Aldosterone Antagonists or Renin-Guided Therapy for Treatment-Resistant Hypertension: A Comparative Effectiveness Pilot Study in Primary Care

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BACKGROUND

Uncontrolled treatment-resistant hypertension (TRH), i.e., blood pressure (BP, mm Hg) $\geq 140/\geq 90$ mm Hg in and out of office on ≥ 3 different BP medications at optimal doses, is common and has a poor prognosis. Aldosterone antagonist (AA) and renin-guided therapy (RGT) are effective strategies for improving BP control in TRH but have not been compared.

METHODS

A comparative effectiveness TRH pilot study of AA vs. RGT was conducted in 4 primary care clinics with 2 each randomized to AA or RGT. The primary outcome was change in clinic BP defined by means of 5 automated office BP values. Eighty-nine patients with apparent TRH were screened and 44 met criteria for true TRH.

RESULTS

Baseline characteristics of 20 patients in the AA (70% Black, 45% female, mean age: 57.4 years) and 24 patients in RGT (79% Black, 50% female, 57.8 years) arms were similar with baseline BP $162 \pm 5/90 \pm 3$

vs. $153 \pm 3/84 \pm 3$, respectively, $P = 0.11/0.20$. BP declined to $144 \pm 5/86 \pm 4$ in AA vs. $132 \pm 4/75 \pm 3$ in RGT, $P = 0.07/0.01$; BP was controlled to JNC7 (Seventh Joint National Committee Report) goal in 25% vs. 62.5%, respectively, $P < 0.01$. Although BP changes from baseline, the primary outcome, were not different ($-17.6 \pm 5.1/-4.0 \pm 3.0$ AA vs. $-20.4 \pm 3.8/-9.7 \pm 2.0$ RGT, $P = 0.65/0.10$), more BP medications were added with AA than RGT ($+0.9 \pm 0.1$ vs. $+0.4 \pm 0.1$ per patient, $P < 0.01$).

CONCLUSIONS

In this TRH pilot study, AA and RGT lowered BP similarly, although fewer additional medications were required with RGT. A larger comparative effectiveness study could establish the utility of these treatment strategies for lowering BP of uncontrolled TRH patients in primary care.

Keywords: aldosterone antagonists; blood pressure; clinical effectiveness; renin-guided therapy; treatment-resistant hypertension.

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Hypertension control in the United States rose from 32.2% in 1999–2000 to 53.8% in 2009–2010.¹ Progress in hypertension control reflected increases in the proportion of adults on treatment and the number of antihypertensive medications taken by treated patients.² Among treated, uncontrolled hypertensive patients in the United States, percentages on ≥ 3 medications increased from 16% in 1988–1994 to 28% in 2005–2008.² In an outpatient quality improvement network, the proportion of treated uncontrolled hypertensive adults prescribed ≥ 3 antihypertensive medications during 2007–2010 was 30.3%,³ which is comparable to the national finding.²

Treatment-resistant hypertension (TRH) is defined as blood pressure (BP) above goal on ≥ 3 or controlled to goal on ≥ 4

BP medications prescribed at optimal doses and preferably including a diuretic.⁴ When information on medication dose, adherence, or out-of-office BP are unavailable in patients who otherwise meet the TRH definition, the term apparent TRH (aTRH) is used. In a practice-based network, $\sim 1/2$ of uncontrolled hypertensive adults with aTRH prescribed ≥ 3 different BP medications were not receiving a diuretic and 2 other antihypertensive medication classes at $\geq 50\%$ of the maximum recommended dose, an arbitrary definition of optimal treatment.³ Other major contributors to aTRH include measurement artifacts, e.g., office resistant hypertension in which BP is nonhypertensive outside but hypertensive in the clinic, and suboptimal adherence.^{4–6}

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Among patients with treated, uncontrolled hypertension, 2 efficacious pharmacological approaches to improving BP control include addition of an aldosterone antagonist (AA) and renin-guided therapy (RGT) changes.^{7–12} However, the comparative clinical effectiveness of these 2 approaches in TRH has not been assessed. Comparative effectiveness of these 2 strategies is important in usual care practices, since most patients with TRH are managed in these settings.¹³ This pilot study was conducted to test the feasibility and preliminary effectiveness of either adding an AA or using RGT in adults with uncontrolled TRH in usual primary care settings. The feasibility analysis from this pilot study was published.¹⁴ The current report focuses on preliminary effectiveness of AA and RGT for BP reduction in uncontrolled TRH.

METHODS

Patients

Adults with hypertension uncontrolled on ≥ 3 different BP medications were screened for inclusion in the pilot TRH study. The protocol was reviewed and approved by the Office of Research Integrity at the Medical University of South Carolina and written informed consent was obtained from each participant prior to initiating screening procedures. The first patient was screened on 14 September 2011 and the last patient visit occurred on 30 December 2014.

Setting

Patients were recruited from 4 community practice sites with limited research experience, comprised of 1 private internal medicine practice, 1 private family medicine practice, and 2 family medicine residency training sites. Each site was randomly assigned to one of 2 treatment protocols, RGT or AA treatment.

Inclusion criteria required patients to be legally competent, provide an informed consent, and 18–80 years old. Eligibility criteria included elevated BP on 2 separate screening visits, while taking ≥ 3 different classes of antihypertensive medications at $\geq 50\%$ of maximum recommended dose per the Seventh Joint National Committee Report (JNC7) or the FDA maximum approved dose for medications not included in JNC7.

Exclusion criteria included a legal guardian or non-English speaking, with known or suspected secondary hypertension, symptomatic or significant orthostatic hypotension, defined as BP falling $\geq 15/\geq 10$ mm Hg upon standing, life-threatening or severe illness likely to worsen during the next 6 months, myocardial infarction or stroke within the last 6 months, and nonadherence with antihypertensive medications. Medication adherence was indirectly assessed by the clinician's assessment and review of prescription refills on medication bottles relative to initial fill date. All patients provided written informed consent for study personnel to verify prescription fill history with the dispensing pharmacy, which was rarely done. Based on guidance from the External Data and Safety Monitoring Board, patients with estimated glomerular filtration rate (eGFR) < 50 mL/1.73 m²/min were excluded for safety considerations associated with AA.¹⁵

Baseline examination

At the first screening visit, demographic information and medical history were obtained and a physical examination was performed. BP, vital signs, and an ECG were recorded. Urine and blood specimens for assessing eligibility were obtained from each patient.

BP (mm Hg) measurements

Each clinic received a BpTRU automated monitor and staff training in its use prior to starting the study.¹⁶ Clinic staff ensured patients were seated and rested prior to applying the BP cuff on the patient's nondominant arm and then remained with the patient during the first recording. Staff were not present in the examination room for the 2nd through 6th BP measurements, which were obtained at 1-minute intervals.¹⁷ Staff then returned to obtain a BP after 3 minutes standing with the BpTRU to screen for orthostatic hypotension. If the average of the 5 readings was $\geq 135/\geq 85$ in patients without diabetes or $\geq 125/\geq 75$ in patients with diabetes or chronic kidney disease (CKD), the patient was scheduled for a second screening BP visit. Qualifying BP values were reduced 5/5 from BP values defining control in JNC7, since automated office BP values obtained with the protocol described are roughly 5/5 lower than usual office readings.^{18,19}

Patients were enrolled in the study if the home and second office screening BP remained elevated at the predetermined levels assuming no other exclusions were identified. To exclude office resistant hypertension,^{4,5} patients were required to have the mean of home BP values, measured twice daily for 1 week between the first and second screening visits, of $\geq 135/\geq 85$ in the absence of diabetes or CKD and $\geq 125/\geq 75$ in the presence of either or both conditions.

Laboratory assays

Blood specimens were obtained at the first screening visit for a complete metabolic panel in all patients. Plasma renin activity (PRA, ng angiotensin I/mL/h) was obtained only for patients in clinics assigned to RGT. PRA samples were obtained in upright patients on their usual diet and antihypertensive medications, i.e., no special preparation. The PRA assays were performed by LabCorp. eGFR was computed using the CKD-EPI (Chronic Kidney Disease Epidemiology Collaboration) equation.²⁰

Protocol

After 2 screening visits with antihypertensive medications held constant to establish baseline BP, eligible patients were enrolled in the study. TRH patients in clinics assigned to the AA arm continued to receive usual care with the addition of spironolactone at a starting dose of 12.5–25 mg once daily. Physicians were encouraged to manage patients assigned to the RGT arm according to the baseline PRA (ng angiotensin I/mL/h) value, yet given latitude to use their clinical judgment. For patients with low PRA, i.e., < 0.65 , physicians were encouraged to discontinue renin-angiotensin system

blockers or “R” drugs, e.g., angiotensin-converting enzyme inhibitors, angiotensin receptor blockers, and β -blockers in the absence of compelling indications, while adding or increasing anti-volume or “V” medications, e.g., diuretics, α_1 antagonists, and calcium channel blockers. The converse was true for patients with high PRA,⁹ i.e., >4.5 .^{21,22} For patients with mid-range PRA 0.6–4.5, physicians were encouraged to add R-drugs if the regimen were mainly “V” medications and vice versa. All patients were followed for a maximum of 6 study visits, including the 2 screening visits and 4 follow-up visits over a 6-month period. The study was concluded after the screening visits and prior to the 6th follow-up visit if automated office BP reached goal, i.e., <135 / <85 for patients without and <125 / <75 for patients with diabetes or CKD.

Data collection and analysis

Case Report Forms were completed by clinic staff and sent to the central study coordinator for entry into an electronic database. Entries were double-keyed and verified. Queries were returned to clinic sites for resolution. Data were exported into SAS for the intention-to-treat analysis and performed at the patient level. Continuous type data were reported as means and SEs. Categorical data were reported as frequencies and percentages. Baseline BP values were determined by the mean of the 2nd–6th readings obtained using the BpTRU from the 2 screening visits. The mean of the 2nd–6th reading at the last follow-up visit defined final BP. The primary study outcome was change in clinic BP measured with the BpTRU. Change in clinic BP was obtained by subtracting BP at the final follow-up visit from the mean of the 2 screening visit BP values. For categorical responses, between-group comparisons were assessed with either chi-square tests or Fisher’s exact test in cases where counts were

less than 5. For continuous measures, pooled *t*-tests were used with Satterthwaite’s method employed in cases where variances between groups were not equal. Due to the small sample size, results for continuous measures were verified with nonparametric methods, and no discernable differences were noted. Two-tailed tests were used without adjustments for multiple comparisons. Logistic regression models were used to estimate relative risk of BP control adjusted for age, body mass index, and baseline BP. The *a priori* level of statistical significance was 0.05.

RESULTS

Among 89 patients consented for the study, 45 did not meet inclusion criteria leaving 44 patients for the intention-to-treat analysis (Figure 1). The primary reasons for exclusion included not completing the initial enrollment or withdrawing from the study ($n = 19$), office BP below the threshold for inclusion ($n = 14$), home BP not recorded or below threshold ($n = 7$), and not currently prescribed ≥ 3 medications at predefined optimal dose at the screening visits ($n = 5$). Demographic and baseline measures shown in Table 1 were similar in both treatment arms. Mean eGFR values were similar in both groups and well above levels denoting CKD, i.e., $\text{eGFR} < 60 \text{ ml}/1.73 \text{ m}^2/\text{min}$. Mean values for body mass index and BP were not significantly higher in the AA than RGT arm. Almost half of the patients were women and nearly half of the patients had diabetes. A majority ($\geq 70\%$) were African-American in both treatment groups. The average ages were 57 and 58 years in the AA and RGT arms, respectively.

Clinic BP (mm Hg), measured with the BpTRU, declined in both treatment arms (Table 1). At the last follow-up visit, systolic BP was marginally lower ($P = 0.07$) and diastolic BP

Figure 1. The process is depicted for identifying eligible subjects for the TRH pilot study comparing addition of an aldosterone antagonist and renin-guided therapy. Abbreviations: BP, blood pressure; PRA, plasma renin activity; TRH, treatment-resistant hypertension.

Table 1. Comparative demographic, baseline, and outcome measures between treatment groups

	Aldosterone antagonist (N = 20)	Renin-guided therapy (N = 24)	Comparison between groups ^a
Baseline characteristics			
Women, n (%)	9 (45.0)	12 (50.0)	0.742
African-American, n (%)	14 (70.0)	19 (79.2)	0.509
Age, years	57.4 ± 2.1	57.8 ± 1.8	0.898
BMI, kg/m ²	36.5 ± 2.1	32.8 ± 1.4	0.132
Diabetes, n (%)	9 (45.0)	11 (45.8)	0.956
Serum K ⁺ , mEq/l	3.9 ± 0.1	4.0 ± 0.1	0.439
eGFR, ml/1.73 m ² /min	84.0 ± 5.0	79.2 ± 5.6	0.525
Chronic kidney disease, n (%)	1 (5.0)	0 (0.0)	0.454
SBP ^b , mm Hg	162 ± 5	153 ± 3	0.112
DBP ^b , mm Hg	90 ± 3	84 ± 3	0.202
BP medications, N	3.9 ± 0.2	3.5 ± 0.1	0.128
Outcomes ^c			
SBP, mm Hg	144 ± 5	132 ± 4	0.068
DBP, mm Hg	86 ± 4	75 ± 3	0.014
BP controlled ^d , n (%)	5 (25.0)	15 (62.5)	0.017
BP < 140/90, n (%)	7 (35.0)	16 (66.7)	0.036
BP < 130/80, n (%)	3 (15.0)	12 (50.0)	0.025
Change in SBP, mm Hg	−17.6 ± 5.1	−20.4 ± 3.8	0.655
Change in DBP, mm Hg	−4.0 ± 3.0	−9.7 ± 2.0	0.103
BP medications, mm Hg	4.8 ± 0.2	4.0 ± 0.1	0.003
Change BP medications, N	0.9 ± 0.1	0.4 ± 0.1	0.009

Data are presented as mean ± 1 SE of the mean or as number (N [entire sample], n [sub-sample]) and percentage. Abbreviations: BMI, body mass index; BP, blood pressure; DBP, diastolic blood pressure; eGFR, estimated glomerular filtration rate; SBP, systolic blood pressure.

^aProbability levels determined from chi-square or Fisher's exact test for categorical responses; from pooled *t*-tests for continuous data with Satterthwaite's method for unequal variances. ^bAverage (mean) BP determined from first 2 screening visits. ^cLast available BP for patients returning for at least 1 follow-up visit. ^dControl defined according to Seventh Report of the Joint National Committee on Prevention, Detection, Evaluation, and Treatment of High Blood Pressure (JNC7) as <130/<80 for patients with diabetes or chronic kidney disease and <140/<90 for all others. Control BP was adjusted 5/5 mm Hg downward for the 5 mm Hg lower BP with BpTRU than usual clinic BP measurements.¹⁸

was lower ($P = 0.01$) in the RGT than AA arm. The change of systolic (−20.4 vs. −17.6, $P = 0.65$) and diastolic (−9.7 vs. −4.0, $P = 0.10$) BP from baseline failed to reach statistical significance between the 2 groups. The proportion of patients obtaining BP control at <140/<90 ($P = 0.04$) and <130/<80 ($P = 0.025$) was greater for the RGT arm. Adjusting for age, body mass index, and baseline BP, there was a nonsignificant increase in the odds ratio of BP control at the last follow-up visit for patients in RGT than AA (odds ratio = 3.1; 95% confidence interval: 0.65–15.28).

The number of BP medications increased for patients in the AA and RGT treatment arms but was greater for patients in the AA arm (Table 1). All 20 patients in the AA group had spironolactone added to the baseline medications (Table 2), and serum potassium rose 0.3 mEq/l and eGFR decreased 2.7 ml/1.73 m²/min. Other medication changes in this group included discontinuation of a diuretic for 2 patients, including 1 patient on 2 different diuretics at baseline, discontinuation of an α_1 -blocker for 1 patient, and

a decrease in β -blocker dose for another patient. In RGT, the mean number of antihypertensive medications per patient increased from 3.5 to 4.0. The total number of BP medications increased for 12 patients, decreased for 2, and did not change for 10.

PRA (ng angiotensin I/ml/h) levels among the 24 patients in the RGT arm ranged from 0.15 to 42.2 (median: 0.59). PRA was missing in the study records of 1 patient. PRA was obtained on the screening visit and retrieved from the clinic's laboratory database as permitted in the written consent form. Renin values were categorized into low (<0.65), middle (0.65–4.5), and high (>4.5). Changes in medications are shown for each RGT group (Table 3). Figure 2 shows the changes in systolic and diastolic BP for each treatment with designation by PRA level for those patients in the RGT arm. The low PRA group had the greatest change in BP (−27.0 ± 5.8/−13.4 ± 2.7), followed by the mid (−13.0 ± 4.43/−6.0 ± 2.7), and high PRA groups (−10.5 ± 2.5/−2.5 ± 6.5).

Table 2. Baseline and last visit medications in the AA treatment arm

	Baseline		Last visit	
	N (%)	DEq	N (%)	DEq
ACEI	18 (90.0)	0.81	18 (90.0)	0.81
α_1 -Blocker	4 (20.0)	0.28	3 (15.0)	0.29
ARB	1 (5.0)	1.00	1 (5.0)	1.00
β -Blocker	15 (75.0)	0.76	15 (75.0)	0.74
dCCB	15 (75.0)	0.97	15 (75.0)	0.97
ndCCB	2 (10.0)	0.66	2 (10.0)	0.66
Diuretic ^a	15 ^a (75.0)	0.56	14 (70.0)	0.54
Aldosterone antagonist	0 (0.0)	NA	20 (100.0)	0.70
Central α_2 agonist	5 (25.0)	0.63	5 (25.0)	0.63
Nitrate	0 (0.0)	NA	0 (0.0)	NA
Renin inhibitor	0 (0.0)	NA	0 (0.0)	NA
Other vasodilator	1 (5.0)	0.25	1 (5.0)	0.25

Data are presented as number and percentage. Abbreviations: AA, aldosterone antagonist; ACEI, angiotensin-converting enzyme inhibitor; ARB, angiotensin receptor blocker; dCCB, dihydropyridine calcium channel blocker; DEq, dose equivalent, i.e., mean proportion of maximum recommended or approved dose; NA, not applicable; ndCCB, nondihydropyridine calcium channel blocker.

^aTwo patients taking more than 1 diuretic at baseline; 1 diuretic was discontinued in one of these patients.

Two serious adverse events were reported including one each with AA and RGT. A 47-year-old Black woman in the AA arm had baseline BP 152/96. Spironolactone 25mg was added after the second screening visit, and her BP declined to 134/90 at follow-up visit 1. At follow-up visit 2, BP was 169/100. She reported stress-related nonadherence with medications the prior 2 days. At follow-up visit 3, she reported headaches, blurred vision, and vomiting. Her BP was 204/124, and she was admitted to the hospital. BP at the fourth and final follow-up visit off spironolactone was 183/103, and further observation was scheduled outside the study.

The second patient was a 49-year old Black man in the RGT arm with diagnoses of poorly controlled hypertension, type 2 diabetes, and congestive heart failure. Qualifying BP was 162/100 mm Hg with baseline PRA 0.15. He was hospitalized following the second screening visit with heart failure. Atenolol, thiazide diuretic, and renin inhibitor were discontinued and carvedilol, spironolactone, and a long-acting nitrate begun. Therapeutic changes in this patient likely reflect efforts to adhere to the RGT protocol and manage heart failure. For example, while carvedilol and atenolol are both β -blockers, carvedilol, unlike atenolol, has a strong evidence-base for systolic heart failure.¹⁸ Carvedilol also blocks α_1 -adrenoceptors, an effective strategy for reducing BP in low-renin hypertension.⁹ While renin-angiotensin system blockers and AA are both evidence based for heart failure, discontinuing the renin inhibitor and adding spironolactone is an appropriate change for improving BP control in this low-renin patient. The patient concluded the study on the first follow-up visit with BP 108/70.

Table 3. Baseline and last visit medications in RGT arm by PRA level

	Baseline		Last visit	
	n (%)	DEq	n (%)	DEq
Low PRA (n = 13)				
β -Blocker	9 (69.2%)	0.73	5 (38.5%)	0.95
ndCCB	1 (7.7%)	1.00	1 (7.7%)	1.00
dCCB	5 (38.5%)	0.90	5 (38.5%)	0.90
Diuretic	11 (84.6%)	0.43	10 (76.9%)	0.44
ACEI	7 (53.9%)	0.61	6 (46.2%)	0.63
α_1 -Blocker	2 (15.4%)	0.13	11 (84.6%)	0.34
ARB	4 (30.8%)	0.55	4 (30.8%)	0.57
Central α_2 agonist	3 (23.1%)	0.42	2 (15.4%)	0.50
Nitrate	1 (7.7%)	2.00	2 (15.4%)	1.25
Antimineralocorticoid	0 (0.0%)	NA	1 (7.7%)	3.00
Renin inhibitor	1 (7.7%)	0.50	0 (0.0%)	NA
Other vasodilator	1 (7.7%)	1.50	1 (7.7%)	1.50
Mid PRA (n = 9)				
β -Blocker	5 (55.6%)	0.43	8 (88.9%)	0.59
ndCCB	2 (22.2%)	0.36	2 (22.2%)	0.36
dCCB	5 (55.6%)	0.95	6 (66.7%)	0.92
Diuretic	7 (77.8%)	0.50	9 (100.0%)	0.50
ACEI	6 (66.7%)	0.75	6 (66.7%)	0.75
α_1 -Blocker	0 (0.0%)	NA	1 (11.1%)	0.25
ARB	3 (33.3%)	1.00	3 (33.3%)	1.00
Central α_2 agonist	1 (11.1%)	0.75	1 (11.1%)	0.75
Nitrate	0 (0.0%)	NA	0 (0.0%)	NA
Antimineralocorticoid	0 (0.0%)	NA	0 (0.0%)	NA
Renin inhibitor	0 (0.0%)	NA	0 (0.0%)	NA
Other vasodilator	2 (22.2%)	0.88	2 (22.2%)	0.88
High PRA (n = 2)				
β -Blocker	0 (0.0%)	NA	1 (50.0%)	0.25
ndCCB	0 (0.0%)	NA	0 (0.0%)	NA
dCCB	2 (100.0%)	0.75	1 (50.0%)	1.00
Diuretic	2 ^a (50.0%)	0.50	2 ^a (50.0%)	0.50
ACEI	2 (100.0%)	0.50	2 (100.0%)	0.50
α_1 -Blocker	0 (0.0%)	NA	1 (50.0%)	0.50
ARB	0 (0.0%)	NA	0 (0.0%)	NA
Central α_2 agonist	0 (0.0%)	NA	0 (0.0%)	NA
Nitrate	0 (0.0%)	NA	0 (0.0%)	NA
Antimineralocorticoid	0 (0.0%)	NA	0 (0.0%)	NA
Renin inhibitor	0 (0.0%)	NA	0 (0.0%)	NA
Other vasodilator	1 (50.0%)	1.50	1 (50.0%)	1.50

Abbreviations: ACEI, angiotensin-converting enzyme inhibitor; ARB, angiotensin receptor blocker; dCCB, dihydropyridine calcium channel blocker; DEq, dose equivalent, i.e., mean proportion of maximum recommended or approved dose; NA, not applicable; ndCCB, nondihydropyridine calcium channel blocker; PRA, plasma renin activity.

^aOne patient had 2 diuretics at enrollment and last visit.

Figure 2. Blood pressure at baseline and at the final follow-up visit is shown for individuals in the aldosterone antagonist and renin-guided therapy arms of the TRH pilot study. Abbreviations: PRA, plasma renin activity; TRH, treatment-resistant hypertension.

DISCUSSION

AA and RGT were both effective for lowering BP among adults with TRH managed in primary care settings. Adding an AA lowered BP (mm Hg) 17.6/5.1 mm Hg from 162/90 at baseline to 144/86 on the last follow-up visit among 20 adults with TRH. As expected, the mean number of antihypertensive medications per patient rose nearly 1 from 3.9 to 4.8 as all 20 patients had an AA added per protocol.

Previous reports documented that adding an AA reduced BP ~20–25/~9.5–12.^{7,8} Given small numbers of patients in our pilot study, we cannot conclude that adding an AA is less effective for managing uncontrolled TRH in usual care settings than in more specialized and research clinics. Removing the single patient with a large increase of BP from the screening to last follow-up visit (Figure 2) led to a mean decline of 20.8/5.7 in the remaining 19 adults in the AA arm. This decline in BP with AA is better aligned with previous reports,^{7,8} and more similar to the decline of BP seen with RGT in this pilot study. The mean dose of spironolactone given to patients in the AA arm was 35 mg (Table 2), and serum potassium increased 0.3 mEq/l. The doses given in this pilot study are within the 12.5–50 mg range that lowered clinic systolic BP 20–25 mm Hg in patients with TRH.^{4,7} Of note, spironolactone 25–50 mg daily was superior to bisoprolol and doxazosin, for lowering home BP among patients with uncontrolled TRH.²³

With RGT, BP fell 20.4/9.7 from a baseline of 153/84 to 132/75 (Table 2, Figure 2), while the mean medication number rose 0.4 from screening to last visit. Comparing changes in BP and BP control achieved in the AA and RGT groups is complicated by the 9/6 mm Hg difference in baseline BP, albeit nonsignificant. When baseline BP values are higher, BP typically falls more with treatment interventions, but attaining control is more difficult.

The low-renin group was the largest with 13 patients (54%). Previous reports identified a large proportion of low renin in patients with TRH who responded well to amiloride.²⁴ In this study, 9 low-renin patients had an α_1 -receptor antagonist added consistent with prior reports that BP responses to α_1 -blockers are better in low- than high-renin hypertension.^{9,10,25} One patient each had a AA and calcium channel antagonist added, whereas 4 had a β -blocker and one each an ACE inhibitor, calcium antagonist, and renin inhibitor discontinued. Except for discontinuation of a calcium antagonist, these changes are consistent with recommendations to add “anti-volume” or “V” drugs for low-renin hypertension, e.g., diuretics, calcium channel, and α_1 -receptor antagonists, and to subtract anti-renin-angiotensin system drugs including β -blockers.⁹ Two patients (9%) had high baseline PRA. One patient had a β -blocker added and a calcium channel blocker discontinued, which is consistent with guidance for

this patient subset, while the addition of an α_1 -blocker in the other patient is not.⁹

In our prior RGT study implemented by hypertension specialists in patients with treated, uncontrolled hypertension, BP fell 29/14, while the number of antihypertensive medications did not change.¹¹ The findings on RGT implemented by primary care physicians in community-based settings are similar, i.e., substantial BP reduction with a modest increment in the number of antihypertensive medications. Moreover, the increase in the number of antihypertensive medications per patient was significantly less with RGT than AA (Table 1). Patients requiring more medications for hypertension control appear to have worse outcomes.^{26,27} The need for fewer medications to lower BP with RGT than AA may have potential benefits on medication costs, adverse effects, and cardiovascular outcomes, which could be assessed in future studies.

Approximately 30% of adults with treated, uncontrolled hypertension are prescribed or report taking ≥ 3 antihypertensive medications to lower BP, i.e., uncontrolled aTRH.^{2,3} Uncontrolled aTRH impacts ~ 7.5 million US adults, with roughly half having true TRH, which exceeds the number that can be practically managed through referral.¹³ The prevalence of aTRH requires effective management strategies in usual primary care settings. aTRH is more common in Black than White adults.^{2–4} Black adults, which comprised the majority of patients in our pilot study, are more likely to be low income and uninsured than White adults and to receive healthcare in settings with fewer resources.^{28,29} Practical, effective management strategies for aTRH that can be implemented in most care settings are important, especially for Black adults who are disproportionately impacted. Adherence to the AA and RGT protocols was strong, which suggests that primary care physicians can successfully implement proven strategies for lowering BP in adults with TRH.

Limitations of our pilot study include the relatively small sample size. Thus, power for detecting clinically and statistically significant differences between the 2 interventions is limited. The study as originally designed had 4 arms. However, referral to a hypertension specialist alone and together with RGT was stopped early by the Data Safety Monitoring Board, since very few eligible patients were referred to a hypertension specialist. Two serious adverse events highlight the risk associated with true TRH and the importance of effective management strategies, especially in usual care settings. The mean age of patients in this study was approximately 10 years younger than adults with aTRH in a national sample,¹¹ yet comparable to adults with uncontrolled aTRH in our clinical practice network.³ Moreover, patients in this report were disproportionately Black. Given safety considerations when adding AA in patients with CKD,¹⁵ patients with baseline eGFR < 50 mL/1.73 m²/min were excluded. Yet, patients with CKD are more likely to have TRH. Thus, our pilot study findings may not adequately reflect patients who are older, White, or who have eGFR < 50 .

In this pilot study, adding an AA and implementing RGT both led to large reductions in systolic BP. Thus, both treatment strategies were effective for lowering BP among patients with TRH in primary care settings. With lessons

learned from the qualitative analysis,¹⁴ our pilot study provides support for a larger comparative effectiveness trial of strategies for improving BP control in adults with uncontrolled TRH in primary care.

SUPPLEMENTARY MATERIAL

Supplementary materials are available at *American Journal of Hypertension* (<http://ajh.oxfordjournals.org>).

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DISCLOSURE

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