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Accuracy and Longevity of an Implantable Continuous Glucose Sensor in the PRECISE Study: A 180 Day, Prospective Multi-center Pivotal Trial

Running title: The PRECISE-trial

Jort Kropff, MD¹, Pratik Choudhary MD², Sankalpa Neupane MD³, Katharine Barnard, PhD⁴, Steve C. Bain, MD⁵, Christoph Kapitza, MD⁶, Thomas Forst, MD⁷, Manuela Link, MD⁸, Andrew Dehennis, PhD⁹ J. Hans DeVries, MD¹

¹Department of Endocrinology, Academic Medical Centre, University of Amsterdam, Amsterdam, the Netherlands; ²King's College London (KCL), London, UK; ³Cambridge University Hospitals NHS Foundation Trust, Cambridge, UK; ⁴Bournemouth University, Bournemouth, UK; ⁵Joint Clinical Research Facility, Swansea University, Swansea, UK; ⁶Profil, Neuss, Germany; ⁷Profil, Mainz, Germany, ⁸Institut für Diabetes-Technologie Forschungs- und Entwicklungsgesellschaft mbH an der Universität Ulm, Ulm, Germany; ⁹Research, Senseonics Inc., Germantown, USA

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Correspondence to: Jort Kropff MD, Academic Medical Centre, Department of Endocrinology, Room F4-215, PO Box 2260, 1100DD, Amsterdam, the Netherlands

E-mail: j.kropff@amc.nl Tel: +31205664573

Objective It is known that continuous glucose monitoring systems can lower mean glucose compared to episodic self-monitoring of blood glucose. Implantable CGM systems may provide additional benefits.

Research Design and Methods We studied the Eversense (Senseonics Inc. Germantown, MD) implantable continuous glucose monitoring sensor in 71 participants aged 18 years and older with Type 1 and Type 2 diabetes in a 180 day multinational-multicenter pivotal trial. Participants used the CGM system at home and in-clinic. CGM accuracy was assessed during eight in-clinic visits with the mean absolute relative difference (MARD) for venous reference glucose values greater than 4.2 mmol/L as the primary endpoint. Secondary endpoints included Clarke Error Grid analysis and alarm performance. The primary safety outcome was device related serious adverse events. This trial is registered with ClinicalTrials.gov, number NCT02154126.

Results The MARD value against reference glucose values above 4.2 mmol/L was 11.1% (95% confidence interval 10.5-11.7%). Clarke Error Grid analysis showed 99.2% of samples in the clinically acceptable error zones A and B. Eighty-one percent of hypoglycemic events were detected by the CGM system within 30 minutes. No device related serious adverse events occurred during the study.

Conclusions Our results indicate the safety and accuracy of this new type of implantable CGM-system and support it as an alternative for transcutaneous CGM.

People with diabetes frequently use fingerstick capillary glucose measurements to guide their dosing decisions (1). Continuous glucose monitoring systems (CGM) can provide glucose data in real-time and reduce the need for fingerstick testing (2). Additionally, people with diabetes can receive temporal information, trend information and alarms for impending hypoglycemic and hyperglycemic events (2). When used regularly, CGM can effectively lower mean glucose compared to fingerstick glucose measurements only (3). Unfortunately wear time of current transcutaneous CGM is low in some populations which might partially be explained by usability issues (4,5). Accuracy of CGM systems have improved over the years but could be improved further, especially in the hypoglycemic range (2). Transcutaneous CGM systems consist of a wired sensor containing glucose sensing enzymes, a transmitter and a display device. The wired sensor is placed just below the skin in the subcutaneous fat and is continuous with the transmitter base. The transmitter is placed in the transmitter base and sends data wirelessly to a display device such as a dedicated receiver or a smartphone. Several transcutaneous CGM systems are currently on the market (6–8). Implantable CGM systems may provide additional ease of use over transcutaneous CGM since frequent sensor insertions through the skin are not needed and the transmitter can be removed easily without the need for sensor replacement, for example during personal care. Furthermore, weekly sensor replacement with warm-up time and the risk of damage to the inserted sensor is no longer applicable. However, the need for implantation and removal through a minor surgical procedure imposes some discomfort on the patient. Currently no long term data on implanted sensor accuracy or longevity are available.

In this multinational-multicenter European trial, we aimed to investigate the safety and accuracy of a new type of CGM system using an implantable glucose sensor. In addition, we assessed

sensor lifetime, system wear time, participant reported outcome measures and measures of glycemic control.

Research design and Methods

Study design and participants

This was a 180 day, prospective, multicenter, pivotal trial. The study was executed between November 2014 and November 2015 and performed at seven clinical sites in Europe. Participants were 18 years or older and had a clinically confirmed diagnosis of type 1 or type 2 diabetes mellitus for over one year and used insulin therapy. People were excluded from study participation if they had any of the following: a history of severe hypoglycemia, diabetic ketoacidosis, symptomatic coronary artery disease, unstable angina, myocardial infarction or stroke in the past 6 months prior to study, known severe microvascular complications including proliferative diabetic retinopathy, macular edema, active non-proliferative retinopathy and renal failure, a hematocrit above 50% or below 30%, lactation, pregnancy or intending to become pregnant during the course of the study or a condition likely to require magnetic resonance imaging (MRI).

A study design diagram is given in supplementary data S1. The study consisted of eleven clinic visits: a screening visit, a sensor insertion visit, five 24-hour and three 8-hour device performance assessment visits, and a sensor removal visit. Finally, a follow-up visit was planned two weeks after sensor removal. The study was performed in accordance with the Declaration of Helsinki and was approved by the institutional ethics review board at each site. Written and verbal informed consent was given by all participants.

Procedures

During the screening visit, laboratory measurements, a physical examination and an electrocardiogram (ECG) were performed. Participants received training in the use of study devices and written instruction materials were provided. At the sensor insertion visit, a glucose sensor for continuous glucose measurement was implanted in both upper-arms of the participant. Participants were free to choose the exact location of sensor implantation within the upper-arm region. Participants decided which of the two implanted sensors was to be designated as the primary sensor. Further information on the insertion and removal procedure is given in study supplementary data S2. Participants were asked to wear the transmitter over the primary sensor and to perform calibration twice daily using the study self-monitoring of blood glucose device (SMBG, Accu-Chek Aviva, Roche Diagnostics, Mannheim, Germany). The secondary sensor was used and calibrated during the eight device performance assessment visits only. Participants and study personnel were display-blinded to CGM glucose values during the device performance assessment visits. For the remainder of the study, continuous glucose data was available to the participants. Participants were asked to confirm the CGM glucose reading using the study SMBG device before making treatment decisions. The maximum study participation was 180 days depending on end of sensor life which was indicated on the CGM display. The sensor was replaced if sensor functionality was found to be lost due to electronics or mechanical failure prior to visit 7 (study day 90).

Study visits started with a glucose measurement ensuring that current blood glucose was <16.7 mmol/L or 300 mg/dL, and ketone blood content ≤ 0.6 mmol/L. Safety laboratory tests were

performed according to local clinic standard operating procedures. Body temperature (99.5°F or <37.5°C) was registered. If needed visits were rescheduled. During each study visit, venous plasma samples were taken for determination of dexamethasone concentration to investigate possible systemic absorption of dexamethasone used in the sensor system. This was done in a highly sensitive liquid chromatography-tandem mass spectrometry method, with a lower limit of detection of 2 ng/mL (9). Venous blood samples were taken every 15 minutes or more frequently during episodes of hypoglycemia (≤ 4.4 mmol/L or 80 mg/dL reference glucose) using an IV-line inserted in the dorsal or cubital vein of the participant's arm. During night-time (2300-0700h), samples were collected every two hours. After bedside centrifuge and visual check for dilution and hemolysis, venous plasma glucose samples were analyzed using a YSI 2300 STAT PLUS glucose and lactate analyzer (YSI, Yellow Springs, OH, USA). Samples were kept on ice and stored in tubes containing dipotassium EDTA to allow for re-analyses. Induction of hypoglycemia and hyperglycemia was performed in a part of the participants per decision of the site investigator (39 completed in 23 subjects). Finally, visits for sensor removal and follow-up were performed. Insertion and sensor removal sites were inspected. Adverse events were registered throughout the study. Participants were asked to complete questionnaires at the start, after 90 days and at the end of the study.

The continuous glucose monitoring system (Senseonics Incorporated, Germantown, MD, USA) used in this study consisted of three components, an implantable fluorescence-based cylindrical glucose sensor sized 3x16 mm, a smart transmitter sized 40x40x14 mm and a handheld device (iPod Touch, Apple Inc. CA, USA) running a mobile medical application. The transmitter had to be worn over the implanted sensor for continuous read-out of glucose data but could be removed

and re-placed without the need for sensor replacement. The transmitter stored the glucose data and provided the participants with on-body vibrations for notification of hypoglycemia and hyperglycemia. Data was continuously transferred to the iPod per secured low-energy Bluetooth transmission which allowed participants and study staff to review current and historical glucose data in real-time. Further product information can be found in study supplementary data S2.

Outcomes

Primary, secondary and exploratory outcomes, were predefined in a statistical analysis plan, additional analyses were added as indicated. The primary efficacy endpoint was the mean absolute relative difference (MARD) for reference glucose values greater than 4.2 mmol/L (75 mg/dL), defined as the average of the absolute difference of paired CGM system and YSI readings (reference) divided by the YSI reading multiplied by 100 (10). The secondary efficacy endpoints included Clarke Error Grid analyses and alarm performance. Alarm performance was defined as confirmed and missed event detection rates and true and false alarm rates given for low and high glucose alarm (<3.9 mmol/L and >10 mmol/L or <70 mg/dL and >180 mg/dL). Confirmed event detection rate was defined as a CGM measurement beyond the alarm threshold within 30 minutes from the start of the event, expressed as the percentage of total number of events. The true alarm rate was defined as a CGM measurement beyond the alarm threshold confirmed by a YSI measurement within 30 minutes expressed as percentage of the total number of alarms. The missed event detection rate and false alarm rate were defined as the inverse of the confirmed event detection rate and true alarm rate, respectively. Primary safety endpoint was incidence of device-related or procedure-related serious adverse events, secondary safety

endpoints included all device-related or procedure-related adverse events. Quality of life was assessed using the Short Form Health Survey (SF-36) and a device specific questionnaire developed for the study. Exploratory outcomes included sensor lifetime analyzed using Kaplan-Meier analysis, calibration stability, sensor stability, accuracy (MARD) over sensor life, system lag time, within subject precision and person to person variability. Additional analyses included MARD over the full glycemic range (2.2-22.0 mmol/L or 40-400 mg/dL) and over the hypoglycemic, normoglycemic and hyperglycemic ranges (≤ 4.2 mmol/L, 4.2-10 mmol/L, >10 mmol/L or ≤ 75 mg/dL, 76-180 mg/dL, >180 mg/dL), system wear-time and glycemic control assessed per HbA1c measurement at the first and last study visit. Also real-time re-analyses of the raw study data using a new data algorithm and analysis of change in HbA1c over the study duration based on HbA1c strata $<7.5\%$ and $\geq 7.5\%$ (58 mmol/mol) was performed.

Statistical analysis & Power calculation

An intention-to-treat analysis for the primary efficacy analysis and additional outcome measures was performed based on all evaluable data from all participants with at least one paired glucose reading. We reported variables as mean with standard deviation or median with interquartile range where appropriate. Confidence intervals for the paired difference (Δ) between outcomes were computed. All reported p-values are two-tailed, and values <0.05 were considered statistically significant. Sensor failures due to mechanical or electrical failure, for which processes of improvements have been implemented, were excluded from sensor life analyses. Impact of a new data algorithm on the system performance was assessed through re-analyses of the raw study data.

Power calculation was based on a test of superiority over a pre-specified performance goal of 20% MARD (reference glucose values >4.2 mmol/L or >75 mg/dL) with a conservative estimate of the investigational device performance of MARD $<18\%$, a standard deviation of $\leq 14\%$, a power of 80% and a one sided significance level of 0.0125. Considering within-subject correlation, data distribution, expected drop-out percentage of 20% and inclusion of up to 7 training subjects the total required number of participants was estimated 82. SAS® 9.1, IBM/SPSS Version 21 and Cytel Version 10 were used for statistical analyses. This trial is registered with ClinicalTrials.gov, identification number NCT02154126.

Results

Eighty-one participants were included of which 5 were used for platform and procedure evaluation, 5 were designated for site training (further information can be found in supplementary data S3). The intention-to-treat analyses of the primary efficacy outcome included 71 patients. Participant baseline characteristics are given in table 1.

The primary efficacy outcome over the study duration showed a MARD for reference samples >4.2 mmol/L of 11.1% (95%CI 10.5 - 11.7%). Performance of the CGM system in the hypoglycemic range (≤ 4.2 mmol/L or ≤ 75 mg/dL) was less than the overall performance (2.2-22.0 mmol/L or 40-400 mg/dL), 21.7% versus 11.6% MARD ($p < 0.001$). A statistically significant reduction of CGM accuracy occurred in the last month of use (Table 2). Table 3 provides further data on the accuracy of the continuous monitoring system per glycemic range. Real-time re-analyses of the raw study data using a new data algorithm indicated improved performance over the currently used algorithm (MARD 2.2-22.0 mmol/L (40-400mg/dL); 10.5% vs. 11.6%, 95%CI of Δ -1.1%; -0.9%, $p < 0.001$; MARD ≤ 4.2 mmol/L; 18.6 vs 21.7%, 95%CI of

Δ -3.8%; -2.3%, $p < 0.001$). Further information can be found in the study supplementary data S7. A Kaplan-Meier analysis for sensors survival estimated 100%, 82% and 40% of sensors functional through day 45, day 90 and day 180 in-clinic evaluation sessions, respectively (figure 1, median sensor life 149 days, IQR 97; 180). Twelve sensors were considered censored in the survival analysis due to either subject withdrawing consent ($n=6$) or electronic or mechanical failure ($n=6$), five sensors were replaced due to electronic or mechanical failure within 3 months after study start.

HbA1c improved in the study group from 7.54% (59 mmol/mol) at baseline to 7.19% (55 mmol/mol) at end of study (Δ 0.35% (4 mmol/mol); 95%CI Δ -0.55% (6 mmol/mol); -0.21% (2 mmol/mol), $p < 0.001$). A post-hoc analyses of participants with a baseline HbA1c $< 7.5\%$ (58 mmol/mol) showed unchanged HbA1c at the last study visit (-0.04%; 95%CI Δ -0.21%; 0.14%, $p=0.669$) (-0 mmol/mol; 95%CI Δ -2 mmol/mol; 2 mmol/mol) whereas participants with a baseline HbA1c $\geq 7.5\%$ (58 mmol/mol) showed a reduction of -0.66% (95%CI Δ -0.91%; -0.42%, $p < 0.001$) (-7 mmol/mol; 95%CI Δ -10 mmol/mol; -5 mmol/mol). The clinical performance of the CGM-system estimated per Clarke Error Grid analysis showed 99.2% of samples in the clinically acceptable error zones A (84.3%) and B (14.9%) (supplementary data S4). The in-clinic alarm performance for the hypoglycemia (< 3.9 mmol/L or < 70 mg/dL) and hyperglycemia (> 10 mmol/L or > 180 mg/dL) threshold indicated a confirmed detection rate of 81% and 88%, and an event true rate of 67% and 90% respectively (supplementary data S4). No indication for change in glucose variability over time was found (data not shown). Transmitter wear compliance was a median 23.5 hours per day (IQR: 23.2; 23.7).

Quality of life measured per SF-36 questionnaire demonstrated unchanged quality of life scores from baseline to end of study. Results from a study specific questionnaire indicated high device acceptance with 84% rating 'I would want to be inserted with a sensor again' and 90% rating 'Using the system helped minimize the burden of diabetes in my life' a score of 5 or higher (scoring range 1-7 points).

The primary safety outcome showed no severe procedure or device related serious adverse events. Fourteen device or procedure-related non-severe adverse events occurred in 11 out of 71 patients with a total number of 147 sensors implanted, used and removed. Five cases of skin reaction were recorded. In all cases, therapy could be continued after a temporary stop of 1-3 weeks. Two cases of incision site infection occurred, one patient received antibiotic treatment, the other infections resolved without need for further medical intervention. Four participants withdrew consent because of study burden (n=2) and inability to obtain venous access (n=2), two subjects withdrew consent due to an adverse event thought to be unrelated to the device. Implantation and removal of sensors was performed by non-surgically trained doctors (endocrinologist/MDs) in most sites (5 out of 7), the remaining sites (2 out of 7) used non-surgically trained doctors or surgeons depending on daily availability. No level of dexamethasone was measured in any of the venous samples. Further information on safety and adverse events and non-primary outcomes can be found in the study supplementary data S4.

Conclusions

The present study, investigating the accuracy, longevity and impact on patients experience of a novel implantable CGM system, showed safety and accurate performance of the investigational device over the full sensor life. Participants acceptance of the device was high. The current

system was accurate with an overall MARD of 11.1% for samples above 4.2 mmol/L (75 mg/dL). CGM performance was less in the hypoglycemic range as is also seen with other CGM products (7,8,11,12). A limited but statistically significant reduction of CGM measurement accuracy occurred in the last month of use, possibly due to long term degradation of the glucose indicating gel before end of sensor life was reached.

Device use coincided with a significant reduction in Hb1Ac, consistent with results of a meta-analysis showing that HbA1c lowering with CGM use depends on baseline HbA1c and device wear-time (3). The Clarke Error Grid analysis estimated high clinical performance with 99.2% of samples in the clinically acceptable error zones A and B.

Results from questionnaire data indicated high participant acceptance of the system but did not register improved perceived generic quality of life as assessed per SF36 questionnaire. Nonetheless study participants did describe the ease of use, ability to remove the transmitter without removing the sensor and availability of on-body vibration alerts as beneficial features of the system. Participants used the CGM for more than 23 hours per day over the full study duration, indicating high acceptance of the system. The implantation, use and removal of 147 glucose sensors in 71 participants resulted in a limited number of mild to moderate skin reactions and skin infections, no device or procedure related serious adverse events were reported.

A previous implantable glucose sensor was described by Garg and colleagues (13), although the authors described acceptable accuracy and longevity of this approach, this CGM system was never commercialized perhaps due to acceptability issues with the surgical implantation procedure related to the sensor size (similar to an AA-battery) (13). Other investigators have shown proof of concept of an implantable self-powered CGM in animals, but no human data is

available (14). Currently no implantable glucose sensors are on the market. Based on the results of this study, the Eversense implantable sensor received a CE mark on May 10, 2016.

The multicenter approach with real-life use of the system at home and the long duration of the study allowed for assessment of glycemic outcomes, device acceptance and impact on quality of life on top of system performance. It should be noted that these are uncontrolled observational data. As in most studies testing novel diabetes technology, it can be expected that a more technology enthusiastic population was included in the study. Also, participants with type 2 diabetes and participants of non-Caucasian descent were underrepresented in this study, as such one should be careful to directly translate the outcomes of the current study to the wider population.

Based on mathematical models it was recently proposed that an inaccuracy of less than 10% MARD is not expected to lead to further improvements in clinical outcomes of CGM use (2), although this might be negated by future trials with clinically relevant outcomes. This and competing products are approaching the 10% mark, except for the hypoglycemic range, for which improvements are needed. Results from a real-time re-analyses of the raw study data using a new data algorithm indicated improved performance over the currently used algorithm. The CGM system including the new algorithm is currently investigated in a 90 day United States pivotal trial (ClinicalTrials.gov identifier: NCT02647905).

The results from this study indicate that the use of a long term implantable continuous glucose sensor is both effective and safe and provides specific usability benefits. The results support implantable CGM as a worthy alternative to current transcutaneous CGM.

Author Contributors

All authors reviewed and provided edits and comments on manuscript drafts. In addition, authors had the following responsibilities: J. K.: main study physician responsible for the trial in Amsterdam, design of the protocol, data collection, review of data reports and drafting of manuscript; P. C. principal investigator of the London Kings college trial site; S. N. principal investigator of the University of Cambridge trial site; K. B. drafting and execution of system specific questionnaire; S.C.B. principal investigator of the Swansea trial site; C. K. principal investigator of the Profil, Neuss trial site; T. F. principal investigator of the Profil, Mainz trial site; M. L. principal investigator of the Ulm trial site; A. D.: design of the study protocol, data-analyses, review of data reports, review of the study manuscript; J. H. D.: principal investigator of Amsterdam trial site and lead principal investigator for the study, design of the protocol, data analyses and drafting of the manuscript.

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Declaration of interests

J. K. received research support from Senseonics and Dexcom; P. C. none to declare; S. N. none to declare; S.C.B. none to declare; K. B. none to declare; C. K. none to declare; T. F. received research support and is consultant/advisor/speaker for Astra Zeneca, Ely Lilly, BMS, Sanofi, Boehringer Ingelheim, Novartis, Novo Nordisk, Berlin Chemie; M. L. none to declare; A. D. is an employee of Senseonics Incorporated; J. H. D. received research support and is a consultant/advisor/speaker for Senseonics, Dexcom, Johnson & Johnson (Animas, LifeScan) and Roche Diagnostics. No other potential conflicts of interest relevant to this article are reported.

Role of Funding Source

The study was funded by Senseonics Incorporated, Germantown, MD, USA. The principal investigator and corresponding author were involved in the development of the study protocol and statistical analyses plan. Data-analyses was performed by company employees, and then checked and approved by an external statistical consultant. The manuscript was written by the corresponding author, co-authors and company representatives were invited to provide feedback to the first draft of the manuscript. The corresponding author takes full responsibility for the submission of the final data and manuscript.

Figure references

Figure 1. Sensor survival per Kaplan-Meier analyses

Sensor survival is given per individual sensor per Kaplan-Meier analyses. The 71 primary sensors were included in the survival analyses. End of sensor lifetime is indicated by the CGM-system. Median sensor lifetime is 149 days.

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Tables

Table 1. baseline patient characteristics

Variable	ITT population (n=71)
Age (years) (SD)	41.7 (12.6)
Sex	
male (n) (%)	42 (59.2)
female (n) (%)	29 (40.8)
Type 1 Diabetes Mellitus (n) (%)	66 (93.0)
Type 2 Diabetes Mellitus (n) (%)	5 (7.0)
Diabetes duration (years) (SD)	22.2 (12.5)
Insulin delivery mode, CSII (n) (%)	42 (59.2)
Body mass index (BMI) (kg/m ²) (SD)	27.0 (4.2)
HbA1c (%) (SD)	7.6 (1.1)
HbA1c (mmol/mol) (SD)	60 (12)
Any history of	
Ketoacidosis (n) (%)	15 (21.1)
Severe hypoglycemia (n) (%)	17 (23.9)
Long term diabetes complications	
retinopathy (n) (%)	16 (22.5)
nephropathy (n) (%)	0 (0)
neuropathy (n) (%)	7 (9.9)
cardiovascular disease (n) (%)	21 (29.6)
foot problems (n) (%)	4 (5.6)

For categorical variables n (%) is presented. For continuous variables mean (SD) is presented.
CSII: continuous subcutaneous insulin infusion

Table 2. Accuracy of the continuous monitoring system versus YSI over time

<i>Sensor accuracy, MARD (%) over the range of 2.2-22 mmol/L or 40-400 mg/dL</i>				
<i>Day</i>	<i>MARD% (n)</i>	<i>SD</i>	<i>95%CI</i>	<i>15mg/dL;20%* - transitioning at 75mg/dl</i>
0-180	11.6 (21527)	11.2	11.5; 11.8	84.0%
1-30	11.6 (10761)	11.4	11.4; 11.8	83.9%
31-60	11.2 (4382)	9.8	10.9; 11.5	85.5%
61-90	11.4 (1429)	10.5	10.9; 11.9	84.3%
91-120	11.9 (2672)	11.6	11.5; 12.3	82.6%
121-150	12.0 (975)	12.6	11.2; 12.8	84.3%
151-180	12.9 (1308)	12.6	12.2; 13.6	81.9%

MARD, mean absolute relative difference between device measurement and reference measurement. In-clinic accuracy is assessed per venous YSI reference measurement. *Performance of the Sensor stability was assessed by calculating the percentage of system readings within 15 mg/dL (for YSI \leq 4.2 mmol/L or 75 mg/dL) or 20% (for YSI $>$ 4.2 mmol/L or 75 mg/dL) of the paired YSI values.

Table 3. Accuracy of the continuous monitoring system per glycemic range and rate of change

Sensor accuracy, MARD (%)							
Glycemic range				Rate of Change			
Venous mmol/L (mg/dL)	MARD (n) MAD (n)	SD	95%CI	Venous mmol/L/min (mg/dL/min)	Mean mmol/L (n) (mg/dL)	SD	95%CI
≤4.2 (75)	21.7 (1057) 14.2 (1057)	21.5 13.5	20.4; 23.0 13.4; 15.0	Decreasing glucose < -0.055 (-1)	15.6 (1964) 280	16.5	14.9; 16.3
4.2-10.0 (75-180)	11.9 (14274) --	10.9 --	11.8; 12.1 --	Stable glucose -0.055;0.055 (-1; 1)	10.7 (14909) 193	10.0	10.5; 10.8
>10.0 (180)	9.2 (6196) --	7.8 --	9.0; 9.4 --	Increasing glucose >0.055 (1)	13.6 (2443) 245	10.7	13.2; 14.1

MARD, mean absolute relative difference between device measurement and reference measurement. Accuracy is assessed per venous YSI reference measurements.