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Reduced rates of diabetic retinopathy complications with use of continuous glucose monitoring

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Elucidating the outcomes of patients using continuous glucose monitoring (continuous glucose monitoring) in day-to-day clinical practice could help expand optimal practice guidelines in prevention and mitigation of diabetic retinopathy (DR). Retrospective cohort study. Subjects, Participants, and/or Controls: 13,302 patients with NPDR initiated on continuous glucose monitoring, compared with 179,079 patients with NPDR not initiated on continuous glucose monitoring before propensity score matching (propensity score matching) at one year. TriNetX (Cambridge, MA, USA), was used to identify patients diagnosed with NPDR stratified by initiation of continuous glucose monitoring or not with at least six months of follow-up. propensity score matching controlled for baseline demographics and medical comorbidities. After propensity score matching, 12,730 patients were subsequently analyzed in each cohort. Use of continuous glucose monitoring was associated with lower risk of vision threatening complications (DME: hazards ratio [HR], 0.87, 95% CI, 0.82–0.93; *P* < .001; PDR: HR, 0.74, 95% CI, 0.66–0.82; *P* < .001; VH: HR, 0.55, 95% CI, 0.47–0.66; *P* < .001; TRD: HR, 0.42, 95% CI, 0.27–0.68; *P* = .027), and need for ocular intervention (anti-VEGF injection: HR, 0.72, 95% CI, 0.65–0.80; *P* < .001; PRP: HR, 0.53, 95% CI, 0.44–0.64; *P* < .001; PPV: HR, 0.37, 95% CI, 0.26–0.51; *P* < .001) among patients with NPDR when compared with matched patients not using continuous glucose monitoring at 1 year. Similar associations at two years were found. continuous glucose monitoring use in patients with NPDR without prior ocular therapy was associated with lower risk of progression to vision threatening complications as well as need for ocular intervention at one year and two years, highlighting that glycemic variability and time in range are important factors influencing the risk of complications from diabetic eye disease.

Keywords Continuous glucose monitoring, Diabetic macular edema, Panretinal photocoagulation, Pars plan vitrectomy, Proliferative diabetic retinopathy, Vascular endothelial growth factor

Abbreviations

CGM	Continuous glucose monitoring
CPT	Current procedural terminology
DME	Diabetic macular edema
DRCR.net	Diabetic retinopathy clinical research network
glycemic variability	Glycemic variability
HIPPA	Health insurance portability and accountability act
ICD-10	International classification of diseases, tenth revision
PRP	Panretinal photocoagulation
PPV	Pars plana vitrectomy
PDR	Proliferative diabetic retinopathy
time in range	Time in range
TRD	Tractional retinal detachment
VEGF	Vascular endothelial growth factor
VH	Vitreous hemorrhage

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Diabetic retinopathy (DR), a microvascular complication of both type 1 and type 2 diabetes, is a leading cause of vision impairment worldwide[1]. Established risk factors for DR includes longer duration of disease and poor glycemic control[2]. The seminal findings of the Diabetes Control and Complications Trial (DCCT) reinforced the importance of intensive insulin therapy and hemoglobin A1c (HbA1c) reduction in order to decrease the risk of development and progression of DR[3]. Yet, despite demonstrating similar HbA1c levels, higher risk of DR progression was associated with the conventional insulin treatment cohort compared to the intensive insulin treatment cohort in the landmark trial[4]. While HbA1c is an integral assay for assessing glycemic control over the preceding three months, it does not accurately measure glycemic variability, which refers to dynamic fluctuations in blood glucose levels during the course of a day[5,6]. As such, it is plausible that other measures of glycemic control beyond HbA1c may influence the risk of microvascular complications of diabetes, including DR[7–9]. Supporting this, glycemic variability has been demonstrated as an independent risk factor for DR among patients with type 1 and type 2 diabetes[9–11]. Moreover, time spent within target glucose ranges (3.9–10.0 mmol/L), a variable known as time in range, has been shown to be significantly associated with the risk of developing mild, moderate, and severe non-proliferative diabetic retinopathy (NPDR) among patients with type 2 diabetes mellitus, even after controlling for HbA1c[10].

Continuous glucose monitoring (continuous glucose monitoring) refers to the ability to constantly measure an individual's blood glucose levels throughout the day and night, which is achievable with the advent of novel minimally invasive monitors which work on the skin or can be implanted subcutaneously. More recently, real-time sensors have been introduced where glucose values are transmitted to a receiver/smartphone continuously, constituting a rapidly growing field of IoT (internet of things)-enabled wearable medical devices. Currently there are four major continuous glucose monitoring product lines that have been approved by the FDA and available for use in the USA: Dexcom G6 and G7, (DexCom, San Diego, CA), Eversense E3 (Senseonics, Germantown, MD), FreeStyle Libre 2 and 3 (Abbott Laboratories, Chicago, IL), and Guardian Connect (Medtronic, Minneapolis, MN)[12]. To date, these all require a physician prescription for use; however, recently in March 2024, the FDA approved the first over-the-counter continuous glucose monitoring, Stelo (DexCom, San Diego, CA), which will become commercially available in 2024[13].

As a group, CGMs have shown demonstrable benefits in optimizing time in range, reducing HbA1c levels, reducing variability in glucose levels, decreasing the incidence of diabetic ketoacidosis, hypoglycemic events, and even hospitalization rates related to diabetic complications[14–19]. However, little is known about the effect of continuous glucose monitoring on DR outcomes among patients with both type 1 and 2 diabetes, the latter of which is becoming an increasingly popular indication for continuous glucose monitoring usage.

Elucidating the outcomes of CGMs in day-to-day clinical practice could help expand optimal practice guidelines in prevention and mitigation of DR. The aim of this study was to analyze the risk of developing vision-threatening complications (VTCs), including diabetic macular edema (DME), proliferative diabetic retinopathy (PDR), vitreous hemorrhage (VH), and diabetic tractional retinal detachment (TRD), as well as need for ocular intervention with intravitreal anti-vascular endothelial growth factor (VEGF) injection therapy, panretinal photocoagulation (PRP), and/or pars plana vitrectomy (PPV) among patients with preexisting NPDR initiated on continuous glucose monitoring compared with a matched control cohort.

Mthods, intervention, or testing

A retrospective cohort study was conducted using the TriNetX network (TriNetX, LLC, Cambridge, MA). TriNetX is compliant with the Health Insurance Portability and Accountability Act (HIPPA) rule and is certified to the ISO 27001:2013 standard. All data from the TriNetX platform is displayed in aggregate and deidentified form. As this study only contained deidentified patient electronic medical records, the WIRB-Copernicus Group (WCG) Institutional Review Board (IRB) reviewed the study protocol and determined that ethical approval was not required, and a waiver of informed consent was granted in accordance with U.S. federal regulations (45 CFR § 46.104). This study is retrospective in nature, and the requirement for informed consent was waived by WCG IRB in accordance with the relevant guidelines and regulations. The research performed was in accordance with the Declaration of Helsinki.

The most updated data analyzed in this study was collected on April 25, 2024, from the TriNetX Health Research Network, which provided access to de-identified electronic health records. At the time of data querying, 125,139,732 patients were included in the TriNetX research network database. Our study used a retrospective cohort design by reviewing electronic health records available from April 25, 2010 through April 25, 2024, and followed the Strengthening the Reporting of Observational Studies in Epidemiology (STROBE) guidelines for reporting cohort studies[20].

Two patient cohorts were identified for analyses. Each group included patients with pre-existing NPDR without DME or PDR, which were identified by their respective International Classification of Diseases, Tenth Revision (ICD-10) codes: Type 1 DM with mild (E10.329*), moderate (E10.339*), or severe (E10.34*) NPDR, and Type 2 DM with mild (E11.329*), moderate (E11.339*), or severe (E11.349*) NPDR. These patients were then stratified by initiation of continuous glucose monitoring (CGM cohort) or not (Control cohort) using Current Procedural Terminology codes 95,249, 95,250, and 95,251. Patients were excluded from their respective cohort if they had six months or less of follow-up prior to enrollment and after the index date. Patients in the control cohort were excluded if they had any instance of continuous glucose monitoring use before or during the study period, as identified by the respective Current Procedural Terminology codes. Additionally, patients were excluded if they had any of the following at the index date: prior history of PDR (E10.35, E11.35, H43.1), prior diagnosis of DME (E10.321, E10.331, E10.341, E11.321, E11.331, E11.341) previous ocular intervention (intravitreal injection, laser photocoagulation, or surgical PPV). Finally, individuals were also excluded from analyses if they developed retinovascular/exudative diseases that could confound the need for intravitreal

injections at any time point during the study: neovascular age-related macular degeneration (AMD; H35.32), branch retinal vein occlusion with cystoid macular edema (H34.83), or central retinal vein occlusion with cystoid macular edema (H34.81). The flow diagram is depicted in Fig. 1.

The index date for the continuous glucose monitoring cohort was the first date in which the diagnosis of NPDR and the use of continuous glucose monitoring was documented. The index date for the control cohort was the first date in which the diagnosis of NPDR was documented. Analyses were performed at follow-up periods of one year and two years. Baseline demographics were recorded. Race and gender were determined based on the presence of these designations within the electronic medical record. Because the data are from a range of health care organizations, there may be variation if self-reported gender and race vs. institutionally classified sex and race were used.

The use of insulin (HS501), sodium-glucose cotransporter-2 inhibitors (SGLT2; A10BK), glucagon-like peptide-1 analogues (GLP-1; A10BJ), and other hypoglycemic agents (HS509) were queried in both groups. Regular insulin, insulin glargine, insulin aspart, insulin degludec, and insulin detemir were all classified as insulin. Acarbose, alogliptin, empagliflozin, glimepiride, glipizide, pioglitazone, and metformin were all classified as other oral or injectable hypoglycemic agents.

Next, propensity score matching was performed on the continuous glucose monitoring and control cohort to account for differences in age, gender, race, hemoglobin A1C (HbA1c), and use of insulin, SGLT2, GLP-1, or other oral and injectable systemic diabetes agents. Severe NPDR was also included in the model, but early and moderate NPDR was not matched given limitations in the number of variables included in the model. The propensity score matching was performed using the TriNetx built-in analysis platform (1:1 matching by nearest neighbor greedy matching algorithm with a caliper of 0.25 standard deviations).

The primary outcome measured was progression to VTCs (DME or PDR) in each group during the study period. Secondary outcome measures were need for ocular intervention to treat DR as reported by their respective Current Procedural Terminology codes: intravitreal injections (CPT: 67028), panretinal laser photocoagulation (CPT: 67228), and/or surgical PPV (CPT: 67040, 67113). One- and two-year outcomes after the index date were compared between both cohorts after propensity score matching. The data analysis was performed using the TriNetX analytical platform.

The standardized mean difference (SMD) for the continuous and categorical variables stratified by use of continuous glucose monitoring or not was calculated and SMD less than or equal to 0.1 was considered to be balanced. Cox proportional hazard regression was implemented to compare the matched cohorts, and the proportional hazard assumption was tested with the generalized Schoenfeld approach. Hazard ratios (HRs) were calculated to investigate the risk ratio of DR VTC and need for ocular intervention in the continuous glucose monitoring and control cohorts. All analyses were conducted using 95% confidence intervals (CIs) to determine statistical significance. Kaplan–Meier analysis was implemented for the cumulative incidence of DME, PDR, VH, and TRD. All patients were right censored to diagnosis date or 1 year after, whichever came first. For continuous data, analyses were conducted using independent t-tests. For categorical data analyses were conducted using chi-square tests. All P values were two-sided and statistical significance was indicated at $p < .05$. Finally, the following analysis does not directly address the statistical assumption for comparing baseline characteristics.

Results

A total of 13,302 patients in the continuous glucose monitoring cohort and 179,079 patients in the control cohort were initially identified prior to propensity score matching at one year. After propensity score matching methods and inclusion/exclusionary criteria were applied, 12,730 patients were subsequently analyzed in each cohort at one year. propensity score matching was based on age, sex, race, HbA1c level, use of insulin or other oral and

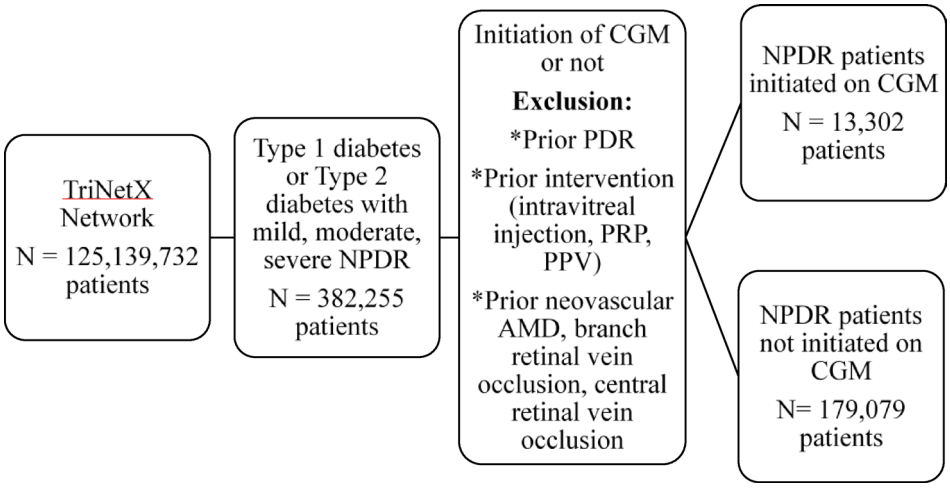


Fig. 1. Flow diagram of patient selection from TriNetX database. CGM: continuous glucose monitoring; NPDR: non-proliferative diabetic retinopathy; PDR: proliferative diabetic retinopathy; AMD: age-related macular degeneration.

injectable systemic diabetes agents, presence of baseline severe NPDR, and other systemic associations (Table 1). After propensity score matching methods were applied, baseline characteristics were balanced between the groups. At two years, total of 10,228 patients in the continuous glucose monitoring cohort and 148,070 patients in the control cohort were identified prior to propensity score matching and after propensity score matching, 9,797 patients were analyzed in each cohort.

Among patients who were followed for one year, 14.3% (1824) patients in the continuous glucose monitoring cohort developed subsequent DME compared with 16.1% (2052) patients in the control cohort. Patients with NPDR initiated on continuous glucose monitoring were associated with a lower risk of developing subsequent DME when compared with patients with NPDR not initiated on continuous glucose monitoring at one year (hazard ratio [HR], 0.87, 95% CI, 0.82–0.93; $P<.001$) and two years (HR, 0.80, 95% CI, 0.75–0.86; $P<.001$) (Table 2).

Furthermore, 4.6% (583) patients in the continuous glucose monitoring cohort developed subsequent PDR compared with 6.1% (780) patients in control cohort at one year of follow-up. Patients with NPDR initiated on continuous glucose monitoring were associated with lower rates of developing subsequent PDR when compared with patients with NPDR not initiated on continuous glucose monitoring at one year (HR, 0.74, 95% CI, 0.66–0.82; $P<.001$) and two years (HR, 0.70, 95% CI, 0.62–0.79; $P<.001$). In addition, patients with NPDR initiated on continuous glucose monitoring were associated with lower rates of developing subsequent VH and TRD when compared with patients with NPDR not on continuous glucose monitoring at one year (VH: HR, 0.55, 95% CI, 0.47–0.66; $P<.001$; TRD: HR, 0.42, 95% CI, 0.27–0.68; $P=.027$) and two years (VH: HR, 0.52, 95% CI, 0.43–0.63; $P<.001$; TRD: HR, 0.39, 95% CI, 0.23–0.66; $P=.003$) (Table 2).

Finally, patients with NPDR initiated on continuous glucose monitoring were associated with lower rates of requiring subsequent intravitreal anti-VEGF injection, PRP, and PPV when compared with patients with NPDR not initiated on continuous glucose monitoring followed for one year (anti-VEGF: HR, 0.72, 95% CI, 0.65–0.80; $P<.001$; PRP: HR, 0.53, 95% CI, 0.44–0.64; $P<.001$; PPV: HR, 0.37, 95% CI, 0.26–0.51; $P<.001$) and two years (anti-VEGF: HR, 0.64, 95% CI, 0.57–0.72; $P<.001$; PRP: HR, 0.50, 95% CI, 0.40–0.62; $P<.001$; PPV: HR, 0.38, 95% CI, 0.26–0.54; $P<.001$) (Table 3).

Kaplan-Meier analysis demonstrated significant differences in developing DME, PDR, VH, TRD, as well as requiring subsequent intravitreal anti-VEGF injection, PRP, and PPV between patients in the continuous glucose monitoring cohort compared to the control cohort throughout the follow-up periods. (Fig. 2. A-D). Finally, this study implemented subgroup analyses according to age, sex, race, and different medication use (Table 4). The higher risk of VTCs (DME, PDR, VH, TRD) in the control cohort compared with that of the continuous glucose monitoring cohort remained unchanged in further subgroup analysis across different age groups, sex, and insulin use.

	Before PSM			After PSM		
	CGM Cohort (*N* = 13,302)	Control Cohort (*N* = 179,079)	SMD	CGM Cohort (*N* = 12,730)	Control Cohort (*N* = 12,730)	SMD
Age, years (Mean +/- SD)	60.6 +/- 15.6	68.6 +/- 13.3	0.55	60.6 +/- 15.7	61.0 +/−15.0	0.04
Gender (%)						
Female	48.8%	47.8%	0.02	48.8%	48.8%	< 0.001
Male	47.2%	47.1%	0.01	47.2%	47.2%	< 0.001
Race (%)						
Hispanic or Latino	7.2%	15.3%	0.26	7.0%	6.1%	0.04
Asian	3.1%	5.0%	0.10	3.1%	3.1%	< 0.001
Black	12.7%	20.0%	0.20	12.5%	12.9%	0.01
White	69.2%	53.8%	0.32	68.3%	69.1%	0.03
Unknown Race	16.3%	25.6%	0.16	16.3%	16.7%	0.04
Systemic Associations (%)						
Hypertension	79.1%	57.7%	0.26	78.7%	73.4%	< 0.001
Hyperlipidemia	77.5%	59.7%	0.39	76.9%	77.6%	0.02
Severe non-proliferative diabetic retinopathy	4.3%	0.0%	0.26	0.0%	0.0%	NA
HbA1c, % (Mean +/- SD)	8.51 +/- 1.83	8.20 +/- 2.08	0.16	8.50 +/- 1.82	8.49 +/- 2.11	0.01
Medications (%)						
Insulin	87.4%	42.2%	1.1	87.2%	87.5%	0.01
Sodium-glucose cotransporter-2 inhibitors	20.1%	7.1%	0.39	19.9%	19.2%	0.02
Glucagon-like peptide-1	31.7%	9.6%	0.56	31.4%	31.4%	< 0.001
Other hypoglycemic agents	31.0%	8.7%	0.58	30.8%	29.4%	0.02

Table 1. Baseline characteristics of patients with NPDR initiated on CGM compared to matched patients not initiated on CGM (control) before and after PSM at one year. CGM: continuous glucose monitoring; PSM: Propensity score match; SD: standard deviation; NPDR: non-proliferative diabetic retinopathy; SMD: standardized mean difference.

	CGM Cohort	Control Cohort		
	n (%)	*n* (%)	HR (95% CI)	*p* value
DME				
One year (*N* = 12730)	1824 (14.3)	2052 (16.1)	0.87 (0.82–0.93)	< 0.001
Two years (*N* = 9797)	1450 (14.8)	1759 (18.00)	0.80 (0.75–0.86)	< 0.001
PDR				
One year (*N* = 12730)	583 (4.6)	780 (6.1)	0.74 (0.66–0.82)	< 0.001
Two years (*N* = 9797)	462 (4.7)	649 (6.6)	0.70 (0.62–0.79)	< 0.001
VH				
One year (*N* = 12730)	204 (1.6)	365 (2.9)	0.55 (0.47–0.66)	< 0.001
Two years (*N* = 9797)	160 (1.6)	305 (3.1)	0.52 (0.43–0.63)	< 0.001
TRD				
One year (*N* = 12730)	25 (0.2)	59 (0.5)	0.42 (0.27–0.68)	0.027
Two years (*N* = 9797)	20 (0.2)	51 (0.5)	0.39 (0.23–0.66)	0.003

Table 2. Incidence of developing DME, PDR, VH, and TRD in patients with NPDR initiated on CGM compared to control. SD: Standard deviation; CI: Confidence interval; CGM: continuous glucose monitoring; PDR: proliferative diabetic retinopathy; VH: vitreous hemorrhage; TRD: tractional retinal detachment; DME: diabetic macular edema; n: number of events; HR: hazard ratio.

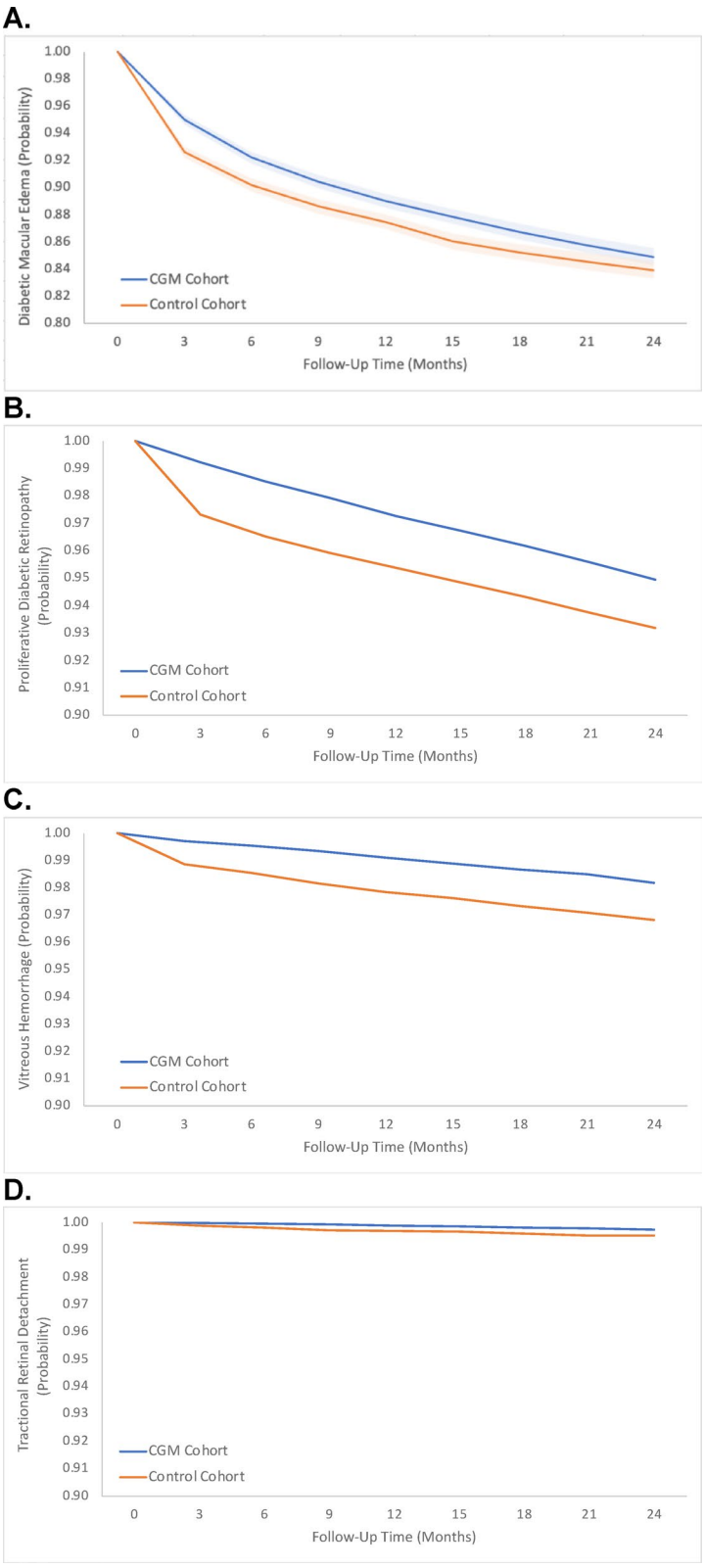
	CGM Cohort	Control Cohort		
	n (%)	*n* (%)	HR (95% CI)	*p* value
Intravitreal Injection				
One year (*N* = 12730)	655 (5.2)	894 (7.0)	0.72 (0.65–0.80)	< 0.001
Two years (*N* = 9797)	475 (4.8)	726 (7.4)	0.64 (0.57–0.72)	< 0.001
PRP				
One year (*N* = 12730)	158 (1.2)	298 (2.3)	0.53 (0.44–0.64)	< 0.001
Two years (*N* = 9797)	122 (1.3)	242 (2.5)	0.50 (0.40–0.62)	< 0.001
PPV				
One year (*N* = 12730)	48 (0.4)	131 (1.0)	0.37 (0.26–0.51)	< 0.001
Two years (*N* = 9797)	41 (0.4)	109 (1.1)	0.38 (0.26–0.54)	0.008

Table 3. Incidence of requiring intravitreal injection, PRP, and PPV in patients with NPDR initiated on CGM compared to control. SD: Standard deviation; CI: Confidence interval; CGM: continuous glucose monitoring; PRP: panretinal photocoagulation; PPV: pars plana vitrectomy; n: number of events; HR: hazard ratio.

Discussion

An increase in utilization of continuous glucose monitoring in the US has improved the management of patients with type 1 and type 2 diabetes. continuous glucose monitoring is also being promoted as a biofeedback wellness tool for healthy patients without diabetes. Despite its broad use, how and whether continuous glucose monitoring benefits patients remains unclear. In the present study, initiation of continuous glucose monitoring was associated with a decreased risk of developing subsequent DME, PDR, VH, and TRD in patients with NPDR when compared to a matched cohort of patients not initiated on continuous glucose monitoring. Further, patients with NPDR initiated on continuous glucose monitoring had less risk of requiring intravitreal anti-VEGF injection, PRP, and PPV when compared with a match cohort of patients not initiated on continuous glucose monitoring. These findings were observed even after adjusting for HbA1c levels and remained consistent across subgroup analyses regardless of age, sex, and insulin use. The findings of the current study suggesting that additional glycemic factors assayed by continuous glucose monitoring, including glycemic variability and time in range, may influence the risk of microvascular changes associated with type 1 and type 2 diabetes.

In clinical practice, glycemic status is primarily assessed by HbA1c, which measures average glycemia over 3 months. Clinical trials also use HbA1c measurement to evaluate risk of diabetic complications[3,21]. Despite its widespread use, limitations in the HbA1c test exist, including incomplete expression of glycemic variability and time in range[7,9,22,23]. Independent of HbA1c, increased glycemic variability and decreased time in range have been established as risk factors for microvascular complications associated with diabetes type 1 and type 2, including DR. In a large single-center cohort study, Lu et al. demonstrated that development of DR was inversely correlated with higher time in range (Pearson correlation coefficient = −0.147; *P*<.001) in patients with type 2 diabetes, independent of HbA1c levels[10]. Further, by inducing oxidative stress and endothelial dysfunction, glycemic variability is recognized as an independent predictor of microvascular complications in type 1 and type 2 diabetes[24,25]. Given the growing literature suggesting the limitations of HbA1c, as well as the importance



of glycemic variability and time in range in predicting diabetic complications, innovative methods to evaluate glycemic status have emerged.

Point-of-care blood glucose monitoring (BGM) and continuous glucose monitoring are two other commonly used methods to assess glucose control in patients with type 1 and type 2 diabetes. BGM with a point-of-care capillary or finger-stick device is integral to the management of patients with severe insulin deficient diabetes and may augment continuous glucose monitoring use, though require frequent and burdensome capillary or finger-stick devices[26]. By increasing time in range, reducing variability in glucose levels and incidence of hypoglycemic events, as well as diabetic ketoacidosis, continuous glucose monitoring provides unique protection

◀**Fig. 2**. A-D. Kaplan-Meier analysis of cumulative incidence of VTCs with the solid line representing the estimated survival function and shaded areas indicating the upper and lower 95% confidence intervals. **A**: Kaplan-Meier analysis of cumulative incidence of DME in patients with NPDR initiated on continuous glucose monitoring compared to the control cohort at 2 years. **B**: Kaplan-Meier analysis of cumulative incidence of PDR in patients with NPDR initiated on continuous glucose monitoring compared to the control cohort at 2 years. **C**: Kaplan-Meier analysis of cumulative incidence of VH in patients with NPDR initiated on continuous glucose monitoring compared to the control cohort at 2 years. **D**: Kaplan-Meier analysis of cumulative incidence of TRD in patients with NPDR initiated on continuous glucose monitoring compared to the control cohort at 2 years.

Covariates	HR (95% CI)	*p* value
Gender		
Male	1.05 (1.03–1.08)	< 0.001
Age Group (years)		
30 < = Age < 40	1.37 (1.23–1.50)	< 0.001
40 < = Age < 50	1.61 (1.48–1.74)	< 0.001
50 < = Age < 60	1.78 (1.65–1.92)	< 0.001
Age > = 60	1.62 (1.50–1.75)	< 0.001
Medications		
Insulin	1.14 (1.11–1.17)	< 0.001

Table 4. Risk of VTC among patients with NPDR stratified by patient demographic information. CGM: continuous glucose monitoring; VTC: vision threatening complications; NPDR: non-proliferative diabetic retinopathy.

against diabetes complications[11,14,16,24,25]. Despite growing literature to support the use of continuous glucose monitoring in type 1 and type 2 diabetes, there is limited data quantifying its benefit in preventing diabetic complications[27,28]. Sartore et al. revealed that increased standard deviation of blood glucose rate of change and continuous overlapping net glycemic action calculated every two hours during the monitoring period, both intended to estimate glycemic variability using continuous glucose monitoring, were associated with an elevated odds of DR in patients with type 1 and type 2 diabetes (odds ratio [OR],1.03; P=.01 and OR, 1.02; P=.04, respectively)[29]. The significance of this association was lost after correction for the presence of hypertension and hypercholesterolemia. Moreover, Liu et al. showed that continuous glucose monitoring use, a proxy for reduced glycemic variability, was associated with lower odds of DR and PDR when compared with no continuous glucose monitoring use among patients with type 1 diabetes with private insurance and predominately of white race (OR, 0.52; P=.008 and OR, 0.42; P=.004, respectively)[14]. It remains unknown whether the outcomes highlighted by Liu et al. can be generalized to all adult populations with type 1 and type 2 diabetes or may be extrapolated to increased risk of diabetic VTCs and need for ocular interventions among patients using continuous glucose monitoring compared to those not using continuous glucose monitoring. Though the present study did not directly measure glycemic variability, use of continuous glucose monitoring among patients with NPDR likely resulted in reduced variability in glucose levels and was associated with a reduced risk of developing subsequent DME (HR, 0.80; P<.001), PDR (HR, 0.70; P<.001), VH (HR, 0.52; P<.001), and TRD (HR, 0.39; P=.003) in a large, heterogenous real-world database of matched patients with type 1 and type 2 diabetes and NPDR at two years.

The present study has several limitations that warrant consideration. As a retrospective analysis of large sets of de-identified aggregated medical health records data, potential confounding factors not addressed may impact the findings of this study. For example, socioeconomic status and lifestyle factors could not be controlled for in this analysis, and therefore selection bias in patient access to continuous glucose monitoring may impact results. Moreover, adherence to using a continuous glucose monitoring may reflect a more compliant patient overall, and manifest in other areas of their care that cannot be readily measured in this type of a study design. Medication adherence, healthy dietary intake, and exercise may all directly impact the incidence and progression rates of microvascular complications. However, continuous glucose monitoring use is becoming standard of care for type 1 diabetes and recent FDA approval for marketing of Stelo biosensor has made continuous glucose monitoring available to patients with type 1 and type 2 diabetes without prescription[13]. An emergence of other continuous glucose monitoring systems on the market and newer versions with improved accuracy and usability has also expanded the use of continuous glucose monitoring in patients with type 1 and type 2 diabetes. Future studies may also evaluate how the use of hybrid close looped technology or insulin pumps may be associated with risk of developing diabetic complications and/or undergoing ocular interventions among patients with type 1 and type 2 diabetes. Furthermore, it is unclear how often patients in the continuous glucose monitoring cohort of our study are using continuous glucose monitoring after enrollment. As most continuous glucose monitoring last for 2 weeks, repeated use of continuous glucose monitoring, glycemic variability and time in range stabilization after continuous glucose monitoring use, or selection bias for motivated patients may explain the improved ocular outcomes among patients in the continuous glucose monitoring cohort compared to the

control cohort. Diabetes type and disease duration was not included in the analysis and differences between both cohorts could confound the results. Next, this study relies on accurate ICD-10 diagnosis and coding, and results may be impacted by inaccuracy of true coding for DME, PDR, VH, TRD, PPV, PRP, and intravitreal anti-VEGF injection. With relatively low rates of developing VTCs and requiring ocular interventions among patients in each cohort of this study, our study only included 4% and 0% of patients in the continuous glucose monitoring and control cohort, respectively, with severe NPDR before propensity score matching. While this may impact the findings of our study, 0% of patients with severe NPDR were included after propensity score matching. Finally, patients who received ocular interventions for the treatment of NPDR prior to the index date were excluded from each cohort but treatment during the study period may affect the development of NPDR VTCs. However, despite being at an increased risk of requiring intravitreal anti-VEGF pharmacotherapy, PRP, and PPV during the study period, patients enrolled in the continuous glucose monitoring cohort also developed VTCs at an increased rate, when compared to matched patients not initiated on continuous glucose monitoring. The analysis does not directly address the statistical assumption for comparing baseline characteristics and interaction tests were not performed. At last, despite relatively stable practice patterns for the past two decades, differences in management of PDR may exist in the enrollment period and impact the findings of the study. Despite its limitations, this study reinforces the growing support for continuous glucose monitoring in the co-management of diabetic patients with DR and provides valuable insight for patients and providers in clinical practice and during counseling.

Using a large real-world patient dataset, this study demonstrated decreased risk of developing subsequent DME, PDR, VH, and TRD in patients with NPDR initiated on continuous glucose monitoring when compared to a matched cohort of patients not initiated on continuous glucose monitoring, even when HbA1c levels was controlled between both cohorts. Those initiated on continuous glucose monitoring had less risk of requiring intravitreal anti-VEGF pharmacotherapy, PRP, and PPV when compared with a match cohort of patients not initiated on continuous glucose monitoring. While continuous glucose monitoring use has rapidly increased in patients with type 1 diabetes, the findings of the present study highlight additional benefit in patients with type 2 diabetes as well. Future studies are needed to investigate the benefit of continuous glucose monitoring, as well as the impact of glycemic variability and time in range, among patients with type 1 and type 2 diabetes with NPDR.

Data availability

The datasets generated and/or analyzed during the current study are not publicly available due TriNetX compliance and ISO 27001 Certification, but are available from the corresponding author on reasonable request.

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Author contributions

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Declarations

Competing interests

The authors declare no competing interests.

Additional information

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