The Renin-Angiotensin System

Where Do We Stand, and What Is the Future?

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Pharmacologic modulation of the renin-angiotensin system (RAS) is the universally recognized first-line strategy in the treatment of hypertension and cardiovascular disease. According to evidence that has been accumulating, the widely used RAS modulators, the angiotensin-converting enzyme (ACE) inhibitors, appear to differ from the angiotensin II type 1 receptor blockers (ARB) not only in terms of their mechanisms of action at different levels of the RAS but also in terms of clinical outcomes.

The weight of this evidence is underscored by the article by Alistair S. Hall in which he discusses the role of different RAS modulators in the treatment of patients with an increased global cardiovascular risk. He draws attention to the distinct pharmacologic profiles and modes of action of ACE inhibitors and ARB as related to the outcomes of major clinical trials, suggesting the use of appropriate ACE-inhibitor regimens, although not ARB, for the prevention of cardiovascular events. This concept is supported by the results of the Heart Outcomes Prevention Evaluation (HOPE) study and the EUROpean trial on Reduction Of cardiac events with Perindopril in stable coronary Artery disease (EUROPA), which showed the efficacy of ramipril and perindopril, respectively, in the secondary prevention of major cardiovascular events.

At present, there is no proof that a beneficial outcome with any of the ACE inhibitors is caused either by a class effect or by a specific drug effect; but at least suggestive evidence is provided by Canadian investigators looking at claims-based, nonrandomized studies comparing the efficacy of different ACE inhibitors in reducing mortality among elderly survivors of myocardial infarction. These studies have clearly demonstrated the superiority of perindopril and ramipril compared with captopril, enalapril, fosinopril, lisinopril, and quinapril. Further evidence comes from the recently published results of the Prevention of Events with Angiotensin-Converting Enzyme inhibition (PEACE) study, in which trandolapril failed to provide further benefits in a population that was similar to that of EUROPA.

Supportive evidence at the level of pharmacokinetics but also “beyond” blood pressure control is examined by Roberto Ferrari in the PERindopril—Thrombosis, Inflammation, Endothelial dysfunction and Neurohormonal activation Trial (PERTINENT) on the antiproliferative, antithrombotic, plaque-stabilizing, and antioxidative properties of perindopril. Ferrari and colleagues found that the improvement in endothelial function brought about by perindopril correlated with the increase in bradykinin and nitric oxide (NO) levels, a mechanism partly explaining its ability to prevent the development and progression of atherosclerosis through ACE inhibition.

Stéphane Laurent points out that modern strategies for the treatment of hypertension should not only target blood pressure reduction but also normalize vascular structure and function. He provides evidence for the benefits of perindopril by its impact on aorta and carotid artery wall hypertrophy as well as on the structure and function of small resistance arteries and the heart.

We have explored the actions of angiotensin as a cytokine implicated in stepped-up cellular turnover, which we have proposed as a basis of accelerated aging in cardiovascular disorders. We propose that modulation of the RAS system may impact on accelerated aging in persons affected by cardiovascular diseases via its effects on proliferation and apoptosis. In fact, in the heart, ACE inhibitors and ARB selectively increase apoptosis in fibroblasts, an effect independent of angiotensin II type 2 (AT2) receptors and consistent with a possible role of angiotensin II type 1 (AT1) receptors in cell survival.

Bernard I. Levy has underlined the importance of differences between angiotensin system modulators affecting AT1 or AT2 receptors. He points out the need for more in-depth understanding of the role of AT2 receptors in the cardiovascular system. Accumulating evidence suggests that long-term AT2 stimulation, as a result of selective AT1 blockade, might exert a hypertrophic and antiangiogenic influence on cardiovascular tissues, especially on the myocardium.

We believe that the future will lead us to assess pharmacologically a relatively new player in the RAS, that is, angiotensin-converting enzyme–2 (ACE2). Its gene, local-
ized in human beings and rodents on chromosome X, was initially discovered in the search for blood pressure determinants on chromosome X and was later found to be a regulator of heart function. Currently there is evidence that ACE2 expression is increased in rats as well as in human beings after myocardial infarction; and from the recent results of Kittleson et al., ACE2 appears to be a component of shared genes in the development of heart failure. Evidence reported from Igase et al. has demonstrated that the AT1 receptor regulates ACE2 expression in the aorta. Based on our cohort of French Canadians from the Saguenay-Lac-St-Jean area in Quebec, Canada, we have uncovered a significant number of chromosomal loci for blood pressure and its metabolic component. In this population, our group recently obtained preliminary data on the association of polymorphisms in the ACE2 gene with hypertension and hypertension-related phenotypes.

Only the future will demonstrate whether safer and more effective drug development and use will be facilitated by the pharmacogenetic approach. It is entirely conceivable that high-throughput, high-density mapping, which now attains 500,000 single-nucleotide polymorphisms using microarray chip technology, will help us to determine alleles and haplotypes of susceptibility not only to disease but also to drug responses, and will potentially help to predict outcomes. It is entirely possible that novel technologies will modify not only pathophysiological research but clinical trials as well.

References


15. Levy BI. How to explain the differences between renin angiotensin system modulators. Am J Hypertens 2005;18:134S–141S.


