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Journal

American Journal of Hypertension, 25(3)

ISSN

0895-7061

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Publication Date

2012-03-01

DOI

10.1038/ajh.2011.216

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Plasma Renin Activity (PRA) Levels and Antihypertensive Drug Use in a Large Healthcare System

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BACKGROUND

Although hypertension guidelines have utility in treating uncomplicated hypertension, they often overlook the pathophysiologic basis and heterogeneity of hypertension. This may explain the relatively poor hypertension control rates. A proposed approach is to guide addition and subtraction of medications using ambulatory plasma renin activity (PRA) values. To evaluate the heterogeneity of hypertension and the medication burden associated with it, we investigated medication usage in relation to PRA among hypertensive patients within a large ethnically diverse organization.

METHODS

A cross sectional data analysis was performed of hypertensive subjects with PRA measurements in the Kaiser Permanente Southern California database between 1 January 1998 and 31 October 2009.

RESULTS

Among 7,887 such patients 0, 1, 2, ≥3 medication usage was 16%, 20%, 24%, 40% respectively. PRA levels ranged 1000-fold. Across PRA quartiles (Q1 to Q4) ≥3 meds were prescribed to 50%, 40%, 34%, 37%. From low to high PRA quartiles there was no usage trend for angiotensin converting enzyme inhibitors (ACEIs)/ angiotensin receptor blockers (ARBs) (71%), but diuretics increased (52%, 53%, 57%, 68%), calcium channel blocker's (CCB) fell (56%, 53%, 51%, 42%), and β-blockers fell (77%, 61%, 49%, 41%). Moreover, systolic BP fell (146, 142, 140, 135 mm Hg), blood urea nitrogen (BUN) rose (16, 17, 18, 20 mg/dl), serum uric acid rose (6.1, 6.3, 6.5, 6.9 mg/dl), and chronic kidney disease rose (22%, 22%, 23%, 27%).

CONCLUSIONS

Polytherapy was the norm for treating hypertension. Lower PRAs were associated with higher blood pressures and more medications. Higher PRAs were associated with lower pressures and fewer medications. The results indicate that opportunities exist to simplify antihypertensive therapy by using current ambulatory PRA levels to guide drug selections and subtractions.

Keywords: *ACEI; antihypertensive medications; ARB; β-blocker; blood pressure; CCB; diuretic; hypertension; plasma renin; PRA*

American Journal of Hypertension, advance online publication 8 December 2011; doi:10.1038/ajh.2011.216

Hypertension affects some 72 million adults in the United States. While awareness and initiation of treatment have been increasing, control rates in those prescribed medications are estimated at 50–70%.[1–3] Uncontrolled hypertension is a leading risk factor for preventable cardiovascular and renal diseases.[4,5] Moreover, resistant hypertension is not uncommon prompting the American Heart Association to advocate further research in this area.[6,7] The Seventh Report of the Joint National Committee on Prevention, Detection, Evaluation, and Treatment of High Blood Pressure (JNC7) recommends initiating treatment with a natriuretic/diuretic drug, either alone or in combination with an anti-renin system drug type, and then adding agents of other drug classes until blood pressure reaches goal.[8] This stepped care strategy does not advocate subtracting drugs even when ineffective, except for side effects or toxicity. Nor does it make official recommendations about follow-up medications except that they should be based on individual patient comorbidities, adverse effects, and cost. Thus the current state of hypertension treatment is not ideal and there is room for improvement in medication burden, cost, and overall control.[9,10]

Poor blood pressure control is frequently ascribed to sub-optimal medication regimens and lack of adequate volume control.[9,11,12] Hypertensive patients have long been known to differ in their blood pressure response to the various classes of antihypertensive medications.[13–18] This heterogeneity has underscored the need for treatment approaches based upon individual patient characteristics. One such approach identifies

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Received 5 July 2011; first decision 4 August 2011; accepted 1 October 2011.

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the underlying pathophysiology by determining the ambulatory (outpatient without specific pre-phlebotomy instructions) plasma renin activity (PRA) level.[13,14,17] Those with low PRA are presumed to have a body sodium-volume excess form of hypertension (V-type) to account for the efficacy of natriuretic drugs (anti-V drug types).[19] Conversely, hypertensive patients with higher ambulatory PRA levels are considered to have some degree of renin–angiotensin vasoconstrictor dependent hypertension and respond well to treatment with anti-renin angiotensin, anti-vasoconstrictor (anti-R drugs). In one such study of patients with treated but uncontrolled hypertension, a PRA guided treatment algorithm led to clinically significant reductions in blood pressure and a decrease in the number of antihypertensive medications.[20] Thus, renin guided therapy has been successfully demonstrated and further clinical trials have been advocated.[10,21]

In the current study, we examined antihypertensive medication usage patterns among hypertensive patients in relation to concurrent PRA levels within a large, ethnically diverse, and integrated healthcare system. We sought to evaluate the heterogeneity of the hypertensive population based on PRA ranges and the associated medication burden.

METHODS

Study population. Subjects were members of the Kaiser Permanente Southern California (KPSC) healthcare system, a prepaid integrated health plan providing comprehensive care at 12 medical centers and over 100 satellite clinics and service sites throughout Southern California. As of 2009, KPSC had an active membership of 3.3 million. The patient population is ethnically and socioeconomically diverse, reflecting the population of the practicing area. All members have similar coverage benefits for health care services, including access to healthcare facilities, procedures, and co-pays for medications and healthcare services. All healthcare encounters are tracked using a common electronic medical record database. The study protocol was approved by the regional institutional review board and was exempted from informed consent.

This retrospective cross sectional study includes subjects of age 18 years and older with documented hypertension and outpatient measurement of PRA, drawn as part of routine clinical practice from 1 January 1998 to 31 October 2009. Subjects with solely an inpatient PRA were excluded. For subjects with multiple PRA values, the first value in the study period was used and all data were relative to that date. All individuals were required to have continuous enrollment in the healthcare plan for 3 months prior to and 3 months after the PRA date and be coded for hypertension using the International Statistical Classification of Diseases and Related Health Problems (ICD).

Another population of subjects coded as hypertensive between 1 January 2006 and 31 December 2007, regardless of PRA levels, was identified for comparison purposes. This population was evaluated to determine if the findings from the PRA cohort applied to the hypertensive population as a whole. The comparison population also had a minimum of 6 months continuous enrollment in the health plan.

Data extracted from internal computerized databases includes laboratory databases, disease registries, and electronic medical charts. Kidney function was determined by estimated glomerular filtration rate (eGFR) using the 4 point abbreviated Modification of Diet in Renal Disease formula[22] and considered chronic kidney disease (CKD) when eGFR <60 ml/min/1.73 m^2. Additional comorbidities were assessed based on inpatient and outpatient ICD diagnoses coding.

Kaiser Permanente Hypertension Treatment Algorithms during the survey period. From January 2005 and onward, Kaiser Permanente recommended an algorithm to all physicians managing hypertension. Prior to 2005, no internal hypertension guidelines were established or recommended. For patients with systolic blood pressure 140–159 and diastolic blood pressure 90–99 mm Hg, the guideline suggests initiating treatment with either a diuretic alone or an angiotensin converting enzyme inhibitor (ACEI)/diuretic combination. The ACEI/diuretic combination was suggested for all patients with systolic blood pressure ≥160 and/or diastolic blood pressure ≥100 mm Hg. If blood pressure was still not in control with full doses, the third medication was a β-blocker to full dose. If blood pressure was still not controlled, the fourth medication was a calcium channel blocker (CCB). Given the fact that an algorithm was implemented for a portion of the study period, medication usage data was separately analyzed for the time periods 1 January 1998 through 31 December 2004, and 1 January 2005 through 31 October 2009.

Identification of hypertension and blood pressure reporting. Hypertension was identified by inpatient and outpatient ICD codes specific to hypertension (401.xx, 402.xx, 403.xx, 404.xx, 405.xx). The accuracy of ICD coding for the diagnosis of hypertension was internally validated by The Permanente Medical Group (Rhonda Woodling HTN Task Force) and previously described.[23] In 1999, the internal hypertension registry, which included 386,710 patients, was used to determine the positive predictive value of ICD coding for hypertension based on the number of times an individual had hypertension coded. A subject who had hypertension coded once had a positive predictive value of 88.7% for hypertension whereas subjects coded at least twice had a positive predictive value of 98.1%. ICD codes were used to identify and exclude patients with secondary hypertension such as renovascular disease, aldosteronism, coarctation of the aorta, pheochromocytoma, and Cushing's syndrome but not CKD from the PRA cohort.

Blood pressure data were not entered into the data base until late 2005 and thus only blood pressures after 2005 were extracted and available for analysis. Blood pressure data within 30 days prior to the PRA date were extracted and then the measurement closest to the PRA date was analyzed. A total of 3,709 subjects met these criteria.

Evaluation of medication usage. Antihypertensive medication usage data were extracted using internal pharmacy dispensation records and pharmacy claims. It was defined as any medication prescribed within 60 days prior to the PRA date,

and was considered zero medication use if <7 days supply was prescribed. Similarly for the comparison population, medication usage was defined and assessed relative to the date of the first ICD coded hypertension. Patients were considered to be on concurrent antihypertensive medications if there was a ≥7 days overlap in medication dispensation within the 60 days before PRA date. Medications were categorized based on their effects on renal sodium handling and on the renin–angiotensin system. CCB's were categorized as anti-V drugs due to their natriuretic effects.[24] Medications were classified as anti-V drugs: diuretic/natriuretics (i.e., mineralocorticoid receptor blockers, thiazide diuretics, CCB, α-blockers, loop diuretics) or anti-R drugs: (i.e., blocking drugs: ACEI, angiotensin receptor blockers (ARBs), direct renin inhibitors; or suppressors of renin secretion (β-adrenergic receptor blockers, centrally acting α-agonists, reserpine, methyldopa). To evaluate the effects of the 2005 algorithm on prescribing patterns, medication usage data were further sub analyzed for periods 1 January 1998 to 31 December 2004 and 1 January 2005 to 31 October 2009.

PRA analysis. PRA values were single measurements obtained during outpatient encounters as part of routine clinical practice for various indications as determined by healthcare practitioners. There was no standardization of pre-draw activity. The PRA levels were drawn in an outpatient/ambulatory environment where patients were seated but they were drawn throughout the day, with the usual variations in physical activity prior to phlebotomy. PRA measurements were made with a PRA enzyme kinetic assay that quantifies the rate of angiotensin I generation by radioimmunoassay. PRA values are reported as ng/ml/h. PRA variance in normal subjects on random diets studied once a week for 4 weeks averaged 29%.[25] The PRA test was performed at Quest Diagnostics Nichols Institute using the Sealey PRA assay.[26] Subjects were categorized into quartiles according to PRA levels.

Statistical analysis. The primary objective was to determine antihypertensive medication usage in the population at large and to evaluate if there were differences based on the treatment PRA level. The percentage of patients who were prescribed 0, 1, 2, or ≥3 medications were determined across quartiles. The average number of medications across quartiles were compared by analysis of variance with Tukey–Kramer multiple comparisons adjustment.

Classes of antihypertensive medications used, and frequency within each PRA quartile were also evaluated. Trend across quartiles was investigated based on Cochran–Armitage trend test. Within each PRA quartile, the prevalence of comorbidities was determined and comparisons between quartiles were made based on χ^2 test. Additional data on age, gender, race, and laboratory values were determined for each PRA quartile. Multivariate logistic regressions analysis was used to evaluate odds ratios (ORs) for diuretic usage among PRA quartiles. Linear regressions analysis adjusting for age, gender, black race, CKD, and PRA quartile was performed to evaluate the relationship between systolic blood pressure and medication usage. Comparisons were made for age and laboratory values using the non-parametric Kruskal–Wallis test. For gender and race, χ^2 was used. PRA was treated as a continuous variable to evaluate the linear trend for blood pressure across the PRA quartiles.

All statistical results were generated using SAS Version 9.2 (SAS Institute, Cary, NC) statistical software and results with *P* values <0.05 considered statistically significant.

RESULTS

A total of 7,887 individuals had a diagnosis of hypertension, a PRA measurement, and met the inclusion criteria for the PRA cohort. Overall, 91.3% had two or more hypertension related ICD diagnoses. Blood pressure data had been transcribed into the data base for 3,709 of these subjects. By time period, 2,766 subjects were identified between 1998 and 2004 and 5,121 subjects between 2005 and 2009 for the PRA cohort. In the 2006–2007 general hypertensive cohort, 498,896 individuals were identified. Renovascular hypertension and aldosteronism identified by ICD coding accounted for 0.25% of this population. Secondary hypertension patients were excluded from the PRA cohort although CKD patients were included and accounted for 23.5% of the PRA cohort.

There was a 1000-fold range in PRA values. Neither PRA nor log PRA was normally distributed (skewed to the right). The PRA ranges in quartiles were: Q1 <0.43, Q2 0.43–1.30, Q3 1.30–3.70, and Q4 3.7–159 ng/ml/h.

Patient characteristics

The characteristics of the PRA cohort and each PRA quartile are shown in **Table 1**. The mean age was 58 years; 60% were female. Across PRA quartiles there were trends for age and race. Thus, Q4 was significantly younger than Q1 ($P < 0.001$) but only by 5 years. The highest proportion of whites (38%) was in Q4 and the lowest in Q1 (32%). Blacks comprised 30% of Q1 but only 17% of Q4. The prevalence of CKD, defined by an eGFR <60 ml/min/1.73 m^2, was 24% in the overall population and increased from 22% to 27% across PRA quartiles ($P < 0.001$). Congestive heart failure rates also showed a non-significant trend toward higher rates with higher PRA quartiles. Conversely, cerebrovascular disease rates were highest in the lowest PRA quartile and showed a declining trend with higher PRA ($P = 0.012$). There were no significant trends for rates of diabetes or ischemic heart disease across PRA quartiles.

Laboratory characteristics are reported in **Table 2**. Although median PRA increased 40-fold across the quartiles, there was no such trend in plasma aldosterone. Small (<10%) but significant serial trends were observed across PRA quartiles for serum creatinine (it rose), eGFR (it fell), serum sodium (it fell), serum potassium (it rose) and serum bicarbonate (it fell). In contrast, both serum uric acid, and blood urea nitrogen (BUN) increased gradually, significantly, and by more than 10% between Q1 and Q4.

Medication usage

All hypertension subjects vs. PRA cohort. The PRA cohort was prescribed more medications than the general hypertension

Table 1 | Characteristics of plasma renin activity (PRA) cohort

		PRA distribution				
Characteristics	All	Quartile 1 (<0.43)	Quartile 2 (0.43–1.30)	Quartile 3 (1.30–3.70)	Quartile 4 (>3.70)	
	(*N* = 7,887)	(*N* = 1,969)	(*N* = 1,929)	(*N* = 2,015)	(*N* = 1,974)	*P* value
PRA (ng/ml/h)[a]	1.30 (0.43, 3.70)	0.20 (0.16, 0.30)	0.81 (0.70, 1.00)	2.07 (1.60, 2.70)	7.82 (5.10, 13.60)	n/a
Age (Years)	58.0 (15.1)	60.5 (12.9)	59.0 (14.5)	57.0 (15.9)	55.7 (16.5)	<0.001
Mean (s.d.)						
Gender						
Female (%)	59.6	58.1	61.5	58.9	60.0	0.146
Male (%)	40.4	42.0	38.5	41.1	40.0	
Race						
White (%)	34.4	31.5	32.2	35.5	38.4	<0.001
Black (%)	22.7	29.6	25.4	19.0	16.9	
Hispanic (%)	19.0	18.3	18.9	19.6	19.0	
Asian/Pacific (%)	9.3	7.9	11.2	10.0	8.1	
Other (%)	14.6	12.7	12.3	15.9	17.6	
Diabetes (%)	29.1	29.6	29.1	28.0	29.6	0.655
Ischemic heart disease (%)	22.9	25.1	21.2	22.4	22.9	0.032
Congestive heart failure (%)	9.8	9.1	9.6	9.9	10.4	0.617
Cerebrovascular disease (%)	10.5	12.1	10.9	9.1	9.9	0.012
CKD (eGFR, ml/min/1.73 m^2)						
<30 (%)	3.8	2.5	4.3	4.0	4.7	<0.001
<60 (%)	23.5	21.7	22.4	22.8	27.2	
≥60 (%)	67.1	71.1	67.3	67.6	62.6	
No test (%)	5.5	4.7	6.0	5.7	5.6	

Comparisons were made by non-parametric Kruskal–Wallis test for age and laboratory values, and χ^2 test for gender and race.
CKD, chronic kidney disease; eGFR, estimated glomerular filtration rate; n/a, not applicable.
[a]Median (interquartile range).

Table 2 | Laboratory characteristics of PRA cohort

	All		Quartile 1 (PRA <0.43 ng/ml/h)		Quartile 2 (0.43–1.30)		Quartile 3 (1.30–3.70)		Quartile 4 (>3.70)		
Laboratory findings (SD)	(*N* = 7,887)		(*N* = 1,969)		(*N* = 1,929)		(*N* = 2,015)		(*N* = 1,974)		*P* value
Aldosterone (ng/dl)[a]	10.4	*N* = 7,887	11.0	*N* = 1,969	9.2	*N* = 1,929	10.0	*N* = 2,015	12.0	*N* = 1,974	n/a
	(5.0, 19.0)		(5.9, 19.0)		(5.0, 17.0)		(5.0, 18.0)		(6.0, 23.1)		
Creatinine (mg/dl)	1.1 (0.8)	*N* = 7,453	1.1 (0.7)	*N* = 1,876	1.1 (0.9)	*N* = 1,813	1.1 (0.8)	*N* = 1,901	1.2 (0.8)	*N* = 1,863	<0.001
Serum BUN (mg/dl)	17.8 (10.7)	*N* = 5,535	15.9 (8.6)	*N* = 1,419	17.4 (10.3)	*N* = 1,374	18.1 (11.1)	*N* = 1,347	19.6 (12.1)	*N* = 1,395	<0.001
eGFR (eGFR, ml/min/1.73 m^2)	74 (30)	*N* = 7,453	75 (24)	*N* = 1,876	74 (31)	*N* = 1,813	75 (28)	*N* = 1,901	73 (34)	*N* = 1,863	<0.001
Serum potassium (meq/l)	3.9 (0.6)	*N* = 7,483	3.8 (0.6)	*N* = 1,882	3.9 (0.6)	*N* = 1,820	4.0 (0.6)	*N* = 1,909	4.0 (0.6)	*N* = 1,872	<0.001
Serum uric acid (mg/dl)	6.5 (2.2)	*N* = 1,117	6.1 (1.9)	*N* = 264	6.3 (2.1)	*N* = 286	6.5 (2.3)	*N* = 283	6.9 (2.3)	*N* = 284	<0.001
Serum sodium (meq/l)	139 (4)	*N* = 7,256	139 (4)	*N* = 1,828	139 (4)	*N* = 1,770	139 (3)	*N* = 1,834	138 (3)	*N* = 1,824	<0.001
Serum bicarbonate (meq/l)	28 (3)	*N* = 7,197	29 (3)	*N* = 1,811	28 (3)	*N* = 1,760	28 (3)	*N* = 1,816	28 (3)	*N* = 1,810	<0.001
Hemoglobin A_{1C} (%)	6.9 (1.5)	*N* = 2,621	6.9 (1.6)	*N* = 657	7.0 (1.6)	*N* = 616	6.9 (1.5)	*N* = 652	6.8 (1.5)	*N* = 696	0.585

BUN, blood urea nitrogen; eGFR, estimated glomerular filtration rate; n/a, not applicable; PRA, plasma renin activity.
[a]Median (interquartile range).

population (2.69 vs. 1.97, $P < 0.001$), indicating the likelihood that the PRA cohort may have been more difficult to control (Table 3). Although similar proportions of each cohort were not prescribed any medications (16 and 17%, $P = 0.09$), 40% of the PRA cohort and only 21% of the general hypertensive population were prescribed ≥3 medications ($P < 0.001$, Figure 1, Table 4). The prevalence of anti-V medications (diuretic/natriuretic) was greater in the PRA cohort (1.23 vs. 0.84/person, $P < 0.001$) (Table 3). The PRA cohort had 81% who were taking any anti-V medication vs. 67% in the general hypertension population ($P < 0.001$). Anti-R drug (1.45 vs. 1.14/person, $P < 0.001$) usage was also greater in the PRA cohort. Those taking any anti-R drug were similar (85% and 84%) which suggests that the PRA cohort had more patients taking multiple anti-R drugs.

The Kaiser Permanente protocol recommended diuretics as the first drug of choice or ACEIs/ARBs in combination with diuretics. Compared to the general hypertensive population,

Table 3 | Medication usage for those prescribed medications, organized according to anti-V and anti-R medication categories

	All KPSC hypertensives 2006–2007[a]		PRA cohort	PRA quartiles				
		P value		Q1	Q2	Q3	Q4	*P* value for trend
Anti-V meds	67%	**<0.001**	81%	80%	80%	81%	83%	0.031[b]
Distal diuretics	51%	**<0.001**	55%	49%	50%	54%	65%	<0.001[b]
Loop diuretics	8%	**<0.001**	12%	11%	12%	13%	13%	0.130[b]
CCBs	22%	**<0.001**	48%	54%	50%	48%	40%	<0.001[b]
(Anti-V meds/person)	(0.84)	**<0.001**	(1.23)	(1.23)	(1.20)	(1.24)	(1.27)	0.076[c]
Anti-R meds	84%	**0.017**	85%	91%	86%	80%	84%	<0.001[b]
ACEI	54%	**<0.001**	51%	54%	49%	47%	55%	<0.001[b]
ARBs	10%	**<0.001**	17%	17%	17%	17%	17%	0.718[b]
β-Blockers	45%	**<0.001**	55%	74%	59%	47%	40%	<0.001[b]
Other renin suppressors	4%	**<0.001**	19%	24%	21%	16%	14%	<0.001[b]
(Anti-R meds/person)	(1.14)	**<0.001**	(1.45)	(1.73)	(1.50)	(1.29)	(1.28)	<0.001[c]
Meds/person	(1.97)	**<0.001**	(2.69)	(2.95)	(2.70)	(2.52)	(2.56)	<0.001[c]

The *P* values in bold are for comparisons between pre-2005 and post-2005. χ^2 test was used for drug use (yes/no) and *t*-test was used for the number of medications. ACEIs, angiotensin converting enzyme inhibitors; ARBs, angiotensin receptor blockers; CCB, calcium channel blocker; KPSC, Kaiser Permanente Southern California.
[a]General Hypertensive Population (2006–2007). [b]*P* values are based on Cochran–Armitage test for trend. [c]*P* values are for linear trend.

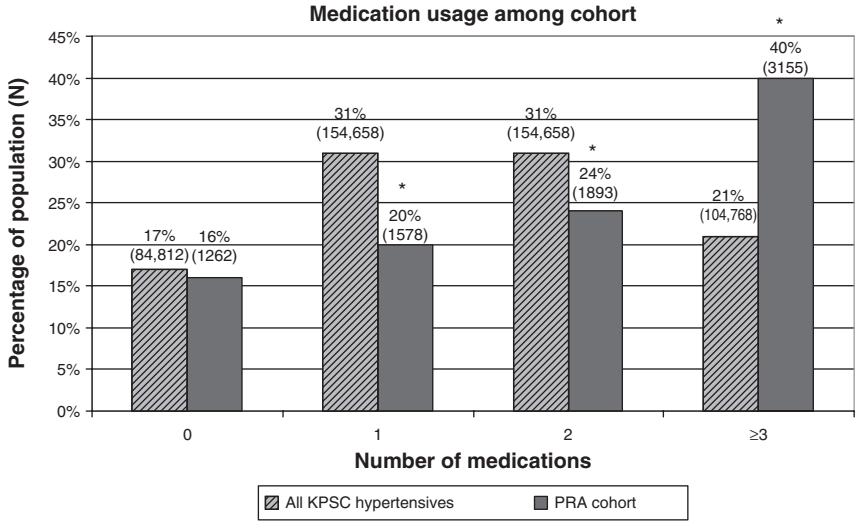

Figure 1 | Number and percentage of subjects prescribed zero, 1, 2 or ≥3 antihypertensive medications. Blue bars, all hypertensives 2005–2006. Red bars, plasma renin activity (PRA) cohort 1998–2009. A color version of the figure is available online. *$P < 0.05$ when comparing the two cohorts. KPSC, Kaiser Permanente Southern California.

Table 4 | Medication usage for general hypertensive population, PRA cohort and PRA quartiles

Medication Number	All KPSC hypertensives 2006–2007	PRA cohort		PRA quartiles				
			P value[a]	Q1	Q2	Q3	Q4	*P* value[b]
0	17%	16%	0.090	12%	18%	20%	16%	<0.001
1	31%	20%	<0.001	16%	20%	23%	20%	0.002
2	31%	24%	<0.001	21%	22%	24%	28%	<0.001
≥3	21%	40%	<0.001	51%	40%	33%	36%	<0.001
Patient *N*	498,896	7,887		1,969	1,929	2,015	1,974	

KPSC, Kaiser Permanente Southern California; PRA, plasma renin activity.
[a]*P* values are based on χ^2 test of proportions between all KPSC cohort and the PRA cohort. [b]*P* values are based on Cochran–Armitage test for trend.

Table 5 | Medication usage for PRA cohort before and after 31 December 2004 (<2005/≥2005)

Medication number	PRA cohort		PRA quartiles							
			Q1		Q2		Q3		Q4	
		P value		*P* value		*P* value		*P* value		*P* value
0	16/17%	0.611	12/12%	0.985	17/19%	0.304	18/21%	0.081	18/15%	0.102
1	22/18%	<0.001	20/15%	0.003	22/19%	0.055	26/21%	0.014	20/20%	0.706
2	25/23%	0.141	23/20%	0.119	25/19%	0.007	25/23%	0.485	26/29%	0.231
≥3	37/42%	<0.001	45/53%	<0.001	36/43%	0.002	31/34%	0.184	36/37%	0.670
Patient *N*	2,766/5,121		641/1,328		862/1,067		651/1,364		612/1,362	

PRA, plasma renin activity.

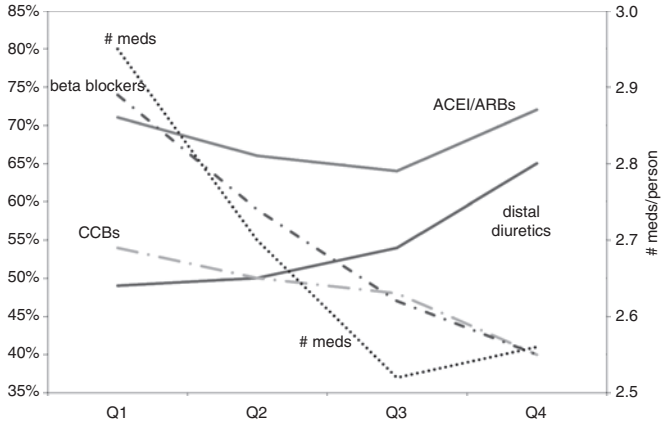

Figure 2 | Plasma renin activity (PRA) quartiles (Q1, Q2, Q3, Q4). Number of medications prescribed (right axis), and percentage of each quartile taking β-blockers, CCBs, ACEIs/ARBs, and/or diuretics acting in the distal nephron for patients prescribed medications. ACEIs, angiotensin converting enzyme inhibitors; ARBs, angiotensin receptor blockers; CCB, calcium channel blocker.

a slightly higher proportion of patients in the PRA cohort were prescribed diuretics (67% vs. 59%, $P < 0.001$) and ACEIs/ARBs (68% vs. 64%, $P < 0.001$). β-Blockers were added next if blood pressure was not controlled. Here, usage was also higher among the PRA cohort: 55% vs. 45% ($P < 0.001$). CCBs were the fourth drug of choice; their overall usage was more than twice as high in the PRA cohort as in the general hypertension cohort (48% vs. 22%) ($P < 0.001$).

PRA quartiles. Among the PRA cohort, the lowest quartile were prescribed more medications as 51% were prescribed ≥3 medications averaging 2.95 meds/person compared to 36% and 2.56 meds/person in Q4. β-Blocker usage paralleled medication number across the quartiles (Figure 2). Among the anti-R drugs, there was no trend across PRA quartiles in usage of renin–angiotensin system blockers (ACEIs/ARBs) but β-blocker usage was almost twofold higher in Q1 vs. Q4 (74% vs. 40%, $P < 0.001$)(Figure 2). There was a trend toward greater anti-V drug use overall across the PRA quartiles from 80 to 83% ($P = 0.031$) particularly in terms of diuretic usage (Table 3, Figure 2). However, CCB use actually declined with higher quartiles (54 to 40%; $P \leq 0.001$).

Medication usage for pre-2005 vs. 2005 onward

The majority (65%) of the PRA cohort was identified after 31 December 2004 and that period was associated with higher medication usage overall (2.7 vs. 2.6, $P < 0.001$). From 2005 onward, the percentage of patients prescribed ≥3 medications increased from 37% to 42% ($P < 0.001$) with the greatest increase occurring in Q1 patients (45% to 53%, $P < 0.001$) (Table 5). Among drug types, distal diuretics (48–58%, $P < 0.001$), ACEIs (47–53% $P < 0.001$), and ARBs (13–19%, $P < 0.001$) increased; β-blockers remained essentially unchanged (54–56%, $P = 0.85$); while other renin suppressors (25–16%, $P < 0.001$) and loop diuretics fell (14–11% $P < 0.001$) (Table 6 and Figure 3).

Table 6 | Medication usage for those prescribed medications, before and after 31 December 2004 (*N* = 2,316/4,265, <2005/≥2005)

	PRA Cohort	*P* value	PRA Quartiles	*P* value		*P* value		*P* value		*P* value	*P* value for trend
			Q1		Q2		Q3		Q4		
Anti-V meds	79/82%	**0.013**	76/82%	**0.004**	78/82%	**0.064**	81/81%	**0.855**	83/83%	**0.868**	0.002/0.793
Distal diuretics	48/58%	**<0.001**	42/52%	**<0.001**	43/56%	**<0.001**	51/56%	**0.069**	61/67%	**0.019**	<0.001[a]/<0.001[a]
Loop diuretics	14/11%	**<0.001**	12/11%	**0.433**	12/11%	**0.497**	15/12%	**0.104**	18/11%	**<0.001**	0.005[a]/0.982[a]
CCBs	49/47%	**0.187**	52/54%	**0.440**	51/50%	**0.730**	48/48%	**0.816**	45/38%	**0.008**	0.009[a]/<0.001[a]
(Anti-V meds/person)	1.2/1.3	**0.001**	1.1/1.3	**0.001**	1.1/1.3	**<0.001**	1.2/1.2	**0.596**	1.3/1.3	**0.060**	<0.001[b]/0.310[b]
Anti-R meds	82/87%	**<0.001**	89/92%	**0.035**	84/87%	**0.101**	74/83%	**<0.001**	81/86%	**0.006**	<0.001/<0.001
ACEI	47/53%	**<0.001**	51/56%	**0.097**	48/50%	**0.515**	44/48%	**0.106**	45/59%	**<0.001**	0.010[a]/0.194[a]
ARBs	13/19%	**<0.001**	13/18%	**0.002**	11/21%	**<0.001**	12/20%	**<0.001**	15/17%	**0.315**	0.151[a]/0.457[a]
β-Blockers	54/56%	**0.085**	70/75%	**0.019**	58/60%	**0.243**	43/49%	**0.035**	41/39%	**0.592**	<0.001[a]/<0.001[a]
Other Renin suppressors	25/16%	**<0.001**	30/21%	**<0.001**	26/18%	**<0.001**	22/13%	**<0.001**	21/11%	**<0.001**	<0.001[a]/<0.001[a]
(Anti-R meds/person)	1.4/1.5	**0.002**	1.7/1.8	**0.057**	1.5/1.5	**0.091**	1.2/1.3	**0.028**	1.2/1.30	**0.182**	<0.001[b]/<0.001[b]
Meds/person	2.6/2.7	**<0.001**	2.8/3.0	**0.001**	2.6/2.8	**<0.001**	2.4/2.6	**0.067**	2.6/2.6	**0.708**	0.003[b]/<0.001[b]

The *P* values in bold are for comparisons between pre-2005 and post-2005. χ^2 test was used for drug use (yes/no) and *t*-test was used for the number of medications.
ACEIs, angiotensin converting enzyme inhibitors; ARBs, angiotensin receptor blockers; CCB, calcium channel blocker; PRA, plasma renin activity.
[a]*P* values are based on Cochran–Armitage test for trend. [b]*P* values are for linear trend.

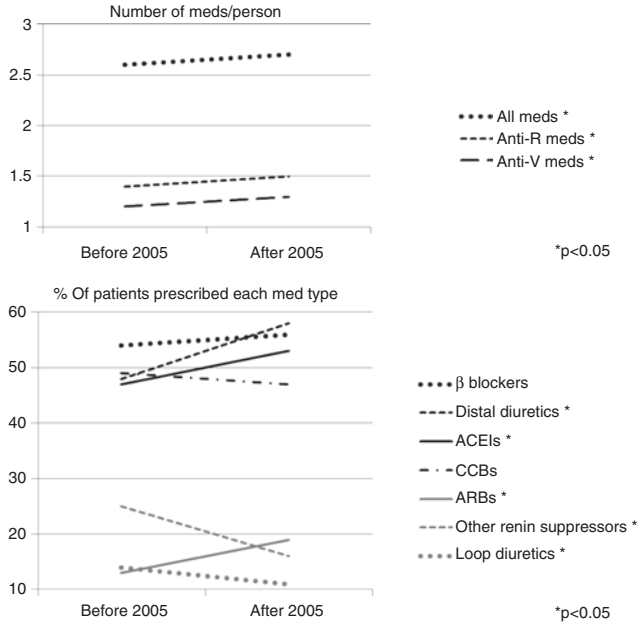

Figure 3 | Number of meds by category and class pre 2005 and 2005 onward for patients who were prescribed medications. ACEIs, angiotensin converting enzyme inhibitors; ARBs, angiotensin receptor blockers; CCB, calcium channel blocker.

Among PRA quartiles (Table 6), medication usage increased in Q1 (2.8 to 3.0 meds/person, $P < 0.001$) Q2 (2.6 to 2.8, $P < 0.001$) and Q3 (2.4 to 2.6, $P = 0.067$). In Q4 medication usage remained at 2.6 per person as increases in diuretic, ACEI and ARB usage were offset by reduced usage of loop diuretics, CCBs, β-blockers and other renin suppressors. Overall, the recommendation of diuretics as first line in the algorithm appears evident as there were no differences in anti-V drug use across PRA quartiles. This is in contrast to the pre-2005 period where the higher PRA quartiles were associated with greater anti-V drug usage (Table 6).

Chronic kidney disease and diuretic usage

Although there was no trend across PRA quartiles for the anti-V drugs as a group, diuretics acting in the distal nephron were prescribed less frequently in the lowest quartile (49% vs. 50%, 54%, 65% Q1 to Q4; $P < 0.001$ for trend) (Figure 2). CKD rates also paralleled the increase in diuretics usage, specifically loop diuretics (data not shown). Multivariate logistic regressions analysis to calculate OR for diuretic usage adjusting for CKD (eGFR <60 ml/min/1.73 m^2), age >59 years, black race, and gender is shown in Table 7. Higher PRA quartiles were associated with greater diuretic usage and increasing OR (95% confidence interval of 1.0 (0.9–1.2), 1.3 (1.1–1.5), and 1.9 (1.7–2.3) in Q2, Q3, and Q4 vs. Q1 respectively after adjusting for CKD, age, gender, and black race. Presence of CKD (eGFR <60 ml/min/1.73 m^2) was associated with higher OR for diuretic usage OR = 1.6 (1.4–1.8) as was black race OR = 1.4 (1.2–1.5) and age >59 OR = 1.1 (1.0–1.3).

Blood pressures

Among patients prescribed medications, systolic and diastolic blood pressures were highest in the lowest PRA quartile (146/81 (mm Hg)) and fell across quartiles to 134/76 in Q4 ($P < 0.001$ for linear trend) (Table 8). In all of the quartiles, blood pressures ranged from moderately high (150–160 systolic) to medium/low. The lowest blood pressures were present in the

highest PRA quartile where one SD below the mean averaged only 114/62 compared to 123/67 in Q1.

Among the PRA quartiles, greater medication usages were associated with higher systolic blood pressure (**Figure 4**). Q1 averaged 146 and 2.95 meds while Q4 averaged 134 and 2.56 meds. Linear regressions after adjusting for age, gender, black race, CKD, and PRA quartile demonstrated that every 10 mm Hg increase in systolic blood pressure was associated with a 0.1 increase in medications ($P < 0.001$).

DISCUSSION

Summary of findings

Polypharmacy, defined as two or more antihypertensive medications, was the norm and increased over time in this large ethnically diverse hypertensive population that had PRA levels measured, and in whom treatment was in part driven by a JNC7 based algorithm. This population of mostly treated hypertensive patients exhibited an enormous range of PRA levels, from 0.1 to >100 ng/ml/h. When evaluated by PRA quartiles, the lowest PRA quartile had the poorest blood pressure control and the greater increase in medication usage between the early and later years. In contrast, the highest PRA quartile had the best blood pressure control, the least antihypertensive medication usage, and no increase in medication usage between early and later years. The higher PRA quartiles had higher BUN, uric acid levels, and rates of CKD.

Drug type usage differed across the PRA quartiles. Compared to the highest PRA quartile, the lowest PRA quartile had more PRA suppressing medications such as β-blockers (74% vs. 40%), more CCBs (54% vs. 40%), similar proportions of ACEIs or ARBs (71% vs. 72%) and lesser usage of diuretic medications (49% vs. 65%). These differences reflect both the stimulating and suppressing effects of antihypertensive drugs on PRA as well differences in number of medications to control blood pressure. The PRA level did not affect drug choice as medications were analyzed prior to the PRA value.

Table 7 | Multivariate logistic regressions analysis for diuretic usage

Odds ratios (ORs) for any diuretic use adjusting for age, gender, race, and CKD

Variable	OR	95% CI	*P* value
Q2 vs. Q1	1.0	0.9–1.2	0.681
Q3 vs. Q1	1.3	1.1–1.5	0.002
Q4 vs. Q1	1.9	1.7–2.3	<0.001
CKD (eGFR <60 ml/min/1.73 m^2)	1.6	1.4–1.8	<0.001
Age >59 vs. 18–59	1.1	1.0–1.3	0.027
Male	0.9	0.8–1.0	0.262
Black race	1.4	1.2–1.5	<0.001

CI, confidence interval; CKD, chronic kidney disease ; eGFR, estimated glomerular filtration rate.

Implications

Polypharmacy is currently the norm in hypertension treatment and is deemed by many as necessary[6,27,28] since initial therapy with multiple medications is reported to improve blood pressure control in uncomplicated hypertension populations.[29,30] Our current study illustrates the limitations of this "one size fits all" approach to hypertension management. These approaches neither address the underlying pathophysiology, nor the possibility that paradoxical increases in blood pressure by antihypertensive drugs[19] might reduce efficacy and increase the number of drugs needed for blood pressure control. This approach often means polytherapy for life, when monotherapy might be achievable. Thus, in a small clinical trial, Dickerson *et al.*[18] demonstrated, after assessing the effect of four different medications in uncomplicated hypertensive patients, that blood pressure control could be achieved with monotherapy in over 73%.

The goal of monotherapy is laudable since medication adherence is an important factor in controlling blood pressure and

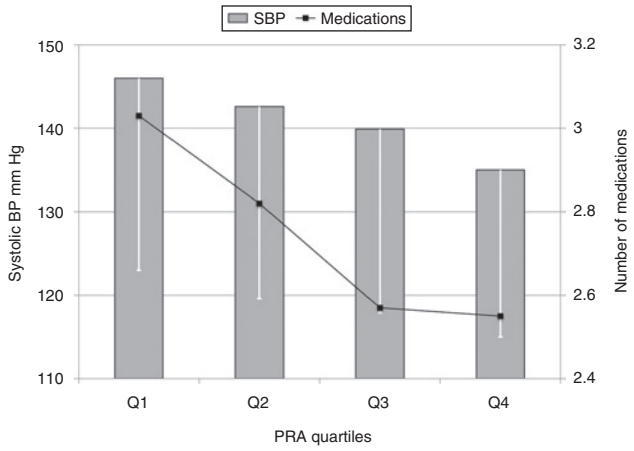

Figure 4 | Plasma renin activity (PRA) quartiles (Q1, Q2, Q3, Q4). Mean systolic blood pressure (SBP) and average number of medications prescribed. *Linear regressions adjusting for age, gender, black race, chronic kidney disease, and PRA quartile demonstrated every 10 mm Hg increase in SBP was associated 0.1 increase in # meds ($P < 0.001$)

Table 8 | Blood pressures (for those prescribed medications) in PRA quartiles

	Q1 (*n* = 835)	Q2 (*n* = 642)	Q3 (*n* = 780)	Q4 (*n* = 850)	*P* value for linear trend
SBP (SD)	146 (23)	143 (23)	139 (22)	134 (20)	<0.001
DBP (SD)	81 (13)	79 (14)	78 (14)	76 (14)	<0.001
SBP 1 SD range	169–123	166–120	161–118	155–114	
DBP 1 SD range	94–67	92–65	93–64	90–62	

BP data were available for analysis from 2006 to 2009 ($N = 3,107$).
DBP, diastolic blood pressure; SBP, systolic blood pressure; PRA, plasma renin activity.

falls with increasing medication usage.[31] Successful blood pressure control has been directly associated with medication adherence[32] and lack of adherence increases health utilization costs.[33] Additionally, monotherapy can minimize adverse reactions, drug interactions, and drug costs. Minimizing medication burden if possible should always be a consideration in hypertension management.

An individualized approach to drug selection has been proposed based on volume-vasoconstriction concepts of blood pressure control and plasma renin test guided therapy.[14] Low renin patients do not respond as well to anti-rennin–angiotensin system drugs and respond better to natriuretic drugs and vice versa.[17,20,34–36] Egan *et al.* successfully applied this approach in a small trial of uncontrolled hypertensive patients who were already taking multiple drugs.[20] Moreover, Turner *et al.* showed that hypertensives with higher PRA levels, either at baseline or during treatment, respond most favorably to atenolol, an anti-renin drug type, while those with lower PRA levels respond better to hydrochlorothiazide, a natriuretic anti-volume drug type.[16]

In the current observational study PRA was not used to guide treatment. PRA was measured on or after the day that medication usage was codified, and could not have influenced medication choice. Volume-vasoconstriction concepts clearly did not guide treatment strategy as anti-R medication usage was greatest in the lowest PRA quartile and least in the highest. Blood pressures were also highest in the lowest PRA quartile. In fact, it is likely that the medication differences influenced the PRA levels. β-Blockers decrease PRA while ACEIs, ARBs, and CCBs increase PRA levels and also proportionately affect the aldosterone/renin ratio.[25,37,38] It is therefore not surprising that 77% of the lowest PRA quartile was taking renin suppressing β-blockers compared to only 41% of the highest quartile.

At the other end of the renin spectrum, some patients with the highest PRA levels may have been excessively volume depleted since they were nearly twice as likely (OR 1.9) to be prescribed diuretics and they had lower blood pressures together with higher BUN and serum uric acid levels. This latter difference may indicate a lesser ability to excrete the products of metabolism. Alternatively, the higher PRA may have been the result of an increased rate of CKD, as defined by eGFR <60 ml/min/1.73 m^2 though the mechanism of this relationship has not yet been established.[39] This study demonstrated greater CKD rates and more diuretic usage with rising PRA quartiles even after adjusting for age, gender, and race.

It might be useful to determine if high PRA levels in successfully controlled hypertensive patients can be used to indicate excessive volume depletion where the PRA elevation is reactive. However, in such a trial it would be important to take into account the fact that the PRA level in patients taking an ACEI or ARB overestimates by about 90% the *in vivo* activity of the renin–angiotensin system because these drugs only block renin–angiotensin system activity *in vivo*, not *in vitro*.[40] In the PRA cohort, 68% of the treated patients were taking an ACEI or ARB, therefore the true activity of their circulating renin–angiotensin system *in vivo* was overestimated.

Limitations

The data from the PRA cohort are not representative of the hypertensive population at large. Among the treated patients, usage averaged 2.0 meds/person in the general hypertensive population and 2.7 meds/person in the PRA cohort. Additionally, 3 or more meds were prescribed for only 21% of the general hypertensive population but for 40% of the PRA cohort. In all likelihood, PRA was ordered as part of an aldosterone/renin ratio to rule out secondary hypertension, including primary aldosteronism. Moreover, since the PRA cohort appeared more difficult to control they most likely included a higher proportion of the resistant and refractory hypertensive subjects.

This selection bias affected medication usage as medications were calculated based on the first PRA value in the PRA cohort and not identified by date of the first hypertension diagnosis whereas in the general hypertension cohort, medication usage was assessed relative to the first coded diagnosis of hypertension. It is possible that the medication usage in the general hypertensive population was less than in the PRA cohort because it was associated with the first blood pressure coding and therefore likely to have been earlier in the treatment work-up. In all likelihood, the PRA cohort had longer follow-up and more frequent treatments for their hypertension. This also speaks to a greater duration of hypertension in the PRA cohort. This cross sectional study however could not assess or compare the duration of hypertension in the PRA cohort or the general hypertensive population.

Additional limitations are that the data base entries were not confirmed and there is no information concerning adherence to medications. Finally, close to 50% did not have blood pressure measurements available for analysis since these data became available in the data base half way through the dates chosen for analysis.

Strengths

The strengths are the size of the population of hypertensive patients, ethnic diversity that is representative of the general population within the practicing area, and a large number of PRA measurements using a sensitive assay method that was performed in a national diagnostic laboratory. Additionally, the findings from 2005 to 2009 also portray the results of an algorithm driven, hypertension treatment program within a large integrated health system.

Summary

This report describes a wide range of PRA levels among mostly treated hypertensive patients. It demonstrates that low and high treatment PRA levels are associated with differences in blood pressure control, in number of drugs prescribed, and in blood levels of BUN and creatinine. Polypharmacy was highly prevalent, as 40% of the PRA cohort and 50% of the low renin quartile was prescribed three or more antihypertensive medications. The wide range of PRA levels, the different medication usage in relation to PRA levels, and the availability of a pathophysiological concept to interpret them illustrates that opportunities exist for clinical trials to investigate if a plasma renin test

guided treatment strategy will improve blood pressure control with fewer medications.[21]

Acknowledgment: This study was partially funded by an investigator initiated research grant from Novartis Pharmaceuticals (J.J.S. PI) and supported by Kaiser Permanente Southern California Regional Research. The study was supported by a research grant from the National Institute of Diabetes, Digestive and Kidney Disease of the National Institute of Health (R01 DK078106) for K.K.Z. The authors would like to thank Federico B. Calara, PhD for his contributions in conceptualizing the study and data interpretation. J.J.S. and J.S. had full access to the data and took responsibility for the accuracy and the integrity of the data analysis.

Disclosure: J.H.L.: Patent #09/657027 "Method for evaluating and treating hypertension". The other authors declared no conflict of interest.

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