EDITORIAL COMMENT

The Race for ACE

A Simple Answer to the Controversial Puzzle of Angiotensin-Converting Enzyme (ACE) Polymorphisms*

Bernhard Schieffer, MD, Helmut Drexler, MD
Hannover, Germany

For over a decade now, clinical and experimental researchers have hunted for gene polymorphisms as a major cause of hypertension, coronary artery disease (CAD) or heart failure, such as angiotensin-converting enzyme (ACE) polymorphisms, which were accused to be a major contributor of cardiovascular diseases (1,2). Sequence variants of the components of the renin-angiotensin-aldosterone system were suggested to have significant influences on cardiovascular homeostasis (2,3). Both gene targeting and studies using transgenic mice suggested a critical role of the ACE gene in blood pressure regulation. Moreover, since an up-regulation of myocardial ACE gene expression has been observed in patients with heart failure, the ACE gene was one of the favorites within the known gene polymorphisms and a top candidate for cardiovascular researchers. Over 100 of base-pair (bp) switches, insertions (I) or deletions (D) were identified within the ACE-gene but only a few, namely the ACE I/D, D/D, or I/I polymorphisms seemed to have a significant impact on either CAD, hypertension or restenosis following coronary stenting (CS). The ACE I/D polymorphism of a 287-bp Alu element within the intron 16 of the ACE gene has attracted significant attention and has been extensively investigated in a spectrum of cardiovascular phenotypes because of its positive correlation with serum ACE activity (4). In addition, several studies showed a positive association between the ACE D/D genotype and an increased risk of myocardial infarction (2). Yet the association for hypertension, left ventricular hypertrophy, cardiomyopathy, CAD and restenosis after percutaneous transluminal coronary angioplasty remains controversial (4–6). Even meta-analysis of several studies, statistical mimics and studies in very selected patients populations provided a rather confusing puzzle of results which ultimately leaves it to the individual researcher, clinician, and journal reviewer whether or not to believe the presented results (2,3). Nevertheless, why should a single base pair polymorphism within the ACE gene result in such a complex pathophysiological problem like restenosis following CS?

In this regard, neointimal hyperplasia, but not lumen narrowing by arterial remodeling, controls the restenotic process after CS. It remains to be determined, however, whether chronic inflammatory processes induced by the stent’s metal struts or components of the renin-angiotensin system, namely ACE and angiotensin II are major contributors to the development of neointimal hyperplasia. Nevertheless, it is well accepted that polymorphisms within the ACE gene may modulate the process of in-stent restenosis. In addition, ACE polymorphisms may also affect the response to ACE inhibitors although there is no consensus as to which allele confers a more pronounced effect (7,8). The ACE DD genotype of the ACE gene is associated with higher circulating angiotensin II levels (4,9), but the pathological implication of enhanced angiotensin II levels with regard to in-stent restenosis remained unclear. Moreover, because plasma ACE activity is under genetic control of a functional mutation located within the ACE locus in almost complete linkage disequilibrium with the ACE ID polymorphism, the ACE ID genotypes were proposed to predict in-stent restenosis (10).

In this issue of the Journal, the study by Koch et al. (11) reported that carrier of the ACE DD polymorphism following CS are not at higher risk of restenosis or recurrent myocardial infarction when treated with ACE inhibitors. This study investigates the largest cohort of patients (2,222 ID genotype patients with symptomatic CAD, 622 ACE DD carrier) and conclusively shows that the ACE polymorphism is of minor clinical importance following CS in patients treated with ACE inhibitors. A variety of angiographic parameters were investigated including minimal lumen diameter, diameter stenosis or late lumen loss all of which were associated with ACE genotype. This association may appear puzzling with regard to a parameter such as in-stent restenosis or lumen gain with stenting that may also depend on skills and experience of the interventional cardiologists. However, the convincing results of the present study imply that pharmacological ACE inhibition can overcome genetic determination by ACE polymorphisms.

However, this analysis has several limitations. First, the duration of treatment with an ACE inhibitor prior to CS, the tissue specificity of the ACE inhibitor used or the daily dose varied. Yet, the beneficial effect was observed in 95% of the study population receiving either enalapril or captopril. Moreover, only 5% of the patients received ramipril, an ACE inhibitor with a particularly high tissue ACE affinity. These observations may be consistent with the notion that ACE inhibition, independent of its tissue ACE affinity elicits beneficial effects following CS and may overcome the deleterious effects of specific ACE polymorphisms.

*Editorials published in the Journal of the American College of Cardiology reflect the views of the authors and do not necessarily reflect the views of JACC or the American College of Cardiology.

From the Abteilung Kardiologie und Angiologie, Medizinische Hochschule Hannover, Hannover, Germany.
Moreover, this trial was not randomized and was performed in a retrospective manner (11). Clearly, randomized placebo-controlled trials without an ACE inhibitor are needed to answer this question. However, these studies will be difficult to design for ethical reasons since ACE inhibition by ramipril in patients with CAD showed a dramatic reduction of cardiovascular events in the HOPE trial (Heart Outcome and Prevention Evaluation) (12).

Finally, whether or not chronic angiotensin II type 1 (AT1)-receptor blockade will be equally effective as ACE inhibition in the prevention of in-stent restenosis in patients with various ACE polymorphisms is of particular clinical interest and needs further evaluation. It is speculated that ACE inhibition may be more effective in ACE DD carriers as compared to AT1-receptor blockade, based on observations that both, AT1-receptor blockade and ACE DD polymorphism are associated with higher serum levels angiotensin II. Therefore, it is postulated that AT1-receptor blockade in ACE DD carriers would increase angiotensin II levels in addition to already elevated angiotensin II serum levels. This latter would synergistically enhance detrimental cardiovascular effects of angiotensin II such as smooth muscle cell hyperplasia for in-stent restenosis.

Moreover, the ACE ID polymorphism is associated with higher ACE activity and should therefore be more effectively treated with ACE inhibitors with high tissue ACE affinity (e.g., quinapril or ramipril).

In summary, the study by Koch et al. (11) should have clinical implications, since it solves some of our problems with the ACE polymorphisms in the daily practice. With regard to in-stent restenosis, we do not have to select our treatment for patients with a specific genotype. The study by Koch et al. (11) provides a very practicable clinical solution: treat all patients with an adequate dose of an ACE inhibitor and this will overcome the negative impact of ACE polymorphisms on in-stent restenosis following CS.

REFERENCES