

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

New-Onset Diabetes in Treated Hypertensive Patients—Is It Clinically Significant?

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Following a symposium on hypertension in Chicago on September 22, 2004, a roundtable discussion was held to discuss one of the emerging controversies in hypertension management, specifically the occurrence of new-onset diabetes in treated nondiabetic hypertensive patients. How frequent is it? Is it just part of the metabolic syndrome that is common in hypertension, or do certain medications predispose patients to hyperglycemia? The question of the effect of other specific medications on insulin sensitivity and the possible reduction in the occurrence of diabetes in the hypertensive population with these agents was also discussed. Dr. Marvin Moser of the Yale University School of Medicine, New Haven, CT, moderated the discussion with Dr. James Sowers of the Missouri College of Medicine, Columbia, MO, Dr. Suzanne Oparil of the University of Alabama at Birmingham, Birmingham, AL, and Dr. Henry Black of the Rush College of Medicine, Chicago, IL. (J Clin Hypertens. 2005;7:90–95) ©2005 Le Jacq Ltd.

DR. MOSER: Jim, it's appropriate that we start with you. You're the expert, you've read the literature, and looked at all the clinical trials. Is this a new controversy about new-onset diabetes? The question is: Do certain medications increase new-onset diabetes in a susceptible population? It is well known that hypertensives develop more diabetes than normotensives. Is it just that, over 5 years, some people will become diabetic or do certain medications decrease insulin sensitivity and result in more than the expected number of new-onset diabetics?

DR. SOWERS: I wish I could give you a definitive answer. I think that there probably is a little propensity for β blockers and diuretics to increase the rate of development of incipient diabetes or to worsen insulin sensitivity over a finite period of time, say 3–5 years. It's not very striking though. If you go back and look at all the data, in the Gress article published in *The New England Journal of Medicine* in 2001, in a large group of patients, the only antihypertensive medication that predisposed to the development of diabetes was a β blocker.

DR. MOSER: And that was about a 25%–28% increase.

DR. SOWERS: Something like that, I've forgotten exactly what it is, Marvin, but diuretics did not predispose, and calcium channel blockers (CCBs) and angiotensin-converting enzyme (ACE) inhibitors did not predispose. The data from the Antihypertensive and Lipid-Lowering Treatment to Prevent Heart Attack trial (ALLHAT), which was the largest trial by far, would suggest that there are some differences. I'm not terribly convinced that diuretics cause diabetes without perturbing potassium and magnesium. So, in an uncontrolled situation where you would get a certain number of people with hypomagnesemia, hypokalemia, or both, I think there may be some predisposition to the development of type 2 diabetes. Beta blockers, on the other hand, do cause weight gain. I think that's the reason that, in some studies, they have been shown to increase the propensity for diabetes. I don't think it's striking, but there's no question there is weight gain. In the United Kingdom Prospective Diabetes Study (UKPDS), for instance, patients on β blockers gained 2.2 kg more than



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patients on an ACE inhibitor, captopril. Fred Luft has done several smaller studies and clearly documented weight gain with β blockers.

DR. MOSER: And that may account for the increase in insulin resistance.

DR. SOWERS: Yes. I think that may be part of it. There may be some aspects of blood flow to peripheral tissues related to β blockers that play some role. Now, having said that, I think that there is probably more of an impact of angiotensin receptor blockers (ARBs) and ACE inhibitors on improving insulin sensitivity than there is any detrimental effect of diuretics, or β blockers, on insulin sensitivity. I think the differential we see is relative to these agents. There are some differences. This is just an educated guess that is based on several recent trials comparing ACE inhibitors and diuretics.

DR. MOSER: Henry, what are your thoughts about this?

DR. BLACK: I think Jim summarized it very well. I have a couple of concerns about where we are right now. One is a fact. If you already had diabetes in ALLHAT, you did best on chlorthalidone. I don't understand how it can cause diabetes and then if you get it, you do better on an agent that might have caused it. This line of thinking might lead you, if you wanted to follow it to a regimen where you would treat people who weren't diabetic yet and if they got it, you would switch them to another therapy. This doesn't really make sense. I think there is, indeed, some serious inconsistency.

DR. MOSER: But did diabetics in ALLHAT do better or worse in terms of coronary disease events on diuretics?

DR. BLACK: Blood pressures (BPs), and all outcomes, showed no advantage of other agents in diabetics compared to diuretics. There was actually some advantage in diabetics who were on chlorthalidone.

MOSER: Were you able to track what diabetes control was like on the diuretic? Did these patients require more antidiabetic drugs?

DR. BLACK: That I don't know. We are currently looking at people with the metabolic syndrome; and people with impaired glucose tolerance compared to diabetics compared to nondiabetics. In all instances, the data seem to be the same, not surprisingly.

DR. MOSER: So are you concerned at all about the possibility of new-onset diabetes with specific medications?

DR. BLACK: I think it just is paradoxical that the drug you think is responsible for causing a particular problem is also the one that treats it best.

We have to figure that out. The thing that's pretty hard to argue with is the consistency among the trials we have, that drugs that block the renin angiotensin system, ACEs or ARBs, seem to reduce the incidence of new diabetes, whenever they're compared to other agents. That's something I believe is probably true that I would like explained. I don't understand this unless it has something to do with insulin resistance rather than just a diagnosis based on how high glucose is.

The important thing that we still haven't proven, but is suggested, is that new-onset diabetes has the same prognosis as established diabetes. That flies in the face of the ALLHAT results, but the difference may be due to the shorter follow-up in ALLHAT compared to other studies with longer observation periods. Right now I think we're at a point where we don't have enough information to really be sure. I believe that it's going to be a matter of time before we learn the magnitude of this problem; what causes it and what to do about it.

DR. MOSER: Suzanne?

DR. OPARIL: I think I lie somewhere in the middle. I definitely believe that once diabetes has developed, the same rules apply to antihypertensive treatment as in nondiabetics. As a matter of fact, there are unpublished data from the trialists showing that diabetics and nondiabetics in this huge meta-analysis, with hundreds of thousands of patients, behave the same way. What counts is lowering the systolic BP to get the greatest benefit.

On the other hand, if you're going to use moderate doses of diuretics as a major treatment modality, I think you have a few obligations. Number one, you need to watch the potassium. In ALLHAT, there was a potassium problem. And, many of the patients who were assigned to the diuretic chlorthalidone also got a β blocker to help control BP. That combination may predispose to insulin resistance and diabetes development. Replacing potassium is important. I think we do not know the long-term consequences of new-onset diabetes. We can't dismiss it lightly. That area needs more work, longer studies, and different designs. I think Dr. Sowers knows the mechanism of preventing insulin resistance with ACE inhibitors and ARBs.

DR. MOSER: I had the occasion to look over most of the studies that have been done and I summarized them by looking at the absolute percentage difference between ACEs and conventional therapy, including β blockers. We also compared CCBs to conventional therapy, ARBs and other therapy, and ACEs to CCBs (Table). As noted, the difference between ACE and ARBs

Table. Incidence of New-Onset Diabetes in the 3- to 8-Year Hypertension Treatment Trials

TRIAL	THERAPY	DURATION (YR)	% NEW-ONSET DIABETES		% ABSOLUTE DIFFERENCE
			ACEI	UC OR D/ β -B	
I. ACEI COMPARED WITH CONVENTIONAL RX			ACEI	UC OR D/ β -B	
CAPP	ACEI/ β -B/D	6.1	6.5	7.5	1.0
STOP-2	ACEI/ β -B/D	6+	4.7	4.9	0.2
ANBP-2	ACEI/D	4+	4.5	6.6	2.1
ALLHAT	ACEI/D	4.9	8.1	11.6	3.5
II. CCB COMPARED WITH CONVENTIONAL RX			CCB	UC	
NORDIL	CCB/ β -B/D	4.5	4.3	4.9	0.6
ALLHAT	CCB/D	4.9	9.8	11.6	1.8
INVEST	CCB/ β -B	4.0	6.2	7.3	1.1
INSIGHT	CCB/D	3.5	5.4	7.0	1.6
STOP-2	CCB/ β -B/D	6+	4.8	4.9	0.1
III. ARB vs. OTHER RX			% ARB	% OTHER RX	
VALUE	ARB/CCB	4.2	13.1	16.4	3.3
LIFE	ARB/ β -B	4.8	6.0	8.0	2.0
SCOPE	ARB/UC	5	4.3	5.3	1.0
CHARM	ARB/other Rx	3+	6.0	7.4	1.4
IV. ACEI vs. CCB			ACEI	CCB	
ALLHAT	ACEI/CCB	4.9	8.1	9.8	1.7

Approximate overall difference ACEI or ARB vs. D/ β -B: 2.0%; ACE/CCB: 2.0%; CCB vs. D/ β -B: 1.5%
 ACEI=angiotensin-converting enzyme inhibitor; UC=usual care; D=diuretic; β -B=beta blocker; CAPP=Capotopril Prevention Project; ANBP-2=Second Australian National Blood Pressure trial; CCB=calcium channel blocker; NORDIL=the Nordic Diltiazem study; ARB=angiotensin receptor blocker; LIFE=Losartan Intervention For End Point Reduction in Hypertension study; SCOPE=Study on Cognition and Prognosis in the Elderly; CHARM=the Candesartan in Heart Failure Assessment of Reduction in Mortality and Morbidity; other trial names expanded in the text. Reproduced with permission from Moser M. New-onset diabetes in the hypertension treatment trials: a point of view. *J Clin Hypertens (Greenwich)*. 2004;6:610–613.

and conventional therapy, mostly diuretics and β blockers, is about 2%. ALLHAT reported the greatest difference. There is no question that there is a difference. New-onset diabetes was about 1% less with CCBs compared to β blockers/diuretics. ARBs, about 2%. So, we are talking about something that looks like it's real. Apparently, the use of agents that block the renin-angiotensin-aldosterone system results in fewer cases of new-onset diabetes than with other agents.

But, do these data justify comments in the literature suggesting that the recommendations of the Seventh Report of the Joint National Committee on Prevention, Detection, Evaluation, and Treatment of High Blood Pressure (JNC 7) for the use of diuretics as initial therapy in most cases, or as part of combination therapy be changed? If there are really going to be thousands of cases of new-onset diabetes with "conventional therapy," and if it is proven that they have the same prognosis as established diabetics, should we change our recommendations? I do not believe that we should. Years ago, we had occasion to review the issue of new-onset diabetes in the placebo-controlled diuretic studies.

There was a less than a 1% increase in this entity in treated compared to placebo patients.

Another comment; I agree with Dr. Sowers, I believe that the ACEs and ARBs are improving insulin sensitivity rather than the other agents making it worse, except perhaps for β blockers, which do appear to have a long-term negative effect on insulin resistance. In the Valsartan Antihypertensive Long-term Use Evaluation (VALUE) study, the use of a CCB, which is metabolically neutral, resulted in more new-onset diabetes than the ARB tested. Another point to reemphasize—new-onset diabetes is more common over a 3–5 year period of time in hypertensive subjects than normotensives, regardless of therapy.

DR. BLACK: Those are interesting numbers, but I wouldn't trivialize a 1%–2% absolute increase. If you treated 100 people with a diuretic and one new case of diabetes developed, this would be important. But I don't know how you could tell whether the epidemic of diabetes we're experiencing is due to obesity, which is my guess, or to how many people use diuretics or, especially, β blockers. So, we have a way to go before we understand this. I wouldn't change recommendations because so few people get

a single agent anyway, and an ACE or an ARB as a second drug is very likely to be used.

DR. SOWERS: Now that we've made the full circle, let me come back to something Suzanne said. In the trialists' analyses, the diabetic group had the same benefits from quantitative lowering of systolic pressure as nondiabetics. We have data on that from the UKPDS. If you look at that trial, BP lowering even in the β blocker/diuretic group completely trumped glucose lowering. It was just more powerful. The message I get from ALLHAT, The International Verapamil-Trandolapril Study (INVEST), and the VALUE trial is it's very important to treat systolic pressure early, and get it as close to goal as possible—and JNC 7 says exactly that.

Now having said that, I think we have to get smart enough to use diuretics in most patients. But my guess is that we have to be just a little wiser, we have to watch metabolic parameters, potassium, and magnesium. Probably more importantly is do more definitive studies to show that when you put a diuretic with an ACE or an ARB, you get this great benefit without any metabolic effects. In the VALUE study, a majority of patients were on a diuretic with an ARB. Perhaps beneficial metabolic effects may be noted. We don't use just one drug and no one is saying that we should.

I certainly don't have a solid answer to the new-onset diabetes problem. The one thing I'm relatively confident of, is that treating BP trumps everything else when it comes to high-risk patients such as the diabetic patient. Any subtle metabolic effects are overwhelmed by BP lowering, particularly systolic BP.

DR. MOSER: Your point about metabolic changes is well taken. We should be aware that the people who tended to develop diabetes in the trials were usually obese and had some evidence of the metabolic syndrome—with higher baseline blood sugar levels, etc.—so these people should be watched more carefully. Jim, in the UKPDS, diabetes control wasn't very good in a large number of patients.

DR. SOWERS: Well the differential was not as great as the investigators wanted it to be. That's why we're doing a study in this country looking at a more defined differential to see if there is a reduction in cardiovascular disease from changing HbA_{1c}. We know that it may be more complicated than lowering BP and we have better medications in hypertension. We have medications that definitively work by different mechanisms, whereas with antidiabetic medications, they primarily act on insulin resistance or insulin secretagogue mechanisms. I think you're right about the UKPDS study,

Marv, but the point is, it was a shock to people in the diabetes field to see this tremendous effect of what, at that time, was considered a small BP difference in terms of diabetic outcomes, both microvascular and macrovascular outcomes. After all, a difference of only $-10/-5$ mm Hg resulted in a dramatic difference in outcome.

DR. MOSER: Suzanne?

DR. OPARIL: I agree. I think that the editorials to which you are referring may be focused on the wrong thing. The focus should be control of systolic BP which, in the cases of most older, high-risk individuals involves a minimum of two drugs. Arguing about whether it should be a diuretic, ARB, or ACE first is irrelevant.

DR. BLACK: It seems to me the people who are critical of the JNC 7 recommendations never read them or never read them carefully. That's too bad because they are very clear. If you had certain comorbid conditions or compelling indications, JNC 7 wasn't always recommending diuretics first. We were recommending them as part of at least a two drug combination. This is very consistent with present thinking.

DR. SOWERS: You know, even though I've been a strong proponent of using renin-angiotensin-aldosterone blockers in diabetes, I'm not so sure that you gain much from using one of them compared to a calcium antagonist or a diuretic, particularly over the first couple of years. I think the idea is to get the BP down. When we think about subtleties like albuminuria and insulin sensitivity, maybe some other metabolic effects, those drugs do have an advantage, but clearly, if you look at the VALUE study, if you look at the INVEST study, if you look at ALLHAT, the most important factor is BP control. So even though I still lean a little bit towards recommending ACEs and ARBs for diabetics as first line therapy, I'm a little less adamant about that than I was a couple years ago. I think that where you're going to use two drugs, you should use a drug like a diuretic that will get the BP down quickly and then add something to it. This is just as logical as starting with an ACE or an ARB and then adding a more powerful medication. I'm not so sure that I have the answers I did a couple years ago.

DR. MOSER: Is it fair to summarize this by saying that everyone agrees that there may be differences in the occurrence of new-onset diabetes with different agents, and that the difference may be small? It appears from data that an ARB or an ACE may be beneficial rather than other agents being harmful. At the moment, however,

projections that some investigators are making and suggestions that we change recommendations are premature. Is that fair?

DR. SOWERS: I think that's fair. And the other point I'd like to make, Marv, which we haven't really talked about, is that it's fairly clear that the calcium antagonists are good drugs too. We've kind of glossed over that but the truth of the matter is that the calcium antagonists have fared well in the big trials. As far as I'm concerned, we have three drugs that are very good to use in high risk patients such as diabetics. There are cost differentials, there's no question about that and these should be taken into consideration. Basically I think what we've learned from the last three major trials is that the use of calcium antagonists results in beneficial outcomes.

DR. BLACK: I'd just like to make one point about cost. I agree with everything you said. I don't think we need to change JNC 7 because it allowed for choosing something other than a thiazide-like diuretic for people with certain diseases like diabetes. But the thing about cost that has been bothering me lately is we seem to have no historical perspective. When diuretics were introduced in the 1950s, they were extremely expensive if we adjust for inflation. As data were accumulated, competition came about and they became generic; they became less expensive. So, we really need to understand how the generic drugs of the future are going to work because calcium antagonists, ACE inhibitors, and ARBs are not going to continue to be branded and pricey. In time, they're going to be generic and inexpensive. If we don't study them now and understand how they compare to the other generic and less expensive drugs, we're going to be lost when that time comes.

DR. MOSER: Good point Henry. A comment about the CCBs. There's no doubt that recent studies have demonstrated their value. What do you think about data from the Swedish Trial in Old Patients with Hypertension 2 (STOP-2) that showed that the ACE-inhibitor based program was more effective in terms of myocardial infarctions and heart failure? What do you think about the smaller studies like Fosinopril Versus Amlodipine Cardiovascular Events Randomized Trial (FACET), Appropriate Blood Pressure Control in Diabetes Trial (ABCD), and African-American Study of Kidney Disease and Hypertension (AASK)? Should we still differentiate in cases of diabetic nephropathy? Is there truly a difference in outcome that we should still pay some attention to?

DR. SOWERS: These last few are small trials.

DR. MOSER: Yes they are.

DR. SOWERS: They're small and they are not as well designed as some of the more recent trials. I think their results are negated by studies like ALLHAT, VALUE, and INVEST.

DR. MOSER: Okay. How about STOP-2?

DR. BLACK: Well, STOP-2 is a useful, rather large, trial. But still, when you put all the data together as the trialists have done, what matters is BP, not a particular agent. There is no question that if we were clever enough to be able to estimate what it was we were trying to prevent in an individual patient, we might be able to more cleverly make a first choice, but the first choice doesn't matter as much, since so many people are going to require a combination of drugs.

DR. MOSER: Especially diabetics.

DR. BLACK: Especially high-risk people and diabetics.

DR. OPARIL: And, so many people require statin treatment, which completely changes the equation. I think one thing that we need to remember, even though we're talking about medications here, is the one panacea—increased physical activity and weight loss. If we could get people to do that, all the risk factors would decrease. Lifestyle modification actually is very effective in preventing diabetes.

DR. BLACK: I want to make one comment. I almost have a flashback when we talk about calcium antagonists to the time of Senator McCarthy saying that I have in my hand 20 trials that show how bad calcium antagonists are. We had to respond to it. I don't think there is much basis for that claim at this time.

Enormous amounts of energy went into discussions about that claim, and I certainly hope that it's finally put to rest. CCBs are very effective BP-lowering drugs. They became popular because you didn't have to worry about age or ethnicity. There are some situations where they may not be as effective as other drugs, and some where they are, just like all the other medications.

DR. MOSER: So Jim, for the record, a brief summary of the new-onset diabetes problem, what do we do with it. Do we ignore it or do we wait for further studies? Do we change anything? A final comment.

DR. SOWERS: Well, the NIH is interested in preventing diabetes because it's endemic and epidemic in this nation. It's a huge problem. Over the long run, the costs are horrendous in terms of medical, social, environmental, and political issues. We have to try to prevent people from developing diabetes. Suzanne said the best way

to prevent diabetes is to lose weight and exercise. She's right, there is about a 55% reduction if you do it right, as in the Diabetes Prevention Trial. There are drugs that have clearly been shown to stave off the development of diabetes and to reduce the prevalence of incipient diabetes over a 3–4 year period of time. These include metformin, glitazones, and some of the other antidiabetic drugs. There are retrospective data suggesting that ACEs and ARBs might inhibit the development of diabetes. Where this probably plays more prominently is in patients who have hypertension, but are not yet diabetic, or who have the metabolic syndrome. That's a large group of patients. I think those drugs may have an impact on the rate of development of diabetes. We'll know more definitively when we get the results of two ongoing prospective trials. Until that time, we can't say definitively that this is the case.

In terms of treating hypertension, I think that aggressive treatment, with relatively rapid lowering of systolic BPs—which is the most difficult thing to accomplish particularly in high-risk patients like the diabetic—should be the number one goal. That usually requires combination medications; almost always the use of a diuretic along with one of these other drugs.

DR. OPARIL: I think that was a wonderful summary. It was great.

DR. MOSER: Thank you.

Addendum: A paper presented at the American Heart Association meeting in November 2004 reviewed 14 years of follow-up data of the Systolic Hypertension in the Elderly Study. The study concluded that: 1) diabetes developing during diuretic therapy did not have a significant long-term association with cardiovascular or total mortality; and 2) chlorthalidone-based treatment results in improved long-term outcomes in diabetes. Diabetes related to chlorthalidone therapy has a better prognosis than diabetes at baseline. These new data appear to confirm the opinions of the panelists regarding the continued recommendations for the use of diuretics as one of the preferred medications in the management of hypertension.