Continuous Glucose Monitoring in People with Type 1 Diabetes on Multiple Dose Injection Therapy – The Relationship between Glycemic Control and Hypoglycemia

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Full Title: Continuous Glucose Monitoring in People with Type 1 Diabetes on Multiple Dose Injection Therapy – The Relationship between Glycemic Control and Hypoglycemia

Short running title: Glycemic control and hypoglycemia

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Abstract

Objective The inverse relationship between overall glucose control and hypoglycemia risk is weakened by the use of real-time continuous glucose monitoring (rtCGM). We assess the relationship between glucose control and hypoglycemia in people with type 1 diabetes using multiple dose injection regimens (MDI), including those at highest risk of hypoglycemia.

Research Design and Methods CGM data from the intervention (rtCGM) and control (self-monitored blood glucose (SMBG)) phases of the DIAMOND and HypoDE studies were analysed. The relationship between glucose control (HbA$_1c$ and mean rtCGM glucose levels) and percentage time spent in hypoglycemia was explored for thresholds of 3.9 mmol/L (70 mg/dL) and 3.0 mmol/L (54 mg/dL), and analysis of variance across the range of HbA$_1c$ and mean glucose was performed.

Results A non-linear relationship between mean glucose and hypoglycemia was identified at baseline, with the steepest relationship seen at lower values of mean glucose. The use of rtCGM reduces the exposure to hypoglycemia at all thresholds and flattens the relationship between overall glucose and hypoglycemia with the most marked impact at lower values of mean glucose and HbA$_1c$. Exposure to hypoglycemia varied at all thresholds across the range of overall glucose at baseline, in the SMBG group, and with rtCGM but the relationships were weaker in the rtCGM group.

Conclusions Usage of rtCGM can flatten and attenuate the relationship between overall glucose control and hypoglycemia, exerting its greatest impact at lower values of HbA$_1c$ and mean glucose in people with type 1 diabetes using MDI regimens and at highest risk of hypoglycemia.
Achieving optimal glucose in people with type 1 diabetes is challenging. Intensified insulin therapy by means of an insulin pump or a multiple dose injection (MDI) regimen, supported by structured education, can effectively lower HbA\textsubscript{1c} with associated reductions in the long-term risk of micro- and macrovascular complications and their associated morbidity and mortality\textsuperscript{1–3}. However, an improvement in glycemia is also associated with an increase in exposure to hypoglycemia and an increase in the risk of severe hypoglycemic events (requiring assistance from a third party to treat)\textsuperscript{4,5}, a relationship that has be shown for mean glucose levels as well as HbA\textsubscript{1c}\textsuperscript{6}.

Use of real time continuous glucose monitoring (rtCGM) with real-time alerts and alarms helps to improve glycemic control and reduces exposure to hypoglycemia in adults with type 1 diabetes, while also reducing hypoglycemia fear\textsuperscript{7–9}. Such benefits are seen in people using insulin pumps or MDI, and have also been shown in people with HbA\textsubscript{1c} values close to target at baseline\textsuperscript{10}. Real-world data suggest rtCGM system usage may also reduce work absenteeism and hospital admissions for extremes of glucose (severe hypoglycemia or diabetic ketoacidosis)\textsuperscript{11}.

A re-analysis of the data obtained in the ‘JDRF CGM study’ suggested that, despite changes to insulin administration, adoption of insulin analogs and implementation of education, the relationship between time spent in low glucose values (equivalent to hypoglycemia risk) and HbA\textsubscript{1c} remains strongest at lower levels of HbA\textsubscript{1c}. However, the same re-analysis also suggested that rtCGM usage was able to abolish the relationship between HbA\textsubscript{1c} and hypoglycemia with no increased exposure to hypoglycemia below 54 mg/dL across the HbA\textsubscript{1c} range\textsuperscript{12}. The data used for the reanalysis were collected using three different rtCGM systems that have been superseded by next generation systems with improved accuracy and usability while the recruited participants included a large number of people with HbA\textsubscript{1c} values approaching target, and a large number of people using insulin pump therapy. The JDRF CGM study additionally excluded those people at highest risk of hypoglycemia, with a recent history of severe hypoglycemia or impaired awareness of hypoglycemia.

The aim of this analysis is to explore the relationship between HbA\textsubscript{1c}, mean glucose levels and hypoglycemia reported using one, more advanced, rtCGM system in a large cohort of adult people.
with type 1 diabetes using an MDI regimen, including participants with an HbA1c value above target 
and those at highest risk of hypoglycemia.
Research design and methods

Data Sources

Data for analysis were obtained from the DIAMOND\textsuperscript{8} and HypoDE\textsuperscript{13} studies. In brief, the DIAMOND study involved 158 adults with type 1 diabetes, age 25 or older and using MDI. Study participants had an HbA\textsubscript{1c} of 7.5 to 10\% (58 to 86 mmol/mol) at baseline and, following a two week run-in using a blinded CGM system, were randomized to an intervention group using rtCGM (Dexcom G4 with 505 algorithm), or a control group who were asked to self-monitor capillary blood glucose (SMBG) four times daily or more. Follow-up visits were at 4, 12 and 24 weeks.

In the HypoDE study, 149 participants aged 18 or older with type 1 diabetes and an HbA\textsubscript{1c} at baseline $\leq$9\% (75 mmol/mol) were recruited. Again, all participants used a MDI insulin regimen. All recruits were at high risk of hypoglycemia, reporting either severe hypoglycemia in the preceding 12 months, or impaired awareness of hypoglycemia (Clarke score $\geq$4). Participants underwent a four-week blinded CGM run-in phase before being randomized to a rtCGM system (Dexcom G5) or SMBG for 22 weeks.

Unlike the DIAMOND study, the HypoDE study did not measure the HbA\textsubscript{1c} following the run-in phase; thus, all baseline blinded CGM data occurred after their initial HbA\textsubscript{1c} measurement. Study visits occurred at 4, 12 and 22 weeks. In both studies the control groups had blinded CGM system for a minimum of two weeks at the end of the study.

Analysis Design

The analysis plan used the previously published methodology exploring the relationship between CGM-derived hypoglycemia data and mean glucose\textsuperscript{12}. For the follow-up analyses and baseline analyses involving mean glucose levels, the data obtained in the DIAMOND and HypoDE studies were combined into one dataset. All baseline analyses involving HbA\textsubscript{1c} only included data from the DIAMOND study due to the nature of the HypoDE study design. Baseline data for HbA\textsubscript{1c}, time in hypoglycemia and mean glucose were recorded for participants with a minimum of 6 complete days of blinded CGM data in the run-in phase. Time below 54 mg/dL was reported as the primary
hypoglycemia metric, in line with the recommendations of the International Hypoglycemia Study Group. Endpoint CGM data are taken from the final two weeks of the intervention and control phases, again where a minimum of 6 complete days of data are available. Relationships were analyzed using linear regression, and variance of percentage time below 54 mg/dL was assessed across groups of mean glucose partitioned based on increments of 20 mg/dL and across groups of HbA1c categorized based on increments of 0.5%. Cubic smoothing splines were used to visually display the relationship between each of these variables and time spent in hypoglycemia.

**Statistical Analysis**

The distribution of the data was assessed for normality and nonparametric tests were used as appropriate. Linear regression models were employed to assess relationships between hypoglycemia and mean glucose or HbA1c. Kruskal-Wallis tests were used to assess variance of time in hypoglycemia across the range of mean glucose and HbA1c. Statistical tests were two-tailed, and the significance level was set at p<0.05.
Results

Descriptive data are reported as mean (SD) where normally distributed and as median with interquartile range (IQR) when skewed. A complete set of CGM data were available for 307 participants (158 DIAMOND, 149 HypoDE) at baseline and 270 participants (133 DIAMOND, 137 HypoDE) at follow-up. For the participants with available baseline data, the overall mean age at baseline was 47 years (SD 12) (DIAMOND 48 years [13]; HypoDE 47 years [12]), overall baseline HbA$_1c$ was 8.1% (1.0%) (DIAMOND 8.6% [0.6%]; HypoDE 7.5% [1.0%]), and 42% of the participants were female (44%, 40%) (Table 1). In total 180 participants were randomized to rtCGM (DIAMOND 105, HypoDE 75).

Baseline data

HbA$_1c$, mean glucose, and time spent in hypoglycemia at baseline are summarized in Table 2. At baseline, mean glucose was associated with time below 54 mg/dL and time below 70 mg/dL (p<0.001 for both outcomes). However, the association did not appear to be linear, so a cubic smoothing spline was subsequently used to model the relationship with time below 70 mg/dL (Supplemental Figure S1). The estimated curve shows a monotone decreasing trend flattening out as the amount of hypoglycemia approaches zero.

At baseline, there was no detectable association between HbA$_1c$ and time below 54 mg/dL (p=0.56) or time below 70 mg/dL (p=0.50). The relationship between HbA$_1c$ and time below 70 mg/dL was also modelled using a cubic smoothing spline, which showed a slight linear decrease (Supplemental Figure S1).

SMBG endpoint data

HbA$_1c$, mean glucose, and time spent in hypoglycemia at the study endpoint in the SMBG arm are summarized in Table 2. In the SMBG group, mean glucose was associated with time below 54 mg/dL and time below 70 mg/dL (p<0.001 in both cases). As above, the smoothing spline for time below 70 mg/dL was decreasing with greater changes for lower mean glucose values (Supplemental Figure S2). There was also an association between HbA$_1c$ and time below 54 mg/dL (p=0.006) and time
below 70 mg/dL (p<0.001) in the SMBG arm. The smoothing spline displayed a decreasing relationship that levelled off around an HbA\textsubscript{1c} value of 8.5% (69 mmol/mol).

rtCGM endpoint data

HbA\textsubscript{1c}, mean glucose, and time spent in hypoglycemia at the study endpoint in the rtCGM arm are summarized in Table 2. In the rtCGM group, there was a significant association between mean glucose and time below 54 mg/dL and time below 70 mg/dL (p<0.001 for both cases). Time below 70 mg/dL was reduced for most participants (79%) using the rtCGM system, including those with a high baseline HbA\textsubscript{1c} and mean glucose where the hypoglycemia rate was lowest. The smoothing spline was approximately linear with a small negative slope (Supplemental Figure S3).

There was an association between HbA\textsubscript{1c} and time spent in hypoglycemia in the rtCGM group for time below 70 mg/dL (p<0.001), but an association was not detectable for time below 54 mg/dL (p=0.10). The smoothing spline resembled a line with a small negative slope (Supplemental Figure S3). Figure 1 displays the relationship between times spent in hypoglycemia and mean glucose or HbA\textsubscript{1c} for the two treatment groups overlaid for comparison purposes.

Between group differences

Time spent in hypoglycemia across groups of mean glucose at baseline, in the control group and in the rtCGM intervention groups for the combined dataset and in each study are presented in Figure 2. At baseline, the distributions of time below 54 mg/dL (p<0.001) and 70 mg/dL (p<0.001) were significantly different across mean glucose groups. In the rtCGM arm at follow-up, the distributions of time spent in hypoglycemia also differed between groups (p=0.002 for time below 54 mg/dL and p<0.001 for time below 70 mg/dL). In the SMBG group, the distributions of time below 54 mg/dL (p<0.001) and 70 mg/dL (p<0.001) also were significantly different between mean glucose groups.

Contrarily, the distributions of time below 54 mg/dL (p=0.10) and 70 mg/dL (p=0.42) were not significantly different across HbA\textsubscript{1c} groups at baseline. In the rtCGM group, the distributions varied across HbA\textsubscript{1c} groups for time below 54 mg/dL (p=0.02) and 70 mg/dL (p=0.001). In the SMBG arm, the distribution of time below 54 mg/dL was significantly different between HbA\textsubscript{1c} groups (p=0.04), and a
difference was observed for time below 70 mg/dL (p=0.005). Boxplots of time spent in hypoglycemia across groups of HbA\textsubscript{1c} at baseline and in each treatment group at follow-up are shown in Figure 2.
Conclusions

This analysis of the data obtained in two large randomized controlled studies using the same rtCGM system shows that rtCGM is able to convert the relationship from nonlinear at the lower end of glucose to an approximately linear relationship, shown most clearly in Figure 1, and emphasizes the relatively greater impact of rtCGM usage on hypoglycemia risk at lower mean blood glucose values and lower HbA$_1c$ values. This suggests that rtCGM usage can empower adults with type 1 diabetes to achieve their target glucose without a major increase in hypoglycemia exposure. Furthermore, hypoglycemia continued to decrease at higher HbA1c levels in the rtCGM group, emphasizing that rtCGM usage can effectively reduce hypoglycemia in people with an HbA1c above target.

In the analysis, at baseline, there is a nonlinear relationship between hypoglycemia and mean glucose levels with a decreasing trend that flattens out as it approaches zero at the higher HbA$_1c$ levels. Analysis of the baseline relationship between hypoglycemia and HbA$_1c$ is limited by the HbA$_1c$ inclusion criteria of the DIAMOND study and the HbA$_1c$ testing schedule of the HypoDE study, in which a baseline HbA$_1c$ was only assessed prior to the run-in phase.

The relationships between glycemic control (mean blood glucose or HbA$_1c$) and hypoglycemia were modelled using cubic smoothing splines because some of the relationships appeared to be nonlinear. Smoothing splines were chosen because they are more flexible to fit nonlinear trends.

At the study endpoints, for participants randomized to SMBG, the relationship between hypoglycemia and mean glucose is unchanged from baseline, and a similar nonlinear relationship between hypoglycemia and HbA$_1c$ emerges as a wider distribution of HbA$_1c$ values is observed, again with an upward inflection in risk at lower values of HbA$_1c$.

In the participants randomized to rtCGM, the nonlinear relationship with mean blood glucose seen at baseline changes to become approximately linear with an increased time spent in hypoglycemia as mean glucose decreases. A similar linear relationship is seen between HbA$_1c$ and time spent below 70 mg/dL. There is also a weak linear relationship between time below 54 mg/dL and
HbA\textsubscript{1c}, although the slope did not reach significance due to the low hypoglycemia rate among most rtCGM participants.

In the analysis of variance, clear variation in exposure to hypoglycemia across the range of mean blood glucose was shown at baseline, and across mean blood glucose and HbA\textsubscript{1c} at follow up in the SMBG group. In the rtCGM group at follow up, a weaker variance in exposure to hypoglycemia was seen across the HbA\textsubscript{1c} range, especially for time spent below 54 mg/dL.

In keeping with the previous analysis based on the JDRF dataset\textsuperscript{12}, for people with type 1 diabetes self-monitoring blood glucose the highest risk of hypoglycemia occurs at the lower extreme of HbA\textsubscript{1c} and this signal is additionally true for mean blood glucose. The finding, that usage of rtCGM systems reduces hypoglycemia risk across the range of glucose, measured by HbA\textsubscript{1c} or mean blood glucose, is confirmed. In the rtCGM group, there was less ability to detect a relationship between glycemia and hypoglycemia because time spent in hypoglycemia was very low among most participants, including those with lower values of HbA\textsubscript{1c}.

In contrast to the previous analysis the J-shaped association was not confirmed in this analysis with no demonstrable increase in hypoglycemia risk at higher overall glucose values. This may reflect the participants recruited using MDI insulin regimens only and fewer insulin correction boluses being delivered compared to the largely insulin-pump using cohort in the JDRF study. The impact of pump therapy when added to rtCGM suggests an increase in time in hypoglycemia with a change in HbA\textsubscript{1c} or variability as assessed by the coefficient of variation\textsuperscript{15}. Further studies are required to assess the impact of insulin administration on the relationship between HbA\textsubscript{1c}, glucose variability, and hypoglycemia. Additionally, a large type 1 diabetes registry found a slight J-shaped association between HbA\textsubscript{1c} and severe hypoglycemia\textsuperscript{16}; the impact of rtCGM on this relationship would be of interest.

Guidelines for treatment targets for people with type 1 diabetes at highest risk of hypoglycaemia suggest adopting a less stringent HbA1\textsubscript{c} target of <8% (64mmol/mol)\textsuperscript{17} to minimise the risk of severe hypoglycemia and the associated morbidity and mortality. This pragmatic approach to
hypoglycemia avoidance may be effective but the impact of rtCGM in addressing hypoglycemia exposure at the lower end of overall glycemia demonstrated here suggests that lower HbA1c targets for people at high risk may be supported with rtCGM usage.

The strengths of this study include the large dataset taken from two large-scale rtCGM studies with participants using MDI insulin regimens. The participants were recruited to studies with broadly similar study designs and the inclusion of participants at high risk of hypoglycemia using more accurate rtCGM systems is a particular strength. Previous studies of rtCGM in adults and pediatric groups with type 1 diabetes have included a high proportion of insulin pump users, and have excluded people with impaired awareness of hypoglycemia or a history of severe hypoglycemia. By including those groups and focusing on people using an MDI insulin regimen only this analysis addresses a gap in the evidence base.

The study designs limit the inclusion of a broad range of HbA1c at baseline, but this effect was mitigated by including mean sensor glucose throughout. Another potential limitation is that the relationship between hypoglycemia and mean glucose at follow-up uses blinded CGM data in the SMBG group, but unblinded rtCGM data in the rtCGM group, while the baseline CGM data are blinded. However, the trends identified in the mean blood glucose analysis are the same as those in the HbA1c group, suggesting that this potential limitation does not have a meaningful impact.

This data analysis compliments the main results from the DIAMOND and HypoDE datasets showing the reduction in exposure to hypoglycemia with rtCGM usage, and provides further evidence that this benefit can be achieved throughout the glycemia range in a diverse group of people with type 1 diabetes using MDI, including those at highest risk of hypoglycemia.
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Duality of interest NO has received honoraria for speaking, and research funding for investigator-initiated studies from Dexcom. MG and VM reports no disclosures concerning this work. PC was a former Dexcom employee and shareholder. NC has received research support through their respective institution from Dexcom. MR has received research funding for an investigator-initiated study from Dexcom. NH and LH received an unrestricted research grant to perform the HypoDE study. GF has received research support and honoraria for speaking through their respective institution from Dexcom.

Author Contributions NO, MG, MR, GF, NH, and LH directed the statistical analysis, interpreted the data, and wrote the manuscript. VM designed the analysis and contributed to interpreting the results. PC and NC undertook the analysis and contributed to the manuscript. NO and LH are the guarantors of this work and, as such, had full access to all of the data in the study and take responsibility for the integrity of the data and the accuracy of the data analysis.

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References

Table 1. Baseline characteristics of the analysis cohorts.

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<tr>
<th>Characteristic</th>
<th>Overall (N=307)</th>
<th>DIAMOND (N=158)</th>
<th>HypoDE (N=149)</th>
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<tr>
<td>Age (years) mean ± SD</td>
<td>47 ± 12</td>
<td>48 ± 13</td>
<td>47 ± 12</td>
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<tr>
<td>Gender – Female n (%)</td>
<td>130 (42%)</td>
<td>70 (44%)</td>
<td>60 (40%)</td>
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<tr>
<td>Diabetes Duration (years) mean ± SD</td>
<td>21 ± 14</td>
<td>21 ± 14</td>
<td>21 ± 14</td>
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<tr>
<td>% Time &lt;54 mg/dL median (quartiles)</td>
<td>1.5% (0.6%, 3.4%)</td>
<td>1.5% (0.6%, 3.2%)</td>
<td>1.7% (0.7%, 3.7%)</td>
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<tr>
<td>% Time &lt;70 mg/dL median (quartiles)</td>
<td>5.1% (2.6%, 8.5%)</td>
<td>4.6% (2.3%, 7.7%)</td>
<td>5.7% (3.0%, 9.2%)</td>
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<tr>
<td>Mean Glucose (mg/dL) mean ± SD</td>
<td>174 ± 31</td>
<td>187 ± 28</td>
<td>160 ± 28</td>
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<tr>
<td>HbA1c (%) mean ± SD</td>
<td>8.1 ± 1.0</td>
<td>8.6 ± 0.6</td>
<td>7.5 ± 1.0</td>
</tr>
<tr>
<td>HbA1c (mmol/mol) mean ± SD</td>
<td>65 ± 11</td>
<td>71 ± 7</td>
<td>58 ± 11</td>
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</table>
Table 2. HbA\textsubscript{1c}, mean glucose, and percentage time spent in hypoglycemia by study.

<table>
<thead>
<tr>
<th></th>
<th>Overall (N=307)</th>
<th>DIAMOND (N=158)\textsuperscript{a}</th>
<th>HypoDE (N=149)\textsuperscript{b}</th>
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<tr>
<td><strong>Baseline</strong></td>
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<tr>
<td>HbA\textsubscript{1c} (%) mean ± SD</td>
<td>8.1 ± 1.0</td>
<td>8.6 ± 0.6</td>
<td>7.5 ± 1.0</td>
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<tr>
<td>HbA\textsubscript{1c} (mmol/mol) mean ± SD</td>
<td>65 ± 11</td>
<td>71 ± 7</td>
<td>58 ± 11</td>
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<tr>
<td>Hours of CGM data median (quartiles)</td>
<td>466 (315, 638)</td>
<td>316 (307, 322)</td>
<td>639 (613, 658)</td>
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<td>% Time &lt;54 mg/dL median (quartiles)</td>
<td>1.5% (0.6%, 3.4%)</td>
<td>1.5% (0.6%, 3.2%)</td>
<td>1.7% (0.7%, 3.7%)</td>
</tr>
<tr>
<td>% Time &lt;70 mg/dL median (quartiles)</td>
<td>5.1% (2.6%, 8.5%)</td>
<td>4.6% (2.3%, 7.7%)</td>
<td>5.7% (3.0%, 9.2%)</td>
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<tr>
<td>Mean Glucose (mg/dL) mean ± SD</td>
<td>174 ± 31</td>
<td>187 ± 28</td>
<td>160 ± 28</td>
</tr>
<tr>
<td><strong>Follow-up (SMBG Group)</strong></td>
<td></td>
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<td></td>
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<tr>
<td>HbA\textsubscript{1c} (%) mean ± SD</td>
<td>7.6 ± 0.9</td>
<td>8.1 ± 0.7</td>
<td>7.3 ± 0.8</td>
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<tr>
<td>HbA\textsubscript{1c} (mmol/mol) mean ± SD</td>
<td>59 ± 10</td>
<td>65 ± 8</td>
<td>56 ± 9</td>
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<tr>
<td>Hours of CGM data median (quartiles)</td>
<td>289 (164, 312)</td>
<td>158 (152, 165)</td>
<td>305 (285, 317)</td>
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<tr>
<td>% Time &lt;54 mg/dL median (quartiles)</td>
<td>1.9% (0.4%, 4.4%)</td>
<td>1.1% (0.1%, 2.7%)</td>
<td>2.1% (0.6%, 5.7%)</td>
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<tr>
<td>% Time &lt;70 mg/dL median (quartiles)</td>
<td>5.4% (2.3%, 10.5%)</td>
<td>3.6% (2.0%, 7.7%)</td>
<td>6.7% (2.9%, 13.3%)</td>
</tr>
<tr>
<td>Mean Glucose (mg/dL) mean ± SD</td>
<td>171 ± 32</td>
<td>191 ± 30</td>
<td>160 ± 28</td>
</tr>
<tr>
<td><strong>Follow-up (rtCGM Group)</strong></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>HbA\textsubscript{1c} (%) mean ± SD</td>
<td>7.5 ± 0.8</td>
<td>7.6 ± 0.8</td>
<td>7.4 ± 0.8</td>
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<tr>
<td>HbA\textsubscript{1c} (mmol/mol) mean ± SD</td>
<td>59 ± 9</td>
<td>60 ± 8</td>
<td>57 ± 9</td>
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<tr>
<td>Hours of rtCGM data median (quartiles)</td>
<td>313 (300, 321)</td>
<td>319 (305, 325)</td>
<td>309 (296, 316)</td>
</tr>
<tr>
<td>% Time &lt;54 mg/dL median (quartiles)</td>
<td>0.4% (0.1%, 1.1%)</td>
<td>0.6% (0.2%, 1.2%)</td>
<td>0.2% (0.1%, 0.7%)</td>
</tr>
<tr>
<td>% Time &lt;70 mg/dL median (quartiles)</td>
<td>2.3% (1.0%, 4.2%)</td>
<td>2.5% (1.3%, 4.8%)</td>
<td>1.4% (0.7%, 3.6%)</td>
</tr>
<tr>
<td>Mean Glucose (mg/dL) mean ± SD</td>
<td>177 ± 30</td>
<td>181 ± 29</td>
<td>172 ± 32</td>
</tr>
</tbody>
</table>

\textsuperscript{a} Twenty-five subjects in the DIAMOND study did not have enough data to be included in follow-up analyses. \textsuperscript{b} Twelve subjects in the HypoDE study did not have enough data to be included in follow-up analyses.
Figure 1. Time spent in hypoglycemia as a function of mean glucose and HbA\textsubscript{1c} by treatment arm at follow-up.

Figure 2. Time spent in hypoglycemia across groups of mean glucose (Panel A) or HbA\textsubscript{1c} (Panel B). Dots denote the mean time below threshold, and boxes denote the median (25\textsuperscript{th}, 75\textsuperscript{th} percentiles) time below threshold.
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Figure S1. Relationships between %time spent below 70mg/dL (3.9mmol/L) and mean glucose and HbA1c at baseline
Figure S2. Relationships between %time spent below 70mg/dL (3.9mmol/L) and mean glucose and HbA1c at the endpoint in the SMBG group.
Figure S3. Relationships between %time spent below 70 mg/dL (3.9 mmol/L) and mean glucose and HbA1c at the endpoint in the rtCGM group.