ORIGINAL ARTICLE

Plasma Renin-guided Therapy in Patients of Primary Hypertension on Antihypertensives: A Prospective Cohort Study

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Abstract

Background: Most guidelines for hypertension overlook the underlying pathophysiologic basis in deciding antihypertensives. Based on renin levels, hypertension may be classified as high-renin hypertension (HRH), low-renin hypertension (LRH), and normal-renin hypertension (NRH). The study examined the renin levels in a hypertensive population and assessed the effect of renin-guided antihypertensive management on blood pressure (BP) control.

Materials and methods: This study was a single-center prospective cohort study. Subjects with primary hypertension (aged 20–60 years) on antihypertensives were included in the study. Initial BP was recorded and subsequently, all antihypertensives were discontinued. After 2 weeks, second BP was recorded and plasma renin assay (PRA) sample was collected. All patients were restarted on the previous antihypertensives and further modification of medication was performed based on their PRA. Anti V drugs, such as diuretics and calcium channel blockers (CCBs) were used in LRH while beta-blockers and antirenin drugs (Anti R drugs) were used in HRH.

Results: The study included 918 patients with hypertension and 896 cases were finally analyzed. Of these patients, 287 (32.03%) had LRH (<0.51 ng/mL/hr), 412 (45.98%) had HRH (>2.64 ng/mL/hr), while 197 (21.99%) had NRH (0.51–2.64 ng/mL/hr). Renin-guided management caused significant BP reduction. In controlled BP group, the systolic BP (SBP)/diastolic BP (DBP) before and after modification were 133.83 ± 3.36/84.77 ± 3.12 and 123.87 ± 10.59/84.05 ± 1.84, respectively (p-value < 0.05). In uncontrolled BP group, the corresponding SBP/DBP were 152.17 ± 2.95/90.36 ± 5.02 and 138 ± 1.23/87.78 ± 0.84, respectively (p-value < 0.05). The number of hypertensives used in patients also reduced with reduction in patients on two, three, or four drugs.

Conclusions: Renin-guided therapy is useful for improving BP control in both controlled and uncontrolled hypertensive patients and in reducing the number of antihypertensive drugs.

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Background

Hypertension is a common public health problem worldwide affecting approximately 25.3% of Indian population.[1] The Eighth Joint National Committee (JNC 8) guidelines recommend initiating treatment of hypertension with one of the four agents—angiotensin-converting enzyme inhibitor (ACEI), angiotensin receptor blocker (ARB), CCB, or thiazide-type diuretic, with a target BP of less than 140/90 mm Hg.[2] However, most national and international guidelines overlook the underlying pathophysiologic basis for deciding the antihypertensive therapy. The selection of the initial drug and any add-on drug is arbitrary, and therefore is alike to the principle that "one size fits all."[3] Therefore, in significant number of patients, BP is inadequately controlled which predisposes them to end-organ damage and vascular complications.[4] Moreover, the use of a pathophysiologically "improper" antihypertensive drug may lead to a lesser BP reduction, and can induce a paradoxical pressor response that contributes to increase in the prevalence of resistant hypertension.[4,5]

The primary determinants of BP are vascular tone and circulating volume.[6] Vascular tone (the "resistance" or "R-factor") is mainly related to renin-angiotensin II system (RAS) dependent vasoconstriction and, therefore, to renin activity. Circulating volume (the "volume" or "V-factor") may increase due to excessive sodium intake or primary aldosteronism, leading to renin suppression.[7] The interaction between "R-factor" and "V-factor" maintains the BP in the normal range.[6] Based on renin levels, hypertension may be classified as HRH, LRH, and NRH.[8] High-renin hypertension is associated with increase of peripheral resistance and is likely to respond to Anti R drugs, whereas LRH may represent primary sodium-volume overload and is likely to respond to diuretics and CCB (Anti V drugs).[9]

Renin-guided therapy, to guide the use of antihypertensive drugs, evolved in the early 1970s[10,11] and was tried for the management of hypertension, particularly poorly controlled hypertension.[12,13] However, this concept has not gained much acceptance as past studies have reported ambivalent results with renin-guided therapy.[3,12] A major reason has been the cost and difficulty in conducting the test and complicated patient preparation for sampling.[9] However, with the advent of plasma-based commercially available tests, sample collection has been rendered easier.[13] Only a few studies on renin-guided hypertension therapy in Asian population have been reported. The present study was designed to examine the pattern of PRA levels of a group of multiethnic hypertensive population on medication and modify the antihypertensive therapy based on their PRA levels to assess the effect on control of BP.

Materials and Methods

Study Design

This study was a single-center open-label prospective cohort study.

Study Population

Adult cases of primary hypertension in the age group of 20–60 years on follow-up in a tertiary care hospital in Mumbai were considered for the study. The study included cases with primary hypertension on antihypertensive medication, who agreed on discontinuation of ongoing medication for 2 weeks prior to PRA assessment. Patients

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with features of secondary hypertension, poorly controlled diabetes, chronic kidney disease stages 3–5, liver disease, congestive heart failure, renovascular hypertension, patients on oral contraceptive pills (OCPs) or nonsteroidal anti-inflammatory drugs (NSAIDs), any life-threatening illness, Cushing's syndrome, genetic causes of hypertension, any active disease process requiring new diagnostic and therapeutic plans, inability to discontinue antihypertensive medications, mental illness or personality disorder that might interfere with adherence to study protocol, were excluded from the study. Patients having a BP of >180/120 mm Hg on discontinuation of antihypertensives during the 2 weeks in the run-up to PRA assessment were also excluded, and advised to resume medication to prevent any possible adverse outcomes.

Baseline Assessment

A history and physical examination were performed for all subjects at the initial visit. A complete biochemistry, hemogram, metabolic panel, lipid profile, thyroid hormone level, electrocardiogram, and urinalysis with 24-hour urine protein were obtained at the time of the initial visit. Blood pressure was recorded at baseline. Those already on medication were advised to report after 2 weeks of abstinence from medication with close monitoring of BP at home. Thereafter, all the abovementioned tests were performed on them. Blood pressure was recorded at the initial visit after abstinence and thereafter, at each visit. Any symptoms or problems encountered were recorded.

Measurement of BP

In the hospital, BP was recorded using a digital sphygmomanometer (HEM-712 CLC; Omron Healthcare, Vernon Hill, Illinois) with appropriately sized arm cuff, after 5 minutes of rest in a quiet room, in sitting position. The mean of three readings was obtained and considered as the final SBP and DBP. All subjects were trained to measure BP at home or nearby suitable place with the use of any standard manual or digital sphygmomanometer. The patients recorded their BP twice daily in the week prior to each visit.

Measurement of PRA

Plasma renin assay was performed using plasma renin activity kits (RIAZEN, R-EX-125, Zentech Company). After lying in supine position for at least 15 minutes, 2 mL of blood was withdrawn from the patient in a fasting state and collected in chilled ethylenediaminetetraacetic acid vacu-container. Plasma was immediately frozen to avoid inadvertent conversion of pro-renin to active renin. The PRA value given in the renin kit, 0.51–2.64 ng/mL/hr was considered as the baseline normal PRA for the study.

Protocol

The study group of hypertensive subjects included diagnosed and followed-up cases fulfilling the mentioned inclusion or exclusion criteria. Informed consent from all the patients was taken. Appropriate clearance from the institutional ethical committee was obtained. Initial BP was recorded and patients were advised to discontinue all antihypertensives from the first day. Patients were advised to check their BP daily. In case of any symptoms, adverse events, or high BP (SBP ≥ 180 and DBP ≥ 120 mm Hg), patients were advised to resume their previous antihypertensives. These patients were excluded from the study.

After 2 weeks, second BP was recorded in the clinic and PRA sample was collected as per the study protocol. All patients were restarted on the same medication that they were using 2 weeks back. After 2 weeks, once the PRA levels were available, patients were recalled to the hospital for further action.

Categorization of Hypertensives as per PRA

- Low-renin hypertension was defined as hypertension with PRA <0.51 ng/mL/hr.
- High-renin hypertension was defined as hypertension with PRA >2.64 ng/mL/hr.
- Normal-renin hypertension was defined as hypertension with PRA 0.51–2.64 ng/mL/hr.

Management based on PRA

Patients were categorized as HRH, NRH, or LRH. The choice of antihypertensive is given in Table 1. If a patient was only on a single drug of one class (LRH or HRH) he/she was allowed to continue the same medication. In case a patient was on two drugs, one of R and the other of V class, treatment was adjusted as per PRA values, and if previously on three or more drugs, only one drug was initiated based on PRA value. Provision for fourth medicine, if required, was left to the individual judgment of the physician. Anti V drugs, such as diuretics (hydrochlorthiazide and indapamide) and CCBs (amlodipine) were used in LRH. In HRH, beta-blockers (atenolol and metoprolol), ACEI (ramipril and enalapril), or ARB (losartan and telmisartan) were used.

All medication was given once a day dose to start with. Care was taken to introduce minimal changes in existing medications as far as possible. No specific preference was given to any drug in each class and standard antihypertensive prescribing practice was followed. Medication was initiated from minimum therapeutic dose and was gradually increased till optimal response. Second drug was introduced only after maximum mentioned dose of first drug was exhibited. If BP was >140/90 mm Hg, relative efficacy of either drug in controlling BP was analyzed. All routine lifestyle recommendations were continued. Patients were recalled every 2 weeks until BP was controlled or until the clinician was satisfied that appropriate therapeutic adjustments had been made. When hypertension control was optimum on two occasions, follow-up was performed on monthly basis.

Outcomes

Primary outcome was defined as achieving BP <140/90 mm Hg with a single drug, while secondary outcome was defined as achieving BP <140/90 mm Hg with two or more drugs.

Statistical Analysis

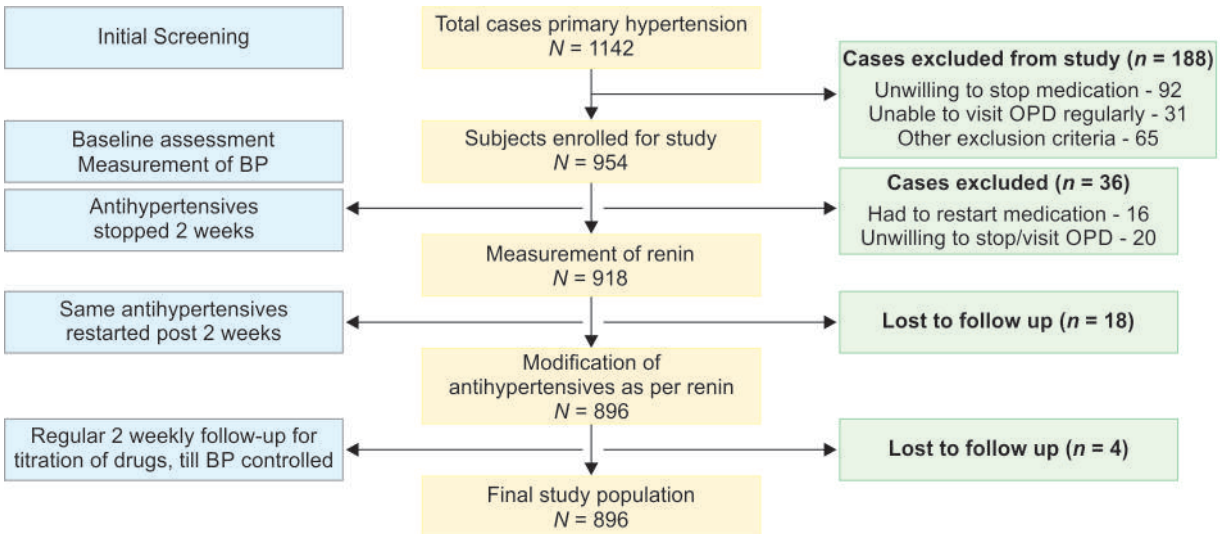
The expected sample size was calculated to be 394, with an expected incidence of 10% (of uncontrolled hypertension), confidence interval of 0.95, power of 0.8, and assumed relative risk of 2. Statistical analysis of the data was performed using appropriate statistical packages (SPSS version 18). Frequency, percentage, and paired *t*-test were used for comparison. *P*-value less than 0.05 was considered statistically significant. Data were reported as mean ± standard deviation (SD). Changes in BP from initial and subsequent control were tested using the Student's *t*-test for paired observations.

Results

In total, 1,142 patients with essential hypertension who visited the hospital from November 2015 to July 2017 were enrolled in the study, of which 188 cases were excluded (as given in Flowchart 1). Subsequently, 918 cases which were initially included in the study, underwent baseline assessment and BP measurements, and their antihypertensive medications were discontinued. Thirty-six cases had to be excluded further as 16 cases had to resume their medication and 20 cases withdrew from the study citing unwillingness to discontinue medication or visit hospital frequently. Renin levels were assessed in 918 subjects and subsequent modification of antihypertensives was possible in 896 subjects as 22 were lost to follow-up. The consort diagram of the study is shown in Flowchart 1.

Baseline Characteristics

Majority were males [531 (59.26%)] and were in the age group of 50–60 years [431 (48.10%)].



Flowchart. 1: Consort diagram of the study

Of the total subjects, 813 (90.73%) had controlled BP while 83 (9.27%) had uncontrolled BP, despite medication. In the controlled BP group, 234 (28.78%) were on single drug, 381 (46.86%) on two drugs, 84 (20.34%) on three drugs, and 114 (14.02%) were on four or more drugs. The initial SBP and DBP (mean ± SD) (mm Hg) were 131 ± 26.22 and 82 ± 16.35, respectively, which increased to 166 ± 34.42 and 98 ± 19.33, after discontinuation of antihypertensives for 2 weeks.

The most commonly used antihypertensives used were diuretics in 529 (65.06%) cases, followed by CCB and beta-blockers used in approximately 50% of the population. In patients on four drugs or patients with uncontrolled BP, more than 90% were already on the above four groups of drugs.

Plasma Renin Assay Measurements

The estimation of PRA showed that 287 patients (32.03%) had low PRA levels (<0.51 ng/mL/hr), 412 (45.98%) had high PRA levels (>2.64 ng/mL/hr), while 197 (21.99%) had PRA in the normal range (0.51–2.64 ng/mL/hr). Among the patients on a single drug, 118 (50.42%) had low PRA and 116 (49.57%) had high PRA, while majority of the subjects on two or three drugs had high PRA, as given in Table 2. In uncontrolled BP group, all patients had normal PRA levels.

Blood Pressure Control after Renin-guided Management

The antihypertensives of the subjects were modified as per the protocol given in Table 1. Compared to the initial therapy, there was a significant reduction in BP after renin-guided management. In subjects

Table 1: Protocol for modification of antihypertensive drugs based on the renin levels

Present type of drug	*Status of BP*	*Modification advised*
Low-renin hypertension (LRH)		
≥1 V drug, no R drug	If BP controlled	Same V drugs
	If BP >140/90	Increase dose or add V drugs
≥1 R drug, no V drug	Initial step	Stop R drugs, add V drugs
	If BP controlled	Same V drugs
	If BP >140/90	Increase dose or add V drugs
≥1 R drug + ≥1 V drug	Initial step	Stop R drugs, same V drugs
	If BP controlled	Same V drugs
	If BP >140/90	Increase dose or add V drugs
Normal-renin hypertension (NRH)		
≥1 V drug, no R drug	If BP controlled	Same V drugs
	If BP >140/90	Add R drugs
	If still BP >140/90	Increase dose V/R drugs, additional V/R agent
≥1 R drug, no V drug	If BP controlled	Same R drugs
	If BP >140/90	Add V drugs
	If still BP >140/90	Increase dose V/R drugs, additional V/R agent
≥1 R drug + ≥1 V drug	If BP controlled	Same V + R drugs
	If BP >140/90	Increase dose V/R drug, additional V/R agent
High-renin hypertension (HRH)		
≥1 R drug, no V drug	If BP controlled	Same R drugs
	If BP >140/90	Increase dose or add V drugs
≥1 V drug, no R drug	Initial step	Stop V drugs, add R drugs
	If BP controlled	Same R drugs
	If BP >140/90	Increase dose or add R drugs
≥1 R drug + ≥1 V drug	Initial step	Stop V drugs, same R drugs
	If BP controlled	Same R drugs
	If BP >140/90	Increase dose or add R drugs

Anti V drugs include diuretics (hydrochlorthiazide and indapamide), CCBs (amlodipine); Anti R drugs include beta-blockers (atenolol and metoprolol), ACEI (ramipril and enalapril), or ARBs (losartan and telmisartan)

with controlled BP, the SBP before and after modification was 133.83 ± 3.36 and 123.87 ± 10.59, respectively (p-value < 0.05), while the corresponding DBP was 84.77 ± 3.12 and 84.05 ± 1.84, respectively (p-value < 0.08). The change in both SBP and DBP was statistically significant in the three- and four-drug group, as shown in Table 3. In subjects with uncontrolled BP, the SBP before and after modification was 152.17 ± 2.95 and 138 ± 1.23, respectively (p-value < 0.05), while the corresponding DBP was 90.36 ± 5.02 and 87.78 ± 0.84, respectively (p-value < 0.05).

The adequacy of BP control was compared before and after renin-guided antihypertensive therapy. In the initial stage, 234 patients (26.12%) were on single drug, 381 (42.52%) on two drugs, eight (9.38%) on three drugs, and 114 (12.72%) were on four drugs for BP control. However, after renin-guided therapy, better control was achieved with 679 patients (75.78%) on single drug, 103 (11.50%) on two drugs, 94 (10.49%) on three and/or four drugs, respectively; with no patient needing more than four drugs, with a statistically significant p value, as shown in Table 4. The 83 subjects (9.26%) with uncontrolled hypertension despite multiple drugs earlier, responded well to renin-guided approach and had a controlled BP on four or less drugs.

Table 2: Levels of renin in subjects with variable number of antihypertensives

Sl. no.	*LRH Low PRA (<0.51 ng/mL/hr)*	*NRH Mod PRA (0.51–2.64 ng/mL/hr)*	*HRH High PRA (>2.64 ng/mL/hr)*
One drug (n = 234) (% of n)	118 (50.42%)	–	116 (49.57%)
Two drugs (n = 381) (% of n)	138 (36.22%)	–	243 (63.77%)
Three drugs (n = 84) (% of n)	31 (36.90%)	–	53 (63.09%)
Four drugs (n = 114) (% of n)	–	114 (100%)	–
Controlled total (n = 813) (% of n)	287 (35.30%)	114 (14.02%)	412 (50.67%)
Uncontrolled (n = 83) (% of n)	–	83 (100%)	–
Total (n = 896) (% of n)	287 (32.03%)	197 (21.99%)	412 (45.98%)

Discussion

This study assessed the renin levels in hypertensive patients after discontinuation of antihypertensives for 2 weeks. Most subjects had high renin levels (45.98%) while low or normal renin was observed in 32.03% and 21.99%, respectively. Thereafter, the antihypertensives were modified based on renin-based algorithm. This resulted in better control of BP with significant reduction in both mean SBP and DBP in patients on two, three, or four drugs and those with uncontrolled BP. Furthermore, there was reduction in the number of drugs

Table 3: SBP and DBP before and after renin-guided therapy

Sl. no.	*SBP (mm Hg) (mean ± SD)*				*DBP (mm Hg) (mean ± SD)*			
	Pre-BP	*Post-BP*	*Paired t-test*	*p-value*	*Pre-BP*	*Post-BP*	*Paired t-test*	*p-value*
One drug (n = 234)	128.78 ± 4.56	126.44 ± 3.39			80.23 ± 1.45	80.66 ± 1.78		
Two drugs (n = 381)	133.82 ± 3.35	122.37 ± 10.40	20.24	<0.05	84.04 ± 3.06	84.11 ±1.60	5.41	<0.05
Three drugs (n = 84)	133.73 ± 3.47	114.24 ± 5.98	25.28	<0.05	85.08 ± 2.85	83.86 ± 1.48	3.51	<0.05
Four drugs (n = 114)	141.58 ± 9.60	125.08 ± 12.25	38.05	<0.05	86.54 ± 5.23	85.85 ± 2.24	2.96	<0.05
Controlled BP (n = 813)	133.83 ± 3.36	123.87 ± 10.59	26.13	<0.05	84.77 ± 3.12	84.05 ± 1.84	5.38	<0.05
Uncontrolled BP (n = 83)	152.17 ± 2.95	138 ± 1.23	41.69	<0.05	90.36 ± 5.02	87.78 ± 0.84	4.58	<0.05

Paired t-test was performed to compare the pre- and post-BP in each group and the p-value was calculated

Table 4: Requirement of antihypertensives before and after renin-guided therapy

Number of antihypertensive drugs	*Before renin-guided therapy (% of 896)*	*After renin-guided therapy (% of 896)*	*Chi-square*	*p-value*
One drug (n = 234)	234 (26.12%)	679 (75.78%)	441	p < 0.0001
Two drugs (n = 381)	381 (42.52%)	103 (11.50%)	218	p < 0.0001
Three drugs (n = 84)	84 (9.38%)	94 (10.49%)	0.61	p = 0.43
Four drugs (n = 114)	114 (12.72%)	20 (2.2%)	71.5	p < 0.0001
Controlled total (n = 813)	813 (90.73%)	896 (100%)		
Uncontrolled (n = 83)	83 (9.26%)	0		
Total (n = 896)	896 (100%)	896 (100%)		

used by patients who were initially on two or four drugs.

High-renin hypertension is seen in renovascular hypertension, pheochromocytoma, reninomas, or drugs such as ACEI/ARBs, diuretics, and OCPs.[14,15] Low-renin hypertension is seen in several secondary conditions like chronic kidney disease, Cushing's syndrome, genetic monogenic causes, primary aldosteronism, drugs such as beta-blockers, or other sympatholytic agents like clonidine, alpha-methyl dopa, and NSAIDs.[16] Most studies in the past have shown that HRH with nonsuppressed renin values is observed in approximately 70% of patients, while LRH is noted in 30% of cases.[6,8,9]

The renin-guided treatment algorithm is based on the vasoconstriction volume analytical model,[7] which supports the view that there are two reciprocating long-term supports of BP levels.[12] Laragh and Sealey first developed the renin-guided approach to choose antihypertensives and refined their observations over the years.[9] Anti V drugs are natriuretic drugs which reduce sodium-related circulating volume and include CCBs, thiazides, loop diuretics, and mineralocorticoid receptor antagonists. Anti R drugs are antirenin/angiotensin II drugs which reduce renin/angiotensin II-related vasoconstriction and include ACEI/ARBs, beta-blockers, and alpha-2 adrenergic receptor antagonists.[16] It, therefore, becomes logical to treat LRH patients (PRA < 0.65 ng/mL/hr) primarily with a natriuretic "V" drug and to discontinue "R" drugs in the absence of compelling indications. Similarly, HRH patients (PRA ≥ 0.65 ng/mL/hr) may be treated with an antirenin "R" medication, while subtracting any "V" drugs.[13]

Renin-guided management has been used in the past. Turner et al. showed that the renin levels and pretreatment BP were the main parameters which can predict systolic and diastolic response to both atenolol and hydrochlorothiazide, and observed an association between in-treatment renin levels and response to add-on therapy.[17] The study also showed that hypertensive patients with higher renin, either at baseline or during treatment, responded most favorably to atenolol, an anti-R drug, while those with lower renin responded better to hydrochlorothiazide (anti-V drug).[17] In a randomized controlled trial (RCT), Dickerson et al. reported superior efficacy of beta-blockers and ACEI in a population of young white patients with high renin, wherein PRA levels were also associated with BP response to ACEI.[18] Schwartz et al. observed that renin profiling was superior to the "age-race rule" in predicting BP response to a therapy with candesartan or hydrochlorothiazide.[19]

However, an RCT by Weir and Saunders observed a lack of correlation between BP reduction and pretreatment renin levels in a cohort of predominately low-renin African-American hypertensive patients treated with trandolapril.[20] Another study in older adult (>70 years old) hypertensive patients, failed to recognize an association between renin levels and BP response to valsartan and/or hydrochlorotiazide.[21]

To date, studies conducted on renin-guided treatment demonstrate conflicting conclusions regarding the predictive role of renin profiling, which may be likely due to the use of concomitant medications, such as NSAIDs or OCPs which may interfere with renin levels and RAS, and due to differential activity of tissue-specific RAS and systemic RAS in a patient, in whom the tissue-specific RAS cannot be adequately measured.

Renin profiling may be used successfully in the management of refractory hypertension.[22] Egan et al. randomized 77 uncontrolled hypertension cases to renin-guided therapy and standard clinical therapy, and found that BP control was better in the former group (74 *vs* 59%, $p = 0.17$), and SBP fall was more in the former group (29.1 *vs* 19.2 mm Hg, $p = 0.03$).[13] Eide et al. found that as many as 67% of their drug-resistant hypertensive patients had low PRA which was successfully managed with a diuretic, amiloride (Anti V drug).[16] In PATHWAY-2 study of resistant hypertension, renin levels were estimated in 269 cases and it was found that most patients had low renin due to salt retaining state, which was successfully treated with spironolactone.[23] In a hypertensive patient on multiple drugs, there always exists a possibility that few drugs are less effective and may be replaced with different class of drugs which may be more effective.[24] Renin-guided therapy offers a possible option to add or titrate drugs based on renin levels. In this study, with renin-guided therapy, the proportion of patients taking polypharmacy (two, three, or four) drugs reduced and more patients could be maintained on a single drug. Minimizing medication burden is important in hypertension management as it reduces pill burden, reduces costs, prevents undue side effects, minimizes drug interactions, and ensures better adherence.[24] The cost of renin estimation and its economic burden is a major concern in renin-guided hypertension management. However, a cost-effectiveness study performed by Smith and Campbell suggested that a renin-guided strategy may be more cost-effective in the longer run, particularly for patients with uncontrolled BP.[25]

The strengths of this study are the size of the study population, ethnic diversity of the population representing the general population, and a large number of PRA measurements using a sensitive assay method. The present study has a few drawbacks. Firstly, PRA levels may be affected by drugs and other conditions. Though these conditions were excluded, there is a likelihood that few unknown factors could have affected the assay. Second, the adherence to medication and BP measurements at home could not be closely monitored which may lead to variation in BP control. Third, few patients were excluded from the study due to resumption of medication within 2 weeks of discontinuation of antihypertensives and could have led to variation in results.

Renin-guided therapy is a practical and objective method for improving BP control in both controlled and uncontrolled hypertensive patients, and in reducing the number of antihypertensive drugs. This renin-guided algorithm can be used in most clinical settings by a wide range of health care providers for addressing the public health burden of hypertension. Reliable commercially available plasma renin assays are becoming widely available and cheaper, and in the future, renin testing may be more accessible and easy. Further RCTs are recommended to study the effectiveness of renin test-guided treatment in a larger study population, different clinical settings, and patient subgroups.

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