COMMENTS AND RESPONSES

Differences in Glucose Tolerance Between Fixed-Dose Antihypertensive Drug Combinations in People With Metabolic Syndrome

Response to Bakris et al.

We read with great interest the recent article by Bakris et al. (1). The authors reported that in patients with impaired glucose tolerance (IGT), the combination of losartan and hydrochlorothiazide resulted in an increased rate of new-onset diabetes when compared with trandolapril and verapamil. Indeed, we agree that thiazide diuretics have a history of producing adverse metabolic effects; however, we contend that losartan is an inappropriate angiotensin receptor blocker (ARB) choice. Losartan has inadequate peroxisome proliferator–activated receptor γ (PPARγ) activity when compared with the other drugs in its class, limiting its ability to neutralize the detrimental glucose effects of thiazide diuretics (2).

It has been shown that the PPARγ activity of thiazolidinediones reduces the risk of new-onset diabetes in patients with IGT (3). Several ARBs have been evaluated for PPARγ activity. Specifically, telmisartan has demonstrated PPARγ agonism at a much higher rate than losartan in vivo (2). In fact, in vitro studies have shown that telmisartan has ~25% of the PPARγ activity of pioglitazone (2). In contrast, losartan fails to demonstrate significant PPARγ effect, even at higher concentrations in humans (2). Thus, telmisartan may have been a more favorable choice as a glycemic ARB/thiazide combination than losartan.

Concerning patients with IGT, an ACE inhibitor or ARB is considered the first-line antihypertensive of choice; however, according to current guidelines, two or more antihypertensive medications are typically required to achieve blood pressure goals, and a thiazide diuretic is considered second-line treatment for most (4). The results of the STAR (Study of Trandolapril/Verapamil SR and Insulin Resistance) trial suggest that use of a thiazide diuretic (regardless of ACE inhibitor or ARB) is inappropriate for treating hypertension in patients with IGT, which is corroborated by the findings of a recent prospective cohort (5). This cohort also reported that calcium channel blockers were not associated with an increased onset of symptomatic diabetes, paralleling the STAR trial results (1,5). While higher-affinity PPARγ ARBs (i.e., telmisartan) are undergoing studies to assess risk of new-onset diabetes (ONTARGET [Ongoing Telmisartan Alone and in Combination With Ramipril Global Endpoint Trial] and TRANSCEND [Telmisartan Randomized Assessment Study in ACE-I Intolerant Subjects With Cardiovascular Disease]), alternative ACE inhibitor or ARB combinations (with calcium channel blockers or doxazosin) should be considered before thiazide diuretics as second-line agents in patients with IGT (6).

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