The Evidence Base for Continuous Glucose Monitoring

Anne L. Peters, MD, *Keck School of Medicine of the University of Southern California, Los Angeles, CA*

Twenty-seven published randomized controlled trials (RCTs) assessing outcomes of continuous glucose monitoring (CGM), involving a total of 3,826 patients, have been published to date. Although the number of patients in each study has been small compared to drug trials, cumulative evidence indicates a benefit of CGM for patients treated with either continuous subcutaneous insulin infusion (CSII) or a multiple daily injection (MDI) insulin regimen. Additionally, some data suggest that CGM may benefit people with type 2 diabetes who do not use insulin therapy.

Overall, RCTs have shown improved glucose control in patients with higher initial A1Cs (often in the range of 7.8–8.8%) using CGM compared to self-monitoring of blood glucose (SMBG). People who wear their CGM device most consistently derive the most benefit. Time spent in the designated hypoglycemia range (usually <70 mg/dL) was reduced in some studies, particularly in those with patients selected for having a higher risk of hypoglycemia. These patients tended to have lower baseline A1Cs (in the range of 6.5–7.5%). Rates of severe hypoglycemia generally have not differed between CGM and non-CGM groups, and these rates have been low across all studies.

Studies fall into a few basic categories: adults with type 1 diabetes (8 trials, 698 patients), adults with type 2 diabetes (4 trials, 547 patients), children with type 1 diabetes (2 trials, 227 patients), adults plus children with type 1 diabetes (7 trials, 1,084 patients), adults with type 1 or type 2 diabetes (3 trials, 655 patients), and women during pregnancy with either type 1 diabetes or gestational diabetes mellitus (GDM) (3 trials, 585 patients). Table 1 lists general findings from all of these trials. It is important to note that some trials used A1C or time in range as the primary endpoint, whereas others used time in a hypoglycemic range as the primary outcome. Readers should also be aware that Table 1 is not a meta-analysis per se, but rather includes studies identified through a literature search of PubMed and Ovid MEDLINE, as well as all prior reviews and studies in their reference lists. Only RCT data are included; observational studies and extension phases of RCTs also have been performed but are not represented here.

The first trials, from the early 2000s, used intermittent CGM. Some used "professional" CGM, in which patients were blinded to the CGM data (see the article on p. 8 of this compendium), and others followed an intermittent use schedule. As time progressed, the trials reflected evolving use of CGM to the current day. That is, earlier studies began to suggest that CGM could improve outcomes, but lack of access to real-time data limited benefit. More recent studies of real-time CGM, in which around-the-clock data are available, have shown more benefit in terms of reduction in both A1C and time spent in a hypoglycemic range.

A major impediment to interpreting CGM studies is that no uniform standard has been employed for teaching people with diabetes how to use continuous data, and no standard follow-up is provided to ensure that dose adjustments are made. In some trials, written instructions were provided to patients regarding insulin dose adjustments, but in many others, targeted education was not provided beyond how to use the device. Additionally, rapid advances in technology are not well represented in the literature, although data from newer systems, such as the Dexcom G5 Mobile (Dexcom, San Diego, CA) and the FreeStyle Libre (Abbott, Alameda, CA), are becoming available.

TABLE 1 Summary of CGM Research Studies

Study	Design	Primary Outcome / Type of CGM	A1C Outcomes	Hypoglycemia Change/Other
ADULTS WITH T1D: A1C PRIMARY OUTCOME				
Beck et al. (1,2)	▸ Adults with T1D on MDI ▸ *n* = 158 ▸ Baseline A1C: ~8.6% ▸ Parallel arms, 24 weeks	A1C reduction / Dexcom G4 Platinum	–0.6%, *P* <0.001	▸ Time <70 mg/dL was 43 vs. 80 min/day, *P* = 0.002 ▸ No difference in severe lows
Lind et al. (3)	▸ Adults with T1D on MDI ▸ *n* = 161 ▸ Baseline A1C: 8.6% ▸ Crossover, 26-week arms	A1C reduction / Dexcom G4 Platinum	–0.43, *P* <0.001	▸ Numerically less time in a hypoglycemic range with CGM
Sequeira et al. (4)	▸ Underserved adults with T1D MDI ▸ *n* = 25 ▸ Baseline A1C: 8.5% ▸ Crossover, 28-week arms	A1C reduction / Dexcom SEVEN	No significant difference between groups	▸ No change in rates of hypoglycemia

continued on page 4

continued from page 3

Study	Design	Primary Outcome / Type of CGM	A1C Outcomes	Hypoglycemia Change/Other
Tumminia et al. (5)	▸ Adults with T1D on MDI or CSII ▸ *n* = 20 ▸ Baseline A1C: ~8.65% ▸ Crossover, 24-week arms	A1C reduction / Medtronic Guardian REAL-Time	Only analyzed 14 patients who used CGM ≥40% of the time; in these patients, there was a significant reduction in A1C (*P* <0.05)	Risk for hypoglycemia was reduced (time spent <70 mg/dL/day), *P* <0.05
ADULTS WITH T1D: HYPOGLYCEMIA PRIMARY OUTCOME				
Bolinder et al. (6)	▸ Adults with T1D on MDI or CSII ▸ *n* = 241 ▸ Baseline A1C: 6.7% ▸ Parallel arms, 6 months	Change in time in hypoglycemic range (<70 mg/dL) / Abbott FreeStyle Libre	NS	▸ Overall, 38% reduction in time in hypoglycemia (–1.24 hours/day, *P* <0.0001) ▸ Time in range (3.9–10.0 mmol/L [70–180 mg/dL]; mean difference) improved by 1.0 ± 0.30 hour, *P* = 0.0006
Hermanns et al. (7)	▸ Adults with T1D, most on MDI ▸ *n* = 41 ▸ Baseline A1C: 8.2% ▸ Crossover design, 5-day arms; patients were free-living within inpatient research setting	Proportion of time spent hypoglycemic / Dexcom SEVEN PLUS	N/A	Reduction in time in hypoglycemic range: 125 ± 89 vs. 181 ± 125 min/day, *P* = 0.005
van Beers et al. (8)	▸ Adults with T1D on MDI or CSII with a Gold score ≥4 ▸ *n* = 52 ▸ Baseline A1C: 7.5% ▸ Crossover, 16-week arms	Mean difference in time in range (4–10 mmol/L [72–180 mg/dL]) / Medtronic Enlite with a MiniMed Paradigm Veo system (used as a monitor)	NS	▸ Reductions in hypoglycemia (≤3.9 mmol/L [70.2 mg/dL]) –4.7%, *P* <0.0001 ▸ Severe hypoglycemia: 14 events with CGM vs. 34 events with SMBG, *P* = 0.033 ▸ Time in range (mean difference) improved by 9.6%, *P* = 0.0001
ADULTS AND CHILDREN WITH T1D: A1C/TIME IN RANGE PRIMARY OUTCOME				
Battelino et al. (9)	▸ Adults and children with T1D on CSII ▸ *n* = 153 ▸ Baseline A1C: 8.1% for adults, 8.6% for children ▸ Crossover, 6-month arms	A1C reduction / Medtronic Guardian REAL-Time	A1C difference –0.43% in favor of sensor on, *P* <0.001	▸ Time spent <3.9 mmol/L (70.2 mg/dL) was 19 vs. 31 min/day, *P* = 0.009 ▸ Four severe hypoglycemic episodes in sensor on mode, two in sensor off mode
Deiss et al. (10)	▸ Adults and children with T1D on MDI or CSII ▸ *n* = 156 ▸ Baseline A1C: 9.5% in arm 1, 9.7% in arm 2 ▸ Three parallel arms: continuous CGM (arm 1) vs. biweekly 3-day CGM (arm 2) vs. control for 3 months	A1C reduction / Medtronic Guardian REAL-Time	Arm 1: –0.6%, *P* = 0.003; Arm 2: no difference in A1C	One episode of severe hypoglycemia in each arm
JDRF CGM Study Group (11)	▸ Adults and children with T1D on MDI or CSII ▸ *n* = 322 ▸ Three age-groups: ≥25 years (*n* = 98), 15–24 years (*n* = 110), and 8–14 years (*n* = 98) ▸ Baseline A1C: ≥25 years, 7.6%; 15–24 years, 7.9–8.0%; and 8–14 years, 7.9–8.0% ▸ Parallel arms, 26 weeks	A1C reduction / DexCom SEVEN, Medtronic MiniMed Paradigm REAL-Time insulin pump and CGMS, and Abbott FreeStyle Navigator	▸ A1C difference: in those ≥25 years of age, –0.53%, *P* <0.001; in those <25 years of age, no difference ▸ A1C response related to use of CGM	No difference in time spent in a hypoglycemic range or in number of severe hypoglycemic episodes

Study	Design	Primary Outcome / Type of CGM	A1C Outcomes	Hypoglycemia Change/Other
O'Connell et al. (12)	▸ Adults and adolescents with T1D on CSII ▸ *n* = 55 ▸ Baseline A1C 7.3% for intervention group, 7.5% for control group ▸ Parallel arms, 3 months	Time in range during the 3-month study period / Medtronic MiniMed Paradigm REAL-Time insulin pump and CGMS	▸ No difference in primary outcome ▸ A1C was –0.43% lower in the CGM group, *P* = 0.009 ▸ Greater reduction in group with more use	No difference in time in range, variability, or hypoglycemia
ADULTS AND CHILDREN WITH T1D: HYPOGLYCEMIA PRIMARY OUTCOME				
JDRF CGM Study Group (13)	▸ Adults and children with T1D on MDI or CSII ▸ *n* = 129 ▸ Baseline A1C: 6.4% for CGM group, 6.5% for control group ▸ Parallel arms, 26 weeks	Change in time ≤70 mg/dL / DexCom SEVEN, MiniMed Paradigm REAL-Time insulin pump and CGMS, and Abbott FreeStyle Navigator	A1C treatment difference favoring CGM, *P* <0.001	▸ Time ≤70 mg/dL numerically less frequent (54 vs. 91 min/day) but not significant, *P* = 0.16 ▸ Median time with blood glucose ≤60 mg/dL was 18 vs. 35 min/day, *P* = 0.05 ▸ Severe hypoglycemia 10 and 11% for CGM and control groups, respectively, *P* = 1.0
Battelino et al. (14)	▸ Adults and children with T1D on MDI or CSII ▸ *n* = 120 ▸ Baseline A1C: 6.9% ▸ Parallel arms, 26 weeks	Time spent in hypoglycemic range / Abbott FreeStyle Navigator	A1C treatment difference favoring CGM: –0.27%, *P* = 0.008	▸ Time spent <63 mg/dL shorter in CGM group; ratio of means 0.49, *P* = 0.03 ▸ No severe hypoglycemia
Heinemann et al. (15)	▸ Adults and children with T1D on MDI with a history of impaired hypoglycemia awareness or severe hypoglycemia ▸ *n* = 149 ▸ Baseline A1C: 7.3% for control group, 7.6% for CGM group ▸ Parallel arms, 26 weeks	Baseline-adjusted hypoglycemia events (glucose ≤3.0 mmol/L [54 mg/dL] for ≥20 minutes) / Dexcom G5 Mobile	No difference in A1C	Adjusted between-group difference in low glucose events: 0.28, *P* <0.0001
CHILDREN WITH T1D				
Ludvigsson et al. (16)	▸ Children with T1D on MDI or CSII ▸ *n* = 27 ▸ Baseline A1C: ~7.7% ▸ Cross-over, 12-week arms; wore CGM for 3 days every 2 weeks	A1C reduction/ Medtronic CGMS	A1C difference at 12 weeks during open vs. blind CGM: ~–0.39%, *P* = 0.011	No significant differences in hypoglycemia
Chase et al. (17)	▸ Children with T1D ▸ *n* = 200 ▸ Baseline A1C: 8.0% ▸ Parallel arms, 6 months	A1C reduction / GlucoWatch G2 Biographer	No significant change in A1C	Sensor use declined from 2.1 to 1.5 times/week because of skin irritation and other issues
ADULTS WITH T2D				
Beck et al. (18)	▸ Adults with T2D on MDI ▸ *n* = 158 ▸ Baseline A1C: 8.5% ▸ Parallel arms, 24 weeks	A1C reduction / Dexcom G4 Platinum with an enhanced algorithm	Adjusted mean A1C difference: –0.3%, *P* = 0.022	No change in hypoglycemia
Ehrhardt et al. (19)	▸ Adults with T2D not on prandial insulin (half on oral medication alone) ▸ *n* = 100 ▸ Baseline A1C: 8.2% for SMBG group, 8.4% for CGM group ▸ Parallel arms, 2 weeks on/1 week off, 4 cycles over 12 weeks	A1C reduction / Dexcom SEVEN	Difference in A1C: –0.6%, *P* = 0.002	▸ Hypoglycemia data NA ▸ Most improvement in people who used CGM per protocol

continued on page 6

continued from page 5

Study	Design	Primary Outcome / Type of CGM	A1C Outcomes	Hypoglycemia Change/Other
Haak et al. (20)	▸ Adults with T2D on prandial-only insulin on MDI or CSII ▸ *n* = 224 ▸ Baseline A1C: 8.74% in intervention group, 8.88% in control group ▸ Parallel arms, 2:1 randomization, 6 months	A1C reduction / Abbott FreeStyle Libre	No difference in A1C overall; difference in A1C if <65 years of age, *P* = 0.03	Time in hypoglycemia (<70 mg/dL) was reduced by 43%, *P* = 0.0006
Yoo et al. (21)	▸ Adults with T2D on oral agents or insulin ▸ *n* = 65 ▸ Baseline A1C: 8.7% in SMBG group, 9.1% in CGM group ▸ Parallel arms, real-time CGM for 3 days once per month for 12 weeks	A1C reduction / Medtronic Guardian REAL-Time	Improvement in A1C greater in CGM group, ~0.5%, *P* = 0.004 (CGM: from 9.1 ± 1.0 to 8.0 ± 1.2%, *P* <0.001; SMBG: from 8.7 ± 0.7 to 8.3 ± 1.1%, *P* = 0.01)	▸ No significant changes in hypoglycemia ▸ In real-time CGM, reduced caloric intake, weight, BMI, and postprandial glucose level; increased physical activity
ADULTS WITH T1D OR T2D				
Garg et al. (22)	▸ Adults with T1D or T2D on insulin ▸ *n* = 91 ▸ Baseline A1C: 7.6% in control group, 8.0% in CGM group ▸ Parallel arms, 3-day CGM for three consecutive 72-hour periods	Time spent in high, low, and target glucose zones / Dexcom STS sensor	▸ 23% less time in hyperglycemia (≥240 mg/dL) ▸ 26% increase in time in range (81–140 mg/dL) ▸ *P* <0.001 for each comparison	CGM group spent 21% less time in hypoglycemia (<55 mg/dL), *P* <0.0001
New et al. (23)	▸ Adults with T1D or T2D on MDI or CSII ▸ *n* = 160 ▸ Baseline A1C: 8.2% ▸ Parallel arms, 100 days	Time spent outside of target range / Abbott FreeStyle Navigator; 1/3 CGM with no alarm, 1/3 CGM with alarm, 1/3 SMBG	No difference in A1C or time spent outside of target range	Less time in hypoglycemia range in group with alarms compared to SMBG group, *P* = 0.03
Cooke et al. (24)	▸ Adults with T1D or T2D treated with at least twice-daily insulin injections ▸ *n* = 404 ▸ Baseline A1C: 9.1% ▸ Parallel arms, 18 months; GlucoWatch group wore device at least four times in the first 3 months and then as needed; Medtronic group wore device for 72 hours three times during first 3 months and on three more occasions thereafter	A1C reduction / GlucoWatch G2 Biographer vs. Medtronic MiniMed CGMS (blinded)	No significant difference in A1C reduction	No reduction in hypoglycemia; possibly an increase
PREGNANT PATIENTS WITH T1D, T2D, OR GDM				
Feig et al. (25)	▸ Adult women with T1D on MDI or CSII who were pregnant or planning pregnancy ▸ *n* = 325 (215 pregnant, 110 planning pregnancy) ▸ Baseline A1C: 6.83% in CGM group and 6.95% in control group (pregnant) and 7.57% in both CGM and control group (planning pregnancy) ▸ Parallel arms, to 34 weeks in pregnant women; for 24 weeks in those planning pregnancy	A1C reduction / Medtronic Guardian REAL-Time or MiniMed MiniLink	A1C difference –0.19%, *P* = 0.0207 in pregnant women; no A1C difference in women planning pregnancy	▸ Comparable severe hypoglycemia events (18 vs. 21) and time spent hypoglycemic (3 vs. 4%) ▸ Neonatal health outcomes: fewer LGA babies, fewer neonatal ICU stays for >24 hours, and fewer neonatal hypoglycemia events
Secher et al. (26)	▸ Adult women with T1D or T2D who were pregnant ▸ *n* = 154 ▸ Baseline A1C: 6.6% in CGM group, 6.8% in control group ▸ Parallel arms, 6 days of CGM at 8, 12, 21, 27, and 33 weeks vs. routine care	LGA babies / Medtronic Guardian REAL-time CGM with Sof-Sensor	No difference in A1C	▸ No difference in number of LGA babies ▸ No difference in hypoglycemia

Study	Design	Primary Outcome / Type of CGM	A1C Outcomes	Hypoglycemia Change/Other
Wei et al. (27)	▸ Adult women with GDM at 24–28 weeks of pregnancy ▸ *n* = 106 ▸ Baseline A1C: 5.8% in SMBG group, 5.7% in CGM group ▸ Parallel arms; women were asked to wear CGM intermittently early (second trimester) or late (third trimester) or perform SMBG	Prenatal or obstetrical outcomes / Medtronic Gold CGMS	No significant reduction in A1C	▸ No difference in obstetrical outcomes ▸ Some reduction in maternal weight gain

JDRF, Juvenile Diabetes Research Foundation; LGA, large-for-gestational-age; NA, not applicable; NS, non-significant; T1D, type 1 diabetes; T2D, type 2 diabetes.

REFERENCES

1. Beck RW, Riddlesworth T, Ruedy K, et al.; DIAMOND Study Group. Effect of continuous glucose monitoring on glycemic control in adults with type 1 diabetes using insulin injections: The DIAMOND randomized clinical trial. JAMA 2017;317:371-378

2. Riddlesworth T, Price D, Cohen N, Beck RW. Hypoglycemic event frequency and the effect of continuous glucose monitoring in adults with type 1 diabetes using multiple daily insulin injections. Diabetes Ther 2017;8:947–951

3. Lind M, Polonsky W, Hirsch IB, et al. Continuous glucose monitoring vs conventional therapy for glycemic control in adults with type 1 diabetes treated with multiple daily insulin injections: the GOLD randomized clinical trial. JAMA 2017;317:379-387

4. Sequeira PA, Montoya L, Ruelas V, et al. Continuous glucose monitoring pilot in low-income type 1 diabetes patients. Diabetes Technol Ther 2013;15:855–858

5. Tumminia A, Crimi A, Sciacca L, et al. Efficacy of real-time continuous glucose monitoring on glycaemic control and glucose variability in type 1 diabetic patients treated with either insulin pumps or multiple insulin injection therapy: a randomized controlled crossover trial. Diabetes Metab Res Rev 2015;31:61–68

6. Bolinder J, Antuna R, Geelhoed-Duijvestijn P, Kröger J, Weitgasser R. Novel glucose-sensing technology and hypoglycaemia in type 1 diabetes: a multicentre, non-masked, randomised controlled trial. Lancet 2016;388:2254–2263

7. Hermanns N, Schumann B, Kulzer B, Haak T. The impact of continuous glucose monitoring on low interstitial glucose values and low blood glucose values assessed by point-of-care blood glucose meters: results of a crossover trial. J Diabetes Sci Technol 2014;8:516–522

8. van Beers CA, DeVries JH, Smits MM, et al. Continuous glucose monitoring for patients with type 1 diabetes and impaired awareness of hypoglycaemia (IN CONTROL): a randomised, open-label, crossover trial. Lancet Diabetes Endocrinol 2016;4:893–902

9. Battelino T, Conget I, Olsen B, et al.; SWITCH Study Group. The use and efficacy of continuous glucose monitoring in type 1 diabetes treated with insulin pump therapy: a randomised controlled trial. Diabetologia 2012;55:3155–3162

10. Deiss D, Bolinder J, Riveline JP, et al. Improved glycemic control in poorly controlled patients with type 1 diabetes using real-time continuous glucose monitoring. Diabetes Care 2006;29:2730–2732

11. Juvenile Diabetes Research Foundation Continuous Glucose Monitoring Study Group. Continuous glucose monitoring and intensive treatment of type 1 diabetes. N Engl J Med 2008:359;1464–1476

12. O'Connell MA, Donath S, O'Neal DN, et al. Glycemic impact of patient-led use of sensor-guided pump therapy in type 1 diabetes: a randomized controlled trial. Diabetologia 2009;52:1250–1257

13. Juvenile Diabetes Research Foundation Continuous Glucose Monitoring Study Group. The effect of continuous glucose monitoring in well-controlled type 1 diabetes. Diabetes Care 2009;32:1378–1383

14. Battelino T, Phillip M, Bratina N, Nimri R, Oskarsson P, Bolinder J. Effect of continuous glucose monitoring on hypoglycemia in type 1 diabetes. Diabetes Care 2011;34:795–800

15. Heinemann L, Freckmann G, Ehrmann D, et al. Real-time continuous glucose monitoring in adults with type 1 diabetes and impaired hypoglycaemia awareness of severe hypoglycaemia treated with multiple daily insulin injections (HypoDE): a multicentre, randomised controlled trial. Lancet 2018; 391:1367–1377

16. Ludvigsson J, Hanas R. Continuous subcutaneous glucose monitoring improved metabolic control in pediatric patients with type 1 diabetes: a controlled crossover study. Pediatrics 2003;111:933–938

17. Chase HP, Beck R, Tamborlane W, et al. A randomized multicenter trial comparing the GlucoWatch Biographer with standard glucose monitoring in children with type 1 diabetes. Diabetes Care 2005;28:1101–1106

18. Beck RW, Riddlesworth TD, Ruedy K, et al.; DIAMOND Study Group. Continuous glucose monitoring versus usual care in patients with type 2 diabetes receiving multiple daily insulin injections: a randomized trial. Ann Intern Med 2017;167:365–374

19. Ehrhardt NM, Chellappa M, Walker MS, Fonda SJ, Vigersky RA. The effect of real-time continuous glucose monitoring on glycemic control in patients with type 2 diabetes mellitus. J Diabetes Sci Technol 2011;5:668–675

20. Haak T, Hanaire H, Ajjan R, Hermanns N, Riveline JP, Rayman G. Flash glucose-sensing technology as a replacement for blood glucose monitoring for the management of insulin-treated type 2 diabetes: a multicenter, open-label randomized controlled trial. Diabetes Ther 2017;8:55–73

21. Yoo HJ, An HG, Park SY, et al. Use of a real time continuous glucose monitoring system as a motivational device for poorly controlled type 2 diabetes. Diabetes Res Clin Pract 2008;82:73–79

22. Garg S, Zisser H, Schwartz S, et al. Improvements in glycemic excursions with a transcutaneous, real-time continuous glucose sensor: a randomized controlled trial. Diabetes Care 2006;29:44–50

23. New JP, Aijan R, Pfeiffer AF, Freckmann G. Continuous glucose monitoring in people with diabetes: the randomized controlled Glucose Level Awareness in Diabetes Study (GLADIS). Diabet Med 2015;32:609–617

24. Cooke D, Hurel SJ, Casbard A, et al. Randomized controlled trial to assess the impact of continuous glucose monitoring on HbA(1c) in insulin-treated diabetes (MITRE Study). Diabet Med 2009;26:540–547

25. Feig DS, Donovan LE, Corcoy R, et al.; CONCEPTT Collaborative Group. Continuous glucose monitoring in pregnant women with type 1 diabetes (CONCEPTT): a multi-centre international randomised controlled trial. Lancet 2017:390:2347–2359

26. Secher AL, Ringholm L, Andersen HU, Damm P, Mathiesen ER. The effect of real-time continuous glucose monitoring in pregnant women with diabetes: a randomized controlled trial. Diabetes Care 2013;36:1877–1883

27. Wei Q, Sun Z, Yang Y, Yu H, Ding H, Wang S. Effect of a CGMS and SMBG on maternal and neonatal outcomes in gestational diabetes mellitus: a randomized controlled trial. Sci Rep 2016;6:19920