

### Association of heart rate variability with progression of retinopathy in type 2 diabetes

**Aims:** To study the association of heart rate variability (HRV) with incident vision-threatening diabetic retinopathy (DR) and DR progression among adults with type 2 diabetes.

**Methods:** A total of 5810 participants without vision-threatening DR and with HRV measures assessment at baseline were recruited from the ACCORD (Action to Control Cardiovascular Risk in Diabetes) study. HRV was assessed at baseline using 10 sec 12-lead digitalized electrocardiograms by calculating two HRV time-domain indices, i.e., standard deviation of all normal-to-normal intervals (SDNN) and root mean square of successive differences between normal-to-normal intervals (rMSSD). Low SDNN was defined as SDNN <8.2 ms and low rMSSD as rMSSD <8.0 ms. Participants were classified in Low HRV (both low SDNN and low rMSSD) and Normal HVR. To study DR progression outcome, a subgroup of 2184 patients, who had eye examinations [color fundus photographs (FP)] at baseline and at the 4-year-visit, was selected from the ACCORD Eye Study population. DR progression was defined as the composite of either progression of DR by at least three steps on the Early Treatment Diabetic Retinopathy Study (ETDRS) scale or progression to proliferative DR, requiring photocoagulation and/or vitrectomy.

**Results:** Over a median of 4.7 years, 280 incident vision-threatening DR cases occurred. Low HRV (vs. Normal HRV) was associated with higher risk of incident vision-threatening DR (adjusted hazard ratio 1.32 and 1.14 for low SDNN and rMSSD, respectively). In the subgroup of 2184 participants from the ACCORD Eye Study, Low HRV was associated with a higher risk of DR progression (adjusted relative risks 1.36 and 1.36 for low SDNN and rMSSD, respectively). After multivariable adjustment for covariates, Low HRV was associated with a higher risk of incident DR compared to Normal HRV.

**Conclusions:** Low HRV was independently associated with increased risks of incident vision-threatening DR and DR progression in a large cohort of adults with type 2 diabetes.

**Comments.** In the recent literature, the possible influence of autonomic dysfunction on the risk of DR has not been valued enough, after the first reports of an associations between DR and CAN, mainly in type 1 diabetes, and the emphasis on a possible CAN involvement in DR pathogenesis (Smith SE et al *Diabetologia*. 1981;21:525-8; Giardullo A et al *Acta Diabetol Lat*. 1989;26:245-55; Krolewski AS et al *Diabetes*. 1992;41:430-7). After decades, this is the first study to suggest a connection between the autonomic nervous system and retinal neurodegeneration, supporting the idea that early-stage DR should be viewed as a neuropathy that affects the retinal parenchyma (Srinivasan S et al *Curr Eye Res*. 2016;41:1359-1366). Despite some limitations, such as the observational nature of the study and the use of two domain indexes of HVR instead of gold standard of cardiovascular autonomic reflex tests, this study confirms the need to go beyond the glycemic control to monitor DR (Hirsch IB et al *JAMA*. 2010;303:2291-2). Another important limitation is the use of only FP or clinical manifestations to evaluate the DR progression: the optical coherence tomography would have allowed to identify the early thinning of the inner retinal layers, making the data more accurate. Further research is needed to clarify the meaning of this association.

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**Reference.** Kaze AD, Yuyun MF, Ahima RS, Sachdeva MM, Echouffo-Tcheugui JB. Association of heart rate variability with progression of retinopathy among adults with type 2 diabetes. *Diabet Med*. 2022 Apr 25:e14857. doi: 10.1111/dme.14857. Epub ahead of print.  
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