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Clinical use of a 180-day implantable glucose sensor improves glycated haemoglobin and time in range in patients with type 1 diabetes*

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Abstract

Aims: This real-world study evaluated the changes in glycated haemoglobin (HbA1c) and continuous glucose monitoring (CGM) metrics associated with use of the implantable 180-day Eversense CGM System (Eversense) in patients with type 1 diabetes.

Materials and methods: This was a prospective, multicentre, observational study among adult participants aged ≥18 years with type 1 diabetes across seven diabetes-care centres in Italy who had Eversense inserted for the first time. HbA1c was measured at baseline and at 180 days. Changes in time in range [TIR (glucose 70–180 mg/dL)], time above range [TAR (glucose >180 mg/dL)], time below range [TBR (glucose <70 mg/dL)] and glycaemic variability were also assessed. Data were also analysed by previous CGM use and by mode of insulin delivery.

Results: One-hundred patients were enrolled (mean age 36 ± 12 years, mean baseline HbA1c 7.4 ± 0.92% [57 ± 10 mmol/mol]). Fifty-six per cent of patients were users of the continuous subcutaneous insulin infusion pump and 45% were previous users of CGM. HbA1c significantly decreased in patients after 180 days of sensor wear (−0.43% ± 0.69%, 5 ± 8 mmol/mol, $P < 0.0001$). As expected, CGM-naïve patients achieved the greatest reduction in HbA1c (−0.74% ± 0.48%, 8 ± 5 mmol/mol). TIR significantly increased and TAR and mean daily sensor glucose significantly decreased while TBR did not change after 180 days of sensor wear.

Conclusions: Real-world clinical use of the Eversense CGM System for 180 days was associated with significant improvements in HbA1c and CGM metrics among adults with type 1 diabetes. The study is registered on clinicaltrials.gov (NCT04160156).

*Parts of this study were presented in abstract form at the 55th Scientific Sessions of the European Association for the Study of Diabetes, Barcelona, Spain, 16-20 September 2019.

1 | INTRODUCTION

The adoption of continuous glucose monitoring (CGM) technology has improved the ability of patients with type 1 diabetes to self-manage their disease. Clinical studies have shown commercially available CGM systems are accurate in detecting and are effective in reducing hypoglycaemia and improving glycaemic control.[1-4] CGM systems display the current glucose value and trend, notify the user of actual or predicted high and low glucose values, and provide data summaries that facilitate diabetes treatment optimization.

Although the use of CGM is increasing, barriers remain for further CGM uptake as well as maintenance of CGM use in the long term.[5] Device-related issues that negatively impact patient adherence and long-term use include trouble inserting the sensor, insertion pain, burden of frequent sensor replacement, discomfort from wearing the sensor, dissatisfaction with wearing diabetes devices, sensor dislodgement and skin irritation due to the adhesive.[5,6]

The Eversense CGM System (Eversense; Senseonics, Inc., Germantown, Maryland) was developed to overcome some of the limitations of traditional transcutaneous CGM systems. Eversense consists of a fully implantable sensor lasting up to 180 days, a removable transmitter that provides on-body vibratory alerts and a mobile medical app (MMA) that displays glucose information captured and calculated by the transmitter. Clinical trials supporting regulatory approval have demonstrated that the Eversense CGM System is accurate and safe.[7-9] The system has also been shown to be safe over multiple sensor insertion and removal cycles in a large European registry.[10]

The purpose of this study was to evaluate changes in glycated haemoglobin (HbA1c) and in CGM metrics among patients with type 1 diabetes using the 180-day Eversense CGM System in the real-world clinical setting.

2 | MATERIALS AND METHODS

2.1 | Study design and patients

This is a prospective, multicentre, observational clinical research study among adult participants aged ≥18 years with type 1 diabetes across seven diabetes-care centres in Italy. Patients were required to be Eversense naïve. As described on the label, patients were not candidates for the system if they required an MRI during sensor wear, were critically ill (including hospitalization), had a known contraindication to dexamethasone, required intravenous mannitol or mannitol irrigation solutions, or were pregnant.

The study protocol was submitted and approved by the Ethical Committee "Area Calabria Centro", protocol number 186–19. Eligible patients were informed about the purpose of the study and informed consent was obtained from all study participants.

The study was registered on clinicaltrials.gov (NCT04160156).

2.2 | Study device

The device has been described in detail previously.[7-9] The 180-day duration Eversense CGM System consists of an implantable, fluorescence-based sensor; the smart transmitter worn on top of the skin above the sensor; and the MMA, which operates on a mobile device (smart phone, smart watch or iPad) and provides real-time monitoring of current and historical glucose values.

The MMA generates pop-up messages and alerts for glucose values crossing low and high thresholds, glucose rates of change exceeding pre-set limits, and predicted low and high glucose levels. Glucose data from the MMA are uploaded and stored in the Eversense Data Management System (DMS). DMS data can be analysed to provide different CGM metrics such as time in range (TIR; 70–180 mg/dL), time below range (TBR; <70 mg/dL), time above range (TAR; >180 mg/dL), mean daily glucose levels and standard deviation (SD).

2.3 | Study procedures

Trained endocrinologists implanted the 180-day duration sensor into the subcutaneous tissue of the upper arm at the end of the deltoid muscle. Patients were registered in the DMS, allowing automatic uploading of sensor glucose data. Study participants were contacted to ensure proper healing of the incision 1 week after insertion and then 4 weeks later, which is consistent with standard clinical practice in Italian diabetes centres. Patients returned to the clinic at the end of the study so that the home-use setting could be evaluated and to collect venous samples for the HbA1c measurement.

Patients were trained on use of the Eversense CGM System before sensor insertion, as suggested by the current clinical practice recommendations.[11] Specifically, patients were instructed about the principles of the sensor technology, the operational aspects of the device, and the interpretation of displayed data. No therapeutic adjustments to pre-meal insulin dosing were specified in the study protocol. Patients were advised to take action when alerts were generated according to general recommendations, including checking the glucose value using a traditional blood glucose meter. The following parameters were collected for each patient: HbA1c (measured using high-performance liquid chromatography[12]) within 2 months before sensor implantation and 180 days ±1 week of sensor wear, disease duration, previous use of CGM (defined as continuous sensor use in the previous 6 months) and insulin therapy delivery mode [multiple daily insulin injection (MDI) or continuous subcutaneous insulin infusion (CSII)].

The percentage of readings within the euglycaemic target or TIR (glucose 70–180 mg/dL), TAR (glucose >180 mg/dL), TBR (glucose <70 mg/dL), mean overall daily glucose, and mean SD and coefficient of variation (CV) were collected from the DMS over the first 2 weeks after sensor implantation, which was used for the baseline assessment in this report. The CGM values recorded 2 weeks before the 180-day visit were used for the 180-day assessment.

All adverse events (AEs) thought to be potentially related to the device or procedure that occurred in clinic or during home use were documented. The healthcare provider (HCP) evaluated the site of sensor insertion at the time of insertion or removal and inquired about healing of the incision over the phone at 1 and 4 weeks after insertion. Patients were asked to provide

TABLE 1 HbA1c and CGM metric changes in all patients and by subgroups using CSII and MDI treatment for insulin delivery and either CGM naïve or with previous CGM use

	All (N = 100)	CSII and previous CGM use (N = 35)	CSII and CGM naïve (N = 21)	MDI and previous CGM use (N = 10)	MDI and CGM naïve (N = 34)
HbA1c (%)					
Baseline	7.4 ± 0.92	7.0 ± 0.7	7.8 ± 0.8	7.0 ± 0.6	7.6 ± 1.0
180 days	6.9 ± 0.76	6.8 ± 0.6	7.1 ± 0.7	6.8 ± 0.9	7.1 ± 0.8
Change from baseline	0.43 ± 0.69	0.22 ± 0.54	0.74 ± 0.48	0.22 ± 0.68	0.53 ± 0.85
P-value	<0.0001	0.03	<0.0001	0.33	<0.001
HbA1c (mmol/mol)					
Baseline	57 ± 10	53 ± 8	62 ± 9	53 ± 7	60 ± 11
180 days	52 ± 9	51 ± 7	54 ± 8	51 ± 10	54 ± 9
Change from baseline	5 ± 8	2 ± 5	8 ± 5	2 ± 8	5 ± 10
P-value	<0.0001	0.03	<0.0001	0.33	<0.001
TIR [%; 70–180 mg/dL (3.9–10.0 mmol/L)] per day					
Baseline	63 ± 15	68 ± 14	56 ± 12	70 ± 11	60 ± 16
180 days	69 ± 14	70 ± 14	69 ± 13	68 ± 15	67 ± 12
Change from baseline	5.3 ± 12.2	2.2 ± 10.8	12.4 ± 10.5	1.7 ± 13.2	6.2 ± 12.3
P-value	<0.0001	0.23	<0.0001	0.69	<0.01
TAR [%; >180 mg/dL (10.1–13.9 mmol/L)] per day					
Baseline	32 ± 16	27 ± 15	39 ± 14	26 ± 10	35 ± 16
180 days	26 ± 14	25 ± 14	26 ± 15	26 ± 10	27 ± 13
Change from baseline	5.9 ± 13.4	1.7 ± 10.6	13.0 ± 14.4	0.6 ± 12.8	7.8 ± 13.6
P-value	<0.0001	0.34	<0.001	0.88	<0.01
TBR (%, <70 mg/dL [<3.9 mmol/L]) per day					
Baseline	4.3 ± 3.1	4.6 ± 3.5	4.5 ± 3.0	4.2 ± 2.5	3.9 ± 3.1
180 days	4.9 ± 4	4.6 ± 4.1	4.6 ± 3.5	5.4 ± 3.2	5.1 ± 4.4
Change from baseline	0.6 ± 4.3	0.0 ± 3.1	0.1 ± 4.1	1.2 ± 3.2	1.1 ± 4.2
P-value	0.41	0.98	0.98	0.27	0.12
Mean daily glucose (mg/dL)					
Baseline	154 ± 21	146 ± 21	160 ± 22	151 ± 15	158 ± 20
180 days	147 ± 24	147 ± 24	146 ± 27	149 ± 21	149 ± 23
Change from baseline	6.3 ± 23.2	0.5 ± 18.5	14.5 ± 29.4	1.6 ± 18.9	9.7 ± 22.9
P-value	<0.001	0.87	0.04	0.79	0.02
SD (mg/dL) per day					
Baseline	54 ± 11	49 ± 11	56 ± 10	52 ± 11	56 ± 10
180 days	50 ± 12	48 ± 12	48 ± 13	53 ± 12	52 ± 12
Change from baseline	3.2 ± 12.4	0.7 ± 10.1	7.9 ± 15.8	0.3 ± 11.3	3.9 ± 12.1
P-value	<0.01	0.65	0.04	0.93	0.06
CV (%)					
Baseline	35 ± 5	34 ± 6	35 ± 4	35 ± 5	35 ± 5
180 days	34 ± 6	33 ± 7	33 ± 5	34 ± 4	35 ± 5
Change from baseline	1 ± 5	0.3 ± 6	2 ± 6	0.5 ± 4	0.5 ± 5
P-value	0.21	0.75	0.10	0.72	0.57

Abbreviations: CGM, continuous glucose monitoring; CSII, continuous subcutaneous insulin infusion; CV, coefficient of variation; HbA1c, glycated haemoglobin; MDI, multiple daily injection; SD, standard deviation; TAR, time above range; TBR, time below range; TIR, time in range.

information on any AEs and changes in health status at and between visits or calls.

2.4 | Statistical analyses

Paired *t*-tests were used to compare mean parameters measured at baseline and at 180 days in the overall study population and by four patient subgroups based on method of insulin delivery and previous CGM use: (i) CSII and previous CGM use; (ii) CSII and CGM naïve; (iii) MDI and previous CGM use; and (iv) MDI and CGM naïve. A two-step rank transformation was applied to normalize the variables, or a non-parametric test was used in cases when variables were not normally distributed. $P \leq 0.05$ was statistically significant for all tests. All tests were performed using SPSS 23 for Macintosh (IBM Corp., Armonk, New York).

3 | RESULTS

3.1 | Baseline characteristics

One-hundred patients across seven diabetes-care clinical centres participated in the study. The mean age of patients was 36 ± 12 years (range 18–69), 53% of patients were male and patients had been diagnosed with type 1 diabetes for an average of 16 ± 10 years. Fifty-six per cent of patients used CSII and the remaining 44% used MDI to deliver their insulin. Fifty-five per cent of patients were CGM naïve and the remaining 45% were previous CGM users. The mean ± SD HbA1c at baseline was 7.4% ± 0.92% (57 ± 10 mmol/mol; range, 5.7–10.5% [39–91 mmol/mol]).

3.2 | Glycated haemoglobin and continuous glucose monitoring metrics

Table 1 summarizes HbA1c and CGM metrics at baseline, at 180 days, and change from baseline for all patients and by previous CGM use and insulin delivery method subgroup. Overall, HbA1c declined from a mean of 7.4% (57 mmol/mol) at baseline to 6.9% (52 mmol/mol) at 180 days [mean change −0.43% (5 mmol/mol), $P < 0.0001$]. As expected, the greatest mean HbA1c reductions were observed in the subgroups of patients who were CGM naïve and used either CSII [−0.74% (8 mmol/mol)] or MDI [−0.53% (5 mmol/mol)].

In the overall sample, mean TIR improved from 63% to 69% (mean change six percentage points, $P < 0.0001$). Consistent with the results on HbA1c changes, the greatest improvements in TIR occurred in the subgroups of patients who were CGM naïve; however, numeric improvements were observed among those with previous CGM use, as well. Similar relative magnitudes of improvements were observed for TAR, mean glucose and SD. TBR range and CV did not change significantly overall or in any subgroup.

3.3 | Safety

No related SAEs and two AEs related to the procedure occurred. One related AE was a mild incision site infection, which was treated by oral antibiotics. The other related AE was the inability to remove the sensor on the first attempt; the sensor was removed on the second attempt. The mean sensor duration was 163 ± 21 days.

4 | DISCUSSION

This real-world clinical study of the long-term, implantable 180-day Eversense CGM System in 100 patients with type 1 diabetes demonstrated statistically significant and clinically meaningful reductions in HbA1c and improvements in most CGM metrics. As expected, these improvements were greater in subgroups of patients who were CGM naïve regardless of the insulin delivery method. The safety profile was consistent with other real-world evaluations of Eversense.

The mean change of −0.43% in HbA1c in the overall sample was associated with an average increase of 5.3% TIR. These findings were consistent with previous reports, which have linked a 0.5% decrease in HbA1c to a 10% increase in TIR.[13] As expected, the two CGM naïve subgroups had relatively higher baseline HbA1c values and poorer CGM metrics than those with previous CGM use; consequently, their values improved to a greater degree. However, it is notable that numeric improvements were observed in all subgroups, regardless of previous CGM use or insulin delivery method, and a statistically significant reduction in HbA1c from baseline was observed in the subgroup of patients who used CSII and previously used a traditional CGM. This significant improvement, despite the limited statistical power in a relatively small subgroup, may reflect the benefits of the long-term, implantable CGM.

The average TIR of 69% at 180 days is greater than that observed in other real-world analyses of the Eversense CGM System. An average TIR of 62% was achieved in the first 205 US commercial users[14] and an average TIR of 65% was achieved in the longitudinal assessment of 945 Eversense users outside of the United States over four consecutive Eversense cycles.[15] Patients who were naïve to CGM, who had relatively low TIR at baseline, experienced meaningful improvements of 7–13 percentage points. The TIR values of nearly 70% seen in this study have only been previously reported for hybrid closed loop or closed loop artificial pancreas systems.[16,17] Interestingly, these improvements were achieved without receiving any formal, protocol-specified diabetes education on how to adjust their therapy based on their Eversense data. Lastly, no degradation in glucose control was observed with Eversense in patients with previous CGM experience.

The findings of this study in the context of evidence-based guidelines suggest that the improvements observed with the Eversense CGM System are clinically meaningful. The overall HbA1c after 180 days of Eversense wear was 6.9%, which meets the guideline-directed goal of <7%.[18] Additionally, the 180-day mean TIR of 69%

was nearly at the guideline-directed goal of >70%.[19] These favourable results in the real-world clinical setting provide support for the use of a long-term, implantable CGM system to optimize the management of type I diabetes.

This study represents the first clinical report of Eversense on HbA1c and CGM metrics under real-world use. The pivotal study to evaluate the 180-day implantable CGM system for CE marking, the PRECISE Study, showed a mean change in HbA1c of −0.35% (4 mmol/mol) from a baseline of 7.6% (60 mmol/mol) after 180 days of use,[7] which is similar to the results of this study. The similar results achieved in both the clinical trial and real-world use settings suggests that the benefits observed in the registration trials are attainable in routine clinical practice.

Unlike the present study, the real-world evaluations previously published on the Eversense performance involved the analysis of de-identified data from the Eversense DMS with little to no knowledge of baseline characteristics of the study participants.[14,15] The differences in CGM metrics and HbA1c changes among those using different methods of insulin delivery and by previous CGM use have also not been previously studied.

Results from a European Patient Registry with >3000 patients confirmed the safety of the device over multiple cycles of use in the real-world setting with <1% of patients experiencing incision site infection, secondary procedures to remove the sensor and adhesive patch irritation.[9] The safety profile of the Eversense CGM System in this study corroborated the safety profile observed in the European registry study and the real-world evaluation of the first Eversense users in the United States with a total of 2% of participants experiencing minor adverse events related to the CGM system.[14]

A strength of this study was the multicentre, prospective evaluation under real-world use conditions. The major limitation of this study is the lack of a control group; however, several previous randomized controlled trials have demonstrated that CGM systems provide significantly greater glycaemic control than usual care.[20-23] Another limitation of this study is the evaluation of a single 180-day cycle of sensor wear, whereas Eversense is intended to be used over a lifetime. In addition, the magnitude of the changes in HbA1c (mean −0.43%) are probably naturally limited by the relatively low baseline HbA1c values (mean 7.4%). The study was not designed to enrol specific numbers of patients in subgroups of previous CGM use and pump use, so the numbers of patients in the various CGM and insulin delivery method subgroups varied and limited the statistical power to detect significance within some of the subgroups. An additional limitation is that quality of life surveys were not administered, which may have provided insights into the patient perspectives on satisfaction with the Eversense relative to traditional CGM systems for those with previous CGM experience.

This prospective evaluation of the 180-day, implantable Eversense CGM System in adults with type 1 diabetes in a real-life clinical setting demonstrated improved glycaemic control outcomes among a broad group of individuals with and without previous CGM experience and using different methods of insulin delivery. The Eversense CGM System shows promise as a diabetes management tool to assist patients with achieving guideline-directed targets for TIR with a long-term sensor that addresses several of the limitations that are known to impair compliance with traditional CGM systems.

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CONFLICT OF INTEREST

No funding was received to conduct this study. C.I. is involved in ongoing clinical studies with the Eversense CGM System but was not compensated for her time to prepare this manuscript. Antonio Cutruzzolà, A.N., R.A., B.B., D.P., L.T., Angelo Cignarelli, L.L., G.C., E.L. and A.G. have nothing to disclose. K.S.T. and F.R.K. are employees of Senseonics.

AUTHOR CONTRIBUTIONS

C.I. takes full responsibility for the work as a whole, including the study design, participant recruiting, data acquisition, analysis and interpretation of the study data, preparation of this manuscript, and the decision to submit and publish the manuscript. Antonio Cutruzzolà, A.N., R.A., B.B., L.T., S.D.M., Angelo Cignarelli, G.C. and E.L. contributed to study participant recruiting and data acquisition. D.P. contributed to study participant recruiting and data acquisition and interpretation. L.L. contributed to study design, participant recruiting and data acquisition. A.G. contributed to study design and interpretation. K.S.T. contributed to manuscript preparation. F.R.K. contributed to critical review of the manuscript.

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