was there anybody or was there even a percentage of patients in the ramipril group that even developed proteinuria?

In other words, maybe they had micro albuminuria and paradoxically went on, which is not something that I would have predicted, but you never know, and I'm just asking. I didn't really see that, and I don't even know if that existed. So there may not have been a reason to see it.

DR. GERSTEIN: Well, clearly individuals who are on ramipril, 5.6 percent or actually 6.8 percent according to the lancet definition of individuals on ramipril went on to develop proteinuria or diabetic nephropathy.

DR. BAKRIS: Right.

DR. GERSTEIN: Compared to a higher percentage in those on placebo. I'm not sure if that's --

DR. BAKRIS: Okay. Well, then given that, and I know the numbers will be small, but is there any explanation for that since that really kind of flies in the face of a lot of other literature?

DR. GERSTEIN: Well, I guess the first thing is that it doesn't appear that ramipril totally prevents it from happening at all, individuals. I mean it reduces the risk of progression of the problem, but there are other studies in which individuals on ACE inhibitors do go on and --

DR. BAKRIS: No question about it. Let me ask it a different way. Was there a difference in -- okay, Salim. Go ahead.

DR. GERSTEIN: Which data are you?

Okay. I may have heard the question differently. Maybe it might help if I have Slide 27. Perhaps that might explain that.

DR. BAKRIS: Okay.

DR. GERSTEIN: I think maybe that's what you're asking.

DR. BAKRIS: All right.

DR. GERSTEIN: Okay. These are the results showing the development of overt nephropathy in those with diabetes, those without diabetes according to micro albuminuria status. I'm not sure, George, but maybe that's what you're asking.

DR. BAKRIS: Yeah.

DR. GERSTEIN: So as you can see, for those with diabetes who had micro albuminuria, 18, eight percent on ramipril and 21.6 percent on placebo developed overt nephropathy for a risk reduction of 15 percent. Those without micro albuminuria at baseline, clearly there were much less numbers that went on to go to get nephropathy, but there was a consistent relative risk reduction of 30 percent.

Those without diabetes, you see that there were 823 with micro albuminuria and four, eight, nine, seven without micro albuminuria. There is a reduction in the development of overt nephropathy in both groups, 30 percent reduction with micro albuminuria, and again it's small numbers, but a like reduction.

DR. BAKRIS: Sure.

DR. GERSTEIN: So it's consistent.

DR. BAKRIS: Right. No, that's fine. Let me just ask a quick question regarding that. I know for the whole group, you know, the blood pressures were not significantly different, but in this subgroup, did you look at the differences in blood

pressure to see if that may have accounted for why this percentage went on and the others didn't?

DR. GERSTEIN: We didn't really look at that. The subgroup of those for nephropathy, no.

DR. BAKRIS: Okay.

ACTING CHAIRMAN CALIFF: Dr. Molitch.

DR. LIPICKY: Excuse me. Before you leave this slide, that slide really said that the largest drug effect was in people who had no diabetes and had no micro albuminuria. Is that not correct?

DR. GERSTEIN: Well --

DR. LIPICKY: Relative risk went down to .34.

DR. GERSTEIN: I'm going to make the same argument that was made --

DR. LIPICKY: Just looking -- just looking at point estimates. So --

DR. GERSTEIN: Looking at the point estimates, you're right. The point estimates --

DR. LIPICKY: That's what George saw in the previous slides.

DR. GERSTEIN: Yes.

DR. LIPICKY: And the point estimate -- you know, the question is: is that a fact?

DR. GERSTEIN: Yes.

DR. LIPICKY: And I agree it's not a fact, but in fact, the two slides are consistent with one --

DR. GERSTEIN: Yes. No, this is consistent with the other slides, and it's something that needs to be looked at in other studies.

ACTING CHAIRMAN CALIFF: Okay. Dr. Molitch.

DR. MOLITCH: I have several questions. One, I wasn't quite sure why the number 36 was priced for the albumen and creatinine ratio.

DR. GERSTEIN: Yes.

DR. MOLITCH: If two is equal to 30, then 20 would be equal to 300; is that correct?

DR. GERSTEIN: No.

DR. MOLITCH: Of milligrams per 24 hours?

DR. GERSTEIN: Maybe I can just go through that a little bit more carefully. Micro albuminuria, the albumen-creatinine ratio for micro albuminuria was chosen. The cutoff was chosen as greater than or

equal to two in dipstick negative individuals at the time of recruitment to this study. And that was because at the time in 1993 and 1994, albumen to creatinine ratio was relatively new metric. It was not yet clearly described as to what would be the one that would correlate or the number that correlates best with a 24 hour urine collection of 20 to 200 micrograms per minute. That's why albumen-creatinine ratio greater than two was chosen for micro albuminuria.

DR. MOLITCH: So where would an equivalent of that be in milligrams per gram of creatinine?

DR. GERSTEIN: Well, that's actually --

DR. MOLITCH: Does that use millimoles?

DR. GERSTEIN: About 30, 30 milligrams per gram.

DR. MOLITCH: Which is pretty close to --

DR. GERSTEIN: Micro albuminuria cutoff.

DR. MOLITCH: Which is pretty close to 30 milligrams per 24 hours for most studies that have looked at it.

DR. GERSTEIN: Yeah, the lower limit of

the albuminuria definition, the 24 hour definition, correct.

DR. MOLITCH: Okay. And so the upper limit?

DR. GERSTEIN: Then for 36, there was -- in 1994 and even today actually there's not a lot of data about what albumen to creatinine ratio to choose which might screen for diabetic nephropathy, which is clinical proteinuria.

So at the time we chose the number of 36 because there was some regression curves that have been published in the literature that suggested that numbers greater than 30 were very highly sensitive and specific, and using those curves and using some data, we chose 36 as being a very conservative estimate, and we knew that using 36 we would miss some clear nephropathies.

DR. MOLITCH: Because if you used 20, we should be closed to 300 milligrams per gram of creatinine.

DR. GERSTEIN: Well, 20 is probably a little bit too low. I mean maybe 30 might have been

okay, but we chose prospectively 36, and we published that in the Diabetes Care paper.

DR. MOLITCH: Okay. A few other things. One is I presume a lot of these patients were developing congestive heart failure, which is one of the outcomes that I presume that urine protein was not collected when the patients were in heart failure or in patients who were exercising?

DR. GERSTEIN: Urine protein was -- individuals who had heart failure -- we only collected the urine protein at baseline one year at the routine study visits and at study end.

DR. MOLITCH: Right.

DR. GERSTEIN: So that would have been essentially no patients who would have been given a urine protein at the time that they were in heart failure.

You're alluding to the fact that heart failure may increase proteinuria, I think.

DR. MOLITCH: Yeah. So we know that they weren't; is that correct?

DR. GERSTEIN: I don't think that we were

collecting them in heart failure. We don't have any data.

DR. MOLITCH: Do we know that?

DR. GERSTEIN: We don't know that for an actual fact, but these were at the routine study visits when they were sent centrally, and if they came to a routine study visit in heart failure, I don't think we know whether there may have been one or two people.

Do we have any?

DR. YUSUF: Collected it from everybody?

DR. GERSTEIN: Yeah, in everybody in the study.

DR. YUSUF: But just for what it's worth --

ACTING CHAIRMAN CALIFF: If you could, go to the microphone. You might want to position yourself up there for further questions.

DR. YUSUF: -- 11 percent in the ramipril group and 13.3. So the difference is 2.3 percent. It'll be a little hard to believe that that's what made the difference.

DR. MOLITCH: Does anyone know with what vigor these were collected? I presume also that people with heart disease were put into exercise programs and exercise was not done the same day as their urine protein collection and this type of thing?

DR. GERSTEIN: People were asked to be in a first morning urine collection. In fact, they were given a bottle the previous visit and told to bring in the first morning collection even when the visit was later in the day.

DR. YUSUF: Yeah, we didn't use standardization for that. You just let it happen, you know, because there was a visit scheduled, and at every visit for that one year and four year visit, at that visit it was collected, and it wasn't based on whether they were exercising or not.

DR. MOLITCH: The patients weren't asked to not exercise --

DR. YUSUF: No.

DR. MOLITCH: -- before they came in?

DR. YUSUF: No, no, and that would have randomized out.

DR. MOLITCH: Okay, and these are all on the 24 hour urines when they were done as a second test after the first treating.

DR. GERSTEIN: Twenty-four hour, yes.

DR. MOLITCH: What percentage of patients had, in fact, an elevated 24 hour urine that had the elevated screen?

Do you understand my question?

DR. GERSTEIN: Everybody that had a positive albumen to creatinine ration of 36 or higher or dipstick positive proteinuria, we sent them a message that they were to obtain a local 24 hour urine collection for either albumen or total protein.

DR. MOLITCH: And what percentage of that group that had elevated levels on that initial value then had a subsequent 24 hour urine that showed an elevated level?

DR. GERSTEIN: Well, of all the individuals that we reported, there were 48 individuals that should have had an albumen -- a 24 hour urine collection, who didn't have the 24 hour urine collection. So let me just -- that was 48 --

DR. MOLITCH: How many had an elevated level on the subsequent 24 hour urine collection?

DR. GERSTEIN: I don't think we know the answer to that question. We know that -- well, I can just review the numbers one more time. We know that 373 individuals -- pardon me -- 273 individuals had an albumen-creatinine ratio positive over the 24 hour urine collection, but 225 individuals had just the 24 hour urine collection, which is the 48 individuals who didn't have one or the other.

I'm not sure that answers your question. I don't think we have any other data to answer that.

DR. MOLITCH: You probably have the data. You just haven't looked at it in that fashion.

DR. GERSTEIN: Yeah, that's right.

DR. MOLITCH: Of the oral agents that people were using, did they stratify it across the two groups that were the, for example, thiazoline diones (phonetic) or Metforman. Was there more in the ramipril group?

I presume since it was randomized they should be possibly equal, but that should have been

looked at since they were lower in the urinary protein as well.

DR. GERSTEIN: We did not collect data on which oral agent people were taking. We collected whether they were on oral agents or whether they were on insulin. So we did not collect whether on TZDs or whether they were on Metforman, et cetera.

DR. MOLITCH: Okay. I think with respect to the prevention of micro albuminuria to begin with, whether we really have shown that here, I think, is certainly open to question in the diabetic group, and also I know the Euclid study had difficulties trying to show that also for Type 1 diabetes. So I'm not sure that that case certainly has been proved at this point.

I have a question also about the development of diabetes, and I guess I don't know whether you're going to answer that or --

DR. GERSTEIN: That's a question either me or Salim or both.

DR. MOLITCH: Okay. When we looked at the curves of development of diabetes, and that went by

pretty quickly, it looked like most of the effect was within the first year or so; is that correct? It didn't look --

DR. GERSTEIN: Well --

DR. MOLITCH: -- like there was continued divergence, like we saw with some of these other effects.

DR. GERSTEIN: Well, okay. Go ahead. Why don't you answer?

DR. YUSUF: Can we go back to my tray, that is, Yusuf's tray, and get Slide 48 and then we'll look at 49 as well? Not that one, 48. Of the main presentation, not the back-up; the main presentation.

DR. GERSTEIN: While they're getting that, I mean, you'll see that the results were apparent at the beginning and continued throughout the whole length --

DR. YUSUF: Of the one year, not the --

DR. GERSTEIN: Yeah, after the first visit.

DR. YUSUF: Yeah. Forty-eight. Can we go on? Yes, that's the slide.

So this is essentially the first visit. The curves are already diverging, and then at the next visit they're further apart, and they're further apart, and they're further apart.

DR. MOLITCH: Is there really a further difference after the second year?

DR. YUSUF: Well, just look at the first one there and then look at out here. It's hard to know exactly whether it's, you know --

DR. MOLITCH: It looks like there's at least 50 percent of the curve within the first year and maybe another 45 percent, 35 percent after that. Does your trend analysis clearly show a clear trend to further divergence under --

DR. YUSUF: We haven't done that analysis. All we've done is this curve, and we have the overall numbers, which was reduced, and we have a few other slides that could clarify some of issues on this if you'd like me to show them. I don't know.

DR. MOLITCH: On this particular aspect?

DR. YUSUF: On this particular aspect.

DR. MOLITCH: Please.

DR. YUSUF: The next one, you have already seen this on, you know, 155 versus 102 difference, and the difference was there mainly in the use of oral agents, but also a trend here.

But I also want to go to my back-up slide, if I could, and go to back-up slide number 42. In a sub-study in one center, not one center, five centers, on the secure sub-study on 730 patients we had fasting glucoses at baseline and at two years. We haven't yet analyzed the four year data, but these are the data on fasting glucoses in everybody in that site, and this is the increase in glucose level from baseline, is .42 in the placebo group, and it also increased in the ramipril group, and that was different.

So these are the only data we have on diabetes that overall the new diagnosis was different, the use of drugs was different, and the glucose levels in a subset of 700 patients were different.

You could switch that off. Thank you.

DR. FLEMING: Can you go back, Salim, to your slide one or two back that was looking at time to diabetes?

DR. YUSUF: Sure. So could we go back to 48 of my main presentation again, please? Thank you.

DR. FLEMING: While they're going back, was your point to try to establish that there was a constancy in the relative risk? Is that what you were trying to get at?

DR. YUSUF: We weren't trying to do that, no. We haven't done an analysis for that.

DR. FLEMING: It's very apparent that the relative risk in that first year is in the neighborhood of .5. The incremental relative risk after that first year is pretty close to one. So the excess is predominantly derived in that first year.

DR. YUSUF: I see, and at the end it's .66, isn't it? So that there has to be something in favor.

DR. FLEMING: Well, it's -- it's cumulative as .6, and so the incremental, which in the hazard ratio is, in fact, the incremental hazard, and that is close to --

DR. YUSUF: The only way we can really do is to put the numbers against each other, and we could

put it --

DR. FLEMING: Okay, but if you've eyeballed these enough, it's pretty clear that the relative risk is converging toward one in the incremental hazard. I don't know how compelling that is, but the point is most of the excess is occurring in that first year.

DR. YUSUF: I think -- how about the second year, Tom? Don't you think there is a further absolute difference?

DR. FLEMING: No.

DR. YUSUF: No? Well, we'll have to look at the --

DR. FLEMING: At least in terms of you have to look at how much the blue goes up versus how much the yellow goes up.

DR. YUSUF: I'm just looking at the difference between the yellow and the blue. In the first year it seems to be --

ACTING CHAIRMAN CALIFF: Is this hard, quantitative science here?

DR. FLEMING: Yeah. Well, what it gets at

is whether or not the effect is continuing to grow, and my point was just if that was what you were trying to get at, it's apparent that most of the effects are in the first year.

DR. YUSUF: Yeah, I'm not trying to get at that. I agree with Rob. This is an eyeball P value.

ACTING CHAIRMAN CALIFF: I think you have to be in the third year of your Ph.D. in statistics to be able to do this.

(Laughter.)

ACTING CHAIRMAN CALIFF: Dr. Molitch.

DR. MOLITCH: Yes. Were there any supporting data at all for the diagnosis of diabetes or this is simply a check-off on a box?

DR. GERSTEIN: Self-reported history of diabetes, in addition to whoever the fact that that Dr. Yusuf just showed the slides. Dr. Yusuf just showed the slide showing that they were on agents. In other words, the doctors were substantiating diagnoses essentially by putting them on drugs or therapy for diabetes, but essentially they were asked at each visit do you have diabetes, yes or no.

DR. YUSUF: I think just to give you an overall picture of the thing, it's fair to say we did not pre-specify this as something we were looking for. It's also fair to say in the rationale part of the protocol we did not write any rationale for this. We didn't expect this.

So we then saw the result. It's a striking P value. So in a sense that first slide is data derived. Then we said, "Is this real or is this a fluke?"

And in order to get whether this was real or a fluke, we looked at what do the doctors do, and, well, they followed their diagnosis by differences in treatment, and then we said do we have some objective data in everybody, and that's where we went to the 700 people, and we found a difference.

So I've just given you the whole story.

DR. MOLITCH: Just to try to get at why this might be the case, obviously there's a number of potential mechanisms. One of them is improvement in insulin resistance essentially by the ACE inhibitor itself.

Second, there was also -- it looked like there was a reduction in the total number of people who were on thiozides and beta blockers when they were on manipril is that correct?

And did you look to see whether that could potentially account for this?

DR. YUSUF: Yeah.

DR. MOLITCH: And number third is was there any change in body weight for the two groups?

DR. GERSTEIN: The answer to your question, you saw the slide in Dr. Yusuf's presentation that there was a difference in the use of thiazides and beta blockers, and that clearly is one methodologic explanation that may account for the difference.

I think that -- have we done body weight changes? We haven't done that analysis. We haven't analyzed that, but I think that what you're saying, Dr. Molitch, is that this needs to be tested prospectively, and as Dr. Yusuf has said, we think it's a good idea and we're doing it.

DR. GRABOYS: Just to pick up on the issue

of diuretics, any obvious explanation why the use of beta blockers in the diabetic group was so low, 28 percent versus about 40 percent for the group?

DR. GERSTEIN: Sure. There has been a long and old literature sort of scaring doctors away from using beta blockers in individuals with diabetes. Based on early studies with the early nonselective beta blockers that in Type 1 diabetes, that they may impair the detection of hypoglycemia, so most physicians in medical school were taught to beware of beta blockers, individuals with diabetes, and that's probably why we were seeing that.

Do you want to come up and make the point?

DR. YUSUF: See, the non-diabetics are all people with vascular disease, and so they -- a very high proportion had an MI or other coronary disease, but as the diabetics include people about 50 percent or more who didn't have an MI, so there's a difference in the reasons why you would use a beta blocker, too?

DR. GRABOYS: Yeah, and any data on the potassium levels in the diabetic group.

DR. GERSTEIN: Potassium levels in the

diabetic group were not elevated. In fact, the potassium levels went high. In the run-in period they were excluded from participation in the study, and so there was no problem with potassium in the diabetes group or the group as a whole.

ACTING CHAIRMAN CALIFF: Dr. Pina.

DR. PINA: In the FDA reviewer's comments, I see that at the visit 558 patients have self-ramipril. Was there a difference in rates for the drug in diabetics and the group as a whole? And were reasons for this situation similar in diabetics as the group as a whole?

DR. GERSTEIN: Okay. Could I have the reserve slides, number three? Right.

So I think this may address the question. The adherence to ramipril was similar to what it was in the group as a whole. So at the end of four years, 61 percent were still taking study ramipril, and 12 percent on ramipril were taking open label ramipril, whereas the placebo, 52.7 percent, were on study drug, and 15.4 percent were on open label use.

So at the end of the study 61 plus 12 is

about 73 percent were taking an ACE inhibitor compared to 15 percent on placebo.

DR. PINA: Were the reasons for discontinuation of ramipril in diabetics different than --

DR. GERSTEIN: These are for stopping therapy. If you go to the next slide actually, Slide 4, these are the reasons for stopping therapy in the individuals with diabetes, and you can see that these reasons are, in fact, the same as they were in the group as a whole.

So cough, which I've already alluded to and very low rates of angioedema, et cetera. So essentially there was no different reason for stopping study ramipril in the diabetic subgroup than there was in the group as a whole.

ACTING CHAIRMAN CALIFF: Why did you ask that question?

DR. PINA: Because it looked like the numbers that stopped the trial, well, it does seem to be high.

DR. Di MARCO: Looking at the numbers, how

certain are you that this is or are you certain that this is an effect on the kidney itself or do you think that this is all secondary to the effects on cardiovascular disease? I mean you have more heart failure in the placebo group, more myocardial infarction, more limb ischemia.

I would guess they had more interventions and more diagnostic procedures. Could the changes you see in the kidney be secondary to that rather than a primary effect of the drug?

DR. GERSTEIN: Well, actually, I think that's a very difficult question because the kidney is essentially part of the vascular system, and things that happen to the vasculature also affect the kidney. So it becomes a very difficult mechanistic question to sort out.

I think if we're reducing atherosclerosis or reducing cardiovascular related intermediate things, then it's certainly reducing them in the kidney, and the kidney may very well do better over time.

So I don't know that one can give a

mechanistic. We don't have obviously sort of a --

DR. Di MARCO: Well, could you look at your population and look at people who didn't have events, didn't have heart failure, didn't have an angiogram, didn't have other things, and see if they also had these same changes in kidney function?

DR. GERSTEIN: I don't believe we've done that analysis, in other words, looked at those who sort of got through the whole study without anything and looked at their change in function. That's actually another analysis that we can do.

ACTING CHAIRMAN CALIFF: Dr. Borer.

DR. BORER: I need to preface my comment and question by admitting that the subgroup hazard rate analysis is hazardous, but, you know, we've been shown a lot of analyses that generally sort of go the same way and occasionally reach nominal statistical significance, and that's very nice, but there are clearly important public health implications if we accept the concept that there are biologically important prophylactic effects on the kidney in diabetics as opposed to the more conservative

accepting that there's a possibly associated goodness when you treat patients for the primary endpoint who have diabetes or don't have diabetes.

With that in mind, I'm going to ask for one more subgroup analysis if you have it because I'm trying to isolate a group with diabetes for which there may not be very good evidence that the drug is useful for the kidneys or importantly useful, and I think it's really a follow-on to John's question a minute ago.

Have you looked at that subgroup of diabetics that didn't have evidence of cardiovascular disease to see what the effects of ramipril is on the kidneys?

DR. GERSTEIN: Are you asking me about the CBD negative group of people?

DR. BORER: Right.

DR. GERSTEIN: And that's Slide 8, reserve Slide 8.

So this is expanding some of the stuff that I've already showed you. In those who did not have cardiovascular disease and those with

cardiovascular disease, I'm going to show you these are the primary outcome, the primary and secondary outcome. This is all heart failure, and this is overt nephropathy.

And as you can see, first of all, is that the results are consistent so when those -- when the primary outcome -- those with cardiovascular disease, there was a 24 percent reduction with ramipril. Those without cardiovascular disease, there was a 16 percent reduction with ramipril. I already pointed out the much higher placebo event rate in this group than in this group. There was no interaction. So they were not statistically heterogeneous, and I just want to take a moment to point out that this was a much lower rate than we'd expected.

In order to detect a 25 percent reduction from 9.9 percent, we would have needed well more than the 3,577 patients that we had had in the study. We would have needed in excess of 10,000 diabetics with no previous cardiovascular disease in order to detect the same type of event rate in the study. So that's the primary outcome.

As for the primary and secondary outcome, the same thing for overt nephropathy, which again those with CVD positive versus those with CVD negative, there was an 18 percent reduction in those CVD positive, an eight percent reduction -- pardon me -- an 18 percent -- excuse me -- a 26 percent reduction there, an 18 percent reduction there, no evidence of heterogeneity. The results were consistent across subgroups regardless of how you cut the data in those with or without a history of cardiovascular disease in the past.

And I think that the results say the same thing for both groups.

DR. BORER: And just staying on that last line there, overt nephropathy defined as you've defined it is one possibly interesting endpoint, but, you know, extrapolating from Dr. Brenner's presentation, what about the development of micro albuminuria and other renally related or vascular related or diabetic vascularpathic changes like eye changes requiring laser therapy or what have you?

DR. GERSTEIN: I showed the data earlier

on about developing -- do you mean micro albuminuria in those according to CVD positive or CVD negative?

DR. BORER: Right, right.

DR. GERSTEIN: We haven't cut the data that fine to look at micro albuminuria in that group. As far as eye disease is concerned, we assessed diabetic eye disease using a very simple question. We just ask people at every visit since the last visit if they'd have laser therapy for diabetic eye disease, and so we did not do retinal photographs. We did not do seven field stereoscopic, et cetera, type assessment. So it was just a history of laser therapy for diabetes in the eyes, which is what we used. So we didn't do any -- we did not analyze it according to CVD positive or CVD negative for micro albuminuria development or progression.

ACTING CHAIRMAN CALIFF: Dr. Lindenfeld.

DR. LINDENFELD: To clarify once again, according to our briefing document from the FDA the protocol definition for overt nephropathy was to be greater than one plus proteinuria and/or the albumen excretion rate of greater than 200 and/or the albumen

to creatinine ratio.

And when one analyzes that, the hazard ratio is 1.07, and so again, I'm wondering. That's not the definition that was published, but according to our documents that was the original protocol definition.

Can you clarify how that change was --

DR. GERSTEIN: Yeah, I'd be happy to.

Could I have my main presentation Slide 20, please, my main presentation Slide 20?

Okay. I can't account for the exact numbers that you just said. However, I can tell you that this was the protocol definition for diabetic nephropathy that was published in Diabetes Care, which was a methods paper of the micro HOPE protocol, and the micro HOPE protocol was submitted in 1994 and funded in 1994, and this was the methods paper published in 1996.

So the definition of diabetic nephropathy stated in Table 2, I think, in that paper was exactly as we see above.

As I've already described, for the Lancet

paper we included with that definition the most sensitive and specific first morning albumen to creatinine ration, which was the only -- which was the best screening test that we had for it because we didn't have all of the 24 hour urine collections that we wanted to have.

At no time in the micro HOPE paper or in the subsequent, you know, methods -- micro HOPE protocol or the methods paper in Diabetes Care did we state that one plus proteinuria was going to be a definition for diabetic nephropathy as an outcome.

ACTING CHAIRMAN CALIFF: Could we hear from the FDA about this? Because there is a discrepancy between what you say and what we have in our briefing document.

DR. GERSTEIN: We recognize that there's a discrepancy, and there was -- I should make one comment, that in the original HOPE paper, the original HOPE protocol that was originally funded, which was before the micro HOPE protocol was funded, there was a much less specific and a very general discussion of albuminuria, but the micro HOPE protocol clearly

defined what we would be talking about in terms of diabetic nephropathy.

DR. LIPICKY: I'm not sure that we need to comment. There are two definitions that are applicable here, and after the primary -- after the review that you received, there was an addendum to the review, and I guess that was not transmitted so that there FDA agrees with the numbers that were shown when it is defined this way.

So the problem is there are two definitions, one that was the protocol and the second which was the publication.

Did I say that correctly?

DR. MOLITCH: You're saying this is a case where the protocol is not amended to reflect the publication.

DR. LIPICKY: Right.

DR. MOLITCH: But they both occurred well before the study with --

DR. LIPICKY: Yeah, let Dr. Hung say what I've say. I may have been --

DR. HUNG: Jim Hung, FDA statistician.

These two actually we analyzed, and so we have that addendum dated April 17th, so agree with the sponsor's numbers. So I don't know whether you got that addendum or not.

ACTING CHAIRMAN CALIFF: Okay. Thank you.

DR. FLEMING: Rob, this was the issue I wanted to raise as well. So I'd like to at least pursue it until I understand it.

ACTING CHAIRMAN CALIFF: Okay.

DR. FLEMING: Are we saying that the -- if we look in Table 23 where we see a striking difference in these two definitions, which I guess no matter what the history of this evolution of definition, it's bothersome to me when you see such a strikingly different result, a relative risk of 1.07 versus a relative risk of .81.

DR. GERSTEIN: I must -- I have to just show, I mean, the next slide, and I have to make the point. The 1.07 was -- I'm not sure where that comes from actually, but regardless, the next one after that --

DR. FLEMING: According to this, it comes

from what was the protocol definition.

DR. GERSTEIN: No, but the -- it's incorrect. The protocol definition is this one, the 24 hour test only. That is the protocol definition published in 1996. It said in the protocol in 1994, that the micro HOPE protocol -- and this was the one that we used in the Lancet paper.

DR. FLEMING: We understand what the published paper showed, but what we're interested in is what was in the protocol and was the protocol amended formally.

ACTING CHAIRMAN CALIFF: Dr. Hung.

DR. LIPICKY: We have to ask you whether that 1.07 relative risk was the protocol defined definition or an error on your part.

DR. HUNG: That 1.07, that actually is the definition I thought originally according to the protocol, but then you must clarify that that is not the case. So 1.07 hazard ratio, that one is much more restricted definition than the first one, which is -- I don't know. It doesn't show up here.

DR. LIPICKY: Shari Targum is going to the

microphone.

DR. TARGUM: I'm just going to read the definition from the protocol, and the definition of overt nephropathy in the protocol is greater or equal to one plus proteinuria on dipstick or urinary albumen excretion greater than 200 micrograms per minute or 300 milligrams per 24 hours.

That is in the protocol. That is not the same as the published --

DR. LIPICKY: And that is the analysis that the 1.07 comes from? Well, Jim says no.

DR. HUNG: According to the definitions read by Shari, we have addendum saying that the hazard ratio is .86. (Unintelligible) was .72, 1.02.

DR. LIPICKY: Well --

DR. HUNG: The P value is --

DR. LIPICKY: I'm sorry.

DR. HUNG: According to the definition just read by Shari we call it the protocol definition.

DR. TEMPLE: So the 1.07 is incorrect?

DR. HUNG: No, no, no, no. The 1.07 is not. One, point, oh, seven is much restricted

definition than the protocol definition just read.

DR. LIPICKY: Well, it's an analysis that only Jim did.

DR. HUNG: Right. I'm trying to entertain --

DR. LIPICKY: The sponsor has not represented that same data in any way.

DR. HUNG: Yeah, I'm trying to entertain -- I'm trying to, you know, entertain the sensitivity of the results.

DR. LIPICKY: -- the sponsor define nephropathy according to the rules that Jim did the analysis by.

DR. HUNG: Okay. Let me read again. Okay? According to definition just described by Shari, that the P value for that endpoint is .075, and I think sponsor agree with that and -- I'm sorry -- not sponsor; the HOPE study group, and the hazard ration is .86. (Unintelligible) single is .72, 1.02. That is in the April 17th addendum.

In fact, the Lancet article has three more definitions, you know, more restrictive definitions,

and I can verify that. I was trying to entertain the sensitivity and robustness of the results.

DR. GERSTEIN: Can I just address a couple of issues related to that?

The first one is that the definition that was published and was in the literature is the first one that's on the line here, the 25 urine collection. It's also universally accepted around the world as the definition of diabetic nephropathy, and I see Dr. Bakris nodding his head, which is the top line on the thing, and this was published, and they said many years before the study ended, and so that's the first point.

The second point is I want it to be clear that we used this second definition in the paper for the reasons I mentioned above. However, we also wanted to make sure that this was a real number. So we explored the definition of diabetic nephropathy in the paper, and I'd like to have reserve Slide, if I could, No. 21, please.

Many people -- Number 21, reserve slide -- many people have stated that in order to be really

sure that somebody with diabetes has diabetic nephropathy, you want to see that they've also had evidence of eye disease.

I've already stated that we didn't do eye photographs in patients, but in the Lancet paper, we said, "Well, let's explore this diabetic nephropathy finding. Let's use" -- because, you know, we didn't do kidney biopsies in these people -- "so let's use the most specific definition that the literature would accept on clinical data for diabetic nephropathy," which means a urine collection that shows nephropathy, plus eye disease.

And so, of course, we have very few numbers, but we see that exact same trend showing, that there's a 38 percent relative risk reduction. So it was not that the Lancet paper was making a whole bunch of definitions. We were saying let's be more specific. Let's be even more specific, and let's see what happens to the results.

So this even further emphasizes the point. No matter how you define diabetic nephropathy in the HOPE data set, we get the same consistent results, and

that was the only reason that we did explore it in the Lancet publication.

ACTING CHAIRMAN CALIFF: Tom, are you satisfied now?

DR. LIPICKY: Let me see if I can explain again because this is now confusing, and it's confusing to me.

In the blue books there that you have that came at the conference, there is an addendum. A lawyer in committee management decided that you all didn't need to see that until today, not us. We wanted to get it to you two weeks ago.

So one part of the thing that would have been -- one part of the discussion would have been avoided in the sense that that is the same data in the same analyses that were shown at the meeting now.

We received the HOPE protocol set of case report forms that had sacks with variable names in every block in the original data so that we saw no written material from HOPE or the sponsor for purposes of the reuse that were written. In fact, it was rather difficult from the protocol and from the

publication to figure out how things were defined. That's why there are a bunch of different analyses that you have seen.

There is no discrepancy at all with respect to how the sponsor is represented or how HOPE is representing the data as they defined it, and what you're seeing is that you can take some trips when you interpret how things should be defined a little differently.

ACTING CHAIRMAN CALIFF: Okay. Tom, are you --

DR. FLEMING: All right. I'm now following along on Table 23(r) from the blue book that we were just presented today, and if I understand, then we are to discard the 122, 110, the 1.07 relative risk, as not having been correct. The correct, I understand, per protocol is the .86.

DR. HUNG: Yes. Just ignore the second line because second line seems to entertain the robustness.

DR. FLEMING: You're tell us that is, in fact, the protocol definition, and the protocol in

spite of these more recent developments and publications in '96, et cetera, et cetera, the protocol was never formally amended?

DR. LIPICKY: That's correct.

DR. GERSTEIN: The protocol was never formally amended.

DR. FLEMING: And so essentially what we're seeing here are results showing that they're about 270 events according to the definitions used in Lancet, which are about half the number of events that fit the protocol definition.

The good news is they both now trend in the right direction, relative risk of .86 versus relative risk of .78, if you use the original. If our interpretation is correct in Table 23(r), it continues though to suggest that micro albuminuria is actually only marginally affected, and renal dialysis is slightly in the wrong direction of only 18 cases.

And doubling in creatinine from baseline is slightly in the wrong direction. Are those, in fact, accepted as correct analyses per protocol?

DR. GERSTEIN: The doubling of creatinine,

yes. That is what we found, very few numbers of individuals, and as Dr. Brenner said, we're way back in the course of renal failure.

DR. FLEMING: Right, right.

DR. GERSTEIN: So we would not expect this to have any effect on doubling the creatinine or end stage renal disease.

DR. FLEMING: Or micro albuminuria. That shows almost a relative risk of .94. Is that also correct?

DR. GERSTEIN: Well, I showed the micro albuminuria data already for the diabetes and the non-diabetes group. I can show them again if you like, but --

ACTING CHAIRMAN CALIFF: No, no, no.

DR. FLEMING: Don't have to. I'm just asking if this is, in fact, essentially consistent with what you understand the protocol definition.

ACTING CHAIRMAN CALIFF: It's one, two, three, four --

DR. GERSTEIN: I don't have those numbers, your numbers right in front of me. I can --

DR. YUSUF: Actually while Hertzel is trying to look at that, Tom, can I deal with that first thing?

You know, when FDA did the initial review, they did not have the design paper that we published about four years ago. So we superseded the definition.

Now, it is fair we didn't file an amendment, but you've got to understand there's an investigator driven study, and we don't file amendments every time a slight definition protocol occurred.

However, the key point is: did we define what the outcome was before we looked at the data? And whether our definitions are data derived or not, and the point is three years before the study was completed, we made that definition which is there in the Diabetes Care literature. It's published, and those are the two things that Hertzel showed you. The first one was 24(r) urine where the P values are .08 and the relative risk is .78, and the second one was, because of the early closure, we did not have -- it

wasn't possible to get 24 urines in everybody.

So without him knowing the data, he said, "Let's take the next best thing we have, and that is the albumen creatinine ratio," and he has reported that.

Now, to be fair, they all show a relative risk from .78 to .8, with P values just below or just above PO .05. So it's consistent, and I think it will be fair to say they're borderline P value. Nothing is three zeros, one.

ACTING CHAIRMAN CALIFF: I think we're all in agreement on those points. Now we've moved on to the issue that some of the other renal endpoints tending even in the wrong direction or show no effect, and the one that we were most concerned about, I think, that you were just going to look at was micro albuminuria.

DR. LIPICKY: Yeah, that was confirmed to be the correct number.

DR. GERSTEIN: That is the correct number.

ACTING CHAIRMAN CALIFF: So that has a ratio of .94?

DR. GERSTEIN: Point, nine, four.

ACTING CHAIRMAN CALIFF: With a P value of 0.34.

DR. GERSTEIN: Yes, .33.

ACTING CHAIRMAN CALIFF: Okay. Joann, did you have any further questions?

DR. LINDENFELD:; Well, I have one other question, and I had asked earlier. In the diabetic patients without cardiovascular disease who were entered because they had diabetes in one respect, can you show us those patients and their risk factors?

In other words, what I want to know is how many of those --

DR. GERSTEIN: No. You're asking which of the risk factors those diabetic individuals had? Regarding if they had at least one risk factor, most of them had greater than one. Janice, I don't think we have an analysis broken down according to each risk factors. You can do it, but we haven't cut the data that way.

DR. LINDENFELD: The reason I'm asking just for clarification is when you look at your

patients with diabetes and one risk factor, we know that there are some we would treat anyway, but how does this data apply to those, a diabetic?

DR. GERSTEIN: Well, I should say, I mean, we defined what risk factors they could have. So it's not that any risk factor got them in. They had to have one of those five that we said: hypertension or smoking or micro albuminuria or lipid abnormalities. So they're very carefully defined risk factors based on epidemiologic data showing that those substantially increased the risk of a person with diabetes.

DR. LINDENFELD: I'm asking this mostly for the physician who looks at their patient and say, "Does this study apply to this specific?"

DR. GERSTEIN: Yeah. We haven't cut it that way.

DR. THADANI: Before you go on to the next, although you're showing there might be some subtle changes in micro albuminuria, but the hard endpoints of dialysis, others are not in your favor; is that correct?

DR. GERSTEIN: We have no reason to expect

that dialysis or creatinine change would be in our favor because of the fact that Dr. Brenner was just saying earlier on that the way -- early on in the course of the development of renal disease I think we're seeing just random play of chance.

DR. THADANI: I realize that, but in what you showed, the data, one of the studies was positive, and it's nice to know the endpoint is going in the right direction. So we may not have enough data.

Now, also you've made a comment that your P value went down from .04 to .07 because you say we don't rely too much on one plus dipstick, and yet you excluded all of those patients at baseline. How can you just contradict your own statement? If I had a new patient --

DR. GERSTEIN: It's different --

DR. THADANI: -- if it is one plus, you said those patients could be treated. Forget about that. Now you're saying that's not a good test. So I think I've got a problem with that because your entry criteria -- you're violating all of the entry criteria by doing that.

DR. GERSTEIN: I'd like to address that question. We excluded people with one plus proteinuria at entry for two reasons. One, the main reason is -- there's two points. The first one is it's a difference between an exclusion criteria and an outcome. So that's number one. So we defined an outcome more rigorously than an exclusion criteria.

The second point is that there was even in 1993 a very strong bias in the diabetes community based on the Lewis study and other studies, that anybody with diabetes, regardless of whether they had Type 1 or Type 2 diabetes, should be in an ACE inhibitor, and we felt at the time that if we had included people with one plus or more dipstick proteinuria that we would have had (a) a very hard time recruiting and (b) a lot of violation of recruitment and a lot of use of unblinded ACE inhibitor.

So we thought for methodologic reasons that we should include anybody that's got clinical proteinuria at the time, but that is not the same as an outcome.

DR. THADANI: No, I buy that, but, on the other hand, if you are one plus, the chance are your proteinuria has increased.

ACTING CHAIRMAN CALIFF: Udho, let's maintain the order of questioning here. I think you'll be cleaning up at the end here if we could move on to Dr. Armstrong.

DR. ARMSTRONG: Following this discussion it would help me if we could start first with the methodology and the threshold for this dipstick, how symmetrical the methodology was across the centers.

And you mentioned it had a 70 percent sensitivity, and I wondered if you'd comment on the intra individual variation. Could you tell me something about the methodology and then I could ask my second question?

DR. GERSTEIN: Sure.

DR. ARMSTRONG: I only have two questions.

DR. GERSTEIN: Okay. The sensitivity and specificity data that I showed is not from the HOPE study. It's from the literature at the time. That's the first thing.

There's actually very little good sensitivity and specificity data on a year end dipstick, but just for the committee, again, it's like an Ames dipstick which has got a strip on it and different reagent pads on the strip. You dip it in the urine. It turns a color. You compare it to a reference color on the side of the bottle. If it's a certain color, you call it trace. If it's a darker color, it's one plus. If it's a darker color, it's two plus. It's a qualitative test, and it was simply used in the inter central measurements visits as a screening test.

That figure for sensitivity and specificity actually came from one paper many years ago which tried to look at it compared to 24 urine collections. I'm not aware of any other paper that's looked at it since that time, and which is why we never included that as a definition of nephropathy.

DR. ARMSTRONG: Did all of the centers in HOPE use the same dipstick?

DR. GERSTEIN: No, it would be different. There aren't -- I don't know all of the companies that

make dipsticks, but it's a similar technology. It's an old, you know, technology, and I'm assuming that someone in France may have used a different company's dipstick than somebody in the United States.

DR. ARMSTRONG: To what extent were the quantitative measurements that were driven by a positive dipstick similar or different?

DR. GERSTEIN: Oh, I see. I don't think we've cut the data showing the 24 hour urines driven by a positive dipstick compared to 24 hour urines by a positive central screen.

DR. ARMSTRONG: So finally, could you construct for me some kind of flow diagram so I could understand the patients in your study who had a positive and negative dipstick during the course of the study and then sort of how they came down the hopper to the end?

I'm confused as to how this study unfolded and how many patients actually ended up with a positive versus a negative dipstick and went on to quantitative measurements. I'm really having trouble following this discussion.

If someone could provide a flow diagram, it would facilitate my understanding.

DR. GERSTEIN: We could certainly do that with the data. We haven't done that type of flow diagram with the data to now.

DR. YUSUF: What we did was we collected urines for the albumen-creatinine ratio, and everybody at baseline one year and at the end of the study irrespective of anything else. So that way the mean ACR changes are really good data. Plus they're central labs, all that stuff, and that's audit.

Now, the dipstick at the beginning excluded people. They were out. Then every year they had a dipstick, and if they had a dipstick, then two things happened. They were asked to provide the morning urine because it was the urine they brought anyway that was done. That was sent to a central lab.

So two things, two events could trigger a 24 hour urine. One is a positive dipstick. Another thing is if any urine that we collected at one year and four years went over that threshold, then we again asked for that.

So that in a sense the ACR is an objective measure, and it's a standardized measure. The dipstick is a qualitative measure, and the mean ACRs at one year and at four years are unbiased by anything, and it's standardized and it's complete. So that's all I can tell you.

ACTING CHAIRMAN CALIFF: Okay. Dr. Fleming, are you finished?

DR. FLEMING: I'm done.

ACTING CHAIRMAN CALIFF: Dr. Thadani.

DR. THADANI: On that question, why didn't you show if you -- Salim says that ACR is the most sensitive. Why did you not show ACR alone? Because you never --

DR. GERSTEIN: Well, we had the gold standard. I mean --

DR. THADANI: No, I realize that, but you are saying that the most sensitive method of estimating, that's the definition. I know you showed a composite of three.

DR. GERSTEIN: Yes.

DR. THADANI: You must have analyzed ACR

alone because you've written papers. Somebody in the review must have asked you that.

DR. GERSTEIN: No, I think that would have been almost a little bit disingenuous. I mean what we said is we have the gold standard. We wouldn't go to the ACR alone, and in fact, you know, if there was a patient who had an CAR who was less than 36, but they did have a 24 hour urine collection, we believed the 24 hour urine collection because that is the gold standard.

The ACR is only 93 percent sensitive and 98 percent specific compared to that gold standard.

DR. THADANI: I realize that. Give the problems with the dipstick, missing it on some patients, you must have data on the issue on everybody, right?

So you --

DR. GERSTEIN: We have ACR on most --

DR. THADANI: Why don't you who us what happened with ACR?

DR. GERSTEIN: We analyzed the data just with the ACR without looking --

DR. THADANI: What's the significance on that?

DR. GERSTEIN: -- at the 24 hour urine collection. I don't think we have done the cut yet, yet. We haven't done that cut yet.

DR. THADANI: And what happens if there's no trend or anything on that?

DR. GERSTEIN: There's no reason to believe that -- sorry.

DR. YUSUF: It's unlikely, given the (inaudible).

DR. THADANI: All right. The other point is that you talked about micro angiopathy in the diabetes. It's a tough issue unless you do photographs, as you said.

DR. GERSTEIN: Yes.

DR. THADANI: And my ophthalmologist colleagues tell me that you really can't even diagnose it. You know, they're talking about the micro angiopathy, especially the retinal one, unless you're doing routine photographs, which you said you did not do.

DR. GERSTEIN: We did not do.

DR. YUSUF: What is the confidence level? Because if you take diabetes, a lot of them will have small, you know, aneurysms which you pick up on the regular limits. So how much confidence we have, these are really bad eyesight with a laser or in order to address that issue, really a prospective study on that?

DR. GERSTEIN: Well, clearly one could take the same model that Dr. Brenner showed for diabetic renal disease progression and apply it to diabetic eye disease progression. You have people that have no diabetic eye disease. They then get a couple of micro albuminuria -- micro aneurysms. We then get a couple of hard extrudates and soft extrudates, and et cetera, et cetera.

So for the eye disease we just asked people about the very, very end of the spectrum, and that's why we have two events, and it's one that most people who say they have laser therapy for diabetic eye disease do have laser therapy for diabetic eye disease, but we don't miss those who don't --

ACTING CHAIRMAN CALIFF: Udho.

DR. THADANI: But be sure that --

ACTING CHAIRMAN CALIFF: Udho.

DR. THADANI: -- the biopsy is --

ACTING CHAIRMAN CALIFF: Udho.

DR. THADANI: Yeah?

ACTING CHAIRMAN CALIFF: Your co-panelists are urging just one more question.

DR. THADANI: The last question is if the (inaudible) retinopathy is in the same direction, then why there's no difference. Actually there are 170 patients in ramipril group and 186 in placebo. It's going in the wrong direction.

DR. GERSTEIN: Sure. Could I have reserve slide, just to maybe answer that, number -- give me a moment -- yeah, Number 24. Reserve Slide 24, please.

Okay. We included this in the paper, and I'll show you the results. We did then come up with a post hoc, post hoc definition, composite outcome of microvascular disease defined as either diabetic nephropathy or laser therapy or dialysis.

So in direct answer to your question, you

see that 9.4 percent of people on ramipril compared to 10.5 percent of people on placebo did report a history of laser therapy for their eyes with a 12 percent relative risk reduction. I've already showed you the nephropathy. We threw in dialysis as a fair measure of part of the microvascular outcome, .6 versus .5, going in the wrong direction.

When you combine all three as a composite measure of microvascular complications, 15.4 percent versus 17.8 with a relative risk reduction of 15 percent of the nominal P value of .05. So I think that answers your question directly.

Slide off.

ACTING CHAIRMAN CALIFF: Okay. I have two questions to which I would like a brief answer, which I know you can do after having been through the grilling you've already been through.

There are two things here that at least for this committee we've had kind of a standard that to recommend an indication it has to either cause the patient to live longer, feel better, or avoid an unpleasant experience of some kind.

And you've got two things here: the delayed onset of diabetes and albumen in the urine as measures that you're considering important. Could you make a case for each as briefly about -- and obviously the implications to the public health, as Dr. Furberg is going into, I guess, in terms of cost, on the other hand, could be substantial if this was seen as a very important surrogate or way to interrupt a disease pathway.

Could you just speak briefly to each?

DR. GERSTEIN: All right.

ACTING CHAIRMAN CALIFF: As to how we should view this as a panel?

DR. GERSTEIN: I'll first address the diabetes and then the micro albuminuria.

From a diabetes perspective, the most important thing about diabetes is that it's a really bad risk factor for really bad outcomes. So people with diabetes are at high risk for many bad things down the line, including microvascular and macrovascular disease and things like erectile dysfunction and everything else.

If you can have a therapy which even on average delays that development by two to three years, then you can make a substantial differences in diabetes. After all, in 1992, diabetes cost the American taxpayer $100 billion a year just in that year alone. Anything that delays the development of that disease obviously is going to be cost savings and a difference to the individual's health.

Micro albuminuria can be viewed in a very similar way. You've got end stage renal disease, which is a serious outcome. Dr. Brenner has alluded to the cost and the numbers of people with end stage renal disease. Clearly if you can slow down the progression of renal disease even with an ACE inhibitor, then you can make a big impact on the serious outcomes down the line.

And so that's I think the best answer I can give.

ACTING CHAIRMAN CALIFF: Great. All right. Thank you.

Now, Dr. Furberg, if we can ask you to briefly summarize, perhaps even more briefly than you

had planned.

(Laughter.)

ACTING CHAIRMAN CALIFF: Like in about three minutes, if possible.

(Laughter.)

DR. FURBERG: Well, I'll try to be brief.

Members of the panel, ladies and gentlemen, let me just skip the slides. I was going to cover the composition of the experience board, going to comment on the prespecified outcomes and how we focused on the primary outcome, but also on all cause mortality and on safety.

I was going to say that we have adequate power to see meaningful differences in the various subgroups, those with various stages of disease and diabetes ranging from 11 to 16 percent, that before we looked at the data established monitoring boundaries that were really restricted during the first half of the trial, and strictly for benefit than for harm, and that we had planned annual visits.

And here is the experience I ant to spend a little bit of time on. At our first look when we

had less than one year of data, the Z score was 1.1. So nothing too exciting. Almost a year later we had tests, the nominal P value of .05, which was well below the boundary of four. So we decided to take another look a year later, and at that time the Z score was 2.75. We dropped the boundary well below at that time.

And we made some projections. We decided on the next meeting and projected that maybe by a year later it would cross the boundary and be able to stop the study. To our surprise, I mean, in November the Z score had jumped up and reached 4.3, but at that time it was clear that we needed to take some action and stop the study, and that was in November.

The problem we had at that time was that 40 percent of all of the primary events had not been duplicated, and we didn't know how many events were in the pipeline. So we wanted to give the investigator some time to clean up the data, get complete data, do the classification so that the data would generate discussion like you've had today, very clear.

And that's why we gave them a few more

months, and we also asked for some specific analyses and stratified analysis looking at MI by type, stroke by type, et cetera.

Here are the Z scores over time just so that you can see what you lived through for the primary, and the pattern is very consistent. It started off with lower -- low values in the increase. You accumulated more events. The typical pattern for basically all of it, and it's interesting to note that in November '97 for some of these maybe we're around two and a half. All cause mortality was just one and a half.

So I don't think we had any problem saying let's go for another year, and that's when we got these fairly striking results and took the action that I had talked about, but the subgroup -- I think this is important -- has not maybe -- should even receive more attention. The two major subgroups, patients with vascular disease of various kinds and the diabetics, and again, the pattern is fairly striking here, the marked increase over time and with Z scores well over four for the larger group with vascular

disease and three and a half for the diabetics.

We noted at that time while it didn't affect the monitoring that the benefit was primarily in the older people in men, and the fact that we extended -- the study went to March mean that a few of these now reached nominal significance.

We were not concerned about safety at all. ACE inhibitor is well established, and we saw a fourfold increase in cough, and it led to discontinuation of treatment, and as you've talked about earlier, some cases of angioedema, nothing beyond what we expected. So safety was never an issue.

I think it's important to get back to the bigger picture. We had a good discussion today and really considered the primary outcome, and I would like to sort in closing to make some comments as a person who had no involvement in the conduct and analyses of the data.

The public health implications are substantial. The reduction we see here and for the major outcome of 22 percent with a remarkable P value

is similar to that we've seen with other important interventions, beta blockers, similastaten (phonetic) and pravostaten (phonetic), the statens, and also with aspirin. So they're adding important information from that point of view.

But what's so remarkable about the study is that ramipril was shown to be effective on top of these proven interventions, making, I think, the findings particularly important.

The documented benefit in patients with the various manifestations, the important subgroups, those with vascular manifestations of atherosclerosis in the heart, brain and peripherally, and the diabetics, they all had significant benefits, and I think that's where the importance of the trial lies, is because they extend the potential indications of ramipril to maybe as many as 15 to 20 million Americans, and the absolute benefit, again, as has been pointed out is also substantial.

A reduction of 43 events per 1,000 patients treated for four and a half years is important in the area of prevention, and that

translates as you heard to a number needed to treat of 23, and that number is obviously higher if you include some of the secondary outcomes.

So in summary, and Mr. Chairman, I think HOPE was a very well designed trial with important scientific findings that also had substantial public health importance.

Thank you.

ACTING CHAIRMAN CALIFF: All right. Thank you.

I think it's time now to move to the questions.

DR. TEMPLE: Rob, can I ask one?

ACTING CHAIRMAN CALIFF: Sure.

DR. TEMPLE: I just wanted to ask Curt something.

I mean in some ways the robustness of the findings was something of an accident because instead of stopping it earlier, you didn't really have the overwhelming finding early and then the curve went up.

One of the things we've been suggesting to people is that the monitoring committee only count

mortality, perhaps even total mortality, a more conservative endpoint which means more trials will go longer.

Do you have any thoughts about that? Would you all have felt comfortable operating under that termination rule or wouldn't it have made any difference or did you sort of do that anyway?

DR. FURBERG: I think we do it anyway. As you know, I'm sure we agree on this point. I mean, with my NIH background, total mortality is often the primary outcome. That is always the yardstick, the comparison, and we kept an eye on that, and mortality was lagging a little bit behind the other outcomes.

So by going the other year, I think we got important results on all cause mortality, and it makes me feel much better both in terms of efficacy and safety about the time.

DR. TEMPLE: But your official stopping rules were based on the combined endpoint.

DR. FURBERG: That's correct.

DR. TEMPLE: So it could have been that you would have been confronted with a consideration to

stop it much earlier.

DR. FURBERG: I think that typically you use the primary outcome for your stopping guidelines. These are guidelines only, but we always kept an eye on all cause mortality.

ACTING CHAIRMAN CALIFF: So, Bob, if I interpret your question right, you're saying that you would recommend from the FDA perspective that people not stop for non-fatal endpoints if mortality is not --

DR. TEMPLE: Yeah. Look. Obviously we have no rule or official guidance on this, but you know, endpoints are evanescent. Death is not. You know, you don't have to really worry it's going to go away, and you don't stop a major endeavor prematurely.

But in addition, I have to say having studies go longer has some appeal. First of all, we like easy regulatory decisions than more difficult ones, but I don't want to advertise that.

But you do get to look at subsets. You get to look at all of the people under -- you get tons more information if you can go a little longer.

Obviously there's the ethical difficulty of continuing when you know the answer, and I was just fresh from this recent experience. I was wondering what Curt thought.

ACTING CHAIRMAN CALIFF: Okay.

DR. FURBERG: Well, it was made easy when we had that jump in Z score. If we at the November '98 meeting had a Z score just about three, I think we would have had a lengthy discussion, but it was made easy, and then when mortality passed the -- reached .01, I think it was very clear.

ACTING CHAIRMAN CALIFF: All right. Now, we move into the panel session. As I understand it, everyone who's here on the panel can vote except Dr. Bakris, who is not a special government employee. So you're welcome to participate in the discussion though as we go through the questions.

And I'm going to ask Dr. Lindenfeld to lead the discussion. The first question is: does the HOPE study adequately establish the beneficial effect of ramipril compared to placebo on the combined endpoint of MI, stroke, and death and cardiovascular

causes?

DR. LINDENFELD: Yes, I would say absolutely it does.

ACTING CHAIRMAN CALIFF: Is there any disagreement?

(No response.)

ACTING CHAIRMAN CALIFF: Okay. Well, then we move to 1.1. Does the proposed labeling adequately describe the risk factors of the HOPE study population?

DR. LINDENFELD: Well, I think in general it does. The one concern I still have is as written at least to me this implies that diabetics with a single risk factor, not necessarily with coronary disease, and with any single risk factor the study applies to them, and I'm a little bit concerned that that's not the case here.

Although the trends were suggestive that diabetics without coronary disease had a benefit, many of those probably would be treated anyway. Many of them probably had micro albuminuria as a single risk factor and some with hypertension. So I'm a little

bit more hesitant about the wording of this.

ACTING CHAIRMAN CALIFF: Are there other opinions on this issue?

DR. THADANI: Just one minor point on that with the low exterior levels and divudex (phonetic) because now you've got Jim Fabrils (phonetic) who study very positive in that group, too. I think just a bit of concern, but given the data, it's positive, but perhaps more questions than answers from the studies.

ACTING CHAIRMAN CALIFF: Would you propose a change in the wording of the label, Joann?

DR. LINDENFELD: Well, I might say in patients both diabetic and non-diabetic 55 years or older, and then stop it at coronary disease, stroke, peripheral vascular disease, period.

ACTING CHAIRMAN CALIFF: Would it be safe to say based on the questions that if the HOPE group or the sponsor came up with more analyses that justified the statement about diabetics with one risk factor, I mean, you have some questions, I think. They just hadn't looked at the data now.

DR. LINDENFELD: Yeah, right. I think if we saw the data there where there was significant, sure, we'd add that.

ACTING CHAIRMAN CALIFF: Does anyone else on the panel feel that there's any change needed in the label?

DR. Di MARCO: I don't. I agree completely with Joann. I think one issue one might raise if one were to do the analysis that Joann is suggesting, since the numbers would be relatively small, you know, we've got to consider what the level of significance, of statistical significance would need to be to accept the implications of the diabetics with one risk factor clause.

I mean I don't want to make a concrete suggestion here, but I think that's something that's going to have to be considered in the discussion about the labeling. Small numbers. How compelling do the results have to be to accept the mandate that would be implicit in this label?

DR. PINA: It might be difficult -- correct me if I misinterpret it -- but that it was not

-- the P value was greater than .05 in diabetics without cardiovascular disease. So it wouldn't even meet the .05 criteria.

ACTING CHAIRMAN CALIFF: But it is a subgroup with trending in the same direction as the overall study.

DR. PINA: Right, right.

ACTING CHAIRMAN CALIFF: Well, maybe at this point, the question 1.2 actually raised looks a little bit tricky to me. Does the proposed label have what we describe the characteristics of the population that should be treated -- underline the word "should." So maybe we could go ahead and vote on the main Question 1.

I'm assuming this will be quick based on the fact that no one had discussion.

DR. TEMPLE: Yeah, Rob, I have a question. The wording in the indication section is written the way we usually write combined endpoint wording, and it says "or." That is, myocardial infarction, stroke, or death. Is that what people mean, or do they believe as Salim did that it, in fact, has shown an effect on

each of those, in which case you would write it differently?

You might start with "and." I would put an "of" in front of each one to make it clear if I wanted to convey that impression. Do you see what I mean?

ACTING CHAIRMAN CALIFF: Yes. I think that's a good question.

Joann, the question is: are you convinced that an individual effect was shown on each component?

DR. LINDENFELD: Yes.

DR. LIPICKY: That's sort of part of 1.3.

ACTING CHAIRMAN CALIFF: Well, I interpreted 1.3 to be a different question.

DR. LIPICKY: Well, okay. Then it was poorly written.

(Laughter.)

DR. LIPICKY: But, in fact, that discussion would appear if one started to add things that were not part of the combined endpoint. Okay? So that really is part of 1.3, and right now I think all one is talking about is if one defines the

population the way in which it was defined in the protocol, is that sufficient, and that's one to describe it in the indications, and secondly, if that's how it's described in the indications, you'd think people like that should be treated.

So those are the questions that are being discussed now.

DR. TEMPLE: Ray, I was asking about the endpoint, not the population.

DR. LIPICKY: Well, but we're talking about the population now.

DR. TEMPLE: I know. I was trying to go back to the first question.

ACTING CHAIRMAN CALIFF: Well, let me try -- well, all right. So let's go back to the main Question 1, and the question there is for the components of the composite, MI, stroke, and death from cardiovascular causes.

Are we convinced there is an effect on each of those endpoints?

DR. LINDENFELD: I was convinced there was an effect on each one.

ACTING CHAIRMAN CALIFF: Tom? As the panel statistician, do you have a comment on that?

DR. FLEMING: The much easier question to answer is the one that have answered all unanimously positively, and that was what was the study designed to address as its primary goal, and that was the composite endpoint, and did it achieve that, and the answer is, yes, it did, and in fact, as Curt showed, with one chance in a half a million. Five hundred thousand to one is the P value.

We have also, because of the robustness of that result, seen that when you split this in innumerable ways you get, because of the compellingness of the result, which is what Bob Temple was saying, it's nice when your study can go that long so that you can get such a compelling result, so that when you split it in so many different ways, it's still convincing.

We never gave the same level of rigorous inquiry to the individual components. I don't know the answer. I certainly am more inclined to think that those individual components have been established

than I am for mortality, which is an 05, which is a 200 to one or 2,500-fold more convincing is the composite endpoint than mortality, and mortality is secondary and the composite was primary.

And I haven't looked in subgroups, and I don't know what happens when we look in the U.S. or in the non-Canadian setting, and is at least the point estimate consistent for mortality?

Now, you're asking, and I see some were in between my reluctance to say mortality has been shown and my complete acceptance at the composite endpoint has been shown. Somewhat in between you're asking Rob has the individual components of the composite been shown.

Is this a question that we have to answer? Can the labeling essentially reflect that the study established compelling evidence of benefit on this composite with these three components?

ACTING CHAIRMAN CALIFF: Well, I think, Bob, if I --

DR. TEMPLE: It could, but that's not nearly as good as telling people who happened if

that's not the only thing you can conclude. That's why -- I mean you're right. The other question is easier. The P value is as long as your arm, but this is still a relevant question. Was there a mortality effect or was there a stroke factor?

DR. FLEMING: Yeah. The mortality question I'm more concerned about than the individual component question. The mortality question, because of the incredible importance of mortality and the fact that it is the least compelling of the five things, the composite, the three components of the composite, and mortality; mortality is the least compelling, and data has not been presented to us to look at how robust the mortality result is.

We don't even know what the result point estimate is in the U.S. or in the non-Canadian setting. So it seems to me we have focused, as makes sense, on, as Salim keeps telling us to: focus on what you said you would do as the primary endpoint, and that has been compelling.

DR. TEMPLE: No matter what the results, once you've set up --

DR. FLEMING: No, not true, not true, but what I'm saying is at least as so far as mortality is concerned, if we wanted to conclude that we have established with this one study on a secondary measure mortality as having been convincing, I would have wanted to have had more insight presented to us today about what the mortality results show, in the same way that we spent an enormous time spending -- looking at what the composite results show.

DR. TEMPLE: Tom, let me be clear. The cardiovascular death significance level is .0002, and overall mortality, which is obviously a compromise measure since half of the deaths aren't affectable, was significant nominally at .005.

DR. FLEMING: Right, right. Twenty-five times less convincing.

DR. TEMPLE: I guess to me I contrast this with our usual use of combined endpoints where we just throw the three out together and somewhere in clinical pharmacology can find out what actually happened to each of them, but in some ways that doesn't seem as satisfactory if you don't have to do it.

So I'm pressing you on this because it seems to me if there were a good basis for it, you'd like the label to give all of the things that were reasonably likely to have been found.

ACTING CHAIRMAN CALIFF: Tom, I want to press on you a little bit, too, on this because, you know, I'm consistently finding as I'm a guest panelists on other groups that 90 percent of clinicians can't deal with saying the composite was different. They always want to know the individual.

And most patients, if you say this prevents death, stroke or heart attack, may say, "Well, what does it do to stroke?" and you say, "Well, we can't say," that's a problem.

And this is a trial that's, I think, so robust. I mean we rarely get a .005 for cardiovascular death, and here we have it for all cause mortality.

DR. FLEMING: I understand, and your question is?

ACTING CHAIRMAN CALIFF: Why is .005 not persuasive to you? You say you want to know the North

American or U.S. results. I'm surprised.

DR. FLEMING: Well, .005, this is very important, but nevertheless a secondary endpoint, a single study. Traditionally we would have assumed if this was the primary endpoint in a single study the general guideline, and it's only a guideline, would be .025, and is how many -- I mean, one of the reasons that to me this single study carries the day is the overwhelming evidence that it provides on the composite endpoint, which was the primary endpoint.

And yet we still spent a considerable amount of time dissecting this in many different ways to understand strength of evidence, and I'm suggesting that on a secondary measure whose strength of measure is 2,500-fold less, that we haven't even been shown what these patterns are for consistency of effects on mortality over various subgroups.

If we wanted to answer this question, shouldn't we have seen more of the evidence on mortality, which would have been a much less obvious answer than the composite endpoint. My sense is the composite endpoint is absolutely shown, and there is

potentially enough evidence to even say that the individual components have been shown. I'm not sure that the distinction between those two is so important, but the distinction with overall mortality is important.

And we've understood that we didn't expect to have effects on non-cardiovascular mortality, and the study properly showed us, the investigators properly showed us that we didn't have an adverse effect, but in fact, it certainly did, as you would expect, dilute the overall strength of evidence, and that strength of evidence is on the margin I'm saying for what I would have typically expected we would have looked at even if it was a single study as the primary endpoint. This is a secondary endpoint.

ACTING CHAIRMAN CALIFF: Ray, you had your hand raised?

DR. LIPICKY: Well, no. I can't say it better than Tom. I just want to support him.

ACTING CHAIRMAN CALIFF: Are there other views?

DR. THADANI: I think it's important. You

know, the composite endpoint is positive, and as Tom has said, why we have to say that mortality went down with the composite endpoint is clear. They're all hard endpoints. There's no ischemia driven endpoint here.

So I think directing that, myocardial infarction and stroke, which matter a lot, so why do you want -- perhaps one important area, you could give a table how each contribution was rather than mentioning in words, just give the numbers. What were the mortality, the morality at each point? Could you add that?

DR. FLEMING: The three components were not overall mortality, stroke, and myocardial infarction. They were cardiovascular mortality, stroke, and myocardial infarction. Cardiovascular mortality is significant at, you know, .0001, which makes most people's test for robustness, at least compared to anything else we've ever seen.

I guess I want to throw something out because this comes up a lot. I think in a trial where there are a lot of noncardiovascular deaths, total

mortality is a robustness test. It may or may not, however, be the best description of what the drug did.

The fact that a total mortality still comes out favorable makes you feel you haven't lost any -- there's nothing weird going on, and that's all to the good, but we already know this drug isn't going to interfere with death due to cancer. We don't expect it to.

So I would argue that at least in some of these cases, the best measure of what the drug did is, in fact, cardiovascular mortality.

In any case, this seems the one thing I do think is that you want to tell people as much as you responsibly can and not let them guess about what the combined endpoint means. We use combined endpoints as something we have to do to get enough endpoints, but it's quite undesirable. You'd rather know the answer for each of them. That's a second best approach which you usually have to take because there aren't enough endpoints.

Here, for better or worse, there were lots of endpoints.

ACTING CHAIRMAN CALIFF: John, you had a comment?

DR. GRABOYS: Just a comment. The nice thing about total mortality though is that you don't have to worry about adjudication then, and I think of reasons why, you know, people with pneumonia, if they've had a prior infarct or if they've had renal failure might do less well, and so the fact that total mortality doesn't move in the wrong direction takes away a lot of the uncertainty, and so I like that.

And the cardiovascular mortality is very strong. So I think that those very hard endpoints are good.

I'm a little uncomfortable about the myocardial infarction because of the way it was -- in the fatal events at least it covered a lot of things.

DR. TEMPLE: But that finding is not the fatal events. It's the non-fatal events.

DR. GRABOYS: Yeah.

DR. TEMPLE: The fatal ones are already in the test.

ACTING CHAIRMAN CALIFF: Are there more

comments on --

DR. THADANI: Yeah. Even on the cardiovascular mortality, there are patients who died off a pulmonary embolism, which one presumes had nothing to do with it. I've got some patients have died.

PARTICIPANT: (Inaudible.)

DR. THADANI: I realize that. So, again, that's the trouble with the cardiovascular mortality. They're encountered in that. So I think total mortality is a better endpoint than dissecting everything else out.

DR. PINA: Rob, are you asking for comments beyond the mortality issue or are you back into the statement here toward the bottom?

ACTING CHAIRMAN CALIFF: I'll entertain anything on Question 1 now you want to comment on because we're about to close it out.

DR. PINA: Right. I have a problem in the last sentence with the secondary endpoint of heart failure because that was not a prespecified secondary endpoint.

ACTING CHAIRMAN CALIFF: Oh, we're going to get to that. That's Question 9.

By the way, Question 9 is the last one in case you don't have it in front of you.

DR. PINA: Right.

ACTING CHAIRMAN CALIFF: We need to discuss 1.2 just for a minute. Does the proposed labeling adequately describe the characteristics of the population that should be treated?

Now, Ray, I thought that our job was not to define who should be treated. That's the doctor's job.

DR. LIPICKY: Yeah, that's okay, and that's a perfectly good answer. That means that then the people who are described as having been enrolled in the trial will sound like they should be treated, and the question was meant to just see whether you had any problem with that, and if you don't that's okay.

ACTING CHAIRMAN CALIFF: Okay. So that would roughly be the same as Question 1.1 then.

DR. THADANI: Rob, on that issue, a patient who was diabetic in one respect or

hypertension, the new guidelines would suggest that one should lower the blood pressure to below 130 or 120, and one of the difficulties you might run into, I don't know what this drug will do if you follow that correctly here, too.

So are you concerned at all or are the panel concerned that that -- you find the therapy? Because one possibility, you would just stop with this, but I understand the recommendation now is to lower the pressure to 120 or 130 in those patients. And would this probably still hold?

DR. TEMPLE: The way it's written now, it lists as the people who should be treated -- and make no mistake. Labeling does suggest who should be treated. It doesn't command it, but it suggest is -- is the exact people who were in the study. That's what all those listings of factors are.

That isn't the only thing one could do. One could say it's for people at high risk of coronary artery disease and here's what we mean, or of these events, and here's what we mean by that, which is a somewhat more flexible definition, and I think one has

some choice there.

ACTING CHAIRMAN CALIFF: Okay.

DR. LIPICKY: Maybe the right way to think about the answer to these questions, the 1.1 and 1.2, is that if one thinks one needs a lot of words written in parentheses or two or three more sentences that describe the patients, if that would help any, or if the few words or the one sentence that reasonably reflects the population randomized is sufficient, I think that maybe is what those were getting at.

ACTING CHAIRMAN CALIFF: Right.

DR. LIPICKY: Because, clearly, we could write a textbook on, you know, what this is all about and how you tell whether there's coronary artery disease and how you know the EST segment.

ACTING CHAIRMAN CALIFF: Yeah, my sense of the panel is that people are pretty happy with the way it's written except for the question of the people with diabetes, and one risk factor is how robust that population is.

And I think the concern, if I'm sensing the panel, is that that's a huge population. This is

one study and sort of the first time out of the box with it. So --

DR. LIPICKY: But the primary endpoint is met.

ACTING CHAIRMAN CALIFF: Yeah, the primary endpoint was met.

DR. LIPICKY: Rather adequately, right?

ACTING CHAIRMAN CALIFF: Quite adequately. No question about that. It was met, and so what I'd like to do is just to move to a formal vote on Question 1, and then we'll quickly vote on 1.1, 1.2, and 1.3 so people can formally express their opinion on it.

Does the HOPE study adequately establish the beneficial effect of ramipril compared to placebo in the combined endpoint of MI, stroke, and death?

If we could just start at the right-hand side.

DR. MOLITCH: Yes.

DR. GRABOYS: Yes.

DR. PINA: Yes.

DR. Di MARCO: Yes.

ACTING CHAIRMAN CALIFF: Yes.

DR. BORER: Yes.

DR. LINDENFELD: Yes.

DR. ARMSTRONG: Yes.

DR. FLEMING: Yes.

DR. THADANI: Yes.

ACTING CHAIRMAN CALIFF: This is a first for me, I think, on this panel, a unanimous vote.

(Laughter.)

PARTICIPANT: Six zeros in front of the one will do that.

ACTING CHAIRMAN CALIFF: Now, I think we can combine 1.1 and 1.2, and I think the primary proposition is that the labeling, which describes the population enrolled in the trial, is adequate and the reasoning being that the primary endpoint was met for the subgroups that we've discussed.

So if we could take a vote on that.

Yes?

DR. MOLITCH: Sorry, Rob. One question. Is this what we have here in front of us or what was shown up on the slide, which I think included all

cause morality?

ACTING CHAIRMAN CALIFF: This is -- until we get to 1.3, this pertains only to the primary composite endpoint.

DR. MOLITCH: Okay.

ACTING CHAIRMAN CALIFF: And you can go ahead and start with your vote.

DR. ARMSTRONG: Can I just ask, Rob, before?

ACTING CHAIRMAN CALIFF: Yes, sir.

DR. ARMSTRONG: On 1.2 are we talking then about the preselected secondary endpoints in the context of this question? Is that right?

ACTING CHAIRMAN CALIFF: No. We're only talking about it with regard to the primary endpoint.

DR. ARMSTRONG: Sorry. Okay.

DR. GRABOYS: Yes.

MR. MOLITCH: Yes.

DR. PINA: Yes.

DR. Di MARCO: Yes.

ACTING CHAIRMAN CALIFF: Yes.

DR. BORER: No.

ACTING CHAIRMAN CALIFF: Could I -- yeah, just comment.

DR. BORER: Yeah. Before I could accept this, I would want to see the data on what appears to have been a very small group of patients who had diabetes and only one risk factor.

DR. LINDENFELD: No for the same reason.

DR. ARMSTRONG: Yes.

DR. FLEMING: Yes.

DR. THADANI: Yes.

ACTING CHAIRMAN CALIFF: Okay. So I'm sure that there will be an opportunity for the sponsor to bring back more data regarding that subpopulation, although the panel vote is clearly in favor also.

Now, 1.3, should all cause mortality be included in the indications portion of the labeling?

DR. MOLITCH: No.

DR. GRABOYS: Yes.

DR. PINA: No.

DR. Di MARCO: Yes.

ACTING CHAIRMAN CALIFF: Yes.

DR. BORER: Yes.

DR. LINDENFELD: Yes.

DR. ARMSTRONG: Yes.

DR. FLEMING: No.

DR. THADANI: No.

ACTING CHAIRMAN CALIFF: What was the final vote there? Six yes, four no. So --

DR. TEMPLE: Rob, that was all cause mortality as distinct from cardiovascular mortality.

ACTING CHAIRMAN CALIFF: Yes.

DR. TEMPLE: How did we understand? Is that right?

ACTING CHAIRMAN CALIFF: That was all cause mortality, correct.

Okay. So we now move on to Question 2.

DR. TEMPLE: Well, before you leave, can I ask a question? If you had a drug that unequivocally reduced cardiovascular mortality and carried along the rest of the death, would that lead you to say there's an effect on all cause mortality or on cardiovascular mortality, or maybe that's what that vote just told us? I don't know.

ACTING CHAIRMAN CALIFF: I'm not sure the

vote exactly addressed that, but I would certainly feel that if all cause mortality is reduced, that trumps everything else, and for what John said. I have -- and you're an expert in this. I think your career in a way started with an investigation of all cause.

DR. TEMPLE: Oh, no, that was highly cause specific. Cardiovascular mortality in the entry in reinfarction trial was just fine. There was only one noncardiovascular death. So it was not a big issue.

ACTING CHAIRMAN CALIFF: Okay.

DR. TEMPLE: Cause specific mortality is a whole different thing, I think.

ACTING CHAIRMAN CALIFF: You know, personally I'm not very interested in cause specific mortality except as an interesting scientific question. I mean as a patient, I really care about whether I'm dead or alive. So --

(Laughter.)

DR. TEMPLE: Yeah.

ACTING CHAIRMAN CALIFF: If I'm dead, I'm not going to ask what I died from.

DR. TEMPLE: But my reasons for asking is that it seems somewhat misleading to me to suggest that you have an effect on all causes of death, which is one way to read that, when in fact you're only having an effect on one part.

Certainly all cause mortality needs to be in the labeling somewhere so that people know it happened. That's not the debate. It's what the indication should be.

DR. Di MARCO: But you could just say "mortality."

DR. TEMPLE: You could, but it worries me as being somewhat misleading for the same reason. All of the effects on one kind of death, it doesn't affect cancer. There were equal numbers of cancer death. So it sound like it sort of captures that, too, which is not what one wants.

ACTING CHAIRMAN CALIFF: But you appear to have a lot more faith in classification of cause of death. I have -- I think it's rubbish for the most part, and so, you know, I would see --

DR. TEMPLE: Even cancer versus

cardiovascular?

ACTING CHAIRMAN CALIFF: People with cancer have thrombogenic substrate and are more likely to have clotting related causes of death. I mean, there are now clear data showing that if you have cancer and you have coronary disease, your risk of dying of coronary disease is higher.

DR. TEMPLE: The observation here that the noncardiovascular deaths tend to be equally distributed even though you've had a profound effect on cardiovascular death is a fairly consistent finding. So I'm sure there's an error rate. I have no doubt about that at all, but I think it's probably trumped by a substantially accurate measure.

Okay. Well, I just wanted to hear what you thought.

ACTING CHAIRMAN CALIFF: Okay. Question 2, and this is an interesting question. Were there differences in the primary endpoint with respect to, first the easy one, gender?

Joann?

DR. LINDENFELD: No differences.

ACTING CHAIRMAN CALIFF: Any disagreement with that?

(No response.)

ACTING CHAIRMAN CALIFF: Now we get to another easy one, age.

DR. LINDENFELD: Again, no differences.

ACTING CHAIRMAN CALIFF: Now we get to a not so easy one, race.

DR. LINDENFELD: Well, race is very difficult because, again, the numbers were so small I don't think that we can tell if there's a difference or not.

ACTING CHAIRMAN CALIFF: Any further comments on the race issue?

DR. THADANI: The race issue is worrisome. I realize the sample size is very small. Given the ACE inhibitor data and hypertension, I realize there's no uniformity, but all our response, that might be lower. It would be nice to be sure that it works in all across. It's not the problem with the investigator. I think they're separately very small, but especially in blacks and Asians there might be

concern. We might be giving a therapy which may not benefit, and one may forget about therapies which by reflector say take a patient with diabetes who also has hypertension. Maybe diuretics might save their lives, and we might be giving the wrong drug which may have no impact.

So I think I have big concerns on that.

ACTING CHAIRMAN CALIFF: Dr. Borer?

DR. BORER: Yeah. I have concerns about this not because the populations are so small, because a lot of the other subpopulations are small, too, but because the apparent discrepancy that we see, small subpopulations notwithstanding, intuitively has potential biological basis, and therefore, I think that it would be important at least somewhere in the label to reflect the fact that this discrepancy exits.

I don't know that you can make anything more of it than that, but certainly prescribers ought to be aware that this is an unresolved discrepancy because it's not -- and the reason I'm concerned about it, again, is not just small numbers so that we can't make a statement, but rather because there is a