

## COMMENTS AND RESPONSES

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

Response to O'Malley, Bouldin,  
and Riche

Unfortunately, O'Malley, Bouldin, and Riche (1) are laboring under the impression that the peroxisome proliferator-activated receptor- $\gamma$  (PPAR $\gamma$ ) effects, described for some angiotensin receptor blockers (ARBs), such as telmisartan, in animal and cell models, are clinically relevant (2–4); sadly, this is not the case. The authors anchor their argument on data that evaluated telmisartan on PPAR $\gamma$  activity but unfortunately had no comparator ARB (5). Moreover, there are no published head-to-head comparisons of ARBs-with-PPAR $\gamma$  activity with those that lack this activity to demonstrate differences on glucose tolerance effects. In fact, every retrospective analysis of clinical trials performed with all ARBs tested show a benefit on reducing new-onset diabetes, including losartan and valsartan, the latter compared with a calcium antagonist (6,7). There is no question that treatment with agents that activate PPAR $\gamma$  activity, such as rosiglitazone, reduce the risk of new-onset diabetes (8). However, equating this clinical effect with a minimally detectable PPAR $\gamma$  activity, seen by

some ARBs, is an inappropriate extrapolation. Perhaps the most convincing outcomes come from a study sponsored by the makers of telmisartan on prevention of new-onset diabetes in over 100 participants, all of whom were normotensive and nondiabetic but had insulin resistance as assessed by euglycemic clamp. Unfortunately, even though this study was registered on the clinical trials website and completed almost 3 years ago, it is unpublished. This may say something about the outcome, i.e., negative studies are generally not reported. This data, coupled with the fact that the PPAR $\gamma$  activity in ARBs with this activity has not been found to affect blood glucose in any significant way and does not have an indication for such use by the Food and Drug Administration, should lead one to further question the clinical validity and usefulness of this concept. Hence, while all ARBs reduce incidence of new-onset diabetes, it does not appear that the magnitude of PPAR $\gamma$  effect is the mechanism.

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