The Impact of Continuous Glucose Monitoring on Low Interstitial Glucose Values and Low Blood Glucose Values assessed by Point of Care Blood Glucose Meters

FIDAM FORSCHUNGSINSTITUT DIABETES

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ABSTRACT

The impact of CGM on the duration of periods with low glucose measured in interstitial fluid is well known. But studies showing an impact of CGM on low blood glucose values, measured by POC-GM are rare. This cross-over study examines the impact of CGM on duration of periods spent in low interstitial glucose range (<70 mg/dl) as well as on the proportion of low blood glucose (BG) values measured by POC-GM (Glukometer 3000, Bio Sensor Technology, Germany) and time until detection of low BG by use of POC-GM.

41 type 1 diabetic patients (age 42.0±11.3 yrs, diabetes duration 15.3 ±10.1; A1c 8.2 ±1.4%) used the DEXCOM 7 Plus CGM system twice; once participants were blinded against the results and in the other study phase (Open CGM) patients received real-time glucose values and current glucose trends, used the CGM data to determine their insulin dose and were alerted if hypoglycemic or hyperglycemic glucose ranges were approached. In addition, BG was routinely measured 6 times a day by POC-GM. The order of study phases was randomized. The time spent in a hypoglycemic glucose range (< 70 mg/dl) was reduced by open CGM from 181±125 to 125± 89 minutes per day (p=.005). Also time spent in the euglycemic glucose range was increased from 946±176 to 1023±168 minutes per day (p=.003). Open CGM reduced the proportion of low BG measurements by POC-GM from 10.3±7.6% to 7.4±5.8% (p=.039), whereas the euglycemic POC readings was increased from 68.3 ±12.1% to 73.7 ±12.1% (p=.007). The time until a hypoglycemic BG value was detected by POC-GM was significantly (p.028) shortened by 33.1 (95% CI 3.8 -62.3) minutes.

These results demonstrate that CGM used for insulin dosing and hypoglycemia alerts not only diminishes low interstitial glucose values but also reduces the proportion of low BG measured by POC-GM. In addition the time for the detection of a hypoglycemic episode by POC-GM was significantly shortened.

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INTRODUCTION

The meta-analysis from Pickup et al. (BMJ, 2011, 343, d3805) indicates that **C**ontinuous **G**lucose **M**onitoring (CGM) use can improve glycemic control by 0.3 HbA1c percentage points. Furthermore, exposure to hypoglycemia can be reduced by 23%. However, while the improvement of glycemia can be assessed by an external laboratory measure, the improvement of exposure to hypoglycemia relies on the measurement of glucose values in the interstitial fluid measured by the CGM systems itself. Nevertheless, measurement precision of CGM in the hypoglycemic range is less concordant with a reference method than measurement in eu- or hyperglycemic ranges. CGM systems are indicated for use as an adjunctive device to complement, not replace, information obtained from standard blood glucose measurements by **P**oint **O**f **C**are **G**lucose **M**eters (POC-GM). Therefore blood glucose values from POC-GM should be used for treatment decisions, such as how much insulin should be taken or should low blood glucose be treated by the consumption of extra carbohydrates.

This study examines the impact of CGM on duration of periods spent in low interstitial glucose range (< 70 mg/dl) as well as on the proportion of low blood glucose values measured by POC-GM and the time until detection of low blood glucose values by use of POC-GM.

METHODS

This cross-over-study with two phases was conducted in an inpatient setting. The order of the study phases was randomized (see Figure 1). All participants wore the CGM device (DEXCOM Seven Plus, Nintamed) twice. Sensors were deployed in the late morning or afternoon. After a calibration period of 2 hours the active measurement phase started. The calibration was done by capillary blood glucose measurement using a POC - GM (Glucometer 3000, Bio Sensor Technology, Germany), which was subjected to laboratory quality control. In addition, capillary blood glucose was measured routinely 6 times a day (fasting, post breakfast, pre-lunch, post lunch, pre-dinner and before bedtime) in both study phases.

In one phase (CGM-blind), participants wore the CGM device, but were blinded against the results. Also, no alerts were given when glucose values reached certain critical hypoglycemic (< 80 mg/dl) or hyperglycemic (> 180 mg/dl) thresholds. In the other study phase (CGM-open), CGM results and trend information were available for patients. If critical hypoglycemic or hyperglycemic thresholds were exceeded an alert was given. Patients had to confirm possible hypo- or hyperglycemia by a capillary blood glucose measurement using POC-GM. Adjustments of insulin dose at mealtime could be based on CGM measurements if POC-GM measurement did deviate less than 20% from CGM measurement (checked by a medical staff).

Outcome measures were the duration of periods with low interstitial glucose. In addition, it was analyzed if a beneficial impact of CGM on the avoidance of hypoglycemia could be demonstrated with POC-GM measurement (proportion of low blood glucose measurements) and if a low blood glucose value could be detected earlier by POC-GM measurement. Significance tests were adjusted for order effects of the study phases.

RESULTS

41 diabetic patients took part in this study (for sample characteristics see Table 1). The mean time of CGM use during the CGM-open and CGM-blind phase was highly comparable (see Figure 2). Additionally, in both phases a highly comparable number of POC-GM measurements was found (see Figure 3).

The system accuracy according to ISO 15197 is depicted in Figure 4. Approximately 70% of all pairs of CGM and POC-GM measurements fell within the range established by ISO 15197. There was no major difference between the CGM-open and CGM-blind phase. The overall Mean Absolute Relative Difference (MARD) was also comparable in both study phases. Interestingly, in both study phases the MARD was significantly higher in the hypoglycemic range compared to the eu- or hyperglycemic glucose range (see Figure 5).

The overall mean glucose value was not affected by CGM use (see Figure 6 and 7). However, during the CGM-open phase the duration of hypoglycemic periods measured in the interstitial fluid was significantly reduced and the duration of the euglycemic phase was significantly increased (see Figure 8). There was no impact on the duration of the hyperglycemic periods in the interstitial fluid. All significance tests were adjusted for order of study phase. No significant order effects were observed.

The beneficial effects of open CGM on the shortening of hypoglycemic periods and the extension of euglycemic periods per day could also be demonstrated by using POC-GM measurements. The proportion of blood glucose values in the hypoglycemic range could be significantly reduced, whereas the proportion of euglycemic glucose readings could be significantly increased (see Figure 9). The time between the last euglycemic glucose measurement and the hypoglycemic blood glucose measurement could be significantly shortened by the use of CGM (see Figure 10 + 11).

CONCLUSION

These results demonstrate that CGM used for insulin doses and use of trend information and hypoglycemic alerts does not only diminish low interstitial glucose values, but also reduces the proportion of low blood glucose values measured by POC-GM. In addition, the time for the detection of a hypoglycemic episode by POC-GM was significantly shortened. Thus, the impact of CGM on decreasing the number of hypoglycemia could not only be demonstrated by CGM measurements itself but also by the use of a more precise POC-GM measurement as a reference method.

Table 1: Sample Characteristics

	mean ± Std; respectively %
Mean age (yrs.)	42.0 ± 11.3
Mean diabetes duration (yrs.)	15.3 ±10.1
% female	22,0
Mean BMI (kg/m²)	26.1 ± 4.3
Mean A1c (%)	8.2 ± 1.4
% with hypoglycemia problems	31.7
Mean insulin dose (IU/kg)	0.72 ± 0.22

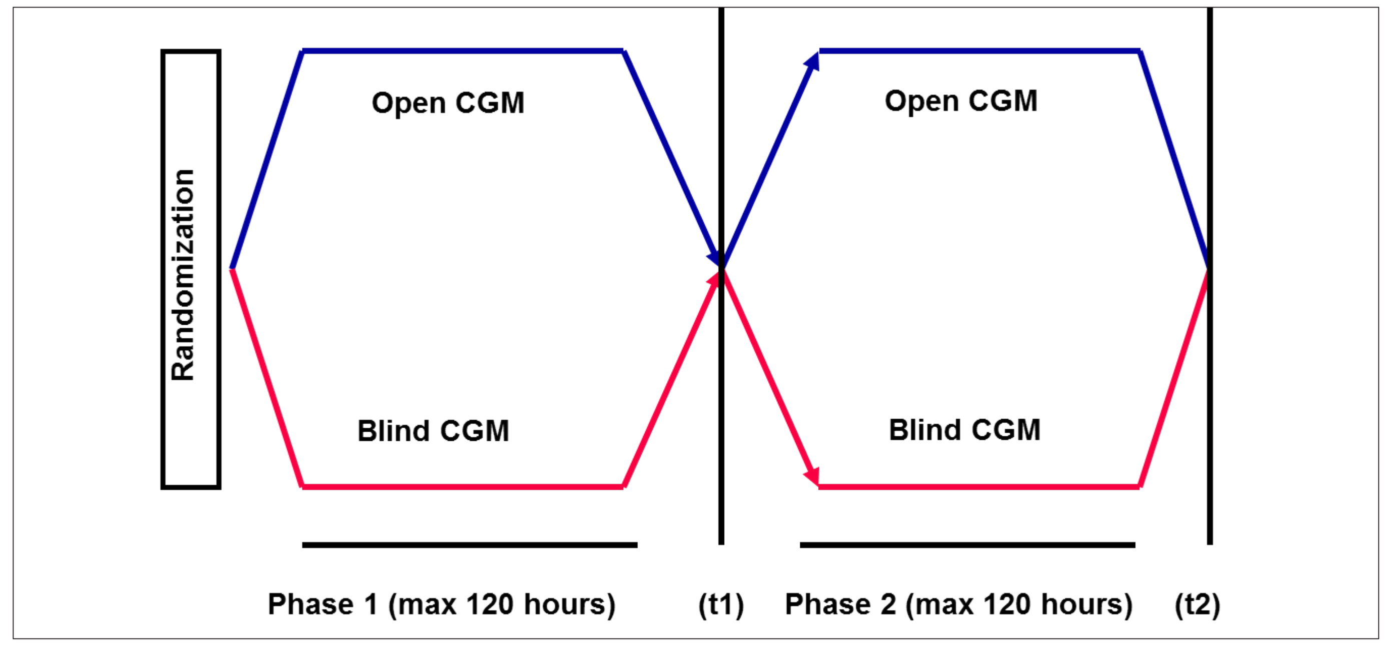

Figure 1: Cross-over study design

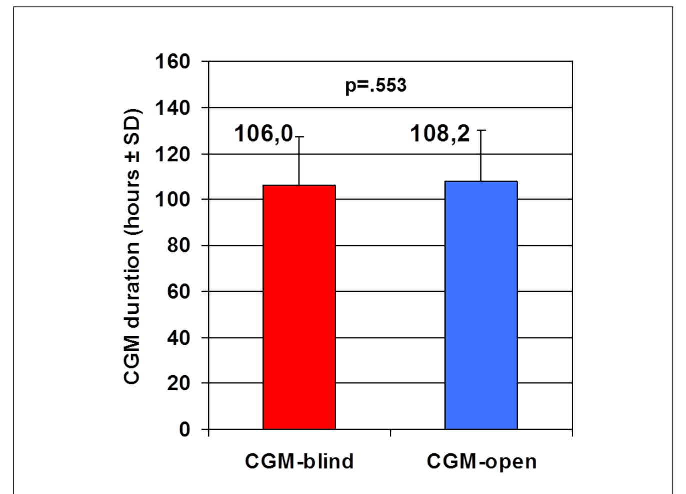

Figure 2: Duration of CGM phases

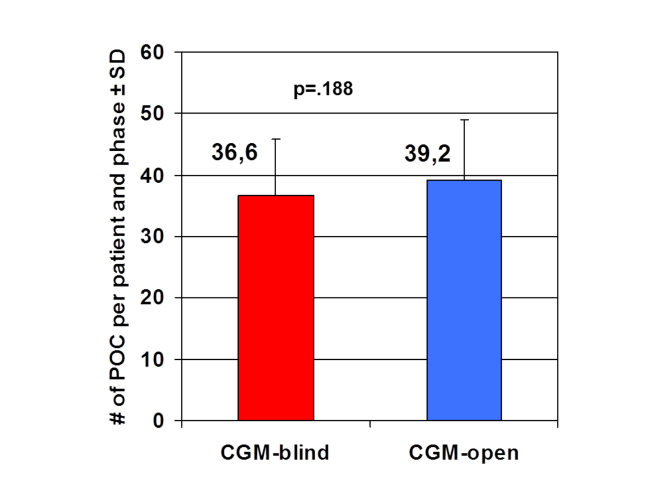

Figure 3: Number of POC-GM measurements

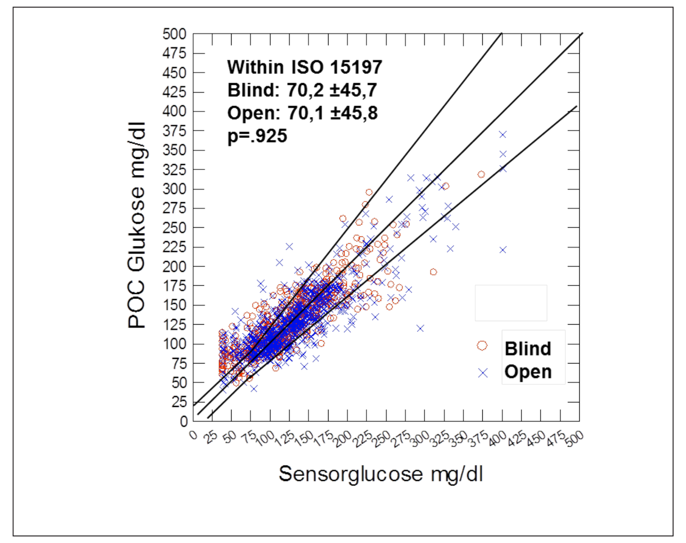

Figure 4: System accuracy according to ISO 15197

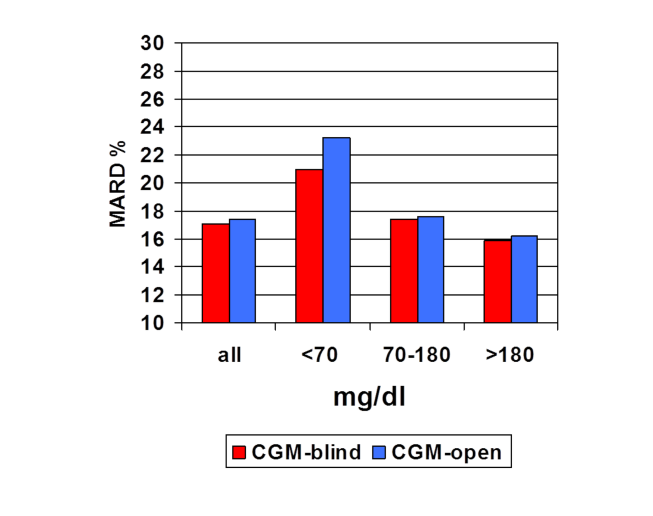

Figure 5: Mean absolute relative difference (MARD)

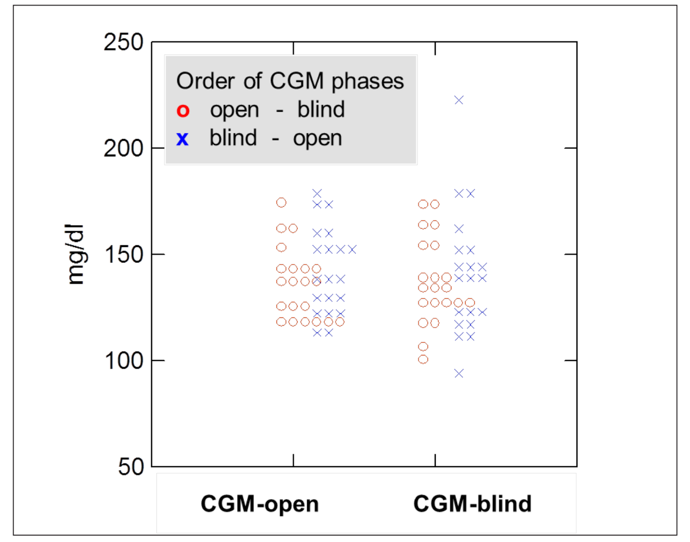

Figure 6: Dot density plot of mean glucose values during CGM

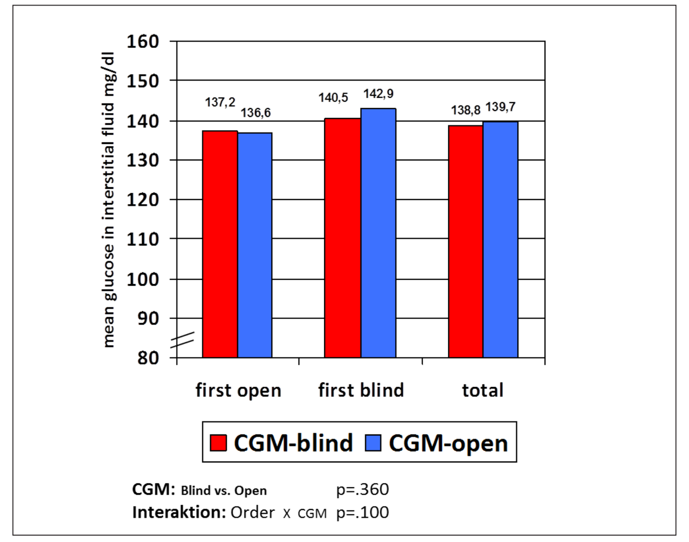

Figure 7: Mean glucose in interstitial fluid

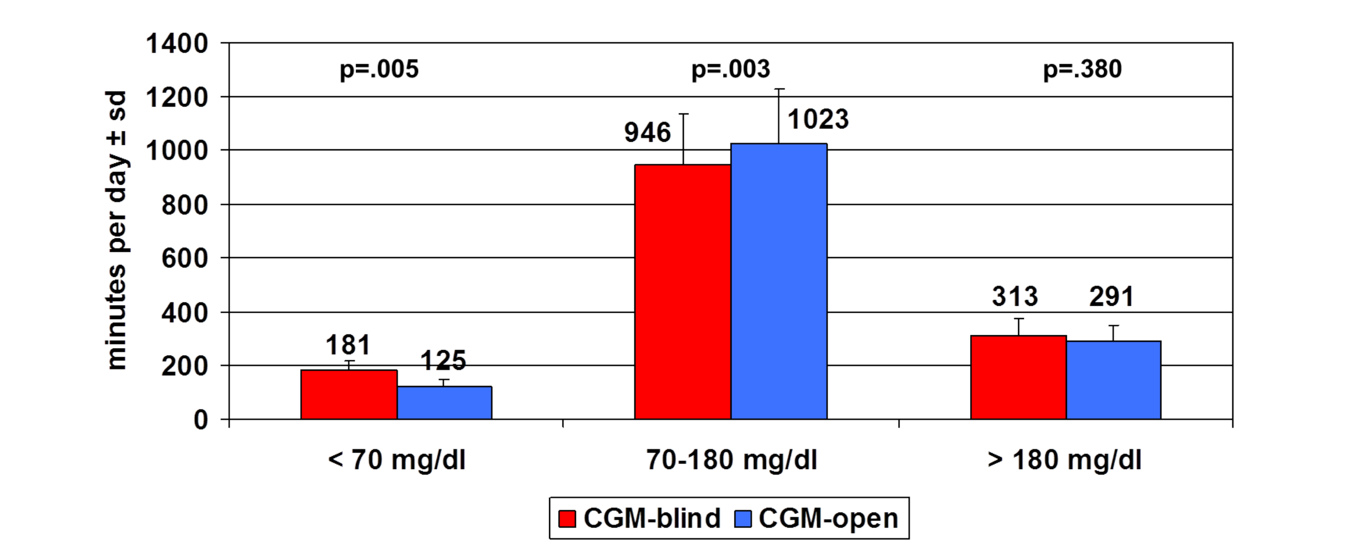

Figure 8: Duration of hypo-, eu- and hyperglycemic glucose phases measured by CGM

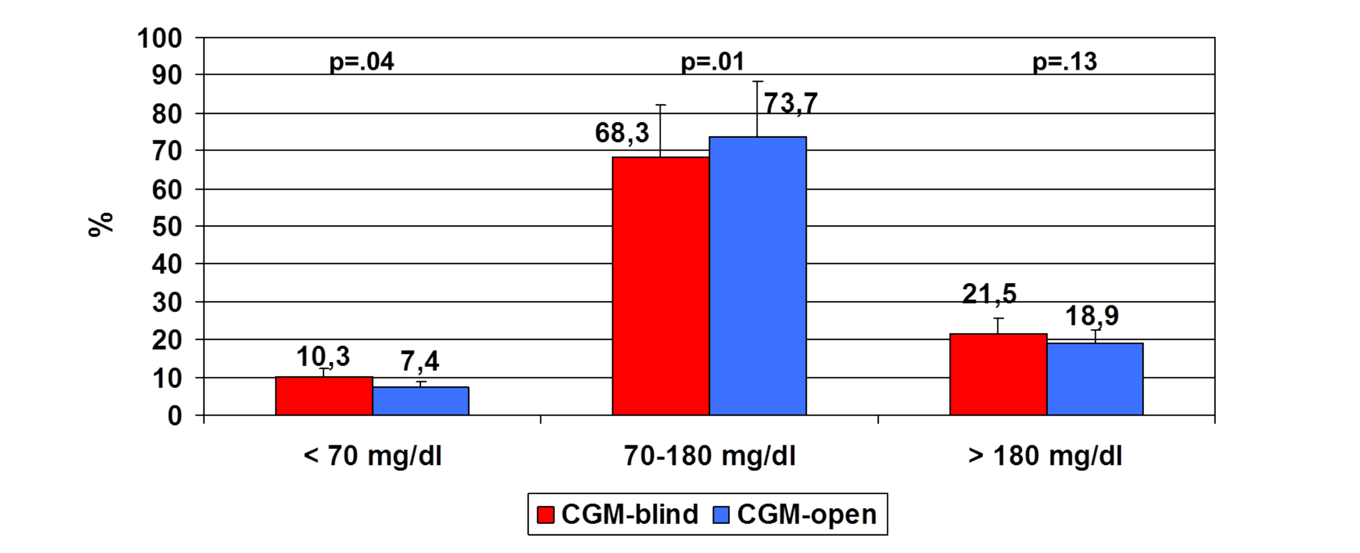

Figure 9: Proportion of POC-GM blood glucose values in the hypo-, eu- and hyperglycemic range

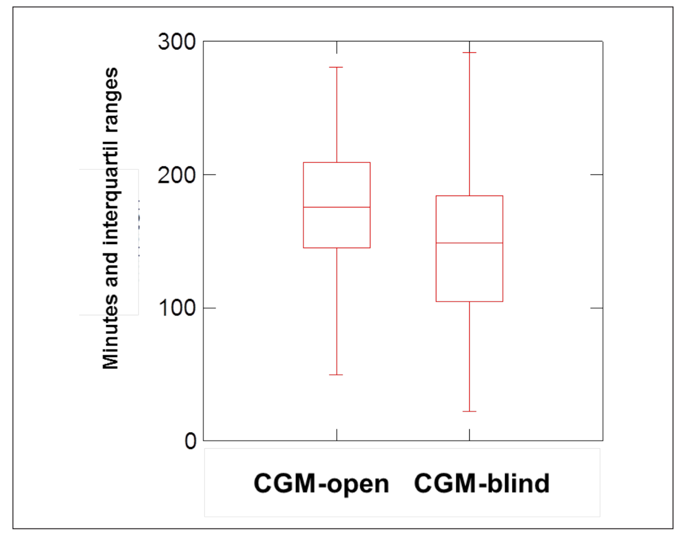

Figure 10: Box plot time until detection of hypoglycemia by POC

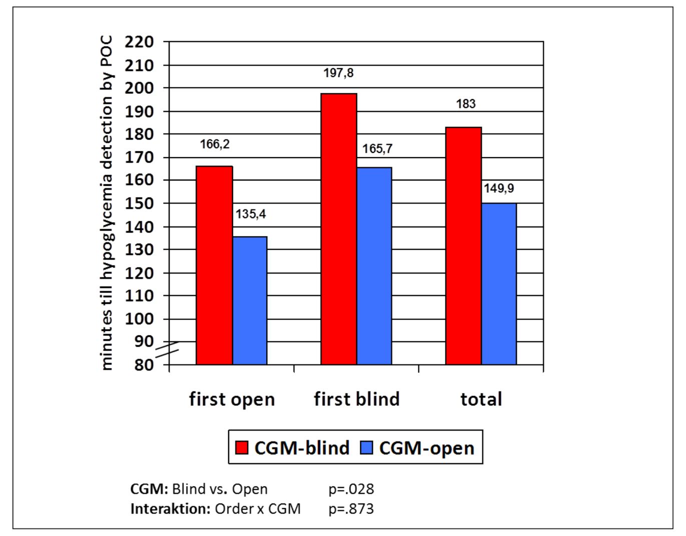

Figure 11: Duration till hypoglycemia detection by POC-GM