Antagonists and inhibitors of the renin-angiotensin system for the treatment of hypertension

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The renin-angiotensin system has two roles in clinical hypertension: its vasoconstrictor properties directly govern blood pressure, and its actions on arterial smooth muscle, connective tissue, and endothelial integrity affect cardiovascular prognosis. Additionally, the direct actions of angiotensin II on the function and structure of the heart and renal vasculature influence clinical events. Angiotensin-converting enzyme (ACE) inhibitors have produced functional and clinical outcome benefits in clinical trials of patients with congestive heart failure, systolic dysfunction after myocardial infarction, and diabetic nephropathy. Similar favorable trends have been noted in observational studies in hypertension. Because such enzymes as chymase can substitute for ACE, the ACE inhibitors may not completely block angiotensin II formation, although they enhance bradykinin accumulation and secondarily stimulate nitric oxide and vasodilatory prostaglandins. Angiotensin II receptor blockers (ARB) selectively block the angiotensin II type 1 (AT1) receptor that not only mediates the known effects of angiotensin II but, according to recent reports, might be responsible for sequestering angiotensin II molecules in renal and cardiac cells. Moreover, by increasing plasma concentrations of angiotensin II, the ARB stimulate the unblocked angiotensin II type 2 (AT2) receptors, which-if they exist in meaningful numbers in human hypertension-mediate additional vasodilatory and antiproliferative effects. The contrasting actions of these two classes of drugs might be clinically relevant. For example, they may have additive antihypertensive efficacy; they have differing effects on renal plasma flow; and in a small pilot study of patients with congestive heart failure, the ARB demonstrated an apparent advantage in survival. Ongoing clinical trials will try to determine whether the effects of ARB can equal or even exceed the beneficial effects of ACE inhibitors on cardiovascular prognosis.