

R o u n d t a b l e D i s c u s s i o n

Conflicting and Confusing Data From the Hypertension Treatment Trials: Whom and What Should You Believe?

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Following a hypertension symposium in Atlanta, GA on March 30, 2005, a roundtable was convened to discuss a confusing topic: "Conflicting Information from the Hypertension Treatment Trials: Whom and What Should You Believe?" Dr. Marvin Moser, Clinical Professor of Medicine at the Yale University School of Medicine, New Haven, CT, moderated the panel discussion. Participants included Dr. Thomas Giles, Professor of Medicine at Louisiana State University Health Sciences Center, New Orleans, LA and President of the American Society of Hypertension, and Dr. Suzanne Oparil, Professor of Medicine at the University of Alabama at Birmingham, Birmingham, AL. (J Clin Hypertens. 2005;7:403–408) ©2005 Le Jacq Ltd.

DR. MOSER: There are indeed conflicting data about the results of specific therapies in the management of hypertension. We have good information in placebo-controlled trials that therapy will reduce morbidity and mortality, not just from cerebrovascular but from cardiovascular disease. We also have data that the use of pharmaceutical interventions augments the use of nonpharmaceutical interventions in reducing morbidity and mortality. However, in the past 10 or 15 years, a series of studies designed to show that drug A is better than drug B or a combination of drug A and B is better than C and D have been reported, and this has led to some confusion. This is especially true since several large controlled studies, like the Antihypertensive and Lipid-Lowering Treatment to Prevent Heart Attack Trial (ALLHAT), the second Australian National BP Study (ANBP2), the Anglo-Scandinavian Cardiac Outcomes Trial (ASCOT), and the Swedish Trial in Old Patients With Hypertension-2 (STOP-2) appeared to report different findings. Tom, why don't you start off by giving us your impression of studies before the last few years, studies like the Fosinopril vs.

Amlodipine Cardiovascular Events Trial (FACET), the Appropriate BP Control in Diabetes (ABCD) trial, the Irbesartan in Patients With Type 2 Diabetes and Microalbuminuria (IRMA) Study, the Irbesartan Diabetic Nephropathy Trial (IDNT), and several others that indicated that the use of an agent that blocks the renin-angiotensin system (RAS) should be part of a therapy program, especially in high-risk or diabetic patients. We should remember, however, that none of these trials was a study of monotherapy. How about their validity—how have they stood up and should we adhere to conclusions that in diabetics or patients with renal disease there is a difference in outcome that depends not just on blood pressure (BP) changes but on the use of specific medications?

DR. GILES: Yes, I think that in diabetics, and particularly when you're talking about problems with the renal circulation, there really is a benefit to using drugs that perturb the RAS. It's mechanistic. It is similar to giving an antibiotic for a specific pathogen. Contrast that to the large cardiovascular morbidity and mortality trials where you've got a whole host of substrates. Here there are different mechanisms for elevating BP in the first place. Drugs work through a multiplicity of actions. I think that



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if one really adopted a Bayesian approach, the prior conviction or skepticism regarding outcome would suggest that these trials are not confusing. These large cardiovascular outcome trials probably all show the same thing—that lowering BP is a good thing to do and accounts for the benefit.

DR. MOSER: So you believe that most of the benefit—except perhaps in certain subsets of patients like diabetics or individuals with renal disease—depends on the BP level achieved and not on how we achieve it.

DR. GILES: Not only that, but of course the higher the BP is when you start, the better the outcome. I think that the lowering of BP is so powerful that it probably disguises almost every attempt you could make to discern differences in outcomes among drugs. The thing is we don't specify the phenotype. We take everybody with an elevated BP and assume that they're pretty much the same, but as Suzanne and I would both say, if you get into a laboratory and you've got a Dahl salt-sensitive rat, a spontaneously hypertensive rat, a stroke-prone rat, and a salt-insensitive rat and a variety of models, no drug would ever act the same in each of these. If you did a trial and you mixed all these different rats together and sent it in to a journal, they'd laugh at you. But that's exactly what our clinical trials do—the patients often represent many different phenotypes. That is why all of the trials had to use multiple medications to achieve results.

DR. MOSER: Suzanne?

DR. OPARIL: Well, it's tough. I agree with Tom. I think that at least in some patients, reducing BP is necessary but not sufficient to get the outcome that we would like—the prevention of cardiovascular disease morbidity and mortality. Some added factors have to do with different mechanisms and also with patient subgroups. If we want to look specifically at the 900-lb gorilla of outcomes trials, ALLHAT, the results in the African Americans who constituted 36% of the 42,000 participants were somewhat different than in other patient groups. In African Americans, the diuretic was better than the other classes of agents with regard to heart failure and, especially, with stroke outcome. BP was lowered to a greater degree in this group with a diuretic compared with an angiotensin-converting enzyme (ACE) inhibitor. With respect to Caucasians, calcium channel blocker (CCB)-based treatment reduced BP to a similar degree, and while there was no difference in stroke prevention, heart failure was more frequent with a CCB than with a diuretic-based regimen. Yes, the phenotype is important.

DR. MOSER: But are you saying that in ALLHAT the difference in stroke outcome was on the basis of a BP difference between groups? Was it the BP rather than the particular drug?

DR. OPARIL: The BP did play a major role in the ALLHAT results, especially for stroke in blacks. I think people who say that BP is an intermediate end point and is not important are foolish and wrong. Clearly the BP, particularly the systolic BP, is a dominant determinant of success in treatment. But, as we have noted, other factors may be important, particularly with respect to prevention of stroke and renal failure.

DR. MOSER: Tom, would you say, for example, that the difference between the ALLHAT results, which suggested that strokes were lowered more with a regimen based on a diuretic than with an ACE inhibitor treatment program, especially in black patients, are not greatly different from ANBP2, which studied mostly white patients? In this trial, as you know, the ACE inhibitor seemed to be a little more effective—but just in a subset of male patients.

DR. GILES: Absolutely—and that's what I meant by constructing a prior conviction relative to the analysis. I think part of our problem has to do with the way we analyze trials. The observation that Suzanne just mentioned is exactly right. When you think about it from a conventional point of view, ALLHAT showed no overall difference among the three different medication groups.

DR. MOSER: The primary end point was equal among the three medications—the subgroups were the areas that showed a difference.

DR. GILES: Correct. In other words, when you start doing repetitive analyses, conventional statistics would tell you that you're treading on very thin ice. From a Bayesian point of view, you could actually do that and come to conclusions that might be quite different. So if you'd asked me ahead of time what I thought ANBP2 was going to show, I would have been happy to say that I thought it could show almost anything. It didn't surprise me. I would have been prepared to accept any result that came out of it. Remember that this trial was not blinded—actually, the outcomes in these two studies are really not that different—different demographics, different results.

DR. MOSER: I happen to agree that it's primarily the BP that accounts for outcome—but what about the differences in heart failure events that have been fairly consistent in the trials showing that ACE inhibitors and diuretics may be more effective, for example, than CCBs. This held in the ALLHAT study. Even

though CCBs and diuretics are both effective in lowering BP in black patients, the incidence of heart failure was greater with the CCB. Is that a drug-specific difference relating to a different mechanism, since there were no real BP differences?

DR. GILES: Yes, I believe so. If you look at heart failure, you're talking about a syndrome that is characterized by salt and water retention. You cannot manage patients with heart failure without diuretics. That was tried in the very early days of ACE inhibitors. People actually did some head-to-head trials and they couldn't complete them because in the people who actually had heart failure, you couldn't manage them without a diuretic. In ALLHAT, I rather suspect that at least some of what was seen in terms of "increases in heart failure" in some of the patients may have been a manifestation of diuretic withdrawal. A lot of those patients who were on diuretics before the trial may have had some forms of compensated heart failure—and ACE inhibitors also affect volume—so I believe that this explains a different outcome.

DR. MOSER: I don't remember, Tom, whether in ALLHAT the heart failure manifested itself in the first couple of months.

DR. GILES: It was early on, yes. And this was particularly obvious with the α blocker, where heart failure incidence was twice as frequent as with the diuretic. We knew from prior trials, for example the first Vasodilator Heart Failure Trial (VHeFT-I), that α blockers are basically neutral in heart failure. That is why I believe that the pre-randomization diuretic withdrawal may have had something to do with the outcome.

DR. MOSER: So, you have no problem with the differences between ALLHAT and ANBP2 even though quite a few of our colleagues have emphasized them.

DR. GILES: I'll tell you, Marv, I think most of these trials show the same thing. You have to lower BP. I still believe that you can get very specific about a subtype. For example, a diabetic with proteinuria. There I think you can show some differences in outcome between different classes of drugs.

DR. MOSER: Suzanne.

DR. OPARIL: Let me comment on ALLHAT a little bit more. First of all, we talked about different phenotypes. I can tell you that ALLHAT heavily over-sampled African Americans because they have much worse BP and target organ problems and worse outcomes than either whites or non-black Hispanics. But it also heavily over-sampled the southeastern United States because that's where African Americans live. I was the southeastern

regional coordinator for ALLHAT and we had 11,000 of the 42,000 participants. Many of these were lower socioeconomic status persons, many of whom had poor dietary habits and were obese. The average body mass index was almost 30. So the ALLHAT participants were very different from the Scandinavians in several large trials and from the relatively affluent white people who were in ANBP2. So sensitivity to drugs is an issue. One other comment—clearly chlorthalidone is therapeutic in early heart failure, not just because it helps to lower BP. The hospitalized and fatal cases of heart failure in ALLHAT were validated in a post hoc study because ALLHAT drew so much criticism, but as Tom noted, some of the early nonhospitalized cases may have resulted from diuretic withdrawal.

DR. MOSER: Again I agree that it's mostly BP, but what about studies like the Losartan Intervention for End Point Reduction (LIFE) study, where an angiotensin receptor blocker (ARB)-based treatment program was compared with a β -blocker-based program and where it appeared that in patients with left ventricular hypertrophy before treatment, strokes were decreased more by the ARB-based treatment.

DR. OPARIL: In my expounding about what's important in hypertension, I always cite LIFE as the only trial that has shown some actual benefit beyond BP lowering in people who were hypertensive. In this case it was hypertension plus left ventricular hypertrophy by electrocardiogram that qualified a patient for the LIFE trial, which means a combination of a big heart, big myocytes, and probably some ischemia in many of these older patients. Remember, most participants were in their 60s and 70s in LIFE as well as in other outcome trials for hypertension. In LIFE, 90% of the participants in both the ARB and β -blocker arms got hydrochlorothiazide, and 40% also got a CCB. The ARB-based treatment reduced strokes 25% more than β -blocker-based treatment—but remember, it was a mixed bag of treatment. The ARB group also had 25% fewer cases of new-onset diabetes. There are many theories about why the ARB was more effective. They all have to do with blocking the effects of the RAS, particularly angiotensin II.

DR. MOSER: But β blockers block renin release, perhaps with less of an effect on RAS activity than the other drugs, and they also reduce cardiac work and reduce cardiac O_2 demand. Why didn't those drugs regress left ventricular hypertrophy and prevent strokes as much as the ARB?

DR. GILES: There are a few things you have to consider. If I were going to choose a β blocker to

put into a trial, first of all I would give an adequate dose. Atenolol, which was the comparator drug in LIFE, is a b.i.d. drug. If you look at trials where they actually dosed atenolol up to good doses and used it b.i.d. it actually winds up being just as effective as the opposite arms of a study. In the LIFE trial, doses may have been inadequate.

DR. MOSER: In other words the dosage should have been at least 100 mg.

DR. GILES: That's correct. The other side of the coin is this: what were the central pressures? Beta blockers classically do not lower central aortic pressures as well as other drugs. If you're measuring pressures in the brachial artery, you may believe that the pressure is the same. In point of fact, the effective pressure in the aorta may not be the same. Since stroke is a pressure-dependent phenomenon, this might explain the stroke difference. Strangely enough, none of the other major events in this trial were different between the two groups. In angina, the results with the β blocker looked better.

The time has come to get out of the Middle Ages with statistical analyses. If you looked at a study in advance and you constructed a prior, and this has been done, results might be different. George Diamond analyzed the LIFE data doing that, and with even a modestly skeptical prior, that trial was negative. So, I don't know if the trial actually was positive. And remember something else. If the N of a trial is big enough, because of its position as the denominator of the calculation, this will tend to make everything significant with a p value <0.05 , whether it's absolute or not. So I don't know what to make out of that. In other words, analyses of some of the trials are suspect and drawing treatment conclusions may be problematic.

DR. MOSER: You're not convinced then that the use of an ARB-based program might be more effective in preventing strokes than a β -blocker-based program?

DR. GILES: For any degree of BP reduction? Not really.

DR. MOSER: Okay. We started out with the statement about conflicting results and interpretations of the trials—I guess that there truly are some. Now what about the two latest trials that have gotten so much publicity? The Valsartan Antihypertensive Long-Term Use Evaluation (VALUE) trial was designed to show that an ARB is superior to a CCB, based on previous estimates that the CCBs were not as effective in reducing myocardial infarctions or heart failure as some of the other drugs. The VALUE study appeared to indicate that the CCB may be a little bit better at reducing events. Is that

based on a BP difference, Suzanne, or is that based on a specific activity of the drug? Again, these were multiple drug studies, since almost everyone received two or more medications.

DR. OPARIL: In VALUE it is unfortunate that there was a failure to balance the BP in the two arms. There was a 4 mm Hg greater decrease in systolic BP in the first few months in the CCB (amlodipine) arm compared with the ARB (valsartan) arm, and there were fewer events in that period of time in the CCB arm. The BP differences tended to decrease over time, but BPs were always higher in the valsartan arm. I think that accounted for the results. There was an attempt by some to use a procedure of questionable statistical validity called serial median matching, picking the patients who had equal BPs. Obviously this destroys the benefits of randomization. With that adjustment, the outcomes were a little bit different but hard to interpret.

It also brings up the importance of not tampering with the BPs in high-risk patients. If you have a high-risk person who's on two or three drugs, it's not wise to stop them all when they are put into a trial and put them on monotherapy for any period of time.

DR. MOSER: So is your conclusion about the VALUE study that the two drugs may have been equal with regard to events if the BP had not been lowered more with the CCB, especially in the first few months?

DR. OPARIL: My conclusion is I don't know.

DR. MOSER: Okay.

DR. OPARIL: Marv, it's also a dose effect. It's easy to sit here and criticize clinical trials. We should recognize that these studies cost hundreds of millions of dollars, they have to be carefully designed, and once the train is on the tracks it's very difficult to change doses or protocols. Over the years of the trial new things may have been learned about drug actions and dosages, but the protocols must be followed.

DR. MOSER: Tom, did the VALUE trial suggest to you as it has to some of our colleagues that we have been going too slowly in getting BP down in older people?

DR. GILES: Let's back up a minute. I tend to agree with almost everything that Suzanne said about that trial. You don't take somebody who's on two or three drugs, knowing that you've had about a 10-mm Hg reduction for each drug, and take them off therapy. Their pressure is going to go up 20–30 mm Hg and then you're going to give them only one study drug to start and even then at a modest dose. I think we learned something there.

DR. MOSER: Was there a wash-out period in the VALUE study?

DR. GILES: No, they just stopped therapy...

DR. MOSER: And the next day started them on one of the trial drugs.

DR. GILES: That's correct.

DR. MOSER: Like ALLHAT.

DR. GILES: The story with the dihydropyridines is instructive. We were one of the first groups to describe myocardial infarction after "bite and swallow" nifedipine. So people tended to go the whole route the other way. So there's this reaction saying you can't lower BP quickly. Obviously lowering BP in seconds to minutes in somebody who's not having a hypertensive emergency is not something you should be doing in the first place. But there is a long way between that and saying, "Well, come back in 6 months and we'll see what the BP is." The observation about BP differences—particularly in the early part of the VALUE trial—is right on target. It tells you that you don't sit around and wait for 4–6 months, with a small dose of a drug, a little diet, and a little exercise. Patients may pay a price for that if they're at high risk and they've got elevated BPs. They need to have those BPs brought down.

DR. MOSER: So you would say lower the BP a little faster than some physicians have been advising, probably over 1–2 months rather than over 4–6 months.

DR. GILES: That's what I would say.

DR. OPARIL: I agree with Tom. But I think there's a practical lesson for people in practice who are going to read this article. If you have someone who's uncontrolled on two or three medicines, it's not a good idea to stop everything and start over. My practice is to always continue everything, add things until you can get control—and then subtract. Multiple switches can be dangerous for the patient.

DR. MOSER: I've forgotten, in the VALUE trial, were the baseline BPs high even though people had been on two or three medications?

DR. OPARIL: Not dramatically, but elevated.

DR. MOSER: So speeding up management doesn't mean, as some people are interpreting, that BP should be reduced within a week or so. In older people, that's going to cause some trouble. Lower it over a period of a month or 2 instead of 3, 4, or 5.

Now we have another study, the ASCOT trial, which has not as yet been published. The study reported that therapy with a CCB-based program is better than therapy which was β -blocker-based. What do you think of the ASCOT study? A CCB was given as initial therapy and titrated upward, an

ACE inhibitor was added, and if that didn't work, doxazosin was added. This was compared with a β blocker (atenolol 50 mg/d, titrated to 100 mg/d) as initial therapy. A diuretic was added as a third step after titration of the β blocker. This is not the way I would have designed the study. I would have started with a diuretic and then added the β blocker. The newer medications reduced BP to a slightly greater degree than the β -blocker-based treatment. What do you think of the results, Tom?

DR. GILES: Well, there was also another arm which was the lipid-lowering arm.

DR. MOSER: There were 10,000 people who received a statin compared with a placebo and the results were quite dramatic—no question about the benefits of lowering lipids.

DR. GILES: Spectacular. Now in terms of the trial design, here again if you look at this from a point of view of saying okay, from what I know about the totality of the data, what would I predict and then I'll run this trial and see if I modify my hypothesis. I would have predicted that if you lower BP and you do it well, that you would get a good outcome. And if there's an uneven distribution of BP between the two arms, the arm that has the lower BP will do better. I'm waiting to see a trial where that doesn't hold, that is to say that a drug that lowers BP 5 or 6 mm Hg better than another one yields worse results. I haven't seen that yet.

So my take on ASCOT is first of all that it pays to lower BP, and there are multiple ways in which to do that. I hate to say it, but here is atenolol again dosed at 50 mg q.d., and that's not an adequate dose of a β blocker. At the end of the day, there was a BP difference.

DR. MOSER: It wasn't much though, Tom—only about 2 or 3 mm Hg systolic BP. Do you think that's enough to make a difference over time?

DR. GILES: But we don't know what the 24-hour BP load was. You see here again the most critical measurement in the whole trial receives the least attention. We do these finite analyses of lipids and all that stuff—yet the most critical measurement may not be highlighted.

DR. MOSER: It's like the Heart Outcome Prevention Evaluation (HOPE) study where there was a reported difference of only 2 or 3 mm Hg in the office BP between an ACE-based group and patients on other medications. However, the ambulatory pressures in the small number of patients where it was measured showed a much greater difference, especially in nighttime pressures. Some investigators believe that this difference may have

accounted for the benefit in the ACE inhibitor-treated group. So you think the BP difference of about 2/1 mm Hg at the end of the ASCOT study may not have reflected what was really going on?

DR. GILES: I think it shows that we've got multiple drugs that we can use to lower BP. I wouldn't be unhappy with any of them, to tell you the truth.

DR. MOSER: Suzanne?

DR. OPARIL: Well I think the BP issue in ASCOT is a serious one. We have not seen the final results. We know from ALLHAT in the African-American cohort and we know from VALUE that excess BP of 4 mm Hg systolic early on is a really bad story for the patient. And we know that although β -blocker treatment has been shown to be helpful and diuretic treatment has been shown to be helpful, a little atenolol and a little bendroflumethiazide in VALUE may not have been quite as robust as amlodipine, which is a very potent drug, plus an ACE inhibitor. So I don't think we're out of the woods with the BP story yet.

DR. MOSER: So is it fair to summarize—the results of these trials appear to be somewhat confusing, but may not be too different. Every few months, a new study announces that one drug or treatment is better than another. This happened after ALLHAT and ANBP2. ALLHAT said ACE inhibitors may not be as good in certain subsets of patients as a diuretic. ANBP2 said the ACE inhibitors were better in certain patients. Confusion has been noted with VALUE, and it's certainly going to be evident when the ASCOT results are finally published. We all seem to agree that BP lowering is most important in reducing events; in a few subsets of people with diabetes or renal disease, specific medications may make a difference. Even here though, BP lowering is most important. In general,

even allowing for statistical manipulations, we should advocate lowering BP with whatever combination works. And do it reasonably quickly but not within 20 minutes. Is that fair?

DR. GILES: I think that's right. I think that some small mechanistic trials that have good hypotheses and a reasonably well defined phenotype are invaluable. I think the problem comes in sometimes with the mega-trials, where the ability to distinguish between drugs is almost nonexistent.

DR. MOSER: Okay. Suzanne, any final words of wisdom?

DR. OPARIL: Yes, a couple of things. I think dosage is extremely important. No matter if it's the best drug available out of the 100 that we have, if you use the wrong dose, the patient will not have a good outcome. Smaller doses will not provide 24-hour BP control. The other uniform deficiency of the mega-trials is they only follow the patient for an average of 3.5–4.5 years. What happens in Year 10? Maybe some of the metabolic effects, which are dismissed by the trialists, might be important in longer-term follow-up. So we just need more information.

DR. MOSER: Yes, the approximately 8–10-year follow-up studies that have been done, like the Hypertension Detection and Follow-up Program (HDFP), the Multiple Risk Factor Intervention Trial (MRFIT), and the 14-year Systolic Hypertension in the Elderly Program (SHEP) do tell us something. It appears that treatment benefit persists. But there are few carefully collected data from the day these studies stopped until mortality data are collected 8–13 years later. People could have dropped out of therapy or gone on different treatments. But we probably never will have a well controlled, randomized 10–15-year study—so we have to use the data we have to make treatment decisions. Thank you.