Choosing Initial Therapy for Hypertension
A Personal View

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With numerous safe and effective antihypertensive drugs now available, the clinician should no longer choose only diuretic agents or β-adrenergic receptor blockers (β-blockers) as initial therapy. Five classes of agents, including angiotensin converting enzyme inhibitors, β-blockers, calcium entry blockers, peripheral α₁-adrenergic receptor blockers, and thiazide diuretic agents, are all appropriate monotherapy in properly selected patients. The choice depends on efficacy, side effects, demography, comorbidity, dosage schedule, cost, mechanism of drug action, and the pathophysiology of the patient’s hypertension. Extensive data are now available that will assist the clinician in choosing an agent that has the greatest probability of success without the need for extensive biochemical or hemodynamic evaluation. (Hypertension 1989;13[suppl I]:I-149–I-153)

Once the diagnosis of hypertension has been established and the initial evaluation completed, the clinician must decide whether to initiate drug therapy and, if so, with which of the vast array of agents now available. I propose that it is no longer appropriate to start treatment only with thiazide diuretic agents or with β-adrenergic receptor blockers (β-blockers) in all patients, as recommended in the third report of the Joint National Committee on Detection, Evaluation, and Treatment of High Blood Pressure.¹

Nonpharmacological Therapy

Nonpharmacological therapy alone is a safe and inexpensive option for patients whose diastolic blood pressures are in the range 90–99 mm Hg and who have no evidence of end-organ damage or other cardiovascular risk factors as determined by simple clinical or laboratory examination. Nondrug therapy has become especially appealing in appropriate patients for a number of reasons. First, the Australian Therapeutic Trial in Mild Hypertension showed that a large percentage of mild hypertensive patients have a clinically meaningful reduction in blood pressure when they take a placebo.² Second, several clinical trials have suggested that the usually recommended drugs for monotherapy, thiazide diuretic agents and β-blockers, frequently cause intolerable side effects.³–⁵ Third, these and other studies continue to imply that treatment with thiazide diuretic drugs does not reduce the frequency of ischemic heart disease and sudden death, perhaps because of the effects of these drugs on electrolytes (hypokalemia and hypomagnesemia) and other metabolic parameters (hyperglycemia and hypercholesterolemia) that may independently worsen an individual’s risk factor status.⁶–⁹ Although these metabolic abnormalities appear ominous, no one has proven conclusively that the abnormalities actually contribute to an enhanced cardiovascular risk. Thus, patients who respond to nondrug therapy may have their blood pressures reduced without any of the risks of pharmacological treatment.

Unfortunately, the long-term efficacy of nondrug therapy has not been proven, and there are no data whatever to show that these strategies reduce the complications of hypertension. Furthermore, the supporters of nondrug treatment often overlook the difficulties that many patients have in adhering to a sodium-restricted hypocaloric diet or in maintaining a regular exercise or behavior modification program. Although compliance with medication is notoriously poor, compliance with major lifestyle changes is even worse.

Many types of nonpharmacological therapy have been advocated. I agree with the report of the subcommittee on nonpharmacological therapy of the 1984 Joint National Committee that concluded that there are adequate data to recommend modest sodium restriction, weight loss if obesity is present, and limitation of alcohol intake to less than 2 oz/day for all hypertensive patients.¹⁰ I also agree that the data supporting potassium, calcium, or polyunsaturated fat supplementation; aerobic exercise; or behavioral therapy are not convincing enough to
necessarily include these as part of a nonpharmaceutical treatment program.

Factors Involved in Choosing Pharmacological Therapy

In my view, most hypertensive patients neither will be candidates for nondrug therapy alone nor will respond to it; therefore, they will require pharmacological treatment. Deciding which class of drugs with which to begin therapy depends on efficacy, side effects, demography, comorbidity, dosage schedule, cost, mechanism(s) of drug action, and pathophysiology of the patient's hypertension.

When making this choice, the clinician also must decide on which data to rely. Should the clinician depend only on large and long clinical trials? These types of studies generally focus on older and established antihypertensive agents and tend to provide information not only on efficacy and side effects but also on the ability of a drug to reduce hypertension-related complications. Can the clinician use the results of smaller and shorter trials and case reports that accompany the introduction of newer antihypertensive drugs? These smaller studies focus on the short-term efficacy and side effects but rarely on the reduction of complications. Should the clinician make a choice based on theoretical constructs of the action of a particular drug or on the presumed or actually evaluated pathophysiology of a patient's hypertension? Alternatively, should the clinician disregard any but the most routine evaluation and start therapy on an empirical basis?

Classes of Agents for Hypertension Monotherapy

In my view, five classes of drugs (angiotensin converting enzyme [ACE] inhibitors, β-blockers, calcium entry blockers, peripheral α1-adrenergic receptor blockers [α1-blockers], and thiazide diuretic agents) are all appropriate choices for initial therapy in selected patients. Other antihypertensive drugs (central α2-agonists, peripheral sympathetic blockers, and vasodilators) should be reserved for double- and triple-drug therapy either because they eventually require concomitant diuretic therapy or because, although effective as monotherapy, their side effects tend to be less acceptable than those of the agents recommended for monotherapy.

Efficacy

In appropriate doses and in properly selected patients, all the agents proposed as monotherapy will work. A proper understanding of the differing response in certain populations will increase the probability that the initial drug of choice will be successful in controlling blood pressure and obviate the need to switch or to add a second agent. In my view, only two trials, the Veterans Administration "Propazide" Trial and the Medical Research Council Study of the Treatment of Mild Hypertension, provide adequate comparative data on the use of thiazide diuretic agents and β-blockers as monotherapy.3-5 These studies investigated the long-term efficacy of these drugs for blood pressure control and for the prevention of complications. In general, the thiazide agents were more effective and better tolerated, but the doses used in both studies were higher than we would now recommend. In the Propazide trial, the thiazide drugs worked better in blacks than in whites and lowered systolic blood pressure further than did the β-blockers. The Medical Research Council trial suggested that the thiazide drugs prevented strokes better than did β-blockers and that the β-blockers as monotherapy offered little protection against hypertension-related complications in cigarette smokers. The International Primary Prevention Study in Hypertension trial confirmed this finding, but the recently published Heart Attack Primary Prevention in Hypertensives trial did not concur (reference 11 and L. Wilhelmson, unpublished observations). There are no other adequate studies that can be used to compare other agents as monotherapy.

Side Effects

All antihypertensive agents have tolerable as well as serious side effects. The clinician must be aware of the common and predictable side effects of each agent. Again, the clinician must judge the probability of occurrence of each side effect and must decide just how much trouble such a side effect would be for an individual patient. For a patient whose job requires maximum alertness, for example, the fatigue caused by β-blockers could be a very serious problem. For a recreational athlete, the potential for electrolyte and volume depletion could make diuretic drugs a poor choice, and the reduction in cardiac output could make β-blockers less appealing. Certainly, for patients with gout or asthma, we no longer need to rely on diuretic drugs or β-blockers, respectively.

Demography

The probability that certain agents are more likely to work in certain population subgroups than in others is well established. Diuretic drugs, for example, are particularly effective in blacks and the elderly.4,5,12 β-Blockers may be safer in the young, calcium entry blockers may work better in the elderly, and ACE inhibitors are more effective as monotherapy for whites than they are for blacks.13,14 There does not appear to be any differential age effect for ACE inhibitors or for age or racial effect in the case of peripheral α1-blockers.

Comorbidity

The presence of comorbid disease, which can be either helped or worsened by antihypertensive treatment, should be a major factor in the choice of initial therapy for hypertension. Many hypertensive patients have other diseases like gout or asthma that can be adversely affected by the thiazide drugs or the β-blockers, respectively, and these agents should not be used first in patients with these problems. On
the other hand, hypertensive patients with coronary artery disease should be given β-blockers or calcium entry blockers. Those patients with congestive heart failure due to systolic dysfunction should receive diuretic drugs or ACE inhibitors. Perhaps those patients with hypercholesterolemia would benefit from treatment with peripheral α₁-blockers that lower low density lipoprotein cholesterol although these drugs have not been shown to prevent ischemic heart disease.

Comorbidity may also affect the choice of initial therapy in other ways. For example, appropriately evaluated patients with hypercalciumia or calcium oxalate nephrolithiasis should receive diuretic drugs; patients with migraines, hyperthyroidism, or excessive anxiety should receive β-blockers; those patients with paroxysmal atrial tachycardia or documented diastolic dysfunction, verapamil; and those patients with peripheral vascular disease or Raynaud’s phenomenon are likely to benefit from nifedipine, a dihydropyridine calcium entry blocker. In obese patients in whom total body volume is elevated, diuretic drugs are a wise choice. Patients with arthritis, whose disease is severe enough to require treatment with nonsteroidal anti-inflammatory agents, perhaps should not be given ACE inhibitors, which may not work if the renal prostaglandin system is suppressed. In patients with chronic renal failure, diastolic blood pressure is positively correlated with plasma volume, and effective natriuretic agents (loop-active diuretic drugs) should be the first agents used to lower blood pressure. 16

Diabetic patients are a particularly important subgroup of hypertensive patients and a troublesome one to treat. The characteristic pathophysiological abnormality in these patients is an increase in total body sodium. Yet, diuretic agents may worsen glucose tolerance unless total body potassium is maintained. β-Blockers, especially the noncardioselective ones, may suppress insulin secretion and also worsen glucose tolerance. These agents may also mask symptoms of hypoglycemia. Neither peripheral α₁-blockers nor calcium entry blockers adversely affect glucose metabolism, but there are no clear data concerning their specific efficacy in this population. ACE inhibitors have been shown to reduce proteinuria in diabetic patients with nephrotic syndrome, and small studies have suggested that treatment with these drugs in diabetic patients may lower blood pressure and improve renal function.

Dosage Schedule

Now that representatives of each of these classes are available for once-a-day or twice-a-day therapy, dosage schedule and its effect on compliance is no longer a major consideration in the choice of initial treatment.

Cost

The cost of drugs is a vital issue not only to patients who pay for their own medication but also to the increasing numbers of physicians who are members of prospective payment health care delivery systems. By far, the least expensive agents that are recommended for monotherapy are the thiazide diuretic agents. A month’s supply of hydrochlorothiazide as a generic drug, for example, will cost the pharmacist less than $1/mo. If potassium supplementation is needed, the cost may increase as much as fivefold (a month’s supply of 20 meq of potassium chloride or Micro K⁺ [A.H. Robins, Richmond, Virginia] costs between $5 and $6/mo, wholesale). Potassium-sparing combinations are approximately 50% more expensive than is the combination of generic hydrochlorothiazide and 20 meq/day of potassium supplementation. β-Blockers cost between $13 and $20/mo (wholesale) for minimally effective doses, although some preparations of generic propanolol cost less than $5/mo (wholesale). Peripheral α₁-blockers are priced similar to nongeneric β-blockers. ACE inhibitors and calcium entry blockers are the most expensive agents recommended for initial therapy for hypertension, costing between $20 and $30/mo (wholesale) for minimally effective doses. Generic verapamil is less expensive, but the single daily dose sustained-release preparation is not available as a generic drug. The wholesale prices mentioned above do not necessarily represent the actual cost to the patients.

Mechanism of Drug Action and Pathophysiology of Patient Hypertension

In my opinion, these factors are the least important considerations in choosing the agent with which to begin treatment. Instead, I favor an empirical approach based on the other factors mentioned previously. I am not certain that we fully understand precisely how available agents work. For example, β-blockers and ACE inhibitors were originally thought to be indicated specifically for patients with “renin-dependent” hypertension based on the assumption that the primary mechanism of drug action was their ability to block the renin-angiotensin-aldosterone system. However, it became clear that patients whose hypertension was not judged to be renin-dependent also responded to these drugs, and therefore other or multiple mechanisms of action seemed to better fit the accumulated clinical experience. Similarly, the usual hemodynamic profile of the elderly (reduced cardiac output, increased total peripheral resistance, and decreased plasma volume) would suggest that diuretic agents would not be good treatment for this patient subgroup. Yet, it is clear that diuretic agents are extremely effective and safe in this age group. Hemodynamic or metabolic profiling of each individual we treat will significantly add to the cost of antihypertensive therapy, but, at this time, this profiling adds little to a well-reasoned choice based on clinical and demographic factors.
Strategy for Choosing Initial Therapy for Hypertension

Strategies for choosing an initial antihypertensive therapy include the following: 1) Start with nondrug treatment as the sole treatment only for those hypertensive patients with diastolic blood pressures between 90 and 99 mm Hg and who have no evidence of end-organ damage, a negative family history of cardiovascular disease, and no comorbid conditions or habits (smoking or alcoholism) that will independently increase cardiovascular risk. Use drug therapy in the remaining patients once the diagnosis is certain, and rely on nonpharmacological therapy only as adjunctive treatment. 2) Rely on short-term trials and personal experience for enumerating side effects and rare complications, but use large clinical trials for understanding comparative efficacy and the ability of an agent to prevent complications. 3) Choose an agent based on the probability of success (based on demography and comorbidity), but strongly consider costs and the problems that would be caused if predictable or even unusual side effects occur. 4) Pay less attention to the potential adverse effects or drug-induced metabolic abnormalities that have not been proven to cause long-term problems, but pay more attention to clinical apparent side effects. 5) Pay less attention to theoretical pathophysiological or pharmacological considerations than to other factors, and avoid excessive evaluation in most patients.

Recommendations for Monotherapy

Thiazide Diuretic Agents

If renal function is normal, use the thiazides first in blacks; in patients over 50; in patients with asthma, primarily systolic hypertension, congestive heart failure, hypercalcuria or calcium oxalate nephrolithiasis, and obesity; and in those patients with limited funds. Avoid thiazide diuretic agents as initial therapy in patients with gout, in those taking digitalis where the arrhythmogenic potential of hypokalemia may be enhanced,23 and in athletes, especially those living in hot climates. These agents should probably not be the first drug of choice in patients with preexisting complex ventricular ectopy, clinically apparent coronary artery disease, hypercholesterolemia, or diabetes mellitus. Loop-active agents are preferred for patients with chronic renal failure.

β-Blockers

Use β-blockers first in whites under 50 years of age, in all patients with coronary artery disease, and patients with gout, migraine headaches, excessive anxiety, or hyperthyroidism. Avoid the use of β-blockers in smokers; in athletes; and in patients with asthma, congestive heart failure with systolic dysfunction, preexisting bradycardia or high-degree atrioventricular block, intermittent claudication, and diabetes mellitus.

ACE Inhibitors

Use ACE inhibitors first as an alternative to β-blockers in athletes, in whites regardless of age, and in patients with congestive heart failure due to systolic dysfunction. These may be the drugs of choice in patients with unilateral renal artery stenosis,24 diabetes, and scleroderma25 with normal renal function. Avoid the use of ACE inhibitors in patients with bilateral renal artery stenosis,26 in patients taking nonsteroidal anti-inflammatory drugs, and in patients with limited funds.

Calcium Entry Blockers

Use calcium entry blockers first as an alternative to diuretic agents in the elderly and in blacks and as an alternative to β-blockers in patients with coronary artery disease. Use these drugs first in patients with peripheral vascular disease or Raynaud’s phenomenon (nifedipine) or in those patients with paroxysmal atrial tachycardia or diastolic dysfunction (verapamil). Avoid calcium entry blockers in patients with systolic dysfunction and bradycardia (verapamil) and in those with limited funds. These agents may be useful in patients with gout, diabetes, or asthma.

Peripheral α2-Blockers

Consider initial antihypertensive therapy with these agents in patients with hypercholesterolemia, and avoid them in patients with a history of dizziness or syncope and in those with limited funds. Peripheral α2-blockers may be useful in diabetic patients, athletes, and those with gout or asthma. These agents are likely to be the least effective of the recommended drugs. Although tolerance is unusual, increases in plasma and extracellular fluid volume have been reported with long-term therapy; despite these effects, antihypertensive efficacy may not be lost.25

Choosing antihypertensive therapy continues to be an inexact science. The proliferation of effective and safe drugs with useful ancillary properties has ushered in an era in which rigid adherence to a particular drug regimen with one or two classes of agents is no longer appropriate. The well-reasoned use of many of these drugs is more likely to guarantee that we can successfully lower blood pressure without causing intolerable side effects or exacerbating coexisting conditions.

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