

## Expert Panel Discussion

## Control of Blood Pressure: Does It Matter Which Agent You Use?

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*A panel was convened to discuss the question, "Is blood pressure lowering the sole determinant of outcome, or do specific drugs make a difference?" The panel was moderated by Marvin Moser, MD, Clinical Professor of Medicine at the Yale University School of Medicine, New Haven, CT. Panelists included Norman Kaplan, MD, Clinical Professor of Medicine at the University of Texas Southwestern Medical Center at Dallas, TX, and William Cushman, MD, Professor of Medicine at the University of Tennessee in Memphis, TN. The discussion was supported by Boehringer Ingelheim, and each author received an honorarium from Boehringer Ingelheim for time and effort spent participating in the discussion or 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. 2007;9:964-973) ©2007 Le Jacq*

DR MOSER: Norm, we have data from clinical trials and from extensive clinical experience to suggest that blood pressure (BP) lowering itself makes the difference in outcome, that the degree to which you lower BP is the determinant of regression of left ventricular hypertrophy, reduction of strokes, reduction of heart failure, and decrease in coronary heart disease events. There are some experts, especially in Europe, who have concluded that based on several meta-analyses, it is clear that benefit accrues just from lowering BP. On the other hand, there are some experts who claim that some medications produce benefits beyond BP, and have specific effects beyond lowering of BP that account for benefit.

Would you like to start by giving us some examples of the first part of this equation? Are there studies to indicate that whether you use a treatment regimen based on a  $\beta$ -blocker, a diuretic, an angiotensin-converting enzyme (ACE) inhibitor, a calcium channel blocker (CCB), or an angiotensin receptor blocker (ARB), there appears to be little difference in outcome? The lower the BP, whatever

you use, the better the outcome. Give us examples of some of these trials.

DR KAPLAN: In almost all the trials that have shown any difference in outcome, there were also differences in BP control. In an analysis of the results of comparative trials published within the past 2 years, there appeared to be no significant difference in outcomes with all the different classes of drugs if the BP reduction was similar.

That is probably the strongest single piece of evidence for BP level and not specific drugs making the difference. There's one exception that I'm aware of. The Losartan Intervention for Endpoint Reduction (LIFE) trial, in which there appeared to be equal BP reduction but a difference in outcome. An ARB-based treatment decreased cardiovascular events, especially stroke, to a greater degree than a  $\beta$ -blocker-based regimen.

An example of the importance of the degree of BP reduction is the Anglo-Scandinavian Cardiac Outcomes Trial (ASCOT), where the trial ended with most patients receiving a combination of either a CCB plus an ACE inhibitor or a  $\beta$ -blocker plus a diuretic. There was a better outcome with the ACE inhibitor/CCB combination but there was



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a 5/2-mm Hg difference in the BP level reached. The difference in outcome is likely to be explained by the fact that there was a difference in BP.

DR MOSER: So you seem to favor the concept that it's mainly the BP level that makes the difference in outcome.

DR KAPLAN: Absolutely. I think that there are a number of analyses that have been done, including that of the Blood Pressure Lowering Treatment Trialists' Collaboration, that have reviewed the data from all clinical trials and concluded that lowering BP is really the main determinant of outcome.

DR MOSER: Okay. Bill, do you want to add any comment about specific trials that confirm what Norm is saying? The United Kingdom Prospective Diabetes Study (UKPDS) is always referred to to pin down that concept. Do you want to describe that trial for us?

DR CUSHMAN: I think it's perhaps a bit more complex than just looking at one trial. First, let me say that I do think that BP reduction is extremely important based on the evidence we have, but it's not entirely clear that it doesn't matter which drugs you use. Actually, if it didn't matter which drugs we used, we certainly would be using reserpine and certain other drugs a lot more frequently, even as initial therapy. But I think we all believe that we should predominantly use the drugs that have done the best in outcome studies, including several classes of drugs that lower BP but are also well tolerated.

There are several trials like UKPDS, in which the lower BP group benefitted and, as Dr Kaplan mentioned, throughout history where we have lowered BP effectively, we've generally gotten beneficial effects on outcomes. But there are exceptions.

DR MOSER: Bill, we are going to cover the differences between classes of drugs, but UKPDS is always pointed out as a clear example, where a  $\beta$ -blocker-based regimen was compared with an ACE inhibitor-based group and the overall outcome was no different. There was a great difference, however, in one group that had a 10/5-mm Hg greater decrease in BP compared with a group with less effective BP control. In the patients in whom this lower BP was achieved, outcome was significantly improved but there was no difference between different medication groups.

DR CUSHMAN: Let me comment on that. UKPDS is certainly one of our landmark studies to imply that lowering BP is effective, particularly in diabetic patients, where they achieved a BP of around 144 mm Hg systolic in the intensively treated group. Both treatments were equally beneficial, and, if anything, there may have been a trend for

the  $\beta$ -blocker group to do better. But UKPDS was too small a study to really look at comparisons between drugs. We need much larger sample sizes, with thousands of patients in a group, to tell with much confidence the difference in major outcomes between 2 drugs. Differences have been seen in some other studies.

The other study that is often used to show the benefit in reducing BP in diabetes is the Hypertension Optimal Treatment (HOT) study. In the HOT trial, similar to UKPDS in this respect, a nice benefit was observed in the diabetic group that had a diastolic BP goal  $\leq 80$  mm Hg, compared with the group with a diastolic BP goal  $\leq 90$  mm Hg.

DR MOSER: There was only a difference of 4 mm Hg or 81 mm Hg compared with 85 mm Hg between the lowest group and the highest. So just a 4-mm Hg difference in diastolic BP made a great difference.

DR CUSHMAN: That's right, and yet if you look at the entire HOT study, which included almost 19,000 participants, there was no benefit to achieving the lower BP.

DR MOSER: Right, except in diabetic persons.

DR CUSHMAN: But the benefit of lower BP was only seen in the diabetic subgroup, which was a smaller proportion of the study. We have some other examples where lower BP has not achieved anything additional in terms of further reducing cardiovascular or renal events.

DR MOSER: Norm, what about studies like the Heart Outcomes Prevention Evaluation (HOPE), which is an example of an ACE inhibitor-based program. By the way, all of the clinical trials are not monotherapy trials: they are all trials of multiple drugs compared with multiple drugs. In the HOPE trial, an ACE inhibitor was used with other drugs in some participants in whom results were compared with those in a group of people who did not receive the ACE inhibitor. A dramatic difference in outcome in favor of the ACE inhibitor group was noted between groups despite what appeared to be little difference in BP levels between the groups. Only about a 2–3/1-mm Hg difference was seen. Will you comment on that trial?

DR KAPLAN: Yes, there was a small difference observed with BP readings taken in the morning. Ramipril was given at bedtime, which was likely to result in a bigger morning effect because of the morning surge of BP. For whatever reason, the medication was given at bedtime and BP was obtained some time during the day after the medication had been given at night. This major difference in outcome was found with minimal BP effects, but 3/1 mm Hg is still a significant difference. When you

look at large population data, the difference that looks small really can be compounded into a much greater difference, at least in some patients. If the average was 3/1 mm Hg, that means that some patients had a much greater BP effect. Clearly, some patients had greater BP reductions.

But there is a set of data from a small group, 38 patients altogether, from the HOPE population, in which 24-hour ambulatory BP levels showed a much greater BP difference of about 17/9 mm Hg during the night.

DR MOSER: As you might expect with a drug being given at bedtime.

DR KAPLAN: At bedtime, exactly. I believe that many have commented that with a 3/1-mm Hg difference, it was clear that this BP difference was not based on the peak of the medication's action. If it had been, a greater BP difference would have been reported between those who were given ramipril and those who were not.

I think there's no clear answer. No other ambulatory BP readings were obtained in the majority of patients, and we should be careful to extrapolate the effect noted in some 38 patients compared with almost 10,000 patients in the HOPE trial. But it does bring up the probability that, again, it's not the medication as much as it is the effect of the medication on BP. We can keep coming back to that same argument.

DR MOSER: Now there are going to be some studies we'll talk about in which there seemed to be a difference with use of different drugs. Bill, do you want to comment on the Antihypertensive and Lipid-Lowering Treatment to Prevent Heart Attack Trial (ALLHAT)? In ALLHAT there was a statistically significant reduction in heart failure with the diuretic- compared with the CCB-based treatment regimen and significantly fewer strokes and heart failure with the diuretic- compared with lisinopril-based treatments, although the primary coronary heart disease outcome among the diuretic, ACE inhibitor, and CCB groups was not different. Do you think the differences in BP outcome made that difference? I know that you analyzed these data and I believe that you concluded that the BP difference may not have been enough to explain the difference in outcome. Perhaps the difference in medications made a difference.

DR CUSHMAN: I think ALLHAT illustrates the fact that there are different effects on different cardiovascular and renal outcomes. So in ALLHAT, for example, none of the 4 drugs that were used (a diuretic, an ACE inhibitor, a CCB,

and an  $\alpha$ -blocker) showed any differences in coronary heart disease outcomes.

DR MOSER: By the way, this is the only double-blind trial of all the trials we're going to discuss. Most of the others were not blinded to drugs; they were blinded to outcome, the so-called prospective, randomized, open-label, blinded end point evaluation (PROBE) design. But ALLHAT was a very well-designed blinded study.

DR CUSHMAN: Of course, many of the other trials used  $\beta$ -blockers or diuretics as the control group. There has been a lot of concern about whether  $\beta$ -blockers really should be included as a "standard of care" in hypertension, especially in the elderly, who were the predominant age group studied in many of the trials. Within ALLHAT, as I said, we found no differences in the coronary outcomes despite the fact that on average there was about a 1- to 2-mm Hg lower systolic BP with the diuretic than with the other classes. CCB use actually resulted in about a 1-mm Hg lower diastolic BP level. So there was very little difference in BP levels between the CCB and the diuretic.

DR MOSER: To account for the difference in heart failure.

DR CUSHMAN: Right. So what we saw were differences in heart failure and stroke. Heart failure was almost twice as common in the  $\alpha$ -blocker arm, for example, and about 40% higher in the CCB arm than in the diuretic arm. As a matter of fact, if you compare the CCB with the ACE inhibitor, even though the CCB lowered BP to a greater extent, the ACE inhibitor actually lowered heart failure rates more than the CCB.

DR MOSER: So, in this case, there is a difference that may not depend on BP; it may depend on some other physiologic changes.

DR CUSHMAN: Right. We've done many statistical analyses to try to explain the differences in outcomes based on BP. We have been unable to show that BP explained the differences in outcomes based on several analyses; however, that doesn't mean that it's not the BP difference, because we're not measuring BP 24 hours a day, every day. It is possible that BP levels, whether overnight, 24-hour, or central BP readings could, in fact, be accounting for these differences in outcome. The important clinical point is that we can't just say, for example, if you use an  $\alpha$ -blocker and can lower the BP to <140/90 mm Hg, you're going to get good results. As a matter of fact, it's strongly suggested in the data that you're still going to have many more strokes and many more heart failure cases if you lower BP with an  $\alpha$ -blocker as opposed to other drug classes that we commonly use.

DR MOSER: In ALLHAT, was there a major difference in BP between the diuretic component and the  $\alpha$ -blocker component?

DR CUSHMAN: There was a 2- to 3-mm Hg difference in systolic BP.

DR MOSER: That's all there was? And yet a major difference in heart failure.

DR CUSHMAN: The doxazosin group had 80% more heart failure cases. And stroke rates were 26% higher with the  $\alpha$ -blocker.

DR KAPLAN: But that comes back to the issue about what we call small differences really having a fairly large population-wide impact. We all know that the ALLHAT differences were just a few mm Hg, but that small a difference could make a difference as far as outcomes were concerned.

DR CUSHMAN: Certainly, I agree. A lot of things we're not measuring could explain the difference, too. All medications have a variety of effects. If the differences we saw are from BP effects only, then I think we have to say that lowering BP with a thiazide-type diuretic does a better job of lowering BP in ways that we didn't measure and that we can't fully appreciate in this study. But it is entirely plausible that some benefits of thiazides are independent of effects on BP.

Now to get back to what Norman has said, in most studies that showed differences, it turned out that the medications or the regimen that lowered BP better did do better at least in certain categories of outcome.

DR MOSER: In ALLHAT, a good part of the stroke benefit with diuretics compared with the other drugs occurred in black patients, in whom BP was lowered more with a diuretic than, for example, with an ACE inhibitor. Is that correct?

DR CUSHMAN: Actually, the BP differences, in the context of what we're talking about, were fairly substantial in black patients between the diuretic and the ACE inhibitor: 3- to 5-mm Hg systolic over the course of the trial. But time-dependent BP adjustment did not significantly alter differences in outcomes for the lisinopril to chlorthalidone comparison in blacks.

DR MOSER: And you can't attribute the difference between the diuretic and the CCB in terms of heart failure to BP difference. Was there any difference in BP outcomes in blacks? Because CCBs are just as effective in blacks as diuretics are in terms of BP. Was there a difference in heart failure outcomes?

DR CUSHMAN: Yes, the heart failure difference was equally higher with the CCB in the black and the nonblack populations.

DR MOSER: Despite the equal degree of BP lowering?

DR CUSHMAN: That's right, with no real difference in BP. Now the heart failure rates with the ACE inhibitor in blacks was 30% higher than with the diuretic; although there was still a difference in whites, it was less substantial. These results are consistent with reports of worse BP control with lisinopril in blacks. The majority of the blacks, however, had BP levels <140/90 mm Hg with lisinopril, so this wasn't terrible BP control, and yet we did see this difference.

I want to comment further on ACE inhibitors and ARBs. There probably is, in my opinion, a beneficial effect of renin-angiotensin system inhibition on heart failure if you look at both the Valsartan Antihypertensive Long-term Use Evaluation (VALUE) and ALLHAT. The CCB lowered BP as well or better than the ACE inhibitor or ARB in both studies. But after 3 years or so, you started seeing a benefit of the ACE inhibitor and ARB on heart failure prevention compared with the CCB, despite the fact that the CCB was better at lowering BP. I think there is something there, but it's not as dramatic as people may think in terms of the remodeling effect of ACE inhibitors and ARBs. In VALUE, the difference actually wasn't statistically significant I think, in part, because both groups frequently received a diuretic. But the pattern is similar to what we saw in ALLHAT, in which the ACE inhibitor, after 3 years or so, started doing better at preventing heart failure than the CCB (-13%;  $P=0.007$ ).

So, for certain events, I think there are differences in outcomes between drugs that are not explained by BP differences, even though I certainly believe that the majority of benefit, although we've not proved it from all the studies, is from BP lowering.

DR MOSER: We are going to get to some specifics, but you make a point and that was shown in very small studies; the Fosinopril vs Amlodipine and Cardiovascular Event Trial (FACET) study and the Appropriate Blood Pressure Control in Diabetes (ABCD) study reported some differences in outcome. ACE inhibitors apparently were more effective in reducing events than the CCBs. Those are small studies. Do you agree with that, Norm?

DR KAPLAN: I was just going to say that the only trial in which I think there was a clear difference between effects on BP and outcome was the LIFE trial. I don't know of any other study where there was a virtual identical BP reduction but with different outcomes. As you pointed out, about 80% of patients in this trial were also taking a diuretic, but the comparators were an ARB and a  $\beta$ -blocker. Those who were taking the ARB losartan did have better outcomes.

DR MOSER: Tell us what that trial was, Norm.

DR KAPLAN: This was a comparison between losartan plus other medications necessary to lower the BP vs an atenolol-based treatment regimen in hypertensive patients with left ventricular hypertrophy (LVH). The primary end point was cardiovascular morbidity and death, a composite end point of cardiovascular death, myocardial infarction, and stroke.

DR MOSER: By the way, in almost all the comparator trials with a  $\beta$ -blocker, atenolol was given once a day. In the International Verapamil-Trandolapril Study (INVEST), it was twice a day.

DR KAPLAN: That, of course, brings up the fact that atenolol is probably not a once-a-day drug, but that's another issue.

DR MOSER: Norm, most of the benefit in the LIFE trial was in stroke reduction, although overall the cardiovascular events were not statistically different between groups. Is that correct? The ARB group had fewer strokes than the  $\beta$ -blocker group.

DR KAPLAN: Yes. That, of course, poses an interesting question. Why should protection against coronary disease and stroke differ? In fact, myocardial infarction was slightly more prevalent in the ARB group. I believe that it comes around to the issue of central BP. That issue was brought up with the results of the Conduit Artery Function Evaluation (CAFE) substudy of the ASCOT trial, in which both central and peripheral BP levels were measured in about 200 patients. There was a difference; there was an equal BP effect peripherally with a  $\beta$ -blocker-based vs a CCB-based regimen, but there was a difference in central BP.

The  $\beta$ -blocker, presumably by slowing the heart rate, allowed the pulse pressure wave to come back and increase the central systolic pressure, whereas with the other drugs, CCBs or ACE inhibitors, there was a significant reduction in the central BP. Since the brain is fed blood from the central area, the brain vessels were presumably exposed to higher pressures, even though the peripheral pressures were the same. The fact that the central pressure was different means that the brain was exposed to a higher level of pressure than would have been expected.

DR MOSER: So in the LIFE study, it may have been that the  $\beta$ -blocker regimen was reducing the peripheral BP almost the same as the ARB, but not the central BP.

DR KAPLAN: That's right.

DR MOSER: When you do a meta-analysis of the trials,  $\beta$ -blockers turn out not to reduce stroke as much as CCBs, for example, but reduce coronary events to an equivalent degree.

DR KAPLAN: Right. The Swedish investigators and others have published a number of meta-analyses that have shown that  $\beta$ -blockers, at least as they have been used in these clinical trials, have been associated with a 13% higher prevalence of stroke when compared with comparator drugs. It is important to again point out that most of the studies used once-daily atenolol, and this may not have provided early morning BP protection.

I think it is important to appreciate that no one has said that  $\beta$ -blockers are causing stroke. It's just that they do not appear to be as protective against stroke as other drugs with equal BP reduction as we measure it in usual practice.

DR MOSER: One caveat, though. All the studies that we're talking about, and correct me if I'm wrong, are studies in the elderly. We know that  $\beta$ -blockers do not reduce BP in the elderly as much as, for example, CCBs or diuretics.

DR KAPLAN: Right.

DR MOSER: I personally believe that the Europeans are wrong in saying that  $\beta$ -blockers are not first-, second-, third-, or even fourth-step drugs in the management of hypertension.

DR KAPLAN: Oh, I think that we all appreciate that for certain conditions—post-myocardial infarction, congestive heart failure, tachyarrhythmias—there are definite indications that  $\beta$ -blockers should be a primary drug. They should be selectively given for particular indications, particularly in the elderly.

DR MOSER: Let me summarize what we've said so far, and then we're going to go into some other trials in which it appears that specific drugs did make a difference.

So far, I believe that we agree that most of the benefit in reduction of cardiovascular as well as cerebrovascular events accrues from the degree to which you lower BP. We have evidence from UKPDS, the HOT study, and other trials. Now in 2 of the large recent trials, the VALUE trial and the ASCOT, the differences in BP appeared to be minimal. But, as Dr Kaplan pointed out, a minimal difference of 3 to 5 mm Hg in a population may make a big difference. In VALUE, the difference was in the first few months of the trial, where a CCB was more effective in lowering BP than an ARB; in ASCOT, the CCB was more effective in lowering BP than the  $\beta$ -blocker during the first few months. Many experts believe that this difference may have made the difference in outcome, that reduction of BP in the first 4 to 6 months of a trial may carry over and may account for better outcome. In both of these trials, primary outcomes

were no different, but secondary cardiovascular disease outcomes favored the drugs that reduced BP to a greater degree.

So we believe that there is good evidence that the BP makes the difference in most cases. But in ALLHAT, as Dr Cushman pointed out, it looks as if the specific drugs made some difference in that the investigators couldn't account for all the benefit differences based on BP differences.

Bill, describe some examples of studies that suggest the benefit of one medication over another. We have mentioned already that CCBs and diuretics are probably drugs of choice in the elderly, that  $\beta$ -blockers are probably not the drug of choice except, as Norm pointed out, in post-myocardial infarction, angina, and congestive heart failure, for example. Are there any specific trials in which it was apparent that drug A is better than drug B? I know the ASCOT investigators have claimed that contemporary therapy is better than old treatment. Basically, what this study really showed was that a CCB was better than a  $\beta$ -blocker-based regimen in older people. There are some trials in which it does appear that certain drugs are more effective than others.

DR CUSHMAN: I've already mentioned that there was a 40% higher risk of heart failure in ALLHAT, with very similar BP levels in those treated with CCBs compared with those who received the thiazide diuretic.

DR MOSER: With the CCB.

DR CUSHMAN: Right. That actually comes out of meta-analyses as well. CCBs don't cause heart failure; they probably do reduce heart failure some compared with placebo or no treatment, but when you pair a CCB against something like a thiazide diuretic that lowers heart failure by 50% compared with placebo, then we do see a difference in heart failure favoring the diuretic, despite the fact that there is no difference in BP reduction.

Also, in ALLHAT the ACE inhibitor and the thiazide were very similar in reducing BP in the non-black population. In that population, strokes were no different but heart failure was still significantly higher with the ACE inhibitor compared with the thiazide diuretic.

DR MOSER: So you would say that ALLHAT showed that the diuretic appeared to be superior to a CCB and to an ACE vis a vis reduction of heart failure events?

DR CUSHMAN: Right. But in blacks there was a big BP difference; however, it is difficult statistically to explain the differences just on the BP. It may be BP levels that we didn't measure within the study, but maybe it is a specific drug effect difference.

I believe that we have a whole series of studies that show that ACE inhibitors and ARBs are better than alternative therapies, usually a CCB or a  $\beta$ -blocker, in slowing the decline in renal function. Certainly, that was seen in the African American Study of Kidney Disease and Hypertension (AASK) in hypertensive renal disease in blacks, and it was seen in studies like the Irbesartan in Diabetic Nephropathy Trial (IDNT) and the Reduction of End Points in Type 2 Diabetes With the Angiotensin II Antagonist Losartan (RENAAL) trial in diabetic nephropathy.

There are studies even in nondiabetics that suggest that ACE inhibitors and ARBs do have some additional effect beyond BP lowering. I know that there are people who believe that in some of those studies the BP outcome may have explained some of the difference, but we believe that mechanistically there's a reason that ACE inhibitors and ARBs would do better in patients with renal disease.

You mentioned ASCOT. There was about a 3/2-mm Hg difference in BP between the CCB and  $\beta$ -blocker groups, which makes it difficult to interpret the difference in outcome. I think it's important, however, to point out that when they added a diuretic to the  $\beta$ -blocker, the dose of the diuretic was one-quarter to one-half lower than what had been used in previous outcome trials with diuretics. This may have influenced the BP and the outcomes.

DR MOSER: The study should probably have used a diuretic first and then added a  $\beta$ -blocker.

DR CUSHMAN: To use 2 different drugs without being randomized as the second drug makes it difficult to say much about it. But I will say that in several studies now (ASCOT is an example, and the recent Action in Diabetes and Vascular Disease: Preterax and Diamicron MR Controlled Evaluation [ADVANCE] in diabetes is another example), the dose of the diuretic was smaller than what we've used in successful outcome studies with diuretics. The bendroflumethiazide dose in ASCOT that was added to the  $\beta$ -blocker was only one-quarter to one-half of the dose that was used in previous outcome studies with bendroflumethiazide. So ASCOT had a few problems.

DR MOSER: That was 1.25 mg, wasn't it, going up to 2.5 mg?

DR CUSHMAN: That's right. Studies using bendroflumethiazide, including the Medical Research Council trial in younger patients, used bendroflumethiazide in doses of 5 to 10 mg. There is concern about using too small of a dose of a thiazide to obtain the optimal outcomes benefits with thiazide-type diuretics.

DR MOSER: What was the ADVANCE study?

DR CUSHMAN: More than 11,000 participants with diabetes were randomized in a double-blind fashion to indapamide, a diuretic, plus perindopril, an ACE inhibitor, compared with a placebo, both on top of other therapy. But the investigators could also use an open-label ACE inhibitor, which they did in 50% of the treated group and 60% of the control group, so it didn't really achieve differential ACE inhibitor treatment. The indapamide dose was 1.25 mg, which was about half of the dose used in the previous Perindopril Protection Against Recurrent Stroke Study (PROGRESS), in which a lot of these same investigators were involved.

DR MOSER: PROGRESS showed that an ACE inhibitor plus a diuretic was very beneficial in preventing recurrent strokes.

DR CUSHMAN: Right, if both were used together. In the ADVANCE study, benefit noted with one of the primary outcomes, macrovascular and microvascular disease combined (which was a later addition in terms of a primary outcome), was statistically significant ( $P=.04$ ), and that was with a 5.6/2.2-mm Hg lower BP. So, with this large-sized trial, one would think that the large difference in BP levels would result in larger outcome differences. It suggests to me that the dose of diuretic may have been too small to reduce events robustly; therefore, it does matter which drugs at which doses are used to treat hypertension, despite that there was a much bigger difference in BP than we've seen in some other trials, such as HOPE and ASCOT.

DR MOSER: And your conclusion on this issue is yes, there are some trials where it does appear to make a difference which medication is used. It looks as if the use of a diuretic may be more effective in preventing heart failure than the use of a CCB. It looks as if the use of a  $\beta$ -blocker may not be as effective in preventing strokes as a CCB or an ACE inhibitor, and that in patients with nephropathies, especially diabetic nephropathy, it looks as if an ACE inhibitor or an ARB should be part of the treatment program because outcome appears to be more beneficial than if, for example, a CCB regimen was used. Is that fair?

DR CUSHMAN: Absolutely.

DR MOSER: Norm, what do you think?

DR KAPLAN: Well, I do think that there is good evidence that ACE inhibitors and ARBs reduce proteinuria to a greater degree than any of the other drugs. Nephrologists have learned that the presence of protein in the tubule, in itself, damages the kidney. The reduction in proteinuria is now a primary end point that is used clinically to evaluate benefit.

It's easy to measure, and it is more useful than having to perform echocardiography and all sorts of other tests to look for effects. And in most studies, ACE inhibitors or ARBs in high doses reduce proteinuria. The nondihydropyridine CCBs verapamil and diltiazem have also been shown to have some effect on proteinuria, whereas the dihydropyridines like amlodipine appear not to do much. So, in that regard, I think there is a differential.

There's a very easy physiologic explanation for these benefits, because the highest concentration of angiotensin goes into the efferent arteriole of each glomerulus and that is where the drug presumably has its main effect. A renin-angiotensin-aldosterone system blocker blocks that effect and thereby allows those vessels to dilate and lower intraglomerular pressure, which would reduce the degree of proteinuria.

DR MOSER: A recent editorial in *The Journal of Clinical Hypertension*<sup>1</sup> pointed out that the data are good for patients with diabetes with evidence of albuminuria. But the evidence in patients without albuminuria is not that good. Would we still favor the use of these agents in diabetics without proteinuria?

DR KAPLAN: Probably not. You're absolutely right. The addition of ACE inhibition in people who have <500 mg/d of total proteinuria may have minimal effect, whereas in those who had heavier proteinuria, a benefit is noted. The presence of significant proteinuria certainly would point us toward the use of ACE inhibitors and ARBs. I know of no good evidence that one needs both of these agents, although many nephrologists are using the combination on the basis of some small studies. Another larger study showed that when they combined ramipril with irbesartan, there was no real additional benefit compared with what they were able to accomplish with only ramipril.<sup>1</sup>

DR MOSER: Despite that the literature does contain some data reporting that when you add an ACE inhibitor to an ARB, you decrease proteinuria more rapidly.

DR KAPLAN: There was a study from Japan, but it was relatively small, whereas a recent study by Bakris and colleagues<sup>2</sup> involved a fairly large number of patients. So that will probably shake up the issue as to whether the 2 agents really are better. I think we all appreciate that there is no good evidence that BP control is improved by combining ACE inhibitors and ARBs.

DR MOSER: Aren't there some data suggesting that BP is lowered further when an ARB is added to an ACE inhibitor?

DR KAPLAN: Most of these studies unfortunately used only medium or moderate doses of one drug and then added the second. Of course they see greater benefit. What we really have to do is maximize dosages. I don't know that we can define what maximal is, but it should be at the top of its approved dosage, then adding a second drug. In those circumstances, there's really very little evidence that the use of two is better than the single drug.

DR MOSER: What about an ACE inhibitor or an ARB plus a CCB in terms of decreasing proteinuria and improving renal function? Any evidence?

DR KAPLAN: I think that is coming. I know that there are numerous combinations of amlodipine, which has become generic, with either ACE inhibitors or ARBs.

DR MOSER: Lots of data on the fact that a CCB and an ARB lower BP significantly, as you would expect, but do we have any data on renal function?

DR CUSHMAN: I don't think so. I guess there's some suggestion that if you add other drugs to lower BP further that you may get some further benefit, but lowering BP goals well below <140/90 mm Hg has not generally been successful in further slowing renal function decline.

DR MOSER: One last point about whether it is the BP level alone that determines outcome. Are there other factors that may come into play? A quick summary about new-onset diabetes: We know, for example, that the use of an ARB- or an ACE inhibitor-based regimen results in less new-onset or incipient diabetes than a program based on a diuretic or a  $\beta$ -blocker. Bill, is this new-onset diabetes of significance? You have data from ALLHAT, you have data from the follow-up of the Systolic Hypertension in the Elderly Program (SHEP). What do you think we should tell physicians about this?

DR CUSHMAN: I think that, in general, there appears to be about a 4- to 6-mg/dL higher fasting glucose level in patients receiving thiazides or  $\beta$ -blockers compared with other regimens. Many but not all studies show that, but that seems to be fairly consistent even in short-term studies. Alternatively, there are a number of studies that suggest that ACE inhibitors and ARBs may reduce the incidence of diabetes. But the best study to test that prospectively so far is the Diabetes Reduction Approaches with Medication (DREAM) study, which compared ramipril, at a dose similar to what seemed to be beneficial in preventing diabetes in HOPE, with a regimen that did not use an ACE

inhibitor. In the DREAM trial, in more than 3000 patients with impaired fasting glucose or impaired glucose tolerance, there was not a significant difference in diabetes incidence and, ironically, there was no difference whatsoever in fasting glucose levels. Here was a high-risk population in which the use of an ACE inhibitor didn't make a difference in diabetes incidence. But I think there is some small benefit on glycemia with ACE inhibitors and ARBs and some small adverse effect on glycemia with some other drugs. I would like to make 2 important points, however. The differences in glucose are small, and so small that even from a statistical perspective you wouldn't expect them to have much effect on outcomes. Also, long-term follow-up within clinical trials or after many years, such as in the SHEP follow-up study, has found no relationship between new-onset diabetes associated with the use of a thiazide diuretic and coronary heart disease or cardiovascular disease outcomes.

In the Action to Control Cardiovascular Risk in Diabetes (ACCORD) trial, a National Heart, Lung, and Blood Institute diabetes study, we are looking at different levels of BP and different levels of glucose control as they relate to cardiovascular and microvascular outcomes. It was estimated that we would need 10,000 participants with about a 1.5% difference in hemoglobin A<sub>1c</sub> to detect a significant and clinically important difference in cardiovascular events. So that is about 10 times the usual 4- to 5-mg/dL differences in glucose levels that we see with antihypertensive medications.

The effect on glucose should not be an important determining factor on what we do unless we get further data that it makes a difference. We're also looking at the relationship between glucose changes during the trial and outcomes years after the trial is completed in ALLHAT.

DR MOSER: Let's play the devil's advocate. I've got 2 drugs like an ARB or an ACE inhibitor that may improve insulin sensitivity and certainly won't make it worse. Let's leave the  $\beta$ -blockers out because they're probably the worst offenders, but let's compare these medications with a diuretic that may increase glucose levels by 4 to 6 mg/dL and may show a difference in new-onset diabetes of 1% to 3% compared with the ACE inhibitor or ARB. Although I am aware that outcome may not change, why shouldn't I just use an ACE inhibitor or an ARB and forget the diuretic? That's a question you're asked all the time, isn't it?

DR KAPLAN: I think, first of all, the addition of a low-dose diuretic to any other class of drug increases the effectiveness of the second drug, so

the diuretic seems to me to be a fundamental part of virtually every hypertensive patient's treatment. But we're talking now about low doses, and I think most of the evidence of an increase in the incidence of diabetes with diuretics has been with fairly large doses. That was certainly true when they looked at insulin sensitivity and used 50 to 100 mg of hydrochlorothiazide.

In ALLHAT, the majority of patients ended up taking 25 mg of chlorthalidone equivalent to 40 mg of hydrochlorothiazide, which is not a small dose. So we have to expect that there should be a somewhat higher level of blood sugar and incidence of diabetes with that dose. As you pointed out, the use of  $\beta$ -blockers may result in an increase in blood sugar related to a decrease in insulin sensitivity.

DR MOSER: So right now you wouldn't pay much attention to the changes in glucose levels as a factor in choosing therapy?

DR KAPLAN: I'm not too concerned with low-dose diuretics. I think part of the problem with  $\beta$ -blockers and why they did not show better benefit on cardiac events is likely to be because they adversely influence both sugar and lipids. We get adverse effects on other risk factors at the same time we're lowering BP. With low-dose diuretics, I'm much less concerned, but I still believe that in many early diabetics in whom proteinuria is the main issue that the use of a naked ACE inhibitor or an ARB would be appropriate. But for most hypertensive patients, I think a low-dose diuretic and then whatever else seems to be logical for the patient should be used. Many times, it will be ACE inhibitors and ARBs with the low-dose diuretic.

DR MOSER: Bill, do you agree? We should remember that new-onset diabetes is much more common in hypertensives with or without medication.

DR CUSHMAN: For the most part. I am concerned, as I mentioned before, about using too low a dose of a diuretic compared with what we've used in outcome studies: 12.5 to 25 mg of chlorthalidone and 12.5 to 50 mg of hydrochlorothiazide, which are appropriate doses. Basically, I wouldn't routinely only use the ACE inhibitor or ARB even in a patient who may have some impaired glucose metabolism already. That is because within a number of trials, but certainly within ALLHAT, we see important differences in major cardiovascular events that favor the diuretic within the 4 to 5 years of follow-up. So, the theoretical effect of the glucose changes would not concern me.

Now given that, I will say that I try to get virtually every patient with diabetes on both an ACE inhibitor or ARB and a thiazide diuretic and if they need a third drug, a CCB. I actually may include the CCB before the ACE inhibitor or ARB in an African American patient if he or she doesn't have renal disease or other indications for the ACE inhibitor. This is because they respond better to the CCB than to an ACE inhibitor. An overwhelming majority of patients with hypertension are going to need at least 2 or 3 drugs, and so in my opinion, we should get them on those classes for which we have the best outcome data: thiazide-type diuretics, ACE inhibitors or ARBs, and CCBs.

DR MOSER: In summary, again, I think we all agree that most of the benefit accrues to lowering BP: the lower the pressure, the better the outcome, whichever drug you use. But there are certain caveats. For example, CCBs and diuretics apparently work better in the elderly and in black patients. ACE inhibitors and ARBs probably work a little better in white patients and in younger people. In patients with diabetes or certainly those with proteinuria, an ACE inhibitor or an ARB should be part of the treatment program. The metabolic effects of diuretics usually do not overwhelm the beneficial effects of lowering BP on cardiovascular outcomes, and the majority of the clinical trials indicate that getting the BP <140/90 is beneficial.

Whether a CCB/diuretic, CCB/ACE inhibitor, or CCB/ARB combination will improve outcome compared to other medications will have to await other studies, but we certainly have enough data now to show that they are effective in lowering blood pressure. In many clinical trials that claim the superiority of one drug over another, superiority may, in some cases, be partially or fully explained by BP differences. Final words, anybody?

DR KAPLAN: The main message is to lower the BP. And how you lower the BP is probably less important than the fact that you lower it. We obviously have to avoid all the known adverse effects of high doses of diuretics and  $\beta$ -blockers, but basically I think our major message should be to lower the BP by whatever means are available.

DR MOSER: Bill?

DR CUSHMAN: I would also mention that I would still be more comfortable using the classes of drugs that have been shown to be beneficial in major outcome studies, giving priority to thiazide-type diuretics. I'm not sure we're going to know anytime soon whether the outcome benefits and differences are all from BP lowering.

DR MOSER: Thank you, Bill and Norm.

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