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ORIGINAL ARTICLE

Accuracy of two continuous glucose monitoring systems: a head-to-head comparison under clinical research centre and daily life conditions

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Aims: To assess the accuracy and reliability of the two most widely used continuous glucose monitoring (CGM) systems.
Methods: We studied the Dexcom®G4 Platinum (DG4P; Dexcom, San Diego, CA, USA) and Medtronic Paradigm Veo Enlite system (ENL; Medtronic, Northridge, CA, USA) CGM systems, in 24 patients with type 1 diabetes. The CGM systems were tested during 6-day home use and a nested 6-h clinical research centre (CRC) visit. During the CRC visit, frequent venous blood glucose samples were used as reference while patients received a meal with an increased insulin bolus to induce an aggravated postprandial glucose nadir. At home, patients performed at least six reference capillary blood measurements per day. A Wilcoxon signed-rank test was performed using all data points ≥15 min apart.
Results: The overall mean absolute relative difference (MARD) value [standard deviation (s.d.)] measured at the CRC was 13.6 (11.0)% for the DG4P and 16.6 (13.5)% for the ENL [$p < 0.0002$, confidence interval of difference (CI Δ) 1.7–4.3%, $n = 530$]. The overall MARD assessed at home was 12.2 (12.0)% for the DG4P and 19.9 (20.5)% for the ENL ($p < 0.0001$, CI Δ = 5.8–8.7%, $n = 839$). During the CRC visit, the MARD in the hypoglycaemic range [≤3.9 mmol/l (70 mg/dl)], was 17.6 (12.2)% for the DG4P and 24.6 (18.8)% for the ENL ($p = 0.005$, CI Δ 3.1–10.7%, $n = 117$). Both sensors showed higher MARD values during hypoglycaemia than during euglycaemia [3.9–10 mmol/l (70–180 mg/dl)]: for the DG4P 17.6 versus 13.0% and for the ENL 24.6 versus 14.2%.
Conclusions: During circumstances of intended use, including both a CRC and home phase, the ENL was noticeably less accurate than the DG4P sensor. Both sensors showed lower accuracy in the hypoglycaemic range. The DG4P was less affected by this negative effect of hypoglycaemia on sensor accuracy than was the ENL.
Keywords: type 1 diabetes, CSII

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Introduction

Although sensor accuracy and reliability of subsequent sensor generations have improved over the years, patients still cannot fully rely on continuous glucose monitoring (CGM) readings when making treatment decisions [1]. This results in the need for frequent self-monitoring of blood glucose (SMBG) and relates negatively to the quality of life benefits of CGM [2]. Although standards for SMBG accuracy have been developed (e.g. ISO 15197:2013), it is not easy to compare the performance of CGM systems from different manufacturers as there is no widely accepted reference method for assessing sensor accuracy. Although it is known that accuracy may be worse with blood glucose in the hypoglycaemic range, CGMs are often not assessed over all glycaemic ranges or the accuracy is not presented in a manner that facilitates comparison across systems [1,3,4]. Also, the clinical research centre (CRC) environment chosen to investigate the CGM often does not reflect daily life conditions or the circumstances of intended use. Much of the published data on the performance of newly approved CGM systems are based on studies performed by the device manufacturers for regulatory purposes and have not been conducted by academic researchers.

The comparative performance of CGM systems is not just an academic question. Doctors and other healthcare providers must make recommendations to patients everyday about the advantages and disadvantages of CGM systems that are commercially available. A head-to-head comparison of CGM accuracy, including assessment over all glycaemic ranges but also reflecting daily life conditions, is so far not available for the two most widely used systems, the Dexcom G4 platinum (DG4P; Dexcom, San Diego, CA, USA) and the Medtronic Paradigm Veo Enlite system (ENL; Medtronic, Northridge, CA, USA).

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We therefore aimed to assess and compare the accuracy of the DG4P and ENL CGM systems in a way that includes both a highly standardized assessment within a CRC and usage at home.

Methods

This was a multinational open-label single-arm parallel study, performed in patients with type 1 diabetes treated with insulin pump therapy or multiple daily injections of insulin. The main inclusion criteria were a diagnosis of type 1 diabetes for at least 6 months, a body mass index of <35 kg/m^2 and a glycated haemoglobin (HbA1c) level of <10% (86 mmol/mol). The main exclusion criteria were pregnancy and the use of medication that impacts glucose metabolism other than those used to treat diabetes. Drugs that may impair enzymatic measurement of glucose by the sensors could not be used during the investigation (e.g. acetaminophen). The study was performed in the medical centres of the universities of Amsterdam, Graz, Montpellier and Padua. A total of 24 patients participated, with six patients per centre. The study was performed in accordance with the Declaration of Helsinki and was approved by the institutional ethics review board at each site. All patients completed an inclusion visit during which informed consent was obtained, they received training in the use of the two CGM systems, a blood sample was taken for haemoglobin and HbA1c assessment and pregnancy was excluded with a urine test in females of child-bearing potential. The two sensors were placed under the guidance of the study personnel during a visit to the research centre. The CGM systems were tested during 6 days of home use, including a nested 6-h CRC visit performed on the third day of the study period. During home use, CGM measurements were compared with capillary blood finger stick measurements, while in the CRC, venous blood glucose was used as reference. The end of study was based upon the 6-day ENL manufacturer-specified lifetime, after which the patient made a final visit. For the DG4P this lifetime is 7 days. Patients continued their normal activities of daily life during the study.

Intervention

The sensors of both CGM systems were inserted in the abdominal region of each patient during the initial hospital visit. If sensor failure occurred before the third study day (the CRC visit) the sensor was replaced. Patients were asked to calibrate the CGM according to the manufacturers' specifications (twice a day after initial calibration) against capillary blood finger stick measurements using an Accu-Chek Aviva series blood glucose meter (Roche Diagnostics, Mannheim, Germany), provided for the study. Patients were advised to avoid calibration directly after meals or strenuous activity. In addition, patients were asked to perform SMBG at least six times per day (preferably: pre- or postprandially and at bedtime). The glucose strips provided to the patient for calibration and SMBG were from the same production lot.

Clinical Research Centre

Patients arrived after fasting at the CRC on day 3. After recalibration of both CGM systems, venous blood sampling started at 8:00 h and was performed every 5 min for the first 15 min and every 15 min thereafter. The blood sampling rate was increased to every 10 min between 09:00 and 10:00 h to register the glucose peak after breakfast and from 11:00 to 12:00 h to register the glucose nadir. After bedside centrifuging, venous plasma was analysed using the YSI 2300 STAT PLUS glucose and lactate analyser (YSI, Yellow Springs, OH, USA). Samples were visually checked for dilution and haemolysis. At 8:15 h patients received a regular breakfast. Mealtime insulin dose was calculated using patients' carbohydrate-to-insulin ratio. An additional 80% insulin bolus was given to induce a period of minor hypoglycaemia [3.0–3.9 mmol/l (54–70 mg/dl)]. A correction insulin bolus was administered to patients arriving with a fasting glucose >5.0 mmol/l (90 mg/dl). Patients received rescue carbohydrates when fasting glucose was <3.0 mmol/l (54 mg/dl) or earlier at the physicians' discretion. Patients left the CRC at 14:00 h while continuing to wear the two sensors until the sixth day of the study, or earlier if both sensors stopped functioning prematurely. The end of functioning was defined as: sensor end of life indicated by the CGM display or inability to recalibrate.

Evaluation of Continuous Glucose Monitoring Accuracy

The overall mean absolute relative difference (MARD) and the MARD in the hypoglycaemic [≤3.9 mmol/l (70 mg/dl)], euglycaemic [3.9–10 mmol/l (70–180 mg/dl)] and hyperglycaemic [≥10 mmol/l (180 mg/dl)] ranges (according to reference measurements) were used as the main study outcomes, both for the CRC and home study phases. Also, the proportion of ARD values ≤15%, or at a reference glucose <5.6 mmol/l (100 mg/dl), the proportion of values with an absolute difference of ≤0.83 mmol/l (15 mg/dl), were calculated (ISO15197:2013). CGM and reference values were also compared using the Bland–Altman analysis [5] and the percentage of data points in zone A of the Clarke error grid (CEG) [6]. The MARD was calculated as the mean of the relative difference between the CGM values and the respective reference glucose values. Venous plasma glucose was used as the reference value during the CRC visit, while capillary glucose, measured by finger stick, was used as the reference value in the home phase of the study. CGM values and reference glucose values were matched in time by linear interpolation of CGM glucose values. Interpolated CGM glucose values were only used if the original sample was taken within 5 min of the available reference value. To prevent interdependency of datapoints, only CGM–reference pairs at least 15 min apart from the next CGM–reference pairs were used for analysis. SMBG values used for (re)calibration were not included in the accuracy analysis.

A *post hoc* subanalysis was performed to assess the effect of the inadvertent use of the Paradigm Real Time (RT) receiver in two patients, where the Paradigm Veo should have been used.

Statistical Analysis

Univariate analyses were performed for descriptive statistics of evaluated variables. The Wilcoxon signed-rank test was used to compare non-normally distributed continuous data and the chi-squared test was used for the comparison of categorical

variables, such as the percentage of values in the CEG A-zone. Histogram and cumulative distribution plots were used to visually assess the difference between the MARD of individual sensors per CGM. All comparisons were conducted at an $\alpha = 0.05$ level of significance using two-tailed tests. The study was designed to detect a 1% difference in CGM accuracy with 85% power, assuming a standard deviation (s.d.) of 0.75%, and 507 independent samples. Outcomes are given in mean (s.d.) with 95% confidence interval of difference (CI Δ). Statistical analysis was performed using IBM SPSS statistics version 20.0.0 (IBM Corp., Armonk, NY, USA).

This study is registered with ClinicalTrials.gov, with the number NCT01751932.

Role of the Funding Source

The present study was funded by Dexcom, San Diego, USA through an unrestricted research grant. Dexcom personnel did not participate in the study or data analysis, nor did they have access to the data until the study was completed and the manuscript was written. The authors developed the study protocol with full academic freedom, the basis of the protocol was developed with the support of a European Community Framework Programme 7 grant (FP7-ICT-2009-4 grant number 247138).

Results

The present study was performed in 2013. The 24 patients had a mean (s.d.) age of 40 (11.8) years and 16 (67%) were male. The mean (s.d.; range) time since diagnosis of type 1 diabetes was 23.5 (13.5; 4–46) years and the mean (s.d.; range) HbA1c was 8.0 (3.0; 6.7–10.0)% [64 (9; 50–86) mmol/mol]. Four ENL sensors failed before the end of the study period as indicated by the display on the receiver. Two of these were replaced, as failure occurred before the third CRC study day; thus, a total of 26 ENL sensors and 24 DG4P sensors were used during the study. In addition, three DG4P and three ENL sensors did not complete the 6-day study period as skin adherence was lost after the CRC day. The DG4P sensor provided more CGM readings than the ENL (99.2 vs. 98.1% of calculated maximum; $p < 0.0001$). Further details can be found in Table 1. Figure 1 (Bland–Altman plot) provides information on sensor accuracy over the range of absolute glucose values, as defined by the reference glucose value. No adverse events occurred during the study.

Clinical Research Centre Phase

Overall sensor accuracy at the CRC phase expressed as MARD (s.d.) was 13.6 (11.0)% for the DG4P (n = 532) and 16.6 (13.5)% for the ENL [n = 530 ($p = 0.0002$, CI Δ = 1.7–4.3%)]. The MARD (s.d.) in the hypoglycaemic range [≤3.9 mmol/l (70 mg/dl)] was 17.6 (12.2)% (n = 117) for the DG4P and 24.6 (18.8)% (n = 117) for the ENL ($p = 0.005$, CI Δ = 3.1–10.7%). The MARD (s.d.) in the hyperglycaemic range [≥10 mmol/l (180 mg/dl)] was 6.2 (5.0)% (n = 28) for the DG4P and 17.1 (8.8)% (n = 28) for the ENL ($p < 0.0001$, CI Δ = 6.9–14.8%). The DG4P had a significantly higher percentage of values in the CEG zone A (79.9 vs. 72.3%; $p = 0.004$, CI Δ = 2.5–12.8%; Figure 2A). Figure 3A shows the cumulative distribution of sensor MARD values, indicating a wider range of MARDs per individual sensor for the ENL compared with the DG4P. The proportion of data pairs in the hypoglycaemic range was 22.1% in the CRC.

Home Phase

The overall sensor accuracy expressed as MARD (s.d.) at the home phase of the study was 12.2 (12.0)% for the DG4P (n = 987) and 19.9 (20.5)% for the ENL [n = 839 ($p < 0.0001$, CI Δ = 5.8–8.7%)]. The MARD (s.d.) in the hypoglycaemic range [≤3.9 mmol/l (70 mg/dl)] was 21.2 (21.8)% (n = 56) for the DG4P and 36.5 (42.6)% (n = 47) for the ENL ($p = 0.014$, CI Δ = 3.6–25.4%). The MARD (s.d.) in the hyperglycaemic range [≥10 mmol/l (180 mg/dl)] was 11.6 (10.6)% (n = 327) for the DG4P and 18.0 (16.7)% (n = 287) for the ENL ($p < 0.0001$, CI Δ = 3.5–8.1%). The DG4P had significantly better average accuracy on each day (Figure 4) and a significantly higher percentage of values in the CEG zone A (83.0 vs. 64.6%; $p < 0.0001$, CI Δ = 14.4–22.4%; Figure 2B). Figure 3B shows the cumulative distribution of sensor MARD values indicating a wider range of MARDs per individual sensor for the ENL compared with the DG4P. The proportion of data pairs in the hypoglycaemic range was 5.7%.

Discussion

The present study, investigating the accuracy of the two most recently approved and widely used CGM systems, shows that the DG4P is significantly more accurate than the ENL system. This holds true both in the highly standardized and controlled CRC environment (MARD 13.6 vs. 16.6%; $p < 0.0002$) as well as under home conditions (MARD 12.2 vs. 19.9%; $p < 0.0001$). As expected, CGM performance was less accurate in the hypoglycaemic range than in the euglycaemic range for both CGM systems. Nonetheless, the DG4P was less affected by this negative effect of hypoglycaemia on sensor accuracy than the ENL and outperformed ENL in all glycaemic ranges. While MARD is the most concise measure of CGM accuracy, CEG analysis adds clinical relevance [6]. Cumulative distribution plots show individual sensor performance (Figure 3A and B), while the Bland–Altman plot (Figure 1) provides information on variations in sensor accuracy over the range of measured glucose concentrations [5], indicating lower accuracy in the hypoglycaemic range for both CGM systems. The results of the cumulative distribution plots, Bland–Altman plot and the % values in zone A of the CEG (home phase: DG4P, 83%, ENL, 65%; $p < 0.0001$) further substantiate the clinical relevance of the difference in CGM accuracy found in the present study. A 30% difference in a major performance measure between two competitor products is quite unusual in medicine. Over time, this difference is likely to translate into clinically meaningful intermediate outcomes, such as better patient acceptance through increased trust in the device, fewer false-positive hypoglycaemia alarms, better prevention of hypoglycaemia and lower mean glucose values.

The accuracy of both CGM systems presented in this study is in line with previous reports (MARD for DG4P in the CRC:

Table 1. Glucose sensor accuracy assessed for the Dexcom G4 Platinum and Medtronic Paradigm Veo Enlite systems in patients with type 1 diabetes under clinical research centre and home conditions.

Variable	DG4P	ENL	p	CI Δ/IQR Δ
Number of sensors used (n)	24	26	—	—
Number of CGM–reference pairs: CRC (n)	532	530	—	—
Number of CGM–reference pairs: home (n)	987	839	—	— —
Number of CGM–reference pairs <3.9 mmol/l: CRC (n)	117	117	—	—
Number of CGM–reference pairs <3.9 mmol/l: home (n)	56	47	—	—
Available CGM readings (% of maximum)	99.2	98.1	<0.0001	1.1–1.2
MARD CRC (%)	13.6	16.6	0.0002	1.7–4.3
MARD home (%)	12.2	19.9	<0.0001	5.8–8.7
MAD CRC (mmol/l)	0.73	0.91	<0.0001	0.1–0.3
MAD home (mmol/l)	1.03	1.68	<0.0001	0.5–0.7
MARD <3.9 mmol/l CRC (%)	17.6	24.6	0.0058	3.1–10.7
MARD <3.9 mmol/l home (%)	21.2	36.5	0.0142	3.6–25.4
MARD 3.9–10 mmol/l CRC (%)	13.0	14.2	0.08	0.03–2.6
MARD 3.9–10 mmol/l home (%)	11.7	19.5	<0.0001	5.5–9.1
MARD ≥10 mmol/l CRC (%)	6.2	17.1	<0.0001	6.9–14.8
MARD ≥10 mmol/l home (%)	11.6	18.0	<0.0001	3.5–8.1
Median ARD CRC (%)	10.9	13.9	0.0002	17.7
Median ARD home (%)	8.9	14.4	<0.0001	18.8
Median ARD <3.9 mmol/l CRC (%)	16.8	22.0	0.0058	23.5
Median ARD <3.9 mmol/l home (%)	12.7	23.1	0.0142	37.2
ARD ≤20% CRC (%)	77.1	67.2	0.0003	4.5–15.3
ARD ≤20% home (%)	82.2	63.5	<0.0001	14.6–22.7
ARD ≤20% or 1.1 mmol/l CRC (%)	86.1	77.5	0.0003	3.9–13.2
ARD ≤20% or 1.1 mmol/l home (%)	83.9	65.2	<0.0001	14.7–22.7
ARD ≤15% or 0.8 mmol/l CRC (%)	75.2	60.8	<0.0001	8.8–20.1
ARD ≤15% or 0.8 mmol/l home (%)	74.0	53.6	<0.0001	15.9–24.7
CGM >3.9 mmol/l, when reference <3.1 mmol/l home (%)	33.3	43.75	0.5327	−22.3 to 43.2
CGM <3.1 mmol/l, when reference >3.9 mmol/l home (%)	0.5	1.3	0.1062	−0.3 to 1.5
CGM >3.9 mmol/l, when reference <3.1 mmol/l CRC (%)	8	28	0.0657	*
CGM <3.1 mmol/l, when reference >3.9 mmol/l CRC (%)	0	0.72	0.0820	*
CEG zone A CRC (%)	79.9	72.3	0.0036	2.5–12.8
CEG zone A home (%)	83.0	64.6	<0.0001	14.4–22.4

Available CGM readings = percentage of calculated maximum number of CGM readings. YSI = reference value measured with the YSI blood glucose analyzer. Self monitoring of blood glucose = reference value measured with finger prick. 20%/1.1 mmol/l = below 4.4 mmol/l (80 mg/dl) reference glucose, deviation is defined as absolute deviation of ≤1.1 mmol/l (20 mg/dl), above 4.4 mmol/l (80 mg/dl) reference glucose, deviation is defined as ≤20%. 15%/0.8 mmol/l = below 5.6 mmol/l (100 mg/dl) reference glucose, deviation is defined as absolute deviation of ≤0.8 mmol/l (15 mg/dl), above 5.6 mmol/l (100 mg/dl) reference glucose, deviation is defined as ≤15% ARD (ISO 15197:2013). CGM >3.9 mmol/l when reference <3.1 mmol/l home = percentage of CGM values above 3.9 mmol/l (70 mg/dl) when reference is below 3.1 mmol/l (55 mg/dl) (a measure for false negative sensor alarms) [7]. CGM <3.1 mmol/l when reference >3.9 mmol/l home = percentage of CGM values below 3.1 mmol/l (55 mg/dl) when reference is above 3.9 mmol/l (70 mg/dl) (a measure for false-positive sensor alarms). ARD, absolute relative difference; CGM, continuous glucose monitoring; CRC, clinical research centre; CEG, Clarke error grid; CI Δ, 95% confidence interval of difference; DG4P, Dexcom G4 Platinum; ENL, Medtronic Paradigm Veo Enlite; MARD, mean absolute relative difference; IQR Δ, interquartile range of difference, given for median ARD; MAD, mean absolute difference.
*Confidence interval of difference was not calculated because of too few cases per cell, respectively 2 and 0 for DG4P.

13.0% [7]; MARD for the ENL at home: 18.9% and in the CRC: 16.4% [8]). The improved accuracy of the new-generation CGM system (compared with, for example, the DG4A [8]), the DG4P, might be explained by changes in the calibration algorithm and physical design of the sensing element of the sensor; for example, changes in the sensor membrane material designed to prevent foreign body response and the shrinkage in sensor wire volume to attenuate tissue trauma [7]. The difference in accuracy between the two sensors did not translate into a difference in clinically more relevant outcomes, such as sensitivity for hypoglycaemia and false-positive hypoglycaemia alarm rate; however, the study was powered for accuracy, not for indicating differences in hypoglycaemia <3.1 mmol/l (34 events) detection or false-positive alarms (15 events). It might be expected that, with long-term use, a 30–40% relative difference in accuracy would translate into better clinical outcomes, such as better patient acceptance through increased trust in the device, fewer false-positive hypoglycaemia alarms, better prevention of hypoglycaemia and lower mean glucose values. Of course this requires further investigation.

The present international study was performed in four university hospitals resulting in an investigated patient group with a broad range of eating habits and diabetes management cultures. CGM accuracy was assessed in a way that includes both a highly standardized assessment in a CRC as well as usage at home. We were able to assess sensor accuracy in all glycaemic ranges by ensuring an adequate number of hypoglycaemic values in the CRC. We therefore believe that methodology

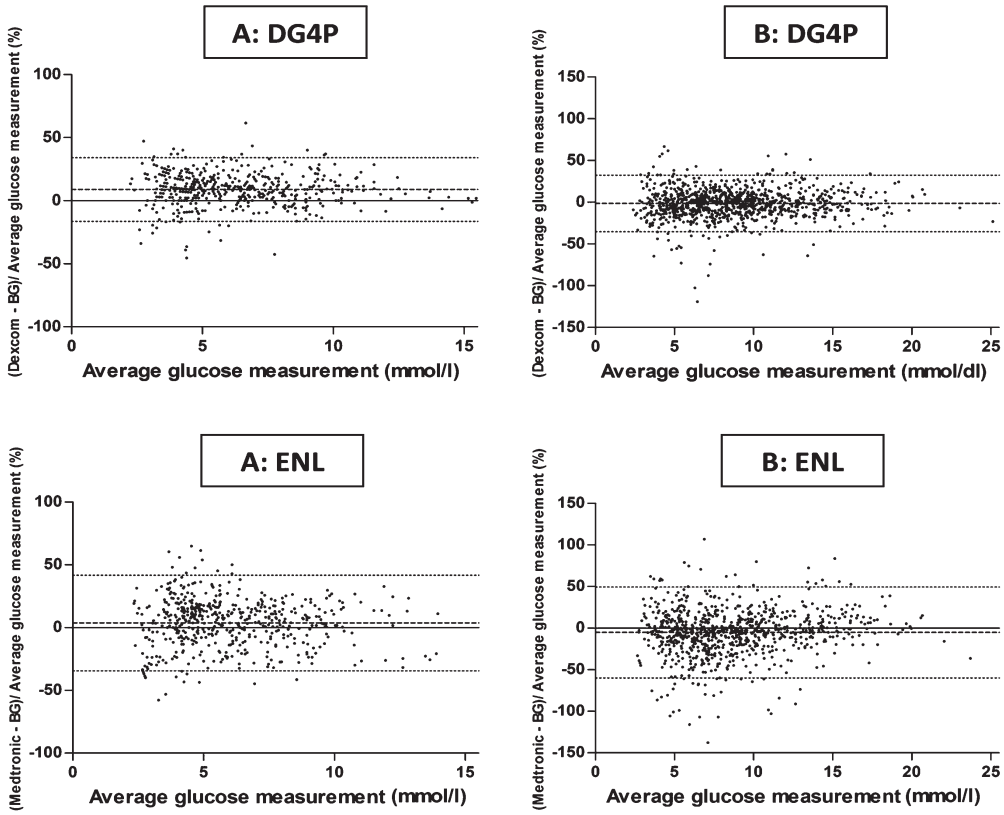

Figure 1. Bland–Altman plots for the Dexcom®G4 Platinum (DG4P) and Medtronic Paradigm Veo Enlite system (ENL). Panel A: clinical research centre (CRC) phase and panel B: home phase. The *x*-axis represents the average reference and continuous glucose monitoring (CGM) glucose measurements, the *y*-axis represents the difference (CGM – reference) versus the average of values measured by CGM expressed as a percentage. The long dashed line is drawn at the mean difference; dotted lines are drawn at the mean difference ± 1.96 times the standard deviation of the mean difference.

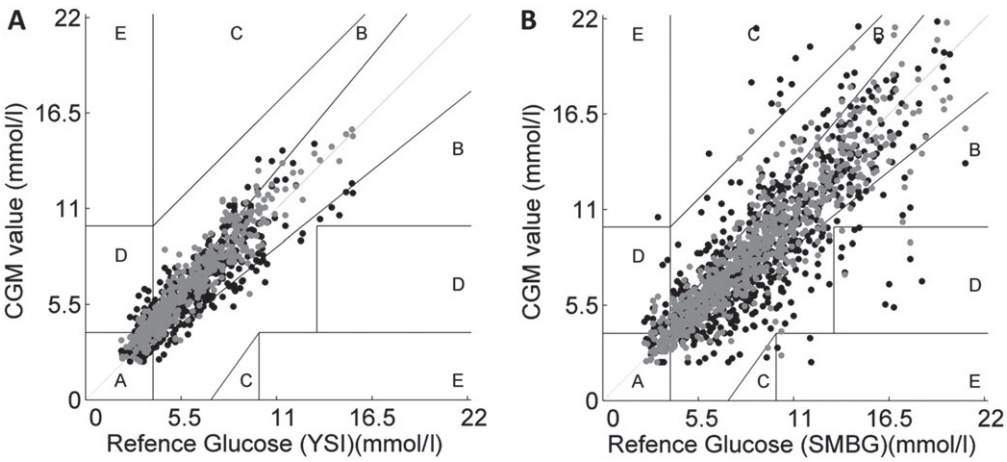

Figure 2. Clarke error grid analysis combined for the Dexcom®G4 Platinum (DG4P; grey dots) and the Medtronic Paradigm Veo Enlite (ENL; black dots) during the clinical research centre (CRC) phase (A) and the home phase (B). CRC phase: based on a total of 532 DG4P – YSI pairs, the DG4P had 79.9% of values in zone A, 15.0% in zone B, 0% in zone C, 5.1% in zone D and 0% in zone E. Based on a total of 530 ENL–YSI (reference value measured with the YSI blood glucose analyser) pairs, the ENL had 72.3% of values in zone A, 20.0% in zone B, 0% in zone C, 7.7% in zone D and 0% in zone E. Home phase: based on a total of 987 DG4P – self-monitoring of blood glucose (SMBG) pairs, the DG4P had 83.0% of values in zone A, 15.0% in zone B, 0.3% in zone C, 1.6% in zone D and 0.1% in zone E. Based on a total of 839 ENL – SMBG pairs, the ENL had 64.6% of values in zone A, 29.8% in zone B, 1.6% in zone C, 3.6% in zone D and 0.5% in zone E.

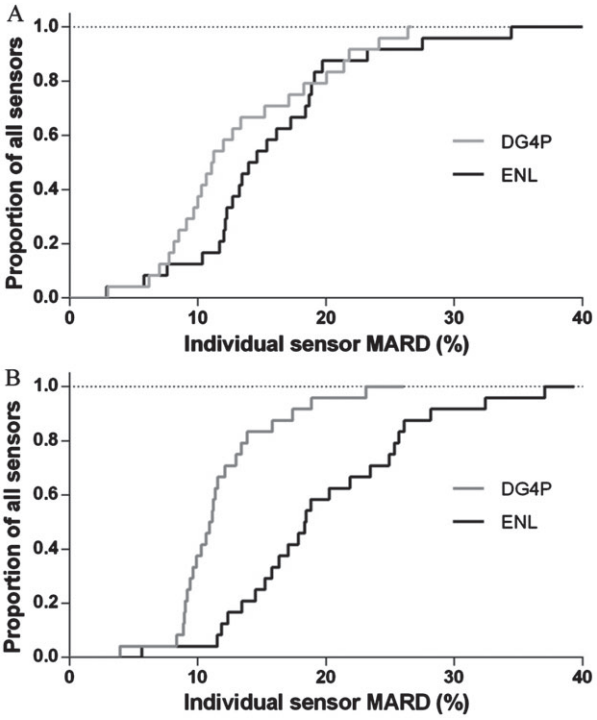

Figure 3. (A) Cumulative distribution of individual continuous glucose monitoring (CGM) performance (in the clinical research centre). (B) Cumulative distribution of individual CGM performance (at home). DG4P, Dexcom®G4 Platinum system; ENL, Medtronic Paradigm Veo Enlite system; MARD, mean absolute relative difference.

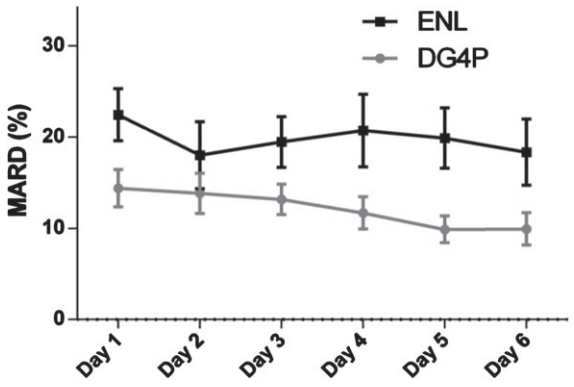

Figure 4. Average continuous glucose monitoring accuracy per day (mean absolute relative difference (MARD) ± 95% confidence interval) for the Dexcom®G4 Platinum (DG4P) and the Medtronic Paradigm Veo Enlite (ENL) systems.

and execution are brought to a level that should guarantee a standard for CGM evaluation and will make comparison between sensor systems less cumbersome. Manufacturers frequently update their products, and during our studies a new version of one of the studied sensors has been presented, the Enlite® (2013). No claims for better accuracy have been made for this updated version [9].

As was stated above, in breach of protocol, 2 out of 24 patients used a Paradigm RT-receiver in combination with the ENL instead of the Paradigm Veo-receiver. The Medtronic Paradigm Veo CGM system uses an updated CGM algorithm. Results from the *post hoc* subanalysis indicated that none of the reported outcomes' level of significance changed when excluding Paradigm RT-sensor systems (data not shown). Moreover, results as indicated by the ENL sensor package insert indicate a slight improvement in sensor accuracy in the hypoglycaemic range [2.2–4.4 mmol/l (40–80 mg/dl)] using the Paradigm Veo (MARD from 14.7 to 12.6%) but a decrease in sensor accuracy in the other glycaemic ranges and overall accuracy. We therefore feel confident that use of the Paradigm RT in two patients had no negative impact on ENL performance.

The DG4P devices were obtained directly from Dexcom and the ENL devices through the local Medtronic affiliated company. In theory this may have caused a bias, but unless independent funding can be obtained [8], this is unavoidable.

In the present study we investigated sensor accuracy in the CRC as well as in the home environment. The reference method used in the CRC was the YSI Analyzer, a reference laboratory instrument. In view of the high sampling frequency in the CRC, finger pricks are not feasible and also venous reference methods show better accuracy than does SMBG; thus, while capillary blood is used to calibrate the CGM, the reference method in CRC is venous plasma which can have a different glucose concentration. Testing a CGM system in a home environment allows accuracy assessment without the confounding effect of the venous-to-capillary offset and allows evaluation over a longer period of time. In addition, the home environment may better reflect the performance of CGM systems in real life by patients using the devices for routine management of diabetes; however, in the home setting, the lack of supervision may raise questions about the validity of gathered data [10]. The use of a CRC phase in addition to the home phase mitigates this problem, complementing assessment at home with a period of frequent highly accurate reference samples and an adequate number of reference pairs in the hypoglycaemic range by inducing a period of minor hypoglycaemia. Assessment of sensor accuracy in the hypoglycaemic range is essential because accurate CGM readings, especially in this range, are of great importance to patients with type 1 diabetes. Figure 4 indicates better sensor performance of the ENL on days 2 and 3 compared with the other study days; this may partly explain the wider difference in sensor accuracy between sensor systems in the home phase versus the CRC phase of the study. Nonetheless, previous studies investigating earlier CGM systems with similar study methods indicate that there is no consistent relationship between sensor accuracy assessed in the CRC and the home phase of the study [8,10]. We therefore believe that there is added value of combining assessment at home and in the CRC, as both assessment methods complement each other and neither of the two methods is superior.

The DG4P is significantly more accurate than the ENL CGM system. The developed assessment method, combining the benefits of the controlled CRC environment including a relatively high amount of time spent in hypoglycaemia, with the challenge of daily life conditions, provides a standard for future CGM evaluations.

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Conflict of Interest

J. K. had full access to all of the data in the study and takes responsibility for the integrity of the data, the accuracy of the data analysis and the decision to submit for publication. Y. M. L. wrote the protocol and reviewed the manuscript. J. K. reviewed the protocol, gathered data, performed data analysis and wrote the manuscript. T. R. P. and W. D. reviewed the protocol and reviewed the manuscript. S. G., A. F. and J. P. gathered data and reviewed the manuscript. F. B. reviewed the manuscript. D. B. reviewed the protocol, gathered data and reviewed the manuscript. E. R., J. K. M. and J. H. D. reviewed the protocol and manuscript.

J. K. M. has received speaker honoraria from NovoNordisk A/S. T. R. P. is a member of the advisory board of Novo Nordisk A/S and has received speaker honoraria from NovoNordisk A/S and Roche Diagnostics. E. R. is a consultant/advisor at A. Menarini Diagnostics, Abbott, Cellnovo, Dexcom, Eli-Lilly, Johnson & Johnson (Animas, LifeScan), Medtronic, Novo-Nordisk, Roche Diagnostics and Sanofi-Aventis and has received research grants/material support from Abbott, Dexcom, Insulet and Roche Diagnostics. J. H. D. is a consultant/advisor at Johnson & Johnson, Novo Nordisk, Roche Diagnostics and Sanofi and has received research grants/material support from Dexcom, Insulet, Medtronic Speaker Bureau, Dexcom, Eli Lilly, Novo Nordisk and Roche Diagnostics. The remaining authors have no conflicts to declare.

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