

REPLY

We appreciate the interest by Dr. Rasi 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 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.

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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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We agree with Dr. Standing that a pediatric formulation of bosentan is needed. The pharmaceutical development of a pediatric formulation, in the form of an orodispersible tablet with a flexible dosage of 8 to 32 mg, is currently undergoing clinical evaluation in children in Europe and in the U.S.

However, during the course of development and validation of the pediatric formulation, the current adult formulation of bosentan was used to begin evaluation of the pharmacokinetics and safety of bosentan in children (1). We acknowledge that we do not describe in detail in our study (2) the technical aspects associated with cutting the adult tablets for the treatment of children. However, several studies have shown the adult formulation is suitable to this situation:

1. The active bosentan substance is uniformly spread throughout the bosentan tablet.
2. Seventy-five percent of the tablet weight is drug substance, thereby limiting the possibility of nonuniformity of the medication dose.
3. The weight of halved tablets, split with a commercially available tablet cutter, was within European and U.S. Pharmacopeia specifications (Actelion, personal communication, 2001). In addition, dissolution rates were measured and found to be similar for both whole and halved tablets.

Therefore, the use of split tablets was considered appropriate for conducting a pharmacokinetic study (1). Quartered tablets were not tested at that time. In our study (2), we followed the sponsor's recommendations of using a commercially available cutter to split the tablets, with no crushing of halved/quartered tablets, and direct oral administration.

Whereas the pharmaceutical development of the pediatric formulation of bosentan was ongoing, we treated children with symptomatic pulmonary arterial hypertension (PAH) at our clinics with the adult bosentan formulation following the sponsor's recommendation for dosing in children at that time (i.e., based on a conservative extrapolation by weight of the recommended adult dosages). Using this approach, these data demonstrated the safety and efficacy of bosentan for pediatric PAH. However, we also agree with Dr. Standing that pediatric dosing needs to be studied further. We anticipate that the current evaluation of a pediatric bosentan formulation will lead to optimal bosentan dosing regimens for children with PAH.

References


Limitations of Crush Technique

Ge et al. (1) reported the results of a prospective study on long-term outcomes of “crush technique” (CT) with drug-eluting stents. This study raises, in our opinion, two main issues.

First, as pointed out by Williams and Abbott in their editorial (2), this study reports a clearly worse outcome as compared to studies with “provisional T stenting” (PTS) and serious concerns about safety profile (4.4% incidence of stent thrombosis). Moreover, the success rate in recrossing the stent struts for final kissing balloon is not reported in the study. Because 36% of patients did not undergo final kissing balloon postdilation, we may assume that, at least in some of them, it was not possible to recross the stent struts. This is an important limitation as any further therapy of side-branch restenosis in “unrecrossable” patients (40% incidence) becomes virtually impossible by means of percutaneous coronary intervention (PCI). From this perspective, PTS appears also to be superior as a second stent is needed in only 15% to 33% of cases, and final kissing balloon is possible in >95% of cases (3).

Additionally, in case of side-branch restenosis it is always possible to perform additional PCI. Taken together these limitations may “crush” down the clinical role of CT, a conclusion not clearly underlined by the investigators.

Second, the modest results of CT reported in the study by Ge et al. (1) are not surprising. In fact, CT results in three drug-eluting stent (DES) layers crushed on an arterial wall at a site of high hemodynamic turbulence, with high chances of the stents’ incomplete expansion where the coverage should be maximal. This...