EDITORIAL (SEE TAYLOR ET AL., P. 1065)

Antihypertensive Therapy and the Risk of New-Onset Diabetes

Numerous studies have consistently demonstrated that certain classes of antihypertensive medications have differential effects on carbohydrate and lipid metabolism in humans. In general, higher doses of thiazide diuretics (i.e., ≥25 mg/day hydrochlorothiazide) and β-blockers, at any antihypertensive dose, worsen glycemic control, with β-blockers worsening insulin sensitivity (1). Conversely, ACE inhibitors, angiotensin II receptor blockers, and calcium channel blockers (CCBs) have neutral or beneficial effects on these variables (2,3). It is noteworthy, however, that not all drugs within the same class have similar effects on insulin sensitivity. This is exemplified by the effects of vasodilating β-blockers failing to worsen insulin resistance and consequently having neutral effects on glycemic control (4,5).

These aforementioned observations are evident in 11 randomized clinical outcome trials where development of new-onset diabetes was evaluated as a secondary end point (Table 1) (6–11). In contrast to this general trend, the STOP-2 (Swedish Trial in Old Patients with Hypertension 2) reported no difference in diabetes incidence between conventional treatment (β-blockers or diuretics) and either ACE inhibitor– or CCB-based treatment (12). Moreover, in addition to prospective randomized trials, some long-term epidemiological studies, such as the ARIC (Atherosclerosis Research in Communities) study, have linked different classes of antihypertensive agents with development of new-onset diabetes (13).

All of these studies, however, have limitations to their conclusions. First, all had cardiovascular outcomes rather than incidence of new-onset diabetes as a primary end point. Second, it is difficult to assess the effects of a single class of agents since many studies added other agents to the randomized drug that also affect insulin sensitivity (6,7,10–12). Lastly, studies that used an open-label with blinded end point evaluation may suffer from detection bias (6,10,12), as diabetes may have been more intensively sought in those who were randomized to conventional treatment.

In this issue of *Diabetes Care*, a long-term observational study involving three large cohorts by Taylor et al. (14) provides additional information on the issue of new-onset diabetes. To investigate the association between drugs from different antihypertensive classes and the risk for new-onset diabetes, the authors followed three cohorts, including 41,193 older women from the NHS (Nurses' Health Study) I, 14,151 younger women from the NHS II, and 19,472 men from the HPFS (Health Professionals' Follow-up Study), all of whom had hypertension, for 8, 10, and 16 years, respectively. Using alternative ways to adequately confirm the diagnosis of new-onset diabetes, the authors documented 3,589 incident cases of diabetes.

After adjustment for multiple confounders, including the use of other antihypertensive medications, the relative risk for incident diabetes in individuals taking a thiazide diuretic compared with those not taking one was 20% higher in the cohort of older women, 45% higher in younger women, and 36% higher in men. The relative risk for new-onset diabetes in participants taking a β-blocker compared with those not taking one was 32% greater in older women and 20% greater in men. It is noteworthy that the authors addressed the possibility that surveillance for diabetes was more intense in patients treated with diuretics and β-blockers. They did this by doing analyses only on cases that reported more than one typical symptom of diabetes on the screening physical examination over the 2 years before the diagnosis. In spite of this, they still found that use of diuretics or β-blockers conferred a significantly greater risk for development of new-onset diabetes. Their data are consistent with previous reports in that neither ACE inhibitors nor CCBs conferred a higher risk for new-onset diabetes (14).

This analysis, because of its denominator and duration, adds substantive strength to the panoply of other studies supporting the notion that most β-blockers and thiazide diuretics increase the risk of new-onset diabetes. While this study clearly has some strength, in that the authors confirmed the self-reported cases of diabetes by medical record review and minimized the effect of differences in testing frequency for diabetes for individual antihypertensive agents with additional analyses that adjusted for multiple known and suspected risk factors for diabetes development, it also has some limitations. These limitations include the following: *1*) the use of self-reporting of antihypertensive medications, *2*) the use of the four antihypertensive drug classes was obtained only in the first cohort of older women from NHS I, and *3*) data for the specific use of ACE inhibitors were missing for men in the HPFS, whereas in younger women from the NHS II study, only the specific use for diuretics was recorded.

Taken together with all other studies, these data support the concept that thiazide diuretics and most β-blockers increase the risk for development of new-onset diabetes. The question is, however, does this development of diabetes detract from their cardiovascular risk reduction?

One observational study of >700 untreated hypertensive patients with a median follow-up of 6 years suggested that the development of new-onset diabetes after the initiation of antihypertensive treatment carried a risk for subsequent cardiovascular events that was similar to that of patients who already had diabetes at the onset of the study (15). On closer inspection, however, this was driven by <10 patients and could not be attributed to use of thiazide diuretics. Moreover, intervention trials, like the HDFP (Hypertension Detection and Follow-Up Program) (16) and the SHEP (Systolic Hypertension in the Elderly Program) (17) demonstrated that a thiazide diuretic–based antihypertensive regimen was associated with improved cardiovascular outcomes but an increase in new-onset diabetes was also noted. Similarly, in the ALLHAT (Antihypertensive and Lipid-Lowering Treatment to Prevent Heart Attack Trial), treatment with chlorthalidone, lisinopril, or amlodipine yielded similar cardiovascular outcomes, even though chlorthalidone was associated with the highest incidence of new-onset diabetes (9).

A rational argument for the discordance

Table 1—*Randomized trials that examined incidence of new-onset diabetes*

Trial	Primary treatment	Increase in new-onset diabetes by primary treatment	Comparator
SHEP	Placebo	↓ 5%	Thiazide diuretic ± BB
STOP-2	BB/thiazide diuretic	No difference from comparator	ACEI/CCB
CAPPP	Thiazide diuretic/BB	↑ 13%	ACEI
HOPE	Placebo ± BB/thiazide diuretic	↑ 52%	ACEI
INSIGHT	Thiazide diuretic/BB	↑ 43%	DHP-CCB
LIFE	BB/thiazide diuretic	↑ 32%	ARB ± thiazide diuretic
ALLHAT	Thiazide diuretic	↑ 16%/30%	DHP-CCB/ACEI
INVEST	BB ± thiazide diuretic	↑ 17%	Non–DHP-CCB based
CHARM	Placebo ± BB/thiazide diuretic	↑ 17%	ARB ± BB/thiazide diuretic
VALUE	DHP-CCB	↑ 25%	ARB based
ASCOT	BB ± thiazide diuretic	↑ 32%	DHP-CCB based

ACEI, ACE inhibitor; ARB, angiotensin II receptor blocker; ASCOT, Anglo-Scandinavian Cardiac Outcomes Trial; BB, β-blocker; CAPP, Captopril Prevention Project; CHARM, Candesartan Cilexetil (Candesartan) in Heart Failure: Assessment of Reduction in Mortality and Morbidity; DHP, dihydropyridine; HOPE, Heart Outcomes Prevention Evaluation; INSIGHT, Intervention as a Goal in Hypertension Treatment; INVEST, International Verapamil-Trandolapril Study; LIFE, Losartan Intervention For Endpoint reduction in hypertension; VALUE, Valsartan Antihypertensive Long-Term Use Evaluation.

between thiazide diuretic–associated increases in new-onset diabetes and reduced cardiovascular events in these studies is that the observation period after new-onset diabetes development was too short (9,16,17). This has been addressed, however, by Kostis et al. (18), who provide 14.3 years mean follow-up data from the SHEP trial. They report that presence of diabetes at baseline and diabetes that developed during the trial among subjects on placebo yielded similar increases in risk for cardiovascular and total mortality. However, new-onset diabetes that developed among those randomized to a thiazide diuretic conferred no significant increase in risk for cardiovascular or total mortality (18). Taken together, these studies provide for the concept that achievement of adequate blood pressure control eliminates the expected increase in cardiovascular risk resulting from development of new-onset diabetes in the absence of treatment.

Clinically, physicians and health care professionals should focus on achievement of glucose, lipid, and blood pressure goals, since only 7.3% of those with diabetes achieve all three guideline goals (19). While cost of medications and preexisting conditions of the patients (i.e., other cardiovascular risk factors) should be considered when prescribing medications, these concerns need to be tempered by the cardiovascular/renal benefits of achieving guideline goals. Agents that do not predispose to the development of diabetes should be preferred in those with metabolic syndrome, but a diuretic will be needed in almost everyone as a second agent to achieve further blood pressure reduction. This is due to the increased sodium reabsorption and volume expansion that results from high circulating insulin levels in people with metabolic syndrome and type 2 diabetes. β-Blockers can be avoided more easily as first-line agents in patients predisposed to develop diabetes but may be needed for specific indications in some people. In such circumstances, it is important to use the appropriate agents while ensuring that guideline goals are achieved.

PANTELEIMON A. SARAFIDIS, MD
GEORGE L. BAKRIS, MD

From the Department of Preventive Medicine, Hypertension/Clinical Research Center, Rush University Medical Center, Chicago, IL.

Address correspondence to George L. Bakris, MD, Hypertension/Clinical Research Center, Department of Preventive Medicine, Rush University Medical Center, 1700 West Van Buren, Suite 470, Chicago, IL 60612. E-mail: gbakris@earthlink.net.

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