COMMENTS AND RESPONSES

PPARγ Variant Influences Angiographic Outcome and 10-Year Cardiovascular Risk in Male Symptomatic Coronary Artery Disease Patients

Response to Schneider et al.

The effects of peroxisome proliferator–activated receptor (PPAR)γ are largely unknown, and studies of genetic variation are one approach to confirm and estimate its impact on disease in humans. Vasculoprotective effects have been observed preclinically with small-molecule stimulation of the PPARγ pathway. Therefore, it constitutes a potential target of secondary prevention to further reduce cardiovascular risk in patients with manifest vascular disease. Other than our current report, there is no evidence on the impact of genetic variation in PPARγ on cardiovascular prognosis in a secondary prevention setting. Hence, we fully share the opinion of Schneider et al. (1) that the current data are not generalizable and only pertain to patients with manifest vascular disease. We greatly encourage further studies on the role of PPARγ in recurrent cardiovascular events and progression of atherosclerosis. Our conclusion therefore remains that our long-term findings in patients with manifest coronary artery disease (CAD) support an important role of PPARγ in determining vascular risk (2).

Regarding the fist comment related to the metabolic profile of the REGRESS (Regression Growth Evaluation Statin Study) population, it is important to realize that known type 1 or type 2 diabetes at baseline was an exclusion criterion for the study and there were no data available on insulin sensitivity and insulin excretion. Lack of significant differences in fasting glucose and BMI among genotypes is therefore easily understood.

A second comment relates to confounding in our study. Confounding factors by definition affect both the determinant (genotype) and the outcome (clinical end point). As a concept, when observing the relation between genotype and clinical outcome, confounding is therefore difficult to imagine, except if as a selection mechanism. We therefore did not correct for either smoking or age. As described, all multivariate models have been intended to explore potential intermediate factors.

A third comment relates to previous reports of cross-sectional analyses of the relation between Pro12Ala genotype and angiographic end points such as the number of vessels diseased. The discrepancy of our data with the report by von Eynatten et al. (3), using the severity score and extent score assessments of CAD, is intriguing. The fact that no baseline characteristics of the 171 study participants were given in that report makes it impossible to provide an explanation underlying this discrepancy. Our current data from REGRESS show that the number of coronary vessels diseased does not vary by Pro12Ala genotype group, and—contrary to the suggestion made by Schneider et al. (1)—these data are fully in keeping with the report by Rhee et al. (4). Furthermore, it is important to note that we assessed the extent of CAD in REGRESS by means of quantitative coronary angiography. This robust and highly standardized measure of atherosclerosis has been widely employed in angiographic clinical trials of atherosclerosis progression. The quantitative coronary angiography analysis uncovered less widespread CAD in carriers of the 12Ala allele of PPARγ.

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