Washington State Health Care Authority

Glucose monitoring – re-review

Topic selection and draft key questions:

Public comment and response

September 11, 2017

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Glucose Monitoring – Re-review

Provided by:

Aggregate Analytics, Inc.

Topic Selection and

Public Comment on Topic Selection and Key Questions

Public Comment & Response

September 11, 2017

Responses to clinical and peer reviewers

Aggregate Analytics is an independent vendor, contracted to produce evidence assessment reports for the Washington Health Technology Assessment (HTA) program. For transparency, all comments received during public comment periods are included in this document and attachments. Comments related to program decisions, process or other matters not pertaining to the evidence report, are acknowledged through inclusion only.

Responses to public comment during topic selection are included **Table 1.**
Comments from:

- Laura Keller, Director, State Government Affairs and Advocacy Washington, American Diabetes Association
- Tomas C. Walker, DNP, APRN, CDE, Senior US Medical Director, Dexcom, Inc.
- Anne L. Carroll, RN, CDE, Dexcom, Inc.

Responses to public comments to the draft key questions are found in **Table 2**.
Comments from:

- Irl B. Hirsch, MD | Medical Director Diabetes Care Center, University of Washington
- Tomas Walker | Senior US Medical Director, Dexcom
- Laura Keller, Director, State Government Affairs and Advocacy Washington, American Diabetes Association

Full text of public comments on topic selection and the draft key questions follow the tables.

Table 1. Responses to comments regarding topic selection

Comment	Response
Laura Keller, Director, State Government Affairs and Advocacy Washington, American Diabetes Association	
Specific comments	
Commenter includes the following recommendations from the Association's Standards of Medical Care in Diabetes—2017: • When used properly, continuous glucose monitoring (CGM) in conjunction with intensive insulin regimens is a useful tool to lower A1C in selected adults age 25 and over with type 1 diabetes • Although the evidence for A1C lowering is less strong in children, teens and younger adults, CGM may be helpful in these groups. Success correlates with adherence to ongoing use of the device • CGM may be a supplemental tool to SMBG in those with hypoglycemia unawareness and/or frequent hypoglycemic episodes Commenter also separately recommends the following: • Anyone on multiple doses of insulin or for whom continuous subcutaneous insulin infusion is being considered, initiated, or utilized with recurrent hypoglycemic episodes or persistently high HbA1c levels be given the option of real-time CGM	Thank you for your comments
Commenter provides general information on CGM and statistics on the economic burden of diabetes.	Thank you for your comments
Tomas C Walker, DNP, APRN, CDE, Senior US Medical Director, Dexcom, Inc	
Specific comments	
Commenter stated that previous systematic reviews and meta-analyses included information from obsolete CGM systems that had low accuracy.	Thank you for your comments
Commenter provided information and RCTs on newly published evidence on real time CGM for both adult and pediatric populations	Thank you for your comments
Commenter gave a summary of guidelines from the American Diabetes Association, from the American Association of Clinical Endocrinologists Consensus Conference, and from the Endocrine Society.	Thank you for your comments
Commenter provided information on the therapeutic implications of the Dexcom G5 Mobile CGM system	Thank you for your comments

Comment	Response
Commenter provided information on the CMS classifications of "therapeutic" and "non-therapeutic" CGM systems and lists the requirements for coverage for therapeutic CGM systems.	
The following are attachments and articles that Dexcom, Inc believes will be useful in the HTAP's review of glucose monitoring: • Formulary dossier of G5™ Mobile CGM system • DIAMOND randomized controlled trial publication: http://jamanetwork.com/journals/jama/fullarticle/2598770 • GOLD randomized controlled trial publication: http://jamanetwork.com/journals/jama/fullarticle/2598771 • IN CONTROL randomized controlled trial publication: http://www.sciencedirect.com/science/article/pii/S2213858716301930 • REPLACE-BG randomized controlled trial publication: http://care.diabetesjournals.org/content/40/4/538	Thank you for your comments. Articles and dossier received. All publications will be considered for inclusion based on the inclusion/exclusion criteria for the evidence report
Anne L. Carroll, RN, CDE, Dexcom, Inc	
Specific comments	
Commenter stated: "Coverage for the Dexcom Continuous Glucose Monitoring System is a marvelous way to help stay off the horrific and tremendously expensive complications which can arise from uncontrolled diabetes. I feel support for patients who have a desire to improve their blood glucose control should be provided by means of a Dexcom device."	Thank you for your comment.

Table 2. Responses to comments on DRAFT Key Questions

2017 Comments on DRAFT Key Questions		Response
Commenter: Irl B. Hirsch, MD | Medical Director Diabetes Care Center, University of Washington		
	Specific comments	
General comments; Utilization Still too low.	I was the Principal Investigator for the "JDRF Sensor Study" publiched in the New England Journal of Medicine. I have been the PI for man other trials including STAR 1 REPLACE,-BG, and we are now starting the WISDM (Wireless Innovation for Seniors with Diabetes Mellitus) trial. The University of Washington is involved with a large type 1 diabetes registry, funded by the Helmsley Charitable Trust. This registry started in 2010, and includes approximately 26,000 patients with type 1 diabetes of all age groups. Here at the University of Washington, at the Diabetes Care Center, we have approximately 600 patients enrolled in this registry. I would like to provide you with some data that is not published. It is related to the results of our yearly questionnaire, which ended in March, 2017. I just want to focus on the CGM data. While CGM is increasing in use, my opinion is that utilization is still too low. At the beginning of 2017, when we look at adults between the ages of 26 and 65 years-old, one-third of patients were using CGM routinely. That is twice the amount that used it between the years of 2010 and 2012. In those years, 7% of all patients used CGM overall, compared to about a quarter of patients now. What is interesting is that even though Medicare did not fund CGM as of the end of last year, 23% of participants in this group still use it. To me, the most interesting part of our data is that for children under the age of six, 45% of participants used continuous glucose monitoring with 28% in the 6 to 13 year-old age group.	Thank you for your comment.
Hypoglycemia Reduction	There are many reasons why CGM is increasing in use. Obviously the technology has improved, and this includes the accuracy of the devices. The data has clearly shown improvements in hemoglobin A1c when the device is used. Here in Washington State, the biggest change that has happened over the last three years is better coverage from the local and regional commercial payers. For the older patients, and this would include the Medicare patients, the main reason for CGM is not hemoglobin A1c improvement, but rather reduction of hypoglycemic exposure. In a different study from the T1D Exchange, we showed that with 40 years duration of type 1 diabetes are spending 99 minutes per day hypoglycemic (defined as blood glucose less than 70mg/dL). That should not be surprising when one sees earlier data from our registry showing that for patients with 40 years duration of diabetes, approximately 20% have a hypoglycemic coma or seizure *per year.* One in five patients, independent of age, with 40 years of diabetes will have an episode of severe hypoglycemia that is life-threatening. We have learned that the risk of severe hypoglycemia is more dependent on duration of diabetes than age, although we see severe hypoglycemia at every age.	Thank you for your comment.

2017 Comments on DRAFT Key Questions		Response
Duration of Diabetes & Risk of Severe Hypoglycemia	We have also shown [severe hypoglycemia] is not at all dependent on hemoglobin A1c level. At all ages we see the same risk of severe hypoglycemia (seizure or coma) with hemoglobin A1c levels near normal or above 10%. We were surprised that severe hypoglycemia was not dependent on hemoglobin A1c but was on duration of diabetes."	Thank you for your comment.
CGM can lead to lower HbA1c levels	The other point to make is that in the T1D Exchange, even though not a randomized trial, we have shown lower hemoglobin A1c levels with the use of CGM. In those under the age of 12 years-old, the difference was 0.9%: 8.7% hemoglobin A1c for those without CGM and 7.8% for those with. For those between the ages of 13 and 26, we saw a similar difference at 9.1% for those without CGM and 8.3% for those with. For Thank you for your comment. all of those individuals above the age 26 without CGM, the hemoglobin A1c was 7.9% compared to 7.4% with.	
Accuracy of Test Strips	All CGM requires appropriate calibration, generally with two fingerstick glucose tests per day. Over the years, we have documented poor accuracy strips which are generally "off-shore" meters, which are FDA approved, but cheaper. In the summer of 2017 the Diabetes Technology Society published their blood glucose test strip surveillance program assessing the accuracy of 18 different blood glucose test strips. Using the latest iso standard they tested each meter with three different studies in over 1000 subjects. The results are extremely concerning, and important to users of CGM since only 6 of the 18 meters passed the current iso accuracy standard. Many of our strips we use are dangerous, especially for those who use insulin, but perhaps even more for those using CGM https://www.diabetestechnology.org/surveillance.shtml	
Endorsement	From the point-of-view of an endocrinologist who actively sees approximately 500 patients with type 1 diabetes, a researcher, and a patient, CGM has been one of the most, if not the most, important advancement in diabetes technology in the past 30 years. The only thing that may come close to this was the introduction of fingerstick glucose testing in the early 1980s. I do not know where we would be without CGM given the large number of patients we are now seeing with more than 40 years of type 1 diabetes since the vast majority of my patients in this demographic uses CGM." "I urge you to consider for this technology to be available to all appropriate patients in Washington State.	Thank you for your comment.
Commenter: Tomas Walker | Senior US Medical Director, Dexcom		
Evidence of Efficacy and Effectiveness	Intensive insulin therapy that lowers average glucose levels has been shown to reduce the risk of the long-term complications of diabetes, but also increases the risk of hypoglycemia.[1-3] Severe hypoglycemia (defined as requiring assistance from another individual to treat[4]) can be debilitating or catastrophic and represents a major barrier to optimal glucose control. Recurrent hypoglycemia contributes to impaired awareness of hypoglycemia (IAH) and increases the	Thank you for your comment. All publications will be considered for inclusion based on the a priori

2017 Comments on DRAFT Key Questions		Response
	risk of severe hypoglycemia (SH), which often requires costly emergency care. Tools are therefore needed that can help patients on insulin therapy lower their average blood glucose to near-normal levels without increasing their risk of hypoglycemia. Real-time CGM provides as many as 288 measurements per day that can provide reassurance or alert patients to the need for interventions. For patients with IAH, the alarm function of CGM devices may be their only warning of impending hypoglycemia, which is of particular importance when driving or sleeping. By contrast, conventional self-monitoring of blood glucose (SMBG) provides intermittent and limited information about blood glucose concentrations, and may miss potential problems even if diligently performed. In many patients with diabetes, CGM is therefore medically necessary to detect trends and patterns in glucose levels over time, optimize glycemic control, and reduce the frequency and severity of hypoglycemic and hyperglycemic events.	inclusion/exclusion criteria for the evidence report
Evidence in Adults with T1DM: Diamond, Gold, Comisair, and In Control studies	The first phase of the Diamond study[5] established that use of CGM, compared to use of SMBG therapy, was associated with a greater mean HbA1c reduction at 24 weeks, and with less time in hypoglycemia. Subjects in the CGM group also experienced significant reductions in diabetes distress and fear of hypoglycemia, and significant improvements in hypoglycemia confidence and well-being compared with conventionally-monitored patients.[7] An optional extension phase offered to people who had used CGM during the first phase studied the impact of insulin delivery method (MDI versus continuous subcutaneous insulin infusion or CSII), and found that transitioning to CSII therapy offered improved time in range, but no corresponding improvement in HbA1c and an increase in biochemical hypoglycemia.[8] The Gold study[6] had a multicenter, randomized, open-label, crossover design and evaluated the impact of CGM on glycemic outcomes, well-being, diabetes distress, and hypoglycemic fear and confidence. After 26 weeks, CGM use resulted in a mean HbA1c level that was 0.43 percentage points less than in the group receiving conventional blood glucose monitoring; patients treated with CGM also reported significantly less fear of hypoglycemia and significantly improved well-being compared to conventional SMBG. The Comisair[9] study followed 65 subjects with T1D for up to 1 year and found that CGM used with MDI was as effective as CGM used with CSII therapy with respect to HbA1c reduction. Both insulin delivery modalities combined with CGM also provided significant and comparable decreases in time spent in hypoglycemia compared to insulin therapy with conventional SMBG. The In Control study[10] was a randomized, open-label, crossover study conducted in adults with poorly controlled T1D and IAH. The study concluded that CGM increased the time spent in normoglycemia and	

2017 Comments on DRAFT Key Questions		Response
	reduced the incidence of severe hypoglycemia by 59% compared with conventional SMBG.	
Evidence in Adults with T2DM	The Diamond study[5] included an independently-powered arm that investigated the effects of CGM in patients using MDI therapy to manage their type 2 diabetes (T2D). The results, published last week in Annals of Internal Medicine[11], demonstrated that after 24 weeks, participants using CGM lowered their HbA1c levels by an average of 0.8 percentage points from baseline. Compared to the Control Group, the CGM Group also spent less time in hyperglycemia and more time spent in the target range. The CGM Group increased time in range by 1.3 hours compared to baseline, and 0.6 hours compared to the Control Group. The HbA1c reductions did not depend on age, educational attainment, or numeracy skills, and adherence to the CGM therapy was remarkably high, with 93% of participants using CGM six or seven days per week at the end of the study. Participants also reported a high level of satisfaction and a relatively low level of perceived hassles.	
Children with T1D	The T1D Exchange Clinic Registry follows over 26,000 patients with T1D, almost 15,000 of whom are younger than 18. Recent Registry publications have confirmed that CGM use is increasing rapidly, especially among very young children. The mean HbA1c values among CGM users and non-users in the Registry were recently reported as 8.1% and 8.9%, respectively.[12] CGM use in every age cohort examined was associated with lower HbA1c values, as shown in the Figure.[13] Separate data from two sensor accuracy studies in youth ages 2-17 years[14] showed that use of CGM had the potential to increase glucose time in range and improve glycemic outcomes.	
Safety	On July 21, 2016, the Clinical Chemistry and Clinical Toxicology Devices Panel of the U.S. Food and Drug Administration (FDA) agreed that there is reasonable assurance Dexcom G5 is safe, effective, and the benefits outweigh the risks with the proposed indications for use. The FDA followed expert recommendation and approved the Dexcom G5 as a replacement for fingerstick glucose testing for diabetes treatment decisions,[15] positioning the device as the new standard of care in glucose monitoring for diabetes management.	
Efficacy and Safety in Sub-populations	In 2017, the REPLACE-BG study[16] of adults with T1D tested whether using CGM data as the basis for diabetes-related treatment decisions, independent of confirmatory SMBG values (“nonadjunctive use”), was as safe and effective as using CGM data with SMBG confirmations (“adjunctive use”). The study confirmed that nonadjunctive use of CGM data was not inferior, in terms of safety and efficacy, to using it as an adjunct to SMBG data. Subjects randomized to the CGM-only group were still required to use SMBG values to calibrate their CGM devices, but performed significantly fewer SMBG tests per day than those in the CGM+SMBG group.	

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	The Dexcom G5 Mobile CGM System has not been evaluated or approved for pregnant women, persons on dialysis, or in critically ill patients. We know of no differential safety issues between sub-populations.	
Cost Effectiveness	A recent publication in the Journal of Medical Economics … was done from a Canadian perspective, and the incremental cost effectiveness ratio (ICER) for Dexcom G5 CGM vs. traditional SMBG was $33,789 Canadian dollar/quality adjusted life year (QALY).[18] Additional studies have been done on the cost effectiveness of CGM, but have included the cost of an insulin pump in the analysis.[19] The range of ICERs are from £12,223 to $98,679 per QALY. The difference in the ICER has been due to the inclusion of sensor augmented pumps, specific target populations and rapidly evolving technology which confounds the results.	
Hospitalizations	The cost of CGM systems must be balanced against the fact that it helps patients avoid costly and potentially catastrophic episodes of severe hypoglycemia. In a randomized clinical trial, CGM use was associated with a 59% reduction in severe hypoglycemia (SH).[10] Of the approximately 1,903,717 people in Washington enrolled in Medicaid, 34,756 have insulin-treated diabetes and, of these, about 4464 have IAH. Reducing the incidence of SH via CGM use in this population of people with IAH has the potential to impact the current State expenditures as follows: 5% of SH episodes among patients with T1D and 13% of SH episodes among patients with insulin requiring T2D require hospitalization[4] and the average cost of a hospitalization for SH is $12,787.[20] Applying a budget impact model, the cost associated with hospitalizations for SH without CGM use is $27,210,736/year; with CGM use is $11,163,051/year.	
ER Visits	10% of SH episodes among patients with T1D and 21% of SH episodes among patients with T2D require an ER visit,[4] and the average cost of an ER visit for SH is $777.[20] Applying a budget impact model, the cost associated with ER visits for SH without CGM use is $2,731,068/year; with CGM use is $1,120,434/year.	
Ambulance Transport	31% of SH episodes among patients with T1D and 23% of SH episodes among patients with T2D require ambulance transport,[4] and the average cost of an ambulance transport for SH is $1,704.[21] Applying a budget impact model, the cost associated with ambulance transport without CGM use is $9,087,717/year; with CGM use is $3,724,944/year.\	
Direct Costs/Net Costs	The average cost per patient for personal CGM is $2,800/year and the total cost for all insulin-requiring patients with IAH is $12,499,200/year. Applying a budget impact model, it was found that the net savings of providing personal CGM to all insulin-requiring Medicaid beneficiaries with IAH in Washington is $10,521,551/year. The results of the budget impact model show that providing Dexcom CGM systems to patients on intensive insulin therapy who are at high risk for SH may result in cost savings for	

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	Washington Medicaid. Because this model neglects the potential cost savings that would be accrued by reducing HbA1c and subsequent risk of long-term diabetes complications, the estimated cost savings are conservative.	
Summary	CGM is a significant advancement in diabetes care with demonstrated clinical benefits. As such, we urge the HTCC to examine the current evidence and consider CGM coverage for patients on intensive insulin therapy who are not at their glycemic goals or are experiencing problematic hypoglycemia. At your request, I am happy to share the referenced material, answer questions, or provide additional detail. Thank you for the opportunity to provide comments.	
Citations	1. The Diabetes Control and Complications Trial Research Group. Epidemiology of severehypoglycemia in the diabetes control and complications trial. Am J Med. 1991;90(4):450-459.1. 2. The Diabetes Control and Complications Trial Research Group. The effect of intensive treatment of diabetes on the development and progression of long-term complications in insulin-dependent diabetes mellitus. N Engl J Med. 1993;329(14):977-986. 3. Zammitt NN, Frier BM. Hypoglycemia in type 2 diabetes: pathophysiology, frequency, andeffects of different treatment modalities. Diabetes Care. 2005;28(12):2948-2961. 4. Heller SR, Frier BM, Herslov ML, Gundgaard J, Gough SC. Severe hypoglycaemia in adults with insulin-treated diabetes: impact on healthcare resources. Diabet Med. 2016;33(4):471-477. 5. Beck RW, Riddlesworth T, Ruedy K, et al. Effect of continuous glucose monitoring on glycemic control in adults with type 1 diabetes using insulin injections: The DIAMOND randomized clinical trial. JAMA. 2017;317(4):371-378. 6. 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(4):379-38 7. Polonsky WH, Hessler D, Ruedy KJ, Beck RW, Group DS. The impact of continuous glucose monitoring on markers of quality of life in adults with type 1 diabetes: Further findings from the DIAMOND randomized clinical trial. Diabetes Care. 2017;40(6):736-741. 8. Beck RW, Riddlesworth TD, Ruedy KJ, et al. Effect of initiating use of an insulin pump in adults with type 1 diabetes using multiple daily insulin injections and continuous glucose monitoring (DIAMOND): a multicentre, randomised controlled trial. Lancet Diabetes Endocrinol. 2017. 9. Soupal J, Petruzelkova L, Flekac M, et al. Comparison of Different Treatment Modalities for Type 1 Diabetes, Including Sensor-Augmented Insulin Regimens, in 52 Weeks of Follow-Up: A COMISAIR Study. Diabetes Technol Ther. 2016;18(9):532-538. 10. van Beers CA, DeVries JH, Kleijer SJ, 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(11):893-902 11. Beck RW, Riddlesworth TD, Ruedy K, et al. Continuous Glucose	

2017 Comments on DRAFT Key Questions		Response
	Monitoring Versus Usual Care in Patients With Type 2 Diabetes Receiving Multiple Daily Insulin Injections: A Randomized Trial. Ann Intern Med. 2017 Aug 22. doi: 10.7326/M16-2855. 12. Miller K, Foster N, DeSalvo D, et al. Continuous glucose monitoring (CGM) use in type 1 diabetes: An update from the T1D exchange clinic registry. Pediatric Diabetes. 2016;17:49. 13. Miller KM, Foster NC, Beck RW, et al. Current state of type 1 diabetes treatment in the U.S. updated data from the T1D Exchange clinic registry. Diabetes Care. 2015;38(6):971-978. 14. Laffel L. Improved accuracy of continuous glucose monitoring systems in pediatric patients with diabetes mellitus: Results from two studies. Diabetes Technol Ther. 2016;18 Suppl 2:S223-233 15. FDA expands indication for continuous glucose monitoring system, first to replace fingerstick testing for diabetes treatment decisions [press release]. U.S. Food and Drug Administration 2016. Available at: http://www.fda.gov/NewsEvents/Newsroom/PressAnnouncements/ucm534056.htm. Accessed August 25, 2017. 16. Aleppo G, Ruedy KJ, Riddlesworth TD, et al. REPLACE-BG: A randomized trial comparing continuous glucose monitoring with and without routine blood glucose monitoring in adults with wellcontrolled type 1 diabetes. Diabetes Care. 2017;40(4):538-545. 17. AMCP Formulary Dossier: Dexcom G5 Mobile Continuous Glucose Monitoring System Economic Value and Modeling Report. 2017:146-152. Available upon request from Dexcom. 18. Chaugule S, Graham C. Cost-effectiveness of G5 Mobile continuous glucose monitoring device compared to self-monitoring of blood glucose alone for people with Type 1 diabetes from the Canadian societal perspecitve. Jrnl Med Economics. 2017 https://doi.org/10.1080/13696998.2017.1360312 19. Graham C. Continuous Glucose Monitoring and Global Reimbursement: An Update. Diabetes Technology & Therapeutics. 2017 (19): S60-S66 20. Curkendall, S.M., et al., Incidence and cost of hypoglycemia among patients with type 2 diabetes in the United States: Analysis of a health insurance database. Journal of Clinical Outcomes Management, 2011. 18(10): p. 455.462 21. Centers for Medicare & Medicaid Services. Ambulance Fee Schedule Public Use Files. [cited 2017 February 14]; Available from: https://www.cms.gov/Medicare/Medicare-Fee-for-Service-Payment/AmbulanceFeeSchedule/afspuf.html	
Commenter: Laura Keller, Director, State Government Affairs & Advocacy Washington, American Diabetes Association		
General	I am writing on behalf of the American Diabetes Association in support of increasing coverage for CGM for beneficiaries with diabetes in Washington.	Thank you for your comments.
ADA Standards of Medical Care in Diabetes -2017	1. When used properly, continuous glucose monitoring (CGM) in conjunction with intensive insulin regimens is a useful tool to lower A1C in selected adults age 25 and over with type 1 diabetes. 2. Although the evidence for A1C lowering is less strong in children, teens and younger adults, CGM may be helpful in these groups. Success correlates with adherence to ongoing use of the device.	All publications will be considered for inclusion based on the a priori inclusion/exclusio

2017 Comments on DRAFT Key Questions		Response
	3. CGM may be a supplemental tool to SMBG in those with hypoglycemia unawareness and/or frequent hypoglycemic episodes.	n criteria for the evidence report
CGM Recommendation	Research has shown benefits for CGM in individuals with type 1 diabetes on intensive insulin therapy, through either an insulin pump or multiple daily injections. As such, we recommend anyone on multiple doses of insulin or for whom continuous subcutaneous insulin infusion is being considered, initiated, or utilized with recurrent hypoglycemic episodes or persistently high HbA1c levels be given the option of real-time CGM.	
Cost Effectiveness	There is evidence to support the cost-effectiveness of continuous glucose monitoring. A study has shown that those who use insulin experience disproportionately high rates of emergency room use, instances of hospitalization, and mortality. i The Centers for Disease Control and Prevention report 282,000 emergency room visits for adults experiencing hypoglycemia in 2011 alone. ii Furthermore a study published in the American Journal of Managed Care found "the mean costs for hypoglycemia visits were $17,564 for an inpatient admission, $1,387 for an [emergency department] visit, and $394 for an outpatient visit." iii CGM can reduce short-term costs by reducing severe hypoglycemic events in high-risk populations.	
Conclusion	Diabetes is a complex disease to manage and can lead to short and long term complications. The goal of diabetes care is to avoid the devastating and costly complications of the disease. The economic cost of diagnosed diabetes in the U.S. is $245 billion per year. Much of the economic burden of diabetes is related to its complications including blindness, amputation, kidney failure, heart attack, and stroke. Yet, we have made major strides in effectively managing diabetes and reducing the risk for these devastating – and costly – complications through necessary medical care, medications and other tools, patient self-management, education, and support. We appreciate the opportunity to provide comments regarding CGM. Should you have any questions or if the Association can be of any assistance, please feel free to contact me at 1-800-676-4065 x 7207 or lkeller@diabetes.org. <u>Citations:</u> 1. Virnig BA, Shippee ND, O'Donnell B, et al. Use of and access to health care by Medicare beneficiaries with diabetes: impact of diabetes type and insulin use, 2007-2011: Data Points # 18. 2014 Jan 29. In: Data Points Publication Series [Internet]. Rockville (MD): Agency for Healthcare Research and Quality (US); 2011-. from: http://www.ncbi.nlm.nih.gov/books/NBK202115/. 2. Virnig BA, Shippee ND, O'Donnell B, et al. Use of and access to health care by Medicare beneficiaries with diabetes: impact of diabetes type and insulin use, 2007-2011: Data Points # 18. 2014 Jan 29. In: Data Points Publication Series [Internet]. Rockville (MD): Agency for Healthcare Research and Quality (US); 2011-. from:	

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CSII), and found that transitioning to CSII therapy offered improved time in range, but no corresponding improvement in HbA1c and an increase in biochemical hypoglycemia.[8]

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The Comisair study[9] followed 65 subjects with T1D for up to 1 year and found that CGM used with MDI was as effective as CGM used with CSII therapy with respect to HbA1c reduction. Both insulin delivery modalities combined with CGM also provided significant and comparable decreases in time spent in hypoglycemia compared to insulin therapy with conventional SMBG.

The In Control study[10] was a randomized, open-label, crossover study conducted in adults with poorly-controlled T1D and IAH. The study concluded that CGM increased the time spent in normoglycemia and reduced the incidence of severe hypoglycemia by 59% compared with conventional SMBG.

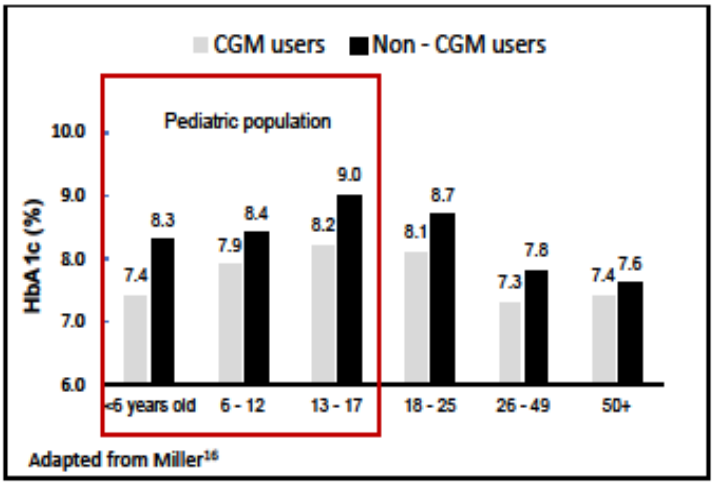
Evidence in Adults With Type 2 Diabetes

The Diamond study included an independently-powered arm that investigated the effects of CGM in patients using MDI therapy to manage their type 2 diabetes (T2D). The results, published last week in *Annals of Internal Medicine*,[11] demonstrated that after 24 weeks, participants using CGM lowered their HbA1c levels by an average of 0.8 percentage points from baseline. Compared to the Control Group, the CGM Group also spent less time in hyperglycemia and more time spent in the target range. The CGM Group increased time in range by 1.3 hours compared to baseline, and 0.6 hours compared to the Control Group. The HbA1c reductions did not depend on age, educational attainment, or numeracy skills, and adherence to the CGM therapy was remarkably high, with 93% of participants using CGM six or seven days per week at the end of the study. Participants also reported a high level of satisfaction and a relatively low level of perceived hassles.

Evidence in Children and Adolescents With T1D

The T1D Exchange Clinic Registry follows over 26,000 patients with T1D, almost 15,000 of whom are younger than 18. Recent Registry publications have confirmed that CGM use is increasing rapidly, especially among very young children. The mean HbA1c values among CGM users and non-users in the Registry were recently reported as 8.1% and 8.9%, respectively.[12] CGM use in every age cohort examined was associated with lower HbA1c values, as shown in the Figure.[13] Separate data from two sensor accuracy studies in youth ages 2-17 years[14] showed that use of CGM had the potential to increase glucose time in range and improve glycemic outcomes.

Figure: HbA1c values for CGM vs. non-CGM users in T1D Exchange Registry



Key question: What is the evidence of the safety of CGM?

On July 21, 2016, the Clinical Chemistry and Clinical Toxicology Devices Panel of the U.S. Food and Drug Administration (FDA) agreed that there is reasonable assurance Dexcom G5 is safe, effective, and the benefits outweigh the risks with the proposed indications for use. The FDA followed expert recommendation and approved the Dexcom G5 as a replacement for fingerstick glucose testing for diabetes treatment decisions,[15] positioning the device as the new standard of care in glucose monitoring for diabetes management.

In 2017, the REPLACE-BG study[16] of adults with T1D tested whether using CGM data as the basis for diabetes-related treatment decisions, independent of confirmatory SMBG values ("nonadjunctive use"), was as safe and effective as using CGM data with SMBG confirmations ("adjunctive use"). The study confirmed that nonadjunctive use of CGM data was not inferior, in terms of safety and efficacy, to using it as an adjunct to SMBG data. Subjects randomized to the CGM-only group were still required to use SMBG values to calibrate their CGM devices, but performed significantly fewer SMBG tests per day than those in the CGM+SMBG group.

Key question: What is the evidence that glucose monitoring has differential efficacy or safety issues in sub-populations?

For evidence of efficacy in type 1, type 2, pediatric and adolescent sub-populations, please see above section **What is the evidence of efficacy and effectiveness of CGM?** The Dexcom G5 Mobile CGM System has not been evaluated or approved for pregnant women, persons on dialysis, or in critically ill patients. We know of no differential safety issues between sub-populations. Please see above section **What is the evidence of the safety of CGM?** for overall evidence of safety.

Key question: What is the evidence of cost-effectiveness of CGM?[17]

Enclosed with this response is a recent publication in the Journal of Medical Economics, examining the cost effectiveness of stand alone CGM systems. The analysis was done from a Canadian perspective, and the incremental cost effectiveness ratio (ICER) for Dexcom G5 CGM vs. traditional SMBG was $33,789 Canadian dollar/quality adjusted life year (QALY)[18]. Additional studies have been done on the cost effectiveness of CGM, but have included the cost of an insulin pump in the analysis[19]. The range of ICERs are from £12,223 to $98,679 per QALY. The difference in the ICER has been due to the inclusion of sensor augmented pumps, specific target populations and rapidly evolving technology which confounds the results.

The cost of CGM systems must be balanced against the fact that it helps patients avoid costly and potentially catastrophic episodes of severe hypoglycemia. In a randomized clinical trial, CGM use was associated with a 59% reduction in severe hypoglycemia (SH).[10] Of the approximately 1,903,717 people in Washington enrolled in Medicaid, 34,756 have insulin-treated diabetes and, of these, about 4464 have IAH. Reducing the incidence of SH via CGM use in this population of people with IAH has the potential to impact the current State expenditures as follows:

Total cost of hospitalizations for SH: 5% of SH episodes among patients with T1D and 13% of SH episodes among patients with insulin requiring T2D require hospitalization[4] and the average cost of a hospitalization for SH is $12,787.[20] Applying a budget impact model, the cost associated with hospitalizations for SH without CGM use is $27,210,736/year; with CGM use is $11,163,051/year.

Total cost of ER visits for SH: 10% of SH episodes among patients with T1D and 21% of SH episodes among patients with T2D require an ER visit,[4] and the average cost of an ER visit for SH is $777.[20] Applying a budget impact model, the cost associated with ER visits for SH without CGM use is $2,731,068/year; with CGM use is $1,120,434/year.

Total cost of ambulance transports for SH: 31% of SH episodes among patients with T1D and 23% of SH episodes among patients with T2D require ambulance transport,[4] and the average cost of an ambulance transport for SH is $1,704.[21] Applying a budget impact model, the cost associated with ambulance transport without CGM use is $9,087,717/year; with CGM use is $3,724,944/year.

Direct costs of CGM: The average cost per patient for personal CGM is $2,800/year and the total cost for all insulin-requiring patients with IAH is $12,499,200/year.

Net cost impact of CGM adoption: Applying a budget impact model, it was found that the net savings of providing personal CGM to all insulin-requiring Medicaid beneficiaries with IAH in Washington is $10,521,551/year.

The results of the budget impact model show that providing Dexcom CGM systems to patients on intensive insulin therapy who are at high risk for SH may result in cost savings for Washington Medicaid. Because this model neglects the potential cost savings that would be accrued by reducing HbA1c and subsequent risk of long-term diabetes complications, the estimated cost savings are conservative.

In summary, CGM is a significant advancement in diabetes care with demonstrated clinical benefits. As such, we urge the HTCC to examine the current evidence and consider CGM coverage for patients on intensive insulin therapy who are not at their glycemic goals or are experiencing problematic

hypoglycemia. At your request, I am happy to share the referenced material, answer questions, or provide additional detail. Thank you for the opportunity to provide comments.

Respectfully,

Tomas C. Walker, DNP, APRN, CDE
Senior US Medical Director
Dexcom, Inc
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glucose level is less than 70 mg/dL, or for that matter, less than 50 mg/dL. I urge you to consider for this technology to be available to all appropriate patients in Washington State.

I may be reached at ihirsch@uw.edu or 206-598-2482 should there be any questions.

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COMMENTER #3: Laura Keller

American Diabetes Association.

August 28, 2017

Washington Health Care Authority
Cherry Street Plaza
626 8th Avenue SE
Olympia, WA, 98501

Re: Comments on Key Questions Continuous Glucose Monitoring (Real-time) Equipment and Supplies

I am writing on behalf of the American Diabetes Association in support of increasing coverage for continuous glucose monitors (CGM) for beneficiaries with diabetes in Washington. Per the Association's Standards of Medical Care in Diabetes – 2017:

- When used properly, continuous glucose monitoring (CGM) in conjunction with intensive insulin regimens is a useful tool to lower A1C in selected adults age 25 and over with type 1 diabetes.
- Although the evidence for A1C lowering is less strong in children, teens and younger adults, CGM may be helpful in these groups. Success correlates with adherence to ongoing use of the device.
- CGM may be a supplemental tool to SMBG in those with hypoglycemia unawareness and/or frequent hypoglycemic episodes.

Research has shown benefits for CGM in individuals with type 1 diabetes on intensive insulin therapy, through either an insulin pump or multiple daily injections. As such, we recommend anyone on multiple doses of insulin or for whom continuous subcutaneous insulin infusion is being considered, initiated, or utilized with recurrent hypoglycemic episodes or persistently high HbA1c levels be given the option of real-time CGM.

Individuals with diabetes who use insulin must diligently monitor their blood glucose in order to give themselves the best chance of avoiding long and short term complications. Long term complications caused by high blood glucose levels include blindness, amputation, heart disease, stroke, and kidney failure. But in the short term, both high and low blood glucose levels are dangerous. CGMs monitor blood glucose frequently and alert individuals with an alarm when their blood glucose reaches dangerously high or low levels in a way that traditional, finger stick measurement cannot because it only shows a snapshot of blood glucose at that moment, but does not warn of rapidly rising or falling levels.

There is evidence to support the cost-effectiveness of continuous glucose monitoring. A study has shown that those who use insulin experience disproportionately high rates of emergency room use, instances of hospitalization, and mortality.[i] The Centers for Disease Control and Prevention report 282,000 emergency room visits for adults experiencing hypoglycemia in 2011 alone.[ii] Furthermore a study published in the *American Journal of Managed Care* found "the mean costs for hypoglycemia visits were $17,564 for an inpatient admission, $1,387 for an [emergency

department] visit, and $394 for an outpatient visit." [iii] CGM can reduce short-term costs by reducing severe hypoglycemic events in high-risk populations. [iv]

Conclusion

Diabetes is a complex disease to manage and can lead to short and long term complications. The goal of diabetes care is to avoid the devastating and costly complications of the disease. The economic cost of diagnosed diabetes in the U.S. is $245 billion per year. Much of the economic burden of diabetes is related to its complications including blindness, amputation, kidney failure, heart attack, and stroke. Yet, we have made major strides in effectively managing diabetes and reducing the risk for these devastating – and costly – complications through necessary medical care, medications and other tools, patient self-management, education, and support.

We appreciate the opportunity to provide comments regarding CGM. Should you have any questions or if the Association can be of any assistance, please feel free to contact me at 1-800-676-4065 x 7207 or lkeller@diabetes.org.

Sincerely,

[redacted]

Laura Keller
Director, State Government Affairs & Advocacy Washington
American Diabetes Association

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From: Carroll, Anne L
To: HCA ST Health Tech Assessment Prog
Subject: Dexcom CGM
Date: Monday, June 26, 2017 12:54:36 PM

Coverage for the Dexcom Continuous Glucose Monitoring System is a marvelous way to help stay off the horrific and tremendously expensive complications which can arise from uncontrolled diabetes. I feel support for patients who have a desire to improve their blood glucose control should be provided by means of a Dexcom device. Anne Carroll, RN, CDE

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June 27, 2017

Health Technology Clinical Committee (HTCC)
Washington State Health Care Authority
Cherry Street Plaza
626 8th Avenue SE
Olympia, WA 98501

Dear members of the HTCC,

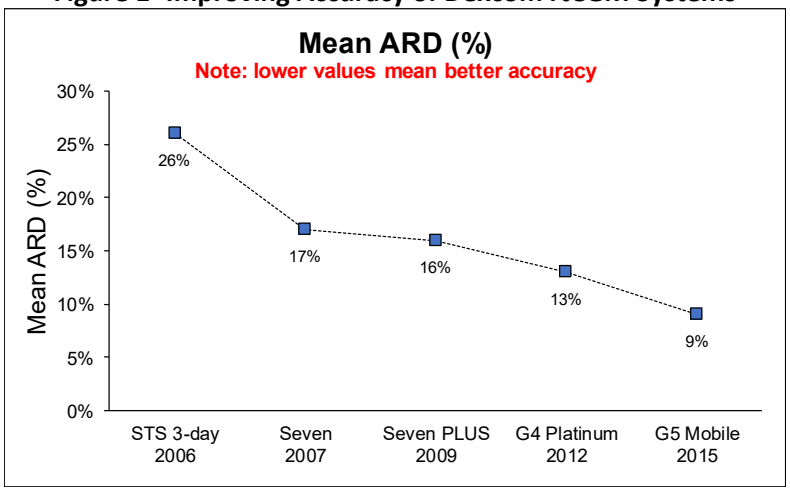
On behalf of Dexcom, Inc., I'm writing to express my appreciation for selecting continuous glucose monitoring (CGM) for re-review and the opportunity to provide comment. With this letter, I'd like to address the use of obsolete CGM technology in systematic reviews and meta-analyses (SRMAs), provide new clinical evidence, and share important information regarding Medicare coverage for *Therapeutic CGM*.

Obsolete Technology in Meta-Analyses

The CGM Rapid Review Report (April 2016) was based upon SRMAs that include obsolete and discontinued CGM systems with relatively poor accuracy, as measured by the mean absolute relative difference (MARD) between CGM and contemporaneous blood glucose values measured by a laboratory standard. Several referenced sources, including Hayes,[1] base their conclusions on early systems with MARD values in the 16-26% range (Figure 1), which are significantly worse than the 9% MARD of the Dexcom G5 Mobile System.

In general, findings from SRMAs for medical devices can be limited as technological advancements preclude differentiation of past and current devices.[2] Findings from older SRMAs may significantly underestimate the potential benefits of the latest devices.

Figure 1- Improving Accuracy of Dexcom rtCGM Systems



New Published Evidence - Adults

Many randomized controlled trials (RCTs) have studied the benefits of personal, real-time CGM (rtCGM) in heterogeneous populations including subjects with either type 1 or type 2 diabetes using continuous subcutaneous insulin infusion (CSII) or multiple daily injection (MDI) therapy, adult and pediatric age groups, those with high or low A1C values, and those with or without problematic hypoglycemia. Among these studies are the Juvenile Diabetes Research Foundation CGM trial[3,4], Battelino et al.[5], and Vigersky et al.[6] These studies all demonstrate significant clinical benefit from CGM, including reductions in A1C and/or hypoglycemia improvements.

Several recent studies have added to the already compelling data establishing the benefit of CGM in patients with poorly-controlled type 1 diabetes. The DIAMOND prospective, randomized, controlled trial[7] examined the effects of CGM use in patients (n=158) with A1C values ranging from 7.5% to 9.9%, in 24 sites across the United States. Subjects randomized to CGM used the technology and demonstrated consistent and sustained use at 6 months (93% used it 6 or 7 days/week). Those using CGM experienced a mean A1C decrease of 1 percentage point from baseline at week 24, compared to a 0.4 percentage point reduction in the control group. The A1C reductions were accompanied by reductions in hypoglycemia. Similar benefits were observed across all subsets, including people with lower education levels, lower numeracy skills, with higher A1C levels, and at older ages. Notably, the glycemic benefits were slightly better for subjects treated at community practices than at academic endocrinology centers. A subset of patients participated in a separate 28-week continuation phase study, which demonstrated sustained A1C benefits and near-constant use of CGM, with 96% of subjects using the system 6 or 7 days per week during the final month.[8]

Results of a second prospective, randomized, controlled trial conducted in clinical sites across Sweden (the GOLD study) were published in the same issue of JAMA,[9] and again showed significant associations between use of CGM use, lower A1C values, and reduced hypoglycemia in people with sub optimally-controlled type 1 diabetes.

Of recent note and significant interest, there are now data supporting the utility of CGM in patients with type 2 diabetes using MDI. The DIAMOND study had a separate, independently powered cohort of 158 such patients. As a group, these subjects used CGM 6.7±0.9 days/week, were highly satisfied with the technology, and significantly reduced their A1C values.[10]

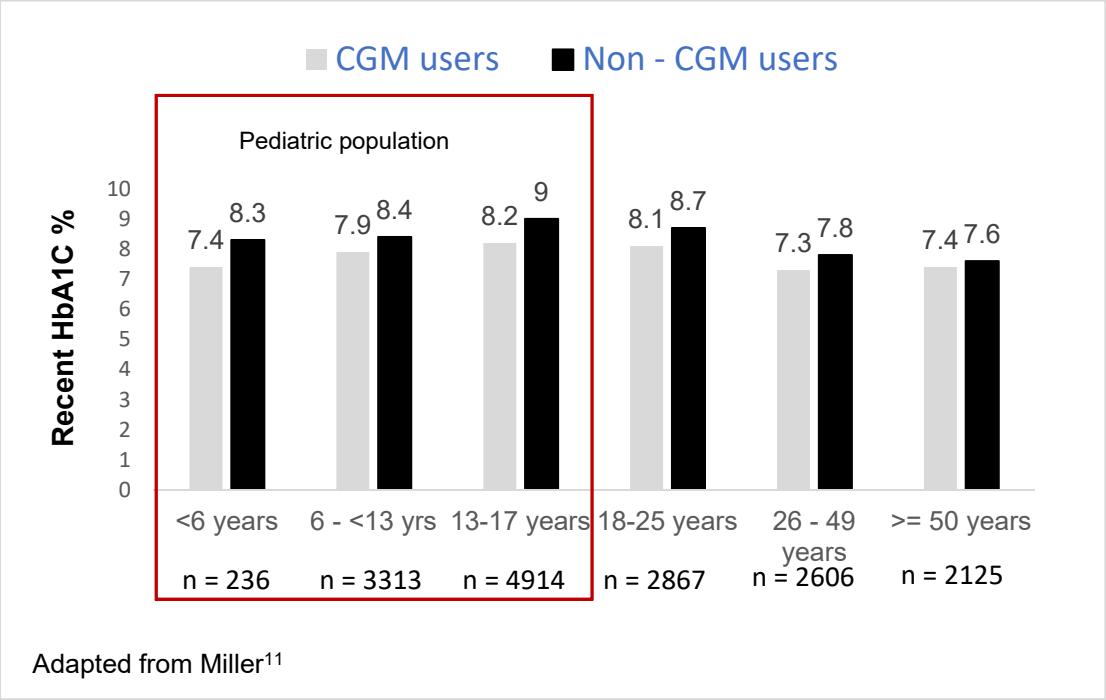
In summary, clinical outcomes from studies such as DIAMOND and GOLD that use up-to-date CGM systems show clinically meaningful and statistically significant benefits for patients with either type 1 or type 2 diabetes. These favorable results are likely to extend to larger populations with access to tools and technologies in the rapidly-evolving category of *Therapeutic CGM*.

New Published Evidence – Pediatrics

The T1D exchange registry was established 8 years ago with the intent to study how diabetes technology translates into better diabetes control in patients (in particular children) with type 1 diabetes in the U.S. Today there are 76 clinical sites geographically distributed with over 25,000 individuals participating (14,593 patients under 18 years of age).[11]

In the T1D exchange registry, on average, participants wearing rtCGM have lower A1C values than those not wearing rtCGM. The largest difference in A1C between rtCGM and non-rtCGM users was found in registry participants less than 18 years old.[11] As shown below, this real-world evidence shows that children wearing rtCGM have lower A1C values than those not wearing rtCGM (Figure 2).

Figure 2: HbA1C values for rtCGM vs. non-rtCGM users in T1D Exchange Registry in the US



This finding is consistent with a separate study[12] study conducted in youth (ages 2-17 yrs.) that showed that the use of rtCGM with improved accuracy and performance had the potential to increase glucose time in range and improve glycemic outcomes.

Studies show adherence to rtCGM at least 60% of the time increases the effectiveness in children and adults. Again, recent publications which use current rtCGM devices have significantly greater accuracy and usability, and hence compliance, than studies from even 6 years ago. The recent DIAMOND[7] and GOLD[9] studies in adults found that the use of rtCGM more than 70% of the time was associated with significant reduction in HbA1C levels. In children with type 1 diabetes, consistent and durable rtCGM use was associated with treatment adherence and improved glycemic control without increasing psychosocial distress.[13]

Professional Society Recommendations

The rapid acceptance of rtCGM is evidenced by an American Diabetes Association position statement[14] asserting that CGM, used in conjunction with intensive insulin therapy, is a useful tool to lower A1C in adults (ages ≥ 25 years) with type 1 diabetes and can be helpful in lowering A1C in children, teens and younger adults. The guidelines recognize that success correlates with adherence to ongoing use of the device.

The American Association of Clinical Endocrinologists[15] Consensus Conference participants unanimously agreed that rtCGM should be available to all insulin-using patients regardless of diabetes type. The AACE glucose monitoring consensus statement[16] recommended personal CGM for patients with type 1 diabetes and with history of severe hypoglycemia, hypoglycemia unawareness and to assist in the correction of hyperglycemia in patients not at goal. CGM usage has improved clinical diabetes outcomes by reducing hypoglycemia and should be used in all patients who have severe hypoglycemia. The current consensus of experts calls for wider use of CGM, recognizing its potential to significantly improve the care of persons living with diabetes.

The Endocrine Society[17] recommends CGM for adult patients with type 1 diabetes whose A1C is above 7% who are able to wear the devices on a daily basis, or in patients who experience significant hypoglycemia.

Therapeutic CGM

Our fifth-generation product, the G5 Mobile system, accurately tracks and reports on glucose values and trends, and provides timely hyperglycemia and hypoglycemia alerts.[18,19] Dexcom CGM technology allows patients to make better-informed decisions for their diabetes management based on their current glucose level and glucose trend. Because of significant improvements in device accuracy and reliability, the FDA recently extended the labeled indication for the G5 Mobile system, allowing Dexcom G5 CGM data to be used for routine diabetes management decisions in lieu of glucose values from finger-sticks using blood glucose meters.[20] This non-adjunctive use indication contributed to a recent CMS decision that established a new category of durable medical equipment, *Therapeutic CGM*.

Medicare

On January 12, 2017, CMS announced the benefit category of non-adjunctive CGMs.[21] The ruling classified CGMs into "therapeutic" and "non-therapeutic" systems, with the former defined as those that can be used to replace fingerstick blood glucose testing for diabetes treatment decisions. Such systems are classified as durable medical equipment within the scope of Medicare Part B.

Currently, *Dexcom G5 Mobile is the only device which meets the Therapeutic CGM device classification*.

On May 18, 2017, a Glucose Monitors Local Coverage Determination (LCD) and Related Policy Article was revised[22] to reflect the CMS ruling. Per the LCD, *Therapeutic CGM* may be covered by Medicare when all of the following are met:

- The beneficiary has diabetes and,
- Has been using a blood glucose meter (BGM) and performing frequent (four or more times a day) testing; and,
- Is insulin-treated with MDI or a Medicare-covered CSII pump; and,
- The insulin regimen requires frequent adjustment on the basis of BGM or CGM testing results; and,
- Within six months prior to ordering the CGM, the treating practitioner has an in-person visit with the beneficiary to evaluate their diabetes control and determined that criteria are met; and,
- Every six months following the initial prescription of CGM, the treating practitioner has an in-person visit with the beneficiary to assess adherence to their CGM and treatment plan.

In conclusion, *Therapeutic CGM* is a significant advancement in CGM technology with demonstrated clinical benefits. As such, we urge the technology research team to examine the current evidence, clinical expertise, and Medicare criteria when developing key questions for the CGM review.

Thank you,

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Academy of Managed Care Pharmacy (AMCP) Formulary Dossier

Dexcom G5™ Mobile
Continuous Glucose Monitoring System

Date: May 2 2017

Dexcom, Inc.
6340 Sequence Drive
San Diego, CA 92121

G5™ Mobile Continuous Glucose Monitoring System
AMCP Formulary Dossier
IMPORTANT INFORMATION

Table of Contents

1.0 EXECUTIVE SUMMARY

1.1 CLINICAL BENEFITS

Diabetes is a group of metabolic diseases characterized by chronic hyperglycemia resulting from defects in insulin secretion, insulin action, or both.[1] An estimated 1 to 3 million people in the United States (U.S.) are diagnosed with type 1 diabetes mellitus (T1DM)[2] and require insulin to survive.

Diabetes is a leading cause of morbidity and mortality and associated with substantial healthcare and societal costs.[3, 6] Intensive therapy that lowers average glucose levels has been shown to reduce the risk of the long-term complications of diabetes but also increases the risk of hypoglycemia,[7-9] which results in significant morbidity and mortality and causes fear of hypoglycemia which is a major barrier to optimal glucose control.

Recurrent hypoglycemia induces a maladaptive response that impairs the ability of patients to detect the early warning signs of hypoglycemia, a condition known as hypoglycemia unawareness (HUA). HUA significantly increases the risk of severe hypoglycemia, which requires assistance from a third party to treat[10] and often requires costly emergency medical care.[11] Tools are needed that can help patients on insulin therapy lower their blood glucose levels without increasing their risk of hypoglycemia and to reduce the incidence of severe hypoglycemia in patients at risk for this costly and potentially fatal adverse event.

Real-time continuous glucose monitoring (RT-CGM*) is advanced glucose monitoring technology that continuously measures interstitial glucose levels, displays the current blood glucose level and direction and rate of change, and uses alarms and alerts to inform patients when blood glucose is exceeding or falling below specified thresholds.[12, 13] This complete picture of glycemic activity helps guide disease management decisions (e.g., insulin dosage adjustments, changes in diet) to avoid glycemic excursions.[12, 13] For patients with HUA, the alarm function of RT-CGM devices may be their only warning of emerging hypoglycemia. In contrast, traditional fingerstick self-monitoring of blood glucose (SMBG), which provides intermittent and limited information about blood glucose concentrations at single points in time,[12, 14] may fail to detect potentially dangerous glycemic excursions even when diligently performed.[12, 13]

Two recently published randomized controlled trials (RCTs) [15] [16] have shown that RT-CGM in conjunction with multiple daily injections (MDI) therapy significantly improves glycemic control in insulin-treated patients with diabetes compared to MDI with conventional SMBG. The DIAMOND RCT evaluated the effectiveness of RT-CGM in 158 patients with poorly-controlled T1DM who were treated with MDI.[15] At 24 weeks, the HbA1c level was 0.6% ($P<0.001$) lower in the group that received RT-CGM than in the group that received conventional blood glucose monitoring. Patients who received RT-CGM also spent significantly less time in hypoglycemia ($P=0.002$), had reductions in diabetes distress ($P<0.001$), less hypoglycemic fear ($P=0.02$), and increases in hypoglycemic confidence ($P<0.001$) and well-being ($P=0.01$) compared with conventionally monitored patients.[15, 17]

The G5™ Mobile CGM System is the only RT-CGM device approved for therapeutic decision making, as a replacement of SMBG. In addition, the Centers for Medicaid & Medicare (CMS) ruling CMS-1682-R, which created a classification of therapeutic CGM that is reimbursable under Medicare Part B, designated the G5™ Mobile CGM System as the only device meeting criteria as therapeutic CGM. The G4 PLATINUM with 505 software and G5 Mobile are equivalent in performance and accuracy. The primary differences are: 1) G5 Mobile is indicated for use as a

* *Personal RT-CGM technology is distinguished from professional CGM. Professional CGM is owned by the clinician and provided to the patient for a short term basis (3-7 days), and often does not display real time glucose values to the patient. Results are for later download by a healthcare professional, who analyzes the data to optimize diabetes management. Personal RT-CGM technology displays real-time glucose values and is used by patients in the home setting to self-manage diabetes on an ongoing basis. This technology also stores blood glucose values, which can be downloaded to analyze patterns of care and optimize treatment. The term RT-CGM used in this dossier exclusively refers to personal use of RT-CGM technology.*

replacement for SMBG in treatment decisions; 2) the G5 Mobile CGM can be used without a receiver and CGM readings can be displayed on a smart phone (in the non-Medicare population); 3) The G5 Mobile can “share” readings with up to 5 “followers (i.e. caregivers) at any time. With Dexcom G5 Mobile CGM System, insulin doses can be adjusted based on the glucose trends and several sequential readings over time.

Detection of episodes of hyperglycemia and hypoglycemia also facilitate long-term insulin dose adjustments. With wireless Bluetooth® technology built into the device transmitter, the G5 Mobile CGM System is the first and only fully mobile CGM system that sends glucose data directly to a smart device, freeing users from the need to carry a separate receiver. The device transmitter securely sends vital glucose information every five minutes directly to an app on iOS-enabled devices for real-time diabetes management. The Dexcom Share feature allows users to select up to five designated recipients, or "followers" so that they can remotely monitor the user's glucose information and receive alert notifications for added protection and peace of mind, particularly for parents of children and for the loved ones of elderly individuals who may not be fully competent in measuring their own blood glucose values reliably and making insulin dosing decisions on their own. Finally, the G5 Mobile System is flexible in that it can be used as a stand-alone device when insulin is administered as basal bolus injections or it can be used in conjunction with continuous insulin infusion via a pump.

1.2 ECONOMIC BENEFITS

Cost-Benefit Analysis Overview

Evaluating the long-term cost-effectiveness of RT-CGM necessarily involves developing complex models that estimate the lifetime likelihood of developing long-term diabetes complications. These cost effectiveness analysis, which may be of limited use to health plans; rather, Dexcom has created a short term budget impact model to examine the economic impact of RT-CGM technology on direct costs associated with emergency medical treatment due to severe hypoglycemia.

This cost-benefit analysis (CBA) evaluates the short-term (1-year) net cost impact associated with a reduction in emergency treatment (ambulance transport, ER visits, and hospitalizations) for severe hypoglycemia conferred by RT-CGM use among insulin-treated patients with diabetes who have hypoglycemia unawareness (HUA).

Medicaid Plan

In a Medicaid plan with 1 million enrollees, the target population consists 869 enrollees with T1DM and HUA and 1,475 enrollees with insulin-treated T2DM and HUA. Table 1 summarizes the key parameters of the model and Table 2 the outcomes for the Medicaid plan (Refer to SECTION 4 for more details and references).

TABLE 1. MODEL PARAMETERS: MEDICAID PLAN

Parameter	T1DM			Insulin-treated T2DM		
	Children	Adults	Elderly	Children	Adults	Elderly
Prevalence of hypoglycemia unawareness	25%	19%	45%	25%	10%	10%
No. of severe hypoglycemia in general population per patient-year	0.32	1.1	1.1	0.12	1.0	1.0
No. of severe hypoglycemia in patients with HUA per patient-year	0.5	6.2	6.2	0.6	5.0	5.0
% of severe hypoglycemic events requiring ambulance transport	31.0%	31.0%	31.0%	23.3%	23,3%	23.3%
% of severe hypoglycemic events requiring an ER visit	9.5%	9.5%	9.5%	20.7%	20.7%	20.7%
% of severe hypoglycemic events requiring hospitalization	5.0%	5.0%	5.0%	12.9%	12.9%	12.9%
Cost of an ambulance transport	$1,704					
Cost of an ER visit	$777					
Cost of hospitalization	$12,787					
Cost of RT-CGM	$4,700					

TABLE 2. NET COST IMPACT OF RT-CGM FOR MEDICAID PLAN

Outcome	Without RT-CGM (SMBG)	With RT-CGM
No. of severe hypoglycemia events	10,841	4,446
No. of events requiring ambulance transport	2,800	1,147
Cost of ambulance transport	$4,771,590	$1,954.488
No. of events requiring an ER visit	1,846	756
Cost of ER visits	$1,434,098	$587,412
No. of events requiring hospitalization	1,118	458
Cost of hospitalization	$14,295,866	$5,856,446
Total cost of emergency treatment	$20,501,554	$8,398,346
Total cost of RT-CGM	$0	$10,548,000

NET COST IMPACT of RT-CGM (savings in emergency treatment for severe hypoglycemia minus cost of RT-CGM)	**$1,555,208**

1.3 CONCLUSIONS

RT-CGM is expected to reduce the short- and long-term complications associated with diabetes by decreasing average blood glucose levels, glycemic variability, and the incidence of hypoglycemia. A strong body of evidence has demonstrated the efficacy of RT-CGM for reducing HbA1c levels and glycemic variability in children and adults with T1DM; although similar benefits are expected in patients with insulin-treated T2DM, more research is needed to confirm efficacy of RT-CGM in this population. A recent RCT has shown that RT-CGM reduces the incidence of severe hypoglycemia by 59% in particularly vulnerable T1DM patients (those with HUA). Assuming RTCGM is able to reduce the incidence of costly emergency treatment in insulin-treated patients with HUA, RT-CGM is estimated to confer cost savings in this high-risk population over a 1-year period. Additional cost savings would be expected to accrue over a patient's lifetime as RT-CGM has been shown to significantly reduce the long-term microvascular and neuropathic complications of diabetes.

Patients receiving the G5™ Mobile CGM System are expected to experience the general benefits of RT-CGM, as summarized above, and have a lower burden of fingersticks, as the G5 device is approved for replacement of BGM for therapeutic decision making. In addition, the superior accuracy of the G5™ Mobile CGM System may enhance patient confidence in device blood glucose readings and more aggressive actions in response to information provided by the device. [18]

2.0 PRODUCT INFORMATION AND DISEASE DESCRIPTION

2.1 PRODUCT DESCRIPTION

The G5™ Mobile Continuous Glucose Monitoring System (G5™ Mobile CGM System) is a glucose-monitoring system that provides real-time continuous glucose measurements every 5 minutes for up to 7 days to detect trends and track patterns in glucose levels in people aged ≥2 years with diabetes.[19] The G5™ Mobile CGM System is designed to replace fingerstick blood glucose testing for diabetes treatment decisions. These measurements aid in the detection of episodes of hyperglycemia and hypoglycemia, facilitating both acute and long-term therapy adjustments, which may minimize these excursions and their associated adverse health consequences.[19]

a. Product Name and Therapeutic Class

The G5™ Mobile CGM System is a glucose monitoring device consisting of three major components: Sensor, Transmitter, and Receiver.

1. Sensor – The Sensor is a flexible, round, miniature wire that is placed just under the skin to read glucose levels (Figure 1). The Sensor attaches to the skin with its adhesive patch, and comprises the Applicator, Sensor Probe, and Sensor Pod. The Applicator is a disposable portion of the Sensor that the patient uses to insert the Sensor Probe. There is a needle inside the Applicator that inserts the Sensor and then is withdrawn once the Sensor Probe has been inserted underneath the skin. The Sensor Probe is the portion of the Sensor that is inserted under the skin and measures glucose levels in surrounding tissue fluid. The Sensor Pod is the small base adhered to the patient's abdomen that holds the Transmitter in place. 2 SMBG calibrations are required per day for proper functioning of the CGM sensor.

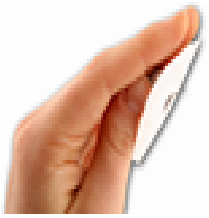


FIGURE 1. G5™ MOBILE CGM SYSTEM SENSOR

2. Transmitter – The Transmitter (Figure 2) wirelessly sends glucose information to the Receiver or optional smart phone. The Transmitter snaps into the Sensor Pod.

FIGURE 2. G5™ MOBILE CGM SYSTEM TRANSMITTER

3. Receiver – This is a pager - sized device programmed to collect and process data from the Sensor and to display the results as a glucose value (Figure 3).

FIGURE 3. G5™ MOBILE CGM SYSTEM RECEIVER

The Sensor Pod and Transmitter are all that remain on the patient's skin during each Sensor wear period (Figure 4).

FIGURE 4. SENSOR POD AND TRANSMITTER ON PATIENT

The G5™ Mobile Application (Dexcom Share® App) allows the patient to use their smart device as their receiver. Just like the dedicated G5 Mobile Receiver, the Mobile App receives data from the Sensor and displays glucose sensor readings, trend graphs, trend arrows, and alerts. As shown in Figure 5, Dexcom Share® in the Dexcom G5™ Mobile App allows patients to remotely view their sensor glucose readings, trends, and to share their data with up to five people ("followers"). After being invited by the "Sharer," and by downloading the Dexcom Follow® App, an individual becomes a "Follower." The user determines what a Follower can see, including the

user's sensor glucose readings, trends, alarm/alerts when the user's glucose is low or high, and messages. The Dexcom Share G5™ CGM System has been developed with technology that provides a high level of security for Personally Identifiable Information and Private Health Information of registered users.

FIGURE 5. DEXCOM SHARE®

Dexcom Clarity® is a data management software program that allows the transfer of glucose data from the Dexcom G5™ Mobile CGM System to remote servers for data management. The cloud-based Dexcom Clarity® software is intended for use by both home users and healthcare professionals to assist people with diabetes in the review, analysis, and evaluation of historical CGM data to support effective diabetes management. The software provides summary reports, which include average glucose, frequency of calibrations, and patterns of low and high glucose (Figure 6). Healthcare professionals can use the retrospective information presented in Dexcom Clarity® to modify their recommendations for a patient's diabetes management plan.

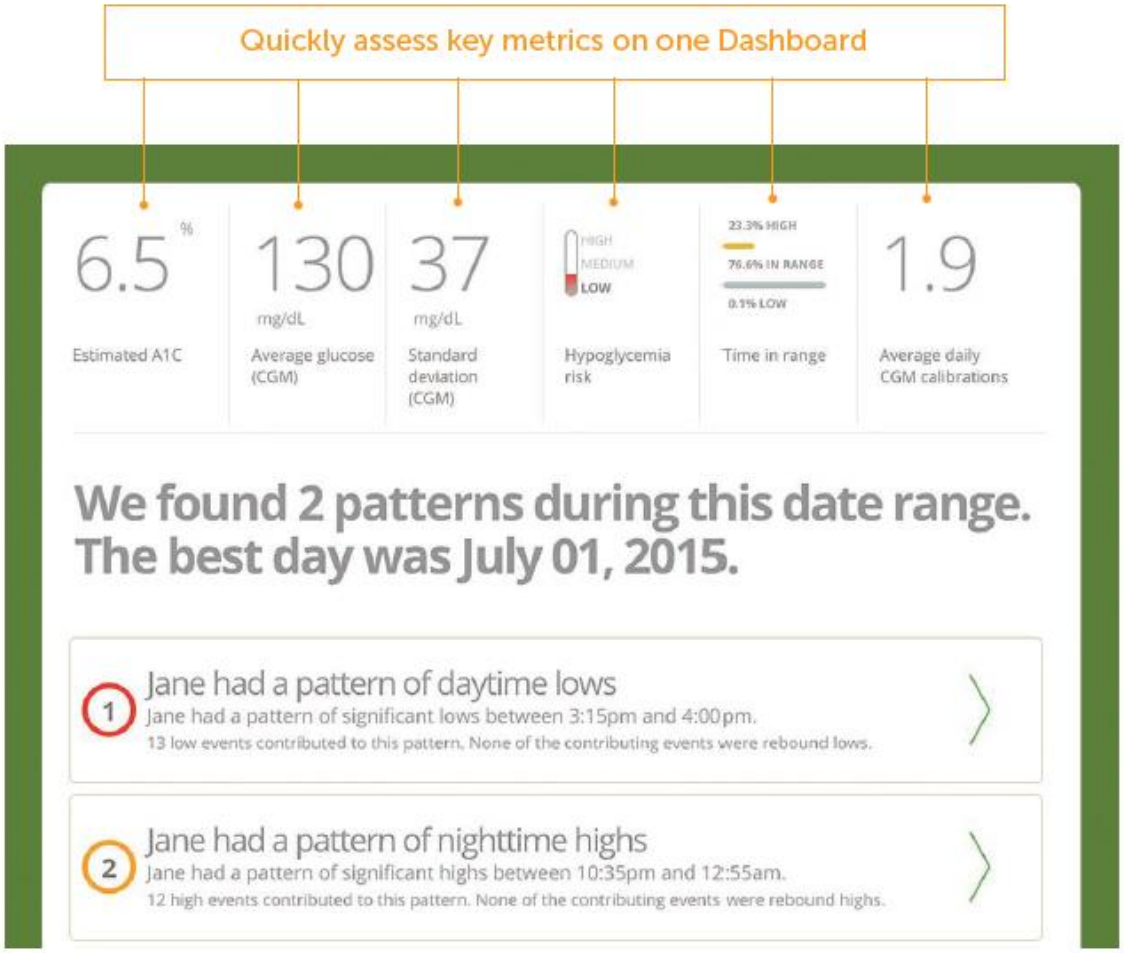


FIGURE 6. CLARITY® OVERVIEW REPORT

b. National Drug Code

The National Drug Code (NDC) for each component of the G5™ Mobile CGM System is shown in Table 3.

TABLE 3. NDCS FOR G5™ MOBILE CGM SYSTEM COMPONENTS

Component	NDC
Transmitter Kit	08627-0014-01
Adult Receiver Kit (Black)	08627-0080-11
Adult Receiver Kit (Pink)	08627-0080-21
Adult Receiver Kit (Blue)	08627-0080-31
Sensor 4 Pack	08627-0051-04

c. Cost

The list prices for the G5™ Mobile CGM System are shown in Table 4. Contracted pricing for individual payers is proprietary.

TABLE 4. COST OF G5™ MOBILE CGM SYSTEM COMPONENTS

Component	List Price
Transmitter (3-month warranty) *	$453.68
Receiver (1-year warranty)	$793.80
Sensor (box of 4)	$566.69
*Transmitter life is approximately 9 months.	

d. Classification

The G5™ Mobile CGM System is a Class III medical device.

e. FDA-Approved Indications

Information regarding premarket approval (PMA) of Dexcom CGM devices that are no longer marketed can be found at: https://www.accessdata.fda.gov/scripts/cdrh/cfdocs/cfpma/pma.cfm?start_search=1&sortcolumn=do_desc&PAGENUM=500&pmanumber=P050012. A timeline for approvals of Dexcom RT-CGM devices is shown in Figure 5.

On October 5, 2012, PMA was granted for the G4™ PLATINUM CGM System for use in adults aged ≥18 years. On February 3, 2014, PMA was granted for the G4™ PLATINUM CGM System for use in children aged 2-17 years. On November 3, 2014, the FDA approved new software (Software 505) for the G4™ PLATINUM CGM System that features an advanced algorithm to improve system accuracy. On December 2, 2014, the FDA approved the Animas® Vibe™ Insulin Pump with the G4™ PLATINUM CGM System for the management of insulin-requiring diabetes in adults aged ≥18 years.

On August 19, 2015, the FDA approved the G5™ Mobile CGM System for the management of diabetes in individuals aged 2 years and older.

On December 20, 2016, the FDA expanded the indication for the G5™ Mobile CGM System to replace fingerstick blood glucose testing for diabetes treatment decisions.*

* On January 12, 2017, Centers for Medicaid and Medicare Services (CMS) ruling CMS-1682-R created a classification “therapeutic CGM” as “durable medical equipment” under Medicare Part B. The G5™ Mobile CGM System is the only RT-CGM device on the market that meets the definition of therapeutic CGM under this ruling.

f. Contraindications/Warnings/Precautions/Adverse Effects

See Section 6.3

g. Interactions

See Section 6.3

h. Dosing and Administration

See Section 6.3

i. Access

There are no anticipated limitations in supply or restrictions on distribution of the G5™ Mobile CGM System. U.S. federal law restricts the sale of the G5™ Mobile CGM System by physician prescription.

j. Co-prescribed/Concomitant Therapies

The G5™ Mobile CGM System is indicated to replace fingerstick blood glucose testing for diabetes treatment decisions.

k. Comparison with Comparator Products

Comparison of the attributes and performance of the G5™ Mobile CGM System and other commercially available RT-CGM devices are shown in Table 5. The G5™ Mobile CGM System can be used separately or in conjunction with an insulin pump. The MiniMed® 530G System is an integrated RT-CGM device and an insulin pump.

TABLE 5. COMPARISON OF PRODUCT ATTRIBUTES AND PERFORMANCE

Product Attributes and Performance	G5™ Mobile CGM System (Dexcom)*	MiniMed® 530G System with Enlite™ Sensor (Medtronic)
Indication	≥2 years[19]	≥16 years[20]
Can be used to make treatment decisions without confirmatory SMBG	Yes[19]	No[20]
Sensor & Transmitter Specifications		
Sensor/Transmitter dimensions	1.5 x 0.9 x 0.5 in[19]	2.0 x 1.5 x 0.75 in[21]
Sensor/Transmitter weight	0.4 oz[19]	0.41 oz[20]
Sensor probe gauge	26 mm[19]	27 mm[22]
Sensor duration	7 days[19]	6 days[20]
Sensor start-up time	2 h[19]	2 h[20]
Moisture protection	Water resistant up to 8 feet for 24 h[19]	Water resistant up to 8 feet for 30 min[23]
Transmitter power	Non-rechargeable; silver oxide batteries[19]	Rechargeable (full charge lasts 14 days) [23]
Communication range	20 feet[19]	6 feet[20]
Receiver Specifications		
Receiver dimensions	4.0 x 1.8 x 0.5 in[19]	551 pump: 2.0 x 3.3 x 0.81 in[20] 771 pump: 2.0 x 3.7 x 0.82 in[20]
Receiver weight	2.4 oz[19]	551 pump: 3.35 oz[20] 771 pump: 3.67 oz[20]
Memory storage	30 days of glucose data, 7 days of tech support data[19]	32 days of glucose data[20]
Receiver power	Rechargeable (full charge lasts 3 days)[19]	1 AAA battery[20]
Calibration		
Minimum calibration	2 h after Sensor insertion, then every 12 h[19]	2 and 6 h after Sensor insertion, then every 12 h[20]
Range	40-400 mg/dL[19]	40-400 mg/dL[20]
Restrictions	Do not calibrate when glucose levels are changing at more than 2 mg/dL per minute[19]	None[20]
Interaction with BG meter	Manually enter reading from any meter[19]	Manually enter reading from any meter, or wirelessly upload readings using the Bayer Contour® Next Link meter[20]

Product Attributes and Performance	G5™ Mobile CGM System (Dexcom)*	MiniMed® 530G System with Enlite™ Sensor (Medtronic)
Alarms		
Hypoglycemia fixed alarm	Set at 55 mg/dL and cannot be adjusted or disabled[19]	Not available
Customizable alarms	Optional; set by user	Optional; set by user
Performance Characteristics		
Overall Accuracy MARD (average % discrepancy between CGM and reference YSI, 40-400 mg/dL)	9.0% (adults) 10.4% (children)[19]	14.2%[24]
Hypoglycemia Accuracy (% of CGM readings within 20% of reference YSI, 40-80 mg/dL)	40-80 mg/dL: 94% (adults) 61-80 mg/dL: 96% (adults) 40-60 mg/dL: 74% (children) 61-80 mg/dL: 82% (children)[19]	Not reported
Hyperglycemia Detection Rate (% of time BG level was at or above alert setting 200 mg/dL and alert sounded)	98% (adults) 97% (children ages 6-17 years) 93% (children ages 2-5 years)[19]	Not reported
Hypoglycemia Detection Rate (% of time BG level was at or below alert setting 70 mg/dL and alert sounded)	91% (adults) 75% (children ages 6-17 years) 100% (children ages 2-5 years)[19]	97.5%[24]
Accuracy Over Time MARD (average % discrepancy between CGM and reference YSI, 40-400 mg/dL)	Day 1: 10.7% (adults) Day 1: 14.8% (children) Day 4: 8.0% (adults) Day 4: 10.7% (children) Day 7: 8.5% (adults) Day 7: 11.3% (children)[19]	Day 1: 16.2%[24] Day 2: 15.1%[24] Day 3: 11.1%[24] Day 4: 13.0%[24] Day 5: 14.4%[24] Day 6: 14.2%[24]
Sensor Life (% Sensors working at end of maximum indicated use)	98% @ 7 days (adults) 94% @ 7 days (children)[19]	91% @ 6 days[24]

BG=blood glucose; MARD=mean average relative difference; YSI=Yellow Springs Instrument.
*Performance data are for the G5™ Mobile CGM System with the 505 software. All G5™ Mobile CGM Systems use the 505 software. Unless otherwise specified, the age range for children is 2-17 years.

2.2 PLACE OF THE PRODUCT IN THERAPY

2.2.1 Disease Description

Diabetes is a group of metabolic diseases characterized by chronic hyperglycemia resulting from defects in insulin secretion, insulin action, or both.[1]

a. Epidemiology of Diabetes

Prevalence of Diabetes in the U.S. General Population

In 2015, an estimated 29.9 million Americans, or 9.3% of the population had diabetes, and 21.5 million or 6.7%[3, 25] were diagnosed with diabetes (Table 6).

The projected prevalence of diabetes in the U.S. adult population in 2050 ranges from a low of 21% to a high of 33%.[26] Factors contributing to the future increased prevalence of diabetes include an aging population, the growing size of at-risk minority populations, and longer survival of people with diabetes.[26] The number of adults living with T1DM is increasing due to both the rising number of new-onset cases of T1DM in adults, including those diagnosed with latent autoimmune diabetes, and longer lifespans among individuals with childhood-onset diabetes.[27]

Prevalence of Diabetes in Children

Combined results from the SEARCH for Diabetes in Youth Study[28] and 2015 U.S. Census Bureau demographic information[25] indicate that the prevalence of T1DM in youth is 0.197%, with an estimated 180,620 affected individuals in 2015, and that the prevalence of T2DM in youth is 0.024%, with an estimated 19,704 affected individuals in 2015.

The estimated number of youth with T1DM is expected to increase by 23%, from 166,018 in 2010 to 203,385 in 2050, primarily due to the projected absolute increases in the minority youth population.[28] The number of U.S. youth with T2DM is expected to increase by 49% (from 20,203 to 30,111) between 2010 and 2050.[28]

Prevalence of Diabetes in Adults

From 2011-2014, the prevalence of diagnosed diabetes was 2.6% (2.3 million) among adults aged 20-44 years; 12.3% (10.3 million) among adults aged 45-64 years; and 21.9% (10.5 million) among adults aged ≥65 years.[25, 29]

T2DM generally accounts for 95% of all diabetes cases in adults aged 20-64 years[3] and 97.5% of adults aged ≥65 years.[30] The estimated prevalence rates of T1DM and T2DM by age group are shown in Table 6.

TABLE 6. U.S. ESTIMATED PREVALENCE OF DIAGNOSED DIABETES IN THE GENERAL POPULATION BY DIABETES TYPE AND AGE GROUP

Age Group	N (million) [25]	% of Population [25]	Diagnosed Diabetes		T1DM		T2DM	
			N (million)	%	N (million)	%	N (million)	%
All ages	321.4	100	21.5	6.7[3]	1.08	0.34	12.42	6.36
<20 years	82.1	25.6	0.18	0.22[28]	0.16	0.197[28]	0.02	0.024[28]
20-44 years	87.2	27.1	2.3	2.6[29]	0.10[a]	0.13	2.2	2.47
45-64 years	84.1	26.2	10.3	12.3[29]	0.50[a]	0.6	9.8	11.7
≥65 years	47.8	14.9	10.5	21.9[29]	0.30[b]	0.55	10.2	21.35

Note: Rates (% of U.S. population within age group) were extrapolated to July 1, 2015 using U.S. Census data.[25]
[a]Assumes 95% of diabetes cases are T2DM and 5% are T1DM in adults aged 20-64 years.[3]
[b]Assumes 97.5% of diabetes cases are T2DM and 2.5% are T1DM in adults aged ≥65 years.[30]

Incidence of Diabetes in the U.S.

Table 7 presents the estimated number and rate of new cases of diagnosed diabetes among U.S. adults in 2012.[31] The precise incidence of new-onset T1DM cases among adults is unknown, possibly due to both the prolonged phase of onset and the subtleties in distinguishing the different types of diabetes.[27]

TABLE 7. ESTIMATED U.S. ANNUAL INCIDENCE OF NEW CASES OF ALL DIAGNOSED DIABETES AMONG ADULTS, 2012[3]

Age Group	Number and Rate of All New Diabetes Cases	
	Number	Rate per 1000
≥20 years	1,700,000	7.8
20-64 years	1,300,000	3.6 (20-44 years)
		12.0 (45-64 years)
≥65 years	400,000	11.5

In 2009, an estimated 18,436 U.S. youth were newly diagnosed with T1DM and 5,089 youth were newly diagnosed with T2DM.[3]

b. Use of Insulin Therapy

Insulin is the requisite treatment for all individuals with T1DM.[32]

Among U.S. youth with T2DM who participated in the SEARCH for Diabetes in Youth Study, 43.3% reported receiving insulin therapy.[4]

In 2013, analysis of a large claims database of privately insured and Medicare Advantage adult patients (aged ≥18 years) with T2DM revealed that 23.0% were using insulin.[33]

The Kaiser Diabetes and Aging Study, a cohort study of approximately 73,000 older adults (aged ≥60 years) with T2DM, revealed that 28.5% of patients received insulin.[34]a

c. Diagnosis and Clinical Presentation

Diagnosis and Classification

According to the ADA, the diagnosis of diabetes may be made based on A1c, fasting plasma glucose, or postprandial plasma glucose (Table 8).[1] Measurement of pancreatic autoantibodies should be considered to confirm the diagnosis of T1DM.[27]

TABLE 8. CRITERIA FOR THE DIAGNOSIS OF DIABETES[1]

A1c ≥6.5%
OR
Fasting plasma glucose ≥126 mg/dL (7.0 mmol/l)
OR
2-h plasma glucose ≥200 mg/dL (11.1 mmol/l) during an oral glucose tolerance test
OR
In a patient with classic symptoms of hyperglycemia or hyperglycemic crisis, a random plasma glucose ≥200 mg/dL (11.1 mmol/l)

d. Clinical Presentation and Course

T1DM

There is considerable variability in the initial presentation of T1DM in children and adults.[27] T1DM is usually diagnosed based on the classic catabolic symptoms suggestive of insulin deficiency, including polyuria, polydipsia, weight loss, and marked hyperglycemia.[27] Children with T1DM often present with acute, severe symptoms of polyuria, polydipsia, and ketonemia.[27] In adults, T1DM presents with a more gradual onset that may initially appear consistent with T2DM.[27] The progressive β-cell destruction associated with T1DM means that all patients require exogenous insulin for survival.[27]

Chronic complications of diabetes, including retinopathy, nephropathy, and neuropathy, rarely have been reported in prepubertal children and children with T1DM duration of only 1-2 years, but may occur after the onset of puberty or after 5-10 years of T1DM.[27] Because hyperglycemia defines diabetes and is directly related to the incidence of complications, it is important to control blood glucose and HbA1c levels prior to puberty to reduce risk for both micro- and macrovascular complications.[27] Additionally, there is burgeoning evidence that elevated blood glucose levels and glycemic variability (periods of hypo- and hyperglycemia) in very young children with diabetes may adversely affect short-term neurocognitive function and the central nervous system.[27]

Most older adults with T1DM have longstanding disease.[27] Some may have advanced complications, and others may have lived with diabetes for many years without the development of complications.[27]

T2DM

Patients with T2DM may present with a wide range of symptoms, depending on the degree of insulin resistance and β-cell dysfunction at presentation.[35] T2DM often is undetected for many years because hyperglycemia develops gradually and at earlier stages is often not severe enough for the patient to notice any of the classic symptoms of diabetes.[36] Although some patients with T2DM are diagnosed after developing the classic acute symptoms, the first symptoms in others are nonspecific, (e.g., fatigue, poor wound healing, dry mouth) and may not be recognized as diabetes.[35] Often, T2DM is not diagnosed in adults until complications occur.[1]

In general, children and adolescents diagnosed with T2DM present with glycosuria without ketonuria, mild thirst, some increase in urination, and little-to-no weight loss; however, up to 33% will have ketonuria at diagnosis, with 5% to 25% having ketoacidosis unrelated to stress, illness, or infection.[35]

Weight reduction and/or pharmacological treatment of hyperglycemia may improve but rarely normalizes insulin resistance.[1] Due to the progressive nature of T2DM, many people with the disease eventually require insulin.[32]

e. Complications of Diabetes

Hypoglycemia

The ADA defines hypoglycemia as “any abnormally low plasma glucose concentration that exposes the subject to potential harm” with a proposed threshold plasma glucose value <70 mg/dL (<3.9 mmol/L).[10] Mild hypoglycemia is associated with the presence of autonomic symptoms manifested as a cause of activation of the sympathetic nervous system and include trembling, palpitations, sweating, anxiety, hunger, nausea, and tingling; individuals are able to self-treat mild hypoglycemia.[37] Moderate hypoglycemia is associated with both autonomic and neuroglycopenic symptoms, and the individual is also able to self-treat.[37] Neuroglycopenic symptoms are manifested in response to decreased levels of glucose to the brain and include difficulty concentrating, confusion, weakness, drowsiness, vision changes, difficulty speaking, headache, dizziness and tiredness.[37] Severe hypoglycemia requires the assistance of another person to treat and can lead to seizures, coma, and even death.[10]

Hypoglycemia is the most common and serious adverse event caused by insulin treatment[38] and is a major barrier to optimal diabetes management.[39] Large landmark randomized clinical trials (RCTs) have shown that intensive diabetes therapy, which aims to achieve lower average blood glucose results, increases the risk of severe hypoglycemia by 2- to 3-fold in patients with T1DM and T2DM.[8, 40-42]

Health Consequences of Hypoglycemia

Recurrent and severe hypoglycemia can cause significant morbidity and mortality. Profound and prolonged hypoglycemia may cause transient or persistent neurological deficits. Repeated episodes of severe hypoglycemia are associated with impaired cognitive function in children, and can have potentially deleterious and cumulative long-term effects on intellectual function.[43] Severe hypoglycemia in older patients has been associated with an increased risk of dementia.[44] A recent history of severe hypoglycemia is the single most significant factor associated with driving collisions for drivers with diabetes,[45, 46] and severe hypoglycemia may contribute to fatal vehicular accidents by impairing cognitive, motor, and perceptual functioning.[45, 47] Among patients who receive emergency inpatient treatment for severe hypoglycemia, 22% experience persistent neurological deficits that cause disability after discharge.[48]

Among individuals with T1DM, 4-10% of all deaths are attributed to severe hypoglycemia,[49, 50] and risk of death 5 years after an episode of severe hypoglycemia is 3.4-fold in those who report severe hypoglycemia.[51] Severe hypoglycemia is associated with an increased risk of cardiovascular events and sudden cardiac death, although it is not yet clear whether hypoglycemia is causally linked to cardiovascular risk or is marker of frailty and predictor of adverse outcomes in patients with diabetes.[52]

Quality of Life

Regardless of severity, hypoglycemia substantially reduces well-being and impairs quality of life by interfering with physical, mental and social functioning, sleep, work productivity, and enjoyment of recreational and leisure activities.[39, 53, 54] A literature review found that studies consistently demonstrate a lower health-related utility associated with hypoglycemia.[55] Studies also have demonstrated that health-related quality of life decreases with increasing severity and increasing frequency of non-severe hypoglycemic episodes.[55] Nocturnal hypoglycemia, a particularly feared event, negatively affects well-being and increases fatigue.[56]

The negative emotional and physical impact of hypoglycemia extends beyond the individual with diabetes to their family members. A survey of 2,057 family members of people with diabetes found that 61% experienced distress over a family member experiencing a hypoglycaemic event.[57] Parents of children with diabetes worry about their child's ability to detect/report hypoglycemia and factors that impacted their child's blood glucose levels and over which they could exercise little control, including leaving their child with other caregivers who could not be trusted to detect hypoglycemia, difficulties remotely monitoring and regulating their child's food consumption and activity, and physical and social changes accompanying childhood development.[58]

Fear of Hypoglycemia

The development of fear of hypoglycemia is associated with both the severity and frequency of past episodes of hypoglycemia.[55, 59] Fear of hypoglycemia is associated with psychological distress, particular increased anxiety,[60, 61] which can make it difficult for patients to differentiate anxiety and hypoglycemic symptoms[60] and consequently delay or prevent the patient from responding appropriately to hypoglycemia to prevent a more severe hypoglycemic episode.[55]

In addition to causing psychological distress, fear of hypoglycemia can have a negative impact on diabetes management and metabolic control. Fear of hypoglycemia is strongly associated with poor adherence to prescribed insulin regimens.[62, 63] The impact of hypoglycemia and fear of future hypoglycemic episodes was assessed via a self-administered survey in 202 patients with T1DM and 133 patients withT2DM.[64] Following a mild or moderate hypoglycemic episode, 37.8% of T1DM and 29.9% of T2DM patients reported increased fear of future episodes; and 74.1% and 43.3%, respectively, reported modifying their insulin dose. After episodes of severe hypoglycemia, most patients with T1DM and T2DM expressed fear of future events (63.6% and 84.2%, respectively) and reduced their doses of insulin. A survey of 1404 employed individuals

with diabetes across the U.S., U.K., Germany, and France found that, of the 1,024 individuals taking insulin, 25% decreased their insulin dose following a non-severe hypoglycemic episode.[65]

Fear of hypoglycemia is also common among the parents of children with diabetes.[66]. Scores on the behavior scale of the Hypoglycemia Fear Survey, particularly of mothers, suggest that they may maintain slightly higher than optimal glucose levels in their children to avoid hypoglycemia.[67, 68]

Fear of hypoglycemia is a major contributor to the decrease in health-related quality-of-life of patients with diabetes. Patients with hypoglycemia symptoms report more fear and worry of hypoglycemia and are more affected by their diabetes compared with those without hypoglycemia symptoms.[69]

Incidence of Non-Severe Hypoglycemia

In a survey of 3,859 people with diabetes in 7 European countries, rates of non-severe hypoglycemia were 1.8 episodes per week for patients with T1DM and 0.4-0.7 episodes per week for patients with insulin-treated T2DM.[70] These figures likely represent underestimates of the true rate of non-severe hypoglycemia as a majority of respondents in this study had either impaired or absent ability to recognize symptoms of hypoglycemia.

Prevalence and Incidence of Severe Hypoglycemia

Approximately 30-40% of adults with T1DM,[71-74] 22% of insulin-treated adults with T2DM,[75] and 6% of youth with insulin-treated T2DM[74] experience at least 1 severe hypoglycemic event annually.

Five studies of children and adolescents with T1DM have reported rates of severe hypoglycemia ranging from 0.16 to 0.38 episodes per patient-year.[76-79] Incidence rates for severe hypoglycemia in adults with T1DM range from 0.5 to 3.2 events per patient-year, with most studies reporting an incidence of ~1 episode per patient-year.[70-73, 80-83]

The incidence of severe hypoglycemia in children and adolescents with insulin-treated T2DM is 0.12 episodes per patient-year.[84] A systematic literature review (1998-2014) of 11 studies involving 6851 adults with insulin-treated T2DM found that the incidence of severe hypoglycemia was 1.0 episodes per patient-year.[85]

Hypoglycemia Unawareness and Risk of Severe Hypoglycemia

HUA is an acquired complication of insulin therapy, whereby the ability to perceive the onset of hypoglycemia becomes absent often due to defective counter-regulatory hormonal responses to hypoglycemia.[86, 87] The prevalence of HUA increases with diabetes duration, and is found in 10-58% of adults with T1DM,[70, 71, 73, 83, 88-96] 21-29% of children and adolescents with T1DM,[79, 97] and 8-20% of adults with insulin-treated T2DM.[70, 83, 93, 98, 99]

The reduced ability to detect the acute autonomic warning symptoms of hypoglycemia creates a vicious cycle of recurrent hypoglycemia and increases the risk of severe hypoglycemia.[100, 101] HUA is associated with a 3-10 times greater incidence of severe hypoglycemia in patients with T1DM[70, 83, 88, 89, 91, 93, 97, 102, 103] and a 2-17 times greater incidence of severe hypoglycemia in patients with insulin-treated T2DM.[83, 93, 98, 99]

Cost of Emergency Treatment for Severe Hypoglycemia

Severe hypoglycemia requires assistance by a third party to restore glycemic control and may require ambulance/EMS services/transport, ER visits, and hospitalization. Vigersky estimated the total annual cost of hospitalizations for hypoglycemia for the US T1DM population to be between $1.8 billion and $5.9 billion.[104] Over a 5-year period, ER visits for severe hypoglycemia cost the US health care system an estimated $600 million ($120 million per year).[31]

A history of emergency treatment for hypoglycemia substantially increases the risk for future events requiring emergency care. In a large case control study, a prior ER visit for hypoglycemia

increased the odds of a subsequent inpatient admission for hypoglycemia by 9-fold (odds ratio [OR] 9.5, 95% confidence interval [CI] 5-18) in patients with T2DM.[105] In a prospective cohort study, a history of previous hypoglycemic episode requiring hospitalization was associated with a 6-fold increase for another episode over the next 8 years (HR 5.7, 95% CI 2.2-15).[106]

Hypoglycemia is associated with higher diabetes-related healthcare costs. In a retrospective analysis of administrative claims data, patients with T2DM who had at least 1 episode of confirmed hypoglycemia had a 71% ($P \leq 0.001$) increase in diabetes-related healthcare costs during a 12-month period compared with patients with no hypoglycemia when adjusted for age, gender, geographic region, socioeconomic status, race, health status, comorbid conditions, medication adherence, and treatment patterns.[107] In another retrospective study, patients with T2DM who experienced a severe hypoglycemic event after initiating basal insulin had 4 times higher diabetes-related healthcare costs during the first post-titration follow-up year than patients who did not experience a severe hypoglycemic event.[108]

Chronic Microvascular Complications

The microvascular complications of diabetes include retinopathy, nephropathy, and neuropathy due to chronic hyperglycemia.[109]

Retinopathy

Most people with diabetes will develop some form of retinopathy, damage to the small blood vessels in the retina that may result in loss of vision.[110] Diabetic retinopathy is the leading cause of blindness in U.S. adults aged 20-74 years.[111] In 2005-2008, of U.S. adults with diabetes aged ≥40 years, 4.2 million (28.5%) people had diabetic retinopathy and 655,000 (4.4%) had advanced retinopathy that could result in vision loss.[3] After 15 or more years of disease, 85% of persons with insulin-dependent diabetes will develop diabetic retinopathy and 20% will develop vision-threatening proliferative diabetic retinopathy.[112]

Nephropathy

Approximately 20-30% of people with diabetes will develop nephropathy.[113] Without specific interventions, microalbuminuria progresses to overt nephropathy or clinical albuminuria in 80% of patients with T1DM and 20-40% of patients with T2DM.[113] In T1DM, overt nephropathy will progress to renal failure in 50% of patients within 10 years and 75% within 20 years.[113] Approximately 20% of patients with T2DM who develop overt nephropathy will progress to renal failure within 20 years.[113] In 2011, a total of 228,924 people of all ages with kidney failure due to diabetes were living on chronic dialysis or with a kidney transplant.[3]

Neuropathy

Diabetic neuropathy affects up to 70% of people with diabetes.[111] The symptoms of diabetic neuropathy may include pain and loss of sensation in the feet or hands, problems with digestion and urination, carpal tunnel syndrome, erectile dysfunction, and other nerve problems.[111] Nerve and blood vessel damage can easily lead to foot infections and ulcers, which increase the risk of amputation.[110] The risk of amputation is up to 25 times greater in people with diabetes than in those without diabetes.[110] Diabetic neuropathy is responsible for 60% of all non-traumatic lower-extremity amputations in the U.S., with approximately 73,000 such amputations occurring annually in U.S. adults with diabetes.[3]

Ethnic and racial minorities suffer a disproportionate burden of complications from diabetes. Non-Hispanic blacks and Native Americans have higher rates of retinopathy, kidney disease (including end-stage renal disease), and lower limb amputation than non-Hispanic whites.[114-116] Hispanics have higher rates of retinopathy and kidney disease (including end-stage renal disease) than non-Hispanic whites.[114-116] Blindness due to diabetes occurs half as frequently in non-Hispanic whites as in racial and ethnic minority groups.[117]

Chronic Macrovascular Complications

Cardiovascular disease (CVD), including angina, myocardial infarction, stroke, peripheral artery disease, and congestive heart failure, is the most common cause of diabetes-related death and disability.[110] U.S. adults with diabetes have a 1.5 to 1.8 times increased risk of heart attack, stroke, and death from CVD compared with those without diabetes.[3] Heart disease and stroke account for 68% and 16% of diabetes-related deaths, respectively, in the U.S.[111]

Mortality

Diabetes is the 7th leading cause of death in the U.S.[3] Between 2003-2006, after adjusting for population age differences, rates of death from all causes were about 1.5 times higher among adults aged 18 years or older with diagnosed diabetes than among adults without diagnosed diabetes.[3]

Although the mortality rate associated with T1DM has improved over time, individuals most recently diagnosed with childhood-onset T1DM have a 5 times greater mortality rate than that of the general population.[118] The gap in life expectancy between people diagnosed with T1DM and the U.S. general population is 4 years for those diagnosed between 1965 and 1980.[119] Life expectancy is estimated to be reduced by 5 years for males with T2DM.[120]

Non-Hispanic black people are twice as likely to die from diabetes as non-Hispanic whites.[118, 121, 122] Most (73%) of this disparity is explained by economic inequality.[121] The diabetes mortality rate is 2.5 to 3.5 times higher among American Indians[123] and 1.3 times higher among Hispanics[124] than non-Hispanic whites.

Effects of Early Tight Glycemic Control on Risk of Long-term Diabetes Complications and Hypoglycemia

Landmark RCTs, such as the Diabetes Control and Complications Trial (DCCT)[8] and the Stockholm Diabetes Intervention Study (SDIS) in T1DM and the UKPDS (United Kingdom Prospective Diabetes Study)[125] and Kumamoto study[126] in T2DM, have established that intensive diabetes therapy, which aims to reduce HbA1c, delays or prevents long-term diabetes complications. Table 9 summarizes the reduction in risk of complications in the intensive treatment groups in these landmark studies. In all studies, glycemic control was directly related to the risk of diabetes complications. For example:

- In the DCCT, a 10% reduction in HbA1c was associated with a 35% risk reduction for retinopathy and a 25-44% risk reduction for nephropathy.[127]
- In the UKPDS, each 1% decrease in HbA1c was associated with a 37% reduction in the risk of microvascular complications, a 16% reduction in heart failure, and a 21% reduction in diabetes-related and all-cause mortality.[128]

TABLE 9. RISK REDUCTION FOR INTENSIVE VERSUS CONVENTIONAL THERAPY BY DECREASE IN HBA1C

Complication	% Risk Reduction (95% Confidence Interval)			
	DCCT[129]	SDIS[130]	Kumamoto[131]	UKPDS[125]
Retinopathy	57 (48-65)‡	25 (6-44)†	69 (24-81)†	25 (7-40)‡
Nephropathy	59 (28-77)‡	16 (4-27)†	70 (14-89)†	
Neuropathy	68 (50-60)‡	—	—	
Macrovascular disease	41 (-10-68)	—	—	16 (71-100)[a]

[a]Fatal or non-fatal myocardial infarction.
*P<0.05
†P≤0.01
‡P<0.001
DCCT=Diabetes Control and Complications Trial; SDIS=Stockholm Diabetes Intervention Study; UKPDS=United Kingdom Prospective Diabetes Study.

An observational follow-up study to the DCCT, the Epidemiologic Diabetes Interventions and Complications (EDIC) study, demonstrated the importance of achieving early glycemic control in reducing the risk of long-term complications. During the EDIC study, patients who had received

conventional treatment during the DCCT were encouraged to switch to intensive diabetes therapy and those who had received intensive therapy in the DCCT continued receiving this care.[132] During the first 7 years of the EDIC, metabolic control converged between the former DCCT treatment groups (HbA1c of 8.1% for the intensive and 8.3% for the conventional group).[132] Despite the delayed improvement in HbA1c in the former DCCT conventional treatment group, patients in the former DCCT intensive therapy group continued to experience a significantly reduced risk of developing microvascular complications during the EDIC.[133-135] This prolonged protective effect of early glycemic control has been called “metabolic memory,” and it highlights the importance of early and aggressive interventions to reduce the risk of long-term diabetes complications.[136]

Prevalence of Poor Glycemic Control

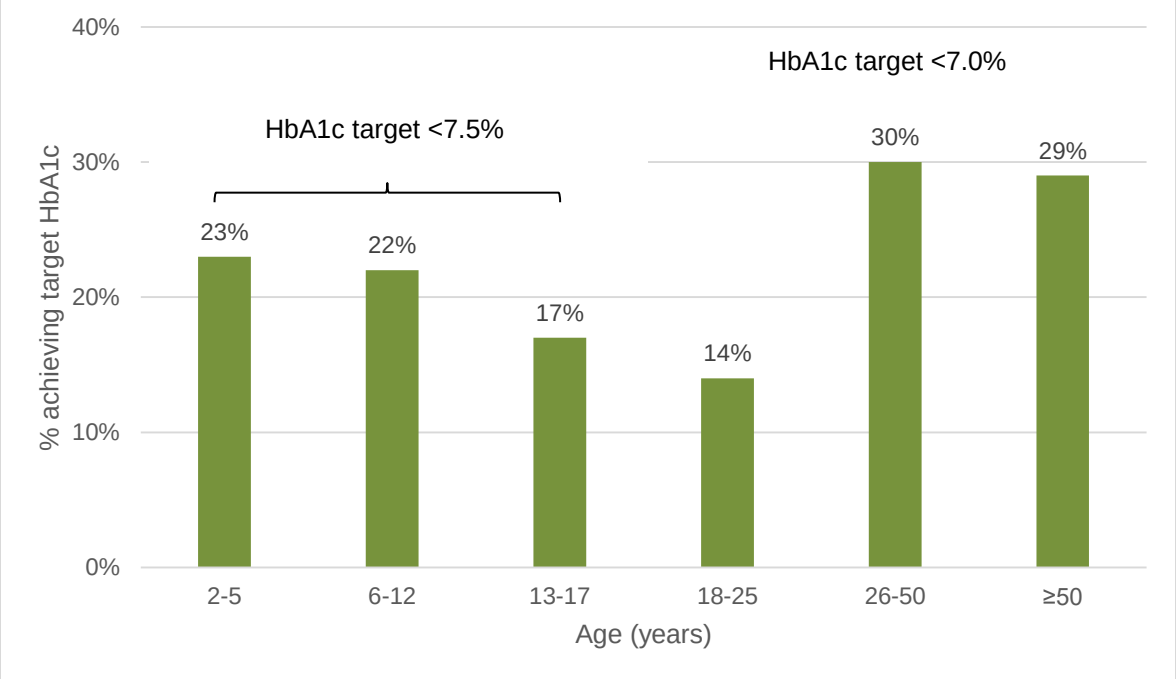
Despite adoption of intensive diabetes therapy as the standard of care in diabetes treatment, data from NHANES 2007-2010 indicate that 48% of U.S. adults with diabetes have poor glycemic control (A1c ≥7.0%).[137] Individuals aged 18-44 years with complications who were receiving less intensive diabetes therapy had the lowest rate of achieving target HbA1c levels (28%), while 70% of adults aged 45-64 years and 84% of those aged ≥65 years with complications who were receiving moderately intensive therapy achieved their HbA1c targets.[137] A lower proportion of older adults with diabetes have poor glycemic control, with 38% of those aged ≥65 years compared with 51% aged <65 years achieving HbA1c of ≥7.0% in NHANES 2003-3006.[138]

A 2007-2008 retrospective claims analysis of a large U.S. managed care organization (MCO) revealed low rates of poor glycemic control among adults with diabetes, with 68% and 44% of individuals with T1DM and T2DM, respectively, at or above the HbA1c target of 7.0%.[139]

In the SEARCH Study, 56% of U.S. youth with T1DM and 46% with T2DM had poor glycemic control, as defined by failing to meet the age-specific ADA target or, for individuals aged <6 years, having an HbA1c ≥8.5%.[140]

Recent data from the US T1D Exchange Registry indicate that about more than three quarters of children and two thirds of adults with T1DM fail to achieve target glucose levels (Figure 8).[141]

FIGURE 7. HBA1C LEVELS AMONG PATIENTS WITH T1DM[141]



f. Humanistic, Societal, and Economic Burden

Aggregate Cost of Diabetes

Diabetes-related complications exert a substantial economic burden to the healthcare system and society. In 2012, the total cost of diabetes in the U.S. was estimated at $245 billion ($274 billion in 2016 USD), with $176 billion ($197 billion in 2016 USD) for direct medical costs and $69 billion ($77 billion in 2016 USD) for costs of lost productivity due to disability, work loss, and premature mortality.[6] A study conducted in 2007 found that T1DM accounted for approximately 9.1% of direct medical costs and 7.5% of indirect costs.[30] Table 10 allocates those figures to the 2012 diabetes cost data to show the cost of diabetes overall and expenditures specifically for T1DM and T2DM.

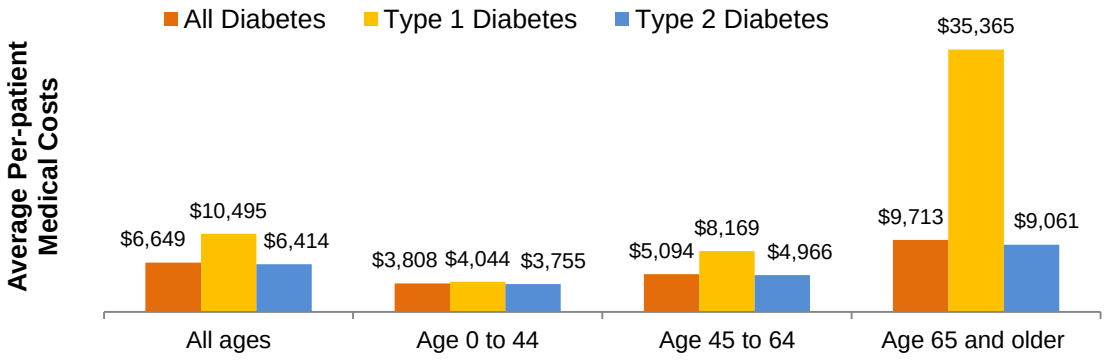
TABLE 10. ECONOMIC BURDEN OF DIAGNOSED DIABETES IN THE U.S. IN 2012[6, 30]

Cost Component	Annual Costs (Billions) in 2016 USD*		
	All Diabetes	T1DM	T2DM
Medical Costs	$197	$17.9	$179.1
Indirect Costs	$77	$7.0	$70.0
Total Costs	$274	$24.9	$249.1
*Costs reported in 2012 USD were inflated to 2016 USD using the Consumer Price Index medical care component.			

Per Capita Cost of Diabetes

In 2012, people with diagnosed diabetes incurred average medical expenditures of about $13,700 ($15,310 in 2016 USD), of which $7,900 ($8,828 in 2016 USD) was attributed to diabetes.[6] Average annual per capita medical costs are higher for individuals with T1DM than for those with T2DM (Figure 9).[30] Although medical costs increase with age in both T1DM and T2DM, they increase at a much faster rate in people with T1DM. Medical costs for individuals aged ≥65 years with T1DM are 8.7 times higher than costs for T1DM patients aged <45 years.

FIGURE 8. AVERAGE ANNUAL MEDICAL COSTS PER PERSON WITH DIABETES (2007 USD)[30]



Cost to Private Payers

Commercial health plan members with diabetes have significantly higher costs than members without diabetes.

- Analysis of data from 40 million individuals with employer-sponsored insurance revealed that per capita annual medical costs were more than 3.5 times higher ($14,999 vs. $4,305) for members with diabetes than for those without diabetes.[142]
- In 2009, seniors from a large sample of UnitedHealth Group's Medicare Advantage members with diabetes had average costs that were 33% higher than Medicare Advantage members without diabetes.[138]

- A study of healthcare costs among 49,356 privately insured youth (aged ≤19 years) found the following:
    - Youth with diabetes had a 6.2 times higher mean annual medical expenditure than youth without diabetes ($9,061 vs. $1,468, P<0.05).[143]
    - Diabetic youth treated with insulin had a $3,650 higher mean annual medical cost than diabetic youth who were not treated with insulin ($9,333 vs. $5,693, P<0.05).[143]

Costs to Medicaid

Medicaid enrollees with diabetes are a high-cost population with significant complications and high levels of healthcare use. Total Medicaid spending for diabetes in 2015 is estimated at $88.6 billion.[144] In 2009, Medicaid enrollees with diabetes spent $13,492 per capita compared with $5,133 for Medicaid enrollees without diabetes.[145] Medicaid enrollees with diabetes had a greater number of annual office visits (12.3 vs. 6.2, P<0.05) and monthly prescription drug fills (5.3 vs.1.4, P<0.05), and were more likely to have an inpatient stay (29% vs. 16%, P<0.05), than enrollees without diabetes.[145]

Tight Glycemic Control Reduces Diabetes Medical Costs

Many studies have shown that improving glycemic control reduces medical costs associated with diabetes.

- In a retrospective analysis of administrative data from a large Washington health maintenance organization, patients with diabetes who achieved a 1% sustained reduction in HbA1c had statistically significant annual cost savings of $685-$950 per patient in the subsequent year.[146]
- A prospective study in a large Minnesota health plan found that for patients with T1DM or T2DM and HbA1c >7.5%, higher HbA1c predicted higher total 3-year healthcare costs.[147]
- A study of T2DM patients in a large managed care organization (MCO) found that diabetes-related costs during a 1-year follow-up period were 32% higher for patients above the target HbA1c level than for patients at or below the target level.[148]
- In a sample of over 10,000 managed care patients with T2DM, patients with good glycemic control (HbA1c ≤7.0%) had 20% lower diabetes-related medical costs than those with poor glycemic control (HbA1c >9.0%).[149]
- Among nearly 10,000 MCO patients with T1DM or T2DM and at least 1 diabetes-related hospital stay, the average cost of hospitalization was more than double for patients with poor glycemic control (HbA1c >10.0%) compared with those with good glycemic control (HbA1c <7%).[150]
- In a large U.S. MCO with about 15 million covered lives:[139]
    - A 1% increase in HbA1c was associated with a corresponding 6% (P=0.006) and 4.4% (P<0.0001) increase in 12-month follow-up medical costs among patients with T1DM and T2DM, respectively, after controlling for age, sex, comorbid conditions, diabetes treatment, and healthcare plan type. This corresponds to an increase in annual diabetes-related medical costs of $445 ($588 in 2016 USD) and $250 ($330 in 2016 USD) for T1DM and T2DM, respectively.
    - Additionally, a 1% increase in HbA1c is associated with an increase in annual diabetes-related pharmacy costs of $109 and $59 ($144 and $78 in 2016 USD) for T1DM and T2DM, respectively.
    - Similarly, a 1% decrease in HbA1c is, on average, associated with a decrease in diabetes-related costs of 5.7% for T1DM and 4.2% for T2DM. This correlates to a

reduction in annual diabetes-related medical costs of $423 and $239 ($559 and $316 in 2016 USD) for T1DM and T2DM, respectively.

2.2.2 Approaches to Treatment

a. Principle Options and Practices

Goals for Glycemic Control

Although HbA1c and blood glucose targets are needed, the ADA[151] and the Association of Clinical Endocrinologists (AACE) and American College of Endocrinology (ACE)[152] emphasize that glycemic targets should be individualized with the goal of achieving the best possible control while minimizing the risk of severe hyperglycemia and hypoglycemia. Table 11 presents the ADA and AACE/ACE recommendations for HbA1c targets for different patient subgroups.

TABLE 11. SUMMARY OF ADA AND AACE/ACE GLYCEMIC RECOMMENDATIONS FOR NON-PREGNANT ADULTS WITH DIABETES

Parameter	ADA[151]	AACE/ACE[152]
A1c	<7.0*	≤6.5%‡
Preprandial capillary plasma glucose	80-130 mg/dL (4.4-7.2 mmol/L)*	
Peak postprandial capillary plasma glucose†	<180 mg/dL (<10.0 mmol/L)*	

*More or less stringent glycemic goals may be appropriate for individual patients. Goals should be individualized based on duration of diabetes, age/life expectancy, comorbid conditions, known CVD or advanced microvascular complications, hypoglycemia unawareness, and individual patient considerations.

†Postprandial glucose may be targeted if HbA1c goals are not met despite reaching preprandial glucose goals. Postprandial glucose measurements should be made 1-2 h after the beginning of the meal – generally when levels peak in patients with diabetes.

‡Glucose targets should be individualized and take into account life expectancy, disease duration, presence or absence of micro- and macrovascular complications, CVD risk factors, comorbid conditions, and risk for hypoglycemia, as well as the patient's psychological status.

Insulin Therapy and Other Anti-Diabetes Medication

T1DM

According to the ADA, the recommended therapy for T1DM includes:

- Multiple daily injections (MDI) of prandial insulin and basal insulin or continuous subcutaneous insulin infusion (insulin pump therapy);
- Matching prandial insulin doses to carbohydrate intake, premeal blood glucose levels, and anticipated physical activity;
- Use of rapid-acting insulin analogs to reduce hypoglycemia; and
- Continued access to insulin pump therapy after age 65 years in individuals who have successfully used this treatment.[32]

T2DM

Interventions designed to impact an individual's physical activity levels and food intake are critical parts of T2DM management.[153] A patient-centered approach should be used to guide the choice of pharmacologic agents and include considerations of efficacy, hypoglycemia risk, impact on weight, potential side effects, cost, and patient preferences.[32] Metformin is the initial preferred pharmacotherapy for patients with T2DM.[32] In newly diagnosed T2DM patients who are markedly symptomatic and/or have HbA1c ≥10%, insulin therapy (with or without additional agents) should be considered from the outset.[32] If noninsulin monotherapy at maximum

tolerated dose does not achieve or maintain the HbA1c target after 3 months, a second oral agent, glucagon-like peptide 1 receptor agonist, or basal insulin should be added.[32] Insulin therapy should not be delayed in T2DM patients who are not achieving glycemic goals.[32] In patients with long-standing suboptimally controlled T2DM and established atherosclerotic CVD, empagliflozin or liraglutide should be considered as they have been shown to reduce cardiovascular and all-cause mortality when added to standard care.

Glucose Monitoring Recommendations

Patients who are receiving MDI or insulin pump therapy should perform SMBG prior to meals and snacks, at bedtime, occasionally postprandially, prior to exercise, when they suspect low blood glucose, after treating low blood glucose until they are normoglycemic, and prior to critical tasks such as driving.[151] For many patients, this will require testing 6-10 (or more) times daily.[151]

Guidelines and consensus statements from The American Diabetes Association, the American Assocciation of Clinical Endocrinology and The Endocrine Society regarding the use of RT-CGM for monitoring glucose in patients with diabetes are described in detail in Section 5.1 and are summarized below. RT-CGM should be available to all insulin-treated patients with diabetes.[154] In addition, patients with HUA, other patients at risk from hypoglycemia, including the elderly, patients with renal impairment, and athletes would also benefit from RT-CGM.[154] T2DM patients who use antihyperglycemic agents other than insulin might also benefit from RT-CGM, but the evidence base is inadequate to make a strong recommendation.[154]

A1c tests should be performed at least twice yearly for patients who meet treatment goals and have stable glycemic control.[151] HbA1c tests should be performed quarterly for patients whose therapy has changed or who are not meeting glycemic control goals.[151]

b. Alternative Treatments

Intensive insulin therapy (MDI or insulin pump therapy) is the standard recommended pharmacologic treatment for patients with T1DM.[32] Most patients with T2DM can be successfully treated with lifestyle intervention and oral antidiabetic agents after initial diagnosis.[32, 155] However, T2DM is a progressive disease that requires increasing the intensity of treatment to maintain glycemic control, and many patients will eventually require insulin.[32]

c. Place and Anticipated Uses of Proposed Therapy

The anticipated uses of the G5™ Mobile CGM System, summarized below, are consistent with the policies of large commercial health plans in the U.S regarding coverage of RT-CGM.[156-158]

The G5™ Mobile CGM System should be considered as replacement to conventional SMBG in people aged ≥2 years with diabetes (ICD-9-CM 250.x), and is particularly appropriate in insulin-treated people with diabetes who meet any of the following criteria:

- Suboptimal glycemic control, as evidenced by HbA1c exceeding the target specified by consensus guidelines
    - The ADA has defined suboptimal glycemic control in adults and children as HbA1c >7.0% and >7.5%, respectively.[151]
- Wide fluctuations in blood glucose levels regardless of A1c
    - Research indicates that the combination of ambient hyperglycemia, glucose variability, and hypoglycemia (the “glycemic triumvirate”) accelerates the development and progression of diabetes complications more so than the additive contribution of the individual glycemic disorders.[159]
- Frequent hypoglycemia
    - Hypoglycemia includes all episodes of an abnormally low plasma glucose concentration that expose the individual to potential harm.[39]

- All episodes of hypoglycemia substantially increase the risk of subsequent hypoglycemia.[39]

- Severe hypoglycemia
  - Severe hypoglycemia is defined as an event requiring assistance of another person to actively administer carbohydrate, glucagon, or other resuscitative actions.[39]

- Hypoglycemia Unawareness (HUA)
  - HUA is defined as the inability to detect the early neurogenic warning symptoms of hypoglycemia.[39] The presence of HUA increases the risk of severe hypoglycemia by 3-10 times in patients with T1DM[70, 83, 88, 89, 91, 93, 97, 102, 103] and 2-17 times in patients with insulin-treated T2DM.[83, 93, 98, 99]

d. Ancillary Disease or Care Management Strategies

The Dexcom G5 Mobile Continuous Glucose Monitoring System (Dexcom G5 Mobile) is a glucose monitoring system indicated for the management of diabetes in persons age 2 years and older. The Dexcom G5 Mobile is designed to replace fingerstick blood glucose testing for diabetes treatment decisions. Interpretation of the Dexcom G5 Mobile results should be based on the glucose trends and several sequential readings over time. The Dexcom G5 Mobile also aids in the detection of episodes of hyperglycemia and hypoglycemia, facilitating both acute and long-term therapy adjustments.
The Dexcom G5 Mobile is intended for single patient use and requires a prescription..

e. Expected Outcomes of Therapy

Limitations of Conventional Glucose Monitoring (SMBG)

Frequent SMBG, a core component of intensive diabetes therapy, provides limited information upon which to base diabetes management decisions. Each SMBG measurement offers only a “snapshot” of blood glucose concentration at a single point in time, and cannot provide information about the direction and rate of change or the duration, frequency, and causes of fluctuations in blood glucose values.[14] As a result, even with diligently administered SMBG, individuals with insulin-treated diabetes may be at risk for potentially dangerous glycemic excursions that escape detection and may make inappropriate treatment decisions due to lack of information about glucose values. For example, a recent study found that, despite a high frequency of daily SMBG (10 tests per day), only 32% of hypoglycemic events were detected in children with T1DM younger than 7 years.[160]

Nocturnal hypoglycemia, which occurs frequently in patients treated with intensive insulin therapy,[161-163] is the primary concern motivating prescription of RT-CGM in two thirds of cases.[164] Most of these hypoglycemic episodes are asymptomatic and remain undetected by standard SMBG, as fingerstick glucose measurements are rarely performed at night.[13]

Even diligent SMBG may negatively impact clinical decision making and glucose control[165-167] because many commercially available blood glucose meters used for SMBG fail to meet International Organization for Standardization (ISO) standards for accuracy.[167-171] For example, in a recent study, SMBG measurements of children and adolescents with T1DM taken under “real life conditions” failed to meet both old and new ISO standard criteria and large deviations of SMBG values for the “true” glucose levels results in higher HbA1c levels and markedly increased rates of hypoglycemic events.[167]

Advantages of RT-CGM Technology and the G5™ Mobile CGM System

RT-CGM technology represents a significant advance over SMBG alone because this technology reports glucose every 5 minutes, which facilitates the detection of impending low or high glucose levels that may otherwise be missed with intermittent data captured by SMGB.[172] For patients with HUA, the alarm function of RT-CGM devices may be their only warning of emerging

hypoglycemia. Furthermore, RT-CGM technology provides information on the direction, rate, and trend in glycemic activity, thereby offering additional data to guide disease management decisions (e.g., insulin dosage adjustments, changes in diet), which may enable patients to reduce glycemic variability and increase the time spent in the target glucose range.[12, 13] Glucose changes in response to diet, medication, physical activity, and other lifestyle factors can be continually observed, providing cues for immediate and retrospective blood glucose management.

The G5™ Mobile CGM System is the only RT-CGM device approved for making treatment decisions and the replacement of confirmatory SMBG. In addition, CMS ruling CMS-1682-R, which created a classification of therapeutic CGM that is reimbursable under Medicare Part B, designated the G5™ Mobile CGM System as the only device meeting criteria as therapeutic CGM. Evidence from REPLACE-BG, a multicenter, randomized, noninferiority clinical trial conducted to determine whether the use of RT-CGM without confirmatory BGM is as safe and effective as using RT-CGM adjunctive to BGM in well-controlled adults with T1DM.[173] Both the RT-CGM only and RT-CGM + BGM groups used a Dexcom G4™ Platinum CGM System with an enhanced algorithm (Software 505) that provides the same accuracy as the G5™ Mobile CGM System. Mean time in 70-180 mg/dL (primary endpoint) was 63 ±13% at both baseline and 26 weeks in the RT-CGM-only group and 65 ± 13% and 65 ±11% in the RT-CGM + BGM group (adjusted difference 0%; one-sided 95% CI 22%). No severe hypoglycemic events occurred in the RT-CGM-only group, and one occurred in the RT-CGM + BGM group. These results indicate that patients using the G5™ Mobile CGM System can reduce their burden of multiple daily finger sticks when using RT-CGM without loss of efficacy or safety, and that the cost of RT-CGM may be lowered by reducing the number of BGM test strips required.

Two recently published RCTs (the DIAMOND and GOLD trials) have shown that RT-CGM in conjunction with MDI therapy significantly improves glycemic control in insulin-treated patients with diabetes compared to MDI with conventional SMBG. The DIAMOND RCT evaluated the effectiveness of RT-CGM in 158 patients with poorly-controlled T1DM who were treated with MDI.[15] At 24 weeks, the HbA1c level was 0.6% ($P<0.001$) lower in the group that received RT-CGM than in the group that received conventional blood glucose monitoring. Patients who received RT-CGM also spent significantly less time in hypoglycemia ($P=0.002$), had reductions in diabetes distress ($P<0.001$), less hypoglycemic fear ($P=0.02$), and increases in hypoglycemic confidence ($P<0.001$) and well-being ($P=0.01$) compared with conventionally monitored patients.[15, 17]

The GOLD trial, a multicenter, randomized, open-label, crossover study conducted in 161 patients with poorly-controlled T1DM treated with MDI, evaluated the impact of RT-CGM on glycemic outcomes, well-being, diabetes distress, and hypoglycemic fear and confidence.[16] After 26 weeks, RT-CGM resulted in a mean HbA1c level that was 0.43% less than in the group receiving conventional blood glucose monitoring ($P<0.001$); patients treated with RT-CGM also reported less fear of hypoglycemia ($P<0.001$) and improved well-being ($P=0.02$) compared to conventional SMBG.

Data from two recently published real-world studies show that RT-CGM used in conjunction with MDI is as effective as the combination of RT-CGM and insulin pump therapy for improving glycemic control. In a nonrandomized, prospective, real-life clinical trial in which T1DM patients received MDI or insulin pump therapy in combination with either RT-CGM or SMBG, both insulin delivery modalities combined with RT-CGM provided significant and comparable decreases in HbA1c with concurrent reduction in time spent in hypoglycemia compared to insulin therapy with conventional blood glucose monitoring (i.e., SMBG) after 1 year.[174] An analysis of real-world data from the T1D Exchange registry examined the impact of RT-CGM on HbA1c in T1DM patients treated with MDI or insulin pump therapy.[175] Among 17,731 eligible participants, 8,783 (35%) used MDI + SMBG, 8,783 (50%) used an insulin pump + SMBG, 2,316 (13%) used an insulin pump + RT-CGM, and 410 (2%) used MDI +RT-CGM. Among RT-CGM users, mean HbA1c was similar in the MDI and insulin pump groups (7.6% vs. 7.7%, $P=0.82$); however,

HbA1c in both RT-CGM groups was lower than among patients using insulin pump + SMBG (8.3%, P<0.0001) and MDI + SMBG (8.8%, P<0.0001). Results were similar in adults and youth.

The results of these recent RCTs and real-world studies support the findings of earlier RCTs, including the landmark JDRF studies, that established the efficacy of RT-CGM in T1DM patients treated with either MDI or insulin pump therapy.[176-183] These studies have shown that, compared to SMBG, RT-CGM significantly reduces HbA1c, glycemic excursions, and glycemic variability without increasing hypoglycemic episodes in children and adults with poorly-controlled T1DM and in adults with well-controlled T1DM who are receiving MDI or insulin pump therapy.[176-180] Similar improvements in glycemic control are seen when RT-CGM is continued or initiated in a routine clinical practice environment [179, 181, 182] The greatest reductions in HbA1c occur in patients who consistently use RT-CGM. .[15, 16, 179] [177, 179, 180, 182, 184]

It is important to note that the majority RCTs conducted to date have not been designed or powered to detect significant changes in the rate of severe hypoglycemia, have often excluded individuals with recurrent severe hypoglycemia from the study samples, and have not robustly measured hypoglycemic episodes.[185] However, two studies indicate that RT-CGM may have a substantial impact on the incidence of severe hypoglycemia. In a 6-month, open-label, extension study of the JDRF clinical trial, children and adults with poorly-controlled T1DM receiving intensive insulin treatment who were initiated on RT-CGM experienced a 46% reduction in the incidence of severe hypoglycemia.[15, 16, 179] Similarly, in a randomized, open-label, crossover study conducted in adults with poorly-controlled T1DM and HUA, RT-CGM reduced the incidence of severe hypoglycemia by 59% compared with SMBG.[186]

f. Post-marketing Obligations

Dexcom adheres to the FDA's standard requirements for Class lll (PMA) manufacturer reporting of medical device-related adverse events. There are no additional FDA requirements for post-marketing surveillance for the G5™ Mobile CGM System.

In addition to reporting adverse events to the FDA, Dexcom is committed to continuous quality improvement of products. Following standard operating procedures, Dexcom monitor multiple inputs for customer feedback: Technical support is responsible for recording customer feedback that will be evaluated, tracked, and trended for product complaints. Marketing compiles marketing solicited data from such sources as surveys, focus groups, etc., into the customer feedback process. Dexcom may also provide product for third-party or physician-sponsored studies, andl have access to the product feedback information and many times will be asked to review data from these studies. This information is fed into the design control process to be evaluated as design inputs for product iterations and next-generation devices.

g. Other Key Assumptions

Not applicable.

3.0 SUPPORTING CLINICAL EVIDENCE

3.1 KEY CLINICAL STUDIES

3.1.1 Clinical Studies Supporting Labeled Indications

RT-CGM is indicated in children and adults with diabetes. Below, we summarize RCTs and other supporting studies evaluating the efficacy and safety of RT-CGM in children and adults with T1DM or insulin-treated T2DM. In the first subsection, we summarize a pivotal trial demonstrating that use of the most accurate available RT-CGM without regular use of confirmatory BGM is as safe and effective as using RT-CGM with BGM in well-controlled adults with T1DM receiving insulin pump therapy. In the second subsection, we summarize all studies that included a comparison of MDI + RT-CGM versus MDI + SMBG. In the third subsection, studies that evaluated the impact of RT-CGM in patients treated with either MDI or insulin pump therapy are summarized. Studies that compared sensor-augmented insulin pump therapy with insulin pump therapy and conventional blood glucose monitoring are omitted from this section because these comparisons provide no information about the relative contributions of RT-CGM and insulin pump therapy on study outcomes. A fourth subsection describes other supporting studies. Quality grades were derived from a 2012 AHRQ meta-analysis[187] or based on criteria similar to those used in the AHRQ review.

RT-CGM Only Versus RT-CGM + Blood Glucose Measurements in Adults with T1DM

Aleppo G, Ruedy KJ, Riddlesworth TD, Kruger DF, Peters AL, Hirsch I, et al. REPLACE-BG: A randomized trial comparing continuous glucose monitoring with and without routine blood glucose monitoring in well-controlled adults with type 1 diabetes *Diabetes Care.* 2017.[173]

Study Description: This was a 26-week randomized non-inferiority clinical trial to determine whether use of RT-CGM without confirmatory blood glucose measurements (BGM) is as safe and effective as using RT-CGM adjunctive to BGM in well-controlled adults with T1DM. The study was conducted from March 2015 to October 2016 14 sites in the US T1D Exchange Clinic Network.

Funding Source: Dexcom, Inc.

Methods: Major eligibility criteria included age ≥18 years, T1DM for ≥1 year with insulin pump treatment for at least 3 months (and not currently using a low glucose suspend function), and point-of-care HbA1c ≤9.0% (≤75 mmol/mol). Exclusion criteria included the occurrence of a severe hypoglycemia event resulting in seizure or loss of consciousness in the past 3 years or an event without seizure/loss of consciousness requiring the assistance of another individual in the past 12 months; >10.0% of baseline CGM glucose concentrations <60 mg/dL (3.3 mmol/L); >1 episode of DKA in the past year; history of seizures other than due to hypoglycemia; current use of a threshold suspend pump feature; myocardial infarction or stroke in the past 6 months; estimated glomerular filtration rate <30 mL/min/1.73 m^2; abnormal thyroid function; use of a systemic β-blocker; regular use of oral corticosteroids; initiation of a noninsulin drug for glucose control during the past 3 months; pregnant; inpatient psychiatric treatment in past 6 months; and presence of a contraindicated medical condition or medication including ongoing use of acetaminophen.

Patients were randomly assigned from a computer-generated sequence to the RT-CGM-only or RT-CGM+BGM group in a 2:1 ratio based on a permuted block design with stratification by clinical site. Both groups used a Dexcom G4™ Platinum CGM System with an enhanced algorithm (Software 505) (referred to as the study RT-CGM), which measures glucose concentrations from interstitial fluid in the range of 40-400 mg/dL (2.2-22.2 mmol/L) every 5 min for up to 7 days. The study BGM was the Contour® Next (Ascensia Diabetes Care US, Inc., Parsippany, NJ). The Abbott Precision Xtra® (Abbott Diabetes Care, Alameda, CA) was used to measure blood ketone levels.

The run-in phase, which was initiated by 276 participants, lasted for 2-10 weeks, depending on whether the participant was a RT-CGM user at the time of study entry. There were two parts of the run-in phase of which participants completed various portions, depending on whether they were using RT-CGM at study entry: 1) Dexcom RT-CGM system configured to record glucose concentrations not visible to the participant (referred to as a blinded CGM) for 14 days to collect baseline data and 2) standard RT-CGM for 2-8 weeks for RT-CGM training. In both phases, the participant's willingness and ability to use the study RT-CGM and BGM were assessed.

Participants who used a Dexcom RT-CGM for at least 21 of the 28 days before study enrollment skipped the blinded CGM phase and were required to have only 2 weeks of unblinded study RT-CGM use. Participants who used a Medtronic CGM for at least 21 of the 28 days before enrollment skipped the blinded CGM phase and were required to have at least 4 weeks of unblinded study CGM use. All other participants completed the 14-day blinded phase and 8 weeks of unblinded RT-CGM use. Successful completion of the blinded phase required study CGM wear on a minimum of 11 of 14 days and an average of three blood glucose measurements per day by the study BGM. Successful completion of the unblinded CGM phase required CGM use on ≥21 days during the past 28 days and an average of four or more BGM measurements on at least 90% of days; for participants whose run-in phase was shortened, the number of days of CGM use were reduced accordingly. Of 276 participants who entered the run-in phase, 50 did not enter the randomized trial for the following reasons: 24 did not meet the BGM criterion, 6 had >10% of CGM readings of <60 mg/dL, and 20 were withdrawn for a variety of other reasons.

After randomization, participants in both groups were instructed to calibrate the study RT-CGM per Dexcom specifications and to use it daily. Both groups also were instructed to perform a BGM measurement when the fasting RT-CGM glucose concentration was <300 mg/dL or when the RT-CGM glucose concentration during the day was >300 mg/dL for 1 h. In both instances, if the BGM measurement confirmed that the glucose level was >300 mg/dL, the participant was instructed to perform a blood ketone measurement with the study ketone meter.

The RT-CGM+BGM group was instructed to perform a BGM measurement with the study meter for RT-CGM calibrations whenever an insulin bolus was administered, when treating or attempting to prevent hypoglycemia, and before going to bed. The RT-CGM only group was instructed to dose insulin and make management decisions on the basis of the RT-CGM sensor glucose concentration, except in the following circumstances that required BGM testing: 1) for 12 h after insertion of a new sensor, 2) on a sick day (e.g., nausea, vomiting), 3) for 4 h after taking acetaminophen, 4) for symptoms suggestive of hypoglycemia but the RT-CGM sensor glucose concentration was not hypoglycemic or dropping rapidly, 5) for 20 min after treating a low RT-CGM sensor glucose concentration if the RT-CGM sensor glucose level had not begun to rise, 6) before administering an insulin bolus when the RT-CGM sensor glucose concentration was >250 mg/dL, and 7) for a fasting RT-CGM glucose >300 mg/dL or RT-CGM glucose concentration during the day >300 mg/dL for 1 h. If a RT-CGM calibration measurement coincided with a meal, the participant was instructed to base the meal bolus on the RT-CGM sensor value and then perform a BGM measurement to calibrate the RT-CGM.

Clinical Outcomes: Analyses followed the intention-to-treat principle. The primary outcome was a treatment group comparison of time in range of 70-180 mg/dL (3.9-10.0 mmol/L) during the 26-week trial by using an ANCOVA model adjusted for baseline time in range and site as a random effect. Confounding was assessed by repeating the analysis with the inclusion of potential confounding variables as covariates. To be included in the analyses of the primary and secondary outcomes of CGM metrics, patients were required to have at least 200 hours of RT-CGM data during the trial. Secondary outcomes included CGM measures of mean glucose, glycemic variability (coefficient of variation), and hypoglycemia (time <70 mg/dL, 60 mg/dL, and 50 mg/dL; area above curve 70 mg/dL; and percentage of days with ≥20 consecutive min of glucose concentrations <60 mg/dL), hyperglycemia (time >180 mg/dL, 250 mg/dL, 300 mg/dL; area under the curve 180 mg/dL; and percentage of days with ≥20 consecutive min of glucose concentrations >300 mg/dL), change in HbA1c, and proportion of participants with both no worsening of HbA1c by >0.3% (3.3 mmol/mol) and no severe hypoglycemic event.. Safety outcomes included severe

hypoglycemia (defined as an event that required assistance from another person to administer carbohydrate, glucagon, or other resuscitative actions); DKA, hyperglycemia not meeting the definition of DKA for which emergency evaluation or treatment was obtained from a health care provider, or blood ketone levels ≥0.6 mg/dL or ≥1.0 mmol/L; and other occurrences meeting the definition of a SAE.

Sample Characteristics: A total of 226 patients were randomly assigned to the RT-CGM group (n=179) or the RT-CGM+BGM group (n=77). The mean age of patients was 44 ± 14 years and mean duration of T1DM was 24 ± 12 years. The mean HbA1c was 7.0% ± 0.7%. Almost half (47%) of patients were RT-CGM users.

One participant in the RT-CGM-only group was determined after randomization to have been ineligible (percentage of time <60 mg/dL during blinded baseline CGM wear was >10%). Seven participants in the RT-CGM-only group and two in the RT-CGM+BGM group withdrew from the trial. Thus, the trial was completed by 142 (95%) of the RT-CGM-only group participants and by 75 (97%) of the RT-CGM+BGM group participants.

Among participants completing the trial, all in both groups were using RT-CGM in month 6. CGM use averaged 6.76 ± 0.5 and 6.86 ± 0.4 days/week in the RT-CGM-only and RT-CGM+BGM groups, respectively, over the 26-week trial, with 91% and 95% averaging ≥6 days/week. All participants in the RT-CGM+BGM group and all but one in the RT-CGM-only group averaged ≥5 days/week over the entire 26 weeks. Among the completers of the trial, BGM tests per day from meter downloads (including the two required daily BGM tests) averaged 2.86 ± 0.9 in the RT-CGM-only group and 5.4 ± 1.4 in the RT-CGM+BGM group (P<0.001).

Outcome (Time in Normoglycemia): Mean percentage time in normoglycemia (70-180 mg/dL) was 63 ± 13% at both baseline and 26 weeks in the RT-CGM group. In the RT-CGM+BGM group, mean percentage time in normoglycemia was 65 ± 13% at baseline and 65% ± 11% at 26 weeks (adjusted difference = 0%; one-side 95% CI -2.0%).

Outcome (Glucose Control): Other CGM metrics of glucose control for mean glucose, hyperglycemia, hypoglycemia, and glycemic variability also showed little change from baseline to 26 weeks and no significant differences between groups (Table 1).

TABLE 1. STUDY OUTCOMES

CGM Outcome	RT-CGM Only Group		RT-CGM+BGM Group		P value
	Baseline (n=149)	26-week study period (n=148)	Baseline (n=77)	26-week study period (n=76)	
% time in range (70-180 mg/dL)	63 ±13	63 ±13	65 ±13	65 ±11	0.81
Mean glucose (mg/dL)	162 ± 22	162 ± 23	158 ± 22	158 ± 20	>0.99
Coefficient of variation (%)	36 (33-41)	37 (34-41)	37 (33-40)	37 (34-40)	0.58
Hypoglycemia					
% time <70 mg/dL	2.9 (1.5-4.5)	3.0 (1.6-5.1)	3.6 (1.9-4.8)	3.7 (1.9-4.9)	0.95
% time <60 mg/dL	1.1 (0.6-0.9)	1.3 (0.5-2.4)	1.4 (0.6-2.3)	1.6 (0.6-2.2)	0.57
% time <50 mg/dL	0.3 (0.2-0.5)	0.3 (0.1-0.6)	0.4 (0.2-0.7)	0.5 (0.2-0.8)	0.75
Area above curve 70 mg/dL	0.3 (0.2-0.5)	0.3 (0.1-0.6)	0.4 (0.2-0.6)	0.4 (0.2-0.5)	0.76
% days with ≥20 consecutive min glucose values <60 mg/dL	25 (15-43)	28 (13-42)	33 (15-43)	32 (16-46)	0.68
Hyperglycemia					
% time <>180 mg/dL	33 (25-43)	35 (25-41)	31 (22-40)	31 (24-38)	0.88
% time >250 mg/dL	8 (4-15)	9 (5-13)	7 (3-11)	7 (4-11)	0.65
% time >300 mg/dL	2 (1-5)	2 (1-4)	2 (1-4)	2 (1-3)	0.72

CGM Outcome	RT-CGM Only Group		RT-CGM+BGM Group		P value
	Baseline (n=149)	26-week study period (n=148)	Baseline (n=77)	26-week study period (n=76)	
Area under curve 180 mg/dL	17 (10-25)	17 (10-23)	20 (10-37)	20 (8-36)	0.90
% days with ≥20 consecutive min glucose values >300 mg/dL	25 (12-48)	27 (14-40)	20 (8-36)	20 (10-37)	0.72
HbA1c (%)	7.1 ± 0.7	7.1 ± 0.7	7.0 ± 0.7	7.0 ± **0.6**	
HbA1c (mmol/mol)	54 ± 7.7	54 ± 7.7	53 ± 7.7	53 ± 6.6	
Change in HbA1c from baseline (%)		0.0 ± 0.5		0.0 ± 0.5	0.41
Change in HbA1c from baseline mmol/mol)		0.0 ± 5.5		0.0 ± 5.5	0.41
No worsening of HbA1c by >0.3% (3.3 mmol/mol) and no severe hypoglycemic event		115 (81)		54 (72)	0.15
Data are median (interquartile range), mean ±SD, or n (%) unless otherwise specified.					

Outcome (Severe Hypoglycemia): No severe hypoglycemia events occurred in the RT-CGM only group and one occurred in the RT-CGM+BGM group.

Outcome (Adverse Events): There were no occurrences of DKA in either group. Other SAEs, unrelated to the study intervention, occurred in four (3%) of participants in the RT-CGM only group and three (4%) in the RT-CGM+BGM group. A blood ketone level ≥0.6 mmol/L (10.8 mg/dL) occurred at least once in 48 (32%) participants in the RT-CGM only group and 26 (34%) in the RT-CGM+BGM group (P=0.79).

Study Limitations: The major limitation of the trial relates to the generalizability of the results based on the participant inclusion and exclusion criteria. The trial cohort included adults with T1DM who used an insulin pump and were well controlled and likely to adhere to the study protocol and excluded individuals with significant hypoglycemia unawareness or a substantial amount of CGM-measured hypoglycemia. Although the trial only included pump users to be able to document when an insulin bolus was given, it seems reasonable to apply the results to individuals who use MDI who otherwise fit the profile of the study participants because the impact of sensor inaccuracy in determining the amount of a bolus should be similar in pump users and injection users.

Conclusion: In well-controlled adults with T1DM at low risk for severe hypoglycemia, RT-CGM without regular use of confirmatory BGM is as safe and effective as using RT-CGM with confirmatory BGM for insulin dosing.

Quality Grade: Good

MDI + RT-CGM Versus MDI + SMBG

Beck RW, Riddlesworth T, Ruedy K, Ahmann A, Bergenstal R, Haller S, et al. Effect of continuous glucose monitoring on glycemic control in adults with type 1 diabetes using insulin injections: The DIAMOND randomized clinical trial. *JAMA.* 2017;317:371-8.[15]

Study Description: This was a 24-week randomized, open-label, parallel-group multicenter clinical trial conducted from October 2014 and May 2016 at 24 endocrinology practices in the US. The trial was conducted to evaluate the effect of RT-CGM in adults with T1DM who have elevated HbA1c levels and use MDI.

Funding Source: Dexcom, Inc.

Methods: Major eligibility criteria included age 25 years or older, diagnosis of T1DM treated for at least 1year with MDI, central laboratory-measured HbA1c level of 7.5% to 10.0%, no home use of a personal CGM device in the 3 months before the trial, and a negative pregnancy test for women of childbearing potential.

Each participant was required to complete a 2-week prerandomization phase using a CGM system that was configured to record glucose concentrations not visible to the participant (referred to as a “blinded” CGM). Eligibility required that the blinded CGM be worn on at least 85% of possible days, the CGM be calibrated at least 2 times per day, and blood glucose meter testing be performed at least 3 times daily. Fourteen participants did not meet these criteria and did not continue into the randomized trial. One participant had a sudden death during the prerandomization phase.

On the study website, after verification of eligibility from data entered, each participant was assigned randomly from a computer-generated sequence to either the RT-CGM or control group in a 2:1 ratio, with a permuted block design (block sizes of 3 and 6) stratified by HbA1c level (<8.5% and ≥8.5%). A 2:1 randomization was used rather than 1:1 to provide a larger sample size for a separate follow-on randomized trial assessing glycemic benefits of initiating pump therapy in RT-CGM users using insulin injections.

Participants in the CGM group were provided with a RT-CGM system (Dexcom G4™ Platinum CGM System with an enhanced algorithm, software 505) that measured glucose concentrations from interstitial fluid in the range of 40 to 400 mg/dL every 5 minutes for up to 7 days. Participants in both groups were provided with a Bayer Contour Next USB meter and test strips. The RT-CGM group was instructed to use RT-CGM daily, calibrate the RT-CGM device twice daily, and verify the RT-CGM glucose concentration with the blood glucose meter before injecting insulin. General guidelines were provided to participants about using RT-CGM, and individualized recommendations were made by their clinician about incorporating RT-CGM trend information into their diabetes management. The control group was asked to perform home blood glucose monitoring at least 4 times daily. Participants in both groups were provided general diabetes management education, and clinicians were encouraged to review downloaded glucose data at each visit to inform treatment recommendations, which were at clinician discretion and not prescriptive in the protocol.

Follow-up visits for both treatment groups occurred after 4, 12, and 24 weeks. The RT-CGM group had an additional visit 1 week after randomization. The control group had 2 additional visits 1 week before the 12- and 24-week visits, at which a CGM sensor in blinded mode was inserted to collect glucose data for 1 week. Telephone contacts for both groups occurred 2 and 3 weeks after randomization.

Clinical Outcomes: The primary outcome was change in the central laboratory-measured HbA1c level. Prespecified secondary outcomes included percentage of participants with HbA1c level less than 7.0%; CGM-measured time in range (70-180 mg/dL), duration of hypoglycemia (<70 mg/dL, <60 mg/dL, and <50 mg/dL), duration of hyperglycemia (>180 mg/dL, >250 mg/dL, and >300

mg/dL), and glucose variability (coefficient of variation); change in HUA; and change in frequency of blood glucose meter testing.

Prespecified exploratory outcomes included CGM-measured mean glucose concentration and the following binary HbA1c outcomes to assist in translation of the primary HbA1c analysis to a participant level: HbA1c level less than 7.5% and relative HbA1c reduction greater than or equal to 10%. Post hoc outcomes included HbA1c reduction of 1% or more, HbA1c level less than 7.0% or reduction of 1% or more, CGM-measured area above the curve 70 mg/dL and area under the curve 180 mg/dL, change in insulin dose, and change in body weight.

Satisfaction with CGM was assessed by completion at 24 weeks of the CGM Satisfaction Survey (44 items on a 1-5 Likert scale, with the computed score representing the mean of the 44 items and subscales of benefits and lack of hassles).

Safety outcomes included severe hypoglycemia (defined as an event that required assistance from another person to administer carbohydrate, glucagon, or other resuscitative actions), DKA, and serious adverse events regardless of causality.

Analyses followed the intent-to-treat (ITT) principle. The following change was made from the protocol and statistical analysis plan before the data lock: the primary analysis was a treatment group comparison of the change in HbA1c level from baseline to 24 weeks, adjusted for baseline HbA1c level and clinical site as a random effect, in a repeated measures linear model in the protocol and with analysis of covariance in the statistical analysis plan. Confounding was assessed by repeating the analysis, including potential confounding variables as covariates. The Rubin method was used to impute for missing data.

Sample Characteristics: A total of 158 participants were assigned to the RT-CGM group (n=105) or control group (n=53). Mean (SD) age was 48 (13) years (range, 26-73 years, with 34 participants [22%] ≥60 years); 44% were women. Median diabetes duration was 19 years (IQR, 10-31 years), and mean baseline HbA1c level was 8.6% (SD, 0.6%; range, 7.5%-9.9%).

The 24-week primary study outcome visit was completed by 102 participants (97%) in the RT-CGM group and all 53 (100%) in the control group. Overall visit completion was 99% and 98%, respectively. Three participants in the RT-CGM group (4 total visits) and 3 in the control group (3 total visits) had additional visits, not required in the protocol, for diabetes management.

Outcome (HbA1c): Mean reduction in HbA1c level from baseline was 1.1% at 12 weeks and 1.0% at 24 weeks in the RT-CGM group and 0.5% and 0.4%, respectively, in the control group (primary analysis repeated-measures P<0.001). At 24 weeks, the adjusted treatment group difference in mean change in HbA1c level was -0.6% (95% CI, -0.8% to -0.3%; P<0.001; Figure 1). There was no significant interaction of the effect of treatment on 24-week HbA1c level according to baseline HbA1c, age (Figure 2), education level, or type of site.

FIGURE 1. MEAN HBA1C TREATMENT GROUP DIFFERENCES

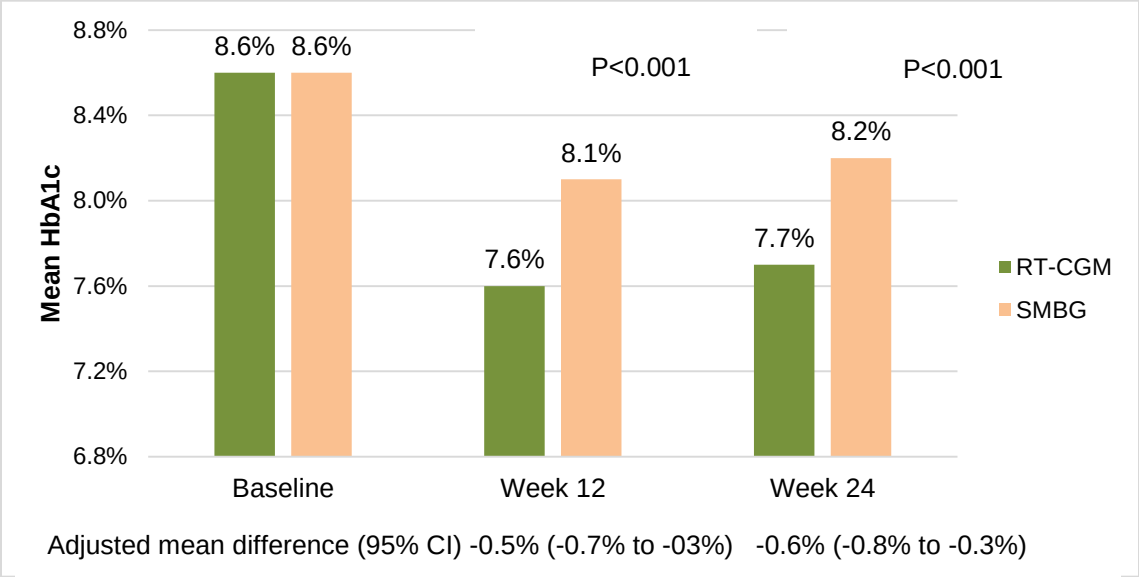
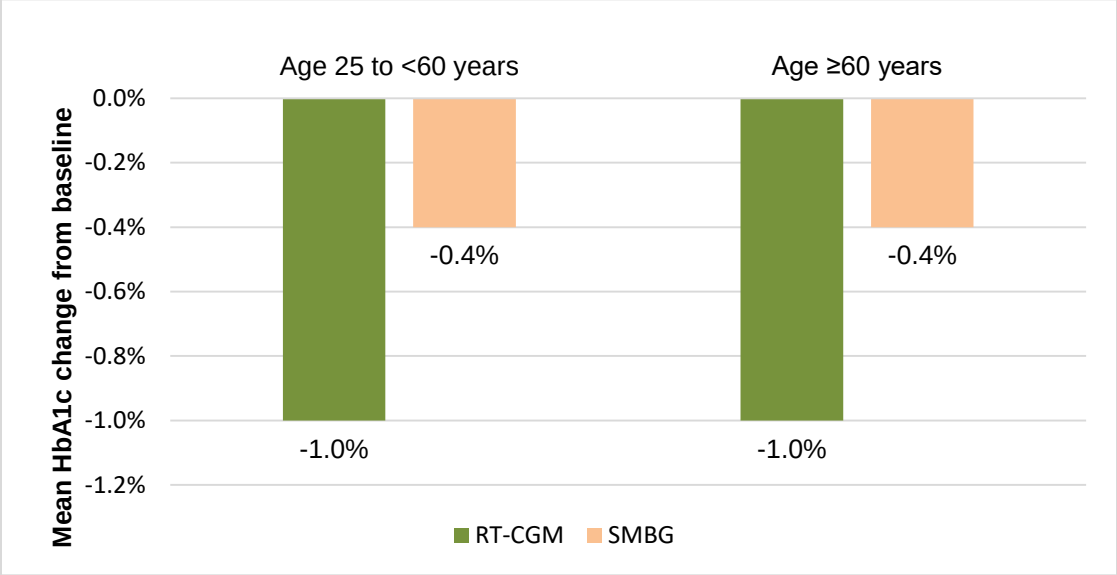


FIGURE 2. MEAN HBA1C CHANGE BY AGE



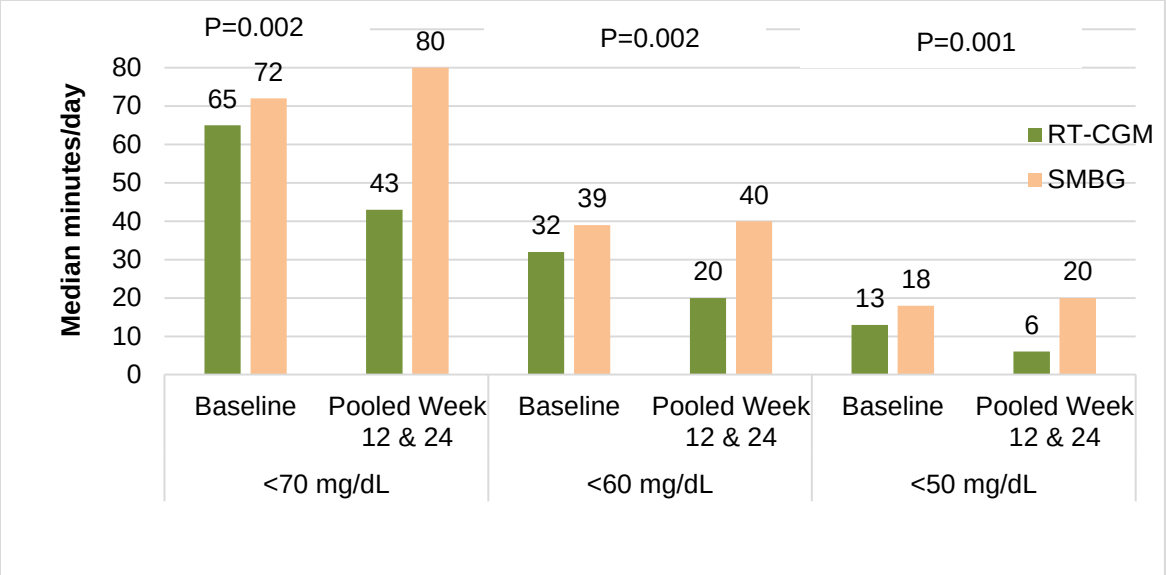
Outcome (Sensor Use): Among the 102 participants in the RT-CGM group who completed the trial, median RT-CGM use was 7.0 days/week (IQR, 7.0-7.0) at 4, 12, and 24 weeks; only 2 (2%) discontinued RT-CGM before the 24-week visit. During month 6 (weeks 21-24), RT-CGM use was 6 or more days/week for 93% of the 102 participants.

Outcome (SMBG): Mean (SD) frequency of SMBG was 5.1 (1.8) per day in the RT-CGM group and 5.1 (1.4) per day in the control group during the baseline period of blinded CGM wear and 3.6 (1.6) per day and 4.6 (1.6) per day, respectively, at 24 weeks (adjusted mean difference for the change, -1.0; 99% CI, -1.7 to -0.4; P<0.001).

Outcome (Time in Normoglycemia, Hyperglycemia, and Hypoglycemia): CGM metrics for time in the range of 70 to 180 mg/dL, hyperglycemia, hypoglycemia (Figure 3), and glycemic variability favored the RT-CGM group compared with the control group. In exploratory analyses, hypoglycemia treatment group differences favored the RT-CGM group during both daytime and

nighttime, but hyperglycemia treatment group differences favoring the RT-CGM group were present only during the daytime.

FIGURE 3. TIME SPENT IN HYPOGLYCEMIA



Outcome (Insulin Use): At 24 weeks, in post hoc analyses there were no significant differences between the RT-CGM group and control group in median change in total daily insulin dose per kilogram of body weight (-0.02 vs 0.03 U/kg; P=0.23), median ratio of long-acting to rapid-acting daily insulin dose (0.9 vs 1.0; P=0.54), or proportion of participants with an increase in number of injections of rapid-acting insulin per day (26% vs 26%; P=0.90).

Outcome (Body Weight): At 24 weeks, there were no significant differences between the RT-CGM group and control group in mean change in body weight (1.7 vs 0.7 kg; mean difference, 1.0 kg; 99% CI, -0.7 to 2.8; P=0.12).

Outcome (HUA): Clarke Hypoglycemia Unawareness scores did not differ between groups at 24 weeks (mean difference, -0.1; 99% CI, -0.7 to 0.5; P=0.64).

Outcome (Satisfaction with RT-CGM): In the RT-CGM group, satisfaction with use of RT-CGM was high, as indicated by the mean (SD) score of 4.2 (0.4) on the CGM Satisfaction Survey, with mean (SD) scores of 4.2 (0.5) on the benefits subscale and 4.3 (0.5) on the subscale for lack of hassles.

Outcome (Severe Hypoglycemia): Severe hypoglycemic events occurred in 2 participants in each group (P=0.67).

Outcome (Adverse Events): There were no occurrences of diabetic ketoacidosis. Other serious AEs, unrelated to the study intervention, occurred in 2 participants in the RT-CGM group and none in the control group.

Study Limitations: In light of the eligibility criteria, the results may not apply to individuals with T1DM who are younger than 26 years or have HbA1c levels outside the range of 7.5% to 9.9% and should not be applied to individuals with T2DM who receive MDI. The informed consent process and the run-in phase had the potential to exclude individuals who might be less adherent with RT-CGM than the cohort that was studied.

Conclusion: Among adults with T1DM who use MDI, the use of RT-CGM compared with usual care resulted in a greater decrease in HbA1c level during 24 weeks. Further research is needed to assess longer-term effectiveness, as well as clinical outcomes and adverse effects.

Quality Grade: Good

Ruedy, K. Riddlesworth, TD, Graham C. Continuous glucose monitoring in older adults with type 1 and type 2 diabetes using multiple daily injections of insulin: results from the DIAMOND trial. *J Diabetes Sci Technol* 1-9, 2017. DOI: 10.1177/1932296817704445 **.[188]**

Study Description: This was a 24-week randomized, open-label, parallel-group multicenter clinical trial conducted from October 2014 to May 2016 at 27 endocrinology practices in the US and Canada. This analysis was conducted to evaluate the effectiveness of RT-CGM in adults aged ≥60 years with T1DM or T2DM using MDI.

Funding Source: Dexcom, Inc.

Methods: Major eligibility criteria included age ≥60 years, diagnosis of T1DM or T2DM treated for at least 1year with MDI, central laboratory-measured HbA1c level of 7.5% to 10.0%, stable diabetes medication regimen and weight over the prior 3 months, and an estimated glomerular filtration rate ≥45. Major exclusion criteria were use of real-time CGM within 3 months of screening and any medical condition(s) that would make it inappropriate or unsafe to target an HbA1c of <7.0%.

Each participant was required to complete a 2-week prerandomization phase using a CGM system that was configured to record glucose concentrations not visible to the participant (referred to as a "blinded" CGM). Eligibility required that the blinded CGM be worn on at least 85% of possible days, the CGM be calibrated at least 2 times per day, and blood glucose meter testing be performed at least 3 times daily (T1DM) or 2 times daily (T2DM). Fourteen participants did not meet these criteria and did not continue into the randomized trial. One participant had a sudden death during the prerandomization phase.

On the study website, after verification of eligibility from data entered, each participant was assigned randomly from a computer-generated sequence to either the RT-CGM or control group in a 2:1 ratio, with a permuted block design (block sizes of 3 and 6) stratified by HbA1c level (<8.5% and ≥8.5%). A 2:1 randomization was used rather than 1:1 to provide a larger sample size for a separate follow-on randomized trial assessing glycemic benefits of initiating pump therapy in RT-CGM users using insulin injections.

Participants in the CGM group were provided with a RT-CGM system (Dexcom G4™ Platinum CGM System with an enhanced algorithm, software 505) that measured glucose concentrations from interstitial fluid in the range of 40 to 400 mg/dL every 5 minutes for up to 7 days. Participants in both groups were provided with a Bayer Contour Next USB meter and test strips. The RT-CGM group was instructed to use RT-CGM daily, calibrate the RT-CGM device twice daily, and verify the RT-CGM glucose concentration with the blood glucose meter before injecting insulin. General guidelines were provided to participants about using RT-CGM, and individualized recommendations were made by their clinician about incorporating RT-CGM trend information into their diabetes management. The control group was asked to perform home blood glucose monitoring at least 4 times daily. Participants in both groups were provided general diabetes management education, and clinicians were encouraged to review downloaded glucose data at each visit to inform treatment recommendations, which were at clinician discretion and not prescriptive in the protocol.

Follow-up visits for both treatment groups occurred after 4, 12, and 24 weeks. The RT-CGM group had an additional visit 1 week after randomization. The control group had 2 additional visits 1 week before the 12- and 24-week visits, at which a CGM sensor in blinded mode was inserted to collect glucose data for 1 week. Telephone contacts for both groups occurred 2 and 3 weeks after randomization.

Clinical Outcomes: The primary outcome was change in the central laboratory-measured HbA1c level from baseline to Week 24. Prespecified secondary outcomes included percentage of participants with HbA1c level less than 7.0%; CGM-measured time in range (70-180 mg/dL), duration of hypoglycemia (<70 mg/dL, <60 mg/dL, and <50 mg/dL), duration of hyperglycemia

(>180 mg/dL, >250 mg/dL, and >300 mg/dL), and glucose variability (coefficient of variation); change in HUA; and change in frequency of blood glucose meter testing.

Sample Characteristics: A total of 116 patients were enrolled (T1DM, n=34; T2DM, n=82). Participants with mean age of 67 ± 5 years were randomly assigned to the RT-CGM group (n=63) or Control group (n=53). Median (IQR) of diabetes duration was 21 (14, 30) years and mean baseline HbA1c was 8.5 ± 0.6%. The groups were well-balanced with respect to education level and diabetes durations. The 24-week primary study outcome visit was completed by 97% (n=61) of the RT-CGM group and 100% (n=53) of the Control group.

Outcome (HbA1c): Mean HbA1c at baseline (8.4 ± 0.6% in the RT-CGM group and 8.6 ± 0.7% in the Control group) decreased to 7.5 ± 0.7% and 8.0 ± 0.8%, respectively, at 12 weeks with an adjusted difference in mean change of -0.3% (P=0.005). At 24 weeks, HbA1c reduction from baseline was greater in the RT-CGM group than Control group (-0.9 ± 0.7% vs. -0.5 ± 0.7%) with an adjusted difference in mean change of -0.4 ± 0.1% (P<0.001).

Outcome (CGM Outcomes): CGM metrics are shown in Table 1. Significant between-group differences in improvements in CGM-measured mean glucose, glycemic variation and in the average time within glucose range (70-180 mg/dL) and in hyperglycemia (>250 mg/dL) at 24 weeks were observed; however, there was minimal hypoglycemia at baseline in both the RT-CGM and Control groups (median time <60 mg/dL was 10 vs. 8 minutes/day, respectively), which affected the ability to detect a difference in hypoglycemia.

Outcome (Glucose Monitoring): Among the 61 RT-CGM participants completing the trial, mean RT-CGM use was 6.9 ± 0.2 days/week in month one (weeks 1-4); and 6.8 ± 1.1 days/week in month 6 (weeks 21-24); 97% used RT- CGM ≥6 days/week in month 6. The mean reduction in the number of daily blood glucose tests from baseline to week 24 was significantly greater for the RT-CGM group compared with the Control group (-1.2 ± 1.6 vs. -0.2 ± 1.4, P=0.001).

Outcome (RT-CGM Satisfaction): In the RT-CGM group, satisfaction with use of RT-CGM was high as indicated by the mean score of 4.2 ± 0.4 on the CGM Satisfaction Survey (possible score range 1 to 5), with mean scores of 4.3 ± 0.5 on the 'Benefits' subscale and 1.8 ± 0.5 on the 'Hassles' subscale, indicating that perceived benefits were high while perceived hassles were few.

Outcome (Adverse Events): There were no severe hypoglycemia or diabetic ketoacidosis events in either group.

Study Limitations: The study did not address the question of whether RT-CGM would reduce severe hypoglycemia events in vulnerable populations (e.g., patients with hypoglycemia unawareness).

Conclusion: This randomized trial demonstrates that RT-CGM can be beneficial for elderly adults with T1DM and T2DM treated with basal-bolus insulin therapy, as has been shown in prior studies in younger adults with diabetes. A high percentage of the study participants used RT-CGM on a daily or near-daily basis over 6 months with a limited number of visits and phone contacts. RT-CGM use was associated with a high degree of patient satisfaction, reduction in HbA1c, hyperglycemia and glycemic variability and an increase in time in glucose range. Given these significant benefits, RT-CGM should be considered for older adults with diabetes using MDI.

Quality Grade: Good

TABLE 1. CGM OUTCOMES

	RT-CGM			Control			P value†
	Baseline (n=63)	12 Weeks (n=61) *	24 Weeks (n=58) *	Baseline (n=53)	12 Weeks (n=52) *	24 Weeks (n=50) *	
Mean ± SD glucose, mg/dL	175 ± 25	167 ± 27	168 ± 29	179 ± 30	178 ± 28	180 ± 28	0.01
Glycemic variability, coefficient of variation, %	34 (28, 42)	33 (28, 37)	31 (28, 36)	34 (29, 38)	33 (28, 38)	33 (27, 39)	0.02
Time spent 70-180 mg/dL, min/day	796 ± 236	892 ± 256	88 9± 251	753 ± 253	767 ± 265	732 ±2 52	<0.001
Time spent >250 mg/dL, min/day	172 (83, 281)	93 (30, 180)	89 (37, 208)	208 (112, 294)	180 (81, 251)	179 (83, 316)	0.006
Time spent <60 mg/dL, min/day	10 (1, 38)	4 (0, 15)	3 (0, 15)	8 (1, 23)	4 (0, 27)	4 (0, 24)	0.11

Median (IQR) is reported for glycemic variability and for time in the hypoglycemic and hyperglycemic ranges. Mean ± SD is reported for mean glucose and time in normoglycemia.
*CGM metrics were not calculated for participants with < 72 h of data: 1 RT-CGM /1 Control at 12 Weeks; 3 RT-CGM/3 Control at 24 Weeks.
† P values are from analysis of covariance models adjusted for the corresponding baseline value, baseline HbA1c and clinical site as a random effect using pooled data from 12 and 24 weeks. Due to skewed distributions, the models for glycemic variability and time in the hypoglycemic and hyperglycemic ranges were based on ranks using van der Waerden scores.

Polonsky WH, Hessler D, Ruedy KJ, Beck RW. The impact of continuous glucose monitoring on markers of quality of life in adults with type 1 diabetes: further findings from the DIAMOND clinical trial. *Diabetes Care* 2017 Apr 7. pii: dc170133. doi: 10.2337/dc17-0133. [Epub ahead of print][17]

Study Description: This was a 24-week randomized, open-label, parallel-group multicenter clinical trial conducted from October 2014 and May 2016 at 24 endocrinology practices in the US. The trial was conducted to evaluate the effect of RT-CGM in adults with T1DM who have elevated HbA1c levels and use MDI.

Funding Source: Dexcom, Inc.

Methods: Major eligibility criteria included age 25 years or older, diagnosis of T1DM treated for at least 1year with MDI, central laboratory-measured HbA1c level of 7.5% to 10.0%, no home use of a personal CGM device in the 3 months before the trial, and a negative pregnancy test for women of childbearing potential.

Each participant was required to complete a 2-week prerandomization phase using a CGM system that was configured to record glucose concentrations not visible to the participant (referred to as a "blinded" CGM). Eligibility required that the blinded CGM be worn on at least 85% of possible days, the CGM be calibrated at least 2 times per day, and blood glucose meter testing be performed at least 3 times daily. Fourteen participants did not meet these criteria and did not continue into the randomized trial. One participant had a sudden death during the prerandomization phase.

On the study website, after verification of eligibility from data entered, each participant was assigned randomly from a computer-generated sequence to either the RT-CGM or control group in a 2:1 ratio, with a permuted block design (block sizes of 3 and 6) stratified by HbA1c level (<8.5% and ≥8.5%). A 2:1 randomization was used rather than 1:1 to provide a larger sample size for a separate follow-on randomized trial assessing glycemic benefits of initiating pump therapy in RT-CGM users using insulin injections.

Participants in the CGM group were provided with a RT-CGM system (Dexcom G4™ Platinum CGM System with an enhanced algorithm, software 505) that measured glucose concentrations from interstitial fluid in the range of 40 to 400 mg/dL every 5 minutes for up to 7 days. Participants in both groups were provided with a Bayer Contour Next USB meter and test strips. The RT-CGM group was instructed to use RT-CGM daily, calibrate the RT-CGM device twice daily, and verify the RT-CGM glucose concentration with the blood glucose meter before injecting insulin. General guidelines were provided to participants about using RT-CGM, and individualized recommendations were made by their clinician about incorporating RT-CGM trend information into their diabetes management. The control group was asked to perform home blood glucose monitoring at least 4 times daily. Participants in both groups were provided general diabetes management education, and clinicians were encouraged to review downloaded glucose data at each visit to inform treatment recommendations, which were at clinician discretion and not prescriptive in the protocol.

Follow-up visits for both treatment groups occurred after 4, 12, and 24 weeks. The RT-CGM group had an additional visit 1 week after randomization. The control group had 2 additional visits 1 week before the 12- and 24-week visits, at which a CGM sensor in blinded mode was inserted to collect glucose data for 1 week. Telephone contacts for both groups occurred 2 and 3 weeks after randomization.

Clinical Outcomes/Analyses: Analyses followed the ITT principle. The primary analysis was a treatment group comparison of the change in quality of life from baseline to 24 weeks that used linear regression models adjusted for baseline levels of the outcome and clinical site as a random effect. Analyses were repeated to include potential confounding variables of age, sex, and diabetes duration as covariates. The World Health Organization (Five) Well-being Index (WHO-5)

and the EQ-5D-5L were used to assess non-diabetes-specific quality of life. The Diabetes Distress Scale (DDS), the Hypoglycemia Fear Survey (HFS-III), and the Hypoglycemia Confidence Scale (HCS) were used to assess diabetes-specific quality of life. Treatment satisfaction was measured in the RT-CGM group at 24 weeks.

Sample Characteristics: A total of 158 participants were assigned to the RT-CGM group (n=105) or control group (n=53) and the 24-week primary study outcome visit was completed by 102 participants (97%) in the RT-CGM group and all 53 (100%) in the control group. Mean (SD) age was 48 (13) years (range, 26-73 years); 45% were female. Mean diabetes duration was 12 ± 14 years, and mean baseline HbA1c level was 8.6% ± 0.6%.

Outcome (Quality of Life): RT-CGM participants reported significantly greater increases in hypoglycemic confidence than SMBG participants (Table 1). Modest decreases in diabetes-related distress in the RT-CGM group and increases in the control group resulted in a mean ± SE cumulative difference for total distress of 0.23 ± 0.07 between groups (P=0.02). Between-group differences for diabetes-related distress and hypoglycemia confidence persisted in models that further adjusted for participant demographic factors.

No significant group differences were observed in hypoglycemic worry or in the non-diabetes-specific quality of life measures.

Outcome (Satisfaction with RT-CGM): In the RT-CGM group, satisfaction with use of RT-CGM was high, as indicated by the mean (SD) score of 4.2 (0.4) on the CGM Satisfaction Survey, with mean (SD) scores of 4.2 (0.5) on the perceived benefits subscale and 4.3 (0.5) on the subscale for lack of hassles. Overall RT-CGM satisfaction was moderately related to decreases in total diabetes-related distress (B = -0.31, P<0.001) and hypoglycemic worry (B = -4.22, P=0.03) and increases in hypoglycemic confidence (B = 0.49, P<0.001) and overall well-being (WHO-5: B = 7.61, P=0.02).

Study Limitations: The study included only adults with T1DM who use MDI and may not generalize to other patient groups of interest, such as teens and insulin pump users with T1DM or individuals with T2DM. Study participants were racially homogenous, with the majority of participants being non-Hispanic white with a high education level. The study was limited to a 24-week period, so it is not known whether the observed benefits would be maintained over longer periods. Although the noted effect sizes were small/moderate to moderate, improvement within the RT-CGM group itself was modest, and the potential clinical significant in unknown.

Conclusion: RT-CGM compared with SMBG contributes to statistically significant improvements in diabetes-specific quality of life as well as enhances glycemic control in adults with T1DM who use MDI.

Quality Grade: Good

TABLE 1. QUALITY OF LIFE OUTCOMES BY STUDY ARM

	RT-CGM Group		Control Group		Model 1			Model 2		
	Baseline	**24 weeks**	**Baseline**	**24 weeks**	**Mean difference in change between arms**	**95% CI**	**P value**	**Mean difference in change between arms**	**95% CI**	**P value**
WHO-5	71.28 ± 14.71	70.47 ± 16.68	69.06 ± 14.89	67.32 ± 86	-1.26	-5.42 to 2.91	0.62	-1.63	-5.88 to 2.61	0.50
EQ-5D-5L	0.90 ± 0.11	0.89 ± 0.10	0.89 ± 0.11	0.88 ± 0.10	0.00	-0.03 to 0.03	0.86	0.00	-0.03 to 0.03	0.92
Diabetes distress										
Total	1.78 ± 0.65	1.61 ± 0.48	1.69 ± 0.62	1.78 ± 0.65	0.22	0.08 to 0.36	0.009	0.23	0.09 to 0.36	0.03
Regimen	2.09 ± 0.87	1.81 ± 0.68	2.08 ± 0.99	2.05 ± 0.87	0.25	0.05 to 0.46	0.04	0.26	0.05 to 0.47	0.04
Emotional burden	2.06 ± 0.90	1.93 ± 0.80	1.91 ± 0.83	2,03 ± 0.95	0.21	0.01 to 0.41	0.08	0.21	0.00 to 0.41	0.09
Interpersonal	1.54 ± 0.63	1.43 ± 0.61	1.45 ± 0.70	1.73 ± 1.04	0.37	0.16 to 0.56	0.009	0.37	0.16 to 0.58	0.01
Physician	1.19 ± 0.63	1.09 ± 0.25	1.12 ± 0.25	1.18 ± 0.69	0.10	-0.04 to 0.24	0.21	0.12	-0.03 to 0.27	0.18
Hypoglycemia confidence	3.27 ± 0.57	3.47 ± 0.55	3.15 ± 0.57	3.18 ± 0.63	0.23	0.06 to 0.40	0.03	0.23	0.05 to 0.41	0.03
HFS-III Worry Subscale	15.75 ± 12.30	13.48 ± 10.63	17.30 ± 13.22	17.71 ± 14.92	3.17	0.19 to 6.14	0.07	2.46	-0.58 to 5.51	0.15

Data are unadjusted mean ± SD by group unless otherwise indicated. Model 1 values resulted from mixed linear regression models adjusted for baseline levels of the outcome and clinical site and random effects. Model 2 values are further adjusted to age, sex, and number of years since diagnosis. P values are adjusted for multiple comparisons by using the Benjamini-Hochberg procedure.
CI = confidence interval; HFS = Hypoglycemia Fear Scale; WHO-5 = World Health Organization Well-Being Index.

Lind M, Polonsky W, Hirsch IB, Heise T, Bolinder J, Dahlqvist S, et al. Continuous glucose monitoring vs conventional therapy for glycemic control in adults with type 1 diabetes treated with multiple daily insulin injections: The GOLD randomized clinical trial. *JAMA.* 2017;317:379-87.[16]

Study Description: This was a randomized, open-label, multicenter clinical trial with a crossover design conducted from February 2014 and June 2016 at 15 sites in Sweden. After a run-in period of up to 6 weeks, patients were randomized to receive RT-CGM or conventional SMBG for 26 weeks with a 17-week washout between treatment periods. The aim of this study was to analyze the effect of RT-CGM on glycemic control, hypoglycemia, well-being, and glycemic variability in individuals with T1DM treated with MDI.

Funding Source: The NU Hospital Group, Trollhättan and Uddevalla, Sweden

Methods: Individuals aged ≥18 years with HbA1c of at least 7.5% (58 mmol/mol) treated with MDI were included. Patients were required to have a fasting C-peptide level of less than 0.91 ng/mL (0.30 nmol/L) and diabetes duration of >1 year. Patients treated with insulin pumps were excluded.

During a 6-week run in, patients completed masked CGM for 2 weeks and questionnaires regarding the following characteristics: subjective well-being (World Health Organization-5 [WHO-5]), treatment satisfaction (Diabetes Treatment Satisfaction Questionnaire [status version and change version]), fear of hypoglycemia (Hypoglycemia Fear Survey), hypoglycemic confidence (Hypoglycemia Confidence Questionnaire), and diabetes-related distress (Problem Areas in Diabetes Scale). During masked CGM, glucose levels were recorded but were not seen by the patient. After masked CGM, patients were excluded if they either did not believe they would wear the CGM sensor more than 80% of the time or did not perform adequate calibrations during the run in (on average ≥12 of 14 during a 7-day period).

Patients were randomized 1:1 into the first treatment period to RT-CGM using the Dexcom G4™ Platinum CGM system or conventional therapy. Randomization was performed by a centralized web-based program stratifying patients by site according to a predefined sequence; random block size varied between 1 + 1 and 2 + 2.

RT-CGM was compared with conventional therapy using only SMBG. Patients were not blinded to treatment. All patients received basic instruction on insulin dosing, such as bolus correction, food choices, and the effect of physical activity on glucose control. A graph was displayed for patients showing the proportion of insulin at time of injection (100%) and the proportion of insulin remaining to give effect at various time points after injection. The patients received general guidelines for interpreting glucose levels and trends obtained by RT-CGM.

During the first week, no alarms were set on the RT-CGM device for low glucose levels except for acute hypoglycemia (<55 mg/dL or 3.05 mmol/L). Alarm settings were introduced no later than 2 weeks after randomization. At each visit, patients were encouraged to use RT-CGM information at least every1 to2 hours during daytime. In the conventional group, patients were encouraged to measure blood glucose levels according to guidelines (i.e., ≥4 times daily). Insulin dosing was based on self-measurement of blood glucose and not RT-CGM values. Assessment of HbA1c was blinded to treatment status. During the 17-week washout period, patients used conventional therapy and masked CGM was performed for 2 weeks.

Patients were assessed at the start of each treatment period and at weeks 2, 4, 13, and 26. HbA1c was measured at all visits in each treatment period except week 2. Masked CGM was performed 2 weeks before both treatment periods. During conventional therapy, masked CGM was also performed during 2 of the 4 last weeks to evaluate total time in hypoglycemia, euglycemia, hyperglycemia, and glycemic variability. At all visits, CGM and self-measurements of blood glucose data were downloaded and used to assess glucose levels, number of self-measurements of blood glucose, time CGM was in use, and for optimizing glycemic control. To

maintain an equal number of visits for both treatment periods, the study did not permit extra patient visits for improving glycemic control.

Clinical Outcomes: The study was powered to detect a difference of 0.3%(3mmol/mol) in HbA1c between weeks 26 and 69 at 90% power and assuming a standard deviation of 1.1%, which required 144 participants. Assuming a dropout rate of 10%, 160 individuals were required for enrollment.

The full analysis set (FAS) consisted of all randomized patients who had at least 1 follow-up measurement in each treatment period. The safety analysis consisted of all randomized patients who received treatment (RT-CGM or conventional therapy) at any time with patients assigned to treatment administered but not randomized treatment. The last observation carried forward (LOCF) principle was applied for any missing efficacy measurements from the last weeks of each treatment period.

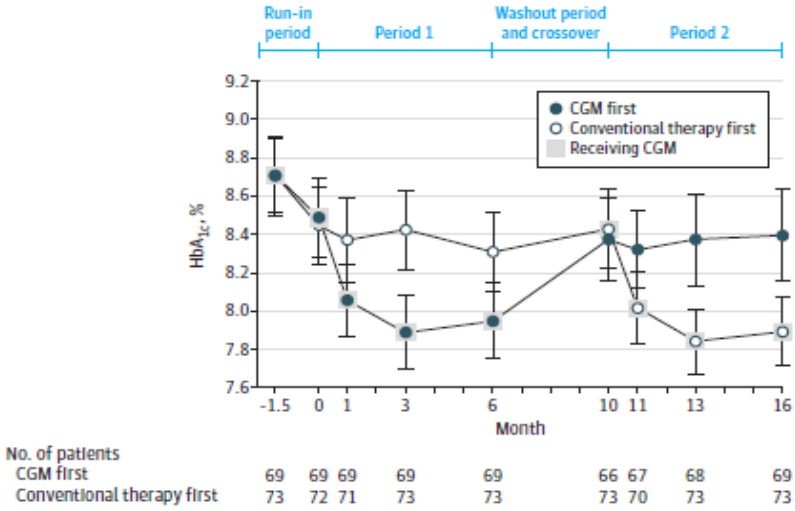
The primary endpoint was the difference in HbA1c between RT-CGM and conventional therapy at weeks 26 and 69 for the FAS with adjustment for treatment period and patient effects using procedure for generalized linear models in SAS software, with sequence, patient (sequence), period, and treatment as class variables. A post hoc sensitivity analysis of primary outcome was performed by multiple imputation with 50 study samplings on all patients randomized by using demographics, baseline characteristics, baseline comorbidities, and HbA1c values at run in and randomization as imputation variables. A second post hoc sensitivity analysis investigating the effect of the site and interaction between site and treatment modeled as fixed effects on the primary outcome was performed.

Secondary endpoints included mean amplitude glycemic excursions; the SD of glucose levels; and the amount of time in hypoglycemia, hyperglycemia, and euglycemia during RT-CGM use. Other endpoints included Diabetes Treatment Satisfaction status (range 0-36) and change in satisfaction (range -18 to 18), WHO-5 Well-Being Index (range 0-100), Hypoglycemic Fear Behavior Scale (range 0-4) and Hypoglycemic Fear Worry Scale (range 0-4), and the Problem Areas in Diabetes scale (range 0-100). Other endpoints were the number of self-measurements of blood glucose and rate of severe hypoglycemia, defined as unconsciousness from hypoglycemia or requiring assistance from another person.

Sample Characteristics: There were 161 patients randomized with a mean age was 43.7 years; 45.3% were women, and mean HbA1c was 8.6% (70 mmol/mol). Of the 161 randomized patients, 142 (88.0%) had follow-up data during both treatment periods in the FAS population. The FAS population had a mean (SD) age of 44.6 (12.7) years; 56.3% were men and 99.3% were white. Mean HbA1c was 8.7% (SD, 0.8%) (72mmol/mol), and mean diabetes duration was 22.2 (11.8) years. For the primary efficacy outcome HbA1c, FAS population, the LOCF imputation was done for 2 (2.9%) patients at the end of RT-CGM therapy and 3 (4.1%) at the end of conventional therapy.

Outcome (HbA1c): Mean (SD) HbA1c during RT-CGM use was 7.92% (0.8%) (63 mmol/mol) and during conventional treatment was 8.35% (0.9%) (68 mmol/mol) (mean difference, -0.43% [95% CI, -0.57%to -0.29%] or -4.7 mmol/mol [95%CI, -6.27 to -3.13 mmol/mol]); P<0.001). HbA1c was lower in RT-CGM-treated patients during the first and second treatment periods, whereas levels were similar at the beginning of both periods.

FIGURE 1. HBA1C VALUES AT INCLUSION, RANDOMIZATION, AND DURING THE TWO DIFFERENT PERIOD OF TREATMENT



In a sensitivity analysis (performed by using multiple imputation) of the primary outcome, including all participants in the trial (n=161), the effect on HbA1c by RT-CGM was 0.39% (95% CI, 0.24%-0.55% [P<0.001]). The second sensitivity analysis of primary outcome (adjusted for the site effect and interaction between site and treatment) showed an HbA1c reduction of 0.43% (95% CI, 0.22%-0.64% [P<0.001]) for RT-CGM use vs conventional therapy. The interaction between site and treatment term was not significant (P=0.84).

Outcome (Glycemic Variability): The SD of blood glucose estimated by CGM and compared with masked CGM during conventional treatment was lower during RT-CGM use than conventional therapy (68.49 vs 77.23 mg/dL; P<0.001) as was the case for mean amplitude of glycemic excursions (161.93 vs 180.96 mg/dL; P<0.001).

Outcome (Well-being, Treatment Satisfaction, Diabetes Distress, and Hypoglycemic Fear and Confidence): Overall well-being, estimated with the WHO-5 questionnaire, improved during RT-CGM use (66.1 vs 62.7; P=0.02). Treatment satisfaction was higher during RT-CGM use as measured by the Diabetes Treatment Satisfaction Questionnaire status version (30.21 vs 26.62; P<0.001) and change version (13.20 vs 5.97; P<0.001). The Hypoglycemia Confidence Questionnaire scale showed less hypoglycemia fear in favor of RT-CGM (3.40 vs 3.27; P<0.001).

Outcome (Sensor Use): Overall mean time of RT-CGM use, estimated by the proportion of CGM data downloaded in relation to follow-up time, was 87.8% during RT-CGM treatment periods. RT-CGM use ranged between 86.5% and 91.9% during various study visits. HbA1c was reduced by 0.46% (0.31%-0.61%) in patients using the CGM sensor more than 70% of the time, and there was no significant difference inHbA1c for those using the CGM sensor for less than 70% of the time.

Outcome (SMBG): Patients performed a mean (SD) of 2.75 (1.39) self-measurements of blood glucose during RT-CGM therapy and 3.66 (2.30) during conventional therapy.

Outcome (Hypoglycemia): During RT-CGM use, the mean (SD) percentage of time patients were in a hypoglycemic range (<70 mg/dL) was 2.79% (2.97%) and 4.79% (4.03%) during conventional therapy and for glucose levels of <54 mg/dL, the percentage of time was 0.79% (1.23%) during RT-CGM use and 1.89% (2.12%) during conventional therapy. There were 5 events of severe hypoglycemia during conventional treatment (event rate, 0.19 per 1000 patient-years) and 1 event occurred during RT-CGM therapy (event rate, 0.04 per 1000 patient-years). There were 7 severe hypoglycemia events during the washout period when patients were undergoing conventional therapy (event rate, 0.41 per 1000 patient-years).

Outcome (Adverse Events): In total, there were 77 patients with 137 AEs during RT-CGM and 67 patients with 122 AEs during conventional therapy. There were no obvious numerical differences for any AE between the treatments. One patient in the RT-CGM group discontinued use because of an allergic reaction to the sensor. There were 7 patients with a total of 9 serious AEs during RT-CGM treatment and 3 patients with total of 9 serious AEs during conventional treatment. Ketoacidosis was not reported during the study.

Study Limitations: Nineteen patients (~12.0%) had no follow-up data in the second treatment period and were not included in the primary analysis. Generally, in a parallel-group study, this can lead to an imbalance between groups. However, in the current study, patients served as their own controls and thus no such problem existed. It has therefore been proposed that the full analysis set population should be used in crossover studies as the main analysis. In addition, with the crossover design, it can be determined whether results are going in the same direction during the first treatment period from a parallel design perspective. Sixteen of the 19 patients who had no follow-up data in the second treatment period hadHbA1c data during the first follow-up period. Among these patients, those with RT-CGM had a 1.0% decrease in HbA1c, whereas those with conventional therapy had an increase of 0.1%. There were more patients treated with RT-CGM than conventional therapy who discontinued treatment during the first treatment period. This was due to patients wanting to continue RT-CGM and therefore not completing the study while receiving conventional therapy in the second period and due to patients experiencing device-related problems. A second limitation is that the study could not be blinded and hence patients were aware of the intervention. In addition, the current results are restricted to patients with HbA1c of at least 7.5%.

Conclusion: Among patients with inadequately controlled T1DM treated with MDI, the use of RT-CGM compared with conventional treatment for 26 weeks resulted in lower HbA1c. Further research is needed to assess clinical outcomes and longer-term adverse effects.

Quality Grade: Good

Soupal J, Petruzelkova L, Flekac M, Pelcl T, Matoulek M, Dankova M, et al. Comparison of different treatment modalities for type 1 diabetes, including sensor-augmented insulin regimens, in 52 weeks of follow-up: a COMISAIR study. *Diabetes Technol Ther.* 2016.[174]

Study Description: This was a nonrandomized, prospective, real-life clinical trial designed to compare the efficacy of long-term use of sensor-augmented insulin regimens (SAIRs), that is, RT-CGM combined with either insulin pumps or MDIs, on glycemic control compared with more common schemes based on classical SMBG in patients with T1DM seeking treatment at an academic medical center in the Czech Republic.

Funding Source: Agency for Healthcare Research of the Czech Republic

Methods: Participants were included if they were aged >18 years, had a duration of T1DM of more than 2 years, and had an HbA1c level between 7.0% and 10% (53 and 86 mmol/mol). Only patients with insulin analogs were enrolled in this study. Subjects who had used RT-CGM during the past 3 months were excluded from the study. Patients with ketoacidosis within the past 3 months and/or severe noncompliance and/or any concomitant therapy influencing glucose metabolism, pregnant women, and women planning pregnancy were not allowed to participate either.

A total of 65 patients were divided into three groups with comparable baseline parameters, taking into account their preferences and diabetologist's recommendation. At the baseline, 27 patients started to use RT-CGM as part of an SAIR, 20 patients initiated insulin pump therapy (without RT-CGM), and 18 patients continued MDI and SMBG only. In the SAIR group, after a further consultation with the diabetologist, subjects could choose a combination of RT-CGM with either an insulin pump (SAP) or MDI. Fifteen of them started to use SAP and the remaining 12 continued with MDI (MDI + RT-CGM). A prerequisite for participation in the SAIR group was the willingness to use sensors >70% of the time. Similarly, patients in the groups without RT-CGM had to be willing to perform SMBG at least 4 times a day.

Subjects were scheduled for a total of seven clinic visits (initial, at 2 weeks, 1 month, then 3, 6, 9, and 12 months). Initially, all patients were monitored by professional CGM for 6 days. Throughout the study, subjects in the groups not using SAIR had professional CGM every 3 months. Participants in the insulin pump group wore one of two types of insulin pumps: MiniMed Paradigm Veo (Medtronic, Northridge, CA) and Animas Vibe (Animas Corporation, West Chester, PA). Participants in the SAP subgroup used either the MiniMed Paradigm Veo System with Enlite sensors (Medtronic) or Animas Vibe system with Dexcom G4 sensors (Dexcom, San Diego, CA). The subgroup of patients with MDI + RT-CGM used a Dexcom G4 CGM system comprising a 7-day transcutaneous sensor, a transmitter, and a receiver. The patients were provided with a personal blood glucose meter, which was used for diabetes self-management purposes and calibration of RT-CGM. At the baseline, all subjects underwent a structured 4-day training program. In the first part of this program, specialists reviewed general principles of T1DM management. Patients were educated on how to prevent hypoglycemia and deal with it in a variety of situations. They were informed about the appropriate timing of preprandial insulin dosing. All patients underwent theoretical and practical education in carbohydrate counting and were encouraged to use flexible dosing of insulin throughout this study. Only patients in the SAIR and insulin pump groups completed theoretical training on the relevant devices, followed by treatment initiation and practical training with investigators.

Participants on SAIR were encouraged to make self-adjustments to their treatment using RT-CGM values, hyper- and hypoglycemic alerts and trends, and to incorporate results of SMBG into treatment changes. The target range for glucose was usually initially relatively wide, but we emphasized to patients that its successive narrowing is usually necessary for reduction of mean blood glucose and glycemic variability. Subjects in non-SAIR groups were encouraged to measure their blood glucose at least 4 times a day.

Clinical Outcomes: The primary endpoint was the difference in HbA1c between the groups after 52 weeks of follow-up. HbA1c values were measured at the baseline, then every 3 months, and at the end of this trial. Prespecified secondary endpoints were changes of glycemic variability expressed by the total SD of blood glucose, average daily glucose from CGM, % of time spent in range (4.0-10.0 mmol/L or 70-180 mg/dL), and the incidence of hypoglycemia (% of time below 3.9 mmol/L or 70 mg/dL).

At each clinic visit, patients were screened for AEs and sensor insertion sites were inspected. Severe hypoglycemia was defined as an episode requiring assistance from another person or neurological recovery in response to restoration of plasma glucose to normal. Ketoacidosis was defined as an episode of hyperglycemia (>14 mmol/L) with low serum bicarbonate (<15 mmol/L), low pH (<7.3), or both together with either ketonemia or ketonuria that required treatment in a healthcare facility.

Sample Characteristics: Baseline characteristics were similar in the three groups (Table 1). Of the 65 patients enrolled, 62 completed all study visits. One subject from the insulin pump group and one from the SAIR group withdrew from the study after the third visit because of personal reasons. One patient from the MDI group was excluded from the analysis due to significant protocol violation.

TABLE 1: BASELINE CHARACTERISTICS OF PATIENTS

	RT-CGM	Insulin pump + SMBG	MDI + SMBG
No. of patients	27	20	18
Age (years), mean (SD), years	34 (10)	35 (9)	38 (17)
Duration of diabetes (years), mean (SD)	15 (9)	13 (10)	14 (9)
HbA1c (%), mean (SD)	8.3% (0.9%)	8.4% (0.6%)	8.3% (0.8%)
MDI=multiple daily injections of insulin; RT-CGM=real-time continuous glucose monitoring; SMBG=self-monitoring of blood glucose			

Outcome (HbA1c): After a year, the SAIR group of patients had significantly lower HbA1c (8.3% ± 0.9% vs. 7.1% ± 0.8% [67.5 ± 10.4mmol/mol vs. 54.5 ± 9.1mmol/mol]; P<0.0001). This improvement in HbA1c was observed both in the subgroup with SAP (8.2% ± 0.9% vs. 7.1% ± 0.9% [66 ± 9 mmol/mol vs. 53.9 v10 mmol/mol]; P=0.0025) and with MDI + RT-CGM (8.5% ± 1.1% vs. 7.2% ± 0.8% [69.3 v 12 mmol/mol vs. 55.3 ± 8.7 mmol/mol]; P=0.0034) compared with the study baseline.

Insulin pump therapy alone also led to significant reduction of HbA1c (8.4% ± 0.9% vs. 7.9% ± 0.7% [68.3 ± 9 mmol/mol vs. 62.7 ± 8 mmol/mol]; P=0.048), while in the group just on MDI, no significant decrease of HbA1c was observed (8.3% ± 0.8% vs. 8.0% ± 0.9% [67.2 ± 9 mmol/mol vs. 64.4 ± 10 mmol/mol]; P=0.40).

At 1 year, the mean difference in HbA1c between the SAIR group and the MDI group was -0.91% (-9.81 mmol/mol) (95% confidence interval [CI], -1.47% to -0.35% [-15.96 to -3.67 mmol/mol]; P=0.002). Moreover, both SAIR strategies were superior to insulin pump therapy alone; the mean difference was -0.75% (-8.11 mmol/mol) (95% CI, -1.23% to -0.26% [-13.41 to -2.81 mmol/mol]; P=0.0032). The difference in HbA1c between the SAIR group and the MDI group was significant from the third month and the difference between the SAIR group and the insulin pump group was significant from the ninth month. Importantly, superiority of both SAIRs in comparison with insulin pump only was not observed just for the SAP version of SAIR but also for the MDI version of SAIR for a between-group difference favoring the MDI + RT-CGM subgroup of -0.66% (-7.4 mmol/mol) (95% CI, -1.23% to -0.10% [-13.64 to -1.6 mmol/mol]; P=0.022). The difference in HbA1c between insulin pump only and MDI + RT-CGM groups started to be significant from the ninth month of this study.

At the baseline, no patient met the ADA/ESDA goal for HbA1c (<7.0% [53 mmol/mol]), while at the end of this trial, 48% of subjects in the SAIR group (eight patients in SAP and five patients in

MDI subgroups), 16% (n=3) of patients in the insulin pump group, and 18% (n=3) of individuals on MDI achieved the HbA1c target.

Outcome (Sensor Use): Mean sensor percentage use in the SAIR group was 85% ± 10% of the time (median 85%) with no significant differences between the two subgroups—SAP or MDI + RT-CGM (85% ± 10% [median 84%] vs. 85% ± 10% [median 87%]; P=0.98).

Outcome (SMBG Frequency): At the end of the study, the average number of blood glucose tests in non-SAIR groups was 3.7 ± 1.1 per day (median 3.6/day), with no significant differences between the groups with MDI and insulin pump therapy (3.7 ± 1.4 [median 3.3/day] vs. 3.6 ± 0.7 [median 3.5/day]; P=0.8). In comparison with SMBG groups, the average frequency of finger-stick tests performed per day was numerically, but not statistically, lower in the SAIR group (3.2 ± 1.0 [median 3.1/day] vs. 3.7 ± 1.1 [median 3.6/day]; P=0.08). However, regardless of the type of insulin delivery (SAP or MDI + RT-CGM), there was lower frequency of SMBG in subjects who were using the Dexcom G4 sensor (n=19) in comparison with users of the MiniMed Paradigm Veo System with Enlite sensors (n=8) (2.7 ± 0.6 vs. 4.3 ± 0.7, P<0.001).

Outcome (Insulin Use): Compared with the baseline, at the end of this study in the SAIR group, there was a significantly higher number of boluses per day and the relative proportion of bolus insulin was higher, while no significant change in these parameters was seen in either SMBG group. No change in the total daily dose of insulin between the baseline and the end of the study was observed for any study group. The average number of boluses per day at the end of the study was lower in both SMBG groups in comparison with the SAIR group (6.8 ± 2.2 vs. 4.3 ± 1.2; P<0.0001). A higher frequency of boluses was seen in patients with insulin pump therapy versus the self-reported boluses in the MDI only group (4.7 ± 1.4 vs. 3.9 ± 0.8; P=0.04), while no significant difference between SAP and MDI + RT-CGM was observed (7.2 ± 2.3 vs. 6.2 ± 2; P=0.25). At the end of this trial, the total daily dose of insulin and the relative proportion of bolus insulin were not different between study groups.

Outcome (Body Weight): No significant change in body weight between the beginning and the end of the study was found for any study group.

Outcome (Glycemic Variability): At 1 year, the average daily glucose level, as measured by RT-CGM or professional CGM, was significantly lower, both in the SAIR group (10.6 ± 1.5 mmol/L vs. 8.7 ± 1.4 mmol/L; P<0.001) and in the insulin pump group (10.7 ± 1.2 mmol/L vs. 9.8 ± 1.1 mmol/L; P=0.04). This improvement in average CGM glucose was accompanied by an increase in the time in range (4.0–10.0 mmol/L or 70-180 mg/dL); 50% ± 11% versus 69% ± 11%; P<0.0001, for SAIR and 51% ± 10% versus 59% ± 11%, P=0.03, for insulin pump.

Compared with the baseline, glycemic variability was lower in the groups on SAIR (SD of blood glucose: 4.0 ± 0.7 mmol/L vs. 3.0 ± 0.5 mmol/L; P<0.0001) and with insulin pump therapy (SD of blood glucose 3.9 ± 0.6 mmol/L vs. 3.4 ± 0.6 mmol/L; P<0.05). Additionally, significant reduction of the time spent in hypoglycemia was observed only in patients with SAIR (8% ±4% vs. 6% ± 3%; P< 0.01). For patients just on MDI, no significant change in SD of blood glucose (3.8 ± 1.0 mmol/L vs. 3.8 ± 1.1 mmol/L; P=0.93) and in hypoglycemia (6% ± 4% vs. 7% ± 5%; P=0.68) was observed.

No difference in HbA1c (7.2% ± 0.8% vs. 7.3% ± 0.9% [54 ± 9 mmol/mol vs. 56 ± 10 mmol/mol]; P=0.87), hypoglycemia (6% ± 4% vs. 6% ± 3%; P=0.91), and SD of blood glucose (2.9 ± 0.5 mmol/L vs. 3.0 ± 0.4 mmol/L; P=0.67) was observed in patients with the two types of RT-CGM systems (Dexcom G4 and Enlite sensor).

Outcome (Severe Hypoglycemia): Throughout the study, two severe episodes of hypoglycemia were reported, one in the insulin pump only group and one in the MDI group. No severe hypoglycemia in the SAIR group was reported.

Outcome (Adverse Events): There was no ketoacidosis or sensor insertion site infection requiring assistance during a year of follow-up.

Study Limitations: This was a nonrandomized study. Thus, although baseline HbA1c was similar, the more motivated patients might have selected the insulin pumps and/or RT-CGM. Another possible limitation is the different types of insulin pumps and RT-CGM systems used in this study. However, this reflects real-life and day-to-day clinical practice.

Conclusion: In patients with T1DM with suboptimal glycemic control, both SAIRs, that is, SAP and MDI + RT-CGM, were superior to MDI or insulin pump therapy in reducing HbA1c, hypoglycemia, and the other endpoints. Both SAIRs provided comparable glycemic benefits. Hence, a combination of RT-CGM and MDI can be considered as an equivalent alternative to SAP therapy for patients who are not willing to or cannot use insulin pumps.

Quality Grade: Fair

Foster NC, Miller, KM, Tamborlane WV, Bergenstal RM, Beck RW. Continuous glucose monitoring in patients with type 1 diabetes using insulin injections. *Diabetes Care* 2006;39:e81-e82.[175]

Study Description: This observational, cross-sectional, real-world analysis assessed the impact of RT-CGM on patients with T1DM using different methods of insulin delivery.

Funding Source: The Leona M. and Harry B. Helmsley Charitable Trust

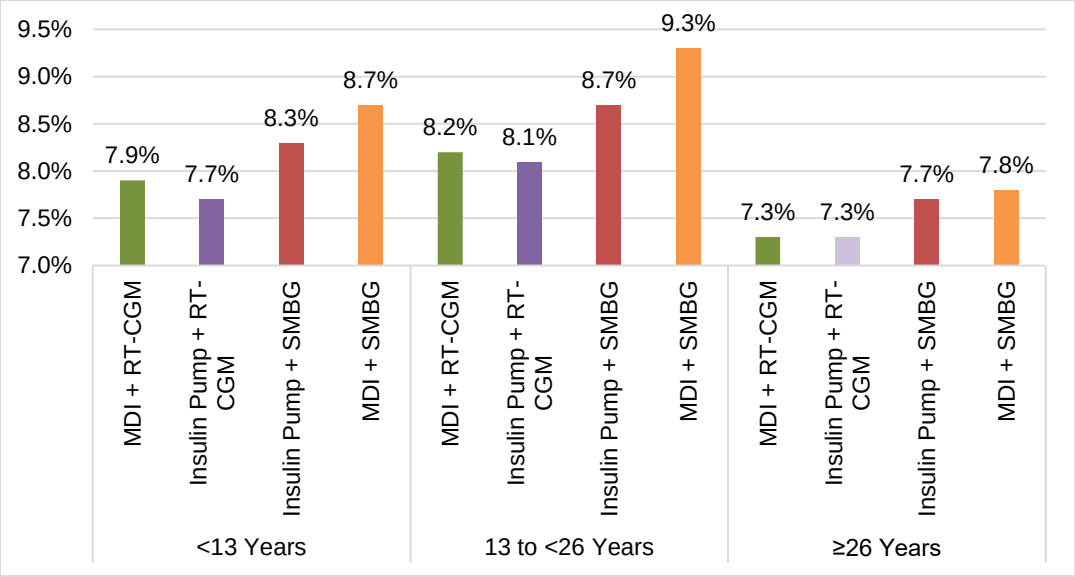
Methods: Participants in the T1D Data Exchange Registry who were diagnosed with T1DM for >1 year; had a clinic visit between June 2014 and October 201e; and used RT-CGM for real-time diabetes management during the 30 days prior to the clinic visit were eligible for the study.

Clinical Outcomes: The primary endpoint was mean HbA1c.

Sample Characteristics: Among the 17,731 registry participants who met eligibility criteria, 6,222 (35%) used MDI + SMBG, 8,783 (50%) used an insulin pump + SMBG, 2,316 (13%) used an insulin pump with RT-CGM, and 410 (2%) used MDI with RT-CGM. A Dexcom RT-CGM device was being used by 97% of the MDI + RT-CGM users and by 58% of the insulin pump + RT-CGM users. Of the 2,726 participants using RT-CGM, 85% were receiving insulin pump treatment, and only 15% were receiving MDI. The median number of boluses of short-acting insulin per day was 3 (interquartile range 3, 4) in both participants using MDI + SMBG and participants using MDI with RT-CGM.

Outcome (HbA1c): Among RT-CGM users, mean HbA1c was similar in MDI and insulin pump users (7.6 6 ±.3% vs. 7.7 ± 1.1%, P value from a linear mixed model adjusted for age, diabetes duration, race/ethnicity, education level, insurance status, annual income, and blood glucose meter testing frequency =0.82) and lower in RT-CGM users than in non-RT-CGM users in the insulin pump group (8.3 ± 1.5%, adjusted P<0.001) and in the MDI group (8.8 ± 1.9%, adjusted P <0.001). As shown in Figure 1, this pattern was seen in both adults and youth.

FIGURE 1. MEAN HBA1C ACCORDING TO INSULIN MODALITY/RT-CGM USE STATUS



Study Limitations: Cross-sectional analyses are subject to potential bias. For instance, there was no available information on how many injection users tried RT-CGM and discontinued it, and thus, the cohort of injection RT-CGM users in the study may be self-selected to be those who are more likely to have lower HbA1c levels.

Conclusion: In this analysis of T1D Exchange registry data, RT-CGM users, irrespective of insulin delivery method, had lower HbA1c levels than non-RT-CGM users even after adjustment

for potential confounding factors. Importantly, RT-CGM users who were using MDI for insulin delivery had HbA1c levels similar to those of RT-CGM users using an insulin pump.

Quality Grade: Fair

Parkin CG, Graham C, Smolskis J. Continuous glucose monitoring use in type 1 diabetes: longitudinal analysis demonstrates meaningful improvements in HbA1c and reductions in healthcare utilization. *J Diabetes Sci Technol*.1-7, 2017 DOI: 10.1177/1932296817693253**.[189]**

Study Description: This retrospective, longitudinal analysis utilized datasets from T1DM patients enrolled in a commercial health plan to assess changes in HbA1c using RT-CGM versus SMBG.

Funding Source: Dexcom, Inc.

Methods: The study population included patients with a diagnosis code for T1MD, continuous enrollment in the health plan, use of MDI or insulin pump therapy, and at least one claim for insulin during the study period. Patients who were pregnant or had prior experience with RT-CGM were excluded from all analyses. Study patients were divided into two groups: patients who initiated RT-CGM use with the Dexcom G4™ Platinum CGM System (Dexcom, Inc., San Diego, CA, USA) and patients documented use of SMBG at a frequency of ≥4 test strips per day within the baseline period as indicated by medical claims.

The identification period for eligible patients was from November 2012 through December 2013. The index date for each patient was the date of the first claim for initiation of either RT-CGM or SMBG at a frequency of ≥4 test strips per day. The baseline period for each group was one year prior the index date; whereas, the measurement period was a year following the index date, including the index date itself.

Data for the study were obtained from the Optum Research Database (Optum, Eden Prairie, USA), which contains eligibility, pharmacy claims, medical claims and laboratory data for more than 14 million enrollees in fully-insured and self-funded healthcare plans. Medical and demographic information, including diagnosis, utilization of healthcare services (e.g., inpatient admissions, ER visits, pharmacy costs), age, gender and geographic regions were obtained from health plans' administrative records for this study.

Clinical Outcomes: The primary outcome measure was change in HbA1c between and within study groups by insulin delivery method (insulin pump vs. MDI). Secondary outcomes included within- and between-group differences in hospitalizations and ER visits. The primary analysis included patients who had at least one HbA1c value documented in both the baseline and the measurement periods. For the secondary analysis, propensity score matched analysis was performed to reduce selection bias due to imbalances in study covariates. The two groups were extensively matched on baseline per-member per-month (PMPM) medical and pharmacy costs, gender, region, Charlson Index Score and sixteen comorbidity Charlson indices. Patients in the RT-CGM group were matched to those in the SMBG group in a 1:1 ratio, based on the resultant propensity score probabilities. However, patients were not matched for HbA1c due to the relatively smaller number RT-CGM patients with *baseline* and *measurement* period values.

Sample Characteristics: A total of 6,467 patients, with 187 in the RT-CGM group and 6,280 in the SMBG group, were included in the primary analysis. The distribution of baseline HbA1c values in the two groups was similar.

Outcome (HbA1c): Patients in both the RT-CGM and SMBG groups experienced statistically significant reductions in HbA1c from baseline (RT-CG: -0.5%, P=0.004; SMBG: -0.2%, P<0.0001). Comparison of change in HbA1c by insulin administration method showed a clinically and statistically significant HbA1c reduction in patients treated with RT-CGM plus MDI (-0.6%, P<0.01) but not with RT-CGM plus insulin pump therapy (-0.3%, P=0.16); however, the between-group difference was not statistically significant (P=0.06).

Outcome (Healthcare Utilization): The number of all-cause inpatient admissions among RT-CGM patients was significantly lower compared with SMBG patients (-42.2%, P=0.013), resulting in 17.4% (P=0.556) lower PMPM costs. The number of diabetes-specific inpatient admissions and costs were also lower among RT-CGM users than those using SMBG, although these

differences were not statistically significant. The number of inpatient admissions coded for DKA among SMBG patients was more than double the number reported for RT-CGM patients during the *measurement* period (36 vs. 16, P=0.068).

The number of all-cause ER visits was 17% lower among RT-CGM patients vs. SMBG patients (P=0.303) with associated lower PMPM costs (p=0.491). (**Figure 3B**) The number of diabetes-specific ER admissions was also lower among RT-CGM patients vs. SMBG patients but with higher associated costs. The number of ER visits coded for DKA among SMBG patients was more than four times higher than reported for RT-CGM patients during the *measurement* period (17 vs. 4, P=0.0318). Similar differences between RT-GM vs. SMBG patients also were seen in the number of ER visits coded for hypoglycemia (2 vs. 7, P=0.353).

Study Limitations: A key limitation of the study is the small sample size of RT-CGM users with pre and post HbA1c test values; a larger sample size would have provided a more robust assessment of the impact of RT-CGM use on glycemic control and health service utilization. Another limitation was the design of the study. It is well known that retrospective analyses inherently include confounding variables, which may go unrecognized because of inadequate knowledge of how they interrelate with the outcomes. Although the analyses showed associations between treatment modalities and outcomes, causal relationships cannot be inferred. Additionally, the Optum data set provided no information regarding the socioeconomic, educational characteristics or participation in a formal diabetes self-management education program, all of which could have affected outcomes.

Conclusion: Use of RT-CGM was associated with reduced HbA1c and utilization of health services compared with SMBG use regardless of insulin delivery method. Additionally, RT-CGM use was associated with notably fewer inpatient admissions and ER visits coded for DKA and hypoglycemia, which can have long-term effects on patient adherence.

Quality Grade: Fair

MDI or Insulin Pump + RT-CGM versus MDI or Insulin Pump + SMBG

van Beers CA, DeVries JH, Kleijer SJ, Smits MM, Geelhoed-Duijvestijn PH, Kramer MH, 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.[186]

Study Description: This was a randomized, open-label, controlled, clinical trial with a crossover design conducted from March 2013 and February 2016 at 2 sites in the Netherlands. After screening and a 6-week run-in period, patients were randomized to receive RT-CGM or conventional SMBG for 16 weeks with a 12-week washout between treatment periods. The aim of this study was to investigate the effect of RT-CGM compared with SMBG on glycemic control in adult patients with T1DM and impaired awareness of hypoglycemia.

Funding Source: Eli Lilly and Sanofi

Methods: Individuals with T1DM aged 18-75 years with HbA1c of 7.0% to 10%, who treated with insulin pump therapy or MDI and performing ≥3 SMBG measurements per day, and who had impaired awareness of hypoglycemia as defined by a Gold score ≥4 were included. Patients were excluded if they had a history of renal, liver, or heart disease, current untreated proliferative diabetic retinopathy, current malignancy, current use of non-selective β blockers, current psychiatric disorders, current substance abuse or alcohol abuse, pregnancy, current use of CGM other than for a short period (3 consecutive months), any hearing or vision impairment that could hinder perception of the glucose display and alarms, poor command of the Dutch language or any disorder that precluded full understanding of the purpose and instructions of the study, participation in another clinical study, and any known or suspected allergy to trial-related products.

After screening and a 6-week run-in phase (including reeducation about diabetes management given 2 weeks before randomization), patients were randomly assigned (1:1) using a computer-generated allocation sequence (block size of four) to either 16 weeks of RT-CGM followed by 12 weeks of washout and 16 weeks of SMBG, or 16 weeks of SMBG followed by 12 weeks of washout and 16 weeks of RT-CGM, where the SMBG phase was the control. The allocation sequence (RT-CGM–SMBG or SMBG–RT-CGM) was generated by the institutional trial pharmacist, and masked to the physicians (by use of sealed envelopes) at the time of randomization (ensuring low risk of allocation bias). After randomization, the sequence was no longer masked for both study physicians (who also assessed outcomes and analyzed the data) and patients.

During both intervention periods, patients attended monthly follow-up visits followed by telephone consultations 2 weeks after each follow-up visit, involving inquiry about adverse events, all episodes of hypoglycemia including severe episodes, use of study device and related technical issues, and to check current medication. Treatment goals were equal in both study periods and in concordance with the ADA Standards of Medical Care. Patients continued using their own blood glucose meters. Therapy adjustments were made based on RT-CGM data in the RT-CGM phase or SMBG data in the SMBG phase.

The RT-CGM system used during the intervention phase consisted of the Paradigm Veo system used solely as a monitor with a MiniLink transmitter (Medtronic, Northridge, CA, USA for both), and the Enlite glucose sensor. Insulin pump-treated patients continued using their own pump for insulin treatment. The low-glucose limit during this trial was preset at 4.5 mmol/L and the low glucose suspension function was not used. CGM data were uploaded before every follow-up visit. Patients were encouraged to use CGM continuously, although this use was not mandatory. During the SMBG phase, patients wore the masked CGM system continuously throughout the intervention phase and uploaded the masked CGM data each week.

Clinical Outcomes: Since the results from a published RT-CGM trial showed a difference of 1.5 h (6.25%) in time spent in normoglycemia between RT-CGM and SMBG, this study aimed to

detect such a difference, assuming an SD of 3.5 h, an α of 0·05, a power of 80%, and a correlation of 0.5 between repeated measures. Assuming that about 15% of patients would drop out, a sample size of 52 patients was needed. The primary endpoint was analyzed in the intention-to-treat population using a linear mixed-model analysis with the percentage of time spent in normoglycemia as the dependent variable, the treatment group (RT-CGM or SMBG) as a factor, and the participant as a random factor. Because of the crossover design of the trial, the carryover effect was assessed by including the sequence allocation as a factor in the mixed model. If a carryover effect was detected ($p<0.1$), only the first study period was analyzed (treating it as a parallel randomized controlled trial). Additionally, insulin treatment modality (MDI or insulin pump) was included as a covariate in the model and a p value for interaction of 0.1 was regarded as significant.

The primary outcome was the mean difference in the percentage of time that patients spent in normoglycemia (4.0-10.0 mmol/L) between RT-CGM and SMBG calculated over the total intervention periods. Secondary endpoints were time spent in normoglycemia each month to show an effect over time, severe hypoglycemia (defined as a hypoglycemic event requiring third-party assistance), the percentage of time patients spent in a hypoglycemic state (blood glucose ≤70 mg/dL) and a hyperglycemic state (>180 mg/dL), average daily area under the curve (AUC) of 70 mg/dL or less (expressed as mg/dl/min), frequency (episodes per week) and duration (min per episode) of CGM-derived hypoglycemic episodes (≥three sequential sensor values ≤70 mg/dL), frequency (episode per night) and duration of CGM-derived hypoglycemic episodes at night-time (0000-0600 h), and within-day and between-day glucose variability (calculated as within-day SD of glucose concentration, coefficient of variation, mean absolute change in glucose concentration, mean of daily differences, and continuous overall net glycemic action). Other secondary endpoints were baseline and 16-week HbA1c measurements, self-reported hypoglycemia awareness (based on Gold and Clarke methods), diabetes-specific measures of quality of life, and satisfaction with use of CGM assessed by the CGM-SAT questionnaire. We also assessed post hoc the frequency of CGM-derived hypoglycemic episodes with cutoffs of less than 63 mg/dL and less than 50 mg/dL.

The primary endpoint was analyzed in the intention-to-treat population using a linear mixed-model analysis with the percentage of time spent in normoglycemia as the dependent variable, the treatment group (RT-CGM or SMBG) as a factor, and the participant as a random factor. Because of the crossover design of the trial, the carryover effect was assessed by including the sequence allocation as a factor in the mixed model. If a carryover effect was detected ($p<0.1$), only the first study period was analyzed (treating it as a parallel randomized controlled trial).

Sample Characteristics: A total of 57 patients attended the screening visit, and 52 were randomly assigned to either the RT-CGM-to-SMBG sequence (n=26) or to the SMBG-to-RT-CGM sequence (n=26). Five patients were deemed ineligible. Of the 52 randomized patients, 46% were women and the mean age and duration of diabetes was 48.6 years and 30.5 years, respectively. Forty-four percent of patients were receiving insulin pump therapy. The mean HbA1c was 7.5% and number of daily SMBG measurements was 5. After randomization, six patients (12%) withdrew early: two discontinued after the RT-CGM period because of motivational issues, one had personal circumstances necessitating discontinuation, two withdrew because they could not upload the masked CGM device, and one withdrew because of poor adherence to RT-CGM.

Outcome (% Time in Normoglycemia): The percentage of time that patients spent in a normoglycemic state during the 16-week intervention period was higher during RT-CGM than during SMBG (65.0% [95% CI 62.8-67.3] vs 55.4% [53.1-57.7]; mean difference 9.6%, 95% CI 8.0-11.2; P<0·0001).

Outcome (% Time in Hypoglycemia and Hyperglycemia): The percentage of time that patients spent in a hypoglycemic state during the 16-week intervention period was lower during RT-CGM than during SMBG (6.8% [95% CI 5.2-8.3] vs 11.4% [9.9-13.0]; mean difference -4.7%, 95% CI -5.9 to -3.4; P<0·0001). The percentage of time that patients spent in a hyperglycemic state during

the 16-week intervention period was lower during RT-CGM than during SMBG (28.2% [95% CI 25.1-31.3] vs 33.2% [30.0-36.3]; mean difference -5.0%, 95% CI -6.9 to -3.1; P<0·0001).

Outcome (Number of Hours/Day Spent in Normoglycemia, Hypoglycemia, and Hyperglycemia): The number of hours per day that patients spent in the normoglycemic state was higher during RT-CGM than SMBG (mean difference 2.3 h/day; 95% CI 1.9-2.7, P<0.0001). Similarly, the number of hours per day that patients spent in hypoglycemia (mean difference -1.1; 95% CI -1.4 to -0.8; P<0.0001) and hyperglycemia (mean difference -1.2; 95% CI -1.6 to -0.7; P<0.0001 were lower during RT-CGM than SMBG.

Outcome (CGM-derived Hypoglycemic Events per Week): The number of CGM-derived hypoglycemic events was lower during RT-CGM than SMBG (mean difference -1.1; 95% CI -2.1 to -0.1; P=0.028).

Outcome (Duration of CGM-derived Hypoglycemic Events): The duration (min/event) of CGM-derived hypoglycemic events was lower during RT-CGM than SMBG (mean difference -37.8; 95% CI -44.6 to -30.9; P<0.0001).

Outcome (Nocturnal Hypoglycemia): The percentage time spent in nocturnal hypoglycemia (mean difference -5.7%; 95% CI -8.2 to -3.2; P<0.0001), number of CGM-derived nocturnal hypoglycemic events (mean difference -0.07; 95% CI -0.11 to -0.02; P=0.003), and duration of CGM-derived nocturnal hypoglycemic events (mean difference -52.7; 95% CI -62.7 to -42.7; P<0.0001) was lower during RT-CGM than SMBG.

Outcome (Glycemic Variability): All measures of glycemic variability (mean glucose concentration, within-day SD of glucose concentration, coefficient of variation of glucose concentration, mean absolute glucose change, mean of daily difference, and continuous overall net glycemic action at 1-h intervals were statistically significantly lower during RT-CGM than SMBG.

Outcome (Severe Hypoglycemia): Fewer severe hypoglycemic events occurred during RT-CGM than with SMBG (14 vs. 24, P=0.033). During both the RT-CGM and SMBG phases, four severe hypoglycemic events occurred resulting in seizure or coma, and one severe hypoglycemic event resulted in the patient being admitted to the hospital. Ten patients (19%) had one or more severe hypoglycemic event during RT-CGM, compared with 18 (35%) during SMBG (uncorrected odds ratio [OR] 0.45, 95% CI 0.23-0.87; P=0.018), with no interaction for insulin treatment modality (insulin pump vs MDI; P=0.348).

Outcome (Hypoglycemia Awareness): There were no relevant differences in self-reported hypoglycemia awareness scores, with no relevant between-group differences in 16-week hypoglycemia awareness scores or change in hypoglycemia awareness scores from baseline to endpoint.

Outcome (Quality of Life): There were no between-group differences in quality of life from scores on the Hypoglycemia Fear Scale (HFS) Behavior subscale, Problem Areas in Diabetes Scale (PAID)-5, Confidence in Diabetes Self-Care scale, EuroQol five-dimensional questionnaire (EQ5D), or World Health Organization Well-being Index (WHO)-5 between the RT-CGM and SMBG phases. Scores on the HFS Worry subscale, transformed to a 0-100 scale, were lower after the RT-CGM phase compared with the SMBG phase (32.5 vs 38.9; mean difference 6.4, 95% CI 1.4-11.4; P=0.014). CGM-SAT scores after the RT-CGM phase were higher than neutral (3.0 on a 5.0 scale), with a mean score of 3.8 (SD 0.6).

Outcome (Adverse Events): Five SEAs other than severe hypoglycemia occurred during the trial, but none were deemed related to the study intervention. 11 mild to moderate AEs occurred during the RT-CGM phase, 16 mild to moderate AEs occurred during the SMBG phase, and two mild to moderate AEs occurred during the wash-out phase. The mild to moderate AEs were deemed unrelated to the study intervention.

Study Limitations: The RT-CGM devices used in the trial might have been outdated, since next generation RT-CGM systems came to market during the trial, with improvements in lag time and

accuracy, and with new features (e.g., predicted low-glucose suspension). Additionally, the masked and real-time CGM devices used in our trial are known to differ somewhat in accuracy, which needs to be taken into account when interpreting the CGM-derived data. The real-time CGM device is calibrated in real time, but the masked CGM device is retrospectively calibrated (which allows the calibration algorithm to use information both before and after the timepoint of interest to obtain an optimum calibration to each reference point, leading to better accuracy). By contrast, real-time CGM displays a glucose value in real-time and the calibration algorithm can only use previous data for calibration. This difference might explain why the real-time CGM device tends to report glucose concentrations that are lower than the reference over the entire range of glucose values. However, if anything, this result would have caused an overestimation of the reported CGM-derived hypoglycemia during the real-time CGM phase compared with the SMBG phase. The difference between RT-CGM and SMBG might therefore be larger than shown in this trial. Other limitations were that the study could not be powered for severe hypoglycemia as a primary outcome, and that data for the frequency of adjustments to SMBG or therapy during the intervention periods were not collected. RT-CGM with predictive low-glucose suspension could further reduce the incidence of severe hypoglycemia in adult patients with impaired awareness of hypoglycemia.

Conclusion: In patients with T1DM and impaired awareness of hypoglycemia, RT-CGM improved glycemic control by decreasing both time spent in a hypoglycemic state and time spent in a hyperglycemic state. Additionally, it diminished severe hypoglycemia. These results support the use of RT-CGM in this high-risk population.

Quality Grade: Good

Tamborlane WV, Beck RW, Bode BW, et al. Continuous glucose monitoring and intensive treatment of type 1 diabetes. N Engl J Med. 2008;359:1464-76.[176]

Beck RW, Buckingham B, Miller K, et al. Factors predictive of use and of benefit from continuous glucose monitoring in type 1 diabetes. Diabetes Care. 2009;32:1947-53.[184]

Beck RW, Lawrence JM, Laffel L, et al. Quality-of-life measures in children and adults with type 1 diabetes: Juvenile Diabetes Research Foundation Continuous Glucose Monitoring randomized trial. Diabetes Care. 2010;33:2175-7.[190]

Study Description: This was a 26-week, randomized, controlled, multicenter trial in adults and children with poorly-controlled T1DM despite intensive insulin therapy. After a 1-week blinded CGM run-in period, patients were randomized to RT-CGM or SMBG (control). Randomization was stratified by clinical center, age group (≥25 years, 15 to 24 years, and 8 to 14 years) and HbA1c level (≤8.0% and >8.0%). The study was conducted between December 2006 and July 2008 at 10 centers in the U.S.

Funding Source: Juvenile Diabetes Research Foundation

Methods: Included were individuals age ≥8 years who were diagnosed with T1DM for ≥1 year before randomization; were receiving intensive insulin therapy (insulin pump or MDI); had an HbA1c level of 7.0 to 10.0%; had had not used CGM at home in the 6 months leading up to the trial; and, during the run-in period, wore a RT-CGM sensor at least 6 of 7 days and performed SMBG at least 3 times per day.

Patients randomized to the RT-CGM group received 1 of 3 RT-CGM devices with a sensor life of 3 to 7 days. Patients were instructed to use the device on a daily basis and to verify the accuracy of the glucose readings with a home blood glucose meter before making management decisions. Patients randomized to the control group were given blood glucose meters and test strips and asked to perform SMBG at least 4 times per day. The control group wore blinded RT-CGM devices.

Clinical Outcomes: The primary endpoint was change in the mean HbA1c level from baseline to 26 weeks. A sample size of 110 patients in each of three age groups (≥25 years, 15 to 24 years, and 8 to 14 years) was planned to have a power of 90% within each age group to detect a difference in the mean HbA1c level between study groups, assuming a population difference of 0.5%, a standard deviation of 0.9 at 26 weeks, a correlation between baseline and 26-week values of 0.58, an alpha level of 0.05, and a loss to follow-up of no more than 15%.

All analyses were performed according to the intention-to-treat principle. The primary analysis was a comparison between the two study groups of the change in the HbA1c levels from baseline to 26 weeks in analysis of covariance models, conducted separately in each of the three age groups and adjusted for the baseline HbA1c level and clinical center.

Secondary endpoints included five pre-specified binary outcomes for HbA1c at 26 weeks (a relative decrease of ≥10%, a 26-week level of <7.0%, an absolute decrease of ≥0.5%, a relative increase of ≥10%, and an absolute increase of ≥0.5%) and a post-hoc binary outcome of an HbA1c level of less than 7.0% with no severe hypoglycemic events at 26 weeks. Other secondary endpoints were the amount of time per day the glucose level was hypoglycemic (≤70 mg/dL), hyperglycemic (>180 mg/dL) and in the target range (71 to 180 mg/dL). Adherence to sensor use and quality of life also were assessed. For patients age >18 years, quality of life measures included the Hypoglycemia Fear Survey (HFS), Problem Areas in Diabetes Scale (PAID) and Social Functioning (SF-12) Health Survey version 2. HFS included questions about hypoglycemia fear (Worry subscale) and behaviors to prevent low blood glucose (Behavior subscale). PAID assesses psychosocial adjustment related to diabetes, including questions about anger, interpersonal distress, and frustration with diabetes treatment. The SF-12 is a generic quality of life measure assessment mental and physical functioning. Patients <18 years of age completed the HFS Worry Subscale and selected subscales from the PedsQL-Generic and Type 1 Diabetes

Module developed by Dr. James W. Varni. Parents of participants <18 years completed the HFS Worry Subscale, the Parent-PAID survey evaluating parental burden associated with diabetes care; and parent-proxy versions of the same PedsQL-Generic and Type 1 Diabetes Module subscales completed by their children. Additionally, the CGM Satisfaction (CGMSAT) questionnaire was administered to the CGM group (participants and parents) at 26 weeks to assess satisfaction with and perceived therapeutic impact of CGM.

Safety endpoints included the proportion of patients who had at least one severe hypoglycemic event (defined as an event that required assistance from another person to administer oral carbohydrate, glucagon, or other resuscitative actions) and the incidence of severe hypoglycemic events. These outcomes also were examined for the subgroup hypoglycemic events associated with seizure or coma. Other safety outcomes were rates of hyperglycemia resulting in ketoacidosis, unexpected study-related or device-related events, and serious adverse events regardless of cause.

Patients who did not provide HbA1c or blinded CGM data at study end were excluded from analyses of these outcomes.

Sample Characteristics: A total of 322 patients were randomized, with 165 assigned to the RT-CGM group and 157 to the control group. Of those patients, 98 patients were age ≥25 years, 110 were age 15 to 24 years and 114 were age 8 to 14 years. The majority of patients were non-Hispanic white; using insulin pump therapy; measuring glucose levels >5 times per day with a home glucose meter; and had a mean HbA1c level of 8.0% or less. Demographic characteristics were well balanced between groups. Discontinuations included 3 (1.8%) patients in the RT-CGM group and 2 (1.3%) in the control group.

Outcome (Glycemic Outcomes): Glycemic outcomes by treatment and age group are shown in Table 1.

TABLE 1: GLYCEMIC OUTCOMES AT 26 WEEKS BY AGE GROUP

Outcome	≥25 Years			15-24 Years			8-14 Years		
	RT-CGM (n=52)	Control (n=46)	P value	RT-CGM (n=57)	Control (n=53)	P value	RT-CGM (n=56)	Control (n=58)	P value
HbA1c†									
At baseline, %	7.6 ± 0.5	7.6 ± 0.5		8.0 ± 0.7	7.9 ± 0.8		8.0 ± 0.7	7.9 ± 0.6	
Change from baseline to 26 weeks, %‡	-0.50 ± 0.56	0.02 ± 0.45	<0.001	-0.18 ± 0.65	-0.21 ± 0.16	0.52	-0.37 ± 0.90	-0.22 ± 0.54	0.29
Relative decrease by ≥10%, N (%)	13 (26)	2 (4)	0.003	8 (14)	5 (10)	0.46	16 (29)	7 (12)	0.04
Absolute decrease by ≥0.5%, N (%)	24 (48)	5 (11)	<0.001	20 (36)	19 (37)	0.57	30 (54)	18 (31)	0.009
Relative increase by ≥10%, N (%)	0	1 (2)	0.48	2 (4)	2 (4)	0.98	5 (9)	2 (3)	0.24
Absolute increase by ≥0.5%, N (%)	0	5 (11)	0.02	7 (13)	7 (14)	0.84	12 (21)	7 (12)	0.18
<7.0% at 26 weeks, N (%)	17 (34)	4 (9)	0.005	8 (14)	9 (18)	0.90	15 (27)	7 (12)	0.01
<7.0% and no severe hypoglycemia at 26 weeks, N (%)	15 (30)	3 (7)	0.006	7 (13)	7 (14)	0.67	14 (25)	6 (10)	0.02
Glucose levels (mean min/day @ baseline/26 weeks)§									
71 to 180 mg/dL	854/986	811/840	<0.001	691/761	697/761	0.79	646/750	710/746	0.53
>180 mg/dL	497/394	549/519	0.002	650/591	641/591	0.85	745/643	671/635	0.58
≤70 mg/dL	159/101	181/161	<0.001	271/215	265/242	0.44	343/242	282/268	0.18
Mean mg/dL/min @ baseline/26 weeks¶	0.040/0.038	0.040/0.041	0.07	0.047/0.047	0.048/0.048	0.48	0.047/0.045	0.046/0.046	0.66

Plus–minus values are means ±SD.
† At 26 weeks, data regarding HbA1c levels were not available for five patients who dropped out of the study (in the CGM group, two patients who were age ≥25 years and one who was age 15 to 24 years; in the control group, two who were age 15 to 24 years).
‡ The between-group difference was significant among patients age ≥25 years (mean difference, -0.53%; 95% confidence interval [CI], -0.71 to -0.35) but not among those age 15 to 24 years (mean difference, 0.08; 95% CI, -0.17 to 0.33) nor those age 8 to 14 years (mean difference, -0.13; 95% CI, -0.38 to 0.11).
§ Data regarding CGM were obtained after completion of the 26-week visit with the use of an unblinded device in the CGM group and a blinded device in the control group. Data were missing in the CGM group for two patients who were age ≥25 years, seven patients who were age 15 to 24 years, and two patients who were age 8 to 14 years; data were missing in the control group for two patients who were age 8 to 14 years.
¶ This value was the absolute rate of change.
RT-CGM=real-time continuous glucose monitoring; SH=severe hypoglycemia.

Outcome (Adverse Events): Adverse events by age group are shown in Table 2.

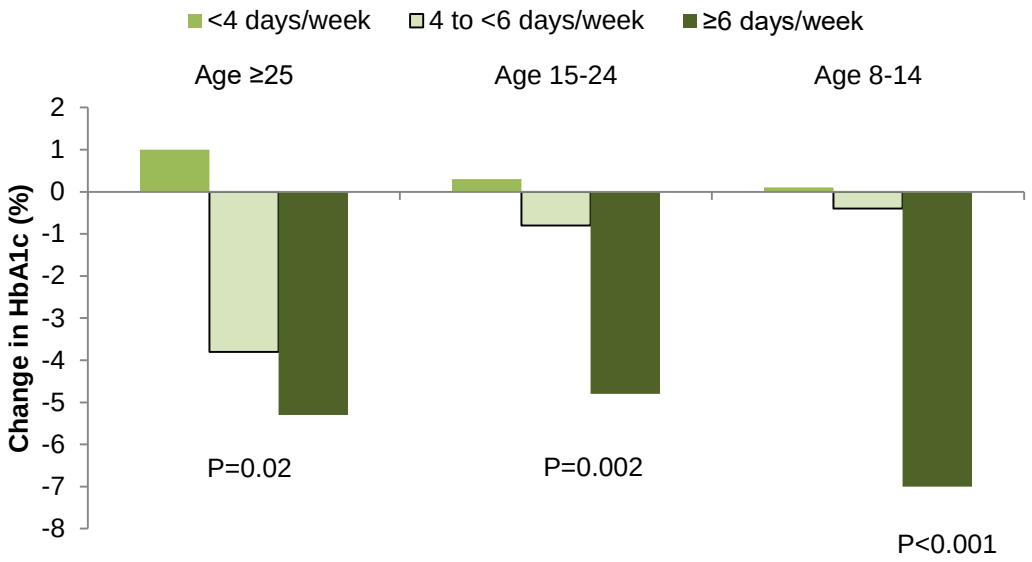
TABLE 2: ADVERSE EVENTS BY AGE GROUP

Adverse Event	≥25 Years			15-24 Years			8-14 Years		
	RT-CGM (n=52)	Control (n=46)	P value†	RT-CGM (n=57)	Control (n=53)	P value†	RT-CGM (n=56)	Control (n=58)	P value†
Severe hypoglycemic event‡									
≥1 event, N (%)	5 (10)	4 (9)	1.0	3 (5)	5 (9)	0.48	4 (7)	6 (10)	0.74
Events per 100 person-years, N	43.4§	26.3	0.66	17.9	23.	0.64	17.9	24.4	0.64
Severe hypoglycemic episode with seizure or coma¶									
≥1 event, N (%)	1 (2)	1 (2)	1.0	1 (2)	3 (6)	0.35	0	0	NA
Events per 100 person-years, N	23.7	4.4	0.85	3.6	11.9	0.14	0	0	NA
≤70 mg/dL	89/60	80/81	0.41	90/99	102/88	0.79	49/47	59/59	0.29
≤50 mg/dL	32/11	22/23	0.11	39/29	42/31	0.99	17/10	18/13	0.50
Other adverse events, N									
Diabetic ketoacidosis	0	0		0	1		0	0	
Cellulitis related to sensor use	0	0		0	0		2	0	
Dizziness during blood draw	0	0		0	0		0	1	
Anxiety or depression	0	0		1	0		0	0	
Kidney laceration	0	0		0	1		0	0	
Seizure not caused by hypoglycemia	0	0		1	0		0	0	

† Fisher's exact test was used to compare the percentages of patients in each study group who had at least one hypoglycemic event; permutation tests were used to compare the incidence rates and compute the confidence intervals.
‡ The between-group difference was 17.1 (95% confidence interval [CI], -37.4 to 73.5) for patients age ≥25 years, -6.0 (95% CI, -35.8 to 23.7) for those who were age 15 to 24 years, and -6.5 (95% CI, -33.4 to 20.6) for those who were age 8 to 14 years.
§ One patient in the CGM who was age ≥25 years had six episodes of seizure or coma. During this period, he reported that he had not used any long-acting insulin; for four of the six episodes, he reported that he had not used short-acting insulin on the day of the event. With the exclusion of data from this patient, the incidence rate for severe hypoglycemia was 20.0 per 100 person-years, and the incidence rate for seizure or coma was 0.
¶ The between-group difference was 19.3 (95% CI, -12.8 to 56.3) for patients who were age ≥25 years and -8.3 (95% CI, -23.4 to 7.0) for those who were age 15 to 24 years. For patients who were 8 to 14 years of age, there were no events.
|| Data were obtained from CGM after completion of the 26-week visit with the use of an unblinded device in the CGM group and a blinded device in the control group. Data were missing in the CGM group for two patients who were age ≥25 years, seven patients who were age15 to 24 years, and two patients who were age 8 to 14 years; data were missing in the control group for two patients who were age 8 to 14 years.
NA=not applicable; RT-CGM=real-time continuous glucose monitoring.

Outcome (Sensor Use): RT-CGM use averaging >6.0 days/week in study month 6 was highest in patients age ≥25 (79%) and lowest in patients age 14 to 25 years (29%); 46% of children age 8-14 years used the sensor at least 6 days/week. Patients averaging at least 6 days per week of RT-CGM use had substantially greater improvement in HbA1c compared with those who used RT-CGM less often (Figure 1).

FIGURE 1. CHANGE IN HBA1C BY SENSOR USE



Outcome (Quality of Life): None of the quality of life measures showed meaningful differences between the RT-CGM and control groups after 26 weeks, which may be due to lack of benefit of RT-CGM use on quality of life, insensitivity of the measures used to detect changes, or high baseline levels of quality of life in this population yielding a ceiling effect. CGM satisfaction scores were positive and indicative of substantial satisfaction with CGM.

Study Limitations: With respect to the generalizability of the results, it is important to recognize that before the study, patients were receiving intensive insulin therapy with either an insulin pump or MDI and frequent home blood glucose monitoring, and most had better-than-average HbA1c levels. In addition, to be eligible for the study, patients needed to show the ability to wear a sensor and insert a new sensor at home. Therefore, the results do not shed light on the use of such devices in a less well controlled, less motivated population of patients with T1DM. Although the results in patients using MDI were similar to the results in those using an insulin pump, the number of patients using MDI was too small for a definitive assessment.

Conclusion: In patients who were age 25 or older, RT-CGM significantly reduced HbA1c without increasing risk of severe hypoglycemia. RT-CGM yielded less benefit among patients who were 8 to 14 years of age and no benefit among those who were 15 to 24 years of age. With respect to generalizability, prior to randomization, patients in this study were receiving intensive insulin therapy; conducting frequent home blood glucose monitoring; had generally better-than-average HbA1c levels; and demonstrated the ability to wear a sensor. Therefore, the results do not shed

light on the use of CGM in a less well controlled, less motivated population of patients. In addition, patients who dropped out of the study before providing end-of-study HbA1c and CGM data (1.8% of patients in the RT-CGM group and 1.3% in the control group) were excluded from efficacy analyses.

Quality Grade: Fair

Beck RW, Hirsch IB, Laffel L, et al. The effect of continuous glucose monitoring in well-controlled type 1 diabetes. Diabetes Care. 2009;32:1378-83.[183]

Study Description: This was a 26-week, randomized, controlled, multicenter trial in adults and children with well controlled T1DM who were receiving intensive insulin therapy. After a 1-week blinded CGM run-in period, patients were randomized to RT-CGM or SMBG (control). Patients were randomly assigned to either the RT-CGM group or the control group using a permuted blocks design stratified by clinical center. The study was conducted between December 2006 and July 2008 at 10 centers in the U.S.

Funding Source: Juvenile Diabetes Research Foundation

Methods: Included were individuals age ≥8 years who had been diagnosed with T1DM ≥ 1 year before randomization; were receiving intensive insulin therapy (insulin pump or MDI); had an HbA1c level of <7.0%; had had not used CGM at home in the 6 months leading up to the trial; and, during the run-in period, wore a blinded CGM sensor at least 6 of 7 days and performed SMBG at least 3 times per day.

Patients randomized to the RT-CGM group received 1 of 3 RT-CGM devices with a sensor life of 3 to 7 days. Patients were instructed to use the device daily and to verify the accuracy of the glucose readings with a home blood glucose meter before making management decisions. Patients randomized to the control group were given blood glucose meters and test strips and asked to perform SMBG at least 4 times per day. The control group wore blinded RT-CGM devices.

Clinical Outcomes: All analyses were performed using a modified ITT approach, in which patients who did not provide HbA1c or CGM data at study end were excluded analyses of those outcomes. The primary outcome was change in the amount of time per day with glucose values ≤70 mg/dL from baseline to 26 weeks. A sample size of 120 subjects was planned to have 90% power to detect a difference in this outcome between treatment groups, assuming a population difference of 29 minutes per day, standard deviation of the 26-week values of 59 minutes per day, correlation between baseline and 26-week values of 0.66 (based on data from a prior study), an alpha level of 0.05, and no more than 15% losses to follow up.

Secondary included change in HbA1c from baseline to 26 weeks (adjusted for baseline HbA1c and clinical center); and 26-week binary HbA1c outcomes (decrease in HbA1c from baseline by ≥0.3%, increase in HbA1c from baseline by ≥0.3%, 26-week value <7.0%). Analyses also were conducted to assess consistency of the treatment effect in subgroups based on age. Four outcome measures were created by combining HbA1c and hypoglycemia data: a) decrease in HbA1c of ≥0.3% from baseline to 26 weeks and no severe hypoglycemic events; b) decrease in HbA1c of ≥0.3% from baseline to 26 weeks and CGM-measured hypoglycemia (≤70 mg/dL) not

increased from baseline to 26 weeks by ≥43 minutes a day (3% of the day); c) HbA1c not increased by ≥0.3% from baseline to 26 weeks and CGM-measured hypoglycemia (≤70 mg/dL) not increased from baseline to 26 weeks by ≥43 minutes a day (3% of the day); and d) either outcome b or c. Compliance with sensor use was assessed.

Safety endpoints included the proportion of patients who had at least one severe hypoglycemic event (defined as an event that required assistance from another person to administer oral carbohydrate, glucagon, or other resuscitative actions) and the incidence of severe hypoglycemic events.

Sample Characteristics: A total of 129 patients underwent randomized, with 67 assigned to the RT-CGM group and 62 to the control group. Baseline characteristics were balanced between groups. Approximately half of patients were female. The majority was non-Hispanic white (94%) and using insulin pumps (86%). Patients were measuring glucose levels about 7 times per day with a home glucose meter, and had a mean HbA1c level of ~6.5%. All patients in the RT-CGM a0nd all but 2 (3.2%) in the control group completed the study.

Outcome (Glycemic Control): Tables 1 and 2 present the blinded CGM-derived glycemic outcomes and change in A1c, respectively.

TABLE 1: CGM-MEASURED OUTCOMES BY TREATMENT GROUP

Outcome	RT-CGM (n=67)		Control (n=62)		P value§
	Baseline	Week 26†	Baseline	Week 26‡	
Median glucose level (minutes/day)					
≤70 mg/dL	91	54	96	91	0.05
≤60 mg/dL	40	18	40	35	0.01
≤50 mg/dL	7	4	9	8	0.05
71-180 mg/dL	1063	1063	972	949	<0.001
>180 mg/dL	255	283	331	341	0.03
>250 mg/dL	40	48	63	83	0.005
Median AUC (≤70 mg/dL)	0.64	0.26	0.60	0.49	0.03
Median SD of values	48	50	56	60	0.008
Median MAGE	93	96	106	108	0.26
Median absolute rate of change (mg/dL/min)	0.60	0.66	0.65	0.66	0.39

†One subject in RT-CGM group was missing sensor data.
‡Two subjects in control group dropped out before the 26-week visit.
§ P value is for between-group differences based on an ANCOVA model based on ranks of the 26-week values using van der Waerden scores, adjusted for the baseline value, clinical center, and type of continuous glucose monitor.
AUC=area under the curve; MAGE=mean amplitude of glycemic excursions; RT-CGM=real-time continuous glucose monitoring; SD=standard deviation; SH=severe hypoglycemia.

TABLE 2: HBA1C AT 26 WEEKS BY TREATMENT GROUP

Parameter	RT-CGM (n=67)	Control* (n=62)	P value
A1c (%) @ baseline, mean ± SD	6.4 ± 0.5	6.5 ± 0.3	
A1c (%) @ 26 weeks, mean ± SD	6.4 ± 0.5	6.8 ± 0.5	
Change in HbA1c (%) from baseline to 26 weeks, mean ± SD†	+0.02 ± 0.45	+0.33 ± 0.43	
Treatment group difference (95% CI) (%)†	−0.34 (−0.49 to −0.20)		<0.001
Decrease in HbA1c by ≥0.3% from baseline to 26 weeks, N (%)	21 (31)	3 (5)	<0.001
Increase in HbA1c by ≥0.3% from baseline to 26 weeks, N (%)	19 (28)	31 (52)	0.02
A1c <7.0% @ 26 weeks, N (%)	59 (88)	38 (63)	<0.001

*26-week data were not available for two control patients.
†Adjusted for baseline HbA1c and site. Negative value denotes lower HbA1c in RT-CGM group compared with control group.
CI=confidence interval; RT-CGM=real-time continuous glucose monitoring; RT-CGM=real-time continuous glucose monitoring; SD=standard deviation.

In three pre-specified age groups (≥25 years, 15 to 24 years, and 8 to 14 years), results of treatment group comparisons generally were similar to the overall analysis for the amount of time per day ≤70 mg/dL. More patients in the RT-CGM group than the control group had a decrease in HbA1c of ≥0.3% without experiencing a severe hypoglycemic event (28% vs. 5%, P<0.001). More patients in the RT-CGM group than the control group also had a decrease in HbA1c of ≥0.3% without an increase of ≥43 minutes a day (3% of the day) in CGM-measured glucose values ≤70 mg/dL (18% vs. 2%, P=0.007), and more had a ≥43 minutes a day decrease in the time per day with the glucose level ≤70 mg/dL without an increase in HbA1c of ≥0.3% (29% vs. 15%, P=0.005).

Outcome (Sensor Use): Over the 26 weeks of the study, median RT-CGM use was 6.8 days/week in patients age ≥25 years, 6.2 days/week in those age 15 to 24 years, and 6.4 days/week in those ages 8 to 14 year (P=0.07), averaging >6 days/week in 79%, 53%, and 61%, respectively.

Outcome (Adverse Events): Seven subjects (10%) in the RT-CGM group and seven (11%) in the control group experienced at least one severe hypoglycemic event, with no significant differences between groups. There were no significant differences in the rate of severe hypoglycemic events between treatment groups. No serious adverse events attributable to the study interventions occurred.

Study Limitations: This study included a unique population of children, adolescents, and adults withT1DM as noted by their entry HbA1c levels being <7.0% and their attention to intensive diabetes management principles with frequent blood glucose monitoring at baseline, averaging about seven times per day.

Conclusion: Almost all measures of glycemic control favored the RT-CGM group. Limitations include selection of well-motivated and -controlled patients with T1DM who were closely followed in a clinical trial setting and exclusion of study drop-outs from the efficacy analyses.

Quality Grade: Good

Bode B, Beck RW, Xing D, et al. Sustained benefit of continuous glucose monitoring on HbA1c, glucose profiles, and hypoglycemia in adults with type 1 diabetes. Diabetes Care. 2009;32:2047-9.[181]

Study Description: This was a 6-month, open-label, extension study following the 6-month JDRF RCT in patients with poorly or well controlled T1DM. Adult patients who were randomized to the RT-CGM group during the 6-month RCT were eligible to participate in the extension during which they continued to receive RT-CGM in a less intense clinical care environment. The study was conducted between December 2006 and February 2009 at 10 centers in the U.S.

Funding Source: Juvenile Diabetes Research Foundation

Methods: Included were individuals age ≥25 years who were diagnosed with T1DM for ≥1 year before randomization; were receiving intensive insulin therapy (insulin pump or MDI); had a baseline HbA1c ≥7.0 or <7.0% prior to randomization; and had received RT-CGM during the 6-month JDRF RCT. Follow-up visits during the extension study occurred at 9 and 12 months post-randomization.

Clinical Outcomes: Outcomes were change in HbA1c and glycemic variability at 6 and 12 months. The incidence of severe hypoglycemia (defined as an event that required assistance from another person to administer resuscitative actions) also was assessed at 6 and 12 months.

Sample Characteristics: Twelve-month follow-up data were analyzed for 83 of the 86 adults who were initially randomized to the RT-CGM group in either the ≥7.0% (n=49) or <7.0% (n=34) baseline HbA1c cohorts; two patients discontinued study participation during the first 6 months and one after completion of the 9-month visit. An insulin pump was used by 75 (90%) patients and MDI by 8 (10%).

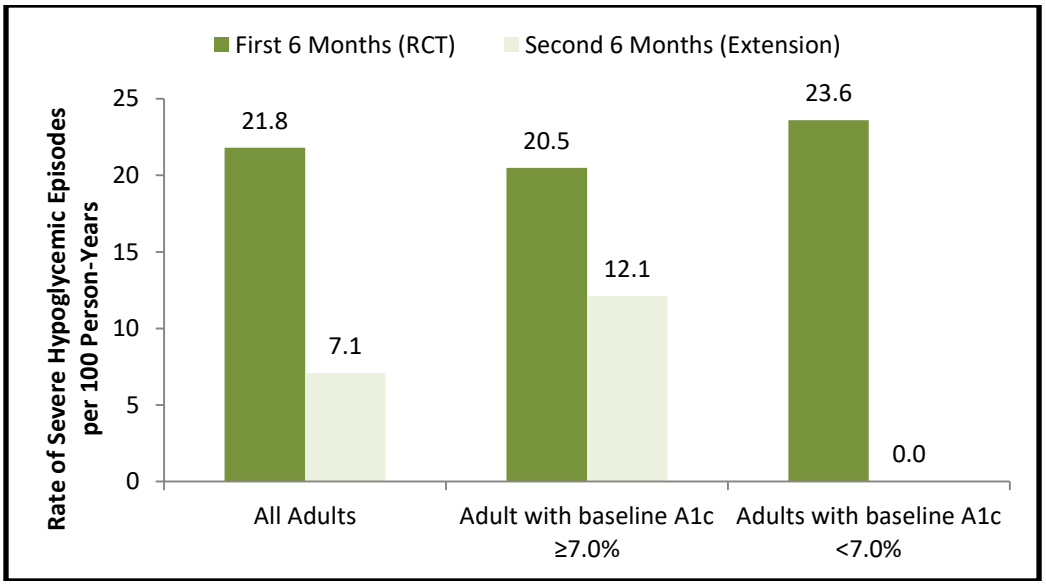
Outcome (HbA1c): Among patients with baseline HbA1c ≥7.0%, mean change in HbA1c from baseline to 12 months was -0.4 ± 0.6% (P<0.001), similar to the change from baseline to 6 months. The reduction in HbA1c occurred mainly in the first 8 weeks and then remained relatively stable through the next 44 weeks. Among patients with baseline HbA1c <7.0%, HbA1c remained within the target range over the entire 12 months of the study (6.4%, 6.3% and 6.4% at baseline, 6 and 12 months, respectively; P=0.42 for change from baseline to 12 months).

Outcome (Sensor Use): Median RT-CGM use was 7.0 days/week in month 6 and 6.8 days/week during month 12. Use in month 12 did not vary with baseline HbA1c level (Spearman r=-0.10, P=0.38).

Outcome (Glycemic Variability): The median amount of time per day with Page | 72glucose in the range of 71 to 180 mg/dL increased significantly (P=0.02) from baseline to 12 months, reflecting a decrease in both hypoglycemia and hyperglycemia. Similar trends were seen both in the HbA1c ≥7.0% and HbA1c <7.0% cohorts. The increase in time in range was seen during both daytime and nighttime. Variability assessed with the standard deviation of glucose values (P=0.02) and mean amplitude of glycemic excursions (MAGE) (P=0.03) were reduced with RT-CGM use from baseline to 12 months. Body weight, daily insulin dose and frequency of daily SMBG did not change meaningfully during the study.

Outcome (Severe Hypoglycemia): A severe hypoglycemic event was experienced by 8 (10%) of the 83 subjects (9 events) during the first 6 months and 3 (4%, 3 events) in the second 6 months. Rates of severe hypoglycemic events during the first and second 6 months of the study are shown in Figure 1. Although rates declined for all groups, these reductions were not statistically significant.

FIGURE 1. RATES OF SEVERE HYPOGLYCEMIA DURING THE FIRST AND SECOND 6 MONTHS



Study Limitations: None specified.

Conclusion: Most adults continued to use RT-CGM on a daily or near-daily basis and had sustained benefits of improved glucose control noted by HbA1c levels and the amount of time sensor glucose values were in the target range. These benefits persisted despite less intensive follow up, designed to approximate usual clinical practice. An additional important observation was the remarkably low rate of severe hypoglycemic events during the extension phase of the study. The total absence of severe hypoglycemia during the second 6 months of the study in the subjects who had a baseline HbA1c <7.0% is particularly striking, especially since these subjects were able to maintain a mean HbA1c of 6.4%. This was an uncontrolled, open-label extension study. It is not known whether comparable improvements in glycemic control were seen in patients not receiving RT-CGM. Further, patients who volunteered for the extension study may have been particularly motivated to improve their diabetes management, and thus results may not generalize to the broader population of diabetes patients.

Quality Grade: Fair

Chase HP, Beck RW, Xing D, et al. Continuous glucose monitoring in youth with type 1 diabetes: 12-month follow-up of the Juvenile Diabetes Research Foundation continuous glucose monitoring randomized trial. Diabetes Technol Ther. 2010;12:507-15.[182]

Study Description: This was a 6-month, open-label, extension study following the 6-month JDRF RCT in youth aged 8-17 years with poorly-controlled T1DM. Youth who were randomized to the RT-CGM group during the 6-month RCT were eligible to participate in the extension during which they continued to receive RT-CGM in a less intense clinical care environment. The study was conducted between December 2006 and February 2009 at 10 centers in the U.S.

Funding Source: Juvenile Diabetes Research Foundation

Methods: Eligible were youth age 7-17 years who were diagnosed with T1DM for ≥1 year before randomization; were receiving intensive insulin therapy (insulin pump or MDI); had a baseline HbA1c 7.0 to <10%; and had received RT-CGM during the 6-month JDRF RCT. Follow-up visits during the extension study occurred at 9 and 12 months post-randomization.

Clinical Outcomes: Outcomes were change in HbA1c and glycemic variability at 6 and 12 months. The incidence of severe hypoglycemia (defined as an event that required assistance from another person to administer resuscitative actions) also was assessed at 6 and 12 months. The CGM Satisfaction Scale, a 44-item 5-point Likert scale questionnaire, was administered at months 6 and 12 to both parents and subjects to assess the satisfaction with and perceived therapeutic impact of CGM. Subjects were categorized into three groups 9based on RT-CGM use in months 6 and 12: (A) ≥6 days/week in month 12; (B) ≥6 days/week in month 6 but <6 days/week in month 12; and (C) <6 days/week in both months 6 and 12. Analyses included only subjects completing the 12-month visit.

Sample Characteristics: Participants included 80 patients who were randomized to RT-CGM during the 6-month JDRF RCT. Five other randomized subjects did not complete the 52-week visit: one patient discontinued study participation during the first 6 months, three after completion of the 26-week visit, and one after completion of the 39-week visit.

The mean age of the 80 subjects was 13.0 years, with 42 (53%) being 8-12 years old and 38 (48%) being 13 to <18 years old; 74 (93%) were Caucasian, four (5%) were Hispanic, and two (3%) were other races. Mean baseline HbA1c was 8.0 ± 0.7%. An insulin pump was being used by 63 (79%), with the others being treated with MDI that included long- and rapid-acting insulin analogs.

Outcome (Sensor Use): Seventy-six of the 80 (95%) youth were still using RT-CGM after 6 months (median usage 5.5 days/week) compared with 67 (84%) after 12 months (median usage 4.0 days/week). Seventeen (21%) of the 80 patients were using RT-CGM ≥6 days/week in month 12 (14 were using RT-CGM ≥6 days/week in month 6 and three <6 days/week in month 6 [usage in month 6 in these three patients averaged 2.0, 3.6, and 5.8 days/week]), 17 (21%) were using it ≥6 days/week in month 6 but <6 days/week in month 12, and 46 (58%) were using it <6 days/week in both months 6 and 12. Use of RT-CGM ≥6 days/week was more likely in younger children and less likely in adolescents. Other baseline characteristics including baseline HbA1c were similar in the three subgroups based on use.

Outcome (HbA1c): HbA1c at baseline, 6 months and 12 months by RT-CGM use is shown in Table 1.

TABLE 1. HBA1C AT BASELINE, 6 MONTHS AND 12 MONTHS IN SUBGROUPS BASED ON RT-CGM USE

	RT-CGM Use			P value[a]
	(A) ≥6 days/week in month 12 (n=17)	(B) ≥6 days/week in month 6 & <6 days/week in month 12 (n=17)	(C) <6 days/week in both month 6 and 12 (n=46)	
HbA1c (mean ± SD)				<0.001 (0.01, <0.001, 0.19)
Baseline	8.2 ± 0.6	7.8 ± 0.5	8.0 ± 0.7	
6 months	7.3 ± 0.6	7.3 ± 0.6	8.0 ± 0.9	
12 months	7.4 ± 0.5	7.7 ± 0.6	8.1 ± 0.7	
ADA target met[b]				0.03 (0.06, 0.02,>0.99)
Baseline	5 (29%)	8 (47%)	18 (39%)	
6 months	11 (65%)	13 (76%)	16 (35%	
12 months	12 (71%)	7 (41%)	15 (33%)	

[a]P values from analysis of covariance model for HbA1c at 12 months and from logistic regression for the percentage of subject meeting ADA target at month 12, adjusted for baseline value and age. The first P value for each variable is for the three-group comparisons, followed by the three two-group comparisons (A vs. B, A vs. C, and B vs. C).
[b]<8.0% for 8-12 years of age and <7.5% for 13-17 years of age.
ADA=American Diabetes Association; RT-CGM=real-time continuous glucose monitoring.

Outcome (Glycemic Variability): In subjects using RT-CGM ≥6 days per week in month 12, CGM glucose data paralleled the HbA1c results, with a substantial increase in the time the glucose level was in the target range of 71-180 mg/dL from baseline to 6 months, sustained through 12 months (P=0.006 comparing baseline and 12 months) because of a reduction in time spent hyperglycemic. Moreover, lowering HbA1c and mean sensor glucose values did not increase the frequency of sensor glucose levels in the hypoglycemic range, which was low at baseline and remained low at 6 and 12 months.

Outcome (CGM Satisfaction): Scores on the CGM Satisfaction Scale were higher at 12 months for the subjects who used RT-CGM ≥6 days per week at 12 months compared with those using RT-CGM <6 days/week at 12 months (mean 4.0 vs. 3.3, P<0.001 for patients; 4.2 vs. 3.7; P<0.001 for parents).

Outcome (Severe Hypoglycemia): The incidence of severe hypoglycemic events was low during the 12 months of the study irrespective of the amount of RT-CGM use. Seven subjects (two of 17 using RT-CGM ≥6 days/week in month 12, two of 17 using RT-CGM ≥6 days/week in month 6 and <6 days/week in month 12, and three of 46 using RT-CGM <6 days/week in both months 6 and 12) experienced a total of nine events (incidence 11.2 events per 100 person-years).

Study Limitations: The participants in the trial were receiving intensive insulin management with either an insulin pump or MDI and prior to the trial most were measuring blood glucose frequently with a home glucose meter and had HbA1c levels in the good to excellent range. In a less well-controlled, less-motivated population of patients with T1DM, RT-CGM use after 12 months might even have been lower than what was found in this study.

Conclusion: Results demonstrated a substantial lowering of HbA1c levels and a corresponding decreased frequency of sensor glucose values above the target range in young patients with baseline values ≥7.0% if they used the RT-CGM device on a near daily basis. The severe hypoglycemia rate of 11.2 events per 100 patient-years during the 12 months of the study is the

lowest rate ever reported for youth with T1DM receiving intensive treatment. Generalizability may be limited as participants were receiving intensive insulin therapy, frequently performed SMBG and had HbA1c levels in the good to excellent range. The exclusion from analyses of patients who dropped out of the study was another limitation.

Quality Grade: Fair

Juvenile Diabetes Research Foundation Continuous Glucose Monitoring Study Group. Effectiveness of continuous glucose monitoring in a clinical care environment: evidence from the JDRF-CGM trial. Diabetes Care. 2010;33:17-22.[179]

Study Description: This was a 6-month, open-label, extension study following the 6-month JDRF RCT in patients with poorly or well controlled T1DM. Patients who were randomized to the control group during the 6-month RCT were eligible to participate in the extension during which they continued to receive RT-CGM in a standard care environment. The study was conducted between December 2006 and February 2009 at 10 centers in the U.S.

Funding Source: Juvenile Diabetes Research Foundation

Methods: Eligible people were age ≥8 years who were diagnosed with T1DM for ≥1 year before randomization with HbA1c ≤10% while receiving intensive insulin therapy (insulin pump or MDI) and had been assigned to the control group during the 6-month JDRF RCT. After completion of the 6-month RCT, each control group patient was provided with one of three RT-CGM devices: the Dexcom SEVEN® (Dexcom, Inc., San Diego, CA), the MiniMed Paradigm® REAL-Time Insulin Pump and Continuous Glucose Monitoring System (Medtronic MiniMed, Inc., Northridge, CA), or the FreeStyle Navigator™ (Abbott Diabetes Care, Inc., Alameda, CA). The RT-CGM initially was used in a blinded fashion for one week to obtain baseline data for evaluating change during follow up. After completion of the blinded use, patients were instructed to use the device daily and to verify the accuracy of glucose measurements with a home blood glucose meter before making management decisions. Target glucose values were pre-meal 70 to 130 mg/dL, peak post-meal <180 mg/dL, and bedtime/overnight 100 to 150 mg/dL. Instructions for insulin dosing included determination of pre-meal bolus doses based on the glucose level, the carbohydrate content of the upcoming meal, rate and direction of glucose change, and guidelines for correcting glucose levels outside the target range at other times. Follow-up visits during the clinical care RT-CGM phase occurred after 1, 4, 13 and 26 weeks, with phone contacts 3 days after RT-CGM initiation and 7 days after the one-week visit.

	All	RT-CGM Use at Month 6			
		0 Days/Week	>0 to <4 Days/Week	4 to <6 Days/Week	≥6 Days/Week
All Ages	**n=154**	**n=26**	**n=45**	**n=23**	**n=60**
Mean baseline A1c†	7.8%	8.0%	7.7%	7.8%	7.6%
∆ HbA1c from baseline to Month 6					

Mean change	-0.1 ± .6%	0.2 ± 0.9%	0.0 ± 0.6%	-0.4 ± 0.7%	-0.2 ± 0.4%
Improved ≥0.5%	49 (32%)	8 (31%)	8 (18%)	13 (57%)	20 (33%)
Worsened ≥0.5%	27 (18%)	8 (31%)	13 (29%)	2 (9%)	4 (7%)
A1c <7.0%	29 (19%)	2 (8%)	5 (11%)	9 (39%)	13 (22%)
Mean Δ from 0-6 Months in Prior RCT	0.0 ± 0.6%	-0.1 ± 0.5%	0.1 ± 0.6%	0.0 ± 0.7%	0.1 ± 0.5%
Age Group ≥25	**n=51**	**n=4**	**n=4**	**n=6**	**n=37**
Mean baseline A1c	7.6%	8.0%	7.6%	7.5%	7.6%
Δ HbA1c from baseline to Month 6					
Mean change	-0.4 ± 0.5%‡	0.1 ± 0.9%	-0.4 ± 0.7%	-0.5 ± 0.3%	-0.4 ± 0.4%
Improved ≥0.5%	23 (45%)	1 (25%)	2 (50%)	4 (67%)	16 (43%)
Worsened ≥0.5%	3 (6%)	1 (25%)	1 (25%)	0	1 (3%)
A1c <7.0%	15 (29%)	0	2 (50%)	3 (50%	10 (27%)
Mean Δ from 0-6 Months in Prior RCT	0.2 ± 0.5%	0.4 ± 0.5%	0.3 ± 0.6%	0.3 ± 0.5%	0.1 ± 0.4%
Age Group 15-24	**n=56**	**n=11**	**n=26**	**n=7**	**n=12**
Mean baseline A1c	7.9%	8.1%	7.9%	8.1%	7.7%
Δ HbA1c from baseline to Month 6					
Mean change	0.0 ± 0.7%	0.4 ± 1.2%	0.0 ± 0.5%	-0.6 ± 0.3%	0.0 ± 0.3%
Improved ≥0.5%	14 (25%)	4 (36%)	4 (15%)	5 (71%)	1 (8%)
Worsened ≥0.5%	10 (18%)	4 (36%)	5 (19%)	0	1 (8%)
A1c <7.0%	6 (11%)	0	2 (8%)	3 (43%)	1 (8%)
Mean Δ from 0-6 Months in Prior RCT	0.1 ± 0.7%	-0.1 ± 0.5%	0.1 ± 0.6%	-0.1 ± 0.8%	0.2 ± 0.7%
Age Group 8-14	**n=47**	**n=11**	**n=15**	**n=10**	**n=11**
Mean baseline A1c	7.8%	7.8%	7.6%	7.9%	7.8%
Δ HbA1c from baseline to Month 6					
Mean change	0.0 ± 0.7%	-0.1 ± 0.6%	0.2 ± 0.6%	-0.2 ± 0.9%	0.0 ± 0.6%
Improved ≥0.5%	12 (26%)	3 (27%)	2 (13%)	4 (40%)	3 (27%)
Worsened ≥0.5%	14 (30%	3 (27%)	7 (47%)	2 (20%)	2 (18%)
A1c <7.0%	8 (17%)	2 (18%)	1 (7%)	3 (3.0%)	2 (18%)
Mean Δ from 0-6 Months in Prior RCT	-0.2 ± 0.6%	-0.2 ± 0.4%	-0.1 ± 0.6%	-0.2 ± 0.7%	-0.1 ± 0.5%

*Baseline refers to the time of initiation of RT-CGM use (following the 6 months in the RCT as control group).
†One patient was missing a baseline lab HbA1c and the point of care HbA1c was imputed using least squares regression model.
‡P<0.001 vs. baseline.
RCT=randomized, controlled trial; RT-CGM=real-time continuous glucose monitoring.

Clinical Outcomes: Outcomes were change in HbA1c from initiation of RT-CGM to 6-month follow-up evaluated with a paired t test. Analysis of HbA1c was limited to subjects with a value ≥7.0% at baseline. The incidence of severe hypoglycemia (defined as an event that required assistance from another person to administer resuscitative actions) also was assessed at 6 and 12 months. RT-CGM use was determined by examining downloads of the RT-CGM devices at

each visit. The association between change in HbA1c and RT-CGM use in month 6 was assessed with least squares regression models adjusting for baseline A1c. The incidence of severe hypoglycemia (defined as an event that required assistance from another person to administer carbohydrate, glucagon, or other resuscitative actions) during the 6-month RCT (as the control group) versus the incidence during the subsequent RT-CGM use phase was compared using a signed rank test. The association of severe hypoglycemic events with baseline HbA1c was assessed with a Spearman correlation coefficient. All analyses included only patients completing the 6-month visit.

Sample Characteristics: A total of 214 of the 219 patients who were enrolled in the RCT control group participated in the extension study. Of the five patients who did not enroll in the extension study, four did not complete the RCT and one decided not to continue after completing the trial. The 214 patients included 80 who were ≥25 years old at the time of initiation of RT-CGM use, 73 who were 15 to 24 years old, and 61 who were 8 to 14 years old. Among the 214 patients, 199 (93%) were Caucasian, mean HbA1c at the time of initiation of RT-CGM was 7.4 ± 0.7% (range 5.8% to 10.1%), with 156 (73%) >7.0% and 58 (27%) <7.0%. An insulin pump was being used by 171 (80%), with the others being treated with MDI. The study was completed by 212 (99%) of the 214 subjects.

Outcome (HbA1c): Table 1 shows the change in HbA1c by RT-CGM use among patients with HbA1c ≥7.0% at the time of RT-CGM initiation. As shown in Table 1, among the 154 patients who completed the 6-month visit, change in HbA1c from baseline to 6 months varied with age group (P=0.002). There was a significant decrease in patients age ≥25 years (-0.4 ± 0.5%, P<0.001) but not in those age 15 to 24 years (mean change +0.01 ± 0.7%, P=0.95) or in those age 8 to 14 years (mean change +0.02 ± 0.7%, P=0.85).

Outcome (Sensor Use): The association of change in HbA1c and age group was related to the amount of RT-CGM use. Greater RT-CGM use was associated with a greater HbA1c decrease (P=0.01 adjusted for age group), and after adjusting for RT-CGM use, the relationship between age group and change in HbA1c was weaker (P=0.07).

TABLE 1. CHANGE IN HBA1C FROM BASELINE* TO MONTH 6 BY AMOUNT OF RT-CGM USE IN MONTH 6 IN PATIENTS WITH HBA1C ≥7.0% AT TIME OF RT-CGM INITIATION

Outcome (Glycemic Variability): In the ≥25 years group, there was an increase in time per day with the glucose level in the range of 71 to 180 mg/dL (882 vs. 980 min, P<0.001), with a decrease in both the time in hypoglycemia ≤70 mg/dL (55 vs. 45 min, P=0.02) and hyperglycemia >180 mg/dL (439 vs. 390 min, P=0.02). In patient age 15 to 24 years, there was a decrease in time in the hypoglycemia ≤70 mg/dL (93 vs. 55 min, P=0.005), but no consistent change in hyperglycemia. In patients age 8 to 14 years, there was no substantial change in time hypoglycemic or hyperglycemic. Results were similar for both daytime and nighttime and in subgroups based on baseline HbA1c (<7.0% and ≥7.0%).

Outcome (Severe Hypoglycemia): The incidence rate of severe hypoglycemic events was 15.0 events per 100 person-years during the 6 months of the follow-up. This trended lower than the rate in these subjects in the 6 months of the RCT that preceded this study period (27.7 events per 100 person-years, P=0.08). A similar trend was present in all 3 age groups as seen in Table 2. The severe hypoglycemia incidence rate during the 6 months of RT-CGM use was not significantly associated with baseline HbA1c (P=0.26).

TABLE 2. RATE OF SEVERE HYPOGLYCEMIA IN 6 MONTHS PRIOR TO RT-CGM USE AND DURING 6 MONTHS OF RT-CGM USE

	6 Month Control Period	6 Month RT-CGM Use Period
Age ≥25 Years	n=78 38.5 Person-Years	n=78 39.1 Person-Years
Severe hypoglycemia		
No. events (No. seizure or loss of consciousness)	13 (2)	9 (2)
No. (%) patients with ≥1 event	9 (12%)	8 (12%)
Incidence rate (per 100 person-years	33.7	23.0
Age 15-24 Years	n=73 35.9 Person-Years	n=73 36.6 Person-Years
Severe hypoglycemia		
No. events (No. seizure or loss of consciousness)	8 (3)	3 (2)
No. (%) patients with ≥1 event	7 (10%)	3 (4%)
Incidence rate (per 100 person-years	22.3	8.2
Age 8-14 Years	n=61 30.3 Person-Years	n=61 30.8 Person-Years
Severe hypoglycemia		
No. events (No. seizure or loss of consciousness)	8 (1)	4 (2)
No. (%) patients with ≥1 event	6 (10%)	3 (5%)
Incidence rate (per 100 person-years	26.4	13.0
RT-CGM=real-time continuous glucose monitoring.		

Study Limitations None specified.

Conclusion: In patients receiving RT-CGM in a standard care environment, significant reductions in HbA1c were seen in adults with baseline HbA1c ≥7.0%. As in the JDRF RCT, no reduction in HbA1c was seen in the two younger age groups. As in the RCT, after adjusting for frequency of RT-CGM use, there was no significant relationship between age and change in A1c. Despite less intensive implementation of RT-CGM in this study, the exposure to biochemical hypoglycemia was reduced in all three age groups, although the difference did not achieve statistical significance. While the study was not powered to detect a difference in severe hypoglycemic events, it is noteworthy that the rate of severe hypoglycemia was reduced by almost 50% when the former control subjects switched to RT-CGM. The limitations of this study include the lack of a control arm, and the exclusion of data from patients who discontinued the study (although the drop-out rate was quite small at 1%). Almost all patients who completed the 6-month RCT opted to enroll in the extension study.

Quality Grade: Fair

Chamberlain JJ, Dopita D, Gilgen E, et al. Impact of frequent and persistent use of continuous glucose m (CGM) on hypoglycemia fear, frequency of emergency medical treatment, and SMBG frequency after one *Sci Technol* 2015.[191]

Study Description: This was a single-center survey to assess changes in hypoglycemia fear, incidence of emergency medical treatment, and utilization of SMBG before and after 1 year of RT-CGM use.

Funding Source: Dexcom, Inc.

Methods: Study participants were individuals with T1DM who were treated with intensive insulin regimens and had used their current RT-CGM device (Dexcom G4 Platinum CGM System) for at least 1 year. Participants were recruited on an "as-seen" basis from a major, urban internal medicine clinic that sees between 700 and 800 patients per year on both an inpatient and outpatient basis and an associated diabetes education center that sees between 500 and 600 outpatients per year. The average HbA1c level among clinic patients was 7.4%. Participants were asked to complete a 16-item questionnaire.

Clinical Outcomes: The survey assessed changes in hypoglycemia fear, daily SMBG testing frequency and emergency medical treatment, comparing the year prior to RT-CGM to 1 year after CGM use in respondents who reported "almost daily" wear of their RT-CGM device.

Sample Characteristics: A total of 74 patients (38 male, 36 female) completed the survey from June 2014 to March 2015. The average age of participants was 42.9 years (range, 23-71 years). Fifty-nine participants had 10-25+ years duration of diabetes, and 59 were currently using an insulin pump. Approximately 76% (n=56) of participants reported participating in at least 1 formal training session with a trainer.

Outcome (Frequency of Use): Survey results showed that 84% of respondents reported wearing their devices "almost daily" (n=58) or 3 weeks per month (n=4). Among frequent users, "improved glycemic control" and "knowing glucose at all times" were most commonly reported as primary reasons for frequent use. Among less frequent RT-CGM users (≤3 weeks per month), the most common reasons reported were "tired of wearing 2 devices" and "sensor did not remain attached." Seventy (94.6%) respondents indicated that they would purchase the Dexcom G4 again.

Outcome (SMBG Utilization): "Almost daily" RT-CGM users reported a significant reduction in daily frequency of SMBG after 1 year of RT-CGM use compared with the prior year of no RT-CGM use (6.8 ± 3.2 vs. 3.2 ± 1.7, P<0.001).

Outcome (Healthcare Utilization): "Almost daily" RT-CGM users reported an 86% reduction in the number of events requiring emergency medical treatment after 1 year of RT-CGM use compared to the year prior to RT- CGM use (0.4 ± 0.9 events vs. 0.1 ± 0.3 events, P=0.0013).

Outcome (Fear of Hypoglycemia): Among respondents who indicated "almost daily" RT-CGM use, 45 (78%) reported worrying about hypoglycemia "most of the time" or "frequently" prior to RT-CGM use. After 1 year of RT-CGM use, no respondents reported worrying about hypoglycemia "most of the time" and 1 (2.0%) reported frequent worry, a 98% decrease in significant hypoglycemia fear (P=0.7359).

Study Limitations: A significant limitation of this study was the use of self-reported data, which may not accurately reflect participants' actual SMBG utilization or history incidence of emergency medical treatment. Lack of objective measurements of clinical and financial outcomes (e.g.,

change in HbA1c, insurance data regarding emergency room visits, SMBG data) further limit the interpretation of our findings. Another limitation was the small sample size; a larger number of participants would likely have increased the generalizability of findings, particularly if a larger number included more patients who used RT-CGM less frequently.

Conclusion: After 1 year of RT-CGM use, high-frequency users reported notable reductions in SMBG utilization, incidence of emergency medical treatment/hospitalizations, and hypoglycemia fear.

Quality Grade: Fair

Other Supporting Studies

Laffel L. Improved accuracy of continuous glucose monitoring systems in pediatric patients with diabetes mellitus: results from two studies. *Diabetes Technol Ther.* 2016;18 Suppl 2:S223-33.[192]

Study Description: Two 1-week open-label single-arm multicenter studies including youth treated with MDI or insulin pump therapy were conducted to compare the performance of two recently available RT-CGM systems, the Dexcom G4™ Platinum RT-CGM (G4P) and Dexcom G4™ Platinum with Software 505 algorithm (SW505). Study 1 was conducted from September 2012 to October 2012 at 6 centers in the US. Study 2 was conducted from May 2014 to September 2014 at 5 centers in the US.

Funding Source: Dexcom, Inc.

Methods: Patients were youth 2-17 years of age with T1DM or T2DM who were using MDI or insulin pump therapy. Exclusion criteria included hematocrits beyond the range recommended by the study glucose meters, pregnancy, hypoglycemic unawareness (other than that usually expected for toddlers with diabetes), need for treatment with acetaminophen, and any significant illness that would pose a risk to the patient or to the staff handling the blood specimen.

In Study 1, participants wore two CGM systems simultaneously for a 7-day sensor wear period (amounting to 168 h), with one receiver providing real-time data and the other masked. In Study 2, participants wore a single unmasked sensor for the 7-day sensor wear period with CGM data displayed in real time. Sensors were inserted in the abdomen and/or upper buttocks by the patients or parents/guardians after self-training using a tutorial and/or one-on-one training by study staff.

Subjects in both studies were required to use a study provided BG meter (the LifeScan [Milpitas, CA] OneTouch® Verio® IQ in Study 1 and the Bayer [Whippany, NJ] Contour® Next USB BG meter in Study 2) and study-provided BG test strips for all BG measurements performed during sensor wear. In both studies, participants were asked to perform a minimum of seven fingersticks per day for home use for calibration (performed twice daily per labeling recommendations), comparative purposes, and all insulin dose selections as well as any other diabetes management decisions. All subjects avoided use of acetaminophen during the sensor wear period and for at least 24 h prior to sensor insertion. In both studies, participants were required not to inject insulin or wear an insulin pump insertion set within 3 inches of the sensor sites during wear. During home use, although the CGM data were displayed on the receiver screen, participants and families were to base all diabetes management decisions on results from the BG meter.

In both studies, subjects 6-17 years of age participated in one in-clinic session on either Day 1, 4, or 7 of sensor wear to allow for comparison of both the G4P and SW505 sensor glucose measurements with a reference glucose measurement (YSI BG analyzer; YSI, Yellow Springs, OH) obtained every 15 ± 5 min using arterialized venous blood and with glucose meter results using fingerstick capillary samples obtained every 30 ± 5 min. For youth 2–5 years of age, only fingerstick capillary samples were obtained every 30 ± 5 min. The CGM systems were calibrated using BG meter results at the start of the clinic session. During the in-clinic sessions, all receivers were masked, avoiding any display of sensor glucose results.

The preschool-aged subjects (2-5 years of age) participated in a 4-h clinic session in both studies. School-aged subjects (6-12 years of age) participated in the clinic session for up to 6 h. Teen subjects (13-17 years of age) participated in the clinic session for up to 6 h in Study 1 and for up to 12 h in Study 2. Those 6-17 years of age underwent intravenous catheterization of the dorsal hand, lower arm, or antecubital region for venous blood sampling for YSI plasma glucose determinations. In the teen sample in Study 2, glucose levels during the in-clinic session were manipulated under close supervision according to protocol guidelines in efforts to achieve glucose levels across the range of sensor performance (40-400 mg/dL) by either adjusting the timing of meals (delaying meals after insulin administration to induce controlled hypoglycemia) or the timing of insulin administration (delaying insulin dosing with food intake to induce hyperglycemia). For youth of all ages in Study 1 and for those 2-12 years of age in Study 2, the participants checked their BG levels, took insulin, and ate as per their usual practice. At the end of the clinic session, study staff unmasked the receivers, and all receivers and glucose meters were downloaded using a sponsor-provided clinical laptop. For both studies, on Day 7, participants returned to the clinic, removed the sensors themselves (or the sensors were removed by parents/guardians, as applicable), and returned the CGM systems and BG meters to the study staff. Study staff assessed adverse events related to study procedures, device use, and skin irritation. Staff carefully inspected the skin at the sites of sensor insertions and used the Draize scale to grade skin irritation.24 Sensors were inspected by the study staff and the sponsor to assess any sensor breakoff during use.

Clinical Outcomes: The RT-CGM values were compared with the temporally matched glucose values from the reference YSI and BG meter values. The MARD, as well as median ARD, in percentages and the proportion of the CGM system values that were within ± 20% of the relative difference from the reference value at glucose levels >80 mg/dL (4.4 mmol/L) and within ± 20 mg/dL of absolute difference at glucose levels ≤80 mg/dL (hereafter referred to as %20/20) were used to evaluate the overall accuracy performance of the CGM devices.

Similarly, performances of the G4P and SW505 systems were assessed within glucose ranges of 40-60 mg/dL (2.2-3.3 mmol/L), 61-80 mg/dL (3.4-4.4 mmol/L), 81-180 mg/dL (4.5-10.0 mmol/L), and >180 mg/dL (10.0 mmol/L) as well as within each day of sensor use, from Day 1 through Day 7. The mean absolute difference (MAD), as well as median absolute difference, was also used to assess performance in the hypoglycemic range, 40-80 mg/dL (2.2-4.4 mmol/L). Modified Bland–Altman plots were used to depict the data distribution and bias between the CGM and the reference glucose determinations. Error grid analyses, including the Clarke Error Grid and Parkes Error Grid, were used to quantify the clinical accuracy of the RT-CGM devices. CGM diagnostic features were evaluated in the hypoglycemic range ≤80 mg/dL (4.4 mmol/L) and in the hyperglycemic range ≥240 mg/dL (13.3 mmol/L) by assessing concordance of CGM values within 15 min of the reference YSI results at these levels. Rate of both low and high false RT-CGM alerts was also assessed based on CGM readings in the hypoglycemic or hyperglycemic ranges, respectively, when the matched YSI values within 15 min were not out of range.

Sample Characteristics: Study 1 consisted of 176 subjects, with 29 in the 2-5-year age group, 69 in the 6-12-year age group, and 78 in the 13- 17-year age group. Study 2 included 79 subjects, with 16 in the 2-5-year age group, 17 in the 6-12-year age group, and 46 in the 13-17-year age group. Almost all patients had T1DM, with an average duration about 5 years; the majority received insulin pump therapy. Mean HbA1c values were 8.2 ± 1.3% and 8.5 ± 1.5% in Studies 1 and 2, respectively. In Study 1, 40% of participants had previous exposure to RT-CGM,

whereas only 13% used RT-CGM devices on a routine basis; in Study 2, 57% had previous exposure to RT-CGM, whereas only 19% used it on a routine basis. Characteristics of the youth participants in Studies 1 and 2 are displayed in Table 1.

TABLE 1: PATIENT CHARACTERISTICS

Characteristic	GAP (n=176)	SW505 (n=79)
Age (years)	**11.4** ±4.2	12.2 ± 4.6
Diabetes duration (years)	4.8 ± 3.7	5.6 ± 4.2
z-BMI, mean ± SD	0.5 ± 1.0	0.7 ± 0.7
z-BMI, range	-4.7 to 2.6	-1.4 to 2.2
SMBG (times/day)	6.7 ± 2.9	6.7 ± 2.3
HbA1c (%)	8.2 ± 1.3	8.5 ± 1.5
Sex (% male)	57%	52%
Race (% white)	94%	96%
Type 1 diabetes (%)	99%	100%
Pump use (%)	72%	60%
Previous RT-CGM use (%)	40%	57%
Frequent RT-CGM use (≥50% of the time) (%)		
Age 2-5 years	16%	20%
Age 6-12 years	39%	22%
Age 13-17 years	44%	58%
BMI=body mass index; G4P=G4 Platinum; RT-CGM=real-time continuous glucose monitoring; SMBG=self-monitoring of blood glucose; SW505=Software 505 algorithm.		

Outcome (CGM Performance): For assessment of CGM accuracy against YSI glucose measurements during the in-clinic sessions, there were 2,922 paired results (CGM and YSI temporally matched) in Study 1 and 2,262 paired results in Study 2 (Table 2). The overall MARD was 17% in Study 1 of the G4P, with a significant improvement in the MARD to 10% in Study 2 with the SW505 (P<0.0001). Median ARD was 14% in Study 1 and 8% in Study 2. For assessment of CGM accuracy against SMBG meter results during the 1 week of sensor wear, there were 16,318 paired results (CGM and meter temporally matched) in Study 1 and 4,262 paired results in Study 2. The overall MARD was 15% in Study 1 and 13% in Study 2 (P<0.00001). The median ARD was 11% in Study 1 and 10% in Study 2.

For both the G4P and SW505, CGM accuracy improved after Day 1 of sensor use. For CGM accuracy against the YSI, MARD improved from 21% on Day 1 to 16% on Day 4 and then to 15% on Day 7 for the G4P; MARD improved from 13% on Day 1 to 8% on Day 4 and then to 10% on Day 7 for the SW505. For CGM accuracy against SMBG, MARD improved from 19% on Day 1 to 12% on Day 7 for the G4P; MARD improved from 15% on Day 1 to 11% on Day 7 for the SW505.

The Clarke Error Grid results indicated superior clinical accuracy with the SW505 algorithm compared with the G4P in the comparison of CGM versus YSI glucose values. Assessment of CGM accuracy using the Parkes Error Grid yielded a similarly improved performance with the SW505 compared with the G4P, with greater percentages of CGM falling within the clinically accurate Zone A and the combined Zone A plus the benign error Zone B for CGM versus YSI and CGM versus SMBG. Notably, 100% of the CGM values fell within Zones A and B for CGM versus YSI and for CGM versus SMBG with the SW505. CGM performance was also assessed across various CGM glucose ranges where the SW505 performance was also superior to the G4P.

TABLE 2. CGM PERFORMANCE ACCURACY DURING CLINIC (CGM VS REFERENCE YSI) AND HOME USE (CGM VERSUS SMBG)

	CGM versus YSI		CGM versus SMBG	
	G4P	SW505	G4P	SW505
Number of matched pairs	2,922	2,262	16,318	4,264
Mean/median ARD (%)	17/14	10/8	15/11	13/10
CEG Zone A (%)/A + B (%)	68/98	90/99	75/98	83/93
PEG Zone A (%)/A + B (%)	79/99	93/100	80/99	86/100
%20/20/%30/30 (%)	68/85	91/96	76/89	84/94
Within CGM ranges				
40 ≤ CGM ≤60 mg/dL				
Number of matched pairs	19	86	487	240
Mean/median AD (mg/dL)	19/9	16/13	24/18	17/14
60 < CGM ≤80 mg/dL				
Number of matched pairs	76	142	1,340	399
Mean/median AD (mg/dL)	13/11	12/8	17/11	14/10
80 < CGM ≤180 mg/dL				
Number of matched pairs	1,155	805	7,084	1,650
Mean/median AD (mg/dL)	17/13	11/8	15/11	14/10
CGM >180 mg/dL				
Number of matched pairs	1,672	1,229	7,407	1,975
Mean/median AD (mg/dL)	18/14	9/7	14/10	11/8
CGM >250 mg/dL				
Number of matched pairs	724	608	3,604	964
Mean/median AD (mg/dL)	18/15	10/7	14/10	11/8

AD=absolute differences; ARD=absolute relative difference; CEG=Clarke Error Grid; G4P=G4 Platinum; PEG=Parkes Error Grid; SW505=Software 505 algorithm.

The SW505 performed superiorly to the G4P with respect to detection of hypo- and hyperglycemia. With a low glucose alert of 80 mg/dL, CGM detected true hypoglycemia according to YSI measurements ≤80 mg/dL 55% of the time within 15 min with the G4P and 91% of the time within 15 min with the SW505. In this hypoglycemic range, there was a false alert rate of 34% with the G4P and 14% with the SW505. With a high glucose alert of 240 mg/dL, CGM detected true hyperglycemia according to YSI measurements ≥240 mg/dL 96% of the time within 15 min with the G4P and 94% of the time within 15 min with the SW505. In this hyperglycemic range, there was a false alert rate of 33% with the G4P and 12% with the SW505.

Outcome (Adverse Events): There were no SAEs or device-related SAEs for either the G4P or the SW505 among the pediatric patients in either study. There was no sensor break-off or infection at the site of sensor insertion. There was mild skin irritation in some patients in the adhesive area, occurring at a low rate.

Study Limitations: Longer-term studies are needed to assess whether the substantially improved performance of the SW505 algorithm results in greater uptake, sustained use, and improvements in glycemic control without an increase in severe hypoglycemia.

Conclusions: This report describes the performance of the G4P CGM system as well as the improved performance of the G4P with the SW505 algorithm in pediatric patients with diabetes.

Quality Grade: Fair

3.1.2 Summary of Clinical Data Supporting Off-label Indications

Off-label indications include pregnant women with T1DM or T2DM who are treated with insulin. To date, no well defined RCTs have been conducted evaluating the use of continuous RT-CGM in pregnant women with diabetes.

3.1.3 Clinical Evidence Spreadsheet

Citation/Funding Source	Study Dates	Design, Treatments & Sample Size	Inclusion/Exclusion Criteria	Clinical Outcomes & Outcome
RT-CGM Only Versus RT-CGM + Blood Glucose Measurements				
Aleppo G, Ruedy KJ, Riddlesworth TD, Kruger DF, Peters AL, Hirsch I, et al. REPLACE-BG: A randomized trial comparing continuous glucose monitoring with and without routine blood glucose monitoring in well-controlled adults with type 1 diabetes *Diabetes Care.* 2017. Funding: Dexcom, Inc. Quality Grade: Good	Start: 52015 End: 9/2015	Design: 26-week, randomized, non-inferiority trial Setting: 14 centers in the U.S. T1D Exchange Clinic Network Treatments: G4 Platinum (G4P) G4 Platinum with 505 software (SW505) Sample Size: G4P (n=176) SW505 (n=79)	Inclusion: • Age ≥18 years • T1DM ≥1 year • Insulin pump therapy (without low glucose suspend feature) ≥3 months • Point-of-case HbA1c ≤9.0% (≤75 mmol/mol) Exclusion: • Occurrence of a severe hypoglycemia event resulting in seizure or loss of consciousness in past 3 years or an event without seizure or loss of consciousness requiting the assistance of another	Primary: % time in range (70-180 mg/dL): • RT-CGM only: ○ Baseline: 63 ±13 ○ 26-week study period: 63 ± 13 • RT-CGM+BGM: ○ Baseline: 63 ±13 ○ 26-week study period: 65 ± 11 • P=0.81 Secondary: Mean glucose (mg/dL): • RT-CGM only: ○ Baseline: 162 ±22 ○ 26-week study period: 162 ± 23

Citation/Funding Source	Study Dates	Design, Treatments & Sample Size	Inclusion/Exclusion Criteria	Clinical Outcomes & Outcome

			individual in the past 12 months
			• Significant HUA
			• >10.0% of baseline CGM glucose concentrations <60 mg/dL
			• >1 episode of DKA in past year
			• History of seizures other than those due to hypoglycemia
			• Current use of threshold-suspend pump feature
			• Myocardial infarction or stroke in past 6 months
			• Estimated GFR <30 mL/min/1.73 m2
			• Abnormal thyroid function
			• Use of a systemic β-blocker
			• Regular use of oral corticosteroids
			• Initiation of a noninsulin drug for glucose control during past 3 months
			• Pregnancy
			• Inpatient psychiatric treatment in past 6 months
			• Presence of a contraindicated medical
				• RT-CGM+BGM:
				  ○ Baseline: 158 ±22
				  ○ 26-week study period: 158 ± 20
				• P>0.99
				
				Coefficient of variation (%):
				• RT-CGM Only:
				  ○ Baseline: 36 (33-41)
				  ○ 26-week study period: 37 (34-41)
				• RT-CGM+BGM:
				  ○ Baseline: 37 (33-40)
				  ○ 26-week study period: 37 (34-40)
				• P=0.58
				
				% time in <70 mg/dL:
				• RT-CGM only:
				  ○ Baseline: 2.9 (1.5-4.5)
				  ○ 26-week study period: 3.0 (1.6-5.1)
				• RT-CGM+BGM:
				  ○ Baseline: 3.6 (11.9-4.8)
				  ○ 26-week study period: 3.7 (1.9-4.7)
				• P=0.95
				
				% time in <60 mg/dL:
				• RT-CGM only:
				  ○ Baseline: 1.1 (0.6-1.9)

Citation/Funding Source	Study Dates	Design, Treatments & Sample Size	Inclusion/Exclusion Criteria	Clinical Outcomes & Outcome
			condition, including ongoing use of acetaminophen.	○ 26-week study period: 1.3 (0.5-2.4) • RT-CGM+BGM: ○ Baseline: 1.4 (0.6-2.3) ○ 26-week study period: 1.6 (0.6-2.2) • P=0.57 % time in <50 mg/dL: • RT-CGM only: ○ Baseline: 0.3 (0.1-0.6) ○ 26-week study period: 0.4 (0.2-0.8) • RT-CGM+BGM: ○ Baseline: 0.4 (0.2-0.7) ○ 26-week study period: 0.5 (0.2-0.8) • P=0.75 Area under curve 70 mg/dL: • RT-CGM only: ○ Baseline: 0.3 (0.2-0.5) ○ 26-week study period: 0.3 (0.1-0.6) • RT-CGM+BGM: ○ Baseline: 0.4 (0.2-0.6) ○ 26-week study period: 0.4 (0.2-0.5) • P=0.76

Citation/Funding Source	Study Dates	Design, Treatments & Sample Size	Inclusion/Exclusion Criteria	Clinical Outcomes & Outcome

				% days with ≥20 consecutive min glucose values <60 mg/dL:
				• RT-CGM Only:
				  ○ Baseline: 25 (15-43)
				  ○ 26-week study period: 28 (13-42)
				• RT-CGM+BGM:
				  ○ Baseline: 33 (15-43)
				  ○ 26-week study period: 32 (16-46)
				• P=0.68
				
				% time in >180 mg/dL:
				• RT-CGM only:
				  ○ Baseline: 33 (25-43)
				  ○ 26-week study period: 35 (25-41)
				• RT-CGM+BGM:
				  ○ Baseline: 31 (22-40)
				  ○ 26-week study period: 31 (24-38)
				• P=0.88
				
				% time in >250 mg/dL:
				• RT-CGM only:
				  ○ Baseline: 8 (4-15)
				  ○ 26-week study period: 9 (5-13)
				• RT-CGM+BGM:
				  ○ Baseline: 7 (3-11)

Citation/Funding Source	Study Dates	Design, Treatments & Sample Size	Inclusion/Exclusion Criteria	Clinical Outcomes & Outcome
				○ 26-week study period: 7 (4-11) • P=0.65 % time in >300 mg/dL: • RT-CGM only: ○ Baseline: 2 (1-5) ○ 26-week study period: 92 (1-4) • RT-CGM+BGM: ○ Baseline: 2 (1-4) ○ 26-week study period: 2 (1-3) • P=0.72 Area under curve 180 mg/dL: • RT-CGM only: ○ Baseline: 17 (10-25) ○ 26-week study period: 17 (10-23) • RT-CGM+BGM: ○ Baseline: 14 (-8-22) ○ 26-week study period: 15 (9-21) • P=0.90 % days with ≥20 consecutive min of glucose values >300 mg/dL: • RT-CGM only: ○ Baseline: 25 (12-48)

Citation/Funding Source	Study Dates	Design, Treatments & Sample Size	Inclusion/Exclusion Criteria	Clinical Outcomes & Outcome
				○ 26-week study period: 27 (14-40) • RT-CGM+BGM: ○ Baseline: 20 (8-36) ○ 26-week study period: 20 (10-37) • P=0.72 Change in HbA1c from baseline: • RT-CGM only: 0.00 ±0.5 • RT-CGM+BGM: 0.00 ±0.5 • P=0.41 No worsening in HbA1c by >0.3% and no severe hypoglycemia: • RT-CGM only: 115 (81) • RT-CGM+BGM: 54 (72) • P=0.15 No. of severe hypoglycemia events: • RT-CGM only: 0 • RT-CGM+BGM: 1
MDI + RT-CGM Versus MDI +SMBG				
Beck RW, Riddlesworth T, Ruedy K, Ahmann A, Bergenstal R, Haller S, et al. Effect of continuous glucose monitoring on glycemic	Start: 10/2014 End: 5/2016	Design: 24-week randomized clinical trial Setting: Multicenter study in the U.S. Treatments:	Inclusion: • Age ≥25 years • T1DM ≥1 years • HbA1c between 7.5% and 10.0% • Receiving MDI	Primary: Mean change in HbA1c after 24 weeks: • MDI + RT-CGM: -1.0% • Control: -0.4%

Citation/Funding Source	Study Dates	Design, Treatments & Sample Size	Inclusion/Exclusion Criteria	Clinical Outcomes & Outcome

control in adults with type 1 diabetes using insulin injections: The DIAMOND randomized clinical trial. *JAMA* 2017; 317:371-78.
 	
Funding: Dexcom
 	
Quality Grade: Good
		MDI + RT-CGM
		Control (MDI + SMBG)
		
		<u>Sample Size</u>:
		Randomized:
		• MDI + RT-CGM (n=105)
		• Control (n=53)
		Completed:
		• MDI + RT-CGM (n=102)
		• Control (n=53)
			• Patients in groups without RT-CGM willing to perform SMBG ≥4 times/day
			• Negative pregnancy test
			• During 2-week pre-randomization phase, use sensor on ≥85% of possible days, perform 2 blood glucose calibrations per day, and perform SMBG ≥3 times per day.
			
			<u>Exclusion</u>:
			• CGM use during past 3 months
				• Mean adjusted group difference: -0.6% (95% CI -0.8% to -0.3%, P<0.001)
				
				<u>Secondary</u>:
				% achieving HbA1c<7.0% after 24 weeks:
				• MDI + RT-CGM: 18%
				• Control: 4%
				• Mean adjusted group difference: 15 (0 to 30)
				• P=0.01
				
				Glucose variability (coefficient of variation):
				• Mean adjusted group difference: -4 (-6 to -2)
				• P<0.001
				
				Median (IQR) min/day in range of 70-180 mg/dL:
				• Mean adjusted group difference: 77 (6 to 147)
				• P<0.001
				
				Median (IQR) min/day <70 mg/dL:
				• Baseline
				  ○ MDI + RT-CGM: 65 (33 to 103)
				  ○ Control: 72 (35 to 136)
				• Pooled 12 & 24 weeks:

Citation/Funding Source	Study Dates	Design, Treatments & Sample Size	Inclusion/Exclusion Criteria	Clinical Outcomes & Outcome
				○ MDI + RT-CGM: 43 (27 to 69) ○ Control: 80 (36 to111) ○ P=0.002 Median (IQR) min/day <60 mg/dL: • Baseline ○ MDI + RT-CGM: 32 (15 to 61) ○ Control: 39 (15 to 78) • Pooled 12 & 24 weeks: ○ MDI + RT-CGM: 20 (9 to 30) ○ Control: 40 (16 to 68) ○ P=0.002 Median (IQR) min/day <50 mg/dL: • Baseline ○ MDI + RT-CGM: 13 (5 to 29) ○ Control: 18 (4 to 39) • Pooled 12 & 24 weeks: ○ MDI + RT-CGM: 6 (2 to 12) ○ Control: 20 (4 to 42) ○ P=0.001 Median (IQR) min/day >180 mg/dL: • Baseline ○ MDI + RT-CGM: 687 (554 to 810)

Citation/Funding Source	Study Dates	Design, Treatments & Sample Size	Inclusion/Exclusion Criteria	Clinical Outcomes & Outcome
				○ Control: 725 (537 to 798) • Pooled 12 & 24 weeks: ○ MDI + RT-CGM: 638 (503 to 807) ○ Control: 740 (625 to 854) ○ P=0.03 Median (IQR) min/day >250 mg/dL: • Baseline ○ MDI + RT-CGM: 301 (190 to 401) ○ Control: 269 (184 to 383) • Pooled 12 & 24 weeks: ○ MDI + RT-CGM: 223 (128 to 351) ○ Control: 347 (241 to 429) ○ P<0.001 Median (IQR) min/day >300 mg/dL: • Baseline ○ MDI + RT-CGM: 129 (66 to 201) ○ Control: 109 (71 to 204) • Pooled 12 & 24 weeks: ○ MDI + RT-CGM: 78 (36 to 142) ○ Control: 167 (89 to 226) ○ P<0.001 <u>Exploratory:</u> % achieving HbA1c<7.5% after 24 weeks: • MDI + RT-CGM: 38%

Citation/Funding Source	Study Dates	Design, Treatments & Sample Size	Inclusion/Exclusion Criteria	Clinical Outcomes & Outcome

				• Control: 11%
				• Adjusted group difference: 31 (12 to 51)
				• P<0.001
				
				Relative reduction in HbA1c ≥10.0% after 24 weeks:
				• MDI + RT-CGM: 57%
				• Control: 19%
				• Adjusted group difference: 37 (16 to 58
				• P<0.001
				
				Mean glucose, mean (SD), mg/dL:
				• Baseline:
				  ○ MDI + RT-CGM: 187 (27)
				  ○ Control: 186 (30)
				• Pooled 12 & 24 weeks:
				  ○ MDI + RT-CGM: 180 (27)
				  ○ Control: 189 (25)
				• Mean adjusted difference: -9 (-19 to 0)
				  ○ P=0.01
				
				<u>Post Hoc Outcomes:</u>
				Reduction in HbA1c ≥1%:
				• MDI + RT-CGM: 52%
				• Control: 19%
				• Adjusted group difference: 33 (11 to 54)

Citation/Funding Source	Study Dates	Design, Treatments & Sample Size	Inclusion/Exclusion Criteria	Clinical Outcomes & Outcome

				• P<0.001
				
				Reduction in HbA1c ≥1% or HbA1c <7.0%:
				• MDI + RT-CGM: 52%
				• Control: 21%
				• Adjusted group difference: 31 (9 to 52)
				• P<0.001
				
				Median (IQR) area above curve 70 mg/dL:
				• Baseline:
				  ○ MDI + RT-CGM: 0.5 (0.3 to 1.1)
				  ○ Control: 0.7 (0.2 to 1.4)
				• Pooled 12 & 24 weeks:
				  ○ MDI + RT-CGM: 0.3 (0.2 to 0.5)
				  ○ Control: 0.7 (0.2 to 1.3)
				• P<0.001
				
				Median (IQR) area under curve 180 mg/dL:
				• Baseline:
				  ○ MDI + RT-CGM: 34 (25 to 46)
				  ○ Control: 33 (26 to 45)
				• Pooled 12 & 24 weeks:
				  ○ MDI + RT-CGM: 27 (17 to 40)
				  ○ Control: 40 (31 to 51)
				• P<0.001

Citation/Funding Source	Study Dates	Design, Treatments & Sample Size	Inclusion/Exclusion Criteria	Clinical Outcomes & Outcome
				Severe Hypoglycemia: • MDI + RT-CGM: n=2 • Control: n=2 Serious adverse events unrelated to RT-CGM: • MDI + RT-CGM: n=2 • Control: n=0 RT-CGM Satisfaction: • Mean (SD) total score: 4.2 (0.4) • Mean (SD) benefits subscale: 4.2 (0.5) • Mean (SD) lack of hassles subscale: 4.3 (0.5)

Ruedy K, Riddlesworth TD, Graham C. Continuous glucose monitoring in older adults with type 1 and type 2 diabetes using multiple daily injections of insulin: results from the DIAMOND trial. *J Diabetes Sci Technol* In press.
 	
Funding: Dexcom
 	
Quality Grade: Good
	Start:
	10/2014
	
	End:
	5/2016
		Design:
		24-week randomized clinical trial
		
		Setting: Multicenter study in the U.S.
		
		Treatments:
		MDI + RT-CGM
		Control (MDI + SMBG)
		
		Sample Size:
		Randomized:
		• T1DM (n=34)
		• T2DM (n=82)
		• MDI + RT-CGM (n=63)
			Inclusion:
			• Age ≥60 years
			• T1DM or T2DM
			• HbA1c between 7.5% and 10.0%
			• Receiving MDI ≥1 year
			• SMBG ≥2 times/day (T2DM or ≥3 times/day (T1DM)
			• Estimated glomerular filtration rate ≥45
			
			Exclusion:
			• CGM use during past 3 months
				Primary:
				Change in HbA1c from baseline to 24 weeks:
				• MDI + RT-CGM: -0.9 ± 0.7%
				• Control: -0.5 ± 0.7%
				• Mean adjusted difference: -0.4 ± 0.1%
				• P<0.001
				
				Secondary:
				Mean glucose (mg/dL):
				• Baseline:
				  ○ MDI + RT-CGM: 175 ± 25
				  ○ Control: 179 ± 30

Citation/Funding Source	Study Dates	Design, Treatments & Sample Size	Inclusion/Exclusion Criteria	Clinical Outcomes & Outcome

		• Control (n=53)
		Completed:
		• MDI + RT-CGM (n=61)
		• Control (n=53)
			• Medical condition contraindicating a target HbA1c <7.0%	• 24 weeks:
				  ○ MDI + RT-CGM: 168 ± 29
				  ○ Control: 180 ± 28
				• P=0.01
				
				Median (IQR) coefficient of Variability (%):
				• Baseline:
				  ○ MDI + RT-CGM: 34 (28 to 42)
				  ○ Control: 34 (29 to 38)
				• 24 weeks:
				  ○ MDI + RT-CGM: 31 (28 to 36)
				  ○ Control: 33 (27 to 39)
				• P=0.02
				
				Mean (SD) time spent 70-180 mg/dL (min/day):
				• Baseline:
				  ○ MDI + RT-CGM: 796 ± 236
				  ○ Control: 753 ± 253
				• 24 weeks:
				  ○ MDI + RT-CGM: 889 ± 251
				  ○ Control: 732 ± 252
				• P<0.001
				
				Median (IQR) spent >250 mg/dL (min/day):
				• Baseline:

Citation/Funding Source	Study Dates	Design, Treatments & Sample Size	Inclusion/Exclusion Criteria	Clinical Outcomes & Outcome
				○ MDI + RT-CGM: 172 (83 to 281) ○ Control: 208 (112 to 294) • 24 weeks: ○ MDI + RT-CGM: 89 (37 to 208) ○ Control: 179 (83 to 316) • P=0.006 Median (IQR) spent <60 mg/dL (min/day): • Baseline: ○ MDI + RT-CGM: 10 (1 to 38) ○ Control: 8 (1 to 23) • 24 weeks: ○ MDI + RT-CGM: 3 (0 to 15) ○ Control: 4 (0 to 24) • P=0.11 Use of RT-CGM: • Month 1: 6.9 ± 0.2 days/week • Month 6: 6.8 ± 1.1 days/week • % ≥ 6 days/week in Month 6: 97% Change in SMBG frequency over 24 weeks: • MDI + RT-CGM: -1.2 ± 1.6 times/day • Control: 0.2 ± 1.4 times/day • P=0.0001

Citation/Funding Source	Study Dates	Design, Treatments & Sample Size	Inclusion/Exclusion Criteria	Clinical Outcomes & Outcome
				Mean RT-CGM Satisfaction: • Total score: 4.2 ± 0.4 • Benefits subscale: 4.3 ± 0.5 • Lack of hassles subscale: 1.8 ± 0.5 Adverse Events: • No DKA or severe hypoglycemic events in either group
Polonsky WH, Hessler D, Ruedy KJ, Beck RW. The impact of continuous glucose monitoring on markers of quality of life in adults with type 1 diabetes: futther findings from the DIAMOND randomized clinical trial. *Diabetes Care* 2017; 40:1-6. Funding: Dexcom Quality Grade: Good	Start: 10/2014 End: 5/2016	Design: 24-week randomized clinical trial Setting: Multicenter study in the U.S. Treatments: MDI + RT-CGM Control (MDI + SMBG) Sample Size: Randomized: • MDI + RT-CGM (n=105) • Control (n=53) Completed/Analyzed: • MDI + RT-CGM (n=102) • Control (n=53)	Inclusion: • Age ≥25 years • T1DM ≥1 years • HbA1c between 7.5% and 10.0% • Receiving MDI • Patients in groups without RT-CGM willing to perform SMBG ≥4 times/day • Negative pregnancy test • During 2-week pre-randomization phase, use sensor on ≥85% of possible days, perform 2 blood glucose calibrations per day, and perform SMBG ≥3 times per day. Exclusion: • CGM use during past 3 months	Primary: WHO-5 (Model 1): • Mean difference in change: -1.26 (-5.42 to 2.91) • P=0.62 WHO-5 (Model 2): • Mean difference in change: -1.63 (-5.88 to 2.61) • P=0.50 EQ-5D-5L (Model 1): • Mean difference in change: 0.00 (0.08 to 0.36) • P=0.86 EQ-5D-5L (Model 2): • Mean difference in change: 0.00 (-0.03 to 0.03) • P=0.92 Diabetes Distress Scale Total (Model 1):

Citation/Funding Source	Study Dates	Design, Treatments & Sample Size	Inclusion/Exclusion Criteria	Clinical Outcomes & Outcome
				• Mean difference in change:0.22 (0.08 to 0.36) • P=0.009 Diabetes Distress Scale Total (Model 2): • Mean difference in change:0.23 (0.09 to 0.36) • P=0.03 Diabetes Distress Scale - Regimen (Model 1): • Mean difference in change:0.25 (0.05 to 0.46) • P=0.04 Diabetes Distress Scale - Regimen (Model 2): • Mean difference in change:0.26 (0.05 to 0.47) • P=0.04 • Diabetes Distress Scale - Emotional Burden (Model 1): • Mean difference in change:0.21 (0.01 to 0.41) • P=0.08 Diabetes Distress Scale - Emotional Burden (Model 2): • Mean difference in change:0.21 (0.00 to 0.41) • P=0.09

Citation/Funding Source	Study Dates	Design, Treatments & Sample Size	Inclusion/Exclusion Criteria	Clinical Outcomes & Outcome
				Diabetes Distress Scale - Interpersonal (Model 1): • Mean difference in change:0.37 (0.16 to 0.56) • P=0.0009 Diabetes Distress Scale -Interpersonal (Model 2): • Mean difference in change:0.37 (0.16 to 0.58) • P=0.01 Diabetes Distress Scale - Physician (Model 1): • Mean difference in change:0.10 (-0.04 to 0.25) • P=0.21 Diabetes Distress Scale -Physician (Model 2): • Mean difference in change:0.12 (-0.03 to 0.27) • P=0.15 Hypoglycemia confidence (Model 1) • Mean difference in change:0.23 (0.06 to 0.40) • P=0.03 Hypoglycemia confidence (Model 2) • Mean difference in change:0.23 (0.05 to 0.41) • P=0.03

Citation/Funding Source	Study Dates	Design, Treatments & Sample Size	Inclusion/Exclusion Criteria	Clinical Outcomes & Outcome
				Hypoglycemia fear (Model 1): • Mean difference in change:3.17 (0.19 to 6.14) • P=0.07 Hypoglycemia fear (Model 2): • Mean difference in change:2.46 (-0.58 to 5.51) • P=0.15 Association between CGM total satisfaction and change in WHO-5: • B (SE): 7.61 (2.80) • 95% CI: 2.05 to 13.17 • P=0.02 Association between CGM total satisfaction and change in EQ-5D-5L: • B (SE): 0.04 (0.02) • 95% CI: -0.01 to 0.08 • P=0.08 • Association between CGM total satisfaction and change in Diabetes Distress Scale: • B (SE): -0.31 (0.08) • 95% CI: -0.47 to -0.16 • P<0.001 Association between CGM total satisfaction and change in Hypoglycemia Confidence:

Citation/Funding Source	Study Dates	Design, Treatments & Sample Size	Inclusion/Exclusion Criteria	Clinical Outcomes & Outcome
				• B (SE): 0.49 (0.10) • 95% CI: 0.29 to 0.70 • P<0.001 Association between CGM total satisfaction and change in Hypoglycemia Worry: • B (SE): -4.22 (1.73) • 95% CI: -7.66 to -0.78 • P=0.03
Lind M, Polonsky W, Hirsch IB, Heise T, Bolinder J, Dahlqvist S, et al. Continuous glucose monitoring vs conventional therapy for glycemic control in adults with type 1 diabetes treated with multiple daily insulin injections: The GOLD randomized clinical trial. *JAMA* 2017; 317:379-87. Funding: NU Hospital Group, Trollhattan and Uddevalla, Sweden Quality Grade: Good	Start: 2/2014 End: 6/2016	Design: 26-week open-label randomized crossover Setting: Multicenter study in Sweden Treatments: MDI + RT-CGM Control (MDI + SMBG) Sample Size: Randomized: • MDI + RT-CGM first (n=82 • Control first (n=79) Full Analysis Set: • MDI + RT-CGM first (n=69) • Control first (n=73)	Inclusion: • Age >18 years • T1DM > 1 year • HbA1c ≥7.5% • Using MDI • Fasting C-peptide <0.91 ng/mL Exclusion: • Did not believe they could wear sensor >80% of the time or did not perform adequate calibrations during 6-week run-in	Primary: HbA1c at end of each 6-month period, mean (95% CI): • MDI + RT-CGM: 7.92% (7.79 to 8.05) • Control: 8.35 (8.19 to 8.51) • Mean difference: -0.43 (-0.57 to -0.29) • P<0.001 Secondary: Mean glucose level (mg/dL): • MDI + RT-CGM: 186.93 (181.66 to 192.20) • Control: 193.68 (188.31 to 199.04) • Mean difference: -6.61 (-12.01 to -1.20) • P=0.02 Mean amplitudes of glycemic excursions (mg/dL):

Citation/Funding Source	Study Dates	Design, Treatments & Sample Size	Inclusion/Exclusion Criteria	Clinical Outcomes & Outcome
				• MDI + RT-CGM: 161,93 (156.94 to 166.91) • Control: 180.96 (175,72 to 186.20) • Mean difference: -19.36 (-24.26 to -14.46) • P<0.001 SD of glucose levels (mg/dL): • MDI + RT-CGM: 68.49 (66.36 to 70.63) • Control: 77.23 (74.96 to 79.50) • Mean difference: -19.36 (-24.26 to -14.46) • P<0.001 DTSQ status version, total scale: • MDI + RT-CGM: 30.21 (29.47 to 30.96) • Control: 26.62 (25.61 to 27.64) • Mean difference: 3.43 (2.31 to 4.54) • P<0.001 DTSQ change version, total scale: • MDI + RT-CGM: 13.20 (12.13 to 14.28) • Control: 5.97 (3.64 to 8.30) • Mean difference: 3.76 (1.70 to 5.82) • P<0.001 WHO-5 Well-being Index:

Citation/Funding Source	Study Dates	Design, Treatments & Sample Size	Inclusion/Exclusion Criteria	Clinical Outcomes & Outcome
				• MDI + RT-CGM: 66.13 (62.94 to 69.32) • Control: 62.74 (60.18 to 65.31) • Mean difference: 3.54 (0.61 to 6.48) • P=0.02 Hypoglycemia Fear Scale Behavior/Avoidance: • MDI + RT-CGM: 1.93 (1.83 to 2.03) • Control: 1.91 (1.81 to 2.00) • Mean difference: 0.03 (-0.05 to 0.10) • P=0.45 HCQ Scale: • MDI + RT-CGM: 3.40 (3.32 to 3.47) • Control: 3.27 (3.18 to 3.35) • Mean difference: 0.12 (0.05 to 0.19) • P<0.001 Mean time of CGM use: 87.8% Reduction in HbA1c by sensor use: • >70% of the time: -0.46% (0.31-0.61) • <70% of the time: NS difference % of time <70 mg/dL: • MDI + RT-CGM: 2.79% (2.97%) • Control: 4.79% (4.03%)

Citation/Funding Source	Study Dates	Design, Treatments & Sample Size	Inclusion/Exclusion Criteria	Clinical Outcomes & Outcome
				% of time <54 mg/dL: • MDI + RT-CGM: 0.79% (1.23%) • Control: 1.89% (2.12%) No. of severe hypoglycemic events: • MDI + RT-CGM: 1 event (rate: 0.04 per 1000 patients-years) • Control: 5 events (rate: 0.19 per 1000 patient-years) No. adverse events: • MDI + RT-CGM: 77 patients with 137 AEs • Control: 67 patients with 122 AEs No. serious adverse events: • MDI + RT-CGM: 7 patients with 9 SAEs • Control: 3 patients with 9 SAEs
Soupal J, Petruzelkova L, Flekac M, Pelcl T, Matoulek M, Dankova M, et al. Comparison of different treatment modalities for type 1 diabetes, including sensor-augmented insulin regimens, in 52 weeks of follow-up: a COMISAIR study.	Start: Not reported End: Not reported	Design: 1-year, prospective, nonrandomized, real-life clinical trial Setting: Single site in the Czech Republic Treatments: • SAIR (n=27) ○ SAP (n=5)	Inclusion: • Age >18 years • T1DM ≥2 years • HbA1c between 7.0% and 10% • Receiving insulin analogs • Patients in SAIR group willing to use sensors >70% of the time	Primary: HbA1c after 1 year: • SAIR: 7.1% ± 0.8% • SMBG: 8.3% ± 0.9% • P<0.0001 Δ in HbA1c from baseline to 1 year: • SAP: ○ Baseline: 8.2% ± 0.9% ○ 1 year: 7.1% ± 0.9%

Citation/Funding Source	Study Dates	Design, Treatments & Sample Size	Inclusion/Exclusion Criteria	Clinical Outcomes & Outcome
Diabetes Technol Ther. 2016. Funding: Dexcom Quality Grade: Fair		○ MDI + RT-CGM (n=12) • Insulin pump + SMBG (n=20) • MDI + SMBG (n=18) <u>Sample Size</u>: Total (n=65) Completed Study (n=62)	• Patients in groups without RT-CGM willing to perform SMBG ≥4 times/day <u>Exclusion</u>: • CGM use during past 3 months • Ketoacidosis in past 3 months • Severe noncompliance • Concomitant therapy affecting glucose metabolism Pregnant or planning pregnancy	○ P=0.0025 • MDI + RT-CGM: ○ Baseline: 8.5% ± 1.1% ○ 1 year: 7.2% ± 0.8% ○ P=0.0034 • Insulin pump + SMBG: ○ Baseline: 8.4% ± 0.9% ○ 1 year: 7.9% ± 0.7% ○ P=0.048 • MDI + SMBG: ○ Baseline: 8.3% ± 0.8% ○ 1 year: 8.0% ± 0.9% ○ P=0.40 Difference in groups in HbA1c @ 1 year: • SAIR vs. MDI + SMBG: -0.91% (95% CI, -1.47% to -0.35%, P=0.002) • SAIR vs. insulin pump + SMBG: -0.75% (95% CI, -1.23% to -0.26%, P=0.0032) • MDI + RT-CGM vs. MDI + SMBG: -0.66% (95% CI, -1.23% to -0.10%, P=0.022) % with HbA1c <7.0% @ 1 year: • SAIR: 48% • Insulin pump + SMBG: 16% • MDI + SMBG: 18% <u>Secondary</u>

Citation/Funding Source	Study Dates	Design, Treatments & Sample Size	Inclusion/Exclusion Criteria	Clinical Outcomes & Outcome

				Δ in mean ±SD daily glucose level from baseline to 1 year (nmol/L):
				• SAIR: 10.6 ± 1.5 vs. 8.7 ± 1.4
				• P<0.001
				• Insulin pump + SMBG: 10.7 ± 1.2 vs. 9.8 ± 1.1
				• P=0.04
				
				Increase in time in target glucose range (4.0-10.0 nmol/L):
				• SAIR
				  ○ Baseline: 50% ± 11%
				  ○ 1 year: 69% ± 11%
				  ○ P<0.0001
				• Insulin pump + SMBG:
				  ○ Baseline: 51% ± 10%
				  ○ 1 year: 59% ± 11%
				  ○ P=0.03
				
				Δ from baseline in SD of blood glucose (nmol/L):
				• SAIR
				  ○ Baseline: 4.0 ± 0.7
				  ○ 1 year: 3.0 ± 0.5
				  ○ P<0.0001
				• Insulin pump + SMBG
				  ○ Baseline: 3.9 ± 0.6
				  ○ 1 year: 3.4 ± 0.6
				  ○ P<0.05
				• MDI + SMBG
				  ○ Baseline: 3.8 ± 1.0

Citation/Funding Source	Study Dates	Design, Treatments & Sample Size	Inclusion/Exclusion Criteria	Clinical Outcomes & Outcome
				○ 1 year: 3.8 ± 1.1 ○ P=0.93 Δ from baseline in time spent in hypoglycemia (<4.0 nmol/L): • SAIR ○ Baseline: 8% ± 4% ○ 1 year: 6% ± 3% ○ P<0.01 • MDI + SMBG ○ Baseline: 6% ± 4% ○ 1 year: 7% ± 5% ○ P=0.68 Severe hypoglycemia: • SAIR: 0 • Insulin pump + SMBG: 1 • MDI + SMBG: 1 Adverse events: • There was no DKA or sensor insertion site infection requiring assistance during the study.
Foster NC, Miller KM, Tamborlane WV, Bergenstal RM, Beck RW. Continuous glucose monitoring in patients with type 1 diabetes using insulin injections.	Start: 6/2014 End: 10/2015	Design Cross-sectional observational study usingT1D Exchange registry data Setting: Multinational patient registry Treatments: MDI +RT-CGM	Inclusion: • T1DM > 1 year • Using insulin pump or MDI • Had clinic visit between 6/2014 and 10/2015 Exclusion:	Primary: Mean MbA1c: MDI + RT-CGM: 7.6 ± 1.3% Insulin pump + RT-CGM: 7.7 ± 1.1% P=0.82 MDI + RT-CGM: 7.6 ± 1.3%

Citation/Funding Source	Study Dates	Design, Treatments & Sample Size	Inclusion/Exclusion Criteria	Clinical Outcomes & Outcome
Diabetes Care 2016; 39:e81-2. Funding: The Leona M. and Harry B. Helmsley Charitable Trust Quality Grade: Fair		MDI + SMBG Insulin pump + RT-CGM Insulin pump + SMBG Sample Size: MDI +RT-CGM (410) MDI + SMBG (n=6,222) Insulin pump + RT-CGM (2,316) Insulin pump + SMBG (n=8,783)	• None	MDI + SMBG: 8.3 ± 1.5% P<0.001 Insulin pump + RT-CGM: 7.7 ± 1.1% Insulin pump + SMBG: 8.8 ± 1.9% P<0.001 <13 Years: MDI +RT-CGM: 7.9% MDI + SMBG: 8.7% Insulin pump + RT-CGM: 7.7% Insulin pump + SMBG: 8.3% 13 to <26 Years: MDI +RT-CGM: 8.2% MDI + SMBG: 9.3% Insulin pump + RT-CGM: 8.1% Insulin pump + SMBG: 8.7% ≥26 Years: MDI +RT-CGM: 7.3% MDI + SMBG: 7.8% Insulin pump + RT-CGM: 7.3% Insulin pump + SMBG: 7.7%
Parkin CG, Graham C, Smolskis J. Continuous glucose monitoring use in type 1 diabetes: longitudinal analysis demonstrates meaningful	Start: 11/2012 End: 8/2013	Design Pre/post case-control study using retrospective claims data Setting: U.S healthcare plans Treatments:	Inclusion: • Age ≥18 years • Identified as eligible from 11/2011-12/2012 • Diagnosis code for T1DM • Continuous enrollment in health plan	Primary: Reduction inHbA1c from baseline: • G4: -0.5% (P=0.004) • SMBG: -0.2% (P<0.0001) Reduction inHbA1c from baseline by insulin delivery method:

Citation/Funding Source	Study Dates	Design, Treatments & Sample Size	Inclusion/Exclusion Criteria	Clinical Outcomes & Outcome
improvements in hba1c and reductions in healthcare utilization. *Diabetes Care* In press. Funding: Dexcom Quality Grade: Fair		G4 Platinum CGM System SMBG <u>Sample Size</u>: Total (n=6,467) • G4 (n=187) • SMBG (n=6,280)	• At least 1 claim for insulin during study period <u>Exclusion</u>: • Pregnant • Prior experience with RT-CGM before index date	• G4 + MDI: -0.6% (P<0.01) • G4 + insulin pump: -0.3% (P=0.16) <u>Secondary</u>: Mean no. all-cause inpatient admissions per 1000 patients: • G4: 126 • SMBG: 218 • Difference: 42.2% (P=0.013) Mean no. diabetes-specific inpatient admissions per 1000 patients: • G4: 35 • SMBG: 74 • Difference: 52.7% (P=0.061) Mean PMPM all-cause inpatient costs: • G4: $299 • SMBG: $362 • Difference: 17.4% (P=0.556) Mean PMPM diabetes-specific inpatient costs: • G4: $101 • SMBG: $211 • Difference: 52.1% (P=0.297) Mean no. all-cause ER visits per 1000 patients: • G4: 950

Citation/Funding Source	Study Dates	Design, Treatments & Sample Size	Inclusion/Exclusion Criteria	Clinical Outcomes & Outcome
				• SMBG: 1,145 • Difference: 17.0% (P=0.303) Mean no. diabetes-specific ER visits per 1000 patients: • G4: 89 • SMBG: 106 • Difference: 16.0% (P=0.492) Mean PMPM all-cause ER costs: • G4: $17 • SMBG: $20 • Difference: 15.0% (P=0.491) Mean PMPM diabetes-specific ER costs: • G4: $13 • SMBG: $7 • Difference: 85.7% (P=0.441) No. DKA inpatient admissions: • G4: 36 • SMBG: 16 • P=0.0675 No. DKA ER visits: • G4: 17 • SMBG: 4 • P=0.0318 No. hypoglycemia ER visits:

Citation/Funding Source	Study Dates	Design, Treatments & Sample Size	Inclusion/Exclusion Criteria	Clinical Outcomes & Outcome
				• G4: 2 • SMBG: 7 P=0.353
MD or /Insulin Pump + RT-CGM Versus MDI or Insulin Pump +SMBG				
van Beers CA, DeVries JH, Kleijer SJ, Smits MM, Geelhoed-Duijvestijn PH, Kramer MH, 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. Funding: Eli Lilly and Sanofi Quality Grade: Good	Start: 3/2013 End: 2/2015	Design: 16-week, randomized, open-label, crossover with 12-week washout Setting: Two sites in the Netherlands Treatments: RT-CGM SMBG Sample Size: Randomized (n=52) Completed study (n=46)	Inclusion: • Age 18-75 years • T1DM • Use of insulin pump or MDI • Perform SMBG ≥3 times/day • Impaired hypoglycemia awareness Exclusion: • History of renal, liver, or heart disease • Current untreated proliferative diabetic neuropathy • Current malignancy • Current use of non-selective β blockers • Current psychiatric disorders or substance/alcohol abuse • Current use of CGM for other than a short period • Hearing or visual impairment that could hinder perception of glucose displays and alarms	Primary: % of time spent in normoglycemia (70-180 mg/dL): • RT-CGM: 65.0% • SMBG: 55.4% • Difference: 9.6% (95% CI, 8.0 to 11.2) • P<0.0001 Secondary: % of time spent in hypoglycemia (≤70 mg/dL): • RT-CGM: 6.8% • SMBG: 11.4% • Difference: -4.7% (95% CI, -5.9 to -3.4) • P<0.0001 % of time spent in hyperglycemia (>180 mg/dL): • RT-CGM: 28.2% • SMBG: 33.2% • Difference: -5.0% (95% CI, -6.9 to -3.1) • P<0.0001

Citation/Funding Source	Study Dates	Design, Treatments & Sample Size	Inclusion/Exclusion Criteria	Clinical Outcomes & Outcome
			• Inability to understand study instructions • Participation in another study • Known or suspected allergy to trial-related products	Time (h/day) spent in normoglycemia (70-180 mg/dL): • RT-CGM: 15.6 • SMBG: 13.3 • Difference: 2.3 (95% CI, 1.9 to 2.7) • P<0.0001 Time (h/day) spent in hypoglycemia (≤70 mg/dL): • RT-CGM: 1.6 • SMBG: 2.7 • Difference: -1.1 (95% CI, -1.4 to -0.8) • P<0.0001 Time (h/day) spent in hyperglycemia (>180 mg/dL): • RT-CGM: 6.8 • SMBG: 8.0 • Difference: -1.2 (95% CI, -1.6 to -0.7) • P<0.0001 CGM-derived hypoglycemic events per week: • RT-CGM: 10.1 • SMBG: 11.1 • Difference: -1.1(95% CI, -2.1 to -0.1)

Citation/Funding Source	Study Dates	Design, Treatments & Sample Size	Inclusion/Exclusion Criteria	Clinical Outcomes & Outcome
				• P=0.028 Duration (min) of CGM-derived hypoglycemic events: • RT-CGM: 60.7 • SMBG: 98.5 • Difference: -37.8 (95% CI, -44.5 to -30.9) • P<0.0001 AUC ≤70 mg/dL per 24 h (mg/dL per min): • RT-CGM: 1132.2 • SMBG: 2082.6 • Difference: -165.6 (95% CI, -1225.8 to -678.6) • P<0.0001 % of time spent with BG ≤70 mmol/L during the night: • RT-CGM: 7.6% • SMBG: 13.3% • Difference: -5.7% (95% CI, -8.2 to -3.2) • P<0.0001 CGM-derived hypoglycemic events per night: • RT-CGM: 0.26 • SMBG: 0.33

Citation/Funding Source	Study Dates	Design, Treatments & Sample Size	Inclusion/Exclusion Criteria	Clinical Outcomes & Outcome
				• Difference: -0.07 (95% CI, -0.11 to -0.02) • P=0.003 Duration (min) of CGM-derived nocturnal hypoglycemic events: • RT-CGM: 78.7 • SMBG: 131.4 • Difference: -52.7 (95% CI, -62.7 to -42.7) • P<0.0001 Mean glucose concentration (mg/dL): • RT-CGM: 149.4 • SMBG: 156.6 • Difference: -7.2 (95% CI, -10.8 to -3.6) • P=0.001 Within-day SD of glucose concentration (mg/dL): • RT-CGM: 50.4 • SMBG: 59.4 • Difference: -9.0 (95% CI, -10.8 to -7.2) • P<0.0001 Coefficient of variation of glucose concentration (overall): • RT-CGM: 39.5

Citation/Funding Source	Study Dates	Design, Treatments & Sample Size	Inclusion/Exclusion Criteria	Clinical Outcomes & Outcome
				• SMBG: 46.3 • Difference: -6.7 (95% CI, -8.0 to -5.5) • P<0.0001 Coefficient of variation of glucose concentration (within day): • RT-CGM: 33.5 • SMBG: 38.0 • Difference: -4.5 (95% CI, -5.5 to -3.6) • P<0.0001 Coefficient of variation of glucose concentration (between days): • RT-CGM: 18.4 • SMBG: 23.1 • Difference: -4.7 (95% CI, -5.9 to -3.5) • P<0.0001 MAG (mg/dL per h): • RT-CGM: 30.6 • SMBG: 32.4 • Difference: -1.8 (95% CI, -1.8 to 0.0) • P=0.04 MODD (mg/dL): • RT-CGM: 59.4

Citation/Funding Source	Study Dates	Design, Treatments & Sample Size	Inclusion/Exclusion Criteria	Clinical Outcomes & Outcome
				• SMBG: 75.6 • Difference: -16.2 (95% CI, -19.8 to 1.26) • P<0.0001 CONGA (mg/dL): • RT-CGM: 30.6 • SMBG: 32.4 • Difference: -1.8 (95% CI, -3.6 to 0.0) • P=0.002 No. of severe hypoglycemic events: • RT-CGM: 14 • SMBG: 34 • P=0.033 % patients with ≥1 severe hypoglycemic event: • RT-CGM: 19% • SMBG: 35% • OR 0.48 (0.2 to 1.0) • P=0.062 HbA1c at study endpoint (%): • RT-CGM: 7.3% • SMBG: 7.3% • Difference: 0.0% (95% CI, -0.01 to 0.0) • P=0.81

Citation/Funding Source	Study Dates	Design, Treatments & Sample Size	Inclusion/Exclusion Criteria	Clinical Outcomes & Outcome
				HbA1c at study endpoint (mmol/mol): • RT-CGM: 56.0 • SMBG: 56.3 • Difference: 0.2 (95% CI, -1.4 to 1.9) • P=0.812 Δ from baseline in HbA1c (%): • RT-CGM: -0.1% • SMBG: -0.1% • Difference: -0.1% (95% CI, -0.2 to 0.1) • P=0.449 Δ from baseline in HbA1c (mmol/mol): • RT-CGM: -0.5 • SMBG: -1.3 • Difference: -0.8 (95% CI, -2.8 to 1.2) • P=0.449 Gold score at study endpoint: • RT-CGM: 4.6 • SMBG: 5.0 • Difference: -0.4 (95% CI, -0.7 to 0.0) • P=0.035 Δ in Gold score from baseline: • RT-CGM: -0.5

Citation/Funding Source	Study Dates	Design, Treatments & Sample Size	Inclusion/Exclusion Criteria	Clinical Outcomes & Outcome
				• SMBG: -0.1 • Difference: -0.4 (95% CI, -0.8 to 0.0) • P=0.076 Clarke score at study endpoint: • RT-CGM: 4.4 • SMBG: 4.4 • Difference: 0.0 (95% CI, -0.4 to 0.4) • P=0.953 Δ in Clarke score from baseline: • RT-CGM: -0.1 • SMBG: -0.4 • Difference: -0.3 (95% CI, -0.9 to 0.2) • P=0.216 Median sensor use during CGM: 89.4% (IQR 80.8 to 95.5) Number of adverse events related to study intervention: • RT-CGM: 0 • SMBG: 0
Tamborlane WV, Beck RW, Bode BW, et al. Continuous glucose monitoring and intensive treatment of type 1	**Start**: 2/2007 **End**: 6/2008	Design: 26-week, randomized, controlled Setting: Multicenter study in the U.S.	Inclusion: • Age ≥8 years • T1DM ≥1 year before randomization	Primary: Mean change in HbA1c from baseline to 26 weeks: • Significant between-group difference in the change in HbA1c

Citation/Funding Source	Study Dates	Design, Treatments & Sample Size	Inclusion/Exclusion Criteria	Clinical Outcomes & Outcome
diabetes. N Engl J Med. 2008;359:1464-76. Beck RW, Buckingham B, Miller K, et al. Factors predictive of use and of benefit from continuous glucose monitoring in type 1 diabetes. Diabetes Care. 2009;32:1947-53. Beck RW, Lawrence JM, Laffel L, et al. Quality-of-life measures in children and adults with type 1 diabetes: Juvenile Diabetes Research Foundation Continuous Glucose Monitoring randomized trial. Diabetes Care 2010;33:2175-77. Funding: JDRF Quality Grade: Fair		Treatments: RT-CGM Control (SMBG) Sample Size: Randomized (n=322) • Age ≥25 years (n=98) • Age 15-25 years (n=110) • Age 8-14 years (n=114) RT-CGM (n=165) • Age ≥25 years (n=52) • Age 15-25 years (n=57) • Age 8-14 years (n=56) Control (n=157) • Age ≥25 years (n=46) • Age 15-25 years (n=53) • Age 8-14 years (n=58) Completers (n=317) RT-CGM (n=162) • Age ≥25 years (n=50) • Age 15-25 years (n=56) • Age 8-14 years (n=56) Control (n=155) • Age ≥25 years (n=46) • Age 15-25 years (n=51) • Age 8-14 years (n=58)	• Used an insulin pump or received ≥3 daily insulin injections • A1c 7.0-10.0% • No use of RT-CGM in 6 months leading up to the trial • During run-in period, wore a RT-CGM sensor at least 6 of 7 days and performed SMBG at least 3 times per day. Exclusion: None	was seen in adults who used RT-CGM (-0.51%, P<0.001), but not in adolescents (0.08%, P=0.52) or children (-0.13, P=0.29). Secondary: % achieving relative decrease in HbA1c ≥10%: • Adults: RT-CGM (26%) vs. Control (4%), P=0.003 • Adolescents: RT-CGM (14%) vs. Control (10%), P=0.46 • Children: RT-CGM (29%) vs. Control (12%), P=0.04 % achieving absolute decrease in HbA1c of ≥0.5%: • Adults: RT-CGM (48%) vs. Control (11%), P<0.001 • Adolescents: RT-CGM (36%) vs. Control (37%), P=0.57 • Children: RT-CGM (54%) vs. Control (31%), P=0.009 % achieving relative increase in HbA1c ≥10%: • Adults: RT-CGM (0%) vs. Control (2%), P=0.48 • Adolescents: RT-CGM (4%) vs. Control (4%), P=0.98

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				• Children: RT-CGM (9%) vs. Control (3%), P=0.24 % achieving absolute increase in HbA1c of ≥0.5%: • Adults: RT-CGM (0%) vs. Control (11%), P=0.02 • Adolescents: RT-CGM (13%) vs. Control (14%), P=0.84 • Children: RT-CGM (21%) vs. Control (12%), P=0.18 % achieving HbA1c <7%: • Adults: RT-CGM (34%) vs. Control (9%), P=0.005 • Adolescents: RT-CGM (14%) vs. Control (18%), P=0.80 • Children: RT-CGM (27%) vs. Control (12%), P=0.01 % achieving HbA1c <7% & no severe hypoglycemia: • Adults: RT-CGM (30%) vs. Control (7%), P=0.006 • Adolescents: RT-CGM (13%) vs. Control (14%), P=0.67 • Children: RT-CGM (25%) vs. Control (10%), P=0.02

Citation/Funding Source	Study Dates	Design, Treatments & Sample Size	Inclusion/Exclusion Criteria	Clinical Outcomes & Outcome
				Mean min/day spent in hyperglycemia (>180 mg/dL) @ BL/26 weeks: • Adults: RT-CGM (854/986) vs. Control (811/840), P<0.001 • Adolescents: RT-CGM (691/761) vs. Control (697/761), P=0.79 • Children: RT-CGM (646/750) vs. Control (710/746), P=0.53 Mean min/day spent in hypoglycemia (<70 mg/dL) @ BL/26 weeks: • Adults: RT-CGM (497/394) vs. Control (549/519), P=0.002 • Adolescents: RT-CGM (650/591) vs. Control (641/591), P=0.85 • Children: RT-CGM (745/ 643) vs. Control (671/635), P=0.58 Mean min/day spent in target range (71-180 mg/dL) @ BL/26 weeks • Adults: RT-CGM (149/101) vs. Control (181/161), P<0.001 • Adolescents: RT-CGM (271/215) vs. Control (265/242), P=0.44 • Children: RT-CGM (343/242) vs. Control (282/268), P=0.18 Mean mg/dl/min glucose @ BL/26 weeks: • Adults: RT-CGM (0.73/0.68) vs. Control (0.72/0.74), P=0.07

Citation/Funding Source	Study Dates	Design, Treatments & Sample Size	Inclusion/Exclusion Criteria	Clinical Outcomes & Outcome
				• Adolescents: RT-CGM (0.85/0.84) vs. Control (0.86/0.87), P=0.48 • Children: RT-CGM (0.84/0.82) vs. Control (0.83/0.83), P=0.66 % of patients with ≥1 severe hypoglycemic event: • Adults: RT-CGM (10%) vs. Control (9%), P=1.0 • Adolescents: RT-CGM (5%) vs. Control (9%), P=0.48 • Children: RT-CGM (7%) vs. Control (10%), P=0.74 No. severe hypoglycemic events per 100 patient-years: • Adults: RT-CGM (43.4) vs. Control (26.3), P=0.66 • Adolescents: RT-CGM (17.9) vs. Control (23.9), P=0.64 • Children: RT-CGM (17.9) vs. Control (24.4), P=0.64 % of patients with ≥1 severe hypoglycemic episode w/seizure or coma: • Adults: RT-CGM (2%) vs. Control (2%), P=1.0 • Adolescents: RT-CGM (2%) vs. Control (6%), P=0.35

Citation/Funding Source	Study Dates	Design, Treatments & Sample Size	Inclusion/Exclusion Criteria	Clinical Outcomes & Outcome
				• Children: RT-CGM (0%) vs. Control (0%) No. severe hypoglycemic events w/seizure or coma per 100 patient-years: • Adults: RT-CGM (23.7) vs. Control (4.4), P=0.85 • Adolescents: RT-CGM (3.6) vs. Control (11.9), P=0.14 • Children: RT-CGM (0) vs. Control (0) Mean min/day glucose ≤70 mg/dL – baseline/26 weeks: • Adults: RT-CGM (89/60) vs. Control (80/81), P=0.41 • Adolescents: RT-CGM (99/88) vs. Control (102/88), P=0.79 • Children: RT-CGM (49/47) vs. Control (59/59), P=0.29 Mean min/day glucose ≤50 mg/dL – baseline/26 weeks • Adults: RT-CGM (32/11) vs. Control (22/23), P=0.10 • Adolescents: RT-CGM (39/29) vs. Control (42/31), P=0.99 • Children: RT-CGM (17/10) vs. Control (18/13), P=0.50

Citation/Funding Source	Study Dates	Design, Treatments & Sample Size	Inclusion/Exclusion Criteria	Clinical Outcomes & Outcome
				Average sensor use >6.0 days/week in study month 6: • Adults (79%) • Adolescents (29%) • Children (46%) Adherence to sensor use and change in A1c: • Patients averaging at least 6 days per week of RT-RT-CGM use had substantially greater improvement in HbA1c compared with those who used RT-RT-CGM less often (P=0.02 in ≥25 age group, P=0.002 in 15 to 24 age group, and P<0.001 in 8 to 14 age group). Change in quality of life: None of the quality of life measures showed meaningful differences between the RT-RT-CGM and control groups after 26 weeks.
Beck RW, Hirsch IB, Laffel L, et al. The effect of continuous glucose monitoring in well-controlled type 1 diabetes. Diabetes Care. 2009;32:1378-83. Funding: JDRF Quality Grade: Fair	**Start**: 2/2007 **End**: 6/2008	Design: 26-week, randomized, controlled Setting: Multicenter study in the U.S. Treatments: RT-CGM Control (SMBG) Sample Size: Randomized (n=129)	Inclusion: • Age ≥8 years • T1DM ≥1 year before randomization • Used an insulin pump or received ≥3 daily insulin injections • A1c <7.0% • No use of RT-CGM in 6 months leading up to the trial	Primary: Change in median min per day in hypoglycemia (≤70 mg/dL) from baseline to 26 weeks: • RT-CGM: Baseline vs. 26 weeks (19 vs. 54) • Control: Baseline vs. 26 weeks (96 vs. 91) • Between-groups P=0.05 • Similar results seen in age ≥25 years, 15-24 years and 8-14 years)

Citation/Funding Source	Study Dates	Design, Treatments & Sample Size	Inclusion/Exclusion Criteria	Clinical Outcomes & Outcome
		• RT-CGM (n=67) • Control (n=62) Completers • RT-CGM (n=67) • Control (n=60)	• During run-in period, wore a RT-CGM sensor at least 6 of 7 days and performed SMBG at least 3 times per day. Exclusion: None	Secondary: Change in median min per day in hypoglycemia (≤60 mg/dL) from baseline to 26 weeks: • RT-CGM: Baseline vs. 26 weeks (40 vs. 18) • Control: Baseline vs. 26 weeks (40 vs. 35) • Between-groups P=0.01 Change in median min per day in hypoglycemia (≤50 mg/dL) from baseline to 26 weeks: • RT-CGM: Baseline vs. 26 weeks (7 vs. 4) • Control: Baseline vs. 26 weeks (9 vs. 8) • Between-groups P=0.05 Change in median min per day in hyperglycemia (>180 mg/dL) from baseline to 26 weeks: • RT-CGM: Baseline vs. 26 weeks (40 vs. 48) • Control: Baseline vs. 26 weeks (63 vs. 83) • Between-groups P=0.005

Citation/Funding Source	Study Dates	Design, Treatments & Sample Size	Inclusion/Exclusion Criteria	Clinical Outcomes & Outcome
				Change in median min per day in hyperglycemia (>250 mg/dL) from baseline to 26 weeks: • RT-CGM: Baseline vs. 26 weeks (40 vs. 48) • Control: Baseline vs. 26 weeks (63 vs. 83) • Between-groups P=0.005 Change in median min per day in target glycemia (71-180 mg/dL) from baseline to 26 weeks: • RT-CGM: Baseline vs. 26 weeks (1063 vs. 1063) • Control: Baseline vs. 26 weeks (972 vs. 949) • Between-groups P<0.001 Change in median AUC (750 mg/dL) from baseline to 26 weeks: • RT-CGM: Baseline vs. 26 weeks (0.64 vs. 0.26) • Control: Baseline vs. 26 weeks (0.60 vs. 0.49) • Between-groups P =0.03 Change in median standard deviation of values from baseline to 26 weeks: • RT-CGM: Baseline vs. 26 weeks (48 vs. 50)

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				• Control: Baseline vs. 26 weeks (56 vs. 60) • Between-groups P =0.008 Change in median MAGE from baseline to 26 weeks: • RT-CGM: Baseline vs. 26 weeks (93 vs. 96) • Control: Baseline vs. 26 weeks (106 vs. 108) • Between-groups P =0.26 Change in median absolute rate of change (mg/dl/min) from baseline to 26 weeks: • RT-CGM: Baseline vs. 26 weeks (0.60 vs. 0.66) • Control: Baseline vs. 26 weeks (0.65 vs.0.66) • Between-groups P =0.39 Change in mean HbA1c from baseline to 26 weeks: • RT-CGM vs. Control (-0.34, P<0.001) % Decreasing HbA1c by ≥0.3% from baseline to 26 weeks: • RT-CGM vs. Control (31% vs. 5%, P<0.001)

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				% Increasing HbA1c by ≥0.3% from baseline to 26 weeks: • RT-CGM vs. Control (28% vs. 52%, P=0.02) % HbA1c <7.0% at 26 weeks: • RT-CGM vs. Control (88% vs. 63%, P<0.001) % Decreasing HbA1c by ≥0.3% without severe hypoglycemic event: • RT-CGM vs. Control (28% vs. 5%, P<0.001) % Decreasing HbA1c by ≥0.3% without an increase of ≥43 min/day in glucose values <70 mg/dL: • RT-CGM vs. Control (18% vs. 2%, P=0.007) ≥43 min/day decrease in glucose values <70 mg/dL without an increase in HbA1c of ≥0.3%: • RT-CGM vs. Control (29% vs. 15%, P=0.005) Median no. days per week of RT-CGM use” • Age ≥25 years: 6.8 • Age 15-24 years: 6.2 • Age 8-14 years: 6.4

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				% using RT-CGM >6.0 days/week: • Age ≥25 years: 79% • Age 15-24 years: 53% • Age 8-14 years: 61% % with ≥1 severe hypoglycemic event: • RT-CGM: 10% • Control: 11% • P=NS Adverse events: There were no serious adverse events attributable to the study interventions.
Bode B, Beck RW, Xing et al. Sustained benefit of continuous glucose monitoring on HbA1c, glucose profiles, and hypoglycemia in adults with type 1 diabetes. Diabetes Care. 2009;32:2047-9. Funding: JDRF Quality Grade: Fair	Start: 12/2006 End: 2/2009	Design: 6-month, open-label, single-arm, extension study of adults age ≥25 years who were randomized to the RT-CGM arm in the 6-month JDRF RCT Setting: Multicenter study in the U.S. Treatments: RT-CGM Sample Size: RT-CGM (n=83) • A1c ≥7.0%	Inclusion: • Age ≥25 years • T1DM ≥1 year before randomization • Used an insulin pump or received ≥3 daily insulin injections • A1c ≥7% or <7.0% • Assigned to RT-CGM arm during JDRF RCT Exclusion: None	Primary: Mean change in HbA1c from baseline to 12 months for patients with baseline HbA1c ≥7.0% • Mean change was -0.4 ± 0.6% (P<0.001), similar to change from baseline to 6 months. Mean change in HbA1c from baseline to 12 months for patients with baseline HbA1c <7.0% • A1c remained in target range over the entire 12 months (6.4%, 6.3% and 6.4% @ baseline, 6 months and 12 months, respectively).

Citation/Funding Source	Study Dates	Design, Treatments & Sample Size	Inclusion/Exclusion Criteria	Clinical Outcomes & Outcome
		Completers (n=80)		P=0.042 for change from baseline to 12 months. <u>Secondary</u>: Sensor use: • Median sensor use was 7.0 days/week in month 6 and 6.8 days/week during month 12. • Sensor use in month 12 did not vary with baseline HbA1c level (P=0.38). Median time per day glucose 71-180 mg/dL: • Increased significantly (P=0.02) from baseline to 12 months, reflecting a decrease in both hypoglycemia and hyperglycemia. • Similar trends seen in HbA1c ≥7.0% and HbA1c <7.0% cohorts. • Increase in target range was seen in both daytime and nighttime. Change in SD of BG values from baseline to 12 months: • Significant reduction in SAP group (P=0.02). Change in MAGE from baseline to 12 months: • Significant reduction in SAP group (P=0.03).

Citation/Funding Source	Study Dates	Design, Treatments & Sample Size	Inclusion/Exclusion Criteria	Clinical Outcomes & Outcome
				Body weight, daily insulin dose, SMBG frequency: • No significant between-group changes. % with a severe hypoglycemic event: • First 6 months: 8 (10%) • Second 6 months: 3 (4%) No. severe hypoglycemic events per 100 person-years among all adults: • First 6 months: 21.8 • Second 6 months: 7.1 No. severe hypoglycemic events per 100 person-years among all adults with baseline HbA1c ≥7.0%: • First 6 months: 20.5 • Second 6 months: 12.1 No. severe hypoglycemic events per 100 person-years among all adults with baseline HbA1c <7.0%: • First 6 months: 13.6 Second 6 months: 0
Juvenile Diabetes Research Foundation Continuous Glucose	Start: 12/2006	Design:	Inclusion: • Age ≥8 years	Primary:

Citation/Funding Source	Study Dates	Design, Treatments & Sample Size	Inclusion/Exclusion Criteria	Clinical Outcomes & Outcome
Monitoring Study Group. Effectiveness of continuous glucose monitoring in a clinical care environment: evidence from the JDRF-CGM trial. Diabetes Care. 2010;33:17-22. Funding: JDRF Quality Grade: Fair	End: 2/2009	6-month, open-label, single-arm, extension study of 6-month JDRF RCT Setting: Multicenter study in the U.S. Treatments: RT-CGM Sample Size: Total (n=214) RT-CGM (n=214) Completers (n=212)	• T1DM ≥1 year before randomization • Used an insulin pump or received ≥3 daily insulin injections • A1c ≤10% • Assigned to control group during JDRF RCT Exclusion: None	Mean change in HbA1c from baseline (initiation of RT-CGM) to 6 months for A1c≥7.0%: • Significant reduction for age ≥25 (-0.4 ± 0.5%, P<0.001) but for age 15-24 (+0.01 ± 0.7%, P=0.95) or age 8-14 (+0.2 ± 0.7%, P=0.85). Secondary: Sensor use and HbA1c reduction: • Among the 154 patients with HbA1c ≥7.0% who completed the study, greater sensor use was associated with a greater reduction in HbA1c (P=0.01 adjusted for age group. • After adjusting for RT-CGM use, the relationship between age group and HbA1c change was weaker. Time per day in glucose range 71-180 mg/dL: • Among age ≥25, there was a significant increase (882 vs. 980 min, P<0.001). Time per day in hyperglycemia >180 mg/dL: • Among age ≥25, there was a significant decrease (430 vs. 390 min, P=0.02). Time per day in hypoglycemia ≤70 mg/dL:

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				• Among age ≥25, there was a significant decrease (55 vs. 45 min, P=0.02). Time per day in glucose range 71-180 mg/dL: • Among age 15-24, there was no significant change. Time per day in hyperglycemia >180 mg/dL: • Among age 15-24, there was no significant change. Time per day in hypoglycemia ≤70 mg/dL: • Among age 15-24, there was a significant decrease (93 vs. 55 min, P=0.005). Time per day in glucose range 71-180 mg/dL: • Among age 8-14, there was no significant change. Time per day in hyperglycemia >180 mg/dL: • Among age 8-14, there was no significant change. Time per day in hypoglycemia ≤70 mg/dL: • Among age 8-14, there was no significant change.

Citation/Funding Source	Study Dates	Design, Treatments & Sample Size	Inclusion/Exclusion Criteria	Clinical Outcomes & Outcome
				No. severe hypoglycemic events per 100 patient-years: • 27.7 during 6-month RCT • 15.0 during 6-month extension P=0.08
Chase HP, Beck RW, Xing D, et al. Continuous glucose monitoring in youth with type 1 diabetes: 12-month follow-up of the Juvenile Diabetes Research Foundation continuous glucose monitoring randomized trial. Diabetes Technol Ther. 2010;12:507-15. Funder: JDRF Quality Grade: Fair	Start: 12/2006 End: 2/2009	Design: 6-month, open-label, single arm, extension study to JDRF RCT, Setting: Multicenter study in the U.S. Treatments: RT-CGM Sample Size: Total (n=80) RT-CGM (n=80)	Inclusion: • Age 7-17 years • T1DM ≥1 year before randomization • Used an insulin pump or received ≥3 daily insulin injections • Baseline HbA1c 7.0 to <10% • Received RT-CGM during 6-month JDRF RCT Exclusion: None	Primary and Secondary: Mean change in HbA1c from baseline to end of JDRF RCT (6 months and 12 months (end of 6-month extension) for patients using sensor ≥6 days/week (A) vs. ≥6 days/week in month 6 (B) and <6 days/week in month 12 vs. <6 days/week in month 6 & 12 (C) • Baseline: 8.2% (A) • 6 months: 7.3% (A) • 12 months: 7.4% (A) • Baseline: 7.8% (B) • 6 months: 7.3% (B) • 12 months: 7.7% (B) • Baseline: 8.0% (C) • 6 months: 8.0% (C) • 12 months: 8.1% (C) • P<0.001 three-group comparison @ 12 months • P=0.01 A vs. B @ 12 months • P<0.001 A vs. C @ 12 months • P=0.19 B vs. C @ 12 months % achieving A1c<7.0% at baseline, end of JDRF RCT (6 months and 12 months (end of

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				6-month extension) for patients using sensor ≥6 days/week (A) vs. ≥6 days/week in month 6 (B) and <6 days/week in month 12 vs. <6 days/week in month 6 & 12 (C) • Baseline: 29% (A) • 6 months: 65% (A) • 12 months: 71% (A) • Baseline: 47% (B) • 6 months: 76% (B) • 12 months: 41% (B) • Baseline: 39% (C) • 6 months: 35% (C) • 12 months: 33% (C) • P=0.03 three-group comparison @ 12 months • P=0.06 A vs. B @ 12 months • P=0.02 A vs. C @ 12 months • P>0.99 B vs. C @ 12 months Time in glucose 71-180 mg/dL: • RT-CGM with sensor use ≥6 days/week in month 12 had a significant increase in time in target glucose range from baseline to 6 months and sustained through 12 months (P=0.006). Time in hypoglycemia <70 mg/dL • RT-CGM with sensor use ≥6 days/week in month 12 had no

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				increase in time spent during hypoglycemia at 6 and 12 months CGM Satisfaction Scale: • Significantly higher scores at 12 months for RT-CGM patients using sensor ≥6 days/week at 12 months compared with those using sensor <6 days/week at 12 months (mean 4.0 vs. 3.3, P<0.001 for patients; 4.2 vs. 3.7, P<0.001 for parents). Incidence severe hypoglycemia during 12 months: • 7 patients (2/17 using sensor ≥6 days/week in month 6 & 12, 2/17 using sensor ≥6 days/week in month 6 and <6 days/week in month 12, and 3/46 using sensor <6 days/week in month 6 & 12). There were 9 severe hypoglycemic events for an incidence rate of 11.2 per 100 person-years.
Chamberlain JJ, Dopita D, Gilgen E, et al. Impact of frequent and persistent use of continuous glucose monitoring (CGM) on hypoglycemia fear,	Start: 6/2014 End: 3/2015	Design: Patient survey Setting: Single center in the U.S. Treatments: G4 Platinum CGM System	Inclusion: • Age ≥18 years • T1DM • Intensive insulin therapy • Used RT-CGM device for at least 1 year	Primary: Frequency of RT-CGM wear: • Almost daily: 78.3% (n=58) • 3 weeks/month: 5.4% (n=4) • 2 weeks/month: 5.4% (n=4) • ≤1 week/month: 10.8% (n=8)

Citation/Funding Source	Study Dates	Design, Treatments & Sample Size	Inclusion/Exclusion Criteria	Clinical Outcomes & Outcome
frequency of emergency medical treatment, and SMBG frequency after one year *J Diabetes Sci Technol* 2015. Funding: Dexcom		Sample Size: Total (n=74) •	Exclusion: None	Primary reason for frequent RT-CGM wear (almost daily to 3 weeks/month): • Improved glucose: 36.2% • Avoid high glucose: 1.7% • Avoid low glucose: 15.5% • Directional arrows: 10.3% • Knowing glucose at all times: 32.8% • Felt safer: 1.7% • Other: 1.7% Primary reason for infrequent RT-CGM wear (≤3weeks/month): • Cost: 6.3% • Perceived accuracy: 6.3% • Frequent alarms: 6.3% • Tired of wearing 2 devices: 12.5% • Sensor errors: 6.2% • Other: 62.5% % worrying about hypoglycemia “most of the time” or “frequently” (almost daily RT-CGM users only): • Before RT-CGM use: 78% • After 1 year RT-CGM use: 2.0% • P=0.7359 Mean number of ER visits/year (almost daily RT-CGM users only): • Before RT-CGM use: 0.4

Citation/Funding Source	Study Dates	Design, Treatments & Sample Size	Inclusion/Exclusion Criteria	Clinical Outcomes & Outcome
				• After 1 year RT-CGM use: 0.1 • P=0.0013 Daily SMBG frequency (almost daily RT-CGM users only): • Before RT-CGM use: 6.8 • After 1 year RT-CGM use: 3.2 • P<0.0001
Other Supporting Evidence				
Laffel L. Improved accuracy of continuous glucose monitoring systems in pediatric patients with diabetes mellitus: results from two studies. *Diabetes Technol Ther.* 2016;18 Suppl 2:S223-33. Funding: Dexcom	**Study 1** Start: 9/2012 End: 10/2012 **Study 2** Start: 5/2014 End: 9/2014	Design: Two prospective, 1-week, single-arm, open-label studies with 7 days of home use and 1 in-clinic session Setting: Six centers in the U.S. (Study 1) Five centers in the U.S. (Study 2) Treatments: G4 Platinum (G4P) G4 Platinum with 505 software (SW505) Sample Size: G4P (n=176) SW505 (n=79)	Inclusion: • Age 2-17 years • T1DM or T2DM • Insulin pump therapy or MDI Exclusion: • Pregnancy • Hematocrits beyond the range recommended by the study glucose meters, • Hypoglycemic unawareness (other than that usually expected for toddlers with diabetes) • Need for treatment with acetaminophen, Any significant illness that would pose a risk to the patient or to the staff handling the blood specimen.	Mean ARD: • G4P: 17% • SW505: 10% Median ARD: • G4P: 14% • SW505: 8% CEG Zone A: • G4P: 68% • SW505: 90% CEG Zone A + B: • G4P: 98% • SW505: 99% PEG Zone A: • G4P: 79% • SW505: 93% PEG Zone A + B:

Citation/Funding Source	Study Dates	Design, Treatments & Sample Size	Inclusion/Exclusion Criteria	Clinical Outcomes & Outcome
				• G4P: 99% • SW505: 100% %20/20: • G4P: 68% • SW505: 91% %30/30: • G4P: 85% • SW505: 96% 40 < CMG ≤60 mg/d: • Mean ARD: ○ G4P: 19% ○ SW505: 16% • Median ARD: • G4P: 9% • SW505: 13% 60 < CMG ≤80 mg/d: • Mean ARD: ○ G4P: 13% ○ SW505: 12% • Median ARD: ○ G4P: 11% ○ SW505: 8% 80 < CMG ≤180 mg/d: • Mean ARD: ○ G4P: 17%

Citation/Funding Source	Study Dates	Design, Treatments & Sample Size	Inclusion/Exclusion Criteria	Clinical Outcomes & Outcome
				○ SW505: 13% • Median ARD: ○ G4P: 11% ○ SW505: 8% CMG >180 mg/d: • Mean ARD: ○ G4P: 18% ○ SW505: 9% • Median ARD: ○ G4P: 14% ○ SW505: 7% CMG >250 mg/d: • Mean ARD: ○ G4P: 18% ○ SW505: 10% • Median ARD: ○ G4P: 15% ○ SW505: 7% True hypoglycemia (<80 mg/dL) alert rate: • G4P: 55% • SW505: 91% False hypoglycemia (<80 mg/dL) alert rate: • G4P: 34% • SW505: 14% True hyperglycemia (>240 mg/dL) alert rate:

Citation/Funding Source	Study Dates	Design, Treatments & Sample Size	Inclusion/Exclusion Criteria	Clinical Outcomes & Outcome
				• G4P: 96% • SW505: 94% False hyperglycemia (>240 mg/dL) alert rate: • G4P: 13% • SW505: 12% There were no SAEs or device-related SAEs in either group. There was no sensor break-off or infection at the site of insertion. Some patients had mild skin irritation in the adhesive area.

ARD=absolute relative difference; BG=blood glucose; CEG=Clarke error grid; CG=capillary glucose; CG-EGA=continuous glucose error grid analysis; CEG=Clarke Error Grid; CI=confidence interval; DKA=diabetic ketoacidosis; DTSQ=Diabetes Treatment Satisfaction Questionnaire; HRQoL=health-related quality of life; HUA = hypoglycemia unawareness; IQR = interquartile range; ITT=intent to treat; MAD=mean absolute difference; MAGE=mean absolute glycemic excursions; MDI=multiple daily injections of insulin; NS=nonsignificant; PEG=Parkes Error Grid; PG=plasma glucose; RD=relative difference; RT-CGM=real-time continuous glucose monitoring; SAP=sensor-augmented insulin pump; SD=standard deviation; SH=severe hypoglycemia; SMBG=self-monitoring of blood glucose; T1DM=type 1 diabetes mellitus; T2DM= type 2 diabetes mellitus.

4.0 ECONOMIC VALUE AND MODELING REPORT

4.1 ABSTRACT

Introduction/Background: Intensive glycemic management, the standard of care for patients with insulin-treated diabetes, increases the risk for hypoglycemia, which is associated with significant morbidity, reduced quality of life, and fear of hypoglycemia. Fear of hypoglycemia causes patients to treat their diabetes less aggressively and contributes to poor glycemic control. Patients with insulin-treated diabetes and HUA are at particularly high risk for severe hypoglycemia, which may require costly emergency medical treatment. RT-CGM is a tool that provides patients with continuous information about their blood glucose levels and trends, allowing them to make management decisions to avoid both hyperglycemia and hypoglycemia.

Methods: We conducted a cost-benefit analysis (CBA) to examine the short-term (1 year) cost impact of providing RT-CGM to diabetes patients at high risk for severe hypoglycemia. The target group for intervention was children and adults with insulin-treated diabetes and HUA. Information from peer-reviewed published literature and other publicly available data were used to estimate key parameters.

Results:

In a Medicaid plan with 1 million enrollees, an estimated 2,344 have insulin-treated diabetes and HUA. With conventional blood glucose monitoring, these patients are expected to experience a total of 10,841 severe hypoglycemic events each year, including 2,800 requiring ambulance transport, 1,866 requiring an ER visit, and 178 requiring hospitalization, for a total cost of $20,501,554. RT-CGM is expected to avert 1,653 ambulance transports, 1,090 ER visits, and 660 hospitalizations; the total cost for emergency treatment of severe hypoglycemia in patients receiving RT-CGM is $8,398,346. The annual cost of RT-CGM is $10,548,000. Thus, the net cost impact of RT-CGM in the Medicaid plan is $1,555,208 in savings [$20,501,554 – ($8,398,346 + $10,548,000)].

Limitations: The assumptions and parameters used in the CBA were derived from multiple studies that had variable strengths and weaknesses. This CBA focuses on the potential cost benefits of providing RT-CGM to a highly select subgroup of patients with insulin-treated diabetes.

Discussion: This CBA indicates that the cost of RT-CGM for individuals with insulin-treated diabetes and HUA is more than offset by reductions in the incidence of severe hypoglycemic events requiring emergency treatment. The BIA was sensitive to assumptions about the cost of hospitalization, increased risk for severe hypoglycemia associated with HUA, and efficacy of RT-CGM for reducing the incidence of severe hypoglycemia.

4.2 INTRODUCTION/BACKGROUND

There is a large body of compelling evidence demonstrating the long-term benefits of intensive treatment in people with diabetes. Intensive treatment halts the onset of some diabetes complications when initiated early in the course of the illness and mitigates the progression and severity of complications when initiated in the mid-course of the illness. Although intensive therapy substantially reduces long-term diabetes complications in insulin-treated patients, these benefits are not realized until 5-10 years after treatment initiation,[193] and therefore may be of less interest to health plans that retain members for shorter periods of time.

Although RT-CGM is often prescribed for the main purpose of reducing hypoglycemia,[164] evaluating the impact of RT-CGM on the incidence of severe hypoglycemia has been made difficult by inadequately powered RCTs and the exclusion of high-risk patients (e.g., patients with HUA).[185] Nonetheless, the ability of RT-CGM to mitigate severe hypoglycemia, and reduce short-term costs associated with emergency treatment, may be of considerable interest to health plans.

We conducted a cost-benefit analysis (CBA) to examine the economic impact of RT-CGM technology on annual direct costs associated with emergency treatment (ambulance transport, ER visits, and hospitalization) for severe hypoglycemia in patients at high risk for these events. The model's overview assumptions, inputs, and results are summarized below.

The objective of this model is to evaluate the short-term (1-year) cost offset associated with RT-CGM use among insulin-using patients with diabetes who have HUA.

- The country of origin is the U.S.
- The target population is insulin-using individuals with diagnosed diabetes and HUA.
- The setting of care is outpatient.
- The time horizon is 1 year.
- The model assumes the perspective of the payer for private health plans and Medicaid.

The source of information is peer-reviewed published literature and other publicly available data.

4.3 MEDICAID CBA: METHODS

4.3.1 Clinical Parameters

a. Medicaid Eligibility Groups and Diabetes Prevalence

The eligibility distribution for a hypothetical plan with 1,000,000 Medicaid enrollees and diabetes prevalence is shown in Table 1.

TABLE 1. PREVALENCE OF DIAGNOSED DIABETES AMONG MEDICAID ENROLLEES BY DIABETES TYPE AND ELIGIBILITY GROUP

Age Group	% of Medicaid Population[194][a]	N	Percent of Enrollees with Diabetes[145, 195][b]	Number with Diabetes	Number with T1DM[c]	Number with T2DM[c]
Children	49.5%	495,000	0.3%	1,485	1,292	193
Adults	34.3%	433,000	9%	38,970	1,948	37,022
Elderly	7.2%	72,000	22%	15,840	396	15,444
Total	**100%**	**1,000,000**	—	**56,296**	**3,637**	**52,659**

[a]The distribution of Medicaid enrollees by eligibility group was derived from Medicaid enrollment during 2015 and Medicaid enrollment by eligibility status for 2012.[194]
[b]The prevalence of diabetes in non-elderly adult Medicaid enrollees was derived from published data from 2009.[145] The prevalence of diabetes in children and elderly Medicaid enrollees was derived from published data from 2003.[195]
[c]For individuals aged <20 years, T1DM was assumed to account for 87% and T2DM for 13% of all diabetes cases.[196] For individuals aged 20-64 years, T1DM was assumed to account for 5% and T2DM for 95% of all diabetes cases.[3] For individuals aged ≥65 years, T1DM was assumed to account for 2.5% and T2DM for 97.5% of all diabetes cases.[30]

b. Number of Enrollees with Diabetes Receiving Insulin

All members with T1DM are assumed to be receiving insulin (Table 2). An estimated 43.3% of youth with T2DM receive insulin.[4] Studies reporting rates of insulin use among adults with T2DM report prevalence rates ranging from 19.6% to 28.5%.[5, 34, 197] For the purpose of the model, we used the rate of 24.7% for adults aged 20-64 years[5] and 28.5% for adults aged ≥65 years.[34]

TABLE 2. NUMBER OF MEDICAID ENROLLEES WITH DIABETES RECEIVING INSULIN

Age Group	T1DM	T2DM

	N	%	N	%
Children	1,284	100	83	43.3**[4]**
Adults*	1,948	100	10,144	27.4**[5]**
Elderly	396	100	4,402	28.5**[34]**
*Adults included non-disabled and disabled adults.				

C. Number of Enrollees with Diabetes Receiving Insulin with HUA

- Among children and adolescents with insulin-treated diabetes, 21% and 29% have HUA;[79, 97] the median of these values is 25%.
- Among adults with T1DM, 10-58% have HUA (Table X);[70, 71, 73, 83, 88-96] the median of these values is 19%.
- Among adults with insulin-treated T2DM, 8-20% have HUA (Table X);[70, 83, 93, 98, 99] the median of these values is 10%.
- Adults elderly adults with T1DM, 45% have HUA.[198]

The number of enrollees with diabetes receiving insulin who have HUA is shown in Table 3.

TABLE 3. NUMBER OF MEDICAID ENROLLEES WITH DIABETES RECEIVING INSULIN WHO HAVE HUA

Age Group	T1DM		T2DM	
	N	%	N	%
Children	321	25	21	25
Non-elderly Adults*	370	19	1,014	10
Elderly	178	45	440	10
*Non-elderly adults included non-disabled and disabled adults aged 18-64 years.				

d. Number of Severe Hypoglycemic Events per Enrollee per Year

Studies of children and adolescents with T1DM and HUA have reported rates of severe hypoglycemia of 0.37 and 0.63.[76, 79] Thus, the median rate of severe hypoglycemia among children and adolescents with T1DM and HUA is 0.5 episodes per patient-year.

In adults with T1DM, the median incidence of severe hypoglycemia is 1.1 episodes per patient-year (Table X). HUA is associated with a median 5.6-fold increased risk of severe hypoglycemia in patients with T1DM (Table X); thus, the rate of severe hypoglycemia in adults with T1DM is calculated as: 1.1 x 5.6= 6.2 episodes per patient-year.

The incidence of severe hypoglycemia in children and adolescents with insulin-treated T2DM is estimated at 0.12 episodes per patient-year.[84] HUA is associated with a median 5-fold increased risk of severe hypoglycemia in patients with insulin-treated T2DM; thus, the rate of severe hypoglycemia in children and adolescents with insulin-treated T2DM is calculated as: 0.12 x 5 = 0.6 episodes per patient-year.

A systematic literature review (1998-2014) of 11 studies involving 6851 adults with insulin-treated T2DM found that the incidence of severe hypoglycemia was 1.0 episodes per patient-year.[85] HUA is associated with a median 5-fold increased risk of severe hypoglycemia in patients with insulin-treated T2DM (Table x); thus, the rate of severe hypoglycemia in adults with insulin-treated T2DM is calculated as: 1.0 x 5 = 5.0 episodes per patient-year.

The number of annual severe hypoglycemic events per enrollee with insulin-treated diabetes and HUA is shown in Table 4.

TABLE 4. NUMBER OF ANNUAL SEVERE HYPOGLYCEMIC EVENTS FOR ENROLLEES WITH INSULIN-TREATED DIABETES WITH HUA

Age Group	T1DM		T2DM	
	N of Events	Annual Rate of Events	N of Events	Annual Rate of Events
Children	161	0.5	13	0.6
Non-elderly Adults*	2,294	6.2	5,070	5.0
Elderly	1,104	6.2	2,200	5.0
*Non-elderly adults included non-disabled and disabled adults aged 18-64 years.				

e. Proportion of Severe Hypoglycemic Events Averted with RT-CGM

RT-CGM reduces the incidence of severe hypoglycemia by 59% in adults with poorly-controlled T1DM and HUA.[186] Similar efficacy is assumed in children/adolescents with T1DM and children/adolescents and adults with insulin-treated T2DM.

f. Number of Severe Hypoglycemic Events Requiring Ambulance Transport

Approximately 31.1% and 23.3% of severe hypoglycemic events occurring in enrollees with insulin-treated T1DM and T2DM, respectively, require ambulance transport.[11] The number of annual severe hypoglycemic events requiring ambulance transport in enrollees with insulin-treated diabetes and HUA without and with RT-CGM is shown in Table 5.

TABLE 5. NUMBER OF SEVERE HYPOGLYCEMIC EVENTS REQUIRING AMBULANCE TRANSPORT

	Without RT-CGM		With RT-CGM	
	N of Events Requiring Ambulance	% of Events Requiring Ambulance	N of Events Requiring Ambulance	% of Events Requiring Ambulance
T1DM	1,103	31.0	452	31.0
T2DM	1,697	23.3	695	23.3

g. Number of Severe Hypoglycemic Events Requiring ER Visits

Approximately 9.5% and 20.7% of severe hypoglycemic events occurring in enrollees with insulin-treated T1DM and T2DM, respectively, require an ER visit.[11] The number of annual severe hypoglycemic events requiring ER visits in enrollees with insulin-treated diabetes and HUA without and with RT-CGM is shown in Table 6.

TABLE 6. NUMBER OF SEVERE HYPOGLYCEMIC EVENTS REQUIRING AN ER VISIT

	Without RT-CGM		With RT-CGM	
	N of Events Requiring ER Visit	% of Events Requiring ER Visit	N of Events Requiring ER Visit	% of Events Requiring ER Visit
T1DM	338	9.5	138	9.5
T2DM	1,508	20.7	618	20.7

h. Number of Severe Hypoglycemic Events Requiring Hospitalization

Approximately 5.0% and 12.9% of severe hypoglycemic events occurring in enrollees with insulin-treated T1DM and T2DM, respectively, require hospitalization.[11] The number of annual severe hypoglycemic events requiring hospitalization in members with insulin-treated diabetes and HUA without and with RT-CGM is shown in Table 7.

TABLE 7. NUMBER OF SEVERE HYPOGLYCEMIC EVENTS REQUIRING HOSPITALIZATION

	Without RT-CGM		With RT-CGM	
	N of Events Requiring Hospitalization	% of Events Requiring Hospitalization	N of Events Requiring Hospitalization	% of Events Requiring Hospitalization
T1DM	178	5.0	73	5.0
T2DM	940	12.9	385	12.9

4.3.2 Economic Parameters

a. Cost of Ambulance Transport for Severe Hypoglycemia

The Medicare rate for ambulance transport is $1704.[199]

b. Cost of ER Visit for Severe Hypoglycemia

In a retrospective cohort analysis of claims data (MarketScan) that assessed the rate and costs of hypoglycemia among adults patients with T2DM treated with insulin alone, the average cost of an ER visit due to hypoglycemia was $610 in 2008 USD.[200] Updating this value to 2016 USD (using the Consumer Price Index for Medical Care) yields a cost of $777 per ER visit for severe hypoglycemia.

c. Cost of Hospitalization for Severe Hypoglycemia

In a retrospective cohort analysis of claims data (MarketScan) that assessed the rate and costs of hypoglycemia among adults patients with T2DM treated with insulin alone, the average cost of hospitalization (without an ER admission) due to hypoglycemia was $10,040 in 2008 USD.[200] Updating this value to 2016 USD (using the Consumer Price Index for Medical Care) yields a cost of $12,787 per severe hypoglycemia hospitalization.

d. Cost of RT-CGM

The annual cost of RT-CGM, which includes the Receiver, Transmitter, and Sensors, is assumed to be $4,500.

4.4 MEDICAID HEALTH PLAN CBA: RESULTS

4.4.1 Costs Averted for Severe Hypoglycemia Ambulance Transport

Without RT-CGM, there are 2,800 annual severe hypoglycemia episodes requiring ambulance transport; the total annual cost for hypoglycemia-related ambulance is estimated at $4,711,590.

Of the 2,800 severe hypoglycemia episodes requiring ambulance transport, RT-CGM technology is expected to avert 1,653.

The cost of annual ambulance transport due to severe hypoglycemia with RT-CGM technology is $1,954,488.

Therefore, RT-CGM technology is expected to reduce hypoglycemia-related ambulance costs by $2,817,102 (cost without RT-CGM of $4,711,590 minus cost with RT-CGM of $1,954,488.

4.4.2 Costs Averted for Severe Hypoglycemia ER Visits

Without RT-CGM, there are 1,846 annual severe hypoglycemia ER visits; the total annual cost for hypoglycemia ER visits is estimated at $1,434,098.

Of the 1,846 ER visits due to severe hypoglycemia, RT-CGM technology is expected to avert 1,090.

The cost of annual ER visits due to severe hypoglycemia with RT-CGM technology is $587,412.

Therefore, RT-CGM technology is expected to reduce hypoglycemia hospitalization costs by $846,686 (cost without RT-CGM of $1,434,098 minus cost with RT-CGM of $587,412).

4.4.3 Costs Averted for Severe Hypoglycemia Hospitalizations

Without RT-CGM, there are 1,118 annual severe hypoglycemia hospitalizations; the total annual cost for hypoglycemia hospitalizations is estimated at $14,295,866.

Of the 1,118 hospitalizations due to severe hypoglycemia, RT-CGM technology is expected to avert 660.

The cost of annual hospitalizations due to severe hypoglycemia hospitalizations with RT-CGM technology is $5,856,446.

Therefore, RT-CGM technology is expected to reduce hypoglycemia hospitalization costs by $8,439,420 (cost without RT-CGM of $14,295,866 minus cost with RT-CGM of $5,856,446).

4.4.4 Cost Offset Due to RT-CGM Reductions in Severe Hypoglycemia Emergency Treatment

If all insulin-treated Medicaid enrollees with HUA received the G5™ Mobile CGM System, the cost to this plan would be $10,548,000.

The annual cost offset due to the impact of RT-CGM on severe hypoglycemia hospitalizations (cost of averted hospitalizations minus cost of RT-CGM technology) is $1,555,208 for Medicaid enrollees.

4.4.5 Sensitivity Analyses

Table 8 shows the results of one-way sensitivity analyses conducted for the Medicaid plan CBA. Results are most sensitive to assumptions about the cost of hospitalization, increased risk for

severe hypoglycemia in patients with HUA, and the efficacy of RT-CGM for reducing the incidence of severe hypoglycemia.

TABLE 8. SENSITIVITY ANALYSIS FOR MEDICAID PLAN CBA

	NET COST IMPACT
Base Case Scenario	$1,555,208
Cost of RT-CGM decreased by 20%	$3,664,808
Cost of hospitalization decreased by 20%	($132,678)
Cost of ER visit decreased by 20%	$1,385,871
Prevalence of HUA assumed to be 58% in adults with T1DM (highest estimate)	$1,574,737
Prevalence of HUA assumed to be 10% in adults with T1DM (lowest estimate)	$1,535,294
Prevalence of HUA assumed to be 20% in adults with insulin-treated T2DM (highest estimate)	$4,473,742
Prevalence of HUA assumed to be to 8% in adults with insulin-treated T2DM (lowest estimate)	$962,681
Risk of severe hypoglycemia in patients with T1DM and HUA assumed to be 3 times higher than in patients without HUA (lowest estimate)	$388,557
Risk of severe hypoglycemia in patients with T1DM and HUA assumed to be 2 times higher than in patients without HUA (lowest estimate)	($4,127,155)
Reduction in severe hypoglycemia due to RT-CGM assumed to be 46% (JDRF trial in patients without HUA)	($1,109,828)

4.5 LIMITATIONS

The assumptions and parameters used in the CBA were derived from multiple studies that had variable strengths and weaknesses. To maximize the external validity of our findings, we selected the median among a range of values reported in the literature regarding the prevalence of HUA, incidence of severe hypoglycemia, and increased risk of severe hypoglycemia associated with HUA. In addition, sensitivity analyses, which examined outcomes using the lowest and highest values in the ranges were conducted. This CBA focuses on the potential cost benefits of providing RT-CGM to a highly select subgroup of patients with insulin-treated diabetes. A longer-term perspective may be needed to demonstrate the cost-effectiveness of RT-CGM for the broader population of patients with insulin-treated diabetes who are at normal risk for severe hypoglycemia but have a high risk for developing long-term complications of diabetes due to chronic hyperglycemia.

4.6 DISCUSSION

This CBA indicates that the cost of RT-CGM for individuals with insulin-treated diabetes and HUA is more than offset by reductions in the incidence of severe hypoglycemic events requiring costly emergency treatment. Cost savings associated with RT-CGM were observed in both the private health plan and Medicaid populations. Results were sensitive to assumptions about the cost of hospitalization due to severe hypoglycemia, the magnitude of the increase in risk for severe hypoglycemia associated with HUA, and the efficacy of RT-CGM for reducing the incidence of severe hypoglycemia.

5.0 OTHER SUPPORTING EVIDENCE

5.1 CLINICAL PRACTICE GUIDELINES

American Diabetes Association

In the 2017 *Standards of Medical Care in Diabetes*,[151] the ADA found strong evidence supporting the value of RT-CGM in conjunction with intensive insulin therapy in lowering HbA1c without increasing hypoglycemia in adults aged ≥25 years with T1DM (Grade A) and supportive evidence that RT-CGM can help reduce HbA1c in children, teens, and younger adults with T1DM (Grade B). The guidelines also note that RT-CGM technology may be particularly useful in people with HUA and/or frequent hypoglycemic episodes (Grade C). People who have successfully used RT-CGM should have continued access after age 65 (Grade E). Given the variable adherence to RT-CGM, clinicians should assess individual readiness for continuing RT-CGM use prior to prescribing. (Grade E). When prescribing RT-CGM, robust diabetes education, training, and support are required for optimal CGM implementation and ongoing use (Grade E).

American Association of Clinical Endocrinologists/American Academy of Endocrinology (AACE/ACE)

On the basis of available evidence, the 2016 AACE/ACE Consensus Conference on Glucose Monitoring made the following recommendations:[154]

- Consensus conference attendees unanimously agreed that RT-CGM should be made available for all insulin-using patients regardless of diabetes type although this conclusion is based entirely on studies conducted in T1DM.
- Few studies have been conducted in patients with HUA due to challenges recruiting a suitable patient population, but it is likely that this population would also benefit from RT-CGM.
- Other patients at risk from hypoglycemia, including the elderly, patients with renal impairment, and athletes should receive next priority.
- T2DM patients who use antihyperglycemic agents other than insulin might also benefit from RT-CGM, but the evidence base is inadequate to make a strong recommendation.

Endocrine Society

The Endocrine Society strongly recommends RT-CGM for adult patients with T1DM who have HbA1c levels above target and those with well-controlled T1DM who are willing and able to use RT-CGM on a nearly daily basis (high-quality evidence).[201] The Endocrine Society suggests short-term, intermittent RT-CGM use in adult patients withT2DM (not on prandial insulin) who have HbA1c levels ≥7% and are willing and able to use the device (low-quality evidence).

National Institute for Health Care Excellence (NICE)

The most current NICE guidelines for the diagnosis and management of adults with T1DM (NG17) recommend that RT-CGM be considered for adults with T1DM who are willing to commit to using RT-CGM at least 70% of the time and to calibrate it as needed, and who have any of the following despite optimized use of insulin therapy and conventional blood glucose monitoring:[202]

- More than 1 episode a year of severe hypoglycaemia with no obviously preventable precipitating cause;
- Complete loss of awareness of hypoglycaemia;
- Frequent (more than 2 episodes a week) asymptomatic hypoglycaemia that is causing problems with daily activities;
- Extreme fear of hypoglycaemia; or
- Hyperglycaemia (HbA1c level of 75 mmol/mol [9%] or higher) that persists despite testing at least 10 times a day.

RT-CGM should be continued only if HbA1c can be sustained at or below 5 mmol/mol (7%) and/or there has been a fall in HbA1c of 2 mmol/mol (2.5%) or more.

The principles of flexible insulin therapy with either a MDI insulin regimen or insulin pump therapy should be used for adults with T1DM who are using RT-CGM.

RT-CGM should be provided by a centre with expertise in its use, as part of strategies to optimise a person's HbA1c levels and reduce the frequency of hypoglycaemic episodes.

The most current NICE guidelines for the diagnosis and management of diabetes in children and young people (NG18) recommend the use of RT-CGM with alarms in children with T1DM who have:[203]

- Frequent severe hypoglycemia;
- Impaired awareness of hypoglycemia associated with adverse consequences (for example, seizures or anxiety); or
- Inability to recognize, or communicate about, symptoms of hypoglycemia (for example, because of cognitive or neurological disabilities).

In addition, the guidelines specify that RT-CGM should be considered for:

- Neonates, infants and pre-school children;
- Children and young people who undertake high levels of physical activity (for example, sport at a regional, national or international level); and
- Children and young people who have comorbidities (for example anorexia nervosa) or who are receiving treatments (for example corticosteroids) that can make blood glucose control difficult.

Lastly, intermittent (real-time or retrospective) CGM should be considered to help improve blood glucose control in children and young people who continue to have hyperglycemia despite insulin adjustment and additional support.

European Society for Pediatric Endocrinology (ESPE), Pediatric Endocrine Society (PES), and International Society for Pediatric and Adolescent Diabetes (ISPAD)

A panel of expert physicians convened by the ESPE, the PES, and the ISPAD provided a consensus statement in 2012 regarding the use of RT-CGM in pediatric and adolescent patients with T1DM.[204] The group recommended that RT-CGM be considered in children and adolescents with T1DM who:

- Are performing frequent SMBG;
- Have experienced severe hypoglycemic episodes;
- Have hypoglycemic unawareness (especially in young children);
- Have nocturnal hypoglycemia;
- Have wide glucose excursions; or
- Have HbA1c exceeding target range or who wish to have in-target glycated hemoglobin levels but limit the risk of hypoglycemia.

International Diabetes Federation (IDF)/ISPAD

A global guideline for diabetes in childhood and adolescence, developed by the IDF/ISPAD in 2011, noted that RT-CGM may allow near-normalization of blood glucose and HbA1c while decreasing risk of hypoglycemia.[205] In addition, the guideline states that RT-CGM may particularly benefit patients with HUA.

5.2 OTHER ECONOMIC EVIDENCE

Huang ES, O'Grady M, Basu A, et al. The cost-effectiveness of continuous glucose monitoring in type 1 diabetes. Diabetes Care. 2010;33:1269-74.[206]

Study Description: The purpose of this study is to evaluate the cost-effectiveness of RT-CGM compared with SMBG in patients with T1DM from the societal perspective.

Timeframe: Lifetime

Population: Adult (≥25 years) patients with T1DM who completed the 6-month JDFR RCT and had baseline HbA1c <7.0% or ≥7.0%.

Location: Diabetes treatment centers in the U.S.

Economic Clinical Outcomes: Incremental cost-effectiveness ratio (ICER) expressed as cost per quality-adjusted life year (QALY).

Outcomes & Data Sources: The estimated effect of RT-CGM was based on the reduction in HbA1c observed in the 6-month JDRF RCT for the adult cohorts with baseline HbA1c <7.0% and ≥7.0%. This effect was projected to continue throughout the patient's lifetime. Utility data were collected from trial participants for both immediate (experienced) QoL effects of RT-CGM and for the QoL effects of potential long-term complications. Experienced utility data were derived from the Health Utility Index and by eliciting time tradeoff (TTO) utilities for overall experience. In the TTO method, patients were asked to consider their current state of health in comparison to life in perfect health. For complication utilities, we used the TTO method to elicit utilities for life with blindness, end-stage renal disease, lower-extremity amputation, chronic angina, and stroke.

For all microvascular complications, investigators used the original DCCT prediction models for intermediate complications that relate HbA1c with the cumulative probability of developing these intermediate complications. For the transitions from intermediate to end-stage microvascular complications, they used annual probabilities found in the literature. For macrovascular complications and mortality, investigators used prediction models for T2DM.

Costs associated with long-term microvascular and macrovascular complications were derived from the literature.

Modeling Methodology: A Monte Carlo-based Markov simulation model was developed that uses framework and data inputs shared by prior cost-effectiveness analyses of treatments in T1DM. The model is framed by the simultaneous progression of disease through major categories of complications and their associated Markov states. After assignment of characteristics of hypothetical subjects, the model simulates the natural history of diabetes based on these characteristics.

Sensitivity Analyses: To assess the relative contributions of immediate QoL and long-term glucose control benefits, analyses were run in which the only benefit was due to improved glucose control. Investigators also evaluated the impact of variation in the daily cost of RT-CGM and utilization of conventional SMBG. The effect of future costs, including medical costs for unrelated illnesses, nonmedical costs, and future earnings, on the overall cost-effectiveness results were estimated separately.

Outcome (Base Case Analysis): For the HbA1c ≥7.0% cohort, the ICER for the base case was $98,679/QALY (95% CI -60,007 [fourth quadrant, dominant] to -86,582 [second quadrant, dominated]). The CIs reflect a large degree of uncertainty about the ICER point estimate. For the HbA1c <7.0% cohort, the ICER for the base case was $78,943/QALY (95% CI 14,644 [first

quadrant] to -290,780 [second quadrant, dominated]). The CIs for this cohort were narrower than for the HbA1c ≥7.0% cohort but still reflect considerable uncertainty around the ICER.

Outcome (Sensitivity Analysis): If the benefit of RT-CGM was limited to glucose lowering and subsequent complication prevention, RT-CGM would not be cost-effective by most conventional thresholds. In the HbA1c ≥7.0% cohort, the average gain in QALYs would be 0.08 and the ICER would be $701,397/QALY. In the HbA1c <7.0% cohort, the average gain in QALYs would be 0.07 and the ICER would be $1,185,384/QALY. If the daily costs of RT-CGM were reduced from $13.85/day ($4,335/year) to $9.89/day ($3,096/year) or below, the ICER would be below $70,000/QALY. If test strip use among RT-CGM patients was two test strips per day as recommended for calibration, RT-CGM would be cost saving compared with SMBG. When accounting for future costs, the ICERs for the two populations did not qualitatively change from the base case.

Limitations and potential biases: Patients in the study cohorts had high baseline utilities, which effectively placed a ceiling on the magnitude of potential QoL benefits that could be brought about by RT-CGM. Patients in the HbA1c ≥7.0% cohort had a mean baseline HbA1c of 7.5%; therefore, results may not be generalized to patients with higher HbA1c levels. The assumptions used to model the long-term complications of T1DM may not reflect the natural history of T1DM.

Quality Grade: Fair

McQueen RB, Ellis SL, Campbell JD, Nair KV, Sullivan PW. Cost-effectiveness of continuous glucose monitoring and intensive insulin therapy for type 1 diabetes. Cost Eff Resour Alloc. 2011;9:13.[207]

Study Description: The objective of this analysis is to assess the societal cost-effectiveness of RT-CGM with intensive insulin therapy relative SMBG with intensive insulin therapy in a general U.S. population of individuals with T1DM.

Timeframe: Lifetime.

Population: Adult (≥25 years) patients with T1DM who completed the 6-month JDRF RCT and had baseline HbA1c ≥7.0%.

Location: Diabetes treatment centers in the U.S.

Economic Clinical Outcomes: The main outcome of interest was the ICER expressed as cost per QALY.

Outcomes & Data Sources: Reductions in the risk of diabetes complications conferred by RT-CGM were based on a 0.5% reduction in HbA1c observed among adults treated with RT-CGM in the JDRF RCT. Risk reduction parameters were drawn from the DCCT for microvascular complications and a meta-analysis relating to macrovascular complications by Selvin et al. Utility values for each disease state were taken from the EQ-5D catalogue by Sullivan et al.

Model inputs and assumptions were based on the CDC Cost-Effectiveness Group, other literature sources, and the expertise of the research team. The CDC Cost-Effectiveness Group used similar modeling inputs and assumptions as were used in the CORE Diabetes Model (i.e., inputs derived from DCCT, UKPDS, and other literature sources).

Costs were derived from evidence published by the ADA. The annual mean cost of diabetes represents the per capita expenditures for people with diabetes at all age groups for hospital inpatient visits, nursing/residential facility visits, physician's office visits, emergency department trips, hospital outpatient visits, home health care, hospice care, podiatry care, insulin, diabetic supplies, oral agents, retail prescriptions, other supplies, and patient time. Lost wages served as a proxy for patient time. Other costs in the model include marginal annual costs for each disease state, such as blindness, end-stage renal disease, lower-extremity amputation and neuropathy, retinopathy, neuropathy, nephropathy, and CHD, along with the concomitant disease states. The marginal costs for each disease state were calculated using average length of stay in an inpatient hospital setting and the cost per medical event, estimated from the ADA. The concomitant disease states were estimated by summing the marginal cost for each disease state, with the exception of blindness, lower-extremity amputation, and end-stage renal disease. Annual and initial costs are an average based on the three RT-CGM devices used during the trial.

Modeling Methodology: A population-level Markov cohort simulation was employed to model the long-term disease progression of patients with T1DM. Long-term complications for each arm were modeled based on reductions in HbA1c levels. The baseline characteristics of this population cohort reflect those of the adult population (i.e., ≥25 years) in the JDRF RCT. Patients had T1DM of approximately 20 years' duration, a mean age of 40 years, and a mean HbA1c level of 7.6% (± 0.5%). A cycle length of one year was used for the Markov analysis, with a time horizon of 33 years, assuming a life expectancy of 73 years. RT-CGM with SMBG was compared to SMBG alone. All costs are in 2007 US dollars, and a discount rate of 3% was used for costs and QALYs. The initial RT-CGM cost estimate is included in the zero cycle of the Markov model node RT-CGM. The annual cost of RT-CGM is then included in all disease states including no complications after cycle zero.

Sensitivity Analyses: Probabilistic sensitivity analysis was performed using Monte Carlo simulation to evaluate the multivariate uncertainty in the model. The input parameters were varied simultaneously over specified ranges. Various probability distributions were chosen based on assumptions for each input parameter. The beta distribution was specified for the probability, utility, and risk reduction parameters. The Gamma distribution was specified for the cost parameters. The Monte Carlo simulation drew values for each input parameter and calculated expected cost and effectiveness for each arm of the model. This process was repeated 10,000 times to give a range of all expected cost and effectiveness values. Additionally, univariate sensitivity analysis was conducted to identify variables that had the largest impact on the model results. For the univariate sensitivity analysis, parameters were varied by ±15%. The parameters that had the largest impact on the model results were presented in a tornado diagram. The top ten variables from the tornado diagram were individually varied by 50% to estimate the effect on the model results.

Outcome (Base-case Analysis): The mean total lifetime costs for SMBG were $470,583. The mean total lifetime costs for SMBG and RT-CGM totaled $494,135, resulting in an incremental cost of $23,552. Lifetime effectiveness for SMBG was 10.289 QALYs. Lifetime effectiveness for SMBG with the addition of RT-CGM was 10.812 QALYs, resulting in an incremental effectiveness of 0.523 QALYs. The ICER was $45,033 per QALY for RT-CGM. Mortality was not directly reduced by RT-CGM; it simply reduced the probability of entering disease states, thereby delaying the increased mortality from complications.

Outcome (Sensitivity Analyses): Resulted indicated that 48% of the observations were cost-effective for a willingness-to-pay (WTP) of US$50,000 per QALY and 70% for a WTP of $100,000/QALY. The variables with the largest impact on model results were the utility of diabetes with no complications, the annual cost of CHD, and the probability of going from diabetes with no complications to the CHD disease state. When the utility of diabetes with no complications was decreased by 50%, the ICER exceeded $300,000/QALY. When the utility of diabetes with no complications was increased by 50%, the ICER was decreased to $30,000/QALY. When the annual cost of CHD was decreased by 50%, the ICER was $86,000/QALY. When the annual cost of CHD was increased by 50% the ICER was $12,000/QALY. When the probability of going from diabetes with no complications to the CHD disease state was decreased by 50%, the ICER was $66,000/QALY. When the probability of entering the CHD disease state was increased by 50%, the ICER was $32,000/QALY.

Limitation and Biases: Patients were assumed to have a baseline HbA1c of 7.5%; therefore, results may not be generalized to patients with higher HbA1c levels. The probability values are from different sample populations. The probabilities are constant with each cycle, indicating no increase in the risk of complications due to diabetes over time. This may result in underestimating the benefit of reducing HbA1c on the risk of long-term complications. The model did not include hypoglycemic events, which may be reduced by RT-CGM.

Quality Grade: Fair

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6.0 DOSSIER APPENDICES

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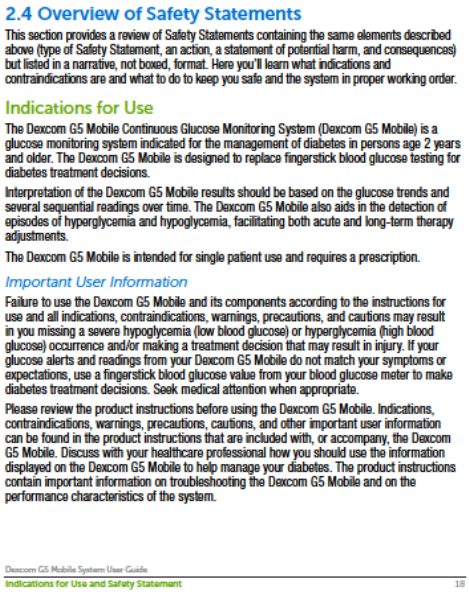
6.2 ECONOMIC MODELS

See interactive models.

6.3 INSTRUCTIONS FOR USE

SEE ATTACHMENT
LBL013445-G5-MOBILE-CGM-SYSTEM-UG-US



2.4 Overview of Safety Statements

This section provides a review of Safety Statements containing the same elements described above (type of Safety Statement, an action, a statement of potential harm, and consequences) but listed in a narrative, not boxed, format. Here you'll learn what indications and contraindications are and what to do to keep you safe and the system in proper working order.

Indications for Use

The Dexcom G5 Mobile Continuous Glucose Monitoring System (Dexcom G5 Mobile) is a glucose monitoring system indicated for the management of diabetes in persons age 2 years and older. The Dexcom G5 Mobile is designed to replace fingerstick blood glucose testing for diabetes treatment decisions.

Interpretation of the Dexcom G5 Mobile results should be based on the glucose trends and several sequential readings over time. The Dexcom G5 Mobile also aids in the detection of episodes of hyperglycemia and hypoglycemia, facilitating both acute and long-term therapy adjustments.

The Dexcom G5 Mobile is intended for single patient use and requires a prescription.

Important User Information

Failure to use the Dexcom G5 Mobile and its components according to the instructions for use and all indications, contraindications, warnings, precautions, and cautions may result in you missing a severe hypoglycemia (low blood glucose) or hyperglycemia (high blood glucose) occurrence and/or making a treatment decision that may result in injury. If your glucose alerts and readings from your Dexcom G5 Mobile do not match your symptoms or expectations, use a fingerstick blood glucose value from your blood glucose meter to make diabetes treatment decisions. Seek medical attention when appropriate.

Please review the product instructions before using the Dexcom G5 Mobile. Indications, contraindications, warnings, precautions, cautions, and other important user information can be found in the product instructions that are included with, or accompany, the Dexcom G5 Mobile. Discuss with your healthcare professional how you should use the information displayed on the Dexcom G5 Mobile to help manage your diabetes. The product instructions contain important information on troubleshooting the Dexcom G5 Mobile and on the performance characteristics of the system.

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Indications for Use and Safety Statement 18

6.4 PATIENT INFORMATION

SEE APPENDIX 6.3

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6.5 MATERIAL SAFETY DATA SHEET

N/A

7.0 ADDENDUM

7.1 PRODUCT DESCRIPTION

i. Other Studied Indications

None

j. Length of Course of Treatment

After initiation, continued use of RT-CGM is anticipated. The sensor is indicated for up to 7 days, although data indicate that the sensor may provide reliable readings for longer periods. In a study examining the feasibility of 10 days of sensor use (using the Dexcom SEVEN® PLUS CGM System) in 30 adults with T1DM, the accuracy of the sensor was maintained throughout the 10-day study duration, with a MARD of 12.6%, 11.3% and 14.5% on days 2, 7, and 10, respectively (P=0.63).[208]

k. Patents

TABLE 12. CURRENT PATENTS

Patent Number	Expiration Date
7,310,544	12/18/2025
7,497,827	3/10/2025
7,654,956	11/5/2027
7,713,574	8/14/2028
7,885,697	3/10/2025
7,949,381	7/18/2026

l. Pharmacovigilance

Dexcom is committed to continuous improvement of our products. We monitor multiple inputs for customer feedback. Technical Support is responsible for logging customer feedback that will be evaluated, tracked and trended for product complaints. The Marketing department will compile marketing solicited data such as surveys, focus groups, etc., into the customer feedback process. Dexcom may also provide product for third party or physician sponsored studies; we will have access to the product feedback information and many times be asked to review data from the studies that will be used for publication. This information is fed into the design control process to be evaluated as design inputs for product iterations and next generation devices.

7.2 FUTURE INDICATIONS

None

7.3 TARGET POPULATION

SEE APPENDIX 6.3

7.4 CLINICAL ASSESSMENT

Literature Search Procedures for Studies Summarized in Section 3.1.1.

Databases searched:

- Medline
- Cochrane Controlled Trials Registry
- Clinicaltrials.gov

Secondary sources:

- Cited literature in retrieved articles
- Cited in 2012 Cochrane review[209]
- Cited in 2012 AHRQ review[187]

Medline search terms: (“Diabetes Mellitus”[Mesh] OR "Diabetes Mellitus, Type 1"[Mesh] OR "Diabetes Mellitus, Type 2"[Mesh]) AND ("continuous glucose monitor*" OR "continuous subcutaneous glucose monitor*" OR "CGMS" OR "CGM" OR "sensor-augmented insulin pump" OR "continuous glucose measur*")

Search terms for Cochrane Controlled Trials Registry **and Clinicaltrials.gov**: “diabetes mellitus,” “diabetes mellitus type 1,” diabetes mellitus type 2,” “continuous glucose monitoring,” “clinical trial,” and “meta-analysis”

Restrictions on Medline search: English, Humans, published to 5/31/2014, type of article (clinical trial, meta-analysis, RCT)

Time period for search: Studies published from 1996 (introduction of first CGM device) to February 1, 2016

Inclusion/exclusion criteria: Studies included in the review were clinical studies in which RT-CGM was compared with SMBG in the management of patients with T1DM or T2DM who were being treated with MDI or insulin pump therapy. The studies had to be of at least 3 months’ duration and have at least one arm that evaluated the continuous use of RT-CGM. Extension studies of RCTs were included.

We excluded studies that compared sensor-augmented pump therapy with insulin pump therapy alone; short-term clinical trials (<3 months duration); studies in non-insulin-dependent T2DM and pancreas/islet-cell transplant patients; trials evaluating the use of retrospective or intermittent CGM; studies performed in non-ambulatory settings; and studies reported in languages other than English. Studies exclusively using the GlucoWatch G2 Biographer were excluded because this device was withdrawn from the market due to side effects. Studies that included Abbott FreeStyle Navigator and also Guardian RT were excluded from the study because they are now obsolete from the US market.

The reasons for excluding specific studies of CGM are shown in Table 33.

TABLE 13. EXCLUDED STUDIES

Study	Reason for Exclusion
Bailey KJ, Little JP, Jung ME. Self-monitoring using continuous glucose monitors with real-time feedback improves exercise adherence in individuals with impaired blood glucose: a pilot study. Diabetes Technol Ther. 2016;18:185-93.	Inadequate duration
Battelino T, Conget I, Olsen B, Schutz-Fuhrmann I, Hommel E, Hoogma R, et al. The use and efficacy of continuous glucose monitoring in type 1 diabetes treated with insulin pump therapy: a randomised controlled trial. *Diabetologia* 2012; 55:3155-62.	SAP versus Insulin Pump
Battelino T, Liabat S, Veeze HJ, Castaneda J, Arrieta A, Cohen O. Routine use of continuous glucose monitoring in 10 501 people with diabetes mellitus. *Diabet Med* 2015; 32:1568-74.	SAP versus Insulin Pump
Bergenstal RM, Tamborlane WV, Ahmann A, Buse JB, Dailey G, Davis SN, et al. Effectiveness of sensor-augmented insulin-pump therapy in type 1 diabetes. *N Engl J Med* 2010; 363:311-20.	SAP versus Insulin Pump

Study	Reason for Exclusion
Bergenstal RM, Klonoff DC, Garg SK, Bode BW, Meredith M, Slover RH, Ahmann AJ, Welsh JB, Lee SW, Kaufman FR; ASPIRE In-Home Study Group. Threshold-based insulin-pump interruption for reduction of hypoglycemia. N Engl J Med. 2013;369:224-32.	No comparison CGM versus SMBG
Bode B, Gross K, Rikalo N, et al. Alarms based on real-time sensor glucose values alert patients to hypo- and hyperglycemia: the guardian continuous monitoring system. Diabetes Technol Ther 2004;6:105-13.	Inadequate duration
Bode B, Shelmet J, Gooch B, et al. Patient perception and use of an insulin injector/glucose monitor combined device. Diabetes Educ 2004;30:301-9.	No CGM (InDuo)
Buckingham BA, Cameron F, Calhoun P, Maahs DM, Wilson DM, Chase HP, Bequette BW, Lum J, Sibayan J, Beck RW, Kollman C. Outpatient safety assessment of an in-home predictive low-glucose suspend system with type 1 diabetes subjects at elevated risk of nocturnal hypoglycemia. Diabetes Technol Ther. 2013;15:622-7.	No comparison CGM versus SMBG
Chase HP, Kim LM, Owen SL, et al. Continuous subcutaneous glucose monitoring in children with type 1 diabetes. Pediatrics 2001;107:222-6.	Intermittent CGM
Chase HP, Roberts MD, Wightman C, et al. Use of the GlucoWatch biographer in children with type 1 diabetes. Pediatrics 2003;111:790-4.	GlucoWatch
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;28:1101-6.	GlucoWatch
Chico A, Vidal-Rios P, Subira M, Novials A. The continuous glucose monitoring system is useful for detecting unrecognized hypoglycemias in patients with type 1 and type 2 diabetes but is not better than frequent capillary glucose measurements for improving metabolic control. Diabetes Care 2003;4:1153-7.	Intermittent CGM
Cooke D, Hurel SJ, Casbard A, et al. Randomized controlled trial to assess the impact of continuous glucose monitoring on HbA1c in insulin treated diabetes (MITRE Study). Diabetic Med 2009;26:540-54.	Intermittent CGM
Cosson E, Hamo-Tchatchouang E, Dufaitre-Patouraux L, et al. Multicentre, randomised, controlled study of the impact of continuous sub-cutaneous glucose monitoring (GlucoDay) on glycaemic control in type 1 and type 2 diabetes patients. Diabetes Metab 2009;35:312–8.	Intermittent CGM
Davey RJ, Stevens K, Jones TW, Fournier PA. The effect of short-term use of the Guardian RT continuous glucose monitoring system on fear of hypoglycaemia in patients with type 1 diabetes mellitus. Prim Care Diabetes. 2012;6:35-9.	Not RCT
Deiss D, Hartmann R, Schmidt J, Kordonouri O. Results of a randomised controlled cross-over trial on the effect of continuous subcutaneous glucose monitoring (CGMS) on glycaemic control in children and adolescents with type 1 diabetes. Exp Clin Endocrinol Diabetes 2006;2:63-7.	Intermittent CGM

Study	Reason for Exclusion
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;5:668-75.	Intermittent CGM
Feldman B, Brazg R, Schwartz S, Weinstein R. A continuous glucose sensor based on wired enzyme technology - Results from a 3-day trial in patients with type 1 diabetes. Diabetes Technol Ther 2003;5:769–79.	Inadequate duration
Fiallo-Scharer R. Eight-point glucose testing Versus the continuous glucose monitoring system in evaluation of glycemic control in type 1 diabetes. J Clin Endocrinol Metab 2005;6:3387-91.	Inadequate duration, no control group
Fonda SJ, Salkind SJ, Walker MS, Chellappa M, Ehrhardt N, Vigersky RA. Heterogeneity of responses to real-time continuous glucose monitoring (RT-CGM) in patients with type 2 diabetes and its implications for application. Diabetes Care. 2013;36:786-92.	Intermittent RT-CGM
Garg S, Zisser H, Schwartz S, et al. Improvement in glycemic excursions with a transcutaneous, real-time continuous glucose sensor: a randomized controlled trial. Diabetes Care 2006;29:44-50.	Inadequate duration
Garg SK, Bookout TR, McFann KK, et al. Improved glycemic control in intensively treated adult subjects with type 1 diabetes using insulin guidance software. Diabetes Technol Ther 2008;10:369-75.	No CGM
Garg SK, Voelmle MK, Beatson CR, et al. Use of continuous glucose monitoring in subjects with type 1 diabetes on multiple daily injections versus continuous subcutaneous insulin infusion therapy: a prospective 6-month study. Diabetes Care 2011;34:574-9.	Non-randomized
Garg S, Brazg RL, Bailey TS, Buckingham BA, Slover RH, Klonoff DC, Shin J, Welsh JB, Kaufman FR. Reduction in duration of hypoglycemia by automatic suspension of insulin delivery: the in-clinic ASPIRE study. Diabetes Technol Ther. 2012;14:205-9.	No comparison CGM versus SMBG
Głowińska-Olszewska B, Tobiaszewska M, Łuczyński W, Bossowski A. Monthly use of a real-time continuous glucose monitoring system as an educational and motivational tool for poorly-controlled type 1 diabetes adolescents. Adv Med Sci. 2013;58:344-52.	Not RCT
Haupt A, Berg B, Paschen P, Dreyer M, et al. InDuo, a novel combined insulin injection and blood glucose monitoring device - effective and safe as other devices, and patient preference. Exp Clin Endocrinol Diabetes 2005;113:541-4.	No CGM (InDuo)
Hermanides J, DeVries JH. Sensor-augmented insulin pump more effective than multiple daily insulin injections for reducing HbA1C in people with poorly controlled type 1 diabetes. *Evidence Based Medicine* 2011; 16:46-48.	SAP versus Insulin Pump
Hermanns N, Kulzer B, Gulde C, et al. Short-term effects on patient satisfaction of continuous glucose monitoring with the glucoday with real-time and retrospective access to	Inadequate duration

Study	Reason for Exclusion
glucose values: A crossover study. Diabetes Technol Ther 2009;5:275-81.	
Hirsch IB, Abelseth J, Bode BW, Fischer JS, Kaufman FR, Mastrototaro J, et al. Sensor-augmented insulin pump therapy: results of the first randomized treat-to-target study. *Diabetes Technol Ther* 2008; 10:377-83.	SAP versus Insulin Pump
Jeha GS, Karaviti LP, Anderson B, et al. Continuous glucose monitoring and the reality of metabolic control in preschool children with type 1 diabetes. Diabetes Care 2004;27:2881-6.	Not RCT
Kordonouri O, Pankowska E, Rami B, Kapellen T, Coutant R, Hartmann R, et al. Sensor-augmented pump therapy from the diagnosis of childhood type 1 diabetes: results of the Paediatric Onset Study (ONSET) after 12 months of treatment. *Diabetologia* 2010; 53:2487-95.	SAP versus Insulin Pump
Kordonouri O, Hartmann R, Pankowska E, Rami B, Kapellen T, Coutant R, et al. Sensor augmented pump therapy from onset of type 1 diabetes: late follow-up results of the Pediatric Onset Study. *Pediatr Diabetes* 2012; 13:515-8.	SAP versus Insulin Pump
Lagarde WH, Barrows FP, Davenport ML, Kang M, et al. Continuous subcutaneous glucose monitoring in children with type 1 diabetes mellitus: A single-blind, randomized, controlled trial. Pediat Diabetes 2006;3:159-64.	Intermittent CGM
Lee SW, Sweeney T, Clausen D, Kolbach C, Hassen A, Firek A, et al. Combined insulin pump therapy with real-time continuous glucose monitoring significantly improves glycemic control compared to multiple daily injection therapy in pump naive patients with type 1 diabetes; single center pilot study experience. *J Diabetes Sci Technol* 2007; 1:400-4.	SAP versus Insulin Pump
Logtenberg SJJ, Kleefstra N, Groenier KH, et al. Use of short-term real-time continuous glucose monitoring in type 1 diabetes patients on continuous intraperitoneal insulin infusion: A feasibility study. Diabetes Technol Ther 2009;5:293–9.	Inadequate duration
Ludvigsson J, Hanas R. Continuous subcutaneous glucose monitoring improved metabolic control in pediatric patients with type 1 diabetes: A controlled crossover study. Pediatrics 2003;5:933–8.	Intermittent CGM
Ly TT, Nicholas JA, Retterath A, Lim EM, Davis EA, Jones TW. Effect of sensor-augmented insulin pump therapy and automated insulin suspension vs standard insulin pump therapy on hypoglycemia in patients with type 1 diabetes: a randomized clinical trial. JAMA. 2013;310:1240-7.	No comparison CGM versus SMBG
Murphy HR, Rayman G, Lewis K, et al. Effectiveness of continuous glucose monitoring in pregnant women with diabetes: Randomised clinical trial. BMJ 2008;7675:907-10.	Intermittent CGM
New JP, Ajjan 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; 32:609-17.	Inadequate duration

Study	Reason for Exclusion
Newman SP, Cooke D, Casbard A, et al. A randomised controlled trial to compare minimally invasive glucose monitoring devices with conventional monitoring in the management of insulin-treated diabetes mellitus (MITRE). Health Technol Assess 2009;13:iii-iv, ix-xi, 1-194.	Intermittent CGM
Nørgaard K, Scaramuzza A, Bratina N, Lalić NM, Jarosz-Chobot P, Kocsis G, Jasinskiene E, De Block C, Carrette O, Castañeda J, Cohen O; Interpret Study Group. Routine sensor-augmented pump therapy in type 1 diabetes: the INTERPRET study. Diabetes Technol Ther. 2013;15:273-80.	Not RCT
Peyrot M, Rubin RR. Patient-reported outcomes for an integrated real-time continuous glucose monitoring/insulin pump system. *Diabetes Technol Ther* 2009; 11:57-62.	SAP versus Insulin Pump
Phillip M, Battelino T, Atlas E, Kordonouri O, Bratina N, Miller S, Biester T, Stefanija MA, Muller I, Nimri R, Danne T. Nocturnal glucose control with an artificial pancreas at a diabetes camp. N Engl J Med. 2013;368:824-33.	No comparison CGM versus SMBG
Raccah D, Sulmont V, Reznik Y, Guerci B, Renard E, Hanaire H, et al. Incremental value of continuous glucose monitoring when starting pump therapy in patients with poorly controlled type 1 diabetes: The RealTrend study. *Diabetes Care* 2009; 32:2245-50.	SAP versus Insulin Pump
Radermecker RP, Saint Remy A, Scheen AJ, Bringer J, Renard E. Continuous glucose monitoring reduces both hypoglycaemia and HbA1c in hypoglycaemia-prone type 1 diabetic patients treated with a portable pump. *Diabetes Metab* 2010; 36:409-13.	SAP versus Insulin Pump
Rowen M, Schneider DJ, Pratley RE, Sobel BE. On rendering continuous glucose monitoring ready for prime time in the cardiac care unit. Coron Artery Dis 2007; 18:405-9.	Non-ambulatory care setting
Rubin RR, Peyrot M. Health-related quality of life and treatment satisfaction in the sensor-augmented pump therapy for A1C teduction 3 (STAR 3) trial. *Diabetes Technol Ther* 2012; 14:143-51.	SAP versus Insulin Pump
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;36:1877-83.	Intermittent CGM
Tanenberg R, Bode B, Lane W, Levetan C, Mestman J, Harmel AP, et al. Use of the Continuous Glucose Monitoring System to guide therapy in patients with insulin-treated diabetes: a randomized controlled trial. Mayo Clinic Proc 2004;79:1521-6.	Intermittent CGM
Tumminia A, Crimi S, Sciacca L, Buscema M, Frittitta L, Squatrito S, et al. Efficacy of REAL-Time continuous glucose monitoring on glycemic control and glucose variability in Type 1 diabetic patients treated with either insulin pumps or multiple insulin injection therapy: a randomized controlled cross-over trial. Diabetes Metab Res Rev. 2014.	Intermittent CGM
Vigersky RA, Fonda SJ, Chellappa M, Walker MS, Ehrhardt NM. Short- and long-term effects of real-time continuous	Intermittent CGM

Study	Reason for Exclusion
glucose monitoring in patients with type 2 diabetes. Diabetes Care 2012;35:32-8.	
Weinzimer S, Xing D, Tansey M, et al. FreeStyle navigator continuous glucose monitoring system use in children with type 1 diabetes using glargine-based multiple daily dose regimens: Results of a pilot trial diabetes research in children network (DirecNet) study group. Diabetes Care 2008;3:525-7.	No control group
Wilhelm B, Forst S, Weber MM, Larbig M, Pfutzner A, Forst T. Evaluation of CGMS during rapid blood glucose changes in patients with type 1 diabetes. Diabetes Technol Ther 2006;2:146-5.	No control group
Wysocki T. Youth and parent satisfaction with clinical use of the GlucoWatch G2 Biographer in the management of pediatric type 1 diabetes. Diabetes Care 2005;8:1929-35.	GlucoWatch
Yates K, Milton AH, Dear K, Ambler G. Continuous glucose monitoring-guided insulin adjustment in children and adolescents on near-physiological insulin regimens: A randomized controlled trial. Diabetes Care 2006;7:1512-7.	No comparison CGM versus SMBG
Yogev Y, Ben-Haroush A, Chen R, Kaplan B, Phillip M, Hod M. Continuous glucose monitoring for treatment adjustment in diabetic pregnancies--a pilot study. Diabet Med 2003;20:558-62.	Not RCT
Yogev Y, Chen R, Ben-Haroush A, Phillip M, Jovanovic L, Hod M. Continuous glucose monitoring for the evaluation of gravid women with type 1 diabetes mellitus. Obstet Gynecol 2003;101:633-8.	Not RCT
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;82:73-9.	Non-insulin-treated patients included
Zick R, Petersen B, Richter M, Haug C. Comparison of continuous blood glucose measurement with conventional documentation of hypoglycemia in patients with Type 2 diabetes on multiple daily insulin injection therapy. Diabetes Technol Ther 2007;9:483-92.	Inadequate duration
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(4):795-800. doi:10.2337/dc10-1989.	Freestyle Navigator used and it is now obsolete from the US market.
Mauras N, Beck R, Xing D, et al. A Randomized Clinical Trial to Assess the Efficacy and Safety of Real-Time Continuous Glucose Monitoring in the Management of Type 1 Diabetes in Young Children Aged 4 to <10 Years. *Diabetes Care*. 2012;35(2):204-210. doi:10.2337/dc11-1746.	Freestyle Navigator used as one of the devices and it is now obsolete from the US market
Riveline J-P, Schaepelynck P, Chaillous L, et al. Assessment of Patient-Led or Physician-Driven Continuous Glucose Monitoring in Patients with Poorly Controlled Type 1 Diabetes Using Basal-Bolus Insulin Regimens: A 1-year multicenter study. *Diabetes Care*. 2012;35(5):965-971. doi:10.2337/dc11-2021.	Freestyle Navigator used and it is now obsolete from the US market.

Study	Reason for Exclusion
Deiss D, Bolinder J, Riveline J-P, Battelino T, Bosi E, Tubiana-Rufi N, Kerr D, Phillip M. Improved Glycemic Control in Poorly Controlled Patients with Type 1 Diabetes Using Real-Time Continuous Glucose Monitoring. Diabetes Care Dec 2006, 29 (12) 2730-2732; **doi:** 10.2337/dc06-1134	Guardian RT used and it is now obsolete from the US market

JAMA | Original Investigation

Effect of Continuous Glucose Monitoring on Glycemic Control in Adults With Type 1 Diabetes Using Insulin Injections
The DIAMOND Randomized Clinical Trial

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IMPORTANCE Previous clinical trials showing the benefit of continuous glucose monitoring (CGM) in the management of type 1 diabetes predominantly have included adults using insulin pumps, even though the majority of adults with type 1 diabetes administer insulin by injection.

OBJECTIVE To determine the effectiveness of CGM in adults with type 1 diabetes treated with insulin injections.

DESIGN, SETTING, AND PARTICIPANTS Randomized clinical trial conducted between October 2014 and May 2016 at 24 endocrinology practices in the United States that included 158 adults with type 1 diabetes who were using multiple daily insulin injections and had hemoglobin A_{1c} (HbA_{1c}) levels of 7.5% to 9.9%.

INTERVENTIONS Random assignment 2:1 to CGM (n = 105) or usual care (control group; n = 53).

MAIN OUTCOMES AND MEASURES Primary outcome measure was the difference in change in central-laboratory–measured HbA_{1c} level from baseline to 24 weeks. There were 18 secondary or exploratory end points, of which 15 are reported in this article, including duration of hypoglycemia at less than 70 mg/dL, measured with CGM for 7 days at 12 and 24 weeks.

RESULTS Among the 158 randomized participants (mean age, 48 years [SD, 13]; 44% women; mean baseline HbA_{1c} level, 8.6% [SD, 0.6%]; and median diabetes duration, 19 years [interquartile range, 10-31 years]), 155 (98%) completed the study. In the CGM group, 93% used CGM 6 d/wk or more in month 6. Mean HbA_{1c} reduction from baseline was 1.1% at 12 weeks and 1.0% at 24 weeks in the CGM group and 0.5% and 0.4%, respectively, in the control group (repeated-measures model $P < .001$). At 24 weeks, the adjusted treatment-group difference in mean change in HbA_{1c} level from baseline was −0.6% (95% CI, −0.8% to −0.3%; $P < .001$). Median duration of hypoglycemia at less than <70 mg/dL was 43 min/d (IQR, 27-69) in the CGM group vs 80 min/d (IQR, 36-111) in the control group ($P = .002$). Severe hypoglycemia events occurred in 2 participants in each group.

CONCLUSIONS AND RELEVANCE Among adults with type 1 diabetes who used multiple daily insulin injections, the use of CGM compared with usual care resulted in a greater decrease in HbA_{1c} level during 24 weeks. Further research is needed to assess longer-term effectiveness, as well as clinical outcomes and adverse effects.

TRIAL REGISTRATION clinicaltrials.gov Identifier: NCT02282397

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Group Information: The DIAMOND Study Group members are listed at the end of this article.

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Only approximately 30% of individuals with type 1 diabetes meet the American Diabetes Association goal of hemoglobin A_{1c} (HbA_{1c}) level of 7.5% (58 mmol/mol) for children (<18 years) and 7.0% (53 mmol/mol) for adults (≥18 years),[1] indicating the need for better approaches to diabetes management. Continuous glucose monitoring (CGM) with glucose measurements as often as every 5 minutes, plus low and high glucose level alerts and glucose trend information, has the capability of better informing diabetes management decisions than blood glucose meter testing performed several times a day. Randomized clinical trials have demonstrated the benefit of CGM in adults with type 1 diabetes, but not consistently in children, to improve glycemic control as measured by HbA_{1c} level and to reduce hypoglycemia.[2-6] These previous trials have either completely or predominantly included insulin pump users,[2,4,5] although the majority of adults with type 1 diabetes deliver insulin via injections.[7,8]

Only a small proportion of individuals with type 1 diabetes who inject insulin use CGM, although the limited available observational data suggest that the glycemic benefit may be comparable to that for pump users. In T1D Exchange registry 2015 data, mean HbA_{1c} level in the 410 adult insulin injecters using CGM was similar to that in 2316 pump users using CGM (7.6% vs 7.7%, respectively) and lower than mean HbA_{1c} level in the 6222 injection users not using CGM (7.6% vs 8.8%; $P < .001$).[9]

Whether individuals receiving insulin injections would be willing to regularly wear CGM sensors and would derive glycemic benefits from CGM needs investigation. Accordingly, this randomized multicenter clinical trial was conducted to evaluate the effect of CGM in adults with type 1 diabetes who have elevated HbA_{1c} levels and use multiple daily injections of insulin.

Key Points

Question For adults with type 1 diabetes who are using multiple daily insulin injections, does continuous glucose monitoring improve hemoglobin A_{1c} (HbA_{1c}) levels compared with self-monitored blood glucose management?

Findings In a randomized clinical trial of 158 adults with type 1 diabetes, there was a significantly greater decrease in HbA_{1c} level during 24 weeks with continuous glucose monitoring vs usual care (−1.0% vs −0.4%).

Meaning Continuous glucose monitoring resulted in better glycemic control compared with usual care, but further research is needed to assess clinical outcomes, as well as effectiveness, in a typical clinical population.

Methods

The trial was conducted at 24 endocrinology practices in the United States (19 community-based and 5 academic centers). The protocol and Health Insurance Portability and Accountability Act–compliant informed consent forms were approved by institutional review boards (central commercial board for 17 sites and local boards for the other 7 sites). Written informed consent was obtained from each participant. The protocol is provided online and the statistical analysis plan is available in Supplement 1.

Study Participants

Major eligibility criteria included age 25 years or older, diagnosis of type 1 diabetes treated for at least 1 year with multiple daily insulin injections, central laboratory–measured HbA_{1c} level of 7.5% to 10.0%, no home use of a personal CGM device in the 3 months before the trial, and a negative pregnancy test for women of childbearing potential (eTable 1 in Supplement 2 has a complete listing of the inclusion and exclusion criteria).

Synopsis of Study Design

Each participant was required to complete a 2-week prerandomization phase using a CGM system that was configured to record glucose concentrations not visible to the participant (referred to as a "blinded" CGM). Eligibility required that the blinded CGM be worn on at least 85% of possible days, the CGM be calibrated at least 2 times per day, and blood glucose meter testing (with a study-provided meter and test strips) be performed at least 3 times daily. Fourteen participants did not meet these criteria and did not continue into the randomized trial (**Figure 1**). One participant had a sudden death during the prerandomization phase.

On the study website, after verification of eligibility from data entered, each participant was assigned randomly from a computer-generated sequence to either the CGM or control group in a 2:1 ratio, with a permuted block design (block sizes of 3 and 6) stratified by HbA_{1c} level (<8.5% and ≥8.5%). A 2:1 randomization was used rather than 1:1 to provide a larger sample size for a separate follow-on randomized trial assessing glycemic benefits of initiating pump therapy in CGM users using insulin injections.

Participants in the CGM group were provided with a CGM system (Dexcom G4 Platinum CGM System with an enhanced algorithm, software 505, Dexcom Inc) that measured glucose concentrations from interstitial fluid in the range of 40 to 400 mg/dL every 5 minutes for up to 7 days. Participants in both groups were provided with a Bayer Contour Next USB meter and test strips. The CGM group was instructed to use the CGM daily, calibrate the CGM twice daily, and verify the CGM glucose concentration with the blood glucose meter before injecting insulin (as per the regulatory labeling of the device at the time the trial was conducted). General guidelines were provided to participants about using CGM, and individualized recommendations were made by their clinician about incorporating CGM trend information into their diabetes management. The control group was asked to perform home blood glucose monitoring at least 4 times daily. Participants in both groups were provided general diabetes management education, and clinicians were encouraged to review downloaded glucose data at each visit to inform treatment recommendations, which were at clinician discretion and not prescriptive in the protocol. eTable 2 in Supplement 2 describes the participant education as well as guidelines for clinicians. CGM guidelines for participants are included in Supplement 1.

Follow-up visits for both treatment groups occurred after 4, 12, and 24 weeks. The CGM group had an additional visit 1 week after randomization. The control group had 2 additional visits 1 week before the 12- and 24-week visits, at which a CGM sensor in blinded mode was inserted to collect glucose data for 1 week. Telephone contacts for both groups occurred 2 and 3 weeks after randomization.

Hemoglobin A_{1c} level was measured at baseline, 12 weeks, and 24 weeks at the Northwest Lipid Research Laboratories, University of Washington, Seattle, with the Diabetes Control and Complications Trial standardized analyzer (TOSOH, Biosciences Inc).

Outcomes

The primary outcome was change in the central laboratory-measured HbA_{1c} level. Prespecified secondary outcomes included percentage of participants with HbA_{1c} level less than 7.0%; CGM-measured time in range (70-180 mg/dL), duration of hypoglycemia (<70 mg/dL, <60 mg/dL, and <50 mg/dL), duration of hyperglycemia (>180 mg/dL, >250 mg/dL, and >300 mg/dL), and glucose variability (coefficient of variation); change in hypoglycemia unawareness[10]; and change in frequency of blood glucose meter testing (longitudinal changes in blood glucose meter testing were not assessed). Prespecified exploratory outcomes included CGM-measured mean glucose concentration and the following binary HbA_{1c} outcomes to assist in translation of the primary HbA_{1c} analysis to a participant level: HbA_{1c} level less than 7.5% and relative HbA_{1c} reduction greater than or equal to 10%. Post hoc outcomes included HbA_{1c} reduction of 1% or more, HbA_{1c} level less than 7.0% or reduction of 1% or more, CGM-measured area above the curve 70 mg/dL and area under the curve 180 mg/dL, change in insulin dose, and change in body weight.

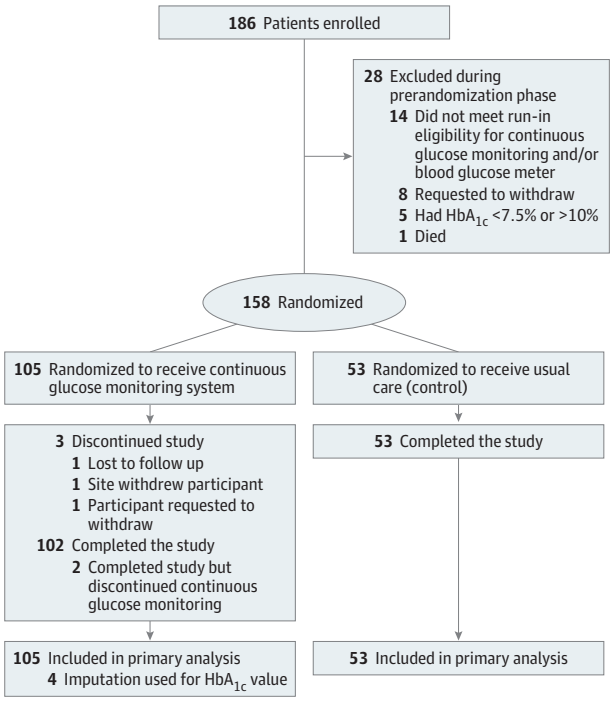
Satisfaction with CGM was assessed by completion at 24 weeks of the CGM Satisfaction Survey (44 items on a 1-5 Likert scale, with the computed score representing the mean of the 44 items and subscales of benefits and lack of hassles).[11] Quality-of-life and health economic outcomes will be reported in separate articles.

Safety outcomes included severe hypoglycemia (defined as an event that required assistance from another person to administer carbohydrate, glucagon, or other resuscitative actions), diabetic ketoacidosis, and serious adverse events regardless of causality.

Statistical Methods

A sample size of 147 for the 2:1 randomization was calculated to have 90% power to detect a difference in mean HbA_{1c} level between treatment groups, assuming a population difference of 0.4%, standard deviation of the 24-week values of 0.7 adjusted for the correlation between baseline and 24-week values (based on data from the Juvenile Diabetes Research Foundation CGM randomized trial[5]), and a 2-sided α level of .05. Sample size initially was increased to 169 to account for potential loss to follow-up. When it was recognized by the coordinating center that the trial completion rate was higher than anticipated, the recruitment goal was changed to a minimum of 150, with the approval of the steering committee and the sponsor.

Figure 1. Flowchart of Continuous Glucose Monitoring Study Completion



All enrolled participants started the run-in phase; 28 did not proceed to randomization for the reasons indicated in the figure. The number eligible for screening who did not sign the informed consent form was not recorded.

Analyses followed the intent-to-treat principle. The following change was made from the protocol and statistical analysis plan before the data lock: the primary analysis was a treatment group comparison of the change in HbA_{1c} level from baseline to 24 weeks, adjusted for baseline HbA_{1c} level and clinical site as a random effect, in a repeated-measures linear model in the protocol and with analysis of covariance in the statistical analysis plan; both are reported in this article. Confounding was assessed by repeating the analysis, including potential confounding variables as covariates. The Rubin method was used to impute for missing data.[12] Exploratory analyses were conducted to assess for interaction between the treatment effect on the change in HbA_{1c} level from baseline to 24 weeks and baseline factors by including interaction terms in analysis of covariance models. The following changes were made from the protocol and statistical analysis plan during the peer-review process: in post hoc analyses, binary HbA_{1c} outcomes were evaluated with propensity scores[13] instead of logistic regression, adjusted for baseline HbA_{1c} level and clinical site; and for secondary, exploratory, and post hoc analyses, 99% CIs instead of 95% CIs are reported.

For CGM outcomes, treatment group comparisons using the CGM data collected in each group for 7 days at 12 and 24 weeks were made with analysis of covariance models based on ranks using van der Waerden scores if the metric was

Table 1. Baseline Participant Characteristics

	Group, No. (%)	
	CGM (n = 105)	Control (n = 53)
Age, y		
25-<45	53 (50)	16 (30)
45-<60	32 (30)	23 (43)
≥60	20 (19)	14 (26)
Mean (SD) [range]	46 (14) [26-72]	51 (11) [26-73]
Diabetes duration, median (IQR), y	19 (9-29)	19 (11-35)
Female sex	47 (45)	23 (43)
Highest education[a]		
<Bachelor's degree	47 (47)	22 (43)
Bachelor's degree	43 (43)	19 (37)
Graduate degree	10 (10)	10 (20)
BMI, mean (SD)	28 (6)	27 (5)
Weight, mean (SD), kg	84 (20)	81 (18)
HbA_{1c}, %		
7.5-<8.5	47 (45)	24 (45)
8.5-≤9.9	58 (55)	29 (55)
Mean (SD) [range]	8.6 (0.7) [7.5-9.9]	8.6 (0.6) [7.5-9.9]
Self-reported No. of self-monitoring blood glucose tests per day, mean (SD)	3.9 (1.3)	4.1 (1.6)
Event in previous 12 mo		
≥1 Severe hypoglycemia	8 (8)	9 (17)
≥1 Diabetic ketoacidosis	1 (<1)	1 (2)
Use of noninsulin glucose-lowering medication	8 (8)	4 (8)
Total daily insulin dose, median (IQR), U/kg/d	0.7 (0.5-0.9)	0.6 (0.5-0.9)
No. of long-acting insulin injections per day		
1	78 (74)	34 (64)
2	26 (25)	19 (36)
3	1 (<1)	0
No. of rapid-acting insulin injections per day		
2	0	1 (2)
3	71 (68)	32 (60)
4	23 (22)	15 (28)
≥5	11 (10)	5 (9)
CGM use previously	17 (16)	9 (17)

Abbreviations: BMI, body mass index (calculated as weight in kilograms divided by height in meters squared); CGM, continuous glucose monitoring; HbA_{1c}, hemoglobin A_{1c}; IQR, interquartile range.

SI Conversions: to convert HbA_{1c} to the SI units of mmol/mol, multiply the HbA_{1c} percentage value × 10.93 and subtract 23.5 from the product.

[a] Education data missing for 5 in the CGM group and 2 in the control group.

skewed, adjusted for the corresponding baseline value, baseline HbA_{1c} level, and clinical site as a random effect. Similar analyses were performed separately for daytime and nighttime. Frequency of blood glucose monitoring was compared between groups with an analysis of covariance model, adjusted for the baseline frequency and clinical site as a random effect.

Statistical methods for other analyses are described in table footnotes. Standard deviations are reported for means and interquartile ranges (IQRs) for medians where applicable. Reported point estimates are unadjusted unless otherwise noted. Analyses were conducted with SAS version 9.4. All *P* values are 2 sided. $P < .05$ was considered significant for the primary analysis and $P < .01$ for all other analyses to account for multiple comparisons (with 99% CIs accordingly provided).

SI Unit Conversions

Throughout, to convert HbA_{1c} to the SI units of mmol/mol, multiply the HbA_{1c} percentage value × 10.93 and subtract 23.5 from the product. For example, an HbA_{1c} value of 7.0% corresponds to 53 mmol/mol. To convert glucose to mmol/L, multiply the values × 0.0555.

Results

Between October 2014 and December 2015, 158 participants were assigned to the CGM group (n = 105) or control group (n = 53). Mean age was 48 years (SD, 13) (range, 26-73 years, with 34 participants [22%] ≥60 years); 44% were women. Median diabetes duration was 19 years (IQR, 10-31 years), and mean baseline HbA_{1c} level was 8.6% (SD, 0.6%; range, 7.5%-9.9%). Participant characteristics according to randomized group are shown in **Table 1.**

The 24-week primary study outcome visit was completed by 102 participants (97%) in the CGM group and all 53 (100%) in the control group (Figure 1). Overall visit completion was 99% and 98%, respectively. Three participants in the CGM group (4 total visits) and 3 in the control group (3 total visits) had additional visits, not required in the protocol, for diabetes management.

Among the 102 participants in the CGM group who completed the trial, median CGM use was 7.0 d/wk (IQR, 7.0-7.0) at 4, 12, and 24 weeks; only 2 (2%) discontinued CGM before the 24-week visit. During month 6 (weeks 21-24), CGM use was 6 or more d/wk for 93% of the 102 participants (eTable 3 in Supplement 2). No participant in the control group initiated unblinded CGM use before the primary outcome.

According to meter downloads, mean blood glucose self-monitoring was 5.1 tests per day (SD, 1.8) in the CGM group and 5.1 tests per day (SD, 1.4) in the control group during the baseline period of blinded CGM wear and 3.6 tests per day (SD, 1.6) and 4.6 tests per day (SD, 1.6), respectively, at 24 weeks (adjusted mean difference for the change, -1.0; 99% CI, -1.7 to -0.4; $P < .001$).

Glycemic Control and Other Outcomes

Primary Outcome

Mean reduction in HbA_{1c} level from baseline was 1.1% at 12 weeks and 1.0% at 24 weeks in the CGM group and 0.5% and 0.4%, respectively, in the control group (primary analysis repeated-measures $P < .001$). At 24 weeks, the adjusted treatment group difference in mean change in HbA_{1c} level was -0.6% (95% CI, -0.8% to -0.3%; $P < .001$) (**Table 2**). For each treatment group, baseline and 24-week HbA_{1c} values for each

Table 2. Primary Outcome and Hemoglobin A_{1c} Outcomes at 12 and 24 Weeks[a]

	12 Weeks		24 Weeks			
	CGM Group (n = 103)	Control Group (n = 52)	CGM Group (n = 105)[b]	Control Group (n = 53)	Between-Group Difference[c,d]	*P* Value[c,d]
Primary outcome, mean (SD), %					Mean adjusted difference, % (95% CI)	
HbA_{1c}	7.6 (0.7)	8.1 (0.7)	7.7 (0.8)	8.2 (0.8)		
Change in HbA_{1c} from baseline	−1.1 (0.7)	−0.5 (0.7)	−1.0 (0.8)	−0.4 (0.7)	−0.6 (−0.8 to −0.3)	<.001
Prespecified secondary outcome, No. (%)					Mean adjusted difference, % (99% CI)	
HbA_{1c} <7.0%	14 (14)	2 (4)	18 (18)	2 (4)	15 (0 to 30)	.01
Prespecified exploratory outcomes, No. (%)						
HbA_{1c} <7.5%	49 (48)	6 (12)	39 (38)	6 (11)	31 (12 to 51)	<.001
Relative reduction in HbA_{1c} ≥10%	62 (60)	12 (23)	58 (57)	10 (19)	37 (16 to 58)	<.001
Post hoc outcomes, No. (%)						
Reduction in HbA_{1c} ≥1%	55 (53)	12 (23)	53 (52)	10 (19)	33 (11 to 54)	<.001
Reduction in HbA_{1c} ≥1% or HbA_{1c} <7.0%	57 (55)	12 (23)	53 (52)	11 (21)	31 (9 to 52)	<.001

Abbreviations: CGM, continuous glucose monitoring; HbA_{1c}, hemoglobin A_{1c}.

SI Conversion: to convert HbA_{1c} to the SI units of mmol/mol, multiply the HbA_{1c} percentage value × 10.93 and subtract 23.5 from the product.

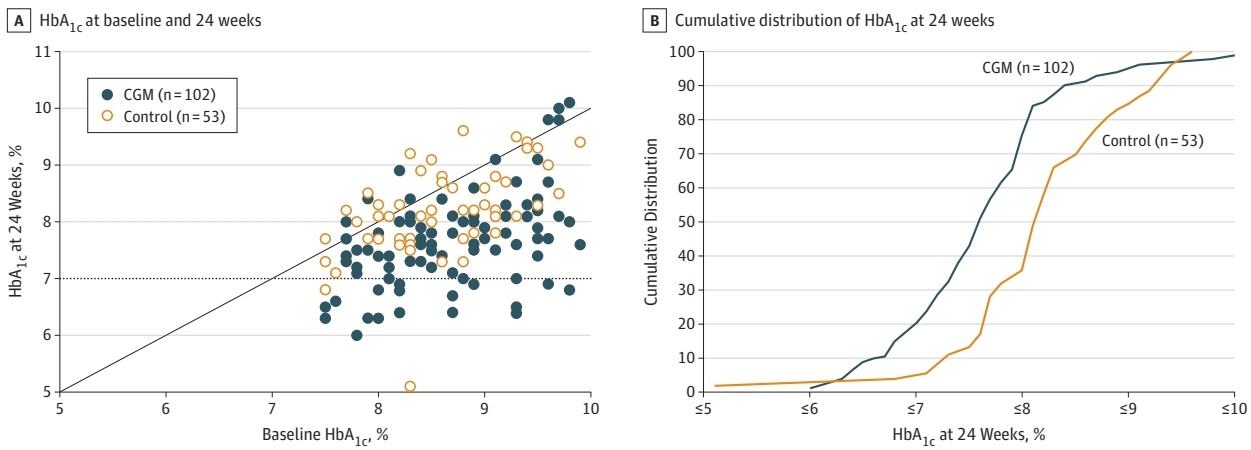
[a] Mean baseline HbA_{1c} level was 8.6% in each group. For all analyses, missing HbA_{1c} values in which the central laboratory value was missing but the local laboratory value was known were imputed with a regression line based on the site's local HbA_{1c} measurements (CGM/control: 1/0 at 12 weeks; 1/0 at 24 weeks).

[b] For the 24-week primary outcome only, the Rubin method was used to impute missing HbA_{1c} values when both the central and local laboratory values were missing (3 in the CGM group and 0 in the control group). For the secondary, exploratory, and post hoc analyses, n = 102.

[c] For the primary analysis, treatment group comparisons were made with analysis of covariance models, adjusted for baseline HbA_{1c} level and clinical site as a random effect. Model residuals were verified to have an approximate normal distribution.

[d] For the secondary, exploratory, and post hoc outcomes, treatment group comparisons were made with propensity scores, adjusted for baseline HbA_{1c} level and clinical site. $P < .01$ was considered significant to account for multiple comparisons (with 99% CIs accordingly provided).

Figure 2. Hemoglobin A_{1c} Values at Baseline and 24 Weeks, by Group



A, Scatterplot of 24-week hemoglobin A_{1c} (HbA_{1c}) levels by baseline HbA_{1c} level. The horizontal line at 7.0% represents the American Diabetes Association HbA_{1c} goal for adults with type 1 diabetes. Points below the diagonal line represent cases in which the 24-week HbA_{1c} level was lower than the baseline HbA_{1c} level, points above the diagonal line represent cases in which the 24-week HbA_{1c} level was higher than the baseline HbA_{1c} level, and points on the diagonal line represent cases in which the 24-week and baseline HbA_{1c} values were the same. B, Cumulative distribution of 24-week HbA_{1c} values. For any given 24-week HbA_{1c} level, the percentage of cases in each treatment group with an HbA_{1c} value at that level or lower can be determined from the figure. To convert HbA_{1c} to the SI units of mmol/mol, multiply the HbA_{1c} percentage value × 10.93 and subtract 23.5 from the product.

participant are shown in **Figure 2**A, and the cumulative distribution of the 24-week HbA_{1c} values is shown in Figure 2B.

Secondary, Exploratory, and Post Hoc HbA_{1c} Outcomes

The greater HbA_{1c} improvement in the CGM group also was reflected in multiple participant-level secondary, exploratory, and post hoc HbA_{1c} outcomes (Table 2). There was no significant interaction of the effect of treatment on 24-week HbA_{1c} level according to baseline HbA_{1c}, age, education level, or type of site (eTable 4 in Supplement 2).

Secondary and Exploratory CGM Outcomes

As secondary outcomes, CGM metrics for time in the range of 70 to 180 mg/dL, hyperglycemia, hypoglycemia, and glycemic

Table 3. Continuous Glucose Monitoring Metrics

	Baseline		12 and 24 Weeks Pooled[a]			
	CGM Group (n = 105)	Control Group (n = 53)	CGM Group (n = 103)	Control Group (n = 53)	Mean Adjusted Difference (99% CI)[b]	*P* Value[b]
Hours of data, mean (SD)	322 (50)	325 (51)	301 (41)	301 (54)		
Prespecified secondary outcomes						
Glucose variability: coefficient of variation, mean (SD), %	42 (7)	42 (7)	38 (6)	42 (7)	−4 (−6 to −2)	<.001
Minutes per day in range 70-180 mg/dL, mean (SD)	660 (179)	650 (170)	736 (206)	650 (194)	77 (6 to 147)	.005
Hypoglycemia, median (IQR)						
Minutes per day <70 mg/dL	65 (33 to 103)	72 (35 to 136)	43 (27 to 69)	80 (36 to 111)		.002
Minutes per day <60 mg/dL	32 (15 to 61)	39 (15 to 78)	20 (9 to 30)	40 (16 to 68)		.002
Minutes per day <50 mg/dL	13 (5 to 29)	18 (4 to 39)	6 (2 to 12)	20 (4 to 42)		.001
Hyperglycemia, median (IQR)						
Minutes per day >180 mg/dL	687 (554 to 810)	725 (537 to 798)	638 (503 to 807)	740 (625 to 854)		.03
Minutes per day >250 mg/dL	301 (190 to 401)	269 (184 to 383)	223 (128 to 351)	347 (241 to 429)		<.001
Minutes per day >300 mg/dL	129 (66 to 201)	109 (71 to 204)	78 (36 to 142)	167 (89 to 226)		<.001
Prespecified exploratory outcome						
Mean glucose, mean (SD), mg/dL	187 (27)	186 (30)	180 (27)	189 (25)	−9 (−19 to 0)	.01
Post hoc outcomes, median (IQR)[c]						
Area above curve 70 mg/dL	0.5 (0.3 to 1.1)	0.7 (0.2 to 1.4)	0.3 (0.2 to 0.5)	0.7 (0.2 to 1.3)		<.001
Area under curve 180 mg/dL	34 (25 to 46)	33 (26 to 45)	27 (17 to 40)	40 (31 to 51)		<.001

Abbreviations: CGM, continuous glucose monitoring; IQR, interquartile range.

SI Conversion: to convert glucose to mmol/L, multiply the values × 0.0555.

[a] Excludes 2 participants in the CGM group with less than 72 hours of data (a prespecified condition).

[b] Treatment group comparisons made with analysis of covariance models, adjusted for the corresponding baseline value, baseline hemoglobin A_{1c} level, and clinical site as a random effect, using pooled data from 12 and 24 weeks. Because of skewed distributions for the hypoglycemia and hyperglycemia metrics (including area above the curve 70 mg/dL and area below the curve 180 mg/dL), these models were based on ranks using van der Waerden scores. $P < .01$ was considered significant to account for multiple comparisons (with 99% CI accordingly provided for the metrics that are approximately normally distributed).

[c] Area above (the glucose) curve 70 mg/dL reflects both percentage and severity of glucose values in the hypoglycemic range. Area under (the glucose) curve 180 mg/dL is the analogous measure for hyperglycemia.

variability favored the CGM group compared with the control group (**Table 3**, eTable 5 in Supplement 2). In exploratory analyses, hypoglycemia treatment group differences favored the CGM group during both daytime and nighttime, but hyperglycemia treatment group differences favoring the CGM group were present only during the daytime (eTables 6 and 7 in Supplement 2).

Other Analyses

At 24 weeks, in post hoc analyses there were no significant differences between the CGM group and control group in median change in total daily insulin dose per kilogram of body weight (-0.02 vs 0.03 U/kg; $P = .23$), median ratio of long-acting to rapid-acting daily insulin dose (0.9 vs 1.0; $P = .54$), proportion of participants with an increase in number of injections of rapid-acting insulin per day (26% vs 26%; $P = .90$), or mean change in body weight (1.7 vs 0.7 kg; mean difference, 1.0 kg; 99% CI, -0.7 to 2.8; $P = .12$) (eTable 8 in Supplement 2). Clarke Hypoglycemia Unawareness scores did not differ between groups (mean difference, -0.1; 99% CI, -0.7 to 0.5; $P = .64$).

Severe Hypoglycemia and Other Adverse Events

Severe hypoglycemic events occurred in 2 participants in each group ($P = .67$). There were no occurrences of diabetic ketoacidosis. Other serious adverse events, unrelated to the study intervention, occurred in 2 participants in the CGM group and none in the control group (eTable 9 in Supplement 2).

CGM Satisfaction

In the CGM group, satisfaction with use of CGM was high, as indicated by the mean (SD) score of 4.2 (0.4) on the CGM Satisfaction Survey, with mean (SD) scores of 4.2 (0.5) on the benefits subscale and 4.3 (0.5) on the subscale for lack of hassles (eTable 10 in Supplement 2).

Discussion

Among adults with type 1 diabetes using multiple daily insulin injections, the use of CGM compared with usual care resulted in a greater decrease in HbA_{1c} level during 24 weeks. The HbA_{1c} benefit in the CGM group was consistently present across the age range of 26 to 73 years, the baseline HbA_{1c} level range of 7.5% to 9.9%, and all education levels. In addition, CGM use was associated with a high degree of participant satisfaction with CGM, increased time with glucose concentrations between 70 and 180 mg/dL, decreased time with glucose concentrations less than 70 mg/dL, and decreased glycemic variability, measured with the coefficient

of variation. The trial was not designed to demonstrate a benefit in reducing clinical severe hypoglycemia events, and the low event rate in the control group precluded a meaningful analysis. However, less biochemical hypoglycemia, as was observed in the trial, has been associated with a lower risk for subsequent severe hypoglycemic events[14,15] and improved quality of life.[16-18]

The amount of CGM use by the participants was high (median CGM use 7 d/wk in month 6) despite a protocol approximating usual practice, with only 1 visit after week 4 and no visits or other protocol-specified contacts between 12 and 24 weeks. The amount of use was similar to or greater than the frequency of use in pump-using adults with type 1 diabetes in previous trials and observational studies,[2-5,19] which could be related to CGM accuracy being significantly improved from the generation of sensors in previous trials.[20-22] The observed benefits of CGM occurred despite the CGM group's having significantly less blood glucose meter testing per day than the control group.

The magnitude of benefit of CGM on HbA_{1c} levels relative to control in this trial of insulin injection users is comparable to the magnitude of benefit of CGM observed in pump users in previous randomized trials.[2,4,5] This finding was not a foregone conclusion. Insulin injection users have less flexibility in adjusting their insulin delivery in response to CGM glucose concentrations and trends than do pump users. Basal insulin delivery for pump users is continuous, can be programmed to vary at different times of the day, and can be temporarily changed in response to decreasing or increasing glucose concentrations or planned activities such as exercise. In contrast, injection users have fixed basal insulin based on the absorption of their long-acting insulin and can make adjustments only to rapid-acting insulin boluses.

The strengths of the trial included a high retention rate, high adherence to treatment group assignment, central laboratory measurement of HbA_{1c} level, a protocol approximating usual clinical practice, and participation in the trial by both community-based and academic sites. Assignment to the CGM and control groups could not be blinded because of the nature of the intervention; however, the groups had a similar number of visits. The 0.4% mean improvement in HbA_{1c} level in the control group likely reflects both a study effect related to clinical trial participation and more structured training in using blood glucose monitoring in adjusting insulin regimens than was occurring for these individuals before the study.

This study also had several limitations. In light of the eligibility criteria, the results may not apply to individuals with type 1 diabetes who are younger than 26 years or have HbA_{1c} levels outside the range of 7.5% to 9.9% and should not be applied to individuals with type 2 diabetes who receive multiple daily injections of insulin. The informed consent process and the run-in phase had the potential to exclude individuals who might be less adherent with CGM than the cohort that was studied.

Conclusions

Among adults with type 1 diabetes who use multiple daily insulin injections, the use of CGM compared with usual care resulted in a greater decrease in HbA_{1c} level during 24 weeks. Further research is needed to assess longer-term effectiveness, as well as clinical outcomes and adverse effects.

ARTICLE INFORMATION

Author Contributions: Dr Beck had full access to all the data in the study and takes responsibility for the integrity of the data and the accuracy of the data analysis.
Concept and design: All authors.
Acquisition, analysis, or interpretation of data: All authors.
Drafting of the manuscript: Beck, Riddlesworth.
Critical revision of the manuscript for important intellectual content: All authors.
Statistical analysis: Riddlesworth, Kollman.
Obtained funding: Price.
Administrative, technical, or material support: All authors.
Supervision: All authors.

Conflict of Interest Disclosures: All authors have completed and submitted the ICMJE Form for Disclosure of Potential Conflicts of Interest. Dexcom Inc provided funding for the trial to each investigator's institution. Dr Beck reports receiving a study grant from Dexcom and that his institution received supplies for research from Dexcom and Abbott Diabetes Care for other studies. Dr Ahmann reports receiving grants for the study and consulting for Dexcom Inc; receiving grants for research support from Medtronic, Novo Nordisk, Lexicon, and Sanofi; consulting for Novo Nordisk, Sanofi, and AstraZeneca; and serving on advisory boards for Lilly, Janssen, and AstraZeneca. Dr Bergenstal reports receiving a study grant from Dexcom and NIH; reports serving on the advisory boards for and/or receiving study funding from Abbott Diabetes Care, AstraZeneca, Becton Dickinson, Boehringer Ingelheim, Calibra, Eli Lilly, Halozyme, Hygieia, Johnson & Johnson, Medtronic, Novo Nordisk, Roche, Sanofi, and Takeda; and reports holding stock in Merck. Ms Kruger reports holding stock in Dexcom. Dr McGill reports receiving grant funding from Novartis, Novo Nordisk, Lexicon, Bristol-Myers Squibb, and Dexcom; and consulting fees from Boehringer Ingelheim, Dexcom, Lilly, Merck, Novo Nordisk, Intarcia, Dynavax, Valeritas, Janssen, and Calibra. Dr Polonsky reports consulting for Dexcom. Dr Wolpert reports receiving grant funding from Abbott Diabetes Care. Dr Price is an employee of Dexcom, Inc and reports holding stock in the company. No other disclosures were reported.

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Role of the Funder/Sponsor: Dr Price, a Dexcom employee, participated in the steering committee, which was responsible for designing the study, writing the protocol, reviewing and approving the manuscript, and interpreting the data. Dexcom did not participate in collection, management, analysis, and interpretation of the data; or, except for the role of Dr Price as a coauthor, in the preparation or revision of the manuscript or in the decision to submit the manuscript for publication. Dexcom staff participated in onsite audit visits. All other monitoring was performed by staff of the Jaeb Center for Health Research.

Meeting Presentation: The trial results were presented at the American Diabetes Association meeting, June 12, 2016, New Orleans, Louisiana.

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JAMA | Original Investigation

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

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IMPORTANCE The majority of individuals with type 1 diabetes do not meet recommended glycemic targets.

OBJECTIVE To evaluate the effects of continuous glucose monitoring in adults with type 1 diabetes treated with multiple daily insulin injections.

DESIGN, SETTING, AND PARTICIPANTS Open-label crossover randomized clinical trial conducted in 15 diabetes outpatient clinics in Sweden between February 24, 2014, and June 1, 2016 that included 161 individuals with type 1 diabetes and hemoglobin A_{1c} (HbA_{1c}) of at least 7.5% (58 mmol/mol) treated with multiple daily insulin injections.

INTERVENTIONS Participants were randomized to receive treatment using a continuous glucose monitoring system or conventional treatment for 26 weeks, separated by a washout period of 17 weeks.

MAIN OUTCOMES AND MEASURES Difference in HbA_{1c} between weeks 26 and 69 for the 2 treatments. Adverse events including severe hypoglycemia were also studied.

RESULTS Among 161 randomized participants, mean age was 43.7 years, 45.3% were women, and mean HbA_{1c} was 8.6% (70 mmol/mol). A total of 142 participants had follow-up data in both treatment periods. Mean HbA_{1c} was 7.92% (63 mmol/mol) during continuous glucose monitoring use and 8.35% (68 mmol/mol) during conventional treatment (mean difference, −0.43% [95% CI, −0.57% to −0.29%] or −4.7 [−6.3 to −3.1 mmol/mol]; $P < .001$). Of 19 secondary end points comprising psychosocial and various glycemic measures, 6 met the hierarchical testing criteria of statistical significance, favoring continuous glucose monitoring compared with conventional treatment. Five patients in the conventional treatment group and 1 patient in the continuous glucose monitoring group had severe hypoglycemia. During washout when patients used conventional therapy, 7 patients had severe hypoglycemia.

CONCLUSIONS AND RELEVANCE Among patients with inadequately controlled type 1 diabetes treated with multiple daily insulin injections, the use of continuous glucose monitoring compared with conventional treatment for 26 weeks resulted in lower HbA_{1c}. Further research is needed to assess clinical outcomes and longer-term adverse effects.

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Intensive insulin therapy resulting in good glycemic control has been shown to prevent and reduce the progression of diabetes-related complications in patients with type 1 diabetes.[1] Today, intensive glycemic control is generally achieved through multiple daily insulin injections or continuous subcutaneous insulin infusions through an insulin pump.[2] Regular self-measured capillary blood glucose values have been crucial to optimal insulin dosing for good glycemic control.[3-5]

In recent years, continuous glucose monitoring (CGM) has become an option for optimal insulin dosing and other activities.[6] The advantages of CGM include providing continuous feedback on estimated glucose values and illustrating glucose trends. CGM systems include a subcutaneous sensor with a transmitter attached and continuous reporting of glucose levels and trends to the patient by a handheld monitor.

Data from clinical trials of CGM have been mixed regarding its effect on glycemic control.[7] Such trials have, for example, consisted only of patients with the following characteristics: (1) continuous subcutaneous insulin infusions; (2) initiated CGM and continuous subcutaneous insulin infusions simultaneously; or (3) included patients with both multiple daily insulin injections and continuous subcutaneous insulin infusions.[7-10] Post hoc findings have also been mixed, in that glycemic control appears to differ when CGM is combined with either multiple daily insulin injections or continuous subcutaneous insulin infusions.[8-10] Although the majority of adults with type 1 diabetes in the United States and Europe are treated with multiple daily insulin injections, to our knowledge, clinical trials evaluating CGM vs conventional therapy in persons treated with multiple daily insulin injections have not been performed.

The aim of this study was to analyze the effect of CGM on glycemic control, hypoglycemia, well-being, and glycemic variability in individuals with type 1 diabetes treated with multiple daily insulin injections.

Key Points

Question Does continuous glucose monitoring improve glycemic control in adults with type 1 diabetes treated with multiple daily insulin injections?

Findings In this randomized clinical trial of 161 adults with type 1 diabetes, glycemic control was improved during continuous glucose monitoring compared with conventional treatment (hemoglobin [HbA_{1c}] of 7.92% vs 8.35% [63 vs 68 mmol/mol]). The mean difference in HbA_{1c} was 0.43% (4.7 mmol/mol).

Meaning Continuous glucose monitoring may result in better glycemic control compared with conventional treatment, but further research is needed to assess clinical outcomes and longer-term adverse effects.

Methods

The GOLD trial was approved by the ethics committee at the University of Gothenburg, Gothenburg, Sweden. All participants provided verbal and written informed consent (trial protocol in Supplement 1).

The study was an investigator-initiated randomized, open-label, clinical trial with a crossover design conducted at 15 sites in Sweden. The study took place from February 24, 2014, to June 1, 2016. After a run-in period of up to 6 weeks, patients were randomized to receive CGM or conventional treatment for 26 weeks with a 17-week washout between treatment periods (**Figure 1**).

Screening

Individuals aged 18 years or older with hemoglobin A_{1c} (HbA_{1c}) of at least 7.5% (58 mmol/mol) treated with multiple daily insulin injections were included. Patients were required to have a fasting C-peptide level of less than 0.91 ng/mL (to convert to nmol/L, multiply by 0.331) and diabetes duration of greater than 1 year. Race and ethnicity were classified by the investigator or other research staff; if there was any uncertainty, the final decision was made in collaboration with the participant.

Patients treated with insulin pumps were excluded. The study design, including other inclusion and exclusion criteria, have been described elsewhere.[11] All laboratory tests were analyzed at a central laboratory (Research Centre for Laboratory Medicine, Karolinska University Hospital, Stockholm, Sweden). Gothia Forum (Gothenburg, Sweden) performed trial monitoring.

Run-in Period

During a 6-week run in, patients completed masked CGM for 2 weeks and questionnaires regarding the following characteristics: subjective well-being (World Health Organization-5 [WHO-5]),[12] treatment satisfaction (Diabetes Treatment Satisfaction Questionnaire [status version and change version]),[13-15] fear of hypoglycemia (Hypoglycemia Fear Survey),[16-18] hypoglycemic confidence (Hypoglycemia Confidence Questionnaire), and diabetes-related distress (Problem Areas in Diabetes Scale).[19,20] During masked CGM, glucose levels were recorded but were not seen by the patient. After masked CGM, patients were excluded if they either did not believe they would wear the CGM sensor more than 80% of the time or did not perform adequate calibrations during the run in (on average ≥12 of 14 during a 7-day period).

Randomization

Patients were randomized 1:1 into the first treatment period to CGM using the Dexcom G4 PLATINUM stand-alone system or conventional therapy. Randomization was performed by a centralized web-based program stratifying patients by site according to a predefined sequence; random block size varied between 1 + 1 and 2 + 2 (eAppendix in Supplement 2).

Treatment

CGM was compared with conventional therapy using only self-monitoring of blood glucose. Patients were not blinded to treatment. All patients received basic instruction on insulin dosing, such as bolus correction, food choices, and the effect of physical activity on glucose control. A graph was displayed for patients showing the proportion of insulin at time of injection (100%) and the proportion of insulin remaining to give effect at various time points after injection.[21] The patients received general guidelines for interpreting glucose levels and trends obtained by CGM.[11]

During the first week, no alarms were set on the CGM device for low glucose levels except for acute hypoglycemia (<55 mg/dL

[to convert to mmol/L, multiply by 0.0555]). Alarm settings were introduced no later than 2 weeks after randomization. At each visit, patients were encouraged to use CGM information at least every 1 to 2 hours during daytime. In the conventional group, patients were encouraged to measure blood glucose levels according to guidelines (ie, ≥4 times daily). Insulin dosing was based on self-measurement of blood glucose and not CGM values. Assessment of HbA_{1c} was blinded to treatment status. During the 17-week washout period, patients used conventional therapy and masked CGM was performed for 2 weeks.

Clinical Assessments

Patients were assessed at the start of each treatment period and at weeks 2, 4, 13, and 26. HbA_{1c} was measured at all visits in each treatment period except week 2.

Masked CGM was performed 2 weeks before both treatment periods. During conventional therapy, masked CGM was also performed during 2 of the 4 last weeks to evaluate total time in hypoglycemia, euglycemia, hyperglycemia, and glycemic variability. At all visits, CGM and self-measurements of blood glucose data were downloaded and used to assess glucose levels, number of self-measurements of blood glucose, time CGM was in use, and for optimizing glycemic control. To maintain an equal number of visits for both treatment periods, the study did not permit extra patient visits for improving glycemic control.

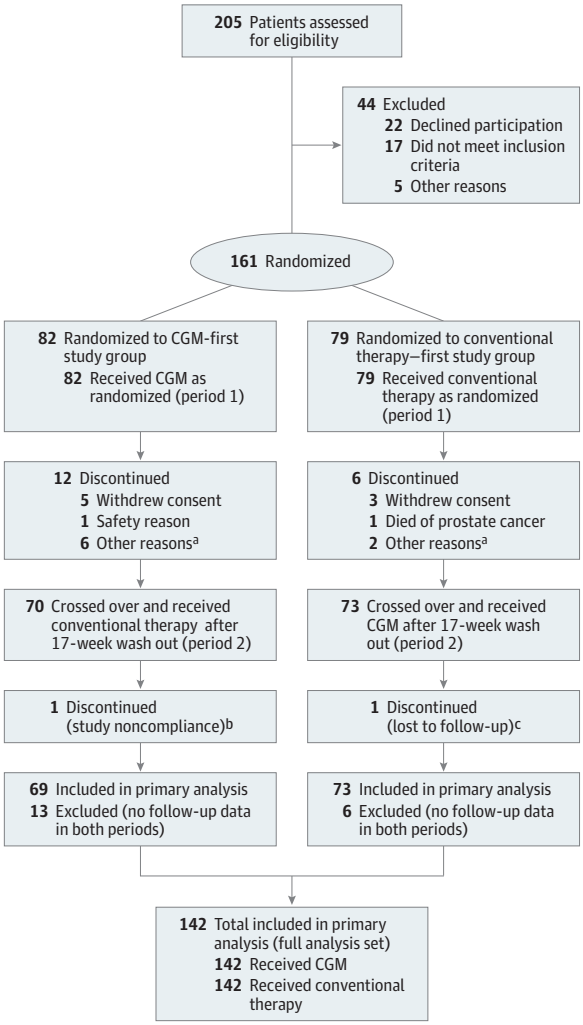
End Points

The primary end point was the difference in HbA_{1c} between CGM and conventional therapy at weeks 26 and 69. Secondary end points included mean amplitude glycemic excursions[22]; the standard deviation of glucose levels; and the amount of time in hypoglycemia, hyperglycemia, and euglycemia during CGM use. Other end points included the following questionnaire results: Diabetes Treatment Satisfaction status (minimum score, 0; maximum, 36; higher value indicates better satisfaction) and change in satisfaction (minimum, −18; maximum, 18; higher value indicates better change in satisfaction), WHO-5 Well-Being Index (minimum, 0; maximum, 100, higher value indicates better well-being), Hypoglycemic Fear Behavior Scale (minimum, 0; maximum, 4; higher value indicates greater fear) and Hypoglycemic Fear Worry Scale (minimum, 0; maximum, 4; higher value indicates greater fear), and the Problem Areas In Diabetes scale (minimum, 0; maximum, 100; higher value indicates greater problems). Other end points were the number of self-measurements of blood glucose and rate of severe hypoglycemia, defined as unconsciousness from hypoglycemia or requiring assistance from another person. All end points were described in the original protocol submitted to the ethical committee before study start (Supplement 1). At study start, the protocol was amended to substitute number of self-measurements of blood glucose as an end point for total insulin dose, and the Hypoglycemia Confidence Questionnaire was added.

Statistics

The reduction 0.3% (3 mmol/mol) in HbA_{1c} is generally considered a clinically meaningful reduction to reduce diabetic long-term complications.[23,24] The study was powered to detect a difference of 0.3% (3 mmol/mol) in HbA_{1c} between weeks 26 and 69 at 90% power and assuming a standard deviation of 1.1%, which required 144 participants. Assuming a dropout rate of 10%, 160 individuals were required for enrollment. No interim analysis was performed.

Figure 1. Screening, Randomization, and Analysis for Continuous Glucose Monitoring and Conventional Treatment Groups



CGM indicates continuous glucose monitoring.

[a] Other reasons for the CGM-first group were dermatological reaction (1), preference to continuing use of CGM (2), preference to switch to insulin pump (1), paracetamol (acetaminophen) use for shoulder pain (1), and unwillingness to proceed (1); for the conventional therapy–first group, other reasons were lack of time (1) and patient request (1).

[b] Patient had no follow-up data reported during period 2 of the study.

[c] Follow-up data maintained during period 2 of the study.

The full analysis set consisted of all randomized patients who had at least 1 follow-up measurement in each treatment period. The safety analysis consisted of all randomized patients who received treatment (CGM or conventional therapy) at any time with patients assigned to treatment administered but not randomized treatment.

The primary efficacy analysis was the difference in HbA_{1c} at weeks 26 and 69 between CGM and conventional therapy

for the full analysis set, with adjustment for treatment period and patient effects using procedure for generalized linear models in SAS software, with sequence, patient (sequence), period, and treatment as class variables.

The last observation carried forward principle was applied for any missing efficacy measurements from the last weeks of each treatment period. Last observation carried forward was not applied to measurements at the first visit in each treatment period. A post hoc sensitivity analysis of primary outcome was performed by multiple imputation with 50 study samplings on all patients randomized by using demographics, baseline characteristics, baseline comorbidities, and HbA_{1c} values at run in and randomization as imputation variables. A second post hoc sensitivity analysis investigating the effect of the site and interaction between site and treatment modeled as fixed effects on the primary outcome was performed.

Secondary efficacy analyses of normally distributed variables were also adjusted for treatment period and patient effects on the full analysis set. For other secondary efficacy variables, the Fisher nonparametric 2-sample permutation test was used to test between treatment sequences on period changes (except for analysis of the occurrence of severe hypoglycemic events in which the treatment groups were handled as 2 independent samples and tested using the Fisher exact test).

The theory of sequential multiple test procedures was applied for the primary and secondary confirmatory analyses. If a 2-sided test gave a significant result at the .05 significance level, the total test mass of .05 was transferred to the next variable in the test sequence until a nonsignificant result was achieved. All these significant tests were then considered confirmatory. All other end points are considered descriptive and are presented in eTable 3 (in Supplement 2).

Calculations were performed using SAS statistical software version 9.4.

Results

Patient Characteristics

The numbers of patients screened, randomized, and not completing the study are shown in Figure 1. There were 161 patients randomized between February and December 2014. The mean age was 43.7 years, 45.3% were women, and mean HbA_{1c} was 8.6% (70 mmol/mol). Of the 161 randomized patients, 142 (88.0%) had follow-up data during both treatment periods in the full analysis set population. Characteristics of patients in the full analysis set population by treatment sequence are shown in **Table 1**. The mean (SD) age was 44.6 (12.7) years, and 56.3% were men. Mean HbA_{1c} was 8.7% (SD, 0.8%) (72 mmol/mol), and mean diabetes duration was 22.2 (11.8) years. Data from the run-in visit are provided in **Table 2**. For the primary efficacy outcome HbA_{1c}, full analysis set population, the LOCF imputation was done for 2 (2.9%) patients at the end of CGM therapy and 3 (4.1%) at the end of conventional therapy.

Glycemic Outcomes

Results of prespecified analyses of the primary and secondary end points are shown in **Table 3**. For the primary efficacy analysis, mean (SD) HbA_{1c} during CGM use was 7.92% (0.8%) (63 mmol/mol) and during conventional treatment was 8.35% (0.9%) (68 mmol/mol) (mean difference, −0.43% [95% CI, −0.57% to −0.29%] or −4.7 mmol/mol [95% CI, −6.27 to −3.13 mmol/mol]); $P < .001$). HbA_{1c} was lower in CGM-treated patients during the first and second treatment periods, whereas levels were similar at the beginning of both periods (**Figure 2**). The standard deviation of blood glucose estimated by CGM and compared with masked CGM during conventional treatment was lower during CGM use than conventional therapy (68.49 vs 77.23 mg/dL; $P < .001$) as was the case for mean amplitude of glycemic excursions (Table 3).

Well-being, Treatment Satisfaction, Diabetes Distress, and Hypoglycemic Fear and Confidence

Results of prespecified analyses of patient-reported outcomes of well-being and diabetes treatment satisfaction are shown in Table 3. Overall well-being, estimated with the WHO-5 questionnaire, improved during CGM use (66.1 vs 62.7; $P = .02$). Treatment satisfaction was higher during CGM use as measured by the Diabetes Treatment Satisfaction Questionnaire status version (30.21 vs 26.62; $P < .001$) and also for the change version (13.20 vs 5.97; $P < .001$). The Hypoglycemia Confidence Questionnaire scale showed less hypoglycemia fear in favor of CGM (3.40 vs 3.27; $P < .001$)(Table 3). Using the theory of sequential tests, the analysis of the primary variable (HbA_{1c}) and the secondary variables (mean glucose levels, mean amplitude of glycemic excursions, standard deviation of glucose levels, Diabetes Treatment Satisfaction Questionnaire status and change versions, and WHO-5 Well-Being Index) were considered confirmatory. Other secondary end points were not tested, and descriptive data for these variables are shown in eTable 3 (in Supplement 2).

Treatment Adherence

Overall mean time of CGM use, estimated by the proportion of CGM data downloaded in relation to follow-up time, was 87.8% during CGM treatment periods. CGM use ranged between 86.5% and 91.9% during various study visits (eTable 1 in Supplement 2). HbA_{1c} was reduced by 0.46% (0.31%-0.61%) in patients using the CGM sensor more than 70% of the time, and there was no significant difference in HbA_{1c} for those using the CGM sensor for less than 70% of the time.

Self-measurement of Blood Glucose

Patients performed a mean (SD) of 2.75 (1.39) self-measurements of blood glucose during CGM therapy and 3.66 (2.30) during conventional therapy.

Patients Not Included in the Full Analysis Set Population

There were 19 patients (11.8%) excluded from the full analysis set population (Figure 1) for lack of follow-up data in the second treatment period. Patient characteristics are shown in eTable 2 in Supplement 2). These patients were younger (37.2 vs 44.6 years; $P = .02$), had higher HbA_{1c} (9.4% vs 8.5%; $P < .001$), and had a history with more severe hypoglycemia events both during the last year (0.37 vs 0.07; $P = .01$) and the past 5 years (1.79 vs 0.60; $P = .04$) compared with individuals in the full analysis set population. In the first treatment period, 16 of these 19 patients had

follow-up data of the primary effect variable HbA_{1c}. Of these, patients treated with CGM (n = 11) had reduced HbA_{1c} from randomization to follow-up—from 9.4% to 8.4% (reduction, 1.0%)—whereas patients with conventional therapy had increased HbA_{1c} from 9.9% to 10.0% (increase, 0.1%).

Hypoglycemia

During CGM use, the mean (SD) percentage of time patients were in a hypoglycemic range (<70 mg/dL) was 2.79% (2.97%) and 4.79% (4.03%) during conventional therapy and for glucose levels of less than 54 mg/dL, the percentage of time was 0.79% (1.23%) during CGM use and 1.89% (2.12%) during conventional therapy. There were 5 events of severe hypoglycemia during conventional treatment (event rate, 0.19 per 1000 patient-years) and 1 event occurred during CGM therapy (event rate, 0.04 per 1000 patient-years). There were 7 severe hypoglycemia events during the washout period when patients were undergoing conventional therapy (event rate, 0.41 per 1000 patient-years).

Adverse Events

In total, there were 77 patients with 137 adverse events during CGM and 67 patients with 122 adverse events during conventional therapy (eTable 4 in Supplement 2). There were no obvious numerical differences for any adverse event between the treatments. One patient in the CGM group discontinued use because of an allergic reaction to the sensor. There were 7 patients with a total of 9 serious adverse events during CGM treatment and 3 patients with total of 9 serious adverse events during conventional treatment (eTable 5 in Supplement 2). Ketoacidosis was not reported during the study.

Sensitivity Analyses of the Primary Outcome HbA_{1c}

In a sensitivity analysis (performed by using multiple imputation) of the primary outcome, including all participants in the trial (n = 161), the effect on HbA_{1c} by CGM was 0.39% (95% CI, 0.24%-0.55% [P < .001]). The second sensitivity analysis of primary outcome (adjusted for the site effect and interaction between site and treatment) showed an HbA_{1c} reduction of 0.43% (95% CI, 0.22%-0.64% [P < .001]) for CGM use vs conventional therapy. The interaction between site and treatment term was not significant (P = .84).

Post hoc Analysis

The weight at the end of conventional therapy was 82.5 kg and for CGM therapy was 83.1 kg (mean difference, 0.63 [P = .01]) and total daily insulin dose was 57.8 U (0.69 units/kg) at the end of conventional therapy and 56.5 U (0.67 units/kg) for CGM therapy (mean difference for total dose in U/kg, −0.02 [P = .01]).

Discussion

In this crossover study of persons with type 1 diabetes treated with multiple daily insulin injections, CGM was associated with a mean HbA_{1c} level that was 0.43% (4.7 mmol/mol) less than conventional treatment. Moreover, glycemic variability was reduced by CGM. Subjective well-being and treatment satisfaction were greater during CGM than conventional therapy.

Table 1. Clinical Characteristics of the Full Analysis Set Population at Baseline and Randomization[a]

Variable	CGM First (n = 69)	Conventional Therapy First (n = 73)
Demographic and Clinical Data		
Age at inclusion visit, mean (SD), y	46.7 (13.0)	42.6 (12.2)
Sex, No. (%)		
Men	37 (53.6)	43 (58.9)
Women	32 (46.4)	30 (41.1)
Race, No. (%)		
Black	0	1 (1.4)
White (including Middle East and North Africa)	69 (100.0)	72 (98.6)
Hispanic ethnicity	0	0
Weight at randomization visit, mean (SD), kg	81.3 (14.7)	83.0 (17.1)
Body mass index at randomization visit, mean (SD)	27.0 (4.1)	27.2 (4.8)
HbA_{1c} (NGSP) at inclusion visit, mean (SD), %	8.71 (0.8)	8.70 (0.9)
HbA_{1c} (NGSP) at randomization visit, mean (SD), %	8.49 (0.9)	8.45 (0.9)
Time from diabetes onset to inclusion visit, mean (SD), y	23.4 (11.9)	21.0 (11.7)
Smoking at inclusion visit, No. (%)		
Current	7 (10.1)	10 (13.7)
Previous	17 (24.6)	15 (20.5)
Never	45 (65.2)	48 (65.8)
Treatment Use at Randomization Visit		
Base insulin type, No. (%)		
Insulatard (NPH insulin)	2 (2.9)	1 (1.4)
Glargine	55 (79.7)	57 (78.1)
Detemir	8 (11.6)	12 (16.4)
Degludec	4 (5.8)	3 (4.1)
Meal insulin type, No. (%)		
Lispro	28 (40.6)	25 (34.2)
Aspart	35 (50.7)	45 (61.6)
Glulisine	4 (5.8)	3 (4.1)
Insulin regular human	2 (2.9)	0 (0.0)
Total daily meal insulin dose, mean (SD), U	26.8 (14.1)	28.2 (12.7)
Total daily base insulin dose, mean (SD), U	29.6 (11.9)	30.9 (15.5)
Total daily insulin dose, U		
Mean (SD)	56.4 (21.6)	59.1 (24.7)
No. of insulin injections, mean (SD), per d	4.90 (1.06)	4.75 (0.86)
Median (range)	5.00 (1.00-7.00)	5.00 (2.00-8.00)
No. of insulin injections (categories), No. (%), per d		
<3	2 (2.9)	1 (1.4)
≥3	67 (97.1)	72 (98.6)
Metformin used, No. (%)	2 (2.9)	0
Other glucose-lowering medication, No. (%)	0	0

Abbreviations: CGM, continuous glucose monitoring; HbA_{1c}, hemoglobin A_{1c}; NGSP, National Glycohemoglobin Standardization Program.

[a] Categorical variables are reported as No. (%), continuous variables as mean (SD), and not normally distributed continuous variables are reported as mean (SD), median (range).

Table 2. Clinical and Questionnaire Data at Run-in Visit[a]

Variable	CGM First (n = 69)	Conventional Therapy First (n = 73)
Glucose Data		
Glucose level, mean (SD), mg/dL[b]	193.7 (31.4)	194.5 (31.3)
Mean amplitude glycemic excursions, mean (SD), mg/dL[c]	183.5 (31.8)	180.3 (29.1)
Glucose levels, mg/dL, mean (SD)[b]	80.1 (13.2)	77.5 (12.7)
Percent of time with low glucose levels <54 mg/dL[b]		
Mean (SD)	2.31 (2.39)	2.06 (2.42)
Median (range)	1.75 (0.00-10.02)	1.11 (0.00-12.33)
Percent of time with low glucose levels <70 mg/dL[b]		
Mean (SD)	5.52 (4.33)	5.12 (4.24)
Median (range)	4.89 (0.00-16.12)	4.32 (0.09-19.97)
Percent of time with high glucose levels >180 mg/dL, mean (SD)[b]	45.4 (14.3)	49.8 (13.4)
Percent of time with high glucose levels above 250 mg/dL, mean (SD)[b]	22.1 (11.6)	23.0 (11.3)
Percent of time with euglycemic levels 99-180 mg/dL, mean (SD)[b]	29.8 (11.1)	31.2 (13.3)
Percent of time with euglycemic levels 70-180 mg/dL, mean (SD)[b]	37.9 (14.6)	39.5 (16.6)
Medical history at inclusion visit, No. (%)		
Previous laser photocoagulation of the retina	14 (20.3)	14 (19.2)
Previous myocardial infarction	3 (4.3)	0
Previous stroke	1 (1.4)	1 (1.4)
Previous bypass graft	1 (1.4)	0
Previous PCI	2 (2.9)	0
Previous amputation	0	1 (1.4)
Previous diabetic foot (or leg) ulcer	1 (1.4)	5 (6.8)
Current diabetic foot (or leg) ulcer	0	3 (4.1)
No. of hypoglycemia events/wk during the last 2 months at inclusion visit[c]		
Mean (SD)	1.90 (1.48)	2.36 (2.23)
Median (range)	1.75 (0.00-7.00)	2.00 (0.00-12.00)
No. of patients	66	68
No. of severe hypoglycemia events during the past year[d]		
Mean (SD)	0.101 (0.425)	0.042 (0.262)
Median (range)	0.0 (0.0-3.0)	0.0 (0.0-2.0)
No. of patients	69	72
No. of severe hypoglycemia events in past 5 y[d]		
Mean (SD)	0.884 (3.042)	0.319 (0.709)
Median (range)	0.0 (0.0-20.0)	0.0 (0.0-4.0)

(continued)

Table 2. Clinical and Questionnaire Data at Run-in Visit[a] (continued)

Variable	CGM First (n = 69)	Conventional Therapy First (n = 73)
Questionnaires		
DTSQ total scale		
Mean (SD)	25.8 (6.1)	24.6 (5.8)
Median (range)	27.0 (4.0-36.0)	25.0 (5.0-36.0)
No. of patients	68	73
WHO-5 Well-Being Index		
Mean (SD)	62.8 (16.6)	57.3 (18.0)
Median (range)	68.0 (12.0-92.0)	64.0 (20.0-100.0)
No. of patients	68	73
SWE-HFS Behavior/Avoidance		
Mean (SD)	1.99 (0.58)	1.85 (0.58)
Median (range)	2.00 (1.00-3.70)	1.80 (0.60-3.30)
No. of patients	68	73
SWE-HFS Worry		
Mean (SD)	0.808 (0.740)	0.880 (0.609)
Median (range)	0.6 (0.0-3.6)	0.8 (0.0-2.8)
No. of patients	68	72
SWE-PAID-20 total scale		
Mean (SD)	24.4 (17.6)	26.8 (16.8)
Median (range)	21.9 (0.0-83.8)	23.8 (2.5-72.5)
No. of patients	68	73
HCQ total scale		
Mean (SD)	3.25 (0.47)	3.22 (0.48)
Median (range)	3.22 (2.13-4.00)	3.28 (2.11-4.00)
No. of patients	67	70

Abbreviations: CGM, continuous glucose monitoring; DTSQ, the Diabetes Treatment Satisfaction Questionnaire; HbA_{1c}, hemoglobin A_{1c}; HCQ, Hypoglycemic Confidence Questionnaire; NPH, negative pH; PCI, percutaneous coronary intervention; SWE-HFS, Swedish Hypoglycemic Fear Scale; SWE-PAID-20, Swedish Problem Areas in Diabetes-20 scale; WHO-5, World Health Organization-5.

SI conversion factor: To convert glucose to mmol/L, multiply values by 0.0555.

[a] Categorical variables are reported as No. (%), continuous variables as mean (SD), and not normally distributed continuous variables are reported as mean (SD), median (range).

[b] Number of patients in the CGM-first group was 63; number in the conventional therapy–first group was 69.

[c] Subjective estimation not based on blood glucose values.

[d] Severe hypoglycemic events are defined as unconsciousness due to hypoglycemia or need of assistance from another person to resolve the hypoglycemia.

The population evaluated in the current study differs to a great extent from earlier clinical trials of CGM.[7-10,25,26] The current study aimed to include a more general population of persons with type 1 diabetes. In contrast to earlier trials, the current study had no upper limit of HbA_{1c} for inclusion, which includes the group of patients with the greatest excess mortality[27,28] and the highest risk of diabetic complications since an exponential relationship exists between higher HbA_{1c} levels and diabetic complications.[23] Hence, finding treatment options for reducing HbA_{1c} in these patients is of great concern. Baseline HbA_{1c} was also high (8.7%) in the current population, and not only was mean HbA_{1c} reduced but fewer patients also had very high HbA_{1c} levels during CGM therapy.

Table 3. Primary and Secondary End Points

	CGM, Mean (95% CI)	Conventional Therapy, Mean (95% CI)	Least Square Means or Mean for Difference: CGM−Conventional Treatment (95% CI)[a]	*P* Value
Primary end point				
HbA_{1c}, %[b]	7.92 (7.79 to 8.05)	8.35 (8.19 to 8.51)	−0.43 (−0.57 to −0.29)	<.001
HbA_{1c}, mmol/mol	63 (61.6 to 64.5)	68 (66.0 to 69.4)	−4.7 (−6.27 to −3.13)	
No. of patients	142	142		
Secondary end points (sequential testing performed)[c]				
Mean glucose level, mg/dL[d]	186.93 (181.66 to 192.20)	193.68 (188.31 to 199.04)	−6.61 (−12.01 to −1.20)	.02
No. of patients	133	133		
Mean amplitude glycemic excursions, mg/dL[d]	161.93 (156.94 to 166.91)	180.96 (175.72 to 186.20)	−19.36 (−24.26 to −14.46)	<.001
No. of patients	123	127		
SD of glucose levels, mg/dL[d]	68.49 (66.36 to 70.63)	77.23 (74.96 to 79.50)	−8.69 (−10.76 to −6.61)	<.001
No. of patients	133	133		
DTSQ status version, scale total	30.21 (29.47 to 30.96)	26.62 (25.61 to 27.64)	3.43 (2.31 to 4.54)	<.001
No. of patients	136	137	131	
DTSQ change version, scale total[e]	13.20 (12.13 to 14.28)	5.97 (3.64 to 8.30)	3.76 (1.70 to 5.82)	<.001
No. of patients	69	67	136	
WHO-5 Well-Being Index	66.13 (62.94 to 69.32)	62.74 (60.18 to 65.31)	3.54 (0.61 to 6.48)	.02
No. of patients	139	140		
Hypoglycemic Fear Scale Behavior/Avoidance	1.93 (1.83 to 2.03)	1.91 (1.81 to 2.00)	0.03 (−0.05 to 0.10)	.45
No. of patients	140	140		
HCQ, scale total[f]	3.40 (3.32 to 3.47)	3.27 (3.18 to 3.35)	0.12 (0.05 to 0.19)	<.001
No. of patients	137	137	135	
Follow-up time, d	182 (180 to 187)	182 (175 to 187)		
No. of patients	142	142		

Abbreviations: CGM, continuous glucose monitoring; DTSQ, the Diabetes Treatment Satisfaction Questionnaire; HCQ, Hypoglycemic Confidence Questionnaire; WHO-5, World Health Organization-5.

[a] Least-square means (95% CIs) and *P* value were calculated using SAS procedure PROC GLM with sequence, patient (sequence), treatment period, and treatment as class variables (calculated only for normally distributed variables). For other variables in which nonparametric tests were performed, values are reported as mean (95% CI).

[b] Values are reported as last observation carried forward with HbA_{1c} measurement standardized by the National Glycohemoglobin Standardization Program.

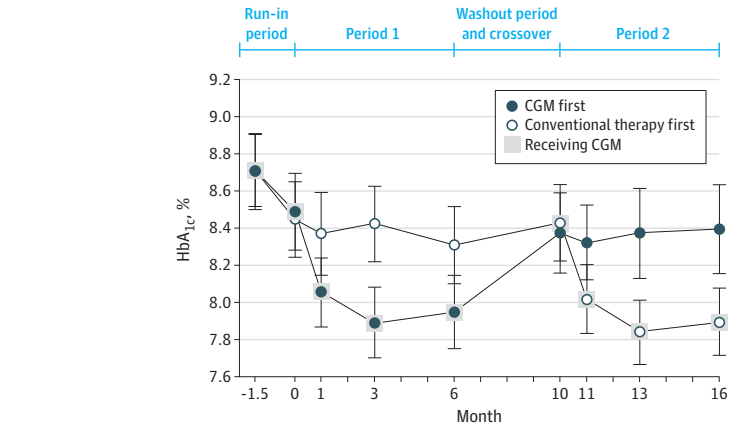
[c] Other prespecified secondary end points and descriptive data (eTable 3 in Supplement 2) were not tested due to the rule of sequential testing (hypoglycemic fear scale-worry, problem areas in diabetes scale, percent of time with high and euglycemic levels, number and percent of patients reducing their HbA_{1c} by 0.5% and by 1%).

[d] Data were measured by CGM during 2 weeks.

[e] Data for the DTSQ change version is collected only at the end of period 2. For the CGM therapy column, it is showing the change in satisfaction from conventional therapy to CGM therapy, and for conventional therapy column, it is showing the change from CGM therapy to conventional therapy.

[f] End point defined as exploratory in the trial protocol.

Figure 2. HbA_{1c} Values at Inclusion, Randomization, and During the 2 Different Periods of Treatment



Hemoglobin A1c (HbA_{1c}) was measured according to the National Glycohemoglobin Standardization Program (NGSP). Data markers and error bars indicate mean (95% CIs). Data were plotted using the last-observation-carried-forward approach.

Also in contrast to earlier CGM-studies,[7-10,25,26] the current trial had no limit on the number of self-measurement of blood glucose patients were required to perform for inclusion. Patients who do not perform self-measurement of blood glucose regularly have higher HbA_{1c} levels.[4] Despite the availability of free glucose meters and test strips in Sweden, less than 50% of patients perform self-measurement of blood glucose according to guidelines (>4 times/d). Hence, evaluating alternative glucose monitoring strategies for these patients is also important. In the present study, patients performed self-measurement of blood glucose less during CGM than conventional therapy (2.7 vs 3.7 measurements/d).

When used in connection with an insulin pump, CGM may ease adjusting insulin doses with respect to observed CGM patterns.[2] Certain processes in the pump can also be guided by CGM information, such as halting the insulin infusion during a rapid decline in glucose.[26] Conversely, most adults with type 1 diabetes are treated with multiple daily insulin injections.[29] Therefore, novel complementary treatment strategies are needed on a broad level. In the intervention/control sequence, HbA_{1c} reverted back to prestudy levels during the washout period (Figure 2), indicating that there was no carry-over effect. In accordance with earlier findings,[9] these results also suggest that the effectiveness of CGM depends on uninterrupted use during multiple daily insulin injections treatment. Our study increases knowledge in the field of type 1 diabetes in reporting that CGM may be a beneficial option for multiple daily insulin injections-treated patients with respect to HbA_{1c} levels.

A novel feature of this trial is a more comprehensive investigation of psychosocial variables, which are now recognized as a high priority in clinical diabetes guidelines.[30] To our knowledge, this trial is the first to demonstrate a significant improvement in subjective well-being and treatment satisfaction in adults using CGM in comparison with conventional therapy. The positive effect on well-being is consistent with previous studies that have shown a significant effect due to CGM on the physical component subscale of the SF-36 (Short Form Health Survey).[10,31] In total, these psychosocial benefits may be at least partially due to the significant HbA_{1C} improvement,[32] as well as to the reduction in time spent in hypoglycemia. Indeed, less time in hypoglycemia is known to be associated with better quality of life[33,34] and a lower risk of severe hypoglycemia.[35,36] Furthermore, hypoglycemic confidence improved during CGM therapy, but it should be interpreted with greater caution since this was an exploratory end point. Of note from a safety perspective, there were numerically more severe hypoglycemic episodes (5 vs 1) during conventional compared with CGM therapy. In addition, 7 severe hypoglycemia events occurred during the washout period of 4 months when patients used conventional therapy.

This study had a number of limitations. First, 19 patients (approximately 12.0%) had no follow-up data in the second treatment period and were not included in the primary analysis. Generally, in a parallel-group study, this can lead to an imbalance between groups. However, in the current study, patients served as their own controls and thus no such problem existed. It has therefore been proposed that the full analysis set population should be used in crossover studies as the main analysis.[37] In addition, with the crossover design, it can be determined whether results are going in the same direction during the first treatment period from a parallel design perspective. Sixteen of the 19 patients who had no follow-up data in the second treatment period had HbA_{1c} data during the first follow-up period. Among these patients, those with CGM had a 1.0% decrease in HbA_{1c}, whereas those with conventional therapy had an increase of 0.1%. There were more patients treated with CGM than conventional therapy who discontinued treatment during the first treatment period. This was due to patients wanting to continue CGM and therefore not completing the study while receiving conventional therapy in the second period and also due to patients experiencing device-related problems (Figure 1).

A second limitation is that the study could not be blinded and hence patients were aware of the intervention. It cannot be excluded that this, to some extent, could have influenced the treatment effect. Although the current reduction in HbA_{1c} may be clinically important, other treatment alternatives are needed for persons with type 1 diabetes to obtain good glycemic control on a broad level. In addition, the current results are restricted to patients with HbA_{1c} of at least 7.5%.

Conclusions

Among patients with inadequately controlled type 1 diabetes treated with multiple daily insulin injections, the use of CGM compared with conventional treatment for 26 weeks resulted in lower HbA_{1c}. Further research is needed to assess clinical outcomes and longer-term adverse effects.

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Continuous glucose monitoring for patients with type 1 diabetes and impaired awareness of hypoglycaemia (IN CONTROL): a randomised, open-label, crossover trial

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Summary

Background Patients with type 1 diabetes who have impaired awareness of hypoglycaemia have a three to six times increased risk of severe hypoglycaemia. We aimed to assess whether continuous glucose monitoring (CGM) improves glycaemia and prevents severe hypoglycaemia compared with self-monitoring of blood glucose (SMBG) in this high-risk population.

Methods We did a randomised, open-label, crossover trial (IN CONTROL) at two medical centres in the Netherlands. Eligible participants were patients diagnosed with type 1 diabetes according to American Diabetes Association criteria, aged 18–75 years, with impaired awareness of hypoglycaemia as confirmed by a Gold score of at least 4, and treated with either continuous subcutaneous insulin infusion or multiple daily insulin injections and doing at least three SMBG measurements per day. After screening, re-education about diabetes management, and a 6-week run-in phase (to obtain baseline CGM data), we randomly assigned patients (1:1) with a computer-generated allocation sequence (block size of four) to either 16 weeks of CGM followed by 12 weeks of washout and 16 weeks of SMBG, or 16 weeks of SMBG followed by 12 weeks of washout and 16 weeks of CGM (where the SMBG phase was the control). During the CGM phase, patients used a real-time CGM system consisting of a Paradigm Veo system with a MiniLink transmitter and an Enlite glucose sensor (Medtronic, CA, USA). During the SMBG phase, patients were equipped with a masked CGM device, consisting of an iPro 2 continuous glucose monitor and an Enlite glucose sensor, which does not display real-time glucose values. The number of SMBG measurements per day and SMBG systems were not standardised between patients, to mimic real-life conditions. During both intervention periods, patients attended follow-up visits at the centres each month and had telephone consultations 2 weeks after each visit inquiring about adverse events, episodes of hypoglycaemia, etc. The primary endpoint was the mean difference in percentage of time spent in normoglycaemia (4–10 mmol/L) over the total intervention periods, analysed on an intention-to-treat basis. Severe hypoglycaemia (requiring third party assistance) was a secondary endpoint. This trial is registered with ClinicalTrials.gov, number NCT01787903.

Findings Between March 4, 2013, and Feb 9, 2015, we recruited and randomly assigned 52 patients to either the CGM–SMBG sequence (n=26) or the SMBG–CGM sequence (n=26). The last patient visit was on March 21, 2016. Time spent in normoglycaemia was higher during CGM than during SMBG: 65·0% (95% CI 62·8–67·3) versus 55·4% (53·1–57·7; mean difference 9·6%, 95% CI 8·0–11·2; p<0·0001), with reductions in both time spent in hypoglycaemia (ie, blood glucose ≤3·9 mmol/L [6·8% *vs* 11·4%, mean difference 4·7%, 3·4–5·9; p<0·0001]) and time spent in hyperglycaemia (ie, blood glucose >10 mmol/L [28·2% *vs* 33·2%, mean difference 5·0%, 3·1–6·9; p<0·0001]). During CGM, the number of severe hypoglycaemic events was lower (14 events *vs* 34 events, p=0·033). Five serious adverse events other than severe hypoglycaemia occurred during the trial, but all were deemed unrelated to the trial intervention. Additionally, no mild to moderate adverse events were related to the trial intervention.

Interpretation CGM increased time spent in normoglycaemia and reduced severe hypoglycaemia in patients with type 1 diabetes and impaired awareness of hypoglycaemia, compared with SMBG. Our results support the concept of using CGM in this high-risk population.

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Introduction

Maintaining near-normal glucose concentrations lowers the risk of microvascular and macrovascular complications and reduces mortality in patients with type 1 diabetes.[1,2] However, satisfactory glycaemic control is difficult to achieve[3] and hypoglycaemia is a major limiting factor in reaching glycaemic targets.[4]

Hypoglycaemia has important physical and psychological consequences[5,6] and can even be fatal.[7] In adults with type 1 diabetes, the mean incidence of mild hypoglycaemia is one to two events per patient per week, and the incidence of severe hypoglycaemia (ie, hypoglycaemia requiring third-party assistance for recovery) is about 0·2 to 3·2 events per patient per year.[6]

Research in context

Evidence before this study

We searched the PubMed database up to May 9, 2016, using the search terms "continuous glucose monitoring", "sensor-augmented pump therapy", "low-glucose insulin suspension", predictive low-glucose suspension", "automated insulin pump suspension", "threshold insulin pump interruption", and "diabetes mellitus, type 1" for full reports of observational trials, randomised controlled trials and systematic reviews that investigated the effect of continuous glucose monitoring (CGM) on glycaemia in patients with type 1 diabetes and impaired awareness of hypoglycaemia. Our search identified one observational study and two randomised controlled trials. Findings from the observational study showed a reduction of severe hypoglycaemia in patients with impaired awareness of hypoglycaemia, reinforcing the need for randomised studies in patients with such impaired awareness. Investigators of one of the randomised trials reported improved hypoglycaemia awareness and glycaemic control from baseline to endpoint (24 weeks), which did not seem related to use of CGM, but was rather attributed to extensive interventions including weekly contact, monthly follow-up visits, and use of a bolus calculator to determine the insulin dose, whether or not an insulin pump was used. Moreover, sensors were used for a median of 57% of the time; only 17 of the 42 individuals achieved the 80% sensor usage threshold, which is often considered the frequency required for meaningful benefit. Findings from the second randomised controlled trial, which used CGM with low-glucose suspend, showed a reduction in severe hypoglycaemia in patients with impaired awareness of hypoglycaemia, but the population studied was quite young (mean age 18·6 years) and the reduction of severe hypoglycaemia lost significance when two outliers in the youngest age groups were excluded from the analysis. Since most patients with impaired awareness of hypoglycaemia are usually older than 40 years and have more than 25 years of diabetes duration, whether CGM adds any benefit (such as less hypoglycaemia and improved glycaemic control) in patients with impaired awareness of hypoglycaemia is still unknown.

Added value of this study

We report the findings from our randomised, crossover trial assessing the effect of CGM without low-glucose suspend on glycaemic control in adult patients with type 1 diabetes affected by impaired awareness of hypoglycaemia. CGM improved percentage of time patients spent in normoglycaemia compared with self-monitoring of blood glucose, by reducing both the percentage of time spent in hypoglycaemia and percentage of time spent in hyperglycaemia. Importantly, the results also showed CGM reduced severe hypoglycaemia in this typical population of patients with type 1 diabetes with impaired awareness of hypoglycaemia. In addition, the absence of an interaction between insulin treatment modality (multiple daily injections or continuous subcutaneous insulin infusion), and both the percentage of time spent in normoglycaemia and the proportion of patients affected by at least one severe hypoglycaemic event are of clinical importance.

Implications of all the available evidence

In earlier trials, CGM did not live up to the expectations of the diabetes community regarding its ability to reduce severe hypoglycaemia. However, our findings here support the benefit of CGM, both with and without combining it with continuous subcutaneous insulin infusion, for improving glycaemic control and diminishing severe hypoglycaemia in adult patients with type 1 diabetes and impaired awareness of hypoglycaemia, who are at highest risk of severe hypoglycaemia.

The risk of severe hypoglycaemia increases with increasing duration of type 1 diabetes. In patients who have had the disease for a long time (>15 years), a prevalence of up to 46% for severe hypoglycaemia, and a mean frequency of 3·2 episodes per patient-year have been reported.[8] Recurrent hypoglycaemia induces defective glucose counter-regulation and impaired awareness of hypoglycaemia.[9] This impaired awareness occurs in roughly 25% of adult patients with type 1 diabetes[10] and renders patients at a three to six times increased risk of severe hypoglycaemia.[10,11]

Continuous glucose monitoring (CGM) reduces HbA_{1c} without increasing hypoglycaemia, with the largest effect in patients with the highest HbA_{1c} at baseline.[12] Current marketed CGM systems are used as standalone devices, or are connected to insulin pumps (sensor-augmented pump therapy), with or without a (predicted) low-glucose suspend feature, which automatically interrupts insulin administration for up to 2 h when glucose concentration falls below a pre-set threshold.[13]

Findings from an observational study[14] have suggested that CGM reduces the risk of severe hypoglycaemia in patients with type 1 diabetes and impaired awareness of hypoglycaemia. This finding was supported by results from a randomised controlled trial using sensor-augmented pump therapy with low-glucose suspension.[15] However, the population studied in the trial was quite young (mean age 18·6 years) and the reduction of severe hypoglycaemia was not significant when two outliers in the youngest age groups were excluded from the analysis. Since most patients with impaired awareness of hypoglycaemia are older than 40 years and have had diabetes for more than 25 years,[16] whether CGM improves glycaemia more than self-monitoring of blood glucose (SMBG) in a typical adult type 1 diabetes population with impaired awareness of hypoglycaemia has yet to be determined.[17]

Therefore, the primary objective of this trial was to investigate the effect of CGM compared with SMBG on glycaemic control in adult patients with type 1 diabetes and impaired awareness of hypoglycaemia.

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Methods

Study design and participants

A detailed description of the study protocol has been previously published.[18] Briefly, we did a two-centre, randomised, crossover, open-label trial (IN CONTROL) at the VU University Medical Center (Amsterdam, Netherlands) and the Medical Center Haaglanden (The Hague, Netherlands). Ethical approval was granted by the medical ethical committee of the VU University Medical Center.

We recruited patients from the outpatient clinics of both medical centres, and from outpatient clinics at affiliated hospitals. To be eligible, patients had to be diagnosed with type 1 diabetes (based on American Diabetes Association [ADA] criteria),[19] aged 18–75 years, be treated with either continuous subcutaneous insulin infusion (CSII) or multiple daily insulin injections (MDI), be undertaking at least three SMBG measurements per day, and have impaired awareness of hypoglycaemia as defined by Gold criteria (ie, with a Gold score ≥4).[11] The Gold method has previously been validated in adult patients with type 1 diabetes and is easy to use.[11] Patients were excluded if they had a history of renal, liver, or heart disease, current untreated proliferative diabetic retinopathy, current malignancy, current use of non-selective β blockers, current psychiatric disorders, current substance abuse or alcohol abuse, pregnancy, current use of CGM other than for a short period (3 consecutive months), any hearing or vision impairment that could hinder perception of the glucose display and alarms, poor command of the Dutch language or any disorder that precluded full understanding of the purpose and instructions of the study, participation in another clinical study, and any known or suspected allergy to trial-related products. We obtained written informed consent from the patients before any trial-related procedures began. In accordance with the risk assessment used in the Netherlands to establish the need for a data safety monitoring board, the present study did not need to have a data safety monitoring board.

Randomisation and masking

After screening and a 6-week run-in phase (including re-education about diabetes management given 2 weeks before randomisation), we randomly assigned patients (1:1) using a computer-generated allocation sequence (block size of four) to either 16 weeks of CGM followed by 12 weeks of washout and 16 weeks of SMBG, or 16 weeks of SMBG followed by 12 weeks of washout and 16 weeks of CGM, where the SMBG phase was the control. The allocation sequence (CGM–SMBG or SMBG–CGM) was generated by the institutional trial pharmacist, and masked to the physicians (by use of sealed envelopes) at the time of randomisation (ensuring low risk of allocation bias). After randomisation, the sequence was no longer masked for both study physicians (who also assessed outcomes and analysed the data) and patients.

Procedures

The (re)education about diabetes management given to all patients before randomisation covered the basic principles of SMBG, hyperglycaemia and hypoglycaemia, glucose fluctuations, insulin and carbohydrates, impaired awareness of hypoglycaemia, and safe and effective use of CGM. No education about the technique of carbohydrate counting was given, in case patients did not practise this technique before enrolment. Patients were equipped with a masked CGM system consisting of an iPro 2 continuous glucose monitor and an Enlite glucose sensor (Medtronic, Northridge, CA, USA), for 2 weeks. This masked CGM system does not display real-time CGM data or glucose trends or allow alarms to be set. The Enlite sensors have a mean absolute relative difference between sensor and reference values of less than 20%.[20,21] Patients were eligible for randomisation if the maximum number of sensor values per day (288) for at least 4 days per week had been obtained, three to four valid calibrations per day had been done, and a daily mean absolute difference less than 18% (in case of a difference between the highest and the lowest calibration value <5·6 mmol/L) or a daily mean absolute difference less than 28% (in case of a difference between the highest and the lowest calibration value ≥5·6 mmol/L) was noted. These cutoff values are used in our clinical practice, and were based on CGM manufacturers' advice (Medtronic, personal communication). In case of low quality or missing CGM data, the run-in phase was extended until satisfactory CGM data for at least 4 days per week had been obtained.

During both intervention periods, patients attended monthly follow-up visits followed by telephone consultations 2 weeks after each follow-up visit, involving inquiry about adverse events, all episodes of hypoglycaemia including severe episodes, use of study device and related technical issues, and to check current medication. Treatment goals were equal in both study periods and in concordance with the ADA Standards of Medical Care.[22] Patients continued using their own blood glucose meters. Therapy adjustments were made on the basis of CGM data in the CGM phase or SMBG data in the SMBG phase. No specific educational issues were addressed other than those stated in the ADA Standards of Medical Care, no treatment or insulin titration protocols were used, and SMBG was not standardised between patients, to mimic real-life conditions and avoid additional interventions. After the first intervention period, patients entered a 12-week washout phase, during which they only received telephone consultations for taking recent medical history and monitoring of potential adverse events every 2 weeks. At the end of the washout period, the general diabetes education was repeated and patients wore a masked CGM device again for 2 weeks to gather baseline data for the second intervention period. At baseline and endpoint of both intervention periods, HbA_{1c} was measured by

high-performance liquid chromatography and self-reported hypoglycaemia awareness was assessed with the Gold[11] and Clarke[23] methods.

The CGM system used during the intervention phase consisted of the Paradigm Veo system used solely as a monitor with a MiniLink transmitter (Medtronic, Northridge, CA, USA for both), and the Enlite glucose sensor. CSII-treated patients continued using their own pump for insulin treatment. The low-glucose limit during this trial was preset at 4·5 mmol/L and the low-glucose suspension function was not used. CGM data were uploaded before every follow-up visit. Patients were encouraged to use CGM continuously, although this use was not mandatory. During the SMBG phase, patients wore the masked CGM system continuously throughout the intervention phase and uploaded the masked CGM data each week. Because of frequent issues with uploading data from the masked CGM device, we assessed the quality of the CGM data and included these data in the analysis if at least 4 days per week's worth of satisfactory CGM data, based on the same criteria as in the run-in phase, were obtained. In case of low quality or missing CGM data, the intervention phase was extended until at least 2 weeks of satisfactory CGM data in a 4-week period had been obtained.

Outcomes

The primary outcome was the mean difference in the percentage of time that patients spent in normoglycaemia (4·0–10·0 mmol/L) between CGM and SMBG calculated over the total intervention periods. In the original protocol, time spent in range was expressed as h per day, but this was redefined as percentages because CGM trials most often report this outcome in this way.[15,17,18] (The change was included on April 2, 2015, but no official protocol amendment was made because this change was not considered substantial.) Secondary endpoints were time spent in normoglycaemia each month to show an effect over time, severe hypoglycaemia (defined as a hypoglycaemic event requiring third-party assistance), the percentage of time patients spent in a hypoglycaemic state (blood glucose ≤3·9 mmol/L) and a hyperglycaemic state (>10·0 mmol/L), average daily area under the curve (AUC) of 3·9 mmol/L or less (expressed as mmol/L min), frequency (episodes per week) and duration (min per episode) of CGM-derived hypoglycaemic episodes (≥three sequential sensor values ≤3·9 mmol/L), frequency (episode per night) and duration of CGM-derived hypoglycaemic episodes at night-time (0000–0600 h), and within-day and between-day glucose

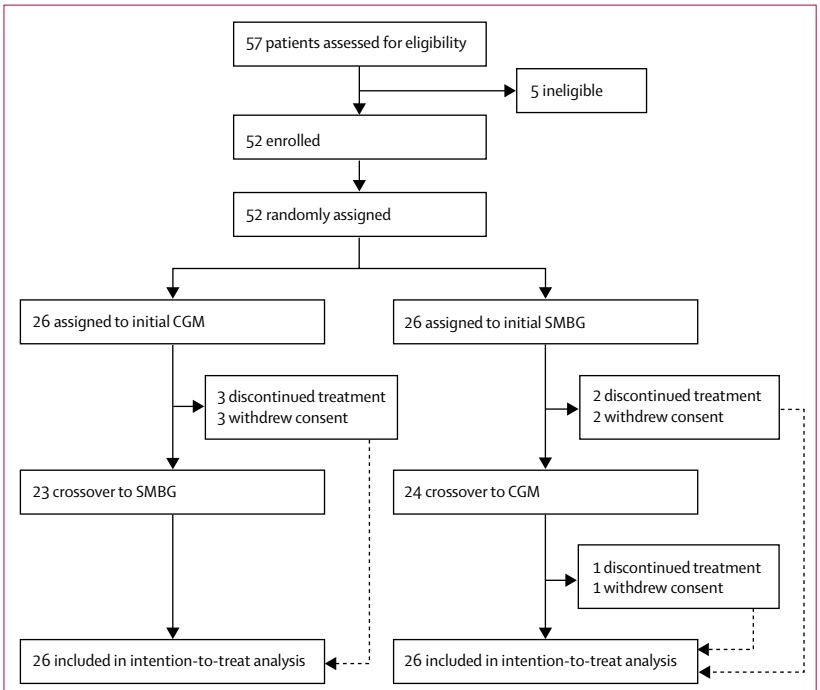

***Figure 1*: Trial profile**
CGM=continuous glucose monitoring. SMBG=self-monitoring of blood glucose.

	Intention-to-treat population (n=52)
Women	24 (46%)
Age (years)	48·6 (11·6)
Weight (kg)	76·9 (14·2)
BMI (kg/m²)	25·0 (3·8)
Diabetes duration (years)	30·5 (18·5–40·8)
HbA_{1c} (%)	7·5% (0·8)
HbA_{1c} (mmol/mol)	58·1 (8·7)
CSII insulin treatment modality	23 (44%)
Duration of CSII therapy (years)	10·2 (4·7–18·7)
Total daily insulin dose (U/kg)	0·5 (0·4–0·7)
Self-reported daily home glucose-meter readings (number per day)	5·0 (4·0–6·0)
Carbohydrate counting	18 (35%)
Retinopathy*	24 (46%)
Peripheral neuropathy†	14 (27%)
Microalbuminuria‡	8 (15%)
Gold score[11]	5·4 (0·7)
Clarke score[23]	5·0 (1·3)
Impaired awareness of hypoglycaemia (Gold[11] and Clarke[23])	45 (87%)
Frequency of severe hypoglycaemia§	
More than one episode per week	2 (4%)
More than one episode per month	7 (15%)
4–12 episodes per year	9 (20%)
1–3 episodes per year	14 (30%)
<1 episode per year	11 (24%)
Never had severe hypoglycaemia	3 (7%)

Data are mean (SD), median (IQR), or n (%). CSII=continuous subcutaneous insulin infusion. *Based on medical history or fundus photography. †Based on medical history or physical examination. ‡Based on an increased albumin-to-creatinine ratio (>2·5 mg/mmol for men and >3·5 mg/mmol for women) or current treatment for microalbuminuria. §46 of 52 participants filled out the severe hypoglycaemia questionnaire.

***Table 1*: Baseline characteristics of the intention-to-treat population**

variability (calculated as within-day SD of glucose concentration, coefficient of variation, mean absolute change in glucose concentration, mean of daily differences, and continuous overall net glycaemic action).[24,25] Other secondary endpoints were baseline and 16-week HbA1c measurements, self-reported hypoglycaemia awareness (based on Gold[11] and Clarke[23] methods), diabetes-specific measures of quality of life (PAID-5, HFS, CIDS, EQ5D, and WHO-5),[18] and satisfaction with use of CGM assessed by the CGM-SAT questionnaire.[18] We also assessed post hoc the frequency of CGM-derived hypoglycaemic episodes with cutoffs of less than 3·5 mmol/L and less than 2·8 mmol/L. Other outcomes specified in our protocol (qualitative analysis of experience with CGM and function of autonomic nervous system) are beyond the scope of this report and will be reported elsewhere.

Statistical analysis

Since the results from a published CGM trial[26] showed a difference of 1·5 h (6·25%) in time spent in normoglycaemia between CGM and SMBG, we aimed to detect such a difference, assuming an SD of 3·5 h, an α of 0·05, a power of 80%, and a correlation of 0·5 between repeated measures. Assuming that about 15% of patients would drop out, we calculated that a sample size of 52 patients was needed.

We did all statistical tests at a two-tailed significance level of 0·05. We analysed the primary endpoint in the intention-to-treat population using a linear mixed-model analysis with the percentage of time spent in normoglycaemia as the dependent variable, the treatment group (CGM or SMBG) as a factor, and the participant as a random factor. Because of the crossover design of our trial, we assessed the carryover effect by including the sequence allocation as a factor in the mixed model. If a carryover effect was detected ($p<0·1$), only the first study period was analysed (treating it as a parallel randomised controlled trial). Additionally, insulin treatment modality (MDI or CSII) was included as a covariate in the model and a p value for interaction of 0·1 was regarded as significant. The percentage of time spent in normoglycaemia was also analysed per month by including the time since the start of the trial in months as a covariate in the mixed model. All other outcomes were also analysed in the intention-to-treat population. We analysed the outcomes with a Gaussian distribution using a similar model, and analysed non-Gaussian distributed data using the Wilcoxon matched-pair signed-rank test.

	CGM phase	SMBG phase	Mean difference (95% CI)	p value
Percentage of time spent with glucose concentration in a specific range				
4·0–10 mmol/L	65·0% (62·8–67·3)	55·4% (53·1–57·7)	9·6% (8·0 to 11·2)	<0·0001
≤3·9 mmol/L	6·8% (5·2–8·3)	11·4% (9·9–13·0)	–4·7% (–5·9 to –3·4)	<0·0001
>10 mmol/L	28·2% (25·1–31·3)	33·2% (30·0–36·3)	–5·0% (–6·9 to –3·1)	<0·0001
Time spent with glucose concentration in a specific range (h per day)				
4·0–10 mmol/L	15·6 (15·1–16·2)	13·3 (12·7–13·8)	2·3 (1·9 to 2·7)	<0·0001
≤3·9 mmol/L	1·6 (1·3–2·0)	2·7 (2·4–3·1)	–1·1 (–1·4 to –0·8)	<0·0001
>10 mmol/L	6·8 (6·0–7·5)	8·0 (7·2–8·7)	–1·2 (–1·6 to –0·7)	<0·0001
CGM-derived hypoglycaemic events (events per week)	10·1 (8·7–11·4)	11·1 (9·8–12·5)	–1·1 (–2·1 to –0·1)	0·028
Duration of CGM-derived hypoglycaemic events (min per event)	60·7 (54·9–66·4)	98·5 (92·6–104·3)	–37·8 (–44·6 to –30·9)	<0·0001
AUC ≤3·9 mmol/L per 24 h (mmol/L per min)	62·9 (45·1–80·7)	115·8 (97·8–133·8)	–52·9 (–68·1 to –37·7)	<0·0001
Nocturnal hypoglycaemia (0000–0600 h)				
Percentage of time spent with glucose concentration ≤3·9 mmol/L	7·6% (5·3–9·8)	13·3% (11·0–15·5)	–5·7% (–8·2 to –3·2)	<0·0001
CGM-derived hypoglycaemic events per night	0·26 (0·21–0·31)	0·33 (0·28–0·38)	–0·07 (–0·11 to –0·02)	0·003
Duration of CGM-derived hypoglycaemic events at night (min per event)	78·7 (69·3–88·1)	131·4 (121·9–140·9)	–52·7 (–62·7 to –42·7)	<0·0001
Mean glucose concentration (mmol/L)	8·3 (8·0–8·6)	8·7 (8·4–9·0)	–0·4 (–0·6 to –0·2)	0·001
Within-day SD of glucose concentration (mmol/L)	2·8 (2·7–2·9)	3·3 (3·1–3·4)	–0·5 (–0·6 to –0·4)	<0·0001
Coefficient of variation of glucose concentration				
Overall	39·5 (38·2–40·8)	46·3 (44·9–47·6)	–6·7 (–8·0 to –5·5)	<0·0001
Within day	33·5 (32·4–34·6)	38·0 (36·9–39·1)	–4·5 (–5·5 to –3·6)	<0·0001
Between days	18·4 (17·5–19·4)	23·1 (22·2–24·1)	–4·7 (–5·9 to –3·5)	<0·0001
MAG (mmol/L per h)	1·7 (1·7–1·8)	1·8 (1·7–1·9)	–0·1 (–0·1 to –0·0)	0·049
MODD (mmol/L)	3·3 (3·1–3·5)	4·2 (4·0–4·4)	–0·9 (–1·1 to 0·7)	<0·0001
$CONGA_1$ (mmol/L)	1·7 (1·6–1·8)	1·8 (1·7–1·9)	–0·1 (–0·2 to –0·0)	0·002

Data are mean (95% CI). CGM=continuous glucose monitoring. SMBG=self-monitoring of blood glucose. AUC=area under the curve. MAG=mean absolute glucose change. MODD=mean of daily difference. $CONGA_1$=continuous overall net glycaemic action at 1 h intervals.

Table 2: **CGM-derived outcomes**

We analysed the proportion of patients with at least one severe hypoglycaemic event using a generalised estimating equation (GEE) with a logistic link function. We preferred to use GEE rather than generalised linear mixed models, because problems of convergence are more likely to occur when using the linear mixed models method. We used an exchangeable correlation to account for correlation between repeated observations for the same patient. We did all analyses with SPSS 22.0 for Windows.

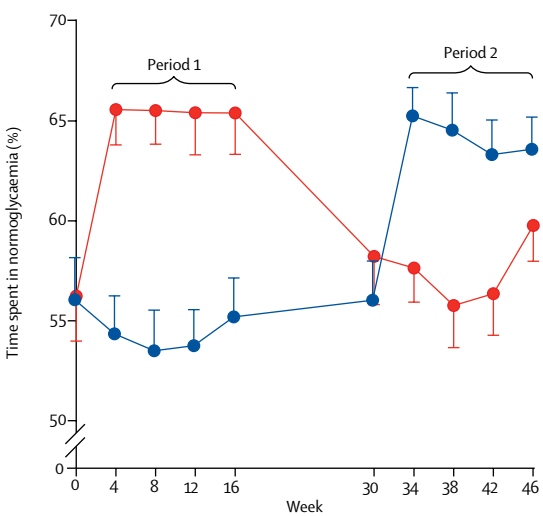

***Figure 2*: Percentage of time spent in normoglycaemia**
Datapoints represent mean (SE) percentage of time spent in normoglycaemia (4·0–10·0 mmol/L) during the preceding 4 weeks in patients allocated to the CGM–SMBG sequence (red line) and SMBG–CGM sequence (blue line). CGM=continuous glucose monitoring. SMBG=self-monitoring of blood glucose. Datapoints at week 0 and week 30 represent mean (SE) percentage of time spent in normoglycaemia during preceding 2 run-in weeks. Period 1: red line=CGM, blue line=SMBG. Period 2: red line=SMBG, blue line=CGM.

This trial is registered with ClinicalTrial.gov, number NCT01787903.

Role of the funding source

The funders of the study had no role in study design, data collection, data analysis, data interpretation, or writing of the report. CAJvB, SJK, MMS, PHG-D, and EHS had access to the raw data. The corresponding author had full access to all the data in the study and had final responsibility for the decision to submit for publication.

Results

Between March 4, 2013, and Feb 9, 2015, 57 patients attended the screening visit, and 52 were randomly assigned to either the CGM-to-SMBG sequence (n=26) or to the SMBG-to-CGM sequence (n=26; figure 1). The first patient was enrolled on March 4, 2013, and the final patient's last visit was on March 21, 2016. Five patients were deemed ineligible: two had a Gold score of 3, one had type 2 diabetes, one had a malignancy, and one was deemed unable to adhere to the study protocol, because he could not attend the monthly follow-up visits. After randomisation, six patients (12%) withdrew early: two discontinued after the CGM period because of motivational issues, one had personal circumstances necessitating discontinuation, two withdrew because they could not upload the masked CGM device, and one withdrew because of poor adherence to CGM (baseline characteristics presented in table 1). 18 patients (35%) of 52 practised the technique of carbohydrate counting.

All 52 randomly assigned patients were included in the primary analysis. Only one participant had used CGM before, during a marathon more than 6 months before randomisation. Median sensor use during the CGM period was 89·4% (IQR 80·8–95·5). Means of 13·0 weeks

	CGM phase	SMBG phase	Odds ratio (95% CI)	Mean difference (95% CI)	p value
Severe hypoglycaemia					
Number of severe hypoglycaemic events	14	34	..	..	0·033*
Patients with ≥1 severe hypoglycaemic event	10 (19%)	18 (35%)	0·48 (0·2 to 1·0)†		0·062
HbA_{1c}					
Value at study endpoint‡ (%)	7·3% (7·1 to 7·5)	7·3% (7·1 to 7·5)	..	0% (–0·1 to 0·2)	0·812
Value at study endpoint‡ (mmol/mol)	56·0 (53·9 to 58·1)	56·3 (54·1 to 58·3)	..	0·2 (–1·4 to 1·9)	0·812
Change from baseline (%)	–0·1% (–0·2 to 0·1)	–0·1% (–0·2 to 0·0)	..	–0·1% (–0·2 to 0·1)	0·449
Change from baseline (mmol/mol)	–0·5 (–1·9 to 0·9)	–1·3 (–2·7 to 0·1)		–0·8 (–2·8 to 1·2)	0·449
Self-reported hypoglycaemia awareness					
Gold score[11] at study endpoint‡	4·6 (4·3 to 5·0)	5·0 (4·6 to 5·4)	..	–0·4 (–0·7 to 0·0)	0·035
Change in Gold score from baseline	–0·5 (–0·8 to –0·1)	–0·1 (–0·4 to 0·2)	..	–0·4 (–0·8 to 0·0)	0·076
Clarke score[23] at study endpoint‡	4·4 (3·9 to 4·8)	4·4 (3·9 to 4·8)	..	0·0 (–0·4 to 0·4)	0·953
Change in Clarke score from baseline	–0·1 (–0·5 to 0·3)	–0·4 (–0·8 to 0·0)	..	–0·3 (–0·9 to 0·2)	0·216

Data are n (%) or mean (95% CI), unless otherwise indicated. CGM=continuous glucose monitoring. SMBG=self-monitoring of blood glucose. *Result of related-samples Wilcoxon signed-rank test done for 16-week severe hypoglycaemia event rates per 100 patient-months. †Result of generalised estimating equation analysis adjusted for study duration. ‡measured after the 16-week intervention phase.

***Table 3*: Severe hypoglycaemia, HbA_{1c}, and self-reported hypoglycaemia awareness**

(SD 1·8) of masked CGM data and 13·6 weeks (1·9) of real-time CGM data were obtained per patient during the study phases, so differences in the amount of CGM data between the CGM and SMBG phases in our analyses did not need to be controlled for.

The percentage of time that patients spent in a normoglycaemic state during the 16-week intervention period was higher during CGM than during SMBG (65·0% [95% CI 62·8–67·3] *vs* 55·4% [53·1–57·7]; mean difference 9·6, 95% CI 8·0–11·2; p<0·0001; table 2, figure 2), and the number of h per day that patients spent in the normoglycaemic state was higher during CGM. All other outcomes were lower during CGM than during SMBG (table 2).

Fewer severe hypoglycaemic events occurred during CGM than with SMBG (table 3, figure 3). During both the CGM and SMBG phases, four severe hypoglycaemic events occurred resulting in seizure or coma, and one severe hypoglycaemic event resulted in the patient being admitted to the hospital. Ten patients (19%) had one or more severe hypoglycaemic event during CGM, compared with 18 (35%) during SMBG (uncorrected odds ratio [OR] 0·45, 95% CI 0·23–0·87; p=0·018), with no interaction for insulin treatment modality (CSII *vs* MDI; p=0·348). However, because of issues with uploading the masked CGM device, the median duration of the SMBG phase was 18·0 weeks (IQR 16·3–20·9) versus 16·0 weeks (16·0–16·9) in the CGM phase. Correction for study duration in the GEE model did not substantially affect the point estimate for the OR (0·48, 0·22–1·04; p=0·062), although the finding was not significant after this correction was made. After completion of the CGM phase, time spent in the normoglycaemic state reverted towards baseline values after the 12-week washout period (figure 2). The sequence allocation had no effect on the primary endpoint (p=0·548) and the effect was constant over both study periods (p=0·157). We noted no differences for the percentage of time that patients spent in a normoglycaemic state between those on MDI versus CSII (figure 4), or between patients who used or did not use the technique of carbohydrate counting ($p_{interaction}$ 0·634, and 0·938, respectively). One patient who spent less time in normoglycaemia during the CGM phase (52·7%) compared with the SMBG phase (57·3%) also spent less time in hypoglycaemia during the CGM phase (4·8%) compared with the SMBG phase (16·5%). The mean HbA_{1c} after both intervention periods and the change in HbA_{1c} from baseline to endpoint were equal in the CGM and SMBG groups (table 3).

We noted no relevant differences in self-reported hypoglycaemia awareness scores, with no relevant between-group differences in 16-week hypoglycaemia awareness scores or change in hypoglycaemia awareness scores from baseline to endpoint (table 3). No between-group differences were noted in quality of life from scores on the HFS Behaviour subscale, PAID-5, CIDS, EQ5D, or WHO-5 between the CGM and SMBG phases (data not shown). Scores on the HFS Worry subscale, transformed to a 0–100 scale, were lower after the CGM phase compared with the SMBG phase (32·5 *vs* 38·9; mean difference 6·4, 95% CI 1·4–11·4; p=0·014). CGM-SAT scores after the CGM phase were higher than neutral (3·0 on a 5·0 scale), with a mean score of 3·8 (SD 0·6).

Five serious adverse events other than severe hypoglycaemia occurred during the trial, but none were deemed related to the study intervention. In the washout phase, one event each of anaphylactic reaction to eye drops, cerebral contusion, rupture of the Achilles tendon, and rupture of the biceps tendon occurred; one hospital admission for erysipelas (not at the CGM insertion site) occurred during the CGM phase. No ketoacidosis occurred during the trial. 11 mild to moderate adverse

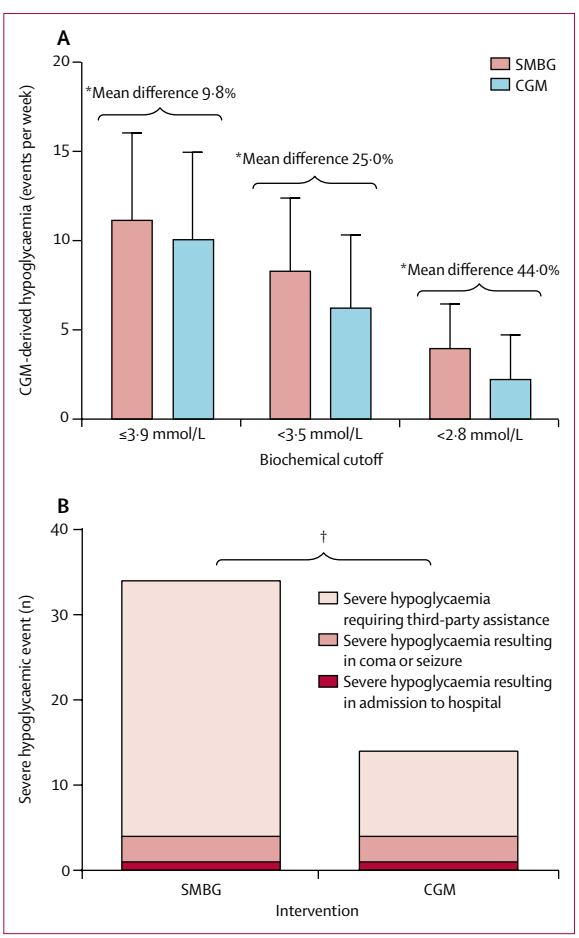

***Figure 3*: (A) CGM-derived hypoglycaemia and (B) severe hypoglycaemia**
(A) Bars represent mean (SD) frequency of CGM-derived hypoglycaemic events per week during the total SMBG period (red bars) and the total CGM period (blue bars), grouped per biochemical cutoff. (B) Number of severe hypoglycaemic events requiring third-party assistance, resulting in coma or seizure, or resulting in admission to hospital are shown for the SMBG period and the CGM period. SMBG=self-monitoring of blood glucose. CGM=continuous glucose monitoring. *Denotes p<0·05 for the comparisons between CGM and SMBG per biochemical cutoff. †Result of the related-samples Wilcoxon signed-rank test done on rates of 16-week severe hypoglycaemic events (requiring third-party assistance) per 100 patient-months (p=0·033).

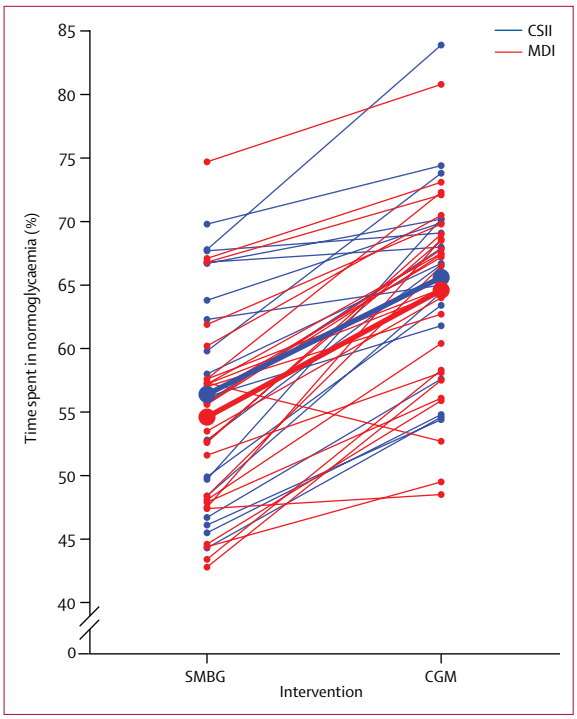

***Figure 4*: Percentage of time spent in normoglycaemia for each patient**
Data are the mean percentage of time spent in normoglycaemia (4·0–10·0 mmol/L) for each patient for the total SMBG period, which is connected to the percentage of time spent in normoglycaemia for the total CGM period. Blue lines represent patients treated with CSII. Red lines represent patients treated with MDI. Thicker lines connect the mean percentage of time spent in normoglycaemia in the total SMBG period and the total CGM period for all patients treated with CSII (blue line) and for all patients treated with MDI (red line). CSII=continuous subcutaneous insulin infusion. MDI=multiple daily injections. SMBG=self-monitoring of blood glucose. CGM=continuous glucose monitoring.

events occurred during the CGM phase, 16 mild to moderate adverse events occurred during the SMBG phase, and two mild to moderate adverse events occurred during the wash-out phase. The mild to moderate adverse events were deemed unrelated to the study intervention and consisted of adverse events related to the musculoskeletal system (CGM phase, n=2; SMBG phase, n=6), urinary tract infection (CGM phase, n=2), dermal infection(CGM phase, n=2; SMBG phase, n=1; wash-out, n=1), gastrointestinal infection (CGM phase, n=1; SMBG phase, n=3), dermal burn (CGM phase, n=1), fever for less than 1 week (CGM phase, n=2; SMBG phase, n=3), excision of lipoma (CGM phase, n=1), dyspnoea (wash-out, n=1), periodontitis (SMBG phase, n=1), infection of the upper respiratory tract (SMBG phase, n=1), and glaucoma (SMBG phase, n=1). No adverse events resulted in discontinuation of the study.

Discussion

The results from our randomised controlled crossover trial in adult patients with type 1 diabetes and impaired awareness of hypoglycaemia showed that a 16-week intervention with CGM (without low-glucose suspension) significantly improved time that the patients spent in a normoglycaemic state, with less time spent in hypoglycaemia and hyperglycaemia, compared with SMBG. Additionally, CGM decreased the frequency of severe hypoglycaemic events in this high-risk population, and produced less glucose variability, but without a change in HbA_{1c}. Our findings suggest that CGM is a valuable tool for the treatment of adult patients with type 1 diabetes and impaired awareness of hypoglycaemia. Our reported differences in time spent in normoglycaemia between SMBG and CGM are similar to the difference between patients using CGM less than 50% and 50% or more of the time, as reported in another intervention trial[17] in patients with impaired awareness of hypoglycaemia. The findings of our trial lend support to the belief that CGM does not have an effect beyond the actual intervention, because withdrawal of CGM resulted in a reversal of the time spent in the normoglycaemic state to baseline values after 12 weeks.[27]

In addition to reducing the frequency of CGM-derived hypoglycaemia and severe hypoglycaemia, the 16-week CGM phase also saw a smaller proportion of patients affected by severe hypoglycaemia than did the SMBG phase. Importantly, this effect occurred without increasing HbA_{1c}, which is often the price paid when trying to avoid hypoglycaemia. No differences occurred in the frequency of severe hypoglycaemic events resulting in seizure or coma, or in the frequency of severe hypoglycaemic events resulting in admission to hospital. The lower the biochemical cutoff for hypoglycaemia was set, the larger the reduction in hypoglycaemia with CGM, which might suggest that patients in our trial took action only when their glucose concentration was already 3·9 mmol/L or lower, or perhaps they defined a lower threshold for self-treating hypoglycaemia. Importantly, CGM did reduce the frequency of hypoglycaemic episodes of less than 2·8 mmol/L, which can cause cognitive dysfunction as a result of neuroglycopenia.[28] We were not able to show a clinically relevant difference in self-reported hypoglycaemia awareness between CGM and SMBG after 16 weeks, possibly because CGM did not prevent all hypoglycaemia, but only reduced its duration and depth. More rigorous avoidance of hypoglycaemic events for a longer period of time might be needed to improve hypoglycaemia awareness.[17] Our results suggest that CGM enables patients to worry less about hypoglycaemia, but does not have a profound measurable effect on other markers of quality of life.[17]

These data add to the discussion about the value of CGM in preventing hypoglycaemia in patients with impaired awareness of hypoglycaemia. Findings from a Cochrane collaboration systematic review meta-analysis[29] showed no difference in the incidence rates of severe hypoglycaemia between CGM and SMBG (risk ratio 1·05, 95% CI 0·63–1·77); however, this analysis was based on data published up to June, 2011, and included studies from which patients with impaired awareness of

hypoglycaemia had mostly been excluded. In a later observational study 1 year later, Choudhary and colleagues[14] reported a reduction of severe hypoglycaemia with CGM in patients with impaired awareness of hypoglycaemia, reinforcing the need for targeted randomised studies in patients with impaired awareness of hypoglycaemia. A trial using CGM with low-glucose suspend seemed to support the idea of a benefit with CGM by showing a reduction of severe hypoglycaemia in patients with impaired awareness of hypoglycaemia.[15] However, the population studied was quite young (mean age 18·6 years) and the reduction of severe hypoglycaemia was not significant when two outliers in the youngest age groups were excluded from the analyses. Since patients with impaired awareness of hypoglycaemia are usually older than 40 years and have had diabetes for more than 25 years,[16] these findings left important questions unanswered. This issue was addressed in another randomised controlled trial (HypoCOMPaSS), which specifically focused on adults with type 1 diabetes and impaired awareness of hypoglycaemia.[17] The investigators reported improved hypoglycaemia awareness and glycaemic control from baseline to endpoint (24 weeks) with the use of extensive patient guidance that included weekly contact, monthly follow-up visits, and use of a bolus calculator to determine the insulin dose, whether or not an insulin pump was used. However, no added benefit of CGM was shown. Importantly, sensors were used for a median of 57% of the time in the HypoCOMPaSS study; only 17 of 42 individuals achieved 80% sensor usage threshold, which is often considered the frequency required for meaningful benefit. Our data add to these findings by showing that in typical adult patients with long-standing type 1 diabetes and impaired awareness of hypoglycaemia, CGM with median sensor usage of 89·4% (IQR 80·8–95·5) reduces severe hypoglycaemia.

When treating patients with type 1 diabetes who have impaired awareness of hypoglycaemia and severe hypoglycaemia in clinical practice, health-care professionals frequently first try to improve glycaemia by optimising self-management (eg, by giving structured education about flexible insulin therapy) and changing the insulin delivery method from MDI to CSII, before considering CGM, since structured education programmes (such as DAFNE and BGAT) and CSII[30–32] have been shown to prevent severe hypoglycaemia and cost less than CGM. In our study population, 18 (35%) of 52 patients used carbohydrate counting and 23 (44%) of 52 patients were on CSII. Our data showed equal benefit from CGM in both patients on CSII and MDI, and in patients who did and did not use carbohydrate counting, with no interaction for insulin treatment modality or the use of carbohydrate counting on the primary outcome. This findings suggests that CGM can be used in various patients, including those not willing or able to change to CSII or practise carbohydrate counting.

Our study has several strengths. Its crossover design removed between-patient variation, and the washout period prevented any substantial carryover effects. Moreover, all data were analysed on an intention-to-treat basis. Furthermore, we showed benefit of CGM in a typical adult type 1 diabetes population with impaired awareness of hypoglycaemia, with a mean age of 48·6 years (SD 11·6), median diabetes duration of 30·5 years (IQR 18·5 to 40·8), and a mean baseline HbA_{1c} value of 7·5% (SD 0·8), which is similar to adult patients with type 1 diabetes who have impaired awareness of hypoglycaemia included in other trials.[14,16,17] The treatment goals and guidance in our study were equal in both intervention periods, with an equal number of follow-up visits and telephone consultations during both periods.

A limitation of our study is that the CGM devices used in the trial might have been outdated, since next-generation CGM systems came to market during the trial, with improvements in lag time and accuracy, and with new features (eg, predicted low-glucose suspension). Additionally, the masked and real-time CGM devices used in our trial are known to differ somewhat in accuracy, which needs to be taken into account when interpreting the CGM-derived data. The real-time CGM device is calibrated in real time, but the masked CGM device is retrospectively calibrated (which allows the calibration algorithm to use information both before and after the timepoint of interest to obtain an optimum calibration to each reference point, leading to better accuracy). By contrast, real-time CGM displays a glucose value in real-time and the calibration algorithm can only use previous data for calibration. This difference might explain why the real-time CGM device tends to report glucose concentrations that are lower than the reference over the entire range of glucose values.[20] However, if anything, this result would have caused an overestimation of the reported CGM-derived hypoglycaemia during the real-time CGM phase compared with the SMBG phase. The difference between CGM and SMBG might therefore be larger than actually shown in this trial. Other limitations were that the study could not be powered for severe hypoglycaemia as a primary outcome, and that data for the frequency of adjustments to SMBG or therapy during the intervention periods were not collected. CGM with predictive low-glucose suspension could further reduce the incidence of severe hypoglycaemia in adult patients with impaired awareness of hypoglycaemia, and clinical trials investigating this possibility should be prioritised.

In conclusion, in patients with type 1 diabetes and impaired awareness of hypoglycaemia, CGM improved glycaemic control by decreasing both time spent in a hypoglycaemic state and time spent in a hyperglycaemic state. Additionally, it diminished severe hypoglycaemia. These results support the use of CGM in this high-risk population.

Contributors
MD and SJK conceived and designed the trial. EHS was the principal investigator in Amsterdam (Netherlands), and was involved in the design of the protocol, coordination of the study, and drafting of the report. PHG-D was the principal investigator in The Hague (Netherlands), and was involved in the design of the protocol, coordination of the study, and drafting of the report. CAJvB, JHD, MHHK, and FJS participated in the study design. CAJvB was the main study physician responsible for obtaining data in both trial centres, data analysis, and drafting of the first draft of the report. SJK obtained a substantial proportion of the data in the VU University Medical Center (Amsterdam, Netherlands). PHG-D supervised the study physicians CAJvB and SJK. MD obtained funding for the trial. CAJvB and MMS did the data analysis and JHD, PHG-D, MHHK, FJS, and EHS made substantial contributions to the data analysis. JHD, SJK, MMS, PHG-D, MHHK, FJS, and EHS reviewed and commented on drafts of the report.

Declaration of interests
Through MHHK and MD, the VU University Medical Center (Amsterdam, Netherlands) received research grants from AstraZeneca, Boehringer Ingelheim, Novo Nordisk, and Sanofi. JHD (or his institution) has received research support and speaker's fees from Abbott, Dexcom, Medtronic, Roche Diabetes Care and Seneonics. PHG-D has received speaker fees from Abbott and Medtronic and is a member of the advisory board of Medtronic. All other authors declare no competing interests.

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IN CONTROL of type 1 diabetes, despite hypoglycaemia unawareness

Even during the 1940s, with insulin's use as an anti-diabetes drug still in its infancy, hypoglycaemia (ie, a blood glucose concentration of less than 70 mg/dL [3·9 mmol/L], as defined by the American Diabetes Association[1]) was well recognised for its symptoms, its severity—and its peculiar absence of effect in some patients.[2] Specifically, the absence of forewarning adrenergic symptoms, which include sweating, tremulousness, palpitations, and anxiety made it difficult to avoid the consequences of neuroglycopenia, such as confusion, seizures, coma, and even death.[3] Although there is still debate over whether this is a maladaptive or adaptive effect of repeated events,[4] the risks from severe hypoglycaemia (blood glucose <50 mg/dL [2·8 mmol/L], or hypoglycaemia requiring assistance to treat) are a burden among the estimated 20% of adults with type 1 diabetes who have hypoglycaemia unawareness.[5]

Historically, proper patient education and adherence to diabetes management strategies have been the mainstays of hypoglycaemia prevention, but recent technological developments have provided additional approaches.[6] Continuous subcutaneous insulin infusion, for example, might be associated with less risk of severe hypoglycaemia than multiple daily injections of insulin,[7] but assessing this risk among patients with impaired awareness of hypoglycaemia is difficult without studies designed specifically to look at this group.

In *The Lancet Diabetes & Endocrinology*, Cornelis van Beers and colleagues[8] report the results of the IN CONTROL trial investigating the use of continuous glucose monitoring (CGM) in patients with type 1 diabetes and impaired awareness of hypoglycaemia. The validated Gold criteria[9] for defining impaired awareness of hypoglycaemia were used to both define this study population and assess the outcome of patient-defined awareness of symptoms. The researchers aimed to investigate whether CGM, consisting of an iPro 2 continuous glucose monitor and an Enlite glucose sensor, improved glycaemia and prevented severe hypoglycaemia compared with self-monitoring of blood glucose (SMBG) in this high-risk population in a randomised, crossover, open-label, 16-week trial. Their results show a significant improvement in the primary outcome of time spent in normoglycaemia (mean difference 9·6%, 95% CI 8·0–11·2; p<0·0001) and a reduction in severe hypoglycaemia in the CGM group compared with the SMBG group, However, no between-group differences were noted in self-reported hypoglycaemia awareness scores after 16 weeks. This result occurred despite 89·4% median sensor use during the CGM period, a measure that distinguishes this study from a similar randomised study by Little and colleagues (HypoCOMPaSS),[10] for which only a median 57% CGM use was reported.

As suggested by van Beers and colleagues,[8] the HypoCOMPaSS study probably showed improvements in hypoglycaemia awareness mostly because of extensive intervention and education, an interpretation supported by results from a meta-analysis from Yeoh and colleagues[11] in which structured education to reduced hypoglycaemia over longer durations resulted in significant improvement in hypoglycaemia awareness. Yet, the reason for the absence of improvement in hypoglycaemia awareness over the 16-week period in van Beers and colleagues' study is unclear. A more significant reduction of time spent in hypoglycaemia might have been needed, or a longer study period for assessing return of symptoms, but perhaps sensor accuracy during hypoglycaemia was problematic as well. The investigators reported on previously published values (mean absolute relative difference less than 20% for the Enlite sensor), but assessing CGM accuracy during this study, especially if consistent positive bias was apparent in the hypoglycaemic range, might have provided helpful information on this issue. Kropff and colleagues reported a mean absolute difference of almost 25% in the hypoglycaemic range for the Enlite sensor over 6-day home use.[11] Additionally, although time in severe hypoglycaemia was reduced with CGM in the IN CONTROL trial, it was not completely eliminated, and even a small amount of time spent at very low glucose ranges could limit improvement in hypoglycaemia unawareness.

Despite the study's limitations, van Beers and colleagues'[8] conclusion that appropriate CGM use can reduce the risk of hypoglycaemia while maintaining, and even improving, time in normoglycaemia, despite

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the presence of hypoglycaemia unawareness, adds further evidence in support of CGM use in patients with type 1 diabetes. Until these data became available, whether appropriate CGM use (with either continuous subcutaneous insulin infusion or multiple daily insulin injections) truly affects hypoglycaemia was unclear. Although perhaps not providing a final verdict, van Beers and colleagues' findings strengthen the evidence in favour of obtaining approval from regulatory agencies for CGM use in this setting, certainly in patients who have clearly defined impaired awareness of hypoglycaemia. Furthermore, CGM use in other technological advancements, such as in sensor-augmented pump therapy, sensor-driven hypoglycaemia minimisers, and fully closed-loop insulin delivery, continues to push the boundaries for reducing hypoglycaemic events, especially during the overnight period, in people with type 1 diabetes.

Still, many questions remain. Improvement in hypoglycaemia unawareness with use of CGM is not clearly proven. Can CGM use completely eliminate hypoglycaemia? Could CGM or other technological advancements also assist in the return of hypoglycaemia awareness with more long-term use, beyond that which is obtained with proper education about hypoglycaemia prevention? Certainly more information needs to be gathered to provide answers to these questions, but dedicated randomised controlled trials, such as IN CONTROL, will continue to fill the gaps in the evidence.

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REPLACE-BG: A Randomized Trial Comparing Continuous Glucose Monitoring With and Without Routine Blood Glucose Monitoring in Well-Controlled Adults With Type 1 Diabetes

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OBJECTIVE

To determine whether the use of continuous glucose monitoring (CGM) without confirmatory blood glucose monitoring (BGM) measurements is as safe and effective as using CGM adjunctive to BGM in well-controlled adults with type 1 diabetes (T1D).

RESEARCH DESIGN AND METHODS

A randomized noninferiority clinical trial was conducted at 14 sites in the T1D Exchange Clinic Network. Participants were ≥18 years of age (mean 44 ± 14 years), had T1D for ≥1 year (mean duration 24 ± 12 years), used an insulin pump, and had an HbA_{1c} ≤9.0% (≤75 mmol/mL) (mean 7.0 ± 0.7% [53 ± 7.7 mmol/mol]); prestudy, 47% were CGM users. Participants were randomly assigned 2:1 to the CGM-only (*n* = 149) or CGM+BGM (*n* = 77) group. The primary outcome was time in range (70–180 mg/dL) over the 26-week trial, with a prespecified noninferiority limit of 7.5%.

RESULTS

CGM use averaged 6.7 ± 0.5 and 6.8 ± 0.4 days/week in the CGM-only and CGM+BGM groups, respectively, over the 26-week trial. BGM tests per day (including the two required daily for CGM calibration) averaged 2.8 ± 0.9 and 5.4 ± 1.4 in the two groups, respectively ($P < 0.001$). Mean time in 70–180 mg/dL was 63 ± 13% at both baseline and 26 weeks in the CGM-only group and 65 ± 13% and 65 ± 11% in the CGM+BGM group (adjusted difference 0%; one-sided 95% CI −2%). No severe hypoglycemic events occurred in the CGM-only group, and one occurred in the CGM+BGM group.

CONCLUSIONS

Use of CGM without regular use of confirmatory BGM is as safe and effective as using CGM with BGM in well-controlled adults with T1D at low risk for severe hypoglycemia.

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*A complete list of members of the REPLACE-BG Study Group can be found in the Appendix.

In the past decade, continuous glucose monitoring (CGM) has evolved as an essential part of diabetes management for many people with type 1 diabetes (T1D) (1–3). This technology offers advantages to traditional self-monitoring of blood glucose by providing real-time information on high- and low-glucose patterns, directions and rate of glucose changes, and hypo/hyperglycemia alerts. Several multicenter randomized controlled trials have demonstrated the benefits of CGM in reducing HbA_{1c} and hypoglycemia, particularly in adults with T1D (2,4–11).

Before December 2016, the CGM systems commercially available in the U.S. were approved by the Food and Drug Administration (FDA) for use only as adjunctive devices to information obtained from standard home blood glucose monitoring (BGM). Therefore, according to the labeling of these CGM systems, a BGM measurement was required to confirm the CGM sensor glucose concentration before making an insulin dosing decision. This regulatory decision presumably was made because the accuracy of the CGM systems was considered to be inadequate for dosing insulin without BGM confirmation. However, with each new generation of sensors, accuracy has improved (12–17), suggesting that CGM may now be sufficiently accurate to be safely implemented as a stand-alone tool for glucose monitoring and therapeutic decisions. In December 2016, the FDA expanded the indications for the Dexcom G5 sensor (Dexcom, San Diego, CA) to allow for replacement of fingerstick blood glucose testing for diabetes treatment decisions.

Even when the FDA labeling limited CGM use to an adjunct-only tool, many CGM users were making insulin dosing decisions by CGM alone. Among adult participants in the T1D Exchange clinic registry, only 26% of 999 surveyed CGM users indicated that they always confirmed the CGM glucose concentration with a BGM measurement before administering an insulin bolus, and 41% indicated that they dosed insulin based on CGM alone more than one-half of the time (R.W.B., unpublished data). In another survey of 222 CGM users, 50% of respondents indicated that during the night, they would treat a CGM low-glucose alert without a confirmatory fingerstick glucose, and 34% would dose insulin for hyperglycemia without a confirmatory BGM measurement (18).

To date, no clinical trials have confirmed the safety and effectiveness of CGM used without BGM to make therapeutic decisions in people with T1D. We conducted a multicenter randomized noninferiority clinical trial to determine whether the routine use of CGM without BGM confirmation is as safe and effective as CGM used as an adjunct to BGM in adults with T1D.

RESEARCH DESIGN AND METHODS

The trial was conducted at 14 endocrinology practices in the U.S. of which 4 were community-based and 10 were academic centers. The protocol and Health Insurance Portability and Accountability Act–compliant informed consent forms were approved by institutional review boards. Written informed consent was obtained from each participant. An investigational device exemption was obtained from the FDA to conduct the trial. The full protocol is available at http://t1dexchange.org/pages/resources/clinic-network/studies and is summarized below.

Study Participants

Major eligibility criteria were age $\geq$18 years, T1D for $\geq$1 year being treated with an insulin pump for at least 3 months (and not currently using a low-glucose-suspend function), and point of care HbA_{1c} $\leq$9.0% ($\leq$75 mmol/mol). Exclusion criteria included the occurrence of a severe hypoglycemic event resulting in seizure or loss of consciousness in the past 3 years or an event without seizure or loss of consciousness requiring the assistance of another individual in the past 12 months, significant hypoglycemia unawareness based on the Clarke Hypoglycemia Unawareness Survey (19), >10.0% of baseline CGM glucose concentrations <60 mg/dL, more than one episode of diabetic ketoacidosis (DKA) in the past year, history of seizures other than those due to hypoglycemia, current use of a threshold-suspend pump feature, myocardial infarction or stroke in the past 6 months, estimated glomerular filtration rate <30 mL/min/1.73 m^2, abnormal thyroid function, use of a systemic β-blocker, regular use of oral corticosteroids, initiation of a noninsulin drug for glucose control during the past 3 months, pregnancy, inpatient psychiatric treatment in the past 6 months, and presence of a contraindicated medical condition or medication, including ongoing use of acetaminophen. (Supplementary Table 1 provides a complete list of the inclusion and exclusion criteria.)

Synopsis of Study Design

A run-in phase of 2–10 weeks preceded the 6-month randomized trial. After successful completion of the run-in phase and after verification of eligibility from data entered on the study Web site, each participant was randomly assigned from a computer-generated sequence to the CGM-only or CGM+BGM group in a 2:1 ratio on the basis of a permuted block design with stratification by clinical site. Both groups used a Dexcom G4 Platinum CGM System with an enhanced algorithm (Software 505) (referred to as the study CGM), which measures glucose concentrations from interstitial fluid in the range of 40–400 mg/dL every 5 min for up to 7 days. The study BGM was the CONTOUR NEXT (Ascensia Diabetes Care US, Parsippany, NJ). The Abbott Precision Xtra (Abbott Diabetes Care, Alameda, CA) was used to measure blood ketone levels (β-hydroxybutyrate).

Run-in Phase

Informed consent was signed by 295 individuals, 19 of whom did not pass the screening assessment. The run-in phase, which was initiated by 276 participants, lasted for 2–10 weeks, depending on whether the participant was a CGM user at the time of study entry. There were two parts of the run-in phase of which participants completed various portions, depending on whether they were using CGM at study entry: *1*) Dexcom CGM system configured to record glucose concentrations not visible to the participant (referred to as a blinded CGM) for 14 days to collect baseline data and *2*) standard CGM for 2–8 weeks for CGM training. In both phases, the participant's willingness and ability to use the study CGM and BGM were assessed. Participants who used a Dexcom CGM for at least 21 of the 28 days before study enrollment skipped the blinded CGM phase and were required to have only 2 weeks of unblinded study CGM use. Participants who used a Medtronic CGM for at least 21 of the 28 days before

enrollment skipped the blinded CGM phase and were required to have at least 4 weeks of unblinded study CGM use. All other participants completed the 14-day blinded phase and 8 weeks of unblinded CGM use. Successful completion of the blinded phase required study CGM wear on a minimum of 11 of 14 days and an average of three blood glucose measurements per day by the study BGM. Successful completion of the unblinded CGM phase required CGM use on ≥21 days during the past 28 days and an average of four or more BGM measurements on at least 90% of days; for participants whose run-in phase was shortened, the number of days of CGM use were reduced accordingly. Of 276 participants who entered the run-in phase, 50 did not enter the randomized trial for the following reasons: 24 did not meet the BGM criterion, 6 had >10% of CGM readings of <60 mg/dL, and 20 were withdrawn for a variety of other reasons (Supplementary Figs. 1 and 2).

Randomized Trial

After randomization, participants in both groups were instructed to calibrate the study CGM per Dexcom specifications and to use it daily. Both groups also were instructed to perform a BGM measurement when the fasting CGM glucose concentration was >300 mg/dL or when the CGM glucose concentration during the day was >300 mg/dL for 1 h. In both instances, if the BGM measurement confirmed that the glucose level was >300 mg/dL, the participant was instructed to perform a blood ketone measurement with the study ketone meter.

The CGM+BGM group was instructed to perform a BGM measurement with the study meter for CGM calibrations whenever an insulin bolus was administered, when treating or attempting to prevent hypoglycemia, and before going to bed. The CGM-only group was instructed to dose insulin and make management decisions on the basis of the CGM sensor glucose concentration, except in the following circumstances that required BGM testing: *1*) for 12 h after insertion of a new sensor, *2*) on a sick day (e.g., nausea, vomiting), *3*) for 4 h after taking acetaminophen, *4*) for symptoms suggestive of hypoglycemia but the CGM sensor glucose concentration was not hypoglycemic or dropping rapidly, *5*) for 20 min after treating a low CGM sensor glucose concentration if the CGM sensor glucose level had not begun to rise, *6*) before administering an insulin bolus when the CGM sensor glucose concentration was >250 mg/dL, and *7*) for a fasting CGM glucose >300 mg/dL or CGM glucose concentration during the day >300 mg/dL for 1 h. If a CGM calibration measurement coincided with a meal, the participant was instructed to base the meal bolus on the CGM sensor value and then perform a BGM measurement to calibrate the CGM.

Follow-up visits for both groups occurred at 3, 6, 13, 19, and 26 weeks, with a ±1-week window. Data were uploaded from the study CGM and BGM devices and the participant's personal insulin pump by using the Tidepool platform (http://tidepool.org). For insulin pumps that were unable to be uploaded to the Tidepool platform, the data were obtained by using Diasend (Chicago, IL) software. At each visit, compliance with CGM and BGM use was assessed, and additional training was given as needed. Glucose and pump data were reviewed to determine whether changes were indicated in diabetes management.

HbA_{1c} was measured at baseline, 13 weeks, and 26 weeks at the Northwest Lipid Research Laboratories, University of Washington, by using the Diabetes Control and Complications Trial standardized analyzer (Tosoh Bioscience, South San Francisco, CA). The following questionnaires were completed at baseline and 26 weeks: the Diabetes Technology Questionnaire, which consists of 30 questions about diabetes self-treatment practices and the impact of living with diabetes on the individual (20), and the Hypoglycemia Fear Survey, which consists of 23 questions about the effect of or worry about hypoglycemia on the individual with diabetes (21).

Study Outcomes

The primary outcome was CGM-measured time in the range of 70–180 mg/dL over the entire 26-week trial. To be included in the primary and secondary analyses of CGM metrics, the participant had to have at least 200 h of CGM data during the 26 weeks of the trial. Secondary outcomes included CGM measures of mean glucose, glycemic variability (coefficient of variation), hypoglycemia (time <70 mg/dL, 60 mg/dL, and 50 mg/dL; area above curve 70 mg/dL; and percentage of days with ≥20 consecutive min of glucose concentrations <60 mg/dL), hyperglycemia (time >180 mg/dL, 250 mg/dL, 300 mg/dL; area under the curve 180 mg/dL; and percentage of days with ≥20 consecutive min of glucose concentrations >300 mg/dL), change in HbA_{1c}, and proportion of participants with both no worsening of HbA_{1c} by >0.3% (3.3 mmol/mol) and no severe hypoglycemic event. Safety outcomes were severe hypoglycemia (defined as an event that required assistance from another person to administer carbohydrate, glucagon, or other resuscitative actions); DKA; hyperglycemia not meeting the definition of DKA for which emergency evaluation or treatment was obtained from a health care provider or blood ketone levels ≥0.6 or ≥1.0 mmol/L; and other occurrences meeting the regulatory definition of a serious adverse event.

Statistical Methods

Sample size was determined for a noninferiority limit of 7.5% for the difference between treatment groups in the time in the range of 70–180 mg/dL over the course of 26 weeks. For 90% power, a one-sided α of 0.05, and assuming an SD of 14% with correlation of 0.48 between the baseline and outcome time in range (based on data from the JDRF CGM randomized trial [8]), the required sample size was estimated to be 122. However, to better assess CGM-only safety, the sample size was selected to be 225 participants randomly assigned 2:1 to the CGM only group or CGM+BGM group.

Analyses followed the intention-to-treat principle. The primary analysis was a treatment group comparison of time in range (70–180 mg/dL) during the 26-week trial by using an ANCOVA model adjusted for baseline time in range and site as a random effect. Confounding was assessed by repeating the analysis with the inclusion of potential confounding variables as covariates. Prespecified exploratory analyses were conducted to assess for interaction between the treatment effect on the time in range (70–180 mg/dL) during the 26-week trial and baseline factors by including interaction terms in the ANCOVA

models. For the remaining CGM outcomes, treatment group comparisons were made by using ANCOVA models based on van der Waerden score rankings if the metric was skewed and adjusted for the corresponding baseline value and clinical site as a random effect.

Change in HbA_{1c} from baseline was compared between groups by using an ANCOVA model adjusted for baseline HbA_{1c} and site as a random effect. The proportions of participants with both no worsening of HbA_{1c} by >0.3% (3.3 mmol/mol) and no severe hypoglycemic event were compared between treatment groups by using a logistic regression model adjusted for baseline HbA_{1c} and site as a random effect. The percentages of subjects with at least one blood ketone level ≥0.6 mmol/L (and ≥1.0 mmol/L) were compared between treatment groups by using a logistic regression model adjusted for site as a random effect. The mean scores on the Diabetes Technology Questionnaire were compared between treatment groups by using ANCOVA models adjusted for site as a random effect. For the Hypoglycemia Fear Survey, the overall total score, the total score for the low–blood glucose questions (1–10), and the total score for the worrying questions (11–23) were each compared between treatment groups by using an ANCOVA model adjusted for the baseline value and site as a random effect.

Analyses were conducted with SAS 9.4 software (SAS Institute, Cary, NC). All *P* values are two-sided.

RESULTS

Between 22 May 2015 and 11 March 2016, 226 participants were assigned to either the CGM-only group (*n* = 149) or the CGM+BGM group (*n* = 77). Mean age was 44 ± 14 years (35 [15%] ≥60 years old), mean diabetes duration was 24 ± 12 years, and mean baseline HbA_{1c} was 7.0 ± 0.7% (53 ± 7.7 mmol/mol); 107 (47%) were CGM users, and 119 (53%) were not using CGM when enrolled. Participant characteristics according to treatment group are listed in Table 1.

One participant in the CGM-only group was determined after randomization to have been ineligible (percentage of time <60 mg/dL during blinded baseline CGM wear was >10%). Seven participants in the CGM-only group and two in the CGM+BGM group withdrew from the trial. Thus, the trial was completed by 142 (95%) of the CGM-only group participants and by 75 (97%) of the CGM+BGM group participants (Supplementary Figs. 2 and 3).

Among participants completing the trial, all in both groups were using CGM in month 6. CGM use averaged 6.7 ± 0.5 and 6.8 ± 0.4 days/week in the CGM-only and CGM+BGM groups, respectively, over the 26-week trial (Table 2), with 91% and 95% averaging ≥6 days/week. All participants in the CGM+BGM group and all but one in the CGM-only group averaged ≥5 days/week over the entire 26 weeks. Among participants ≥60 years old who completed the study, 95% in the CGM-only group (*n* = 21) and 92% in the CGM+BGM group (*n* = 13) averaged ≥6 days/week, and among participants <60 years old, 90% (*n* = 121) and 95% (*n* = 62) averaged ≥6 days/week. Among the completers of the trial, BGM tests per day from meter downloads (including the two required daily BGM tests) averaged 2.8 ± 0.9 in the CGM-only group and 5.4 ± 1.4 in the CGM+BGM group ($P < 0.001$).

Table 1—Participant characteristics at enrollment (*N* = 226 randomized)

	CGM-only group(*n* = 149)	CGM+BGM group(*n* = 77)
Age (years)	44 ± 14	45 ± 13
Range	19–78	25–69
Diabetes duration (years)	23 ± 12	25 ± 12
Range	2–64	4–58
BMI (kg/m^2)	27.7 ± 4.1	26.5 ± 4.9
Female sex	71 (48)	41 (53)
Race/ethnicity		
White non-Hispanic	139 (93)	68 (88)
Hispanic or Latino	4 (3)	5 (6)
Black/African American	4 (3)	1 (1)
Asian	2 (1)	2 (3)
Other/unknown	0 (0)	1 (1)
Annual household income ($)*		
<50,000	18 (16)	7 (12)
>50,000–100,000	39 (35)	17 (30)
≥100,000	54 (49)	33 (58)
Highest education*		
Less than bachelor's degree	35 (24)	12 (16)
Bachelor's degree	75 (51)	35 (48)
Postbachelor's degree	38 (26)	26 (36)
Insurance*		
Private	132 (89)	66 (88)
Other	15 (10)	7 (9)
None	2 (1)	2 (3)
CGM use before study		
Never used CGM	26 (17)	14 (18)
In past, but not current	54 (36)	25 (32)
Current Dexcom CGM user	49 (33)	28 (36)
Current Medtronic CGM user	20 (13)	10 (13)
Central laboratory HbA_{1c} value†		
<7.0% (53 mmol/mol)	59 (40)	39 (51)
7.0–8.0% (53–64 mmol/mol)	79 (53)	31 (40)
≥8.0% (64 mmol/mol)	11 (7)	7 (9)
% (mmol/mol)	7.1 ± 0.7 (54 ± 7.7)	7.0 ± 0.7 (53 ± 7.7)
Self-reported BGM testing times/day	5.2 ± 2.1	4.9 ± 1.9
Clarke Hypoglycemia Unawareness Survey total score		
0	100 (67)	53 (69)
1	34 (23)	14 (18)
2	15 (10)	10 (13)

Data are mean ± SD or *n* (%) unless otherwise indicated. *Missing data for CGM-only and CGM+BGM groups: annual income for 38 and 20, education for 1 and 4, and insurance for 0 and 2, respectively; †The local laboratory HbA_{1c} value was used for one participant in the CGM+BGM group whose central laboratory value was unavailable.

Table 2—CGM use over the 26-week study period in participants completing the trial

CGM use (days/week)	CGM-only group (*n* = 142)	CGM+BGM group (*n* = 75)
Median (interquartile range)	7.0 (6.5–7.0)	7.0 (6.7–7.0)
Mean ± SD	6.7 ± 0.5	6.8 ± 0.4
3 to <4	1 (<1%)	0
4 to <5	0	0
5 to <6	12 (8)	4 (5)
6 to <7	55 (39)	34 (45)
7 days/week	74 (52)	37 (49)
<6	13 (9)	4 (5)
≥6	129 (91)	71 (95)

Data are *n* (%) unless otherwise indicated.

Glycemic Control and Other Outcomes

Mean time spent in the range of 70–180 mg/dL was 63 ± 13% at both baseline and 26 weeks in the CGM-only group and 65 ± 13% and 65 ± 11%, respectively, in the CGM+BGM group (adjusted difference 0%; one-sided 95% CI −2%). Other CGM metrics of glucose control for mean glucose, hyperglycemia, hypoglycemia, and glycemic variability also showed little change from baseline to 26 weeks and no significant differences between groups (Table 3). Mean change in HbA_{1c} was 0.0% (0.0 mmol/mol) in each group (P = 0.41) (Table 3). Results were similar in subgroups based on age, duration, education, CGM use before study enrollment, baseline HbA_{1c}, and baseline time in range (Table 4). CGM and HbA_{1c} results also were similar between groups in the subset ≥60 years old (Supplementary Table 2).

Severe Hypoglycemia and Other Adverse Events

No severe hypoglycemic events occurred in the CGM-only group, and one

Table 3—Study outcomes

	CGM-only group		CGM+BGM group		
CGM results	Baseline (*n* = 149)	26-week study period (*n* = 148)*	Baseline (*n* = 77)	26-week study period (*n* = 76)*	*P* value†
Hours of CGM data	640 (620–650)	4,007 (3,709–4,166)	641 (619–651)	4,021 (3,725–4,136)	
Range	306–663	467–4,399	270–684	811–4,535	
% time in range (70–180 mg/dL)	63 ± 13	63 ± 13	65 ± 13	65 ± 11	0.81
Mean glucose (mg/dL)	162 ± 22	162 ± 23	158 ± 22	158 ± 20	>0.99
Coefficient of variation (%)	36 (33–41)	37 (34–41)	37 (33–40)	37 (34–40)	0.58
Hypoglycemia‡					
% time <70 mg/dL	2.9 (1.5–4.5)	3.0 (1.6–5.1)	3.6 (1.9–4.8)	3.7 (1.9–4.9)	0.95
% time <60 mg/dL	1.1 (0.6–1.9)	1.3 (0.5–2.4)	1.4 (0.6–2.3)	1.6 (0.6–2.2)	0.57
% time <50 mg/dL	0.3 (0.1–0.6)	0.4 (0.2–0.8)	0.4 (0.2–0.7)	0.5 (0.2–0.8)	0.75
Area above curve 70 mg/dL	0.3 (0.2–0.5)	0.3 (0.1–0.6)	0.4 (0.2–0.6)	0.4 (0.2–0.5)	0.76
% Days with ≥20 consecutive min glucose values <60 mg/dL	25 (15–43)	28 (13–42)	33 (15–43)	32 (16–46)	0.68
Hyperglycemia‡					
% time >180 mg/dL	33 (25–43)	35 (25–41)	31 (22–40)	31 (24–38)	0.88
% time >250 mg/dL	8 (4–15)	9 (5–13)	7 (3–11)	7 (4–11)	0.65
% time >300 mg/dL	2 (1–5)	2 (1–4)	2 (1–4)	2 (1–3)	0.72
Area under curve 180 mg/dL	17 (10–25)	17 (10–23)	14 (8–22)	15 (9–21)	0.90
% days with ≥20 consecutive min of glucose values >300 mg/dL	25 (12–48)	27 (14–40)	20 (8–36)	20 (10–37)	0.72
HbA_{1c} results	Baseline (*n* = 149)	Week 26 visit (*n* = 142)	Baseline (*n* = 77)	Week 26 visit (*n* = 75)	
HbA_{1c}					—
%	7.1 ± 0.7	7.1 ± 0.7	7.0 ± 0.7	7.0 ± 0.6	
mmol/mol	54 ± 7.7	54 ± 7.7	53 ± 7.7	53 ± 6.6	
Change in HbA_{1c} from baseline					0.41
%		0.0 ± 0.5		0.0 ± 0.5	
mmol/mol		0.0 ± 5.5		0.0 ± 5.5	
No worsening of HbA_{1c} by >0.3% (3.3 mmol/mol) and no severe hypoglycemic event		115 (81)		54 (72)	0.15

Data are median (interquartile range), mean ± SD, or *n* (%) unless otherwise indicated. *One participant in the CGM-only group and one in the CGM+BGM group never came in for a follow-up visit and therefore had no CGM data; †Two-sided P value for the CGM metrics and change in HbA_{1c} are from ANCOVA models adjusted for the corresponding baseline value and site as a random effect. Because of the skewed distributions for the CGM coefficient of variation, and the CGM hypoglycemia and hyperglycemia metrics, these models were based on van der Waerden score rankings. The P value for the HbA_{1c}/severe hypoglycemia combined outcome is from a logistic regression model adjusted for baseline HbA_{1c} and site as a random effect. Results were similar for the % time in range when also adjusting for education; ‡One-percent time equals 14.4 min/day.

Table 4—Time in range (70–180 mg/dL) by group according to baseline factors

	CGM-only group (n = 148)*			CGM+BGM group (n = 76)*			
	n	Baseline	26-Week Study Period	n	Baseline	26-Week Study Period	P value for interaction†
Age							0.08
<50 years	94	60 ± 13	60 ± 13	45	65 ± 13	65 ± 13	
≥50 years	54	68 ± 12	67 ± 12	31	64 ± 11	65 ± 9	
Diabetes duration							0.74
<25 years	87	62 ± 13	63 ± 12	41	67 ± 12	66 ± 11	
≥25 years	61	63 ± 14	63 ± 14	35	62 ± 13	63 ± 12	
Education‡							0.71
Less than bachelor's degree	34	59 ± 14	59 ± 13	12	65 ± 9	63 ± 11	
Bachelor's degree or higher	113	64 ± 13	64 ± 13	61	66 ± 13	65 ± 11	
CGM use before study							
Never used	25	64 ± 12	65 ± 10	14	65 ± 10	63 ± 13	0.26
In past, but not current	54	58 ± 13	57 ± 14	24	62 ± 14	63 ± 13	
Current Dexcom user	49	67 ± 12	67 ± 12	28	69 ± 12	68 ± 10	
Current Medtronic user	20	64 ± 13	63 ± 11	10	59 ± 8	61 ± 7	
Baseline HbA_{1c}							0.20
<7.5% (58 mmol/mol)	108	67 ± 11	66 ± 11	60	69 ± 10	68 ± 9	
≥7.5% (58 mmol/mol)	40	51 ± 10	52 ± 12	16	50 ± 9	52 ± 10	
Baseline time in range (70–180 mg/dL)							0.39
<60%	61	50 ± 8	53 ± 11	24	51 ± 7	54 ± 9	
≥60%	87	72 ± 8	69 ± 10	52	72 ± 8	69 ± 9	

Data are mean ± SD. *One participant in the CGM-only group and one in the CGM+BGM group never came in for a follow-up visit and therefore had no CGM data; †P values obtained by including an interaction term in each ANCOVA model adjusted for baseline value and site as a random effect. Continuous variable used in the models for age, duration, HbA_{1c}, and baseline time in range; ‡Education missing for one participant in the CGM-only group and three participants in the CGM+BGM group.

occurred in the CGM+BGM group. No occurrences of DKA occurred in either group. Other serious adverse events, unrelated to the study intervention, occurred in four (3%) participants in the CGM-only group and three (4%) in the CGM+BGM group (Supplementary Table 3). A blood ketone level ≥0.6 mmol/L occurred at least once in 48 (32%) participants in the CGM-only group and 26 (34%) in the CGM+BGM group (P = 0.79); the ketone level was ≥1.0 mmol/L at least once in 27 (18%) and 15 (19%) participants, respectively (P = 0.84).

Questionnaires

Mean scores on the Diabetes Technology Questionnaire were 3.6 ± 0.6 in the CGM-only group and 3.8 ± 0.6 in the CGM+BGM group at baseline and 3.6 ± 0.6 in each group at 26 weeks (P = 0.58). There also was no significant difference between groups on the section of the questionnaire inquiring about change from prestudy (P = 0.28) (Supplementary Table 4). On the Hypoglycemia Fear Survey, total scores were 29 ± 11 in the CGM-only group and 28 ± 9 in the CGM+BGM group at baseline and 32 ± 11 and 31 ± 11 at 26 weeks, respectively (P = 0.88) (Supplementary Table 5).

CONCLUSIONS

This multicenter randomized trial was conducted to determine whether using CGM alone to make insulin dosing decisions is as safe and effective as using CGM as an adjunct to BGM. For the primary outcome of CGM-measured time in the glucose range of 70–180 mg/dL, use of CGM alone was shown to be noninferior to using CGM and BGM together. For this metric and all other efficacy outcomes for CGM-measured hyperglycemia, hypoglycemia, and glucose variability, results in the CGM-only and CGM+BGM groups were virtually identical as were the HbA_{1c} results. Scores obtained from the Diabetes Technology Questionnaire and Hypoglycemia Fear Survey also were similar in the two groups. From a safety perspective, no DKA events or severe hypoglycemic episodes occurred in the CGM-only group. Comparable results were found in participants who were experienced CGM users at study entry, in those who were CGM naive, in older versus younger participants, and in those with higher and lower education levels. In both treatment groups, mean time in range was similar at baseline and during follow-up, likely reflecting the excellent glycemic control of most participants entering the trial.

To our knowledge, this randomized trial is the first to assess the effectiveness and safety of insulin dosing by using CGM alone in adults with T1D. In addition to randomization and multiple center participation, the strengths of this study include a high degree of participant retention, CGM use, and treatment group adherence. Notably, there was good separation between the treatment groups in the number of BGM tests per day, particularly when recognizing that two of the BGM measurements per day were required for CGM calibration and that according to the protocol, the calibrations were performed at times such that they would not influence insulin bolusing.

The major limitation of the trial relates to the generalizability of the results based on the participant inclusion and exclusion criteria. The trial cohort included adults with T1D who used an insulin pump and were well controlled

(mean HbA_{1c} 7.0% [53 mmol/mol]) and likely to adhere to the study protocol and excluded individuals with significant hypoglycemia unawareness or a substantial amount of CGM-measured hypoglycemia. Although the trial only included pump users to be able to document when an insulin bolus was given, it seems reasonable to apply the results to individuals who use multiple daily injections of insulin who otherwise fit the profile of the study participants because the impact of sensor inaccuracy in determining the amount of a bolus should be similar in pump users and injection users (8,22). The results of this study support the need for future studies to assess the safety of CGM used without routine BGM testing in youth and in less-compliant adults than those included in this study, such as individuals with higher HbA_{1c} levels, who perform BGM testing fewer than four times a day, and with hypoglycemia unawareness (23).

The application of this trial's results to clinical practice can benefit people with T1D by reducing their burden of multiple daily fingersticks when using CGM and can enhance the cost-effectiveness of CGM therapy by reducing the number of daily BGM test strips. Furthermore, the demonstration that insulin dosing based on CGM alone is safe has applicability to assessing risk involved with artificial pancreas systems that automate insulin delivery based on CGM sensor glucose measurements.

In conclusion, in well-controlled adults with T1D meeting the eligibility criteria for this trial, use of CGM without regular use of confirmatory BGM is as safe and effective as using CGM with a confirmatory BGM measurement for insulin dosing.

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Duality of Interest. G.A. has served on a scientific advisory board for Diasend and Novo Nordisk and received consultancy payments from Dexcom. G.A.'s employer has received research support from Novo Nordisk and Bristol-Meyers Squibb/AstraZeneca with no personal income to G.A. D.F.K. has served on a scientific advisory board for Novo Nordisk, Abbott, Eli Lilly, Sanofi Aventis, and Janssen. D.F.K. has received speaker fees from Janssen, Valeritas, AstraZeneca, Eli Lilly, Novo Nordisk, and Dexcom. D.F.K.'s employer has received research support from AstraZeneca, Eli Lilly, Novo Nordisk, Dexcom, and Lexicon. D.F.K. holds stock in Dexcom. A.L.P. has served on a scientific advisory board and consulted for Abbott, Becton Dickinson, Bigfoot Biomedical, Boehringer Ingelheim, Eli Lilly, AstraZeneca, Intarcia, Janssen, Lexicon, Medtronic-Minimed, Merck, Novo Nordisk, Omada Health, OptumRx, Sanofi, and United Healthcare and received editorial fees from Medscape. A.L.P.'s employer has received research support from Dexcom. I.H. has received consultancy fees from Abbott Diabetes Care, Roche, and Intarcia. R.M.B. has served on a scientific advisory board and received consultancy fees from Abbott, Boehringer Ingelheim, Bristol-Meyers Squibb/AstraZeneca, Dexcom, Eli Lilly, Halozyme, Inc., Johnson & Johnson, Medtronic, Novo Nordisk, Roche, Sanofi, and Takeda. R.M.B.'s employer has contracts with the listed companies for his services with no personal income to R.M.B.: Abbott, Boehringer Ingelheim, Bristol-Meyers Squibb/AstraZeneca, Dexcom, Eli Lilly, Halozyme, Inc., Johnson & Johnson, Medtronic, Novo Nordisk, Roche, Sanofi, Takeda, and Merck. R.M.B. has inherited Merck stock. A.J.A. has received consultancy fees from Dexcom, Lexicon, Medtronic, and Novo Nordisk. A.J.A.'s nonprofit employer has received research support from Dexcom, Lexicon, Medtronic, and Novo Nordisk with no personal compensation to A.J.A. V.N.S. has received speaking fees from Dexcom. A.P.-T. has served on a scientific advisory board and received consultancy fees from Boehringer Ingelheim, Bristol-Meyers Squibb/AstraZeneca, Dexcom, Eli Lilly, Halozyme, Inc., Lexicon, Merck, Medtronic, Mylan, Novo Nordisk and Sanofi. A.P.-T.'s employer has contracts with the listed companies for her services with no personal income to A.P.T.: Boehringer Ingelheim, Bristol-Meyers Squibb/AstraZeneca, Dexcom, Eli Lilly, Halozyme, Inc., Lexicon, Merck, Medtronic, Mylan, Novo Nordisk and Sanofi. H.R. has served on a scientific advisory board for Elli Lilly, Merck, Novartis, and Novo Nordisk. H.R. received research grant support from BMS, Daiichi Sankyo, and Lexicon. H.R.'s employer has received research support from Medtronic and Merck. A.B. has served on a scientific advisory board for Abbott and Janssen and received speaker fees from AstraZeneca and Sanofi. A.B. has received research grant support from Novo Nordisk, Eli Lilly and Company, AbbVie, MannKind Corporation, Orexigen Therapeutics, Inc., Sanofi-Aventis, Jaeb, Merck, GlaxoSmithKline, University of Oxford, Bristol Myers Squibb, Boehringer Ingelheim Pharmaceuticals, Inc., Duke University Medical Center, Medtronic, Astra Zeneca, and Halozyme. R.W.B.'s employer has received research support and study supplies from Dexcom and Abbott Diabetes Care. No other potential conflicts of interest relevant to this article were reported.

Author Contributions. G.A., K.J.R., and R.W.B. contributed to the data interpretation and wrote/edited the manuscript. T.D.R. performed statistical analyses and wrote/edited the manuscript. D.F.K., A.L.P., I.H., R.M.B., E.T., A.J.A., V.N.S., M.R.R., B.W.B., A.P.-T., R.P.-B., H.R., E.E., A.B., and C.K. contributed to the data interpretation and reviewed/edited the manuscript. R.W.B. is the guarantor of this work and, as such, had full access to all the data in the study and takes responsibility for the integrity of the data and accuracy of the data analysis.

Appendix

Participating T1D Exchange Clinic Network sites with the principal investigator (PI), co-investigator (I), and coordinator (C) in order by the number of participants randomized per site as of 4 November 2016. Detroit, Michigan, Henry Ford Health System (*n* = 27), Davida Kruger (PI), Terra Cushman (C); Los Angeles, California, University of Southern California–Community Diabetes Initiatives (*n* = 19), Anne Peters (PI), Mark Harmel (C); Seattle, Washington, University of Washington, Diabetes Care Center (*n* = 19), Irl Hirsch (PI), Dori Khakpour (C); Minneapolis, Minnesota, International Diabetes Center/Park Nicollet Adult Endocrinology (*n* = 18), Richard Bergenstal (PI), Beth Olson (C); Chicago, Illinois, Northwestern University (*n* = 18), Grazia Aleppo (PI), Elaine Massaro (C), Teresa Pollack; Boston, Massachusetts, Joslin Diabetes Center–Adult (*n* = 16), Elena Toschi (PI), Astrid Atakov-Castillo (C); Portland, Oregon, Harold Schnitzer Diabetes Health Center at Oregon Health and Science University (*n* = 15), Andrew Ahmann (PI), Kristin Jahnke (C); Aurora, Colorado, University of Colorado/Denver, Barbara Davis Center for Childhood Diabetes (*n* = 15), Viral N. Shah (PI), Terra Thompson (C); Philadelphia, Pennsylvania, University of Pennsylvania Perelman School of Medicine/Rodebaugh Diabetes Center (*n* = 15), Michael Rickels (PI), Amy Peleckis (I), Shannon O'Brien (I), Cornelia Dalton-Bakes (C); Atlanta, Georgia, Atlanta Diabetes Associates (*n* = 14), Bruce Bode (PI), Siana Tyler (C); San Diego, California, Scripps Whittier Diabetes Institute (*n* = 14), Athena Philis-Tsimikas (PI), Rosario Rosal (C); Ann Arbor, Michigan, University of Michigan (*n* = 13), Rodica Pop-Busui (PI), Cynthia Plunkett (C); Tampa, Florida, University of South Florida Diabetes Center (*n* = 12), Henry Rodriguez (PI), Emily Eyth (C); Des Moines, Iowa, Iowa Diabetes and Endocrinology Research Center (*n* = 8), Anuj Bhargava (PI), Lisa Borg (C).

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American Diabetes Association®

July 5, 2017

Washington Health Care Authority
Cherry Street Plaza
626 8th Avenue SE
Olympia, WA, 98501

Re: Comments on Continuous Glucose Monitoring (Real-time) Equipment and Supplies

I am writing on behalf of the American Diabetes Association in support of increasing coverage for continuous glucose monitors (CGM) for beneficiaries with diabetes in Washington.

The Association's Standards of Medical Care in Diabetes – 2017 includes the following recommendations:

- When used properly, continuous glucose monitoring (CGM) in conjunction with intensive insulin regimens is a useful tool to lower A1C in selected adults age 25 and over with type 1 diabetes.
- Although the evidence for A1C lowering is less strong in children, teens and younger adults, CGM may be helpful in these groups. Success correlates with adherence to ongoing use of the device.
- CGM may be a supplemental tool to SMBG in those with hypoglycemia unawareness and/or frequent hypoglycemic episodes.

Research has shown benefits for CGM in individuals with type 1 diabetes on intensive insulin therapy, through either an insulin pump or multiple daily injections. As such, we recommend anyone on multiple doses of insulin or for whom continuous subcutaneous insulin infusion is being considered, initiated, or utilized with recurrent hypoglycemic episodes or persistently high HbA1c levels be given the option of real-time CGM.

American Diabetes Association. Standards of Medical Care in Diabetes – 2014. Diabetes Care January 2014; 37 (Supplement 1): S21-S22. Available at: http://care.diabetesjournals.org/content/37/Supplement_1/S14.full.pdf+html Tamborlane WV, Beck RW, Bode BW, et al.; 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.

Individuals with diabetes who use insulin must diligently monitor their blood glucose in order to give themselves the best chance of avoiding long and short term complications. Long term complications caused by high blood glucose levels include blindness, amputation, heart disease, stroke, and kidney failure. But in the short term, both high and low blood glucose levels are dangerous. CGMs monitor blood glucose frequently and alert individuals with an alarm when their blood glucose reaches dangerously high or low levels in a way that traditional, finger stick measurement cannot because it only shows a snapshot of blood glucose at that moment, but does not warn of rapidly rising or falling levels.

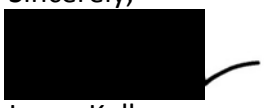
Those who use insulin experience disproportionately high rates of emergency room use, instances of hospitalization, and mortality.i The Centers for Disease Control and Prevention report 282,000 emergency room visits for adults experiencing hypoglycemia in 2011 alone.ii A study published in the American Journal of Managed Care found "the mean costs for hypoglycemia visits were $17,564 for an inpatient admission, $1,387 for an [emergency department] visit, and $394 for an outpatient visit."iii CGM can reduce short-term costs by reducing severe hypoglycemic events in high-risk populations.iv

Conclusion

Diabetes is a complex disease to manage and can lead to short and long term complications. The goal of diabetes care is to avoid the devastating and costly complications of the disease. The economic cost of diagnosed diabetes in the U.S. is $245 billion per year. Much of the economic burden of diabetes is related to its complications including blindness, amputation, kidney failure, heart attack, and stroke. Yet, we have made major strides in effectively managing diabetes and reducing the risk for these devastating – and costly – complications through necessary medical care, medications and other tools, patient self-management, education, and support.

We appreciate the opportunity to provide comments regarding CGM. Should you have any questions or if the Association and be of any assistance, please feel free to contact me at 1-800-676-4065 x 7207 or lkeller@diabetes.org.

Sincerely,



Laura Keller
Director State Government Affairs and Advocacy Washington
American Diabetes Association

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UW Medicine
UNIVERSITY OF WASHINGTON
MEDICAL CENTER

August 25, 2017

Washington State Healthcare Authority
RE: Continuous Glucose Monitoring for Diabetes
shtap@hca.wa.gov

To whom it may concern,

By way of introduction, I am an endocrinologist and diabetologist at the University of Washington. I should also point out, for full transparency, I am also a patient with 53 years of type 1 diabetes, in addition to the brother and uncle of two others with type 1 diabetes. All three of us wear continuous glucose monitors (CGMs). I am the Medical Director for the Diabetes Care Center at the University of Washington, and I have spent the last 30 years involved in numerous research studies focusing on better treatments of diabetes.

I have no doubt that you will have all of the data from the various randomized controlled trials that have been performed with regards to CGM, both in adolescents and adults. In fact, I was the principal investigator (PI) for the first large randomized trial, the "JDRF Sensor Study" published in the New England Journal of Medicine. I have been the PI for many other trials including STAR 1, REPLACE-BG, and we are now starting the WISDM (Wireless Innovation for Seniors With Diabetes Mellitus) trial. From a research point-of-view, I have seen the studies improve, as well as the technology. This has improved our efficacy for both glucose control and reduction of hypoglycemia.

I did however want to inform you about another study which my guess is that no one else will address. The University of Washington is involved with a large type 1 diabetes registry, funded by the Helmsley Charitable Trust. This registry started in 2010, and includes approximately 26,000 patients with type 1 diabetes of all age groups. Here at the University of Washington, at the Diabetes Care Center, we have approximately 600 patients enrolled in this registry.

While we do publish the registry results every few years as a snapshot of diabetes care in the United States, I would like to provide you with some data that is not published. It is related to the results of our yearly questionnaire, which ended in March, 2017. I just want to focus on the CGM data.

My first comment is that while continuous glucose monitoring is increasing in use, my opinion is that utilization is still too low. At the beginning of 2017, when we look at adults between the ages of 26 and 65 years-old, one-third of patients were using CGM routinely. That is twice the amount that used it between the years of 2010 and 2012. In those years, 7% of all patients used continuous glucose monitoring overall, compared to about a quarter of patients now. What is interesting is that even though Medicare did not fund CGM as of the end of last year, 23% of participants in this group still use

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it. To me, the most interesting part of our data is that for children under the age of six, 45% of participants used continuous glucose monitoring with 28% in the 6 to 13 year-old age group.

There are many reasons why CGM is increasing in use. Obviously the technology has improved, and this includes the accuracy of the devices. The data has clearly shown improvements in hemoglobin A1c when the device is used. Here in Washington State, the biggest change that has happened over the last three years is better coverage from the local and regional commercial payers. For the older patients, and this would include the Medicare patients, the main reason for CGM is not hemoglobin A1c improvement, but rather reduction of hypoglycemic exposure. In a different study from the T1D Exchange, we showed that patients with 40 years duration of type 1 diabetes are spending 99 minutes per day hypoglycemic (defined as blood glucose less than 70mg/dL). That should not be surprising when one sees earlier data from our registry showing that for patients with 40 years duration of diabetes, approximately 20% have a hypoglycemic coma or seizure *per year*. One in five patients, independent of age, with 40 years of diabetes will have an episode of severe hypoglycemia that is life-threatening. We have learned that the risk of severe hypoglycemia is more dependent on duration of diabetes than age, although we see severe hypoglycemia at every age.

I want to also point out that while discussing severe hypoglycemia, we have also shown it is not at all dependent on hemoglobin A1c level. At all ages we see the same risk of severe hypoglycemia (seizure or coma) with hemoglobin A1c levels near normal or above 10%. We were surprised that severe hypoglycemia was not dependent on hemoglobin A1c but was on duration of diabetes.

The other point to make is that in the T1D Exchange, even though not a randomized trial, we have shown lower hemoglobin A1c levels with the use of CGM. In those under the age of 13 years-old, the difference was 0.9%: 8.7% hemoglobin A1c for those without CGM and 7.8% for those with. For those between the ages of 13 and 26, we saw a similar difference at 9.1% for those without CGM and 8.3% for those with. For all of those individuals above the age 26 without CGM, the hemoglobin A1c was 7.9% compared to 7.4% with.

One other point relevant to this conversation is that all CGM requires appropriate calibration, generally with two fingerstick glucose tests per day. Over the years, we have documented poor accuracy strips which are generally "off-shore" meters, which are FDA approved, but cheaper. We appreciate that the US FDA is not able monitor the quality of all of the strips on the market. In the summer of 2017 the Diabetes Technology Society published their blood glucose test strip surveillance program assessing the accuracy of 18 different blood glucose test strips. Using the latest iso standard they tested each meter with three different studies in over 1000 subjects. The results are extremely concerning, and important to users of CGM since only 6 of the 18 meters passed the current iso accuracy standard (https://www.diabetestechnology.org/surveillance.shtml). Many of our strips we use are dangerous, especially for those who use insulin, but perhaps even more for those using CGM.

In conclusion, from the point-of-view of an endocrinologist who actively sees approximately 500 patients with type 1 diabetes, a researcher, and a patient, CGM has been one of the most, if not the most, important advancement in diabetes technology in the past 30 years. The only thing that may come close to this was the introduction of fingerstick glucose testing in the early 1980s. I do not know where we would be without CGM given the large number of patients we are now seeing with more than 40 years of type 1 diabetes since the vast majority of my patients in this demographic uses CGM. Forty years of type 1 diabetes used to be a relatively rare event, but it is now my most common patient. CGM has literally saved the lives of many of my patients who have absolutely no knowledge of when their

glucose level is less than 70 mg/dL, or for that matter, less than 50 mg/dL. I urge you to consider for this technology to be available to all appropriate patients in Washington State.

I may be reached at ihirsch@uw.edu or 206-598-2482 should there be any questions.

Sincerely,

[redacted]

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August 28, 2017

Health Technology Clinical Committee (HTCC)
Cherry Street Plaza
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Dear members of the HTCC,

I am Tomas Walker, Senior US Medical Director for Dexcom, and I'm writing to express my appreciation for the Committee's selection of continuous glucose monitoring (CGM) for a second review. This letter is in response to the draft key questions.

Key question: What is the evidence of efficacy and effectiveness of CGM?

Intensive insulin therapy that lowers average glucose levels has been shown to reduce the risk of the long-term complications of diabetes, but also increases the risk of hypoglycemia.[1-3] Severe hypoglycemia (defined as requiring assistance from another individual to treat[4]) can be debilitating or catastrophic and represents a major barrier to optimal glucose control. Recurrent hypoglycemia contributes to impaired awareness of hypoglycemia (IAH) and increases the risk of severe hypoglycemia (SH), which often requires costly emergency care.[4] Tools are therefore needed that can help patients on insulin therapy lower their average blood glucose to near-normal levels without increasing their risk of hypoglycemia.

Real-time CGM provides as many as 288 measurements per day that can provide reassurance or alert patients to the need for interventions. For patients with IAH, the alarm function of CGM devices may be their only warning of impending hypoglycemia, which is of particular importance when driving or sleeping. By contrast, conventional self-monitoring of blood glucose (SMBG) provides intermittent and limited information about blood glucose concentrations, and may miss potential problems even if diligently performed. In many patients with diabetes, CGM is therefore medically necessary to detect trends and patterns in glucose levels over time, optimize glycemic control, and reduce the frequency and severity of hypoglycemic and hyperglycemic events.

Evidence in Adults With Type 1 Diabetes

The Diamond[5] and Gold[6] studies examined the safety and efficacy of CGM among people with type 1 diabetes (T1D) who used multiple daily injection (MDI) therapy and had above-target HbA1c values. Both studies used current-generation Dexcom CGM systems. The first phase of the Diamond study established that use of CGM, compared to use of SMBG therapy, was associated with a greater mean HbA1c reduction at 24 weeks, and with less time in hypoglycemia. Subjects in the CGM group also experienced significant reductions in diabetes distress and fear of hypoglycemia, and significant improvements in hypoglycemia confidence and well-being compared with conventionally-monitored patients.[7] An optional extension phase offered to people who had used CGM during the first phase studied the impact of insulin delivery method (MDI versus continuous subcutaneous insulin infusion or

CSII), and found that transitioning to CSII therapy offered improved time in range, but no corresponding improvement in HbA1c and an increase in biochemical hypoglycemia.[8]

The Gold study had a multicenter, randomized, open-label, crossover design and evaluated the impact of CGM on glycemic outcomes, well-being, diabetes distress, and hypoglycemic fear and confidence. After 26 weeks, CGM use resulted in a mean HbA1c level that was 0.43 percentage points less than in the group receiving conventional blood glucose monitoring; patients treated with CGM also reported significantly less fear of hypoglycemia and significantly improved well-being compared to conventional SMBG.

The Comisair study[9] followed 65 subjects with T1D for up to 1 year and found that CGM used with MDI was as effective as CGM used with CSII therapy with respect to HbA1c reduction. Both insulin delivery modalities combined with CGM also provided significant and comparable decreases in time spent in hypoglycemia compared to insulin therapy with conventional SMBG.

The In Control study[10] was a randomized, open-label, crossover study conducted in adults with poorly-controlled T1D and IAH. The study concluded that CGM increased the time spent in normoglycemia and reduced the incidence of severe hypoglycemia by 59% compared with conventional SMBG.

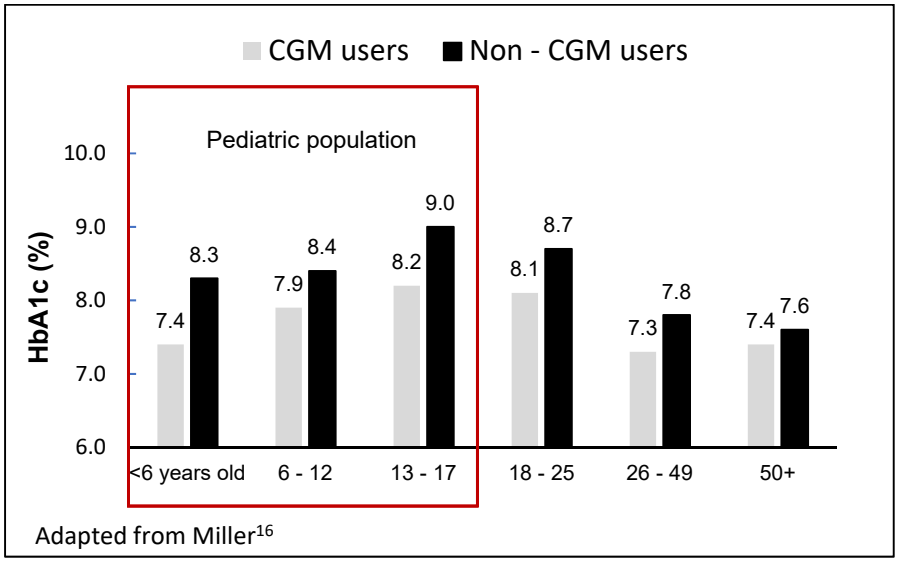
Evidence in Adults With Type 2 Diabetes

The Diamond study included an independently-powered arm that investigated the effects of CGM in patients using MDI therapy to manage their type 2 diabetes (T2D). The results, published last week in *Annals of Internal Medicine*,[11] demonstrated that after 24 weeks, participants using CGM lowered their HbA1c levels by an average of 0.8 percentage points from baseline. Compared to the Control Group, the CGM Group also spent less time in hyperglycemia and more time spent in the target range. The CGM Group increased time in range by 1.3 hours compared to baseline, and 0.6 hours compared to the Control Group. The HbA1c reductions did not depend on age, educational attainment, or numeracy skills, and adherence to the CGM therapy was remarkably high, with 93% of participants using CGM six or seven days per week at the end of the study. Participants also reported a high level of satisfaction and a relatively low level of perceived hassles.

Evidence in Children and Adolescents With T1D

The T1D Exchange Clinic Registry follows over 26,000 patients with T1D, almost 15,000 of whom are younger than 18. Recent Registry publications have confirmed that CGM use is increasing rapidly, especially among very young children. The mean HbA1c values among CGM users and non-users in the Registry were recently reported as 8.1% and 8.9%, respectively.[12] CGM use in every age cohort examined was associated with lower HbA1c values, as shown in the Figure.[13] Separate data from two sensor accuracy studies in youth ages 2-17 years[14] showed that use of CGM had the potential to increase glucose time in range and improve glycemic outcomes.

Figure: HbA1c values for CGM vs. non-CGM users in T1D Exchange Registry



Adapted from Miller[16]

Key question: <u>What is the evidence of the safety of CGM?</u>

On July 21, 2016, the Clinical Chemistry and Clinical Toxicology Devices Panel of the U.S. Food and Drug Administration (FDA) agreed that there is reasonable assurance Dexcom G5 is safe, effective, and the benefits outweigh the risks with the proposed indications for use. The FDA followed expert recommendation and approved the Dexcom G5 as a replacement for fingerstick glucose testing for diabetes treatment decisions,[15] positioning the device as the new standard of care in glucose monitoring for diabetes management.

In 2017, the REPLACE-BG study[16] of adults with T1D tested whether using CGM data as the basis for diabetes-related treatment decisions, independent of confirmatory SMBG values ("nonadjunctive use"), was as safe and effective as using CGM data with SMBG confirmations ("adjunctive use"). The study confirmed that nonadjunctive use of CGM data was not inferior, in terms of safety and efficacy, to using it as an adjunct to SMBG data. Subjects randomized to the CGM-only group were still required to use SMBG values to calibrate their CGM devices, but performed significantly fewer SMBG tests per day than those in the CGM+SMBG group.

Key question: <u>What is the evidence that glucose monitoring has differential efficacy or safety issues in sub-populations?</u>

For evidence of efficacy in type 1, type 2, pediatric and adolescent sub-populations, please see above section **What is the evidence of efficacy and effectiveness of CGM?** The Dexcom G5 Mobile CGM System has not been evaluated or approved for pregnant women, persons on dialysis, or in critically ill patients. We know of no differential safety issues between sub-populations. Please see above section **What is the evidence of the safety of CGM?** for overall evidence of safety.

Key question: <u>What is the evidence of cost-effectiveness of CGM?</u>[17]

Enclosed with this response is a recent publication in the Journal of Medical Economics, examining the cost effectiveness of stand alone CGM systems. The analysis was done from a Canadian perspective, and the incremental cost effectiveness ratio (ICER) for Dexcom G5 CGM vs. traditional SMBG was $33,789 Canadian dollar/quality adjusted life year (QALY)[18]. Additional studies have been done on the cost effectiveness of CGM, but have included the cost of an insulin pump in the analysis[19]. The range of ICERs are from £12,223 to $98,679 per QALY. The difference in the ICER has been due to the inclusion of sensor augmented pumps, specific target populations and rapidly evolving technology which confounds the results.

The cost of CGM systems must be balanced against the fact that it helps patients avoid costly and potentially catastrophic episodes of severe hypoglycemia. In a randomized clinical trial, CGM use was associated with a 59% reduction in severe hypoglycemia (SH).[10] Of the approximately 1,903,717 people in Washington enrolled in Medicaid, 34,756 have insulin-treated diabetes and, of these, about 4464 have IAH. Reducing the incidence of SH via CGM use in this population of people with IAH has the potential to impact the current State expenditures as follows:

<u>Total cost of hospitalizations for SH:</u> 5% of SH episodes among patients with T1D and 13% of SH episodes among patients with insulin requiring T2D require hospitalization[4] and the average cost of a hospitalization for SH is $12,787.[20] Applying a budget impact model, the cost associated with hospitalizations for SH without CGM use is $27,210,736/year; with CGM use is $11,163,051/year.

<u>Total cost of ER visits for SH:</u> 10% of SH episodes among patients with T1D and 21% of SH episodes among patients with T2D require an ER visit,[4] and the average cost of an ER visit for SH is $777.[20] Applying a budget impact model, the cost associated with ER visits for SH without CGM use is $2,731,068/year; with CGM use is $1,120,434/year.

<u>Total cost of ambulance transports for SH:</u> 31% of SH episodes among patients with T1D and 23% of SH episodes among patients with T2D require ambulance transport,[4] and the average cost of an ambulance transport for SH is $1,704.[21] Applying a budget impact model, the cost associated with ambulance transport without CGM use is $9,087,717/year; with CGM use is $3,724,944/year.

<u>Direct costs of CGM:</u> The average cost per patient for personal CGM is $2,800/year and the total cost for all insulin-requiring patients with IAH is $12,499,200/year.

<u>Net cost impact of CGM adoption:</u> Applying a budget impact model, it was found that the net savings of providing personal CGM to all insulin-requiring Medicaid beneficiaries with IAH in Washington is $10,521,551/year.

The results of the budget impact model show that providing Dexcom CGM systems to patients on intensive insulin therapy who are at high risk for SH may result in cost savings for Washington Medicaid. Because this model neglects the potential cost savings that would be accrued by reducing HbA1c and subsequent risk of long-term diabetes complications, the estimated cost savings are conservative.

In summary, CGM is a significant advancement in diabetes care with demonstrated clinical benefits. As such, we urge the HTCC to examine the current evidence and consider CGM coverage for patients on intensive insulin therapy who are not at their glycemic goals or are experiencing problematic

hypoglycemia. At your request, I am happy to share the referenced material, answer questions, or provide additional detail. Thank you for the opportunity to provide comments.

Respectfully,

[redacted]

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Cost-effectiveness of G5 Mobile continuous glucose monitoring device compared to self-monitoring of blood glucose alone for people with type 1 diabetes from the Canadian societal perspective

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ORIGINAL RESEARCH

Cost-effectiveness of G5 Mobile continuous glucose monitoring device compared to self-monitoring of blood glucose alone for people with type 1 diabetes from the Canadian societal perspective

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ABSTRACT

Aims: To evaluate the cost-effectiveness of real-time continuous glucose monitoring (CGM) compared to self-monitoring of blood glucose (SMBG) alone in people with type 1 diabetes (T1DM) using multiple daily injections (MDI) from the Canadian societal perspective.

Methods: The IMS CORE Diabetes Model (v.9.0) was used to assess the long-term (50 years) cost-effectiveness of real-time CGM (G5 Mobile CGM System; Dexcom, Inc., San Diego, CA) compared with SMBG alone for a cohort of adults with poorly-controlled T1DM. Treatment effects and baseline characteristics of patients were derived from the DIAMOND randomized controlled clinical trial; all other assumptions and costs were sourced from published research. The accuracy and clinical effectiveness of G5 Mobile CGM is the same as the G4 Platinum CGM used in the DIAMOND randomized clinical trial. Base case assumptions included (a) baseline HbA1c of 8.6%, (b) change in HbA1c of –1.0% for CGM users vs –0.4% for SMBG users, and (c) disutilities of –0.0142 for non-severe hypoglycemic events (NSHEs) and severe hypoglycemic events (SHEs) not requiring medical intervention, and –0.047 for SHEs requiring medical resources. Treatment costs and outcomes were discounted at 1.5% per year.

Results: The incremental cost-effectiveness ratio for the base case G5 Mobile CGM vs SMBG was $33,789 CAD/quality-adjusted life-year (QALY). Sensitivity analyses showed that base case results were most sensitive to changes in percentage reduction in hypoglycemic events and disutilities associated with hypoglycemic events. The base case results were minimally impacted by changes in baseline HbA1c level, incorporation of indirect costs, changes in the discount rate, and baseline utility of patients.

Conclusions: The results of this analysis demonstrate that G5 Mobile CGM is cost-effective within the population of adults with T1DM using MDI, assuming a Canadian willingness-to-pay threshold of $50,000 CAD per QALY.

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Introduction

Diabetes is a complex, progressive, and costly disease. There are an estimated 3.4 million people living with diabetes in Canada, and diabetes prevalence is estimated to increase by 44% between 2015–2025[1]. The economic burden of diabetes was estimated at ~CAD 12.2 billion in 2010, accounting for 3.5% of public healthcare spending in Canada, and is expected to increase in the coming years. Direct medical costs accounted for ~17% of the total diabetes expenditure and costs associated with premature death due to diabetes accounted for about two thirds of the total cost[2].

Diabetes is a chronic disease with significant long-term costs associated with disease-related complications. People with diabetes are more than 3-times as likely to be hospitalized with cardiovascular disease, 12-times more likely to be hospitalized with end-stage renal disease, and almost 20-times more likely to be hospitalized with non-traumatic lower limb amputations than the general population[3]. Diabetes is the leading cause of acquired blindness in Canadians under the age of 50, and diabetic retinopathy affects ~500,000 Canadians[4,5]. Given the chronic nature of diabetes and its high direct and indirect costs, long-term cost-effectiveness analyses are critically important to inform health technology assessment decision-makers regarding the reimbursement/funding for new therapeutic technologies intended to reduce the burden of disease.

Approximately 90% of all the diabetes cases in Canada are type 2 diabetes, and the remaining 10% are type 1 diabetes[2]. People with type 1 diabetes (T1DM) require life-long treatment with insulin. Proper management of diabetes requires both achieving optimal glycemic control and avoiding hypoglycemia. Long-term follow-up data from studies such as the Diabetes Control and Complications Trial (DCCT) have demonstrated a beneficial effect of improved glycemic control on cardiovascular (CV) outcomes. After ~11 years follow-up, compared with patients who received conventional diabetes management, patients who were intensively treated during the DCCT experienced a significant (42%) reduction in CV events, as well as a significant (57%) decrease in non-fatal myocardial infarctions, strokes, and CV deaths[6]. Analyses

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Supplemental data for this article can be accessed here.

performed 20 years after the DCCT showed that a mean of 6.5 years of intensive therapy aimed at achieving near-normal glucose levels reduced the risk of development and progression of retinopathy by as much as 76%, and was associated with a modestly lower all-cause mortality rate, compared with conventional therapy[7,8].

The Canadian Diabetes Association 2013 Guidelines recommended that therapy for most people with type 1 or type 2 diabetes should be targeted to achieve HbA1c $\leq$7.0% to reduce the risk of microvascular (retinopathy, nephropathy, and neuropathy) and, if implemented early in the course of disease, macrovascular (angina, myocardial infarction, stroke, peripheral artery disease, and congestive heart failure) complications. To achieve this target, it is recommended that adults with T1DM receive insulin delivered as basal-bolus injections (or use of a pen) or via continuous subcutaneous insulin infusion (CSII) using an insulin pump[9].

Despite advances in diabetes management and treatment, achieving optimal HbA1C levels still remains a challenge[10]. Multi-center clinical trials, such as the Juvenile Diabetes Research Foundation (JDRF) CGM study and the SWITCH study, have demonstrated the effectiveness of real-time CGM over SMBG in improving glycemic control[11,12]. Subsequent research has confirmed the efficacy of standalone real-time CGM when used in patients receiving multiple daily injections (MDI) of insulin to reduce HbA1c and glycemic variability[13,14]. In the recently conducted DIAMOND randomized controlled clinical trial in people with T1DM on multiple daily injections with a mean baseline HbA1c of 8.6%, there was a 1.0% reduction in HbA1c for the CGM group compared with 0.4% reduction in HbA1c for the SMBG group at 24 weeks from baseline ($p < .001$)[13]. In the DIAMOND RCT, Dexcom G4 Platinum CGM system (with 505 software) was used which is equivalent to the Dexcom G5 Mobile CGM system in terms of accuracy and performance[15–17].

The Dexcom G5 Mobile CGM System is unique by virtue of its indication for making treatment decisions without fingerstick blood glucose confirmation and integration with a smart phone device which obviates the need for a separate CGM receiver[16]. These advantages result in less utilization of resources (fewer blood glucose testing strips) and improved patient usability and satisfaction, thus impacting the cost-effectiveness of CGM. Given the clinical benefits of standalone real-time CGM, a cost-effectiveness analysis of G5 Mobile CGM compared to self-monitoring blood glucose (SMBG) was performed from the Canadian societal perspective for adults with T1DM.

Methods

The QuintilesIMS CORE Diabetes Model (CDM; QuintilesIMS Health, Basel, Switzerland) version 9.0 was chosen to perform the cost-effectiveness analyses of Dexcom G5 Mobile compared to SMBG in T1DM patients on multiple daily injections in this assessment. The IMS CDM has been previously used by the National Institute of Health and Care Excellence (NICE)[18] and other health technology assessment bodies in their economic evaluations of new technologies for people with T1DM, and is a commonly used model in the literature that has been extensively validated[19].

Model perspective, time-horizon, and discount rate

We used a cohort-based (bootstrap) model simulation over a 50-year time horizon as per convention with 1,000 simulation iterations containing 1,000 patients each; this approach was taken to create robust estimates and minimize errors.

Costs were estimated from the Canadian healthcare perspective. Consequences were expressed in quality-adjusted life years (QALYs) gained. As per Canadian Agency for Drugs and Technologies in Health (CADTH) guidelines for cost-effectiveness analyses in Canada, clinical and cost outcomes were discounted at a rate of 1.5% (Table 1)[20].

Model description

The IMS CDM is an internet-based, interactive simulation model that predicts the long-term health outcomes and costs associated with the management of diabetes. The IMS CDM is widely validated, and the latest validation publication from 2014 is the basis for the technical model description provided in this report[19]. This description is consistent with the latest version of the model (version 9.0). Given the degree of validation of the model, it was deemed important not to use an alternative model or develop a *de novo* cost-effectiveness model for this evaluation.

The IMS CDM comprises 17 inter-dependent sub-models, which represent the most common diabetes-related complications: angina pectoris, myocardial infarction (MI), congestive heart failure (CHF), stroke, peripheral vascular disease (PVD), diabetic retinopathy, cataracts, hypoglycemia, diabetic ketoacidosis (DKA), nephropathy, neuropathy, foot ulcer/amputation, macular edema, lactic acidosis (T2DM only), peripheral edema (T2DM only), and depression[19]. A sub-model for non-specific mortality is also included. Each of these sub-models is a Markov model that includes different health states reflecting the severity/stage of the complication. Transition probabilities between the states of a complication sub-model can be dependent on time, demographics, health state, physiological factors, and diabetes type[19]. The analysis used QuintilesIMS CORE Diabetes model's default 'minimum approach' for quality-adjusted life-year (QALY) estimation. In this approach, the quality-of-life for a patient with multiple complications is assumed to take the minimum of the utility values associated with these complications[32].

An important limitation of the model is that it is not suitable for modeling long-term outcomes for children or adolescent populations, because the background risk adjustment/risk factor progression equations are all based on adult populations. Hence, we had to limit all our analyses to the adult population[19].

Model inputs and assumptions

Cohort patient characteristics

The DIAMOND clinical trial population had a mean baseline HbA1c of 8.6% (SD = 0.7%) for both the CGM and SMBG

Table 1. Key base case parameter values and sources for IMS CORE modelling.

Base case parameter	Assumption	References
Patient demographics		
Mean cohort baseline HbA1c	8.6% (SD 0.7%)	Beck *et al.*[13]
Mean age	46 years	Beck *et al.*[13]
Mean duration of diabetes	19 years	Beck *et al.*[13]
Proportion of male	53%	Beck *et al.*[13]
Treatment effects		
Mean change in HbA1c		
SMBG only	–0.4% (SD 0.7%)	Beck *et al.*[13]
CGM + SMBG	–1.0% (SD 0.7%)	Beck *et al.*[13]
Hypoglycemia event rates		
SMBG only		
NSHE	2,900/100 patient years	UK Hypoglycemia Study Group[21]
SHE 1	278/100 patient years	UK Hypoglycemia Study Group[21]
SHE 2	42/100 patient years	UK Hypoglycemia Study Group[21]
% requiring medical services	13%	Foos *et al.*[22]
CGM + SMBG		
NSHE	26% reduction	Battelino *et al.*[23]
SHE 1	50% reduction	JDRF Continuous Glucose Monitoring Study Group[24,25]
SHE 2	50% reduction	JDRF Continuous Glucose Monitoring Study Group[24,25]
Key utility inputs		
Starting utility for people with type 1 diabetes adult cohort	0.90	Solli *et al.*[26]
Disutilities for hypoglycemic events		
NSHE	–0.0142	Currie *et al.*[27]; Beaudet *et al.*[28]
SHE 1	–0.0142	Currie *et al.*[27]; Beaudet *et al.*[28]
SHE 2	–0.047	Currie *et al.*[27]; Beaudet *et al.*[28]
Approach to hypoglycemia disutility progression	Stable impact	CDM default assumption
Key acute event costs		
Direct costs hypoglycemic events		
NSHE	4.79	Harris *et al.*[29]
SHE 1	29.47	O'Brien *et al.*[30]
SHE 2	2,101.6	CADTH[31]
Simulation time horizon	50 years	Convention
Discount rate	1.5%	CADTH[20]

NSHE, non-severe hypoglycemic event; SHE 1, severe hypoglycemic event requiring non-medical assistance; SHE 2, severe hypoglycemic events requiring medical assistance from a third party; SMBG, self-monitoring of blood glucose; CGM, continuous glucose monitoring; CDM, Core Diabetes Model.

groups for people with Type 1 diabetes on multiple daily injections. The mean age of the patients in the clinical trial was 46 years, and the mean duration of diabetes for these patients was 19 years[13]. The patient demographics and clinical characteristics in Table 1 reflect those in the DIAMOND clinical trial.

Treatment effects

The treatment effects for this analysis were sourced from the DIAMOND RCT. Results from this trial demonstrated a 1.0% reduction in HbA1c for the CGM group compared to 0.4% reduction for the SMBG group at 24 weeks from baseline (Table 1)[13].

A post-hoc analysis was done of CGM data collected from patients in the DIAMOND RCT, where a 33% median reduction was seen in *non-severe* hypoglycemic events (NSHEs), which were defined as events with a glucose level <54 mg/dL with a duration of at least 20 min[33]. By some standards, a hypoglycemic event with blood glucose <54 mg/dl lasting at least 20 min may be considered a severe hypoglycemic event[34]. However, for this cost-effectiveness analysis, we conservatively estimated that CGM would result in a 26% reduction in NSHEs, based on published data from earlier generation CGM devices.

The DIAMOND RCT was not designed or powered to detect severe hypoglycemic events (SHEs); therefore, in order to assess the effect of a reduction in *severe* hypoglycemic events, we conservatively assumed that CGM would result in a 50% reduction of severe hypoglycemia compared to SMBG alone. This is supported by data (83 individuals $\geq$25 years of age) demonstrating a 46% reduction in the rate of severe hypoglycemia in the "home use" continuation phase following the end-point of the Juvenile Diabetes Research Foundation (JDRF) randomized clinical trial. In this trial, the incidence rate of severe hypoglycemia was 21.8 per 100 person-years for the SMBG group and 7.1 events per 100 person-years for the CGM group in the first and last 6 months, respectively. As more recent CGM devices have demonstrated greater accuracy and are more "user friendly", we assumed a 50% reduction in severe hypoglycemic events associated with CGM in the base-case analysis[24,25]. The IN CONTROL RCT, which evaluated the impact of the addition of CGM to MDI or pump in T1DM patients with hypoglycemia unawareness, found that there was a 59% reduction in severe hypoglycemic events for patients in the CGM group compared to the control group of SMBG[35].

Sensitivity analyses were performed around reduction in severe and non-severe hypoglycemic events to determine the robustness of the results.

Utilities and costs

The base-line utilities for the T1DM patient cohort and for acute events can be seen in Table 1. The utilities associated

with each of the diabetes-related complications related health states were sourced from published literature and are available in Supplemental material 1.

According to a 2014 review of utility values in economic modeling for diabetes[28], the disutilities associated with acute hypoglycemic events vary widely. The disutilities associated with severe hypoglycemic event (SHE) and non-severe hypoglycemic event (NSHE) from the Marrett *et al.*[36] publication were –0.160 and –0.050, respectively, and the disutilities for SHE and NSHE from the Vexiau *et al.*[37] publication were –0.270 and –0.070, respectively. However, in this analysis (Table 1), we conservatively assumed the disutility associated with an SHE event to be –0.047 and with an NSHE to be –0.0142, based on Currie *et al.*[27,28]. Several studies have demonstrated that fear of hypoglycemia (FoH) is associated with decreases in health-related quality-of-life (HRQoL)[38–45]. The Currie *et al.*[27] 2006 study modeled the degree of FoH as well as changes in utility, with different levels of self-reported hypoglycemia by severity and frequency.

Only direct costs related to CGM, SMBG, and diabetes-related complications were included. All costs were adjusted to 2016 Canadian dollars (CAD). Costs related to insulin treatment were not included in the analyses, as those were assumed to be equivalent for both groups. The cost of CGM was based on the list price, and was sourced from the manufacturer (Table 2). The G5 Mobile CGM system is indicated as a replacement for fingerstick blood glucose testing[46]. However, G5 Mobile CGM still requires two fingersticks per day for calibration. In this analysis, we conservatively considered 2.3 fingersticks/day for calibration with G5 Mobile CGM (Table 2). In the long-term DCCT trial, fingerstick testing was done at least 4-times per day to meet the target HbA1c level in the intensively treated group of diabetes patients[47]. In this analysis, we conservatively assumed that patients in the SMBG comparator group use four fingersticks per day for blood glucose testing (Table 3). All unit costs for diabetes-related complications were inflated to 2016 values, and were sourced from published literature and are available in Supplementary material 2.

Table 2. Price of Dexcom G5 Mobile CGM (list price).

Annual intervention costs		G5 Standalone (CAD)
Transmitter	1,556	Dexcom communication. $389 per transmitter (4 transmitters per year)
Receiver	No receiver	Dexcom communication
Sensor	4,420	Dexcom communication $340 for a pack of 4; 13 packs per year
Finger stick calibration	612	Ontario Drug Benefit Program (×2.3 per day @ $0.729 per finger stick)[48]
Total G5 stand-alone costs	6,588	

Sensitivity analyses

One-way sensitivity analyses were conducted for key parameters, such as discount rate, baseline HbA1c level, hypoglycemia-related disutilities, HbA1c reduction conferred by CGM vs SMBG, percentage reduction in NSHEs and SHEs, starting utility of patients in the simulation cohort, and fingersticks per day, to determine the robustness of the results. Probabilistic sensitivity analysis was performed to derive the acceptability curve.

Results

The base-case results show that G5 Mobile CGM was associated with an improvement of 3.35 quality adjusted life-years (QALYs) compared to SMBG alone in T1DM adults receiving MDI. The total direct lifetime costs were $339,196 for the G5 Mobile CGM and $225,862 for SMBG alone. The incremental cost-effectiveness ratio (ICER) for G5 Mobile CGM compared to SMBG alone is $33,789/QALY in Canadian dollars (Table 4). The mean time to onset for each of the complications can be seen in Supplemental material 3.

Extensive one-way sensitivity analysis was conducted on key input parameters (Table 5). Base-case results were not impacted by a change in the discount rate, baseline starting utility, or baseline starting %HbA1c level. However, in the sensitivity analysis, when the severe hypoglycemic event reduction rate on G5 Mobile CGM compared with SMBG alone is increased from 50% to 75%, the ICER becomes $29,140/QALY gained and,on the other hand, when this rate is decreased to 25%, the ICER becomes $39,662/QALY. Thus, the ICER was moderately impacted by the reduction in severe hypoglycemic events due to G5 Mobile CGM in this analysis. However, when the hypoglycemia-related disutilities were increased and decreased by 50%, it resulted in ICERs of

Table 3. SMBG group list price.

Annual intervention costs		SMBG (CAD)
Base-case		
SMBG group – 4 fingersticks per day	1,064	Cost is $0.729 per test strip[48]
SMBG group – 6 fingersticks per day	1,597	Cost is $0.729 per test strip[48]
SMBG only – 8.2 fingersticks per day	2,182	Cost is $0.729 per test strip[48]
		Ontario Drug Benefit Program reimburses 3000 test strips per patient, i.e. 8.21 test strips per patient per day[49]

Table 4. Base case cost-effectiveness results for G5 Mobile RTCGM vs SMBG alone for individuals with Type 1 diabetes in Canada (list price).

Outcomes	CGM + SMBG, Mean	SMBG, Mean	Difference, Mean
Life expectancy (years)	23.233 (CI: 23.216–23.25)	23.197 (CI: 23.18–23.213)	0.037 (CI: 0.013–0.061)
Quality-adjusted life years (QALYs)	8.382 (CI: 8.375–8.388)	5.027 (CI: 5.023–5.032)	3.354 (CI: 3.346–3.326)
Total lifetime direct costs (CAD)	339,196 (CI: 338,567–339,825)	225,862 (CI: 225,278–226,447)	113,334 (CI: 112,468–114,199)
Incremental costs/QALY gained (CAD)			33,789 (CI: 33,558–34,079)

CGM, continuous glucose monitoring; ICER, incremental cost-effectiveness ratio; QALY, quality-adjusted life year; SMBG, self-monitoring of blood glucose.

$65,363/QALY gained and $22,783/QALY gained, respectively. Increasing the number of fingersticks used by patients per day in the SMBG group from 4 fingersticks to 6 and 8.2 fingersticks per day improved the cost-effectiveness for the G5 Mobile CGM compared to SMBG alone (Table 5). The cost-effectiveness acceptability curve for the G5 Mobile CGM can be seen in Figure 1.

Discussion

Cost-effectiveness analyses are important to consider for health technology assessment decision-making. Healthcare systems should consider the costs to society resulting from the failure to give patients access to CGM, including costs of managing severe and non-severe hypoglycemic episodes, costs of failing to achieve optimal glycemic control, and reductions in quality-of-life experienced by people suffering from diabetes. Costs are difficult to estimate because of the long-term nature of health outcomes in diabetes. CGM technology is improving (in accuracy and usability) at a rate which may make cost-effectiveness analyses obsolete by the time newer data are published[50]. The accuracy of the CGM devices has improved significantly over time. For example, the G5 Mobile CGM system is approved for the replacement of confirmatory self-monitoring blood glucose measurements when making therapeutic decisions in Canada (CGM G5 still requires two fingersticks for calibration)[46]. Evidence from REPLACE-BG, a multi-center, randomized, non-inferiority clinical trial, demonstrated that the use of the G5 Mobile CGM without confirmatory SMBG is as safe and effective as using CGM adjunctive to SMBG in adults with T1DM and an HbA1c close to target[50]. Also, a smart phone (or mobile device) can be used in lieu of the dedicated receiver. Both (1) the reduction in SMBG usage from 4–8-times a day to 2-times a day and (2) the ability to use a CGM with a mobile device instead of a receiver introduce cost savings for the healthcare system and impacts the cost-effectiveness of CGM. The ICER for G4 Platinum CGM that requires a receiver and SMBG confirmation is $40,120 CAD/QALY, compared with $33,789 CAD/QALY for G5 Mobile CGM.

An important aspect of cost-effectiveness analysis is determining the optimal "baseline" utility value and the appropriate set of dis-utilities, and this involves challenges comparable to those for other input parameters. For example, differences in reported utility values may be due to a variety of factors including cohort age, comorbidities[39], and use of different utility-assessment procedures[40]. Sensitivity analysis demonstrates that the results of this analysis were robust to changes in the baseline utility value of people with T1DM. In this analysis, the highest ICER was observed when

Table 5. Sensitivity analyses (base-case—G5 Mobile CGM vs SMBG alone).

Parameter	ICER (CAD) (CI)
Discount rate = 0%	$34,411 (33,166–33,785)
Discount rate = 3%	$33,729 (33,550–34,078)
Cohort baseline HbA1c = 7.6%	$34,781 (34,579–35,067)
Cohort baseline HbA1c = 9.5%	$32,816 (32,530–33,129)
Hypoglycemia disutilities decrease by 50%	$65,363 (65,394–66,617)
Hypoglycemia disutilities increase by 50%	$22,783 (22,618–22,977)
Non-severe hypoglycemic events reduction = 50%	$19,715 (19,569–19,868)
Severe hypoglycemic event reduction = 25%	$39,662 (39,417–39,987)
Severe hypoglycemic event reduction = 75%	$29,140 (28,922–29,387)
Starting utility of cohort = 0.71	$34,382 (34,137–34,655)
Starting utility of cohort = 0.95	$33,656 (33,429–33,951)
G5 Mobile CGM vs SMBG with 6 fingersticks per day	$29,871 (29,642–30,138)
G5 Mobile CGM vs SMBG with 8.2 fingersticks per day	$25,731 (25,496–25,990)
% HbA1c reduction for CGM vs SMBG = 0.3	$34,738 (34,453–35,023)
% HbA1c reduction for CGM vs SMBG = 0.9	$32,723 (32,463–32,984)
G4 Platinum CGM (with receiver) vs SMBG	$40,160 (39,896–40,425)

CGM, continuous glucose monitoring; CI, confidence interval; ICER, incremental cost-effectiveness ratio; QALY, quality-adjusted life year; SMBG, self-monitoring of blood glucose.

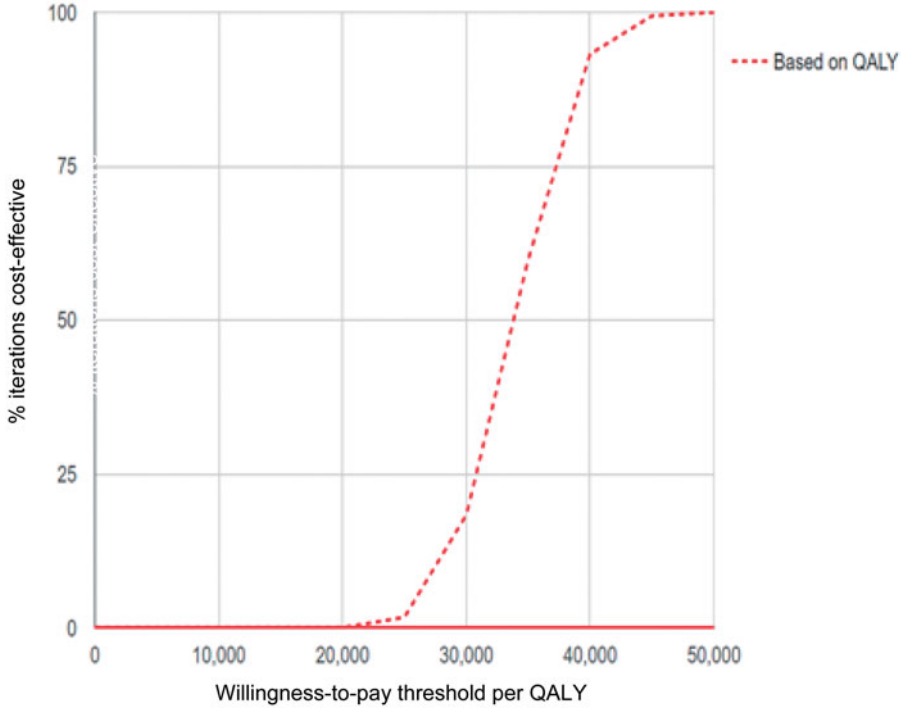

Figure 1. Probabilistic analysis cost-effectiveness analysis acceptability curve for G5 Mobile vs SMBG from the Canadian perspective.

the hypoglycemia-related disutilities were decreased by 50% (ICER = $65,363 CAD/QALY). Several studies have demonstrated that fear of hypoglycemia (FoH) can impact the health-related quality-of-life in diabetes patients[38,40,42,51]. In Canada, 40% of the persons with diabetes are worried about hypoglycemia risks, and this negative impact of the worry about hypoglycemia was found to be independent of the type of diabetes and treatment[52]. Recent RCTs such as that in the Diamond clinical trial demonstrate that CGM significantly increases hypoglycemia related confidence compared with SMBG. The most striking group differences were seen in staying safe from serious hypoglycemic problems while sleeping and while driving[53]. This improvement in quality-of-life of patients with T1DM due to CGM use is reflected by the incremental quality adjusted life years (QALYS) seen for G5 Mobile compared with SMBG in this analysis. The Currie *et al.*[27] study was considered appropriate for deriving dis-utilities related to fear of hypoglycemia for this analysis, because the objective of the Currie *et al.*[27] study was to model the degree of fear of hypoglycemia experienced by individuals ($n = 1305$) with T1DM or T2DM (45% on insulin), as well as change in utility with different levels of self-reported hypoglycemia severity and frequency. Given these insights, the greatest value of CGM may be in the high-risk sub-group of patients with an increased risk and frequency of hypoglycemic events. These include sub-groups of people with T1DM, such as those with a history of hypoglycemic events[54]; impaired awareness of hypoglycemia (risk of hypoglycemic events is 6-fold higher)[55]; and those experiencing nocturnal hypoglycemia (since this is difficult to detect with SMBG)[56].

This review of published literature indicates that only two of all published studies assessed the cost-effectiveness of standalone CGM[57,58], while the remainder assessed the cost-effectiveness of integrated insulin pump therapy and CGM[18,59–62]. The two published studies evaluating the cost-effectiveness of standalone CGM were from the US societal perspective, and were based on outcomes from the JDRF trial that included patients who used CGM integrated with an insulin pump. The ICER for the Huang *et al.*[57] study with lifetime time-horizon was $98,679 USD/QALY and for the McQueen *et al.*[58] study with a 33-year time-horizon was $45,033 USD/QALY. Other studies, such as Kamble *et al.*[59], assessed the cost-effectiveness of SAP (sensor augmented pump that includes the addition of two technologies: pump plus CGM) compared with MDI, while Ly *et al.*[60], Roze *et al.*[61] (France) and Roze *et al.*[62] (UK) assessed the cost-effectiveness of SAP (with low glucose suspend feature) compared with standard pump therapy, and the Riemsma *et al.*[18] study was an economic evaluation of integrated sensor augmented pumps.

To our knowledge, the current analysis is the first one to demonstrate the cost-effectiveness of standalone CGM compared with SMBG from the Canadian societal perspective. The base case ICER in the present study is more in line with the ICER reported in McQueen *et al.*[58], and the more favorable ICER seen in our analysis is more likely because of the improved CGM performance over time that results in greater patient trust in their device, promoting better adherence to CGM and sustained improvements in HbA1c.[63]

Conclusions

The results of this cost-effectiveness analysis demonstrate that the base case incremental cost-effectiveness ratio (ICER) for G5 Mobile CGM compared to SMBG alone is $33,789 CAD/QALY (CI = $33,558–$34,079). The base case ICER is robust to changes in discount rate, baseline HbA1c level, and starting utility of the people with the T1DM cohort. The base case ICER is impacted by the increase in SMBG usage, increase or decrease in hypoglycemia-related disutilities, and increase or decrease in the reduction in the rate of severe hypoglycemic events associated with CGM. The results of this cost-effectiveness analysis conducted with IMS CORE Diabetes model for G5 Mobile CGM compared with SMBG alone in a cohort of people with T1DM over a 50-year time horizon demonstrate that G5 Mobile is a cost-effective intervention at a willingness-to-pay threshold of $50,000 CAD/QALY[64].

Transparency

Declaration of funding

This study was supported by funding from Dexcom, Inc.

Declaration of financial/other relationships

At the time of study completion and manuscript development, SC and CG were employees of Dexcom, Inc.

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