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COMMENTARY

Intensive risk factor management and cardiovascular autonomic neuropathy in type 2 diabetes in the Action to Control Cardiovascular Risk in Diabetes trial: A post-hoc analysis

In people with type 1 or 2 diabetes, cardiovascular autonomic neuropathy (CAN) is associated with the development of atherosclerotic cardiovascular disease (CVD), and with a high risk of lethal arrhythmias and sudden death[1,2]. In the Action to Control Cardiovascular Risk in Diabetes (ACCORD) trial, which included people with type 2 diabetes, participants with CAN at baseline were 1.55–2.14-fold more likely to die than participants without CAN, and the presence of orthostatic hypotension at baseline was also associated with an increased risk of total death (hazard ratio 1.61) and death or hospitalization due to heart failure (hazard ratio 1.85)[3]. Thus, CAN is emerging as an independent risk factor for all-cause mortality or cardiovascular death in people with type 2 diabetes.

At advanced stages, CAN manifests itself as exercise intolerance, orthostatic hypotension, and silent myocardial infarction and ischemia[1]. However, early-stage CAN is asymptomatic and, thus, easily overlooked and underdiagnosed[1]. A reduction in heart rate variability (HRV) might be the only finding[1], so early diagnosis of CAN on the basis of electrocardiogram-derived indices of HRV is important to improve the prognosis in people with diabetes.

HRV is a measure of the beat-to-beat fluctuation in heart rate over time, and provides information about cardiac parasympathetic (vagal) and sympathetic activity. Reduced HRV indicates a predominant parasympathetic denervation, which results in a compensatory increase of sympathetic tone. HRV can be assessed by statistical analysis (time domain analysis) and power spectral analysis (frequency domain analysis) of the R-R intervals[1]. Power spectral analysis of HRV allows R-R intervals to be divided into two bands: low-frequency power (low-frequency band; 0.04–0.15 Hz) and high-frequency power (high-frequency band; 0.15–0.40 Hz). Low frequency is thought to reflect both sympathetic and parasympathetic activity, whereas high frequency reflects only parasympathetic activity[4]. The low frequency-to-high frequency ratio is considered to be a measure of sympathovagal balance and to reflect any shift toward sympathetic or parasympathetic activation[4].

Among the various measures of HRV, the coefficient of variation of the R-R interval during deep breathing, a time domain analysis, might be the most sensitive and valuable for detecting CAN. The coefficient of variation of the R-R interval is simple and widely available for use in everyday clinical practice. The Toronto Consensus Panel on Diabetic Neuropathy recommends that diagnosis of CAN be based on the use of cardiovascular autonomic reflex tests; that is, heart rate response to deep breathing, standing up from sitting, and the Valsalva maneuver and blood pressure response to standing up or handgrip[1]. According to the Panel, cardiovascular autonomic reflex tests still represent the gold standard in cardiac autonomic testing, although they are complex and time-consuming. The Panel recommends that all patients with type 2 diabetes should be screened for CAN, irrespective of diabetes duration. Because people with type 2 diabetes often have ischemic heart disease or heart failure, an early diagnosis of CAN might improve their prognosis and reduce adverse cardiac events.

The pathophysiological mechanisms responsible for the development of CAN are multifactorial. In people with type 1 diabetes, the main risk factor is poor glycemic control, and the usefulness of intensive glycemic control in preventing and slowing the progression of CAN is well known. In the Diabetes Control and Complications Trial, the prevalence of CAN was reduced by 53% in the intensive glycemic control arm[2]. In the follow-up Diabetes Control and Complications Trial/Epidemiology of Diabetes Interventions and Complications study, intensive therapy during the Diabetes Control and Complications Trial reduced the subsequent incidence of CAN by 31% in Epidemiology of Diabetes Interventions and Complications year 13/14[2], supporting the hypothesis that tight control of blood glucose in patients with type 1 diabetes is critical for preventing CAN and slowing its progression.

In people with type 2 diabetes, risk factors for CAN include elevated blood pressure, dyslipidemia (elevated triglyceride levels), smoking, high body mass index

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(obesity), insulin resistance and chronic hyperglycemia. The Intensified Multifactorial Intervention in Patients with Type 2 Diabetes and Microalbuminuria (Steno-2) trial showed a 63% reduction in the rate of progression to CAN with intensive multifactorial interventions targeting hyperglycemia, hypertension, dyslipidemia and lifestyle[2]. Therefore, multifactorial interventions might be effective for preventing CAN in people with type 2 diabetes.

The ACCORD trial originally investigated the effects of intensive glycemic, blood pressure, and lipid interventions on CVD events in participants with type 2 diabetes and high cardiovascular risk[3]. The trial had a factorial design that allowed each intervention to be examined independent from the other two. It aimed to achieve almost normal glycemic levels and found a median hemoglobin A1c of 6.4% (46 mmol/mol) in the intensive glycemic therapy arm compared with 7.5% (58 mmol/mol) in the standard therapy arm. After 3.5 years of follow up, the ACCORD trial reported a beneficial effect of an intensive glucose-lowering strategy on non-fatal cardiovascular events, but this decrease was accompanied by a paradoxical increase in mortality[3]. Based on these findings, the current guideline-recommended strategy in patients with type 2 diabetes is to individualize the glycemic target.

In a recent article published in *Diabetes Care*, Tang *et al.*[5] assessed the effects of glycemia, blood pressure and lipid interventions on CAN during the study period in a post-hoc analysis of the ACCORD trial. The group examined the effect of intensively treating traditional risk factors for CAN, including hyperglycemia, hypertension and dyslipidemia in ACCORD trial participants with type 2 diabetes and high cardiovascular risk[5]. CAN was defined as the combination of: (i) a standard deviation of all normal-to-normal R-Rs in the lowest quartile; and (ii) a QT index in the highest quartile of the ACCORD population. Compared with the standard intervention, intensive glucose treatment reduced CAN risk by 16% (odds ratio [OR] 0.84; $P = 0.003$), an effect that was driven by individuals without CVD at baseline (OR 0.73; $P < 0.0001$) rather than by those with CVD (OR 1.10; $P = 0.34$) (Figure 1a). Intensive blood pressure intervention decreased CAN risk by 25% (OR 0.75; $P < 0.001$), especially in patients aged ≥65 years (OR 0.66; $P = 0.005$; Figure 1b). However, no significant evidence was found for deviation from additivity of the two interventions ($P = 0.18$). Fenofibrate did not have a beneficial effect in CAN (OR 0.91; $P = 0.26$). The results confirm a beneficial effect of intensive glycemic therapy in reducing CAN in type 2 diabetes, and show for the first time a similar benefit of intensive blood pressure control. They also show that patients with a negative history of CVD especially benefit from intensive glycemic control for CAN prevention, and indicate that a more intensive application of these interventions might further improve their effectiveness in preventing CAN. Furthermore, because the targets of the Steno-2 trial approximately corresponded to those of the

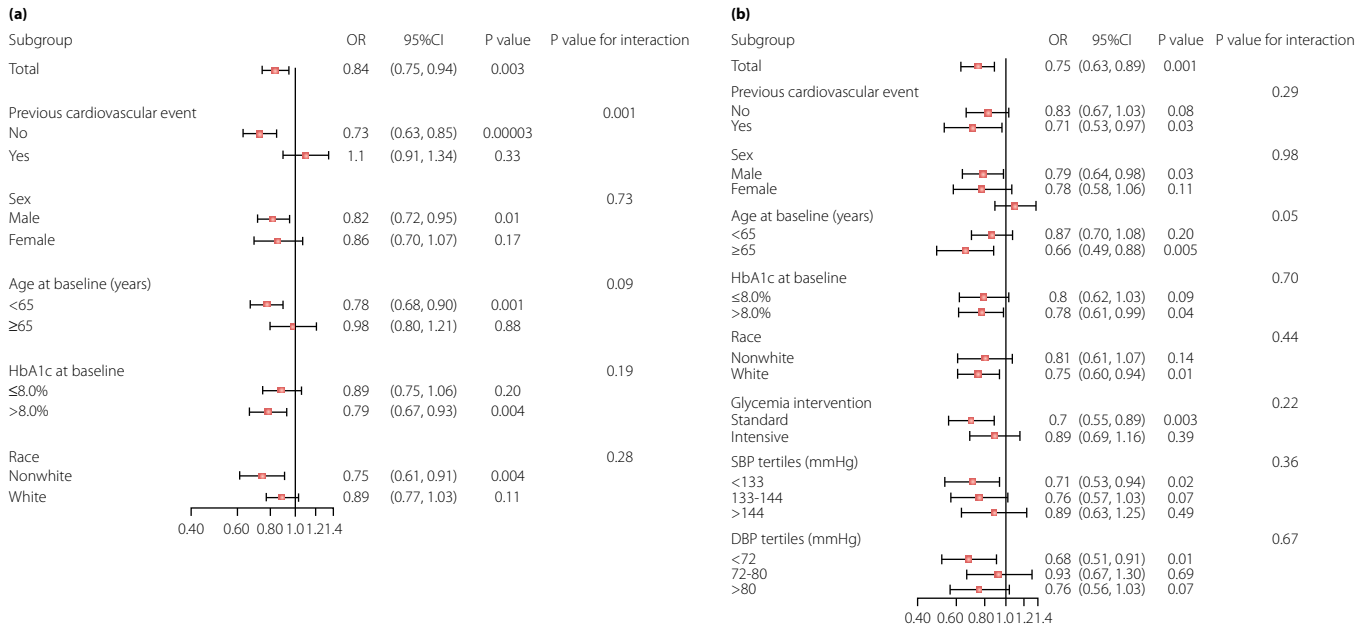

Figure 1 | Effects of the Action to Control Cardiovascular Risk in Diabetes (ACCORD) interventions on cardiovascular autonomic neuropathy (CAN) risk in the subgroups prespecified for the analysis of the ACCORD primary outcome. (a) Glycemic trial: effect of intensive versus standard glycemic control on cardiovascular autonomic neuropathy. (b) Blood pressure trial: effect of intensive versus standard blood pressure control on cardiovascular autonomic neuropathy. CI, confidence interval; HbA1c, hemoglobin A1c; OR, odds ratio.

standard treatments in the ACCORD trial, these results suggest that a more intensive application of these interventions might further improve their effectiveness in preventing CAN.

However, the results of this post-hoc analysis should be interpreted carefully, because the ACCORD trial was not designed to investigate the effects of intensive glycemic, blood pressure and lipid interventions on the risk of CAN. Another major limitation is the method used to diagnose CAN in the ACCORD trial, because HRV was not assessed during provocative physiological maneuvers, including deep breathing and the Valsalva maneuver.

In conclusion, the present post-hoc analysis of the ACCORD trial showed beneficial effects of intensive glycemic or blood pressure control on the development of CAN in high-risk patients with type 2 diabetes, and also found possible heterogeneity in the effectiveness of intensive glycemic control, depending on the history of CVD or age-related blood pressure changes. We recommend that all patients with diabetes should be screened for CAN by assessing electrocardiogram-derived indices of HRV, because early diagnosis of CAN might enable its progression to be slowed through intensive blood glucose or blood pressure interventions or both. Identifying CAN as early as possible is important and clinically relevant, because it allows physicians to decide when and how to implement optimal strategies for risk factor management in a personalized approach.

DISCLOSURE

The author declares no conflict of interest.

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