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D. R. Witte · S. Tesfaye · N. Chaturvedi · S. E. M. Eaton · P. Kempler · J. H. Fuller · EURODIAB Prospective Complications Study Group

Risk factors for cardiac autonomic neuropathy in type 1 diabetes mellitus

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Abstract *Aims/hypothesis:* Cardiac autonomic neuropathy (CAN) is associated with increased morbidity and mortality in type 1 diabetes. Apart from glycaemic control, risk factors for CAN have not been extensively studied. *Methods:* As part of the EURODIAB Prospective Complications Study, CAN—defined as either a loss of heart rate variability or postural hypotension on standing—was assessed at baseline and follow-up (7.3±0.6 years from baseline) in patients with type 1 diabetes. *Results:* Follow-up measurements were available for 956 participants without CAN at baseline (age at baseline 31.3±8.9 years, duration of diabetes 13.5±8.3 years). During follow-up, 163 (17%) subjects developed CAN, yielding an incidence of 23.4 per 1,000 person-years. Blood pressure, weight, the presence of cardiovascular disease, albuminuria, distal symmetrical polyneuropathy (DSP) and retinopathy at baseline were associated with the incidence of CAN after adjustment for sex, duration of diabetes and HbA_1c. In a multivariate regression model, baseline factors associated with an increased risk of developing CAN were age [odds ratio (OR)=1.3 per decade, 95% CI 1.1–1.7], HbA_1c (OR=1.2 per percentage point, 95% CI 1.1–1.4), systolic blood pressure (OR=1.1 per 10 mmHg, 95% CI 1.0–1.3), feeling faint on standing (OR=2.0, 95% CI 1.2–3.2), DSP (OR=1.9, 95% CI 1.2–3.0) and retinopathy (OR=1.7, 95% CI 1.1–2.6). *Conclusion/interpretation:* This study confirms the importance of exposure to hyperglycaemia as a risk factor for CAN. A small set of variables, including HbA_1c, hypertension, DSP and retinopathy, predict the risk of CAN. Clinical trials are needed to address the impact of intensive antihypertensive treatment on CAN in type 1 diabetes.

Keywords Cardiac autonomic neuropathy · Cardiovascular risk factors · Diabetic neuropathy · Epidemiology · Hypertension · Type 1 diabetes mellitus

Abbreviations CAN: cardiac autonomic neuropathy · CVD: cardiovascular disease · DCCT: Diabetes Control and Complications Trial · DSP: distal symmetrical polyneuropathy · EDC: Epidemiology of Diabetic Complications · EURODIAB PCS: EURODIAB Prospective Complications Study · OR: odds ratio · ROC: receiver operating characteristic

D. R. Witte (✉) · J. H. Fuller
Department of Epidemiology and Public Health, Royal Free and University College London Medical School,
1-19 Torrington Place,
London, WC1E 6BT, UK
e-mail: d.witte@ucl.ac.uk
Tel.: +44-207-6791728
Fax: +44-207-8130288

S. Tesfaye · S. E. M. Eaton
Diabetes Research Unit, Royal Hallamshire Hospital,
Sheffield, UK

N. Chaturvedi
Department of Epidemiology and Public Health, Faculty of Medicine, Imperial College of Science, Technology and Medicine,
London, UK

P. Kempler
Department of Medicine, Semmelweis University,
Budapest, Hungary

Introduction

Cardiac autonomic neuropathy (CAN) is a common complication of type 1 diabetes. Reported prevalence rates vary between 2.4% for those with a recent diagnosis of diabetes without other complications [1] and 36% for the clinic-based EURODIAB population at baseline [2]. All-cause mortality is markedly increased in diabetic subjects with CAN [3–5], and this has been attributed to the increased incidence of silent myocardial infarction [5], the increased mortality after myocardial infarction [6], QT interval prolongation leading to an increased risk of sudden cardiac death [7–9] and to the nephropathy-mediated risk of cardiovascular disease (CVD) [10].

Although neural damage by chronic hyperglycaemia, vascular insufficiency in the vessels supplying the nerves, and autoimmune mechanisms have been suggested as

possible causes of CAN, its pathogenesis remains poorly understood [5, 11, 12]. As in the case of distal symmetrical polyneuropathy (DSP), disease duration and long-term poor glycaemic control are important risk factors for the development of CAN [1, 10, 13]. During the 5-year follow-up of the Diabetes Control and Complications Trial (DCCT), intensive therapy reduced the incidence of new cases of CAN by 53% [1]. However, this intervention did not entirely eliminate the risk of CAN, indicating that other therapies should be sought. Reduced cardiovascular autonomic reactivity can be observed in young patients with type 1 diabetes [14], suggesting that other risk factors besides glycaemic control are likely to be involved in its pathogenesis. However, it remains unclear what these factors are and whether they can be modified in such a way so as to prevent this complication. Cross-sectional analysis of the baseline data from the EURODIAB study showed a relationship between prevalent CAN and triglycerides, AER, CVD, proliferative retinopathy and DSP, in addition to the established risk factors (age, duration of diabetes and HbA_1c) [2]. Advanced nephropathy has been suggested as an independent predictor of CAN [13]; however, the complex relationship between hypertension, nephropathy and CAN has not yet been fully elucidated.

Establishing the role of a wider range of risk factors, or risk indicators, for the development of CAN in prospective studies is of great clinical importance, since it will help to identify those at high risk. Furthermore, insight into the aetiology of CAN may help to identify potential targets for new risk-lowering strategies. We therefore investigated which risk factors determined the occurrence of CAN during the 7.3 years of follow-up in participants of the EURODIAB Prospective Complications Study (PCS) who were free of CAN at baseline.

Subjects and methods

Study design The EURODIAB PCS was set up in 1989. Participants were seen twice, once at the baseline visit that took place between 1989 and 1991, and subsequently at a follow-up visit between 1997 and 1999. At baseline, 3,250 subjects were studied (1,668 males and 1,582 females, mean age 32.7±10.2 years, mean duration of diabetes 14.7 ±9.3 years, and mean HbA_1c 6.7±1.9%) [15]. Subjects with type 1 diabetes were randomly selected in a stratified manner from 31 European diabetic clinic populations. The selection criteria and methods have previously been described in detail [15]. The study was approved by the ethics committee of each participating centre and all subjects provided written informed consent.

Aliquots of baseline blood samples, fasting if possible, were sent to central laboratories. Measurements included total cholesterol, HDL cholesterol and triglycerides [16–18]. LDL cholesterol was calculated according to the method of Friedewald et al. [19]. The reference range for HbA_1c was 2.9–4.8% [20]. Fibrinogen was measured by a clotting assay based on the prothrombin time, as previously described [21, 22]. Levels of von Willebrand factor were measured by ELISA using von Willebrand factor antigen [23] incorporating Dako antibody (Dako, Carpinteria, CA, USA) to coat the micro-wells [24]. Urinary AER was measured from a single 24-h urine collection [25]. An AER between 20 and 200 μg/min was defined as microalbuminuria, while >200 μg/min was defined as macroalbuminuria. The presence and severity of diabetic retinopathy was assessed from centrally graded retinal photographs (two fields per eye) taken with a wide-angle camera [26]. Retinopathy was classified as being either non-proliferative or proliferative.

CVD was defined as a history of doctor-diagnosed CVD (previous myocardial infarction, angina, coronary bypass grafting or stroke) or ischaemic changes on a 12-lead ECG (classified by two observers according to the Minnesota Code) [27].

The protocol used to assess DSP was similar in detail to a number of recently published protocols [1, 28, 29]. A diagnosis of DSP was made if abnormalities were found in two or more of the following three domains:

1. Symptoms of distal neuropathy. The presence of the following symptoms over the previous 6 months was ascertained: (a) “asleep” numbness or “dead feeling” in the feet; (b) a prickling sensation in the feet; (c) deep, aching or burning pains in the legs; and (d) unusual difficulty in climbing stairs. The presence of one or more symptoms was classed as abnormal.
2. Neurological examination. Ankle and knee tendon reflexes were assessed, with reinforcement if necessary. The absence of two or more ankle or knee reflexes was classed as abnormal.
3. Assessment of vibration perception threshold (VPT). The VPT was measured using centrally calibrated biothesiometers (Biomedical, Newbury, OH, USA). [30] Three readings were taken on the right big toe and right medial malleolus, with values rounded up to the nearest unit and their average used for analysis. The results were classified according to age-related criteria [30].

Assessment of CAN There are several techniques available for assessing CAN [7]. The techniques used in the EURODIAB study were chosen based on their ability to assess CAN with reasonable validity and on their ease of use. The presence of CAN was identified by testing two cardiovascular reflex responses: the change in heart rate and the change in systolic blood pressure (measured by a Hawksley random-zero sphygmomanometer) on standing after resting in the supine position for at least 5 min. The ratio of the longest ECG R–R interval between the 28th and 32nd beats following standing to the shortest interval between the 13th and 17th beats (R–R ratio) was calculated by a single observer. CAN was defined as a loss of heart rate variability (R–R ratio <1.04) and/or postural hypotension (a decrease in systolic blood pressure of >20 mmHg) [31]. Participants were encouraged to avoid consuming beverages containing caffeine, alcoholic beverages and tobacco products during the 12 h prior to

the autonomic function tests. Patients were also asked to refrain from taking any non-prescription drugs 48 h before testing.

Participants completed a questionnaire that included questions about symptoms of autonomic dysfunction; however, the questions concerning bladder control, nocturnal diarrhoea and problems with erections and sexual intercourse were answered positively by only a small number of participants, making them unsuitable for further analysis. The question "Have you felt faint on standing up in the last 6 months?" was answered positively by a sufficient number of subjects (n=138) to be included in the analyses.

Baseline investigations and CAN assessment were repeated after a period of 7.3±0.6 years. Figure 1 shows a flow diagram for all participants and the study population for this paper. Of the 3,250 subjects, 243 did not have a complete CAN assessment at baseline. This was mostly due to the ECG recording being of insufficient quality to establish a valid R–R interval. Four of the 31 centres did not participate in the follow-up of the study, leading to the exclusion of 395 subjects (centre drop-out). A further five subjects were excluded because it became apparent at follow-up that they had not met the initial inclusion criteria (protocol violation). These 643 individuals were excluded from all further analyses. For the analysis of incident cases of CAN, subjects with CAN at baseline (n=881) were also excluded. Additional exclusions were due to death and to loss to follow-up (with and without information on life status), as shown in Fig. 1. Thus, the primary study population consisted of 956 individuals without CAN at baseline and with a full CAN assessment both at baseline and at follow-up.

Statistical analysis The data were analysed using the STATA Statistical Software Package, Release 7.0 (STATA, College Station, TX, USA). In order to assess the possibility of selective loss to follow-up, the baseline characteristics (age, sex, duration of diabetes, HbA_1c, insulin dose per kg body weight, systolic and diastolic blood pressure, weight, BMI, WHR, AER, total cholesterol and triglycerides) of the final study population and those who were somehow lost to follow-up were compared. Differences were assessed using an independent-sample t-test for normally distributed variables, and a Mann–Whitney U-test for variables with a skewed distribution. Within the study population, the baseline characteristics of those with and without incident CAN were compared. In the case of variables with a normal distribution, means±SD are reported. For variables with a skewed distribution, medians (5th and 95th percentiles) are shown. The relationships between the incidence of CAN and potential baseline risk factors were assessed by logistic regression, first adjusting for age and sex, and subsequently adjusting for duration of diabetes, sex and HbA_1c. Three multivariate logistic regression models were compared. These models were based on age and glycaemic control (HbA_1c), with subsequent addition of variables from medical history and clinical examination in one step, and diabetic complications in a further step. These models yielded mutually adjusted odds ratios (ORs) for the development of CAN. For each model the area under the receiver operating

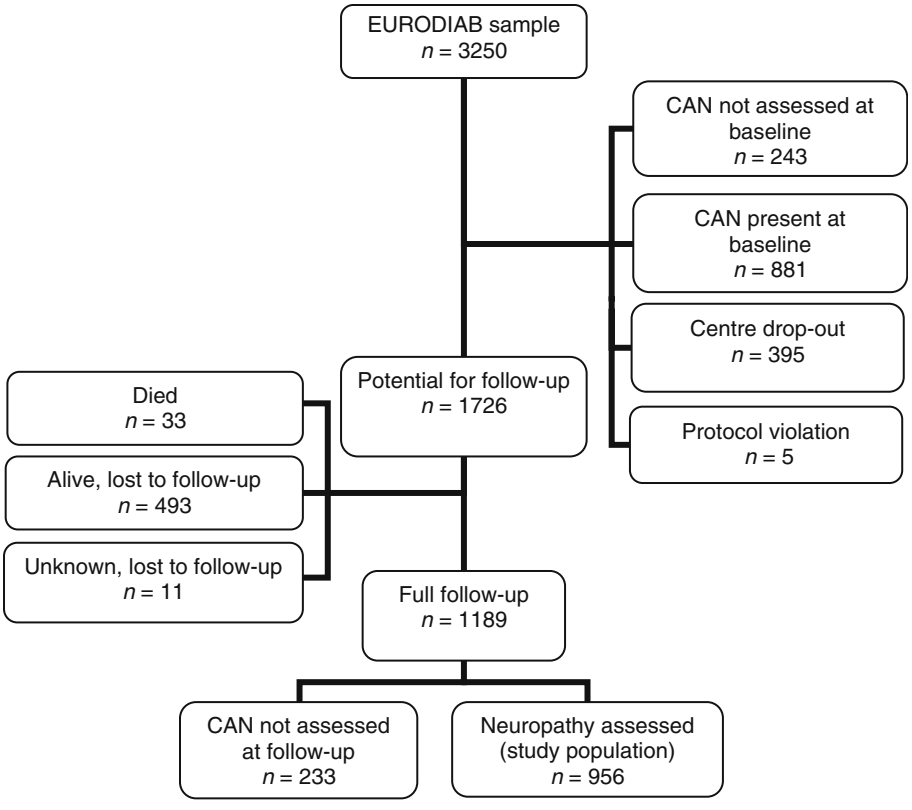

Fig. 1 Flow chart for the study population

characteristic (ROC) curve was calculated and compared with that for the other models. The area under the ROC curve indicates how informative each model is for the prediction of CAN. To assess the potential effect of medication on our results, all regression analyses were repeated excluding subjects who used antihypertensives, lipid-lowering drugs, drugs prescribed for angina pectoris or for other cardiac conditions. Important changes to the results are reported. A p value lower than 0.05 was considered statistically significant.

Results

We compared the baseline characteristics of the study population (n=956) with those of subjects with potential for follow-up who died, were lost to follow-up for any reason, or did not have a full CAN assessment at the follow-up visit (n=770). The study population was younger than the excluded subjects (31.3±8.9 vs 32.8±9.7 years), had a lower systolic blood pressure (118±14 vs 120±16 mmHg) and had lower total cholesterol levels (5.2±1.0 vs 5.3±1.1 mmol/l). Other differences were not statistically significant.

Of the 956 subjects in the study population, 163 (17%) developed CAN over the 7.3 years of follow-up. This is equivalent to an incidence rate of 23.4 per 1,000 person-years of follow-up. The baseline characteristics of both groups are summarised in Table 1. In an unadjusted comparison, subjects who developed CAN were older, heavier, had a longer duration of diabetes, and had a higher WHR and systolic blood pressure than those who did not. They also had a higher percentage of HbA_1c and higher levels of triglycerides and von Willebrand factor. At baseline, albuminuria, retinopathy, a positive history of CVD and feeling faint on standing up were present in a greater proportion of those who developed CAN compared with those who did not.

Table 2 shows the ORs for developing CAN at two levels of adjustment: (1) age and sex; and (2) sex, duration of diabetes and HbA_1c. When adjusted for age and sex, duration of diabetes was no longer related to the incidence of CAN. HbA_1c was a major determinant of future CAN, with an increase in risk of 20% per percentage point increase in HbA_1c. Total cholesterol, triglycerides, HDL, LDL and smoking were not related to the risk of developing CAN. Diastolic and systolic blood pressure and the diagnosis of hypertension carried an increased risk of CAN when the entire study group was considered. The relationship with blood pressure was attenuated on exclusion of those receiving antihypertensive therapy at baseline (n=59) and lost statistical significance in the age- and sex-adjusted model. Adjustment for sex, duration of diabetes and HbA_1c yielded a significantly increased risk of 16% per 10 mmHg increase in systolic blood pressure in those not using antihypertensive medication. Following adjustment for age and sex, a tenfold increase in AER (one point on the log scale) was associated with a 55% increase

Table 1 Baseline characteristics of subjects with and without CAN at follow-up

	Progression to CAN (n=163)	No progression to CAN (n=793)
Age (years)	34.5±10.3	30.7±8.4
Duration of diabetes (years)	15.4±9.8	13.1±8.0
Male	58	53
Ever smoked	52	45
Height (cm)	170±9	169±9
Weight (kg)	69±11	67±11
BMI (kg/m^2)	23.9±2.9	23.4±2.6
WHR	0.86±0.11	0.84±0.09
HbA_1c (% of Hb)	6.89±1.81	6.38±1.79
Insulin dose per kg body weight (IU/kg)	0.67±0.20	0.68±0.22
Total cholesterol (mmol/l)	5.33±1.12	5.19±1.03
LDL cholesterol (mmol/l)	3.37±1.02	3.22±0.89
HDL cholesterol (mmol/l)	1.46±0.41	1.53±0.45
Triglycerides (mmol/l)	0.97 (0.50, 2.66)	0.88 (0.49, 2.22)
Fibrinogen (g/l)	3.20 (1.69, 4.83)	3.14 (1.76, 4.64)
von Willebrand factor (U/ml)	1.21 (0.68, 2.28)	1.08 (0.55, 2.08)
Systolic blood pressure (mmHg)[a]	121±16	117±14
Diastolic blood pressure (mmHg)[a]	75±11	74±10
AER (μg/min)	12 (3, 578)	11 (3, 125)
Hypertension	30	27
Macroalbuminuria	10	4
Microalbuminuria/macroalbuminuria	34	25
Any retinopathy	59	38
Proliferative retinopathy	14	5
History of CVD	11	5
Feeling faint on standing up	22	13

Data are means±SD, medians (5% centile, 95% centile) or percentages

[a]Excluding those using antihypertensive therapy

Table 2 Risk factors for the development of CAN

	Adjusted for age and sex		Adjusted for sex, duration of DM and HbA_1c	
	OR	95% CI	OR	95% CI
Age (per decade)[a]	1.58	1.31–1.90[b]		
Sex (male)[b]	1.23	0.87–1.74		
Duration (per decade)	1.01	0.79–1.30		
HbA_1c (per % Hb)	1.20	1.09–1.32[b]		
Insulin dose per kg body weight (per IU/kg)	1.12	0.50–2.52	0.69	0.30–1.57
Height (per 10 cm)	1.05	0.82–1.35	1.16	0.90–1.49
Weight (per 10 kg)	1.11	0.92–1.34	1.21	1.01–1.46[d]
BMI (per kg/m^2)	1.03	0.97–1.10	1.06	0.99–1.13
WHR (per SD)	1.17	0.96–1.42	1.17	0.97–1.42
Log AER [per 10-fold increase (μg/min)]	1.55	1.16–2.09[e]	1.30	0.96–1.76
Smoking (ever vs never)	1.09	0.77–1.54	1.19	0.84–1.68
Systolic blood pressure (per 10 mmHg)[f]	1.09	0.96–1.24	1.16	1.02–1.32[d]
Diastolic blood pressure (per 10 mmHg)[f]	1.11	0.94–1.33	1.15	0.97–1.36
Systolic blood pressure (per 10 mmHg)	1.15	1.03–1.28[d]	1.20	1.07–1.34[e]
Diastolic blood pressure (per 10 mmHg)	1.21	1.03–1.42[d]	1.23	1.05–1.44[e]
Total cholesterol (per mmol/l)	1.05	0.89–1.24	1.05	0.89–1.24
Triglycerides (per mmol/l)	1.12	0.93–1.36	1.06	0.87–1.30
HDL cholesterol (per mmol/l)	0.66	0.43–1.02	0.79	0.52–1.21
LDL cholesterol (per mmol/l)	1.10	0.87–1.39	1.11	0.88–1.40
Fibrinogen (per g/l)	1.01	0.77–1.31	0.94	0.73–1.23
von Willebrand factor (U/ml)	1.58	1.04–2.38[d]	1.47	0.98–2.22
Hypertension	1.77	1.19–2.65[e]	1.96	1.31–2.92[d]
CVD	1.88	1.02–3.47[d]	2.18	1.19–4.03[d]
DSP	2.46	1.67–3.64[b]	2.29	1.53–3.41[b]
Macroalbuminuria	2.65	1.38–5.08[e]	2.16	1.12–4.18[d]
Microalbuminuria or macroalbuminuria	1.58	1.09–2.31[d]	1.25	0.85–1.85
Proliferative retinopathy	2.76	1.46–5.21[e]	2.96	1.50–5.84[e]
Any retinopathy	2.10	1.41–3.13[b]	2.17	1.38–3.44[d]
Feeling faint on standing up	1.94	1.25–3.00[e]	1.93	1.25–2.98[e]

[a]Adjusted for sex
[b]$p<0.001$
[c]Adjusted for age
[d]$p<0.05$
[e]$p<0.01$
[f]Excluding those using antihypertensive therapy

in the risk of developing CAN. After further adjustment, this relationship was attenuated and was no longer statistically significant. In the age- and sex-adjusted model, von Willebrand factor carried an increased risk of CAN. This association also lost statistical significance after adjustment for sex, duration of diabetes and HbA_1c. All diabetic complications at baseline were associated with an increased risk of developing CAN after adjustment for age and sex. Most relationships remained statistically significant in the model adjusted for sex, duration of diabetes and HbA_1c. In both models the risk of developing CAN was almost doubled in those who gave a positive answer to the question "Have you felt faint on standing up in the past 6 months?" The positive predictive value of 'feeling faint on standing' was 0.26 and the corresponding negative predictive value was 0.84.

Multivariate logistic regression models based on the most important variables from the adjusted models are displayed in Table 3. Model B includes variables from the medical history, the clinical examination and those associated diabetic control, and Model C is further adjusted for diabetic complications. Model B shows that age, HbA_1c, systolic blood pressure and feeling faint on standing up are all independent risk factors/risk indicators. In Model C, the presence of DSP and any form of retinopathy at baseline were additionally predictive of new CAN. In this model the roles of age and systolic blood pressure were somewhat attenuated.

The area under the ROC curve of the model that included diabetic complications (Model C) was slightly, but not significantly larger than that of Model B. However, Model C was significantly better than the basic model that only included age and HbA_1c (Model A).

Re-analysis excluding all subjects who used antihypertensive therapy, lipid-lowering drugs, or drugs prescribed for angina pectoris or other heart conditions at either baseline or follow-up (n=67) yielded lower ORs for von Willebrand factor, CVD, microalbuminuria or macroalbuminuria, and proliferative retinopathy. The ORs were 1.41 (95% CI 0.90–2.22), 1.28 (95% CI 0.60–2.74), 1.20 (95% CI 0.78–1.84) and 2.14 (95% CI 0.97–4.71), respectively, in the age- and sex-adjusted model, and 1.36 (95% CI 0.87–2.15), 1.58 (95% CI 0.75–3.35), 1.89 (95% CI 0.79–4.53) and 2.22 (95% CI 0.97–5.09), respectively, in the model adjusted for sex, duration of diabetes and HbA_1c.

Table 3 Logistic regression models with ORs for relationships between key risk factors and the incidence of CAN

	OR	95% CI	*p* value
Model A: diabetic control			
Age (per decade)	1.65	1.37–1.98	<0.001
HbA_1c (per % Hb)	1.20	1.09–1.31	<0.001
Area under ROC curve	0.64	0.60–0.69	–
Model B: addition of medical history and clinical examination			
Age (per decade)	1.51	1.25–1.84	<0.001
HbA_1c (per % Hb)	1.21	1.10–1.33	<0.001
Feeling faint on standing up	1.91	1.23–2.98	0.004
Systolic blood pressure (per 10 mmHg)	1.18	1.06–1.32	0.003
Area under ROC curve	0.67	0.63–0.72	–
Model C: addition of complications			
Age (per decade)	1.34	1.06–1.69	0.01
HbA_1c (per % Hb)	1.23	1.10–1.37	<0.001
Feeling faint on standing up	1.97	1.20–3.22	0.007
Systolic blood pressure (per 10 mmHg)	1.13	0.99–1.29	0.06
DSP	–	1.21–3.04	0.005
Any retinopathy	1.70	1.11–2.60	0.01
Area under ROC curve	0.70	0.65–0.76	–

Test for areas under ROC curves being different: Model A vs Model B, p=0.10; Model B vs Model C, p=0.07; Model A vs Model C, p=0.02

Other adjusted relationships (Table 2) and the multivariate regression models (Table 3) were not materially affected.

Discussion

In the present study of subjects with type 1 diabetes, the incidence of CAN during 7.3 years of follow-up was related to age, HbA_1c, systolic blood pressure, and the presence of DSP and retinopathy at baseline. The incidence of CAN was 23.4 per 1,000 person-years, which is lower than the incidence of 59 per 1,000 person-years found in the Epidemiology of Diabetic Complications (EDC) analysis [13]. This difference may be explained by the fact that EDC participants had a longer duration of diabetes and higher HbA_1c values at baseline compared with those in our study population.

Potential limitations Our study population consisted of 956 of the 1,726 subjects with potential for follow-up. The 770 (45%) subjects who were not included in the final study population were older and had slightly higher systolic blood pressures and total cholesterol levels. As a consequence of this, our results may underestimate the true incidence of CAN. However, these differences are unlikely to bias the observed associations between risk factors and disease, as a situation in which high cholesterol or blood pressure reduces the risk of CAN in those lost to follow-up but increases the risk in those attending follow-up is unlikely.

Main observations We observed a relationship between feeling faint on standing and the risk of developing CAN, confirming our previous cross-sectional findings [32]. Although feeling faint on standing is a non-specific symptom, it may act as an indicator of early phases of autonomic neuropathy in some individuals. A recent study demonstrated that diabetic subjects with CAN and orthostatic hypotension show instability in cerebral blood flow on active standing [33]. A higher rate of medication use among those who felt faint on standing could not explain our findings, since the multivariate logistic regression models did not change materially after the exclusion of those on medication. Although the low positive predictive value of this symptom limits its role in isolation, the multivariate models suggest that it may be a helpful addition to the other determinants of CAN. However, the practical utility and reliability of this finding needs to be confirmed in other studies.

The cross-sectional baseline report on CAN in the EURODIAB population found that the presence of CAN was associated with age, duration of diabetes, HbA_1c, triglycerides, AER, cardiovascular disease, severe retinopathy and DSP [2]. In this prospective analysis, we have not confirmed a role for triglycerides or AER as risk factors for the development of new cases of CAN. Conversely, CVD at baseline was predictive of CAN, irrespective of duration of diabetes, sex or HbA_1c. However, it was a less powerful predictor than the other diabetic complications, as can be observed from its absence in the multivariate models.

The close relationship between measures of CAN and DSP has been well documented [34, 35]. Our analyses excluded all subjects with CAN at baseline, and our definition of DSP did not include items used in the diagnosis of CAN, thereby excluding the possibility of finding a relationship through overlapping definitions. Our findings confirm previous reports of DSP as a risk factor for CAN, independently of diabetes duration and HbA_1c [10], thus strengthening the case for a shared aetiology.

The lack of a relationship between AER or albuminuria and the development of CAN may seem surprising. The EDC study reported that macroalbuminuria was a stronger predictor of CAN than blood pressure was. However, among those without overt nephropathy, neither AER nor mild albuminuria was predictive of CAN development [13]. Our study revealed that, in a population with a lower baseline prevalence of macroalbuminuria (5.0% in the EURODIAB PCS vs 15.6% in the EDC), neither AER nor the presence of either microalbuminuria or macroalbuminuria was predictive of CAN, whereas systolic blood pressure was. The absence of a relationship between AER or microalbuminuria and CAN in the present study may be due to the larger proportion of participants without advanced nephropathy, in whom neither AER nor albuminuria is related to CAN [36]. We considered the possibility that, in excluding those with CAN at baseline, we had selected a population with different pathophysiological mechanisms. However, when we scrutinised the baseline characteristics of those with CAN at baseline and

those who developed the complication during follow-up, we found no evidence for selection (data not shown). Furthermore, when we used the follow-up values for AER we found a cross-sectional relationship between AER and the presence of CAN (after adjusting for sex, duration of diabetes and HbA_1c at follow-up). Thus, AER deterioration appears to occur simultaneously with the development of CAN, but does not precede it to a sufficient extent to independently predict the risk of CAN.

Further studies Experimental studies and animal models have provided ample evidence for a microvascular origin of DSP in diabetes through structural changes in the vasa nervorum which reduce the endoneurial blood flow producing neural hypoxia [11]. These previous findings are in agreement with the important relationships observed between CAN development and the baseline presence of retinopathy and systolic blood pressure in the present study. Both may be regarded, albeit indirectly, as indicators of a microvascular pathway. Although this potentially common pathophysiological mechanism needs to be further evaluated using direct vascular measures, our observations give rise to the important possibility that tight blood pressure control may have added value for the prevention of CAN over intensive glycaemic control alone. This hypothesis has previously been postulated [13]; however, a randomised controlled trial comparing the effect of adding antihypertensive therapy to intensive glycaemic control has not yet been conducted in type 1 diabetes. The Steno-2 study, a randomised controlled trial, has studied the effect of tight glycaemic control, lipid lowering, antioxidants and antihypertensive therapy in type 2 diabetes. In this study, subjects in the intensive treatment group showed a 63% reduction in the risk of developing CAN and an 11-mmHg reduction in systolic blood pressure [37]. Our results suggest that a similar reduction in systolic blood pressure may decrease the incidence of CAN by 15–20%, in addition to the 40–50% decrease which may be achieved by matching the 1.9-percentage-point reduction in HbA_1c obtained in the DCCT study [1]. Such results would be of clear clinical relevance, markedly reducing the morbidity and possibly also the excess mortality associated with CAN.

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The EURODIAB Prospective Complications Study Group includes:

B. Karamanos, A. Kofinis, K. Petrou (Hippokration Hospital, Athens, Greece).

F. Giorgino, G. Picca, A. Angarano, G. De Pergola, L. Laviola, R. Giorgino (Internal Medicine, Endocrinology and Metabolic Diseases, Department of Emergency and Organ Transplantation, University of Bari, Italy).

C. Ionescu-Tirgoviste, A. Coszma, C. Guja (Clinic of Diabetes, Nutrition and Metabolic Diseases, Bucharest, Romania).

M. Songini, A. Casu, M. Pedron, S. Pintus, M. Fossarello (Diabetes Unit, San Michele Hospital, Cagliari, Italy).

J. B. Ferriss, G. Grealy, D. O. Keefe (Cork University Hospital, Cork, Ireland).

M. Toeller, C. Arden (Diabetes Research Institute, Heinrich-Heine University, Dusseldorf, Germany).

R. Rottiers, C. Tuyttens, H. Priem (University Hospital of Gent, Belgium).

P. Ebeling, M. Kylliäinen, V. A. Koivisto (University Hospital of Helsinki, Finland).

B. Idzior-Walus, J. Sieradzki, K. Cyganek, B. Solnica (Department of Metabolic Diseases, Jagiellonian University, Krakow, Poland).

H. H. P. J. Lemkes, J. C. Lemkes-Stuffken (Leiden University Medical Centre, Leiden, The Netherlands).

J. Nunes-Correa, M. C. Rogado, L. Gardete-Correia, M. C. Cardoso, A. Silva, J. Boavida, M. Machado Sa Marques (Portuguese Diabetic Association, Lisbon, Portugal).

G. Michel, R. Wirion, S. Cardillo (Centre Hospitalier, Luxembourg).

G. Pozza, R. Mangili, V. Asnaghi (San Raffaele Hospital, Milan, Italy).

E. Standl, B. Schaffler, H. Brand, A. Harms (Schwabing City Hospital, Munich, Germany).

D. Ben Soussan, O. Verier-Mine, P. Fallas, M. C. Fallas (Centre hospitalier, Valenciennes, France).

J. H. Fuller, J. Holloway, L. Asbury, D. J. Betteridge (University College London, UK).

G. Cathelineau, A. Bouallouche, B. Villatte Cathelineau (Saint-Louis Hospital, Paris, France).

F. Santeusanio, G. Rosi, V. D'Alessandro, C. Cagini, P. Bottini, G. P. Reboldi (Department of Internal Medicine, Perugia, Italy).

R. Navalesi, G. Penno, S. Bandinelli, R. Miccoli, M. Nannipieri (Department of Endocrinology and Metabolism, University of Pisa, Italy).

G. Ghirlanda, C. Saponara, P. Cotroneo, A. Manto, A. Minnella (Catholic University of the Sacred Heart, Rome, Italy).

J. D. Ward, S. Tesfaye, S. Eaton, C. Mody (Royal Hallamshire Hospital, Sheffield, UK).

M. Borra, P. Cavallo Perin, S. Giunti, G. Grassi, G. F. Pagano, M. Porta, R. Sivieri.

F. Vitelli, M. Veglio (Department of Internal Medicine, University of Turin and ASO CTO/CRF/Maria Adelaide, Turin, Italy).

N. Papazoglou, C. Manes (General Hospital Papageorgiou, Diabetes Unit, Thessaloniki, Greece).

M. Muggeo, M. Iagulli, V. Cacciatori (Division of Metabolic Disease, University of Verona Medical School, Verona, Italy).

K. Irsigler, H. Abrahamian (Vienna Lainz Hospital, Austria).

S. Walford, J. Sinclair, S. Hughes, V. McLelland, J. Ward (New Cross Hospital, Wolverhampton, UK).

G. Roglic, Z. Metelko, Z. R. Pepeonik (Vuk Vrhovac Institute for Diabetes, Zagreb, Croatia).

The steering committee members are:

J. H. Fuller (London), B. Karamanos, Chairman (Athens), A. K. Sjolie (Odense), N. Chaturvedi (London), M. Toeller (Dusseldorf), G. Pozza, Co-chairman (Milan), J. B. Ferriss (Cork), M. Porta (Turin), R. Rottiers (Gent), G. Michel (Luxembourg).

The coordinating centre includes:

J. H. Fuller, N. Chaturvedi, J. Holloway, D. Webb, L. Asbury (University College London, UK).

The central laboratories include:

G. C. Viberti, R. Swaminathan, P. Lumb, A. Collins, S. Sankaralingham (Guy's and St Thomas' Hospital, London, UK).

The retinopathy grading centre includes:

S. Aldington, T. Mortemore, H. Lipinski (Royal Postgraduate Medical School, Imperial College, London, UK)

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