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Results of ADVANCE Diabetes Trial

GLYCEMIC CONTROL IN CARDIOVASCULAR DISEASE

You are listening to ReachMD, The Channel for Medical Professionals. Hi, this is Dr. Thomas Bersot, President of the National Lipid Association and I would like to welcome you to Lipid Luminations hosted by Dr. Larry Kaskel and presented by the National Lipid Association.

Welcome to Lipid Luminations, I am Dr. Larry Kaskel, your host and joining me today is Dr. Eliot Brinton, Director of the Metabolism Section of Cardiovascular Genetics and associate professor at the University of Utah School of Medicine.

DR. LARRY KASKEL:

Dr. Brinton, welcome to Lipid Luminations.

DR. ELIOT BRINTON:

Thank you very much, glad to be with you.

DR. LARRY KASKEL:

I would like to start out talking a little bit about glycemic control in cardiovascular disease. It has been in the news a lot this year with the ACCORD trial, the ADVANCE trial, and VA Diabetes Trial. Could you talk a little bit about what we learned from the ADVANCE trial?

DR. ELIOT BRINTON:

Let me start with ACCORD, as that was the one that came out first. ACCORD was the one that hit the news rather strongly, rather strikingly. There was an announcement made that the trial was being stopped early and the reason it was being stopped early was little bit of a surprise and that was an increase in both total mortality and cardiovascular disease mortality with the intensive controlled arm and this was not what was anticipated. The whole reason for doing these 3 trials that you mentioned was the considerable amount of evidence that tighter glycemic control had a favorable impact on cardiovascular disease. So, we were really brought up short. I think with this announcement that came from the Data and Safety Monitoring Board of ACCORD where they just felt it was unethical to continue

the aggressive treatment arm of this trial because of the increasing total mortality and cardiovascular disease mortality. Now, you mentioned the ADVANCE trial, the ADVANCE trial was another large trial with a somewhat similar design, but there are some differences between getting into a <_____> that I think may be critical in terms of understanding why the outcome seemed to be different and the ADVANCE trail actually they presented an interim analysis shortly after this surprise announcement from the ACCORD trial in which they stressed that their results were not the same, that they did not have an increase in total mortality nor an increase in cardiovascular disease mortality. So, the ADVANCE trial was almost completed, but they did have a look at this, they had been following that very question throughout the trial so they were able to just pull up what they had looked at in their most recent interim analysis and so it was, I suppose, reassuring in a sense to have the ADVANCE as a counterpoint to the ACCORD, but left everybody very much up in the air until we then went on to have the full presentations of those 2 trials plus a third trial at the American Diabetes Association meeting. So, there really were these 3 trials, the ACCORD hitting first, the ADVANCE second and then the VA Diabetes Trial is the one that was first presented in June and actually still has not been published in full manuscript form whereas these other 2 we know just a little bit more about that, but all 3 of them together, I think, are needed to give us a balanced picture of this question because it is a very, very complicated one and may be somewhat troubling. I will have to say that for those of us to do both athero-prevention and diabetes treatment, it was a little bit disconcerting to see how this came out, but I think perhaps we can see our way through this and I can, may be, weave for you the right picture that will may be get us back out of the woods here.

DR. LARRY KASKEL:

Well, that would be nice to kind of elucidate the findings. Let's start with the ADVANCE trial. How many people were in that trial compared with the other trials. How big was it?

DR. ELIOT BRINTON:

The ADVANCE trial was very large. ADVANCE and ACCORD were all around the 10,000 range in terms of the number subjects. So, as big as it gets in terms of diabetes trials and for that reason, I think these 2 trials carry a little bit more weight. Now, the VA trial was much smaller. It only had a little over 1700 subjects, but as I said a minute ago, I think each one of these gives us an interesting perspective and a valuable perspective on the same issue and I think if we put the 3 of them together we have really a 3-dimensional view of something that otherwise would be very, very puzzling and very troubling if we had just either one of the 2 larger trials, either the ACCORD or the ADVANCE.

DR. LARRY KASKEL:

And what about the timeframes of these studies? How long did each of them continue and were they long enough trials?

DR. ELIOT BRINTON:

Well, that is one of the critical questions. It's perhaps one of the key takeaways as exactly how long does it take to see benefit and let me just back up 1 second before I get to that question because I think something we need to get into before we look specifically at the question of the duration is the question of exactly how were these trials set up. All 3 trails were comparing "intensive" versus "standard care," but in each trial, those terms had very different meaning. In ACCORD, the baseline A1c was 8.1%. The intensive treated group had a goal to get less than 6. Now, we don't hardly ever talk about getting diabetics to less than 6 because it is so difficult to do, but the rationale was that is the non-diabetic range and <_____> diabetics and brought their A1cs in a non-diabetic range, wouldn't that be wonderful. Well potentially it might have been wonderful, but it turns out that it wasn't so much and it turns out it was very, very hard to do. They felt short of that goal. The average A1c in the intensively treated group despite really heroic treatment was 6.4%. The standard treated arm of that trial had a 0.6% drop down to 7.5%. So, now keeping that in mind, let's go on to ADVANCE, ADVANCE started at 7.2%, so almost a 4% is point below ACCORD and for them the intensive goal was less than 7 and they did achieve that, they had a 6.5.

So, their goal was much higher, but the achieved A1c was almost identical to that of accord and yet the drop in A1c was much less; in ACCORD, it was about 1.7% drop whereas in ADVANCE, the intensive treated group had only a 0.7% drop so much less of a drop and yet the achieved A1c was almost the same and then the standard treated group had 7.0, which was actually lower than it was in the standard treated group with ACCORD, but remember that they started out much lower, so they had really a trivial 0.2% change in their A1c. At VA Diabetes Trial, they confuse things a little bit further, was quite different. It also had a goal of less than 7%, but they started out at 9.5%. So, higher thankfully than the average diabetic patient in the US, but not necessarily higher than average in a given population such as the veteran population and they didn't really, I mean, they excluded people with normal A1c to begin with, but they didn't go out of their way to get a high A1c, that's just what they found and I think a lot us will have patients in the 7 range, the 8 range, and the 9 range at baseline. So, you have 3 trials here in 3 different starting ranges. I think it's actually perhaps beneficial, although we are not quite sure fully how to take advantage of this baseline spread and then the on treatment A1c in the VA Diabetes Trial was 6.9, which was a little higher than 6.4 and 6.5 of ACCORD and ADVANCE, but if you look at the change from baseline, they actually had the greatest drop. They had a drop of about 2.5 points and then the standard treatment group had an 8.4%, so by far higher than the other standard treated groups, but noticed that they had the greatest drop and they had a little over 1-point drop in their standard treatment group. So, some very, very interesting difference and we are not quite yet certain what to make it out, but that has to be kept in mind as we interpret these studies because otherwise I think it's rather difficult to make sense of them. Another thing that was somewhat different is the types of medications used all 3 of them, all 3 of the studies used kind of a toolbox approach. There were several different medications from which to choose. There was no randomization of the actual treatment, but rather just randomization of the intensity of the treatment. In the 2 stateside studies ACCORD and the VA Trial, there was much more use of thiazolidinediones, the majority of both of those trials used TZDs whereas in the ADVANCE trial, which was not done in the US, only 17% and 11% of the intensity in standard treatment arm received that. So, there is that difference, although it turns out that may not have made as much of a difference as you might think. There was a lot of use of metformin, pretty extensive use of sulfonylurea, especially in the ADVANCE trial. Over 90% of the patients in the intensive treatment arm had sulfonylureas, a little bit of incretin use in the ACCORD and the VADT, a lot of insulin use - especially in ACCORD and VADT, a little bit less so in ADVANCE. So, there are some interesting differences in terms of the types of medications used, although it's rather hard to draw firm conclusions in that regard because there was quite a bit of similarity in the use of these drugs between intensive and standard treatment in each of the 3 trials. So, very, very complicated issue and we are, I think, just beginning to get to the bottom of. You mentioned the issue of duration of the trial, the longest of these 3 trials was actually the VA Diabetes Trial and perhaps not coincidentally, it had an average duration of over 7 years and whereas ADVANCE was shorter and ACCORD was shorter still, they were in the neighborhood of 3.5 years or so for ACCORD, now that was stopped a year or so early because of this finding of excess mortality. So, they had actually planned to go little bit longer in ADVANCE, went about 5 years. So, one of the questions is duration of treatment and it turns out that the longer the study went, the more positive it was. The VA Diabetes Trial still did not have any statistically significant reduction in cardiovascular events in the intensively treated group, but they had a trend in the right direction much more so than either ADVANCE or ACCORD. The other question is what about any longer-term followup, may be even after you have stopped an intervention and it turns out that just a couple of months ago, there was a followup publication from the UKPDS, a much earlier trial and they found that in extended followup in the UKPDS, there was continued benefit as far as cardiovascular events. Cardiovascular events trended somewhat lower during the initial period of intervention in the UKPDS, which was either with insulin, sulfonylurea, or metformin. In the case of metformin in the obese patients, there actually was a significant reduction in cardiovascular events. In case of insulin and sulfonylurea, not significant during the initial trial, but with extended followup to about 18 years or so, they found that the cardiovascular disease events continued to separate and actually became statistically significant. So, there is something we call a legacy effect or metabolic memory where more intensive treatment with glycemic control seems to have somewhat sluggish uptake that may take 5 or even 10 years to see the initial benefit, but then once you have seen that benefit and you had a long enough intervention, then even if you stop the differential between the 2 groups, there will continue to be a spread between the 2 groups as far as actual cardiovascular disease, that also has been seen in type 1 diabetes and DCCT, the followup for that was called EDIC, that was also published fairly recently and in the long-term followup of that intensive treatment and type 1, they saw the same thing. Borderline benefit by the end of the trial, in fact in the first few years of the trial, it looked actually a little bit adverse and then as it went out to 10 and 15 and even 20 years, that's when they saw significant reduction in cardiovascular event. So, it's kind of like your 41K, your investment in the stock market. If you are expecting a quick turn around and you only get a 5-year time whenever, you may lose money. If you can be patient and go to 10, 15, 20 years, you are pretty much guaranteed to see a benefit. So, in terms of glucose control and cardiovascular disease, I think the single most important takeaway is don't be in too big of a hurry. Another very important thing that came out of the VA Trial was that there seemed to be a striking difference in benefit or harm from the intensive treatment based on the duration of diabetes. They had everywhere from newly diagnosed diabetics up to individuals, who had diabetes for 15 and 20 years and they found that up to about 12 to 15 years, the more intensive treatment was beneficial for his cardiovascular events whereas if you go beyond that time window, then it was actually harmful. So, early treatment relatively early in the first decade or so and relatively intensive, it may be not overly intensive, remember the one study that showed the definite harm was a study where they

were actually trying to beat these people below 6%, so may be there is a takeaway there, don't be quite so aggressive, but if you start early and you have a more gentle and more reasonable and more realistic approach to intensive control, that is you are trying to get below 7, then chances are you are going to see benefit whereas if you are being too aggressive or if you don't have more than say may be 3 or 4 years, may be don't see the benefit yet, but starting at 5, 6, 7 years, you will see the benefit and going out to 10, 15, and 20 years, you probably are going to see even more benefit. So very, very interesting situation with these 3 trials, we are still trying to piece it together, awaiting for some followup publications from ACCORD and ADVANCE, we are awaiting for initial publication with VA Diabetes Trial. We are learning that lipid control was very important, blood pressure control very important, but the final answers are not yet in.

DR. LARRY KASKEL:

Dr. Eliot Brinton from the University of Utah School of Medicine, thank you very much for coming on the show.

DR. ELIOT BRINTON:

Thank you very much. I have really enjoyed it.

DR. LARRY KASKEL:

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