SUPPLEMENT TO
MANAGED Care

Effective Hypertension Management With New Treatment Paradigms

Based on a meeting in New Orleans, March 11–12, 2004

HIGHLIGHTS

- JNC-7 and the New Therapeutic Approaches
- Role of Fixed-Dose Combination Therapy
- Economic Impact of Poor Diagnosis and Management

ROUNDTABLE DISCUSSIONS

- Effective Diagnosis, Management, and Treatment
- Minimizing Costs and Maximizing Outcomes in the Real World Setting

Continuing education credit sponsored by The Chatham Institute

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INTRODUCTION

Despite the release of report after report by the esteemed Joint National Committee on Prevention, Detection, Evaluation, and Treatment of High Blood Pressure — beginning in 1977 — the United States has made scant progress in recent years with respect to increasing the percentage of Americans who are aware that they have hypertension, whose hypertension is being treated, or whose hypertension is under control. Literally scores of drugs exist to treat hypertension, and Americans spend billions of dollars on them each year. Nevertheless, many more billions are involved in the direct and indirect costs associated with stroke, heart attack, and kidney disease stemming from hypertension that has gone undetected or been inadequately treated.

In this context, a distinguished panel recently convened in New Orleans to discuss the scope of this health care crisis and the steps that might be taken to at long last improve rates of hypertension control. Their deliberations are contained in this supplement.

Dean G. Smith, PhD, professor and chair of the Department of Health Management and Policy at the University of Michigan School of Public Health, described the economic burden imposed by hypertension on the U.S. health care system. Joel M. Neutel, MD, medical director of the Orange County (Calif.) Research Center, presented arguments for initiating drug treatment of hypertension with combination therapy instead of the long-recommended additive approach.

During and following these presentations, representatives of health plans and medical institutions reinforced — and sometimes challenged — the faculty members' recommendations. Edited versions of their spirited discussions are presented herein, in the hope that the panelists' remarks will provide insight for readers who are eager to improve the way that their health plans approach the treatment of patients with hypertension.

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Continuing Education Section

Effective Hypertension Management With New Treatment Paradigms

Continuing education credit is offered to physicians and pharmacists who read pages 5 through 26 of this publication, complete the post-test on page 27, and fill out the evaluation form on page 28. Estimated time to complete this activity is 2 hours.

PURPOSE AND OVERVIEW

These articles are derived from "Effective Hypertension Management With New Treatment Paradigms," a meeting that took place in New Orleans, March 11–12, 2004.

This activity focuses on new treatment approaches in the cost-effective management of patients with hypertension. The roundtable convened a select group of thought leaders and experts from managed care organizations, employer groups, and patient advocacy groups, as well as cardiologists and nephrologists, who shared their reactions to the content of feature presentations as well as their informed professional perspectives on the challenge of managing hypertension. The faculty panel also discussed implementation of the Joint National Committee (JNC) 7 guidelines, overcoming barriers to diagnosis and treatment of hypertension, the role of combination therapy, and other key issues in hypertension as they relate to managed care medical and pharmacy executives and physicians.

Educational needs assessment

Hypertension is easy to diagnose, yet 30 percent of hypertensive patients are unaware that they are hypertensive. A quarter of those who are aware that they have hypertension receive less-than-adequate treatment, and more than 10 percent receive no treatment at all.

Recent National Health and Nutrition Examination Survey (NHANES) data show that only about a third of hypertensive patients have their blood pressure under control. Facing increasingly complicated drug regimens and increasingly complex responsibilities for paying for a greater proportion of their pharmacy bills, some patients tend not to comply with or even fill their prescriptions. Antihypertensive therapy is clearly beneficial, with its associated reductions in incidence of stroke, heart attack, and heart failure. Uncontrolled hypertension and its sequelae exert a huge financial burden on the health care system. Managed care organizations are seeking cost-effective ways to optimize treatment for hypertension patients while lessening the economic burden associated with uncontrolled disease. JNC-7 came about due to the publication of many new clinical and observational studies, the need for a new, clear, and concise guideline that would be useful for clinicians, the need to simplify the classification of blood pressure, and the clear recognition that previous JNC reports were not being used to maximum benefit.

JNC-7 blood pressure goals are difficult to achieve through a monotherapeutic approach, and these guidelines recognize that typically two or more drugs are needed. Fixed-dose combination antihypertensive treatments available as single pills and containing agents from two different classes of medications may produce additive blood pressure control, reduce dose-dependent adverse effects of monotherapy, and reduce the complexity of (and therefore noncompliance with) drug regimens for patients. A clear need exists to educate managed care decision makers about the optimal approach to improving outcomes for these patients based on the newest recommendations.

Educational objectives

After reading this publication, the participant should be able to:

- Establish rational, effective treatment strategies with the goal of lowering blood pressure in hypertensive patients to less than 140/90 mm Hg and below 130/80 mm Hg in hypertensive patients with diabetes or renal disease, per JNC-7 guidelines
- Incorporate into his or her disease management approach an understanding of the societal impact of hypertension from the perspectives of overall health, quality of life, and economics
- Address the barriers to effective hypertension management and take positive steps to improve patient compliance with treatment to help achieve blood pressure goals and lower health care expenditures in a broader range of patients

Target audiences

Managed health care professionals, including physicians, pharmacists, medical directors, chief medical officers, pharmacy directors, and other senior managers in managed care organizations.

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Combination Therapy as Initial Treatment For Hypertension

JOEL M. NEUTEL, MD
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In the last century, hypertension emerged as a disease process as the result of epidemiologic studies conducted by the insurance industry. In the early 1930s, Metropolitan Life began searching for a clinical marker that would identify people who were poor risks for life insurance, owing to their high risk of dying at a young age. By the mid-1950s, a review of the company's actuarial databases led Metropolitan Life to conclude that patients whose blood pressure exceeded 140/90 mm Hg should pay higher premiums for life insurance, if not be barred from purchasing it altogether.


JOEL M. NEUTEL, MD

It was not until 1977 that the Joint National Committee (JNC) on Detection, Evaluation, and Treatment of High Blood Pressure issued its first set of recommendations, which suggested that people whose diastolic blood pressure was higher than 100 mm Hg be considered for treatment. Systolic blood pressure was considered unimportant and part of the normal aging process. It also was thought that therapy aimed at reducing systolic blood pressure was likely to precipitate the very events it was intended to prevent.

Today, we know that hypertension is a major risk factor for cardiovascular disease (CVD), and that coronary artery disease (CAD) is by far the most common cause of death in the industrialized world. Blood pressure is merely the marker of hypertension; success in treating hypertension must be assessed in terms of a decrease in CVD (along with decreases in heart failure and kidney disease). As a patient's blood pressure increases, so does the risk of CVD. Among adults age 40 to 69, each increase of 20 mm Hg in systolic blood pressure or 10 mm Hg in diastolic blood pressure was found to double a person's risk of CVD, whether the baseline blood pressure was as low as 115/75 mm Hg or as high as 185/115 mm Hg (Lewington 2002).

Shortly after the publication of the first JNC report, data collected through the second National Health and Nutrition Examination Survey (NHANES II, 1976–1980) showed that only 51 percent of U.S. adults (age 18 to 74) with high blood pressure (≥140/≥90 mm Hg) were aware they had hypertension (Burt 1995). Moreover, only 31 percent of the hypertensive adults were receiving antihypertensive treatment. Control of hypertension was achieved in 32 percent of the treated group or 10 percent of the overall hypertensive population.

Seven reports, little progress

To reflect advances in biomedical knowledge and completion of important clinical trials, the JNC has issued new reports periodically since its initial report (specifically, in 1980, 1984, 1988, 1993, 1997, and 2003; see reference list). At first, increased attention to hypertension provided by the JNC resulted in an improvement in the rate of awareness of the condition among people with hypertension. Over the course of the next decade, awareness rose to 73 percent according to data from phase 1 of NHANES III (1988 to 1991) — along with a near tripling of the control rate, which reached 29 percent (55 percent of the treated hypertensive patients) (Burt 1995).

Since then, there has been no evidence of further improvement in rates of hypertension awareness, treatment, and control. In fact, data from phase 2 of NHANES III (1992 to 1994) showed a slight decrease in patient awareness of hypertension, which decreased from 73 to 68 percent. The control rate also dropped slightly, from 29 to 27 percent (Hyman 2001).

The most recent NHANES data show that only 31 to 34 percent of hypertensive patients have their hypertension under control despite publication of three new sets of recommendations by the JNC between 1988 and 1997; introduction of two new classes of antihypertensive drugs, angiotensin-converting enzyme (ACE) inhibitors and angiotensin receptor blockers (ARBs); availability of more than 80 drugs for treating hypertension; and expenditure of about $15 billion annually for these agents (Hajjar 2003, JNC 2003). An improvement of just a few percentage points in control rates for such an important risk factor for CAD strongly suggests that the JNC reports have been ineffective in advancing the management of hypertension.

The percentage of hypertensive patients receiving treatment has remained approximately 55 percent, but the majority of treated patients do not have their hypertension controlled. It must be remembered that treated

patients whose hypertension is inadequately controlled still are at substantial risk for developing CVD. In a population of patients with type 2 diabetes, patients whose mean blood pressure was reduced from 161/94 mm Hg to 144/82 mm Hg ("tight" control) over the course of 9 years experienced a 44 percent reduction in stroke (*P*=.013), a 21 percent reduction in myocardial infarction (*P*=.13), an 18 percent reduction in all-cause mortality (*P*=.17), and a 32 percent decrease in death related to diabetes (*P*=.019), relative to patients whose mean blood pressure was reduced from 161/94 mm Hg to 154/87 mm Hg (UKPDS 1998).

The JNC currently recommends that hypertensive patients strive for a blood pressure goal of 140/90 mm Hg — 130/80 mm Hg if they have diabetes or chronic kidney disease; normal blood pressure is regarded as systolic blood pressure less than 120 mm Hg and diastolic blood pressure less than 80 mm Hg. Future JNC reports are likely to incorporate lower goals. The Prospective Studies Collaboration, a meta-analysis, pooled data from 61 prospective observational studies involving over 1 million subjects with no vascular disease at baseline. In middle-aged and older patients, results showed that an increase in blood pressure from usual pressure as low as 115/75 mm Hg is directly related to vascular mortality (Lewington 2002). In addition, the Multiple Risk Factor Intervention Trial (MRFIT) showed that a statistically significant link between systolic blood pressure and CHD mortality becomes evident at systolic pressures greater than 118 mm Hg (Stamler 1993). Once systolic blood pressure exceeds 150 mm Hg, the risk of death is about four times greater than it is among patients whose systolic blood pressure is less than 112 mm Hg. Considering the results of the Prospective Studies Collaboration and MRFIT, it is conceivable that a goal of 120/80 mm Hg may soon be recommended for hypertensive patients.

Should such a goal become a JNC recommendation in the near future, it is reasonable to ask what percentage of patients could be expected to reach it via monotherapy. If our goal is to reduce blood pressure efficiently, and if drugs are selected on the basis of efficacy, then combination therapy should be recommended because it is dramatically more effective than monotherapy, regardless of which antihypertensives are used. For example, in a double-blind, 8-week study of adults with essential hypertension, the use of valsartan in combination with hydrochlorothiazide (HCTZ) was found to reduce mean sitting systolic blood pressure to a greater extent than monotherapy with either agent (Table 1).

Similarly, another study showed that patients receiving the ACE inhibitor benazepril and the calcium channel blocker (CCB) amlodipine achieved a greater reduction in mean sitting systolic blood pressure compared with those receiving either agent alone (Weir 1999). The combination of amlodipine/benazepril 5/20 mg reduced mean sitting systolic blood pressure by 27.5 mm Hg, compared with reductions of 18.1 mm Hg and 14.8 mm Hg among patients receiving amlodipine 5 mg or benazepril 20 mg, respectively.

Improved adverse effect profile with combination therapy

In addition to being more efficacious, antihypertensive combination therapy also offers a superior adverse-effect profile. Physicians worry that combination therapy will result in more adverse effects, but in fact combination therapy causes no more adverse effects than monotherapy. Moreover, combination therapy even may minimize adverse effects, which could improve rates of compliance. For example, patients receiving combination therapy with amlodipine/benazepril 5/20 mg achieved considerably greater reduction in blood pressure than did patients receiving either agent alone. Furthermore, the adverse-event profile compared favorably with that of the placebo group (Table 2).

Combination therapy with the CCB verapamil SR and the ACE inhibitor trandolapril provides another example of the benefits of using antihypertensives from two different classes (Table 3). Compared with patients receiving the CCB alone, patients receiving the combination of verapamil SR and trandolapril showed a lower rate of edema. This also was the case in the previously mentioned study combining the CCB amlodipine with the ACE inhibitor benazepril. In placebo-controlled U.S. trials of amlodipine/benazepril, the increase in the incidence of edema in patients receiving amlodipine monotherapy was statistically significant compared with patients receiving the combination product.

The edema associated with CCBs occurs because they are extremely powerful vasodilators, affecting the arterial but not the venous side of the vascular tree.

TABLE 1 Reduction from baseline in systolic blood pressure among patients (N=871) receiving valsartan alone or in combination with hydrochlorothiazide*

	Placebo	Valsartan 80 mg	Valsartan 160 mg
Placebo	1.7	8.2	12.6
Hydrochlorothiazide 12.5 mg	7.6	16.8	18.7
Hydrochlorothiazide 25 mg	12.1	20.0	23.2

**P*<.001 for all treatments vs. placebo.
SOURCE: BENZ 1998

TABLE 2 Reduction in blood pressure and adverse events with first-line use of amlodipine, benazepril, or the combination

	Placebo (n=77)	Amlodipine 5 mg (n=77)	Benazepril 20 mg (n=77)	Amlodipine/benazepril 5/20 mg (n=77)
Reduction in blood pressure (mm Hg)				
Systolic		16.2	12.4	24.7
Diastolic		8.8	6.7	13.2
Adverse events (%)				
Drug-related adverse events	11.7	24.7	6.5	15.6
Dizziness	0.0	1.3	3.9	5.2
Edema	5.2	16.9	1.3	7.8
Cough	0.0	0.0	0.0	5.2
Headache	7.8	2.6	3.9	2.6

SOURCE: KUSCHNIR 1996

The opening of the arterioles results in increased flow to the capillaries — the venous sites that remain constricted — with a consequent increase in hydrostatic pressure that causes the capillaries to leak. Physicians routinely prescribe furosemide for CCB-induced edema, but it is ineffective for this purpose. Yet, adding an ACE inhibitor to the CCB dilates the veins, reducing pressure in the capillaries and alleviating the edema. In this way, blood pressure is reduced through a much more generalized effect on the entire cardiovascular tree, rather than on just one side of it. By using two complementary agents, an aphysiologic reduction in blood pressure is changed to a physiologic reduction, resulting in a greater reduction in blood pressure, fewer side effects, and greater compliance.

Accepting inadequate control

In general, however, physicians and patients dislike polypharmacy. To avoid polypharmacy, physicians will even accept inadequate control of a condition. Since 1977, the JNC has advocated a start-low, go-slow approach to the treatment of hypertension: start a patient on a low dose of a drug, increase that dose to the maximum, if necessary, and then, if control has not been achieved, either switch to a different drug or add a second drug. Although it is true that increasing the dose of an antihypertensive reduces blood pressure, the increased dose also leads to more dose-dependent adverse effects. Knowing this, clinicians rationalize inadequate control on the basis of protecting patients from adverse effects associated with higher doses. For example, if a patient's blood pressure is almost controlled, doubling the dose may be needed to gain full control. A physician may decide against doubling the dose, however, as it could result in noncompliance due to increased side effects. Therefore, the physician accepts inadequate control on the basis that some treatment is better than none. This

TABLE 3 Reduction in blood pressure and adverse events with first-line use of verapamil SR, trandolapril, or the combination

	Placebo (n=152)	Verapamil SR 240 mg (n=155)	Trandolapril 4 mg (n=155)	Verapamil SR/ trandolapril 240/4 mg (n=163)
Reduction in blood pressure (mm Hg)				
Systolic		8.0	9.0	12.9
Diastolic		4.5	4.3	8.1
Adverse events (%)				
Dizziness	2.6	3.8	2.5	4.3
Edema	3.3	1.3	1.3	0.6
Cough	2.6	0.6	7.5	5.5
Headache	10.5	12.1	10.7	6.7

SOURCE: MESSERLI 1998

TABLE 4 Selected fixed-dose combination antihypertensives

Trade name (manufacturer)	Nonproprietary names of active ingredients	Drug classes	Available strengths (mg)
Atacand HCT *(AstraZeneca)*	Candesartan/hydrochlorothiazide	ARB/diuretic	16.0/12.5, 32.0/12.5
Avalide *(Bristol-Myers Squibb)*	Irbesartan/hydrochlorothiazide	ARB/diuretic	150/12.5, 300/12.5
Capozide *(Bristol-Myers Squibb)*	Captopril/hydrochlorothiazide	ACE inhibitor/ diuretic	25/15, 25/25, 50/15, 50/25
Diovan HCT *(Novartis)*	Valsartan/hydrochlorothiazide	ARB/diuretic	80.0/12.5, 160/12.5, 160/25
Hyzaar *(Merck)*	Losartan/hydrochlorothiazide	ARB/diuretic	50.0/12.5, 100/25
Inderide *(Wyeth-Ayerst)*	Propranolol/hydrochlorothiazide	Beta blocker/ diuretic	40/25, 80/25
Lexxel *(AstraZeneca)*	Enalapril/felodipine	ACE inhibitor/CCB	5.0/2.5, 5.0/5.0
Lotensin HCT *(Novartis)*	Benazepril/hydrochlorothiazide	ACE inhibitor/ diuretic	5.00/6.25, 10.0/12.5, 20.0/12.5, 20/25
Lotrel *(Novartis)*	Amlodipine/benazepril	CCB/ACE inhibitor	2.5/10, 5/10, 5/20, 10/20
Micardis HCT *(Boehringer Ingelheim)*	Telmisartan/hydrochlorothiazide	ARB/diuretic	40.0/12.5, 80.0/12.5
Prinzide *(Merck)*	Lisinopril/hydrochlorothiazide	ACE inhibitor diuretic	10.0/12.5, 20.0/12.5, 20/25
Tarka *(Abbott)*	Trandolapril/verapamil SR	CCB/ACE inhibitor	2/180, 1/240, 2/240, 4/240
Ziac *(Lederle)*	Bisoprolol/hydrochlorothiazide	Beta blocker/ diuretic	2.50/6.25, 5.00/6.25, 10/6.25

ACE inhibitor=angiotensin-converting enzyme inhibitor, ARB=angiotensin receptor blocker, CCB=calcium channel blocker
SOURCE: PRESCRIBING INFORMATION FOR ALL DRUGS

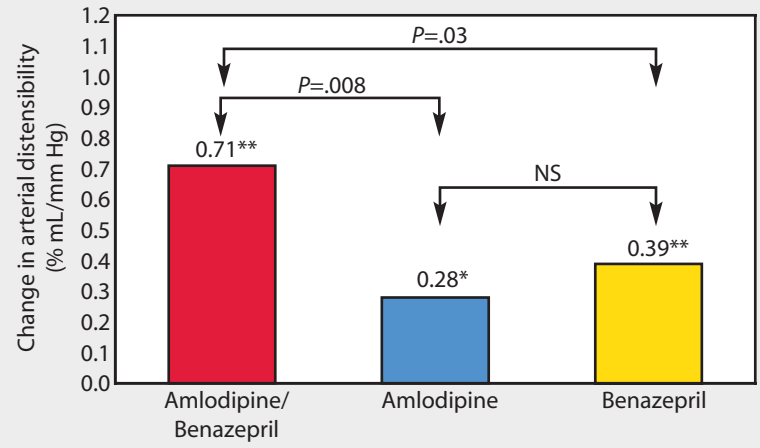
pattern of thought is suggested by the utilization of amlodipine, the most commonly used antihypertensive in the United States. Although the response rate increases with the size of the dose, so does the rate of adverse events (Frick 1988). Thus, the majority of patients receiving amlodipine are on amlodipine 5 mg instead of amlodipine 10 mg despite the greater efficacy of amlodipine 10 mg.

Patients dislike the complicated regimen associated with taking several pills and they become less compliant. Indeed, a recent meta-analysis of randomized controlled trials of strategies for improving adherence with antihypertensive therapy concludes that simplification of the dosing regimen seems to be the most fruitful approach (Schroeder 2004). A number of products offering fixed doses of antihypertensive agents from two different classes are available today (Table 4), offering a solution for physicians and patients seeking the power of combination therapy with the convenience of monotherapy. It always should be remembered, however, that the goal of antihypertensive therapy is not a reduction in blood pressure but a reduction in clinically important events (e.g., death, myocardial infarction, stroke). Selecting an antihypertensive solely on the basis of efficacious blood pressure reduction can mislead clinicians, as was demonstrated in the Fosinopril Versus Amlodipine Cardiovascular Events Randomized Trial (FACET). In this trial, which enrolled hypertensive patients with diabetes, patients randomized to fosinopril 20 mg (n=189) or amlodipine 10 mg (n=191) achieved a reduction of 8 mm Hg from baseline in diastolic blood pressure. The greater reduction of 19 mm Hg in systolic blood pressure in the amlodipine group was statistically significant compared with the reduction of 13 mm Hg in the fosinopril group (Tatti 1998). Yet, patients receiving fosinopril were about 50 percent less likely to experience major vascular events than patients receiving amlodipine during 3.5 years of follow-up (fosinopril group, 14 events [2.6 per 100 person-years]; amlodipine group, 27 events [5.0 per 100 person-years]).

In FACET, if a patient's hypertension was not controlled using the initial agent, the other drug was added. The risk of experiencing a major vascular event was slightly less among patients receiving the combination of fosinopril and amlodipine than among patients receiving fosinopril alone, although the difference was not statistically significant (Tatti 1998).

Another ACE inhibitor/CCB combination, benazepril plus amlodipine, also appears to be more cardioprotective than double doses of either agent used alone (Neutel 2004). Subjects with mild to moderate hypertension were randomized to 2 weeks of treatment with amlodipine 5 mg or benazepril 20 mg. Subsequently, they were force-titrated to 22 weeks of treatment with amlodipine 10 mg, benazepril 40 mg, or amlodipine/benazepril 5/20 mg. The combination therapy and amlodipine monotherapy both reduced blood pressure by the same amount, but arterial stiffness — an important noninvasive measure of atherosclerotic disease — was reduced to a greater extent in the group receiving combination therapy than in either of the groups receiving monotherapy (Figure). Likewise, mean left ventricular mass was reduced by 65 g in the combination group versus 28 g in the amlodipine group ($P<.02$) and 42 g in the benazepril group ($P<.14$).

FIGURE Change in arterial distensibility



* $P<.05$ vs. baseline
** $P<.01$ vs. baseline
SOURCE: NEUTEL 2004

The Safety of Lotrel and Amlodipine in a Comparative Efficacy (SOLACE) trial included patients (N=364) randomized to treatment initially with amlodipine 5 mg monotherapy or amlodipine/benazepril 5/20 mg (Neutel 2003). If patients reached a target blood pressure less than 130/85 mm Hg after 2 weeks, they continued on the starting therapy. Otherwise, their treatment was increased to amlodipine 10 mg or amlodipine/benazepril 10/20 mg, and at week 5 HCTZ 12.5 mg could be added if control was not obtained. By week 12, the target level had been reached by 54 percent of patients receiving amlodipine monotherapy compared with 74 percent of patients receiving the combination. Moreover, in the subpopulation of patients with severe hypertension (systolic blood pressure >180 mm Hg), a greater reduction in systolic blood pressure was seen in the group receiving amlodipine/benazepril (42.3 mm Hg, n=28) than among those receiving amlodipine monotherapy (30.4 mm Hg, n=26, $P=.001$). Notably, as in other studies, patients receiving amlodipine/benazepril reported edema less often than those receiving amlodipine monotherapy (12.6 percent vs. 23.0 percent, $P=.01$).

This confirms what numerous studies have shown: many patients with stage 2 hypertension (systolic ≥160 mm Hg, diastolic ≥100 mm Hg) need combination therapy to achieve their target blood pressure. Indeed, the JNC now recommends two-drug combination therapy as initial therapy for such patients.

TABLE 5 Low-dose combination therapy compared with the ideal antihypertensive

Ideal antihypertensive	Low-dose combination therapy
Effectively reduces blood pressure	Effectively reduces blood pressure
Effective over 24 hours with once-daily dosing	Maintains blood pressure control over 24 hours with once-daily dosing
High response rate	Effective in all hypertensive patients
Reduced adverse events	Reduced adverse events
Reduced negative metabolic side effects	Reduced negative metabolic side effects
End-organ protection beyond blood pressure control	End-organ protection beyond blood pressure control
Affordable	Less expensive than multiple-drug therapy

Nevertheless, JNC continues to recommend monotherapy with a thiazide-type diuretic as initial therapy for most patients with stage 1 hypertension (systolic blood pressure, 140 to 159 mm Hg; diastolic blood pressure, 90 to 99 mm Hg). Although this approach may appear attractive on the grounds of efficacy and cost, it is not supported by a consideration of what happens in clinical practice (Caro 1999). Retrospective review of a database showing outpatient prescriptions filled for 22,918 patients newly diagnosed with hypertension showed that overall persistence with drug therapy was poor (84 percent persisting with antihypertensive treatment after 6 months), but it differed according to the physician's initial choice of therapy (diuretics, 80 percent; beta blockers, 85 percent; CCBs, 86 percent; ACE inhibitors, 89 percent). Moreover, 27 percent of patients whose initial drug was a diuretic did not persist beyond three prescriptions compared with 20, 16, and 13 percent of patients starting with a beta blocker, CCB, or ACE inhibitor respectively. Because a diuretic was the most commonly selected initial therapy received by 42 percent of patients (ACE inhibitor, 32 percent; CCB, 14 percent; beta blocker, 12 percent), these findings have important implications for treatment of hypertension. When all factors are considered, low-dose combination therapy comes close to matching the characteristics of the ideal antihypertensive (Table 5, page 9).

Ideally, a step-care approach would be most desirable for treating hypertension, because minimizing the number of drugs is desirable. If a patient can achieve control with one drug, then monotherapy would be the best approach for that patient. Yet, this approach has been tried for 40 years, and it has failed to increase the rate of hypertension control substantially.

The question then becomes, would combination therapy harm patients who do not need it? The answer is no; patients who might reach their goal with monotherapy would have their blood pressure lowered even further with combination therapy, which is desirable, and would also be likely to experience fewer adverse effects, which is desirable as well. A once-daily combination product obviously satisfies patients' needs for a simpler regimen. In short, from multiple perspectives, combination therapy constitutes a win-win situation.

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Strategies for Overcoming Barriers to Effective Diagnosis and Treatment of Hypertension

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BEN PARK, MD: Isn't it more difficult to control hypertensive patients who now are 50 pounds overweight than it was 20 years ago when they weren't? Lifestyle choices enter into this.

JOEL M. NEUTEL, MD: That is absolutely correct, but the obesity problem is not diminishing. Today, 65 percent of the American population and 20 percent of adolescents are considered obese. Yet to control this disease, we cannot simply wait for people to lose weight.

DEAN G. SMITH, PHD: You suggest that the Joint National Committee recommendations have failed. Has there been any opposition in the medical community to the JNC, or any lack of support for it?

NEUTEL: Well, no, it hasn't been opposed. Through the last 2 decades or so, we've tried to give it a chance to work. Now, however, we have to come to terms with the fact that it's not working. Even the JNC is going in that direction.

Ben's point is important, because we have always suggested that patients change their lifestyle habits. In the real world, though, it is extraordinarily difficult — and it's causing many problems. I've been villanized for no longer believing that the first step in managing hypertension should be nonpharmacologic. For whatever reason, doctors continue to try to make lifestyle changes occur first. Physician habits demonstrate that the nonpharmacologic approach spans 3 months to 5 years. Looking at the success rate of nonpharmacologic treatment, it's extraordinarily small — in the single digits. Despite continuing attempts in my unit all the time, we fail to reach our goals in 96 percent of our patients.

I've shown that while trying a nonpharmacologic approach, stiffening of the vessels occurs within a year if the blood pressure remains elevated. Why not treat pharmacologically first, protecting patients throughout the period when lifestyle changes are to be made, and then make the "reward" stopping the drug if the patients are successful? You've lost nothing except a few dollars for the treatment, but you've protected their vessels.

PARK: My point was that we probably are doing a better job than we realize, because if you adjusted the blood pressure for the weight gain, chances are improvement would have been much greater than 2 percent.

BRADLEY K. KOZAR: Today, there actually may be more to overcome.

D. SMITH: Well, yes, and treading water is always a good thing to do when the sea is rising.

NEUTEL: It is certainly a difficult situation, irrespective of the reason.

PARK: I have been trying to assist my patients in making these changes. I've given them books, and we've put a gym in our practice. We have an exercise specialist, and we have these patients follow an exercise program for 3 months.

NEUTEL: We have done the same. Patients see a nurse practitioner — an expert in hypertension who educates them. They see a dietician — an expert in managing diet in hypertensive patients. We also started a gym, where we still failed in about 96 percent of patients.

KHAN NEDD, MD: You said 5 years; I would tell you 13 to perhaps 20 years for people to actually get there. Our patients die of these diseases, even while we continue to debate the issue. You have to go the pharmaceutical route at the starting point for treatment.

CHARLES SMITH, MD, MBA: Nevertheless, don't you think that just in the last 1 or 2 years that public awareness of obesity has been heightened substantially? I read that 30 million people are restricting their carbohydrate intake now.

NEDD: Weight loss as a goal in the general population is not about reducing blood pressure; it is driven by concerns about personal appearance.

NEUTEL: I have many patients who have been on the Atkins diet, and they have lost anywhere from 10 to 100 pounds. Yet, within 6 months, as soon as they start reintroducing carbohydrates, the weight comes back. Exercise is most effective and what we ought to advocate, but it also is difficult to see through.

Given that we are on this topic of lifestyle changes, if we had the executive committee of the JNC sitting in this room, would you be comfortable advocating using a first-line nonpharmacologic approach simultaneously with pharmacologic treatment?

PARK: We are seeing that as patients pay more and more of their share of the pharmaceutical bill, they're more motivated to make lifestyle changes. They really are.

C. SMITH: Unfortunately, as they pay more of their pharmaceutical bill, they are less likely to get their prescriptions refilled.

NEUTEL: That's a big problem.

KOZAR: What is the role of the employer in this?

MARCIA A. PALMER, PHARMD, MBA: Today, the direction in managed care is consumer choice. From my perspective, it would be more important to incentivize the consumer in some way, probably financially. For example, if you achieve specific goals with exercise, then you might not have a copayment, or if you don't reach your goals, then you might have a higher premium. I think the time has come to implement employee incentive benefit designs.

C. SMITH: Not many employers incentivize their employees.

PAMELA A. HYMEL, MD, MPH: We do. If the employees have hypertension or high cholesterol, we reduce their health care premiums by $300 for participating in a risk-reduction program.

PARK: How well does it work?

HYMEL: We have about a 65 percent participation rate, and we have seen a decrease in cardiovascular events among participants. Yet it concerns me that we only have a 65 percent participation rate among people with lifestyle habits that put them at risk. We're going to have to watch trends in the future to see that employers are not overpricing medication or creating barriers to obtaining medication that's free, when it is appropriate, as with hypertension, diabetes, and asthma. Employers tend to approach this in different ways, but we need to help our employees get the right medication so that they can have healthier lifestyles and be more productive.

D. SMITH: I saw an article that was promoting a benefit-based copayment, where copayments are directly related to the medical benefit of the drug. In some cases, the copayment should be a negative number. Imagine going to the drugstore, and the pharmacist gives you your medication and 5 dollars.

C. SMITH: It makes sense, but it is extremely difficult to accomplish.

NEUTEL: That's why this is such an interesting meeting. I go to many formulary committee meetings in California, and the feeling is that the people involved in making the decisions are not interested in the savings in 5 years. They are worried about balancing the budget at the end of this year; something that might have benefits for patients 5 years from now doesn't register as clearly.

C. SMITH: That was common 5 years ago. Now, from a managed care perspective, there's the recognition that one plan is going to end up getting another plan's patients next year. So, there are heightened concerns about what happens in 2 to 5 years. Previously, we all thought it would cost too much, but now we do look at outcomes.

NEUTEL: I'm pleased to hear that, because I haven't seen evidence of that change as yet. Nevertheless, as you all know, preventing one heart attack or stroke will pay for the drug for many, many of your participants.

NEDD: I think that's the key. JNC-7 evidently is a wonderful document, and it influences us all with respect to how we treat hypertension. There is a disconnection, however, relative to what patients understand about this whole issue. For instance, in our African American Health Institute in Grand Rapids, our goal is to focus not on patient education but on system change. Even if you give people money, you still end up preach-

ing to the choir. People who join those programs already are healthy or have a history of lifestyle changes.

NEUTEL: You bring up another good point relative to managing hypertension, which is education. The length of time that doctors get to spend with their patients is diminishing. Internists are told that they have to see a patient in 10 minutes; so, when they note a hypertensive patient on the schedule, they think "Oh, an easy patient, 5 minutes for him — and 15 for the next, more difficult patient." They run in, look at the readings, the patient complains about something else, and they tell the patient to make another appointment. They run out, having adjusted the medication or left it the same, and the patient still holds a list of questions.

A few months ago, I gave a lecture on hypertension at a local hospital. About 500 people showed up. But they weren't interested in my lecture; all they wanted to do was ask about drug interactions and side effects, what blood pressure monitor to buy for themselves at home, what the goals of blood pressure should be, and all these things. What they wanted to do was to ask the questions they had not been given the opportunity to ask in their visit to their doctor. So, that's another thing we have to think about, direct-to-consumer education. Maybe that's where the pharmaceutical industry can help us.

NEDD: Or even better, provider education.

NEUTEL: Exactly. But providers are working long hours, they're tired, and they are just not doing it as much.

D. SMITH: Specialists in health behavior and health education, nurses and other health professionals, are likely to be much better at this process of educating.

PARK: As with any chronic disease, you will have more effective management with a team-based approach. The other day I got a call from a fitness center in a nursing home, asking if I would give a talk on high blood pressure. They said that they receive more questions about that than anything. I was shocked.

NEDD: In our hospitalist group, we ask questions of patients all the time, so I think we have some impact. When it comes to hypertension, we ask patients their goals, and they don't know. That means providers aren't providing patients with a vital piece of knowledge with respect to a definitive goal that they can go home with.

NEUTEL: There are two important issues here. We are questioning whether there should be major changes in our approach to patient and provider education. Second, we all acknowledge that nonpharmacologic treatment works, but there are questions about whether a nonpharmacologic approach should be used simultaneously with pharmacologic management as well as about the extent of patient cooperation we can get.

KOZAR: Managed care has historically been slow to accept combination therapy.

NEUTEL: The concept out there is that combination therapy is more expensive.

KOZAR: The bias actually is more than cost, or at least it used to be — a bias against combination therapy that was unrelated to the copayment issue.

PARK: It is. If you look at asthma, you can't get the insurance companies to pay for Advair [fluticasone propionate/salmeterol] combination inhalation therapy. But, if you write the two components individually — which costs about $40 more, they're happy to pay for that.

NEUTEL: I have been through this with Lotrel. If you look at the cost of Lotrel, which is amlodipine plus benazepril, it was about $45 a month for a 30-pill supply. Amlodipine 5 mg was around $37, so it was cheaper, and benazepril 20 or 10 mg was around $25 at the time. The point, however, was that they were more expensive if you used them as separate tablets.

The pharmacist didn't realize how many patients in his database were on an ACE [angiotensin-converting enzyme] inhibitor plus a CCB separately. When I asked him to do an analysis, he found that about 30 percent of the hypertensive patients were on the two drugs separately, and that putting Lotrel on the formulary would save a lot of money. But he didn't recognize that until someone advised him to look at the database. So, there is a lack of recognition about what's actually happening in clinical practice.

PALMER: Let's put this into some perspective. Drug cost is not the sole determinant of managed care acceptance. Our discussion of drug costs and utilization is not going to solve the antihypertensive adherence problem.

NEUTEL: What solves the problem is formulary availability, and that depends on cost. Doctors will tell you that if it's not on the formulary, they're not going to write it, because getting a prior authorization is just not worth the time it takes.

PALMER: Our health plan closely followed patients who were candidates for Advair with their primary care physicians. We found no difference in adherence with Advair or the two individual medications. So, having the drug on the formulary did not solve the problem.

C. SMITH: Relative to Advair, studies show increased compliance using only one drug rather than two, so we accepted that. In the past we were concerned about whether the two drugs would have increased side effects. Nevertheless, there's a tremendous pressure on pharmacy directors for cost, and giving up a copayment is always a consideration. It goes back to whether we look long-term for improvements. When a study shows synergy between two drugs, the study can show increased compliance. We'll give relative to the cost in exchange for improved outcomes.

HYMEL: I'm really surprised about this pharmacy copayment issue. I know that if you can get better com-

pliance, employers will put those drugs on the first tier. The idea is that you may as well pay for the medication, because in the long run with the right medication, you are getting better effects for your employee population.

KOZAR: Nevertheless, in hundreds of meetings with managed care pharmacy and medical directors on new drugs, I always hear them say that they don't pay extra for convenience or compliance.

HYMEL: These are the managed care organizations, right?

KOZAR: Right.

HYMEL: Well, that's where employers have to start stepping up and having these kinds of discussions.

NEUTEL: This is why this meeting is so important. I do hundreds of lectures with doctors, and they tell me over and over that if it's not on formulary, they can't write the script. Often, though, the reason that a drug is not on formulary is cost. I have been to formulary committees, and if I don't have outcomes studies for a given drug, it doesn't go on formulary. If another drug has an outcomes study, however, but there is a cheaper drug that doesn't have an outcomes study, then the outcomes study doesn't matter. There is a mixed message as to what they're seeking.

NEDD: As somebody who sometimes sits on the formulary committee, I find that there are many individuals having conflicting issues that never really surface. The pharmacist is concerned about losing a copayment, yet the discussion never really surfaces. Everybody comes in with their issues. We generally see decisions being based on an issue that doesn't present itself at pharmacy and therapeutics committee meetings.

Those silos make it difficult to come up with a great way of making a decision. As a physician, as an advocate for patients, I may have great arguments for why I want to do something. I may even hear good arguments for why it could be, but I don't know what's occurring behind the scenes. Ten days later, such issues arise; for example, "We couldn't really do that because we have a deal with this company that bundles these products together."

PARK: I worked at a major health plan for 6 years. I've gone to them time and time again trying to get these things changed. It's not that individuals within the organization don't care, but overall what drives publicly traded companies is maximizing quarterly earnings.

NEDD: Ultimately it comes down to whether the consumers will comply or not. In African-American patients as a general rule, how they deal with the issue of *potential* adverse effects is really the key. In the African American population, you have to understand their historical level of trust with respect to relationships with physicians and pharmaceutical companies.

NEUTEL: It's made even worse for us by the fact that pharmacists, who really are trying to be helpful, will spend time going through side effects in the package insert with patients. Before they have even started, patients have had this list of side effects diligently explained to them, which scares them off.

HYMEL: So they won't even take the medication….

NEUTEL: They don't start the first drug.

NEDD: In the population I'm talking about, adverse effects do occur, but it's not the issue.

NEUTEL: I handle it by giving them the package insert for aspirin, and they tend to get the picture. But it is a big problem, and the compliance rate is no better among patients who get their drugs for free. When you ask why, patients say they didn't want to deal with the side effects or that they'd rather deal with the nonpharmacologic treatment advocated by the doctor.

NEDD: That's where the discussion must occur. We did that by going around the room and telling people about the side effects associated with some common drugs. When we asked whether they'd take this drug, it was interesting how many people wouldn't take acetaminophen or aspirin. While we are making the argument that adverse reactions shouldn't be an issue, consumers are sometimes speaking in a different language on this subject.

D. SMITH: If you pay attention to modern pharmacy education, pharmacists are talking more about side effects and identifying them early on. A key area is ACE inhibitors; clinical trials show 5 percent coughing rates, and physicians are saying that in practice, when they move away from the patients with isolated hypertension to the people who are on six and seven medications, the cough rate goes into the 15 to 20 percent range.

PALMER: If I remove my pharmacist and managed care hats — as a yuppie with 145/95 mm Hg blood pressure — I would want to start with lifestyle management for at least a 3- to 6-month period, and then just hydrochlorothiazide before I would initiate combination therapy.

KOZAR: Is there anyone else who feels that way?

PARK: I've got to tell you, patients don't know whether it's a combination or not. I give them one pill, and they respond with "Okay, great."

NEUTEL: In their minds, a single tablet is one medication. As for lifestyle modification, my line to my patients in Orange County is, "I want you to go out and exercise, lose weight, cut salt, cut smoking. I'm then going to start you on this medication, and in 3 months we will reassess it. And if you have done what you told me you'll do, I will stop your medication, I promise you." That seems to work just fine.

NEDD: In the JNC-7 standard of prehypertension, is there a role for monotherapy?

NEUTEL: That's a good point. I believe there is, and I'll tell you why. When I was studying the normotensive young adult children of hypertensive parents, I found that the normotensive children had all the other signs we look for in hypertension. They had elevated norepinephrine, elevated renins, left ventricular hypertrophy. They had stiffer vessels than normotensive matched young adults of normotensive parents. They had all this, but they hadn't developed high blood pressure. They are what I refer to as the normotensive hypertensives; they have the syndrome, but they haven't yet developed the high blood pressure.

Now, in terms of risk, they probably are at the same level as hypertensive people. We never treat them, though, because they don't have high blood pressure. And blood pressure is a marker to isolate this group of patients and put them into the treatment group. Should we be treating those patients? We should, I think. Perhaps, that is where the monotherapy will come in.

An ongoing study is looking at that. They are taking a group of patients and randomizing half to placebo and half to an angiotensin receptor blocker, and watching them for 5 years, with the end point being development of overt hypertension. I think you can prevent it if you get in early enough; you can only control it once they've developed it. So it's a whole other discussion.

PARK: Do you believe blood pressure can be too low if someone is asymptomatic?

NEUTEL: No.

PARK: Also, is there is a role for impedance cardiography?

NEUTEL: I don't do it anymore. Within 2 years, we will have a three-drug combination in one tablet that will get 85 or 90 percent of patients to goal.

NEDD: Patients come in with other issues. I tell them up front: You've got to be on anywhere between 2.3 to 4.6 drugs, and as long as you are standing we'll treat you, especially patients who come in with other issues.

PARK: In general, you get the behavior that you pay for, whether it's for a physician, medical director, employer, or insurance company. I've seen a lot of improvement in our physicians when we have started paying them for outcomes. I haven't seen any CEOs of major health plans who have specific health care quality outcome measures as part of their compensation package, and they ultimately make the decisions.

C. SMITH: I have seen some medical directors who have been able to show statistical significance in improving effectiveness-of-care measures and have received bonuses, but not at the CEO level.

D. SMITH: I like the idea of CEOs doing it.

PARK: The CEO brings the resources of the organization to bear. Until those people have some compensation at risk for specific clinical outcomes, I don't think you'll see the organization caring as much as it could otherwise.

The Health Economics of Hypertension

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Determining the economic impact of hypertension or any illness is a vexatious matter, fraught with methodologic pitfalls. Faced with the need to allocate funds for health research, members of the Senate Committee on Appropriations in 1994 found themselves among the sorely vexed. They turned to the National Institutes of Health for guidance, asking the NIH to provide cost estimates and number of deaths associated with the 15 leading causes of death listed by the Centers for Disease Control and Prevention (CDC). The NIH issued its report as directed in 1995 and has since updated it. The NIH report comes with this caveat: "Disease-specific cost of illness estimates are uneven and essentially noncomparable…. Economic costs are an incomplete index of disease-specific burden and an insufficient criterion for priority setting" (Kirschstein 2000).


DEAN G. SMITH, PHD

Nevertheless, whether at the level of a nation or a health plan, priorities must be set because economic resources are limited. Relatively simple economic analyses (e.g., cost-effectiveness) often are used to help inform a wide range of decisions, from selecting a treatment for a patient to setting health care policy. But while doing so, as the NIH points out, it also is important to remember that any estimate of the economic cost of a health condition is an incomplete measure of the total burden the condition presents, owing to the difficulty in measuring important aspects of the condition, such as impaired function, diminished quality of life, and the emotional and psychological impact on people with whom patients interact. The unquantifiable aspects of illness are especially burdensome in the conditions most closely associated with hypertension, owing to the debilitating nature of stroke, heart attack, and heart failure, to name some prominent examples, and their high prevalence.

Patients with uncontrolled hypertension are 2 or 3 times more likely to develop heart failure than patients who either do not have hypertension or whose hypertension is controlled (Levy 1996). Furthermore, patients with uncontrolled hypertension have a higher incidence of stroke and stroke-related morbidity and mortality. Trials have found that controlling blood pressure with medications decreases the risk of stroke, coronary heart disease, myocardial infarction (MI), congestive heart failure, and progression of renal disease, as well as morbidity and mortality resulting from other causes. Left untreated or undercontrolled, hypertension and related sequelae represent a potentially significant burden on the health care system and society as a whole.

Nevertheless, estimating the costs of hypertension is complicated by the fact that hypertension is but one factor among many involved in the etiology of a given illness. In fact, in a recent study by the CDC of the actual causes of death in the United States (Table 1, page 18), the authors excluded the effects of high blood pressure and high cholesterol (Mokdad 2004). They instead focused on factors that often underlie the development of hypertension, dyslipidemia, and other risk factors for heart disease and other leading causes of death (Table 2, page 18). Note that the top three actual causes of death in Table 1 are major modifiable risk factors associated with cardiovascular disease or hypertension or both. Deaths attributed to poor diet and physical inactivity, which is manifested largely as overweight, increased by one third between 1990 and 2000, the largest increase of any single cause.

To the extent that individuals, health plans, and governments desire to devote economic resources to addressing modifiable risk factors, it is possible to prevent hypertension and its attendant ills from arising in the first place. In its seventh report (JNC-7), the Joint National Committee on Prevention, Detection, Evaluation, and Treatment of High Blood Pressure endorses lifestyle modification as the foundation for treating hypertension, as it has been shown that systolic blood pressure can be reduced by 5 to 10 mm Hg through weight loss of 10 kg (22 pounds), 8 to 14 mm Hg through a low-fat diet rich in fruits and vegetables, 2 to 8 mm Hg through restriction of sodium, 4 to 9 mm Hg through regular physical activity, and 2 to 4 mm Hg through moderate alcohol consumption (JNC-7 2003).

Quantifying costs

Despite the difficulties in isolating the costs of hypertension, some researchers have made the attempt. The CDC's National Center for Health Statistics has estimated that direct medical care expenditures attributable to hypertension totaled $108.8 billion in 1998 —

TABLE 1 Leading actual causes of death in the United States

Actual cause	2000*		1990	
	Percent	*Number*	*Percent*	*Number*
Tobacco	18.1	435,000	19	400,000
Poor diet and physical inactivity	16.6	400,000 (overweight, 385,000)	14	300,000
Alcohol	3.5	85,000	5	100,000
Microbial agents	3.1	75,000	4	90,000
Toxic agents	2.3	55,000	3	60,000
Motor vehicle	1.8	43,000	1	25,000†
Firearms	1.2	29,000	2	35,000
Sexual behavior	0.8	20,000	1	30,000
Illicit drug use	0.7	17,000	<1	20,000
Total	48.2	1,159,000	50	1,060,000

*Some deaths for 2000 have been included in more than one category (e.g., alcohol and motor vehicle).
†Alcohol-related motor vehicle deaths were assigned to the alcohol category.
SOURCES: 2000 ESTIMATES FROM MOKDAD 2004; 1990 ESTIMATES FROM MCGINNIS 1993, QUOTED IN MOKDAD 2004

TABLE 2 Leading causes of death in the United States in 2000

Cause of death	Number	Deaths per 100,000 population
Heart disease	710,760	258.2
Malignant neoplasm	553,091	200.9
Cerebrovascular disease	167,661	60.9
Chronic lower respiratory tract disease	122,009	44.3
Unintentional injuries	97,900	35.6
Diabetes mellitus	69,301	25.2
Influenza and pneumonia	65,313	23.7
Alzheimer's disease	49,558	18.0
Nephritis, nephrotic syndrome, and nephrosis	37,251	13.5
Septicemia	31,224	11.3
Other	499,283	181.4
Total	2,409,351	873.1

SOURCE: MININO 2002, QUOTED IN MOKDAD 2004

12.6 percent of all U.S. medical spending that could be associated with diagnoses (Hodgson 2001). Of this amount, $22.8 billion was directly associated with a diagnosis of hypertension, $29.7 billion with cardiovascular complications of hypertension, and $56.4 billion for other diagnoses. The average amount spent for a hypertensive condition was $3,787. Per capita spending increased with age (younger than 65, $249; 85 and older, $3,007). (Despite the age-related increase in per capita spending and a recommendation by the U.S. Preventive Services Task Force, a bill that would have expanded Medicare coverage to include hypertension screening and other preventive measures, the Medicare Wellness Act of 2001 [S 982/HR 2058], died in committee.)

Comparable results were obtained in a study using data from the 1996 Medical Expenditure Panel Survey, which also demonstrated the extent of comorbidity associated with hypertension and other chronic conditions (Druss 2001). In this nationally representative sample of 22,230 U.S. residents, hypertension was the most prevalent chronic condition (10.2 percent), with diabetes and heart disease being found among 3.6 and 1.3 percent of the population, respectively. Among patients with heart disease, 44.0 percent also had hypertension (and 21.2 percent also had diabetes). Among those with diabetes, 45.8 percent also had hypertension (and 7.9 percent also had heart disease).

Including direct costs for hypertension and costs for comorbid conditions, the mean per capita health care cost for patients with hypertension was $4,073. When extended to the U.S. population, costs for hypertension and comorbid conditions totaled $110.3 billion. Of this total, only 13.4 percent was for direct treatment of hypertension, with the remaining 86.6 percent attributable to treatment of comorbid conditions. In this survey, 67 percent of patients carried private health insurance, with 34 percent reporting enrollment in managed care (defined as care provided by an HMO or the need to go through a gatekeeper for all health care). Including the costs of lost work, the total costs for persons with hypertension were estimated at $121.8 billion. Due to the high prevalence of hypertension, its total costs were more than twice those of diabetes ($57.6 billion) or heart disease ($42.4 billion).

Defining hypertension as systolic blood pressure higher than 139 mm Hg or diastolic blood pressure higher than 89 mm Hg, the JNC-7 report cites hypertension as one of the most common chronic medical conditions in the United States, affecting some 50 mil-

lion Americans. In addition, 22 percent of American adults are believed to have prehypertension, defined as systolic blood pressure of 120 to 139 mm Hg or diastolic blood pressure of 80 to 89 mm Hg.

It should be no surprise, then, that hypertension accounts for a substantial amount of physician activity. During 2001, the number of office visits for ambulatory care was 880.5 million, with an overall rate of 314 visits per 100 persons (Cherry 2003). Patients cited hypertension as the principal reason for 10.5 million of these visits (1.2 percent). Nevertheless, 34.5 million visits (3.9 percent) resulted in a primary diagnosis of essential hypertension — the most common illness-related primary diagnosis, leading arthropathies (3.2 percent), acute upper respiratory infections (3.2 percent), and diabetes (3.1 percent).

Although the cause of hypertension is unknown in most cases, the vast majority of cases are easily detectable and treatable, in theory. Despite the relative ease of diagnosis, 30 percent of patients are unaware that they have high blood pressure. Among those who are aware, 11 percent do not receive any treatment and another 25 percent receive suboptimal treatment. As of 2000, it was estimated that less than 35 percent of hypertensive patients are controlled to below 140/90 mm Hg (JNC-7 2003).

To gain a better appreciation of the costs that would be involved in identifying and treating persons whose hypertension is untreated or undercontrolled, it is necessary to assess the demographic characteristics of these populations. They might be expected to be people on the outskirts of mainstream society — impoverished, lacking access to regular health care. That is not the case. An examination of data from the Third National Health and Nutrition Examination Survey (NHANES III) — the source of the widely cited estimates of rates of hypertension awareness and control in the United States — disclosed that most cases of uncontrolled hypertension consist of isolated mild systolic hypertension in older adults who have access to health care and relatively frequent contact with physicians (Hyman 2001). Among treated patients, control rates declined with age from 65 percent among patients 25 to 44 years old, to 52 percent among those 45 to 64 years old, and to 34 percent among those 65 or older. Among patients with uncontrolled hypertension, blood pressure levels rose with age. In those unaware of their hypertension, mean blood pressure was 138/91 mm Hg in persons 25 to 44 years old, 148/86 mm Hg in those 45 to 64 years old, and 153/83 mm Hg in those 65 or older. In those aware of their hypertension but not treated, mean blood pressure was 141/94, 152/89, and 160/81 mm Hg in each respective age group. Finally, in those whose hypertension remained uncontrolled despite treatment, mean blood pressure was 147/95, 150/87, and 159/78 mm Hg in each respective age group.

Having health insurance did not distinguish one group from another: among patients who were unaware that they had hypertension, 90.2 percent had health insurance; patients with acknowledged but untreated hypertension, 89.5 percent; and patients with treated but uncontrolled hypertension, 95.7 percent. Among patients whose hypertension was treated and controlled, 93.5 percent had health insurance. Among patients whose hypertension was treated and controlled, 95.2 percent had a usual source of care — but, so did 97.0 percent of the patients whose hypertension was treated and uncontrolled.

Multivariate analysis showed that persons age 65 or older had the greatest risk of uncontrolled hypertension — this despite the fact that people in this age group have the most frequent contact with the health care system and are most likely to have medical insurance.

Which treatment?

The goal of antihypertensive therapy is to reduce cardiovascular and renal morbidity and mortality. The JNC-7 guidelines indicate that for most patients with uncomplicated hypertension, drug therapy begins with a thiazide-type diuretic, either alone or in combination with an antihypertensive from another class (JNC-7 2003). This recommendation is supported by a recent meta-analysis of 42 recent randomized controlled trials evaluating the efficacy of various antihypertensive agents for major cardiovascular events over the course of at least 1 year in at least 400 subjects (Psaty 2003). (The study was published in the same issue of *JAMA* that contained the JNC-7 report.) Trials enrolling patients with heart failure or a history of MI were excluded, as well as those trials that involved other therapies such as smoking cessation or lowering lipids. The qualifying trials enrolled 192,478 subjects who were followed for an average of 3 to 4 years.

The meta-analysis included the controversial Antihypertensive and Lipid-Lowering Treatment to Prevent Heart Attack Trial (ALLHAT 2002), which relied solely on secondary end points to conclude that thiazide diuretics should be preferred as first-line antihypertensives (Messerli 2003). The second Australian National Blood Pressure Study also was included, which showed somewhat conflicting results — a slight advantage of the diuretic hydrochlorothiazide over the angiotensin-converting enzyme (ACE) inhibitor enalapril in elderly patients, especially men (Wing 2003).

For every outcome in the meta-analysis, low-dose diuretics were superior to placebo. Furthermore, no outcome showed that any other first-line therapy was superior to low-dose diuretics — although some were superior to placebo. In eight comparisons, low-dose diuretics were statistically significantly superior to the other treatments. Although 13 other comparisons fa-

vored low-dose diuretics, results did not reach statistical significance.

Because the most effective drug in this analysis also was the least expensive, the authors pointed out that cost-effectiveness analyses were not needed to justify recommending low-dose diuretics as first-line treatment for most patients requiring drug therapy for uncomplicated hypertension. An earlier cost-minimization study that applied wholesale drug costs to the numbers needed to treat (NNT) to prevent a stroke, MI, or death in middle-aged and elderly patients with uncomplicated hypertension found that diuretics were more cost-effective than the newer agents (ACE inhibitors, alpha blockers, beta blockers, or calcium channel blockers [CCBs]). The cost-effective advantage of diuretics held even if the newer agents were 50 percent more effective than diuretics in preventing major events and even if the cost of potassium supplementation was considered (Pearce 1998).

Yet, in real-world conditions — in contrast to the artificial conditions of clinical trials — patient behavior shows that diuretics do not enjoy the status that might be expected of an agent that costs less and is as effective or more effective than any other antihypertensive. An analysis of a large Canadian database containing pharmaceutical records for patients newly diagnosed with hypertension showed that patients initially treated with a diuretic were least likely to persist with antihypertensive therapy after 5 years of treatment, while those initially treated with an ACE inhibitor or CCB were most likely to persist with therapy (Caro 1999). Rates of persistence were poor regardless of the agent used initially: after only 6 months, persistence rates with diuretics, beta blockers, CCBs, and ACE inhibitors were 80, 85, 85, and 89 percent, respectively; after 4.5 years, respective persistence rates were 40, 49, 47, and 53 percent.

The JNC-7 report notes that most patients who require drug therapy for hypertension will need combination therapy to meet their blood pressure goals. Physicians therefore need not be overly concerned about weighing the cost-effectiveness of diuretics against the possibility that giving patients a diuretic increases the likelihood that they will stop using antihypertensives altogether. Insights into the benefits of antihypertensive combination therapy are presented in the article, on page 5 of this supplement, by Joel M. Neutel, MD.

Part of the explanation for undertreatment of hypertension in the United States may stem from the outmoded belief that systolic blood pressure naturally rises with age, and that a good rule of thumb for determining a person's normal systolic blood pressure is to add 100 to the person's age. Even stage 1 isolated systolic hypertension (systolic 140–159 mm Hg, diastolic <90 mm Hg) has been shown to increase cardiovascular morbidity and mortality, however (Sagie 1993). In the Framingham Heart Study, 80 percent of subjects with systolic blood pressure in this range at baseline progressed, after 20 years of follow-up, to a systolic pressure of 160 mm Hg or higher, compared with 45 percent of subjects who were normotensive at baseline. Furthermore, compared with normotensive subjects, those with stage 1 isolated systolic hypertension had a 47 percent greater risk of cardiovascular disease and 57 percent greater risk of death from cardiovascular disease.

Because blood pressure in U.S. cohorts increases with age (but not via natural processes), it is important to monitor patients periodically whose blood pressure is not optimal but who are not yet hypertensive. In the JNC-6 report, these patients were classified as having normal blood pressure (systolic 120–129 mm Hg or diastolic 80 to 84 mm Hg) or high-normal blood pressure (systolic 130–139 mm Hg or diastolic 85–89 mm Hg). The ter-

TABLE 3 Rates of progression to higher blood pressures in Framingham Heart Study (% progressing)

	Blood pressure on follow-up after 4 years			
Blood pressure at baseline	***<120/ <80 mm Hg***	***Systolic 120–129 or diastolic 80–84 mm Hg***	***Systolic 130–139 or diastolic 85–89 mm Hg***	***Systolic >140 or diastolic >90 mm Hg***
Age 35–64 years				
<120/<80 mm Hg	64.4	22.0	8.5	5.1
Systolic 120–129 or diastolic 80–84 mm Hg	27.5	31.9	22.5	18.1
Systolic 130–139 or diastolic 85–89 mm Hg	11.0	21.1	28.5	39.4
Age 65–94 years				
<120/<80 mm Hg	38.2	28.0	15.3	18.5
Systolic 120–29 or diastolic 80–84 mm Hg	21.1	24.2	25.7	29.0
Systolic 130–139 or diastolic 85–89 mm Hg	7.9	16.2	23.4	52.5

SOURCE: VASAN 2001B

minology has been altered in the JNC-7 report, with normal being described as systolic blood pressure less than 120 mm Hg and diastolic blood pressure less than 80 mm Hg, and with prehypertension described as systolic blood pressure between 120 and 139 mm Hg or diastolic blood pressure between 80 and 89 mm Hg. Applying the JNC-6 definitions to subjects in the Framingham Heart Study who did not initially have hypertension, it was found that older subjects and those with blood pressure just below the threshold for hypertension were more likely to progress to hypertension than younger subjects and those with blood pressures farther below the hypertension threshold (Table 3).

In the Framingham population, men and women with blood pressure just below the hypertension threshold (systolic pressure of 130–139 mm Hg or diastolic pressure of 85–89 mm Hg) were found to be at 1.6 and 2.5 greater risk for cardiovascular disease, respectively, compared with subjects whose blood pressure was less than 120 mm Hg systolic and less than 80 mm Hg diastolic (Vasan 2001a). In subjects who were at least 65 years old and on the border of hypertension, the crude cardiovascular event rates for women and men were 19.5 and 28.1, respectively, per 1,000 person-years. The authors speculated that if antihypertensive therapy could lower the absolute 5-year risk of cardiovascular disease by 25 percent in this population, 28 men or 41 women would need to be treated for 5 years to prevent one major cardiovascular event. A clinical trial, however, would be needed to confirm the benefits of drug therapy in this population.

Conclusion

Owing to medical advances, patients who once may have died from a heart attack now survive, only to develop heart failure. Owing to medical advances, patients who once may have died from a stroke also survive, often for many years (though often without regaining full function). Owing to less welcome changes, some of which are incapable of being modified (the inevitable aging of the large Baby Boom cohort) and some quite amenable to modification, at least in theory (sedentary lifestyles, poor diets), risk factors for cardiovascular disease are burgeoning nationally. Americans are becoming increasingly overweight and obese, with the prevalence of obesity conservatively estimated at 21 percent in 2001 — a 74 percent increase beyond the 12 percent prevalence rate in 1991 (Mokdad 2003).

For more than 40 years, the prevalence of diagnosed diabetes has been rising inexorably, from less than 1 percent in 1960 to nearly 5.3 percent today (14 million Americans) — and about one third of Americans with diabetes remain undiagnosed (Engelgau 2004). Moreover, metabolic syndrome, a constellation of risk factors for coronary heart disease, is found in nearly a quarter of the U.S. adult population, and its prevalence rises steeply with increasing weight (Park 2003). Hypertension is a criterion that helps to define metabolic syndrome (along with abdominal obesity, low levels of HDL cholesterol, elevated triglyceride levels, and elevated fasting glucose levels).

From this perspective, hypertension is but one factor in a set of interrelated factors that contribute substantially to the nation's disease burden. Most people who have hypertension or who are at risk of developing hypertension already are known to the health care system. Many will benefit from one or more of the numerous antihypertensive agents that are available. Nevertheless, instead of regarding hypertension as a specific illness to be treated with specific pharmaceutical agents (and hypercholesterolemia as another, and diabetes as yet another), a large-scale reallocation of resources to improve the lifestyles of Americans might simultaneously reduce the prevalence of hypertension, dyslipidemia, and insulin resistance; reduce the resulting morbidity and mortality; and improve overall quality of life. Economic analyses could inform a decision to allocate more funds for disease prevention in the hope of reducing expenditures for treating illness, but such a decision ultimately would be an expression of political will beyond the province of economics alone.

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Minimizing Costs and Maximizing Outcomes In the Real World Setting

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BEN PARK, MD: It would seem that about half the people in America have hypertension or prehypertension.

DEAN G. SMITH, PHD: The problems are centered on how to get the patients who are not controlled on medication to continue taking medication or to start a new medication, and how to get the patients who are unaware that they have a problem to come into the office. That is a bigger challenge than getting them to initiate treatment.

CHARLES SMITH, MD, MBA: Have you looked into the pharmacoeconomic data presented by the pharmaceutical companies?

D. SMITH: The content of any dossier is difficult to interpret, given that they are generated by the pharmaceutical companies that have an interest in presenting the data in such a way that their drugs would be considered for inclusion in your formulary. Furthermore, data are lacking on combination treatments. If data on hypertension are presented, those should be the direct costs of hypertension. Often, though, the cost savings include the cost savings related to stroke and heart failure. The problem is then isolating the cost savings related to hypertension.

BRADLEY K. KOZAR: More and more managed care organizations are asking drug companies for the NNT [number needed to treat].

D. SMITH: Economists don't think in terms of the NNT. They usually think about the cost of the treatment, the benefits of saved dollars later on, and making that sort of analysis in a given a population. I think pharmacists, however, may use the NNT.

KOZAR: Marcia, what does the NNT tell you as a pharmacist?

MARCIA A. PALMER, PHARMD, MBA: Pharmacists look at that number, because often data from studies do not include a large population. The NNT is used to help determine the validity of the study.

KOZAR: What do those numbers tell you, Chuck?

C. SMITH: They tell us that some of these medications are extremely expensive when it comes to obtaining a good outcome. For some drugs, such as cancer agents, we look more at life expectancy and how much we are gaining versus the cost. My pharmacy and therapeutics committee accepts the NNT, but there is often a request by one or more members for more information.

D. SMITH: In the case of hypertension, it is fairly straightforward, with the drug cost representing a relatively small fraction of the total expenditures. Sometimes we

can be penny wise and pound foolish with respect to decisions not to be treating people.

KHAN NEDD, MD: Do you have any data on the added costs, such as for absenteeism?

D. SMITH: As far as hypertension is concerned, absenteeism is rarely evaluated thoroughly.

NEDD: It seems like it makes sense and is logical for an effective argument.

D. SMITH: Employers need to request that information.

JOEL M. NEUTEL, MD: Can you capture the extent to which absenteeism is correlated to various disease processes?

PAMELA A. HYMEL, MD, MPH: We spent a long time developing a database allowing us to integrate our medical and pharmacy data with our absenteeism and disability data. With hypertension, though, most of the related absenteeism is from the sequelae. To me, that is where we need the pharmaceutical companies and employers to focus their efforts.

D. SMITH: Yes, and hypertension has been slow to come into focus. It is one of the progressive illnesses that people continue to ignore until catastrophic events occur.

NEDD: In an evidence-based setting, do we actually know that for sure?

D. SMITH: Well, we have the observations but the issue is how high the numbers actually are. We don't have precision on the numbers yet.

NEDD: Certainly, the knowledge that somebody has hypertension has an effect on his or her personal life.

D. SMITH: We see those patients going to the physician's office more, which in some employed populations actually means being away from work.

HYMEL: That would be the presenteeism issue. The patients are worried about the sequelae, the side effects from the medication, and the problems arising from the hypertension itself.

NEDD: In some populations, the knowledge of the existence of disease may create a virtual disability characterized by frequent visits to the physician's office and time off from work, which will translate into cost.

D. SMITH: When you consider the relationship between hypertension control and medication costs, you will notice that people who are somewhat controlled have fewer health care costs than those who are poorly controlled.

NEDD: I would just like to remind everyone that the data don't represent women, minorities, or the elderly.

D. SMITH: That is correct; most of the available data are for white males.

NEDD: It's not something you can exactly extrapolate from these studies. To some degree you can, but I don't think you can fully do so until you look at studies that are much more inclusive, especially with respect to women and elderly populations.

D. SMITH: There are various issues to consider when thinking about combination therapy. ACE [angiotensin converting enzyme] inhibitors, ARBs [angiotensin receptor blockers], and diuretics are increasingly recommended as first-line therapy. When we get to fixed-capsule, fixed-dose combinations and single-capsule, fixed-dose combinations, there is an opportunity for significantly greater adherence and to use fewer medical resources. Remember, too, that there have been a variety of studies on tolerability and compliance issues. Findings suggest that one third of the patients titrate their medication down or take fewer drugs than are prescribed.

C. SMITH: This supports being aggressive and using combination therapy for most of your hypertensive patients. By doing this, more of your patients are going to be better, with fewer side effects, and you'll achieve greater efficacy and compliance.

D. SMITH: If you simplify patient treatment regimens, will patients be more compliant? Among single-line therapy for hypertension, we see wide variations with respect to compliance. Overall, when first introduced to an antihypertensive agent, patients only take it about a third of the time during the first year.

C. SMITH: But that may be due to a lack of response.

NEUTEL: Perhaps it is due to side effects?

D. SMITH: Follow-up studies show higher rates of noncompliance.

NEUTEL: There are outcome studies with diuretics that show a reduced incidence of cardiovascular disease. But outcome studies are without value if patients are not taking their medications.

NEDD: We have done better in propagating ARBs and ACE inhibitors as truly antihypertensive agents, whereas historically, diuretics have been sold as symptomatic relief for peripheral edema. So there are a lot of patients who probably look at the agents very differently.

D. SMITH: Prescribing fewer drugs, in general, is better, but there could be certain combinations that make sense to patients and result in higher total compliance. Still, the problem of compliance generally increases when more than one agent is used.

PARK: In the case of diabetes, fixed-ratio insulin was developed for exactly the same reason — because people weren't compliant when it came to mixing their insulins.

D. SMITH: Yes.

PARK: So premixed insulin combinations became available to combat the patient noncompliance.

D. SMITH: With fixed-dose combinations, one might argue that you are not optimizing treatment in some patients. But, because you are getting so many more patients to be compliant, the suboptimal outcome in individual patients is acceptable.

NEDD: Will the price increase with the higher dose, or will we see flat pricing?

KOZAR: You will see more and more flat pricing. Pharmaceutical companies are not penalizing you for increasing the dose.

NEUTEL: That's very interesting, because the initial thinking with the development of combination therapy was to come out with just a couple doses to simplify it for doctors. It turns out, though, that doctors want the flexibility to change any component of the regimen and weren't happy with the limited options made available by the pharmaceutical companies.

NEDD: Everything included, if you isolate hypertension, what is the overall impact in terms of cost to an MCO or to a patient?

PARK: The question was whether you could isolate the benefits of a single disease, treating a single disease versus treating multiple ones. I don't believe you can, because you have to treat a patient with cholesterol medications if you know they have high cholesterol.

NEDD: I assume that there are places where the data exist but they have to be teased out. Can we wrap some science around this that says if you do this, you yield this benefit?

PALMER: There has to be some way to express the benefit of antihypertensives visually. Perhaps DTC [direct-to-consumer] advertising is the answer. If it is, then how do we visually represent the effects of hypertension to the consumer?

D. SMITH: There are several issues that need to be addressed. One is getting patients to the office to be evaluated. The other is getting people who are unwilling to accept that they might have hypertension to go to the office. Then, there are patients who come to the office but don't continue treatment. Any DTC campaign would need to appeal to all these groups effectively.

PALMER: I agree. So, how do we make the effects of hypertension clear to the public?

D. SMITH: Do you think that's the next step? To tell the health plans we have enough information and that it now is time to take it to the public?

PARK: Most of the people the ads should target — older Americans of Medicare age — don't have coverage for antihypertensives. So, the majority of the people who need treatment will have to pay for it themselves and therefore have to be convinced that there is real value in obtaining the treatment.

PALMER: Due to the national publicity surrounding high cholesterol, most people know what their numbers should be for LDL and HDL. Yet most people don't know their optimal blood pressure.

HYMEL: They don't know what good systolic and diastolic values are and what those numbers mean. With hypertension being an asymptomatic disease in most individuals, the patients are not convinced that they need to be treated. The message that strokes and myocardial infarctions are very real risks related to hypertension isn't getting across to the public. I just don't think the public is completely convinced that hypertension is dangerous.

NEUTEL: The reason for that is that the media have shifted away from hypertension to focus on cholesterol and diabetes.

C. SMITH: I checked with four health plans to see if they educate their members about hypertension, via direct mail, etc. The answer was no.

NEUTEL: This trend is emerging in medical schools, too. At my institution, students have two lectures on hypertension at the clinic and receive no formal training in this area, despite the fact that it is one of the most common conditions they will confront in clinical practice.

NEDD: I think there is room to get the message across; we just have to think about it from a different point of view than we have historically.

D. SMITH: Would more HEDIS [Health Plan Employer and Data Information Set] measures help to justify the value of educational efforts to health plans?

PALMER: No question.

NEDD: The guidelines and algorithms need to be tied to an incentive to gain wider acceptance.

PARK: I'm suggesting a program that displays the algorithm as a flow chart and allows the clinicians to simply click on it as they make decisions about, for example, drug therapy, testing, or frequency of visits, in the office/hospital setting. To take it a step further, it should document what choices are made, provide feedback on a measurable result, and allow for comparison to the entire population of physicians using the algorithm.

PALMER: What I learned from JNC-7 is that we need to be more aggressive and make changes on a quicker basis.

HYMEL: Once you get a patient under control, how do you keep the patient compliant? I think that that is where we don't do a good job of follow-up health education. I'm convinced that personal health coaches can help narrow this gap.

D. SMITH: At Care America Health Plan, which once had roughly 250,000 enrollees — mostly in southern California, including 80,000 Medicare patients — employed persons called assigned patients on the telephone to check up on medication use, any problems, etc. It not only saved the plan money but also achieved high compliance rates.

KOZAR: I would like to gain some concluding insight as to what you can do, from your perspective, as a patient-advocacy group. What can you do within your employee base, as an employer, to ensure that follow-up health education happens?

NEDD: I want every initiative, whether it comes from a hospital, an HMO, or wherever, to be inclusive of the broader community.

HYMEL: From an employer's perspective, I see four things we can do to help our employees change their behavior. The first would be education. We need to continue to supply lifestyle management and disease management programs to our employees to make sure they understand the conditions and to get them appropriate coaching where indicated.

The second would be to ensure there aren't barriers to getting the appropriate medication. Employers need to rethink the formulary issue, when they're driving the formularies, and to make sure that the appropriate medications are on the right tier.

The third point is to make sure we align physician incentives to outcomes. The last point is just that employers need to work together with physicians and economists to understand the benefits of early treatment in terms of productivity. There will be more funding for this kind of thing if there is evidence that productivity is increased due to preventative measures and early treatment.

PARK: I need speakers to come and show these data to the physicians. Furthermore, I need a set of slides that I can use when I, or other physicians in my group, give presentations in the community. These slides have to be created at a level that the layperson can easily understand.

C. SMITH: A lot of employers look only at the bottom line and how to curb premium increases. If we can offer them financial incentives, they will do what it takes to earn that money.

PALMER: There are things that all of us can do within our own organizations — the employer group, the physician group, whatever it may be. I still am very much behind the thought of DTC advertising and a public awareness campaign, so that everyone knows the adverse effects of less than optimal blood pressure.

D. SMITH: Organizations need to convince themselves of the cost-effectiveness of hypertension control and the best avenues to achieve control. A key problem also lies with getting patients to take and continue taking their medications once the health plans and doctors have been convinced of the drugs' value.

CONTINUING EDUCATION POST-TEST

Effective Hypertension Management With New Treatment Paradigms

On the combined answer sheet/evaluation form on page 28, please place an X through the box of the letter corresponding with the correct response for each question. There is only ONE correct answer to each question.

1. **According to JNC-7, initial therapy for most patients with stage 1 hypertension should be:**
   a. Monotherapy with an angiotensin converting enzyme inhibitor.
   b. Monotherapy with an angiotensin receptor blocker.
   c. Monotherapy with a calcium channel blocker.
   d. Monotherapy with a thiazide-type diuretic.
   e. Combination therapy with an angiotensin converting enzyme inhibitor/calcium channel blocker.
2. **If a patient has edema induced by a calcium channel blocker, the edema can be relieved by adding:**
   a. An angiotensin converting enzyme inhibitor.
   b. An angiotensin receptor blocker.
   c. Furosemide.
   d. Fluvoxamine.
3. **The JNC currently defines normal blood pressure as:**
   a. <140/<90 mm Hg.
   b. <130/<80 mm Hg.
   c. <120/<90 mm Hg.
   d. <120/<80 mm Hg.
4. **In studies in which patients received both amlodipine and benazepril, rates of edema were:**
   a. Similar to those seen among patients receiving amlodipine monotherapy.
   b. Slightly higher than those seen among patients receiving amlodipine monotherapy.
   c. Much higher than those seen among patients receiving amlodipine monotherapy.
   d. Lower than those seen among patients receiving amlodipine monotherapy.
5. **When the dose of an antihypertensive agent is increased, adverse events can be expected to:**
   a. Increase.
   b. Decrease slightly.
   c. Decrease dramatically.
   d. Remain the same.
6. **A meta-analysis suggests that the best strategy for improving adherence with antihypertensive therapy may be to:**
   a. Reduce the average wholesale price.
   b. Simplify the dosing regimen.
   c. Use a diuretic as initial therapy.
   d. Use a beta blocker as initial therapy.
   e. Reduce the copayment.
7. **The edema associated with calcium channel blocker (CCB) therapy occurs because:**
   a. CCBs are powerful vasoconstrictors that affect only the arterial side of the vascular tree.
   b. CCBs are powerful vasoconstrictors that affect only the venous side of the vascular tree.
   c. CCBs are powerful vasodilators that affect only the arterial side of the vascular tree.
   d. CCBs are powerful vasodilators that affect only the venous side of the vascular tree.
8. **If a patient has failed to reach his or her blood pressure goal with monotherapy, the best strategy for achieving greater reduction in blood pressure while minimizing adverse effects is to:**
   a. Double the dose of the initial agent.
   b. Switch to a different agent in the same class.
   c. Add another antihypertensive from a different class.
   d. Switch to a different agent in a different class.
9. **Since 1988, rates of hypertension control have:**
   a. Improved by a few percentage points.
   b. Improved dramatically.
   c. Declined by a few percentage points.
   d. Declined dramatically.
10. **In a retrospective review of prescriptions given to patients newly diagnosed with hypertension, the rate of persistence was lowest among patients whose initial prescription was for a/an:**
    a. Angiotensin converting enzyme inhibitor.
    b. Angiotensin receptor blocker.
    c. Beta blocker.
    d. Calcium channel blocker.
    e. Diuretic.
11. **According to JNC-7, prehypertension is:**
    a. Systolic 130 to 139 mm Hg and diastolic 80 to 89 mm Hg.
    b. Systolic 130 to 139 mm Hg or diastolic 80 to 89 mm Hg.
    c. Systolic 120 to 139 mm Hg and diastolic 80 to 89 mm Hg.
    d. Systolic 120 to 139 mm Hg or diastolic 80 to 89 mm Hg.
12. **The majority of patients who are unaware that they have hypertension lack health insurance.**
    a. True.
    b. False.
13. **Systolic blood pressure rises with age as part of the normal aging process.**
    a. True.
    b. False.
14. **According to JNC-7, normal blood pressure is:**
    a. Systolic 120-129 mm Hg and diastolic 80-84 mm Hg.
    b. Systolic 120-129 mm Hg or diastolic 80-85 mm Hg.
    c. Systolic <120 mm Hg and diastolic <80 mm Hg.
    d. Systolic <120 mm Hg or diastolic <80 mm Hg.
15. **The leading actual cause of death in the United States in 2000 was:**
    a. Tobacco.
    b. Poor diet and physical inactivity.
    c. Alcohol.
    d. Microbial agents.
16. **The greatest risk of having uncontrolled hypertension is posed by:**
    a. Lack of health insurance.
    b. Lack of a usual source of health care.
    c. Being age 65 or older.
    d. Being younger than 65.
17. **Which of the following lifestyle modifications is *not* mentioned by JNC-7 as a means of lowering systolic blood pressure?**
    a. Low-fat diet rich in fruits and vegetables.
    b. Moderation of alcohol consumption.
    c. Smoking cessation.
    d. Sodium restriction.
    e. Weight loss.
18. **Nearly all patients with heart disease also have hypertension.**
    a. True.
    b. False.
19. **Which age group has the highest rate of blood pressure control?**
    a. 25 to 44.
    b. 45 to 64.
    c. 65 and older.
    d. Control rates are similar in each age group.
20. **The most common illness-related primary diagnosis that is made during office visits for ambulatory care is:**
    a. Acute upper respiratory infection.
    b. Arthropathy.
    c. Diabetes.
    d. Hypertension.

CONTINUING EDUCATION ANSWER SHEET/CERTIFICATE REQUEST

Effective Hypertension Management With New Treatment Paradigms

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Please allow up to 6 weeks for processing.

This activity is provided at no charge to the participant.

EXAMINATION: Place an X through the box of the letter that represents the best answer to each question on page 27. There is only ONE answer per question. Place all answers on this form:

	A.	B.	C.	D.	E.
1.	☐	☐	☐	☐	☐
2.	☐	☐	☐	☐	
3.	☐	☐	☐	☐	
4.	☐	☐	☐	☐	
5.	☐	☐	☐	☐	
6.	☐	☐	☐	☐	☐
7.	☐	☐	☐	☐	
8.	☐	☐	☐	☐	
9.	☐	☐	☐	☐	
10.	☐	☐	☐	☐	☐
11.	☐	☐	☐	☐	
12.	☐	☐			
13.	☐	☐			
14.	☐	☐	☐	☐	
15.	☐	☐	☐	☐	
16.	☐	☐	☐	☐	
17.	☐	☐	☐	☐	☐
18.	☐	☐			
19.	☐	☐	☐	☐	
20.	☐	☐	☐	☐	

PROGRAM EVALUATION
So that we may assess the value of this self-study program, we ask that you please fill out this evaluation form.

Have the activity's objectives been met?

1. Establish rational, effective treatment strategies with the goal of lowering blood pressure in hypertensive patients to less than 140/90 mm Hg and below 130/80 mm Hg in hypertensive patients with diabetes or renal disease, per JNC-7 guidelines
☐ Yes ☐ No

2. Incorporate into his or her disease management approach an understanding of the societal impact of hypertension from the perspectives of overall health, quality of life, and economics
☐ Yes ☐ No

3. Address the barriers to effective hypertension management and take positive steps to improve patient compliance with treatment to help achieve blood pressure goals and lower health care expenditures in a broader range of patients
☐ Yes ☐ No

Was this publication fair, balanced, and free of commercial bias? ☐ Yes ☐ No

If no, please explain: _____

Did this educational activity meet my needs, contribute to my personal effectiveness, and improve my ability to:

Strongly agree — *Strongly disagree*

Treat/manage patients?
5 4 3 2 1 N/A
Communicate with patients?
5 4 3 2 1 N/A
Manage my medical practice?
5 4 3 2 1 N/A
Other _____
5 4 3 2 1 N/A

Effectiveness of this method of presentation:

Excellent	*Very good*	*Good*	*Fair*	*Poor*
5	4	3	2	1

Time spent reading this publication:

Hours _____ Minutes _____

What other topics would you like to see addressed? _____

Comments: _____