

Letter to editor

Relationship between plasma ACE activity and the proliferative healing process in coronary vessel injury after coronary stenting[☆]

The recent publication by Agerholm-Larsen B. et al. addressed the important issue of the degree of association between the insertion/deletion (I/D) polymorphism of the angiotensin converting enzyme (ACE) gene and its phenotypic expression in terms of basal plasma level of the enzyme in a large population of healthy Danes [1]. The I/D polymorphism explained up to 30–40% of the total phenotypic variance of plasma ACE level in women and men irrespective of age. This is in agreement with previous studies [2,3] and confirms that this genetic marker plays a role also in a population that previously had shown no association between the D allele of the ACE gene and the risk of myocardial infarction (MI) [4]. The authors point out that despite this good correlation between genotype and phenotype, diseases possibly affected by enhanced ACE activity (such as hypertension or left ventricular hypertrophy) do not show conclusive evidence of this association, and that plasma ACE level has not been demonstrated to be a cardiovascular risk factor so far. Their conclusion ‘New studies should focus on pathologic conditions involving diseases known or suspected to be associated with elevated levels of serum ACE’ has stimulated our comments below.

The usefulness of a genetic marker in clinical practice is based on the possibility of screening populations at risk for a certain event, and to predict or prevent its occurrence. Accurate prediction is directly dependent on the number of variables involved in the phenomenon and on the knowledge about their interactions with the environment. In this respect, atherosclerosis and MI may represent the paradigms of multifactorial disease, where each factor has a different weight in different subjects.

The I/D polymorphism of the ACE gene has been studied as a risk factor for many different cardiovascu-

lar disorders; however, current evidence of its importance is not conclusive. These controversial findings may have many explanations: selection bias by mortality in retrospective analysis; bias against studies with small samples; the different role played by a genetic marker in different populations (different ethnic groups or levels of cardiovascular risk throughout the studies, and the different kind of interaction between individuals and environment); use of ACE-inhibitors in the study population (with significant effects on plasma ACE levels, blood pressure, and more importantly, reduction of the incidence of MI, or recurrent angina in ischemic patients); and most interestingly, different association with different pathophysiologic processes, bearing in mind that common polymorphisms with frequent alleles and relatively small effects interact with each other and the environment, and are likely to account for most of the genetic background of coronary artery disease.

From these considerations, one could assume that some diseases, even if multifactorial, are controlled by fewer factors and pathophysiological interactions than are atherosclerosis or MI, and may express a phenotype likely to be related to the renin-angiotensin system (RAS), and marked by the I/D polymorphism. The process of left ventricular remodeling after MI [5,6] and of vascular repair after percutaneous injury [7–9] seem to be examples of these associations.

We have previously shown that plasma activity of ACE is indeed associated with in-stent restenosis, and that this process is marked by the I/D polymorphism of the ACE gene [9]. This is consistent with the known effects of the ACE through the activation of angiotensin II (a potent vasoconstrictor and stimulus for cell proliferation) and the inhibition of bradykinin (a potent vasodilator and inhibitor of cell proliferation) [10]. In fact, the main cause of in-stent restenosis is neointimal hyperplasia [11]. A different case is that of restenosis after balloon dilatation in which the mechanism leading to chronic lumen loss is mainly vessel shrinkage [12], and a correlation with the I/D polymorphism has not been found [13,14].

The data on the phenotypic variance explained by the I/D polymorphism shown by Agerholm-Larsen and co-workers [1] are in full agreement with our previous

[☆] Response to: [Agerholm-Larsen B, et al., ACE Gene polymorphism explains 30–40% of variability in serum ACE activity in both women and men in the population at large. The Copenhagen City Heart Study. *Atherosclerosis* 1999;147:425–7].

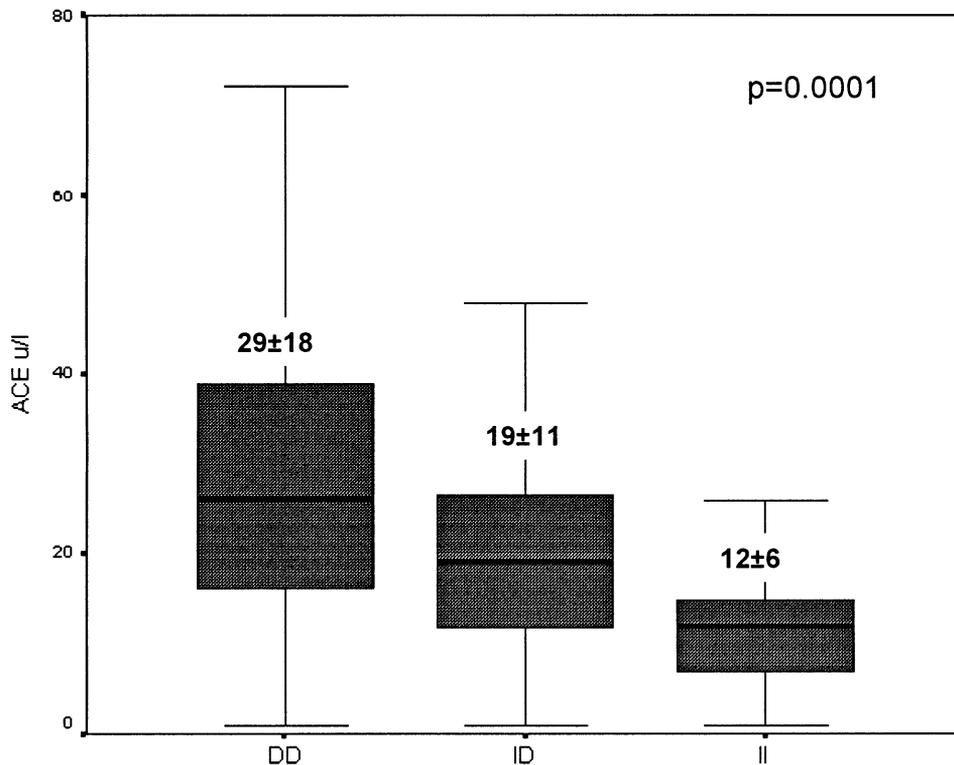


Fig. 1. Plasma ACE level according to the I/D polymorphism determined in a series of 657 non ACE-inhibited patients with coronary artery disease prior to coronary intervention (Differences of plasma ACE level between the three genotypes were tested by Kruskal–Wallis analysis of variance, ANOVA).

investigation performed in a much smaller population of ischemic patients [9]; furthermore, both studies are comparable since the same laboratory method for the determination of plasma ACE activity was used (quantitative kinetic determination at 340 nm with the use of FAPGG substrate from Sigma Diagnostics). Plasma ACE levels for each genotype, measured in a population of 657 patients with coronary artery disease, consistently support the codominant effect of the ACE gene (Fig. 1). Furthermore, the correlation between the phenotype (plasma ACE) and the pathologic condition investigated (in-stent restenosis) is clearly displayed in Fig. 2.

If ACE activity is involved in the proliferative process of in-stent restenosis, plasma ACE itself may be a more direct marker of these phenomena than the ACE genotype. In fact, although plasma and cellular ACE levels are genetically controlled, the I/D polymorphism may be only a marker in linkage disequilibrium with a functional mutation located within or close to the ACE gene [3].

Increasing evidence shows that ACE is up-regulated during the healing process that follows balloon injury of the arterial wall [7–15], and that the degree of the proliferative response is correlated to the deeper damage of the vessel caused by the use of metallic prosthesis or high expansion pressures [16]. The long-lasting ACE

activity in the cells of the in-stent restenotic plaque close to the metallic wires was demonstrated, for the first time, by our group in a preliminary report [17]; more complete results will follow in the near future.

Thus the example of the ACE I/D polymorphism makes apparent the association between a genetic marker, the corresponding phenotype (represented by the low, intermediate or high plasma level of the en-

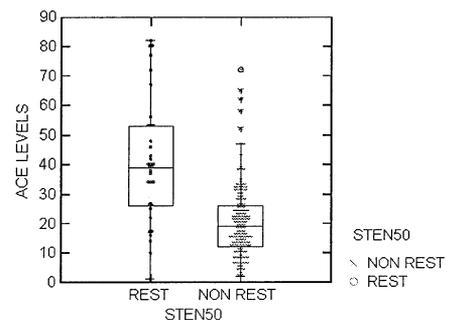


Fig. 2. Plasma ACE level in patients with restenosis (REST) and without in-stent restenosis (NON-REST) at the angiographic follow-up represented in a box plot. Restenosis is defined as a lumen obstruction $\geq 50\%$ (STEN 50). The box bounds the first and the third quartiles (interquartile range), encompasses 50% of the data, and includes the median (line within the box). Reproduced from Ribichini et al. [9] with permission. (Copyright 1998, Lippincott, Williams & Wilkins, USA).

zyme), and the pathophysiological effect expressed in different degrees of reparative initial proliferation after vessel injury. These findings are consistent with the observation that in-stent restenosis shows a bimodal distribution [18]; indeed patients undergoing stent implantation are distributed in two sub-populations with a different susceptibility for in-stent restenosis. This susceptibility to develop initial hyperplasia is patient-related and likely to be genetically determined.

If a strong association between a genetic marker and the risk of restenosis can be found, this knowledge could be implemented in the individual treatment strategy of patients. The role of the RAS seems more important in the proliferative phenomenon of in-stent restenosis than in other cardiovascular disorders, suggesting that patients with in-stent restenosis may represent an appropriate target for studying the role of the I/D polymorphism in coronary artery disease.

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