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Resistant Hypertension: Mechanisms and Treatment

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Abstract
Purpose of Review Emerging evidence suggests that multiple mechanisms may be responsible for the development of treatment-resistant hypertension (TRH). This review aims to summarize recent data on potential mechanisms of resistance and discuss current pharmacotherapeutic options available in the management of TRH.
Recent Findings Excess sodium and fluid retention, increased activation of the renin-angiotensin-aldosterone system, and heightened activity of the sympathetic nervous system appear to play an important role in development of TRH. Emerging evidence also suggests a role for arterial stiffness and, potentially, gut dysbiosis. Therapeutic approaches for TRH should include diuretic optimization and the addition of aldosterone antagonists as the preferred fourth agent in most patients. Further therapeutic approaches may be guided by the suspected underlying mechanism of TRH in conjunction with other patient-specific factors.
Summary The pathophysiology of TRH is multifaceted; however, increasing evidence supports several mechanisms that may be targeted to improve blood pressure control among patients with TRH. Further studies are needed to determine whether such approaches may be more effective than usual care.

Keywords Resistant hypertension · Mechanisms · Antihypertensive · Treatment

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Introduction

The concept of "treatment-resistant" hypertension (TRH) has existed, with varying operational definitions, almost since the advent of modern antihypertensive drug therapy in the 1950s [1, 2]. Early references to this phenotype generally described patients with continually elevated BP despite use of multiple antihypertensive drugs [3]. Consensus guidelines in the early 2000s made explicit reference to resistant hypertension and its link with secondary causes of hypertension [4, 5]. Yet, relatively little attention was paid to TRH in the literature until the last decade. In 2008, the American Heart Association published a scientific statement focused explicitly on the identification and management of TRH, defined as uncontrolled BP despite the use of ≥3 antihypertensive agents or use of ≥4 antihypertensive agents regardless of BP control [6]. Since that time, numerous studies have documented the clear and consistent increased risk of adverse cardiovascular outcomes and death [7–12] and impaired health-related quality of life [13, 14], associated with TRH. Moreover, the epidemiology of TRH has been relatively well characterized, particularly in the West. Approximately 86 million adults in the USA and 1.4 billion individuals worldwide have hypertension [15, 16], and, of these, an estimated one in ten has TRH [17]. And, with relatively frequent follow-up and drug titration, some 2% of

individuals with newly diagnosed hypertension may develop TRH within a year [18].

However, much less is known regarding the mechanisms underlying development of TRH. Numerous mechanisms have been proposed, but few have been adequately studied in patients with well-characterized TRH. In turn, this incomplete understanding of pathophysiologic mechanisms underpinning TRH has hampered efforts towards identifying optimal approaches to treating these patients. A reasonably robust literature base has clearly documented a role for spironolactone, but beyond that, evidence guiding treatment remains relatively sparse. Herein, we review possible pathophysiologic mechanisms for TRH and discuss approaches to the management of TRH, with a focus on antihypertensive drug therapy.

Mechanisms

Current evidence suggests that development of TRH is likely multifactorial, but our understanding of pathophysiologic causes remains incomplete. Compared to patients with nonresistant hypertension, patients with TRH are more likely to be older, obese, black, and have higher prevalence of cardiovascular disease (e.g., coronary artery disease) and chronic kidney disease (CKD) [9, 19, 20]. However, the observed associations between such patient factors and TRH are highly dependent on the context under which such observational studies are performed. That is, in addition to reflecting potential direct or shared causal mechanisms, such associations likely also reflect, at least in part, the conditions under which therapy is likely to be titrated, for example, in patients perceived by prescribers to be at higher cardiovascular risk. Thus, while these factors, particularly in tandem, are useful in identifying persons at high risk of having TRH, they offer an incomplete picture of the pathophysiologic mechanisms underpinning TRH. Nevertheless, several potential mechanisms have been identified, which largely comport with the aforementioned patient characteristics. As described in more detail below, these mechanisms include excess fluid retention (due to numerous causes, including excess sodium ingestion), excess circulating aldosterone due to activation of the RAAS, activation of the sympathetic nervous system (SNS), and vascular remodeling and arterial stiffness (Fig. 1).

Sodium and Fluid Retention

Excess sodium intake and the resultant increase in fluid retention play an important role in the pathophysiology of hypertension. Under normal conditions, hemodynamic changes decrease vascular resistance and increase sodium excretion to maintain a consistent BP in the setting of excess volume. However, patients with TRH may have increased sodium sensitivity, leading to a blunted impact of these counter-regulatory changes. Moreover, chronic intake of excess sodium may lead to endothelial dysfunction, even among sodium-resistant individuals [21]. The sodium sensitivity of patients with TRH is exemplified by a small, randomized study showing remarkable BP reductions in patients placed on a low-sodium (50 mmol/day) diet compared to those on a high-sodium (250 mmol/day) diet [22]. The role of excess volume in TRH is suggested by previous studies showing significant improvement in BP control through optimization of diuretic therapy [23–25]. Additionally, studies have documented intravascular expansion among patients with TRH by evaluating various markers of fluid retention, such as increased thoracic impedance and higher natriuretic peptide concentrations [23, 26].

Although the exact mechanism of excess fluid retention is unclear, potential contributing factors include CKD, obesity, and hyperaldosteronism. It is estimated that the prevalence of TRH in patients with CKD is approximately 25%, which is significantly higher compared to the general hypertensive population [27]. Chronic kidney disease can contribute to further sodium and volume retention due to the impaired renal-pressure natriuresis. This inability to increase sodium excretion in the setting of high sodium intake leads to the expansion of the extracellular fluid, thereby increasing BP [28, 29]. Additionally, tubular sodium reabsorption may be increased in part due to impaired renal function, and may also contribute to reduced renal-pressure natriuresis [28]. The degree of volume expansion also appears to be correlated to the degree of kidney impairment [27]. Obesity has also been associated with higher-volume status in patients with TRH due to impairment of the renal-pressure natriuresis and activation of the RAAS [30, 31]. Increased visceral and retroperitoneal fat causes physical compression of the kidneys, which may lead to an impairment of renal-pressure natriuresis and increased intrarenal pressures. Obesity has also been associated with a dysfunction of the natriuretic peptides, further contributing to impaired sodium and fluid excretion [31].

Renin-Angiotensin-Aldosterone System

The RAAS plays an important role in the homeostasis of BP regulation and vascular resistance. Angiotensin II, through the activation of the angiotensin II receptor type 1 (AT_1), is a potent vasoconstrictor in the arterioles and promotes sodium and fluid retention [32]. By contrast, sodium excretion occurs through the activation of angiotensin II receptor type 2 (AT_2) in the kidneys [33]. Chronic activation of the RAAS may further contribute to the increased volume expansion in patients with TRH, especially in the setting of impaired pressure natriuresis. In particular, both CKD and obesity have been associated with increased activation of the RAAS, which appear to be sustained even in the setting of high-volume status

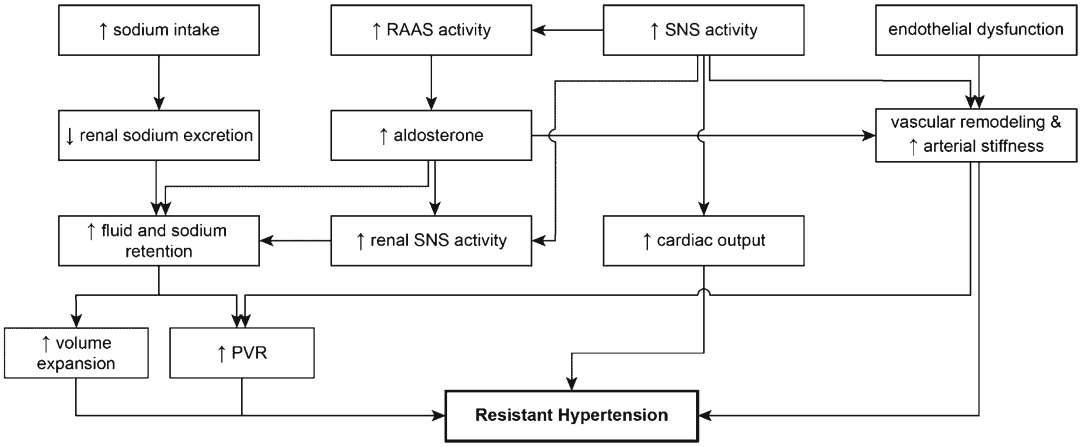

Fig. 1 Schematic of mechanisms involved in development of TRH. *PVR* peripheral vascular resistance, *RAAS* renin-angiotensin-aldosterone system, *SNS* sympathetic nervous system

[27, 31]. Additionally, the endothelial nitric oxide synthase pathway helps to regulate the vascular effects of the RAAS [34]. This pathway may be impaired in patients with TRH, and therefore, the BP-elevating effects of the RAAS enhanced [35].

Aldosterone, a mineralocorticoid secreted by the adrenal cortex in response to angiotensin II, plays an intricate role in regulating sodium and water balance in the distal collecting duct of the kidneys. Its classical action in hypertension pathogenesis is to promote sodium and fluid retention in the nephrons, but recent evidence suggests additional effects in the vasculature to promote inflammation, arterial stiffening, and oxidative stress, which may contribute to TRH development [32, 33, 36]. Interestingly, certain comorbidities, such as obesity and obstructive sleep apnea (OSA), have been associated with increased levels of aldosterone, which appear to be unrelated to the activity of the RAAS [30, 37]. Classically defined primary aldosteronism (PA) is prevalent in approximately 14 to 21% of patients with TRH, and is a major cause of apparent resistance [38]. However, even in cases not reaching the usual threshold for diagnosing PA, excess aldosterone production may promote the development of TRH. Low renin (consistent with excess aldosterone) is common in patients with TRH. Previous studies have shown significant BP-lowering effects with amiloride and eplerenone in patients with low-renin hypertension [39, 40].

The brain's RAAS pathway also may be implicated in development of TRH [33, 41]. Unlike the renal RAAS, where a down-regulation occurs in the setting of high sodium intake, the brain RAAS becomes activated in response to increased sodium loading, and through a positive feedback cycle, the kidneys promote further sodium retention. Much of these effects are believed to be mediated by the AT_1 receptor in the brain; however, activation of the brain AT_2 receptor appears to impart a counter-regulatory effect to suppress the sympathetic tone on the kidneys and induce a diuresis effect [33]. Under these circumstances, an increased production of aldosterone in the brain also occurs, leading to increased activity of the renal SNS. Increased renal SNS activity reduces renal excretion of sodium by decreasing renal blood flow and by increasing renal tubular sodium reabsorption [41].

Sympathetic Nervous System

The role of the SNS has previously been characterized in the development and maintenance of hypertension. Peripheral sympathetic nerve activity and the rate of norepinephrine spillover from the kidneys appear to be increased in the general hypertensive population [42]. Moreover, increased renal nerve activity through sympathetic activation may also enhance renal tubular sodium reabsorption and promote renin secretion [28]. Enhanced SNS activity also appears to be associated with various comorbidities, including obesity, OSA, and CKD, and may contribute to insulin resistance [30, 42, 43].

Emerging evidence further suggests SNS involvement in patients with TRH. In a cross-sectional study that included 424 patients with TRH, reduced heart rate variability was associated with a blunted nocturnal fall in BP [44•]. Reduced heart rate variability is a marker for enhanced SNS activity and may be associated with worse cardiovascular outcomes [45], which may partly explain the increased cardiovascular risk associated with TRH. Furthermore, greater SNS activation may be particularly pertinent in truly refractory hypertension, which appears to be less volume-dependent compared to TRH. Dudenbostel and colleagues found that patients with refractory hypertension (uncontrolled BP on ≥5 antihypertensive drugs) have higher 24-h ambulatory heart rate (HR) and reduced HR variability compared to patients with controlled TRH [46••]. Of note, patients with refractory hypertension were also younger (48 vs. 56.5 years) compared to their controlled TRH counterparts. Additionally, higher levels of 24-h urinary normetanephrine were measured in those with refractory hypertension compared to those with controlled TRH. Arterial stiffness and peripheral vascular resistance were also higher in the patients with refractory hypertension, suggesting a contribution of elevated sympathetic tone [46••].

Other Potential Mechanisms

Some degree of arterial stiffness is usually present in patients with TRH, and its absence may be suggestive of pseudoresistance [47]. Nevertheless, the extent to which vascular remodeling is a cause of TRH is not well elucidated. Likely causes of arterial stiffness in patients with TRH include increased sympathetic tone (particularly in refractory hypertension), excess aldosterone, and the long-standing uncontrolled hypertension common among patients with TRH [48–50]. Advanced age and certain comorbidities (e.g., diabetes, obesity) may contribute to increased arterial stiffening and an impaired central hemodynamic response to elevated BP. Further, isolated systolic hypertension, which is common in the setting of TRH, may be indicative of significant arterial stiffening.

Recent research has suggested an involvement of the gut microbiota in the pathophysiology of hypertension. Altered gut microbiota have been associated with several cardiometabolic diseases, including insulin resistance, obesity, hyperlipidemia, and hypertension [51, 52]. Though the exact mechanism is unclear, gut microbiota may exert hypertensive effects through altered bacterial production of short-chain fatty acids, which influence epithelial cell-related inflammation and sympathetic nerve activity, or by producing toxic by-products (e.g., hydrogen sulfate) that directly increase BP [51, 53]. Recent work has documented a "leaky gut" due to epithelial cell dysfunction associated with gut dysbiosis in animal models, which likely contributes to excess fluid water and solute accumulation [54]. An alternative hypothesis is that altered microbiota may influence antihypertensive drug metabolism, thus reducing (or enhancing) effectiveness of some drugs. Whether the gut microbiota plays a significant role in development of TRH in humans, specifically, is unknown, but a recent case report has highlighted the possible relationship of the gut bacterial flora and BP regulation in TRH [55].

Approaches to Management and Treatment

The major goal of treatment of TRH is to reduce the risk of morbidity and mortality related to cardiovascular events and prevent adverse complications of therapy. Optimization of medical therapy is important to improve BP control, reduce medication burden, and maximize health-related quality of life. Because TRH requires a multidrug regimen, close follow-up is imperative in these patients to prevent adverse drug events and monitor for potential drug interactions, especially those that may promote poor BP control [56]. Below, we discuss general approaches and supporting evidence (or lack thereof), but note that specific antihypertensive regimen for a given patient should be personalized based on the presence of comorbidities and previous medical therapy experience.

In the general hypertensive population, the goal BP recommended by most national guidelines to date has been less than 140/90 mmHg. The 2008 AHA scientific statement endorsed the prevailing (then, JNC 7 [4]) target BP for patients with TRH [6]. However, robust evidence guiding BP targets in this patient population is lacking. Previous retrospective studies have shown that BP control to less than 140/90 mmHg appears to be associated with significant reductions in stroke, but not in other cardiovascular outcomes [9, 10]. In the absence of well-designed prospective studies in patients with TRH, it seems reasonable to follow the prevailing general hypertension BP targets in those with TRH.

Appropriate patient evaluation to rule out pseudoresistance and potential secondary causes should be performed prior to initiating pharmacological management for TRH. A thorough medication history with assessment of adherence to antihypertensive medications, and confirmation of elevated BP using out-of-office measurements uncovers most cases of pseudoresistance. Patient presentation suggestive of secondary hypertension should warrant screening, referral, and treatment, as appropriate [57]. In most cases, these patients do not have true TRH and therapy targeting the secondary cause usually reduces antihypertensive regimen burden substantially. Thereafter, antihypertensive medication changes should be pursued, as described in more detail below, in combination with any necessary lifestyle changes. Figure 2 displays a potential mechanism-based approach to antihypertensive therapy selection, though it should be noted that such an approach has not been prospectively studied.

Optimization of Three-Drug Antihypertensive Regimens

Optimization of a patient's existing antihypertensive regimen should be considered initially. The most often recommended three-drug backbone consists of the so-called "A + C + D" regimen: an angiotensin-converting enzyme inhibitor (ACE-I) or angiotensin receptor blocker (ARB) ("A"), plus a (usually dihydropyridine) calcium channel blocker (CCB; "C") plus a thiazide-type diuretic ("D") [58]. One third of patients with TRH in the USA are not on this three-drug combination, suggesting a sizeable opportunity for improving BP management before adding additional agents that are often poorly tolerated [59]. Doses of each antihypertensive agent should be titrated to the maximum effective dose, when possible, prior to the addition of other agents, to reduce medication burden. Table 1 provides a summary of the starting and maximum effective doses of common antihypertensive agents [60, 61].

Optimization of diuretic therapy is particularly important given the volume overload often present in TRH. The choice of diuretic likely also matters because pharmacologic properties differ significantly between these agents [62]. Chlorthalidone is recommended as the preferred thiazide-type diuretic, in part because of its substantially longer elimination half-life (50–

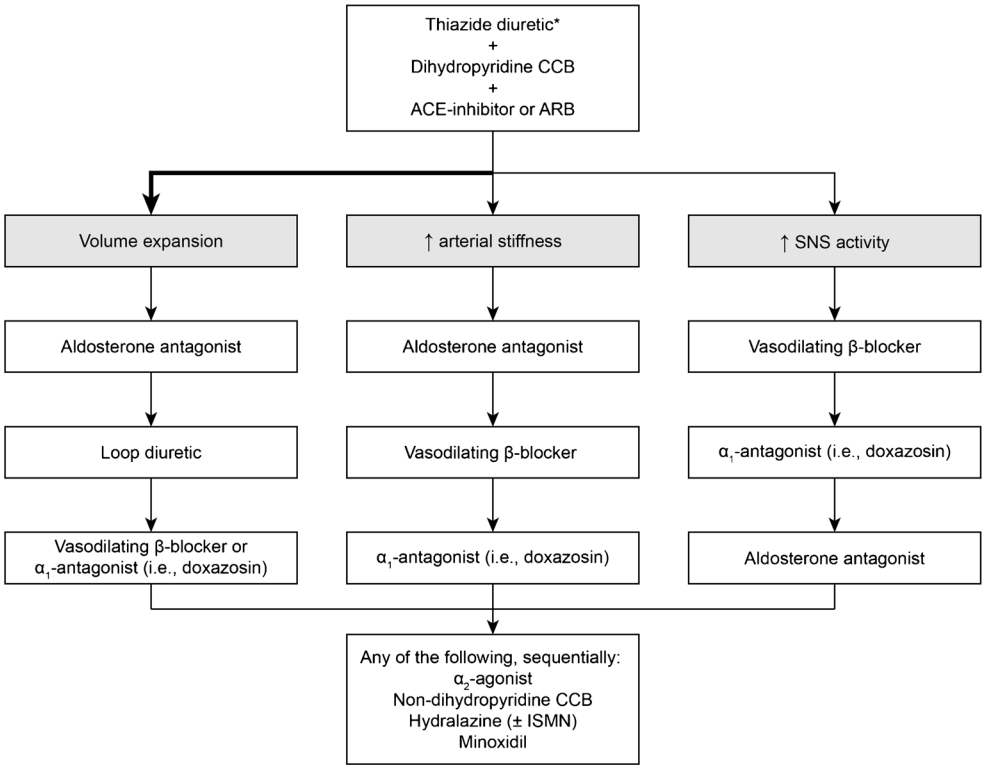

Fig. 2 Possible mechanism-based treatment algorithm for treatment-resistant hypertension. The ideal three-drug antihypertensive backbone regimen should consist of a thiazide diuretic (*asterisk* indicates preferably chlorthalidone or alternatively indapamide or twice-daily hydrochlorothiazide), a calcium channel blocker (preferably dihydropyridine), and either an angiotensin-converting enzyme inhibitor or an angiotensin receptor blocker. If blood pressure remains elevated after optimizing this regimen and pseudoresistance has been excluded, consideration may be given to the likely cause of treatment resistance. Most patients are likely to have volume expansion and low-renin hypertension, in which case an aldosterone antagonist is the clear first choice, barring contraindications. Beyond this recommendation, the evidence base is relatively sparse

60 h) compared with other thiazide-type diuretics (i.e., 9 h for bendroflumethiazide and 10 h for hydrochlorothiazide), allowing for more consistent BP-lowering throughout the 24-h dosing interval; this longer half-life also supports BP-lowering in cases of occasional missed doses. And, secondly, because the evidence on reducing hard endpoints, at least in the general hypertension population, is more robust with chlorthalidone compared with other thiazides [63, 64]. Although thiazide diuretics have not been directly compared in patients with TRH, strong consideration should be given to switching patients who are not already treated with chlorthalidone to this agent, as tolerated. Indapamide is a reasonable alternative and likewise has evidence of benefit on hard outcomes, albeit less than chlorthalidone. If hydrochlorothiazide is continued—as remains the case in greater than three in four US patients with TRH [59]—it should be administered twice daily (i.e., 25 mg twice daily).

Aldosterone Antagonists

Current evidence supports the use of aldosterone antagonists as the preferred fourth agent in patients with TRH. Spironolactone, in particular, has been shown to significantly reduce systolic BP without significant incident hyperkalemia or acute kidney damage in carefully selected patients. The efficacy and safety of spironolactone in the TRH population is now supported by an increasingly robust literature, including observational data and RCTs. The landmark PATHWAY-2 trial investigated the optimal fourth-line agent for patients with TRH already taking the ideal three-drug regimen (A + C + D) [65••]. After 12 months, spironolactone exhibited greater reduction in mean home systolic BP from baseline (−12.8 mmHg) compared to doxazosin (−8.7 mmHg), bisoprolol (−8.3 mmHg), or placebo (−4.1 mmHg), and appeared to be the most effective agent in approximately 60% of patients. An inverse relationship was observed with the BP-lowering effects of spironolactone and baseline plasma renin activity (PRA), where a greater reduction in BP was observed in patients with low baseline PRA. These findings would suggest a particularly important role for spironolactone in patients with volume overload. The overall adverse event rate was relatively low, and all agents were well tolerated with low rates of discontinuation due to adverse events.

Eplerenone is less well studied in TRH but appears to be approximately equally effective. A small prospective study in

Table 1 Starting doses and maximal/optimal doses of common antihypertensive agents

Drug	Initial dose	Max target dose
ACE-I		
Benazepril	10 mg daily	40 mg daily
Captopril	25 mg twice daily	150 to 200 mg twice daily
Enalapril	5 mg daily	20 mg daily (10 mg twice daily)
Lisinopril	10 mg daily	40 mg daily
Ramipril	2.5 mg daily	10 mg daily
ARB		
Candesartan	4 mg daily	12 to 32 mg daily
Eprosartan	400 mg daily	600 to 800 mg daily (400 mg twice daily)
Irbesartan	75 mg daily	300 mg daily
Losartan	50 mg daily	100 mg daily (50 mg twice daily)
Olmesartan	20 mg daily	40 mg daily
Telmisartan	40 mg daily	80 mg daily
Valsartan	40 mg daily	160 to 320 mg daily
Thiazide diuretic		
Chlorthalidone	12.5 mg daily	25 mg daily
Hydrochlorothiazide	12.5 mg daily	50 mg daily (25 mg twice daily)
Indapamide	1.25 mg daily	2.5 mg daily
Loop diuretics		
Bumetanide	0.5 mg daily	1 mg daily
Furosemide	20 mg twice daily	40 mg twice daily
Torsemide	5 mg daily	10 mg daily
Dihydropyridine CCB		
Amlodipine	2.5 mg daily	10 mg daily
Felodipine	5 mg daily	20 mg daily
Nicardipine SR	30 mg daily	90 mg daily
Nifedipine LA	30 mg daily	120 mg daily

ACE-I angiotensin-converting enzyme inhibitor, *ARB* angiotensin receptor blocker, *CCB* calcium channel blocker, *LA* long-acting, *SR* sustained release

patients with TRH found significant reductions in both clinic and 24-h BP when eplerenone was initiated as a fourth agent [66]. An advantage of eplerenone is its reduced side effect profile compared to spironolactone, with the former associated with fewer sexual side effects (e.g., gynecomastia, menstrual irregularities).

Aldosterone antagonists appear most effective in patients with low-renin (high volume) hypertension; therefore, baseline measurement of PRA may be informative. Whether aldosterone antagonists are as effective in truly refractory hypertension is not known, but as volume overload appears to play a smaller role, agents targeting the SNS may prove more effective (Fig. 2). Prior to the initiation of an aldosterone antagonist, baseline serum potassium and serum creatinine should be obtained to assess appropriateness of therapy, and these laboratory parameters should be monitored routinely to avoid hyperkalemia or acute renal failure. Aldosterone antagonists are contraindicated in patients with severe CKD, acute renal failure, and hyperkalemia.

Other Antihypertensive Agents

Far less robust evidence is available regarding the use of other classes of antihypertensive drugs as add-on therapy for TRH in the modern era. Recent literature suggests the use of α_1-blockers, α_2-agonists, β-blockers, and peripheral vasodilators as potential second-line agents for TRH, and in some cases, as an alternative to aldosterone antagonists [60, 61, 66, 67]. The choice of specific agent depends greatly on multiple patient-related factors, such as age, drug tolerance, comorbidities, and underlying mechanism of TRH. Table 2 summarizes dosing and other caveats for these agents [60, 61, 68].

β-blockers should be strongly considered among patients with comorbidities (e.g., systolic heart failure, acute myocardial infarction), where these agents have been shown to have morbidity and mortality benefits. β-blockers also may be preferred in patients where increased SNS activity is suspected to contribute substantially to persistent BP elevation, as may be the case in refractory hypertension [69]. Mixed-action β-

Table 2 Dosing regimen of potential first- or second-line antihypertensive agents for treatment resistant hypertension

Drug	Usual dosing	Drug Class Comments
Aldosterone antagonists		
Eplerenone	25 to 100 mg daily	Preferred as first-line for resistant hypertension
Spironolactone	12.5 to 50 mg daily	Avoid in patients with severe CKD, acute renal failure, and hyperkalemia
β-blockers		
Atenolol	25 to 100 mg daily	Associated with worsened lipid profile, decreased insulin sensitivity, impaired glucose control
Bisoprolol	5 to 10 mg daily	
Carvedilol[a]	6.25 to 25 mg twice daily	Suggested use as add-on therapy in patients with increased SNS activity (i.e., elevated HR, decreased HR variability)
Labetalol[a]	100 to 300 mg twice daily	Strongly recommended in patients with comorbidities (e.g., systolic HF, acute MI), where β-blockers have proven morbidity and mortality benefits
Metoprolol succinate	50 to 200 mg daily	
Metoprolol tartrate	25 to 100 mg twice daily	
Nebivolol[b]	5 to 10 mg daily	
Propranolol	40 to 160 mg twice daily	
α_1-blockers		
Doxazosin	1 to 2 mg daily	Associated with improvement in lipid profile and insulin sensitivity
Prazosin	1 to 5 mg twice daily	
Terazosin	1 to 2 mg daily	Consider as alternative to aldosterone antagonists or β-blockers due to intolerance or contraindications
α_2-agonists		
Clonidine	0.1 to 0.2 mg twice daily (PO); 1 to 3 mg once weekly (TTS)	Associated with rebound hypertension Suggested use as add-on therapy in patients with increased SNS activity (e.g., elevated HR, decreased HR variability)
Methyldopa	250 to 500 mg twice daily	
Peripheral vasodilators		
Hydralazine	25 to 100 mg twice daily[c]	Associated with volume retention and reflex tachycardia; minoxidil also associated with ↑ aldosterone
Minoxidil	10 to 40 mg daily (divided into two or three doses)	Both agents usually require concurrent use with diuretic and β-blocker; hydralazine is sometimes combined with long-acting nitrates

HR heart rate, *PO* oral, *TTS* transdermal therapeutic system

[a] Additional α_1-blocking activity

[b] Additional nitric oxide-dependent vasodilation activity

[c] May require three times per day dosing

blockers (i.e., nebivolol, carvedilol, labetalol) are often employed in this setting because of their dual mechanisms of action in lowering BP, potentially decreasing medication burden in this high-risk population. However, very little data exist to support their greater efficacy in TRH. Nebivolol, in particular, is sometimes recommended on the basis of evidence suggesting improvements in arterial stiffness, although the evidence is mixed [70]. In PATHWAY-2, bisoprolol (on top of an A + C + D regimen) significantly reduced home systolic BP compared to placebo (−8.3 vs. −4.1 mmHg), but the difference was significantly less than that observed between spironolactone and placebo [65••]. In a small prospective study, patients with TRH who received sequential renin-angiotensin system (RAS) blockade with ramipril plus bisoprolol had a mean decrease in daytime ambulatory BP by 7/6 mmHg from baseline [71]. Interestingly, the majority of patients randomized to the RAS blockade group required the addition of a β-blocker, with 20% of patients achieving BP control after the addition of bisoprolol. The forthcoming APROPRIATE study is comparing propranolol vs. placebo on 24-h ambulatory BP in patients with TRH [72].

α_1-blockers, such as doxazosin, are clearly inferior as first-line agents in terms of reducing major outcomes [73], but few studies have investigated their role as add-on therapy in TRH. Despite these limited data, α_1-blockers are frequently used in TRH and may be indicated as alternative agents in patients unable to tolerate aldosterone antagonists or β-blockers, particularly in patients with evidence of arterial stiffness. Retrospective studies of doxazosin as a fourth- or fifth-line agents have shown relatively large reductions in systolic and diastolic BP ranging from 16 to 33 mmHg and 7 to 19 mmHg, respectively [74, 75]. In the PATHWAY-2 trial, doxazosin

significantly decreased home systolic BP from baseline by 8.7 mmHg, similar to bisoprolol [65••]. Whether such BP reduction translates to reduced morbidity or mortality in TRH is not known.

The centrally acting α_2-agonists, clonidine and methyldopa (and to a lesser extent, guanfacine), have been used as second-line therapy in essential hypertension [69], but few data exist on their effectiveness in TRH. These centrally acting sympatholytic agents may be attractive second-line agents for TRH, particularly when increased sympathetic tone is suspected. However, the use of α_2-agonists may be limited due to frequent dosing and common side effects, such as xerostomia and somnolence. Rebound hypertension is also a significant concern with these medications, particularly in the setting of nonadherence which is thought to be frequent in TRH. Therefore, patients should be counseled extensively to maintain adherence and avoid abrupt discontinuation.

The peripheral vasodilators, hydralazine and minoxidil, have been used as second-line therapy in essential hypertension, but evidence supporting their use is scarce. No randomized clinical trials have been performed with hydralazine, and most data supporting its use in hypertension come from pre-/post-studies [76]. Genetic variations in the metabolism of hydralazine may play a role in its BP-lowering efficacy in patients with TRH [77]. Moreover, hydralazine is associated with numerous side effects, including headache (most often, early in therapy) and a low risk of lupus-like syndrome. Minoxidil has slightly more evidence, including a retrospective study in hospitalized patients with TRH that found that minoxidil initiated as a fourth agent was associated with a significant BP reduction from 162/83 to 136/73 mmHg upon discharge [78•]. An advantage of the peripheral vasodilators is that they require no dose adjustment in renal impairment and may be preferred in patients with CKD. However, their use is also limited due to the risk of volume retention and reflex tachycardia, and therefore, they generally must be combined with a diuretic (sometimes dual diuretics) and a β-blocker [69]. Minoxidil also increases aldosterone production, and its use in patients already taking an aldosterone antagonist may be prudent.

Other Potential Pharmacotherapy Strategies

Nitrate therapy (i.e., isosorbide mononitrate) is sometimes used in TRH, generally in combination with hydralazine, and particularly in settings with evidence supporting the combination (i.e., stage C systolic heart failure). Combined nitrate and phosphodiesterase-5 inhibitor therapy can also profoundly decrease BP, for example, by 26/18 mmHg in one small study [79], but this combination would require careful monitoring and is unlikely to be appropriate for many patients in the outpatient setting. A sequential nephron blockade strategy (i.e., addition of a loop diuretic to existing regimen with thiazide-type diuretic) significantly reduces daytime ambulatory BP in patients with TRH [71], and may be most appropriate in patients with high-volume (low-renin)-mediated TRH. Dual calcium-channel blockade therapy with a dihydropyridine CCB plus a nondihydropyridine CCB provides additional BP-lowering, apparently through a pharmacokinetic interaction that increases concentrations of the dihydropyridine CCB [80]. Additionally, chronotherapy has recently gained traction as a potential strategy in the management of hypertension. This concept aims to target the specific timing of antihypertensive therapy to maximize nocturnal BP-lowering, which is a good predictor for future cardiovascular risk [81]. A prospective study in patients with TRH showed improvements in nighttime BP and normalization of circadian BP patterns just by changing the administration of one antihypertensive to bedtime [82•]. In the general hypertensive population, chronotherapy has been shown to reduce cardiovascular outcomes [83], while further investigation is needed to assess whether this benefit also translates to the TRH population.

Investigational Agents

Given the difficulty in attaining and maintaining appropriate BP control, novel therapeutic agents are being developed to expand the options in the treatment of hypertension. Many of these agents are aimed at targeting different mechanisms within the complex pathophysiology of hypertension with the goal of providing complementary actions to existing treatment options. Examples include targets for novel receptors within the RAAS (i.e., angiotensin type II, Mas-R, MrgD), compounds inhibiting the production of angiotensin III in the brain RAAS, and agents that inhibit neprilysin [84]. Though the majority of these agents are in the pre-clinical phases, a few have started phase IIb or phase III clinical trials.

Conclusion

Treatment-resistant hypertension is common and associated with significant adverse consequences including higher risk of cardiovascular events and death, and reduced health-related quality of life. The precise mechanisms underpinning the development of TRH remain unclear, although several mechanisms have been proposed. Excess fluid retention and increased aldosterone levels appear to play a critical role in the development of TRH, whereas enhanced activation of SNS seems to be a substantial contributor to refractory hypertension. In patients with true TRH, optimization of the antihypertensive regimen should be the initial pharmacotherapeutic approach, which includes transitioning to the ideal three-drug combination (ACE-I or ARB plus dihydropyridine CCB plus thiazide-type diuretic) and utilizing a long-acting thiazide-

type diuretic (i.e., chlorthalidone or indapamide). Aldostone antagonists are the preferred first-line agents for TRH, given the significant BP-lowering effects observed in clinical trials. Data guiding second-line options for TRH are scarce, and the choice of an agent should be based on patient-related factors, including the suspected mechanism of resistance, and presence of comorbidities warranting specific therapies.

Compliance with Ethical Standards

Conflict of Interest The authors declare no conflicts of interest relevant to this manuscript.

Human and Animal Rights and Informed Consent This article does not contain any studies with human or animal subjects performed by any of the authors.

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Papers of particular interest, published recently, have been highlighted as:
- • Of importance
- •• Of major importance

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