SAGE-Hindawi Access to Research
International Journal of Hypertension
Volume 2011, Article ID 598694, 10 pages
doi:10.4061/2011/598694

Review Article

Resistant Hypertension Workup and Approach to Treatment

Anastasios Makris, Maria Seferou, and Dimitris P. Papadopoulos

European Excellent Center of Hypertension, Laiko University Hospital, 24 Agiou Ioannou Theologou Street, 155-61 Athens, Greece

Correspondence should be addressed to Dimitris P. Papadopoulos, jimpapdoc@yahoo.com

Received 30 September 2010; Accepted 18 November 2010

Academic Editor: Konstantinos Tsioufis

Resistant hypertension is defined as blood pressure above the patient's goal despite the use of 3 or more antihypertensive agents from different classes at optimal doses, one of which should ideally be a diuretic. Evaluation of patients with resistive hypertension should first confirm that they have true resistant hypertension by ruling out or correcting factors associated with pseudoresistance such as white coat hypertension, suboptimal blood pressure measurement technique, poor adherence to prescribed medication, suboptimal dosing of antihypertensive agents or inappropriate combinations, the white coat effect, and clinical inertia. Management includes lifestyle and dietary modification, elimination of medications contributing to resistance, and evaluation of potential secondary causes of hypertension. Pharmacological treatment should be tailored to the patient's profile and focus on the causative pathway of resistance. Patients with uncontrolled hypertension despite receiving an optimal therapy are candidates for newer interventional therapies such as carotid baroreceptor stimulation and renal denervation.

1. Introduction

Hypertension is the most common chronic disease in the developed world affecting up to 25% of the adult population [1]. It remains the most important modifiable risk factor for coronary heart disease, stroke, congestive heart failure, renal disease, and peripheral vascular disease. Suboptimal blood pressure control is responsible for 62% of cerebrovascular disease, 49% of ischemic heart disease, and an estimated 7.1 million deaths a year [2]. Because of the associated morbidity, mortality and economic cost to society early diagnosis and treatment within the established guidelines is imperative. A sizeable percentage of the hypertensive population does not manage to achieve adequate control in spite of receiving 3 or more antihypertensive medications. These are the patients with resistant hypertension.

Resistant hypertension is defined by the Joint National Committee 7 as blood pressure that is above the patient's goal despite the use of 3 or more antihypertensive agents from different classes at optimal doses, one of which should ideally be a diuretic [3]. Patients whose blood pressure is controlled but require 4 or more medications to do so should also be considered resistant to treatment. However, the definition does not include newly diagnosed hypertensives. Resistant hypertension is not synonymous with uncontrolled hypertension. The latter includes both patients with inadequately treated blood pressure due to poor adherence or inadequate treatment, as well as those with true resistant hypertension [3, 4]. The importance of resistant hypertension lies in the identification of patients who are at high risk of suffering complications from reversible causes of hypertension and patients who may benefit from a particular diagnostic or therapeutic approach [3].

The exact prevalence of resistant hypertension is unknown, in part because of its arbitrary definition. However, small studies estimate prevalence from 5% in general medical practice up to 50% in nephrology clinics [5]. In a prospective analysis of Framingham study data, a higher baseline systolic blood pressure along with older age, the presence of LVH and obesity (BMI $> 30\,kg/m^2$) were the strongest predictors of lack of blood pressure control [6, 7]. Results were similar in ALLHAT where the older, obese patients with higher baseline systolic blood pressure and LVH required 2 or more antihypertensive agents [8]. The strongest predictor however was serum creatinine over 1.5 mg/dL. Other patient characteristics associated with resistant hypertension include excessive salt ingestion, diabetes, black race, and female gender. Both studies showed greater difficulty in controlling systolic blood pressure compared to diastolic. Up to 92% of patients achieved target diastolic blood pressure while only 60%–67% achieved systolic blood pressure goals [6, 8]. It is likely that this condition will become increasingly common because of the aging population and a progressive increase in obesity and comorbidities such as diabetes.

There are also a few studies implicating gene mutations. A Finnish study found that certain variants of the β and γ subunits of the epithelial sodium channel gene ENaC were significantly more prevalent in patients with resistant hypertension [9]. Other studies associate the allele of the CYP3A5*1 enzyme with both higher blood pressure levels in normotensive people of black race, as well as with hypertension resistant to treatment [10, 11]. This particular enzyme is involved in the metabolism of cortisol and corticosterone. These and other genes that may be identified in the future hold the potential for the development of novel therapeutic targets.

2. Pseudoresistance Evaluation

The workup of patients with suspected resistant hypertension is summed up in Table 3.

The first step in evaluating a patient with uncontrolled blood pressure is to establish whether it is a case of true resistant hypertension or just pseudoresistance. The latter refers to a lack of blood pressure control despite receiving treatment without true resistance. This can be caused by easily reversible causes such as suboptimal blood pressure measurement technique, poor adherence to prescribed medication, suboptimal dosing of antihypertensive agents or inappropriate combinations, the white coat effect, and clinical inertia. It is important to exclude these causes before labeling a patient as having resistant hypertension.

Poor blood pressure measurement technique is quite common, usually the result of not letting the patient rest before measurement and using a small cuff [12]. Patients should always rest in a chair with their back supported for a minimum 5 minutes prior to measurement and the cuff's air bladder must encircle at least 80% of the arm circumference. The average of two readings taken a minute apart represents the patient's blood pressure.

Approximately 40% of newly diagnosed patients will discontinue their antihypertensive medication the first year of treatment [13, 14]. Eventually, less than 40% will continue taking their medication after 5 to 10 years [13, 15]. The most common causes are poor patient-physician communication concerning blood pressure goals and the importance of achieving them, potential side effects, high cost of treatment, and complex regimens [16, 17]. Adherence can be improved by choosing affordable agents with minimal side effects that are given once daily alone or in fixed dose combinations. Older patients with memory deficits or psychiatric illness can benefit from using pill boxes.

Clinical inertia can be described as a physician's ignorance of treatment guidelines or reluctance to adhere to them due to lack of training or inexperience in antihypertensive medication, underestimation of cardiovascular risk, and overestimation of the treatment provided [18, 19]. This results in suboptimal dosing or inappropriate combinations of agents. A large part of this problem could be resolved if physicians familiarize themselves with one or two drugs in each class of antihypertensives. Proper training is imperative so that physicians realize the importance of treating to reach a goal blood pressure level of less than 140/90 mmHg and knowing when to refer patients to a hypertension specialist.

A white coat effect should be suspected in patients whose clinical blood pressure measurements are consistently and significantly higher than reliable out of office measurements. Other signs include repetitive symptoms of overtreatment such as orthostatic hypotension and persistent fatigue as well as absence of target organ damage including left ventricular hypertrophy, retinopathy, and chronic kidney disease [20, 21]. These cases must be confirmed with 24-hour ambulatory blood pressure monitoring. One study found that 20 to 30% of a patient population believed to have resistant hypertension was actually well controlled when measured by 24-hour ambulatory blood pressure monitoring [22]. Accurate home blood pressure values are the best guide for therapy. In elderly patients, especially diabetics, arterial stiffness may cause pseudoresistance because less compressible arteries cause falsely elevated blood pressure [23].

3. Concomitant Conditions

As was previously mentioned, obesity is associated with resistant hypertension. Obese patients have increased sympathetic activity, higher cardiac output, and a rise in peripheral vascular resistance due to reduced endothelium-dependent vasodilation. Plasma aldosterone and endothelin are also increased, while excessive surrounding adipose tissue results in increased intrarenal pressures and changes in renal architecture [24]. As the body mass index increases, progressively higher doses of antihypertensive drugs are required to control blood pressure [25]. Weight loss has been found to reduce both systolic and diastolic blood pressure [3, 26].

Another common concomitant condition in hypertensive patients is diabetes. Insulin resistance increases sympathetic nervous activity, vascular smooth muscle cell proliferation, and sodium retention leading to elevated blood pressure resistant to treatment [3]. The common comorbidities of obesity, hypertension, and diabetes induce renal dysfunction, further hindering blood pressure treatment.

Dietary factors include increased salt and alcohol consumption. Although small amounts of alcohol (2 drinks/day) have vasodilating effects and may lower blood pressure, consumption of more than 30 mL daily raises blood pressure and may increase cardiovascular risk. Older patients, patients of African origin, and patients with chronic kidney disease are particularly susceptible to salt intake [3]. Current guidelines recommend that dietary sodium for a hypertensive person should be under 100 mmol/day (2.4 g sodium or 6 g sodium chloride) and even lower in salt sensitive patients [27]. Excessive salt intake can be assessed by measuring sodium excretion in a 24-hour urine collection.

Several common medications can cause elevated blood pressure and hinder treatment. Perhaps the most common are nonsteroidal anti-inflammatories including COX-2 inhibitors and aspirin, decongestants (phenylephrine and pseudoephedrine), stimulant agents used for weight loss, narcolepsy or attention deficit disorder, contraceptives, cyclosporine, and erythropoietin [3]. Corticosteroids increase blood pressure through fluid retention, particularly but not limited to those with increased mineralocorticoid activity. Licorice and herbal medication that contains stimulants such as ephedra can also cause hypertension.

Table 1: Causes of resistant hypertension.

Exogenous substances
Drug related (see Table 2)
Herbal preparations (licorice, ephedra, ginseng, yohimbine, ma huang, and bitter orange)
Alcohol consumption
Excess sodium intake
Concomitant conditions
Obesity
Insulin resistance
Smoking
Pseudoresistance
White-coat hypertension
Pseudohypertension in the elderly
Measurement artifact
Physician inertia
Secondary causes of hypertension
(i) Common causes
Renovascular disease
Renal parenchymal disease
Primary aldosteronism
Pheochromocytoma
Cushing syndrome
Thyroid and parathyroid disease
Coarctation of the aorta
(ii) Rare causes
Aneurysm located at the bifurcation of the right renal artery
Arterial thrombosis from abdominal aorta to both common iliac arteries
Occlusion of the left renal artery
Hypercalcemia
Carcinoid syndrome
Central nervous system tumors
Premenstrual syndrome

4. Assessment of Secondary Causes of Hypertension

Secondary causes of hypertension are common in patients with resistant hypertension, particularly in the elderly. These include obstructive sleep apnea, renal parenchymal disease, renal artery stenosis, and primary aldosteronism [28, 29] (Table 1).

Obstructive sleep apnea is particularly frequent in patients with resistant hypertension. A small study of 41 patients with resistant hypertension discovered that 83% suffered from sleep apnea [30]. The severity of sleep apnea is positively associated with the likelihood of resistant hypertension [31, 32]. Several mechanisms are believed to contribute to this effect. Intermittent hypoxemia and increased upper airway resistance induce a sustained increase in sympathetic nervous system activity [33, 34]. Also, there seems to be a significantly higher prevalence of primary aldosteronism in patients with sleep apnea [35, 36]. Alternatively, obesity may be the common factor that increases risk for both obstructive sleep apnea and excess aldosterone production [35]. A sleep study is indicated in patients with resistant hypertension and other signs and symptoms of sleep apnea including obesity, large neck size, excessive loud snoring, interrupted sleep, daytime somnolence, polycythemia, and carbon dioxide retention [37, 38]. Treatment with a continuous positive airway pressure device (CPAP) has been shown to reduce blood pressure and thus is beneficial in resistant hypertension patients with obstructive sleep apnea [3].

The recent studies suggest that primary aldosteronism is a much more common cause of hypertension than originally believed. Particularly in patients with resistant hypertension, the prevalence of primary aldosteronism has been found between 10% and 20% [3, 39, 40]. Aldosterone exerts a number of effects leading to increased systemic vascular resistance, such as endothelial dysfunction, vascular remodeling through collagen deposition, vascular damage, impairment of the baroreflex leading to loss of compensation for elevated blood pressure, and hypovolemia [41–43]. It has been suggested that obesity is involved, causing a generalized activation of the renin-angiotensin-aldosterone system, perhaps through excretion of cytokines from adipocytes [44, 45].

Primary aldosteronism may be suggested by hypokalemia; however this is often a late manifestation preceded by the development of hypertension [46–48]. Screening should be done with plasma renin and serum aldosterone ratio measurement (which has a high sensitivity but low specificity) and confirmed with sodium loading or fludrocortisone suppression testing [39, 49].

Renal parenchymal disease is both a cause and a complication of poorly controlled hypertension [50, 51]. As was previously mentioned, in ALLHAT serum creatinine above 1.5 mg/dL was the strongest predictor of failure to achieve goal blood pressure [8]. Resistant hypertension in chronic kidney disease is mainly due to activation of the renin-angiotensin system, sodium retention, and the resulting intravascular volume expansion [52]. Other factors include activation of the sympathetic nervous system due to decreased blood flow to the kidney, alterations in vasoconstrictor and vasodilator excretion from the endothelium, and increased arterial stiffness [52].

Table 2: Drug related causes of resistant hypertension.

Drug-related causes
Nonadherence
Suboptimal medication regimen
Inappropriate combinations
Drug actions and interactions
(i) Drugs that regularly raise blood pressure:
Anabolic steroids
Sympathomimetic amines (midodrine)
Cocaine
Nicotine
(ii) Drugs that often raise blood pressure:
Ethanol (in excess)
Corticosteroids
Cyclosporin
Erythropoietin
Anorectics
NSAIDs including COX-2 inhibitors
Ergot alkaloids
(iii) Drugs that occasionally raise blood pressure:
Caffeine
Phenothiazines
Tricyclics
Oral contraceptives
(iv) Drugs that cause hypertension on withdrawal:
Clonidine
B-blockers
(v) Drugs that cause hypertension by interaction:
MAOIs

Table 3: Resistant hypertension workup.

Identify and correct pseudoresistance
(i) Perform proper measurements of blood pressure.
(ii) Evaluate white coat hypertension with reliable home or 24-hour blood pressure measurements.
(iii) Evaluate patient adherence and improve it with education, prescription of the least costly effective drug regimen with the fewest potential adverse effects. Prefer once daily fixed-dose combination products.
Lifestyle modifications
(i) Ask the patient about use of any pharmacological/herbal substances that may increase blood pressure.
(ii) Evaluate of the amount of alcohol intake.
(iii) Evaluate dietary salt intake and recommend sodium restriction to <100 mmol (2.4 g) per day.
(iv) Assess the degree of obesity, abdominal obesity, and physical activity and recommend weight reduction and regular aerobic exercise (at least 30 min/day, most days of the week).
Identify factors contributing to true resistance
(i) Evaluate renal function with estimation of glomerular filtration rate and modify treatment accordingly.
(ii) Search for causes of secondary hypertension

Tailor treatment according to patient characteristics using optimal doses of appropriate medications. If all fails refer to hypertension specialist.

Renal artery stenosis is a relatively common finding in hypertensive patients undergoing cardiac catheterization with approximately 20% of patients having unilateral or bilateral stenosis above 70% [53]. However the causative role of these stenosis in hypertension remains unknown since only a few patients actually benefit from surgical or endovascular revascularization [54, 55]. The majority of cases (90%) are due to atherosclerotic lesions and are seen in older patients, smokers, patients with known atherosclerotic disease and unexplained renal insufficiency [56]. The other 10% are fibromuscular lesions, commonly in women under 50 years of age, and these are the patients that will usually improve blood pressure control after revascularization [3]. Bilateral renal artery stenosis should be suspected in patients with a history of "flash" pulmonary edema with preserved systolic heart function. Screening can be done using magnetic resonance angiography (MRA), computer tomographic angiography (CTA), Doppler ultrasonography, or angiotensin converting enzyme (ACE) inhibitor renography [49, 57].

Pheochromocytoma is a rare cause of resistant hypertension with a prevalence of 0.1%–0.6% among hypertensives [58, 59]. The average time between initial symptoms and diagnosis is 3 years, and many cases are missed altogether according to autopsy studies [60]. Clinical signs include episodic headaches, palpitations, and sweating. The best screening test for pheochromocytoma is 24-hour urinary metanephrines or plasma free metanephrines (normetanephrine and metanephrine) which carries a 99% sensitivity and an 89% specificity [61].

Hypertension is a common manifestation of Cushing's syndrome. Up to 90% of patients are hypertensive and 17% have resistant hypertension [62, 63]. The primary mechanism is increased mineralocorticoid activity that leads to increased intravascular volume [64]. However, other factors such as obstructive sleep apnea and insulin resistance also contribute substantially [65, 66]. Target organ damage in Cushing's syndrome is more severe than in primary hypertension because it is associated with many other cardiovascular risk factors such as diabetes, obstructive sleep apnea, obesity, and dyslipidemia [67, 68].

Thyroid and parathyroid dysfunction are common reversible causes of secondary hypertension. Patients with hyperthyroidism usually present with systolic hypertension and those with hypothyroidism have diastolic hypertension. Most patients with primary hyperparathyroidism are diagnosed because of routine findings of hypercalcemia [69, Table 1-2].

5. Pharmacological Treatment

Pharmacological treatment should be based on the most common causes of resistant hypertension and focused on blocking all the physiological pathways to blood pressure elevation [18, 70]. Antihypertensive agent doses should be titrated upward until blood pressure is controlled or the maximum recommended dosage is reached, unless the patient experiences dose related adverse effects. It is then appropriate to add a drug from another class that has additive or synergistic effects with the first drug. In general, a typical regimen should include a diuretic, an ACE inhibitor or angiotensin receptor blocker (ARB), a calcium channel blocker (CCB), and a β-blocker.

The timing of medication administration can also affect blood pressure control. Switching one of 3 or more medications from morning to bedtime administration can result normalization of blood pressure in 21.7%–37% of patients [71, 72]. This is particularly important in nondippers. Since volume overload is the most frequent underlying pathophysiology and suboptimal dosing the most frequent cause of resistant hypertension, adding, increasing or changing diuretic therapy is the key to successful treatment and will help over 60% of patients achieve target blood pressure [18, 73–77].

Patients with normal kidney function should receive 12.5–25 mg/day of hydrochlorothiazide although some will benefit from doses up to 50 mg/day [73]. Chlorthalidone at 25 mg/day is an alternative that offers greater 24-hour blood pressure reduction than 50 mg/day hydrochlorothiazide with the greatest difference occurring overnight and may be preferred in certain patients with resistant hypertension [78]. When given at the same dose as hydrochlorothiazide, chlorthalidone will reduce blood pressure an additional 8 mmHg according to a small study [79]. Patients should be monitored for hyponatremia and hypokalemia, and caution is warranted in patients with a history of prediabetes and gout. A common pitfall is not realizing that the patient's kidney function is deteriorating and not switching diuretic class when it does. Thiazide diuretics are not effective in chronic kidney disease. Therefore, they must be replaced with loop diuretics when the estimated glomerular filtration rate (eGFR) falls below 40 mL/min/1.73 m^2 [27, 73, 80]. In a study of 12 elderly patients with hypertension whose blood pressure was uncontrolled on multidrug regimens the use of furosemide significantly improved blood pressure control [81]. Furosemide and bumetanide have a relatively short half-life and should be dosed twice daily in order to avoid reactive sodium retention due to intermittent natriuresis and consequent activation of the renin-angiotensin system [73, 80, 82].

When optimal diuresis fails, other medications should be considered. Since subclinical aldosteronism is a common occurrence in resistant hypertension, low doses of spironolactone (25–50 mg/day) or eplerenone can be particularly helpful. Patients most expected to benefit from mineralocorticoid blockade include those with primary hyperaldosteronism, the obese, and those suffering from obstructive sleep apnea. According to one study, the addition of spironolactone 12.5–25 mg/day to 76 patients with uncontrolled hypertension taking an average of 4 antihypertensive agents resulted in an average 25/12 mmHg reduction after 6 months [83]. The blood pressure lowering arm of the ASCOT study had similar results for patients who were unselected for aldosterone/plasma renin activity. When spironolactone was added as a fourth line agent, blood pressure dropped by 21.9/9.5 mmHg. At this dosage spironolactone is safe, well tolerated and provides significant additive blood pressure reduction [84, 85]. Eplerenone may be more suitable for patients requiring spironolactone doses above 25 mg/day because breast tenderness is a common adverse effect at higher doses [86]. Hyperkalemia is another risk that must be monitored.

Amiloride is an alternative indirect aldosterone antagonist that is better tolerated than spironolactone. One small study found that the addition of 2.5 mg/day amiloride decreased blood pressure by 31/15 mmHg [40]. However, it has been shown that 10 mg of amiloride has half the blood pressure reduction capability of 25 mg spironolactone and therefore should be considered only when spironolactone is not tolerated [87].

Blockade of the renin angiotensin system with ACE inhibitors or ARBs in patients that are intolerant of ACE inhibitors is particularly recommended in patients with diabetes mellitus, heart failure, postmyocardial infarction, chronic kidney disease, high coronary disease risk, and recurrent stroke prevention [27, 88]. Dosage should be increased to the maximum recommended dosage as long serum creatinine does not increase more than 35% above baseline and hyperkalemia does not develop [1–11]. Dual ACE and ARB therapy is no longer recommended in most cases because of the possibility of adverse renal outcomes [89, 90].

Aliskiren, the only available direct renin inhibitor, is at least as effective as ARBs in reducing end target organ damage but has not been directly tested in resistant hypertension. The ALLAY trial showed that aliskiren monotherapy was as effective as losartan in reducing LVMI, although the combination of both did not achieve a statistically significant further LVMI regression [91]. The addition of aliskiren to losartan did however seem to have additional renoprotective effects in another study, reducing the mean urinary albumin creatinine ratio by 20% in patients with diabetic nephropathy [92]. The additional blood pressure reduction was marginal and therefore the role of direct rennin inhibitors in resistant hypertension remains undetermined.

Polypharmacy is difficult to avoid because blood pressure can be controlled by using one drug in only about 50% of patients. Fixed dose combinations offer the convenience of taking fewer pills, combining antihypertensive agents with additive or synergistic effect and reducing dose-dependant adverse effects of individual components. The latter is evident in ACE inhibitor or ARB combinations with CCBs, as the ACE inhibitors/ARBs reduce the peripheral edema that frequently develops with dihydropyridine calcium channel blocker therapy. Another popular fixed dose combination with synergistic effects is ACE inhibitors/ARBs with diuretics, since the latter enhance the antihypertensive efficacy of all the other classes. The recent introduction of triple agent combinations containing dihydropyridine CCBs as well is expected to lessen the burden of polypharmacy and further improve adherence [86].

CCBs are particularly indicated in black and elderly patients. The ACCOMPLISH study suggested that combining ACE inhibitors with CCBs was more effective at preventing major cardiovascular and renal events than ACE inhibitors with diuretics despite achieving similar blood pressure control rates [93]. Both regimens are available as fixed dose combinations and are useful options in different circumstances. In cases of true resistant hypertension, there are also data to support adding a complementary non dihydropyridine CCB to a regimen including a RAS blocker, diuretic, and dihydropyridine CCB. Such a combination of complementary CCBs results in additive BP reduction with a low-side effect profile and makes pharmacological sense [94, 95].

Beta-blockers are indicated in the setting of coronary artery disease, congestive heart failure, and postmyocardial infarction. When adding on combinations already including a diuretic, an ACE inhibitor or ARB and a calcium channel blocker, vasodilating β-blockers should be preferred [73, 96]. Beta-blockers as well as loop diuretics are also usually necessary when administering direct vasodilators to overcome the reflex tachycardia and fluid retention, respectively [97]. If BP control is still not achieved with full doses of a 4-drug combination, use of other agents such as centrally acting alpha-agonists (methyldopa and clonidine) or vasodilators (hydralazine or minoxidil) is needed. These agents are very effective for lowering BP but have poor tolerability, require frequent dosing, and lack positive outcome data [27]. At this stage, the intervention of a hypertension specialist is warranted. Besides these established treatments, new antihypertensive agents are being developed.

Endothelin receptor antagonists are a new family of antihypertensive medications that are currently being evaluated. Darusentan is a selective antagonist for type A endothelin receptors, activation of which causes vasoconstriction and proliferation of vascular smooth muscle [98]. It has demonstrated significant dose-dependant reductions in both systolic and diastolic blood pressures and has been positively evaluated in resistant hypertension [98, 99]. Unfortunately, another unpublished phase 3 clinical trial failed to meet its coprimary end point and the drug's future remains uncertain [100]. Atrasentan is another highly selective endothelin receptor antagonist that has shown positive results in blood pressure reduction for 72 patients [101]. Interestingly, it also had a positive influence on the patients metabolic profile. Another promising category under development is medication that combines inhibitors of vasoconstrictive mediators with drugs that potentiate vasodilating mediators by inhibiting their breakdown by neutral endopeptidases (NEPs). Omapatrilat is such an agent that has been evaluated favorably in the OCTAVE trial [102]. Vaccines targeting angiotensin I and II are also being developed and tested [103, 104].

In any case, treatment should be tailored to the patient's profile, lifestyle, and comorbidities. Constructing a regimen that is acceptable to the patient, well tolerated and will maintain long-term compliance is important. Yet in some patients, optimal blood pressure control will not be achieved even with the most carefully designed regimen. In these cases, new device-based approaches for blood pressure control are being evaluated (Tables 1 and 2).

One of these devices is the Rheos device (CVRx, Maple Grove, Minn) which stimulates the carotid baroreceptors for better blood pressure control by taking advantage of chronic electrical activation of the afferent limb of the carotid baroreflex. The device consists of a pulse generator and bilateral perivascular carotid sinus leads that are implanted under narcotic anesthesia. According to the findings from the Device-Based Therapy of Hypertension (DEBuT-HT) study that were recently presented, after four years of treatment, Rheos reduced systolic blood pressure by an average of 53 mmHg (193 mmHg versus 140 mmHg). Blood pressure was reduced significantly each year, with the largest decrease occurring in year four. Many of these patients were able to reach their blood pressure goal and reduce the number of medications that patients were taking to treat their hypertension from an average of 5 at baseline to 3.4 medications at 4 years. Baroreflex activation therapy also improved functional capacity and reduced left ventricular mass without any evidence of carotid injury or stenosis [105].

Another target for the interventional treatment of resistant hypertension is catheter-based renal nerve ablation. Renal sensory afferent nerve activity directly influences sympathetic outflow to the kidneys and other highly innervated organs involved in cardiovascular control, such as the heart and peripheral blood vessels, by modulating posterior hypothalamic activity [106, 107]. All these components are stimulated in hypertension and contribute to blood pressure elevation.

Renal sympathetic nerve ablation is achieved percutaneously via the lumen of the renal artery, using a catheter connected to a radiofrequency generator. Treatment has been administered to 45 patients with resistant hypertension taking a median of 4.7 antihypertensive agents. Followup at 1 and 2 years has shown a sustained blood pressure reduction of 27/11 mmHg [108, 109]. The multicentre Simplicity HTN-1 study that was recently presented at the European Society of Hypertension's 20th meeting included 108 patients with persistently elevated blood pressure despite treatment with an average of five medications. Catheter-based renal denervation produced a mean blood pressure reduction of 33/15 mmHg at 24 months without evidence of vascular or renal abnormalities. Results from the Simplicity HTN-2 study comparing renal denervation treatment to rigorous medical therapy are expected by the end of 2010.

6. Conclusions

Resistant hypertension remains a challenging clinical problem that will increasingly become more common. Causes of resistance should be considered when blood pressure does not respond satisfactorily to a rational triple antihypertensive regimen that includes a diuretic. The workup of patients with resistive hypertension should be a two-step approach (Table 3): first, confirmation that it is indeed true resistant hypertension by ruling out or correcting factors associated with pseudoresistance, and second, identification of the true factors involved in treatment resistance. The cornerstone of therapy remains a rigorous evaluation followed by correction of contributing causes and appropriate pharmacological treatment. Newer interventional therapies may become a viable option in the future for those patients with uncontrolled hypertension despite receiving an optimal multiple medication antihypertensive regimen and those who cannot tolerate the medication.

References

[1] K. Wolf-Maier, R. S. Cooper, J. R. Banegas et al., "Hypertension prevalence and blood pressure levels in 6 European countries, Canada, and the United States," *Journal of the American Medical Association*, vol. 289, no. 18, pp. 2363–2369, 2003.

[2] World Health Organization, "Reducing risks, promoting healthy life," World Health Report, World Health Organization, Geneva, Switzerland, 2002.

[3] D. A. Calhoun, D. Jones, S. Textor et al., "Resistant hypertension: diagnosis, evaluation, and treatment: a scientific statement from the American Heart Association Professional Education Committee of the Council for High Blood Pressure Research," *Circulation*, vol. 117, no. 25, pp. e510–e526, 2008.

[4] M. Epstein, "Resistant hypertension: prevalence and evolving concepts," *Journal of Clinical Hypertension*, vol. 9, no. 1, pp. 2–6, 2007.

[5] N. M. Kaplan, "Resistant hypertension," *Journal of Hypertension*, vol. 23, no. 8, pp. 1441–1444, 2005.

[6] D. M. Lloyd-Jones, J. C. Evans, M. G. Larson, C. J. O'Donnell, E. J. Roccella, and D. Levy, "Differential control of systolic and diastolic blood pressure factors associated with lack of blood pressure control in the community," *Hypertension*, vol. 36, no. 4, pp. 594–599, 2000.

[7] D. M. Lloyd-Jones, J. C. Evans, M. G. Larson, and D. Levy, "Treatment and control of hypertension in the community: a prospective analysis," *Hypertension*, vol. 40, no. 5, pp. 640–646, 2002.

[8] W. C. Cushman, C. E. Ford, J. A. Cutler et al., "Success and predictors of blood pressure control in diverse North American settings: the antihypertensive and lipid-lowering treatment to prevent heart attact trial (ALLHAT)," *Journal of Clinical Hypertension*, vol. 4, no. 6, pp. 393–404, 2002.

[9] T. Hannila-Handelberg, K. Kontula, I. Tikkanen et al., "Common variants of the beta and gamma subunits of the epithelial sodium channel and their relation to plasma renin and aldosterone levels in essential hypertension," *BMC Medical Genetics*, vol. 6, article 4, 2005.

[10] R. C. Givens, Y. S. Lin, A. L. S. Dowling et al., "CYP3A5 genotype predicts renal CYP3A activity and blood pressure in healthy adults," *Journal of Applied Physiology*, vol. 95, no. 3, pp. 1297–1300, 2003.

[11] H. Ho, A. Pinto, S. D. Hall et al., "Association between the CYP3A5 genotype and blood pressure," *Hypertension*, vol. 45, no. 2, pp. 294–298, 2005.

[12] T. G. Pickering, J. E. Hall, L. J. Appel et al., "Recommendations for blood pressure measurement in humans and experimental animals—part 1: blood pressure measurement in humans—a statement for professionals from the Subcommittee of Professional and Public Education of the American Heart Association Council on high blood pressure research," *Circulation*, vol. 111, no. 5, pp. 697–716, 2005.

[13] J. J. Caro, J. L. Speckman, M. Salas, G. Raggio, and J. D. Jackson, "Effect of initial drug choice on persistence with antihypertensive therapy: the importance of actual practice data," *Canadian Medical Association Journal*, vol. 160, no. 1, pp. 41–46, 1999.

[14] G. Mazzaglia, L. G. Mantovani, M. C. J. M. Sturkenboom et al., "Patterns of persistence with antihypertensive medications in newly diagnosed hypertensive patients in Italy: a retrospective cohort study in primary care," *Journal of Hypertension*, vol. 23, no. 11, pp. 2093–2100, 2005.

[15] B. L. G. van Wijk, O. H. Klungel, E. R. Heerdink, and A. de Boer, "Rate and determinants of 10-year persistence with antihypertensive drugs," *Journal of Hypertension*, vol. 23, no. 11, pp. 2101–2107, 2005.

[16] R. P. Wildman, D. Gu, P. Muntner et al., "Alcohol intake and hypertension subtypes in Chinese men," *Journal of Hypertension*, vol. 23, no. 4, pp. 737–743, 2005.

[17] N. C. Henningsen, O. Ohlsson, I. Mattiasson, E. Trell, H. Kristensson, and B. Hood, "Hypertension, levels of serum gamma glutamyl transpeptidase and degree of blood pressure control in middle-aged males," *Acta Medica Scandinavica*, vol. 207, no. 4, pp. 245–251, 1980.

[18] J. P. Garg, W. J. Elliott, A. Folker, M. Izhar, and H. R. Black, "Resistant hypertension revisited: a comparison of two university-based cohorts," *American Journal of Hypertension*, vol. 18, no. 5, pp. 619–626, 2005.

[19] J. P. Forman, M. J. Stampfer, and G. C. Curhan, "Non-narcotic analgesic dose and risk of incident hypertension in US women," *Hypertension*, vol. 46, no. 3, pp. 500–507, 2005.

[20] C. L. Trewet and M. E. Ernst, "Resistant hypertension: identifying causes and optimizing treatment regimens," *Southern Medical Journal*, vol. 101, no. 2, pp. 166–173, 2008.

[21] D. G. Vidt, "Pathogenesis and treatment of resistant hypertension," *Minerva Medica*, vol. 94, no. 4, pp. 201–214, 2003.

[22] M. A. Brown, M. L. Buddle, and A. Martin, "Is resistant hypertension really resistant?" *American Journal of Hypertension*, vol. 14, no. 12, pp. 1263–1269, 2001.

[23] T. G. Pickering, "Arterial stiffness as a cause of resistant hypertension?" *Journal of Clinical Hypertension*, vol. 9, no. 5, pp. 390–395, 2007.

[24] J. E. Hall, "The kidney, hypertension, and obesity," *Hypertension*, vol. 41, no. 3, pp. 625–633, 2003.

[25] B. Kroon et al., "European Society of Hypertension 20th Meeting," Abstract 01, Oral Session 9D.

[26] D. A. Calhoun, "Resistant or difficult-to-treat hypertension," *Journal of Clinical Hypertension*, vol. 8, no. 3, pp. 181–186, 2006.

[27] A. V. Chobanian, G. L. Bakris, H. R. Black et al., "Seventh report of the Joint National Committee on Prevention, Detection, Evaluation, and Treatment of High Blood Pressure," *Hypertension*, vol. 42, no. 6, pp. 1206–1252, 2003.

[28] T. Young, M. Palta, J. Dempsey, J. Skatrud, S. Weber, and S. Badr, "The occurrence of sleep-disordered breathing among middle-aged adults," *New England Journal of Medicine*, vol. 328, no. 17, pp. 1230–1235, 1993.

[29] O. Olivieri, A. Ciacciarelli, D. Signorelli et al., "Aldosterone to renin ratio in a primary care setting: the Bussolengo study," *Journal of Clinical Endocrinology and Metabolism*, vol. 89, no. 9, pp. 4221–4226, 2004.

[30] A. G. Logan, S. M. Perlikowski, A. Mente et al., "High prevalence of unrecognized sleep apnoea in drug-resistant hypertension," *Journal of Hypertension*, vol. 19, no. 12, pp. 2271–2277, 2001.

[31] L. Grote, J. Hedner, and J. H. Peter, "Sleep-related breathing disorder is an independent risk factor for uncontrolled hypertension," *Journal of Hypertension*, vol. 18, no. 6, pp. 679–685, 2000.

[32] P. Lavie and V. Hoffstein, "Sleep apnea syndrome: a possible contributing factor to resistant," *Sleep*, vol. 24, no. 6, pp. 721–725, 2001.

[33] V. K. Somers, M. E. Dyken, M. P. Clary, and F. M. Abboud, "Sympathetic neural mechanisms in obstructive sleep apnea," *Journal of Clinical Investigation*, vol. 96, no. 4, pp. 1897–1904, 1995.

[34] G. Grassi, A. Facchini, F. Q. Trevano et al., "Obstructive sleep apnea-dependent and -independent adrenergic activation in obesity," *Hypertension*, vol. 46, no. 2, pp. 321–325, 2005.

[35] D. A. Calhoun, M. K. Nishizaka, M. A. Zaman, and S. M. Harding, "Aldosterone excretion among subjects with resistant hypertension and symptoms of sleep apnea," *Chest*, vol. 125, no. 1, pp. 112–117, 2004.

[36] M. N. Pratt-Ubunama, M. K. Nishizaka, R. L. Boedefeld, S. S. Cofield, S. M. Harding, and D. A. Calhoun, "Plasma aldosterone is related to severity of obstructive sleep apnea in subjects with resistant hypertension," *Chest*, vol. 131, no. 2, pp. 453–459, 2007.

[37] J. F. Setaro and H. R. Black, "Current concepts: refractory hypertension," *New England Journal of Medicine*, vol. 327, no. 8, pp. 543–547, 1992.

[38] P. J. Strollo Jr. and R. M. Rogers, "Obstructive sleep apnea," *New England Journal of Medicine*, vol. 334, no. 2, pp. 99–104, 1996.

[39] S. Douma, K. Petidis, M. Doumas et al., "Prevalence of primary hyperaldosteronism in resistant hypertension: a retrospective observational study," *The Lancet*, vol. 371, no. 9628, pp. 1921–1926, 2008.

[40] I. K. Eide, P. A. Torjesen, A. Drolsum, A. Babovic, and N. P. Lilledahl, "Low-renin status in therapy-resistant hypertension: a clue to efficient treatment," *Journal of Hypertension*, vol. 22, no. 11, pp. 2217–2226, 2004.

[41] M. Epstein, "Resistant hypertension: prevalence and evolving concepts," *Journal of Clinical Hypertension*, vol. 9, no. 1, supplement 1, pp. 2–6, 2007.

[42] M. Epstein and D. A. Calhoun, "The role of aldosterone in resistant hypertension: implications for pathogenesis and therapy," *Current Hypertension Reports*, vol. 9, no. 2, pp. 98–105, 2007.

[43] D. A. Duprez, "Aldosterone and the vasculature: mechanisms mediating resistant hypertension," *Journal of Clinical Hypertension*, vol. 9, no. 1, supplement 1, pp. 13–18, 2007.

[44] S. Engeli, J. Böhnke, K. Gorzelniak et al., "Weight loss and the renin-angiotensin-aldosterone system," *Hypertension*, vol. 45, no. 3, pp. 356–362, 2005.

[45] M. Ehrhart-Bornstein, V. Lamounier-Zepter, A. Schraven et al., "Human adipocytes secrete mineralocorticoid-releasing factors," *Proceedings of the National Academy of Sciences of the United States of America*, vol. 100, no. 2, pp. 14211–14216, 2003.

[46] L. Mosso, C. Carvajal, A. González et al., "Primary aldosteronism and hypertensive disease," *Hypertension*, vol. 42, no. 2, pp. 161–165, 2003.

[47] C. E. Fardella, L. Mosso, C. Gómez-Sánchez et al., "Primary hyperaldosteronism in essential hypertensives: prevalence, biochemical profile, and molecular biology," *Journal of Clinical Endocrinology and Metabolism*, vol. 85, no. 5, pp. 1863–1867, 2000.

[48] R. D. Gordon, M. Stowasser, T. J. Tunny, S. A. Klemm, and J. C. Rutherford, "High incidence of primary aldosteronism in 199 patients referred with hypertension," *Clinical and Experimental Pharmacology and Physiology*, vol. 21, no. 4, pp. 315–318, 1994.

[49] J. Park and V. Campese, "Clinical characteristics of resistant hypertension: the importance of compliance and the role of diagnostic evaluation in delineating pathogenesis," *Journal of Clinical Hypertension*, vol. 9, no. 1, supplement 1, pp. 7–12, 2007.

[50] V. M. Buckalew Jr., R. L. Berg, S. R. Wang, J. G. Porush, S. Rauch, and G. Schulman, "Prevalence of hypertension in 1,795 subjects with chronic renal disease: the modification of diet in renal disease study baseline cohort," *American Journal of Kidney Diseases*, vol. 28, no. 6, pp. 811–821, 1996.

[51] S. Klahr, A. S. Levey, G. J. Beck et al., "The effects of dietary protein restriction and blood-pressure control on the progression of chronic renal disease," *New England Journal of Medicine*, vol. 330, no. 13, pp. 877–884, 1994.

[52] V. M. Campese, N. Mitra, and D. Sandee, "Hypertension in renal parenchymal disease: why is it so resistant to treatment?" *Kidney International*, vol. 69, no. 6, pp. 967–973, 2006.

[53] R. A. Aqel, G. J. Zoghbi, S. A. Baldwin et al., "Prevalence of renal artery stenosis in high-risk veterans referred to cardiac catheterization," *Journal of Hypertension*, vol. 21, no. 6, pp. 1157–1162, 2003.

[54] J. J. Crowley, R. M. Santos, R. H. Peter et al., "Progression of renal artery stenosis in patients undergoing cardiac catheterization," *American Heart Journal*, vol. 136, no. 5, pp. 913–918, 1998.

[55] N. J. Ives, K. Wheatley, R. L. Stowe et al., "Continuing uncertainty about the value of percutaneous revascularization in atherosclerotic renovascular disease: a meta-analysis of randomized trials," *Nephrology Dialysis Transplantation*, vol. 18, no. 2, pp. 298–304, 2003.

[56] R. D. Safian and S. C. Textor, "Renal-artery stenosis," *New England Journal of Medicine*, vol. 344, no. 6, pp. 431–442, 2001.

[57] A. Kawashima, I. R. Francis, D. A. Baumgarten et al., *Renovascular Hypertension*, American College of Radiology, Reston, Va, USA, 2007.

[58] M. Omura, J. Saito, K. Yamaguchi, Y. Kakuta, and T. Nishikawa, "Prospective study on the prevalence of secondary hypertension among hypertensive patients visiting a general outpatient clinic in Japan," *Hypertension Research*, vol. 27, no. 3, pp. 193–202, 2004.

[59] A. M. Sinclair, C. G. Isles, I. Brown, H. Cameron, G. D. Murray, and J. W. Robertson, "Secondary hypertension in a blood pressure clinic," *Archives of Internal Medicine*, vol. 147, pp. 1289–1293, 1987.

[60] J. M. Sutton, S. G. Sheps, and J. T. Lie, "Prevalence of clinically unsuspected pheochromocytoma. Review of a 50-year autopsy series," *Mayo Clinic Proceedings*, vol. 56, no. 6, pp. 354–360, 1981.

[61] J. W. M. Lenders, G. Eisenhofer, M. Mannelli, and K. Pacak, "Phaeochromocytoma," *Lancet*, vol. 366, no. 9486, pp. 665–675, 2005.

[62] M. H. Moneva and C. E. Gomez-Sanchez, "Pathophysiology of adrenal hypertension," *Seminars in Nephrology*, vol. 22, no. 1, pp. 44–53, 2002.

[63] G. Arnaldi, T. Mancini, B. Polenta, and M. Boscaro, "Cardiovascular risk in Cushing's syndrome," *Pituitary*, vol. 7, no. 4, pp. 253–256, 2004.

[64] P. Ferrari, "Cortisol and the renal handling of electrolytes: role in glucocorticoid-induced hypertension and bone disease," *Best Practice and Research: Clinical Endocrinology and Metabolism*, vol. 17, no. 4, pp. 575–589, 2003.

[65] S. I. McFarlane, M. Banerji, and J. R. Sowers, "Insulin resistance and cardiovascular disease," *Journal of Clinical Endocrinology and Metabolism*, vol. 86, no. 2, pp. 713–718, 2001.

[66] A. Sacerdote, K. Weiss, T. Tran, B. R. Noor, and S. I. McFarlane, "Hypertension in patients with Cushing's disease: pathophysiology, diagnosis, and management," *Current Hypertension Reports*, vol. 7, no. 3, pp. 212–218, 2005.

[67] M. L. Muiesan, M. Lupia, M. Salvetti et al., "Left ventricular structural andnfunctional characteristics in Cushing's syndrome," *Journal of the American College of Cardiology*, vol. 41, no. 12, pp. 2275–2279, 2003.

[68] A. Faggiano, R. Pivonello, S. Spiezia et al., "Cardiovascular risk factors and common carotid artery caliber and stiffness in patients with Cushing's disease during active disease and 1 year after disease remission," *Journal of Clinical Endocrinology and Metabolism*, vol. 88, no. 6, pp. 2527–2533, 2003.

[69] D. P. Papadopoulos and V. Papademetriou, "Resistant hypertension: diagnosis and management," *Journal of Cardiovascular Pharmacology and Therapeutics*, vol. 11, no. 2, pp. 113–118, 2006.

[70] M. Yakovlevitch and H. R. Black, "Resistant hypertension in a tertiary care clinic," *Archives of Internal Medicine*, vol. 151, no. 9, pp. 1786–1792, 1991.

[71] R. C. Hermida, D. E. Ayala, C. Calvo et al., "Effects of time of day of treatment on ambulatory blood pressure pattern of patients with resistant hypertension," *Hypertension.*, vol. 46, no. 4, pp. 1053–1059, 2005.

[72] R. C. Hermida, D. E. Ayala, J. R. Fernández, and C. Calvo, "Chronotherapy improves blood pressure control and reverts the nondipper pattern in patients with resistant hypertension," *Hypertension*, vol. 51, no. 1, pp. 69–76, 2008.

[73] M. Moser and J. F. Setaro, "Clinical practice. Resistant or difficult-to-control hypertension," *New England Journal of Medicine*, vol. 355, no. 4, pp. 385–392, 2006.

[74] J. W. Graves, R. L. Bloomfield, and V. M. Buckalew Jr., "Plasma volume in resistant hypertension: guide to pathophysiology and therapy," *American Journal of the Medical Sciences*, vol. 298, no. 6, pp. 361–365, 1989.

[75] S. J. Taler, S. C. Textor, and J. E. Augustine, "Resistant hypertension: comparing hemodynamic management to specialist care," *Hypertension*, vol. 39, no. 5, pp. 982–988, 2002.

[76] K. A. Jamerson, G. L. Bakris, B. Dahlö et al., "Exceptional early blood pressure control rates: the ACCOMPLISH trial," *Blood Pressure*, vol. 16, no. 2, pp. 80–86, 2007.

[77] H. R. Black, W. J. Elliott, G. Grandits et al., "Principal results of the controlled onset verapamil investigation of cardiovascular end points (CONVINCE) trial," *Journal of the American Medical Association*, vol. 289, no. 16, pp. 2073–2082, 2003.

[78] M. E. Ernst, B. L. Carter, C. J. Goerdt et al., "Comparative antihypertensive effects of hydrochlorothiazide and chlorthalidone on ambulatory and office blood pressure," *Hypertension*, vol. 47, no. 3, pp. 352–358, 2006.

[79] N. Khosla, D. Y. Chua, W. J. Elliott, and G. L. Bakris, "Are chlorthalidone and hydrochlorothiazide equivalent blood-pressure-lowering medications?" *Journal of Clinical Hypertension*, vol. 7, no. 6, pp. 354–356, 2005.

[80] P. A. Sarafidis and G. L. Bakris, "State of hypertension management in the United States: confluence of risk factors and the prevalence of resistant hypertension," *Journal of Clinical Hypertension*, vol. 10, no. 2, pp. 130–139, 2008.

[81] H. L. Vlase, G. Panagopoulos, and M. F. Michelis, "Effectiveness of furosemide in uncontrolled hypertension in the elderly: role of renin profiling," *American Journal of Hypertension*, vol. 16, no. 3, pp. 187–193, 2003.

[82] P. A. Sarafidis, "Proteinuria: natural course, prognostic implications and therapeutic considerations," *Minerva Medica*, vol. 98, no. 6, pp. 693–711, 2007.

[83] M. K. Nishizaka, M. A. Zaman, and D. A. Calhoun, "Efficacy of low-dose spironolactone in subjects with resistant hypertension," *American Journal of Hypertension*, vol. 16, no. 11 I, pp. 925–930, 2003.

[84] A. B. Alper Jr. and D. A. Calhoun, "Contemporary management of refractory hypertension," *Current hypertension reports*, vol. 1, no. 5, pp. 402–407, 1999.

[85] M. K. Nishizaka and D. A. Calhoun, "The role of aldosterone antagonists in the management of resistant hypertension," *Current Hypertension Reports*, vol. 7, no. 5, pp. 343–347, 2005.

[86] E. Pimenta, K. K. Gaddam, and S. Oparil, "Mechanisms and treatment of resistant hypertension," *Journal of Clinical Hypertension*, vol. 10, no. 3, pp. 239–244, 2008.

[87] D. A. Lane and D. G. Beevers, "Amiloride 10 mg is less effective than spironolactone 25 mg in patients with hypertension resistant to a multidrug regime including an angiotensin-blocking agent," *Journal of Hypertension*, vol. 25, no. 12, pp. 2515–2516, 2007.

[88] J. M. Dora, C. K. Kramer, and L. H. Canani, "Standards of medical care in diabetes—2008: response to Hirsch, Inzucchi, and Kirkman," *Diabetes Care*, vol. 31, no. 5, article e45, 2008.

[89] S. Yusuf, K. K. Teo, J. Pogue et al., "Telmisartan, ramipril, or both in patients at high risk for vascular events," *New England Journal of Medicine*, vol. 358, no. 15, pp. 1547–1559, 2008.

[90] M. A. Pfeffer, J. J. V. McMurray, E. J. Velazquez et al., "Valsartan, captopril, or both in myocardial infarction complicated by heart failure, left ventricular dysfunction, or both," *New England Journal of Medicine*, vol. 349, no. 20, pp. 1893–1906, 2003.

[91] S. D. Solomon, E. Appelbaum, W. J. Manning et al., "Effect of the direct renin inhibitor aliskiren, the angiotensin receptor blocker losartan, or both on left ventricular mass in patients with hypertension and left ventricular hypertrophy," *Circulation*, vol. 119, no. 4, pp. 530–537, 2009.

[92] H. H. Parving, F. Persson, J. B. Lewis, E. J. Lewis, and N. K. Hollenberg, "Aliskiren combined with losartan in type 2 diabetes and nephropathy," *New England Journal of Medicine*, vol. 358, no. 23, pp. 2433–2446, 2008.

[93] K. Jamerson, M. A. Weber, G. L. Bakris et al., "Benazepril plus amlodipine or hydrochlorothiazide for hypertension in high-risk patients," *New England Journal of Medicine*, vol. 359, no. 23, pp. 2417–2428, 2008.

[94] J. J. Saseen, B. L. Carter, T. E. R. Brown, W. J. Elliott, and H. R. Black, "Comparison of nifedipine alone and with diltiazem or verapamil in hypertension," *Hypertension*, vol. 28, no. 1, pp. 109–114, 1996.

[95] C. N. Gashti and G. L. Bakris, "The role of calcium antagonists in chronic kidney disease," *Current Opinion in Nephrology and Hypertension*, vol. 13, no. 2, pp. 155–161, 2004.

[96] S. J. Mann, "Combined alpha/beta-blockade: an underused approach to the treatment of resistant hypertension," *Journal of Clinical Hypertension*, vol. 9, no. 9, pp. 663–666, 2007.

[97] D. A. Sica, "Minoxidil: an underused vasodilator for resistant or severe hypertension," *Journal of Clinical Hypertension*, vol. 6, no. 5, pp. 283–287, 2004.

[98] H. R. Black, G. L. Bakris, M. A. Weber et al., "Efficacy and safety of darusentan in patients with resistant hypertension: results from a randomized, double-blind, placebo-controlled dose-ranging study," *Journal of Clinical Hypertension*, vol. 9, no. 10, pp. 760–769, 2007.

[99] R. Nakov, E. Pfarr, and S. Eberle, "Darusentan: an effective endothelin receptor antagonist for treatment of hypertension," *American Journal of Hypertension*, vol. 15, no. 7, part 1, pp. 583–589, 2002.

[100] M. P. Schlaich, H. Krum, and M. D. Esler, "New therapeutic approaches to resistant hypertension," *Current Hypertension Reports*, vol. 12, no. 4, pp. 296–302, 2010.

[101] E. Raichlin, A. Prasad, V. Mathew et al., "Efficacy and safety of atrasentan in patients with cardiovascular risk and early atherosclerosis," *Hypertension*, vol. 52, no. 3, pp. 522–528, 2008.

[102] J. B. Kostis, M. Packer, H. R. Black, R. Schmieder, D. Henry, and E. Levy, "Omapatrilat and enalapril in patients with hypertension: the Omapatrilat Cardiovascular Treatment vs. Enalapril (OCTAVE) trial," *American Journal of Hypertension*, vol. 17, no. 2, pp. 103–111, 2004.

[103] M. J. Brown, J. Coltart, K. Gunewardena, J. M. Ritter, T. R. Auton, and J. F. Glover, "Randomized double-blind placebo-controlled study of an angiotensin immunotherapeutic vaccine (PMD3117) in hypertensive subjects," *Clinical Science*, vol. 107, no. 2, pp. 167–173, 2004.

[104] P. M. Ambühl, A. C. Tissot, A. Fulurija et al., "A vaccine for hypertension based on virus-like particles: preclinical efficacy and phase I safety and immunogenicity," *Journal of Hypertension*, vol. 25, no. 1, pp. 63–72, 2007.

[105] L. A. Sanchez, K. Illig, M. Levy et al., "Implantable carotid sinus stimulator for the treatment of resistant hypertension: local effects on carotid artery morphology," *Annals of Vascular Surgery*, vol. 24, no. 2, pp. 178–184, 2010.

[106] V. M. Campese and E. Kogosov, "Renal afferent denervation prevents hypertension in rats with chronic renal failure," *Hypertension*, vol. 25, no. 4, part 2, pp. 878–882, 1995.

[107] V. M. Campese, E. Kogosov, and M. Koss, "Renal afferent denervation prevents the progression of renal disease in the renal ablation model of chronic renal failure in the rat," *American Journal of Kidney Diseases*, vol. 26, no. 5, pp. 861–865, 1995.

[108] H. Krum, M. Schlaich, R. Whitbourn et al., "Catheter-based renal sympathetic denervation for resistant hypertension: a multicentre safety and proof-of-principle cohort study," *The Lancet*, vol. 373, no. 9671, pp. 1275–1281, 2009.

[109] M. P. Schlaich, P. A. Sobotka, H. Krum, E. Lambert, and M. D. Esler, "Renal sympathetic-nerve ablation for uncontrolled hypertension," *New England Journal of Medicine*, vol. 361, no. 9, pp. 932–934, 2009.