

Measures of Heart Rate Variability improve prediction of cardiovascular outcomes and all-cause mortality

Aim: To investigate whether tests for cardiovascular autonomic neuropathy (CAN) and heart rate variability (HRV) improve the predictive power, beyond traditional risk factors, for future cardiovascular outcomes and all-cause mortality.

Methods: This study was a prospective longitudinal study, with 541 participants with type 2 diabetes (with either any microvascular or macrovascular complication or 2 cardiovascular risk factors) who were followed-up for a median of 12-years. All participants underwent CAN testing using Ewing's criteria, and a subsample (n=313) underwent 24-hour Holter monitoring with time-domain HRV parameter measurement (the standard deviation of all normal RR intervals [SDNN] and the standard deviation of the averaged normal RR intervals for all 5 min segments [SDANN]). The primary outcomes were the occurrence of any cardiovascular event (CVE) and all-cause mortality. Multivariate Cox regressions examined the association between CAN/HRV with cardiovascular events and all-cause mortality.

Results: 25% of participants at baseline had definite CAN (2 abnormal tests out of 5) and 17-18% low HRV parameters (SDNN <70 ms or SDANN <50 ms). Over 12-years follow-up there were 177 CVEs and 236 deaths in the whole cohort, and 96 CVEs and 129 all cause deaths in the subsample of 313 patients undergoing 24-hour HRV. As expected, lower HRV values and CAN were associated with adverse outcomes. When added to a standard risk factor model, CAN (Ewing's) did not improve risk discrimination for outcomes when assessed by the C-statistic. However, HRV measures improved risk discrimination for CVEs and mortality with increases in C-statistics up to 0.039 and Integrated Discrimination Improvement indices by 25%.

Conclusions: Low HRV variables were a better predictor of outcomes than standard tests for CAN, and improved risk discrimination models.

Comments. CAN is a common complication of diabetes, which is independently associated with increased cardiovascular morbidity and all-cause mortality. Various measures of CAN are available, but are not widely used in the clinical setting, as their clinical utility is uncertain. This prospective, observational cohort study shows that HRV parameters improved risk discrimination for cardiovascular outcomes and mortality. The strengths of the study include the large patient numbers, long duration of follow-up and utilization of 24-hour Holter monitoring, the traditional method of HRV assessment, with standard previously-described cut-off values indicative of abnormally reduced HRV. A limitation is the inclusion of participants with only type 2 diabetes and exclusion of those with common co-morbidities associated with the condition (e.g. morbid obesity and advanced renal failure). Moreover, the authors highlight that as with any cohort study residual confounding due to unmeasured or unknown factors cannot be ruled out, indeed participants with CAN and/or low HRV had a greater burden of micro/macrovascular risk factors. Further studies are now necessary in different cohorts (including type 1 diabetes) to determine whether HRV measures are applicable to clinical practice, in particular, determining the impact of treatment (e.g. tight glucose control / multifactorial risk factor management).

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Reference. Cardoso CRL, de Oliveira VAG, Leite NC, Salles GF. Prognostic importance of cardiovascular autonomic neuropathy on cardiovascular and mortality outcomes in individuals with type 2 diabetes: The Rio de Janeiro type 2 diabetes cohort. *Diabetes Res Clin Pract.* 2022 Dec 21;196:110232. doi: 10.1016/j.diabres.2022.110232. Epub ahead of print. PMID: 36563882.

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