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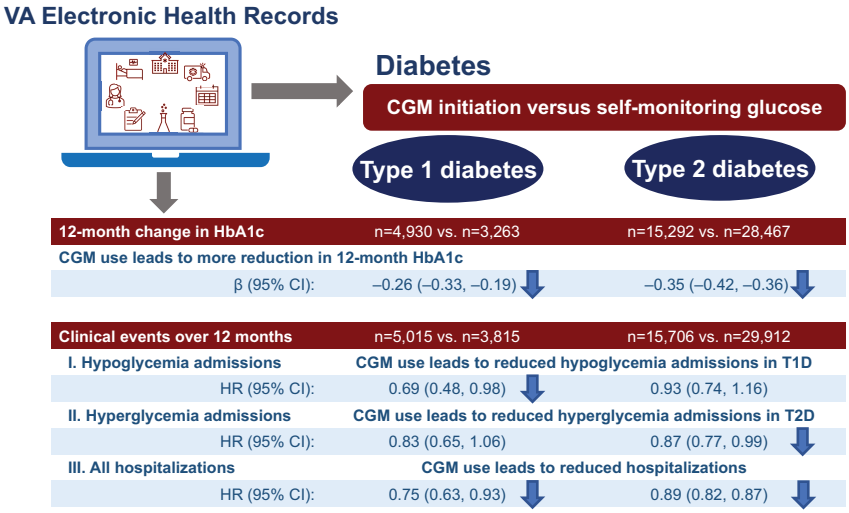

CGM, continuous glucose monitoring; HR, hazard ratio; T1D, type 1 diabetes; T2D, type 2 diabetes; VA, Veterans Administration.

ARTICLE HIGHLIGHTS

- There is a paucity of real-world data on the effects of continuous glucose monitoring (CGM) on clinically important end points.
- We sought to determine whether CGM initiation improves glycemic management and reduces risk of admission to an emergency room or hospital.
- Initiation of CGM was associated with lower HbA_{1c} and overall lower risk of admission to an emergency room or hospital for hypoglycemia or hyperglycemia and of all-cause hospitalization.
- Several clinically relevant subgroups demonstrated greater benefits from CGM initiation.

Initiation of Continuous Glucose Monitoring Is Linked to Improved Glycemic Control and Fewer Clinical Events in Type 1 and Type 2 Diabetes in the Veterans Health Administration

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ORIGINAL ARTICLE

OBJECTIVE

To determine the benefit of starting continuous glucose monitoring (CGM) in adult-onset type 1 diabetes (T1D) and type 2 diabetes (T2D) with regard to longer-term glucose control and serious clinical events.

RESEARCH DESIGN AND METHODS

A retrospective observational cohort study within the Veterans Affairs Health Care System was used to compare glucose control and hypoglycemia- or hyperglycemia-related admission to an emergency room or hospital and all-cause hospitalization between propensity score overlap weighted initiators of CGM and nonusers over 12 months.

RESULTS

CGM users receiving insulin (*n* = 5,015 with T1D and *n* = 15,706 with T2D) and similar numbers of nonusers were identified from 1 January 2015 to 31 December 2020. Declines in HbA_{1c} were significantly greater in CGM users with T1D (−0.26%; 95% CI −0.33, −0.19%) and T2D (−0.35%; 95% CI −0.40, −0.31%) than in nonusers at 12 months. Percentages of patients achieving HbA_{1c} <8 and <9% after 12 months were greater in CGM users. In T1D, CGM initiation was associated with significantly reduced risk of hypoglycemia (hazard ratio [HR] 0.69; 95% CI 0.48, 0.98) and all-cause hospitalization (HR 0.75; 95% CI 0.63, 0.90). In patients with T2D, there was a reduction in risk of hyperglycemia in CGM users (HR 0.87; 95% CI 0.77, 0.99) and all-cause hospitalization (HR 0.89; 95% CI 0.83, 0.97). Several subgroups (based on baseline age, HbA_{1c}, hypoglycemic risk, or follow-up CGM use) had even greater responses.

CONCLUSIONS

In a large national cohort, initiation of CGM was associated with sustained improvement in HbA_{1c} in patients with later-onset T1D and patients with T2D using insulin. This was accompanied by a clear pattern of reduced risk of admission to an emergency room or hospital for hypoglycemia or hyperglycemia and of all-cause hospitalization.

Clinical trials and observational studies of continuous glucose monitoring (CGM) have most often been conducted in traditional type 1 diabetes (T1D) patient populations

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(i.e., those characterized by early onset of disease, autoimmune destruction of islets, and more rapid and complete dependence on insulin). Because most studies have been shorter in duration, they have focused on changes in HbA_{1c} or metrics such as time in range or time below range (1,2). Although some, but not all, studies have suggested potential reductions in the number of serious hypoglycemia and possibly hyperglycemia events, more data on these clinically relevant outcomes are clearly needed (1–4).

Despite a rapid expansion of CGM use in T2D, even less is known about the nature and duration of benefits of CGM use in this population. Although randomized clinical trials have shown trends toward improvement in HbA_{1c}, they provide less consistent evidence for reduction in time in hypoglycemia or hyperglycemia and minimal evidence of effects on clinically important hypoglycemia or hyperglycemia events (5–7). In a relatively large retrospective observational study of patients with T1D (with a smaller number of patients with T2D) within the Kaiser health system, Karter et al. (8) confirmed CGM-related improvement in HbA_{1c}, overall and in both groups separately, but reported more mixed results regarding hospitalization for hypoglycemia or hyperglycemia.

The cost of CGM devices along with the provision of technical and educational support to patients and providers to initiate and maintain broad CGM use in health care institutions is substantial. It is therefore of great importance to understand existing CGM use patterns among both patients with T1D and those with T2D and potential benefits regarding overall glycemic control and adverse events such as emergency room (ER) visits and hospitalizations.

The objective of this study was to use the large population of patients with T1D or T2D and their comprehensive medical records within the Veterans Health Administration (VHA) health care system to determine differences in glucose control and adverse diabetes outcomes over 12 months in those who initiated CGM compared with those using glucose strip–based monitoring. We also examined these outcomes by key baseline characteristics and CGM use patterns.

RESEARCH DESIGN AND METHODS

Study Design

A retrospective observational cohort design was used to compare glucose control and several clinically relevant events over 12 months of follow-up. The protocol was approved by the Phoenix Veterans Affairs Health Care System Institutional Review Board, which provided a waiver of consent for this analysis of secondary data. We extracted all relevant electronic health record data from the VHA Corporate Data Warehouse, a national repository of clinical and administrative information from VHA encounters that includes both inpatient and outpatient visits, diagnoses, pharmacy and medication use, vital signs records, laboratory measurements, and general patient demographic information.

Study Population

To identify patients with diabetes initiating CGM from 1 January 2015 to 31 December 2020, all available ICD-9 and ICD-10 diagnostic codes were extracted from medical encounters among U.S. veterans age ≥21 years with at least one diagnosis of diabetes (ICD-9 250 or ICD-10 E10, E11, O24.0×, or O24.1×) between 2002 and 2020. Initiators of CGM (also subsequently referred to as CGM users) were identified as those with their first prescription (defined as index date) between 1 January 2015 and 31 December 2020. CGM prescriptions were identified if they matched a glucose sensor for the devices available in the VHA during this time period (Dexcom, Freestyle Libre, and Medtronic). Initiation of specific CGM sensors for T1D and T2D were, respectively, Dexcom (50% and 34%), Freestyle Libre (10% and 63%), and Medtronic (40% and 3%).

All remaining patients with no record of a filled prescription for a CGM glucose sensor were selected as nonusers and randomly assigned an index date between 1 January 2015 and 31 December 2020 if they were prescribed blood glucose test strips for self-monitoring in the year before their assigned index date. Additional criteria for inclusion in the cohort (detailed in Supplementary Fig. 1) included classification as a patient with T1D or T2D and having sufficient baseline and follow-up participation in VHA care (defined below).

Identification of T1D and T2D followed a modified Klompas algorithm (9) (Supplementary Methods). Individuals included in the cohort had to have at least 2 years of preindex activity within the VHA, at least one clinical encounter in primary care or endocrinology in the year before their index date, and a postindex date interaction within the VHA. To achieve balanced propensity scores (PSs) in T2D, it was necessary to limit both CGM users and nonusers to those using insulin in the year before the index date but not receiving insulin pumps. Because diabetes is an exclusion criterion for enrollment in the military, T1D in the current cohort reflects adult-onset disease.

Data Extraction Procedures

We used ICD-9 Clinical Modification and ICD-10 Clinical Modification codes to identify prevalent medical conditions or outcomes. Visit types were identified by associated clinic stop codes and were linked with dates, services provided, and diagnoses. Laboratory measurements were captured using LOINC (Logical Observation Identifiers Names and Codes) codes. Calculation of proportion of days covered (PDC) by medication refills was used as an estimate of duration and consistency of medication use.

We extracted outpatient medical records for visits, demographics, medications, diagnoses, and general laboratory measures in the 12 months before the index date. However, baseline HbA_{1c} was selected as the HbA_{1c} value closest to the index date (within 6 months), and information for comorbidity indices was collected up to 24 months preindex date. Inpatient admissions or ER visits were identified from inpatient admission records.

A large number of demographic and clinical variables were considered to build PSs for CGM users and nonusers (highlighted in Tables 1 and 2 and Supplementary Methods).

Outcomes

Primary outcomes included *1*) glycemic control (change in HbA_{1c} at 6 and 12 months after the index date), *2*) hypoglycemia events (the first postindex date occurrence of an ER or hospital admission if hypoglycemia was listed as one of the diagnostic codes), *3*) hyperglycemia events (defined similarly as hypoglycemia), and *4*) all-cause hospitalization (the first postindex date occurrence of any inpatient admission). We used a 12-month postindex date observation window to assess the change in HbA_{1c} and the onset of these outcomes. A secondary outcome included the change in the percentage of patients achieving HbA_{1c}

Table 1—Baseline characteristics before and after PS overlap weighting in individuals with T1D (n = 8,533)

	Unweighted			Overlap weighted		
T1D	Nonusers (n = 3,518)	CGM users (n = 5,015)	SMD	Nonusers (n = 3,518)	CGM users (n = 5,015)	SMD
Index year, %			0.546			<0.001
2015	19.9	8.3		10.0	10.0	
2016	18.1	10.5		12.4	12.4	
2017	17.2	11.3		13.9	13.9	
2018	17.3	23.0		18.7	18.7	
2019	15.2	25.7		21.5	21.5	
2020	12.4	21.2		23.5	23.5	
Mean (SD) age at index, years	64.5 (11.7)	59.4 (11.3)	0.438	61.7 (11.6)	61.7 (11.3)	<0.001
Male sex, %	95.3	91.4	0.156	93.5	93.5	<0.001
Mean (SD) BMI, kg/m^2	28.5 (6.20)	28.0 (5.1)	0.094	27.7 (5.9)	27.7 (5.3)	<0.001
Ethnicity, %			0.231			<0.001
White, non-Hispanic	73.8	83.2		79.7	79.7	
African American	20.5	12.8		15.3	15.3	
White, Hispanic	4.1	3.0		3.5	3.5	
Other	1.6	1.1		1.5	1.5	
U.S. region, % of total			0.029			<0.001
South	40.5	39.4		38.5	38.5	
Midwest	24.6	25.5		24.0	24.0	
West	22.6	23.2		26.0	26.0	
Northeast	12.3	11.9		11.4	11.4	
Endocrinologist visit, %	34.8	91.1	1.435	72.1	72.1	<0.001
Median (IQR) total PCP and endocrine visits	3 (2, 6)	6 (4, 9)	0.610	5 (3, 8)	5 (3, 8)	<0.001
Mean (SD) LDL cholesterol, mg/dL	85 (33)	86 (32)	0.040	86 (34)	86 (32)	<0.001
Mean (SD) HDL cholesterol, mg/dL	49 (16)	55(16)	0.338	53 (17)	53(16)	<0.001
Mean (SD) total cholesterol, mg/dL	159 (41)	162 (40)	0.073	161 (42)	161 (40)	<0.001
Median (IQR) triglycerides, mg/dL	100 (69, 152)	84 (60, 124)	0.220	91 (64, 139)	88 (63, 133)	<0.001
Mean (SD) SBP, mmHg	134 (15)	133 (14)	0.137	133 (14)	134 (14)	0.020
Mean (SD) DBP, mmHg	74 (9)	75 (8)	0.066	75 (8)	74 (8)	0.039
Median (IQR) creatinine, mg/dL	1.1 (0.9, 1.3)	1.0 (0.9, 1.2)	0.152	1.0 (0.9, 1.3)	1.0 (0.9, 1.3)	<0.001
Mean (SD) eGFR, mL/min/1.73 m^2	73 (25)	78 (23)	0.202	75 (25)	75 (24)	<0.001
Mean (SD) HbA_{1c}, %	8.2 (1.6)	8.4 (1.4)	0.102	8.5 (1.6)	8.5 (1.4)	0.019
Mean (SD) HbA_{1c}, mmol/mol	66 (17.5)	68 (15.3)	0.102	69 (17.5)	69 (15.3)	0.019
Any insulin use, %	100.0	100.0	<0.001	100.0	100.0	<0.001
Dual basal and bolus use	81.5	67.1	0.334	79.3	77.9	0.034
Basal use only	10.3	0.7	0.427	2.2	2.2	0.004
NPH insulin	10.0	3.3	0.273	4.0	4.0	<0.001
Long/basal insulin	76.4	66.4	0.222	78.2	78.2	<0.001
Mixed insulin	8.8	1.4	0.342	2.0	2.0	<0.001
Short/rapid insulin	89.7	99.3	0.427	97.8	97.8	0.004
Insulin pump use, %	5.6	49.7	1.134	18.8	18.8	<0.001
Glucagon, %	10.9	33.6	0.568	21.4	21.4	<0.001
Statin use, %	71.4	75.9	0.102	75.1	75.1	<0.001
Antihypertensive medication use, %	77.7	69.5	0.188	74.0	74.0	<0.001
Hypoglycemic risk score			0.132			<0.001
Low	71.1	76.3		72.9	72.9	
Intermediate	19.2	14.4		16.6	16.6	
High	9.6	9.3		10.5	10.5	
Noninsulin diabetes medication, %	23.3	16.3	0.177	20.4	20.4	<0.001
Metformin	20.3	13.5	0.183	16.7	16.3	0.013

Continued on p. 857

Table 1—Continued

	Unweighted			Overlap weighted		
T1D	Nonusers (*n* = 3,518)	CGM users (*n* = 5,015)	SMD	Nonusers (*n* = 3,518)	CGM users (*n* = 5,015)	SMD
Private insurance, %	30.6	46.4	0.329	37.0	37.0	<0.001
Medicare, %	60.3	42.3	0.366	51.6	51.6	<0.001
Medicaid, %	2.0	1.4	0.046	2.2	2.2	<0.001
Extended care, %	8.9	5.1	0.150	7.8	7.8	<0.001
Housing insecurity, %	4.4	2.9	0.083	4.0	4.0	<0.001
Hospice care, %	0.8	0.5	0.043	0.9	0.9	<0.001
ER visits, %			0.070			<0.001
0	78.1	75.7		75.5	75.5	
1	11.7	14.1		13.3	13.3	
≥2	10.2	10.2		11.2	11.2	
Elixhauser comorbidity score, %			0.111			0.024
0	7.7	10.3		8.1	8.1	
1	24.7	25.9		23.6	24.2	
2	25.7	25.8		26.0	25.1	
≥3	41.9	37.9		42.3	42.3	
DCSI weighted score, %			0.094			0.054
0	25.6	21.9		22.4	22.2	
1	21.6	24.2		22.7	20.9	
2	18.4	19.0		17.3	18.9	
≥3	34.3	34.9		37.5	38.0	
Hypoglycemia event, %	3.6	3.6	0.004	4.0	4.0	<0.001
Hypoglycemia event or outpatient glucose <54 mg/dL, %	9.0	9.4	0.016	9.7	9.9	0.007
Hyperglycemia event, %	7.2	7.2	0.003	7.9	7.9	<0.001
Hospitalization, %	16.6	13.6	0.083	16.0	16.0	<0.001

The baseline period is the period before the index date. SMD <0.1 indicates a covariate is balanced between groups. Hypoglycemia and hyperglycemia were identified by ICD-9/10 diagnostic codes from inpatient or ER settings. Hypoglycemia or glucose <54 mg/dL includes diagnoses or outpatient glucose laboratory values <54 mg/dL. Hospitalizations were identified by inpatient admissions. Extended care includes long-term inpatient stays, nursing home consults, or skilled home care consults. The baseline period for events and values is standardized for all participants to 1 year before the index date, except for HbA_{1c} values that are within 6 months before the index date and Elixhauser comorbidity and DCSI weighted scores that are within 24 months before the index date. DBP, diastolic blood pressure; DCSI, Diabetes Complications Severity Index; eGFR, estimated glomerular filtration rate; IQR, interquartile range; NPH, neutral protamine hagedorn; PCP, primary care provider; SBP, systolic blood pressure.

values below 7%, 8%, and 9% during this time window.

Negative control outcomes assessed potential bias resulting from possible residual confounding factors between CGM users and nonusers (10). They share the same potential sources of bias as primary outcomes but are less plausibly related to CGM use. Two negative control outcomes were considered in outpatient and inpatient settings: *1*) specific musculoskeletal diagnoses associated with back, joint, and soft tissue disorders or injuries and *2*) upper respiratory infections.

Statistical Analyses

Baseline characteristics are presented as mean (SD), median (interquartile range), or percentage. To handle missing data, multiple imputation by chained equations (11) was performed to create five imputed data sets, which were subsequently combined.

Overlap PS weighting was used to balance baseline covariates between CGM users and nonusers. We calculated PSs by logistic regression models that predicted CGM initiation using >40 candidate predictors (Tables 1 and 2 and Supplementary Methods). All PS models demonstrated excellent discrimination (C statistic ≥0.93 for each). To improve balance between CGM users and nonusers in T2D, we applied downsampling and randomly selected 10% of the nonusers for comparison.

Overlap weights equaled 1 − PS for CGM users and PS for nonusers. Covariate differences before and after overlap weighting were assessed using standardized mean difference (SMD). An absolute SMD value of <0.1 was considered a negligible group imbalance.

We compared the changes in HbA_{1c} between CGM users and nonusers using linear mixed models (LMMs). We compared the percentage of individuals achieving HbA_{1c} targets between CGM users and nonusers using generalized estimating equations (GEEs). Difference in differences was then calculated, and the Δ method was used to derive CIs (12).

Our primary clinical outcomes and negative control events were analyzed using Cox proportional hazards models with overlap weighting. Individuals were censored if they were lost to follow-up, died, or had no event in the 12-month

Table 2—Baseline characteristics before and after PS overlap weighting in individuals with T2D (*n* = 45,618)

	Unweighted			Overlap weighted		
T2D	Nonusers (*n* = 29,912)	CGM users (*n* = 15,706)	SMD	Nonusers (*n* = 29,912)	CGM users (*n* = 15,706)	SMD
Index year, %			1.421			<0.001
2015	17.0	0.7		2.1	2.1	
2016	16.9	1.2		2.9	2.9	
2017	16.8	2.0		4.5	4.5	
2018	16.7	9.8		14.1	14.1	
2019	16.6	34.4		32.4	32.4	
2020	16.0	51.8		44.0	44.0	
Mean (SD) age at index, years	68.3 (9.5)	66.7 (9.8)	0.167	67.7 (9.7)	67.7 (9.6)	<0.001
Male sex, %	96.3	94.0	0.106	95.0	95.0	<0.001
Mean (SD) BMI, kg/m^2	33.0 (6.6)	32.7 (6.8)	0.048	33.0 (6.7)	33.0 (6.8)	<0.001
Ethnicity, %			0.125			<0.001
White, non-Hispanic	69.9	75.0		73.2	73.2	
African American	20.6	17.4		18.5	18.5	
White, Hispanic	6.8	4.8		5.4	5.4	
Other	2.8	2.8		3.0	3.0	
U.S. region, %			0.277			<0.001
South	44.6	39.2		40.3	40.3	
Midwest	23.8	22.5		24.3	24.3	
West	19.9	16.6		18.8	18.8	
Northeast	11.7	21.8		16.6	16.6	
Endocrinologist visit, %	19.4	67.8	1.119	43.8	43.8	<0.001
Median (IQR) total PCP and endocrine visits	4 (2, 6)	6 (4, 9)	0.499	5 (3, 8)	5 (3, 8)	<0.001
Mean (SD) LDL cholesterol, mg/dL	81 (34)	80 (35)	0.045	80 (34)	80 (34)	<0.001
Mean (SD) HDL cholesterol, mg/dL	40 (11)	41 (13)	0.161	41 (12)	41 (12)	<0.001
Mean (SD) total cholesterol, mg/dL	152 (42)	154 (44)	0.025	152 (44)	152 (43)	<0.001
Median (IQR) triglycerides, mg/dL	145 (100, 218)	145 (97, 225)	0.048	146 (100, 222)	145 (97, 222)	<0.001
Mean (SD) SBP, mmHg	135 (14)	134 (13)	0.059	135 (14)	134 (13)	0.019
Mean (SD) DBP, mmHg	74 (8)	74 (8)	0.040	74 (8)	74 (8)	0.052
Median (IQR) creatinine, mg/dL	1.1 (0.9, 1.4)	1.2 (0.9, 1.5)	0.097	1.2 (0.9, 1.5)	1.2 (0.9, 1.5)	<0.001
Mean (SD) eGFR, mL/min/1.73 m^2	68 (24)	66 (25)	0.106	66 (25)	66 (25)	<0.001
Mean (SD) HbA_{1c}, %	8.1 (1.6)	8.7 (1.7)	0.366	8.5 (1.7)	8.5 (1.6)	0.008
Mean (SD) HbA_{1c}, mmol/mol	65 (17.5)	72 (18.6)	0.366	69 (18.6)	69 (17.5)	0.008
Any insulin use, %	100	100	<0.001	100	100	<0.001
Dual basal and bolus use	56.7	87.4	0.730	79.2	78.4	0.021
Basal use only	41.0	6.6	0.884	16.4	15.8	0.017
NPH insulin	12.9	4.9	0.284	6.0	6.0	<0.001
Long/basal insulin	76.9	89.7	0.348	87.0	87.0	<0.001
Mixed insulin	11.7	6.0	0.203	7.2	7.2	<0.001
Short/rapid insulin	48.9	91.1	1.039	79.3	79.3	<0.001
Glucagon, %	1.1	10.9	0.419	3.8	3.8	<0.001
Statin use, %	81.1	83.6	0.067	83.0	83.0	<0.001
Antihypertensive medication use, %	86.8	86.0	0.023	86.1	86.1	<0.001
Hypoglycemic risk score			0.153			<0.001
Low	71.3	65.7		69.4	69.4	
Intermediate	24.9	27.6		25.6	25.6	
High	3.8	6.7		5.0	5.0	
Noninsulin diabetes medication, %	67.4	67.7	0.006	67.8	67.1	0.016
Metformin	54.6	48.8	0.118	51.3	51.3	<0.001
Sulfyonureas	27.0	12.1	0.384	16.1	16.1	<0.001
DPP-4 inhibitor	7.5	11.9	0.148	11.5	11.5	<0.001

Continued on p. 859

Table 2—Continued

	Unweighted			Overlap weighted		
T2D	Nonusers (*n* = 29,912)	CGM users (*n* = 15,706)	SMD	Nonusers (*n* = 29,912)	CGM users (*n* = 15,706)	SMD
SGLT-2 inhibitor	4.2	18.2	0.455	13.3	13.3	<0.001
Thiazolidinediones	2.8	4.8	0.107	4.1	4.1	<0.001
GLP-1 agonists	6.5	22.8	0.474	17.7	17.7	<0.001
α-Glucosidase inhibitors	1.2	0.6	0.064	0.8	0.8	<0.001
Glinides	0.2	0.2	0.005	0.2	0.2	<0.001
Amylin	0.0	0.1	0.017	0.0	0.1	0.030
Private insurance, %	33.4	38.1	0.100	36.7	36.7	<0.001
Medicare, %	71.7	69.9	0.39	71.5	71.5	<0.001
Medicaid, %	1.5	1.7	0.018	1.6	1.6	<0.001
Extended care, %	8.6	12.5	0.128	11.2	11.2	<0.001
Housing insecurity, %	3.3	2.7	0.034	2.8	2.8	<0.001
Hospice care, %	1.0	1.4	0.038	1.3	1.3	<0.001
ER visits, %			0.183			<0.001
0	75.7	67.9		71.9	71.9	
1	13.1	15.6		14.2	14.2	
≥2	11.2	16.5		13.9	13.9	
Elixhauser comorbidity score, %			0.241			0.027
0	2.7	2.3		2.3	2.4	
1	18.1	12.6		14.6	14.3	
2	26.3	20.6		23.4	22.4	
≥3	52.9	64.5		59.8	60.9	
DCSI weighted score, %			0.306			0.028
0	20.2	11.9		15.7	15.4	
1	22.4	19.0		20.4	21.0	
2	20.3	18.5		20.2	19.3	
≥3	37.1	50.6		43.7	44.3	<0.001
Hypoglycemia event, %	1.3	3.1	0.121	2.0	2.0	0.003
Hypoglycemia event or glucose <54 mg/dL, %	3.6	7.2	0.163	5.1	5.1	0.004
Hyperglycemia event, %	5.2	9.9	0.179	7.8	7.8	0.006
Hospitalization, %	15.9	19.0	0.081	17.0	17.0	0.006

The baseline period is the period before the index date. A covariate with SMD <0.1 is considered balanced between groups. Hypoglycemia and hyperglycemia identified by ICD-9/10 diagnostic codes from inpatient or ER settings. Hypoglycemia or glucose <54 mg/dL includes diagnoses or outpatient glucose laboratory values <54 mg/dL. Hospitalizations were identified by inpatient admissions. Extended care includes long-term inpatient stays, nursing home consults, or skilled home care consults. The baseline period for events and values is standardized for all participants to 1 year before the index date, except for HbA_{1c} values that are within 6 months before the index date and Elixhauser comorbidity and DCSI weighted scores that are within 24 months before the index date. DBP, diastolic blood pressure; DCSI, Diabetes Complications Severity Index; DPP-4, dipeptidyl peptidase 4; eGFR, estimated glomerular filtration rate; GLP-1, glucagon-like peptide 1; IQR, interquartile range; NPH, neutral protamine hagedorn; PCP, primary care provider; SBP, systolic blood pressure; SGLT-2, sodium–glucose cotransporter 2.

follow-up period. The proportionality of all model predictors was confirmed.

Sensitivity analyses were conducted using variations in outcomes and definitions of hypoglycemia and hyperglycemia events and within a subpopulation characterized by narrower inclusion criteria to increase the likelihood of reasonable health and VHA participation at baseline (Supplementary Results). We also tested excluding any follow-up after March 2020 to remove COVID-19 pandemic influences on outcomes. To demonstrate the validity of the PS approach, we also compared CGM effects between groups using Cox proportional hazards models while simply adjusting for key differences. To determine if insulin pump use modified the effects of CGM within T1D, we tested for an interaction between CGM use and insulin pump use and performed analyses excluding insulin pump users to determine the effects of CGM in their absence.

Stratified subgroup analyses within CGM users were conducted based on baseline age, HbA_{1c}, hypoglycemic risk score, and PDC calculated using CGM sensor fills. LMMs and GEE models were used for these subgroup analyses to compare outcomes pre- and postindex dates. To assess the dose-response effect of CGM use, we assessed the effects of CGM across increments of 25% in PDC.

All statistical analyses were performed using R version 4.1.2 (https://www.r-project.org). The R package MatchThem (13) was used for calculating PSs; survival was used for Cox proportional hazards analyses;

geepack was used for GEEs (14,15); lmerTest (16) was used for LMM analyses. A two-sided test with $P < 0.05$ was considered statistically significant, and we did not adjust for multiple testing.

Data and Resource Availability

Individual patient data are protected by the federal government and Veterans Affairs, and the data are not available for sharing. Detailed information on the study protocol and code is available upon request from the corresponding author.

RESULTS

Cohort Construction and Characteristics

Supplementary Figure 1 illustrates the selection of patients into the T1D (Supplementary Fig. 1*A*) and T2D (Supplementary Fig. 1*B*) cohorts. Applying exclusion criteria (as outlined in *Research Design and Methods*) resulted in 5,015 CGM initiators and 3,815 nonusers with T1D. Applying similar criteria among nonusers with T2D, and after downsampling to 10%, 15,706 CGM initiators and 29,912 nonusers with T2D were included in the same period. At least 1 year of follow-up within the VHA was available for >90% of patients with T1D and T2D.

Tables 1 and 2 show the baseline characteristics of the T1D and T2D cohorts before and after PS overlap weighting. Initiation of CGM for T1D increased over the 5-year interval from 2015 to 2020. Compared with nonusers with T1D, CGM users tended to be younger and less frequently male, have more frequent visits with primary care and endocrinology providers, and have greater use of insulin pumps and glucagon (Table 1). African American and Hispanic American groups had lower percentages of CGM users than nonusers, whereas the percentage of CGM users was higher for White patients with T1D. General indicators of health, such as indices of hypoglycemia risk, comorbidities, and diabetes complications, were relatively similar between groups. After overlap weighting, baseline characteristics demonstrated small SMDs (<0.1), indicating well-matched groups (Table 1 and Supplementary Fig. 2*A*).

In comparison with those with T1D, patients with T2D (Table 2) were on average older and more obese, used far more noninsulin diabetes medications and less glucagon, and had lower rates of hypoglycemia. Initiation of CGM in T2D increased dramatically from 2015 through 2020. Similar disparities, as noted in T1D, were seen in percentages of CGM users among racial/ethnic groups. CGM users (vs. nonusers) tended to have more clinical visits, higher HbA_{1c} values, lower estimated glomerular filtration rate, greater use of insulin and glucagon, greater use of other diabetes medications, more visits to ERs, and higher risk and comorbidity scores. After PS overlap weighting, baseline features demonstrated small SMDs (<0.1) between CGM initiators and nonusers (Table 2 and Supplementary Fig. 2*B*).

Differences in Glycemic Control Between CGM Initiators and Nonusers

Declines in HbA_{1c} (differences in difference) were significantly greater in CGM users with T1D compared with nonusers at 6 (−0.26%; 95% CI −0.31, −0.21%) and 12 (−0.26%; 95% CI −0.33, −0.19%) months (Table 3). The percentages of patients with T1D achieving HbA_{1c} <8 and <9% after 12 months were greater in CGM users, with a nearly 10–percentage point increase among CGM users achieving a <9% target.

The declines in HbA1c were also significantly greater in CGM users with T2D compared with nonusers at 6 (−0.39%; 95% CI −0.42, −0.36%) and 12 (−0.35%; 95% CI −0.40, −0.31%) months (Table 3). The percentages of patients with T2D achieving <8 and <9% after 12 months were greater in CGM users than in nonusers. Of note, declines in HbA_{1c} in the smaller subsets of women with T1D or T2D were in line with overall cohort results (Supplementary Table 1).

Risk of Hypoglycemia, Hyperglycemia, and All-Cause Hospitalization Between CGM Initiators and Nonusers

In patients with T1D, CGM initiation was associated with a significantly reduced risk of hypoglycemia (Table 4), with a hazard ratio (HR) of 0.69 (95% CI 0.48, 0.98). If a hypoglycemia event included an outpatient blood glucose level <54 mg/dL, this difference remained significant (HR 0.72; 95% CI 0.57, 0.91). Risk reduction for admission for hyperglycemia was not statistically significant (HR 0.83; 95% CI 0.65, 1.06). All-cause hospitalization was significantly reduced in CGM users (HR 0.75; 95% CI 0.63, 0.90).

In patients with T2D (Table 4), no difference in risk of admission for hypoglycemia was seen between CGM users and nonusers, but there was a reduction in risk of hyperglycemia in CGM users (HR 0.87; 95% CI 0.77, 0.99). The risk of all-cause hospitalization was reduced in CGM users (HR 0.89; 95% CI 0.83, 0.97).

For T1D and T2D, sensitivity analyses (Supplementary Table 2) excluding less healthy individuals, censoring those whose follow-up included years in which COVID was active, or using alternative definitions of hypoglycemia and hyperglycemia (Supplementary Table 3) or excluding patients with T1D using insulin pumps at baseline resulted in reduced cohort sizes but did not change the pattern of results meaningfully. In T1D, we found no significant interaction (at P value <0.05) between CGM use and insulin pump use for any outcome.

For T1D and T2D, neither outpatient nor inpatient diagnosis of a musculoskeletal disorder or upper respiratory infection (as negative control) indicated there was a bias favoring CGM users resulting from unmeasured confounding factors (Supplementary Table 4).

Subgroup and Other Analyses

As shown in Supplementary Figure 3*A–D*, certain subsets seemed to gain more benefit over 6 to 12 months of CGM use. In patients with T1D, both declines in HbA_{1c} and risks of admission for hyperglycemia and all-cause hospitalization were greater in those age <65 than in those age ≥65 years. Declines in HbA_{1c}, but not admissions for hypoglycemia, hyperglycemia, or any causes, were greater in those with higher baseline HbA_{1c} values (vs. those with lower HbA_{1c} values). In contrast, in those with intermediate or high risk of hypoglycemia (vs. low risk) at baseline, declines in HbA_{1c} were similar, but declines in risk of admissions for hyperglycemia, hypoglycemia, and all causes were significantly greater. Those with excellent compliance with CGM throughout the 12 months, defined as a PDC score of ≥0.80, demonstrated greater declines in HbA_{1c} as well as in risk of admissions for hypoglycemia and hyperglycemia. In T2D, generally very similar patterns of response to CGM initiation were seen in these same subsets (Supplementary Figure 3*A–D*). Patients with T2D with

Table 3—Comparison of glycemic control over 12 months among CGM users and nonusers with T1D or T2D

	CGM users			Non-CGM users			Weighted difference in differences	
Analysis	Before baseline	After baseline	Difference	Before baseline	After baseline	Difference	Estimate (95% CI)	*P*
T1D (CGM users, *n* = 4,930; nonusers, *n* = 3,263)								
Mean (SD) HbA_{1c} at 6 months, %	8.54 (1.45)	8.26 (1.33)	−0.28	8.39 (1.56)	8.36 (1.55)	−0.03	**−0.26 (−0.31, −0.21)**	**<0.001**
Mean (SD) HbA_{1c} at 12 months, %	8.54 (1.45)	8.22 (1.35)	−0.32	8.39 (1.56)	8.39 (1.55)	0.0	**−0.26 (−0.33, −0.19)**	**<0.001**
HbA_{1c} <7%, %	11.5	14.8	+3.3	16.5	16.4	−0.1	3.4 (−17.7, 24.5)	0.75
HbA_{1c} <8%, %	38.9	47.0	+8.1	43.2	44.5	+1.3	**6.9 (0.1, 13.6)**	**<0.05**
HbA_{1c} <9%, %	66.0	75.7	+9.7	70.0	69.9	−0.1	**9.7 (7.7, 11.8)**	**<0.001**
T2D (CGM users, *n* = 15,292; nonusers, *n* = 28,467)								
Mean (SD) HbA_{1c} at 6 months, %	8.70 (1.71)	8.17 (1.42)	−0.53	8.26 (1.61)	8.13 (1.58)	−0.13	**−0.39 (−0.42, −0.36)**	**<0.001**
Mean (SD) HbA_{1c} at 12 months, %	8.70 (1.71)	8.21 (1.46)	−0.49	8.26 (1.61)	8.10 (1.60)	−0.16	**−0.35 (−0.40, −0.31)**	**<0.001**
HbA1c <7%, %	12.2	17.2	+5.0	19.2	23.7	+4.5	0.4 (−8.2, 9.0)	0.92
HbA1c <8%, %	36.6	49.6	+13.0	49.1	54.7	+5.6	**7.4 (4.6, 10.2)**	**<0.001**
HbA1c <9%, %	63.1	76.2	+13.1	73.2	76.3	+3.1	**10.0 (9.1, 10.9)**	**<0.001**

Abbreviations: CGM, continuous glucose monitoring; CI, confidence interval; HbA1c, hemoglobin A1c (%); n, sample size; mo, months; T1D, type 1 diabetes; T2D, type 2 diabetes. *P* values <0.05 and associated estimates are in bold. Values presented before or after baseline as mean (SD) or percentage. Sample size is slightly reduced for HbA_{1c} outcomes because those included must have either a preindex HbA_{1c} value, a 6-month postindex value, or a 12-month postindex value. Difference-in-differences estimates reflect LMMs and GEEs with HbA_{1c} status within 6 months before and 12 months after the index date adjusted by overlap weighting from PS models. The reference group for comparisons is CGM nonusers. To convert HbA_{1c} from percentage to mmol/mol, use the formula HbA_{1c}, mmol/mol = (HbA1c, % − 2.152) ÷ 0.09148.

excellent compliance with CGM throughout the 12 months showed greater improvements in all outcomes. As shown in Supplementary Table 5, declines in HbA_{1c} increased across increments of PDC.

CONCLUSIONS

This study indicates, in a large national cohort, that initiation of CGM was associated with meaningful improvements in HbA_{1c} in both patients with T1D and those with T2D using insulin. Importantly, these improvements in glycemic control were accompanied by a general trend toward reduced risk of admission to an ER or hospitalization for hypoglycemia or hyperglycemia. There was an even more consistent reduction in risk of all-cause hospitalization in both T1D and T2D.

Effects of CGM Initiation on Glycemic Control

The declines in HbA_{1c} (−0.26 to −0.39%) are in line with those seen in most randomized clinical trials of real-time CGM in T1D (1,2). Some variation in published results in T2D likely results from heterogeneous medication regimens and initial HbA_{1c} levels in the cohorts studied. In one relatively large and well-conducted trial of CGM in patients with T2D using basal insulin and with HbA_{1c} levels >8% (17), CGM use was associated with a 0.4% greater decline in HbA_{1c}.

However, most randomized clinical trials of CGM effects were shorter in duration (3–6 months), and, therefore, the current results provide a more intermediate-/longer-term assessment of the effects of CGM on glycemic control. Finding

Table 4—HRs for glucose control–related events and all-cause hospitalizations for CGM users versus nonusers over 12 months

	T1D (*n* = 5,015 CGM users; *n* = 3,815 nonusers)		T2D (*n* = 15,706 CGM users; *n* = 29,912 nonusers)	
Outcome	HR (95% CI)	*P*	HR (95% CI)	*P*
Hypoglycemia event	**0.69 (0.48, 0.98)**	**0.04**	0.93 (0.74, 1.16)	0.52
Hypoglycemia event or glucose <54 mg/dL	**0.72 (0.57, 0.91)**	**0.01**	0.97 (0.83, 1.12)	0.65
Hyperglycemia event	0.83 (0.65, 1.06)	0.14	**0.87 (0.77, 0.99)**	**0.04**
All-cause hospitalization	**0.75 (0.63, 0.90)**	**0.002**	**0.89 (0.82, 0.97)**	**0.004**

Results associated with *P* values <0.05 are in bold. HR estimates reflect Cox proportional hazards model with time to event as the first occurrence of an event within 12 months after the index date and adjusted by overlap PS weighting. The reference group is CGM nonusers. Hypoglycemia and hyperglycemia were identified by ICD-9/10 diagnostic codes in ER or inpatient setting. Hypoglycemia or glucose <54 mg/dL includes hospital diagnoses or outpatient glucose laboratory values <54 mg/dL. Hospitalizations were identified by inpatient admissions. HR, hazard ratio.

similar declines in HbA_{1c} values at 6 and 12 months indicates that the benefit of initiating CGM seems relatively stable for at least 12 months. This is consistent with the persistently lower HbA_{1c} in T1D after 16 months of follow-up reported in the SILVER (Sustained Intensive Treatment and Long-Term Effects on HbA1c Reduction) trial after randomization to CGM for 26 weeks (18). CGM initiation in the current study also increased the percentage of individuals achieving HbA_{1c} values of <8 and $<9\%$ in both T1D and T2D at 12 months, targets at or below the inflection point for greater risk of diabetes complications (19–22). Because baseline HbA_{1c} levels were relatively similar between patients with T1D and those with T2D, the greater decline in T2D certainly highlights that CGM use in this group can also be quite effective.

The large size of these cohorts allowed us to compare effects of CGM initiation on changes in HbA_{1c} among unique subsets of individuals. Individuals with T1D or T2D who were younger (age <65 years), had higher baseline HbA_{1c} levels, or had excellent CGM compliance (PDC >0.8) all demonstrated greater reductions in HbA_{1c}. Because the rationale for starting CGM in those with high hypoglycemic risk is primarily to prevent additional low-glucose episodes, it is not surprising that this baseline determinant did not influence change in HbA_{1c} value in either T1D or T2D.

The decline in HbA_{1c} associated with CGM initiation seemed clinically meaningful, particularly in patients with T2D, in whom changes approached 0.4%. Moreover, some subsets of individuals, such as those with higher baseline HbA_{1c} values, showed robust declines in HbA_{1c} ranging from -0.71% in those with T1D to -1.14% in those with T2D.

Effects of CGM Initiation on ER or Hospitalization Outcomes

Reductions in risk of ER or hospital admission for hyperglycemia, hypoglycemia, or any cause ranged from 17 to 30% in T1D. Overall, these results suggest a fairly robust effect of CGM initiation in T1D to reduce relatively common but potentially serious diabetes complications that can increase the need for costly ER and hospital admissions.

Generally similar, but less overall favorable, patterns for clinical events were seen in CGM initiators with T2D. Although risk of admission related to hypoglycemia was not reduced, the risk of hyperglycemia declined. And again, CGM initiation in T2D was linked to a significant 11% decline in risk of all-cause hospitalization. These results raise the possibility that decreases in health care use could offset the excess costs of supporting CGM initiation and use within appropriate patient groups.

As seen with declines in HbA_{1c}, certain subgroups of CGM users seemed to achieve greater risk reduction for ER or hospitalization admissions from initiation of CGM. However, this did not follow the same patterns as those seen for glycemic control. Indeed, for several subgroups, admission for hypoglycemia or hyperglycemia or all-cause hospitalization did not appear related to changes in glycemic control. For example, those with higher baseline hypoglycemia risk, who had shown little difference in change in HbA_{1c} values versus those at lower hypoglycemia risk, had lower risk of all three clinical outcomes. This further highlights the potential value of initiating CGM in those with recurrent hypoglycemia. More consistent use of CGM during the 12 months of follow-up (higher PDC) was also an important determinant of admissions related to hypoglycemia and hyperglycemia, with less consistent trends toward decreases in risk of all-cause hospitalization for T1D and T2D. This relationship between PDC and hospitalization suggests efforts to educate patients about consistent use of CGM may have a positive impact on reducing diabetes-related hospitalizations.

Exploration of Mechanisms Accounting for the Apparent Benefits of CGM

We speculated that CGM benefits may be an indirect function of increased frequency of health care interactions, but several factors suggest that this is not the case. First, effects of CGM on glycemic control were in line with results from randomized clinical trials. Second, compliance with CGM, as measured by PDC, was directly related to improvements in both glycemic control and outcomes. Third, although we recognize that simple visit frequency may not capture the potential benefit of health care visits for all patients, accounting for any excess visits postinitiation of CGM in analysis models did not seem to be an important mediator of CGM effects on change in HbA_{1c} (Supplementary Materials). Overall, these findings suggest that it is the direct effects of CGM (in comparison with self-monitoring of blood glucose) to provide better information about glucose levels and facilitate shared decision making between patients and providers about diabetes management that improve outcomes.

Limitations and Strengths

Although the VHA has a relatively diverse racial and ethnic patient population and growing female enrollment, the number of women included in our cohorts was low. However, CGM-associated changes in HbA_{1c} in women were consistent with overall results. We also excluded patients with T2D not receiving insulin, limiting generalizability to the broader T2D population. Although overlap weighting provided excellent balancing of characteristics between groups, there remains the possibility that CGM users and nonusers may not have been well matched on variables not considered. We also acknowledge that ICD codes associated with hospital visits may not always reliably identify hypoglycemia- and hyperglycemia-related admissions. However, several sensitivity analyses using alternative definitions, including more objective laboratory data, did not meaningfully alter the results. The current study included CGM users who met inclusion criteria across a 6-year period (2015–2020), which likely resulted in patients using multiple types of CGM devices during a period in which newer CGM models have improved accuracy and usability compared with older models. CGM devices also vary in their frequency of glucose measurements, need for calibration, ability to provide alerts at high or low glucose levels, and other attributes. Our analyses do not provide insight into the potential effects these different types of CGM devices or features may have on outcomes.

The VHA cohorts of CGM users and nonusers are the largest reported to date worldwide and permitted examination of CGM effects on not just changes in HbA_{1c} but also clinically relevant outcomes such as ER visits and hospitalizations. This also allowed study of two groups, those with T1D developing in adulthood and those with T2D, who have been less commonly evaluated, thus providing novel and complementary information to previously published studies. Importantly, the current findings demonstrate that benefits in these groups

were generally similar to those reported in the more frequently studied childhood-onset T1D. We also examined key subgroups of CGM users, demonstrating the types of benefits that might be anticipated based on baseline characteristics and with consistent use of CGM. An additional strength was the number of additional sensitivity analyses conducted to exclude potential confounding explanations for the associations found between CGM and outcomes. Importantly, several of the study results were consistent with those from a retrospective observational analysis conducted within Kaiser Permanente suggesting consistency of CGM effects across large health care systems (8). Because the VHA health care system provides relatively comprehensive and inexpensive medical care for all enrolled veterans, access to providers and devices such as CGM and the resulting outcomes should be less influenced by disparities in finances or health care availability.

In conclusion, this large real-world study demonstrated CGM initiation in T1D and T2D was linked to clinically meaningful and sustained improvements in glucose control and reductions in risk of hypoglycemic and hyperglycemic events contributing to ER or hospital admissions as well as to all-cause hospitalizations. Study results also highlight that patient baseline characteristics and consistency of CGM use seem important determinants of the types of outcomes most likely to improve with initiation of CGM.

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