Can CGM Discriminate Between Type 1 Diabetes Patients With and Without Severe Hypoglycaemia? Results of the Baseline Assessment from the HypoDE Study

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BACKGROUND AND AIMS

People with type 1 diabetes and hypoglycaemia unawareness have an increased risk for severe hypoglycaemia (SH), defined as the need of third party assistance for recovery. Continuous glucose monitoring (CGM) offers valuable data about glycaemic control and hypoglycaemic exposure in these high-risk patients. However, it is unknown to which extent CGM can provide data that enables identifying people who experienced an episode of severe hypoglycaemia in the past year in this high-risk group. Therefore, we analysed baseline data of the HypoDE study to examine the following problems:

1. Is the hypoglycaemic CGM footprint different in people with and without SH?
2. Can CGM data be used to identify people with severe hypoglycaemia in this high-risk group?
3. What is the screening performance of the hypoglycaemic CGM footprint to identify people with SH?

MATERIALS AND METHODS

Patients with type 1 diabetes on a multiple daily insulin injections (MDI) regimen and hypoglycaemia problems were eligible for the HypoDE study. Hypoglycaemia problems were defined as having suffered a SH episode during the past 12 months or having reduced hypoglycaemia awareness.

Baseline data of 149 participants of the HypoDE study were analysed. Participants wore blinded rtCGM (Dexcom G4) for 28 days. We used the duration of time per day spent in different hypoglycaemic ranges (≤70 mg/dl, ≤60mg/dl, ≤55 mg/dl, ≤50 mg/dl) and the number of hypoglycaemic events with glucose readings of ≤55 mg/dl for at least 20 minutes as hypoglycaemic CGM footprint. We used receiver operating characteristics (ROC) curves to evaluate the ability of the above-mentioned parameters to identify people with SH. We calculated sensitivity, specificity as well as positive and negative predictive values to determine the screening performance of these parameters.

RESULTS

- Sample characteristics are described in Table 1. Participants had a long diabetes duration and a rather good glycaemic control as indicated by a mean A1c of 7.5%. 90 participants reported at least one episode of SH and 59 reported reduced hypoglycaemia awareness without SH. Participants with SH had a lower HbA1c, a higher hypoglycaemia unawareness score, more hypoglycaemia related worries and avoidance behaviour as well as higher diabetes-related distress.
- Table 2 and Figure 1 depict the hypoglycaemic CGM footprint for participants with and without SH. Using parametric and non-parametric statistics indicated that all parameters of the hypoglycaemic CGM footprint were significantly different in participants with and without SH.
- Participants with SH spend significantly less time in the hyperglycaemic range (>180 mg/dl: 440.9 ± 220.7 vs. 563.3 ± 244.5 min per day, p=.002). The duration in time-in-range (>70 - ≤180 mg/dl) did not differ (868.6 ± 191.5 vs. 805.7 ± 223.4, p=.08).
- The ROC and the area under the ROC curve are depicted in Figures 2 and 3. The ROC for all parameters was clearly above the 0.5 diagonal line (Figure 2), indicating better screening performance than a classification by chance. The 95% confidence intervals of the area under the ROC curves did not cut the 0.5 line (Figure 3), which indicates that the different parameters of the hypoglycaemic footprint can significantly better identify people with SH than a classification by chance.
- Sensitivity and specificity as well as positive and negative predictive values are shown in Figures 4 and 5. Although sensitivity and specificity are reasonable high, there is still room for improvement.
- In Figure 6, the hazard ratio of SH is shown. The risk of SH is roughly doubled to tripled when one of the parameter showed an increase of one standard deviation.

CONCLUSION

In a high-risk group of patients with type 1 diabetes and hypoglycaemia problems, the hypoglycaemic CGM footprint can clearly discriminate people with and without previous SH. The screening performance of this hypoglycaemic CGM footprint is significantly better than a classification by chance. There is also a high concordance of different parameters of the hypoglycaemic footprint. The choice of the hypoglycaemic cut-off-values does not play a decisive role, since the screening performance of all indicators of the hypoglycaemic footprint are rather similar. However, the sensitivity and especially the specificity showed room for improvement. Since the screening performance was tested in a high-risk group of people with type 1 diabetes, it cannot be ruled out that the sensitivity, specificity as well as the positive and negative predictive values would have been different in a sample of people with good hypoglycaemia awareness. The hazard ratios showed a two- to three-fold increase in the risk of severe hypoglycaemia when the parameters of the hypoglycaemic CGM footprint increased by one standard deviation. The analysis of the CGM footprint with respect to detecting signs indicative for SH risk might provide meaningful information for patients at risk.

Table 1: Sample characteristics

Sample characteristics Mean (SD) or %	All N=149	With SH n = 90	Without SH n = 59	p
Age in years	46.5 (11.9)	46.1 (11.5)	47.2 (12.5)	.578
% female	40.3 %	42.2 %	37.3%	.551
Diabetes duration in years	21.3 (13.9)	22.6 (13.9)	19.1 (13.7)	.125
HbA1c in %	7.5 (1.0)	7.2 (1.0)	7.8 (0.9)	.001
Hypoglycaemia Unawareness Score (range 0 – 7)	4.9 (1.2)	5.0 (1.5)	4.6 (0.6)	.018
Insulin dose in IU/KG	0.5 (0.3)	0.5 (0.3)	0.6 (0.3)	.431
HFS II - worry scale	32.4 (14.9)	34.6 (14.4)	29.2 (15.3)	.032
HFS II - behaviour scale	20.8 (8.9)	22.2 (9.1)	18.7 (8.3)	.018
Diabetes Distress Scale	2.5 (0.8)	2.7 (0.8)	2.3 (0.7)	.003

Table 2: Hypoglycaemic CGM footprint

CGM characteristics Mean (±SD)	All N=149	With SH n = 90	Without SH n = 59	p
CGM wearing time in days	26.8 (2.1)	26.9 (2.2)	26.6 (1.8)	.233
Duration of glucose ≤ 70 mg/dl in min/day	106.9 (89.3)	130.5 (98.9)	71.0 (56.2)	<.001
Duration of glucose ≤ 60 mg/dl in min/day	63.4 (63.9)	79.9 (72.7)	38.3 (35.5)	<.001
Duration of glucose ≤ 55mg/dl in min/day	46.5 (52.0)	59.6 (60.1)	26.5 (26.4)	<.001
Duration of glucose ≤ 50mg/dl in min/day	32.7 (41.0)	42.9 (48.0)	17.1 (18.8)	<.001
Number of events ≤ 55mg/dl per 28 days	13.0 (11.5)	15.7 (12.5)	8.9 (8.2)	<.001

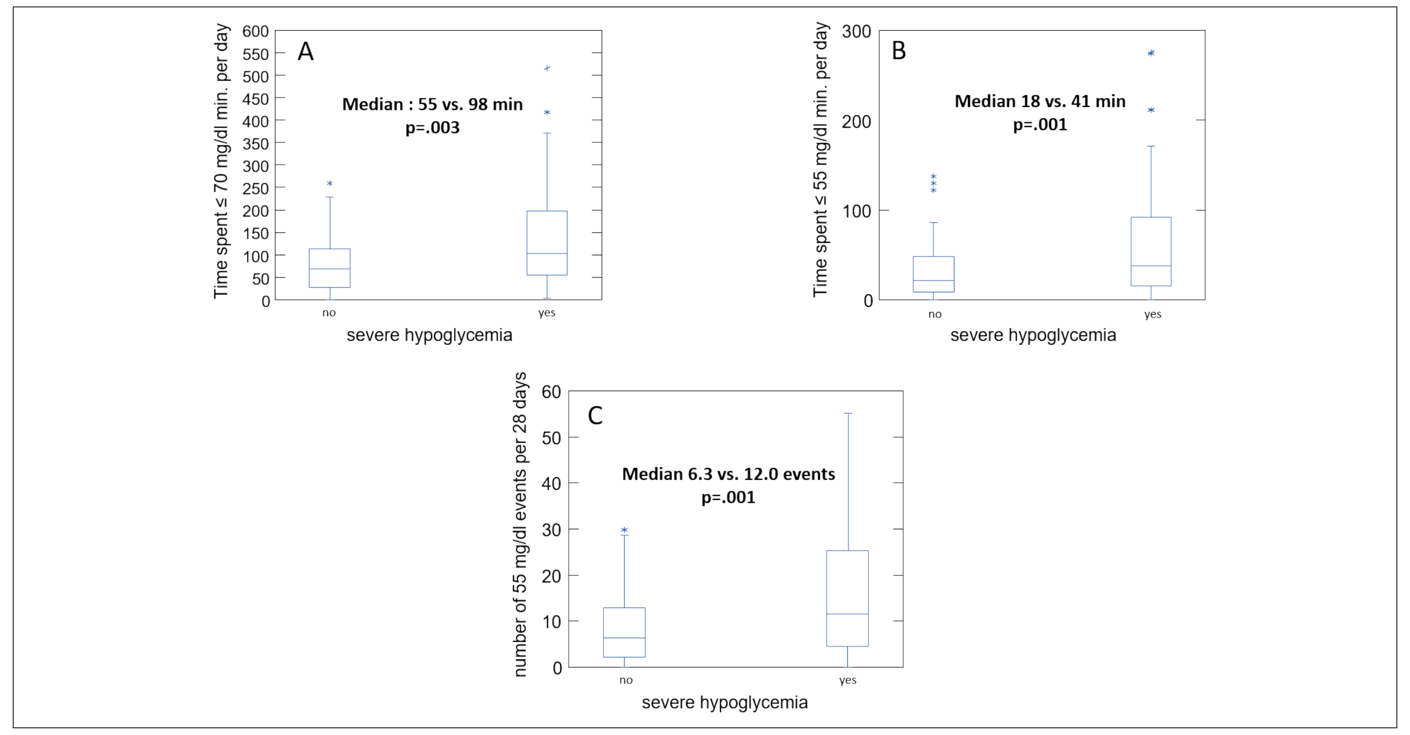

Figure 1: Difference of duration of different hypoglycaemic phases or number of ≤ 55 mg/dl hypoglycaemic events in people with and without severe hypoglycaemia (A ≤ 70 mg/dl; B ≤ 55 mg/dl; C # of ≤ 55 mg/dl events)

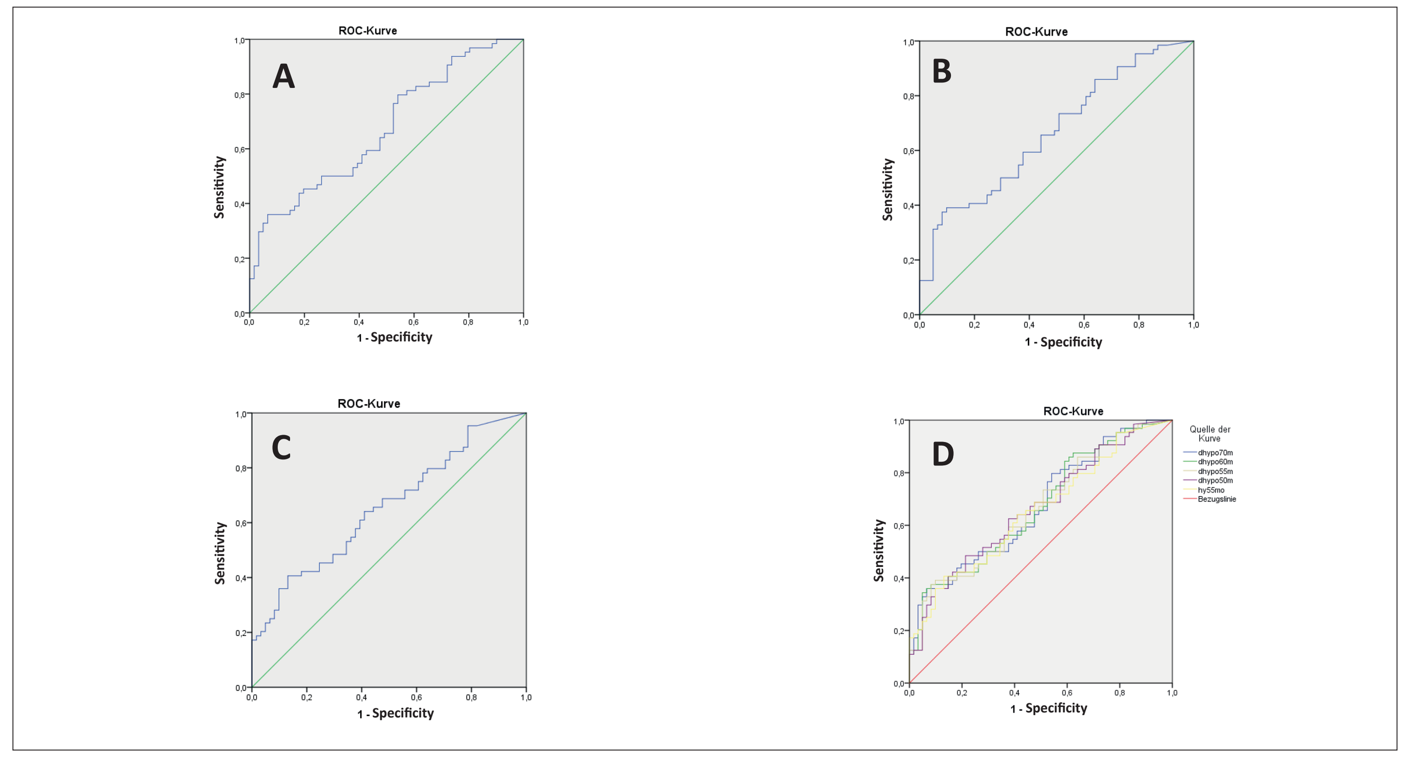

Figure 2: ROC curves of the screening performance of the duration of different hypoglycaemic phases for the identification of particpants with severe hypoglycaemia (A ≤ 70 mg/dl; B ≤ 55 mg/dl; C # of ≤ 55 events; D = all ROC)

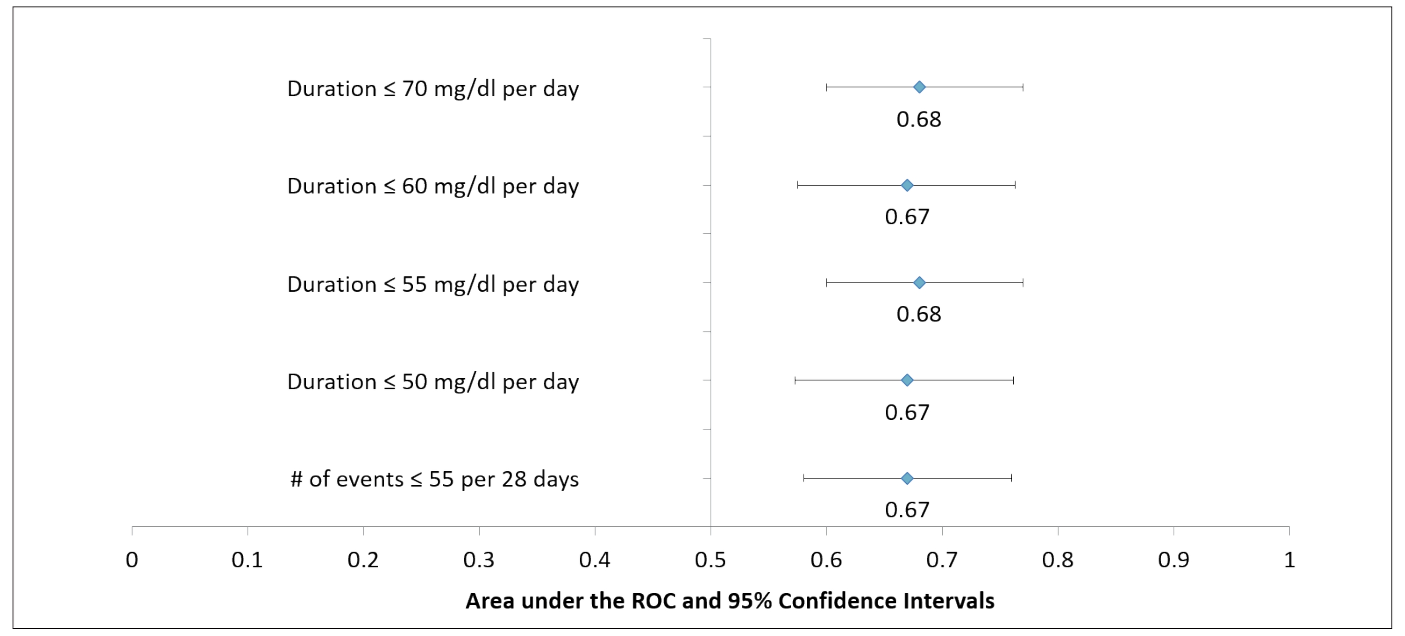

Figure 3: Area under the ROC curves for duration of different hypoglycaemic ranges or for number of events ≤ 55 mg/dl with 95% confidence interval

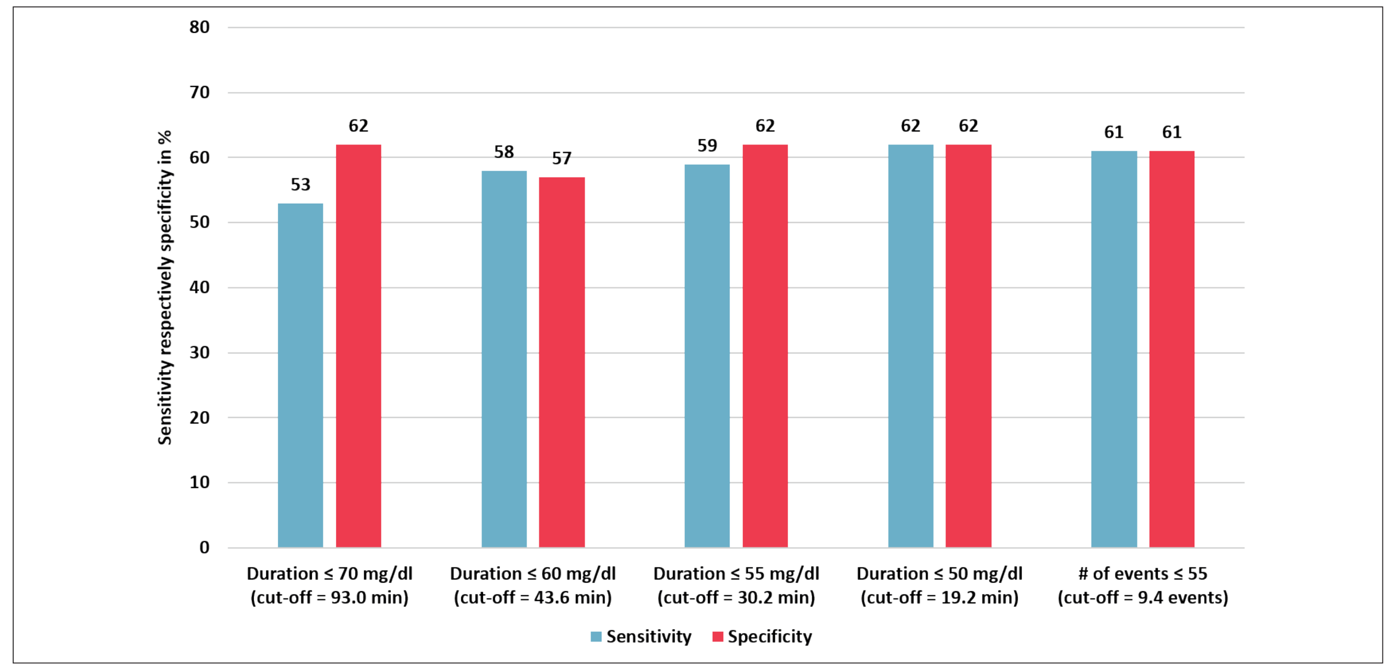

Figure 4: Sensitivity and specificity of CGM data for identification of people with severe hypoglycaemia

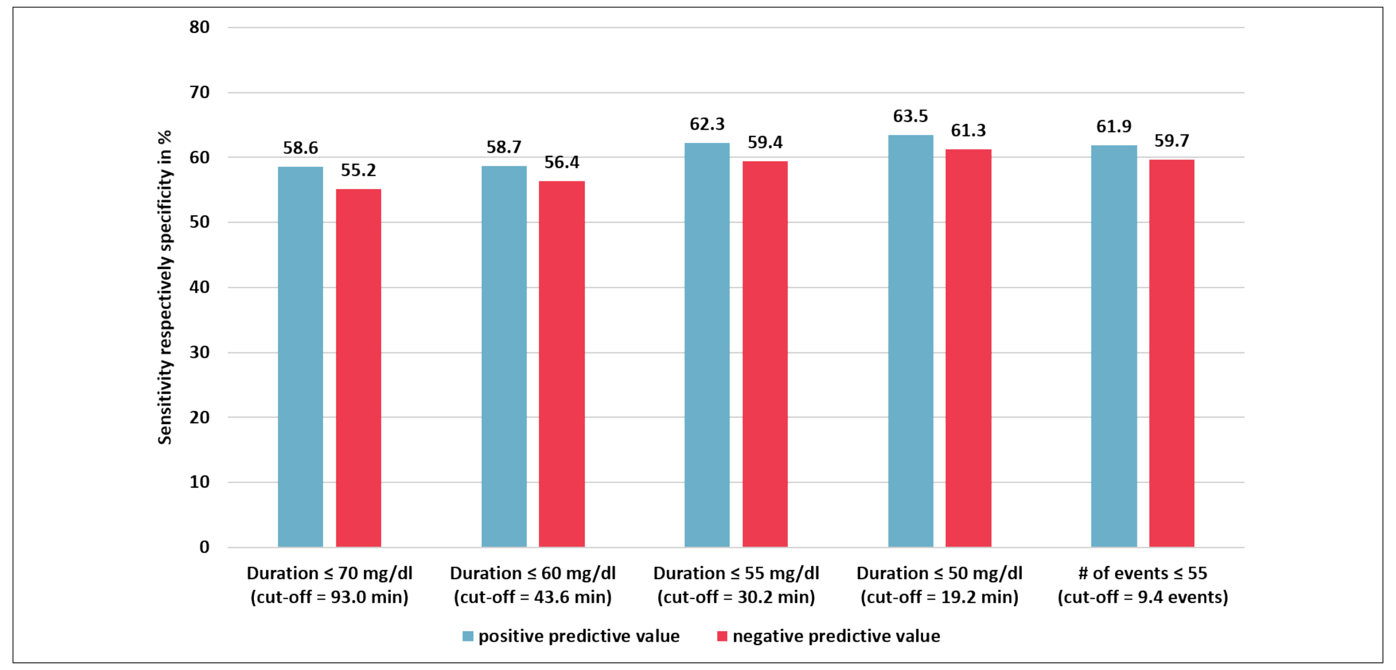

Figure 5: Positive and negative predictive values of CGM data for identification of people with severe hypoglycaemia

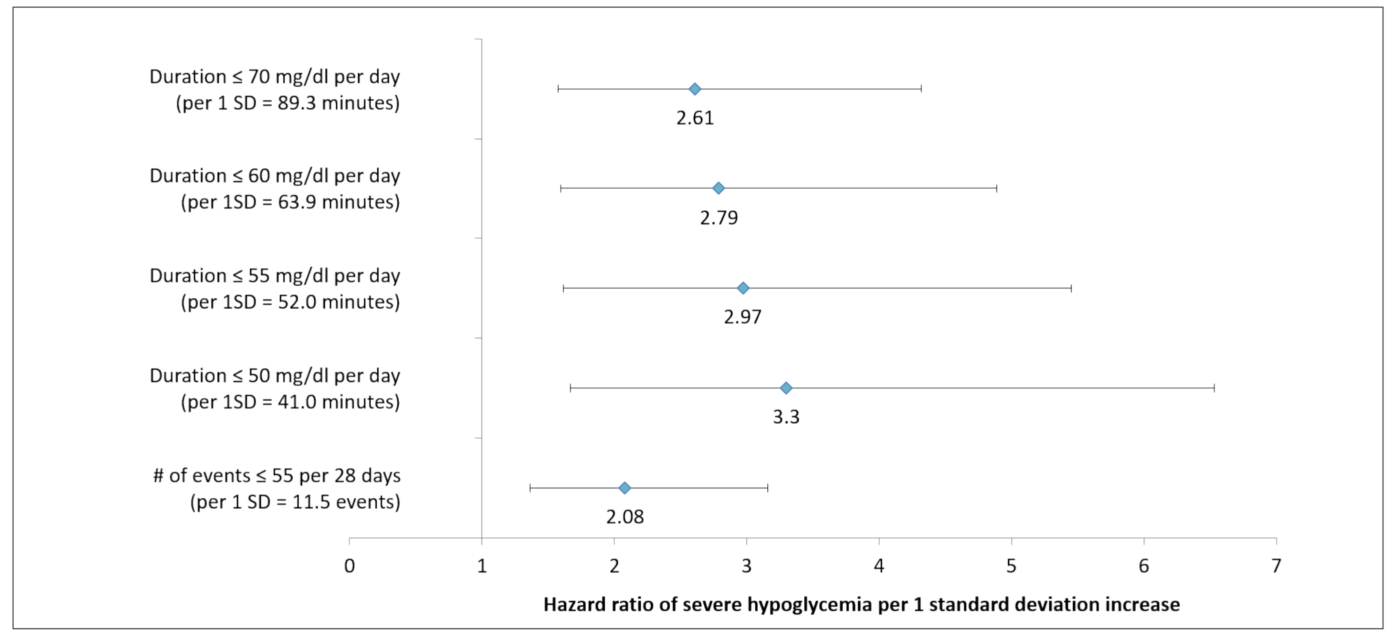

Figure 6: Hazard ratio of SH in dependence from an increase of different parameters of the CGM footprint by 1 SD

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