FOOD AND DRUG ADMINISTRATION

NINETY-FIFTH MEETING OF THE

CARDIOVASCULAR AND RENAL DRUGS ADVISORY COMMITTEE

8:30 a.m.

Thursday, January 17, 2002

Kennedy Ballroom
Holiday Inn
8777 Georgia Avenue, N.W.
Washington, D.C.

ATTENDEES

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ATTENDEES (Continued)

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GEORGE WILLIAMS

C O N T E N T S

NDA 20-757/S-021, Avapro (irbesartan)
Sanofi-Synthelabo (c/o Bristol-Myers Squibb)
for the Treatment of Hypertensive Patients
with Type 2 Diabetic Renal Disease

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P R O C E E D I N G S

(8:30 a.m.)

DR. BORER: I'd like to welcome you and begin the 95th meeting of the Cardiovascular and Renal Drugs Advisory Committee of the FDA.

Before we begin the formal presentations, we'll hear the conflict of interest statement by Jaime Henriquez, the Executive Secretary of the committee.

MR. HENRIQUEZ: The conflict of interest statement. The following announcement addresses the issue of conflict of interest with regard to this meeting and is made a part of the record to preclude even the appearance of such at this meeting.

Based on the submitted agenda for the meeting and all the financial interests reported by the committee participants, it has been determined that all interests in firms regulated by the Center for Drug Evaluation and Research present no potential for an appearance of conflict of interest at this meeting with the following exceptions.

In accordance with 18 U.S.C. 208(b)(3), a full waiver has been granted to Dr. JoAnne Lindenfeld for her unrelated consulting for one of the sponsors. She received less than $10,000 a year. And to Dr. Alan Hirsch for unrelated speaking for the sponsor. He received between $5,000 and $10,000 a year.

A copy of the waiver statements may be obtained by submitting a written request to the agency's Freedom of Information Office, room 12A-30 in the Parklawn Building.

In the event that the discussions involve any other products or firms not already on the agenda for which FDA participants have a financial interest, the participants are aware of the need to exclude themselves from such involvement and their exclusion will be noted for the record.

With respect to all other participants, we ask in the interest of fairness that they address any current or previous financial involvement with any firms whose products they may wish to comment upon.

DR. BORER: Thank you.

We'll begin then. This morning we're going to consider an NDA related to irbesartan, Avapro, for the treatment of patients with hypertension and type 2 diabetic renal disease. I think the presentation will be introduced by Dr. Daniels.

DR. DANIELS: Thank you and good morning, members of the advisory panel. It's a pleasure to be here today to discuss information about Avapro and its use in the treatment of type 2 diabetic renal disease. I'm Brian Daniels, the Vice President for the Pharmaceutical Research Institute at Bristol-Myers Squibb.

Briefly let me review our agenda and speakers. After my introduction, Dr. Ed Lewis, a Muehrcke Professor of Nephropathy and Director of the Nephropathy Section at the Rush Medical College, will present important background information on type 2 diabetic nephropathy with an emphasis on the endpoints used in our renal studies. Dr. Lewis was a principal investigator for the IDNT study.

Then Dr. Melisa Cooper, a nephrologist and a vice president in the Pharmaceutical Research Institute at Bristol-Myers Squibb, will give the efficacy and safety data for IDNT.

Then Hans-Henrik Parving, Professor and Chief Physician at the Steno Diabetes Center, Denmark, will present the efficacy and safety data for IRMA 2. Dr. Parving was an investigator for the IRMA 2 trial.

Finally, Dr. Lewis will then return to discuss the overall risk-benefit profile of irbesartan in the treatment of type 2 diabetic renal disease.

We have some additional consultants that the panel can use to answer their questions. Dr. Julia Breyer Lewis is a Professor of Medicine at Vanderbilt University. Dr. Lloyd Fisher is a Professor Emeritus in biostatistics at the University of Washington, and Dr. Marc Pfeffer is a Professor of Medicine in the Cardiovascular Division at Brigham and Women's Hospital. All three were involved with

the conduct of the IDNT trial.

Just to remind everyone that Avapro is an angiotensin II receptor blocker, active at the AT1 receptor subtype. It's current indication is for the treatment of hypertension. It's available in over 79 countries, with over 3.6 million patient-years of experience worldwide. It's recommended starting dose for hypertension is 150 milligrams daily with a maximum dose of 300 milligrams daily.

Two complementary trials constitute the Avapro development program in type 2 diabetic renal disease. Together they studied over 2,300 patients along the continuum of type 2 diabetic renal disease. These trials were designed as specific renal studies using endpoints appropriate for the severity of renal disease being investigated.

The irbesartan diabetic nephropathy trial, or IDNT, investigated renoprotection in 1,715 hypertensive patients with type 2 diabetic nephropathy, defined as overt proteinuria. Irbesartan microalbuminuria in type 2 diabetic subjects, or IRMA 2, studied 590 hypertensive patients at an earlier point along their disease continuum, specifically those patients with microalbuminuria.

The proposed indication for Avapro for patients with hypertension and type 2 diabetic renal disease:

Avapro is indicated for the treatment of type 2 diabetic renal disease.

Now I would like to introduce Dr. Ed Lewis who will give important information on the background of type 2 diabetic renal disease. Dr. Lewis?

DR. EDMUND LEWIS: Thank you. Good morning.

Type 2 diabetic nephropathy is a growing problem worldwide. Type 2 diabetes is epidemic and approximately 40 percent of patients with type 2 diabetes will get nephropathy. Currently approximately 45 percent of patients entering our dialysis transplantation programs in this country are entering with the primary diagnosis of diabetic nephropathy, and the cost of this is enormous.

The natural history of type 2 diabetic nephropathy does not differ greatly from that of type 1, and that is that there is an inexorable progression from early nephropathy to overt nephropathy with progressive structural and functional changes which ultimately lead to a decrease in the glomerular filtration rate and end-stage renal disease.

Virtually all patients with type 2 diabetic nephropathy have hypertension. One difference between the course -- and there are many differences in terms of the patient populations -- of the patient with type 2 diabetic nephropathy as opposed to type 1 diabetic nephropathy is

that there is cardiovascular morbidity and mortality throughout the course which represents a second system involved, a competing endpoint, which has to be taken into consideration in the design of any trial.

We can define renal failure as a decrease in the ability of the kidney to carry out its primary function of filtering impurities in the blood, and this is measured by measuring either the glomerular filtration rate, the creatinine clearance being one approximation of that, or evidence of the retention of filterable molecules, particularly creatinine.

As you know, the creatinine clearance represents the estimation of the amount of blood cleared of a molecule in a unit time, so that the numerator in the formula is the concentration of that substance, creatinine, in the blood and the volume of urine per unit time, and the denominator is the serum creatinine so that when one plots the clearance of creatinine against the serum creatinine, you have a hyperbolic function.

Now, creatinine measures the glomerular filtration rate because it is freely filtered and it is not reabsorbed by the kidney. However, there is some secretion of creatinine so that it is not an ideal measure, but it is clinically the most convenient measure of the glomerular filtration rate. The ideal measure is a molecule that is

not secreted at all.

Given the fact that we have a hyperbolic function, it's important to note that whenever the serum creatinine doubles along this curve, the creatinine clearance halves. Early then in the course of renal disease, a relatively large change in creatinine clearance is associated with a relatively small change in the serum creatinine. However, doubling means halving of the clearance. Late in the curve, relatively small changes in clearance are associated with large changes in the serum creatinine because it's a hyperbolic function.

So, in designing a trial, the goal is to have an entry criterion where patients enter in an area where changes in the glomerular filtration rate are reflected by readily measurable changes in the serum. Later in the course of renal disease, small changes cause large changes in the serum creatinine, and so again in the design of a clinical trial, we're looking at the changes here being reflective of the phenomenon that we are measuring.

A number of years ago, we, the collaborative study group, carried out the study of ACE inhibition with captopril in type 1 diabetic nephropathy, and we used, as an endpoint in that study, doubling of serum creatinine, meaning halving of the glomerular filtration rate relative to the baseline. When we compared the doubling of

creatinine to the clearances in those patients who had doubled, we looked at iothalamate clearance and creatinine clearance. Now, iothalamate happens to be a molecule that is ideal for measuring the glomerular filtration rate. It is freely filtered. It is not reabsorbed and it is not secreted. As you can see, among the patients who doubled their creatinine in that study, there was at least a halving of the glomerular filtration rate. So, we felt that that justified our use of doubling of serum creatinine for that definition of halving of the glomerular filtration rate.

End-stage renal disease is the clinical requirement for renal replacement therapy. The Medicare definition of end-stage renal disease for patients with diabetic nephropathy is a serum creatinine of greater than 6 or a creatinine clearance of less than 15 mls per minute, so that in order to use an objective definition and get away from variances in practice of nephrology in terms of the use of dialysis in patients with kidney disease. The objective definition of end-stage renal disease is taken as the federal Medicare definition of serum creatinine of greater than 6, and that again comes into the design of the study that you'll be hearing today.

This relationship then between the creatinine clearance and the serum creatinine actually defines renal

function. Creatinine parameters are not surrogates; they are not substitutes. The creatinine parameters define the ability of the kidney to filter the blood.

To reflect further on the type 1 diabetic nephropathy trial which preceded our type 2 diabetic nephropathy trial, when we looked at the so-called hard endpoints of death, dialysis, or transplantation in the captopril trial of type 1 diabetic nephropathy patients, there was a risk reduction of 50 percent for that endpoint among the patients who received captopril as opposed to placebo.

When we looked at the Kaplan-Meier curve for doubling of serum creatinine, we had the same risk reduction and approximately the same curve. And the reason for that is that the median time from a halving of the glomerular filtration rate to end-stage renal disease was only 9 months so that a halving of the baseline glomerular filtration rate in diabetic nephropathy, with its inexorable downhill course, is a very important milestone. And as you will see, this is true in the type 2 patients as well. And that explains why a doubling of serum creatinine correlated so well with the hard endpoints in the previous study.

Now, I want to remind you about the structure of the glomerular filter because what we're really studying

is the function of the glomerular filter. What this graphic shows is that the glomerular capillary bed -- glomerular capillaries having three layers basically, endothelial cell, basement membrane, and epithelial cells, so the filtration is going on here -- and it is built on an architectural structure of connective tissue which is known, here in pink, as the glomerular mesangium.

Now, in a normal glomerulus, the black here is silver staining of the glomerular basement membrane, and you can see these beautiful, graceful basement membranes of the capillary loops, and one can barely see the architectural structure on which these glomerular capillary loops lie.

This is the face of the enemy for a nephrologist. This happens to be from a biopsy that was taken during a pilot trial that the collaborative study group did prior to the irbesartan diabetic nephropathy trial that you'll be hearing about. In this pilot trial, we utilized entry criteria which approximated those which are used for the IDNT, and we did renal biopsies on these patients with type 2 diabetic nephropathy in order to determine the nature of the glomerular lesion which we would be studying.

This is quite typical of what we found. As you can see, typical of diabetic nephropathy, there is a marked

increase in the connective tissue of the glomerular mesangium, and it is the progression of that connective tissue which leads to scarring and obliteration of the glomerular capillaries which is ultimately responsible for renal failure in diabetic nephropathy.

In this case, as is true in the average case entering the IDNT, the patient had already lost 50 percent of their renal function so that in the irbesartan diabetic nephropathy trial, what we have are patients who have this advanced abnormality and what we're trying to do is prevent further progression of that abnormality.

In the design of a therapeutic program, given the goal of preventing progression of the established lesion, it would seem appropriate to not only try to tell doctors to try to prevent progression of that lesion, but it would appear appropriate to tell doctors to treat a patient so that they can prevent this advanced lesion from ever occurring. And for that reason, it is logical to study early diabetic nephropathy to see whether you can, in fact, tell a physician that they can treat a patient to prevent them from going on to advanced disease.

Now, there are a number of abnormalities that can be measured in early diabetic nephropathy. Structurally the abnormal connective tissue metabolism which occurs in diabetic nephropathy occurs very early so

that there is marked thickening of the glomerular basement membrane in patients who are biopsied very early with the first evidences of diabetic nephropathy and there is expansion of the glomerular mesangium, which you saw. If one wanted to look for the signal for connective tissue metabolism, say, mRNA for type IV collagen, you will find an increase in the signal very early, and I'll show you some data about that.

Structurally, functionally the earliest evidence of diabetic nephropathy is an alteration in the selective permeability characteristics of the glomerular capillary wall, which means that the normal permeability characteristics, which means exclusion of the filtration of macromolecules, begins to be breached, and from a clinical point of view, a reliable and reproducible way of measuring that is to measure small amounts of albumin which begin to appear in the urine at the earliest stages of diabetic nephropathy.

So, the first functional alterations are associated with increased filtration of albumin, and some of that is reabsorbed by the renal tubules. That which is not reabsorbed is excreted in the urine, and that is referred to by the term microalbuminuria.

Now, microalbuminuria is defined as a urinary excretion of abnormal quantities of urine, more than 20

micrograms per minute, which is approximately 30 milligrams per 24 hours, and less than 200 micrograms per minute, which is approximately 300 milligrams per day.

Now, the reason for the upper limit is it is somewhat artificial but it is the borderline between microalbuminuria and the definition of overt proteinuria or overt nephropathy. The reason that it's the borderline is in fact that is where the routine clinical tests that doctors use for proteinuria, the dip stick, turns positive. So, if you want to find out whether there is an abnormality in the selective permeability characteristics of the glomerular capillary earlier, you have to do specific tests for albumin. The clinical dip stick is negative. So, that's what defines overt nephropathy.

This is from a biopsy of a patient who has very early diabetic nephropathy and microalbuminuria, and as you can see, there is basement membrane thickening here, but there is a beginning of the increase in glomerular mesangial material which ultimately leads to the florid lesion that you've already seen.

Most studies of microalbuminuria or early nephropathy have been done in type 1 patients for a variety of reasons. I'll be glad to answer questions about that later. However, it has been consistent to find thickening of the glomerular basement membrane of the order of

magnitude similar to patients who have overt nephropathy in patients with early nephropathy, and there is a beginning, as you saw, of mesangial expansion in these patients.

In a study carried out by Sharon Adler, she looked at normal patients who were living related donors, biopsies from normal patients, biopsies from patients with diabetes who had normal albumin excretion, meaning less than 20 micrograms per minute, patients who had microalbuminuria, and patients with overt nephropathy. So, as you can see, among this group the serum creatinine would naturally be normal in normals, it's normal in patients with diabetes and no microalbuminuria, and it's normal in patients with microalbuminuria because early in the course of diabetes, you don't have changes in the ability of the filter to function. Of course, in overt nephropathy, the creatinine is going up because your glomerular filtration rate is going down, as you see here. The albumin excretion rate in the microalbuminuric patients is 56 and in overt nephropathy 4 grams.

And she measured the glomerular collagen mRNA for type IV. As you can see, the signal in microalbuminuric patients is elevated the same as in overt nephropathy, so that the biochemical abnormality for the development and continuation of diabetic nephropathy is there early, giving us good reason to intervene as early as

possible.

If one were to study early diabetic nephropathy then, it is not practical to study the structural abnormalities which occur early. It would mean doing renal biopsies on hundreds, if not thousands, of patients, and these are not easy patients to biopsy. They are very obese.

The functional abnormality of altered capillary wall perm selectivity is what we are left with in order to study early diabetic nephropathy. And as I've said, the macromolecule of clinical relevance which can be measured and is accurately measured and reproducibly measured is albumin.

Now, the very quantity of microalbuminuria in a study could be measured and a conclusion made from the study, or a study can use as an endpoint the movement from the microalbuminuric state to the overt nephropathy state, meaning that the patient has crossed the border of 200 micrograms per minute. So, they have progressed.

The importance of that is that in this progression of diabetic nephropathy, that's what happens. Patients go from small amounts of albuminuria to clinically overt proteinuria/albuminuria and then the glomerular filtration rate starts going down. You cannot get a patient having decreased glomerular filtration rate going

to end-stage renal disease without them going through the period of overt proteinuria. So, in the design of a trial -- and the IRMA 2 trial is so designed -- what we are looking for is an endpoint which accurately measures the movement from microalbuminuria to overt nephropathy.

The rationale for the clinical development program then was to determine whether inhibition of the renin-angiotensin system is renoprotective in type 2 diabetic nephropathy just as it is in type 1 diabetic nephropathy. And renoprotection is the term applied to the the effect of a drug in protecting the kidney from progressive renal disease which is independent of other systemic effects that that drug might have such as blood pressure lowering.

Now, there are several reasons why interruption of the renin-angiotensin system could be renoprotective in diabetic nephropathy. The glomerular capillary tuft is an arteriole portal system, meaning that the capillaries have an arteriole feeder and an arteriole drains the capillary tuft, so that the pressure within the glomerular capillary tuft is under the control of changes in the two arterioles.

In a normal kidney, there is autoregulation of the blood pressure within the capillaries, meaning that in a normal person, if your blood pressure goes up, there is constriction of the afferent arteriole so that the pressure

within the glomerular capillary tuft remains constant. In the diabetic state, which has been directly measured in animals, but of course not directly measured in humans, there is deficiency of that autoregulation meaning that any elevation in the systemic blood pressure is more directly transmitted to these capillaries and there is the barotrauma opportunity there. So, any drug that lowers the systemic blood pressure will lower glomerular capillary tuft pressure because of this deficient autoregulation.

More importantly in the diabetic state, there is constriction of the efferent arteriole for reasons that are not clear, and that is under the influence of angiotensin II. So, in the diabetic state, there is an increase in glomerular capillary tuft pressure directly measured by Dr. Brenner and associates many years ago because of this increase in the tone of the draining arteriole. So, inhibition of the renin-angiotensin system at that level relieves that pressure and diminishes barotrauma.

Furthermore, abnormal matrix metabolism -- and I've shown you histologic examples of that -- is under the control of angiotensin II modulation through TGF-beta which controls collagen type IV metabolism in the kidney, as well as other connective tissue proteins.

Lastly, there is an issue of whether increased

amounts of protein trafficking through the kidney is nephrotoxic and angiotensin II, in addition, does decrease glomerular filtration of macromolecules. So, it is possible that a decrease in proteinuria traffic is also a protective mechanism. So, there is good reason to believe that the therapeutic interruption of the renin-angiotensin system can be renoprotective in this disease.

So, we will be presenting studies of early diabetic nephropathy, the IRMA 2 study, the goal of which was to show whether one could stabilize the perm selectivity abnormality in the kidney so that the patient did not go on to overt proteinuria and nephropathy and the irbesartan diabetic nephropathy trial which looked at the therapy of the advanced lesion to see whether the progression of advanced nephropathy could be inhibited.

The goal then of the irbesartan diabetic nephropathy trial is to take patients whose substrate glomeruli looked like this and prevent the progression of this advanced lesion.

With that, I'm very pleased to introduce Dr. Melisa Cooper who will review with you the results of the irbesartan diabetic nephropathy trial. Thank you.

DR. BORER: Thank you very much, Dr. Lewis.

Before Dr. Cooper begins, I want to determine if there are any committee questions. We have some new

people on the committee and some guests, so I'd like to set some early ground rules and make a statement.

One of the over-arching issues we're facing here -- and I think you've outlined it really extraordinarily for us -- is to determine what the drug may do, once we hear the data, that causes clinical benefit, makes a patient feel better or live longer, versus what are pharmacological effects, that is, what makes the tests look better but may not have an impact in a significant way on making the patient feel better or live longer. So, that's an over-arching issue that we're going to have to consider because we really need to see some evidence of clinical benefit, which we may well.

With that in mind and with that lovely presentation having been given, I want to ask if there are questions of Dr. Lewis, and I'd like to structure that just a little bit. I want to begin with the committee reviewer, JoAnne Lindenfeld, and then we have two nephrologists who are ad hoc members of the committee today, Dr. Kopp and Dr. Brem, Dr. Kopp from the NIH and Dr. Brem from Rhode Island Hospital. So, after JoAnne, I'd like to hear from the two nephrologists and then we can ask if anybody else has any questions about the presentation of Dr. Lewis.

DR. LINDENFELD: I'd like to echo that was a lovely presentation. Thank you.

Just some questions I have about clarification. One, could you tell us something about the progression of renal disease in diabetics in blacks and Hispanics compared to whites?

DR. EDMUND LEWIS: Yes. Well, of course, in type 1 diabetic nephropathy, it's basically so few patients from those ethnic groups that we don't know a lot except that the few patients who are black, African Americans, who have type 1 diabetic nephropathy do progress faster than whites.

In type 2 diabetic nephropathy, overall patients who are Hispanic certainly tend to have a more rapid progression than patients who are white, and I think that the relevant literature on this actually is Native American literature. It's the Pima Indian data because I think genetically the Hispanic problem for type 2 diabetic nephropathy is probably based there as far as we can tell from the course of that disease. So, it occurs earlier in patients who are Hispanic and it is certainly inexorably progressive.

In terms of whether the absolute rate of progression is worse, that is not entirely clear. Reflecting on the Pima Indian data, the rate of progression of early, meaning microalbuminuria to overt proteinuria, actually approximates the white population and the rate of

progression of the disease itself also might be a little faster, but it also approximates the white population. So, it's a bigger health problem, but in terms of what one can expect from the course, other than its occurring earlier in the life of a patient, the courses aren't that dissimilar.

Again, there's less information about African Americans, but I think as a general statement one can say that kidney disease, not just diabetic kidney disease, but hypertensive kidney disease and the like, appears to be more progressive in the African American population and more refractory to any therapies.

DR. LINDENFELD: So, to just follow up on that, in a study that evaluates progression of renal disease, you would like to see those groups, blacks, Hispanics, be equal in all treatment groups.

DR. EDMUND LEWIS: Well, I suppose that you would like to see that, but the problem is that you have to find these patients. I think it would be a more accurate reflection of what I would say is that in a study of type 2 diabetic nephropathy, it would be appropriate to make every effort to get minority groups in the sample. There's no doubt about that.

To get parity I think would be extremely difficult. I think that as you will see in the IDNT, when you start talking about multinational studies and so forth,

the representation, for example, among the blacks in the United States in that study was certainly equivalent to the relative population of blacks and so forth, but then when you start to get European involvement, there are no blacks. So, it's harder to construct a study where you have parity there. I don't know exactly how you would come to that.

DR. LINDENFELD: I guess my question relates to whether or not one would design the study for stratify for race, for instance, to make sure that different races were equally represented among the groups.

DR. EDMUND LEWIS: Yes, I don't know. I think conceivably one of the biostatisticians in the group might want to address that. I think that the pre-stratification of a clinical trial such as this I think brings in certain complexities, not the least of which is you expand your sample size tremendously and make the study even harder to do.

There are other issues about bringing minorities into clinical trials which also are a little difficult, and I think the AASK trial at the NIH showed that it's hard sometimes to get minority populations into clinical trials such as this.

DR. LINDENFELD: Right. I'm not just talking about recruiting, but rather making sure that the minority groups are equally represented among the treatment groups.

DR. EDMUND LEWIS: Oh, yes. No, I agree with that. Absolutely.

DR. LINDENFELD: And I think that's going to be an important point. At least the literature would suggest there is an increased rate of progression of diabetic renal disease in minority groups, suggesting that you'd want those to be equal.

Just a second point just for my own understanding. Can you tell us if there are any commonly used drugs -- and we use a lot more drugs in these patients now than we did when the captopril study was done -- that affect the secretion of creatinine or the absorption of albumin?

DR. EDMUND LEWIS: In this trial -- actually it was true in the captopril trial too -- in order to control blood pressure, in addition to the coded medications, at least three antihypertensives and diuretics were used. So, the treatment of hypertension, which of course, actually both from a cardiovascular and a renal point of view, is terribly important in this patient population, is a polypharmacy issue and that is a very relevant question.

None of the antihypertensives -- actually we had this data in the type 1 study because it was a much smaller study. We had iothalamate clearances in those patients, so we were able to determine whether drugs

altered creatinine secretion better because we had both the creatinine clearance and the iothalamate GFR. We can compare those.

The antihypertensive agents generally used, which is what was used in the study, and the diuretics generally used would not alter significantly the creatinine secretion course. And I think this sort of goes back to your first question. The randomization of these patients and the fact that all of these drugs were being used in all patients would sort of cancel things out if there was a minor difference, but to our knowledge there is no difference.

And in terms of albumin excretion, I think all that you can say about that is that there is certainly a relationship between the variance in albumin excretion and the systemic blood pressure so that if you lower the systemic blood pressure, you will have less albumin excretion over a very broad range of albumin excretion. Therefore, in designing a study where one's endpoints are albumin excretion, you have to account for the blood pressure lowering effect.

DR. LINDENFELD: And then just one final question. In the type of patient that was entered in the IDNT trial, a patient with gross albuminuria and elevated creatinine, how much would you expect the initiation of

diuretics to change the serum creatinine?

DR. EDMUND LEWIS: I wouldn't. I think what we found is that -- you see, it's hard for me to answer this question for the trial because in a very complex group of patients like this, physicians were using more and less diuretics according to how much edema the patient had. We were really all over these doctors in terms of controlling blood pressure and stuff. So, there were variances in dosing even of diuretics.

But the only direct answer that I can give you about that is that we did have a protocol about elevation of the serum creatinine early because what we were concerned about was whether, using an agent like irbesartan, something that interrupted the renin-angiotensin system, a patient with bilateral renal artery stenosis would go into acute renal failure.

Now, as it turned out, that didn't happen during the study, but there were patients who raised their serum creatinine early in the study because they suddenly had their blood pressure controlled, and you will see the data on that. Most of the patients coming into the study were way out of control relative to any standards, and once they had their blood pressure controlled, which included diuretics, there would be a bump in creatinine in a number of these patients, and we at the clinical coordinating

center of the collaborative study group would be advised about these patients I think generally, usually. Certainly if they doubled their serum creatinine, we would, but if they raised it by 25 percent, we would be advised about that, and we would talk through the clinical problem and invariably the creatinines came back to normal once diuretic therapy was modulated. So, these are very complex patients.

I think that we had the appropriate feedback to figure out that this was happening, and it was not a study-long issue. It was an issue that would occur early in the study when these patients were getting their blood pressure controlled.

DR. BORER: Dr. Kopp?

DR. KOPP: Thank you. I'd like to echo a second time that that was an excellent presentation of a complicated topic.

I'd like to get your thoughts about a topic that I'm sure will come up again which is the role of macroproteinuria as a surrogate endpoint for both diabetic nephropathy and in the future nondiabetic nephropathy. We know that the level of proteinuria represents a graded spectrum of risk for rates of progression. Do we know quantitatively what level of reduction in proteinuria is clinically significant, and is there data in terms of a

similar quantitative reduction in risk of progression?

DR. EDMUND LEWIS: Well, you know, I think nephrologists are on the same wavelength on this issue, and I think that the wavelength that we're on is that I think we're all beginning to understand that the more proteinuria you have, the worse your course will be. I think that we can all agree with that.

I think the other thing that we have to say for certain is that no clinical trial has been designed to test the answer to your question. You can tell me if I'm wrong on this, but I think that it would require a design where you're actually shooting for two different levels of reduction of proteinuria, for example, and that hasn't happened. So, all of the data that we're working with is post hoc.

Having said that, I think that when one looks at a given disease like diabetic nephropathy, given the problem of constraints of how long you're actually going to be able to follow these patients in a clinical trial, I think the best that we can say is that one group did or didn't progress in terms of their proteinuria more than the other, implying that the patients who had greater progression of proteinuria are at greater risk of continuing renal damage.

I think that almost for certain any study of

kidney disease where the patient does well, well being progression or regression of renal disease, the proteinuria goes down. And any patient who does poorly, that is, their GFR keeps going down, the proteinuria is likely to go up. But it becomes a chicken and egg thing then because is the proteinuria going up or down because you're treating the glomerulus or is it going up or down because proteinuria is a determinant of nephrotoxicity let's say. And I don't think that any of these trials, including the ones you'll be hearing today, necessarily -- Dr. Parving might have different feelings about this, but I don't think they necessarily help in terms of answering your question.

DR. KOPP: So, I guess I hear you saying perhaps it's not quite time to begin to use proteinuria as an endpoint in and of itself. Is that the implication?

DR. EDMUND LEWIS: No, I'm not saying that because what I'm saying is that I think that -- well, the first thing that I have to say is that -- and I think again nephrologists understand this in general together well. When you're studying a filtration system, there are so many things you can study, and it doesn't matter whether you're an industrial engineer or a bioengineer studying dialysis membranes or a renal physiologist. What you can study is either the capacity of the membrane -- and in terms of the kidney, it's the glomerular filtration rate -- or the

selective permeability characteristics of the membrane, which in glomerular disease is proteinuria.

So, I think that it is time for us to recognize that if one prevents going from low amounts of protein excretion to high amounts of protein excretion, certainly we have enough correlations there to be able to say that that is progression of the renal disease. So, I would argue that a study, the goal of which was to show that you didn't go from one stage of the disease to the next stage of the disease, more proteinuria, is a valid study of the intervention in the course of renal disease. But that's just my opinion.

DR. KOPP: Thank you.

DR. BORER: Dr. Brem?

DR. BREM: I'd like to ask again a question about glycemic control. One of the things that people have stressed in the past is adequate glycemic control for patients and that that is a major factor in progression of disease. Yet, there wasn't any discussion about that in your presentation. I was wondering if you might comment a bit about that and perhaps how it may affect outcome.

DR. EDMUND LEWIS: Well, glycemic control in either the type 1 or type 2 patients is certainly not easy, but in the type 2 patient, it is extremely difficult because of the fact that you can't just give them insulin

and get the response you want. I think we have the UK PDS, for example, which says that a glycemic control is important.

In the IDNT, there was a tremendous range in terms of hemoglobin A1C's which narrowed over the course of the disease. However, there was still a range. These people are extremely hard to control.

One of the investigators who was on our executive committee, Dr. Rudy Bilous of Great Britain, who's I think a well-respected diabetologist worldwide, looked at our hemoglobin A1C data relative to data that they had gotten in the United Kingdom of control of type 2 diabetes and found that basically the distribution of our hemoglobin A1C's was exactly what was the case in the general population of type 2 diabetic patients.

More important to your question is that irrespective of how difficult it is to control hemoglobin A1C's, the level of hemoglobin A1C throughout the study in all three treatment groups was equal.

DR. BREM: Right. Well, I guess the question I was asking is if the hemoglobin A1C were in the lower range, did those patients progress more slowly in all the different categories of treatments from these different studies, sort of an analysis of variance.

DR. EDMUND LEWIS: I think that neither the

collaborative study group nor Bristol-Myers Squibb has looked at quartiles or quintiles of hemoglobin A1C and the rate of progression. I think we just haven't looked at that. I think that it is an interesting question, but I think that for us the two really burning issues were: one, was our glucose control what is seen in patients in the wild, which was true; and two, was it equivalent in all three groups. Of the many, many analyses that we've done through, I'm sorry to say we haven't done the one that would satisfy you for that question.

DR. BREM: The other was a minor thing I guess in terms of the creatinine doubling. That I guess is assuming that the creatinine in most people is 1. As a pediatric nephrologist, I would point out that many children have creatinines considerably below 1 and perhaps small adults have creatinines that are below 1 as well, as creatinine reflects muscle mass. If the creatinine is below 1, for instance, and doubles, it may go into what's still considered a normal range and yet be doubled and, in fact, probably represents a 50 percent reduction in renal function. Does that 9 months apply to those patients?

DR. EDMUND LEWIS: Yes. No, I agree with that although I just want to expand on that for non-nephrologists who don't think about creatinine clearance on an hourly basis during the course of the week. The

hyperbolic curve that I showed you, that particular curve would have been 100 over the serum creatinine. In very muscular people, the daily creatinine production would be much higher, which would shift the entire curve to the left, but it remains a hyperbolic curve with the same shape and so forth. In small people, children, very elderly people and so forth, the curve might be shifted to the left rather than the right because they're making much less creatinine but it's still a hyperbolic curve.

In our study -- and you'll be hearing more about this -- the creatinine entry was such that you could not double your serum creatinine and remain in the normal range. If you doubled your serum creatinine, you were in the high 2's or 3's. I think a woman could have a lower creatinine and come into the study, but still, when they doubled, their creatinine was quite elevated. So, we don't have information about patients who doubled their serum creatinine and it's still in the normal range.

I think because of the hyperbolic curve, which would be much steeper in a child, it would be much harder to know exactly where you've doubled and halved your creatinine clearance because you're really on that down slope which is why, in the design of the clinical trial, we're going to the linear part of the hyperbolic curve not up the vertical axis.

DR. BREM: So, those patients probably already had evidence of significant renal disease or impairment at the start perhaps of their study.

DR. EDMUND LEWIS: Yes. The mean GFR coming into our study was 50 and the mean urine protein was 900 milligrams. The glomerulus that I showed you was not the worst glomerulus that I picked out of 30 renal biopsies. We really were studying advanced disease.

But I think that you hit upon the issue which we just discussed, and that is the patient with early diabetic nephropathy, which is where you really want to intervene, is in many ways analogous to the patient who is a child. That is, you start to get evidence of renal disease, but you can't actually measure it accurately by measuring the glomerular filtration rate. So, all that is left for us is measuring the other parameter of filter function which is permeability. I mean, that's all that's left.

DR. BORER: Before we go on to other questions, let me ask Bristol-Myers Squibb to sort of make a bookmark because you may have some data which we haven't heard yet, so I don't want an explanation now, relevant to Dr. Brem's question. My recollection is you did Cox model analyses on these data, so you could at least tell Dr. Brem and the rest of us whether the effect on proteinuria and the other

endpoints is independent of the effect on glycemic control or on glucose or on hemoglobin A1C even though you may not be able to give specific data. Don't tell us now but when you present the data.

Are there any other questions from people around the table about the pathophysiology of renal disease? Ray, you had a question?

DR. LIPICKY: I guess I'd like to just clarify something as a non-nephrologist. I think I heard you saying two things, and maybe you did and maybe you didn't. But you're saying, I think, that if you understand kidney disease, the creatinine is not a surrogate measure of anything. It is a measure of disappearance of functional glomeruli, and consequently although patients don't feel anything and there is no morbid/mortal consequence that is associated with any creatinine, it is a direct measure of how many functional nephrons you have and that may be just an exaggeration. So, that's part one.

Then part two is that although progression from microalbuminuria to overt proteinuria again is not a symptom, that if you understand the nature of the disease, that is a sure sign that something has happened to the glomeruli, and if you do not see that happen, then that's a sign that nothing has happened to the glomeruli. Did I say that in the right way?

DR. EDMUND LEWIS: Let me think about it for a second.

Now, one thing you should understand, Dr. Lipicky, is that in the profession we consider you a nephrologist.

(Laughter.)

DR. EDMUND LEWIS: So, I just want to make that clear.

In terms of the creatinine parameter, yes, I think that you state it correctly, and that is in terms of kidney diseases, in terms of the fact that there's disease going on in the kidney, not just type 2 diabetes, but a whole variety of kidney diseases are silent. And if you are trying to measure the progression of renal disease, you are left with measuring the functional ability of the kidney as a filter, and creatinine is a direct measure of that filter. That's why I say it's not a surrogate because it is measuring the function.

And in terms of the proteinuria question, yes, once again, I think that in proteinuria studies you have to be careful because there are, on a day-to-day basis, many factors which can alter the excretion of protein, including if you run up to the top floor of this hotel and run back down, you will excrete more albumin than if you were just walking around here. You have to be careful about that

because there are alterations in the tendency of that filter to leak protein under a variety of conditions, chain smoking cigarettes for a while, running around, running marathons, and so forth. But when you get fixed increases in the level of protein excreted and you start crossing borders, like the border into overt dip stick positive proteinuria, you are then talking about changes which reflect the early changes in the course of disease.

DR. BORER: Any other questions? I think Alan and Steve each had a concern. Alan?

DR. HIRSCH: My question is again a follow-up to Dr. Kopp's and my nephrology colleague's question. When we talk about surrogate markers, obviously, we have to place some kind of value on the surrogate, and later today we'll be talking about combined endpoints and value to the patients. I want to come back one more time.

With some surrogate markers, there's a percent reduction in LDL cholesterol. I know pretty well what that does to the patient in terms of any cardiovascular risk. There must be some threshold below which intraocular pressure decrease will prevent blindness, some nadir wedge pressure change which alters shortness of breath and mortality.

What I struggle with as a non-nephrologist is what level of microalbuminuria change has any impact down

the road in some time frame on a clinical outcome. Do we have any information, or is it merely at this point a qualitative improvement in the natural history?

DR. EDMUND LEWIS: Tell me if this is adequate or not. What I would like to do, since Dr. Parving is probably the most logical person in the world to discuss this topic, I really want you to hear his opinion about this.

But to just go back to my answer to Dr. Lipicky, I think the problem is the goal being early intervention. I think that your confidence about measuring something that doesn't have a symptom and that is a point in time during the course of a disease is dependent upon how much information you have about the natural course of this disease. One of the things that you can be sure of in diabetic nephropathy is that the course is inexorable, so that when you start to see increases in urine protein excretion, you can be certain that that will progress if there is not an effective intervention. I think we know enough about the course of diabetic nephropathy to be able to say that, but to a certain extent, I'd like to defer to Dr. Parving who's done I think most of the really truly valid publishable studies in this area.

DR. BORER: Maybe we can hold that for Dr. Parving's presentation.

Final question, Steve?

DR. NISSEN: The cause of mortality in these patients of diabetic hypertensive disease, if I'm correct, isn't about 80 percent of the mortality cardiovascular?

DR. EDMUND LEWIS: Yes.

DR. NISSEN: Myocardial infarction and stroke being the most common.

DR. EDMUND LEWIS: Yes.

DR. NISSEN: So, would not one test of this surrogate of doubling creatinine be the relationship between the ability to affect the doubling of creatinine and the ability to affect cardiovascular mortality, death, myocardial infarction, nonfatal infarct, stroke, et cetera?

DR. EDMUND LEWIS: See, I think it's not a one to one. It's a relative increase. And we're talking about populations now.

You get into a very interesting, complex issue, and these are interesting and complex patients let me tell you. There's no pleasure to do a clinical trial with this group of patients.

Microalbuminuria in the nondiabetic population -- let's say the hypertensive population -- is a marker of cardiovascular disease. People, for example, with hypertension who have microalbuminuria have a much worse prognosis over the next 10 years in terms of myocardial

infarction, cardiovascular death and so forth than people with hypertension who don't have microalbuminuria. And we don't know why that is. We don't know what the vascular issue is that explains that.

But I think that at this point I have to say that because there are a number of clinical states associated with decreased perm selectivity and microalbuminuria, it doesn't negate the importance of that parameter in diabetic nephropathy just as decreased glomerular filtration rate is seen in many diseases, it doesn't mean that studying that in diabetic nephropathy is not valid.

So, the microalbuminuria means that, indeed, that is a population of patients who have increased cardiovascular risk. Obviously, type 2 diabetic patients have increased cardiovascular risk. But I don't think that one can draw the conclusion that you can use a renal parameter in patients with overt or even latent diabetic nephropathy with a cardiovascular index and say the cardiovascular event is the hard endpoint even though the albumin is the renal parameters --

DR. NISSEN: But if that's what happens, if your renal function gets worse, you ultimately go on and die a cardiovascular death, then wouldn't one want to see that a drug that slows the development of end-stage renal

disease would have a beneficial effect on the hard cardiovascular endpoints? What I'm getting at is, as a way of validating the surrogate, whether or not we ought to see such a relationship.

DR. EDMUND LEWIS: You know, you're undermining my concluding statements.

(Laughter.)

DR. EDMUND LEWIS: The thing is that if you look at the cardiovascular course of patients with type 2 diabetic nephropathy, certainly there are excess cardiovascular events throughout nephropathy and those patients with type 2 diabetes who have proteinuria have many more cardiovascular events than those who don't, and those who have a decrease in GFR have more still than those who don't. And when they go on dialysis programs, the cardiovascular events go way up. Of course, that is why, in terms of preventing cardiovascular events, the one dramatic thing that we can do is prevent them from going on to end-stage renal failure.

But I think that in this patient population, what I've come to see is that the cardiovascular disease in patients with advanced renal disease -- so, we're talking about the IDNT patients -- is so advanced when you start to study those patients that I don't think that you can use a cardiac endpoint to indicate that you've done something as

far as -- you know, that altering the progression of kidney disease can alter that. I think that that's what it comes down to.

DR. BORER: I made a misstatement. We have one final question from the far side of the table there.

DR. TEMPLE: The previous discussions are interesting. They go to the heart of surrogacy and all kinds of things. I would say we've certainly accepted the idea that creatinine doubling is an anatomical finding that has something to do with whether you're going to have renal failure. That's not a big stretch in many ways for reasons you just gave.

It would be true, though, that something that had a physiologic effect or a pharmacologic effect on creatinine might not be very persuasive because what you're saying is when you see a creatinine doubling, that's really an anatomic effect. You're describing the state of the glomeruli. So, something that had a transient effect wouldn't be nearly as persuasive. You wouldn't know what to make of that. JoAnn was sort of asking about that before.

My question goes to the microalbuminuria. Do we know whether any of the drugs being studied here might have a sort of physiologic effect -- I'm not sure what that would be -- that would decrease the amount of albumin but

not really reflect the state of the kidney?

Just by analogy when people wanted to say that use of ACE inhibitors at the time of an infarction would prevent remodeling, we always said, well, that's nice but just showing a change in ejection fraction while still on drug is not very impressive because that just may be that you're a vasodilator. So, that doesn't prove anything. Take the drug away and show us that you still have an impact on ejection fraction. That would be convincing.

So, my question is how, does that apply to the microalbuminuria findings here? Is there anything these drugs might do that could be fooling us about whether they're really making an anatomic change or just sort of changing the hemodynamics in the kidney to alter protein excretion? What's known about that?

DR. EDMUND LEWIS: I think that that's the important question for you. It's the important question for us when we're designing trials, and in a way it is very, very difficult to come up with a concrete answer unless you follow these patients for 10-15 years. So, we do have the constraint of coming up with a parameter within the period of some reasonable clinical trial.

I think that Dr. Parving will address this because in the IRMA 2 trial, the higher dose angiotensin receptor blocker actually was associated with continued

decrease of urine albumin excretion even after the drug is stopped. And I think that that's probably the best that you can ask for if you want to say it's physiological. It's not physiological.

I think in terms of the preamble to your question, there's very, very little known about tubular reabsorption of albumin, and I think that you will see in the IRMA 2 trial data with two doses of ARBs and so forth. I don't think that there is a reason to believe that decreased albumin excretion is because the same amount has been filtered and more is being reabsorbed. That certainly does occur for sure with lowering the blood pressure and that has been accounted for in this trial. So, I think my goal here is to get off this podium.

(Laughter.)

DR. EDMUND LEWIS: After Dr. Parving's talk, I hope you will grill him about this.

(Laughter.)

DR. BORER: This is really the final question. Tom?

DR. FLEMING: Well, I think my colleagues have asked a lot of the key issues here, as I've been thinking about it, but I think Dr. Temple just got at something that I've been thinking about as I've been listening to you.

You had mentioned creatinine clearance is, in

essence, not a surrogate. It is truly the clinical event of interest. And listening to your presentation, it strikes me that what would be the truer measure would be something that's fundamentally structural progression, structural abnormality versus functional abnormality. I'm motivated to ask the question by Bob's question because it seems as though there are more factors that could influence the functional abnormalities. Wouldn't we best be served, although it may not be so achievable, to be looking at something that is directly structural progression, structural abnormalities?

DR. EDMUND LEWIS: Well, no. I think in an ideal world -- and I think it's not unreasonable to make that demand. You know, this is coming out of a life where my focus has not been diabetes. It's been lupus actually. So, we're more interested in structural and functional issues there.

First of all, I think that is to me not conceivable that one could do a study of multiple biopsies in this patient population. This happens to be a dangerous population for renal biopsies, and I think we were very fortunate in many ways that we did the pilot trial and that was fine because this is a very obese population of patients and they have hypertension. So, their risk with renal biopsy is greater than the usual patients whom we

biopsy.

The ethics of doing multiple biopsies I am not sure that any IRB would approve of, but I can't speak for IRBs in the future and so forth. And I know that comment probably doesn't mean anything in terms of what's going on here, but that is my opinion.

The other thing about that -- and we've certainly seen this in doing multiple biopsies in other diseases like lupus -- is that there is a sampling issue so that if you want to find a difference between two biopsies, certainly there are morphometric ways of measuring things, but in the end, even though it sounds like that might be the gold standard, the fact of the matter is that the accurate and reproducible way of studying renal function is the functional issue which is the ability of the kidney to filter and not the morphologic issue which in this case, especially with the advanced disease, would mean that you would be trying to show stability. That would become a real statistical issue in terms of morphology.

So, in answer to your question, I think that ideally certainly at the bench with experimental animals, that's what you do, but in terms of our ability to actually study clinically patients with type 2 diabetes, I don't think we could do it.

DR. FLEMING: Well, I can readily be persuaded

with what you've said, that measuring these functional abnormalities may be more measurable and even potentially more reproducible. My concern is more uncertainty about what is the magnitude of effect, duration of effect, and other factors that could influence those functional abnormalities that aren't necessarily integral to what it is that we're trying to do here.

DR. EDMUND LEWIS: Well, let me just ask you, are you referring to the perm selectivity issue, which is the proteinuria issue, or are you referring to the filtration issue?

DR. FLEMING: Actually my concerns would apply to any of these markers.

DR. EDMUND LEWIS: I guess the key term here with type 2 diabetic nephropathy is "inexorable." As you will see, using the serum creatinine as a direct measure of renal function, you can expect progression, you can expect doubling, indicating having the glomerular filtration rate. Shortly after that, you can expect the patient to get to a level of renal function where they require dialysis and transplantation, and that is progressive, and I think that you will see in our data that that in fact is what happens.

So, if one uses doubling of serum creatinine, as we have, as the index of significant loss of renal function, those patients invariably progress to the hard

endpoint, if you will, which is requiring end-stage renal failure management. And it's there where it's undeniable that you've actually got a clinical event.

So, we are not talking about a measure. We're not talking about creatinine as a surrogate any longer; we're talking about it as a measure. But we're not talking about it as a measure that doesn't have serious clinical significance; we're talking about it as a measure that ultimately we can expect a hard endpoint, if in fact we were to follow the patient long enough.

DR. BORER: JoAnn?

DR. LINDENFELD: Just one final question. You showed very nice data in the captopril trial that creatinine clearance and iothalamate clearance were exactly equal. Do we have any data at all like that in this type of patients before the institution of therapy and after the institution of therapy?

DR. EDMUND LEWIS: No. Well, I'm not sure I get your question.

DR. LINDENFELD: To be sure that secretion is not an issue.

DR. EDMUND LEWIS: No, we don't have --

DR. LINDENFELD: It seems like that's a physiologic measure that would help us understand that, as Dr. Temple brought up, we're not seeing sort of a

physiologic change that's not reversible. So, that kind of measurement would be enormously helpful to show that, before and then after treatment, those two things don't change.

DR. EDMUND LEWIS: Yes. Again, I want to emphasize that patients entering the IDNT were patients who had really advanced disease. As you will see, their blood pressures were high even on antihypertensive medication before they got to us, and this is not a clinical situation where we can just stop drugs and do clearances. I don't think that it's something that is a practical thing in this patient population. I don't believe that one can get the data that you're asking for, which is creatinine dynamics off the drugs that these patients are going to have to be on. So, it's a problem there. What I'm saying is I don't think there's an answer to your question.

DR. BORER: Dr. Lewis, I want to thank you very much. I must say I wish you had been speaking about this to my class when I was in medical school.

(Laughter.)

DR. BORER: We'll go on and while we're doing that, I want clarification that requires only a yes or a no from Dr. Cooper or maybe from Dr. Daniels. Is it true that the proposed indication is for the treatment of patients with type 2 diabetic renal disease, not for the patients

with hypertension and type 2 diabetic renal disease? Is that correct?

DR. COOPER: With hypertension.

DR. BORER: Because that's not what was given to us. So, we have to make that clarification.

DR. COOPER: In both studies all the patients had hypertension.

DR. BORER: I know they did, but the proposed indication, your slide A-6, doesn't say that. That's why I'm asking. But now you've clarified it. You're asking for approval for treatment of patients who have hypertension and type 2 diabetic renal disease.

Having clarified that, let's move on. Dr. Cooper?

DR. COOPER: Good morning, Chairman, members of the advisory committee and the FDA and invited participants from the academic community. I have been involved with the irbesartan diabetic nephropathy trial since its inception working with Dr. Lewis and the collaborative study group to design this trial between 1993 and 1995. I am here today to share the results with you.

The presentation is divided into four segments: the study design and conduct, the demographic and baseline data, the efficacy results, and the safety.

The irbesartan diabetic nephropathy trial, or

IDNT, was designed as a single trial that tested two hypotheses. Does interruption of the renin-angiotensin system with the angiotensin II receptor antagonist irbesartan provide renoprotection in subjects with type 2 diabetic nephropathy independent of blood pressure lowering? Specifically, would irbesartan be superior to placebo in the primary comparison and would irbesartan be superior to amlodipine in the secondary comparison?

The primary endpoint was a composite of doubling of baseline serum creatinine, end-stage renal disease, or death. The design of the study was carried out according to the principles that the collaborative study group had established in the type 1 diabetic nephropathy study with captopril. An irreversible doubling of serum creatinine is a direct measure of the decline in the kidney's ability to filter blood and corresponds to the loss of 50 percent of renal function. When a subject reached doubling of serum creatinine as an endpoint, coded medication was stopped to allow the study investigator to treat the subject outside of protocol. Verification of doubling of serum creatinine as an endpoint required submission of two consecutive samples for measurement of serum creatinine by the central laboratory at Rush Presbyterian Hospital after all corrective actions defined by the protocol had been undertaken to confirm there were

not reversible causes.

End-stage renal disease was defined as renal transplantation, the need for dialysis, or a serum creatinine equal to or greater than 6.0 milligrams percent. This threshold for serum creatinine was selected because it is the trigger for initiating dialysis in diabetics as endorsed by Medicare.

All-cause mortality was included in the primary composite endpoint due to the competing risk of cardiovascular disease in these type 2 diabetic subjects.

The secondary endpoint involved cardiovascular events that affect these subjects: cardiovascular death, nonfatal myocardial infarction, hospitalization for heart failure, permanent neurological deficit attributed to stroke, and amputation.

All primary and secondary outcome measures were adjudicated by the outcome confirmation and classification committee or the mortality committee without knowledge of coded medication assignment. These committees were independent, non-BMS entities.

In order to qualify for study entry, subjects had to be 30 to 70 years old with type 2 diabetes, hypertension, as defined here, and a urine protein excretion exceeding 900 milligrams. Serum creatinine was between 1.0 and 3.0 milligrams percent in women and 1.2 and

3.0 milligrams percent in men to assure that renal function was on the linear slope of decline.

Subjects from 209 sites located in 27 countries were randomized to one of three treatments: placebo, irbesartan, or the calcium channel blocker amlodipine.

When the trial was first designed, the relative importance of blood pressure lowering alone versus unique benefits of antihypertensives with mechanisms of action, other than interruption of the renin-angiotensin system, in type 2 diabetic nephropathy remained to be determined. Published reports of studies in experimental models and in patients with either microalbuminuric or proteinuric diabetic renal disease suggested that administration of calcium channel blockers could be renoprotective. Furthermore, amlodipine at that time was the most frequently prescribed antihypertensive used in diabetics.

In order to test the two study hypotheses, aggressive management of blood pressure control was essential. Multiple antihypertensives, with the exception of those disallowed by the protocol, angiotensin II receptor antagonists, ACE inhibitors, and calcium channel blockers, were added for all subjects to ensure that the target blood pressure level, 135 over 85 millimeters of mercury, was reached. An independent committee of physicians, the clinical management committee, reviewed

data periodically in a blinded manner to ensure a blood pressure lowering to target levels for each subject and across the three treatment groups.

Subjects were followed for an average of 2.9 years and were seen every 3 months until the end of the study. A data safety monitoring committee reviewed unblinded safety and efficacy results periodically throughout the study.

1,715 subjects were randomized to one of the three treatment groups and all were included in the intent-to-treat analysis. 16 subjects did not receive study drug. All of the 1,699 subjects who received at least one dose of study drug were included in the safety analysis.

408 subjects discontinued study drug early. Of these subjects, 161 reached one of the endpoints and 121 were followed until study closure without an endpoint. 118 subjects were missing measurement of serum creatinine at study closure. Dialysis, transplantation and mortality status was known in 89 of these subjects. Mortality status was known in the remainder. 8 subjects were lost to follow-up. The remaining 1,291 subjects completed double-blind therapy as defined by the protocol.

The incidence of discontinuation of study drug was similar across the three treatment groups.

The baseline characteristics of all randomized

subjects is demonstrated here. It was similar across the three treatment groups. Subjects were close to 60 years of age, predominantly male and caucasian, with type 2 diabetes for an average of 15 years. In response to one of the earlier questions, distribution of the races across the three treatment groups was similar.

Consistent with the natural history of the disease and the duration of known diabetes, subjects had mild to moderate renal insufficiency with a mean serum creatinine of 1.7 milligrams percent, and notice here the creatinine clearance at baseline was 57 to 59 milliliters per minute. Normal creatinine clearance in this population would be considerably higher.

The mean urine protein excretion was close to the nephrotic range.

Blood pressure measurements at baseline were also similar across all treatment groups.

Here are the mean systolic and diastolic blood pressures plotted over time. Reductions in systolic and diastolic blood pressure from baseline were observed in all three treatment groups. The attained blood pressure levels were clinically indistinguishable in the irbesartan group, which is in yellow, and the amlodipine group in blue. There was a 3.9 millimeter of mercury and a 2.7 millimeter of mercury difference observed between the irbesartan group

and the placebo group in pink in the mean systolic and diastolic blood pressures, respectively. While these differences are statistically significant, analyses of the primary efficacy endpoint, to be shared with you shortly, confirm that these differences are not clinically meaningful in this study.

On average, two to four antihypertensives were required to achieve this level of blood pressure control. The most frequently prescribed antihypertensives were beta-adrenergic blockers, central adrenergic agonists, and peripheral adrenergic blockers. The use of all classes of agents was slightly more common in the placebo group. The majority of subjects used either thiazide diuretics or, as renal disease progressed, loop diuretics.

As you recall, the primary efficacy measure is the time to the composite endpoint of doubling of serum creatinine, ESRD, or death. This slide shares the primary results of the study. As seen here, irbesartan in yellow significantly increased the time to the primary composite endpoint when compared to placebo in pink, demonstrating a 20 percent relative risk reduction, with a p value of 0.023. The treatment benefit was apparent as early as 18 months and was maintained throughout the study.

In the secondary comparison with amlodipine in blue, a 23 percent relative risk reduction was observed.

Again, this difference was statistically significant with a p value of 0.006. This treatment effect was seen in the setting of clinically indistinguishable blood pressure levels.

To confirm that the blood pressure differences between irbesartan and the placebo groups were not clinically meaningful, the primary analysis was adjusted using blood pressure levels as a time dependent covariate in the Cox regression model. The results for the primary efficacy endpoint were similar with a relative risk reduction of 19 percent and a p value of 0.035.

A similar analysis, adjusting for the levels of hemoglobin A1C, was also conducted, and once again, the results for the primary composite endpoint were similar.

Lastly, the amlodipine group behaved similarly to the placebo group with no observed benefit in the primary composite endpoint.

This slide displays the Kaplan-Meier curves for the renal outcomes, a predefined endpoint consisting of doubling of serum creatinine or ESRD. Treatment with irbesartan in yellow significantly delays the progression of diabetic nephropathy compared with placebo in pink with an observed relative risk reduction of 26 percent. This was statistically significant with a p value of 0.012.

For the secondary treatment comparison with

respect to amlodipine in blue, a 34 percent relative risk reduction in favor of irbesartan was observed. This again was statistically significant with a p value less than 0.001.

The Kaplan-Meier curves suggest that the treatment benefit was observed as early as 18 months and was maintained for the duration of the study. The Cox regression analysis confirmed that the observed renal benefit of irbesartan was independent of blood pressure lowering.

Together, these results prove that blockade of the renin-angiotensin system with irbesartan delays the progression of diabetic nephropathy and that these benefits were in addition to blood pressure reduction alone.

Data on the next two slides provides insight into the relationship between doubling of serum creatinine and ESRD.

Patients with proteinuria who double their serum creatinine have advanced to the stage of the disease characterized by progressive and irreversible loss of renal function. This is evident in this analysis showing the cumulative rate of reaching ESRD for subjects who have doubled their serum creatinine. The median time to ESRD, defined as renal transplantation or the need for dialysis or serum creatinine of at least 6.0 milligrams percent,

once halving of the GFR has occurred, was 9.8 months and is similar to that observed in the captopril trial of type 1 diabetics, which was 9.3 months.

The relationship between serum creatinine and ESRD is further defined on this slide showing dialysis and transplantation events that occurred in subjects after doubling of serum creatinine or in subjects who experienced ESRD as defined by a serum creatinine of at least 6.0 milligrams percent as a first event. Of the 322 subjects who doubled their serum creatinine, 133, or 41 percent of subjects, underwent dialysis or transplantation during the period of follow-up. In contrast, only 5 percent of subjects who never experienced a serum creatinine event reached ESRD. These results indicate that progressive decline in renal function increases the risk of subsequent outcomes.

Of the 71 subjects whose first event was ESRD, as defined by the serum creatinine, the overwhelming majority, 59 or 83 percent of subjects, went on to dialysis or transplantation, and this occurred in a relatively short time frame. The mean time until dialysis was initiated in these subjects was only 2.5 months.

Based on these results, it is reasonable to conclude that with longer follow-up, all subjects who doubled their serum creatinine would reach ESRD unless

death intervened. Furthermore, these results mirror practice in the nephrology community. The standard approach to the treatment of diabetics with advanced nephropathy is to periodically monitor serum creatinine and initiate dialysis once the serum creatinine reaches 6.

The next series of slides portray the results for the components of the primary composite endpoint and the secondary endpoint analysis, cardiovascular morbidity and mortality.

This slide displays the relative risk reductions of the primary composite endpoint and the individual components. In order to assess the impact of treatment on the individual components, all occurrences of that component event were included in the time-to-event analyses. When a subject reached doubling of serum creatinine as an endpoint, coded medication was stopped to allow the study investigator to treat the subject outside of protocol. Thus, the intent-to-treat analyses presented for each of the components include events which occurred in subjects who were no longer on coded medication.

The first panel displays the risk reductions for the comparison of irbesartan and placebo and the second panel for the comparison between irbesartan and amlodipine. The observed benefit of irbesartan, when compared to placebo, was driven primarily by the two renal outcomes,

doubling of serum creatinine and ESRD. The consistency of the results are apparent in the comparison with the second control group. The relative risk reduction of 23 percent was also driven by the renal outcomes, doubling of serum creatinine and ESRD.

For all-cause mortality, the point estimates are close to 1 for each comparison, suggesting that treatment with irbesartan had no adverse effect on subject safety.

As you'll recall, the secondary composite measure was time to cardiovascular morbidity and mortality and it was evaluated to assess potential risk in the type 2 subjects given the competing risk of cardiovascular disease and to exclude evidence of harm. There was no difference observed between any of the treatment groups.

The sample size here, less than 600 subjects per arm, was smaller than has been typically required to detect differences in cardiovascular events due to blood pressure lowering using drugs with different mechanisms of action. These results reinforce the benefits of optimizing blood pressure control.

The next slide displays the relative risk reductions of the secondary composite endpoint and the individual components for the comparisons between irbesartan and placebo and irbesartan and amlodipine.

Cardiovascular events which occurred in subjects who were no longer on coded medication were included in these intent-to-treat analyses. Furthermore, by protocol, cardiovascular events that occurred after ESRD was reached were not captured because the initiation of dialysis and other therapeutic interventions are known to influence cardiovascular risk factors.

There were no statistically significant differences in the comparisons between irbesartan and placebo for any of the individual events, indicating that there was no overall increased cardiovascular risk associated with treatment with irbesartan.

In the comparisons between irbesartan and amlodipine, the result for hospitalization for heart failure favored treatment with irbesartan. The point estimates indicate directional trends for cardiovascular death, nonfatal myocardial infarction, and stroke in favor of amlodipine treatment. However, the confidence intervals for these risk reductions overlap 1 and did not reach statistical significance.

In view of these results, a post hoc analysis combining the renal and cardiovascular endpoints was conducted to assess the overall benefit/risk of therapy. This combined composite endpoint provides equal weight to both the renal and the cardiovascular events and assesses

the time to the first occurrence of any detrimental outcome, whether it be renal, cardiovascular morbidity, or all-cause mortality. In this analysis in which the cumulative event rate approached 80 percent, irbesartan retains its treatment effect compared with either placebo or amlodipine, a 19 percent relative risk reduction compared to placebo and a 21 percent relative risk reduction compared to amlodipine, thus suggesting that the overall benefit of treatment with irbesartan is preserved.

The final segment of this presentation will focus on irbesartan's safety profile. In general, treatment with irbesartan in this patient population was safe and well-tolerated and resulted in few discontinuations. This table presents the incidents of adverse events, serious adverse events, discontinuations due to any adverse event, and death. There were no substantial differences between any of the treatment groups in these important safety measures.

Just to address one of the earlier questions, there were approximately 260 deaths reported in the study. Slightly greater than 50 percent of them were due to cardiovascular events.

The next slide includes those adverse events of special interest that are likely to occur in subjects with renal disease which resulted in discontinuation of study

drug: hyperkalemia, inability to control blood pressure, edema, orthostatic symptoms, and the early rise in serum creatinine.

It is well known that agents that interfere with the renin-angiotensin system increase the risk of hyperkalemia due to hypoaldosteronism. Although the incidence of hyperkalemia due to these agents is infrequent in patients with normal serum creatinine, in patients with impaired renal function that continues to worsen, the risk of hyperkalemia will increase.

As expected, subjects treated with irbesartan experienced a higher incidence of hyperkalemia compared with either placebo or amlodipine. This resulted in permanent discontinuation of study medication in 12 of the 577 subjects. Periodic monitoring and appropriate intervention reduced the severity of this electrolyte disturbance. No subject with documented hyperkalemia attributed to treatment with irbesartan experienced death associated with hyperkalemia.

Inability to control blood pressure was a concern in this patient population because of the severity of the hypertension. Discontinuation of coded medication for this adverse event occurred more frequently in the placebo arm.

Edema, requiring discontinuation, occurred more

frequently in the amlodipine arm.

Orthostatic symptoms were also a concern because of autonomic neuropathy, and discontinuation of study drug due to orthostatic symptoms was similar across all three treatment groups.

Lastly early rise in serum creatinine, a well-documented risk in patients with bilateral renal artery stenosis treated with ACE inhibitors, only occurred in one placebo-treated subject.

In summary, irbesartan significantly reduced the time to progression of advanced diabetic nephropathy as demonstrated by the beneficial effects on the composite endpoints, renal outcomes and total mortality. There was a 20 percent reduction in the primary endpoint compared with placebo and a 23 percent relative risk reduction with respect to amlodipine.

Importantly, renoprotective benefits of irbesartan were independent of blood pressure reduction.

Finally, in this patient population, irbesartan was generally safe and well-tolerated.

Before I introduce Dr. Parving, I guess I wanted to know if you had any questions.

(Laughter.)

DR. BORER: Yes, we will, and I don't think we'll be able to complete them all before the break that

I'm now told is mandatory for FDA people. Other parts of the Government sometimes tough it out.

(Laughter.)

DR. BORER: But I'm told that this group can't compete. In just about 5 minutes, we will take a break, so we'll have a few questions first. Then we'll complete after we come back from a 15-minute break.

But I would like to ask you a question now so that, since you may not have the answers readily available, during the break you can try to pull the relevant data together.

Granted that ESRD as the first event was relatively uncommon compared with doubling of the serum creatinine, nonetheless you show us an evaluation with ESRD as first event that suggests that this occurred earlier, not quite significantly earlier, but earlier, in patients who were not on irbesartan than in patients who were on irbesartan. Therefore, since all the patients who doubled their serum creatinine were allowed to receive drugs that are presumed to prevent the progression of renal disease, which I guess would in virtually all cases have included an ACE inhibitor or an AT1 receptor blocker -- you can correct me if I'm wrong about that -- I'd like to know, first of all, what drugs were they put on.

And secondly, what happened to the rate at

which ESRD developed in those patients who went from placebo to a presumably effective drug or from amlodipine to a presumably effective drug compared with the rate that was seen before the cut point in the patients who were still on randomized therapy at the time that they hit their first endpoint, being ESRD? That may be sort of complicated and maybe I didn't say it quite right, but I think you get the idea.

If you don't have those data right now, that's fine, but I'd like to know what those results are after the break. Do you have any idea of that right now?

DR. COOPER: No. I'd prefer to take a break and we will compile the data, to the best of our ability, to address your question.

DR. BORER: Okay, that's great.

I'll tell you what. Rather than have at you here, is it okay if we break 5 minutes earlier than you said? Yes, okay.

Tom?

DR. FLEMING: Given, Jeff, that you're putting on the table issues that we might discuss after the break so they have time to get it, one thing I'd like to see is the numbers of people who had dialysis or transplant, and so specifically two analyses: dialysis-free survival analysis and dialysis/transplant-free survival analysis.

I.e., the first being events are either death or dialysis; the second events being either death, transplantation, or dialysis.

DR. BORER: We'll take a break now and we will begin again precisely at 20 minutes of 11:00.

(Recess.)

DR. BORER: I assume that the requirement of the FDA that it get a break will also mean that people who work for the FDA want to have lunch. That's another thing we don't often do in other parts of the world. But to be able to stop in time to do that, we're going to have to start right now. So, let's sit down, get together, and begin the questioning of Dr. Cooper.

Where do we want to start here? Dr. Kopp?

DR. KOPP: Dr. Cooper, I had two questions. You may have mentioned this and I may have missed it. But were beta-blockers similarly used in all three groups, the issue being those also have an antirenin effect.

DR. COOPER: The use of all agents was slightly more common in the placebo group. So, the beta-blockage use in the placebo group was approximately 50 patients of the patients; in the irbesartan group, it was 43 percent; and it was a little bit less in the amlodipine group. So, it was slightly more common in the placebo group.

Your second question?

DR. KOPP: The second question actually -- well, I guess I'll launch in -- is the issue that Tom Hostetter raised in the editorial in the New England Journal, which was the noncomparison with ACE inhibitors. I guess one of the issues here is that as a practitioner with a patient with type 2 diabetes, you can look back on the type 1 diabetic study and see that captopril had a 50 percent reduction in doubling of creatinine, or you can look at this agent with a roughly 25 to 30 percent reduction, and you have to choose. Do you go with an agent that might potentially be more potent or go with the agent that has been used in the particular subset that you're looking at, type 2 diabetes?

So, the question would be you must have given thought to the use of ACE inhibitors. Any comment about why that arm was not used?

DR. COOPER: Yes. Can I please have subtalk 2.4?

There's no data in type 2 diabetics with renal disease as to what class of drug, whether or not it interrupts the renin-angiotensin system, could be effective. This was the first trial conducted in this patient population. There was much discussion, especially because we were doing this study in collaboration with an academic group, about the choice of the comparator.

For using a calcium channel blocker as a comparator, there were three points. The first was we wanted to evaluate blood pressure lowering due to a different mechanism of action other than interruption of the renin-angiotensin system. The second point suggested that calcium channel blockers could possibly be renoprotective, and at the time that the study was designed, between 1993 and 1995, there was a fair amount of literature and much discussion about calcium antagonists in all patients with renal disease. And lastly, because amlodipine was the agent of choice for this patient population, we wanted to assess whether or not this drug could be renoprotective.

Specifically addressing your question about why we did not select an ACE inhibitor as a comparator, there were three points. The first was that we would be testing a mechanism of action that's similar. It's similar but it's not the same. With irbesartan, which is an angiotensin II receptor antagonist, you have complete blockade of the angiotensin I receptor. With an angiotensin converting enzyme inhibitor, you have other pharmacological activity, and specifically you have an entire series leading to potentiation of such things as bradykinin that were not yet tested in this patient population. No one could make any assumptions without data

and without evidence that type 2 diabetics with this extent of renal disease would do well with an ACE inhibitor.

And lastly, we're just being very pragmatic. Should we have conducted a study with an ACE inhibitor, we would have had to conduct a non-inferiority study, and the sample size would have been prohibitive.

DR. BORER: Let's keep on around this side of the table here. Bev?

DR. LORELL: I'd like to hear a bit more information about the actual strategies that were used in the trial when an increase in creatinine, albeit later found to be transient, occurred. Clearly in the real world, certainly in treating heart failure, the major reason for stopping an ACE inhibitor and probably also ARBs in patients for whom ACE inhibitors clearly reduce mortality is seeing transient rises in creatinine. That will impact the use of your drug in the real world.

What strategies were actually used and what was the mean and median absolute magnitude of transient bumps in creatinine that were addressed and reversed?

DR. COOPER: In answer to your last point, we do not have specific data about mean or median transient increases in serum creatinine. What I can share with you is the protocol that was used.

There were approximately five reasons that were

identified that could lead to reversible changes in renal function. The investigators were all instructed to first repeat serum creatinine measurements and determine whether or not any of these five reasons could be contributing to a transient increase in serum creatinine. They then needed to wait an additional 4 weeks before sampling the blood again. If there was still a transient increase, the protocol actually allowed for dose reduction of study drug to determine if there was some dose-related effect. If the increase in serum creatinine was sustained, then measurements from the first aliquot and from the second aliquot were subsequently sent to the central laboratory for confirmation of the serum creatinine. So, on average, there were approximately 4 weeks between the first serum creatinine being drawn and the last serum creatinine being drawn to protect against the possibility that we weren't dealing with a situation which was reversible acute renal failure.

DR. LORELL: But during those 4 weeks, did the investigators embark on the protocol of interventions on those five potential factors?

DR. COOPER: Yes.

DR. LORELL: They did.

DR. COOPER: Yes.

DR. BORER: Blase?

DR. CARABELLO: Let me try to understand better what happened to patients who doubled their serum creatinine. At that point, coded drug was stopped, and they were treated openly and presumably aggressively. How were they then treated statistically? Were they censored from the initial group that they were in, or did they continue on in that group? What happened to them in terms of follow-up?

DR. COOPER: In order to address that question, I'm going to ask the statistician responsible for the results from Bristol-Myers Squibb, Dr. Natarajan.

DR. NATARAJAN: Hi. My name is Kannan Natarajan from Bristol-Myers Squibb. I'm in the Biostatistics Department.

To answer your question, we treated them as intent-to-treat, so we did not actually discard any events that might have happened after they stopped coded medication. All of these patients were analyzed as they were randomized.

DR. BORER: Steve?

DR. NISSEN: Yes. I want to come back to that in a minute.

But first, I wonder if you could put up your slide C-16. Is that possible?

DR. COOPER: Core slide C-16 please.

DR. NISSEN: There are a variety of endpoints listed there, and those of us in cardiovascular medicine tend to think of the hard cardiovascular endpoints as being the composite of cardiovascular death, MI, and stroke. Now, one interpretation of the data -- and I want to see if you concur with this -- is that in the comparison with amlodipine, you saw a 23 percent decrease in the risk of reaching your renal endpoint, but at the cost of, at the expense of, a 36 percent increase in the risk of cardiovascular death, a 51 percent increase in the risk of nonfatal MI, and an 86 percent increase in the risk of stroke.

Each of those point estimates overlap a relative risk of 1, but the hard cardiovascular endpoints, if you lump those together, my guess is -- and I actually did some statistics here myself and Tom probably could do it very quickly. I got a p value of around .01. So, it looks to me like there's actually stronger evidence for an increased risk of hard cardiovascular endpoints than there is evidence for a beneficial effect on the softer endpoint of an increase in creatinine. Is that an accurate reflection of the data?

DR. COOPER: Is Dr. Pfeffer here?

DR. JULIA LEWIS: The FDA has asked for a hold on the question. They're with Dr. Pfeffer right now.

Members of the FDA are with Dr. Pfeffer.

DR. COOPER: Okay. Can we come back to addressing your question when Dr. Pfeffer returns? Thank you.

DR. BORER: I wonder if you've had time to look for the data that I asked about earlier and that Tom asked about?

DR. COOPER: I'm going to begin with the second question that you asked specifically about transplantation and dialysis, with the caveat that in order to produce specific slides with time-to-event analyses, et cetera, we're actually putting those together now and we can share them with you probably after lunch. So, if we could start with subtalk 5.8.

The first slide displays the actual number of events that occurred within end-stage renal disease. So, you have the number of dialysis, transplant, and serum creatinine events. This is all events that occurred, not just those that were part of the initial composite component.

If you look at the irbesartan events, you'll see that 77, 73 plus 4, events occurred in the irbesartan group, and if you look at the placebo group, you'll see that 88 plus 6, or 94, events occurred in the placebo group. So that the incidence of occurrence of

transplantation or dialysis events was less in the irbesartan group than in the placebo group.

I do not have a risk reduction or a p value for that result, but I would be happy to remind you that in the FDA questions, the actual risk reduction of time to dialysis was included, and that's .8. Confidence intervals do overlap 1.

Given that in this study, the progression of renal disease, you would have needed to follow these patients for a continued length of time in order to observe a statistically significant result. Also, the composite endpoint was a composite, and none of the individual components were powered in order to achieve a significant result.

The next slide. This is the total incidence of the events, dialysis, transplantation. Of course, we include serum creatinine since it was part of the ESRD definition for the components. So, we have 77. This is the same slide. 77 and 94.

Let's move on to slide 361 which is the Kaplan-Meier curve of time to ESRD. For the Kaplan-Meier curve here, this is ESRD. This includes serum creatinine of 6. We're trying to pull together the other Kaplan-Meier curve now. The relative risk reduction for irbesartan versus placebo was 23 percent. This was not statistically

significant. It was .07, but it trends in the appropriate direction.

Once again, if you look at irbesartan and amlodipine curves -- excuse me -- if you look at the amlodipine and placebo curves, they're superimposed on each other, indicating that there's no difference in the event rate in those two groups.

DR. LINDENFELD: Could I just add something here? Correct me if I'm wrong about this, but in the captopril trial, there was a 50 percent reduction in end-stage renal disease, and they did not use a definition of creatinine greater than 6.

DR. COOPER: Right.

DR. LINDENFELD: In this trial, all of the difference in end-stage renal disease is in creatinine greater than 6. None of it is in transplants or dialysis. So, there would be no reduction in end-stage renal disease if one didn't use creatinine greater than 6. Is that correct? I believe it is.

DR. COOPER: No, I disagree with that. As I shared with you before, the incidence of transplant and dialysis events was lower in the irbesartan group, and at least for time to dialysis, there appears to be a relative risk reduction in favor of treatment with irbesartan. And that's your last point.

In the comparison of the data between the captopril and the irbesartan trials, there are a couple of points that I think are important to communicate. The first is the relative incidence of death in the type 1 patients who, at the time of the study, were 35 years old and not 58 years old, was very, very different. We had just a handful of deaths, and that's one point.

The second point is in the discussion of the captopril study, in the communications with the FDA as we were designing the study, the feedback that we received at that time was that we needed to have as firm a definition of ESRD as possible.

When you consider that this trial was conducted in 27 countries and the number of investigators, all of whom need to make a decision about when to initiate dialysis, there is no standard in the nephrology community on when to initiate dialysis. We felt very strongly that by including a serum creatinine of 6 or greater as part of the definition of ESRD, we were making that endpoint less arbitrary, and it was a clear definition. That's reinforced by the results that I shared with you earlier in the presentation where the time to dialysis following a serum creatinine of 6 was only 2.5 months.

DR. LINDENFELD: I understand the reasons that you said, and other people may want to comment on this.

But in fact if you exclude the creatinine of 6 and use transplant or dialysis, it was 22 versus 24. So, there was not even a trend to a change. I'm just saying this is different.

DR. COOPER: That's incidence.

DR. LINDENFELD: Right.

DR. COOPER: Okay, we need to have the data for time to.

DR. LINDENFELD: Right.

DR. BORER: Tom?

DR. FLEMING: I think part of what you're saying, JoAnn, is my understanding, and I think what Dr. Cooper has said is in part my understanding as well. Let me just get that out and see if we have a consensus here.

In the captopril trial, they did specifically look only at transplantation, dialysis, survival. It did show a 50 percent reduction and p was .006. I'm still interested in knowing what the results of that endpoint would show in this trial, specifically what does transplant, dialysis, death, as a composite endpoint, show in this trial.

I agree with Dr. Cooper. My understanding is the contributions of the elements will be different. In the captopril trial, only 30 percent of those endpoints in the composites were death, although death did show a

reduction. There was a 43 percent reduction in the death rate, although it was less of the dominant contribution. There were proportionately more dialysis/transplantation events. Here we would see in the composite endpoint, which I'm still waiting -- we still haven't been shown it -- we will have more dominance by death.

My understanding is where you're right, JoAnn, when you look at time to the primary endpoint -- and dialysis is the first event -- there's no evidence of a reduction there, 24/22. But if you continue to follow people past creatinine increases and look at whether or not this translates into a reduction in dialysis -- I believe it's what we're seeing now, which is the data you're showing us -- there's evidence of a 20 percent reduction, but it's not significant.

But clearly when you get this composite endpoint of transplantation, dialysis, death, that relative risk reduction is going to be a fair amount less than 20 percent and not at all close to the 50 percent reduction of captopril in that corresponding analysis. So, I'd still like to see that analysis.

I'd like to move on to a related point, but did you want to say any more about this?

DR. LINDENFELD: No. Go ahead.

DR. FLEMING: Steve brings up another very key

point and that is if we're looking at clinical endpoints looking at the aggregation of clinical endpoints, certainly it's appropriate to focus on those that are renal related. Certainly it's appropriate to look at a transplantation/dialysis-free survival endpoint separately.

But it's also very clinically relevant to say, especially if we're going to compare to amlodipine, what is globally happening here that's really clinically important? When we keep seeing these meta-analyses, we keep seeing the creatinine changes included in those, and of course, they continue to dominate.

There's no question there is a difference in time to doubling. There's no question, and amlodipine doesn't provide that benefit. But if we look at how that translates into true, tangible clinical outcomes, looking first with a focus toward renal, i.e., dialysis, transplantation, death, we haven't seen it yet, but my guesstimate is it's going to be a reduction of 10 to 12 percent relative risk, compared to 50 percent with captopril.

We haven't at all yet seen an analysis that's, in essence, in the spirit of what Steve wants to see, which is let's look at all events that really matter. Let's look at transplantation, dialysis, survival, but then also factor in those important cardiovascular events, such as MI

and stroke, where it would appear that there's no longer an advantage over amlodipine. And in fact, it's not clear to me whether there's a disadvantage. It would certainly be important at some point soon to see those two composite analyses.

DR. COOPER: So, if I understand you correctly, Dr. Fleming, what you're requesting is the time to a combined composite endpoint, excluding the serum creatinine events, that focus just on dialysis, transplantation, cardiovascular events, and death.

DR. FLEMING: Indeed, because essentially what we're looking at here is a continuum. What we're looking at in the primary endpoint is an endpoint that is dominated by time to doubling of serum creatinine. We've seen, however, that there's only about a 9-month lag from that endpoint to end-stage renal disease, and in fact a large number of people have achieved end-stage renal disease endpoints. But those endpoints are still heavily influenced by having serum creatinines hitting 6. And we're told that that, in fact, is a trigger for intervention, although interestingly there is some lag in when that intervention occurs.

But if it's in fact a short lag, then we presumably should be fully adequately powered to see the tangible effects. Does this translate in tangible effects

in terms of reducing the renal-focused endpoint, which is transplantation, dialysis, death? So, let's look at that composite endpoint, numbers of people that had that endpoint, relative risk estimates.

Then looking more globally, as Steve had pointed out, let's look at the more global clinical consequences, because we've acknowledged that in this setting cardiovascular events dominate what are the bad things that happen to people. So, at least I would like to know what is the relative outcomes in bad things. Take your secondary endpoints and add transplantation and dialysis or take Steve's three endpoints, which are stroke, MI, cardiovascular death, and add dialysis and transplantation, and let's see. There's a lot of data here on these clinical endpoints. Let's see what those results show.

DR. COOPER: Dr. Fisher, would you like to comment?

DR. FISHER: Yes, I'd like to make a few comments. I'm a little bit shocked, for example, to hear Dr. Fleming think that 50 percent in type 1 diabetics, who are not required to be hypertensive, by the way, for that trial, so that a substantial proportion were not -- so, the concurrent therapy was very different and anything you observed could, in part, be related to hypertension as well

because it was a placebo-controlled trial. And there were 35 and this is 58. So, I don't really understand the relevance.

A second point I'd like to make -- and I'm not a clinician.

DR. FLEMING: Lloyd, the relevance of what?

DR. FISHER: The relevance of the captopril data in young type 1 diabetics to demonstrate nephropathy, everybody hypertensive type 2 diabetics. I mean, granted we are treating diabetes and things are somewhat --

DR. FLEMING: You can put captopril aside if you wish. The interest in looking at what are the direct clinical outcomes stands on its own as being intrinsically of interest.

DR. FISHER: Just a second. We've heard about the cardiovascular death, and I think that's very relevant. However, the overall death rate is essentially unity, if you take into account deaths from all causes, total mortality. So, I personally would focus on that. I don't think the patient is too concerned about why they died. Well, they're not concerned about why they died actually, I think it's fair to say. The patient survivors are probably not too concerned about why the patient died but whether in fact there is an excess risk. Of course, that point estimate, including everything, is there.

There may be analyses that haven't been run, but certainly the fairly strong trend, when you look at -- and I imagine there are curves. I can't remember. There are umpty-doodle backup slides. Does anybody know if the cardiologist speaker is going to be allowed to speak?

DR. BORER: Not for a bit. There are some issues that have to be resolved first. So, we'll have to hold that.

DR. FISHER: Okay, because that's very important. It's not as if nobody thought of these issues. There's a very nice presentation by a person involved in the classification of that, a card-carrying, well-known cardiologist, who indeed could address these issues and is prepared to address the issues.

But one of the points he makes, in case this doesn't get through, is he was surprised, when they got done, that there were many more renal endpoints than cardiovascular endpoints. Both are very important. And if you put them together, this is a sick population.

But I don't know if the sponsor has every analysis Tom would desire, but there are a number of analyses that can be presented with backup slides looking at those endpoints.

I would only like to point out the study was not designed nor powered for longer-term follow-up. Maybe

it should have been. But I think it's a little unfair to say, well, gee, if you didn't reach the components that I personally like, then you know, it doesn't mean much. That's kind of a stretch to me. You may say, well, gee, it was a great trial, but unfortunately it didn't have the best endpoint for the state of the science at this point in time, and I could understand that and that would be somewhat defensible.

But all the additional evidence, while not totally persuasive at the same significance level with fewer events, points that everything does go on as you've seen. You can throw things together and it looks nice and so on and so forth.

DR. BORER: Ray?

DR. LIPICKY: Well, but I guess to my mind there is some relevance of the captopril trial in the sense that there's this elegant schema for understanding the progression of kidney disease, and that if you can look at the captopril trial, you see that there is a clinically relevant endpoint that is easily met, and you should accept the creatinine as not a surrogate but a real thing. And the trouble here is, it seems to me, that the clinically relevant stuff that was measured sort of undermines that basic philosophy. So that although FDA has said doubling creatinine is an endpoint that is okay, FDA may be wrong,

and perhaps one shouldn't accept that as a reasonable thing.

DR. COOPER: Can I just make a couple of comments?

We're going to do our best to collect all the data and be able to respond. But there are a couple other comments here that are pertinent to the conversation, and then I'd like Dr. Lewis to be able to comment as well.

The first comment is that, Dr. Lipicky, if you will recall the first advisory committee on captopril, most of the cardiologists at that time were concerned that all of the benefit for captopril was because of its effect on heart failure, and that was driving the results of the study, which is why we felt very much that it was critical to include heart failure in the analysis.

The second comment -- and I think Dr. Lewis will be able to address this -- is with respect to the delay between serum creatinine of 6 and initiating dialysis. There are clear explanations for why that, quote, apparent delay would occur.

Dr. Lewis?

DR. EDMUND LEWIS: Well, I've spent the last 8 years discussing the captopril trial, so I don't see why today should be any different.

First of all, I want to make sure that we're

all on the same page as far as who was studied in the captopril trial and who is being studied here because the common denominator may be diabetes, but we're talking about two very different trials and two very different populations of patients. So, let me just establish that first and then we can go on from there.

We have slide 10-1, please.

So, as you can see, we have a population of patients that's 24 years older. They are obese, whereas the type 1's were slim. Their blood pressures were considerably higher, particularly the systolic. However, I also want to emphasize that in the trial that we're talking about, IDNT, 100 percent of the patients were hypertensive, and in the captopril trial, 75 percent of the patients were hypertensive. So, 25 percent of the patients in the captopril trial had a very different course, particularly the ones in the placebo group.

In addition, the type 2 patients that we're studying had a significantly worse level of renal function with a mean serum creatinine of 1.7 compared to the patients in the captopril trial.

So, we're talking about two different populations of patients here. They're older. They're obese. They all smoke. They have an enormous history of cardiovascular disease, as you can see, 45 percent having

had a cardiovascular event. You couldn't get into the captopril trial if you had a cardiovascular event. And their blood pressure is a problem over years. These patients have chronic hypertension compared to the type 1 patients.

Can I have subtalk 48-6 please? Yes.

DR. LINDENFELD: Dr. Lewis, while you're on that subject, the levels of proteinuria were the same, though, between the two trials.

DR. EDMUND LEWIS: Well, actually those are the geometric means. So, we've had a little interaction here because, of course, I represent BMS today, but we are the collaborative study group, and if you look at our paper, our actual means, not geometrical, but the actual means of urine protein excretion in the irbesartan trial is considerably higher than it was in the captopril trial, just meaning that we had more patients with a lot more proteinuria which kind of evens out when you do geometric means. So, you'll have to take my word for it on this. The patients in the type 2 trial on average had higher proteinuria. We had more patients with massive proteinuria than in the type 1 trial.

Now, in terms of doubling of serum creatinine and ESRD, one thing that I do want to point out to the panel: times change, as well as issues about various

diseases. And the reason why our hard endpoint in the type 1 study was death, dialysis, or transplantation -- and my recollection is there were 22 deaths in the type 1 study. It was 14 in the placebo group and 8 in the captopril group, which was not statistically significant, but it was that trend.

And the reason we bundled those in the type 1 study was because when we designed the type 1 study, we included death with dialysis and transplantation because at that time it was very difficult for a patient with end-stage renal disease due to diabetic nephropathy to actually get on a dialysis program. So, we saw those deaths not being as cardiovascular deaths but as renal deaths, which is no longer an issue because, as I say, 45 percent of patients on our dialysis programs today have diabetes.

So, it was a different time, and that's why that design was put in. But I think that it points out that you can't really exactly take even definitions such as death as being identical between the two studies because we're talking about the 1980s as compared to now, and things have changed.

Now, if you look at doubling of serum creatinine, which I hope we have established as being a very important clinical event in this course, which presages end-stage renal disease -- I mean, this isn't an

episodic disease. This is a continuum here. So, if you look at that, you can see that in fact in the two arms here, we have a substantial decrease in the likelihood of reaching that milestone.

Now, one of the things about this and the apparently stronger results in the captopril trial is that, first of all, we did not have cardiovascular death as a serious competing endpoint in that trial. People are dying during this trial before they ever have a chance to double or go into end-stage renal disease, for that matter. And in addition, the placebo group in the captopril trial was losing renal function at such a rate that it was easier to show a difference between the two groups because in those days blood pressure was not controlled as rigidly, and that group of patients, the placebo group, certainly was losing renal function faster.

So, in terms of comparing the two trials, from my point of view, having been the PI for both of these trials, the only thing that I think that really can be said about the two trials is that the results for both trials are strongly in the same direction. To compare the numbers from the two trials I really personally don't think is valid.

Now, as far as the end-stage renal disease or death issue, I think that to a certain extent, of course,

we've said that we had a composite endpoint. These people could have a renal endpoint or a cardiovascular endpoint, and the cardiovascular endpoints were not statistically significant. Looking at the published data in, say, just hypertensive populations, the blood pressure trialists collaborative meta-analysis, clearly irrespective of what agent you're going to use, it's whether you lower the blood pressure or not that's going to really determine what your cardiovascular events are. So, we're not too surprised about the cardiovascular deaths really determining this.

And as far as the ESRD is concerned, I think that you can see from our data about the way people are moving, doubling serum creatinine, getting up to 6, going on to dialysis, that I think that we're really talking about in this trial an issue of length of follow-up. I can't imagine how we can be talking about end-stage renal disease -- our data not showing that we have a serious effect in altering the course of renal disease because we're altering the course in a very positive way with irbesartan all the way up to renal disease. The only reason we don't have a significant p value with that is because we didn't follow them quite long enough. I think that you can assume that everybody who doubles is ultimately going to reach 6, and then they'll go on dialysis in a very short period of time.

So, in looking at the course of renal disease, not looking at the specific p value numbers at each stage, I believe that what we're showing here is not really different from the captopril trial when you take into consideration patient population and all of that kind of thing.

DR. BORER: Dr. Lewis, before you sit down, can you clarify something for me? I know you didn't collect these data, they're not reported, and it's not going to be a primary basis for decision making, but just so I can understand. When somebody reaches a creatinine of 6, let's say he doesn't get dialyzed, are there lifestyle changes that we can infer would occur? For example, is the diet very restricted? Are there other limitations? Can you tell us something about that?

DR. EDMUND LEWIS: Yes, I would be glad to address that.

The reason actually for the Medicare definition of a creatinine of 6 in this population is that the goal of the nephrologist is to get the patient on dialysis before they have uremic complications because once they start having uremic complications, for example, just pericarditis, the road back is a long road. So, what we're trying to do is to prevent the adverse effects of uremia which are systemic by putting the patient on dialysis

before they get any of this.

One of the things that has not come up, which I would point out to the committee, is that the Medicare criteria of a creatinine of at least 6 or a creatinine clearance of less than 15 mls per minute applies to the population of patients with diabetic nephropathy. What that means, which is important to the nephrologist, of course, is that Medicare has no problem paying for dialysis when people have reached that level. They have made the decision that that is an appropriate level. It prevents complications, hospitalizations, nausea and vomiting, further inanition or whatever is occurring because the patient is feeling sick, plus the anemia and all of that. They will pay for that.

Now, if a patient does not have diabetic nephropathy and has advancing renal disease, the Medicare definition of end-stage renal failure is not the same. The Medicare definition of renal failure is now creatinine equal to or greater than 8 or a creatinine clearance equal or less than 10. And the reason for that is it is recognized in the community and by the federal government that patients with diabetic nephropathy are, in fact, sicker than patients with chronic renal failure due to other diseases and, therefore, deserve to be dialyzed earlier. I think that my last statement there probably

answers your question.

DR. JULIA LEWIS: Can I add a comment to that? I have an advantage as a younger nephrologist. These are still all the patients in my clinic. At a creatinine of 6, the patients are fatigued. They've lost their sleep cycle, and very importantly, their serum albumin as a key marker of nutrition has begun to fall. The serum albumin is actually the single most important predictor of survival in a dialysis patient. So, they've already begun to have signs and symptoms that they complain of. Within 2 or 3 weeks of initiating dialysis, most of my patients, both diabetic and nondiabetic, will say I feel better than I have felt in a year. So, they've had a gradual decline in energy level, nutritional status, and other factors.

DR. BORER: Thank you.

Bev?

DR. COOPER: May I just intercede here? One of the other observations has to do with hospitalizations, and Dr. Pfeffer is now available and can address some of the questions we have about the cardiovascular events.

DR. BORER: Let's just follow through on this idea. We'll come back to that. There are several interlocking issues here.

Bev?

DR. LORELL: I'd like to ask a question that

may be a segue to Dr. Pfeffer's comments. I am not a statistician, but I am a cardiologist that deals all the time with incidents of death and interventional cardiology trials in heart failure.

I guess I would like a comment from one of the card-carrying statisticians either on our panel or elsewhere. If you look at the incidence of cardiovascular death in this population, it is actually remarkably low. It's about 8 percent in the placebo group. It may be in part because they're being treated with antihypertensives and the cardioprotective class of drugs of beta-blockers.

So, looking at the incidence of cardiovascular death over a 57-month treatment period, if I were going to design a trial with the primary endpoint of reducing cardiovascular death, I would suspect that would be a trial that would need several thousand people in the treatment and placebo arms. And perhaps before Dr. Pfeffer, representing the company, speaks, we could hear a statistician's comment on that.

DR. BORER: Lloyd, Tom?

DR. FLEMING: If you're asking about whether it would take an enormous trial if one were focusing only on cardiovascular death --

DR. LORELL: That's my question.

DR. FLEMING: -- it would take a very large