

EDITORIAL

The Role of Double Renin-Angiotensin System Blockade

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ABSTRACT

Blockade of the renin-angiotensin system (RAS) is now recognized as an effective means of lowering blood pressure and protecting hypertensive patients from end-organ damage. There are three pharmacologic approaches to blockade of the RAS, with angiotensin-converting enzyme (ACE) inhibitors, with angiotensin II receptor blockers (ARBs), and with direct renin inhibitors. Clinical studies with the first two classes have shown that neither one achieves complete blockade of the RAS. However, an almost complete blockade of the RAS can be achieved by combination of an ACE inhibitor plus an ARB, albeit not with consistent benefits. A complete blockade of the RAS can also be obtained by combination of an ARB with a renin inhibitor. Further outcome trials are needed to show which combination offers long-term advantages in terms of end-organ protection.

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KEY WORDS: *hypertension; renin-angiotensin system; angiotensin-converting enzyme inhibitors; angiotensin receptor blockers; renin inhibitors; combination therapy*

LIST OF ABBREVIATIONS:

ACE = angiotensin-converting enzyme
Ang II = angiotensin II
ARB = angiotensin receptor blocker
RAS = renin-angiotensin system

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Blockade of the renin-angiotensin system (RAS)¹⁻⁸ is now recognized as an effective means of lowering blood pressure and protecting hypertensive patients from end-organ damage. There are nowadays three pharmacologic approaches to blockade of the RAS: with angiotensin-converting enzyme (ACE) inhibitors, introduced in the 1970s, with angiotensin II (Ang II) AT₁ receptor blockers (ARBs), introduced in the 1990s, and with direct renin inhibitors, a new class whose first agent, aliskiren,⁸ was introduced in 2006. Clinical studies with the first two classes have shown that neither one achieves complete blockade of the RAS. With chronic use of ACE inhibitors, there is a gradual return of Ang II towards pretreatment levels because enzymes other than ACE, e.g., chymase and others, can cleave off two aminoacids from the decapeptide angiotensin I, even though there is no evidence of “escape” in terms of blood pressure control. With ARBs there is a partial blockade of AT₁ receptors of variable degree and duration, depending on the affinity of each agent for the receptor and of the duration of the blockade (surmountable or insurmountable).

It has now been shown that an almost complete blockade of the RAS can be achieved by combination of an ACE inhibitor plus an ARB.⁹ There has been clinical evidence that a more complete blockade of the RAS may offer benefits in terms of end-organ protection even beyond those of optimal blood pressure control, e.g. by arresting or reversing the progression of diabetic or other nephropathies (COOPERATE trial).¹⁰ One such trial, the ONTARGET study of telmisartan and ramipril combination, published recently,¹¹ showed that combination of the two agents achieved

a small additional blood pressure lowering compared to monotherapy with either one. Not surprisingly, telmisartan tended to be better tolerated than ramipril. However, there was no advantage with the combination in terms of outcome; in fact, there was a trend to increased adverse reactions, especially renal impairment, which was puzzling. Nevertheless, these data are not much different from those reported in the past for treatment of acute myocardial infarct with valsartan and captopril alone or in combination (the VALIANT study).¹² This is in contrast to two heart failure studies of ACEI plus ARB combinations, the Val-HeFT and CHARM trials, in which the ARBs valsartan and candesartan, respectively, showed additional benefits when added to ACE inhibitor therapy.^{13,14}

A complete blockade of the RAS can also be obtained by combination of an ARB with a renin inhibitor. One such study¹⁵ demonstrated that combination of the ARB valsartan with the renin inhibitor aliskiren, produced a significantly greater blood pressure decrease than either agent given as monotherapy. Such combination would be particularly desirable in cases, where total suppression of the RAS is desirable, but the patient is intolerant to ACE inhibition (because of cough or angioedema). Further outcome trials are needed to show whether ARB plus renin inhibitor combination offers additional long-term advantages in terms of end-organ protection when compared to different drug combinations achieving the same degree of blood pressure lowering.

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