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Research: Treatment

Routine use of continuous glucose monitoring in 10 501 people with diabetes mellitus

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Abstract

Aims To analyse blood glucose control according to continuous glucose monitoring use in data from the CareLink™ database, and to identify factors associated with continuation of sensor use during sensor-augmented pump therapy.

Methods The analysis used data from 10 501 people with Type 1 and 2 diabetes mellitus, of whom 7916 (61.7%) had used glucose sensors for ≥ 15 days during any 6-month period over a 2-year observation period. Data were analysed according to the extent of sensor use (< 25%, 25–49%, 50–74% and ≥ 75% of the time). Time to discontinuation of sensor use was also analysed in new users of glucose sensors.

Results Compared with patients in the lowest sensor usage group and non-users, the highest glucose sensor usage group had significantly ($P < 0.0001$) lower mean blood glucose and blood glucose SD, were more likely to achieve a mean blood glucose concentration < 8.6 mmol/l, (odds ratio 1.5, 95% CI 1.3–1.7; $P < 0.0001$), and had 50% fewer hypoglycaemic (blood glucose concentration < 2.8 mmol/l) episodes. Among new users, sensor use during the first month of therapy was an important predictor of subsequent discontinuation. Lack of full reimbursement was also significantly associated with early discontinuation, whereas measures of glycaemic control were predictive of discontinuation during long-term treatment.

Conclusions The use of continuous glucose monitoring was significantly associated with reductions in hypoglycaemia and improved metabolic control during insulin pump therapy. Sensor use during the first month was strongly associated with long-term adherence; patient education and training may be helpful in achieving this.

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Introduction

In sensor-augmented insulin pump therapy, the pump receives continuous glucose monitoring (CGM) data from a subcutaneous sensor allowing online monitoring by patients and clinicians, and suspension of insulin delivery if blood glucose decreases below a pre-set threshold ('low glucose suspend' function). This technique has been shown to produce effective glycaemic control without increasing the risk of hypoglycaemia [1]. Prospective controlled studies have shown significant and sustained HbA_{1c} reductions of ~ 0.8–1.78 mmol/mol (0.5–1.1%), compared with multiple daily injections and self-monitoring of blood glucose [2–4]. Similar results were obtained in other studies [5–8] on CGM in people with Type 1 diabetes, most of whom were receiving insulin pump therapy. Together, these studies show that sensor-augmented pump therapy is associated with a significant increase in the time spent within normal glycaemic ranges, and decreases in the number of hypoglycaemic events and duration of hypoglycaemia [3,5–10]. The introduction of this technology, however, has raised issues regarding the widespread use of CGM [11–13]. In particular, the generalizability to the 'real world' situation of results obtained with CGM in controlled clinical trials remains to be established. Registry-based studies [14,15] have found improvements in glycaemic control similar to those seen in controlled clinical trials, but these studies were small and were restricted to specialist centres. Robust outcomes data during routine CGM could potentially be obtained from large databases [16]. The potential benefits of this approach are highlighted by the finding that, despite clear evidence that CGM should be used

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What's new?

- The generalizability to routine clinical use of results obtained on continuous glucose monitoring under the controlled conditions pertaining in clinical trials remains to be established.
- This study, which involved data from > 10 000 people with diabetes, is the largest study to have analysed objective data derived from a self-uploaded patient electronic database.
- The analysis showed that the routine home use of continuous glucose monitoring was significantly associated with a reduction in hypoglycaemia and improved metabolic control in people with diabetes receiving insulin pump therapy.

for at least 70% of the time to ensure optimum benefits [2,3,5,7,14,15,17], this level of adherence is rare [15,18]. The aim of the present study, therefore, was to analyse glycaemic control from self-monitoring of blood glucose data in relation to patterns of CGM use in people with diabetes included in the CareLink™ database (Medtronic), and to identify the factors associated with discontinuation of sensor use.

Patients and methods

In the present analysis, we used anonymized CareLink data collected between 1 September 2011 and 31 October 2013 from 21 196 people with diabetes in Western Europe, Israel and Canada. Patients provided informed consent for the use of their data before the first download; this consent did not include the use of demographic and other clinical data, and hence these data were not recorded. Reimbursement status of sensor-augmented pump therapy was described as full (reimbursement by the public healthcare system or national funding with universal coverage), partial (significant restrictions or regional variations in coverage, or case-by-case funding) or none, depending on the patients' countries of residence.

The CareLink database includes only patients receiving insulin pump therapy (insulin pumps or sensor-augmented pumps from Medtronic) with blood glucose meters from various manufacturers. All individuals included in the analysis had at least 6 months' downloadable data and at least one sensor reading in CareLink. In order to exclude anecdotal and transient diagnostic use of the sensor, sensor users were defined as patients with at least 15 days of sensor usage within any 6-month period starting from 1 September 2011: the date of the first sensor reading was defined as the date of first consistent sensor use. Patients with < 15 days of sensor use within any 6-month period were considered to be non-users. In addition to the non-user group, four user groups were defined: patients using the sensor < 25%, 25–49%, 50–74% or ≥ 75% of the time.

Because the sensor provides 288 readings within a 24-h period, the expected number of readings over any period of time could be calculated. For sensor users, the proportion of time wearing a sensor was calculated as the observed number of sensor readings divided by the expected total number of readings from the time of first consistent sensor reading to the end of the observation period, expressed as a percentage. In occasional instances where the device's memory capacity was reached before the data were uploaded to CareLink, data from the relevant period were excluded from the analysis.

Measures of glycaemic variability were derived from self-monitoring of blood glucose measurements, rather than sensor glucose values, because this approach provides greater consistency in the number of blood glucose measurements between groups. Variability measures included mean (SD) blood glucose, the proportion of blood glucose measurements below 2.8, 3.3 and 3.9 mmol/l, the proportion of measurements between 3.9 and 10.0 mmol/l, and the proportion of measurements above 10.0 mmol/l and 13.9 mmol/l. Blood glucose measurements were also used to estimate HbA_{1c} levels and the proportion of patients achieving an HbA_{1c} level < 53 mmol/mol (7.0%), as described by Nathan *et al.* [19].

Hypoglycaemic events were defined as blood glucose values below 2.8, 3.3 and 3.9 mmol/l. Two low blood glucose measurements within 20 min were regarded as one event, as described previously [9].

Statistical analyses

Comparisons of blood glucose measures between sensor usage groups were performed using ANOVA with weighting for unequal numbers of blood glucose measurements between patients [20]. Odds ratios of achieving specific HbA_{1c} targets between groups were compared by logistic regression, with sensor usage group as covariate. Adjustment for multiple comparisons was performed using the Hommel test. No imputation of missing data was performed.

Time to discontinuation of sensor use was analysed in patients who were already receiving pump therapy but were new to sensor therapy. These patients were defined as individuals with a date of first consistent sensor use later than 1 October 2011 (at least 1 month after the start of the observation period). Sensor discontinuation was defined as < 14 days of sensor use within any 6-month period starting from the last day of the observation period (31 October 2013) and finishing at the date of first consistent sensor use. Kaplan–Meier curves were used to estimate the proportion of patients remaining on sensor therapy at different times within each group, and a Cox proportional hazard model was used to identify factors associated with discontinuation of sensor use, and to compare the risk of sensor discontinuation between sensor usage groups. All statistical analyses were performed using SAS (version 9.3) software (Cary, North Carolina, USA), and P values < 0.05 were considered to indicate statistical significance.

Results

At the time of the analysis, the CareLink database included 21 196 patients, of whom 10 695 had < 6 months of data and were therefore excluded. Of those included in the analysis (n = 10,501), 7916 had at least 15 days of sensor use within a 6-month period, and 2585 were non-users; 3028 of the sensor users (38.3%) were identified as being new to sensor therapy. Of the 7916 sensor users, 1760 (22.2%) used the sensor ≥ 75% of the time, and 2782 (35.1%) used sensors < 25% of the time (Table 1).

The mean (SD) daily insulin dose was 43.6 (22.1) units, and the median daily dose was 40.4 units. Full reimbursement of sensor-augmented pump therapy was available to 4005 patients (38.1%), and partial coverage was available to 6002 (57.2%). Where treatment was fully reimbursed at national level, ~ 50% of sensor users used their sensors > 50% of the time, whereas lower rates of sensor use were seen when reimbursement was only partial (Table 1).

Glycaemic control with sensor-augmented pump therapy

The mean (SD) blood glucose concentration among non-users was 9.3 (4.5) mmol/l, compared with 9.3 (4.4) mmol/l in patients using the sensor < 25% of the time, 9.3 (4.3) mmol/l in those using the sensor 25–49% of the time, 9.3 (4.1) mmol/l in those using the sensor 50–74% of the time, and 9.1 (3.8) mmol/l in those using the sensor ≥ 75% of the time; the mean concentration and SD in the latter group were both significantly (P < 0.0001) lower than the corresponding values in all other groups. The mean decrease in blood glucose in the highest sensor usage group, compared with non-users, was 0.26 mmol/l, which corresponds to a decrease in HbA_{1c} concentration of 0.2% [19]. A mean blood glucose concentration < 8.6 mmol/l was achieved in 699 patients (39.7%) using the sensor for ≥ 75% of the time, compared with 30.5–32.1% of patients in other sensor usage groups and 31.1% in non-users (P < 0.0001 for all comparisons with the highest sensor use group); the odds ratios for achieving this level of glycaemic control in the highest users were 1.4 (95% CI 1.2–1.6) compared with those using the sensor 50–74% of the time, and 1.5 (95% CI 1.3–1.7) compared with all other groups (P < 0.0001 for all comparisons). The mean proportion of blood glucose concentrations < 2.8, 3.3 and 3.9 mmol/l, 3.9–10.0 mmol/l, and > 10.0 mmol/l in each group are shown in Table 2. The mean proportion of blood glucose values in the range 3.9–10.0 mmol/l increased significantly with sensor use (P < 0.0001 for the highest users compared with all other users); compared with non-users, the mean proportions of blood glucose values < 3.9 mmol/l or > 10.0 mmol/l were 30.5 and 3.9% lower, respectively, in the highest user group,

Table 1 Participant characteristics according to sensor usage group

	Sensor usage group				
	Non-sensor users	< 25% of the time	25–49% of the time	50–74% of the time	≥ 75% of the time
Number of participants, *n*	2585	2782	1789	1585	1760
Mean (SD) total daily insulin dosage, units	43.4 (21.7)	43.5 (21.4)	43.7 (22.5)	44.8 (22.2)	42.4 (22.8)
Median number of self-monitoring of blood glucose measurements per week	33.9	31.5	32.2	34.5	37.4
Sensor users, *n* (%)	NA	1375 (49.4)	1548 (86.5)	1556 (98.2)	1755 (99.7)
Sensor drop-outs, *n* (%)	NA	1407 (50.6)	241 (13.5)	29 (1.8)	5 (0.3)
Number of participants using low glucose suspend feature (%)	NA	1091 (39%)	980 (55%)	947 (60%)	1152 (65%)
Mean number of activations of the low glucose suspend feature per week*	NA	2.1	2.2	2.3	2.8
Mean duration of low glucose suspension per week† (h:min:s)	NA	3:00:39	2:57:33	3:15:31	3:30:35
Mean duration of individual activations of low glucose suspend feature§ (h:min:s)	NA	1:41:40	1:35:08	1:35:32	1:22:11
Reimbursement level‡, *n* (%)					
National	823 (31.8)	805 (28.9)	691 (38.6)	800 (50.5)	886 (50.3)
Partial	1613 (62.4)	1853 (66.6)	1044 (58.4)	706 (44.5)	786 (44.7)
None	149 (5.8)	124 (4.5)	54 (3.0)	79 (5.0)	88 (5.0)

NA, not applicable.
Totals may not equal 100% because of rounding.
*During the time when the low glucose suspend feature was active and sensor was on. All group comparisons vs. ≥ 75% usage group are P < 0.0001.
†P = 0.0035, 0.0018, 0.1573 each group respectively vs. ≥ 75% usage group.
§P = 0.0002, 0.0133, 0.0110 each group respectively vs. ≥ 75% usage group.
‡National reimbursement: reimbursement by the public healthcare system or national funding; partial reimbursement: reimbursement with significant restrictions or case by case funding or regional variations; None: no reimbursement by the public healthcare system or not funded at national or regional level.

Table 2 Results of self-monitoring of blood glucose according to sensor usage group

	Mean (SD) proportion of blood glucose values, %				
	Non-users n = 2585	Sensor usage < 25% n = 2782	Sensor usage 25–49% of the time n = 1789	Sensor usage 50–74% of the time n = 1585	Sensor usage ≥ 75% of the time n = 1760
< 2.8 mmol/l	2.0 (0.04)	1.9 (0.04)	1.6 (0.04)	1.4 (0.04)	1.2 (0.03)
< 3.3 mmol/l	5.1 (0.07)	4.8 (0.07)	4.2 (0.08)	3.8 (0.08)	3.3 (0.07)
< 3.9 mmol/l	9.1 (0.10)	8.5 (0.01)	7.7 (0.11)	7.0 (0.12)	6.3 (0.11)
3.9–10.0 mmol/l	53.4 (0.23)	54.1 (0.23)	54.7 (0.30)	55.3 (0.32)	57.6 (0.32)
> 10.0 mmol/l	37.6 (0.27)	37.3 (0.26)*	37.6 (0.33)†	37.7 (0.36)‡	36.1 (0.36)
≥ 13.9 mmol/l	16.2 (0.2)	15.6 (0.19)	15.3 (0.24)	14.7 (0.25)	13.0 (0.23)

*P = 0.007, †P = 0.001, ‡P = 0.0009 vs. ≥ 75% usage group. All other comparisons vs. ≥ 75% usage group are P < 0.0001.

Table 3 Mean daily number of hypoglycaemic (blood glucose concentration < 2.8, < 3.3 and < 3.9 mmol/l) events according to sensor usage

	Non-users	Sensor usage < 25%	Sensor usage 25–49%	Sensor usage 50–74%	Sensor usage ≥ 75%
< 2.8 mmol/l					
Number of events per patient per year	45.0*	41.0*	36.0†	32.1*	27.5
Increase in mean number of hypoglycaemic events, compared with highest sensor usage group, %	50	37.5	25	12.5	–
Incidence rate ratio (95% CI), vs. ≥ 75% usage group	1.64* (1.50, 1.80)	1.49* (1.36, 1.63)	1.31* (1.17, 1.50)	1.17§ (1.04, 1.31)	–
< 3.3 mmol/l					
Number of events per patient per year	115.3*	105.7*	92.55*	84.34†	76.9
Increase in mean number of hypoglycaemic events, compared with highest sensor usage group, %	52.3	38.1	19.0	9.5	–
Incidence rate ratio (95% CI), vs. ≥ 75% usage group	1.50* (1.39, 1.61)	1.37* (1.28, 1.48)	1.20* (1.10, 1.31)	1.10§ (1.01, 1.20)	–
< 3.9 mmol/l					
Number of events per patient per year	203.6*	188.8*	167.4*	154.9	148.9
Increase in mean number of hypoglycaemic events, compared with highest sensor usage group, %	36.5	26.8	12.2	2.4	–
Incidence rate ratio (95% CI), vs. ≥ 75% usage group usage group	1.36* (1.28, 1.45)	1.27* (1.19, 1.35)	1.12†(1.04, 1.21)	1.04 (0.96. 1.12)	–

*P < 0.0001, †P = 0.001, §P = 0.04 vs. ≥ 75% usage group.

while the mean proportion of blood glucose values within this range was 7.9% higher. Based on these results, a prediction analysis showed that patients using the sensor > 75% of the time would have a 50% greater chance of achieving a mean blood glucose level < 8.6 mmol/l, compared with the lower usage groups (odds ratio 1.5, 95% CI 1.3–1.7).

The mean numbers of hypoglycaemic episodes in each sensor usage group are shown in Table 3. With a threshold of 2.8 mmol/l, the mean annual number of episodes per patient was 43.8 among non-users, and this figure decreased to 32.9 in patients using the sensor for 50–74% of the time and 29.2 in those using the sensor ≥ 75% of the time. Compared with the highest sensor usage group, the mean annual number of hypoglycaemic events was decreased by up to 50% in non-users or lower usage groups (Table 3). Statistically significant reductions in hypoglycaemic events with increasing sensor usage were also seen when higher hypoglycaemic thresholds were used (Table 3). The frequency and total duration of low glucose suspension increased with sensor use (Table 1).

Factors associated with sensor use discontinuation

Survival analyses were conducted to investigate the likelihood of discontinuing sensor use during the overall observation period among patients who were new to sensor-augmented pump therapy (n = 3028). Of these, 1117 (37%) used the sensor for > 50% of the time, of whom 570 (19%) used the sensor for ≥ 75% of the time. Overall, 769 patients (25.4%) discontinued sensor use during the observation period: the mean (SD) time on sensor-augmented pump therapy during the observation period ranged from 244 (184) days in the lowest sensor usage group to 432 (147) days in the highest. Only 0.4% of patients in the highest sensor usage group discontinued treatment during the observation period, compared with 52.9% of those using the sensor for < 25% of the time, 13.7% of those using the sensor for 25–49% of the time, and 1.3% of those using the sensor for 50–74% of the time. This suggested that the risk of discontinuation was related to the degree of sensor use, and this was confirmed by survival analysis focusing on the first month of sensor use only. During this period, ~ 65% of participants used the sensor > 50% of the time, and 41.6% used the sensor > 75% of the time. In this analysis, the treatment discontinuation rate was 15.6% in the highest usage group, compared with 31.7–32.9% in the lower usage groups; thus, patients in the lower usage groups during the first month were approximately twice as likely to discontinue sensor use as those in the highest usage group. During the first month and over the entire treatment period, patients in the lowest sensor usage group were significantly (P < 0.001) more likely to discontinue sensor-augmented pump therapy than those in the higher usage groups (Fig. 1). Multivariate analysis showed that the groups with lower sensor use during the first month had approximately twice the risk of sensor discontinuation, compared with the highest sensor usage group. Other factors associated with sensor discontinuation were lack of full reimbursement, the mean number of blood glucose measurements per day before sensor therapy, and mean total daily dose before sensor therapy. Compared with full reimbursement, partial or no reimbursement was associated with a 50% greater risk of sensor discontinuation; similarly, each additional blood glucose measurement per day above the mean increased the risk of discontinuation by 3.5%, and each 1-unit increment above the mean total daily dose increased the risk by 0.4%.

Discussion

To date, this is the largest study to have analysed objective data derived from a self-uploaded patient database. As such, it reflects a growing trend towards the use of real-life data to

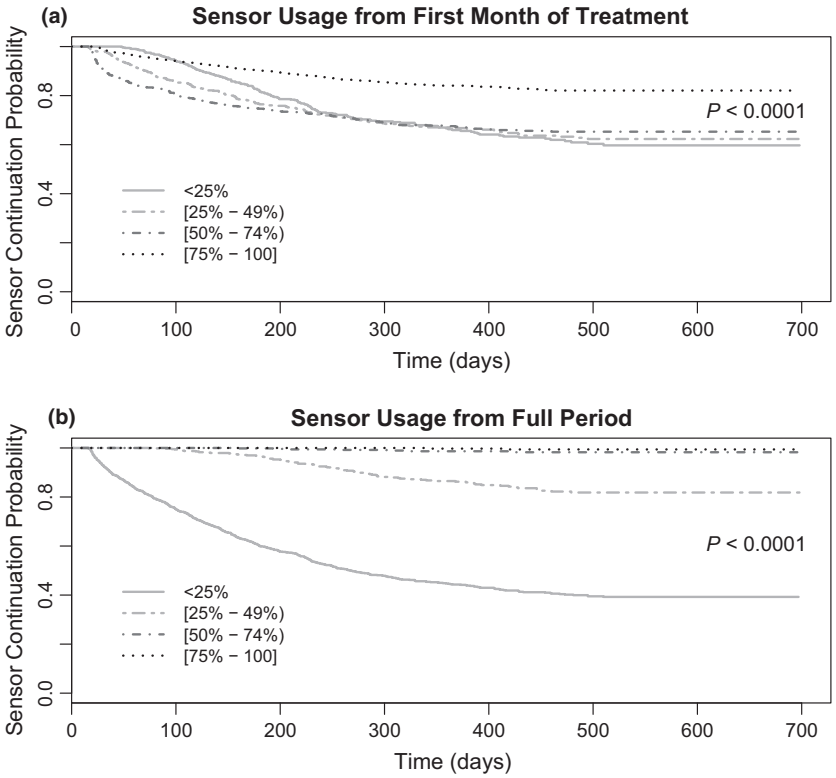

FIGURE 1 Kaplan–Meier analysis of time to discontinuation of sensor-augmented pump therapy according to sensor usage group. (a) Groups by first month of treatment usage. (b) Groups by full study period usage.

improve clinical outcomes and resource use in people with diabetes [18]. This approach may identify treatment effects that are not apparent in randomized controlled trials, which usually include strictly defined patient populations that may not be representative of the broader patient population [21,22]. The most clinically relevant result in the present study was that CGM was associated with a 12.5–50% reduction in the frequency of hypoglycaemia. This is consistent with a previous suggestion [23] that the benefit of CGM in individuals with low HbA_{1c} concentrations may be in reducing hypoglycaemia rather than mean HbA_{1c} values. Although the absolute reduction in predicted HbA_{1c} achieved in the present study in the highest sensor usage group (0.2%) was lower than those previously reported in randomized trials [2–4], this can be at least partly explained by the fact that the present study involved a large, diverse, patient population with relatively low mean blood glucose concentrations, in whom a large decrease in HbA_{1c} would not be expected. As in randomized trials [5–7], significant improvements in glycaemic control were observed during sensor use: based on the results of the present study, a prediction analysis showed that, with a sensor use of > 75%, patients had a 50% greater chance of achieving a mean blood glucose level < 8.6 mmol/l [estimated HbA_{1c} level below 53 mmol/mol (7.0%)]. Significant lowering of glucose was observed with higher sensor use, even when self-monitoring of blood glucose was performed six times per day (data not shown).

As in randomized controlled studies [9,10], sensor-augmented pump therapy was associated with a substantial reduction in the number of hypoglycaemic events, compared with non-use. The observed event rate among non-users (43.8 events per patient per year) was similar to that achieved in the ASPIRE study [9], and in patients with Type 1 diabetes mellitus included in a population-based study [24]. The finding that the highest sensor usage was associated with reductions in hypoglycaemic events of up to 50% is particularly noteworthy, given the diverse nature of the patient population and the small decrease in HbA_{1c}. Use of the 'low glucose suspend' feature increased significantly with higher sensor use, with shorter and more frequent activations and longer duration of insulin suspension. This feature may augment the favourable effect of CGM on hypoglycaemia.

Although 25% of new users discontinued sensor use during the study, the mean time to discontinuation was 339 days: even in the lowest sensor usage group, the mean time to discontinuation was 244 days. Overall, 75% of patients continued using the sensor either permanently or intermittently for up to 2 years. These data compare favourably with those reported in the T1D Exchange Clinic registry study, in which 41% of patients discontinued CGM within 1 year [25]. The most common reasons for discontinuation in that study were problems or discomfort when wearing the device and technical problems with the device. It is possible that the lower discontinuation rates found in the present study may reflect technological improvements in the CGM devices available in Europe. Survival analysis showed that patients in the lower sensor usage groups during the first month of sensor use were approximately twice as likely to discontinue treatment as those in the highest usage group. Hence, educational strategies to facilitate sensor use during the first month of therapy might be helpful in promoting long-term adherence.

The absence of full reimbursement was strongly associated with sensor discontinuation. It is possible that other factors led to withdrawal during long-term treatment, such as issues relating to quality of life or treatment burden. This might suggest that different approaches to improving adherence may be required for patients with differing levels of experience with CGM. On initiation of CGM, patient education should focus on technical and quality of life issues, while managing patients' expectations during the first 30 days; subsequently, adherence to sensor usage could be improved by emphasizing and demonstrating attainment of glycaemic goals and reduction of hypoglycaemia.

There are a number of potential technical issues that can cause data gaps during sensor use, such as infrequent data uploading and limited pump memory. In the present study, however, the median proportion of lost data was 9%; in a large cohort, such as that included in the present study, a data loss of this size will have only a small effect on the overall analyses.

A potential limitation of the present study is that, because of the nature of the data collection process, it was not possible to obtain data on patient-related factors that can influence adherence to therapy and subsequent metabolic control, such as age, gender, duration of diabetes, socio-economic status, educational level or diabetes education. Similarly, no data were available on outcomes in different practice settings, or on the use of healthcare resources by the patients. A further potential limitation is that patients downloading data to CareLink might be expected to be those most adherent to sensor-augmented pump therapy, although the potential impact of this may be offset by the large population size.

In conclusion, this analysis from a large patient database showed that patients on sensor-augmented pump therapy have less hypoglycaemia and slightly better glycaemic control in everyday life. Importantly, sensor use during the first month was strongly associated with long-term adherence. These novel observations can be used to develop specific clinical strategies to optimize metabolic control through CGM.

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Competing interests

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