

## Expert Panel Discussion

# The ASCOT Trial—Are $\beta$ -Blockers Still Useful as Antihypertensive Medication?

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*Following a hypertension symposium in New York, NY in March 2006, an expert panel was convened to discuss the Anglo-Scandinavian Cardiac Outcomes Trial (ASCOT) and the future of  $\beta$ -blocker therapy. Dr Marvin Moser of the Yale University School of Medicine, New Haven, CT chaired the panel, which included Dr Thomas D. Giles, President of the American Society of Hypertension and Professor of Medicine at Louisiana State University School of Medicine, New Orleans, LA; Dr Thomas G. Pickering, Director of Behavioral Cardiovascular Health at Columbia University College of Physicians and Surgeons, New York, NY; and Dr Ronald G. Victor, Professor of Internal Medicine and Division Chief of Hypertension at the University of Texas Southwestern Medical Center, Dallas, TX. (J Clin Hypertens. 2006;8:723–728) ©2006 Le Jacq*

**DR MOSER:** Ron, the Anglo-Scandinavian Cardiac Outcomes Trial (ASCOT), which was a comparative drug trial of calcium channel blocker (CCB) therapy with angiotensin-converting enzyme inhibitors (ACEIs) added, compared with a  $\beta$ -blocker treatment regimen with a diuretic added, reached some definite conclusions. The authors concluded, first, that this trial demonstrated that so-called contemporary therapy was clearly better than older therapy in reducing cardiovascular morbidity and mortality and, second, that the results were generalizable. What's your interpretation of ASCOT? Were there any flaws in the study; was it well conducted?

**DR VICTOR:** The strengths of the study were positive outcomes, large numbers of subjects, and multiple centers. Although initially ASCOT was comparing a  $\beta$ -blocker with a CCB, many of the patients were on 2 medications, such as a  $\beta$ -blocker and a diuretic, or a CCB and an ACEI. These are the strengths.

The study was stopped early because the Data Safety Monitoring Board (DSMB) thought that the outcomes were sufficiently different with therapy with a CCB/ACEI compared with older therapy with a  $\beta$ -blocker/diuretic. But there has been some

debate about this, since there were no differences between groups with the primary outcome: coronary heart disease events were similar. The people who like the trial say that you don't need statistics when the DSMB stops a trial early. The investigators who are on the other side claim that you have to hold the standard of evaluation to positive outcomes—and ASCOT was negative for the primary outcome. Nevertheless, numerous secondary outcomes were positive.

Some of the negative aspects of the study include that it was a prospective, randomized, open, blinded end point (PROBE) design, which is not a randomized, controlled, double-blinded study. If I understand the PROBE design, investigators are allowed to assign medications, but the end points are analyzed in a blinded fashion. More and more trials are being done this way because they're cheaper. In addition, there were many people who took other drugs or crossed over from one group to another.

There was a lipid-lowering arm as well, which was blinded, and the results were unequivocal.

**DR MOSER:** Clearly, the lipid-lowering plus blood pressure (BP)-lowering regimen was dramatically effective in reducing cardiovascular events.

**DR VICTOR:** The other interesting aspects of the study were that it was Anglo-Scandinavian:



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largely whites over the age of 60 years, and more males—a very select group of patients.

DR MOSER: Was the primary end point different at all between the 2 groups?

DR VICTOR: As I mentioned, it was not, but proponents of the study say that's because the DSMB stopped it early. Can the results be generalized, as the authors claim? Probably not. This is relevant because people of African and Asian descent have a higher incidence of cough and angioedema with ACEIs, and different groups and ages respond differently to different medications. For example, CCBs and diuretics are more effective in the elderly and blacks than ACEIs or  $\beta$ -blockers—so that, for example, comparing a  $\beta$ -blocker-based treatment to a CCB-based program in the elderly may favor the CCB.

Among the secondary outcomes in this trial was less new-onset diabetes in the CCB/ACEI group compared to  $\beta$ -blocker/diuretic therapy.

DR MOSER: What's your take-home message? Do you believe that national guidelines and our approach to therapy should be changed on the basis of the ASCOT data?

DR VICTOR: That's a good question. I'm not much of a proponent of  $\beta$ -blockers for uncomplicated hypertension. The  $\beta$ -blocker arm of ASCOT didn't work out too well.

DR MOSER: So you seem to suggest that this study was basically a  $\beta$ -blocker compared with a CCB, at least for the first 4–6 months, when there was a BP difference—the CCB was more effective.

DR VICTOR: About half the subjects were on the 2 drugs,  $\beta$ -blocker/diuretic, or CCB/ACEI, after the first 4–6 months, so it wasn't exactly a long-term study of monotherapy compared with combined therapy. Based on the results of this study, I would not select a  $\beta$ -blocker or a thiazide/ $\beta$ -blocker combination for patients who are prediabetic or at the first step of treatment for uncomplicated hypertension.

DR MOSER: Okay. So you seem to lump the  $\beta$ -blocker and diuretic together and are concerned about the problem of metabolic changes with these agents. Yet in the Antihypertensive and Lipid-Lowering Treatment to Prevent Heart Attack Trial (ALLHAT), morbidity and mortality on a diuretic-based regimen was similar to that on a regimen with an ACEI or CCB in patients who were normoglycemic, or who had elevated fasting blood glucose levels, or who were diabetics. Should the ASCOT investigators have used the term  *$\beta$ -blocker-based* compared with *CCB-based* instead of *old* compared with *contemporary*?

DR VICTOR: That's an open question. The thing that really needs to be pointed out is that BP lowering was more rapid and greater with the CCB- than the  $\beta$ -blocker-based program.

DR MOSER: So BP lowering was better with the CCB during the first 4–6 months than it was with the  $\beta$ -blocker.

DR VICTOR: And that's not surprising.

DR MOSER: No, not at all, in that population. Well, Tom, what's your take-home message from ASCOT?

DR PICKERING: For me, I wasn't that impressed with the differences between the old and the new drugs. I think the big issue with all of these studies is that they tend to be overinterpreted when they're first published, because people want to get them into a good journal and make a big splash. That's true with pharmaceutical company-funded studies, but may also have been true of ALLHAT, which was funded by the National Institutes of Health (NIH). The big question with all of these is, "Is there an effect independent of the BP lowering?" With ASCOT as with ALLHAT, there was a difference in the BPs between groups, and my own feeling is that probably most of the different results can be explained by the differences in BP. This was borne out by the ASCOT-Conduit Artery Function Evaluation (CAFE), a substudy that measured the effects of the drugs on the central aortic pressure, and found even bigger differences than seen in the brachial artery pressure. Having said that, I too have some reservations about using  $\beta$ -blockers as initial treatment in hypertension.

I was on the US Food and Drug Administration (FDA) panel that reviewed the data from the Losartan Intervention for End Point Reduction (LIFE) study, which was another  $\beta$ -blocker comparison trial where the angiotensin receptor blocker (ARB) group did better than the  $\beta$ -blocker group. The big debate was whether it was because the ARB was so good or because  $\beta$ -blockers aren't so good. I tend to believe that  $\beta$ -blockers are not as good at preventing primary events as other drugs, including diuretics, especially in the elderly.

DR MOSER: Your conclusion about the ASCOT study, then, is that the data are interesting but you were not as impressed as much as some people have been by the results. Perhaps it was the BP differences in those first 4–6 months between the CCB-treated compared with the  $\beta$ -blocker-treated patients that made the difference. This study does add to other data from studies like LIFE and probably the Medical Research Council (MRC) elderly trial, that  $\beta$ -blockers may not be the initial drug of choice in patients without angina, myocardial

infarction (MI), or heart failure. Dr Giles, what's your take?

DR GILES: Well, I believe that one of the reasons all of these trials are so confusing is because they're doomed from the beginning. If you look at the responder/nonresponder rates in the population with respect to any class of antihypertensive drugs, they are widely distributed. Then, if 4 different drugs are studied in a single clinical trial, the results are bound to be confusing. If you were going to use a comparator drug such as a  $\beta$ -blocker, however, then it should be given at an effective dose, and the BPs should be comparable between the treatment arms.

DR MOSER: So the dose of the  $\beta$ -blocker in this case may not have been appropriate?

DR GILES: Fifty milligrams of atenolol once a day is somewhere between homeopathy and treatment. Also, an issue that continues to come up is, "Can you assess the BP lowering of a  $\beta$ -blocker by measuring brachial artery BP?" I'm persuaded by data that you cannot. Central BP is not lowered by  $\beta$ -blockers to the same degree as brachial artery BP. For example, in the LIFE trial, where stroke reduction drove the end point, central BPs were likely not lowered as much with the  $\beta$ -blocker as with the ARB. On the other hand, the effect on ischemic heart disease in the LIFE trial favored the  $\beta$ -blocker.

DR MOSER: So in LIFE, although we're told that the cardiovascular events were reduced significantly more with the ARB compared with the  $\beta$ -blocker, it really was the difference in stroke that accounted for most of the difference.

DR GILES: Which, as I've noted, is more sensitive to central pressures. So I didn't find the ASCOT study results particularly surprising. My guess is there could be another one coming out tomorrow using the exact same design and showing different things. I think it all depends on looking at it from a Bayesian point of view. If you wanted to look at this study design and say, "Based on the totality of the data, will whatever result I get out of this trial change what I think about specific drugs?" my answer is, "Not likely."

DR MOSER: As we have suggested, in this particular study, the  $\beta$ -blocker used was given once daily when it should have been given twice daily; what you were comparing was an inadequate dose of the  $\beta$ -blocker to an adequate dose of a CCB. The other issue we might talk about is the population studied in ASCOT, LIFE, and in ALLHAT. These were elderly people. In ALLHAT, about one third of the people were black, and they, as well as the elderly, respond better to CCBs than to  $\beta$ -blockers.

But I would agree that the questions about  $\beta$ -blockers and their effectiveness have been around for a long time.  $\beta$ -Blockers initially increase vascular resistance. Over time, it may decrease. As you have noted, the difference between central pressure that vessels respond to and peripheral pressure that we measure may account for the difference in outcome. So now that you've seen this study, Tom, do you conclude that old therapy is out or do you limit your conclusions? Is ASCOT just another reason why we shouldn't consider  $\beta$ -blockers as preferred initial therapy?

DR GILES: I'll tell you, Marv, I'm pretty much an individualist when it comes to prescribing for patients. I think it's wonderful to have all these drugs available, but the debate about which drug is best may be moot. Only a few people remain on monotherapy. Even for patients with systolic BPs <140 mm Hg, I generally give them 2 drugs as initial therapy. One of them usually is a diuretic or a CCB, and the other is usually a drug that blocks the renin-angiotensin system, unless, as you point out, there's a compelling indication for something else. In other words—multidrug therapy. If you look at the LIFE trial, it certainly was not just a  $\beta$ -blocker vs an ARB; hydrochlorothiazide was given to most patients in both groups.

DR MOSER: Eighty percent in both groups got hydrochlorothiazide. You're right, Tom, all the trials have been multidrug studies. I agree that it is difficult to conclude that drug A is better than drug B, because most of the time multiple drugs have been used.

I think that we all pretty much agree that ASCOT did confirm previous observations. ASCOT showed that a CCB/ACEI combination is safe and that there are fewer cases of new-onset diabetes with this combination than with a  $\beta$ -blocker/diuretic combination. Although the primary outcome wasn't different, the secondary outcome differences were statistically significant. Although the authors use the term *old therapy*, this study was basically a comparison of a  $\beta$ -blocker to a CCB over the first 4–6 months of the trial.

Perhaps we should not lump  $\beta$ -blockers and diuretics together. There are many studies demonstrating that diuretics are as effective as other medications.

So, why have we been using  $\beta$ -blockers as initial therapy all these years? Where did we get the idea that we should use a  $\beta$ -blocker as initial treatment? The first Joint National Committee on Detection, Evaluation, and Treatment of High Blood Pressure (JNC I) advocated diuretics. Later on, we included  $\beta$ -blockers because we had some

data on propranolol.  $\beta$ -Blockers continued to be listed as initial therapy until JNC VI, when we said that in the elderly, diuretics should be first and then a  $\beta$ -blocker can be used as additional therapy. All the other guidelines continue to list diuretics,  $\beta$ -blockers, ACEIs, ARBs, and CCBs as possible initial therapies. Should that be changed? Should  $\beta$ -blockers be dropped as one of the initial agents? The recent recommendations of the British Medical Society suggest that they should. In fact, these suggest that they should not be considered as second- or even third-step agents unless a specific condition is present.

DR VICTOR: My cardiologic colleagues know that  $\beta$ -blockers are great drugs for angina, and in people with ischemic heart disease and heart failure,  $\beta$ -blockers are extremely useful. So I believe that quite a few physicians, especially cardiologists, are influenced by the positive outcomes in these settings. But in the patient with isolated systolic hypertension, the  $\beta$ -blockers may not be drugs of initial choice and may not be as protective against stroke for equal BP reduction as some of the other medications. In a younger person, the concern is about a lifetime of treatment that might, over decades, have some diabetogenic potential.

DR MOSER: And yet in many young people with a so-called hyperactive sympathetic nervous system,  $\beta$ -blockers clearly lower BP better than diuretics or CCBs.

DR VICTOR: Sure. But the other issue is that  $\beta$ -blockers may cause depression in some people, and may have some sexual side effects. So I personally believe that the  $\alpha/\beta$ -blockers will replace the pure  $\beta$ -blockers.

DR MOSER: Because of more favorable effects on vascular resistance and fewer metabolic effects.

DR VICTOR: More favorable. Labetalol, for example, is a good drug for severe hypertension.

DR MOSER: Tom, what are your opinions about the data on  $\beta$ -blockers? Have they been proven to be effective as antihypertensive agents?

DR PICKERING: Propranolol was one of the first of the major antihypertensive drugs after diuretics. I remember we used to give 1–2 g of propranolol a day.

DR MOSER: And sometimes 2 or 3 g.

DR PICKERING: And it worked; it lowered BP. At that time there were no CCBs, ACEIs, or ARBs.

DR MOSER: And it was a lot better than  $\alpha$ -methyl dopa.

DR PICKERING: And some other medications. It should be remembered that the original MRC trial, which compared propranolol, a thiazide, and placebo, did show some reduction in morbid

events. So I don't think they are useless drugs. It is just that we now have more drugs to choose from, and I do think that the newer drugs cause fewer side effects and in older people, these other agents may actually be slightly better in terms of reducing morbid events. But I wouldn't say that necessarily about younger patients.

DR MOSER: So at the time  $\beta$ -blockers were introduced, they were an advance over what we had before...

DR PICKERING: Absolutely.

DR MOSER: ...and in combination with a diuretic, they were effective and did appear to reduce morbidity and mortality. The MRC trial was a trial that produced results that were unexpected. The  $\beta$ -blockers turned out to be no more effective than placebo in reducing MIs, and diuretics proved to be much more effective. That was not the pretrial prediction.

DR PICKERING: Right.

DR GILES: Weren't  $\beta$ -blockers the first antirenin drugs? Initially, as we know, they may cause some peripheral vasoconstriction. But as I recall,  $\beta$ -blockers modulate renin release and, over time, lower peripheral vascular resistance. This provides an explanation for reducing BP through  $\beta$ -blockade. If not by this mechanism, then how would they do it—do we know?

DR MOSER: Initially, we all believed that they lowered BP because they reduced cardiac output and heart rate. After a while there is some sort of autoregulation change. Whether it is due to reducing renin release or not, no one is quite sure.

DR PICKERING: It is certainly possible that there is some autoregulation over time.

DR VICTOR: They're supposed to lower central sympathetic output. We tried to show this but couldn't prove it.

DR MOSER: Well, where do you think  $\beta$ -blockers fit in now? We all are going to agree without too much discussion that they're not preferred initial therapy, especially in the elderly, where perhaps they might not be too effective.

DR GILES: I think that in the absence of a compelling indication,  $\beta$ -blockers aren't the first drugs that I would select. I think we've all said that the ARBs can be given without concern for side effects. So, if you're going to give a drug to someone who doesn't have any symptoms, ARBs make a very attractive choice as a first step. And, the ARBs make an excellent combination when used with a low dose of a diuretic, or a CCB.

DR MOSER: Well what about the young person who comes in with a resting heart rate of 85 with

systolic BP elevations, BP 145/85 mm Hg, a young athletic kid. Do  $\beta$ -blockers have a place in therapy? Don't they control BP? And sympathetic overdrive?

DR GILES: That's a tough question. You know, they were giving  $\beta$ -blockers for stage fright and for anxiety states. Clearly they block that component of the sympathetic nervous system. But, of course, it's a 2-edged sword.  $\beta$ -Blockade heightens  $\alpha$ -adrenergic responses.

I personally think the phenotype of this individual doesn't necessarily dictate that you have to go in that direction. For example, ARBs decrease sympathetic outflow by working on the presynaptic adrenergic nerve terminal. So that's a way of addressing that situation.

Below 100 bpm, resting heart rate is under vagal control. It's not driven by adrenergic activity. When someone has a resting tachycardia, vagal withdrawal has already occurred. It's only when you begin to bring in the catecholamines that you start getting higher rates.

DR MOSER: Let me ask a question. We all believe in evidence-based medicine. We have 3 studies in elderly patients that are always quoted to demonstrate that  $\beta$ -blockers are passé. Do we have any data on 40–60-year-olds that tell us that  $\beta$ -blockers are useful or not? I'm not defending their use, just trying to clarify a point.

DR VICTOR: There are not going to be too many studies like that, because most young people don't have enough events to get a positive outcome.

DR MOSER: That's right. There aren't going to be any.

DR VICTOR: So...I think it's the side effect profile that we're worried about in younger people, and in older people you have better choices.  $\beta$ -Blockers will still be used, but they may just not be the preferred drugs in uncomplicated hypertensives.

DR MOSER: So, basically what we are all saying is that these drugs may reduce BP, reduce stroke compared with placebo, but not as much as other medications; they reduce recurrent MIs and improve heart failure outcome as much as other drugs, but we have other choices that may be just as effective in most situations without some of the side effects.

DR PICKERING: There's another issue to discuss. Are all  $\beta$ -blockers alike, and what are the class effects? We know, for example, that in post-MI patients, all  $\beta$ -blockers are not alike; I believe that atenolol was not found to be effective in post-MI or heart failure patients, but whether this was because of underdosing or lack of adequate data I don't know. There are only 3  $\beta$ -blockers that are

currently approved for each of these indications, and atenolol is not one of them. And if you look at the evidence for adverse effects of  $\beta$ -blockers in hypertension trials, it was nearly always atenolol that was used. So that raises the question of whether or not these comments should apply to all  $\beta$ -blockers, or just atenolol.

DR MOSER: What do you think? Forget the  $\alpha/\beta$ -blockers for a minute, because obviously drugs like labetalol and carvedilol are different physiologically and metabolically, and they're very effective. They do cause some dizziness and postural changes. But forget that. Do you believe that there is a major difference in the other  $\beta$ -blockers, selective or nonselective?

DR PICKERING: For hypertension, I don't think there are really enough data to say. I certainly would not include the  $\alpha/\beta$ -blockers like labetalol and carvedilol in the same group because, as you know, there is some evidence that in diabetes the use of carvedilol may result in fewer metabolic effects than a simple  $\beta$ -blocker.

DR MOSER: Tom, do you think there is a class effect for  $\beta$ -blockers, or can't we say? Most of the studies were done with propranolol and atenolol.

DR GILES: I guess I have to retreat into the notion that there is no such thing as class effect. That is not a pharmacologic term. There may be class labeling for drugs, but all these molecules are clearly different. I think the ARBs are probably more similar in the sense that nobody can demonstrate much more than the effects on the angiotensin II type 1 receptor. But  $\beta$ -blockers have different effects.

While I agree with you about needing evidence upon which to base therapeutic decisions, I would submit that the totality of the evidence doesn't necessarily reside with randomized trials. Furthermore, as you pointed out, the randomized trials, unless they're done correctly, can end up causing more confusion than enlightenment. We now have a new  $\beta$ -blocker, nebivolol, which will be marketed soon. This is a vasodilating  $\beta$ -blocker; its dilatation appears to be based on a nitric oxide (NO)-dependent mechanism and not dependent on  $\alpha$ -blockade. It is an NO-releasing  $\beta$ -blocker. You can't paint all  $\beta$ -blockers with the same brush.

DR MOSER: If each of you had to present a summary statement about the ASCOT trial and the future of  $\beta$ -blockers, what would you say?

DR VICTOR: I think the ASCOT data are consistent with the increasing body of evidence that we have better choices than  $\beta$ -blockers, especially a  $\beta$ -blocker as initial therapy for hypertension in people older than 60 years.

DR MOSER: The ASCOT investigators have listed  $\beta$ -blockers and diuretics together as old therapy. Are there data showing that there are better choices than a diuretic?

DR VICTOR: No, not a diuretic by itself—but a  $\beta$ -blocker/diuretic combination, and certainly a  $\beta$ -blocker alone, would not be a first choice. A diuretic is definitely initial therapy for isolated systolic hypertension, no question. I believe that  $\beta$ -blockers are unquestionably good drugs for hypertension in the setting of coronary disease and congestive heart failure. For uncomplicated hypertension, I think there are better choices.

DR MOSER: Do we have to change the JNC recommendations, or are they still okay?

DR VICTOR: Yes, we need to change the JNC recommendations, because as new data have come to life, parts of JNC 7 are out of date. Along these lines, the British Hypertension Society recently amended their guidelines to remove  $\beta$ -blockers as first-line—or, even second-line—therapy for uncomplicated hypertension.

DR MOSER: But the JNC doesn't suggest  $\beta$ -blockers as initial therapy except in special situations. The report suggests diuretics as initial therapy in most patients and other drugs as possibilities. Do we have to rewrite that?

DR VICTOR: I think so.

DR MOSER: Okay.

DR VICTOR: An important thought. All the studies, including the Valsartan Antihypertensive Long-Term Use Evaluation (VALUE) and ASCOT, have proved that getting the BP down, no matter how you do it, is terribly important and should be the Holy Grail in our business.

DR MOSER: Tom?

DR PICKERING: I basically agree. I think my philosophy is it's the BP, stupid, and I don't think ASCOT has really changed that belief.

$\beta$ -Blockers are still on my list of antihypertensive drugs, but they're near the bottom rather than the top. I would not start with them, except possibly in a young person with a hyperdynamic circulation. Otherwise I rarely start with a  $\beta$ -blocker as the drug of first choice, but will add one when necessary.

DR MOSER: Tom, any parting words?

DR GILES: I agree. I think that ASCOT reinforces the notion that lowering BP is of great importance. It points out that the combination of a CCB with an ACEI is effective in reducing morbidity and mortality, just as we've shown in the past with diuretics and  $\beta$ -blockers. The choice in an individual patient is probably dependent upon other things. For that reason, we're lucky that we have a lot of medications to choose from.

DR MOSER: Thank you.