

## $\beta$ -Blockers as First-Line Therapy for Hypertension in the Elderly

*Based on a presentation by Franz H. Messerli, MD*

### *Presentation Summary*

The efficacy and safety of the calcium channel blockers (CCBs) and  $\beta$ -blockers were the focus of this presentation. The CCB class of antihypertensives comprises a heterogeneous group of agents. Safety concerns over their use in patients with hypertension arose because of inappropriate and unapproved use of short-acting CCBs. It has been known for some time that nifedipine, when used to treat hypertensive emergencies, can lead to an increased incidence of adverse cardiac events. The results of large recently completed trials of long-acting CCBs in elderly hypertensive patients, however, attest to the efficacy and safety of these agents and have also prompted their endorsement in the Sixth Report of the Joint

National Committee on the Detection, Awareness, and Treatment of Hypertension (JNC-VI) as first-line antihypertensive agents in the elderly.

$\beta$ -blockers are ineffective as first-line therapy for elderly hypertensive patients, concludes a recently published review that analyzed 10 trials in which diuretics or  $\beta$ -blockers were used as first-line drugs.  $\beta$ -blockers were 50% less effective in lowering blood pressure and conferred no primary cardioprotection in elderly patients compared with diuretics. A pathophysiologic mismatch may explain the poor performance of  $\beta$ -blockers in older patients. The JNC no longer considers  $\beta$ -blockers appropriate for first-line monotherapy in elderly patients with hypertension.

The safety and efficacy of certain antihypertension drug classes, in particular, the calcium channel blockers (CCBs), has recently been called into question.<sup>1,2</sup> In addition, controversy also surrounds the benefits of  $\beta$ -blocker therapy in elderly patients.<sup>3,4</sup> Several multibillion dollar, multicenter, hard endpoint trials that in total have enrolled approximately 200,000 patients are in progress or have

recently been completed and should help clarify the safety and efficacy issues surrounding many of the antihypertensive drug classes currently in use. "The only drug class for which there are ironclad data in terms of morbidity and mortality in hypertension at the present time remain the diuretics," stated Franz Messerli, MD, Medical Director, Division of Research, Ochsner Clinic, New Orleans, Louisiana.

### Calcium Channel Blockers

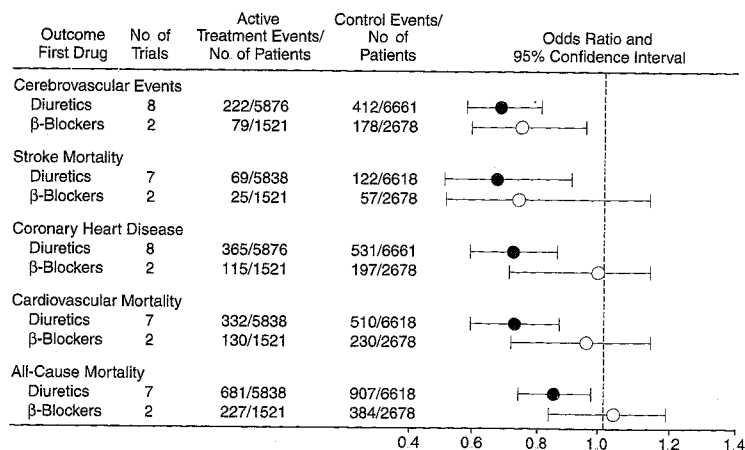
As Dr. Messerli explained, the CCB class of antihypertensive agents is heterogeneous. The evidence fueling the CCB controversy stemmed from inappropriate use of short-acting CCBs.<sup>5</sup> From the regulatory viewpoint, short-acting sublingual nifedipine has never been approved for the treatment of any form of hypertension, emergent or other, and its use for this purpose would be considered off-label. No benefits whatsoever of nifedipine capsules have been identified in hypertensive emergencies, and there are no outcome data. On the contrary, serious adverse effects have been reported after sublingual administration of fast-acting nifedipine for hypertensive emergencies,<sup>6</sup> and numerous fatalities have been reported. The Sixth Report of the Joint National Committee on

Prevention, Detection, Evaluation, and Treatment of High Blood Pressure (JNC-VI) has clearly identified sublingual nifedipine as unacceptable.<sup>7</sup> Even when given three times a day, the short-acting formulation still leads to distinct fluctuations in plasma level, as opposed to the long-acting preparations. Thus, there are distinct differences within the drug class.

The efficacy and safety of CCBs have been confirmed in the Systolic Hypertension in Europe (Syst-Eur) trial,<sup>8</sup> a very thorough, prospective, randomized trial with the dihydropyridine CCB nitrendipine in more than 4000 elderly hypertensive patients with isolated systolic hypertension. The study was terminated prematurely because a significant benefit for stroke was demonstrated after the interim analyses. Active treatment reduced the stroke rate by 42%, and all cardiovascular disease mortality was also significantly reduced. Reductions in heart failure and myocardial infarction rate showed a favorable trend. Based on these results, JNC-VI labeled long-acting dihydropyridine CCBs as appropriate first-line therapy in older patients.

Dr. Messerli added that the benefits of CCBs are even more pronounced in diabetic hypertensive patients. When one compares the overall results of the Systolic Hypertension in the Elderly Program (SHEP) trial<sup>9</sup> in which a diuretic was the first-line agent, with the results from Syst-Eur with the CCB, there is really not much difference in terms of mortality and cardiovascular endpoints in nondiabetic patients. A calcium antagonist-based therapeutic strategy was clearly superior to a diuretic-based therapeutic strategy in terms of all-cause and cardiovascular morbidity and mortality. Also, in a substudy of the SYST-EUR, the calcium antagonist reduced total mortality and cardiovascular mortality significantly better in the diabetic than in the nondiabetic patient. This

**Figure.** Meta-Analysis of Prospective Clinical Trials in Elderly Patients with Hypertension According to First-Line Treatment Strategy



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clearly would indicate that blood pressure lowering with a dihydropyridine calcium antagonist confers substantial benefits in the diabetic hypertensive patient. However, when just the diabetic patients from the Syst-Eur trial were analyzed, the CCB reduced total mortality twice as much and the cardiovascular mortality three times as much in the diabetic patients compared with the nondiabetic patients. A recent study, the Appropriate Blood Pressure Control in Diabetes (ABCD) Trial,<sup>10</sup> compared a CCB with an angiotensin-converting enzyme (ACE) inhibitor as a first-line antihypertensive agent and showed an increased protective effect of the ACE inhibitor. Thus, in diabetic hypertensive patients, ACE inhibitors may be considered more beneficial, but as a second-line agent one should consider a calcium antagonist, Dr. Messerli said.

### **β-Blockers**

"Practicing physicians are just getting a little bit confused," according to Dr. Messerli, referring to recent contradictory findings on the risk of sudden cardiac death among patients receiving β-blocker therapy published just 1 month apart in *The Annals of Internal Medicine*.<sup>3,4</sup>

Clearcut data in support of a protective function of β-blockers in elderly patients with hypertension are not available. To clarify indications for use of β-blockers in the elderly, Dr. Messerli and his colleagues systematically analyzed 10 trials that lasted at least 1 year, that used diuretics and/or β-blockers as first-line therapy, and that reported morbidity and mortality outcomes.<sup>11</sup> The findings were surprising. In contrast to diuretic therapy, β-blockers did not reduce coronary heart disease morbidity, cardiovascular mortality, or all-cause mortality (Figure). A small reduction in nonfatal strokes was obtained with β-blockers, but here also, the diuretics were superior.

The conclusion from this study was that β-blockers should no longer be considered for first-line therapy in uncomplicated hypertension in the elderly. Although β-blockers are beneficial in patients after a myocardial infarction, their use in elderly patients with uncomplicated hypertension exposes 6.4 million patients to their adverse effects without conveying any real benefits, according to Dr. Messerli.

### **Why Are β-Blockers Not Effective in the Elderly?**

In reference to the blood pressure-lowering ability of β-blockers, Dr. Messerli said that from the analysis, the response rate in the elderly to diuretics calculates to 60% compared with only 30% for the β-blockers.<sup>11</sup> Thus, β-blockers are less effective than diuretics in lowering blood pressure in the elderly.

Several pathologic changes associated with aging may render β-blockers ineffective in older patients (Table). The hemodynamic profile in the elderly is characterized by low cardiac output, low heart rate, and high peripheral resistance, with all the conditions being exacerbated by β-blockers. The elderly have predominantly systolic hypertension, which is not affected much by β-blockers. Also, because β-adrenergic responsiveness is diminished in the elderly, higher doses of the β-blocker would be required.

Hypertensive heart disease, hypertensive renal disease, and hypertensive vascular disease are common in older patients. β-blockers are the least effective of various antihypertension agents in reducing hypertensive heart disease. In studies that have compared the relative effectiveness of various agents in reducing left ventricular hypertrophy, β-blockers trail the angiotensin-converting enzyme (ACE) inhibitors, CCBs, and diuretics.<sup>12,13</sup> The elderly often present with comorbidities such as chronic obstructive pulmonary disease, cardiovascular dis-

ease, diabetes, depression, dementia, and sexual dysfunction, all of which are adversely affected by  $\beta$ -blockers.

In conclusion, for the treatment of older patients, Dr. Messerli said that JNC-VI asserts that diuretics are superior to  $\beta$ -blockers and that  $\beta$ -blockers are no longer an option as monotherapy in the elderly.

... DISCUSSION HIGHLIGHTS ...

**Medical Aspects of  $\beta$ -Blocker and CCB Therapy**

**Dr. Schulman:** Is there any role for the new third generation  $\beta$ -blockers in hypertension in the elderly?

**Dr. Messerli:** From a purely theoretical point of view, yes. The rates for vasodilating  $\beta$ -blockers should be better in the elderly, but they do the wrong thing. They make the elderly hypertensive patients hemodynamically unstable. All of them lower cardiac output and increase peripheral resistance. However, there are no outcome studies that prove this concept.

**Dr. Schulman:** When we read the data on the postinfarct patient and look at the large subgroup of elderly postinfarct patients, many will also have hypertension. What should we recommend to physicians in that important subgroup?

**Table.** Possible Reasons for Diminished Efficacy of  $\beta$ -Blockade in the Treatment of Hypertension in Elderly Patients

Pathophysiologic Entity	Specific Changes in the Elderly*	Effect of $\beta$ -Blockade†
Systemic hemodynamics	Decreased cardiac output, heart rate, and elevated systemic vascular resistance	Further decrease in cardiac output, heart rate; further increase in vascular resistance
Blood pressure pattern	Predominantly systolic hypertension	Lesser effect on systolic blood pressure
Hypertensive heart disease	Left ventricular hypertrophy is common	Least efficient in reducing left ventricular hypertrophy
Hypertensive renal disease	Decreased renal blood flow, glomerular infiltration rate, and increased microproteinuria	Further decrease in renal blood flow and glomerular infiltration rate; no effect on microproteinuria
Hypertensive vascular disease	Increased arterial stiffness, vascular hypertrophy	No effect on arterial stiffness or hypertrophy (in contrast to other drugs)
Metabolic effects	Insulin resistance, glucose intolerance, and lipid abnormalities are common	Increase the risk of developing diabetes by 4 to 6; increase in triglycerides and decrease in high-density lipoprotein cholesterol
$\beta$ -Adrenergic responsiveness	Decreased	Diminished efficacy
Exercise tolerance	Decreased	Further decrease in exercise tolerance
Comorbidity	Chronic obstructive pulmonary disease, peripheral vascular disease, diabetes mellitus, depression, dementia, and sexual dysfunction are common	Affecting all of these comorbid conditions adversely

\*Compared with younger patients with similar blood pressure elevation

†With the exception of the vasodilating  $\beta$ -blockers.

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**Dr. Messerli:** There is no question in my mind that the post-MI [myocardial infarction] patient of 10 or 15 years ago is a good  $\beta$ -blocker candidate. That patient was very different from today's post-MI patient who undergoes stenting and angioplasty and CABG [coronary artery bypass grafting]. I'm not sure that we can really translate the efficacy of the  $\beta$ -blockers to today's post-MI patient. Nevertheless, I think that these patients probably should continue to be treated with a  $\beta$ -blocker.

Why is it then that the  $\beta$ -blockers clearly are cardioprotective in secondary prevention post-MI, whereas there seems to be no primary cardioprotective effect? I think what we're doing post-MI is treating manifest severe coronary heart disease and there, clearly, slowing the heart to a diminishing heart rate and cardiac output is beneficial. For primary prevention, what we are doing is lowering blood pressure with a drug that has a hemodynamically inappropriate effect. Therefore, I think the two situations are different.

The question that comes up in the post-MI patient who has hypertension is, "Can you be satisfied if the blood pressure is controlled with the  $\beta$ -blocker alone?" I would say probably not. We probably should have an ACE inhibitor or maybe even a low dose of a calcium blocker, in addition to the  $\beta$ -blocker, in other words, one drug for cardioprotective effect and the other for lowering the blood pressure.

**Dr. Gerstenblith:** To what extent are your conclusions relevant in a younger population regarding the use of  $\beta$ -blockers?

**Dr. Messerli:** There is only one study looking at  $\beta$ -blockers in the younger population and comparing it to placebo and that's the MRC [Medical Research Council] trial.<sup>14</sup> The MRC trial was a fairly large study done in middle-aged patients, and it basically showed that in nonsmoking men,  $\beta$ -

blockers were somewhat beneficial when compared with placebo. When the smokers were included, the benefits evaporated. There are two other studies comparing  $\beta$ -blockers with a diuretic in the middle-aged population, showing that there's not much difference in morbidity and mortality, at least in the nonsmokers. So probably in the younger population there is some benefit, but it's relatively weak.

**Dr. Gerstenblith:** Do you have a concern about  $\beta$ -blockers in diabetic patients?

**Dr. Messerli:** The diabetic patients have insulin resistance, and  $\beta$ -blockers may adversely affect these patients. Surprisingly, there was no difference in outcome in a recent British study in which a  $\beta$ -blocker was compared to an ACE inhibitor in a large diabetic population.

**Dr. Brunton:** Now the data show that dihydropyridine calcium channel blockers [CCBs] are protective in the elderly, can you then extend that to nondihydropyridine CCBs?

**Dr. Messerli:** I'm not so sure we really can extrapolate. In my own practice, I do. I think that drugs such as diltiazem and verapamil are probably as good, and that in certain situations they may have an advantage.

**Dr. Schulman:** Do you recommend diuretics in the elderly at a low dose or a high dose? At low dose, if the blood pressure isn't controlled, do they receive a second drug or go up to a higher dosage?

**Dr. Messerli:** A low dose of a diuretic drug is excellent initial therapy in the elderly. I usually use a combination of hydrochlorothiazide and a potassium-sparing compound, half a tablet, once a day. This is a fair way of proceeding in the elderly; it is effective and has very few side effects. However, I'm a bit concerned about dehydration dur-

ing the hot summer months, especially if the patients are working outside. I've seen significant hyponatremia. ACE inhibitors also are prone to produce significant drops in blood pressure in the heat, so I'm a bit concerned about that. But I do think a low-dose diuretic is good.

#### Affecting Community Practice

**Dr. Jacobs:** I'd like to try and make what you just presented very practical.

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***The Syst-Eur [Systolic Hypertension in Europe] trial, which clearly showed for the first time in a prospective randomized study that a calcium blocker is beneficial, was nowhere to be seen in the press.***

— Franz H. Messerli, MD

Having gone through a rigorous analysis that draws rather strong conclusions regarding management of hypertension in a high-prevalence and a high-risk population, how have you taken that data from your own organizational environment to try to change the practice of medicine, so that patients receive optimal care? What seems to work?

**Dr. Messerli:** What seems to work is if the article appears in *The Wall Street Journal* or the *New York Times*. That seems to make it more newsworthy. For instance, you have the whole CCB controversy, which was based on defective studies dealing with short-acting drugs. The Syst-Eur [Systolic Hypertension in Europe] trial, which clearly showed for the first time in a prospective randomized study that a calcium blocker is beneficial, was nowhere to be seen in the press. It's unfortunate, but a lot of these decisions are made on the basis of the reporting in the press.

**Dr. Schulman:** We really have to think about press reporting, because certainly *The Wall Street Journal* is business oriented, and what we're talking about are some important products for selected businesses. How do we tie in the pharmaceutical industry and those of us who provide healthcare?

**Dr. Messerli:** That's really extremely difficult because obviously the pharmaceutical industry has another agenda.

**Dr. Shepard:** Is there any mechanism for the FDA [Food and Drug Administration] to review the data that you've just published<sup>11</sup> that shows that  $\beta$ -blockers aren't indicated in the elderly, to review the indication labeling for  $\beta$ -blockers and to consider removing that or modifying that indication to indicate they should not be used as primary treatment?

**Dr. Messerli:** That's a very good point. I can give the example of some labeling for nifedipine. In 1985 I was on the FDA advisory committee, and the manufacturer wanted labeling with nifedipine as an indication for hypertensive emergencies. We turned down the request unanimously because there were no safety data or outcome data. There was nothing which proved that the drug did anything for the patient. It lowered blood pressure, but we didn't know how fast or how low; it was completely unpredictable. Nevertheless, despite this decision, in every single emergency room in the country, sublingual nifedipine was used, until the results of their hazards were published 10 years later.<sup>6</sup> This just shows that even if the FDA makes a decision, it's not necessarily going to change the practice of physicians. It needs more than that.

**Dr. Cabana:** A recent article reviewed the records of all prescriptions between 1992 and 1995. It bemoaned the fact that  $\beta$ -blocker and diuretics

aren't being used as first-line therapy for hypertension.<sup>15</sup> Is that something to really be worried about, and how prevalent is the problem of inappropriate  $\beta$ -blocker use?

**Dr. Messerli:** I don't know. At a recent Grand Rounds, I asked the audience that if any among them had hypertension, who would start himself or herself on the  $\beta$ -blocker or the diuretic? One hand went up. All of the others would start themselves on the ACE inhibitor or calcium blocker. Physicians don't always preach what they practice.

**Dr. Wilson:** We did the same thing and got a similar response from a managed care group that we were talking to about hypertension and appropriate use of drugs.

#### Importance of 24-Hour Blood Pressure Control

**Dr. Wilson:** One of the big issues we've always emphasized is 24-hour control. We may think a patient is well controlled because the blood pressure is usually measured some time during the day when the drug effect is at a maximum; but in fact, at other times in the day, the blood pressure may not be well controlled. So we tried to determine what the extent of that problem might be. We studied about 75 patients who were treated and were well controlled based on office pressures obtained with excellent technique.<sup>16</sup> Then, we did ABPM [ambulatory blood pressure monitoring] on these patients. We also did HBPM [home blood pressure monitoring] to look at correlations. We quantified the degree of control or lack of control based on two factors—average blood pressure and the blood pressure load in those patients. We found that of the patients who were treated and well controlled, based on office pressures, more than 50% had blood pres-

sure loads greater than 30% throughout the 24-hour period, which was especially pronounced in the morning. From these results, we extrapolated carefully that the minority of the patient population with hypertension, who we think are treated and well controlled, in fact, may not be well controlled.

**Dr. Messerli:** I think that's an extremely important issue, because obviously most of the morbidity and mortality occurs in the early morning hours and this has been documented for coronary heart disease and for stroke. Although, we do not know whether the early morning rise in blood pressure is associated or causally related to this, it behooves us at least to control blood pressure during that time as well.

The patients take their medicine in the morning and come to the office during the daytime hours; therefore, when they see the doctor, their blood pressure is at its lowest, at the peak effect of the antihypertensive drug. It is therefore extremely important to assess the early morning hours. The FDA advisory committee has recommended a peak-to-trough ratio of 50% for antihypertensive drugs. This number is completely arbitrary, but it's better than nothing. What is important is to use long-acting drugs, particularly for the CCBs. The long-acting ones actually provide smoother control of arterial pressure. Did you look in terms of what you did in your study?

**Dr. Wilson:** We were unable to stratify on the basis of drug therapy or even class because there were only 75 patients. Now these patients were all dosed once a day on the therapy, but it may have been with one drug or two drugs or three drugs. Very few were on three drugs; most were on either one or two drugs. We noted that those patients on more than one drug were a lot less likely to have blood pressure fluctuation than those on a single drug.

We strive for single-drug therapy, and part of our concern is whether that is realistic. In reality, atenolol should be dosed twice a daily to get the best 24-hour control.

**Dr. Brunton:** Should the patients be taking the medications at night rather than in the daytime since many of the supposedly once-a-day medications still have a 20-hour framework?

**Dr. Messerli:** That's a good concept, but the concern is that those who have to empty the bladder at night may have hypotensive episodes at that time because blood pressure is lower during the night anyway, and then, you lower it even further because you have the peak effect of the antihypertensive drug at that time.

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