RESPONSE TO COMMENT ON INZUCCHI ET AL.

Pioglitazone Prevents Diabetes in Patients With Insulin Resistance and Cerebrovascular Disease. Diabetes Care 2016;39:1684–1692

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Katsiki and Mikhailidis (1) raise the possibility that reduced uric acid may have been a mechanism of the cardiovascular benefits of pioglitazone in the Insulin Resistance Intervention after Stroke (IRIS) trial. Unfortunately, we did not measure urate levels during the trial, so the question cannot be answered. One small trial suggested modest reductions in hyperuricemia from pioglitazone, on the order of 14% (<1 mg/dL) (2). Data regarding the association between uric acid and cardiovascular disease remain highly controversial, however, and whether lowering urate confers a cardiovascular advantage remains to be demonstrated convincingly.

The issue of effects of pioglitazone on nonalcoholic fatty liver disease is also raised. As Katsiki and Mikhailidis (1) describe, modest decreases in alanine aminotransferase levels were in fact measured in IRIS participants assigned to the pioglitazone group. Because we did not measure liver fat directly, we do not know whether pioglitazone actually improved steatosis, but this is a reasonable inference based on previous trials (3). We agree that another mechanism for the potential cardiovascular benefits of this drug may involve a reduction in liver fat (4), which is commonly increased in patients with insulin resistance and prediabetes. Improvement in liver fat content may also partially mediate the diabetes prevention effects of pioglitazone, since steatosis, an important reflection of hepatic insulin resistance, appears to contribute independently to the progression of hyperglycemia in at-risk individuals (5).

Finally, we agree that postprandial lipemia, also reduced by pioglitazone (6), is apt to be another factor that might aggravate cardiovascular risk. We did not perform meal tolerance testing in this large cardiovascular outcomes trial, but fasting triglycerides were reduced 13% over 5 years in patients randomized to pioglitazone compared with a 2% decline in patients randomized to placebo.

Clearly, pioglitazone has multiple actions that may influence cardiovascular risk, including favorable effects on insulin sensitivity, lipoprotein profile, blood pressure, and inflammation. Although associations of any or all of these with pioglitazone treatment may be demonstrated, a trial such as IRIS cannot determine which effects are causally related to clinical outcomes. Moreover, peroxisome proliferator–activated receptor γ agonists such as pioglitazone may have direct effects on the very cells involved in the atherosclerotic process, including vascular endothelium and smooth muscle, monocytes, and macrophages (7). Further studies in both animal models and humans will be necessary to fully understand the mechanisms by which pioglitazone reduces cardiovascular events.

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