Three question set from Michigan Neuropathy Screening Instrument add independent prognostic information on cardiovascular outcomes: analysis of ALTITUDE trial

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Abstract

Aims/hypothesis: The patient self-administered Michigan Neuropathy Screening Instrument (MNSI) is used to diagnose diabetic peripheral neuropathy. We examined whether MNSI might also provide information on risk of death and cardiovascular (CV) outcomes.

Methods: We divided 8463 patients with type 2 diabetes, chronic kidney disease (CKD) and/or CV disease from ALTITUDE into independent training (n=3252) and validation (n=5211) sets. In the training set we identified specific questions independently associated with a CV composite outcome [CV death, resuscitated cardiac arrest, non-fatal myocardial infarction/stroke, heart failure hospitalization (HF)]. We then evaluated the performance of these questions in the validation set.

Results: In the training set, three questions (Are your legs numb? Have you ever had an open sore on your foot? Do your legs hurt when you walk?) were significantly associated with the CV composite outcome. In the validation set, after multivariable adjustment for key covariates, one or more positive responses (n=3079, 59.1%) was associated with higher risk of CV composite outcome (HR 1.54, 95% CI 1.28-1.85, p<0.001), HF (HR 1.73, 95%CI 1.28-2.33, p<0.001), myocardial infarction (HR 1.86, 95%CI 1.25-2.76, p=0.002) and stroke (HR 1.74, 95%CI 1.19-2.53, p= 0.004) relative to those who answered "no" to all questions. Associations were stronger if patients answered positively to all three questions (n=552, 11%). The addition of the total number of affirmative responses to existing models significantly improved Harrell's C statistic for CV composite outcome (0.70 vs 0.71, p= 0.010), continuous net reclassification improvement (+22%, (+10%, +31%), p=0.027) and integrated discrimination improvement (+0.9%, (+0.4%, +2%), p=0.007).

Conclusions/interpretation: We identified three questions from MNSI that add additional prognostic information in patients with type 2 diabetes, CKD and/or CV disease. If externally validated, these questions may be integrated into the clinical history to augment prediction of CV events in high-risk type 2 diabetes patients.

Keywords: Type 2 diabetes, chronic kidney disease, cardiovascular disease, Michigan Neuropathy Screening Instrument, death, cardiovascular outcomes.

Abbreviations

ALTITUDE The Aliskiren Trial in Type 2 Diabetes Using Cardio-Renal Endpoints

CKD Chronic kidney disease

CV Cardiovascular

DPN Diabetic peripheral neuropathy

HF Heart failure hospitalization

MNSI Michigan Neuropathy Screening Instrument

Introduction

Diabetic peripheral neuropathy (DPN) is a common complication of both type 1 and type 2 diabetes. It is one of the major causes of foot ulcers and subsequent amputations, and is also associated with a higher risk of all-cause and cardiovascular (CV) mortality than in patients without DPN (1-3). Poor glycemic control is the strongest risk factor for the development of DPN, while age and duration of DM, as well as other co-morbidities (dyslipidemia, hypertension, diabetic retinopathy, nephropathy, smoking), are also associated with DPN (4,5). Previous studies have shown that DPN is present in 30-50% of patients with DM (6,7). Therefore, screening and timely diagnosis of DPN is important for improving foot care and highlighting the risk of adverse CV outcomes.

While electromyography, electroneurography and sural nerve biopsy are the gold standard for diagnosing DPN, the Michigan Neuropathy Screening Instrument (MNSI), introduced in 1994, is considered to be an alternative diagnostic tool. The MNSI includes two separate assessments, a 15-item self-administered questionnaire about symptoms and a lower extremity examination that includes inspection and assessment of vibratory sensation and ankle reflexes (8). The MNSI was developed to diagnose DPN in clinical practice and is also used in large clinical trials (9-11). However, its' value in risk stratification has not been ascertained. Therefore, we investigated whether the MNSI questionnaire offers additional information about risk of death and major CV events in high-risk patients with type 2 diabetes, and chronic kidney disease (CKD) and/or CV disease.

Methods

Participants The Aliskiren Trial in Type 2 Diabetes Using Cardio-Renal Endpoints (ALTITUDE, NCT00549757) was a double-blind, randomized, controlled trial conducted among 8561 patients with type 2 diabetes and CKD and/or CV disease who were randomly assigned to receive 300 mg of aliskiren per day or placebo, added to an angiotensin-converting-enzyme inhibitor or angiotensin II receptor blocker. Patients were followed up for a median of 2.6 years (IQR 2.0-3.2). The trial design and results are published (12,13).

Out of the 8561 randomized patients, 8463 completed the self-administered MNSI questionnaire (Supplementary material 1) at baseline and were included in this post-hoc analysis (the remaining 98 patients did not complete the questionnaire). Based on the time of randomization, we divided this cohort into an independent training (n=3252, randomized 2007-2008) and validation set (n=5211, randomized 2009-2011).

Study design In the training set, we identified specific questions that were independently associated with the CV composite outcome [CV death, resuscitated cardiac arrest, non-fatal myocardial infarction/stroke, heart failure hospitalization (HF)]. These questions were then evaluated in the validation set in unadjusted and adjusted models to confirm their potential independent association with clinical outcomes.

Statistical analysis

Baseline characteristics were stratified by patient group (training/validation set). Continuous data are presented as the mean ± standard deviation except for triglycerides and urinary albumin-to-creatinine ratio, which are presented as median [25–75th percentile]. Categorical variables are expressed as proportions and were compared by the chi-square test, while continuous variables were compared using t-tests or Wilcoxon rank-sum tests, as appropriate. Using patients in the

training data set, forward stepwise-selection techniques were used with threshold p-value = 0.05 to identify specific questions that were independently associated with the CV composite outcome without adjustment for any other variables. We further tested the null hypothesis that all selected questions were equally associated (i.e. equal hazard ratios (HR)) with the outcome of interest versus the alternative that one or more of the selected questions were differentially related to the outcome (i.e. one or more HRs different from the others). These selected questions were then tested as predictors in adjusted Cox proportional hazards models using the validation data set. We used these questions in two models. First we estimated the risk associated with an affirmative answer to any of the three questions compared to those with no affirmative answers. Next, we estimated the risk associated with each specific number of affirmative answers compared to a reference of zero affirmative answers. Proportional hazards regression models were used to assess the association between the questions and CV outcomes. Model 1 was adjusted for the randomized study treatment. Model 2 was adjusted for baseline covariates: age, sex, race, smoking status, systolic blood pressure, eGFR, urinary albumin to creatinine ratio, history of heart failure, myocardial infarction, stroke, atrial fibrillation, diabetic nephropathy, diabetic retinopathy, amputation, claudication, unstable angina, coronary revascularization, duration of diabetes, HbA1c, and randomized treatment (14). Harrell's C statistics (compared using a transformation of the equivalent Somers' D parameters (15)), continuous net reclassification improvement (NRI) and integrated discrimination improvement (IDI) were obtained by comparing the described multivariable Cox models with and without the inclusion of the variable identifying the number of "yes" responses from among the chosen MNSI questions and was assessed at 3 years post-randomization. Assessment of the proportional hazards assumption was performed using Schoenfeld residuals. Two-sided P-values <0.05 were

considered statistically significant. Analyses were performed using Stata version 13.1 (Stata Corp., College Station, TX, USA).

Results

The 8463 participants were divided into a derivation (n=3252) and a validation group (n=5211). Baseline characteristics in these two groups are presented in Table 1. Patients included in the training and validation groups were qualitatively similar. All pair-wise correlations between MNSI questions were less than +0.40. In the training data set, we identified three questions which were independent predictors of the CV composite outcome: question 1- Are your legs and/or feet numb? (HR 1.25 95% CI 1.04-1.50, p=0.019), question 8-Have you ever had an open sore on your foot? (HR 1.45, 95% CI 1.18-1.76, p<0.001) and question 12- Do your legs hurt when you walk? (HR 1.63, 95% CI 1.36-1.95, p<0.001). The associations of three questions with specific CV outcomes in the training data set are shown in Supplementary Table 1. After adjusting for other baseline covariates, we found no evidence that the HRs associated with any of the three questions were significantly different from the others with respect to any of the outcomes.

In the validation set, 3079 patients (59.1%) answered "yes" to at least one of these three questions. Of these, 29.7% answered positively to one, 18.8% to two and 10.6% to three questions.

We then analyzed the associations between different combinations of individual questions and CV outcomes in the validation dataset (Table 3, Graph 1). In unadjusted models, patients who answered "yes" to at least one of the three questions demonstrated a higher risk of the CV

composite outcome (HR 1.77, 95% CI 1.48-2.11, p<0.001), all-cause death (HR 1.48, 95% CI 1.19-1.84, p<0.001), CV death (HR 1.51, 95% CI 1.14-2.01, p=0.004), heart failure hospitalization (HR 2.00, 95%CI 1.50-2.68, p<0.001), myocardial infarction (HR 2.20, 95%CI 1.51-3.21, p<0.001) and stroke (HR 1.95, 95%CI 1.36-2.78, p<0.001), relative to those who answered "no" to all of the questions. After multivariable adjustment, the excess risk associated with a positive answer to a question was reduced by a quarter to a half, but remained clinically important and retained statistical significance (with the exceptions of all-cause death and CV death). These associations became even stronger if patients answered positively to multiple questions in relation to all CV outcomes, except stroke (Supplementary Table 2). The addition of the total number of affirmative responses to existing models significantly improved Harrell's C statistic for CV composite outcome (0.70 vs 0.71, p= 0.010), continuous net reclassification improvement (+22%, (+10%, +31%), p=0.027) and integrated discrimination improvement (+0.9%, (+0.4%, +2.1%), p=0.007). For all other outcomes, C-statistic was improved by +0.00 to +0.02, NRI by +17% to +25% and IDI by +0.3% to ++0.8% (details in Table 4).

Discussion

This study identified three out of 15 simple questions from the MNSI which provided additional prognostic information about the risk of all-cause death, CV death and a composite CV outcome, as well as its components, in patients with type 2 diabetes and CKD and/or CV disease. While the MNSI questionnaire has previously been used to screen for DPN (9-11), this is the first time these questions have been used as predictors of risk of CV events. A positive answer to any one of the three identified questions was associated with a higher risk of adverse CV events, and the relationship was even stronger if the answer to multiple questions were positive. Furthermore, when patients' characteristics and other CV risk factors were considered, a positive answer to

each of these three questions provided additional prognostic information concerning the risk of the outcomes described.

The DCCT/EDIC study investigators examined the performance of each item in the MNSI questionnaire and examination in confirming the diagnosis of DPN. These investigators concluded that a reduced index of four questions performed nearly as well as the more extensive instrument (11). Two of these four questions (question 1- Are your legs and/or feet numb? and question 8-Have you ever had an open sore on your foot?) were also identified by us as important predictors of CV outcomes.

As CV risk factors and microvascular disease are associated with both DPN and CVD in people with type 2 diabetes, it is perhaps unsurprising that instruments designed to detect DPN might also predict future CVD. That the risks associated with simple, questions are strong, and only marginally attenuated by multivariable adjustment that accounts for variables associated with the risk of experiencing the primary outcome of the study is more striking. Etiologic explanations for this are unclear. Alternatively, or additionally, these questions may capture unmeasured pathways (for example chronic inflammation in association with a history of an open sore), or more global aspects of vascular damage in association with type 2 diabetes. A similar hypothesis has been invoked to account for the repeated observation that abnormalities of retinal vascular architecture, which are thought to mimic patterns in the cerebrovascular territory, predict outcomes independent of other vascular risk factors (16,17).

It is well known that CV events are a leading cause of morbidity and mortality in patients with type 2 diabetes. Therefore, in clinical settings, there is a growing need for tools which could help accurately assess the risk of adverse events in type 2 diabetes patients. While study of residual confounding and alternative pathways are of interest in understanding mechanisms to identify

new therapeutic targets, current clinical practice should be more concerned with identification of high risk individuals to whom existing therapies can be targeted. In clinical practice, complication assessment will also suffer from similar levels of imprecision as in ALTITUDE and other studies, and performance of additional tests, such as markers of inflammation are time consuming and expensive. Inclusion of just three simple, yet strongly predictive, questions may therefore be of substantial importance to clinical practice. Prediction models are widely used in medicine as potential aids in clinical understanding and therapeutic decision-making, as well as better assessment of prognosis. However, before a new risk prediction model could be adapted in clinical practice and widely used, it needs to be externally validated, to assess its generalizability (18-20). In this analysis, we demonstrated internal validation by showing that three questions identified from the derivation set provided statistically significant prognostic information in an independent validation set.

There are several limitations of this study that need to be noted. First of all, all patients were included in ALTITUDE based on same inclusion criteria, and although divided into statistically independent derivation and validation groups, the two groups were overall similar. Therefore, the lack of external validation, as well as the fact that these findings may not be generalizable to other population of patients with type 2 diabetes is considered an important limitation. In addition, we are limited by the fact that the cohort included in this clinical trial were high-risk type 2 diabetes patients, who were therefore more susceptible to adverse CV outcomes.

In conclusion, we believe that these three questions represent a simple, non-invasive and inexpensive tool which could potentially provide additional prediction information in clinical practice. If externally validated in type 2 diabetes patients with lower CV risk, these questions

may be integrated into the clinical history to augment the prediction of CV events in high-risk type 2 diabetes patients.

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Duality of interest

Drs Seferovic and Claggett report no conflicts.

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Authors' contributions

All authors contributed to the interpretation of the results, writing or revision of the manuscript, and approved the decision to submit the article for publication.

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Table 1. **Baseline characteristics by patient group**

Characteristic	Derivation N=3252	Validation N=5211
Age, years	65.2 ± 9.6	64.1 ± 9.8
Female sex, n (%)	944 (29.0)	1760 (33.8)
Race, n (%)		
White	2024 (62.2)	2778 (53.3)
Black	96 (3.0)	179 (3.4)
Asian	861 (26.5)	1810 (34.7)
Native American	3 (0.1)	6 (0.1)
Pacific Islander	8 (0.2)	6 (0.1)
Other	260 (8.0)	432 (8.3)
Weight, kg	84.7 ± 19.5	81.8 ± 19.3
Body mass index, kg/m^2	30.3 ± 5.9	29.7 ± 5.9
Duration of diabetes, n (%)		
< 1 years	106 (3.3)	180 (3.5)
1-5 years	416 (12.8)	793 (15.2)
>5 years	2730 (83.9)	4238 (81.3)
Smoking history, n (%)		
Never	1539 (47.3)	2709 (52.0)
Ex-smoker	1270 (39.1)	1825 (35.0)
Current smoker	443 (13.6)	677 (13.0)
Systolic blood pressure, mmHg	137.4 ± 16.1	137.2 ± 16.6
Diastolic blood pressure, mmHg	74.2 ± 9.7	74.2 ± 9.9
Glycated hemoglobin, %	7.7 ± 1.6	7.9 ± 1.7
Glycated hemoglobin, mmol/mol	61±18	63±19
Total cholesterol, mmol/l	4.4 ± 1.1	4.6 ± 1.2
LDL cholesterol, mmol/l	2.5 ± 0.9	2.6 ± 1.0
HDL cholesterol, mmol/l	1.2 ± 0.3	1.2 ± 0.3
Triglycerides, mmol/l	1.8 [1.3, 2.6]	1.8 [1.2, 2.5]
eGFR, ml/min/1.73m^2	54.3 ± 21.3	57.7 ± 24.0
Urinary albumin-to-creatinine ratio (geometric mean)	26.9 [4.2,82.0]	36.3 [8.5,111.5]
Medical history, n (%)		
Chronic heart failure	374 (11.5)	489 (9.4)
Cardiovascular disease	1554 (47.1)	2065 (39.3)
Unstable angina	364 (11.2)	441 (8.5)
Percutaneous coronary intervention	500 (15.4)	707 (13.6)
Coronary artery bypass surgery	493 (14.9)	564 (10.7)
Hospitalization for myocardial infarction	585 (18.0)	828 (15.9)
Hospitalization for stroke	359 (11.0)	477 (9.2)
Transient ischemic attack	170 (5.2)	174 (3.3)
Atrial fibrillation	289 (8.9)	435 (8.3)
Amputation of toe/foot/leg	129 (4.0)	209 (4.0)
Diabetic nephropathy	2070 (63.7)	3575 (68.6)
Diabetic retinopathy	1170 (36.0)	1968 (37.8)
Antihyperglycemic agents, n (%)		
Sulfonylurea	1156 (35.5)	1551 (29.8)
Metformin	1553 (47.8)	2351 (45.1)
Insulin	1748 (53.8)	3046 (58.5)

Data are n (%), mean (SD), or median (IQR). HDL=high density lipoprotein, LDL=low density lipoprotein, eGFR=estimated glomerular filtration rate

Table 2. Association of the questions and outcomes, unadjusted and adjusted models in patients who were randomized 2007-2008 (derivation group n=3252)

	Unadjusted			Adjusted*		
Question	**HR, 95 % CI**	**p-value**	**p-value (equality)**	**HR, 95 % CI**	**p-value**	**p-value (equality)**
CV composite outcome						
	524 events		0.19	**517 events**		0.73
Question 1	1.25 (1.04-1.50)	0.019		1.23 (1.02-1.49)	0.033	
Question 8	1.44 (1.18-1.76)	<0.001		1.38 (1.13-1.70)	0.002	
Question 12	1.63 (1.36-1.95)	<0.001		1.33 (1.09-1.61)	0.004	

Question 1- Are your legs and/or feet numb? Question 8-Have you ever had an open sore on your foot? Question 12- Do your legs hurt when you walk? *Model adjusted for age, sex, race, smoking status, systolic blood pressure, eGFR, urinary albumin to creatinine ratio, HF history, myocardial infarction, stroke, atrial fibrillation, diabetic nephropathy, diabetic retinopathy, amputation, claudication, unstable angina, coronary revascularization, duration of diabetes, HbA1c, and randomized treatment.

Table 3. Association of the questions and outcomes, Model 1 and 2 in patients who were randomized 2009-2011 (validation group n=5211)

	Model 1		Model 2	
Answer	**HR, 95 % CI**	**p-value**	**HR, 95 % CI**	**p-value**
CV composite outcome				
	595 events		587 events	
Any "yes"	1.77 (1.48-2.11)	<0.001	1.54 (1.28-1.85)	<0.001
All "yes"	2.08 (1.61-2.70)	<0.001	1.70 (1.30-2.23)	<0.001
All-cause death				
	369 events		366 events	
Any "yes"	1.48 (1.19 -1.84)	<0.001	1.23 (0.98-1.54)	0.072
All "yes"	2.06 (1.51-2.81)	<0.001	1.58 (1.14-2.19)	0.006
CV death				
	222 events		220 events	
Any "yes"	1.51 (1.14-2.01)	0.004	1.24 (0.93-1.66)	0.15
All "yes"	2.14 (1.44-3.18)	<0.001	1.62 (1.06-2.46)	0.025
Heart failure hospitalization				
	235 events		232 events	
Any "yes"	2.00 (1.50-2.68)	<0.001	1.73 (1.28-2.33)	<0.001
All "yes"	2.20 (1.44-3.36)	<0.001	1.75 (1.13-2.71)	0.013
Myocardial infarction				
	145 events		143 events	
Any "yes"	2.20 (1.51-3.21)	<0.001	1.86 (1.25-2.76)	0.002
All "yes"	2.75 (1.63-4.65)	<0.001	2.19 (1.26-3.80)	0.005
Stroke				
	152 events		149 events	
Any "yes"	1.94 (1.36-2.78)	<0.001	1.74 (1.19-2.53)	0.004
All "yes"	1.70 (0.97-2.99)	0.066	1.42 (0.78-2.59)	0.25
3 point MACE (CV death, non-fatal myocardial infarction, non-fatal stroke)				
	436 events		431 events	
Any "yes"	1.75 (1.42-2.15)	<0.001	1.49 (1.51-1.85)	<0.001
All "yes"	2.10 (1.56-2.84)	<0.001	1.69 (1.23-2.31)	0.001

Model 1 adjusted for the randomized study treatment; Model 2 adjusted for age, sex, race, smoking status, systolic blood pressure, eGFR, urinary albumin to creatinine ratio, HF history, myocardial infarction, stroke, atrial fibrillation, diabetic nephropathy, diabetic retinopathy, amputation, claudication, unstable angina, coronary revascularization, duration of diabetes, HbA1c, and randomized treatment. Footnote to Table 3: For all reported hazard ratios above, no significant violations of the proportional hazards assumption were detected ($p>0.05$ for all)

Table 4. Harrell's C statistics, continuous net reclassification improvement (NRI) and integrated discrimination improvement (IDI)

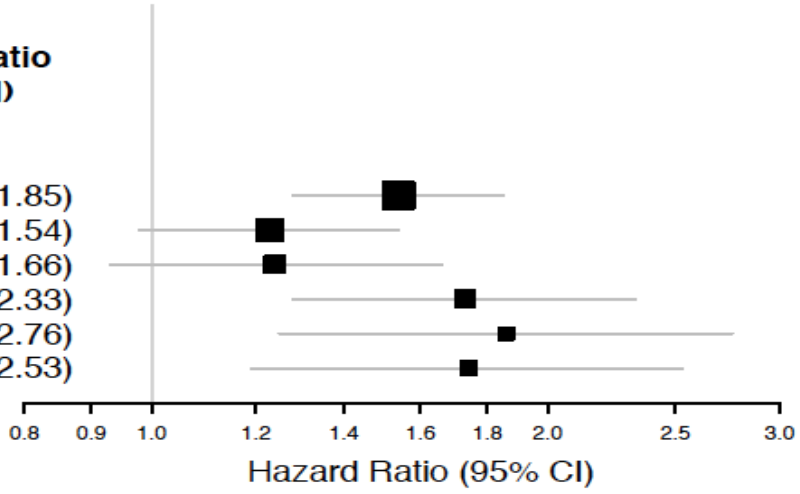
Outcome	With vs. without MNSI questions		
	Harrell's C	**NRI**	**IDI**
CV composite outcome	C=0.70 vs 0.71, p= 0.010	+22%, (+10%, +31%), p=0.027	+0.9%, (+0.4%, +2.1%), p=0.007
All-cause death	C=0.71 vs 0.71, p= 0.12	+22%, (-3%, +36%), p=0.09	+0.5%, (+0.1%, +1.8%), p=0.020
CV death	C=0.72 vs 0.73, p= 0.15	+17%, (-5%, +31%), p=0.13	+0.3%, (0.0%, +1.6%), p=0.040
Heart failure hospitalization	C=0.78 vs 0.79, p= 0.003	+25%, (+11%, +33%), p<0.001	+0.4%, (-0.1%, +1.6%), p=0.11
Myocardial infarction	C=0.74 vs 0.75, p= 0.27	+24%, (+10%, +34%), p=0.013	+0.7%, (+0.2%, +2.8%), p<0.001
Stroke	C=0.70 vs 0.72, p= 0.045	+23%, (-13%, +48%), p=0.09	+0.4%, (-0.1%, +2.0%), p=0.07
3 point MACE	C=0.70 vs 0.72, p= 0.045	+22%, (+6%, +36%), p=0.033	+0.8%, (+0.3%, +2%), p=0.007

CV-cardiovascular; 3 point MACE: CV death, non-fatal myocardial infarction, non-fatal stroke

Figure Legend

Figure 1. **The association of answer "yes" to any of the three questions (upper panel) and all three questions (lower panel) with adverse outcomes in patients who were randomized 2009-2011 (validation group n=5211)**

Outcome	Events	Hazard Ratio (95% CI)
Any yes		
CV composite	587	1.54 (1.28–1.85)
All cause death	366	1.23 (0.98–1.54)
CV death	220	1.24 (0.93–1.66)
HF hospitalization	232	1.73 (1.28–2.33)
Myocardial infarction	143	1.86 (1.25–2.76)
Stroke	149	1.74 (1.19–2.53)



Outcome	Events	Hazard Ratio (95% CI)
All yes		
CV composite	587	1.70 (1.30–2.23)
All cause death	366	1.58 (1.14–2.19)
CV death	220	1.62 (1.06–2.46)
HF hospitalization	232	1.75 (1.13–2.71)
Myocardial infarction	143	2.19 (1.26–3.80)
Stroke	149	1.42 (0.78–2.59)