AACE Guidelines

AMERICAN ASSOCIATION OF CLINICAL ENDOCRINOLOGISTS MEDICAL GUIDELINES FOR CLINICAL PRACTICE FOR THE DIAGNOSIS AND TREATMENT OF HYPERTENSION

AACE Hypertension Task Force

American Association of Clinical Endocrinologists Medical Guidelines for Clinical Practice are systematically developed statements to assist health-care professionals in medical decision making for specific clinical conditions. Most of the content herein is based on literature reviews. In areas of uncertainty, professional judgment was applied.

These guidelines are a working document that reflects the state of the field at the time of publication. Because rapid changes in this area are expected, periodic revisions are inevitable. We encourage medical professionals to use this information in conjunction with their best clinical judgment. The presented recommendations may not be appropriate in all situations. Any decision by practitioners to apply these guidelines must be made in light of local resources and individual patient circumstances.

AACE Hypertension Task Force

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Abbreviations:
AACE = American Association of Clinical Endocrinologists; **ABCD** = Appropriate Blood Pressure Control in Diabetes; **A1C** = hemoglobin A1c; **ACEIs** = angiotensin-converting enzyme inhibitors; **ACTH** = adrenocorticotropic hormone (corticotropin); **ARBs** = angiotensin receptor blockers; **ARR** = aldosterone/plasma renin activity ratio; **AT_1** = angiotensin II type 1; **BBs** = β-adrenergic blocking agents; **BP** = blood pressure; **CCBs** = calcium channel blockers; **CRH** = corticotropin-releasing hormone; **CT** = computed tomographic; **CVD** = cardiovascular disease; **DOC** = deoxycorticosterone; **ENaC** = epithelial sodium channel; **FACET** = Fosinopril Versus Amlodipine Cardiovascular Events Randomized Trial; **GFR** = glomerular filtration rate; **GRA** = glucocorticoid-remediable aldosteronism; **IVC** = inferior vena cava; **JNC** = Joint National Committee on Prevention, Detection, Evaluation, and Treatment of High Blood Pressure; **MEN** = multiple endocrine neoplasia; **MI** = myocardial infarction; **MIBG** = metaiodobenzylguanidine; **MRI** = magnetic resonance imaging; **RAAS** = renin-angiotensin-aldosterone system; **RCTs** = randomized controlled trials; **UKPDS** = United Kingdom Prospective Diabetes Study; **VMA** = vanillylmandelic acid; **WHO** = World Health Organization

I. MISSION STATEMENT

Hypertension is epidemic worldwide; nevertheless, only a minority of subjects with this condition receive effective treatment. In the United States, more than 50 million people have blood pressure (BP) at or above the optimal level of 120/80 mm Hg, yet only approximately half receive treatment and just 31% of those taking antihypertensive medication have their BP controlled to below 140/90 mm Hg (1). The problem may be worse elsewhere, as evidenced by a survey indicating that only 9% of patients with hypertension in the United Kingdom had BP lowered to less than 140/90 mm Hg (2). The World Health Organization (WHO) cites a "second wave" epidemic of cardiovascular disease (CVD) related to hypertension and other factors in developing countries and projects that CVD will likely be the number one cause of death in the world by 2020 (3).

In the United States, inadequate control of hypertension is likely attributable to a combination of factors. Problems with screening and behavioral counseling; controversial definition and classifications of hypertension; unclear treatment goals; and complex or costly pharmacotherapy (or both difficulties) can lead to patient and physician nonadherence to existing guidelines (4-6). An evidence-based approach to the treatment of hypertension is still evolving. Comorbid conditions that increase cardiovascular risk, such as diabetes mellitus, need to be considered in treatment decisions. In addition, controversy still exists over the universal applicability of currently available recommendations.

The American Association of Clinical Endocrinologists (AACE) proposes these guidelines to clarify what is known about the treatment of hypertension based on the best current evidence. Unlike other clinical practice guidelines, however, those presented in this report will focus on identifying and managing hypertension secondary to or coincident with endocrinopathies. The AACE contends that understanding the associated pathophysiologic features of hypertension will guide appropriate treatment and help physicians anticipate the usefulness of evolving therapies, such as blockade of the renin-angiotensin system for retarding the progression of retinopathy and nephropathy in patients with diabetes (7).

An understanding of physiologic aspects of the endocrine system is helpful to the primary care physician in identifying the causes and determining the optimal treatment in even uncomplicated cases of hypertension. Furthermore, the AACE asserts that the clinical endocrinologist can and should make important contributions to the investigation and treatment of patients with difficult-to-manage hypertension, as well as those with complicating endocrine disorders such as diabetes or insulin resistance. Endocrine expertise should facilitate the discovery and treatment of secondary forms of hypertension that can eventuate in effective control or, in some cases, a cure for these conditions.

These guidelines are not a substitute for individual physician expertise and judgment. Rather, they are intended to serve as a decision-making aid and, ultimately, to help clarify some of the confusion surrounding hypertension diagnosis and treatment.

II. SPECIFIC OBJECTIVES AND METHODS

The objectives of this report are as follows:

1. Indicate when to suspect the presence of and pursue further testing for secondary hypertension
2. Provide appropriate examples of the most common causes of endocrine-associated hypertension that physicians may encounter
3. Elucidate the cause of each endocrine disorder underlying hypertension
4. Describe the tests used to confirm each diagnosis
5. Identify the appropriate management options for each condition, based on the available evidence and known pathophysiologic changes
6. Discuss outcomes and potential side effects associated with each management option

The following are target audiences for these guidelines:

1. Endocrinologists
2. Physicians and health-care professionals who wish to learn about management of hypertension secondary to or coincident with endocrinopathies

The AACE Hypertension Task Force consists of experts in the fields of both endocrinology and hemodynamics. All task force participants are active members of the AACE or the American Society of Hypertension (or both). Several contributors have authored publications on endocrine disorders, hypertension, or their association. These guidelines were developed in accordance with the AACE Protocol for Standardized Production of Clinical Practice Guidelines (8). Task force members collected data, reviewed and graded clinical evidence in accordance with established criteria (Tables 1 and 2), and developed a section of the report consistent with their clinical focus or area of specialization. References were obtained through computerized searching of the literature, scanning of incoming journal issues in the medical library, and review

Table 1
American Association of Clinical Endocrinologists
Criteria for Determining Level of Evidence

Level of evidence	Description
1	Well-controlled, generalizable, randomized trial Adequately powered Well-controlled multicenter trial Large meta-analysis with quality ratings All-or-none evidence
2	Randomized controlled trial—limited body of data Well-conducted prospective cohort study Well-conducted meta-analysis of cohort studies
3	Methodologically flawed randomized clinical trials Observational studies Case series or case reports Conflicting evidence with weight of evidence supporting the recommendation
4	Expert consensus Expert opinion based on experience “Theory-driven conclusions” “Unproven claims”

From the American Association of Clinical Endocrinologists Ad Hoc Task Force for Standardized Production of Clinical Practice Guidelines (8).

Table 2
American Association of Clinical Endocrinologists
Criteria for Determining Recommendation Grade

Recommendation grade	Description
A	Homogeneous evidence from multiple well-designed randomized controlled trials with sufficient statistical power Homogeneous evidence from multiple well-designed cohort controlled trials with sufficient statistical power ≥1 conclusive level 1 publications demonstrating benefit >> risk
B	Evidence from at least one large well-designed clinical trial, cohort or case-controlled analytic study, or meta-analysis No conclusive level 1 publication; ≥1 conclusive level 2 publications demonstrating benefit >> risk
C	Evidence based on clinical experience, descriptive studies, or expert consensus opinion No conclusive level 1 or 2 publication; ≥1 conclusive level 3 publications demonstrating benefit >> risk No conclusive risk at all and no conclusive benefit demonstrated by evidence
D	Not rated No conclusive level 1, 2, or 3 publication demonstrating benefit >> risk Conclusive level 1, 2, or 3 publication demonstrating risk >> benefit

From the American Association of Clinical Endocrinologists Ad Hoc Task Force for Standardized Production of Clinical Practice Guidelines (8).

of references in pertinent review articles, major textbooks, and syllabi from national meetings. Final recommendations represent a consensus among the task force members. These recommendations have been approved by reviewers, the AACE Publications Committee, and the AACE Board of Directors. Because many of the endocrine syndromes described herein are uncommon and outcome data are scarce, comments and recommendations on the management of these conditions are based on a combination of available evidence and expert judgment of task force members.

III. EXECUTIVE SUMMARY

In this section, the main findings and recommendations of the task force are summarized and graded on the basis of levels of evidence (Table 3), as previously established by the AACE (8). Further details and referenced discussion providing the basis for these recommendations, as well as other aspects of endocrine hypertension, may be found in the subsequent sections.

Introduction

It is now widely appreciated that the identification and lifelong treatment of hypertension are critical to successful risk reduction in CVD. Data from the National Health and Nutrition Examination Survey, however, clearly demonstrate that treatment and control rates of hypertension have not improved substantially during the past 2 decades, despite a progressively growing and powerful armamentarium of pharmacologic agents. The problem is exacerbated by the increasing incidence of hypertension and other metabolic disorders, such as type 2 diabetes mellitus, associated with lifestyle factors.

The AACE believes that clinical endocrinologists are optimally suited to help direct effective treatment of both uncomplicated and more refractory cases of hypertension. These guidelines combine pathophysiologic and evidence-based approaches to identification and treatment of hypertension, particularly with regard to underlying or related metabolic dysfunctions. It is our hope that these guidelines will be used to facilitate the achievement of accurate diagnosis and effective prevention or treatment of hypertension, and they indicate where more in-depth, focused evaluation is needed.

Lifestyle Modification

A significant observation is that 30% to 65% of patients with hypertension are obese, a problem frequently compounded by high sodium intake, sedentary lifestyle, and excessive use of alcohol. Therefore, lifestyle modifications directed at correcting these contributing factors may benefit the patient regardless of the primary cause of the hypertension and should have an important, first-line

Table 3
Summary of Evidence-Based Recommendations for Management of Hypertension*

Indication	Recommendation	Highest level of evidence	Grade
Lifestyle modification	Weight loss (in overweight patients)	1	A
	Sodium restriction (2.3-3 g/day)	1	A
	Potassium intake ≥3.5 g/day	1	A
	Alcohol restriction ≤1 oz/day	2-3	B
	Exercise ≥30 min/day	3-4	C
Type 2 diabetes	Goal BP ≤130/80 mm Hg	2	A
	Goal BP ≤120/75 mm Hg when severe proteinuria exists	1	A
	ACEI or ARB as first- or second-line agent	1	A
	Thiazide diuretic as first- or second-line agent (in low dosage with adequate potassium replacement or sparing)	1	A
	BB (preferably drugs that block both α and β receptors) as second- or third-line agent	1	A
	CCB (preferably nondihydropyridine) as second-, third-, or fourth-line agent	1	A
Pheochromocytoma	α-Adrenergic blocker as first-line agent, in conjunction with BB or CCB (or both) as needed	3	C
Hyperaldosteronism	Surgical resection for unilateral adenoma	2	B
	Aldosterone antagonists, ACEI, or ARB for hyperplasia	2	B
	Low-dose glucocorticoid for GRA	3	C
Cushing's syndrome	Surgical or ablative therapy for adenoma	1	A
	Medical inhibition of steroid synthesis (especially ketoconazole) in intractable cases	2	B
Pregnancy	All major antihypertensive agents except ACEI/ARB (preferably methyldopa or nifedipine)	1-2	A
	Magnesium for preeclampsia at high risk for seizures	1-2	A

*ACEI = angiotensin-converting enzyme inhibitor; ARB = angiotensin receptor blocker; BB = β-adrenergic blocking agent; BP = blood pressure; CCB = calcium channel blocker; GRA = glucocorticoid-remediable aldosteronism.

role in any therapy. A moderate weight loss of 5 to 10 kg can have a significant beneficial effect on hypertension in obese patients (*grade A*, on the basis of multiple well-controlled trials).

The AACE recommends restricting daily sodium intake to less than 3 g in patients with uncomplicated hypertension or to as low as 2.3 g in patients with refractory hypertension or multiple risk factors, particularly diabetes mellitus (*grade A*). Although not all cases of hypertension are related to sodium intake, sodium restriction is an important adjunct to other lifestyle modifications and pharmacologic therapy. Insufficient potassium intake may also be an etiologic factor in hypertension. The AACE recommends a daily potassium intake of at least 3.5 g (in the absence of renal insufficiency), preferably from fresh fruits and vegetables (*grade A*).

Daily consumption of more than 1 oz of alcohol is associated with elevated levels of BP; even this small quantity may also impair the response to pharmacologic therapy for hypertension. Accordingly, healthy adults should limit alcohol consumption to 2 or fewer average-sized alcoholic drinks per day (*grade B*, because of the absence of any well-controlled randomized trials).

A favorable inverse relationship has been noted between BP and regular physical activity, independent of body weight. Thus, moderately intense exercise for at least 30 minutes daily is recommended for all adults (*grade C*, primarily based on observational studies and expert consensus opinion).

Diabetes and Hypertension

Type 2 diabetes mellitus and hypertension are common across all populations and frequently coexist. This relationship is particularly true in African American subjects, among whom up to 14% of adults may have both disorders. Many of the estimated 49 to 69 million adults in

the United States with insulin resistance also have hypertension, and a quarter of the patients with type 1 diabetes mellitus have hypertension. Obviously, common pathophysiologic processes are at work, which will influence the effectiveness of all treatments for either disorder. Because of the strong correlation of both diabetes and hypertension with risk of CVD, optimal therapy should address both conditions, while including the common benefits of lifestyle modification.

Because angiotensin-converting enzyme inhibitors (ACEIs) and angiotensin receptor blockers (ARBs) are associated with favorable effects on renal function and may improve insulin sensitivity, they are ideal first choices in the treatment of patients with both diabetes and hypertension (*grade A*). Diuretics have also been shown to be effective in the treatment of hypertension, both alone and in combination therapy, and likely are even more effective in patients with excess sodium intake or impaired sodium excretion. Thiazide diuretics, however, can worsen blood glucose control in patients with diabetes and can increase the likelihood of development of diabetes mellitus in insulin-resistant subjects. Thus, diuretics may have an effective role in the treatment of hypertension in these patients, but they should be used in the lowest effective dosage in conjunction with adequate potassium replacement or the addition of a potassium-sparing agent (*grade A*).

β-Adrenergic blocking agents (BBs) may likewise precipitate or exacerbate type 2 diabetes mellitus. This feature, together with a variety of adverse side effects, seems to make BBs less appealing as first-line agents for treatment of hypertension in patients with either type 2 or type 1 diabetes mellitus (*grade A*). BBs, however, have proved effective in the management of the ischemic and congestive cardiomyopathies that are more common in patients with diabetes than in those without diabetes. Because the major adverse effects of BBs may be mediated by peripheral vasoconstriction and increasing insulin resistance, the use of the new third-generation BBs (such as nebivolol) or drugs that block both α and β receptors (such as carvedilol) may prove to be particularly beneficial (*grade A*). These agents cause vasodilatation and an increase in insulin sensitivity.

The use of calcium channel blockers (CCBs) has been associated with both benefits and adverse outcomes in a variety of study populations with diabetes. The nondihydropyridine CCBs (that is, diltiazem and verapamil) may reduce microalbuminuria to an extent comparable to that with the ACEIs, whereas dihydropyridine CCBs may increase it. Increased albuminuria is associated with increased CVD and chronic kidney disease risk. Although not considered optimal agents for first-line therapy or monotherapy in patients with diabetes, CCBs have proved safe and effective in combination regimens with ACEIs, diuretics, and BBs (*grade A*).

In general, combination therapy is needed to achieve the stricter BP goals set for most patients with diabetes mellitus. The seventh report of the Joint National Committee on Prevention, Detection, Evaluation, and Treatment of High Blood Pressure (JNC) recommended achieving systolic BP below 130 mm Hg and diastolic BP below 80 mm Hg in these patients. Although this goal is based largely on level 2 and 3 evidence, the AACE wishes to promote an aggressive approach to the management of hypertension in patients with diabetes and classifies this recommendation as *grade A*. Systolic and diastolic BP goals at or below 120/75 mm Hg may be even more effective in slowing the progression of renal disease and other cardiovascular and cerebrovascular complications, particularly in the presence of substantial proteinuria (>1 g daily) (*grade A*).

In light of the plethora of data showing that patients with diabetes have, on average, a 2-fold greater risk of renal disease and a 3-fold greater risk of CVD in comparison with subjects without diabetes, AACE recommends an early aggressive approach in the management of hypertension as part of overall risk factor reduction. In addition to lifestyle modifications, the use of an ACEI or ARB, in conjunction with a low-dose diuretic, a CCB, a third-generation BB, or some combination of these agents, currently seems to be the preferred initial therapeutic regimen for patients with diabetes (*grade A*).

Endocrine Hypertension

The potential to "cure" someone's hypertension or to avoid a serious complication is of paramount importance but occasionally must be weighed against the costs, particularly the health risks, of attempting to do so. At times, the clinical situation may suggest the likelihood of a secondary cause of hypertension. The index of suspicion for an underlying cause may be raised by the absence of usual accompanying factors (including a family history, gradual onset, obesity, or high salt intake) or by unexpected clinical or laboratory findings before or during treatment (including hypokalemia, azotemia, tachycardia, or refractoriness to treatment). Causes of endocrine hypertension include disorders of the adrenal, thyroid, parathyroid, or pituitary glands or a renin-secreting tumor. The most common of these are of adrenal origin—namely, mineralocorticoid, catecholamine, or glucocorticoid excess. Renal artery stenosis is the main treatable cause of secondary hypertension not of a primary endocrine origin.

Pheochromocytoma is one of the less common but more dramatic and most pursued causes of endocrine hypertension. Most pheochromocytomas are benign, but a substantial percentage may be bilateral or extra-adrenal lesions (paragangliomas). The hypertension may be episodic or sustained. Patients with pheochromocytoma may have a family history of pheochromocytoma or multiple endocrine neoplasia (MEN) syndrome. More commonly, the index of suspicion is raised by episodes of pallor and evidence of orthostatic hypotension accompanying the typical symptoms, such as palpitations, diaphoresis, and headache. The diagnosis requires demon-

stration of elevated levels of catecholamines or metabolites in the plasma or urine. Sensitivity and specificity considerations should guide the choice of investigatory procedures, including subsequent imaging techniques. Definitive treatment by surgical excision of the tumor cures the hypertension in about 75% of cases. Underlying essential hypertension, progressive renal disease, or an approximately 10% recurrence rate, usually with malignant histologic findings, may prevent complete cure. Preoperative control as well as management of any residual disease (particularly with malignant involvement) is best accomplished with α-adrenergic blocking agents and addition, as needed, of BBs or CCBs (or both) (*grade C*).

Primary hyperaldosteronism may account for up to 15% of patients with hypertension, particularly in middle age. Although hypokalemia and metabolic alkalosis are classic findings, many patients with primary hyperaldosteronism may not display these findings, particularly when adrenal hyperplasia is the cause. The use of the random serum aldosterone/plasma renin activity ratio (ARR) with a sufficiently high cutoff value has facilitated diagnosis at an acceptable cost and low risk. The diagnosis of primary hyperaldosteronism ultimately depends on demonstration of the following findings: (*1*) hypertension, (*2*) an elevated ARR, and (*3*) an elevated serum aldosterone concentration or urinary aldosterone excretion (or both).

Identifying the specific cause of primary hyperaldosteronism can be difficult but should be pursued. Distinguishing between aldosterone-producing adenoma (unilateral or bilateral) and bilateral adrenal hyperplasia may be particularly difficult, necessitating one or more imaging techniques or selective adrenal vein sampling. Although a laparoscopic surgical procedure is increasingly available and usually the treatment of choice for a unilateral adenoma, medical therapy is preferred for bilateral adrenal hyperplasia (*grade B*). In patients with glucocorticoid-remediable aldosteronism (GRA), low doses of a glucocorticoid may provide effective treatment after exclusion of Cushing's disease or ectopic production of corticotropin (adrenocorticotropic hormone or ACTH) (*grade C*).

Cushing's syndrome is perhaps most frequently suspected as a cause of secondary hypertension and, at the same time, is one of the most elusive diagnoses to make. Many pseudo-Cushing's states have been identified, and because definitive treatment is almost always surgical, considerable care must be exercised to arrive at an accurate diagnosis. Unfortunately, in many cases, this diagnostic difficulty may result in substantial expense, including referral to a tertiary or even quaternary center at times, particularly if corticotropin-releasing hormone (CRH) stimulation and inferior petrosal sinus sampling are necessary.

Identification of Cushing's syndrome, at least in the earlier stages, necessitates an increased index of suspicion among the myriad of patients with similar phenotypic features, including centripetal obesity, hirsutism, and striae. New-onset glucose intolerance and hypertension may be the earliest features of the syndrome. Difficult-to-control hypertension, hypokalemia, and perhaps hyperpigmentation may be the only presenting manifestations when ectopic ACTH production is the initiating abnormality.

The cause of hypertension in most patients with Cushing's syndrome is unclear but likely multifactorial, including increased catecholamine sensitivity and some mineralocorticoid effect of cortisol. Accordingly, no one class or combination of antihypertensive agents tends to be routinely effective at controlling BP, and treatment should include elimination of the pathologic hormone production, usually by surgical intervention (*grade A*). In otherwise inoperable or intractable cases, ketoconazole and mitotane have been used with some success (*grade B*). Even after effective management of excess cortisolemia, however, up to 33% of patients with the endogenous syndrome have persistent systolic hypertension and 75% have persistent diastolic hypertension. As in the other foregoing causes of secondary hypertension discussed, residual or recurrent hypertension should be appreciably easier to manage after effective treatment of the endocrine pathologic condition.

Pregnancy-associated hypertension involves at least 3 different categories of patients, as discussed subsequently in this document. Even when the hormonal milieu of pregnancy is primarily etiologic, termination of the pregnancy is usually not a preferred option for treatment. Although the need to treat mild hypertension (<140/90 mm Hg) during pregnancy remains a matter of debate, the immediate treatment of severe hypertension (>170/110 mm Hg) clearly improves both maternal and fetal outcomes, and most authorities agree that treating moderate hypertension is also beneficial, at least to the mother. Methyldopa or CCBs, particularly nifedipine, are thought to be the most suitable antihypertensive agents for use during pregnancy, but BBs and other classes of antihypertensive drugs, except ACEIs and ARBs, can be used safely in accordance with the experience of the treating physician. Magnesium sulfate is superior to other agents in reducing recurrent eclamptic seizures and is recommended for preeclampsia at high risk for seizures. The levels of evidence for all the aforementioned recommendations warrant a *grade A* classification.

IV. APPROACH TO THE PROBLEM

The Problem

Although the National Health and Nutrition Examination Survey II and III showed a progressive increase in patient awareness (73%), treatment (55%), and satisfactory control (29%) of hypertension up to 1991 (9), in most patients the BP is still not sufficiently controlled. Since 1991, there has been a plateau, or at most modest improvement, in treatment and control rates of hypertension (1,10-12). Furthermore, available evidence indicates that rates of end-stage renal disease, congestive heart fail-

ure, and age-adjusted mortality attributable to stroke have increased during the past decade (10).

Inadequate control of hypertension may derive, in part, from the fact that the approach to identifying and treating hypertension, although evidence based, is subject to change and controversy. Even the definition of hypertension has remained a topic of some debate. Over time, as the database of evidence correlating elevated BP levels with CVD has grown, values defining "normal" BP have declined. The first National Health Examination Survey, conducted from 1960 through 1962, defined hypertension as BP higher than 160/95 mm Hg (1). In 1973, the National High Blood Pressure Education Program, organized at the National Institutes of Health, defined hypertension as BP higher than 140/90 mm Hg, based on available cardiovascular risk data (10,11). In 1993, the fifth report of the JNC lowered the definition of normal BP to 130/85 mm Hg or below, and in 2003, the seventh report of the JNC lowered the definition of normal BP still further to 120/80 mm Hg or below (12,13). Optimal BP levels for those patients with advancing renal insufficiency or substantial proteinuria (or both) have previously been proposed as 120/75 mm Hg or below (14).

The current limited understanding of the initiating factors and pathophysiologic processes involved in hypertension has left the level at which BP is considered "high" subject to interpretation. The clinical context of hypertension has an important role in the consideration of normal BP, because intermittent or borderline high BP levels may be relatively benign in one patient yet pose serious clinical consequences for another, depending on risk factors such as age, sex, ethnicity, habitus, and comorbidities. African American men in the United States, for example, tend to have hypertension at a younger age in comparison with white men, have more severe hypertension, and have a higher rate of end-organ damage (13). In addition, patients with diabetes must achieve a lower BP level than patients without the condition to derive a comparable benefit, inasmuch as diabetes itself increases the risk of CVD. Determination of hypertension is further complicated by the fact that the circumstances under which BP is measured can influence the reading. "White-coat hypertension" is a well-known clinical entity defined as persistently elevated BP levels in the physician's office, whereas BP in other situations is normal. Although this subject is controversial, it is possible that white-coat hypertension may not need treatment when, for example, ambulatory monitoring confirms normal BP values or only intermittent increases.

Identifying and Treating Hypertension

These guidelines focus on identifying hypertension and recommending treatment based on endocrine pathophysiologic conditions. In particular, detailed information for the diagnosis and management of hypertension secondary to or coincident with endocrinopathies is provided and integrated with material from 2 comprehensive documents that reflect the expertise of prominent international hypertension specialists. The first of these documents is the JNC 7 report (12), which, like previous reports of the JNC, draws on the results of randomized controlled trials (RCTs) to guide therapy. Clinicians should realize that RCTs have their limitations, including relatively focused end points, short durations, selective cohorts, and generally limited consideration of potentially different causes of hypertension within each cohort. The second document is the 1999 WHO-International Society of Hypertension guidelines for the management of hypertension, which concentrates on the management of mild hypertension as the most prevalent issue facing clinicians and policy-makers around the world (15).

Understanding the pathophysiologic changes as the basis of therapy will help physicians use a therapeutic agent's mechanism of action to tailor treatment to the clinical need. For example, angiotensin II, produced by the circulating renin-angiotensin-aldosterone system (RAAS) as well as alternative enzymatic and local pathways, has widespread trophic and mitogenic effects on cardiac and vascular cells. These influences are in addition to vasoconstrictive effects on coronary, renal, and cerebral blood vessels. Accordingly, ACEIs and ARBs may, in addition to lowering BP levels, have other roles in preventing end-organ damage, as clearly demonstrated in African American patients with hypertensive renal disease, by slowing the decline in the glomerular filtration rate (GFR) independent of the degree of BP lowering (16-18). Nevertheless, categorizing all patients with essential hypertension into pathophysiology-based treatment groups such as low- or high-renin hypertension has proved to be difficult and may not always be practical. Effective treatment on the basis of available evidence is the more important consideration in such cases. Developing more sensitive ways to assess vascular status and risk—for example, by monitoring endothelial cell dysfunction even before hypertension and atherosclerosis progress—will help to identify the pathophysiologic mechanisms involved.

A recently recognized subset of patients with essential hypertension includes those with isolated systolic hypertension. This common and disproportionate increase in systolic BP often accompanies aging. Isolated systolic hypertension confers a much higher risk of coronary artery disease-related mortality than does elevated diastolic BP, and data from controlled trials indicate that aggressive treatment of this age-related increase in systolic BP reduces cardiovascular morbidity and mortality (19).

Clearly, before prescribing medication, the clinician must rule out artifactual, iatrogenic, and other (nonendocrine) causes of hypertension, such as improper BP measurement technique or inadequate measurements, long-term use of drugs or other products that may raise BP (for example, certain nutritional supplements or nonsteroidal anti-inflammatory drugs), poor adherence to lifestyle modifications, or poor compliance with pharma-

cotherapy. Lifestyle modification, in particular, is an essential, first-line treatment strategy. Unfortunately, promoting a healthful lifestyle is a daunting task in a population that has become increasingly sedentary and persists in high caloric (and high salt) intake. Ultimately, best-practice medicine involves tailoring therapy to address the underlying pathophysiologic abnormalities.

V. ROLE OF LIFESTYLE MODIFICATION

Thirty percent to 65% of the cases of hypertension diagnosed in the Western world can be directly attributed to obesity (20). Because hypertension can often be remedied in this population by weight loss, it should be the cornerstone of any lifestyle modification effort designed to decrease BP. Other lifestyle modifications that decrease BP levels include reduction in sodium intake, moderation of alcohol intake, consumption of an adequate amount of potassium, and increase in physical activity. Collectively, a decreased intake of calories, sodium, and alcohol, along with increased physical activity, is associated with a 50% reduction in the 5-year incidence of hypertension (21,22). Lifestyle modification can also lessen the need for antihypertensive agents and, consequently, decrease the occurrence of side effects while reducing the cost of treatment. As a result, the JNC 7 (12), the WHO (20), and the International Society of Hypertension (15) all support lifestyle modification as an important component of treatment of hypertension.

Weight Loss

Approximately 64% of US adults are either overweight or obese. Usually, the definitions of overweight and obesity are a body mass index in excess of 25 kg/m^2 and ≥30 kg/m^2, respectively (23), with appropriate consideration given to ethnicity, sex, and body habitus. Obesity is associated with a 2- to 6-fold increase in risk of occurrence of hypertension (24-28). On the average, for each 10-kg increase over ideal body weight, systolic BP rises 2 to 3 mm Hg and diastolic BP rises 1 to 3 mm Hg (20). Loss of excess weight can reduce both systolic and diastolic BP levels (21,29-31). Even the moderate loss of 4.5 kg in an obese patient with hypertension can significantly reduce BP (32). In addition, loss of excess weight is effective in the primary prevention of hypertension (25,29-31). Physicians should promote weight loss for all overweight patients and encourage the prevention of weight gain that could result in hypertension. A combination of diet and exercise is more effective in producing weight loss and lowering BP than either modification alone (33).

Nutritional Factors

Sodium

Epidemiologic, clinical, and experimental studies suggest that sodium intake in excess of physiologic requirements is associated with hypertension (34,35). In addition, moderating the intake of sodium may be an important strategy in the primary prevention of hypertension because it helps blunt the age-related increase in BP (35,36). In the INTERSALT study, which included 10,079 men and women 20 to 59 years old from defined populations in 52 centers and 32 countries, for each 100-mmol (2.3-g) decrement in daily sodium intake the study population had average lower systolic BP of 3.7 mm Hg and lower diastolic BP of 2.0 mm Hg (35,36).

Reducing sodium intake also helps decrease BP levels in patients with hypertension and is likely most beneficial for populations with the greatest sodium intake (37). The Dietary Approaches to Stop Hypertension (DASH-Sodium) trial (37) confirmed that low sodium intake in patients with high-normal BP or stage 1 hypertension favorably reduced BP values, particularly in African American patients. A daily sodium intake reduction of about 30% to 40% has also been associated with decreased BP levels in elderly persons (38). Other studies have confirmed the effectiveness of restriction of dietary sodium as an adjunct to pharmacotherapy in patients with hypertension (39-41). Restricting daily sodium intake may also help reduce hypertension-related mortality. An aggressive 100-mmol daily restriction in sodium intake during the first 55 years of life could result in a 16% lifetime reduction in mortality from coronary artery disease, a 23% reduction in mortality attributable to stroke, and a 13% reduction in death from all causes (42).

Patients with hypertension or high-normal BP levels should reduce sodium intake to 3 g or less per day (37). Physicians should advise patients to choose foods low in salt, minimize the use of salt during cooking, and reduce their intake of table salt (36,43).

Potassium

Clinical studies clearly indicate that adequate potassium intake has an important role in BP reduction and that insufficient potassium intake may contribute to the development of hypertension (44-49). A meta-analysis of RCTs showed that potassium chloride supplementation of 60 to 100 mmol/day decreased systolic BP by 4.4 mm Hg and diastolic BP by 2.5 mm Hg (49). High potassium intake has also been associated with a decreased incidence of stroke, independent of its effect on BP (48,50). Ideally, persons with normal renal function should have a daily intake of potassium of approximately 3.5 g, preferably from fresh fruits and vegetables (51).

Other Micronutrients and Macronutrients

Current data suggest that neither micronutrients (for example, calcium, magnesium, and zinc) nor macronutrients (for example, fat, fatty acids, carbohydrate, fiber, and protein) are major, independent determinants of hypertension risk: short-term changes in the consumption of these nutrients do not seem to affect BP levels (20,30,52). A diet

rich in fruits, vegetables, and low-fat dairy foods that is low in both saturated and total fats, however, has been shown to decrease BP values (53,54).

Alcohol

Persons who drink alcohol every day tend to have higher BP levels than those who drink alcohol less often. In one study, subjects who drank alcohol every day had systolic BP levels 6.6 mm Hg higher and diastolic BP levels 4.7 mm Hg higher than once-weekly drinkers, regardless of the total amount of alcohol consumed per week (36). Specifically, consumption of 2 or more alcoholic drinks daily (approximately an ounce of alcohol) is associated with an increase of 1.0 mm Hg systolic BP and 0.5 mm Hg diastolic BP per drink, although it is not clear whether a threshold exists for these effects. These effects are independent of other factors such as obesity, tobacco use, physical activity, age, and sex (55). Excessive intake of alcohol may also be a cause of resistance to antihypertensive medication (56,57). When alcohol consumption is reduced, BP tends to improve consistently and significantly, independent of weight change (55,58-60). Although an intriguing body of literature suggests cardiovascular benefit from a low level of alcohol consumption (61), these associations noted in epidemiologic studies need to be investigated in RCTs. Healthy adults should limit the consumption of alcohol to 2 drinks (24 oz of beer, 10 oz of wine, or 3 oz of 80-proof whiskey) (12) or fewer per day, and consumption should not exceed 14 drinks weekly for men and 9 drinks per week for women (59).

Activity Level

When compared with the fit and active peer, the sedentary and out-of-condition normotensive person typically has a 20% to 50% increase in risk of hypertension (62). Physical activity reduces both systolic and diastolic BP in both normotensive persons and those with hypertension (62-64), and an inverse relationship has been noted between BP and physical activity independent of body weight (65-67). Physically active persons also tend to have smaller age-related BP increases (68-71). Exercise lowers the rate of cardiovascular-related mortality (72), in addition to the many other known physical and psychologic benefits. All adults should be encouraged to participate in regular, moderately intense physical activity (40% to 60% of maximal oxygen consumption) for a minimum of 30 minutes daily to prevent or control hypertension (12,32,73).

Psychosocial Factors and Stress

Although mental stress may immediately increase BP through a variety of mechanisms, stress has not been shown to have long-term effects on BP independent of such confounding factors as socioeconomic or dietary factors (20). Current data do not provide convincing evidence for stress management as part of a hypertension prevention or treatment program (32,74).

Smoking and Tobacco Use

Although tobacco smoking does not cause hypertension, it is a major cardiovascular risk factor and is frequently related to the diet and exercise issues discussed in the foregoing material. A recent study involving 15,152 cases and 14,820 control subjects from 52 countries, representing every inhabited continent, found that persons who smoked cigarettes had nearly triple the risk of myocardial infarction (MI) in comparison with those who had never smoked (75). Physicians can improve these odds: approximately 2% to 15% of patients quit smoking for at least 1 year in response to their physician's advice (76-78). It is strongly recommended that all physicians aggressively promote smoking cessation programs.

Effectiveness of Counseling

Clinical trials demonstrate that counseling to reduce sodium intake, decrease alcohol consumption, lose weight, and increase physical activity can motivate patients and thereby help prevent primary hypertension in high-risk subjects (30,31,40,79). Nevertheless, cognitive behavioral therapies alone (such as biofeedback, relaxation, and meditation), while superior to no therapy at all, have not been shown to be superior to placebo or self-monitoring (80).

VI. TREATMENT OF HYPERTENSION IN PATIENTS WITH DIABETES MELLITUS, INSULIN RESISTANCE, OR BOTH

Diabetes and hypertension are interrelated disorders. In one study, the quartile of subjects with the highest insulin resistance had a 33% greater risk of having hypertension in comparison with the quartile with the highest insulin sensitivity (81). One quarter of the patients with type 1 diabetes (82) and half of those with type 2 diabetes (83,84) have hypertension. In general, the prevalence of hypertension is 1.5 to 3 times higher in the diabetic population than in age-matched groups without diabetes (85). Conversely, diabetes is more than twice as prevalent in patients with hypertension than in those with normal BP (86,87).

The additive effect of diabetes and hypertension strongly predisposes a person to CVD. In the Multiple Risk Factor Intervention Trial (88), in which 347,978 men underwent follow-up for a mean of 12 years, absolute risk of CVD death was overall 3 times higher for men with diabetes than for those without this disorder, and the absolute excess risk for men with diabetes increased progressively as the systolic BP level increased.

Approaches to Treatment of Hypertension in Diabetes

Two physiologic systems underlying the adverse effects of hypertension in patients with diabetes are the RAAS and the sympathetic nervous system (89).

Angiotensin II exerts vasoconstrictive effects directly through stimulation of the angiotensin II type 1 (AT_1) receptor and indirectly through release of endothelin and

norepinephrine. Angiotensin II stimulation of the AT_1 receptor increases oxidative stress and superoxide anions through activation of nicotinamide adenine dinucleotide phosphate or the reduced form of nicotinamide adenine dinucleotide phosphate oxidase. This process also reduces nitric oxide bioavailability through formation of peroxynitrites. In addition, AT_1 stimulation produces inflammation by inducing expression of proinflammatory molecules, such as monocyte chemotactic protein-1 and vascular cell adhesion molecule, as well as a variety of cytokines including tumor necrosis factor α and interleukin-6. Furthermore, angiotensin II promotes vascular remodeling by stimulating smooth muscle migration, hypertrophy, and replication, inducing growth factor expression, and increasing production of matrix glycoproteins and metalloproteinases. Angiotensin II also exerts prothrombotic effects by stimulating synthesis of plasminogen activator inhibitor-1 and activating platelet aggregation and adhesion (90).

Diabetic autonomic neuropathy is associated with augmented sympathetic tone (91), which increases levels of free fatty acids. Myocardial utilization of free fatty acids results in uncoupling of oxidative phosphorylation, inhibiting membrane adenosine triphosphate and leading to increased myocardial oxygen consumption and myocardial ischemia (92). Increased sympathetic tone may also directly decrease cardiac function and induce cardiac arrhythmias, which increase the risk of coronary disease-related mortality (93). Of note, insulin resistance is itself associated with increased sympathetic activity (94). On the basis of the roles of the RAAS and the sympathetic nervous system in the pathogenesis of hypertension in patients with diabetes, therapeutic agents that affect the production or receptor binding of angiotensin II (the ACEIs and ARBs) or block the hormones and neurotransmitters that stimulate the sympathetic nervous system (the BBs) seem to offer particular benefit.

Recommended Therapeutic Agents

On the basis of positive results from RCTs, JNC 7 recommended that diuretics, ACEIs, ARBs, BBs, and CCBs be considered important agents in the treatment of hypertension in patients with diabetes (12).

Diuretics

In patients with diabetes, therapeutic regimens based primarily on thiazide diuretics were associated with a 33% decrease in CVD mortality in the large Hypertension Detection and Follow-Up Program (95). Diuretic treatment in the Systolic Hypertension in the Elderly Program (96,97) was also shown to decrease the risk of major CVD events in patients with diabetes, with an absolute risk reduction approximately twice as great as that seen in elderly patients without diabetes. The largest investigation of diuretic-based treatment of hypertension has been the Antihypertensive and Lipid-Lowering Treatment to Prevent Heart Attack Trial (98), consisting of 42,418 patients with hypertension, 36% of whom had diabetes, randomized to regimens based on chlorthalidone, amlodipine, or lisinopril. After 1 year of treatment, BP had decreased from a baseline of 146/84 mm Hg to 137/79 mm Hg with chlorthalidone, 138/79 mm Hg with amlodipine, and 140/80 mm Hg with lisinopril. At 5 years, the BP levels were 134/75 mm Hg with chlorthalidone, 135/75 mm Hg with amlodipine, and 136/75 mm Hg with lisinopril. The chlorthalidone group had significantly lower levels of systolic BP. Cumulative event rates for the primary outcome (fatal coronary heart disease or nonfatal MI) were similar in all groups, both in the overall study and in the diabetic subset. Among the subset of patients with diabetes, those treated with chlorthalidone versus amlodipine showed no significant difference in total mortality, total coronary heart disease, total CVD, or stroke, although the development of heart failure was 42% lower with chlorthalidone. When chlorthalidone and lisinopril treatments were compared, no significant difference in total mortality, total coronary heart disease, or stroke was noted in the diabetic subset, but an 8% greater risk of CVD and a 22% greater risk of heart failure were found in the group receiving lisinopril. No analysis has been reported correcting for the lower levels of BP achieved with chlorthalidone. In addition, interpretation of the study is also confounded by the fact that patients with hypertension generally need 2 or more agents to control BP; exclusion of diuretics from their usual use as second- or third-line agents after ACEIs in patients with diabetes would be expected to compromise the antihypertensive benefit of the lisinopril-based regimen. Adverse glycemic consequences of chlorthalidone were not uncommon in this trial. Analysis of fasting blood glucose levels showed that, among the initially nondiabetic patients receiving chlorthalidone, diabetes had developed in 11.6% at 4 years, in comparison with 8.1% of patients receiving lisinopril ($P<0.001$) (98).

Angiotensin-Converting Enzyme Inhibitors

Several studies have suggested the benefits of ACEIs in managing hypertension in patients with diabetes. Overall results of the Captopril Prevention Project (99), with almost 11,000 patients who had diastolic BP ≥100 mm Hg, showed that use of the ACEI captopril and conventional treatment with a BB plus a diuretic were equally effective in preventing fatal and nonfatal MI, stroke, and cardiovascular deaths. Among the 572 patients with diabetes, however, the ACEI decreased MI, total CVD, and mortality to a greater extent than the results seen with conventional treatment. In the Fosinopril Versus Amlodipine Cardiovascular Events Randomized Trial (FACET) (100), adverse CVD events were seen in 14 of the 189 patients with diabetes and hypertension treated with the ACEI, in comparison with 27 of the 191 treated with amlodipine.

Although not a hypertensive study, the Heart Outcomes Prevention Evaluation (101) demonstrated the

advantages of prescribing ACEIs in patients with diabetes. Among the 5,720 study participants without diabetes at baseline, diabetes developed in 3.6% of those randomized to treatment with ramipril, in comparison with 5.4% of those randomized to receive placebo ($P<0.001$). In addition, a 44% decrease in the likelihood of requirement for glucose-lowering therapy was noted in patients receiving the ACEI versus placebo. Patients with diabetes at the outset of the study had a 25% decrease in the primary outcomes of MI, stroke, or cardiovascular death. In addition, patients with diabetes who received the ACEI had a 24% decrease in all-cause mortality, a 37% decrease in CVD-related mortality, and a 33% decrease in stroke in comparison with those who received placebo (102).

In the Appropriate Blood Pressure Control in Diabetes (ABCD) study (103), enalapril was associated with 5 fatal or nonfatal MIs during a 5-year period, in contrast to the occurrence of 25 such events with the CCB nisoldipine among the same number of patients (N = 225). This highly significant risk reduction with the ACEI compared with the CCB was found in subgroups with moderate and intensive BP control. Both therapeutic agents led to similar preservation of the GFR, although albuminuria decreased only with enalapril treatment.

In the Swedish Trial in Old Patients With Hypertension-2 (104), which compared the effects of CCBs, ACEIs, and BB plus diuretics, the risk for MI was 49% lower in patients treated with an ACEI in comparison with those receiving a CCB, despite a similar degree of BP lowering. This reduction in MIs seen with use of ACEIs versus CCBs was consistent with that reported in the ABCD trial (103).

Angiotensin Receptor Blockers

In the Losartan Intervention for Endpoint Reduction in Hypertension study (105), losartan was found to decrease cardiovascular mortality by 13% in comparison with atenolol in 9,193 patients with essential hypertension and left ventricular hypertrophy. The ARB produced even greater improvements compared with the BB in the 1,195 patients with diabetes, including a 37% decrease in CVD-related mortality (106).

The Reduction of Endpoints in NIDDM With the Angiotensin II Antagonist Losartan trial (107) showed significant renal benefits in 1,513 patients with type 2 diabetes and nephropathy. During a period of 3.4 years, a 28% reduction in the development of end-stage renal disease was noted with use of the ARB in comparison with placebo, both taken in addition to conventional antihypertensive treatment, including CCBs, diuretics, α-adrenergic blocking agents, BBs, and centrally acting agents. The ARB also exhibited a cardiovascular benefit, reducing the rate of first hospitalization for heart failure by 32% in comparison with that for placebo. The Irbesartan Diabetic Nephropathy Trial (108) randomized 1,715 patients with hypertension and nephropathy due to type 2 diabetes to irbesartan, amlodipine, or placebo. Study subjects had urinary protein excretion of at least 900 mg/day and a serum creatinine concentration between 1.0 and 3.0 mg/dL in women or between 1.2 and 3.0 mg/dL in men. Therapy with irbesartan decreased the risk of doubling of the serum creatinine level by 33% in comparison with placebo and by 37% in comparison with amlodipine. These different outcomes were not attributable to differences in the BP levels achieved.

Calcium Channel Blockers

In the Systolic Hypertension in Europe Trial (109), 4,695 patients with systolic hypertension, including 492 who had diabetes, were treated with nitrendipine or placebo. After 2 years of follow-up, in the diabetic subgroup systolic BP was reduced 8.6 mm Hg and diastolic BP was reduced 3.9 mm Hg in study patients receiving the CCB in comparison with placebo. Similarly in comparison with placebo, use of the CCB was associated with decreased overall mortality, mortality from CVD, and all cardiovascular events, to a significantly greater extent among patients with diabetes than among those without diabetes. The 5-year Nordic Diltiazem study (110) showed that cardiac event rates in 351 diltiazem-treated patients were similar to rates found in 376 patients receiving diuretics in combination with BBs.

It should be noted, however, that certain studies, such as the ABCD (103), Swedish Trial in Old Patients With Hypertension-2 (104), and FACET (100), suggest that use of dihydropyridine CCBs may be associated with worse outcomes than those seen with ACEIs. Other evidence suggests that CCBs may not be optimal agents for patients with diabetes. In the Multicenter Isradipine Diuretic Atherosclerosis Study (111) of isradipine (2.5 to 5 mg) versus hydrochlorothiazide (12.5 to 25 mg), angina occurred in 2.5% versus 0.7% of patients, respectively. Moreover, an increase was noted in major vascular events (MI, stroke, congestive heart failure, angina, and sudden death) with administration of the CCB versus the diuretic, which increased as the hemoglobin A1c (A1C) level increased, although patients with diabetes were not included in this study.

β-Adrenergic Blocking Agents

In the United Kingdom Prospective Diabetes Study (UKPDS) 39, a subset of intensively treated patients with hypertension received either the BB atenolol or the ACEI captopril as primary treatment (112). Cumulative diabetes-related end points and specific outcomes, including total and fatal MI, heart failure, angina, stroke, and retinopathy, were similar in the 2 intensive treatment groups. In 35% of patients treated with atenolol and 22% of those receiving captopril, however, the initial antihypertensive treatment was discontinued, with claudication, bronchospasm, and erectile dysfunction being more common with use of the BB. Furthermore, the mean A1C value was 7.5% in the atenolol-treated group versus 7% in the captopril-treated group during the first 4 years of follow-up, despite 25%

more patients in the atenolol group receiving additional glucose-lowering treatment. The mean weight gain was 3.4 kg in the atenolol group, in comparison with 1.6 kg in the captopril group.

Long-term elevation of norepinephrine can provoke a variety of deleterious effects that are mediated through actions on α_1-, β_1-, and β_2-adrenergic receptors. Therefore, it may be relevant that various BBs have different pharmacologic properties, with metoprolol and atenolol acting primarily at the β_1 receptor, propranolol having both β_1 and β_2 receptor antagonist action, and carvedilol acting at the α_1, β_1, and β_2 receptors. Of note, metoprolol, atenolol, and particularly propranolol decrease insulin sensitivity, whereas carvedilol increases insulin sensitivity (113). In addition, metoprolol, atenolol, and propranolol increase triglyceride levels and lower the level of high-density lipoprotein cholesterol, whereas carvedilol again has the opposite effects (114). In a study of patients with type 2 diabetes and hypertension, carvedilol and atenolol had similar BP-lowering effects and action in decreasing left ventricular hypertrophy, but triglyceride, fasting plasma glucose, A1C, and insulin levels decreased with use of carvedilol but increased with atenolol therapy. Moreover, insulin sensitivity increased 27% with carvedilol treatment but decreased 24% with administration of atenolol (115). Recently, a 5-month randomized controlled comparison of the effects of carvedilol and metoprolol tartrate in 1,235 patients with type 2 diabetes and hypertension showed a modest increase in A1C with use of the latter and an improvement in insulin sensitivity with use of the former agent, with evidence as well that progression to microalbuminuria was less frequent with carvedilol than with metoprolol therapy (116).

Combination Hypertension Treatment Regimens

Three or more drugs are typically needed to achieve optimal BP control in patients with diabetes or renal disease (117), and it has been recommended that therapy should be initiated with a combination of 2 or more drugs when BP is 20 mm Hg systolic or 10 mm Hg diastolic (or both) above goal (12). Perhaps the most important role of CCBs in patients with diabetes is as part of such a combination regimen. In the Hypertension Optimal Treatment study (118), the CCB felodipine was associated with a decrease in major cardiovascular events, but most patients also received BBs, ACEIs, and diuretics. In FACET (100), the lowest CVD-related mortality was seen in patients treated with both amlodipine and fosinopril. Renoprotective actions of CCBs include decreased systemic pressure, decreased renal hypertrophy, decreased metabolic activity and mesangial growth, and decreased nephrocalcinosis. Some studies suggest benefits of CCBs similar to those of ACEIs in patients with renal insufficiency, including preservation of the GFR and reduction of albuminuria (119,120). Investigations are in progress to help determine the optimal combination therapy for patients with hypertension and diabetes. It is hoped that these studies will clarify the relative benefits of diuretics, BBs, CCBs, ARBs, and other agents in combination with ACEIs, will determine whether the adverse metabolic effects of BBs and diuretics convey specific disadvantages in patients with diabetes, and will discover the effects of the various therapeutic options on the quality of life.

Goals of Treatment of Hypertension in Diabetes

The Hypertension Optimal Treatment study (118) attempted to randomize patients to achieve diastolic BPs of 90, 85, and 80 mm Hg but achieved instead mean diastolic BPs of 85.2, 83.2, and 81.1 mm Hg. Despite this much smaller degree of separation, the risk of a major cardiovascular event was still 30% less in the lowest in comparison with the highest BP stratum in patients without diabetes, and the corresponding value in those with diabetes was 37% less (118).

In UKPDS 38, patients with diabetes and hypertension were randomized to tight control of BP, with a target level of <150/85 mm Hg (with the use of captopril or atenolol as main treatment), or less tight control with a BP target of <180/105 mm Hg (121). After a median duration of follow-up of 8.4 years, the cohort randomized to tight BP control achieved a mean BP level of 144/82 mm Hg; this result was associated with reductions of 56% in heart failure, 44% in stroke, 37% in microvascular disease events such as the need for laser photocoagulation, 32% in diabetes-related death, and 24% in overall diabetes-related end points in comparison with patients randomized to less tight BP control, who achieved a mean BP level of 154/87 mm Hg. Moreover, epidemiologic analysis of the relationship between systolic BP and events in the overall UKPDS population of patients with diabetes showed that, in comparison with those who had systolic BPs <125 mm Hg, patients with diabetes who had systolic BPs of 125 to 142 mm Hg had a 1.52-fold increase in risk and those with systolic BPs >142 mm Hg had a 1.82-fold increase in risk of developing coronary artery disease. Each decrease of 10 mm Hg in BP was associated with reductions in overall diabetes end point development of 12%, diabetes-related mortality of 15%, total mortality of 11%, MI of 11%, stroke of 17%, microalbuminuria of 13%, and congestive heart failure of 15%. There was no evidence of a J-shaped curve or threshold effect (122).

The UKPDS found evidence of significant interaction between BP and glycemic treatments (123). The effects of BP were more pronounced in the group with the highest A1C: patients with A1C >8% and systolic BP >170 mm Hg had a 10-fold increase in total end points. In contrast, patients with systolic BP <140 mm Hg had little risk of MI regardless of A1C level. Thus, the need for careful treatment of both factors is emphasized. For prevention of one retinal or renal end point in the UKPDS, 14 patients needed to be treated for 10 years with tight control of BP, in comparison with 36 patients treated with tight glycemic control. Only 6 patients needed to be treated with tight control of BP, in comparison with 20 patients treated with

tight glycemic control, to prevent any diabetes-related end point. In this study, most patients received multiple antihypertensive agents for BP control, whereas by trial design most patients received monotherapy for diabetes. This observation suggests that patients were treated more aggressively for hypertension than for diabetes.

VII. DIAGNOSIS OF ENDOCRINE HYPERTENSION

The need to suspect secondary hypertension and to determine its cause depends on the clinical circumstance. In some cases, a high index of suspicion and the potential for long-term cure or control of the primary hypertension might suffice. In other cases, despite adequate BP control, failure to recognize an underlying condition (for example, pheochromocytoma or renovascular disease in the setting of renal failure) might cause harm to the patient, and the benefits of detection and treatment would outweigh the potential risks and cost of the investigation.

The physician should suspect a secondary cause when hypertension has the following characteristics:

- Sudden onset, intermittent, or especially labile
- Unaccompanied by the usual contributing factors (such as obesity or high salt intake)
- Associated with abnormal clinical or laboratory findings (for example, features of Cushing's syndrome or hypokalemia)
- Resistant to therapy (that is, uncontrolled with use of 3 medications, including a diuretic)

New-Onset Hypertension

There is consensus that arterial hypertension develops gradually in susceptible persons over a period of years. Because many patients have not had a BP measurement taken in years or even decades, their hypertension may erroneously appear to be of sudden onset. If a physician is not confident about a gradual onset of hypertension, investigation for a secondary cause should be considered.

No Usual Contributing Factors

The absence of the usual contributing factors (obesity, high salt intake, excessive use of alcohol, and lack of exercise) or a positive family history (history of hypertension in a first-degree relative) may warrant an investigation into the possibility of secondary hypertension. The index of suspicion should be raised by clinical manifestations of other endocrine disorders, whether documented in the history or detected on physical examination. The presence of one or more of the usual contributing factors, with or without a positive family history, however, does not rule out a secondary cause for the hypertension but would lower the index of suspicion and the incentive for a costly investigation (124).

Abnormal Clinical Findings

Coronary or Peripheral Vascular Disease

A large proportion of patients with hypertension have coexistent coronary or peripheral vascular disease and, as such, their renal arteries are likely to be abnormal (125). Medication resistance or intolerance, sudden loss of BP control, or rapidly declining renal function suggests hemodynamically significant renal artery stenosis. Although angiography remains the definitive study for this diagnosis (126), Doppler ultrasonography and computed tomographic (CT) and magnetic resonance angiography offer alternatives for the patient in whom the invasive nature of the procedure is an issue. The need for use of a contrast agent may limit the feasibility of CT angiography in the patient with diabetes who has renal impairment. Before undergoing any imaging of the renal vasculature, the patient should be fully informed of the risks and benefits and should consent to the therapeutic intervention planned.

Glucocorticoid Excess (Cushing's Syndrome)

Hypertension with or without hypokalemia may accompany Cushing's syndrome of endogenous or exogenous origin. Similarly, depressed violaceous striae, moon facies, and a cervicodorsal fat pad take time to develop and, while often diagnostic, may or may not be present, depending on the duration and the severity of the glucocorticoid excess.

Genetic Diseases

The physician should consider the possibility that the hypertension could be a result of pathologic processes underlying genetic diseases. The existence of pheochromocytoma or paraganglioma should be considered in patients with multiple tumors of neural crest origin (MEN type 2). Sustained or intermittent hypertension associated with paroxysmal symptoms or spells, although not pathognomonic, suggests the presence of a pheochromocytoma. In such cases, the diagnosis must be confirmed or excluded with appropriate laboratory testing.

Abnormal Laboratory Findings

The serum potassium level is an established laboratory test for distinguishing between essential hypertension and mineralocorticoid excess. Specifically, spontaneous hypokalemia in the salt-replete state is an indicator of a mineralocorticoid-excess condition, the most common being primary hyperaldosteronism.

VIII. CAUSES AND TREATMENT OF ENDOCRINE HYPERTENSION

The causes of endocrine hypertension include disorders of the adrenal, thyroid, parathyroid, and pituitary

glands, abnormal renal tubular sodium handling, or renin-secreting tumors. These conditions are summarized in Table 4 and discussed in greater detail subsequently, particularly the most common disorders of adrenal origin.

Pheochromocytoma

A pheochromocytoma is usually a benign tumor of the adrenal medulla that secretes excess epinephrine, norepinephrine, or both. A paraganglioma is an extra-adrenal neoplasm of the sympathetic nervous system. The resultant adrenergic receptor stimulation causes persistent or intermittent hypertension. It has an estimated incidence of 2 to 8 cases per million persons annually (127). Typically, a pheochromocytoma manifests as a single adrenal tumor, but in 10% to 20% of cases, it manifests as a single extra-adrenal tumor along the sympathetic chain, 98% of which are below the diaphragm. In 10% to 35% of sporadic cases, patients will have multiple bilateral adrenal or extra-adrenal tumors.

Diagnosis

Elevated free catecholamine excretion or high levels of metabolites (that is, metanephrines or vanillylmandelic acid [VMA]) in the serum or urine establish the diagnosis of pheochromocytoma. Localization of the lesion (or lesions) necessitates use of imaging techniques.

Recommended biochemical tests for diagnosis of pheochromocytoma include the following:

- *Plasma free metanephrines*. The plasma free metanephrine concentration is a highly sensitive test but is considerably less specific than 24-hour urine collection for free metanephrines or VMA. If normal levels are detected, the presence of a neoplasm of the sympathetic nervous system is highly unlikely (127).
- *Timed urine collection (minimum of 4 hours) for metanephrines*. These assays are most effective when performed during or immediately after a symptomatic episode.
- *Urine collection (24-hour specimen) for free catecholamines, metanephrines, and VMA*. Urinary VMA is the most specific of all tests for the diagnosis of pheochromocytoma.

The normal ranges for biochemical urine tests will depend on the laboratory. Usually, however, values associated with a pheochromocytoma are dramatically elevated.

The choice of tests depends on the pretest probability of the presence of a pheochromocytoma. In the more common clinical scenario of resistant or paroxysmal hypertension, perhaps with palpitations, the probability of pheochromocytoma is still low, and one should use tests with higher specificity, such as urinary VMA and metanephrines. In cases in which the pretest probability is high (such as a prior history of pheochromocytoma, familial pheochromocytoma, history of MEN 2, von Hippel-Lindau disease, neurofibromatosis type 1, familial paraganglioma, or pallor and hypertensive spells), tests with higher sensitivity, such as plasma free metanephrines, are more appropriate. In many cases in clinical practice, however, it would be appropriate to perform tests with high sensitivity and high specificity concurrently to arrive at an accurate diagnosis.

The sensitivity and specificity for the various biochemical tests used in the diagnosis of pheochromocytoma are outlined in Table 5. Because the plasma catecholamine levels are labile, the assay is not clinically reliable. Clinicians should also be aware of medications and other factors that can interfere with the interpretation of catecholamine and metanephrine measurements (Table 6). Patients should stop taking these medications for at least 2 weeks before testing (127). Depending on the assay used, particularly with older assays for VMA, other drug or dietary factors may interfere with the measurements, and these should be clarified by the testing laboratory.

Diagnostic Testing

Clonidine suppression testing is useful if the basal plasma catecholamine levels are elevated (1,000 to 2,000 pg/mL), BP is >160/90 mm Hg, and imaging fails to localize a lesion. Clonidine is a centrally acting α_2 agonist that decreases central sympathetic outflow. Blood samples and BP are measured before and 3 hours after oral administration of clonidine (0.3 mg in a 70-kg adult). In most patients, the BP decreases. In addition, plasma catecholamine concentrations decrease to <500 pg/mL if under physiologic control, but they do not decrease in patients with pheochromocytoma. This is a relatively safe test (128).

The AACE does not recommend provocative testing (for example, glucagon, metoclopramide, or naloxone provocation). The objective of such testing is to stimulate the tumor to secrete catecholamines, which can be associated with substantial risk.

Imaging

Imaging options for diagnosing and localizing pheochromocytoma include CT scanning, magnetic resonance imaging (MRI) of the adrenal glands, and sodium iodide I 131-metaiodobenzylguanidine (MIBG) scintigraphy (129). The accuracy of these techniques for this purpose is summarized in Table 7. CT is the best imaging technique to visualize the adrenal glands; however, in the case of a pheochromocytoma, MRI provides better histologic differentiation by means of T2-weighted and spin-echo sequences (130). Similarly, ^{131}I-MIBG scintigraphy is the best imaging method for confirming that a tumor is a pheochromocytoma and for ruling out additional metastatic disease (131). Indium In 111-diethylenetriamine pentaacetic acid-D-phenylalanine-pentetreotide (octreotide) scintigraphy has shown more limited sensitivity and lacks the specificity of ^{131}I-MIBG.

Table 4
Summary of Etiologies of Endocrine Hypertension

Source and condition	Brief description
Adrenal abnormalities:	
Pheochromocytoma	Usually benign tumor of adrenal medulla that secretes excess epinephrine and norepinephrine, causing excessive stimulation of adrenergic receptors. Malignant in 10% of cases; may be extra-adrenal in the sympathetic chain
Hyperaldosteronism (aldosteronism)	Hypersecretion of aldosterone, causing abnormal electrolyte metabolism (sodium retention, hypokalemia). Can be primary (cause lies within adrenal gland) or secondary (stimulus is extra-adrenal). Primary aldosteronism can result from adrenal adenoma or carcinoma or from bilateral cortical nodular hyperplasia. Secondary aldosteronism with hypertension can result from renin overproduction or renin-producing tumors
Dexamethasone-suppressible:	
Glucocorticoid-remediable aldosteronism (GRA) or familial hyperaldosteronism I	GRA is a monogenic disorder and is an autosomal dominant trait with features similar to those of primary aldosteronism. Usually associated with bilateral adrenocortical hyperplasia without progression to adenoma
Hyperplasias:	
Enzyme deficiency (11β-hydroxylase, 17α-hydroxylase)	In 11β-hydroxylase enzyme deficiency, a defect in cortisol biosynthesis leads to excess 11-deoxycorticosterone, which accounts for sodium retention and resulting hypertension
Idiopathic hyperplasia	…
Bilateral adrenal hyperplasia	See hyperaldosteronism
Nodular hyperplasia	See hyperaldosteronism
11β-Hydroxysteroid dehydrogenase deficiency (hereditary or acquired)	When hereditary, it is a rare autosomal recessive trait in which cortisol cannot be converted to cortisone. Congenital condition has a high morbidity and mortality. When acquired, can result from ingestion of carbenoxolone (type 1) or licorice (type 2) or chewing tobacco containing certain forms of licorice that result in sodium retention
Excess deoxycorticosterone (DOC)	Rarely, hypertensive patients with hypokalemic alkalosis have adenoma(s) that secrete DOC
Cushing's syndrome	The endogenous form results from increased cortisol production by the adrenal; in most cases, the cause is bilateral adrenal hyperplasia (Cushing's disease) but can also be nodular hyperplasia. The more common exogenous causes include prolonged use of glucocorticoids or adrenocorticotropic hormone
Thyroid:	
Hypothyroidism	Low-renin form of hypertension associated with increased systemic vascular resistance and contracted plasma volume and cardiac output
Hyperthyroidism	Excess secretion of thyroid hormones results in widened pulse pressure with or without systolic hypertension due to decreased peripheral vascular resistance and increased cardiac contractility
Parathyroid:	
Hyperparathyroidism	Hypertension occurs in 30% to 40% of hyperparathyroid patients, although often this may be coincidental. Ordinarily attributed to renal parenchymal damage due to nephrolithiasis and nephrocalcinosis; severe hypercalcemia can also have a vasoconstrictive effect
Pituitary:	
Acromegaly	Hypertension occurs in about a third of these patients and is characterized by suppressed renin and aldosterone secretion, probably due to volume expansion and increased vascular rigidity
Other:	
Renin-secreting tumor	Results from intrarenal tumor (see hyperaldosteronism, secondary) or extrarenal (ovarian) tumor
Pregnancy-induced	Hypertension occurs in 5% to 10% of pregnancies. Cause is unclear but involves increased vascular responsiveness to vasoconstrictor stimuli and many features of insulin resistance when preeclampsia develops
Liddle syndrome	One of several, apparently rare, inherited disorders resulting in enhanced reabsorption of sodium in the distal tubule, independent of the mineralocorticoid receptor. Plasma renin and aldosterone concentrations are suppressed despite hypokalemic alkalosis

Table 5
Sensitivity and Specificity of Various Biochemical Tests Used in the Diagnosis of Pheochromocytoma

Test	Sensitivity (95% CI) (%)	Specificity (95% CI) (%)
Plasma free metanephrines	99 (96-100)	89 (87-92)
Urinary fractionated metanephrines	97 (92-99)	69 (64-72)
Plasma catecholamines	84 (78-89)	81 (78-84)
Urinary catecholamines	86 (80-91)	88 (85-91)
Urinary total metanephrines	77 (68-85)	93 (89-97)
Urinary vanillylmandelic acid	64 (55-71)	95 (93-97)

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Treatment

Whenever possible, surgical excision or maximal debulking of accessible tumor is the preferred treatment of pheochromocytoma. Preoperative management or control of residual disease should involve primarily α-adrenergic blocking agents, particularly phenoxybenzamine or prazosin hydrochloride, and allowance of adequate time for vascular volume expansion. BBs should be added, as needed, to control tachycardia and arrhythmia. CCBs may also be advantageous as secondary or tertiary agents because they attenuate the pressor response to norepinephrine and can prevent catecholamine-induced coronary spasm (128).

Associated Conditions

Familial pheochromocytoma is associated with MEN syndromes, particularly type 2 (formerly, 2A). This disorder usually consists of bilateral adrenal medullary hyper-

Table 6
Potential Causes of False-Positive Results for Catecholamines and Metanephrines*

Tricyclic antidepressants and antipsychotic agents
Levodopa
Drugs containing catecholamines
Ethanol
Withdrawal from clonidine and other drugs
Acetaminophen and phenoxybenzamine (plasma metanephrines)
Major physical stress (for example, operation, stroke, obstructive sleep apnea)

*Labetalol, sotalol, and buspirone can interfere with the spectrophotometric assay for metanephrines; catecholamines measured by high-performance liquid chromatography and metanephrines measured by tandem mass spectroscopy are not affected to a significant degree by most antihypertensive agents.
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Table 7
Accuracy of Imaging Techniques for Localizing and Diagnosing Pheochromocytoma*

Variable	CT (%)	MRI (%)	MIBG (%)
Sensitivity	98	100	78
Specificity	70	67	100
Positive PV	69	83	100
Negative PV	98	100	87

*CT = computed tomography; MIBG = ^{131}I-metaiodobenzylguanidine; MRI = magnetic resonance imaging; PV = predictive value: based on a prevalence rate of 38% in this highly selected group of 104 patients; includes 30 adrenal gland tumors and 10 extra-adrenal tumors.

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plasia or adenomas, medullary carcinoma of the thyroid, and hyperparathyroidism. The adrenal disease frequently manifests as a unilateral lesion, with the contralateral lesion not becoming apparent until years later. Similarly in affected family members, 1 or 2 tumors may manifest. MEN 2 syndrome is usually diagnosed by genetic testing for the *RET* proto-oncogene on chromosome 10.

Type 3 (formerly, 2B) MEN syndrome consists of 1 or more of the following: adrenal medullary hyperplasia or adenomas, medullary carcinoma of the thyroid, mucosal neuromas of the lips or tongue, marfanoid habitus, thickened corneal nerves, ganglioneuromas of the gastrointestinal tract, and, rarely, hyperparathyroidism.

Familial pheochromocytoma has also been noted in association with neurofibromatosis or with von Hippel-Lindau disease. About 5% of patients with pheochromocytoma have neurofibromatosis, and 1% of patients with neurofibromatosis have pheochromocytoma (132,133).

The approximate frequency of pheochromocytoma is 10% to 20% in patients with von Hippel-Lindau disease, 50% in those with MEN 2, and 20% in those with paraganglioma. (Genetic testing for von Hippel-Lindau disease is available at Johns Hopkins University and at the University of Pennsylvania. Testing for familial paraganglioma is available at the University of Pittsburgh.)

Primary Hyperaldosteronism

Primary hyperaldosteronism usually becomes clinically apparent during the fourth or fifth decade of life and is more common in women than in men. In addition to hypertension, classic features of the disorder include hypokalemia, weakness, cramps, periodic paralysis, increased kaliuresis, metabolic alkalosis, and hypernatremia.

Data suggest that the diagnosis of hyperaldosteronism has increased substantially because of the use of biochemical screening tests. Primary hyperaldosteronism was formerly thought to occur in 0.01% (134) to 1.5% (135) of patients with hypertension. Recent studies using the ARR as a screening test, however, have reported a considerably higher prevalence (136). Currently, primary hyperaldosteronism is thought to account for up to 15% of cases of clinical hypertension (137).

Diagnosis

The physician should consider the potential presence of primary hyperaldosteronism in any patient who has refractory hypertension (receiving more than 3 antihypertensive agents), spontaneous hypokalemia (K^+ less than 3.5 mEq/L), or severe hypokalemia during diuretic therapy (K^+ less than 3.0 mEq/L) in conjunction with an inability to normalize K^+ levels after discontinuation of diuretic therapy for at least 2 to 4 weeks.

Of note, normokalemia has been reported in up to 12% of patients with hypertension and aldosteronoma and in up to 50% of patients with adrenal hyperplasia (138). A 24-hour K^+ urinary excretion of less than 30 mEq/day, however, is highly unusual in patients with hyperaldosteronism (139).

Evaluation of potassium balance in patients with hypertension receiving treatment can be difficult. Diuretic use often leads to hypokalemia, and inhibition of the RAAS by ACEIs and ARBs masks the potassium-wasting effect of the excess mineralocorticoid. Nevertheless, any low or low-normal serum potassium concentration in the setting of ACEI or ARB therapy, alone or with a potassium-sparing diuretic, or a need for potassium supplementation should alert the clinician to the possibility of a primary mineralocorticoid-excess state. Thiazide diuretics, CCBs, ACEIs, and ARBs improve the diagnostic discriminatory power of the ARR. BBs and clonidine suppress plasma renin and are more likely to cause false-positive results.

Algorithms for diagnosing hyperaldosteronism in patients with hypokalemia and for subtype evaluation are presented in Figures 1 and 2 (140). When the physician suspects primary hyperaldosteronism based on the serum K^+ level, an ARR (with a blood specimen obtained with the patient seated) and saline suppression testing can provide valuable additional diagnostic information. Performance of the saline suppression test may be contraindicated in patients with severe hypertension or heart failure.

- *Aldosterone/plasma renin activity ratio*. Blood samples should be obtained in the morning with patients in a seated position (141). The cutoff for the ARR ranges from 25 (140) to 50 (142). A high ARR in the setting of a high-normal plasma aldosterone level (>15 ng/dL) suggests primary hyperaldosteronism.

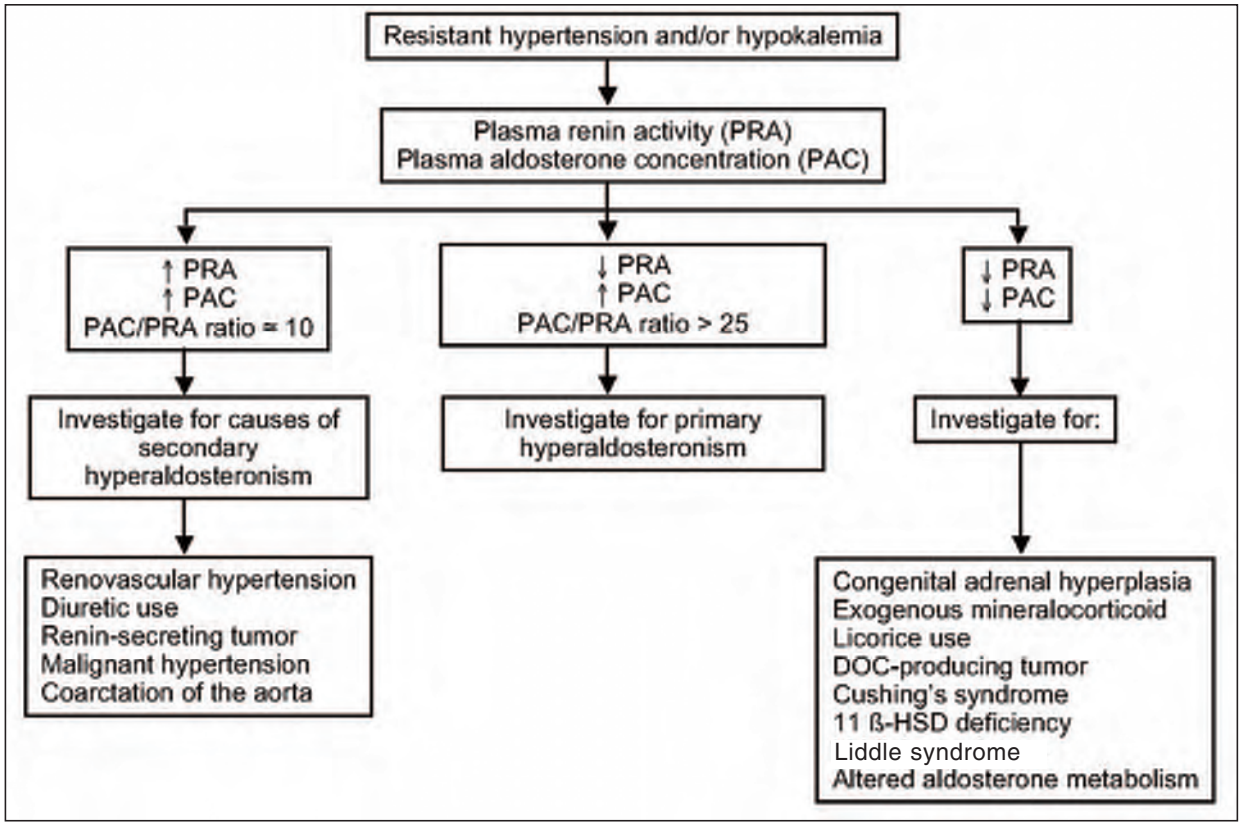

Fig. 1. Algorithm showing use of plasma renin activity (*PRA*) and plasma aldosterone concentration (*PAC*) and their ratio (*PAC/PRA*) for diagnosing hyperaldosteronism in patients with resistant hypertension, hypokalemia, or both. *DOC* = deoxycorticosterone; *HSD* = hydroxysteroid dehydrogenase. Adapted with permission from Young and Hogan (140).

- *Saline suppression test*. Performance of the saline suppression test should be undertaken after the patient has maintained an adequate Na^+ intake (at least 100 mmol/day) for 3 days. Alternatively, the physician may infuse isotonic saline at a rate of 300 to 500 mL per hour for 4 hours. A serum sample is then obtained with the patient in the upright position. Typically, serum aldosterone is suppressed to less than 10 ng/dL in the patient with essential hypertension. Nonsuppression of serum aldosterone confirms a diagnosis of primary hyperaldosteronism and warrants further imaging and localizing procedures (141,143). Severe hypertension may be a contraindication to such testing, and patients must be monitored closely with any salt loading.

Distinguishing Adenoma From Hyperplasia

Adenomas tend to occur in patients at a younger age (<40 years) and with higher aldosterone levels, more severe hypertension, and, frequently, hypokalemia. Serum 18-hydroxycorticosterone, imaging studies, and adrenal venous sampling are helpful in distinguishing an adenomatous from a hyperplastic cause of primary aldosteronism (Fig. 2).

- *18-Hydroxycorticosterone*. In comparison with hyperplasia, adenomas generally have more profound mineralocorticoid effects (that is, hypokalemia and hypertension). In patients with adenomas, serum 18-hydroxycorticosterone is significantly elevated (>100 ng/dL) (144).
- *Imaging studies*. A unilaterally positive CT scan of the abdomen suggests the presence of an adenoma, especially if the patient is younger than 40 years. Because imaging modalities have improved, providing better images with higher resolution than was previously achievable, more micronodules and thickened limbs of the adrenal glands are being diagnosed. Although enhanced imaging sensitivity will certainly decrease the likelihood of a false-negative diagnosis, it may be expected to increase the likelihood of a false-positive diagnosis, in light of the prevalence of nonfunctioning adenomas (incidentalomas). On the basis of imaging alone, inappropriate management decisions could result from a small adenoma being labeled as hyperplasia or from bilateral nodules with a larger, nonfunctioning nodule on one side and a small, hyperactive nodule contralaterally.

  Other imaging options include MRI of the adrenal glands or a ^{131}I-labeled 6β-iodomethyl-19-norcholesterol (NP-59) nuclear scan with dexamethasone suppression. In this latter study, asymmetric uptake after 48 hours suggests adenoma, whereas symmetric uptake after 72 hours indicates hyperplasia (145). Selenium 75-6-selenomethylcholesterol is another radiolabeled

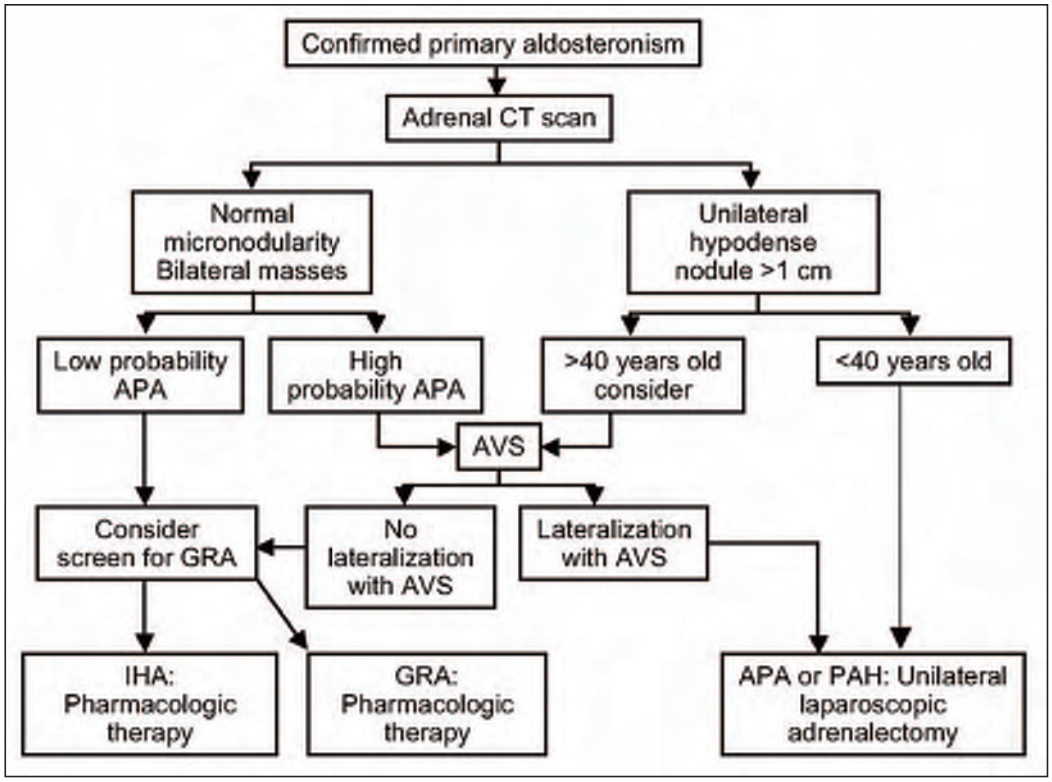

Fig. 2. Algorithm showing subtype evaluation after diagnosis of primary hyperaldosteronism has been established. Imaging studies aid the physician in determining whether any adrenal masses or nodules represent adenoma or hyperplasia. Subsequent adrenal venous sampling (*AVS*) is further helpful in making this distinction, aiding the physician in choice of therapy. *APA* = aldosterone-producing adenoma; *CT* = computed tomographic; *GRA* = glucocorticoid-remediable aldosteronism; *IHA* = idiopathic hyperaldosteronism; *PAH* = primary adrenal hyperplasia. Adapted with permission from Young and Hogan (140).

agent useful for uptake by the pathologic tissue (146). These scans are difficult to interpret, especially in those patients treated with a multidrug regimen.

- *Adrenal venous sampling*. This test is useful for determining whether the imaging study correctly predicts the side of hypersecretion and, accordingly, the surgical response rate (147). This technically challenging procedure should be performed by an experienced interventional radiologist. The crux of the difficulty is sampling the short right adrenal vein, the orifice of which is small relative to the draining area, the inferior vena cava (IVC). After stimulation with ACTH, concomitant measurements of aldosterone and cortisol are made from each adrenal vein and infrarenal IVC, the latter providing a normalized aldosterone:cortisol ratio for comparison.

In unilateral disease, the aldosterone:cortisol ratio would generally be increased by a factor of at least 3 on the diseased side. Measurements of cortisol levels also make it possible to confirm the site of sampling; cortisol levels in the adrenal veins should be 10-fold greater than those in the IVC. Combining this procedure with the short ACTH stimulation test will magnify secretion and the difference in aldosterone production between the 2 adrenal glands.

Management

Surgical resection remains the treatment of choice for a unilateral adenoma unless the potential risks of surgical intervention outweigh the potential benefits. Fortunately, most adenomas can now be removed laparoscopically. Adenomectomy usually corrects the hypokalemia, and the BP may return to normal or at least be more responsive to pharmacotherapy. The severity or duration of the BP elevation or target-organ damage has no bearing on the response of BP to surgical treatment (148). In female patients or elderly patients with a small adenoma or in patients with bilateral adenomas, however, medical therapy with spironolactone may obviate surgical intervention. The side effects of gynecomastia and erectile dysfunction in male patients may make such treatment unacceptable, and a trial of the aldosterone antagonist eplerenone may be warranted (149).

Glucocorticoid-Remediable Aldosteronism

GRA is a low-renin form of inherited hypertension in which aldosterone levels are usually, but not always, high. In GRA, the secretion of aldosterone is primarily regulated by ACTH rather than angiotensin II (150), is therefore subject to diurnal variation, and parallels the cortisol level.

In GRA, aldosterone is hyperresponsive to ACTH, and symptoms can thus be normalized with dexamethasone.

GRA is due to a crossover mutation involving the 11β-hydroxylase and aldosterone synthase genes, which results in a chimeric gene that allows ectopic expression of aldosterone synthase in the zona fasciculata. ACTH normally regulates this layer of the adrenal gland, and the ectopic aldosterone synthetase oxidizes the C-18 carbon of corticosterone and cortisol and thereby results in the production of aldosterone and the hybrid metabolites 18-hydroxycortisol and 18-oxocortisol. These hybrid steroids are further metabolized and eventuate in elevated urinary levels of the tetrahydro compounds 18-hydroxycortisol and 18-oxocortisol (151).

Diagnosis

GRA is diagnosed by demonstrating the presence of the chimeric gene on chromosome 8q21-22 by a long polymerase chain reaction technique or by Southern blot analysis (or both tests). Urinary mineralocorticoid precursors are increased.

Treatment

GRA is treated with the smallest effective dose of a glucocorticoid to suppress the production of ACTH. The typical regimen is dexamethasone, 0.5 mg taken at bedtime.

11β-Hydroxysteroid Dehydrogenase Deficiency

This rare congenital enzyme deficiency (152) is, like acquired aldosteronism resulting from ingestion of carbenoxolone, a syndrome of mineralocorticoid excess. The initial manifestations in affected patients are low plasma renin activity, low aldosterone, and low 11-deoxycorticosterone, slightly elevated urinary free cortisol levels, and increased ratios of urinary tetrahydrocortisol and allotetrahydrocortisol to tetrahydrocortisone. This condition is usually treated with low-dose dexamethasone to suppress ACTH.

Excess Deoxycorticosterone

Excess deoxycorticosterone (DOC) results from 11β-hydroxylase deficiency, which is the second most frequent cause of congenital adrenal hyperplasia, an inherited inability to synthesize cortisol (153). This syndrome is caused by mutations in the *CYP11B1* gene that encodes a mitochondrial cytochrome P-450 enzyme.

Approximately two thirds of patients with the classic form of 11β-hydroxylase deficiency have hypertension, which usually manifests during early infancy. The cause of the elevated BP is unclear. Although it is presumably attributable to excess DOC levels, DOC is a weak mineralocorticoid, and its levels do not correlate with BP. Typically, patients with excess DOC also show signs of androgen excess.

The diagnosis is made by documenting the clinical features and elevated levels of basal or ACTH-stimulated DOC, 11-deoxycortisol (compound S), or 24-hour urinary 17-ketosteroids. Excess DOC is managed by glucocorticoid replacement to suppress ACTH. Hypertension may not respond to glucocorticoid therapy and may necessitate the use of spironolactone, amiloride, or CCBs. Although the hypertension is responsive, hirsutism and virilization are generally refractory to glucocorticoid therapy; androgen receptor blockade should be considered for these effects.

Cushing's Syndrome

Although Cushing's syndrome is not a common cause of secondary hypertension, 75% to 80% of patients with the endogenous syndrome have hypertension (154). Among those patients with iatrogenic Cushing's syndrome, the frequency of hypertension approximates that of the general population (155).

It is unclear how cortisol increases BP, but several mechanisms may be involved. Although considered a glucocorticoid hormone, cortisol has a strong affinity for the mineralocorticoid receptor, equal to that of aldosterone. The effect of cortisol on this receptor is less pronounced than that of aldosterone because of the conversion of cortisol to its inactive form, cortisone, within the kidney by the action of 11β-hydroxysteroid dehydrogenase-2. Experimental evidence suggests that in endogenous Cushing's syndrome, cortisol excess overwhelms this enzyme, as opposed to inhibiting it (156).

Intravascular volume expansion is a feature of the hypertension associated with Cushing's syndrome. Hypokalemia, however, seldom accompanies this hypertension, except in cases of very high ACTH concentrations that can occur in the setting of ectopic production of ACTH. In addition, because the mineralocorticoid inhibitor spironolactone does not affect the cortisol-induced increase in BP, other mechanisms are thought to be responsible for the hypertension associated with Cushing's syndrome (157). For example, this hypertension may be due to increased catecholamine sensitivity. Investigators have demonstrated that, in normal subjects, orally administered hydrocortisone increases BP and enhances pressor responsiveness. The agent causes intra-arterial norepinephrine to increase resistance in local vascular beds in a dose-dependent manner, an indication of increased catecholamine sensitivity after hydrocortisone treatment (158).

Diagnosis

Identification of Cushing's syndrome as a cause of secondary hypertension necessitates an elevated index of suspicion early during the course of the disease, when the glucocorticoid excess may be subtle. New onset of glucose intolerance and hypertension may be the earliest features of the syndrome. When ectopic production of ACTH is the initiating abnormality, the biochemical abnormalities and the severity of the BP elevation may predate the appearance of cushingoid features by years. Hyperpigmentation,

hypokalemia, and difficult-to-control hypertension may be the only presenting features.

Whatever the mechanism of the hypertension accompanying Cushing's syndrome is, definitive treatment should be directed toward correcting the pathologic condition causing the cortisol excess. This strategy necessitates establishing the existence of a cortisol-excess state and identifying the responsible abnormality.

For decades, nonsuppressibility of cortisol production has been the hallmark of endogenous Cushing's syndrome. As illustrated in Figure 3, assessments to determine autonomous secretion of cortisol include late-night measurement of serum and salivary cortisol concentrations, measurement of 24-hour urinary free cortisol excretion, low-dose (2 mg/day in divided doses) dexamethasone suppression of glucocorticoid excretion, and the dexamethasone-CRH test. None of these, however, has sufficient sensitivity, specificity, and predictive value to be considered the "gold standard" diagnostic study (159).

Once the diagnosis of Cushing's syndrome has been established, the subtype must be determined. The absence of ACTH indicates autonomous adrenal function. Normal or increased ACTH concentrations suggest a hypothalamic-pituitary or ectopic ACTH cause. Pituitary imaging and petrosal vein sampling alone and during CRH stimulation can establish the pituitary as the source.

Treatment

Treatment of Cushing's syndrome is almost always surgical and directed against the site of pathologic hormone production. Only in cases of comorbidity or intractable recurrence is medical management appropriate. Effective management of excess cortisolemia ameliorates several features of Cushing's syndrome. Up to 33% of patients with the endogenous syndrome, however, have persistent systolic hypertension, and 75% have persistent diastolic hypertension (160,161).

Most patients with Cushing's syndrome will have a decrease in BP during ketoconazole treatment (162). For those patients with persistent hypertension during ketoconazole treatment, cautious use of antihypertensive therapy is recommended. No specific class of drugs is recommended in this patient population; in determining the pharmacologic choice, the levels of the patient's electrolytes and renal function should be considered.

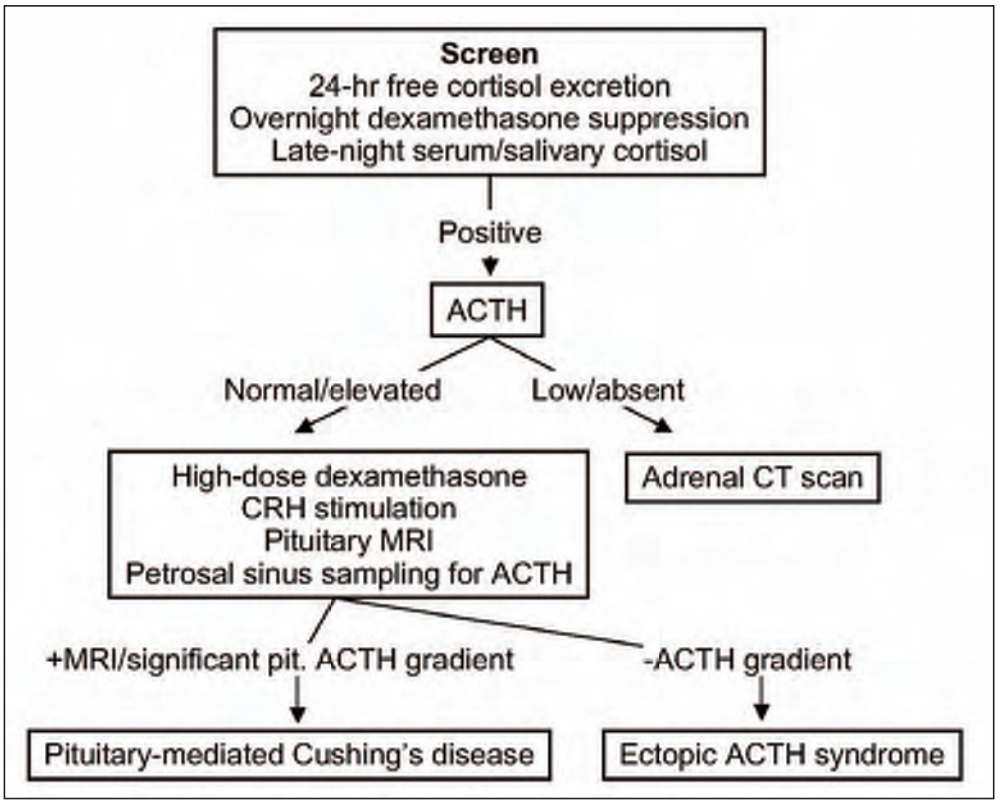

Fig. 3. Algorithm showing assessment for Cushing's syndrome, including establishing that a cortisol-excess state exists and determining the abnormality responsible, so that treatment may be directed toward correcting the pathologic condition causing this excess. Once a diagnosis of Cushing's syndrome has been established, the subtype must be determined. *ACTH* = adrenocorticotropic hormone; *CRH* = corticotropin-releasing hormone; *CT* = computed tomographic; *MRI* = magnetic resonance imaging; *pit*. = pituitary.

Thyroid Disease

Hypothyroidism

Approximately 3% to 5% of all patients with hypertension have hypothyroidism (163). In patients with hypothyroidism, the prevalence of hypertension, particularly elevated diastolic BP, is nearly triple that seen in the general population (164), although the association between hypertension and hypothyroidism has been questioned (165).

Hypothyroidism is associated with a low-renin form of hypertension (166). Systemic vascular resistance is increased (167), plasma volume is contracted, and cardiac output is reduced. The BP often decreases after correction of the hypothyroidism (164). In one study, treatment of the hypothyroid state reduced diastolic BP to <90 mm Hg in all patients younger than 45 years and in 23% of patients 50 to 69 years of age (168). Experimental evidence suggests that, perhaps because of the bradycardia of hypothyroidism, the heart may be protected even when the BP level is elevated in these patients (169). Levothyroxine treatment of patients with hypothyroidism lowers plasma catecholamine levels and reduces the tachycardic response to infusion of norepinephrine (170).

Hyperthyroidism

Hyperthyroidism is usually associated with systolic hypertension. Direct and indirect actions of triiodothyronine increase cardiac contractility (through increased velocity of contraction and diastolic relaxation), whereas excessive vasodilatation results in decreased peripheral vascular resistance (171). Systolic BP levels tend to decrease when hyperthyroidism is effectively controlled (172).

Pregnancy-Associated Hypertension

Hypertension complicates 5% to 10% of pregnancies. In approximately 30% of these cases, the hypertension antedates pregnancy (chronic hypertension), although it is frequently undiagnosed (173). Hypertension that develops during pregnancy may be transient, without associated proteinuria, and resolved after delivery (gestational hypertension), or it may be accompanied by substantial proteinuria and other adverse signs and symptoms (preeclampsia). The risk of developing preeclampsia is approximately 25% when hypertension antedates pregnancy, in comparison with a risk of approximately 5% for normotensive women (174).

Although the causes of pregnancy-induced hypertension and preeclampsia remain unclear, the pathophysiologic changes are known to involve increased vascular responsiveness to vasoconstrictor stimuli. Patients with preeclampsia have activation of the coagulation cascade in conjunction with increased inflammatory markers and evidence of oxidative stress. Many of the features of preeclampsia mimic the insulin resistance syndrome, and insulin resistance is, in fact, a prominent feature of preeclampsia (174). Pregnancy-induced hypertension is associated with a 40% increase in the risk of occurrence of gestational diabetes (175).

The immediate treatment of severe hypertension (>170/110 mm Hg) during pregnancy improves both maternal and fetal outcomes, and most authorities agree that treating moderate hypertension is also beneficial (176). Improved outcomes include reduction in maternal and perinatal mortality, preterm birth, primary cesarean section, and duration of hospital stay. Considerable controversy still exists, however, about the relative benefit of treating mild hypertension (<140/90 mm Hg) during pregnancy, particularly near term. Magnesium sulfate is superior to other agents in reducing recurrent eclamptic seizures and is recommended for patients with preeclampsia at high risk for seizures (173). Methyldopa or CCBs, particularly nifedipine, are thought to be the most suitable antihypertensive agents for use during pregnancy, in part because of the lack of long-term follow-up data in the offspring with use of newer drugs. When necessary, BBs may be prescribed. ACEIs and ARBs are contraindicated during pregnancy because of increased fetal morbidity and mortality, but all other classes of antihypertensive agents can be used safely, and the experience of the treating physician will influence the agent selection (13).

Hyperparathyroidism

Approximately 30% to 40% of patients with hyperparathyroidism have hypertension. Conversely, the frequency of hyperparathyroidism in patients with high BP levels is approximately 1%, or 10 times greater than that in the general population.

No direct correlation has been noted between the severity of the BP elevation and the degree of hypercalcemia or the level of parathyroid hormone (177). After parathyroidectomy, BP levels may or may not normalize (178). Accordingly, although hypercalcemia may cause vasoconstriction, the etiologic factors underlying hypertension in early or mild hyperparathyroidism are uncertain, and the association may be partly coincidental. Renal parenchymal damage due to nephrocalcinosis or nephrolithiasis could be etiologic in the hypertension associated with chronic or severe hyperparathyroidism (179).

Acromegaly

Hypertension occurs in about a third of the patients with acromegaly. Excess growth hormone (endogenous or exogenous) can result in an increase in plasma volume attributable to sodium retention (180) in the absence of hyperaldosteronism and yet induction of a low-renin state (181).

Renin-Secreting Tumors

Renin-secreting tumors are extremely rare. They tend to occur in younger persons and are associated with high plasma renin and aldosterone levels in the absence of renovascular disease. Hypertension and hypokalemia are usu-

ally severe (182). The renin can originate from a juxtaglomerular cell tumor, Wilms' tumor, or ovarian tumor. The extrarenal tumors generally produce higher levels of prorenin (183).

The diagnosis of hypertension attributable to a renin-secreting tumor is one of exclusion in patients with the aforementioned clinical and biochemical features. MRI is the most reliable method of diagnosing these lesions; arteriography and selective renal vein sampling are unreliable for diagnosis. Surgical excision is the treatment of choice. Renin-secreting tumors of the kidney are usually superficial and are readily separated from normal renal tissue. All these lesions reported to date have been benign.

Liddle Syndrome

Liddle syndrome is a rare autosomal dominant monogenically inherited disorder involving mutations in the epithelial sodium channel (ENaC), which has a central role in sodium transport across membranes. In the kidney, the ENaC contributes to the regulation of BP through changes in sodium balance and blood volume (184). The ENaC is a membrane protein consisting of 3 different but homologous subunits (alpha, beta, and gamma) present in the apical membranes of epithelial cells (185). Gain-of-function mutations in the beta and gamma subunits enhance sodium reabsorption and result in hypertension in Liddle syndrome. Other ENaC polymorphisms have been described, often occurring in persons of African descent, which also result in hypertension (186). All these cases have had low plasma renin activity and suppression of aldosterone, which under normal conditions modulates the sodium channel activity in the distal tubule (187). Amiloride and triamterene, which specifically inhibit overactive sodium channels, but not spironolactone, have been found to be particularly effective in controlling hypertension in these patients. Loss-of-function mutations in all 3 subunits of the ENaC cause hypotension, as in pseudohypoaldosteronism type 1, a salt-wasting disease that occurs during infancy.

Although essential hypertension is likely to be a polygenic (and multifactorial) disorder resulting from the inheritance of several susceptibility genes, the potential role of mutations in genes coding for the ENaC is currently an area of considerable interest (185).

IX. CONCLUSION

The guidelines presented focus on identifying and managing hypertension secondary to or coincident with endocrinopathies. An understanding of endocrine physiology and pathophysiology will aid clinicians in not only identifying the causes and determining the best treatment of these complex forms of hypertension but also anticipating the usefulness of evolving therapies.

As always, individual physician expertise and judgment are paramount in making these sophisticated clinical decisions. These guidelines are intended to serve as a decision-making aid to help clarify some of the confusing issues surrounding the diagnosis and management of hypertension, particularly when associated with endocrine disorders.

X. DISCLOSURE

Zachary T. Bloomgarden, MD, FACE, is or has been a speaker or consultant (or both) for Amylin Pharmaceuticals, CV Therapeutics, GlaxoSmithKline, Eli Lilly and Company, Novo Nordisk, Sanofi-Aventis, and Takeda Pharmaceuticals America. Other members of the AACE Hypertension Task Force reported no conflicts of interest.

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