Then we have post intervention deaths, and then we have documented arrythmia, and then dying either due to bradyarrythmia or tachyrhythmia. Then we have a bunch of other categories for cardiovascular, but those are the ones that would be related to --

DR. Di MARCO: So someone found asleep dead in bed, how were they classified?

DR. DAGENAIS: Well, as unexpected cardiovascular death.

DR. Di MARCO: Well, in your table is that an MI?

DR. DAGENAIS: It was unexpected. I mean it was classified as unexpected cardiovascular death.

DR. Di MARCO: Well, in the slide that was shown it says cardiovascular. It says MI/heart failure, documented arrythmia and other cardiovascular.

DR. DAGENAIS: It was among the cardiovascular deaths.

DR. YUSUF: It would be in the other. That is the point.

DR. Di MARCO: I thought you said all of

those were post procedure, and most of those --

DR. DAGENAIS: All those were post procedure.

DR. YUSUF: Sorry. Tell me what it is. It was an MI? Okay. It was an MI.

DR. Di MARCO: So a lot of the MIs were really sudden deaths.

DR. YUSUF: Yes, and for what it's worth, John, there is a significant reduction in sudden deaths, which patterns the reduction in cardiac arrest.

ACTING CHAIRMAN CALIFF: John, I can't resist as the Chair asking you this. Can you really tell a sudden death from an MI death in someone that's having --

DR. Di MARCO: I think that's a terrible misclassification. You know, I mean you can call it an MI, but it's -- I can't take the same statement that this reduces what I think is a myocardial infarction. It may reduce a whole mess of cardiovascular events, but sudden at night most of the time is an arrhythmia that probably may be

ischemically mediated, but may not.

ACTING CHAIRMAN CALIFF: Do you have any further questions?

DR. Di MARCO: No.

ACTING CHAIRMAN CALIFF: Ileana.

DR. PINA: Salim, thank you for a very nice presentation. I want to go back to the heart failure issue, and I know it's been brought up now several times, but I think in your initial definition what you've excluded were patients who had demonstrated congestion as opposed to the broad spectrum of heart failure, and you did SOLVD, and you know how we found some of the prevention patients was by going through the FO lab and trying to find myocardial infarctions so we could pick up the low EFs.

I am quite surprised at seeing this many patients with reasonable rejection fractions of 59. Were those rejection fractions taken at any time or was it after an event or --

DR. YUSUF: Those were taken --

DR. PINA: -- anyone in the chart that had

a --

DR. YUSUF: Those were taken at any time before randomization, and they shouldn't have been after that was done a further event and no further EFs that were below that.

DR. PINA: And in the concomitant medications, there seems to have been an increase in the use of several agents. Diuretics went up, and it looked like they went up in placebo more than in the ramipril group. Was that significant and were those the patients that developed the heart failure?

DR. YUSUF: I know it is significant, but I think it includes the people that developed the heart failure, and it also includes some hypertensives. It's both.

DR. PINA: So some of those diuretics may have been hydroflorothiazide?

DR. YUSUF: Yes.

DR. PINA: There was also a very significant increase in HMG co-reductase use, almost half of the patients. Was there a region, a geographical region difference in that where people

encouraged to do secondary risk modification factors during the trial?

DR. YUSUF: At the very beginning of the trial we encouraged people to use the best possible therapies in their opinion, and as you can see, it was pretty good given we started in '93. That's when we started.

The increase in HMG co -- in lipid lowering therapies was worldwide. We saw that increase in every region. I don't remember the absolute numbers by region, Ileana, but I remember at one of our meetings discussing a worldwide increase and showing it by region.

DR. PINA: I have no more questions.

ACTING CHAIRMAN CALIFF: Dr. Graboys.

DR. GRABOYS: I have no questions at this time.

ACTING CHAIRMAN CALIFF: We're moving along nicely here.

DR. MOLITCH: I don't know whether you would like to bring up the issues of the development of diabetes in this group in people who did not have

diabetes.

ACTING CHAIRMAN CALIFF: I think it would be better to hold on that until we have the diabetes presentation.

DR. YUSUF: If you want, I could deal with that because that's not going to be dealt with by Hertzel, if you want.

ACTING CHAIRMAN CALIFF: I'd still rather handle diabetes all at one and you can come to the microphone when needed during that section.

DR. YUSUF: Okay. Happy to do that then.

DR. MOLITCH: I'll pass then.

DR. BAKRIS: I just have a quick question. Looking through all of the data here, this is more of a curiosity, but did you look at heart rate differences between the groups and look at the impact of heart rate? Was there even a difference?

I didn't see that data, and there are certainly some small studies that suggest ACE inhibitors do affect that, but I'm just curious.

DR. YUSUF: No. As you know, heart rate was balanced at entry, which I showed you, and I know

in the secure study we looked at heart rate and there was no impact of treatment. I don't know if we looked at it in the whole population, but in the 700 we did.

ACTING CHAIRMAN CALIFF: Okay. I have a couple of questions, and actually I'm hoping to engender a little interaction here with Bob and Ray on these issues because I think everything at least that I thought was important has been brought up, and I think it would be useful to have a little bit of FDA questioning on a couple of these.

The first is the race issue, and I think it seems like we're in a bit of a dilemma here because, on the one hand, we can say there aren't enough black people in the trial or any of the trials to say anything meaningful. On the other hand, it's 14 percent of the U.S. population and even more than 14 percent of the population at risk for the problem that we're discussing.

And so it brings up a fundamental question of what is the FDA position on studies that come in without an adequate representation of minorities, and how is the FDA looking at this.

DR. LIPICKY: Okay. I don't have a good answer for you. In general, I guess, I would be entirely in tune with the notion that in this study, it doesn't appear as though there is a signal that is worth worrying about, which is the usual kind of thing that happens. and we kind of take the point of view that if things are consistent across most subgroups and you don't have anything to worry about in one subgroup that doesn't look consistent, then you shouldn't worry. So that's my answer, number one.

And I guess my answer, number two, is that the question of blacks and their responsiveness to ACE inhibitors irrespective of what it is that you look at is really pretty muddy, and I suppose the nicest or the one area where people would be most in agreement is that blacks don't respond as well in terms of decreasing blood pressure, and there, indeed, those are subgroup analysis that if you look at any one study or any one development program, I think you should hardly believe that conclusion from the one development program where it seem to be there in more than one.

And to give you an example of how FDA thinks, in spite of one development program which clearly show in that development program that there was no blood pressure difference in the blacks, that drug is labeled it doesn't work as well in blacks.

So I don't think we have the answer to these questions or know how to address them or actually be able to do a good job of doing that, and I think it's a topic that might be worthy of more general discussion when, indeed, there is a larger group of data to look at because I don't know how you tell when there's a signal you should pay attention to.

ACTING CHAIRMAN CALIFF: Well, this will certainly be a topic of discussion during the panel portion this afternoon.

I wanted to give Salim a chance to make a statement in relation to the trial after hearing the FDA position.

Bob, I don't know if you have anything further.

DR. TEMPLE: Well, there isn't any doubt

that the description of the study results will point out that there is a dearth of black patients in it. It's worth thinking about history. There aren't a lot of blacks in the 4F study. There weren't any blacks in the Scandinavian timilof (phonetic) study.

To the extent that a large trial becomes difficult to repeat is carried out in parts of the world that don't have an appropriate distribution, a distribution relevant to the United States, we are to a degree stuck.

We have one experience that we feel funny about. When the first Canadian trials, mostly Canadian, partly Texas, supported the use of aspirin in patients with TIA, there were very few women in the trials, and to the extent that there were any women, they didn't seem to be showing any benefit. So for many years the drug was labeled as for use in males.

And I think a lot of people questioned whether that was the right thing to do, whether the absence of data should have led to that conclusion, and you have something of the same question here, and there is obviously no perfect answer.

But one of the things I'd be interested in throwing out is whether people believe that you could mount a trial of this kind in a black population since there are no data. It really brings to a head the question of data versus likelihood and a wide variety of other things.

Can I ask a question, too?

ACTING CHAIRMAN CALIFF: Sure.

DR. TEMPLE: This may not matter a great deal, but were the individual components of the combined endpoint explicitly said to be secondary endpoint or co-primaries or something?

DR. YUSUF: Yes, they were.

DR. TEMPLE: Okay. My presumption -- maybe other people will talk about this -- the labeling is not perfectly clear as to whether the proposed claim is that it treats each component of the combined endpoint or the combined endpoint itself. Which did you have in mind, you and the company?

DR. YUSUF: You're asking me?

DR. TEMPLE: I'm asking anybody who will -- you're at the mic. So yeah.

DR. YUSUF: I must confess lack of high level of intelligence on labeling issues. I think I can tell you how I would interpret the data. I'd interpret the data we have clear evidence in each component, you know, and so I would see when I give a talk I would tell people. I'd show the data exactly like this.

Now, how that affects labeling, Bob, you know better than I do, but clearly we have each component significantly different.

DR. TEMPLE: Okay. Well, we'll need to make sure the labeling conveys what people want it to convey.

Do I understand there was one case of fatal angioedema?

DR. YUSUF: Let me tell you what happened. The first thing was this was a patient that the center did not report his angioedema, just reported it as a sudden death or something like that.

When you had concerns about another product and we were preparing for this, we got a call from the medical reviewer, I think, saying were there

any fatal cases or ventilated cases of angioedema, and we went through all of them.

And Janice then came up with one death where she did not tell me what the allocation was and said, "This is the description," and the description was an individual in a given remote hospital who had a short history of shortness of breath and a 24 hour history of -- right, right -- so that case, shortness of breath of only 24 hours, the clinicians did not report heart failure, and this is the report from the wife, not even from the family, and we said we think there may be one case. So that's the history of that case.

DR. TEMPLE: How far into treatment was that patient?

DR. YUSUF: That's interesting. It was at 30 days, and it happened when we went from the five milligram dose to the ten milligram dose. It did not happen early.

The other thing is, you know, because of these issues I looked median time to angioneurotic edema in our eight, and it was something like 48 days

or 48 or 50 days. It wasn't clustering early, which was what I hoped we would see.

DR. TEMPLE: Two more short questions. One just relating to the comment Dr. Di Marco made. There may be debate about whether a death was caused by an MI, but I believe you would say that the definition of MI that you used for non-fatal MIs was fairly rigorous, and that's what the claim is.

The claim is not for fatal MIs. It's cardiovascular deaths. It's for MIs, presumably non-fatal, over all cardiovascular deaths and stroke.

I guess finally I just want to make the observation that this is the first trial I know where a robot was responsible for the conduct of the study. Now, do you know what I mean?

DR. YUSUF: Yeah, I've never been called --

DR. TEMPLE: C3PO is the managing --

DR. YUSUF: I know.

DR. TEMPLE: I thought that was cute.

DR. YUSUF: It's an honor to be called a robot.

The second thing that you don't know --

DR. TEMPLE: Do you know my reference?

DR. YUSUF: I know the C3PO.

DR. TEMPLE: I don't want to be --

DR. YUSUF: It was deliberate.

DR. TEMPLE: I don't want to be obscure. Right. I figured it was.

DR. YUSUF: The other thing that you don't know is that we tried to get a randomization number, 1-800-dot, dot, R2D2, but they wouldn't give it to us.

(Laughter.)

ACTING CHAIRMAN CALIFF: Dr. Lipicky, you have questions?

DR. LIPICKY: Just a couple of questions. One is do you think the angioedema results rebut the notion that angioedema is more common in blacks?

DR. YUSUF: Oh, our numbers are so small, just like on the efficacy subgroup, I would say --

DR. LIPICKY: Yeah, okay.

DR. YUSUF: -- we have -- they're so small that --

DR. LIPICKY: So it's just really a

testament for the few numbers of blacks --

DR. YUSUF: That's right.

DR. LIPICKY: -- that exist and not to say that blacks are not more sensitive than whites.

DR. YUSUF: I mean, if I did a subgroup on the angioedema and I -- of which we did -- and there was, say, two cases in the placebo and zero in the active, it still is not helpful in telling us -- I know where you're going -- you know, about the blacks having more angioedema. I don't think we can say anything from 144.

DR. LIPICKY: Right, and then the next question is: do you think or is it true that I should believe that none of the patients enrolled in the trial were symptomatic?

DR. YUSUF: It is true that you should believe that their physicians told us they weren't symptomatic.

DR. LIPICKY: Okay, fine.

(Laughter.)

DR. YUSUF: Right.

DR. LIPICKY: Then the last question. The

last question is this sort of large, simple trial, do you think that any of the questions that you've been asked to respond to are a reflection of that or the ability to answer any of the questions that were asked just now are a reflection of that?

DR. YUSUF: I don't think so.

DR. LIPICKY: Nor do I. I just wanted to know what your interpretation was.

DR. YUSUF: Yeah.

DR. LIPICKY: And I suppose this study cost around 200 million?

DR. YUSUF: I wish it did, but it didn't. It cost about less than ten percent of that.

DR. LIPICKY: Okay.

ACTING CHAIRMAN CALIFF: Well, let me ask the remainder of my questions then, which are oriented towards these general issues. The first one, and Ray may want to make a comment on this, too, you used words like "compelling," "convincing," et cetera, to describe your P value from a single trial.

We've had some recent experiences in cardiovascular disease where apparently compelling,

convincing results from smaller studies have been overruled by follow-up studies that tried to replicate the Elite 1 and 2, for example, or Praise 1 and 2.

As a general comment, what is it about this P value or this result? What's your mathematical threshold?

DR. YUSUF: Do you want me to?

ACTING CHAIRMAN CALIFF: This is your chance to address it because we'll certainly need to address it as a panel when you're excluded from the discussion.

DR. YUSUF: First, the Praise examples you give, the main results were no value of significant -- it wasn't significant. So it's really not analogous.

But let's think of Westner (phonetic), you know, because that might -- you know, the first set of Westner neuron (phonetic) studies. It was the first trial. It was on a composite endpoint, which is heart failure. That's true, but there were too many inconsistencies within the trial, you know, that those relationships within the trial were not what you'd expect.

Plus, as a plus the PDE inhibitors we were all concerned about at that stage because we had data with Milrinault (phonetic) that was harmful, and of course, you can spin a story, but this is different.

The thing with the HOPE data are two or three things. Coming into this there was already evidence that MI was prevented based on SOLVD and SAVE. Of course, it didn't meet regulated criteria, and there was still some debate.

We had data from other studies that lives were being saved. We knew its safety profile. So there's a body of evidence on which HOPE is built. So HOPE Is not in isolation.

And then we get the meta analysis that's coming out of the Lancet in two weeks' time. The relative risk reduction and MI reduction is identical to what you get from the previous trials from a meta analysis. So there is external data backing it.

The second thing is internally there is a consistent story, say, between two halves of the study, the Y2ME and the non-Y2ME part. It's like two random halves are over three standard deviations. So

the whole thing is five standard deviations on the primary.

Then when you take other endpoints, which are not part of the primary, like revascularization, it fits in with it. So you get a nice, warm, fuzzy feeling that something good is happening overall.

So I think it's the external supporting data, the overwhelming nature of the zed value, which is five standard -- nearly five, 4.89 to 4.9 in the primary, clear results of some of the secondary. All of that put together, I think, make a compelling case.

ACTING CHAIRMAN CALIFF: So, I mean, all of that is warm and fuzzy, but if fundamentally you have a trial with a P value, it's been said if it's mortality, less than .05 is okay in previous cardiorenal meetings, but now we have some examples of a few that are less than .05 in the first trial and nothing in the second trial.

Is .001 something that we should think about or --

DR. YUSUF: I think you and I may be in the same camp on this issue. I really believe we

shouldn't interpret P values in isolation. We should interpret the totality of the evidence, look at the internal coherence of the data, the external coherence of the data.

Let me give you an example. Let us say that we had a P value of 0.045 in a given trial, and that one total, total mortality, and that was a primary endpoint.

That would not be enough for me. I would try to say, like if it was an anti-platelet agent, I would expect to see all of the effect on cardiovascular.

But suppose we see there is very little effect on cardiovascular, but that P of 0.045 is coming from non-cardiovascular. To me that's not plausible. The second thing I'd like is at external data, like are there supportive trials.

For instance, I would disbelieve a trial of an 0.04 if there are no external trial data, if internally it's not coherent, and there aren't supportive data on related endpoint.

So to me the P value is only one part of

the equation, and I know you think that way, too. At least I think so, and so I think any given P value at some stage we'll make a mistake if you only use the P value. I don't know what others fee.

ACTING CHAIRMAN CALIFF: Right. Ray?

DR. LIPICKY: Let's say that HOPE for the combined primary endpoint had a P value of .035, not less than .001, and all of the things that you say are still true. That is, there's external data, and all of the internal data would have lined up the same way as they do now with one or two exceptions.

Would you consider that to have been compelling?

DR. YUSUF: I wouldn't certainly use the word "compelling," but I would say the HOPE results indicate a significant reduction in mortality which is totally supported by external data, and therefore, i believe the concept that these agents reduce events --

DR. LIPICKY: Except that it is an advocacy for treating asymptomatic people who doctors think are bad.

DR. YUSUF: But that's where, you know, we

make other judgments. It's not just the P value that helps you with your judgment. If you prevented a major event, then it's worth -- that is important enough, then it's worthwhile.

If there are side effects, that may detract from it. If there is a beneficial effect on a lesser -- on something that's not stated on your primary, but is a secondary endpoint, less severe or maybe even more severe but less frequent, a similar effect?

Look at the totality of the data.

DR. LIPICKY: I agree, and it's sort of hard to dissociate oneself from what you saw, but let's say you had only studied $1,500 patients. You know, you had a P value of .035 for your parameter endpoint. I think that I would say, "Very interesting," but not believe it.

DR. YUSUF: If that --

DR. LIPICKY: Even with all of the other things that are true, you know, all of the other external data and everything else.

DR. YUSUF: Well, it all depends on how

much that external data are. If the external data using the same drug or very similar drugs is three zeros on the P value and the same endpoint, I would say I could probably over a drink persuade you to believe it, but to approve it, I don't know.

DR. LIPICKY: Two drinks.

(Laughter.)

ACTING CHAIRMAN CALIFF: Speaking of external data, you know that there are several other trials that are ongoing looking at --

DR. YUSUF: Sure.

ACTING CHAIRMAN CALIFF: And this is a big change in indication when we're talking now about people with normal left ventricular function who are at risk of coronary disease, as I'm sure we'll get into with Dr. Furberg's presentation. How should the committee consider the fact that those other trials have not been stopped?

You used words like "compelling" to describe this one trial, and yet there are obviously safety committees of other trials that are saying maybe it's not quite so compelling.

DR. YUSUF: Well, I think we'd be foolish to guess what data they've seen. You know, I just don't know, and I think that would be really hazardous to try to make the decision based on data none of us have seen. I don't know, and I think we can only make decisions based on what we have, Rob. We can't make even educated guesses based on --

ACTING CHAIRMAN CALIFF: Udho, do you have a comment on this?

DR. THADANI: Yeah. I think you mentioned the consistency of data. I think you're right to a certain point, but it's driven by the MI consistent with cardiovascular death in the HOPE trial because I'm really surprised -- no, and stroke, heart endpoints -- I'm really surprised that unstable angina -- because most of the patients with MI, we are doing unstable angina, non-Q MIs, as you see so hard to differentiate. The hospitalizations are really driven by those more than (unintelligible) infarcts now, and I'm really surprised that in a plaque rupture hypothesis of the ASS-2, according to Victor it's not holding here; there were 10,000 patients and there's

no difference within placebo either in unstable angina or need for hospitalization for unstable angina.

So you're driven by heart endpoints I'm not arguing. I think you showed great data. Revascularization, I think you could argue the threshold is different. Somebody got chest pain. He gets angioplasty. It's more biased than other endpoints.

So why do you think there's a dilemma here?

DR. YUSUF: I think this is an interesting issue. First, it could be that unstable angina is a pretty nonspecific endpoint, especially in the North American context where anybody with any chest pain comes in.

And when we said new ECV pic. changes (phonetic), a little squiggle on the T wave is considered that.

The second thing is there is another good example of this apparent paradox, and that's aspirin. We have no doubt that aspirin prevents MI. We all agree, but if you pulled the same data where you can

get it for unstable angina, we did this because of a trial we were designing. There is absolutely no effect on refractory angina or rehospitalization with angina.

DR. THADANI: So I think you can't say it's very nonspecific because if you look at outcomes in unstable angina, all the trials, including your doing the CURE trial and every basis based on the assumption the prognosis is not as good as people have believed, and I think clinicians can tell obviously are wrong. Sometimes patients don't have coronary disease because they have unstable angina.

But I think it would be nice if the hospitalization for unstable angina went in the right direction. It would be great.

DR. YUSUF: I agree.

DR. THADANI: I'm just very confused with that.

ACTING CHAIRMAN CALIFF: But, you know, we've all agreed to that.

DR. THADANI: But the question is is MI is really determined by your changes on annual visit

because only two ECGs were done, one at baseline --

DR. YUSUF: No, no, no.

DR. THADANI: -- one at two years, and one at endpoint. That's what the protocol says.

DR. YUSUF: Wait a minute, wait a minute, wait a minute. MIs were based on clinical MIs. That's the MIs.

DR. THADANI: But also silent MIs are on it.

DR. YUSUF: No, silent MI is not part of the data. We have data on silent MIs, and --

DR. THADANI: It says in there --

DR. YUSUF: Sorry. We have data on silent MIs, and I can show a slide, and there is a numerical trend identical to the clinical MIs, but it's not part of the primary endpoint.

DR. THADANI: So in the patient who is not hospitalized, he has Q wave if he's countered, right?

DR. YUSUF: Not in this, but that's a separate set of MIs which you haven't seen.

DR. THADANI: So you could have missed several MIs in patients in diabetics who have no

symptoms because they got short of breath and they got --

ACTING CHAIRMAN CALIFF: All right, Udho. He said -- he said he has the silent MIs. Would you like to see the data?

DR. THADANI: I think so because I think the whole --

ACTING CHAIRMAN CALIFF: Okay.

DR. THADANI: The definition is that cardiovascular and then MIs and he says MIs have to be symptomatic, and we know diabetic patients don't have symptoms, and the way you do it here, (unintelligible) of MI doing by the FDA, it says silent MIs is a composite MI endpoint.

So why is there difference here? That means you're dissecting the data here.

DR. YUSUF: I can't control everything the FDA does.

DR. THADANI: No.

DR. YUSUF: But when we have --

DR. THADANI: -- your protocol.

DR. YUSUF: Slide 35, please.

DR. THADANI: I'm looking on page --

DR. YUSUF: Would you like to look at this?

DR. THADANI: Yeah, sure. -- page 1351 in your MI definition. "Silent QAMI is composite of the A, B, C, D criteria," which is new QAs. That I would presume you have to do ECGs often enough to account for it.

DR. YUSUF: But it's not, Udho, in what I showed you.

ACTING CHAIRMAN CALIFF: Right. I think you've been clear. I mean the slide here shows that there's a trend for silent MIs and you add them all together.

DR. YUSUF: Could I just show you? If you add silent MIs, it becomes stronger.

DR. THADANI: Okay.

DR. YUSUF: These are the data on clinical MIs, which is what we've, you know -- which is what is in our main papers. This is silent MIs, and you will see it's the same directional effect.

ACTING CHAIRMAN CALIFF: I might

parenthetically add there's several other large studies now showing very little contribution of silent MI in clinical trial populations, the HERS (phonetic) trial, in particular.

DR. YUSUF: And that's why we did not --

DR. THADANI: And this is by CK, CKMP, or triple MIs now?

DR. YUSUF: Which one? Silent MIs?

DR. THADANI: Any MIs, whether enzymes.

DR. YUSUF: Oh, there is about two pages of criteria.

DR. THADANI: So you have that.

DR. YUSUF: Yeah, we needed two out of three criteria.

DR. THADANI: And sine I had a chance to ask, I would come back to your question now for cancer. I think the cancer rate was a bit higher. I know this didn't come out, but the cancer rate is higher in the active treatment on the placebo number-wise, and yet you say you did not ask the physicians to report cancer. Is this --

DR. YUSUF: Wait a minute. What you're

seeing from the FDA is not a reliable analysis I'm sorry to say.

DR. THADANI: What is reliable then?

DR. YUSUF: Okay. What I --

(Laughter.)

DR. YUSUF: Let's come to this. What the FDA has done --

ACTING CHAIRMAN CALIFF: Salim, I think it's important to go through this carefully because actually it was going to be my last question. The adverse events versus what you collected on the case report form.

DR. YUSUF: That's right. I think Rob hit it on the head. Cancers that the FDA reported is from the AE database. The AE database does not include all cancers because we only asked people to report SAEs if they met certain criteria, and if something was part of the natural history of the disease and occurs in a 60 or 70 year old, it's not counted.

Now, I'll tell you what the total number of cancers were. There were 401 in the placebo group, and there was 383 in the ramipril group, and since,

Paul, you were interested in GI, Paul, there were 72 in the placebo group, and there were 69 in the ramipril group. So that's the total cancers.

ACTING CHAIRMAN CALIFF: And, Salim, again to clarify, the reason you know those are the right number of cancers is that you had a page on the case report form that asked about cancer?

DR. YUSUF: No, we didn't. I'll tell you what happened.

ACTING CHAIRMAN CALIFF: How did you collect the cancer data if it was not on the adverse events?

DR. YUSUF: Yes, we did at the end, but not to start with for a certain reason which I cannot disclose because one part of the trial is going on. Okay?

We decided we'd better get a better handle on the cancers, and when we started to look at it, we realized cancers were being reported haphazardly because we didn't have a cancer form.

So at the last visit we had a specific form where we asked them to fill it out on every

patient. So we capture it because they could go back to the notes and get any cancers, and that's how the numbers I've told you are from.

So the SAE report, to be fair to the FDA, they took it out of that component which doesn't capture everything.

ACTING CHAIRMAN CALIFF: Okay. I just had two more points, and then we can -- if we're going to finish today, we're going to have to move along, I think, and my hope would be we're scheduled for lunch at one. My hope would be that we can get through the renal protection presentation and most of the questions by one, then take a lunch break, come back and do the diabetes, and then move into the panel discussion.

So anyway, just a clear statement from you on this because it's very -- we're going to discuss in this trial, and I think you've been clear about it already.

You don't think that trials that are internationally done should routinely look for interactions according to region of enrollment?

DR. YUSUF: I actually think if there is no prestated hypothesis before you start off with, then you shouldn't look, and if you look, you should generally place more emphasis on the overall analysis because that has been a data derived analysis, and just like any data derived subgroup analysis, it's fraught with all kinds of problems. A data derived regional analysis is fraught with the same methodological problems.

On the other hand, if we have good reason to believe there may be different reasons, and we've stated in the protocol, then we are obliged to do two things. One is to insure we have reasonable power to pick up those interactions, and then to test for heterogeneity at the end of it.

In most trials that I've been involved with and most people do, these are not issues. So I think in such circumstances really one should base the results on the totality of the data and not by any subgroup analysis.

DR. FLEMING: On that issue, Salim, do you think you've consistently followed that guideline in

your reporting of results, i.e., that you have recognized that if it wasn't prestated or if there wasn't a biological rationale to in advance justify that you essentially have given little credence to results?

DR. YUSUF: I know I'm walking into a trap here, Tom.

(Laughter.)

DR. FLEMING: Okay. Then let me tell you what the trap is.

DR. YUSUF: Let me answer your question. On subgroups, there are different things that we are looking at. I'm talking about subgroups, and regarding subgroups the answer is yes. That's the way I have consistently looked at the data on subgroups.

DR. FLEMING: Well, certainly subgroups are one type of analysis that presents substantial risk of being misled because of multiplicity of testing, but it's certainly not the only one, and, yes, the trap was just to pull out one example, new diagnosis of diabetes.

DR. YUSUF: I knew what you were going to

put up.

DR. FLEMING: You know, it's of interest to me that those results are being presented, and in your formal presentation there was nothing stated about subgroup analyses by aspirin, subgroup analyses by country, subgroup analyses by race. So it's just -- it's trying to get a sense of what is, in fact, that --

DR. YUSUF: Can I just explain to you what our position on the -- or my position at least is -- on the development of new diabetes?

I think it is an interesting hypothesis that requires testing, and we've designed a trial to test that.

ACTING CHAIRMAN CALIFF: Okay.

DR. YUSUF: So I hope that's consistent with fair methodological thinking.

ACTING CHAIRMAN CALIFF: We'll come back to this, I'm sure.

I just had two more questions. The factorial design, and again, I'm interested here in whether there's any interaction between you and Bob

and Ray in this regard.

It's commonly believed and stated that when you're doing studies for an indication with the FDA that you can't do a factorial design because it's two experimental therapies being given together, obviously you've done it here. But one is a vitamin which is not regulated by the FDA, and the other is a drug.

Would you say the factorial design is a better way to do things, given the number of potential treatments that we have today? And is there a down side to it that you've seen?

DR. YUSUF: Asking me or --

ACTING CHAIRMAN CALIFF: Yeah.

DR. YUSUF: Who, me?

ACTING CHAIRMAN CALIFF: Why don't you start? I'd just be interested in hearing from Drs. Temple and Lipicky.

DR. YUSUF: Well, I tend to be a big believer in factual design for several reasons. One is doing these trials is really tough and expensive, and if you can evaluate more than one treatment in

that trial effectively, one should do it as long as there is no postulate for a negative interaction or bad side effects or anything or the fact that the mechanisms may overlap. You know, you've got to choose your questions carefully.

So I tend to say -- in my writings I always say -- do a factorial design unless you have good reasons not to do so. That's the way I believe, and I think 75 percent of the trials I've been involved with have been factorial designs.

Now, there are obviously certain issues with factorial designs, but in one way you can think of your second factor as background therapy. For instance, let us assume in this population aspirin was not indicated or capitobril (phonetic) was not indicated, and we have two options. We could let aspirin float in as background therapy. If there is an interaction, you'll still get the interaction. If there's no interaction, you've lost nothing. If there is, you learn about aspirin, and you learn about the interaction.

So I think unless there is a strong a

priori reason not to do a factorial design, the starting point should be let's consider a factorial design.

ACTING CHAIRMAN CALIFF: Rob or Ray, do you have guidance on factorial design?

DR. TEMPLE: Well, we've certainly never given to my best knowledge advice that they should not be carried out. This factorial design is where both components were directed at the same endpoint.

For what it's worth, the approval of aspirin and thrombolysis was -- the use of those two together and the knowledge of how they interact was a very important outcome of one of the ISO studies. So, I mean, there's a time honored tradition.

We've occasionally been asked what about throwing in a completely separate randomization not even for the main endpoints, something completely different, and when we've been asked, we've said that's a really good idea, but companies have been nervous that there might be some odd interaction that would bite them and have been reluctant to do it, but it's not because we've advised against it, although

it's perhaps true that an unwelcomed interaction could be troublesome.

Personally I'd like to see a wide variety of alternative medicines tested in the context of, you know, good studies where the resources to study those interventions would not be available. So I think we think they're good.

ACTING CHAIRMAN CALIFF: Isn't it true that such an interaction could still wreck a study even if it wasn't part of the randomization?

DR. TEMPLE: You can imagine outcomes -- oh, I see. Sure. Look at the discussion we just had of aspirin. That's interaction.

ACTING CHAIRMAN CALIFF: Right. Okay. Ray.

DR. LIPICKY: Not to let the opportunity go, we like factorial trials and try to talk people into studying more than one dose that way frequently, not because marketing thinks it's a good idea, but because it makes sense medically.

ACTING CHAIRMAN CALIFF: Okay. My last question has to do with the monitoring, auditing of

this trial, and you obviously didn't reconcile your adverse events database with the main database because you have different numbers. At least from my experience about half of the cost of a trial is spent on chasing down details and adverse events databases, and I just wanted to get a sense from you and from Bob and Ray about what the advantages might have been of spending more time on the details of the adverse events.

There appears to be a consultation going on here.

DR. LIPICKY: I can give you my answer to that, and that would be none.

DR. TEMPLE: There have been a lot of discussions about what necessary monitoring is, as Rob is undoubtedly familiar with. The good clinical practice document that came out of ICH and is now our guidance also says that monitoring, the amount of monitoring and, indeed, the presence of any on site monitoring at all is something you have to figure out depending on the circumstances of the trial.

So in the present case with the mortality

endpoint being at least part of it and some of the other endpoints fairly hard, you might conclude that not a great deal of on site monitoring is necessary because you can check centrally whether the rules are being followed, and we take an open minded attitude toward that.

It certainly is true that the cost of trials go up enormously if you do what would be called conventional drug company on site monitoring. So I think we're open minded about it.

If all of the elements are subjective and you're worried about blind breaking, things like that, there might be reasons to be on site and find out more about it, but you can make a case that it's less necessary when the endpoints are hard, easily verifiable, and which at least some of these are.

ACTING CHAIRMAN CALIFF: So what was done in this trial? What was the auditing procedure?

DR. YUSUF: It was modest and sensible, and what we did was randomization was central and we controlled it. So we knew that was integral. All primary and prestated secondary endpoints, they had to

fax in supporting data. So we knew it actually happened.

So those were the two things that were 100 percent audited.

The second thing is a random ten percent of the patients were reviewed. The charts were reviewed by the company's staff, and at the end of the study every center was visited once at least by the monitors.

So compared to some trials it was much more minimal, and I think there were three factors that were driving this minimalistic approach. One is it was a low cost trial. Second is there were at least some enlightened people in the company who backed us, which was very important. Otherwise we could not have done this trial.

And the third one is I believed methodologically all along monitoring was a waste of money at least to the extreme that it went. But what we also did was what Bob said. We monitored for cause.

When we looked at data and we found sloppy

data or lots of missing data or suddenly in a given region or center the event rates are markedly different, we then got people to go out and check those.

So we did central monitoring very carefully, and then when we had a suspicion something was wrong, we sent people out, and in fact, in all those cases all we found was sloppiness, not fraud or anything like that.

ACTING CHAIRMAN CALIFF: So to be clear, it's frequently said that 100 percent monitoring has to be done because the FDA requires it, but in this case, there's ten percent, and it's okay with the FDA?

DR. LIPICKY: Yes.

DR. TEMPLE: Well, a lot of what Salim described wouldn't even be called monitoring. It's auditing, which is not the same thing at all. The issue is on site monitoring.

We had a workshop under the auspices of the Institute of Medicine on this, and you know, as everybody knows, typical drug trials, you visit every four weeks and go over and do stuff, and we had a lot

of the discussions of this while writing the international guideline, and there was an initial inclination to say that that's what monitoring means. You go every four weeks out to the site and visit every site.

What I said and what Jay Siegel, who was there with us, is that not trial that's ever shown anything really important has ever been monitored like that, so that it didn't really seem like it could be an absolute necessity.

Most NIH trials aren't monitored that way. Most cancer cooperative group trials, you know, the typical study, none of those trials get that kind of monitoring. So the guidance is quite flexible, and for a large outcome trial it's virtually inconceivable that you can go to every site every four weeks. So it's written quite flexibly.

I think the idea is that it should be part of the plan. There should be a reason for choosing the monitoring and follow-up and auditing arrangements that you have and that we're prepared to look at anything reasonable. It's a good idea to think about

it ahead of time, however.

ACTING CHAIRMAN CALIFF: Great. Okay. Well, Tom, last comment.

DR. FLEMING: Very brief. I just wanted to concur with Salim's advocacy for factorial designs, particularly in those settings as you point out where it's not anticipated that there will be negative synergy and the interactions that would, in particular, cause you to have to reduce the dose in the cell in which both interventions are delivered.

Point of information. You had referred to an upcoming Lancet publication that was a meta analysis. What are the other -- in fact, is this a meta analysis in a setting that is specific to HOPE?

DR. YUSUF: No, no, no. It's really the pre-HOPE trials. It just took one and a half years to get reviewed and published.

DR. FLEMING: And which of the studies are included in that?

DR. YUSUF: It is the two SOLVD trials, SAVE, TRACE, and AIRE, and it's about what level, 12,000 or so patients, and it's got about two, 3,000

deaths, another four, 5,000 non-fatal events.

I'd be happy to send you a copy.

DR. FLEMING: Could this be a source of the types of studies to look at, for example, the race issue in larger numbers?

DR. YUSUF: It's not in the paper. We tried to do it, Tom, but what we found was there was so few people who were non-white in these trials. That would have been the best place to look at it, and you're absolutely right in your instincts.

DR. THADANI: Salim, if I may ask you the last question here, given the constant different practices of medicine, especially cardiovascular coronary disease in the States, Europe, Canada -- if you work in three places it's different -- and given some concern regarding that most of the population is coming from Canada, there might be differences in race and also numbers are small in U.S. and elsewhere.

Why don't you when you design the trial -- I realize there are difficulties -- limit the number of patients who can go from each country? So you reach 1,200 patients, 1,400. I know trials are

difficult, but then we won't be arguing with what you're doing today because then we'd be more sure that when you analyze the data for the variability, either its race or region will be more consistent.

Why don't we do that? I know in small trials, say, if you're doing a stable angina exercise, we won't let a center -- it reaches 12 patients and they cut off. Otherwise in the end his results are biased just from that sample.

I'd like your comment on that.

DR. YUSUF: I think it is impractical because you can never predict exactly what the recruitment is going to be in different parts of the world, and then what will happen is your slowest recruiting region will delay your entire program.

The other part is the cost of doing the trial varies by regions, and in the end you have only so much money, and the main thing you're interested in is getting a clear overall result. So you want that money to go really far and Ray made the point this is for the size of the study and the duration of the study not a generously funded study.

The third point is let me take a methodological issue here with you on the variations in treatment. Let us say --

ACTING CHAIRMAN CALIFF: Be brief.

DR. YUSUF: Very brief.

Let us -- the thing that you raised earlier on, Udho, was perhaps revascularization rates differ in different parts of the world. Well, the best way then to do is to take the patients who had revascularization and then look at the treatment effect in them, and in those who didn't have revascularization and look at the treatment effect in them, and then if you see an interaction, your hypothesis would be supported, but if you didn't see an interaction by previous CABG surgery or PTCA, then you'd say, "Well, that's not supported."

And, in fact, in HOPE we've done that analysis. I haven't brought it here, but there's about 35 percent of the people have previous revascularization. Get them into the trial, and the relative risk reductions are identical.

So when you say, yes, practice patterns

may vary by region, then you take each of those practice patterns and do the subgroup analysis by those practice patterns to understand it, and we've done it, and there is no heterogeneity.

ACTING CHAIRMAN CALIFF: Okay. Let's move along now to the renal protective issue.

DR. YUSUF: I'm also standing as the moderator. So if you don't mind, I'll introduce the next speaker.

ACTING CHAIRMAN CALIFF: That will be fine.

DR. YUSUF: The next speaker is Dr. Hertzel Gerstein -- no, it's Dr. Barry Brenner from Harvard, who will give us a perspective on renal disease that will assist us in interpreting the next speaker's presentations.

DR. BRENNER: Thank you, Dr. Yusuf.

Ladies and gentlemen, I feel a little bit as you do when you attend an elegant banquet. There's usually a separation at the beginning of the meal and the main course by some sorbet, and I think I've been asked to provide the sorbet this morning or this

afternoon after this lengthy discussion and simply to introduce the subject of chronic renal disease.

Now, as many of you know, chronic renal disease is a category of many etiologies, but they all have in common one feature, and that is that renal disease of a chronic nature is inexorably progressive. Nobody gets better on their own with chronic renal disease. They only get worse.

There is a progressive march from mild to advanced renal disease that is true whether the renal disease is congenital, hereditary, metabolic as in diabetes, inflammatory as in arthritis, or due to any other etiology.

My first slide shows you the multiplicity of causes of end stage renal disease. At one point in time, 1992, the United States renal data registry provided this information, and what you see is that in 1992 there were roughly three populations making up the whole of end stage renal disease. This is renal disease that has advanced to the point where for life to continue the patient requires either renal replacement therapy in the form of hemodialysis or

rental transplant patient.

In these patients, a third have their renal failure due to diabetes, roughly a third due to hypertension, and a roughly a third due to all other causes.

In 1972, when the United States Congress took the bold step of insuring totally the cost of care for patients with end stage renal disease, roughly 20,000 Americans qualified in the first year, and the cost in that first year was $270 million.

Now, in 1992, 20-some years later, 300,000 Americans are being maintained on chronic renal replacement therapy, and the cost was $15 billion.

The latest figures we have are for 1998, and now we learn that there are nearly 500,000 Americans on renal replacement therapy, and the cost at least in 1999 from the most recent estimate is crossing the $20 billion mark.

So the problem with chronic renal disease, even though we have a life support system called dialysis, is not being met because the growth of this population and the cost of incurring this kind of care

is so great that there has to be an emphasis on providing some regard to the chronic renal disease paradigm.

Now, another element that's shown here is that in 1992 the number of diabetics who made up the whole of end stage renal disease was roughly a third of the total. In 1972, it was less than ten percent, and in 1999, again where we have the latest figures, 44 percent of the total are diabetics, and of course, Type 2 adult onset diabetics are the dominant population here, more than 90 percent being Type 2.

Now, in the year 2015 what should this pie chart look like? By everyone's best guess, diabetes will represent 80 or 90 percent of the total, and that's because our population is aging, and our population is growing in size. I'm talking about this. And more and more people are living to the development of Type 2 diabetes, and equally importantly, are living 20 years with their disease.

So that the complications of advanced microvascular disease, including end stage renal disease, are beginning to accumulate.

The time line for progressive nephropathy in diabetes is very well described. It is well recognized from many natural history studies that it takes approximately 25 to 30 years for the kidney to fail. So a fatal myocardial infarction three years after the onset of Type 2 diabetes will occur in an individual who has relatively normal renal function.

On the other hand, postponing fatal stroke or fatal MI will allow roughly 40 percent of the diabetic population to travel this road toward end stage rental therapy.

In the initial years, there is already abnormalities of the kidney if one looks histologically, but by usual function tests very little abnormality is detected. There's not protein in the urine, not even scanned quantities of protein, the so-called micro albuminuria, and function studies are, by and large, normal.

In a five to 15 year interval there is now evidence that blood vessels everywhere in the body are beginning to leak plasma proteins. The leak is relatively small at first, but can be measured, and

any number of compartments have been measured.

For example, the leak of albumin occurs into the retinal field and can be detected with fluorescein labeled albumin.

The leak of albumin also occurs across capillaries into interstitial fluid around muscle capillaries, for example, but it's difficult to sample.

The largest volume of interstitial fluid is urine. Urine is the interstitial fluid that surrounds the glomerular capillary bed. The glomerular bed, like all other beds in the diabetic, are under higher pressures from the very start of the hyperglycemic state, in part, because of the overload of volume and the increase in flow through the microvascular bed in diabetes, Type 1 and Type 2.

The leak of albumin, this transcapillary escape of albumin, occurs into the fluid surrounding the glomerular capillaries as it does across all capillaries, but recall that the fluid that crosses the glomerular capillary eventuates as final urine and is an easy and readily available fluid source in which

to measure this escape phenomenon.

This process is already evident early in the course of diabetes. After five or so years, many patients with diabetes will develop micro albuminuria, and as it turns out, those individuals who develop micro albuminuria are the ones who will, if left unchecked and live long enough, develop end stage renal failure.

Micro albuminuria in many, many studies has been shown to predict all of the bad events that fall on patients with diabetes with respect to the kidney, but also with respect to other risks.

So the more protein in the urine, the shorter the life span. In diabetics, the more protein in the urine, the greater the cardiovascular event rates. That means myocardial event rate, coronary artery disease event rate, peripheral vascular disease event rates, retinopathy, neuropathy, the entire gamut of microvascular complications increases in risk as the expression of the proteinuria rises.

The proteinuria is not just a renal problem. It is a hallmark of a larger syndrome of

microvascular leakage which is taking place everywhere, and these other organs that I just enunciated are affected by that abnormality.

This diagram indicates something about how clinical trials are done. When it is recognized that in order to convince people about the protective effect of a particular drug, you will expect to have studies that are done near the end stage of renal failure because within a five or ten year interval and as short as a three year interval, the number of events like loss of renal function totally or fatal MIs, all cause mortality will accumulate in this later interval.

Very different would be a trial where the initial enrollment is in HOPE, and you'll hear the data include data of patients with diabetes who have not had any detectable abnormality of renal function. They have not yet proteinuria, micro albuminuria, and they include some patients who do have micro albuminuria.

To wait until those patients develop end stage renal failure would require a study of some 20

years, not a popular study for most of the fellows who come to my laboratory to want to undertake nor the investigators who want to undertake nor the funding sources want to take on.

Very different are the endpoints that accumulate along this line for cardiovascular events. Myocardial infarction is occurring everywhere along this window, and of course, the patients enrolled in HOPE are showing the myocardial infarctions and other all causes of primary outcome event that were documented by Dr. Yusuf. But renal failure won't occur for another 20 years.

The challenge to people working on the kidney has been to try and identify which other factors might serve as risk for mortality and for cardiovascular complications. In diabetics, in particular, glycemic control has been proven, and those studies of glycemic control have been done primarily at the very early stages of diabetes.

And going back again to that line diagram, the DCCT trial was done in here. Some of the patients were normal albuminuric, and some were micro

albuminuric, and the endpoints were to cross the next milestone. For the normal albuminuric did they become micro albuminuric? For the micro albuminuric, did they develop overt nephropathy, which is simply defined as reaching a level of protein in the urine of dip stick positive sensitivity, a half a gram a day or more?

So the milestones here are short in DCCT, short of an endpoint of renal failure. Yet the glycemic control story is now universally accepted. The better the control, the less likelihood the normal albuminuric will develop micro or the micro albuminuric will develop overt nephropathy.

So this time line governs a great deal of what we think about when we try and identify these early events that might predict delayed renal failure.

In addition to glycemic control in the diabetic, we include proteinuria, and we include hypertension as the hallmark risk factor. Control of their of these delays progression to the next milestone, but no study has taken the control of blood pressure, the control of blood glucose or the control

or proteinuria at the earliest stages and followed the patient all the way through because, as I said, the demand of time of 20 years.

You heard from Dr. Yusuf today, and you know from your own experience that the initial studies of cardio protection with ACE inhibitors congregated in patients who had the most advanced heart disease, and then only over time with demonstration of efficacy in the most advanced populations did trials begin working at earlier and earlier stages in the evolution of heart disease, now to the point not only of not asymptomatic left ventricular dysfunction, but now with no left ventricular dysfunction as you heard in HOPE.

The same pattern is emerging in the nephropathy field. The initial renal protective studies in insulin dependent diabetes were done at the late stage where you could affect mortality, expect mortality and renal death to occur, and in both studies, the insulin dependent diabetic, efficacy of ACE inhibition was established, was demonstrated. And the Lewis trial received an FDA approval.

Currently three trials are in progress, not with ACE inhibitors, but with angiotensin receptor antagonists, and they are in the population that had never been studied in detail in this late phase, the non-insulin dependent population, and no data are expected from these trials for another year or two.

We see small trials accumulating in the incipient phase and three published trials completed in the preclinical stage. In the aggregate, eight trials in non-insulin dependent diabetes with micro albuminuria, and five in insulin dependent diabetics where the enrollment criteria in this micro albuminuria and the event is protection of protein in the urine at an overt level, that is, more than a half a gram a day.

These trials have been published, have not received FDA attention, to my knowledge, and now we have data that you will hear again in non-insulin dependent diabetes from the HOPE study with more patients in this HOPE database than in the aggregate of this A trial population already studied.

And HOPE also addresses the earliest phase

of all, patients who are normal albuminuric at enrollment and where the endpoint is the detection of micro albuminuria. Does ramipril protect or not?

And, again, the number of patients in HOPE in this NIDDM trial -- it's primarily NIDDM. There are only a few IDDMs in the database -- exceed those already studied.

So I think what we have from HOPE, and I was not an investigator included in the study, is an opportunity to have more aggregate information looking at trends of protection that are possible with ACE inhibition, and to see whether the accumulation of experience warrants recommendations for general acceptance by the physicians in our communities.

Thank you very much.

ACTING CHAIRMAN CALIFF: Are there questions for Dr. Brenner?

DR. THADANI: In the progression of disease, is there a difference between insulin dependent and non-insulin? You know, you showed the chart from zero to five, five to ten, or is that data really driven from insulin dependent diabetics?

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ACTING CHAIRMAN CALIFF: Are there questions for Dr. Brenner?

DR. THADANI: In the progression of disease, is there a difference between insulin dependent and non-insulin? You know, you showed the chart from zero to five, five to ten, or is that data really driven from insulin dependent diabetics?

DR. BRENNER: The natural history of Type 1 and Type 2 diabetes by most experts today is considered the same. There was a time when it was thought that insulin dependent diabetics had a greater risk of nephropathy than non-insulin dependent diabetics, but that has been shown clearly not to be the case when young, non-insulin dependent diabetics are now included and have the likelihood of living 20 years with their disease.

Before, it was a 50 year old with NIDDM who died three, five, seven years later with an MI, didn't have renal disease, and was, therefore, leading people to think no nephropathy. But now we know that if you study, for example, the American indigenous population around the Hela Reservation or the Canadian Inuit population or the aboriginals in Australia, and in some other populations of young, relatively young onset, maturity onset diabetes with that 20 years of life the time line for the development of nephropathy superimposes exactly on Type 2 or Type 1.

DR. THADANI: What about the question of it won't come in this HOPE trial, but glycemic

controls, especially with the hemoglobin glycemic --

DR. BRENNER: I think there --

DR. THADANI: Were there a difference in the progression if you control it better or you don't?

DR. BRENNER: There are fewer NIDDM glycemia trials, and nothing as rigorous as DCCT, which was done in IDDM. IDDM carried out at the earliest stages of nephropathy clearly influenced recommendations about renal protection, but it's largely been extrapolation from the IDDM study to the NIDDM population. There's no clear, rigorous trial, to my knowledge.

ACTING CHAIRMAN CALIFF: Other questions for Dr. Brenner? Yes, Dr. Fleming.

DR. FLEMING: This issue of valid surrogates for diabetic nephropathy, albumen excretion rates and albumen creatinine rations, and you did show us this plot that looked at the relationship of proteinuria and mortality showing quite a thinning out in survival differences by five years. The question: how much is this the causal agent? How much is this a marker for other differences that are, in fact,

causal?

Was there any expiration in those data to try to understand --

DR. BRENNER: Not in that study.

DR. FLEMING: -- imbalances?

DR. BRENNER: Not in that study. That study in insulin dependent diabetics is one of about eight that shows a similar pattern, that the more the proteinuria, the greater the mortality.

DR. FLEMING: The correlation is undoubtedly real. What's the strength of evidence for this being a causal factor?

DR. BRENNER: I don't think the proteinuria is a cause. The proteinuria tells you that the patient has a transcapillary leak. It's easy to find when you measure urine. It's hard to find when you look at that leak in the organ because you're not accessing the interstitial.

So the question is: what's wrong with the blood vessel wall?

It turns out in diabetes to be, from my viewpoint, rather simple. The pressures in all

capillaries are higher than normal within three days of the onset of diabetes. As soon as you have hyperglycemia, you retain salt and water because in order to reabsorb glucose, the renal tubule does the reabsorption of the glucose in co-transport with sodium. So there is extracellular volume expansion.

And within a few days, you can measure a 30 percent increase in cardiac output. I think Dr. Borer did that study. You can find an increase in retinal flow, muscle forearm flows, and renal blood flow. All of these organs are over profused, and when the pressures are measured in peripheral capillaries, they double.

And when we measured them for the first time in the glomerular capillaries in diabetes, they went up like 35, 40 percent.

The singular benefit of ACE inhibition was to restore those glomerular pressures to normal, more so than any other class of drugs at the time that the studies were done. And that motivated the Lewis trial and what have you.

ACTING CHAIRMAN CALIFF: You seem to be

making the case that albumen in the urine is a valid surrogate for the ultimate permanent loss of renal function. I think that's what Dr. Fleming was getting at, and I'm just wondering whether there's adequate evidence by the criteria that have been developed for validating surrogates that we can really accept.

DR. FLEMING: And just because that's leading into where I'm headed with the next question, which is if you have a patient with pre-clinical nephropathy or incipient, early incipient nephropathy, which as you've noted is patients in the HOPE trial, how do we know what level of change you need to see in proteinuria for as long a period of time as we're following for you to have even a moderately reliable sense that that, in fact, is going to influence long term occurrence of --

DR. BRENNER: Long term recurrence?

DR. FLEMING: Well, the long term clinical course of renal failure.

DR. BRENNER: The renal outlook, the prognosis for the kidney.

DR. FLEMING: Right.

DR. BRENNER: What we have is clear evidence in patients who have macro proteinuria and where the macro proteinuria has been reduced. Studies in diabetic and in non-diabetic alike, the more you reduce the level of albumen in the first year of ACE inhibitor therapy, the greater is the slowing of the rate of loss of GFR in the subsequent three year period.

In other words, the more the proteinuria are based with the therapy, the more the trend down in renal function is stopped.

DR. FLEMING: But that's still not evidence to validate a surrogate, and secondly, that's a more proximal event to the actual occurrence of renal failure than where we are here, and it's much more of a reach.

DR. BRENNER: But it's a look at a later stage, and --

DR. FLEMING: But still it --

DR. BRENNER: But the answer to your question is we don't have the data.

ACTING CHAIRMAN CALIFF: Dr. Lipicky.

DR. LIPICKY: In the slide that you showed with the time line and the Lewis paper --

DR. BRENNER: Yes.

DR. LIPICKY: -- of those studies that are in the late stages of development, the Lewis study certainly did measure clinical endpoints, such as the need for dialysis,a nd things on that order --

DR. BRENNER: Yes.

DR. LIPICKY: -- which were affected by treatment significantly. How many -- where does the REAM (phonetic) study --

DR. BRENNER: The RAIN (phonetic) trial is a study in non-diabetic patients.

DR. LIPICKY: I see. Okay. So --

DR. BRENNER: And it has the same endpoints as Lewis.

DR. LIPICKY: So much of these other studies that are in this --

DR. BRENNER: No, everything here is for diabetes. I didn't --

DR. LIPICKY: Right.

DR. BRENNER: -- address the non-diabetic

study.

DR. LIPICKY: So which of these studies, in fact, have clinically relevant endpoints in addition to Lewis?

DR. BRENNER: Only Lewis.

DR. LIPICKY: Only Lewis.

DR. BRENNER: In what has been reported to date.

DR. LIPICKY: Right. So that --

DR. BRENNER: In all of these other trials that you see where they are used with angiotensin suscepta (phonetic) blockers, I believe -- I know for sure RENALE (phonetic) because I chair it -- IDNT, which is the abisarten (phonetic) diabetic nephropathy trial, has the same hard endpoints that was in Lewis. In fact, Lewis is the director of that trial.

And I believe ABCD-V2 has the same hard endpoints.

DR. LIPICKY: So at the moment with respect to the story that you're evolving, there is one trial in diabetics that actually --

DR. BRENNER: One trial.

DR. LIPICKY: -- would lend support to the notion that seems to be the notion that most nephrologists have.

DR. BRENNER: I don't know what you mean by that. Let me -- let me, I think, say what you were thinking. Lewis is the only study in diabetes, published study in diabetes, that has the hard endpoints of renal death and all cause morality, in addition to having doubling of serum creatinine or changes in proteinuria or less -- let's say less rigorous measures of renal function.

DR. LIPICKY: Right.

DR. BRENNER: Okay, and the only other trial that has that in all of nephrology is the RAIN trial with Altace in non-diabetic patients.

DR. LIPICKY: And those endpoints were --

DR. BRENNER: The same.

DR. LIPICKY: -- thought of afterwards, right? They weren't part of the prospective trial.

DR. BRENNER: I think they are part of the prospective trial.

DR. LIPICKY: Were they?

DR. BRENNER: To my knowledge.

DR. LIPICKY: But they weren't part of the original publication, were they?

DR. BRENNER: They were.

DR. LIPICKY: They were. Okay.

DR. BRENNER: It was composite endpoint of the things I --

DR. LIPICKY: Okay, fine. So then there are two trials in all of kidney disease --

DR. BRENNER: Yes.

DR. LIPICKY: -- that might support the notion that you're forwarding.

DR. BRENNER: Yes.

DR. LIPICKY: Okay.

DR. BRENNER: There are also some other experiences that are worth mentioning. There are some repeat biopsy trials which show that the reduction in proteinuria is matched by some lessening of the histologic changes. In some cases, in the kidney transplant, for example, where the biopsy is often carried out quite frequently to monitor so-called rejection episodes, there is clear regression of

lesion with these kinds of therapies.

So that adds to the sense of confidence we have that early studies on that time line are pertinent to predicting late events, late being loss of renal function or all cause mortality.

DR. THADANI: If I may ask on two minor points.

DR. BRENNER: Yes.

DR. THADANI: When you're assessing proteinuria or micro albuminuria, protein intake has got a lot of influence. If you eat more protein, do you leave more protein?

DR. BRENNER: Not in a normal subject.

DR. THADANI: In the patients with diuretics?

DR. BRENNER: Insofar as their eating more protein will raise their renal blood flow.

DR. THADANI: So it will increase the micro proteinuria, right?

DR. BRENNER: It may provoke a slight --

DR. THADANI: So if you don't control the dietary intake, how confident could you be that on a

given day or one year later your variation in the total 24 hour urinary --

DR. BRENNER: Well, to the extent that you have a randomization --

DR. THADANI: I realize, but with the sample size you get away, but if you don't have the samples, that would be one issue possible. You have a heavy meal with a lot of -- you know.

DR. BRENNER: These protein measurements are typically made on first morning specimens.

DR. THADANI: I suppose --

DR. BRENNER: And whatever meal effect you're contemplating is largely dissipated.

DR. THADANI: Even if you have a heavy meal the night before?

DR. BRENNER: Even if you had dinner the way I did last night.

DR. THADANI: Okay.

(Laughter.)

ACTING CHAIRMAN CALIFF: All right, Udho. Last question. We have a hungry audience here.

DR. THADANI: The last question is in the

Lancet article they define three different -- one is the micro endoneuria. The other one is the ratio of the creatinine --

DR. BRENNER: Which article?

DR. THADANI: I think the renal --

DR. BRENNER: The HOPE study?

DR. THADANI: Yeah.

DR. BRENNER: I don't want to get into that.

DR. THADANI: No, no.

DR. BRENNER: Somebody else will.

DR. THADANI: I just want to say what's your idea of measuring just the albumen. Was it the ratio of albumen to creatinine? Which is more relevant in your judgment to assess the significance of progression?

DR. BRENNER: I would say a change in any of them as long as you try and stay with the same --

DR. THADANI: So you define it for?

DR. BRENNER: Yes.

ACTING CHAIRMAN CALIFF: Okay. Thank you. And with what we'll take a 45 minute break

for lunch and try to start at about ten till two.

(Whereupon, at 1:08 p.m., the meeting was recessed for lunch, to reconvene at 1:50 p.m., the same day.)

A-F-T-E-R-N-O-O-N S-E-S-S-I-O-N

(2:00 p.m.)

ACTING CHAIRMAN CALIFF: If everyone could take their seat, we'd like to get started.

I think we had a good morning covering the general issues in the trial and the cardiovascular outcomes, and we've now had the introduction to the renal outcomes. It's time now to turn to the diabetes sub-study.

Our goal will be to try to get through the sponsor portion in the next hour, and then that will leave us two hours for deliberations.

DR. YUSUF: Sure. Our next speaker is Dr. Hertzel Gerstein, who was the principal investigator of the diabetes component of the HOPE study. He will be discussing the results on the main endpoints amongst diabetics, and also on the nephropathy issue.

DR. GERSTEIN: Mr. Chairman, ladies and gentlemen, it is my pleasure to present the results of the HOPE study as they pertain to individuals in the study who had diabetes.

I will first discuss the cardiovascular

outcomes in the diabetic subgroup in the first half of my presentation. In the second half of the presentation, I will discuss the nephropathy, the renal outcomes in the diabetic subgroup.

Diabetes is well known to be a strong risk factor for cardiovascular disease. Individuals with diabetes are two to four times more likely to die of cardiovascular causes than those without diabetes.

Middle aged individuals with diabetes and other risk factors have an annual risk of a cardiovascular event of four to five percent.

Evidence from other studies show that ACE inhibitors reduce end stage renal disease in people who have Type 1 diabetes, as well as diabetic nephropathy, and it is clear that this reduction may also be due to a cardiovascular benefit in addition to the renal benefit, and there's also evidence that ACE inhibitors may have favorable metabolic effects.

It is important to state that the HOPE study prespecified diabetes as a separate subgroup for separate analysis of the primary outcome, and in fact, at the time that this study was planned, there was a

plan to recruit up to 4,000 individuals with diabetes in the study, which would have given us, assuming an event rate of five percent per year, 90 percent power to detect an 18 percent reduction in the cardiovascular primary outcome.

We were very successful, and as I'll show you, we recruited at least one in three participants with diabetes. So this was a prespecified subgroup.

You've already seen this slide, and this is the same inclusion and exclusion criteria for those with diabetes as those without, with the exception that individuals with diabetes could have been recruited to the study if they'd had a previous cardiovascular disease as in the other individuals or if they had at least one other cardiovascular risk factor, and that would be a systolic greater than 160 or a diastolic greater than 90 or on therapy; cholesterol greater than 5.2 millimeters per liter; HDL less than 0.9; smoker; or micro albuminuria, and I'll show you that micro albuminuria or small amount os albumen in the urine at the time was felt to be a strong cardiovascular risk factor and now clearly is

a very strong cardiovascular risk factor, and we'll discuss that later on.

Just to remind you that individuals with diabetes and, indeed, individuals in the whole study were excluded if they also had dipstick positive proteinuria. So in light of the previous presentation before lunch, we excluded anybody who would have been called overt nephropathy or well on their way to end stage renal disease, and for the diabetes group and, again, for the group as a whole, this was a study of those with either no proteinuria or just micro albuminuria, and I'll come back to that in the second part of the presentation.

The same outcomes apply to the diabetic subgroup as they apply to the group as a whole. Clearly, the exact same primary outcome and the exact same secondary outcomes. I'm just going to highlight for the second part of the presentation that one of the secondary outcomes was overt nephropathy, and this was an outcome that we had discussed fully in a previous sub-study which was funded in 1994, and I'll talk about that later on, the micro HOPE sub-study.

Okay. Now I'm going to present the baseline characteristics for the individuals in the study with diabetes, and this just applies to those with diabetes. As you can see, about 36 to 37 percent of all the diabetic subjects in the study were women, which is one of the largest studies of women with diabetes for cardiovascular outcomes, and the average age was 65.

The duration of diabetes was about 11 years in the study, and it's important to note that the diabetes therapy were balanced across groups as were the other baseline characteristics.

These are the baseline risk factors. Approximately 56 percent of the individuals with diabetes had a history of hypertension at the time of randomization. The other important thing to note on this slide in addition to the balance across groups is the fact that one third, 1,119 individuals with diabetes were enrolled in the study because they had at least one other risk factor, but did not have a previous cardiovascular disease as defined in the protocol. So that was one third of the total group of

individuals with diabetes.

The blood pressure at the time of randomization was about 142 over 80 for the individuals with diabetes, and as you can see, there was a fair bit of abdominal obesity, about 100 centimeters for the waist circumference, and the ankle/brachial index was about .97.

With regards to concomitant drug use, these were balanced across the two groups. Approximately 20 percent of the individuals with diabetes were taking diuretics, 28 percent on beta blockers, and slightly greater than 40 percent on calcium channel blockers, 20 percent on cholesterol lowering drugs.

Finally, with regards to baseline biochemistry, you can see that the glycated hemoglobin in the study was about 7.4 percent, which is typical of what glycemic control would have been in the United States at around the time the study was being conducted. These people had essentially normal renal function at the time that they were recruited into the study, again, emphasizing the fact for later on that

these were very early in any course towards later renal disease. They had normal function at the time of randomization.

One third of the people with diabetes in the study, 1,140 individuals had micro albuminuria, defined as an albumen to creatinine ratio greater than or equal to two in a dipstick negative population.

These are the results for the individuals with diabetes, randomized to ramipril or placebo. This is the slide showing the primary outcome of cardiovascular death, myocardial infarction, or stroke, and as you can see, ramipril reduced the risk of this primary outcome by 25 percent, and the result was fairly clear at the beginning and continued as the study progressed over the four and a half years.

In addition to reducing the primary outcome, ramipril effectively reduced each component of the primary outcome. This is the data for cardiovascular death. There was a 37 percent reduction in the cardiovascular death on ramipril compared to placebo. There was a 22 percent reduction in myocardial infarction on ramipril compared to

placebo, and there was a 33 percent reduction in stroke in individuals randomized to ramipril compared to placebo in just the diabetic subgroup of the study.

We then looked to insure that the results were consistent across various subgroups of the diabetes subgroup, and the next slide will show these subgroups, and I'll go through this a little bit slower since the slide may be a little difficult to read.

These are those with micro albuminuria at baseline and those without micro albuminuria at baseline, and as you can see, there was a very consistent relative risk reduction for both groups. The interaction P value was 0.34 showing no reason to suspect any heterogeneity.

These next two lines are those individuals with a history of a previous cardiovascular event, and these were those 1,119 individuals without previous cardiovascular disease, and as you can see, one thing that we did find was that those without previous cardiovascular disease had a lower event rate than we expected.

We had planned that this group would have an event rate about 18 to 20 percent, and we were somewhat surprised to that it was lower than we expected at 9.9 percent. So we had much less ability to detect a difference. The group with diabetes and a cardiovascular event in the past had a 24 percent placebo rate.

There was no evidence whatsoever of a difference between the results for the two groups. The interaction P value was close to unity at 0.65, showing the results were consistent whether or not there was a history of cardiovascular disease as defined in the protocol.

The next four lines relate to the anti-hyperglycemic agents used by the individuals with diabetes in the study, and regardless of whether they were taking dietary therapy alone, oral agents, insulin or combinations, the results were consistent with an interaction P value of 0.51.

As has already been mentioned, we had very few individuals with Type 2 diabetes, about 2.3 percent of the total -- pardon me -- Type 1 diabetes.

Two, point, three percent of the total had Type 1. Ninety-seven, point, seven percent had Type 2 diabetes. However, the results were again consistent. There's a point estimate for Type 1, the point estimate for Type 2. Large confidence intervals because of a few numbers. No evidence of interaction.

The next slide shows the results in the diabetes subgroup for a total mortality. As in the group as a whole, there was a clear benefit of ramipril on total mortality showing a 24 percent risk reduction with ramipril compared to placebo.

I don't have a slide showing the revascularization benefit, but there was also in the diabetic subgroup a 17 percent relative risk reduction in revascularization with a P value of 0.031.

Finally, as in the group as a whole, the question arises as to whether or not the effect of ramipril in the study was due to its blood pressure lowering effect or whether it was due to another effect, and we tried to analyze that by that have been described for the group as a whole, but we did a simple, multivariate regression, Cox regression

analysis in which we asked the question: after controlling for the mean change in blood pressure during the course of the study, to what degree does ramipril prevent the composite outcome of myocardial infarction, stroke, or cardiovascular death. And you see that there's the exact same relative risk reduction, same relative risk with essentially the same confidence interval even after controlling for the mean change in systolic and diastolic blood pressure.

And if there's questions later, I have time dependent changes on another slide which I can show, suggesting that the effect was over and above that related to blood pressure lowering.

Now, that is the first part of the presentation related to the effect of ramipril on the cardiovascular endpoints that were in the HOPE study.

The second part of the presentation, I will discuss the renal outcomes, and that will be what we're talking about now.

As many of you know, there is evidence that ACE inhibitors may reduce progression of early

renal disease in individuals with diabetes, and indeed, even late renal disease individuals with diabetes. Dr. Brenner has already shown some studies that show that ACE inhibitors work in the late stages of renal disease.

At the time that the study, that the HOPE study began, as I mentioned, we also submitted and received approval for a sub-study called the micro HOPE sub-study, which stands for micro albuminuria, cardiovascular, and renal outcomes in the HOPE study, and the purpose of the micro HOPE sub-study was to assess the effect of ramipril on albuminuria in HOPE study participants.

The methods of the micro HOPE study were subsequently published in a paper in 1996.

I want to remind the committee at this time that in the HOPE study participants with high degrees of proteinuria at baseline were excluded on the basis of a simple urine protein dipstick. So, again, this is a group of individuals that were early in that line of progression of renal disease that was described earlier on.

In this substudy and in the protocol and in the diabetes care paper, we prospectively defined micro albuminuria as a urinary albumen excretion rate of 20 to 200 micrograms per minute, and if you do the urine collection for 24 hours, this is exactly equivalent to a 24 hour urine collection of 30 to 300 milligrams of albumen per day.

We also prospectively defined micro albuminuria to be present if the albumen to creatinine ratio was greater than two milligrams per millimole in a first morning urine collection, and you divide by creatinine in these because you need to control for the volume of the urine.

Now, in the sub-study, we stated that we would define diabetic nephropathy on the basis of the gold standard test for diabetic nephropathy, and I'll show that in the next slide, the gold standard being a 24 hour urine collection for either albumen or protein.

We also stated, however, and we published that, that we would screen using two possible ways of screening for this gold standard. We would screen

centrally at baseline, one year, and study end, and in fact, we did, using a central measurement of first warning albumen to creatinine ratio, and this was done in four different laboratories around the world. Most of them in Europe and North America were all done in Canada and the U.K.

We stratified the results for the lab in which it was measured, and there was no evidence of heterogeneity across the different labs.

At the other visits, those that were not at baseline, one year, and study end, we stated that we would do a less accurate screen for diabetic nephropathy with a urine dipstick, and just to remind the committee, this is a qualitative test where a nurse research assistant dips the color reagent into urine and compares the color on the bottom to see if it's one plus or two plus or trace, et cetera.

And for the purposes of triggering a 24 hour urine collection, we stated that either a first warning albumen to creatinine ratio at baseline, one year, and study end or at the other visits, a urine dipstick being greater than or equal to one plus would

trigger the 24 hour urine gold standard measurement.

And these are the diagnostic characteristics of those two tests. You see the albumen to creatinine ration measured centrally is by far much more accurate with the sensitivity and the specificity of 93 and 98 percent, whereas because of the qualitative nature and other problems with it, the dip stick has only got about 70 percent sensitivity and about 90 percent specificity.

We defined diabetic nephropathy prospectively in the study as a 24 hour urine collection for albumen which was greater than 300 milligrams in 24 hours or if it was an excretion rate, greater than 200 micrograms per minute, and as I've said, those are exactly equivalent.

We also said because the urines were actually measured locally, the 24 hour urines were measured locally, that if the local lab couldn't measure an albumen, we would also accept a 24 hour urine total protein, which includes albumen as well as some other proteins, of greater than 500 milligrams per day, and these are the currently accepted

definitions of diabetic nephropathy today, and they were also in 1993, 1994, and we published this in the methods paper.

So that was the prospectively defined gold standard for diabetic nephropathy that we used. Now, as has already been presented, this study was ended early, and because it was ended early, we were not able to collect all of the 24 hour urines that we needed to collect because -- for two reasons.

One, people were coming in quicker, and also a lot of the local labs were not able or did not go and collect the 24 hour urine collections.

Therefore, prior to analyzing the results for nephropathy and prior to doing the analysis, we thought that we would be very appropriate to include the most sensitive and the most specific screening test that we used as well, and so the final definition that was reported in the Lancet paper was as follows.

The exact same gold standard, but we said if there was no gold standard available, but it should have been done because the albumen to creatinine ratio said it should have been done, that we included an

albumen to creatinine ratio greater than 36 as well. So what was used in the Lancet paper was a 24 hour urine collection being positive, and only if one is not available, an albumen to creatinine ratio greater than 36 in the first morning urine.

Before I show the results of the effect of ramipril on the renal outcome, I just would like to emphasize the point that was made by Dr. Brenner earlier regarding the importance of micro albuminuria as a risk factor for cardiovascular disease and for cardiovascular outcomes.

This is epidemiologic data drawn directly from the HOPE study, and this is just the subgroup of individuals with diabetes who are on placebo throughout the study. This is the primary outcome of MI, stroke, or cardiovascular death.

And as you can see -- and remember only a third of the patients with diabetes and micro albuminuria, two thirds did not have micro albuminuria. As you can see, and I'll walk you through this, close to 30 percent of those with micro albuminuria at baseline had the primary outcome, and

about half of the, 15.3 percent of those with no micro albuminuria at baseline had the primary outcome.

The relative risk for an MI or stroke or cardiovascular death, if you just have micro albuminuria, after adjusting for age and gender and smoking and hypertension and hyperlipidemia and waist to hip ratio and creatinine and the duration of diabetes, the use of diabetes agents and the glycated hemoglobin, even after adjusting for all of those things in a Cox analysis was 1.84.

Very similar thing seen for all cause mortality. The adjusted relative risk was 1.85. For diabetic nephropathy, as you find in the Lancet paper, which as you know is a progression from micro albuminuria to nephropathy or normal albuminuria to diabetic nephropathy, for those with micro albuminuria at baseline, they were 17 times more likely to develop diabetic nephropathy than those without micro albuminuria at baseline.

Now, I'm going to show you the effect of ramipril on the renal outcome of diabetic nephropathy. I will first show you the first line are the results

according to the previously specified and defined definition that was published. Just using the 24 hour urine measurement alone, just using the 24 hours urine measurement alone, there was a 20 percent relative risk reduction that just did not make the nominal P value of 0.05.

When we included the 24 hour urine collection, plus in the absence of a 24 hour urine collection, an albumen to creatinine ratio greater than 36, it's important to note that there were a lot more events, 48 more events in both groups, and clearly we see that there's a 22 percent reduction in the development of overt nephropathy.

If one broadens it further and explores the data by including in the absence of a 24 hour urine collect an albumen to creatinine ratio, and in the absence of that, dipstick positive proteinuria, that less accurate test that I described, you still have a very consistent result of a 20 percent reduction.

And the point to note in this slide is regardless of how you define overt nephropathy, we see

the same result essentially, but a 20 to 22 percent risk reduction in the development of overt nephropathy as the study progresses.

When one measures -- when one analyzes albuminuria as a continuous variable, this is a centrally measured, first morning, albumen to creatinine ratio. We measured it centrally at baseline, one year, and study end, as I've already described.

You can see that the effect of ramipril is apparent immediately within a year's time and continues as the study progresses.

With the last few slides, we thought it would be useful for the committee to see what the effect of ramipril was in those both with and without diabetes. In other words, the whole HOPE study population as a whole. We haven't made a big point of it, but I want to remind the committee that 30 percent of individuals with diabetes had micro albuminuria at baseline, but 15 percent of those without diabetes also had micro albuminuria at baseline.

So when we looked at what the effect of

ramipril is in the group as a whole, what we see is that all patients, 20 percent of individuals who had no micro albuminuria, who were normal albuminuric at baseline went on to develop micro albuminuria, and 23 percent of those on placebo went on to develop micro albuminuria with a relative risk reduction of about nine percent, and this was consistent in those with diabetes and those without diabetes.

The next slide shows the progression from no albuminuria to either micro albuminuria or overt nephropathy for the group as a whole, and that is the same type of finding. Twenty-one percent went from no micro albuminuria at all to any albuminuria compared to 24 percent on placebo with a relative risk reduction of about ten percent, again, consistent across the groups with no heterogeneity.

Finally, another way to look at that is the progression from either no micro albuminuria to any albuminuria or from micro albuminuria to nephropathy, which is the last slide. So this is the progression from one stage to the next stage, and you see that there is 20 percent progressed on ramipril

compared to 22 percent on placebo, with a reduction of 12 percent, again, consistent across the groups.

In summary, ladies and gentlemen, I believe that in the diabetes subgroup of the HOPE study we've shown that in people with diabetes who are at risk for cardiovascular disease, the addition of ramipril to other effective therapies reduces cardiovascular death, strokes, and myocardial infarction, total mortality, revascularization, and diabetic nephropathy.

The effect was independent of the effect on blood pressure of ramipril, and the only substantial adverse effect is as has been described in the group as a whole, was a five percent excess of cough.

Thanks for your attention

ACTING CHAIRMAN CALIFF: Okay. So what we want to do here would be to address questions related to diabetes, renal function, in particular, and maybe we'll reverse direction and start on the far right-hand side with questions or comments.

DR. BAKRIS: A very nice presentation.

You know, I just wanted to ask your opinion about something.

The next to last slide, just before the summary slide, I was looking at the impact on the diabetic and the non-diabetic, and one could make the argument looking at that data that, in fact, you had more of an effect if you didn't have diabetes than if you had diabetes, and I just wanted to get your thoughts on that.

DR. GERSTEIN: I think it's essentially a subgroup analysis. The results were heterogeneous or -- pardon me -- there was no heterogeneity with the result. I don't really think that it means much other than just the play of chance. I think the result were consistent across the groups. It's clearly something that has not been explored in the literature. The whole role of micro albuminuria and the benefits or risks, et cetera, in nondiabetic people is a relatively new area of investigation.

DR. BAKRIS: Right. The other related question, and I didn't see this, and I know you excluded people with frank proteinuria de novo, but