

ATHENS CARDIOLOGY UPDATE 2010

New Developments in the Field of RAS Inhibition

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The renin-angiotensin system (RAS) was extensively investigated and characterized throughout the first half of the 20th century. However, its contribution to the maintenance of high blood (BP) in essential hypertension and to the development of hypertensive cardiac complications remained under debate until the advent of the first pharmacologic probes capable of blocking its actions, namely the angiotensin receptor blocker (ARB) saralasin and the angiotensin-converting enzyme inhibitor (ACEI) teprotide in the early 1970's. Using these probes, we could demonstrate that even in normal-renin and low-renin hypertension, blockade of the RAS produced a fall in BP. And this fall was maximized if the patient had been previously submitted to sodium depletion by diuretics or low salt diet, which might produce only a small and possibly insignificant BP fall by itself, but rendered the hypertension RAS-dependent and far more responsive to RAS blockade.

In parallel, we had found that excess angiotensin II, either exogenous (in experimental animals) or endogenous, in various clinical settings, could produce significant cardiac and renal tissue damage, because the vasculature of these organs is particularly sensitive to the constricting effects of angiotensin. In particular, angiotensin excess was shown to produce widespread foci of necrosis and scarring of the myocardium, leading to replacement of myocardial tissue by fibrotic tissue, eventually progressing to ischemic cardiomyopathy and heart failure.

KEY WORDS: *angiotensin;*
hypertension; heart failure

Early clinical trials found that treatment of heart failure with ACEIs or ARBs leads to significant hemodynamic improvement in terms of increased cardiac output, decreased peripheral arterial resistance, decreased heart rate, increased coronary blood flow and diminished myocardial oxygen consumption. Subsequent large randomized long-term outcome trials with ACEIs or ARBs, such as the HOPE, EUROPA, LIFE, CHARM, etc., confirmed the functional and structural benefits of these therapeutic approaches and have now established treatment with an ACEI or ARB as mandatory therapy for patients with ischemic heart disease, as well as congestive or chronic heart failure.

It is also now universally accepted that initiation of RAS-suppressing therapy with an ACEI or ARB in patients with multiple cardiovascular risk factors, even not necessary including hypertension, offers long-term protection from ischemic heart disease, diastolic and systolic cardiac dysfunction, arrhythmias, as well as protection from renal insufficiency, cerebrovascular accidents and new onset type 2 diabetes mellitus.

Drugs that inhibit the RAS now include, in addition to the ACEIs and ARBs, a new class, the direct renin inhibitors (DRIs), of which only aliskiren is commercially available to date. Several clinical trials have shown aliskiren to be equally effective to ACEIs and ARBs in terms of BP lowering, cardioprotection and nephroprotection.

A large body of literature has now reported additional benefits of ACEI+ARB combination in selected patients, i.e., those with resistant hypertension on multidrug

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therapy and, in particular, those with progressive renal insufficiency and persistent proteinuria, with or without coexisting diabetes mellitus. All studies report better control of proteinuria—a surrogate marker of severity of the nephropathy—although success in terms of final outcomes, such as rate of progression to end-stage renal disease, cardiovascular events or overall morbidity and mortality, has not been consistent. Perhaps because of these mixed results, there has been no effort to proceed to a fixed combination of ACEI+ARB.

The advent of the novel class of DRIs presents a new possibility for dual blockade of the RAS. The pattern of changes in the various components of the RAS under direct inhibition of renin differs from that observed under chronic use of ACEI or ARB. Specifically, despite increase in renin concentration,

the levels of plasma renin activity, angiotensin I, angiotensin II and aldosterone remain consistently suppressed, with no evidence of “escape”. Therefore, a dual blockade of the RAS with a DRI plus either ACEI or ARB would be more absolute. Early studies of such combinations have produced promising results in terms of improved markers of progression of renal disease and severity of heart failure, without significant adverse events. However, there are not yet large longitudinal clinical trials to establish the benefits of such combinations in terms of important change in final outcomes. Notwithstanding these considerations, there is now a large body of clinical evidence supporting the long-term benefits of suppressed RAS for the protection of structure and function of vital organs.