We appreciate the interest by Dr. Rassi in our recent study on the role of angiotensin-converting enzyme (ACE) inhibitors and angiotensin receptor blockers (ARBs) in diabetes prevention (1). We agree that lifestyle modifications that increase physical activity and minimize abdominal obesity are the most rational and cost-effective strategies for preventing type 2 diabetes. Despite this knowledge, compliance with a prescription for daily exercise and lasting weight loss proves difficult for many people; the epidemic of diabetes continues to escalate. Thus, safe pharmacologic approaches for preventing this disease will probably be relevant and important for many individuals.

Screening for new-onset diabetes using the American Diabetes Association criteria of a fasting plasma glucose of ≥126 mg/dl at two different visits in patients with no diabetes at the time of enrollment is a valid initial test to identify this disease at its early stages and prevent its chronic sequelae. However, the use of data from relatively short-term studies to calculate a number-needed-to-treat (NNT) can be misleading, as the risk of diabetes accrues over decades or, indeed, a lifetime.

Insulin resistance is a common pathophysiologic disturbance that plays a causal role in both hypertension and type 2 diabetes. It also results in overactivity of the rennin-angiotensin-aldosterone system leading to hypertrophy and stiffening of smooth muscles in the arterial wall and left ventricle. Angiotensin-converting enzyme inhibitors and ARBs have a proven efficacy for improving outcomes in insulin-resistant conditions, such as hypertension, coronary heart disease (CHD), and congestive heart failure, and they are the most effective antihypertensive agents for regressing smooth muscle hypertrophy commonly seen in these conditions (2). The fact that they also reduce the risk of new-onset diabetes is just one more reason to choose them for these established indications over other antihypertensive agents that worsen insulin sensitivity, such as traditional beta-blockers and diuretics (3).

Metabolic syndrome is a more robust marker for risk of type 2 diabetes and CHD events (4). If the NNT with an ACE inhibitor or ARB to prevent the development of new-onset diabetes in these patients is to be calculated, it will be substantially lower than that found in populations from our study, who were obviously at a lower risk. Therefore, as we have advocated, targeting high-risk prediabetic individuals for use of an ACE inhibitor or ARB therapy will increase the cost-effectiveness of these medications.

REFERENCES


Long-Term Bosentan Treatment in Children With Pulmonary Arterial Hypertension

One of the core principles of scientific research is to provide full details of the experimental methods for replication in further study or clinical practice. As with many published studies (1), Rosenzweig et al. (2) failed to provide details of the drug formulation in their report. Bosentan is currently only commercially available in tablet form, and the dosing used in their study appears to be multiples of halved/quartered tablets. It is widely recognized that splitting tablets causes significant dosing inaccuracy, even when commercially available tablet cutters are used (3,4). Furthermore, many children are unable to swallow whole tablets (5), and crushing the tablets can impair drug absorption (6). Rosenzweig et al. (2) do not report how their patients took the dose (whether or not it was swallowed whole). If the published report does not detail the drug formulation and method of administration, the reliability of any findings is questionable as the methods cannot be repeated accurately. If tablets were cut in half/quartered and crushed, both the amount of drug administered and its absorption are questionable, bringing the validity of the results into doubt.

In their report, Rosenzweig et al. (2) cite a pharmacokinetic study (7) on the dosing of bosentan in pediatric patients that also fails to give formulation and administration details and whose lowest dose is 31.25 mg as opposed to 15.6 mg in Rosenzweig et al. (2). Bosentan may well be a useful agent in the treatment of pulmonary arterial hypertension in children; surely it is now time that a pediatric liquid formulation be developed, the efficacy and dose optimization of which can be addressed in a well-conducted prospective clinical trial.


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