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

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AHA Scientific Statement

Resistant Hypertension: Diagnosis, Evaluation, and Treatment

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David A. Calhoun, MD, FAHA, Chair; Daniel Jones, MD, FAHA; Stephen Textor, MD, FAHA; David C. Goff, MD, FAHA; Timothy P. Murphy, MD, FAHA; Robert D. Toto, MD, FAHA; Anthony White, PhD; William C. Cushman, MD, FAHA; William White, MD; Domenic Sica, MD, FAHA; Keith Ferdinand, MD; Thomas D. Giles, MD; Bonita Falkner, MD, FAHA; Robert M. Carey, MD, MACP, FAHA

Abstract—Resistant hypertension is a common clinical problem faced by both primary care clinicians and specialists. While the exact prevalence of resistant hypertension is unknown, clinical trials suggest that it is not rare, involving perhaps 20% to 30% of study participants. As older age and obesity are 2 of the strongest risk factors for uncontrolled hypertension, the incidence of resistant hypertension will likely increase as the population becomes more elderly and heavier. The prognosis of resistant hypertension is unknown, but cardiovascular risk is undoubtedly increased as patients often have a history of long-standing, severe hypertension complicated by multiple other cardiovascular risk factors such as obesity, sleep apnea, diabetes, and chronic kidney disease. The diagnosis of resistant hypertension requires use of good blood pressure technique to confirm persistently elevated blood pressure levels. Pseudoresistance, including lack of blood pressure control secondary to poor medication adherence or white coat hypertension, must be excluded. Resistant hypertension is almost always multifactorial in etiology. Successful treatment requires identification and reversal of lifestyle factors contributing to treatment resistance; diagnosis and appropriate treatment of secondary causes of hypertension; and use of effective multidrug regimens. As a subgroup, patients with resistant hypertension have not been widely studied. Observational assessments have allowed for identification of demographic and lifestyle characteristics associated with resistant hypertension, and the role of secondary causes of hypertension in promoting treatment resistance is well documented; however, identification of broader mechanisms of treatment resistance is lacking. In particular, attempts to elucidate potential genetic causes of resistant hypertension have been limited. Recommendations for the pharmacological treatment of resistant hypertension remain largely empiric due to the lack of systematic assessments of 3 or 4 drug combinations. Studies of resistant hypertension are limited by the high cardiovascular risk of patients within this subgroup, which generally precludes safe withdrawal of medications; the presence of multiple disease processes (eg, sleep apnea, diabetes, chronic kidney disease, atherosclerotic disease) and their associated medical therapies, which confound interpretation of study results; and the difficulty in enrolling large numbers of study participants. Expanding our understanding of the causes of resistant hypertension and thereby potentially allowing for more effective prevention and/or treatment will be essential to improve the long-term clinical management of this disorder. (***Hypertension.*** **2008;51:000-000.)**

Key Words: AHA Scientific Statements ■ hypertension ■ blood pressure

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Resistant hypertension is defined as blood pressure that remains above goal in spite of the concurrent use of 3 antihypertensive agents of different classes. Ideally, one of the 3 agents should be a diuretic and all agents should be prescribed at optimal dose amounts. Although arbitrary in regard to the number of medications required, resistant hypertension is thus defined in order to identify patients who are at high risk of having reversible causes of hypertension and/or patients who, because of persistently high blood pressure levels, may benefit from special diagnostic and therapeutic considerations. As defined, resistant hypertension includes patients whose blood pressure is controlled with use of more than 3 medications. That is, patients whose blood pressure is controlled but require 4 or more medications to do so should be considered resistant to treatment.

Prevalence

The prevalence of resistant hypertension is unknown. Cross-sectional studies and hypertension outcome studies suggest, however, that it is not uncommon. In a recent analysis of National Health and Nutrition Examination Survey (NHANES) participants being treated for hypertension, only 53% were controlled to <140/90 mm Hg.[1] In a cross-sectional analysis of Framingham Heart Study participants, only 48% of treated participants were controlled to <140/90 mm Hg and less than 40% of elderly participants (>75 years of age) were at a goal blood pressure.[2] Among higher-risk populations and, in particular, with application of the lower goal blood pressures recommended in the Seventh Report of the Joint National Committee on Prevention, Detection, Evaluation, and Treatment of High Blood Pressure (JNC 7) for patients with diabetes mellitus or chronic kidney disease (CKD), the proportion of uncontrolled patients is even higher. Of NHANES participants with chronic kidney disease, only 37% were controlled to <130/80 mm Hg[3] and only 25% of participants with diabetes were controlled to <130/85 mm Hg.[1]

Uncontrolled hypertension is not synonymous with resistant hypertension. The former includes patients who lack blood pressure control secondary to poor adherence and/or an inadequate treatment regimen, as well as those with true treatment resistance. To accurately determine the prevalence of resistant hypertension, a forced titration study of a large, diverse hypertensive cohort would be required. Such a study has not been done, but recent hypertension outcome studies offer an alternative as medications in these studies were usually provided at no charge, adherence was closely monitored, and titration of medications was dictated per protocol. In this regard, the Antihypertensive and Lipid-Lowering Treatment to Prevent Heart Attack Trial (ALLHAT) may be the most relevant as it included a large number of ethnically diverse participants (>33 000): 47% female, 35% African American, 19% Hispanic, and 36% with diabetes.[4]

In ALLHAT, after approximately 5 years of follow-up, 34% of participants remained uncontrolled on an average of 2 medications.[5] At the study's completion, 27% of participants were on 3 or more medications. Overall, 49% of ALLHAT participants were controlled on 1 or 2 medications, meaning that approximately 50% of participants would have needed 3 or more blood pressure medications. This percentage, however, may underestimate the degree of treatment resistance relative to the general hypertensive population, as patients with a history of difficult-to-treat hypertension (needing more than 2 medications to achieve a blood pressure of <160/100 mm Hg) were precluded from enrolling in ALLHAT. Conversely, this percentage might overestimate the prevalence of resistant hypertension as a consequence of the restricted treatment regimens allowed in ALLHAT. Combined use of any 2 of the following classes of medications was discouraged: thiazide-type diuretics, angiotensin-converting enzyme (ACE) inhibitors, calcium channel blockers, and α adrenergic receptor antagonists. Such combinations account for a substantial proportion of current clinical practice.

Prognosis

The prognosis of patients with resistant hypertension compared with patients with more easily controlled hypertension has not been specifically evaluated. Presumably, prognosis is impaired as such patients typically present with a long-standing history of poorly controlled hypertension and commonly have associated cardiovascular risk factors such as diabetes, obstructive sleep apnea, left ventricular hypertrophy (LVH), and/or CKD. The degree to which cardiovascular risk is reduced with treatment of resistant hypertension is unknown. The benefits of successful treatment, however, are likely substantial as suggested by hypertension outcome studies in general and by the early Veterans Administration cooperative studies, which demonstrated a 96% reduction in cardiovascular events over 18 months with use of triple antihypertensive regimens compared with placebo in patients with severe hypertension (diastolic blood pressure 115 to 129 mm Hg).[6] How much of this benefit occurs with successful treatment of resistant hypertension is unknown.

Patient Characteristics

Blood pressure remains uncontrolled most often because of persistent elevations in systolic blood pressure. Among Framingham participants being treated for hypertension, 90% had achieved a diastolic blood pressure goal of <90 mm Hg, while only 49% were at a systolic blood pressure goal of <140 mm Hg.[2] This disparity in systolic versus diastolic blood pressure control worsened with increasing age such that systolic control rates exceeded 60% for younger participants (≤60 years) but was <40% in older subjects (>75 years). Prospectively, ALLHAT demonstrated a similar difficulty in controlling systolic blood pressure in that only 67% of the participants had their systolic blood pressure lowered to <140 mm Hg, whereas 92% of participants achieved a goal diastolic blood pressure of <90 mm Hg.[5]

In an analysis of Framingham study data, the strongest predictor of lack of blood pressure control was older age, with participants >75 years being less than one fourth as likely to have systolic blood pressure controlled compared with participants ≤60 years of age.[2] The next strongest predictors of lack of systolic blood pressure control were the presence of

Table 1. Patient Characteristics Associated With Resistant Hypertension

Older age
High baseline blood pressure
Obesity
Excessive dietary salt ingestion
Chronic kidney disease
Diabetes
Left ventricular hypertrophy
Black race
Female sex
Residence in southeastern United States

LVH and obesity (body mass index [BMI] >30 kg/m^2) (Table 1). In terms of diastolic blood pressure control, the strongest negative predictor was obesity, with blood pressure being controlled about one third less often compared with lean participants (BMI <25 kg/m^2). In a prospective analysis of Framingham participants, in addition to older age, higher baseline systolic blood pressure was associated with increased risk of never reaching goal blood pressure.[7]

In ALLHAT, older age, higher baseline systolic blood pressure, LVH, and obesity all predicted treatment resistance as defined by needing 2 or more antihypertensive medications.[5] Overall, the strongest predictor of treatment resistance was having CKD as defined by a serum creatinine of ≥1.5 mg/dL. Other predictors of the need for multiple medications included having diabetes mellitus and living in the southeastern United States. African-American participants had more treatment resistance, as did women, such that black women had the lowest control rate (59%) and non-black men the highest (70%).

Although the exact prevalence is unknown, the above studies indicate that resistant hypertension is a common clinical problem. Further, with a progressively older and heavier population in association with an increasing incidence of diabetes and CKD, the prevalence of resistant hypertension can be anticipated to increase.

Genetics/Pharmacogenetics

As resistant hypertension represents an extreme phenotype, it seems reasonable to predict that genetic factors may play a greater role than in the general hypertensive population. However, genetic assessments of patients with resistant hypertension are limited. In one of the few genetic evaluations of patients with resistant hypertension, investigators in Finland screened 347 patients with resistant hypertension for mutations of the β and γ subunits of the epithelial sodium channel (ENaC).[8] Mutations of these subunits can cause Liddle's syndrome, a rare monogenic form of hypertension. Compared with normotensive controls, 2 β ENaC and γ ENaC gene variants were significantly more prevalent in the patients with resistant hypertension. The presence of the gene variants was associated with increased urinary potassium excretion relative to plasma renin levels but was not related to baseline plasma aldosterone or plasma renin activity. In addition, when inserted into *Xenopus* oocytes, the most commonly used expression system for ENaC functional studies, the gene variants did not show a significant difference in activity compared with ENaC wild-type, arguing against clinically meaningful effects for these mutations.

The CYP3A5 enzyme (11β-hydroxysteroid dehydrogenase type 2) plays an important role in the metabolism of cortisol and corticosterone, particularly in the kidney. A particular CYP3A5 allele (CYP3A5*1) has been associated in African-American patients with higher systolic blood pressure levels in normotensive participants[9] and hypertension more resistant to treatment.[10] Although based on a very small number of patients, these results are provocative and support additional attempts to identify genotypes that may relate to treatment resistance. Identification of genetic influences on resistance to current therapies might also lead to development of new therapeutic targets.

Pseudoresistance

Poor Blood Pressure Technique

Inaccurate measurement of blood pressure can result in the appearance of treatment resistance. Two of the most common mistakes—measuring the blood pressure before letting the patient sit quietly and use of too small a cuff—will result in falsely high blood pressure readings.[11] Although the degree to which inaccurate measurement of blood pressure results in falsely labeling patients as having uncontrolled hypertension is unknown, assessments of office blood pressure measurement technique suggest that it is likely a common clinical problem.[11]

Poor Adherence

Poor adherence to antihypertensive therapy is a major cause of lack of blood pressure control.[12] Retrospective analyses indicate that approximately 40% of patients with newly diagnosed hypertension will discontinue their antihypertensive medications during the first year of treatment.[13,14] During 5 to 10 years of follow-up, less than 40% of patients may persist with their prescribed antihypertensive treatment.[13,15] While poor adherence is common at the primary care level, it may be less common among patients who are seen by specialists. In a retrospective analysis at a hypertension specialty clinic, it was estimated that poor adherence was a significant contributing factor to the lack of blood pressure control in only 16% of evaluated patients.[16]

Lack of blood pressure control is distinct from treatment resistance. For an antihypertensive regimen to have failed, it has to have been taken correctly. This distinction is clinically important as patients with poorly controlled hypertension secondary to lack of adherence need not be subjected to the evaluations and continued manipulations in treatment regimens that are undertaken for patients with true treatment resistance.

White-Coat Effect

Studies indicate that a significant white-coat effect (when clinic blood pressures are persistently elevated while out-of-

office values are normal or significantly lower) is as common in patients with resistant hypertension as in the more general hypertensive population, with a prevalence in the range of 20% to 30%.[17,18] Also, as with more general hypertensive patients, patients with resistant hypertension on the basis of a "white coat" phenomenon manifest less severe target organ damage and appear to be at less cardiovascular risk compared with those patients with persistent hypertension during ambulatory monitoring.[19–21]

Lifestyle Factors

Obesity

Obesity is associated with more severe hypertension, a need for an increased number of antihypertensive medications, and an increased likelihood of never achieving blood pressure control.[5,22] As a consequence, obesity is a common feature of patients with resistant hypertension.[23] Mechanisms of obesity-induced hypertension are complex and not fully elucidated but include impaired sodium excretion, increased sympathetic nervous system activity, and activation of the renin-angiotensin-aldosterone system.[24]

Dietary Salt

Excessive dietary sodium intake contributes to the development of resistant hypertension both through directly increasing blood pressure and by blunting the blood pressure–lowering effect of most classes of antihypertensive agents.[25–27] These effects tend to be more pronounced in typical salt-sensitive patients, including the elderly, African Americans, and, in particular, patients with CKD.[28] Although excessive dietary sodium is fairly widespread, it has been specifically documented as being common in patients with resistant hypertension. In an analysis of patients referred to a university hypertension center for resistant hypertension, average dietary salt ingestion based on 24-hour urinary sodium excretion exceeded 10 g a day.[23]

Alcohol

Heavy alcohol intake is associated with both an increased risk of hypertension, as well as treatment-resistant hypertension. In a cross-sectional analysis of Chinese adults ingesting ≥30 drinks a week, the risk of having various forms of hypertension increased from 12% to 14%.[29] In a Finnish hypertension clinic, heavy drinkers, as suggested by increases in liver transaminase levels, were much less likely to have their blood pressure controlled during a 2-year follow-up compared with patients with normal transaminase levels.[30] Prospectively, cessation of heavy alcohol ingestion by a small group of patients reduced 24-hour ambulatory systolic blood pressure by 7.2 mm Hg and diastolic blood pressure by 6.6 mm Hg while dropping the prevalence of hypertension from 42% to 12%.[31]

Drug-Related Causes

Several classes of pharmacological agents can increase blood pressure and contribute to treatment resistance (Table 2). The effects of these agents, however, can be highly individualized, with most persons manifesting little or no effect, while other individuals may experience severe elevations in blood pressure.

Table 2. Medications That Can Interfere With Blood Pressure Control

Nonnarcotic analgesics
Nonsteroidal antiinflammatory agents, including aspirin
Selective COX-2 inhibitors
Sympathomimetic agents (decongestants, diet pills, cocaine)
Stimulants (methylphenidate, dexmethylphenidate, dextroamphetamine, amphetamine, methamphetamine, modafinil)
Alcohol
Oral contraceptives
Cyclosporine
Erythropoietin
Natural licorice
Herbal compounds (ephedra or ma huang)

Given their widespread use, nonnarcotic analgesics, including nonsteroidal antiinflammatory agents (NSAIDs), aspirin, and acetaminophen, are probably the most common offending agents in terms of worsening blood pressure control.[32,33] NSAIDs, in particular, are associated with modest but predictable increases in blood pressure. Meta-analyses of the effects of NSAIDs have indicated average increases in mean arterial pressure of approximately 5.0 mm Hg.[34] Additional studies indicate that NSAIDs can blunt the blood pressure–lowering effect of several antihypertensive medication classes, including diuretics, ACE inhibitors, angiotensin receptor blockers (ARBs), and β-blockers.[35,36] Similar effects have been described with the selective cyclooxygenase-2 (COX-2) inhibitors.[37,38]

Although NSAIDs have an overall modest effect on blood pressure levels, in susceptible individuals significant fluid retention, increases in blood pressure, and/or acute kidney disease may occur. These effects presumably occur secondary to inhibition of renal prostaglandin production, especially prostaglandin E_2 and prostaglandin I_2, with subsequent sodium and fluid retention. Elderly patients, diabetics, and patients with CKD are at increased risk of manifesting these adverse effects.

Other medication classes that may worsen blood pressure control include sympathomimetic compounds such as decongestants and certain diet pills, amphetamine-like stimulants, modafinil[39], and oral contraceptives. Glucocorticoids, such as prednisone, induce sodium and fluid retention and can result in significant increases in blood pressure. Corticosteroids with the greatest mineralocorticoid effect (eg, cortisone, hydrocortisone) produce the greatest amount of fluid retention, but even agents without mineralocorticoid activity (eg, dexamethasone, triamcinolone, betamethasone) produce some fluid retention. Herbal preparations containing ephedra (or ma huang) have been associated with worsening blood pressure.[40,41] Licorice, a

Table 3. Secondary Causes of Resistant Hypertension

Common
Obstructive sleep apnea
Renal parenchymal disease
Primary aldosteronism
Renal artery stenosis
Uncommon
Pheochromocytoma
Cushing's disease
Hyperparathyroidism
Aortic coarctation
Intracranial tumor

common ingredient in oral tobacco products, can raise blood pressure by suppressing the metabolism of cortisol, resulting in increased stimulation of the mineralocorticoid receptor.[42,43] In anemic patients with CKD, erythropoietic agents may increase blood pressure in both normotensive and hypertensive patients.

Secondary Causes

Secondary causes of hypertension are common in patients with resistant hypertension, although the overall prevalence is unknown (Table 3). The likelihood of a readily definable secondary cause of hypertension is greater in older patients because of a greater prevalence of sleep apnea, renal parenchymal disease, renal artery stenosis, and possibly primary aldosteronism.[44–46] Uncommon secondary causes of hypertension include pheochromocytoma, Cushing's syndrome, hyperparathyroidism, aortic coarctation, and intracranial tumors.

Obstructive Sleep Apnea

Untreated obstructive sleep apnea is strongly associated with hypertension and in normotensive persons predicts development of hypertension.[47,48] Sleep apnea is particularly common in patients with resistant hypertension. In an evaluation of 41 consecutive patients (24 men, 17 women) with treatment-resistant hypertension, 83% were diagnosed with unsuspected sleep apnea based on an apnea-hypopnea index $\geq$10 events/h.[49] There was a significant gender difference, with sleep apnea being both more common and more severe in the men compared with women patients. Cross-sectional studies indicate that the more severe the sleep apnea, the less likely blood pressure is controlled despite the use of an increasing number of medications.[50,51]

The mechanisms by which sleep apnea contributes to the development of hypertension have not been fully elucidated. A well-described effect is that the intermittent hypoxemia, and/or increased upper airway resistance associated with sleep apnea, induces a sustained increase in sympathetic nervous system (SNS) activity.[52,53] Increases in SNS output would be expected to raise blood pressure through increases in cardiac output and peripheral resistance as well as by increased fluid retention. In addition, sleep apnea has been associated with increases in reactive oxygen species with concomitant reductions in nitric oxide bioavailability.[54,55]

Primary Aldosteronism

Recent studies indicate that primary aldosteronism is a much more common cause of hypertension than had been demonstrated historically. In an evaluation of more than 600 patients with hypertension, the prevalence of primary hyperaldosteronism was found to be 6.1%.[56] In this study, the prevalence of primary aldosteronism varied according to the underlying severity of hypertension, with a prevalence of 13% among patients with severe hypertension (>180/110 mm Hg). Importantly from a clinical standpoint, in this study and others documenting a high prevalence of primary aldosteronism, serum potassium levels were rarely low in patients confirmed to have primary aldosteronism, suggesting that hypokalemia is a late manifestation of the disorder preceded by the development of hypertension.[56–58]

Primary aldosteronism is common in patients with resistant hypertension with a prevalence of approximately 20%. In an evaluation of patients referred to a hypertension specialty clinic, investigators at the University of Alabama at Birmingham found that 18 of 88, or 20%, consecutively evaluated patients with resistant hypertension were diagnosed with primary aldosteronism based on a suppressed renin activity and a high 24-hour urinary aldosterone excretion in the course of a high dietary sodium intake.[59] The prevalence of primary aldosteronism was similar in African-American and white patients. In a study conducted in Seattle, Washington, primary aldosteronism was diagnosed in 17% of patients with resistant hypertension.[60] Similarly, investigators in Oslo, Norway, have reported confirming primary aldosteronism in 23% of patients with resistant hypertension.[61]

As in the general hypertensive population, the stimulus for the aldosterone excess in patients with resistant hypertension has not been identified. Generalized activation of the renin-angiotensin-aldosterone system has been described with obesity, while other studies suggest that adipocytes may release secretagogues that stimulate aldosterone release independent of angiotensin-II.[62–64] In addition, preliminary results relate aldosterone excess to sleep apnea in patients with resistant hypertension.[65] Although cause-and-effect has not been confirmed, these studies suggest that the increased occurrence of primary aldosteronism may be linked to the increasing incidence of obesity.

Pheochromocytoma

Pheochromocytoma represents a small but important fraction of secondary causes of resistant hypertension. The prevalence of pheochromocytoma is 0.1% to 0.6% of hypertensives in a general ambulatory population.[66,67] The exact prevalence of pheochromocytoma as a cause of resistant hypertension is unknown, but the literature is replete with case reports of malignant and difficult-to-control hypertension secondary to pheochromocytoma. Although the clinical presentation of pheochromocytoma is highly variable, approximately 95% of patients demon-

strate hypertension and 50% have sustained hypertension.[68] Furthermore, pheochromocytoma is characterized by increased blood pressure variability,[69] which constitutes an additional independent risk factor beyond increased blood pressure itself for cardiovascular morbidity and mortality.[70,71] The occurrence of a sustained increase and the degree of blood pressure variability are both related to the level of norepinephrine secretion by the tumor.[72]

Despite improved diagnostic techniques that can reduce the time to specific identification of pheochromocytoma in a hypertensive patient, there remains an average of 3 years between the initial symptoms and final diagnosis.[73] Many cases of pheochromocytoma are missed altogether based on autopsy studies in which the tumors contributed to 55% of the deaths and were not suspected in 75% of cases.[74]

The diagnosis of pheochromocytoma should be entertained in a hypertensive patient with a combination of headaches, palpitations, and sweating, typically occurring in an episodic fashion, with a diagnostic specificity of 90%.[75] The best screening test for pheochromocytoma is plasma free metanephrines (normetanephrine and metanephrine), which carries a 99% sensitivity and an 89% specificity.[75]

Cushing's Syndrome

Hypertension is present in 70% to 90% of patients with Cushing's syndrome.[76] Although the main mechanism of hypertension in Cushing's syndrome is overstimulation of the nonselective mineralocorticoid receptor by cortisol,[77] other factors such as sleep apnea and the insulin resistance syndrome are major contributors to hypertension in this disease.[78,79]

Although the exact prevalence of resistant hypertension in patients with Cushing's syndrome is unknown, one group found that 17% had severe hypertension.[80] Furthermore, it is well documented that target organ damage in Cushing's syndrome is more severe than in primary hypertension.[81] The overall cardiovascular risk in Cushing's syndrome is substantial because the disorder is associated with other major risk factors such as diabetes mellitus, the metabolic syndrome, sleep apnea, obesity, and dyslipidemia, in addition to hypertension.[82]

Because the pathogenesis of hypertension in Cushing's syndrome involves activation of mineralocorticoid receptors, the usual antihypertensive agents employed in treating primary hypertension (renin-angiotensin system blockers, calcium channel antagonists, adrenergic blockers, diuretics) may not be effective in lowering blood pressure to goal.[79] Surgical excision of an adrenocorticotropic hormone (ACTH)—or cortisol-producing tumor—effectively lowers blood pressure.[79] The most effective antihypertensive pharmacological agent in Cushing's syndrome is a mineralocorticoid receptor antagonist (spironolactone or eplerenone).[79]

Renal Parenchymal Disease

CKD is both a common cause and complication of poorly controlled hypertension.[83,84] Recent studies reviewing 16 589 participants in the NHANES indicate that 3% of the population have increased serum creatinine above 1.6 mg/dL, corresponding to more than 5.6 million of the general population.[85] Most of this population was receiving antihypertensive drug therapy (75%), but achievement of current goal levels (<130/85 mm Hg) was uncommon. In a recent cross-sectional analysis of patients with CKD being followed in nephrology clinics, less than 15% had their blood pressure controlled to <130/80 mm Hg despite of the use on average of 3 different antihypertensive agents.[86] In ALLHAT, CKD as indicated by a serum creatinine of >1.5 mg/dL was a strong predictor of failure to achieve goal blood pressure.[5] Treatment resistance in patients with CKD is undoubtedly related in large part to increased sodium and fluid retention and consequential intravascular volume expansion.

Renal Artery Stenosis

Renovascular disease is a common finding in hypertensive patients undergoing cardiac catheterization, with more than 20% of patients having unilateral or bilateral stenoses (with a degree of obstruction ≥70%).[87] Unknown, however, is the role of such lesions in causing hypertension. Studies of treatment-resistant hypertension commonly reveal a high prevalence of previously unrecognized renovascular disease, particularly in older patient groups.[45,88] The former series suggested that 12.7% of patients ≥50 years of age referred to a hypertension center had a secondary cause of hypertension, the most common of which (35%) was renovascular disease. A large experience with both surgical and endovascular revascularization indicates that some patients with renovascular disease experience improved blood pressure control after correction of renal artery stenosis, although randomized clinical trials in general have not shown convincing benefit in regard to improvement in renal function or blood pressure control.[89,90]

More than 90% of renal artery stenoses are atherosclerotic in origin.[91] The likelihood of atherosclerotic renal artery stenosis is increased in older patients; in smokers; in patients with known atherosclerotic disease, especially peripheral arterial disease; and in patients with unexplained renal insufficiency. Bilateral renal artery stenoses should be suspected in patients with a history of "flash" or episodic pulmonary edema, especially when echocardiography indicates preserved systolic heart function. Less than 10% of renal lesions are fibromuscular in etiology developing most commonly in women, <50 years of age.

Renal artery stenosis can be difficult to identify with any certainty using noninvasive studies. Duplex ultrasound, magnetic resonance angiography (MRA), renal scintigraphy, and computed tomography (CT) angiography have good test characteristics in published studies,[92] but the true positive and negative predictive value will vary both with the populations at risk and the level of expertise at each institution. Negative imaging studies warrant additional examinations for patients in whom there is a high level of clinical suspicion and for whom renal revascularization is being seriously considered. MRA is highly sensitive for stenosis, but the specificity can be low, and minimal lesions are often characterized as moderate or high grade.[93]

Diabetes

Diabetes and hypertension are commonly associated, particularly in patients with difficult-to-control hypertension. In ALLHAT, diabetes predicted lack of blood pressure control during the course of the study.[5] Clinical trials have indicated that in order to achieve the lower blood pressure goal recommended for patients with diabetes, an average range of 2.8 to 4.2 antihypertensive medications will be needed.[94] The degree to which insulin resistance directly contributes to the development of hypertension versus simply being associated with hypertension because of common underlying causes has not been determined. Pathophysiologic effects attributed to insulin resistance that may contribute to worsening hypertension include increased sympathetic nervous activity, vascular smooth muscle cell proliferation, and increased sodium retention.

Evaluation

The evaluation of patients with resistant hypertension should be directed toward confirming true treatment resistance; identification of causes contributing to treatment resistance, including secondary causes of hypertension; and documentation of target-organ damage (Figure). Accurate assessment of treatment adherence and use of good blood pressure measurement technique is required to exclude pseudoresistance. In most cases, treatment resistance is multifactorial in etiology with obesity, excessive dietary sodium intake, obstructive sleep apnea, and CKD being particularly common factors. Target-organ damage such as retinopathy, CKD, and LVH supports a diagnosis of poorly controlled hypertension and in the case of CKD will influence treatment in terms of classes of agents selected as well as establishing a blood pressure goal of <130/80 mm Hg.[95]

Medical History

The medical history should document duration, severity, and progression of the hypertension; treatment adherence; response to prior medications, including adverse events; current medication use, including herbal and over-the-counter medications; and symptoms of possible secondary causes of hypertension. Daytime sleepiness, loud snoring, and witnessed apnea are suspicious for sleep apnea. A history of peripheral or coronary atherosclerotic disease increases the likelihood of renal artery stenosis. Labile hypertension, in association with palpitations and/or diaphoresis, suggests the possibility of pheochromocytoma.

Assessment of Adherence

Ultimately, adherence in a clinical setting can only be known by patient self-report. Patients should be specifically asked, in a nonjudgmental fashion, how successful they are in taking all of their prescribed doses, including discussion of adverse effects, out-of-pocket costs, and dosing inconvenience, all of which can limit adherence. Family members will often provide more objective assessments of a patient's adherence, but such input should generally be solicited in the presence of the patient.

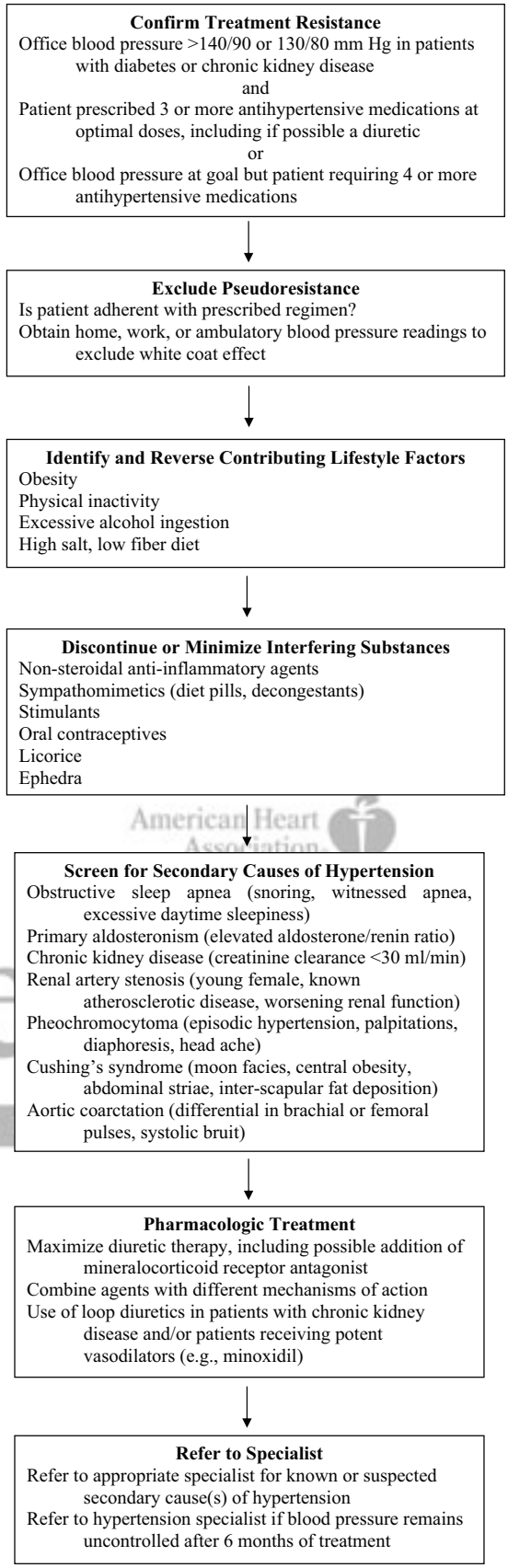

Figure. Resistant hypertension: diagnostic and treatment recommendations.

Blood Pressure Measurement

Use of good blood pressure measurement technique is essential to the accurate diagnosis of resistant hypertension, including having the patient sit quietly in a chair with his or her back supported for 5 minutes before taking the measurement; use of the correct cuff size with the air bladder encircling at least 80% of the arm (the adult large cuff for the majority of patients); and supporting the arm at heart level during the cuff measurement.[11] A minimum of 2 readings should be taken at intervals of at least 1 minute and the average of those readings should be taken to represent the patient's blood pressure. The blood pressure should be measured carefully in both arms and the arm with the higher pressures generally should be used to make future measurements. Supine and upright blood pressures should be measured during follow-up to detect orthostatic complications with treatment.

Physical Examination

A fundoscopic examination should document the presence and severity of retinopathy. The presence of carotid, abdominal, or femoral bruits increases the possibility that renal artery stenosis exists. Diminished femoral pulses and/or a discrepancy between arm and thigh blood pressures suggest aortic coarctation or significant aortoiliac disease. Cushing's disease is suggested by abdominal striae, particularly if pigmented; moon facies; or prominent interscapular fat deposition.

Ambulatory Blood Pressure Monitoring

Documentation of a significant white-coat effect requires reliable assessment of out-of-office blood pressure values. This is accomplished most objectively with the use of 24-hour ambulatory blood pressure monitoring. Alternatively, work site measurements by trained health practitioners and/or out-of-office assessments with use of manual or automated blood pressure monitors can be relied on. In the case of patient self-assessments, use of good blood pressure technique with validation of the accuracy of readings is essential. Cuffs adequately sized for use with extremely obese patients are generally not available with ambulatory or home automated monitors. In such cases, use of wrist monitors may become necessary, but the accuracy of such units can prove variable.[96,97]

A significant white-coat effect should be suspected in patients with resistant hypertension in whom clinic blood pressure measurements are consistently higher than out-of-office measurements; in patients who repetitively show signs of overtreatment, particularly orthostatic symptoms; and in patients with chronically high office blood pressure values but an absence of target organ damage (LVH, retinopathy, CKD). In such cases, 24-hour ambulatory blood pressure monitoring is recommended. A mean ambulatory daytime blood pressure of $>135/85$ mm Hg is considered elevated.[11] If a significant white-coat effect is confirmed, out-of-office measurements should be relied on to adjust treatment.[98]

Biochemical Evaluation

Biochemical evaluation of the treatment-resistant hypertensive should include a routine metabolic profile (sodium, potassium, chloride, bicarbonate, glucose, blood urea nitrogen, and creatinine); urinalysis; and a paired, morning plasma aldosterone and plasma renin or plasma renin activity to screen for primary aldosteronism. Even in the setting of ongoing antihypertensive treatment (excluding potassium-sparing diuretics, particularly aldosterone antagonists), the aldosterone/renin ratio is an effective screening test for primary aldosteronism, having a high negative predictive value.[23,99] A high ratio, however, has a low specificity for primary aldosteronism, likely reflecting the common occurrence of low-renin hypertension in patients with resistant hypertension. The specificity of the ratio is improved if a minimum plasma renin activity of 0.5 ng/mL/h is used in its calculation and/or a plasma aldosterone level $\geq$15 ng/dL is required for the ratio to be considered high. A high ratio (generally 20 to 30 when plasma aldosterone is reported in nanograms per deciliter and plasma renin activity in nanograms per milliliter per hour) is suggestive of primary aldosteronism, but further evaluation is necessary to confirm the diagnosis.

A 24-hour urine collected during ingestion of the patient's normal diet can be helpful in estimating dietary sodium and potassium intake, calculating creatinine clearance, and measuring aldosterone excretion. To do so from the same collection, however, requires that a nonsalt acid (eg, acetic acid) be used as the preservative for aldosterone. If a 24-hour urine is not used to calculate creatinine clearance, renal function can be calculated by any of a number of validated urine-free formulae. Measurement of 24-hour urinary metanephrines or plasma metanephrines is an effective screen for patients in whom pheochomocytoma is suspected.[100]

Noninvasive Imaging

Imaging for renal artery stenosis should be reserved for patients in whom there is an increased level of suspicion. This would include young patients, particularly women, whose presentation suggests the presence of fibromuscular dysplasia and older patients at increased risk of atherosclerotic disease. The preferred imaging modality will vary by institution, depending on the level of training and experience. For patients with CKD, modalities that do not involve iodinated contrast may be preferred over CT angiography. Diagnostic renal arteriograms in the absence of suspicious noninvasive imaging are not recommended. Likewise, due to poor specificity, abdominal CT imaging is not recommended to screen for adrenal adenomas in the absence of biochemical confirmation of hormonally active tumors (hyperaldosteronism, pheochromocytoma, Cushing's syndrome).

Treatment Recommendations

Resistant hypertension is almost always multifactorial in etiology. Treatment is predicated on identification and reversal of lifestyle factors contributing to treatment resistance; accurate diagnosis and appropriate treatment of secondary

causes of hypertension; and use of effective multi-drug regimens (Figure). Lifestyle changes, including weight loss; regular exercise; ingestion of a high-fiber, low-fat, low-salt diet; and moderation of alcohol intake should be encouraged where appropriate. Potentially interfering substances should be withdrawn or down-titrated as clinically allowable. Obstructive sleep apnea should be treated if present.

Maximize Adherence

Treatment adherence worsens with the use of an increasing number of pills, with increasing complexity of the dosing regimen, and as out-of-pocket costs increase. Accordingly, prescribed regimens should be simplified as much as possible, including the use of a long-acting combination of products to reduce the number of prescribed pills and to allow for once-daily dosing. Adherence is also enhanced by more frequent clinic visits and by having patients record home blood pressure measurements.[101,102] Although expensive and labor intensive, use of a multidisciplinary treatment approach including nurse case managers, pharmacists, and nutritionists can improve treatment results.[103] Involving the patient by having him or her maintain a diary of home blood pressure values should improve follow-up and enhance medication adherence, while involvement of family members will likely enhance persistence with recommended lifestyle changes.

Nonpharmacological Recommendations

Weight Loss

Weight loss, although not specifically evaluated in patients with resistant hypertension, has a clear benefit in terms of reducing blood pressure and often allows for reduction in the number of prescribed medications. A recent review of long-term weight loss studies indicated that a 10-kg weight loss is associated with an average 6.0-mm Hg reduction in systolic and a 4.6-mm Hg reduction in diastolic blood pressure.[104] An earlier meta-analysis of randomized, controlled, weight loss trials found that the greatest benefit, at least for diastolic blood pressure reduction, was in patients already receiving antihypertensive therapy.[105] While difficult to achieve and even more difficult to maintain, weight loss should be encouraged in any patient with resistant hypertension who is either overweight or obese.

Dietary Salt Restriction

The benefit of dietary salt reduction is well documented in general hypertensive patients with observed reductions in systolic and diastolic blood pressure of 5 to 10 and 2 to 6 mm Hg, respectively.[106,107] African-American and elderly patients tend to show larger benefit.[107] Dietary salt reduction has not been specifically evaluated in patients with resistant hypertension. However, in an evaluation of patients whose blood pressure was uncontrolled on a combination of an ACE inhibitor and hydrochlorothiazide, a reduced-salt diet lowered systolic and diastolic blood pressure at 1 month follow-up by 9 and 8 mm Hg, respectively.[108] Accordingly, dietary salt restriction, ideally to less than 100 mEq of sodium/24-hour, should be recommended for all patients with resistant hypertension.

Moderation of Alcohol Intake

Whether by undoing negative physiological effects and/or improvements in medication adherence, cessation of heavy alcohol ingestion can significantly improve hypertension control. Daily intake of alcohol should be limited to no more than 2 drinks (1 ounce of ethanol) per day (eg, 24 ounces of beer, 10 ounces of wine, or 3 ounces of 80 proof liquor) for most men and 1 drink per day for women or lighter-weight persons.[95]

Increased Physical Activity

In a small group of African-American men with severe hypertension (untreated systolic $\geq$180 or diastolic blood pressure $\geq$110 mm Hg who received up to 3 antihypertensive agents to lower diastolic blood pressure by 10 mm Hg and/or to $<$95 mm Hg), 16 weeks of an aerobic exercise regimen (stationary cycling 3 times a week) lowered diastolic blood pressure by 5 mm Hg and systolic blood pressure by 7 mm Hg, although the latter change was not statistically significant.[109] Reductions in diastolic blood pressure were maintained after 32 weeks of exercise, even with withdrawal of some antihypertensive medications. In a meta-analysis that included studies of both normotensive and hypertensive cohorts, regular aerobic exercise produced average reductions of 4 mm Hg in systolic and 3 mm Hg in diastolic blood pressure.[110] Based on these observed benefits, patients should be encouraged to exercise for a minimum of 30 minutes on most days of the week.

Ingestion of a High-Fiber, Low-Fat Diet

Ingestion of a diet rich in fruits and vegetables; high in low-fat dairy products, potassium, magnesium, and calcium; and low in total saturated fats (ie, the Dietary Approaches to Stop Hypertension or DASH diet) reduced systolic and diastolic blood pressure by 11.4 and 5.5 mm Hg more, respectively, than the control diet in hypertensive patients.[111] The benefit of such a diet has not been separately evaluated in patients with resistant hypertension, but some degree of blood pressure reduction seems likely.

Treatment of Secondary Causes of Hypertension

When primary aldosteronism, pheochromocytoma, or Cushing's disease is suspected or confirmed, treatment will be specific for that particular disorder. Effective management of these diseases may require referral to an appropriate specialist.

Treatment of Obstructive Sleep Apnea

Treatment of sleep apnea with continuous positive airway pressure (CPAP) likely improves blood pressure control, although the benefit in CPAP intervention trials has been variable. In a well-controlled evaluation that included both normotensive and mildly hypertensive subjects, 9 weeks of

CPAP use (5.5 hours per night) lowered 24-hour mean ambulatory systolic and diastolic blood pressure by 10.3 and 9.5 mm Hg, respectively.[112] In an uncontrolled evaluation of 11 patients with resistant hypertension, 2 months of CPAP use was associated with reductions in nighttime and daytime ambulatory systolic blood pressure of 14.4 and 9.3 mm Hg, respectively, and a 7.8 mm Hg reduction in nighttime diastolic blood pressure.[113] CPAP use averaged 4.2 hours per night. The large blood pressure reductions observed in these 2 studies, however, need to be reconciled with other studies that have reported modest or no antihypertensive benefit with CPAP use.[114,115] Review of randomized CPAP intervention trials suggests that CPAP use can be expected to lower blood pressure in hypertensive patients, with the largest benefit being seen in patients with severe sleep apnea and in patients already receiving antihypertensive treatment.[116]

Treatment of Renal Artery Stenosis

Angioplasty of fibromuscular lesions almost always benefits, and is often curative, of the associated hypertension and therefore is the recommended treatment of choice.[117] Restenosis, however, may occur in excess of 20% of patients after 1 year. Whether endovascular revascularization is needed for most atherosclerotic lesions is controversial. In patients with either controlled blood pressure or resistant hypertension, the relative benefit of intensive medical therapy versus angioplasty with stenting has not been clearly established.[118] Poorly controlled hypertension imparts a major level of cardiovascular risk, however, and endovascular angioplasty, with or without stenting, should be considered when drug therapy alone is unsuccessful. Valuable information on this topic should come from the Cardiovascular Outcomes in Renal Atherosclerotic Lesions (CORAL) trial, which is an ongoing NIH-funded study designed to determine more precisely whether percutaneous intervention with stenting plus medical therapy versus medical therapy alone improves long-term cardiovascular outcomes in patients with renal artery stenosis. Pending the results of the CORAL trial, available evidence does not support a relative advantage of either medical treatment versus revascularization procedures for treatment of renal stenosis.[119] However, if the blood pressure remains poorly controlled in spite of optimal medical therapy, revascularization is recommended, recognizing that a significant blood pressure response is not assured.

Pharmacological Treatment

Withdrawal of Interfering Medications

Medications that may interfere with blood pressure control, particularly NSAIDs, should be avoided or withdrawn in patients with resistant hypertension. However, as this is often clinically difficult, the lowest effective dose should be used with subsequent down titration whenever possible. When initiating treatment with these agents, blood pressure should be monitored closely while recognizing that adjustments to the antihypertensive regimen may become necessary.

Like other nonnarcotic analgesics, acetaminophen is associated with an increased risk of developing hypertension,[33] although when compared with ibuprofen it was less likely to worsen blood pressure control in treated subjects.[35] Therefore, if analgesics are necessary, acetaminophen may be preferable to NSAIDs in subjects with resistant hypertension, recognizing, however, that acetaminophen will provide little if any antiinflammatory benefit.

Diuretic Therapy

Evaluations of patients with resistant hypertension referred to specialty clinics have been consistent in finding that treatment resistance was in part related to a lack of, or underuse of, diuretic therapy. After measuring cardiac output, vascular resistance, and intravascular volume, investigators at Mayo Clinic found that patients referred for resistant hypertension often had occult volume expansion underlying their treatment resistance.[120] Blood pressure control was improved primarily through the use of increased doses of diuretics. In a retrospective evaluation of patients referred to Rush University Hypertension Clinic, lack of blood pressure control was attributed most often to the use of a suboptimal medical regimen, which was modified most frequently by adding a diuretic, increasing the dose of the diuretic, or changing the class of prescribed diuretic based on the underlying renal function.[16] In a separate study it was reported that increased diuresis with the use of furosemide significantly improved blood pressure control in 12 elderly patients with hypertension whose blood pressure was uncontrolled on multidrug regimens.[121]

The above studies indicate that patients with resistant hypertension frequently have inappropriate volume expansion contributing to their treatment resistance such that a diuretic is essential to maximize blood pressure control. In most patients, use of a long-acting thiazide diuretic will be most effective. In a blinded comparison of hydrochlorothiazide 50 mg and chlorthalidone 25 mg daily, the latter provided greater 24-hour ambulatory blood pressure reduction, with the largest difference occurring overnight.[122] Given the outcome benefit demonstrated with chlorthalidone and its superior efficacy compared with hydrochlorothiazide, chlorthalidone should be preferentially used in patients with resistant hypertension.[4,123–125] In contrast to hydrochlorothiazide, chlorthalidone is available in very few fixed-dose combinations and so its use will generally require separate dosing. In patients with underlying CKD (creatinine clearance <30 mL/min), loop diuretics may be necessary for effective volume and blood pressure control. Furosemide is relatively short acting and usually requires at least twice-daily dosing. Alternatively, loop diuretics with a longer duration of action, such as torsemide, can be used.

Combination Therapy

An abundance of studies demonstrate additive antihypertensive benefit by combining 2 agents of different classes. This is particularly true of thiazide diuretics, which significantly improve blood pressure control when used in combination with most if not all other classes of agents. In the Veterans Affairs Single Drug Therapy Cooperative Study, patients not controlled (diastolic blood pressure ≥ 90 mm Hg) on one randomly assigned antihypertensive medication (thiazide di-

uretic, ACE inhibitor, β-blocker, calcium channel blocker, α-blocker, or a centrally acting α agonist) were then randomized to one of the other medications. If diastolic blood pressure was still not controlled, the first medication was added back in to test the various 2-drug combinations: the combinations that included a thiazide diuretic were consistently more effective than combinations that did not include the diuretic.[126]

Beyond studies of 2-drug combinations, there is little data assessing the efficacy of specific combinations of 3 or more drugs. Accordingly, recommendation of specific multidrug combinations is largely empiric and/or anecdotal. Intuitively, it seems most appropriate to continue to combine agents of different mechanisms of action. In that regard, a triple drug regimen of an ACE inhibitor or ARB, calcium channel blocker, and a thiazide diuretic is effective and generally well tolerated. This triple regimen can be accomplished with 2 pills with use of various fixed-dose combinations.

Although β-antagonists are indicated in the setting of coronary heart disease or congestive heart failure, combined α-β-antagonists, because of their dual combination of action, may be more effective antihypertensives,[127] although head-to-head comparisons of maximal doses are lacking. Recent studies indicate an add-on antihypertensive benefit of aldosterone antagonists in patients uncontrolled on multidrug regimens. Centrally acting agents are effective antihypertensive agents but have a higher incidence of adverse effects and lack outcome data. Lastly, potent vasodilators such as hydralazine or minoxidil can be very effective, particularly at higher doses, but adverse effects are common. With minoxidil especially, reflexive increases in heart rate and fluid retention occur such that concomitant use of a β-blocker and a loop diuretic is generally necessary.

Ultimately, combinations of 3 or more drugs must be tailored on an individual basis taking into consideration prior benefit, history of adverse events, contributing factors, including concomitant disease processes such as CKD or diabetes, and patient financial limitations. Treatment recommendations in this setting cannot be overly standardized, particularly when going beyond 3 drugs.

The widespread difficulty in controlling blood pressure has lead to a proliferation of treatment algorithms for prescription of antihypertensive agents as monotherapy and in combination.[128–130] These algorithms rely primarily on the likely presence or absence of inappropriate volume expansion as suggested by suppressed renin levels. Renin levels are recommended to be measured directly or presumed based on ethnicity and age. These algorithms have not been validated in large, diverse cohorts such that the recommendations are largely empiric. In addition, as suggested by the studies discussed above, patients with resistant hypertension typically have refractory volume expansion such that treatment recommendations dichotomized according to volume status are likely less relevant.

Recent reports have suggested that the combined use of an ACE inhibitor and ARB or a dihydropyridine and non-dihydropyridine calcium channel blocker provides significant additional antihypertensive benefit compared with monotherapy with the different agents.[131,132] These studies, however, have not generally used maximal doses of either of the combined agents, so it is not possible to know whether the additional blood pressure reduction is really unique to the combination or simply a titration effect. Accordingly, it is premature from a purely blood pressure perspective to recommend the use of same-class combinations over use of agents from different classes. Such a recommendation is supported by a recent evaluation of patients whose blood pressure was uncontrolled on an ARB. In this study, adding a diuretic or calcium channel blocker was more effective than adding an ACE inhibitor.[133]

Mineralocorticoid Receptor Antagonists

Consistent with reports of a high prevalence of primary aldosteronism in patients with resistant hypertension have been studies demonstrating that mineralocorticoid receptor antagonists provide significant antihypertensive benefit when added to existing multidrug regimens. In an evaluation of 76 patients referred to a university hypertension clinic for poorly controlled hypertension, spironolactone (12.5 to 50 mg daily) in an open-label evaluation lowered blood pressure on average by an additional 25 mm Hg systolic and 12 mm Hg diastolic.[134] The antihypertensive benefit was similar in both African American and white patients. In this study, patients were being treated with an average of 4 medications, which included in all patients a diuretic and an ACE inhibitor or ARB. Interestingly, the blood pressure response was not predicted by the baseline plasma aldosterone or 24-hour urinary aldosterone, plasma renin activity, or plasma aldosterone/renin ratio. These results are similar to an earlier study demonstrating that spironolactone lowered systolic and diastolic blood pressure by 24 and 10 mm Hg, respectively, when added to the regimen of patients whose blood pressure was uncontrolled with at least 2 medications.[135] In most patients, this included an ACE inhibitor or ARB and diuretic.

Amiloride antagonizes the epithelial sodium channel in the distal collecting duct of the kidney, thereby functioning as an indirect aldosterone antagonist. In a study of 38 patients with low-renin hypertension whose blood pressure was uncontrolled with multiple drugs, including a diuretic, substitution with the combination of amiloride 2.5/hydrochlorothiazide 25 mg daily for the prior diuretic lowered systolic and diastolic blood pressure by 31 and 15 mm Hg, respectively.[61] In 26 patients, the amiloride/hydrochlorothiazide doses were doubled with an additional reduction in systolic and diastolic blood pressure of 11 and 4 mm Hg, respectively.

In a blinded comparison, amiloride 10 mg daily, spironolactone 25 mg daily, or a combination of both were used as add-on therapy in African-American patients whose blood pressure was uncontrolled on a 2-drug regimen consisting of a diuretic (a thiazide diuretic in 92% of the subjects and a loop diuretic in the remaining 8%) and a calcium channel blocker.[136] The mean decreases in systolic and diastolic blood pressure compared with placebo were, respectively, 12.2 and 4.8 mm Hg for amiloride, 7.3 and 3.3 mm Hg for spironolactone, and 14.1 and 5.1 mm Hg for the combination. Accordingly, both agents lowered blood pressure but amiloride somewhat more so. Amiloride was associated with significant

increases in plasma renin activity while spironolactone was not, suggesting that with continued titration of the spironolactone additional blood pressure lowering may have occurred.

In these studies of spironolactone and amiloride, both agents were generally safe and well tolerated. The most common adverse effect of spironolactone is breast tenderness with or without breast enlargement, particularly in men. Hyperkalemia is uncommon with either agent, but it can occur, necessitating close monitoring. Risk of hyperkalemia is increased in older patients, patients with diabetes and/or CKD, or when added to ongoing treatment with ACE inhibitors, ARBs, and/or NSAIDs. The mechanism of mineralocorticoid receptor blockade in the treatment of resistant hypertension likely involves more effective diuresis than is provided with thiazide diuretics alone; however, confirmation of such an effect or demonstration of non–volume-related effects are lacking.

Dosing

A recent cross-sectional analysis of ambulatory blood pressure control indicated that patients taking at least one of their hypertensive agents at bedtime had better 24-hour mean blood pressure control and, in particular, lower nighttime systolic and diastolic blood pressure values.[18] This latter difference may be particularly relevant as recent studies have suggested that nighttime blood pressure levels better predict cardiovascular risk than do daytime values.[137,138] It may be that twice-daily dosing of nondiuretic blood pressure medications will improve control rates in patients with resistant hypertension. This potential benefit, however, would have to be reconciled with reductions in adherence that would likely occur with use of less convenient and potentially more expensive dosing regimens.

Hypertension Specialist

Studies of clinical outcomes indicate that patients with resistant hypertension do benefit from referral to a hypertension specialist. In a retrospective evaluation of patients referred to a university hypertension clinic for resistant hypertension, blood pressure had declined by 18/9 mm Hg at 1-year follow-up, and control rates had increased from 18% to 52%.[139] In a separate retrospective analysis, hypertension specialists at the Rush University Hypertension Center were able to control blood pressure to <140/90 mm Hg in 53% of patients referred for resistant hypertension.[16]

If a specific secondary cause of hypertension is suspected in a patient with resistant hypertension, referral to the appropriate specialist is recommended as needed. In the absence of suspected secondary causes of hypertension, referral to a hypertension specialist is recommended if the blood pressure remains elevated in spite of 6 months of treatment.

Controlled Resistant Hypertension

With the current definition of resistant hypertension, patients whose blood pressure is controlled but who use 4 or more medications should still be considered resistant to treatment. In needing so much medication, such patients are at increased risk of reversible and/or secondary causes of hypertension and may benefit from the diagnostic considerations outlined above. Whether or not to adjust the treatment regimen in this situation should be decided on an individual basis with the primary objective being to maintain blood pressure control but use fewer medications and/or use a regimen that minimizes adverse effects. In this regard, patient preference will be an important consideration.

Research Challenges and Needs

Resistant hypertension as a specific subgroup remains understudied. Experimental assessment of patients with resistant hypertension is complicated by the associated high cardiovascular risk, which limits the safe withdrawal of medications and which restricts the types and duration of experimental interventions that can be used to explore proposed etiologies. Studies are further limited by concomitant disease processes such as diabetes, CKD, sleep apnea, and atherosclerotic disease. These concurrent diseases and their treatments are difficult to systematically control for and confound interpretation of study results. Enrolling adequate numbers of participants is also a significant research challenge, particularly in regard to assessing efficacy of experimental treatment modalities. Overcoming such a challenge will likely require a consortium of hypertension centers allowing for multicenter participation. Lastly, even among patients with resistant hypertension, subgroups of patients with different etiologies undoubtedly exist. As an extreme example, the young patient with combined systolic and diastolic resistant hypertension is undoubtedly different in terms of etiology, prognosis, and likely effective treatment than the elderly patient with severe, isolated, resistant systolic hypertension. Also likely different is the patient with true refractory hypertension, that is, whose blood pressure is never controlled despite maximal medical therapy. Meaningful differentiation of these subgroups will likely speed identification of respective causes of treatment resistance and development of specific treatment strategies.

Much additional knowledge is needed to better identify and treat patients with resistant hypertension. While the prevalence and prognosis of resistant hypertension can be estimated and presumed, neither is known. Cross-sectional and outcome studies have identified patient characteristics associated with resistant hypertension, but underlying mechanisms of treatment resistance, particularly potential genetic mechanisms, have not been widely investigated. Efficacy assessments of specific multidrug regimens are needed to better guide therapy. Also needed is an accurate means of assessing adequacy of diuretic treatment. While multiple studies indicate that treatment resistance is often related to refractory volume expansion, there is little objective information on adjusting diuretic therapy, including alternative use and dosing of different types of diuretics.

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Writing Group Disclosures

Writing Group Member	Employment	Research Grant	Other Research Support	Speakers' Bureau/Honoraria	Ownership Interest	Consultant/ Advisory Board	Other
David A. Calhoun	University of Alabama, Birmingham, Center for Sleep/Wake Disorders	Novartis†; AstraZeneca†; NIH/NHLBI†; AHA†	None	Merck†; AstraZeneca†; Pfizer†; Novartis†	None	Pfizer*	None
Robert M. Carey	University of Virginia School of Medicine	Sankyo Ltd†	None	None	None	Takeda NA Ltd†	None
William C. Cushman	University of Tennessee Health Science Center	None	None	None	None	None	None
Bonita Falkner	Thomas Jefferson University	AstraZeneca†; Pfizer†; Novartis†	None	Bristol-Myers Squibb*	None	Merck*; Pfizer*	None
Keith Ferdinand	Heartbeats Life Center	AstraZeneca†; Nitromed†; Merck*; Pfizer*; Bristol-Myers Squibb*	None	None	None	None	None
Thomas D. Giles	Louisiana State University Medical Center	Novartis†; AstraZeneca†; Abbott†; Amgen†	None	Novartis†; AstraZeneca†	None	Mylan*; Novartis*; Biovail*; Merck*; Bortelu*	None
David C. Goff	Wake Forest University School of Medicine	None	Pfizer*	None	None	None	None
Daniel Jones	University of Mississippi Medical Center	None	None	None	None	None	None
Timothy P. Murphy	Brown Medical School	None	None	None	None	None	None
Domenic Sica	Medical College of Virginia	Novartis†; GlaxoSmithKline†	None	Novartis†; Bristol-Myers Squibb†	None	Reliant Pharmaceuticals†; Novartis†; Pfizer†	None
Stephen Textor	Mayo Clinic	None	None	None	None	None	None
Robert D. Toto	University of Texas Southwestern Medical School	None	None	None	None	None	None
Anthony White	American Heart Association	None	None	None	None	None	None
William White	University of Connecticut Health Center	None	None	None	None	None	None

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*Modest.

†Significant.

Reviewer Disclosures

Reviewer	Employment	Research Grant	Other Research Support	Speakers' Bureau/Honoraria	Expert Witness	Ownership Interest	Consultant/Advisory Board	Other
Theodore L. Goodfriend	Medical College of Wisconsin	None	None	None	None	None	None	None
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Matthew R. Weir	VA Hospital, University of Wisconsin	None	None	None	None	None	None	None

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