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Effects of Prior Intensive Insulin Therapy on Cardiac Autonomic Nervous System Function in Type 1 Diabetes Mellitus

The Diabetes Control and Complications Trial/Epidemiology of Diabetes Interventions and Complications Study (DCCT/EDIC)

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Background—The Epidemiology of Diabetes Interventions and Complications (EDIC) study, a prospective observational follow-up of the Diabetes Control and Complications Trial (DCCT) cohort, reported persistent benefit of prior intensive therapy on retinopathy and nephropathy in type 1 diabetes mellitus. We evaluated the effects of prior intensive insulin therapy on the prevalence and incidence of cardiac autonomic neuropathy (CAN) in former DCCT intensive and conventional therapy subjects 13 to 14 years after DCCT closeout.

Methods and Results—DCCT autonomic measures (R-R variation with paced breathing, Valsalva ratio, postural blood pressure changes, and autonomic symptoms) were repeated in 1226 EDIC subjects in EDIC year 13/14. Logistic regression models were used to calculate the odds of incident CAN by DCCT treatment group after adjustment for DCCT baseline covariates, duration in the DCCT, and quantitative autonomic measures at DCCT closeout. In EDIC year 13/14, the prevalence of CAN using the DCCT composite definition was significantly lower in the former intensive group versus the former conventional group (28.9% versus 35.2%; $P=0.018$). Adjusted R-R variation was significantly greater in the former DCCT intensive versus the former conventional group (29.9 versus 25.9; $P<0.001$). Prior DCCT intensive therapy reduced the risks of incident CAN by 31% (odds ratio, 0.69; 95% confidence interval, 0.51 to 0.93) and of incident abnormal R-R variation by 30% (odds ratio, 0.70; 95% confidence interval, 0.51 to 0.96) in EDIC year 13/14.

Conclusions—Although CAN prevalence increased in both groups, the incidence was significantly lower in the former intensive group compared with the former conventional group. The benefits of former intensive therapy extend to measures of CAN up to 14 years after DCCT closeout. (*Circulation*. 2009;119:2886-2893.)

Key Words: autonomic nervous system ■ diabetic neuropathies ■ diabetes mellitus, type 1 ■ glucose

Autonomic innervation is the primary extrinsic control mechanism regulating heart rate variability and cardiac performance. Chronic hyperglycemia promotes progressive autonomic neural dysfunction and cardiovascular autonomic neuropathy (CAN). The presence of CAN may be documented by abnormal heart rate variability. It may be the most overlooked complication of type 1 diabetes mellitus. CAN is associated with an increased prevalence of silent myocardial ischemia and is an independent predictor of increased cardiac mortality.¹⁻⁴

Editorial see p 2865 Clinical Perspective on p 2893

The Diabetes Control and Complications Trial (DCCT) demonstrated that intensive insulin therapy for type 1 diabetes mellitus reduced the onset and progression of diabetic retinopathy, nephropathy, and neuropathy⁵⁻⁷ and reduced the incidence of CAN by 53% compared with conventional therapy.⁷ The Epidemiology of Diabetes Interventions and Complications (EDIC) is a prospective observational study of

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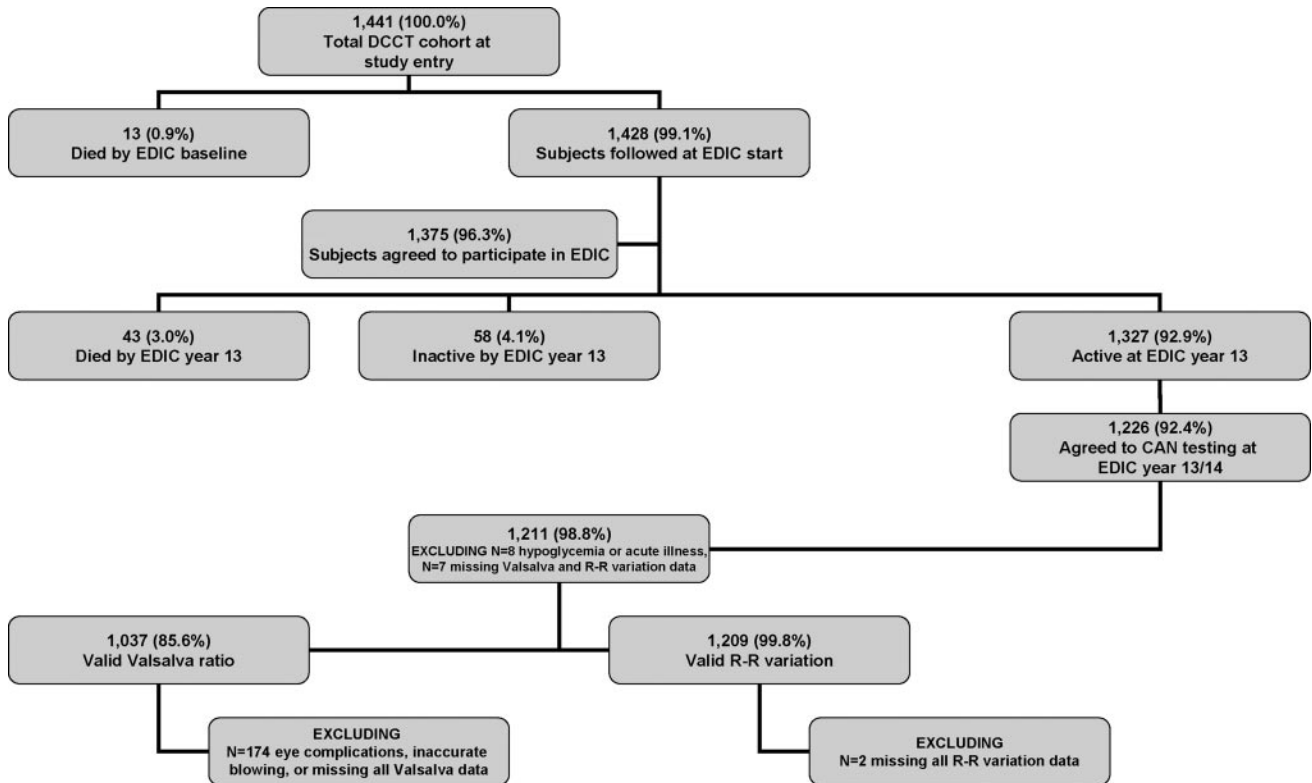


Figure 1. Flow diagram of NeuroEDIC participation.

the DCCT cohort.⁸ Its goal is to describe the long-term effects of prior intensive therapy compared with conventional insulin therapy on the development and progression of microvascular complications and cardiovascular disease in type 1 diabetes mellitus. EDIC follow-up has shown that the differences in retinal and renal outcomes observed at the end of the DCCT between the former intensive and conventional treatment groups have persisted and even increased for as long as 8 years despite the loss of glycemic separation.^{8,9} The persistent beneficial effect of past glucose control has been called “metabolic memory.”¹⁰ Preliminary results have suggested that metabolic memory may apply to peripheral neuropathy.¹¹

Using data obtained during the 13th or 14th year of EDIC follow-up, we evaluated CAN in EDIC participants and asked whether the former DCCT intensive treatment group continues to experience a lower prevalence and incidence of CAN compared with the former DCCT conventional treatment group despite no differences in levels of glycemic control after the close of the DCCT.

Methods

Study Design and Participants

The DCCT has been described elsewhere.⁵ Briefly, 1441 subjects who had diabetes mellitus for 1 to 15 years with no (primary prevention cohort) or minimal (secondary intervention cohort) diabetic retinopathy were eligible to participate. Subjects were randomly assigned to either intensive treatment or conventional treatment and were followed up for 3 to 9 years (mean, 6.5 years).⁵ At the end of DCCT, intensive therapy was recommended for all subjects, and subjects in the conventional treatment group were trained in intensive therapy and returned to their own healthcare providers for diabetes care. Annual EDIC study examinations began in 1994, 1

year after completion of the DCCT; 1375 (96%) subjects agreed to participate in the follow-up evaluations. A detailed description of EDIC study procedures and baseline characteristics has been published.¹² Clinical and biochemical end points were obtained annually from a standardized history, physical examination, and laboratory testing protocol.¹² Evaluation of glycemic control was based on measurements of hemoglobin A_{1c} (HbA_{1c}) using the same methods previously described for the DCCT.⁵

The DCCT and EDIC study procedures were approved by the institutional review boards of all participating centers, and all participants provided written informed consent. CAN testing (as performed during the DCCT) was repeated in 1226 subjects 1 time during year 13/14 of the EDIC follow-up (EDIC neurology protocol [NeuroEDIC]; Figure 1).

CAN Evaluations

During the DCCT, CAN was assessed at baseline and biennially with R-R response to paced breathing (R-R variation), Valsalva maneuver, and postural changes in blood pressure.⁷ Reported autonomic symptoms (for postural hypotension, gastroparesis, diabetic diarrhea, colonic atony, genitourinary dysfunction, sudomotor abnormality, and hypoglycemic unawareness) also were assessed.

During NeuroEDIC, the same CAN evaluations were performed once by EDIC nurse coordinators who were centrally trained and certified. The Autonomic Symptom Profile instrument¹³ was used to assess autonomic symptoms.

Because autonomic function may be altered by a variety of factors, all subjects were required to fast and avoid caffeine and tobacco products, as well as prescription and over-the-counter medicines (except for their usual insulin regimen), for at least 8 hours before CAN testing.⁷ Subjects who experienced hypoglycemia after midnight (defined as a blood glucose ≤ 50 mg/dL [2.775 mmol/L]) and/or signs or symptoms of hypoglycemia ($n=4$) or subjects with acute illness 48 hours before testing ($n=4$) were excluded. Subjects with active proliferative retinopathy, history of laser therapy or vitrectomy, or suspected (unconfirmed) proliferative retinopathy and/or no

eye examination in the last 4 years and those who could not accurately perform the required forced expiration ($n=174$) were excluded from performing the Valsalva maneuver (Figure 1).

Testing was performed with the Hokanson ANS 2000 device (Hokanson Inc, Bellevue, Wash), and results were analyzed at a single reading center. All CAN measurements were reviewed for quality control purposes by a single masked investigator (P.A.L.) at the reading center, who decided whether the technical quality of the recording and conditions of the test met study criteria. The R-R variation was certified as usable on the basis of whether the test was performed according to protocol, whether cardiac arrhythmia interfered with interpretation of the test, and whether the patient paced his/her breathing appropriately. Valsalva testing was done twice as previously described,¹⁴ and the average was calculated. Acceptable recordings were submitted for data entry and analysis. The postural change in blood pressure consisted of 2 supine measurements at least 6 minutes apart, followed by blood pressure measurements at 1, 2, 3, 4, 5, and 10 minutes after standing. The reproducibility of the CAN measurements was evaluated at the reading center, where a random sample of 10% of tests were reread, demonstrating a coefficient of reliability between the primary and the repeat readings of 0.999.

Measures and Definition of CAN in the DCCT and EDIC

R-R variation is the measurement of the magnitude of cardiac sinus arrhythmia, predominantly a function of the parasympathetic nervous system.^{14,15} It is computed as a dimensionless circular mean vector of R-R intervals.¹⁴ The Valsalva ratio evaluates cardiovagal function in response to a standardized increase in intrathoracic pressure and is influenced by both parasympathetic and sympathetic activity.¹⁴ Blood pressure response to standing reflects mainly sympathetic activity. This battery of tests is well suited to explore long-term changes in the autonomic nervous system function because they have been validated, shown to be reliable and reproducible, shown to have prognostic value,^{15–20} and recommended for assessment of autonomic neuropathy.^{3,18,20}

In the DCCT, abnormal R-R variation was defined as <15 , abnormal Valsalva ratio as ≤ 1.5 , and orthostatic hypotension as a postural decrease of >10 mm Hg in diastolic blood pressure.⁷ Presence of CAN was defined as either an R-R variation <15 or an R-R variation between 15 and 19.9 in combination with a Valsalva ratio ≤ 1.5 or a decrease of >10 mm Hg in diastolic blood pressure.⁷ Several studies published since the DCCT have demonstrated that heart rate variation is affected by age and possibly by gender.^{14,17} Therefore, we have analyzed these data, making adjustments for age, sex, and other covariates as described in Statistical Analyses. Orthostatic hypotension was defined in EDIC using both the DCCT criteria (without catecholamine measurements) and the consensus criteria.²¹

Outcome Measures

The primary outcome measures were the prevalence and incidence of CAN during EDIC. Secondary outcomes included changes in the continuous measures of R-R variation and Valsalva ratio during EDIC between the former intensive and conventional therapy cohorts, the prevalence of abnormal R-R variation and of abnormal Valsalva ratio at EDIC year 13/14, and the prevalence of autonomic symptoms.

Statistical Analyses

Demographic and clinical characteristics were compared between treatment groups with the Wilcoxon rank-sum test for ordinal or continuous variables and the contingency χ^2 test for categorical variables. Normal-error linear models were used to assess treatment group differences in R-R variation and Valsalva ratio at each of the 3 time points separately (DCCT baseline, DCCT closeout, and EDIC year 13/14) with adjustment for DCCT baseline age, sex, primary and secondary cohort, and duration in the DCCT study.

Logistic regression models assessed the treatment group differences in the odds of incident CAN by a specific criterion (eg, R-R variation <15) at EDIC year 13/14 among those free of the condition at DCCT closeout. The percent reduction in odds of incident CAN with intensive therapy compared with conventional therapy was computed as $(1-OR)\times 100$, where OR is the odds ratio. Models for R-R variation <15 also were adjusted for R-R variation at DCCT closeout; models for Valsalva ratio ≤ 1.5 were adjusted for Valsalva ratio at DCCT closeout; and models for abnormal CAN function were adjusted for both quantitative measures. *P* values were calculated with likelihood-ratio tests. The proportion of the treatment group effect explained by the differences in the HbA_{1c} between groups in DCCT and EDIC was calculated as the proportion reduction in the likelihood ratio test for treatment group after adjustment for the mean HbA_{1c} level during both DCCT and EDIC compared with that without adjustment. Statistical analyses were performed with SAS version 8.2 statistical analysis software (SAS Institute, Inc, Cary, NC). Statistical significance was defined as $P<0.05$.

The authors had full access to and take full responsibility for the integrity of the data. All authors have read and agree to the manuscript as written.

Results

After all exclusions were made, we evaluated CAN in 1211 EDIC participants. These included 304 intensive and 306 conventional subjects in the primary prevention cohort and 316 intensive and 285 conventional subjects in the former secondary intervention cohort (Figure 1). There were 1209 valid tests of R-R variation (93% intensive and 89% conventional subjects from the active and surviving DCCT cohort). Lower completion rates were observed for the Valsalva studies (1037 valid tests) because of the restrictions on performing the Valsalva maneuver in subjects with proliferative retinopathy and those unable to sustain the required magnitude and duration of forced expiration (as described above). Thus, Valsalva studies were completed in 84% intensive and 72% conventional subjects.

Table 1 summarizes the characteristics of these participants at DCCT baseline and closeout and EDIC year 13/14 by original treatment group. Data stratified by cohorts are presented in the Appendix of the online-only Data Supplement.

Participants in both former treatment groups (intensive and conventional) were heavier in EDIC year 13/14 than at DCCT closeout (body mass index, 28.3 ± 5.0 versus 25.9 ± 3.8 kg/m²; $P<0.001$). At EDIC year 13/14, participants from the former intensive group were slightly older than the former conventional group (47.8 ± 7.0 versus 47.0 ± 6.9 years; $P=0.040$) and had higher total cholesterol levels (177 ± 36 versus 172 ± 35 mg/dL; $P=0.041$). There were no significant differences in low-density lipoprotein cholesterol, blood pressure (systolic or diastolic), or smoking status. In EDIC year 13/14, the use of β -blockers was significantly greater in the former conventional group (9.1% versus 5.0%; $P=0.005$). There were no differences in the use of any other drugs, including angiotensin-converting enzyme inhibitors, angiotensin receptor blockers, other blood pressure-lowering agents, or statins (Table 1).

There were no significant differences at EDIC year 13/14 in any of the characteristics presented in Table 1 between participants in the NeuroEDIC and subjects who were still actively participating in other EDIC evaluations but did not participate in NeuroEDIC.

Table 1. Characteristics of the 1211 Subjects With Autonomic Measurements at EDIC Year 13/14

Characteristic and Group	DCCT Baseline	DCCT Closeout	EDIC Year 13/14
Age, mean±SD, y			
INT	27.2±7.1	33.9±6.9†	47.8±7.0†
CONV	26.5±7.0	33.0±6.9	47.0±6.9
Female, n (%)			
INT	303 (49)	303 (49)	303 (49)
CONV	271 (46)	271 (46)	271 (46)
Body mass index, mean±SD, kg/m ²			
INT	23.3±2.7	26.6±4.3†	28.6±5.3
CONV	23.4±2.9	25.0±3.0	27.9±4.8
Duration of diabetes, mean±SD, y			
INT	5.7±4.2	12.3±4.9	26.6±4.9
CONV	5.5±4.1	11.9±4.9	26.1±4.9
HbA _{1c} , mean±SD, %			
INT	9.1±1.6	7.4±1.0†	7.9±1.2
CONV	9.0±1.6	9.0±1.5	7.8±1.2
Systolic BP, mean±SD, mm Hg			
INT	113.4±11.5†	116.4±11.3	120.9±14.4
CONV	114.8±11.7	116.2±11.5	119.6±13.8
Diastolic BP, mean±SD, mm Hg			
INT	72.3±8.9	74.8±8.6	73.4±9.1
CONV	72.7±8.8	74.1±8.8	72.4±8.7
Total cholesterol, mean±SD, mg/dL			
INT	177.2±33.2	180.5±30.7	176.6±36.1†
CONV	173.6±32.3	182.3±36.0	172.3±35.1
LDL cholesterol, mean±SD, mg/dL			
INT	110.5±28.9	112.7±27.2	103.2±30.0
CONV	107.8±28.3	113.7±30.6	100.2±30.3
Current smoker, n (%)			
INT	127 (20)	139 (22)	84 (14)
CONV	112 (19)	118 (20)	67 (11)
Any BP-lowering medication, n (%)*			
INT	*	*	200 (32)
CONV	*	*	212 (36)
β-Blockers, n (%)*			
INT	*	*	31 (5)†
CONV	*	*	54 (9)
ACEI, n (%)*			
INT	*	*	243 (39)
CONV	*	*	255 (43)
ARB, n (%)*			
INT	*	*	57 (9)
CONV	*	*	67 (11)
Lipid-lowering medications, n (%)*			
INT	*	*	316 (51)
CONV	*	*	318 (54)

INT indicates intensive (n=620); CONV, conventional (n=591); BP, blood pressure; LDL, low-density lipoprotein; ACEI, angiotensin-converting enzyme inhibitor; and ARB, angiotensin receptor blocker.

*No medication data were collected in the DCCT. The use of blood pressure-lowering medications was an exclusion criterion at DCCT baseline.

† $P<0.05$ for treatment group differences by the Wilcoxon rank-sum test or χ^2 test comparing the intensive and conventional treatment groups.

Glycemic Control in EDIC Year 13/14

At DCCT completion, HbA_{1c} was 7.4% in the intensive group and 9.1% in the conventional group ($P<0.001$). At the first EDIC study examination, HbA_{1c} separation between the DCCT intensive and conventional groups narrowed substantially to 7.9% versus 8.3%, and by the 5th year of the EDIC study, the difference in HbA_{1c} between groups was no longer statistically significant (8.1% versus 8.2%; $P=0.099$).⁸ The difference in HbA_{1c} between the former intensive and conventional groups continued to show no significant difference ($P=0.219$ and $P=0.345$, respectively) at the time of CAN testing in EDIC year 13/14 (Figure 2).

Changes in Measures of CAN From DCCT to EDIC Year 13/14

The prevalence of CAN as assessed by heart rate variability was quite low at DCCT closeout in both treatment groups (4% intensive versus 9% conventional).⁷ Abnormalities were more prevalent in subjects from the secondary intervention cohort and among patients followed up for longer periods.⁷

As shown in Table 2, in EDIC year 13/14, the cross-sectional prevalence of CAN using the DCCT composite definition (R-R <15 or R-R <20 and Valsalva ≤1.5 or a decrease of >10 mm Hg in diastolic blood pressure) was significantly lower in the former intensive group compared with the conventional group (28.9% versus 35.2%; $P=0.018$) in pooled data from the primary prevention and secondary intervention cohorts. The prevalence of abnormal R-R variation (R-R <15) increased during EDIC in both groups but continued to be significantly higher in the former conventional group compared with the former intensive group (30.2% versus 23.8%; $P=0.012$), whereas the prevalence of an abnormal Valsalva ratio (<1.5) did not differ significantly between the former intensive and conventional groups (Table 2).

Table 2 also presents the pooled analysis of the changes in the continuous R-R variation and Valsalva ratio with adjustment for DCCT baseline age, sex, cohort assignment, and duration in the DCCT study. R-R variation was significantly higher within the former intensive group compared with the former conventional group in EDIC year 13/14 in both unadjusted and adjusted analyses (adjusted means, 29.9 versus 25.6; $P<0.001$; Table 2). Although there were no differences in the unadjusted Valsalva ratios between former DCCT groups in EDIC year 13/14, the adjusted means for the Valsalva ratio were higher in the former intensive compared with the former conventional group ($P=0.036$). By EDIC year 13/14, only a very small number of subjects in both cohorts presented with postural hypotension (1.8% intensive versus 1.6% conventional; $P=0.736$; Table 2).

Metabolic Memory

The effects of metabolic memory were assessed for the incidence of abnormal R-R variation, abnormal Valsalva ratio, and abnormal CAN function during EDIC in those subjects who were free of the condition at the end of the DCCT. The primary end point (incidence of CAN using the composite definition) among those without CAN at DCCT closeout was significantly lower in the former intensive group

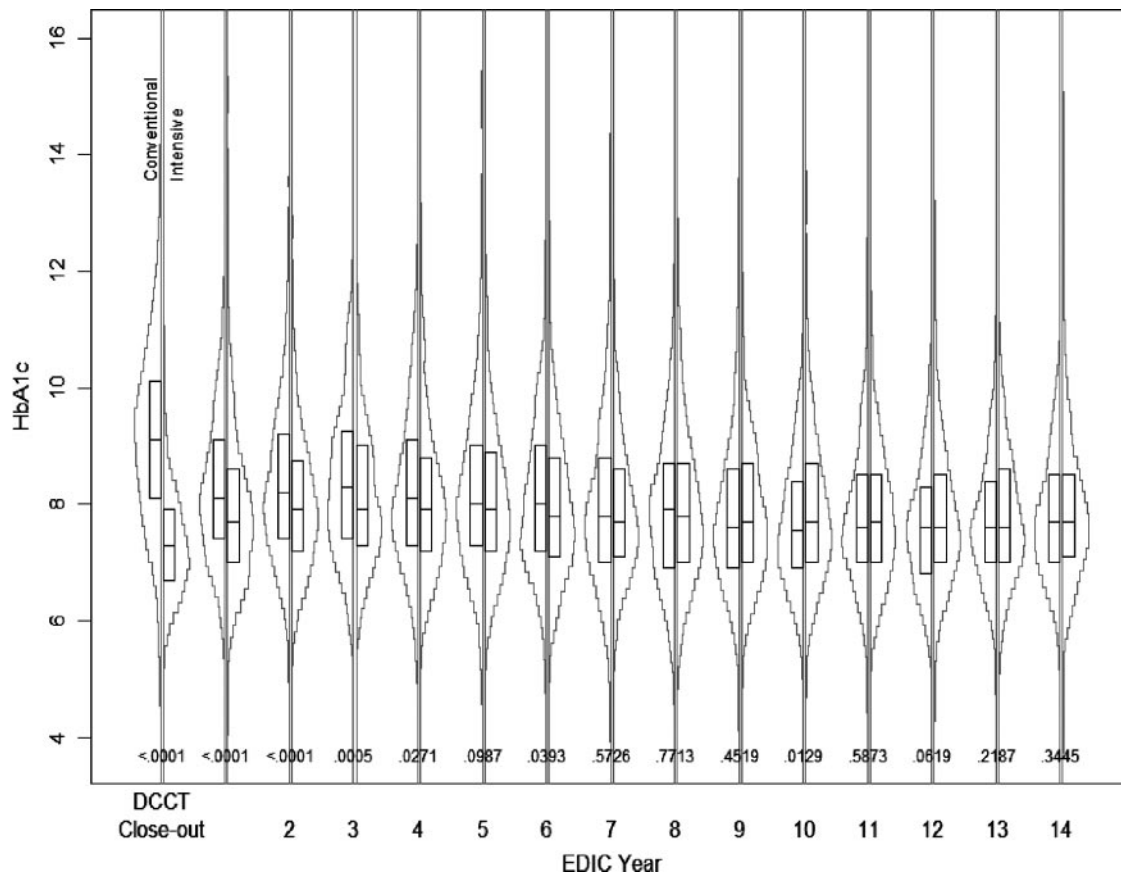


Figure 2. HbA_{1c} at DCCT closeout and through EDIC year 13/14. Box plots show interquartile range; horizontal lines, mean HbA_{1c}.

compared with the former conventional group (24.4% versus 29.8%; $P < 0.05$; Table 3).

Intensive insulin therapy during DCCT reduced the risk of incident CAN by 31% (odds ratio, 0.69; 95% confidence interval [CI], 0.51 to 0.93) and of abnormal R-R variation (< 15) by 30% (odds ratio, 0.70; 95% CI, 0.51 to 0.96) after adjustment for DCCT baseline age, sex, cohort assignment, duration in the DCCT study, and the level of R-R variation at DCCT closeout. Results were not different with the inclusion of β -blocker use during EDIC. With the additional adjustment for the level of Valsalva ratio at DCCT closeout and β -blocker use during EDIC, the odds of incident CAN became barely insignificant (odds ratio, 0.73; 95% CI, 0.54 to 1.004).

An increased incidence of CAN using the composite definition was associated with higher mean HbA_{1c} levels during both DCCT and EDIC. After adjustment for the mean HbA_{1c} levels during both DCCT and EDIC, treatment group differences were no longer significant (odds ratio, 1.31; 95% CI, 0.83 to 2.07). The proportion of the DCCT treatment group effect explained by the group differences in HbA_{1c} in DCCT and EDIC was 77.9%. Thus, virtually all of the difference between treatment groups in the incidence of CAN was explained by the differences in the HbA_{1c} levels between groups. The same is true for the treatment group differences initially observed for abnormal R-R variation (odds ratio, 1.36; 95% CI, 0.84 to 2.19). The proportion of the treatment group difference in R-R variation explained by the group differences in HbA_{1c} was 68.6% (Table 3).

Symptoms

A small number of participants from both former treatment groups reported symptoms consistent with autonomic neuropathy in EDIC year 13/14 (Table II of the online-only Data Supplement). Decreased adrenergic awareness of hypoglycemia (20% intensive versus 25% conventional), male impotence (23% intensive versus 30% conventional; $P = 0.039$), and excessive postprandial epigastric fullness (8% intensive versus 8% conventional) were the most commonly reported symptoms. No significant treatment group differences were found for the rest of the symptoms.

Discussion

During EDIC, CAN progressed substantially in both treatment groups, but the prevalence and incidence of CAN in EDIC year 13/14 remained significantly lower in the former intensive group than in the former conventional group, despite similar levels of glycemic control. Among patients with type 1 diabetes mellitus, the total exposure to hyperglycemia, as assessed by disease duration and degree of glycemic control, is the dominant determinant of risk of progression of microvascular complications, as documented during EDIC for nephropathy and retinopathy.^{8,9} The development of CAN, however, is a function of complex interactions among degree of glycemic control, disease duration, age-related neuronal attrition, and systolic and diastolic blood pressures.^{22,23}

The effects of age on measures of heart rate variability have been demonstrated in several independent cohorts of

Table 2. CAN Outcomes in 1211 Subjects With EDIC Year 13/14 Autonomic Measurements

Test and Group	DCCT Baseline	DCCT Closeout	EDIC Year 13/14
CAN prevalence, n (%) [*]			
INT	24 (3.9)	43 (7.1)	179 (28.9)§
CONV	31 (5.3)	57 (9.9)	208 (35.2)
R-R Variation <15, n (%)			
INT	20 (3.3)	39 (6.6)	147 (23.8)§
CONV	25 (4.3)	53 (9.5)	178 (30.2)
Valsalva ratio ≤1.5, n (%)			
INT	31 (5.2)	42 (7.4)	145 (26.0)
CONV	30 (5.2)	51 (9.3)	146 (30.4)
R-R variation, mean±SD			
INT	48.5±22.6	41.4±20.5	29.6±18.9‡
CONV	47.4±21.2	39.3±20.1	26.1±17.5
Adjusted R-R variation, mean±SD†			
INT	48.8±21.3	41.8±19.5§	29.9±17.4‡
CONV	47.0±21.4	38.9±19.4	25.6±17.5
Valsalva ratio, mean±SD			
INT	2.1±0.4	2.0±0.4	1.8±0.4
CONV	2.0±0.4	2.0±0.4	1.8±0.4
Adjusted Valsalva ratio, mean±SD†			
INT	2.1±0.5	2.0±0.5	1.8±0.2§
CONV	2.0±0.5	2.0±0.5	1.7±0.4
Postural hypotension, n (%)			
INT	2 (0.3)	3 (0.5)	11 (1.8)
CONV	3 (0.5)	4 (0.7)	9 (1.6)

INT indicates intensive; CONV, conventional.

^{*}CAN prevalence is defined as any one of the following conditions: R-R variation <15, R-R variation <20 in combination with Valsalva ratio ≤1.5, or postural hypotension.

†Means adjusted for DCCT baseline age, sex, cohort assignment, and duration in the DCCT study.

‡ $P<0.01$, § $P<0.05$ for treatment group differences by the Wilcoxon rank-sum test or χ^2 test comparing the intensive and conventional treatment groups.

healthy subjects.^{14,17,24} The age-related declines in R-R variation and Valsalva ratio are presumably due to a progressive decline in vagal function and/or alterations in baroreceptor sensitivity and sympathetic adrenergic activity.^{14,17,24} For this reason, we adjusted for the effects of age and found that both the prevalence and incidence of CAN remained significantly lower in the former intensive group compared with the former conventional group. In addition to age, the rate of forced respiration may influence the R-R variation; however, the respiration rate was paced to reduce the effects of hyperventilation.

Blood pressure significantly affects the interpretation of R-R variation. However, in EDIC year 13/14, we found no significant group difference in systolic or diastolic blood pressure among EDIC subjects with valid CAN measurements or in the use of any blood pressure-lowering agents

except β -blockers. No patients used β -blockers at DCCT baseline or at closeout. Treatment with β -blockers was more common at EDIC year 13/14 in subjects from the former conventional group compared with former intensive group, but in both groups, use of β -blockers was very low. Modulation of β -adrenergic activity by β -adrenergic blockade may positively influence heart rate variability.¹⁵ Our analysis therefore adjusted for the difference in β -blocker use during EDIC, resulting in group differences that barely lost significance.

The inconsistent group differences observed in the Valsalva ratio in EDIC year 13/14 suggests that R-R variation is a more sensitive test than the Valsalva maneuver. The reason may be that the major afferent and efferent pathways of the R-R variation with paced breathing are vagal.¹⁴ Other studies have shown that even during carefully standardized conditions, the Valsalva ratio can be an insensitive measure of CAN.¹⁴ Although the heart rate response to changes in blood pressure induced by the Valsalva maneuver is a parasympathetic response, the preceding blood pressure changes reflect complex autonomic functions, including blood volume, venous capacitance, total systemic resistance tone, and cardiac adrenergic tone.^{25,26} It is therefore possible that the Valsalva ratio requires greater parasympathetic impairment before becoming abnormal. However, our ability to interpret the Valsalva ratio in our study was limited in that a substantial number of subjects were not eligible to perform the maneuver because of the presence of severe retinopathy. Selection bias also may explain these findings.

The DCCT cohort was young and generally healthy with a relatively short duration of type 1 diabetes mellitus at baseline. The EDIC cohort has a mean duration of diabetes of ≈ 25 years. CAN studies in EDIC were done only in year 13/14, a substantially longer interval between tests compared with measures of retinopathy (every 4 years in EDIC) and nephropathy (biennial assessments of urine albumin excretion and annual assessments of serum creatinine). Although this may limit our understanding of how glycemic exposure affects measures of CAN, it is clear that the former intensive group had significantly fewer abnormalities in R-R variation and a lower of incidence of CAN relative to the conventional group.

Even after adjustment for the level of autonomic measurements or presence of CAN at the end of the DCCT, there were persistent beneficial effects of intensive versus conventional therapy after 13 to 14 years of follow-up in EDIC. Thus, a metabolic memory effect has occurred for measures of CAN as previously observed for retinopathy and nephropathy. Furthermore, differences between the original DCCT treatment groups in the level of the DCCT and EDIC mean HbA_{1c} explain virtually all of the beneficial effect of intensive versus conventional therapy on risk of incident CAN.

The mechanism of this persistent beneficial effect of DCCT treatment on outcomes assessed during EDIC is unknown. It is possible that early intensive therapy had different impacts on the various pathogenic pathways associated with autonomic neuronal function, including formation of advanced glycation end products, increased oxidative/nitrosative stress with increased free radical production, activation of the polyol and protein kinase C pathways, activation of polyADP ribosylation, and

Table 3. Incidence of Abnormal Autonomic Measurements at EDIC Year 13/14 Among Subjects With Intact Function at DCCT Closeout

Characteristic and Group	Incident Abnormal Function, n (%)	Unadjusted Odds Ratio (95% CI)	Adjusted Odds Ratio (95% CI)*	HbA _{1c} Adjusted Odds Ratio (95% CI)*
R-R variation <15				
INT	109 (18.8)	0.76 (0.57–1.02)	0.70 (0.51–0.96)	1.36 (0.84–2.19)
CONV	125 (23.2)			
Valsalva ratio ≤1.5				
INT	113 (19.7)	0.92 (0.69–1.23)	0.85 (0.62–1.16)	0.86 (0.54–1.36)
CONV	112 (21.1)			
Abnormal CAN function†				
INT	141 (24.4)‡	0.76 (0.59–0.995)	0.69 (0.51–0.93)	1.31 (0.83–2.07)
CONV	159 (29.8)			

INT indicates intensive; CONV, conventional.

*Logistic regression models were adjusted for DCCT baseline age, sex, cohort assignment, and duration in the DCCT study. Models for R-R variation <15 also were adjusted for R-R variation at DCCT closeout; models for Valsalva ratio ≤1.5 were adjusted for Valsalva ratio at DCCT closeout; and models for abnormal CAN function were adjusted for both quantitative measures. HbA_{1c} models include the mean HbA_{1c} levels during both DCCT and EDIC.

†Abnormal CAN function was defined as any one of the following conditions: R-R variation <15, R-R variation <20 in combination with Valsalva ratio ≤1.5, or postural hypotension.

‡*P*<0.05 for treatment group differences by the χ^2 test comparing the intensive and conventional treatment groups.

activation of genes involved in neuronal damage.^{3,27} Such mechanisms could have had persistent effects, although HbA_{1c} levels no longer differed during the EDIC study.

Another important clinical observation is that the prevalence and incidence of CAN from DCCT closeout to EDIC year 13/14 increased substantially in both the former conventional and intensive groups. The prevalence of CAN in EDIC was higher than previously described in other cohorts of patients with type 1 diabetes mellitus.³ Although variability among studies using different diagnostic methods, criteria, and definitions of CAN are expected, this increase in CAN is important because CAN is associated with increased frequency of silent myocardial ischemia³ and major cardiovascular events² and is a predictor of cardiovascular mortality. Ewing et al²⁸ and O'Brien et al²⁹ reported 5-year mortality rates as high as 53% and 27%, respectively, in diabetic patients with CAN, with a high proportion attributed to sudden cardiac death. In another population-based sample of individuals with type 1 diabetes mellitus, Orchard et al³⁰ found a 4-fold higher mortality rate in individuals with CAN at baseline compared with individuals without CAN. A meta-analysis of 15 studies that included 2900 subjects with diabetes mellitus reported a significantly higher relative risk of mortality in patients with CAN compared with patients without CAN.¹

Despite an increase in CAN prevalence in both treatment groups, only a relatively small number of participants reported symptoms consistent with autonomic neuropathy in EDIC year 13/14. Patient unawareness of cardiovascular dysfunction may increase the risks associated with CAN.

The high prevalence and incidence of CAN found in the EDIC cohort 13 to 14 years after the DCCT closeout may have important prognostic consequences considering the still relatively young age of the EDIC cohort. Future prospective analyses will assess the predictive associations between CAN and the risk (hazard) of mortality and cardiovascular events in

type 1 diabetes mellitus. These studies could provide additional important information on the natural history and progression of CAN and would help us better understand the long-term effects of intensive therapy in patients with type 1 diabetes mellitus.

Conclusion

Our results suggest that the benefits of former intensive therapy extend to measures of CAN 13 to 14 years after the end of the DCCT and support the initiation of intensive treatment of type 1 diabetes mellitus as early as is safely possible to provide durable protection from the development and progression of diabetic complications.

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Disclosures

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CLINICAL PERSPECTIVE

We present prospective findings of cardiovascular autonomic neuropathy (CAN) in patients with type 1 diabetes mellitus enrolled in the Diabetes Control and Complications Trial (DCCT) and followed up annually through the Epidemiology of Diabetes Interventions and Complications (EDIC) for an additional 13 to 14 years after the DCCT closeout. CAN is associated with a high risk of cardiac arrhythmias and sudden death, possibly related to silent myocardial ischemia. Our study provides a comprehensive CAN assessment over 25 years in a well-characterized cohort of patients with type 1 diabetes mellitus. The prevalence and incidence of CAN, as assessed by heart rate variability, increased substantially from DCCT closeout to EDIC year 13/14 despite the young age of the cohort, a very low prevalence of CAN at DCCT closeout, and good glycemic control. Even after adjustment for the level or presence of CAN at DCCT closeout, there were persistent beneficial effects of prior intensive versus conventional therapy after 13 to 14 years of follow-up in EDIC. Treatment group differences in the mean level of hemoglobin A_{1c} during DCCT and EDIC explained virtually all of the beneficial effects of intensive versus conventional therapy on risk of incident CAN. These findings support the recommendation that intensive treatment of type 1 diabetes mellitus be initiated as early as possible to provide durable protection from the development and progression of diabetic complications.

SUPPLEMENTAL MATERIAL

Table 1A Characteristics of the 1,211 subjects with autonomic measurements at EDIC Year 13/14 by cohort

Characteristic	Group	Primary Prevention			Secondary Intervention		
		DCCT Baseline	DCCT Closeout	EDIC Year 13/14	DCCT Baseline	DCCT Closeout	EDIC Year 13/14
Age, mean±SD, y	INT	26.8 ± 7.2	32.9 ± 7.0	46.9 ± 7.0	27.5 ± 7.0	34.7 ± 6.8	48.7 ± 6.8
	CONV	26.1 ± 7.5	32.1 ± 7.4	46.1 ± 7.4	26.8 ± 6.4	33.9 ± 6.2	47.9 ± 6.2
Female, No(%)	INT	153 (50)	153 (50)	153 (50)	150 (47)	150 (47)	150 (47)
	CONV	134 (44)	134 (44)	134 (44)	137 (48)	137 (48)	137 (48)
Body Mass Index, mean±SD, kg/m ²	INT	23.1 ± 2.8	26.4 ± 4.5 ^a	28.4 ± 5.2	23.5 ± 2.6	26.8 ± 4.1 ^a	28.7 ± 5.4
	CONV	23.2 ± 2.9	24.9 ± 3.1	28.0 ± 4.8	23.7 ± 2.8	25.2 ± 3.0	27.9 ± 4.7
Duration of diabetes, mean±SD, y	INT	2.6 ± 1.3	8.6 ± 2.3	22.9 ± 2.4	8.8 ± 3.7	15.9 ± 4.0	30.2 ± 4.0
	CONV	2.6 ± 1.4	8.5 ± 2.4	22.7 ± 2.4	8.6 ± 3.7	15.5 ± 4.1	29.8 ± 4.2
Hemoglobin A1c, mean±SD, %	INT	9.0 ± 1.6	7.4 ± 1.0 ^a	8.0 ± 1.2	9.2 ± 1.5	7.3 ± 1.0 ^a	7.9 ± 1.3
	CONV	8.9 ± 1.6	9.1 ± 1.5	7.9 ± 1.2	9.0 ± 1.5	8.9 ± 1.6	7.8 ± 1.2
Systolic BP, mean±SD, mm Hg	INT	112.5 ± 10.8 ^a	114.9 ± 11.2	120.6 ± 14.1	114.2 ± 12.2	117.7 ± 11.3	121.3 ± 14.8
	CONV	114.2 ± 11.6	114.7 ± 10.8	118.8 ± 13.8	115.5 ± 11.8	117.8 ± 12.0	120.5 ± 13.8
Diastolic BP, mean±SD, mm Hg	INT	71.7 ± 8.7	74.2 ± 8.8	74.8 ± 8.8 ^a	73.0 ± 9.2	75.4 ± 8.4	72.1 ± 9.3
	CONV	72.1 ± 8.8	73.3 ± 8.5	72.9 ± 8.3	73.3 ± 8.8	74.8 ± 9.1	71.9 ± 9.0
Total cholesterol, mean±SD, mg/dl	INT	176.0 ± 33.1 ^a	178.5 ± 29.9	181.4 ± 37.0 ^a	178.3 ± 33.3	182.5 ± 31.4	171.9 ± 34.6
	CONV	169.2 ± 32.9	179.1 ± 34.7	171.6 ± 34.3	178.3 ± 31.1	185.7 ± 37.1	173.1 ± 35.9
LDL cholesterol, mean±SD, mg/dl	INT	109.1 ± 29.4	110.6 ± 27.4	106.8 ± 31.1 ^a	111.9 ± 28.4	114.7 ± 26.8	99.6 ± 28.6
	CONV	103.8 ± 28.5	110.2 ± 29.9	100.2 ± 30.0	112.0 ± 27.6	117.4 ± 30.9	100.2 ± 30.7
Current smoker, No(%)	INT	63 (21)	74 (25) ^a	48 (16)	64 (20)	65 (21)	36 (11)
	CONV	54 (18)	61 (20)	34 (11)	58 (20)	57 (20)	33 (12)

Any BP lowering medication, No(%)^b	INT	b	91 (30)	b	b	109 (34)
	CONV	b	95 (31)	b	b	117 (41)
Beta blockers, No(%)^b	INT	b	11 (4) ^a	b	b	20 (6)
	CONV	b	26 (9)	b	b	28 (10)
ACE, No(%)^b	INT	b	105 (35)	b	b	138 (44)
	CONV	b	117 (38)	b	b	138 (48)
ARB, No(%)^b	INT	b	31 (10)	b	b	26 (8)
	CONV	b	32 (10)	b	b	35 (12)
Lipid-lowering medications, No(%)^b	INT	b	146 (48)	b	b	170 (54)
	CONV	b	150 (49)	b	b	168 (59)

CAN Cardiac autonomic neuropathy, EDIC Epidemiology of Diabetes Interventions and Complications, DCCT Diabetes Control and Complications Trial, INT intensive, CONV conventional, BP blood pressure, LDL low density lipoprotein, ACE Angiotensin converting enzyme inhibitors, ARB Angiotensin receptor blockers.

^a $P < 0.05$ for treatment group differences by the Wilcoxon rank-sum test or chi-square test comparing INT and CONV treatment groups.

^b No medication data were collected in the DCCT. The use of blood pressure lowering medications was an exclusion criterion at DCCT baseline.

Table 2 A Presence of autonomic symptoms in EDIC year 13/14 by cohort assignment

Characteristic	Group	Primary Prevention	Secondary Intervention	Combined
		No. (%)		
Weakness on standing relieved by lying down	INT	10 (3)	11 (4)	21 (4)
	CONV	13 (4)	14 (5)	27 (5)
Fainting on standing relieved by lying down	INT	4 (1)	5 (2)	9 (2)
	CONV	7 (2)	14 (5)	21 (4)
Dysphagia (difficulty in swallowing)	INT	5 (2)	9 (3)	14 (2)
	CONV	6 (2)	4 (1)	10 (2)
Anorexia	INT	5 (2)	5 (2)	10 (2)
	CONV	7 (2)	2 (1)	9 (2)
Nausea	INT	8 (3)	8 (3)	16 (3)
	CONV	11 (4)	11 (4)	22 (4)
Vomiting	INT	5 (2)	4 (1)	9 (2)
	CONV	6 (2)	4 (1)	10 (2)
Vague fullness after meal	INT	12 (4)	33 (11)	45 (8)
	CONV	24 (8)	23 (8)	47 (8)
Nocturnal diarrhea	INT	3 (1)	7 (2)	10 (2)
	CONV	4 (1)	7 (3)	11 (2)
Fecal incontinence	INT	3 (1)	3 (1)	6 (1)
	CONV	1 (0.3)	2 (1)	3 (1)
More than 20 bowel movements/day	INT	1 (0.3)	0 (0)	1 (0.2)
	CONV	2 (1)	0 (0)	2 (0.4)
Less than 2 bowel movements/week	INT	4 (1)	7 (2)	11 (2)

	CONV	7 (2)	11 (4)	18 (3)
Less than 1 bowel movement/3 days	INT	7 (2)	9 (3)	16 (3)
	CONV	12 (4)	13 (5)	25 (4)
Impotence (males only)	INT	29 (19)	43 (26)	72 (23)^a
	CONV	53 (30)	45 (30)	98 (30)
Retrograde ejaculation (males only)	INT	5 (3)	8 (5)	13 (4)
	CONV	8 (5)	9 (6)	17 (5)
Overflow bladder incontinence	INT	8 (3)	9 (3)	17 (3)
	CONV	3 (1)	10 (4)	13 (2)
Urinary dribbling	INT	16 (6)	19 (6)	35 (6)
	CONV	14 (5)	22 (8)	36 (6)
Incomplete bladder emptying	INT	16 (6)	10 (3)	26 (4)
	CONV	10 (3)	20 (7)	30 (5)
Increased urinary volume	INT	4 (1)	6 (2)	10 (2)
	CONV	4 (1)	3 (1)	7 (1)
Decreased urinary volume	INT	2 (1)	5 (2)	7 (1)
	CONV	6 (2)	7 (3)	13 (2)
Diminished sweating of legs	INT	7 (2)	9 (3)	16 (3)
	CONV	16 (5)	15 (5)	31 (5)
Feeling of increased sweating elsewhere	INT	15 (5)	22 (7)	37 (6)
	CONV	12 (4)	25 (9)	37 (6)
Decreased adrenergic awareness of hypoglycemia	INT	54 (18)	68 (22)	122 (20)
	CONV	75 (25)	68 (25)	143 (25)

EDIC denotes Epidemiology of Diabetes Interventions and Complications, INT intensive, CONV conventional.

^a $P < 0.05$ for treatment group differences by the Wilcoxon rank-sum test or chi-square test comparing INT and CONV treatment groups.