expert roundtable »

Treating Special Populations with Hypertension: Is a Two-Drug or Fixed-Dose Combination Therapy Appropriate Initial Treatment in Hypertension?

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Moderated by **Jan Basile, MD**[1]
Discussants: **Alan Gradman, MD**[2], **Shawna Nesbitt, MD**[3], and **Matthew Weir, MD**[4]

DR. BASILE: Over 70 million Americans, and 1 billion people worldwide, have hypertension, classified as a blood pressure (BP) greater than or equal to 140/90 mm Hg. With as many as 50% of adults from Westernized societies projected to have hypertension by 2025, physicians will continue to be challenged with treating this major cardiovascular disease.[1]

Currently, physicians are utilizing one or more antihypertensive medications, with lifestyle modifications, to get BP controlled to levels below 140/90 mm Hg. Both in clinical practice and in clinical trials a majority of patients may require two or more antihypertensive drugs to be effectively controlled. Thus, the clinician is challenged to determine whether one or more drugs should be started in patients with hypertension, especially in patients who are part of special populations.

I am Jan Basile, from the Medical University of South Carolina and Ralph H. Johnson VA Medical Center in Charleston, South Carolina. With me today are Dr. Shawna Nesbitt, of the University of Texas Southwestern Medical Center in Dallas, Texas; Dr. Matthew Weir of the University of Maryland Medical Center in Balti-

The following Expert Roundtable Discussion was held on June 27, 2011. Dr. Jan Basile from the Medical University of South Carolina/Ralph H. Johnson VA Medical Center moderated the topic "Treating Special Populations with Hypertension: Is a Two-Drug or Fixed-Dose Combination Therapy Appropriate Initial Treatment in Hypertension?" with Drs. Alan Gradman from Temple University, Shawna Nesbitt from the University of Texas Southwestern Medical Center, and Dr. Matthew Weir from the University of Maryland Medical Center participating.

The discussion focused primarily on: (1) when to use monotherapy compared to combination therapy in newly diagnosed hypertensive patients; (2) the role of baseline blood pressure, age and medical comorbidities as a determinant for monotherapy compared to combination therapy; (3) the barriers to combination therapy including education, side effects, insurance coverage; (4) the tolerability of combination therapy; (5) the use of certain antihypertensives in special populations; (6) the use of preferred combination therapies; (7) the use of monotherapy compared to combination therapy in elderly patients; (8) the use of combination therapy in patients with chronic kidney disease. (*Med Roundtable Cardiovasc Ed.* 2011;2(4):225–234)

TRIALS DISCUSSED:
ACCOMPLISH, ALLHAT, HYVET, SHEP, STITCH

COMPOUNDS DISCUSSED:
amlodipine, chlorthalidone, benazepril, hydrochlorothiazide benazepril, bendrofluazide

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more, Maryland; and Dr. Alan Gradman of Temple University School of Medicine in Pittsburgh, Pennsylvania.

While I realize the three of you are often involved in seeing more complicated cases of hypertension and may not often have an opportunity to begin antihypertensive therapy in a newly diagnosed patient, if you were to see a patient with uncomplicated hypertension, how would you decide if a single agent or two or more agents should be utilized when first initiating hypertensive therapy? Let me first start with you, Shawna. How do you approach that?

DR. NESBITT: You know, I really do use the guidelines to help me to make decisions.[2,3] These suggest that single drug therapy is appropriate in patients with stage 1 hypertension (BP 140/90 mm Hg–159/99 mm Hg without signification target organ involvement. If stage 2 hypertension is present, (BP 160/100 mm Hg or higher), or significant target organ involvement is identified, then two drug therapy is justified. I think that when we start to look at what is the risk of the patient, what is the BP level, and what am I actually treating, this helps me to make the decision. The consensus statement, as it relates to African-American patients who are at distinctly higher risk for target organ damage associated with elevated BP, takes the approach that we ought to increase aggressiveness in order to get BP under control.

In the International Society of Hypertension in Blacks (ISHIB) document, we have taken the treatment guideline a little bit further.[3] We have set the treatment goal from 140/90 mm Hg down to 135/85 mm Hg. For people who have diabetes and renal disease, we've kept the goal at 130/80 mm Hg. If the levels are 15 mm Hg systolic or 10 mm Hg diastolic above these goals, we have to decide whether or not we are going to use two-drug therapy to start, which the guidelines recommend.

DR. BASILE: Okay, thank you. Alan, you were the lead author in the American Society of Hypertension (ASH) Position Paper on combination therapy in hypertension.[4] Would you comment on the evidence base for both Shawna's recommendation of treating BPs of 150/95 mm Hg, or 15/10 mm Hg above the minimum goal of 135/85 mm Hg set for Blacks with two drugs,[3] in comparison with the Seventh Report of the Joint National Committee on Prevention, Detection, Evaluation, and Treatment of High Blood Pressure (JNC 7) criteria of 160/100 mm Hg or 20/10 mm Hg in all patients with hypertension?[2] How do you approach single-drug therapy or combination therapy?

DR. GRADMAN: Generally the level of BP at baseline is the primary determinant of whether two-drug therapy or single-drug therapy is initiated. There is evidence that even in patients with stage one hypertension, initiating patients with two drug therapy results in more rapid goal attainment, as well as a higher percentage of patients who achieve target BPs.[5]

So, even though the current standard of practice is to use baseline BP as the primary determinant, an argument can be made to treat even more patients with initial two-drug or combination therapy than are recommended by various guidelines.

With regard to the evidence base, which was your question, the question is what evidence are you talking about? In terms of end-point reduction I'm not sure that there is much evidence basis to support initiation of two-drug therapy. However, in terms of BP reduction and target BP attainment there is a great deal of information that documents that initiating multiple drug therapy gives you more BP reduction and faster attainment of target BP.[5]

DR. BASILE: Matt, what are your thoughts?

DR. WEIR: Basically, my decisions about using two-drug or combination therapy in patients is based on their current BP and how far they are from the goal. First, I establish what I feel would be the most appropriate goal BP for them based on their age, medical comorbidities, et cetera, and then I estimate how far they are from that goal. My general rule of thumb is that it is probably going to take one medication for every 10 mm Hg of systolic BP reduction.

If they are more than 20 mm Hg from goal, i.e., 160 mm Hg systolic BP or higher, I would start them on a single pill combination, especially if their prescription program would allow this. Obviously, if their program precluded that, I would be left with using two separate medications.

My philosophy for using a combination of two medications is simply grounded on the fact that hypertension is just only one disease treatment process, and patients will often require other medications. I prefer to keep the pill burden to a minimum in order to help compliance.

I would preferably use a single pill combination including a renin-angiotensin system (RAS) blocking drug and either a thiazide diuretic or a calcium channel blocker (CCB), depending on which I thought would be better tolerated.

DR. BASILE: What do you think are some of the obstacles that do not allow clinicians to use two drugs as initial therapy? Alan, let's start with you.

DR. GRADMAN: Well, one of the obstacles may be the education of physicians who, in some cases—and I think this applies more to older physicians—have been taught that it's better from a safety standpoint to initiate one drug and be able to determine its specific effects and side effects. I think that is one barrier. The other barrier is one that Matt just mentioned: Insur-

ance coverage may dictate initiation of a single drug rather than initiation of two drug therapy. These are the two main barriers, I believe to the use of combination therapy.

DR. BASILE: To get around that second one they could use two single pills that may be less expensive if they cannot get a single-dose combination as part of their prescription plan.

DR. GRADMAN: That's another option, yes. I would add, however, that I believe we, as clinicians, must insist on our prerogative to select antihypertensive therapy on the basis of optimal efficacy, and not allow others to obtain our consent to utilize inferior treatments.

DR. BASILE: Shawna, in the population that you often see in Texas, what do you think some of the obstacles are?

DR. NESBITT: I would agree with what's already been stated about the major obstacles—physicians' understanding for the need for multiple drug therapy and the consideration for side effects. Some of the problems may be experience-based and a failure to understand that there is synergy in some combinations that may make management easier.

In fact, there may be contraindications to some of the combinations of antihypertensives. All antihypertensives are not the same. While they all lower BP, the mechanisms of two or more agents given together don't necessarily fit. I think that education for physicians and other providers could go a long way in helping to make better choices in how we put medications together.

Then the other part of it really speaks to how well we can get the system to support improving our outcomes by helping to financially support patients to be more compliant with one pill if this is necessary for treatment.

DR. BASILE: Matt, anything else to add?

DR. WEIR: I would add that the major decision process I use for choosing medications is largely based on tolerability. I have a firm belief that the vast majority of people should be treated with a RAS-blocking drug, in large part because they are so well tolerated. They certainly work well with thiazide diuretics and CCBs in lowering BP.

Plus, I am impressed with the quarter of a century of data that we have, which demonstrates that RAS blockers provide an approximate 20% relative risk reduction benefit in people with evidence of heart disease and kidney disease. Although we lack data on the benefit of these drugs on disease progression early in the disease process, their tolerability plays a role in my choosing them as a first-line therapy.

"I think thiazides offer the advantage of an anti-calciuric effect, so that women will tend to retain calcium, which has been demonstrated to facilitate bone mineralization with older age."

~ Matthew Weir, MD

I prefer using thiazide diuretics with RAS blockers for women, in large part because women prefer being more svelte and really don't have as many problems with gouty arthropathy or libido problems as men might have with thiazides.

For men, I prefer using calcium blockers, in large part because they don't affect libido, and if there are problems with ankle edema it's less of an issue than it is in women because men wear more comfortable shoes and long pants.

Lastly, I think thiazides offer the advantage of an anti-calciuric effect so that women will tend to retain calcium, which has been demonstrated to facilitate bone mineralization with older age.

DR. BASILE: Let's go through some of these special populations. Matt, you've already brought up women. Alan, let me turn to you; in women without a compelling indication for a particular class of antihypertensive drug, what do you use, or how do you approach initial single-agent therapy in women? Do you pretty much agree with Matt?

DR. GRADMAN: For the most part, yes. I tend to prefer RAS drugs as first step treatment and I don't think there is any difference in terms of BP response between men and women. I avoid the use of these agents, however, in women of childbearing age who wish to become pregnant. In such patients, low dose diuretics and CCBs are suitable alternatives.

If I'm using monotherapy it tends to be one of those drugs, although certainly diuretics and CCBs have equal evidence basis in terms of long term end-point reduction and they're all well tolerated agents. But, on balance, I prefer the RAS drugs because they have no dose-dependent side effects and because of their overall tolerability and efficacy.

DR. BASILE: JNC 8 is being put together; what do you think they will say about women? Matt suggested that perhaps for the bone mineral density effects that he uses a thiazide diuretic in women, certainly women at risk for osteoporosis. Do you think that based on gender there is any particular evidence for different classes of drugs as initial therapy?

DR. GRADMAN: Not really. The only thing that I would mention is that

there is a high percentage of hypertensive women and men who are obese and of course those patients tend to have abnormalities of glucose metabolism. One can throw the other side of the metabolic effects of diuretics into the equation. They may improve calcium metabolism, but they may worsen glucose metabolism and I think that's another feature that needs to be kept in mind.

DR. BASILE: Shawna, how do you feel about that?

DR. NESBITT: Well, in the ISHIB consensus statement we opted for the RAS/CCB combination as a preferred agent unless there is a compelling indication for a diuretic because of volume.[3] In the Avoiding Cardiovascular Events Through Combination Therapy in Patients Living With Systolic Hypertension (ACCOMPLISH) trial,[6] which compared the RAS/CCB combination to a RAS agent plus a diuretic, it distinctly showed that even with identical BP control there was a 20% mortality benefit to the RAS/CCB combination. I think that while we don't have a clear explanation for the results, I think it says a lot about what we should be recommending in terms of not just getting BP under control for a patient.[7]

When the data were examined, specifically with respect to the African-American population, which was sizable for a clinical trial in this day and age, we saw the same effect. When you then look at the data with 24-hour ambulatory BP recordings—because some of the suggestions have been, "Could this be because the BP control was not achieved as well on a 24 hour basis?"—there was no difference between the angiotensin-converting enzyme (ACE) inhibitor/CCB and the ACE inhibitor/diuretic groups. I think that it's warranted to suggest that we ought to go for mortality benefit because it's not just about BP control. This is really about target organ damage.

On the other hand, I think there are a number of patients who have volume concerns, and as Matt points out, that the edema from the CCB is unbearable, and in those patients, the diuretic combination is better, but I'd start with a RAS/CCB as my basis for therapy.

DR. BASILE: So from what you said, Shawna, you're pretty much putting the thiazides as a third step agent. But remember, ACCOMPLISH is only one study, and there have been several where thiazide diuretics proved to be effective in reducing morbidity and mortality.

DR. NESBITT: As a third line after RAS/CCB, if a patient is not controlled, but if a patient is not a candidate for the RAS/CCB then they would be on RAS/diuretic, so it would be second step in that case.

"I tend to prefer renin-angiotensin system drugs as first line treatment and I don't think there is any difference in terms of the response between men and women."

~ Alan Gradman, MD

DR. BASILE: What would not make them a candidate for the RAS/CCB?

DR. NESBITT: If someone is volume overloaded, as in patients with kidney disease or who are edematous, I think that patient probably needs a diuretic as part of their therapy.

DR. BASILE: Very interesting. Matt, how do you feel about that?

DR. WEIR: I am a firm believer in the ACCOMPLISH data (despite my conflict of interest: participating on the steering committee of the study and writing several of the papers). We do not have an explanation as to why there was an advantage to the CCB over the thiazide diuretic with the ACE inhibitor. My suspicion is that tolerability is a key factor, but there may also be metabolic differences between the two combinations in favor of the ACE/CCB. In my experience, women have a tougher time tolerating higher doses of amlodipine, compared to men. Realistically, if I can't get to goal with lower doses of well tolerated medicines, I might even use three medications. There are even single pill combinations of thiazides, calcium blockers, and RAS inhibitors. I think this is a very reasonable approach if one needs lower doses of three drugs to avoid side effects.

Since hypertension is a lifelong, progressive, largely asymptomatic disease process, I think we have to be mindful of that as we pursue our therapeutic choices.

DR. BASILE: Alan, how do you feel? JNC 7[2] responded to the results of the Antihypertensive and Lipid-Lowering Treatment to Prevent Heart Attack Trial (ALLHAT), and placed a lot of stock in that particular outcomes trial. Shawna suggested that the ISHIB guidelines put a lot of stock in the ACCOMPLISH trial,[6,7] again, only one trial. It will be interesting to see if JNC 8 changes the philosophy that JNC 7 had, recommending a thiazide-diuretic for "most" as initial therapy or as part of the initial combination therapy in the treatment of hypertension. What is your thinking on that?

DR. GRADMAN: I think ACCOMPLISH is an important trial. Many of us have believed in the efficacy and safety of CCBs for a long time. However, I don't consider it definitive in establishing the superiority of calcium blockers over diuretics. If you go back to ALLHAT,[8] for example, the diuretic chlorthalidone was equal to amlodipine, the same drug that was used in

ACCOMPLISH, at least in terms of primary end-point reduction.

The other thing that we know is that, if you look at some combination therapy studies, there are a significant percentage of patients who require diuretics to achieve BP lowering. Patients who have renal insufficiency of any degree usually require diuretics. In many other patients as well, addressing volume with diuretics also turns out to be critical in terms of controlling BP.

I personally hope that they change the JNC 7 default recommendation for diuretics. On the other hand, I wouldn't necessarily put diuretics in third place behind CCBs as my preferred combination partner.

DR. NESBITT: I guess the statement here is not to suggest that CCBs are better than diuretics; however, I think that we are looking at which combination might be better. In ACCOMPLISH there was a mortality benefit that existed with the CCB that did not exist with the diuretic.

While a single agent may not necessarily be better as exemplified in ALLHAT,[8] when you combine that same agent with another agent, the combination of the two may actually perform better from a mortality standpoint.

I agree with Alan that there are going to be a significant number of patients who clearly need a diuretic, and the recommendation is absolutely that those patients ought to get a diuretic first.

DR. GRADMAN: I do not believe there was a mortality difference in ACCOMPLISH,[7] I think it was the overall endpoint—the composite endpoint that was 20% different. But there was a significant difference in strokes and myocardial infarctions, et cetera, between the ACE inhibitor/CCB and ACE inhibitor/diuretic groups.

DR. WEIR: It was the composite endpoint.

DR. GRADMAN: Yes.

DR. NESBITT: That's correct, I'm sorry I misstated, it was the overall endpoint.

DR. BASILE: So what I'm hearing is that, rather than specifically recommend a particular initial single agent for most patients with hypertension, there are different times when you will prefer to use either a RAS blocker or a CCB like amlodipine or a thiazide diuretic. At the end of the day these are the three classes of drugs as a single agent that you feel most comfortable with in people without a compelling indication. Would you agree with that, Shawna?

> ***"We're suggesting early on in treatment, depending both on the degree of blood pressure elevation and our goal for blood pressure reduction, that there will be many patients that will require two agents as initial therapy"***
>
> *~ Jan Basile, MD*

DR. NESBITT: Yes.

DR. BASILE: Matt?

DR. WEIR: Yes.

DR. BASILE: Alan?

DR. GRADMAN: Agree.

DR. BASILE: Okay. That's single-agent therapy, but we're suggesting early on, depending on the degree of BP elevation, that there are many patients who will require two agents as initial therapy. Let me just turn a little bit to some of these special populations. Shawna has already mentioned the ACCOMPLISH[6,7] trial, which compared a fixed dose combination of the ACE inhibitor benazepril with the dihydropyridine CCB amlodipine as initial therapy compared to benazepril with hydrochlorothiazide—no BP difference, but a benefit for the amlodipine combination for the composite outcome.

Let me ask you, Alan: In the ASH position paper,[4] you actually recommended one of four therapies as preferred dual agent combination therapy. Can you talk about that?

DR. GRADMAN: We did not recommended them as preferred specifically for initial therapy. We recommended them as being the preferred two-drug combination in general. Also, I would agree if one were going to choose initial therapy, then we would pick from among four drug categories. Again, I think we've talked about the reasons that we all prefer RAS blockers in terms of their end-point reduction data in patients with renal disease, in patients with heart failure, and in patients with established vascular disease.

We have also discussed the differences between diuretics and CCBs, in terms of their end-point effects. Beyond that, a positive feature of these combinations relates to the fact that, in addition to having additive effects on BP reduction, they also may improve the tolerability profile of the combination partners.

For example, if you combine a diuretic with either an ACE inhibitor or an angiotensin receptor blocker (ARB), you attenuate the degree of hypokalemia and the frequency with which clinically significant hypokalemia occurs. Maintaining metabolic balance is a very positive feature of these drugs. By the same token, if you combine an ACE or an ARB with a dihydropyridine calcium blocker cer-

tainly, you tend to reduce the magnitude of edema, which is the dose limiting side effect of those CCBs.

I think there are many good reasons, in terms of BP reduction, tolerability, and evidence-based end-point reduction, that favors the use of these medications in combination therapy.

DR. BASILE: Matt, how do you feel about that?

DR. WEIR: I think there are pros and cons as to how you choose the mate for the RAS blocker. I've already given you some specific insights that I use primarily based on tolerability for the different genders.

As Alan mentioned, the beauty of the RAS blocker is that it attenuates some of the metabolic effects of the thiazide diuretics. They attenuate the pedal edema associated with CCBs. It is fair to say also that any of the two drug combinations are equally effective in terms of their abilities to lower BP with RAS blockers.

I think if you add to the improved tolerability with better BP reduction, in one pill, it is a win-win situation. Which approach you use needs to be individualized, based on tolerability.

DR. BASILE: Okay. I want to talk a little bit about the elderly patient with hypertension because I think we're changing some of our thoughts on how to approach these patients. Evidence is available to suggest that they be treated regardless of their age, as in the Hypertension in the Very Elderly Trial (HYVET),[9] where the oldest of the old (mean 84 years of age) benefited with a reduction in mortality when compared to placebo therapy.

Many clinicians are reluctant to start two drugs in elderly patients with hypertension. Alan, let me start with you and ask, are there situations where you might start with two drugs in an elderly patient with hypertension?

DR. GRADMAN: There are situations in which treatment should be initiated with a combination. Remember, however, that the majority of elderly patients with hypertension have isolated systolic hypertension. The target BP in this population is not quite as clear as perhaps JNC 7[2] would indicate. There are some people who state that there is no proven advantage to lowering systolic pressure below 160 mm Hg. HYVET,[9] which enrolled patients over the age of 80, used 150 mm Hg systolic as the target BP.

This is just a lead-in to the fact that the standard approach that we use in younger patients with combined systolic-diastolic BP elevations may not necessarily apply to people who have isolated systolic hypertension with low or normal diastolic BPs. Some data suggest that too low a diastolic BP may be associated with an increased risk of cardiovascular events in patients who have coronary disease. For these reasons I think there is some reluctance to use aggressive initial combination therapy, particularly in very elderly patients who have isolated systolic hypertension.

Now, if you talk about patients who have combined systolic-diastolic hypertension then I believe those patients can be started on two drugs or combination therapy using the same criteria that we previously discussed for other patient subgroups.

DR. BASILE: Matt, should elderly patients be started on two drugs?

DR. WEIR: Well, let me first go on record and say I object to the word "elderly." I think what is more appropriate is "older," because that terminology in all of us is changing as we get older ourselves.

It is a question of where you are with the patient and where you hope to be. I am not against using two medicines in an older patient. Let's say, for example, if they are higher than 25 or 30 mm Hg systolic BP from goal—in other words, with a systolic BP of more than 165 or 170 mm Hg. I am always more cautious in older patients, and I always carefully monitor them for positional changes in BP. As we age, the baroreceptors are not as responsive as they once were, and this increases the risk for orthostatic symptoms, which obviously can be substantial in an older patient who may be infirm, not have as good balance, or neuropathy, et cetera.

As for the medications I would use, I think we have good supportive evidence for the use of thiazide diuretics, CCBs, and drugs that block the RAS. We've already discussed some of the different trials that have supported the use of these medicines, so I would be using those three as treatment considerations.

I would be a little bit more careful about beta-blockers, unless the patient had known heart failure or coronary artery disease, in large part because we know the beta blockers also tend to predispose to some degree of orthostasis, and we also know they tend not to be as protective against incident stroke compared to other drugs like calcium blockers, thiazide diuretics, and RAS-blocking drugs.

DR. BASILE: Yes, the most recent recommendations by the consensus document on the older hypertension patient is that systolic BP values of less than 140 mm Hg are appropriate goals for most patients who are less than 80 years of age, but for those 80 and older, as in the HYVET, 140 to 144 mm Hg, if tolerated, can be acceptable.[10]

The report went on to highlight HCTZ, chlorthalidone, bendroflumethiazide, and indapamide, a thiazide-like diuretic used predominantly in Europe, as diuretics of choice. Based on this recommendation I would like to follow up on the use of chlorthalidone specifically in the elderly.

DR. WEIR: Older!

DR. BASILE: Excuse me, in the older patient. And I guess this recommendation is based on both the ALLHAT[8] and the Systolic Hypertension in the Elderly (SHEP) trials,[11] which reported definite outcome benefits in older patients with chlorthalidone. What are your thoughts on this?

Let's start with you, Shawna, as you already mentioned the ACCOMPLISH trial, which used HCTZ and found it to be a less effective partner with a RAS blocker than the CCB, amlodipine. What are your thoughts on chlorthalidone compared to HCTZ?

DR. NESBITT: You know, it's an interesting debate, and it's one that we don't have a clear answer to, except that we know that chlorthalidone compared to HCTZ, pharmacologically speaking, is more potent. We know it's longer acting, and we know it will lower BP more effectively.

My concerns for older patients, however, are that I worry about giving high dose diuretics to any older patient because of the concern about low sodium, which I do see reasonably frequently in my little old ladies and I worry about low potassium.

Because chlorthalidone is more potent there is a likelihood of seeing those complications even more frequently in that population, although in SHEP and ALLHAT this did not seem to occur. Although I think you can use it, you certainly need to be more vigilant about using a more potent diuretic in this population, where the side effects, like a hip fracture, will be more dangerous. Hip fractures were, however, not more common in the SHEP diuretic-treated cohort compared to placebo.

DR. BASILE: Your points are well taken. We may be guilty of telling our older patients to restrict sodium and they end up taking in a lot of free water, which can result in hyponatremia as well as hypokalemia. So when using a thiazide diuretic, especially in the older patient, sodium as well as potassium has to be followed.

Alan, what are your thoughts on the chlorthalidone dilemma? Should it be the preferred thiazide in the older patient, where the evidence is greatest for its use?

DR. GRADMAN: Good question. One thing I would add is that I would reemphasize indapamide in the list of diuretics where there is evidence of benefit in the elderly. This was the drug that was used in HYVET and, in addition to producing major stroke reduction, there also was a 21% mortality reduction compared to placebo.[9,12] It is one of the only hypertension trials to my knowledge that has shown a reduction in overall mortality. I think I would include indapamide in the list of diuretics to be considered.

"My concerns for older patients, however, are that I worry about giving high dose diuretics to any older patient because of the concern about low sodium, and I worry about low potassium in them and the complications that they will develop from it."

~ Shawna Nesbitt, MD

To get back to your question about chlorthalidone, I would agree with much of what Shawna said. We know that chlorthalidone is a longer acting drug; it's more potent on a milligram per milligram basis, and I would agree that the use of a low dose is preferable.

I don't think we have the answer to the question of chlorthalidone compared to HCTZ from an end-point perspective, but there is no question that the body of evidence favors chlorthalidone at this particular point in time, just because it was used in several US trials.

DR. BASILE: Matt, any thoughts on this?

DR. WEIR: I am in complete agreement with the points that Alan made.

DR. BASILE: In the older hypertensive do we have good evidence to start with two drugs or a combination, i.e., has any clinical trial evaluated the 20/10 mm Hg rule that JNC 7 recommended (i.e., two drugs for BPs greater than 160/100 mm Hg). Matt, do you know how many older people there were in ACCOMPLISH?

DR. WEIR: I can tell you the average age in the study was 63.[7]

DR. WEIR: So that gives you a good clue that many, if not most, of the patients were in their 60s, and obviously a fair number were also into their 70s.

DR. BASILE: Do you think there is an age range or an age where perhaps we shouldn't use two drugs as initial therapy, even when the pressures are high and it may be difficult for BP to get to goal, Matt?

DR. WEIR: I think it is appropriate for older people. It just gives them a leg-up on the ever-advancing pill counts. It will improve compliance; it will probably reduce the likelihood of missing doses. I am not making an argument from day one to start older patients on a single pill combination, but if they can be carefully titrated to their ideal BP goal, one can then consolidate their medications into fewer pills.

DR. BASILE: Okay, Alan, how do you feel, one drug in the oldest of the old to start with?

DR. GRADMAN: My usual practice is to start with one drug. As per your dis-

cussion of the recent consensus document, I don't think we have very clear evidence for selection of target BP in older patients, particularly in the very elderly, and I don't think we have clear evidence as to the basis for whether or not to routinely begin combination therapy.

At this point it's up to the discretion of the physician. I tend to err on the side of caution. It should be noted, however, that if you look at the studies and the literature there has never been an excess of major adverse events in elderly people started on two drugs or combination therapy, so it's probably safe.

DR. BASILE: Shawna, how do you feel?

DR. NESBITT: I tend to agree with what's been said. I guess my only concern about the elderly as it relates to clinical trials is that we don't have combination trials in older patients, meaning over 80. In patients over 80, I have not really started them on combination therapy as the very first step of treatment, although once they are on treatment and are not controlled, I think switching to a combination is appropriate. I think the 140 to 145 mm Hg systolic BP range is probably a reasonable one.

DR. BASILE: That seems reasonable and a practical approach to treating these patients with hypertension. Let me turn last to patients with chronic kidney disease (CKD). Matt, what is your approach to both single- and multi-agent therapy in patients with CKD, and at what estimated glomerular filtration rate (GFR) do you feel that thiazide diuretics may no longer be effective?

DR. WEIR: This is not well studied. My personal opinion is that decisions about diuretic support should be based in part on the physical exam, and the degree of the BP elevation.

As the GFR decreases to 50 ml/min/1.73^2 or below, my thoughts on which thiazide diuretic to use changes more from HCTZ to chlorthalidone, and then eventually towards loop diuretics. The diuretic action of thiazides diminishes as the GFR drops, since they have to be filtered, and then reabsorbed in order to achieve their activity within the kidney.

Obviously as GFR declines you need a larger dose of a drug to provide the same diuretic effect as in someone with a higher GFR. That being said, we also know that thiazides have peripheral vasodilatory activities. The interesting question is whether thiazide diuretics have antihypertensive properties, which are independent of their effects on volume reduction, in patients with lower GFR. That's an area where we do not have good clinical data.

It's an important question, because if thiazides possess antihypertensive activity in lower GFR patients, it may require them to be euvolemic to see the effect, as increased blood volume offsets the antihypertensive properties of all drugs.

DR. BASILE: Do you feel that there is an ideal two-drug combination in patients with CKD?

DR. WEIR: I think a RAS blocking drug is part of the equation for everybody, whether they have kidney disease or not. I think the decision about whether they need a diuretic or a calcium blocker is the next step. This should be based on the degree of renal insufficiency and the assessment of volume.

More often than not, as the GFR decreases, the likelihood of requiring a diuretic goes up substantially. People with kidney disease tend to be salt retainers (although this is not true for all forms of kidney disease).

Decisions about diuretic use need to be individualized. Often people with kidney disease will need three medicines, given the fact that they should be treated to a lower systolic BP goal of about 130 mm Hg.

DR. BASILE: Alan, your thoughts on that?

DR. GRADMAN: Certainly I agree with most of what Matt said. Of course you don't get much additive BP-lowering effect when you combine most beta-blockers with RAS inhibiting drugs. Basically I would agree with Matt. I do think that you need loop diuretics in patients who have significant renal insufficiency—that there may be some advantage to using longer acting loop diuretics like torsemide, for example, as compared to furosemide, and that treating volume is a necessity in patients who have renal insufficiency. Even if they're not constantly volume overloaded, the time course of sodium excretion is changed even in patients with mild renal insufficiency and it's important to avoid transient increases in blood volume, which may adversely affect BP control.

DR. BASILE: Shawna, anything else you'd like to add?

DR. NESBITT: Well, I think, going back to the ISHIB consensus statement, these are the patients that you would want to start with a RAS blockade and a diuretic, rather than the RAS plus the CCB agent, as an initial consideration for combination therapy.

Frequently three agents are needed, and in these cases probably the CCB as the third agent would be the alternative in order to get them to the goal. Again, I think Alan mentioned that with a GFR of less than 30 or so they probably will need a loop diuretic in order to get volume control.

DR. BASILE: Well, we've covered a lot of ground. Let me try to summarize what we have said. I think there has been some agreement that we're not quite sure that there is a best initial antihypertensive medication in patients

without a compelling indication, although there may be some favorites in some special populations.

I heard you all suggest using either a RAS blocker, a CCB—preferably of the dihydropyridines type, mentioning amlodipine—or a thiazide diuretic (preferably chlorthalidone) as possible initial therapy in patients with hypertension. There was less enthusiasm, especially in the older patient, for the use of a beta-blocker unless there is a compelling indication for their use, and there was no mention of a direct renin inhibitor (DRI) as initial therapy in hypertension.

We didn't have time to discuss other medications, such as mineralocorticoid receptor antagonists, like spironolactone or eplerenone, that are more often used in those with resistant hypertension. However, I will ask you all, if you do use a drug like a spironolactone in therapy before these three main classes: RAS blockade, thiazide diuretic, and CCB.

I heard a lot of agreement on the use of initial two drug combinations when there was a larger burden to get to goal BP, either a 15/10 mm Hg as in the ISHIB guideline elevation above goal (greater than 150/95 mm Hg), or a 20/10 mm Hg elevation as in the JNC 7 goal (greater than 160/100 mm Hg). Alan pointed out that the recent Simplified Therapeutic Intervention to Control Hypertension (STITCH) trial suggested that even in stage one hypertension where there is less than a 20/10 elevation in BP that either an ACE/diuretic or an ARB/diuretic as initial therapy allowed patients to get to goal more effectively over six months of treatment without any more side effects.[5]

Finally, which is the best two-drug combination is debatable. Shawna suggested that a CCB and RAS blocker, based on one study, ACCOMPLISH, was better than HCTZand a RAS blocker despite equal BP reduction. Others pointed out the differences in chlorthalidone and HCTZ, especially in the older patient.

Alan mentioned indapamide, another evidence-based thiazide-type diuretic not often thought about in this country that has been used in clinical trials that often originated overseas.

There is always controversy in treating patients with hypertension. Does anyone have any final comments before we wrap it up? Shawna?

DR. NESBITT: Just to clarify points made earlier, I would say that I'm not sure that I intended to suggest that DRIs would be considered that much differently than RAS blockade in my mind. I probably would use them in some patients as an initial agent for the treatment of hypertension.

DR. BASILE: Alan and Matt, do you agree with that?

DR. WEIR: Yes, absolutely, compared to an ACE or an ARB. I consider them therapeutically equivalent, and equally well tolerated for lowering blood pressure.

DR. GRADMAN: Yes, I would agree with that—the only caveat would be that in patients who have specific indications, for example, patients who have type II diabetes with proteinuria in which there are specific Food and Drug Administration indications for ARBs, for example, I would prefer the ARB, but generally speaking I agree with including a DRI in the RAS blocker category.

DR. BASILE: Let me add that I don't know of any clinical trial where the DRIs have been used as initial therapy. We have no outcomes; although they certainly do lower BP and are Food and Drug Administration-approved for hypertension. I would prefer an ACE or an ARB with the outcomes that we have before I'd start with a DRI.

I appreciate what Alan said about adding a DRI to an ARB in nephropathy, et cetera. I think JNC 8 will have a similar approach to this class of antihypertensive agent.

DR. GRADMAN: The only thing is that these are general recommendations, and comorbidities often alter our drug selection. You mentioned diabetic nephropathy in patients with proteinuria. There a combination of an ARB and a DRI might be an appropriate initial treatment. In cardiology we see lots of patients who have coronary disease and heart failure in whom beta-blockers are a very important component of therapy and I don't think we should forget about them. These agents still have a large place in the treatment of hypertension. I think it's very important to pay careful attention to comorbidities.

DR. WEIR: I still think, with a lifelong, progressive, largely asymptomatic disease process, that tolerability of medication is a major concern. Simplicity is important, and our best opportunities to facilitate compliance will require us to pay attention to strategies to consolidate pill counts with well tolerated medications. This will help us get more patients to what we feel is an appropriate goal BP.

DR. BASILE: I want to thank each of you for your expertise and your time.

Dr. Basile is a consultant for Boehringer Ingelheim, Forest Labs, Daiichi-Sankyo, and Takeda Pharmaceuticals and has served on speaker's bureaus for Daiichi-Sankyo, Forest Labs, Eli Lilly/Boehringer Ingelheim and Takeda Pharmaceuticals. Dr. Basile has also received grant/research support from NHLBI. Dr. Weir has served as a scientific advisor to Daiichi-Sankyo. He has no other conflicts of interest to disclose. Dr. Gradman is a consultant for Daiichi-Sankyo, Novartis, Forest Laboratories, and Takeda, is a speaker for Daiichi-Sankyo, Novartis, Forest Laboratories, and Takeda and has

received research support from Novartis. Dr. Nesbitt is a consultant to and speaker for Novartis Corporation. She also reported that she is a consultant to Daiichi-Sankyo, Inc. and a speaker for Forest Laboratories, Inc. and Boehringer Ingelheim Corporation.

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