New-Onset Diabetes, Antihypertensive Treatment, and Outcome

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New-onset diabetes (NOD) confers increased risk for cardiovascular disease and all-cause mortality in different clinical settings. In the specific context of hypertensive subjects exposed to the long-term effects of antihypertensive drugs, a study from our group and a recent 28-year follow-up study from Sweden showed a greater risk of major cardiovascular disease in hypertensive subjects who developed NOD than in those who did not. Notably, the yearly incidence of NOD ranged from 1.0% in the Swedish study to 1.9% in our study.

This issue of Hypertension hosts a posthoc analysis of the Valsartan Antihypertensive Long-term Use Evaluation (VALUE) database, which tested the hypothesis that NOD is a predictor of cardiac morbidity and cardiac and all-cause mortality. The hypertensive subjects who developed NOD showed a 43% higher risk of cardiac morbidity (ie, a composite of sudden death, myocardial infarction, death associated with revascularization, and congestive heart failure requiring hospitalization) when compared with those who did not develop diabetes.

When the determinants of the composite pool of cardiovascular events were examined separately, NOD was associated with a marginally higher risk of myocardial infarction (hazard ratio [HR]: 1.30; 95% CI: 0.99 to 1.70; P = 0.057) and a significantly higher risk of congestive heart failure (HR: 1.41; 95% CI: 1.06 to 1.87; P = 0.017). These findings are in full agreement with a recent report from the ONgoing Telmisartan Alone and in combination with Ramipril Global Endpoint Trial (ONTARGET), in which NOD was associated with a 74% excess risk of congestive heart failure requiring hospitalization.

In the analysis of the VALUE database, all-cause mortality (HR: 0.61; 95% CI: 0.48 to 0.77) and cardiac mortality (HR: 0.44; 95% CI: 0.28 to 0.70) were lower, not higher, in the subjects with NOD than in their nondiabetic counterparts. Despite some obvious caveats, including the relatively small number of fatal events and the shorter follow-up time in the subjects with NOD than in those without NOD, an interesting potential explanation of these results might be the more aggressive treatment reserved by the VALUE trialists to the subjects with NOD. Statins, aspirin, β-blockers, and diuretics were given more frequently to subjects who developed NOD than to those who did not, and all of the differences between the 2 groups were statistically significant. This analysis of the VALUE Study confirms that NOD predicts an excess risk of cardiac morbidity and brings in the hypothesis that intensive treatment of cardiovascular risk factors in these subjects might be a rewarding strategy to reduce mortality.

Prognostic Value of Drug-Induced Diabetes

A recent network meta-analysis of 22 clinical trials showed that angiotensin-converting enzyme inhibitors, angiotensin II receptor blockers, calcium channel blockers, and placebo are associated with a significantly lesser risk of NOD as compared with diuretics. The risk of NOD was similar with diuretics and β-blockers. This and other reports are feeding a controversy over the prognostic impact of NOD in randomized trials of “old” (ie, diuretics and β-blockers) versus “new” (angiotensin-converting enzyme inhibitors, angiotensin II receptor blockers, and calcium channel blockers) antihypertensive drugs. The essence of the controversy is the apparently innocent nature of NOD, supported by a pretended weakness of the association between the incidence of NOD and the excess risk of hard end points in most trials. The crucial issue is to understand why many trials failed to detect an excess risk of hard events in people treated with diuretics and β-blockers if the premise is correct that NOD is an adverse prognostic marker more frequently associated with these drugs.

Indeed, different risks of NOD do not necessarily translate into different risks of hard end points in available trials. Based on previous data on the number of subjects needed to treat to prevent 1 new case of diabetes and the estimated incidence of cardiovascular events, we calculated that 1 cardiovascular event specifically associated with NOD may be prevented for every 385 to 449 subjects treated with new, rather than old antihypertensive drugs for ~4 years. It follows that any attempt to draw solid implications on the prognostic value of NOD from randomized studies may be limited by the inadequacy of sample size of available studies, not by the lack of adverse prognostic value by NOD itself. This line of reasoning is supported by posthoc analyses of the Antihypertensive and Lipid-Lowering Treatment to Prevent Heart Attack Trial and the Systolic Hypertension in the Elderly Study.

In the Antihypertensive and Lipid-Lowering Treatment to Prevent Heart Attack Trial, the incidence of coronary artery disease was 64% higher (95% CI: 15 to 233) in the subjects who developed NOD in the first 2 years of follow-up than in...
those who did not. However, when the chlorthalidone, amlodipine, and lisinopril groups were analyzed separately, the excess risk of coronary artery disease was significant only in the lisinopril group (HR: 2.23; 95% CI: 1.07 to 4.62), not in the other groups, although the P value for the interaction term was not significant (P=0.21). These results suggest that the power of the chlorthalidone and amlodipine groups might have been inadequate to detect the adverse impact of NOD on coronary artery disease, as shown in the total Antihypertensive and Lipid-Lowering Treatment to Prevent Heart Attack Trial cohort. A further potential explanation might be that the lesser blood pressure reduction in the lisinopril group as compared with the other groups may have allowed NOD to unveil its adverse prognostic impact.

Similarly, in the extended follow-up of the Systolic Hypertension in the Elderly Study, NOD was associated with a higher risk of all-cause (HR: 1.35; 95% CI: 1.05 to 1.72) and cardiovascular (HR: 1.56; 95% CI: 1.12 to 2.18) mortality in the placebo group but not in the active treatment group. These data have been interpreted as evidence that NOD induced by treatment is not harmful. However, one could also argue that, in the specific Systolic Hypertension in the Elderly setting composed by elderly subjects with isolated systolic hypertension and high cardiovascular risk in the short term, the highly favorable prognostic effect of blood pressure reduction may have outweighed the adverse prognostic impact of NOD.

In conclusion, we should refrain from the temptation to underestimate the adverse prognostic impact of NOD solely because most randomized trials of old versus new antihypertensive agents failed to disclose a clear-cut association between NOD and outcome. NOD, regardless of its determinants, remains an adverse prognostic marker. The onset of type 2 diabetes may occur earlier in the vital cycle of many subjects as a result of the imbalance between favoring and protective factors. On the other hand, an excess risk of cardiovascular disease may be associated with plasma glucose well before the diagnosis of NOD is established.

In the clinical management of subjects with essential hypertension, the right target to pursue should be not only the control of blood pressure but also the prevention of NOD through appropriate lifestyle measures and, possibly, the preferential use of drugs that do not increase plasma glucose. If required for full control of blood pressure or other compelling reasons, diuretics and β-blockers should certainly be considered, but with careful control of blood glucose evolution. As suggested by the present VALUE report, an intensive treatment of cardiovascular risk factors in hypertensive subjects with NOD is strongly advisable.

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**Disclosures**

None.

**References**

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