Diuretics as Monotherapy or as Part of Combination Therapy for Hypertension: An Update

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At a meeting of The American Society of Hypertension in May 2008, a panel was convened to discuss the use of diuretics. Are they still preferred initial therapy, are they still the preferred agent to add in combination therapy, and is there a difference between or among the diuretics that have been used in the clinical trials? The session was moderated by Marvin Moser, MD, of the Yale University School of Medicine, New Haven, CT. Participants included Domenic Sica, MD, Virginia Commonwealth University, Richmond, VA; William Cushman, MD, University of Tennessee, Memphis, TN; and Ken Jamerson, MD, University of Michigan, Ann Arbor, MI. J Clin Hypertens (Greenwich). *2008;10:726–734.* ©*2008 Le Jacq*

DR MOSER: Bill, let's start with you. There are abundant evidence-based data reporting that diuretic-based treatments have significantly reduced the incidence of stroke, coronary heart disease, congestive heart failure, and progression of renal disease. Despite the availability of those data, the use of diuretics has consistently decreased since the 1970s, when the information became available, to the late 1990s, when the Antihypertensive and Lipid-Lowering Treatment to Prevent Heart Attack Trial (ALLHAT) was published. Explain ALLHAT to us and review some of the other data on results of treatment with diuretics. Are diuretics alone or with the addition of other drugs still acceptable treatments? And does it make a difference which diuretic is given?

DR CUSHMAN: Starting with the VA Cooperative Study in the 1960s, there have been a number of studies that were diuretic-based that showed consistent benefits in reducing morbidity and mortality in hypertension. This was particularly true of strokes and heart failure but also of coronary heart disease. Obviously, there were a variety of different regimens that were used, but before the 1990s the newer agents that we commonly use now as add-on drugs were not available. By the 1990s, the prescription of thiazide-type diuretics had fallen to about 20% of hypertensive patients despite the fact that at that time, the only outcome data that we had in hypertension trials were with thiazide diuretics and, less compellingly, with β-blockers.

DR MOSER: Why do you believe that diuretic use decreased when we had the VA Cooperative Study, Hypertension Detection and Follow-Up Program (HDFP), and the Systolic Hypertension in the Elderly Program (SHEP), all of which were diuretic-based and all of which showed benefit?

DR CUSHMAN: Well, we know that the use of diuretics in high doses has biochemical effects in terms of reducing potassium, increasing uric acid, and increasing glucose to some degree. All of those are relatively small effects unless you use very high doses. It was also true that there was no longer the same degree of marketing of diuretics when some of the newer drugs came along in the 1980s and 1990s. In particular, angiotensin-converting enzyme (ACE) inhibitors and calcium channel blockers (CCBs), the new kids on the block in the 1980s, were heavily promoted. The theories behind their potential benefits were intriguing, and the potential adverse effects of thiazides, and to some degree β-blockers, were highlighted. There was a consistent decrease in use of thiazides despite that there

doi: 10.1111/j.1751-7176.2008.00010.x

were no outcome data from hypertension clinical trials with those newer classes of drugs until the late 1990s.

ALLHAT was designed in the early 1990s to determine whether these newer classes of drugs were in fact superior to the thiazide-type diuretic class. ALLHAT was a randomized double-blind clinical trial designed to determine whether the incidence of fatal coronary heart disease or nonfatal myocardial infarction (the primary outcome) and other cardiovascular outcomes was lower for high-risk hypertensive patients initially treated with a CCB (amlodipine 2.5–10 mg/d), an ACE inhibitor (lisinopril 10–40 mg/d), or an α-blocker (doxazosin 2–8 mg/d) compared with a thiazide-type diuretic (chlorthalidone 12.5–25 mg/d). It showed that chlorthalidone was at least as good as amlodipine or lisinopril for lowering blood pressure and preventing cardiovascular and renal end points. Chlorthalidone was superior to all 3 other drugs in preventing heart failure and superior to the ACE inhibitor and α-blocker in preventing stroke and combined cardiovascular disease events; the stroke benefit over the ACE inhibitor was only in African Americans. These findings are largely consistent with those of other relevant trials and meta-analyses.

DR MOSER: Dom, how much of this change in treatment practices was a result of concern about hypokalemia and possible ventricular arrhythmias? Hypokalemia was probably the finding that bothered physicians the most. How much of that was real, and how much of it was dosage-related or specific to the drugs that were used?

DR SICA: The hypokalemia was, without question, real and related to the high-dosages (50–100 mg/d) of either hydrochlorothiazide or chlorthalidone commonly used at that time. It took us some time to adjust our thinking relative to diuretic dosing and to adopt a more low-dose strategy for diuretic administration.

DR MOSER: Fifty to 100 mg of chlorthalidone as well as hydrochlorothiazide?

DR SICA: Yes. Unfortunately, lessons learned from high-dose therapy were ill advised. We believed that the electrolyte disturbances at the high doses were so significant that we erred on the side of extreme caution and began using ultralow doses, which then took away some of the blood pressure–lowering benefits of these drugs. We also moved away from the use of chlorthalidone, which was the thiazide-type diuretic most extensively studied from an outcomes viewpoint. In so doing, there was a subtle shift to the belief that all thiazide-type diuretics were equal and that the outcomes results would be the same whether hydrochlorothiazide or chlorthalidone was being used.

DR MOSER: So what's the difference between the two drugs?

DR SICA: Well, the belief has been that there's a class effect for thiazide-type diuretics, yet they are fairly different from one another and they may be fundamentally different in their outcomes effects. We know that you can get a substantially greater blood pressure reduction with one vs the other, that is, chlorthalidone compared with hydrochlorothiazide.

DR MOSER: Is that because of potency or duration of action?

DR SICA: It's an interesting phenomenon. Nobody quite knows, because when you have a pharmacologic attribute for a compound, it's tough to distinguish which attribute you can assign causality to a positive effect. Chlorthalidone has a very long duration of action. It is a true diuretic, compared with hydrochlorothiazide, in that there's a net volume loss for blood pressure reduction, but with thiazide-type diuretics there is vasodilation; however, chlorthalidone may have a little more staying power than hydrochlorothiazide. Recent studies with ambulatory blood pressure monitoring would seem to suggest this. In the one study I am speaking of, 50 mg of hydrochlorothiazide was compared with 25 mg of chlorthalidone. The difference was an overnight decrease in blood pressure with chlorthalidone of several mm Hg or more. This, to me, was a pretty significant decrease in nocturnal blood pressure and separates these two compounds in a meaningful fashion.

That being said, what we're left with is that we have different drugs, different durations of action, and potentially different mechanisms of action. But we're saddled with a belief that these two diuretics are equal. Many have promulgated this message, but I've got a strong belief that there's a within-class distinction, an important intraclass difference.

DR MOSER: Do you think that some of the perceived problems with diuretics were that we were using chlorthalidone in the clinical trials in dosages that were high, with more hypokalemia? Did we frighten doctors away from using it?

DR SICA: I think we did. We did that with hydrochlorothiazide, too. I also believe that the fixed-dose combination products began to dominate but none of them included chlorthalidone except two: one with clonidine and another with atenolol. We just became more and more familiar with the hydrochlorothiazide-containing combinations, and we all but forgot that a drug such as chlorthalidone existed.

DR MOSER: I think you're right; "HCTZ" [hydrochlorothiazide] is also easier to write out than "chlorthalidone."

DR SICA: It's easier and doctors kind of grew up with it. The fixed-dose combination products with ACE inhibitors only contained hydrochlorothiazide, as is the case with the angiotensin receptor blocker fixed-dose combinations; thus, anyone being trained in the 1980s and 1990s was left with little choice but fixed-dose combinations containing hydrochlorothiazide. Unfortunately, this prescription practice was neglectful of the within-class differences among the thiazide-type diuretics.

DR MOSER: Ken, the thiazides, whether chlorthalidone in clinical trials or hydrochlorothiazide by perception, had all these positive study findings that showed reduction of cardiovascular events to an extent that hadn't been proven with anything else. But there were some other problems with thiazides besides hypokalemia that bothered people. There were some effects on lipids and on glucose. Are those important problems with the doses we use now, or have they been overemphasized?

DR JAMERSON: I think that the possible metabolic effects resulted in clinicians' seeing patients more often for blood tests. But there may be an important problem that we're missing to explain why the usage of diuretics decreased. Working adults who take them have to urinate frequently, and it may interrupt their lives. If one can have similar blood pressure control without having to do this, why should he or she continue with a diuretic? This may be a very important limitation. So the lower the dose went, the smaller the metabolic effect, but the urge to have to stop and urinate was still there to some extent.

Quite frankly, heretofore I thought that whether the diuretic was a thiazide-like hydrochlorothiazide or chlorthalidone, the primary mechanism for reducing cardiovascular disease was lowering blood pressure. There has not been a great deal of information about effects of these agents other than lowering blood pressure and thereby reducing cardiovascular risk.

So whether hydrochlorothiazide or chlorthalidone was used, if blood pressure was reduced and the patient tolerated it, you typically thought your job was done well.

DR MOSER: We could argue that point because, in fact, if you lower the blood pressure and you reduce stroke, coronary disease, and heart failure, that may be all that has to be done. Another point is that in studies that have been blinded and controlled the tolerability of diuretics turns out to be just as good or better than other drugs, despite the perceptions of some physicians. With chlorthalidone, for example, you may have an increase in urination for several hours, and then it becomes less obvious over 48 to 72 hours. It is, of course, true that in some men with prostate disease this can be annoying. But with the dosages we use, 12.5 or 25 mg/d, this is not a major problem in the majority of patients.

DR JAMERSON: I think you're right, but if you look long term, particularly in clinical trials in which you're going to follow patients for 4 to 5 years, the biggest occurrence of complaints would be in the first 3 months. If people stay on therapy for 3 months, the odds are that they will stick it out for the duration of the trial. In trials, you do have extra resources; you have nurses and others to encourage the patient. But to the primary practitioner who has to take care of colds and lots of other issues, it may be a little tougher to get patients to stay with a medication for that initial 3 months, so it is important to achieve blood pressure control without too many adverse effects. So I think that as newer drugs like the ACE inhibitors came along and could lower blood pressure equally, there was little reason to put up with adverse effects, not necessarily with diuretics but with any medications.

DR MOSER: We can argue that, too, because I'm not sure that any of the newer drugs by themselves will lower blood pressure in as high a percentage of patients as seen in many of the clinical trials. With ACE inhibitors, for example, or with angiotensin receptor blockers, more than 60% of people require a diuretic to lower the blood pressures to goal levels.

DR JAMERSON: The best data I recall suggest that, especially in the African American population, the drugs that work best are CCBs. But they too have adverse effects, and CCB-based treatment results in more episodes of heart failure than ACE inhibitor- or diuretic-based treatment.

DR MOSER: Bill, do you want to comment on tolerability?

DR CUSHMAN: I will say that in any blinded studies, even short-term studies, you virtually never see increased urination as an adverse effect. I think a lot of people have that perception and if they think they are going to have a side effect, they often experience it. But we've not seen frequent urination as a deterrent to therapy in even short-term randomized, controlled, blinded studies. And over and over again, I've never seen it in any of the registration-blinded studies.

DR JAMERSON: We never ask, so we don't see it either.

DR SICA: I rarely see it. A thiazide diuretic, at the dosage we now use, is not a potent diuretic. Its action is short-lived.

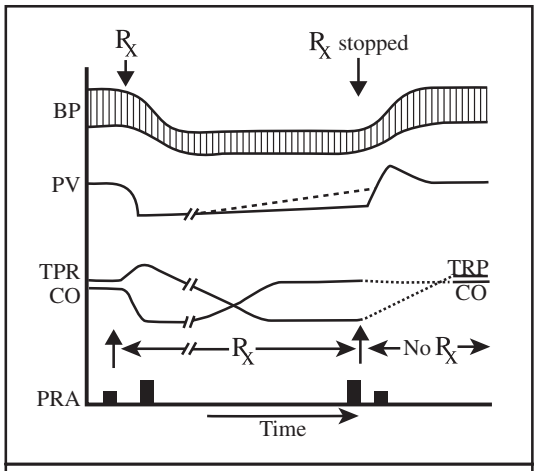
What does happen, though, when you talk to enough patients is that in anticipation of a diuresis, they increase their fluid intake and urine output then matches intake, thus, the origin of their urinating more. This, of course, is not true of patents with heart failure, in whom diuresis can be profuse. We also see this belief in more urination with a diuretic with spironolactone. The spironolactone is given exclusively for blood pressure control, but as soon as the word diuretic is seen on the product brochure, a patient often becomes concerned about increased frequency of urination. I agree that there's a perceptual issue, but anticipatory intake is also very important.

DR MOSER: I think that a valuable point to make is the problem with nonblinded studies. For example, most of the studies with β-blockers are nonblinded. If people know they're on a β-blocker and have read the package insert, they get cold hands and are certain that it was because of the β-blocker. It could be freezing cold weather, but they stop the medication anyway. Similarly, if you get a cough and know that it may be a result of an ACE inhibitor, the drug will be stopped—even if you obviously have a cold. Dom, comment very briefly on the sequence of physiologic changes that occur over the first 4 to 6 weeks when you give a diuretic. Obviously, if the drugs continued to act as a diuretic and the patient kept losing fluid, he or she would look like a shriveled up prune in 3 or 4 days.

DR SICA: There are 3 phases in the response to diuretics. The acute phase is marked by a modest increase in sodium excretion. There is a small volume change during this time period, and the initial drop in blood pressure seems to relate to this volume change.

DR MOSER: So plasma volume decreases?

DR SICA: Yes, and cardiac output also temporarily decreases. Thereafter, there is a transitional phase during which there's an accommodation to the diuretic action of these drugs. This process has been termed the braking phenomenon. The mechanistic basis for this is poorly worked out. This is but one of several factors that return plasma volume back toward pretreatment values. This gain in fluid volume is also shared by the extracellular and interstitial fluid compartments. During this phase of the response to a thiazide-type diuretic, there's probably a resetting of vascular tone that some have held relates to a change in both sodium and calcium content in the vessel wall. As this tissue-leaching effect ensues, there is a gradual



Abbreviations: R_X, drug therapy BP, blood pressure; PV, plasma volume; TPR, total peripheral resistance; CO, cardiac output; PRA, plasma-renin activity.

After about 4 to 6 weeks of treatment, BP remains below pretreatment levels, cardiac output has returned to normal, and vascular resistance is reduced, but plasma volume remains slightly below pretreatment levels, Resistance and BP return to pretreatment levels when the diuretic is stopped.

Modified from Tarazi et al.
Circulation. 1970;41;709-717.

Figure. Hemodynamic effects of chlorothiazide in a hypertensive patient.

vasodilatation. There's something about salt and water depletion that sets the stage for the vessels to dilate over the long term (Figure).

If you have a high salt intake at the time of initial diuretic activity, it seems to blunt the short- and long-term positive blood pressure–lowering effects. Of interest, there have been studies in which diuretics have been infused directly into the brachial arteries and downstream vasodilator effects have been assessed. These studies have shown little if any direct vascular effects.

DR MOSER: So on balance after about 4 to 6 weeks, the cardiac output is back to normal and plasma volume may still not be quite back to pretreatment levels. So that's why the renin angiotensin system is more active. But blood pressure and vascular resistance are reduced.

DR SICA: With most antihypertensive patients, with a few exceptions, there is a dose-response relationship that's timed on a 24-hour basis. We give a drug, obtain measurable blood levels, get the desired effect often equating with the blood level, and then do the same thing the following day with the next dose. A diuretic's vasodilating actions may, to a certain degree, persist despite missed doses once a steady state has been reached; thus,

there is a residual effect that seems to be present upon missing a dose or in some instances discontinuing therapy. Unfortunately, this persistence of effect upon discontinuation of a thiazide-type diuretic is poorly studied, particularly as it relates to head-to-head comparison with other nondiuretic antihypertensive drug classes. It is interesting that over the years a common clinical practice in the elderly has emerged, which is to give a thiazide-type diuretic, but 3 to 4 times a week to "lessen" net weekly diuresis. At least anecdotally there does not appear to be much loss of antihypertensive effect when such an approach is used.

DR MOSER: The ALLHAT study, which was blinded and randomized and included 42,000 people, should be reemphasized. A diuretic-based regimen was compared with an ACE inhibitor or CCB-based treatment program. CCBs and ACE inhibitors are clearly effective, very useful antihypertensive agents, and their use with other drugs has resulted in reduction in cardiovascular events. Ken, what's your take on this study, which was designed to determine whether chlorthalidone—in this case in modest dosages, 12.5 to 25 mg/d—was as effective in reducing cardiovascular events as an ACE inhibitor or CCB? In subsets of patients—in diabetics, different racial groups, heart failure patients, and angina patients—the diuretic-based treatment was just as effective as treatment based on an ACE inhibitor or CCB. In fact, there was less heart failure with a diuretic than with a CCB and fewer strokes with the diuretic when compared with the ACE inhibitor, especially in African Americans.

DR JAMERSON: ALLHAT is clearly one of the largest head-to-head trials, and you summarized it quite well. The intent was to compare the diuretic with newer drugs. Within the study design of ALLHAT, the newer agents did not prove themselves to be better. Groups were titrated to a target blood pressure and add-on therapy was used, but the add-on therapy may not have been appropriate. For example, if you give a diuretic and add a β-blocker, if blood pressure can be reduced to goal, that seems appropriate, but if a CCB doesn't work, an ACE inhibitor probably should be added, and this was not allowed by the protocol. Instead, a β-blocker was added.

DR MOSER: In other words, if the diuretic was ineffective, you could add a β-blocker, which is logical.

DR JAMERSON: Right.

DR MOSER: But if an ACE inhibitor was ineffective, you couldn't add a CCB or a diuretic because of the study design.

DR JAMERSON: Right. But about 25% of the patients did receive diuretics in the ACE inhibitor and CCB groups. It did answer some questions, but in terms of how physicians manage patients, it didn't answer all the questions.

DR MOSER: And yet, we talk about the adverse metabolic effects of diuretics and β-blockers, especially when combined; in ALLHAT, in which 30% of patients receiving a diuretic also got a β-blocker, new-onset diabetes was more common, but the outcome data are as good or better than with other regimens, whether you look at coronary disease, angina, or heart failure. How do we explain that?

DR JAMERSON: The regimen looks good for lowering blood pressure. But, if I had my choice, to achieve the same blood pressure control without having abnormal metabolic milieu or tipping you over to diabetes, I would prefer to have the blood pressure control without the diabetes. Even though you tell me that mathematically it doesn't matter, it's my body, they're my numbers, and I don't want it. I think it's more logical and reasonable to not give patients metabolic aberrations. Why would you want to do it, why would you want a diuretic and a β-blocker if there's equal efficacy with a method that won't give you these metabolic aberrations?

DR MOSER: I agree with some of that, but the metabolic changes were small and did not appear to be clinically relevant. But I agree, a diuretic as a base plus an ACE inhibitor, an angiotensin receptor blocker, or a CCB makes a lot of sense in terms of good blood pressure control and potentially fewer metabolic changes than with a β-blocker. Bill, in ALLHAT there was about a 3.5% increase in new-onset diabetes with diuretic-based therapy, compared with the ACE inhibitor–based regimen, and yet outcome was not affected at all in terms of patients with pretreatment impaired glucose tolerance or diabetes. Describe the extent to which glucose levels changed. Was it 2, 3, or 10 mg/dL?

DR CUSHMAN: Well, I agree with Ken that if you had two drugs that did the same thing in terms of blood pressure lowering or outcomes, yet the use of one of them either resulted in adverse events or caused significant metabolic abnormalities, then obviously you wouldn't use that one. I think that's one good reason not to use β-blockers routinely, because they do not have any advantage on outcomes in hypertension. As a matter of fact, they fairly consistently—not always, but fairly consistently–underperform, yet they have metabolic effects particularly on glucose and triglycerides. However, if a drug is more effective at preventing major cardiovascular events despite having some

metabolic changes, as is true for the diuretic, then that agent should be used in preference.

DR MOSER: So if you had had your choice in ALLHAT, it might have been an ACE inhibitor plus a diuretic or a CCB plus a diuretic?

DR CUSHMAN: Right, although in 1992 when ALLHAT was done—we have to remember, that's an awfully long time ago—there were just no outcome data at all with CCBs, ACE inhibitors, or α-blockers. So the very large group of experienced investigators who put the study together felt that we should not mix up the groups and just routinely add something else. Even in practice, adding the drugs that we added, β-blockers and clonidine, was very commonly done. We tried to encourage the more frequent use of reserpine, since it is better tolerated than clonidine, is long-acting, and had been used in many other studies as a second agent. I would add that the investigators did not have a strong bias as to which regimen would be proven best in ALLHAT. As a matter of fact, if you had polled us, I think most of us would have guessed that the ACE inhibitor–based program probably would have won the day in terms of outcomes. And it did not.

DR MOSER: If you had to design that study today, would you use a diuretic first and then add an ACE inhibitor, an angiotensin receptor blocker, or even a CCB if goal blood pressures were not achieved?

DR CUSHMAN: Well, you wouldn't design the same study. It confounds a study too much to routinely add the other study drugs being compared, so you really have to ask a different question. One of the considerations is to look at various combinations, just as the Avoiding Cardiovascular Events Through Combination Therapy in Patients Living With Systolic Hypertension (ACCOMPLISH) study looked at two different combinations. But in ALLHAT, the metabolic effects like hypokalemia were fairly trivial and were fairly easy to treat. As a matter of fact, if we could have routinely used potassium-sparing drugs, it would have been even less of an issue. The glucose difference between chlorthalidone and the ACE inhibitor was about 5 mg/dL. As you know, some studies with ACE inhibitors show a benefit on glucose, but some don't. The Diabetes Reduction Assessment With Ramipril and Rosiglitazone Medication (DREAM) did not suggest a benefit with the ACE inhibitor, which may have surprised some people. The difference in ALLHAT's blood glucose levels corresponds to only a 0.1% to 0.2% difference in hemoglobin A_{1c}. By comparison, the Action to Control Cardiovascular Risk in Diabetes (ACCORD) study was powered for a 1.5% difference in hemoglobin A_{1c} with more than 10,000 participants to detect whether there was a significant cardiovascular benefit in reducing hemoglobin A_{1c}.

DR MOSER: Could you tell us what the ACCORD study is?

DR CUSHMAN: Sure. The ACCORD study is a large National Heart, Lung, and Blood Institute study comparing the effects on cardiovascular events of a hemoglobin A_{1c} goal of <6% compared with 7% to 7.9%. We now know from 3 major trials, including ACCORD, that there is no benefit in reducing cardiovascular events even by reducing hemoglobin A_{1c} by >1%. Much smaller differences in glucose seen sometimes with antihypertensive agents would not be expected to have an important effect on outcomes.

DR MOSER: And these possible metabolic changes don't worry you?

DR CUSHMAN: They don't worry me if the drug you're using is superior. So, for example, if you're using a β-blocker post–myocardial infarction, which we know improves survival, I would not worry about a small difference in glucose or triglycerides from the β-blocker. Similarly, in hypertension, if the diuretic did not have the advantages that were seen in ALLHAT and other studies in terms of heart failure and stroke and overall cardiovascular events, then I would not favor it. But certainly with these relatively small metabolic differences, I am not concerned. In the VA Cooperative Single-Drug Therapy Study, for example, we looked very carefully at lipids over a 1- to 2-year period and reported that the thiazide had no significant effect on lipids or lipoproteins. It did have an effect on glucose, just as we've seen in other studies, but we've already discussed the net benefits of the thiazide on outcomes.

Now, to step back 16 years after ALLHAT was started and look at all the data that we have on how effective various drugs are in lowering event rates, clearly our best data are with thiazide-type diuretics, ACE inhibitors, angiotensin receptor blockers, and CCBs. And the CCBs look much better than what was thought to be the case 10 years ago.

DR MOSER: We will be asking Dom about specific combinations and Ken about the ACCOMPLISH study, but first, Bill, did you think that the difference in outcome—especially with stroke and heart failure being more common with the ACE inhibitor than with the diuretic or heart failure being more common with the CCB when compared with the diuretic—was due to a blood pressure difference? In stroke especially, in the black cohort, which was about 30% of the total group, there

was a big difference in blood pressure between the ACE inhibitor and diuretic. Is it the blood pressure difference, or was there perhaps some specific effect of the diuretic?

DR CUSHMAN: We carefully measured office blood pressure and tried to retrain people, but that's never perfect. Based on these blood pressures, the CCB and the diuretic were virtually identical in terms of blood pressure change, a mm Hg here or there, one way or the other.

There is no way, therefore, that the difference in heart failure, either clinically or statistically, can be attributed that to these blood pressure differences.

DR MOSER: Why does the diuretic appear to be better?

DR CUSHMAN: You can't say from a clinical trial mechanistically why things work, but I think that we've seen such persistent benefits of diuretics in preventing heart failure, on average about a 50% reduction compared with placebo, that it doesn't surprise me that something else that has never come close to that would do worse. I don't believe that the CCB caused heart failure; it just didn't reduce it as much as the diuretic.

DR MOSER: Do you think it may result from a slight degree of volume depletion over time?

DR CUSHMAN: I think an appropriately dosed thiazide diuretic has an effect that would be like putting somebody on a very low–sodium diet. Otherwise, the CCB and the diuretic were similar. In addition, in the non–African American population in ALLHAT, there was no difference in blood pressure change between the ACE inhibitor and the diuretic, but there was about 15% to 20% more heart failure with the ACE inhibitor when compared with the diuretic-based treatment.

DR MOSER: How did you reconcile this? Blocking the renin system should help to prevent heart failure, yet the ACE inhibitor did not turn out to be the most effective drug.

DR CUSHMAN: Right. If you look at studies like the Valsartan Antihypertensive Long-Term Use Evaluation (VALUE) and ALLHAT and you compare the ACE inhibitor or angiotensin receptor blocker to amlodipine in both studies, the curves look very similar. You have no difference in heart failure for the first 2 to 3 years, and then beyond that you see some benefit of the ACE inhibitor or the angiotensin receptor blocker over amlodipine. In ALLHAT the difference was significant, but in VALUE the difference did not achieve significance, perhaps because a diuretic was added frequently in both groups. I think there is probably a different effect mechanistically; again, we can't prove mechanisms from clinical trials, but it appears that something is different, because of the immediate benefit of the diuretic on heart failure. There was less than half the incidence of heart failure with the diuretic compared with the other drugs within the first 6 to 12 months. And so there was an immediate effect with the diuretic. It was very dramatic and it persisted.

DR MOSER: And this was true in people who had angina, who had ischemic heart disease, who had diabetes, etc?

DR CUSHMAN: The heart failure differences were seen in every subgroup.

DR MOSER: Dom, what about combination therapy, that's the buzzword of the 2000s; everybody's doing it and we all recognize that at least half of our patients, especially with stage 2 hypertension or worse, are going to need ≥2 drugs to control blood pressure. Should we start patients on 2 drugs separately or in combinations? Which patients? Should it be hydrochlorothiazide, chlorthalidone, indapamide, or some other thiazide that we should use as part of the therapy? What's your present take on this?

DR SICA: Well, I think the Seventh Report of the Joint National Committee on Prevention, Detection, Evaluation, and Treatment of High Blood Pressure guidelines were fairly progressive in recommending that 2 drugs be started at the inception of therapy if blood pressure was >20/10 mm Hg above goal.

DR MOSER: In other words, 160/100 mm Hg for most people.

DR SICA: Yes, 160/100 for nondiabetics, without chronic kidney disease, but if you do that computation, it means that at 150/90 mmHg in a diabetic patient, you're already 20/10 mm Hg above goal. The 2-drug therapy paradigm has been there for some time for many clinicians. Many drugs have a fixed ability to reduce blood pressure with a systolic blood pressure decrease of maybe 10 to 15 mm Hg on average. Because of this aspect of blood pressure–lowering response to most monotherapies, physicians should really become more familiar with 2-drug combinations, either given as individual therapies or as a fixed-dose combination.

DR MOSER: Are we at a place now where we might wish to question the present recommendations for combination therapy? Should a thiazide be one of the components, whether it's a thiazide ACE inhibitor, a thiazide angiotensin receptor blocker, or even a thiazide CCB? Or do we now have data that say that perhaps these are not the ideal combinations for most people?

DR SICA: I would say that we have to reexamine past beliefs to try to understand the role of

renin-angiotensin system (RAS) blockade combined with a CCB compared with a diuretic and an ACE inhibitor. We do not have the answers to that question. I'd personally reserve my judgment. We should discuss the ACCOMPLISH study before you try to answer this question.

DR MOSER: All right, Ken. What is the ACCOMPLISH study?

DR JAMERSON: ACCOMPLISH compared 2 different fixed-dose combinations with 2 different classes of drugs. In all, 11,464 individuals were randomized to one of two strategies, a diuretic and RAS inhibitor or a CCB and an RAS inhibitor.

DR MOSER: Was the study blinded?

DR JAMERSON: Yes. In ACCOMPLISH, the RAS inhibitor was a foundation of therapy, with a diuretic or the CCB on top. The study was stopped early when it was clear that one strategy was superior to the other. Ultimately, if you were receiving a combination of a CCB with an ACE inhibitor, there was 20% superiority compared with receiving an RAS inhibitor plus a diuretic.

DR MOSER: Was the primary outcome different, or are these different secondary outcomes?

DR JAMERSON: This was a primary outcome composed of several composite measures. The composite measures were cardiovascular death, heart attack, stroke, hospitalization for unstable angina, coronary revascularization procedures to prevent myocardial infarction and bypass, and resuscitation from sudden death.

DR MOSER: And in both regimens, were blood pressures reduced equally? The diuretic/RAS inhibitor when compared with the RAS inhibitor/CCB?

DR JAMERSON: About as equal as we can get in a clinical trial. There was a 0.7-mm Hg difference in systolic blood pressure between the two arms.

DR MOSER: So your and the ACCOMPLISH investigators' conclusions were that the combination of an RAS inhibitor and a CCB was superior to an RAS inhibitor plus a diuretic. Bill, you've studied the ACCOMPLISH trial; would you like to comment?

DR CUSHMAN: I'm on the steering committee even though I didn't help design the study, but I think the results are clear and they're consistent, even if you take out the revascularizations.

DR JAMERSON: I think one thing that's clear is that the amlodipine, a CCB, and benazepril or an ACE inhibitor combination is a good regimen.

DR MOSER: What dose of hydrochlorothiazide did they use in that study?

DR JAMERSON: The dose of hydrochlorothiazide was 12.5 to 25 mg.

DR MOSER: So 25 mg was the maximum?

DR JAMERSON: Right, and clearly that's what's been used; that's what almost all combinations in recent years have contained.

DR MOSER: Is that a reasonable and effective dose?

DR CUSHMAN: I think it's too little, but we don't know for sure. If you consider chlorthalidone at 12.5 or 25 mg as being effective for lowering blood pressure, the dose of 25 mg of hydrochlorothiazide may be too small.

DR MOSER: Do you think that if they'd used a larger dose, a better blood pressure reduction would have been noted with the diuretic/RAS inhibitor?

DR CUSHMAN: There may have been a better blood pressure reduction, but as we discussed, we can't attribute the benefits in ALLHAT to blood pressure change alone.

DR MOSER: So that may be something else that might have occurred in the ALLHAT patients to account for the better response to the diuretic?

DR CUSHMAN: You know, we have indirect data showing that a low-dose diuretic may not work very well. Let's look at the Anglo-Scandinavian Cardiac Outcomes Trial (ASCOT), in which a CCB/ACE inhibitor improved secondary outcomes more than a β-blocker/diuretic regimen. In that trial, the dose of bendroflumethiazide was one-fourth to one-half of what had been used in previous outcome studies, although a great part of the outcome difference could have been a result of using a β-blocker first. In the recent Action in Diabetes and Vascular Disease (ADVANCE) trial, a very small dose of indapamide was used, much smaller than what was used in the Perindopril Protection Against Recurrent Stroke Study (PROGRESS), a study of an ACE inhibitor and diuretic in poststroke patients in which recurrent stroke was reduced by the combination. In ADVANCE, they had much less reduction in cardiovascular events. The ACE inhibitor was also used in a lower dose than a full dose, and there was only about a 9% reduction in cardiovascular events in a diabetic population. So, to me, there's some suggestion and evidence now from several trials that we have to be careful in terms of underdosing any medication, especially diuretics.

DR MOSER: Do you think ACCOMPLISH may have underdosed the diuretic?

DR CUSHMAN: Relative to older studies, it is a lower dose, but clearly we have to do other studies. We do not have studies of chlorthalidone in combination with an ACE inhibitor or a CCB.

DR MOSER: Also, Ken, why wasn't heart failure considered an end point in the ACCOMPLISH study?

DR JAMERSON: The dose of diuretics in previous trials has been primarily driven by the need to control blood pressure. Heretofore, there has not been significant discussion of diuretics possessing unique attributes that confer benefit beyond lowering the blood pressure alone. The introduction of an argument suggesting that the dose of diuretic could influence cardiovascular outcomes can neither be substantiated nor negated by current trials. The issue of paramount importance regarding the ACCOMPLISH dosing of diuretics is that it captures the dosing strategy of more than 80% of prescribing clinicians and therefore has direct implications for millions of hypertensive patients. The results provide compelling evidence that the diuretic dose that the vast majority of patients receive (in combination with benazepril) is inferior to the combination of amlodipine and benazepril.

DR MOSER: Last comment, Dom, and then I'll summarize.

DR SICA: I don't know that it was the lower dose per se, because even if chlorthalidone was substituted in ACCOMPLISH, you still would have gotten to the same blood pressures as were recorded. You would not have had blood pressure differences per se. You might have had a blood pressure difference overnight with chlorthalidone that you may not have had with hydrochlorothiazide. There were no data about blood pressures at night. We know that chlorthalidone works for a longer portion of the 24-hour dose interval. The blood pressure differences at night may have made the difference.

DR JAMERSON: I just wanted to point out that there's an academic question here. Perhaps what most clinicians are using is not the right diuretic, and academically maybe it should have been chlorthalidone in ACCOMPLISH. But there's a message here that if you're using combination tablets that are available, there is one that's superior to the other, and it turns out that the ACE inhibitor with 12.5 to 25 mg of hydrochlorothiazide may not be the way to go.

DR CUSHMAN: I think there should be a strong message not to abandon diuretic use but clearly not to use doses that have not been proven beneficial in trials. In terms of blood pressure differences, one thing we have seen repeatedly is that if one regimen starts out more effective in lowering blood pressure, even if you titrate or add other drugs, it remains the superior regimen, usually both for blood pressure efficacy and for outcomes. Because of therapeutic inertia even among very good investigators, you never completely overcome the early difference in blood pressure. We have seen that now in every single trial in which there's even a small difference in blood pressure.

DR MOSER: Let me summarize. Diuretics have been in use since 1957, and we probably have more accumulated data on these drugs than any other antihypertensive drug. We have excellent outcome data in the young, the elderly, diabetics, and nondiabetics that these are effective as monotherapy in some studies and in combination with other medications in reducing not just stroke and heart failure but coronary heart disease events and progression to renal failure.

The question is, do we continue to use hydrochlorothiazide, which is the drug that most physicians have become accustomed to? This may be because when we were using other diuretics, such as chlorthalidone, we were giving dosages of 50, 100, or even 200 mg/d. A great deal of hypokalemia occurred and people were concerned about it. Should we begin to use more chlorthalidone in doses of 12.5 or 25 mg, which we think are equivalent to about 25 or 37.5 mg of hydrochlorothiazide? This is the agent used in the clinical trials in the United States with good results and with a longer duration of action than hydrochlorothiazide.

Another question is this: We've all gotten used to using a thiazide plus an RAS inhibitor, a thiazide and a β-blocker, or a thiazide and CCB as therapy in a large number of cases, and the results of treatment have been good. But now these combinations have been challenged by the results of a large randomized blinded study that suggest that a combination of an RAS inhibitor and a CCB may indeed be more effective in preventing events than a thiazide (hydrochlorothiazide)/RAS combination.

These results should be considered when we advocate therapeutic interventions. We should also consider that if the diuretic had been given in larger doses or a different diuretic was used, the results might have been different. At present, this question cannot be answered.

Disclosure: This expert panel discussion was supported by Takeda Pharmaceuticals North America, Inc., including an honorarium for each author for time and effort spent participating in the discussion and/or reviewing the transcript for important intellectual content before publication. The authors maintained full control of the discussion and the resulting content of this article; Takeda Pharmaceuticals North America, Inc., had no input in the choice of topic, speakers, or content.