



expert roundtable » The JNC 8—What Might Be Expected?

Moderated by **Marvin Moser, MD¹**

Discussants: **Jan Basile, MD²**; **Norman Kaplan, MD³**; and **Ronald Victor, MD⁴**

DR. MOSER: In 2003 the Joint National Committee (JNC) on the Prevention, Detection, Evaluation and Treatment of Hypertension published the seventh edition of their recommendations and guidelines. The next report is probably going to be released sometime in 2011.

I'm Dr. Marvin Moser, Clinical Professor at Yale. Our panel will be discussing some of the possible recommendations in JNC 8 that may influence clinical practice. As a disclaimer, I chaired the first JNC and was involved in all of the 6 others, but I am not, however, on the JNC 8 committee, and have not been informed of the possible content of this report.

With me today is Dr. Norman Kaplan, Clinical Professor of Medicine at the Southwestern Medical School in Dallas. Norm has had a long experience in hypertension and was involved in JNC 3 to JNC 6.

In addition, Dr. Ronald Victor, who is Associate Director of the Cedars-Sinai Heart Institute and Director of the Hypertension Center there, is joining us. Ron has had no involvement in any of the JNCs to date and is also not on the JNC 8 committee.

Finally, Jan Basile, who is a Professor of Medicine at the Medical University of South Carolina in Charleston. Jan was involved in JNC 7, and also has not had any involvement in JNC 8.

What we're going to do today is discuss some of the possible recommendations or changes that might appear in JNC 8, recognizing that our opinions are based

The following Expert Roundtable Discussion was held on October 27, 2010. Dr. Marvin Moser from the Yale School of Medicine moderated the topic "The JNC 8 – What Might Be Expected?" with Drs. Jan Basile from the Medical University of South Carolina, Norman Kaplan from UT Southwestern Medical School at Dallas, and Ronald Victor from Cedars-Sinai Medical Center, Los Angeles participating.

The discussion focused primarily on: (1) Joint National Committee (JNC) reports prior to the forthcoming JNC 8, (2) progress in controlling hypertension, including special populations (3) blood pressure goals, (4) diagnostic evaluation of the hypertensive patient, (5) lifestyle changes that impact blood pressure, (6) initial therapy, including the use of beta-blockers and direct renin inhibitors, including elderly and obese populations, (7) combination therapy, (8) safety of ARBs and cancer, and (9) predictions on the recommendations that might be included in the forthcoming JNC 8 report. (*Med Roundtable Cardiovasc Ed.* 2010;1(4):267–275) ©2010 FoxP2 Media, LLC

TRIALS DISCUSSED:

ACCOMPLISH, ASCOT, DASH, HYVET, LIFE, MRC, NHANES, PREMIER, SHEP, STICH

COMPOUNDS DISCUSSED:

atenolol, carvedilol, chlorthalidone, eplerenone, hydrochlorothiazide, indapamide, reserpine, spironolactone, telmisartan

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Published online: www.themedicalroundtable.com • Search for ID: CV2166

on our knowledge and experience in hypertension and not as a result of discussions with the JNC 8 committee.

Norm, let's start with you. Let's try to follow the outlines of previous JNCs and first discuss the scope of the hypertension problem. How many people do we now think have hypertension in the US? Have the numbers changed? Have the percentages of people who are aware that they have hypertension, or who are under treatment, and under control changed? Are we making progress or have we stood still since 2003?

DR. KAPLAN: Well, we've definitely made progress, but we're still not quite close to the overall goal of getting a large majority of patients under good control. I think that you and other people who have been involved with the Joint National Committee reports since the very first one, have been gratified by the increase in the number of people being recognized, treated and controlled since 1977.

The latest figures that I've seen from the National Health and Nutrition Examination Surveys (NHANES) are that

about 50% of all hypertensives are now being controlled at goal levels of 140/90 mm Hg or below. This is certainly a very significant difference from the 10% or 12% that were being adequately treated back in the '70s, so, yes, we are doing better. More people are being identified. More people are being treated and more people are being controlled, but we still have large numbers of people who need to be treated more vigorously.

DR. MOSER: Encouraging numbers. The Harris Survey that was done for the Hypertension Education Foundation two years ago came up with some very encouraging numbers. More than 90% of hypertensive individuals knew they had hypertension, which, again, is a far cry from what we noted in JNC 1 in 1977. More than 80% were under specific treatment and 55% or 60% stated they were at goal levels at some point.

Is there a group of people who are not being controlled? We still talk about 40% or 50% of people who are uncontrolled. Are they resistant? Are they difficult to treat? Are they young? Are they old? Are they in different ethnic groups? What are they?

DR. BASILE: Marv, as Norm points out, about 50% of all patients with hypertension are now controlled. If we look at the NHANES report more closely, about 80% of Americans 20 years of age and older with hypertension are aware of their having hypertension and 73% of patients with hypertension are receiving treatment. But of those actually treated for hypertension, the proportion of patients with hypertension over the past 20 years who achieved a BP <140/90 mm Hg has increased from 51% to almost 70%. Thus, only about 30% of those being treated from the most recent NHANES 2007-2008 report still have BPs at or above 140/90 mm Hg.

DR. MOSER: So you believe that we are really controlling about 70% of those who are being treated?

DR. BASILE: Yes, according to this NHANES report.

DR. KAPLAN: But we're still not adequately treating an awful lot of people. Is that still correct?

DR. BASILE: That is true, Norm. About 1 in 4 with hypertension are still not being treated, and of those with hypertension, about 30% are not being adequately controlled. So there certainly is room for improvement.

DR. MOSER: Of interest, in the Harris poll, the number of people who were unaware that they were hypertensive, were very low, and the number treated was more than 80%. I think that is consistent with the behavioral risk factor study in about 28,000 people.

DR. VICTOR: At the recent High Blood Pressure Research Council meeting the new NHANES data were reported. It was almost unbelievable how much hypertension control had increased—from 35% to 50% in the past decade. The other point to make is that NHANES' numbers, which represent only one set of blood pressure measurements, likely underestimate control rates.

There's still work to be done. In answer to your question, the Mexican-American population seems to have the worst control rates.

DR. MOSER: In the elderly the control rate isn't good either. Isn't that true? The majority of uncontrolled patients are elderly, aren't they, or am I wrong?

DR. KAPLAN: I think they are, but then JNC 8 will probably address the question of how controlled blood pressure should be defined in people over age 65. As one of these, who has systolic hypertension, I'm not so sure that 140 is the correct end-point that we should be considering as "controlled."

In the HYVET trial, which is by far the best trial in the very elderly, with the average patient age of 84, baseline BPs

were 173/90, and all patients had to have a systolic above 160. The average achieved systolic pressure was not below 140 but rather 154, and yet remarkable reductions in strokes, mortality, heart failure, and all CV events were reported. I know we're going to talk about the trials later, but I think that there is an issue that should be addressed: What should we call an adequately controlled blood pressure in the elderly?

DR. MOSER: Since the JNC 8 will be evidence-based, Jan, do you want to comment on that? Norm makes a good point; national statistics on control are based on 140/90, but perhaps in a large segment of the population this level may not have to be achieved to obtain significant benefit. Should we change the 140/90 goal in some populations or should we keep it? Intuitively we still believe that as close to 120/80 mm Hg as possible may be a desired goal, but what does the evidence show?

DR. BASILE: As far as the clinical trial evidence is concerned, although we recommend <140/<90 mm Hg in all patients, including the elderly and the oldest of the old, the evidence does not confirm that we've really ever achieved this recommendation of <140 mm Hg in a well designed clinical trial involving the elderly.

DR. MOSER: As an average you mean?

DR. BASILE: Yes, as a mean pressure, in the elderly, including the oldest of the old. If you look at the Systolic Hypertension in the Elderly Program (SHEP), that compared initial thiazide-diuretic antihypertensive drug therapy with placebo, we achieved a final mean systolic blood pressure (BP) of about 143 mm Hg in the actively treated arm. In the Hypertension in the Very Elderly Trial (HYVET), that also compared the initial use of the thiazide-like drug, indapamide, with placebo, we also achieved a mean systolic BP around 144 mm Hg in the actively treated group, with only 49%

achieving a systolic BP <150 mm Hg. Yet the benefits of active antihypertensive drug therapy was overwhelming.

The point is that strokes and cardiovascular events were prevented in these elderly trials that have often been placebo controlled without achieving a systolic BP goal of less than 140 mm Hg in most people. Remember though that most of these patients had initial systolic BPs of 160 mm Hg or greater. I think what we're doing here is reducing risk by reducing BP significantly from the baseline in these elderly and very elderly patients with hypertension. I think that's an important concept. The delta change in millimeters of mercury from baseline that we can achieve in a given patient and their individual risk with stage 2 hypertension when they first are being treated are important concepts that define benefit in a given patient. Based on their individual cardiovascular risk, outcome has been improved by lowering systolic BP close to 30 mm Hg in many of them and yet, we haven't achieved the systolic BP goal of <140 mm Hg recommended in JNC 7 for all patients. I expect JNC 8 will review the evidence before finalizing their recommendations for goal BPs in the elderly hypertensive, and may conclude that, despite lack of good clinical trial evidence, the goal should still remain at <140 mm Hg. Perhaps they will go with <150 mm Hg while trying to get as close to <140 mm Hg as possible.

The clinical point I would make is that, despite lack of good evidence, I would still try to achieve less than 140 mm Hg as the systolic BP goal. However, if you can't achieve it because of side effects or intolerance to medication or autonomic insufficiency, you are probably still achieving benefit by reducing the BP about 20 mm Hg from a baseline of >160 mm Hg and close to 30 mm Hg when the baseline BP is >170 mm Hg.

DR. MOSER: There is good evidence from SHEP and other studies that a

reduction of about -12/-4 or -5 mm Hg more than placebo is enough to reduce events. Ron, based on present evidence, if you were writing this section in JNC 8, what would you say now about goals and population control?

DR. VICTOR: For super seniors, 150/80 based on HYVET. For most of the population, office blood pressures of 140/90 and for diabetics, I guess that 130/80 mm Hg is a reasonable compromise. For the high-risk patients with heart disease, the ACCHA guidelines recommend less than 130/80, with incomplete evidence. The other problem to address is that we're basing all of these recommendations on office or clinic blood pressures. Out-of-office blood pressures are probably better predictors.

DR. MOSER: JNC 8 will probably review this but at present the data we have are for clinic BPs.

So, to summarize this section, we can honestly say, based on evidence, that we've achieved at least a 50% control rate and that most hypertensives, probably 70%, 80% or maybe even 90% are aware that they have hypertension, are aware that it's a major risk factor and are doing something about it. Is that fair for this section?

DR. BASILE: Yes, I think this is a fair summary.

DR. MOSER: JNC 8 is going to be based very carefully on evidence, so let's back up a little. Norm, can you agree that what we have just concluded is based on evidence? I think intuitively we all agree, but that's a different story.

DR. KAPLAN: As you suggest, the evidence simply does not exist for the large portion of the elderly whose blood pressures are between 140 and 160. We really don't have evidence. The only evidence we have are some scattered data from the elderly over age 65. There was a decrease in both events and mortality by active treatment, but

the number of the patients, however, was only about 1,000.

In the HYVET trial in the very elderly, the investigators did not try to get BPs below 150. So I would use 150 as the recommended goal based on the evidence, which admittedly is not adequate, particularly for the population with BPs of 140–160.

DR. MOSER: So you would agree with Ron that, in terms of defining the problem nationally, we might want to redefine the level at which we say people are controlled or not controlled, especially in the elderly?

DR. KAPLAN: Yes.

DR. MOSER: Jan, let's switch to something else; the diagnostic evaluation. Since 1977 the initial workup for hypertensives hasn't changed much. It includes a urine and a blood count, a lipid profile and blood glucose. An EKG is also included in the recommendations, although some people argue that that doesn't add much. That's about it. Now, is there any evidence that adding an echo, an APBM, other biomarkers, or pulse wave tracings will improve our diagnostic abilities, improve our risk estimates, and change our method of treatment?

DR. BASILE: Well, it's an excellent question and I think one of the key points that JNC 8 must address that was lacking in JNC 7 and was included in JNC 6 is, how to better predict CV risk in patients with hypertension. This allows us to better stratify patients with hypertension, who may have differing CV risk that is not always appreciated by just knowing the BP. For example, you can have a BP of 145/90 mm Hg with no other risk factors for CV disease, and be low-risk, but be at high-risk with a BP of 132/88 mm Hg if you are an 80-year-old person with one additional risk factor. Just being aware of the elevation in BP does not always stratify risk appropriately.

DR. MOSER: I agree. Let me follow up on this. A blood glucose will predict

diabetes. A BUN, creatinine and urine will provide information about renal disease. There are ethnic differences in blood pressure risk. A cardiogram provides evidence of previous ischemic disease and arrhythmias. It may not define LVH in many cases, but shouldn't determine whether or not blood pressure should be lowered. We're going to do that whether or not LVH is present. Being the devil's advocate, we have defined risk by doing these simple studies. Do other diagnostic procedures change our approach to management or add to predicting risk—and is this important?

DR. BASILE: Well, although other tests do add to predicting risk, we don't necessarily have outcome trials that suggest that any of the particular markers that some physicians advocate will better allow us to treat the patient. For example, microalbuminuria is a very important predictor of risk, but there is no evidence that reducing microalbumin in a clinical trial as a primary target improves outcome in patients with hypertension. In fact, the FDA will not even look at it as an effective end-point to approve a drug for hypertension.

Echocardiography is an expensive tool that may allow us to better stratify risk, but I think we're still going to be using the EKG. This may not be as sensitive, but it is still very specific when LVH is noted in a given patient. The LIFE trial did use EKG evidence of LVH. They had very strict criteria. They did show better outcomes with initial therapy with an ARB than a beta-blocker, but that's only one trial. I don't think that LVH, *per se*, gives us a particular therapeutic class that would be recommended as initial therapy, so I wouldn't be in favor of using the echo as a routine screening test. Lowering blood pressure over time seems to be the single most important factor in reversing LVH.

Marv, I don't think JNC 8 will be including other initial markers of risk that will better allow us to understand

when to begin treatment. I wait to see what risk score JNC 8 uses, but once again I know of no validated risk appraisal that they will be able to endorse, that will be evidence-based. While I would like them to give us a better risk score than clinicians currently use, I am not sure there is one they can endorse other than the Framingham risk score, with its inherent concerns.

DR. MOSER: To summarize what Jan just said: Some of these other procedures, like echocardiography or pulse wave tracings may help to more carefully define risk, but thus far there is little evidence that the results of these treatments will have a major effect on

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treatment. We are going to treat people based on the blood pressure whether or not they have LVH or abnormal pulse wave tracings. These tests are of interest and some investigators may believe that to omit them is anti-academic, but in the long run it does not appear that the results of these studies affect therapy in a large majority of cases

Ron, do you want to talk about home blood pressures, which may help in determining outcome? Is there evidence that these are important?

DR. VICTOR: There is no way to get an accurate picture of a patient's usual blood pressure just from office measurements. Doing home monitoring twice a day for a week, tossing out the first day's

readings and averaging all of the rest is the current recommendation.

DR. MOSER: Is there evidence to show that this is going to improve your outcome? JNC 8 is going to be based on evidence. We all believe that home blood pressures are helpful and give you a picture of what's going on over time.

DR. VICTOR: It's clear that they're more predictive of events and they add information to the office blood pressure.

DR. MOSER: So JNC 8 might say that home BPs will be helpful in determining what the pressure is over time, but presently there is no trial evidence that knowing home blood pressures will decrease events. But if knowing these numbers and finding them helpful in lowering BPs then there probably is a benefit. Norm?

DR. KAPLAN: I think that home blood pressures should be recommended, and I think JNC 8 will say that. It is clear that home blood pressure monitoring improves the degree of blood pressure control. We don't know whether it then translates into fewer events, which is really what the evidence would have to say, but I think that the committee will say that we know that it will help reduce people's blood pressure if they do home monitoring and therefore we do recommend it for virtually everyone to get out-of-office readings.

DR. MOSER: Instinct tells us without definitive evidence that the lower the pressure the better the outcome. Now, what about ambulatory monitoring? Is the JNC 8 going to recommend that as a routine, as many of our colleagues would suggest?

DR. KAPLAN: Absolutely not. I mean it's a wonderful research tool and could be used in a certain group of people, particularly people who appear to be resistant in the office, but it's never going to be used for the majority of people. There are people who believe that

it should be. Dr. O'Brien from Ireland is one of those advocates. He points out that if you could do an ambulatory monitor on everyone you would improve your accuracy in diagnosing hypertension and then if you did another one after they were on treatment you would also improve your accuracy as to whether they're well controlled. One problem is that nobody in the US is willing to pay for 60 million people having two or more ambulatory monitors, so I think it's a moot question. We believe that it's useful and it could be used in a selective way, but not as an overall technique for the majority of patients.

DR. MOSER: Is it better than just using home monitoring the way Ron described, where you get a picture of BPs over a week or two instead of one 24-hour snapshot?

DR. KAPLAN: No. I don't believe that. In fact, there are papers that show very close similarity between the daytime ambulatory monitoring and the patient's home pressures. There is, of course, the issue of the nighttime BPs, which at present cannot be obtained by any kind of home device. That clearly is an important part of the overall risk of a patient, as is the early morning surge of blood pressure, which is also critical and often times will not be obtained by home monitoring alone.

DR. MOSER: Do both of you agree with the fact that ambulatory monitoring is not yet ready for primetime and that home pressures probably will be recommended as the preferred method of getting out-of-office pressures? This despite the limitations of not obtaining nighttime pressures.

DR. VICTOR: Yes.

DR. BASILE: I agree that home monitoring should be recommended, both to improve adherence with medication and blood pressure control rates, but we need to have insurance and third party agencies allow us to prescribe

home monitoring devices that can be paid for without the patient being responsible for out-of-pocket expenses in the same way that diabetics can get glucose monitors through their health insurance plans.

DR. MOSER: Do you believe that JNC 8 is going to address that?

DR. BASILE: I would hope so.

DR. MOSER: Okay. What about pulse wave tracings and measuring augmentation indexes, etc? Do we need central blood pressures, for example, to treat the majority of patients? Is there any evidence to support the use of these procedures?

DR. KAPLAN: Well, again, a pulse pressure is a pretty good indicator of

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- Ron Victor, MD

the central pressure. If it's very high we know that there is going to be a very high central systolic pressure. I don't think at the moment obtaining central pressures adds anything to clinical management. Again, it's a nice research tool, but it doesn't go beyond that; we also have to recognize that there are all kinds of procedures that some have recommended that we could add to the list, all of which are interesting but may not be necessary to improve outcomes.

C-reactive protein (CRP) is a very obvious one. I don't think CRP has added anything to improving outcomes, and I don't think we ought to be adding it or most any of the other studies that have been recommended as additional, routine procedures. Obviously, there will be some instances where all or any of these additional

procedures might turn out to be useful, but right now I think the Framingham risk score can tell us 99% of what we need to know about risk.

DR. MOSER: I happen to agree with Norm, but, Ron, what's your comment?

DR. VICTOR: Marv, I agree. Many of our colleagues in cardiology would say that EBCT calcium score and CRP help to risk stratify in the intermediate risk group. I don't agree with that; I agree with Norm; these procedures don't add enough information to justify their routine use.

DR. MOSER: The CT studies add a lot of radiation, that's for sure.

DR. VICTOR: And a lot of cost. But to get back to the Framingham risk score, by the time a man is over 55 or a woman over 65, as Norm said, the risk is already so steeply age dependent that it's hard to add additional tests to improve on it.

DR. MOSER: So you're going to lower the blood pressure in a 65-year-old man or woman with elevated blood pressure even without many of the newer risk defining tests because they're at high risk?

DR. VICTOR: I would certainly treat them. Yes.

DR. MOSER: Let's review lifestyle changes that impact blood pressure. Have any newer trials been carried out to determine benefits of non-pharmacologic intervention in the past 5-6 years to warrant changes in the JNC recommendations?

DR. VICTOR: My short answer would be no. It's great to attempt to change habits to prevent diabetes, but in the real world the effect on blood pressure is very small. The DASH trial, which was a feeding trial, does demonstrate the full benefits of a fruit-and-vegetable diet with low-fat dairy products, but in the PREMIER trial, where people had to buy their own food, the effect was much less.

DR. MOSER: Would all of us agree that lifestyle changes are again going to be emphasized, as they should be? Reduction of sodium intake, weight loss, exercise and moderation of alcohol intake should be part of any program, but new evidence is apparently not available that will require a major change in previous JNC recommendations.

DR. BASILE: Yes. I would say that. I would agree. There is tremendous evidence regarding the importance of lifestyle changes in hypertension, but unfortunately, it has been shown in mostly short-term studies with forced-feeding programs. The major problem for both economic or social reasons is that patients find it difficult to achieve the same lifestyle changes that were noted in the clinical trials that showed benefit. I would point out the importance of a dietician as part of a treatment team if at all possible.

DR. VICTOR: Let me add something: The Institute of Medicine has advocated a 10% reduction in the sodium content of food over the next ten years to reduce population level pressures. I'd be very surprised if the JNC 8 doesn't come out to endorse that as a societal change. There is some evidence for this. In Finland this has had a huge impact.

DR. MOSER: And in Belgium. All right, let's get on to the next part of the guidelines: Initial therapy. Is there evidence that suggests that the recommendations will be the same as in JNC 7 or different?

DR. KAPLAN: That's the major point. There will be an eight-year hiatus between the 7th and 8th reports. In the interim, beta-blockers have gotten reclassified; the British have already said in their guidelines that they will not support the use of any traditional beta-blocker for primary protection, only for certain secondary situations. Clearly, they are still indicated for those.

DR. BASILE: Yes, I would agree with Norm. I think that JNC 8 should go a

step further and tell clinicians that there is more recent evidence since JNC 7 that the use of atenolol, especially when used once a day as initial therapy in many clinical trials, is not only an ineffective comparator, but its use also results in poorer outcomes compared to other anti-hypertensive agents. So I think not only will JNC 8 distance themselves from the traditional beta-blockers as initial therapy, but I hope that they will come out stronger about a caution on the use of atenolol.

DR. MOSER: Can I play the devil's advocate again? Much, but not all, of the data that the British conclusions are based on were from the MRC trial, which was a very poorly controlled clinical trial. It wasn't blinded, and the

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dropout rate was about 40% in the beta-blocker group. I'm not saying that beta-blockers should remain an initial choice, but they do have a place in therapy for several subgroups of patients. Does anybody want to comment?

DR. KAPLAN: Well, there were more than just the MRC trial that were looked at to decide the beta-blocker issue. Most of the trials, of course, have not been just with a beta-blocker. In fact, there are relatively few trials where one drug has been the only drug used. Almost all of the trials wound up as multi-drug trials. But I'm convinced that what the meta-analysis said was that with beta blockers (mainly atenolol), heart attacks were not reduced more than with other drugs, and their use provided less protection against

stroke. This presumably relates to their hemodynamic mechanism of action.

DR. MOSER: So that's fair. So should we relegate their use to patients with ischemic heart disease and heart failure to be used as one of several drugs?

DR. BASILE: Post MI and heart failure with reduced ejection fraction stand out.

DR. MOSER: Okay, what about the other initial therapy recommendations that the JNC 8 might suggest compared to JNC 7?

DR. VICTOR: Well, I would say that carvedilol, a beta blocker with vasodilating properties, is now generic and has a better metabolic profile than the older beta blockers. This might be considered as an optional initial therapy. I know of no outcomes data for treating hypertension with carvedilol, but it is excellent add-on therapy for resistant hypertension.

DR. MOSER: So the beta-blockers with vasodilating properties, whether it's due to nitric oxide enhancement or alpha-adrenergic blockade, may be one of the beta-blockers to be used, if you're going to use a beta-blocker. Is that fair?

DR. VICTOR: Yes.

DR. KAPLAN: Yes.

DR. BASILE: Yes. I think both carvedilol and nebivolol, the vasodilating beta-blockers should not be lumped as a "one size fits all" within that class. There are mechanistic differences without outcome studies in hypertension with these drugs.

DR. MOSER: What is the initial therapy recommendation going to look like? What does the evidence tell us? Should we continue to list diuretics as the preferred drug, or should they just be one of the preferred drugs? Will JNC 8 suggest that you could start with a diuretic, an ACE or ARB, or a calcium-channel blocker, depending on age or ethnic backgrounds? What do you think the committee will recommend?

DR. BASILE: Another question: Should the direct renin inhibitor class also get a JNC 8 recommendation for initial therapy? Although they do lower blood pressure, there are no outcome studies in patients with hypertension; I'm wondering if they're going to place the direct renin inhibitor class in a similar position as the traditional beta-blockers. Not for initial therapy, but for use in special situations.

DR. KAPLAN: That's a good point, because they're being very heavily promoted. The one that is now available—there will presumably be more—has not been put to the test of outcome data. Therefore, I see no reason to use the direct renin inhibitor in place of either ACE inhibitors or ARBs, where we've got a lot of strong outcome data.

DR. MOSER: If you were to structure the algorithm for the treatment of hypertension what would you list in terms of initial therapy, monotherapy, two-drug therapy? Would you start with an ACE, an ARB, a calcium-channel blocker, or diuretic? Would you start differently in an older person? Would you start differently in a diabetic? Each of you tell us, based on the evidence, what you think JNC 8 is going to recommend? Then we'll talk about side effects.

DR. BASILE: I think the evidence would support that the strongest recommendation for initial therapy be either a thiazide diuretic, a dihydropyridine calcium channel blocker or an ACE inhibitor or ARB for initial therapy.

DR. MOSER: In all patients?

DR. BASILE: Yes, in all with hypertension and no compelling indication. I think that we could argue over which drug class is best within those three for initial therapy, but ALLHAT withstanding, we don't have good evidence to support specific positions about those specific drug classes. I think globally, when we look at these three classes of drugs, similar outcomes are achieved

and with all of them now being generic at a similar price I would not favor one over the other as initial therapy.

DR. MOSER: Norm, would you agree with that?

DR. KAPLAN: Yes. What I would put in the JNC 8 would be to use a low dose of chlorthalidone, which is a different type of drug than hydrochlorothiazide, and often to combine it with a low dose of an aldosterone receptor blocker, either spironolactone or eplerenone. To me, that's a very appropriate starting therapy for the majority of people. I don't think the JNC 8 should say that therapy should never start with a calcium channel blocker or renin-inhibiting drug, but for most

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hypertensives the recommendation should be to start with a low-dose diuretic, hopefully with an aldosterone blocker for the majority of patients.

DR. MOSER: Now, is there a difference in the response of the elderly, for example, to a drug that effects the renin angiotensin system, like an ACE or an ARB and a diuretic or a CCB? Do we have enough data to suggest there should be a differentiation of therapy in the elderly?

DR. KAPLAN: There are some small studies that have shown that the renin inhibiting drugs such as an ACE inhibitor or an ARB, are more effective in Caucasians and young people. They're less effective in elderly and black patients, but if they are used

with a low-dose diuretic then all of that difference disappears.

DR. MOSER: Do you agree with that, Jan?

DR. BASILE: I do agree with that, but it is only one piece of a large puzzle and I would also point out that most patients in clinical trials required two or more medications to get their blood pressure effectively controlled. So the first drug is often not the final drug that patients need to be on to get their blood pressure effectively controlled.

So, getting back to Norm's comment on chlorthalidone and aldosterone blockade, I hope that JNC 8 will differentiate within the thiazide diuretic class and point out the lack of evidence with hydrochlorothiazide at 12.5 mg to 25 mg a day and the strong clinical trial evidence, for chlorthalidone at the same dose of 12.5 mg to 25 mg once a day. Although we know that reactive hyperaldosteronism occurs in a good number of patients, especially in patients with resistant hypertension, I don't think JNC 8 will recommend an aldosterone (mineralocorticoid receptor) blocker as a second agent, only because there isn't good clinical trial evidence for that strategy. Norm may be right, but there isn't the clinical trial evidence for them to support that.

DR. MOSER: The clinical trial evidence includes two-drug therapy with ACE and a calcium channel blocker, or ACE-diuretics, and newer data on the use of ARBs and diuretics. Norm's point though is well taken. In the obese resistant hypertensive there is some evidence that visceral obesity increases aldosterone secretion and that may be why in some of these resistant hypertensives blood pressures come down when you add spironolactone or eplerenone. Norm, the obesity data are very interesting.

DR. KAPLAN: Yes they are. By the way, I checked with the local pharmacy. Eplerenone, which is now generic and is the preferable aldosterone blocker, still

costs \$114 for a 30-pill prescription. So even though it's generic it has not yet come down to the level that it should be, which would be a \$4 a month drug, like a lot of other generics. By the way, there are some old data with spironolactone that do show good outcomes. If we use it appropriately at a low dose it's a good addition to a low dose of diuretic, but I agree that JNC 8 will probably not make that recommendation.

DR. MOSER: What's your maximum dose of spironolactone? We used to use 400 mg/day all of the time.

DR. KAPLAN: That's like three grams of Aldomet. No, we use dosages of 25–50 mg a day at most, with a diuretic.

DR. BASILE: Should JNC 8 recommend a thiazide diuretic, and perhaps specifically chlorthalidone, as the initial therapy in most patients as they did in JNC 7?

DR. MOSER: What do you think they're going to do?

DR. BASILE: I do not think they're going to go in that direction.

DR. MOSER: I don't either. I think they'll do what you have suggested; either a diuretic or an ACE, an ARB or a CCB; and in most cases, eventually you'll get to two drugs, which include a diuretic. The question is, do you start people on two drugs? What are they going to say about that? In JNC 7 it was recommended in many of the elderly and in people with diabetes and renal disease: Start right out on two drugs, rather than wait the three or four months and add something. That's where you're going to end up anyway. Any validity to that argument?

DR. KAPLAN: Well, I agree with Jan, who said that most people are going to end up on two drugs. However, if it's a relatively uncomplicated, relatively early stage one hypertensive (BPs between 140/90 mm Hg and 160/100 mm Hg), I still like the idea of starting

with one drug. The idea is that some people really do respond remarkably well to one drug and therefore, they likely will not need a second drug.

DR. MOSER: I agree with you. Jan?

DR. BASILE: Yes, I would agree with you on that too. I think JNC 8, being an evidence-based document, will not be able to support the 20/10 rule that JNC 7 endorsed or the 15/10 rule that the International Society of Hypertension in Blacks continues to endorse for initial two-drug, combination therapy in patients with hypertension.

DR. MOSER: What they're referring to is stage two hypertension, like 160/100.

DR. BASILE: Correct. Stage two hypertension or 150/90 mm Hg in a diabetic as recommended in JNC 7. There are some data regarding the benefits of early use of a two-drug regimen. In the STICH trial published in *Hypertension* in 2009, patients with higher stage one hypertension (mean 154/88 mm Hg) over a six-month period were more likely to reach their BP goal of <140/<90 by starting with either an ACE/diuretic or an ARB/diuretic compared to the group that began with a step-care approach with single agent therapy. Not only were the two drugs given initially more likely to get BP controlled by 6 months, but the patients also felt better with no more side effects occurring when starting with the two drugs.

So getting to Norm's point, perhaps if the patient is 10 mm Hg or less to goal when they are first treated, one drug can be suggested and if they're 10–20 mm Hg from goal you can start with one or two drugs (based on the STICH trial), and if they're more significantly elevated it can be recommended that two drugs be used as initial therapy (a realistic approach). There is no evidence, however, that by utilizing this strategy you will improve hard clinical outcomes.

DR. KAPLAN: Let me just make a small point. Both the ASCOT trial and the HYVET trial did look at outcomes. In these trials, about 60% of the patients ended up on two drugs because they could not be adequately controlled with the first medication. So if you open the gate a little bit you do have some outcome data with combination therapy. Again, the trials didn't start with two agents, but they ended up with them. But I would agree. We'll likely see the JNC 8 recommend that you should start with one drug, but be relatively quick to add a second drug if control is not accomplished.

DR. VICTOR: We are all aware that ARBs cause very few side-effects; what do you think about the recent data on ARBs and cancer?

DR. KAPLAN: Although these data are of concern, a more thorough examination of all data with telmisartan, the ARB used in over 80% of the trials with an ARB, found no increase in the incidence of cancer. Remember that reserpine, diuretics and CCBs were all said to cause cancer, but no such evidence was ever well documented.

DR. BASILE: I do not think there is much scientific evidence to cause any concern for the clinical use of ARBs and I don't believe JNC 8 will have much to say on this since it will be an evidence-based document. The concern was raised from a recent meta-analysis suggesting a relationship between ARBs and cancer. But the limitations of this type of analysis are well known. As opposed to prospective randomized clinical trials where investigators pre-specify their methodology, meta-analyses are conducted retrospectively and are prone to "cherry picking" inclusion criteria and endpoint definitions that often bias the results and lead to misleading and unreliable conclusions. This is my conclusion of that meta-analysis. Clinicians should feel comfortable about using ARBs in the treatment of hypertension without the fear of them causing cancer.

DR. MOSER: I'm going to ask both of you now to summarize the major differences that may, and we have to use the word "may," appear in JNC 8 compared to JNC 7, keeping in mind that the committee will adhere to evidence to as great a degree as possible. What will the major differences be, in the workup, evaluation and treatment. Norm?

DR. KAPLAN: I think 140/90 will still be the dividing line between normal and high; that lower goal blood pressures may be recommended, but not if this can only be achieved with excessive therapy. That is not by having to give patients three and four drugs to get them below 140/90, particularly in the elderly. I doubt if there is going to be many additional diagnostic evaluations recommended, and I think for therapy we'll still go back to starting with one drug. A diuretic will still be generally recommended, but there will be an opening to the other classes of drugs where there are good outcome data and that a second agent should be considered for some patients.

DR. MOSER: Jan?

DR. BASILE: Yes, I agree with Norm. One thing we should mention is the ACCOMPLISH trial, which compared an ACE/diuretic to an ACE/CCB. In this trial overall cardiovascular outcome was better with the ACE/CCB. I don't believe that the JNC 8

committee will put too much stock in this one particular trial as a means of recommending one combination over another, but it will certainly be mentioned and perhaps support initial two-drug fixed-combination therapy.

DR. MOSER: What would you say are the bottom-line, three or four points about JNC 8?

DR. BASILE: I would say JNC 8 will embellish lifestyle modification with more evidence than in JNC 7, but recognize the limitations of the data. I do not think that they will add any new diagnostic tests to their algorithm, but they should have a risk stratification scoring system that will better enable clinicians to understand differences in risk in patients with similar blood pressures, even if it has not been validated in a clinical trial. I do not think that they will recommend thiazide diuretics as the preferred medication in most patients with hypertension.

DR. MOSER: As initial therapy?

DR. BASILE: As initial therapy. I think they'll recommend a thiazide diuretic, preferably chlorthalidone or an ACE, an ARB, or a dihydropyridine calcium channel blocker, especially now that most of those classes are generic and very economically priced.

I don't think they'll recommend combination therapy with a preferred

particular combination, but they will put more emphasis on the importance of getting blood pressure to less than 140/90 sooner than later, except in the oldest of the old. I do think that they'll cull some of the data from clinical trials that suggest getting blood pressure controlled sooner rather than later improves outcome. So I think that will be embellished as well.

DR. MOSER: Ron, your summary?

DR. VICTOR: I think JNC 8 will recommend initial therapy with either 1) an ACE inhibitor or ARB, 2) a CCB (amlodipine), or 3) a thiazide-type diuretic. I would hope the committee recommends low-dose combination therapy if blood pressure is ≥ 10 mm Hg above goal. ACE inhibitor/CCB may be the preferred combination, based on ASCOT and ACCOMPLISH. I think a mineralocorticoid receptor antagonist and a vasodilating beta-blocker will be recommended as fourth- and fifth-line therapy for difficult hypertension.

DR. MOSER: Thank you for a very comprehensive discussion. Now we will have to await the JNC 8 recommendations to see if they agree with at least some of our conclusions.

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