Does Renin Cause Cardiovascular & Kidney Disease in Non-hypertensive Patients?

PJR: As Hans Selye was fond of advising me, theories are not important, only facts are. Some theories are meritorious for their heuristic value, in that they encourage others to discover new facts that lead to improved theories. In that regard, the existing facts confirm your hypothesis about the role of renin in essential hypertension. Studies now show that antirenin drugs are effective in treating or preventing cardiovascular and kidney disease not only in hypertensive patients but others with normal blood pressure. Doesn’t this imply a much larger role for renin in these disorders than is currently recognized?

JHL: You are absolutely correct. The antirenin drugs (ACE inhibitors, ARB’s and beta blockers) have been shown to have salutary effects on proteinuria due to kidney disease that are not achieved with other antihypertensives like thiazides and calcium channel blockers. Thus, the angiotensin II receptor blockers losartan and irbesartan were recently approved for the treatment of diabetic nephropathy in hypertensives with type 2 diabetes. In addition to diabetes, diuretics can cause acute interstitial nephritis, their overuse is the most common cause of dehydration in patients with diabetic nephropathy and they are contraindicated in chronic renal failure. Yet, JNC VII does not consider diabetes or impaired kidney function to be a contraindication to thiazide therapy and never mentions the benefits of ACE inhibitors or ARB’s in this regard.

As you pointed out, ACE inhibitors reduce albumin excretion in both normotensive and hypertensive patients with type 1 or type 2 diabetes and angiotensin II receptor blockers have also been shown to reduce albuminuria in type 2 diabetes. A recently published double-blind, randomized crossover trial reported that adding the ARB candesartan to treatment with maximal recommended doses of ACE inhibitors provided superior renoprotection in diabetic nephropathy that was completely independent of blood pressure changes. Candesartan has also been shown to reduce cardiovascular mortality and hospital admissions for congestive heart failure in a broad spectrum of patients already receiving "best treatment” with other drugs. The EUROPA study just reported that the ACE inhibitor perindopril reduced the risk of myocardial infarction and death in patients with stable coronary artery disease, including those with a history of a past myocardial infarction and angina so significantly that it should be considered for chronic therapy in all patients with coronary disease. It seems quite possible that we have only scratched the surface with respect to the role of renin in the pathophysiology of vasculotoxic events in normotensive patients at increased risk from diabetes, cardiovascular or renal disease. Gaining insight into what induces overactivity of renin-angiotensin-aldosterone cascade in all these events could be the key to learning how to prevent or treat essential hypertension. At present, blocking or counteracting these harmful responses with antirenin drugs is the best approach based on our research.

JR: I suspect that the primary stimulus will be found to originate in the brain, possibly the cerebral cortex. If this proves true, stress could play a crucial role in hypertension, as Hans Selye always alleged. - Stay tuned!

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