Editorial

Can cardiac autonomic neuropathy be a predictor of cardiovascular outcomes in diabetes?

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Unexpected Results

As various cardiovascular outcome trials conducted in persons with type 2 diabetes reach publication, scientific debate arises as to the interpretation of their results. Outcomes that follow expected lines are easily understood, while findings that are unusual have to be explained to a discerning audience of information-savvy patients and knowledgeable physicians.

A recent example is the finding of increased risk of hospitalization in patients randomized to saxagliptin, as reported by the saxagliptin assessment of vascular outcomes recorded in patients with diabetes mellitus–thrombolysis in myocardial infarction (SAVOR-TIMI) 53 trial.[1] This unexpected result, which stemmed from analysis of one component of a secondary endpoint, has attracted more debate than the primary end point results, which showed that saxagliptin neither increased nor decreased the rate of ischemic events in persons with type 2 diabetes. No reason has been found so far to explain the association between saxagliptin and hospitalization. Results from the Vildagliptin in Ventricular Dysfunction Diabetes (VIVIDD) study regarding the effect of vildagliptin on cardiac function are also open to interpretation.[2]

Modern cardiovascular outcomes trials follow strict guidance for industry, as laid down by the United States Food and Drug Administration.[3] Thus, they represent a marked improvement over earlier generation trials such as the University Diabetes Group Programme study,[4] which attracted considerable criticism for methodological flaws.[5]

Trial design specialists take multiple factors into consideration while writing protocols, and try to ensure that as many variables as possible are captured in data collection. The SAVOR-TIMI trial, for example, assessed various parameters at baseline including hypertension; dyslipidemia; history of prior myocardial infarction, heart failure, and coronary revascularization, and the presence of established atherosclerotic diabetes.[6] All these variables, however, have not been able to predict or explain the occurrence of increased hospitalization for heart failure.

Unheralded Predictor

One important comorbid condition, which has not been assessed in these trials, though, is cardiovascular autonomic neuropathy (CAN). We hereby highlight the importance of assessing CAN as a determinant of cardiovascular outcomes in diabetes, and propose inclusion of CAN measurement in all cardiovascular outcome trials being conducted on antidiabetic drugs.

Rationale of Assessment

Cardiovascular autonomic neuropathy is a frequently encountered chronic complication of diabetes, defined as the impairment of autonomic control of the cardiovascular system in the setting of diabetes after exclusion of other causes.[7] CAN has been found to be a better predictor of major cardiac events than assessment of silent myocardial ischemia.[8] A meta-analysis of 15 studies showed that CAN is associated with increased risk of mortality, and this association is stronger if 2 or more abnormalities are used to define CAN.[9] The presence of CAN suggests a grave prognosis, with the risk of sudden death.[10] The higher mortality is observed in

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patients with CAN even in the absence of other clinically detectable microvascular and macro vascular complications.

Cardiovascular autonomic neuropathy is also directly linked with left ventricular dysfunction. Analysis of a large cohort of type 1 diabetes patients has shown that persons with CAN have significantly higher left ventricular mass, mass-to volume ratio, and cardiac output, independent of other factors.[11] Thus, CAN is certainly a predictor of cardiovascular outcomes in persons with diabetes.

Feasibility of Assessment

The assessment and quantification of CAN have been standardized to a great extent, and validated methods of assessment are available.[12] The American Diabetes Association suggests that screening for signs and symptoms of CAN should begin at diagnosis in type 2 diabetes, thus highlighting its importance.[13] It suggests CAN assessment as a means of cardiovascular risk stratification in persons with diabetes. Cardiovascular reflex tests are considered the gold standard for diagnosis.[14]

The Cinderella of Cardiology

Unfortunately, however, CAN seems to have been neglected by cardiology researchers and policy makers alike. The European Society of Cardiology (ESC) guidelines on diabetes, prediabetes, and cardiovascular diseases developed in collaboration with the European Association for the Study of Diabetes, for example, are an extremely comprehensive and exhaustive review of the subject.[15] They too, fail to mention the role of CAN in the pathogenesis of cardiovascular morbidity in diabetes

Summary

Assessment of CAN in diabetes clinical trials is both rational, and feasible. It is possible that the cardiac autonomic health, which was not considered during randomization, may have modified the response of subjects to therapy in the SAVOR-TIMI and VIVIDD trials. Keeping this in mind CAN should be, and must be, considered as a significant factor while designing randomization strategies in future cardiovascular outcome trials. This is especially true for trials involving incretin-based therapies, as their mechanism of action and response is closely linked with the autonomic nervous system.[16] This conjecture, however, is open to debate.

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