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ReachMD
www.reachmd.com
info@reachmd.com
(866) 423-7849

Can Diuretics Prevent Heart Failure?

You are listening to ReachMD, The Channel For Medical Professionals. Welcome to our series focussed on the heart on ReachMD. I am your host, Dr. Matthew Sorrentino, from the University Of Chicago and with me today is Dr. Barry Davis. Dr. Davis is the Guy S. Parcel Chair in Public Health. He is the director of the Coordinating Center for Clinical Trials at University of Texas School of Public Health in Houston Texas. Dr. Davis and his colleagues recently published a paper in circulation, entitled Heart failure with preserved and reduced left ventricular ejection fraction in the ALLHAT trial.

DR. MATTHEW SORRENTINO:

Dr. Davis welcome to the program.

DR. BARRY DAVIS:

Thank you glad to be here.

DR. MATTHEW SORRENTINO:

I thought first we should just give a brief overview of what the ALLHAT trial is. ALLHAT stands for Antihypertensive and Lipid-Lowering Treatment to Prevent Heart Attack Trial. What was the general design and purpose of this trial?

DR. BARRY DAVIS:

Well the general design and purpose was to see if any of the newer blood pressure drugs back in the early 90s were better than the standard blood pressure drug used at that time which was a diuretic and up to that point in time there had been several new classes of drugs that had been developed. One was an alpha blocker, another was an ACE inhibitor and another kind of drug was a calcium channel blocker, and all these drugs had been approved to lower blood pressure, but the key question was that would any of these drugs have additional benefits beyond lowering blood pressure or in other words if you put patients on these drugs and they achieve equivalent blood pressure lowering and if you follow them for several years, would there be any difference in the kinds of serious consequences you get from hypertension such as heat attacks, heart failure, stroke, so the trial was designed to compare these 3 newer drugs to the diuretic, try and achieve equivalent blood pressure over time and then after a period of time, which in our case is about 5 years, see which drug did best at preventing heart attacks and strokes and heart failure.

DR. MATTHEW SORRENTINO:

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So, as I understand the trial, there were 4 groups, there was the active competitor group, there was the chlorthalidone, the diuretic, and there were 3 other groups. What were the agents that were used in the 3 other groups to compare against chlorthalidone?

DR. BARRY DAVIS:

Well, the calcium channel blocker was represented by amlodipine. The ACE inhibitor was represented by lisinopril and the alpha-blocker was represented by doxazosin.

DR. MATTHEW SORRENTINO:

And I would expect that none of these groups achieve perfect blood pressure on a single agent. Where the individuals in the trial able to use agents from the other groups or they had to stay away from those agents?

DR. BARRY DAVIS:

The desire was to get people to stay away from those agents. The study actually provided additional agents that weren't represented by the 4 classes to try and control blood pressure. You are absolutely right in that. There was a good number of people that required additional medication to achieve blood pressure control. Although, there was about 30% that were able to achieve good blood pressure control on just 1 drug. So, in the course of the study, if the blood pressure was not well controlled, they were allowed to go on additional agents.

DR. MATTHEW SORRENTINO:

Now, part of your trial was called the heart failure validation study. Can you tell us a little bit about the purpose of this analysis of the ALLHAT trial?

DR. BARRY DAVIS:

Well the study was designed as a large simple trial which means that we need a lot of patients, study had 42,000 patients, but we also wanted to make this trial done in a real, real setting, out the community, out in physicians offices, and we wanted to make it simple so that a lot of information, detailed information need not be collected. One of the criteria was in determining outcome such as heart failure or heart attacks or strokes. We had established criteria for this and doctors are supposed to follow advice, but they would check a box as to whether these things happened and they will provide some documentation. Before ALLHAT was done, it was known that ACE inhibitors were good at treating people with heart failure. Once they had established heart failure, ACE inhibitors were good at lowering the death rate, but before ALLHAT, people weren't sure about necessarily which drugs might be good at preventing these outcomes of, as I mentioned, heart failure, heart attack, and stroke. Well, it turned out in the course of ALLHAT, it seemed that the diuretics were best at preventing heart failure whether you compared it to the calcium channel blocker, the ACE inhibitor, or the alpha blocker. In fact, the alpha-blocker arm because the study was stopped early because of the higher heart failure rate. There were many people who looked at ALLHAT and thought that our criteria were not stringed in that for heart failure, so we undertook a heart failure validation study wherein we took all the heart failure cases and cut an additional documentation on them and had it blind it to panel of experts and they were able to go through and determine whether people had certain symptoms and signs. We then took all that information and ran it though an algorithm based upon our criteria for heart failure, but also on algorithm defined by the Framingham study for heart failure,

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and it turns out that the number of heart failure cases was reduced a little bit because there was probably some noise in the system, but the treatment differences that we noted between the drugs remained intact whether we use what the physicians down the community said, whether we used our criteria, whether we used the Framingham criteria. So, the patterns were made exactly the same in that the diuretic was best at preventing heart failure and then perhaps the ACE inhibitor came next and they both beat out the calcium channel blocker and the alpha-blocker.

DR. MATTHEW SORRENTINO:

One of the distinctions you made in the trial was between heart failure with preserved ejection fraction and heart failure with reduced ejection fraction. Was there a particular definition of ejection fraction that you used to divide this group?

DR. BARRY DAVIS:

Yes, we used the cut point of 50%. This concept of preserved and reduced ejection fraction has been around for a little while, little bit older than that. It's been the concept of systolic heart failure versus diastolic heart failure and the thinking now a days is to not call at that, but to look at how well the heart pumps blood and to base it upon the ejection fraction and this can be measured before one enters the study or at the time they have heart failure, but we have this cut point at 50% with certain consensus among the panel of experts who would participate in other heart failure studies. Sometimes 40% is used, sometimes even 45%, but 50% seemed very reasonable.

DR. MATTHEW SORRENTINO:

If you are just joining us, you are listening to our series Focus On The Heart from ReachMD, The Channel For Medical Professionals. I am Dr. Math Sorrentino and I am speaking with Dr. Barry Davis from Houston Texas for talking about the ALLHAT trial and the prevention of heart failure in that trial.

Lets talk specifically about that group of patients who had preserved ejection fraction. Do these patients also have benefit from the chlorthalidone over the other agencies in the trial.

DR. BARRY DAVIS:

Oh! yes, in fact, this was the clear winner for people who have heart failure with preserved ejection fraction. The chlorthalidone, a diuretic, beat out the other 3 groups. With reductions in risk of, like I say, anywhere from 20% to 30%.

DR. MATTHEW SORRENTINO:

With a particular patient type that seemed to typify this patient with preserved ejection fraction and they've got the benefit.

DR. BARRY DAVIS:

As in the case in our study as in past studies, this condition of heart failure with preserved ejection fraction seems to be more prevalent among women than among men, and I think at our study it was on the order of over something like 56% were women with heart failure

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with preserved ejection fraction whereas much higher number for reduced ejection fraction among men.

DR. MATTHEW SORRENTINO:

Now, I am looking at the patient's with reduced ejection fraction. Did any of the other groups, the lisinopril, the ACE inhibitor, the calcium channel blocker or the alpha-blocker also show any benefit if your ejection fraction was reduced.

DR. BARRY DAVIS:

Yes, in the case of heart failure with reduced ejection fraction, the ACE inhibitor, lisinopril, and the diuretic chlorthalidone seemed to be equally good at preventing this kind of heart failure. They beat out the calcium channel blocker and the alpha-blocker.

DR. MATTHEW SORRENTINO:

I recall when this study was first coming out and the alpha-blocker arm was stopped prematurely. There was some thought that may be the alpha-blocker caused heart failure. Is there any way to tell from this trial if chlorthalidone and lisinopril is actually preventing things or is it that the other groups cause more heart failure? Can we tell that from this type of data?

DR. BARRY DAVIS:

Now that's a prominent active control trial to combination of one has no effect and the others benefiting or the other one has no effect and the other one is harmful or could be a combination of the two. Without a placebo arm, it's almost impossible to tell. One can look at other studies where there was placebo arms and trying guess, I mean, the closest thing was the study called the Systolic Hypertension in the Elderly Program where it was just chlorthalidone against placebo and they didn't measure the ejection fractions, but the heart failure reduction rates were in the order of 15% compared to placebo. So, it's still not quite clear whether there was a combination of benefit, arm, or either one alone.

DR. MATTHEW SORRENTINO:

That's interesting that in this trial and in the SHEP trial that you just mentioned the systolic hypertension and the elderly program that chlorthalidone was the thiazide diuretic that was chose. It seems in clinical practice we don't use that diuretic as much. Many of us use hydrochlorothiazide. Do you think this could be a class effect of all the thiazides or is there something magical about chlorthalidone?

DR. BARRY DAVIS:

Well, there has been a lot of controversy since ALLHAT came out about this and we didn't know how to try to explore this in great detail. My feeling is that there may be something special about chlorthalidone, but one of the problems is chlorthalidone and hydrochlorothiazide are not equivalent in terms of that dosing. It's sort of about 2 to 1 from all the literature we can see and that if a person is on 12.5 mg of chlorthalidone, the equivalent dose would be 25 mg of hydrochlorothiazide or if you are on 25 mg of chlorthalidone, then you should be on 50 mg of hydrochlorothiazide. And lot of treatment in the community with hydrochlorothiazide may not have gone up to the higher levels that we would have been equivalent in the levels that we used in these trials of chlorthalidone. One of the other problems is that that chlorthalidone is not as widely available as you said as hydrochlorothiazide. People are talking

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about doing further studies to try and compare them. If you look at the big trials where the proper dosing of hydrochlorothiazide and chlorthalidone were used, they seemed to have pretty equivalent results. Some of the new trials have a new sort of the equivalent doses for hydrochlorothiazide as one would use for chlorthalidone.

DR. MATTHEW SORRENTINO:

One of the concerns I think a lot of people has had about this trial. Could the diuretic just have been masking symptoms or preventing symptoms, but really had no impact on the heart. In another words if were preventing fluid retention, patients may not get breathless or may not have edema, so they may not get diagnosed with heart failure. Can we tell from this trial if the diuretic worked only because it kept patients more on the dehydrated side or do you think there might be some direct cardiac effect lowering filling pressures, for example, or changing remodeling something like that?

DR. BARRY DAVIS:

I have 2 things to say about that. People of voice put up their argument, but the problem is, is that in all who have diagnosed heart failure, you have to have those symptoms and signs, so if you use a drug that prevents those symptoms and signs and how can you have the condition. So, when you call that masking or unmasking you are not having the condition. If there was another definition of heart failure that didn't use symptoms and signs then one could argue about that. The other thing is we have done further analysis. Its not in this paper, its been presented and hope to get published soon. Looking at the people who had heart failure immediately after the study started to see what kind of medications that were on before the study started, what kind of medications that were randomized to when the study started, and to see if there is any interaction between the type of treatment aide been on before hand and the treatment they were assigned in terms of resulting in heart failure and we didn't find anything. That doesn't mean that still may not have been something, but we've looked a lot at this question and nothing has really jumped out _____ oh! yeah that is true. It doesn't seem to be the case that we can see.

DR. MATTHEW SORRENTINO:

So it seems that we have more data suggesting that diuretics should still remain first-line therapy for hypertension with this fairly robust finding that heart failure is prevented. Do you think this data supports that it especially in our elderly female patients we should be reaching chlorthalidone before some of the newer agents.

DR. BARRY DAVIS:

Yes, I think that they should and we have always may be argument that lot of people do need to be on 2 drugs, but at least 1 of the drug should be a diuretic. In our study, and remember ALLHAT had a very large population and it was very diverse and some of the results were very very robust. Very good at lowering blood pressure, it's very good at preventing heart failure compared to the others and we have looked at these as I said along many criteria, not only what the investigative setting _____ but using stricter criteria such as in Framingham, the same results held up and its also good at preventing strokes, so it seems that diuretics have been used as a name say of therapy for probably 50 years and they are still around and they are still cheap and they are still very good treatment for high blood pressure.

DR. MATTHEW SORRENTINO:

Well, I want to thank Dr. Barry Davis, who has been our guest. We have been discussing the prevention of heart failure in the ALLHAT

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trial where the chlorthalidone, arm of the ALLHAT trial, seemed to be the winning drug in preventing heart failure, both in patients with preserved and reduced ejection fraction.

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