Plasma Renin Activity- Little Foot or Big Step for Blood Pressure Management?

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Lecture Objectives:
1. Provide a basic overview of hypertension
2. Discuss treatment methods for hypertension
3. Evaluate the literature pertaining to the utilization of plasma renin activity to guide treatment of hypertension
4. Recommend optimal pharmacotherapeutic regimens in an adult with resistant hypertension given plasma renin activity levels
## Hypertension Background

### 1.1 Impact of Hypertension (HTN)

- Utilizing the American College of Cardiology and American Heart Association (ACC/AHA) 2017 HTN definition, 45.6% of US adults have HTN.
- From 2005 to 2015 there has been a significant increase in death rates attributable to elevated blood pressure (BP) from 10.5% up to 37.5% (78,862 deaths).
- Projections show that by 2035, the total direct cost of high BP could increase to an estimated $220.9 billion.

### 1.2 Pathophysiology of Primary Hypertension

- The pathogenesis of primary HTN is multifactorial and highly complex.
- Numerous genetic and environmental factors (polygenic disorders, diet, physical activity, alcohol consumption) result in neurohumoral dysfunction and promote inflammation and insulin resistance.
- These dysfunctions all lead to increased peripheral resistance or increased blood volume, which are 2 primary causes of sustained HTN.

![Figure 2. Pathophysiology of Primary Hypertension](image)
1.3 **CARDIOVASCULAR RISK FACTORS**

- HTN and modifiable cardiovascular risk factors share several mechanisms of action and pathophysiology.
- Treating some of the modifiable risk factors may reduce BP through modification of shared pathology, and cardiovascular risk may be reduced by treating global risk factor burden.

<table>
<thead>
<tr>
<th>Modifiable Risk Factors</th>
<th>Non-Modifiable Risk Factors</th>
</tr>
</thead>
<tbody>
<tr>
<td>▪ Cigarette smoking</td>
<td>▪ Chronic kidney disease</td>
</tr>
<tr>
<td>▪ Diabetes mellitus</td>
<td>▪ Family history</td>
</tr>
<tr>
<td>▪ Dyslipidemia</td>
<td>▪ Increased age</td>
</tr>
<tr>
<td>▪ Overweight/obesity</td>
<td>▪ Low socioeconomic/educational status</td>
</tr>
<tr>
<td>▪ Physical inactivity/low fitness</td>
<td>▪ Male sex</td>
</tr>
<tr>
<td>▪ Unhealthy diet</td>
<td>▪ Obstructive sleep apnea</td>
</tr>
<tr>
<td></td>
<td>▪ Psychosocial stress</td>
</tr>
</tbody>
</table>

1.4 **SECONDARY CAUSES OF HYPTENSION**

<table>
<thead>
<tr>
<th>Common Causes</th>
<th>Prevalence</th>
<th>Clinical Indications</th>
</tr>
</thead>
<tbody>
<tr>
<td>Obstructive Sleep Apnea</td>
<td>25-50%</td>
<td>- Resistant HTN</td>
</tr>
<tr>
<td></td>
<td></td>
<td>- Snoring</td>
</tr>
<tr>
<td></td>
<td></td>
<td>- Fitful sleep</td>
</tr>
<tr>
<td></td>
<td></td>
<td>- Breathing pauses during sleep</td>
</tr>
<tr>
<td></td>
<td></td>
<td>- Daytime sleepiness</td>
</tr>
<tr>
<td>Primary Aldosteronism</td>
<td>8-20%</td>
<td>HTN with:</td>
</tr>
<tr>
<td></td>
<td></td>
<td>- Hypokalemia</td>
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<tr>
<td></td>
<td></td>
<td>- Muscle cramps or weakness</td>
</tr>
<tr>
<td></td>
<td></td>
<td>- Obstructive sleep apnea</td>
</tr>
<tr>
<td></td>
<td></td>
<td>- Family history of early-onset HTN or stroke</td>
</tr>
<tr>
<td>Renovascular Disease</td>
<td>5-34%</td>
<td>- Resistant HTN</td>
</tr>
<tr>
<td></td>
<td></td>
<td>- HTN of abrupt onset or worsening</td>
</tr>
<tr>
<td></td>
<td></td>
<td>- Flash pulmonary edema</td>
</tr>
<tr>
<td></td>
<td></td>
<td>- Early-onset HTN</td>
</tr>
<tr>
<td></td>
<td></td>
<td>- Commonly in women</td>
</tr>
<tr>
<td>Drug or Alcohol Induced</td>
<td>2-4%</td>
<td>- Sodium containing antacids</td>
</tr>
<tr>
<td></td>
<td></td>
<td>- Caffeine</td>
</tr>
<tr>
<td></td>
<td></td>
<td>- Nicotine</td>
</tr>
<tr>
<td></td>
<td></td>
<td>- NSAIDs</td>
</tr>
<tr>
<td></td>
<td></td>
<td>- Oral contraceptives</td>
</tr>
<tr>
<td></td>
<td></td>
<td>- Cyclosporine or tacrolimus</td>
</tr>
<tr>
<td></td>
<td></td>
<td>- Sympathomimetics</td>
</tr>
<tr>
<td></td>
<td></td>
<td>- Cocaine, amphetamines</td>
</tr>
<tr>
<td></td>
<td></td>
<td>- Neuropsychiatric agents</td>
</tr>
<tr>
<td></td>
<td></td>
<td>- Erythropoiesis-stimulating agents</td>
</tr>
<tr>
<td></td>
<td></td>
<td>- Clonidine withdrawal</td>
</tr>
<tr>
<td></td>
<td></td>
<td>- Herbals</td>
</tr>
</tbody>
</table>
### 1.5 Hypertension Guidelines

**Table 2. Comparing Hypertension Guidelines**

<table>
<thead>
<tr>
<th>Guideline</th>
<th>Categories (mmHg)</th>
<th>Goals</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>JNC 7 (2003)</strong></td>
<td>Normal: &lt;120 and &lt;80</td>
<td>CKD or DM: &lt;130/&lt;80</td>
</tr>
<tr>
<td></td>
<td>Pre-HTN: 120-139 or 80-89</td>
<td>Others: &lt;140/&lt;90</td>
</tr>
<tr>
<td></td>
<td>Stage I: 140-159 or 90-99</td>
<td></td>
</tr>
<tr>
<td></td>
<td>Stage 2: ≥160 or ≥100</td>
<td></td>
</tr>
<tr>
<td><strong>JNC 8 (2014)</strong></td>
<td>Age ≥60: ≥150 or ≥90</td>
<td>CKD or DM: &lt;140/&lt;90</td>
</tr>
<tr>
<td></td>
<td>Age &lt;60: ≥140 or ≥90</td>
<td>Age &lt;60: &lt;140/&lt;90</td>
</tr>
<tr>
<td></td>
<td>CKD: ≥140 or ≥90</td>
<td>Age ≥60: &lt;150/&lt;90</td>
</tr>
<tr>
<td></td>
<td>DM: ≥140 or ≥90</td>
<td></td>
</tr>
<tr>
<td><strong>ACC/AHA (2017)</strong></td>
<td>Normal: &lt;120 and &lt;80</td>
<td>All: &lt;130/&lt;80</td>
</tr>
<tr>
<td></td>
<td>Elevated: 120-129 and &lt;80</td>
<td></td>
</tr>
<tr>
<td></td>
<td>Stage I: 130-139 or 80-89</td>
<td></td>
</tr>
<tr>
<td></td>
<td>Stage 2: ≥140 or ≥90</td>
<td></td>
</tr>
</tbody>
</table>

*Blood pressure categories based on an average of ≥2 careful readings obtained on ≥2 occasions

CKD = chronic kidney disease; DM = diabetes mellitus; JNC = Joint National Committee; ACC = American College of Cardiology; AHA = American Heart Association

### 1.6 Recommendations for Treatment and Follow-up

- Per the ACC/AHA 2017 guidelines, treatment and follow-up are dependent on degree of BP elevation as well as the presence of atherosclerotic cardiovascular disease (ASCVD) risk.

**Figure 3. Recommendations for Hypertension Treatment and Follow-Up**
2 Pharmacological Strategies for Hypertension

2.1 Stepped-Care Strategy

- Defined as the step-wise addition of medications until BP control is achieved7
- Example: 2017 ACC/AHA Hypertension Guidelines2
  1. Identify compelling indications:

<table>
<thead>
<tr>
<th>Disease State</th>
<th>1st Line Agents</th>
<th>Other Recommendations</th>
</tr>
</thead>
<tbody>
<tr>
<td>Stable ischemic heart disease</td>
<td>- Beta-blockers</td>
<td>If further control needed:</td>
</tr>
<tr>
<td></td>
<td>- ACE inhibitors/ARBs</td>
<td>- Dihydropyridine CCBs</td>
</tr>
<tr>
<td></td>
<td></td>
<td>- Thiazide diuretics</td>
</tr>
<tr>
<td></td>
<td></td>
<td>- Aldosterone antagonants</td>
</tr>
<tr>
<td>Heart failure with reduced ejection fraction (HFrEF)</td>
<td>- ACE inhibitors/ARBs</td>
<td>Nondihydropyridine CCBs are not recommended</td>
</tr>
<tr>
<td></td>
<td>- Aldosterone antagonists</td>
<td></td>
</tr>
<tr>
<td></td>
<td>- Diuretics</td>
<td></td>
</tr>
<tr>
<td></td>
<td>- Neprilysin inhibitors</td>
<td></td>
</tr>
<tr>
<td></td>
<td>- Beta-blockers (carvedilol, metoprolol succinate, or bisoprolol)</td>
<td></td>
</tr>
<tr>
<td>Heart failure with preserved ejection fraction (HFrEF)</td>
<td>- Diuretics</td>
<td>Limited data exist to guide the choice of alpha-blockers, beta-blockers, and CCBs</td>
</tr>
<tr>
<td></td>
<td>- ACE inhibitors/ARBs</td>
<td></td>
</tr>
<tr>
<td></td>
<td>- Beta-blockers</td>
<td></td>
</tr>
<tr>
<td>Chronic kidney disease</td>
<td>- ACE inhibitors/ARBs</td>
<td></td>
</tr>
<tr>
<td>Cerebrovascular disease</td>
<td>- Thiazide diuretics</td>
<td>Reduction in BP appears to be more important than the choice of specific agents</td>
</tr>
<tr>
<td></td>
<td>- ACE inhibitors/ARBs</td>
<td></td>
</tr>
<tr>
<td>Peripheral artery disease</td>
<td>No specific recommendation</td>
<td></td>
</tr>
<tr>
<td>Diabetes mellitus</td>
<td>- ACE inhibitors (if albuminuria present)</td>
<td></td>
</tr>
<tr>
<td>Atrial fibrillation</td>
<td>- ARBs</td>
<td></td>
</tr>
<tr>
<td>Valvular heart disease</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Aortic disease</td>
<td>- Beta-blockers</td>
<td>ACE inhibitors were not seen to improve survival</td>
</tr>
</tbody>
</table>

ACE= angiotensin-converting enzyme; ARBs= Angiotensin II receptor blockers; CCBs= calcium channel blockers

2. Add any first line agent:
  - Preferred first line agents (thiazide diuretics, long acting CCBs, and ACE inhibitors/ARBs) have been shown to reduce clinical events
  - ACE inhibitors/ARBs are not a preferred first line agent in African Americans

3. Continue adding agents until BP control is achieved

- Efficacy study: “ALLHAT”5
  - In the ALLHAT trial, 66% of patients were controlled to goal of <140/90 mmHg
  - Patients required an average of 2 medications, though there were 13% of patients that required ≥4 medications
  - A subgroup analysis of race noted that in blacks with HTN and without renal disease or HF, thiazide diuretics lowered rates of stroke compared to ACE inhibitors6

- Potential Limitations
  1. Agents that are ineffective or minimally effective are rarely discontinued7
  2. Variable control rates
2.2 Thiazide First Strategy

- Example: JNC 7 Guidelines recommended thiazide diuretics as the preferred initial agent due to studies showing favorable results in preventing the cardiovascular complications of HTN.
- “First-line drugs for hypertension (Review)”

<table>
<thead>
<tr>
<th>Table 4. Mortality and Morbidity Reduction with Different First-Line Agents</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Low-dose thiazide diuretic vs. placebo</strong></td>
</tr>
<tr>
<td>Total Mortality</td>
</tr>
<tr>
<td>Total Stroke</td>
</tr>
<tr>
<td>Total Coronary Heart Disease</td>
</tr>
<tr>
<td>Total Cardiovascular Events</td>
</tr>
<tr>
<td>Withdrawal due to adverse effects</td>
</tr>
</tbody>
</table>

*ARR= absolute risk reduction; NNT= number needed to treat; NNH= number needed to harm

- Objective: to quantify the mortality and morbidity effects from different first-line agents
- Author’s Conclusions:
  - First-line low-dose thiazide diuretics reduced all morbidity and mortality outcomes in adult patients with moderate to severe primary HTN
  - First-line ACE inhibitors and CCBs may be similarly effective, but the evidence was of lower quality
  - First-line high-dose thiazides diuretics and first-line beta-blockers were inferior to first-line low-dose thiazide diuretics
- Efficacy study: “Blood pressure-lowering efficacy of monotherapy with thiazide diuretics for primary hypertension (review)”
  - In a meta analysis, chlorthalidone resulted in 12-point reduction in systolic blood pressure (SBP) and 3.9-point reduction in diastolic blood pressure (DBP)
  - Hydrochlorothiazide resulted in 6.9-point reduction in SBP and 3.3-point reduction in DBP
- Potential Limitations:
  - Responses to BP agents is characterized by marked interindividual response
  - Many people will require treatment with more than one agent to achieve BP control
  - Patients may be unable to tolerate thiazide diuretics

2.3 Age-Race Strategy

- Tailoring therapy decisions to patient demographics such as age or race/ethnicity
- Example: British Hypertension Society guidelines for hypertension management 2004
• This strategy is based on the assumption that younger Caucasians have renin-dependent HTN and other racial ethnic groups and older individuals have predominately low renin\textsuperscript{14}
• Efficacy study: “Age-race subgroups compared with renin profile as predictors of blood pressure response to antihypertensive therapy”\textsuperscript{15}
  o Age-race strategy resulted in 64.5\% of patients achieving goal DBP (<90 mmHg)
  o There was a 13.3-point reduction in SBP and 11.9-point reduction in DBP
• Potential Limitations:\textsuperscript{8}
  o Relies on population statistics that may not be accurate for all persons in a given group
  o Limited use for patients that are already treated, but remain uncontrolled

2.4 \textbf{TREATMENT RESISTANT HYPERTENSION (TRH)}\textsuperscript{16}
• Uncontrolled HTN on ≥3 agents preferably including a diuretic
• Management:
  1. Maximize thiazide diuretics
  2. Add aldosterone antagonist
  3. Add beta-blocker (unless heart rate <70 beats/minutes)
  4. Add hydralazine
  5. Substitute minoxidil for hydralazine
  6. Refer to HTN specialist
• Efficacy studies:
  o Adding spironolactone: “PATHWAY-2”\textsuperscript{17}
    ▪ 58\% control rate in SBP (<135 mmHg)
    ▪ Serum potassium increased by 0.43 mEq/L
    ▪ Hyperkalemia resulted in 2\% of the population
    ▪ Mean eGFR was reduced by 10.02 mL/min/1.73 m\textsuperscript{2}
  o Referal to HTN specialist: “Blood pressure control in the hypertensive clinic” \textsuperscript{18}
    ▪ Referrals to HTN specialist for TRH increased control rates from 18\% to 52\%
• Limitations:\textsuperscript{14}
  o Tolerability issues of aldosterone antagonists, including the development of CKD with an eGFR <45 mL/min/1.73 m\textsuperscript{2} or baseline serum potassium >4.5 mEq/L
  o Prolonged spironolactone use at higher doses may be limited by gynecomastia and erectile dysfunction in men and menstrual irregularities in women
  o Increased pill burden, especially with the twice daily dosing of eplerenone

2.5 \textbf{PLASMA RENIN ACTIVITY (PRA) STRATEGY}
2.5.1 Renin Background\textsuperscript{18}
• Renin: an enzyme secreted by and stored in the kidneys involved in the regulation of fluid volume and arterial vasoconstriction
• BP is sustained by:
  1. Body sodium-volume content (V)
    ▪ Body salt increases or decreases the extracellular fluid volume
    ▪ This increase or decrease in the volume of fluid delivered to the arterial tree affects BP via a hydraulic effect
  2. Plasma renin-angiotensin vasoconstrictor activity (R)
    ▪ Compensatory adjustments in arteriolar caliber are mediated by changes in circulating angiotensin II
    ▪ The renal juxtaglomerular apparatus of each nephron detects changes in body-sodium volume and adjusts angiotensin II levels through PRA
Figure 4. Relationship Between Arterial Volume and Vasoconstriction

- A normal BP can have low, medium, or high PRA levels when it is simultaneously present with reciprocally high, medium or low levels of body sodium volume content.
- HTN occurs when the kidneys fail to sufficiently reduce PRA in response to an increase in body salt (i.e. normal PRA levels x elevated sodium volume = elevated BP).
  - PRA is low in ~30% of hypertensive patients, indicating an appropriate renal baroreceptor response to high pressure.
  - PRA is moderate in ~55% of hypertensives.
  - PRA is high in ~15% of hypertensives.

- PRA Levels
  - Assessed using a blood test that measures the activity of the plasma renin enzyme.
  - PRA levels can be affected by age, race, diet, medications, and disease states.
  - The PRA level test is available commercially, costs less than a urinary albumin and is reimbursed in the United States by Medicare and most insurance carriers.
  - No special patient preparation is needed and there is no need to stop antihypertensive drugs.

<table>
<thead>
<tr>
<th>Category</th>
<th>PRA Level</th>
</tr>
</thead>
<tbody>
<tr>
<td>Low</td>
<td>&lt;0.65</td>
</tr>
<tr>
<td>Moderate</td>
<td>0.65-6.5</td>
</tr>
<tr>
<td>High</td>
<td>≥6.5</td>
</tr>
</tbody>
</table>

2.5.2 Selecting Antihypertensive Drug Types

- All effective antihypertensive drugs lower BP by either reducing sodium-volume content (anti-V drugs) or reducing or blocking the vasoconstrictor activity of the circulating renin-angiotensin system (anti-R drugs).
### Table 7. Drug Class Blood Pressure Lowering Mechanisms

<table>
<thead>
<tr>
<th>Anti-V Drug Types</th>
<th>Anti-R Drug Types</th>
</tr>
</thead>
<tbody>
<tr>
<td>• Thiazide diuretics</td>
<td>• Beta-blockers</td>
</tr>
<tr>
<td>• Aldosterone antagonists</td>
<td>• Alpha-2 agonists</td>
</tr>
<tr>
<td>• Alpha-blockers</td>
<td>• ACE inhibitors/ARBs</td>
</tr>
<tr>
<td>• CCBs</td>
<td>• Direct renin inhibitors (DRIs)</td>
</tr>
</tbody>
</table>

- PRA levels can be used to guide selection of antihypertensive medication:

### Table 8. Studies Assessing Blood Pressure Response with Various PRA Levels

<table>
<thead>
<tr>
<th>Study</th>
<th>Agent(s)</th>
<th>Population</th>
<th>Findings</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Anti-V Drugs</strong></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Vaughan et al. (1973)21</td>
<td>Spironolactone</td>
<td>- 71 patients - PRA levels: 37 low; 36 normal</td>
<td>Reductions in BP were significantly greater in patients with low renin compared with normal renin.</td>
</tr>
<tr>
<td></td>
<td>Chlorthalidone</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Bolli et al. (1980)22</td>
<td>Prazosin</td>
<td>- 27 patients - PRA levels: 12 low; 15 normal</td>
<td>Prazosin monotherapy lowers BP in about 1/3 of hypertensive patients and most effectively in those with low renin-HTN.</td>
</tr>
<tr>
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<td></td>
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</tr>
<tr>
<td>Buhler et al. (1982)23</td>
<td>Verapamil</td>
<td>- 43 patients - PRA levels: 11 low; 24 normal; 8 high</td>
<td>The antihypertensive response to verapamil was greatest in older and low renin patients.</td>
</tr>
<tr>
<td><strong>Anti-R Drugs</strong></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Buhler et al. (1973)24</td>
<td>Propranolol</td>
<td>- 74 patients - PRA levels: 17 low; 38 normal; 19 high</td>
<td>Reductions in BP were greater in patients with high renin levels compared to low and moderate.</td>
</tr>
<tr>
<td>Minami et al. (2008)25</td>
<td>Telmisartan</td>
<td>- 11 patients - PRA levels: 6 low; 5 high</td>
<td>Reductions in BP were significantly greater in patients with high renin levels than those with low renin levels</td>
</tr>
</tbody>
</table>

### 2.5.3 Historical Perspectives26
- The concept of PRA measurements for the prediction of antihypertensive effects is not new
- During the formative years (1960s-1970s), three major issues dissuaded clinicians from using PRA measurements:
  1. Unaware of need to proper pH control of PRA assay
  2. Belief that patients must discontinue antihypertensives prior to PRA tests
  3. Belief that patients had to have sodium-controlled diets prior to PRA tests
- The truth: PRA testing can be done regardless of a patient's drug regimen or salt intake
  - Patients should continue their usual sodium intake and drug therapy before testing to provide the truest picture of what is supporting a patient's elevated BP
- Studies comparing the utility of PRA compared with current antihypertensive management strategies are limited, possibly due to:
  1. Misunderstanding of the potential utility of the modern PRA assay
  2. Lingering methodologic concerns
  3. Assay expense
  4. Extended laboratory turnaround time
  5. The lack of recommendations for PRA testing in practice guidelines
3 CLINICAL QUESTION: SHOULD PLASMA RENIN ACTIVITY LEVELS BE USED TO MANAGE BLOOD PRESSURE?

3.1 INITIAL TREATMENT DECISIONS

Table 9. THE ROLE OF PLASMA RENIN ACTIVITY, AGE, AND RACE IN SELECTING EFFECTIVE INITIAL DRUG THERAPY FOR HYPERTENSION

<table>
<thead>
<tr>
<th></th>
<th></th>
</tr>
</thead>
<tbody>
<tr>
<td>Objective</td>
<td>To compare control rates among 3 drug selection strategies for initial drug therapy: 1. Thiazide diuretic for all 2. Thiazide diuretic for white subjects ≥50 years and all black subjects and a renin-angiotensin system (RAS) blocker for white subjects &lt;50 years 3. Thiazide diuretic for PRA &lt;0.6 and RAS blocker for PRA ≥0.6</td>
</tr>
</tbody>
</table>

METHODS

Study Design  
Retropective analysis of data previously collected in the Genetic Epidemiology Responses to Antihypertensives (GERA) study

Inclusion Criteria  
- Patients 30-59 years of age  
- Essential HTN (BP >140/90 mmHg or diagnosis with current treatment)

Exclusion Criteria  
- Known secondary causes of HTN  
- Women using oral contraceptives  
- BP >180/110 mmHg after washout period

Interventions  
Antihypertensives were stopped and subjects were evaluated every other week during a 4-6 week washout phase  
Antihypertensive therapy was administered for 4-6 weeks with either:  
- Hydrochlorothiazide 25mg daily x 4 weeks  
- Candesartan 16mg daily x 2 weeks then increase to 32mg x 4 weeks

Outcomes  
BP control rates (<140/90 mmHg) for each 3 drug selection categories

Monitoring  
BP was checked at study visits (completed in triplicate)  
Subjects were to maintain a standard sodium intake of 2 mmol/kg/day  
Monitored weekly by 24-hr urine collection alternating with diaries  
Compliance with drug therapy was assessed by pill counts at each study visit

Statistical Analysis  
Utilized p-values for quantitative variables (analysis for variance for normally distributed; Mann-Whitney rank sum test for non-normally distributed)  
The overall difference in control rates between strategies is a weighted average of the 8-stratum-specific (age/race/PRA) differences in control rates

RESULTS

Participant Demographics  
- Overall patients included in the study were obese and had type 1 HTN  
- There were no significant differences between treatment groups

Outcomes  
BP control rates (%) by treatment strategy:

<table>
<thead>
<tr>
<th>Strategy</th>
<th>Overall</th>
<th>Black Subjects</th>
<th>White Subjects</th>
</tr>
</thead>
<tbody>
<tr>
<td>Thiazide only</td>
<td>53.8</td>
<td>55.2</td>
<td>52.4</td>
</tr>
<tr>
<td>Age-race</td>
<td>61.3</td>
<td>55.2</td>
<td>67.1</td>
</tr>
<tr>
<td>PRA</td>
<td>69.4*</td>
<td>62.1*</td>
<td>76.3*</td>
</tr>
</tbody>
</table>

* indicates statistical significance vs. other strategies
AUTHORS' CONCLUSIONS

The results of this study suggest that in patients aged <60 years with uncomplicated essential HTN, choice of initial antihypertensive drug therapy using a PRA strategy is associated with higher control rates than a strategy based on age-race criteria or thiazide only.

CRITIQUE/DISCUSSION

Strengths  o Compared commonly used strategies to determine initial agent
 o Utilized commonly used “maximum” dose of both agents

Limitations  o Retrospective study design
 o Lower upper age limit
 o PRA assays were run for 3 hours (less accuracy for low PRA levels)
 o Different durations between groups
 o Not “real-life” use of PRA levels (sodium restrictions)
 o Only utilized one drug from each category

Discussion  This study provides the beginning basis to consider using PRA levels to guide initial therapy decisions. However, future studies are needed to verify results and demonstrate the applicability into a “real-world” world setting.

Table 10. COMPARISON OF BLOOD PRESSURE CONTROL RATES AMONG RECOMMENDED DRUG SELECTION STRATEGIES FOR INITIAL THERAPY OF HYPERTENSION

BACKGROUND AND OVERVIEW


Objective  To compare control rates among 3 drug selection strategies:
  1. Thiazide diuretic for all
  2. Thiazide diuretic for all black subjects and white subjects ≥50 years and a RAS blocker for white subjects <50 years
  3. Thiazide diuretic for PRA <0.6 and RAS blocker for PRA ≥0.6

METHODS

Study Design  o Retrospective analysis of data previously collected in the PEAR-1 study (prospective, multicenter, randomized, open-label, parallel group study)

Inclusion Criteria  o Patients 17-65 years of age
 o Essential HTN (BP ≥140/90 mmHg or diagnosis with current treatment)

Exclusion Criteria  o Known secondary causes of HTN
 o Isolated systolic HTN
 o Known cardiovascular disease
 o HR <55 beats/minute in the absence of beta-blocker
 o DM or screening fasting blood glucose >126 mg/dL
 o Primary renal disease
 o Concomitant diseases treated with BP-lowering medications
 o BP >180/110 mmHg after washout period
 o Chronic treatment with BP-elevating drug

Interventions  o Antihypertensives were stopped and subjects were evaluated every other week during a 4-week washout phase
 o Antihypertensive therapy was administered for 9 weeks of treatment
  ▪ Hydrochlorothiazide 12.5mg daily (increase to 25mg if BP >120/70)
  ▪ Atenolol 50mg daily (increase to 100mg if BP >120/70)
### Outcomes
- BP control rates (<140/90 mmHg) for each 3 drug selection categories

### Monitoring
- Home BP was measured throughout the 9-week treatment period
- 24-hour ambulatory BP was measured at the beginning and end

### Statistical Analysis
- Utilized p-values for quantitative variables (Analysis for variance for normally distributed; Mann-Whitney rank sum test for non-normally distributed)
- The overall difference in control rates between strategies is a weighted average of the 8-stratum-specific (age/race/PRA) differences in control rates

### RESULTS

#### Participant Demographics
- Patients were obese with a BMI of ~30 kg/m²
- Average baseline BP: 151/98 mmHg
- No significant differences between treatment groups

#### Outcomes
- BP control rates (%) by treatment strategy:

<table>
<thead>
<tr>
<th>Strategy</th>
<th>Clinic BP</th>
<th>Home BP</th>
<th>24-hr Ambulatory BP</th>
</tr>
</thead>
<tbody>
<tr>
<td>Thiazide-only</td>
<td>31.7*</td>
<td>26.4*</td>
<td>43.9*</td>
</tr>
<tr>
<td>Age-race</td>
<td>40.8*</td>
<td>36.1*</td>
<td>51.6*</td>
</tr>
<tr>
<td>PRA</td>
<td>48.9*</td>
<td>42.6*</td>
<td>61.3*</td>
</tr>
</tbody>
</table>

* indicates statistical significance vs. other strategies

Secondary Analysis:
- Preferred agent for each PRA/racial/age subgroup

<table>
<thead>
<tr>
<th>PRA levels</th>
<th>Blacks</th>
<th>Whites</th>
</tr>
</thead>
<tbody>
<tr>
<td>Suppressed</td>
<td>&lt;50 years</td>
<td>≥ 50 years</td>
</tr>
<tr>
<td></td>
<td>HCTZ</td>
<td>HCTZ</td>
</tr>
<tr>
<td>Non-Suppressed</td>
<td>Atenolol</td>
<td>HCTZ</td>
</tr>
</tbody>
</table>

### AUTHORS’ CONCLUSIONS
The results of this study confirm their previous findings that drug selection based on PRA levels is associated with higher BP control rate than either alternative strategy. Based on the observations of this study, a combination of PRA + age-race criteria may be effective (PRA utilized in whites ≥50 years of age and blacks <50 years of age).

### CRITIQUE/DISCUSSION

#### Strengths
- Allowed for medicine titrations
- Slightly higher age limit than previous study
- Assessed home BP readings
- Utilized 24-hour BP readings at beginning and end
- “Real-life” PRA levels (no sodium restrictions)

#### Limitations
- PRA assays were run for 3 hours (less accuracy for low PRA levels)
- Retrospective study design

#### Discussion
This study helps to verify that PRA levels can be utilized to determine initial agents specifically in older white patients and younger black patients.

### 3.2 TREATED, UNCONTROLLED HYPERTENSION

#### Table 11. PLASMA RENIN TEST-GUIDED DRUG TREATMENT ALGORITHM FOR CORRECTING PATIENTS WITH TREATED BUT UNCONTROLLED HYPERTENSION: A RANDOMIZED CONTROLLED TRIAL

#### BACKGROUND AND OVERVIEW

<table>
<thead>
<tr>
<th>Citation</th>
</tr>
</thead>
</table>
**Objective**
To compare change in BP in treated, uncontrolled hypertensives managed using renin test-guided therapeutics (RTGT) vs. clinical hypertension specialists’ care (CHSC)

**METHODS**

**Study Design**
- Randomized, open-label controlled trial
  - Randomized in a 1:1 ratio to be managed using RTGT vs. CHSC
  - Not stratified for any demographic or clinical variables

**Inclusion Criteria**
- Adults ≥21 years of age
- Uncontrolled HTN (Defined as 3 quietly sitting clinic readings at the single baseline visit ≥140/90 mmHg (≥130/80 mmHg if DM and/or CKD present)
- Taking one or more anti-hypertensive agent

**Exclusion Criteria**
- Uncontrolled DM or hyperlipidemia requiring medication changes
- Any active disease process requiring new diagnostic and therapeutic plans
- Any life-threatening illness
- History of alcohol or drug abuse in the last 5 years
- Mental illness or personality disorder that might interfere with adherence to study protocol
- End-stage renal disease/progressive CKD (SCr >2.5 mg/dL)
- Intolerance to 2 or more antihypertensive medications
- Home BP readings <135/85 mmHg at baseline (or <125/75 mmHg in patients with CKD/DM)

**Interventions**
Renin test-guided therapeutics algorithm (RTGT):

<table>
<thead>
<tr>
<th>≥1 V drug; no R drug</th>
<th>≥1 R drug; no V drug</th>
<th>≥1 R drug + ≥V drug</th>
</tr>
</thead>
<tbody>
<tr>
<td>PRA &lt;0.65: add V drug</td>
<td>PRA &lt;0.65: stop R drug, add V drug</td>
<td>PRA &lt;0.65: stop R drug, add V drug</td>
</tr>
<tr>
<td>PRA 0.65-6.5: add R drug</td>
<td>PRA 0.65-6.5: add V drug</td>
<td>PRA 0.65-6.5: add V drug</td>
</tr>
<tr>
<td>PRA &gt;6.5: stop V drug, add R drug</td>
<td>PRA &gt;6.5: add R drug</td>
<td>PRA &gt;6.5: add R drug</td>
</tr>
</tbody>
</table>

*If BP uncontrolled at visit 4 → repeat PRA and proceed to the appropriate protocol
- “R drugs”-ACE inhibitors, ARBs, Beta-blockers
- “V drugs”-Thiazide diuretics, Alpha-1 antagonists, CCBs

Clinical hypertension specialists’ care (CHSC):
- PRA was not available to guide medication changes

**Outcomes**

**Primary Outcome**
- Change in SBP and DBP from baseline to follow-up

**Secondary Outcomes**
- Renin values defining low-, medium-, and high-renin patients
- Medication changes from baseline to follow-up

**Monitoring**
- Patients were managed by 1 of 3 clinical HTN specialists
- Patients were scheduled every 2-4 weeks until BP was controlled
- Clinic BP was an average of 3 readings
- Home BPs were checked twice daily

**Statistical Analysis**
- Estimated sample size: 60 patients to detect a 4-point difference in both SBP and DBP with 90% power
- Intention to treat analysis: Included patients with baseline and ≥1 follow-up visit
- Primary outcome compared using student unpaired t-test

**RESULTS**

**Participant Demographics**
- 77 patients were included in the intention-to-treat analysis (41 RTGT vs. 43 CHSC)
Patients in the RTGT group were older (63 vs. 58 years), mostly Caucasian, and had lower eGFR. Baseline PRA levels were not different between groups. No significant difference in baseline BP between groups (RTGT: 157/87 mmHg vs. CHSC: 153/91 mmHg).

Baseline PRA levels were not different between groups. No significant difference in baseline BP between groups (RTGT: 157/87 mmHg vs. CHSC: 153/91 mmHg).

Outcomes

Primary Outcome
- Change in SBP: RTGT -29.1 mmHg vs. CHSC -19.2 mmHg (p= 0.03)
- Change in DBP: RTGT -14.1 mmHg vs. CHSC -11.3 mmHg (p= 0.32)

Secondary Outcomes
- RTGT group had no change in the number of BP medications, while CHSC saw a slight increase in average number of BP meds 2.7 → 3.0 (p= 0.25)
- Number of clinic visits were similar between groups (3.6 vs 3.4)
- CHSC added mostly V drugs while making few changes in R drugs
- Higher rates of BP control in RTGT group, though this was not statistically significant
- Low-renin: Decreased number of medications in RTGT group while numbers increased in CHSC group (p= 0.01)
- Medium-renin: Significantly greater BP reduction in the RTGT group (p= 0.01)
- High-renin: No significant differences between groups

Outcomes

Primary Outcome
- Change in SBP: RTGT -29.1 mmHg vs. CHSC -19.2 mmHg (p= 0.03)
- Change in DBP: RTGT -14.1 mmHg vs. CHSC -11.3 mmHg (p= 0.32)

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- Medium-renin: Significantly greater BP reduction in the RTGT group (p= 0.01)
- High-renin: No significant differences between groups

The overall success of the RTGT algorithm demonstrates that using ambulatory PRA testing in treated but uncontrolled HTN provides key information about their current sodium-volume status and/or renin status that can be used to improve BP control.

CRITIQUE/DISCUSSION

Strengths
- Randomized control trial
- Ruled out white coat HTN
- Utilized clinic and home BP readings
- Real-life plasma renin activity values (did not require stopping HTN agents)
- Utilized intention-to-treat analysis

Limitations
- Unbalanced treatment groups (race, age, eGFR)
- Potential patient population underrepresented due to changes in BP goals in new guidelines
- No standardization of CHSC group (guidelines, protocols, etc.)
- RTGT guidelines provide no guidance on starting doses of medication or dose titrations

Discussion
- RTGT was able to decline BP without any net change in medication number
  - Lower costs, fewer adverse effects, better compliance
  - May counterbalance or exceed benefits of current recommendations to just add an aldosterone antagonist
- Showed the applicability of PRA levels in the ambulatory care setting

COST EFFECTIVENESS ANALYSIS

A PRA guided strategy that lowered mean SBP by ≥10mmHg than standard of care is likely cost effective.

At least for younger adults or those with higher cardiovascular risk, PRA guided strategy may be a reasonable and cost-effective strategy to aid clinicians in improving BP control.

This study did not take into account medication costs, which can be potentially decreased though PRA guidance.

PRA guided strategy appears to dominate standards of care when PRA tests costs <$70 per test.

This suggests that future reductions in the cost of PRA should warrant increased consideration of PRA guided treatment.
Table 12. ALDOSTERONE ANTAGONISTS OR RENIN-GUIDED THERAPY FOR TREATMENT-RESISTANT HYPERTENSION: A COMPARATIVE EFFECTIVENESS PILOT STUDY IN PRIMARY CARE

<table>
<thead>
<tr>
<th>BACKGROUND AND OVERVIEW</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Objective</strong></td>
</tr>
</tbody>
</table>

<table>
<thead>
<tr>
<th>METHODS</th>
</tr>
</thead>
</table>
| **Study Design** | o Comparative effectiveness TRH pilot study  
  ▪ Patients were recruited from 4 community practice site  
  ▪ Each site was randomly assigned to one of 2 treatment protocols (RGT vs. AA) |
| **Inclusion Criteria** | o Patients 18-80 years old  
  o Elevated BP on 2 separate screening visits, while taking ≥3 different classes of BP meds at ≥50% of maximum recommended dose per JNC7 (or the FDA maximum approved dose if not included in JNC7) |
| **Exclusion Criteria** | o Required legal guardian  
  o Non-English speaking  
  o Known or suspected secondary HTN  
  o Symptomatic or significant orthostatic hypotension (standing BP falling ≥15/10 mmHg)  
  o Life threatening or severe illness likely to worsen during the next 6 months  
  o Nonadherence with BP medications (per refill history)  
  o eGFR <50 mL/min/1.73 m² |
| **Interventions** | **AA arm:**  
  o Received usual care with the addition of spironolactone at a starting dose of 12.5-25mg daily  
  **RGT arm:**  
  o R drugs-ACE inhibitors, ARBs, Beta-blockers  
  o V drugs-Thiazide diuretics, Alpha-1 antagonists, CCBs  
  o Physicians were encouraged to manage patients according to the baseline PRA:  
    | **Low PRA <0.65**  
    | o Discontinue R drugs in the absence of compelling indications  
    | o Add or increase V drugs  
    | **Moderate PRA 0.65-4.5**  
    | o If regimen predominantly V drugs, add an R drug  
    | o If regimen predominantly R drugs, add a V drug  
    | **High PRA >4.5**  
    | o Discontinue V drugs in the absence of compelling indications  
    | o Add or increase R drugs |
| **Outcomes** | **Primary Outcome:**  
  o Change in clinic BP  
  **Secondary Outcomes:**  
  o Final BP reading  
  o Proportion of patients achieving goal  
  o Changes in BP medications |
Monitoring
- BP was tested in the clinic 7 times following appropriate resting period
  - 1st: staff present
  - 2-6th: without staff present (automatic re-inflation at 1 minute intervals)
  - 7th: after standing for 3 minutes to rule out orthostasis
- Readings ≥ 135/85 mmHg (or ≥ 125/75 mmHg in patients with DM or CKD) required second BP screening visit following similar protocol + home BP readings taken twice daily for 1 week
- PRA was collected in upright patients on their usual diet and antihypertensive medications
- Patients were followed for a max of 6 visits over a 6-month period (including 2 baseline visits)
- Patients could be discharged early if BP controlled at earlier visit

Statistical Analysis
- Intention-to-treat analysis
- Categorical data: assessed using Chi square tests (or Fisher’s exact test when count <5)
- Continuous data: assessed using pooled t-test
- Logistic regression models were used to estimate relative risk of BP control adjusted for age, BMI, and baseline BP

RESULTS

Participant Demographics
- 44 patients included in intention-to-treat analysis (20 AA vs. 24 RGT)
- Demographic and baseline measures were similar between treatment arms
- Average age was 57 and 58 years
- High rates of DM (>45%), African Americans (>70%)

Outcomes

<table>
<thead>
<tr>
<th>Outcomes</th>
<th>AA Arm (n= 20)</th>
<th>RGT Arm (n= 24)</th>
<th>p-value</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Primary Outcome</strong></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Change in SBP (mmHg)</td>
<td>-17.6</td>
<td>-20.4</td>
<td>0.655</td>
</tr>
<tr>
<td>Change in DBP (mmHg)</td>
<td>-4.0</td>
<td>-9.7</td>
<td>0.103</td>
</tr>
<tr>
<td><strong>Secondary Outcomes</strong></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Final SBP (mmHg)</td>
<td>144</td>
<td>132</td>
<td>0.068</td>
</tr>
<tr>
<td>Final DBP (mmHg)</td>
<td>86</td>
<td>75</td>
<td>0.014</td>
</tr>
<tr>
<td>“Controlled” (5/5 mmHg less than goal)</td>
<td>5 (25%)</td>
<td>15 (63%)</td>
<td>0.017</td>
</tr>
<tr>
<td>BP &lt;140/90 mmHg</td>
<td>7 (35%)</td>
<td>16 (66%)</td>
<td>0.036</td>
</tr>
<tr>
<td>BP &lt;130/80 mmHg</td>
<td>3 (15%)</td>
<td>12 (50%)</td>
<td>0.025</td>
</tr>
<tr>
<td>BP medications</td>
<td>4.8</td>
<td>4.0</td>
<td>0.003</td>
</tr>
<tr>
<td>Change in BP medications</td>
<td>0.9</td>
<td>0.4</td>
<td>0.009</td>
</tr>
</tbody>
</table>

- Adjusting for age, BMI, and baseline BP, there was a non-significant increase in the odds ratio for BP control at the last follow up with RGT
- The low PRA group had the most significant drop in BP, followed by moderate, then high

Adverse Events
- 2 serious ADRs were reported (one in each group)
  - AA arm: significant HTN with hypertensive symptoms due to nonadherence
  - RGT arm: heart failure exacerbation likely due to following PRA too closely (chose atenolol over carvedilol)
- All 20 patients in the AA arm had spironolactone added and serum potassium levels rose 0.3 mEq/L and eGFR decreased 2.7 mL/min/1.73 m²
**AUTHORS’ CONCLUSIONS**

- The need for fewer medications to lower BP with RGT than AA may have potential benefits on medication costs, adverse effects, and cardiovascular outcomes
- Adherence to both protocols was strong, suggesting either could be successfully implemented in practice
- This pilot study provides support for a larger comparative effectiveness trial

**CRITIQUE/DISCUSSION**

<table>
<thead>
<tr>
<th>Strengths</th>
<th>Limitations</th>
<th>Discussion</th>
</tr>
</thead>
<tbody>
<tr>
<td>Inclusion required elevated readings at 2 separate visits</td>
<td>Potential patient population underrepresented due to changes in BP goals in new guidelines</td>
<td>The results show promise for PRA levels to be utilized in primary care in patients with TRH due to its ability to be effectively implemented in clinic and its ability to lower medication requirements.</td>
</tr>
<tr>
<td>BP measurement protocol helps eliminate “white coat effect”</td>
<td>Inclusion BP were 5/5 mmHg lower than BP goals (based on theory that their BP measurement protocol results in lower readings)</td>
<td></td>
</tr>
<tr>
<td>Considered compelling indications</td>
<td>Different definition of high PRA</td>
<td></td>
</tr>
<tr>
<td>Real-life plasma renin activity values (did not require stopping HTN agents)</td>
<td>Possible type 2 error (small sample size, limited power, etc.)</td>
<td></td>
</tr>
<tr>
<td>Used PRA levels in combination with clinical judgement</td>
<td>Results may not reflect patients who are older, white, or have eGFR &lt;50 mL/min/1.73 m²</td>
<td></td>
</tr>
<tr>
<td>Intention-to-treat analysis</td>
<td>Did not compare timeline to achieve control (Did RTG or AA result in control faster?)</td>
<td></td>
</tr>
</tbody>
</table>

4 **SUMMARY AND RECOMMENDATIONS**

4.1 **INITIAL THERAPY TREATMENT DECISIONS**

- **Summary:**
  - In black patients ≥50 years and white patients <50 years, the age-race strategy effectively selected the most effective medication
  - However, in black patients <50 years or white patients ≥50 years, the age-race strategy was ineffective at selecting the most effective medication
  - The ALLHAT trial showed greater reduction in BP and stroke rates with first line thiazide diuretics compared to ACE inhibitors
- **Recommendation:**
  - Consider a combination of the age-race strategy, thiazide-first (in black patients), and PRA strategy for initial therapy treatment decisions (See Figure 3.)
4.2 TREATED, UNCONTROLLED HYPERTENSION

- Summary:
  o A PRA driven protocol was able to be successfully implemented into a clinic setting for patients with treated, uncontrolled HTN
  o PRA guided therapy lowered BP with either no net change or a decrease in the number of medications patients were taking
  o PRA guided therapy was shown to likely be cost-effective in treated, uncontrolled HTN. Cost-effectiveness was increased when cardiovascular risk factors were present.

- Recommendations:
  o PRA guided therapy should be considered in treated, uncontrolled HTN to help minimize pill burden (See table 13 for algorithm of therapy initiation and de-escalation)
  o In TRH, PRA guided therapy would be preferred in patients already on an aldosterone antagonist or if there are concerns for tolerability to an aldosterone antagonist

<table>
<thead>
<tr>
<th>Table 13. Proposed algorithm for treated, uncontrolled hypertension</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>PRA &lt;0.6</strong></td>
</tr>
<tr>
<td>• Add or maximize Anti-V drug</td>
</tr>
<tr>
<td>• Stop Anti-R drug in the absence of compelling indication</td>
</tr>
</tbody>
</table>

If BP uncontrolled after 4 weeks, repeat PRA labs and follow appropriate protocol
4.3 Future Directions

- The most benefit from PRA levels will likely be in patients with TRH or those with a desire to minimize pill burden.
- Before widespread implementation of PRA levels, we will likely need additional trials and specific recommendations in the treatment guidelines.
- Future trials would preferably be large scale randomized controlled trials comparing usual care to PRA level guided therapy.
- Unanswered questions:
  - Would PRA levels achieve BP control in fewer visits than the standard of care in TRH?
  - If a patient’s BP is controlled, can we utilize PRA levels to remove unnecessary medications while retaining BP control?
  - Would black patients with elevated PRA levels achieve similar reduction in stroke with RAS inhibitors as seen with thiazide diuretics?

5 References


### 6 Appendix

<table>
<thead>
<tr>
<th>Abbreviation</th>
<th>Definition</th>
</tr>
</thead>
<tbody>
<tr>
<td>AA</td>
<td>Aldosterone antagonist</td>
</tr>
<tr>
<td>ACC/AHA</td>
<td>American College of Cardiology and American Heart Association</td>
</tr>
<tr>
<td>ACE</td>
<td>Angiotensin-converting enzyme</td>
</tr>
<tr>
<td>ARB</td>
<td>Angiotensin II receptor blockers</td>
</tr>
<tr>
<td>ARR</td>
<td>Absolute risk reduction</td>
</tr>
<tr>
<td>ASCVD</td>
<td>Atherosclerotic cardiovascular disease</td>
</tr>
<tr>
<td>BP</td>
<td>Blood pressure</td>
</tr>
<tr>
<td>CCB</td>
<td>Calcium channel blocker</td>
</tr>
<tr>
<td>CKD</td>
<td>Chronic kidney disease</td>
</tr>
<tr>
<td>CHSC</td>
<td>Clinical hypertension specialists’ care</td>
</tr>
<tr>
<td>DM</td>
<td>Diabetes Mellitus</td>
</tr>
<tr>
<td>DRI</td>
<td>Direct renin inhibitor</td>
</tr>
<tr>
<td>GERA</td>
<td>Genetic Epidemiology Responses to Antihypertensives</td>
</tr>
<tr>
<td>HFrEF</td>
<td>Heart failure with reduced ejection fraction</td>
</tr>
<tr>
<td>HFpEF</td>
<td>Heart failure with preserved ejection fraction</td>
</tr>
<tr>
<td>HR</td>
<td>Heart rate</td>
</tr>
<tr>
<td>HTN</td>
<td>Hypertension</td>
</tr>
<tr>
<td>JNC</td>
<td>Joint National Committee</td>
</tr>
<tr>
<td>NNH</td>
<td>Number needed to harm</td>
</tr>
<tr>
<td>NNT</td>
<td>Number needed to treat</td>
</tr>
<tr>
<td>NSAIDs</td>
<td>Nonsteroidal anti-inflammatory</td>
</tr>
<tr>
<td>PRA</td>
<td>Plasma renin activity</td>
</tr>
<tr>
<td>R</td>
<td>Plasma renin-angiotensin vasoconstrictor activity</td>
</tr>
<tr>
<td>RAS</td>
<td>Renin-angiotensin system</td>
</tr>
<tr>
<td>RTG</td>
<td>Renin guided treatment</td>
</tr>
<tr>
<td>RTGT</td>
<td>Renin test-guided therapeutics</td>
</tr>
<tr>
<td>SCr</td>
<td>Serum creatinine</td>
</tr>
<tr>
<td>TRH</td>
<td>Treatment resistant hypertension</td>
</tr>
<tr>
<td>US</td>
<td>United States</td>
</tr>
<tr>
<td>V</td>
<td>Body sodium-volume content</td>
</tr>
</tbody>
</table>