# The Association Between Cardiovascular Autonomic Neuropathy and Mortality in Individuals With Diabetes

## A meta-analysis

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**OBJECTIVE** — To examine by meta-analysis the relationship between cardiovascular autonomic neuropathy (CAN) and risk of mortality in individuals with diabetes.

**RESEARCH DESIGN AND METHODS** — We searched Medline for English-language articles published from 1966 to 2001. Fifteen studies having a baseline assessment of cardiovascular autonomic function and mortality follow-up were identified. The analyses were stratified according to whether a single abnormality or two or more measures of cardiovascular autonomic function were used to define CAN. A global measure of association (i.e., relative risk) was generated for each group by pooling estimates across the studies using the Mantel-Haenszel procedure.

**RESULTS** — CAN was significantly associated with subsequent mortality in both groups, although the magnitude of the association was stronger for those studies for which two or more measures were used to define CAN. The pooled relative risk for studies that defined CAN with the presence of two or more abnormalities was 3.45 (95% CI 2.66–4.47; $P < 0.001$) compared with 1.20 (1.02–1.41; $P = 0.03$) for studies that used one measure.

**CONCLUSIONS** — These results support an association between CAN and increased risk of mortality. The stronger association observed in studies defining CAN by the presence of two or more abnormalities may be due to more severe autonomic dysfunction in these subjects or a higher frequency of other comorbid complications that contributed to their higher mortality risk. Future studies should evaluate whether early identification of subjects with CAN can lead to a reduction in mortality.

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One of the most overlooked of all serious complications of diabetes is cardiovascular autonomic neuropathy (CAN) (1). CAN results from damage to the autonomic nerve fibers that innervate the heart and blood vessels. This nerve damage in turn leads to dysfunctional heart-rate control and abnormal vascular dynamics. Clinical manifestations associated with cardiovascular autonomic dysfunction in diabetic individuals include postural hypotension, exercise intolerance, intraoperative cardiovascular lability, and silent myocardial ischemia/infarction (2,3). Collectively, these may contribute to an increased risk of mortality, although the strength of the association is not clear since nearly all of the available studies have been carried out on relatively small numbers of individuals.

A previous review (4) that examined the association of mortality and cardiovascular autonomic dysfunction across several studies reported a mortality rate of 27% among diabetic subjects with CAN compared with 5% among those without. The average follow-up period was 5.5 years. Mortality rates among individuals with evidence of CAN varied, however, from a high of 53% in one study (5) to a low of 9% (6). The variability of mortality rates revealed in these studies may be related to *1*) the study population, *2*) the modality for assessing cardiovascular autonomic dysfunction, *3*) the criteria used to define the presence of CAN, and *4*) the length of follow-up.

The analysis of each study as a single entity includes only a limited number of study subjects. Thus, the focus of this report was to perform a comprehensive evaluation by pooling results across published studies to obtain a more precise estimate of the association of CAN and increased risk of mortality.

## RESEARCH DESIGN AND METHODS

— From a Medline database (1966–2001), we used a combination of keywords (cardiovascular autonomic neuropathy, mortality, diabetes, death, etc.) to identify studies that assessed cardiovascular autonomic dysfunction and its association with mortality in diabetic individuals. We considered only studies published in English for our meta-analysis.

Studies were included in the meta-analysis if there was a baseline assessment

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**Abbreviations:** CAN, cardiovascular autonomic neuropathy; EI, expiration-inspiration.

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

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of cardiovascular autonomic function and a mortality follow-up. The assessment of cardiovascular autonomic function was made on the basis of one or more of the tests described by Ewing et al. (7). Mortality rates for individuals with CAN at baseline versus those without CAN for each study were compared using the $\chi^2$ test or Fisher's exact test, where appropriate. The studies were divided into two groups based on the number of abnormal measures of cardiovascular autonomic function (i.e., a single abnormality or the presence of two or more abnormalities of autonomic function) that were used to define CAN. A global measure of association (relative risk) was generated for each group by pooling estimates across the studies using the Mantel-Haenszel procedure (8).

**RESULTS** — In our literature search of published studies in English, we found 15 studies (5,6,9–21) that could be included in the meta-analysis (Table 1). Four additional studies addressing the relationship between diabetic CAN and mortality were identified by our search (22–25) but could not be included in the meta-analysis. In three (22–24), the raw numbers of case and control subjects among individuals with and without CAN were not presented. In the other study (25), cardiac arrests and mortality were grouped together. These studies did, however, provide additional data suggesting that decreased autonomic function was associated with an increased risk of mortality.

The follow-up intervals of the 15 studies included in the meta-analysis ranged from 0.5 to 16 years. With the exception of one study (20), mortality rates were higher for individuals with CAN at baseline than in those whose baseline assessment was normal, with statistically significant differences in 12 of the studies. The study-specific relative risks ranged from 0.91 for the study by Sawicki et al. (20) to 9.20 for the study by Jermendy et al. (12). Relevant details of each study are described in Table 1. Figure 1 presents the relative risks and 95% CIs for these studies graphically, with the studies divided into two groups based on the number of measures that were used to define the presence of CAN. The Mantel-Haenszel estimate for the pooled relative risk for mortality was 3.45 (95% CI 2.66–4.47; $P < 0.001$) for studies that used two or more measures to define CAN. The pooled estimate for those studies defining CAN with one measure of autonomic function was 1.20 (1.02–1.41; $P = 0.03$). It should be noted that the presentation of results by Gerritsen et al. (21) did not allow for incorporation in the pooled estimate.

**CONCLUSIONS** — These results indicate a strong and consistent association between CAN and increased risk of mortality. The associations are consistent across multiple studies despite the differences between studies in terms of patient cohorts, assessment modalities, and disease definitions (e.g., how many abnormal tests defined the presence of CAN).

The association between CAN and mortality was considerably stronger for the 10 studies for which CAN was defined on the basis of two or more abnormalities than for the studies for which CAN was defined on the basis of only a single abnormal test. These differences may reflect the fact that subjects considered to be affected on the basis of two measures may have had more severe autonomic dysfunction or a higher frequency of other comorbid complications, contributing to their higher mortality risk. Alternatively, studies defining CAN by a single test abnormality may have misclassified unaffected subjects as affected.

Because diabetic individuals with cardiovascular autonomic dysfunction are more likely to have other diabetes-associated complications compared with individuals without CAN, several studies have attempted to address the question of whether cardiovascular autonomic dysfunction predicts mortality independently of other known risk factors. For example, some studies assessing mortality made an effort to minimize the potentially confounding effects of age, sex, and diabetes duration by matching individuals who were $CAN^+$ and $CAN^-$ at baseline on these variables (10,13). In the study by O'Brien et al. (10), individuals with CAN experienced a 3.3-fold higher mortality rate versus those without over the 5-year follow-up interval. Individuals in the $CAN^+$ group, who were matched for sex and diabetes duration with the $CAN^-$ group, had a higher prevalence of vascular and other complications at baseline compared with those in the $CAN^-$ group. However, even after adjusting for these differences through multivariate analysis, autonomic neuropathy still remained significantly associated with mortality (10). In another study, Rathmann et al. (13) matched individuals with and without CAN for age, sex, and duration of diabetes at baseline. In addition, they excluded individuals from the study with advanced renal and/or symptomatic cardiovascular disease. Although the number of subjects in this study was small, those in the $CAN^+$ group experienced an eightfold excess in mortality. Slightly lower risk estimates were reported by Gerritsen et al. (21) from the population-based Hoorn Study. In this study, which included 159 subjects with type 2 diabetes, individuals were followed for an average of nearly 8 years. Most of the tests of cardiac autonomic function used, including the expiration-inspiration (EI) difference, indicated that impaired autonomic function was associated with mortality in subjects with diabetes. The relative risk associated with the EI difference and all-cause mortality was 2.25 after adjusting for age, sex, and known diabetes. No further adjustments, however, were made to account for possible differences in other comorbidities in this study.

A potential relationship between symptomatic CAN and mortality was examined in a study by Sampson et al. (9). The investigators in this study compared the mortality experience of those with and without abnormal heart rate variability and observed a 2.6-fold higher mortality rate for those with the abnormality versus the $CAN^-$ group (20 of 73 vs. 4 of 38). On further analysis, however, the excess risk could be attributed entirely to subjects who were symptomatic for diabetic autonomic neuropathy (18 of 49). Subjects who were asymptomatic but had abnormal heart rate variability experienced mortality rates that were almost identical to those in the $CAN^-$ group (2 of 24 vs. 4 of 38). In contrast, individuals with symptomatic autonomic neuropathy experienced a 3.5-fold higher mortality rate than those in the $CAN^-$ group (18 of 49 vs. 4 of 38).

Previous studies have also examined whether other factors may mediate the relationship between CAN and mortality. For example, Orchard et al. (6) attempted to evaluate the independent contribution of cardiac autonomic dysfunction to mortality risk in a population-based sample of individuals with type 1 diabetes. Individuals for this study were identified through

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**Table 1—*Studies of cardiovascular autonomic neuropathy and mortality***

| Reference | Follow-up (years) | Tests of CAN | Definition of CAN | % (Mortality/ $CAN^+$) | % (Mortality/ $CAN^-$) | Comments |
|---|---|---|---|---|---|---|
| Ewing et al. (5) | 5 | 1. Valsalva maneuver<br>2. Handgrip<br>3. Postural fall in BP | | 53% (21/40) | 15% (5/33)* | Subjects who complained of symptoms suggestive of autonomic neuropathy comprised the study cohort. $CAN^+$ subjects had more complications at baseline. Half of the deaths for the $CAN^+$ subjects were attributed to renal failure. |
| Sampson et al. (9) | 10–15 | 1. HRV during deep breathing | Based on abnormal HRV and the presence of symptomatic autonomic neuropathy† | 37% 18/49 | 11% (4/38)* | Mortality in asymptomatic individuals with an isolated abnormality in HRV was not increased (2/24 vs. 4/38). Excess mortality restricted to those with symptomatic CAN. |
| O'Brien et al. (10) | 5 | HRV in response to<br>1. supine rest<br>2. single deep breath<br>3. Valsalva maneuver<br>4. standing for 60 seconds | Two or more of the four tests were abnormal | 27% (23/84) | 8% (7/84)* | Those with CAN had greater prevalence of other complications, but in multivariate analysis, CAN was the most important predictor of mortality. |
| Ewing et al. (11) | 3 | 1. HRV during deep breathing<br>2. Valsalva maneuver<br>3. 30:15 ratio<br>4. BP response to standing<br>5. BP response to handgrip | Normal = all tests normal or one borderline; early = one of the three heart rate tests abnormal or two borderline; definite = two or more of the heart rate tests abnormal; severe = at least two of the heart rate tests abnormal and one or both of the BP tests abnormal or both borderline | 31% (10/32) | 8% (3/39)‡ | Included men <60 years old. $CAN^+$ subjects who died ($n$ = 10) had longer QT intervals than those who did not. |

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**Table 1—*Continued***

| Reference | Follow-up (years) | Tests of CAN | Definition of CAN | % (Mortality/ $CAN^+$) | % (Mortality/ $CAN^-$) | Comments |
|---|---|---|---|---|---|---|
| Jermendy et al. (12) | 5 | 1. HRV during deep breathing<br>2. Valsalva maneuver<br>3. 30:15 ratio<br>4. SBP response to standing | Results of parasympathetic tests (1, 2, 3) were scored 0 = normal, 1 = borderline, 2 = abnormal. Those with a score of 0–1 = without CAN; score of 2–3 = early CAN; score of 4–6 = definitive CAN‖ | 40% (12/30) | 4% (1/23)* | No patients had an abnormal SBP response to standing. Deceased were older and had more complications at baseline. |
| Rathmann et al. (13) | 8 | 1. Coefficient of variation of R-R intervals with normal respiration<br>2. Coefficient of variation of R-R intervals with deep respiration | Both tests abnormal | 23% (8/35) | 3% (1/35)‡ | Subjects with advanced renal disease, proliferative retinopathy, and CVD were excluded. |
| Hathaway et al. (14) | 2–5 case-control study | 1. HRV during deep breathing<br>2. Valsalva maneuver | Both tests abnormal | 31% (4/13) | 0% (0/16)‡ | Case-control study of transplant recipients (pancreas-kidney or kidney alone). Cases ($n$ = 4) died of sudden cardiac death within 3½ years posttransplant. Control subjects survived 2–5 years posttransplant. |
| Navarro et al. (15) | 1–11.5 | 1. HRV during deep breathing<br>2. Valsalva maneuver | Both tests were abnormal | 28% (101/359) | 5% (6/128)§ | All subjects were candidates for pancreas transplantation. |
| Veglio et al. (16) | 5 | 1. Heart rate (resting)<br>2. HRV during deep breathing<br>3. BP response to standing | Two or more of the tests were abnormal | 13% (10/75) | 4% (10/241)* | QTc prolongation associated with increased mortality risk. |
| Chen et al. (17) | 7.7 | HRV in response to<br>1. single deep breath<br>2. six consecutive breaths<br>3. supine to standing<br>4. Valsalva maneuver<br>BP change sitting to standing | Unique diagnostic criteria defined by scoring 3 or more | 29% (106/371) | 12% (29/241)§ | $CAN^+$ associated with increased mortality even in the absence of postural hypotension. |
| Total for studies with CAN defined by 2 or more abnormalities# | | | | 313/1,088 | 66/878 | |

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**Table 1—*Continued***

| Reference | Follow-up (years) | Tests of CAN | Definition of CAN | % (Mortality/ $CAN^+$) | % (Mortality/ $CAN^-$) | Comments |
|---|---|---|---|---|---|---|
| Orchard et al. (6) | 2 | 1. HRV during deep breathing | Abnormal E/I (expiration/ inspiration) ratio | 9% (8/88) | 2% (9/399)* | Relative risk decreased from 4.03 to 1.37 after controlling for duration, renal disease, hypertension, and coronary heart disease. |
| Sawicki et al. (18) | 5–13 | 1. RR variation between supine and standing position | $RR_{supine}/RR_{standing}$ <1.03 | 62% (16/26) | 29% (17/ 59)* | All subjects with overt diabetic nephropathy. |
| Toyry et al. (19) | 10 | 1. HRV during deep breathing<br>2. SBP decrease during standing | Parasympathetic neuropathy = abnormal E/I (expiration/inspiration) ratio | 50% (3/6) | 17% (20/ 116) | Mortality rates for CVD mortality only. Subjects were newly diagnosed with diabetes. In multivariate analysis, sympathetic $CAN^+$ at 5-year predicted CVD mortality at 10 years, even after adjusting for conventional CVD risk factors. |
| Sawicki et al. (20) | 15–16 | 1. RR variation between supine and standing position | $RR_{supine}/RR_{standing}$ <1.03 | 69% (58/84) | 76% (100/ 132) | Consecutive patients (31% male) enrolled over a 2-year period for improvement in metabolic control. |
| Gerritsen et al (21) | 0.5–9.2 | 1. Spectral analysis during spontaneous breathing for 3 minutes<br>2. EI difference and baroreflex sensitivity during six deep breaths for 1 min | EI difference | NA | NA | Relative risk = 2.25 (1.13–4.45) for EI difference. Diabetic subjects ($n$ = 159) identified through a population survey. |
| Total for studies with CAN defined by a single measure¶ | | | | 85/204†† | 146/706 | |

EI difference = mean expiration-inspiration difference in R-R intervals over six consecutive breaths; R-R interval = time interval between successive electrocardiogram R-waves. *$P < 0.01$; ‡$P < 0.05$; §$P < 0.001$. †Postural hypotension (>20 mmHg fall in SBP) was present for 67% of the patients with symptomatic CAN (i.e., abnormal HRV). Additional tests for CAN, not performed at baseline, were included in this study during the follow-up years. ‖A small number of affected individuals ($n$ = 15) were considered to have early CAN, defined as having 2 to 3 borderline test results, 1 abnormal and 1 borderline test, or a single abnormal test. #Mantel-Haenszel estimate for the pooled relative risk for mortality = 3.45 (95% CI: 2.66– 4.47; $P < 0.001$) for studies with CAN defined by two or more abnormalities. ¶Mantel-Haenszel estimate for the pooled relative risk for mortality = 1.20 (95% CI: 1.02– 1.41; $P = 0.03$) for studies with CAN defined by a single measure. ††The study by Gerritsen et al. (21) was not included in the calculation of these rates (or in the pooled relative risk estimate) because raw numbers were not provided.





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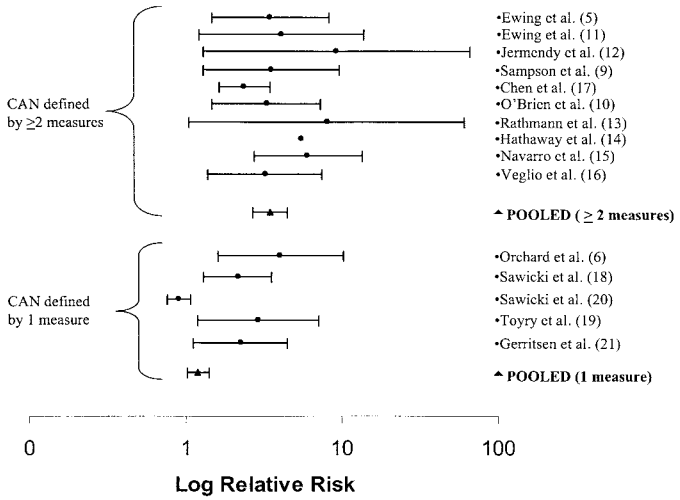


**Figure 1—***Relative risks and 95% CIs for studies of cardiovascular neuropathy (CAN) and mortality. Pooled relative resk for 10 studies with CAN define by two or more measures: 3.45 (95% CI 2.66–4.47). Pooled relative risk for 4 studies with CAN defined by a single measure: 1.20 (1.02–1.41). Data from the study by Gerritsen et al. (21) was not included in the estimate of pooled relative risk.*

a hospital-based registry system and were considered to be representative of all type 1 diabetes patients residing in Allegheny County, Pennsylvania. Initial analyses of 487 participants based on a 2-year follow-up revealed a fourfold higher mortality rate in those with CAN at baseline versus those without. However, after adjusting for baseline differences between the $CAN^+$ and $CAN^-$ groups in markers related to nephropathy, coronary heart disease, duration of diabetes, and hypertension, the relative risk decreased from 4.03 to 1.37 and was no longer statistically significant. Contrary to these results, however, in a study of 146 type 2 diabetic individuals (mean duration of diabetes, 11 years), Wirta et al. (22) observed that cardiovascular autonomic dysfunction (i.e., low Valsalva ratio) and a slightly reduced glomerular filtration rate still in the normal range independently predicted mortality during a 9-year follow-up period.

Although our review of the literature was thorough, there were limitations to the meta-analysis. Our search was limited to English-language published studies. Mortality rates may have been affected by differences in study populations, modalities used to determine the presence of CAN, the length of follow-up, and criteria used to define the presence of CAN. Very few of the published studies matched those with and without CAN for comorbidities at baseline and thus it is difficult to attribute the mortality differences solely to the presence of CAN. In addition, there may be several different pathogenetic mechanisms that explain the association between CAN and the increased risk of mortality (e.g., arrhythmias, renal failure, sudden death).

The associations found from our review of the literature were not as strong as previously reported (4). The discrepancy appears to be due to our inclusion of several studies (e.g., 17–20) with relatively high mortality rates for those without CAN. These additional studies may have included more individuals with severe comorbidities at baseline, emphasizing the difficulty ascertaining the independent effects of CAN on mortality in the presence of other comorbid conditions.

In summary, for individuals with diabetes, dysfunction of the autonomic nervous system appears to be associated with an increased risk of mortality and morbidity. Although the relative risk associated with studies for which CAN is defined on the basis of a single abnormal test confers an increased risk of mortality, a greater risk is clearly associated when CAN is defined on the basis of two or more abnormalities. The exact pathogenic mechanisms are unclear, however, although some deaths may be avoidable through early identification of these higher risk patients and by slowing the progression of autonomic dysfunction and its associated conditions. The results of the Diabetes Control and Complications Trial clearly showed that intensive glycemic treatment can prevent the development of abnormal heart rate variation and slow the deterioration of autonomic dysfunction over time for individuals with type 1 diabetes (26). For individuals with type 2 diabetes, intensive multifactorial treatment slowed the progression of autonomic neuropathy in one study (27), whereas in another study those in the intensely treated group showed a small tendency for improved autonomic function, with deterioration noted in the conventionally treated group (28).

Pharmacological intervention may also improve autonomic dysfunction. The administration of metoprolol to ramipril-treated type 1 diabetic patients with abnormal albuminuria has recently been shown to improve autonomic dysfunction (29). Cardiac autonomic function, however, did not change after 12 months of treatment with trandolapril (30), but increased parasympathetic activity was shown after 3 months of treatment with quinapril (31). The use of antioxidants is also promising. For example, alpha lipoic acid (thioctic acid) was shown to be associated with a slight improvement in CAN for individuals with type 2 diabetes (32). It should be noted, however, that the effect of these interventions on mortality is not known.

The association of mortality and cardiovascular autonomic dysfunction indicates that individuals with abnormal autonomic function tests are candidates for close surveillance. Thus it has been recommended that a baseline determination of cardiovascular autonomic function be performed upon diagnosis in type 2 diabetes and within 5 years of diagnosis for those with type 1 diabetes, followed by a yearly repeat test (33). In addition, the presence of autonomic dysfunction should alert the health care professional to search for associated risk factors of cardiovascular disease and implementation of an intense program to reduce these factors for mortality to be attenuated.

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