Intensive control of blood glucose and blood pressure reduces CAN risk in diabetes

16 December 2020

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Intensive interventions to reduce blood glucose and blood pressure levels in type 2 diabetes reduce the risk of developing cardiovascular autonomic neuropathy (CAN), a frequent but underdiagnosed complication of diabetes that can be life-threatening.

In a study led by Alessandro Doria, MD, Ph.D., MPH, from the Joslin Diabetes Center and Harvard Medical School, and Rodica Pop Busui, MD, Ph.D., of the University of Michigan, published online in *Diabetes Care*, researchers found that intensive glycemic control reduced CAN risk by 17%, while intensive blood pressure control reduced risks by 22%.

They also found that intensive control of blood glucose was more effective in individuals with no history of cardiovascular disease (CVD) and that blood pressure lowering was more effective in individuals older than 65 years, suggesting that some degree of personalization of risk reduction might be possible.

They add that any benefits with the approach should be weighed against risks and costs, particularly because excess mortality has been observed in a trial, following intensification of treatment for glycemia.

The analysis focuses on the Action to Control Cardiovascular Risk in Diabetes (ACCORD) trial, which originally investigated the effects of intensive glycemic, blood pressure control and lipid interventions on cardiovascular events in individuals with type 2 diabetes and high CVD risks.

For their analysis the authors included participants that had an evaluation for CAN at baseline and at least one more assessment after randomization (~7000 individuals). Specifically, they looked at the effects on CAN of intensive glucose treatment, intensive blood pressure treatment and fenofibrate (a lipid lowering agent), compared to standard treatments.

None of the interventions (intensive and standard care) involved the newer drugs class of SGLT2 inhibitors and only few participants received GLP1-receptor agonists towards the end of trial, as the overall trial ran from early 2001 through to 2010 when these drugs were not widely used in clinical practice. The average follow-up was about five years.

They found that intensive treatment to reduce HbA1c (a measure of blood glucose levels) to near normal levels resulted in a 17% reduced risk for CAN (odds ratio: 0.83; confidence interval 0.74-0.93; p=0.002) compared to standard treatment, and that was after adjusting the risk model for a very broad spectrum of confounding factors, including all traditional CAN and

cardiovascular disease risk factors.

The same direction of effect was evident for the intensive treatment of raised blood pressure. That approach resulted in a 22% reduced risk for CAN compared to standard treatment approaches (odds ratio: 0.78; CI 0.65-0.92; p=0.004) after adjusting for confounding factors. Treatment with fenofibrate and a statin compared to placebo and a statin was not as successful, with no significant difference between the interventions.

Additional analyses based on subgrouping showed that the protective effects of intensive treatment of glycemia on CAN risk was only found in individuals without a history of cardiovascular disease events but not in individuals with such a history. Blood pressure interventions was especially evident in older adults over the age of 65 years where CAN risk was reduced by 34%.

Notably, intensive glycemic control applied on top of intensive blood pressure control did not appear to reduce CAN risk more than intensive blood pressure lowering on its own. Taken together, the authors suggest these observations point towards the possible personalization of risk reduction strategies, but that more research will be needed to confirm the usefulness of these approaches.

While concluding that intensive glycemic and blood pressure control is likely to benefit patients in terms of CAN risk reduction, they do urge caution with respect to risks and costs. This is particularly from the perspective that the original ACCORD trial showed that after three and half years of follow-up, intensive glucose-lowering did result in reduced non-fatal cardiovascular events but paradoxically also an increase in overall mortality.

Commenting further on the research, senior co-author Dr. Alessandro Doria said,
"Based on previous smaller studies, we thought that intensive glycemic and blood pressure control would probably work, but these results provide us with definitive proof that these treatments can be used to prevent this serious complication of diabetes."

Co-author Prof Rodica Pop Busui added, "These findings have high clinical care relevance, as we have previously demonstrated that CAN, even in earlier stages, independently predicts cardiovascular and all-cause mortality in type 2 diabetes, and major cardiovascular events and heart failure in type 1 diabetes."

More information: Yaling Tang et al, Intensive Risk Factor Management and Cardiovascular Autonomic Neuropathy in Type 2 Diabetes: The ACCORD Trial, *Diabetes Care* (2020). DOI: 10.2337/dc20-1842

Provided by Joslin Diabetes Center