Cardiac Autonomic Neuropathy Predicts Cardiovascular Morbidity and Mortality in Type 1 Diabetic Patients With Diabetic Nephropathy

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OBJECTIVE — Cardiac autonomic neuropathy (CAN) has been associated with a poor prognosis in patients with diabetes. Because CAN is common in patients with diabetic nephropathy, we evaluated the predictive value of CAN in type 1 diabetic patients with and without diabetic nephropathy.

RESEARCH DESIGN AND METHODS — In a prospective observational follow-up study, 197 type 1 diabetic patients with diabetic nephropathy and a matched group of 191 patients with long-standing type 1 diabetes and normoalbuminuria were followed for 10.1 years (range 0.0–10.3 years). At baseline, CAN was assessed by heart rate variation (HRV) during deep breathing. HRV was evaluated as a predictor of the primary end point: cardiovascular morbidity and mortality. As secondary end points, all-cause mortality and the influence of HRV on progression of diabetic nephropathy (decline in glomerular filtration rate [GFR]) was evaluated.

RESULTS — During the follow-up, 79 patients (40%) with nephropathy reached the combined primary end point vs. 19 patients (10%) with normoalbuminuria (log-rank test, $P < 0.0001$). The unadjusted hazard ratio (HR) for reaching the primary end point when having an abnormal HRV (≤10 bpm) measured at baseline compared with a normal HRV was 7.7 (range 1.9–31.5; $P = 0.004$) in patients with nephropathy. Similarly in the normoalbuminuric patients, the unadjusted HR was 4.4 (1.4–13.6; $P = 0.009$). In patients with nephropathy, abnormal HRV was significantly associated with fatal and nonfatal cardiovascular disease after adjustment for cardiovascular risk factors. The adjusted HR for reaching the primary end point in a patient with nephropathy and an abnormal HRV was 6.4 (1.5–26.3, $P = 0.010$), as compared with a normal HRV. The unadjusted HR for dying when having an abnormal HRV compared with a normal HRV was 3.3 (95% CI 1.0–10.7; $P = 0.043$) in patients with diabetic nephropathy. After adjustment for confounding factors, the impact of HRV on all-cause mortality in patients with nephropathy was no longer significant ($P = 0.293$). There was no relationship between abnormal HRV and rate of decline in GFR.

CONCLUSIONS — HRV is an independent risk factor for cardiovascular morbidity and mortality in type 1 diabetic patients with nephropathy.

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Cardiovascular autonomic neuropathy (CAN) is a severe complication of diabetes, causing death and morbidity and large costs to the welfare system (1). The mechanisms by which CAN exerts negative influence on quality and length of life are controversial, but many relationships have been found, e.g., to exercise intolerance (2–5), silent myocardial ischemia (6–10), and prolongation of the QT interval causing deadly arrhythmias (11,12).

Diabetic nephropathy is another devastating complication affecting ~40% of all type 1 diabetic patients (13). It is known that patients who develop diabetic nephropathy are at greater risk of dying early and that CAN might be of particular importance in this patient group. Patients with CAN have a higher prevalence of proteinuria than patients without CAN (14). In one study of 85 patients with overt nephropathy, 31% were found to have autonomic neuropathy, and here autonomic neuropathy was found to be a predictor of all-cause mortality (15). Also a relationship between progression of renal dysfunction and autonomic dysfunction has been suggested (16).

CAN results from damage to the autonomic nerve fibers to the heart, and the earliest indicator of CAN is a decrease in heart rate variation (HRV) during deep breathing (17), which is easily assessed by a simple bedside test. Because knowledge about CAN in type 1 diabetic patients with diabetic nephropathy is scarce, we assessed factors associated with abnormal HRV in a large cohort of type 1 diabetic patients with and without diabetic nephropathy at baseline. The cohort was followed prospectively for 10 years, and the prognostic value of HRV in relation to the combined end point of cardiovascular morbidity and mortality and to the secondary end points of all-cause mortality and progression of diabetic nephropathy was assessed.

RESEARCH DESIGN AND METHODS

— In 1993, 197 type 1 diabetic patients with diabetic nephropathy who had their glomerular filtration rate (GFR) and HRV measured the same year were recruited from the outpatient clinic at Steno Diabetes Center for a case-control study (18,19). Diabetic nephropathy was diagnosed by the following criteria: persistent albuminuria ≥300 mg/24 h in two of three consecutive 24-h urine collections, the presence of retinopathy, and no clinical or laboratory evi-

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Abbreviations: CAN, cardiac autonomic neuropathy; CVD, cardiovascular disease; GFR, glomerular filtration rate; HRV, heart rate variation.

A table elsewhere in this issue shows conventional and Système International (SI) units and conversion factors for many substances.

dence of other renal or urinary tract disease other than diabetic glomerulosclerosis (20). As control subjects, we recruited 191 patients with long-standing type 1 diabetes and persistent normoalbuminuria. The two groups were matched for sex, age, and duration of diabetes. Age and duration of diabetes were matched within ±5 and ±3 years, respectively. During the follow-up, 13 patients with normoalbuminuria developed microalbuminuria, whereas none developed diabetic nephropathy.

GFR was measured regularly during follow-up approximately every year. Only patients with a minimum of three measurements were used to assess the rate of decline in kidney function (21). There were no interim measurements other than GFR.

In the present study CAN was defined as having an HRV ≤10 bpm at baseline, which was proposed as abnormal by Ewing et al. (22).

In a prospective observational study design, patients were followed up until 31 December 2003 or until death ($n = 76$) or emigration ($n = 3$). All end points were obtained at the follow-up examination. The results of the follow-up examination have been published elsewhere (23). The study was approved by the local ethics committee, and all patients gave fully informed consent.

Baseline clinical and laboratory investigations

Investigations were performed in the morning after an overnight fast (18,19). Arterial blood pressure was measured twice following at least 10 min of rest in the supine position. Urinary albumin concentration was measured by an enzyme immunoassay (24) from 24-h urine collections. Serum creatinine concentration was assessed by a kinetic Jaffé method. GFR was measured in patients with diabetic nephropathy after a single injection of 3.7 MBq ^{51}Cr-EDTA (25).

Diabetic retinopathy was assessed in all patients by fundus photography after pupillary dilatation and graded as nil, simplex, or proliferative retinopathy. Patients were interviewed using the World Health Organization cardiovascular questionnaire (26). At baseline, major cardiovascular events were diagnosed as a history of stroke and/or myocardial infarction. Smoking was defined as persons smoking one or more cigarettes/cigars/pipes per day; all others were considered nonsmokers.

In 149 patients with diabetic nephropathy, GFR was assessed annually (27). HRV was assessed by expiration/inspiration variation in heart rate according to the method described by Hilsted and Jensen (28). To perform the test, the patient was in the supine position and asked to breathe deeply at the rate of 6 breaths/min for 1 min while being monitored by electrocardiogram. The maximum and minimum heart rates during each breathing cycle were measured, and the means of the differences were calculated.

End points

The primary end point was a composite cardiovascular end point of cardiovascular mortality and morbidity. Cardiovascular morbidity was defined as a history of nonfatal myocardial infarction, percutanous coronary intervention, coronary artery bypass grafting, nonfatal stroke, amputation as a result of ischemia, and vascular surgery for peripheral atherosclerotic disease as suggested by Gaede et al. (29). The secondary end point was all-cause mortality and progression of diabetic nephropathy. Information regarding the primary end point was obtained from a World Health Organization questionnaire (26) ($n = 274$) and confirmed in patient files. All patients were traced in the national register in January 2004.

Statistical analysis

HRV, urinary albumin excretion rate, triglyceride levels, and serum creatinine concentrations were non-normally distributed and were therefore log transformed to obtain normal distribution before analysis and given as medians (range). All other values are given as means ± SD. For normal and log-normal distributed variables, comparison between groups was performed by an unpaired Student's t test. Frequencies were compared with a χ^2 test.

All time-to-first-event variables were analyzed with a log-rank test and displayed on Kaplan-Meier plots according to the presence of nephropathy and HRV levels. To evaluate HRV as a predictor of the primary and secondary end points, the patients were divided into categories as suggested by Ewing et al. (22): abnormal, HRV ≤10 bpm; borderline, 11–14 bpm; and normal, ≥15 bpm.

In the analysis of predictors of the primary end point, stepwise Cox regression with backwards selection was used, including variables that in a bivariate analysis were significantly predictive of the primary end point. Prespecified variables were smoking and sex. To avoid overfitting the model, only one parameter for kidney function was used, chosen by the highest overall χ^2 score. The same was done for lipid and blood pressure variables. In total, the following baseline variables were used: smoking, sex, age, history of cardiovascular disease (CVD), total cholesterol level, triglyceride level, urinary albumin excretion rate, systolic blood pressure, HbA_{1c} (A1C), and HRV.

The same method was used when analyzing all-cause mortality. The variables in the final model were the same as above. Results are described as hazard ratios (HRs) with 95% CIs without or with adjustment for other factors that might affect prognosis.

Because our study allows evaluation of CAN in patients with diabetic nephropathy per se, we divided groups for analysis of predictors of the primary end point and all-cause mortality. However, we also performed Cox regression analysis on all patients. In the normoalbuminuric patients, the number of events was limited, and results from the Cox analysis should be interpreted with caution. No difference in results was seen if patients who developed microalbuminuria during follow-up were excluded from the analysis.

Progression in diabetic nephropathy was assessed as the change in GFR with time. Linear regression analysis (least-squares method) using all measured GFR values during follow-up in each patient versus time was used to determine the rate of decline in GFR (slope) for each patient. The individual rates of decline in GFR in patients with normal/borderline/abnormal HRV were compared using one-way ANOVA.

Two-tailed P values <0.05 were considered significant. All calculations were performed with SPSS version 12.0.

RESULTS

Baseline and baseline associations

Baseline characteristics are shown in Table 1. The HRV was significantly different in the two groups. In Table 1, the distribution of patients into categories of Ewing et al. (22) is shown. In Table 2, the frequency of events during the follow-up period within patients divided into the Ewing et al. categories is shown.

At baseline, older age ($r^2 = 0.115$; $P < 0.0001$) and higher systolic blood pressure ($r^2 = 0.068$; $P < 0.0001$) were significantly associated with abnormal

Table 1—*Baseline clinical characteristics in type 1 diabetic patients with and without diabetic nephropathy*

	Patients with diabetic nephropathy	Patients with normoalbuminuria	*P* value
n	197	191	
Sex (male/female)	120/77	117/74	NS
Age (years)	41 ± 9	43 ± 10	NS
Duration of diabetes (years)	28 ± 8	27 ± 8	NS
BMI (kg/m^2)	24.0 ± 3.3	23.6 ± 2.5	NS
A1C (%)	9.5 ± 1.5	8.5 ± 1.1	<0.001
Smoking (%)	50	42	NS
History of stroke	14 (7)	2 (1)	<0.001
History of myocardial infarction	10 (5)	2 (1)	<0.001
History of stroke/myocardial infarction	21 (11)	4 (2)	<0.001
Retinopathy (nil/simplex/proliferative)	0/61/136	67/106/18	<0.001
Urinary albumin excretion (mg/24 h)*	796 (16–14,565)	8 (1–30)	
Serum creatinine (μmol/l)	103 (54–684)	76 (40–116)	<0.001
GFR (ml/min per 1.73 m^2)	74 ± 34		
Systolic blood pressure (mmHg)	151 ± 23	132 ± 18	<0.001
Diastolic blood pressure (mmHg)	86 ± 13	76 ± 10	<0.001
Serum cholesterol (mmol/l)	5.6 ± 1.2	4.8 ± 1.0	<0.001
HDL cholesterol (mmol/l)	1.46 ± 0.5	1.56 ± 0.4	<0.001
LDL cholesterol (mmol/l)	3.54 ± 1.1	2.82 ± 0.9	<0.001
Triglycerides (mmol/l)	1.22 (0.3–9.8)	0.77 (0.28–3.1)	<0.001
HRV (bpm)	6 (0–50)	13 (0–55)	<0.001
HRV (abnormal/borderline/normal)	151/21/25	65/44/82	<0.001
HRV (abnormal/borderline/normal) (%)	76/11/13	34/23/43	
Antihypertensive treatment (%)	81	13	<0.001
Statins (%)	0	0	
Aspirin (%)	11	2	<0.001

Data are means ± SD, *n* (%), or median (range) unless otherwise indicated. *Some patients with previously persistent albuminuria receiving antihypertensive medication had urinary albumin excretion <300 mg/24 h.

HRV in patients with diabetic nephropathy in a linear regression analysis. Similarly, in patients with persistent normoalbuminuria, A1C levels (r^2 = 0.063; $P < 0.0001$) and older age (r^2 = 0.115; $P < 0.0001$) were associated with abnormal HRV.

Follow-up and HRV as a predictor of cardiovascular mortality and morbidity

The mean follow-up until death or follow-up visit was 10.1 years (range 0–10.3 years). During the follow-up, 79 patients (40%) with nephropathy reached the combined primary end point versus 19 patients (10%) with normoalbuminuria (log-rank test $P < 0.0001$).

The 79 nephropathic patients reaching the primary end point experienced a total of 107 events including 25 deaths from cardiovascular causes, 23 coronary interventions or myocardial infarctions, 24 strokes, and 35 lower-limb amputations or peripheral bypass procedures. In patients with normoalbuminuria, there were a total of 23 events in 19 patients, including 8 deaths from cardiovascular causes, 8 coronary interventions or myocardial infarctions, 5 strokes, and 2 lower-limb amputations or peripheral bypass procedures.

In Fig. 1*A* and *B,* the cumulative incidence of the primary end point in patients with diabetic nephropathy and in patients with normoalbuminuria is shown. In patients with nephropathy, the unadjusted HR for reaching the primary end point when having an abnormal HRV compared

Table 2—*Events and all-cause mortality during 10 years of follow-up in patients divided according to HRV during deep breathing*

	Abnormal: HRV ≤10 bpm	Borderline: HRV 11–14 bpm	Normal: HRV ≥15 bpm	Unadjusted HR (95% CI)*	*P* value unadjusted HR	Adjusted HR (95% CI)*	*P* value adjusted HR
All patients	216	65	107				
Fatal/nonfatal cardiovascular events	85 (39)	6 (9)	6 (6)	8.7 (3.8–20.0)	<0.0001	4.9 (2.1–11.5)	<0.0001
All-cause mortality	62 (29)	7 (11)	6 (6)	5.7 (2.5–13.1)	<0.0001	—	NS
Patients with nephropathy	151	21	25				
Fatal/nonfatal cardiovascular events	72 (48)	4 (19)	2 (10)	7.7 (1.9–31.5)	0.002	6.4 (1.5–26.3)	0.010
All-cause mortality	53 (35)	3 (12)	3 (14)	3.3 (1.0–10.7)	0.043	—	NS
Patients with normoalbuminuria	65	44	82				
Fatal/nonfatal cardiovascular events	13 (20)	2 (5)	4 (5)	4.4 (1.4–13.6)	0.009	—	NS
All-cause mortality	9 (14)	4 (9)	3 (4)	3.9 (1.0–14.3)	0.043	—	NS

Data are *n* or *n* (%) unless otherwise indicated. *Comparing patients with abnormal HRV to patients with a normal HRV within categories.

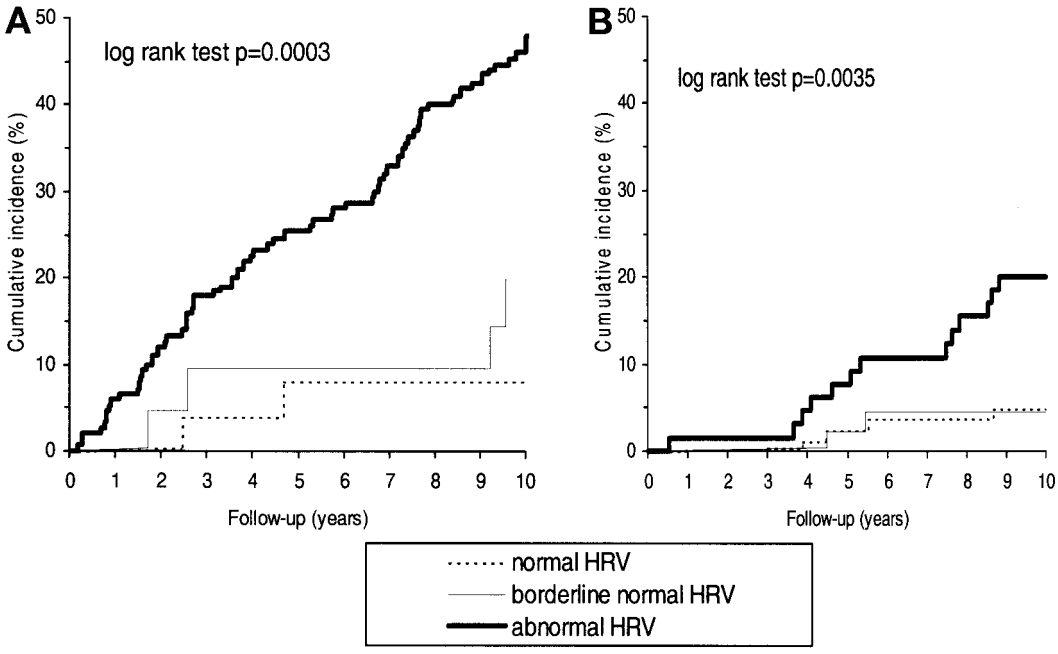

Figure 1—*The cumulative incidence of the primary end point in patients with diabetic nephropathy* (A) *and persistent normoalbuminuria* (B). *Patients are divided into categories as suggested by Ewing et al. (22).*

with a normal HRV was 7.7 (95% CI 1.9–31.5; $P = 0.002$). In patients with diabetic nephropathy, HRV was significantly associated with development of fatal and nonfatal CVD after adjustment for the following confounding factors: current smoking, sex, age, history of CVD, total cholesterol, triglycerides, urinary albumin excretion rate, systolic blood pressure, A1C, and HRV. The HR for reaching the primary end point for a patient with diabetic nephropathy with abnormal HRV was 6.4 (1.5–26.3; $P = 0.010$) after adjustment compared with a patient with nephropathy and a normal HRV. Patients with a borderline normal HRV had an insignificant higher HR of 2.9 (0.5–16.0; $P = 0.221$) compared with patients with a normal HRV.

In normoalbuminuric patients, the unadjusted HR for reaching the primary end point was 4.4 (95% CI 1.4–13.6; $P = 0.009$) when having an abnormal HRV compared with a normal HRV. After adjustment for the above-mentioned risk factors, HRV was not a significant predictor of the primary end point ($P = 0.226$).

When the two groups were analyzed together in the Cox model with adjustment for the above-mentioned risk factors and diabetic nephropathy, HRV was still significantly predictive of the primary end point. The HR in all patients for reaching the primary end point when having an abnormal HRV compared with a normal HRV was 4.9 (95% CI 2.1–11.5; $P < 0.0001$).

Of the 197 patients with nephropathy, 59 (30%) died during follow-up versus 16 (8%) of the 191 patients with normoalbuminuria (log-rank test, $P < 0.0001$). The unadjusted HR for dying when having an abnormal HRV compared with a normal HRV was 3.3 (95% CI 1.0–10.7; $P = 0.043$) in patients with diabetic nephropathy, but after adjustment for the above-mentioned confounding factors, the impact of HRV on all-cause mortality in patients with nephropathy was no longer significant ($P = 0.293$). In patients with normoalbuminuria, the unadjusted risk of dying when having an abnormal HRV compared with a normal HRV was 3.9 (1.0–14.3; $P = 0.043$). After adjustment for the above-mentioned risk factors, the association between HRV and all-cause mortality was no longer significant ($P = 0.47$). If the two groups were analyzed together in the Cox model with the above-mentioned risk factors, the association between HRV and all-cause mortality was no longer significant ($P = 0.101$).

HRV and progression of renal disease

In patients with diabetic nephropathy, the rate of decline in GFR was not significantly different among groups according to HRV. Mean ± SD values of rate of decline were 3.9 ± 4.7, 4.4 ± 3.4, and 3.6 ± 3.4 ml · min^{-1} · year^{-1}, respectively, in the three groups with normal, borderline normal, and abnormal HRV ($P = 0.59$).

CONCLUSIONS

— In the present study, we evaluated HRV as a risk factor in type 1 diabetic subjects with and without diabetic nephropathy prospectively followed for 10 years. In this study, the influence of CAN could be determined in a large, well-defined cohort of type 1 diabetic subjects with and without diabetic nephropathy, which gives us a new understanding of the negative influence of CAN in patients already known to be at high risk. In high-risk individuals with diabetic nephropathy, we found autonomic dysfunction, determined as abnormal HRV, to be a predictor of cardiovascular mortality and morbidity. We also show that autonomic dysfunction is not a promoter of progression of decline in kidney function.

Patients with diabetic nephropathy and abnormal HRV had a higher incidence of fatal and nonfatal CVD and a higher all-cause mortality than patients with nephropathy and a normal HRV. After adjustment for conventional cardiovascular risk factors, HRV was still a significant predictor of fatal and nonfatal CVD in patients with diabetic nephropathy. Furthermore, in patients with persistent normoalbuminuria, a higher incidence of CVD and an unadjusted higher risk was found in patients with abnormal HRV than in patients with a normal HRV. Patients with normoalbuminuria and abnormal HRV experienced significantly more events than patients with normal or borderline HRV. We also evaluated the rate of decline in GFR to see

whether a decreased HRV could predict a faster decline in GFR. We could not find a relationship between rate of decline in GFR and having an abnormal HRV.

Originally the association between CAN and poor prognosis was proposed by Ewing et al. (30). In this early study, risk factors such as nephropathy and known CVD were not assessed, and it is likely that these factors contributed importantly to the increase in mortality in the patients with CAN. In a meta-analysis of 12 published studies, abnormal HRV was shown to be associated with an increased risk of silent myocardial infarction (10). Subsequently, a number of prospective studies have demonstrated increased mortality in patients with CAN (8,31,32). Rathmann et al. (8) investigated a mixture of type 1 and type 2 diabetic subjects, with a total of 35 patients with CAN, and found an 8-year survival rate of 77% in these patients. Ewing et al. (31) showed an increase in sudden death in patients with autonomic neuropathy with 8 sudden deaths among 71 diabetic men followed for 3 years. In a larger study population of 457 type 1 diabetic subjects, Orchard et al. (32) found a fourfold increase in mortality in patients with CAN after 2 years of follow-up. Overall, these three studies correspond closely to the present study in which 35 and 14% of type 1 diabetic patients with and without nephropathy and having abnormal HRV died during 10 years of follow-up.

In the present study, the rate of decline in GFR had a mean value of 4 ml · min^{-1} · $year^{-1}$, comparable with that in other studies of type 1 diabetic patients with overt nephropathy during antihypertensive therapy (33,34). A faster rate of progression of renal dysfunction was suggested in type 1 diabetic patients with autonomic dysfunction (16) in a very small study consisting of 26 patients with albuminuria with and without autonomic dysfunction followed for 1 year with creatinine as a measure of progression of diabetic nephropathy. When decline in kidney function is evaluated long term, follow-up and a precise evaluation method are recommended (21). We could not find a relationship between rates of decline in GFR evaluated with plasma clearance of ^{51}Cr-EDTA, which is a precise and accurate measure of kidney function (with at least three measurements during follow-up) in a large group of patients with diabetic nephropathy followed for 10 years. Thus, autonomic neuropathy is not a progression promoter in diabetic nephropathy because it is not associated with a faster decline in renal function.

Patients with diabetic nephropathy constitute a population with a high risk of CVD and early death compared with patients with persistent normoalbuminuria. Autonomic dysfunction rarely exists as an isolated complication in long-term diabetes (10). Often coexistence with coronary artery disease, cerebrovascular disease, and nephropathy is seen (10). Evidently, CAN is not the only factor responsible for increased mortality in long-term diabetes. CAN is shown to be an independent risk factor in patients with atherosclerotic CVD (35), and in the present study CAN increased cardiovascular risk in both patients with nephropathy and patients with persistent normoalbuminuria.

The mechanisms by which CAN increases cardiovascular morbidity and mortality remain to be settled. One hypothesis involves impaired central control of respiration in patients with CAN (36); other studies found exercise intolerance in patients with CAN (2–4) with a reduced response in heart rate and blood pressure and decreased cardiac output during exercise. An association between CAN and QT prolongation has been shown, with the latter condition being characterized by adverse cardiac events (37,38). Whether patients with diabetes have silent myocardial infarctions more frequently is a matter of debate (7). In 29 type 1 diabetic patients, of whom 1 patient had diabetic nephropathy, a high prevalence of silent coronary atheromatosis shown by intravascular ultrasound was found with an association to long-term glycemic control (39), but the prognostic importance is unknown. Recently, A1C, hypertension, distal symmetrical polyneuropathy, retinopathy, and exposure to hyperglycemia were shown to be risk factors for development of CAN (40). The study could not show that urinary albumin excretion independently predicted CAN, probably due to a small proportion of patients (5%) with overt nephropathy in the study. The authors found a cross-sectional relationship and suggested that urinary albumin excretion rate deterioration occurs simultaneously and therefore should not predict development of CAN. We did not find a relationship between rate of decline in GFR and abnormal HRV in patients with diabetic nephropathy.

In the Diabetes Control and Complications Trial, good glycemic control was shown to slow progression of abnormal autonomic tests (41), and, as recently reviewed, symptomatic treatment of CAN is possible with ACE inhibitors and β-blockers (42). Furthermore, a short-term study has shown an increase in HRV during treatment with an ACE inhibitor (43). Therefore, patients can benefit from early diagnosis and possible prevention or slowing of progression by improved glycemic control and symptomatic treatment to improve quality of life and perhaps early initiation of multifactorial treatment aiming at preventing/reducing CVD and autonomic neuropathy as demonstrated in the Steno-2 study (29).

Our study is limited because we only determined CAN by one test. We are aware that the recommendation is to use three different tests to determine the presence of CAN (44). However, our patient population is very well characterized, with a large homogeneous group of type 1 diabetic patients with and without diabetic nephropathy followed prospectively for 10 years. Earlier studies have been smaller or have included a mixture of type 1 and type 2 diabetic subjects or have had a shorter follow-up time.

In summary, in the present study, we demonstrated that abnormal HRV, which is easily assessed by a simple bedside test, independently predicts fatal and nonfatal CVD in type 1 diabetic patients with diabetic nephropathy. We therefore suggest the use of HRV together with other known risk factors as a clinical tool for risk stratification within this high-risk population.

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