Effect of Prior Intensive Insulin Treatment During the Diabetes Control and Complications Trial (DCCT) on Peripheral Neuropathy in Type 1 Diabetes During the Epidemiology of Diabetes Interventions and Complications (EDIC) Study

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OBJECTIVE — To evaluate the impact of former intensive versus conventional insulin treatment on neuropathy in Diabetes Control and Complications Trial (DCCT) intensive and conventional treatment subjects with type 1 diabetes 13–14 years after DCCT closeout, during which time the two groups had achieved similar A1C levels.

RESEARCH DESIGN AND METHODS — Clinical and nerve conduction studies (NCSs) performed during the DCCT were repeated during the Epidemiology of Diabetes Interventions and Complications (EDIC) study by examiners masked to treatment status on 603 former intensive and 583 former conventional treatment subjects. Clinical neuropathy was defined by symptoms, sensory signs, or reflex changes consistent with distal polyneuropathy and confirmed with NCS abnormalities involving two or more nerves among the median, peroneal, and sural nerves.

RESULTS — The prevalence of neuropathy increased 13–14 years after DCCT closeout from 9 to 25% in former intensive and from 17 to 35% in former conventional treatment groups, but the difference between groups remained significant ($P < 0.001$), and the incidence of neuropathy remained lower among former intensive (22%) than former conventional (28%) treatment subjects ($P = 0.0125$). Analytic models of incident neuropathy that adjusted for differences in NCS results at DCCT closeout showed no significant risk reduction associated with former intensive treatment during follow-up (odds ratio 1.17 [95% CI 0.84–1.63]). However, a significant persistent treatment group effect was observed for several NCS measures. Longitudinal analyses of overall glycemic control showed a significant association between mean A1C and measures of incident and prevalent neuropathy.

CONCLUSIONS — The benefits of former intensive insulin treatment persisted for 13–14 years after DCCT closeout and provide evidence of a durable effect of prior intensive treatment on neuropathy.

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The Diabetes Control and Complications Trial (DCCT) enrolled 1,441 patients with type 1 diabetes and randomly assigned them to intensive or conventional treatment. The DCCT conclusively demonstrated that reducing glucose levels delayed or prevented the development of retinopathy, nephropathy, and neuropathy over a mean of 6.5 years (1). At DCCT closeout, subjects were encouraged to maintain or begin intensive treatment and were invited to participate in a prospective observational study (Epidemiology of Diabetes Interventions and Complications [EDIC]) to evaluate the long-term effects of prior treatment on microvascular, neuropathic, and macrovascular outcomes (2).

At DCCT closeout, the mean A1C was significantly lower in the intensive compared with the conventional treatment group (7.4 vs. 9.1%, $P < 0.0001$). However, within 1 year, the differences in A1C narrowed substantially (7.9% intensive vs. 8.3% conventional, $P < 0.0001$), and within 5 years the A1C levels no longer differed between groups (8.1% intensive vs. 8.2% conventional, $P = 0.11$). Despite similar A1C levels, former intensive treatment subjects continued to have a lower cumulative incidence of retinopathy and nephropathy than conventional treatment subjects (3–5). This persistent effect of past glucose control has been termed metabolic memory (6). Previously published EDIC study results showed a durable effect of former intensive treatment compared with former conventional treatment on symptoms and signs of neuropathy, based on a neuropathy screening tool, 8 years after DCCT closeout (7). The neuropathy screening tool initially used during EDIC differed, however, from the more comprehensive methods used during the DCCT (2,8).

The current study (NeuroEDIC) was performed to determine the impact of

former intensive treatment on distal symmetrical neuropathy during the EDIC study using the same comprehensive measures of neuropathy performed during the DCCT. We report neuropathy outcomes in the EDIC cohort based on original intention-to-treat DCCT treatment group assignments, with glycemic exposure reflecting the differences in A1C during 6.5 years of the DCCT and the subsequent convergence of A1C for almost 14 years after DCCT closeout during the EDIC study. The comprehensive assessment of peripheral neuropathy allowed us to examine whether the significant treatment group differences in symptoms, signs, and electrophysiological features of neuropathy at DCCT closeout have persisted 13–14 years later and if metabolic memory applies to neuropathy.

RESEARCH DESIGN AND METHODS

— The DCCT design has been described elsewhere (1). Briefly, we recruited 1,441 subjects with 1–15 years duration of type 1 diabetes, minimal or no microvascular complications, and no history of neuropathy requiring medical treatment. Subjects were randomly assigned to intensive treatment (three or more insulin injections daily or continuous subcutaneous insulin infusion, guided by frequent self-monitoring of blood glucose) or conventional treatment (one or two insulin injections daily) and followed for 4–9 years (mean 6.5 years) (1,9). The DCCT included a primary prevention cohort and a secondary intervention cohort. The primary prevention cohort had diabetes for 1–5 years (mean 2.6 years) and no retinopathy or microalbuminuria at baseline. The secondary intervention cohort had diabetes for 1–15 years (mean 8.7 years) and mild to moderate retinopathy at baseline. The secondary intervention cohort also had a higher prevalence of confirmed clinical neuropathy at DCCT baseline than the primary prevention cohort (9.4 vs. 3.5%, respectively) (8).

Of 1,305 subjects from the original DCCT cohort who were active in the EDIC study, 1,186 agreed to participate in NeuroEDIC. These included 603 in the former intensive treatment group and 583 in the former conventional treatment group, representing 93 and 91% of eligible participants, respectively.

Clinical neurological examination

Neurologists masked to treatment group assignment performed the clinical examinations as in the DCCT, including neurological history and physical examination to detect the presence of distal symmetrical polyneuropathy, and identified potential causes of neuropathy other than diabetes (1).

Nerve conduction studies

Nerve conduction studies (NCSs) were performed by trained and certified electromyographers on the dominant side median (motor and sensory), peroneal (motor), and sural (sensory) nerves using percutaneous nerve stimulation and surface recording as done in the DCCT (10). NCS responses were evaluated by an independent reviewer to identify outlying or nonphysiological values and measurement, transcription, and calculation errors. Records thought to be in error were returned to the electromyographers for remeasurement and resubmission. Normal values were based on those provided by participating laboratories during the DCCT (10). An abnormal NCS result consistent with neuropathy was defined as a value above or below the absolute threshold of normal among amplitude, conduction velocity, or *F* wave latency in at least two anatomically distinct nerves (1,10).

Neuropathy outcome measures

Neuropathy was defined using clinical and electrodiagnostic criteria (1). As in the DCCT, the classification of definite clinical neuropathy was based on the neurologist's examination and required at least two positive responses among symptoms, sensory signs, or reflex changes consistent with a distal symmetrical polyneuropathy (e.g., symptoms or signs showing a length-dependent gradient in a stocking or stocking-glove distribution). Confirmed clinical neuropathy, the primary outcome measure, also required NCS abnormalities involving two or more nerves among the median, peroneal, and sural nerves. The components of the clinical and NCS examinations were secondary outcome measures. The DCCT definition of confirmed clinical neuropathy permitted confirmation based on abnormal autonomic nervous system test results. However, only 12 subjects fulfilled that criterion, and confirmation of neuropathy in these analyses was based on NCS abnormalities appropriate for a sensory or sensorimotor polyneuropathy without regard to autonomic test results.

The online appendix (available at http://care.diabetesjournals.org/cgi/content/full/dc09–1941/DC1) includes descriptions of the surface temperature measures obtained during the NCSs, the statistical methods, and the results of analyses within the primary prevention and secondary intervention cohorts. Analyses reported here are for the combined cohorts.

RESULTS

Participants

The characteristics of the 1,186 NeuroEDIC participants at DCCT baseline, DCCT closeout, and EDIC years 13–14 are shown in Table 1. Characteristics of the primary prevention and secondary intervention cohorts are shown in supplemental Table 1a. There were no clinically relevant treatment group differences in the characteristics, or in the use of medications to reduce neuropathic pain, or in the use of ACE inhibitors or angiotensin II receptor blockers (ARBs). The NeuroEDIC participants were comparable with 121 active and surviving DCCT participants who did not participate in the NeuroEDIC, except that the NeuroEDIC participants at EDIC years 13–14 were slightly older than nonparticipants (aged 48 vs. 46 years, $P < 0.01$).

Neuropathy status during DCCT and NeuroEDIC

The prevalence of clinical and NCS indicators of neuropathy at DCCT baseline, DCCT closeout, and EDIC years 13–14 are shown in Table 2 by DCCT treatment group in the total cohort. At DCCT baseline, there were no significant between-treatment group differences for any of the results, and the overall prevalence of confirmed clinical neuropathy was low (7% intensive vs. 5% conventional treatment, P = NS). At DCCT closeout, the treatment groups differed in most measures of neuropathy, with lower prevalence of neuropathy in the intensive compared with the conventional treatment group (9 vs. 17%, $P < 0.001$).

At EDIC years 13–14, the prevalence of all indicators of neuropathy had increased relative to DCCT closeout. Although the difference between treatment groups had narrowed, the prevalence of clinical symptoms and signs (abnormal sensation) and of the clinical neuropathy outcome measure remained lower in the former intensive treatment group compared with the former conventional treatment group. The prevalence of abnormal NCS results also increased in both treatment groups relative to DCCT closeout, and the between-treatment group difference

Table 1—*Characteristics of NeuroEDIC participants at DCCT baseline, DCCT closeout, and EDIC years 13–14*

Characteristic	DCCT baseline	DCCT closeout	EDIC years 13–14
Age (years)			
INT ($n = 603$)	27 ± 7*	34 ± 7*	48 ± 7*
CONV ($n = 583$)	27 ± 7	33 ± 7	47 ± 7
Female			
INT	294 (49)	294 (49)	294 (49)
CONV	268 (46)	268 (46)	268 (46)
Height (cm)			
INT	171 ± 10	172 ± 10	171 ± 9
CONV	172 ± 10	172 ± 10	173 ± 10
Weight (kg)			
INT	68 ± 11	78 ± 14†	84 ± 17
CONV	70 ± 13	75 ± 13	84 ± 17
BMI (kg/m^2)			
INT	23 ± 3	27 ± 4†	29 ± 5
CONV	24 ± 3	25 ± 3	28 ± 5
BMI >30 (kg/m^2)			
INT	7 ± 1	115 ± 20†	202 ± 34
CONV	10 ± 2	27 ± 5	173 ± 30
Diabetes duration (years)			
INT	6 ± 4	12 ± 5	26 ± 5
CONV	6 ± 4	12 ± 5	26 ± 5
A1C (%)			
INT	9.1 ± 1.6	7.3 ± 1.0†	7.8 ± 1.2
CONV	8.9 ± 1.6	9.1 ± 1.5	7.8 ± 1.2
Systolic blood pressure (mmHg)			
INT	113 ± 12†	116 ± 11	121 ± 14
CONV	115 ± 12	116 ± 12	120 ± 14
Diastolic blood pressure (mmHg)			
INT	72 ± 9	75 ± 9	74 ± 9
CONV	73 ± 9	74 ± 9	73 ± 9
Total cholesterol (mg/dl)			
INT	177 ± 33	180 ± 31	176 ± 36
CONV	174 ± 33	183 ± 36	173 ± 35
LDL cholesterol (mg/dl)			
INT	111 ± 29	112 ± 27	103 ± 30
CONV	108 ± 29	114 ± 31	100 ± 31
Current smoker			
INT	125 (21)	134 (22)	87 (14)
CONV	111 (19)	119 (20)	79 (14)
Any ACE inhibitors or angiotensin receptor II blockers‡			
INT			290 (48)
CONV			301 (52)
Medication for neuropathic pain in hands/feet			
INT			41 (7)
CONV			35 (6)

Data are means ± SD or *n* (%). *$P < 0.05$ former intensive treatment group (INT) vs. former conventional treatment group (CONV). †$P < 0.01$ INT vs. CONV. ‡Data on medication use was not collected during the DCCT.

continued to be significant (55% former intensive vs. 68% former conventional treatment, $P < 0.001$). Similarly, the prevalence of confirmed clinical neuropathy increased substantially in both treatment groups, and the between-group difference remained significant (25% former intensive vs. 35% former conventional treatment, $P < 0.001$).

The results are shown separately within the primary prevention and secondary intervention cohorts in supplemental Table 2a. At each evaluation, the prevalences of most indicators of neuropathy were higher in the secondary intervention cohort than in the primary prevention cohort. At EDIC years 13–14, the primary prevention cohort showed a significant treatment group difference only in the prevalence of abnormal NCS results, whereas the secondary intervention cohort showed significant treatment group differences in the prevalence of all measures of neuropathy except abnormal reflexes. Similarly, the between-treatment group difference in prevalence of confirmed clinical neuropathy was significant in the secondary prevention cohort (29% former intensive vs. 42% former conventional treatment, $P < 0.01$) but not in the primary prevention cohort (22% former intensive vs. 28% former conventional treatment, P = NS).

NCS results

NCS results at DCCT baseline, DCCT closeout, and EDIC years 13–14 are summarized in Table 3, with the median (50th), 5th, and 95th percentile values for each attribute by treatment group. At DCCT baseline, there were no significant between-group differences for any of the individual NCS attributes or for the overall test of stochastic ordering. At DCCT closeout, there were treatment group differences in most NCS results. Performance was generally worse (e.g., lower amplitude, slower conduction velocity, or longer *F* wave latency) for the conventional treatment group compared with the intensive treatment group. At DCCT closeout, the Wei-Lachin test (11) of the overall difference between groups in all 10 NCS measures simultaneously showed a significant favorable effect of intensive therapy.

During EDIC years 13–14, all NCS results showed substantial deterioration from DCCT closeout. The median (50th percentile) NCS values were characterized by low sensory amplitudes, low sensory and motor conduction velocities, and prolonged *F* wave latencies. Many values approached or exceeded the upper or lower limit of normal. Despite substantial deterioration, NCS performance was still better in the former intensive than the former conventional treatment group. However, the differences between treatment groups were smaller at EDIC years 13–14 than at DCCT closeout, and the level of significance (based on the overall

Table 2—*Prevalence of clinical (symptoms and signs) and NCS results suggestive of distal symmetrical polyneuropathy at DCCT baseline, DCCT closeout, and EDIC years 13–14*

Variable	DCCT baseline	DCCT closeout	EDIC years 13–14
Clinical examination			
Symptoms			
INT	32 (5)	44 (7)*	119 (20)†
CONV	39 (7)	75 (13)	172 (30)
Abnormal sensation			
INT	128 (21)	147 (25)†	248 (41)*
CONV	120 (21)	206 (36)	292 (50)
Abnormal reflexes			
INT	105 (18)	135 (23)†	264 (44)
CONV	93 (16)	212 (37)	292 (50)
Clinical neuropathy			
INT	57 (10)	88 (15)†	204 (34)†
CONV	48 (8)	128 (22)	240 (41)
Electrophysiology			
Abnormal NCS			
INT	185 (31)	164 (28)†	326 (54)†
CONV	196 (34)	288 (50)	401 (69)
Primary outcome			
Confirmed clinical neuropathy			
INT	39 (7)	52 (9)†	152 (25)†
CONV	31 (5)	97 (17)	204 (35)

Data are *n* (%). *$P < 0.01$ former intensive treatment group (INT) vs. former conventional treatment group (CONV). †$P < 0.001$ INT vs. CONV.

test of stochastic ordering *Z* scores) was less (Table 3).

The secondary intervention cohort generally showed poorer NCS performance (greater deviation from normal) than the primary prevention cohort (supplemental Table 3a). The treatment group differences in NCS results at DCCT closeout were consistent across the primary prevention and secondary intervention cohorts. Between-treatment group differences persisted at EDIC years 13–14 but were smaller, particularly among the primary prevention cohort.

Measures of incident neuropathy

Table 4 shows the incidence of clinical and NCS indicators of neuropathy at DCCT closeout and EDIC years 13–14 among subjects who did not fulfill the specific criterion for neuropathy at the preceding evaluation. At DCCT closeout, the incidences of all measures of neuropathy and of confirmed clinical neuropathy (6 vs. 14%, $P < 0.001$) were significantly lower in the intensive treatment group compared with the conventional treatment group. At EDIC years 13–14, the incidences of all measures of neuropathy had increased substantially in both treatment groups relative to DCCT closeout, and the only significant difference between groups was in the incidence of confirmed clinical neuropathy (22% former intensive treatment vs. 28% former conventional treatment, $P = 0.0125$).

The results of the analyses of incident neuropathy for the primary prevention and secondary intervention cohorts are shown in supplemental Table 4a. The incidence of all measures of neuropathy at DCCT closeout and EDIC years 13–14 was higher in the secondary intervention cohort than the primary prevention cohort. At EDIC years 13–14, no significant treatment group differences existed for any measure of incident neuropathy in either cohort.

Supplemental Table 5a presents the odds of developing clinical neuropathy, abnormal NCS results, or confirmed clinical neuropathy at DCCT closeout and at EDIC years 13–14 among subjects who did not fulfill the specific criterion for neuropathy at DCCT closeout. As previously reported (8,10), a significant treatment group effect was found for all measures of incident neuropathy at DCCT closeout favoring intensive treatment compared with conventional treatment ($P < 0.001$). At EDIC years 13–14, the original treatment group assignment continued to affect the incidence of confirmed clinical neuropathy, reducing the odds of developing confirmed clinical neuropathy 13–14 years after DCCT closeout (odds ratio [OR] 0.70 [95% CI 0.52–0.93]). However, as previously shown (12), among subjects without clinical neuropathy at DCCT closeout, the intensive treatment group still had significantly better NCS results versus the conventional treatment group. In additional models that adjusted for the average rank of selected NCS results at DCCT closeout, the former intensive treatment group no longer showed a significant effect on incident neuropathy during the EDIC study. For example, the OR for confirmed clinical neuropathy was 1.17 (0.84–1.63), indicating that the long-term difference in incident neuropathy observed during the EDIC study was explained by these subclinical differences in NCS results at DCCT closeout among subjects who did not have confirmed clinical neuropathy. For each outcome, an optimal subset model was constructed, and the best model was selected based on the lowest value of the Akaike Information Criterion (13). The selected covariates are shown in supplemental Table 5a, although all models gave similar results.

Analyses also investigated the differences between the former treatment groups in the ranks of the NCS measures at EDIC years 13–14 among subjects without confirmed clinical neuropathy at DCCT baseline or closeout after adjusting for the average NCS rank at DCCT closeout. The Wei-Lachin test of no difference between groups for all 10 quantitative NCS measures simultaneously showed an aggregate significant benefit of former intensive versus conventional treatment ($P = 0.0032$). Additional ANCOVA models of each quantitative NCS measure at EDIC years 13–14 that likewise adjusted for DCCT closeout NCS results showed nominally significantly better performance for the former intensive treatment group versus the former conventional treatment group in three of the NCS measures, all in the lower extremity, including peroneal amplitude ($P = 0.0082$), sural amplitude ($P = 0.0070$), and sural conduction velocity ($P = 0.0255$). These results were similar for models with and without limb temperature adjustments.

Influence of glycemic control during the DCCT and the EDIC study on neuropathy

The effect of glycemic control on indicators of incident and prevalent neuropathy

Table 3—*NCS results at DCCT baseline, DCCT closeout, and EDIC years 13–14*

Nerve/attribute	DCCT baseline	DCCT closeout	EDIC years 13–14
Median motor			
Amplitude (abnormal limit <4.2) (mV)			
INT	10.2 (4.5–17.5)	10.1 (5.0–16.0)	8.8 (4.2–14.8)
CONV	10.0 (4.5–17.0)	10.0 (5.0–16.0)	8.9 (4.0–14.4)
Conduction velocity (abnormal limit <49.0) (m/s)			
INT	54.0 (46.5–61.2)	55.0 (48.0–61.1)†	51.4 (42.5–58.2)*
CONV	53.8 (46.9–60.3)	52.3 (44.2–59.3)	51.0 (42.9–57.7)
F wave latency (abnormal limit >31.8) (ms)			
INT	28.0 (24.0–33.0)	27.6 (24.1–32.1)†	29.5 (25.4–35.0)
CONV	28.0 (24.0–32.6)	28.8 (24.8–34.0)	29.9 (25.6–36.4)
Median sensory			
Amplitude (abnormal limit <10.0) (μV)			
INT	19.0 (7.0–47.0)	15.0 (5.0–45.0)	9.0 (0.0–29.0)
CONV	20.0 (7.0–50.0)	14.0 (3.0–40.0)	8.0 (0.0–29.0)
Conduction velocity (abnormal limit <48.0) (m/s)			
INT	51.8 (38.2–63.4)	51.8 (36.8–62.0)†	43.8 (25.9–57.9)
CONV	52.1 (39.4–64.0)	50.0 (33.0–61.0)	43.1 (25.9–56.8)
Peroneal motor			
Amplitude (abnormal limit <2.5) (mV)			
INT	5.6 (2.0–10.0)	5.8 (2.0–10.0)†	4.2 (0.3–9.0)†
CONV	5.5 (2.0–10.9)	5.0 (1.1–10.0)	3.5 (0.1–7.6)
Conduction velocity (abnormal limit <40.0) (m/s)			
INT	43.7 (35.5–51.5)	45.0 (37.0–52.0)†	42.1 (30.5–49.3)†
CONV	43.8 (35.6–50.9)	41.5 (33.0–49.0)	40.6 (25.7–47.8)
F wave latency (abnormal limit >56.0) (ms)			
INT	50.4 (41.6–61.6)	50.6 (42.0–69.8)†	53.3 (43.9–74.0)†
CONV	50.8 (40.4–62.0)	54.5 (42.9–69.8)	55.5 (45.1–74.0)
Sural sensory			
Amplitude (abnormal limit <5.0) (μV)			
INT	12.0 (0.0–28.0)	11.0 (0.0–27.0)†	7.0 (0.0–18.0)†
CONV	13.0 (0.0–30.0)	9.0 (0.0–23.0)	5.0 (0.0–15.0)
Conduction velocity (abnormal limit <40.0) (m/s)			
INT	45.1 (35.0–56.0)	45.2 (35.9–56.0)†	42.4 (29.8–51.9)†
CONV	45.2 (34.1–56.0)	42.4 (34.6–52.0)	40.0 (29.8–50.0)
Overall (test of stochastic ordering)‡	$Z = 1.74$	$Z = 7.99$	$Z = 4.60$
	$P = 0.0819$	$P = <0.0001$	$P = <0.0001$

Data are median (5–95%). *$P < 0.05$ former intensive treatment group (INT) vs. former conventional treatment group (CONV). †$P < 0.01$ INT vs. CONV. ‡The test of stochastic ordering tests whether the majority of the measures show differences in a single direction, thus favoring one treatment group over the other.

was modeled as a function of mean A1C level during the DCCT and during the EDIC study. Supplemental Table 6a presents the OR of developing or having the particular indicator of neuropathy per unit A1C percent increase (e.g., 8 vs. 7%), given that all other variables were held constant. The mean A1C level during the DCCT was significantly associated with the incidence of confirmed clinical neuropathy and with the prevalence of all measures of neuropathy at EDIC years 13–14. Similarly, the mean A1C level during the EDIC was a significant predictor of all measures of incident and prevalent neuropathy at EDIC years 13–14. The odds of developing emergent confirmed clinical neuropathy during the EDIC study increased significantly per unit (%) increase in mean A1C during the DCCT (OR 1.24 [95% CI 1.10–1.41]) and during the EDIC study (1.82 [1.55–2.14]). The odds of having confirmed clinical neuropathy at EDIC years 13–14 (prevalence) likewise increased significantly per unit increase in mean A1C during the DCCT (1.35 [1.35–1.50]) and during the EDIC study (1.80 [1.56–2.07]).

CONCLUSIONS — Intensive treatment designed to achieve near-normal glycemia among patients with type 1 diabetes delayed or prevented the development of neuropathy over an average of 6.5 years in the DCCT (1). The differences in retinopathy and nephropathy associated with intensive versus conventional treatment persisted after differences in A1C levels dissipated, supporting the concept of metabolic memory (6). Less rigorous cross-sectional evaluations of neuropathy performed at EDIC year 8 showed that the benefits of 6.5 years of intensive treatment had persisted (7), a finding consistent with other beneficial effects of metabolic control on neuropathy (14–16). Information about incident or progressive neuropathy among EDIC participants was limited, however, because the neuropathy measures used during the initial EDIC evaluations differed from those used in the DCCT. The current NeuroEDIC evaluations address this concern by using the

Table 4—*Incidence of clinical neuropathy, abnormal NCSs, and confirmed clinical neuropathy at DCCT closeout and EDIC years 13–14 among subjects who did not fulfill the specific criterion for neuropathy at the preceding evaluation*

Variable	DCCT baseline	DCCT closeout	EDIC years 13–14
Clinical neuropathy			
INT	57/600 (10)	57/533 (11)†	145/505 (29)
CONV	48/581 (8)	96/526 (18)	154/448 (34)
Abnormal NCSs			
INT	185/601 (31)	73/410 (18)†	195/430 (45)
CONV	196/582 (34)	137/382 (36)	151/290 (52)
Confirmed clinical neuropathy			
INT	39/600 (7)	32/551 (6)†	117/541 (22)
CONV	31/581 (5)	75/543 (14)	136/479 (28)‡

Data are *n* (%). †$P < 0.001$ former intensive treatment group (INT) vs. former conventional treatment group (CONV). ‡$P = 0.125$.

same neuropathy measures performed during the DCCT.

In the current analyses, prior treatment-group differences in the prevalence of confirmed clinical neuropathy persisted 13–14 years after DCCT closeout, despite the rapid, post-DCCT disappearance of glycemic separation, reflecting both improvement of glycemic control in the former conventional treatment group and worsening of glycemic control in the former intensive treatment group. All significant differences in measures of neuropathy favored the former intensive treatment group over the former conventional treatment group. The absolute risk reduction was relatively small at EDIC years 13–14, but glycemic separation had not existed for nearly a decade. Despite this persistent effect of prior treatment, the current results are disappointing in that 34% of subjects in the former intensive treatment group and 41% of those in the former conventional treatment group developed clinical neuropathy, and 25 and 35% of the former intensive and conventional treatment groups, respectively, developed confirmed clinical neuropathy. The higher prevalence of most indicators of neuropathy at each evaluation in the secondary intervention cohort compared with the primary prevention cohort is consistent with those participants having a longer duration of diabetes. The prevalence of neuropathy 13–14 years after DCCT closeout seems high but may not be when compared with other studies. At EDIC years 13–14, the duration of diabetes averaged 23 years among the primary prevention cohort and 30 years among the secondary intervention cohort. Previous estimates have suggested that >50% of patients with a 25-year history of diabetes have neuropathy (17). By this measure, the prevalence of neuropathy identified in NeuroEDIC may be lower than anticipated.

Analyses show that former intensive therapy had a long-term effect on incident confirmed clinical neuropathy among subjects free of this outcome at DCCT closeout (supplemental Table 5a). However, previous analyses have suggested that the categorical definitions of neuropathy inadequately adjust for the levels of subclinical neuropathy at DCCT closeout (12). When the analysis of each clinical outcome was adjusted for the mean rank of the 10 NCS measures at DCCT closeout, the effect was no longer statistically significant. These findings indicate that the long-term beneficial effects of intensive therapy on clinical neuropathy in the EDIC study could be explained by the residual difference between groups in the NCSs among patients at DCCT closeout.

Analyses also show that intensive treatment had significant long-term beneficial effects on NCS measures in the EDIC study, both individually and overall (Table 3). However, after adjusting for the residual NCS differences at DCCT closeout, differences persisted for 3 of 10 NCS measures, all from the lower extremity and among those most likely to be abnormal in mild diabetic neuropathy. Thus, metabolic memory may apply to neuropathy as well as retinopathy and nephropathy, but part of its long-term effect is mediated by treatment group differences in residual subclinical NCS results at closeout among subjects who remain asymptomatic. However, the current analyses cannot exclude the possibility of a prior and more robust effect attributable to metabolic memory that diminished or resolved 13–14 years after DCCT closeout. Indeed, the magnitude of the effect of prior intensive treatment on diabetic retinopathy has diminished over time (18).

Our study had some limitations. The definition of clinical neuropathy used in the DCCT and the EDIC study required appropriate symptoms and signs, based on the neurologist's interpretation of the neurological examination. Absolute values of normality were then used for electrodiagnostic measures to identify confirmed clinical neuropathy. A criticism of our use of the electrodiagnostic results may be that adjustments were not made for potential confounders, such as height, when determining whether NCS results were normal. Regardless, there was considerable agreement between the clinical and electrodiagnostic measures of neuropathy. The initial analyses also did not exclude subjects identified to have competing cause for neuropathy. In subsequent analyses, history forms were reviewed to identify subjects who were receiving (or who had received) medications associated with peripheral neurotoxicity ($n = 4$) or subjects who had conditions thought by the examining neurologist to contribute to or explain the subject's neuropathy ($n = 5$). Repeat analyses excluding this small number of subjects showed results similar to the original results including all subjects (data not shown).

In summary, we found that the reduced prevalence of neuropathy resulting from former intensive treatment of patients with type 1 diabetes persisted for at least 13–14 years. However, the current findings are disappointing in terms of the cumulative frequency of neuropathy and do not support the initial optimism that the effects of diabetes on the peripheral nervous system attributable to hyperglycemia could be arrested. Intensive treatment appears important but insufficient to delay progression or to prevent development of diabetic neuropathy in many subjects. Although models that adjusted for NCS differences at DCCT closeout based on a composite NCS score failed to show significant treatment group differences for incident neuropathy, we found support for the concept of metabolic memory on the NCS measures when we used more powerful analyses that adjusted for the actual NCS values at closeout.

Despite the substantial prevalence of neuropathy among the NeuroEDIC participants, the results of the current study

provide further evidence of the importance of good glycemic control. Incident and prevalent neuropathy at EDIC years 13–14 were strongly influenced by the mean A1C levels from DCCT baseline through the NeuroEDIC assessment, confirming that poor glycemic control is a significant and robust predictor of neuropathy.

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