When Blockade of the Renin-Angiotensin System Becomes a Two-Edged Sword

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Why do some drugs that inhibit the renin-angiotensin system (RAS) fail to provide cardiovascular protection or possibly even cause harm when added to standard therapies in high-risk patients?¹ ² Why, in comparison with a single drug that inhibits the RAS, is the combination of 2 RAS inhibitors no more effective or even possibly harmful?² ³ ⁴ The reasoned analysis by Sealey et al. ⁵ in this issue of the Journal suggests that excessive sodium-volume depletion caused by overzealous use of diuretics and salt restriction in subsets of patients might help explain why, in some clinical trials, additional treatment with either 1 or 2 RAS inhibitors has failed to improve cardiovascular outcomes or even appeared to be harmful.

Excessive sodium-volume depletion and cardiovascular risk

Sealey et al. ⁶ observed that, compared with patients with relatively low or normal plasma renin activity (PRA) levels, patients with high PRA levels in various clinical trials tended to have greater cardiovascular mortality rates and evidence of greater sodium-volume depletion: lower blood pressures (BPs), lower brain natriuretic peptide levels, and higher blood urea nitrogen and uric acid levels. Use of diuretics was also greater in subjects with high PRA than in those with lower PRA. Although RAS-blocking drugs can cause reactive rises in PRA, the use of RAS-blocking drugs was not greater in the subjects with high PRA. Sealey et al. ⁶ surmise that, in subsets of patients, excessive diuretic use and/or dietary salt restriction induced high PRA levels and contributed to the greater sodium-volume depletion and greater cardiovascular risk. They suggest that in clinical trials of RAS-blocking drugs in high-risk patients, adverse outcomes in the subjects with high PRA and excessive sodium-volume depletion may have offset positive outcomes in other subjects, thereby causing the net trial outcomes to be neutral or even negative. In a subanalysis of the HOPE trial, Verma et al. ⁷ observed that subjects in the highest PRA quintile at baseline had an increased risk of cardiovascular death, even after adjusting for effects of baseline diuretic use and for subsequent allocation to ramipril treatment. However, Verma et al. ⁷ did not adjust for the extent of dietary salt restriction or the strength/dose of diuretics used by those in the different PRA quintiles.

Other prominent investigators have warned that “diuretic therapy is an exceedingly common therapeutic approach in essential hypertension and that diuretic-induced volume depletion may be sufficient to cause harm in some patients on dual RAS blockade.” ⁸ Looking at this from another angle, Sealey et al. ⁶ emphasize the hazards of RAS blockade in normotensive patients with high cardiovascular risk who are excessively volume depleted. Why would one think of administering a drug that blocks the RAS to a patient who is normotensive (i.e., to someone whose BP is inherently normal or is already under good control with other antihypertensive drugs)? The reason is that use of these agents is indicated in many patients who do not necessarily have elevated BP. Some RAS inhibitors are approved for reducing risk of cardiovascular events in patients who either have a history of cardiovascular disease or have diabetes and at least 1 other cardiovascular risk factor, regardless of whether hypertension is present. Some RAS inhibitors are also approved for treatment of heart-failure patients or for treatment of patients after myocardial infarction, whether or not hypertension is present.

Use of PRA to identify patients with excessive sodium-volume depletion

In drug package inserts, the pharmaceutical companies warn about the risks of prescribing RAS blockers to patients who are sodium-volume depleted. The package inserts specifically guide clinicians to be careful about giving these drugs to patients taking high doses of diuretics. However, the drug manufacturers offer little or no practical advice on how to determine which patients being considered for treatment are excessively sodium-volume depleted. Sealey et al. ⁶ contend that such patients can be identified by their high PRA levels. Specifically, in patients with normal BP who are not taking an RAS-blocking agent, Sealey et al. ⁶ consider PRA levels above the normal range as strong evidence of excessive sodium-volume depletion. In patients with normal BP who are taking an RAS-blocking agent, a very high PRA level might also reflect excessive sodium-volume depletion. However, RAS-blocking agents can cause reactive rises in PRA in the absence or presence of sodium-volume depletion. Thus, in a patient taking
a drug that inhibits the RAS, it may be difficult to discern whether an increased PRA level is reflecting the presence of sodium-volume depletion in addition to a reactive rise in PRA secondary to RAS blockade.

Increased PRA: both a warning sign and protective response in patients with excessive sodium-volume depletion

The associations discussed by Sealey et al.\(^6\) do not establish any cause-and-effect relationships or indicate whether use of PRA measurements would have improved cardiovascular outcomes in clinical trials of RAS inhibitors. However, the observations noted by Sealey et al.\(^6\) become more compelling when considered together with the strong teleological reasons discussed below against administering an RAS blocker to a patient with a normal level of BP and a high PRA.

Sealey et al.\(^6\) emphasize that in patients with BP controlled on diuretics or salt restriction or both, a high PRA level not only is an indicator of excessive sodium-volume depletion but also helps protect against circulatory risks posed by excessive sodium-volume depletion (i.e., low BP, reduced organ perfusion pressure, and glomerular hypofiltration). Higher rates of aldosterone secretion induced by increased activity of the RAS also help to protect against the threat of hyperkalemia created by excessive sodium-volume depletion and reduced delivery of sodium and water to potassium secretory sites in the distal nephron. In a high cardiovascular risk patient with a normal level of BP and a high PRA, administration of an RAS inhibitor is not advisable because it will interfere with the effects of the very system that has been activated to protect against the threat of hyperkalemia.

Use of PRA to guide correction of excessive sodium-volume depletion

Sealey et al.\(^6\) suggest that before a high cardiovascular risk patient with a normal BP level and a high PRA be given an inhibitor of the RAS, clinicians should correct excess sodium-volume depletion by gradually tapering natriuretic drugs and or relaxing dietary salt restriction in a manner that reduces PRA levels into the medium range (0.65–4.5 ng/ml/h), provided this does not cause unacceptable increases in BP or hazardous fluid retention. Thus, in high cardiovascular risk patients with BP in the normal range, Sealey et al.\(^6\) propose that measurements of PRA may be helpful for (i) identifying which individuals are likely to be more sodium-volume depleted than necessary and (ii) guiding the correction of excess sodium-volume depletion before initiating treatment with an RAS inhibitor.

It is unlikely that randomized trials will ever be performed to test the clinical outcome benefits and cost effectiveness of using PRA measurements to identify and guide management of normotensive, high cardiovascular risk patients with excessive volume depletion. However, in light of the analysis of Sealey et al.\(^6\) and knowledge of the fundamental biologic role of the RAS, it is logical to consider supplementing clinical judgment with measurements of PRA when contemplating treatment of normotensive, high cardiovascular risk subjects with inhibitors of the RAS. Of course, one should also be cognizant of the costs for PRA measurements. Although costs for a PRA measurement can vary among testing sites, $30 is considered by the Health Care Blue Book to be the fair price for a renin assay, and it is also the National Payment Limit price set by the Medicare Clinical Laboratory Fee schedule.\(^9,10\) In situations where hospital-based laboratories are charging excessive test prices to help cover high overhead costs throughout the medical center, it may be possible for clinicians to refer patients to an outside commercial laboratory where the test charges are more reasonable.

DISCLOSURE

T.W.K. is a recipient of lecture honoraria from and a stockholder in pharmaceutical companies with financial interests in drugs that inhibit the renin-angiotensin system. T.W.K. is a director of the clinical chemistry laboratory at the University of California–San Francisco (UCSF) and does not receive any income related to renin testing performed on UCSF or non-UCSF patients.

REFERENCES