Discussion


Dr. Moser: Dr. Ramsay, you present excellent arguments for using absolute risk and factors other than blood pressure levels as indicators of whom to treat and when. But I have a problem with some of this reasoning—all of the data on benefit of treatment in the clinical trials have been based on just lowering the blood pressure. The trials to date have not attempted to change lifestyle (smoking cessation, etc) or lower lipids. It is possible that results might be better with a broader approach to risk factor reduction, but they haven’t been bad with limited intervention. You seem to indicate that lowering blood pressure really doesn’t contribute much to the reduction in mortality.

The second point has to do with the estimates of number-needed-to-treat (NNT) to prevent an event. Benefit in the trials is underestimated. Many people in the placebo group drop into active therapy as their blood pressures exceed the limits of safety. Individuals in many of the trials are generally low-risk patients with relatively few endpoints in the placebo or control group and events such as prevention of progression to severe disease, the development of left ventricular hypertrophy (LVH), and improvement in quality of life measurements are usually not factored into the benefit equation. Don’t you believe that these factors are important in determining whom to treat, not only in terms of individuals but as part of a national policy?

Prof. Ramsay: The point about underestimating treatment benefit would be correct if we were comparing treatment to total neglect. In other words, if patients were not followed up and treated later if necessary. The Medical Research Council (MRC)1 and Australian trials2 examined the difference in outcome between treating mild hypertension immediately or waiting and treating only if the blood pressures rose to >200/110 mm Hg. These trials define the true marginal benefit from treating at an earlier stage, which was very small.

Regarding your second point, do we benefit patients by just lowering blood pressure—the answer is yes. If we identify people at high risk with elevated blood pressure and lower the blood pressure, we will reverse the increase in risk.

Dr. Moser: Questions from the audience: Dr. Ramsay, why did you ignore the Canadian guidelines, which are similar to those in the US?

Prof. Ramsay: My apologies to the Canadian guidelines. Is there something in these guidelines that we should hear about?

Dr. Moser: The Canadian guidelines advocated early treatment with β-blockers or diuretics as initial therapy. Unlike the British and the World Health Organization (WHO), they were quite specific.

Prof. Ramsay: I hope they said treat vigorously those with sufficient risk but do not treat those who have virtually no risk.

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Dr. Moser: Question from Dr. William Elliot of Chicago.

Dr. Elliott: Thank you, Dr. Ramsay for a very nice discussion. In the United States, our health maintenance organizations (HMO) and the MBAs who run them are very much more interested in an area that you didn’t spend much time on. You spoke a great deal about the 5-year number needed to treat to prevent a death. It’s important to remember that preventing a nonfatal event in young people is also extremely important. If a $17,500 and disability-producing heart attack can be prevented, that’s pretty important.
Prof. Ramsay: I take the point. However, as a Scotswoman, if I had to pay one million dollars to add 1 year to my life, I would think rather hard about it. Having thought hard, I would tell the doctor to take his tablets elsewhere. Perhaps I’d stop drinking and make some other lifestyle changes.

Dr. Moser: What Dr. Elliot was suggesting is that saving an event that might negatively impact your life is extremely worthwhile, ie, if you could prevent a transient ischemic attack (TIA) or LVH or if you could save yourself from progressing to high risk where treatment might be more difficult. You took exception to some of the findings of the Hypertension Detection and Follow-up Program (HDFP). There may be many problems with this trial study, but if you look at individuals in this study who had developed target organ damage prior to therapy, the reduction in mortality/morbidity was as great as for those without target organ delivery, but it was from a much higher level of risk (15.6 versus 4.5). Why wait?

Prof. Ramsay: The question is how much treatment an individual has to take, the chance of benefit, and what his choice would be. I come back to the question of who should make these decisions. We know that young people drive cars recklessly, do bungee jumping, take Ecstasy, and have unsafe sex (although they don’t tell us about that). What makes us think that they are so willing to take pills for 5 years to prevent cardiovascular events that are so rare in this population? I think it should be a matter of personal choice. The NNT tells them the facts. Why are we afraid to give low-risk patients the NNT?

Dr. Moser: I have another question for Dr. Ramsay. This questioner noted that risk factors that we consider today are based on demographics, chemistries, and on lifestyle differences. Wouldn’t we be more accurate if we took 24-h blood pressure monitors to define risk?

Prof. Ramsay: The answer is no. More and more accurate measurement of any single factor will make very little difference to the overall risk estimate. Echo-cardiographic LVH or 24-h ambulatory blood pressure monitoring make only very small marginal differences to risk estimates when used alone. If they were put into a risk equation with other factors, risk prediction would improve slightly but at rather high cost.

Dr. Moser: A question for Dr. Weber: With the knowledge gained from trials or studies since 1993, can we accept angiotensin converting enzyme (ACE) inhibitors and calcium channel blockers (CCB) for initial therapy with the same level of confidence, based on evidence, as the diuretics and β-blockers?

There is little doubt that the ACE inhibitors and probably the angiotensin II (A-II) receptor antagonists are highly effective in congestive heart failure and in individuals with low ejection fractions. However, the hypertensive subset of patients in the Studies of Left Ventricular Dysfunction (SOLVD) study failed to achieve a reduction in myocardial infarctions (MI), angina, or overall mortality despite the definite benefit in congestive heart failure (CHF). Overall cardiovascular events were reduced because of the major reduction in heart failure.

As you noted, the Shanghai Trial of Nifedipine in the Elderly (STONE) study with a long-acting calcium channel blocker was poorly controlled. This showed a reduction in arrhythmias and strokes, but there were only two MI in each group—no chance to determine benefit with coronary heart disease (CHD). The Systolic Hypertension—Europe trial (Syst-Eur) data confirm that strokes are reduced by lowering blood pressure and that it appears that long-acting CCB are safe. At the moment, however, we have little data with CCB re CHD morbidity and mortality but some suggestive better data with the ACE inhibitors and A-II receptor antagonists.

With regard to your comments about the latest paper from Dr. Alderman’s group that suggested a lower cardiovascular event rate with ACE inhibitors compared to β-blockers or diuretics: Dr. Alderman stated that none of these differences were statistically significant. As you noted, this was a retrospective, case-control study, which I don’t believe we should depend on for treatment decisions. The bottom line—do we have enough evidence to recommend that ACE inhibitors and CCB are just as effective as the older drugs and that they should be considered for initial therapy?

Dr. Weber: First of all, I have a lot of difficulty with the expression “evidence-based medicine.” It’s a form of tyranny by statisticians. I think that any study that looks at how a drug works or what it does is evidence. I don’t think evidence consists merely of studies that are highly effective in congestive heart failure and in individuals with low ejection fractions. However, the hypertensive subset of patients in the Studies of Left Ventricular Dysfunction (SOLVD) study failed to achieve a reduction in myocardial infarctions (MI), angina, or overall mortality despite the definite benefit in congestive heart failure (CHF). Overall cardiovascular events were reduced because of the major reduction in heart failure.

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believe the ACE inhibitors would have been significantly better.

**Dr. Moser:** Yes, but the study was retrospective. Dr. Alderman told me that the confidence intervals are so wide that no conclusions should be drawn from these data.

**Dr. Weber:** All retrospective studies have weaknesses, but it seems that every time ACE inhibitors have been used, there have been fewer clinical events. I don’t know what would happen in a pure hypertension study.

**Dr. Moser:** I do agree with that—the ACE studies are suggestive of benefit in several different populations. We have to remember, however, that in all of the studies that used ACE inhibitors, including the diabetic nephropathy studies, other agents were used in combination in about 75% to 80% of patients. For example, >75% of people in the major nephropathy study were also on diuretics and about 50% were on β-blockers to achieve goal blood pressure.

It is clear that the ACE inhibitors have special actions in patients with renal disease and heart failure, but even in heart failure, as you pointed out, combinations were used; almost every patient was on a diuretic and digitalis.

I worry about the data we have thus far on CCB. Yes, the Prospective Randomized Amlodipine Survival Evaluation Study Group (PRAISE) study, which compared a group of amlodipine-treated subjects with heart failure to those just on standard therapy, suggests that there was no increase but also no decrease in mortality in patients with heart failure, but I don’t know of any study, controlled or not, in hypertensives that has shown clear benefit for CHD events with these agents. Am I wrong about that?

**Dr. Weber:** You’re correct about that. There are a lot of studies underway to determine this. The shame of it is that CCB have been around for 25 years and we’re just beginning to collect data about their benefits. What adds to the difficulty is that placebo-controlled hypertension trials are no longer considered ethical, and most patients finish up on combination treatment rather than on simple monotherapy.

**Dr. Black:** My own view, and this is what we’re doing in the ALLHAT trial, is to try and change what the clinical trials look like, so they’re closer to what we actually do from day to day. Trials like ALLHAT and many of the other 32 studies in progress, are more effectiveness studies, which try to take real world doctors treating real world patients in real world settings to get a better estimate of how many we need to treat to prevent an event. Doctors treat patients one patient at a time knowing that they’re all different.

This is a different approach than the trials. I too worry about the tyranny of evidence-based medicine as well as the fundamentalism it brings us.

**Dr. Moser:** Let me defend the trials to some degree. We have data from these less than perfect studies that just lowering blood pressure has achieved quite a bit. We could argue whether there has been a reduction in CHD events of 16% or 12%, but there is no argument that a major reduction in target organ damage, including CHD events, target organ progression and mortality has been achieved—a reduction that has been achieved in diuretic or β-blocker–based trials. Data are actually better with the diuretics. The argument that CHD events have not been reduced by these agents is just not true. Maybe results will be somewhat different in the ongoing trials, but probably not too different—the clinical trials that we have seen to date have been very helpful. As everyone has suggested, benefit of treatment in the highest risk patients will be greatest. In the recent metaanalysis, benefit was greater with low-dose diuretic therapy in the elderly than therapy in younger or less severe hypertensives. While we should not be rigid about evidence-based medicine, I think that we must pay attention to it.

**Prof. Ramsay:** I would also like to defend the controlled trials. Those who downplay the value of such evidence have very short memories indeed. One thing that randomized controlled trials have shown us repeatedly is that we can be wrong. One would have bet a lot of money that β-blockers would be more cardioprotective than diuretics. The Medical Research Council (MRC) trial in the elderly showed the opposite to be true. We thought once that antihypertensive drug treatment in the elderly might actually be harmful. Trials showed benefits much larger than had been expected. Those who believe that they know what the next randomized controlled trial is going to show are deluding themselves. We do need further controlled trials.

**Dr. Moser:** I agree with Dr. Ramsay. To write off the evidence from controlled trials takes us back to the dark ages of therapeutics. And transferring the results of animal data or cellular changes from a particular therapy to clinical outcome is hazardous, as we all have found out. For example, the vascular protective effects that have been demonstrated with CCB in animals at between 20 and 40 times the doses given to humans have not as yet been demonstrated in humans.

**Prof. Ramsay:** One additional point. When we look to new randomized controlled trials, we should not be asking whether the newer classes of drugs are similar to those already established; we should be asking whether they’re superior to diuretics and β-blockers. If
they’re not superior, we come back to the principle that if all else is equal, we should favor the most economic treatments. So we’re not looking for trials to show that the CCB are similar—we’re really looking for evidence that they add to benefit. If they don’t add something, why should we prefer them?

Dr. Weber: First of all, prospective randomized trials take a long time. They’re very interesting and very helpful, but I don’t think it’s appropriate to simply say that because such trials have not been completed and analyzed, we aren’t allowed to make decisions based on what we already know. There are different grades of evidence. Trials do present surprises and appropriately can compel us to make changes in how we treat patients. But in the meantime, I have to take into account what I read and what I see, analyze the available data, such as it is, and reach conclusions.

Dr. Moser: The JNC VI Committee looked at all of the data on the newer agents and considered them in setting up the new guidelines. We concluded that diuretics or β-blockers should be used as initial therapy unless there are specific indications for the use of other drugs, ie, ACE inhibitors or A-II receptor antagonists in heart failure or diabetic nephropathy, certain CCB in angina or the elderly, etc. Of course, Dr. Weber is correct—we should pay some attention to data gathered in smaller, shorter trials or the experience of practitioners who treat large numbers of subjects.

Another question for the panel: How far should blood pressure be lowered in uncomplicated hypertensives, in other words, in a 40-year old male with 145/95 mm Hg, or in a 65-year old with no evidence of target organ involvement? Is there a J-curve? Do we worry about it, or should we just keep on going until we reduce blood pressures to 110/80 mm Hg? This is an important clinical decision that doctors have to make.

Prof. Ramsay: We do not know the answer. Hopefully we will when the Hypertension Optimal Treatment (HOT) study is completed. This study is testing the hypothesis formally.

Dr. Moser: What do you do?

Prof. Ramsay: I’m still impressed by the evidence from the original Veteran’s Administration Study in 1967, showing that even partial control of severe blood pressure affords a major part of the benefit achieved. If I can lower the diastolic blood pressure to 90 or 85 mm Hg, I am perfectly content until new evidence shows that I should strive for more. I suspect there is not a J-curve, but we need new evidence.

Dr. Weber: I agree in principle. Fortunately there are trials now underway that may help to answer this question more precisely.

Dr. Roccella: I have a question for Dr. Ramsay. Help me to understand what is so magical about 5 years. When I look at the data on the number needed to treat, and the long-term follow-up, for example of the HDFP study, treatment for the first 4 or 5 years appears to confer benefit over additional years. So, if you make the decision to treat with the number needed to treat based on 5 years, it’s quite different than if you use the 8 plus-year HDFP or 10-year Multiple Risk Factor Intervention Trial (MRFIT) data.

Dr. Moser: These are softer data, but you’ve got a point.

Prof. Ramsay: Yes, this is a valid point conceptually but not actually true. The initial decision is not a decision for life. It is crucial that any individual who is hypertensive is followed-up regularly. At the end of 5 years risk may well have changed as blood pressure and risk rise with age. The assessment of risk and the need for treatment may be entirely different then. You do not make a decision that treatment will never be needed.

I would also answer with another question—Why, in the trials of the elderly, where many patients have probably had hypertension for many years, were strokes decreased by 40% and myocardial infarctions by 20% with antihypertensive drug treatment that was started after age 60? Was anything lost by waiting?

Dr. Moser: A question for the audience—how many would adhere to the JNC V and JNC VI recommendation that a middle-aged person without other risk factors, whose blood pressures remains at >140/90 mm Hg after 6 months of nonpharmacologic intervention, be introduced to drug therapy?

Less than half of our audience would begin therapy with drugs. So there is a disagreement about when to begin medication.

Dr. Roccella: Let me emphasize something that Dr. Moser talked about—the fact that trial results underestimate the benefit of treatment. The “drop in” effect is very important. For example, in the Systolic Hypertension in the Elderly Program (SHEP),9 45% of people in the placebo group were actually on drugs. So the benefits at 5 years, based on treated versus “non-treated,” is actually lower than it would be if the number on therapy had been compared to the number not on therapy.

Prof. Ramsay: One comment. Those patients in the placebo group did not end up on treatment by accident; they were treated by protocol design. If blood pressure rose above a certain predetermined level, treatment was started. So the trials compared immediate treatment versus waiting to see and treating only if blood pressures exceeded this threshold. The trials are, therefore, an accurate estimate of an early treat-
ment strategy versus a strategy of waiting and treating later if necessary.

Dr. Moser: But the early treatment turned out to be better . . .

Prof. Ramsay: It is better, but the benefit is extremely small in low-risk subjects.

Question from the floor: I’m a little confused about one issue that we’re discussing—whether to treat or not to treat when the blood pressure is above 90 or 100 mm Hg. From what I know, blood pressure varies greatly within a day in some individuals. So what do you really mean by 90 mm Hg? Perhaps these different patients need different treatments and treatment at different times.

Dr. Moser: Let me try to clarify this. All of the data from numerous epidemiologic studies that estimate risk are based on casual blood pressures. The higher the pressure when a person walks into a room, sits down, and has his or her blood pressure taken, the greater the risk. All of our data on outcome are also based on casual pressures.

In the clinical trials people were seen three or four times a year. Those whose blood pressures were lower had a better outcome. I still believe at this point that, even though we recognize variability and diurnal fluctuations and nondippers and dippers, the casual pressure should be the one to use in gauging risk or outcome. In a few cases home pressures might be useful.

Dr. Moser: Dr. Black, what data do you use in deciding whether or not to treat someone?

Dr. Black: I have to use office blood pressure because that’s what we know about. I am very interested in the differences in individual variations but they don’t, in fact, help us.

Prof. Ramsay: We know that averaging repeated blood pressure measurements over a period of months takes out much of the variability. Whether we can do better than that, I don’t know.

Dr. Moser: Last question—Dr. Weber, one of the challenges that you threw out was that the antiproliferative and antiatherosclerotic effects of the new classes of drugs might present an advantage over other agents. Would that translate to clinical benefit? Is there any evidence of this?

Dr. Weber: Almost all the new antihypertensive drug classes, including ACE inhibitors, CCB, and A-II receptor antagonists, have been shown in animals to prevent vascular wall proliferative changes in response to injury or other stresses, and to slow down or, in some cases, completely prevent atherosclerosis.

In the INTACT Study nifedipine trial in humans, which compared this CCB to placebo, new coronary lesions were fewer in the treated group but regression or progression of lesions were not different from placebo.

Dr. Moser: And the treated patients had more vascular events.

Dr. Weber: You are correct. There were more events in patients treated with short-acting nifedipine but they had better looking coronary arteries. This simply emphasizes the importance of hemodynamic effects. We know we have tools that can change what is happening in the vascular wall. The question is, will this actually reduce coronary events in hypertensive humans? We’re working hard to find out.

Dr. Moser: To summarize, this symposium addressed current recommendations for treatment and their validity. A great deal of time was spent, however, on deciding not on how to treat but on whether or not to treat patients with less severe disease. These discussions are worthwhile.

We all agree that we have some very good evidence of benefit when diuretics and β-blockers are used in the management of hypertension. We have some evidence with the newer agents, ie, the ACE inhibitors, A-II receptor antagonists, and CCB, but certainly not definitive evidence. Whether we adhere to evidence-based medicine down the line or use case-controlled studies and clinical experience to help us with our decisions is another matter. There is a strong but not irrefutable case for evidence-based decisions.

Finally, studies strongly suggest that combination therapy with relatively small doses of two different classes of drugs is probably an effective way to treat the majority of our patients in terms of response rates and minimizing side effects. JNC VI has recognized this by suggesting that fixed dose combination therapy is appropriate first-step treatment.

We all await the results of the numerous long-term trials presently underway with the newer agents and studies like ALLHAT, which includes 42,000 subjects and which also addresses reduction of risk factors, such as hyperlipidemia, in addition to hypertension.

REFERENCES

3. HDFP Hypertension Detection and Follow-up Program Cooperative Group: Five-year findings of the Hyper-


