

Prevalence of Neuropathy and Peripheral Arterial Disease and the Impact of Treatment in People With Screen-Detected Type 2 Diabetes

The ADDITION-Denmark study

MORTEN CHARLES, MD¹
 NIELS EJSKJAER, MD²
 DANIEL R. WITTE, PHD³

KNUT BORCH-JOHNSEN, DRMEDSCI⁴
 TORSTEN LAURITZEN, DRMEDSCI¹
 ANNELI SANDBAEK, MD¹

OBJECTIVE—There is limited evidence on how intensive multifactorial treatment (IT) improves outcomes of diabetes when initiated in the lead time between detection by screening and diagnosis in routine clinical practice. We examined the effects of early detection and IT of type 2 diabetes in primary care on the prevalence of diabetic peripheral neuropathy (DPN) and peripheral arterial disease (PAD) 6 years later in a pragmatic, cluster-randomized parallel group trial.

RESEARCH DESIGN AND METHODS—A stepwise screening program in 190 general practices in Denmark was used to identify 1,533 people with type 2 diabetes. General practices were randomized to deliver either IT or routine care (RC) as recommended through national guidelines. Participants were followed for 6 years and measures of DPN and PAD were applied.

RESULTS—We found no statistically significant effect of IT on the prevalence of DPN and PAD compared with RC. The prevalence of an ankle brachial index ≤ 0.9 was 9.1% (95% CI 6.0–12.2) in the RC arm and 7.3% (5.0–9.6) in the IT arm. In participants tested for vibration detection threshold and light touch sensation, the prevalence of a least one abnormal test was 34.8% (26.7–43.0) in the RC arm and 30.1% (24.1–36.1) in the IT arm.

CONCLUSIONS—In a population with screen-detected type 2 diabetes, we did not find that screening followed by IT led to a statistically significant difference in the prevalence of DPN and PAD 6 years after diagnosis. However, treatment levels were high in both groups.

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D diabetes is increasingly considered suitable for screening (1). However, even though modeling studies suggest that screening may be cost effective, there are several critical uncertainties (2). In particular, there is limited evidence that benefit estimates obtained from studies of clinically detected type 2 diabetes also apply to screen-detected populations.

The multicenter Anglo-Danish-Dutch Study of Intensive Treatment in People With Screen-Detected Diabetes in Primary Care (ADDITION) was set to obtain this evidence base. The ADDITION study showed that an intervention to promote target-driven, intensive management of patients with screen-detected type 2 diabetes was associated with a nonstatistically

significant 17% relative reduction in the incidence of a composite cardiovascular event end point over 5 years (3). There is limited trial evidence regarding prevention of diabetic peripheral neuropathy (DPN) and peripheral arterial disease (PAD) in people with diabetes. As current knowledge on PAD and DPN in diabetes has been gained in patients with clinically diagnosed and sometimes longstanding diabetes, and as the prevalence of PAD and DPN in patients with screen-detected diabetes is unknown, our aim was to describe the effect of early detection and intensive multifactorial treatment (IT) on the prevalence of DPN and PAD in patients with screen-detected type 2 diabetes in the Danish arm of the ADDITION study.

RESEARCH DESIGN AND METHODS

Design

The design and rationale of the ADDITION study have been reported (4). In brief, ADDITION-Denmark consists of two phases: 1) a screening phase and 2) a pragmatic, cluster-randomized parallel group trial. In five regions of Denmark, 744 general practices were invited to participate and 190 agreed and were randomized to screening plus routine care (RC) of diabetes or screening followed by IT. Randomization was stratified by region and the number of full-time general practitioners per practice.

A population-based stepwise screening program among people aged 40–69 years without known diabetes was undertaken, and individuals were diagnosed with diabetes according to World Health Organization (WHO) criteria, as previously described (5). Overall 1,533 (RC, 623; IT, 910) eligible participants with screen-detected diabetes agreed to take part in the trial. After an average of 6 years of follow-up, 1,278 participants were re-examined. One hundred eight people were only seen

From the ¹School of Public Health, Aarhus University, Aarhus, Denmark; the ²Department of Endocrinology, Aarhus University Hospital, Aarhus, Denmark; the ³Steno Diabetes Center, Gentofte, Denmark; and the ⁴Research Center for Quality in Health Care, Institute of Public Health, University of Southern Denmark, Odense, Denmark.

Corresponding author: Morten Charles, mc@alm.au.dk.

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by their own general practitioner and nine people were not examined with the tests included in the present analysis and did not answer the questionnaires. These participants were excluded from our analysis, yielding a study sample of 1,161 participants for the analysis presented in this paper. Supplementary Fig. A1 displays the practice and participant flow.

Intervention

The specific characteristics of the interventions to promote IT have been described previously in detail (4). The purpose of the IT was to provide the best possible evidence-based treatment in primary care. We aimed to educate and support general practitioners and practice nurses in target-driven management (using medication and promotion of healthy lifestyle) of hyperglycemia, blood pressure, and cholesterol, based on the stepwise regimen used in the Steno-2 study (6). Intensive treatment was promoted through the addition of several features to existing diabetes care. Practice staff was provided with educational materials for patients, and patients were sent reminders if annual check-up appointments were overdue. Practices received additional funding to support the delivery of extra care added to the usual care and consultations. All treatment targets and algorithms were based on evidence from randomized controlled trials demonstrating the benefits of IT on cardiovascular risk factors in people with type 2 diabetes (3) and are displayed in Supplementary Table A2. Although targets for treatment were specified and classes of medication recommended, decisions on prescriptions, including choice of individual drugs, were made by practitioners and patients.

In the RC group, general practitioners were only provided with diagnostic test results. Patients with screen-detected diabetes received the standard pattern of diabetes care according to the Danish national recommendations (7,8).

Measurements

Health assessments at baseline and follow-up included biochemical, anthropometric, and questionnaire measures and were undertaken by centrally trained staff unaware of study group allocation, according to standard operating procedures. Blood pressure was calculated as the mean of three measurements performed after at least 10-min rest, while participants were

seated with the cuff on the right arm resting at the level of the heart, using Omron blood pressure recorders. Height and weight were measured in light indoor clothing, without shoes, using a fixed rigid stadiometer and a Tanita scale, respectively.

All biochemical measures were analyzed at baseline and follow-up at the Aarhus University Hospital and Steno Diabetes Center. The specific analyses have been described previously. Microalbuminuria was defined as an albumin/creatinin ratio on spot urine: men, 2.5–25 mg/mmol; women, 3.5–25 mg/mmol; macroalbuminuria, >25 mg/mmol (9).

Light touch sensory testing was performed after a standardized protocol at four test sites on each foot (plantar aspect of the great toe and first, third, and fifth metatarsal heads) using a Semmes-Weinstein 10 g/5.07 monofilament (Bailey Instruments, Manchester, U.K.). Inability to feel one or more of the test sites was considered to be abnormal (10). This is a single set level used to detect unequivocal insensitivity. Vibration detection threshold (VDT) was determined on the dorsal side of the great toe proximal to the nail on both feet using a CASE IV and the 4-2-1 stepping algorithm (11), following a standard protocol. If the patient failed to comply with the null stimuli twice, the test was rerun once after reinstruction of the patient. If the patient again did not comply with the null value twice, the test on that foot was aborted. The CASE IV system uses a set of 25 standardized vibratory levels, and for each test the computer calculates the “just noticeable difference” (JND) from the subject’s responses. If the participant was unable to detect the highest vibration level, VDT was set at 26 JND. The CASE IV system also expresses the VDT values in normal deviates and percentiles as compared with a normal population based on age, sex, height, and weight. Values ≥ 95 th percentile were considered abnormal (12). Ankle brachial index (ABI) was measured by trained technicians using a Doppler MiniD900 med Huntleigh Transducer EZ8 Widebeam. After a 10-min rest in supine position, brachial systolic blood pressure was measured twice on both arms. Then the distal systolic blood pressure was determined twice (a third time if there was more than 10 mmHg difference) in the arteria dorsalis pedis and the arteria tibialis posterior, alternating on each foot. ABI for each foot was calculated from the highest distal blood pressure divided by

the highest brachial blood pressure from either side (13). Low ABI was defined as 0.9 or less (13).

Standardized self-report questionnaires were used to collect information on socio-demographic characteristics (education, employment, and ethnicity), lifestyle habits (smoking status and alcohol consumption), and self-reported cardiovascular disease (previous myocardial infarction, stroke, or operation/instrumentation on the heart). The patients were asked to answer the questionnaire part of the Michigan Neuropathy Screening Instrument (MNSI) and scored accordingly. A score ≥ 7 was considered abnormal (14). Patients also completed the Brief Pain Inventory short form (15). Patients were defined as having painful diabetic neuropathy if they indicated having pain in both legs (from knees down) and/or both arms (from elbow down).

ABI was done on all patients in three centers (Holstebro, Aarhus, and Copenhagen), and it was possible to calculate ABI in both legs in 836 out of 863 patients. Monofilament was done on all patients in two centers (Aarhus and Steno, 635 participants); 618 had data from all eight test sites. CASE IV was introduced in the follow-up examination from 8 September 2009 in Aarhus and from 22 September 2009 at Steno Diabetes Center. Three hundred ninety-nine participants were examined with CASE IV, in 28 of whom data were not obtained from both feet (20 aborted tests due to noncompliance with null stimuli, and 8 had different disabilities, making CASE IV impossible to test in both legs). Forty-six participants were not measured with CASE IV even though the machine was available. One thousand one hundred forty eight participants returned the supplementary questionnaire containing the Michigan neuropathy questionnaire and Brief Pain Inventory short form.

The study was approved by local ethics committees in each center and was conducted in accordance with the principles of the 1996 Helsinki Declaration. All participants provided informed consent.

Statistical analysis

Patient characteristics at baseline and at follow-up are presented as unadjusted means or, in case of skewed distributions, as medians. Patient groups that were examined with different measures (CASE IV, monofilament, or ABI) were compared

with all examined patients with the use of Student *t* test or the Mann-Whitney *U* test where appropriate. In case of unequal variances, means were compared by approximate inference based on the *t* distribution. Participants with missing values (CASE IV, monofilament, or ABI) were compared with persons without missing values. Participants with an aborted test on CASE IV were compared with participants without an aborted test. The prevalence for each treatment group of DPN and PAD was calculated as the number of participants with abnormal tests divided by the number who participated in that specific test and did not have a missing value. Data are presented with 95% CI. Odds ratios of an effect of IT as compared with RC were calculated using logistic regression taking cluster effect (general practitioner practice) into account. The mean of the normal deviates of VDT in each intervention group was compared using Student *t* test. Statistical analyses were performed with Stata software (version 11, StataCorp LP, College Station, TX).

RESULTS—Baseline characteristics are shown in Table 1. The average follow-up

time was 5.8 years and 5.9 years for RC and IT, respectively. Median HbA_{1c} did not change over the follow-up period in either group, but there was a similar significant decline in systolic blood pressure and total cholesterol in both groups. There was an overall increase in the proportion of participants using medication during the follow-up time. In the RC group, the proportion taking antihypertensive drugs increased from 44 to 77% at follow-up, whereas lipid-lowering drugs increased from 19 to 73%. In the IT group, the corresponding proportions increased from 47 to 80% and from 23 to 81%. At follow-up, antiglycemic drugs were taken by 52% in the RC group and 63% in the IT group. Numbers of smokers significantly declined in both groups with no difference between groups, and the total alcohol consumption also declined. There was no change in BMI from baseline. Patient characteristics of participants at follow-up are summarized in Supplementary Table A3.

We found no substantial differences between subgroups and the total patient population, and no differences between participants with missing values compared with participants with no missing

values, except for a few small differences in the CASE IV subgroup. The CASE IV-examined group was slightly younger (RC, 58.5 years; IT, 58.3 years at baseline) and had a shorter diabetes duration (RC, 5.1 years; IT, 5.4 years). The 46 patients not tested with CASE IV, even though the test was available at that time, had a significantly higher BMI and larger waist circumference. The 31 tested patients with missing data on CASE IV were significantly older but otherwise did not differ from the other patients tested with CASE IV (data not shown).

The prevalence of low ABI and different measures of DPN are presented in Table 2. The effect of intervention is expressed as an odds ratio and presented in Fig. 1. The means of the normal deviates of VDT in each foot were higher in the RC group compared with the IT group, but the difference was not statistically significant.

CONCLUSIONS—We found no statistically significant effect of IT in general practice, delivered through education and support of general practitioners and practice nurses in evidence-based, target-driven management and strict treatment targets/algorithms, on the prevalence of DPN and PAD in people with screen-detected type 2 diabetes as compared with RC delivered according to the national recommendations.

Intervention studies in people with type 2 diabetes have so far only found modest effects on the prevention of DPN. The UK Prospective Diabetes Study indicated a benefit of tighter glycemic control on microvascular complications, but there was no effect on surrogate end points of DPN (16). In the Action to Control Cardiovascular Risk in Diabetes (ACCORD) trial, intensive glycemic control only had a modest positive impact on the development of neuropathy (17), with a significant difference between treatment groups in light touch measured with monofilament but no differences in MNSI >2 or loss of vibration sense measured with a 128-Hz tuning fork alone. In the Steno-2 study, there was no difference between the treatment groups in the development of peripheral neuropathy measured with biothesiometry (6). With regard to treatment, the inference from the UK Prospective Diabetes Study was that dyslipidemia and blood pressure were potentially modifiable risk factors for the development of peripheral

Table 1—Patient characteristics at baseline

Patient characteristics	RC	IT
No. of patients	459	702
Male, <i>N</i> (%)	269 (59)	421 (60)
Age (years)	59.9 (6.8)	59.6 (6.9)
Glycosylated hemoglobin (% of hemoglobin)*	6.4 (6.0; 7.0)	6.4 (6.0; 7.0)
Systolic blood pressure (mmHg)	149.8 (19.3)	147.0 (19.1)
Diastolic blood pressure (mmHg)	88.3 (11.3)	87.3 (10.6)
Weight (kg)	F: 82.8 (17.0); M: 93.7 (15.9)	F: 84.6 (18.3); M: 94.2 (15.9)
Height (cm)	F: 162.6 (5.9); M: 175.6 (6.7)	F: 163.7; M: 175.9 (6.7)
BMI	F: 31.2 (6.0); M: 30.4 (4.4)	F: 31.5 (6.5); M: 30.4 (3.4)
Total cholesterol (mmol/L)	5.77 (1.14)	5.58 (1.08)
HDL (mmol/L)	1.40 (0.34)	1.36 (0.36)
Triglycerides (mmol/L)*	1.6 (1.1; 2.4)	1.6 (1.1; 2.4)
Smoking daily, <i>N</i> (%)	134 (30)	215 (31)
Smoking less than daily, <i>N</i> (%)	169 (37)	271 (39)
Alcohol (units per week)*	6 (2; 14)	6 (2; 14)
Microalbuminuria, <i>N</i> (%)	52 (13)	78 (13)
Macroalbuminuria, <i>N</i> (%)	6 (2)	14 (2)
Antihypertensive drugs (%)	200 (44)	333 (47)
Lipid-lowering drugs (%)	87 (19)	162 (23)

Data are mean (SD), unless otherwise indicated. Patient characteristics at baseline of participants in the Danish arm of ADDITION, who completed a neuropathy questionnaire and/or were tested for DPN or PAD at follow-up. *Median (25th; 75th percentile). F, female; M, male.

Table 2—Prevalence (% of examined population) of different measures of DPN and low ABI in RC or IT group

Variable	N	RC (95% CI)	IT (95% CI)
ABI \leq 0.9 (%)	329/507	9.1 (6.0; 12.2)	7.3 (5.0; 9.6)
Light touch, 1/8 (%)	231/387	20.3 (15.3; 26.1)	17.8 (14.1; 22.0)
VDT, >95th percentile (%)	136/235	25.7 (18.3; 33.2)	22.6 (17.2; 28.1)
Light touch + VDT (%)	135/229	34.8 (26.7; 43.0)	30.1 (24.1; 36.1)
MNSI Qst, cut \geq 7	430/656	9.3 (6.5; 12.1)	8.7 (6.5; 10.9)
Pain (%)	400/581	4.5 (2.5; 6.5)	4.6 (2.9; 6.4)

Light touch sensation tested with 10 g monofilament. MNSI Qst, MNSI questionnaire; pain, distal peripheral diabetic pain defined by self-reported bilateral pain distal from knees or elbows.

vascular disease in people with type 2 diabetes (18). Prospective data from the Fremantle Diabetes study suggested that treatment with statins or fibrates may protect against the development of DPN (19).

In our study of patients with screen-detected diabetes in primary care, we did not find that IT had a significant impact on the prevalence of DPN or PAD. However, all observed risk estimates favored multifactorial intervention at a nonstatistically significant level. This finding might be due to the relatively early stage in the disease process at which patients with previously undiagnosed diabetes are picked up by screening. It is conceivable that at this stage where the progression of the disease process underlying PAD and DPN is also at its initial stages, a longer duration of IT is necessary to observe an effect. A future repeated examination of our participants after a longer follow-up period will show whether this is the case. It should also be remarked that in the ADDITION study, which was pragmatic in design, both treatment groups saw a

marked improvement in treatment between baseline and follow-up as general population treatment guidelines developed in the same time period (7,8). Consequently, the treatment levels did not differ as much between RC and IT groups as was expected at study inception.

Current knowledge on PAD and DPN in diabetes has been gained in patients with traditionally diagnosed and sometimes longstanding diabetes. Reported prevalence of DPN and PAD estimates vary widely, most likely depending on differences in patient selection, definition, and methods of assessment. In Germany, the MONICA/KORA Augsburg surveys found the prevalence of DPN to be 28% using the MNSI score >2 , and the prevalence of ABI <0.9 to be 16% in 195 patients with diabetes (20). At baseline in the Australian Fremantle Diabetes study, the prevalence of PAD (ABI <0.9) was 13.6% in 1,181 patients assessed for PAD, but the authors state that this is a conservative estimate, as 113 unclassified patients had higher levels of risk factors (21). In the same cohort, the prevalence of DPN using MNSI score >2 was 30.9% (19). A recent Swedish population-based study including 156 patients found a prevalence of DPN of 34% based on inability to feel three out of four test sites with the monofilament or feel a neurothesiometer at a cut point of >25 V (22).

A prevalence study in a U.K. general practice reported the prevalence of painful diabetic neuropathy to be 26.4% (23), but estimates on the prevalence of painful neuropathy are sparse and vary from 8 to 26% in diabetic populations (24).

It is challenging to compare prevalences, especially DPN. But having all objections in mind, our prevalences of PAD and different measures of DPN in our RC group seem slightly lower than previously reported in other studies. This could be a reflection of screening identifying

patients earlier in the trajectory of diabetes and/or that the overall diabetes treatment has improved. However, it is more important to stress that our findings show that even in this group of patients at an early stage of type 2 diabetes, DPN and PAD are present in a sufficiently large proportion of patients to warrant close clinical attention.

ADDITION-Europe is the first international study on the effects of early detection and IT of type 2 diabetes. Only the ADDITION-Denmark population was examined for PAD and DPN, and this study, presenting prevalence in a screen-detected population, is therefore unique. All patients were identified and treated in primary care, and the trained personnel used broadly accepted and standardized methods for diagnosis. This study therefore provides a solid overview of the size of the problem of PAD and DPN in this highly relevant population. At baseline there was a very low level of retinopathy (25), but we did not measure our outcome characteristics during the baseline assessment and can therefore not calculate incidence rates. However, we can assume that the prevalence of abnormal DPN and PAD at baseline was equally distributed among the randomization groups. The reported prevalence differences can therefore be interpreted as differences in cumulative incidence during the follow-up period.

Our study has some selection problems. More patients were included in the intensive care groups, even though there was no difference in number and types of practices in the randomization groups. Randomization of practices was performed before the screening and inclusion of patients started. But it seems that the intervention, which included training doctors and nurses in diabetes treatment, enhanced the focus in the IT group on screening and including patients. Not all patients were tested with all of our measures, but, except for the CASE IV subgroup, we found no substantial difference between those with and without measurement. We are therefore confident that the findings in these groups can be considered representative for all included patients. The patients tested with CASE IV were slightly younger with shorter diabetes duration. As older age and longer diabetes duration are associated with higher levels of DPN, it is possible that our results on VDT slightly underestimate the prevalence in both treatment groups. It is also possible that the small number of aborted

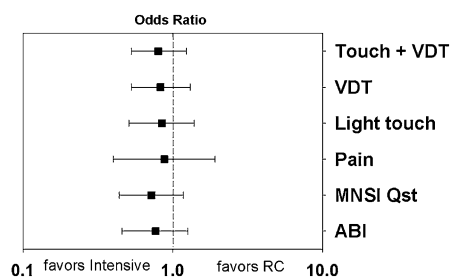


Figure 1—Effect of IT in general practice as compared with RC expressed in odds ratios taking cluster effect into account. Light touch sensation tested with 10 g monofilament. MNSI Qst, MNSI questionnaire \geq 7; pain, distal peripheral diabetic pain defined by self-reported bilateral pain distal from knees or elbows.

VDT tests could be associated with decreased or eradicated sensibility and therefore caused a slight underestimation of the prevalence of VDT. Ideally, summed nerve conduction measures would have been the most objective criterion of DPN.

In a population of people with screen-detected type 2 diabetes, education and support of general practitioners and practice nurses in evidence-based, target-driven management and strict treatment targets/algorithms did not cause a statistically significant difference in the prevalence of DPN and PAD 6 years after diagnosis, as compared with RC delivered according to the national recommendations. The high prevalence of PAD and different measures of DPN in our RC group seem to be only slightly lower than previously reported values among people with clinically diagnosed diabetes. As both DPN and PAD are associated with the development of foot ulcers and cardiovascular disease, clinicians should be aware of these high prevalences when dealing with patients with screen-detected diabetes.

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