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Resistant Hypertension: A Comprehensive Overview

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Abstract

Hypertension is a common, undertreated disease and a major risk factor for cardiovascular, cerebrovascular and renal disease. As many as 20-30% of hypertensive patients have resistant hypertension, defined as uncontrolled blood pressure despite 3 or more antihypertensive drugs including a diuretic, typically combined with a calcium-channel blocker and an angiotensin-converting enzyme inhibitor or angiotensin receptor blocker. Patients with resistant hypertension can often be controlled by adding a mineralocorticoid receptor antagonist and/or vasodilating beta-blocker. A significant number of patients will have a treatable secondary cause of resistant hypertension such as obesity, sleep apnea, renal insufficiency, primary aldosteronism or renal artery stenosis. For patients whose hypertension is refractory to preferred antihypertensives, use of third-line antihypertensives such as sympatholytics or vasodilators may be effective but consideration should be given to investigational device-based antihypertensive therapies. Renal artery angioplasty/stenting can be useful in selected cases of renal artery stenosis, while renal sympathetic denervation holds promise for resistant essential hypertension.

Keywords: Hypertension; antihypertensive drugs; Antagonist; vasodilators

Introduction

Hypertension (HTN) is the most common cardiovascular disease and remains a major risk factor for coronary heart disease, cerebrovascular disease, heart failure and renal failure [1,2]. Fewer than half of patients with HTN in the United States reach their Blood Pressure (BP) goals despite availability of numerous inexpensive generic Antihypertensive Drugs (AHDs) [1,3]. Approximately 5-10% (up to 20-30%) of patients with inadequately-controlled HTN have resistant HTN, defined as BP that remains above goal despite optimal doses of 3 AHDs including a diuretic [4,5]. Resistant HTN includes patients whose BP is controlled on ≥ 4 AHDs but excludes patients whose BP is uncontrolled on a suboptimal AHD regimen or <3 AHDs [4]. Recent studies suggest that the prevalence of resistant HTN may be increasing over time [5]. Predictors of inadequately-controlled BP that characterize resistant HTN patients include older age, obesity, higher systolic BP, diabetes, Left Ventricular Hypertrophy (LVH), and Chronic Kidney Disease (CKD) [4]. Patients with resistant HTN are at elevated risk for adverse cardiovascular outcomes, particularly stroke and hospitalization for heart failure [6]. In this review, we discuss the evaluation and medical management of resistant HTN and describe investigational device-based techniques for management of resistant HTN.

Investigation of Uncontrolled HTN

The first step in the assessment of patients with inadequately-controlled HTN is exclusion of falsely-elevated BP readings or lifestyle factors impairing AHD response ("pseudoresistant" HTN) (Figure 1). Poor BP measurement technique, particularly an undersized BP cuff, can falsely elevate BP readings [1]. "White-coat HTN" describes patients whose in-office BP remains elevated despite controlled ambulatory BP, and occurs in at least 20-30% of patients with apparently resistant HTN [7,8]. Patients with white-coat HTN typically lack target organ damage and appear to have lower cardiovascular risk than patients with sustained HTN [9]. Ambulatory BP measurement can establish the diagnosis of white-coat HTN, and is appropriate for the evaluation of most patients with uncontrolled BP [4].

After confirming elevated BP, correctible lifestyle factors that impair BP control should be identified and ameliorated (Figure 1) [1,4]. Weight loss and increased physical activity can produce independent and potentially additive BP reductions [10-13]. Excess dietary sodium intake is common in resistant HTN, and dietary sodium restriction can improve HTN control [4,14-16]. The Dietary Approaches to Stop Hypertension ("DASH") diet can improve BP beyond sodium restriction alone [1,15]. Smoking cessation and moderation of alcohol intake can further improve BP control [1]. A number of prescription and nonprescription drugs can elevate BP, most notably Non-Steroidal Anti-Inflammatory Drugs (NSAIDs) [1,4]. Finally, AHD adherence is critically important for adequate BP control, although lack of AHD adherence accounts for relatively few cases of resistant HTN [4,17,18].

Medical Treatment of Uncontrolled HTN

The recommended 3-drug AHD regimen in patients with resistant HTN consists of maximum doses of a long-acting Thiazide Diuretic (TD), Calcium-Channel Blocker (CCB) and Angiotensin-Converting Enzyme (ACE) inhibitor or Angiotensin-II Receptor Blocker (ARB) [4,19]. Patients whose AHD regimen differs significantly from this combination should be switched if possible (Figure 1). Any long-acting ACE inhibitor or ARB is acceptable, but valsartan may have superior BP lowering at maximum dose [20]. Amlodipine is a useful long-acting CCB given its safety and efficacy in large HTN trials [21-23]. Hydrochlorothiazide (HCTZ) is commonly available in combination AHD pills, but the longer-acting and more potent TDs chlorthalidone

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and indapamide are superior for BP lowering and cardiovascular prevention [22-28]. Low HCTZ doses (12.5-25 mg daily) show an inferior antihypertensive effect when compared to HCTZ 50 mg daily or chlorthalidone 12.5-25 mg daily [24,29]. We suggest switching HCTZ to chlorthalidone (25-50 mg daily) or indapamide (up to 2.5-5 mg daily) prior to diagnosing resistant HTN [4,19,26]. A recent study showed a 29/12 mmHg BP reduction from substituting chlorthalidone 50 mg ± amlodipine 10 mg (with or without adding aliskiren 300 mg) in patients whose BP was uncontrolled on spironolactone + another diuretic ± another CCB [30].

Investigation of Resistant HTN

Biochemical testing in patients with resistant HTN includes measurement of serum electrolytes, urinalysis, BUN, creatinine, and fasting glucose and lipids [1,4]. Measurement of Plasma Renin Activity (PRA) and Serum Aldosterone Concentration (SAC) on a fasting morning blood sample to calculate an aldosterone-to-renin ratio (ARR, i.e. SAC divided by PRA) is recommended to screen for Primary Aldosteronism (PA) in most patients [4]. A screening electrocardiogram is appropriate to identify LVH [1]. Renal artery imaging and/or nocturnal polysomnography can be considered to screen for Renal Artery Stenosis (RAS) and Obstructive Sleep Apnea (OSA), as discussed below. Confirming dietary sodium intake with a 24-hour urine collection for sodium and creatinine can be useful in selected patients. Screening for uncommon secondary causes of HTN such as pheochromocytoma, Cushing syndrome, hyperparathyroidism, thyroid disease, aortic coarctation or intracranial tumor should be performed when there is clinical suspicion (Table 1) [4].

Secondary HTN and Resistant HTN

A significant number of patients will have a treatable secondary cause of resistant HTN, the most common being obesity, CKD, OSA, RAS and PA (Table 1) [4]. Identification and treatment of secondary causes of HTN should improve BP control and in some cases may even normalize BP without the need for AHDs. Important clues suggesting a secondary cause of HTN include severe or resistant HTN, age <30 years without risk factors for HTN (or HTN onset before puberty), accelerating or malignant HTN, new onset HTN at age >55 years and refractory hypokalemia (Table 2). The common secondary causes of HTN (RAS, PA, OSA, CKD, obesity) are more prevalent in elderly patients, while the suspicion for uncommon secondary causes of HTN may be higher in young patients (Table 1) [31]. One study reported that 12.7% of patients ≥ 50 years old with resistant HTN had a secondary cause of HTN [31]. The prevalence of secondary causes in resistant HTN could increase as the population ages, and the most common secondary etiology underlying resistant HTN remains unclear [31,32].

Obesity may be one of the most common contributors to resistant HTN [10]. Studies have identified OSA in up to 64-83% of patients with resistant HTN, making it perhaps the most common secondary cause of HTN [32-35]. Obesity and OSA directly promote resistant HTN via sympathetic activation and aldosterone-mediated sodium retention; sodium retention may be both a cause and consequence of OSA [36-39]. Screening for OSA using nocturnal polysomnography is appropriate in many patients with resistant HTN, especially those with obesity, snoring, witnessed apneas or daytime sleepiness. Weight loss and exercise are critically important for patients with obesity and resistant HTN, and gastric bypass is a viable treatment for hypertensive patients with severe obesity [11-13]. Treatment of OSA using Continuous Positive Airway Pressure (CPAP) can improve BP control in resistant HTN [40].

PA may be present in up to 17-23% of patient with resistant HTN and is suggested by hypokalemia, which occurs in fewer than half of cases [41-44]. An elevated ARR (>20-30 ng/dl per ng/ml/h), especially with serum aldosterone concentration (SAC) >15 ng/ml, is suggestive but not diagnostic of PA and requires confirmatory testing such as a 24-hour urine collection for sodium and aldosterone while on a high-sodium diet [4,44]. The ARR remains useful to screen for PA in patients taking most AHDs except Potassium-Sparing Diuretics (PSD) [41,44]. Uncertainty regarding the optimal testing strategy for PA may warrant referral to an endocrinologist for confirmatory testing [4, 44]. Patients with PA often respond well to high doses of a Mineralocorticoid Receptor Antagonist (MRA) such as spironolactone, which may be superior to the less potent but more selective MRA eplerenone [45].

RAS is commonly identified in patients with resistant HTN, especially those with atherosclerotic vascular disease, and was previously considered to be the most common secondary cause of HTN [31,46,47]. Screening for RAS using renal artery imaging with ultrasound, CT or MRI is appropriate in many patients with resistant HTN, particularly with abdominal bruits, atherosclerotic vascular disease, elevated PRA, CKD, renal function deterioration on ACE inhibitor or ARB, renal size asymmetry, history of flash pulmonary edema or suspected fibromuscular dysplasia [47-50]. While the majority of RAS is caused by atherosclerosis, a minority of cases are due to fibromuscular dysplasia (particularly in women <50 years old) which may have a more robust response to renal artery intervention [47].

CKD with reduced Glomerular Filtration Rate (GFR) is a common

Common secondary causes of HTN	**Clues suggestive of specific etiology**
Obesity	Elevated body mass index and/or waist circumference, metabolic syndrome
Renal artery stenosis	Recurrent pulmonary edema, abdominal bruit, atherosclerotic vascular disease, renal size asymmetry, renal insufficiency, elevated PRA
Primary hyperaldosteronism	Hypokalemia, hypernatremia, metabolic alkalosis, elevated ARR and SAC, low PRA, edema
Obstructive sleep apnea	Obesity, snoring, daytime sleepiness, witnessed apneas, nocturnal awakening
Chronic kidney disease	Elevated creatinine and BUN, proteinuria, edema
Uncommon secondary causes of HTN	**Clues suggestive of specific etiology**
Cushing syndrome	Moon facies, central obesity, abdominal striae, hypokalemia, low PRA, hyperglycemia
Pheochromocytoma	Intermittent BP surges, episodic spells of headache, diaphoresis, palpitations, tachycardia
Hypercalcemia	Fatigue, gastrointestinal symptoms
Aortic coarctation	Radial-femoral pulse delay, reduced femoral pulses, arm/leg BP discrepancy
Thyroid disease	Fatigue, heat/cold intolerance, skin changes, tachycardia or bradycardia, eye signs, anxiety
Intracranial tumor	Morning headache, neurological deficits

Table 1: Secondary causes of HTN.

• Severe or resistant HTN
• Age <30 without risk factors for HTN
• HTN onset before puberty
• Accelerating or malignant HTN
• New onset HTN at age >55
• Refractory hypokalemia

Table 2: Clues suggesting secondary HTN.

cause and consequence of resistant HTN [51]. Patients with CKD often have occult volume overload causing resistant HTN [4,52]. Patients with creatinine clearance <30 ml/min may not respond to TD and require a more potent Loop Diuretic (LD) such as furosemide (given at least twice daily) or torsemide [4]. Further complicating the treatment of HTN in patients with CKD is the use of lower target BP goals to slow CKD progression, leading to higher rates of resistant HTN in patients with CKD [1,4,51].

Medical Treatment of Resistant HTN

After excusion of secondary causes of HTN and optimization of lifestyle factors, many patients still have uncontrolled BP despite an optimal regimen of chlorthalidone/indapamide, CCB and ACEI or ARB. Patients with resistant essential HTN frequently have low renin with persistent sodium retention and occult volume overload, particularly elderly and/or African-American patients and those with CKD [53,54]. Confirming and reinforcing dietary sodium restriction is critical for these patients [14,16]. Increasing the intensity of existing diuretic therapy is a reasonable initial approach for most patients (especially with serum potassium >4.5 mmol/L), and is the most common intervention performed at many specialty HTN clinics [17,19,55]. Diuretic therapy (or ultrafiltration for patients on dialysis) should be intensified until the patient reaches a dry weight where further fluid loss leads to evidence of hypovolemia. For patients with persistently elevated BP on an optimized 3-drug AHD regimen, preferred second-line AHDs include MRA or Vasodilating Beta-Blockers (VBB) with AHDs such as sympatholytics or Vasodilators (VD) relegated to third-line (Table 3).

AHD treatment can be tailored based on PRA, such that patients with suppressed PRA (PRA <0.65-1 ng/ml/h, implying volume excess) receive intensified diuretic therapy, MRA and/or VD and patients with non-suppressed PRA (≥ 0.65-1 ng/ml/h, implying renin excess) receive intensified renin-angiotensin inhibition with ACE inhibitor, ARB, renin inhibitor and/or Beta-Blocker (BB) [53]. The cut-off between suppressed and non-suppressed PRA can vary by laboratory, but is generally 0.65-1 ng/ml/h. A small study of 77 patients with uncontrolled HTN showed improved systolic BP reduction (29 mmHg vs. 19 mmHg) using PRA-guided therapy compared to specialist care [56]. With PRA-guided therapy, physiologically ineffective AHDs can be withdrawn, such as ACE inhibitor/ARB/BB when PRA is low or diuretic/MRA when PRA is high [53,56]. A recent study of patients with uncontrolled HTN despite irbesartan 300 mg, amlodipine 5 mg and HCTZ 12.5 mg showed improved BP control with addition of spironolactone ± furosemide/amiloride compared to ramipril ± bisoprolol [57]. This study was designed to show that diuretic therapy is more effective than renin-angiotensin inhibition in resistant HTN, but the results are limited by inadequate baseline dosing of amlodipine and HCTZ.

Mineralocorticoid Receptor Antagonists

For most patients with resistant HTN, a low-dose MRA (such as spironolactone 12.5-50 mg daily) is an effective initial therapy, particularly with serum potassium ≤ 4.5 mmol/L (Figure 1) [2,4,19]. Interest in spironolactone as add-on therapy for resistant HTN emerged more than a decade ago with the demonstration that low-dose spironolactone can produce robust BP lowering when added to a multi-drug AHT regimen in resistant HTN patients with or without PA [58]. Several observational studies, including an experience with 1141 patients from the ASCOT trial, have shown impressive BP reductions averaging 22/10 mmHg with addition of low doses of spironolactone in resistant HTN patients without PA [59,60]. The randomized ASPIRANT study showed a much smaller 5.4/1 mmHg reduction in ambulatory BP by spironolactone 25mg daily versus placebo, highlighting the importance of placebo control [61]. Hyperkalemia with MRA and other PSDs is more common in patients with diabetes, CKD and/or elevated baseline potassium levels; many patients with CKD (including selected oligoanuric dialysis patients) will tolerate MRA for resistant HTN [62-64].

In theory, patients with low PRA, high SAC or high ARR (implying excess sodium retention and/or aldosterone activity) should have greater BP reduction with MRA [53]. However, multiple studies have found MRA to be effective for resistant HTN regardless of PRA and SAC, suggesting that ARR may only predict response to MRA in untreated HTN patients [65-69]. MRA may lower BP by different mechanisms based on aldosterone status, producing diuresis in patients with hyperaldosteronism and vasorelaxation in patients without hyperaldosteronism [69].

We prefer MRA over non-MRA PSDs (i.e. amiloride) based on the adverse cardiovascular effects of aldosterone independent of renal sodium/potassium handling, warranting direct inhibition of its receptor [39,69,70]. An early randomized study in low-renin HTN showed superiority of amiloride 10 mg over spironolactone 25 mg for BP lowering [71]. However, a later study of HTN patients with high ARR showed similar BP lowering with amiloride 40 mg and spironolactone 100 mg, and demonstrated that amiloride 40 mg is needed to achieve maximum effect while spironolactone 100 mg has minimal added

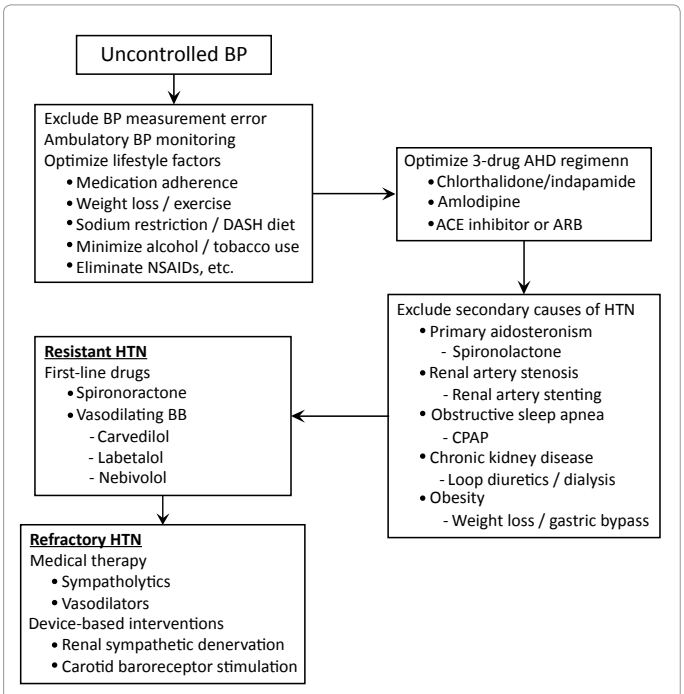

Figure 1: Approach to resistant HTN.

Drug	Class	Usual dose	Max dose	# doses/day	Adverse effects
Spironolactone	MRA	12.5-50 mg	400 mg	1-2	Hyperkalemia, gynecomastia, renal insufficiency
Eplerenone	MRA	25-100 mg	200 mg	1-2	Hyperkalemia, renal insufficiency
Carvedilol	ABB	25-50 mg	100 mg	2	Bradycardia, orthostasis, bronchospasm
Carvedilol CR	ABB	20-80 mg	80 mg	1	Bradycardia, orthostasis, bronchospasm
Labetalol	ABB	200-800 mg	2400 mg	2-3	Bradycardia, orthostasis, bronchospasm
Nebivolol	VBB	5-10 mg	40 mg	1	Bradycardia, headache
Clonidine	A2A	0.2-0.8 mg	2.4 mg	2-3	Fluid retention, orthostasis, sedation, bradycardia
Guanfacine	A2A	1-3 mg	4 mg	1	Fluid retention, orthostasis, sedation, bradycardia
Methyldopa	A2A	250-1000 mg	3000 mg	2-3	Fluid retention, orthostasis, sedation, bradycardia
Reserpine	Other	0.05-0.1 mg	0.25 mg	1	Fluid retention, orthostasis, sedation, depression
Doxazosin	AB	2-8 mg	16 mg	1	Fluid retention, orthostasis, tachycardia
Terazosin	AB	2-10 mg	20 mg	1	Fluid retention, orthostasis, tachycardia
Hydralazine	VD	25-100 mg	300 mg	2-3	Fluid retention, orthostasis, tachycardia
Minoxidil	VD	2.5-20 mg	80-100 mg	1-2	Fluid retention, orthostasis, tachycardia, hirsutism
ISMN	VD	30-120 mg	240 mg	1	Fluid retention, orthostasis, tachycardia, headache

Table 3: AHDs for resistant HTN.

effect over 50 mg [72]. The less-potent selective MRA eplerenone is effective in resistant HTN and avoids the anti-androgenic side effects of spironolactone but may have lower efficacy [45,73]. Investigational aldosterone synthase inhibitors show promise in early phase clinical trials of HTN and could prove to be a valuable alternative to MRA [74].

Beta-blockers

BB provide inferior cardiovascular prevention compared with first-line AHDs, likely due to unfavorable hemodynamic effects that produce a lesser degree of central aortic BP lowering than brachial BP lowering [75-77]. BB is superior for cardiovascular prevention compared with placebo and remains useful second-line AHDs [76]. BB is indicated for patients with resistant HTN and/or compelling indications such as coronary heart disease, heart failure or tachyarrhythmia [1,4]. Vasodilatory BB (VBB), including combined alpha/beta blockers (ABB, i.e. labetalol/carvedilol) and nebivolol (which increases nitric oxide signaling), are the preferred BB for patients with HTN based on more favorable hemodynamic and metabolic effects (Figure 1) [77]. Patients with elevated PRA (≥ 0.65-1 ng/ml/h) and/or elevated resting heart rate (>85 BPM) may have elevated adrenergic tone producing resistant HTN, and could benefit from VBB rather than MRA as their next AHD [53]. Evidence supporting improved HTN outcomes with VBB compared with other BB is scarce, but maximum doses of ABB may lower BP to a greater extent than other BB due to dose-dependent alpha blockade [4,77,78]. Carvedilol is a preferred VBB due to its low cost as well as proven safety and efficacy in multiple large trials, including direct comparison showing benefits over metoprolol [78-80]. Nebivolol is an effective AHD with the advantage of once-daily dosing and improved tolerability [77,81].

Refractory HTN

Refractory HTN includes patients whose BP remains elevated despite use of ≥ 4 AHDs, accounting for about 10% of resistant HTN patients referred to a speciality clinic [82]. These patients may respond poorly to spironolactone and display elevated resting Heart Rate (HR), implicating elevated sympathetic activity rather than sodium retention as the dominant pathophysiology [82]. Medical treatment of uncontrolled HTN despite an effective diuretic, CCB, ACE inhibitor or ARB, spironolactone and VBB remains challenging. Although third-line AHDs may be effective, device-based therapies such as renal sympathetic denervation, carotid baroreceptor stimulation or renal artery stenting should be considered (Figure 1) [83-85]. A thorough search for common and uncommon secondary causes of HTN (Table 1) should be considered and PRA-guided therapy may be useful [4,53]. Several novel AHDs in development could potentially find use in resistant HTN, but new drug development for resistant HTN is hindered by the significant placebo effect on BP and the availability of numerous inexpensive generic AHDs [61,74,86-88].

The third-line AHD classes for refractory HTN are sympatholytics and VD (Figure 1). These AHDs are prone to fluid retention with or without orthostasis, requiring a strong diuretic (often a LD); VD also produces reflex sympathetic activation and tachycardia. Clinical outcomes data are lacking with most of these AHDs despite clear antihypertensive efficacy. For PRA-guided therapy, low PRA (<0.65-1 ng/ml/h) would favor use of a VD while elevated PRA (≥ 0.65-1 ng/ml/h) or elevated resting HR would favor use of a sympatholytic [53]. In selected patients with refractory HTN and persistently elevated PRA, the MRA could be replaced with an ARB or direct renin inhibitor, but a sympatholytic may be preferred given the modest BP lowering and increased adverse events seen with dual renin-angiotensin system blockade [53,89,90]. Triple therapy with MRA plus ACE inhibitor plus ARB or direct renin inhibitor is not recommended due to risk of hyperkalemia and renal dysfunction [4].

Sympatholytics

Sympatholytics include central alpha-2 agonists (A2A, i.e. clonidine/guanfacine/methyldopa) which reduce sympathetic activity and reserpine which reduces neuronal catecholamine release [91]. Clonidine is a potent and highly effective AHD despite a higher rate of adverse effects than first-line AHDs [92]. Clonidine's short duration of action poses a risk of rebound HTN after missed doses leading to chaotic BP control, but this can be overcome by use of a transdermal clonidine patch. The longer-acting and less potent A2A guanfacine requires once-daily dosing and has fewer side effects, but may be less effective [91]. Low-dose guanfacine 1mg daily failed to significantly improve office BP or mean ambulatory BP over placebo in a study of resistant HTN [86]. Methyldopa was effective in a small study of resistant HTN, but off-target adverse effects limit its use [91,93]. Reserpine is long-acting and effective at very low doses (0.05-0.1 mg daily) with established efficacy as add-on therapy in multiple large HTN trials; while psychiatric side effects can limit use of reserpine, these appear minor at low doses [91,94].

Vasodilators

VD include pure AB, long-acting nitrates, Endothelin Receptor Antagonists (ERA) and direct vasodilators (i.e. hydralazine/minoxidil) [91]. Long-acting AB (i.e. terazosin/doxazosin) can be useful in patients who do not tolerate the BB effects of ABB and/or patients with prostatism, but an association between AB and adverse cardiovascular outcomes merits caution [1,95,96]. Long-acting nitrates such as Isosorbide Mononitrate (ISMN) can be useful in selected patients, especially isolated systolic HTN, coronary heart disease and/or heart failure [97,98]. Hydralazine can be highly effective at maximum dose, and the combination of hydralazine with long-acting nitrates is useful in patients with heart failure (particularly systolic dysfunction) [99]. Minoxidil is potent and long-acting, but produces hirsutism and prominent fluid retention. The ERA darusentan is one of the few AHDs evaluated in placebo-controlled studies for resistant HTN. Darusentan 50-300 mg daily reduced BP in resistant HTN by 17-18/10-11 mmHg (vs. 9/5 mmHg with placebo) but increased the risk of fluid retention [87]. In patients with resistant HTN, darusentan 50-300 mg daily was effective for reducing mean ambulatory BP (9 mmHg vs. 4 mmHg with guanfacine 1 mg daily and 2 mmHg with placebo) despite similar in-office BP reduction and a higher rate of adverse effects [86].

Device-based Therapy and Resistant HTN

Combination pharmacologic therapy is currently the preferred approach for most patients with resistant HTN (Figure 1). Nonetheless, an important minority of patients have refractory HTN and/or a correctible cause of HTN that can be addressed using novel device-based therapies. Renal artery angioplasty/stenting has been evaluated in large-scale clinical trials of patients with atherosclerotic RAS [85]. For patients with resistant essential HTN, catheter-based renal sympathetic denervation appears to have favorable efficacy and safety [83,100]. Other novel therapies including carotid baroreceptor stimulation (CBS) are still undergoing evaluation [84,88].

Renal Artery Angioplasty/Stenting (RAAS) has been available for many years, but large-scale clinical trials comparing RAAS with Optimal Medical Therapy (OMT) in atherosclerotic RAS have only occurred recently [47,85,101,102]. RAAS is highly effective for RAS due to FMD and remains standard therapy these patients [47,50]. However, the results of recent trials have cast doubt on the routine use of RAAS in atherosclerotic RAS [85,102]. The large-scale ASTRAL trial randomized 806 patients with atherosclerotic RAS to RAAS + OMT vs. OMT alone and found no significant differences in BP control, renal events, cardiovascular events or death during up to 5 years follow-up [102]. A meta-analysis including 1208 patients confirmed these findings, showing no significant benefit for any major outcome [85]. Anecdotally, there are patients who benefit substantially from RAAS for atherosclerotic RAS. Elevated PRA, renal function deterioration on ACE inhibitor or ARB, renal size asymmetry, history of flash pulmonary edema, accelerating or refractory HTN may identify patients who are more likely to benefit from RAAS [47,49,50]. However, those patients with resistant essential HTN and incidental RAS may not benefit from RAAS. The rate of procedural complications from RAAS in ASTRAL was 9%, further arguing in favor of careful patient selection [102].

Increased renal sympathetic activity is common in patients with HTN, with hyperactivity of both efferent and afferent renal sympathetic nerves contributing to elevated BP [100,103,104]. Newly-developed minimally-invasive techniques using catheter-based radiofrequency ablation to abolish renal sympathetic nerve activity have been compared with medical therapy in resistant HTN [83,100]. The Symplicity HTN-2 trial randomized 106 patients with resistant essential HTN to renal denervation (RD) using the Simplicity catheter system in addition to prior AHDs which were unchanged for 6 months (followed by crossover of all untreated patients to RD), and demonstrated a 33/11 mmHg greater BP reduction with RD at 6 months [83]. A sustained 28/10 mmHg BP reduction at 1 year was seen in patients initially randomized to RD, plus a 24/8 mmHg BP reduction at 6 months in patients who crossed over to RD after initial medical therapy [100]. A systematic review of published RD studies confirmed sustained BP reductions of 18-36/9-15 mmHg over 12 months with infrequent complications [103]. Patients remained on multiple AHDs after RD, so RD should be considered an effective add-on treatment for resistant or refractory HTN rather than a cure [83,100].

Carotid sinus baroreceptors regulate BP via modulation of sympathetic tone, allowing simulation of these baroreceptors to reduce sympathetic activity and BP [105,106]. Observational studies of the surgically-implanted Rheos CBS system in resistant HTN showed improvements in BP over long-term follow-up, with a response rate of 76%, a mean BP reduction of 35/16 mmHg, and a 55% rate of achieving BP goals [107,108]. A subsequent randomized controlled study of CBS failed to meet its primary efficacy endpoint of patients achieving ≥ 10 mmHg reduction in systolic BP at 6 months (54% with the Rheos device vs. 46% with control), despite a greater systolic BP reduction (16 mmHg vs. 9 mmHg) at 6 months and mean systolic BP reduction of 25 mmHg at 1 year [84]. For initial CBS responders, the mean systolic BP reduction was 44 mmHg and 88% of patients had a sustained response [84]. The risk of procedural complications from surgical CBS device implantation did not meet the primary safety endpoint [84].

Conclusions

Resistant HTN is a common clinical problem with a rising prevalence due to increasing rates of risk factors such as older age, obesity, diabetes and CKD. While most patients have resistant essential HTN and/or other identifiable reasons for uncontrolled HTN, a significant number have treatable secondary etiologies such as obesity, OSA, RAS, PA or CKD. We reserve the term resistant HTN for patients whose BP remains uncontrolled despite lifestyle intervention plus 3 first-line AHDs, ideally chlorthalidone or indapamide plus a CCB and an ACE inhibitor or ARB. The pathophysiology of resistant HTN involves occult volume overload and/or sympathetic hyperactivity, and most patients will respond to diuretic intensification plus spironolactone and/or VBB as preferred second-line agents. For patients with HTN refractory to this combination of AHDs, third-line drugs such as sympatholytics or VD can be effective but investigational device-based therapies should be considered. The device-based antihypertensive therapies furthest along in clinical evaluation are RD and CBS, along with RAAS for selected patients with RAS; at this time RD appears the most promising in terms of safety and efficacy. Critical areas of ongoing research include patient selection for these therapies and an evaluation of their risks and benefits. Well-controlled trials will be needed to compare different second- and third-line AHDs with each other and to compare AHD alone with AHD plus device-based therapies in this high-risk patient population.

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