trial, unless one were targeting a very substantial reduction in the death rate on that.

DR. LORELL: Thank you.

DR. BORER: Lloyd, you had a comment?

DR. FISHER: Yes, you are right. It would take a larger trial. Actually, from what I have been informed, it's not as large as Tom would think probably. And the reason is that the cardiovascular event rate really goes up when the people hit dialysis. Now, I'm not familiar with that literature, but everything that I've been hearing, as we've been rehearsing for this meeting, assuming that's true -- and the independent people brought in here could discuss that. So, if you followed long enough, if you're willing to let a lot of people get to dialysis and so on and so forth, and not feel you had to intervene to prevent that in every way you could, then actually surprisingly not just the death rate but the cardiovascular event rate would go up more than you would think.

DR. COOPER: And in that situation, we would have continued coded medication throughout the study rather than discontinuing it at the first event.

DR. EDMUND LEWIS: If I could address that, just to finish Lloyd's statement, the mortality rate, once a patient reaches dialysis, hasn't changed much over the last several years, and it is much greater in patients who

have diabetic nephropathy than it is in patients with other diagnoses on dialysis programs. The one-year mortality for these patients is 25 percent, and the two-year mortality is 50 percent. So, the goal is to prevent the patient from going on to dialysis as long as possible because they're not dying renal deaths, they are dying cardiovascular deaths, and whatever it is about dialysis that does this, these patients do very badly.

DR. BORER: Steve?

DR. NISSEN: I just want to make sure I understand whether any of the cardiovascular endpoints were censored in this trial. Am I or am I not correct? When they reached ESRD, from then on were the cardiovascular events included or were they censored?

DR. COOPER: They weren't captured.

DR. NISSEN: They were not captured.

DR. COOPER: Right.

DR. NISSEN: They were captured or captured and censored?

DR. COOPER: They were not captured. The patients were no longer on study drug, so there's wasn't a safety effect that we were following, and because of the interventions associated with ESRD and the change to the patient's status as a result of those interventions, we did not capture any cardiovascular events that happened once a

subject reached ESRD.

DR. NISSEN: Okay. Well, maybe I'll have more to say in the discussion period, but I'd sure like to see that data.

DR. COOPER: That's the design.

Can we have Dr. Pfeffer now?

DR. BORER: Alan, did you have one question first here?

DR. HIRSCH: This may also just relate and maybe Dr. Pfeffer can answer it as well.

In transition again from the balance of renal benefit to cardiovascular benefit, I want to go back to Steve's point on figure C-16 where you see a reduction in heart failure events with irbesartan, but a relatively favorable effect on the ischemic events in the amlodipine group. You've shown us baseline data for many renal parameters. I just want to make sure there wasn't any misallocation or randomization imbalances. Do you have data on clinical coronary disease, myocardial infarction history, heart failure in the three cohorts you can share with us?

DR. COOPER: We didn't collect data at baseline to that level of degree, but the frequency of prior cardiovascular events at the time of randomization was similar in all three treatment groups.

DR. HIRSCH: I saw that. I was wishing to break that down a little bit.

DR. BORER: Marc?

DR. PFEFFER: I'd like to start with an apology for some of the confusion. I am a member of this group, but my tenure was supposed to start after this meeting because I obviously knew I was working on this project since 1995, and I knew this date. When I was invited to join, I asked that my tenure start after this session. And apparently my paperwork went through faster than anticipated. So, I apologize to --

DR. BORER: A first.

(Laughter.)

DR. PFEFFER: But my history with this trial I think is relevant because it goes back to the design phase. Dr. Lewis and the collaborative group had been working with the sponsor -- and this is relevant to the difference between cardiovascular and renal -- to design a renal study in a patient population that had never been tested with a new class of agents that had never been evaluated.

At that time, I came in and had discussions with Dr. Lewis and the sponsor and said how could you not look at cardiovascular events. That's what will happen with these patients. And he said, Marc, you have to understand. We're getting these people at the point of the

spectrum where they're more likely to have renal events, but why don't we prospectively look at cardiovascular events too but as a clear secondary. As a matter of fact, all the alpha in this project is on the renal events. So, this was a renal study known in a population with a high likelihood to have a propensity for cardiovascular events.

Now, given that, the sample size was based on the renal events. So, it was a sample size of approximately 600 per group with three active comparators. So, there wasn't a chance to talk about cardiovascular death.

If I could have the first slide. We built a composite. Why does one build a composite? First of all, this is a secondary endpoint. And we built a composite knowing that with 600 people, three groups, two comparisons, to get a signal that there was an ability to influence a cardiovascular outcome, we would need as many what we thought were clinically important events as possible.

So, as you've heard, it's cardiovascular death plus nonfatal MI, and I would say prospectively we even built in an ECG core lab where the baseline ECG was looked at 6 months, 1 year, and approximately 6,000 electrocardiograms were looked at. Hospitalization for heart failure required a hospitalization and an

adjudication committee, as did neurologic deficit, and the amputation was clear, above the ankle. So, we felt this is a smorgasbord of bad news cardiovascular events, and let's see, if we have a signal that in these three active comparators, if we can see something.

To give you an idea of where we stood, we also said 600 might not be enough. Let's broaden the definitions and now let's call this a tertiary. That's clearly a definition of where we are. We're in the exploratory phase, but we didn't want to miss something with this new class of agents in this important population.

So, what we added to what you had seen before was nonfatal MIs called by the site. So, if a site called it, we'd add that. We also added revascularization procedures. We now added heart failure that didn't quite require a hospitalization, but the investigator said I'm not comfortable here. We're going to start an ACE inhibitor or an angiotensin receptor blocker, and we also added a different level of amputation and peripheral vascular procedures.

And the results were surprising to me that with that smorgasbord of cardiovascular events adding all these together, in only 2.9 years -- everyone on active blood pressure control, and blood pressure levels are going from about 160 to approximately 140 systolic -- we had a 25

percent event rate overall. Contrast that to the renal where it's 37. So, Dr. Lewis was right. These people were more likely to have a renal event.

But that didn't mean that we didn't prespecify and look at these things. This is the actual numbers. The most common event that happened to one of these randomized patients who was then followed for a cardiovascular event, the most common event was the development of a hospitalization for heart failure.

If we look at the overall composite, I think the conclusion is that this therapy, these three arms, that there's no distinction in the overall cardiovascular event rate.

Now, again, all the groups are receiving antihypertensive therapy. There's a central committee blindly working with all the investigators to try to get the pressures down, not knowing the assignment, and this was the overall.

Now, when the investigators presented this -- and the first time that was done was in Stockholm at the European Congress of Cardiology -- our conclusion was that there was no difference in this prespecified composite, lumping all cardiovascular events.

When you have a composite, I think it's fair to look at the components for hypothesis-generating

information, and we did that. And what that showed was the most important line is the first dot, which is the narrowest confidence interval, which is the overall predefined, and you can see that that is right around the nil, which is what that Kaplan-Meier showed.

But then when you break it down into what were the components, the only thing that really leaves the line -- and we are not making a point of this because it's one component of many -- is this hospitalization, but it's counterbalanced by other factors. The event that we had the narrowest confidence interval, of course, is the overall, and we choose to make the statement that there's no influence on cardiovascular events, some very interesting things here that will need further study.

The tertiary analysis, which is even broader, just confirms what I've just said, and once again, the components go back and forth. Really no difference and nothing that you would say we found something here in this one of six subanalyses in a tertiary analysis, but interesting observations that will require larger studies, which are already underway. There are large studies comparing ARBs to calcium channel blockers. VALUE has approximately 15,000 patients; LIFE has 9,000 patients. That's what's going to be required.

Post hoc for the combined -- you've seen this

-- was let's add the renal bad news to the cardiovascular bad news and see if it's a shallow victory. Are we just offsetting those renal benefits by more cardiovascular adverse events? And that wasn't true.

But I think an even more important analysis to some of the points that I've heard raised appropriately today, what about the patient? The patient doesn't care if they're referred to the nephrologist, the neurologist, or the cardiologist if they had something happen to them. This isn't a "who's my specialist here." It's "how am I doing?"

We looked at the hospitalizations. Now, this is also skewed in a way that the data collection stopped at the development of end-stage renal failure. So, censoring from the time of development of end-stage renal failure means that we had slightly longer exposure in the irbesartan group. With that slightly longer exposure, there were fewer hospital admissions and the time in the hospital was reduced. I think that's a global measure.

Now, of interest, the cardiovascular component of the hospitalizations was not changed in these three arms with all active therapy. So, our conclusion would be that although we did not show a measurable impact on cardiovascular disease, we did show a measurable improvement in global health, best measured I think by the

total hospitalizations.

DR. BORER: Steve or Tom, do you have any other points you want to make?

DR. NISSEN: I tend to look at these events in more of a hierarchical way, and I guess that's why I focused so narrowly on what we would consider the hard cardiovascular endpoints of cardiovascular death, nonfatal MI, and stroke. I would really like to see an analysis where those hard endpoints are looked at. And the reason I say that, Marc, is that most of the "benefit" on the irbesartan versus amlodipine comparison comes from the hospitalization for heart failure, and we all know that amlodipine tends to produce some peripheral edema and that patients with peripheral edema are much more likely to get into a hospital with a diagnosis of heart failure. So, what you're trying to do is equate a soft endpoint like hospitalization for heart failure with much harder endpoints.

And I really want to know what the statistical significance would be if one looked at -- and I recognize it's exploratory and I recognize it's not prespecified, but in terms of looking at overall benefit, I think you have to look at cardiovascular events in that kind of hierarchical way because they have different importance in terms of the overall benefit to the patient. Do we have such an

analysis?

DR. PFEFFER: Well, Steve, I think if we could prespecify the importance of a nonfatal event, then give it a rank, we'd all be in much better shape for designing trials. Your bias is that having a nonfatal MI, you'll do better than getting hospitalized for development of heart failure. Well, there are nonfatal MIs and there are nonfatal MIs, and there are developments of heart failure. And I think that's the whole problem with once you get below death, how do you rank these things. Even with the diagnosis of an MI, sometimes it's a triponin leak versus, wow, this person is not going to get out of their chair again. So, I think that's treading in an area that we can't do within this study or that most studies couldn't do. Therefore, we chose to give you the whole global smorgasbord and let you interpret that.

I think the hospitalizations are a very important component of this.

DR. NISSEN: One follow-up and that is --

DR. JULIA LEWIS: Could I comment?

DR. NISSEN: Sure.

DR. JULIA LEWIS: On the adjudication committee -- and Marc can speak to this too -- we were very sensitive to that issue of peripheral edema associated with amlodipine use that you mentioned. In fact, as we

adjudicated the heart failure hospitalizations, we required the patients to have other manifestations such as rales, a chest x-ray that showed pulmonary congestion, wedge pressure. I mean, there had to be more to it than swollen ankles.

DR. NISSEN: Sure.

Let me just ask one more question, and that is I want to know the justification for not collecting the cardiovascular event data once they got to dialysis. I'm very troubled by that because we don't have data that I think we should have.

DR. EDMUND LEWIS: Well, once a patient goes on to dialysis, their caregiver, their environment, everything really changes. Plus, their clinical course changes in a highly expected way. So, that data was not collected because of that, because in fact the way we looked at it, requiring end-stage renal disease was the endpoint here. And the high mortality rate of these patients, while it would be of interest to know the exact number, I agree, but we didn't anticipate that it would be any different than any other type 2 diabetic nephropathy that reached end-stage renal disease. They, after all, had not been on coded medication for some considerable period of time. They may have had their blood pressure controlled better than the average patient, so maybe they had a more benign

course. But we did not feel that having detail of that stage of the patient's life would actually contribute meaningful information to what we were studying, and what we were studying was does our intervention prevent the patient from requiring dialysis according to what the course of things would be.

DR. NISSEN: But an intention-to-treat analysis says you continue to collect the data as the endpoints occur. I mean, I think it's an unusual approach. I can understand why you might argue that the data might be censored, but I certainly would like to see the data.

DR. JULIA LEWIS: I just want to make two quick comments to add to the reasons why we chose not to do that in the design committee, and that's because there are two ongoing trials, one sponsored by the NIH and one sponsored by a pharmaceutical company, looking at elements of the dialysis membrane interaction with the patient and looking at phosphate binders and certain things that we use to manage them once they're on dialysis that are thought -- the hypothesis is that those things actually impact on cardiovascular events. So, we really thought this was a fairly contaminated population.

Also, recall we only start out with 1,715 patients at the beginning of the trial. Our other feeling was that there were going to be so few patients for a

cardiovascular outcome analysis that actually reached dialysis that it wasn't the appropriate setting in which to do a study in what happens to cardiovascular events in ESRD patients.

DR. BORER: Tom and then Bob and then I have some final questions for you before we break for the FDA-mandated lunch.

DR. FLEMING: There's much to say here. It's in a certain sense philosophically troubling to me because we are -- and I can accept this in a certain sense -- arguing that we need to follow patients long enough to really be able to see the full clinical benefits achieved by an intervention that is effectively extending the time to doubling of creatinine. Yet, at the same time we're hearing, gee, when you get out far enough, there's such a myriad of complicated phenomenon influencing the outcomes of these patients, that we don't really want to capture all of these events because it's difficult to interpret them.

In essence, what I want to understand is what are the true clinical consequences of an intention to deliver an intervention versus not and follow all the patients forward in time. And it may not be possible to expect statistical significance on all the cardiovascular endpoints. That doesn't mean it's not very informative to understand whether there's a pattern here that is

suggestive of benefit or lack of benefit. So, it's a simple question.

Marc, you've indicated that you were a bit surprised that cardiovascular events were about two-thirds what the renal events were. Maybe that's what it is. I have trouble knowing whether that's what it is because we stopped systematically following the cardiovascular events at certain points in time. So, it's a little difficult to understand that.

What I would like to see, Marc, about three slides from the end, you threw something up that is getting at, at least indirectly, what some of us have been really struggling to see. Could you put the slide up again that shows the actual number of documented events of each type when we're looking at the secondary endpoint? And I'd like to have this left up for several minutes so at least we can make some notes as we go on to other discussions.

Fundamentally, what I'd like to see -- descriptive or inferential isn't critical to me. What I want to see is what the data show about the difference between the three intervention arms in the fraction of patients that have the more renal endpoints here, death, dialysis, survival. Show me what that analysis is.

And then it is relevant to be able to see more globally how those renal and cardiovascular outcomes pool

not that I have to prove statistical significance or not. I'd like to understand what the data show about the actual influence of the strategies here in impacting both renal and cardiovascular outcomes. So, at some point before we get into voting, I'm really hoping someone can put those specific analyses before us.

DR. JULIA LEWIS: Can I make just a quick comment? I know you're cardiologists and I know that heart attacks and cardiovascular deaths are really important outcomes for you. But again, as a nephrologist, I have to tell you whether or not you have to go to a dialysis unit three times a week is also a very important outcome, and if the government ran out of money, 100 percent of those people would be dead without dialysis. So, we don't have renal death because we're rich and fortunate in our country. It's a huge factor for patients. Many of them are more frightened of it than they are of a heart attack.

DR. BORER: Bob?

DR. TEMPLE: I guess I have a couple of observations. Maybe this should be left for the discussion, but it seems to me the discussion is bearing on them.

This was not a trial to describe which the best antihypertensive is. A trial of 40,000 people is attempting to do that. We don't know what success it's

having. But you really wouldn't expect a trial of this size to be able to pin down the question of whether amlodipine is better at preventing heart attacks than irbesartan. There are mountains of data on that question. Most of it, I admit, is ACE inhibitors not A2 blockers. But it's obvious that trials go every which way. I mean, a big trial in diabetics -- not so big -- the ABCD trial sort of suggested that calcium channel blockers are death and ACE inhibitors make you live, and then other trials don't show the same thing.

It doesn't seem surprising to me that in people, all of whom are treated apparently appropriately for their blood pressure, you see twists and turns, and I'm not sure how much you can make out of a trial of this size on those endpoints when hundreds of thousands of patients have not allowed anybody but certain individuals to reach a conclusion about whether calcium channel blockers are better or worse. So, I wonder how much one should make of this. So, that's one observation.

The second is -- people have said this repeatedly but I'm not sure whether everybody buys it -- that when you reach a creatinine of 6 or something like that, you are on your way to dying or going on dialysis, although this trial didn't follow that long enough. So, there seems to be a minimization of that because you didn't

die or go on dialysis yet. I wonder about that because the contention is at least you're on your way there. If we followed you another year or two, you'd definitely be there. But those are not counted as serious events because they didn't quite happen yet. So, I wonder about that. It seems to me worth discussing. Does any disagree with that?

Then, of course, the other observation is that there are two comparisons here. One is against placebo which actually translates to a wide variety of other drugs, but not including calcium channel blockers or ACE inhibitors or something like that. And that doesn't show this funny thing on cardiovascular events. So, it's not clear what to make of that.

You might say that these data certainly don't tell you you should always use irbesartan instead amlodipine in everybody because those other events seemed to go the wrong way and it's ambiguous on that. But does that interfere with reaching a conclusion about the effect on renal function? And I think those are somewhat separate questions.

DR. BORER: Thank you.

I have three final questions for you before we break. No discussion, just give me an answer if you can, and they'll probably come up again as we go through the discussion of the formal questions later.

I asked you before about what happened to the people once they were taken off their coded drug. That question had several components. First of all, what were they put on? How were they treated after they were taken off the coded drug, number one? And number two, what happened to their rates of progression compared with the rate of progression in the first portion of the trial before they were taken off the coded drug? So, that's one set that I'd like to hear an answer to.

Second, I want to know something about the exclusions beyond that point at which people were taken off their coded drug. There were several other people who were analyzed one way or another that I'd like to hear about.

And third, you made a point about blood pressure differences not being important, and I think it's useful that Dr. Kopp is here because I think that the data that exists might not support that statement and it may be important for us to know about that.

But we'll go through them one at a time. First of all, what about the patients who stopped their coded drug? How were they treated and what happened?

DR. COOPER: Can we have the first slide on concomitant medication on double-blind therapy please?

This slide displays the use of the different classes of antihypertensives in this patient population

during the double-blind period. As you recall, earlier I was asked a question about beta-blockers, and you see that the frequency of use was 52 percent in the placebo group. In most of the classes, placebo patients by and large received more antihypertensives.

We do not have specific information about the use of agents once patients reached double of serum creatinine because there's no approved indication and it was up to the investigator to decide what to continue to use. Our feeling is everyone was very committed to maintaining blood pressure control and the use of these agents most likely continued subsequent to discontinuing coded medication.

DR. BORER: So had you replaced the coded medication to maintain the blood pressure? By increasing the doses of these others?

DR. COOPER: I don't have that information. We didn't collect that level of detail of information.

DR. BORER: At some point it would be important to know, because I'd like to know if they were put on ACE inhibitors or ARBs. If they were, you'd interpret subsequent data one way; if they weren't, you wouldn't.

DR. COOPER: In the second slide that I'd like to show -- and I believe that this slide is on an overhead and not on a projector, so if we could have the overhead

set up. The reason why halving of GFR as measured by a doubling of serum creatinine was considered a clinically relevant outcome was because the study investigators felt that once you've lost half of your renal function, you needed to allow the study investigator to treat the patient with whatever therapy, even though there's no approved indication, should be used to delay the progression of renal disease.

Interestingly enough, not all investigators put their patients on an ACE inhibitor. I don't have the exact percent, but it's certainly not all. And what this slide shows you is the rate of progression to end-stage renal disease after doubling of serum creatinine in subjects with and without ACE inhibitors following the endpoint. So, with ACE inhibitors is on the lower curve, and there is data here suggesting that if you treat them with an ACE inhibitor, you are going to delay their progression of renal disease.

And subjects who did not receive an ACE inhibitor. And there could have been many reasons for why the patients weren't treated with an ACE inhibitor. These patients could have had severe hyperkalemia because of their progression of disease as an example. The rate of progression was more rapid.

DR. BORER: Okay. That's not the way I would

interpret those curves, but I can be corrected by any statistician sitting here. It looks to me like those lines are parallel. They just have a different 0 offset. Am I wrong about that?

DR. COOPER: If you look at the medians that were calculated until ESRD, it is shorter for those without ACE inhibitors, 6.4 months, rather than those with ACE inhibitors. It's 12.9 months.

DR. BORER: Perhaps we need a little bit more evaluation. Lloyd, can you clarify that for me?

DR. FISHER: I agree with Dr. Borer. What he is saying is the offset are the people who at the time they doubled already were at ESRD, according to the creatinine criteria, reinforcing the point these are different populations. But if you put the offset together mentally, it's not nearly as impressive. So, it's not really clear whether there's benefit or not from these data.

DR. BORER: Well, I'm not sure how much we can infer from this, but I would have been happier to see a real difference between the people who actually were put on renin-angiotensin system affecting agents after the coded drug was stopped than not, and I don't really see that. So, I'm not sure what to make of that.

MR. WILLIAMS: George Williams from Bristol-Myers Squibb.

I think we have to be careful in these kinds of interpretations of different therapeutic events for cohorts, as described here. These are certainly not randomized comparisons.

DR. BORER: Right, I understand.

DR. COOPER: I do have one more slide to show and that's the slide that shares the rate of progression to ESRD by treatment group in subjects who were not put on an ACE inhibitor. So, if they weren't treated with an ACE inhibitor or an A2 receptor antagonist, that's the closest we have to looking at whether or not there was some preserved benefit after study drug was discontinued but they had halved their GFR.

So, you see irbesartan in yellow, placebo in pink, and amlodipine in blue. There is no real difference here statistically, but if you look at the trends, the rate of progression for irbesartan seems to be -- I don't want to say similar because I can't show you the corresponding curve before doubling of serum creatinine, but it is less than it is for the other two groups.

DR. EDMUND LEWIS: May I add something?

DR. BORER: Yes, Dr. Lewis.

DR. EDMUND LEWIS: I just wanted to remind the panel of the hyperbolic relationship that I showed you between creatinine clearance or GFR and the serum

creatinine because now we're talking about a period along that curve that is at the tail where very small changes in glomerular filtration rate are associated with very large changes in the serum creatinine. So, if you actually wanted to have a valid study of anything, ACE inhibitors or where the patient was randomized first and so forth, those changes in GFR leading to large changes in creatinine on your hyperbolic curve are so large that you would really need a lot of patients to get anything other than the sort of identical curves that we're showing you here.

DR. BORER: Well, perhaps it's just not evaluable because the study wasn't designed to do this, but you've shown us the data.

What about the exclusions? Now, you've told us what happened or what you know about what happened to people after they stopped coded drug when they doubled their serum creatinine. What about the others? There were patients who never received any treatment. There were patients who had ESRD and creatinine doubling at the same time and were counted one way rather than another way. Can you tell us what you did about, for example, the patients who never received treatment? How were they handled?

DR. COOPER: Dr. Natarajan?

There were 16 subjects who did not receive a dose of study drug even though they had been randomized.

DR. NATARAJAN: Again, Kannan Natarajan from Bristol-Myers Squibb.

The 16 patients were analyzed as per the intent-to-treat guidelines, in essence, actually as they were randomized.

Can I have that slide for the 16 patients please?

These are the 16 subjects who were randomized but never got a single treatment, never treated. These 6 patients were on placebo, 2 patients on irbesartan, and 8 patients on amlodipine. All of these patients were treated as if they received study drug and they were analyzed by the intent-to-treat principle.

Some of these patients did have an event very soon after the randomization and were counted as having an event. If we were to do a sensitivity analysis, counting in a more demonic way, the irbesartan subject is the only one who is actually going to have the event. Still, it does not change your conclusion.

DR. BORER: How about the people who were lost to follow-up? There were 13, as I recall, or something like that.

DR. COOPER: There were 8 subjects lost to follow-up for which we did not have mortality status, and we have a sensitivity analysis for those 8 subjects as

well.

DR. NATARAJAN: Can I have the slide for the 8 subjects?

Again, 8 subjects were lost to follow-up. We did not get any information on these subjects at the time of the study closure. There were 2 placebo subjects, 4 irbesartan patients, and 2 amlodipine patients. In the sensitivity analysis, we again considered the worst possible scenario in which all the placebo subjects, as well as the amlodipine subjects, didn't have an event. However, all irbesartan subjects did have an event. As you see, the primary composite endpoint is still very similar.

DR. BORER: Okay, that's great.

You also had patients who had some events known but their mortality status wasn't known, and how did you deal with them?

DR. NATARAJAN: Can I have the 19-patient slide?

There were 19 subjects who had variable follow-up. There were 11 patients for whom we had the mortality status known. Most of these subjects had withdrawn consent and the only thing that we know of is actually whether they were dead or alive at the end of the study. One subject died during follow-up and is included in the ITT analysis. Assuming the other 7 subjects had a primary event, this is

how -- and again, this is in the worst case scenario which is highly unlikely to happen in the sense that it's more of a demonic way of looking at it. The placebo subjects and the amlodipine subjects didn't have any event. The irbesartan subjects alone had an event, and this is how it will turn out to be.

DR. BORER: At least we have the data in front of us, and I appreciate that.

The final question before we break. You suggested that although there was a 2 to 3 percent difference in blood pressure between the placebo group and the irbesartan group -- forget for a moment the amlodipine group because I'm going to suggest to you that that issue may or may not be relevant since we haven't considered the possibility that amlodipine might do something bad. But if you just think about the placebo patients versus irbesartan, there was a 2 to 3 percent difference in blood pressure favoring irbesartan, and you suggested that though that was statistically significant, it wasn't clinically relevant.

About 6 months ago, we sat at a meeting listening to data from ALLHAT, and there was a rather formidable presentation, suggesting something very different from what you said, that is, that 2 to 3 millimeters of mercury could account for a lot of

difference. And I wonder if either you or someone from the committee who's familiar with ALLHAT or with the relevant data here can talk about that a little bit.

One might infer that the better results in the irbesartan group versus the placebo group had something to do with the difference in blood pressure control rather than some independent effect of blockade of the renin-angiotensin system. How would you respond to that?

DR. COOPER: Well, that was the reason why we did the Cox regression analysis using blood pressure levels during the study to adjust for the primary composite endpoint, and in that analysis, the relative risk reduction, 19 percent, is similar to what was observed without that analysis. It was 20 percent.

I guess I'm interested in your comment about comparing the amlodipine and irbesartan group because amlodipine could have been doing harm. One of the points is that the amlodipine event rate was similar to the placebo event rate, and it is our interpretation that it is unlikely that amlodipine was doing any harm with respect to this composite endpoint.

DR. BORER: You may well be right. I'm cognizant of the fact -- and in fact I had come to the same conclusion that Bob stated -- we had two different comparisons here, and we're asking several different

questions.

I don't want to lose my train of thought here before we close. Yes, I do remember now.

I don't know technically how one makes adjustments with the Cox model. I don't know how valid it is to say there was 20 percent and 19 percent and whatever. What I would be willing to accept is that there is an independent effect of treatment even when you consider blood pressure differences, which I assume is what you found. Maybe you can expand on that.

DR. NATARAJAN: Yes. Can I have slide 354?

What we did is basically address the issue of the differences in the blood pressure between the treatment groups whether it's clinically relevant or not. From a statistical point of view, we adjusted in a time-dependent manner and these are the results of the analyses, both unadjusted, as well as adjusted for time varying mean arterial pressure. As you can see, the risk reduction change is very small, from 20 percent to 19 percent, and the significance still exists. And with regard to amlodipine, we did not see any difference in the blood pressure, and thus the estimate did not differ, nor does the p value.

DR. BORER: Tom, can you comment on this?

DR. FLEMING: Well, I think what's been

attempted here with the time varying covariate is a reasonable approach. The question is how interpretable or convincing is it really.

Essentially -- and I assume this is what you've done, although there are lots of variations to how you might do this -- what you're saying is we know at baseline that blood pressure is predictive of risk of many types of events, renal and cardiovascular. So, what we'd like to do to fully capture that influence, particularly if there's a difference in the blood pressure profile over time across two different regimens, is put a time varying covariate in that says anytime there's an event, what is that person's blood pressure at that point and adjust for blood pressure, not just at baseline but as it's varying over time.

DR. NATARAJAN: That is correct, yes.

DR. FLEMING: And that's a very reasonable approach to take here.

There are some pretty significant assumptions we're making, though, and that is the way in which blood pressure truly is influencing outcome is fully being captured by whatever that latest measured blood pressure was at that point.

I've attempted these kinds of adjustments in other trials in which we have seen evolving differences in outcomes and evolving differences in blood pressure levels,

and we haven't also been able to explain these differences by the time varying covariate analysis. So, I consider what they've done as a reasonable approach, but it certainly doesn't reliably allow us to conclude that there are not differences in these event rates that could well still be impacted by the difference in blood pressure control between the arms.

DR. JULIA LEWIS: If I may add something. I'm an investigator in the African American study of kidney disease and hypertension, which has been presented at the American Heart Association, and I sit on the writing committee.

We in that NIH-sponsored trial randomized African Americans with kidney disease and hypertension to a mean arterial blood pressure of 102 to 107 versus less than 92. We achieved between a 10 and 11 millimeter mercury difference in mean arterial blood pressure. By any measure of renal function, including time to event and iothalamate GFR, we were unable to demonstrate a beneficial effect of being randomized to the lower mean arterial blood pressure group of less than 92.

Although that's a different group -- it's African Americans with high blood pressure and kidney disease -- I thought I would share that piece of renal data with you, which may suggest that the renal bed is somehow

perhaps different than the cardiac bed in its response or that we're in a range of the continuum where it's less of an impact.

DR. NATARAJAN: I would like to just add one more thing. Whether or not we adjust and do this time-dependent analysis, the thing to keep in mind is that there was no difference with respect to amlodipine and irbesartan, and that would actually suggest that that is independent of the blood pressure lowering.

DR. FLEMING: Although you're making assumptions there about what other mechanisms of action could differ between the two that might offset a difference that would be attributable to blood pressure lowering.

DR. BORER: I think that's been a very informative presentation. I really want to thank you, Dr. Cooper. You've been very clear and concise and given us a lot of numbers.

DR. COOPER: I'm a nephrologist.

(Laughter.)

DR. BORER: Yes. Well, when I was in medical school, our physiology department was primarily skewed towards renal physiology because Robert F. Pitts was the chairman. Knowing that I would be a cardiologist when I grew up, I was very excited when one of the teaching fellows said that he had a grant from the American Heart

Association. So, I said, what are you doing relative to the heart? He said, nothing of course. The only purpose of the heart is to pump blood to the kidneys. Everybody knows that.

(Laughter.)

DR. BORER: So, I understand what you're saying here.

In any case we will take a break until 1 o'clock when public comment will be possible, and then we'll finish the last two formal presentations and go on to the questions.

(Whereupon, at 12:10 p.m., the committee was recessed, to reconvene at 1:00 p.m., this same day.)

AFTERNOON SESSION

(1:15 p.m.)

DR. BORER: We'll begin again.

The meeting is open for public comment. There were no applications for public comment, but are there any individuals who have comments that need to be made?

(No response.)

DR. BORER: If not, we'll go ahead. We have some additional questions and I believe the sponsor has some responses first to Tom Fleming's questions, and once you do that, we have some more questions from JoAnn and from Tom before we get on to the next phase of the presentation.

DR. COOPER: Thank you.

What I'm going to present now are the data to respond to the remaining questions. Can I have the first slide please?

Part of the earlier discussion focused on the effect of treatment on end-stage renal disease, specifically transplantation and dialysis. I did want to share with you the results of the time-to-event analysis for end-stage renal disease, including serum creatinine of 6.0 milligrams percent and greater.

In this Kaplan-Meier curve in which irbesartan is displayed in yellow and amlodipine and placebo are in

blue and pink, respectively, a treatment effect was observed with a 23 percent risk reduction in favor of irbesartan. Once again, this is all patients who had an ESRD event even after they discontinued study medication.

Next slide. This is the first of the analyses that was requested, time to dialysis, transplantation, or death comparing placebo and irbesartan. And in this analysis, the relative risk reduction was 13 percent, the confidence interval between .7 and 1.09.

The next slide --

DR. FLEMING: Could you leave that up for a few seconds please?

DR. COOPER: Yes.

(Pause.)

DR. FLEMING: Thank you.

DR. COOPER: The next slide contains the time to event for dialysis and death. Once again, a relative risk reduction in favor of treatment with irbesartan was observed, 11 percent. Confidence intervals are on the slide.

(Pause.)

DR. COOPER: Next slide please. This is the analysis of time to event of ESRD or death. In this analysis, serum creatinine of 6 is included. The relative risk reduction in favor of treatment with irbesartan

compared to placebo is 15 percent.

(Pause.)

DR. COOPER: And lastly, the new, redefined, combined composite endpoint, which includes dialysis, transplantation, death, and cardiovascular events. The relative risk reduction in favor of treatment with irbesartan observed is 14 percent. It's not expected that any of these post hoc analyses would be statistically significant. They're not powered to detect differences between treatments for any of the components.

DR. FLEMING: Do you happen to know what the amlodipine total is?

DR. COOPER: We do. That's slide MC-128 please.

For the same combined composite endpoint, the relative risk reduction was 10 percent in favor of treatment with irbesartan.

DR. FLEMING: This is much of what we wanted to see. I guess the last was this specific analysis, but only driven by the death, dialysis, and cardiovascular. Did you happen to do that?

DR. COOPER: Death, dialysis, transplantation, cardiovascular events. This does not include a serum creatinine of 6.

DR. FLEMING: This does not.

DR. COOPER: No.

DR. FLEMING: Okay.

DR. COOPER: Our conclusions from these results are that treatment with irbesartan is renoprotective. When you consider this patient population and the fact that you need anywhere between two and four antihypertensives to optimize their blood pressure control, we feel that these data support the use of irbesartan to protect the renal function, but we also recognize that this does not exclude the use of another antihypertensive to protect the heart.

DR. BORER: Thank you very much.

JoAnn, you had several additional questions.

DR. LINDENFELD: Just to make sure I understand here, when a patient was admitted for heart failure or admitted for another event, was that creatinine included in the events? For instance, if a patient was admitted for heart failure in between the routine evaluations and their creatinine had doubled, was that then evaluated as a doubling of creatinine assuming that it was reproduced?

DR. COOPER: All events were adjudicated by the outcome confirmation classification committee. If a patient had two events at the same time, they would have been adjudicated independently of each other, and all of the criteria would have had to have been fulfilled. Certainly there could have been -- and probably were -- a

number of patients who, because of their compromised renal function due to diabetic nephropathy, at the time of the hospitalization where there are other insults to their system, if you will, could have been pushed over into end-stage renal disease at that time and had incurred doubling of serum creatinine.

DR. LINDENFELD: I guess what I'm asking is whether or not patients who had worsening heart failure were sampled more often and they're more likely to reach the endpoint of doubling of creatinine earlier because there was this significant excess of heart failure. That could have made a difference of a number of endpoints.

DR. JULIA LEWIS: Let me see if I can answer the question for you. In order for a patient to reach a doubling of serum creatinine, they had to have a persistent doubling of their serum creatinine on two measurements up to 4 weeks apart. During the time interval between the first measurement of doubling of serum creatinine and the second, the investigator would be encouraged to treat any reversible causes of the rise in serum creatinine.

So if, for example, a patient was in the hospital with heart failure and had a transient rise in their serum creatinine, when they came to their next study visit, the study coordinator would be checking their serum creatinine as part of that visit. If at that visit, the

serum creatinine was doubled, it would then fall into the usual path of confirming the doubling.

Did that answer your question?

DR. LINDENFELD: I think so.

I'd like to just get back to this issue of race just a little bit. Could you show me what the doubling of creatinine was in blacks versus whites? I recognize there was a small number of blacks in the study, but is there a substantial difference?

The reason I ask that is there were 98 doublings of creatinines in the irbesartan group and 135 in the placebo, so a difference of 37 patients. There were 78 black patients in the placebo group, 63 in the irbesartan, and 87 in the amlodipine group. This is several percentage points difference because the total number in each group was slightly different.

So, I'm just concerned. If, as we've heard, the progression of renal disease is significantly different in minorities and there's a difference in minorities, whether or not that's a significant point here.

So, I think to just start that, could you tell me was there a difference in the doubling of creatinine in black patients compared to white patients?

DR. COOPER: The answer is yes. Do we have the subgroup analysis specifically for blacks versus whites?

The subgroup analysis shows that the point estimate for doubling of serum creatinine favors treatment with irbesartan. The effect in white patients is greater with a relative risk reduction of 25 percent compared to nonwhite patients with a relative risk reduction of 5 percent. This is a subgroup analysis with a very small number of patients, and once again the results are going to be driven by the number of patients.

DR. LINDENFELD: It doesn't look like there's enough difference in the baseline to make a difference.

But there is an under-representation of, I think, blacks in the irbesartan group compared to both the placebo and the amlodipine group. There's under-representation in the entire trial, but I think there's about a 5 percentage point difference in the number of blacks here. It just concerns me because if blacks are likely to progress at a higher rate, then a small difference could make an event difference of 10 or 12 in that group, which could change the total number of 37 events substantially. Again, I think this is a problem in this kind of trial of not stratifying for the groups that are more likely to progress.

DR. COOPER: Dr. Lewis, do you want to address the rate of progression of renal disease in black patients?

DR. EDMUND LEWIS: Well, not any further than

what I've said before. I don't think we have information about the rate of loss in black patients in the study in terms of delta creatinine clearance for blacks versus whites. So, I really can't expand very much on what was said before. I think that here you have this data, and I don't think that there's any further that I can say about that, although I will point out that the effect of race on the outcome -- clearly patients who are white had more irbesartan effect, if you will, than blacks. But I really can't comment about your other point.

DR. JULIA LEWIS: I think I can comment a little bit more about it. Can I have my slide 1?

This is true that if you look at the age-adjusted incidence of ESRD, African Americans have a higher age-adjusted incidence of ESRD based on the USRDS data.

Also, there's data out there that suggests that an African American with high blood pressure and kidney disease compared to a white person with high blood pressure and kidney disease, between the ages of 20 and 45, has a 20 times increased risk of developing kidney disease.

However, in the African American study of kidney disease and hypertension, sponsored by the NIH that I alluded to earlier, 1,094 African Americans were randomized in a three-by-two factorial design. I've already commented on the results of the blood pressure

randomization. I will comment that the ACE inhibitors protected their kidneys, but I would also like to comment that the average rate of decline of renal function in this study in African Americans with high blood pressure and kidney disease was 2 mls per minute per year, which would mean that if you started out with a normal kidney function, a GFR of 100, it would take you 50 years to reach end-stage renal disease. So, some of our conceptions based on epidemiologic data on the rate of decline of renal function in African Americans may reflect the fact that unlike in clinical trials, their blood pressure is not under exquisite control.

DR. LINDENFELD: I don't think that helps me much because it isn't a diabetes trial.

Again, actually what you've said concerns me just a little bit more because if there's an over-representation of blacks in the amlodipine and the placebo groups compared to irbesartan and blacks progress faster, then to me that biases the study a bit in favor of irbesartan.

In addition, if irbesartan doesn't appear to work in blacks and it does in whites, from the data you've shown me, then that's an additional problem more than just the fact that renal function progresses more rapidly in blacks. So, that data actually concerns me.

I'm really concerned because these are not very large numbers. I'd be interested. Maybe I'm overdoing it here, but doubling of creatinine is everything here, and there's only 37 patients difference in the doubling of creatinine. Yet, between amlodipine and irbesartan, there are 24 more blacks and 15 more between placebo and irbesartan. You know, just a few patients here makes a difference between a significant and a nonsignificant study.

DR. NATARAJAN: I agree, but I wanted to actually caution the committee in terms of actually over-interpretation of subgroups of very small sizes. Again, yes, actually there are very few blacks, and the differences among the treatment groups, though numerically there, they were not statistically significant. They were not actually any different between any of the treatment groups.

DR. LINDENFELD: Well, I agree with that, but I'm not talking about that. What I'm talking about is the fact that it seems to me from a cardiologist's standpoint, if you just go back and review the reviews, that blacks progress more rapidly and other subgroups too. Maybe Hispanics. But it appears that the literature suggests -- you may have some data that I don't have -- that the progression is more rapid. Again, just help me with this.

Maybe you can explain why that's not a concern.

DR. FLEMING: I think JoAnn is talking more specifically about race in its role as a predictor and hence a potential confounder rather than as an effect modifier, although both are issues. But if in fact it's a predictor such that blacks would have a poor outcome and they are under-represented in the intervention group, then you would have some level of confounding. It's not a serious imbalance, but her point is the strength of evidence here is marginal at the level of significance, so even a minor imbalance could somewhat compromise the convincingness of results.

DR. LINDENFELD: That's exactly right, but it could also be an effect modifier if in fact irbesartan -- there are not enough numbers -- but if it's less effective in blacks than whites, then it becomes an effect modifier too in a sense. They are small numbers, but the study is based on very small differences in numbers.

DR. EDMUND LEWIS: I don't know about helping you. All that I can say about the preconceptions of how much faster or how more malignant a course patients with type 2 diabetic nephropathy have does not take into consideration the fact that these patients do not have their blood pressure controlled to the recommendations that are made. And I think that in this study, we get the

closest that has come actually to blood pressure control recommendations in both the hypertensive and type 2 diabetic population.

So, I think that the assumption that because somebody is African American, they therefore are going to have a much more malignant course is really not exactly an accurate assumption. It's based on literature where the black population, the African American population, has more problems with blood pressure control than does the white population.

I think that once you get into the subgroup analyses, you're getting into small numbers. I personally don't think that our outcomes are that small of numbers. But when you get into the subgroup populations, you are getting into small numbers, and I think that before you make certain assumptions, you have to have the data.

And I don't really believe that you have data showing that the black population -- the natural course of their diabetic nephropathy is that much worse. The natural course of diabetic nephropathy, as we're showing you, is bad and that's with blood pressure control. That's in everybody.

So, I think there's a certain assumption here. I just don't think we can go any further with it because I don't think that there's a number we can put on it. I

don't think that you can say because somebody is African American, their chances of doubling is 1. something compared to a white because that information really doesn't exist.

DR. LINDENFELD: No, I agree, and I certainly don't pretend to be an expert. But if one just goes to the reviews, the reviews all strongly suggested that progression is substantially faster without specific data. But the reviews suggest, from studying the data, that it's faster in blacks and certainly American Indians and perhaps non-white Hispanics.

DR. EDMUND LEWIS: Well, I would be glad to go through whatever data you're picking out of your reviews because I think that I will have no problem showing you that there is a blood pressure issue.

I will say, though, that the Hispanic population and the best study population which is relevant here is the Pima Indian population. The NIH has supported longitudinal studies. 50 percent of the total Pima Indian population gets type 2 diabetes and most of them get nephropathy. And the time from birth to onset of diabetes is very well-known. From the onset of diabetes to proteinuria is very well-known. From proteinuria to decreasing renal function and end-stage renal disease is very well-known in this patient population. They've even

had serial renal biopsies, frankly. And I think that you will see, if you look at that population, which genetically really represents the problem in Hispanic populations in North America, that the curves to those various events are the same as those reported from Germany in type 2 diabetic nephropathy.

So, when you start studying populations carefully, controlling for things like blood pressure and so forth, you won't necessarily come up with the conclusions that you get out of reviews. That's all that I can say.

DR. BORER: Bev and then Dr. Kopp?

DR. LORELL: Thank you.

In a little different subgroup, I'd like you to address the issue of the subgroup of women. The point estimate for women for the primary endpoint is even closer to unity than for non-whites, .98. And perhaps you can address that for us.

DR. COOPER: Yes. Dr. Breyer Lewis?

DR. JULIA LEWIS: I'm going to first remind you of the statistical results, and then I'm going to comment on putting it in some perspective.

First, I would remind you that we were not powered for exploratory subgroup analysis. There were, for example, nearly 900 white males in this trial and only 91

black females.

However, as you can see from this, the common point estimate of .8 crosses all the confidence intervals, suggesting a common risk reduction between males and females.

Similarly, the confidence intervals overlap, again suggesting that there's not a statistically significant difference.

Lastly, when looking at multiple subgroup comparisons, it's important that the point estimate favors irbesartan. That's the statistical response to that question.

In terms of putting it in perspective of what's known about the impact of gender on women in hypertension and renal disease, I would first remind you of the hypertension studies. I'll remind you that when the first studies were done, examining whether or not treating people with hypertension with basically beta-blockers and diuretics versus placebo was of benefit. The first three trials, the MRC done in England, the hypertension detection and follow-up program done here in the United States, and the Australian therapeutic trial, when the subgroup analysis was done in women, not only did they either not find a benefit or actually found that the women had a higher mortality rate in the treated group.

Now, although there was concern expressed when these studies were done, no one at that time advocated strongly that women should be withheld from the treatment of hypertension. Subsequently, the INDANA analysis, which has incorporated seven clinical trials looking at the treatment of hypertension, has concluded what in fact has been I think common medical practice, and in fact women benefitted from the treatment of their hypertension, although not in all the categories as did men, but in key categories, including main cardiovascular events.

In the area of renal disease, I'll just review only clinical trials that have in the definition that you would accept that are randomized, double-blind with sufficient numbers of patients enrolled to have power to look at the group as a whole. But again, the analysis of the impact on women is a subgroup analysis in each of these trials. I also selected trials that have outcomes similar to the one used in IDNT.

The first, of course, is the captopril trial, which you are familiar with, in type 1 diabetics. Males and females had equal outcomes. Males did not have a worse rate of decline of renal function, nor was there any difference in efficacy of the ACE inhibition for males.

A study done in nondiabetic patients with proteinuric kidney disease in Europe found that males had a

worse outcome and that there was worse efficacy of ACE for males. Excuse me. It was better efficacy for ACE in males.

Another study done in nondiabetic proteinuric patients in Europe. Worse outcome for males, no. But better outcome for males.

If you look at the MDRD, which was not a study, looking at an intervention with a specific antihypertensive agent, but at other interventions, males had worse outcomes.

So, in fact, the subgroup analysis in the available renal studies is all over the map, suggesting that perhaps all of these studies are not powered for these exploratory subgroup analyses.

DR. KOPP: I just wanted to make a comment about the progression of diabetic nephropathy in blacks versus whites. My understanding is very close to what Dr. Lewis said, that in the setting of diabetes, blacks are something like 2- to 3-fold more likely to develop nephropathy, but I'm not aware, although he may have come across something that I don't know about, that once diabetic nephropathy appears, that the rate of progression is different.

DR. BORER: Why don't we move ahead with the presentation, and we'll get to any residual -- we have

another speaker down at the end of the table.

DR. TEMPLE: A short question. Going back to the possibility that the greater number of blacks in one group influenced the results, isn't that answered by the breakdown into the black and white populations that we saw in which the effect was larger in the white population? That doesn't seem to be compatible with the whole result being driven by the excess of blacks. Isn't that right?

DR. LINDENFELD: If you think that the progression -- I don't want to make a huge issue of this. I just think these are small numbers. But if you assume that progression is greater in blacks and there are more blacks in the non-treatment group, that group would progress faster.

DR. TEMPLE: No. I agree with that. But then they showed separate results for the white population than the black population. The effect, if anything, was larger in the white population.

DR. LINDENFELD: Right.

DR. FLEMING: One has to be careful, Bob, in keeping these issues of confounding and effect modification separate. If you look at page 73, for example, in the sponsor's briefing document where they present this summary, if you look in the control arm, non-whites have a somewhat higher event rate, 43.5 percent, from whites at

37.3 percent. And as a result, if you end up with some excess of whites in the intervention arm, then there would be a small level of confounding. I don't think this is a very large risk of confounding. It would be very modest. But I think JoAnn's point was in a setting where the significance is very close to the border, this could have some influence.

A separate point entirely, also a relevant point, is is race also an effect modifier, not only is it a predictor such that it appears that non-whites have a somewhat higher rate, does treatment effect differ by race, which is an entirely separate phenomenon from whether race is a confounder. And it also appears here, that in addition to it being a potential confounder because non-whites have a somewhat higher risk, it's also true that the effect seems to be greater in the whites than it is in the non-whites. Two separate issues.

DR. BORER: Without --

DR. NATARAJAN: Could I address that?

DR. BORER: No. Just one moment because I think we may have gone as far as we need to go with this.

There may be some differential effect based on race. It seems plausible to me. We know that renin levels are, by and large, a lot lower in the black population with hypertension than in the white population with

hypertension, and here we're blocking the renin-angiotensin system.

I don't want to go into the realm of speculation. These are the data. Indeed, there may be some comments, if the drug is judged to be approvable, about labeling issues or maybe not. But let's deal with that when we get to the questions, and let's hear the remainder of the data that we're going to hear.

DR. FLEMING: Jeff, there were two quick questions that I wanted to raise.

DR. BORER: Sure, absolutely.

DR. FLEMING: If I could go back to the sponsor's presentation, slide C-13. What you had done there is you had broken out the relationship between having had a creatinine event versus dialysis or transplantation. Surely there is, obviously as this shows, a relationship, as we would fully expect. It's interesting that 26 percent of these events of dialysis or transplantation occur in that right-hand column, people that didn't have a serum creatinine event.

I guess I have two questions. One is trying to understand why a quarter of these people would have gone on dialysis or transplantation without having had a creatinine event is question one.

Question two is how do those 69 break out by

intervention arm? Hopefully not with more of them on the irbesartan group.

DR. COOPER: The answer to your first question is, by and large, when patients presented requiring dialysis, it was because they either missed visits and so we were no longer able to measure their serum creatinine and then assess whether they had had a doubling or an ESRD event, as determined by the serum creatinine, or the other most frequent reason was because these were patients who were on a rapid slope of decline of renal function, hadn't yet doubled, or achieved a serum creatinine of 6, were hospitalized because of an intercurrent and severe illness that compromised whatever remaining function they had left and pushed them over into permanent end-stage renal disease.

DR. FLEMING: So, there's not a fully consistent relationship, at least in terms of documenting a doubling versus having dialysis occur. There are a substantial number that will actually have dialysis occur before you document.

Can you tell us how those 69 broke out in the three groups?

DR. COOPER: I honestly do not remember. Do we have that data?

DR. FLEMING: If you don't have it now, I can

wait and we can get it at the end of the next presentation. It would be useful to know that.

DR. BORER: Yes, let's try and get it.

Just a clarification in response to Tom. If I understood what you said correctly, it's not that there may not have been doubling or far greater than doubling of creatinine in many of these patients who didn't have a doubling event or a 6.0 creatinine before they went on dialysis, but that they went on dialysis in the context of a situation which was not the time at which these events were measured and therefore they wouldn't be captured that way in the data set. They may well have had a creatinine of 6 in the context of another disease, but you didn't count it that way. They just had to go on dialysis. Am I correct in saying that?

DR. COOPER: Yes, that's correct.

DR. BORER: Steve?

DR. NISSEN: I don't want to belabor this, but we talked about other subgroups. I was very struck by the North America versus non-North America data, and I would really like a comment because we've seen an awful lot of studies, particularly recently, where drugs didn't seem to have any effect in the North American population but did in the out-of-U.S. population. I personally am troubled by that, and I want to know if you have any comments or

thoughts or can you help me understand why there was only a 5 percent point estimate for the North American population.

DR. COOPER: Part of that is driven by the fact that all of the black patients that were enrolled and randomized were actually in North America, so a number of those events were in that subgroup. There is no other biological explanation for why the rates of progression would be different or the treatment effect would be different between the different regions. Certainly in Latin America and in the Pacific region, the event rate that was observed -- and there are minority populations in those regions -- was very consistent with what was seen in Europe.

Any other comments?

DR. BORER: Dr. Temple.

DR. TEMPLE: Some people have expressed some degree of nervousness about not having a sort of ultimate endpoint on the people who got their creatinine to 6 or doubled it or something like that. A fair amount of time has now elapsed since you published and collected data. Would it be of interest or a possibility to find out when all the people in the trial went on dialysis?

DR. COOPER: We could certainly do that for all subjects who didn't withdraw consent and for all subjects that didn't participate in a site that was closed.

Actually ascertaining dialysis or ESRD is more difficult than mortality because with mortality you can just access a death certificate. But yes, we can do that.

DR. TEMPLE: Even if the site is closed, they could find out when the person went on dialysis. I'm not saying it would be easy and I'm not even saying it's necessary. I just wondered if you could do it.

DR. COOPER: Yes, we can make an attempt to do that.

DR. FLEMING: Just a follow-up on that. Why wouldn't that be a compellingly obvious thing to do in the sense that what we're hearing is clearly there is a real relationship between creatinine elevation and dialysis, the latter being an obvious clinically important endpoint, the former being at least debatable as to the level of surrogacy that it actually presents? But the answer is there in this database, and the answers that we have in this database are marginal, even if you focus on the primary endpoint, and if it's just a matter of time, which we keep hearing, then wouldn't it be potentially very informative to know what an updated data set would say?

DR. BORER: We could ask the sponsor to do that.

I just want to make one quick comment and then we must move on. We shouldn't get into a debate here. I

have no problem with recognizing that somebody with a creatinine of 6 is sick. I'm just a cardiologist, but even I know that. They don't feel well and Dr. Lewis actually recited the problems that are associated with creatinine at that level left untreated by dialysis. So, I don't think we should spend too much time talking about whether these people are sick or not. If they're not dialyzed, they're real sick, and we can debate that later when we go through the questions. But I don't think that's a key issue.

DR. JULIA LEWIS: Could I expand on that for just one second? In type 2 diabetes, there are 135 million. By the year 2025, there are going to be 325 million, a 100 percent increase in the third world, if you'll forgive me for referring to it, the Asian countries. For them an elevated creatinine is death. We wouldn't be able to go count them going on dialysis later. They're dead because it's not an available therapy.

DR. FLEMING: Then we should be able to see in those people a survival in that as well.

DR. BORER: We should.

DR. COOPER: Right. We will make every effort to collect that data.

It is with great pleasure that I now introduce Dr. Parving --

(Laughter.)

DR. COOPER: -- who will be discussing the IRMA 2 study. You will be hearing about the ability of irbesartan to alter the course of diabetic nephropathy earlier in the disease so that patients do not advance from the stage of microalbuminuria to proteinuria, the onset of which in diabetes heralds the inevitable decline in renal function. Thank you very much.

DR. PARVING: So, I'm supposed to say good afternoon from Denmark.

I am pleased to give you information on the early course of diabetic kidney disease and I'm going to present the data from the study called IRMA 2. It's dealing with irbesartan in type 2 diabetic patients who are suffering from persistent microalbuminuria.

I will present data in two segments, one giving you some background information and then go to the presentation of IRMA 2.

First, the background. This is actually linking up to what you have just been told, dealing with the IDNT study. It's a Kaplan-Meier estimate of the primary composite endpoint in the IDNT study in relation to quartiles of albumin excretion rate at baseline. The message from this baseline estimate is the following. If you have levels of albuminuria, low 1,000 milligrams, the event rate is approximately less than 20. If you go the

very high rate, the upper quartile, then you have an event rate of nearly four-fold higher, at least suggesting that the level of proteinuria or albuminuria is reflecting the underlying cause of the kidney disease as first demonstrated by Bright in 1836 in England.

This cartoon is giving you information on the different levels of albuminuria. We have a log scale and we are dealing with the overnight albumin excretion rate, and the reason why we are dealing with the overnight albumin excretion rate is in an attempt to standardize the collection. So, we are avoiding the marathon runner, we are avoiding other special activities of standing up and lying down because we have that phenomenon. So, we are standardizing it by using overnight collection. So, you collect all the urine during the nighttime.

Normal albuminuria is defined as an albumin excretion rate below 20 micrograms per minute. If you have an excretion rate between 20 and 200 micrograms, we call it microalbuminuria.

This range of albuminuria is usually not depicted by the dip stick test. You need to develop sensitive tests in order to pick it up. This was described the first time 20 years ago by Viberti, Mogensen, and myself as something important in relation to diabetic kidney disease. And we actually have an anniversary this

year.

(Laughter.)

DR. PARVING: Then about the 200 microgram level, we are speaking about overt nephropathy.

You will also appreciate that while the IDNT studies carried out in patients with overt nephropathy having an excretion rate of more than 2,000, way up here, IRMA 2 is a study carried out very early in the course of diabetic kidney disease because, as Ed Lewis already told you, microalbuminuria is an abnormality in the glomerular capillaries leaking protein. So, it's the earliest clinical sign we have of an underlying diabetic kidney disease. So, IRMA 2 is carried out in this range.

Very important information is that 60 percent of our type 2 patients will never, ever develop kidney disease. Unfortunately, 40 percent of our patients in America, in Europe, and in certain parts of Asia, even higher, will develop this devastating kidney disease.

It's also true that in order to develop the disease, you are progressing through the level of microalbuminuria, the earliest state of diabetic kidney disease, into overt nephropathy.

Important to note is that the GFR, meaning the glomerular filtration rate -- the drop in normal man with normal albumin excretion rate is 1 ml per minute per year.

If you have microalbuminuria, the drop in kidney function is ranging between 1 to 3 mls per minute per year and that is based on all the available data. You'll appreciate later on in my speech that the rate of decline in the IRMA 2 is 2 mls per minute per year.

If we go to overt nephropathy, the rate of decline is increasing, and it's ranging between 2 to 20, with the average rate reported in the literature of 10 mls per minute per year. Actually the level of decline from the IDNT study -- we haven't discussed that today -- was 6.5 mls per minute per year. So, you can clearly see if you go from this level of proteinuria to this level, you have a progressive worsening of the kidney function. Consequently the aim of IRMA 2 is to keep the patients within that region. We don't want to get them out of the box.

More background information about microalbuminuria in type 2 diabetes. As already stressed by Ed Lewis, it is an early marker of diabetic kidney disease. We have structural lesions too, and we have discussed that already. That's the alternative. If you don't like the clinical physiology, you need to do repeat biopsies. You have no other alternative if you want to evaluate the lesions. We have biochemical evidence suggesting abnormalities, as also seen later on in the

disease.

Important to note, again based on all available literature, 5 to 10 percent of these type 2 patients with microalbuminuria will convert into overt nephropathy every year.

As already stated, as long as you have microalbuminuria, the rate of decline in the glomerular filtration rate is ranging between normality and slightly elevated, but a very low rate of decline as compared to what happens if you are running with overt nephropathy.

Then I think in all fairness it should be mentioned that the American Diabetes Association and the International Diabetes Federation actually are advocating that we are screening for microalbuminuria, and if we detect it persistently, we need treatment.

The hypothesis in IRMA 2, the earliest study of irbesartan in diabetic kidney disease, is exactly the same as in IDNT. The objective is to evaluate the renoprotective effect of irbesartan above and beyond the blood pressure lowering effect on the progression to overt nephropathy, and we are comparing that with conventional antihypertensive treatment and it's done in hypertensive patients who have type 2 diabetes and persistent microalbuminuria. So, in essence, this is not a blood pressure trial. This is a trial aiming at evaluating the

blockage of angiotensin II. Is angiotensin II nephrotoxic? Yes or no. That's the answer you'll have from this trial.

The study design was carried out in the following way. The patient was run in placebo for at least 4 weeks. We saw them every week at the clinic. They were then randomized either to receive placebo, irbesartan 150 milligrams once daily, or irbesartan, the yellow one, 300 milligrams once daily. We used 4 weeks in the titration period.

The aim of the three arms was to obtain blood pressure equivalence. So, we were actually trying to get exactly the same blood pressure in each and all of the arms, keeping the blood pressure below 135 over 85 millimeters of mercury.

In the placebo arm, it was not allowed to use ACE inhibitor or receptor antagonist. Neither were you allowed to use dihydropyridine calcium antagonists. The reason for that was that in some of the past literature, this kind of compounds, the dihydropyridine calcium antagonist, was reported to elevate proteinuria, and we consequently felt that it was unfair then to use it.

The primary outcome in IRMA 2 is time to the first occurrence of an albumin excretion rate of more than 200 micrograms per minute and an increase of at least 30 percent in albuminuria from the baseline level, and that

had to take place at two consecutive evaluations. This endpoint has been used for the last 10 years within trials trying to evaluate the importance of preventing the occurrence of disease in type 2 and type 1 diabetes. So, we are using exactly the same endpoint that other colleagues have applied in the past dealing with this question.

The secondary endpoint is the changes in the overnight urinary albumin excretion rate, and finally, we are looking also at the changes in estimated creatinine clearance. This is based on the so-called Cockcroft-Gault formula, which is an old formula based on measurement of creatinine knowing the sex of the patient, knowing the weight of the patient, and the age, and then you can calculate this formula. Actually the formula has been validated by ourselves in patients with diabetic kidney disease. It works.

The baseline characteristics in the IRMA 2 study. The good news is that the three arms are balanced dealing with demographic data, dealing with clinical data, and dealing with laboratory data.

We have the same age, 58 years of age.

We have a male preponderance, as we should have in this disease.

We cannot discuss ethnicity in our study from

the point of view we don't have any other than whites because it was done in Europe. I complained about that. Next time we have to do it around the world.

BMI was, as it should be. They're obese.

The known duration is identical.

Hemoglobin A1C -- we were discussing that earlier this morning -- was also at the same level, and that level was equivalent to a mean blood glucose of 8 millimoles per liter. I hope you know millimoles per liter, because I'm not able to convert it so speedily into milligrams per deciliter. It should be all right.

Microalbuminuria, the level in micrograms per minute is also at the same level in the three arms. Of course, there are small differences, and we will adjust for that when we do our risk ratio measurements.

Another important issue compared to the IDNT, which you just heard about where there was already, when they started the study, the GFR was down to 58. So, it was in harmony already when they started the study dealing with IDNT. In this study they had well-preserved kidney function, 109, 109, and 108.

The blood pressure was equivalent in the three arms. The same systolic, 153 in all three arms; 90 in the placebo; irbesartan 90, and 91. There was no statistically significant differences at baseline.

So, what happened to the blood pressures during the trial? If we started at the bottom line, you'll remember that there was identical blood pressure at baseline. They went down and they stayed down during the study. On average, the blood pressure in the three arms was identical. It was 83, 83, and 83 millimeters of mercury. If we go to the mean blood pressure calculated the usual way, the placebo group and the irbesartan 150 group had a mean blood pressure of 103, 103, and the irbesartan 300 group had 102. And that was significant. It was only small reduction but there was a significant difference in blood pressure.

If we then go to the top, the systolic blood pressure. Again, you'll remember that it had identical values at baseline. The values during the 2 years of observation in the placebo group was 144 millimeters of mercury. In the group receiving irbesartan, the green one, 150, it was 143, so there was a 1 millimeter difference. And finally in the group, the yellow one, receiving irbesartan 300 milligrams once daily, the systolic blood pressure was 141 millimeters of mercury, and that was definitely lower than in the placebo group. Again, we adjusted for that in our hazard estimation.

This is the main outcome of IRMA 2. This is the cumulative event rate, a Kaplan-Meier plot, of the

development of diabetic kidney disease, defined as earlier. First of all, I would like to tell you why this has this bumpy appearance. It has to do with the fact that albuminuria at these different time intervals -- it's not measured continuously. It's measured after a certain number of month, 3 months, 6 months, 12 months, and so on, and consequently you can only have events at these time points.

After 3 months, you always see a separation, and the separation is actually persistent during the 2-year study period. At the end of the 2 years, 15 percent in the group receiving placebo on top of standardized treatment -- treatment reduced the blood pressure to nearly the identical level as in the two other arms. There was 15 percent of these patients who progressed to a level of more than 200 micrograms per minute. In the group, the green one, of irbesartan 150, it was 10 percent, and finally in the group of 300 milligrams of irbesartan once daily, it was 5 percent.

At the top you will see the relative risk reduction. The relative risk reduction unadjusted was 70 percent for irbesartan 300 versus placebo, with a p value equal to 0.0004.

If we adjust for the differences in albuminuria at baseline and the blood pressure during the trial, then

the relative risk reduction goes down from 70 percent to 68 percent.

If we then look at the dose of irbesartan 150 once daily versus placebo, we had an unadjusted relative risk reduction of 39 percent. It was not statistically significant with a p value of 0.085.

If we adjust for baseline differences and blood pressure difference, the relative risk reduction actually improved. It was 44 percent and the p value was equal to 0.05.

During the study, patients who developed diabetic kidney disease were discarded. So, when you hit the endpoint, you were out. That's important to understand this slide because this is the percentage change in albuminuria. The expectation for each and all of us would have been a rise in albuminuria, but you have to remember that the bad guys are out. So, when they hit more than 200 micrograms, they leave the study.

The message is then from those who received placebo treatment on top of standardized treatment, there was no major difference in albumin excretion rate during the 2 years of study. At the end it was 9 percent above baseline.

If we look at irbesartan 150, the mean reduction in proteinuria was 24 percent, and this was

highly statistically different from the placebo group.

Then if we look at my favorite, irbesartan 300 milligrams once daily, you see the reduction, and the reduction is actually continuing during the trial period. So, at 2 years, the difference is 54 percent compared to the placebo group.

Another important issue is that if we compare the mean reduction in albuminuria, it was 38 percent compared to the 150 with 24. There was a highly statistically significant difference with a p value of 0.001.

Estimated creatinine clearance. Again, remember that the patients who developed diabetic kidney disease are leaving the study. So, what you're seeing here is, in essence, what is happening in those who remain microalbuminuric. You are seeing a picture of a so-called biphasic response because we have the estimated creatinine clearance, and you see the initial response from time 0 to 3 months when blood pressure is going down. There is rather a steep drop in kidney function, but before giving you that figure, I will just mention that the initial value of creatinine clearance was identical in the three arms, 108, 108, 109. If we look at the initial drop, it was 5 milliliters in the group receiving irbesartan 300 and it was 3 in the group receiving placebo or irbesartan 150.

So, initially when blood pressure is lowered, we are losing filtration power. That is a well-documented phenomenon when blood pressure is lowered. From 3 months and onwards, we are dealing with a so-called sustained rate of drop in kidney function, and the good news is that the rate is flat.

Actually when we look from here to here, the drop in kidney function in the irbesartan 300 milligram group and in the irbesartan 150 milligram group was only amounting to 2 mls per minute per year. You'll remember that the normal drop, just by getting older, is 1 ml per minute per year.

In the group receiving the placebo, the drop was 1 ml per minute per year, and if you remember that we initially started off having a GFR of 110 and you're only losing approximately 2 mls per minute per year, as long as you're microalbuminuric, then it will take you approximately 40 to 50 years to know the states which we have discussed this morning, if that continues. And of course, you will ask me that, so I will give you an answer later on.

The safety profile in the IRMA 2. We are very early, so we don't have a lot of concern actually. If we are looking at the most important one, the serious adverse events, we had 22.8 percent in the placebo group. In the

group of irbesartan, it was less, 15.8, and the group of irbesartan 300, it was 15 percent. So, there were actually less severe events. The number of deaths was equivalent.

So, in summary then, the IRMA 2 study had two messages.

The first is that by using irbesartan in patients with type 2 diabetes and microalbuminuria, we found a 70 percent risk reduction in the progression from microalbuminuria to overt nephropathy.

The second one is that the risk reduction was dose-dependent, meaning that 300 milligrams was superior to 150, which of course is very important when you treat patients, as I do every day.

Furthermore, the effect was an effect above and beyond the blood pressure reducing effect.

And finally, as already stressed by Melisa, it's a safe and well-tolerated compound in these patients.

Thank you very much.

DR. BORER: Thank you very much. Again, a really clear and lucid presentation.

Do we have questions here? We'll start with our two nephrologist members here, if you have any issues to raise. Dr. Brem?

DR. BREM: I was wondering if you could just clarify one point on the slide D-12. The placebo group.

If I understand it, the patients who met the endpoint were not included in this slide for GFR or were they included in the GFR?

DR. PARVING: The patients meeting the endpoint, meaning the development of diabetic kidney disease, were excluded when they met the endpoint. They were in the study until they met the endpoint.

DR. BREM: So, on this particular slide, D-12, were those placebo patients demonstrating a decrease in GFR included in this slide or were they not?

DR. PARVING: All patients, as you can see from the numbers here, were included, but when they developed diabetic kidney disease, they were no longer included because, by design, they had to leave the study. Consequently, we could have no additional value on them. So, we are following each and all of them until the time point where they developed diabetic kidney disease and then they are left out.

DR. BREM: Do those patients have an accelerated decrease in GFR in your particular study in the placebo group as you described in the general population?

DR. PARVING: That's a very important question which cannot be answered from this study because this study, as you see, is only running for 2 years. When you go from microalbuminuria, having a very low level of

progression, to overt nephropathy, you need a couple of years in order to actually be able to pick up the signal that the rate of decline is worsening.

DR. BREM: But I thought you demonstrated at the beginning -- correct me if I'm wrong -- that patients with overt proteinuria have a decline in GFR of about 6 or more milliliters per minute --

DR. PARVING: That's correct.

DR. BREM: And these patients have a GFR decrease of approximately 2. So, if you counted all the placebo patients who reached overt proteinuria in this particular analysis, wouldn't you expect to see a more pronounced decrease in glomerular filtration rate in that population?

DR. PARVING: It's completely correct, as you state, in relation to the initial slide. The drop in kidney function in these patients is minute, and when they go from one level of proteinuria to a next level of proteinuria, it's correct that the rates start to go up. But you need a certain time interval in order to pick up the signal. Actually most nephrologists suggest that you have to follow the patient approximately for 2 years in order to be pretty sure that you have that signal.

DR. BREM: So, you'd have to follow these patients in this group for an additional --

DR. JULIA LEWIS: The overt proteinuria patients are no longer counted. Once they hit overt proteinuria, you're no longer measuring their creatinine clearance.

DR. BREM: Right, but my thought would be, if you did, you would be able to demonstrate efficacy in GFR much more convincingly. And I'm wondering why you wouldn't have included them in this particular analysis because it would be more supportive of your argument.

DR. PARVING: We have data from the literature. I would like to share them with you. I think we can show you 4-3.

This is the review of the literature available to each and all of you. That's a retrospective study, the first one. All the remaining studies are prospective.

The message from this slide is the following. First of all, the conversion from microalbuminuria into overt nephropathy is ranging from 4 to more than 9 percent.

If we look at the drop in kidney function -- and you have to remember that these studies were followed prospectively for 4 to 5 years, so they had a much longer observation period than we have in IRMA 2. The rate of decline in the study from the Pima was 1, from East Welley, it was 2, from our study group at Steno it was 3.2 percent, from India it was 1 percent, from the ABCD trial it was 1

percent. These patients were treated with blood pressure lowering agents here and here, while they were untreated here because they were normotensive. So, in long-term observational study, the rate of decline, as I depicted to you, is between 1 to 3.

And I can expand on that because we have a follow-up of the Steno study, and that will be 4-37.

The Steno study we published a couple of years ago. It's a study dealing with type 2 diabetic patients who have microalbuminuria, the same way as in IRMA 2. They're very much the same. It's a study where we were looking at the potential importance of multifactorial intervention. In this study, we were actually measuring the glomerular filtration rate using an isotope technique initially and during the study period. We reported the data after 4 years, and now just before leaving Denmark, I had the possibility of looking into the data after 8 years. We have 129 patients followed now for 8 years.

Those patients who remained microalbuminuric in this prospective, randomized trial had a rate of decline every year during the 8 years of 3.2, while those patients who developed overt nephropathy, using exactly the same definition as I gave you earlier, had a drop in kidney function of 4.7, again showing to you that when you pass from one category to the next, then you start to have

worsening of kidney function.

But again, the important issue in this very early state of diabetic kidney disease is that you have to do long-term studies, and this is an 8-year study while IRMA 2 is a 2-year study and we could not pick up that signal.

DR. BORER: JoAnn, do you have any specific questions?

DR. LINDENFELD: In the GFR substudy that's mentioned in the briefing booklet -- you've explained the reason for that not changing. But after 4 weeks of withdrawal of drug, certainly in the 150 group, the proteinuria went right back up to baseline. And after 2 years, do you find that disturbing that that doesn't suggest that there's been a persistent change? And then again, it also went up in the 300 milligram group, but not as much. I'm wondering what we would make of that?

DR. PARVING: In the literature, several studies have been carried out and after carrying out the studies, some of us, at least those of us from Denmark, have stopped the treatment and then see what happens. That has been done in type 1 patients, in type 2 patients, early and late.

So, in the IRMA 2 trial, we actually did the same. We followed in a subset of patients kidney function

during, of course, the 2 years of observation, and then after 2 years, we stopped all treatment. So, at this time point, all kind of blood pressure lowering treatment was stopped and we are now looking at the change, after stopping treatment for 1 month, in albuminuria. In the placebo group, the pink one, actually the level goes back to baseline and no change. If we look correctly at the 150 milligram irbesartan group, there's actually a huge rise of 80 percent going back to normal, which may suggest that a major part of the effect in that particular arm was hemodynamic.

The good news, however, is that in the yellow group, the irbesartan 300 group where we saw a significant reduction in development of diabetic kidney disease, we only saw a rise of 13 percent, and this in my mind is one of the first times ever where we have demonstrated that by stopping this kind of treatment, we are not regaining what we expect. Actually it seems to suggest that there is a residual effect of the irbesartan 300 milligrams, but again, that has to be proven in a larger number of patients. So, all in all, it may suggest that the effect of our compound in the high dose has residual renoprotection.

DR. BREM: Were those data controlled for blood pressure?

DR. PARVING: Blood pressure rose. As you may remember, the blood pressure was identical in the three arms, more or less. The diastolic was identical.

DR. BREM: But at the end.

DR. PARVING: All of them had a rise in blood pressure when you stopped treatment because you stopped all kinds of medication. So, in essence, I think if I recall correctly, the rise was less in the placebo group, was biggest in the two groups who no longer had the treatment with irbesartan. So, it's not a blood pressure phenomenon.

You'll also remember that despite the fact that blood pressure was reduced to the same level in the placebo group, as in the irbesartan 150 milligram group, there was actually no difference. There was a huge 24 percent difference in albuminuria. So, even though there are minute changes in blood pressure, this can definitely not explain that. But there was a rise in blood pressure.

And there was also a rise in kidney function, the way it should be, meaning that when you stopped that kind of treatment, you see a regain in kidney function. As I said to you initially, there was a drop the first 3 months, this biphasic pattern, and this is due to a blood pressure drop.

Actually give me the option of mentioning something, which some of you may remember and some of you

may have forgotten, and that's the story about malignant hypertension. The story about malignant hypertension is dating back to the 1950s. When you had malignant hypertension, the survival until end-stage renal failure was 2 years, if you didn't die from stroke before that. It was a devastating condition.

However, when blood pressure lowering was initiated, we saw the following pattern. When you lowered blood pressure, you saw a rise in creatinine and, of course, that always indicates that you may do some harm to the patient. However, the creatinine level then stabilized, stabilized, and stabilized, and the patient no longer went into end-stage renal failure.

So, this initial phenomenon is actually well described more than 50 years ago in malignant hypertension and is documented in each and all of the major trials dealing with kidney outcome. The MDRD study, the captopril study, all of them have this initial drop.

DR. BORER: I'd like to go back to slide D-12 again. I don't want to try to over-interpret data that have been processed in a certain way with all the dropouts that you explained for reaching overt proteinuria. But I'm struck with the observation that the people who were left in the trial in the placebo arm and the irbesartan 150 arm, even though they more frequently had overt proteinuria, as

we can see from the numbers below, and therefore dropped out, even though there were more dropouts, more overt proteinuria, those who are left in seem to have a slightly better response over the 24 months than the group with irbesartan 300. That may be an artifact of all the processing of these data, but I'd just like your comment about that.

DR. PARVING: I think definitely it's fair. From the point of view that I stated initially, that actually the initial drop in kidney function is the important player here because the drop in the irbesartan 300 milligram group, those who gained most in relation to avoiding development of nephropathy, was 5.7 milliliters. So, the absolute drop was 5.7 here and it was 3 here.

You will also appreciate that the level initially was 1 milliliter lower. So, that's another issue.

At the end of the study, after 2 years of observation, the difference between irbesartan 300 milligrams and the two other groups was 3 mls. So, most of the difference is actually explained alone by the fact that the initial drop in kidney function in irbesartan 300 was bigger than in the two other arms. There was no difference in the irbesartan 300 group and in the two arms dealing with the slope. It was identical.

DR. BORER: Should we draw any inferences from the fact that the drop was greater in the 300 milligram group? I mean, is that a bad thing?

DR. PARVING: You could say that, unfortunately -- luckily, it's the opposite. Actually it turned out that in several studies that those who have the biggest initial drop in kidney function have the best long-term prognosis. That has been demonstrated from our group and from the group in Groningen in Holland and also from Italy. It actually suggests that the initial drop in kidney function is reflecting probably the drop in glomerular pressure which is elevated in these patients, at least in animals, as demonstrated by Barry Brenner.

DR. BORER: Blase?

DR. CARABELLO: It's just that those data seem different from the table that we have in our book, table 7, where the initial drop in the irbesartan 300 group in GFR was 2.3 percent and then the late drop at 24 months was 12 percent. This is on page 10 for anyone that doesn't have it. It seems to be the reverse of that.

DR. PARVING: This is the intention to treat. I don't know what you have there.

DR. CARABELLO: This is a GFR substudy.

DR. PARVING: Oh, don't do that.

(Laughter.)

DR. PARVING: Because now we are mixing everything together, but it's all right. I will clear it up.

This is dealing with all patients enrolled in IRMA 2. The substudy is only dealing with a subfraction, actually approximately 130 patients, who participated in the substudy. The substudy was not a random pick because the substudy was dominated by Dr. Parving and his group because we had 50 patients in the group after the 130. So, the substudy is in no way representative or a random sample for the whole population.

Consequently, this is the important player. This is the whole group and all the data based on the Cockcroft-Gault. It's not the substudy.

DR. CARABELLO: So, was the substudy done to confuse cardiologists?

(Laughter.)

DR. CARABELLO: Or was there another purpose?

DR. PARVING: I need to be honest now. We were actually asked by the FDA to do it.

(Laughter.)

DR. PARVING: And I'm pretty sure that the FDA did not want to confuse anybody.

(Laughter.)

DR. PARVING: What the FDA really wanted us to

look at was the effect when stopping the drug. That was actually the aim of the FDA. They would like to see what is the effect when you stop your treatment after 2 years. In the high group, in the group of 300 milligrams of irbesartan, there seemed to be a persistent effect, at least the proteinuria did not go up. And I'm pretty sure that the FDA will be pleased to see that.

DR. PELAYO: I'm the primary reviewer for irbesartan diabetic nephropathy.

I think the issue for the subgroup study -- that was the wrong question to ask because regardless how many patients you study, it doesn't matter for how long you are going to follow them up after you stop the medication, those studies have no -- you can't interpret them because there are multiple scenarios that I could create. So, I would totally disregard those studies not only as the primary reviewer but also as a nephrologist. And I say that to confuse everybody. So, that was the wrong question to ask because there is no answer that can be interpreted.

DR. PARVING: Unfortunately, I happen to disagree slightly because we made a paper a couple of years ago where we actually demonstrated in type 1 patients with microalbuminuria, a randomized trial carried out in Denmark for 8 years. Don't shake your head.

For 8 years we did the study. We published it

in the British Medical Journal, and what we did after 8 years, we measured glomerular filtration rate during the 8 years in these type 1 patients with microalbuminuria, and then we stopped the treatment and remeasured glomerular filtration rate. And the outcome of this study, with the first author as Elizabeth Mathiesen, was the following.

8 years of treatment with the drug called captopril in type 1 patients with microalbuminuria stabilized kidney function. There was no drop whatsoever during 8 years when we reevaluated after stopping the treatment. So, I think actually that FDA was very smart asking us to do that.

DR. KOPP: Just one other question about that. In the GFR substudy group, did you drop patients out who had met the proteinuria endpoint?

DR. PARVING: Sorry. Once more.

DR. KOPP: In the substudy group that we're talking about --

DR. PARVING: In the substudy group, if they developed diabetic nephropathy, they were out.

DR. KOPP: You were out in that study as well.

DR. PARVING: Yes, exactly because the aim of the substudy group was actually to evaluate what happens when we stop the treatment. So, they had continue until 2 years, and then we stopped the treatment.

DR. LINDENFELD: But in this substudy, without belaboring it too much, there really wasn't any difference in the dropout rate.

DR. PARVING: No.

DR. LINDENFELD: So, again I think it does point up that in this study GFR didn't change and you can't explain the substudy on the fact that the patients that developed proteinuria dropped out.

DR. PARVING: No, no, no. The important issue dealing with the glomerular filtration rate from IRMA 2 is the following. I will never, ever dare to claim that there is any difference in the drop in kidney function in these patients. The message is the opposite. The message is as long as the patients stay microalbuminuric, you are only losing 2 mls per minute per year. In other words, it lasts many, many years. If we calculate this, it will take 40 to 50 years to go to the department of nephrology asking for dialysis, and that is the message.

DR. BORER: Ray, you had a question?

DR. LIPICKY: Yes. If you could show slide 4-197 again because I think you said a few words, and I probably missed it.

So, in the very last end there, week 4, there are three data points, and we were sort of led to believe at the beginning of today that you developed proteinuria

when all these things build up in the glomeruli. So, in 4 weeks, in one of the two possible things, the green and the yellow, all of that mass of stuff must have reversed? All of those bluish globs that we saw early in the day went away -- or came back? I'm sorry. Came back.

DR. PARVING: No. I will be very pleased to answer that.

First of all, there is a rebound phenomenon. That is well demonstrated.

DR. LIPICKY: Yes.

DR. PARVING: You have to remember that the expectation is actually the following. When you have 2 years with microalbuminuria, you'll assume, if we have not treated the patient, that it will be up here. However, there was a rebound to the baseline suggesting that a major part of the lowering in this group was due to hemodynamic effect. I quite agree.

DR. LIPICKY: But you have the placebo group there.

DR. PARVING: Sure.

DR. LIPICKY: So, you don't have to refer to something way up there.

DR. PARVING: But the placebo is not a placebo group left untreated.

DR. LIPICKY: No, no. I understand.

DR. PELAYO: You know what is the problem? To interpret that, you have to understand that the antihypertensive medication was discontinued. If it was discontinued in the placebo, it was discontinued in in 150 and it was discontinued in 300.

DR. LIPICKY: No, I --

DR. PELAYO: Wait. Let me finish.

Then if you discontinue the antihypertensive, the blood pressure will go up. That in and of itself can affect glomerular permeability. If you stop abruptly the inhibition of the angiotensin II system, that also can modify hemodynamics and glomerular permeability. Therefore, to me the data is not surprising.

But it still is the wrong question to ask because it doesn't matter what happened after you discontinue the antihypertensive. What matters is what happened before because all this could be due just to a functional effect.

I think Dr. Brenner, who is sitting on my right, could explain this in a more elegant way and without an accent. Dr. Brenner, do you care to enlighten the audience with your knowledge about proteinuria, glomerular hemodynamics, and antihypertensive treatment, and the wrong question and how you can really interpret the data?

DR. BRENNER: I don't think I can improve on

it.

DR. PARVING: Could I have a chance to answer the question?

(Laughter.)

DR. PARVING: And will you answer all the remaining questions for me? That's all right.

DR. LIPICKY: Well, it's getting mixed up. Let me ask the question again.

We were supposed to take the decrease in proteinuria, effect of ARBs, as inducing a morphological change in glomeruli and that the proteinuria occurred because of some morphological effect. And what you have there, at least in one data point, is what looks like something morphological happened in 4 weeks that negated 2 years of therapy. That sort of is mysterious.

DR. PARVING: No. I think that the question raised is quite on target, and I will definitely be very pleased to answer it.

First of all, it's important to realize that this kind of kidney complication is not something which is done overnight. It takes a number of years to develop that kind of lesion, even the early one, with mesangial expansion as increased basement membrane. There's also good reason to assume that the number of years it takes to get rid of it is probably the same. Why should it be

different?

We have one marvelous example from the literature, and that is the beautiful biopsy study carried out by Michael Mauer from Minnesota. He took type 1 patients, biopsied them, and then he gave them a new pancreas. They had this new pancreas working for 10 years with completely normal blood glucose values. No insulin, no nothing. He rebiopsied after 5 years. There was no significant difference. But after 10 years, he saw that there was a significant reversal of the structural damage. I think to my mind that this study demonstrates that it takes a long time to get rid of it.

I think what we are doing here, we are only doing a short-term study. Of course, the message from this study is that the patients are put on the treatment. We will never, ever stop them. We'll continue of course. That's the kind of treatment you need if you need if you want to get reversal of the kidney structural damage. But I think, in essence, that everybody has to realize that it's a very slow process and you need to do it for many, many years in order to gain.

DR. BORER: May I ask? I'll try not to muddy the waters a little bit more. It sounds to me like this is a two-component model. Number one, the morphological changes in the kidney, and number two, superimposed upon

that, acute hemodynamic changes that can change the expression, if you will, of the effects of the morphologic changes.

You took away drugs at week 24 and you said the blood pressure went up. Presumably it went up relatively rapidly, and we saw here the effect of what was sitting there with a new blood pressure level on top of it. And it looks worse for at least two of the arms.

If you followed along further, would you have expected -- or let's say you lowered the blood pressure further with some other drug. Would you then have expected the green point to come back down a little bit again?

DR. PARVING: It depends on what kind of compounds that you're aiming at because all blood pressure reduction will eventually reduce the albumin excretion rate, each and all of them. But some of them are more potent and those that are more potent are those that are blocking the effect of angiotensin II. That goes for ACE inhibition and for receptor antagonist.

DR. BORER: I understand that. I didn't want to get into that. I see that the irbesartan 300 doesn't seem to reverse nearly so much as the others, and that suggests that there's some residual effect, et cetera.

I was only asking the question if you took away the new hemodynamic load on top of the morphological change

that already existed, would you see some tendency towards improvement. That's all.

DR. PARVING: Sure.

DR. BORER: And you would.

DR. PARVING: You will see that.

DR. BORER: Tom?

DR. FLEMING: I'd like to just, one more time for my own sake, go through the interpretation you gave to your slide D-12 just to make sure I understand what you're telling us your interpretation is.

We have had explained to us today a biological progression that occurs with microalbuminuria first, leading to proteinuria, leading to glomerular filtration rate changes, leading to end-stage renal disease, which in essence is dominated by dialysis, transplant, and renal death. This is the progression.

In the IRMA 2 trial, we're really going back to this earlier stage. We're looking at whether or not we can delay this progression to clinical proteinuria. Often what we would want to do, from a statistical perspective to get a sense of the validity of that as a surrogate for ultimate clinical benefit, is to see how that translates into effects on other tangible phenomena that are downstream in terms of clinical consequences. Of course, the next one in line is the filtration rate.

What you're saying is there's not an apparent benefit here, but you're saying be careful because it's going to take more years of effects before you're going to get to a point where you're going to expect to see effects on GFR. Is that correct? Is that a correct interpretation you're giving to why one shouldn't be too concerned about this?

DR. PARVING: I think you're right.

DR. FLEMING: And if I take that then as the interpretation, I can be -- I'll give my interpretation. Jeff, you can comment. Or go ahead. I'll give my interpretation after you.

DR. BORER: No. I just want to ask is that really what you -- I mean, if I'm understanding what you said correctly, it's not that you were waiting for an improvement in GFR. You were waiting to see a worsening and it didn't happen.

DR. PARVING: Exactly.

DR. BORER: You want to, as you said, keep them within the box.

DR. FLEMING: Sure, but I would like to see some evidence of a net benefit relative to placebo. And I'm understanding that we would need to have many more years of effect on delaying progression to increases in proteinuria to be able to expect then, when we look at this

phenomenon downstream, we'll see an effect.

DR. BORER: Maybe yes, maybe no. You dropped out and didn't collect data on the people who developed proteinuria.

DR. FLEMING: Yes, but my initial sense is, looking at the numbers of dropouts -- and it's only a speculation. Unfortunately the trial wasn't designed to truly answer this. It's not clear that that would have reversed this perspective.

DR. PARVING: But could I give an answer? Because exactly what you are saying is that if we should have picked up the signal, then of course we should have kept the patients who developed diabetic kidney disease in the trial. And then we should have told you that those who developed diabetic kidney disease and were followed for 5 or more years did worse than those who didn't. Unfortunately, the design of the study was so that those who were the bad-doers were actually leaving the study.

DR. FLEMING: We understand. We understand that.

But I guess the bottom line conclusion to me is I could be persuaded that the lack of tangible evidence of a benefit on the next phenomenon could, in fact, be that we're looking too early. But at a minimum, I'm left without any substantive basis to say I've got evidence to

validate my surrogate. I know natural history. I know the progression in natural history, but I don't have any direct tangible clinical evidence to show that when I've intervened and achieved this effect in delay of proteinuria, that this is the magnitude and duration of effect that will reliably translate into ultimate clinical benefit downstream. It may or it may not. But I'm left with much less evidence of validating a surrogate here than I would typically expect to have.

DR. JULIA LEWIS: If I could have the slide from the hyperbolic curve from the other Dr. Lewis' talk.

If you'll remember -- and I'm sure it will be up there in a second -- the IRMA 2 trial was not intended nor anticipated nor would we ever design a study to look at the change in rate of decline of renal function in patients who are in this area of the curve for two reasons.

One, in order to, for example, double your serum creatinine, you have to lose a gigantic amount of renal function to measure that.

In addition, in this area of the curve, the measurements of GFR -- the scatter in the measurement itself is almost equal to the rate of decline in renal function when you're in this area of the curve in microalbuminuric patients.

So, in early diabetic kidney disease with

microalbuminuria, you simply can't reliably measure the changes in renal function in those patients, which is why we worked in this area of the curve in IDNT. So, we didn't anticipate to see changes in GFR in IRMA 2 or to be able to detect changes in IRMA 2 in those early microalbuminuric patients over a 2-year period.

DR. LIPICKY: I guess I wanted to follow up on what Tom said because he said what I was trying to say much better, but I'd like to try just one more time to say what I meant.

And that is that the data from IRMA 2 are consistent with the hypothesis that was forwarded. They do not prove the hypothesis that was forwarded. In fact, they sort of don't help it very much.

Then secondly, the creatinine doubling is consistent with the notion that people get into trouble in the first trial, but the actual number of events that were observed don't go along with that. So, this is the nature of the beast that you're evaluating.

DR. PARVING: Could I then add? I will not disagree but I would like to say that the natural history of diabetic kidney disease, where you have such a slow rate of progression in kidney function, which is actually what causes the death of the patient, if you lose filtration power, you're a dead man. Initially the drop is so slow --

DR. LIPICKY: The only thing I said is that if you're a believer, you believe and you don't need data. If you're not a believer, you need data, and that's going to be the problem that's discussed.

DR. PARVING: I think you have the data. I think you have the data telling you that you only have a drop of 2 mls per minute per year in those who are microalbuminuric. That's exactly what you want to know.

DR. BORER: Bev.

DR. LORELL: I think that in this study that you're describing, it seems to me it would be extremely problematic to follow the patients even longer-term to see a more rapid decline in creatinine clearance. And the reason I say that, as a non-nephrologist, is if it is true in the diabetic, that the development of macroalbuminuria precedes this more rapid decline in creatinine from an ethical standpoint for the individual physician investigators, it would have been impossible I think, once a patient reached the point of microalbuminuria, not to use the best data available, which would have been the captopril study, and to have said at this point ethically -- admittedly they're not the same population, but best data available -- I must move to treating with an ACE inhibitor. So, I don't think even today it would be possible to do this study to carry it out long term to look

at events.

DR. LIPICKY: This was done today. What do you mean?

DR. LORELL: No. I'm saying we have another study here now looking at irbesartan and data from losartan.

DR. LIPICKY: So, you think it's ethical to do things you don't know anything about rather than find out whether something works or not?

DR. LORELL: No. I would argue that from the point of view of the physician investigators caring for individual patients --

DR. LIPICKY: But to do something where you do not know what you're doing is correct.

DR. LORELL: I didn't say that.

DR. LIPICKY: Well, why didn't you say that?

DR. LORELL: I'm sympathetic with the stopping endpoint in this trial, given the other data that was available, albeit in type 1 diabetes. So, I actually think it would be very problematic to keep a patient, once they had developed macroalbuminuria, on one of these three treatment arms.

DR. PARVING: That was actually the main reason why that was decided because it was tested out at several of the safety committees in Europe, and they would not

allow us to go ahead. So, that was quite simple. So, what you're saying is at least the notion in Europe. They may be wrong, as Ray Lipicky is saying, but that was the notion.

DR. BORER: Steve?

DR. NISSEN: Bev, I don't agree with you. If it's ethical to take patients at a later stage in the disease, as was done in IDNT, and give them placebo for a long period of time, it certainly would be ethical to do so in an earlier part of the disease curve.

This is an important question because no matter what we decide here, clinicians have to know when in the course of the disease might an intervention such as this be useful. So, we're looking for a signal here that says, well, gee, maybe if you start this therapy very early when you get that first microalbuminuria, you can prevent this whole cascade. So, we're all kind of looking to find some evidence that that's the case, and there isn't any evidence, unfortunately, in the data.

DR. EDMUND LEWIS: Hopefully, I'll get back up there. I should be wearing armor the next time I get back up there, but hopefully I will get back up there to try to convince you otherwise.

There are complex issues here that involve the ethics. First of all, in early type 2 diabetic

nephropathy, microalbuminuria, the study by Ravid from Israel using enalapril showed clearly that ACE inhibitors absolutely stabilized microalbuminuria over a period of -- I forget. I think it was 5 years, and that for that reason, ACE inhibitors were appropriate therapy. So, the physician, seeing the patient with early type 2 diabetic nephropathy using evidence base ethically should be using an ACE inhibitor at least.

Now, in our study, the irbesartan diabetic nephropathy trial, it is not fair to say that since they had two arms that didn't inhibit renin-angiotensin, what about the ethics of that compared to this? Because we were facing an entirely different clinical problem. The clinical problem that we were facing was not only do type 2 patients with diabetic nephropathy perform the same as the type 1's, when their renin-angiotensin system is blocked, but also we're dealing with a much older population of hypertensive patients.

So, the question was also not just benefit, but risk. That is, in this patient population, when you use a renin-angiotensin system antagonist, is there enough bilateral renal artery stenosis to cause serious adverse events with acute renal failure, and do they have enough hyporeninemic, hypoaldosteronism to cause much more severe hyperkalemia during the course of the study than the type 1