Genetic Variability of von Willebrand Factor and Atherosclerosis

To the Editor:

With great interest we read the study by Sramek et al.1 in which they showed that patients with type 3 von Willebrand disease, characterized by an absence of circulating von Willebrand factor (vWF), were not protected against atherosclerosis. The patients in their study were young (mean age 35 years), whereas clinically relevant atherosclerosis typically occurs at a later age. Therefore, we would like to present our study on the association between vWF and atherosclerosis in an elderly population.

We performed a nested case-control study within the Rotterdam Study, a population-based cohort study in individuals ≥55 years of age.2 We examined the association of the −1793 C/G vWF gene polymorphism, of which the G allele is known to be associated with higher vWF levels,3 with peripheral atherosclerosis, as assessed by the ankle-arm index. Within 6 strata defined by age and gender, we selected individuals with an ankle-arm index in the lowest and highest 15% of the distribution as cases (n=459) and controls (n=422). The −1793 C/G polymorphism was determined as described previously.4 Logistic regression analysis was used to calculate age- and gender-adjusted odds ratios and confidence intervals. Overall, no association between the −1793 C/G genotype and the risk of peripheral atherosclerosis was found, as follows: CG versus CC 1.20 (0.91–1.59); GG versus CC 0.90 (0.57–1.44), and CG+GG versus CC 1.14 (0.87–1.49).

Increased vWF levels have been associated with the risk of cardiovascular disease in many epidemiological studies.5 It is still unclear whether increased levels of vWF are a cause of cardiovascular disease or merely a marker of endothelial damage. In addition, it is not clear whether vWF is involved in atherosclerotic plaque formation, progression of atherosclerosis, or rather in thrombosis precipitating cardiovascular events. Recently, we showed that carrying the G allele at position −1793 is associated with an increased risk of myocardial infarction only in subjects with advanced atherosclerosis, which suggests that vWF may be causally involved in cardiovascular disease.6 Therefore, considering the results of Sramek et al1 and our findings that a genetic variation resulting in increased vWF levels is not associated with peripheral atherosclerosis, we suggest that the role of vWF in cardiovascular events is not the formation of atherosclerotic plaques but rather the formation of thrombi precipitating these events in subjects in whom atherosclerosis is already present.

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