Online-Only Appendix to:

"Effect of Prior Intensive Insulin Therapy on Peripheral Neuropathy in Type 1 Diabetes"

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Supplemental data to be made available electronically (Online-Only)

Nerve Conduction Studies

Surface temperatures were measured from the forearm, palm, anterior leg, and calf for the median motor, median sensory, peroneal, and sural recordings, respectively, immediately before and after each recording, as done in the DCCT. Electromyographers were provided with the DCCT closeout temperatures and instructed to approximate the temperatures to the extent possible. The averaged pre- and post-recording temperatures from the forearm, palm, anterior leg, and calf during NeuroEDIC were 33.1º C, 33.0º C, 32.4º C, and 32.0º C, respectively. These temperatures did not differ significantly from the DCCT closeout temperatures, and there were no significant treatment group differences in surfaces temperatures at DCCT closeout or EDIC year 13-14.

Statistical Analyses

When NCS responses were unelicitable, conduction velocity was recoded as the 1st percentile, latency as the 99th percentile, and amplitude as 0. The Wilcoxon rank-sum test assessed group differences in ordinal or quantitative variables, and the contingency Chi-square test for categorical variables. NCS values were ranked from lowest to highest, lower values reflecting greater abnormality, for all attributes except F response latency where higher values (indicating greater abnormality) were assigned lower ranking. Midranks were used for tied ranks. Rank-transformation analysis of covariance (ANCOVA) assessed group differences in the ranks of the 10 NCS measures in EDIC at DCCT baseline or closeout, adjusted for the mean NCS rank at DCCT closeout and both the DCCT and EDIC limb temperature during the nerve conduction study. The overall treatment group difference in the 10 NCS measures was assessed using the nonparametric Wei-Lachin rank test of stochastic ordering (11) that assesses whether one group on average tends to have better outcomes for all 10 measures than the other group.

Logistic regression models assessed group differences in, and other covariate effects on, the odds of an outcome. Analyses of prevalent neuropathy at EDIC year 13-14 employed all subjects assessed, whereas analyses of incident outcomes excluded subjects with the specific neuropathy outcome at the preceding evaluation. Models also adjusted for the average rank of NCS results at DCCT closeout to control for residual differences between groups.(12) Separate models adjusted for the average rank of all NCS measures, all leg measures, leg amplitude and conduction velocity measures, and peroneal and sural amplitude and peroneal conduction velocity. Additional covariates evaluated included age, sex, height, weight, body mass index (BMI), cardiovascular risk factors, and medications (analgesics and ACE/ARBs). A forward

stepwise selection procedure was used, and covariates having a P value <0.10 were included in the models. Interaction terms between treatment group and another covariate with p <0.10 were kept in the final models. For each neuropathy outcome, the 'best' model was selected based on the lowest value of the Akaike Information Criterion (AIC).(13)

Prior glycemic exposure was measured by the mean HbA1c level during DCCT (i.e. from month 3 to closeout) and during EDIC (from year 1 to the NCS at year 13-14).

Statistical analyses were performed using SAS V 8.2 (Cary, NC).

Neurologists and Electromyographers –

B. Katirji, P. Neal, K. Spencer, M.J. Brown, S.J. Bird, J. Christine, M. Rubin, I. Zaprianova, E.J. Angus, B.K. Ahmad, R. Freeman, R. Nardin, C. Gibbons, P. Siao Tick Chong, D. Cros, P.J. Dyck, J.R. Daube, J.E. Kurent, D. Freking, E. Aul, S. Mennen, L. Rios, W. Sebetka, D. Walk, R. Conway, J. Hoerner, D. Lacomis, S. Zivkovic, C. Shipes, S. Boksenbaum, S. Fedorek, T. Bertorini, S. Vernino, B. Brightman, A. Gordon, M. Weiss, G. Meekins, J. Distad, R. Chan, A. Kilroy, M.T. Al-Lozi, J. Goldstein, S., Novella, J. Verghese, S.A. Driss, N. Desai, C. Hafer-Macko, J. Russell, J.E. Chapin, J. Korthals, J. Teener, E.L. Feldman, J.W. Albers

Table 1a. Characteristics of NeuroEDIC participants at DCCT baseline, DCCT closeout, and EDIC year 13-14

		Primary Prevention				Secondary Intervention			
Characteristic	**Group**	**N**	**DCCT Baseline**	**DCCT Closeout**	**EDIC Year 13-14**	**N**	**DCCT Baseline**	**DCCT Closeout**	**EDIC Year 13-14**
Age, mean (SD), years	INT	297	27 (7) *	33 (7) *	47 (7) *	306	28 (7) *	35 (7) *	49 (7) *
	CONV	296	26 (8)	32 (7)	46 (7)	287	27 (7)	34 (6)	48 (6)
Female, N (%)	INT		152 (51)	152 (51)	152 (51)		142 (46)	142 (46)	142 (46)
	CONV		128 (43)	128 (43)	128 (43)		140 (49)	140 (49)	140 (49)
Height, mean (SD), cm	INT		171 (10)	172 (10)	172 (9)		171 (10)	171 (9)	171 (9)
	CONV		172 (10)	173 (9)	173 (9)		171 (10)	172 (10)	172 (10)
Weight, mean (SD), kg	INT		68 (12)	78 (14) †	84 (17)		69 (10)	79 (14) †	84 (18)
	CONV		70 (13)	75 (13)	85 (18)		70 (12)	74 (12)	83 (16)
BMI, mean (SD), kg/m^2	INT		23 (3)	27 (5) †	28 (5)		24 (3)	27 (4) †	29 (5)
	CONV		23 (3)	25 (3)	28 (5)		24 (3)	25 (3)	28 (5)
BMI $\geq$ 30, kg/m^2	INT		4 (1)	54 (19) †	94 (32)		3 (1)	61 (20) †	108 (36) *
	CONV		3 (1)	13 (4)	92 (32)		7 (2)	14 (5)	80 (28)
Diabetes duration, mean (SD), years	INT		2.5 (1.3)	8.6 (2.3)	22.4 (2.4)		8.9 (3.8)	16.0 (4.0)	29.7 (4.0)
	CONV		2.5 (1.3)	8.5 (2.3)	22.2 (2.4)		8.7 (3.7)	15.7 (4.0)	29.4 (4.1)
HbA1c, mean (SD), %	INT		9.0 (1.7)	7.4 (1.0) †	7.9 (1.2)		9.2 (1.5)	7.3 (1.0) †	7.8 (1.2)
	CONV		8.9 (1.6)	9.2 (1.5)	7.8 (1.1)		9.0 (1.6)	9.0 (1.5)	7.7 (1.2)
Systolic BP, mean (SD), mmHg	INT		112 (11) †	115 (11)	121 (14)		114 (12) †	118 (12)	121 (14)
	CONV		114 (12)	115 (11)	119 (14)		116 (12)	118 (12)	122 (14)
Diastolic BP, mean (SD), mmHg	INT		72 (9)	74 (9)	75 (9)		73 (9)	75 (8)	73 (9)
	CONV		72 (9)	73 (9)	74 (9)		74 (9)	75 (9)	73 (9)
Total cholesterol, mean (SD), mg/dl	INT		177 (33)	179 (30)	181 (37)		178 (34)	182 (32)	171 (35)
	CONV		169 (33)	180 (35)	172 (35)		178 (32)	186 (37)	174 (36)
LDL cholesterol, mean (SD), mg/dl	INT		110 (30)	111 (27)	106 (31)		111 (29)	114 (27)	99 (29)
	CONV		104 (29)	111 (30)	101 (30)		112 (28)	118 (31)	100 (31)
Current smoker, N (%)	INT		61 (21)	70 (24) *	47 (16)		64 (21)	64 (21)	40 (13)
	CONV		51 (17)	59 (20)	43 (15)		60 (21)	60 (21)	36 (13)
Any ACE or ARB, N (%) ‡	INT				138 (46)		64 (21)	99 (34)	152 (50) *
	CONV				134 (45)		73 (25)	101 (36)	167 (58)

Pain or numbness in hands/feet, N (%)	INT	82 (28)	103 (34)
	CONV	73 (25)	113 (39)
Medication for neuropathic pain in hands/feet, N (%)	INT	41 (24)	41 (24)
	CONV	35 (20)	35 (20)

INT former intensive treatment group, CONV former conventional treatment group, BMI body mass index
* p<0.05 INT versus CONV
† p<0.01 INT versus CONV
‡ Data on medication use was not collected during the DCCT.

Table 2a. Prevalence of clinical (symptoms and signs) and nerve conduction study results suggestive of distal symmetrical polyneuropathy at DCCT baseline, DCCT closeout, and EDIC year 13-14

		Primary Prevention			Secondary Intervention		
Variable	**Group**	**DCCT Baseline**	**DCCT Closeout**	**EDIC Year 13-14**	**DCCT Baseline**	**DCCT Closeout**	**EDIC Year 13-14**
				No. (%)			
Clinical examination							
Symptoms	INT	11 (4)	15 (5)	52 (18)	21 (7)	29 (10)	67 (22) **
	CONV	16 (5)	28 (10)	71 (24)	23 (8)	47 (16)	101 (35)
Abnormal sensation	INT	51 (17)	67 (23)	120 (40)	77 (25)	79 (26) **	128 (42) **
	CONV	43 (15)	88 (30)	126 (43)	77 (27)	118 (42)	166 (58)
Abnormal reflexes	INT	33 (11)	40 (14) **	110 (37)	72 (24)	95 (32) **	154 (50)
	CONV	27 (9)	81 (28)	126 (43)	66 (23)	131 (46)	166 (58)
Clinical neuropathy	INT	20 (7)	28 (10) **	93 (31)	37 (12)	60 (20) **	111 (36) **
	CONV	12 (4)	43 (15)	101 (34)	36 (13)	85 (30)	139 (48)
Electrophysiology							
Abnormal NCS	INT	59 (20)	60 (21) **	140 (47) **	126 (41)	104 (34) **	186 (61) **
	CONV	64 (22)	119 (41)	185 (63)	132 (46)	169 (59)	216 (75)
Primary Outcome							
Confirmed clinical neuropathy	INT	14 (5)	13 (4)	64 (22)	25 (8)	39 (13) **	88 (29) **
	CONV	5 (2)	28 (10)	83 (28)	26 (9)	69 (24)	121 (42)

* p<0.01; ** p<0.001 INT versus CONV
INT former intensive treatment group, CONV former conventional treatment group, NCS nerve conduction studies

Table 3a. Nerve conduction study results at DCCT baseline, DCCT closeout, and EDIC year 13-14

			Primary Prevention			Secondary Intervention		
Nerve/Attribute	**Abnormal Limit**	**Group**	**DCCT Baseline**	**DCCT Closeout**	**EDIC Year 13-14**	**DCCT Baseline**	**DCCT Closeout**	**EDIC Year 13-14**
Median Motor					**median (5%, 95%)**			
Amplitude, mV	<4.2	INT	10.4	10.2	9.1	10.0	10.1	8.4
			(4.0, 16.6)	(5.4, 16.0)	(4.4, 15.2)	(4.6, 18.0)	(4.8, 16.0)	(3.9, 13.8)
		CONV	10.0	10.2	9.3	10.0	10.0	8.6
			(5.0, 17.0)	(5.5, 16.0)	(4.5, 15.2)	(4.2, 17.0)	(4.8, 16.0)	(3.7, 14.4)
Conduction velocity, M/sec	<49.0	INT	54.9	55.7 **	51.6	53.3	54.3 **	51.2 **
			(48.2, 61.4)	(49.1, 62.0)	(42.4, 58.1)	(46.0, 61.0)	(47.3, 60.2)	(42.9, 58.7)
		CONV	54.7	52.8	51.4	52.8	51.9	50.0
			(48.0, 60.9)	(45.3, 60.1)	(42.9, 58.3)	(46.0, 59.7)	(43.1, 58.8)	(42.3, 57.3)
F-wave latency, msec	>31.8	INT	27.6	27.3 **	29.3	28.6	28.0 **	29.7
			(24.0, 32.0)	(24.0, 31.6)	(25.4, 34.0)	(24.0, 33.3)	(24.4, 32.4)	(25.4, 35.2)
		CONV	27.8	28.5	29.7	28.0	29.2	30.2
			(23.7, 32.2)	(24.7, 33.3)	(25.4, 36.1)	(24.3, 33.3)	(24.8, 35.4)	(25.8, 36.6)
Median Sensory								
Amplitude, μV	<10.0	INT	20.0	17.0	10.0	16.0	12.5	9.0
			(8.0, 50.0)	(6.0, 45.0)	(1.0, 29.0)	(6.0, 41.0)	(5.0, 43.0)	(0.0, 29.0)
		CONV	21.0	16.0	9.0	19.0	12.0	7.0
			(9.0, 55.0)	(3.0, 42.0)	(0.0, 32.0)	(5.0, 45.0)	(2.0, 36.0)	(0.0, 29.0)
Conduction velocity, M/sec	<48.0	INT	53.0	53.1 *	45.0	50.0	50.0 **	43.1
			(41.9, 65.2)	(39.0, 63.7)	(25.9, 59.1)	(36.7, 61.9)	(34.4, 60.8)	(25.9, 55.5)
		CONV	54.0	51.7	43.8	50.4	46.8	41.2
			(40.3, 65.0)	(37.0, 61.9)	(25.9, 58.0)	(38.0, 62.1)	(32.5, 59.0)	(25.9, 54.2)
Peroneal Motor								
Amplitude, mV	<2.5	INT	6.0	6.0 *	4.7 *	5.0	5.2 **	3.8 **
			(2.7, 11.0)	(2.2, 10.3)	(0.8, 9.2)	(1.6, 10.0)	(1.5, 10.0)	(0.2, 8.0)
		CONV	6.0	5.2	3.9	5.0	4.4	3.0
			(2.3, 11.5)	(1.7, 10.5)	(0.3, 7.9)	(1.9, 10.0)	(0.8, 9.5)	(0.1, 7.4)

Conduction velocity, M/sec	<40.0	INT	45.0	45.8 **	42.6 **	42.6	44.0 **	41.7 **
			(38.1, 52.0)	(39.3, 52.4)	(32.6, 50.0)	(34.0, 49.2)	(36.1, 51.7)	(28.7, 49.1)
		CONV	44.8	42.0	41.1	42.7	41.0	40.0
			(37.9, 52.3)	(34.4, 49.5)	(27.7, 48.4)	(34.2, 50.0)	(32.4, 48.2)	(25.4, 46.7)
F-wave latency, msec	>56.0	INT	49.8	49.4 **	52.4 *	51.7	51.6 **	53.9 *
			(40.6, 59.0)	(41.8, 69.8)	(43.9, 74.0)	(43.0, 62.4)	(42.3, 69.8)	(44.4, 74.0)
		CONV	50.4	53.6	54.1	51.0	55.6	56.0
			(39.0, 61.8)	(42.3, 69.8)	(44.4, 74.0)	(41.1, 62.7)	(44.4, 69.8)	(45.8, 74.0)
Sural Sensory								
Amplitude, µV	<5.0	INT	15.0	12.0 **	7.0	10.0	10.0 **	6.0 **
			(2.0, 30.0)	(3.0, 28.0)	(0.0, 20.0)	(0.0, 24.0)	(0.0, 25.0)	(0.0, 17.0)
		CONV	15.0	10.0	7.0	11.0	7.0	4.0
			(1.0, 30.0)	(0.0, 25.0)	(0.0, 18.0)	(0.0, 28.0)	(0.0, 20.0)	(0.0, 13.0)
Conduction velocity, M/sec	<40.0	INT	45.8	46.6 **	42.4 *	42.6	43.8 **	41.2 **
			(36.4, 56.0)	(36.8, 58.3)	(29.8, 53.8)	(32.6, 55.0)	(35.6, 53.8)	(29.8, 50.0)
		CONV	46.6	43.7	41.2	43.7	41.6	38.9
			(36.8, 56.0)	(35.5, 53.8)	(29.8, 51.9)	(32.6, 54.4)	(34.1, 50.3)	(29.8, 50.0)
Overall (test of stochastic ordering)		Z =	0.97	6.05	2.40	1.19	6.01	4.19
		P =	0.3297	<0.0001	0.0164	0.2359	<0.0001	<0.0001

* p<0.01; ** p<0.001 INT versus CONV
INT former intensive treatment group, CONV former conventional treatment group
~ 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

Table 4a. Incidence of clinical neuropathy, abnormal nerve conduction study, and confirmed clinical neuropathy at DCCT closeout and EDIC year 13-14 among subjects who did not fulfill the specific criterion for neuropathy at the preceding evaluation

		Primary Prevention			Secondary Intervention		
Variable	**Group**	**DCCT Baseline**	**DCCT Closeout**	**EDIC Year 13-14**	**DCCT Baseline**	**DCCT Closeout**	**EDIC Year 13-14**
				No. (%)			
Clinical neuropathy	INT	20/295 (7)	20/269 (7)	75/263 (29)	37/305 (12)	37/264 (14) *	70/242 (29)
	CONV	12/294 (4)	35/278 (13)	79/249 (32)	36/287 (13)	61/248 (25)	75/199 (38)
Abnormal NCS	INT	59/295 (20)	35/231 (15) **	94/232 (41)	126/306 (41)	38/179 (21) **	101/198 (51)
	CONV	64/295 (22)	70/228 (31)	81/174 (47)	132/287 (46)	67/154 (44)	70/116 (60)
Confirmed clinical neuropathy	INT	14/295 (5)	7/275 (3) *	53/278 (19)	25/305 (8)	25/276 (9) **	64/263 (24)
	CONV	5/294 (2)	24/285 (8)	65/264 (25)	26/287 (9)	51/258 (20)	71/215 (33)

INT former intensive treatment group, CONV former conventional treatment group, NCS nerve conduction studies
* $p<0.01$; ** $p<0.001$ INT versus CONV; § $p=0.0125$

Table 5a. Adjusted odds of incident clinical neuropathy, abnormal NCS, and confirmed clinical neuropathy at EDIC Year 13-14 among former intensive- and conventional treatment group subjects who did not fulfill the specific criterion for neuropathy at DCCT closeout. The "best" models having the lowest Akaike Information Criteria (AIC) value are shown

	EDIC Year 13-14	
Logistic Regression Models	**Unadjusted**	**Adjusted for average rank over NCS measures and age, sex, height, weight, BMI, cardiovascular risk factors, and medications ***
Variable	**OR (95% CI)**	
Clinical neuropathy	0.77 (0.59-1.01)	0.99 (0.73-1.34)
		Age and height, average rank of 3 leg NCS measures †
Abnormal NCS	0.76 (0.57-1.03)	1.01 (0.72-1.41)
		Weight; average rank of all 10 NCS measures ‡
Confirmed clinical neuropathy	0.70 (0.52-0.93)	1.17 (0.84-1.63)
		*Age and height***,** average rank of all 10 NCS measures ‡

NCS nerve conduction studies, BMI body mass index

* Covariates that entered into the models using a stepwise selection are indicated in *italics* with the OR (95% CI) for each model

† Adjusted for the average rank over 3 leg NCS measures at DCCT closeout: peroneal (amplitude and conduction velocity), sural (amplitude).

‡ Adjusted for the average rank over all 10 NCS measures at DCCT closeout: median motor (amplitude, conduction velocity, and F-wave latency), median sensory (amplitude and conduction velocity), peroneal (amplitude, conduction velocity, and F-wave latency), sural (amplitude, and conduction velocity).

Table 6a. Effect of total DCCT/EDIC glycemic exposure (per one-unit increase in mean HbA1c) on odds of prevalent (at EDIC year 13-14) or incident (during EDIC) clinical neuropathy, abnormal nerve conduction study, and confirmed clinical neuropathy (values in **bold** indicate a significant increase in the OR)

Logistic Regression Models		Prevalent	Emergent *
		OR (95% CI)	**OR (95% CI)**
Clinical neuropathy	DCCT mean HbA1c	**1.17 (1.06-1.29)**	1.07 (0.95-1.20)
	EDIC mean HbA1c	**1.64 (1.44-1.88)**	**1.74 (1.48-2.03)**
Abnormal NCS	DCCT mean HbA1c	**1.43 (1.28-1.60)**	1.14 (0.99-1.32)
	EDIC mean HbA1c	**1.87 (1.61-2.18)**	**1.96 (1.63-2.36)**
Confirmed clinical neuropathy	DCCT mean HbA1c	**1.35 (1.21-1.50)**	**1.24 (1.10-1.41)**
	EDIC mean HbA1c	**1.80 (1.56-2.07)**	**1.82 (1.55-2.14)**

NCS nerve conduction study, HbA1C glycosylated hemoglobin
Data is the proportional odds for a one-unit increase in DCCT or EDIC mean HbA1c on having the outcome, given all other variables are held constant.
* Among those with intact function at DCCT closeout.