

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

## Secondary Hypertension—Whom and How Do You Study? What Type of Therapy Is Appropriate?

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*Following a hypertension symposium in Los Angeles, CA on October 20, 2004, a roundtable was convened to discuss secondary or treatable forms of high blood pressure, when and whom should be studied, and treatment methods. Dr. Marvin Moser, Clinical Professor of Medicine at Yale University School of Medicine, New Haven, CT, moderated the panel discussion. Participants included Dr. Ron Victor, from the Southwestern Medical Center, Dallas, TX and Dr. Joel Handler of the Orange County Kaiser Permanente Hypertension Clinic, Anaheim, CA. (J Clin Hypertens. 2005;7:224–230) ©2005 Le Jacq Ltd.*

DR. MOSER: We all know that there are treatable or secondary causes of high blood pressure (BP) but we also know that they probably account for less than 10% of hypertensives. You don't want to miss one, especially one where specific treatment results in a cure. Joel, whom do you study?

DR. HANDLER: I think we have to be selective. You can't take all comers. If the patient is successfully treated to goal BP with one or two drugs, I'm generally not going to do a work-up.

DR. MOSER: Even in a 7-year-old kid?

DR. HANDLER: I don't deal with pediatrics. My patients are 50 and over. I do see some young adults, but no children.

DR. MOSER: But in an adult person whom you are able to control with reasonable therapy, you would probably not look for a secondary cause.

DR. HANDLER: If, for example, they're on a well-tolerated angiotensin-converting enzyme (ACE) and diuretic regimen, their BP is under control, and their creatinine doesn't bump up, I'm not going to go further with specific studies.

DR. MOSER: What about a 60-year-old whom you have been following for 5 years with BP that has been normal and now, for the first time, BP is 180/110 mm Hg?

DR. HANDLER: I think that is an important point. Natural history studies suggest that when you have untreated hypertension, it accelerates about

10% of the time, but in a patient who is well controlled on drug therapy, studies indicate that only 1% or less will accelerate due to natural disease progression. If somebody is well controlled for several years or has had normal BPs and comes to the clinic with readings characteristic of grade II hypertension, I might consider a post-captopril renogram or aldosterone/renin sampling. Lots of times, I don't even do that. If you performed additional laboratory work and a nuclear medicine study in 1% of 1 million people, you are going to study a lot of people. If I can add additional medication or get them under control fairly easily, I'm not going to pursue it.

DR. MOSER: So you would not necessarily study someone who is well controlled and gets out of control?

DR. HANDLER: That's correct.

DR. MOSER: Ron, when do you study people?

DR. VICTOR: Anyone who has ever been hospitalized for severe or accelerated hypertension deserves to be studied.

DR. MOSER: You are talking about stage 3 or 4 with funduscopic findings of hemorrhages or exudates, or creatinine levels of more than 1.5 to 2.0 mg/dL?

DR. VICTOR: Yes. Because we know that the chances of finding a secondary cause, either renal artery stenosis or primary aldosterone, is much greater in that setting.

DR. MOSER: Now what about someone who has been documented as having had 150/90 mm Hg



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to 160/100 mm Hg for several years? Pressures haven't really been well controlled, but now they present with BPs greater than 200/110 mm Hg with retinal hemorrhages?

DR. VICTOR: The classic teaching is that this may represent new-onset renal artery stenosis. That brings up a whole issue of how you approach any question of secondary hypertension—we're not hedging, but sometimes the decision is difficult and you have to balance benefit to risk, inconvenience, and cost before starting various studies.

DR. MOSER: The secondary causes we are looking for are renovascular hypertension, primary aldosteronism, and pheochromocytoma, which we can usually, but not always, suspect because this is truly symptomatic hypertension. Anyone with palpitations, headaches, sweating, and episodic hypertension should be studied for a pheochromocytoma.

Next, renovascular hypertension. Ron, you've alluded to the fact that one of the groups you would work-up are people with accelerated or malignant hypertension. In another group, some of our colleagues, but not all, would disagree with Joel and insist that if a patient was well controlled and experiences a significant 20, 30, or 40 mm Hg rise in systolic BP and had continued to take medication, then he or she should probably be studied. Joel, are there any people that you would definitely work-up for renovascular disease?

DR. HANDLER: Someone who had a progressive decline in renal function or a sudden decline either unprovoked or as a consequence of an ACE or angiotensin receptor blocker (ARB) might be a candidate for study.

DR. MOSER: How long would you wait? If you had started an ACE inhibitor or an ARB and the creatinine goes from 1.2 to 1.5 or 1.6 mg/dL and you check it in 3 weeks and it is not rising any further, but is not coming down, what do you do? In other words, what is your trigger point before you would say this patient must be studied for renovascular disease?

DR. HANDLER: About a 30% fall in glomerular function rate or a rise in serum creatinine more than 0.5 mg/L. My experience is that in people with mild degrees of renal insufficiency or chronic kidney disease, the creatinine will bump a bit with ACE-inhibitor therapy, but usually will come back toward the baseline or even below the baseline level and hang in there. If the glomerular filtration falls more than 30%, you should stop ACE-inhibitor therapy for a period of time. Sometimes volume status has a lot to do with that.

DR. VICTOR: Studies indicate that when patients have a little increase in creatinine within 4 months, it may indicate improved renal function years later. I think it's appropriate to advise doctors to continue therapy if there is some increase in creatinine because this may be an indication that glomerular hypertension is actually being reduced. There may be a short-term decrease in the glomerular filtration rate which will translate into long-term benefit.

DR. MOSER: So, it's fair to say that if you have someone, for example, a 60-year-old person whose renal function probably isn't perfect to begin with, and creatinine levels go from 1.2 or 1.3 to 1.5 or 1.6 mg/dL, and stay around these levels, that therapy with an ACE inhibitor or ARB should be continued. But what if creatinine goes to 2.4 in 3 months?

DR. VICTOR: You need to stop therapy.

DR. MOSER: And look for renovascular disease?

DR. VICTOR: Two things. I assess volume status, whether there is concomitant use of NSAIDs or diuretics. Then consider if there is a renovascular problem. What we would be worrying about is bilateral renal artery stenosis.

DR. MOSER: So far, the patients whom you would study would include an accelerated or malignant hypertensive, perhaps the person who has been well controlled and who gets out of control and, finally, someone with an adverse renal function response to renin-angiotensin-aldosterone system inhibition. We never have really answered the query about new-onset newly diagnosed stage 2 hypertension with BPs greater than 160/100 mm Hg. Let's say, Joel, you have a patient who was normotensive for years, and then has a BP of 170/110 mm Hg.

DR. HANDLER: First of all, if somebody has a BP that is 20 mm Hg higher than before and I can control them with one or two drugs without an increase in creatinine, that's okay. As far as somebody presenting out of the blue with stage 2 hypertension, we can go back to Perrera's natural history study in 1955 of 500 patients with essential diastolic hypertension. Twelve percent of these essential hypertensives had their onset before the age of 20 and it was rare for essential hypertension to be noted for the first time over age 50. So, if somebody presents with newly diagnosed stage 2 hypertension and is past age 50, secondary hypertension is a consideration. Again, you have to develop a strategy and look ahead and see what makes sense. I think that when it comes to renal artery stenosis due to atherosclerosis, the results and complications of the interventions suggest that

if you can get these patients under control with medication without a decline in renal function, it is probably OK and the patients may be better off.

DR. MOSER: Are you saying that they should not be worked up because...

DR. HANDLER: What I'm saying is that there is a high likelihood of having a secondary etiology, but what are you going to do about it? You can treat a lot of these patients medically.

DR. MOSER: Perhaps the common dictum that anyone who has new-onset stage 2 hypertension or whose hypertension gets out of control or whose creatinine goes up sharply should be worked up may not be the correct way to proceed in all cases. If a patient is studied, what am I going to do about it? So, Joel, if a 70-year-old person is proven to have atherosclerotic renovascular disease after a careful diagnostic study, you might treat them medically anyway. Perhaps the rules that have been pretty well set in guidelines may not be applicable to all of these patients.

DR. HANDLER: That's what I'm saying.

DR. MOSER: You may be right. Joel?

DR. VICTOR: I agree with what Joel said. It is still a difficult process to find patients who are going to really benefit from an invasive procedure. The data are far from perfect. I don't know of any data with drug-eluting stents for renal artery stenosis. These procedures may improve outcome.

DR. MOSER: Let's get back to basics. Any clinical clues to renovascular disease?

DR. VICTOR: Well the old clinical tip is that someone may have flash pulmonary edema.

DR. MOSER: That's rare though, isn't it?

DR. VICTOR: They say 30%.

DR. MOSER: How many cases have you seen.

DR. VICTOR: Not too many and, even then, how many have a correctable lesion is another story.

DR. MOSER: Okay, what else, what other clinical clues? We still do physical exams.

DR. VICTOR: The sensitivity of a flank or epigastric bruit is very low. I mean, it's not a good clinical finding. It is also rare to find it even if you look and listen carefully.

DR. MOSER: Well it is fairly common in older people to hear a low-pitched systolic bruit with aortic or mesenteric artery disease, but when you hear a high-pitched holosystolic murmur with a diastolic component, it may be helpful in detecting renovascular disease. In younger women, this finding has been very helpful. Ron, if you see a young woman with hypertension, would you look for renal disease, specifically fibromuscular dysplasia?

DR. VICTOR: Yes, I would. The bruit is a helpful clue in this case. The success rate with either

surgery or angioplasty is good. This is an unusual finding but should be kept in mind.

DR. MOSER: Angioplasty does produce good results. Do stents help?

DR. VICTOR: I do not know if that's been studied.

DR. HANDLER: In the hypertension primer, they mention that the patients who get a stent had less restenosis. I am not sure that they had data showing that there was better control of the hypertension, but there was a little bit lower percentage of restenosis.

DR. MOSER: Fibromuscular dysplasia is a totally different disease with a different prognosis from atherosclerosis.

DR. VICTOR: We had an 80-year-old woman who had bilateral fibromuscular dysplasia and was treated with improvement in BP.

DR. MOSER: With an angioplasty?

DR. VICTOR: Yes.

DR. MOSER: So in a young woman with hypertension, you certainly will look for bruits and, if there is a bruit or if BP is difficult to control, this might give you a clue to this entity.

DR. VICTOR: If you have a potentially correctable form of hypertension, correct it. It avoids a lifetime of medications and cost.

DR. MOSER: Now let's go back to the other problem. We have a patient whose creatinine keeps rising on an ACE inhibitor. They are not volume depleted. We reduce the dosage of the diuretic, but believe that this 65-year-old man may have renovascular disease. What do you do next, Joel? Will you go further or still just adjust medications?

DR. HANDLER: If these patients have renovascular hypertension, it is overwhelmingly atherosclerotic. They have a high rate of complications from procedures and surgery. Frequently, there is an ostial stenosis where the plaque comes off of the aorta and involves the proximal renal arteries. These patients have a higher rate of cholesterol embolization as a result of a procedure and may suffer acute renal failure as a result of cholesterol embolization and have other cardiovascular or procedural complications. I am reluctant to look further.

DR. MOSER: So the complications may be significant and the procedures do not always result in a cure of the hypertension. You might, therefore, just give him different medications?

DR. HANDLER: Yes.

DR. MOSER: Ron, assume you want to study this patient with possible renovascular hypertension, but you ask the questions—why put him through studies when, in the end, he may improve but won't be cured with a bypass or an

angioplasty? You still have to use medicine, so what's the difference if I only use three pills instead of four? Sorry to belabor the point, but this is an important decision.

DR. VICTOR: It's a tough judgment call in every case. If it looks like there's a high suspicion of bilateral renal artery stenosis and a downhill course in renal function with institution of ACE inhibitor therapy, you will try to preserve the kidney. This would push me toward working the patient up.

DR. MOSER: Will medical therapy with lowering the BP in a patient with renovascular disease slow the progression of renal disease as much as a successful angioplasty? "Successful" defined as not necessarily controlling the pressure to normotensive levels without therapy, but with less medication?

DR. VICTOR: It depends. There are some, but not all data, suggesting this.

DR. MOSER: Interesting insights. Most textbooks present three or four indications for specific RV disease studies, but do not carefully consider what happens when you make the diagnosis. Let's assume that you've made a decision that either renal function is deteriorating or BP control is not achievable and you have decided that intervention would be useful if a lesion were found. What are the two or three best tests you might use to rule out RV disease?

DR. VICTOR: I think it's very institution-dependent. In our institution, the best test is a computed tomography (CT) angiogram.

DR. MOSER: A CT angiogram?

DR. VICTOR: A screening test. We don't do captopril renograms anymore because...

DR. MOSER: Are there too many false negatives and false positives?

DR. VICTOR: Yes, and also it's a pain in the neck to stop all the drugs that are supposed to be stopped—renin-system blocking drugs for 6 weeks, some other drugs for 3 weeks, etc. If someone's pressure is high, it's a mess and you're worried about increasing BPs and strokes.

DR. MOSER: So you go right to an angiogram.

DR. VICTOR: I do a CT angiogram if I'm not worried about contrast-induced nephropathy. If I'm worried about that, I do a magnetic resonance angiogram (MRA) with gadolinium where there is no risk of renal embarrassment. In our institution it's not quite as good, but in some institutions it is as good or better.

DR. MOSER: Will your surgeons operate on the basis of those tests or do they insist on an angiogram?

DR. VICTOR: No, they insist on an angiogram if the results are not absolutely clear. But if we have

a negative CT angiogram, it stops there. And, it is probably really OK not to go any further with a negative MRA.

DR. MOSER: How do you determine function, and does renal size influence you? You can demonstrate a lesion, but it may just be an anatomic lesion with no physiologic effects.

DR. VICTOR: A discrepancy in renal size with the affected size being smaller is very helpful.

DR. MOSER: And how about the physiologic differences?

DR. VICTOR: We do not use the captopril renogram; we just haven't used it.

DR. MOSER: So you don't use any specific measures of physiologic differences? Do you use differential renin levels.

DR. VICTOR: No.

DR. MOSER: Joel, what do you do?

DR. HANDLER: We prefer a renal artery MRA with gadolinium, but I think our interventional radiologists would demand an angiogram if there was a suspicious MRA just because of false positives. I agree with Ron, that it's probably a pretty good screening test to rule out significant renovascular disease. There have been a few times when I've had patients with severe medically refractory hypertension and despite a normal renal artery MRA I've gone ahead with renal angiography to be sure I'm not missing a potentially correctable lesion. The angiogram has always been normal in these cases. These are usually highly selected younger individuals with an experience of multiple medication intolerances. Or, they are truly refractory and very severe hypertensives, where I've already decided that if a significant occlusion is discovered, a try at stenting is warranted without pursuing a functional renal study or renal vein renins.

DR. MOSER: We used to pay a lot of attention to that. Ron, so you find a lesion and the odds are that it's atherosclerotic. Do you operate on it knowing that maybe you may not do any better than if medical therapy were pursued more vigorously?

DR. VICTOR: I agree with Joel. If I can treat the patient's BP with good results medically, I probably would continue with medications.

DR. HANDLER: The bottom line, I believe, should be that if you are convinced that you are going to perform some intervention before you work the patient up, you study them; if you are not convinced that intervention is really going to improve outcome, there is little reason to perform a lot of tests.

DR. VICTOR: If you're not going to do it, there's no point.

DR. MOSER: We won't spend much time on the diagnosis of pheochromocytoma. This is symptomatic hypertension and, if the patient has palpitations, headaches, or profuse and inappropriate sweating, they should be studied. Metanephrine and vanillylmandelic acid levels should be determined. If they are elevated, further studies (CT scan, etc.) should be done to localize the tumor and remove it. Although postoperative BPs are usually reduced to normal, some older people may remain hypertensive after the tumor is removed, but they will not have the preoperative symptoms. A pheochromocytoma is a secondary cause where there is *no* question about treatment.

There is now an emphasis on primary aldosteronism. Are we missing a lot of these cases? Is it important to find them? A majority of hypertensive patients are on ACE inhibitors or ARBs and these medications may keep BP at goal levels even with primary aldosteronism. But what about a patient who is relatively resistant to therapy or, in some but not all cases, has a serum potassium (K) below 3.5 mg/dL off a diuretic or below 3.2 mg/dL on a diuretic? How vigorously should we look for an aldosterone lesion? Ron, briefly summarize when and how you would study such a patient. And then what will you do? Most people with primary aldosteronism will have bilateral hyperplasia and most of them will respond to usual medication plus an aldosterone antagonist like spironolactone. So why should we bother studying them?

DR. VICTOR: Because a lot of these patients have very severe hypertension that is not possible to adequately control. There are two issues. One is the elevated BP and its sequelae and the second is the K level. Hypokalemia, over time, can result in serious metabolic consequences.

DR. MOSER: We used to think aldosteronism was most common in younger women. Is that true?

DR. VICTOR: Typical range is 30–60 years of age.

DR. MOSER: It's a pretty big range; more women than men?

DR. VICTOR: I don't know. In our hands probably about the same, not much gender difference.

DR. MOSER: So you would tend to work-up resistant hypertensives?

DR. VICTOR: I always work-up resistant hypertensives for primary aldosterone regardless of the K levels. The work from the Mayo Clinic suggests that about 20%–30% of patients with this disease have a normal K. You don't know what the K was before they developed primary aldosteronism, but I think that a low K is certainly one reason to go further.

DR. MOSER: Do you have a limit; do you have a cut point where you get suspicious?

DR. VICTOR: A reasonable cut point is an unstimulated K of less than 3.3 mg/dL.

DR. MOSER: Not on a diuretic. What about on a diuretic?

DR. VICTOR: Less than 3.0 mg/dL. If you wait for this finding, you're going to miss some cases and, as noted, some people even have normal K levels. There has been a debate about the incidence of newly diagnosed primary aldosteronism. The percentage went up when the renin-to-aldosterone ratios became the big screening test. The percentage of people with a solitary adenoma where the BP can either be cured or greatly improved by adrenalectomy is probably about 1% of all hypertensives.

DR. MOSER: Do adenomas ever become malignant?

DR. VICTOR: Not to my knowledge.

DR. MOSER: So, that is not the incentive to look for them.

DR. VICTOR: These are microadenomas and the malignant potential to my knowledge is as close to zero as possible.

DR. MOSER: Okay, so first anyone with a low K. Different centers have different criteria. Second, anyone with resistant hypertension where you can't control the BP. These are indications to look for an adrenal lesion. What's the simplest test you can do to detect it?

DR. VICTOR: I get renin and aldosterone levels. This can be done while people are on their medications. If they come in, for example, on an ACE inhibitor and they have a suppressed renin, that's helpful because the renin should be very high on an ACE inhibitor or ARB. You should realize that if the K is low, you can get a falsely low aldosterone level because K is a secretagogue for aldosterone.

DR. MOSER: So, it's just one aldosterone and one renin determination.

DR. VICTOR: Yes, if the renin is low and the aldosterone is high, then I proceed to other studies.

DR. MOSER: What are your criteria for aldosterone and the aldosterone-to-renin ratio levels for the diagnosis of primary aldosteronism?

DR. VICTOR: It depends on the renin laboratory. If the renin comes back below 1, a ratio of 20 to 40 of aldosterone/renin is highly suspicious if the aldosterone level is above 15 and the renin is below 1, I'm suspicious enough to go forward.

DR. MOSER: So an aldosterone/renin ratio of approximately 15–20 is enough suspicion to look further. Joel, what's your cut point?

DR. HANDLER: I work-up all the resistant hypertensives with an aldosterone/renin ratio no

matter what their K is because approximately 40% of hyperaldosterone patients will have normal K levels. It's helpful to know that, with the exception of spironolactone, you don't have to withdraw routine antihypertensive medications when the ratio is performed so long as the K is near normal. When the aldosterone/renin ratio is 20 to 1 with an aldosterone level higher than 15, follow-up is a 24-hour urine test after salt loading. We're looking for a 24-hour urine sodium excretion of more than 200 mEq and an aldosterone level greater than 12 mg. Normally, sodium loading will suppress aldosterone secretion; in primary aldosteronism it is not suppressed. A diagnosis of probable hyperaldosterone on the basis of biochemical testing can be used to tailor medical therapy. Such patients can be started on spironolactone.

DR. MOSER: How about eplerenone?

DR. HANDLER: I don't have much experience with eplerenone because fortunately, in the patients I've put on spironolactone thus far, it's been well tolerated. Calcium channel blockers can also be maximized because there is evidence that calcium is involved in the final common pathway of aldosterone production via several mechanisms.

DR. MOSER: And if the pressure comes down, and the patients feel fine, you don't bother with anything else.

DR. HANDLER: No, I don't image them.

DR. MOSER: Ron, do you agree?

DR. VICTOR: No I don't.

DR. MOSER: So, if you get a ratio of 25 to 1 aldosterone/renin, what do you do?

DR. VICTOR: What I do is stop all the anti-renin-system blocking drugs and wait for about 4 weeks. I try to control them with calcium channel blockers and my least favorite sympatholytics like clonidine and labetalol. I realize that  $\beta$  blockers can affect renin, but I don't care about that so much. And then what I do is I replete the K to make certain that the low K hasn't underestimated the aldosterone levels. We then get a 24-hour urine and put the patient on a whole tablespoon of salt per day (8 g), to try to make sure we have volume expansion and get the urinary sodium above 250 mEq for 24 hours. This is done in an effort to suppress aldosterone production. As noted, in people with normal adrenals, the level will go down with salt loading; in people with primary aldosteronism it will not be suppressed. Then I stop the K and do another 3 days of salt loading—which patients hate—and see if they get inappropriate kaluresis. If aldosterone secretion is decreased by volume expansion, K secretion ordinarily is decreased. In primary aldosteronism, it is not suppressed.

DR. MOSER: Is all of this necessary?

DR. VICTOR: Yes. I'll tell you why. First of all, if you don't have patients salt loaded, you really can't judge whether or not aldosterone secretion was suppressed.

DR. MOSER: But isn't an aldosterone/renin ratio enough to say they have either hyperplasia or adenoma?

DR. VICTOR: No. You really have to do the salt loading if you don't want to have a lot of false positives, if you are really talking about primary aldosteronism.

DR. MOSER: Again, does the same question arise here as with renovascular disease? Does it make a difference if you prove the presence of primary aldosteronism or does empiric treatment work?

DR. VICTOR: There's a difference. The difference is that there is no really good treatment for the small percentage who have a unilateral adenoma instead of bilateral hyperplasia.

DR. MOSER: Wouldn't you find that out just by doing a CT scan even though these lesions are often very small?

DR. VICTOR: Absolutely not. These are microadenomas. It used to be said that if you had an absolutely normal one-sided adrenal and the other one had a clear-cut 1.5 cm or greater adenoma that had a lot of fat in it, you could go ahead and take it out and you'd be right. There are data that you can still make a mistake or that it's really bilateral hyperplasia, even with these small lesions. I don't believe the CT scan at all; I would never send somebody to surgery without adrenal vein sampling for aldosterone levels. You have to be at an institution where they do adrenal vein sampling routinely. If you're at an institution that doesn't do that and you can't send your patient somewhere, then my whole approach would be different.

DR. MOSER: What would you do if you didn't have this capability?

DR. VICTOR: I would send them somewhere that did have it.

DR. MOSER: Okay. What if a patient couldn't go?

DR. VICTOR: That's a problem, but I would not use high-dose spironolactone. Clearly, there is a dose-dependent incidence of irreversible gynecomastia. Eplerenone has changed that, but it's very expensive right now. It seems to be less potent than spironolactone, but much more specific. Patients I have with bilateral adrenal hyperplasia who have had very severe hypertension are on as much as 100 mg per day of eplerenone in divided doses, but they're on three or four other drugs.

DR. MOSER: And they are controlled.

DR. VICTOR: Fairly well, but not great. And their quality of life is an issue because they're on high doses of drugs.

DR. HANDLER: Can I just ask one question? What is your failure rate for right adrenal vein catheterization?

DR. VICTOR: That's an important issue. It's hard to get into because it's at right angles. I can't remember any case where we couldn't get an interpretable adrenal vein sampling, but it is very difficult to do.

DR. MOSER: So, the work-up and confirmation of a functioning adenoma is not always easy but, Ron, you find it necessary in hard-to-control patients, although most cases end up with medical treatment. If you find an adenoma, it should be removed.

DR. VICTOR: Yes, because someone would have to take three or four medications for the rest

of their life and hypokalemia may continue to be an issue. The K is always cured if you make the right diagnosis. The BP is improved but, as you know, even after removal of an adenoma, patients usually have to be on some medications.

DR. MOSER: So to summarize, secondary hypertension may account for cases of resistant hypertension. A clearly treatable form is a pheochromocytoma, and properly selected cases of primary aldosteronism with discrete adenomas and patients with fibromuscular dysplasia of the renal arteries are candidates for surgical intervention with good results. Finally, many cases of RV disease, especially in older patients and patients with aldosteronism secondary to bilateral hyperplasia, may do just as well on medical therapy; some investigators may not agree completely with these approaches to therapy, but I believe that they are reasonable. Thank you.