Correspondence

Differential Effects of Pioglitazone on Advanced Atherosclerotic Lesions

To the Editor-in-Chief:

The recent article by Nakaya and colleagues¹ addresses the role of the insulin-sensitizing thiazolidinedione (TZD) and peroxisome proliferator-activated receptor (PPAR) γ ligand, pioglitazone, on advanced atherosclerosis in low density lipoprotein receptor (LDLR)-deficient mice. Advanced atherosclerotic progression directly precedes acute clinical events; therefore, it is important to understand the consequences of widely prescribed drugs, such as TZDs, on these endpoints.² To specifically study the effects of TZDs on advanced atherosclerosis, the investigators administered pioglitazone to mice with pre-established lesions and found no reduction in advanced aortic lesion size. According to the authors, the rationale for their study was that PPAR γ ligand treatment on advanced atherosclerosis had not been previously evaluated. However, in 2007 in the journal *Circulation*, our group published a similar strategy, also in LDLR-deficient mice with pre-established lesions.³ In contrast to the Nakaya et al study, in which the mice were switched from high-fat feeding to normal chow diet when pioglitazone was added, our strategy was to continue the high-fat diet during the pioglitazone phase. The findings of the two published studies are consistent in that pioglitazone failed to reduce overall lesion burden. However, our report also investigated effects on advanced lesional complexity, which in humans is a much more important lesional endpoint than plaque size. This analysis revealed that pioglitazone actually increased plaque necrosis. In recent unpublished studies, our group also assessed the effects of pioglitazone on advanced lesions using the same dose administered by Nakaya et al, and we again found no effect on lesion size, although plaque necrosis was not elevated at this dose. Thus, despite evidence that TZDs reduce early atherosclerotic lesions in mice,⁴ our study and Nakaya et al indicate that the effects of TZDs on advanced atheromata is

less pronounced. This is consistent with the Prospective Pioglitazone Clinical Trial in Macrovascular Events, in which the primary endpoints of all-cause mortality—nonfatal myocardial infarction, stroke, acute coronary syndrome, and peripheral vascular disease—failed to show a beneficial effect.⁵

Edward Thorp
Ira Tabas

*Columbia University
New York, New York*

References

1. Nakaya H, Summers BD, Nicholson AC, Gotto AM, Jr., Hajjar DP, Han J: Atherosclerosis in LDLR-knockout mice is inhibited, but not reversed, by the PPAR γ ligand pioglitazone. *Am J Pathol* 2009, 174:2007–2014
2. Tabas I: Consequences and therapeutic implications of macrophage apoptosis in atherosclerosis: the importance of lesion stage and phagocytic efficiency. *Arterioscler Thromb Vasc Biol* 2005, 25:2255–2264
3. Thorp E, Kuriakose G, Shah YM, Gonzalez FJ, Tabas I: Pioglitazone increases macrophage apoptosis and plaque necrosis in advanced atherosclerotic lesions of nondiabetic low-density lipoprotein receptor-null mice. *Circulation* 2007, 116:2182–2190
4. Li AC, Binder CJ, Gutierrez A, Brown KK, Plotkin CR, Pattison JW, Valledor AF, Davis RA, Willson TM, Witztum JL, Palinski W, Glass CK: Differential inhibition of macrophage foam-cell formation and atherosclerosis in mice by PPAR α , β / δ , and γ . *J Clin Invest* 2004, 114:1564–1576
5. Dormandy JA, Charbonnel B, Eckland DJ, Erdmann E, Massi-Benedetti M, Moules IK, Skene AM, Tan MH, Lefebvre PJ, Murray GD, Standl E, Wilcox RG, Wilhelmsen L, Betteridge J, Birkeland K, Golay A, Heine RJ, Koranyi L, Laakso M, Mokan M, Norkus A, Pirags V, Podar T, Scheen A, Scherbaum W, Schernthaner G, Schmitz O, Skrha J, Smith U, Taton J: Secondary prevention of macrovascular events in patients with type 2 diabetes in the PROactive Study (PROspective pioglitazone Clinical Trial In macroVascular Events): a randomised controlled trial. *Lancet* 2005, 366:1279–1289