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Pressor Responses to Antihypertensive Drug Types

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BACKGROUND
Pressor responses to antihypertensive drugs are not addressed in treatment guidelines although they have been described in various clinical situations. We now report the incidence of pressor responses to initiation of monotherapy using four antihypertensive drug types, and the influence of plasma renin activity (PRA) status, among participants in a worksite-based antihypertensive treatment program.

METHODS
Systolic blood pressure (SBP) response was evaluated among 945 participants with no prior treatment who were given either a diuretic or calcium-channel blocker (natriuretic antivolume V drugs, $n = 537$) or a β-blocker or angiotensin-converting enzyme (ACE) inhibitor (antirenin R drugs $n = 408$). PRA was categorized by low, middle, and high tertiles (L, M, and H). SBP rise ≥10 mm Hg was considered pressor.

RESULTS
More pressor responses occurred with R than V drugs (11% vs. 5%, $P = 0.001$). L, M, and H renin tertiles had similar frequencies with V drugs (6, 4, and 6%), but low and middle tertiles given R had greater pressor frequencies (17% $P = 0.003$ vs. V and 10% $P = 0.02$ vs. V). Treatment SBP ≥160 mm Hg occurred more frequently with R than V drugs (19% vs. 13%; $P = 0.007$); moreover, in the lowest renin tertile 35% R vs. 13% V ($P = 0.001$) had SBP ≥160 mm Hg. Treatment SBP <130 mm Hg was more frequent in V patients in the lowest tertile (18% vs. 5%; $P = 0.003$), and in R patients in the highest tertile (26% vs. 12%, $P = 0.002$).

CONCLUSIONS
Pressor responses to antihypertensive monotherapy occur sufficiently frequently to be of concern, especially in lower renin patients given a β-blocker or ACE inhibitor (ACEI).

Keywords: *anti hypertensive drugs; blood pressure; hypertension; pressor responses; renin*

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High blood pressure (BP) is treated by many drug types. Roughly half of all patients respond to each of the major classes of antihypertensive agents[1] but the characteristics of responders may differ for each drug class.[2] Moreover, although failure to respond is well recognized, the occurrence or clinical importance of an actual rise in pressure is rarely addressed.

BP responses to antihypertensive therapies are influenced by the interaction of the physiological characteristics of BP regulation with the mechanism of action of the particular pharmacological agent prescribed. For example, therapies that block the renin–angiotensin system are expected to have their least effect in patients with low plasma renin activity (PRA) and their greatest effect in persons with medium-to-high PRA values.[3–5]

In the current report, data were analyzed from subjects who participated in a worksite-based antihypertensive treatment program in New York City.[6] Ambulatory, pretreatment PRA was measured, and baseline and follow-up BP were systematically recorded. We now describe the BP responses to particular antihypertensive drug monotherapies and their relationship to baseline ambulatory PRA levels in these hypertensive patients.

METHODS

The Worksite Hypertension Program (Worksite), an onsite, union-sponsored, systematic hypertension control program, provided data for this study and has been described elsewhere.[7] Entry criteria for Worksite included an elevated BP ≥140/90[8] after three successive visits, or being treated with antihypertensive medication.[6] Beginning in 1981, baseline BP was ascertained and blood for PRA was drawn from seated patients in the usual clinic setting at the third pretreatment visit.

Prescription of drug therapy generally followed recommendations of successive Joint National Committee on Prevention, Detection, Evaluation, and Treatment of High Blood Pressure reports, but was ultimately at the discretion of the program physician. From 1981–1988, a subset of participants in Worksite were randomly allocated to either diuretic or β-blocker monotherapy. After 1990, program physicians were made aware of baseline PRA values and encouraged to prescribe diuretics for those with lower PRA levels, and antirenin agents for those with higher PRA levels, although precise thresholds were not specified.[7]

Inclusion criteria for this retrospective analysis of prospectively collected data were Worksite participants, untreated at

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entry, pretreatment systolic BP (SBP) of at least 140 mm Hg, a PRA measurement, treated with initial monotherapy with a diuretic, calcium-channel blocker (CCB), β-blocker or angiotensin-converting enzyme (ACE) inhibitor, and a first in-treatment revisit within 90 days of entry (mean ± s.d.: 33 ± 18 days) (n = 945).

Measures and statistical analyses. Antihypertensive monotherapy was characterized as either a natriuretic, antivolume (V drug) consisting of diuretic or CCB, or an antirenin agent (R drug) consisting of β-blockers or ACE inhibitors (ACEIs). SBP and diastolic BP (DBP) were measured by a trained nurse with a standard sphygmomanometer while the patient was sitting, and recorded as the average of the last two of three readings. Change in BP was calculated as the value at first in-treatment visit minus the pretreatment baseline value, so that a negative value represents a decline and a positive value a rise. Changes in SBP and DBP were analyzed both as continuous and categorical variables. Categorization was ≥10, −9 through 9, and less than or equal to −10 mm Hg for SBP and ≥5, −4 through 4, and ≤5 mm Hg for DBP. SBP rise ≥10 mm Hg was considered a pressor response and SBP fall ≤10 mm Hg was considered a depressor response. PRA was categorized into low, middle, and high tertiles (<0.74, 0.74–2.00, >2.00 ng/ml/h). An alternate cutpoint of <0.65 to define low renin was also assessed.[9]

Bivariate associations of patient characteristics and BP response by drug group were assessed with χ^2 for categorical variables and t-test for continuous variables and Mann–Whitney U test for PRA, which was non-normally distributed. Spearman rank correlations were used to assess the bivariate association of categories of change in SBP with PRA tertile within drug group. Odds ratios for fall in SBP <10 mm Hg and for a rise of ≥10 mm Hg were calculated in logistic models adjusting for age, race, smoking, diabetes, body mass index, history of cardiovascular disease, and baseline SBP. Goodness of fit for logistic models was assessed with Hosmer and Lemeshow tests. Sensitivity analyses were performed for the subset of patients randomly assigned antihypertensive monotherapy. Statistical analyses were performed with SPSS, version 17 (SPSS, Chicago, IL) and STATA, version 10 (StataCorp, College Station, TX).

RESULTS

Proportions in the three categories of SBP change and the three categories of DBP change did not differ significantly between ACEI and β-blocker (R drugs) or between diuretic and CCB (V drugs) (**Table 1**). There were also no significant differences in the pressor effect within V and R drug categories when broken down by PRA tertile (**Figure 1**). Mean ± s.d. change for SBP were similar for ACEI and β-blockers and for diuretic and CCB (**Table 1**). Mean DBP responses were similar between ACEI and β-blocker, but did differ by 2 mm Hg between diuretic and CCB. In the following analyses, data from patients taking ACEIs or β-blockers are categorized as R and data from patients taking diuretics or CCBs are categorized as V.

Patients prescribed V drugs were older, more likely to be black, and had a higher baseline SBP) (**Table 2**). Those provided R drugs were more likely to be male (P = 0.02) and have higher median PRA. Those with history of diabetes (<5%) were more frequently prescribed an R drug. No significant differences were observed for body mass index, history of cardiovascular disease, baseline DBP, cholesterol, or smoking.

Mean fall in SBP was 4 mm Hg greater among those taking V than R drugs (P < 0.001) (**Table 3**). Overall, 7.7% of patients exhibited a SBP rise ≥10 mm Hg; R drug patients about twice as likely (11% vs. 5.2%, P = 0.001) to experience that rise. A fall in SBP ≥10 mm Hg was more likely to occur in patients given

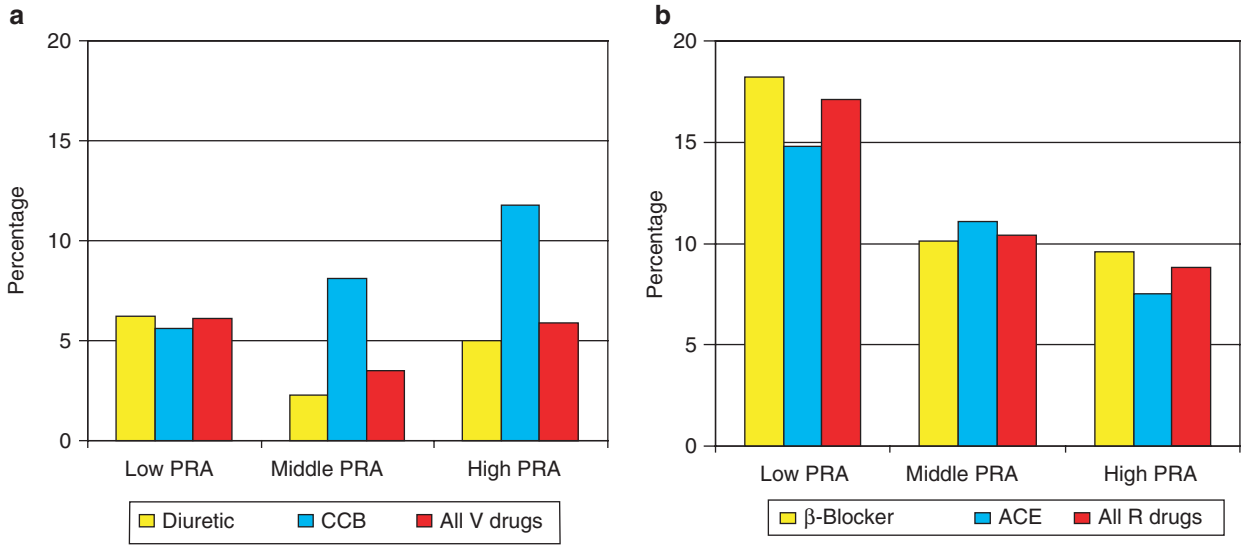

Figure 1 | Percent with systolic pressor response ≥10 mm Hg by plasma renin activity (PRA) category (**a**) for diuretic, calcium-channel blocker (CCB) and all V drug (diuretic or CCB). P for linear trend = 0.52, 0.39, and 0.80, respectively. Comparing diuretic to CCB within each PRA tertile: L: P = 0.86, M: P = 0.09, H: P = 0.27. (**b**) For β-blocker, Angiotensin-converting enzyme inhibitor (ACEI), and all R drug (β-blocker or ACEI). P for (inverse) linear trend = 0.14, 0.27, and 0.06, respectively. Comparing β-blocker to ACEI within each PRA tertile: L: P = 0.70, M: P = 0.85, H: P = 0.63. R, antirenin; V, natriuretic antivolume.

Table 1 | Blood pressure changes comparing ACEI and β blockers (R) and diuretic and CCB (V)

Variable	ACEI (*n* = 139)	β-Blockers (*n* = 269)	*P**	Diuretic (*n* = 429)	CCB (*n* = 108)	*P***
SBP change (mm Hg)	−11 ± 15	−10 ± 15	0.48	−15 ± 15	−13 ± 15	0.15
DBP change (mm Hg)	−7 ± 9	−6 ± 9	0.27	−7 ± 8	−9 ± 10	0.01
Categories of SBP change (%)			0.83			0.23
≥10 mm Hg rise	10	12		5	7	
−9 through +9 mm Hg	33	35		32	37	
≥10 mm Hg fall	57	54		64	56	
Categories of DBP change (%)			0.44			0.17
≥5 mm Hg rise	12	20		6	7	
−4 through +4 mm Hg	25	31		32	23	
≥5 mm Hg fall	66	61		61	70	

Values are presented as mean ± s.d. or % of the column *n*.
ACEI, angiotensin-converting enzyme inhibitor; BP, blood pressure; CCB, calcium-channel blockers; DBP, diastolic BP; R, antirenin drugs; SBP, systolic BP; V, natriuretic antivolume drugs.
**P* for comparison of ACEIs vs. β-blockers. ***P* for comparison of diuretics and CCBs.

Table 2 | Baseline characteristics by V or R drug group

Variable	V drug (*n* = 537)	R drug (*n* = 408)	Either drug (*n* = 945)	*P*
Age (years)	54 ± 8.9	52 ± 9.1	53 ± 9.9	0.002
Male sex (%)	66.1	73.3	69.2	0.02
Race				0.002
White (%)	27.6	31.9	29.4	
Black (%)	31.7	20.3	26.8	
Hispanic (%)	37.6	43.9	40.3	
Other (%)	3.2	3.9	3.5	
BMI (kg/m^2)	28.3 ± 4.8	28.1 ± 3.9	28.2 ± 4.4	0.43
History cardiovascular disease (%)	5.2	5.6	5.4	0.78
Smoker (%)	17.7	19.4	18.4	0.51
Systolic BP (mm Hg)	157 ± 13.3	155 ± 12.4	156 ± 13.0	0.01
Diastolic BP (mm Hg)	98 ± 9.4	98 ± 8.8	98 ± 9.1	0.23
Cholesterol (mmol/l)	219 ± 42	220 ± 44	219 ± 43	0.72
History of diabetes (%)	2.2	6.6	4.1	0.001
Plasma renin activity (ng/ml/h)	0.96 (0.38, 2.00)	1.70 (0.96, 3.08)	1.30 (0.52, 2.50)	0.001
Plasma renin activity tertile (%)				<0.001
Lowest tertile	43.0	20.1	33.1	
Middle tertile	31.7	35.3	33.2	
Highest tertile	25.3	44.6	33.7	

BMI, body mass index; BP, blood pressure; R drug, antirenin drugs (β blockers, angiotensin-converting enzyme inhibitors); V drug, natriuretic drugs (diuretics and calcium-channel blockers).
[a]Results for continuous variables are reported as mean values (with s.d.) with *P* values calculated by *t*-test between drug groups or median (interquartile range) with *P* calculated by Mann–Whitney *U* test. Categorical variables are reported as percentages with *P* values calculated by χ^2.

V drugs (62% vs. 55%, $P = 0.03$). DBP responses did not differ significantly between V and R drugs.

By PRA tertile, without respect to drug type, the mean falls in SBP and DBP were similar (Table 4). However, patients in the lowest renin tertile, treated with a V drug, had a greater mean fall in SBP and DBP, a higher percentage who had a depressor response and who achieved a BP <130 mm Hg than did R drug patients.

Pressor responses also differed by drug use across renin tertiles (see either drug in Table 4). Thus, 17% of patients in the lowest renin tertile given R drugs had an SBP rise ≥10 mm Hg vs. only 6% given V drugs ($P = 0.003$). The percentages were 10% vs. 4% ($P = 0.02$) in the middle renin tertile and 9% vs. 6% in the highest PRA tertile ($P = 0.33$). Overall there was a borderline trend ($P = 0.06$) across PRA tertiles toward an inverse correlation for R drugs with BP rise.

Table 3 | Blood pressure response by V or R drug group

Variable	V drug ($n = 537$)	R drug ($n = 408$)	Either drug ($n = 945$)	*P*
SBP change (mm Hg)	−15 ± 15	−11 ± 15	−13 ± 15	<0.001
DBP change (mm Hg)	−7 ± 9	−7 ± 9	−7 ± 9	0.23
Categories of SBP change (%)				0.002
≥10 mm Hg rise	5.2	11.0	7.7	0.001*
−9 through +9 mm Hg	32.8	34.1	33.3	
≥10 mm Hg fall	62.0	54.9	58.9	0.03*
Categories of DBP change (%)				0.64
≥5 mm Hg rise	6.3	7.8	7.0	
−4 through +4 mm Hg	30.5	29.2	29.9	
≥5 mm Hg fall	63.1	63	63.1	

SBP and DBP change (first clinic visit ≤90 days from initial treatment – baseline), negative values represent a fall in BP.
DBP, diastolic blood pressure; R drug, antirenin drugs (β-blockers, angiotensin-converting enzyme inhibitors); SBP, systolic blood pressure; V drug, natriuretic drugs (diuretics and calcium-channel blockers).
[a]Results for continuous variables are reported as mean values (with standard deviations) with p values calculated by t-test. Categorical variables are reported as percentages with *p* values calculated by χ^2.
**P* value for V compared to R for the specific row relative to else.

Figure 2 shows patients who were given R drugs, compared to V, were significantly more likely to have a treatment SBP ≥160 mm Hg for the group as a whole (19% vs. 13%, $P = 0.007$), and this was particularly so in the low PRA tertile (35% vs. 13%, $P < 0.001$). Altogether, R and V drugs were equally likely (18% vs. 17%, $P = 0.47$) to have an SBP ≤130 mm Hg, but differed significantly in the low and high PRA tertiles. Overall, V drug patients also had a greater average fall in SBP and a more frequent depressor response than R drug patients (**Table 3**), but were not significantly more likely to achieve an SBP <130 mm Hg (**Table 5**). The relative odds for patients taking R vs. V drugs of having either a true pressor response (SBP rise ≥10 mm Hg (top row)) or failing to respond (<10 mm Hg fall in SBP (bottom row)) is presented in **Table 5**. The odds ratios are adjusted for baseline SBP and other potential confounders (see **Table 5**). R drugs were significantly more likely than V drugs to be associated with an SBP rise in all but the highest PRA tertile. On the other hand, the highest renin tertile patients given R drugs were less likely than patients given V drugs to fail to respond ($P = 0.01$). Results were similar after adding an additional adjustment for physicians being blinded or not to renin status. For the subset of 252 participants who had been randomly allocated to V (diuretics) or R (β-blockers) drugs, results were consistent, but not statistically significant. Comparing the randomized subset to the subset whose prescription was informed by renin status ($n = 450$) a slightly but not significantly larger proportion (8.7 vs. 7.3%, $P = 0.51$) had a pressor response of ≥10 mm Hg.

Among patients in the lowest PRA tertile, similar results were obtained using 0.65 and alternately 1.00 ng/ml/h to define low PRA instead of the upper bound of the tertile value of 0.74 (data not shown).

Table 4 | Blood pressure response by V or R drug group within plasma renin activity tertiles

	V drug	R drug	Either drug	*P*
Lowest PRA tertile (<0.74, median 0.34 ng/ml/h)	$n = 231$	$n = 82$	$n = 313$	
Baseline SBP (mm Hg)[a]	158 ± 14	157 ± 13	157 ± 14	0.84
Baseline DBP (mm Hg)	98 ± 9	100 ± 8	98 ± 9	0.18
SBP change (mm Hg)	−16 ± 16	−6 ± 13	−13 ± 16[b]	<0.001
DBP change (mm Hg)	−8 ± 9	−5 ± 9	−7 ± 9[b]	0.008
SBP rise ≥10 mm Hg	6%	17%	9%	<0.001
Systolic change −9 through +9 mm Hg	29%	44%	33%	0.01
SBP fall <10 mm Hg (includes rise)	35%	62%	42%	<0.001
SBP fall ≥10 mm Hg	65%	39%	58%	<0.001
Middle PRA tertile (0.74–2.00, median 1.30 ng/ml/h)	$n = 170$	$n = 144$	$n = 314$	
Baseline SBP (mm Hg)	156 ± 13	155 ± 12	155 ± 13	0.27
Baseline DBP (mm Hg)	98 ± 9	97 ± 8	97 ± 9	0.56
SBP change (mm Hg)	−15 ± 15	−10 ± 15	−13 ± 15[b]	0.006
DBP change (mm Hg)	−7 ± 8	−7 ± 8	−7 ± 8[b]	0.74
SBP rise ≥10 mm Hg	4%	10%	7%	0.02
Systolic change −9 through +9 mm Hg	32%	36%	34%	0.48
SBP fall <10 mm Hg (includes rise)	36%	46%	41%	0.06
SBP fall ≥10 mm Hg	64%	54%	59%	0.06
Highest PRA tertile (>2.00, median 3.1 ng/ml/h)	$n = 136$	$n = 182$	$n = 318$	
Baseline SBP (mm Hg)	157 ± 13	154 ± 12	155 ± 13	0.02
Baseline DBP (mm Hg)	100 ± 9	97 ± 9	98 ± 9	0.01
SBP change (mm Hg)	−12 ± 13	−13 ± 15	−13 ± 15[b]	0.59
DBP change (mm Hg)	−7 ± 8	−8 ± 10	−7 ± 9[b]	0.48
SBP rise ≥10 mm Hg	6%	9%	8%	0.08
Systolic change −9 through +9 mm Hg	40%	28%	33%	0.01
SBP fall <10 mm Hg (includes rise)	46%	37%	41%	0.12
SBP fall ≥10 mm Hg	54%	63%	59%	0.12

DBP, diastolic blood pressure; R drug, antirenin drugs (β-blockers, angiotensin-converting enzyme inhibitors); PRA, plasma renin activity; SBP, systolic blood pressure; V drug, natriuretic drugs (diuretics and calcium-channel blockers).
SBP and DBP change (first clinic visit ≤90 days from initial treatment – baseline), negative values represent a fall in BP.
[a]Results for continuous variables are reported as mean values (with s.d.) with *P* values calculated by *t*-test within tertiles of PRA. Results from categorical variables are presented as % and *P* values comparing V to R drug calculated with χ^2. [b]Comparison of SBP and DBP mean change for either drug group between PRA tertiles by analysis of variance: $P = 0.81$ and 0.76, respectively.

DISCUSSION

These findings identify and describe pressor responses in hypertensive patients during initial antihypertensive monotherapy. These pressor responses are unlikely to be entirely explained by simple random variation as their frequency

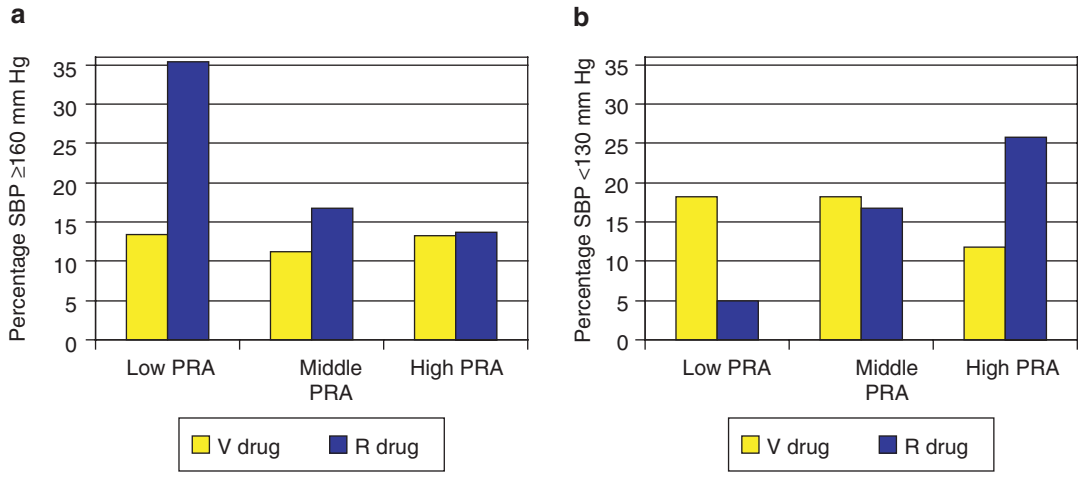

Figure 2 | Comparison of achieved systolic BP by V and R drugs within PRA tertiles. (**a**) Percent with treatment systolic BP ≥ 160 mm Hg by PRA tertile (low PRA $P < 0.01$, middle PRA $P = 0.16$, high PRA $P = 0.90$; P for linear trend = 0.88, and <0.001 for V and R drugs respectively). (**b**) Percent with treatment systolic BP < 130 mm Hg by PRA tertile (low PRA $P \leq 0.003$, middle PRA $P = 0.72$, high PRA $P = 0.002$; P for linear trend = 0.14 and <0.001 for V and R drugs respectively). R, antirenin; V, natriuretic/antivolume.

Table 5 | Adjusted odds ratios of R drug compared to V drug

	Low PRA (<0.74 ng/ml/h), $n = 313$	Middle PRA (0.74–2.0 ng/ml/h), $n = 314$	Highest PRA (>2.0 ng/ml/h), $n = 318$
Rise in SBP ≥10 mm Hg	4.0 (1.6, 9.7), $P = 0.002$	3.9 (1.4, 11.3), $P = 0.01$	1.2 (0.5, 3.1), $P = 0.65$
Fall in SBP <10 mm Hg	3.5 (2.0, 6.4), $P < 0.001$	1.7 (1.0, 2.8), $P = 0.04$	0.5 (0.3, 0.8), $P = 0.01$

Top line for patients whose SBP rose by at least 10 mm Hg. Bottom line for patients whose SBP did not fall by at least 10 mm Hg, reported by PRA tertile. Values are odds ratios (95% confidence intervals) and P values adjusted for age, race, smoking, diabetes, body mass index, history of cardiovascular disease, and baseline SBP, by tertile of PRA. Rise in SBP ≥10 mm Hg is also included within the category of fall in SBP <10 mm Hg) so that odds ratios for fall in SBP ≥10 mm Hg are simply the inverse of fall <10 mm Hg. In the "rise" models, baseline SBP was a significant predictor for low and high PRA; history of diabetes was a significant predictor for middle and high PRA; and race was a significant predictor for middle PRA. In the "fall" models, baseline SBP was a significant in all three PRA strata and age was a significant predictor in the middle PRA. No other covariates were statistically significant in any of the models.
PRA, plasma renin activity; R drug, monotherapy with antirenin drug (β-blocker or angiotensin-converting enzyme inhibitor); SBP, systolic blood pressure; V drug, monotherapy with natriuretic drug (diuretic or calcium-channel blocker).

differed between plasma renin tertiles, and between patients treated with V (diuretic or CCB) or R (β-blocker or ACEI) drugs, although the two drug types classified as R induced similar frequencies of pressure responses, as did the two drugs types classified as V.

This was a retrospective analysis of nearly 1,000 participants in a prospective cohort study in a New York City worksite-based systematic hypertension detection and treatment program during 1981–1998.[6] During initiation of monotherapy, we observed a ≥10 mm Hg decline in SBP in >50% of the patients. Overall, the mean BP fall with V drugs was 4 mm Hg greater than with R agents, but there were differences across the renin tertiles. Thus, V agents lowered average BP by at least 10 mm Hg and achieved SBP <130 mm Hg more frequently in the low and middle renin tertiles, whereas, in contrast, R drugs were least effective in the lowest and most effective in the highest renin tertile.

Pressor responses occurred in all renin tertiles and with all drugs studied but they were less frequent with V than with R drugs and most frequent in patients with lower PRA levels given R drugs. Pressor responses to antivolume natriuretic agents previously reported have often been attributed to drug-induced reactive increases in renal renin secretion, similar to that induced by sodium deprivation.[10–15] In contrast, reports of pressor responses to β-blockers indicate more frequent occurrence in lower renin patients[16] and have been attributed instead to β-blocker facilitated unopposed α-adrenergic activity. Although based upon rather small numbers, an unexpected observation in this study was that pressor responses with ACE inhibitor use occurred in the lowest renin tertile and that pressor response patterns across renin tertiles were quite similar to those associated with β-blocker use, perhaps indicating a common mechanism related to blockade of the renin–angiotensin system. These data also suggest that lower renin levels could sometimes work to keep BP down, perhaps by maintaining an adequate level of glomerular filtration, even though it had been assumed previously that the amounts of renin in the circulation of low-renin patients were too low to be of clinical importance.[9]

Altogether, we found that, without knowledge of PRA status, more patients will have an adequate BP fall with V than R agents. At the same time, the data also indicate that avoiding antirenin system R treatment of the lowest renin subjects, and targeting higher renin patients for antirenin drug treatment would substantially increase the likelihood of achieving BP control with monotherapy, and result in less frequent pressor responses.

The average depressor effects we report herein are consistent with the oft repeated truism that any particular

antihypertensive agent, regardless of its mechanism of action, will lower BP in roughly half of hypertensive subjects. But, this ignores the heterogeneity in individual responsiveness to antihypertensive agents that has been demonstrated over several decades. Awareness of the sodium volume and renin–angiotensin vasoconstriction contributions to BP control led to classification of patients by level of PRA and to the revelation that low-renin subjects preferentially respond to "V" drugs, and higher renin subjects to "R" drugs.[17–22]

Materson demonstrated that BP responses to six classes of antihypertensive agents differed according to race and age in males.[23] Deary *et al*. later demonstrated that the most effective depressor agent could be identified for each hypertensive individual through sequential testing of the different drug classes,[24] and that age, gender, and race were strong predictors of outcome. However, in contrast to findings here, they found that PRA, while associated with BP response, did not increase predictive ability for BP response. The difference may be due to differences in the sensitivity for measuring PRA and/or to differences in the study populations.

The heterogeneity of individual responses to monotherapy, and particularly the paradoxical pressor effects seen here, may have important implications for the interpretation of active comparator clinical trials, and planning of future studies of antihypertensive therapies. Trial results, conventionally report BP as mean and s.e. This obscures any possible heterogeneity in BP response—including a pressor response. Thus, a difference in the average BP fall may be determined as much by the proportions with depressor responses as by the proportions with pressor responses. Because there will be subgroups with different BP responses to the initial drug, the drug patterns achieved (most studies have BP goals) and the number and dose of drugs will vary, and, most importantly, the data here indicate that these variations may not be altogether random. This masked heterogeneity may also affect clinical outcomes. For example, in a trial comparing primary treatment with a "V" and "R" drug, the intention-to-treat analysis may reveal no difference. However, these average findings may mask differences, or even conflicting outcomes, within definable subgroups. To enhance the value of future clinical trials, stratification of participants, before randomization, by elements such as level of PRA that determine heterogeneity among hypertensive patients, could dramatically improve the capacity to better guide the care of individuals.

The possibility of a pressor response also may have immediate clinical relevance. This is particularly true in regard to fixed-dose combination pills. These agents, which often include both an R and a V component, might involve a better than 10% risk that one of the two drugs will make a pressor contribution to the net BP effect. Thus, an optimal antihypertensive agent could be compromised and lead to the need for an unnecessary third or even fourth agent to gain control of BP. In short, there is a fair chance that both the efficacy and efficiency of antihypertensive care will be compromised when therapy is initiated with a fixed combination pill. Without knowledge of concurrent PRA status, a more prudent course would start with a single drug, then use single file one-by-one addition, while subtracting each ineffective drug, and titrating effective drugs until goal pressure is achieved. Then, if a matching fixed-dose combination agent exists, its use could be appropriate.

Strengths of this study include its large size, standardized methodology (including BP determination), ability to detect low PRA, and including subjects drawn from the general working population. Participants received medications without cost and were thus unlikely to have used other agents. While assignment of antihypertensive agents was not random, adjusting for blinding to renin status did not alter results. Moreover, results for the group as a whole were similar to the approximately one-quarter of the subjects randomly assigned either diuretics or β-blockers, In fact, the randomized subset had a slightly, but not significantly higher proportion with pressor responses. This suggests that indication bias (by drug assignment as influenced by knowledge of PRA) had a minimal effect on overall results, and if anything, might have led to an underestimation of the overall pressor response. If assignment had been by chance, more lower-renin patients would have received R drugs. At the same time, because these findings derive from a retrospective analysis, the possibility of latent confounding can not eliminated. Finally, neither the persistence of the pressor response, nor its impact on long-term BP levels or further therapy, nor on clinical outcomes, can be ascertained from these data.

In sum, pressor responses to antihypertensive drug monotherapy appear to be neither rare nor the result of chance alone. Also, our data indicate that patients with low PRA values are at the highest risk of a pressor response when prescribed an R drug. Furthermore, it is important to recognize that ≥10 mm Hg increases in systolic pressure can occur with any antihypertensive drug, and at any level of PRA. Because these pressor responses can be substantial, physicians and patients cannot assume them to be without clinical significance.

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