

Expert Panel Discussion

The Treatment of Hypertension in the Elderly

Marvin Moser, MD; William C. Cushman, MD; Michael G. Ziegler, MD

Following a hypertension symposium in San Francisco in September 2007, an expert panel was convened to discuss the treatment of hypertension in the elderly. Based on recent data, new recommendations may be indicated. The session was moderated by Marvin Moser, MD, Clinical Professor of Medicine at Yale University, New Haven, CT. Participants were William Cushman, MD, Professor of Preventive Medicine and Medicine at the University of Tennessee in Memphis, and Michael Ziegler, MD, Professor of Medicine, University of California at San Diego. The discussion was supported by Novartis Pharmaceuticals and Merck & Company, and each author received an honorarium from Novartis Pharmaceuticals and Merck & Company for time and effort spent participating in the discussion and reviewing the transcript for intellectual content before publication. The authors maintained full control of the discussion and the resulting content of this article. (J Clin Hypertens (Greenwich). 2008;10:58–68) ©2008 Le Jacq

DR MOSER: This session represents an update of previous reviews.¹ Bill, we have come a long way from the time when we believed that elevation of systolic blood pressure (SBP) was not a problem, when some experts believed that a reading of 100 mm Hg plus your age was a normal SBP level and that we should leave people aged 70 to 80 years alone if they had elevated SBP levels, even levels of 160 or 170 mm Hg. The definition of isolated systolic hypertension has been changed from a blood pressure (BP) level $\geq 160 / < 90$ to $\geq 140 / < 90$ mm Hg, and we've accumulated good data on the treatment of these patients. These data indicate that their hypertension should be treated. Would you review some of the classic studies that have shown that treatment is beneficial and tell us about the medications that were used in these studies?

DR CUSHMAN: Indirect evidence came from the earlier diastolic hypertension trials where SBP levels were also concomitantly lowered. When you look back at the benefits of these trials, it was often the SBP lowering that was more closely associated with improvements in outcome. But until the early 1990s, we really didn't have any definitive data showing that if you treated hypertension based only on SBP—particularly isolated systolic hyper-

tension, in which the diastolic BP was low—you would get a benefit. The landmark study that proved that we should treat isolated systolic hypertension was the Systolic Hypertension in the Elderly Program (SHEP). In this trial, 4736 older individuals with SBP levels ≥ 160 mm Hg, documented over several visits, but with diastolic BP levels < 90 mm Hg were randomized to treatment with a thiazide-type diuretic (chlorthalidone)-based regimen or placebo. In the active arm, the β -blocker atenolol or reserpine and then hydralazine could be added to control BP.

DR MOSER: That was a placebo-controlled trial, because at that time we didn't know whether or not BP lowering was effective in this group of patients and it was ethical to do this.

DR CUSHMAN: That's right. There was quite a lot of controversy as to whether these elderly people should even be treated, with the concern that there would be harm in lowering BP levels in people with stiff arteries. The study showed greater reductions in BP in the treated group (SBP, 143 vs 155 mm Hg), and the primary stroke end point was reduced by 36% ($P = .0003$), heart failure by 49% (81% in those with prior myocardial infarction), and coronary events by 27%. All of the things we were worried about with regard to lowering BP in this population were proved to be wrong.



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DR MOSER: Did patients tolerate medications? That was one of the problems that SHEP had to address.

DR CUSHMAN: They did. Treatment was compared with placebo, and there were relatively few adverse effects of active treatment. Only about 4% of patients had hypokalemia (as defined by a potassium level <3.2 mEq/L), but that could usually be treated effectively. There was a small percentage of the treated population who developed diabetes (8.6%), not a large number, but importantly it wasn't statistically significant compared with the placebo group (7.5%). The long-term assessment of these people after 14 years of follow-up showed that there was no increase in all cause mortality or cardiovascular mortality associated with new-onset diabetes in the chlorthalidone arm. So all of the concerns both about lowering BP in that population and about thiazide usage, which in SHEP included 12.5 to 25 mg chlorthalidone daily, seemed to be unfounded.

The other landmark study was the Systolic Hypertension in Europe (Syst-Eur) study, which was reported about 6 years later. This was a study in a group of older patients in whom the diastolic BP just had to be <95 mm Hg but, as in SHEP, SBP was ≥ 160 mm Hg. The participants were randomized to the dihydropyridine calcium channel blocker (CCB) nitrendipine or placebo. In this trial, BP was not lowered quite as effectively as in SHEP, but the benefits were impressive. The study was stopped earlier than anticipated because of a significant reduction in stroke (42% reduction; $P=.003$). Clearly, on the heels of SHEP having been positive, it would have created an ethical problem to continue the study any longer.

DR MOSER: So we had two studies, one was diuretic-based and the other was a dihydropyridine CCB-based study.

DR CUSHMAN: That's right.

DR MOSER: Both of them showed essentially the same thing.

DR CUSHMAN: It is hard to know—these were apples and oranges, certainly different populations, but overall results were good with either a diuretic or CCB-based program. In a more recent head-to-head comparison study, the Antihypertensive and Lipid-Lowering Treatment to Prevent Heart Attack Trial (ALLHAT), in which we had some patients with isolated systolic hypertension and a similarly aged population, the CCB- and diuretic-based regimens reduced coronary outcomes and stroke to a similar degree. The main difference was that the CCB did not reduce heart failure as well as the

diuretic. That is a major problem in older populations because heart failure is the number one reason for admission to the hospital in a Medicare-aged population.

DR MOSER: Mike, have you been convinced? The Syst-Eur trial was a systolic/diastolic hypertension study. SHEP involved isolated systolic hypertension. Are you convinced by these two studies that we have enough evidence to begin to treat hypertension in all patients older than 65 years with antihypertensive drugs if lifestyle changes weren't successful?

DR ZIEGLER: By the time the Syst-Eur findings came out, the data were so striking in terms of benefit that I wasn't sure I really believed them. They were just too good to be true.

DR MOSER: Which parts of the data? The dementia part?

DR ZIEGLER: Largely, the data on dementia. They reported a 55% reduction in dementia, a 42% decrease in stroke, and improvement in some areas that went beyond what SHEP showed. SHEP was tightly controlled, and the data were convincing. Frankly, when the SHEP data came out, my treatment of hypertension changed overnight. Suddenly, I was looking at SBP and starting treatment in patients based exclusively on the SHEP data. Subsequent studies have borne out the SHEP results.

DR MOSER: You worried about Syst-Eur results because they showed something that seemed out of line, that is, the dramatic decrease in dementia with a CCB-based trial.

DR ZIEGLER: At the time that Syst-Eur came out, the Puget Sound Health Alliance suggested that dihydropyridine CCBs were causing lots of cardiovascular problems. Suddenly, the Syst-Eur trial reported that a dihydropyridine CCB showed dramatic benefits. The difference between those two pieces of data was enormous. In retrospect, it appears that the Puget Sound data were based partly on non-sustained-release CCBs in an epidemiologic post hoc study so that the differences can be accounted for.

DR MOSER: These results included outcomes with short-acting nifedipine.

DR ZIEGLER: Yes. I think both studies were valid, but at the time the difference between those really raised questions in the United States and got a lot of attention.

DR MOSER: But you became convinced then that treatment of hypertension in the elderly was beneficial—you had no doubt about it.

DR ZIEGLER: Any doubts rapidly resolved, and subsequent studies have had a relatively easy

time demonstrating benefit. Risk in the elderly population is so high that the incidence of adverse outcomes is higher than in hypertension studies with younger people. As a consequence, it takes a smaller number of elderly people enrolled in the studies to attain statistical significance. Thus, a number of subsequent studies have shown a significant benefit in treating the elderly.

DR MOSER: Alright, so we had data showing that both systolic and diastolic hypertension could be reduced and benefit was clear, but doctors still were not responding to these data and treating hypertension in elderly people, even 5 to 10 years after SHEP was reported. The next step was to evaluate whether one particular medication or one particular combination of medications was better than another. There have been many comparative trials. What have you concluded about specific therapies in the elderly population?

DR ZIEGLER: Well, if I may quote a famous physician who treats hypertension, "It's the BP, dummy." So the number one consideration was the actual reduction in BP. SBP elevations in the elderly are often dramatic. In the clinic, it's not all that rare to see SBP levels of 200 mm Hg with diastolic BP levels of about 80 mm Hg. The most dramatic decreases in BP are seen in people with these levels. And these are the ones who have had the greatest benefit. So mostly it's the BP and not specific medications, but there are some exceptions.

DR MOSER: Bill, many studies aren't always listed as trials in the elderly, but ALLHAT, the Valsartan Antihypertensive Long-Term Use Evaluation (VALUE), the Anglo-Scandinavian Cardiac Outcomes Trial (ASCOT), and the Swedish Trial in Old Patients with Hypertension-2 (STOP-2), really all are studies in the elderly. More than two-thirds of the patients now being studied are older than 60 years and probably half of them are older than 70 years, aren't they, in these trials?

DR CUSHMAN: Virtually all the trials have had an entry criterion of age 50 to 55 years or older to get in, so that there could be a reasonable expectation of enough cardiovascular end points.

DR MOSER: Most of the recent trials compare one regimen with another and attempt to prove superiority of one treatment over another. Based on the data that you've seen, what do you think practitioners should do when they begin therapy in an elderly patient; are there specific medications that work better than others in this population as monotherapy? Should they start with two drugs right away, or start with one?

DR CUSHMAN: First of all, there is no mystery why SHEP and the Syst-Eur trial used a diuretic or a CCB, respectively, because these are the classes of drugs that lower SBP the best as monotherapy, particularly in the elderly.

DR MOSER: Better than β -blockers, angiotensin-converting enzyme (ACE) inhibitors, and angiotensin receptor blockers (ARBs)?

DR CUSHMAN: Better than β -blockers, ACE inhibitors, and ARBs. There are actually some groups in which there is almost no effect from monotherapy with a β -blocker, ACE inhibitor, or ARB, for example, an elderly black patient. So if you're going to start with one drug, it makes sense to start with a CCB or diuretic. I think on balance putting all the data together, even given very similar reductions in BP, the diuretic looks better in head-to-head studies. For example, in ALLHAT (average age at entry, 67 years) the CCB and the diuretic were similar in all outcomes except heart failure, and, as noted, heart failure is the most common reason for older patients to be hospitalized. Heart failure rates were about 40% higher with the CCB than the thiazide-type diuretic chlorthalidone. Results of meta-analyses are consistent with the lesser benefit of CCB on heart failure incidence. The CCBs probably do lower heart failure rates some, but a lot less than diuretics do; as a matter of fact, in the Syst-Eur trial heart failure was reduced by about 30% compared with placebo, although the difference wasn't statistically significant.

DR MOSER: ALLHAT hasn't published data on results in the different age groups from 60 to 80 years and older, but these have been presented. Was the same outcome noted in the 60 to 70 year group and the 70 to 80 years and older group in ALLHAT?

DR CUSHMAN: Yes.

DR MOSER: There was no difference in outcome?

DR CUSHMAN: There's no heterogeneity across age groups no matter where we cut it, although, obviously, the older the population the more events there are. The relative differences among the CCB, diuretic, and ACE inhibitor were similar.²

DR MOSER: Did the diuretics prove to be equally effective with regard to outcomes as the CCB and ACE inhibitor in these patients, regardless of age?

DR CUSHMAN: There were some differences. The diuretic was better in preventing heart failure compared with both of the other agents, and the diuretic was better than the ACE inhibitor in preventing stroke, heart failure, and overall cardiovascular disease (CVD). For the prespecified subgroup of patients aged 65 years or older, combined

Table I. Results of Therapy in the Elderly

	CLINICAL TRIAL							
	AUSTRALIAN	EWPHE	C & W	STOP	MRC	SHEP	HDFP	SYST-EUR
No. of patients	582	840	884	1627	4396	4736	2374	4695
Age range, y	60–69	>60	60–79	70–84	65–74	60–80	60–69	>60
Mean BP at entry, mm Hg	165/101	182/101	197/100	195/102	185/91	170/77	170/101	174/86
	% REDUCTION OF EVENTS IN TREATED PATIENTS COMPARED WITH CONTROLS							
Stroke	33	36	42 ^a	47 ^a	25 ^a	33 ^a	44 ^a	42 ^a
CAD	18	20	+0.03	13 ^b	19	27 ^a	15 ^a	30
CHF	–	22	32	51 ^a	–	55 ^a	–	29
All CVD	31	29 ^a	24 ^a	40 ^a	17 ^a	32 ^a	16 ^a	31 ^a

Abbreviations: BP, blood pressure; C & W, Coope and Warrender; CAD, coronary artery disease; CHF, congestive heart failure; CVD, cardiovascular disease; EWPHE, European Working Party on High Blood Pressure in the Elderly; HDFP, Hypertension Detection and Follow-Up Program; MRC, Medical Research Council; SHEP, Systolic Hypertension in the Elderly Program; STOP, Swedish Trial in Older Patients With Hypertension; Syst-Eur, Systolic Hypertension in Europe. ^aStatistically significant. ^bMyocardial infarction only; sudden deaths decreased from 13 to 4. Adapted with permission from Moser.⁶

Table II. Results of Early Studies of Antihypertensive Drug Therapy in Patients >80 Years

Significant reduction of 35% in strokes (mostly nonfatal) >35% in heart failure >20% in cardiovascular events
Nonsignificant reduction of about 20% in major coronary events
Nonsignificant increase of 10% to 15% in total mortality
Preliminary results of HYVET In 3845 patients with systolic, diastolic, and isolated systolic hypertension, there has been a significant reduction in stroke and mortality

Abbreviation: HYVET, Hypertension in the Very Elderly Trial. Reproduced with permission from Moser.⁶

coronary heart disease, combined CVD, and heart failure rates were all significantly higher with lisinopril than with chlorthalidone, and heart failure rates were higher with amlodipine than with chlorthalidone.¹ Combined CVD and stroke rates were significantly lower in the amlodipine compared with the lisinopril group in this older subgroup.³

DR MOSER: In very old people, aged 75 years and older, did the diuretic decrease BP more than lisinopril, for example? Was that consistent throughout the age group?

DR CUSHMAN: We have not reported the age subgroups cutting off at 75 or 80 years, but we plan to do so. I will be surprised, however, if there is any heterogeneity wherever we cut off the age subgroup. Race was the only subgrouping that showed heterogeneity, with even worse outcomes with lisinopril; the diuretic and CCB did reduce BP more than the ACE inhibitor did in blacks, but we couldn't attribute most of the outcome differences to BP differences.

DR MOSER: We accumulated good data on the benefits of treating hypertension in the elderly, and

these are summarized in Table I. What we were lacking after these trials were data in patients older than 80 years. STOP-2 had some patients aged up to 84 years, and I believe they reported that there were no differences in outcome in those people compared with younger ones. But we've been waiting now for 6 or 7 years for the Hypertension in the Very Elderly Trial (HYVET) report (Table II). That study has been ongoing for many years because of recruiting difficulties. It is a placebo-controlled study that compares placebo with a low-dose diuretic (sustained-release indapamide 1.5 mg/d) and additional ACE inhibitor (perindopril) therapy, if required. Mike, will you comment on these preliminary data from HYVET? Have they helped us in deciding whether to treat people aged 80 years and older?

DR ZIEGLER: These are unpublished data. For a long time, we have had suggestive but not conclusive data to justify treating the very elderly. But this study may have answered the question.

DR MOSER: They stopped it prematurely.

DR CUSHMAN: Yes, they announced that they stopped it because stroke and total mortality were

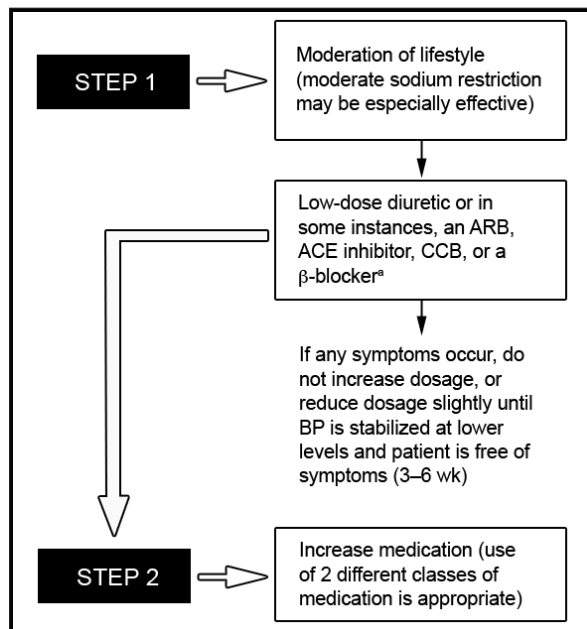


Figure. Approach to the management of elderly patients with hypertension. Abbreviations: ARB, angiotensin receptor blocker; ACE, angiotensin-converting enzyme; CCB, calcium channel blocker; BP, blood pressure. ^aIf initial BP is >180 mm Hg or patient has evidence of renal disease, coronary heart disease, or diabetes, the use of combination therapy for initial treatment represents a reasonable approach. Reproduced with permission from Moser.⁶

significantly reduced in the treated group, although they haven't given any specific numbers yet. It's possible that they are collecting all of the events before they publish the final results, which one would assume will be soon.

DR MOSER: Meta-analyses had reported a decrease in stroke and heart failure in the very elderly, but a statistically nonsignificant decrease in coronary heart disease events. There was no reported treatment benefit for cardiovascular death, and there was a nonsignificant 6% (–5 to 18) relative excess of death from all causes, so some people were worried about that (Table II).

DR CUSHMAN: The meta-analysis, however, included only a relatively small number of patients in this older than 80 years group: 1672. Most of us didn't believe that these findings, especially for mortality, were conclusive, and I think it's very reassuring now that we have definitive data that people older than 80 years do get mortality benefits, as well as other CVD event benefits, from lowering BP.

DR MOSER: Many have argued that if a stroke or heart failure could be prevented in the very old, that was enough to justify therapy despite the equivocal data on mortality. Now, based on other studies and HYVET we can justify treating

the elderly and the very elderly with a diuretic or a CCB or a diuretic plus an ACE inhibitor. It is well known that when you add an ACE inhibitor or an ARB to a diuretic, they are effective in the elderly. But, Mike, there are problems in treating the elderly; you just can't give someone a pill and lower the BP.

DR ZIEGLER: There are many problems in treating the elderly because their physiology is not the same as that of the young. For one thing, the brain of an elderly person senses BP changes poorly because baroreceptor sensitivity is lessened. When we experimentally increase patients' BP, their heart rates fail to lower enough because the patients lack that centrally mediated response.

DR MOSER: Or there's a lag in response.

DR ZIEGLER: This disturbs practitioners because even an adherent patient who measures BP levels 3 times a day gets upset when BP goes up to levels that are scary. They either end up in the emergency department, or they call the doctor because the BP doesn't come down. In a young individual with better baroreflexes, there is less variation in BP; when BP goes up, reflexes kick in, heart rate slows, and BP modulates. So number one, the variation in BP in the elderly is great and presents a therapeutic challenge.

The second consideration that concerned me when we saw the increased mortality data in some meta-analyses in the elderly was whether treatment of hypertension caused periodic hypotension due to poor baroreflexes. Falls in the elderly from dizziness, etc, can be fatal, so we really have to pay attention to the medication and doses because we may decrease standing BP and cause postural hypotension and falls.

DR MOSER: Do you monitor BP in the standing position in the elderly?

DR ZIEGLER: I routinely monitor BP in the standing position in patients who are taking any medication that might decrease standing BP. The monitoring characteristics must be understood, and unfortunately many physicians are unaware of the changes that occur with aging. Some believe that a decrease in SBP on standing is abnormal. As a matter of fact, a 10-mm Hg decrease in SBP on standing in an elderly person is common but is abnormal in a 20-year-old. Diastolic BP should not decrease on standing, even in the elderly. Monitoring is especially important if the patient is taking an α 1-blocker, as many elderly men with prostatism do, or if a patient is taking a high-dose diuretic. These 2 classes of drugs are the worst for causing postural hypotension.

The next thing to look at is diabetic autonomic neuropathy. If patients can't feel their toes, their BP is going to decrease when they stand up and they are at risk of a fall. Those considerations should guide therapy.

DR MOSER: Mike, what you describe is the real world. When you review the clinical trials, the incidence of falls is not increased, orthostatic hypotension (OH) appears to occur in a only few people, and dizziness and syncope were not major problems. Bill, you've participated in many of these trials.

DR CUSHMAN: I also have had quite a bit of clinical experience. My experience has been that, as Mike said, the α -blockers in particular but also the central agonists, such as clonidine, can cause orthostatic changes. Many of the people referred to me with resistant hypertension are still receiving clonidine treatment. α/β -Blockers also may cause OH. The diuretic story is interesting. You would think that these medications would have more effect, and we see that they do in some patients. However, there was a good study years ago with nursing home patients, and those who had the biggest problems with OH were those whose BP was uncontrolled and whose SBP was high. Of interest, diuretic usage predicted a lower incidence of orthostatic changes. But, clearly, there are some patients who will get volume depleted.

DR MOSER: Especially thin women . . .

DR CUSHMAN: . . . Particularly if they're taking other drugs that may promote OH, so you do have to be careful. I believe that controlling BP and avoiding some of the worst-offending drugs is important.

I will say this: we don't have many data on OH in clinical trials. SHEP measured it, but results have not yet been reported, other than baseline prevalence and associations—higher SBP and lower mean body mass index were associated with OH.

DR MOSER: Did they report many falls?

DR CUSHMAN: Falls were reported in 12.8% of the active group and in 10.4% of the placebo group; fractures occurred in 2.4% and 2.0%, respectively. In the Action to Control Cardiovascular Risk in Diabetes (ACCORD) trial, with 100% diabetics, we are systematically measuring orthostatic BP, and hopefully we'll have data on whether specific treatment or treatment goals are associated with increased OH and whether OH is associated with events or adverse effects. This is a group in which we're titrating treatment in many people to reach SBP goals of <120 mm Hg.

DR MOSER: Alright, Mike, if you have an elderly patient and you've decreased SBP from 170

to 150 mm Hg in the sitting position, but in the standing position it's always about 120 mm Hg and he or she feels fine, what do you do?

DR ZIEGLER: I, in fact, have a number of patients exactly like that who are referred to me. The first thing I do is question very closely about postural light-headedness.

DR MOSER: Okay, but the patient says that he or she is absolutely symptom-free.

DR ZIEGLER: Many people have, at one point, felt a little dizzy when they get up out of bed in the morning or when they have the flu or a hangover. Close questioning will bring out some early symptoms of postural light-headedness, and I find it troubling when antihypertensive therapy increases the more subtle signs that come out only with closer questioning. At that point, I worry about 2 things. The first is falls, and the second is hypoperfusion of organs. I don't know how good it is for the brain to not have enough blood for someone to think clearly. So, if there is postural hypotension, I begin to question the antihypertensive therapy. Has it been so aggressive that there is a potential for more harm than good? I look closely at that and individualize therapy to minimize postural hypotension; just as in treating diabetes, we have to watch carefully not to induce hypoglycemia.

DR MOSER: What if you quiz the patient very carefully and standing BP is consistently 120 mm Hg or so but there is no light-headedness or faint feelings, would you just say, okay, let's continue the same therapy?

DR ZIEGLER: Generally, I do say, okay, that is great. In fact, the necessary perfusion pressure for an older person to get blood from the heart to the brain when standing is about 80/50 mm Hg. So some people with very good arteries will tolerate a BP of 90/60 mm Hg while standing without symptoms. If that's the case, that's wonderful: lower is better. But when lower comes along with adverse effects, it's not necessarily better.

DR CUSHMAN: Looking at outcome data, we really don't have studies that have purposely titrated treatment to reach a BP level <140 mm Hg in the elderly population. On-treatment SBP levels in the treated group averaged in the low 140s [mm Hg] in SHEP, and those in the placebo group were 155 mm Hg. Now, obviously many people had BP levels <140 mm Hg.

DR MOSER: Those are sitting pressures?

DR CUSHMAN: Yes, they were sitting pressures. If I'm concerned about postural hypotension but a patient is not symptomatic, I may stop titrating medication when SBP is in the low 140s [mm

Hg]. So, I may not keep pushing to get to <140 mm Hg in a patient who has a substantial decrease in standing BP.

DR MOSER: Alright. We all set goals; we say in the elderly that you've got to decrease the SBP just as much as in the young, to <140 mm Hg. We tell physicians to do that. We often see practicing doctors just shaking their heads and saying, you know, this expert doesn't know what he's talking about. Half of my older patients can't tolerate that kind of BP. As it decreases from 160 to 170 mm Hg to \leq 150 mm Hg, patients often just feel bad—just nonspecific feelings. In fact, if you look at national statistics, most of the patients with uncontrolled BP have uncontrolled SBP. In at least some of these patients, BP may not be controlled because of intolerance to lower BP. Of course, many times doctors don't change therapy when they should. But let's say that you have a patient with a BP of 180/80 mm Hg, you're very conscientious, and you start treatment with a low dose of diuretic. SBP goes down to 160 mm Hg. You add a low dose of a CCB, an ACE inhibitor, or an ARB, and SBP decreases to 150 mm Hg. At this point, the patient calls and says, "I don't care, Doc, I just don't feel right." There is no severe postural hypotension, but the patient just doesn't feel right. He or she felt better with higher BP. Is this common? What do you do?

DR ZIEGLER: It's unfortunately quite common. Many elderly patients do not feel well, and in fact all patients are not going to feel well at some time, which they may or may not blame on medication. We really need to know the medication and be able to confidently tell them that we recognize that they do not feel well, but this particular medication does not cause the adverse effect you are describing. You really have to have confidence that you know the medication well enough to recognize its adverse effects.

DR MOSER: So, you might increase the dosage, with some confidence that it is not the medication causing the problem, in an attempt to get the SBP to <150 mm Hg. But the patient says, "I'm not going to take it; I feel terrible." Bill, what do you do?

DR CUSHMAN: Compliance with therapy is of the utmost importance. If the baseline SBP was 180 mm Hg and you've reduced it to 150 mm Hg with a goal of <140 mm Hg, but you have a patient who is convinced that taking more medication is going to make him or her feel sick, I think the better part of valor is to settle for a BP level of 150 mm Hg and keep the patient on medicine. If you push the patient and make him or her unhappy with your therapy, he or she may just quit all treatment. And then the SBP goes back up to 180 mm Hg.

DR MOSER: So there are some elderly patients for whom you know what the objective should be, but maybe you can't achieve it because of factors of interaction between you and a patient. Alright, what about trying this: your patient feels terrible with a reduction in SBP of 20 to 30 mm Hg, so why not give him or her a month or two to let the baroreceptors reset? Perhaps medication can then be increased and BP reduced after that time (see Figure for treatment algorithm).

DR CUSHMAN: I'm sure we all do this. Obviously, you want the confidence of the patients and you want them to know that you're concerned about them and you're going to work with them. That's one of the main things that I do when patients come to me. I believe that we all tell patients that if they're having problems, we will try to eliminate them. What I often find is that I may ultimately get back to the kind of regimen that I want them on, and they do fine. So, for example, if I start with one drug and then add a second and the patient is feeling bad, I may just switch to the combination of the two, and lo and behold, they tolerate that fine. Oftentimes, when it's those kind of general problems, it's not the drugs.

The other thing I'll do is try to convince patients that the drug they think they don't want to take actually is going to have a good effect on their outcomes. Many patients are willing to come back and actually do pretty well on the same medication if the problems are discussed.

DR MOSER: Do you think that some of this relates to patients' perception of what they read in the paper, for example, that a β -blocker is supposed to make them feel tired or that a CCB is going to cause swelling?

DR CUSHMAN: I think that's probably true; however, some medications are going to cause adverse effects, and we just have to be willing to change therapy if they do. Certainly, we see many patients who have a cough when receiving an ACE inhibitor. I am surprised at how often the cough goes away when we stop the drug. And if somebody has swelling on a high dose of a dihydropyridine CCB and you switch them and they do much better, we gain their confidence.

DR MOSER: What do you think is the percentage of patients older than 65 years with isolated systolic hypertension in whom you can reduce SBP to <140 mm Hg and keep them there? In the real world?

DR ZIEGLER: Even under ideal conditions, the success rate in my referral clinic for resistant hypertension still is only about 50%.

DR MOSER: Even with close follow-up?

DR ZIEGLER: Even under extremely close follow-up.

DR MOSER: Bill?

DR CUSHMAN: I don't have many patients in whom we can't reduce BP to goal levels.

DR MOSER: Are these mostly men?

DR CUSHMAN: I'm treating mostly men, that's right. That may make a difference; there may be more problems in women. In the clinical trials and in practice, however, we often find that goal levels can be achieved. In the Veterans Affairs (VA) health system, we achieve control rates in >70% of patients, with few age differences, and we often see patients with more difficult-to-control hypertension than we put in clinical trials.

So I believe that in the majority of, but obviously not all, older patients, we can get SBP down to goal levels.

DR MOSER: An encouraging note that we should add is that even if you don't reduce BP to goal and you only reduce it from 180 to 150 mm Hg, you're going to achieve a great deal of benefit. In all the clinical trials in the elderly that reported benefit, the difference was about -12 to -15 mm Hg systolic; even a decrease of 15 mm Hg is going to be significant in terms of outcome.

DR ZIEGLER: I think that's an important point. Frequently, we're presented with risk analyses that show a somewhat linear relationship with BP, but that linear relationship breaks down as the BP gets very high. And just clipping the top off of a very high BP has a beneficial effect.

DR MOSER: And, as Bill has pointed out in several publications, most of the clinical trials never achieved anything like the goal in many patients. Some of them obviously did, but the mean treated SBP levels were 145, 150, and 155 mm Hg in the major trials.

So, let's go back to a typical patient—a 75-year-old man with a BP level of 170/80 or 170/70 mm Hg. You are convinced that he ought to be treated. Some people are concerned that if the BP decreases too much and the diastolic BP goes too low, coronary perfusion may decrease. Are you concerned about that?

DR ZIEGLER: The controlled data from prospective trials suggest that that is not a problem and that most of the worry about that came from retrospective looks at trial results. I believe that people who were very ill tended to have low diastolic BP and subsequently did not do so well. That may account for what's called the J-shaped curve. We're still looking for the hook on that J in the prospective trials.

DR MOSER: So you believe that the possible increase in coronary heart disease events may occur in sicker people and has little to do with excessive lowering of diastolic BP?

DR CUSHMAN: I agree with Mike. When you titrate to lower BP levels, there have been few data to suggest increased risk, no matter what that level is. But, of course, we haven't had many trials in which we've titrated BP to very low levels. I actually was a coauthor on the SHEP data where we reported a J-curve when diastolic BP fell to <60 mm Hg.

DR MOSER: But, as reported, when the diastolic BP was <45 mm Hg, the event rate did not go up.

DR CUSHMAN: But again, as you noted, there were very few patients in this group. These people reflecting the so-called J-curve probably had worse disease; they had stiffer arteries so that diastolic BP levels were lower. This should not deter us from achieving the goal SBP levels that were achieved in studies. And, for the most part, I don't let any of the J-curve data deter me from achieving a SBP goal of 140 mm Hg.

DR MOSER: Now, let's ask how you would treat this 75-year-old person. You are convinced that lowering the BP by even by 15 or 20 mm Hg is useful. Other than sodium restriction, which may be especially helpful in the elderly, weight loss and exercise should be encouraged?

DR ZIEGLER: To be honest, I find significant sodium restriction difficult to accomplish, so I don't like to spin my wheels with patients. I would rather recommend that patients do something that may actually work. So I will talk to them about diet and exercise, and then as a first therapeutic option I begin with low-dose thiazide diuretics. I tend to start quite low with, for example, 12.5 mg of hydrochlorothiazide in the elderly because they tend to be fairly sensitive to it. I'm honestly a bit surprised with the physiology of the elderly who have diminished renal function. You would think that it would take a high dose of a diuretic to lower BP, yet my experience is that relatively low doses work fairly well if they don't have kidney disease.

DR MOSER: How often do you see patients with BP levels of 170/70 mm Hg and perhaps some left ventricular hypertrophy, which many of them have, but with no proteinuria and relatively asymptomatic? In other words, a fairly typical patient. How often do you see a patient like this?

DR ZIEGLER: Patients need to understand that there is a benefit to lowering BP, but they also need to understand that treatment doesn't have to break the bank or disrupt their lifestyle. I tend to schedule more frequent visits initially because patients

have questions. After that, I'll stretch out the time between visits.

DR MOSER: Let's say that you see the patient in a month and check potassium levels. BPs are not at goal levels. Do you increase the dosage of the thiazide?

DR ZIEGLER: I tend to either add an ACE inhibitor or switch to one of the generic combinations that have a diuretic/ACE inhibitor combination. These are now inexpensive because they are off-patent.

DR MOSER: Why not a CCB?

DR ZIEGLER: I find that once a person has begun taking a diuretic, an ACE inhibitor will give an additive effect. A CCB will further lower BP, but the BP lowering may be less than the additive effect of the individual diuretic plus the individual CCB.

DR MOSER: So, although an ACE inhibitor may not be as effective as monotherapy in the elderly, it is very effective with a diuretic.

DR ZIEGLER: That's exactly correct.

DR MOSER: What about an ARB with a diuretic? You won't have to be concerned about a cough?

DR ZIEGLER: Either one. The physiology of that patient is that they tend to be a little volume overloaded because they eat a lot of salt and have diminished renal function. If they start with a diuretic, the low renin status changes to a higher renin level and an antirenin agent will work.

DR MOSER: OK, so the patient is on an ACE inhibitor/diuretic or an ARB/diuretic combination, and you see him or her in a month and now BP is controlled at about 135/70 or 135/65 mm Hg. This is the result in about 50% of patients. How often do you see a patient like this?

DR ZIEGLER: At that point, I see the patient relatively infrequently if there are no other health problems. I see him or her more frequently if I'm worried about glucose and cholesterol; ordinarily, every 3 months is quite a reasonable time.

DR MOSER: Do you have patients perform home BP measurements?

DR ZIEGLER: I do. I know a lot of physicians who don't like patients to bother them with home BP readings, but I'm in favor of home BP assessment. If the patient drives me crazy with it, well I guess that's the price of good therapy.

DR MOSER: But you tell them that the BP level might vary by 20 or 15 mm Hg. Some people really worry about changes of 10 or 15 mm Hg.

DR ZIEGLER: I try not to disrupt my patients' lives by making them slaves to monitoring their health all of the time. When I have a patient who measures their BP 3 or more times a day because

they discover occasional high BPs, I tell them to do it 3 times a week.

DR CUSHMAN: Or I'll tell them measure BP at home 3 times in one day, once a week, or something like that.

DR MOSER: Bill, I think you do essentially the same thing as Mike.

DR CUSHMAN: Although I admit that if they have stage 2 hypertension . . .

DR MOSER: . . . Stage 2 is ≥ 160 mm Hg systolic or ≥ 100 mm Hg diastolic.

DR CUSHMAN: If the SBP level is ≥ 160 mm Hg and I don't think the patient is that frail, I'll go ahead and recommend starting with a low dose of two drugs. The main reason for that is that if somebody's got an SBP of, say, 180 or 190 mm Hg, even though the diuretic or CCB is going to lower it by 20 or 30 mm Hg, it's still going to take a long time and a lot more visits to get to goal.

DR MOSER: So you might start right away on the ACE inhibitor 12.5 mg thiazide combination or ARB 12.5 mg thiazide combination.

DR CUSHMAN: Right. Admittedly, because of our ALLHAT data I will use a CCB instead of the ACE inhibitor or ARB in black patients. Most of the time up until we completed ALLHAT, I would have used an ACE inhibitor or an ARB with a diuretic.

DR MOSER: Why wouldn't you just increase the hydrochlorothiazide from 12.5 mg to 25 mg if the patient has responded but BP is not at goal? Why not just double the dose of the diuretic?

DR ZIEGLER: I actually look at my patients closely for volume status, look at neck veins, listen to their lungs, press on their ankles, and try to evaluate whether they are volume overloaded. The majority are not, but in the ones who are indeed volume overloaded, it is just impossible to control BP until volume is controlled, so I will use a diuretic dosage appropriate to the patient's kidney function and sodium intake.

DR MOSER: You might need 25 mg of a diuretic in elderly patients with diminished kidney function?

DR ZIEGLER: Yes, particularly if renal function is diminished, as is often the case in someone who's had hypertension for a long time. In that case, you'd start treatment with a higher dose of a diuretic.

DR MOSER: Alright, last question, Bill. This patient comes in, he or she is taking an ACE inhibitor or an ARB with a diuretic or a CCB and a diuretic, and you see him or her first in a month and then 2 months later. The SBP level is still 155 mm Hg or so. What do you do in terms of getting to goal? Do you give up or say I've done quite a bit but not all that I should?

DR CUSHMAN: First of all, I usually don't stop at 12.5 mg of hydrochlorothiazide. Although everything Mike said is totally reasonable and logical, we have no outcome data with the 12.5-mg dose, even in the elderly. So I will often start with 12.5 mg, but I try never to stop there. I'll almost always go to 25 mg of hydrochlorothiazide. I will usually maximize the ACE inhibitor or ARB dosages within the ranges recommended. At that point, I may add the CCB and go to a reasonable dosage of that. But very often, I will change the hydrochlorothiazide to 25 mg of chlorthalidone, which appears to be more effective. Studies appear to indicate that it probably is.

DR MOSER: Is that too much in an older person?

DR CUSHMAN: It doesn't appear to be. We had patients older than 100 years in ALLHAT, and there wasn't any differential effect on outcomes by sex. Chlorthalidone was also used in the elderly SHEP population, and it had very favorable effects, as we have already discussed.

DR MOSER: And you picked chlorthalidone because it's a longer-acting drug and you have good outcome data with it?

DR CUSHMAN: We picked it because all the recent US studies had used chlorthalidone, and we knew what 12.5 to 25 mg of chlorthalidone would do in terms of outcomes. We didn't know what the lower dose of hydrochlorothiazide, which was and is popular, would do because we don't have any outcome data with the lower doses.

DR MOSER: Why don't doctors in the United States use chlorthalidone?

DR CUSHMAN: I'm sure a lot of it has to do with marketing. Clearly, hydrochlorothiazide, either by itself or in combination (eg, hydrochlorothiazide/triamterene), was widely used in the United States, whereas if you go to other countries, it may be a different thiazide.

Also, there was an early perception that when the 50 to 100 mg of chlorthalidone was used, it caused a lot of metabolic effects.

DR MOSER: Do you think it's worthwhile in a 70- to 75-year-old person who doesn't respond to a diuretic—25 mg chlorthalidone, for example—and a CCB or an ARB or ACE inhibitor to go to a third drug?

DR CUSHMAN: The third drug would be the CCB added to the thiazide, with either an ACE inhibitor or an ARB.

DR MOSER: So you do go to a third drug. Do you think it's worthwhile? In some cases, a patient may end up taking an ACE inhibitor or an ARB/CCB combination plus a diuretic; of course,

patients with diabetes or evidence of nephropathy should be taking an ACE inhibitor or an ARB as part of the treatment regimen.

DR CUSHMAN: Yes. And if the patient's BP remains higher than I want it to be, and he or she doesn't have symptoms, I'll go to a fourth drug. In ALLHAT, we were able to control BP to <140/90 mm Hg in 64.4% of participants aged 70 years or older after 5 years of follow-up; for those aged 55 to 69 years, BP was controlled in 66.3%.⁴

DR MOSER: In addition to the 12 other drugs the patient is taking for diabetes, dyslipidemia, arthritis, etc?

DR CUSHMAN: That's right. It depends on what else is going on whether you use an α -blocker in somebody with benign prostatic hyperplasia symptoms or spironolactone or another potassium-sparing drug if the patient tends to be hypokalemic. Very often, I use reserpine.⁵ The experience in SHEP, ALLHAT, and a number of other trials, including many VA trials, has been good with low-dose reserpine.

DR MOSER: Very low doses of reserpine. But what about α/β -blockers? They vasodilate, and they are physiologically more acceptable than β -blockers. Do you worry about them in the elderly because of postural hypotension?

DR CUSHMAN: I do, because of postural hypotension, but also we have no outcome data in hypertension with the α/β -blockers. Labetalol has always been a twice-daily drug, and I try not to use twice-daily drugs.

DR MOSER: Carvedilol is now a once-daily α/β -blocker.

DR CUSHMAN: Yes, carvedilol obviously was not a once-a-day drug and it was also previously expensive, but now it's once-a-day.

Again, we don't have any outcome data for these agents, but I would rather use something like that than a drug such as clonidine or methyldopa, which obviously cause a lot of adverse effects. I actually believe that α -blockers are not quite as bad as central α -agonists like clonidine, and adverse effects seem to be decreased if an α -blocker is combined with a β -blocker.

DR ZIEGLER: I would just confirm what Bill said. It's not rare in my referral hypertension clinic to have patients taking 5 antihypertensive drugs, if they are combined intelligently and used in low doses so that the adverse effect profile is tolerable. If you use combination agents where 2 agents are contained in a single pill, the patients don't rebel as much due to taking too many pills, and if you're careful to stick with drugs that aren't inordinately

expensive, then you don't get rebellion due to cost. I have many patients who are taking quite a few drugs whose conditions are successfully controlled with them, and they continue to take them. That being said, of course, compliance rates go down as the number of drugs goes up, and you do have to work with the patient more closely.

DR MOSER: So, let me summarize. I think we've come a long way over the past 20 to 30 years in our attitude toward hypertension in the elderly, not just in terms of systolic/diastolic hypertension but isolated systolic hypertension. We have good data on benefit from treatment of isolated systolic as well as systolic/diastolic in patients younger than 80 years, or even older, based upon preliminary data from HYVET. We all agree that a diuretic is a reasonable first-step choice, not in everybody but in the majority of elderly patients because of good response rates and outcome benefits. CCBs also are very useful and effective as monotherapy in the elderly, more so than β -blockers and other agents that block the renin-angiotensin system. But in many of these patients, especially those with diabetes or evidence of nephropathy, a diuretic plus an ARB or ACE inhibitor should be used. In some cases, it may even be prudent if the SBP level is >160 mm Hg to start with a combination of an ACE inhibitor or an ARB and a diuretic right away. We can expect to reduce stroke, heart failure, morbidity, and mortality from coronary heart disease with effective treatment.

There are going to be some patients in whom you will not reduce BP to below the goal of 140 mm Hg

without causing problems, and in those patients it may be prudent to back off and settle for something a little less. Nevertheless, we should continue to try to reduce BP to goal. Any closing remarks?

DR ZIEGLER: I think that is a good summary.

DR CUSHMAN: I agree. We will soon have important new information on treatment goals in the elderly from HYVET, and the ACCORD trial will report by 2009 or 2010 on whether it is safe and beneficial to treat to an SBP goal of <120 mm Hg.

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