Renin-Angiotensin System Blockers May Create More Risk Than Reward for Sodium-Depleted Cardiovascular Patients With High Plasma Renin Levels

Jean E. Sealey,1 Michael H. Alderman,2 Curt D. Furberg,3 and John H. Laragh4

BACKGROUND
Four recent reports revealed differences in survival rates among treated cardiovascular patients taking renin-angiotensin system–blocking drugs. Patients with higher on-treatment plasma renin activity (PRA) levels died sooner of cardiovascular mortality than those with lower levels. We investigated whether excessive sodium depletion might have induced the higher PRA levels and contributed to the greater morbidity and mortality.

METHODS
Using published data, ranges of PRA, blood pressures, drug usage, and biochemical parameters were compared among various groups of cardiovascular patients.

RESULTS
We showed (i) that PRA levels are usually medium to low in treated cardiovascular patients, but are sometimes abnormally high, (ii) that excessive sodium depletion can induce such high PRA levels, (iii) that the higher PRA patients exhibited evidence of sodium depletion: lower blood pressures, more frequent natriuretic drug usage, lower N-terminal pro b-type natriuretic peptide (NT-proBNP), and higher blood urea nitrogen and uric acid levels, with similar usage of renin-angiotensin blocking drugs.

CONCLUSIONS
We hypothesize that patients with high on-treatment PRA levels die sooner of cardiovascular events because they are excessively sodium-volume depleted. Moreover, renin-angiotensin system–blocking drugs may be harmful in such patients because they can functionally interfere with the effects of reactive rises in PRA that are triggered to prevent potentially dangerous falls in blood pressure, increases in plasma potassium, and falls in glomerular filtration rate. Careful liberalization of salt intake and subtraction of natriuretic drugs, sufficient to reduce reactive hyperreninemia without inducing unacceptable increases in blood pressure, might benefit such patients and decrease risk of adverse effects from drugs that block the renin-angiotensin system.

Keywords: angiotensin-converting enzyme inhibitor; angiotensin receptor blocker; blood pressure; cardiovascular mortality; diuretics; hypertension; hypotension; plasma renin; PRA; sodium depletion.

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It has long been observed that hypertensive patients with high pretreatment plasma renin activity (PRA) levels are at greater risk of cardiovascular disease (CVD).1–3 Moreover, renin-angiotensin system–blocking drugs have been shown to dramatically reduce cardiovascular mortality and morbidity4–9 in patients with CVD. In fact, cardiovascular patients are said to have “compelling indications” for taking these drugs.10 At the same time, most such patients are concurrently taking natriuretic drugs and/or low-salt diets to remove excess body fluids.10–12 If the association between high PRA levels and cardiovascular risk represents a causative relationship, this creates a paradox because both renin-angiotensin system–blocking drugs and natriuretic drugs increase PRA13 but can also protect from CVD. Moreover, recent data from patients with a variety of cardiovascular conditions show that these higher on-treatment PRA levels are associated with higher rates of cardiovascular mortality than lower PRA levels, even in those patients already taking renin-angiotensin system–blocking drugs.14–17

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The purpose of this report is to examine the clinical implications of reactively high PRA levels occurring in treated cardiovascular patients. Our hypothesis is that natriuretic drugs and low-salt diets are used excessively in subgroups of patients, causing sodium-volume depletion and reactively rising high PRA levels, and that such patients develop increased risk of cardiovascular mortality, especially when they are also treated with renin-angiotensin system–blocking drugs. This view is based on physiological studies showing that an active circulating renin-angiotensin system is critical to cardiovascular health in the sodium-depleted state because it prevents blood pressure (BP) from falling too low; it sustains higher glomerular filtration rate (GFR) levels via greater efferent than afferent arteriolar vasoconstriction, and it increases adrenal aldosterone secretion to protect from hyperkalemia. This view is also supported by reports that dual renin-angiotensin system blockade is associated with increased risk of hypotension, hyperkalemia, and deteriorating renin function.

We therefore hypothesize that both the reactively high PRA levels and the increased cardiovascular risk are caused by concurrent sodium depletion induced by excessive use of natriuretic drugs and/or low-salt diets. By monitoring PRA levels during natriuretic treatment, cases of iatrogenic hyperreninemia may be identified. Such patients might benefit from restoration of vascular volume by curtailing dietary sodium restriction and/or subtracting natriuretic drugs until PRA levels return to the medium to lower ranges that are associated with improved survival.

METHODS

In this report, we review published data that are relevant to the hypothesis that when sodium depletion becomes excessive, PRA values will exceed the normal range of 0.65–4.5 ng/ml/h and, in that setting, renin system blockade may actually increase cardiovascular mortality. We first review PRA levels in normal subjects and in untreated hypertensive patients. We then review the effect of different degrees of sodium depletion on PRA and BP levels in low- and medium-renin hypertensive subjects.

Finally, we analyze data from 4 recent reports of PRA levels in treated cardiovascular patients to determine whether the patients with the highest plasma renin who had greatest cardiovascular mortality could have been reactively sodium-depleted (Table 1). Muhlestein et al. and Tomaschitz et al. reported plasma renin measurements in observational studies of cardiac catheterized patients; blood was drawn before the procedure. Verma et al. reported PRA data from patients with stable chronic vascular disease and/or diabetes enrolled in the Heart Outcomes Prevention and Evaluation (HOPE) trial currently taking drugs other than renin-angiotensin system blockers; blood was drawn before randomization to either ramipril 10 mg or placebo. Masson et al. reported PRA measurements in heart-failure patients from the Valsartan Heart Failure (Val-HeFT) trial who were currently taking drugs that included an angiotensin converting enzyme inhibitor (ACEI); blood was drawn before randomization to either valsartan 160 mg or placebo.

To normalize PRA results, PRA data from Verma et al. and Muhlestein et al. were multiplied by 1.7 to adjust for the higher concentration of angiotensin I (Ang I) reference standards in the GammaCoat Plasma Renin Activity Radioimmunoassay kit (Diasorin, Stillwater MN). Masson et al. measured PRA using a kit originally sold by New England Nuclear, then marketed by Perkin-Elmer. This kit consistently gives low values because of a 3-fold dilution of plasma angiotensinogen. However, because of the variability of this effect, unadjusted values are reported herein. Plasma renin concentration data from Tomaschitz et al. were divided by 8.0 to convert from μU/ml to ng/ml/h.

Statistical analyses were derived from the original publications. Data from Gonzalez et al. were reanalyzed as quartiles with P values derived from Spearman rho correlation analysis.

RESULTS

Ranges of PRA levels in normal subjects and in untreated and treated hypertensive patients and in patients with CVD

Normal subjects. Although the normal range of PRA levels is influenced by sodium intake, traditionally we have defined the normal range as 0.65–4.5 ng/ml/h. Because, in this report, data from treated patients were analyzed in tertiles, quartiles, or quintiles, we reanalyzed data from the normal subjects in the same three ways (Table 2). The data are from a group of 144 normotensive subjects who were studied yearly at the worksite over several years and had 24-hour urinary sodium excretions between 80 and 200 mmol/day. The median PRA levels of the lowest PRA tertiles, quartiles, and quintiles were 0.65, 0.57, and 0.50 ng/ml/h respectively, whereas the median PRA levels of the highest tertiles, quartiles, and quintiles were 4.0, 4.7 and 5.0 ng/ml/h, very similar to our traditional normal range.

Hypertensive patients. Median PRA levels in PRA quartiles of untreated hypertensive patients reported by Gonzalez et al. were all lower than those of the normal subjects (51%, 60%, 73%, and 85%) (Table 2). Median PRA levels of the three lowest quartiles of treated hypertensive patients reported by Sim et al. were also subnormal (35%, 51%, and 81%), but the highest renin group was 195% of normal. Thus, in contrast with untreated hypertensive patients, close to a quarter of treated hypertensive patients had high PRA levels.

Cardiovascular patients. Median PRA levels in quartiles of patients undergoing cardiac catheterization reported by Tomaschitz et al. (Table 2) were subnormal, except for that of the highest group (79%, 66%, 81%, and 104%). Muhlestein et al. reported PRA data in tertiles of patients with coronary artery disease; the two lowest tertiles were subnormal, whereas the highest was elevated: (44%, 71%, and 186% of normal). Verma et al. reported the PRA levels of cardiovascular patients from the HOPE trial in quintiles; all but the highest renin group were low (58%, 59%, 67%, 74%, and 118%). Masson et al. also reported their heart-failure data from the Val-HeFT trial in tertiles; all values were elevated (130%, 252%, and 568% of normal). Thus, the heart-failure...
<table>
<thead>
<tr>
<th>References</th>
<th>Trial or observational study</th>
<th>Year of first publication</th>
<th>Year of publication of PRA data</th>
<th>Diagnosis</th>
<th>% with hypertension</th>
<th>No. with PRA measurement</th>
<th>Average duration of follow-up</th>
<th>% antihypertensive medications when PRA was measured</th>
<th>Subsequent meds</th>
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<td>Muhlestein et al.</td>
<td>Intermountain Heart Collaborative Study</td>
<td>2010</td>
<td>2010</td>
<td>Coronary artery disease</td>
<td>63%</td>
<td>1,165</td>
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<td>2011</td>
<td>Referred to coronary angiography</td>
<td>68%–79%</td>
<td>3,303</td>
<td>9.9 years</td>
<td>ACEI 83%–94% ARB 3%–7% Beta blocker 56%–74% CCB 14%–17% Diuretics 7%–25%</td>
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<td>2011</td>
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<td>41%</td>
<td>2,913</td>
<td>4.5 years</td>
<td>ACEI/ARB 0% Beta blocker 64%–29% Diuretics 7%–25%</td>
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<td>Val-HeFT trial</td>
<td>2001</td>
<td>2010</td>
<td>Heart failure NYHA class II, III, or IV</td>
<td>6%–7%</td>
<td>3,978 on ACEI</td>
<td>23 months</td>
<td>ACEI 100% Beta blocker 43%–30% Diuretics 78%–92% Spirolactone 2%–7%</td>
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<td>2011</td>
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<td>2012</td>
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<td>7,887</td>
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**Abbreviations:** ACEI, angiotensin converting enzyme inhibitor; ARB, angiotensin receptor blocker; CCB, calcium channel blocker; CV, cardiovascular; HOPE, Heart Outcomes Prevention and Evaluation; LURIC, Ludwigshafen Risk and Cardiovascular Health Study; NA, Not available; NYHA, New York Heart Association; Val-HeFT, Valsartan Heart Failure.
Table 2. Median PRA and mean SBP, BUN, uric acid, eGFR and NT-ProBNP in renin subgroups

<table>
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<tr>
<th>Renin tertiles, quartiles, or quintiles</th>
<th>Patient characteristics</th>
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Bold values indicate that plasma renin activity (PRA) levels are higher than upper limit of the normal range (4.5 ng/ml/h).

Abbreviations: BUN, blood urea nitrogen; cath, catheterized patients; eGFR, estimated glomerular filtration rate; HT, hypertension; NA, data not available; NS, not significant; NT-ProBNP, N-terminal pro b-type natriuretic peptide; SBP, systolic blood pressure.

*PRA data multiplied by 1.7 to adjust for differences in assay reference standards.

**Plasma renin concentration (PRC) data converted to PRA by dividing by 8.0.

c pmol/L.

*P < 0.05; **P < 0.01; ***P < 0.001.
patients enrolled in the Val-HeFT trial stood out from the rest: they had higher PRA levels across the spectrum (Table 2). Nonetheless, even in the heart-failure patients, the lowest PRA tertile remained at the low end of the normal range (1.0 ng/ml/h).

Overall. Altogether these data show heterogeneity of PRA levels among patients with hypertension and/or CVD. The PRA levels of individual patients ranged more than 10-fold, with large fractions of patients having medium to low PRA levels but many having PRAs that exceed those of normal subjects or of untreated hypertensive patients.

Effect of sodium depletion on PRA and BP levels in low- and medium-renin hypertensive patients

In this section, we demonstrate heterogeneity of both baseline and reactive increases in PRA levels in hypertensive patients who were progressively sodium-volume depleted. Published data13 of a study of low- and medium-renin hypertensive patients are reviewed.

Six low-renin and 6 medium-renin hypertensive patients (Figure 1) were instructed by a dietician as outpatients on how to conform to 6 protocols designed to achieve increasing degrees of sodium depletion; 3 different sodium diets (250, 100, or 35 mmol/day) were each given for 3 weeks without a diuretic and then again with a diuretic. Urinary sodium excretion measurements confirmed that the diets were adhered to as instructed. The 6 different protocols were given in random order. Sodium depletion increased from the left to right side of each box.

The low- and medium-renin hypertensives differed in systolic BP (SBP) and PRA responses to the same degree of sodium depletion. Thus, when dietary sodium intake was reduced from 250 to 100 mmol/day in medium-renin patients, SBP fell by 17 mm Hg and PRA levels increased from 1.2 to 2.0 ng/ml/h, whereas the same reduction in sodium intake in low-renin hypertensives reduced SBP by only 5 mm Hg and barely increased PRA levels (increasing from 0.10 to 0.16 ng/ml/h). As the degree of sodium depletion increased, the SBP of the low-renin patients fell toward normal and PRA levels rose into the medium range, whereas the SBP of the medium-renin patients fell only minimally but PRA levels rose above the normal range. When sodium depletion became extreme (by reducing dietary sodium intake from 100 to 35 mmol/day while taking a diuretic), neither hypertensive group exhibited any further fall in SBP, but they both now exhibited large increases in PRA. Thus, among hypertensive patients whose SBP had fallen to ≤140 mm Hg as a result of sodium depletion, there was almost a 10-fold range in PRA levels (1.3, 2.0, 4.0, 5.9, and 11.4 ng/ml/h) (Figure 1).

In sum, the same degree of sodium depletion induced greater reactive increases in PRA in medium-renin hypertensives than in low-renin hypertensives, and changing from moderate to extreme sodium depletion had little effect on BP but induced large reactive increases in PRA. Thus, differences in degrees of sodium depletion and interindividual differences in response could explain the large range of PRA

Figure 1. In low- and medium-renin hypertensive patients, plasma renin activity (PRA) levels rise and systolic blood pressure (SBP) falls with increasing degrees of sodium depletion; but SBP stops falling when PRA levels rise above the normal range. The figure illustrates SBP (total height of each bar) in relation to PRA levels (red component of bar) in 6 low-renin and 6 medium-renin hypertensive patients who were given 3 sodium diets (each for 3 weeks) without (left side of each box) and with (right side of each box) a concurrent diuretic. Eight patients received 2.5 mg indapamide, and 4 patients received 25 mg chlorthalidone daily. Dashed lines indicate the normal range of PRA (0.65–4.5 ng/ml/h).
levels observed in the 4 published reports of treated cardiovascular patients.14–17

**Relationship of PRA levels to cardiovascular mortality**

Figure 2 shows that in 4 different published reports of thousands of cardiovascular patients cardiovascular mortality was higher in treated patients with higher PRA levels than in those with lower PRA levels. Muhlestein et al.15 reported that elevated baseline PRA was significantly associated with increased 3-year morbidity/mortality (log-rank $P = 0.005$), myocardial infarction (log-rank $P = 0.03$), heart-failure hospitalization (log-rank $P = 0.03$), and all-cause death (log-rank $P = 0.007$). Furthermore, Tomaschitz et al.16 reported increased probability of cardiovascular death during follow-up with increasing quartiles of plasma renin; patients with high plasma renin levels continued to be separated throughout a follow-up period of almost 10 years ($P < 0.001$). Verma et al.17 also reported that patients in the upper vs. the lowest PRA quintiles had increased rates of cardiovascular death (log-rank $P = 0.006$). Masson et al.14 also reported that PRA was associated with mortality; the rate of the combined endpoint (time to all-cause mortality and time to mortality or morbidity) increased across tertiles of PRA ($P < 0.0001$). The data in Figure 2 were not adjusted for potential confounders.

The mortality rates in subgroups with the highest plasma renin levels were 1.5- to 2-fold higher than in the lowest plasma renin groups. As expected, the yearly CVD mortality rates in the lowest vs. the highest PRA groups differed markedly between patient types: 0.2% vs. 0.3% per year for hypertensives reported by Gonzalez et al.3 (not shown), 1.0% vs. 1.8% per year for cardiovascular patients in the HOPE trial reported by Verma et al.17, 1.5% vs. 2.2% for cardiac catheterization patients reported by Tomaschitz et al.16, 2.3% vs. 4.7% for cardiac catheterization patients reported by Muhlestein et al.15, and 7.2% vs. 11.6% for the heart-failure patients in the Val-HeFT trial reported by Masson et al.14.

Because treatment is associated with higher PRA levels only in subsets of such cardiovascular patients, we
investigated if there were differences in physical, biochemical, and pharmaceutical parameters between the PRA subgroups that might explain their higher PRA levels.

**SBP differences between plasma renin groups**

The greater cardiovascular mortality of the higher PRA patients cannot be ascribed to higher BPs per se because SBP trended lower as PRA became higher (Table 2). Although the highest PRA subgroup reported by Tomaschitz et al. did not have lower SBPs than the lowest subgroup, the downward trend in SBP across renin subgroups was highly significant ($P < 0.001$). Moreover, comparing the highest and lowest PRA subgroups, SBP averaged $-6$ mm Hg lower in untreated hypertensives reported by Gonzalez et al., $-12$ mm Hg lower in the treated hypertensives reported by Sim et al., $-4$ mm Hg lower in the cardiovascular patients from the HOPE trial reported by Verma et al., and $-18$ mm Hg lower in the heart-failure patients reported by Masson et al. from the Val-HeFT trial. Thus, the heart-failure patients with the highest PRA levels reported by Masson et al. had an average SBP that was almost $20$ mm Hg lower than the lowest PRA group ($115$ vs. $133$ mm Hg) but a death rate that was $1.8$-fold higher.

**Relationship between SBP, PRA, and “effective PRA levels”**

The greater cardiovascular mortality of the higher PRA group of heart-failure patients reported by Masson et al. occurred despite their concurrent use of an ACEI. However, further analysis revealed that plasma renin activity was not completely blocked in the highest renin tertile. At the doses used clinically, ACEIs block the conversion of Ang I to Ang II by only $90\%$, leaving about $10\%$ unblocked. Thus while taking an ACEI, “effective PRA levels” are in fact only one-tenth of reported PRA levels. Comparing the highest renin groups, the treated heart-failure patients had a $31$ mm Hg lower SBP than the untreated hypertensives (Figure 3). At first glance, that appears to have been sustained by $8$ times more renin-angiotensin–mediated vasoconstriction (PRA = $25$ ng/ml/h vs. $3.3$ ng/ml/h). However, because $90\%$ of renin system activity was actually blocked in vivo, this means that “effective PRA levels” were only $2.5$ vs. $3.3$ ng/ml/h, almost identical. Consequently, the BP of the highest renin tertile of heart-failure patients continued to be supported by Ang II–mediated vasoconstriction. In other words, the PRA levels of these heart-failure patients had risen high enough to overcome renin-angiotensin system blockade.
Blood urea nitrogen (BUN), uric acid, estimated GFR (eGFR), and N-terminal pro b-type natriuretic peptide (NT-ProBNP) levels across renin subgroups: evidence for greater sodium-volume depletion of the higher renin subgroups

Blood urea nitrogen and serum uric acid levels reflect the efficiency of removal of metabolic waste products from the blood and are rough indicators of vascular volume. They were reported for only the normal subjects and the untreated and the treated hypertensives (Table 2).23-26 There was a significant trend among the untreated hypertensives (BUN and uric acid levels were 12% and 11% higher, respectively, in the highest PRA quartile compared with the lowest) and among the treated hypertensives (BUN and uric acid levels were 26% and 13% higher, respectively, in the highest group). In contrast, there was no such trend among the normal subjects.

Although there were significant ($P < 0.001$) downward trends in eGFR between low- and high-renin subgroups, the difference was only 1% and 3% for the untreated and treated patients, respectively, and 8% for the heart-failure patients.

There was also a significant downward trend ($P < 0.001$, 20% fall) in NT-ProBNP across PRA levels in the heart-failure patients reported by Masson et al.14 and the cardiovascular patients ($P < 0.001$, 30% fall) reported by Verma et al.17 (Table 2). This was unexpected because the higher PRA patients in the Val-HeFT trial exhibited 1.8 times the cardiovascular mortality; more severe heart failure is expected to bring higher circulating natriuretic peptides.14 In fact, it is instead consistent with the reported inverse relationship between plasma volume and NT-ProBNP levels.30

In summary, the patients with the highest PRA levels had lower BPs, reduced ability to clear metabolic waste products, and lower NT-ProBNP levels despite their greater cardiovascular mortality. All of these parameters are consistent with greater degrees of sodium depletion.

**Drug usage amongst renin subgroups**

Figure 4 illustrates the percentages of each renin subgroup that were taking beta blockers, diuretics, and/or an ACEI or angiotensin receptor blocker (ARB) in relation to the median PRA level of each subgroup. Compared with the highest renin subgroups, the lowest were all taking a higher percentage of beta adrenergic blocking drugs (Sim et al.: 74% vs. 40%; Masson et al.: 43% vs. 30%; Tomaschitz et al.: 74% vs. 56%; Verma et al.: 63% vs. 29%). Nonetheless, although beta blockers clearly suppress renal renin secretion, more than 25% of patients in the highest renin groups were taking beta-blocking drugs, consistent with the fact that, although beta blockers suppress PRA levels in everyone, they do not prevent PRA levels from rising in response to sodium depletion.31

In contrast, in each of the highest renin subgroups compared with the lowest renin subgroups, greater percentages of patients were taking diuretic drugs (Sim et al.: 65% vs. 49%; Masson et al.: 92% vs. 78%; Tomaschitz et al.: 50% vs. 16%; and Verma et al.: 25% vs. 7%).

Figure 4. The percentage of patients in each renin quartile or tertile who were taking either diuretics, an angiotensin converting enzyme inhibitor (ACEI) or angiotensin receptor blocker (ARB), or a beta blocker. Data and $P$ values for trend of diuretic usage were as follows: treated hypertensive patients (Sim et al.: red squares, $P < 0.001$), heart-failure patients in the Valsartan Heart Failure (Val-HeFT) trial (Masson et al.: black triangles, $P < 0.0001$), cardiovascular patients in the Heart Outcomes Prevention Evaluation (HOPE) trial (Verma et al.: blue closed circles, $P = 0.02$) and cardiovascular patients in the observational study (Tomaschitz et al.: lilac open circles, $P < 0.001$). Dotted lines indicate the PRA normal range.
There was no difference in ACEI/ARB usage between the lowest and the highest renin subgroups in Sim et al.26 (71% vs. 72%), Verma et al.17 (0% for each), and Masson et al.14 (both 100%). Only the cardiac catheterization patients in Tomaszczik et al.16 exhibited greater ACEI/ARB usage in the highest renin subgroup (80% vs. 48%).

In sum, there was always a greater use of diuretics in the highest PRA subgroups.

**DISCUSSION**

Recent data from 4 reports of thousands of patients with a variety of cardiovascular conditions have shown that subgroups of patients with higher on-treatment PRA levels have greater cardiovascular mortality than similar patients with lower PRA levels despite their taking renin-angiotensin system–blocking drugs.14–17 In this report, we investigated whether the higher treatment PRA levels might be iatrogenic (i.e., induced by excessive use of natriuretic drugs and/or low-salt diets in subgroups of patients). If so, renin-angiotensin system blockade might increase rather than decrease cardiovascular mortality in those patients.

We first showed that equal degrees of sodium depletion can induce different PRA levels in individual hypertensive patients. We then showed that the highest renin subgroups in the 4 reports had PRA levels that were above the normal range (0.65–4.5 ng/ml/h), in contrast with the other subgroups whose median PRA levels were either medium or often low. Then we showed that the highest renin subgroups differed from the lowest in that the highest renin subgroups were more frequently taking natriuretic drugs, had lower SBPs, had lower NT-proBNP levels, and had higher BUN and uric acid levels but were just as likely to also be taking renin-angiotensin system–blocking drugs (Table 2; Figure 4). Thus, overall, we found that only subsets of treated cardiovascular patients had high PRA levels, that excessive sodium depletion can induce such high PRA levels, and that the highest renin subgroups generally exhibited evidence of excessive sodium depletion.

Renin-angiotensin system–blocking drugs reduce cardiovascular mortality in clinical trials of patients with cardiovascular or chronic kidney disease;5–9,32,33 the data are so convincing that such patients are said to have “compelling indications” for taking these drugs.10 But, natriuretic drugs might seem a more likely candidate for inducing the higher PRA levels than excessive sodium intake and reducing natriuretic drugs in patients whose PRA levels might be elevated because of excessive sodium depletion.

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Because ACEIs and ARBs can increase PRA levels,15 they might seem a more likely candidate for inducing the higher PRA levels in subsets of treated patients than excessive sodium depletion. But ACEIs and ARBs could not be the primary cause because the patients in the HOPE trial were not taking
either an ACEI or ARB when PRA was measured, whereas all of the patients analyzed in the Val-HeFT trial were taking an ACEI (Figure 4). Moreover, ACEIs/ARBs do not induce large increases in PRA levels in low-renin patients, whereas sodium depletion can eventually induce very high PRA levels in everyone, even in low-renin hypertensives (Figure 1).

A weakness of this report is that the PRA levels, BPs, and natriuretic drug usage of the individuals who died in the clinical trials were not compared with those who survived. Moreover, the extent of sodium depletion was based on indirect measures, and even those measures were not available for all of the reports. Also, PRA levels were measured before adding an ACEI or ARB in the HOPE and Val-HeFT trials and were very likely higher during the outcome phase of the trials.

A strength of the report is that thousands of patients had treatment plasma renin levels measured and the relationships of PRA to outcomes were similar despite the use of different plasma renin tests (Figure 2). Moreover, the cardiovascular death rates increased across the range of PRA levels and were not just a feature of the highest renin groups.

Clearly, this hypothesis needs to be tested. That could be done by comparing adverse events (hypotension, falling GFR levels, hyperkalemia) in clinical trials of renin-angiotensin system–blocking drugs among patients given natriuretic drugs who developed low, medium, or high on-treatment PRA levels.

The possibility that excessive sodium depletion counteracts the beneficial effects of renin-angiotensin system–blocking drugs has broad implications for treatment guidelines. It calls into question the practice of sodium depleting patients without concurrently ensuring that PRA levels do not rise above the medium range. But, the good news is that most patients given sodium-depleting regimens do not develop high PRA levels (Figure 4). For the remainder, the high PRA levels can be readily reversed by gradually withdrawing natriuretic drugs and/or increasing dietary salt intake (Figure 1), often without inducing an unacceptable rise in BP. However, initiating treatment with combination pills rather than just 1 drug increases the difficulty of back-titrating individual drug types.

This hypothesis also calls into question whether dual renin-angiotensin system blockade is bad for everyone, as is now proposed, because it is possible that the lesser efficacy of dual blockade in clinical trials is caused by a few sodium-depleted patients. The difference in outcome between 1 and 2 anti–renin system drugs in clinical trials can be explained as follows: 1 renin-angiotensin system blocker benefits the majority of patients but simultaneously increases cardiovascular risk in a few sodium-depleted patients, resulting in net cardiovascular benefit for the group as a whole. The second drug adds little benefit to the majority of patients, whose renin-angiotensin system is now successfully blocked, but further increases risk in those who remain sodium depleted; the net effect of the second drug is an increase in cardiovascular risk for the group as a whole. This would explain why, irrespective of whether the second drug type is an ACEI or ARB or direct renin inhibitor, it is always the second renin-angiotensin system blocker that is associated with an increased number of adverse events.

Another implication relates to the observation that large numbers of treated cardiovascular patients continued to have suppressed PRA levels despite taking natriuretic drugs, suggesting that many remained sodium-volume expanded. That has implications for the interpretation of clinical trials. Thus, if a patient cohort is predominantly volume expanded with low PRA levels, the patients are unlikely to achieve much benefit from renin-angiotensin system–blocking drugs because many will have no renin-angiotensin system activity to block, similar to half of the patients in the CONSENSUS trial with lower Ang II levels. In contrast, a cohort that is predominantly euvolemic with medium to high PRA levels will achieve more benefit, similar to the other half of the patients in the Cooperative North Scandinavian Enalapril Survival Study (CONSENSUS) trial who had higher plasma Ang II levels. It might be argued that the greater benefit of the higher Ang II group in the CONSENSUS trial negates our hypothesis. However, NT-proBNP evidence suggests that the higher Ang II subgroup was comprised of fewer sodium-depleted patients than the highest PRA tertile in the Val-HeFT trial because compared with the lower Ang II subgroup, they had higher NT-proBNP levels, whereas, compared with the lowest PRA tertile, the highest PRA tertile of the Val-HeFT trial had lower NT-proBNP levels.

Finally, the data in Figure 1 indicate that each person may have a critical BP level that triggers a large release of renin from the kidneys, leading to high-renin normotension (Figure 1, right columns in each box). Because the 4 reports show that such high-renin normotension is associated with greater cardiovascular mortality, it calls into question the current practice of only using BP as the endpoint for treatment of hypertension. A better goal might be to maintain BP high enough to keep PRA levels within the normal range because that would mean that the kidneys are being adequately perfused. In sum, cardiovascular health is better maintained when BP (normotension or hypertension) is sustained more by the sodium-volume factor than by PRA-mediated vasoconstriction.

Four recent reports revealed differences in survival rates among treated cardiovascular patients: those with higher treatment PRA levels died sooner of cardiovascular complications than did those with low PRA levels, despite the concurrent use of renin-angiotensin system–blocking drugs. In this report, we showed that the higher PRA groups exhibited evidence of excessive sodium depletion (i.e., lower BPs, more frequent use of natriuretic drugs, lower NT-ProBNP, and higher BUN and uric acid levels) but no difference in the use of renin-angiotensin system–blocking drugs.

We believe that excessive sodium-volume depletion increases risk for cardiovascular events and should generally be avoided. We further believe that excessive sodium-volume depletion should be a contraindication for renin-angiotensin system–blocking drugs in patients with otherwise compelling indications for such drugs, because they put patients at increased risk for hypotension, hyperkalemia, and falling GFR levels. High PRA measurements (>4.5 ng/ml/h) may help to identify such sodium-volume-depleted patients. Then, a gradual increase in salt intake and/or subtraction of natriuretic drugs to suppress PRA levels to the normal range without causing unacceptable increases in BP may benefit...
these patients and reduce the risk for adverse effects if they are concurrently treated with renin-angiotensin system-blocking drugs.

REFERENCES


DISCLOSURE

The authors declared no conflict of interest.

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