

Expert Panel Discussion

The ALLHAT Study Revisited: Do Newer Data From This Trial and Others Indicate Changes in Treatment Guidelines?

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Following a hypertension symposium in Washington, DC, in November 2006, a panel was convened to discuss new data from the Antihypertensive and Lipid-Lowering Treatment to Prevent Heart Attack Trial (ALLHAT) and to revisit the significance of this trial in the management of hypertension. Based on these data and information from other trials, the expert panel also addressed the questions, "Is it time for a new Joint National Committee report?" and "Should the 2003 hypertension treatment recommendations be updated or are they still valid?" The panel was moderated by Marvin Moser, MD, Clinical Professor of Medicine, Yale University School of Medicine, New Haven, CT. On the panel were Suzanne Oparil, MD, Professor of Medicine at the University of Alabama in Birmingham, and President of the American Society of Hypertension (ASH); William Cushman, MD, Professor of Preventive Medicine and Medicine at the University of Tennessee in Memphis and attending physician at the Washington, DC, VA Medical Center; and Vasilios Papademetriou, MD, Professor of Medicine at Georgetown University in Washington, DC, and attending physician at the Washington, DC, VA Medical Center. This expert panel discussion was supported by Pfizer Inc and each author received an honorarium from Pfizer Inc for time and effort spent participating in the discussion and reviewing the transcript for important intellectual content prior to publication. The authors maintained full control of the discussion and the resulting content of this article; Pfizer had no input in the choice of topic, speakers, or content. (Please note that Dr Oparil's comments herein do not represent the official opinion of ASH.) (J Clin Hypertens. 2007;9:372–380) ©2007 Le Jacq

DR MOSER: ALLHAT (the Antihypertensive and Lipid-Lowering Treatment to Prevent Heart Attack Trial) was a landmark study, the largest hypertension study to date. It was randomized and blinded and compared several different modalities of treatment in more than 40,000 people. The results may not have been consistent with what had been anticipated. Bill, I wonder if you could very briefly summarize the design of the trial and the results.

DR CUSHMAN: The important aspect of ALLHAT was that it was a large study, double-blinded, and randomized. There are many other hypertension studies that are smaller and not blinded to what therapies patients receive. These are very important strengths of the ALLHAT study. The primary purpose of ALLHAT was

to determine whether 3 newer classes of drugs, angiotensin-converting enzyme inhibitors (ACEIs), calcium channel blockers (CCBs), or α -blockers, were superior to diuretics in preventing coronary events. This is where the controversy was when the study was designed in the early 1990s. The study also evaluated other events as important secondary outcomes. These included stroke, heart failure, and all other cardiovascular (CV) events, in addition to the coronary event outcome. The study was large to empower it to address the coronary issue, but this also gives it very good power to address other questions.

The ACEI used was lisinopril, which was the most frequently used ACEI at that time; the CCB was amlodipine, the most widely used CCB for the treatment of hypertension; and the α -blocker was doxazosin, a frequently used long-acting α -blocker.



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DR MOSER: These were the initial monotherapies. What if monotherapy did not reduce blood pressure (BP) to goal levels?

DR CUSHMAN: That's very important. The first drug used was blinded, and then we wanted a fairly equal distribution of the second drug. No drugs from the same classes as the blinded drugs could be routinely added as a second drug. For example, a β -blocker was the most frequent second drug class added, but a diuretic could not be added to the ACEI or CCB groups, and a CCB could not be added to the ACEI group.

DR MOSER: At the end of the study, many subjects were on 2 or 3 drugs. What kind of control rates did you achieve?

DR CUSHMAN: At the beginning of ALLHAT, about one fourth of the patients had BP below 140/90 mm Hg. Within 6 months, half of the patients were under control and at 5 years, two thirds of the patients were under control. About 68% were controlled in the diuretic group, 66% with the CCB as initial therapy, and about 61% in the ACEI-based treatment group. At the end of the trial, about 70% of subjects were controlled to below 140/90 mm Hg.

DR MOSER: Because dosages were titrated until goal pressures were achieved?

DR CUSHMAN: That's right.

DR MOSER: Do you believe that these levels of control can be achieved in the real world, not just in a clinical trial, if physicians follow the type of protocol in ALLHAT?

DR CUSHMAN: Absolutely, yes. We didn't think that it was possible in a community setting, but we have achieved this level of control in the Department of Veterans Affairs (VA) nationally.

DR MOSER: Okay. Now, one of the arms of the trial was stopped prematurely.

DR CUSHMAN: This was the only time that an α -blocker had been studied in a major outcomes trial. Doxazosin was stopped after an average of about 3 years of follow-up for 2 reasons. One was that there was a real safety issue. Heart failure was almost twice as frequent and strokes were 25% higher with the α -blocker than with the diuretic. These were both highly significantly different. The second reason was that there was little likelihood of seeing a difference in the primary coronary outcome even if the α -blocker arm had been continued for several more years. In light of the magnitude of the other CV differences, continuing the α -blocker arm was not believed to be ethical.

DR MOSER: So the study was continued with 3 groups—diuretic-, ACEI-, and CCB-based treatments.

DR CUSHMAN: Yes.

DR MOSER: And at the end of the 5-plus-year study in more than 30,000 subjects, the diuretic proved to be equal in terms of primary outcome and better in terms of some secondary outcomes?

DR CUSHMAN: This is also correct. The primary question that had been asked was whether or not the newer drugs were better. The study results indicated that there was no difference among the 3 drugs in coronary outcomes and that the CCB- or ACEI-based groups did not have a better CV disease outcome compared with the diuretic. A major difference between the CCB and the diuretic was about a 40% higher risk of heart failure with the CCB. Diuretic-treated subjects also had fewer strokes and heart failure events than the ACEI-treated subjects. Although BP was lowered more with the diuretic compared with the ACEI in black patients, where stroke outcome strongly favored the diuretic, analyses did not suggest that the BP difference explained all the differences in outcomes.

DR MOSER: Were you surprised about these findings or had other studies suggested that this might be true?

DR CUSHMAN: Other studies have reported that CCBs were not as effective in preventing heart failure. When we started ALLHAT, it wasn't clear that the CCBs were not as effective in preventing heart failure as some other antihypertensive medications, even though it was pretty clear that they didn't treat heart failure very well.

DR MOSER: So the primary outcome of coronary heart disease events among the 3 drugs was equal, but comparing the diuretic to the CCB-based therapy, there were more episodes of heart failure with the CCB?

DR CUSHMAN: Right. And that was true for every subgroup we looked at, whether it was black, white, men, women, older, or younger people.

DR MOSER: Did this include diabetics and nondiabetics?

DR CUSHMAN: Yes, diabetics and nondiabetics.

DR MOSER: What about results with lisinopril compared with the diuretic chlorthalidone?

DR CUSHMAN: As you mentioned, results showed that lisinopril was associated with a higher risk of stroke and a higher risk of heart failure than the diuretic. These differences were statistically significant and noted in most subgroups. In black patients, there was actually a greater difference in heart failure and stroke with the ACEI compared with the diuretic than in the nonblack population. In whites, heart failure was significantly higher in

the ACEI compared with the diuretic group, but stroke rates were not different.

DR MOSER: Many of us believe that it is the BP difference rather than specific drugs that accounts for much of the difference. As noted, there were BP differences between the lisinopril- and the diuretic-treated groups in the black population.

DR CUSHMAN: That's correct. But there really were few BP differences in the nonblack population and despite that, the heart failure rate was still higher. Lack of a BP difference in whites may explain why stroke rates were not different. Although BPs were not lowered in blacks quite as much with lisinopril, more than half of blacks had achieved goal BPs of below 140/90 mm Hg.

DR MOSER: Wasn't there about a 4- to 5-mm systolic difference between the ACEI and the diuretic in black and white subjects?

DR CUSHMAN: Yes, but when time-dependent adjustment for BP was applied, the relative risks for CV events did not change significantly in either racial subgroup. For example, for lisinopril compared with chlorthalidone in blacks, time-dependent BP adjustment only reduced the relative risk from 1.40 to 1.36 for stroke, from 1.30 to 1.26 for heart failure, and from 1.19 to 1.17 for combined CV events.

DR MOSER: But do you believe that might have affected the stroke difference?

DR CUSHMAN: Well, it could have, although as we said in our original paper, no matter how you analyze it statistically, we can't completely explain it. As you know, we did not measure BP 24 hours a day, so it could be the result of BP differences—but perhaps not BP differences that can be appreciated with usual clinic BP measurements.

DR MOSER: It is not surprising to me that lisinopril was not as effective in lowering BP in blacks as the diuretic or the CCB. Are there new data available about subgroups in ALLHAT? You mentioned that there was no difference in the primary outcome among the CCB, ACEI, and diuretic in elderly or young persons or in diabetic men or women, and that the differences noted with secondary outcomes were also consistent across all studied subgroups.

DR CUSHMAN: In general, all of the subgroups looked similar to what the overall results were. Obviously, we're looking further at subgroups and outcomes. One of the events that we have looked at in more detail is heart failure, since that is where the most consistent differences were. We have recently published more heart failure data in *Circulation* (2006;113:2201–2210). These data indicate that within the first year, there is actually a doubling of

the risk of heart failure for both the ACEI and CCB compared with the diuretic-treated subjects. And remember, about one third of people in each drug group were also receiving a β -blocker.

DR MOSER: What about diabetics or people with impaired fasting glucose?

DR CUSHMAN: Can we discuss this later? A few more observations about heart failure—the ACEI did seem to have some better effects after 2 or 3 years compared with the CCB in preventing heart failure. This is not noted for the first couple of years, so it probably is through some different mechanism of action than the diuretic. The ACEI never is better than the diuretic, but it seems that if you are going to prevent heart failure, a diuretic and an ACEI or perhaps an angiotensin receptor blocker (ARB) would be a good combination.

DR MOSER: Suzanne, it has been argued that a heart failure diagnosis may have been made because a lot of these people were on a diuretic before entering ALLHAT. They may have been individuals with left ventricular hypertrophy or borderline failure. When the diuretic was stopped and they were started on an ACEI, a CCB, or an α -blocker as part of the study, they went into heart failure. Another argument has been that the diagnosis was made on the basis of peripheral edema. How did you address these concerns?

DR OPARIL: This has been dealt with. Certainly there were patients who had their original nonprotocol diuretic stopped and did develop edema, but we counted them as edema, not heart failure. In fact, there have been a number of validation studies done, including reviewing data on all patients who had been hospitalized or had experienced fatal heart failure. By case-only analysis, there was no evidence for any statistically significant interaction between prior drug type (eg, diuretic) and treatment group for the outcome of heart failure overall or during the first year.

We did a careful chart review by cardiologists who looked at echocardiograms and magnetic resonance images and used other validation criteria to confirm a heart failure diagnosis. In fact, in the patients who were diagnosed as having heart failure at the site by their provider, the concordance was about 85% (*Am Heart J.* 2007;153:42–53). In other words, the heart failure diagnosis was correct in more than three fourths of all patients. I challenge anybody in general practice to do better than that.

DR CUSHMAN: And in those who weren't validated, it was usually because we just didn't have enough data.

DR MOSER: So the ALLHAT investigators were convinced that the heart failure was real and not secondary to changes in medication, and so on?

DR OPARIL: Absolutely.

DR PAPADEMETRIOU: Another point that confirms the opinion that the heart failure was real is the outcome data. Those patients who developed and were diagnosed as having heart failure in ALLHAT had a 6-fold increase in mortality, compared with those who did not have this diagnosis.

DR MOSER: Are the results of ALLHAT counterintuitive? ACEIs are great drugs in heart failure.

DR PAPADEMETRIOU: Well, ACEIs are great drugs for treating patients with heart failure, but ALLHAT data suggest that diuretics are as good or even more effective in preventing it.

DR CUSHMAN: Probably most of the patients who developed heart failure in ALLHAT did get put on an ACEI after they developed heart failure, although we don't have the data on this.

DR MOSER: Was there a difference in heart failure occurrence in blacks and whites that could be related to the BP difference? Maybe it was the BP, again, that made the difference.

DR CUSHMAN: As I mentioned previously, adjusting for BP differences had little effect on the relative risk for heart failure.

DR MOSER: Okay now, Bill or Suzanne, what about the patients with diabetes? As you know, we have been told by some of our colleagues that diuretics should not be used in diabetics or in people with impaired fasting glucose levels. ALLHAT looked at this very carefully and now has accumulated a great deal of data on this subject. What can you tell us about this? Do the data suggest that a diuretic is not a good idea in a diabetic or a person with impaired glucose tolerance?

DR OPARIL: I think we can say that in ALLHAT, the diabetics had the same outcome as the nondiabetics. The use of a diuretic-based regimen proved just as effective in controlling coronary disease outcome as the ACEI or CCB and proved somewhat more effective in some subgroup analyses.

We have to remember that we did not measure proteinuria specifically and we excluded people who had known chronic kidney disease. So it may be that the subtype of diabetic that might do better with ACEIs or ARBs is someone with more evidence of diabetic nephropathy, but clearly the 16,000 or 18,000 diabetics in ALLHAT did just fine on a diuretic-based regimen compared with the other groups studied.

DR PAPADEMETRIOU: I would say that this is rather good news. The fact that diuretics were as

good as ACEIs and CCBs in preventing CV events gives a lot more leeway to use them in the treatment regimen of diabetics. We need them to control BP. We see a lot of older patients with diabetes; they take a lot of medications and frequently have other comorbidities. Most of these patients have difficult-to-control hypertension and in many of them it is impossible to achieve guideline goals without a diuretic. The only way to control their BP is to make certain that they receive an adequate dose of a diuretic regardless of what else they are taking. Many of the older diabetics have comorbidities such as heart failure, renal disease, and coronary artery disease, and they develop fluid retention. Without diuretics, it's difficult to manage them effectively, alleviate their symptoms, or control their BP. It's good to know that the diuretics do not adversely affect their survival and do not cause more CV events.

DR CUSHMAN: While the diuretic turned out to be better in the diabetics and actually in every subgroup for one or more major outcome, I think one of the messages from ALLHAT is that all 3 of these classes of drugs are very effective. We don't have as much data with the ARBs, although they look like they should be in this group as well, if you look at the LIFE (Losartan Intervention for Endpoint Reduction) study and VALUE (Valsartan Antihypertensive Long-Term Use Evaluation) trial, where BPs were lower during the first few months with a CCB compared with an ARB, there were fewer myocardial infarctions with the CCB. Clearly, these are good drugs. Actually, when you look at CCBs compared with ACEIs, I think there are some surprising results.

DR MOSER: Many people were convinced that CCBs did not reduce myocardial infarction to the same degree as the diuretics or ACEIs.

DR CUSHMAN: CCBs and ACEIs were very similar for many outcomes. The ACEI reduced heart failure more than the CCB, but the CCB was better at reducing stroke and a combined CV disease outcome than the ACEI. On balance, it looks like other than for white men, the CCB actually had an edge in terms of being better than the ACEI, if you look at all the outcomes.

DR OPARIL: In these older high-risk patients in ALLHAT, the protocol did not allow the use of a diuretic in the ACEI group, and that may explain why the ACEI did not come out so well in this population.

DR CUSHMAN: Absolutely.

DR MOSER: Are you suggesting that ACEIs without a diuretic may not be as effective in reducing CV events as we have been led to believe?

DR OPARIL: Yes, without a diuretic.

DR MOSER: I certainly agree, we have to remember that all the studies reporting a benefit of ACEIs in diabetics used ACEIs and diuretics.

DR OPARIL: There had been a myth propagated by endocrinologists, nephrologists, and others that an ACEI is some kind of magic bullet for diabetics and certain other classes of patients. I don't think there's magic there.

DR CUSHMAN: Yes, I agree.

DR MOSER: Vasilios, what's the message that practicing doctors should take from the ALLHAT data indicating that you can control a high percentage of people and showing equivalence with the primary outcome among these 3 drugs, with some possible benefit in subsets in the diuretic-treated group? Have the ALLHAT results been accepted by practitioners?

DR PAPADEMETRIOU: I think the main message from the ALLHAT study and many other large outcomes studies is that treating hypertension to goal is the most important thing we can do for the patient with hypertension. In most patient populations, it doesn't matter how we do it. The benefit that is attributable to specific medications beyond BP control is rather small, if any. If you look at the totality of evidence, from ALLHAT and elsewhere, it's BP control that benefits the patient. There may be some additional benefit, depending on the population studied, but the benefit is small. ALLHAT should, but probably has not, put to rest the myth that diuretic-based regimens are not as effective as treatment with other medications.

In my opinion, at least some of the difference in stroke and heart failure outcomes in the ALLHAT study, in favor of diuretics—compared with the CCB or the ACEI—can be explained by better BP reduction. I think the lower BP in the diuretic-treated groups may explain at least in part the better outcomes.

DR MOSER: So you think that is what made the difference?

DR PAPADEMETRIOU: I think these differences can explain most of the differences in stroke. The differences in overall coronary events were not apparent—they were not obvious. I believe that you need much greater BP differences to see any difference in coronary events or in cardiac outcomes. If you look at the meta-analyses of the data from the BP collaborators, you need at least a 4-mm Hg difference in BP to observe any effect on cardiac events, whereas you can see an effect on stroke even with 1 or 2 mm Hg. In ALLHAT, we had a 2-mm Hg difference and we saw 15% fewer strokes in the diuretic-treated patients compared with the ACEI. In blacks, where we had a

4- or 5-mm Hg difference between the diuretic and the ACEI group, we saw a 40% difference in stroke.

DR MOSER: Did anyone go into the database and determine whether or not the benefit was greater in people with the greatest difference in BP?

DR CUSHMAN: For the most part, as I mentioned, we could not entirely explain the differences in outcome by the differences in BP, except in the α -blocker–chlorthalidone comparison. Here, the difference in stroke was explainable by the BP difference, but the difference in heart failure was not. And as I believe I also mentioned, where we had no differences in BP, we still noted some differences in heart failure outcome.

For the ACEI, diuretic, and CCB comparisons, we couldn't explain much of the outcome differences by BP differences.

DR OPARIL: At least by BP control at 1 year.

DR MOSER: Suzanne, not to belabor the point, but do you believe that the difference in BP between the diuretic and lisinopril can explain the stroke difference?

DR OPARIL: It could not be explained completely by BP differences.

DR CUSHMAN: It was in the black population that a BP difference was noted. But even looking at the integrated BP over the course of the study or at 1 year, we still couldn't statistically explain the differences in outcomes, but that doesn't mean that it's not the BP difference. Nocturnal BPs, which were not measured, could have been much different among the medications. We did look at whether patients who were controlled at goal BP level showed this difference; even though they were controlled, there was still an excess of heart failure with the ACEI and the CCB compared with the diuretic group.

DR MOSER: Suzanne, can you explain this?

DR OPARIL: I think you referred earlier to the fact that our measurements in these large randomized controlled trials are not precise BP measurements. People who make a career out of studying ambulatory BP monitoring for research, not for patient care necessarily, find that nocturnal BP levels count the most in determining outcome. So it is conceivable, as Bill suggested, that the BP patterns were different for the different drugs at night and this made the difference.

DR MOSER: In blacks, there are more nondippers.

DR OPARIL: Yes, and you couldn't pick up these differences in the clinic. That is something that should be studied more. And there are those who believe that benefits in HOPE (Heart Outcomes Prevention Evaluation) may have

resulted from medication being dosed at night even though everybody didn't take it at night.

DR MOSER: Now there have been some recent papers from ALLHAT with data relating to the significance of new-incident or new-onset diabetes (NOD) with various antihypertensive agents. An Italian study suggested that NOD had the same prognosis as pretreatment diabetes. But there were only 63 events in the 3 groups studied. Long-term data from the diuretic-based Systolic Hypertension in the Elderly Program (SHEP) did not confirm this. Many experts have used the study in Italy, however, to convince doctors that NOD, which is about 1% to 3.5% greater with diuretics compared with ACEIs, should be considered when making a decision about medication.

What did the ALLHAT study report about CV outcomes in people with impaired fasting glucose or abnormal glucose tolerance who received a diuretic, a CCB, or an ACEI? Bill and Suzanne, was clinical outcome adversely affected in these patients?

DR CUSHMAN: When the outcome results were compared among randomized groups within those with diabetes, impaired fasting glucose, and normoglycemia, there was no significant difference in the primary coronary heart disease outcome, except for a significantly higher risk of coronary heart disease with amlodipine compared with chlorthalidone in participants with impaired fasting glucose. Stroke was 31% more common in normoglycemic participants assigned to lisinopril compared with chlorthalidone. Heart failure was more common in diabetic and normoglycemic participants assigned to amlodipine or lisinopril than with chlorthalidone. So clearly, there was no evidence of superiority of a CCB or ACEI compared with a thiazide-type diuretic as initial antihypertensive therapy, regardless of glycemia status.

We have also recently reported from ALLHAT that fasting glucose levels increased in older adults with hypertension, regardless of treatment type. Participants taking chlorthalidone had a modestly higher risk of developing fasting glucose levels >125 mg/dL, but there was no conclusive evidence that this diuretic-associated increase in diabetes risk increases the risk of clinical events. For example, there was no significant association of change in fasting glucose at 2 years with subsequent risk for coronary heart disease, stroke, CV disease, total mortality, or end-stage renal disease.

DR OPARIL: One fascinating comment that came out of this analysis is that, when clinical outcomes for those who developed incident diabetes were analyzed by treatment group, those

randomized to lisinopril had an increased risk of developing coronary disease and heart failure, while those randomized to chlorthalidone did not. There is no obvious mechanistic explanation for this finding, but it is interesting to speculate that those who developed diabetes while on an ACE inhibitor treatment had worse underlying metabolic abnormalities and were therefore at increased risk for cardiovascular disease. Clearly, we need more research on the clinical significance of incident diabetes in treated hypertensive patients.

DR MOSER: Okay, so we have had more data from ALLHAT in the past 3 years and results of several studies on angiotensin-2 receptor blockers compared with CCBs. We also have another study comparing ACEIs and CCBs with β -blockers and diuretics and quite a lot in the literature about new modalities for diagnosis and perhaps some new approaches for treatment. Do we need new hypertension treatment guidelines? The last US guideline was in 2003. The British have just released a 95-page document. This was carefully done with good science, and carefully researched, but in my opinion, it is not useful for the practicing physician. Is it time, Vasilios, to do an update of the guidelines, or not? First let's take the diagnostic evaluation. Do we have enough new information in the last few years to change our approach to diagnosis?

DR PAPADEMETRIOU: I don't think the new information is sufficiently different from what we have advocated so far so as to mandate new guidelines and a new manuscript. I think that the most important thing is to try to implement what we have learned over the last 2 or 3 decades and try to evaluate patients who need an evaluation and get them under treatment on the correct regimens.

DR MOSER: What about C-reactive proteins; what about the newer data on ambulatory monitoring; what about new information on echoes? What about recent data on pulse-wave tracings or impedance cardiography? Many of our colleagues are advocating the use of these tests.

DR PAPADEMETRIOU: Well, all these new modalities are important and are scientifically interesting. They certainly enrich our knowledge and understanding of the relationship of elevated BP and vascular disease. But I don't think at the end of the day the results of any of them alter the way we should approach patients.

DR MOSER: So, if people have high BP, you're going to treat them, and if they have other risk factors you're going to treat them, regardless of what the C-reactive protein level is or what an echocardiogram shows?

DR CUSHMAN: What has not been done and what is really needed to determine whether these tests are clinically useful are careful, unbiased studies to determine differences in outcome between patients who receive these tests and those who do not. I just don't think that's been done. These tests correlate with a lot of things, but they don't tell us in this patient population that they're going to benefit from this or another treatment. One example of this is the number of genetic tests in the ALLHAT population. They haven't yet told us that a genetic marker will predict outcomes based on using one drug as opposed to another.

DR OPARIL: Okay, back to whether we need new guidelines or not. No, I don't think that any of the newer diagnostic modalities are ready for prime time in practice and do not have to be added to the JNC (Joint National Committee on Prevention, Detection, Evaluation, and Treatment of High Blood Pressure) recommendations of 2003. I think they are very important research tools, however, because as both of you pointed out, we still don't know exactly how to discriminate who needs treatment and who doesn't. Maybe there is a way to better stratify risk using these modalities, but we certainly do not have enough data to justify their use at this time.

DR MOSER: Okay. I think we seem to agree then that we don't need additions to the diagnostic evaluation recommendations that were in JNC 7. Actually, these recommendations haven't changed much since JNC I in 1977. But what about studies reporting that impedance cardiography helped to guide treatment? I find the data interesting but not convincing.

Studies were performed and treatment was changed based on results. People who had the procedure had better blood pressure control when compared with a group of people treated without the procedure. Most of the trial findings suggested volume overload and treatment were changed in the study group.

DR CUSHMAN: So they gave more diuretics.

DR MOSER: That's correct. This should be one of the things that is done routinely in any hypertensive who is not controlled. Anyway, it appears that we agree that you don't need new diagnostic evaluation guidelines; that recommendations for ambulatory monitoring, echocardiograms, and C-reactive protein levels and so on should be reserved for special situations, and that at present they are interesting research tools. We should continue looking at studies on vascular function; these might change treatment, but at present there are not enough data to recommend these as routine procedures.

What about lifestyle changes? Anything new that should be added in a new guideline?

DR PAPADEMETRIOU: I think that what we have known for the last 2 decades is valid today. Regular exercise, mostly aerobic exercise, weight loss, sodium restriction, moderation of alcohol intake, and so forth. Some data indicate that even resistance exercise may be beneficial and may favorably affect the lipid profile of the patient. Weight reduction is clearly beneficial. For each pound lost, it seems that there is a 1-mm Hg reduction in BP. A low-salt diet of about 100 mmol of sodium a day (or about 1 teaspoonful of sodium) and decreasing the amount of alcohol that is consumed are very helpful measures and we should try to implement them.

DR MOSER: But are there new data that should be added?

DR PAPADEMETRIOU: I don't know of any earthshaking data that mandate a revision of the JNC guidelines.

DR MOSER: Bill, what about the high-fruit and vegetable, low-fat diet or the DASH (Dietary Approaches to Stop Hypertension) low-salt component, is that something that should be reemphasized?

DR CUSHMAN: The problem is that reducing salt in a DASH diet didn't lower BP much more until you got down to 50 mmol a day.

DR MOSER: Very difficult to accomplish.

DR CUSHMAN: Low salt alone was fairly effective, if you could reduce it enough. But most of the benefit was from the DASH diet alone.

One of the lifestyle modalities that has been discussed was the use of a machine to regulate respiratory rate. Reduce this and lower BP. There were several members of the JNC 7 committee who had done studies with this machine. For the most part, they seemed pretty positive, but all of the trials had been done by the company that makes it. So I think that it would still be premature to conclude that this is useful until we get independent confirmation of benefit.

DR MOSER: I used this machine on myself for 2 weeks. I can tell you that it is relatively easy to get the respiratory rate down to below 10/min without the use of a specific instrument. In fact, go home tonight and practice taking a long deep breath and letting it out slowly; you'll find that you can achieve this decrease in respiratory rate. Whether doing this for 30 minutes per day or 2 hours per week will lower BP over the long term is still an open question; even if it does, this could be done without this type of machine. The manufacturer is heavily promoting its use. An ad in *USA Today* quoted someone who had

BP of 160/120 mm Hg and who used this machine. He claims that his BP decreased to 120/80 mm Hg. This type of promotion may do a great deal of harm. This approach is certainly not ready for prime time.

DR CUSHMAN: Right. There are a lot of approaches that don't work. Certainly, there are claims that are made, and I'd like to emphasize that patients should be discouraged from going out and buying something that hasn't been proven effective.

DR MOSER: Vasilios, is there anything significant that we should add to this section if a new report is put together? Should more emphasis be placed on sleep apnea and its treatment?

DR PAPADEMETRIOU: What Bill said I think is important and should be emphasized. People shouldn't spend money and energy on highly publicized tests with unproven benefits. There is little reason for new guidelines to advocate these. The data on sleep apnea are important. Obese patients with resistant or difficult-to-control hypertension should be tested for sleep apnea and should be treated with appropriate devices (continuous positive airway pressure). Effective treatment of sleep apnea has a dramatic effect on BP control. It should be mentioned somewhere that high-calcium or even high-potassium diets don't necessarily lower BP.

DR MOSER: I think the JNCs have always said that the data on calcium, potassium, or magnesium as BP treatments are not definitive.

DR PAPADEMETRIOU: Right.

DR MOSER: A high potassium intake may lower BP by a few mm Hg. What I'm trying to establish here is, is it necessary to formulate a new guideline to add more tests or procedures for the routine diagnostic evaluation and new information about lifestyle changes? If there is not much to add, then a 1- or 2-page reiteration of previous reports would be adequate, with some reemphasis of previous recommendations for nonpharmacologic therapy. Are we in agreement about this?

DRS PAPADEMETRIOU, CUSHMAN, and OPARIL: Yes.

DR MOSER: Now the question is, do we need new guidelines for pharmacologic therapy? Suzanne, what would you do if you were redesigning the pharmacologic treatment algorithm?

DR OPARIL: First, let me present the National Heart, Lung, and Blood Institute's point of view, which is that we need integrated CV disease guidelines. What we're trying to do is prevent stroke, heart attacks, heart failure, and chronic kidney disease. Just treating BP may not do that. I see many patients, particularly older women, who are

being very aggressively treated for their BP but not for comorbidities like peripheral vascular disease or coronary disease. For example, BP is controlled but the patient is not on a statin. Or the patient has had a stroke and is not on appropriate secondary prevention measures. So we do need to consider hypertension guidelines within a broader context.

DR MOSER: What if we were writing an updated hypertension guideline and also emphasized in a strong statement that people with elevated BP and at high CV risk should be on aspirin, statins, etc, etc?

DR OPARIL: Also, some comments about diabetes management. Now that obesity and diabetes are becoming so common, many physicians who were trained more than 10 or 15 years ago don't know as much as they should about treating type 2 diabetes. I think that the most important thing we need in a new guideline (and this is in JNC 7) is a reemphasis on treatment methods. Write things down for patients. Many of us are poor at health services research. We don't know how to get patients to do things, how to get them to be adherent with pills, let alone lifestyle changes. The VA and others such as Kaiser Permanente have demonstrated dramatic improvements in adherence, compliance, and BP control by establishing good follow-up approaches. We'll have to wait a little while to see whether this improves outcome, but physicians in practice should know about these methods. So for that reason, even if there is little difference in what you do for diagnosis or exactly what you do for lifestyle changes, or even if there is nothing new that you do for treatment, we must reaffirm what the best minds think is the state of the art for delivering good care.

DR MOSER: So in the pharmacologic section, you would like more emphasis on overall CV risk management and to improve the delivery of care.

DR CUSHMAN: I think part of the puzzle that is often missing is clinical inertia—the fact that health care providers do not always change or titrate medications to achieve goal BP. This was noted in JNC 7, but I think that since then we've been able to demonstrate that certain systems, for example, the VA, do a reasonable job of follow-up and this may help to overcome clinical inertia and go a long way toward improving BP control. We now have more data on systems improvement and improving physician inertia. That's one thing we could add if a new report is considered.

The only thing I would change in the initial algorithm for the treatment of hypertension would be to give less priority to the β -blockers among the classes that we could use as initial therapy.

DR MOSER: Would you change the basic algorithm?

DR CUSHMAN: Not too much. I personally think that we should emphasize the classes on which we have the best outcome data and the fact that they combine very well. I would emphasize diuretics, ACEIs or ARBs, and CCBs as the mainstay of therapy because those 4 classes have the best outcome data in hypertension and they combine well. I would not, however, recommend routinely combining an ACEI with an ARB. We also have more data on the use of 2 or more drugs, and we should reiterate the concept to always include a diuretic in multidrug regimens. The JNC 7 also did not give very much information on how to combine drugs. That is something we frequently see in patients who are referred to us and are refractory. They are on 2 or 3 classes of drugs that don't add very much to each other.

DR MOSER: And you would note that a CCB/diuretic is an acceptable combination.

DR CUSHMAN: Yes. The VALUE study used that as one arm of the trial, with good results.

DR MOSER: One study many years ago reported that they were not additive, but our data and other studies indicate that they are. So if we were going to have another guideline (and no one is saying we should or should not), you would emphasize overall CV treatment, you would de-emphasize β -blockers, you would keep part of the algorithm that suggests thiazides as initial therapy in most patients and if not, ACEIs, ARBs, or CCBs. We should emphasize the use of multiple drugs—diuretic/ACEI, diuretic/ARB, diuretic/CCB, or CCB/ACEI, and suggest β -blockers as third- or fourth-step agents except in people with angina,

heart failure, or post-myocardial infarction. Is that fair?

DR PAPADEMETRIOU: Or with tachycardias.

DR MOSER: Right. So would this new guideline be helpful for the practitioner?

DR OPARIL: Yes, I think there is recent trial evidence that's relevant and more data about dealing with compelling indications like heart failure and renal disease. So there are some new things that can be presented to busy physicians who may not have time to stay up-to-date. Guidelines also help to give information about the level of evidence. Representatives of pharmaceutical companies who provide a great deal of information to physicians tend to overstate the benefits of one treatment over another, so providing guidelines based on good scientific data is useful. Practitioners want new guidelines.

DR MOSER: So to summarize: there may not be much to add to the diagnostic evaluation or non-pharmacologic approach sections to previous JNCs but based on recent data there are some changes in the pharmacologic treatment algorithm that may be beneficial to the practicing physician. But perhaps we do not need an extensive document.

If the National Institutes of Health decides to do an overall CV risk factor prevention paper, that would be quite different. Perhaps, however, an updated JNC in 3 or 4 pages is indicated at this time. It is difficult to do this with a large committee since there are so many people with different ideas, but it should be tried. Is this fair?

DR OPARIL: That's fair. And of course, every country in the world is planning or is in the process of doing new guidelines. It is not a good idea to ignore this and do nothing.

Thank you.