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-γ (PPARγ) 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 PPARγ activity but unfortunately had no comparator ARB (5). Moreover, there are no published head-to-head comparisons of ARBs-with-PPARγ 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 PPARγ activity, such as rosiglitazone, reduce the risk of new-onset diabetes (8). However, equating this clinical effect with a minimally detectable PPARγ activity, seen by some ARBs, is an inappropriate extrapolation. Perhaps the most convincing outcomes come from a study sponsored by the makers of telemisartan 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even though this study was registered on the clinical trials website and completed almost 3 years ago, it is unpublished.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 PPARγ 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 PPARγ effect is the mechanism.

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References

1. O'Malley KJ, Bouldin MJ, Riche DM: Differences in glucose tolerance between fixed-dose antihypertensive drug combinations in people with metabolic syndrome (Letter). *Diabetes Care* 30:e23, 2007. DOI: 10.2337/dc06-2562.
2. Schupp M, Clemenz M, Gineste R, Witt H, Janke J, Helleboid S, Hennuyer N, Ruiz P, Unger T, Staels B, Kintscher U: Molecular characterization of new selective peroxisome proliferator–activated receptor γ modulators with angiotensin receptor blocking activity. *Diabetes* 54:3442–3452, 2005
3. Tuck ML: Angiotensin-receptor blocking agents and the peroxisome proliferator-activated receptor-gamma system. *Curr Hypertens Rep* 7:240–243, 2005
4. Doggrell SA: Editorial overview: the 'sartans': is it premature to consider PPAR-gamma receptor agonism a bonus? *Curr Opin Investig Drugs* 6:242–244, 2005
5. Benndorf RA, Rudolph T, Appel D, Schwedhelm E, Maas R, Schulze F, Silberhorn E, Boger RH: Telmisartan improves insulin sensitivity in nondiabetic patients with essential hypertension. *Metabolism* 55:1159–1164, 2006
6. Dahlof B, Devereux RB, Kjeldsen SE, Julius S, Beevers G, Faire U, Fyhrquist F, Ibsen H, Kristiansson K, Lederballe-Pedersen O, Lindholm LH, Nieminen MS, Omvik P, Oparil S, Wedel H: Cardiovascular morbidity and mortality in the Losartan Intervention for Endpoint Reduction in Hypertension study (LIFE): a randomised trial against atenolol. *Lancet* 359: 995–1003, 2002
7. Julius S, Kjeldsen SE, Weber M, Brunner HR, Ekman S, Hansson L, Hua T, Laragh J, McInnes GT, Mitchell L, Plat F, Schork A, Smith B, Zanchetti A: Outcomes in hypertensive patients at high cardiovascular risk treated with regimens based on valsartan or amlodipine: the VALUE randomised trial. *Lancet* 363:2022–2031, 2004
8. Gerstein HC, Yusuf S, Bosch J, Pogue J, Sheridan P, Dinccag N, Hanefeld M, Hoogwerf B, Laakso M, Mohan V, Shaw J, Zinman B, Holman RR: Effect of rosiglitazone on the frequency of diabetes in patients with impaired glucose tolerance or impaired fasting glucose: a randomised controlled trial. *Lancet* 368:1096–1105, 2006