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ORIGINAL RESEARCH

Intensive Glycemic Treatment Mitigates Cardiovascular and Mortality Risk Associated With Cardiac Autonomic Neuropathy in Type 2 Diabetes

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BACKGROUND: Hyperglycemia is one of the proposed risk factors for cardiac autonomic neuropathy (CAN). CAN is associated with increased cardiovascular and mortality risk. But it remains unclear whether cardiovascular and mortality risk associated with CAN is mitigated by intensive glycemic treatment.

METHODS AND RESULTS: This secondary analysis included 7866 patients from the ACCORDION (Action to Control Cardiovascular Risk in Diabetes Follow-On) study. CAN was defined using ECG-derived measures. End points included primary outcome (composite of cardiovascular events) and total deaths. During a median follow-up of 8.9 years, a total of 1341 cardiovascular events and 1364 all-cause deaths were ascertained. Compared with standard treatment, intensive treatment reduced risk of primary outcome and total deaths among patients with CAN but not among those without CAN. Compared with absence of CAN, the presence of CAN was associated with increased risk of primary outcome and total deaths in the standard group but not in the intensive group. Significant interactions were found between CAN status and treatment arms on risk of primary outcome and total deaths. Incidence rates per 100 person-years of primary outcome and total deaths were similar between patients without CAN and those with CAN undergoing intensive treatment.

CONCLUSIONS: Intensive glycemic treatment mitigates cardiovascular and mortality risk associated with CAN and may serve as an effective way in the management of CAN.

Key Words: cardiac autonomic neuropathy ■ cardiovascular risk ■ mortality risk ■ type 2 diabetes

Cardiac autonomic neuropathy (CAN), a common microvascular complication of diabetes, is associated with markedly increased cardiovascular and mortality risk,[1–5] as well as risk of severe hypoglycemia.[6,7] Determining the exact prevalence of CAN in patients with diabetes has proved difficult because of the inconsistency of the definition, methods, and patient populations used.[8] Nevertheless, reduced heart rate variability (HRV) is one of the earliest detectable subclinical signs of CAN,[1,8,9] and ECG-derived indices of HRV are commonly used for an early diagnosis of CAN.[6,10]

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CLINICAL PERSPECTIVE

What Is New?

- Compared with standard glycemic treatment, intensive treatment reduced cardiovascular and mortality risk among patients with cardiac autonomic neuropathy (CAN) but not among those without CAN.
- Compared with absence of CAN, the presence of CAN increased cardiovascular and mortality risk in the standard treatment arm but not in the intensive treatment arm.
- The absolute risk of cardiovascular events and death in patients with CAN undergoing intensive treatment was similar to those without CAN.

What Are the Clinical Implications?

- CAN is associated with increased cardiovascular and mortality risk; however, intensive glycemic treatment mitigates cardiovascular and mortality risk associated with CAN and may serve as an effective way in the management of CAN.

Nonstandard Abbreviations and Acronyms

ACCORD	Action to Control Cardiovascular Risk in Diabetes
ACCORDION	Action to Control Cardiovascular Risk in Diabetes Follow-On
CAN	cardiac autonomic neuropathy
HRV	heart rate variability
rMSSD	root mean square of successive differences between normal-to-normal R-R intervals
SDNN	SD of all normal-to-normal R-R intervals
T2D	type 2 diabetes
UKPDS	UK Prospective Diabetes Study

Poor glycemic control in type 2 diabetes (T2D) is associated with occurrence and progression of diabetes-related complications, such as CAN[9,11,12] and cardiovascular disease (CVD).[13,14] Yet large randomized controlled trials have yielded mixed findings with respect to the long-term cardiovascular effects of intensive glycemic treatment.[15–18] In addition, hypoglycemia was more frequent in the intensive group than those in the standard group, which was associated with increased cardiovascular and mortality risk. Accordingly, current guidelines recommend less stringent goals for patients with a history of severe hypoglycemia or advanced microvascular complications.[19] The rationale behind this recommendation is that patients with T2D under these conditions will be more susceptible to the adverse effects of intensive glycemic treatment.

We previously reported that intensive treatment (compared with standard treatment) reduced more cardiovascular events among those with CAN during the ACCORD (Action to Control Cardiovascular Risk in Diabetes) trial phase.[20] T2D patients with CAN could represent a phenotypical subgroup in which the beneficial effects of intensive glycemic treatment in reducing cardiovascular risk persisted beyond the clinical trial. Such hypotheses are supported by data from several randomized controlled trials that have reported long-term microvascular benefits from short-term intensive glycemic treatment in individuals with T2D,[18,21,22] as well as beneficial effects of prior intensive glycemic treatment on CAN.[9,23]

To further confirm that intensive treatment improves long-term prognosis in patients with T2D with CAN, we used data from the ACCORDION (Action to Control Cardiovascular Risk in Diabetes Follow-On) study and explored whether long-term cardiovascular and mortality risk associated with CAN was mitigated by prior intensive glycemic treatment.

METHODS

Study Design

Data of participants enrolled in the ACCORD trial and its observational follow-up, the ACCORDION study, were used. The design and results of these studies have been published previously in detail.[15,24–26] In brief, ACCORD enrolled 10 251 people with T2D and previous evidence or high risk of CVD across the United States and Canada from June 2001 through October 2005. Participants were randomized in a 1:1 ratio to receive intensive (targeting glycated hemoglobin [HbA_{1c}] <6.0%) or standard (targeting HbA_{1c} 7%–7.9%) glycemia-lowering therapy. After a mean of 3.7 years, participants were transferred from the intensive to the standard glucose-lowering therapy arm on February 5, 2008, because of excess deaths in the intensive arm. All participants continued standard therapy until the planned end of the trial in June 2009. The study was approved by an institutional review committee.

All surviving ACCORD participants who could be contacted were subsequently offered the opportunity to participate in the ACCORDION study, during which data on cardiovascular and other health-related outcomes and measurements were collected and analyzed between May 2011 and October 2014. No active therapies were provided by the study during this follow-up period. The study protocol was approved by institutional review boards at each center as well as

by a review panel at the National Heart, Lung, and Blood Institute. All participants gave written, informed consent to participate in ACCORD and ACCORDION. The ACCORD database can be fully available from the National Heart, Lung, and Blood Institute/Biologic Specimen and Data Repository Information Coordinating Center on reasonable request.

Assessment of Cardiac Autonomic Neuropathy

The measures of CAN were obtained from standard 12-lead digitized ECG recorded over 10 seconds, with the participant resting supine after an overnight fast (MAC 1200 electrocardiograph system, GE Healthcare, Chicago, IL) as previously described.[3,27] Two heart rate variability (HRV) time–domain indices were derived: SD of all normal-to-normal R-Rs intervals (SDNN) and root mean square of successive differences between normal-to-normal R-R intervals (rMSSD). CAN was defined in the present analyses as both SDNN and rMSSD being below the 10th percentile in our sample of the ACCORD cohort (SDNN <5.0 ms and rMSSD <5.3ms).[4,20]

ECG recordings that were missing or demonstrated poor quality and recordings from those with artificial pacemaker, atrial fibrillation/flutter, and ectopic beats were excluded, leaving 8060 patients with valid ECG data at baseline. Patients who were missing values of important covariates was also excluded (n=194), leaving a cohort of 7866 patients for the current analysis (Figure S1).

Outcome Measures

The primary outcome of this study was the first occurrence of a cardiovascular event of the entire ACCORD trial and ACCORDION study, including nonfatal myocardial infarction, nonfatal stroke, or CVD death; the secondary outcome measure was total deaths.[24]

Statistical Analysis

We compared the baseline characteristics of participants by groups defined using the glycemic management arms and CAN status. Continuous variables were reported as mean (SD) and compared using Student's *t* tests. Categorical variables were expressed as count (proportion) and compared using χ^2 statistics. The cumulative incidence of adverse outcomes across categories divided by CAN status and glycemic treatment arms was estimated using the Kaplan–Meier method.

First, we compared those receiving intensive glycemic treatment with those receiving standard treatment (reference group) within each CAN status. Second, we compared those with CAN with those without CAN (reference group) within each glucose-lowering treatment group. Multiplicative interactions between CAN status and treatment arms on outcomes were tested by including the product term (ie, CAN status × treatment arms) as well as CAN status and treatment arms in the models. Third, patients were separately divided into 3 mutually exclusive groups: group 1, CAN absent; group 2, CAN present and standard arm; group 3, CAN present and intensive arm; risk of CVD and death was also compared among these 3 risk groups, whereby all patients without CAN (irrespective of treatment arms) served as the reference group for the other 2 groups (patients with CAN in the standard treatment group and patients with CAN in the intensive treatment group). Multivariable Cox proportional hazards regression models were used to compute hazard ratios (HRs) and associated 95% CIs. These models were adjusted for age, sex, race, 7 clinical center networks, smoking status, body mass index, systolic blood pressure, triglycerides, low-density lipoprotein cholesterol, creatinine, HbA_{1c}, diabetes duration, history of CVD, protein in urine, neuropathy, eye disease, depression, and hypoglycemia, and use of angiotensin-converting enzyme inhibitors/angiotensin receptor blockers, β blockers, statins, sulfonylureas, metformin, meglitinides, α-glucosidase inhibitors, thiazolidinediones, and insulin at baseline.

Sensitivity analyses were performed to ensure the robustness of the present findings. The following composite measures were computed to document the presence of CAN: (1) CAN1 was defined as the lowest quartile of SDNN and the highest quartile of QT index[3,28]; (2) CAN2 was defined as the lowest quartile of SDNN and the highest quartiles of QT index and resting heart rate.[3,28] All statistical analyses were performed using Stata (StataCorp, College Station, TX), and a 2-sided *P* value <0.05 was considered to indicate statistical significance.

RESULTS

Patients' Baseline Characteristics

Table S1 displays the baseline characteristics of participants excluded compared with those included in the final sample. Compared with those included in analyses, patients excluded from analyses were more likely to be β blocker users, to be men, and to have a CVD history. A total of 7866 patients (mean age, 62.5±6.5 years, 39.9% women, 62.7% White individuals) were included in our analysis. During a mean follow-up period of 7.8 (median, 8.9) years, 1341 CVD events, and 1364 all-cause deaths were ascertained. The prevalence of CAN denoted by low HRV in our main analyses was 6.7% (n=530). Characteristics of patients with and without CAN in different treatment arms were presented in Table 1. Patients with CAN had a longer duration of diabetes, higher HbA_{1c}, higher prevalence of neuropathy and eye disease, and were more likely to use insulin in both treatment arms.

Table 1. Baseline Characteristics of Participants by Glycemic Treatment Arms and CAN Status

Characteristics	Intensive glycemic treatment			Standard glycemic treatment		
	CAN present	CAN absent	*P* value	CAN present	CAN absent	*P* value
N (total = 7866)	259	3652	-	271	3684	-
Age, y	62.1±6.7	62.5±6.5	0.406	62.6±6.6	62.5±6.5	0.909
Female, %	34.4	40.5	0.053	30.3	40.4	0.001
Race and ethnicity, %			0.596			0.263
White	65.3	62.8		67.5	62.1	
Black	18.9	18.4		14.4	18.8	
Hispanic	5.4	7.5		7.4	7.9	
Others*	10.4	11.3		10.7	11.3	
Current smoking, %	17.0	14.2	0.214	15.9	13.1	0.192
BMI, kg/m^2	32.5±5.6	32.2±5.4	0.313	33.1±5.8	32.2±5.3	0.010
SBP, mm Hg	135.2±17.3	136.1±16.9	0.389	135.5±16.5	136.4±17.1	0.397
Triglycerides, mg/dL	208.8±199.3	189.3±137.8	0.033	208.2±151.5	191.5±146.6	0.073
LDL, mg/dL	103.9±34.6	105.1±33.5	0.553	100.8±33.8	105.2±33.7	0.039
Creatinine, μmol/L	82.1±21.7	79.8±20.7	0.081	83.7±19.9	79.4±19.5	<0.001
HbA_{1c}, %	8.5 (1.1)	8.3 (1.1)	0.001	8.5 (1.2)	8.3 (1.0)	<0.001
Diabetes duration, y	12.9±8.1	10.5±7.4	<0.001	13.7±8.6	10.6±7.4	<0.001
Medical history, %						
Prior CVD	36.7	34.5	0.471	36.9	33.5	0.257
Protein in urine	20.5	19.7	0.770	21.0	19.6	0.559
History of neuropathy	36.3	24.8	<0.001	40.2	27.0	<0.001
Eye disease	37.8	29.5	0.004	41.7	30.5	<0.001
Depression	27.8	24.1	0.176	27.3	24.5	0.298
History of hypoglycemia†	10.4	8.4	0.269	11.1	8.1	0.083
Medications, %						
ACEi/ARBs	69.1	68.8	0.905	71.2	69.6	0.576
β Blockers	26.3	28.7	0.400	28.0	30.2	0.453
Stains	61.4	63.5	0.502	63.1	64.4	0.663
Sulfonylureas	51.4	54.5	0.323	47.6	54.2	0.035
Metformin	60.6	65.4	0.115	60.1	65.5	0.074
Meglitinides	1.2	2.7	0.130	2.6	2.4	0.886
α-Glucosidase inhibitors	0.4	0.8	0.445	1.8	0.7	0.033
Thiazolidinediones	24.3	22.5	0.493	20.7	22.2	0.555
Insulin	45.6	32.4	<0.001	53.1	34.5	<0.001

Values are mean ±SD, unless otherwise indicated. ACCORD indicates Action to Control Cardiovascular Risk in Diabetes; ACEi/ARBs, angiotensin-converting enzyme inhibitors/angiotensin receptor blockers; BMI, body mass index; CAN, cardiac autonomic neuropathy; CVD, cardiovascular disease; HbA_{1c}, glycated hemoglobin; LDL, low-density lipoprotein; SBP, systolic blood pressure.

*Other races include Asian, American Indian, and Alaskan Indian.

†History of hypoglycemia was defined in the ACCORD trial as blood glucose <3.9 mmol/L in the 7 days preceding baseline.

However, they were less likely to be women and sulfonylurea users only in the standard treatment arm.

Long-Term Intensive Treatment Effect on Primary Outcome and Mortality Stratified by CAN Status

Consistent with previous analysis on the ACCORDION study,[15] intensive glycemic treatment for a mean of 3.7 years had a neutral long-term effect on primary outcome and total death (Table S2). However, beneficial effect of intensive treatment was present among patients with CAN (primary outcome: HR, 0.56 [95% CI, 0.38–0.83]; *P* = 0.003; total deaths: HR, 0.54 [95% CI, 0.37–0.79]; *P* = 0.002) but not among patients without CAN (primary outcome: HR, 0.94 [95% CI, 0.84–1.05]; *P* = 0.283; total deaths: HR, 1.02 [95% CI, 0.91–1.14]; *P* = 0.736; Table S2 and Figure S2).

Table 2. Cardiovascular and Mortality Risk Associated With CAN Across the Glycemic Treatment Arms

Treatment arms	Events (%)		Incidence *		CAN present vs CAN absent†		Interaction *P* value
	CAN present	CAN absent	CAN present	CAN absent	HR (95% CI)	*P* Value	
Primary outcome							
Overall	122 (23.0)	1219 (16.6)	2.8	2.1	1.29 (1.07–1.56)	0.009	
Intensive	50 (19.3)	591 (16.2)	2.5	2.1	1.06 (0.79–1.42)	0.694	0.048
Standard	72 (26.6)	628 (17.0)	3.9	2.2	1.58 (1.23–2.03)	<0.001	
Total deaths							
Overall	127 (24.0)	1237 (16.9)	2.7	1.8	1.28 (1.06–1.54)	0.010	
Intensive	49 (18.9)	619 (16.9)	2.1	1.8	0.99 (0.73–1.32)	0.925	0.018
Standard	78 (28.8)	618 (16.8)	3.3	1.8	1.63 (1.28–2.07)	<0.001	

CAN was defined as both SDNN and rMSSD being below the 10th percentile in our sample of the ACCORD cohort (SDNN <5.0 ms and rMSSD <5.3ms). ACCORD indicates Action to Control Cardiovascular Risk in Diabetes; CAN, cardiac autonomic neuropathy; HR, hazard ratio; SDNN, SD of all normal-to-normal R-R intervals; and rMSSD, root mean square of successive differences between normal-to-normal R-R intervals.

*Incidence rate is per 100 person-years and is not adjusted for covariates.

†The full model was adjusted by age, sex, race, 7 clinical center networks, smoking status, body mass index, systolic blood pressure, triglycerides, low-density lipoprotein cholesterol, creatinine, glycated hemoglobin, diabetes duration, history of cardiovascular disease, protein in urine, neuropathy, eye disease, depression, and hypoglycemia, and use of angiotensin-converting enzyme inhibitors/angiotensin receptor blockers, β blockers, statins, sulfonylureas, metformin, meglitinides, α-glucosidase inhibitors, thiazolidinediones, and insulin at baseline.

Cardiovascular and Mortality Risk Associated With CAN Stratified by Treatment Arms

In total population, compared with absence of CAN, the presence of CAN was associated with increased cardiovascular and mortality risk (primary outcome: HR, 1.29 [95% CI, 1.07–1.56]; $P=0.009$; total deaths: HR, 1.28 [95% CI, 1.06–1.54]; $P=0.010$; Table 2 and Figure 1). However, this risk was observed in the standard treatment arm (primary outcome: HR, 1.58 [95% CI, 1.23–2.03]; $P<0.001$; total deaths: HR, 1.63 [95% CI, 1.28–2.07]; $P<0.001$) but not in the intensive treatment arm (primary outcome: HR, 1.06 [95% CI, 0.79–1.42]; $P=0.694$; total deaths: HR, 0.99 [95% CI, 0.73–1.32]; $P=0.925$; Table 2 and Figure 1). We found a significant interaction between treatment arms and CAN status on primary outcome and total deaths (*P* for interaction=0.048 and 0.018, respectively; Table 2).

Cardiovascular and Mortality Risk for Patients With CAN in Intensive or Standard Treatment Arms Compared With Patients Without CAN

Cardiovascular and mortality risk were highest among patients with CAN undergoing standard treatment (primary outcome: HR, 1.59 [95% CI, 1.25–2.02]; $P<0.001$; total deaths: HR, 1.55 [95% CI, 1.23–1.95]; $P<0.001$) and was comparable between patients without CAN and those with CAN undergoing intensive treatment (primary outcome: HR, 1.02 [95% CI, 0.77–1.35]; $P=0.904$; total deaths: HR, 1.00 [95% CI, 0.75–1.33]; $P=0.988$; Table 3 and Figure 2). As for cardiovascular event subtypes, intensive treatment showed more beneficial effects on nonfatal myocardial infarction and nonfatal stroke (Table S3).

Sensitivity Analyses

The prevalence of CAN varied according to the definition used: 7% (n=552) for CAN1 and 3.4% (n=267) for CAN2. Although the HRs for the intensive treatment effect in adverse outcomes were not affected significantly by CAN status for any of the definitions, the larger absolute risk reduction induced by intensive treatment was observed in subjects with CAN1, CAN2 (data not shown). Furthermore, the increased risk of primary outcome and total deaths for participants with CAN1 and CAN2 was observed in the standard treatment arm, but not in the intensive treatment arm (Tables S4 and S5). Finally, the absolute risk of primary outcome and total deaths in patients with CAN1 and CAN2 undergoing intensive treatment was similar to those without CAN1 and CAN2 (Tables S6 and S7).

DISCUSSION

In a large cohort of patients with T2D, we first illustrated that intensive glycemic treatment had long-term beneficial effects only among those with CAN. Then, we demonstrated that CAN was associated with increased cardiovascular and mortality risk in the standard group but not in the intensive group. Finally, we confirmed that there was no difference in risk of primary outcome and death between patients with CAN undergoing intensive treatment and those without CAN.

We previously reported that intensive glycemic treatment had a beneficial effect on cardiovascular events and a neutral effect on death among those

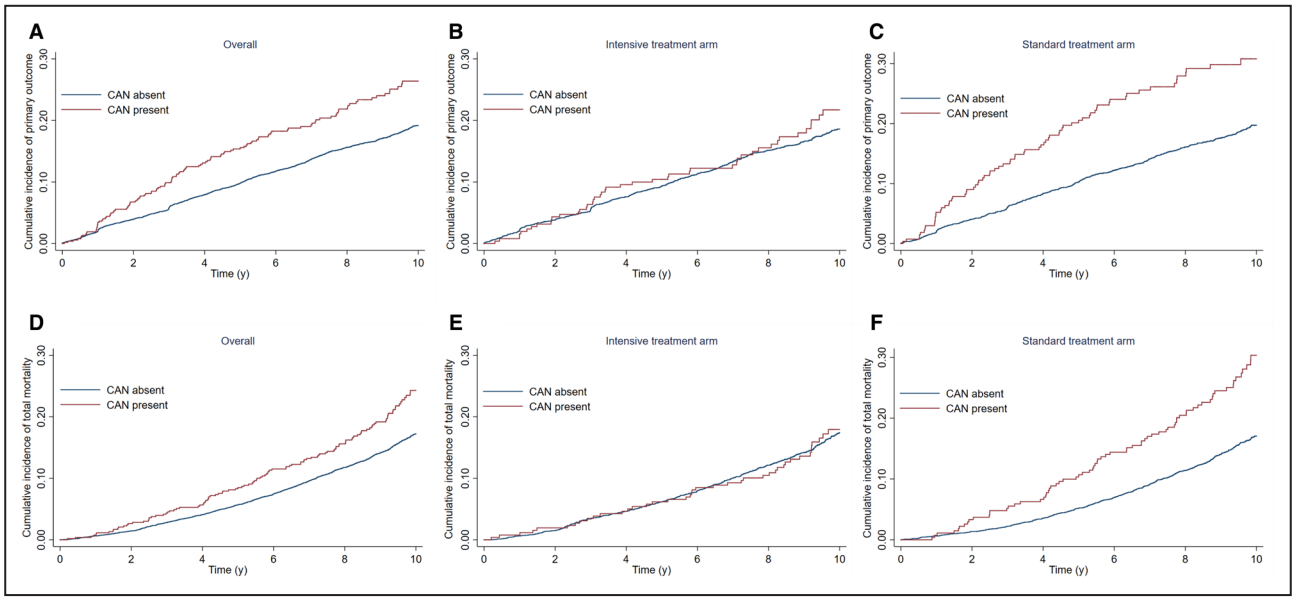

Figure 1. Cumulative incidence of primary outcome (A through C), and total deaths (D through F) by CAN status in overall population and in different glycemic treatment arms.
The primary outcome was a composite of the first occurrence of nonfatal myocardial infarction, nonfatal stroke, or death from cardiovascular causes. CAN indicates cardiac autonomic neuropathy.

with CAN during the ACCORD trial phase.[20] Results in the present analyses added to our prior study and extended them by showing that the beneficial effect on primary outcome persisted beyond the clinical trial. Furthermore, beneficial intensive treatment effect on death among patients with CAN emerged after the clinical trial. Such "legacy" effects were supported by the UKPDS (UK Prospective Diabetes Study), showing that a 10-year posttrial follow-up time might be necessary for emergent risk reductions of myocardial infarction and total deaths.[18]

Previous studies mostly focused on the association between glycemic control status and occurrence and progression of CAN and demonstrated a beneficial effect of intensive glycemic treatment on CAN.[9,11,12,23] An important question that arises is whether intensive glycemic treatment mitigates the cardiovascular and mortality risk associated with CAN. Given that intensive treatment is effective only among those with CAN in our present analyses, it is possible that cardiovascular and mortality risk difference between those with and without CAN may be reduced in the context of intensive treatment. We confirmed this hypothesis by showing that cardiovascular and mortality risk associated with CAN was observed in the standard treatment arm but not in the intensive treatment arm. Our results are consistent with a prior study showing that more aggressive preventive medication treatments may result in weaker associations between HRV and later events.[29] Closer inspection of the Kaplan–Meier

Table 3. Hazard Ratio for Patients With CAN Undergoing Intensive or Standard Treatment Compared With Patients Without CAN

	Primary outcome				Total mortality			
	Events (%)	Incidence *	HR (95% CI)†	*P* value	Events (%)	Incidence*	HR (95% CI)†	*P* value
CAN absent	1219 (16.6)	2.1	1.00 (reference)	-	1237 (16.9)	1.8	1.00 (reference)	-
CAN present and standard	72 (26.6)	3.9	1.59 (1.25–2.02)	<0.001	78 (28.8)	3.3	1.55 (1.23–1.95)	<0.001
CAN present and intensive	50 (19.3)	2.5	1.02 (0.77–1.35)	0.904	49 (18.9)	2.1	1.00 (0.75–1.33)	0.988

CAN was defined as both SDNN and rMSSD being below the 10th percentile in our sample of the ACCORD cohort (SDNN <5.0 ms and rMSSD <5.3 ms). ACCORD indicates Action to Control Cardiovascular Risk in Diabetes; CAN, cardiac autonomic neuropathy; HR, hazard ratio; SDNN, SD of all normal-to-normal R-R intervals; and rMSSD, root mean square of successive differences between normal-to-normal R-R intervals.

*Incidence rate is per 100 person-years and is not adjusted for covariates.

†The full model was adjusted by age, sex, race, 7 clinical center networks, smoking status, body mass index, systolic blood pressure, triglycerides, low-density lipoprotein cholesterol, creatinine, glycated hemoglobin, diabetes duration, history of cardiovascular disease, protein in urine, neuropathy, eye disease, depression, and hypoglycemia, and use of angiotensin-converting enzyme inhibitors/angiotensin receptor blockers, β-blockers, statins, sulfonylureas, metformin, meglitinides, α-glucosidase inhibitors, thiazolidinediones, and insulin at baseline.

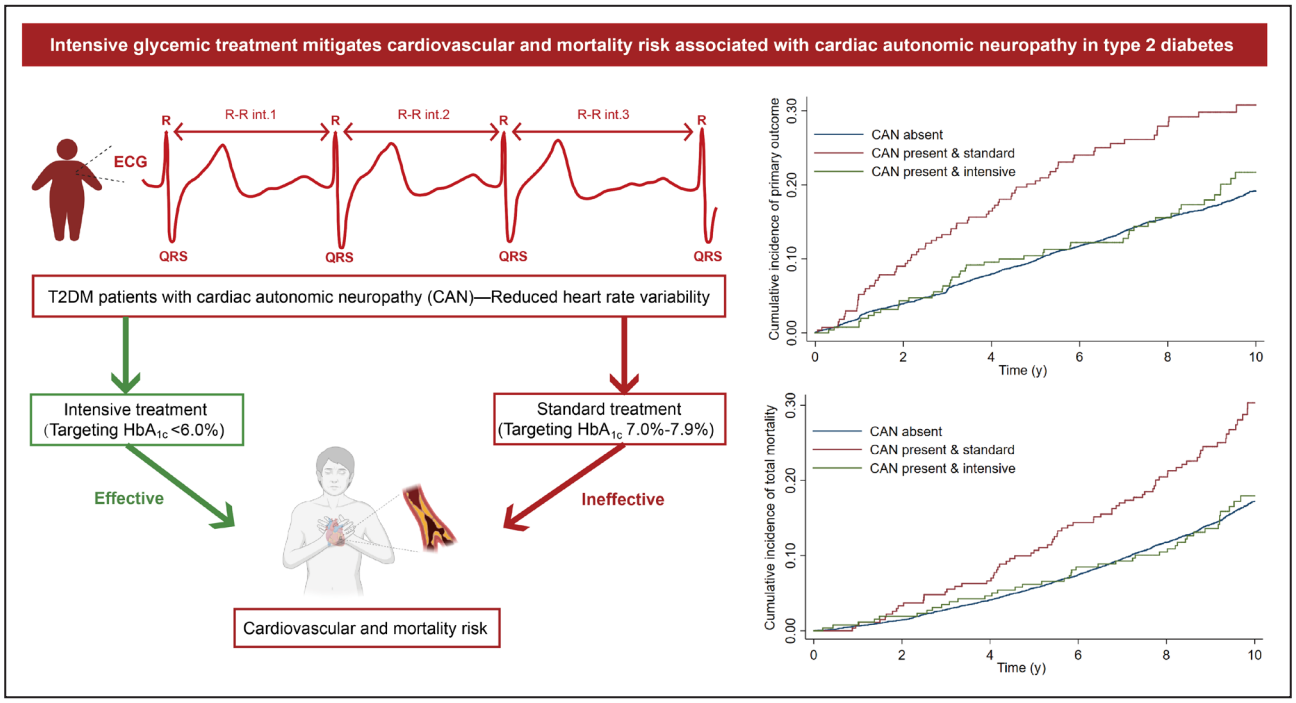

Figure 2. Cumulative incidence of primary outcome, and total mortality in patients with CAN undergoing intensive or standard treatment and in those without CAN.
The primary outcome was a composite of the first occurrence of nonfatal myocardial infarction, nonfatal stroke, or death from cardiovascular causes. CAN indicates cardiac autonomic neuropathy; HbA_{1c}, glycated hemoglobin; and T2D, type 2 diabetes.

curve data (Figure 2) of the present analysis suggests that cumulative incidence of cardiovascular events and total deaths were similar between patients with CAN undergoing intensive treatment and those without CAN, indicating that absolute risk of adverse outcome associated with CAN was greatly mitigated by intensive treatment. This finding is consistent with our prior study,[20] indicating that intensive glycemic treatment but not standard treatment is suitable for patients with CAN.

Current guidelines recommend that less stringent HbA_{1c} goals (such as <8%) may be appropriate for patients with advanced microvascular complications.[19] Our findings challenge this picture and suggest that intensive treatment (targeting HbA_{1c} <6%) may be suitable for patients with CAN. Of note, intensive treatment was much more of a risk factor for hypoglycemia among patients without CAN, and much less so among patients with CAN (Table S8). Therefore, patients with T2D with CAN may receive more benefits and less harm from intensive treatment. Participants with CAN are more likely to develop a variety of pathophysiological factors that themselves increase cardiovascular and mortality risk, such as inflammation,[30] endothelial dysfunction,[31] arterial stiffness,[32] renal insufficiency,[33] and multiple metabolic syndrome.[34] As a result, CAN may represent a phenotype in which hyperglycemia is strongly associated with CVD and death, and subgroups with CAN would be helped by intensive glycemic control. Our findings are supported by another post hoc analysis of the ACCORDION study, which has identified diabetic retinopathy, another subtype of diabetic microvascular complications, as predictor of the long-term beneficial effect of intensive treatment on the risk of CVD and possibly death.[35]

Strengths and Limitations

The strengths of this study include a large sample of patients with T2D with valid ECG data at baseline, the unique ACCORD trial design, and additional long-term follow-up after the clinical trial. The limitations to our study should also be acknowledged. First, CAN status was based on HRV indices obtained from short ECG recordings using time–domain indices only, rather than on 24-hour ECG-derived HRV or dynamic cardiovascular autonomic reflex tests.[36] However, a composite of the SDNN and rMSSD variables was found to be a strong predictor of adverse outcomes,[6,9,28] to the point that current guidelines recommend its use to evaluate CAN in large trials.[1] Furthermore, we also used several definitions of CAN in sensitivity analyses to ensure the robustness of the present findings. Of note, 10-second ECG may have the advantage of being less time consuming and easier to apply in clinical settings while providing comparable predictive value.[37–39] Second, cutoffs used in our analyses were derived

from distribution in the ACCORD cohort. However, previous studies showed that HRV below the 10th percentile was at statistically significantly increased risk of CVD and death in T2D.[4,20] Third, we could not exclude residual confounding, despite the fact that we have adjusted for potential covariates as much as possible. Finally, these findings are in a relatively modest sized subset of individuals and reflect a post hoc analysis of an overall negative study. Further randomized controlled trials are required to explore the intensive treatment effect among patients with T2D with CAN.

CONCLUSIONS

Intensive glycemic treatment exhibited long-term beneficial effects among patients with CAN, and mitigated the cardiovascular and mortality risk associated with CAN. Intensive treatment may serve as an effective way in the management of CAN. Further prospective randomized clinical trials are needed to validate the effects of intensive treatment in improving the clinical prognosis among patients with T2D with CAN.

ARTICLE INFORMATION

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Disclosures

None.

Supplemental Material

Tables S1–S8
Figures S1–S2

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