SPECIAL ARTICLE

SHATTUCK LECTURE

The Hypertension Paradox — More Uncontrolled Disease despite Improved Therapy

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N Engl J Med 2009;361:878-87.

THE TREATMENT OF HYPERTENSION HAS BEEN ONE OF MEDICINE'S MAJOR successes of the past half-century. The remarkable advances in therapy have provided the newfound capability for lowering blood pressure in almost every person with hypertension. Nevertheless, hypertension continues to be a major public health problem whose prevalence is increasing worldwide.[1] Moreover, the number of people with uncontrolled blood pressure is also increasing, despite the therapeutic advances. Here, I discuss the factors responsible for this paradox and the strategies required for addressing the growing problem.

EARLY APPROACHES TO THERAPY

Hypertension is a major risk factor for cardiovascular and renal diseases, and early data indicate that untreated hypertension shortens life expectancy by approximately 5 years.[2] Although data linking increased blood pressure to premature death were long available from insurers,[3] the prevailing medical opinion well into the 1950s was that lowering of elevated blood pressure was detrimental because it would impair perfusion of vital organs and thereby increase the risk of cardiovascular and renal diseases.[4] Three early pioneers who thought otherwise and aggressively pursued blood-pressure lowering were Walter Kempner, Reginald Smithwick, and Robert Wilkins. Each had a different approach: Kempner used dietary manipulation; Smithwick, surgery; and Wilkins, drug therapy.

Kempner prescribed a diet composed primarily of rice and fruits. It was low in calories, fat, protein, and sodium (<30 mmol per day) and caused ketosis, weight loss, and a decrease in blood pressure.[5] The full diet was difficult to follow, but many patients attended Kempner's clinic at Duke Medical Center for the treatment of hypertension or obesity. Some patients' severe hypertension and renal dysfunction improved on Kempner's program, but his work was not taken seriously by the academic medical community for many years.

Smithwick, who chaired the Department of Surgery at Boston University, developed a surgical procedure for the treatment of hypertension that involved bilateral lumbodorsal sympathectomy and splanchnicectomy with resection of the sympathetic ganglia from the lower thoracic through the upper lumbar roots and removal of much of the greater splanchnic nerve.[6] Complications from the surgery, particularly symptomatic orthostatic hypotension, were relatively common, but as with Kempner's diet, some patients with severe hypertension benefited and survived until effective drug therapies became available.

Wilkins, one of my mentors, became chief of cardiology at Boston University in 1945. His interest in hypertension was enhanced by the availability of a large number of Smithwick's patients at the institution. Wilkins was asked by James Shannon, then head of the Squibb Institute and later director of the National In-

stitutes of Health, to work with Squibb on developing antihypertensive drugs. Around the same time, Edward Freis joined Wilkins as a research fellow and was assigned to study the hemodynamic effects of new antihypertensive drugs. One such drug was pentaquine, an antimalarial agent that was observed to cause orthostatic hypotension. Although it had to be abandoned because of a high incidence of side effects, pentaquine appeared to cause reversal of malignant hypertension in a small number of patients.[7] The development of antihypertensive drugs intensified in the late 1940s and early 1950s, and several medications, including *Rauwolfia serpentina*, veratrum alkaloids, ganglionic blocking drugs, and hydralazine, were tested in the laboratories of Wilkins and others.[8,9] Freis was recruited to Georgetown and the Washington Veterans Administration Hospital and continued his work there, competing with his former mentor.

Wilkins became increasingly convinced of the benefits of antihypertensive therapy and wrote in 1952, "No case of hypertension associated with good renal function should be considered impossible to treat until proven otherwise."[8] He and his associates began combining drugs with different modes of action when the initial medication did not adequately lower blood pressure. This "step-care" approach has continued to be a mainstay of therapy. The number of patients with hypertension who received treatment expanded rapidly, particularly when the thiazide diuretics became available in the late 1950s. The first use of chlorothiazide for hypertension was reported almost simultaneously by the research groups of Wilkins and Freis. Both rushed to publish, Wilkins and Hollander in the *Boston Medical Quarterly*[10] and Freis and Wilson in the *Medical Annals of the District of Columbia*.[11] The competition between them was intense, but the work of each was appropriately recognized with the Lasker Award, which Wilkins received in 1958 and Freis in 1971.

BENEFITS OF ANTIHYPERTENSIVE-DRUG THERAPY

In the 50 years since the introduction of the thiazide diuretics, many classes of antihypertensive drugs have been approved for use (Table 1). Five of these — diuretics, beta-receptor blockers, angiotensin-converting–enzyme (ACE) inhibitors, calcium-channel blockers, and angiotensin-receptor blockers (ARBs) — now represent the primary treatment options.[12] In addition, several clinical trials were conducted that showed clear-cut benefits of therapy, beginning with the treatment of malignant hypertension.[13] Subsequently, the landmark Veterans Administration studies showed impressive reductions in cardiovascular events among patients with a pretreatment diastolic blood pressure of 115 to 129 mm Hg[14] and later among those with a diastolic pressure of 90 to 114 mm Hg.[15] The benefits were so impressive in the former study that a highly significant effect (in comparison with placebo) was observed with an intervention group of only 73 patients who were treated for 18 months.

Subsequent placebo-controlled trials showed the importance of blood-pressure lowering in elderly patients with isolated systolic hypertension with therapies based on the use of either diuretics or calcium-channel blockers.[16,17] Most

Table 1. Advances in the Treatment of Hypertension.

Decade and Therapy
1940s
Potassium thiocyanate
Kempner diet
Lumbodorsal sympathectomy
1950s
Rauwolfia serpentina
Ganglionic blockers
Veratrum alkaloids
Hydralazine
Guanethidine
Thiazide diuretics
1960s
α_2-Adrenergic–receptor agonists
Spironolactone
β-Adrenergic–receptor agonists
1970s
α_1-Adrenergic–receptor antagonists
Angiotensin-converting–enzyme inhibitors
1980s
Calcium antagonists
1990s
Angiotensin-receptor blockers
Endothelin-receptor antagonists*
2000s
Renin inhibitors

* This class of drugs has not been approved for clinical use in patients with hypertension.

recently, the studies were expanded to include patients over the age of 80 years, among whom treatment with a diuretic and an ACE inhibitor was associated with a substantial reduction in mortality and morbidity from cardiovascular diseases.[18]

Such reductions that have been achieved with antihypertensive therapy have been truly impressive. In placebo-controlled trials, the incidence of stroke has been reduced by an average of 35 to 40%, the incidence of coronary events by 20 to 25%, and the incidence of congestive heart failure by more than 50%. Malignant hypertension has become a rare entity, and acute hypertensive heart failure and hemorrhagic stroke are now uncommon.

EVOLVING APPROACHES TO TREATMENT

The management of hypertension continues to evolve as newer antihypertensive medications and clinical trial data become available. On the basis of the current information, I would recommend the following approaches.

LIFESTYLE MODIFICATIONS

The adoption of certain lifestyle modifications has been shown to be effective in lowering blood pressure and should be recommended for all patients with hypertension. These modifications include weight control, exercise, dietary sodium restriction and potassium enhancement, moderation of alcohol intake, and adoption of the Dietary Approaches to Stop Hypertension (DASH) eating plan, which emphasizes a high intake of fruits, vegetables, complex carbohydrates, and low-fat dairy products and restriction of saturated fats.[19] The reductions in systolic blood pressure that are achieved with these approaches have averaged 5 to 10 mm Hg for a weight decrease of 10 kg, 8 to 14 mm Hg for the DASH eating plan, 2 to 8 mm Hg for dietary sodium reduction, 4 to 9 mm Hg for increased physical activity, and 2 to 4 mm Hg for moderation of alcohol consumption.

No clinical trial has examined directly the effects of lifestyle interventions on cardiovascular outcomes. However, indirect evidence supporting a favorable effect has been reported from 10-to-15-year follow-up of patients in the Trials of Hypertension Prevention I and II (TOHP I and TOHP II; ClinicalTrials.gov number, NCT00000528), which studied the effects of lifestyle modifications, including salt restriction.[20,21] The groups who were assigned to the sodium-reduction intervention had significantly fewer cardiovascular events during long-term follow-up than the usual-care group.[22] The urinary sodium-to-potassium ratio correlated more strongly with the cardiovascular-event rate than urinary sodium alone, suggesting that a higher potassium intake had a beneficial effect.[23]

DRUGS

In most patients with hypertension, drug therapy is required to achieve target blood-pressure levels. Several excellent agents are available.

Thiazide-type diuretics, beta-blockers, ACE inhibitors, calcium-channel blockers, and ARBs are considered to be the most useful classes of drugs, since they have been shown in clinical trials to reduce cardiovascular complications in patients with hypertension.[12,24] All these classes have broadly similar average effects on blood pressure,[25] although there are differences among patients. In the majority of patients, two or more antihypertensive drugs are required to achieve target blood-pressure levels. As a result, several two-drug fixed-dose combinations have been introduced,[26] and recently even a three-drug preparation that combines a calcium-channel blocker, an ARB, and a thiazide diuretic has become available.

To determine whether a given drug or drug combination is superior to any other, several comparison trials have been performed. In general, these studies have shown minimal differences in primary outcomes among the drug classes, as long as equivalent reduction in blood pressure has been achieved (Table 2).[27-33] Even blood-pressure differences as small as 3/2 mm Hg between treatment groups have been associated with significant differences in certain outcomes.[30,34] A few trials have shown superiority of one drug or a given combination over another. In the Losartan Intervention for Endpoint Reduction in Hypertension (LIFE) study (NCT00338260), losartan-based therapy was associated with fewer cardiovascular events than atenolol-based treatment.[31] In the Second Australian National Blood Pressure Study (ANBP2), ACE inhibition was associated with a somewhat lower incidence of cardiovascular complications than thiazide-based therapy in men but not in women.[32] In the Avoiding Cardiovascular Events through Combination Therapy in Patients Living with Systolic Hypertension (ACCOMPLISH)

Table 2. Comparative Drug Trials in Patients with Hypertension.*

Trial Name	Drug Comparison	Primary Outcome
STOP-2[27]	Thiazide-type diuretic plus beta-blocker vs. ACE inhibitor plus calcium-channel blocker	No significant difference
ALLHAT[28]	Thiazide-type diuretic vs. ACE inhibitor vs. calcium-channel blocker	No significant difference
INVEST[29]	Thiazide-type diuretic plus beta-blocker vs. calcium-channel blocker plus ACE inhibitor	No significant difference
ASCOT[30]	Thiazide-type diuretic plus beta-blocker vs. calcium-channel blocker plus ACE inhibitor	No significant difference
LIFE[31]	Angiotensin-receptor blocker vs. beta-blocker	Angiotensin-receptor blocker superior
ANBP2[32]	Thiazide-type diuretic vs. ACE inhibitor	ACE inhibitor superior in men only
ACCOMPLISH[33]	ACE inhibitor plus thiazide-type diuretic vs. ACE inhibitor plus calcium-channel blocker	ACE inhibitor plus calcium-channel blocker superior

* ACCOMPLISH denotes Avoiding Cardiovascular Events through Combination Therapy in Patients Living with Systolic Hypertension, ALLHAT Antihypertensive and Lipid-Lowering Treatment to Prevent Heart Attack Trial, ANBP2 Second Australian National Blood Pressure Study, ASCOT Anglo-Scandinavian Cardiac Outcomes Trial, INVEST International Verapamil-Trandolapril Study, LIFE Losartan Intervention for Endpoint Reduction in Hypertension, and STOP-2 Swedish Trial in Old Patients with Hypertension 2.

study (NCT00170950), the benazepril–amlodipine combination was superior to a benazepril–hydrochlorothiazide-based regimen.[33] However, the bulk of evidence indicates that by far the most critical aspect of therapy is the lowering of blood pressure, regardless of how this is achieved.

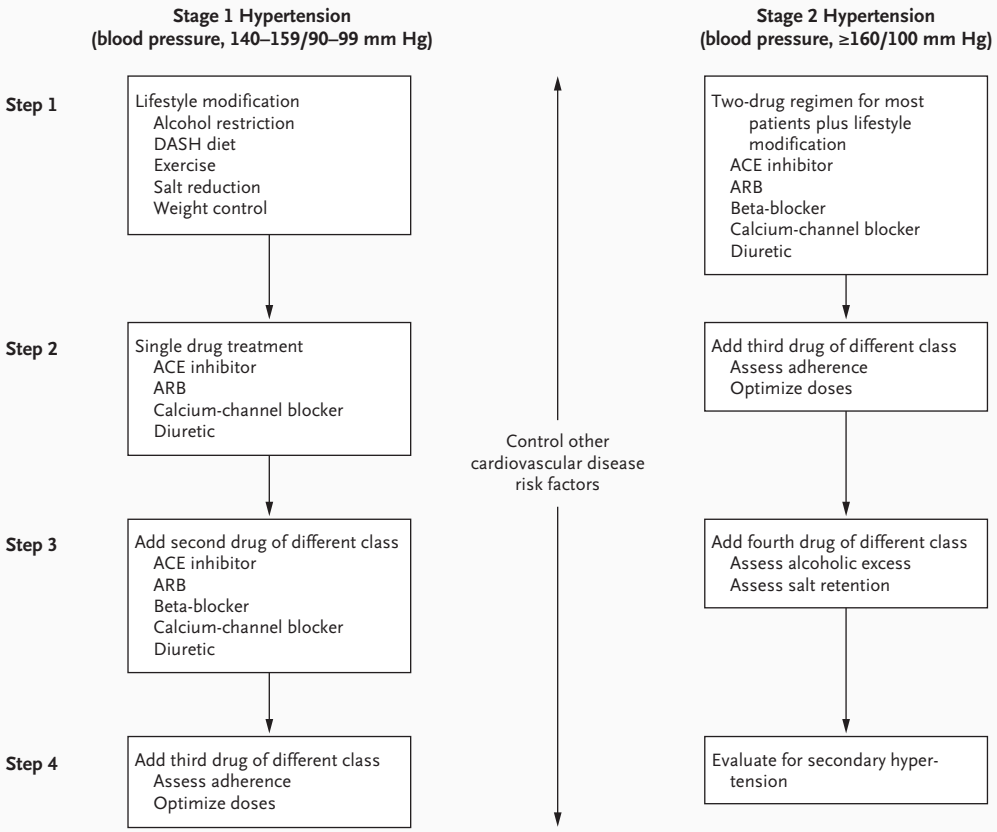
There are situations, however, in which the data demonstrate compelling indications for the use of certain classes of antihypertensive drugs. These include the use of ACE inhibitors and ARBs in patients with chronic renal disease, diabetes, congestive heart failure, or recent myocardial infarction and beta-blockers in those with angina pectoris, recent myocardial infarction, arrhythmias, or heart failure.[12] Selection can also be based on coexisting conditions for which a given drug may provide added benefit (e.g., calcium-channel blockers or beta-blockers for patients with both hypertension and migraine headache).

NEW TREATMENT ALGORITHM

Although thiazide-type diuretics were recommended in the Joint National Committee Guidelines of 2003 as the preferred initial drug therapy for most patients with hypertension, subsequent data from the LIFE study, the Anglo-Scandinavian Cardiac Outcomes Trial (ASCOT),[30] ANBP2, and ACCOMPLISH point to the need for a more flexible approach. Taken together, the studies show that several drug classes with reasonable side-effect profiles can reduce cardiovascular complications to a degree similar to that associated with diuretics. In addition, since generic preparations for each of these drug classes are or will soon become available, the cost advantage of diuretics has become much less of an issue.

The new treatment algorithm that I would recommend is illustrated in Figure 1. The approach varies slightly, depending on the severity of hypertension. In stage 1 hypertension (blood pressure, 140–159/90–99 mm Hg), it is appropriate to begin with lifestyle modifications before drug therapy is initiated. Thiazide-type diuretics, ACE inhibitors, calcium-channel blockers, or ARBs can be considered initially, depending on the physician's experience, the patient's acceptance, and the presence of compelling or coexisting conditions. Because of recent data indicating that traditional beta-blockers, such as atenolol and metoprolol, are not as effective in reducing the risk of stroke as the other four classes,[35] their use as first-line agents, particularly in the elderly, should be restricted to patients with the compelling indications described above. It is uncertain whether the use of newer beta-blockers with vasodilator properties, such as carvedilol, should be similarly restricted.

In stage 2 hypertension (blood pressure, >160/100 mm Hg), drug treatment should be initiated promptly, along with lifestyle approaches. Two-drug combinations may be used as initial therapy in some patients. Evaluation for secondary hypertension should be considered



Compelling Indications	Drug Treatment
Post–myocardial infarction	ACE inhibitor, beta-blocker
Angina pectoris	Beta-blocker, calcium-channel blocker
Heart failure	ACE inhibitor, ARB, beta-blocker, diuretic, aldosterone antagonist
Chronic renal disease	ACE inhibitor, ARB
Diabetes	ACE inhibitor, ARB, and others
High coronary heart disease risk	ACE inhibitor, ARB, beta-blocker, calcium-channel blocker, diuretic

Figure 1. Algorithm for Management of Hypertension.
ACE denotes angiotensin-converting enzyme, ARB angiotensin-receptor blocker, and DASH Dietary Approaches to Stop Hypertension.

when three or more antihypertensive drugs of different classes do not control blood pressure.

It is likely that in the future, pharmacogenetic data will help guide drug choice, but little such information is currently available. There is also a growing interest in instituting antihypertensive-drug therapy on the basis of total cardiovascular risk rather than absolute blood-pressure levels,[36] but direct evidence justifying such an approach is lacking.

Although several excellent antihypertensive drugs are available, the search for new agents continues. Several interesting new therapies for hypertension are under development, including the endothelin receptor type A antagonist darusentan,[37] which may be approved soon for the treatment of resistant hypertension. New treatments in early stages of clinical testing include a vaccine to block the activity of angiotensin II,[38] cannabinoid-1 receptor antagonists,[39] and alage-

brium, which interferes with cross-linkages of collagen and elastin and thereby reduces arterial and myocardial stiffness.[40]

HYPERTENSION CONTROL

The control of hypertension continues to be inadequate despite the excellent array of effective, well-tolerated medications. Recent data indicate that approximately 28% of Americans with hypertension are unaware of their hypertension, 39% are not receiving therapy, and 65% do not have their blood pressure controlled to levels below 140/90 mm Hg (Fig. 2).[41] The control rates are even worse among patients with chronic kidney disease, diabetes, stable angina, the acute coronary syndrome, or left ventricular dysfunction, in whom target blood-pressure levels of 130/80 mm Hg or lower are recommended.[12,42] In large part, the low control rates can be attributed to poor management of elevated systolic blood pressure.

Race, ethnic background, and income status affect control rates of hypertension and other cardiovascular risk factors. The 1999–2000 National Health and Nutrition Examination Survey (NHANES) showed a reduction in blood pressure to below 140/90 mm Hg with treatment in 33% of white patients but only in 28% of black patients and 18% of Hispanic patients.[43] During 25 years of follow-up to the Multiple Risk Factor Intervention Trial (MRFIT) (NCT00000487), the rate of death from cardiovascular disease among black patients was 25% higher than that among white patients. This difference could be explained by differences in blood-pressure levels, the presence of diabetes, smoking prevalence, and income status.[44] The reasons behind these health disparities are complex and involve such factors as the availability of health insurance, access to high-quality health care, and cultural and attitudinal differences between patients and their physicians. The societal costs from such disparities are high, and there is an urgent need to deal with this problem on a broad basis.

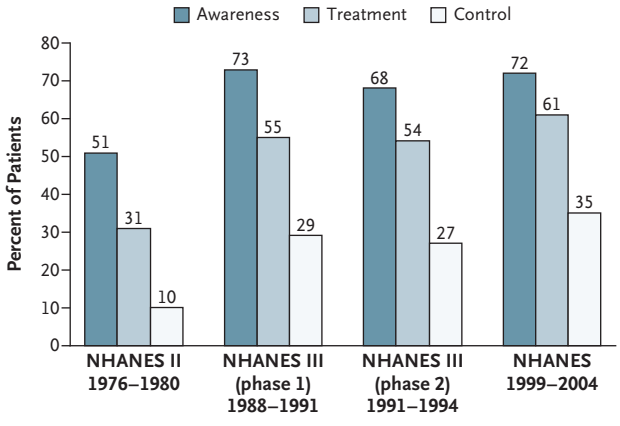


Figure 2. Rates of Awareness, Treatment, and Control of High Blood Pressure in the United States (1976–2004).

High blood pressure is defined as a reading of 140/90 mm Hg or more for persons between the ages of 18 and 74 years. Despite major improvements in blood-pressure therapies in recent years, some 28% of Americans with hypertension do not know they have the condition, 39% are receiving no therapy, and 65% have insufficient blood-pressure control. Data are from Chobanian et al.[12] and Cutler et al.[41] NHANES denotes National Health and Nutrition Examination Survey.

INCREASE IN THE PREVALENCE OF HYPERTENSION

The prevalence of hypertension continues to increase worldwide. NHANES data indicate that prevalence has increased among U.S. adults, from approximately 50 million in the period from 1988 through 1994 to 65 million in the period from 1999 through 2004.[41] The prevalence of hypertension worldwide is projected to increase from approximately 1.0 billion in 2000 to 1.5 billion by 2025.[2] The total number of persons with uncontrolled hypertension in the United States has increased from 37 million to 42 million, despite improvements in treatment and in control rates during the past two decades (Fig. 3).

What can be done to reverse this trend? To reflect the high risk of hypertension in persons with blood pressures of 120–130/80–89 mm Hg, the seventh report of the Joint National Committee on Prevention, Detection, Evaluation, and Treatment of High Blood Pressure reclassified blood pressures in this range as prehypertension.[12] The rate of progression from prehypertension to hypertension can be relatively rapid, and hypertension ultimately develops in most persons if they live long enough. In the Framingham Heart Study population, approximately 90% of persons who had normal blood pressure at 55 or 65 years of age became hypertensive in the subsequent 20 years.[45] In the international Atherosclerosis Risk in Communities (ARIC) study (NCT00005131), which followed more than 15,000 patients between 45 and 64 years of age for 9 years, the average 5-year age-adjusted in-

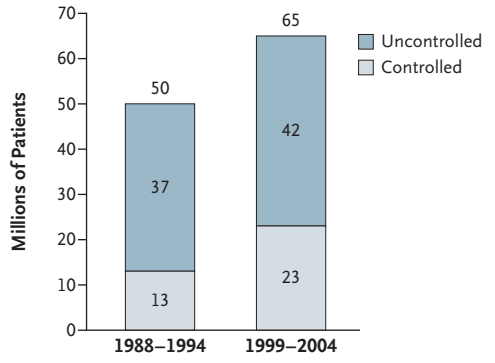


Figure 3. Changes in the Prevalence and Control of Hypertension in the United States (1988–2004).

The total number of persons with uncontrolled hypertension has increased from 37 million to 42 million during the past two decades, even though the rate of control has increased from 27% to 35% during the same period. Data are from Chobanian et al.[12] and Cutler et al.[41]

crease in systolic blood pressure ranged from 4 to 7 mm Hg.[46]

Persons with prehypertension — more than 30% of the U.S. adult population — are at higher-than-average risk for cardiovascular disease.[47] From the prehypertensive range upward, the effect of blood pressure on cardiovascular risk is progressive and continuous, with an average doubling of risk for every increase of 20/10 mm Hg in pressure.[48] Patients with prehypertension also have a higher prevalence of other cardiovascular risk factors, such as dyslipidemias, diabetes, insulin resistance, obesity, and the metabolic syndrome,[47] and have earlier evidence of target organ damage than normotensive persons.[49] Thus, patients with prehypertension should be targeted for lifestyle interventions that reduce blood pressure or delay the onset of hypertension and that help to control other cardiovascular risk factors.

Several factors can contribute to the development of hypertension (Table 3).[26] Recent genome-wide analyses have revealed several single-nucleotide polymorphisms (SNPs) of genetic loci that are associated with blood pressure.[50,51] Whether any of these SNPs will prove to be targets for the prevention or treatment of hypertension remains to be determined. Salt intake and body weight are particularly important in the age-related increase in blood pressure. Such increases are uncommon in societies in which sodium chloride intake does not exceed 50 mmol per day.[52] Salt intake in the United States has increased during the past 25 years and is currently approximately 150 to 170 mmol per day (3.5 to 4.0 g of sodium).[53,54] The increase in dietary salt may also have contributed to the growing obesity problem during this period by causing increased intake of fluids, particularly of high-calorie soft drinks.[55]

The major factors involved in the sensitivity of blood pressure to salt are poorly understood. Several single-gene mutations that directly affect renal sodium reabsorption can cause hypertension, but such variants have been observed in only a few persons.[56] Blacks, the elderly, and persons with chronic renal disease have increased salt sensitivity.[57] Dietary salt reduction lowers blood pressure in persons with both normotension and hypertension and in children as well as adults.[58] Extrapolation of data from the Intersalt study (NCT00005763) suggests that a salt intake of 50 mmol below the current mean level (a decrease of about one third) would reduce blood pressure by an average of 4.0/2.5 mm Hg among persons with hypertension and by 2.0/1.0 mm Hg among persons with normotension.[59]

The ratio of dietary sodium to potassium correlates better with blood pressure than the level of either cation alone.[60] Diets that are composed primarily of processed foods are not only high in sodium but also low in potassium. U.S. dietary potassium intake averages between 50 and 60 mmol per day.[60] An Institute of Medicine panel has recommended a sodium intake for adults of 50 to 65 mmol per day and a potassium intake of 120 mmol per day,[61] but we are far from reaching such goals.

Some countries, such as Finland and Great Britain, have achieved significant reductions in dietary sodium through aggressive efforts. In Finland, average salt intake has decreased by one third during the past 30 years, and there has been an associated population-wide decrease in blood pressure.[62] Finland's intensive program has included broad educational efforts and cooperation by the food industry in developing low-sodium products and attaching warning labels to high-sodium foods. Once salt intake is reduced for a few weeks, most people appear to readjust their taste threshold to become more sensitive to salt,[63] which facilitates long-term reductions in intake.

The increase in body weight in the population

Table 3. Risk Factors for Hypertension.*

Genetic predisposition or family history
Black race
Diagnosis of prehypertension
Increasing age
Obesity
High sodium–low potassium intake
Excessive alcohol intake
Low socioeconomic status
Sleep apnea
Use of certain illegal drugs or over-the-counter medications

* Data are from Chobanian et al.[26]

is a critical factor in the increase in the prevalence of hypertension. Weight loss in overweight or obese persons can prevent or delay the onset of hypertension.[64] Unfortunately, the prevalence of obesity continues to rise.[65]

Societal changes during the past 30 years have had a major negative effect on dietary habits and preferences. The rapid growth of the fast-food industry and in the intake of commercially prepared foods has meant an increased consumption of calories, saturated fat, and salt and a reduced intake of fruits, vegetables, and complex carbohydrates.[55] Daily caloric intake in adults has increased an average of 300 kcal during this period as portion sizes have grown and marketing of high-calorie, less-nutritious foods has increased.[55,66,67]

Deeply ingrained lifestyle habits cannot be changed without a national strategy that creates broad acceptance of the need for such change. The success in reducing tobacco use was facilitated greatly by the passage of legislation against smoking in public areas and the workplace, expansion of educational efforts and public service announcements, increased taxation of cigarettes, elimination of cigarette vending machines in certain areas, limitation of cigarette sales to minors, and risk labeling of cigarette packs.

To combat obesity, support from families, schools, community and religious organizations, government, insurers, food and beverage industries, health care providers, and the general public will be essential. Population-wide strategies — such as redesigning of roads and walkways to promote cycling and walking and the expansion of school health education and physical education programs — should be combined with individually targeted interventions to alter dietary intake and increase physical activity. Recent progress provides some cause for optimism: public awareness of the major contributors to childhood obesity and the health risks involved has increased,[68] and support has grown for making a number of essential changes, some of which are beginning to be mandated in several states.

It is paradoxical that despite the enormous advances in antihypertensive-drug therapy, the number of people with uncontrolled hypertension has continued to rise. The failure to adopt healthy lifestyles has been a critical factor in this increase and must be addressed urgently. To make the necessary changes on a broad basis will be difficult, but the benefits will be well worth the effort.

No potential conflict of interest relevant to this article was reported.

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