

Treatment Resistant Hypertension: A Pragmatic Management Approach

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ABSTRACT

Treatment resistant hypertension (TRH) is defined by office blood pressure (BP) uncontrolled on ≥ 3 or controlled on ≥ 4 antihypertensive medications, preferably at optimal doses and including a diuretic. Among treated hypertensives, $\sim 30\%$ of uncontrolled and 10% of controlled individuals have apparent treatment resistant hypertension (aTRH). Apparent treatment resistant hypertension is used when optimal therapy, patient adherence, and BP measurement artifacts are unknown. In $\geq 50\%$ of aTRH patients, BP measurement artifacts ('office' TRH), suboptimal regimens, or suboptimal adherence are present, i.e. pseudoresistance. Patients with 'office' TRH have fewer cardiovascular events (CVE) than those with persistent hypertension. Patients with suboptimal regimens or adherence and persistent hypertension appear to have excess CVE. 'Office' TRH is minimized by averaging several BP values obtained with an accurate, automated monitor, while the patient is alone in the examination room'. Home or ambulatory BP monitoring directly confirm 'office' TRH or persistent hypertension. Optimal therapy is reasonably defined by ≥ 3 different antihypertensive medication classes, e.g. thiazide-type diuretic, renin-angiotensin blocker and calcium antagonist at $\geq 50\%$ of maximum recommended doses. Intensifying diuretic therapy is effective for controlling many TRH patients who are volume expanded. Personalized strategies, e.g. renin or hemodynamics, can inform successful therapy. Patient blood pressure self-monitoring and attention to adverse effects, medication costs, and pill burden can improve adherence. Suspected secondary hypertension should be evaluated and interfering substances or medications discontinued. These approaches will identify or correct the problem in $\sim 80\%$ of aTRH patients. Referral to a hypertension specialist is recommended for TRH patients not successfully managed with the pragmatic approach outlined.

Keywords: Cardiovascular disease, Nonadherence, Office resistance, Pseudoresistant hypertension, Spironolactone, Treatment resistant hypertension.

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INTRODUCTION

Treatment resistant hypertension (TRH) was defined as blood pressure (BP) uncontrolled on ≥ 3 or controlled on ≥ 4 BP medications prescribed at optimal doses and preferably including a diuretic.¹ The term apparent aTRH is frequently used, since measurement artifacts, suboptimal treatment regimens, i.e. contributors to pseudoresistance, are often unknown.² Prevalent apparent treatment resistant hypertension (aTRH) among treated uncontrolled hypertensives nearly doubled from 16 to 28% between 1988–1994 and 2007–2010. Simultaneously, the proportion of adults with controlled hypertension rose from 27 to 52%. More intensive treatment accounted for the increase in hypertension control together with factors predisposing to TRH including increases in age, obesity, diabetes and kidney disease.^{1,2} The predisposing factors are all associated with insulin resistance, which is more common in adults with TRH.³

Apparent TRH impacts roughly 11% of all hypertensive adults in the US, which includes individuals who are unaware of their hypertensive and aware individuals who are untreated. Among hypertensive adults on treatment, $\sim 30\%$ of treated uncontrolled and 10% of treated controlled adults in the US or ~ 8 million individuals.^{2,4} Given the high prevalence of aTRH and unfavorable prognosis,^{1,2,4} it is important for primary care clinicians to identify and manage most of these individuals as referring all for specialty care is impractical. This review outlines a pragmatic approach to evaluating and treating aTRH that can be implemented in many primary care settings (Table 1).¹

Measurement artifacts are common in uncontrolled aTRH.⁵⁻⁷ Since measurement artifacts are very common and affect 30 to 50% of aTRH patients, a good starting point for evaluation is an accurate and representative BP. In other words, a BP can be measured accurately in the office setting by trained individuals carefully following standardized measurement protocol. However, that carefully measured BP is not necessarily representative of usual daytime readings. Another compelling reason to obtain a BP value more representative of usual daytime values is that 'office' TRH has a better prognosis than true TRH.^{6,7} Patients trained in BP self-monitoring who

Table 1: A seven-step plan for evaluation and management of treatment resistant hypertension¹

1. Confirm treatment resistance: Office blood pressure >140/90 on ≥ 3 antihypertensive medications at optimal doses and preferably including a diuretic.
2. Exclude pseudo-resistance: Is the patient adherent with an optimal treatment regimen? Is out-of-office blood pressure elevated?
3. Identify and address contributing lifestyle factors, e.g. obesity, physical inactivity, excess alcohol and high salt intake
4. Discontinue or reduce interfering substances, e.g. NSAIDs, sympathomimetics, oral contraceptives, erythropoietin, ephedra (nonprescription weight loss)
5. Screen for secondary causes of hypertension, e.g. obstructive sleep apnea, primary aldosteronism, chronic kidney disease, renal artery stenosis, pheochromocytoma
6. Continue to optimize pharmacologic treatment: Enhance diuretic therapy (see text); consider α_1 and β_1 adrenoceptor blockade in patient with an otherwise optimal regimen (avoid combining β -blockade and nondihydropyridine CCB)
7. Refer to a hypertension specialist for definitive evaluation and treatment of known or suspected secondary cause(s) of hypertension or if blood pressure remains uncontrolled after 6 months

use an accurate device can provide reliable out-of-office readings. Using an accurate, validated ambulatory BP monitor is another method for obtaining useful BP values outside the office setting.⁸ Self-monitored BP and ambulatory BP monitoring both provide prognostically important information beyond that of office BP.⁹ With either of these techniques, a nonhypertensive daytime BP is <135/<85 mm Hg. Using an accurate, automated office BP monitor to obtain a series of readings with the patient alone in the examination room minimizes the office effect and better approximates usual daytime readings.¹⁰ The Canadian Hypertension Guidelines recommend using a BP value of <135/<85 as nonhypertensive when the mean of several automated readings is obtained in the office setting as described above.¹¹

Suboptimal Treatment Regimens

In working with several hundred primary care practice settings, we documented that ~50% of patients with uncontrolled aTRH were not prescribed optimal therapy defined as three different antihypertensive medications including a diuretic at $\geq 50\%$ of the maximum recommended or approved doses, e.g. hydrochlorothiazide 25 mg, lisinopril 20 mg, and amlodipine 5 mg daily.³ While some patients may not tolerate optimal therapy, clinicians have many opportunities to improve BP control by optimizing prescribed antihypertensive medications in their patients with aTRH who have hypertension outside the office setting.

Inadequate adherence or failing to take $\geq 75\%$ of prescribed medication, impacts ~10 to 60% of aTRH.^{2,3} Direct questions on medication adherence often elicit unreliable responses. Inviting patients to share concerns about costs, side effects or other barriers can be useful in obtaining clinically useful information. Any admission of nonadherence is often associated with taking <75% of prescribed medication. Concerned and caring family members often times have insight on patient adherence and barriers.

Medication possession ratio (MPR) or the percentage (fraction) of days the patient possesses the medication during a given time period, e.g. 6 to 12 months, is a reasonable proxy for adherence.⁷ A conversation with the pharmacist and examining pill bottles to assess the number of prescription refills relative to the dates of the initial prescription and visit are useful, albeit imperfect assessment of MPR. In other words, most patients do not continue to refill medications they are not taking, especially if their effort and funds are required. Medications that are 'automatically' mailed to the patient's home provide less useful information with regard to the MPR as a proxy for adherence. Reducing out-of-pocket costs and prescribing single-pill combinations can improve adherence and control. Addressing side effects and engaging uncontrolled aTRH patients in BP self-monitoring are proven strategies for improving adherence and control.^{2,8} Self-monitoring as a strategy to improve hypertension control is more effective when linked with relaying BP information to their clinician's office and when the patient receives advice from the clinician or staff to improve blood pressure management between scheduled office visits.

Adherence with a healthy lifestyle is also important in uncontrolled and TRH. The benefits of sodium restriction⁹ and avoiding excess alcohol and drugs, such as amphetamines and cocaine are important.² Most obese patients will have a fall in BP with weight loss.² The dietary approaches to stop hypertension (DASH) eating plan lowers BP without weight loss.¹⁰ Moreover, DASH appears even more effective in lowering BP and reducing other cardiovascular risk factors when it is the nutritional component of a weight loss plan.¹¹

Secondary Hypertension

Once common contributors to pseudo-resistant hypertension are determined to be unlikely explanations for aTRH, further evaluation is important. Suspected secondary causes of hypertension can be assessed in most office settings.¹ Patients with resistant hypertension are often obese and volume expanded, which contributes

to sleep apnea.¹² Better control of volume, e.g. adding spironolactone, can improve BP and sleep apnea.¹³ While treatment of sleep apnea with measures, such as continuous positive airways pressure (CPAP), can improve hypertension control, the impact on BP is often unimpressive, even in patients that adhere with and otherwise benefit from this therapy.¹⁴

Primary aldosteronism is the most common secondary hypertension,¹ but not all patients are hypokalemic. Plasma renin activity is suppressed together with excess aldosterone production.¹⁵ While an ald/renin ratio >20–30:1 is a screening test for primary aldosteronism, patients with low-renin hypertension can satisfy ratio criteria without having aldosterone excess. Marked hypokalemia can reduce aldosterone production and should be corrected prior to evaluation. Preferably, patients are not on medications impacting the renin-angiotensin-aldosterone axis for several weeks prior to the assessment for primary aldosteronism. Practically, a disproportionate share of patients with TRH has suppressed plasma renin activity on treatment, although patients should not be taking aldosterone antagonists or epithelial sodium channel antagonists, e.g. amiloride, when assessing primary aldosteronism. If low plasma renin occurs with excess aldosterone in a 24-hour urine, the diagnosis is confirmed by failure to suppress aldosterone with saline infusion or a high salt diet. The majority of patients with primary aldosteronism have bilateral adrenal hyperplasia, rather than aldosterone-producing adenoma. If a unilateral adrenal lesion is identified on an imaging procedure, such as computerized tomographic scanning, confirmation of excess aldosterone from that gland is important prior to surgery as incidental, inactive adrenal lesions are relatively common. Patients with aldosterone-producing adenoma and bilateral adrenal hyperplasia often respond to aldosterone antagonists with other agents, e.g. thiazide diuretics and calcium antagonists.

Other secondary forms of hypertension including renal artery stenosis, chronic kidney disease, sleep apnea, pheochromocytoma, primary hyperparathyroidism, Cushing's syndrome and disease, aortic coarctation, hypo- and hyperthyroidism.¹ Screening tests for secondary hypertension are provided in Table 2.^{1,15,16} Not unexpectedly, most screening tests listed, while useful, are associated with false negative (imperfect sensitivity) and false positive (imperfect specificity). When the 'pretest' likelihood of a specific secondary form of hypertension is high, then confirmatory testing is appropriate in the event a screening test was used and negative.

Interfering Substances and Medications

Various over-the-counter and prescribed medications, e.g. oral contraceptives, nonsteroidal anti-inflammatory

Table 2: Screening tests for selected causes of treatment resistant hypertension

<i>Suspected secondary hypertension</i>	<i>Screening test</i>
Renal artery stenosis	Duplex Doppler ultrasonography (can be technically difficult), computed tomographic angiography (CTA), magnetic resonance angiography (MRA)
Hypothyroidism, hyperthyroidism	TSH, free T4 and T3
Pheochromocytoma	24-hour urine fractionated metanephrine and normetanephrine
Cushing's syndrome/disease	Overnight dexamethasone suppression test
Primary hyperparathyroidism	Ca ⁺⁺ , serum PTH
Sleep apnea	History, polysomnography (sleep study)

Readers are encouraged to consult up to date for additional specific information on screening test for the various causes on secondary hypertension above (Available at: <http://www.uptodate.com/contents/search>)

drugs, glucocorticoids, and other immunosuppressive agents calcineurin inhibitors (cyclosporine, tacrolimus), erythropoietin, and agents interfering with vascular endothelial growth factor signaling can raise BP.¹ When possible, these agents should be minimized or discontinued.

Additions and Changes to the Pharmacological Regimen

Adding a low-dose aldosterone antagonist, e.g. 12.5 to 50 mg spironolactone, lowers BP in many TRH patients.^{1,15,16} If patients are not ideal candidates for spironolactone, e.g. baseline serum K⁺ >4.5 or eGFR <45 ml/1.7 m²/min,¹⁷ then changing from hydrochlorothiazide (HCTZ) to chlorthalidone can lower BP. Chlorthalidone is more likely than HCTZ to be effective with eGFR 30–44 (stage 3B CKD). Patients with eGFR <30 ml/1.7 m²/min, may require a loop diuretic, e.g. torsemide to improve volume control and lower BP. Patients with eGFR <15 may require dialysis for volume and BP control.

In patients with progesterone and antiandrogenic effects of spironolactone, eplerenone is an aldosterone antagonist devoid of sex-steroid effects. Since aldosterone raises BP in significant part by increasing the number and activity of epithelial sodium channels (ENaCs), amiloride, which blocks ENaCs, is also effective therapy for primary aldosteronism, especially at higher doses of 10 to 40 mg daily. Monitoring for hyperkalemia is important with both aldosterone antagonists and epithelial sodium channel antagonists. Aldosterone antagonists and ENaC inhibitors have a low-risk when started at modest doses in individuals with eGFR >45 and serum potassium <4.6 mmol/l. While these agents can be used cautiously



when essential in individuals with lower eGFR or higher serum potassium, beginning at very low doses and frequent monitoring (e.g. ≤ 7 days), for adverse effects is warranted, especially when initiating treatment or increasing doses.

For patients with neurogenic hypertension, alpha and/or beta-receptor blockade or central sympatholytics, e.g. guanfacine, can lower BP. Hemodynamic, and renin-guided therapy can identify effective medications.^{18,19} With renin-guided therapy, evidence suggests that low-renin patients have a better BP response to diuretics, aldosterone antagonists, α_1 -adrenoceptor blockers, and calcium antagonists. Conversely, high-renin patients can have more robust BP responses to angiotensin converting enzyme inhibitors or angiotensin receptor, β -adrenoceptor, and renin blockers. Middle renin patients can respond well to both groups of medications with preference given to the group not prescribed. For example, in a patient with medium renin values on a beta-blocker and angiotensin receptor blocker, a diuretic or nondihydropyridine calcium antagonist would be preferred and *vice versa*. In the absence of compelling indicating for both the beta-blocker and angiotensin receptor blocker, e.g. heart failure or previous myocardial infarction, then the beta- or angiotensin receptor blocker could potentially be withdrawn with maintenance of hypertension control.

Prognosis in Patients with Controlled and Uncontrolled TRH

Hypertension guidelines generally recommend adding and uptitrating antihypertensive medications until goal BP is achieved.²⁰⁻²³ The implied assumption is that the benefits of treating hypertension are mainly related to BP lowering irrespective of the number of antihypertensive medications required to achieve BP reduction. However, one study reported that patients with aTRH, that included both controlled and uncontrolled aTRH, have worse outcomes than uncontrolled hypertensive patients without aTRH.²⁴ The treat to new targets cholesterol study noted that patients with both controlled and uncontrolled aTRH had a similar and greater risk for cardiovascular events than uncontrolled patients without aTRH.²⁵ Two other reports indicate that patients with aTRH, including controlled aTRH, are at greater risk for one or more CVD events or death than patients without aTRH.^{26,27} Moreover, Valsartan antihypertensive long-term use evaluation (VALUE) trial data indicated that patients controlled on a single medication had significantly fewer cardiovascular events than patients controlled on combination therapy, even after adjusting for baseline BP and history of cardiovascular disease.²⁸

In fact, cardiovascular outcomes were not significantly different between controlled and uncontrolled patients on combination therapy.

Thus, in patients uncontrolled on three or more are controlled on four or more medications, it is important for clinicians to recognize that these individuals likely remain at higher risk for cardiovascular events than patients prescribed fewer medications. To mitigate excess risk, clinicians are encouraged to optimize control of other cardiovascular risk factors with special attention to cholesterol in statin eligible patients.²⁹ In addition, even moderate dose statin, e.g. 10 mg atorvastatin in the Anglo-Scandinavian Outcomes Trial (ASCOT) was associated with a lower likelihood of treatment resistant hypertension.³⁰ This is consistent with other evidence suggesting a mild BP lowering effect of statins, which appears to be greater in patients with hypertension than those with nonhypertensive BP values.³¹ Clinicians are also encouraged to use antihypertensive medications with compelling indications³² in patients with diabetes, chronic kidney disease, and cardiovascular disease, all of which heighten future risk for incident cardiovascular events.

In summary, aTRH is a common condition. Using the pragmatic approach outlined, clinicians can identify and address pseudo-resistance, screen for secondary hypertension and initiate changes to lifestyle and pharmacotherapy to improve BP control. It is likely that $\geq 80\%$ of aTRH patients can be successfully managed in primary care. For complex cases of secondary hypertension and truly refractory hypertension, referral to a hypertension specialist is warranted for further management and consideration of device-based therapies.

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