

How to Achieve Control in Managing Hypertension?

Robert D. Brook, MD, Department of Internal Medicine, Division of Hypertension, University of Michigan, Ann Arbor, Michigan

Hypertension treatment has definitively proven to reduce the incidence of cardiovascular and cerebrovascular morbidity and mortality. Despite improvements in blood pressure awareness and management during the last few decades, the majority of hypertensive adults remain inadequately treated with blood pressure goals not achieved. Most recent estimates demonstrate that only 27.4% of adults in the United States have their blood pressures well-controlled (National Health and Nutrition Examination Survey III, phase 2). The situation among diabetic patients is even worse, as only 12% have their blood pressures <130/85. Other countries with universal access to health care share the same problem or have even poorer control rates (e.g., 16% in Canada).

Given that hypertension is a major independent risk factor for both cardiovascular and cerebrovascular disease, the first and third leading causes of mortality, respectively, poor blood pressure control poses tremendous public health and cost burdens to the industrialized world. An improved understanding among physicians of the barriers to effective hypertension treatment and of methods to improve blood pressure control is therefore important. The aim of this brief review will be to provide a practical approach for health care providers on how to achieve target blood pressure goals in treating hypertension.

Blood Pressure Goals

There is a direct linear relationship without a threshold level between both systolic and diastolic blood pressure and cardio-cerebrovascular disease. Even high-normal blood pressures (130–139/85–89 mm Hg) are associated with an increased relative risk of cardiovascular disease (OR 2.5 for women and 1.6 for men vs. optimal blood pressure <120/80 mm Hg). In the past, treatment of diastolic blood pressure has taken precedence in clinical trials. However, systolic blood pressures and pulse pressures are more closely linked to cardiovascular health, especially in the elderly, and are becoming the focus of modern treatment.

At present, the Joint National Committee VI (JNC VI) has set the goal office blood pressure at <140/90 mm Hg for adults with uncomplicated hypertension. No trial has yet demonstrated that incremental reductions in blood pressure below this level improve outcomes in these patients. The current systolic goal, however, has been the subject of some debate. All patients enrolled in the clinical trials demonstrating the benefits of treating isolated systolic hy-



pertension were limited to those with initial systolic pressures ≥ 160 mm Hg.

The blood pressure targets for adults with certain comorbidities and/or target organ damage are even lower (Figure 1). For example, current evidence supports more aggressive treatment for all diabetic patients. In the Hypertension Optimal Treatment (HOT) trial, all major cardiovascular events could be reduced by approximately 50% by further lowering diastolic blood pressure from <90 to <80 mm Hg in diabetic patients. Future studies will determine if this degree of aggressive treatment is also warranted in other high-risk adults.

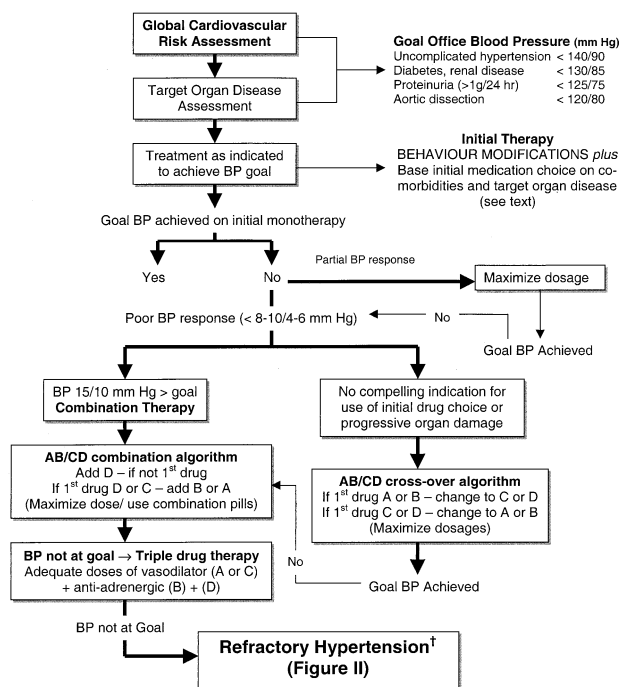
Barriers to Achieving Blood Pressure Targets

A number of factors pose significant obstacles for optimal blood pressure treatment (Tables 1 and 2) and will be discussed in detail during the review of the approach to hypertension management. However, a few points merit highlighting. Despite inadequate blood pressure control throughout the industrialized world, a number of studies have estimated the prevalence of truly refractory hypertension at only 2.9–18%. The majority of under-controlled hypertension occurs in older adults with isolated mild stage I (140–160 mm Hg) systolic hypertension who have adequate access to medical care. These observations underline a very important point; physician under-aggressiveness remains a primary reason for poor hypertension control.

A substantial portion of this dilemma can likely be attributed to the “single-pill myth” that most hypertension can be adequately managed with one medication. On the contrary, several large randomized trials clearly illustrate that hypertension is a heterogeneous disorder that requires more than one blood pressure pill in approximately 50% of patients. In order to achieve a diastolic blood pressure <80 mm Hg in the HOT study, it required an average of 3.6 medications. In the African-American Study of Kidney Disease (AASK), 3.8 drugs were needed daily to reach a goal mean arterial pressure of <92 mm Hg. Despite these findings, a large veterans study and a national survey of primary care physicians have both demonstrated a high prevalence of physician reluctance to increase blood pressure medications in adults with mildly-to-moderately uncontrolled hypertension. It is therefore crucial for health care providers to be aware of the large degree of effort required to achieve the blood pressure goals of existing guidelines.

Management of Hypertension

A suggested approach to achieve blood pressure control while managing hypertension is outlined in Figure 1. Because the primary aim of treating any cardiovascular risk factor is to actually improve patient outcomes, the initial step is to perform a complete cardiovascular history and



[†]Refractory hypertension work-up may be warranted on 1 or 2 drugs in special circumstances (e.g. no risk factors for primary hypertension, young age, evident sign(s)/symptom(s) of secondary hypertension)

A, angiotensin converting enzyme inhibitor; B, beta blocker; C, calcium channel blocker; D, diuretic, BP, blood pressure

Figure 1. General hypertension management outline.

physical exam. The focus should be on global risk assessment in order to establish an absolute cardiovascular risk estimate (e.g., Framingham risk score). Afterward, some degree of hypertension-related target organ disease (TOD) assessment is mandatory. Opinions vary on the extent of TOD work-up that should be routinely performed. For the most part, a more comprehensive TOD assessment is helpful for patients at intermediate cardiovascular risk to help guide the intensity of subsequent treatment. Recent studies demonstrate that obtaining an echocardiogram (left ventricular size measurement) and/or carotid ultrasound (inti-

Table 1. Etiology of Refractory Hypertension

Primary Causes	Examples
Poor adherence to medical regimen	Skipped or missed drugs; Self-discontinuation of drugs; Poor office follow-up; Avoiding behavioral modifications
Dietary interference	Excess salt, caffeine, alcohol
Medication or drug interference	Table 2
White coat (office) effect	Isolated office hypertension; Office refractory hypertension
Pseudo-hypertension	Poor measurement techniques; Decreased arterial compliance; Cuff-inflation artifact; Reactive— anxiety/pain; Paroxysmal hypertension
Sub-optimal medication regimen	Physician under-treatment; Poor medication combinations; Wrong diuretic class; Pseudo-tolerance to medications
Obesity	Metabolic syndrome; Sleep apnea, habitual snoring
Secondary hypertension	Table 3

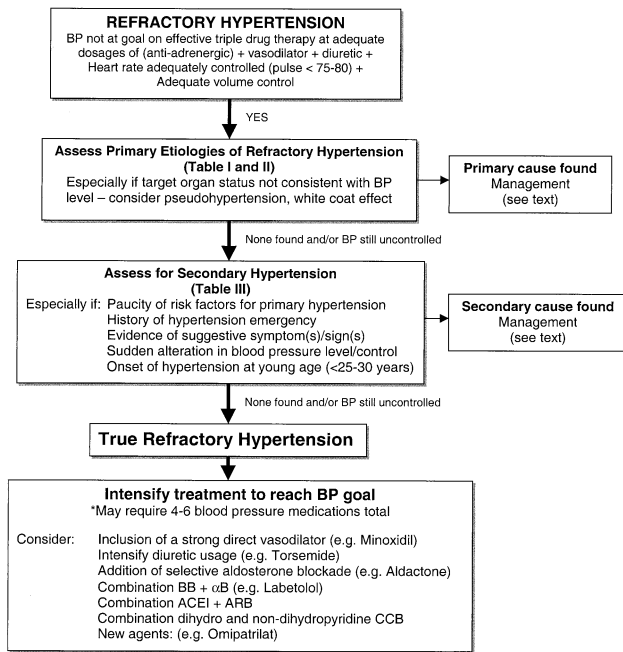
Table 2. Substances That May Interfere With Blood Pressure Control

Medication Class	Examples
Nonsteroidal anti-inflammatory drugs	Indomethacin, Piroxicam, Naproxen
Cyclooxygenase-2 inhibitors	Rofecoxib, Celecoxib
Oral contraceptives	(not hormone replacement therapy)
Nasal decongestants (oral or nasal)	Phenylephrine, Pseudoephedrine
Steroids	glucocorticoids, mineralocorticoids
Cyclosporine	
Erythropoietin	
Anti-depressants	monoamine oxidase inhibitors, tricyclics
Central acting medications	Chlorpromazine, sympathomimetics
Weight loss medications	Sibutramine, Phenylpropanolamine
Migraine and headache medications	ergotamines, Sumatriptan
Beta-agonists	
Drugs	
	Cocaine, amphetamines, caffeine, stimulants
	Acute tobacco smoking, excess alcohol consumption
Herbal Medications (Others)	
	Ephedra (Ma Huang), Ginseng, Saw palmetto, Capsicum
	Licorice/Glycyrrhetic acid (chewing tobacco), Carbenoxolone

ma-media thickness) will significantly alter the management of at least 45% of medium risk patients by leading to the earlier initiation of medications.

Guided by the cardiovascular and TOD assessment, an initial drug of first choice should be chosen based on the recommendations of JNC VI (not reviewed here). In adults with uncomplicated hypertension, recent clinical trials suggest that all four medication classes (not α -blockers) are equally effective in reducing adverse cardio-cerebrovascular events. Therefore, the initial drug choice can be tailored to individual patient and physician preferences. However, some studies suggest that the newer classes of anti-hypertensives, particularly the angiotensin-converting enzyme inhibitors (ACEI), provide vascular protection beyond blood pressure reduction alone (e.g., Heart Outcomes Prevention Evaluation study). In addition to the conditions recommended by JNC VI, ACEI may also be particularly effective in any high-risk patient, such as those with underlying atherosclerosis. Furthermore, the recent LIFE study results suggest that angiotensin-receptor blockers (ARB), may be superior to older antihypertensive agents for reducing cardiovascular events in high-risk hypertensive patients with left ventricular hypertrophy. Whether either ACEI or ARB become the recommended first-line agent will be clarified by ongoing studies.

Once a first agent has been initiated, management should generally proceed as per Figure 1. If adequate control is not achieved (approximately 50% of the time), then a dose escalation, a change to an alternate monotherapy or beginning combination therapy are all viable choices depending on the circumstances (Figure 1). In general, combination therapy should be initiated if rapid achievement of goal blood pressure is desired, a drug indication prohibits discontinuation of the initial medication or the blood pressure is substantially above target values on monotherapy.



BB, beta blocker; α B, alpha blocker; ACEI, angiotensin converting enzyme inhibitor
ARB, angiotensin receptor blocker; BP, blood pressure; CCB, calcium channel blocker

Figure 2. Refractory hypertension assessment.

For the most part, medications that primarily target the renin-angiotensin system (β -blockers, ACEI) combine well with drugs that are more effective in low-renin states (calcium blockers, diuretics). A general AB/CD drug combination and monotherapy medication class crossover strategy has therefore been promoted. The effectiveness of this general rule has recently been demonstrated to increase the blood pressure control success rate of monotherapy from 39% to 73%. Although various patient demographic predictors and the AB/CD algorithm have some limited practical utility in selecting drug therapy, they must never take precedence over the indicated medication of choice based on comorbid conditions as per JNC VI (e.g., ACEI in diabetes).

One-third to one-quarter of hypertension patients will not have their blood pressures adequately lowered on two medications. At this point, triple-drug therapy should be started. The most effective and rational drug combination consists of a vasodilator (e.g., calcium-channel blocker, ACEI) plus an anti-adrenergic (e.g., β -blocker, central acting sympatholytic) plus a diuretic (a loop diuretic may be required in the presence of renal insufficiency or multiple anti-hypertensive medications). If triple therapy is unsuccessful (2.9–18% of the time), then an evaluation for the etiology of refractory hypertension should follow (Figure 2). There are, however, circumstance when this evaluation should be initiated much earlier in the course of therapy (e.g., young patients with limited risk factors for primary hypertension, obvious sign(s)/symptom(s) of secondary hypertension).

Table 3. Strategies To Improve Patient Adherence

- Schedule regular and frequent follow-up visits
 - Emphasize behavioral modifications to reduce medication dependence
 - Patient education about hypertension and the importance of therapy
 - Achieve blood pressure control as rapidly as possible once therapy begins
 - Minimize drug regimen alterations (decrease medicine turbulence)
 - Discuss medication side-effects
 - Use medications with lower side-effect profiles (ACEI, ARB)
 - Set realistic blood pressure and behavioral modification goals
 - Reduce medication costs for patients with financial concerns
 - Use home blood pressure monitoring and home blood pressure logs
 - Electronic pill counters
 - Prescribe combination medications when indicated
- Lowers adverse side-effects due to lower dosages
Pill burden is reduced
Medicine regimen is simplified
More effective in achieving target blood pressures
May be less expensive

Evaluation of Refractory Hypertension

In most cases, special attention should be paid to the primary causes of refractory hypertension prior to initiating a work-up for identifiable secondary etiologies (Table 1). In a commonly cited study, the etiology of refractory hypertension in the vast majority of cases (89%) referred to a tertiary care clinic were due to one of these primary causes. A suboptimal medical regimen accounted for approximately 40% of referrals. In most patients, the blood pressure could be subsequently controlled after identifying and treating a primary cause of refractory hypertension (Table 1) and/or after altering and intensifying the medication regimen.

Patient Non-Adherence

Poor adherence to the prescribed medical regimen is frequently cited as the most common etiology of refractory hypertension. It is estimated that one-half of all patients discontinue taking antihypertensive medications within 1 year. Unfortunately, patient adherence is notoriously difficult to adequately assess. Studies suggest that physicians have only a 50/50 chance of truly determining if a patient is properly following the medical regimen. Pill counting is usually not effective. Some methods to help determine compliance are to openly discuss the issue in a non-judgmental manner, assess for expected drug side-effects (e.g., bradycardia on a β -blocker), measure plasma drug levels and to ask patients to recall their drug names and daily pill-taking routine. Occasionally, it may be necessary to admit patients with poorly controlled hypertension to the hospital for observed therapy to settle the issue.

Table 3 presents some strategies to improve patient adherence. The usual JNC VI recommendation is to begin medications with either a diuretic or β -blocker for patients with uncomplicated hypertension to save health care costs. However, recent data suggest that starting monotherapy with either an ACEI or ARB leads to superior 1-year patient adherence (64% with ARB vs. 38% for diuretics). The improved long-term blood control may actually result in a

more cost-effective outcome due to reduced incidence of hypertension-related cardiovascular events and hospitalizations.

Diet, Medications and Drugs Interfering With Blood Pressure

Table 2 presents a list of many medications, drugs or dietary substances that may raise blood pressure or interfere with medication efficacy. It is important to discuss all over-the-counter medications and herbal remedies with patients, as these are often overlooked during the medication history.

White Coat Effect and Home/Ambulatory Blood Pressure Monitoring

Approximately 16–35% of patients diagnosed with hypertension actually have normal blood pressures at home (white coat hypertension). Physicians should be aware that there is a lower threshold value for hypertension when measured by home recordings (<135/85 mm Hg). Furthermore, some studies demonstrate that one-quarter of all true hypertensives with apparent refractory hypertension have controlled out-of-office blood pressures (pseudo-resistance due to white coat effect). These situations should be particularly suspected when the level of hypertension TOD does not parallel the magnitude of office blood pressure elevations.

Home blood pressure monitoring has shown to improve patient adherence, reduce medical costs and physician visits, lower the amount of drugs required for blood pressure control and lead to a better prediction of long-term cardiovascular outcomes. In general, home monitoring can be accurately done with modern devices (particularly those with memory to avoid patient misreporting of home recordings). Devices that have passed the American Association for Medical Instruments should be used. The most critical issue is to assure that patients are obtaining home readings with the proper technique (e.g., sitting 5 minutes resting prior to recording). Only a few readings per week are required, as studies have demonstrated that 3–6 measurements per week accurately convey average out-of-office levels and rule out white coat hypertension. In certain circumstances (e.g., patient anxiety, uncertain reliability), 24-hour ambulatory blood pressure monitoring is useful or required to obtain accurate blood pressure determinations.

Pseudohypertension

An additional situation that should be suspected when TOD is less severe than would usually result from the degree of office blood pressure elevations is pseudohypertension. Many conditions can lead to inaccurate estimations of actual blood pressure values (Table 1). Great care should be made to assure that office blood pressures are being obtained by the proper technique. Simple mistakes such as inappropriately low arm position, too small of a blood pressure cuff and incomplete back and foot support can falsely raise blood pressure by 5–15 mm Hg.

Calcification of the brachial artery media can also lead to falsely elevated indirect blood pressure measurements (e.g.,

elderly, diabetics). This should be suspected when symptoms of hypotension are being reported despite severe refractory office pressures. A carefully measured oscillometric finger blood pressure, or an intra-arterial reading usually settles this issue.

An often under-appreciated etiology of pseudohypertension is paroxysmal hypertension due to underlying psychologic problems (e.g., anxiety disorders). These situations often occur in the absence of obvious precipitants and mimic a pheochromocytoma, due to the labile hypertension associated with somatic symptoms. Patients usually deny any relation to stress, anxiety, pain or emotional problems. This differentiates it from reactive hypertension, which is clearly related to an environmental precipitant. Ruling out adrenal hormonal abnormalities, while being careful not to add to patient anxiety, with the subsequent pursuit of psychiatric assessment is helpful. This can usually be done by measuring a single plasma metanephrine value due to its extraordinary sensitivity of 99%. In many cases, the use of anti-anxiety or anti-depressant medications can eliminate the labile hypertension. Simply adding more blood pressure pills usually worsens the problem and does not control the severe blood pressure elevations during paroxysms.

Sub-Optimal Medical Therapy

An inadequate medical regimen is often cited as the first or second (behind patient non-adherence) most common primary etiology of presumed refractory hypertension. Beyond physician medication under-aggressiveness, the single most prevalent shortcoming is diuretic under-usage (or inappropriate use of a thiazide diuretic in the presence of renal impairment or multiple strong vasodilators). Triple-drug regimens should include drugs as outlined in Figure 2. Indeed, the diagnosis of true refractory hypertension cannot be made and most work-ups for secondary hypertension should not proceed until the drug dosages and combinations are optimized.

Secondary Hypertension

Once a primary cause of refractory hypertension is no longer suspected, then a tailored work-up for and treatment of secondary hypertension should follow (Table 4). In situations where there are suggestive signs/symptoms or a relative lack of risk factors for primary (essential) hypertension, a secondary hypertension work-up may be warranted earlier in the management. Most very young patients (<30 years old) and those with a clear history of a hypertension emergency should undergo an evaluation of secondary causes.

A complete discussion of secondary hypertension is beyond the scope of this review. However, two particular disorders deserve to be highlighted. Many large studies over the last decade have clearly shown that sleep-related breathing disorders (e.g., sleep apnea, recurrent snoring) are associated with hypertension 50–80% of the time. There is emerging evidence that sleep apnea may be a common

Table 4. Secondary Causes of Hypertension

Cause	Etiologies/Signs/Symptoms	Screening Test(s)/Follow-Up Tests
Common		
Intrinsic renal disease	Any cause of renal insufficiency/edema	Creatinine (>1.4-1.8)/GFR, UA, renal DUS
Renovascular disease	Atherosclerosis, FMD/renal bruit, sudden BP change, underlying atherosclerosis, increase in creatinine with ACEI, intermittent pulmonary edema, FMD—young woman	Renal MRA ± DUS for resistance indices/renal angiography ± pressure gradients
Hyperaldosteronism	Adrenal hyperplasia or adenoma/ ↓ potassium, metabolic alkalosis, ↑ sodium, ↓ ↓ potassium on diuretic, any refractory hypertension	plasma PRA:ALDO/24-hour urine ALDO, saline suppression test, adrenal imaging
Sleep breathing disorders	Sleep apnea, habitual snoring/snoring, witnessed apneas, day-time somnolence, headache, obesity	Sleep study/CPAP trial
Uncommon		
Pheochromocytoma	Adrenal, extra-adrenal (rare)/spells—episodic hypertension, palpitations, sweating, headache, pallor, orthostasis	Plasma metanephrine/24-hour urine metanephrines, clonidine suppression test, adrenal imaging
Hyperglucocorticoidism	Cushing's, adrenal adenoma/Purple striae, trunkal obesity, buffalo hump, lipodystrophy	Plasma cortisol/24-hour urine cortisol, dexamethasone suppression test
Aortic coarctation	Congenital disease/Young age, ↓ Leg pressures, delayed leg pulses	CT scan, angiogram
Hyper/hypothyroidism	Any cause/hyper/hypothyroid symptoms	TSH/T4, thyroid imaging
Hyperparathyroidism	Any cause/hypercalcemia	PTH, calcium/parathyroid imaging

GFR, glomerular filtration rate; UA, urinalysis; FMD, fibromuscular dysplasia; MRA, magnetic resonance angiography; DUS, duplex ultrasonography; ACEI, angiotensin converting enzyme inhibitor; PRA, plasma renin activity; ALDO, aldosterone

cause of refractory hypertension and that treatment with nocturnal CPAP can significantly improve the ease of blood pressure control. Physicians should be alerted to the possibility of sleep apnea and have a low threshold for ordering a sleep study in any patient with refractory hypertension, particularly those with suggestive symptoms (Table 3).

In the past, primary aldosteronism was thought to account for only 0.5–1.0% of hypertension. More current estimates suggest that it may actually underlie 6–14% of cases. Additionally, 30–50% of patients with documented mineralocorticoid-induced hypertension have normal to low-normal serum potassium levels, making the presence of hypokalemia an unreliable screening test. An early assessment with a screening plasma renin activity (PRA) to aldosterone ratio (in ng/dL/ng/mL/hour) in cases of refractory hypertension is helpful even when patients are taking blood pressure medications (except spironolactone). Both PRA and aldosterone measurements are available in most clinical laboratories and can be performed without special patient preparation in the morning hours after being ambulatory. A ratio >20-25 in the presence of a low PRA (<1 ng/mL/hour) and an aldosterone ≥15 ng/dL should be followed up with further confirmatory testing, such as an intravenous saline suppression test. The addition of aldosterone blocking medications, or adrenal adenoma resection as indicated, can be highly successful in normalizing the blood pressure in these cases.

Methods to Achieve Blood Pressure Goals in Refractory Hypertension

In rare cases (2.9–18%), hypertension is truly refractory to triple-drug therapy without an underlying primary or secondary cause of hypertension. These cases are usually due to extreme obesity or elderly age. Often times, patients have a long history of poorly controlled moderate hypertension

that has subsequently progressed to severe refractory hypertension due to vascular and TOD damage. Figure 2 provides suggestions for management.

The most helpful ways to lower blood pressure are to not give up and continue to try different regimens. What works for one patient may not work for another. Make sure that there is an adequate degree of diuretic usage. Use multiple combination pills that may include up to 4–6 medications in only 2–3 different pills. Add a strong acting direct vasodilator such as minoxidil. This often achieves control when other medications fail, especially with renal insufficiency. A heart rate–slowing agent and loop diuretic are almost always required in combination with minoxidil to control reflex sympathetic activation and volume retention. The addition of a selective aldosterone blocker to the medication regimen has been shown to significantly lower blood pressure and reduce the number of pills required to achieve goals, even without overt primary hyperaldosteronism. Finally, referral to a hypertension specialist and/or enrollment in trials of new anti-hypertensive medications is an option for patients where blood pressure control remains elusive.

Questions and Answers

- Can physicians trust home blood pressures and use them clinically?
Yes. Most often, home blood pressures more accurately convey the patient's risk for future cardiovascular events and their average blood pressure than office readings. Most modern devices are accurate if used properly. However, treatment guidelines are based on office readings. Therefore, home monitoring should be used to supplement office readings at the current time (not replace them).
- Should white coat hypertension be treated?
This is debatable at the present time. Prospective

studies show no evidence of increased mortality in white coat hypertensives. However, most studies suggest that white coat hypertension is associated with evidence of mild target organ disease compared to true normotensives. As long as patients have home blood pressures <135/85 and are without evidence of organ damage, then hypertension treatment can be postponed. Close follow-up is mandatory.

3. How common is refractory hypertension?
True refractory hypertension when patients are taking an adequate triple-drug regimen and have no secondary cause of hypertension is uncommon (only 2.9–18% of hypertensives).
4. What is the most common secondary cause of hypertension?
If obstructive sleep apnea is counted as a secondary cause, then it is by far the most prevalent underlying disease contributing to hypertension. Intrinsic renal disease and renal vascular disease are also common. Primary aldosteronism is now recognized as a very common cause of hypertension as well (6–12% of hypertensives).
5. Can most hypertensives be controlled on one pill?
No. In fact, approximately 50% of hypertensives need two or more medications.
6. Are there differences among the blood pressure classes in preventing disease in uncomplicated hypertension?
No. The four most recent studies demonstrate that all classes (except possibly α -blockers) are equally effective in reducing cardiovascular risk in the absence of diabetes, renal insufficiency or previous heart disease or failure (uncomplicated hypertension). Differences

do exist among medication classes that make certain medications superior for patients with comorbidities (e.g., ACEI should be used in diabetes).

Suggested Reading

- Setaro JF, Black HR. Refractory hypertension. *N Engl J Med* 1992;327:543–7.
- Graves JW. Management of difficult to control hypertension. *Mayo Clin Proc* 2000;75:278–84.
- Yakovlevitch M, Black HR. Resistant hypertension in a tertiary care clinic. *Arch Intern Med* 1991;51:1786–92.
- Alper AB, Calhoun DA. Contemporary management of refractory hypertension. *Current Hypertens Rep* 1999;1:402–7.
- Brown MA, Buddle ML, Martin A. Is resistant hypertension really resistant? *Am J Hypertens* 2001;14:1263–9.
- Thakkar RB, Oparil S. Primary aldosteronism: A practical approach to diagnosis and treatment. *J Clin Hypertens* 2001;3:189–95.
- Silverberg DS, Oksenberg A. Are sleep-related breathing disorders important contributing factors to the production of essential hypertension? *Curr Hypertens Rep* 2001;3:209–15.
- Spence JD, Hurley TC, Spence JD. Actual practice in hypertension: Implications for persistence with and effectiveness of therapy. *Curr Hypertens Rep* 2001;3:481–7.
- Sica DA, Gehr TWB. Direct vasodilators and their role in hypertension management: Minoxidil. *J Clin Hypertens* 2001;3:110–4.
- Mann S. Severe paroxysmal hypertension (pseudopheochromocytoma): Understanding the cause and treatment. *Arch Intern Med* 1999;159:670–74.

Address correspondence and reprint requests to Robert D. Brook, MD, Department of Internal Medicine, Division of Hypertension, University of Michigan, 1500 E. Medical Center Drive, 3918 Taubman Center, Ann Arbor, MI 48109.