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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Diabetes Care 2020;43:53–58 | https://doi.org/10.2337/dc19-0977

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 (MDI) regimens, 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 Multiple Daily Injections and Continuous Glucose Monitoring in Diabetes (DIAMOND) and HypoDE studies were analyzed. 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 ANOVA across the range of HbA_{1c} and mean glucose was performed.

RESULTS

A nonlinear 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

Use 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.

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Received 15 May 2019 and accepted 27 August 2019

This article contains Supplementary Data online at http://care.diabetesjournals.org/lookup/suppl/doi:10.2337/dc19-0977/-/DC1.

This article is part of a special article collection available at http://care.diabetesjournals.org/collection/cgm-for-type1-diabetes.

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_{1c} with associated reductions in the long-term risk of micro- and macrovascular complications and their associated morbidity and mortality (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) (4,5), a relationship that has been shown for mean glucose levels as well as HbA_{1c} (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 (7–9). Such benefits are seen in people using insulin pumps or MDI and have also been shown in people with HbA_{1c} values close to target at baseline (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) (11).

A reanalysis 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_{1c} remains strongest at lower levels of HbA_{1c}. However, the same reanalysis also suggested that rtCGM usage was able to abolish the relationship between HbA_{1c} and hypoglycemia with no increased exposure to hypoglycemia $<$54 mg/dL across the HbA_{1c} range (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_{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 among HbA_{1c}, mean glucose levels, and hypoglycemia reported using one, more advanced rtCGM system in a large cohort of adult people with type 1 diabetes who use an MDI regimen, including participants with an HbA_{1c} value above target and those at highest risk of hypoglycemia.

RESEARCH DESIGN AND METHODS

Data Sources

Data for analysis were obtained from the Multiple Daily Injections and Continuous Glucose Monitoring in Diabetes (DIAMOND) (8) and HypoDE (13) studies. In brief, the DIAMOND study involved 158 adults with type 1 diabetes, aged $\geq$25 years, and using MDI. Study participants had an HbA_{1c} of 7.5–10% (58–86 mmol/mol) at baseline and, following a 2-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 perform self-monitoring of 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 $\geq$18 years with type 1 diabetes and an HbA_{1c} at baseline $\leq$9% (75 mmol/mol) were recruited. Again, all participants used an 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 4-week blinded CGM run-in phase before being randomized to an rtCGM system (Dexcom G5) or SMBG for 22 weeks.

Unlike the DIAMOND study, the HypoDE study did not measure the HbA_{1c} following the run-in phase; thus, all baseline blinded CGM data occurred after the initial HbA_{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 2 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 (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 data set. All baseline analyses involving HbA_{1c} only included data from the DIAMOND study due to the nature of the HypoDE study design. Baseline data for HbA_{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 spent at $<$54 mg/dL was reported as the primary hypoglycemia metric, in line with the recommendations of the International Hypoglycaemia Study Group (14). End point CGM data are taken from the final 2 weeks of the intervention and control phases, again in which a minimum of 6 complete days of data are available. Relationships were analyzed using linear regression, and variance of percentage time $<$54 mg/dL was assessed across groups of mean glucose partitioned based on increments of 20 mg/dL and across groups of HbA_{1c} categorized based on increments of 0.5%. Cubic smoothing splines were used to visually display the relationship among 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 used to assess relationships between hypoglycemia and mean glucose or HbA_{1c}. Kruskal-Wallis tests were used to assess variance of time in hypoglycemia across the range of mean glucose and HbA_{1c}. 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 when skewed. A complete set of CGM data were available for 307 participants (158 DIAMOND and 149 HypoDE) at baseline and 270 participants (133 DIAMOND and 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% and 40%, respectively)

Table 1—Baseline characteristics of the analysis cohorts

Characteristic	Overall (N = 307)	DIAMOND (N = 158)	HypoDE (N = 149)
Age (years), mean ± SD	47 ± 12	48 ± 13	47 ± 12
Sex (female), *n* (%)	130 (42)	70 (44)	60 (40)
Diabetes duration (years), mean ± SD	21 ± 14	21 ± 14	21 ± 14
Percent time <54 mg/dL, median (quartiles)	1.5 (0.6, 3.4)	1.5 (0.6, 3.2)	1.7 (0.7, 3.7)
Percent time <70 mg/dL, median (quartiles)	5.1 (2.6, 8.5)	4.6 (2.3, 7.7)	5.7 (3.0, 9.2)
Mean glucose (mg/dL), mean ± SD	174 ± 31	187 ± 28	160 ± 28
HbA_{1c} (%), mean ± SD	8.1 ± 1.0	8.6 ± 0.6	7.5 ± 1.0
HbA_{1c} (mmol/mol), mean ± SD	65 ± 11	71 ± 7	58 ± 11

(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 <54 mg/dL and time <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 <70 mg/dL (Supplementary Fig. 1). The estimated curve shows a monotone decreasing trend flattening out as the amount in hypoglycemia approaches zero.

At baseline, there was no detectable association between HbA_{1c} and time <54 mg/dL ($P = 0.56$) or time <70 mg/dL ($P = 0.50$). The relationship between HbA_{1c} and time <70 mg/dL was also modeled using a cubic smoothing spline, which showed a slight linear decrease (Supplementary Fig. 1).

SMBG End Point Data

HbA_{1c}, mean glucose, and time spent in hypoglycemia at the study end point in the SMBG arm are summarized in Table 2. In the SMBG group, mean glucose was associated with time <54 mg/dL and time <70 mg/dL ($P < 0.001$ in both cases). As above, the smoothing spline for time <70 mg/dL was decreasing with greater changes for lower mean glucose values (Supplementary Fig. 2). There was also an association between HbA_{1c} and time <54 mg/dL ($P = 0.006$) and time <70 mg/dL ($P < 0.001$) in the SMBG arm. The smoothing spline displayed a decreasing relationship that leveled off at an HbA_{1c} value of ~8.5% (69 mmol/mol).

rtCGM End Point Data

HbA_{1c}, mean glucose, and time spent in hypoglycemia at the study end point in the rtCGM arm are summarized in Table 2. In the rtCGM group, there was a significant association between mean glucose and time <54 mg/dL and time <70 mg/dL ($P < 0.001$ for both cases). Time <70 mg/dL was reduced for most participants (79%) using the rtCGM system, including those with a high baseline HbA_{1c} and mean glucose in which the hypoglycemia rate was lowest. The smoothing spline was approximately linear with a small negative slope (Supplementary Fig. 3).

There was an association between HbA_{1c} and time spent in hypoglycemia in the rtCGM group for time <70 mg/dL

Table 2—HbA_{1c}, mean glucose, and percentage time spent in hypoglycemia by study

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

[a]Twenty-five subjects in the DIAMOND study did not have enough data to be included in follow-up analyses. [b]Twelve subjects in the HypoDE study did not have enough data to be included in follow-up analyses.

($P < 0.001$), but an association was not detectable for time <54 mg/dL ($P = 0.10$). The smoothing spline resembled a line with a small negative slope (Supplementary Fig. 3). Figure 1 displays the relationship between times spent in hypoglycemia and mean glucose or HbA_{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 data set and in each study, is presented in Fig. 2. At baseline, the distributions of time <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 <54 mg/dL and $P < 0.001$ for time <70 mg/dL). In the SMBG group, the distributions of time <54 mg/dL ($P < 0.001$) and <70 mg/dL ($P < 0.001$) were also significantly different between mean glucose groups.

Contrarily, the distributions of time <54 mg/dL ($P = 0.10$) and <70 mg/dL ($P = 0.42$) were not significantly different across HbA_{1c} groups at baseline. In the rtCGM group, the distributions varied across HbA_{1c} groups for time <54 mg/dL ($P = 0.02$) and <70 mg/dL ($P = 0.001$). In the SMBG arm, the distribution of time <54 mg/dL was significantly different between HbA_{1c} groups ($P = 0.04$), and a difference was observed for time <70 mg/dL ($P = 0.005$). Box plots of time spent in hypoglycemia across groups of HbA_{1c} at baseline and in each treatment group at follow-up are shown in Fig. 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 Fig. 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 HbA_{1c} levels in the rtCGM group, emphasizing that rtCGM usage can effectively reduce hypoglycemia in people with an HbA_{1c} 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 modeled 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 end points, 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 increased time spent in hypoglycemia as mean glucose decreases. A similar linear relationship is seen between HbA_{1c} and time spent <70 mg/dL. There is also a weak linear relationship between time <54 mg/dL and HbA_{1c}, although the slope did not reach significance due to the low hypoglycemia rate among most rtCGM participants.

In the ANOVA, clear variation in exposure to hypoglycemia across the range of mean blood glucose was shown at baseline and across mean blood glucose and HbA_{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_{1c} range, especially for time spent <54 mg/dL.

In keeping with the previous analysis based on the JDRF data set (12), for people with type 1 diabetes with SMBG, the highest risk of hypoglycemia occurs at the lower extreme of HbA_{1c}, and this signal is additionally true for mean blood glucose. The finding that use of rtCGM systems reduces hypoglycemia risk across the range of glucose, measured by HbA_{1c} or mean blood

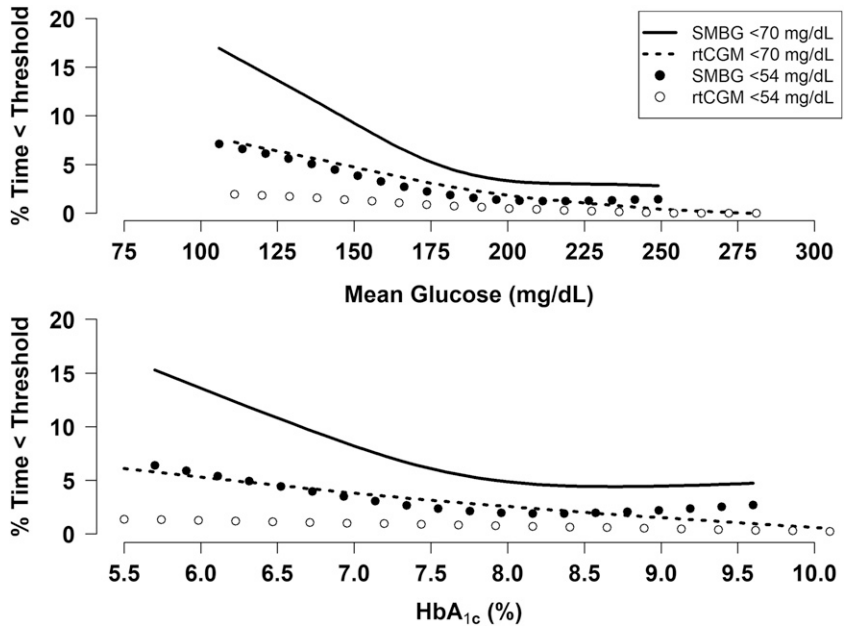

Figure 1—Time spent in hypoglycemia as a function of mean glucose and HbA_{1c} by treatment arm at follow-up.

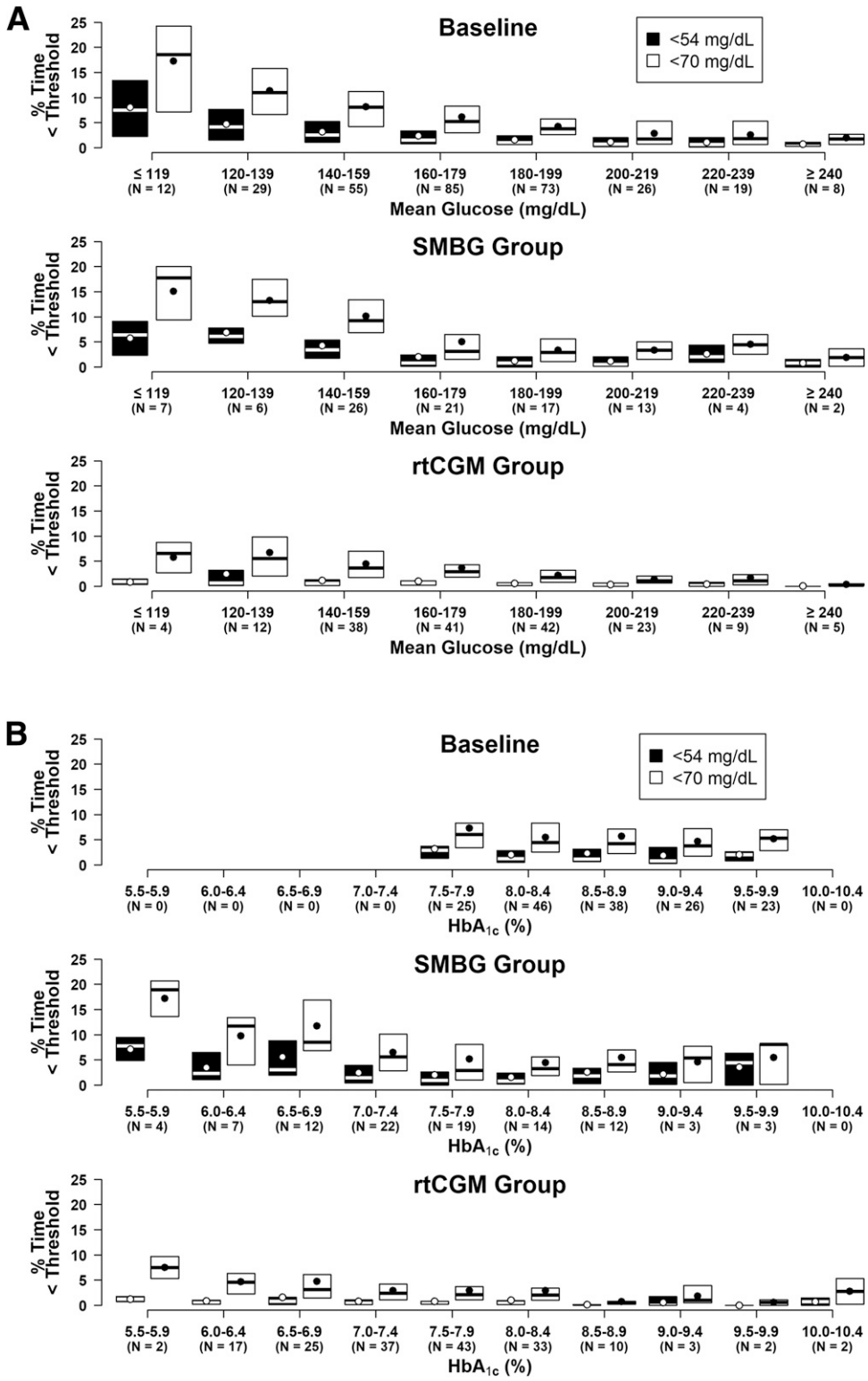

Figure 2—Time spent in hypoglycemia across groups of mean glucose (*A*) or HbA_{1c} (*B*). Dots denote the mean time below threshold, and boxes denote the median (25th, 75th percentiles) time below threshold.

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_{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 with 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_{1c} or variability as assessed by the coefficient of variation (15). Further studies are required to assess the impact of insulin administration on the relationship among HbA_{1c}, glucose variability, and hypoglycemia. Additionally, a large type 1 diabetes registry found a slight J-shaped association between HbA_{1c} and severe hypoglycemia (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 hypoglycemia suggest adopting a less-stringent HbA_{1c} target of $<$8% (64 mmol/mol) (17) to minimize 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 in this study suggests that lower HbA_{1c} targets for people at high risk may be supported with rtCGM usage.

The strengths of this study include the large data set 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 HbA_{1c} 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 HbA_{1c} group, suggesting that this potential limitation does not have a meaningful impact.

This data analysis complements the main results from the DIAMOND and HypoDE data sets 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.

Acknowledgments. The authors thank Dexcom for enabling access to the DIAMOND and HypoDE study data sets.

Funding. This article presents independent research supported by the National Institute for Health Research Biomedical Research Centre at Imperial College Healthcare NHS Trust.

The views expressed are those of the authors and not necessarily those of the National Health Service, the National Institute for Health Research, or the Department of Health.

Duality of Interest. N.O. has received honoraria for speaking and research funding for investigator-initiated studies from Dexcom. P.C. is a former Dexcom employee and shareholder. N.C. has received research support through his respective institution from Dexcom. N.H. and L.H. received an unrestricted research grant to perform the HypoDE study. G.F. has received research support and honoraria for speaking through his respective institution from Dexcom. M.R. has received research funding for an investigator-initiated study from Dexcom.

Author Contributions. N.O., M.G., N.H., G.F., M.R., and L.H. directed the statistical analysis, interpreted the data, and wrote the manuscript. P.C. and N.C. undertook the analysis and contributed to the manuscript. V.M. designed the analysis and contributed to interpreting the results. N.O. and L.H. 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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