Effect of Intensive Glycemic and Blood Pressure Control on QT Prolongation in Diabetes: The ACCORD Trial

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Compared with standard glycemic control, intensive glycemic control caused increased mortality in the Action to Control Cardiovascular Risk in Diabetes (ACCORD) trial. Preliminary data from several studies suggest that intensive glycemic control is associated with QT prolongation, which may lead to ventricular arrhythmias as a possible explanation of this increased mortality. We sought to assess the effects of intensive glycemic control and intensive blood pressure control on the risk of incident QT prolongation. Cox proportional hazards models were used to compare the risk of incident QT prolongation (>460 ms in women or >450 ms in men) in the intensive versus standard glycemic control arms. Over a combined 48,634 person-years of follow-up (mean 4.9), 634 participants (6.4%) developed a prolonged QTc. Participants in the intensive glycemic control arm did not have an increased risk of QT prolongation. Similarly, a strategy of intensive blood pressure control did not result in a significant change in risk of prolonged QTc. Sensitivity analyses using alternative QT correction formulas (Hodges and Bazett) yielded overall similar findings. In conclusion, the increased mortality observed in the intensive glycemic control arm in the ACCORD trial is not likely to be explained by QT prolongation leading to lethal ventricular arrhythmias.

The prevalence of diabetes continues to grow, as does the collective toll it takes on population health (1,2). In response to the observation that patients with type 2 diabetes mellitus (DM2) have a several-fold increased risk of cardiovascular disease and that, among those with DM2, this risk increases exponentially as glycated hemoglobin (HbA_{1c}) increases above 8%, the Action to Control

Cardiovascular Risk in Diabetes (ACCORD) trial was designed (3–6). Among those participants randomized to a strategy of intensive glycemic control, there was an increased risk of death, both all-cause and cardiovascular (7). To date, the mechanism of this harm remains unclear (8).

There is a growing body of literature suggesting that glycemic control can affect cardiac repolarization, which in turn influences the risk of lethal ventricular arrhythmias (9). The heart rate–corrected QT interval is a well-validated and reproducible measure of cardiac repolarization that has been shown to be associated with risk of lethal ventricular arrhythmia (10). A strategy of aggressive glycemic control carries with it a heightened risk of hypoglycemia, which directly induces both QT prolongation (11) and QT dispersion (12). We hypothesized that a strategy of intensive glycemic control would be associated with an increased risk of new QT prolongation in ACCORD and that this might explain the increased risk of cardiovascular and all-cause mortality observed in the intensive glycemic control arm.

RESEARCH DESIGN AND METHODS

Study Design and Population
The design and conduct of ACCORD have previously been described (6). Briefly, ACCORD was a randomized clinical trial designed to assess the utility of two strategies of glycemic control (intensive vs. standard), two strategies of blood pressure control (intensive vs. standard), and two strategies of lipid control (simvastatin plus fenofibrate vs. placebo). Inclusion criteria were a history of DM2, an HbA_{1c} level ≥7.5%, and either age ≥40 years with

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prevalent cardiovascular disease or age ≥55 years with a substantial amount of atherosclerosis, albuminuria, left ventricular hypertrophy, or two or more additional risk factors from the following set: dyslipidemia, hypertension, smoking, or obesity. Exclusion criteria included a BMI of >45 kg/m^2, a serum creatinine level of >1.5 mg/dL, and other serious illnesses. With the sponsorship of the National Heart, Lung, and Blood Institute (NHLBI), the study was conducted at 77 clinical sites through the U.S. and Canada and was approved by the relevant institutional review boards. All participants provided written informed consent.

The trial enrolled 10,251 participants with DM2 at high risk of cardiovascular events. All participants were randomly assigned to either the intensive or standard glycemic control arms as part of the ACCORD glycemia trial (13). Of these, 5,518 were concomitantly enrolled in the ACCORD lipid trial, in which they were randomized to either simvastatin plus fenofibrate or simvastatin plus placebo (14). The remaining 4,733 participants were enrolled in the ACCORD blood pressure trial; they were randomized to either intensive or standard blood pressure control strategies (15).

For our analysis, we included all ACCORD participants with a baseline electrocardiogram (ECG) of quality suitable for interpretation, a normal Framingham QTc interval at baseline, and at least one follow-up ECG. Of the 10,251 participants in the ACCORD trial, 46 were excluded for missing or poor-quality ECGs and 319 were excluded for baseline prolonged QTc, leaving 9,886 eligible participants. Outcomes ascertained by the end of the planned 7-year follow-up period were included in this analysis.

QTc Interval
At all ACCORD sites, baseline and follow-up resting study ECGs were obtained by trained electrocardiographers via standardized protocol on a GE Marquette Medical Systems (Milwaukee, WI) MAC 1200 electrocardiograph at a sampling rate of 500 Hz. All ECGs were digitally transmitted to a central core laboratory for processing and coding: the Epidemiological Cardiology Research Center (EPICARE) at Wake Forest School of Medicine. Study ECGs were visually checked for quality and then automatically processed using the GE Marquette Medical Systems 12SL program, version 2001. QTc interval was calculated using the raw QT interval and the heart rate according to the recommendations of the American Heart Association, American College of Cardiology, and Heart Rhythm Society for the Standardization and Interpretation of the Electrocardiogram (16). The Framingham QT correction for heart rate, where QTc$_{Framingham}$ = QT + 154 * (1 − 60/HR) (17), was used. As a sensitivity analysis to allow for comparison with other studies, we also repeated our analysis using alternative QT heart rate correction formulas, including the Hodges correction, where QTc$_{Hodges}$ = QT + 1.75 * (HR − 60) (18), and the Bazett correction, where QTc$_{Bazett}$ = QT * (HR/60)$^{1/2}$ (19).

$$QT_{Framingham} = QT + 154 \cdot \left(1 - \frac{60}{HR}\right)$$

$$QT_{Hodges} = QT + 1.75 \cdot (HR - 60)$$

$$QT_{Bazett} = QT \cdot \left(\frac{HR}{60}\right)^{1/2}$$

Other Variables
Anthropomorphic measures, including height, weight, and blood pressure, were collected during study visits. Demographic covariates were determined using participant self-report at enrollment. History of cardiovascular disease was defined as prior MI, stroke, arterial revascularization, angina with ischemic changes on ECG at rest, pathological changes on a graded exercise test, or cardiac imaging results suggestive of ischemia.

Outcome Variables
Our outcome of interest was time to first measured QTc meeting criteria for prolongation, which we defined as a QTc >460 ms in women or >450 ms in men. The schedule of ECG recordings performed as part of the ACCORD trial has previously been reported (6).

Statistical Methods
Baseline characteristics of the study population assigned to each treatment arm were compared using mean ± SD for continuous variables and frequency (percentage) for categorical variables.

Kaplan-Meier analyses were used to compare survival free of incident QT prolongation between treatment arms, with the log-rank used to assess for between-group differences. Cox proportional hazards modeling was used to compare the risk of incident QT prolongation as a function of treatment arm assignment, generating hazard ratios (HRs) and 95% CIs. The assumption of time-independent proportionality of risks was assessed by examining the Martingale residual plots and by incorporating the ln of follow-up time as a time-dependent covariate; there was no evidence of substantial deviation from the assumed time-independent proportionality of risk. We then examined the consistency of the observed relationships between treatment arm assignment and the risk of incident QT prolongation in prespecified subgroups, using statistical tests of interaction between the treatment assignment and the subgroup of interest within the Cox models. Two-sided P values <0.05 were considered to be statistically significant. All statistical analyses were conducted at Wake Forest University School of Medicine using SAS, version 9.4 (SAS Institute, Cary, NC).

Data and Resource Availability
The data sets analyzed during the current study are available from the NHLBI Biological Specimen and Data Repository Information Coordinating Center.

RESULTS

The distribution of QTc$_{Framingham}$ at baseline is graphically depicted in Fig. 1. At study enrollment, 316 of 10,205 ACCORD participants had a prolonged QTc$_{Framingham}$. The average QTc$_{Framingham}$ among those who did not have a baseline prolonged QTc$_{Framingham}$ was 411 ± 17 ms. At study exit, the average QTc$_{Framingham}$ among these participants was 417 ± 21 ms. Baseline characteristics of the study population are presented in Table 1. Over a combined 48,634 person-years of follow-up (mean 4.9), 634 participants (6.4%) developed a prolonged QTc$_{Framingham}$.

Compared with those participants randomized to the standard glycemic control arm, participants in the intensive glycemic control arm did not have an increased risk of incident QT prolongation (HR 0.95, 95% CI 0.81–1.11, P = 0.53) (see Table 2 and Fig. 2). Sensitivity analyses using Hodges correction and Bazett correction yielded similar findings.

Our secondary analysis compared the risk of incident QT prolongation in those randomized to intensive blood pressure control, with the standard blood pressure control group as the reference. Here, we found no evidence of

a significant change in risk of prolonged QT (HR 0.84, 95% CI 0.66–1.06, P = 0.15) (see Table 3). Sensitivity analyses demonstrated no effect of intensive blood pressure control on the risk of incident QT prolongation when Hodges correction was used. There was evidence of decreased risk of incident QT prolongation with use of Bazett correction.

To explore how the different QT correction formulas performed, we determined the correlation between the heart rate–corrected QT by each formula and the heart rate. The Framingham correction performed best, with an r^2 of 0.04, while Hodges correction had an r^2 of 0.09 and Bazett correction had an r^2 of 0.10.

DISCUSSION

Principal Findings

In this analysis of the ACCORD trial, we examined the effects of strategies of intensive glycemic control and intensive blood pressure control on the risk of incident QT prolongation. The key findings include the following: *1*) intensive glycemic control compared with standard glycemic control did not result in a higher risk of incident QT prolongation, and *2*) intensive blood pressure control
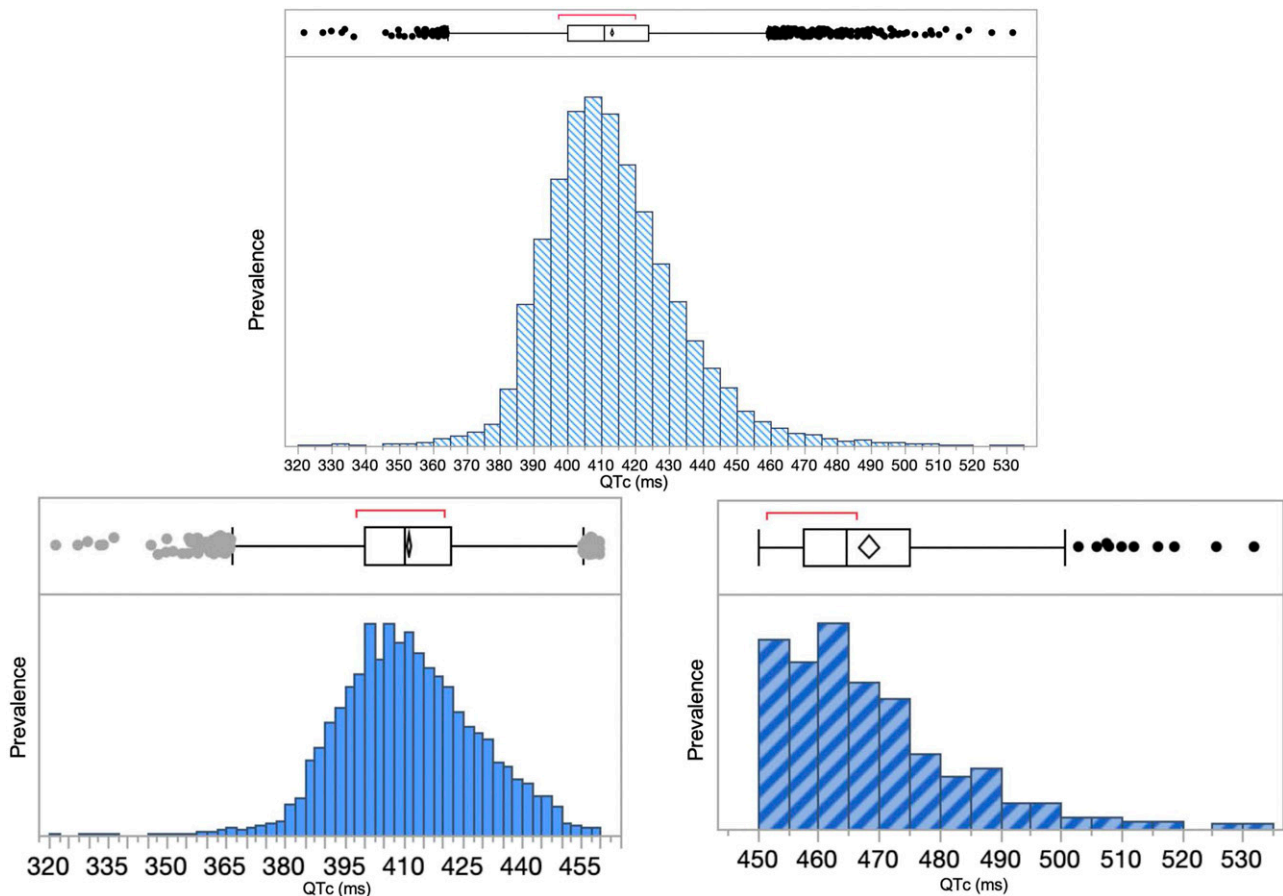

Figure 1 — Baseline QTc (Framingham) of the ACCORD study population (*n* = 10,205). Histogram of the baseline QTc of the study population in 10-ms bins (top) and separated into those with and without baseline prolonged QTc (bottom).

Table 1—Baseline characteristics of the ACCORD participants, stratified by trial arm

	Glycemic control		Blood pressure control	
	Intensive	Standard	Intensive	Standard
n	4,740	4,708	2,210	2,159
Age (years)	62.6 ± 6.6	62.7 ± 6.6	62.7 ± 6.6	62.7 ± 6.7
Sex (% male)	61.2	61.3	52.3	52.0
Race (% white)	62.1	62.2	60.1	57.6
Years with diabetes	10.7 ± 7.6	10.8 ± 7.6	11.0 ± 7.9	10.9 ± 7.7
Current smoking (%)	14.3	13.6	13.1	13.4
Weight (kg)	93.3 ± 18.5	93.4 ± 18.4	91.8 ± 17.5	92.0 ± 19.1
Height (cm)	170.0 ± 9.8	170.0 ± 9.8	169.0 ± 9.8	168.8 ± 10.0
Waist circumference (cm)	106.6 ± 13.7	106.7 ± 13.6	105.3 ± 13.3	105.9 ± 14.1
BMI (kg/m^2)	32.3 ± 5.4	32.2 ± 5.4	32.1 ± 5.4	32.3 ± 5.6
Systolic BP (mmHg)	136.3 ± 17.0	136.5 ± 17.1	139.1 ± 16.0	139.4 ± 15.4
Diastolic BP (mmHg)	74.9 ± 10.6	75.1 ± 10.7	76.0 ± 10.5	76.1 ± 10.2
Heart rate	72.8 ± 11.7	72.6 ± 11.7	73.1 ± 11.8	73.1 ± 11.4
Total cholesterol (mg/dL)	183.6 ± 42.2	183.6 ± 41.7	194.1 ± 45.0	191.6 ± 44.4
HDL (mg/dL)	41.9 ± 11.8	42.0 ± 11.5	46.2 ± 13.2	46.4 ± 14.1
LDL (mg/dL)	105.0 ± 34.0	105.1 ± 33.9	110.9 ± 37.2	108.9 ± 35.9
VLDL (mg/dL)	36.8 ± 25.0	36.5 ± 24.0	37.0 ± 29.2	36.3 ± 28.7
Triglycerides (mg/dL)	191.8 ± 149.6	189.7 ± 149.5	195.8 ± 179.5	191.5 ± 185.6
HbA$_{1c}$ (%)	8.3 ± 1.1	8.3 ± 1.1	8.4 ± 1.1	8.3 ± 1.1

Data for continuous variables are mean ± SD, and data for categorical variables are frequency (percentage). BP, blood pressure. P value as calculated by ANOVA for continuous and χ^2 for categorical variables.

compared with standard blood pressure control did result in a higher risk of incident QT prolongation.

These results suggest that the excess mortality observed in the intensive glycemic control arm of ACCORD is not likely to be explained by an increased rate of QT prolongation as a mechanism of lethal ventricular arrhythmias. Neither intensive glycemic control nor intensive blood pressure control appears to significantly affect the risk of incident QT prolongation in the population as a whole.

Results in Context

The QT interval is a marker of both ventricular depolarization and repolarization. Lengthening of the QT interval is seen in numerous cardiovascular pathologies, including subclinical atherosclerosis (20), coronary artery disease (21), and heart failure (22). Furthermore, a prolonged QT interval is generally associated with worse prognosis, including death (23–25), cardiovascular death (26), coronary artery disease (27), and stroke (28). Beyond the importance of a baseline prolonged QT, new-onset prolonged QT is an emerging marker of risk (29,30). Though prior analyses have demonstrated that medications only account for a minority of the attributable risk of QT prolongation (31), the use of hypoglycemic agents and intensity of glycemic control in patients with diabetes represents a modifiable risk factor for QT prolongation. The ACCORD trial offers an opportunity to explore the relationship

between long-term glycemic control and the risk of QT prolongation.

It has been shown that patients with diabetes have a higher prevalence of prolonged QT and decreased repolarization reserve (32), as well as other electrocardiographic markers of derangements in repolarization with the commensurate increase in risk of arrhythmic death, such as abnormal microvolt T-wave alternans (33). This, coupled with the QT-prolonging effects of commonly used hypoglycemic agents and the demonstrated hypoglycemia-induced QT prolongation during presentations for hypoglycemic crises (34), make patients with diabetes particularly vulnerable to the proarrhythmic effects of QT prolongation. Despite these concerns, we found no increased risk of QT prolongation in those randomized to intensive glycemic control in ACCORD.

There are multiple possible reasons for this null finding. Though hypoglycemic agents can individually prolong the QT interval and cause QT dispersion (35), perhaps the long-term effects of intensive glycemic control have sufficient salutary effects on cardiac remodeling to outweigh the QT-prolonging effects of the medications. Prior studies assessing how short-term intensive glycemic control influences the heterogeneity of repolarization that is present in uncontrolled diabetes have found no improvement, despite a decrease in mean HbA$_{1c}$ from 10 to 7% (36), though it is again difficult to tease out the effects of glycemic control from the effects of the medications used to

Table 2—Effect of intensive glycemic control on the risk of developing new QT prolongation in ACCORD participants

Treatment arm	Participants	Events (n)	Event rate (% per year)	HR (95% CI)	P
Framingham QTc formula (n = 9,886)				0.95 (0.81–1.11)	0.53
Intensive glycemic control	4,929	308	1.27		
Standard glycemic control	4,957	326	1.33		
Hodges QTc formula (n = 9,795)				0.88 (0.77–1.01)	0.07
Intensive glycemic control	4,878	381	1.59		
Standard glycemic control	4,917	437	1.80		
Bazett QTc formula (n = 9,448)				0.87 (0.75–1.01)	0.07
Intensive glycemic control	4,740	330	1.43		
Standard glycemic control	4,708	382	1.63		

The numbers of study participants and events (incident QT prolongation) and HRs from the Cox models are provided for each of three QT heart rate correction formulas. The number of participants differs between analyses because different numbers of participants met criteria for QT prolongation at baseline (which was an exclusion criteria) depending on which heart rate correction formula was used.

achieve this goal. Alternatively, perhaps finer measures of glycemic control than treatment assignment would better tease out the relationship between euglycemia and the QT interval. For example, some studies have found that glycemic variability may be more tightly linked with QT prolongation and dispersion than just median HbA$_{1c}$ (37).

Heart Rate Correction

The results are presented using three QT heart rate correction formulas: Framingham, Hodges, and Bazett. The problems with Bazett correction, which is the formula that was developed first (38) and is in most widespread use, have been well described (39,40). Our analysis of the residual correlation after application of the three rate correction formulas was consistent with prior studies; specifically, we found that the Bazett formula had the highest residual correlation and thus performed most poorly. Application of the Bazett correction also led to the highest prevalence of baseline QT prolongation, with 7.4% of the study population meeting criteria for baseline prolonged QT by the Bazett formula versus 3.1% by the

Framingham formula. With these caveats in mind, the results of the analysis incorporating the Bazett formula should be viewed with some skepticism, and, in fact, they are divergent from the results of the blood pressure treatment analyses using the Framingham and Hodges corrections, though the results of the Bazett analysis are included here for completeness.

Effects on Those With Baseline Prolonged QT

Our primary analysis explored the effects of intensive glycemic control on the risk of incident QT prolongation. However, intensive glycemic control could also lead to harm if it caused more severe QT prolongation among those participants with prolonged QT at baseline, so we performed a supplementary analysis to explore how intensive glycemic control affects QT interval in those participants with baseline QT prolongation. Among those with baseline QT prolongation using the Framingham correction, the QTc was similar in the standard glycemic control and intensive glycemic control arms at 468.6 ± 13.6 and 467.8 ± 15.3, respectively. During the trial, those participants assigned to standard glycemic control had shortening
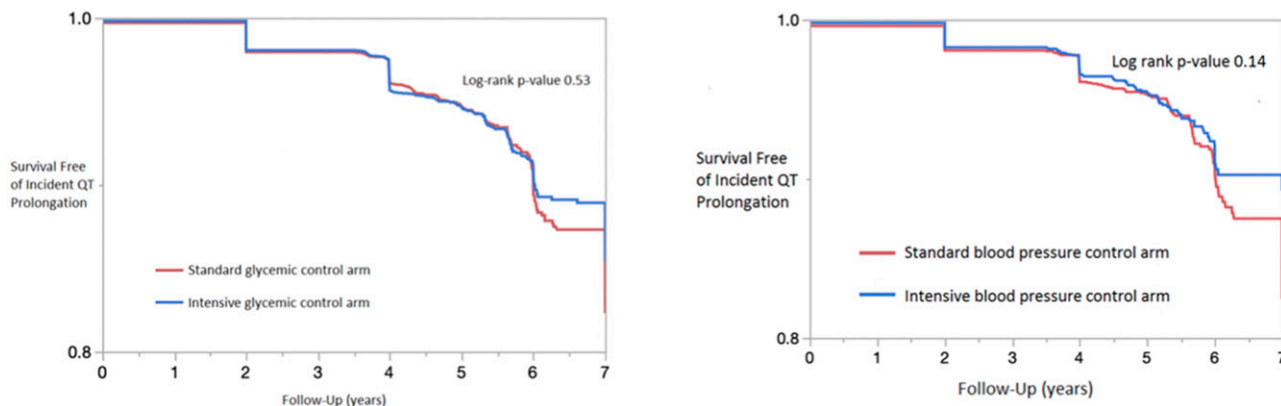

Figure 2—Kaplan-Meier curves of survival free of incident QT prolongation demonstrate that participants in the intensive glycemic control arm and those in the standard glycemic control arm had similar rates of incident QT prolongation (at left); similarly, those in the intensive blood pressure control arm and those in the standard blood pressure control arm had similar rates of incident QT prolongation (at right).

Table 3—Effect of intensive blood pressure control on the risk of developing new QT prolongation in ACCORD participants

Treatment arm	Participants	Events	Event rate (% per year)	HR (95% CI)	P
Framingham QTc formula (n = 4,583)				0.84 (0.66–1.06)	0.15
Intensive blood pressure control	2,304	119	1.05		
Standard blood pressure control	2,279	148	1.30		
Hodges QTc formula (n = 4,550)				1.05 (0.86–1.30)	0.62
Intensive blood pressure control	2,282	178	1.59		
Standard blood pressure control	2,268	176	1.55		
Bazett QTc formula (n = 4,369)				0.79 (0.63–0.99)	0.04
Intensive blood pressure control	2,210	135	1.24		
Standard blood pressure control	2,159	170	1.58		

The numbers of study participants and events (incident QT prolongation) and HRs from the Cox models are provided for each of three QT heart rate correction formulas. The number of participants differs between analyses because different numbers of participants met criteria for QT prolongation at baseline (which was an exclusion criteria) depending on which heart rate correction formula was used.

of their QTc to 453.7 ± 31.0, while those assigned to intensive glycemic control had shortening of their QTc to 455.9 ± 29.4. The average ± SD change in QTc over the course of the trial in those with baseline prolonged QTc was −14.9 ± 28.2 in the standard glycemic control arm and −12.2 ± 26.6 in the intensive glycemic control arm. Therefore, it appears that intensive glycemic control did not cause prolongation of the QTc, even among those participants with baseline QT prolongation.

Interaction With Neuropathy
In light of the fact that prior literature has demonstrated that there may be a differential effect of intensive glycemic control on mortality depending on select baseline participant characteristics, including prevalent self-reported neuropathy, higher baseline HbA$_{1c}$ (>8.5), and regular aspirin use (41), we performed a supplementary analysis in which we assessed for interaction between these participant characteristics and baseline prolonged QT with regard to the outcome of mortality. Interaction P values (before correction for multiple comparisons) ranged from 0.11 to 0.48, suggesting that there is no evidence of a differential effect of intensive glycemic control on mortality due to an interaction between baseline prolonged QT and prevalent self-reported neuropathy, higher baseline HbA$_{1c}$ (>8.5), and regular aspirin use. Though prior literature has identified cardiac autonomic neuropathy being associated with increased mortality risk in ACCORD but not explaining a differential effect of intensive glycemic control (42), we also assessed for interaction between baseline QT prolongation and cardiac autonomic neuropathy with regard to intensive glycemic control and mortality, again finding no evidence of interaction (P value 0.91).

Limitations and Strengths
Our findings should be interpreted in the context of their limitations. Though we sought to assess the effects of intensive glycemic control and intensive blood pressure control on the risk of lethal ventricular arrhythmia, we were limited to examining the effects on the QT interval, which is a marker of this risk but not the clinical end point

of interest. Our outcome variable was incident QT prolongation, defined by exceeding an agreed-upon sex-specific normal upper limit. The QT interval is a continuous variable with no upper limit of risk, so operationalizing QT prolongation in this way may affect our results, though sensitivity analyses using alternative thresholds were concordant. However, population studies assessing the risk of QT prolongation have used this definition, which is also used clinically, which maximizes the external validity of our findings. The heart rate QTc can be calculated using several formulas—we chose the Framingham correction because of the evidence in its favor (43), but sensitivity analyses incorporating other commonly used QT corrections (Hodges and Bazett) yielded overall similar results.

In addition, while we demonstrate the effects of intensive glycemic control and intensive blood pressure control on the QT interval, there are emerging data suggesting that certain components of the QT interval may be more predictive of the risk of sudden cardiac death than others, such as the T wave onset to T peak component (44); thus, it is possible that intensive glycemic control may increase the risk of ventricular arrhythmia by increasing T-wave dispersion, which would not be reflected in the QT interval alone. Unfortunately, our data do not address this question, as our data do not include the raw ECG format, which could be used to analyze the duration and morphologies of the components of the T wave, though this could be valuable in better understanding the effects of intensive glycemic control on cardiac repolarization and the risk of ventricular arrhythmia. Future studies should include detailed morphological analysis of the T wave and its components to better characterize the arrhythmia risk associated with perturbations in ventricular repolarization. Furthermore, given that there were more hypoglycemic episodes in the intensive glycemic control group and that hypoglycemia can induce transient changes in ventricular repolarization, it is possible that intensive glycemic control could have led to a propensity for QT prolongation that was only manifest in the setting of hypoglycemic episodes, which would not have been reflected on study ECG and would not be captured in our analysis.

Because ACCORD was a trial comparing different goals for glycemic and blood pressure control but the choice of agents used was left to the discretion of the treating physicians, we could not separate the QT-prolonging effects of the individual drugs used from the strategy assigned. Some of the agents used more frequently in the intensive glycemic control arm may have had QT-prolonging effects that were drug related rather than being related to the degree of glycemic control per se. However, the drugs used during the trial are reflective of real-world clinical practice, so we would expect the same relationships to hold. It should also be noted that the observed increased mortality in the intensive glycemic control arm of ACCORD may have been due to chance alone, in which case exploration of the QT-prolonging effects of intensive glycemic control would be rendered less important.

Despite these limitations, the ACCORD trial offers the best opportunity for assessing the effects of intensive glycemic control and intensive blood pressure control on the risk of QT prolongation among a nationally representative population with diabetes from a large clinical trial of treatment strategies aimed at the reduction of cardiovascular risk. The strengths of our study include the large sample size, standardized acquisition and interpretation of study ECGs, and duration of follow-up.

Conclusion

In patients with diabetes, a strategy of intensive glycemic control did not result in an increased risk of incident QT prolongation. Similarly, a strategy of intensive blood pressure control did not result in an increased risk of incident QT prolongation. Thus, the increased mortality observed in the intensive glycemic control arm in the ACCORD trial is not likely to be explained by QT prolongation leading to lethal ventricular arrhythmias.

Duality of Interest. No potential conflicts of interest relevant to this article were reported.

Author Contributions. M.J.S. and J.Y. conceived and designed the analysis. M.J.S. performed the analysis. M.J.S., E.Z.S., and J.Y. interpreted the results. M.J.S. drafted the manuscript. A.G.B., S.P.W., P.D.B., E.Z.S., and J.Y. revised the manuscript for critical intellectual content. All authors approved of the final manuscript for submission. M.J.S. is the guarantor of this work and, as such, had full access to all the data in the study and takes responsibility for the integrity of the data and the accuracy of the data analysis.

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