Risk Factors for the Presence and Progression of Cardiovascular Autonomic Neuropathy in Type 2 Diabetes: ADDITION-Denmark

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OBJECTIVE

To examine the course of cardiovascular autonomic neuropathy (CAN) and related cardiometabolic risk factors in patients with type 2 diabetes.

RESEARCH DESIGN AND METHODS

CAN and cardiometabolic risk factors were assessed in the Danish arm of the Anglo-Danish-Dutch Study of Intensive Treatment in People With Screen-Detected Diabetes in Primary Care (ADDITION-Denmark) at 6-year (*n* = 777) and 13-year (*n* = 443) follow-up examinations. Cardiovascular autonomic reflex tests (CARTs)—that is, lying to standing, deep breathing, and the Valsalva maneuver—and 2-min resting heart rate variability (HRV) indices were obtained as the main measures of CAN. Risk factors related to CAN status, as determined by CARTs, were studied by using multivariate logistic regressions. The effects of risk factors on continuous CARTs and HRV indices, and their changes over time, were estimated in linear mixed models.

RESULTS

A progressive yet heterogeneous course of CAN occurred between the 6- and 13-year follow-ups. Higher HbA_{1c}, weight, BMI, and triglycerides were associated with prevalent CAN. No significant effect of risk factors on CARTs was found when they were analyzed as continuous variables. CART indices decreased over time, and a trend of decreasing HRV indices was seen. Higher HbA_{1c} and BMI were associated with lower HRV index values, but these differences diminished over time.

CONCLUSIONS

These data confirm that hyperglycemia, obesity, and hypertriglyceridemia are negatively related to indices of CAN, although these effects diminish over time. The observed heterogeneous course of CAN may challenge the present clinical approach of categorically classifying CARTs to diagnose CAN and the notion of CAN being irreversible.

Cardiovascular autonomic neuropathy (CAN) is a common complication of diabetes and is associated with markedly increased morbidity and mortality (1–5). Damage to the parasympathetic and sympathetic autonomic nerve fibers that innervate the heart and blood vessels causes dysfunction of heart rate control and vascular dynamics, and thereby causes CAN (6). CAN poorly correlates with specific symptoms or clinical signs, implying that this condition frequently remains unrecognized until late in the disease

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trajectory (7). Cardiovascular autonomic reflex tests (CARTs) are the gold standard for diagnosing CAN (5,8), and they mainly characterize parasympathetic function.

Modifiable risk factors such as hyperglycemia, obesity, dyslipidemia, hypertension, and smoking are among the proposed risk factors for CAN (1,9–13). No clear evidence supports glucose-lowering intervention to prevent CAN in type 2 diabetes (14,15). Yet, multifactorial treatment reduced the development of CAN by 68% in the Steno-2 Trial, which included people with type 2 diabetes and microalbuminuria (16).

Few longitudinal studies of CAN exist, and previous research has used cohorts with long-standing diabetes in a hospital setting (3,15,16). Less is known about the course of CAN among cohorts with a short duration of type 2 diabetes treated in a primary care setting. Inspired by the Steno-2 Trial, the Anglo-Danish-Dutch Study of Intensive Treatment in People With Screen-Detected Diabetes in Primary Care (ADDITION) was the first to study the effect of early screening-based detection of type 2 diabetes followed by an intense multifactorial intervention for diabetes compared with the effect of routine care for diabetes (16,17). In the Danish arm of ADDITION (ADDITION-Denmark), intensive multifactorial treatment had no effect on the development of CAN after 6 years of follow-up (18). Nevertheless, CAN was evident, with a prevalence of 15% for early signs of CAN and ~7% for manifest CAN (18). This cohort was followed for another 6.5 years; CAN was assessed during follow-up on the basis of CARTs and resting heart rate variability (HRV) recordings obtained after a median of 13 years of diabetes.

The aim of this longitudinal study was to explore the prevalence, incidence, and progression of CAN during two CAN assessments obtained during ADDITION-Denmark and to investigate the effects of cardiometabolic risk factors on the prevalence and progression of CAN.

RESEARCH DESIGN AND METHODS

This study uses data from participants who attended the 6- and 13-year follow-up examinations in ADDITION-Denmark, which has been described in detail previously (17). Individuals without known type 2 diabetes were enrolled through stepwise screening in primary care throughout 2001–2006. General practices were randomized to deliver either intensive, target-driven, multifactorial care or routine care until the trial concluded in 2009 (~6 years after inclusion) (19,20). In Denmark, 1,533 people with type 2 diabetes were enrolled. Participants have been followed observationally since 2009, and a follow-up examination was conducted in 2015–2016 after a median of 13 years of diabetes.

Cardiometabolic risk factors were obtained at the 6- and 13-year follow-up examinations; these included anthropometric data, blood pressure (BP), and metabolic measures (HbA_{1c}, total cholesterol, LDL cholesterol, HDL cholesterol, triglycerides, and albumin-to-creatinine ratio [ACR]), as previously described (17). Albuminuria was defined as ACR ≥2.5 mg/mmol in men and ≥3.5 mg/mmol in women (19). Estimated glomerular filtration rate (eGFR) was calculated by using the Chronic Kidney Disease Epidemiology Collaboration equation (21). General practitioners provided records of prescribed medications (glucose-lowering drugs, statins, antihypertensive drugs, and aspirin) at the 6- and 13-year examinations. Information on smoking habits (current smoker or nonsmoker) was obtained from questionnaires.

Three of five test centers examined CAN using a Vagus device (Medicus Engineering, Aarhus, Denmark) at the 6-year examination, and all test centers did so at the 13-year examination (22,23). The Vagus device automatically records an electrocardiographic signal. The accuracy of the detection of R-R intervals has been validated according to U.S. Food and Drug Administration guidelines, and the device has been tested against a stationary device (22). Moderate to high reproducibility of CART results has been demonstrated for this device (24). We obtained HRV indices from 2-min resting electrocardography recordings, followed by three standard CARTs—calculating R-R intervals from electrocardiographic traces while moving from lying to standing, deep breathing, and the Valsalva maneuver—as described previously (18,22). All CAN testing was performed by trained examiners and was preceded by a 10-min period of rest in a supine position in a quiet and isolated examination room between 9:00 A.M. and 1:00 P.M. Smoking and intake of food and caffeine-containing beverages were prohibited at least 2 h before testing. Each CART was done once in each participant. HRV indices were analyzed in the time domain (the root mean square of the sum of squared differences [RMSSD] between R-R intervals and the SDs of normal-to-normal intervals [SDNN]) and in the frequency domain (low-frequency power band [LF] [0.04–0.15 Hz], high-frequency power band [HF] [0.15–0.4 Hz], and total power [≤0.4 Hz]) (25). The latter was obtained by using an autoregressive model. The LF-to-HF ratio was calculated post hoc. The HRV indices RMSSD and HF are considered to be primarily measures of parasympathetic activity, whereas SDNN, LF, total power, and the LF-to-HF ratio are measures of both parasympathetic and sympathetic activity (26). Low values of any of these CAN indices were considered to reflect low HRV.

Outcome Measures

The primary outcome measure was CAN status; CAN was defined by using the gold standard CARTs (5): normal CARTs = no CAN, one abnormal CART = early and reversible CAN, two or three abnormal CARTs = manifest CAN (18). Age-dependent cutoffs were used to define abnormal results (8,27).

Secondary Outcomes: Continuous Values for the CARTs and the HRV Indices

At the 6-year follow-up, 863 participants were eligible for CAN assessment. Of these, 64 participants were not examined because of technical problems with the device or a lack of time (n = 42), atrial fibrillation or a pacemaker (n = 14), or disabilities that prevented testing (n = 3). Of the 799 participants examined, 22 participants had missing values for two CARTs and 76 participants had a missing value for one CART; this left a study sample comprising 777 participants with at least two CARTs. At the 13-year follow-up, 585 participants were eligible for CAN assessment. Of these, 108 participants were not examined because of technical problems with the device or a lack of time (n = 67), atrial fibrillation or a pacemaker (n = 35), or recent laser treatment for diabetic eye disease (n = 6). Of the 477 participants examined, 127 participants had a missing value for one CART and 34 participants had missing values for two CARTs; this left a study sample

of 443 participants with at least two CARTs. In total, CAN was assessed in 299 participants at both time points. The flow of participants in whom CAN assessments were completed in ADDITION-Denmark is illustrated in Supplementary Fig. 1. When exploring risk factors associated with CAN, case subjects were defined as participants with manifest CAN, and we pooled participants with early signs of CAN with CAN-free control subjects.

Ethics

The study was approved by the Committee on Health Research Ethics in the Central Denmark Region (file nos. 20000183 and 1-10-72-63-15) and the Danish Data Protection Agency (file no. 2005-57-0002, ID185). The study was conducted in accordance with the ethical principles for medical research stated in the 1996 Declaration of Helsinki (28), and all study participants gave written informed consent before each examination.

Statistics

Participant characteristics were reported on the basis of the prevalence of manifest CAN at the 6- and the 13-year follow-up and incident CAN between the two examinations. Data are presented as the median and interquartile range (IQR) for continuous variables and as frequencies and proportions for categorical variables. Covariates were compared using Kruskal-Wallis and χ^2 tests.

Progression of CAN was evaluated in participants who were reexamined for CAN. First, we illustrated any change in their CAN status. Second, we calculated the median of absolute change in continuous CAN measures (CARTs and HRV indices, as listed below). Third, we calculated the median of the absolute change in continuous CAN measures by change in CAN status for subsets showing improvement or progression of CAN status. The paired *t* test was performed to determine the significance of changes.

We evaluated the risk of prevalent manifest CAN for cardiometabolic risk factors present at the 6- and the 13-year follow-ups. The risk of incident manifest CAN was evaluated on the basis of risk factors present at the 6-year follow-up. Risk factors under study were HbA_{1c}, weight, waist circumference, BMI, diastolic BP, systolic BP, pulse pressure, total cholesterol, HDL cholesterol, LDL cholesterol, triglycerides, eGFR, albuminuria, and smoking status (current smoker). The effect of each risk factor on the risk of CAN was estimated by using multivariate logistic regression models adjusting for sex, age, diabetes duration, and randomization group.

For a direct evaluation of the associations between risk factors and CAN, we studied the effect of risk factors on the continuous measures of CARTs (lying to standing, deep breathing, and the Valsalva maneuver) and HRV indices (RMSSD, SDNN, LF, HF, and total power). Risk factors studied included HbA_{1c}, BMI, diastolic BP, pulse pressure, HDL cholesterol, LDL cholesterol, triglycerides, albuminuria, and smoking status (current smoker). Linear mixed models were used to estimate both the effect of risk factors on CAN measures (time-independent effects) and changes in CAN measures per year (time-dependent effects). We incorporated the time interval between CAN assessments and adjusted for sex, age, diabetes duration, and randomization group. In addition, we adjusted for resting heart rate in models of HRV indices. HRV indices were log-transformed to meet the assumption of linearity and normal distribution of residuals. These models provided optimal use of all available data and accounted for the clustering of participants by general practice.

We tested for effect modification of risk factor associations by sex using a Wald test. The linearity of continuous risk factor associations with CAN measures was confirmed by testing the statistical significance of quadratic terms. We applied a conservative strategy for adjustments including covariates with high evidence of confounding based on prior knowledge; this was done to reduce the risk of adjusting for colliders and of overadjusting. Furthermore, limited adjustments were allowed in the multivariate logistic regressions on the basis of numbers of cases, and a similar strategy for adjustments across models was considered, enabling a straight comparison of results across models.

RESULTS

In the 6-year subset of 777 participants, the median age was 65.0 years (IQR 60.0–70.0), and 466 (60%) were men. In the 13-year subset of 443 participants, the median age was 70.3 years (IQR 65.7–74.5), and 291 (66%) were men. CAN was assessed at both time points for 299 participants. The flow of participants who were reexamined for CAN between various stages of CAN is shown in Fig. 1. Of the 299 participants who were reexamined, the subset of 270 participants who were free of CAN at 6-year follow-up had a median age of 63.0 years (IQR 58.0–67.0), and 189 (70%) were men. In all subsets more than 97% of participants were white. The characteristics of participants by CAN status at the 6- and the 13-year follow-up, and by status of incident CAN, are shown in Supplementary Tables 1–3. At both time points, case subjects with prevalent CAN had higher HbA_{1c}, weight, BMI, and triglycerides and larger waist circumference, and were more often treated with β-blockers, than participants without CAN. Participants who were developing CAN were younger

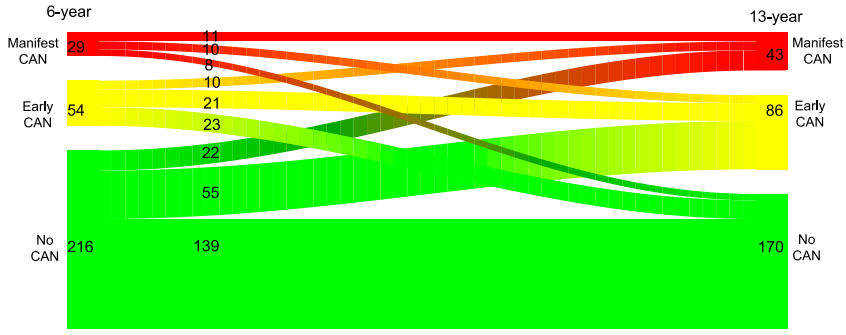

Figure 1—The flow of participants between clinical groups of participants with CAN from ADDITION-Denmark. The chart shows the numbers of participants and changes in their CAN status on the basis of defined categories—no CAN (green), early CAN (yellow), or manifest CAN (red)—from the 6- to the 13-year follow-up.

than participants who stayed free of CAN.

The prevalence of manifest CAN was 9.0% at the 6-year follow-up and 15.1% at the 13-year follow-up. During follow-up of a median of 6.5 years (IQR 6.4–6.9), 32 participants (11.9%) developed incident manifest CAN, corresponding to an annual incidence of 1.8% (18 cases per 1,000 person-years).

Overall, CAN status changed progressively from the 6- to the 13-year follow-up, although the CAN phenotype was heterogeneous (Fig. 1). Eight participants (28%) with manifest CAN at the 6-year follow-up improved and had no CAN at the 13-year follow-up. In a similar way, 23 participants (43%) with early CAN at the 6-year follow-up improved and changed to no CAN at the 13-year follow-up. Conversely, progression occurred in 77 participants (36%) with no CAN and in 10 (19%) participants with early CAN. Stable disease was seen in 11 participants (38%) with manifest CAN and 21 participants (39%) with early CAN.

Changes in continuous CAN measures in reexamined participants are shown in Supplementary Table 4. CARTs decreased significantly between the 6- and the 13-year follow-up. No statistically significant changes were seen in measures of HRV indices. Median changes in CAN measures for subsets of participants whose CAN status improved or progressed are shown in Supplementary Table 5. Continuous changes in CAN measures overall corresponded with a change of CAN status, that is, increasing levels were found in participants with improving CAN status, whereas decreasing levels were found in participants with progressing CAN status. Yet, CARTs increased less in participants in whom CAN status improved, and these changes were not statistically significant, whereas larger and mainly significant decreases were seen in participants in whom CAN status progressed.

The risks of prevalent and incident manifest CAN are shown in Table 1. No difference was found for the risk of CAN by sex or by trial randomization group (intensive group vs. routine group). A higher risk of prevalent CAN was associated with a longer duration of diabetes (odds ratio 1.22 [95% CI 1.02–1.46] per year) and with younger age (odds ratio 0.96 [95% CI 0.92–1.00] per year of age) at the 6-year follow-up. Prevalent CAN was associated with higher HbA_{1c}, weight, BMI, and triglycerides at both the 6- and the 13-year follow-up. In addition, prevalent CAN was associated with larger waist circumference, lower LDL cholesterol, and the presence of albuminuria at the 6-year follow-up and with lower diastolic BP at the 13-year follow-up. Similar risk factor associations were estimated for incident CAN, although these did not reach statistical significance.

The effects of risk factors present at the 6-year follow-up on the continuous and repeated measures of CARTs are shown in Table 2. Higher HbA_{1c} values were associated with lower CART results. Conversely, higher HDL cholesterol was associated with higher CART results. Both of these effects diminished over time, and neither the effects on actual values nor the effects on changes of CAN measures were statistically significant.

Effects of risk factors on HRV indices are depicted in Table 3. In general, higher HbA_{1c} and BMI were associated with lower HRV indices, but the effects diminished over time. We found no effect modification by sex, and we confirmed the linearity of associations between continuous risk factors and outcomes of CAN measures.

CONCLUSIONS

This longitudinal study is to our knowledge the first to evaluate the presence and progression of CAN in a population with type 2 diabetes followed in a "real-life" general practice setting, and it is the first to investigate the effects of cardiometabolic risk factors. We found a progressive yet heterogeneous course of CAN during a median of 6.5 years of follow-up. We confirmed hyperglycemia, obesity, and hypertriglyceridemia as risk factors for the presence of CAN, as determined by CARTs. Furthermore, we demonstrated that hyperglycemia and high BMI negatively affect HRV.

The CAN prevalence of 9% at the 6-year follow-up and of 15% at the 13-year follow-up, and the annual incidence of 1.8%, are fairly low, particularly considering the relatively old age of participants. Other studies have reported a prevalence of up to 60% after 15 years of diabetes and an annual incidence of 6% (1,3,5,16). Still, a direct comparison with other studies is not straightforward because different criteria were used to define CAN.

Overall, we observed progression of CAN among this cohort. This is supported by the transition of participants between the various clinical CAN groups and by the concomitant decrease in the continuous values of CARTs. We found no statistically significant changes in measures of HRV indices for the total group of participants in whom CAN was reexamined. However, for subsets in which CAN status changed, changes in the HRV indices overall corresponded with changes in CAN status.

It is noteworthy that our data also show that CAN status improved in some of the participants. Within the clinical group of manifest CAN, 62% changed to early or no CAN. These changes occurred in concert with increases in several of the continuous CAN measures, although only a few of these reached statistical significance. Several reasons could explain this finding. One possibility is that participants in ADDITION had less advanced CAN overall at baseline, as we did not include late-stage signs of CAN (e.g., orthostatic hypotension) (8,29). Moreover, screening was used to detect diabetes in the participants, which means that the diagnosis of diabetes is likely to have preceded a clinical presentation of diabetes by 3–5 years, equaling the diabetes duration of this cohort, to 8–10 years in cohorts with clinically diagnosed diabetes (30). Furthermore, in ADDITION, a multifactorial treatment was provided and overall good control of risk factors was retained during the 13 years of follow-up (31,32). A positive effect of the treatment provided would be in line with the Steno-2 Trial, which showed a 68% reduction in the development of CAN among participants with type 2 diabetes and albuminuria who received similar treatment (16). In summary, we believe that a less advanced stage of CAN, early detection of diabetes, and positive effects of treatment may to some extent explain the slow disease progression and improvements in CAN found in this study. Conversely, other explanations are possible for the heterogeneous course of CAN. First, we included in our analyses all participants who completed at least two of three CARTs, and CARTs were weighted equally, as proposed in the literature

Table 1—Risk of prevalent and incident manifest CAN, by risk factor, in multivariate logistic regression analyses: ADDITION-Denmark

	Risk of manifest CAN					
	Year 6 (*N* = 777)		Year 13 (*N* = 443)		Risk of incident or manifest CAN (*N* = 270)	
Characteristics	OR (95% CI)	Participants (*n*)	OR (95% CI)	Participants (*n*)	OR (95% CI)	Participants (*n*)
Male sex	0.90 (0.56–1.46)	777	1.28 (0.72–2.30)	443	1.99 (0.73–5.47)	270
Age (years)	0.98 (0.95–1.01)	777	0.96 (0.92–1.00)*	443	0.95 (0.89–1.01)	270
Diabetes duration (years)	1.22 (1.02–1.46)*	777	0.91 (0.76–1.09)	443	0.87 (0.68–1.12)	270
Intensive randomization group	0.99 (0.60–1.72)	777	1.06 (0.63–1.80)	443	1.07 (0.53–2.16)	270
HbA_{1c} (%)	1.55 (1.23–1.94)*	775	1.52 (1.17–1.97)*	441	1.06 (0.70–1.60)	270
HbA_{1c} (mmol/mol)	1.04 (1.02–1.06)*	775	1.04 (1.01–1.06)*	441	1.01 (0.97–1.04)	270
Weight (kg)	1.02 (1.00–1.03)*	777	1.02 (1.00–1.04)*	442	1.00 (0.97–1.02)	270
Waist circumference (cm)	1.02 (1.00–1.04)*	775	1.02 (1.00–1.04)	440	0.99 (0.96–1.03)	269
BMI (kg/m^2)	1.06 (1.01–1.11)*	777	1.06 (1.01–1.11)*	441	1.00 (0.93–1.09)	270
Systolic BP (mmHg)	0.99 (0.98–1.01)	777	1.00 (0.98–1.01)	443	0.98 (0.96–1.00)	270
Diastolic BP (mmHg)	0.98 (0.95–1.01)	777	0.96 (0.93–0.99)*	443	0.97 (0.93–1.00)	270
Pulse pressure (mmHg)	1.00 (0.98–1.03)	777	1.01 (0.99–1.04)	443	0.98 (0.94–1.02)	270
Total cholesterol (mmol/L)	0.77 (0.58–1.03)	775	0.82 (0.64–1.04)	441	0.74 (0.47–1.15)	270
HDL cholesterol (mmol/L)	0.64 (0.30–1.37)	775	0.45 (0.17–1.19)	441	0.44 (0.12–1.51)	270
LDL cholesterol (mmol/L)	0.63 (0.44–0.89)*	762	0.71 (0.51–1.00)	425	0.71 (0.43–1.17)	267
Triglycerides (mmol/L)	1.30 (1.06–1.59)*	775	1.43 (1.13–1.80)*	441	1.18 (0.76–1.84)	270
eGFR ($mL/min/1.73\ m^2$)	0.99 (0.98–1.00)*	775	0.99 (0.98–1.00)	441	0.99 (0.97–1.01)	270
Any albuminuria†	1.82 (1.15–2.89)*	771	1.49 (0.82–2.69)	437	0.72 (0.28–1.84)	270
Current smoking	1.22 (0.79–1.89)	765	0.98 (0.41–2.34)	404	0.72 (0.26–1.97)	269

The risk of prevalent manifest CAN at the 6- and the 13-year follow-up and of incident manifest CAN between the 6- and the 13-year follow-up by risk factors were determined by using multivariate logistic regression models adjusted for sex, age, diabetes duration, and trial randomization group. In the estimates for sex, age, diabetes duration, and randomization group, each variable was adjusted for the other variables. All results are per-unit differences in risk factors, except for albuminuria, which reflects participants with albuminuria vs. participants without albuminuria, and for current smokers, which reflects current smokers vs. nonsmokers. *$P < 0.05$. †Any albuminuria is defined as ACR ≥3.5 mg/mmol for women and ≥2.5 for men.

Table 2—Effects of risk factors on baseline levels and changes in continuous measures of CARTs: ADDITION-Denmark

Risk factors	Lying to standing		Deep breathing		Valsalva maneuver	
	β (95% CI)	*P* value	β (95% CI)	*P* value	β (95% CI)	*P* value
Levels at baseline (time-independent effects)						
HbA_{1c} (%)	−0.127 (−0.435 to 0.182)	0.421	−0.182 (−0.437 to 0.073)	0.163	−0.551 (−1.119 to 0.018)	0.058
HbA_{1c} (mmol/mol)	−0.012 (−0.040 to 0.017)	0.421	−0.012 (−0.040 to 0.007)	0.163	−0.050 (−0.102 to 0.002)	0.058
BMI (kg/m^2)	−0.012 (−0.057 to 0.034)	0.620	−0.013 (−0.051 to 0.024)	0.492	0.024 (−0.066 to 0.115)	0.600
Diastolic BP (mmHg)	0.015 (−0.009 to 0.040)	0.219	−0.012 (−0.032 to 0.007)	0.221	−0.015 (−0.067 to 0.037)	0.577
Pulse pressure (mmHg)	**0.026 (0.003–0.048)**	**0.022**	−0.007 (−0.025 to 0.011)	0.457	−0.037 (−0.081 to 0.008)	0.105
HDL cholesterol (mmol/L)	0.196 (−0.447 to 0.838)	0.551	0.141 (−0.414 to 0.695)	0.619	0.262 (−1.065 to 1.589)	0.699
LDL cholesterol (mmol/L)	−0.007 (−0.313 to 0.299)	0.965	−0.043 (−0.301 to 0.216)	0.747	0.234 (−0.369 to 0.837)	0.447
Triglycerides (mmol/L)	−0.035 (−0.304 to 0.234)	0.797	−0.124 (−0.350 to 0.103)	0.284	0.251 (−0.275 to 0.776)	0.350
Any albuminuria*	0.079 (−0.509 to 0.667)	0.793	−0.251 (−0.745 to 0.244)	0.320	−0.989 (−2.178 to 0.200)	0.103
Current smoking	−0.045 (−0.396 to 0.306)	0.803	0.062 (−0.235 to 0.359)	0.683	−0.302 (−0.986 to 0.382)	0.386
Changes per year (time-dependent effects)						
HbA_{1c} (%)	0.017 (−0.030 to 0.064)	0.471	0.028 (−0.012 to 0.067)	0.166	0.078 (−0.009 to 0.165)	0.079
HbA_{1c} (mmol/mol)	0.002 (−0.003 to 0.006)	0.471	0.003 (−0.001 to 0.006)	0.166	0.007 (−0.001 to 0.015)	0.079
BMI (kg/m^2)	0.002 (−0.005 to 0.009)	0.651	0.002 (−0.004 to 0.008)	0.542	−0.004 (−0.018 to 0.010)	0.533
Diastolic BP (mmHg)	−0.002 (−0.006 to 0.001)	0.238	0.002 (−0.001 to 0.005)	0.214	0.002 (−0.006 to 0.010)	0.573
Pulse pressure (mmHg)	**−0.004 (−0.007 to 0.001)**	**0.025**	0.001 (−0.002 to 0.004)	0.535	0.005 (−0.001 to 0.008)	0.118
HDL cholesterol (mmol/L)	−0.029 (−0.127 to 0.069)	0.566	−0.022 (−0.107 to 0.063)	0.609	−0.023 (−0.225 to 0.180)	0.828
LDL cholesterol (mmol/L)	0.001 (−0.045 to 0.048)	0.961	0.007 (−0.032 to 0.046)	0.727	−0.034 (−0.126 to 0.058)	0.472
Triglycerides (mmol/L)	0.004 (−0.036 to 0.045)	0.832	−0.124 (−0.350 to 0.103)	0.262	−0.043 (−0.123 to 0.037)	0.287
Any albuminuria*	−0.011 (−0.101 to 0.080)	0.820	0.038 (−0.038 to 0.114)	0.324	0.145 (−0.038 to 0.328)	0.120
Current smoking	0.006 (−0.047 to 0.060)	0.817	−0.010 (−0.055 to 0.036)	0.676	0.045 (−0.060 to 0.149)	0.406

Time-independent and time-dependent effects of risk factors on CARTs were derived from linear mixed models adjusted for sex, age, diabetes duration, and trial randomization group. Statistically significant effects (represent by $P < 0.05$) are shown in boldface type. All results are per-unit differences in risk factors, except albuminuria, which reflects participants with albuminuria vs. participants without albuminuria, and current smokers vs. nonsmokers. *Any albuminuria is defined as ACR ≥3.5 mg/mmol for women and ≥2.5 for men.

(5,8,33). This strategy implies that participants' CAN status might be defined by different combinations of CARTs at the two examinations. Whether this could hinder a proper evaluation of change in CAN status is unknown; however, the literature does not suggest this. Second, we used age-specific cutoffs (by decade) to evaluate CARTs (8,27). This could be of special importance in our cohort, which spans the seventh-decade cutoff (median age increased from 65.0 to 70.3 years between the two examinations). This means that while some participants had the same decade-specific cutoff at baseline and at follow-up, others had a different cutoff at follow-up. Furthermore, the normative data applied were not developed by using the Vagus device. However, the normative data used cover the age range of our cohort and were used for CAN at the 6-year examination (18). We consider the normative data we used to be the most optimal data available, although we acknowledge the need for better normative material. Third, although CARTs have been shown to be reproducible, intrapatient variability of CARTs might to a minor extent have caused heterogeneity in CAN status (8,33). Last, CARTs were performed only once for each participant, which could have prevented the detection of some measurement errors by the Vagus device.

Our study showed no difference in the risk of CAN by sex, which is in line with previous studies (1). Age showed no clear association with the presence of CAN, yet participants with incident CAN were slightly younger than the participants not developing CAN between the two examinations. This might be explained by the inclusion criteria in ADDITION, as older age was among the predefined risk factors leading to diabetes screening (17). Therefore, younger participants had a relatively higher cardiometabolic risk. No difference in the prevalence or the incidence of CAN was found when comparing randomization groups. This is similar to findings at the 6-year follow-up and is likely explained by the minor differences in treatment intensity achieved in this pragmatic trial (18).

We confirm hyperglycemia, obesity, and hypertriglyceridemia as risk factors for prevalent CAN on the basis of categorical classifications of CARTs (1,33,34). We were not, however, able to confirm

Table 3—Effects of cardiometabolic risk factors on baseline levels and changes in HRV indices from linear mixed models

	Log RMSSD		Log SDNN		Log LF		Log HF		Log total power	
Risk factors	β (95% CI)	*P* value	β (95% CI)	*P* value	β (95% CI)	*P* value	β (95% CI)	*P* value	β (95% CI)	*P* value
Levels at baseline (time-independent effects)										
HbA_{1c} (%)	**−1.232 (−2.417 to −0.046)**	**0.042**	**−1.237 (−2.193 to −0.280)**	**0.011**	**−2.647 (−5.045 to −0.249)**	**0.031**	−2.257 (−4.763 to 0.249)	0.077	**−2.215 (−4.197 to −0.233)**	**0.028**
HbA_{1c} (mmol/mol)	**−0.113 (−0.221 to −0.004)**	**0.042**	**−0.113 (−0.201 to −0.026)**	**0.011**	**−0.242 (−0.462 to −0.023)**	**0.031**	−0.207 (−0.436 to 0.023)	0.077	**−0.203 (−0.384 to −0.021)**	**0.028**
BMI (kg/m^2)	**−0.295 (−0.472 to −0.118)**	**0.001**	**−0.180 (−0.323 to −0.037)**	**0.013**	−0.118 (−0.487 to 0.250)	0.529	**−0.506 (−0.875 to 0.138)**	**0.007**	−0.177 (−0.482 to 0.127)	0.254
Diastolic BP (mmHg)	−0.085 (−0.192 to 0.022)	0.118	**−0.096 (−0.180 to −0.012)**	**0.026**	0.013 (−0.208 to 0.233)	0.952	0.020 (−0.216 to 0.256)	0.866	−0.049 (−0.240 to 0.142)	0.614
Pulse pressure (mmHg)	−0.066 (−0.153 to 0.020)	0.134	−0.030 (−0.101 to 0.040)	0.395	−0.101 (−0.277 to 0.075)	0.261	−0.069 (−0.252 to 0.114)	0.458	−0.076 (−0.222 to 0.069)	0.304
HDL cholesterol (mmol/L)	0.158 (−2.343 to 2.658)	0.902	−0.402 (−2.426 to 1.621)	0.697	0.782 (−4.227 to 5.790)	0.760	−1.229 (−6.498 to 4.041)	0.648	−1.225 (−5.453 to 3.002)	0.570
LDL cholesterol (mmol/L)	−0.309 (−1.507 to 0.888)	0.613	−0.101 (−1.061 to 0.859)	0.836	−0.252 (−2.688 to 2.185)	0.840	−1.033 (−3.541 to 1.476)	0.420	−0.740 (−2.752 to 1.273)	0.471
Triglycerides (mmol/L)	0.331 (−0.693 to 1.355)	0.527	0.245 (−0.584 to 1.074)	0.563	0.911 (−1.160 to 2.982)	0.389	0.491 (−1.674 to 2.657)	0.656	0.437 (−1.298 to 2.172)	0.621
Any albuminuria*	−0.054 (−2.386 to 2.278)	0.964	0.181 (−1.698 to 2.060)	0.850	0.471 (−4.251 to 5.194)	0.845	−1.520 (−6.438 to 3.398)	0.545	−0.056 (−4.029 to 3.917)	0.978
Current smoking	−1.015 (−2.384 to 0.354)	0.146	−0.500 (−1.605 to 0.606)	0.375	0.147 (−2.618 to 2.912)	0.917	−2.225 (−5.108 to 0.658)	0.130	−0.762 (−3.069 to 1.545)	0.517
Changes per year (time-dependent effects)										
HbA_{1c} (%)	**0.195 (0.014–0.376)**	**0.035**	**0.190 (0.044–0.336)**	**0.011**	**0.402 (0.036–0.768)**	**0.032**	0.355 (−0.028 to 0.738)	0.069	**0.339 (0.036–0.642)**	**0.028**
HbA_{1c} (mmol/mol)	**0.018 (0.001–0.034)**	**0.035**	**0.017 (0.004–0.031)**	**0.011**	**0.037 (0.003–0.070)**	**0.032**	0.032 (−0.003 to 0.068)	0.069	**0.031 (0.003–0.059)**	**0.028**
BMI (kg/m^2)	**0.045 (0.018–0.072)**	**0.001**	**0.027 (0.005–0.049)**	**0.015**	0.015 (−0.042 to 0.071)	0.607	**0.077 (0.021–0.133)**	**0.007**	0.026 (−0.021 to 0.073)	0.273
Diastolic BP (mmHg)	0.013 (−0.003 to 0.029)	0.124	**0.015 (0.002–0.028)**	**0.024**	−0.001 (−0.035 to 0.033)	0.952	−0.004 (−0.040 to 0.032)	0.833	0.008 (−0.021 to 0.037)	0.600
Pulse pressure (mmHg)	0.010 (−0.004 to 0.023)	0.153	−0.030 (−0.101 to 0.040)	0.428	0.015 (−0.012 to 0.042)	0.275	0.010 (−0.018 to 0.038)	0.484	0.011 (−0.011 to 0.033)	0.327
HDL cholesterol (mmol/L)	−0.012 (−0.392 to 0.368)	0.951	0.074 (−0.233 to 0.382)	0.636	−0.052 (−0.814 to 0.711)	0.894	0.192 (−0.610 to 0.993)	0.640	0.212 (−0.431 to 0.855)	0.518
LDL cholesterol (mmol/L)	0.050 (−0.132 to 0.232)	0.587	0.023 (−0.123 to 0.169)	0.761	0.046 (−0.324 to 0.416)	0.808	0.155 (−0.226 to 0.536)	0.425	0.119 (−0.187 to 0.425)	0.444
Triglycerides (mmol/L)	−0.045 (−0.203 to 0.107)	0.546	−0.039 (−0.164 to 0.087)	0.545	−0.146 (−0.460 to 0.167)	0.360	−0.063 (−0.390 to 0.265)	0.709	−0.066 (−0.328 to 0.197)	0.624
Any albuminuria*	0.020 (−0.334 to 0.378)	0.913	−0.024 (−0.312 to 0.264)	0.869	−0.086 (−0.810 to 0.639)	0.817	0.246 (−0.509 to 1.000)	0.524	0.000 (−0.609 to 0.610)	0.999
Current smoking	0.161 (−0.045 to 0.370)	0.133	0.079 (−0.090 to 0.248)	0.359	−0.022 (−0.445 to 0.401)	0.919	0.351 (−0.090 to 0.793)	0.118	0.128 (−0.225 to 0.481)	0.478

Time-independent and time-dependent effects of risk factors on HRV indices were calculated from linear mixed models adjusted for sex, age, diabetes duration, trial randomization group, and resting heart rate. Statistically significant ($P < 0.05$) effects are shown in boldface type. Results are per-unit differences in risk factors, except that albuminuria reflects participants with albuminuria vs. participants without albuminuria and current smokers reflects current smokers vs. nonsmokers. *Any albuminuria was defined as ACR ≥3.5 mg/mmol for women and ≥2.5 for men.

these risk factors for incident CAN. Albuminuria was associated with CAN at the 6-year follow-up, which is in line with previous research (1). Conversely, at the 6-year follow-up, higher levels of LDL cholesterol were associated with lower risk of CAN, which conflicts with the findings of other studies (1). This and other paradoxical findings for LDL cholesterol in ADDITION are likely explained by bias caused by treatment with statins (32,35).

The study has a risk of selection bias because of loss to follow-up. Post hoc analyses showed that women, slightly older participants (median age difference of 1.4 years), and participants treated with β-blockers were more likely to be lost to follow-up. Because CAN case subjects were more frequently treated with β-blockers than participants without CAN, an underestimation of the true incidence of CAN is possible. Conversely, the younger age of participants attending the follow-up examinations could also have caused overestimation.

Studying associations between risk factors and continuous levels of CARTs revealed no significant risk factor associations. However, we showed trends for higher HbA_{1c} being associated with lower levels of all three CARTs. We also saw a trend for HDL cholesterol being positively associated with CART levels. The HbA_{1c} results were replicated and statistically significant in analyses of HRV indices; higher HbA_{1c} was associated with lower HRV indices, yet effects diminished over time. Also, higher BMI was associated with lower levels of most HRV indices, with effects diminishing over time.

Many different kinds of medication used in diabetes may affect CAN measures. Most important are β-blockers, which may increase both CART levels and HRV (8,36). Adjusting for medical treatment in this study is not straightforward, as we have only yes/no information regarding treatment with different medications, and this information was obtained at the 6-year examination but on average 1 year before the 13-year examination, and a relatively large amount of data was missing (~20% at the 13-year examination). Post hoc analyses were conducted to adjust for β-blocker treatment at the 6- and the 13-year follow-up in linear mixed models (data not shown). We looked at two

extreme scenarios to impute missing data on β-blocker treatment at the 13-year follow-up: "all on treatment" versus "no one treated." Whereas most estimates of risk factor associations remained unchanged, these adjustments affected the estimates for the associations between HbA_{1c} and CAN measures, diminishing the effects (up to 50%) and losing statistical significance. It is possible that β-blocker treatment in this study acts as an indicator of an overall worse risk profile of participants, as this drug was not a first-line drug for the treatment of hypertension, and participants treated with β-blockers were more likely to be lost to follow-up than those not receiving β-blockers. However, we do not have the data to answer this question. In conclusion, we consider an effect of β-blocker treatment possible, but we think it unlikely that the effect of β-blockers drives the associations between risk factors and CAN.

The main strengths of our study are its relatively large size, the applicability of the results to most people with diabetes who are being treated in general practice, and CAN assessments obtained by the Vagus device. Also, participants' age at diabetes onset is very relevant, as this age (60 years) is just around the peak for the prevalence and the incidence of type 2 diabetes (27). However, our study also has limitations. Most important, no optimal normative data for CARTs were available, and our results stress the need for better normative data. CARTs were performed only once for each participant, which could have prevented the detection of some measurement errors. To reduce the burden of examinations on the participants, we did not evaluate orthostatic hypotension. This may have prevented the identification of more severe cases of CAN. However, we consider this of little relevance in this cohort of early-stage diabetes. Resting HRV was assessed without controlling the breathing rate. Controlling the breathing rate enables an easier separation of the LF and HF. At the same time, however, controlled breathing may affect HRV indices by shifting the sympathovagal balance toward vagal predominance (37). We found rather homogeneous levels of risk factors, which varied little, and this may have hindered the identification of further significant risk factor associations (31,32). Last, because this is an observational study, on the basis of these data we cannot state mechanistic associations between separate risk factors or treatment components and CAN.

In conclusion, this study of people with screening-detected type 2 diabetes showed an overall progressive yet heterogeneous course of CAN. CAN progressed less than in previous studies of type 2 diabetes, and we observed improvements in CAN. Our results suggest a positive effect of early detection of diabetes and multifactorial treatment in preventing the progression of CAN. At the same time, our study questions the clinical approach of categorizing CAN status by decade-specific cutoffs for CARTs. We confirm hyperglycemia, obesity, and hypertriglyceridemia as risk factors for CAN. Furthermore, hyperglycemia and obesity showed a negative effect on continuous CAN measures, which further underlines these modifiable risk factors as being important in the development of CAN. Studies applying repeated measures of both risk factors and CAN measures are called for to explore further the influence of risk factors on the presence and progression of CAN.

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Author Contributions. S.T.A. collected data, performed the statistical analyses, and wrote the manuscript. D.R.W., J.F., H.A., T.L., M.E.J., T.S.J., R.P.-B., and M.C. designed the study, provided input on statistical analyses, contributed to the discussion, and reviewed and edited the manuscript. J.F. processed data from the Vagus device. M.C. collected data. S.T.A. is the guarantor of this work and, as such, had full access to all the data in the study and takes responsibility for the integrity of the data and the accuracy of the data analysis.

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