Cardiac Effects of Sulfonylurea-Related Hypoglycemia

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OBJECTIVE

To determine the effect of sulfonylurea-related hypoglycemia on cardiac repolarization and ectopy in the setting of well-controlled type 2 diabetes.

RESEARCH DESIGN AND METHODS

Thirty subjects with sulfonylurea-treated type 2 diabetes underwent 48 h of concurrent continuous glucose monitoring and ambulatory electrocardiography. Ventricular repolarization (QTc) and QT dynamicity were analyzed during periods of hypoglycemia (<3.5 mmol/L for >20 min) and compared with periods of euglycemia and hyperglycemia combined. Cardiac ectopy rates during hypoglycemia were compared with ectopy rates when blood glucose was 4–10 mmol/L.

RESULTS

Mean HbA_{1c} was 6.9% (52 mmol/mol). Hypoglycemia was detected in 9 of 30 subjects (30%); episodes were typically nocturnal (67%) and asymptomatic (73%). Hypoglycemia-associated QTc prolongation was seen in five of nine subjects with a large variation in individual response. Higher QT dynamicity, a poor prognostic factor in cardiac disease, was seen in subjects who experienced hypoglycemia compared with subjects who did not (0.193 vs. 0.159 for the nocturnal period; $P = 0.01$). This finding persisted after the hypoglycemic event. The rates of ventricular and supraventricular ectopy demonstrated a nonsignificant trend toward an increase during hypoglycemia (median rate ratio 1.58 and 1.33, respectively). Similar, nonsignificant results were observed in a separate insulin-treated cohort.

CONCLUSIONS

Hypoglycemia, often unrecognized, is a frequent finding in well-controlled sulfonylurea-treated type 2 diabetes. It is associated with the novel finding of increased QT dynamicity and QTc prolongation in some individuals. Our findings suggest sulfonylurea-related hypoglycemia can have detrimental cardiovascular sequelae. Similar effects are also seen in the setting of insulin therapy.

Landmark trials of intensively treated type 2 diabetes, including ACCORD (Action to Control Cardiovascular Risk in Diabetes) (1), ADVANCE (Action in Diabetes and Vascular Disease: Preterax and Diamicron MR Controlled Evaluation) (2), and the VADT (Veterans Affairs Diabetes Trial) (3), have implicated hypoglycemia as a risk marker and renewed interest in exploration of the role iatrogenic hypoglycemia plays in cardiovascular outcomes in the setting of excellent glycemic control (4). Insulin, glinides, and sulfonylureas are the agents most likely to be involved in iatrogenic hypoglycemia. Historically, hypoglycemia was considered to be predominantly a problem of insulin-treated subjects. However, increasing use of continuous glucose monitoring (CGM) has resulted in the identification of hypoglycemia as a common problem in sulfonylurea-treated

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subjects (5,6). Apart from the adverse effect that hypoglycemia can have on quality of life, there is accumulating evidence that hypoglycemia is associated with poor cardiovascular outcomes (7).

Preclinical and clinical studies of the cardiac effects of iatrogenic hypoglycemia have centered mainly on insulin-induced hypoglycemia. Furthermore, relatively few studies have looked at this issue in the free-living setting (8–12). These studies have described increased rates of ectopy, prolongation of ventricular repolarization, and increased rates of ischemia during insulin-related hypoglycemia. The effects of sulfonylurea-related hypoglycemia are less well established.

Certainly, questions regarding the cardiovascular safety of sulfonylurea therapy have been asked for many years (13). There remain theoretical concerns that sulfonylurea therapy may adversely affect action potential propagation throughout the myocardium (14). While sulfonylureas exert their glucose-lowering effect via the binding of the sulfonylurea receptor (SUR1) on pancreatic β-cells, which facilitates closure of an inward rectifying potassium channel and insulin release, the presence of another isoform of the sulfonylurea receptor (SUR2) on cardiac myocytes is a concern. Cross-reactivity between a sulfonylurea and the SUR2 receptor could disrupt potassium influx and myocardial depolarization.

Although observational evidence has suggested an association between sulfonylurea therapy and adverse cardiovascular outcomes, evidence from randomized controlled trials has not been conclusive. In the absence of firm evidence of cardiovascular harm and in the setting of proven blood glucose–lowering efficacy and low cost, sulfonylureas remain prominent second-line treatment options in type 2 diabetes treatment guidelines worldwide (15–17). Individualization of therapy is evidently an important consideration, but the advent of sound evidence questioning the cardiovascular safety of sulfonylureas would challenge the placement of sulfonylurea therapy as a second-line treatment option.

In this context we assessed the cardiovascular effects of second-generation sulfonylurea-related hypoglycemia in a free-living setting. We examined three particular aspects of cardiac electrophysiology known to be associated with poor outcomes, namely, QT prolongation, increased QT dynamicity, and dysrhythmia. QT dynamicity is an index of QT adaptation to heart rate (18), and increased QT dynamicity has been associated with increased mortality after myocardial infarction and in chronic heart failure (19,20). To explore whether our findings were specific to sulfonylurea treatment or to hypoglycemia per se, supplementary analyses of data from ambulant, insulin-treated subjects were undertaken.

RESEARCH DESIGN AND METHODS

This was a single-center observational study of subjects with well-controlled type 2 diabetes who were receiving treatment with sulfonylurea therapy. In addition to sulfonylurea therapy, participants were permitted to be prescribed other antidiabetic agents apart from insulin or glinides. The other inclusion criteria included prior experience of symptomatic hypoglycemia and an ability to perform calibrating finger-prick capillary blood glucose monitoring. Exclusion criteria comprised a diagnosis of type 1 diabetes, current treatment with insulin, presence of left bundle branch block on electrocardiogram, family history of long QT syndrome, and concurrent treatment with any medication known to prolong ventricular repolarization. Consecutive subjects who attended the Royal Prince Alfred Hospital Diabetes Centre and fulfilled the selection criteria were approached to participate. The Sydney Local Health District Ethics Review Committee based at Royal Prince Alfred Hospital granted approval for this study.

Monitoring

All subjects underwent 48 h of blinded CGM and ambulatory electrocardiography (Holter monitoring). After monitoring devices were attached, subjects were asked to go about their usual day-to-day activities and to continue to take their regular medications. The only caveat was that subjects were asked not to immerse the Holter monitor in water because the device used in this study was not waterproof.

The Holter monitoring system used was the GE Seerlight Extend Compact Digital Holter (GE Medical Systems, Milwaukee, WI). Holter electrodes were applied to standard points on the chest and abdomen. Routine monitoring leads were used to connect the electrodes to a recorder that was attached to a holster and worn by the study subject for the study period.

Subjects wore a blinded, time-synchronized CGM for the duration of the study (iPro2; Medtronic, Northridge, CA). Subjects were requested to perform at least four calibrating blood glucose measurements daily using their personal blood glucose meter. They were also asked to record a description of and the time at which any symptoms of hypoglycemia were experienced. Hypoglycemia (blood glucose $<$3.5 mmol/L) on CGM without simultaneous documentation of symptoms in the subject's diary was considered asymptomatic.

CGM Analysis

The iPro2 system determined an average interstitial glucose reading at 5-minute intervals. The calibrating finger-prick capillary blood glucose measurements were manually entered into the cloud-based CareLink Pro software provided by Medtronic at the time of data upload. Data were processed remotely by Medtronic, and a blood glucose reading for each interstitial glucose reading was generated. Hypoglycemia was defined as a blood glucose of $<$3.5 mmol/L. To be considered a valid hypoglycemic episode, the blood glucose was required to remain $<$3.5 mmol/L for $>$20 min, reflecting a clinically significant event. The methodology used here is in keeping with previously reported studies (9,21,22).

Ambulatory Electrocardiography Analysis

The Holter monitoring data were analyzed with MARS ambulatory electrocardiography software (version 8.0 SP3, General Electric 2013). QT interval and heart rate data (in 5-min averages), corresponding to the time-synchronized CGM periods of hypoglycemia, euglycemia, and hyperglycemia, were obtained for each subject. The QT interval used in further analyses was taken as the median QT interval from the available Holter channels.

Corrected QT intervals for each subject were calculated using individually optimized correction formulae. The individual correction method used was based on the parabolic model ($QTc = QT/[RR^{\alpha}]$). The value of α was determined individually for each subject such that the correlation coefficient between QT and RR was minimized (and in all cases $<$0.01). This

method was used in preference to general correction formulae (such as the Bazett or Fridericia correction formulae) because individual heart rate correction has been shown to produce more accurate results (23). As a result of circadian variation of the QT interval, this process was performed for separate daytime (0700–2300) and nocturnal (2300–0700) periods.

Assessment of QTc prolongation was based on guidelines endorsed by the International Society for Computerized Electrocardiology (male: borderline prolongation 430–450 ms, frank prolongation >450 ms; female: borderline prolongation 450–460 ms, frank prolongation >460 ms) (24). In the event that a subject experienced hypoglycemia, a ΔQTc level was calculated. The ΔQTc level was determined by subtracting the average QTc during the period in which the blood glucose was >3.5 mmol/L from the average QTc during the period in which the blood glucose was ≤3.5 mmol/L.

The most commonly used measure of QT dynamicity is the gradient of the linear regression between uncorrected QT and RR intervals (18). To perform QT dynamicity analysis in this study, uncorrected average QT measurements (in ms) at 5-min intervals were plotted against corresponding 5-min average RR measurements (in ms) for each subject. Plots were made for separate daytime (0700–2300) and nocturnal (2300–0700) periods. A linear regression line was fitted to each data set, and the corresponding QT dynamicity was determined by calculating the gradient of this regression line. By this method, QT dynamicity is unitless.

For the purpose of ventricular and supraventricular ectopy analysis, the MARS system performed a fully automated examination of each subject's Holter data set. Individual ectopic beats, couplets, and short runs of ectopy were identified. All ectopic events were combined into a single hourly ectopic event count, and periods of hypoglycemia were compared with periods in which the subject's average blood glucose level remained in the target range (4–10 mmol/L).

Insulin-Treated Cohort

Supplementary analyses were undertaken to examine whether findings of this study apply to hypoglycemia generally or whether they more specifically apply to sulfonylurea-related hypoglycemia. Raw data from a similar CGM and Holter monitoring study of 14 subjects with insulin-treated diabetes were reviewed. The methods and results of that study have been published previously (11). For the insulin study, hypoglycemia was defined as blood glucose <3.9 mmol/L. QT dynamicity and ectopy rate calculations were performed with the methodology used for the sulfonylurea-treated cohort.

Statistical Analysis

Data were analyzed using NCSS 2007 statistical software (NCSS, LLC, Kaysville, UT). Continuous data were checked for normality and are expressed as mean ± SD or as median and interquartile range (IQR). Categorical data are presented as a number with the corresponding percentage. Data were stratified according to whether subjects experienced hypoglycemia during the study period. The Fisher exact test was used to assess for differences in categorical variables, and *t* tests were used to assess for differences in continuous variables. A χ^2 test for independence was performed to assess for differences in the distribution of sulfonylurea dosing between hypoglycemic and nonhypoglycemic groups. Statistical significance was accepted at $P < 0.05$.

On the basis of an anticipated rate of hypoglycemia of 27% (5) and an anticipated increase in QTc during hypoglycemia of 8 ± 6 ms (11), a sample size of 30 subjects was calculated to have 80% power with $\alpha = 0.05$.

RESULTS

Subject Characteristics

The study recruited 30 sulfonylurea-treated subjects, and 9 subjects experienced a total of 15 distinct episodes of hypoglycemia during the study period. Of those subjects who experienced hypoglycemia, the median number of hypoglycemic episodes per study was two (IQR: one episode per study). Subjects were stratified according to the presence or absence of hypoglycemia observed during the study period.

Demographic and baseline characteristics of the hypoglycemic (*n* = 9) and

Table 1—Demographic and baseline characteristics by analysis group

	Hypoglycemic group (*n* = 9)	Nonhypoglycemic group (*n* = 21)	*P* value
Age (years)	62.8 ± 10.2	68.3 ± 7.4	0.1
Male	6 (67)	12 (57)	0.7
Caucasian	7 (78)	17 (81)	1.0
Diabetes duration (years)	15.0 (4.0–16.0)	14.0 (11.0–18.0)	0.4
Oral hypoglycemic therapy			
Mono or dual	5 (56)	9 (43)	0.6
Triple or quadruple	4 (44)	12 (57)	
HbA_{1c} (%) [mmol/mol]	6.6 ± 0.8 [49 ± 6]	7.0 ± 0.9 [53 ± 7]	0.2
BMI (kg/m^2)	31.8 ± 6.3	31.2 ± 5.0	0.8
Overweight	3 (33)	6 (29)	1.0
Obese	5 (56)	12 (57)	1.0
Waist circumference (cm)			
Male	113 ± 13	107 ± 11	0.4
Female	108 ± 10	108 ± 11	1.0
Blood pressure (mmHg)			
Systolic	122 ± 10	131 ± 10	0.03*
Diastolic	72 ± 7	71 ± 9	0.8
Smoking			
Lifelong nonsmoker	3 (33)	15 (71)	
Former smoker	4 (44)	6 (29)	0.1†
Current smoker	2 (22)	0 (0)	
Abstainer from alcohol	4 (44)	4 (19)	0.2
Microvascular complications	1 (11)	8 (38)	0.2
Macrovascular complications	0 (0)	5 (24)	0.3
Hypertension	6 (67)	15 (71)	0.4
Dyslipidemia	5 (56)	18 (86)	0.2

Data are *n* (%), mean ± SD, or median (IQR). *Significant *P* value on *t* test. †For lifelong nonsmoker vs. former and current smoker.

nonhypoglycemic (n = 21) groups are reported in Table 1. The distribution of sex, ethnicity, and obesity were comparable between the two groups, and the median time since diagnosis of type 2 diabetes was similar. The distribution of diabetes treatment regimens was also similar, with approximately half of the subjects in each group receiving mono or dual oral hypoglycemic therapy and half of the subjects in each group receiving triple or quadruple oral hypoglycemic therapy (refer to Supplementary Table 1 for further details). At study enrollment, 29 participants reported gliclazide and 1 participant reported glimepiride as their sulfonylurea treatment. The median daily dose of sulfonylurea (calculated as the modified-release gliclazide dose equivalent) was 60 mg in both the hypoglycemic and nonhypoglycemic groups. The distribution of sulfonylurea dosing was not significantly different between the groups (P = 0.72). There was no significant difference in baseline serum potassium, magnesium, and calcium concentrations between the hypoglycemic and nonhypoglycemic groups (K^+: 4.4 ± 0.2 mmol/L vs. 4.4 ± 0.3 mmol/L, P = 0.96; Mg^{2+}: 0.78 ± 0.05 mmol/L vs. 0.77 ± 0.06 mmol/L, P = 0.65; Ca^{2+}: 2.36 ± 0.09 mmol/L vs. 2.41 ± 0.10 mmol, P = 0.28).

The subjects were well controlled (mean HbA_{1c} 6.9 ± 0.9% [52 ± 7 mmol/mol]) reflecting selection criteria. Neither age nor average HbA_{1c} level was statistically significantly different between the hypoglycemic and nonhypoglycemic groups. There was a nonsignificant excess of macrovascular complications in the nonhypoglycemic group. Baseline systolic blood pressure was significantly lower in the hypoglycemic subjects (122 mmHg vs. 131 mmHg, P = 0.03). Interestingly, both of the current smokers who participated in this study experienced hypoglycemia during the monitoring period. Exclusion of current smokers did not significantly alter ΔQTc, QT dynamicity, or relative rates of cardiac ectopy (Supplementary Table 2).

Hypoglycemia and Ventricular Repolarization

An overview of the experience of hypoglycemia for each of these nine subjects is outlined in Table 2. A predominance of asymptomatic hypoglycemic episodes (11 of 15 [73%]) was identified. This was particularly marked overnight; 9 of 10 (90%) nocturnal hypoglycemic episodes were asymptomatic. There was greater awareness of hypoglycemia during the day; three of the five daytime hypoglycemic episodes were symptomatic. The duration of hypoglycemic episodes ranged from 20 min to more than 4 h. Longer episodes were generally associated with a lower blood glucose nadir.

There was a heterogeneous QTc response to hypoglycemia: some subjects recorded a shortening of QTc (of up to 8 ms), and other subjects recorded a lengthening of QTc (of up to 15 ms). No clear relationship was found between the duration or the depth of hypoglycemia and the change in QTc length during hypoglycemia. Within the subgroup of individuals who experienced QTc prolongation during hypoglycemia, the greatest QTc prolongation was observed overnight.

QT Dynamicity

Results of average pooled daytime and nocturnal QT dynamicity for hypoglycemic and nonhypoglycemic subjects are presented in Fig. 1. Significantly higher nocturnal QT dynamicity was present in the hypoglycemic group compared with the nonhypoglycemic group (0.193 vs. 0.159; P = 0.01). There was a similar higher daytime QT dynamicity in the hypoglycemic group compared with the

Table 2—The hypoglycemic experience of subjects with hypoglycemia

Subject no.	Sex	Time spent in hypoglycemia (min)	Hypoglycemic episodes with duration (min)		Blood glucose nadir (mmol/L)	Average QTc when BGL <3.5 mmol/L (ms)	ΔQTc* (ms)
			Symptomatic	Asymptomatic			
				Daytime (0700–2300)			
24	M	20	0	1 (20)	3.4	430	−1
19	M	155	2 (80, 75)	0	2.2	413	3
20	M	135	1 (25)	1 (110)	2.3	404	3
				Overnight (2300–0700)			
19	M	90	0	1 (90)	2.2	423	−8
10	F	25	0	1 (25)	3.4	448	−6
15	M	25	0	1 (25)	3.3	427	−4
5	F	180	0	2 (80, 100)	3.1	437	−2
16	M	130	0	1 (130)	2.5	433	−1
4	M	75	0	1 (75)	2.7	450	4
1	M	525	1† (280)	1 (245)	2.2	430	10
24	M	25	0	1 (25)	3.2	464	15

QTc measurements in the borderline and frankly prolonged ranges (on the basis of sex) are underlined. F, female; M, male. *ΔQTc = Average QTc for duration BGL ≤3.5 mmol/L – Average QTc for duration BGL >3.5 mmol/L (for separate day time and nocturnal time periods). †This hypoglycemic episode for subject 1 was classified as symptomatic because he reported symptoms consistent with hypoglycemia at the beginning of the episode. His initial treatment of the hypoglycemia was insufficient to resolve the episode, and he went to sleep without confirming correction of the hypoglycemia. As a consequence, his blood glucose level remained low for more than 4 h.

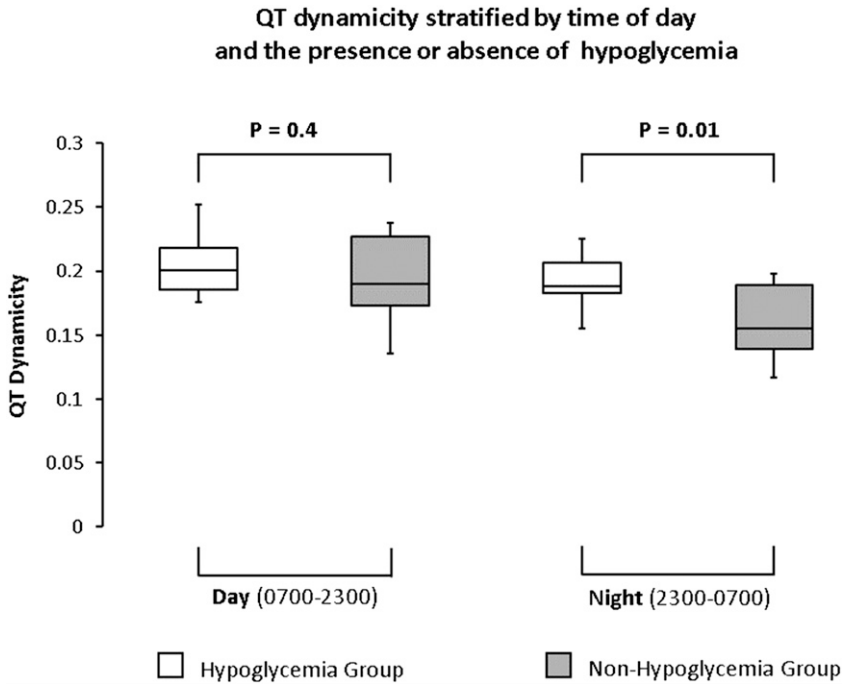

Figure 1—QT dynamicity stratified by glycemic experience (hypoglycemia vs. nonhypoglycemia) and time of day (day 0700–2300 and night 2300–0700). The whiskers of the box-and-whiskers plot represent the 10th and 90th percentiles for each group, and the outer margins of the boxes represent the 25th and 75th percentiles.

nonhypoglycemic group, but this was not statistically significant (0.209 vs. 0.194; P = 0.4). The QT dynamicity results were not significantly different for the hypoglycemic group when analysis was restricted to the pre- and post-hypoglycemic period (nocturnal QT dynamicity: 0.197 vs. 0.159, P = 0.005; daytime QT dynamicity: 0.209 vs. 0.194, P = 0.4).

Ectopy and Arrhythmia

The results of the analysis of ventricular and supraventricular ectopy for the nine subjects who experienced at least one episode of hypoglycemia during monitoring are presented in Table 3. There was considerable intersubject variation in the rate of ventricular and supraventricular ectopy when a subject's blood glucose level was in the 4–10 mmol/L range (classified as euglycemia in Table 3). Ectopic event rates ranged from 0 to 17 events/h. Most subjects had increased rates of ventricular and supraventricular ectopy during hypoglycemia (five of nine and seven of nine, respectively). Although not statistically significant, the point estimate for the median rate ratio for ventricular (1.58) and supraventricular ectopic events (1.34) was greater than 1.0, suggesting a trend toward increased ectopy during sulfonylurea-related hypoglycemia.

With regard to arrhythmias, episodes of atrial fibrillation (n = 1) and nonsustained ventricular tachycardia (n = 1) were observed; these episodes were unrelated to hypoglycemia. Of the 30 participants, 29 were transiently observed to have a heart rate of <60 bpm during sleep; however, no clinically significant bradycardia (heart rate <40 bpm) was detected at any level of glycemia.

Insulin-Treated Cohort

Characteristics of the insulin-treated cohort are outlined in Supplementary Table 3. In summary, the insulin-treated cohort were of a similar age (62 ± 8 years) and had a similar duration of diabetes (average >15 years) as the main study cohort but with a high prevalence of ischemic heart disease (8 of 14 participants [57%]). Of the 14 insulin-treated subjects, 5 experienced hypoglycemia.

Within the insulin-treated cohort, average pooled daytime QT dynamicity was numerically greater in the subgroup that experienced hypoglycemia than in the subgroup that did not (0.180 vs. 0.164; P = NS). Similarly, average pooled nocturnal QT dynamicity was greater in the subgroup that experienced hypoglycemia (0.186 vs. 0.175; P = NS) (Supplementary Fig. 1). Restricting the cohort to subjects who received insulin without concurrent sulfonylurea therapy gave comparable results (P = NS) (Supplementary Figs. 2 and 3).

The median ventricular ectopy rate ratio in the insulin-treated cohort for those

Table 3—The average hourly rate of ventricular and supraventricular ectopic events during hypoglycemia and euglycemia for the nine subjects who experienced hypoglycemia during monitoring

	Ventricular ectopic events per hour			Supraventricular ectopic events per hour		
Subject	During hypoglycemia	During euglycemia	Rate ratio	During hypoglycemia	During euglycemia	Rate ratio
1	1.14	0.56	2.03	5.43	4.19	1.30
4	17.0	10.8	1.58	1.33	1.00	1.33
5	0	0.03	0	1.23	1.06	1.16
10	2.00	2.67	0.75	1.38	0.45	3.03
15	0	0.07	0	0	0.02	0
16	0.44	0.61	0.73	15.11	8.45	1.79
18	1.22	0.17	7.09	0.22	0.41	0.54
19	1.14	0.54	2.11	0.86	0.60	1.43
24	2.50	1.16	2.15	3.33	2.24	1.49
	Median rate ratio for group (95% CI)		1.58 (0–2.15)	Median rate ratio for group (95% CI)		1.33 (0.54–1.79)

subjects who experienced hypoglycemia was 2.1, and the median supraventricular ectopy rate ratio in the insulin-treated cohort was 0 (Supplementary Table 4).

CONCLUSIONS

Cardiovascular disease remains the leading cause of death for subjects with diabetes (25). The evidence base supporting the maintenance of stringent glycemic control targets to prevent complications in subjects with diabetes has grown during the past 20 years, and the cardiovascular sequelae of such an approach has gained much attention after the publication of results from ACCORD, ADVANCE, and VADT. In the context of both excellent glycemic control and sulfonylurea treatment, we observed frequent, asymptomatic nocturnal hypoglycemia and a heterogeneous QTc response to hypoglycemia with clinically significant prolongation in some but not all individuals. In addition, we report the novel observation of an unfavorable, increased QT dynamicity in hypoglycemia-prone individuals warranting further investigation.

Our findings are somewhat concerning given the frequency of hypoglycemia detected: 30% of study participants experienced at least one episode of hypoglycemia during a relatively short period of monitoring. Most hypoglycemia was nocturnal and asymptomatic. Previous studies that did not use CGM and instead relied on self-reported hypoglycemia likely overlooked many nocturnal hypoglycemic episodes because they were not detected by study participants. In a recent meta-analysis of two clinical trials involving 1,040 patients taking gliclazide, the rate of mild hypoglycemia attributable to gliclazide was 1.4% per year (26).

The consequence of sulfonylurea-related hypoglycemia on the cardiovascular system is an issue of central importance. The hypothesis that hypoglycemia prolongs ventricular repolarization (potentially predisposing to arrhythmia) certainly has support (10,27). Although QTc prolongation predisposes to the phenomenon of early afterdepolarization and torsades de pointes, whether severe hypoglycemia causes increased rates of sudden cardiac death and whether it is by this mechanism remains unclear. There are certainly other factors associated with hypoglycemia (including hypokalemia and catecholamine excess) that could contribute to adverse cardiac outcomes (28). Nonetheless, QTc prolongation during hypoglycemia is a clinical concern that can be readily identified during routine Holter monitoring.

Interestingly, the results of this study do not suggest that there is a uniform ventricular response to sulfonylurea-induced hypoglycemia. Heterogeneous findings have been reported by others studying QTc during hypoglycemia in type 2 diabetes, albeit while on insulin therapy (9), and the reason for this intersubject variation is unclear. Neither the duration nor the depth of hypoglycemia seems to be able to explain the discrepancy of ΔQTc response (refer to the Supplementary Analysis online for further details). Cardiac preconditioning to hypoglycemia may be postulated to explain some of the difference in intersubject ventricular repolarization response (28,29); however, testing this hypothesis during our observational study was not possible.

Although detection of QTc prolongation is an important means of identifying those subjects who may be at risk for arrhythmia, it is a static measure. As its name suggests, QT dynamicity is a dynamic measure and provides complementary information to QTc regarding ventricular repolarization. Our novel finding of increased nocturnal QT dynamicity in hypoglycemia-prone subjects is concerning in light of previously reported associations of increased QT dynamicity with increased mortality (19,20). QT dynamicity reflects sympathoadrenal activation and has a circadian rhythm, with higher QT dynamicity during daylight hours corresponding to the period in which there is higher sympathetic tone (30). Lower QT dynamicity is generally observed at night during sleep when there is a predominance of parasympathetic tone. Because a steeper QT/RR gradient reflects decreased vagal tone and/or increased sympathetic tone, it has been proposed that higher QT dynamicity might contribute to a greater vulnerability to arrhythmias (18).

An association between increased QT dynamicity and the occurrence of nocturnal hypoglycemia may surprise some clinicians. Sleep-related hypoglycemia-associated autonomic failure, described by Banarer and Cryer (31) in the setting of hyperinsulinemic clamp-induced hypoglycemia in type 1 diabetes, would be expected to blunt the sympathoadrenal response to hypoglycemia and thereby reduce QT dynamicity. Consequently, it would seem that sleep-related hypoglycemia-associated autonomic failure did not significantly affect our subjects with type 2 diabetes. Our results are consistent with a sustained elevation of sympathetic tone that persisted outside the time of hypoglycemia. Our findings are similar to the prolonged counterregulatory response observed by Jennum et al. (32) in their study of the effect of nocturnal hypoglycemia on sleep in subjects with type 2 diabetes.

Collectively, the results observed in our study of sulfonylurea-treated subjects suggest an association between hypoglycemia and abnormal ventricular repolarization. In the absence of a comparator group not treated with sulfonylurea, whether the results apply to hypoglycemia per se or whether the results more specifically apply to sulfonylurea-related hypoglycemia is unclear. Analyses of data from an insulin-treated cohort have helped to provide preliminary insights into this question.

In a study of insulin treated subjects, Lee et al. (11) found hypoglycemia was associated with a relatively small (8 ± 6 ms) average increase in QTc (Bazett correction). This contrasts with the heterogeneous response in QTc (individually optimized correction) observed in the current study. We note that each study used different correction formulae, which could potentially account for this variation.

Nevertheless, in an analysis of raw data from this insulin-treated cohort, we observed higher QT dynamicity in those subjects who experienced hypoglycemia. Although not statistically significant, this observation is in keeping with our observations in the sulfonylurea-treated cohort and suggests an association with iatrogenic hypoglycemia rather than sulfonylurea treatment specifically. Although these QT dynamicity results are concerning, they are from a small number of individuals and suggest the need for larger, more detailed studies and longitudinal follow-up to be more definitive, including to further determine the strength and temporal association of hypoglycemia propensity with QT dynamicity.

Frequent ventricular ectopy has been associated with increased cardiac mortality in subjects with established heart disease, and a recent meta-analysis has suggested that this finding also holds

true in the general population (33). Stahn et al. (8) reported increased rates of atrial and ventricular dysrhythmia during hypoglycemia in a combined CGM and Holter monitoring study of 30 subjects with type 2 diabetes and cardiovascular disease. In our sulfonylurea-treated cohort (with lower rates of cardiovascular disease), a similar trend in increased ventricular and supraventricular ectopy during hypoglycemia was observed, and although these results failed to demonstrate statistical significance, they are in concordance with previous work.

This study has a number of strengths. To our knowledge, this was the first real-world, simultaneous CGM and Holter monitoring study focusing on sulfonylurea-treated subjects. This study considered a novel approach to the analysis of changes in ventricular repolarization during hypoglycemia by way of assessment of QT dynamicity. The analysis of data from sulfonylurea-treated patients and data from insulin-treated patients has also provided insight into some of the underlying issues.

This research had a number of limitations. We were only able to study a small number of sulfonylurea-treated subjects, and for logistical reasons, these subjects could only be monitored for a relatively short period of time. The inclusion of smokers in the study cohort may be criticized as introducing smoking as a potential confounder. Smokers were observed to have a higher incidence of hypoglycemia in our study, and this finding has been documented in the literature (34,35). Smoking has been postulated to reduce insulin clearance, leading to hyperinsulinemia and increased hypoglycemia (36). However, supplementary analyses of our data (with current smokers excluded) demonstrated that smoking did not significantly alter the results of any of our end points of interest.

In addition, we are unable to comment on the effects of sulfonylurea-related hypoglycemia in the setting of established cardiovascular disease; none of the sulfonylurea-treated subjects with a history of cardiovascular disease experienced hypoglycemia during monitoring.

Overall, the finding of significantly increased nocturnal QT dynamicity associated with sulfonylurea-related hypoglycemia suggests a need for further studies in this area. However, the data from this study can be seen to add to a growing body of evidence that identifies hypoglycemia as an important management issue with respect to cardiovascular safety and adds perspective to the recommendation that an emphasis be placed on pharmacotherapy with low hypoglycemic risk and benign cardiovascular outcome data (37–40).

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Author Contributions. T.L.M., J.W., and T.W. designed the study and developed the methodology. T.L.M. and L.M. performed the analysis. T.L.M., J.W., S.M.T., and T.W. contributed to the analysis and interpretation of the data. T.L.M. wrote the manuscript. J.W., B.A.B., D.K.Y., S.M.T., and T.W. reviewed and edited the manuscript. T.L.M. and T.W. are the guarantors of this work and, as such, had access to all study data and take responsibility for the data integrity and accuracy of the data analysis.

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