

## Critical Overview of Antihypertensive Therapies: What Is Preventing Us From Getting There?

Based on a presentation by Mark A. Munger, PharmD

### **Presentation Summary**

Hypertension is by far the most prevalent form of cardiovascular disease in the United States, affecting between 43 million and 50 million adults. Although uncontrolled hypertension is well recognized as a modifiable risk factor associated with long-term target-organ damage, many are unaware they have hypertension, as many as 50% are not receiving treatment, and an estimated 70% of those being treated do not achieve adequate blood pressure control. Why? Despite the effectiveness of antihypertensive therapy and considerable evidence that morbidity and coronary disease have decreased between 1950 and 1990, it appears that the

progress made during those decades has not continued into the 1990s. Age-adjusted stroke rates for 1990 to 1994 rose slightly, and the rate of decline in coronary disease during this same period has leveled off. Moreover, both the rate of end-stage renal disease and the prevalence of heart failure increased during the early 1990s. The reasons for inadequate blood pressure control are numerous, including the multifactorial nature of hypertension; the presence of environmental factors such as diet, smoking, and concomitant drug therapy; poor adherence to therapy; insufficient therapeutic effort on the part of the treating physician; and adverse side effects of hypertensive agents.

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Nearly 60 million adult Americans, or more than 1 in 5, have 1 or more forms of cardiovascular disease. Hypertension is by far the most prevalent form, affecting between 43 million and 50 million people.<sup>1</sup> Although uncontrolled hypertension is well recognized as an important modifiable risk factor associated with coronary heart disease,

stroke, congestive heart failure, end-stage renal disease, and peripheral vascular disease, many people with hypertension remain unaware of their condition. Up to 50% are not receiving treatment, and an estimated 70% of those who are being treated do not achieve adequate blood pressure control.<sup>1</sup> As a result, controlling blood pressure adequately remains a daunting challenge

to both the medical community and the population in general as we enter the 21st century.

That the challenge of controlling blood pressure still exists is disheartening, because the effectiveness of antihypertensive therapy in reducing morbidity and mortality in people with mild to moderate hypertension has been demonstrated again and again. During the past few decades, death rates from stroke have fallen by 50%, whereas those from coronary heart disease have fallen by about 53%.<sup>2</sup> Antihypertensive drugs have contributed to these declines and have probably saved more than 1 million lives over a 16-year period.<sup>3</sup> In addition, the improvement in the quality of life for the millions of hypertensive Americans who were spared the damaging sequelae of stroke and heart disease because of antihypertensive

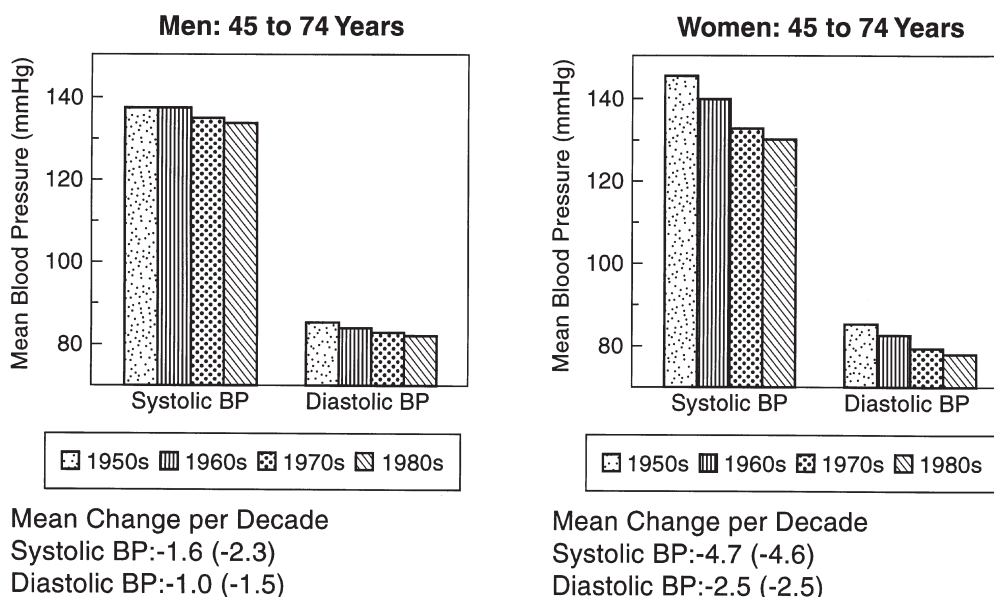
treatment is undoubtedly enormous, although largely immeasurable.

### Obstacles to Reducing Cardiovascular Disease With Antihypertensive Drugs

There are numerous reasons why the goal of reducing cardiovascular disease with appropriate antihypertensive therapy has not been met. Among them are:

- The role of genetics in the pathophysiology of hypertension
- The multifactorial nature of hypertension
- Environmental factors such as smoking, alcohol consumption, caloric intake, and concomitant drug therapy
- Poor adherence or lack of adherence to therapy
- Reluctance of physicians to treat

**Figure.** Age-Adjusted Trends in Blood Pressure Levels



Age-adjusted values are given, followed in parentheses by the values adjusted for age and body-mass index.  
Source: Reference 4.

aggressively enough so that adequate control is achieved

- Side effects of antihypertensive drugs

To put this in perspective, it is necessary to review the progression of hypertension management in this country from the 1950s to the present, examine current standards of hypertension treatment, and discuss the obstacles mentioned above in greater detail.

### The Framingham Heart Study

The landmark Framingham Heart Study was begun in 1948 and continues to this date. Sponsored by the National Heart, Lung, and Blood Institute (NHLBI), this longitudinal study of the population of Framingham, Massachusetts, was the first to document the natural history of hypertension and coronary artery disease. A recently published report involving 10,333 men and women between the ages of 45 and 74 in the primary and offspring Framingham Heart Study examined age-adjusted trends in systolic and diastolic blood pressure, use of antihypertensive drugs, severity of high blood pressure, and the effects on left ventricular hypertrophy (LVH) during the past 4 decades: the 1950s, 1960s, 1970s, and 1980s.<sup>4</sup>

The mean change per decade in age- and body mass-adjusted systolic and diastolic blood pressure levels for men and women are shown in the Figure. The greater decrease in blood pressure levels in women compared with men may reflect an increase in body mass index in men and a decrease in women over this observation period.

The percent decline in blood pressure levels over 4 decades reflected a greater proportion of decline in the higher stages of hypertension. In men, there was a 29% decrease in stage 2 hypertension, a 42% decrease in stage 3, and a 63% decrease in stage 4. The corresponding decreases in women were 43%, 54%, and 68%.<sup>4</sup>

The percent decline in blood pressure levels was also paralleled by an increase in the use of antihypertensive medications, from 2.3% for men and 5.7% for women in the 1950s to 24.6% for men and 27.7% for women in the 1980s. As a result, over the 4-decade period of observation, the use of antihypertensive medications increased by 128% in men and 70% in women.<sup>4</sup>

In the 1950s, the predominant antihypertensive agents used were hexamethonium and hydralazine. In the 1960s, the predominant agents were hydrochlorothiazide, reserpine, and propranolol. Calcium channel blockers predominated in the 1970s, as did angiotensin-converting enzyme (ACE) inhibitors in the 1980s. The increased use of antihypertensive therapy over these 4 decades may reflect the more favorable efficacy, safety, and side-effect profiles of the agents used in each successive decade.

Also paralleling the decline in blood pressure levels and the increased use of antihypertensive agents were the lower rates of electrographically confirmed LVH in the Framingham population. Over the 4 decades of observation, LVH decreased by 23% in men and 41% in women.<sup>4</sup> This is an important finding, because LVH represents target-organ damage from high blood pressure and increases the risk for ischemic syndromes, stroke, heart failure, and sudden cardiac death.

Although a cause-and-effect relationship cannot be proved, the decline in blood pressure levels, the increased use of antihypertensive drugs, and the decline in LVH seen between the 1950s and the 1980s contribute strong evidence that substantial progress has been made in decreasing morbidity and mortality from hypertension in the United States during these 4 decades.<sup>4</sup> Why then is the goal of reducing cardiovascular disease with antihypertensive drugs not being met? And why has the Joint National

Committee on Prevention, Evaluation and Treatment of High Blood Pressure, in its Sixth Report, challenged the medical profession to improve its management of hypertension?<sup>2</sup>

### Losing Ground in the 1990s

The first evidence that ground gained in the 1970s and 1980s is being lost in the 1990s comes from the NHLBI.<sup>5</sup> While age-adjusted rates for stroke and coronary artery disease declined by approximately 59% and 53%, respectively, from 1972 to 1994, the stroke rates rose slightly between 1990 and 1994, and the rate of decline for coronary disease leveled off during the same 5-year period.

Moreover, both the rate of end-stage renal disease, for which high blood pressure is the second leading cause, and the prevalence of heart failure have increased during the early 1990s.<sup>6</sup> As a result, the favorable trends demonstrated in the Framingham Heart Study do not appear to have continued into the 1990s. In addition, the increased awareness, treatment, and control of

hypertension seen in the 1970s and 1980s seem to have leveled off or declined slightly in the 1990s.<sup>1</sup> Epidemiologic data from separate studies done in Minnesota and Iowa showing decreases in hypertension awareness, treatment, and control support these findings.<sup>7-11</sup>

### The Role of Genetics and Environmental Factors

Recent advances in genetics have shed light on its role in hypertension, which results from the interaction of major genes, polygenes, and environmental factors. The major genes include those that code for angiotensin production, the presence of diabetes, obesity, and race. These genes blend with polygenes and with individual environmental factors that are present in individuals and within families. Indeed, genetic analyses of communities, families, twins, and individuals all support the premise that genes lead to the development of hypertension. Moreover, such analyses have shown that mutations in at least 10 genes can alter blood pressure.<sup>12</sup> Specific genetic mutations, for example, affect various sites in the renin-angiotensin pathway, altering salt and water reabsorption in the kidney and, ultimately, blood pressure levels. Oral contraceptives also exert effects on this pathway and alter blood pressure levels as well.

It is also important to recognize that hypertension is not simply a disease of elevated blood pressure levels, but is in many cases an inherited syndrome of cardiovascular risk factors, including lipid abnormalities, insulin resistance, changes in renal function, endocrine changes, obesity, LVH, diastolic dysfunction, and abnormalities in vascular structure and elasticity. In describing this inherited syndrome, Neutel and Smith note that high blood pressure is a late manifestation of this syndrome in many patients and that it is often preceded

**Table 1.** Potential Risks of Intermittent Compliance or "Drug Holidays"

<ul style="list-style-type: none"><li>■ Period without effective drug action<ul style="list-style-type: none"><li>○ Short-acting <math>\alpha</math>-1 blockers such as prazosin</li><li>○ Short-acting ACE inhibitors (captopril)</li><li>○ Short-acting dihydropyridines (nifedipine capsules)</li></ul></li> <li>■ Rebound effects when dosing suddenly stops<ul style="list-style-type: none"><li>○ Clonidine</li><li>○ Short-acting <math>\beta</math>-blockers (propranolol, atenolol, metoprolol)</li><li>○ Short-acting ACE inhibitors (possibly)</li></ul></li> <li>■ Excessive drug effects when dosing resumes<ul style="list-style-type: none"><li>○ <math>\alpha</math>-1 blockers</li><li>○ ACE inhibitors</li><li>○ Short-acting dihydropyridines</li></ul></li></ul>
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Source: Leenen FHH. Intermittent blood pressure control: Potential consequences for outcome. *Can J Cardiol* 1999;15(suppl C):13C-18C.

by some or all of the associated cardiovascular risk factors.<sup>13</sup>

In light of the contribution of genetics to hypertension, early intervention may be necessary to reverse or allay the disease process.

Environmental factors play a significant role in hypertension. These factors include salt and potassium intake, alcohol consumption, tobacco use, caloric intake, and concomitant drug therapy. Any of these factors may adversely affect blood pressure control.

In some individuals, the presence of only 1 of these factors may be sufficient to elevate blood pressure levels or reduce the efficacy of antihypertensive agents. Although changes in lifestyle—such as a low-fat, low-cholesterol diet, more exercise, reduced salt intake, reduced alcohol consumption, and smoking cessation—have been shown to have favorable effects on blood pressure control, long-term adherence to these nonpharmacologic measures is generally poor. They should, however, be recommended on a trial basis for a limited period of time before instituting pharmacologic therapy in patients with borderline or mild hypertension and as adjunctive therapy to increase drug efficacy in patients who are taking antihypertensive medications.

### Adherence to Therapy

Poor adherence to antihypertensive therapy remains a major therapeutic challenge, contributing to inadequate blood pressure control in more than two thirds of patients with hypertension.<sup>14</sup> The importance of adherence to therapy can be demonstrated by examining the events that occur while the patient is on treatment, because these events do not appear to be related only to the blood pressure level at the initiation of treatment but also to the absence of blood pressure control over the subsequent years of treatment.

Inadequate blood pressure control may relate to the treating practition-

er, who may not make a sufficient therapeutic effort or who may select a drug with insufficient efficacy or too many side effects, or it may relate to the patient, who fails to comply with therapy or complies only partially. Examples of patient noncompliance include:

- Failure to fill or refill a prescription
- Taking less than the prescribed dose by splitting tablets
- Taking medication once in a while, or taking it for a short time, then stopping for a period of time and resuming (intermittent compliance or “drug holidays”)

The potential risks of intermittent compliance are listed in Table 1.<sup>15</sup> Variable control may occur with drugs that have a short duration of action, because of wide variations in blood pressure response during the dosing intervals; in other words, intermittent use of these drugs results in periods of time when there is no effective drug action.

Rebound effects can occur when dosing stops suddenly and is discontinued for a few days. There is a rapid disappearance of  $\beta$ -blockade, followed by a period of enhanced beta responsiveness, which can increase the risk

**Table 2.** Promising Strategies for Improving Adherence to Therapy

<ul style="list-style-type: none"> <li>■ Patient education</li> <li>■ Self-monitoring</li> <li>■ Social support</li> <li>■ Telephone follow-up</li> <li>■ Tailoring/individualizing therapy</li> <li>■ Use of combination therapy                             <ul style="list-style-type: none"> <li>○ Better blood pressure control than with monotherapy</li> <li>○ Fewer side effects</li> <li>○ Improved adherence to therapy</li> <li>○ Lower cost of therapy</li> </ul> </li> </ul>
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for new-onset angina or a myocardial infarction.<sup>16</sup>

Conversely, excessive drug effects can occur with certain agents when dosing resumes because of marked increases in plasma drug concentrations, which are associated with a rapid drop in blood pressure, followed by a quick return to baseline. These effects are not seen with longer-acting agents such as the  $\beta$ -blocker nadolol, the calcium channel blocker amlodipine, or the ACE inhibitors trandolapril and ramipril.<sup>15</sup>

The most promising strategies for improving adherence to therapy are combinations of the interventions listed in Table 2. When trying to ascertain who is most likely to adhere to therapy and who is not, compliance with therapy during the first month of treatment appears to be the most powerful predictor of long-term compliance.<sup>17-20</sup>

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...DISCUSSION HIGHLIGHTS ...

#### **Adherence to Therapy**

**Dr. Gradman:** One area in which managed care in particular can make a positive contribution is by encouraging adherence to therapy. What strategies are being used to improve adherence?

**Dr. Lee:** Two major obstacles to successful antihypertensive therapy are patients who don't come back for follow-up and patients who come back to the physician but don't take their medications. In these areas, managed care has the potential—although it's largely unrealized at this time—to be vastly superior to fee-for-service medicine because no one in fee-for-service is keeping track of this kind of thing.

While it is not easy to merge pharmacy claim data with medical claim data to look at this question, it's certainly feasible. Once you do it and

create a pharmacy/medical claim data warehouse, you can track which patients with high blood pressure have stopped filling their prescriptions and which patients are taking them at a rate below what one would expect. We've all seen data on statins showing that patients take roughly one half the number of pills prescribed for them, and I'd be surprised if it was qualitatively different for hypertension medications.

Regarding patients who are lost to follow-up, who are diagnosed with hypertension and then don't come back for 2 years, there already are databases to identify them. Someone has to telephone them or write to them and say, "Come on back to the doctor." I think that this is going to happen much more in managed care administrations in the next few years.

**Dr. Steinberg:** I think we are probably not likely to get as much benefit from managed care in these areas as one might think, although it is true that managed care is clearly better positioned with information and organization to accomplish some of the things that aren't currently being accomplished as well in fee-for-service medicine.

As Dr. Lee pointed out, it is clearly possible for managed care organizations either on their own, through their manipulation of their pharmacy data, or with the assistance of the pharmacy benefit manager organizations, to identify patients who are not taking or renewing their medicine as frequently as it should be taken or renewed. In a study related to the development of the HEDIS [Health Employer Data and Information Set] hypertension project, we collected computerized administrative data that included pharmacy data from 4 HMOs [health maintenance organizations], which we supplemented with data abstracted from the charts of approximately 2000 patients. After adjusting for age, gender, and comorbid conditions such as diabetes, we

were able to look at hypertension control as a function of those characteristics as well as the antihypertensives the patients were taking.

The problem—or the challenge, as I see it—is that the types of interventions which are likely to be effective, such as patient education, close follow-up, and spending time with the patient, are very expensive.

It's unclear whether managed care organizations that invest time and dollars in this labor-intensive and data-intensive approach will ever be in a position to recover an economic return on that investment. The one entity that is most likely to is the federal government because these patients are going to wind up on Medicare. In fact, if you step back and look at it, the government is the entity that is likely to gain the most from hypertension control before the time a patient becomes eligible for Medicare.

### Preventive Interventions

**Dr. Gradman:** Today's public perception of managed care tends to be rather negative. A recent issue of *Newsweek* featured "HMO Hell" on the cover, which I thought was a bit extreme. Nevertheless, managed care has an image problem, despite the fact that it has the organization, the follow-up, the recordkeeping, and the other necessary building blocks to put together an effective preventive program that would save healthcare costs in the long run.

Surely, there's no doubt that the health system as a whole would benefit costwise if long-term complications were prevented. However, preventive interventions are expensive, the costs are front loaded, and the benefits accrue years later. How can the healthcare system be changed so that implementing preventive strategies is rewarded sooner? Managed care has something important to contribute, because fee-for-service medicine is not as systematic.

**Dr. Steinberg:** Actually, the same opportunities are available to fee-for-service medicine. The only thing stopping fee-for-service doctors from educating patients, spending time with them, and having their nurses follow up is the same thing that's stopping everybody else: it's very time consuming and expensive.

I don't think it's fair to say that managed care is uniquely positioned to do this. Every physician is positioned to do this. We need to look beyond what has to be done to encourage managed care and look at what needs to be done to encourage the entire medical profession.

For example, specialty clinics focused only on hypertension have done very well in this regard, because they have highly motivated nurses, nurse-practitioners, and other professionals who are really spending time with the patients, focusing on particular patient needs, and so on. It isn't so much a matter of huge organizational capabilities as it is professional commitment and the time and the costs associated with it.

**Dr. Munger:** In the last 5 to 10 years, we've seen an explosion of multidisciplinary programs to follow patients with heart failure. We've seen substantial decreases in morbidity, mortality, costs, and especially hospitalizations for heart failure.

Is there a chance that we're looking at something different with hypertension? You can follow heart failure patients and find that 50% of them are going to die in 5 years. In hypertension, we're talking about decades of follow-up, decades of maintaining these patients on their drugs before an end-stage process will occur. Is that a difference in the commitment of resources based on acuity and dollars?

**Dr. Lee:** That's a very interesting question. I think the situations are analogous. It's just that the intensity of the intervention with hypertension

is lower, and it's stretched over a much longer period of time.

Although there are heart failure teams and heart failure programs for managed care patients, there are very few home care programs for fee-for-service patients with heart failure. Where they do exist, they are usually funded by the hospital's marketing department rather than the cardiology division, which usually can't find any stream of revenue to support a home care nurse. Fee-for-service patients are not getting state-of-the-art care, although most people don't understand that when they bash managed care. I think the same is true for hypertension, but it's hard for the managed care organizations to rise to the challenges there because 20% of their patients are going to be in another HMO next year and they're not going to realize those financial benefits.

In addition, I'm not really sure that there are real cost savings when you add up everything at the end of the day, down the line. I'd like to believe there are, but I don't think the data support it. The real reason to provide long-term follow-up and care is that it's the right thing to do.

**Dr. Gradman:** Why don't you think there are any cost savings?

**Dr. Lee:** When people study it, they find that you spend more money than you save.

**Dr. Steinberg:** It's cost beneficial, but it's not cost saving.

**Dr. Lee:** It's got an attractive cost-effectiveness ratio if you're using  $\beta$ -blockers and diuretics. When you start using calcium blockers, it's not so attractive.

**Dr. Gradman:** Over what time frame does the cost become unfavorable? If you take a 20-year time frame, I can't believe that prevention of all these

strokes, myocardial infarctions (MIs), end-stage renal disease, and congestive heart failure won't save money.

**Dr. Steinberg:** Studies suggest that it doesn't.

**Dr. Gradman:** Over 20 years?

**Dr. Lee:** Yes, because you're paying for drugs for many, many people for many, many years. That doesn't mean that patients shouldn't take their anti-hypertensive drugs, but we shouldn't kid ourselves and say that we're going to save money.

**Dr. Steinberg:** While the armamentarium of antihypertensive drugs has improved markedly, its cost has increased as well.

**Dr. Munger:** If you go back to what I presented, the 1-month follow up is very predictive of long-term compliance, you may not need to spend much money to take the time to talk to patients and convince them how important it is to take their drugs for that 1 month. The data we have now predict that if they stay on their drugs for 1 month, they'll stay on them for a long period of time.

**Dr. Steinberg:** Right. But the question is, whose money are you spending? For that type of interaction with a patient to be effective, it isn't a 1-minute discussion. It's probably more like a 10- or 15-minute discussion or more. It's not clear to me that having that discussion is cost effective, and it's not clear to me that physicians are interested in spending their time having that discussion. It's also not clear to me that physicians are necessarily good at having that discussion compared with other people who may be specifically interested in and trained to conduct it.

**Dr. Munger:** The literature suggests that nurses, physician assistants,



nurse-practitioners, and pharmacists are better suited to talk about these issues. This would involve a much lower up-front cost than it would for a physician to take the time.

**Dr. Lee:** Our network has 6 full-time pharmacists working with our managed care patients, doing follow-up with patients who are being weaned from omeprazole (Prilosec) over a 2-week time period. We haven't done that for hypertension yet, but it's clearly a strategy we should be looking at.

### Cost Effectiveness

**Dr. Gradman:** It would be interesting to look at the recent Framingham data showing a reduction in the incidence of target-organ damage with antihypertensive treatment<sup>4</sup> in the context of the lack of cost effectiveness, because there is a longer time frame and the data are up to date.

**Dr. Lee:** Until now, no one had the data to redo that cost-effectiveness analysis perfectly. The ways in which you could increase the savings from treatment of hypertension would be to have better compliance and a greater number of people with controlled blood pressure. You could have a fabulous drug that really lowers long-term complication rates, but if only a quarter of your patients are actually taking the pills and are under control, it's not going to change the cost effectiveness.

**Dr. Steinberg:** One other thing that may increase the cost effectiveness of hypertension management is an increase in the costs associated with treating complications. When you factor in the higher cost interventions developed over the past 20 years for MI and heart failure, you will find that it clearly has a favorable effect on the cost-effectiveness ratio.

**Dr. Munger:** In addition, when you

choose an antihypertensive drug, you also have to look at the cost of concomitant therapy associated with that drug, such as laboratory tests, potassium supplements, and so on. How does that factor into the cost? So far, only 1 small study has done that, and it shows that most of the drug costs over a 1-year period range from about \$900 to about \$1400, depending on the drug chosen and its concomitant therapy.<sup>21</sup>

**Dr. Gradman:** We've talked about patients in the managed care system. What about the one third of patients who don't even know they have hypertension?<sup>1</sup> How can that problem be approached?

*“You could have a fabulous drug that really lowers long-term complication rates, but if only a quarter of your patients are actually taking the pills and are under control, it's not going to change the cost effectiveness.”*

—Thomas H. Lee, MD

### Hypertension Awareness

**Dr. Lee:** It amazes me that one third of people with hypertension don't know they have it. I can believe there may be one third who deny they know it but not that they didn't know it at all. Whenever we do screening for cholesterol and blood pressure, we find that people with high lipids, high cholesterol, and high blood pressure knew it all along but went for screening to confirm that they still have it.

Another factor is that a sizable proportion of the population does not have access to the healthcare system

in any given year. For the most part, they tend to be young and healthy. However, I think most of them are indeed having their blood pressure taken and are being told what it is. It seems like there's a conspiracy between the providers and the patients; they're letting it slide, and they're not acting on it.

**Dr. Gradman:** So you don't believe those figures from the NHANES [National Health and Nutrition Examination Survey] study?<sup>1</sup>

**Dr. Lee:** I don't believe people who say they've never had their blood pressure taken or that people who have been screened have never been told that their pressure is high. Either the providers doing the screening weren't forceful enough in recommending follow-up with a doctor or the people being screened are in denial.

**Dr. Steinberg:** Until we do a better job with what goes on downstream, it doesn't matter as much that there's a large reservoir of people who don't yet know that they have hypertension. Letting them know doesn't do much if we're not controlling their blood pressure effectively. Once we get much better at control, there's more to be accomplished by increased detection efforts.

**Dr. Gradman:** That is a very important point. Another important issue is that physicians are often not very aggressive in treating to goal. It's not only the patient's fault that he or she doesn't take the medicines or show up for visits; it's also that physicians are not sufficiently committed to treating their patients to attain a goal blood pressure.

**Dr. Munger:** That's an interesting point. Sometimes it's better to look back to find out where we should be going now. If you go back to 1972, when the National High Blood

Pressure Education Program was started, it had 2 goals. One was to educate physicians about high blood pressure, its consequences, and its treatment. The second one, which was communicated to the public, was to know your blood pressure or know your number.

Given some of the genetic data that we have now, we could improve hypertension awareness if we focused on checking patients with a family history of high blood pressure.

**Dr. Lee:** At this point, I think any physician who doesn't have an idea of what hypertension is has been out of the loop for the last 30 years. I also think the HEDIS measure might be a very effective strategy for both patients and physicians, in terms of pressuring them to do something about it.

**Dr. Munger:** That's not the point. Physicians know what blood pressure is; they just don't persuade people to get it checked and seek treatment. They don't lower blood pressure to the goal numbers.

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