

Vibration Perception Threshold as a Measure of Distal Symmetrical Peripheral Neuropathy in Type 1 Diabetes

Results from the DCCT/EDIC study

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OBJECTIVE — To describe the sensitivity, specificity, positive predictive value, and negative predictive value of vibration perception threshold (VPT) testing in subjects with type 1 diabetes relative to gold standard assessments of peripheral neuropathy.

RESEARCH DESIGN AND METHODS — VPT was determined in 1,177 adults with type 1 diabetes 13–14 years after participating in a study of intensive (INT) versus conventional (CONV) diabetes treatment. Abnormal VPT was defined by values exceeding 2.5 SD above age-specific normal values. Signs and symptoms of peripheral neuropathy were assessed and electrodiagnostic studies were performed to establish definite clinical neuropathy, abnormal nerve conduction, and confirmed clinical neuropathy (the presence of both definite clinical neuropathy and abnormal nerve conduction).

RESULTS — Thirty-seven percent of subjects had definite clinical neuropathy, 61% had abnormal nerve conduction, and 30% had confirmed clinical neuropathy. Abnormal VPT was more common among former CONV than among INT subjects (64 vs. 57%, $P < 0.05$) and was associated with older age. VPT was a sensitive measure of confirmed clinical neuropathy (87%) and of definite clinical neuropathy (80%) and a specific measure of abnormal nerve conduction (62%). Higher VPT cut points improved test sensitivity and lower cut points improved specificity. Areas under the receiver operating characteristic curves ranged from 0.71–0.83 and were higher for older than for younger subjects and highest for those with confirmed clinical neuropathy.

CONCLUSIONS — VPT was a sensitive measure of peripheral neuropathy. Future researchers may choose to select VPT cut points for defining abnormality based on the population studied and clinical outcome of interest.

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In the Diabetes Control and Complications Trial (DCCT), distal symmetrical peripheral neuropathy (DSPN) was defined categorically on the basis of clinical findings and electrodiagnostic (nerve conduction) studies (1–3). At the conclu-

sion of the DCCT, subjects were invited to participate in the Epidemiology of Diabetes Interventions and Complications (EDIC) study, a long-term observational follow-up of the DCCT cohort (4). In the EDIC study, DSPN was assessed annually

using the Michigan Neuropathy Screening Instrument (4,5). Beginning in 2007, during the 13th and 14th years of EDIC study follow-up (EDIC 13/14), the assessments of DSPN performed during DCCT were repeated. In keeping with consensus recommendations to include quantitative sensory testing in the diagnosis of diabetic neuropathy (6,7), vibration perception threshold (VPT) testing was added to the battery of neurological assessments performed at EDIC 13/14. Herein we describe VPT studies among EDIC study subjects 13–14 years after the conclusion of the DCCT and evaluate the performance of VPT as a stand-alone method for identifying DSPN relative to gold standard assessments involving neurologists' examinations and electrodiagnostic studies.

RESEARCH DESIGN AND

METHODS — At baseline, the DCCT studied 1,441 subjects aged between 13 and 39 years with type 1 diabetes for 1–15 years who were generally in good health. Subjects were randomly assigned to intensive (INT) or conventional (CONV) therapy and were followed for a mean of 6.5 years (1). The EDIC study enrolled 1,375 of the surviving DCCT subjects in 1994 (687 INT and 688 CONV). During EDIC 13/14, VPT studies were performed on 624 (94%) of former INT and 601 (91%) of former CONV subjects (4). Characteristics of subjects with VPT assessment did not differ from those of subjects who did not have VPT assessment performed (data not shown). Concurrent DSPN assessments were performed on 1,177 subjects.

VPT

VPT was assessed using the Vibratron II (Physitemp Instruments, Clifton, NJ). The device produces vibration amplitudes from 0.005–200 microns, expressed as vibration units (0.005 microns = 0.1 vibration unit; 200 microns = 20.0 vibration units), with a higher vibration unit value indicating

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worse performance or greater sensory dysfunction. A forced-choice algorithm was used to determine VPT at the dominant index finger and dominant great toe. The examiner controlled which of two metal posts (labeled A and B) was vibrating and controlled the vibration units using a predetermined algorithm. The subject placed his or her digit (finger or toe) first on post A and then on post B using light pressure for about 1 s and was asked to state which was vibrating. Subjects were encouraged to guess if uncertain and were not told if they were correct or incorrect. Subjects were positioned to prevent them from seeing the device settings. Vibration intensity was increased by 10% after incorrect responses and was decreased by 10% after correct responses. Stimuli at vibration units of ≤ 1.0 were repeated before increasing or decreasing the vibration intensity. The test was stopped when the subject made five errors over a minimum of 18 trials. Vibration units corresponding to the subject's first five errors and the five lowest correctly identified vibration units were rank ordered; the highest and lowest of these 10 were discarded. The average of the remaining eight values was recorded as the VPT. During a central training session, the study coordinator or research nurse from each EDIC study site was trained and was required to submit at least two VPT tests on non-EDIC study subjects to demonstrate competency in test administration and scoring.

Ninety-four subjects, two to six from each clinical site, were randomly selected for repeat VPT testing of the great toe on the same day and by the same examiner as a measure of test reproducibility. Examiners were instructed to wait at least 30 min between tests. In the interval, subjects re-wore any footwear worn before the primary test (8).

VPT results are expressed both as continuous and categorical variables using age-specific normal values provided by Physitemp Instruments (9). Values within 2.5 SD of the age-specific mean were categorized as normal, and those exceeding 2.5 SD were categorized as abnormal.

Definition of DSPN in DCCT and EDIC

Board-certified neurologists and electromyographers were identified, trained, and certified in the EDIC study to conduct neurological evaluations and electrodiagnostic studies using the protocol

Table 1—Characteristics of subjects evaluated for VPT in EDIC 13/14

| Characteristic | Total cohort | INT | CONV |
|------------------------------------|----------------|----------------|----------------|
| n | 1,177 | 599 | 578 |
| Age (years) | 47 \pm 7 | 48 \pm 7 | 47 \pm 7* |
| Men (%) | 622 (53) | 307 (51) | 315 (55) |
| Duration of diabetes (years) | 26 \pm 5 | 26 \pm 5 | 26 \pm 5 |
| A1C (%) | 7.8 \pm 1.2 | 7.8 \pm 1.2 | 7.8 \pm 1.2 |
| Height (cm) | 172 \pm 10 | 171 \pm 9 | 173 \pm 10 |
| BMI (kg/m ²) | 28.2 \pm 5.0 | 28.4 \pm 5.2 | 28.0 \pm 4.7 |
| Lower extremity ulcers (%) | 90 (8) | 37 (6) | 53 (9) |
| Definite clinical neuropathy (%) | 438 (37) | 201 (34) | 237 (41)† |
| Abnormal nerve conduction (%) | 722 (61) | 324 (54) | 398 (69)† |
| Confirmed clinical neuropathy (%)‡ | 353 (30) | 151 (25) | 202 (35)† |

Data are means \pm SD or n (%). Data are presented for same year in which the VPT test was performed. * $P < 0.05$; † $P < 0.01$ for treatment group differences by the Wilcoxon rank sum test or contingency χ^2 test. ‡Presence of signs and symptoms consistent with distal symmetrical polyneuropathy with abnormal electrodiagnostic tests in at least two of three nerves tested.

for the DCCT (1–3). Three analytic definitions were used in the DCCT and subsequently in the EDIC study to define DSPN. The first, definite clinical neuropathy, indicates the presence of symptoms and signs consistent with DSPN based on history and physical examination by a board-certified neurologist. The second, abnormal nerve conduction, represents one or more abnormal nerve conduction results (amplitude, conduction velocity, or F response latency) in two different peripheral nerves among the median (sensory or motor), peroneal motor, or sural sensory studies. Finally, confirmed clinical neuropathy was defined as the presence of both definite clinical neuropathy and abnormal nerve conduction (1–3).

Statistical analysis

Groups were compared using Wilcoxon rank sum tests for ordinal or continuous variables and contingency χ^2 tests for categorical variables. The performance of VPT in predicting definite clinical neuropathy, abnormal nerve conduction, and confirmed clinical neuropathy was assessed by determining sensitivity, specificity, positive predictive value (PPV), negative predictive value (NPV), and the Cohen κ (10) in the full cohort and separately for those aged 36–50 and 51–65 years. Sensitivity is the probability of having an abnormal VPT test in the presence of neuropathy. Specificity is the probability of having a normal VPT test in the absence of neuropathy. PPV is the proportion of subjects with neuropathy among those with abnormal VPT test results, reflecting both the sensitivity of the test and the prevalence of the condition in the population. NPV is the proportion of sub-

jects without neuropathy among those with normal VPT tests. The Cohen κ measures agreement between two methods. κ measures the percentage of data values in the main diagonal of a 2×2 table and then adjusts these values for the amount of agreement that could be expected due to chance alone. Perfect agreement results in the maximum value for κ of 1.0, values between 0.20 and 0.39 indicate fair agreement, values between 0.4 and 0.59 indicate moderate agreement, and values ≥ 0.6 indicate good agreement. Receiver operating characteristic (ROC) curves show the relationship between the true-positive ratio (sensitivity) and false-positive ratio ($1 - \text{specificity}$) of a test and can be used to define cut points to identify abnormal test results (11). Areas under the ROC curve (AUC) measure the performance of a test in predicting the outcome of interest. Generally, AUC values of 0.5 indicate that a test performs no better than chance, values between 0.70 and 0.79 indicate fair performance, values between 0.80 and 0.89 indicate good performance, and values ≥ 0.9 indicate excellent test performance.

RESULTS— Characteristics of the 1,177 participants with both DSPN and VPT assessment are shown in Table 1. DSPN was more prevalent among former CONV than among former INT participants ($P < 0.01$) using all three analytic definitions. DSPN prevalence among all participants was highest when defined by abnormal nerve conduction (61%). Definite clinical neuropathy was present in 37% of subjects and confirmed clinical neuropathy in 30% of subjects.

Subjects selected for repeat VPT test-

Table 2—VPT results for subjects evaluated in EDIC 13/14 by treatment group and age category

| Characteristic | Total cohort | Treatment group | | Age categories | | |
|------------------|--------------|-----------------|--------------|----------------|-------------|--------------|
| | | INT | CONV | ≤35 years | 36–50 years | 51–65 years |
| <i>n</i> | 1,177 | 599 | 578 | 59 | 693 | 425 |
| VPT great toe | 3.78 ± 2.35 | 3.53 ± 2.19 | 4.03 ± 2.47† | 2.38 ± 1.61 | 3.44 ± 1.97 | 4.53 ± 2.75† |
| Abnormal | 710 (61) | 341 (57) | 369 (64)* | 20 (34) | 401 (58) | 289 (69)† |
| VPT index finger | 1.05 ± 0.51 | 0.99 ± 0.42 | 1.11 ± 0.58† | 0.96 ± 0.42 | 1.00 ± 0.47 | 1.13 ± 0.58† |
| Abnormal | 71 (6) | 24 (4) | 47 (8)† | 2 (3) | 41 (6) | 28 (7) |

Data are means ± SD vibration units or *n* (%). **P* < 0.05; †*P* < 0.01 for treatment group or age-group differences by the Wilcoxon rank sum test or contingency χ^2 test.

ing were representative of the EDIC study cohort with respect to age (47.3 ± 7.3 years), sex (52% male), diabetes duration (24.8 ± 4.3 years), and frequency of confirmed clinical neuropathy (40%) and were equally distributed between treatment groups (*n* = 50 INT; *n* = 44 CONV). Eighty-three subjects had repeat testing. The mean primary and repeat test scores did not differ (3.8 ± 2.7 vs. 3.9 ± 2.8 vibration units, *P* = 0.38). The calculated test-retest coefficient of reliability was 0.85.

Mean VPT was higher at both the great toe and index finger among former CONV versus INT subjects (4.03 vs. 3.53, *P* < 0.01 at the great toe; 1.11 vs. 0.99, *P* < 0.01 at the index finger) (Table 2). VPT was abnormal at the great toe in a majority (61%) of subjects but was abnormal at the index finger in only 6% of subjects. VPT abnormalities were more prevalent among former CONV than among former INT subjects at both the toe and finger. Older age, regardless of former treatment group, was associated with higher mean VPT and greater prevalence of abnormal VPT (Table 2). Mean VPT values were higher at both the index finger (1.26 ± 0.67 vs. 1.03 ± 0.49 , *P* <

0.001) and great toe (5.86 ± 3.21 vs. 3.62 ± 2.20 , *P* < 0.001) among subjects reporting a lower extremity ulcer during the EDIC study compared with subjects with no reported lower extremity ulcers.

VPT was a sensitive predictor of all three DSPN outcome measures (Table 3), with the highest sensitivity noted for confirmed clinical neuropathy (87%). The sensitivity of VPT to predict definite clinical neuropathy and abnormal nerve conduction was 80 and 75%, respectively. For all three outcomes, sensitivity increased with age. Specificity of VPT was highest for abnormal nerve conduction (62%) and lowest for definite (51%) or confirmed clinical neuropathy (51%) (Table 3). For all outcome measures, specificity decreased with age.

The PPV of VPT was higher for abnormal nerve conduction (76%) than for definite (49%) or confirmed clinical neuropathy (43%) and increased with age (Table 3). The NPV of VPT was higher for confirmed (90%) and definite clinical neuropathy (81%) than for abnormal nerve conduction (61%) and did not vary substantially by age (Table 3). κ values indicated at least fair agreement between VPT and all three outcome measures and

were higher (indicating better agreement between VPT and the neurological outcome measures) in older participants.

ROC curves were generated to plot the performance of great toe VPT against all three DSPN outcome measures. Figure 1 shows the relationship between the true-positive ratio (sensitivity) and the false-positive ratio (1 – specificity) for various VPT values to predict definite clinical neuropathy (Fig. 1A), abnormal nerve conduction (Fig. 1B), and confirmed clinical neuropathy (Fig. 1C). For the full cohort, VPT values that provided ~80% sensitivity were 4.30, 3.55, and 4.29 for definite clinical neuropathy, abnormal nerve conduction, and confirmed clinical neuropathy, respectively. VPT values that provided ~80% specificity were 2.61 for definite clinical neuropathy, 2.34 for abnormal nerve conduction, and 3.31 for confirmed clinical neuropathy. AUC ranged from 0.71–0.83, indicating fair to good performance and were highest for confirmed clinical neuropathy. Separate ROC curves were created for subjects aged 36–50 (Fig. 1D–F) and 51–65 years (Fig. 1G–I) (together accounting for 95% of the total cohort). AUC was higher for older participants:

Table 3—Performance of VPT testing on the great toe

| | <i>n</i> * | Sensitivity | Specificity | PPV | NPV | % correct | κ |
|-------------------------------|------------|-------------|-------------|-----|-----|-----------|----------|
| Definite clinical neuropathy | | | | | | | |
| Total cohort | 1,170 | 80 (76–84) | 51 (47–54) | 49 | 81 | 62 | 0.271 |
| Aged 36–50 years | 691 | 75 (69–81) | 50 (46–55) | 42 | 81 | 58 | 0.208 |
| Aged 51–65 years | 420 | 87 (82–92) | 47 (41–54) | 59 | 80 | 66 | 0.330 |
| Abnormal nerve conduction | | | | | | | |
| Total cohort | 1,170 | 75 (72–78) | 62 (58–67) | 76 | 61 | 70 | 0.271 |
| Aged 36–50 years | 691 | 72 (68–77) | 63 (57–68) | 74 | 61 | 68 | 0.350 |
| Aged 51–65 years | 420 | 81 (76–85) | 57 (48–65) | 80 | 58 | 73 | 0.377 |
| Confirmed clinical neuropathy | | | | | | | |
| Total cohort | 1,170 | 87 (84–91) | 51 (47–54) | 43 | 90 | 62 | 0.296 |
| Aged 36–50 years | 691 | 84 (78–89) | 51 (46–55) | 37 | 90 | 59 | 0.241 |
| Aged 51–65 years | 420 | 93 (89–97) | 47 (41–53) | 53 | 91 | 65 | 0.348 |

Data are % (95% CI) unless otherwise indicated. **n* = 7 subjects who are missing a great toe measurement.

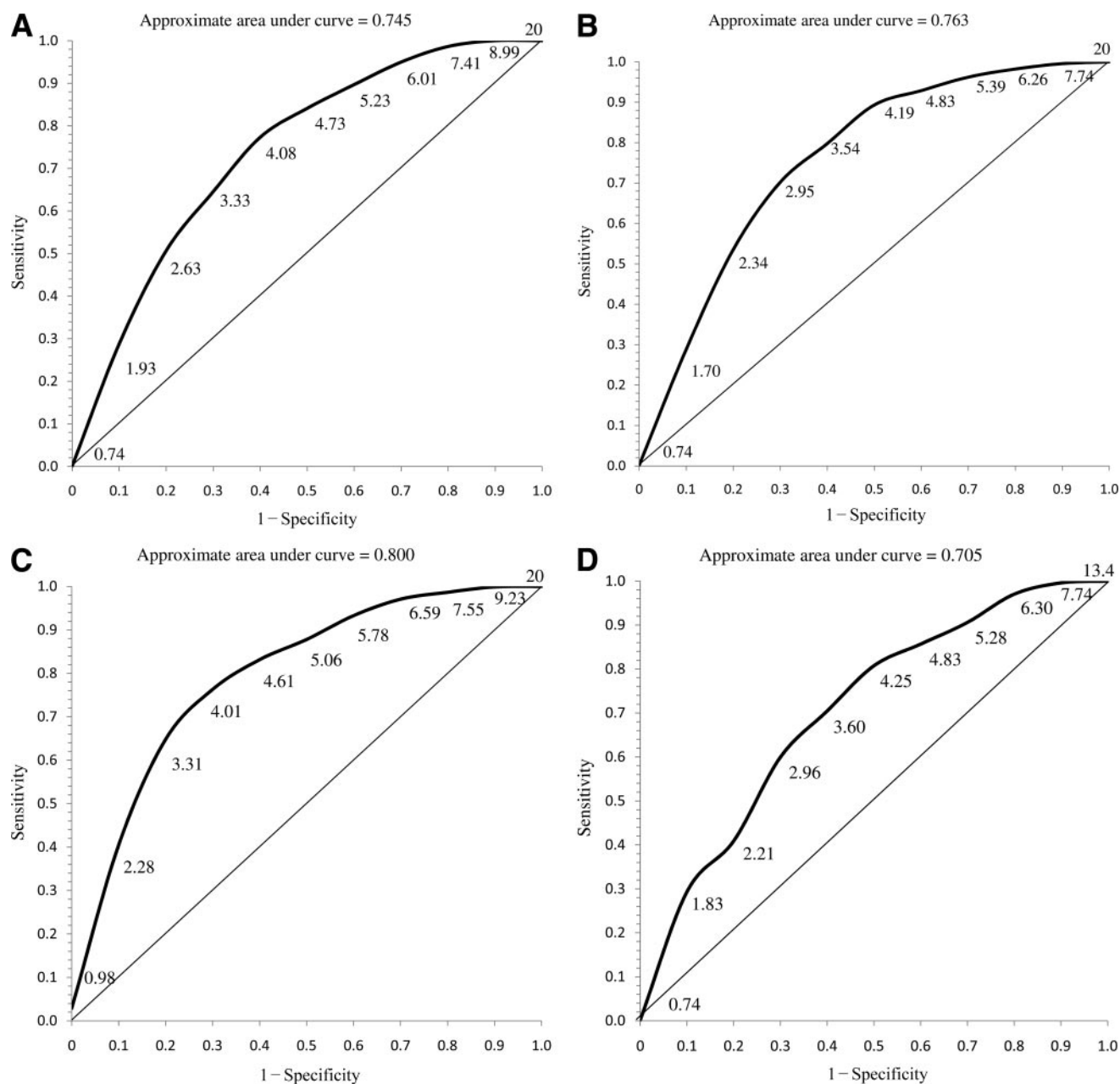


Figure 1—ROC curves for the accuracy of VPT testing at the great toe for predicting definite clinical neuropathy (A), abnormal nerve conduction (B), and confirmed clinical neuropathy (C) in all subjects. The ROC curves shown in D–F are for the accuracy of VPT in predicting definite clinical neuropathy (D), abnormal nerve conduction (E), and confirmed clinical neuropathy (F) among subjects aged 35–50 years, whereas G–I show ROC curves for the accuracy of VPT testing at the great toe for predicting definite clinical neuropathy (G), abnormal nerve conduction (H), and confirmed clinical neuropathy (I) for subjects aged 51–65 years. For each ROC curve, the VPT value corresponding to each decile of 1 – specificity is shown.

0.78 vs. 0.71 for definite clinical neuropathy, 0.78 vs. 0.75 for abnormal nerve conduction, and 0.83 vs. 0.76 for confirmed clinical neuropathy.

CONCLUSIONS— We determined VPT and the prevalence of abnormal VPT in 1,177 subjects with type 1 diabetes during the 13th or 14th year of their participation in the EDIC study. VPT was a reliable measure of DSPN and a sensitive

and specific measure of definite clinical neuropathy, abnormal nerve conduction, and confirmed clinical neuropathy in this large cohort of patients with long-standing type 1 diabetes and a high prevalence of DSPN.

VPT tests at the index finger and great toe were performed concurrently with detailed neurological assessments and electrophysiological studies. To ensure uniformity in test administration, all EDIC

study sites used the same devices and had centralized training. VPT testing was performed on the same day as the subject's neurological assessment and electrophysiological studies to minimize temporal variability when results were compared. To verify VPT test reproducibility, we performed repeated, same day testing in a randomly selected subset of subjects and determined that the test-retest coefficient of reliability was good (0.85).

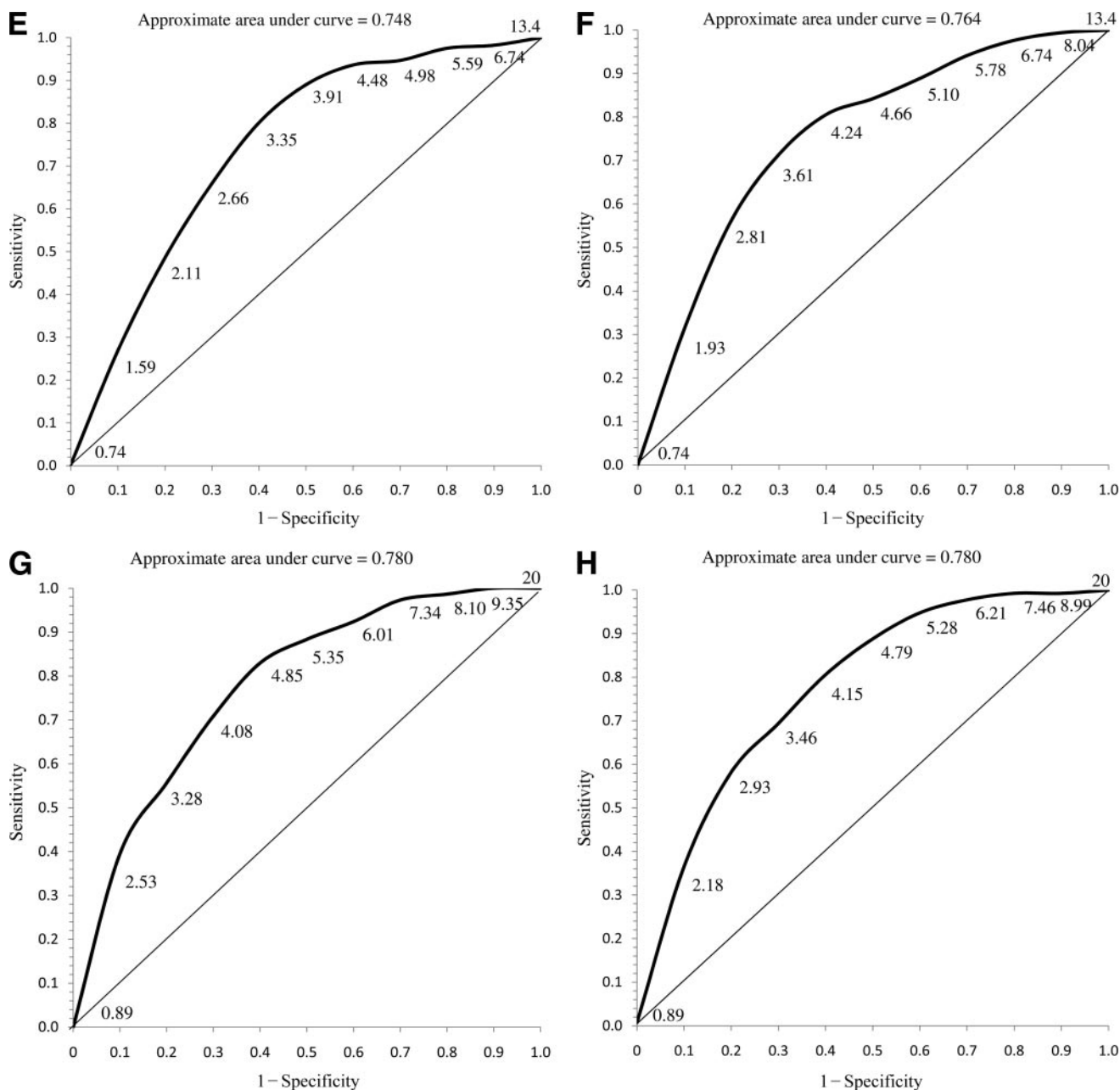


Figure 1—Continued.

VPT may provide important, clinically meaningful information about large nerve fiber dysfunction in diabetes. The neurological impairments associated with large fiber neuropathy account for >80% of the morbidity associated with DSPN (12). Abnormal VPT values have been shown to predict the long-term complications of ulceration and amputation (13) and have been associated with foot ulcers, gangrene, amputation and lower extremity bypass, or angioplasty in type 1 diabetes (14). Common criticisms of VPT testing are that it is not sufficiently specific to large fiber or even to peripheral

nerve dysfunction, that the results are influenced by subject attentiveness, motivation, and fatigue (15–18), that reproducibility may vary in nondiabetic and diabetic populations, and that results may vary depending on the device used (15,18). VPT testing has the advantages of being simple, quick to perform, painless, and generally well tolerated. VPT results are not significantly affected by the presence of foot callus or by limb temperature (15). These advantages and the availability of standardized testing algorithms make VPT an attractive option for DSPN assessment in research settings.

The higher prevalence of abnormal VPT observed at the great toe versus the index finger in our study was not unexpected, given the characteristic length-dependent (stocking distribution) pattern of DSPN. Likewise, higher mean VPT values and increased prevalence of abnormalities among older subjects is not wholly unexpected, given the known effects of aging on peripheral nerve function. The higher prevalence of abnormal VPT values in former CONV than in former INT participants is consistent with the higher prevalence of definite clinical neuropathy, of abnormal nerve conduc-

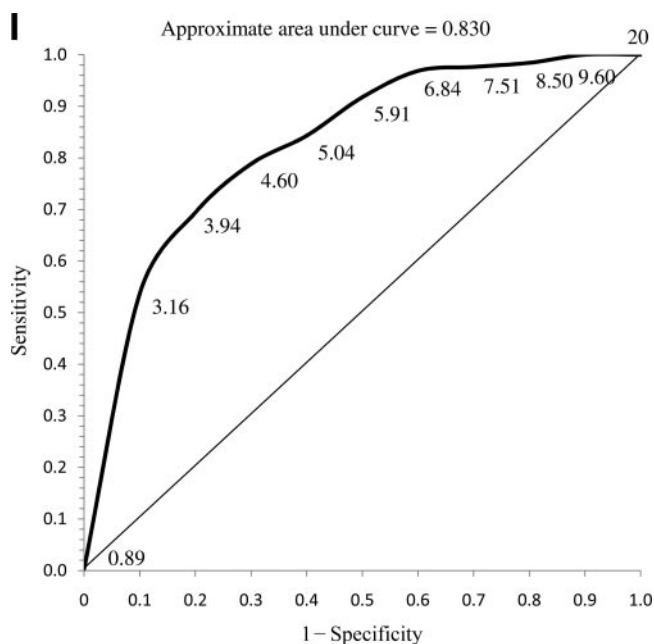


Figure 1—Continued.

tion, and of confirmed clinical neuropathy in the CONV group as reported previously (19).

Sensitivity and specificity, PPV, NPV, and ROC curves relating VPT at the great toe to each of the analytic definitions of neuropathy used in the EDIC study were used to evaluate the utility of VPT to predict DSPN. VPT at the index finger was not used because <8% of all subjects had abnormal VPT at the finger. As a practical consideration, inclusion of the VPT test at the finger, conducted before testing at the toe, gives the subject an opportunity to become familiar with the test procedure and gives the examiner an opportunity to assess the subject's attentiveness and willingness to undergo testing.

We show that VPT at the great toe is a sensitive predictor of both definite clinical neuropathy and confirmed clinical neuropathy. Because sensory examination of large nerve fibers (e.g., vibration and position sense) is a component of the neurologists' evaluation, this finding is not unexpected. VPT was a less sensitive indicator of abnormal nerve conduction, probably reflecting inclusion of upper extremity nerves in the definition of abnormal nerve conduction, and identification of subclinical neuropathy as mild abnormalities of physiological function determined by electrodiagnostic criteria but without clinically discernible signs or reported symptoms as we have previously reported (20). Specificity of VPT was greatest for abnormal nerve conduction.

Overall, the sensitivities and specificities obtained in our study compare favorably to those of others who have reported sensitivities between 58 and 84% and specificities between 61 and 86% for VPT (21–24) measured by a variety of test devices and test methods.

The ROC curves demonstrate the clear tradeoff between sensitivity and specificity when VPT is used as a predictor of DSPN. For example, to attain 90% sensitivity for VPT testing as a predictor of confirmed clinical neuropathy, the cut point to determine abnormal VPT would be 5.5. That would, however, provide a specificity of only ~40% (Fig. 1C). Optimizing specificity at 90% sets the cut point at 2.2 but limits sensitivity to ~40%. With use of the ROC curves, cut points can be chosen to optimize sensitivity and/or specificity according to the outcome of interest and age-group under study. The AUCs suggest that VPT performance is fair to good, with VPT best at predicting confirmed clinical neuropathy and with greater predictive value in older age-groups (again, not unexpected given the known effects of aging). With κ as another measure of agreement, VPT had at least fair agreement with nerve conduction studies. Abnormal nerve conduction was more prevalent than either definite clinical neuropathy or confirmed clinical neuropathy; therefore, the PPV of VPT was highest as a measure of abnormal nerve conduction. NPV was higher for confirmed clinical neuropathy and defi-

nite clinical neuropathy and lower for abnormal nerve conduction, reflecting the lower prevalence of the confirmed and definite clinical neuropathy. Although these analyses do not address the utility of VPT as a measure of disease severity or the ability of VPT to measure change in neuropathy status over time, they may inform future investigations that use the same methodology, providing appropriate thresholds for determining the presence of DSPN.

In general, VPT was best as an indicator of confirmed clinical neuropathy, which was especially true among older participants. VPT as measured in the EDIC study may be useful in future studies of type 1 diabetes with cut points selected to optimize sensitivity and specificity, depending on both the characteristics of the population studied and the clinical outcome selected.

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C.L.M. wrote the manuscript. B.H.W. researched data and performed analysis. R.P.-B., J.W.A., E.L.F., and W.H.H. contributed to discussion and reviewed/edited the manuscript. P.A.C. researched data and reviewed/edited the manuscript. S.C. reviewed/edited the manuscript.

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