

## FLORIDA DEPARTMENT OF HEALTH

**Moderator: Natalie Gibson**  
**December 8, 2004**  
**11:00 a.m. CT**

Operator: Good day, everyone. Welcome to this Hypertension and Diabetes Conference Call. Today's call is being recorded.

For opening remarks and introductions, I would like to turn the conference over to Natalie Gibson, Program Epidemiologist and Evaluator for the Florida Diabetes Prevention and Control Program. Please go ahead.

Natalie Gibson: Thank you. Good afternoon.

Continuing with our series of audio teleconferences, the Florida Department of Health, Bureau of Chronic Disease Prevention and Health Promotion, and the Diabetes Prevention and Control Program welcomes Dr. Errol D. Crook, who will discuss the topic of hypertension and diabetes.

Dr. Crook joins us from Wayne State University School of Medicine in Detroit, Michigan, where he is an Associate Professor and Acting Chairman of the Department of Internal Medicine.

He holds a B.A. in Chemical Engineering and an M.D. from Columbia College in New York. Dr. Crook completed his residency and Nephrology Fellowship in Birmingham, Alabama at the University of Alabama.

He is the former President of the American Federation of Medical Research, member of the Scientific Advisory Board of the National Kidney Foundation, Associate Editor of American

Journal of Medical Sciences, and is involved as a reviewer or editor for several other journal publications. He is also the Principal Investigator on a National Institute of Health funded study on the mechanism of excess cardiovascular disease in patients with chronic kidney disease.

At this time, I ask that everyone please refer to the program syllabus. Continuing education credits have been approved for the following healthcare professionals; nurses and dietitians, the Big Bend Area Health Education Center has approved this program for 1.5 contact hours. The nurse provider number SBN2654. This is not a national provider. Nurses and health educators in other states, states other than Florida, must request approval from the professional boards and their States. All CE credits will be reported to Florida's CE broker monitoring system. Nurses who want to receive CE credits must complete the appropriate CEU paperwork with the correct license number and legible name and address.

The Commission on Dietetic Registration has approved this program for nationwide dietetic continuing education credits. CPEU level three, 1.5 major session, topic code CL0312.

Dietetic practitioners who are not in the PDP process should sign and return the CDR Commission on Dietetic Registration Prior Approval CPE reporting form.

If there are no RDs or DPRs in attendance please return the reporting form and indicate no RDs, DTRs attended, at the top.

Dietetic practitioners who are under the professional development portfolio should not sign the CDR Prior Approval CPE reporting forms. These individuals should sign-in on the RD, DTR, PDP education program sign-in with the Florida Diabetes Prevention and Control Program logo at the top.

In addition, these individuals should record this activity on the step four learning activity log.

Please read the flier attached to the CDR form for more information.

General attendance certificates will automatically be provided for all participants. Dieticians will be provided attendance certificates either directly through CDR or to the dietician base on the program.

Nurses will receive CEU certificates approximately four weeks on the receipt of complete, legible paperwork. Paperwork received after December 15th or paperwork with incorrect or illegible names and license numbers will not be eligible for CEU credit.

All participants should have already completed the pretest. In addition, each participant needs to sign-in on the participant attendance sheet, complete the evaluation form, and pertinent CEU paperwork.

Each site administrators should send in the sign-in sheet and completed form to Natalie Gibson, Florida Department of Health, 4052 Bald Cypress Way, Bin # A18, Tallahassee, Florida, 32399, or fax to 850-245-4391 by December 15th. It is not necessary to fax and mail your forms.

CE credits will not be issued to participants who have not signed in, provided their license number, and legible address, and completed the required forms by that date.

Dr. Crook, I will now turn it over to you.

Dr. Errol Crook: Thank you, Natalie.

I am happy to have the opportunity to speak to everyone today on this most important topic. I thank Natalie for that gracious introduction. I will add that I am also a Staff Physician at the John D. Dingle VA Medical Center and an employee of the Federal Government.

As we move forward, I will go through the slide presentation, and I am told it's been made available to everyone. And we'll try to stay on track so that we all are looking at the same thing.

As we go to slide two here, just to sort of set the scope of the problem. And this is the prevalence of diagnosed diabetes in the United States. I hope you all have it and are able to see it in a color version. Coming off of this year's recent election we got used to a lot of red and blue. And we see a lot of red and blue on the slide, in looking at prevalence of diabetes in 1991, with red being a 4 to 6 percent prevalence in any particular state, and blue being a 7 to 8 percent prevalence.

And you'll notice over a decade that the prevalence rates have drastically increased, and, in fact, you'll see prevalence rates, including the state of Florida hosting this event, with prevalence rates of greater than 10 percent of diabetes and their general population.

I should also mention that these prevalence rates would mirror what you would see if this slide were showing data for obesity, for example. And in many cases, it would mirror this for hypertension. And it's just that the timeframes for hypertension would have been moved back 30 to 40 years, as we became much more aware of that disease quite awhile ago.

So we move to the next slide, which will be slide three, we have the prevalence rate according to race and ethnicity, and which gives us some indication of the groups that may be, or not may be, but are at higher risk for the disease. And clearly, the non-Hispanic blacks, Hispanics, and native Americans are at significantly higher risk for diabetes than non-Hispanic whites.

However, the overall prevalence rates as shown on the previous slide and on this slide remain incredibly high with upwards of one out of every 10 people, almost, that are in the country, having diabetes, and, therefore, putting really the rest of the country of the adult population at risk.

As we move to the next slide it sort of shows how these prevalence rates have increased for both men and women over the course of the last decade, or so. And you notice that really started from the mid-90's onward that the curves really moved from being relatively flat to having fairly steeper slopes of increase for diabetes. And, again, this trend would, is basically paralleled by the increased rates of obesity that are seen in the country at this time.

Now, when we move to the next slide it gives us some ideas about the natural history of type 2 diabetes, and this slide and a few of the following slides are going to be dealing with that and help us to understand this important link between diabetes and hypertension, and the coexisting illnesses.

So, in -- at the time someone has their diabetes developed, and notice I did not say the word diagnose. When I said developed, would be say year zero is shown on the bottom graph, you see at that point lots of things have already started to happen. For example, insulin levels have already started to increase and some resistance has already started to develop for the previous 10 years if not more prior to the time when they may become clinically a diabetic which would be manifested by an elevation in fasting or postprandial glucose.

So, particularly in the type 2 diabetic which is 90 percent or more of all diabetics in this country, the process that are involved in leading to some of the things we're going to talk about today, such as cardiovascular disease, and vascular dysfunction, are operative well before the time of the disease being clinically apparent.

And then, we add on top of that the fact that in many cases diabetes is not diagnosed until in some cases five to 10 years after it actually is clinically present, and it moves someone along this timeline, some cases 20 years, of having insulin resistance and elevated glucose levels, doing their dastardly deeds to the vasculature and to the target organs.

We've talked, as we move to the next slide, it demonstrates this continuum where we, and particularly in the type 2 diabetic where we have insulin resistance developed for a multitude of reasons and a lot of investigators out there, including myself, are looking at this.

And it develops over time, it gets worse, leading eventually to elevating those blood levels impaired glucose tolerance and then type 2 diabetes. While the type 1 diabetics typically start with the impaired beta cell function from auto immune destruction, and they end up with insulin resistance and impaired glucose tolerance and then type 1 diabetes, with everything happening from that point forward really being very similar between the two groups.

The organs that are involved to produce these metabolic abnormalities are shown on the next slide, which are the pancreas, the liver, and the skeleton muscle. And as we'll see as we go through the talk, the relative import of the, particularly the skeleton muscle and the adipose tissue to build raw development and later treatment of insulin resistance. And, therefore, vascular disease, is very important. So, it is a multi-organ disease in both its effects, as well as in its patho-physiology.

And the next slide, is now slide number eight, demonstrates that insulin resistance carries with it associated, several associated conditions. I'd like to point out that many of these conditions are in and of themselves independent risk factors for cardiovascular disease, such as hypertension, such as dyslipidemia, such as obesity, particular central obesity, and such as things like the atherosclerosis being one of the just clinical results of this constellation of events.

So, the insulin resistance that is associated with diabetes is very important, and that it is likely to be in many respects directly responsible for the very high rates of hypertension seen in this population. In addition, in this instance resistance is responsible for the very high rates of cardiovascular disease as demonstrated on the next slide and association of insulin resistance with the cardiovascular risk factors and the metabolic syndrome, which is now gaining in, we recognize this importance as we address these diseases in patients, have come to the forefront, we see an insulin resistance is one of the underlying themes and foundations on which this increased cardiovascular disease seen in diabetics is built. And on this foundation you have the many processes ongoing, such as increased inflammation, increased intra vascular thrombosis, lead into increased atherosclerosis, and unstable plaque.

Prior to getting to those points of increased atherosclerosis relief events typically lead to hypertension as one of its most common clinical correlates. And this same point is made, again, on the next slide, it's showing that this continuum from having insulin resistance, impaired glucose tolerance, eventually to cardiovascular impact, with the most severe being death, or the significant complications of diabetes such as blindness, renal failure, coronary heart disease and amputation, are really go along and continuum.

And the fact remains, as we stated earlier, that we get involved as healthcare providers often times when we are very far along the continuum. In fact, probably three quarters of the way along this time line is shown here. And aggressive intervention at this point with blood pressure control is probably the most important thing we can do to prevent those significant disabling complications that I mentioned.

I think the most important thing that we can do is to try to intervene as early in this timeline as possible, with preventative factors, and doing that requires that we understand the several risk factors out there for this disease process, and understanding that hypertension, in fact, is one of the strongest risk factors for diabetes tells us that when any patient with hypertension, diabetic, or

non-diabetic have got aggressive intervention and prevention of long-term complications is of the up most importance.

And for the next few slides we're going to turn our attention to hypertension in and of itself. This is a disease process that had the attention of the healthcare providers and investigators worldwide, but particularly in this country, for decades. I think diabetes and obesity, and dyslipidemia really haven't received this type of attention really until the last two decades. And the reason being is that, you know, five or six decades ago we did not have extremely high rates of hypertension, of obesity or diabetes, and it was hypertension that was causing the significant impact on cardiovascular disease at that time.

And with a very focused effort nationally on hypertension awareness, treatment and control, there's been considerable gains made in this area. And this slide, which is slide number 11 of the group, demonstrates that when you compare data from the National Health and Nutrition Examination Survey from the 1970s to data taken about a decade later that the awareness of hypertension significantly increased, the treatment of hypertension significantly increased, and the control of hypertension significantly increased.

However, when you look now, as we go forward, over the last two decades, the awareness, in fact, has decreased, the treatment has remained at about the same levels, and control has not significantly improved either. Such that with regards to this cardiovascular risk factor which is arguably of the most import with regards to cardiovascular death, we really have not made significant gains, and built upon that earlier foundation that was built.

The important number, I think, for all of us to remember here is that 31 percent controlled, from 1999, 2000 which was based on JNC 6 criteria, and we'll be talking about these criteria as we go through the talk. But if only 30 percent of patients are at control, and we really are not doing the job we need to do in order to reduce the affects of hypertension on cardiovascular outcomes.

And the most important take-home message is that is controlled, not necessarily treatment that is most importantly reducing these outcomes as particularly true in the diabetic population.

There are several factors out there that affect the prevalence rates of hypertension, and you notice that many of these are the same factors that affect the prevalence rate for diabetes. And diabetes itself is at risk factor for a very strong risk factor for hypertension, therefore, you see that the link between these two diseases is very, very strong.

And as we go to the next slide, I'm sorry, which is now slide number 13, we talk about the metabolic syndrome which has definitely gained a lot of attention over the course of the last five years as it is a syndrome that pulls together several of the risk factors for cardiovascular disease together.

And as you can see, that hypertension is a strong part of that, as well as insulin resistance, the obesity that you see associated particularly with type 2 diabetes, and in fact, diabetes, itself, being the most severe form of insulin resistance is a part of this syndrome. And it is clear now that patients who have the metabolic syndrome are at higher cardiovascular risk than those who do not.

It has also been established that amongst all these factors listed here that go into determining whether or not someone has metabolic syndrome, the factor that is the most commonly seen across all groups is hypertension.

So, on the next slide, which is now slide 14, we start our conversation specifically regarding hypertension in patients with diabetes. It is -- hypertension is very, very common in the type 2 patients. At the time, all type 2 diabetic patients have their diabetes diagnosed. At least 40 percent of them already have a diagnosis of hypertension. I think in certain populations, for example, in African-Americans that number is actually significantly higher, probably in the range

of 60 to 70 percent of African-Americans who are diagnosed with type 2 diabetes will have hypertension at the time their diabetes is diagnosed.

When you look at patients with type 2 diabetes and nephropathy. And this does not necessarily mean reduced kidney function but it means evidence of urine and protein leak consistent with diabetic kidney disease, up to and over 80 percent of these patients will have hypertension. And in our clinic population, and I do not show the data here, but we published this in a few data sets over time, when you have patients with established nephropathy, i.e., and a decreased glomerular filtration rate established proteinuria, you're talking 97 percent of those patients will have hypertension, as mentioned in the last bullet there.

As we go to the next slide, it is now slide number 15, we have outlined here the criteria for the classification and management of blood pressure for adults from the Joint National Committee on the Detection, Treatment, and Evaluation of Blood Pressure. JNC 7, which came out now about one-and-a-half years ago.

And with this iteration of the JNC reports they established normal blood pressure to be less than 120 over 80, and that's very important for us to understand. It is, you know, what we used to call that was optimal, and now we want to use stronger language and call this normal. It is important to understand that if you start with a blood pressure of approximately 115 over 65, that for each 10 millimeter mercury increase in your systolic blood pressure, and 5 millimeter mercury increasing your diastolic blood pressure, that your risk for coronary heart disease doubles. So 120 over 80 and less is, in fact, normal.

And the group now that was somewhat of a controversial definition, but a group between 120 and 139 systolic, and 80 and 89 diastolic are now called pre-hypertension. And so by doing this overnight they sort of created a group of about 20 million to 50 million people depending upon which source you read, with a new label, that being pre-hypertension.

And this was done, though, based on data from Framingham, and a couple of other cohorts that show that if you were, particularly if you were 55 and over, and you had a systolic blood pressure of 135 to 139, and a diastolic of 85 to 89 that 70 percent of those patients would have high blood pressure, or a diagnosis of hypertension within four years. Therefore, by bringing in the pre-hypertension diagnostic classification we're bringing attention to the fact that these people are at high risk of developing hypertension.

Stage 1 hypertension is 140 to 159, systolic at 90 to 99, diastolic in stage 2 is greater than 150 systolic and greater than and equal to 100 diastolic. And on the next slide, which is now slide 16, we want to talk a bit about chronic kidney disease and this epidemiology, as this is, as kidney disease is actually one of the biggest morbidities and causes of mortality in the diabetic population.

So, chronic kidney disease is present in probably 11 million, if not more people, in the United States. And by far the vast majority of these people are not people who require dialysis or kidney transplant. However, that number continues to grow exponentially with over 370,000 persons requiring transplant or dialysis in the year 2000.

And it's important for us to understand that by some of the parameters, the most common parameter that we would use to determine whether someone has chronic kidney disease is by looking at the serum creatinine, but using that in and of itself is not adequate to determine whether or not someone actually has normal renal function. There are a lot of factors that go into making that determination, and, therefore, we are, and the renal community now recommend using the GFR. And we will be talking about that in a couple of slides.

When you look, and the reason that kidney disease is very important for us to discuss, and talk about diabetes and hypertension is shown on the next slide, which is slide 17. The first quadrant,

first group of four columns are the basically incidence rates for in-stage renal disease among, with the primary diagnosis of diabetes as the cause of the kidney disease among whites to the left, African-Americans the second column, native Americans the third column, and Asian Americans in the fourth column. And you would note that African-Americans and the native Americans have significantly higher rates four to five times those of Caucasians in this country for diabetic nephropathy.

The set of four columns to the right of that are the same numbers for hypertension as a primary cause of kidney disease, and you will note that African-Americans have up to six times to seven times the rates of hypertension, hypertensive nephrosclerosis as the cause of end stage renal disease as Caucasians. And it is interesting to note that, in fact, diabetes was, is now the number one cause of end stage renal disease in this country when you look at all causes of end stage renal disease.

It was the number one cause of end stage renal disease in all ethnic groups except African-Americans, starting as far back as the mid '80's. And African-Americans because of their such high prevalence rates and severity of hypertension, diabetes did not become the number one cause of end stage renal disease in that group until about 1997. But as you can still see that these two disease processes are still sort of neck-and-neck with regards to their cause of end stage renal disease, particularly in African-Americans.

Now, as I mentioned earlier, and we go to the next slide, we do not like to simply use the creatinine as a measure of kidney functions because it -- there are several factors that also impact the true determination of kidney function. And, therefore, we in the nephrology community, are advocating the use of a glomerular infiltration rate, which we think should be calculated on every patient.

And there are a multitude of methods by which one can measure it out there, and that are readily available. Some are easier calculations than others, but in this day and age of handheld PDAs, et cetera, with the easily used calculators, it doesn't make a whole lot of difference which one you use, and they're all fairly facile.

When, in fact, we're also advocating that all clinical labs around the country don't just report a creatinine for a patient, but they also go ahead and report the GFR so that the provider when looking at that number understands that they may have a patient with significant reduction in estimated glomerular filtration rates.

Taking a page from the cardiologists and the way they sort of have classified heart failure over the last couple of decades where the Kidney Foundation has decided to use stages of renal disease, as well. And they are shown on this slide, with stage 1 being patients with relatively preserved glomerular filtration rate but the presence of proteinuria are even microalbuminuria. Stage 2, 3, 4, and 5 are shown here with graduate reductions in estimated glomerular filtration rate, with stage 5 really being patients who are just about on or already on dialysis or a need for transplantation.

The next slide, slide 19, shows the prevalence of chronic kidney disease, by stage of disease, and you'll see that last group down there, stage 5, we are talking about 300,000 people or so, but note how many people have stage 2 disease and stage 1 disease, where we have albuminuria or a slight reduction in GFR, with those two groups alone, you're talking about over six and approaching seven percent of the population. And this is based on data from the early '90s in NHANES 3, and those numbers I think today and our best estimates are, in fact, higher.

And so, why do I make this point of the GFR? If this slide actually demonstrates that if you look at the prevalence of hypertension by GFR that hypertension becomes much more common in groups as the renal function declines. So that stage 1 hypertension, greater than 140 over 90, by

the JNC 7 criteria, at stage 2 which is greater than 160 over 100 or greater, by JNC 7 criteria are shown here. With up to 55 percent of patients having at least stage 1 hypertension with a GFR of 60, or stage 2 disease, and 10 percent of people having stage II disease, putting that together you have 65 to 70 percent of patients with a reduction in kidney function having hypertension.

And remember, as I said, if you have diabetes and reductions in kidney function of some sort then those numbers typically go up to 80 to 90 percent of that population specifically would have hypertension.

The next slide, slide 21 of the set, demonstrates that hypertension, specifically the systolic blood pressure, are very strongly related to coronary heart disease death. This data is from, this to fit screenee's, which is the multiple risk factor intervention trial which took patients with hypertension and treated them, and with cardiovascular end point. And it shows that as you look at the access on the right, the systolic blood pressure increases so the coronary heart disease death rate. And as you look at the axis along the X axis, going from right to left, as diastolic blood pressure increases so do coronary heart disease death rate.

But what it shows is the group with the roughly highest risk is that group would be systolic blood pressure of greater than 160, and in fact, the group of systolic blood pressures are greater than 140. And the systolic blood pressure is a relatively more import than the diastolic blood pressure. And it's from data such as these and some other studies that we would talk about that led to the recommendations for blood pressure control that we will hit on throughout this talk.

The next slide uses the same data set, and shows you the risk of having a death from stroke by systolic and diastolic blood pressure. And the lowest decile of risk is that a systolic blood pressure of less than 112 and a diastolic of less than 71. And if you notice, if you go up to the fourth decile, where the systolic blood pressure is 121, the diastolic is 79, that the risk of having

stroke death has already gone up 2.5 fold, at a rate, at a blood pressure that one would consider optimal, and in fact, normal by JNC 6, and almost by JNC 7 criteria.

So, our awareness of the importance of blood pressure has to be heightened as the level of blood pressure itself, not just whether or not you were at 140 over 90 or not, but the level of blood pressure itself has impact on what your outcomes may be.

So, on the next slide, slide 23 of your packet, talks about reasons to be aggressive in the treatment of hypertension in patients for chronic kidney disease. So, the adverse outcomes for chronic kidney disease such as kidney failure, cardiovascular disease and premature death can be prevented or delayed, and that's shown clearly in several studies.

The treatment of earlier stages of chronic kidney disease is effective in retarding the progression of kidney failure and in preventing the systemic complications that develop during the course of progressive chronic kidney disease. And the initiation of therapy for cardiovascular risk factors at earlier stages of chronic kidney disease can be effective in reducing the very hard cardiovascular morbidity and mortality in these patients.

And we're going to spend a little time now, once we proceed through these slides, talking about the link between chronic kidney disease and cardiovascular disease which is really one of the sort of lynch pins for aggressive blood pressure control in the diabetic patient. This study, this data looks at five year prediction of the probability of having cardiovascular risk and disease. It's taken from the atherosclerosis risk and communities trial, and it basically shows you that as your GFR declines that your risk of cardiovascular disease actually increases.

I think, and we've talked about GFR, but on the next slide we also see that there are other predictors of bi-renal risk factors that predict cardiovascular outcomes. And one that we talk a lot about in the diabetic is that of urinary albumen excretion. And we talk about it in the diabetic,

specifically, with regards to risk of having progression of diabetic kidney disease, but when you look in the general population urinary albumen excretion, even at very low levels, are predictive of cardiovascular and non-cardiovascular mortality. This data is from the PREVEND Trial which demonstrates that cardiovascular death, that third column, and non-cardiovascular death both significantly increase as the urine albumen excretion ratio increases.

And I will just tell you that the 20 to 200 milligram per liter group there is what we would typically call microalbuminuria in the diabetic. And you can see that when you hit that threshold that compared to the groups that have less than 20 you're really about almost, you're almost four times higher risk of cardiovascular death. And when you go above that 200 to what we call microalbuminuria your risk goes up 16 times for cardiovascular death.

The prevalence rates for these estimated total population are demonstrated in the second column, and you can see these actually are very common issues, and things that I think we have to keep our eye on not just on our diabetic patients.

As we go to the next slide, and I won't go through all of this in detail, but suffice it to say that proteinuria in and of itself is a very strong cardiovascular risk factor. And if you have gross proteinuria on a dip stick, there have been several trials to demonstrate that this is perhaps one of the most powerful predictors of cardiovascular disease.

Now, a word about albuminuria and proteinuria, it doesn't necessarily mean that they, themselves, are the cause of the cardiovascular disease. I suspect that they're more likely just a sign as to kidney, it's a very vascular organ. These are signs of vascular disease that are definitely seen in the diabetic and patients with hypertension, and they are manifestation, a clinical manifestation of what's going on in the vascular bed throughout the body.

As we go on to slide number 28, I wanted to bring your attention to two studies that were in the New England Journal in September which really have brought a lot of attention to the relationship between renal dysfunction and cardiovascular outcomes. They were both published in the same issue of the Journal.

And one valiant trial which looked at treatment, blood pressure, and patients' post acute myocardial infarction went back and looked at that data with regards to the impact of the initial renal function on outcome, and basically showed an inverse relationship between an initial renal function and subsequent death.

The next trial, which was a community based sample from the Kaiser Permanente Group out in Oakland looked at a cross-sectional analysis from data back in the mid '90's, had over 1 million patients from which they were able to estimate GFR using the abbreviated MDRD equation, and they demonstrated by using that equation to estimate GFR. And those patients had a reduction in GFR, but in their case about less than 50 MLs per minute and a significantly increased risk for cardiovascular death. So, they're using death as an end point, and adjusted for diabetes status, the relationship among diabetes was actually even stronger among non-diabetics.

So, the scope of cardiovascular complications in patients with renal disease, as we go to the next slide, is quite significant. It is not just creatinine or elevation of creatinine, it's a reduction in GFR, but it also involves proteinuria or albuminuria and this risk, increased risk of cardiovascular disease is seen even at what we would call normal serum creatinine levels, and this, and the renal disease is a stronger risk factor for cardiovascular disease as smoking and diabetes.

Now, let's start linking these together here. The next slide, slide 30 of the set, shows the relationship for cardiovascular disease risk between patients who do not have diabetes and do not have cardiovascular disease, in the first column. And we set that at a reference level of one.

The next column basically shows a patient who does not have diabetes but has past previous cardiovascular disease, so they have approximately a four times higher risk of having a cardiovascular than the non-diabetic who has not had cardiovascular disease.

A patient with diabetes but no history of cardiovascular disease actually has equal cardiovascular risk, and therefore, we call, therefore, when you have diabetes we basically say that you have vascular disease. It is an equivalent to other cardiovascular or already have had a stroke or a myocardial infarction.

Now, add in chronic kidney disease on top of the diabetes and you see that the risks of having a cardiovascular event goes up another six to seven fold, such that the diabetic with kidney disease is probably 25 or 27 times more likely to have a cardiovascular event than the patient without diabetes or cardiovascular disease.

And when you look at, in the next slide, we see a similar sort of risk stratification for the level of proteinuria, and this is a World Health Organization study in diabetics that looks at cardiovascular mortalities of, you have light proteinuria versus heavy proteinuria, and heavy proteinuria basically means detectable to one plus on a dipstick of light proteinuria sort of being micro, higher levels of microalbuminuria. You see that the risk of having cardiovascular disease goes up significantly there, as well.

So, there are several cardiovascular risk factors that are strongly associated with diabetes and renal disease, and they're listed on the next slide here. And you can see that basically these, all of these risk factors tend to cluster.

Now, in the next slide, I talk about studies that support the recommendation for blood pressure level control in patients with diabetes. And I've listed several of them here, and we're going to focus some time on some of them. I will say up front that the recommendations that are currently

out there with regards to treating blood pressure, JNC 7, and we'll talk about those for the National Kidney Foundation in a little bit, are based upon data, some data directly, but a lot of what's been extrapolated from these and some other studies out there. And without there necessarily being one study that asks the question specifically of what's the best blood pressure for a diabetic.

One of the studies that I think is actually one of the most illuminating is the hypertension optimal treatment trial, and I'm now on slide 34 of the set. This trial, I'll also call HOT, it rolled over 18,000 patients with hypertension. And between 50 and 80 years of age. The overall goal was to try to determine what an optimal level of blood pressure might be, and they went by diastolic blood pressure. They had people randomized to either achieve a diastolic blood pressure less than 90 millimeters of mercury, less than 85 millimeters of mercury, or less than 80 millimeters of mercury. And the treatment that they chose was Felodipine, a ( di-- ) calcium channel blocker.

The study had over, had 1,501 diabetics to study entry, and in that diabetic population the observation was made that cardiovascular disease and cardiovascular disease mortality was significantly lower in that lowest target group, the diastolic blood pressure less than 80, when you compared it to the other two groups. Supporting the notion that the lower the blood pressure in diabetics with hypertension the better with regards to cardiovascular outcomes.

The next study I want to focus some time on was the United Kingdom Perspective Diabetes study, the UKPDS, a well-published and reported study, that basically had an overall hypothesis that aggressive glycemic control in a type 2 diabetic would lower their micro as well as macro vascular outcomes. Now, embedded within the study they actually had a blood pressure study which looked at usual blood pressure versus low blood pressure. You have to remember that this study was actually designed in the '70's and started in the implementation in the '80's, so their usual blood pressure group had a systolic that was up around, allowed to go up to 180, and a

diastolic allowed to go up to 105 to 110. And the low blood pressure group target was 140 to 150 systolic and 80 to 90 diastolic. What we could call stage 1 hypertension by JNC criteria, now.

Now, having said that, the achieved blood pressures in this study were probably as low as one would see in many of the trials and in most clinics that we see today. But the important end point is that the low blood pressure group tended to have better outcomes with regards to micro vascular and macro vascular complications. And embedded actually within this blood pressure study was a study of treatment with those who are randomized to lower blood pressure half got atenolol, half got an ace inhibitor captopril, and there was no significant difference between those two agents in outcome.

But they went on to actually put their -- took all comers, and they put their blood pressures into deciles by systolic blood pressure, there was a clear correlation between blood pressure, systolic blood pressure, and micro vascular outcomes, and the lowest risk was at a systolic blood pressure of 110 to 120, indicating that the optimal blood pressure, systolic blood pressure in a diabetic should be quite low, down less than, at 120 or so.

Another trial that broke-down many of our misconceptions regarding treatment of blood pressure in diabetics and in the general population, as well, was the Systolic Hypertension in the Elderly Program, so-called SHEP. And this study was designed to examine isolated systolic hypertension, i.e., people who have systolic blood pressures of 160 and above what the normal diastolic blood pressure. A very common entity seen in older people. And there had been some contention up until the time the study was designed and done that we should not be too aggressive in treating blood pressure in this group of people as it would actually lower perfusion of vital organs, particularly the brain.

But they challenged that with the hypothesis that lowering the blood pressure in this group would be of benefit. They looked at cardiovascular outcomes. They used chlorthalidone as the first

agent, and they show that they with treatment and achieving a target systolic blood pressure of 140 was their goal, that they could decrease the incidence of heart failure, and if there was previous evidence of a myocardial infarction on an EKG the reduction of heart failure, subsequent heart failure went down as much as 80 percent.

I should tell you, as shown on the next slide now, slide 37, that if you looked at the, broke it down between diabetics and non-diabetics, the effects were seen in both groups. However, the diabetics definitely had a much larger impact from blood pressure lowering than the non-diabetic group supporting the importance of blood pressure treatment in this population.

The next study I want to spend some time on, this is now slide 38, is the Appropriate Blood Pressure Control in Diabetes Trial. And this trial was led by Bob Estacio of Colorado and his group. It has some very important findings with regards to the goal blood pressure in patients with type 2 diabetes. It had several targets. And there were a couple of cohorts. And in this particular one, they wanted to compare a constant channel blocker to an ace inhibitor, and in this case, nisoldipine to enalapril. And they wanted to determine what the appropriate blood pressure level was in type 2 diabetics for reduction, particularly in small vessel complications, like retinopathy, neuropathy, and nephropathy, but they also looked at the large fails complication of a stroke.

And when they looked at myocardial infarction they found that there was a significant difference between the ace inhibitor group and the calcium channel blocker group leading the data safety monitoring board to stop the part of the study that looked at the comparison between the two drugs early. However, they went on to continue their analysis of data and their two cohorts, and subsequently, reported that information.

And on the next slide, slide 39, they looked at their hypertensive cohorts, and so these were groups that start off of a diagnosis of hypertension, blood pressure greater than 140 over 90, type

2 diabetes. They had two blood pressure groups. They had a group they wanted to get intensive control. 132 over 78 is what they were able to achieve. They were going for mean arterial pressure between 90 and 95. And the group that had moderate control they were willing to accept a mean arterial blood pressure of around 100 to 105. And the differences between the blood pressure groups is shown here, it's 132 over 78 versus 138 over 86.

And when they looked at that data with regards to just blood pressure, not agent, they found that the group that had the intensive therapy had lower overall incidents of death. But there was no difference in that they noted on the progression of retinopathy and neuropathy, and there was no difference on the progression of renal disease, indicating that maybe if you can get to 140 over 85, to 90, or so, you may be able to lower, that may be a threshold at which you could lower a progression of micro vascular complications. But the effects of lower blood pressure were clearly seen on death. And hence, supporting in part the recommendations for more aggressive blood pressure control in diabetic patients.

In addition to that, they also had what they called a normal tensive cohort, and these were patients who started off with blood pressures of less than 140 over 90. And they asked a question of whether lowering blood pressure further in this group would actually give you additional benefit. And so, they, again, took half of the group when they treated them with the goal of lowering the diastolic blood pressure by 10 millimeters of mercury.

In that group they achieved a blood pressure of 128 over 75, and in the moderate control group they achieved a blood pressure of 137 over 81. And, again, they showed that, and in this case, among this group, they started off at that time with the definition of normal retention. Remember, this was early '90's, early to mid '90's when this was designed, that those patients in the lower blood pressure group had less progression of retinopathy and lower rates of stroke.

And you see that, in fact, the group that had the higher blood pressure was at 137 over 81. We don't, and there was no difference in progression of kidney disease in this group, or differences in neuropathy. But there was a significant lowering of progression of retinopathy and a lower risk of stroke, indicating that, again, blood pressures, in this case, 120 over 75, were superior to a blood pressure of 137 over 81, giving support, again, to the recommendations of JNC 7, and the National Kidney Foundation, and the American Diabetes Association, that aggressive blood pressure lowering goal should be set in patients with hypertension.

Now, when you look at these two studies you can see that the moderate control blood pressure groups in both of these cohorts is actually much better than what we would see in most clinics out there today with regards to the treatment of blood pressure in diabetic patients.

There have been several other studies that have looked at agents, specific agents to use in lowering end points in people with kidney disease. The next study, which is RENAAL looks at our using Losartan ARB in treatment of blood pressure and patients with diabetic nephropathy. And the group that got treated had, with Losartan had lower first time admits for heart failure and a reduction in end stage renal disease and death.

And I put this up here not to talk about the drug but to make the point that although there was a difference in treatment and the contention by the investigators writing this data up that this was seen in the absence of a difference in blood pressure. In fact, that was not fully true. And one year of follow-up the group that received the Losartan had a significantly lower blood pressure than the group that was on placebo. And I believe, indicating that lowering of blood pressure aggressively and early is going to give you benefit.

And this, I believe, the same concept has been recently shown in the, in a trial called VALUE which sort of compared valsartan, another ARB, to a calcium antagonists in patients with coronary heart disease and heart failure. And it basically demonstrated that the patients who got

the calcium antagonist did better. And one of the reasons they believe they did is because at six months they had a significantly lower blood pressure than the other group, again indicating that aggressive and early lowering of blood pressure is probably best.

I'm going to skip the next slide, number 42. We're going to get to it in another part of the talk. And I'm going to actually do the same with the next slide, number 43, which again just gives some data for your information there, to talk about other studies, to talk about not just blood pressure control but also what type of agents may reduce blood pressure, affects of cardiovascular disease in patients with diabetes.

The next slide I'm going to look at is slide number 44, which lays out some of the trials to demonstrate risk reduction in cardiovascular disease outcomes with lower blood pressure in diabetics. We have talked about the top four, six-year-old, the fifth one here, is from, it's a very similar study to SHEP, but instead of using a diuretic they used nitrendipine, so it was looking at an isolated systolic hypertension in older individuals.

And you can see that when you look at the achieved blood pressures, and in every one of these studies the lower blood pressure group did better, so lowering blood pressure as a concept is significantly important in patients with hypertension. The achieved blood pressures in these studies are sort of 140s over 80s except for the ABCD, which got down to less than 130 over 80. And when you sort of, and what has happened to all of these information has been put together to arrive at the recommendations for hypertension in diabetics.

So, if we go to the next slide, we'll start talking quickly in the last few minutes about hypertension in diabetics with kidney disease. And the next slide, now slide 46, shows the recommendations of the National Kidney Foundation which pretty much mirror those of JNC 7, as the target blood pressure for patients with diabetic kidney disease is less than 130 over 80. If the blood pressure is greater than 130 over 80 and you have diabetic kidney disease we'll initiate treatment with a

(renal --) system inhibitor, either an ace or an ARB. If the blood pressure is less than 130 over 80 and you have diabetic renal disease you still should be treated. They still should get an ace inhibitor because what appears to be improvement in cardiovascular outcome in that population when an ace inhibitor is used.

The next slide, now slide 47, I always include in my talks when I'm talking about treatment of diabetic kidney disease and blood pressure diabetic kidney disease with regards to kidney outcomes. Because it indicates that, in fact, it don't, it's not necessary if you can get a very similar effect by using the drug regiment that doesn't necessarily have an ace inhibitor in it.

It was shown in the early '80's by Heinz Parving Group in the Netherlands where they took type 1 diabetics and used them as their own controls. They treated them with blood pressure lowering medications, beta blockers, vasodilators and diuretics, lowered their blood pressure to 128 over 84, and show that they're albumen excretion rate and the rate at which their GFR declined decreased significantly. And so, it is not as much, it's not so much important as to what drug you use, it's just important that you achieve goals, and notice that 128 over 84 is where we were able to get to.

The next slide, I see sort of corroborates that point a bit more in the collaborative study group which done in this country looked to show that Captopril lowered renal disease progression in type 1 diabetics. But if you look at the risk of doubling the serum creatinine in the group who've had normal blood pressure at the start, there was really no significant difference. There was not a significant difference in the number who doubled their creatinine, so risk reduction was not significant.

And if you look at the next slide, which is slide 49, it shows there's someone in graphic form. And it plots the amino to your blood pressure versus the risk per 100 patient years of doubling the creatinine in this cohort of type 1 diabetics with nephropathy. So they're type 1 diabetics with

retinopathy and proteinuria, established diabetic nephropathy, part of the cohort got Captopril, and part got a placebo.

You will notice that the risk of doubling their creatinine was exactly the same for both groups up until the mean arterial blood pressure somewhere around 92 to 94. That correlates to a blood pressure of say 125 over 75. And as you went above that number then you saw benefit of Captopril as it related to placebo.

So, that number there, mean arterial pressure of 92 to 94, or blood pressure lowering of somewhere around 125 over 75 appears to be a good threshold which we should try to achieve in our patients with diabetic kidney disease.

The next slide, number 50, I'm going to skip this, so it just outlines more recent studies with ARBs and diabetic kidney disease.

And we're going to go to, which is slide number 51, which is really the compilation of data from several studies done by George Bakris in examining the role of blood pressure and renal survival in diabetics. And you can see that the decline in GFR, and each of these data points is data on achieved blood pressure, changed to mean arterial blood pressure from a specific study.

So, we have data from about nine studies plotted on this continuum here. And you can see then those areas where the mean arterial blood pressure has gotten down, particularly less than 100 which is around 140 over 90, and getting down to 94 to, as we said, 92, so which is 125 over 75, that the risk goes down in large support of what we think is the threshold we want to achieve in our diabetic patients.

The next slide, slide 52, is a graphic depiction of the risk from myocardial infarction by systolic blood pressure from the United Kingdom Perspective Diabetes studies. I alluded to these earlier,

per the slide there. But so you can see that the systolic blood pressure increases from a reference variable of around 114, that the risk of myocardial infarction per 100 patient years goes up significantly, just before an increase up to 142. And again, up to 170. So, aggressive blood pressure lowering in this high risk population is important.

As we start winding down the next slide talks about ALLHAT, which is something we always have to talk about when we talk about high blood pressure trials, as is the largest blood pressure lowering trial to date. And it compared Amlodipine, a (---) like diuretic to a calcium antagonist and Lisinopril, and (los centera) ace inhibitor. Both cardiovascular outcomes being the primary outcome, but one of the secondary outcomes was end stage renal disease. They excluded all patients who had a creatinine above two, so there was a relatively low risk population. However, they had an over representation of diabetics by design with a 30 to 35 percent, 35 percent of this cohort being diabetic.

And it basically shows that there was no significant difference between Chlorthalidone and Lisinopril, or Chlorthalidone and Lisinopril with regards to end stage renal disease. However, both comparisons it did favor the diuretic, which was somewhat counterintuitive, particularly with regards to the ace inhibitor.

Now, when we talk about agents to choose to treat blood pressure out there, I think in the non-diabetic population we need to think about the risk of diabetes. As I mentioned, just having diabetes automatically gives you the -- puts you at an equivalent there for cardiovascular disease. And there are data from ARIC, the Hope Trial, Life Trial, and from ALLHAT, itself, that show that (renal ---) inhibitors are probably the drugs that lower your incidence of diabetes in hypertensive patients, when compared to other drugs, particularly (thiazide), (thiazide) light diuretics and beta blockers.

And on the next slide, slide 55 sort of shows that data for ALLHAT where of the group of non-diabetic patients who were put on chlorthalidone approximately 16 percent of them developed diabetes over the course of follow-up, and that's versus 10 percent and 9 percent in the calcium antagonist and ace inhibitor groups.

Now, as we have said, as we go to slide 56, it is very important to achieve aggressive blood pressure targets and JNC criteria of less than 130 over 80 in diabetic patients. This reduces their cardiovascular outcomes, most importantly, and their heart attack and stroke rates. And also, reduces the progression of diabetic kidney disease, as well as retinopathy.

And rather than focus on what drug one should use to achieve these goals it is most important to focus on achieving goals and realize that it's actually going to require multiple drugs to get there. This slide, slide 56, demonstrates that in several trials all of which, except for the bottom three, were primarily hypertension trials, and the bottom three included several hypertensive patients that in some cases up to four drugs are required to reach to achieve blood pressure goals.

And you'll notice that the number then of blood pressure medications required is high enough that you don't have to spend your time quibbling about which one drug this patient ought to be on or not be on, and which one is better, because quite frankly you're looking at using multiple drugs.

ALLHAT and that population of patients, they were able to get most of their patients to a blood pressure of 130 to 135 over 65 to 70, and they required at least two medications in two-thirds of their cohort. And this is a cohort of over 30,000 patients. So, the argument about which drug to use is not one that should be as important as it is, that we achieve the goals that we need to achieve in our diabetic patients, that being a blood pressure of less than 130 over 80.

And the last slides are some things that we've already talked about. I want to bring your attention to that diabetics with kidney disease particularly have a very high prevalence rate of anemia,

something that we have coming out in Kidney International very soon. And these have prevalence rates of anemia can be seen in even moderate reductions of the renal function, and that will increase their cardiovascular risk, making it all the more important to lower, to be aggressive and lowering their blood pressure further.

So, that completes my talk. I think I might have gone a minute or two over, but I'm happy to answer any questions at this time.

Operator: Thank you.

Dr. Errol Crook: You're welcome.

Operator: The question-and-answer session will be conducted electronically today. If you would like to ask a question please press the star key, followed by the number one on your telephone. If you are joining us today using a speaker phone please turn off your mute function before signaling to allow your signal to reach our equipment. Once again, if you would like to ask a question please press star, one now. And we'll pause for a moment.

We'll take a question from Kathy Moore with Leesburg Regional Medical Center.

Kathy Moore: This question is regarding medication choice for someone that is categorized as pre-diabetes, specifically blood sugar is just slightly over 100. Should patients like that be switched off of beta blockers since that seems to increase the rate of the development of diabetes?

Dr. Errol Crook: Yes, a very good question. And if you -- it depends upon who you would talk to. Now, I think the group, the data suggests that diuretics and beta blockers compare to other blood pressure lowering medications may increase your risk of developing diabetes.

Now, the folks who, there are lots of people out there who argue vehemently that if you look at diabetes as an all or none phenomenon that it, you know, you have a fasting blood sugar of 124, 125, you're not diabetic. You have a fasting blood sugar of 126, you're diabetic. And then, it is not that your fasting blood pressure went from 124 to 126 to increase your cardiovascular risk, and that, in fact, your cardiovascular risk goes up on a continuum.

Now, I'm actually of the group that believes, however, that you have to look at each patient and look at their risk profile for development of diabetes going forward. So, if there are, have a very strong family history, if they are significantly obese, the two biggest things I think I would look at, and you can look at this person and say this is someone who is extremely likely to become diabetic going forward, then I need to do all I can to lower their cardiovascular risk, and that includes addressing their cardiovascular risk as if they're almost diabetic now.

Now, having said that, it's important to note that blood pressure lowering in and of itself lowers your risk for diabetes. I don't advocate at this point taking people who are on a blood pressure medicine, that is successful, and making a change because they want to lower their diabetes risk. I do, however, think you need to take it into consideration and nuance hypertension patients who come to you with a BMI that is extremely high and a very strong family history of diabetes, than when you make your initial choice for drug.

Kathy Moore: Thank you.

Dr. Errol Crook: You're welcome.

Operator: We'll now hear from Margaret Burton with Collier County Health Department.

Margaret Burton: Dr. Crook, I enjoyed your presentation very, very much, for personal reasons as well as professional. My question is do you have any experience with complications from the ARBs causing a fibro **myalgia** like syndrome?

Dr. Errol Crook: I personally have not seen that. There's, I think in general when you compare aces to ARBs, the ARBs are better tolerated, with a much, much lower levels of angiodema and lower levels of cough, as well. I think that like any drugs out there as they enter into the market and we have more time with them, you end up getting more and more things. I personally have not had that particular complication, experience with that particular complication.

Margaret Burton: The only reason I mention it, myself, another nurse, and a nurses aid, all three of us have had that, and as soon as we stopped the ARB within two days we improved.

Dr. Errol Crook: OK. And what particular ARB was it?

Margaret Burton: I -- it started when I was on (avolide) and it continued when it was switched to (cozar).

Dr. Errol Crook: Oh, really.

Margaret Burton: After about 10, 12 months of use. And I tried it 10 times. I'd restart it. Within a couple of weeks I was nearly crippled. Two days after stopping it I'm getting better.

Dr. Errol Crook: Wow. Well, you know, I have to admit, I haven't had that experience. I have to -- maybe I didn't recognize it. You know, I have to tell you, and this sort of goes along with the talk, when you talk about patients with hypertension, the very high prevalence rates of diabetes in that group, and the other thing you have is (dyslipidemia), so...

Margaret Burton: Yes.

Dr. Errol Crook: So, most of the patients show-up, they're on something to lower their blood pressure, and they're on a statin nowadays. And when a patient shows up with those type of complaints we typically will stop the statin first, and you know, we'll check the CPK, and move from there. And I suspect that in most of us providers are looking at those set of drugs with those complaints. And I guess if they continue to persist with discontinuing the statin then we need to take a look at the other drugs. But I personally haven't had that experience. I thank you for sharing that with us.

Margaret Burton: Thank you.

Operator: And once again, if you do have a question please press the star, one now. If your question has been answered you can remove yourself by pressing the pound key.

We'll now hear from Theoria McNeil in Central Florida Healthcare Incorporated.

(Ann): Hi. This is (Ann) with Theoria. I have a question on the use of (chlondine) in African-Americans and Hispanic population. We find that it tends to lower their ability to stay awake. I wanted to know if the doctor had any input on that?

Dr. Errol Crook: Well, yes, that's true, I think, in anybody using it. And, you know, there are a lot of issues with (chlondine), and one of my colleagues here, Wayne, who sits right next to me, (John Flack), who is an expert in hypertension, he avoids that drug. I, but it gives you dry mouth, it makes you (somalat), if you get to really high levels and your patients aren't compliant you get the rebound. And they just don't feel well.

So, I typically reserve it for folks who have resistant hypertension. And I see a lot of that being a nephrologists with interest in diabetes, I see a lot of resistant hypertension. And working in an

area where we have a lot of people who don't have significant financial resources it is a very affordable medication.

So, it is effective in lowering blood pressure. You do have the side effects. To (some) of this, I would tell you actually with time become a bit more tolerate it, and patients as they in the beginning it can be quite ((inaudible)), or have a personal -- my Dad is one of the personal, my own personal experience for me. He told me about him starting. When he started this drug, at the time he had a job where he had to drive a good bit, and would often have to pull off the road and go to sleep. So it -- that's something, though, that with time you begin to tolerate.

But because of it's affect, it's very effective at blood pressure lowering, and is affordable, it's a drug that we have to keep in (armamentarium).

(Ann): Would you, do you recommend it then being used acutely? Say a patient walking into clinics with an extreme high blood pressure, and this is the way you're going to treat?

Dr. Errol Crook: I think it's one of the best drugs to use in an acute situation. In fact, you know, you can sort of load the (moreley) right in front of you, start with .1, check their blood pressure, 20 to 30 minutes later, and if you don't get it you give them another .1 and go to .2.

And then, actually, the lowering that you get in the blood pressure with that drug when given orally is actually pretty smooth. It's not a drastic thing. It lasts for awhile, and you can start them on that therapy while, and as opposed to other drugs that we've talked about that you may have used long-term, it has in some cases two to four weeks before you see the maximum affect on blood pressure lowering there.

(Ann): OK. Thank you.

Dr. Errol Crook: You're welcome.

Operator: And, once again, if you do have a question please press star, one now. We'll pause for a moment.

There are no questions in the queue at this time, but once again, that is star, one if you have a question.

Natalie Gibson: Hello, Dr. Crook?

Dr. Errol Crook: Yes.

Natalie Gibson: This is Natalie Gibson. We had a question submitted via electronically.

Dr. Errol Crook: OK.

Natalie Gibson: (Erin Kiegerie), she's an (RN MSM) from Jackson Health Systems. She writes, 'at the last diabetes seminar I attended from physicians representatives from the National Institute of Health. It was mentioned that diabetes is being treated as a cardiovascular disease rather than an endocrine problem. Do you have any reference material or suggestions on where I may find where the theory might have originated from, or whether you agree or disagree, and why?'

Dr. Errol Crook: OK. Well, I agree. If she goes to slide number -- I'll find it here -- slide number 30 of my talk shows the rationale for that. It shows that, and this data is, was originally and best illustrated in a paper by (Steven Hafner), in the New England Journal, I believe in 1998, where he showed that patients with diabetes had the same risk of a cardiovascular event as a non-diabetic who had already had a cardiovascular event. And, therefore, it was thought of as being a cardiovascular equivalent.

Natalie Gibson: Thanks.

Dr. Errol Crook: And I believe as to why this happens is because of the affects on the (vaculature), both large and small vasculature, and the enhanced (atherosclerosis) that you see in diabetics as shown in the earlier part of the talk when we focused on some of the patho physiologic mechanisms and consequences or insulin resistance.

Operator: There are no further questions in the queue. I'll turn the conference back over to Ms. Gibson for any additional or closing remarks.

Natalie Gibson: Thank you. I would like to thank everyone for participating in today's call. We appreciate Dr. Crook for giving us his time and expertise. These insights will be useful in improving diabetes care nationwide.

I want to remind nurses and dietitians who would like CEU credit for this program, you should mail or fax all completed forms to me by December 10th to ensure that your forms are received by the December 15th deadline. The fax number is 850-245-4391.

Once again, thank you. I hope that you all have a wonderful day.

I will now turn it over to the Operator for call conclusion.

Operator: That concludes today's conference. We thank you for your participation, and you may now disconnect.

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