about the appropriate use of omapatrilat. Unit-of-use packaging will reinforce key risk messages, and the plan includes a novel and mandatory risk counseling program for patients.

A post-marketing surveillance plan would include a prospective observational cohort study and a plan for ongoing assessment of program effectiveness, including the use of an expert panel. We're also committed to providing extensive pre- and post-marketing testing of risk message comprehension and are confident that the proposed plan would be effective in minimizing the risk of life-threatening angioedema.

At this point, I'd like to make a few comments on benefit-risk. In general, the target population proposed for this drug would include those identified by the WHO IHS classification system as being at very high risk for cardiovascular disease or at high risk for cardiovascular disease, with an absolute risk of major cardiovascular events of at least 2 to 3 percent per annum and perhaps higher.

In these patients, a greater reduction in blood pressure by 3 over 2 millimeters of mercury, such as that observed with omapatrilat relative to enalapril in OCTAVE, would be projected to be associated with a 10 percent relative risk reduction, which would correlate to the

reduction of 20 to 30 major cardiovascular events per 10,000 treated per year. A greater reduction in blood pressure by 5 over 3 millimeters of mercury, such as that observed with omapatrilat over other agents in other studies would be associated with at least a 15 percent relative risk reduction, which correlates to a reduction in 30 to 45 major cardiovascular events per 10,000 patients treated per year. As I've described, the observed incidence of angioedema with airway compromise over 24 weeks in OCTAVE was 1.6 per 10,000, with a 95 percent confidence interval of 0.2 to 5.7.

Now, these observations suggest that at those at high or very high cardiovascular risk, the projected number of life-threatening cardiovascular events prevented would substantially exceed the number of life-threatening angioedema events caused by at least an order of magnitude and perhaps more. If one takes the worst case estimate, the upper bound of the 95 percent confidence interval, as the basis for comparison, the benefit-risk relationship is still favorable.

Special consideration needs to be given to black patients and to current smokers as the overall risk of angioedema is higher in these patients. While BMS recognizes the increased risk in these patients and recommends that omapatrilat be used with special caution,

we believe that carefully selected black patients and current smokers may benefit from omapatrilat treatment.

To conclude, in patients at high risk for cardiovascular events, the number of major cardiovascular events prevented would be projected to exceed the number of life-threatening angioedema events caused by at least an order of magnitude and possibly much more.

Now, when projecting cardiovascular benefit based on blood pressure reduction, there may be a concern about any unintended cardiovascular consequences of the therapy which could undermine or diminish the benefit. In this regard, I'd like to introduce Dr. Packer to review available CV event data with omapatrilat.

DR. BORER: Let's hold that just for a second, if we can. First of all, we're going to want to ask you some questions before we hear from Milton about heart failure. But it is 10:13 and 32 seconds, not by the satellite, and we'll take a break until 10:25 right now and then come back, ask you some questions, and then we'll go on with the presentation.

DR. LEVY: Thank you.

(Recess.)

DR. BORER: Before we begin the questions, there are two issues we need to deal with. There were no requests for public comment, but I want to determine that

there is no one here who wants to comment about the issues that we're discussing today.

(No response.)

DR. BORER: If not, one other matter. The statement about Dr. Beverly Lorell's involvement and the reason for her exclusion wasn't really precisely stated. She is one of the principal investigators in the OVERTURE trial. She has no direct financial interest. For reasons of public disclosure, I think it's useful to know that.

Let's go on then with questions about safety. I'd like to begin with a request for clarification on two slides, and then we can get into more substantive safety issues.

Slide number 43. The issue here is that the female patient is listed as having become hypotensive. Can you give us a little bit of detail here? How hypotensive? Was this a clinically evident problem or did somebody measure a low blood pressure and record the patient as being hypotensive? What happened there?

DR. LEVY: She lost consciousness and didn't have a measurable blood pressure, and with an initial epinephrine injection, she regained consciousness. She received a second subcutaneous epinephrine injection, and over about 3 to 5 minutes, she regained a blood pressure of 110.

DR. BORER: This was not presumably -- or was it -- one of the patients who would have been your high-risk groups that's being targeted for the drug in the proposed labeling, or in your proposal I mean.

DR. LEVY: No, she wouldn't have been.

DR. BORER: Just for my information, were there other patients who developed hypotension or lost consciousness with the drug?

DR. LEVY: The rate of hypotension was extremely low with the drug. It was on the order of a 10th of a percent of all patients.

DR. BORER: And how did that compare with the comparator?

DR. LEVY: They were very similar.

DR. BORER: And then a comment more than a question. The risk factors that you defined in your last slide included seasonal allergies. Now, that's not overwhelmingly surprising, but a little surprising in view of the information that Dr. Kaplan gave us. I don't expect that you could possibly have an explanation for it, but it suggests that the biology we're dealing with here is more complex than perhaps we fully understand at this point. Is there any comment you want to make about --

DR. LEVY: Can I have that slide again?

DR. BORER: And perhaps Dr. Kaplan wants to

comment on it.

DR. LEVY: As I mentioned, there was a prior hypothesis, a relatively strong one, regarding black race based on both our experience and --

DR. BORER: I'm specifically talking about seasonal allergies.

DR. LEVY: Right, I understand. My point is that there was no prior hypothesis for seasonal allergies, nor was there a reason to believe that this would be identified as a risk factor. We looked at a wide variety of characteristics and showed these modest changes, increases or decreases, in risk in some. The information that's reported here makes no attempt to correct for multiplicity of analyses. The confidence intervals are nominal, 95 percent confidence intervals. And in the absence of some pathophysiologic rationale or prior hypothesis, this should really be regarded as hypothesis-generating.

I'll ask Dr. Kaplan to comment on it, if he would.

DR. KAPLAN: I think in terms of the issues there in terms of where the relative risk was higher or lower, I don't think I could have predicted any one of them in particular. The incidence, if you look at the seasonal allergies, was a little bit higher, but I don't know I

could have related the two or necessarily predicted that the risk would be somewhat higher.

Female gender. The incidence of angioedema, irrespective of cause, is higher in women. That might be consistent with it.

Nor could I tell you why somebody with diabetes or atherosclerosis would have lesser risk. So, I can't help much with the way those data came out in terms of what we know or what we could have predicted.

The only possible one would be in terms of blacks perhaps having more risk for angioedema. The only data related to that is responsiveness to intradermal bradykinin seems to be heightened blacks. Therefore, they may have end organ responsiveness that's a little bit higher than caucasians, and that would predispose to more angioedema.

DR. BORER: Thank you.

Tom, do you have any specific safety issues before we go on to Susanna and to Steve?

DR. PICKERING: Well, there are some questions I'd like to ask relating to the generalizability of the findings and the OCTAVE design.

I wonder if you could tell us a bit more about how the centers were selected. I believe there was something about being close to a major medical center.

Also, were any of the episodes occurring during the first 2 hours while the patient was still in the hospital setting? And finally, what information was given to the patients about the risks and symptoms that they might expect?

DR. LEVY: Well, those are very good questions. The first question regarding selection of study centers, this is an enormous trial with 3,300 centers in 12 countries. They represent both experienced clinical trialists as well as physicians skilled in the treatment of hypertension, but without prior experience in clinical trials. The issue you've just cited, in prequalifying we did require that they be within 1 hour of a medical facility with resuscitation equipment.

Your last question, if I could ask you to restate it.

DR. PICKERING: What information were the patients given about expected symptoms or side effects?

DR. LEVY: Patients were provided with a detailed informed consent, and that informed consent described the phenomenon of angioedema, swelling of the anatomic sites, provided rather detailed information about the quantitative risk of angioedema, as it was known at the time so they could evaluate the risk of study participation, and concluded with a sentence instructing

them to seek medical attention should it occur. It's very consistent with what's done in trials. We propose in our risk management program a level of patient education that goes very far beyond that.

DR. PICKERING: The third part of the question was relating to episodes during the first 2 hours after the dose.

DR. LEVY: Yes. As I showed you, a total of 88 episodes occurred on the first day of treatment. 56 of those occurred within 2 hours of administration of the first dose.

DR. BORER: Susanna.

DR. CUNNINGHAM: You've defined the target population that you anticipate using this drug in. I want to know what percentage of that target population is African American, what percent are current smokers, have renal disease, seasonal allergies, et cetera. So, what's the risk profile going to look like in your defined high risk population?

DR. LEVY: I can certainly refer you to the trial data. Those are excellent questions.

For instance, overall, 10 percent of subjects in the study were black, 13 percent of those with diabetes were black. So, there is some association, but overall, the vast majority of patients with diabetes who would be

candidates for the drug are not black.

Prevalence of smoking overall in the study was about 18 percent, and it was fairly consistent across all study subgroups, including those that we've identified as potential target populations for the drug.

So, I guess the short answer is that blacks would probably be represented somewhere between 10 to 13 percent in the potential target population, perhaps a little bit greater than their overall prevalence in the population, and smoking probably around 18 percent.

DR. CUNNINGHAM: And how about those other potential new risk factors that we don't know for sure about, the other ones, the seasonal allergies, the former smokers?

DR. LEVY: The population is 51 percent women; former smokers, maybe another 20 percent. Again, those are characteristics that are, at this point, hypothesis-generating associated with small differences in risk.

DR. BORER: Blase.

DR. CARABELLO: You indicated the proportion of patients that developed angioedema at which dose and that it was much higher at 20 milligrams than at 10. But of the patients that developed angioedema, how many did not have it at lower doses and then subsequently developed it as the dose was up-titrated?

DR. LEVY: Well, it's a great question, general question about the dose relationship of angioedema. This study, of course, was not designed to really characterize the relationship of incidence to dose. You'd need a true parallel group study to do that, in which patients started off at each dose and were titrated upwards, so you didn't filter people.

What we saw is that over time the incidence of angioedema decreased despite the up-titration of patients to higher levels of drug. But there were a significant proportions of patients who did develop angioedema on 80 milligrams, having tolerated 10, 20, 40 milligrams.

DR. BORER: Steve.

DR. NISSEN: I want to explore one of the principal hypotheses of the trial which was that by starting at a low dose and then gradually working our way up, that we could avoid the more catastrophic problems. It's difficult to answer that question obviously because the way that the angioedema was adjudicated is different in the two trials, but help me a little bit, if you will.

The raw rate of angioedema in percent in the pre-OCTAVE trials I have at about 1.96 percent. Do you agree with that? It looks like angioedema 1.03 and then head and neck edema, another .93. So, your slide number 36 would suggest that the rate of was around 1.96 percent pre-

OCTAVE. Is that right?

DR. LEVY: Well, we didn't know exactly what it was pre-OCTAVE because not all those head and neck edema cases were angioedema, and conversely, there might have been other events that were called allergic reactions that were angioedema. But to the best of our knowledge, that's a reasonable, very rough estimate.

DR. NISSEN: Do you think that's a high estimate?

DR. LEVY: If we knew exactly what the incidence was before OCTAVE, we wouldn't have done OCTAVE. I think it's a reasonable rough estimate.

DR. NISSEN: All right.

And then in OCTAVE, the rate was 2.17 percent. So, again, obviously there's an issue here, but it looks to me like the actual incidence, about 1 in 50 patients pre-OCTAVE had angioedema and about 1 in 50 patients in OCTAVE had angioedema. So, it looks like the strategy of starting low and working up may not have been effective. Is that a reasonable assumption?

DR. LEVY: I think that's quite possible. Just bear in mind that the study wasn't designed to compare 10 and 20 milligram doses. There's an enormous difference in the way in which physicians were solicited to provide angioedema reports in OCTAVE. We know from other trials,

like the SOLVD trial, what when you ask physicians to report this event, the reporting rate goes up dramatically.

DR. NISSEN: Yes. The reason I think it's relevant is that there was a difference in the number of very severe cases pre-OCTAVE and in OCTAVE. But because those numbers are so small, the confidence intervals are quite wide. So, I wanted to go back and look just at the raw rates of any angioedema to get a sense for whether the strategy of starting low would be protective or not. To me, there doesn't look like there's any evidence that that strategy is going to work in protecting patients, at least not from what we can see in the data.

Now, just before we broke, you said that you thought that this drug would be acceptable in smokers and blacks. The word you used is you said in "selected" smokers and blacks. What I guess I would like to know is how are we to select those people. The incidence was about 1 in 18 or 1 in 19 in blacks. So, what criteria should I use to select those African American patients that can successfully be given omapatrilat?

DR. LEVY: They would be patients with very high cardiovascular risk and hypertension that can't be controlled with existing medications.

DR. NISSEN: But that's the same criteria you told us for the rest of the population. So, you'd apply

the same criteria to the African Americans that you would to the non-African Americans.

DR. LEVY: The same principles, but one might set the bar higher.

DR. NISSEN: All right, fair enough.

Now, I guess I had a question for Mike Weber because you obviously spend your life treating this, and I know you deal with this. The issue relates to compliance in a clinical trial versus compliance in practice. In the great State or country of Brooklyn --

(Laughter.)

DR. NISSEN: -- what are compliance rates like?

DR. BORER: Tread lightly there.

(Laughter.)

DR. NISSEN: As we know from those who live in the great State of Manhattan.

(Laughter.)

DR. NISSEN: But what are compliance rates like among populations with severe hypertension in your setting?

DR. WEBER: Well, as you know, Steve, the largest population group by far in our setting happens to be African American or Caribbean American. They do actually extraordinarily well with hypertension treatment because the African American community is, in fact, highly educated about hypertension and takes it very seriously.

In fact, even if you look at NHANES data, there is a suggestion that blacks overall have very comparable adherence to treatment as compared with non-blacks.

So, I would say compliance is good. Now, what do I mean by good? I would say that about 50 percent of patients who start on a medication are still taking it about 6 months later or taking some sort of appropriate treatment 6 months later.

DR. NISSEN: How frequently, in your experience, do patients miss a few doses, skip a weekend, go off somewhere, and stop the medication, and then restart it again?

DR. WEBER: I would say about 70-75 percent of hypertensive patients make those sorts of errors or omissions.

DR. NISSEN: The reason I get to that is because I'm worried about a risk here, and the risk is you've titrated somebody up to 80 milligrams of omapatrilat. They take a long weekend with their spouse somewhere and they forget to take their medicines with them. They've been off the drug for three or four days. They come back home and they restart it. I'm trying to assess what the risk is going to be in clinical practice compared to the risk in a clinical trial. So, I need your thoughts about that.

DR. WEBER: Well, it is going to happen and it does happen all the time in clinical trials as well as in regular clinical practice. So, we do know that starting almost de novo on an extraordinarily high dose of a treatment, omapatrilat or anything else, is happening all the time, presumably with relatively little side effects or adverse effects that we are aware of.

We had quite a few people in the early omapatrilat experience who, in fact, did start directly on higher doses or were accelerated quite quickly to higher doses in the parallel group studies, and to the best of my knowledge, with the exception of some people who had some hypotension -- and there were not many of those -- in fact, it was pretty well tolerated.

DR. NISSEN: But you made the case that the incidence of those severe cases was worse in the pre-OCTAVE experience, and the suggestion is here that we can prevent those. I guess I'm worried here that in the general population where people start and stop drug, that the risk of somebody being off the drug for a few days and then going back to an 80 milligram dose might be pretty significant over a period of years. See, the question is whether the risk of angioedema is going to tail off with time and kind of get vanishingly small or whether we're going to see year after year an ongoing risk of this. And

that relates to whether intermittent therapy is likely I think.

DR. WEBER: I don't think there's an answer to that question, Steve.

DR. LEVY: I might just provide a few facts from the trial that you might find helpful. We did ask patients at each visit if they had been compliant with medications. Compliance was defined essentially as taking at least two-thirds of their prescribed medication from the previous visit, and at each visit about 3 percent of patients admitted that they hadn't been compliant, which is a small number, but it's still 300 to 400 patients at each visit on omapatrilat who admitted they had missed at least a third of their medication from the previous visit.

We very carefully characterized dose interruptions in subjects who developed angioedema, and we found 3 subjects who developed what was essentially mild angioedema following a period of dose interruption. So, there certainly is no signal that there's an increased risk in patients who take their drug intermittently.

DR. NISSEN: The reason I ask is one of your really bad cases was a patient that missed a dose. One of your severe cases of angioedema in the database that I reviewed, the patient took a dose about 8 hours late and immediately got into trouble. I can refer you to that.

DR. LEVY: No. That is the subject in OCTAVE. She typically took her dose at 8:00 in the morning. She reported she took it at 4:00 that afternoon instead. I think given the half-life of the drug, 14 to 19 hours, it would be difficult to link those two.

DR. NISSEN: A second question I guess relates to how to assess the risk in general use. I'm sure many other members of the panel have the same concern, that when you administer a drug in a clinical trial, there's a certain kind of a protected environment that's involved. You know, you strictly mandate that the patients stay for 2 hours after every dose titration. The physicians know they have to look for this side effect. They've been educated at an investigator meeting. There's a lot of stuff that goes on.

What I worry about is what happens in Sioux Falls, South Dakota when a patient kind of goes in a rural office where it's a much less protected environment. Because once you let a drug out of a clinical trial environment, you're less protected.

Given the fact that this is a pretty serious side effect, my worry is that patients won't make it in time or won't be recognized in time because they're not going to be as protected as they would be in a clinical trial. I'd appreciate any insight about what kind of a

risk that represents here.

DR. LEVY: Maybe I can just make a comment on it. It's an excellent question. One of the reasons why we did a 25,000-patient trial at 3,300 sites in 12 countries was to provide as much information as possible about how the drug would be used and what the results would be in real-life practice. Of course, there were many clinics in places like Sioux Falls, South Dakota, very remote locations in Russia, all over the world.

It's also worth pointing out that by and large, when patients experienced angioedema, they sought medical attention at a facility other than the investigator's office. So, the question is whether those facilities in a small town can provide epinephrine and, if necessary, in the rare cases mechanical airway protection.

DR. NISSEN: I guess the final comment -- and perhaps it's a rhetorical one -- is on page 114 of your document, you say that treatment of life-threatening angioedema does not require specialized training. Angioedema associated with omapatrilat is managed in the same fashion as angioedema due to any other cause. Treatment of serious allergic reactions is a core skill for physicians and nurses, and airway protection is a routine procedure for emergency personnel, et cetera.

Well, one of the things that was most

troubling, in reading the case narratives, is that 3 of the 6 patients required cricothyroidotomy. Other than my friend here, Blase Carabello, who does everything well, I would doubt if any of us on this panel with a Bic pen -- I mean, I'm glad to hear that Dr. Temple is skilled in this.

(Laughter.)

DR. NISSEN: But I'm standing in the shoes of being somewhere and giving the drug and having a patient get laryngeal edema. And those 3 patients could not be intubated. So, somebody that was skilled enough to take a scalpel and pierce the cricothyroid membrane was necessary to save the life of the patient. So, to say that this is a core skill I think is to trivialize the problem. I guess I would like your comment, but 3 of the 6 serious cases had to have a cricothyroidotomy in order to protect their airway.

DR. LEVY: Perhaps one of the clinicians on the panel would care to speak to that.

DR. NISSEN: Mike Weber, do you do these cricothyroidotomies?

(Laughter.)

DR. WEBER: Well, I have done them in rabbits.

(Laughter.)

DR. WEBER: I'm working my way up to humans.

But no, this clearly is an issue. I think the

most important thing I can say about it is what Dr. Kaplan and Elliott have also pointed out, that fortunately these cases do not suddenly announce themselves as sudden respiratory embarrassment. There is a fairly long prodrome. So, as long as the patient knows that they ought to be going to an emergency room, hopefully that will allow us to deal with those patients. But if you can ask for some sort of a guarantee that there would be a 100 percent system to get absolutely everyone taking an ACE inhibitor who's going to have angioedema, I guess we can't guarantee that. But luckily, we do seem to have those several hours for the patient, as long as they know that they ought be doing it, to get to the emergency room.

DR. NISSEN: I'm going to, Jeff, hold further questions. I did have some further questions on the risk management program, but I thought it would be better not to do those now because, obviously, there's an issue about how do you manage the risk here.

DR. PACKER: Jeff, I just wanted to comment one thing about the need for a cricothyroidotomy. I actually have done a couple, having trained in a city hospital, but it has been a while.

I just wanted to emphasize that the core message, I think, which needs to be conveyed to physicians is the importance of epinephrine because epinephrine is the

most effective treatment to prevent progression of this disease. Antihistamines don't work and steroids work but they work too late to have an impact on progression. And what is striking is the fact that in so many cases the use of epinephrine was delayed. In all the cases you're talking about, epi wasn't even given or epinephrine was delayed. I think part of the educational program is to remind physicians as to what really is the appropriate treatment for a serious and potentially life-threatening angioedema.

DR. BORER: I think that's a very important point. The only problem is, as Dr. Kaplan pointed out, if the drug is actually given to the people that you're targeting, there's going to have to be more known than that you give epinephrine. There's going to have to be something known about how you deal with the problems that may develop when you give epinephrine to that target population. So, it's a somewhat more complicated problem.

DR. PACKER: But we're talking about what might be called a risk-benefit relationship. You're not giving epi to everybody. You're only giving epi to people in whom the risk-benefit relationship is favorable. Someone who is going to die from angioedema -- the risk-to-benefit relationship is extremely favorable.

DR. BORER: Right. I'm not suggesting you

wouldn't give epinephrine. I'm suggesting that you have to know how to do more than give epinephrine. You have to be able to deal with the consequences of it.

DR. NISSEN: It's a little more complicated also. Let me just tell you that you have an educational program. You educate people like me that treat hypertension on the importance of epinephrine. But the patient goes to an emergency department somewhere where there's not been any omapatrilat education given, and that doctor there has to know that the first thing you've got to do is give epi to the patient, not steroids or something else. I question. Because so many of these patients were treated elsewhere for their angioedema, the ability to educate people about this is challenging.

DR. PACKER: See, the patient and the patient's family play such an important role here because they can have a card that says I'm at risk of angioedema or whatever. This is the appropriate treatment.

DR. BORER: Paul.

DR. ARMSTRONG: I have a couple of questions for Dr. Levy and perhaps for Dr. Kaplan.

Dr. Levy, I may have missed it, but if you look at the 95 percent confidence limits on the estimates of angioedema in the 10 milligram versus the higher dose, do they overlap? You showed that there was a difference in

the frequency, but I didn't see the confidence estimates around those.

DR. LEVY: Again, we've not directly compared the incidence. We didn't intend to. We provided two estimates of risk.

DR. ARMSTRONG: The second question is that you reminded us that this was a trial of international scope and very large. As someone who's had the experience of doing some of these trials, one of the things that one finds amongst events that are of fairly low frequency is that there's sometimes a difference in the surveillance detection when it's left to physicians who are participating. We've been finding, for example, that things like bleeding detected in Russia are less frequent with the same exposure and have hypothesized that that might lead to a better understanding of how different countries survey these phenomenon. So, with that background, what is the difference in the frequency of angioedema across the countries which participated in this 25,000-patient trial?

DR. LEVY: We looked at the incidence of angioedema by region comparing North America with Europe, which is where almost all the other patients were treated. And the incidence of angioedema was a little bit lower in Europe than in North America, as you'd expect, since there

are essentially no patients of African descent in Europe.

DR. ARMSTRONG: And in Russia?

DR. LEVY: We didn't look at it by country.

DR. ARMSTRONG: Perhaps you or Dr. Kaplan can help me then. You've identified that Afro-Americans have a higher frequency. Do other ethnic groups also have a higher frequency of angioedema if one looks at Southeast Asians or Chinese or Japanese? What do we know from the ACE inhibitor data and other data vis-a-vis ethnicity and angioedema?

DR. LEVY: We're not aware of any other described ethnic associations, and there aren't sufficient data in OCTAVE to look at that question.

DR. ARMSTRONG: Dr. Kaplan, when you inject bradykinin subcutaneously to other ethnic groups, what do you find? You commented on that being a detection --

DR. KAPLAN: Yes, but it hasn't been done. That study was strictly Afro-Americans versus whites. I think the answer to your question, like people in Southeast Asia or Japanese or so on, has not really been looked at. There are just no data on that in terms of the incidence of angioedema. I know of nothing to suggest that it's accentuated in some way, but there's basically no data on it.

I'd like to make a comment with regard to when

angioedema occurs because we mentioned that there was no way we could predict. There's no test. There's no way you could tell who was at risk. I'm going to make a statement that's really just theoretical, but just think about it a little bit because part of it has a certain randomness to it. It would be logical that if you take more, that you might see more angioedema, but that doesn't necessarily hold uniformly.

I have seen patients on ACE inhibitors who had a few multiple episodes, say, of facial angioedema and it was not recognized that it was due to their ACE inhibitor. And they come to me, now taking it for 3 months more, and they haven't had a swelling. When they come in, once I see that there's no other available cause, I immediately stop the drug. So, there's something that we truly don't understand about when the angioedema occurs.

I'll tell you what I think is going on, but it's right out of my head, and that is obviously it's got to relate in some way to bradykinin levels, which has to do with the rate of formation versus the rate of degradation. If you're taking a drug and you've reached a reasonable steady state, there's no question on an ACE inhibitor that you get some elevation of the kinin level. But if you're measure blood levels, they're a little bit up but you're not struck that it's tremendously high. I'm suspicious

that when the angioedema occurs, something that is not yet identified is occurring to the person that produces bradykinin. They have a cold. They have an infection. They fell. They bumped their hip against the corner of their table, something of that sort. Then it doesn't take much to have levels soar sky-high.

And let me emphasize the lability of it. If I measure a blood bradykinin, just put a tourniquet on, stick the needle in, versus do the same procedure, get the needle in, remove the tourniquet, take 10 mls of blood and throw it in the garbage, and measure the bradykinin in the 11th ml, the difference between those two is 50-fold in bradykinin level, just from the needle stick and a little pressure. So, it's exquisitely labile.

So, I have a hunch that there are unknowns here that relate to when the actual attack of angioedema occurs, and that's why it has such a random feel.

DR. ARMSTRONG: If I may, Mr. Chairman, with Dr. Kaplan, I'm sure one of the easiest places to develop consensus today will be what's not known. But as we pursue this, can you just again help me with the epidemiology of angioedema that's not drug-related, that's spontaneous as it relates to age? With several hundreds of thousands of patients treated with ACE inhibitors, is the distribution by age any different with patients on ACE inhibitors than

it is spontaneously, sir?

And when you explore co-factors or factors that you believe produce bradykinin and then engender an episode of angioedema, do you reckon that those co-factors are any different in patients on ACE inhibitors as opposed to other agents and, by inference, with the drug that we're discussing today?

DR. KAPLAN: To my knowledge, the angioedema that one would see with an ACE inhibitor is not going to vary particularly, let's say, between the ages of 20 and 80. I don't think anyone has looked at it in terms of age groups but I don't think it would be dramatically different. The most common form of angioedema that we see, regardless of etiology, is that autoimmune one that I mentioned to you. It persists for a long time. It's recurrent. It's like there all the time, and it's often associated with hives. First of all, it's two-thirds women and one-third men. So, it's skewed by sex. And the peak is between 20 and 40, and it's at both tails. As you get older and in youngsters, it's quite a bit less. I'm positive that although I don't know the details, that the ACE inhibitor situation would not parallel that. My best estimate is that it would be fairly level among age groups.

DR. BORER: We have a question from Mike and then a comment from Doug.

DR. ARTMAN: This may be more theoretical and perhaps Dr. Kaplan might be the one best to address it, but I'm just wondering if these risk factors for angioedema are additive. In other words, if you're a black female, smoker with renal disease and seasonal allergies, is your relative risk up to 10 to something?

DR. LEVY: No. The answer is no. The two major risk factors identified were black race and current smoking. You put them together and the incidence of angioedema is identical to that you see in blacks. It's 5.6 percent.

DR. THROCKMORTON: And yet, Elliott, the timing of those angioedema events for those two particular populations was quite different, as I recall. Could you show those two curves? The time to angioedema events for blacks and for smokers.

DR. LEVY: Yes.

DR. THROCKMORTON: Because those seemed very different. Again, going to the question of are all risk factors equal and are we talking about a single angioedema thing or are there different kinds of angioedema.

DR. LEVY: They're certainly not additive. There is a difference in the time to onset of angioedema amongst blacks and current smokers. In current smokers, the risk is greatest at the initiation of therapy. There

were 45 cases in smokers on the first day of therapy, and then the rate declined fairly dramatically to a level that was near that seen in other patients.

In blacks, on the other hand, the risk was not dramatically greater on the first day of therapy than it was in whites, but it remained at a higher level for a longer time and the risk decayed more slowly.

So, there is a difference in the time course of angioedema in patients with each of those risk factors.

DR. CUNNINGHAM: Yes. You got me to wondering. What are the risk factors for angioedema in the group that was on enalapril. Are they the same?

DR. LEVY: The risk factors were quite similar with the exception of current smoking which did not appear to be a risk factor for enalapril associated angioedema.

DR. CUNNINGHAM: Because one of our questions is whether or not the two are the same, and if they have different risk factors, that makes you wonder.

DR. LEVY: It's a little hard to look at the enalapril group because of the relatively small number of events. The profile is quite similar with that one exception.

DR. BORER: Tom and then Steve.

DR. PICKERING: Yes. I'd like to pursue the question of the definition of black a little further. In

this country it usually refers to African American, but I practice in northern Manhattan and a lot of patients look black to me but define themselves as Latino or Hispanic. And the distribution of risk factors is not necessarily the same as in African Americans. Can you tell us what the definition was and also how many of the blacks were U.S. African Americans as opposed to some other dark-skinned group?

DR. LEVY: Well, they're almost all U.S. The investigators were provided with one of four categories and simply asked the subjects to identify which of the four they belonged to. They were white, black, Asian Pacific, and other. So, it's not possible to tell you where the black subjects came from, whether they were Afro-Caribbean or of Spanish descent.

DR. BORER: Steve.

DR. NISSEN: None of us has asked you about cough, and obviously cough is an ACE inhibitor side effect that I think we believe is bradykinin related. Was there a difference in incidence of cough across all your trials in ACE inhibitors and omapatrilat?

DR. LEVY: No. They're pretty much spot-on, identical.

DR. NISSEN: Can anybody give me an explanation for that? It seems surprising.

DR. KAPLAN: The data on cough are not as good as the data on angioedema in terms of relating a kinin level to the actual event. Most people think that it is related to bradykinin, however.

DR. PACKER: I think that from the understanding that I have, there may be multiple mediators of cough. Bradykinin may be one. Substance P, a whole host of other factors have been implicated. So, I think it's probably much more multifactorial, which is why we're not seeing a signal here.

DR. THROCKMORTON: Steve, if you're interested, the incidence of cough was looked at by Dr. Pelayo in the original safety review, and that's on page 23 of his tab, which I guess is tab 4. As they said, the numbers are fairly small, but there does seem to be an ordering where the majority of the events were in the omapatrilat group and not placebo.

DR. NISSEN: Statistically speaking, there's no difference?

DR. THROCKMORTON: It's 2.1 percent versus 0.3 percent. It was a safety analysis. So, we wouldn't have normally don't statistical.

DR. NISSEN: I see, okay.

DR. LEVY: I'm sorry. I couldn't hear that data. Could you repeat that?

DR. THROCKMORTON: It's page 23 of Dr. Pelayo's. This is comparing against placebo. Is that what you were interested in, Steve?

DR. NISSEN: No.

DR. THROCKMORTON: You were interested in enalapril.

DR. NISSEN: Yes. Again, tolerability compared to enalapril. It sounds like it's a wash.

DR. LEVY: Well, you can see there's --

DR. NISSEN: No difference.

DR. LEVY: -- no difference.

DR. NISSEN: Very good. That's helpful.

Let me just ask one more final question for me, and then I'll pass this along. Part of your risk management program is to try to keep patients in physicians' offices for a couple of hours after they get that first dose. I assume that that's going to be a recommendation. Am I correct?

DR. LEVY: It's a consideration. The program is under development now.

DR. NISSEN: But I guess one of the things that I know about physicians and their levels of patience is -- I'll ask you a question and see if the clinicians agree with this. When you do something like that and you have an event that's relatively rare, like angioedema, physicians

may start out keeping patients for a couple of hours. They won't see an event and they will start to get a little complacent, and they'll start letting people go sooner. And I guess I'm worried that in a big program that goes on for a while, because the events themselves are rare, any individual physician is not likely to see one. And there's going to be a tendency to get increasingly complacent until something catastrophic happens. It's a just a question of behavior and it's something that worries me. Any thoughts that any of the clinicians have about whether this is a real concern or not a real concern I'd be interested in.

DR. BLACK: I haven't even done trachs in rabbits, so I'm not sure I'm really qualified to talk about it. But I've had angioedema that, in fact, had to do with something else in Charlotte Hungerford Hospital in Torrington, Connecticut, which is near Russia actually.

(Laughter.)

DR. BLACK: My own feeling just in general is every emergency room, in fact, can do this procedure. The care that I got was exactly what you heard. It was shotgun. I got the right stuff and it got better. But I think, in fact, this program will really improve the care and awareness of angioedema whatever the cost. And we know there are cases from ACE inhibitors also. So, I think it's going to really help out. The people who are going to do

most of the care are going to be people in ERs. It's not going to be in the first few hours in the doctor's office. So, I'm not as concerned.

I think a program that asks you to stay there for a while is probably going to be, as you say, not in fact -- and it probably wouldn't make too much difference. The anaphylactic case was the only one, and those are clearly by chance.

DR. LEVY: I think it might be useful for the committee just to know a little bit more about the risk management program at this point, if you'd be interested, because the topic has come up a few times.

DR. BORER: If we can hold that just a little bit because that ultimately will be part of our discussion in terms of risk-benefit and we will want to hear a little bit about it. You know, we got a lot in our handouts and materials about what you submitted.

Why don't we just go through this OVERTURE data quickly and then we can come back and clean up.

DR. FLEMING: Jeff.

DR. BORER: Oh, I'm sorry. Tom.

DR. FLEMING: I had two or three questions on safety. I'd like to pursue a little bit more what Steve and I think Paul were getting at earlier about what is the evidence that there is, in fact, a relationship here and a

safety risk with starting dose.

Can you put up slide 36? As Steve was alluding to, in slide 36 there appears to be evidence that there may be a two- or three-fold lower risk of angioedema when you're starting below a 20 milligram dose. In fact, in this experience, there were no cases of airway obstruction, airway compromise, in the less than 20 dose. So, in a certain sense, the OCTAVE study is a disappointment when you look at the fact that the 10 milligram starting dose gave a higher overall occurrence rate of 2.17 percent.

Yet, as you point out, that readily could be under-detection in this setting here. One piece of evidence of that is when you look at the rate of airway compromise, it turns out that in OCTAVE it's 1.6 per 10,000. Here, if you look at the greater than 20 milligram group, it's almost 10-fold larger. It's 15 per 10,000. So, there really is evidence when you look at airway compromise that there really is a relationship with dose.

To try to get a better sense about this, beyond just relying on the airway compromise rates, we know that in OCTAVE there were these two cases, but there were overall 19 cases that were hospitalized. Can you give us for these two columns here, the below 20 and the greater than or equal to 20, how these cases break out relative to hospitalization? Because that may give us further

reinforcement to the airway compromise data that there really is a dose-response relationship.

DR. LEVY: Let me just see if I understand. You want to know from these data in this program what proportion of patients required mechanical airway protection, what proportion were hospitalized.

DR. FLEMING: Yes. We know it's 0 and 4 for airway compromise. So, in these two columns, of the 18 cases in the less than 20 milligram setting, how many of them were hospitalized, and of those 66 in the greater than 20 milligram, how many were hospitalized?

In essence, what I'm getting at is if there's under-detection, as I'm almost certain there is here, it's less likely to be under-detected in the most serious cases. Airway compromise I'm assuming you're going to see. Hospitalization I would think you would be more likely to see. So, we'll get a better clue, along with the airway compromise, that there really is a dose response.

DR. LEVY: In those who were started at 20 milligrams or more, there were 4 patients who were hospitalized for angioedema without requiring airway compromise. I'll ask my team to verify it for me. My recollection is that in those less than 20 milligrams, it was 1 patient hospitalized, but I'll ask them to check for me.

DR. FLEMING: Okay, and they can give that to us later after they check.

Let me go on to a second question.

DR. KAPLAN: Could I make a comment on the 19 hospitalized patients? In looking those over, I read all of them to see what was the criteria for hospitalization. If you look at it carefully, you will see that about 8 or 9 out of the 19, upon arrival to the emergency room, were almost asymptomatic, had either a little bit of lip swelling that was left or had nothing, but gave a history of having had tongue swelling or pharyngeal swelling or drooling or something that had happened hours before and they were then hospitalized for observation. That's a safe thing to do and it's exactly what you might consider doing if it were anaphylaxis.

But the fact is, if you read them individually, of course, they were all hospitalized overnight. Nothing happens. They're discharged the next morning. And the fact that about 8 or 9 of them, by our criteria I think and by my judgment as an allergist, ought not to have been hospitalized because if you understand what happens with an ACE inhibitor, you get the swelling, it crescendos. That time may vary depending upon the person and severity, and then it finally abates, and it does not recur. So, it doesn't rebound, which is the reason why steroids are of no

value actually in treating them in contrast to anaphylaxis.

So, I think that those who have respiratory embarrassment on arrival are the obvious. But I think hospitalization may not be the best criteria as we look at this study for the actual incidence of the "severity" because a substantial proportion of those patients resolved spontaneously and really didn't need hospitalization.

DR. FLEMING: Let me go on to the second question and that's slide 39. Having seen in the prior experience before OCTAVE no cases of the airway obstruction and evidence of lower rates, the intention here was to see if we could show that the rate was below 2. So, the null hypothesis was a rate of 2. The alternative was something discernibly less than 2. Ultimately what we see here in the bottom confidence interval is that we cannot only not rule out that the rate is less than 2. We can't even rule out the rate is less than 4, and the data suggests that the rate is actually 3.2.

I see Jim Neaton here. I don't know if it's because he was on a DSMB for this study. I'm just guessing.

How was the DSMB monitoring this phenomenon as the study was ongoing? Because it appeared your null hypothesis was 2 and the alternative, I'm assuming, was 1 or 1.5 or something like that. And you're entirely way

inconsistent with that with these data. How was this being factored in during the monitoring of the trial?

DR. LEVY: Let me comment on that. Jim was actually not on the DSMB.

But the DSMB was provided with these data, as well as safety data. In their view, it was very important to weigh both potential harm and potential benefit in assessing whether this study was to continue or not, and they didn't apply a simple stopping rule based on whether or not the prespecified hypothesis for angioedema was reached. In their view, there was clear evidence not only of increased risk of angioedema, but also of greater blood pressure reductions.

DR. FLEMING: So, the protocol simply said the null hypothesis is 2, alternative is less, and there was no stopping guideline specified in the protocol.

DR. LEVY: There was no prespecified stopping rule.

DR. FLEMING: The last question. When we look at angioedema by severity, you've given us that data in the aggregate. The add-on group with 4,751 patients is an important subgroup here. In this subgroup, do you have the breakdown of the cases of angioedema by grade?

DR. LEVY: Yes, we do, but let me just make a point and that's that in that group and all other groups,

there's a remarkable consistency across this database. What you'll see is that the incidence of angioedema in group 3 is similar to that seen overall, and that 60 percent of the cases received no treatment or antihistamines only as they did overall. So, we'll be happy to show you those data, but they're quite consistent with the overall data.

DR. FLEMING: Okay, and please do so, though. At some point bring those back to us.

DR. BORER: If there are no other questions of fact here, maybe we can go on here about OVERTURE, and then we'll come back to some of the other safety issues.

DR. PACKER: Before I begin, I just want to note that in light of my status as an SGE but also in light of my role as principal investigator of the OVERTURE study, the Advisors and Consultants Staff of the FDA has consented to my participation and presentation in today's meeting.

I also wanted to correct Steve's comment, and I think this is particularly sensitive to both Jeff's and Tom's views. I think those who live in Manhattan neither characterize it as a State or a country. I think they characterize it as a universe.

(Laughter.)

DR. PACKER: With that in mind, at yesterday's meeting on candesartan, the advisory committee indicated it

was comfortable believing that an incremental decrease in blood pressure would be translated into a reduction in cardiovascular events if it could be reassured that the experimental drug did not exert an adverse effect independent of its antihypertensive action that could increase the risk of a cardiovascular event. Therefore, the committee implied it would feel comfortable, assuming that a decrease in blood pressure would produce a predictable reduction in cardiovascular risk, if the drugs being compared were in the same class, but they might not feel such comfort if the drugs were in different classes. And I think Steve in particular made this point.

DR. FLEMING: Some of us, though, might not have been as comfortable with such a broad generalization as you have stated.

DR. PACKER: Even in the same class. Right.

So, I'd like to consider the present situation which is that both omapatrilat and enalapril are both ACE inhibitors and that's in part reassuring, but omapatrilat differs from enalapril in also being a NEP inhibitor. So, the question is, how comfortable can the committee be that NEP inhibition does not produce adverse cardiovascular effects that could negate the cardiovascular benefits expected from its incremental ability to lower blood pressure?

This table shows the cardiovascular events that were observed during the 6 months' treatment with omapatrilat and enalapril in the OCTAVE study. Now, although this was a prespecified analysis, the study was not designed to compare the two drugs on the risk of cardiovascular events. So, I think these data need to be interpreted very cautiously. Having said that, there were 105 cardiovascular events in the omapatrilat group and 121 in the enalapril group.

This slide shows the Kaplan-Meier plots for these events. The hazard ratio of omapatrilat to enalapril is 0.87, with an upper bound of the 95 percent confidence interval of 1.13, I think in and of itself suggesting that NEP inhibition is unlikely to exert a meaningful adverse effect that might detract from the expected clinical benefits of the drug.

Now, although these data might be considered to be reassuring, my own view is that these data need to be interpreted very carefully since the duration of follow-up in the study is only 6 months.

I also think that it is likely that Tom might ask for an analysis of these data according to the characteristics that the sponsor is proposing. It might form the basis of use of the drug. And I just want to let you know we are working on that as we speak, including

trying to address the issue of the blood pressure lowering effects in all of those individual subgroups at high risk.

Well, in light of the limitations of these data, I think it's important to consider the results of OVERTURE. Preliminary results of this trial were presented at the ACC in March. Final results will appear in Circulation online in about a week from now, and before reviewing the results, I want to emphasize that although these data have been presented to the FDA, they have not been reviewed by the FDA. Therefore, they are being presented with the proviso that if they have any influence on your judgments, they will need to be confirmed by the agency.

The OVERTURE trial evaluated 5,770 patients with class II, III, or IV heart failure. All patients had an ejection fraction less than or equal to 30 percent. All were hospitalized for the treatment of heart failure within the past year. All patients were receiving excellent background therapy for heart failure, including beta blockers in 50 to 60 percent of patients and spironolactone in over 40 percent.

Importantly, about 1,300 patients, or about 20-25 percent of the population, were hypertensive. I just want to mention that hypertension is a particularly important problem in patients with heart failure since it

is so critical to lower blood pressure in these individuals. Yet, there is a sizeable risk for frequency of hypertension in people with heart failure. It's 20-25 percent in moderate to severe heart failure. It's over 40 percent in milder degrees of heart failure. And these patients are already receiving diuretics, ACE inhibitors, beta blockers, and they can't take calcium channel blockers. So, I think that an analysis of that subgroup would, in part, address Tom's request for additional data, including outcomes data, in high-risk individuals.

Now, eligible patients for this trial had any prior with an ACE inhibitor discontinued and were randomized in a 1-to-1 fashion to either omapatrilat or enalapril. The target dose of omapatrilat was 40 milligrams once daily, which had shown promising results in earlier heart failure trials, and the target dose of enalapril was 10 milligrams b.i.d., which was the target dose used in the SOLVD Treatment trial. I think this remains the most definitive study showing a favorable effect of ACE inhibitors on morbidity and mortality.

What I'd like to do is to make two points about these doses. First, the target doses of both drugs was half the target dosage used in the OCTAVE trial, and second, because this was a heart failure trial, enalapril was given twice a day, whereas the drug is conventionally

given only once a day in the treatment of hypertension and, as Steve has mentioned, the use of a b.i.d. regimen arguably provided a tougher test for omapatrilat.

Now, the primary endpoint in this study was the combined risk of all-cause mortality or hospitalization for heart failure. This endpoint was used prospectively in the original protocol to test two hypotheses, a non-inferiority hypothesis and a superiority hypothesis. According to the original protocol, omapatrilat would be considered non-inferior to enalapril if the upper bound of the 97.5 percent one-sided confidence interval was less than 1.09, and if this were achieved, we would have been able to conclude that omapatrilat would have retained at least 80 percent of the effect of enalapril seen in the SOLVD Treatment trial, which was the protocol-specified reference standard, greater than 80 percent. Of course, if the upper bound of the one-sided 97.5 percent one-sided confidence interval was less than 1, then we would have concluded that omapatrilat was superior to enalapril.

Now, here are the results on the primary endpoint. There were 973 patients who died or were hospitalized for heart failure in the enalapril, 914 such patients in the omapatrilat group. It translates into a 6 percent lower risk of the primary endpoint in the omapatrilat group. The upper bound is 1.03, which is

greater than 1 but less than 1.09. Therefore, we could not conclude omapatrilat was superior to enalapril, but we could conclude that omapatrilat was not inferior to enalapril.

Now, this slide shows the effect of omapatrilat and enalapril on the combined risk of cardiovascular death or cardiovascular hospitalization. This was a prespecified secondary endpoint in the study, and it represented the most comprehensive cardiovascular endpoint specified in the original protocol. For this endpoint, omapatrilat had a 9 percent lower risk of a cardiovascular event which was nominally significant.

Now, as I said at the beginning, over 1,300 patients in OVERTURE were hypertensive in that they had a systolic blood pressure that was greater than 140.

Now, this slide shows the influence of baseline systolic blood pressure on the magnitude of the difference between omapatrilat and enalapril on the primary endpoint of death or hospitalization for heart failure, and on the secondary endpoint of cardiovascular death and cardiovascular hospitalization. And as can be seen, the higher the systolic blood pressure, the greater difference in favor of omapatrilat, and this was true for both endpoints. The difference in favor of omapatrilat in patients with a systolic blood pressure greater than 140

was a 16 percent lower risk of death or hospitalization, and a 21 percent lower risk of cardiovascular death or cardiovascular hospitalization.

I guess, Tom, these are probably the best estimates we now have with respect to outcomes data in hypertensive patients, albeit it in hypertensive patients with heart failure.

I would like to close with a brief note about safety. This slide lists selected adverse events that were seen in the OVERTURE trial. As can be seen, omapatrilat had more reports of hypotension and dizziness, but fewer reports of heart failure and fewer reports of impaired renal function. Angioedema was seen in 14 enalapril patients, 24 omapatrilat patients, and of these, 3 patients were hospitalized, 2 in the enalapril group and 1 in the omapatrilat group, and none had airways compromised.

Now, in summary, I think the results of OVERTURE are at least suggestive and certainly I think consistent with the hypothesis that in patients with hypertension and heart failure, omapatrilat might reduce cardiovascular events when compared with enalapril even when enalapril is given twice daily.

But I want to emphasize a much more important point, and that is, I think these data provide considerable reassurance that NEP inhibition does not detract from the

cardiovascular benefits one can expect from the incremental antihypertensive effects of omapatrilat.

With that, I'd be delighted to answer any questions the committee might have.

DR. BORER: How were heart failure events defined in the protocol, Milton?

DR. PACKER: Heart failure was defined by the investigator, which in most heart failure protocols, heart failure is defined by the clinician. The qualifications for heart failure are based relatively on the severity of the disease. So, they had to have class II, III, and IV symptoms limited by dyspnea and/or fatigue.

DR. BORER: No, no. I'm sorry. That's not what I'm asking.

DR. PACKER: Oh, I'm sorry.

DR. BORER: These are adverse events. Everybody in the trial had heart failure.

DR. PACKER: Oh, I understand. I think, as you may appreciate, in a trial where the -- and we see this all the time in heart failure trials. Investigators are asked to report all AEs. There is no guidance given to investigators as to how they should report AEs or not. In general, heart failure as an AE is by far the most frequent AE reported in heart failure trials. In general, in drugs that work in heart failure, the reports of AEs in heart

failure tend to be lower in the active treatment than in the placebo. But there is no quality control here. There is no guidance as to how heart failure as an AE should be defined. It's really up to the judgment of the investigator.

DR. BORER: And similarly I assume for hypotension.

DR. PACKER: Similar for hypotension. All the AEs are reported at the discretion of the investigator in a spontaneous manner without any specific instructions as to what they should or should not report or how to define specific terms.

DR. BORER: Can you tell us what doses of the two drugs actually were achieved? I see the design, but what was actually achieved?

DR. PACKER: I know the estimates, and Jeff, we can give you the actual numbers, but it's in the range of about 80 to 82 percent in both treatment groups received target dose. We will check on whether that's -- that's correct? It's 82.7 percent and -- we'll get you the data, but that's the range.

DR. BORER: Steve, do you have any questions?

DR. NISSEN: I just wanted to come back to the blood pressure issue since what's on the table here is the application for approval of this drug for hypertension. I

want to hear again your thoughts, Milton, on why there was no blood pressure difference between omapatrilat and enalapril in the hypertensive heart failure patients because, again, this does shed some light on whether b.i.d. enalapril might be as good as omapatrilat.

DR. PACKER: I just want to, again, emphasize the points, but let me supplement them as well since you're asking me to do that.

First of all, again this wasn't a hypertension study. This was a heart failure trial, and heart failure investigators in general view blood pressure as a range as opposed to a number. I don't know another way of saying that. There's a complete difference in the quality of the blood pressure data in the context of a hypertension trial than in the context of a trial done for another indication.

Having said that, I think that the most important point is the trough blood pressures were similar, but there is evidence from other trials in heart failure, not from OVERTURE, that during most of the day the blood pressure is considerably lower in the omapatrilat group than in the ACE inhibitor group. And the difference, by the way, in previous heart failure trials has been in the realm of about 7 to 8 millimeters of mercury greater in omapatrilat than, for example, in the previous trial with lisinopril.

In that trial, Steve -- and the trial I'm referring to IMPRESS. Lisinopril is a once-a-day drug. The blood pressures came down and were very similar at trough in that trial, but during the day the blood pressures were dramatically different in the two treatment groups. I think that reinforces the point that the committee made yesterday, which is it isn't just trough blood pressure that affects cardiovascular events, it's the delta blood pressure throughout the day.

DR. NISSEN: I'm not sure I get the argument. What you're sort of saying is blood pressure isn't measured as well by heart failure docs as it is hypertension docs. But that variability would occur in both arms of the trial. By most blood pressure standards, it's a pretty big trial. The number of patients with hypertension. OVERTURE is 5,700 patients and of that, what, 1,500 of them are hypertensive. That's a pretty big sample. So, when you see spot-on same trough effects -- I recognize there might have been differences in peak effects, but the most important metric that's used in hypertension evaluation is that trough blood pressure. When given b.i.d., these two drugs had an indistinguishable effect on trough blood pressure. So, it's troubling me.

DR. PACKER: Obviously, there are other hypotheses, but the other hypothesis, at least suggested by

the data, is that NEP inhibition has cardiovascular benefits independent of blood pressure lowering. Obviously, we can't say that from the data. Both of those hypotheses are possible.

I actually feel more comfortable with the delta blood pressure during the day than I am suggesting to you that NEP inhibition has an incremental effect on the biology of this disease that is independent of blood pressure.

DR. BORER: From the AEs, at some point during the day, 8 percent more on omapatrilat are having a lower blood pressure. They were hypotensive.

DR. PACKER: Steve, the blood pressures had to be lower at peak because hypotension and dizziness was much more frequent in the omapatrilat group than in the enalapril group. I know we didn't measure it, but it had to be that way.

DR. NISSEN: I agree although, again, conceivably there is a very early effect. It doesn't last very long. The patients get kind of dizzy and syncopal for an hour or two, but then the levels track together. Without having ambulatory blood pressure data, we really don't know. But again, at least at trough, which is what you measured, there really wasn't much difference.

DR. BORER: Are there any other questions?

Tom.

DR. FLEMING: Milt, could you put your last slide 13 up again?

You seem to be saying that we're looking at two mechanisms that omapatrilat would have. One is through NEP inhibition and the other is through whatever mechanisms that lead to the incremental antihypertensive effects, and that somehow this study is telling us that the favorable benefits on cardiovascular endpoints mediated through that second mechanism aren't in some way offset or compromised by NEP inhibition. And where does that come from --

DR. PACKER: Oh, no, no, no.

DR. FLEMING: That's what the technical wording seems to say.

DR. PACKER: This addresses specifically the concern that you raised yesterday, which is if you compare an ACE inhibitor and ACE inhibitor -- and let's assume for a moment that one reflected the committee's view that they would feel comfortable doing that. That may not precisely reflect your view, but ACE inhibitor and ACE inhibitor -- then if the one ACE inhibitor or an angiotensin II antagonist lowered blood pressure and another one lowered blood pressure more, that the delta that one observed in blood pressure would be translated into a cardiovascular benefit is because there was no other mechanisms that these

drugs had that had been identified that might detract or modify the relationship between delta blood pressure and delta events. That's a hypothesis, but that's the concept that I think was promulgated yesterday.

If you go across classes, you're less certain. What I wanted to emphasize here is that there is an overlap between the mechanism of omapatrilat and an ACE inhibitor. Everyone is comfortable with what an ACE inhibitor might do. So, I want to put forward the OVERTURE data as reassurance that the incremental action of omapatrilat -- there is no evidence that that would have an unfavorable effect on cardiovascular events especially if you think that blood pressures were the same. Therefore, whatever you see in hypertension, that you could translate the delta in blood pressure to the delta in events without being concerned that there's some other action of the drug that might be adversely affecting cardiovascular events.

DR. FLEMING: Milt, it would seem, to follow through on this argument, you would have to be saying you know somehow that if you take away NEP inhibition, that the remaining mechanisms that omapatrilat would have would yield overall better antihypertensive effects than an ACE inhibitor alone.

DR. PACKER: No. I'm actually suggesting that if this drug were not a NEP inhibitor, it would look like

an ACE inhibitor.

DR. FLEMING: The argument that we were saying yesterday is if you're comparing two agents that yield different antihypertensive effects and we want to infer from that difference a difference in cardiovascular benefits, that is a perfectly acceptable inference so long as there aren't any other mechanisms out there that would offset that.

So, therefore, for the logic to carry over to here, what you're having to conclude here is that omapatrilat has mechanisms relative to enalapril that yield a better antihypertensive effect and NEP inhibition is not in any way compromising the corresponding beneficial effects you would expect to see on the endpoints.

Let's move on, though, to maybe an even more fundamental question. This is sort of a negative in a certain sense. Basically when I'm looking at omapatrilat against enalapril, another way of interpreting this is to say, well, at least with omapatrilat we didn't make things worse, or we're not less effective than enalapril. And there's a little bit of that even in your hypothesis of non-inferiority. Yes, we're trying to maintain at least 80 percent of the benefit.

I'm always troubled in a non-inferiority argument, though, when the experimental arm is not

anticipated to be more favorable in some way. I believe strongly in non-inferiority when I have an experimental intervention that has a safety profile or a convenience or a cost profile that would make it more favorable in that domain such that if efficacy is the same, then I come out ahead. And as a result, because of that, I'm willing to potentially give up a little bit of efficacy.

So, bottom line here is for this trial to be interpreted as positive, it's positive only in the sense that we can say we're ruling out that omapatrilat is meaningfully worse, and hence that's a win as long as in the safety domain we're all convinced omapatrilat is better than enalapril. But I think what this whole discussion is about today is that that's not where we are. So, shouldn't you have expected to be required to show at least superiority here for it to be win?

DR. PACKER: Could I have my backup slides, please, on the SOLVD Treatment definition and the slide that follows that?

DR. BORER: As you go through this, I think it's important to remember you did a heart failure trial, and we're not evaluating this drug for its efficacy for heart failure. We're trying to evaluate it for its efficacy as a treatment for people with high blood pressure. So, I think that's really Tom's point.

DR. PACKER: I think what Tom is saying -- and we have certainly learned this lesson many, many times in heart failure trials -- is that in spite of the prior hypothesis of non-inferiority, one would be a lot more comfortable if this trial had met its primary endpoint. In light of the fact that it didn't meet its primary endpoint, one has to be particularly cautious of subgroup analyses on either primary or secondary endpoints.

In light of that, I just want to mention one aspect of OVERTURE which is new. This was not presented at the ACC, but it does appear in our publication in Circulation.

Let me emphasize that the primary endpoint was death or hospitalization for heart failure. This was the definition of hospitalization used in the OVERTURE trial. It included all hospitalizations attributable to heart failure as adjudicated by the endpoint committee which required IV treatment and had a duration of more than 24 hours. This was exactly what was said in the protocol.

The reference standard for this trial was SOLVD Treatment. This was the reference standard for non-inferiority. We recognized only after the trial was over that the definition for hospitalization for heart failure in SOLVD Treatment was different than for OVERTURE. In SOLVD Treatment, the hospitalization for heart failure was

all hospitalizations attributed to heart failure by the investigator regardless of treatment or duration. And there was no adjudication process in the SOLVD Treatment trial.

So, I just want to, for purposes of curiosity, show you what the data would look like if one had used the reference standard definition.

DR. FLEMING: If this is in interest of answering my question, just because time is short, I don't know that we have to go into this because I don't think this is getting at that separate issue that I was asking.

DR. PACKER: Jeff, I'll be done in one second.

This is the results you've already seen, a 6 percent lower risk with a p value. This is the primary endpoint using the SOLVD definition, 11 percent lower. This is obviously a post hoc analysis. But I offer it only to suggest the fact that had we been wise enough or whatever, if we had used the same definition used in our reference standard, maybe things would have worked out better. I don't want to put too much emphasis in it. I only provide it for whatever reassurance it would give you.

DR. BORER: Bob, did you have a comment?

DR. TEMPLE: Only that, I guess while Milton is suggesting there might be something really good going on here, the main purpose I think was to make the case that at

least nothing bad happened other than the angioedema, so you don't have to worry. And that point would be fairly strong I think.

DR. BORER: Yes. I think that the issue that we're trying to focus in on here is that we're considering this drug as an antihypertensive. We want to be sure that the safety is acceptable for the intended use. It certainly is nice to know that it might turn out to be a real good drug for people with heart failure where the benefit-risk issues are very much different. But in the hypertensive population, what are we going to see?

And what we saw was that, for whatever reason, the measure that was used showed no difference in the efficacy of the drug for the hypertensive population here and perhaps no additional cardiovascular risk. So, we're still talking about the angioedema as being our primary concern. And that's reassuring to know. I mean, that's useful.

DR. FLEMING: Just in a single sentence, Bob, in view of the angioedema, all I'm saying is it's not enough to convince me that nothing bad is happening. I want to see something good happening.

DR. TEMPLE: Right, and I don't think it's being alleged, although perhaps it's being suggested, that there was any finding like that. All it does is give you

some assurance that it doesn't do anything bad.

DR. BORER: That there's no new problem.

DR. TEMPLE: Given the choice of primary endpoint, you really can't say much more than that probably.

DR. PACKER: I'd like to introduce Dr. Black for the next presentation, if that's all right.

DR. BORER: Henry, just tell me approximately how long do you think you'll be taking?

DR. BLACK: Well, if I use my Manhattan speed, it will be 5 minutes. I do want to bring us back to blood pressure and I think this is a good way to do it.

DR. BORER: Okay. Why don't you go ahead.

DR. BLACK: Thanks. I do appreciate it. I realize how late it is and how tired everybody is, but I do think it would be useful to talk a little bit about where we are on high blood pressure now and to answer one question in particular, which is whether omapatrilat's greater efficacy does add to the value of current agents. I'm not going to talk about safety at this point.

In order to do this, I want to review what we did in the Joint National Committee to try to improve hypertension care. You heard yesterday from Dr. Kannel that overall we were controlling 27 percent of hypertensives in America. This is actually considerably

better than any of the rest of the world, and this is only people from 18 to 74. The data for older people are considerably worse.

In order to educate physicians and also patients about how we would do this, we borrowed somewhat from ATP II and we talked about goals rather than control, understanding this was dichotomous and you could be a millimeter above or beyond or not and be at goal. But that's what we thought was easier for people, in fact, to operate with.

The goal for most hypertensives was less than 140 and less than 90. For high-risk individuals like diabetics or people with heart failure or chronic renal failure, we set that goal lower, even though at that point in time, with the possible exception of SHEP, there was no trial that confirmed that more aggressive therapy was beneficial in diabetics in particular. Syst-Eur, UKPDS, HOT, and other studies as well, LIFE, have really suggested this was a good call even though it wasn't at that time evidence-based. And for those with proteinuria, it was even lower still. This goal was not dependent on age, gender, or other forms of comorbidity.

What I want to do is show you, with that in mind, three clinical trials and my own clinical experience as to whether we can achieve that goal and why we can't.

I'll begin with LIFE, which was completed this year. This was a comparison of two regimens, one beginning with an ARB losartan, one beginning with a beta blocker atenolol, and only about 11 or 12 percent of individuals took only those drugs. It was a large trial. It was a long trial. And the goals here are shown, as you see it.

Overall, those who reached diastolic goal of less than 90 for both arms was quite impressive, almost 90 percent. However, for those who reached the systolic goal -- and as you heard yesterday, again it's systolic pressure, especially in older people, that's a better predictor of outcomes -- it was under 50 percent. And those who reached both goals, it was also about 45 to 48 percent.

In the diabetics, the highest risk group, you had quite similar data or you didn't do quite as well, 85 and 82 percent for losartan and atenolol, respectively, but under 40 percent for both arms to get systolic pressure under 140. That's not the 130 goal that we're talking about.

Two other studies, one of which is published and one of which is not yet published, I also want to show you. This is the ALLHAT trial, which was just completed. It's 42,000 high-risk hypertensives. Everybody enrolled was over 55 and had another risk factor. There were 15,000

diabetics in ALLHAT. There were about 15,000 African Americans in ALLHAT. And everybody had to have something else.

What I want to call your attention to is not the outcomes, because those aren't available yet, but how we did with respect to blood pressure. In this study, 90 percent of people were on treatment when they started and only 27 percent of that 90 percent overall were at the JNC VI goals, not even again using the diabetic goals. What happened here was you got switched to one of the treatment regimens which was a diuretic or lisinopril or amlodipine or doxazosin. And there was very, very careful nagging of our clinicians to titrate to a goal, and the goal was less than 140 over 90.

We accomplished a lot. In one year, we got 86 percent to diastolic goal, 58 to systolic goal, and this was maintained throughout. Now, this suffers from patients we can no longer follow and not having blood pressures, from people with events not being followed, people who died not being followed, but it's a good look at what happens.

However, for systolic blood pressure, which began at 31 percent under 140, we got only up to 70 percent. So, there's still a large number of high risk older people whose systolic blood pressure we could not get to below 140 in spite of these efforts, and overall, 69

percent at 6 years reached both. These numbers approximate 30,000 hypertensives.

In the CONVINCE trial, which we just presented in May, we see very similar data. Here we were comparing a non-dihydropyridine verapamil to diuretics or beta blockers as the comparators. 16,000 individuals, 13 countries. Began with 20 percent at the JNC VI goals of less than 140 over 90. Once again, no problem getting diastolic under control in this older high-risk group, but a lot of difficulty getting equally good results for systolic pressure. Started with 20, got to 67 percent. That's quite good. That's as good really as any study so far, but there's a large group of people untreated.

Now, what we did -- and you don't have this slide in your book. We added it after some of the earlier discussion -- is to show how we did it. At the end of titration, almost by definition, people were on one drug. Step 1 is monotherapy. But with time, the number of people who could reach and maintain that goal has slipped. So, by 30 months, which is the last data we have, only about 24 percent were on single agents, 44 percent were on one or two agents, many were on third agents or open label. Our physicians could use just about anything they wanted. We nagged them unmercifully to get there, and this was the best we could achieve.

Well, that's fine. Let's look at how we do in a specialist clinic. These are clinical trial patients at one end of a spectrum. They're watched closely. What about people who are refractory? And that's what we see mostly in our clinic.

We used HEDIS criteria here to see if they were reasonable, and then we had to follow everybody for at least a year. We just looked at that visit to see how well we were doing. This is 437 consecutive patients and we saw how often we achieved the goal of less than 140 and less than 90. This is where we started.

These are people sent to us because their doctors couldn't control them, and I would want to parenthetically say that main reason in two studies we've done of refractory hypertension why that doesn't happen is that people do not in practice use the right drugs in the right doses. That's simply a reality. Those are two studies separated by 10 years with exactly the same findings.

So, we started with 35 percent at systolic goal, 51 percent at diastolic goal, and that's same interesting 28 percent at both. When we got done -- and we think we're pretty good at doing this -- we came very close to the clinical trial results. 86 percent were under 90, 63 percent were under 140, and 60 percent were at both.

But that's still as good as we can do.

If you look at the diabetics, it's a little more interesting. HEDIS goals at that point are less than 140 over 90, just the way the trials were. This is how we did. 87 of those 437 had diabetes. 52 percent at both goals, but if you look at JNC VI now, which was less than 130 over 85, we were only controlling 22 percent. And the biggest gap was, of course, in systolic pressure. Diastolic, we weren't doing too badly.

If you look at ADA or NKF, it's considerably worse. Now we can only get 15 percent of this high-risk subset at the goals set by expert committees.

And how did we do this? We weren't afraid to use drugs. Most of our patients were on three or four or two. Occasionally we could use non-drug therapy, but very rarely. So, of the diabetics, 50 percent were on three or more and 30 percent were on two drugs at least. And we used everything. We didn't have the restrictions you have in a trial of not having availability of a class. We used diuretics. We used calcium antagonists. We used ACE inhibitors in about 60 percent, ARBs in about 20 percent. So, we're practicing according to guidelines. That was nice to see. We looked at the few people who weren't on one of those and there was a good reason in almost every one. And we used minoxidil, central acting agents, beta

blockers, alpha blockers without any particular bias.

So, I think right now we can conclude -- and I don't know if I've quite made my 5 minutes -- that we've failed to reach systolic goals in a substantial number of patients despite what we currently have to do and despite expertise and despite what happens in a trial. So, I think regimens that include omapatrilat will greatly improve our ability to achieve goals, especially systolics.

Thanks.

DR. BORER: Thank you, Henry. I didn't mean to suggest that you had to hurry. It was just that we have to take a break at some point so people can check out of the hotel and then come back.

DR. BLACK: I do understand.

DR. BORER: Why don't we take just a few minutes to ask you questions. Then we'll break for lunch.

DR. BLACK: Sure.

DR. BORER: Steve.

DR. NISSEN: Actually, Jeff, I had questions that are probably more complex than we can do in a few minutes. I think I would prefer everybody take a break. I think what Henry raises is the issue of benefit to risk. You've now given us the benefit side and I want to explore that, but I don't think I can do that quickly.

DR. BORER: Why don't we then break now and

we'll come back here at 12:50.

(Whereupon, at 12:00 p.m., the committee was recessed, to reconvene at 12:50 p.m., this same day.)

AFTERNOON SESSION

(12:55 p.m.)

DR. BORER: We'll begin again.

It occurs to me, Dr. Waclawski, perhaps you want to make your concluding statements and then we'll get into the issues that we want to get into in terms of the questioning about safety and risk-benefit, to the extent that we have questions about these things.

DR. WACLAWSKI: If you would just let me clarify one thing. Did you intend to have questions specifically with respect to Dr. Black's presentation?

DR. BORER: Yes.

DR. WACLAWSKI: And you'd do that after the concluding statements.

DR. BORER: Yes. We'll wait for you to finish.

DR. WACLAWSKI: Very good.

Good afternoon again. I'm Anthony Waclawski. We'd first like to thank the committee and FDA for their kind attention and the chance to present these data to you.

As you continue your discussion today and you consider the target population, we would welcome the committee to consider our proposal for a target population. But we fully realize that there may be other subsets of this population where the committee considers the benefit-to-risk ratio for omapatrilat to be favorable. We're

looking forward to your continued deliberations on these points.

That concludes our formal presentations for the day. Thank you again.

DR. BORER: Thank you.

DR. WACLAWSKI: Elliott Levy can now return to the podium.

DR. BORER: Let me ask you, because I think we want to be absolutely fair in hearing everything you think is important. You presented us or we were presented with extensive documentation of the risk management plan. Is there something that's changed since the document that was submitted to us? Because if not, I don't think we need an extensive presentation here. If it has changed in some substantial way and you think that's important, then you should be able to tell us about it.

DR. WACLAWSKI: I think we'll agree that what you've seen we've sufficiently clarified through our presentations and made the points that we felt we needed to make, mainly about the objectives of the plan and why we think that an education-based program is one that could have some success, and that we're confident with working with the agency going forward.

DR. BORER: With that having been said, let's get into the questions of the committee, the remaining

questions regarding safety and the risk-benefit issues. We'll start with the committee reviewer. Steve.

DR. NISSEN: Thanks, Jeff.

Again, we left with Henry up there and we didn't get a chance to interact with you, Henry, and I really would like to. I'm going to make a couple of statements and then ask you some questions.

I assume you would agree with me that the long-term effects of vasopeptid ACE inhibitors on morbidity and mortality are not known.

DR. BLACK: Yes, I would agree.

DR. NISSEN: And that we've seen demonstration of very perhaps superior blood pressure reduction with omapatrilat in these studies. So, what I'm grappling with is how or whether we can translate the blood pressure differences for this new class of drugs into estimates for event reduction. And I want to ask you a hypothetical question because in my mind what we're all balancing here is benefit versus risk, which you were obviously addressing in your presentation. So, here's my question.

If we had a diuretic that reduced 24-hour ambulatory blood pressure by 12 millimeters of mercury and an ACE inhibitor that decreased ambulatory blood pressure by 10 millimeters of mercury, would we be confident that the diuretic arm would result in reduced events? So, you

have a diuretic that decreases by 12 and you've got an ACE inhibitor that reduces by 10, using the most elegant 24-hour measures available.

DR. BLACK: This is if compared to each other?

DR. NISSEN: Yes, compared to each other.

DR. BLACK: I think in general I can't answer that specific question without having some real data to back it up.

I do think -- and I think this point was talked about a lot yesterday -- that incremental drops in blood pressure, even small ones, seem to result in considerable reduction in outcome events.

DR. NISSEN: I guess what I'm trying to get at is whether, in fact, one can predict that a drug that has a modestly greater blood pressure reduction will result in a greater reduction in events. Because isn't that what we're being asked to assume here in terms of the benefit of this agent?

DR. BLACK: Yes, I understand. There have been some attempts to do this. Some have used epidemiological estimates. I think you saw some of that yesterday from Dr. Kannel. Dr. Stamler has used similar things to predict reductions in mortality, of small reductions in systolic pressure leading to fairly large reductions in mortality. And there's been a large meta-regression done by Jahn

Staessen suggesting that small differences in systolic pressure could result in 20 to 25 percent reductions in cardiovascular mortality. Now, those studies are always up for some interpretation, but there's a consistency about them based on 31 clinical trials that have been done so far.

DR. NISSEN: Mike Weber, do you want to offer us some advice here? Because there are some calculations that appear in here about this relationship between how many events are prevented versus the risks.

DR. WEBER: Yes, but underlying that, Steve, is exactly the conversation you had yesterday morning and that the difference in blood pressure has its greatest meaning when you're comparing the same kinds of pharmacology. So, if you had one ACE inhibitor that was minus 10 and the other was minus 12, then I'm going to favor the one that's minus 12. But you gave us a diuretic at minus 12 and an ACE inhibitor at minus 10, and that's a very difficult situation because they clearly have very different profiles, and I suspect there are some patients who are going to do a lot better with one than with the other. But I think what we're talking about here, of course, is within the ACE inhibitor family.

DR. NISSEN: Well, see, it was a deliberately difficult question because for me to make a judgment here,

I have to believe that vasopeptide ACE inhibitors fundamentally will act on events in the same way that the ACE inhibitors act on events. Yet, we're talking about the first drug in a new class that does different things. So, I'm asking you guys -- I respect both of you. You've done tremendous work over the years in hypertension -- whether you can justify that sort of assumption, and if so, how you can justify that assumption.

DR. WEBER: Well, I think we would both depend quite heavily actually on what Milton showed us just before lunch because a concern you would always have is that what it is that is different about omapatrilat didn't just mean more blood pressure reduction but everything else stays the same, but whether there is something about adding in this NEP inhibition that's going to cause something that's unexpected or adverse.

I think the two things that Milt showed us, first of all, the major cardiovascular endpoints in OCTAVE were certainly moving in the right direction, for whatever that's worth, but certainly not moving in an adverse direction, and secondly, in the OVERTURE study, the heart failure trial, where again you could have a pretty strong level of confidence, particularly in the hypertensive patients, that if anything, things were favoring omapatrilat, for whatever that's worth. But I think we can

at least lay to rest the concerns that Tom Fleming was expressing yesterday about comparing different classes.

DR. NISSEN: Well, I guess the problem we see with using the OVERTURE data isn't the problem that that's not the population that this drug is being proposed to treat. It's not being proposed for heart failure. It's being proposed for hypertension. So, the reassurance is obviously going to be limited, is it not, by the fact that it was studied in a different population than is being proposed to be used here?

DR. WEBER: That's right, albeit a high risk population with hypertension, but I acknowledge that.

Dr. Hennekens, I wondered, would you have a comment?

DR. HENNEKENS: Well, on this point, Steve, I'm a recent addition to this advisory group because of work I had done at Harvard on hypertension, some of which included collaboration with the Oxford Group. We looked at 14 randomized trials, including over 30,000 subjects that were treated for 2 to 3 years with blood pressure lowering agents. We predicted going in that the 3 to 5 millimeter reductions would be associated with about a 40 percent lowered risk of stroke and a 30 percent lowered risk of CHD and about a 20 percent lowered risk of cardiovascular mortality.

What we found is that 2 to 3 years of blood pressure lowering led to the predicted 42 percent lower risk of stroke, about a 16 percent reduction in heart disease, and about a 21 percent reduction in vascular mortality, so that the stroke and the vascular mortality reductions, over 2 to 3 years with this amount of blood pressure lowering, were very similar to the epidemiology. Where there was the shortfall was in CHD.

We speculated that chance in the trials might explain it. We speculated that there might be a more immediate and direct effect on the brain, a more delayed and indirect effect on the heart via atherogenesis. We also speculated that the first-line drugs, the diuretics and beta blockers, which have a 5 percent adverse effect on LDL, might be increasing the risk of coronary heart disease events.

The issue here becomes complicated in terms of the application of those data to the risk-benefit ratio on this drug, and I think that's why the sponsors have correctly tried to define a target population, all of whom have a 10-year risk of about 20 percent or greater, and if we add uncontrolled hypertension to that risk, it's probably closer to a 40 percent 10-year risk of adverse cardiovascular outcomes. And it's in these patients where I think the claim is that the benefits will outweigh the

risk, but that does presume a 2- to 3-year sustained difference in blood pressure of that amount.

DR. NISSEN: I've looked at these data very carefully as the primary reviewer here, and as I think we all at this table know, there is no long-term exposure data to omapatrilat available. So, we don't know what happens down the road.

DR. HENNEKENS: No, but what we do know, though -- and I will yield to Dr. Levy in just a second -- is that you see a sustained advantage over 24 weeks in 25,000 subjects, and that's not the same as a 2- to 3-year reduction, but it's at least heading down the right path.

DR. BORER: Bob, did you have a comment about this?

DR. TEMPLE: Slightly different.

DR. LEVY: May I just respond? A point of clarification. We do actually have quite a bit of long-term experience with omapatrilat. We have patients treated for up to 5 years. Patients have been treated in controlled trials for up to a year, and the antihypertensive effects are sustained and they're superior to comparator. Over 5 years, there's no indication that the antihypertensive effect is lost. In fact, we did a withdrawal study in which patients who were maintained on the drug for over a year and had stable blood pressures

were withdrawn from therapy to demonstrate that it retained its antihypertensive effect.

DR. NISSEN: But let me just make sure I understand what you know. The differential effect against, say, enalapril is sustained in those longer-term trials?

DR. LEVY: We have comparative data versus losartan not enalapril in a trial that lasted a year, and the difference between the two drug regimens is sustained.

Our longer-term experience is in primarily open-label, uncontrolled trials.

So, of course, we can't speculate what would happen if patients were to be followed for 5 or 10 years. On the other hand, in the patient population we've identified who don't seem to be able to get to target with existing meds, it seems highly likely that there would be some lasting benefit if they can stay on this one.

DR. NISSEN: But there's no hard data on differential effects beyond 12 months.

DR. LEVY: Yes, that's right.

DR. NISSEN: Now, the second question --

DR. BORER: But just before you go on to that, Steve, Bob.

DR. TEMPLE: I have an observation about this. Steve is obviously asking the fundamental surrogate question. You always, when you rely on blood pressure, are

making some assumptions, and they're not always right. I'm absolutely positive you get better blood pressure control with 100 milligrams of chlorthalidone than you do with 25 milligrams of hydrochlorothiazide, and there are even well-controlled studies that show improved survival or improved stroke anyway in those people. But it turns out you pay a price for the better control in the form of arrhythmias and other things. So, it turned out there was an additional effect in addition to the one that you were relying on that was a worry.

Nonetheless, for what's it worth, we do act -- and the whole community acts -- as if lowering blood pressure to goal is a desirable thing however you do it, with whatever drugs you do it, even though they can't prove that. ALLHAT is supposed to get you some further insight on that question, is lowering blood pressure equivalent, to the same extent the same, no matter how you do it?

DR. NISSEN: I guess the spirit of my question relates to trials like LIFE where a similar blood pressure reduction has different effects on events. So, what I said yesterday I'm kind of repeating today, which is when you cross classes, there may be class-specific effects that are unknown, uncertain, and it's particularly germane when it's the first drug in the class were we don't really know, over a period of time, what the effect of morbidity and

mortality are, let alone know what it is relative to some other agent.

DR. TEMPLE: Yes. But of course, every time you approve a new drug, especially of a new class, you don't know that. Some people would tell us we should make people know that and do an ALLHAT each time, but we have not adopted that policy.

DR. NISSEN: Well, Bob, again, the difference here is that there's risk. If the drug had a similar risk profile, we wouldn't have this conversation.

DR. TEMPLE: That's fair.

The other observation I guess -- I've written this, so I want to say it -- is it doesn't seem out of the question about you can learn about some unexpected bad news from studies in different populations. So, I've always felt some of the concerns about calcium channel blockers in hypertension were, to some extent, resolved by the post-infarction studies, a fragile group, and it didn't seem to do anything bad in those, other than cause heart failure. And I believe that's the argument they're making about OVERTURE, that it should reassure you that nothing unexpectedly awful is happening even though it's a different population.

DR. NISSEN: So, for me the most powerful evidence would be obviously direct evidence on morbidity

and mortality, but there is less powerful evidence that might be germane here, and I wanted to give you an opportunity to give us your perspective on it, and that is the issue of target organ protection. So, I wanted to know if there is any evidence here of superior target organ protection for omapatrilat in comparison to other available agents.

So, this would obviously be another kind of surrogate, but it would be one that we probably ought to weigh in our deliberations. So, I'd be interested in anything you can provide that might help us there.

DR. LEVY: Some of this information was cited briefly in the briefing documents. Let me just review that.

DR. NISSEN: But we haven't discussed them. That's what I want to discuss now.

DR. LEVY: Yes. There's a presentation on this issue.

We conducted a number of studies designed to examine the effect of omapatrilat on target organ damage. Three of them were cited in your briefing document.

DR. NISSEN: Now, keep in mind now we're talking about in comparison to other agent, not just against placebo.

DR. LEVY: Yes. I'm going to show you the

findings from three studies and briefly cite a fourth.

In your briefing document, the first is a trial that was conducted in patients with chronic stable angina. We had noted in preclinical studies that omapatrilat had an anti-anginal effect that wasn't shared by ACE inhibitors. And we conducted a trial -- it was a placebo-controlled trial -- in which omapatrilat was shown to improve exercise tolerance. That was this study.

And if I could go to the next slide. We demonstrated significant improvements in various measures of ischemia, including maximal exercise duration, time to onset of angina, and time to ST segment depression. So, not an active-controlled trial, but a novel finding that hasn't been described with ACE inhibitors.

DR. NISSEN: Unfortunately, it wasn't germane to what I was asking because I'm looking for evidence that there is some target organ protection here not afforded by an active control agent. In other words, is there anything that says that omapatrilat improves angina in comparison to enalapril or lisinopril or amlodipine or anything like that?

DR. LEVY: Right. Well, again, this hasn't been described with the ACE inhibitors, so we thought it was worthwhile.

DR. NISSEN: Also, certainly with amlodipine

it's been described.

DR. LEVY: If I could have the next slide. We conducted a study to examine the effects of the drug on proteinuria. This was actually a study conducted early in the clinical development program. We used amlodipine as the comparator because of its potent effects on blood pressure and its apparently neutral effects on proteinuria. We found in this trial, if I could have the next slide, that omapatrilat produced significant reductions in urine albumin excretion rate that in magnitude were about comparable to that seen with the ACE inhibitors.

DR. NISSEN: Were there any direct comparisons made between omapatrilat and, say, ARBs, which I guess are about to be labeled for this indication, or ACE inhibitors?

DR. LEVY: Not for this purpose.

Now, the next study we have a comparison with losartan in patients with left ventricular hypertrophy. The primary endpoint here was change in echocardiographically determined LV mass after 24 weeks of therapy with omapatrilat or losartan, and then patients remained on therapy for up to a year. At the primary time point, at week 24, both drugs reduced left ventricular mass to a significant degree with a trend towards greater reduction with omapatrilat.

DR. BORER: What were the blood pressure

responses to the two drugs?

DR. LEVY: Can I see the tracing, summarized blood pressure changes over the full duration of the study?

These are the blood pressure changes over the full 52 weeks of the trial. In the first 24 weeks, patients remained primarily on monotherapy, and then they went on to add adjunctive therapy. About 34 percent of those treated with omapatrilat received another agent; about 60 percent of those treated with losartan. And there's a difference in systolic blood pressure of about 4 millimeters of mercury that's pretty well sustained from week 24 in the trial on.

You had asked me before about what evidence we had that there's a long-term superiority. This is an interesting trial, much smaller than OCTAVE, but one in which, despite a much greater discrepancy in the rate of adjunctive therapy use, you still see a preserved difference of about 4 millimeters of mercury in systolic blood pressure.

DR. NISSEN: But I guess I was looking more for evidence. I guess what I'm trying to understand is it would help me if there were evidence that in comparison to ACE inhibitors or calcium channel blockers or diuretics, that some organ system was protected in some way.

DR. LEVY: Let me show you one more study, if I

could just have the primary finding from the CHOIR study. These are data that were not included in the NDA, and so the FDA hasn't reviewed them. If there of interest to you, I'd certainly like them to review the study.

But this was a study that we conducted in patients with systolic hypertension, randomized to treatment with omapatrilat or enalapril, in which we assessed the effect of the drug essentially on conduit vessel stiffness, which is a major finding in older patients with primarily systolic hypertension and is thought to have a pathogenic role. Now, in animal studies the natriuretic peptides were shown to have a favorable effect on the large arteries.

In this study -- can I just have the primary results?

DR. NISSEN: I'm not sure I would call that an end organ, though.

DR. LEVY: Well, there's a degenerative change in these vessels over time that seems to be associated with poor outcomes.

Anyway, the drug produced a reduction in central pulse pressure that's not seen with enalapril, and it indicates that there's a distinct effect on the pathologic change in these conduit vessels.

So, we certainly have a variety of information

about target organ damage. At the very least, the drug appears to share the beneficial effects of existing drugs. It may be superior in some areas.

DR. NISSEN: Yes, I would agree with that conclusion, from what I've seen in the documents, that it does appear to share those properties. But again, looking for superiority as a way to justify the increased risk, that was what I was really probing for.

That's all I have.

DR. WEBER: I just wanted to remind Steve that, in fact, that in previous trial with losartan, the differential effects on left ventricular hypertrophy were really quite clear. And that's interesting because in the LIFE study, if you remember, losartan was clearly superior to the beta blocker in regressing LVH. So, this is, if you like, one good example of a target organ difference to the favor of omapatrilat against a standard comparator.

DR. NISSEN: Well, Mike, the differences were highly significant compared to placebo, but there was not a significant difference compared to losartan. The p value was nonsignificant. So, again, it was a demonstration of equivalence, not necessarily of superiority.

DR. WEBER: I think it was 7 versus 4.

DR. NISSEN: Well, but the p value was greater than .1.

DR. LEVY: You're correct. There was a trend towards greater reduction with omapatrilat.

I have data on some of the subgroup analyses that were requested before the break.

DR. BORER: Why don't you go ahead and then we'll get on to some other questions.

DR. LEVY: Dr. Fleming had asked about efficacy and safety in the proposed target population. If I can have the first slide there. This is the proposed target population. These patient populations are identified based on review of the clinical guidelines to determine patient populations that would increase CV risk and therefore might stand to gain the most from incremental reductions in blood pressure. Of course, the second criteria, hypertension difficult to control with existing agents, patients who can't benefit elsewhere.

We presented these data by subgroup because they're post hoc analyses, and it's very important to be able to examine each of the subgroups for consistency.

Can I have the next slide? I showed you these results earlier. I call your attention to the right-hand panel. There's a very consistent reduction in blood pressure in all these high-risk groups, ranging from 3 to 5 millimeters of mercury more with omapatrilat than with enalapril.

But for the sake of clarity, we've prepared a pooled analysis in which we put together these populations. This is what a population looks like. Again, the two largest risk groups that were represented in OCTAVE were diabetes and atherosclerotic disease with 3,300 and 2,300 patients respectively, and then smaller numbers with renal disease and heart failure. So, there are about 6,000 patients represented in this analysis. They tend to be a little bit older than the overall study population, but otherwise they're not remarkable in terms of demographic characteristics.

DR. FLEMING: And do all of these patients also satisfy the criterion of having had a difficulty to control hypertension?

DR. LEVY: This is all subjects. I wanted to show you the largest group possible. We've also done these analyses for those who entered the study uncontrolled on medication and the results are very similar.

DR. FLEMING: If you have it, because time is short, it would be adequate just to drill down to that target group rather than including this bigger group that includes a number of people who wouldn't be in your target, if you have it.

DR. LEVY: I'll call it up, but there really are only two slides to show and one is that, as you'd

expect, when you see groups that are consistent, you see a consistent difference in efficacy of about 4 millimeters of mercury in the target population at week 24. As I showed you earlier, the rate of angioedema in the study was lower in those with diabetes or atherosclerotic disease than in others. So, the risk of angioedema in the target population is also lower. The two events that are subject to that airway compromise were not in the target population and the number of patients hospitalized was also quite small.

DR. FLEMING: So, it's just not been possible at this point still to produce the actual target population subgroup? I'm presuming that the target population subgroup would only be half that size or two-thirds.

DR. LEVY: I'm sorry. If we were to focus on those patients who entered the trial uncontrolled on therapy with the same comorbid characteristics, there are about 2,000 subjects in the analysis. Again, the reduction in blood pressure is 3.6 millimeters of mercury more with omapatrilat than with enalapril.

DR. FLEMING: And do you happen to know what the distribution is for the clinical events and also for the safety events?

DR. LEVY: Yes. As you know, there were 226 clinical events in the trial. In this group there were

102, 58 in subjects randomized to enalapril and 54 in subjects randomized to omapatrilat. So, the hazard ratio is .91. It's very consistent with what we saw overall.

DR. FLEMING: And the angioedema? Did you have that data?

DR. LEVY: Well, this is the angioedema.

DR. FLEMING: That's still a bigger group. Right? That doesn't focus or drill down on only those people that were difficult to control hypertension at baseline.

DR. LEVY: In those who had these comorbid characteristics and who entered the study on medication uncontrolled, there were 18 angioedema events out of 1,140 subjects on omapatrilat, an incidence of 1.58 percent, and 8 events out of 1,053 subjects on enalapril, .76 percent. In both cases, most of the events were severity class I.

DR. FLEMING: Do you have how many were at III-IV?

DR. LEVY: I'm sorry?

DR. FLEMING: Severity class III-IV.

DR. LEVY: Well, as you can see here, in the larger group, there were 2 patients who were hospitalized, neither with airway compromise, and there were no patients who required mechanical airway protection. In the smaller group, there were also 2 subjects hospitalized without

airway compromise.

Does that answer your question?

DR. BORER: Not quite. Just so it's on the record here, people who entered the trial uncontrolled are not actually the group that Tom is focusing on. I'm sure you don't have these data, and nobody expects you to put them together in 2 minutes. But it's the people who couldn't be controlled, not the people who weren't controlled.

Henry Black showed us that there are people in his own clinic -- and he's an expert -- on maximal therapy who aren't controlled. So, they exist but those aren't the people who came in uncontrolled into this clinical practice population for a study.

The question we would really have to define the risk-benefit ratio we want most precisely would be the people who, on maximal medical therapy under optimal care, could not be controlled without omapatrilat and now could be controlled with omapatrilat. What's their risk?

I don't think you have that group, but it's different from your group 3 in the OCTAVE trial. Again, you may have those data. I don't know.

DR. LEVY: We've showed you data from a variety of groups that are relatively difficult to control. I think what you can conclude is that the efficacy advantage

is preserved, no matter how difficult the patient is to control, and we got some very difficult-to-control patients represents in OCTAVE. In patient populations where there's a higher risk of diabetes or atherosclerotic disease, there's less angioedema.

DR. BORER: All the data you've shown us are consistent with what you're suggesting.

One of the reasons that I'm sort of not fully satisfied -- and it may be impossible without some additional trial to provide that satisfaction -- is that the argument that routine clinical practice does it this way and they don't make it just isn't really a very good argument to me, as I suggested earlier.

One of the reasons that I'm concerned about this and the underuse of appropriate medications and whatever are the data that Ray Lipicky presented I think the first time two years ago, although maybe he put them together earlier than that, about the dose-response curve of antihypertensive drugs showing that, by and large, probably everybody underdoses most antihypertensive drugs, and if you just push the dose a little bit more, you'd get the blood pressure down with conventional agents that have already been approved.

So, to assuage my concern about that, the most convincing thing I've heard and seen was the slide that

Henry showed earlier from his own clinic where there are people who are really expert at this who have --

DR. BLACK: I can perhaps try to give you some idea. I don't think it's possible with what you saw here to make that guess. But in our diabetic group, which is not large, where we are very aggressive using the real guidelines for diabetics -- and diabetics are one of the groups that this is being recommended to use -- we could only achieve goal in about 20 percent of people with what we currently have. And we use large doses. We use four or five or six drugs if necessary. So, there's a big gap in that group alone.

DR. LEVY: If I could show one slide just to clarify a point. If I could have the slide from the 73 study.

We're proposing that the drug be used in the patients that Henry Black is talking about, the patients who can't be brought to control despite very honest attempts to get them there. In the right-hand panel here, you've got patients who were on very high dose ACE inhibitor therapy plus one or two or three other medications. They remain far from target with systolic pressures at baseline in the 150s. The substitution of omapatrilat for their prior ACE inhibitor therapy produced further reduction in blood pressure of around 10

millimeters of mercury. There are few alternatives for these patients.

The question was raised before about whether one could achieve the same results with b.i.d. enalapril or with the addition of a thiazide. In patients who can reach those with those manipulations, this is not the role of the drug. But there is a very substantial incremental blood pressure reduction which may be of value in patients who are very difficult to control with existing drugs.

DR. BORER: You don't really believe that if the drug were approved and marketed, that it would only be used in the group that Henry Black couldn't control with six other drugs.

DR. LEVY: I think Henry has shown data that there are 30 to 40 percent of patients who can't be controlled.

DR. BORER: I understand, but I'm asking you do you really believe that that's the way the drug would be used if it were marketed. It's a rhetorical question.

(Laughter.)

DR. CARABELLO: But it's a question I'd like to go into a little bit further. I see this drug perhaps as somewhat akin to amiodarone where you have the nettlesome problem of atrial fibrillation, very few drugs to control it, and we have a very toxic, not particularly safe drug,

but its risk is mitigated by the fact that it's only prescribed by a few people, those people who have a special knowledge of the drug and of arrhythmias. My question would be is, could we limit the drug in terms of who prescribes for what, where, and when? And would that not be yet a strategy we haven't talked about for mitigating risk?

DR. WACLAWSKI: Excuse me, Dr. Borer. Could I just add to your rhetorical question perhaps? It's certainly something we have been discussing on the risk management side within the company for some time, and it certainly is one of our concerns as well, which is that if and when the drug were to be approved with a target population, it would be necessary to show that we could limit the use to those patients where the benefit-to-risk is clearly favorable.

And that's important to us not only for the good of the patients, but also because even if the benefit-risk was to be expanded beyond that later, it's important to focus on a group that has the highest benefit-to-risk initially for the initial marketing of the product. We recognize that as a risk and we've worked internally try to work through that. And there may be some tools, some ways to build the risk management plan around that, and that's something certainly we would welcome input on. But your

concern is well taken.

DR. BORER: 15 years ago -- and I guess it's 17 years ago now -- this same discussion revolved around amiodarone, and the consultants who were speaking for the drug insisted that it should be approved only for use by experts who were the six of them sitting in the front row --

(Laughter.)

DR. BORER: -- and shouldn't be used by anyone else. I don't think we achieved that, but perhaps that's okay.

Bob.

DR. TEMPLE: I have a slightly different question. Let's say we were willing to assume that it really was good for outcome to be able to lower blood pressure 3 millimeters of mercury more than you otherwise could. That's sort of what Henry is saying in some ways.

There are two sets of data. One is moderately convincing evidence I think that this works a little better than other ACE inhibitors. At least with lisinopril, how many times a day you give it probably doesn't matter, and they seem to have some data there. So, that's one thing.

What I hear Henry saying is, look, if this is as well as you can do with available therapy without omapatrilat, you're going to do 3 millimeters of mercury

better when you substitute this for your other ACE inhibitor. So, that's one line of argument.

The other line of argument is that OCTAVE actually showed that you could get 3 millimeters of mercury better with this than without it, but I have some questions about that. These are all points raised by Dr. Stockbridge in his review.

It's quite striking that even though people were allowed to increase the dose of enalapril to gain control, only about 40 percent of people got on the maximum dose, and just to save Steve from having to say it, they didn't get an opportunity to have it twice a day. So, you don't really know what would have happened if they had gone to the right dose. Maybe that 3 over 2 would be 1 over .5.

In addition, the fairly simple expedient of adding another drug was only used in a very small fraction of patients. So, I recognize the idea that is implicit in what Henry said, which is, well, it works better, so you've got to end up better. And I guess I raise the question, don't you have to know in practice how different these resistant patients will be when you actually do it as opposed to sort of the theoretical advantage which is, well, how can it not, which is I think what Henry's argument is.

So, I'd be interested in some response to why,

given the opportunity to use the proper dose or the maximum dose, if you like, of enalapril and given the opportunity to add therapies which they could have, nobody really did it. So, do we really know how much better this is than conventional therapy in an actual "I can't control this patient" setting?

I take your point. A lot of people can't be controlled, but if this were available, do we actually know in a hands-on way and a demonstrated way how much difference it would make? That's really what Norm was asking in this review.

DR. BLACK: Bob, if I could, I'd try to give you two impressions. We've done two assessments of our clinic when I was in New Haven and again in Chicago about 10 years later to look at our patients who were resistant and see what the reasons were and what we could about it. The most common reason both times was that the patients that we got were not properly dosed, did not get the right drugs in the right order, didn't have them long enough, exactly the practice gaps we see.

We were able with our manipulations to get control in about 60 percent, very similar to what you saw here, both times. In 1990, it was using diuretics when people didn't know how to use them, and there are newer things now. That wasn't quite the problem. So, I think

that's going to be an issue. I don't think you can address exactly what would happen if omapatrilat were around, but I think that's the pattern of practice.

In our trials, where we do lay out a protocol, we reward people for getting control and punish them when they don't and let them use whatever they want. We still can't do any better than, in fact, what we're seeing.

DR. TEMPLE: But I'd still like to hear a little bit about -- I mean, you had a difference of 3 over 2, or thereabouts, with people on inadequate doses of enalapril. You've got to imagine that if the dose had gone up or if it had been b.i.d., the difference would be less than that, and you certainly have to imagine if they'd added a drug, which in many cases they did not, the difference would have to be reduced. Now, Norm had an estimate based on what happened when you did add a drug, that it wouldn't be very hard to get control by adding another drug, and yet they didn't.

Obviously, the question is, okay, on the one hand, I can get away without this other drug. On the other hand, I have the angioedema. So, you sort of have to know how you do with another drug. Or maybe you don't think you do. So, what do you think about that?

DR. FLEMING: Henry, just for my understanding of your response to Bob's question just now, you've made