

Clinical Study: Resistant Hypertension Optimal Treatment Trial (ReHOT)

Spironolactone Versus Clonidine as a Fourth-Drug Therapy for Resistant Hypertension

The ReHOT Randomized Study (Resistant Hypertension Optimal Treatment)

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Abstract—The aim of this study is to compare spironolactone versus clonidine as the fourth drug in patients with resistant hypertension in a multicenter, randomized trial. Medical therapy adherence was checked by pill counting. Patients with resistant hypertension (no office and ambulatory blood pressure [BP] monitoring control, despite treatment with 3 drugs, including a diuretic, for 12 weeks) were randomized to an additional 12-week treatment with spironolactone (12.5–50 mg QD) or clonidine (0.1–0.3 mg BID). The primary end point was BP control during office (<140/90 mmHg) and 24-h ambulatory (<130/80 mmHg) BP monitoring. Secondary end points included BP control from each method and absolute BP reduction. From 1597 patients recruited, 11.7% (187 patients) fulfilled the resistant hypertension criteria. Compared with the spironolactone group (n=95), the clonidine group (n=92) presented similar rates of achieving the primary end point (20.5% versus 20.8%, respectively; relative risk, 1.01 [0.55–1.88]; $P=1.00$). Secondary end point analysis showed similar office BP (33.3% versus 29.3%) and ambulatory BP monitoring (44% versus 46.2%) control for spironolactone and clonidine, respectively. However, spironolactone promoted greater decrease in 24-h systolic and diastolic BP and diastolic daytime ambulatory BP than clonidine. Per-protocol analysis (limited to patients with $\geq 80\%$ adherence to spironolactone/clonidine treatment) showed similar results regarding the primary end point. In conclusion, clonidine was not superior to spironolactone in true resistant hypertensive patients, but the overall BP control was low ($\approx 21\%$). Considering easier posology and greater decrease in secondary end points, spironolactone is preferable for the fourth-drug therapy.

Clinical Trial Registration—URL: <http://www.clinicaltrials.gov>. Unique identifier: NCT01643434.

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Resistant hypertension is an emerging clinical and public health problem with increasing incidence because of increasing life expectancy^{1,2} and the growing global epidemic of obesity, diabetes mellitus, and obstructive sleep apnea.³⁻⁶ Likewise, the excessive dietary salt ingestion reported in many countries⁷ can contribute substantially to the risk of resistant hypertension. Identifying and treating patients with resistant hypertension is of paramount importance because compelling evidence has shown that this subgroup of hypertensive patients presents with a significantly higher rate of target-organ damage, a higher risk of cardiovascular events, and a significantly poorer prognosis than those of nonresistant hypertensive patients.^{8,9}

Despite advancements in hypertension diagnosis, the prevalence of resistant hypertension is not well established.⁸ Poor medical adherence, poor blood pressure (BP) measuring technique, and white-coat effect are relevant challenges to figuring out the real burden of resistant hypertension.⁸ Until recently, the prevalence of resistant hypertension was mainly derived from post hoc analyses of clinical trials.¹⁰ Recent data from the National Health and Nutrition Examination Survey indicate that the estimated prevalence of resistant hypertension has been increasing progressively during the last decades, reaching 11.8% between 2005 and 2008.¹¹ Whether these statistics can be extrapolated to other countries is largely unknown. Moreover, identifying good predictors of resistant hypertension may help in screening these patients and providing appropriate BP control.

Finally, the most suitable fourth drug to be added to the commonly prescribed triple antihypertension regimen (a diuretic, an angiotensin-converting enzyme inhibitor or an angiotensin-receptor blocker, and a calcium channel blocker) is not well established.¹²⁻¹⁴ A recent randomized study compared active treatments added to the triple regimen and concluded that spironolactone was the most effective add-on drug for the treatment of resistant hypertension.¹⁵ However, this conclusion was based only on systolic home BP, and no potent central sympatholytic candidates, such as clonidine, were tested.

In the current study, we have prospectively assessed the following: (1) the prevalence of true resistant hypertension in a cohort of outpatients with stage 2 hypertension (BP \geq 160/100 mmHg), (2) the clinical predictors of resistant hypertension, and (3) the effects of spironolactone versus clonidine when added to the triple regimen in patients with resistant hypertension. We wanted to test that a significant minority of patients with stage 2 hypertension are truly resistant to antihypertensive treatment that we can identify clinical predictors of resistant hypertension using demographic medical history and laboratorial exams and that the sympatholytic drug clonidine would promote greater BP control than spironolactone, as determined by both office and 24-hour ambulatory BP monitoring (ABPM). The main reason for speculating clonidine superiority relies on the fact that patients with resistant hypertension were already on use of a diuretic (approaching hypervolemia) and renin-angiotensin inhibitors.

Methods

The ReHOT study (Resistant Hypertension Optimal Treatment) was approved by the institutional review board (No. 0758/09). All

participants provided written informed consent. This investigation was conducted in accordance with the Declaration of Helsinki and good clinical practice guidelines. The ReHOT investigators, including the Writing Committee and Steering Committee, are listed in the Appendix. The authors declare that all supporting data are available within the article ([online-only Data Supplement](#)).

The detailed methodology, including the inclusion and exclusion criteria, can be found in the study design paper.¹⁶ Briefly, we describe the 2 main steps below:

Step 1: determining the prevalence of resistant hypertension using a 12-week open-label forced-titration regimen of 3 antihypertensive drugs (chlorthalidone, enalapril or losartan, and amlodipine):

The ReHOT study included patients with hypertension stage 2 (never treated or under previous antihypertensive treatment) to detect resistant hypertension prevalence in 26 sites in Brazil. We excluded secondary forms of hypertension (except obstructive sleep apnea because of the lack of available sleep laboratories at all centers).¹⁶ Resistant hypertension was defined as BP that remains above goal, despite the concurrent use of 3 antihypertensive agents of different classes, including a diuretic, and all agents were prescribed at optimal dose amounts (in our study: chlorthalidone, 25 mg QD; enalapril, 20 mg BID; losartan, 50 mg BID; and amlodipine, 5 mg BID).⁸ At each visit, the physician measured the patient's BP in a seated position after a 10-minute rest period with the validated Omron HEM-742 automatic device. At least 3 measurements, or until 2 consecutive measurements differed $<$ 4 mmHg, were obtained. The mean value of the last 2 measurements was calculated and used as the office BP value.

At visit 0, all patients underwent a clinical evaluation, including anthropometric data, sleep questionnaires, and BP measurements. All patients received lifestyle modification counseling, including dietary sodium reduction and physical activity. Patients were initially treated with chlorthalidone 25 mg/d and enalapril 20 mg BID (or losartan, 50 mg BID if side effects, such as cough, were presented). For ethical reasons, previous antihypertensive treatment other than the ones included in our study was suspended without prior washout. During all visits, medication adherence was monitored by pill count. All medications were provided to the patients, and there was a log form in the case report form of the study to control and calculate drug compliance. We considered adherent patients as those taking all medications correctly \geq 80% of the time on all days.¹⁶ Nonadherence to treatment was considered in the analysis.

After 4 weeks, on visit 1, patients underwent routine laboratory tests (including glucose, cholesterol levels, estimated glomerular filtration rate, and serum K⁺), electrocardiography, and 24-hour ABPM. During the 24-hour ABPM (SpaceLabs device, model 90207; SpaceLabs Medical, Inc, Snoqualmie, WA), BP was measured every 10 minutes during the day and every 20 minutes during the night with an appropriate cuff placed on a nondominant arm. Activities, bedtime, and time of awakening from sleep were recorded by the participants in diaries. The participants were instructed to perform their ordinary daily activities and not to move their arm during the ongoing measurement. If uncontrolled BP (systolic BP \geq 140 mmHg and diastolic BP \geq 90 mmHg) was observed, we introduced 5 mg/d amlodipine that could be titrated to 10 mg/d after 4 weeks at visit 2 if the BP goal was not achieved. At visit 3, patients underwent another ABPM, and those with office BP \geq 140/90 mmHg and ABPM 24-hour mean \geq 130/80 mmHg, despite good adherence to medical therapy, were considered resistant hypertensives.¹³

Step 2: open-label, parallel randomized study comparing the 2 drugs in patients with true resistant hypertension

True resistant hypertensive patients were randomized (simple randomization generated by a computer) into 2 treatment groups: treatment with spironolactone 12.5 mg QD or with clonidine 0.100 mg BID. On visits 4 and 5 (4-week intervals), the dosage could be increased for spironolactone to 25 or 50 mg/d and clonidine to 0.200 or 0.300 mg BID if indicated. Clonidine is a Food and Drug Administration-approved drug acting as a centrally acting α_2 adrenergic agonist reducing the sympathetic activity. The maximum dose is 2.4 mg orally per day in divided doses, but in this trial, we used the maximum dose of 0.6 mg. In our clinical practice, this schedule is tolerated by significant proportion of patients. Patients with controlled

BP on visit 3 received pharmaceutical assistance every 4 weeks (visits 4 and 5) and were evaluated after 12 weeks (visit 6). At visit 6, all patients underwent a medical examination, routine laboratory tests, ECG, and ABPM. After 24 weeks, we were able to define the hypertensive patients controlled with 2 or 3 drugs and the patients who remained uncontrolled after treatment with 4 antihypertensive drugs. Adverse events were recorded at each visit paying special attention to potential recognized adverse effects of clonidine and spironolactone treatments, as well as potential, serious adverse events related to the resistant hypertension profile and multiple antihypertensive drugs: syncope, cerebrovascular events, myocardial infarction, death, among others.

Outcomes

The primary end point was effective BP control determined by both office BP (defined as a systolic BP <140 mmHg and diastolic BP <90 mmHg) and ABPM (defined as a 24-hour mean BP <130/80 mmHg) after the 12-week randomized period of treatment with clonidine or spironolactone. Secondary end points included effective BP control by each evaluation method (office BP/ABPM) and absolute BP reduction in each study arm.

Statistical Analysis

We estimated the prevalence of true resistant hypertension to be 20%. For the randomization phase, we calculated that it would be necessary to enroll 189 patients in each treatment arm. Because of the lack of evidence comparing the effects of spironolactone versus clonidine in the same trial, we made an empirical estimation of a difference of 5 mmHg in BP between treatment groups and an SD of 15 mmHg in each group, for a 2-sided test. We anticipate a statistical power of 90%.

Continuous measurements are presented as the mean and SD or median and interquartile range. Categorical measurements are presented as absolute and relative frequencies. Comparisons between the resistant and nonresistant hypertension groups were performed using Student *t* test or nonparametric Mann–Whitney *U* tests and χ^2 tests. Significant variables (except absolute BP values) adjusted for age and sex were used for determining the predictors of resistance to BP treatment by a logistic regression model.

Our primary analysis was based on a modified intention-to-treat population (only patients with BP data were included in the final analysis). Additional per-protocol analyses were performed to investigate the performance of the 2 antihypertensive drugs in patients who were adherent ($\geq 80\%$) to the assigned treatments. The primary end point was evaluated using Fisher exact test and is presented as the relative risk, estimated with its respective 95% CI. To evaluate the secondary end points, the BP measurements are presented with 95% CIs. To examine the changes in systolic and diastolic BP, repeated measures analysis of variance was performed, including an indicator variable for time (baseline, 4, 8, and 12 weeks), an interaction term for treatment by time, and the variable treatment in the model. The analyses were performed using the R software 3.2.3 (R Core Team, 2015), and the tests were considered significant at a level of 5%.

Results

Prevalence and Predictors of Resistant Hypertension

From October 2010 to February 2014, we initially recruited 1893 patients with hypertension stage 2. After excluding the patients who refused to participate, patients who did not come back for the regular visits, and patients with incomplete evaluations, 1597 participants were studied. Details about the study recruitment and exclusions are presented in Figure 1. The characteristics of the studied patients are described in Table 1. Overall, this is a middle-aged sample of predominantly men who were obese and carried a significant

prevalence of comorbidities, such as diabetes mellitus, dyslipidemia, and high risk for obstructive sleep apnea (Table 1). After 12 weeks of follow-up, we found that 11.7% (187 patients) fulfilled the resistant hypertension criteria. Table 1 also shows the characteristics of patients with and without resistant hypertension. The patients with true resistant hypertension had a higher proportion of participants with a history of stroke, a higher frequency of diabetes mellitus, a lower estimated glomerular filtration rate, and a higher proportion of participants with systolic plus diastolic nondipping BP. As expected, the patients with resistant hypertension presented with higher BP levels as determined by office BP and ABPM. Table S1 in the [online-only Data Supplement](#) shows the predictors of resistant hypertension in our population. According to this table, a history of stroke, diabetes mellitus, and office BP $\geq 180/110$ mmHg at study entry were independently associated with a confirmed diagnosis of resistant hypertension. Data on the adherence to medications in phase 1 are presented in Table S2. Table S3 shows the characteristics of the randomized patients who continued ($n=162$) or discontinued ($n=25$) the study.

Comparison of Spironolactone Versus Clonidine

Table 2 shows the baseline characteristics of the true resistant hypertensive patients who were randomized to the spironolactone or clonidine treatment groups. Overall, the groups were homogeneous regarding the clinical variables. Data on the adherence to medications in phase 2 are presented in Table S4. No significant differences in medical adherence were observed (including the comparison of randomized drugs). The mean dose of spironolactone and clonidine at study end were 40 mg and 0.35 mg, respectively. Figures 2 and 3 report the data on office BP and ABPM, respectively. From baseline to 3 months, the following respective systolic and diastolic decreases were observed (Figure 2): 15.1 (10.6–19.7) and 7.7 (5.0–10.3) mmHg for spironolactone and 13.7 (9.0–18.4) and 6.4 (3.7–9.1) mmHg for clonidine. When comparing treatments, neither drug was significantly better ($P=0.624$ for systolic BP, $P=0.454$ for diastolic BP). However, the patients randomized to spironolactone had a greater decrease in their 24-hour systolic and diastolic BP (Figure 3A). Indeed, from baseline to 3 months, the following respective systolic and diastolic decreases were observed: 11.8 (8.6–15.0) and 6.3 (4.5–8.2) mmHg for spironolactone and 7.3 (4.1–10.6) and 3.9 (2.0–5.8) mmHg for clonidine. When comparing treatments, spironolactone was significantly better ($P=0.030$ for systolic BP, $P=0.045$ for diastolic BP). Regarding daytime BP, the following respective systolic and diastolic decreases were observed from baseline to 3 months: 11.7 (8.5–14.9) and 6.9 (4.9–8.8) mmHg for spironolactone and 8.0 (4.8–11.3) and 4.3 (2.4–6.6) mmHg for clonidine. When comparing treatments, spironolactone was not superior to clonidine for systolic BP ($P=0.071$) but significantly better for diastolic BP ($P=0.039$). No differences were observed in the night-time BP (Figure 3C). From baseline to 3 months, the following respective systolic and diastolic decreases were observed: 9.2 (4.8–13.8) and 5.8 (3.5–8.2) mmHg for spironolactone and 6.6 (2.2–11.0) and 3.4 (1.0–5.7) mmHg for clonidine.

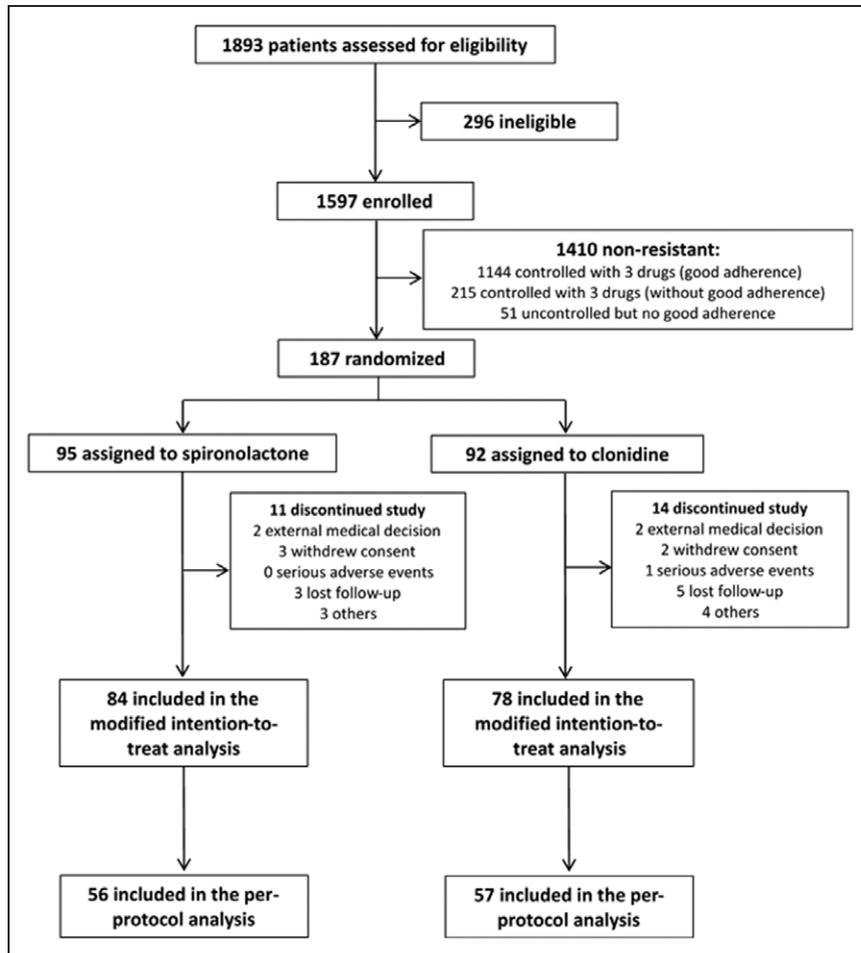


Figure 1. Trial profile.

When comparing treatments, neither drug was significantly better ($P=0.358$ for systolic BP, $P=0.097$ for diastolic BP). Table 3 summarizes the rate of primary and secondary outcomes in an intention-to-treat analysis. Table 3 showed that $\approx 21\%$ of patients displayed controlled BP at both the office BP monitoring and ABPM after the fourth drug was administered. We found similar office BP (33.3% versus 29.3%) and ABPM (44% versus 46.2%) control for spironolactone and clonidine, respectively. The per-protocol analysis (limited to those with $\geq 80\%$ adherence to spironolactone or clonidine use) showed similar results for the primary end point (Table S5). Table S6 shows the adverse effects of spironolactone or clonidine. Overall, the rate of side effects reported for both spironolactone and clonidine was low. Not a single case of gynecomastia related to spironolactone. The patients randomized to clonidine, however, presented with a higher frequency of somnolence than those who received spironolactone, but no substantial impact on daily living was observed, and the vast majority of them continued treatment. No differences were observed in the heart rate in both drugs (spironolactone, 71 ± 15 ; clonidine, 70 ± 14 bpm; $P=0.65$). In contrast, patients randomized to spironolactone had a slight increase in the creatinine levels compared with clonidine (1.12 ± 0.38 versus 0.98 ± 0.35 mg/dL; $P=0.01$) and a higher percentage of hyperkalemia (Table S6). Despite this higher percentage of hyperkalemia after spironolactone, no related complications were reported. Adherence to clonidine and

spironolactone was not different (Table S4). No other differences were observed.

Discussion

In this systematic multicenter study comprising stage 2 hypertensive patients from all regions of Brazil, we found that $\approx 12\%$ of patients under regular use of the most common triple therapy for hypertension (thiazide, an angiotensin-converting enzyme inhibitor or angiotensin-receptor blocker, and calcium channel blockers) presented with resistant hypertension. A history of stroke, diabetes mellitus, or BP $\geq 180/100$ mm Hg at study entry was independently associated with a resistant hypertension diagnosis. More importantly, data from the randomized controlled phase showed that spironolactone and clonidine treatment resulted in similar BP control, as determined by both office BP monitoring and 24-hour ABPM. Per-protocol analysis (limited to those with $\geq 80\%$ adherence to spironolactone or clonidine use) showed similar results in the primary end point. Overall, the adherence and tolerance of both drugs were similarly good. However, data from the secondary end points showed that patients randomized to the spironolactone group had a greater decrease in their 24-hour systolic and diastolic BP and diastolic daytime ambulatory BP than the clonidine group. Our results suggest that good adherence to the antihypertensive treatment can control the vast majority of patients with stage 2 hypertension. Based on our initial

Table 1. Characteristics of the Patients Included in Phase 1

Variable	Total (n=1597)	Nonresistant (n=1410)	Resistant (n=187)	P Value
Age, y	54±10	54±10	55±11	0.141*
Men, %	40.5	39.8	45.5	0.16†
White, %	41.6	42	39	0.49†
Body mass index, kg/m ²	30.8±6.4	30.8±6.5	30.7±5.1	0.903†
Heart failure, %	0.6	0.6	0.5	1†
Previous stroke, %	3.8	3.0	10.2	<0.001†
Previous myocardial infarction, %	1.1	0.9	2.1	0.252†
Diabetes mellitus, %	18.7	16.9	32.6	<0.001†
Dyslipidemia, %	29.2	28.4	35.8	0.043†
Smoker, %	9.2	9.2	9.1	1†
High risk for sleep apnea—Berlin Questionnaire, %	61.4	61.5	61.3	1†
Serum creatinine, mg/dL	0.9 (0.7–1.1)	0.9 (0.7–1.1)	0.9 (0.8–1.2)	0.008‡
Potassium, mEq/L	4.1 (3.8–4.4)	4.1 (3.8–4.4)	4.1 (3.7–4.4)	0.559‡
Estimated glomerular filtration rate, mL/min	94.9 (75.4–119.9)	95.2 (76.6–120.7)	88.9 (68.5–116.9)	0.008‡
Office BP				
Systolic BP at study entry	172.5±15.7	171.4±15.1	180.6±17.5	<0.001*
Diastolic BP at study entry	102.4±11.6	101.9±11.3	106.1±13.4	<0.001*
BP ≥180/110 mm Hg at study entry, %	37.6	34.6	60.4	<0.001†
Systolic BP after 3 mo, mm Hg	129.7±16.7	126.5±13.8	153.6±17.1	<0.001*
Diastolic BP after 3 mo, mm Hg	81.1±10.2	79.6±9.1	92.4±10.7	<0.001*
ABPM				
24-h systolic BP, mm Hg	122.6±18.9	119.8±17.9	142.5±13.1	<0.001*
24-h diastolic BP, mm Hg	74.9±12.3	73.4±11.8	86.2±9.8	<0.001*
Daytime systolic BP, mm Hg	125.3±19.5	122.6±18.6	145.2±12.9	<0.001*
Daytime diastolic BP, mm Hg	77.8±12.8	76.2±12.3	89.2±10.6	<0.001*
Night-time systolic BP, mm Hg	115.3±21.8	112.6±20.9	135.3±17.4	<0.001*
Night-time diastolic BP, mm Hg	68±13.8	66.5±13.5	79.4±9.8	<0.001*
Systolic BP nondipping, %	63.2	62.4	69	0.095†
Diastolic BP nondipping, %	39.4	38.5	46	0.059†
Systolic and diastolic BP nondipping, %	53.9	52.5	63.6	0.006†

ABPM indicates ambulatory blood pressure monitoring; and BP, blood pressure.

**t* test.

†Fisher exact test.

‡Mann–Whitney *U* test.

hypothesis, the ReHOT study results indicated that clonidine was not superior to spironolactone as a fourth-drug therapy in patients with resistant hypertension. Spironolactone is preferable considering that it is taken once a day and displayed better outcomes in some ABPM parameters. Because only 21% of resistant hypertensives controlled in both office and ABPM with either fourth drug, additional efforts should be aimed at identifying indicators for the best responders to each drug and novel drug associations.

The main aim of the ReHOT study was to explore the best fourth medical treatment for resistant hypertension patients under regular use of the most common triple regimen. Resistant hypertension is a heterogeneous state that

requires attractive alternatives to treatment, such as acting against fluid retention and sympathetic activity mechanisms. Because of the complexity and challenge of selecting patients with true resistant hypertension, it is not surprising that the data on this important area of study are relatively scarce in the literature. Thus far, the available evidence highlights spironolactone—a drug that acts primarily through competitive binding of receptors at the aldosterone-dependent sodium-potassium exchange site in the distal convoluted renal tubule, as the best fourth option for treating resistant hypertension. Previous studies have shown advantages of spironolactone versus placebo¹⁷ in combination with other diuretics, such as furosemide and amiloride

Table 2. Baseline Characteristics of the Patients Randomized to Spironolactone or Clonidine Treatment in Phase 2

Variable	Clonidine (n=92)	Spironolactone (n=95)	P Value
Age, y	56.3±9.7	54±11.1	0.133*
Men, %	46.7	44.2	0.841†
White, %	39.1	38.9	1†
Body mass index, kg/m ²	30±5	31.5±5.2	0.051†
Heart failure, %	1.1	0	0.987†
Stroke, %	9.8	10.5	1†
Myocardial infarction, %	3.3	1.1	0.591†
Diabetes mellitus, %	31.5	33.7	0.873†
Dyslipidemia, %	39.1	32.6	0.439†
Smoker, %	12	6.3	0.277†
High risk for OSA—Berlin Questionnaire, %	65.2	57.4	0.349†
Serum creatinine, mg/dL	0.9 (0.7–1.1)	1 (0.8–1.2)	0.171‡
Potassium, mEq/L	4.1 (3.8–4.4)	3.9 (3.7–4.4)	0.37‡
Estimated glomerular filtration rate, mL/min	94.5 (69.5–115.1)	86 (66.3–117)	0.311‡
Office BP			
Systolic BP at study entry—first phase, mm Hg	181.1±18.5	180.1±16.5	0.708*
Diastolic BP at study entry—first phase, mm Hg	107.1±14	105.2±12.8	0.348*
BP ≥180/110 mm Hg at study entry, %	62	58.9	0.786†
Systolic BP after 3 mo of triple treatment, mm Hg	151.8±16.3	155.3±17.7	0.162*
Diastolic BP after 3 mo of triple treatment, mm Hg	91.3±12	93.5±9.3	0.176*
Ambulatory blood pressure monitoring			
24-h systolic, mm Hg	141.7±12.8	143.3±13.5	0.392*
24-h diastolic, mm Hg	85.6±9.7	86.7±9.9	0.456*
Daytime systolic, mm Hg	144.5±13.1	145.9±12.6	0.467*
Daytime diastolic, mm Hg	88.6±10.6	89.9±10.7	0.382*
Night-time systolic, mm Hg	135.4±15.3	135.3±19.2	0.953*
Night-time diastolic, mm Hg	79±9.6	79.8±10	0.552*
Systolic BP nondipping, %	69.6	68.4	0.991†
Diastolic BP nondipping, %	52.2	40	0.128†
Systolic and diastolic BP nondipping, %	65.2	62.1	0.772†

BP indicates blood pressure; and OSA, obstructive sleep apnea.

**t* test.

†Fisher exact test.

‡Mann–Whitney *U* test.

versus ramipril and bisoprolol (in patients already using an angiotensin-receptor blocker),¹⁸ even compared with renal denervation.^{19,20} However, to the best of our knowledge,

only 1 randomized study has compared spironolactone with other potential drug candidates. In the PATHWAY-2 trial (Prevention and Treatment of Hypertension With Algorithm-Based Therapy Number 2),¹⁵ a double-blind, crossover trial performed at 12 secondary and 2 primary care centers in the United Kingdom showed that spironolactone was superior to doxazosin, bisoprolol, and placebo to decrease systolic home BP (primary aim) for 12 weeks in 230 patients who completed all treatment cycles.¹⁵ In the ReHOT trial, we found comparable BP control of spironolactone versus clonidine during a similar follow-up period. There are several differences in the PATHWAY-2 and ReHOT trials that deserve discussion. First, the ReHOT trial recruited patients from all regions of Brazil, which has a highly admixed population. Moreover, several of the involved centers have characteristics of secondary/tertiary care. Second, the ReHOT trial used clonidine instead of doxazosin to promote sympathetic blockade. Although no previous direct comparisons of the effectiveness of BP control of clonidine versus doxazosin are available,²¹ clonidine seems to have a greater bioavailability and lower dependence of protein binding²² than doxazosin.²³ Third, although PATHWAY-2 focused on systolic home BP (primary aim), the ReHOT trial used both the systolic and diastolic BP from the office and ABPM. Our primary aim was based on BP control (guided by Hypertension Guidelines)¹³ rather than absolute values. Moreover, the available data from the 24-hour BP allowed us to evaluate BP during sleep and non-dipping status. These differences in BP measurements may explain the percentage of BP control in PATHWAY-2 (on average, 68.9%) versus 21% in the current study. If ABPM control is considered alone, we observed a 44% and 46.2% control for spironolactone and clonidine, respectively. Moreover, the BP control differences observed between office and ABPM may be partially explained by the well-known white-coat effect. Further studies evaluating the predictors of spironolactone or clonidine BP response are warranted in the ReHOT trial.

In the present study, we found 11.7% of resistant hypertension, which is comparable with the rates reported for population studies, such as National Health and Nutrition Examination Survey (11.8%)¹¹ and the Brazilian Longitudinal Study of Adult Health (11%).²⁴ However, it is important to emphasize that unlike the previous studies, our sample is restricted to stage 2 hypertension (to decrease the rate of white-coat hypertension), and we relied on office BP and ABPM to ascertain BP and took special care to assess adherence through pill counting. Our results have important clinical implications for our National Health System, which is responsible for attending to ≈75% of the Brazilian population. The 3-drug regimen used in this study is available for prescribing to the hypertensive population, and it was able to control BP in the vast majority of patients. Moreover, the presence of comorbidities (such as stroke and diabetes mellitus) and stage 3 BP (≥180/110 mm Hg) at study entry were independent predictors of resistant hypertension. Some of these predictors (such as diabetes mellitus and higher BP values) were already reported in the literature.⁸ In our clinical practice, there are no systematic protocols for identifying patients with true resistant

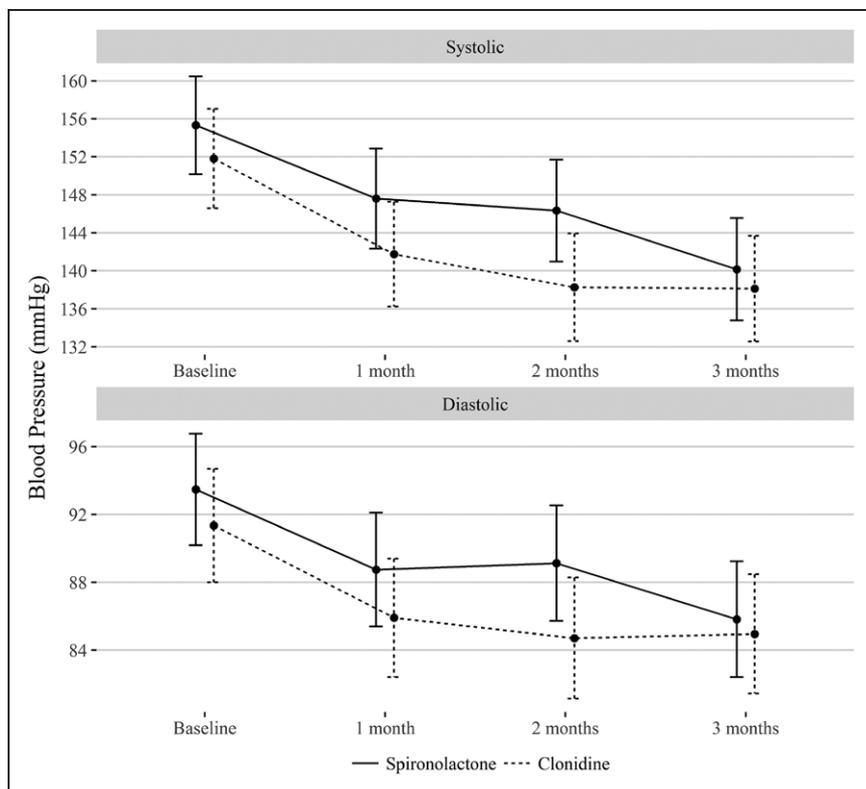


Figure 2. Office blood pressure data in patients randomized to spironolactone or clonidine treatment.

hypertension and any evaluation of medical adherence is performed. Every year, thousands of patients with high values of BP are inadvertently referred for evaluation in tertiary centers for false suspicion of resistant hypertension. This approach carries increased costs and unnecessary appointments in tertiary centers, therefore, increasing the waiting list and return intervals. Our results underscore the need to improve adherence to medical therapy. Although no ideal medication adherence technique is available, the ReHOT trial results suggest that a local program for counting pills during treatment is highly desirable.

The current study has several strengths that need to be addressed. First, this is a multicenter randomized trial involving several regions in Brazil. Second, this trial monitored and reported pill counting like previous randomized study.¹⁵ Poor medical adherence is a particularly major issue in the diagnosis of resistant hypertension.⁸ Another important issue is the potential Hawthorne effect observed in previous investigations that observed BP decrease in the control group.¹⁷ This fact is mainly explained by improving the first 3-drug adherence after entering in the study. The ReHOT trial did not have a placebo group but took special attention to this possibility performing

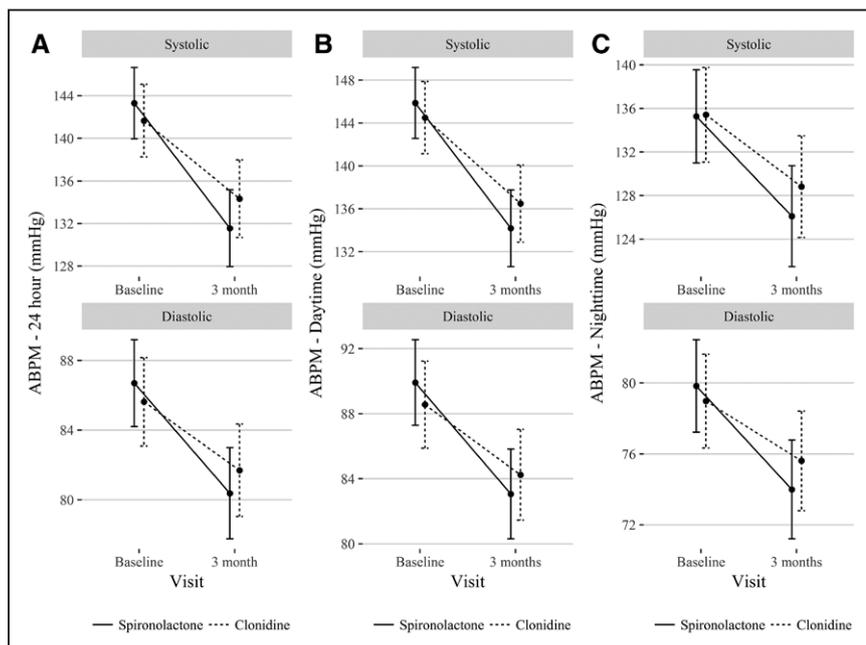


Figure 3. Ambulatory blood pressure monitoring (ABPM) data in patients randomized to spironolactone or clonidine treatment. **A**, 24-h blood pressure; **B**, daytime blood pressure; and **C**, night-time blood pressure.

Table 3. Primary and Secondary Outcomes Analysis (Modified Intention to Treat)

End Point	Spironolactone (n=84)	Clonidine (n=78)	Relative Risk	P Value
Primary end point				
Office BP and 24-h ABPM control, %	20.5	20.8	1.01 (0.55 to 1.88)	1
Secondary end points				
Office blood pressure <140/90 mmHg, %	33.3	29.9	0.9 (0.56 to 1.43)	0.771
24-h ABPM <130/80 mmHg, %	44	46.2	1.05 (0.75 to 1.47)	0.911
Office BP, mmHg				
Systolic	140.1±18.8	138±19	-2.08 (-7.95 to 3.8)	0.486*
Diastolic	85.9±11.1	85±13.2	-0.91 (-4.71 to 2.89)	0.635*
ABPM, mmHg				
24-h systolic	131.3±12.8	133.9±13.8	2.68 (-1.55 to 6.9)	0.212*
24-h diastolic	80.4±10.1	81.4±9.9	1 (-2.17 to 4.18)	0.533*
Daytime systolic	133.8±12.7	136.1±13.6	2.32 (-1.87 to 6.51)	0.275*
Daytime diastolic	83±10.3	83.9±10.3	0.91 (-2.35 to 4.17)	0.583*
Night-time systolic	125.9±15.2	128.4±17.1	2.52 (-2.62 to 7.66)	0.334*
Night-time diastolic	74.1±10.8	75.3±11	1.17 (-2.29 to 4.63)	0.505*

ABPM indicates ambulatory blood pressure monitoring; and BP, blood pressure.

*Mean difference (spironolactone vs clonidine).

a 12-week first phase before starting the randomized phase. Third, the ReHOT trial performed measurements using both office BP measurements and 24-hour ABPM, which showed that the percentage of patients with controlled BP is much less than observed for each BP method. The potential limitations also deserve attention. The sample size determination considered a superiority test, and the estimated rate of resistant hypertension (20%) reported in our study design¹⁶ was higher than what we observed. The study power may compromise our findings. However, the estimated relative risk was close to 1 (1.01 with 95% CI, 0.55–1.88), but the noninferiority margin for a significance level of 2.5% is wide (considering 80% power). Therefore, noninferiority of clonidine to spironolactone cannot be claimed in this study. Another limitation is that this is an open-label study. However, we used automatic devices (no BP rounding using this technique), and all ABPM measurements were analyzed in a blinded fashion. Third, the current study compared relatively low doses of clonidine versus optimized doses of spironolactone. In fact, the mean dose of clonidine after 12 weeks represents ≈60% of the maximum possible dose. This finding is partially explained by the higher rate of somnolence to clonidine and may likely be enhancing the effectiveness of spironolactone compared with clonidine in resistant hypertension. Finally, the ReHOT trial did not test other antihypertensive classes nor did it evaluate hard end points. Nonetheless, BP is a powerful surrogate of cardiovascular events, especially in patients with resistant hypertension. Based on our stringent criteria for selecting true resistant hypertension, we speculate that the randomized studies addressing the impact of treatment on fatal and nonfatal cardiovascular events in patients with resistant hypertension will require a huge effort from multiple countries and substantial financial support.

Perspectives

Results from ReHOT trial showed an 11.7% of resistant hypertensives among a cohort of Brazilians outpatients with stage 2 hypertension. Although the rate of BP control was similar between the 2 tested drugs, spironolactone is preferable as a fourth drug considering the dosage facilities and higher impact in some ABPM secondary end points. Identification of indicators for best responders for both drugs or novel drug associations are needed considering that only 21% of patients are controlled in a restricted criteria, including both the office BP and the 24-hour ABPM.

Appendix

The ReHOT investigators are as follows: the Writing Committee consisted of Eduardo M. Krieger, Luciano F. Drager, Dante Marcelo Artigas Giorgi, Jose Eduardo Krieger, Alexandre C. Pereira, José Augusto Soares Barreto-Filho, Armando da Rocha Nogueira, and José Geraldo Mill. The Steering Committee consisted of Eduardo M. Krieger, Dante Marcelo Artigas Giorgi, Jose Eduardo Krieger, Alexandre C. Pereira, Luciano F. Drager, Alessandro Betito, Diogo Duarte Fagundes Moia, and Silvia Beatriz Paulino Cavasin de Souza. The Statistical Analyses Committee consisted of Paulo A. Lotufo and Alexandre C. Pereira. The Adjudication Committee consisted of Jose Eduardo Krieger, Alexandre C. Pereira, Dante Marcelo Artigas Giorgi, and Luciano F. Drager. Participating sites (Brazilian population [%]—patients included [%]): North region (8.3%–5.9%) UFPA: Universidade Federal do Pará (Eduardo Augusto de Silva Castro). Northeast region (27.8%–22.7%) HAN, Hospital Ana Nery da Universidade Federal da Bahia (Armênio Costa Guimarães); HSI, Hospital Santa Izabel da Santa Casa de Misericórdia, Escola Bahiana de Medicina e Saúde Pública (Gilson Soares Feitosa); Universidade Federal do Ceará (Carlos Roberto Martins Rodrigues Sobrinho); Universidade Federal de Pernambuco (Hilton de Castro Chaves Júnior); UFS, Universidade Federal de Sergipe (José Augusto Soares Barreto-Filho). Middle-west region (5.5%–2.8%) UFG: Universidade Federal de Goiás (Paulo César Brandão Veiga Jardim).

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Disclosures

None.

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Novelty and Significance

What Is New?

- In patients with true resistant hypertension, clonidine was not superior to Spironolactone as a fourth-drug therapy in blood pressure control, as determined by both office blood pressure monitoring and 24-hour ambulatory blood pressure monitoring, but spironolactone is easier to take and displayed a greater decrease in 24-hour systolic and diastolic blood pressure.

What Is Relevant?

- The ReHOT study (Resistant Hypertension Optimal Treatment) showed that appropriate treatment for resistant hypertension can control >85% of patients with hypertension stage 2 using the most prescribed triple-antihypertensive regimen available in the Brazilian National Health System (a public healthcare service covering >100 million people).

Summary

Our results underscore the need to improve adherence to the medical therapy worldwide, avoiding unnecessary prescriptions and appointments in tertiary centers. Results from our randomized phase provided good options for the fourth-drug treatment in resistant hypertension, but additional analysis for identifying subgroups that best respond to spironolactone or clonidine are needed.