Expert Panel Discussion

Improving Blood Pressure Control Rates: Is There More We Can Do?

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A panel discussion was convened on November 10, 2006, to discuss methods of improving blood pressure control rates and future study focus. The expert panel was moderated by George L. Bakris, MD, Director, Hypertension Center, Endocrine Division, the University of Chicago School of Medicine, Chicago, IL, and included Matthew R. Weir, MD, Division of Nephrology, the University of Maryland School of Medicine, Baltimore, MD, and Henry R. Black, MD, Roberts Professor of Preventive Medicine, Rush University Medical Center, Chicago, IL. (J Clin Hypertens. 2007;9:134–142) ©2007 Le Jacq

DR BAKRIS: Well, what we are here today to talk about is improving blood pressure (BP) control rates and methods and new research to help achieve better percentages of goal in the US population. We're going to go through some questions today to engage our panel and see what insights they can give us in terms of BP goals. Now let me start off with you, Henry. Looking at the evaluation of patients presenting with refractory or complicated hypertension, what kinds of things do you look at, assuming now that they're on one medication? What kinds of things do you look at in terms of deciding whether they need a combination up front or whether you start with another agent? Why don't you walk us through that?

DR BLACK: Well, when I first see a patient, whether they're on treatment or not and almost no matter what else they're on, I first determine whether they're at the goal I expect them to be. Now I understand that goals are somewhat arbitrary and dichotomous and there's really not that much difference between someone who's 1 or 2 mm Hg above goal compared with someone who is 1 or 2 lower and is thus at goal. Once I decide that they're not where I want them to be (at goal), then I have a series of factors that I assess, some relatively "simple" things such as whether they are actually taking their medicine. While that question may appear to be simple, it may be a very difficult thing to assess accurately. Patients don't always confess that they aren't following "doctor's orders." But, in general, the people that we see at a tertiary center are at least committed to taking their medicines. In a primary care setting, however, noncompliance is probably the major reason treated hypertensive patients fail to reach goal.

After deciding that the patient is adherent to the recommended regimen, I then look for some clinical clues for a secondary cause of his or her hypertension. While I don't necessarily or routinely do an extensive workup for secondary hypertension in all resistant patients, I will pursue a specific diagnosis if I have some baseline laboratory data from another source that suggests the diagnosis or if I find something in the history and physical examination that raises my index of suspicion (a poor man's prior probability). Examples would be a low serum potassium, either untreated or while on diuretics, or in a patient with refractory hypokalemia (one whose serum potassium remains low in spite of potassium supplementation or while on angiotensin-converting enzyme [ACE] inhibitors, angiotensin receptor blockers [ARBs], or aldosterone blockers). This is a patient in whom mineralocorticoid excess state should be excluded. Some patients will have symptoms consistent with a pheochromocytoma, but they usually do not present with refractory hypertension. I would monitor patients with the typical clinical

characteristics of renovascular hypertension (bruits, renal insufficiency without an active sediment, or proteinuria). I also look at their lifestyle to see whether they are overweight, how much salt they eat, and whether they are sedentary or not. Then I would formulate my plan. It's a little bit different for patients with certain conditions such as diabetes, heart failure, or chronic kidney disease, but, for the most part, the initial evaluation is similar.

DR BAKRIS: Let me ask you, Matt, is there anything you want to add to that?

DR WEIR: I always focus on the use of lifestyle modification, but I also will not wait for a miracle to happen, and I am most interested in earlier treatment for people with higher cardiovascular risk to support nonpharmacologic maintenance. If they're more than 10 mm Hg systolic from goal, I think it's an unrealistic expectation to assume that lifestyle will get them to goal. So, if repeated BPs are more than 10 mm Hg from where I feel they are desirable, I will usually start a medication in conjunction with lifestyle modification.

DR BAKRIS: Okay, that's very good. Now in keeping with that, the Seventh Report of the Joint National Committee on Prevention, Detection, Evaluation, and Treatment of High Blood Pressure (JNC 7) states that more than about 20/10 mm Hg above the goal should be an indication for starting with combinations up front. Do you subscribe to that, Matt?

DR WEIR: Well, I've always been a believer of what I affectionately call the rule of 10s, and that's how I like to educate my patients. If you look at the wealth of clinical trial data that are available, most medications will reduce systolic BP by about 10 mm Hg at best, particularly if you subtract out the placebo effect. So what I like to explain to my patients is that if they're more than 20 mm Hg from systolic BP goal, I invariably will prescribe 2 medications right from the start, preferably in the form of a fixed-dose combination, as an effort to facilitate reaching goal.

DR BAKRIS: Alright, Henry, do you agree with that?

DR BLACK: I think, in principle, yes. There are a couple of things that I would do a little bit differently, but I think the main point that Matt made, namely not to consider a lifestyle modification regimen adequate, is something I really think is true. We don't have any reliable long-term data on how well these work, with an occasional exception in certain other conditions. For the most part, we're going to need a combination of treatments—some nondrug treatments and some drug treatments—to get to where we want to be. What is new and very important to emphasize now is that we have learned that we need to get people to goal relatively quickly, especially if they are at high risk. By quickly, I don't mean days or hours, I mean weeks to months. So trusting an ineffective treatment or depending on 1 drug to get you there and then stopping that and starting another one, so-called sequential monotherapy, is not a good idea. Therefore, I discuss the regimen with the patient and tell them about the medications I plan to use; I say much the same thing that Matt does. So, first, I tell them the goal I want them to get to and that since, in my assessment, their BP is too high to get to that goal with a single drug, I'm going to start 2 drugs at the beginning. I also like fixed-dose combinations because I feel they improve adherence and, more importantly, they help get BP under control relatively quickly.

DR WEIR: I would like to support Henry's statement by saying that I also shoot for a 2- to 6-month window in terms of getting to goal, in large part because a number of the recently published studies indicate that more prompt control of BP in this period of time is associated with reduction in cardiovascular events.

DR BAKRIS: Okay, that's fine, and I think this is an issue I was going to talk about later, but since you both brought it up, I think we can deal with it right now. You gave a range of 2 to 6 months to get BP to goal. I'm assuming now that if you have an 80-year-old woman or a 75-year-old woman, you're not going to shoot to get to goal in 2 months. You're going to try to go slower and wait for 6 months, is that correct?

DR WEIR: We need to individualize our approach carefully, particularly with older patients. I always like to check older patients to make sure they don't have orthostasis. Positional changes in BP can make them more susceptible to the effect of BP-lowering medications.

DR BAKRIS: Wait a minute. Let's assume that these older patients are not orthostatic, and let's assume that they don't have a pulse pressure of 100 mm Hg, that they've got a pulse pressure of, say, 75 or 70 mm Hg … In those types of patients, in whom the vasculature is still kind of healthy relative to somebody with a much wider pulse pressure, would you still take your time or would you be more aggressive?

DR WEIR: If I had a 65-year-old individual at 170/75 mm Hg, let's say …

DR BAKRIS: Okay.

DR WEIR: I more likely than not would give them a fixed-dose combination.

DR BAKRIS: Okay. Henry, do you agree with that?

DR BLACK: I want to go back to your first question.

DR BAKRIS: Okay.

DR BLACK: Should we be more gentle in our treatment in older people? We used to preach "go slow and not too low." That was a way to summarize our approach and emphasize our concerns about overtreatment, but I think we were denying them the benefits that we've learned since trials such as the Antihypertensive and Lipid-Lowering Treatment to Prevent Heart Attack Trial (ALLHAT) and Valsartan Antihypertensive Long-Term Use Evaluation (VALUE) and probably the Anglo-Scandanavian Cardiac Outcomes Trial (ASCOT). In those studies, the average age of the patients was in the high 60s and the benefit of getting to goal promptly was clear. In VALUE, for example, a trial of high-risk hypertensives, the biggest discrepancy between the 2 treatments in stroke incidence happened during the initial 3 months. We mustn't be too timid about treating our oldest patients. Surely there are some who develop hypotension and even syncope, but those cases are unusual and the overwhelming majority of patients will benefit from prompt treatment. We need to see them more often than younger patients to be sure they are able to tolerate what we have prescribed.

That's not that different from what I was saying. I referred to patients in their 60s. In any case, I think right now we're not trying to get them too low or get there too slow. In fact in VALUE, where the median age was in the high 60s, there were still a number of people who were in the age group that we tend to worry about. And, for strokes, at least in this high-risk group, the biggest discrepancy between the 2 treatments in increasing stroke rates occured during initial treatment and up to 3 months. So I think we can't be too timid about this, we can't be too concerned about the patient who's passed out as representing other people being denied. I also think we have to see them more often, perhaps—maybe we start a little slower and make up for that by seeing them more frequently if they tolerate what they start with.

DR BAKRIS: Well Henry, for perspective, because you were involved with this, how would you put this into context? You mentioned some very recent trials, how would you put Systolic Hypertension in the Elderly Program (SHEP) in that context, because patients in that traial were clearly those with predominant systolic hypertension.

DR BLACK: Right. We haven't done that as yet. It would be a good idea to look at those data to see when stroke rates began to diverge. We have enough data from trials in people older than 70 or 75 to see whether the people who had strokes were those we treated aggressively or whether early treatment reduced the stroke rates. We need to emphasize that we are not advocating the urgent approach so prevalent 15 or 20 years ago, when sublingual nifedipine was used in everyone whose BP seemed to need to be lowered quickly. That is not what we are talking about.

DR BAKRIS: I think that's a very important point. I just want to come back to this, that from a basic common-sense approach, all of these situations require a good physical examination be performed, that the patient be assessed for volume and orthostatic changes, and that you use appropriate medicines wisely in the individual, and, certainly in people with diabetes who may have autonomic neuropathy as well, one has to be very cautious.

DR BLACK: We're going to palpate the neck and listen for bruits and be a little slower in someone who has them, but a lot of people at that age who are coming in as we're initiating treatment are reasonably healthy. They are going to benefit from having reduced BP within 2 to 6 months.

DR BAKRIS: Now we have more than 125 different antihypertensive medications to select from, and one would argue that is more than enough if you know what you're doing In addition, we have probably at least 2 dozen if not more combinations of various ACE inhibitors or ARBs du jour and diuretics. We have some ACE-calcium channel blockers (CCBs), we have ARB-CCBs coming on the horizon, and we have ACE-β-blockers coming on the horizon. First let's talk about what is preferred if you're going to start with a fixed-dose combination, or even 2 different medicines. What do you prefer to start with, Matthew, in someone who is well above the goal at initial therapy? Which one of those combinations would you pick and why?

DR WEIR: I am a little bit different in my approach and I'm sure both you and Henry will have your own thoughts, but I always think that something that modifies the activity of the renin–angiotensin system (RAS) should be the anchor of the regimen. The reason for this is that the RAS is pivotal not only in the regulation of systemic BP, but it also regulates vascular injury and repair responses. So, I feel we need to modify the RAS as part of an effective BP-lowering regimen. This is not to say it should be the first choice, but it should be part of the long-term perspective. So, in a sense, it's not as important what you start with, it's what you finish with.

Now as far as using an RAS blocker, I don't want to get into an ACE or ARB argument, because they're both good therapeutic classes. For me, the real question is what is the best drug to use with it. In terms of providing more robust reduction of BP, I feel either a thiazide diuretic or a CCB is the optimal choice. Invariably I will use one or the other in conjunction with a drug that blocks the RAS as part of my approach, preferably as a fixed-dose combination.

DR BAKRIS: Okay, not so fast. Not so fast. I've got to pin you down here. This is a multiple choice question, I want you to select the best answer … diuretic married to an RAS blocker or CCB married to an RAS blocker? What are your criteria for selecting to whom you would give which regimen? Is there something on the physical examination, is there something in the laboraty results, something in the history? What is guiding you one way or the other? Or is it cost?

DR WEIR: You mean you're asking about the difference between a thiazide- or a CCB-based RAS-blocking regimen?

DR BAKRIS: Yes, exactly.

DR WEIR: That's a tough call. That's a very tough call, George. I'll be honest with you. My long-term belief is that a CCB-based approach with an RAS-blocking drug will likely be more metabolically friendly, specifically with regard to lipids and glycemic control, compared with a thiazide-based approach, particularly if higher-dose thiazide (25 mg or more) is used, That is grounded on the recent studies I've seen published, that thiazide-based approaches, although very effective and which have certainly stood the test of time in terms of providing BP reduction, are suspect with regard to metabolic changes.

DR BAKRIS: Alright, that's fine. Now I'm going to give Henry a shot here, but I'm going to set him up a little bit. I would come back and say, well that's interesting, but so what, because in SHEP, ALLHAT, and in other trials where diuretics clearly caused metabolic havoc, they also ended up being pretty good for reducing events. Henry …

DR BLACK: For 5 years. For 5 years, George.

DR BAKRIS: Yes, I understand.

DR BLACK: Well let's again go back to your question. My approach right now given our armamentarium of 150 drugs or so, is that there are 3 classes of drugs I would consider to be tier 1 drugs, borrowing now from managed care terminology. Those would be diuretics, calcium antagonists, and blockers of the renin-angiotensin-aldosterone system, the ACEs, or ARBs. I won't make a distinction between those 3 classes of drugs for the moment. If one looks at the trials that we have to base our judgment, the most effective regimen in VALUE was a combination of a calcium antagonist and a diuretic. It was not an RAS blocker at all. In these high-risk volunteers, the treatment group who had fewer strokes (although not statistically significant at the end) and fewer myocardial infarctions were those who started with a calcium antagonist with a diuretic added if needed. These were the volunteers who had better and prompter BP control, something that was maintained throughout. In fact, they never received an RAS blocker. So I think to make the judgment that a good regimen needs to include that class of drug is not grounded in what we currently know.

Now, I would modify that approach in patients with certain comorbidities. For example, if your patient has diabetes and proteinuria, or heart failure, or you think might be in incipient heart failure or renal disease, an agent that blocks the RAS should definitely be part of a complicated regimen. But one must bear in mind that CCBs and diuretics are very effective at lowering BP and that is the primary objective of therapy. Diuretics do have metabolic consequences, but when given together with an RAS blocker, which is what VALUE did, many of these problems are obviated and the rate of new diabetes is statistically less than the group that received a calcium antagonist first. There is little doubt that diuretics do increase new diabetes, but the real consequences of this are not certain. John Kostis has analyzed the 14-year follow-up data from SHEP and found that those who developed new diabetes on a diuretic–β-blocker combination did not have the same long-term risk as did those in SHEP who entered the program with diabetes. While diuretic- and β-blocker–induced diabetes is of concern, the true significance is unclear. In any case, as found in VALUE, the combination of an ARB with a diuretic had a more reduced incidence of new diabetes compared with a calcium antagonist-diuretic regimen.

DR BAKRIS: Okay.

DR WEIR: I would support Henry's statements. I appreciate his modification based on what I said, but I also want to make sure that I come across as stating that BP goal attainment is always the first priority. It's not what you start with, it's what you finish with. And I am consistently impressed that in the clinical trials of people with clinically evident heart disease and kidney disease, there is always an advantage to receiving a therapy that modifies the RAS as part of an effective BP-lowering regimen.

This is the issue that we need to consider over the long term of 20 to 30 years. Due to the cost of these

later trials, we have only 5-year data to compare the evidence of different therapies. I would also agree with Henry's point that I don't use thiazide diuretics or CCBs alone without drugs that block the RAS.

DR BLACK: Matt, could I ask you to speculate a bit?

DR WEIR: Sure.

DR BLACK: If I could come up with a scenario where your patient's BP was at or under goal with a 2-drug regimen without an RAS blocker or one that is 2 mm Hg systolic higher with a regimen that includes one, would you trade those 2 mm Hg to have the RAS blocked?

DR WEIR: Well, I don't think that is a fair comparison.

DR BLACK: That's what I'm asking you to do. I want you to say, or probe your statement a little bit, that BP trumps everything, which is what I think and therefore would not sacrifice a few mm Hg just to have the RAS blocked.

DR WEIR: I would agree with you. I would do both. I would both get to goal and block the RAS.

DR BAKRIS: Okay, that's fine, but if you have a choice and you get a little bit better BP control without blocking the RAS, would that be okay with you?

DR WEIR: No, it wouldn't. I mean another way of looking at it, if I had a patient let's say with diabetes …

DR BAKRIS: Yeah.

DR WEIR: …who had a recommended goal BP below 130 mm Hg and was at 128 mm Hg while on a CCB and a thiazide; would I adjust their regimen to use an ACE inhibitor or an ARB to lower their BP more or back off on some of the medication to make sure I could get an RAS-blocking drug into the regimen?

DR BAKRIS: What if they weren't diabetic?

DR WEIR: Well if they weren't at goal …

DR BAKRIS: No, what I meant was if that same patient you described, who didn't have diabetes or the metabolic syndrome or microalbuminuria or any of the things that a lot of patients don't have.

DR WEIR: Well that's a very good question. Again, it may boil down to tolerability, ability to pay for medications, and of course more careful assessment of whether they do or do not have risk factors for cardiovascular disease or subclinical measures of atherosclerosis. Given any evidence of risk factors, I would be more aggressive with modifying the RAS. If the patient had absolutely no evidence of risk, I would probably still be inclined to do it if I could, although this is not well grounded in evidence of clinical trials. These drugs also have excellent tolerability.

DR BAKRIS: Alright, alright. I'm going to move the direction of the discussion a little bit and try to get an answer to this by looking at the Avoiding Cardiovascular Events Through Combination Therapy in Patients Living With Systolic Hypertension (ACCOMPLISH) trial, which is an ongoing trial of almost 12,000 patients with very high cardiovascular risk and kidney disease who are being randomized to either an ACE-CCB or an ACE-diuretic. So, since we're here, I want you to take a stand based on everything you've said. Do you think there will be a winner and, if so, which drug will it be? Remember now, this is event driven, not time driven.

DR WEIR: Well, I'll give you my bias. There are 3 thoughts that come to my mind. One, will a full dose of an ACE inhibitor, because all participants are receiving 40 mg of benazepril, level the playing field for 5 years so that the accompanying medications (assuming equivalent BP control) will not make a difference. You might need more time to see a differential. So that's one question.

DR BAKRIS: Okay.

DR WEIR: The second thought I have is, will the CCB component facilitate earlier control of BP compared with the thiazide. Although there are no good studies comparing them head to head in this regard, I think there are suggestions in clinical trial data to indicate that thiazides take a little longer to get people to goal, whereas CCBs tend to provide more robust control of BP earlier on, particularly in people who tend to consume more salt. Also, CCBs' BP-lowering effects are independent of ethnicity and age. Now if that is the case, then there might be a differential in outcome.

DR BAKRIS: Okay, very good. Henry of course can't answer that because he's head of the data and safety monitoring board. But I wanted to try to get you at that. I personally think, based on the data, that it's going to be very very close, and I'm not sure if there's a clear winner. I think for tolerability and overall side effects, though, the ACE-CCB is probably going to win. But we'll see.

DR BLACK: George, going back to the point I made first, ACEs are great drugs, particularly when fully dosed, and they may level the playing field. However, the other area of interest that I have, which is similar to much of the work you've done in the past few years, has to do with metabolic friendliness of regimens. A lot of the studies show that drugs that block the RAS reduce the likelihood of developing new diabetes by 25% to 30% in patients who often require multiple drugs to control their BP.

So, is there a difference between a thiazide-based regimen and a CCB-based regimen? I wonder whether the CCB-based regimen might be more metabolically neutral over the course of this 5-year study. Now, again, that may or may not translate into events (it probably won't), but given the fact that we treat people with these medications over many decades, that may prove to be important.

DR BAKRIS: Well it's true, that is an unanswered question. So, we'll see. Having said all of this, I want to move to another related topic. You talk about RAS blockade and beyond ACE and ARB inhibition, but let's not forget that β-blockers also block the RAS. Aldosterone doesn't block the whole system but it blocks a component of the system. Where do you think these agents fit into combinations? Because there are diuretic combinations (for example, spironolactone with hydrochlorothiazide, or bisoprolol with hydrochlorothiazide), how would you compare those with ACE-CCBs? Are they more user-friendly or less?

DR BLACK: In my view, the newer generation of β-blockers, carvedilol and nebivolol, have distinct advantages over the older ones, with respect to both metabolic friendliness and tolerability. These drugs seem to be better tolerated than older β-blockers and, in work you've done, do not have the metabolic side effects often seen with the older generation of β-blockers. We've been using this class of drugs since the 1960s, so we mustn't ignore the many benefits we have discovered in patients with compelling and specific indications, such as heart failure, migraines, coronary artery disease, angina, and arrhythmias. It would be wrong to ignore them but, to me, they're in the tier 2 group, which are to be used for hypertension only after the 3 tier 1 classes I mentioned earlier. We also shouldn't forget that β-blockers are also RAS blockers and therefore surpress renin secretion by the kidney. They were the first class of drugs developed to reduce BP by that mechanism in addition to other effects. Once we became aware of the metabolic consequences, and once other options for treating hypertension became available, they were used for hypertension. In addition, β-blockers are not as effective for lowering BP in important patient groups. For example, these agents are not very effective in older people or in African Americans when given as monotherapy. As part of a combination regimen, however, they are an excellent complement to diuretics. In SHEP, for example, we used atenolol as the second drug, with further reduction in BP. Many other studies have also used similar combinations. We must put their use into perspective. I consider them for treating hypertension in the same category as α-blockers and aldosterone blockers. These classes of drugs are usually indicated as initial therapy, but are certainly very valuable as adjunct therapy or if there is a specific or compelling indication for their use.

DR BAKRIS: Matthew, do you agree or disagree?

DR WEIR: Well no, I support many of Henry's statements. I use β-blockers in practice primarily to provide heart rate control. Given the fact that the vast majority of coronary artery perfusion occurs during diastole, it makes sense in people who have or are at risk for coronary artery disease to slow heart rate. And so I tend to be much more inclined to use these drugs to facilitate heart rate control in my higher cardiovascular risk patients.

Certainly, these drugs have clear indications in people with angina pectoris, people who are post–myocardial infarction, those with systolic heart failure, and those with hypertrophic cardiomyopathy. But you also have to balance these benefits with tolerability, metabolic neutrality, and of course weight gain, which can occur. As Henry stated, some of the newer β-blockers may provide important opportunities to achieve all the goals that we've seen with selective and nonselective β-blockers but without a lot of the adverse events and metabolic consequences, which could limit their long-term use. So, I do prescribe β-blockers, but invariably I do not use them alone. I almost always use them with a drug that blocks the RAS along with a thiazide or a CCB to facilitate achieving goal BP.

As far as the aldosterone blockers go, I think still more needs to be learned about their optimal place in antihypertensive regimens. We've used triamterene for many many years as a fixed-dose combination with thiazide. I think spironolactone may have important opportunities, particularly in people with resistant hypertension; however, it may have adverse effects that could limit its use, particularly in men, although a newer chemical, eplerenone, does not have as many associated side effects in men.

DR BAKRIS: Okay, very good. Because you brought up triamterene, which I was hoping you wouldn't, we should discuss the very clear distinction between triamterene and spironolactone. While they both preserve potassium, one is affecting aldosterone and the other is not. And I think that is a very important distinction since aldosterone, especially in obese African American patients, is now a key player in terms of BP control.

Now, before I ask the final question, which do you think is going to be better, an ACE-CCB or an

ARB-CCB, because those are right around the corner and will be with us imminently. Do you think in fact there will be a difference, first in outcome and second in tolerability? Henry?

DR BLACK: Well, I'd like to weigh in on this one. When ARBs first came along, their major advantage was their excellent tolerability. Their side effect profile was as good as placebo and maybe even better. They didn't cause the cough so commonly seen in patients taking ACE inhibitors and they didn't cause angioedema, a potentially fatal side effect, which is uncomfortably common in African Americans. What ARBs didn't have when they were introduced in the mid-'90s was the extensive and impressive clinical trial portfolio that ACE inhibitors did; now they do. So I don't see any reason to accept the risks (angioedema) of ACE inhibitors or to accept the additional cost of having to change a medication from an ACE inhibitor to something else because of a cough, So, yes, I think ARBs, assuming BP control is equally good, have significant advantages over ACE inhibitors in tolerability and a very robust clinical trial portfolio to support their use.

DR BAKRIS: Okay. Matthew?

DR WEIR: I don't disagree with anything Henry said, but I will say this: about 10 or 15 years ago we were extolling the advantages of ACE inhibitors over other antihypertensive therapies due to their excellent quality-of-life profile and tolerability. I won't disagree that cough can be an issue in a small percentage of patients and can lead to discontinuation of the medicine. We also recognize that there are certain types of patients who are at greater risk for angioedema, particularly people of African American ethnicity and smokers; but it's important to realize these side effects are infrequent and even rare. I think it's an individual choice for each physician in terms of working with their patients. I think it's a tough call in deciding between these 2 agents because they are both well tolerated and they do not have a dose-related side-effect profile. Thus, you can use the fully approved dose for lowering BP without increasing the risk for adverse events. This is why I'm a big fan of using these drugs with other medications in my patients as part of an effective BP-lowering regimen.

DR BAKRIS: Okay, very good. Before I leave this topic, we haven't talked about something that is very common. A combination either with an ACE or an ARB and a CCB clearly provides a much lower incidence of pedal or peripheral edema. And Matt, you've done some key studies on this. Why don't you just give a very brief overview as to what the mechanism is and why it is in fact more beneficial to use an ACE or an ARB with a CCB for this reason rather than a diuretic.

DR WEIR: Well, George, you're pointing out an intriguing observation that's been consistently noted in a number of clinical trials: when a drug that blocks the RAS is utilized with a CCB, there appears to be less pedal edema. We're not really sure of the mechanistic interrelationship. Some theories are that since calcium blockers are potent peripheral arteriolar dilators, when people assume the upright posture, there will be gravity-dependent capillary leakage. If you coadminister a drug that dilates the venules, particularly in the distal areas where the capillaries connect, you could lower capillary pressure and reduce some of the extravasation of fluid.

I think it's an intriguing hypothesis, but it has not been proven. What I think is clear, however, is that this type of approach, using a venous capacitance dilator like an ACE or an ARB, consistently reduces pedal edema more effectively when coadministered with CCBs, even compared with thiazide or loop diuretics. So it does support the hypothesis that this is a local vascular phenomenon and is not related to sodium and water retention.

DR BLACK: Matt, you've done some of the best work in this area. Do you think there's likely to be any difference between the ability of an ACE or an ARB to reduce edema in people on a full dose of a dihydropyridine?

DR WEIR: No, I don't think there is any difference, Henry. In fact, I've seen even newer data with renin inhibitors indicating that they too have this same type of an effect. So I think this may be really something having to do with venous capacitance improvement, which lessens the likelihood of capillary leak. We don't have an explanation for the biologic effect, but the bottom line is it appears to work in a large percentage of the population.

DR BAKRIS: Okay, thank you very much. And in fact you've given a very nice segue into the next topic, which, in fact, is not even beyond the RAS, it is in fact the RAS, and another whole new class of agents that's out there, the renin inhibitors. These agents have actually been around since the 1980s, but because of very bad bioavailability, they really haven't made it to prime time. So we have one that will be coming out very soon; what do you think this is going to add to what we already have in the armamentarium? We're already blocking the RAS in 2 different spots, we've got very good data for cardiovascular outcomes with both these agents, and now we have the rate-limiting enzyme that's

driving the system being blocked. What do you guys speculate in terms of additional benefit, if there is going to be additional benefit. Henry?

DR BLACK: Tough question, George, and I know you knew it was. In this era, we now have at least 4 distinct ways to interfere with the renin-angiotensin-aldosterone system. We can block the system at the top of the cascade with direct inhibition of renin secretion (β-blockers), in the middle with ACE inhibitors (which block the conversion of angiotensin I to angiotension II) and ARBs (which prevent the activation of the angiotensin II type 1 receptor), and at the end with aldosterone receptor blockers. I am a little skeptical that a drug that blocks the RAS at the start of the cascade, where there are lots of opportunities for compensatory mechanisms, will be better tolerated or more effective than ARBs. Furthermore, they don't as yet have the trial portfolio that we now have with the other 4 classes of drugs.

Now, whether they have additional effects beyond simply renin inhibition that provide special advantages still remains to be proven. There are some data that I think both you and Matt have helped generate to suggest that these agents might have such advantages or, perhaps, be more effective at lowering BP in combination with other drugs. We will have to see.

DR BAKRIS: Matthew?

DR WEIR: Well thank you, George, for asking the intriguing question. I completely support Henry's points, and would step further and say I don't know that we will ever develop what I would describe as a silver bullet in the antihypertensive armamentarium, meaning a drug that is so effective that it will be a monotherapy success. So, I think in the future, all drug development will be based on regimen-based pharmacotherapy. Even with the new renin inhibitors—I don't think they're going to be a solution for controlling BP alone. But I think they'll be helpful as part of effective BP-lowering regimens. Now, they are different than ACEs and ARBs in that they do not result in a reflex increase in production of angiotensin I, angiotensin II, or plasma renin activity and, because of this difference, they may have benefits at the vascular level that we have not yet fully appreciated. That said, renin inhibitors need to be tested in large-scale clinical trials to show that they provide the same cardiovascular benefits as those we've seen with other RAS-blocking drugs like ACEs and ARBs.

The 3 therapeutic classes that may provide the greatest opportunity for BP reduction with the renin inhibitors are drugs that, when given alone, result in an increase in plasma renin activity, which would include thiazide diuretics, ACE inhibitors, and ARBs. I think those are the 3 classes that need to be studied more carefully to see whether there may be some additivity with the renin inhibitor in terms of lowering BP. The CCB works well with everything, so I am sure they will also work effectively with the renin inhibitor

I recently presented some data at the World Congress of Cardiology that clearly indicate that there may be some opportunity with the thiazides, ACEs, and CCBs in reducing BP with the renin inhibitor, aliskiren. Whether this is going to be true with ARBs is not yet known, but larger studies are being performed to test that relationship right now.

DR BAKRIS: Alright. You know, from a theoretical standpoint, if you look at the data on renin inhibitors, at least on studies in the kidney, one of the things that is consistent is not only do they reduce levels of angiotensin II, but they also reduce aldosterone levels far better than ACE inhibitors and, for that matter, better than ARBs. Having said that, would you think that a renin inhibitor should be combined with a diuretic or should it be combined with a CCB in the context of combinations to provide greater reductions in BP? Arguing that, and I realize this is theoretical, if you get a drug that's reducing aldosterone levels better than the traditional RAS blockers but not as well obviously as an aldosterone blocker and all the benefits of aldosterone blockade in diabetes and heart failure, etc, and for BP certainly I've seen some data, as you alluded to, that using this agent in combination gives you slightly better BP reductions as you'd expect. How about combining it with a CCB? Would you think that would be a good way to go, over a diuretic?

DR WEIR: Well, I can tell you, George, I've already analyzed the data combining the renin inhibitor with a thiazide and a CCB …

DR BAKRIS: Yes.

DR WEIR: … and it does look quite effective. They provide similar overall reductions in BP. However, not as many people have been studied in this regard, so I think we need to gather more information.

DR BAKRIS: Okay, very good. Henry?

DR BLACK: I think that the question underlying all of this that I'd like to comment on before you ask it is, why, with all that we currently have to treat hypertension at our disposal, aren't we doing a better job in treating this condition and preventing the complications of elevated BPs?

We have 150 drugs right now and we have new drugs and new combinations coming out annually, so why do we need new drugs? Perhaps because with the addition of a new drug or drug class we may take advantage of new ways to prevent or treat target organ damage and we may add some additional mm Hg reductions by adding these agents to what we already use. Either scenerio would be something I would really welcome. Whether a new class or an improvement on a class that we have become conversant with comes in and replaces an older class cannot be predicted with certainty. For the most part, newer drugs were either more effective or better tolerated or both. Diuretics and sympathetic blockers replaced ganglionic blockers and direct vasodilators; β-blockers replaced more complete sympatholytics; peripheral α-blockers and calcium antagonists replaced direct vasodilators; ACE inhibitors supplemented and replaced β- and α-blockers; and ARBs improved the tolerability of ACE inhibitors. So, in general, we do put older, less well tolerated agents out to pasture when improvements make that possible. The only drug class that has been different are diuretics, as we now enter the 50th year of their clinical use. So, yes, we do need new approaches. Bring them on and let's see how well they they work and in whom they work best. We still have a long way to go to make the most of our knowledge.

DR BAKRIS: So, as a summary, to bring this to a close, I'm going to make some statements and see whether you agree or disagree with me.

Statement number 1 is that fixed-dose combinations, especially with ACE inhibitors and CCBs, are metabolically better tolerated and offer very good BP control. I think we'd agree with that.

DR BLACK: I would.

DR BAKRIS: Matt?

DR WEIR: Oh, yes.

DR BAKRIS: Okay, so now number 2. I think that as far as using these agents, the issue of adherence to therapy that many authorities talk about (ie, the Food and Drug Administration…), think these are convenience drugs, that fixed-dose combinations do nothing but make it convenient and, thus, taking one fewer pill improves adherence. There is nothing pharmacologically special about them. But would you agree that at least from the studies that are out there, the published studies that have carefully looked at this in a relatively nonbiased way, actually improve adherence to medications and as a result give you longer-term better BP control than using individual pills?

DR BLACK: I'm not as persuaded of that as I wish I were. My own feeling about what patients do with complicated regimens is that they figure out a system that works for them, whether they have to lay out 8, 12, or 2 pills, they still figure out a system. Unfortunately, when you're talking about using a fixed-dose combination to reduce the pill burden from 8 pills to 7 pills or 9 pills to 8 pills, I am sure there is some marginal benefit, but we need a better understanding of how much this approach really changes adherence behavior.

DR BAKRIS: Matthew?

DR WEIR: I would agree exactly with what Henry said. I think CCBs have been part of the winning team of so many different BP-lowering studies, that it's hard to argue against them. I wouldn't use them alone but I'll certainly use them with drugs that block the RAS.

DR BAKRIS: Good. Well, you know, I think this brings us to a close. I think we've made the points about getting to BP goal quickly, using agents that are meaningful in terms of their pharmacologic mechanisms or complementary in terms of their pharmacologic mechanisms, and at the same time looking at new combinations that may provide potentially better tolerability and perhaps lower morbidity and maybe equivalence in terms of reducing mortality.

DR BLACK: If we use what know and what we've got, there are going to be fewer people who have strokes, heart attacks, heart failure, and chronic renal disease and probably a lot less dementia; that's what we should be working on.

DR WEIR: I really think that future clinical trials will focus on whether certain types of patients need earlier management of BP, particularly in the 120s or 130s, because these are gray areas that we have not traditionally focused on. Ultimately we may be able to prevent the requirement of more complicated multiple-drug regimens, but also make a difference in terms of long-term risk for cardiovascular events.

DR BAKRIS: Of course you bring up now the whole issue of the Trial of Preventing Hypertension (TROPHY) and we're not going to go there because unfortunately our time is up. And so I'm bringing this to a close. Thank you both very much for participating in this forum.

DR BLACK: Thank you.

DR WEIR: Thank you, gentlemen.