

Expert Panel Discussion

Resistant or Difficult-to-Treat Hypertension

Marvin Moser, MD; William Cushman, MD; Joel Handler, MD

Following a hypertension symposium in Los Angeles, CA, in October 2005, an expert panel discussion was held to discuss resistant hypertension. Are there patients whose blood pressures cannot be controlled? Do inappropriate uses of medications or drug combinations or, on the other hand, poor adherence on the part of patients, play a major role in resistance? Dr. Marvin Moser, Clinical Professor of Medicine at the Yale University School of Medicine, New Haven, CT, moderated the discussion. Participants on this panel included Dr. William Cushman of the University of Tennessee College of Medicine, Memphis, TN, and Dr. Joel Handler of the Kaiser Permanente Group in Anaheim, CA. (J Clin Hypertens. 2006;8:434–440)

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DR. MOSER: Bill, we hear a lot about resistant hypertension. For many years we blamed this on the patient—lack of cooperation, not taking their medication, missing appointments, or just not being very concerned about blood pressure (BP). Then we blamed resistant or poorly controlled hypertension on drug side effects—patients stopping therapy because of symptoms. In recent years, however, it has been reported in the few studies that have been performed that drug side effects may play only a minor role in resistance and that patient discontinuance of therapy may not be a major factor. Even drug interactions with cocaine, NSAIDs, and others are not the major reasons for resistance. Many experts now believe that perhaps it is physician inertia, their inappropriate use of medications, or underuse of diuretics that are more important reasons for failure to reduce BP to goal levels. How do you feel about this? Would you comment about the inappropriate use of medications and inappropriate combinations?

DR. CUSHMAN: Yes. I think Dan Berlowitz's article in the *New England Journal of Medicine* in 1998 really focused our attention for the first time on what we've come to call "therapeutic" or "clinical inertia" in hypertension management. He studied a group of Veterans Affairs (VA) patients in New England who were getting free medications

and coming to clinics at least 5 or 6 times a year for BP-related visits. Yet, only 25% were controlled below 140/90 mm Hg. What he found was that the providers were not titrating or adding medications.

DR. MOSER: People would come to the clinic, their pressures would be 150/95 mm Hg or higher and no change in medicine was made.

DR. CUSHMAN: That's right. About 40% of patients had BPs above 160 mm Hg systolic or above 90 mm Hg diastolic and these uncontrolled patients had no change in medication dosage 94% of the time. That was not unique to the VA; that was universal in the 1990s, when the study was conducted. I believe that we hadn't properly taught or encouraged providers to titrate to full doses of medications and to add different medications if the first one didn't work. I don't think many of us were teaching that until the late 1990s.

DR. MOSER: Was it because everyone hadn't fully appreciated the dramatic results of the clinical trials? There were many trials that had been finished by the late 1980s and 1990s.

DR. CUSHMAN: Possibly. Clinicians weren't applying in practice the type of titration schemes that had been used in the clinical trials.

DR. MOSER: Berlowitz's study showed that doctors were not paying much attention to patients who hadn't achieved goal BPs. As we said, they were coming back every few months, their pressures were still elevated and medication wasn't



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changed. Had the benefits of reducing BP to goal levels been established at the time of his study?

DR. CUSHMAN: I believe the guidelines were pretty clear throughout that period of time and that goal BP was less than 140/90 mm Hg. The Systolic Hypertension in the Elderly Program (SHEP) trial in 1991 had shown that treating systolic BP to at least the low 140s reduced events compared with systolic BP in the mid-150s.

DR. MOSER: Was it fear of decreasing the pressure too much in this elderly population that may have resulted in the poor results?

DR. CUSHMAN: Certainly there was fear. I think it was a combination of that and many mantras out there about using low doses of antihypertensive medications. Clinicians didn't know about or were reluctant to titrate to fuller doses or use multiple medications. There had never been a study looking at what was necessary to lower both systolic below 140 as well as diastolic below 90. ALLHAT was really the first study that I'm aware of that treated to a combined goal of <140/90 mm Hg.

DR. MOSER: Most studies had focused on the diastolic pressure—and in the elderly that wasn't the problem.

DR. CUSHMAN: Absolutely.

DR. MOSER: And the FDA had just required efficacy results with diastolic BP to approve a drug. So, you believe that at least some of the problem of resistance, at least 5–10 years ago, related to the fact that an SBP goal had not been clearly defined?

DR. CUSHMAN: Right. Or, how important it was to actually get the systolic below 140 mm Hg. Even though SHEP had been published in 1991, it took a while for clinicians to get the message that they really needed to reduce the systolic BP.

DR. MOSER: Joel, in your experience, is it physician inertia or lack of appreciation for the benefits of therapy that results in the large number of patients who are not being treated to goal pressures? Or are there just some patients who would never get to goal pressures even if a doctor was conscientious and added and subtracted drugs appropriately?

DR. HANDLER: Well, I think the latter category is probably a small part of the problem. For resistant hypertensives in my clinic, I'll always have a few patients who, no matter what I do, I can't get under control. But even in these patients, getting the BP down to some degree is beneficial in reducing their cardiovascular risk.

DR. MOSER: You mean reducing the BP without achieving goal?

DR. HANDLER: That's right. SHEP sought to reduce initial systolic pressures >180 mm Hg to

<160 mm Hg and demonstrated a large impact in reducing stroke and MI. The larger hypertension treatment trials only achieved about 65% control rates of systolic pressure <140 mm Hg compared with about 90% attaining diastolic pressures <90 mm Hg. This shows us the relative degree of difficulty in getting systolic pressure under optimal control. Many times we have to be satisfied with systolic pressures in the 150s if we feel we've made our best effort and can reassure the patient that there has been significant risk reduction nonetheless. However, a larger group of patients, for whatever reason, has their hypertension ignored by physicians. Patients who have not had a medication change for a year or more come to our clinic with elevated BPs. Usually the patient has seen the physician for a symptomatic complaint and they are focused on that complaint.

DR. MOSER: Is this mostly in the elderly? It is quite natural to focus on arthritis complaints, on diabetes control, or symptoms of prostatic hypertrophy. Meanwhile the BP remains elevated and nothing is done about it. Is it a problem or concern that if the BP is decreased in an older person, they may feel bad? Maybe many physicians are worried about this.

DR. CUSHMAN: I think a lot of the problem is that most physicians who are treating hypertension don't realize how few of their patients are controlled unless someone is measuring response rates and giving them feedback. I mentioned that in the VA study, only 25% were below 140/90 mm Hg. This was in the early 1990s. It turns out that by the late 1990s, more than 40% were controlled in the VA nationally. That was after electronic medical records were established. People could see over time how well the BP was controlled. Starting in about 2000, the VA instituted a national monitoring system, a performance measure for BP control. Hospitals and providers got feedback as to how well they were doing globally, not just with individual patients. As a result of these procedures, control rates continued to climb year by year, and in 2004 they were 67%.

DR. MOSER: These results are consistent with clinical trials with established protocols for goal BPs and where medications were given in appropriate amounts and dosages. In these trials, about 60% or more achieved goal systolic pressures.

DR. CUSHMAN: That's right. If you look at trials like the Antihypertensive and Lipid-Lowering Treatment to Prevent Heart Attack Trial (ALLHAT) and Controlled Onset Verapamil Investigation of Cardiovascular Endpoints (CONVINCE), an

identical BP control rate was achieved as has been achieved within the VA (67%). Even in these trials, however, most of the patients who were not controlled, probably were not controlled because of clinical inertia.

DR. MOSER: Even though the protocol strongly suggested specific approaches if goal BPs were not achieved?

DR. CUSHMAN: That's right.

DR. HANDLER: I fully support what Bill is saying about the effectiveness of organizational support systems. We are addressing therapeutic inertia within the Kaiser organization and have also seen our hypertension control rate rise over 60%. We looked at regional control rates and examined best practices. This analysis led to the development of a model of care we are promoting at our Southern California facilities. We learned first of all that some kind of BP alert for elevations is an important action trigger. We have an electronic alert for BPs and in the areas that do not have electronic messaging, we highlight the elevated BPs on the progress note sheet that is handed to the provider. The second part of the process, as Bill has pointed out, is performance feedback reporting. At our department meetings, we provide this information in an unblinded fashion. The physicians know how they stand compared with their peers with regard to BP control in patients who have a diagnosis of hypertension.

The third part of the program that we've found helpful is to get physicians in nonprimary care areas involved. Many times, BP elevations will be recorded by a head and neck surgeon, an allergist, or a urologist. We are establishing systems whereby people with elevated BPs in nonprimary care areas are referred back to primary care or to a nurse-run clinic. A mentored treatment algorithm is then followed in some of these nurse clinics.

DR. MOSER: This sounds fine in a large managed care program and in the VA where nurses and personnel are available to handle clinics and feedback. But what about a private practitioner who is seeing 30–40 people a day? He or she is concerned about an asthmatic with an acute attack, a severe diabetic, or someone with crippling arthritis. It is difficult to get them to focus on managing a disease where the patient is not in pain or has significant symptoms. Doctors have gotten the message that hypertension poses a risk and that treatment is beneficial and prevents cardiovascular events. But somehow, to make further progress, we have to keep management simple and keep expense as low as possible. This can be done if hypertension experts don't make the process too complicated. A system of flagging

patients with hypertension and patients whose BPs remain >140/90 mm Hg can be introduced without additional cost or time. This can and should be done. While a more elaborate system is great with a health maintenance organization, with the VA, or in a university clinic, the real problem may be that it is the family practitioner who sees most of the hypertensive patients. I really believe that part of the management problem is the fear of lowering pressure too much, especially in the elderly. Another possible problem with a "resistant hypertensive," as Bill pointed out, is not realizing the importance of reaching goal BPs, the use of appropriate combinations, and dosages of the commonly used drugs like diuretics, angiotensin-converting enzyme (ACE) inhibitors, angiotensin receptor blockers (ARBs), and calcium channel blockers (CCBs). Do we have specific data to guide us?

DR. CUSHMAN: I think that the first thing we have to pay attention to are outcome data from the clinical trials. We have good data with the thiazide-type diuretics, ACE inhibitors, ARBs, CCBs, and various combinations of these medications. The nice thing is that all of these medications, except the ACE inhibitor and ARB, combine well with each other.

DR. MOSER: So, a diuretic with an ACE inhibitor, an ARB, a β blocker, or CCB is more effective than high-dose monotherapy.

DR. CUSHMAN: Yes, that's right.

DR. MOSER: There were some data years ago that reported that the CCBs and diuretics were not more effective than monotherapy when given together. If you adhere to the renin theory, they shouldn't be, since both of these classes of drugs are effective in low renin subjects. But this combination is a good one, isn't it?

DR. CUSHMAN: Yes, and it was certainly used quite effectively in the Valsartan Antihypertensive Long-Term Use Evaluation (VALUE) study where a diuretic was added to the calcium blocker with somewhat better results than with the ARB plus a diuretic.

DR. MOSER: Now you downplayed β blockers in your recommendation. These are renin inhibitors, aren't they?

DR. CUSHMAN: Right. You could use a β blocker instead of an ACE inhibitor or ARB. All of the β blockers combine well with either a diuretic and/or a calcium blocker as long as the calcium blocker is a dihydropyridine CCB (DHP-CCB). However, I would not use a β blocker early in therapy because of the poor track record in hypertension outcome trials, unless there was a compelling indication for the β blocker.

DR. MOSER: So, what you're saying is that appropriate combinations should not be a major problem. A diuretic plus an ACE inhibitor, ARB, or CCB, a diuretic/ β blocker, a β blocker plus a DHP-CCB, or even in some cases a nondihydropyridine and a DHP-CCB are all appropriate?

DR. CUSHMAN: Right. Now what we often see are patients who are on an ACE inhibitor, an ARB, and/or a β blocker. These medications are similar enough, even though they don't have identical mechanisms of action, so that they don't add a lot of efficacy to each other. They're safe to use together but basically you're not going to get nearly as much added efficacy as you will if a diuretic, for example, is added to either one.

DR. MOSER: So, if a patient came in on a β blocker and an ACE inhibitor and they weren't controlled, you might stop the β blocker and use a diuretic along with the ACE inhibitor instead, unless there was a specific reason (such as angina or post-myocardial infarction) for the use of a β blocker.

DR. CUSHMAN: Absolutely. Conversely, if they need to be on both of these agents for coronary disease, then that's fine—you can still add the diuretic or a calcium blocker.

DR. MOSER: So, appropriate use of medications should not be a major problem.

DR. CUSHMAN: It doesn't have to be, but it often is. The other thing is that, in addition to the major classes of drugs, there probably are some drugs that we can add that are also effective, although we don't have an overwhelming amount of data to decide which works best. Historically, we've used direct vasodilators, like hydralazine, added to other medications and I think that reserpine in small doses is still a good drug to consider. Aldosterone antagonists may also be used.

DR. MOSER: In a resistant patient, the addition of an aldosterone antagonist has proven very effective in lowering BP; not in all patients, but certainly enough to warrant consideration.

DR. CUSHMAN: If a patient is receiving full doses of three medications, including a diuretic, and their BP is not controlled, there are even more drugs that can be added. I believe that primary care providers can be comfortable using other medications. I tend not to use clonidine and certainly very few people use methyl dopa. Both of those drugs cause more than 50% of patients to have some side effects, and this leads to a much higher drug withdrawal rate.

DR. MOSER: Would you use one of these in a truly resistant patient?

DR. CUSHMAN: Rarely, because I think reserpine is a much better alternative—it's much better tolerated, very long-acting, and inexpensive.

DR. MOSER: If you can find it.

DR. CUSHMAN: It is available. We haven't had trouble finding it. And there are still other options.

DR. MOSER: Alpha blockers for one...

DR. CUSHMAN: Alpha blockers...

DR. MOSER: ...as a third- or fourth-step drug.

DR. CUSHMAN: Absolutely. And, in many recent studies, α blockers have often been the third drug added. They're going to cause more side effects than some other medications, but there are patients who benefit from their use. I would usually reserve an α blocker for fourth line. However, they are useful in patients with lower urinary tract symptoms, e.g., from benign prostatic hyperplasia. Remember, the α -blocker arm was stopped early in ALLHAT because of excess cardiovascular events, so an α blocker should not be used as initial or possibly even one of the first additional agents in a patient.

DR. MOSER: Joel, you have a patient who comes to see you on 12.5 mg of hydrochlorothiazide and 20 mg of enalapril. They are not controlled. Do you add a third drug or do you think about dosage changes?

DR. HANDLER: In a case like that, I would maximize the dosages of the diuretic and the ACE inhibitor.

DR. MOSER: What's the maximum dose of a diuretic you'd use?

DR. HANDLER: I use 25 mg of hydrochlorothiazide and then I'll usually switch to chlorthalidone.

DR. MOSER: At what dosage?

DR. HANDLER: 25 mg.

DR. MOSER: Okay, you'd go to 25 of hydrochlorothiazide. BP is still uncontrolled. You switch to 25 mg of chlorthalidone, which may be equivalent to 37.5 or maybe even 50 mg of hydrochlorothiazide, and the pressure still isn't controlled. Do you want to continue with just these two drugs? Would you ever go to 50 mg of chlorthalidone?

DR. HANDLER: Before I'd go to 50 mg of chlorthalidone, I'd add on or maximize another medication.

DR. MOSER: Bill, do you agree? Many physicians and some of the clinical trials used inadequate doses of diuretics.

DR. CUSHMAN: I think the standard dose of hydrochlorothiazide based on outcome studies and BP efficacy studies should probably be 25 to 50 mg of hydrochlorothiazide and 12.5 to 25 mg of chlorthalidone. Certainly we have a wealth of outcome data with the 12.5- to 25-mg doses of chlorthalidone. We have no outcome data with 12.5 mg of hydrochlorothiazide. I may start some patients on 12.5 mg, particularly an elderly patient, but I rarely keep them at this dosage.

DR. MOSER: We've been brainwashed to use lower and lower doses. Dr. Freis once said that we can get so low that the effectiveness is lost.

DR. CUSHMAN: You're right about that. Now, about going above 50 mg of hydrochlorothiazide or 25 mg of chlorthalidone, there are several good studies showing that you get very little, if any, added antihypertensive benefit, but you do get more biochemical changes. At the doses we now recommend, there is a relatively low frequency of significant hypokalemia. Hypokalemia is even less of a problem if the diuretic is combined with an ACE inhibitor, an ARB, or an aldosterone antagonist.

DR. HANDLER: We often have patients referred to our hypertension clinic on 25 mg of hydrochlorothiazide and then are switched to 25 mg of chlorthalidone, which often has additional BP-lowering efficacy. One of the other reasons for making this change is that 50 mg of hydrochlorothiazide appears to be less acceptable to clinicians. Physicians who will not use 50 mg of hydrochlorothiazide often readily accept 25 mg of chlorthalidone. The main drawback is that we don't have many combinations with chlorthalidone.

DR. MOSER: Just one or two...

DR. HANDLER: ...so very often if somebody is on a combination, then I may go to a combination that includes 50 mg of hydrochlorothiazide, and referring physicians seem to be more accepting of that as long as it's in the combination.

DR. MOSER: Hopefully we'll have more chlorthalidone combinations soon. Joel, the nephrologists are telling us that some clinical trials with angiotensin II receptor blockers didn't report better results because correct dosages of these agents were not being given. What do you think about the dosages of ARBs? And how high would you go before you say that a particular ARB is not going to work?

DR. HANDLER: Well, I have to tell you that I don't use a lot of ARBs. For our therapeutic algorithms and regimens, we use a sequence of a diuretic, ACE inhibitor, and then go to a β blocker or CCB, but I do agree that some of the trials did not use full doses of some of the ARBs.

DR. MOSER: Talk about the CCBs. If you're using 10 mg of amlodipine, could you go to 20 mg or even 40 mg? Where do you think the benefit-to-risk ratio changes? Is there an increase in BP benefits up to a point and then nothing further?

DR. HANDLER: I'm glad you brought up CCBs because I believe that they probably are underdosed to some extent. As Bill has pointed out, we need to go to higher doses. Table X in the full

Seventh Report of the Joint National Committee on Prevention, Detection, Evaluation, and Treatment of High Blood Pressure (JNC 7) in 2003 is a helpful guide for many agents, because it indicates the dose ranges for the commonly used antihypertensives. For example with felodipine, I think most practitioners will stop at a dose of 10 mg, but really can go to 20 mg according to that table.

DR. MOSER: What about amlodipine or nisoldipine?

DR. HANDLER: Our top dose of amlodipine would be 10 mg according to the JNC table. We don't use much nisoldipine.

DR. MOSER: So you wouldn't go higher than 10 mg of amlodipine?

DR. HANDLER: Not usually. We occasionally use combinations of DHP- and non-DHP-CCBs for resistant patients. If a patient is not on a β blocker or another rate-slowing agent, a useful strategy may be to add a non-DHP-CCB to the DHP-CCB. I find that this combination works well in some elderly women with resistant hypertension who cannot tolerate a diuretic due to hyponatremia.

DR. MOSER: Give me an example of that. A patient is on 10 mg of amlodipine.

DR. HANDLER: I would add 120 mg of diltiazem extended release to the 10 mg of amlodipine, and consider a diltiazem dosage advance depending on the BP response and patient tolerability to the CCB combination.

DR. MOSER: Bill, what about the dosages of angiotensin II receptor blockers? Do you believe that we're underdosing patients, especially since most people who are on an ARB are also on a diuretic? How high can you go before the risk-benefit ratio changes?

DR. CUSHMAN: I don't think we're underdosing if we follow the recommended doses in the Physician's Desk Reference or the JNC 7 tables. However, I think that in practice, virtually all of these classes of drugs are underdosed. Physicians often use smaller doses of the ARB or other drugs than what they actually can.

DR. MOSER: What's the cutoff point? I'm a practitioner—I've read all about the ARBs and I'm told that these must be titrated. I use either losartan, valsartan, irbesartan, telmisartan, or olmesartan and start with the lowest dose recommended. Let's say with losartan at 50 mg, can I go to 100 mg q.d.? Does it make any difference or should I stop at 50 mg/d?

DR. CUSHMAN: The data we have from outcome studies with ARBs indicate that half of the maximal dose is not as effective as the maximal dose.

For example, in the Irbesartan Microalbuminuria Type 2 Diabetes Mellitus in Hypertensive Patients (IRMA-2) study, irbesartan 150 mg/q.d. was not as effective as 300 mg in reducing renal complications. So, I think that we need to assume that it's good to try and go to the maximum doses with those drugs, if at all possible.

DR. MOSER: How about with the ACE inhibitors?

DR. CUSHMAN: Probably with the ACE inhibitors, too. Now, super maximal doses might have some theoretic benefit, but we don't have the data to say that we should go above the maximum recommended doses. At this point, I would not recommend doing that. Maybe down the road we'll find out that there are some renal benefits to going to higher doses, but we don't have evidence for those higher doses that they lower BP more effectively. Secondly, even though I'm not too

concerned about it, we don't have safety data on much higher doses. I think the main point is that we don't have the evidence yet to use higher than currently recommended doses of ARBs or ACEIs.

Now, with calcium blockers, there probably is a further BP-dose response when going to higher doses, but clearly the side effects start going up a lot when you go to higher doses of calcium blockers than those that are currently recommended, and we have no outcome data with higher doses.

DR. MOSER: The JNC table (Table) gives some examples of maximum doses recommended.

So, let me summarize. We seem to all agree that resistant hypertension does exist, and that there are some people in whom you really can't get the BP to normal or optimal levels without changing their enjoyment of life, especially in the elderly. A major problem, however, appears to be related to physician

Table. Suggested Dosage Ranges for Commonly Used Antihypertensive Drugs* (From JNC 7)

CLASS	DRUG	USUAL DOSE RANGE (MG)	DAILY FREQUENCY
Thiazide diuretics	Hydrochlorothiazide	12.5–50	1
	Chlorthalidone	12.5–25	1
Aldosterone receptor blockers	Spironolactone	25–50	1–2
	Eplerenone	50–100	1
β Blockers	Atenolol	25–100	1–2
	Metoprolol (extended-release)	50–200	1
α-β Blockers	Carvedilol	12.5–50	2
Angiotensin-converting enzyme inhibitors	Enalapril	2.5–40	1–2
	Lisinopril	10–40	1
	Ramipril	2.5–20	1
Angiotensin II antagonists	Candesartan	8–32	1
	Eprosartan	400–800	1–2
	Irbesartan	150–300	1
	Losartan	25–100	1–2
	Olmesartan	20–40	1
	Telmisartan	20–80	1
	Valsartan	80–320	1
Calcium channel blockers (nondihydropyridines)	Diltiazem (extended-release)	180–420	1
	Verapamil (long-acting)	120–360	1
Calcium channel blockers (dihydropyridines)	Amlodipine	2.5–10	1
	Felodipine	2.5–20	1
	Isradipine	2.5–10	2
α ₁ Blockers	Doxazosin	1–16	1
	Prazosin	2–20	2–3
Central α ₂ -agonists and other centrally acting drugs	Clonidine	0.1–0.8	2
	Clonidine patch	0.1–0.3	1/wk
	Reserpine	0.05–0.25	1
Direct vasodilators	Hydralazine	25–200	2

*Not all drugs listed in the Seventh Report of the Joint National Committee on Prevention, Detection, Evaluation, and Treatment of High Blood Pressure (JNC 7) are included. Adapted with permission from *JAMA*. 2003;289:2560–2572.

or health care provider inertia about changing, altering, adding, or substituting medications. We cannot be certain whether this is related to consideration of “side effects” or lack of appreciation of treatment benefits. With combinations, which can include a diuretic and a β blocker, diuretic/ACE, diuretic/ARB, diuretic/CCB, an ACE inhibitor/CCB or, in some cases, two different CCBs, a DHP and a non-DHP drug, goal pressures of <140 mm Hg can probably be achieved in many “resistant” patients. This assumes that causes of resistance have been ruled out, i.e., secondary causes, interfering substances, sleep apnea, etc. Goals pressures are most difficult to achieve in elderly patients, even if

they are adherent and are taking three medications, including a diuretic. The addition of drugs like the aldosterone antagonists or, in some cases, even less widely used drugs like an α blocker, reserpine, hydralazine, or clonidine may be helpful.

DR. CUSHMAN: The only other thing I would add is that there is a very rare patient whom you believe was compliant and that you have decided after some time they’re truly resistant to therapy, and subsequently found out that they really weren’t taking their medications consistently or as prescribed. It is unusual to have a truly resistant patient to currently available medications.

DR. MOSER: Thank you.