

EDITORIAL COMMENT

Do We Need Yet Another Blocker of the Renin-Angiotensin System?*

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As of the latest count in the U.S., there are 10 angiotensin-converting enzyme (ACE) inhibitors and 7 angiotensin receptor blockers (ARBs) in the therapeutic arsenal. Although in meta-analyses some outcome differences were documented between ACE inhibitors as a class and ARBs as a class, the main differences within both classes seem to be mostly related to pharmacokinetics, perhaps with the exception of the antihypertensive efficacy that has been shown to vary from one ARB to another by a very few millimeters of mercury (1). To merit the label “better,” a new drug has to be either more efficacious or safer (or both) than existing drugs. In hypertensive cardiovascular disease,

See page 1157

more efficacious means a better reduction of heart attacks, strokes, and end-stage renal disease, and safer means fewer adverse effects than ARBs or ACE inhibitors. Some but not all ACE inhibitors and ARBs have been shown to confer protection of the heart, the kidneys, and the brain. As a class, ACE inhibitors seem to be somewhat more effective than ARBs for cardioprotection, whereas the reverse may be true for cerebroprotection. However, whether and to what extent such protection is independent of the fall in blood pressure remains the subject of an ongoing debate.

With regard to safety, most clinicians have the impression that both classes are well tolerated, the only adverse effect being cough (common) and angioedema (rare) with the

ACE inhibitors. There seems little doubt that the new class (i.e., renin inhibitors [2]) will beat the ACE inhibitor in terms of side effects. However, to outdo the ARBs either in terms of efficacy or safety will be a formidable challenge. One may therefore appropriately ask whether the introduction of yet another class of renin-angiotensin-aldosterone system (RAAS) blockers will fulfill a clinical need or merely add to the bottom line of the product manufacturer.

A comparison of the biochemical features clearly shows that there are differences among the 3 drug classes (Table 1). The question is whether any of these differences will ultimately translate in clinically meaningful differences in outcome. In other words, for the same decrease in blood pressure, will renin inhibitors confer more organ protection than do ARBs or ACE inhibitors, i.e., is the patient at a lesser risk of heart attack, congestive heart failure, stroke or renal failure? This question has not been conclusively answered in a head-to-head comparison between an ACE inhibitor and an ARB. It therefore seems unlikely that a pharmaceutical company would be courageous enough to mount a large outcome trial comparing a renin inhibitor with either an ARB or an ACE inhibitor. The most likely scenario is that practicing physicians will periodically be spoon-fed small potboiler studies showing some improvement of surrogate end points (such as left ventricular mass or albuminuria) with renin inhibitors.

The study by Oh et al. (3) in this issue of the *Journal* shows that the antihypertensive efficacy of aliskiren is very similar to what we have seen with ACE inhibitors and ARBs. A 4-fold escalation of the dose (from 150 to 600 mg) merely yielded a 2.5 or 2.2 mm Hg additional fall in blood pressure. When placebo was subtracted from the blood pressure fall with the 2 well-tolerated aliskiren doses (150 and 300 mg) a single-digit decrease in systolic and diastolic pressure was observed. Thus, similar to ACE inhibitors and ARBs, the dose response of blood pressure with aliskiren seems to be shallow and to plateau at or even below the FDA-approved maximal dose.

However, renin inhibitors could also be attractive if they were shown to have fewer adverse effects but similar organ protection and outcome as ACE inhibitors and ARBs. We should remember that angioedema is a rare but potentially fatal adverse effect of ACE inhibitors. Given that millions of patients are exposed to these drugs, a substantial number of drug-associated fatalities can be estimated to occur every year (4). In contrast, ARBs are exceedingly well tolerated and have often been shown to have even fewer adverse effects than placebo. The fact that ARBs are well tolerated allows us to test the hypothesis that some features of target organ protection may not be related to the fall in blood pressure. The hypothesis of enhanced organ protection with higher than FDA-approved doses is currently explored by 3 different studies with 640 mg valsartan, 128 mg candesartan, and 900 mg irbesartan. Should this concept bear fruit and indeed enhanced target organ protection be conferred

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Table 1 Endocrine Differences Among Renin-Angiotensin-Aldosterone System Blockers

	ACE Inhibitors	ARBs	Renin Inhibitors
Enzymes			
Plasma renin activity	Increased	Increased	Inhibited
Plasma renin concentration	Increased	Increased	Increased
Plasma ACE/tissue ACE	Inhibited	Not inhibited	Not inhibited
Substrate concentrations			
Angiotensinogen	Decreased	Decreased	No change
Ang I	Increased	Increased	Decreased
Bradykinin	Increased	No change	No change
End products			
Ang II	Decreased	Increased	Decreased
Non-ACE-dependent Ang II	Present	Blocked	Blocked
Ang III, Ang IV	Decreased	Increased	Decreased
Ang ₍₁₋₇₎	Increased	Increased	Decreased
Aldosterone	Decreased	Decreased	Decreased

ACE = angiotensin-converting enzyme; Ang = angiotensin; ARB = angiotensin receptor blocker.

by high ARB doses, then the question of combination therapy efficacy and safety would have to be reassessed. Will the addition of a renin inhibitor to high-dose ARB and/or ACE inhibitor therapy further enhance target organ protection, and, most importantly, will susceptible patients (i.e., those with diabetes and chronic renal failure) tolerate such combinations? That said, it is now clear that (pro)renin receptors of various sorts exist and that binding of prorenin to at least one of these receptors is associated both with increased angiotensin II generation at the target cell surface and with direct stimulation of intracellular second messenger signaling pathways (5). Indeed, Luetscher et al. (6), more than 20 years ago, related prorenin levels to microvascular complications in diabetic patients. In diabetic animal models, prorenin binding to this receptor has been shown to exert angiotensin-independent, unlike ACE inhibitors or ARBs, pathologic effects in target tissues such as the kidney (5). If renin inhibitors, unlike ACE inhibitors or ARBs, effectively block either the enhanced generation of angiotensin II at the cell surface receptor or alter the ability of prorenin to directly signal at the receptor, a new mechanism for the inhibition of the cardiovascular complications of diabetes—a condition associated with high circulating prorenin concentrations—and hypertension could be at hand. It will be interesting to see how this plays out (5).

With regard to adverse effects of renin inhibitors, the report of Oh et al. (3) is not entirely reassuring. Diarrhea was a dose-dependent adverse effect and occurred in more than 10% of patients with the 640 mg dose. Gastrointestinal adverse effects with any RAAS blocker invariably raise the issue of intestinal angioedema which has been reported with ACE inhibitors (4,7). We also should consider that long-term adverse effects have been poorly documented with all antihypertensive drug classes with the exception perhaps of the diuretics and beta-blockers. The fact that these drugs are “safe” when taken for a few months or a year does not allow us to extrapolate that they will be safe when taken for years and decades which is common for antihypertensive therapy (8).

Modern antihypertensive therapy has spoiled patients and physicians. Blood pressure can now be lowered with comfort and convenience in most patients. Although the arrival of a new drug class such as the renin inhibitors is exciting and should be welcomed, its exact place in the antihypertensive arsenal will depend on extensive documentation of efficacy and safety.

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