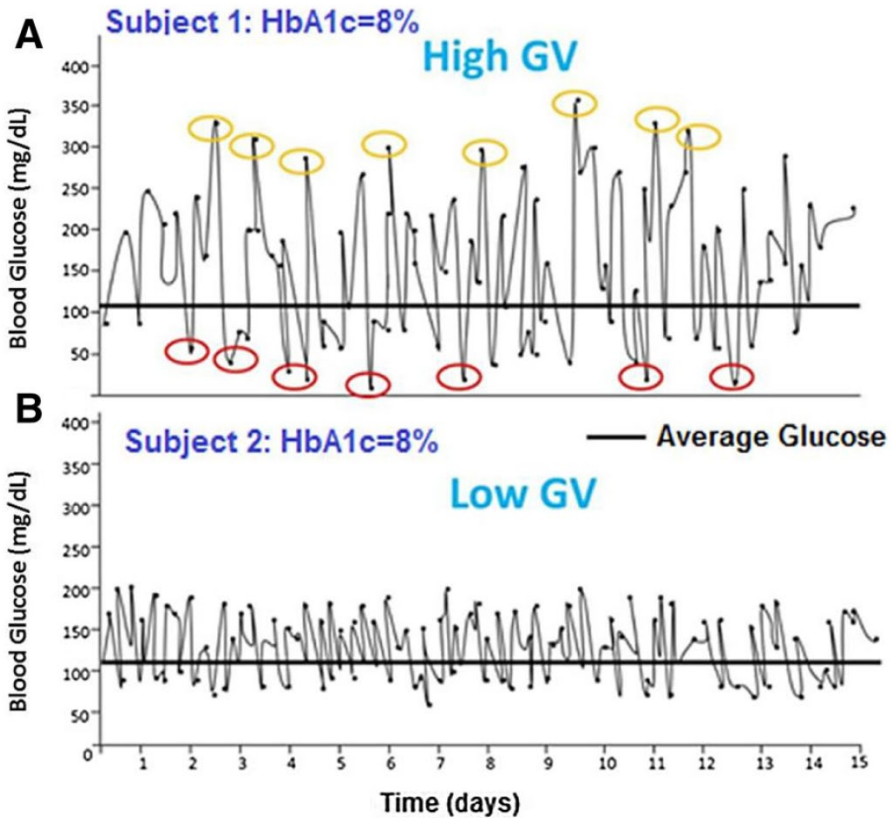
Limitations of A1C for Assessment of Glycemic Control

- Variability in the measurement of A1C
- Conditions that affect red blood cell turnover cause A1C discrepancies:
  - Hemolytic and other anemias
  - Glucose-6 phosphate dehydrogenase deficiency
  - Erythropoietic drugs
  - Recent blood transfusion
  - End-stage renal disease
  - Pregnancy
- Unreliable results in the presence of hemoglobinopathies
- Racial differences in A1C

ADA. *Diabetes Care*. 2019 Jan;42(Suppl 1):S61-S70.

Glycemic Variability

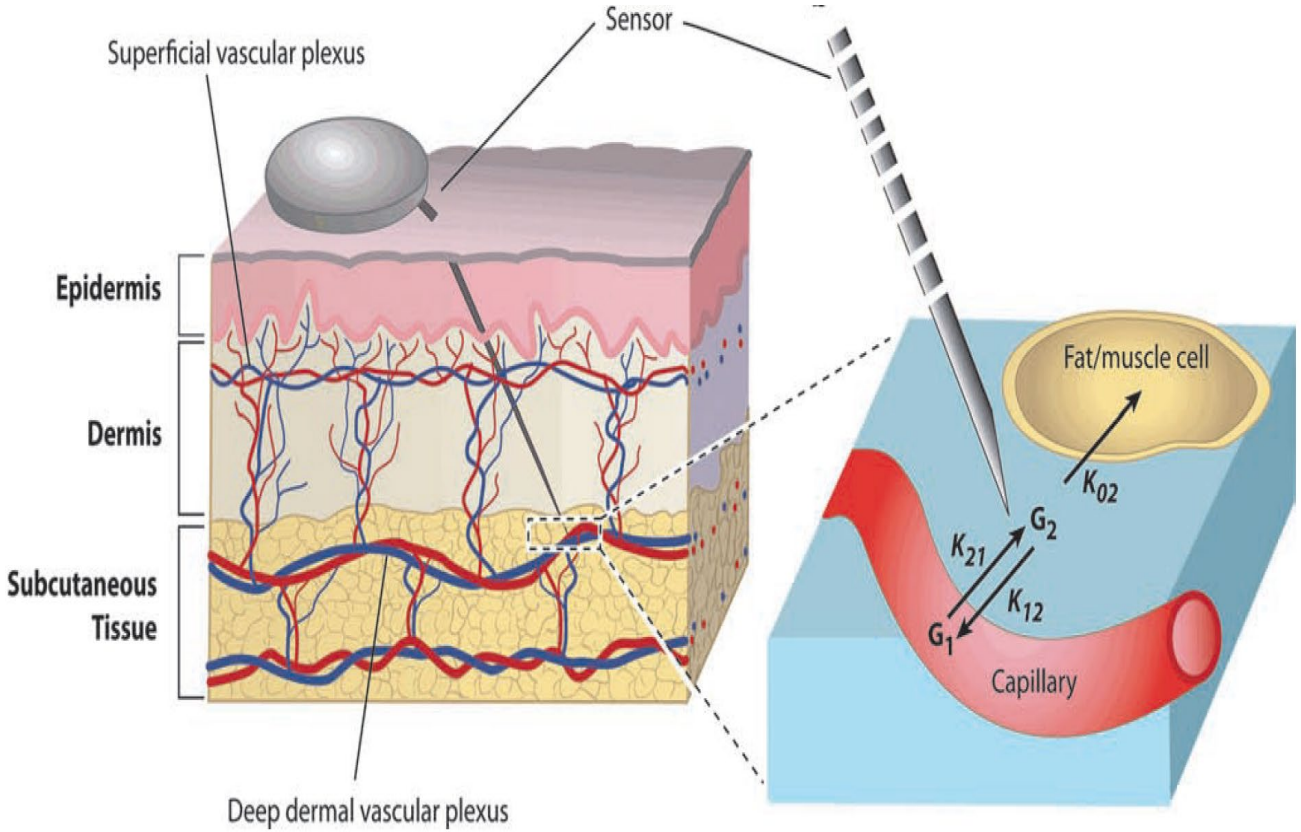
- A1C is easy to measure but provides limited insight into glucose control patterns
- Wide range of mean glucose variability can correspond to the same 3 month A1C measurement
- Short-term glycemic variability or hypoglycemic events can be missed
- CGM metrics can give a better picture of glycemic variability



Foster NC, Beck RW, Miller KM, et al. State of Type 1 Diabetes Management and Outcomes from the T1D Exchange in 2016-2018 [published correction appears in Diabetes Technol Ther. 2019 Apr;21(4):230]. *Diabetes Technol Ther*. 2019;21(2):66-72. doi:10.1089/dia.2018.0384

A1C, hemoglobin A1C; CGM, continuous glucose monitoring.

Monitoring Glycemic Control: Continuous Glucose Monitoring (CGM)



- A1C cannot capture glycemic variability or glucose excursions, including hypoglycemic events[1]
- With CGM, a small sensor is placed under the skin, to measure the interstitial glucose levels in intervals of 5 to 15 minutes[1]
- CGM provides a more comprehensive assessment of glycemic control
- CGM can inform patients of impending glucose excursions using glucose trend arrows and influence treatment decisions[2]
- CGM devices continue to become easier to use, more accurate, and more accessible to patients[2]

Figure: Cengiz and Tamborlane. Diabetes Technol Ther. 2009. Jun;11 (Suppl 1)

1. Bergenstal et al. *Diabetes Care*. 2018 Nov;41(11):2275-2280.
2. Ajjan et al. *Adv Ther*. 2019 Mar;36(3):579-596.

Current Commercially-Available CGM systems

Abbott

No user calibration required

Medtronic

Dexcom®
CONTINUOUS GLUCOSE MONITORING

eversense®
Continuous Glucose Monitoring System

No user calibration required

Key Features of Current CGM Devices

	Personal							Professional		
	rt-CGM						is-CGM			
CGM Category	Dexcom G6[13]	Dexcom G5[12]	Dexcom G4 Platinum[16]	Medtronic Guardian 3[10,11]	Medtronic Enlite 2[17]	Senseonic Eversense[18]	Abbott Freestyle Flash Libre[19,20]	Medtronic Enlite iPro2[21]	Dexcom G4 Professional[22]	Abbott Freestyle Libre Pro[23]
Population Age (y)	≥2	≥2	≥2	≥7	≥16	≥18	United States: ≥18 Non–United States: ≥4	≥7	≥2	United States: ≥18
Pregnancy Approval	No	No	No	No	No	No	United States: no Non–United States: yes	No	No	No
Warm-up time (h)	2	2	2	2	2	24	10 d: 12 14-d: 1	2	2	2
Sensor wear (d)	10	7	7	7	6	United States: 90 Non–United States: 180	10–14	6	7	14
Calibrations	None	2/d	2/d	2–4/d	2/d	2/d	None	NA	2/d	NA
Nonadjunctive Use	Yes	Yes	No	No	No	Yes	Yes	NA	NA	NA
Audible Alarms/Alerts	Yes Hypoglycemia predictive alerts	Yes	Yes	Yes Predictive alerts	Yes Predictive alerts	Yes Predictive alerts (vibrates)	No	NA	Blinded: no Unblinded: yes	NA
Trend Arrows	Yes	Yes	Yes	Yes	Yes	Yes	Yes	NA	Blinded: no Unblinded: yes	NA

1. Kravarusic J, Aleppo G. *Endocrinol Metab Clin North Am.* 2020 Mar;49(1):37-55.

Key Features of Current CGM Devices cont.

	Personal							Professional		
	rt-CGM						is-CGM			
CGM Category	Dexcom G6[13]	Dexcom G5[12]	Dexcom G4 Platinum[16]	Medtronic Guardian 3[10,11]	Medtronic Enlite 2[17]	Senseonic Eversense[18]	Abbott Freestyle Flash Libre[19,20]	Medtronic Enlite iPro2[21]	Dexcom G4 Professional[22]	Abbott Freestyle Libre Pro[23]
Share features	Yes	Yes	Yes	Guardian Connect Mobile only (Apple)	No	Yes	14-d system only (LibreLink)	NA	NA	NA
Pump integration	Tandem t:slim X2 with Basal IQ	Tandem t:slim X2	Animas Vibe Tandem t:slim G4	Medtronic 670G	Medtronic Revel, 530G, 630G	None	None	NA	NA	NA
Software Compatibility	Dexcom CLARITY Glooko Tidepool	Dexcom CLARITY Glooko Tidepool	Dexcom Studio Glooko Tidepool	Medtronic CareLink Tidepool	Medtronic CareLink	Glooko	LibreView Tidepool (reader only)	iPro CareLink	Dexcom Studio	LibreView
Acetaminophen Interference	No	Yes	Yes	Yes	Yes	No	No	Yes	Yes	No
MARD (%)	9	9	9	Abdominal 10.6[a]-9.6[b] Arm 9.1[a]-8.7[b]	13.6	8.8	10 d: 9.7 14 d: 9.4	13.6	9	12.3
Radiograph/MRI Compatible	No	No	No	No	No	Yes	No	No	No	No

Abbreviations: is-CGM, intermittent scanned CGM; NA, not available; rt-CGM, real-time CGM.
[a] Two calibrations per day.
[b] Four calibrations per day.
Data from Refs.[10–13,16–23]

1. Kravarusic J, Aleppo G. *Endocrinol Metab Clin North Am.* 2020 Mar;49(1):37-55.

Indications for CGM Therapy

International Consensus:[1]
- All patients with T1D
- T2D treated with intensive insulin therapy, not meeting glycemic goals
- Those with problematic hypoglycemia

AACE:[3]
- T1D with hypoglycemia/unawareness or not meeting glycemic goals
- T2D on intensive insulin therapy, high risk for hypoglycemia, or unappreciated hyperglycemia

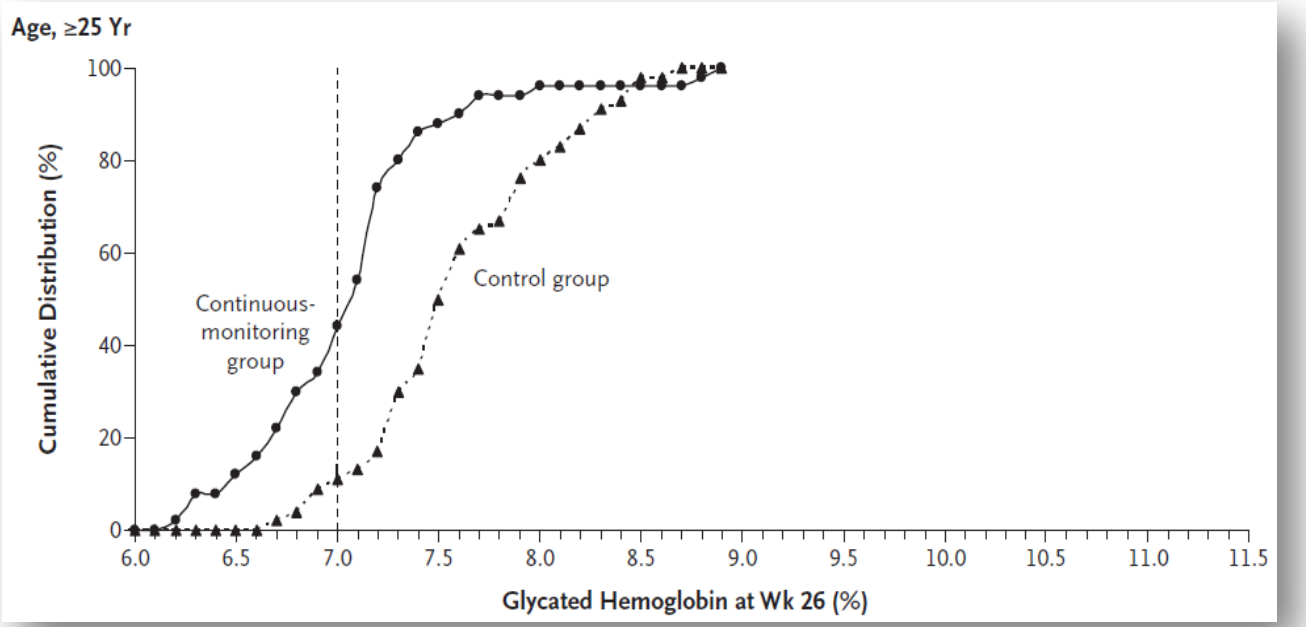
American Diabetes Association:[2]
- T1D not meeting glycemic goals (consider in T2D)
- Hypoglycemia/unawareness
- Sensor-augmented pump therapy
- Consider in pregnancy

1. Danne et al. *Diabetes Care* 2017; 40:1631-1640.
2. ADA. *Diabetes Care*. 2019 Jan;42(Suppl 1):S71-S80.
3. Handelsman et al. *Endocr Pract*. 2015 Apr;21 Suppl 1:1-87.

Evidence for CGM Therapy: Hemoglobin A1C

CGM and Intensive Treatment of T1D

- **Randomized, multicenter clinical trial that assessed the efficacy and safety of CGM in adults and children with T1D**
- **Population:** Age ≥8 years, T1D diagnosis for ≥1 year, insulin pump use or ≥3 insulin injections daily, A1C 7-10%, no CGM use prior 6 months
- **Primary outcome**: Mean change in A1C from baseline to 26 weeks
- **Results**: Mean change in A1C in adults (age ≥25 years) at 26 weeks with use of CGM were significant (-0.53%, *P*<0.001). Results were not significant for those age 15-24 (0.08, *P*=0.52) or age 8-14 (-0.013, *P*=0.29)



Legend: A1C, hemoglobin A1C; CGM, continuous glucose monitoring; T1D, type 1 diabetes.

Tamborlane WV et al. *N Engl J Med*. 2008 Oct 2;359(14)

Greater A1C Reduction in Patients Who Look at CGM Display

Comparison of Bottom and Top Quartiles of CGM Attention and A1C Reduction at 12 Weeks

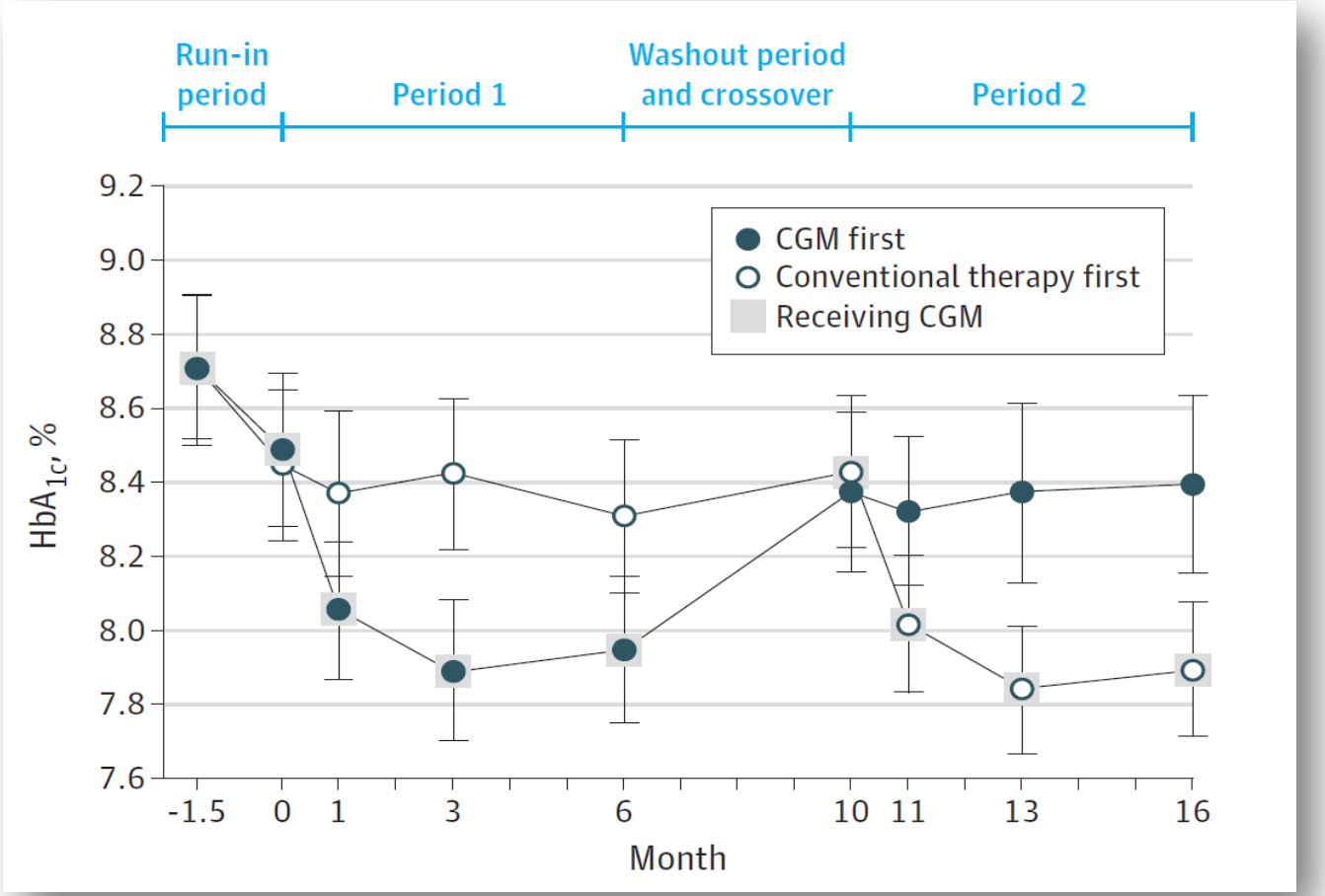
	Bottom Quartile (n=32)	*Top Quartile (n=31)*	*P value*
1-h trend screen views per day	9.8 ± 2.7	37.7 ± 11.3	<0.001
A1C change at 12 weeks (%)	-0.11 ± 0.61	-0.61 ± 0.76	0.008
3-h trend screen views per day	1.4 ± 0.7	5.8 ± 3.0	<0.001
A1C change at 12 weeks (%)	-0.23 ± 0.66	-0.84 ± 0.93	0.006
9-h trend screen views per day	0.9 ± 0.4	3.7 ± 2.3	<0.001
A1C change at 12 weeks (%)	-0.19 ± 0.49	-0.78 ± 0.94	0.004
All trend screen views per day[a]	12.2 ± 3.3	47.2 ± 13.4	<0.001
A1C change at 12 weeks (%)	-0.08 ± 0.58	-0.61 ± 0.75	0.004

Data are mean ± SD values
[a]Combined number of trend screen views (1-, 3-, and 9-h) per day
Legend: A1C, hemoglobin A1C; CGM, continuous glucose monitoring; SD, standard deviation.

Bailey et al. *Diabetes Technol Ther* 2007;9(3)

CGM vs Conventional Therapy in T1D: The GOLD Trial

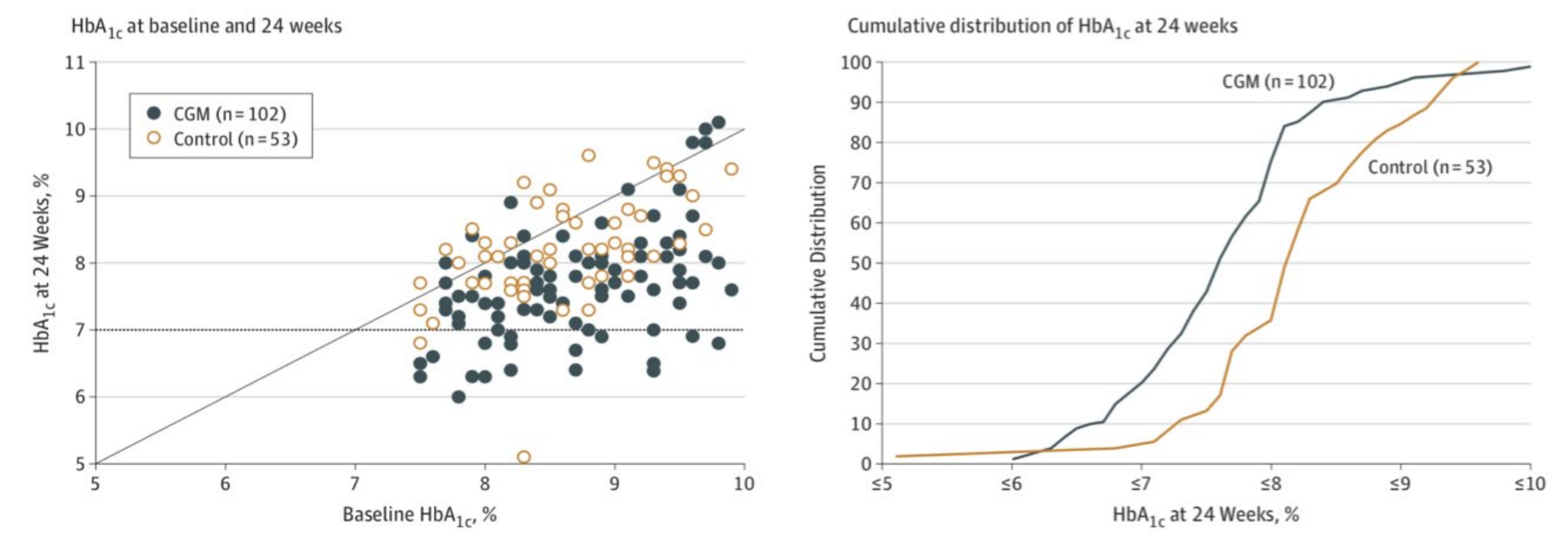
- **An open-label, randomized crossover trial in adults withT1D comparing the effect of CGM vs. conventional therapy (SMBG) on glycemic control**
- **Population:** ≥18 years, T1D for ≥1 year on MDI, with A1C >7.5%
- 1:1 randomization CGM vs SMBG
- **Primary outcome**: Difference in A1C between CGM and conventional therapy at weeks 26 and 69.
- **Results**: Mean difference in A1C of -0.43% (*P*<0.001) during CGM vs conventional therapy after 26 weeks



Legend: A1C, hemoglobin A1C; CGM, continuous glucose monitoring; GOLD, Glycemic control & Optimization of Life quality in type 1 Diabetes; MDI, multiple daily injections; SMBG, self-monitoring of blood glucose; T1D, type 1 diabetes.

Lind et al. *JAMA*. 2017;317:379-387

CGM vs SMBG in T1D: The DIAMOND Trial



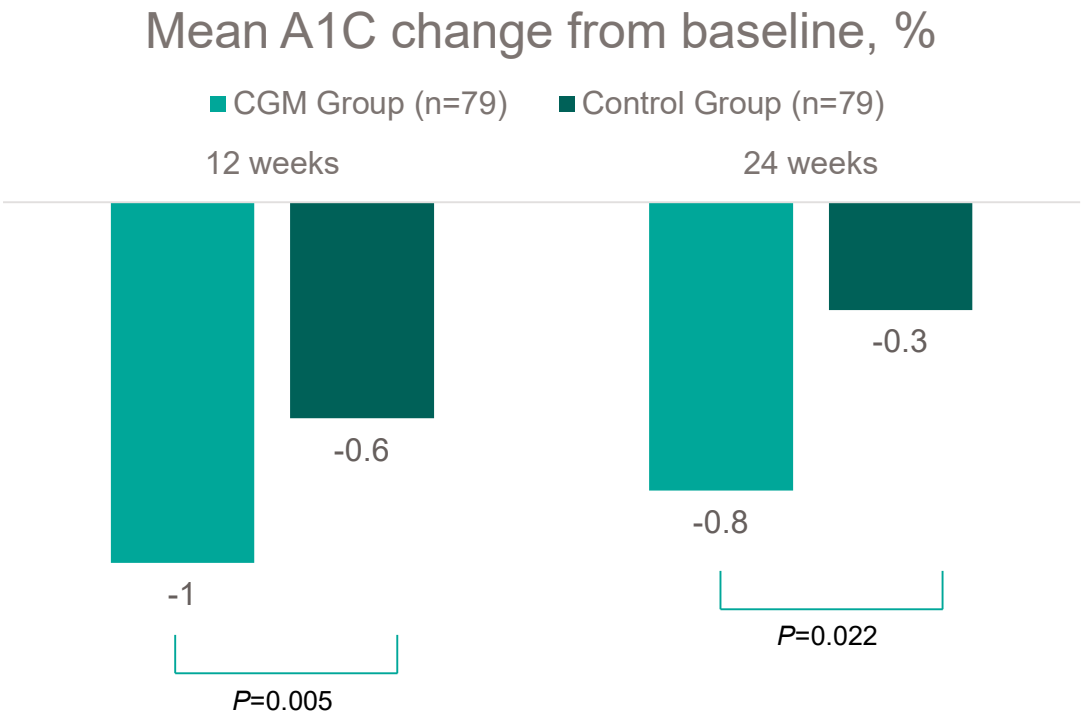
- **Prospective RCT in adults with T1D comparing the effect of CGM to SMBG on glycemic control**
- **Primary outcome**: Change in A1C from baseline to 24 weeks
- **Results**: At 24 weeks, mean A1C reduction from baseline of 1.0% in CGM group (from 8.6% to 7.7%) vs 0.4% in SMBG group (*P*<0.001). A1C decreased from 8.6% to 7.7% in CGM group. Time spent in hypoglycemia <70 mg/dL was 43 min/day with CGM vs 80 min/day with SMBG (*P*=0.002)

Beck, RW et al, *JAMA*.2017;317(4):371-378

Legend: DIAMOND, Multiple Daily Injections and Continuous Glucose Monitoring in Diabetes; RCT, randomized controlled trial; SMBG, self-monitoring of blood glucose

CGM vs SMBG in T2D

- **Prospective RCT in adults with T2D comparing the effect of CGM to SMBG on glycemic control**
- Enrollment criteria: Age ≥25 years, T2D on MDI ≥1 year, A1C 7.5%-10.0%, stable medication regimen and weight over past 3 months, SMBG ≥2 per day, without significant renal dysfunction
- **Primary outcome:** A1C reduction at 24 weeks. Secondary outcomes: hypoglycemia, QOL, and CGM satisfaction
- **Results**: Mean adjusted change in A1C of -1.0% from baseline to 24 weeks in CGM group compared with control group change of -0.6% (*P*=0.005) with adjusted difference of -0.3% (*P*=0.022)
- No difference in hypoglycemia or QOL; high CGM satisfaction scores



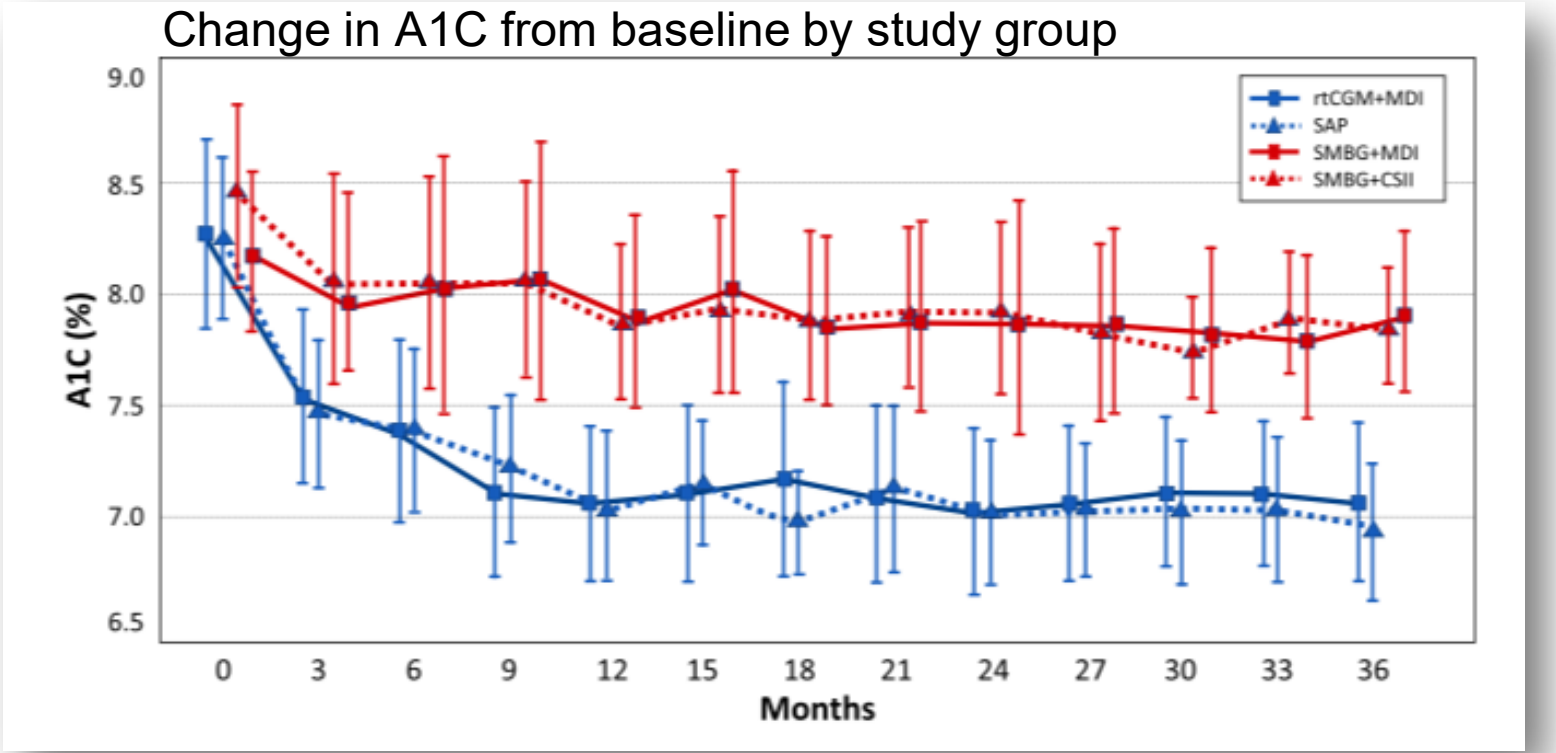
	Mean A1C, %		
	Baseline	12 Weeks	24 Weeks
CGM Group	8.5	7.5	7.7
Control Group	8.5	7.9	8.0

Beck R et al. *Annals of Internal Medicine*. 2017; 167 (4).

Legend: RCT, randomized controlled trial; SMBG, self-monitoring of blood glucose; T2D, type 2 diabetes; A1C, hemoglobin A1C; QOL, quality of life

CGM vs SMBG in T1D: COMISAIR Study 3-Year Outcomes

- **A 3-year prospective, nonrandomized, real-world study comparing CGM with SMBG in patients receiving MDI or CSII**
- Patients were divided into 4 groups: CGM+MDI, CGM+CSII (SAP), SMBG+MDI, and SMBG+CSII
- **Primary outcome**: Between-group difference in A1C at 3 years
- **Results**: At 3 years, both CGM groups had a mean A1C of 7%, a significant difference from both SMBG+CSII (7.7%) and SMBG+MDI (7.7% and 8.0%, respectively; *P*<0.0001 for both)



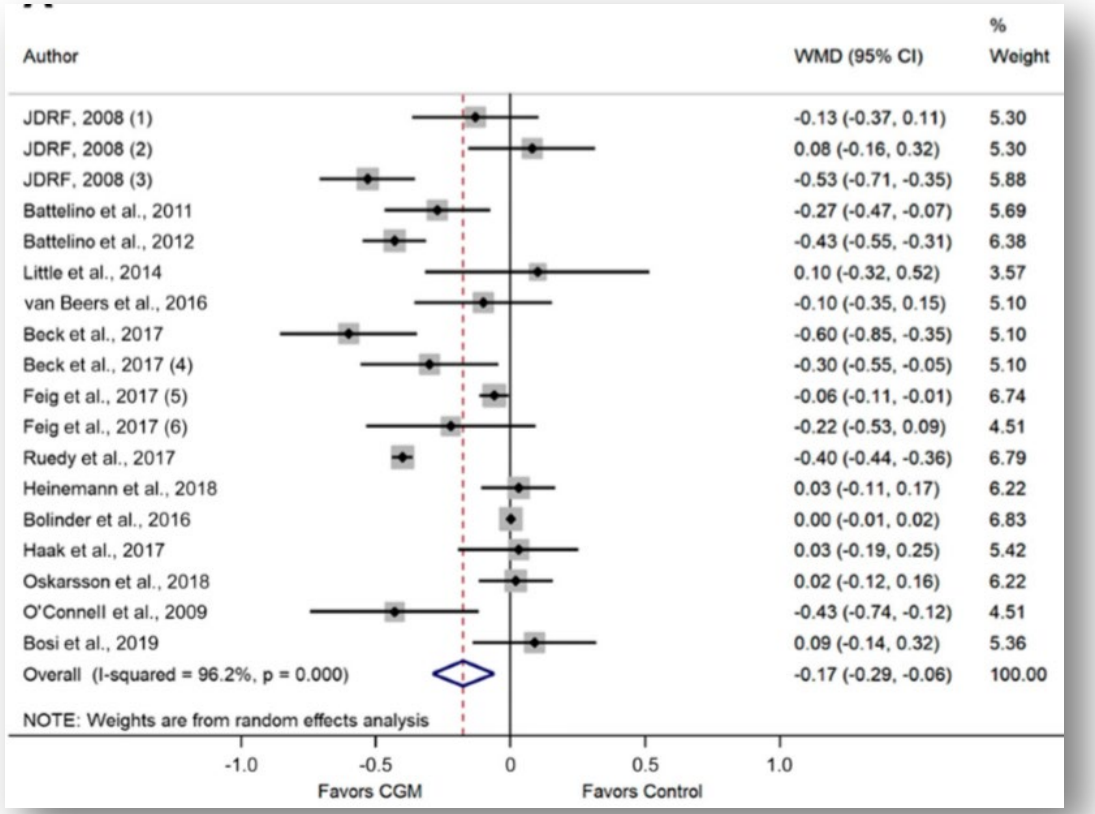
Legend: COMISAIR, Comparison of Different Treatment Modalities for Type 1 Diabetes Including Sensor-Augmented Insulin Regimens; CSII, continuous subcutaneous insulin infusion; MDI, multiple daily injections; rt, real-time; SAP, sensor-augmented pump; SMBG, self-monitoring of blood glucose; T1D, type 1 diabetes.

Šoupal J et al. *Diabetes Care*. 2019 Sep 17.

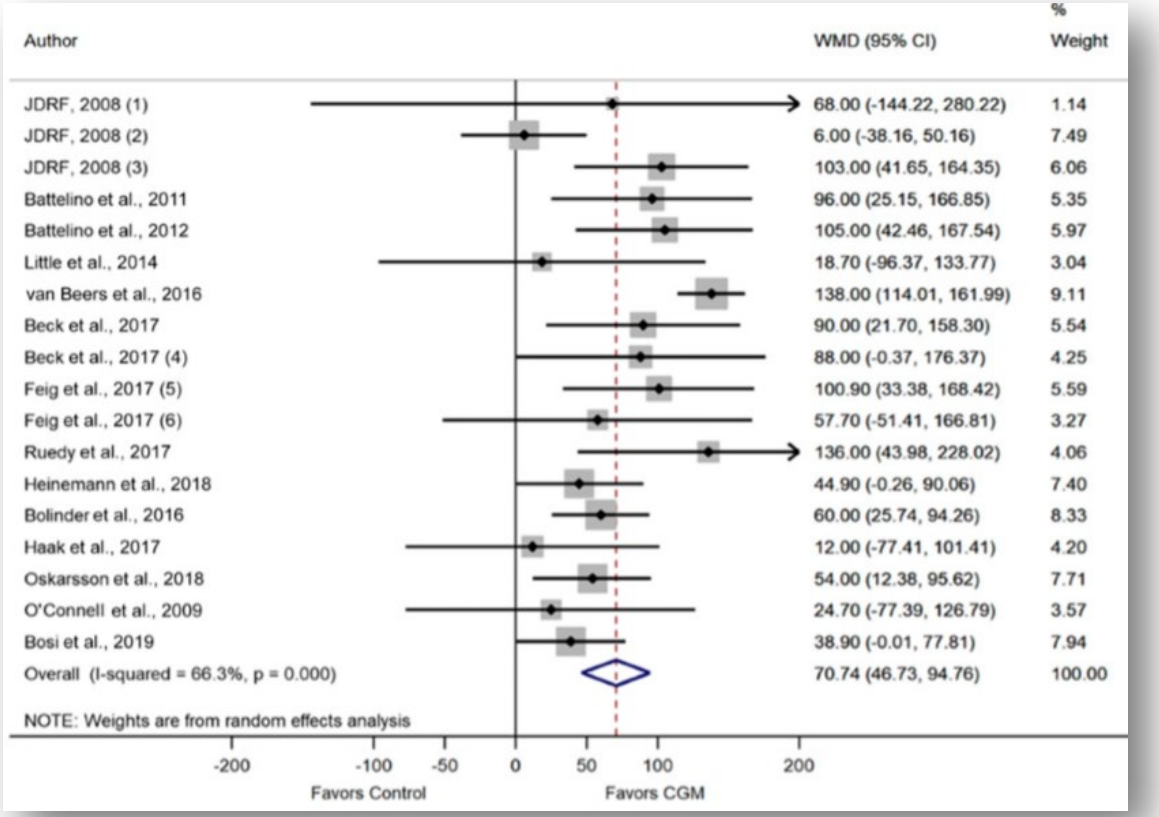
Evidence for CGM Therapy: Time in Range

Meta-analysis of CGM trials in T1D and T2D

Change in Hemoglobin A1C



Time in Target Glucose Range



Maiorino et al. *Diabetes Care*. 2020;43:1146–1156.

Continuous Glucose Monitoring Metrics

Continuous Glucose Monitoring Metrics

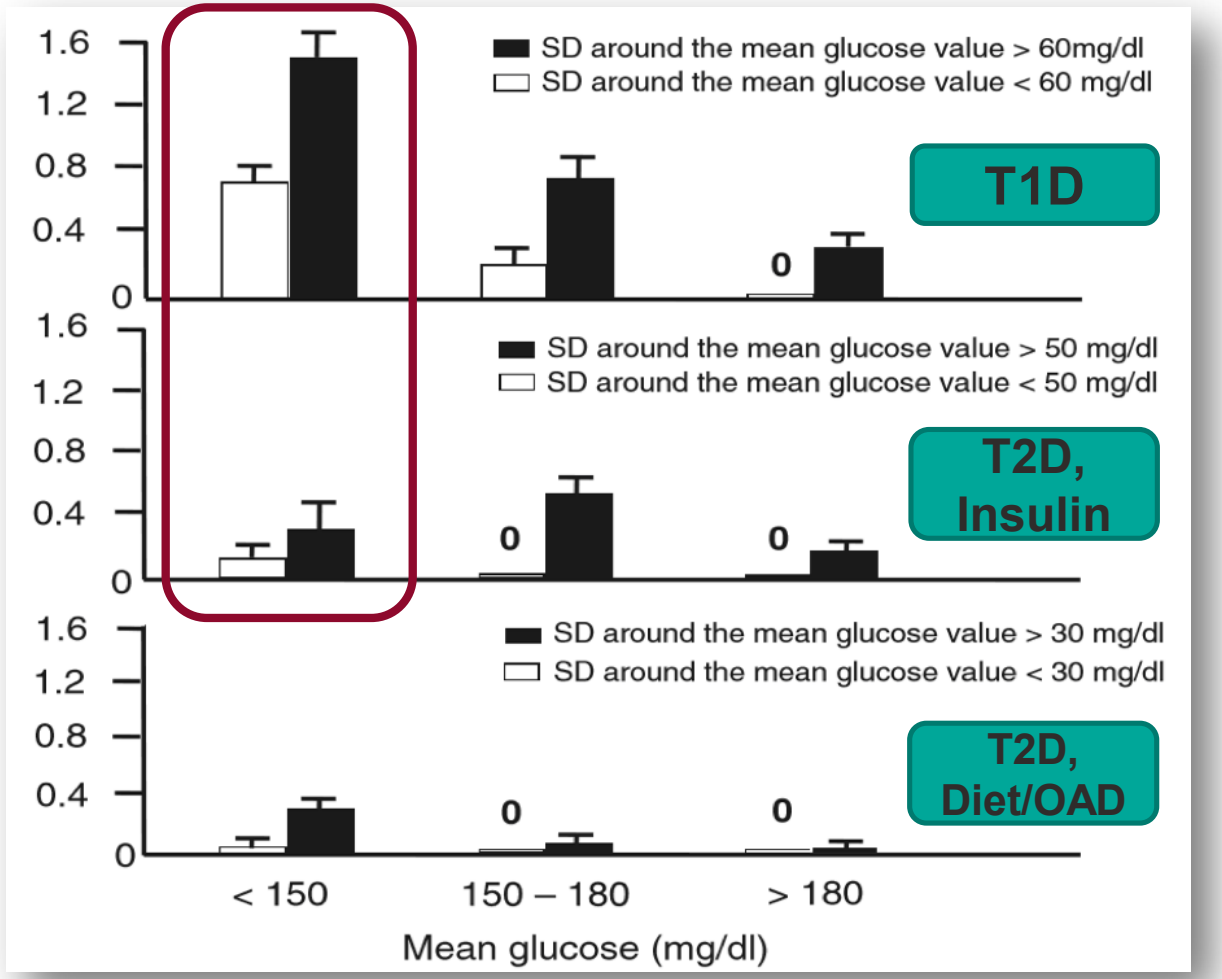
Standardized CGM Metrics for Clinical Care: 2019	
1. Number of days CGM worn (recommend 14 days)	
2. Percentage of time CGM is active (recommend 70% of data from 14 days)	
3. Mean glucose	
4. Glucose management indicator	
5. Glycemic variability: Coefficient of Variation (%CV) target ≤36%*	
6. Time above range: % of readings and time >250 mg/dL (>13.9 mmol/L)	Level 2
7. Time above range: % of readings and time 181-250 mg/dL (10.1-13.9 mmol/L)	Level 1
8. Time in range: % of readings and time 70-180 mg/dL (3.9-10.0 mmol/L)	In range
9. Time below range: % of readings and time 54-69 mg/dL (3.0-3.8 mmol/L)	Level 1
10. Time below range: % of readings and time <54 mg/dL (<3.0 mmol/L)	Level 2

- 2019 International Consensus Group streamlined 14 core metrics to 10 most applicable to clinical practice
- Provide more data for assessment of glycemic control compared with A1C

*Some studies suggest that lower %CV targets (<33%) provide additional protection against hypoglycemia for those receiving insulin or sulfonylureas

Battelino T et al. *Diabetes Care*. 2019 Aug;42(8):1593-1603

Glycemic Variability and Hypoglycemia



- Measures of Glycemic Variability
  - Standard Deviation (SD)
  - Coefficient of Variation (CV)
  - MAGE
- Stable glucose levels: CV<36%
- Glycemic variability is a consistent predictor of hypoglycemia
- **Figure:** highest rates of hypoglycemia in those with high variability (SD) and a lower mean glucose value (rectangle)

Legend: A1C, hemoglobin A1C; CV, coefficient of variation; MAGE, mean amplitude of glycemic excursion; OAD, oral antidiabetic drugs; SD, standard deviation; T1D, type 1 diabetes; T2D, type 2 diabetes.

Monnier L et al. *Rev Endocr Metab Disord* (2016) 17:91–101

Electronic AGP Report with Key CGM Metrics

AGP Report

Name

MRN

GLUCOSE STATISTICS AND TARGETS

26 Feb 2019 - 10 Mar 2019	**13 days**
% Time CGM is Active	**99.9%**

Glucose Ranges	**Targets** [% of Readings (Time/Day)]
Target Range 70-180 mg/dL	Greater than 70% (16h 48min)
Below 70 mg/dL	Less than 4% (58min)
Below 54 mg/dL	Less than 1% (14min)
Above 250 mg/dL	Less than 5% (1h 12min)

Each 5% increase in time in range (70-180 mg/dL) is clinically beneficial.

Average Glucose	**173 mg/dL**
Glucose Management Indicator (GMI)	**7.6%**
Glucose Variability	**49.5%**

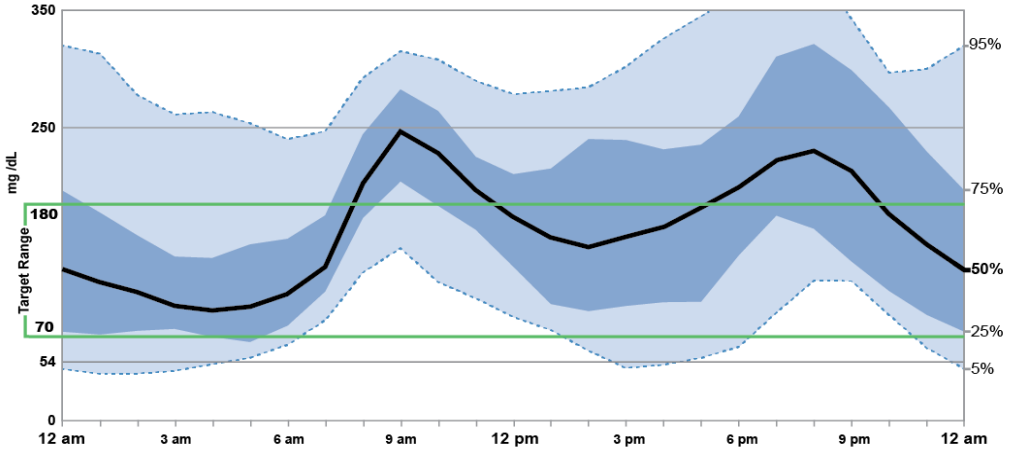
Defined as percent coefficient of variation (%CV); target ≤36%

TIME IN RANGES

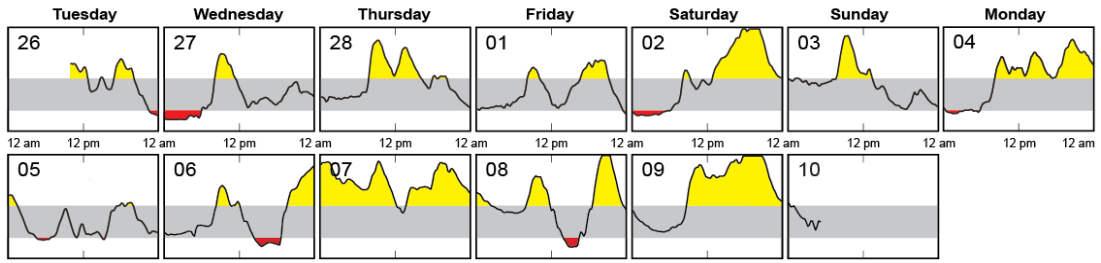
- **Very High** (>250 mg/dL) **20%** (4h 48min)
- **High** (181–250 mg/dL) **23%** (5h 31min)
- **Target Range** (70–180 mg/dL) **47%** (11h 17min)
- **Low** (54–69 mg/dL) **4%** (58min)
- **Very Low** (<54 mg/dL) **6%** (1h 26min)

AMBULATORY GLUCOSE PROFILE (AGP)

AGP is a summary of glucose values from the report period, with median (50%) and other percentiles shown as if occurring in a single day.



DAILY GLUCOSE PROFILES



Each daily profile represents a midnight to midnight period.

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AMERICAN ASSOCIATION OF CLINICAL ENDOCRINOLOGISTS
AACE

CGM Data: Glucose Management Indicator (GMI)

- Using 10-14 days of data, CGM-derived mean glucose values can be used to find an “estimated A1C” (eA1C)[1]

- GMI has been proposed as a new term to replace eA1C, as this better conveys the use of this metric
  - GMI helps inform or guide diabetes treatment decisions, but is not necessarily a perfect match with A1C levels[1]

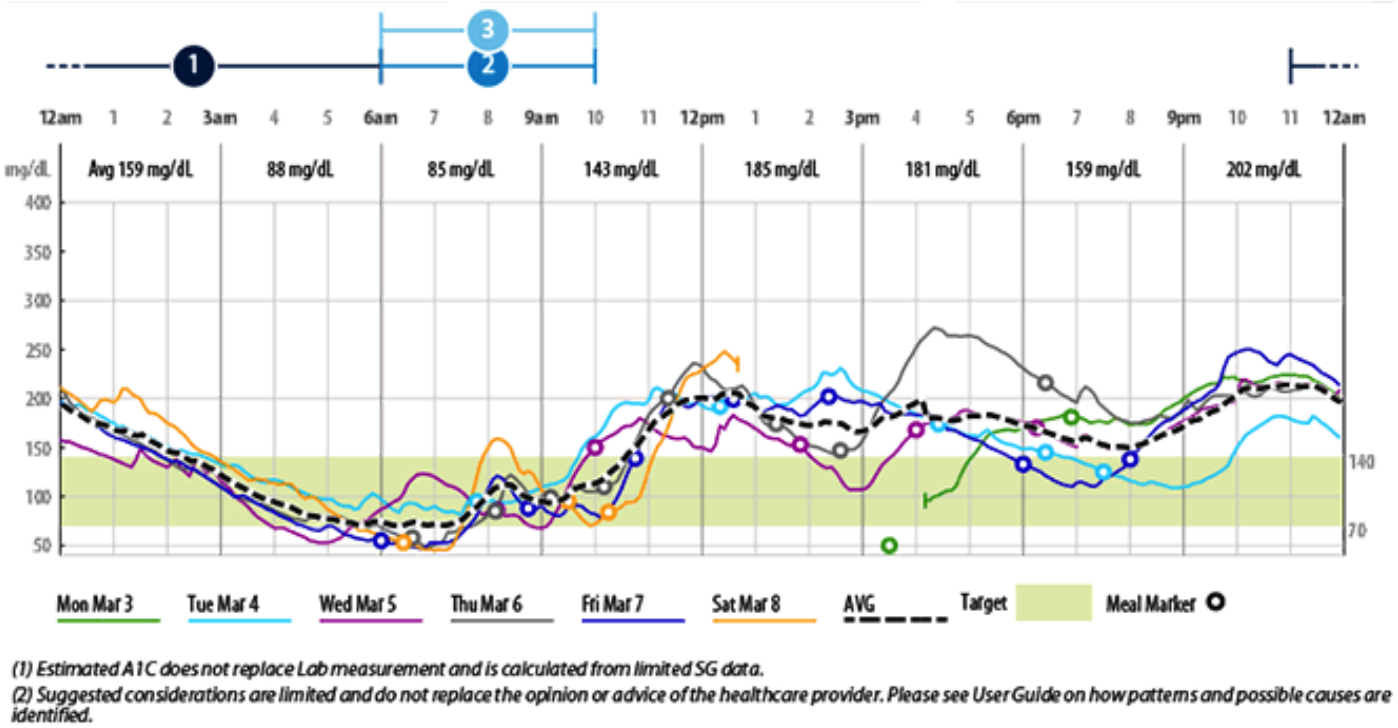
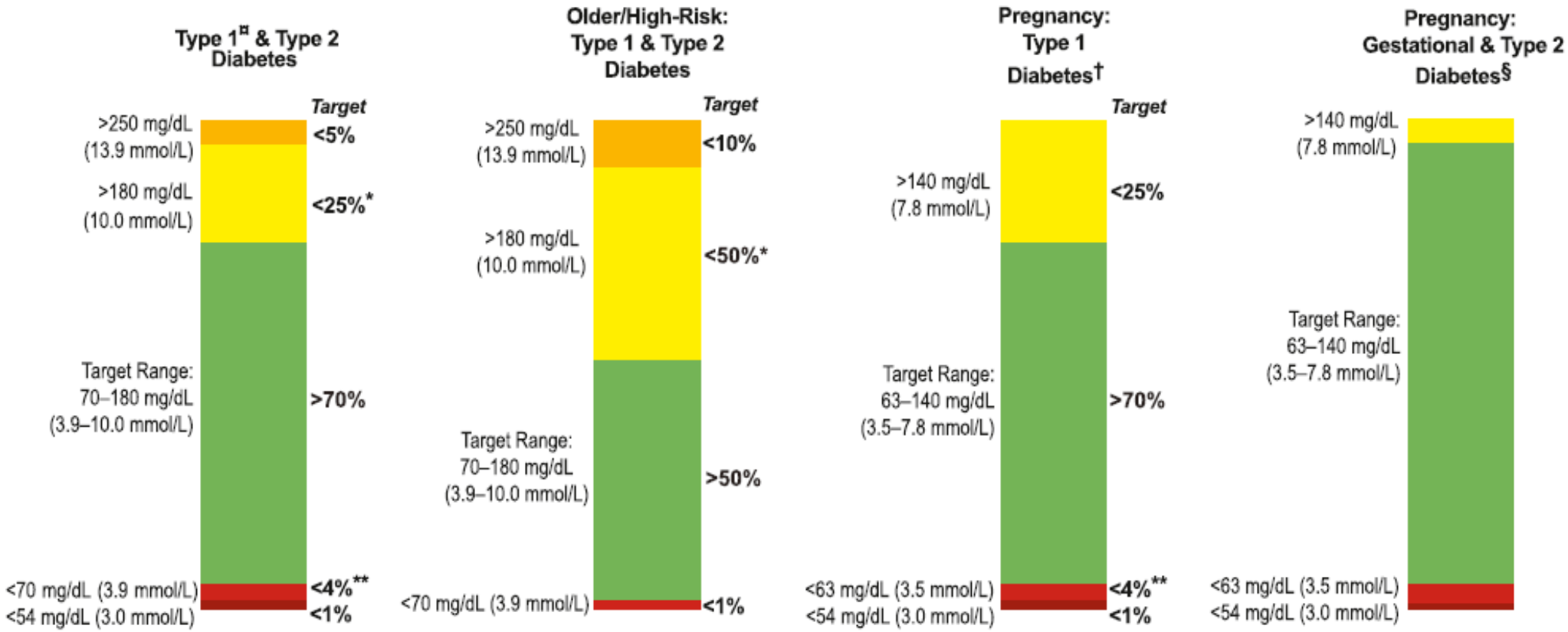


Image: https://professional.medtronicdiabetes.com/ipro2-professional-cgm. Accessed on January 9, 2020

1. Bergenstal et al. *Diabetes Care*. 2018 Nov;41(11):2275-2280.

Individualizing Glycemic Control Goals Using CGM Metrics



Battelino T et al. *Diabetes Care*. 2019 Aug;42(8):1593-1603

Contributors

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