

RESISTANT HYPERTENSION

Clinical Perspective

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ABSTRACT

Resistant or difficult-to-treat hypertension is a common clinical problem affecting 10 to 15% of treated hypertensive patients. Effective management of resistant hypertension firstly requires distinguishing pseudo-resistant from true resistant hypertension. Common causes of pseudo-resistance include inaccurate blood pressure (BP) measurement, white coat effect, poor medication adherence, and undertreatment. Pharmacologic treatment of resistant hypertension requires use of effective multidrug antihypertensive regimens, including especially diuretic therapy. An initial three-drug regimen of an angiotensin-converting enzyme (ACE) inhibitor or an angiotensin receptor blocker (ARB), amlodipine, and a long-acting thiazide diuretic is recommended. Chlorthalidone is recommended as the preferred thiazide diuretic of choice given its long half-life and superior efficacy. A large body of literature now clearly establishes spironolactone as the most effective fourth medication for treatment of resistant hypertension. Renal nerve denervation (RND) is under intensive investigation to determine its true antihypertensive benefit, especially for treating uncontrolled resistant hypertension. Recent studies suggest that while the technique will likely provide some benefit in terms of additional BP reduction, it will not likely cure patients of their resistant hypertension as most subjects participating in studies of RND have generally continued medical therapy with use of the same or nearly the same number of medications. Accordingly, clinicians, even with the availability of renal nerve derivation, will have to remain facile in prescribing multiple drug combinations for treating resistant hypertension.

Keywords: Chlorthalidone, Renal nerve denervation, Resistant hypertension, Spironolactone.

How to cite this article: Calhoun DA. Clinical Perspective. *Hypertens J* 2016;2(3):153-159.

Source of support: This work was supported by NIH grant RO1 HL113004.

Conflict of interest: Dr Calhoun has received grant support from Medtronic and Valencia Technologies. He also serves as a consultant for Valencia Technologies.

INTRODUCTION

Resistant hypertension is defined as high blood pressure (BP) requiring use of three or more antihypertensive

agents, ideally one of which is a diuretic.¹ Resistant hypertension is defined as such to identify patients with difficult-to-treat hypertension who may benefit from special diagnostic and/or therapeutic considerations. In 2008, the American Heart Association (AHA) Scientific Statement on resistant hypertension expanded the definition to include patients whose BP was controlled, but with use of four or more medications, so-called controlled resistant hypertension.¹ The rationale for creating this category was that, even though their BP could be controlled, the need for four or more antihypertensive medications was unusual, and such patients may likewise benefit from the same special consideration recommended for patients with uncontrolled resistant hypertension.

PREVALENCE

Based simply on needing four or more medications, whether controlled or uncontrolled, resistant hypertension is common. Multiple cross-sectional analyses of different cohorts worldwide indicate that resistant hypertension affects approximately 10 to 20% of the patients being treated for hypertension.²⁻⁶ For example, de la Sierra et al² determined the prevalence of resistant hypertension among more than 68,000 hypertensive patients included in the Spanish Ambulatory Blood Pressure Monitoring Registry. The authors reported that the overall prevalence of resistant hypertension in this largely primary care-based cohort was 14.8% of all treated hypertensives. The large majority of these patients had uncontrolled resistant hypertension (12.2% of the treated hypertensives), i.e., elevated office BP with use of three or more medications, with the remaining percentage having controlled resistant hypertension, i.e., controlled BP with use of four or more medications.

In a longitudinal analysis of the National Health and Nutrition Examination Survey (NHANES), Roberie and Elliot⁴ estimated the change in the prevalence of resistant hypertension in the United States. Using the results of the NHANES datasets between 1998 and 2008, the authors found the prevalence of resistant hypertension to have increased progressively from an estimated prevalence of 8.8% between 1988 and 1994, to 14.5% between 1999 and 2004, and 20.7% between 2005 and 2008. These results are important in highlighting that resistance is common, perhaps as high as 20% of the overall hypertensive population and that the prevalence is seemingly increasing quite dramatically. This observed increase in the prevalence of

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resistant hypertension is not surprising, given that two of the most common risk factors for developing resistant hypertension are older age and obesity,⁷ which are increasingly typical of most populations worldwide.

CONFIRMING TRUE RESISTANT HYPERTENSION

The first step in evaluating suspected resistant hypertension is to confirm the presence of true resistant hypertension. While the prevalence of resistant hypertension is high simply based on having prescribed three or more antihypertensive medications, in reality, at least half of the patients likely have “apparent” *vs* “true” resistant. Apparent resistant hypertension refers to patients whose BP pressure is seemingly uncontrolled in spite of receiving three or more antihypertensive agents. Pseudo-causes of treatment resistance are, however, common among patients with apparent resistant hypertension. The most common of these causes are inaccurate BP measurement, white coat effect, poor medication adherence, and undertreatment. It is essential for the treating clinician to consider and exclude these causes of pseudo-resistance before considering a patient to be truly resistant to antihypertensive treatment.

Poor BP Technique

Poor BP technique resulting in accurate BP measurement is common in most routine clinical situations. The most common mistakes made during BP measurement include not having the patient sitting relaxed in a quiet area for several minutes before measuring the BP, using too small of a BP cuff, and placing the BP cuff over clothing during the measurement. These errors in technique all tend to result in a falsely high BP reading. This effect was recently quantified in a comparison of routine BP clinic measurements *vs* measurements done by trained hypertension experts using a standardized measurement routine, including use of an automated BP device that averaged serial, unattended BP readings.⁸ In this analysis, Bhatt et al found that 33% of 130 patients referred to a hypertension specialty clinic for resistant hypertension were misdiagnosed as having uncontrolled resistant hypertension because of inaccurate measurements during routine triage assessments compared with the expertly done measurements using the strict, automated-based routine. These findings emphasize the importance of well-done office BP assessments to confirm true, uncontrolled resistant hypertension. In addition to application of good BP techniques in general, use of automated devices that average serial readings is preferred to manually obtained measurements in order to avoid operator-dependent mistakes and biases, which are commonplace in routine clinical settings.⁹⁻¹¹

White Coat Effect

A prominent white coat effect is common in patients with resistant hypertension, with estimates ranging from 20 to 40% of patients with uncontrolled office BP. For example, de la Sierra et al found that of the 8,295 patients with resistant hypertension participating in the Spanish Ambulatory Blood Pressure Monitoring Registry, 37.5% had white coat resistant hypertension, i.e., elevated office BP levels while prescribed three or more antihypertensive agents, but 24-hour ambulatory BP levels <130/80 mm Hg. Grigoryan et al¹² retrospectively evaluated primary care participants in a study relating medication adherence to BP control. Of the 140 study participants with resistant hypertension, 22% were identified as having white coat resistant hypertension.

While studies clearly demonstrate that white coat resistant hypertension is common, it is also important to recognize that such patients are also likely, over time, to progress to having true resistant, i.e., having both elevated office and ambulatory BP levels. This progression was demonstrated by Muxfeldt et al¹³ who did serial ambulatory BP monitoring at 3- or 6-month intervals on patients identified as originally having white coat resistant hypertension. The investigators found that with each repeat ambulatory monitoring, about 30% of the patients no longer had white coat resistant hypertension but had progressed to having true uncontrolled resistant hypertension. Combined, these studies emphasize the importance of accurately measuring out-of-office BP assessments when evaluating patients with uncontrolled resistant hypertension. As serial ambulatory BP monitoring is not practical, practitioners should encourage patients to invest in an automated home BP monitor and instruct them in good home BP technique. These out-of-office readings should then be used to confirm the diagnosis of true resistant hypertension and to guide treatment decisions, especially in patients with white coat effects.

Medication Nonadherence

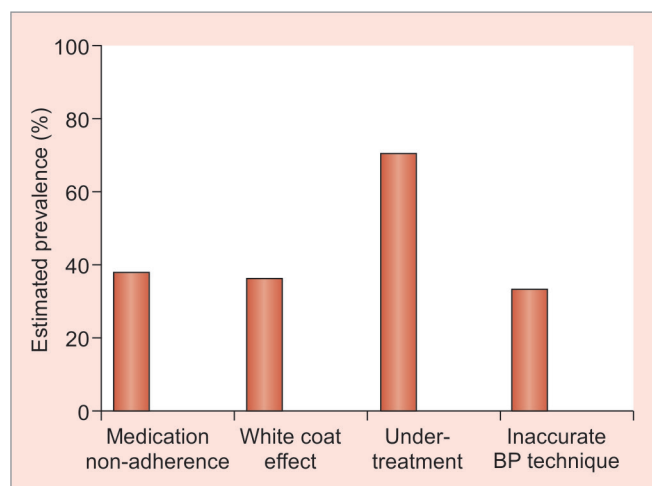
Poor medication adherence is likely one of the most common causes of pseudo-resistant hypertension. Obviously, if a patient is not taking his or her medications as prescribed, then he or she cannot be considered to be truly resistant to that regimen. In direct assessments of urinary or serum drug levels in patients referred to hypertension specialty clinics, direct assessments of urinary or serum drug levels (or appropriate metabolites) have found that up to 70% of patients prescribed three or more antihypertensive agents are nonadherent with one or more of the prescribed medications. Jung et al¹⁴ determined adherence by toxicological assessment of spot urine samples

in patients referred to a university-based hypertension clinic for uncontrolled resistant hypertension. Of the 375 patients tested, only 30% were fully adherent with the prescribed antihypertensive medications. Of the 70% of patients that were nonadherent, about 85% were taking less than half of their prescribed medications and 30% were taking none. A similarly done study of 339 patients being evaluated for controlled resistant hypertension reported a prevalence of nonadherence of 47% (24% nonadherent with any medications and 23% partially nonadherent).¹⁵

A large degree of nonadherence should not be surprising in patients prescribed multiple medications. With each additional medication, out-of-pocket costs likely increase and development of adverse events is more likely. Further, it is well known that as the number of prescribed medications increases and the complexity of the dosing regimen increases, adherence suffers. Accordingly, it is incumbent upon clinicians treating complicated hypertension to anticipate and monitor as best as possible for poor medication adherence with multidrug combinations. As toxicological assessment of drug levels is not practical on a routine basis, clinicians instead must rely on patient self-admission and/or monitoring of prescription refills. Being attentive to medication costs for patients in the context of all their prescribed prescriptions and use of combination pills, if affordable, can serve to improve medication adherence.

Undertreatment

Undertreatment also contributes importantly to lack of BP control in patients with apparent resistant hypertension. In an assessment of hypertensive patients attending primary clinics that allowed for electronic monitoring of patient records, Egan et al¹⁶ found that about 30% of the 468,877 hypertensive patients were controlled, and of those, 44,684 were being prescribed three or more antihypertensive medications. However, of these with uncontrolled resistant hypertension, only 15% were prescribed a regimen that was considered optimal, defined multidrug combinations of different classes of agents, including a diuretic, and with all agents prescribed at $\geq 50\%$ of the maximum recommended dose for treatment of resistant hypertension. Use of chlorthalidone and/or an aldosterone antagonist was especially low in patients with uncontrolled BP ($<10\%$). These findings emphasize the frequent lack of intensification of antihypertensive treatment by clinicians in spite of continued uncontrolled BP. Admittedly, individual patient regimens have to be individualized based on medication intolerances, regimen affordability, and perceived effectiveness, but three-drug regimens of an angiotensin-converting enzyme (ACE) inhibitor or angiotensin receptor blocker



Graph 1: Estimated prevalence of causes of pseudo-resistant hypertension. Modified from Bhatt et al⁸

(ARB), amlodipine, and a long-acting thiazide diuretic or thiazide-like diuretic (i.e., chlorthalidone) are widely available, inexpensive, and generally well tolerated even at maximum or near maximum doses, allowing for use in most patients.

Clearly, causes of pseudo-resistance to antihypertensive treatment are common. Graph 1 highlights this in summarizing the estimated prevalence rates from different studies of the different causes of pseudo-resistance including white coat effect, undertreatment, poor adherence, and inaccurate BP measurement.⁸ The study of Grigoryan et al¹² is especially informative in having determined the prevalence of white coat effect and poor adherence in the same cohort. They found that 50% of patients were being misdiagnosed as having resistant hypertension because of these two factors alone, and that almost all of the patients were being undertreated, including none of the patients being treated with chlorthalidone or spironolactone. While discouraging, these findings highlight the challenge hypertension experts face in accurately diagnosing and treating true resistant hypertension.

PHARMACOLOGIC TREATMENT OF RESISTANT HYPERTENSION

Multiple studies suggest that development of resistant hypertension is generally related, at least in part, to inappropriate fluid retention. For example, Taler et al¹⁷ found that patients with resistant hypertension have evidence of increased thoracic fluid content as measured by thoracic impedance. The authors demonstrated that BP control in these patients is best achieved with intensification of diuretic therapy. Gaddam et al¹⁸ in a series of studies reported that patients with resistant hypertension, even in the absence of apparent chronic kidney disease (CKD), have excessive intravascular fluid retention as indicated

by elevated natriuretic peptide levels in spite of standard thiazide diuretic use. In a separate study, these same investigators linked the excess fluid retention to hyperaldosteronism.¹⁹ Indexing changes in intracardiac heart volume as measured by magnetic resonance imaging, it was demonstrated that an aldosterone antagonist, i.e., spironolactone, added to the existing treatment regimen substantially lowered BP in relation in reductions in intravascular volume.¹⁹ These findings implicate excessive fluid retention attributable to hyperaldosteronism as a common cause of antihypertensive treatment resistances such that effective management of resistant hypertension is generally predicated on intensification of diuretic therapy, including specifically preferential use of chlorthalidone, or a comparable long-acting thiazide diuretic, and spironolactone, an aldosterone antagonist.

Preferential use of Chlorthalidone

The AHA Scientific Statement on resistant hypertension recommended a standardized three-drug regimen – an ACE inhibitor or ARB, a calcium channel blocker, and a thiazide diuretic – for treatment of uncontrolled hypertension.¹ This recommendation was based on studies demonstrating the tolerability and efficacy of the three classes of agents. Chlorthalidone was specifically recommended as the diuretic to be used. Although its efficacy has not been specifically tested in patients with resistant hypertension, chlorthalidone has been demonstrated to be superior to hydrochlorothiazide (HCTZ) on a milligram per milligram basis when receiving one of the other agent as monotherapy.²⁰ This demonstration of superiority is consistent with retrospective assessments reporting increased antihypertensive benefit when switching patients who have uncontrolled BP with HCTZ to the same dose amount of chlorthalidone.²¹ In light of these observations, chlorthalidone (or a long-acting equivalent) should be preferentially used as the diuretic of choice for treatment of resistant hypertension, either as part of the initial three-drug regimen or especially if the patient remains uncontrolled on a multidrug combination utilizing HCTZ.

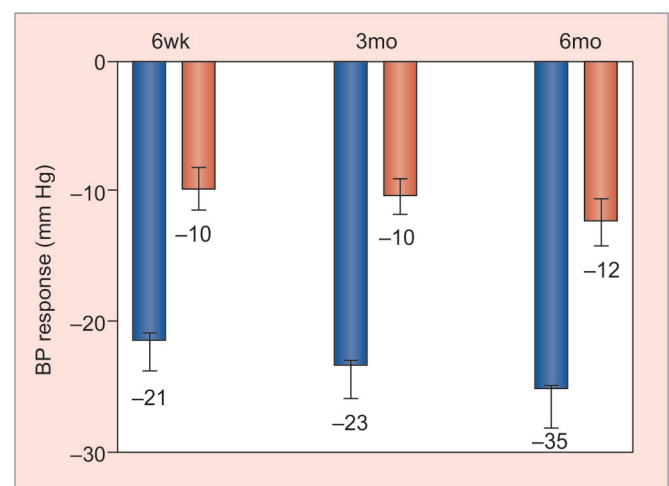
Spironolactone: The Standard Fourth Medication for treating Resistant Hypertension

Primary aldosteronism is common in patients with resistant hypertension. In an evaluation done at the University of Alabama at Birmingham, Calhoun et al²² reported that 20% of 88 consecutive patients referred for uncontrolled resistant hypertension met the classical diagnostic criteria for primary aldosteronism. This finding of a prevalence of primary aldosteronism in patients with resistant hypertension has been confirmed in multiple other clinics

worldwide.²³⁻²⁵ Additional studies further suggest that even beyond the 20% of patients with classical primary aldosteronism, there is large proportion of patients with resistant hypertension with lesser degrees of hyperaldosteronism that may not fulfill the strict criteria for having true primary aldosteronism, but nonetheless likely contributes to excess fluid retention and antihypertensive treatment resistance.^{18,19}

Given the high prevalence of hyperaldosteronism in patients with resistant hypertension, it is not surprising that use of aldosterone antagonists, specifically spironolactone, has been shown to provide substantial antihypertensive benefit for treatment of resistant hypertension. Nishizaka et al²⁶ reported that addition of low doses of spironolactone (25–50 mg) to existing regimens of three or more antihypertensive medications reduced systolic and diastolic BP at 6 months follow-up on average by 25 and 12 mm Hg respectively (Graph 2). These findings have been consistent with multiple other studies demonstrating the large antihypertensive benefit of spironolactone for treating resistant hypertension.²⁷⁻²⁹ Importantly, these studies demonstrate broad benefit of spironolactone for treatment of resistant hypertension in that the large antihypertensive benefit is not simply limited to patients with demonstrably high aldosterone levels, but significant BP reductions occur even in patients with seemingly normal or low serum or aldosterone levels.

The recent publication of the Prevention and Treatment of Hypertension With Algorithm-based therapy (PATHWAY-2) results clearly establishes spironolactone as the most appropriate fourth medication for treatment of resistant hypertension.³⁰ This study is particularly compelling in having been done as a randomized, double-blind, cross-over comparison of placebo, a beta antagonist (bisoprolol 5–10 mg daily), an alpha



Graph 2: Spironolactone-induced reduction in systolic (filled bars) and diastolic BP (open bars) at 6 weeks, 3 months, and 6 months in subjects with resistant hypertension²⁶

antagonist (doxazosin 4–8 mg daily), and spironolactone (25–50 mg daily) in patients uncontrolled on a standardized triple-drug regimen of an ACE inhibitor or ARB, a thiazide diuretic, a calcium channel blocker, and a thiazide diuretic. After 12 weeks of treatment with each randomized medication or placebo, spironolactone was clearly the most effective. The average reduction in home systolic BP (the primary endpoint) induced with spironolactone was superior to that of placebo (–8.70 mm Hg), bisoprolol (–4.48 mm Hg), and doxazosin (–4.03 mm Hg).

The findings of PATHWAY-2 are definitive in firmly establishing spironolactone as the most effective fourth medication for treating resistant hypertension after use of an ACE inhibitor or ARB, a calcium channel blocker, and a thiazide diuretic.³⁰ The PATHWAY-2 findings are further important in confirming that spironolactone was broadly effective across the entire cohort. However, in PATHWAY-2 it was also observed that the antihypertensive benefit of spironolactone was especially pronounced in patients with evidence of excess fluid retention as indicated by suppressed renin levels. In patients with low renin levels and resistant hypertension, the antihypertensive benefit of spironolactone approached on average 20 mm Hg. This observation highlights the potential benefit of spironolactone in overcoming the fluid retention thought to generally underlie resistant hypertension, a degree of benefit unlikely to be surpassed by other classes of agents.

SPIRONOLACTONE AND RENAL NERVE DENERVATION

The initial, uncontrolled studies of renal nerve denervation (RND) for treatment of uncontrolled resistant hypertension indicated a reduction in office systolic BP of 20 to 30 mm Hg.^{31,32} Subsequent double-blind, sham-controlled assessments of RND did not confirm a significant treatment benefit in patients with uncontrolled resistant hypertension.^{33,34} In the case of SYMPPLICITY HTN-3, there was a large reduction in office BP in patients who had true RND done, but there was a similarly large reduction in the sham-treated group, such that there was no statistical difference between the two treatment arms. There is much ongoing discussion as to why there was a large reduction in BP in both the truly treated and the sham treated groups, including possibly a large regression to the mean phenomena in both groups, variable changes in medication adherence in the two groups both during the run-in period and during the trial, and/or incomplete RND because of operator inexperience. Multiple studies designed to overcome these and other study limitations are ongoing with use of different

devices. To avoid the confounding effects of poor or variable adherence by study participants, the ongoing studies include both hypertensive cohorts that are untreated and cohorts of patients with resistant hypertension who are being treated with standardized triple-drug regimens. Such an approach should allow for definitive determination of the true treatment effects of RND.

Pending those results, recent findings provide important insight into the relative benefit of RND *vs* medical therapy that includes spironolactone as the fourth medication. The Renal Denervation for Hypertension (DENERHTN) trial was a prospective, open-label randomized controlled comparison of a standardized stepped-care antihypertensive treatment regimen, including spironolactone as the fourth medication, *vs* the same stepped-care approach in combination with RND.³⁵ The study cohort consisted of patients with resistant hypertension whose BP remained uncontrolled in spite of receiving a standardized three-drug regimen of indapamide, ramipril or irbesartan, and amlodipine. There were 48 subjects in the RND plus stepped-care group and 53 in the stepped-care alone group.

After 6 months of treatment, the mean change in daytime ambulatory systolic BP was –15.8 mm Hg in the RND group and –9.9 mm Hg in the medical treatment group, a baseline adjusted difference of –5.9 mm Hg, which was statistically different.³⁵ The number of antihypertensive medications prescribed and medication adherence was same between the two groups. The DENERHTN trial is clinically informative in indicating that RND is additive to pharmacologic treatment that includes use of spironolactone. But the findings also demonstrate that RND is not likely to be a cure of RHTN. The number of medications utilized in the two treatment arms was the same, and there was no indication of patients being overtreated, *i.e.*, needing downtitration or withdrawal of medications in patients who had undergone RND. So while RND provided additional benefit, study participants still needed use of multidrug regimens for BP control.

The continued importance of the use of antihypertensive medications, including especially spironolactone, *vs* RND for treatment of resistant hypertension is also highlighted by the recent Sympathetic Renal Denervation Versus Increment of Pharmacological Treatment in Resistant Arterial Hypertension (DENERVHTA) trial.³⁶ In this study, the antihypertensive benefit of RND *vs* adding spironolactone in patients with uncontrolled resistant hypertension was compared. After 6 months of treatment, spironolactone ($n = 13$) was far superior to RND ($n = 11$), having reduced 24-hour systolic BP by –23.6 and –5.7 mm Hg respectively. Although a small study, the findings indicate that in patients with resistant

hypertension, medical treatment, including especially use of spironolactone, provides antihypertensive benefit that surpasses that of RND. Combined, DENERHTN and DENERVHTA suggest that while RND may prove to be an important adjunct to medical therapy for treatment of resistant hypertension, it is unlikely to replace it. Accordingly, clinicians will have to remain facile in prescription of multidrug antihypertensive regimens for treatment of resistant hypertension.

CONCLUSION

Resistant hypertension, based on needing four or more antihypertensive medications, remains a common clinical problem and is likely to remain so, given that two of the most common risk factors for developing resistant hypertension are older age and obesity, both of which are increasingly prevalent problems worldwide. Effective management of resistant hypertension firstly requires accurate diagnosis, including obtaining accurate BP measurements, excluding white coat effects, confirming medication adherence, and distinguishing undertreatment from true treatment resistance.

Causes of resistant hypertension are multifactorial, but often an important underlying factor is excess intravascular fluid retention. Such fluid retention is in itself usually multifactorial in etiology, including CKD, hyperaldosteronism, and high dietary sodium intake. Pharmacologic treatment of resistant hypertension is in general predicated on overcoming that recalcitrant fluid retention with use of effective multidrug regimens, including especially appropriate intensification of diuretic therapy. A standard three-drug regimen of an ACE inhibitor or ARB, amlodipine, and a long-acting thiazide diuretic is recommended when possible. Given its clear superiority over HCTZ in terms of efficacy, chlorthalidone is recommended as the preferred diuretic in this initial three-drug regimen.

A large body of literature, including the recent publication of the very compelling PATHWAY-2 results, clearly establishes spironolactone as the most effective fourth drug for treatment of resistant hypertension. Doses of up to 50 mg have been shown to provide continued antihypertensive benefit when added to a thiazide diuretic.

The true antihypertensive efficacy of RND continues to be debated, with testing with ongoing, scientifically rigorous trials in both untreated hypertensive cohorts and cohorts of uncontrolled resistant hypertension. No doubt, those studies will quantify the antihypertensive benefit of RND both as monotherapy and as add-on therapy to existing multidrug regimens. While those study results are awaited, recent findings suggest that RND will more likely serve as an adjunct to pharmacologic therapy as

opposed to being curative of resistant hypertension, such that clinicians will need to continue prescribing multiple drug antihypertensive regimens for difficult-to-treat hypertension.

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