When Does New Onset Diabetes Resulting From Antihypertensive Therapy Increase Cardiovascular Risk

George L. Bakris, James R. Sowers

The report in this issue of Hypertension by Verdecchia et al., a prospective study in a relatively large group of patients with uncomplicated essential hypertension, demonstrated two important findings. First, baseline level of plasma glucose and use of diuretics after a median follow-up of 6 years were independent predictors for development of new onset diabetes. Second, they observed that the occurrence of a new onset of diabetes in treated hypertensive patients carried a risk for subsequent cardiovascular disease (CVD) events that was not statistically different from those who already had diabetes and hypertension at the onset of the study. Indeed, the risk of CVD events in those with new onset diabetes was not substantially different compared with those who already had diabetes at the onset of the investigation, with both groups having much higher risk than those who remained free of diabetes. These are important and clinically relevant observations.

It is increasingly recognized that persons with hypertension have a high prevalence of insulin resistance and are at substantially higher risk of developing type 2 diabetes mellitus. Verdecchia et al.’s data support prior observations that certain antihypertensive drug classes (diuretics and β-blockers) may increase this propensity of patients with hypertension to develop type 2 diabetes. Use of diuretics or β-blockers compared with angiotensin-converting enzyme inhibitors or calcium antagonists was associated with an increased incidence of new diabetes in the Captopril Prevention Project (CAPP) and the Intervention as a Goal in Hypertension Treatment Study (INSIGHT). In a prospective study of the Atherosclerosis Risk in Communities study and the Losartan Intervention for End-Point Reduction (LIFE), use of a β-blocker was associated with an 18% to 27% higher incidence of new diabetes. In the recent Antihypertensive and Lipid Lowering Treatment to Prevent Heart Attack Trial (ALLHAT), the incidence of new diabetes was highest in the chlorthalidone group compared with either the amlodipine or lisinopril groups. In the recently reported Controlled Onset Verapamil Investigation of Cardiovascular End Points (CONVINCE) trial, there was a tendency for lesser new onset diabetes for patients randomized to verapamil versus conventional therapy (ie, β-blockers).

The very recently reported International Verapamil SR-trandolapril Study (INVEST), demonstrated a significantly lower incidence of new onset diabetes in the verapamil group compared with the β-blocker group. In both CONVINCE and INVEST, verapamil provided similar CVD risk reduction to a β-blocker with better tolerability. Thus, the totality of data from clinical trials indicates that thiazide diuretics and β-blockers increase risk for new onset diabetes. The current report in this journal indicates that the associated development of diabetes significantly increases the risk for CVD. It is now generally recognized that macrovascular disease starts long before the presentation of patients with clinical diabetes, as several studies have shown the increased risk of CVD in patients with impaired glucose tolerance even after adjusting for conventional risk factors. The current study suggests that the accelerated development of clinical diabetes associated with antihypertensive therapy further enhances the risk for CVD in patients with essential hypertension. This increased risk, however, is not appreciated for at least 6 or more years after its development, a duration much longer than any of the follow-up trials. The current study also suggests that patients with elevated fasting glucose are at a particularly high risk for new onset diabetes and associated enhanced CVD risk. Collectively, these observations suggest that thiazide diuretics and β-blockers should be initiated cautiously in hypertensive patients with elevated fasting glucose is, above 100 mg/dL or those who have a body mass index of ≥30.

Further, the risks of new onset diabetes and associated CVD risk should be factored into further recommendations of antihypertensive therapy. This will be increasingly important as the numbers of hypertensive patients with insulin resistance increase in parallel with increases in obesity and aging of the essential hypertension population throughout the world.

References


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