

## Clinical Overview of Antihypertensive Classes—Clinically Relevant Differences: Myths or Facts?

Based on a presentation by Alan H. Gradman, MD

### **Presentation Summary**

The goals of antihypertensive therapy are to lower blood pressure and prevent end-organ damage without side effects, which affect quality of life. The antihypertensive drugs, regardless of class, all lower blood pressure, but they vary in their mechanisms of action, side-effect profiles, suitability for patients with other comorbid conditions, and ability to protect against the long-term sequelae of hypertension. The Sixth Report of the Joint National Committee on Prevention, Evaluation, and Treatment of High Blood Pressure (JNC-VI) recommends diuretics and  $\beta$ -blockers as first-line therapy for uncomplicated hypertension, with diuretics also being strongly preferred for patients with isolated systolic hypertension or hypertension and heart failure and  $\beta$ -blockers being strongly preferred for patients who have had a myocardial infarction (MI) and those with hypertension and angina, atrial tachycardia, or atrial fibrillation.

Because angiotensin-converting enzyme (ACE) inhibitors have been shown to be cardioprotective and renoprotective in patients with diabetes or impaired left ventricular (LV) function, the JNC-VI recommends them as first-line therapy in patients with diabetes with proteinuria, heart failure, and MI complicated by LV dysfunction. It recommends calcium channel blockers for hypertensive patients with angina, long-acting dihydropyridines for those with isolated systolic hypertension, and the nondihydropyridines for those with atrial tachycardia or fibrillation, diabetes, and proteinuria. The angiotensin II receptor blockers (ARBs) share many of the organ-protective effects of ACE inhibitors when studied in animal models. They are effective in lowering blood pressure and have a very benign side-effect profile; however, these agents have not been available long enough to ascertain their efficacy in protecting against long-term complications.

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The goals of antihypertensive treatment are to normalize blood pressure and prevent long-term complications without

adversely affecting the quality of life. The evolution of antihypertensive therapy reflects this latter goal, in that newer drugs do not necessarily

lower blood pressure more effectively than older drugs but do so without adversely affecting the quality of life to the same extent.

Blood pressure is the product of cardiac output and peripheral vascular resistance. Because many physiologic factors affect these variables, there are many ways to reduce blood pressure. One can lower it by reducing heart rate and contractility, as is the case with  $\beta$ -blockers, or one can decrease intravascular volume with diuretics, thereby decreasing left ventricular (LV) filling. Both these drug classes reduce cardiac output. Peripheral vascular resistance can be reduced with direct-acting vasodilators, calcium channel blockers, peripheral  $\alpha$ -blockers, or central sympathetic agonists. Interference with the renin-angiotensin system produces vasodilation as well as favorably influencing salt and water balance.

There are many different pharmacologic strategies for lowering blood pressure, including dozens of effective drugs, which are grouped into several classes and are currently on the market. Evolution of these agents dates from the 1950s. Selection of an individual agent is determined in large part by its clinical utility and cost, elements of which are shown in the Table.

**Table.** Determinants of Utility of an Antihypertensive Agent

■ Pharmacokinetics/pharmacodynamics
■ Effectiveness in reducing blood pressure
○ Responder/control rates
○ Comparison with other agents
○ Efficacy in subpopulations
■ Safety and tolerability
■ End-organ protection

### Diuretics

The short-term effects of diuretics are increased salt and water excretion, decreased intravascular volume and cardiac output, increased total vascular resistance, and activation of the renin-angiotensin system. For reasons that are not fully understood, these agents, especially the thiazides, also decrease peripheral vascular resistance when they are administered on a long-term basis.

The thiazide diuretics are associated with a number of side effects, many of which are dose dependent and can be minimized by using lower dosages. In the past, it was common to use doses of hydrochlorothiazide as great as 100 mg daily; today lower doses of 12.5 mg and 25 mg are recommended.

Diuretics are associated with side effects including muscle cramps, erectile dysfunction, elevated uric acid levels, hypokalemia, and hypomagnesemia. Their use is associated with elevated low-density lipoprotein levels as well as glucose intolerance and hyperinsulinemia. The use of low doses of diuretics minimizes side effects and is associated with better long-term outcomes.

Diuretics, especially at low dosages, reduce the incidence of stroke and coronary events, as demonstrated in the Systolic Hypertension in the Elderly Program (SHEP).<sup>1</sup> In the SHEP study, elderly patients with isolated systolic hypertension, which has been shown to be a potent risk factor for long-term morbid events, were treated with low-dose chlorthalidone.  $\beta$ -blockers were used as second-line drugs. In addition to a significant reduction in stroke of 37%, a reduction in coronary events was seen that was not observed in many earlier studies using higher diuretic doses. There was also a reduction, of borderline statistical significance in all-cause mortality.<sup>1</sup>

According to the Sixth Report of the Joint National Committee on Prevention,

Evaluation, and Treatment of High Blood Pressure (JNC-VI), diuretics and  $\beta$ -blockers are preferred first-line therapy for uncomplicated hypertension. Diuretics are also strongly recommended for patients with isolated systolic hypertension or hypertension coexisting with heart failure. They should be used with caution in hypertensive patients with dyslipidemia, diabetes, or gout. Potassium-sparing diuretics are not recommended for patients with significant renal insufficiency, because of the risk of hyperkalemia.<sup>2</sup>

### $\beta$ -Blockers

$\beta$ -blockers reduce blood pressure by several mechanisms. For example, by reducing heart rate and contractility, they lessen cardiac output. By decreasing renin release, they also lessen activation of the renin-angiotensin system.  $\beta$ -blockers also reduce blood pressure by affecting central sympathetic activity and baroreceptor reflexes.

Widely used in the treatment of myocardial infarction (MI), angina, and cardiac arrhythmias as well as hypertension,  $\beta$ -blockers are well tolerated in the majority of patients. Side effects experienced by some patients who receive these agents include depression, fatigue, nightmares, sleep disturbances, reduced exercise tolerance, erectile dysfunction, atrioventricular block, and bronchospasm.  $\beta$ -blockers also have unfavorable metabolic effects, in that they decrease high-density lipoprotein cholesterol levels and increase insulin resistance, and also mask the signs of hypoglycemia, although the clinical relevance of these observations is unclear.

The JNC-VI recommends  $\beta$ -blockers as first-line treatment for patients with uncomplicated hypertension as well as those who have sustained an MI. These agents have been shown to reduce mortality by about 25% in the post-MI patient population.  $\beta$ -blockers are also preferred in hyperten-

sives with angina, atrial tachycardia, or atrial fibrillation, but they are not recommended as first-line therapy for hypertensive patients with bronchospastic disease or insulin-dependent diabetes.<sup>2</sup>

### Diuretics vs $\beta$ -Blockers as First-Line Agents

Several studies have compared diuretics with  $\beta$ -blockers as first-line agents for hypertension, including a recent meta-analysis of major long-term randomized trials. Although there was considerable variability among the studies in terms of dosing and patient population (ie, the patients in the studies using high-dose diuretics were primarily younger individuals with predominantly diastolic hypertension. Those in the studies using low-dose diuretics were, for the most part, older people with isolated or disproportionate systolic hypertension), the meta-analysis represents a useful approach to complex literature.<sup>3</sup>

The results of the meta-analysis can be summarized as follows:

- Low-dose diuretics appeared to be somewhat superior to  $\beta$ -blockers as first-line agents in reducing coronary events, cardiovascular mortality, and total mortality.
- Diuretics and  $\beta$ -blockers were roughly equivalent in their effects on the incidence of stroke and congestive heart failure.

In another meta-analysis comparing diuretics with  $\beta$ -blockers in elderly patients with hypertension, Messerli and coworkers also found that diuretics were more effective in reducing the incidence of coronary heart disease, cardiovascular mortality, and all-cause mortality. Diuretics and  $\beta$ -blockers were roughly equivalent in reducing the incidence of stroke.<sup>4</sup>

The findings of these and other studies suggest that low-dose diuretics are the preferred agents for first-line therapy in patients with uncomplicated hypertension.

### Calcium Channel Blockers

Calcium channel blockers lower blood pressure by reducing peripheral vascular resistance. This is accomplished by blocking the influx of calcium through voltage-sensitive channels located in the membranes of vascular smooth muscle cells, which in turn decreases intracellular calcium concentration and arterial contractility. These agents represent a heterogeneous group of compounds with differing ancillary properties, particularly with regard to their electrophysiologic effects. Diltiazem and verapamil, which lower heart rate and decrease atrioventricular nodal conduction, are quite different from nifedipine and its derivatives, which function primarily as pure peripheral vasodilators. The latter are more potent as antihypertensive agents and are used extensively in the management of hypertension.

In general, calcium channel blockers are better tolerated than high-dose diuretics and  $\beta$ -blockers. Calcium antagonists do not exert any effects on the central nervous system. Side effects associated with the use of the dihydropyridines (ie, nifedipine, amlodipine, felodipine, and related compounds) include flushing, headache, dizziness, and peripheral edema. Edema, a dose-limiting side effect, is the result of unopposed arteriolar dilation and not sodium retention. The nondihydropyridines, diltiazem and verapamil, are associated with gastrointestinal disturbances (notably constipation with verapamil) and changes in the cardiac conduction system, which may produce sinus bradycardia and atrioventricular block in susceptible patients.

There has been some concern in recent years about the safety of the calcium channel blockers, particularly short-acting nifedipine, which has been associated with an increased risk for acute coronary events in some studies. In other studies, particularly in patients with diabetes, long-acting dihydropyridines have been

found to be less effective compared with angiotensin-converting enzyme (ACE) inhibitors in reducing long-term vascular complications. The results of the Systolic Hypertension in Europe (Syst-Eur) study, which used the long-acting dihydropyridine nitrendipine, demonstrated long-term efficacy equal to that of low-dose diuretics. These results strongly suggest the safety concerns regarding calcium channel blockers have been overstated.<sup>5</sup>

The Syst-Eur study, a large, long-term, randomized study evaluating nitrendipine in 4695 patients with isolated systolic hypertension, was similar in design to the SHEP study and produced almost identical results. The dihydropyridines reduced the incidence of stroke and cardiac events, including a 30% reduction in the incidence of MI, although the latter reduction was not statistically significant.<sup>5</sup>

On the basis of this and other studies, the JNC-VI recommended calcium channel blockers for hypertensive patients with angina, the long-acting dihydropyridines for patients with isolated systemic hypertension, and the nondihydropyridines for patients with atrial tachycardia or atrial fibrillation, as well as those with diabetes and proteinuria. Because they may worsen long-term outcome, calcium channel blockers other than amlodipine and felodipine have no place in the treatment of heart failure. These latter agents, which have a neutral effect on both symptoms and prognosis, may be used in the treatment of angina and hypertension that coexist with congestive heart failure. The short-acting dihydropyridines may precipitate ischemic events and should be avoided.<sup>2</sup>

### Angiotensin-Converting Enzyme Inhibitors

Angiotensin-converting enzyme (ACE) inhibitors reduce blood pressure by decreasing the production of angiotensin II, elevating bradykinin levels, reducing salt and water reten-

tion, and producing vasodilation. They reduce angiotensin II production by interfering with ACE, an enzyme responsible for much of the conversion of angiotensin I to angiotensin II and for the metabolism of bradykinin. As a result, ACE inhibitors also elevate bradykinin levels, which contribute to the antihypertensive effects of these drugs and is also responsible for many of the side effects associated with their use.

Compared with earlier generations of antihypertensive drugs, the ACE inhibitors have an excellent side-effect profile. They do, however, cause cough, which is thought to be the result of the elevation of bradykinin and other vasoactive peptides metabolized by ACE, and angioneurotic edema, which is occasionally life threatening. ACE inhibitors also increase serum potassium levels and may cause hyperkalemia, primarily in patients with renal insufficiency and in those taking potassium supplements and nonsteroidal antiinflammatory drugs (NSAIDs).

According to the JNC-VI report, diabetes with proteinuria, heart failure, and previous MI with reduced LV systolic function are compelling indications for the use of ACE inhibitors. They should not be used in patients with bilateral renal stenosis, because they will induce renal insufficiency caused by efferent arteriolar dilation, resulting in reduced glomerular filtration pressure. They also should not be given to pregnant women, because they are known to be teratogenic, particularly in the third trimester.<sup>2</sup>

Dihydropyridine calcium channel blockers are generally more potent in terms of blood pressure reduction compared with ACE inhibitors. In a study that compared the ACE inhibitor enalapril with the dihydropyridine calcium channel blocker felodipine, for example, felodipine was able to reduce blood pressure to a significantly greater extent.<sup>6</sup> Therefore, dihydropyridines are particularly valuable

in patients with severe or resistant hypertension.

### Angiotensin Receptor Blockers

Because there are metabolic pathways other than ACE that lead to the production of angiotensin II, ACE

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inhibitors produce only partial inhibition of the renin-angiotensin system. The newest group of antihypertensives, the angiotensin receptor blockers (ARBs), differ from ACE inhibitors in that they directly block the action of angiotensin II at the receptor site rather than interfering with its production. As a result, these agents block the effects of angiotensin II, whether it is produced through the action of ACE or through alternate metabolic pathways. The ARBs bind to the AT<sub>1</sub> receptor, the primary receptor for angiotensin II, and prevent angiotensin II from binding to it. It is through the AT<sub>1</sub> receptor that vasoconstriction, aldosterone production, sodium retention, and growth promotion\*—all of which are deleterious in hypertensive patients—are mediated. Among the drugs in this

\*NOTE: Angiotensin II causes trophic changes in cardiomyocytes, cardiac fibroblasts, vascular smooth muscle cells and renal mesangial cells. Growth promotion is a synonym for trophic changes. These structural changes that result from trophic effects are important in the development of left ventricular hypertrophy, arterial hypertrophy, and glomerulosclerosis, independent of angiotensin's effect on blood pressure.

class are losartan, valsartan, candesartan, irbesartan, telmesartan, and eprosartan.

The ARBs are clearly the best tolerated of the antihypertensive agents. In submitting a new drug application for losartan to the Food and Drug Administration, the manufacturer provided data on drug-related adverse events in a wide range of hypertensive patients who were enrolled in clinical trials. Interestingly, the incidence of drug-related adverse events was the same for both losartan and placebo, and it was also less than the adverse event rates associated with diuretics,  $\beta$ -blockers, calcium channel blockers, and ACE inhibitors. All agents in this class have reported similar tolerability profiles.

Studies have shown that the blood pressure-lowering effect of ARBs is similar to that of the ACE inhibitors. Comparative studies suggest that candesartan and irbesartan are somewhat more potent than losartan in this regard. In a recently published trial, for example, the maximum dose of candesartan (32 mg) lowered blood pressure by approximately 2 mm Hg more than the maximum dose of losartan (100 mg).<sup>7</sup> Addition of low-dose diuretics to ARBs is an effective strategy in patients who require more than 1 antihypertensive agent.

As mentioned, drugs that interfere with the renin-angiotensin system are generally less potent than dihydropyridine calcium channel blockers. Interestingly, the Candesartan Versus Losartan Efficacy Comparison (CAN-DLE) study, which compared candesartan with the calcium channel blocker amlodipine, found that candesartan was equipotent to amlodipine in lowering systolic blood pressure and almost equipotent in lowering diastolic blood pressure (data on file, AstraZeneca).

### **End-Organ Protection Through Interference With the Renin-Angiotensin System**

In addition to its hemodynamic effects—vasoconstriction and sodium

retention—the renin-angiotensin system is involved in the development of many hypertensive sequelae that are not related exclusively to elevated blood pressure. As a result, angiotensin II stimulates arteriolar and myocardial hypertrophy, mesangial cell hypertrophy in the kidney, endothelial dysfunction, and other effects thought to be important in the development of atherosclerosis, left ventricular hypertrophy (LVH), and glomerulosclerosis. The clinical sequelae, which include coronary artery disease, renal disease, and heart failure, are multifactorial in origin, with high blood pressure constituting only part of the pathophysiology leading to clinical disease.

In patients with coronary disease who have sustained an MI and have LV dysfunction but are not necessarily hypertensive, ACE inhibitors have been shown to be cardioprotective in that they slow the progression of LV dysfunction and reduce the incidence of recurrent MI.<sup>8</sup>

Animal models of diabetic and nondiabetic nephropathy have shown that both ACE inhibitors and ARBs are renoprotective. In patients with nephropathy related to type 1 diabetes mellitus, when compared with placebo the ACE inhibitor captopril was shown in a 4-year study to reduce the incidence of death and the need for dialysis or transplantation by approximately 50%.<sup>9</sup> Renal protection has also been observed in other patient populations without diabetes.

Left ventricular hypertrophy is a powerful risk factor for long-term cardiovascular complications in the hypertensive population. Both angiotensin II and aldosterone contribute to the cellular events involved in the development of LVH. Several meta-analyses have shown that the ACE inhibitors are more effective than diuretics,  $\beta$ -blockers, or calcium channel blockers in promoting LVH regression.

The ACE inhibitor ramipril was recently shown in the Heart

Outcomes Prevention Evaluation (HOPE) trial to provide vascular protection in patients older than age 55 who have established coronary disease, peripheral vascular disease, or stroke or in patients with diabetes as well as another cardiovascular risk factor. Many of the patients in the study had hypertension, but blood pressure levels were controlled before study entry. The results of the HOPE trial, which were reported at the November 1999 meeting of the American Heart Association, indicated that ramipril produced a 22% reduction in the primary endpoint of the study—cardiovascular death, MI, or stroke—and a 17% reduction in all-cause mortality in this broad spectrum of study patients.<sup>10</sup> Its favorable effect in diabetics confirms earlier data indicating the particular value of renin-angiotensin system blockade in patients with diabetes. As a result, the Fosinopril Versus Amlodipine Cardiovascular Events Randomized Trial (FACET) showed that compared with the calcium channel blocker was the ACE inhibitor more effective in reducing long-term cardiovascular endpoints in patients with hypertension and type 2 diabetes.<sup>11</sup>

In unselected hypertensive patients, however, ACE inhibitors may be no more effective than other antihypertensive agents in preventing long-term hypertensive complications. The Captopril Prevention Project (CAPPP), a large European trial that compared captopril with diuretics and  $\beta$ -blockers as first-line therapy, found that there was no difference in the primary endpoint (a composite of fatal and nonfatal MI, stroke, and other cardiovascular deaths), except in patients with diabetes, who did do better with the ACE inhibitor.<sup>12</sup>

Although the ARBs lower blood pressure and have a benign side-effect profile, they have not been available long enough to ascertain their effects in preventing long-term complica-

tions. In animal models, the protective effects of the ARBs are similar to those of the ACE inhibitors, but these results have not yet been confirmed in humans. Currently, trials are under way to evaluate whether the ARBs are cardioprotective and/or renoprotective in groups of patients with hypertension, diabetic nephropathy, and congestive heart failure.

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### Summary

Blood pressure reduction is critical to preventing long-term complications in patients with hypertension, and all agents that have been evaluated in long-term clinical trials appear to be effective. Current strategies emphasize the importance of achieving a goal blood pressure, which in most patients is below 140/90 mm Hg. There are a number of important determinants of the clinical utility of individual antihypertensive agents. These include their pharmacokinetics and pharmacodynamics, their side-effect profiles, their efficacy in patients with comorbid conditions, and their ability to provide protection against end-organ damage. Drugs that are effective when taken once daily and produce minimal side effects are preferred. Therapy should be individualized, particularly with respect to coexisting conditions that influence the long-term efficacy of specific drug classes.

...DISCUSSION HIGHLIGHTS ...

**JNC-VI Guidelines**

**Dr. Steinberg:** Why do so many physicians fail to comply with the JNC-VI [Sixth Report of the Joint National Committee on Prevention, Evaluation, and Treatment of High Blood Pressure] recommendations? Is it simply a different prioritization of antihypertensives?

**Dr. Gradman:** If you are referring to the use of diuretics and  $\beta$ -blockers as first-line therapy, the JNC-VI recommends that patients with uncomplicated hypertension be preferentially treated with these agents. I think that's an arguable recommendation, but let's say we accept it as a reasonable approach.

We have to remember that far less than half of the hypertensive patients we see have uncomplicated hypertension. Many of those who do are young people who are otherwise healthy and don't want to take  $\beta$ -blockers. If you have a young patient who is an athlete,  $\beta$ -blockers are not the best choice, because they reduce peak exercise tolerance. Low-dose diuretics are a more reasonable option for such patients. The major point is that the number of patients who fall into those first-line recommendations is not as great as you think.

Another issue is that many physicians don't know the literature or the JNC-VI recommendations very well. Although there is certainly a need to educate patients about hypertension, there is also a need to educate physicians.

**Dr. Lee:** I haven't seen a drug representative promoting low-dose thiazides in a long time.

**Dr. Munger:** I was going to mention the same thing. Marketing plays a tremendous role in product use.

**Dr. Lee:** In my provider organization, which includes a teaching hospital, physicians who stray from the JNC-VI

guidelines most often are the house staff. You would think they would be most familiar with the guidelines, but they are prescribing calcium channel blockers as the first antihypertensive much more often than physicians who have been in practice longer.

**Dr. Steinberg:** Why do you think that is?

**Dr. Lee:** I think they're being bombarded with—or are influenced by—journal ads more than older physicians do.

**Dr. Steinberg:** Data from the HOPE [Heart Outcomes Prevention Evaluation] trial suggest that ACE [angiotensin-converting enzyme] inhibitors provide beneficial long-term effects in patients who are hypertensive and have either diabetes, peripheral vascular disease, or some type of coronary heart disease. Should all these patients be on an ACE inhibitor?

**Dr. Gradman:** That's an important question. If I had hypertension, I would take an ACE inhibitor as first-line therapy, but that's contrary to the JNC-VI recommendations. Is there absolute, incontrovertible proof that an ACE inhibitor is more effective than other drugs in patients with diabetes or coronary heart disease? No, but I believe that available data are highly suggestive.

The expansion of indications for ACE inhibitors suggested by the HOPE trial plays into that, because these agents seem to have vascular-protective effects, which are most clearly demonstrated in patients with diabetes and coronary disease. Although we need to look at the different subgroups in this study, it seems that a benefit in such a broad spectrum of patients will expand the indications for ACE inhibitors.

**Dr. Lee:** The PEACE [Prevention of Events with Angiotensin-Converting



Enzyme Inhibition] trial, which has a similar design, will provide further insight that may confirm the HOPE trial findings; that will make the case more compelling. The tough issue is that there is a spectrum of risk. How far down that spectrum do you go? Do you give ACE inhibitors to every male, because males have a higher risk for heart disease? It's a difficult decision; on the other hand, it makes sense scientifically.

As for therapeutic strategies, I am very impressed with the low-dose diuretics. I use 12.5 mg or 25 mg of hydrochlorothiazide before adding another agent.

**Dr. Gradman:** I think your strategy is very reasonable, in terms of both cost effectiveness and medical therapy. However, if you look critically at the amount of placebo-corrected blood pressure reduction that you get with 12.5 mg of hydrochlorothiazide, it's only 3 mm Hg or 4 mm Hg. The numbers may look better in elderly and African-American patients, but the average hypertensive patient is not going to be controlled with 12.5 mg of hydrochlorothiazide.

To control the majority of hypertensives, you need multiple drug agents given simultaneously. In this regard, I think there has been an overemphasis of the question, "What's the first-line drug?" because not that many patients are adequately controlled on the first-line drug, especially if it's 12.5 mg of hydrochlorothiazide.

### β-Blockers

**Dr. Lee:** I like to use a salt-and-pepper approach, that is, sprinkle a little bit of a second drug on top of whatever your first choice is, and things go much better. I was impressed by the Merck Medco data showing that low-dose diuretics had a lower side-effect rate than calcium blockers and ACE inhibitors. I also believe that the cardioprotective effects of β-blockers are

so compelling in so many settings, particularly post MI [myocardial infarction], I look for any excuse I can to put people on β-blockers.

**Dr. Gradman:** I'm less impressed by the cardioprotective effects of β-blockers than I used to be, although I certainly agree they should be used preferentially in post-MI patients.

**Dr. Lee:** My take on the literature is that β-blockers are good drugs for people with coronary disease if the drugs don't have side effects. The combination of a generic β-blocker and 12.5 mg of hydrochlorothiazide is probably the most common regimen I use for my patients with hypertension. The fact is, the majority of patients don't have side effects to a β-blocker. Most people do fine with that regimen, and that's what I use first.

**Dr. Munger:** Is activation of the sympathetic nervous system a consideration for you in choosing a drug for hypertension? There are compelling data showing that a heart rate of greater than 85 beats per minute increases the risk for cardiovascular events substantially. Do you choose a rate-limiting antihypertensive based on the heart rate?

**Dr. Gradman:** Although it has been shown that heart rate reduction with β-blockers correlates with outcome in post-MI patients, to my knowledge, it has not been shown in hypertensives. Nevertheless, if I see patients with a heart rate of 88 or 90 beats per minute, I tend to put them on either a β-blocker or on a drug like verapamil or diltiazem, that is, agents that lower the heart rate. However, if a patient has a low heart rate—say, in the 50s—I might use a dihydropyridine, which increases the heart rate a bit.

**Dr. Munger:** When I put patients on β-blockers, they almost invariably

report some degree of fatigue. That doesn't mean they won't stay on medication, but they're going to complain that they just don't have the pep and energy they had before they started taking these drugs.

**Dr. Lee:** That's not supported by the literature. Whereas  $\beta$ -blockers have a high side-effect rate compared with some other drugs, the majority of patients do not have side effects. Studies have shown that people with hypertension or another chronic disease report that their quality of life is worse once they're diagnosed and taking a pill every day. That may account for some of what you're hearing.

**Dr. Munger:** It could be the altitude. Salt Lake City is 4500 feet above sea level. There are differences in oxygenation and fatigue when you put patients who live at high altitudes on drugs. For example, I see a lot more edema with dihydropyridines in Salt Lake City than I did when I was in Cleveland.

**Dr. Gradman:** Every study that has looked at peak exercise tolerance with  $\beta$ -blockers shows it is reduced. Sometimes our adverse-event reporting underestimates the effects of drugs on quality of life, although there is little support for that statement in the literature.

**Dr. Lee:** I have very few patients who push themselves to peak exercise tolerance. I like  $\beta$ -blockers and prescribe them often, but I always ask about side effects. Specifically, I ask about impotence.

#### Managed Care Perspectives and Formulary Issues

**Dr. Gradman:** Are managed care strategies affected by some of the data we've talked about?

**Dr. Steinberg:** As in the nonmanaged care world, data from the managed

care environment suggest that patients are being treated, but they aren't being treated to goal. I suspect, but don't have any way of proving it, that there are many physicians who do not believe, despite the available data, that treating to below 140 mm Hg over 90 mm Hg is a good idea. That is another phenomenon that we have to deal with if we are going to improve overall blood pressure control.

So far, this discussion has focused on adverse effects especially related to drugs. There's been no discussion of side effects perceived and reported by the patient, particularly the elderly, that are associated with blood pressure reduction per se.

**Dr. Gradman:** That's a good point. I don't prescribe  $\alpha$ -blockers very often because they frequently produce orthostatic hypotension.

Another issue is formulary restrictions. One of the things doctors dislike about managed care is the concept that they can't prescribe any drug they want. They feel it runs counter to a basic responsibility of a physician, that is, to try to match the right drug to a given patient. How do formulary restrictions play into managed care strategies?

**Dr. Lee:** Some data—and they are weak—suggest that closed formularies may actually increase admissions to the hospital. Ideologically, my colleagues and I are against closed formularies. However, we recognize that there are huge differences in cost among drugs within classes and that we have a responsibility to try to make the healthcare system work.

Most of my colleagues are actually comfortable with the development of 3-tiered formularies, where there are sizable differences in copayments. We're against having a drug blocked out, but we can live with the benefit structure of a plan with a \$25 copayment for a drug. Usually, we can help the patient find a drug that will pro-

vide effective treatment without side effects that's in the \$5 or \$10 copayment range.

The provider organization with which I'm associated is not an insurance company but an organization that contracts with managed care organizations. We've actually gotten the other providers to organize a P&T [pharmacy and therapeutics] committee to compile a list of drugs that we believe should be included in every managed care formulary.

It drives us crazy when the most cost-effective option is locked out by one payer because it has gotten a fabulous deal, often with a completely different class of drugs. For example, if it got a great deal on asthma drugs, it locks out a cardiovascular drug. After encouraging our doctors to prescribe the cost-effective options, they may find that option has been locked out.

In response, Partners Health Care has been meeting with other provider organizations and will be presenting soon a list to the insurance companies of drugs that should be on all of their formularies.

**Dr. Steinberg:** We really have to ask whether closed formularies are a good thing or a bad thing, and whether it is a good thing for doctors to use whatever drug they think is the right drug. I served on the P&T committee at Johns Hopkins Hospital for a couple of years. Most hospitals have formularies; it's not just managed care organizations that have them. I believe there is a role for formularies, but they should be focused primarily on comparative effectiveness and safety. In addition, if a P&T committee is convinced that 2 drugs are therapeutically equivalent, then there's no reason to pay more for the more expensive drug.

**Dr. Gradman:** I don't mean to interrupt, but the idea of therapeutic equivalence across a large population of patients may be very different from

therapeutic equivalence in an individual patient; this is something of which we often lose sight. It's true that if you look at the whole population, drug X and drug Y may be absolutely equal, but the tolerability in individual patients may be different.

**Dr. Steinberg:** I agree, but I'm not convinced that individual clinicians are as capable of making these distinctions in as reliable and valid a way as they may think.

From my perspective, there are many circumstances where there is such an overwhelming, compelling rationale for using a particular drug that it becomes virtually indefensible not to be using it. Yet we see far too many circumstances where that drug isn't being used. Although I believe that the benefits of formulary restriction are not well documented, there is also substantial interphysician variation in the use of drugs that cannot have a scientific rationale underlying it.

**Dr. Gradman:** That's absolutely true, but if the decision-making ability of the physician to take care of his or her patient is to be removed, who is better able to make that decision than the physician? In other words, isn't that the physician's professional responsibility? Isn't that what being a physician is all about?

**Dr. Steinberg:** That's right, but it doesn't mean the physician shouldn't be held accountable for his or her performance in fulfilling that professional responsibility.

### Economic Issues

**Dr. Lee:** Right again. In our system, the framework we use for discussing these issues is that there are only 3 options for dealing with the economic issues facing healthcare, and that means pharmacy as well. Those 3 options are: You can reduce access, you

can reduce cost, or you can try to manage the care.

Reducing access in pharmacy means prior authorizations or locking drugs out, and no one likes that. As for reducing costs, we can expect that whoever is paying for the healthcare is going to be hit pretty hard on price in the years ahead. That's still not going to eliminate the rising cost issue, however.

The real issue is that management of care has got to happen, and insurance companies cannot do it. Inevitably, the management burden is going to fall on physicians and patients. They have to take it on together and manage it together. It shouldn't happen by locking out drugs, but by physicians and patients recognizing that the patient's pocketbook is going to be affected differently by different drugs. If patients need a special drug because it's the right one for them, they're probably going to have to pay more.

**Dr. Munger:** I think physicians are going to spend time working with patients to try to find a strategy that takes care of the problem with minimal damage to the patient's pocketbook; that's the way I see the formulary system working. It still boils down to the practitioner/patient relationship. If you close a formulary out—let's say we're going to close  $\beta$ -blockers out—and you strongly believe in using  $\beta$ -blockers, that's going to affect your relationship with your patient if you now have a drug to which you are denied access.

**Dr. Lee:** Another objection to lock-outs is avoidance of a diminished sense of responsibility and accountability among physicians. If the formulary is locking out a drug, it encourages the physician not to take responsibility.

**Dr. Gradman:** That is a really good point. If you remove responsibility, or

if you remove decision making and autonomy, I think it results in a big loss in terms of physician accountability and the doctor/patient relationship. You have disempowered the physician.

### Accountability

**Dr. Lee:** Dr. Gradman, how would you recommend incorporating financial accountability into the lives of physicians as they practice medicine? How should physicians feel accountable?

**Dr. Gradman:** When you're in your office taking care of a patient, you've got to think about the patient and do what you think is best for that patient, period. So I start from that standpoint, not from the standpoint that I am charged with lowering or controlling the healthcare costs of the nation. So I have a different philosophy there.

We all recognize resources are not unlimited and cost containment in some form or another is essential. I like Dr. Lee's approach to the copayment, because it forces the physician and the patient to work together and arrive at a compromise. If money is no object for a patient, and he or she can afford to pay for whatever drug may have a minor benefit in terms of tolerability or whatever, great. The patient should be allowed to pay for it, and that decision can be made between the patient and the physician without regard for the total cost to the economy. If, on the other hand, money is an issue for the patient, then a reasonable compromise should be reached regarding treatment and cost.

I agree that financial accountability is very difficult to introduce into medical practice. You have to fall back on the old "if it were my mother, what would I want done" test. In that case, maybe you'd want a CT [computed tomography] scan done for a headache

or the latest and best drug given for a common condition. There are no easy solutions.

**Dr. Steinberg:** I'd like to pick up on that and clarify something I was saying before. I believe that there is no one better than the physician to make clinical decisions in concert with the patient. However, I think that with decision-making responsibility should come professional accountability.

In my view, professional organizations have not stepped up to the plate and dealt with the fact that if there are compelling data that diabetics with renal disease should be on ACE inhibitors, they have a responsibility to determine whether physicians caring for those patients are prescribing ACE inhibitors for them. If they aren't, there ought to be either a compelling explanation or accountability for the fact that they're not doing so.

**Dr. Gradman:** I agree with that 100%. I don't think accountability has ever been part of medical practice, partly because it's very difficult. Certainly, the development of methods for record keeping, tracking, and the assessment of professional performance is enormously important, but we can't minimize how incredibly difficult it is to do well. I don't know of anybody or any system that's been able to do it.

Of course, you can choose 1 item, such as "Do they give  $\beta$ -blockers post MI?" That's the government's approach, and it's fine. But we all know that medical treatment involves dozens of decisions for each patient. To analyze all those decisions in a comprehensive and valid way is an enormous task. It's not as if the professional organizations could simply decide to do this tomorrow and be able to do it. You've all served on quality assurance and similar committees where you review outcomes of patients and know that it's very difficult to sort out

exactly whether good treatment decisions have been made.

**Dr. Steinberg:** Right, but we can't just throw up our hands and say that we're not going to do it because it's difficult; that's not a very satisfying outcome either. That's really what we've been saying for the past 20 or 30 years, that the medical profession is ultimately going to have to be accountable.

I believe we ought to start with clinical accountability before we get to fiscal accountability, because no one disputes the fact that physicians should be considering the clinical issues when they're taking care of their patients. It's debatable on the financial side. All I'm saying is that if there were greater adherence to what we already know is the optimal thing to do, costs would likely be considerably lower than they are now.

**Dr. Lee:** I agree. One thing we're doing in our network now, but only for our capitated patients, is outpatient chart reviews. We're picking the areas where we're spending a lot of money, but we're also pulling random charts from outpatient offices for patients receiving certain services. Then I, sometimes with one of my colleagues, look at the whole chart and comment on quality and efficiency. When one of our physicians lets a hypertensive patient putter along at 160 mm Hg over 95 mm Hg, we point that out.

The only reason our physicians are allowing us to go into their offices to look at their charts is because they recognize that financially, for this capitated population, we've got to go to a new level in terms of tightening up our care. If you proposed opening up patient charts randomly to pick out things where you practice, you would meet tremendous resistance. Culturally, chart review has been precipitated by a collective sense of financial crisis.

On the other hand, I believe that the net result of this will be to improve the quality of care physicians provide. They will know that if they let a patient "slide" at 160 mm Hg over 95 mm Hg, someone might pull that chart and look at it. They might be embarrassed in front of their colleagues. That kind of pressure is likely to make them feel more accountable. As a result, one of the pluses of managed care is that it could improve care if you can get providers to work together and review the care they are giving their patients.

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