EDITORIAL (SEE P. 1578 AND P. 1585)

Neuropathy: The Crystal Ball for Cardiovascular Disease?

Cardiovascular disease (CVD) is a major cause of death in patients with type 2 diabetes. Unclear, however, is the effect of intensive therapy in reducing the development of cardiovascular complications. The UK Prospective Diabetes Study (UKPDS), involving patients with newly diagnosed disease, showed a nonsignificant trend in the reduction of rates for myocardial infarction (MI) (1). However, data 10 years after cessation of the trial showed a 15% reduction in the risk of MI for those in the original intensive therapy group (2). This benefit from early intensive therapy persisted despite the fact that the within-trial differences for A1C between the intensive and conventional therapy groups were lost within 1 year of completion of the trial. The sustained benefit from early aggressive treatment is referred to as the legacy effect or metabolic memory.

The question of more intensive therapy and reduction in cardiovascular complications was addressed for people with type 2 diabetes of long duration in three other studies (i.e., the Action to Control Cardiovascular Risk in Diabetes [ACCORD] [3], the Action in Diabetes and Vascular Disease: Preterax and Diamicron Modified Release Controlled Evaluation [ADVANCE] [4], the Veterans Affairs Diabetes Trial [VADT] [5]). Although the three studies utilized different patient cohorts, with varying durations of diabetes (ACCORD, 10 years; VADT, 11.5 years; and ADVANCE, 8 years) and had different treatment regimens, the results of these trials indicated that intensive glucose control did not reduce CVD events. In fact, the ACCORD trial was terminated early because an increased rate of mortality was found to be associated with intensive control of hyperglycemia (6). A higher rate of mortality for those on intensive treatment was not, however, found in ADVANCE and VADT. Recent articles from the ACCORD trial, by Pop-Busui et al. (7) and Calles Escandon et al. (8), examined whether the effects of cardiovascular autonomic neuropathy (CAN) or self-reported history of neuropathy at baseline could have been a contributor to the higher mortality risk in the intensive glycemic arm.

Physiological activities of the cardiovascular system are under the control of the autonomic nervous system. Damage to the autonomic nerves that innervate the heart and blood vessels results in dysfunction in heart rate control and vascular dynamics (i.e., CAN) (9). Autonomic imbalance between the sympathetic and parasympathetic nervous systems' regulation of cardiovascular function contributes to metabolic abnormalities (10) and significant morbidity and mortality for individuals with diabetes (11–13). Clinical manifestations of cardiovascular autonomic dysfunction (e.g., exercise intolerance, intraoperative cardiovascular liability, orthostatic tachycardia and bradycardia syndromes, silent myocardial ischemia) can result in life-threatening outcomes (11,12). In fact, the ultimate outcome of increased risk of mortality is clearly associated with the presence of autonomic dysfunction (12). Results from the ACCORD trial again confirmed the association of CAN and mortality. These investigators showed that the individuals in this trial with baseline CAN were 1.55–2.14 times as likely to die as individuals without CAN (7). Furthermore, CAN in the presence of peripheral neuropathy was the highest predictor of CVD mortality (i.e., hazard ratio [HR] 2.95, $P = 0.008$). Indeed, combining indexes of autonomic dysfunction have been shown to be associated with the risk of mortality (12–14).

In the ACCORD trial, assessment of CAN included heart rate (reflecting overall autonomic function and cardiorespiratory fitness), a measure of heart rate variability (i.e., time domain marker of overall autonomic function–SD of normally conducted R-R intervals [SDNN]), and QT index (reflecting sympathetic function) computed from 10-s resting electrocardiograms (7). The investigators did not find that the presence of CAN appeared to contribute to the increased mortality observed in the intensive versus standard glycemic therapy group. Unfortunately, there is no consensus on the best measures for assessing CAN, thus it is possible that there was an underestimation of the impact of autonomic dysfunction based on methodological issues. It should be noted that a nonstatistically significant ($P = 0.07$) trend toward an increased incidence of CAN (based on the development of autonomic symptoms) in patients on intensive versus standard therapy was shown in the VADT (5). Results from the Detection of Ischemia in Asymptomatic Diabetics (DIAD) study showed that the presence of cardiac autonomic dysfunction (defined via change in heart rate from lying to standing, a measure reflecting parasympathetic dysfunction) was among the highest HR (4.33) associated with the primary events (i.e., cardiac death or nonfatal MI) (15). Just as the number and type of assessment modalities used to identify the presence of CAN affects prevalence rates and the association with mortality (12), the methods in the ACCORD trial used to assess CAN may have affected the ability to determine an association with intensive glucose therapy and mortality.

It is well known that prior hypoglycemic episodes attenuate the response of the autonomic nervous system to subsequent hypoglycemia (16). Recently, it has been suggested that prior hypoglycemia could attenuate the autonomic response to specific cardiovascular stresses (17). These findings have significant clinical implications given that antecedent hypoglycemia attenuates cardiovascular autonomic control and thus could impact the use of rigorous glycemic control in individuals with diabetes. Nonetheless, antecedent hypoglycemia associated with CAN did not appear to explain the increase in mortality associated with rigorous control reported in the ACCORD study (7). It should be noted, however, that in post hoc comparisons between the intensive and standard glycemic arms in the ACCORD trial, a differential effect on mortality was found for those that self reported history of neuropathy (8). The disparity between different forms of neuropathy as a predictor of outcomes has been shown by others. In the ACCORD study (8), the Michigan Neuropathy Screening Instrument (MNSI) detected peripheral neuropathy in 4,357 patients, whereas only 2,737 reported a history of neuropathy. Of those who reported a history of neuropathy, 61% had a MNSI score that indicated neuropathy. In the DIAD study, a relationship with CVD was found with numbness and absent sensa-

tion but not with pain, tingling, absent vibration, or absent reflexes (15). Painful neuropathy, however, is associated with abnormal autonomic function, which may be a consequence of the pain (18). Gaede et al. (19) showed that multifactorial treatment improved CAN without an impact on peripheral neuropathy, measured with a biothesiometer. Johnson et al. (20) found that almost three-fourths (119 of 148) of diabetic individuals with long-standing diabetes and peripheral neuropathy, who were potentially eligible for an intervention trial, had baseline functional cardiac abnormalities but no association with autonomic neuropathy. The DIAD study showed an HR of 2.83 for absent sensation and primary events, with CAN, however, being more strongly associated (15). The reason for the disparity between the association of intensive therapy, mortality, and different forms of neuropathy is unclear. Further study on the difference between somatic and autonomic neuropathy as predictors of, or contributors to, CVD is warranted.

Mortality occurred in both treatment arms of the ACCORD trial. Excessive risk with intensive versus standard strategy occurred when patients in the intensive group failed to reduce A1C within the first year (8). It was the individuals who failed to achieve goal easily who suffered events. As suggested by Calles-Escandon et al. (8), individuals with poorer glycemic control at baseline may be those with disease that is more difficult to manage or perhaps those who were less adherent to treatment. It may well be that the presence of polyneuropathy or CAN should caution against aggressive and rapid blood glucose lowering if it cannot be achieved easily. Results generated from the U.K. General Practice Research Database showed a U-shaped association of glycemic control and events, with the lowest HR at an A1C of ~7.5% (21). This mean glycated hemoglobin value of ~7.5% was associated with lowest all-cause mortality and lowest progression to large-vessel disease events. Low and high mean A1C values were associated with increased mortality and cardiac events (21). Although these were observational analyses, knowledge that individuals have somatic or autonomic dysfunction may warrant relaxation of intensity and haste to achieve control.

Given that intensive glucose therapy has been shown to be affective in reducing risk for any diabetes-related end point for patients with newly diagnosed type 2 diabetes (2), attention by health care providers should be made for the early identification of individuals with diabetes and treatment according to the current guidelines early on in the disease process. Post hoc subgroup analysis of the VADT showed that intensive glycemic control had a greater CVD benefit for those individuals with duration of diabetes <15 years compared with those with longer duration (5). The window of opportunity is early.

The lack of effect of intensive glycemic control on the reduction of CVD events in individuals with type 2 diabetes of longer duration heightens the importance of other risk factors in the disease process and emphasizes the need for a multifactorial approach of treatment. In the Steno-2 Study (19), where people with type 2 diabetes received intensive multifactorial treatment (e.g., targeting hyperglycemia, hypertension, dyslipidemia, and microalbuminuria, along with secondary prevention of CVD with aspirin), the approach reduced the risk of cardiovascular events by 53% and also reduced autonomic dysfunction by 63%. In terms of the multifactorial approach, the glucose-lowering agents appeared to have the least effect when compared with antihypertensive treatment, lipid-lowering agents, aspirin, and vitamin-mineral supplements. It should also be noted that the findings of the multifactorial approach were seen after 7.8 years of follow-up. Given that this multifactorial approach took ~8 years for the difference to emerge, and the overall mortality rate at 3.5 years in the ACCORD trial was lower than seen in earlier studies of similar patients (22,23), it is possible that the intensive arm was terminated prematurely with the benefit potentially emerging later.

The lesson to be learned from the ACCORD study is that somatic and autonomic dysfunction are significant risk factors for CVD with HRs that transcend traditional risk factors. It should be emphasized that patients with neuropathy represent a high-risk group in which aggressive diabetes treatment strategies have to be weighed against the risk. Identification of the presence of neuropathy is pivotal. In addition, there is something more that should be learned from the use of markers of somatic/autonomic nerve function in predicting outcomes. These observations should guide investigators into what creates this distinction and how this should impact further trials on reducing cardiovascular risk. Whether it will suffice to use simple examination of heart rate variability and heart rate using electrocardiogram strips and a history of peripheral neuropathy to predict major adverse cardiovascular events remains to be studied.

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Received 19 April 2010 and accepted 20 April 2010.
DOI: 10.2337/dc10-0745

Acknowledgments— No potential conflicts of interest relevant to this article were reported.

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