DEPARTMENT OF HEALTH AND HUMAN SERVICES

FOOD AND DRUG ADMINISTRATION

CENTER FOR DRUG EVALUATION AND RESEARCH

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CARDIOVASCULAR AND RENAL DRUGS

ADVISORY COMMITTEE

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90th MEETING

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Monday, May 1, 2000

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The Advisory Committee met at 10:00 a.m., in the Masur Auditorium, Building 10, National Institutes of Health, 900 Rockville Pike, Rockville, Maryland, Dr. Robert Califf, Acting Chairman, presiding.

PRESENT:

ROBERT CALIFF, M.D., Acting Chairman

JOHN Di MARCO, M.D., Member

THOMAS GRABOYS, M.D., Consumer Representative

ILEANA PINA, M.D., Member

PRESENT:

JOHN C. STANDAERT, Executive Secretary

PARTICIPANTS:

PAUL ARMSTRONG, M.D.

JEFFREY BORER, M.D.

THOMAS FLEMING, Ph.D.

JOANN LINDENFELD, M.D.

UDHO THADANI, M.D., FRCP

INVITED GUESTS:

GEORGE BAKRIS, M.D.

MARK MOLITCH, M.D.

FDA PARTICIPANTS:

JAMES HUNG, Ph.D.

RAYMOND LIPICKY, M.D.

SHARI TARGUM, M.D.

ROBERT TEMPLE, M.D.

SPONSOR REPRESENTATIVES:

BARRY M. BRENNER, M.D.

GILES DAGENAIS

CARL FURBERG, M.D., Ph.D.

HERTZEL GERSTEIN, M.D., M.Sc.

THOMAS K. ROGERS, III, M.S.

SPONSOR REPRESENTATIVES (Continued):

SALIM YUSUF, D.Phil., M.D.

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(10:04 a.m.)

ACTING CHAIRMAN CALIFF: Good morning. I'm Rod Califf, and it's now time to start our Cardiovascular and Renal Drugs Advisory Committee meeting.

This morning we have some invited guests and some new participants to this committee, in addition to the return of some old participants to help us out. We'll have time to introduce everyone as we get into the discussion, but we'd like to open the meeting by asking if there's anyone who would like to make a public comment.

(No response.)

ACTING CHAIRMAN CALIFF: Hearing no public comment, we'll now turn it over to Joan Standaert, who will acknowledge the conflicts.

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

Based on the submitted agenda and information provided by the participants, the Agency has determined that all reported interest in firms regulated by the Center for Drug Evaluation and Research present no potential for a conflict of interest at this meeting with the following exceptions.

Drs. Milton Packer and Marvin Konstam have been excluded from participating in today's discussion and vote concerning Altace.

Further, in accordance with 18 USC 208(b), full waivers have been granted to Drs. George Bakris, Thomas Fleming, Udho Thadani, Ileana Pina, Joann Lindenfeld, and Mark Molitch. Copies of these waiver statements may be obtained by submitting a written request to FDA's Freedom of Information Office located in Room 12A30 of the Parklawn Building.

In addition, we would like to disclose for the record that Drs. Robert Califf, Udho Thadani, and George Bakris have interests which do not constitute financial interest within the meaning of 18 USC 208(a), but which could create the appearance of a

conflict.

The agency has determined notwithstanding these interests, that the interests of the government in their participation outweighs the concern that the integrity of the agency's programs and operations may be questioned.

Therefore, Drs. Robert Califf, Udho Thadani, and George Bakris may participate fully in all matters relating to Altace.

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

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

This concludes the conflict of interest statement for this meeting.

I have been asked by the management of the

auditorium to make a general announcement regarding food and drink in the auditorium. They are concerned that people have been leaving papers and leaving the site in not too nice a condition. So they are asking that you please respect the building and take all of your papers and everything that you bring with you back.

ACTING CHAIRMAN CALIFF: Thank you.

We'll move on now with the presentation from the sponsor, and I think what we'll do is we'll hear from each speaker, each individual speaker, and then we'll let the panel ask questions of each individual.

MR. ROGERS: Good morning, Mr. Chairman, distinguished members of the panel. We are pleased that today you will be considering a supplement to King Pharmaceuticals' NDA for Altace, or ramapril capsules.

Altace has been approved for the treatment of hypertension sine 1991. It is also indicated for the treatment of congestive heart failure in patients who have sustained acute myocardial infarctions.

The supplemental application being considered today seeks approval of additional indications for Altace. The proposed new indications are for the prevention of cardiovascular death, myocardial infarction, and stroke.

Based upon positive comments from the FDA's review, all cause mortality has also been added to the indications shown on this slide. Of course, we understand that the text of final labeling will be the result of meaningful discussions with the agency after the conclusion of today's meeting.

The supplement is based upon the findings of the Heart Outcomes Prevention Evaluation Study, known as the HOPE study. The study was conceived and independently conducted by Dr. Salim Yusuf of McMaster University and administered by members of the International Steering Committee for HOPE.

The study evaluated the long-term benefits of ramipril in an extremely large patient population that was followed for approximately four and one-half years.

Today Drs. Yusuf, Brenner, Gerstein, and

Furberg will present and discuss the findings of the study. We're also joined today by additional consultants, Dr. Giles Dagenais, who was co-chair of the study, and by Dr. Craig Pratt.

From a public health perspective, the implications of the HOPE Study are dramatic, and we are fortunate and appreciative that Dr. Yusuf persevered to obtain funding necessary to conduct an independent study of such magnitude and duration. Dr. Yusuf will be our first presenter and will also facilitate further discussions as the morning proceeds.

Thank you.

ACTING CHAIRMAN CALIFF: I'm assuming the panel has no questions at this point.

Obviously in the redesign of this auditorium they didn't take us into consideration up here. We're sort of packed in like sardines, but we'll make the best of --

DR. FLEMING: Rob, it's correct then that the labeling indication differs from what has just been sent to us on paper?

ACTING CHAIRMAN CALIFF: Only for the --

DR. FLEMING: All cause mortality?

ACTING CHAIRMAN CALIFF: -- all cause mortality. That's correct.

DR. YUSUF: Dr. Califf, Dr. Lipicky, ladies and gentlemen, it's my pleasure on behalf of the HOPE Steering Committee and investigators to present to you the results of the study.

HOPE stands for Heart Outcomes Prevention Evaluation Study. It's a large, simple, randomized trial of ramipril ACE inhibitor and Vitamin E in patients at high risk for cardiovascular events.

I'm not going to show you data related to Vitamin E. Suffice to say that Vitamin E proved to be ineffective in this trial.

Now, as you all know, there is a long history of the evaluation of ACE inhibitors in cardiovascular disease going back some 20 years. A series of trials initially high risk and sick patients were conducted. This was initially in people with heart failure, and we know it reduces mortality and heart failure hospitalizations, and some of these

trials also suggested a reduction in myocardial infarction which has not been fully accepted.

There have been similar data in patients with asymptomatic LV dysfunction, post myocardial infarction, some data on acute myocardial infarction, and in diabetics at least in the literature there's a range of studies that have indicated a benefit on progression of renal disease.

Looking at the literature amongst hypertensives, it seems to be similar in reducing clinical events likely to be better than calcium blockers in diabetics, and there's a meta analysis in press at the moment.

However, there's a large body of people, those with other manifestations of coronary artery disease and without LV dysfunction or heart failure, those with strokes, those with peripheral arterial disease or other diabetics in which we do not know if ACE inhibitors prevent clinically important outcomes.

The starting point for me in the design of HOPE was my experiences in the SOLVD trial. In this trial of 6,700 people with low ejection fractions,

half of whom had heart failure; the other had asymptomatic LV dysfunction; we had a surprising finding, and the finding was a reduction in myocardial infarction by about 23 percent, which was statistically significant and consistent in the two parts of the study.

Nevertheless, these data generated a lot of interest, but was not seen to be convincing to most people. When we looked at the literature and looking at the literature, we find epidemiological data that would suggest the possibility that modifying the renin angiotensin system may be helpful.

These are data from one such study by Mickey Alderman, where he took 2,000 hypertensives, treated them with diuretics, controlled their blood pressure, then profiled their renin levels, and whether they were smokers or nonsmokers, the risk of myocardial infarction increased with the risk or with the levels of renin; the same thing after controlling for cholesterol; the same thing after controlling for glucose.

In addition, there were animal data, and

these are one such studies, indicating in the radum (phonetic) centric artery that use of an ACE inhibitor decreases vascular wall thickening and also leads to dilatation of the artery.

Victor Zahl (phonetic) has done a large amount of work in this area at the molecular level and has come up with a unifying hypothesis. In this hypothesis, he thinks of the classical respecters as increasing oxidative stress in the vascular wall leading to endothelial dysfunction. This then leads to a decrease in nitric oxide activity, and the secretion of a number of local mediators, including an increase in tissue ACE levels and adjutants in two levels.

This has a prothombotic effect, an effect in stimulating inflammation in the vessel wall. It could lead to vasoconstriction. It could lead to hypertrophy both of the heart as well as the vessel wall, and my promote plaque rupture by inducing the secretion of various hormones, various enzymes that are proteolytic, such as the metallo-proteinasis (phonetic).

So this was the basis on which several years ago, eight years ago, we embarked on this trial. This is the summary of the study. The main name of the study was to assess the effects of ramipril on Vitamin E or all Vitamin E versus its placebo on the primary composite endpoint of cardiovascular death, myocardial infarction or strokes.

This was a randomized, double blind study utilizing a two-by-two factorial design. We deliberately chose wide entry criteria. The study was large, and it was simple.

Nine and a half thousand patients were followed for about four to six years. The study had high power to detect relative risk reductions in the primary endpoint in the range of 11 to 13 percent. In addition, the study was designed specifically to examine the results in a few key subgroups and on a number of secondary endpoints.

The study was organized in 267 hospitals in 19 countries in North and South America and in Europe, and it was coordinated by the Canadian Cardiovascular Collaboration Project Office at

McMaster University in Hamilton, Canada.

These are the key inclusion and exclusion criteria. Patients over the age of 55 and at high risk of cardiovascular events, if they had any evidence of vascular disease, as long as they did not have markers of low risk or have heart failure. This could be any evidence of coronary heart disease, strokes, or peripheral arterial disease, or if they were diabetics and in addition had one of the coronary risk factors or had vascular disease.

We also excluded patients who had heart failure or those with low ejection fraction because that was clear proof of the value of ACE inhibitors in this population.

In addition, if anybody was taking ACE inhibits for hypertension or any other reason, or they were on Vitamin E, they were excluded.

These are the main outcomes of the study. As stated before, the primary outcome was the composite of myocardial infarction, stroke or cardiovascular death.

The secondary outcomes were the individual

components of this composite, and in addition, we wanted to look at hospitalizations for unstable angina, hospitalizations for heart failure, total mortality, revascularization, overt nephropathy, and for the Vitamin E part, cancer, and that part of the study is still continuing.

There were other outcomes that were prespecified, and these were two: that with diabetic complications and other forms of heart failure, all forms of heart failure.

In addition, the phones recorded at regular intervals cardiac arrest, worsening angina, and development of diabetes, but they were not prespecified as hypotheses in the protocol.

These are the sample size and power calculations. The study was due to get 8,000 patients by formal calculations, followed for three and a half years, and the event rate expected was about five percent per year.

Using that, we would have high power to detect 15 to 17 percent risk reductions. At the very beginning, we inflated the sample size by an

additional 1,000 patients to overcome unexpected eventualities, such as lower event rates or poor compliance.

In the end, we ended up with nine and a half thousand patients, followed for longer periods of time, and I shall explain to you why this happened.

The original follow-up was meant to be to follow patients for three years after the first 18 months of recruitment so that the mean follow-up was going to be about 3.6 years.

However, because of the consistent results from the anti-hypertensive trials and the cholesterol lowering trials, we were concerned that there would be a lag in the manifestations of the effects of ACE inhibitors because we were postulating an anti-atherosclerotic mechanism.

So we thought perhaps the first two years we would have no treatment effect, and treatment would only -- the differences would only emerge later. As you will see, we were wrong in this assumption, but nevertheless, this is the assumption that we in with.

Furthermore, we had a lower event rate

than expected. Instead of five percent, we had 4.2 percent.

The process by this decision was made was as follows. It was made by the Steering Committee who had absolutely no knowledge of any of the blinded data other than the overall event rate. We then requested and sought funding both from the Medical Research Council of Canada and from the sponsors in two steps, and we eventually managed to get a two year extension so that the mean follow-up would be comparable to that seen in the cholesterol lowering trials.

There are certain additional aspects of the study organization that's worth pointing out. In each country there were national coordinators and regional coordinators.

In addition to the CCC project office in Hamilton, there were regional coordinating centers in Europe, in Brazil, and in Argentina. These constituted the International Steering Committee.

There were three important subcommittees. Two of them were made of members of the Steering Committee and one was independent. This committee,

the Events Adjudication Committee, adjudicated all of the primary and prestated secondary endpoints blindly.

In addition, the Data and Safety Monitoring Board, consisting of outside experts, independently reviewed the progress of the study.

The study was funded through 14 sources. What is listed here are the key sources. The primary peer reviewed funding came from Medical Research Council of Canada and the Heart and Stroke Foundation of Ontario.

The primary pharmaceutical funding came from Hoechst Marion Roussel in Canada and internationally. Astra-Zeneca, King Pharmaceuticals were also major funders, as were contributions from the Vitamin E manufacturers.

I should, however, stress that the study was independently designed, organized, conducted, analyzed, and reported by the Canadian Cardiovascular Collaboration and the HOPE Steering Committee, and the company only received the database after the publication of the results and the data being sent directly by us to the FDA.

As you know, the study was terminated early because of clear evidence of benefit in favor of ramipril. This occurred on March 22nd, when the Data Monitoring Committee recommended early terminations.

On April 17th and 24, we presented the results to the investigator, and we had formally stated that all events up to April 15th would be counted. Close-out visits were completed by August 1999. Database was closed on November 1999 at which time vital status was ascertained in all but six out of the nine and a half thousand patients.

Non-fatal outcomes were ascertained in 99.3 percent of patients. Adjudication was completed and possible in 99.9 percent of patients, and out of the 700,000 forms, 99.4 percent were declared clean.

The data were first published electronically in the New England Journal on November 10th, 1999, and in print version in two papers, in January in the New England Journal and another one in the Lancet in the third week of January.

Now, this is the process or screening and run-in. Screening first. Ten thousand seven hundred

and ten patients were initially invited to an eligibility visit. However, 134 were found to be ineligible at that time. The vast majority of these were due to proteinuria or the use of ACE inhibitors, and a small number for using Vitamin E.

Ten thousand five hundred and seventy-six, or 98.7 percent, were considered to be eligible and entered a run-in phase. The run-in phase consisted initially of seven to ten days of two and a half milligrams of ramipril used in a single blind fashion, at the end of which creatinine and potassium were checked.

This was then followed by a ten to 14-day period of placebo, which is also single blind. Ten thousand five hundred and seventy-six patients entered the run-in, and 9,541 were randomized. Approximately 1,000 were excluded after run-in. The main reasons were due to nonadherence or the patient changing his or her mind. A few patients had elevations of creatinine, cough, or hypotension or dizziness, and these are not mutually exclusive.

Eventually we randomized nine and a half

thousand patients to the overall program. However, for the evaluation of ramipril, there was a sub-study, a secure sub-study, of 750 patients in which one third were also randomized to two and a half milligrams of ramipril, and that is this dose.

So the main analysis of ramipril that I'll present to you is based on 9,300 patients. However, the data adding this to this slightly strengthened the results and has no material impact on any conclusions we come to.

These are the baseline characteristics. There are two things to note: first, that all the baseline characteristics were balanced. The second thing to note are key findings. The mean age was 66. The blood pressure was 139 by 79. The ankle-arm ratio was .98. Heart rate was 69. Body mass index was 28, and serum creatinine and potassium were as follows.

This was a well treated group with about three quarters of patients receiving anti-platelet agents, four percent receiving anticoagulants. Fifteen percent received diuretics for hypertension. Forty percent received beta blockers. Forty-six

percent received calcium blockers, and about 29 percent receive cholesterol lowering agents, and this proportion increased over time as I'll show you in a minute.

The key aspects of history as follows. About two and a half thousand patients were women, making this one of the largest trials in cardiovascular disease to include women. Eighty percent had coronary artery disease, out of which about 50 percent of the overall population had a remote myocardial infarction. Eleven percent had cerebrovascular disease, and in 40 percent they either had clinical peripheral arterial disease or an abnormal ankle-arm blood pressure ratio.

Forty-seven percent had hypertension, but these people have to have their blood pressures controlled before they enter the trial. We were very much interested in the diabetic component and had a target of 40 percent of diabetics, but recruitment strategies insured that at least one third of the patients would be diabetics, and this is one of the larger trials of diabetes and cardiovascular

prevention.

These are the data on the change in concomitant drugs over time. As you will see, three quarters of patients were on anti-platelets at the beginning. At the end of the study you will see there is a slightly lower rate in the group receiving ramipril, and this is probably because there were more clinical events in this group compared to this group.

Lipid lowering therapy increase in both groups and was nearly half by the end of the study. Beta blocker use remained approximately constant, increasing in the placebo group and decreasing slightly in the ramipril use.

Diuretic use increased in both groups, but to a greater extent in the placebo group. Calcium channel blockers decreased in both groups, and that is consistent with the worldwide trend towards lower calcium blocker use.

These are the data on adherence to the medications. At one year, 85 percent of the patients receiving ramipril remained on study medications compared to 89 percent. At four years, 68 percent

compared to 71 percent.

In addition, the proportion taking ACE inhibitors as an open label fashion was low in both groups, both at one year and at four years, but as you can see, it was higher in the placebo group compared to the control groups, compared to the ramipril group.

These are the doses once a patient decided to take the medication. These are the people who stopped taking the medication, and you will see in the majority of patients, if they were on the medication, they were tolerating and using the ten milligram dose.

So we did achieve the goal that we wanted of getting the dose up to ten milligrams in the vast majority of patients.

Now, these are the reasons why either ramipril or placebo was stopped. Cough as a reason for stopping, as expected, was more common with ramipril, as was hypotension and dizziness. There were lower rates of stopping blinded medication for hypertension because a clinical event occurred or for the use of non-study ACE inhibitors.

This slide tells you -- summarizes data on

the most important side effect that we are all concerned about about this class of agents. During the run-in, there were five cases out of ten and a half thousand patients of angioneurotic edema. All of them were mild and did not require hospitalizations.

After randomization, there were 16 cases in the ramipril group compared to seven in the placebo group. One was fatal in the ramipril group. There was no such event in the placebo group. There was one hospitalization here, none here. Nobody required ventilation.

We only had 141 patients who were blacks in the study, and they had no events in either the active or the placebo group.

These are the primary results of the study. The composite of myocardial infarction, stroke, and cardiovascular death. There were 826 events in the placebo group. That is 17.8 percent compared to 651 with ramipril, or 14 percent. This represents a 22 percent relative risk reduction or relative risk, with relatively tight confidence limit, and it's clearly statistically significant.

Each component of this primary was reduced, like cardiovascular deaths were reduced by 26 percent. Myocardial infarction was reduced by 20 percent. Strokes were reduced by 32 percent, and each of these three components was statistically significant.

We postulated a neutral effect on non-cardiovascular deaths, and that's exactly what we found. Overall, total mortality was reduced from 12.2 percent down to 10.4 percent, a 16 percent relative risk reduction. That is also statistically significant.

These are the survival curves for the composite primary endpoint, and you will see the curves diverge early and keep on diverging throughout the study.

These are the data on myocardial infarction, and we see the same pattern of divergence and then continued divergence.

These are data on strokes. We again see a somewhat larger effect, but the same pattern of divergence within the first year and then continuing

to go apart.

Now, these are details of several vascular events. These are the total number of strokes based on the previous slides, at 32 percent risk reduction with reasonably tight confidence intervals.

In addition, we had a reduction in transient ischemic attacks, and if you take the composite of these two, that, too, is clearly reduced.

Fatal strokes were reduced, as were non-fatal strokes.

In addition, when you look at the types of strokes, you will see a significant reduction in ischemic strokes, a tendency towards lower hemorrhagic strokes, although these were less common, and strokes where we were not able to classify whether they were ischemic or hemorrhagic, but also tended to be lower with ramipril.

These are data on the degree of disability and severity based in those having strokes. You will see strokes that were associated with full recovery on nonlimiting were reduced. Those that left the patient somewhat impaired was also lower, 56 down to 43.

Those that left the patient severely incapacitated or needing constant help was also lower, and these are the data that I showed you before on a reduction in fatal strokes.

Therefore, the impact on strokes was across different types of strokes and different severities of strokes.

These are the data on cardiovascular deaths. Again, a divergence by about a year and continuing divergence throughout. These are similar curves on total mortality, which again shows a slightly more delayed divergence, but then it keeps on diverging throughout the end of the study.

Now, these are further details on the causes of death. At the bottom are noncardiovascular deaths that I showed you. At the top are the total cardiovascular deaths, which is where we found the difference, and we found that difference in myocardial infarction, in strokes, in a small trend towards heart failure deaths, little difference in documented arrhythmia, but there was also a clear difference in those with other cardiovascular deaths, and these are

mainly periprocedural, either CABG surgery or PTCA or cardiac causes after noncardiac surgery.

These data are on the primary composite endpoint stratified by the allocation to Vitamin E on no Vitamin E. You can see in the half of the patients who were randomized to receive placebo for Vitamin E there is a clear benefit. Similarly, in those receiving Vitamin E as the second randomization, there's a 21 percent risk reduction that is clearly significant.

What this means is that if you divide the data into two random halves, we have clearly significant results in each of those two random halves.

It also means that the randomization to Vitamin E in no way interfered with the evaluation of ramipril compared to placebo, a point that I wish other sponsors would take note of. It's a very efficient way of answering two questions for the price of one.

Now, these are data on the subgroup analysis utilizing the primary endpoint. We have pre-

specified two sets of subgroup analysis to examine consistency, in those with cardiovascular disease and those without cardiovascular, those with diabetes and those without diabetes.

As we only had about 1,100 people without cardiovascular disease, the event rates were lower in this group compared to the placebo group, but the relative risk reductions are consistent with the relative risk reductions seen in the overall study, which is what this dotted line is, although the confidence limits are wide, but nevertheless, they overlap, and the P value for interaction indicates no evidence of heterogeneity.

In those with diabetes and those without diabetes, in each of these two subgroups there is clear statistical significance compared to placebo, and again, no evidence of heterogeneity.

These are data on other subgroups, and these are mainly being examined for consistency. In those under the age of 65, those over the age of 65, the results were similar. In men and women in both groups, the results were similar, and just to

emphasize the point, we had two and a half thousand women, and the results in women by themselves are statistically significant, and because the upper confidence limit does not cross one.

Those with hypertension history or those without hypertension history, the results are consistent. Those with coronary artery disease, those without coronary artery disease, the results are consistent.

Again, in those with a history of cerebral vascular disease, those without cerebral vascular disease, although we had only 1,000 people, this was a high risk subgroup, and again, the risk reductions are identical and there is no evidence of heterogeneity.

In those with evidence of peripheral arterial disease and no peripheral arterial disease, similar results. Those with micro albuminuria or no micro albuminuria at the randomization visit, similar results.

So these three slides indicate to you that the results were consistent across many different

subgroups and broad populations.

These are the data on secondary outcomes. We had a significant reduction in revascularization procedures, 18.4 percent down to 16 percent, representing a relative risk of .85, which is nominally significant.

Hospitalizations for unstable angina, there was no impact, even overall or when we looked at the data in those who had ECG changes when they were hospitalized.

Hospitalizations for heart failure was numerically lower in the ramipril group compared to the placebo group at 13 percent risk reduction with wide confidence limit, and it's not statistically significant.

These are the data on other outcomes that I had shown you in one of my earlier slides. Complications related to diabetes mellitus was significantly lowered, and these data will be elaborated to a greater extent by Dr. Hertzel Gerstein. So I request that you hold any questions on that for him.

I will show you more data on heart failure, and heart failure, any manifestation of heart failure, was also significantly reduced by 23 percent with relatively tight confidence limits.

Cardiac arrests were lower. These are non-fatal cardiac arrests and are not counted in mortality.

Worsening angina based on the patient's report was also lower, and much to our surprise, new diagnosis of diabetes mellitus was also lowered by 34 percent.

These are the survival curves on revascularization. You will see it took some time for the curves to diverge, and then it diverged throughout the duration of follow-up. These are details on the types of revascularization. You will see that coronary revascularizations were reduced by 17 percent, but there was also a similar trend towards reduced non-coronary revascularizations, such as peripheral angioplasty or surgery, limb amputation, or carotid endarterectomy.

Now, before I show you further details on

heart failure, I want to put the heart failure data in perspective. As you know, heart failure and ACE inhibitors have a long history. The first major trial in heart failure was done in the CONSENSUS 1 trial using an allopril (phonetic) in Class 4 heart failure some ten to 15 years ago.

At that time, since we did not have a clear indication for the use of ACE inhibitors, when patients deteriorated, ACE inhibitors were hardly used, under ten percent of the patients. I was easy, therefore, to show an impact on total mortality.

By the time the SOLVD treatment trial was being done, we already had the results of consensus. At that time we included people with low ejection fraction and heart failure, and in this study we saw an impact of mortality being reduced, but the risk reductions were smaller than this, and this may well be because of the lower risk patients, but also because of the higher rate of noncompliance.

In addition, we showed an impact on heart failure hospitalization. However, when we did the SOLVD prevention trial, which was being simultaneously

run as the treatment trial, when people deteriorated and had signs or symptoms of heart failure, up to 40 percent of patients received open label ACE inhibitors, and this was also a lower risk group which had low ejection fraction alone and no heart failure, and in this group we weren't able to show a clear reduction in mortality, but we showed a clear reduction in out-patient manifestations of heart failure and heart failure hospitalization.

It is in this context that we should review the HOPE data. The HOPE data included people without low ejection fraction, that is, preserved ejection fraction, and they had no heart failure.

When they deteriorated, they were allowed to use ACE inhibitors even if the patient did not reach a primary or second endpoint, and 60 percent of the people, when they developed heart failure as an out patient, received an ACE inhibitor, and we found a clear reduction in all manifestations of heart failure, and I'll show you those data now.

These are the data that I've shown you before on heart failure hospitalizations. There is a

trend in favor, but it's not statistically significant. These are the data on all manifestations of heart failure, including the ones that I showed you previously.

You will see a 23 percent reduction. That is clearly significant and keeps on diverging throughout the study, parallelling what we saw on other endpoints.

These are further details. This is the top line. On all manifestations of heart failure, there's a 23 percent risk reduction with tight confidence limits.

This was contributed due to a variety of different forms. One is the use of open label ACE inhibitors for heart failure was also reduced by 28 percent. When you take most of your manifestations, there's a 13 percent risk reduction, and when you take death, there's a 12 percent risk reduction.

If you take the composite of cardiovascular death or all heart failure, there's a 24 percent risk reduction. If you take the composite of cardiovascular death plus heart failure

hospitalization, there's a 23 percent risk reduction. That is significant, and all of these are consistent.

There are two reasons to use the composites in formal statistical evaluation. First, death is a competing event. So when you take a secondary endpoint, it is methodologically more rigorous to use deaths plus heart failure hospitalization, although of course each of them contribute to the difference observed.

The second reason is because -- gosh, I can't remember what the second reason is. I'll go on.

Now, these are data now on development of heart failure. Sorry. These are data now on the diagnosis of diabetes mellitus. The way this was recorded was on an annual check box in the forms. No tests were required, but I'll show you the data. That's why you get these in steps annually.

Remember this is a blinded study, and the total number of people unblinded in the study was under 20; is that right? In five years.

So essentially this diagnosis was being made unbiased, and there's a 34 percent risk reduction

that is statistically significant.

These are further details of what the physician did when he or she diagnosed diabetes. You will see oral agents were described in 53 patients in the ramipril group compared to 101 in the placebo group. Insulin alone or in combination with oral agents, six here and four there. And diet alone as a strategy was used in 43 patients in the ramipril group and 15 in the placebo group.

Now, this study did not perform ejection fractions in everybody at baseline. The protocol recommended that if you knew somebody had a low ejection fraction, please exclude them, but it wasn't demanded, given the fact this was an international study, and also the fact this was a cheap study.

So, however, in 4,775 patients ejection fraction was available pre-randomization and was normal. The mean ejection fraction was .59 in this group with this standard deviation. The primary outcome was reduced from 18.8 percent to 13.9 percent, a 27 percent risk reduction, which is at least as large as what we saw in the overall population.

Again, we see reductions in cardiovascular deaths, reductions in myocardial infarction, reductions in strokes, reductions in all manifestations of heart failure, and reductions in revascularization.

So focusing just on the subgroups of patients where we know for sure have a preserve EF, the results are consistent and clear.

These are the data on blood pressure because one of the questions that could be asked is: how much of the benefits can be explained due to blood pressure lowering?

The first thing to note is that the blood pressure at entry was about 139 systolic by 79 diastolic. That would not conventionally be called hypertension. Some may call this borderline elevated blood pressure.

You will see that in the middle of the trial, the difference in systolic blood pressure was just over three millimeters or just over -- this is about 1.8 millimeters diastolic. So the difference in blood pressure was modest.

Now, based on this and based on external data, we can project what degree of the benefit, what amount of the benefit can be explained by blood pressure lowering.

Based upon previous trials of hypertensive patients who all had higher blood pressures coming into those trials, a ten to 15 millimeter difference in systolic blood pressure leads to a 40 percent lower stroke rates and a 15 percent lower myocardial infarction rates.

We saw a 3.3 millimeter difference in systolic blood pressure. Using these data, we would expect a 13 percent difference in strokes, but we saw a 32 percent reduction.

We would have expected a five percent myocardial infarction reduction solely based on the blood pressure lowering, but we observed a somewhat larger effect.

So we would be able to say or we would at least surmise that only a small proportion of the benefits are due to the blood pressure lowering effects of the agent and the rest may be due to other

effects.

This is further explored in the next few slides. Here we divided people into quartiles by diastolic blood pressure and the next one by systolic. So the quartiles we used were 70, 71 to 79, 80 to 85, and over 86. We, in order to overcome regression to the mean, we calculated usual blood pressures, and interestingly the usual mean blood pressure in this group is higher than the cutoff, and the usual mean blood pressure here is lower than the cutoff. That's just a methodological point.

And you will see the relative risk reductions though are consistent across the four quartiles.

The same holds true for systolic blood pressure. The lower systolic blood pressure is, the blood pressure of under 124, 125 to 139, 140 to 150, or over 151, and you will see consistent reductions across the whole range, although it may appear visually there's a slightly higher benefit out here at the highest levels.

Now, a third way that we looked at the

data was to do a time dependent covariate analysis within our trial, adjusting for the observed reduction in blood pressure. These are the unadjusted, crude results, a relative risk of .78. After adjustment it was virtually unchanged.

When we look at each of the individual components, you will see for myocardial infarction there is very little difference. If anything, this is slightly more in favor of treatment, but for strokes you will see there is a slight attenuation of the benefit, and for cardiovascular deaths, again, there is only a slight attenuation of the benefit.

So these three different approaches to the analysis suggest to us that the benefits are probably independent of blood pressure lowering.

In my reserve slides, I have additional slides on atherosclerosis prevention, and if the committee would like to discuss it at a later time, I'd be happy to show them.

Now, as a clinician, we were very pleased with the results of the study because as a clinician it meant this would be of great importance to my

patients.

If we treated 1,000 people for four years, we would prevent 18 deaths, 16 myocardial infarctions, and nine strokes for a total of 43 events, which means the number needed to treat to prevent one event is 23. Since some of these occur in the same patients and to take into account overlapping events, the number of people in whom you'd prevent an event is 36, and the number needed to treat would be 28 people to prevent one event.

As you know, there was 20 percent when it's noncompliant, and you can kind of crudely calculate what it might have theoretically looked had everybody taken the drugs. Of course, that's theory.

Now, in addition to these three major endpoints, a number of other clinically important endpoints or roles are prevented. Now, if you put all of this into the equation, you will see 128 events were prevented in about 60 people, and the number needed to treat understandably gets smaller.

Either analysis, the previous slide or this slide, indicates that clinically important and

useful results have emerged.

Therefore, ladies and gentlemen, in conclusion, there is convincing evidence that ramipril prevents cardiovascular death, myocardial infarction, and strokes. It prevents the need for revascularization.

These benefits are consistently observed in a very broad range of high risk patients and in addition to other effective therapies.

In addition to those observations, we found there was significant reductions in any manifestation of heart failure, in new diagnosis of diabetes, which was not prespecified, and in nephropathy, which Dr. Gerstein will devote an entire presentation to.

The only major uncommon side effect or only common side effect is a five percent excess of cough.

Thank you very much.

ACTING CHAIRMAN CALIFF: Okay. What I'd like to suggest is that we focus the questions on the general study design, the organization of the study,

and the primary results, and we save questions on diabetes and renal outcomes until those speakers present.

And maybe we could just start, Udho, with you at your end and just work our way down and let everyone ask the questions that they have.

DR. THADANI: I suppose they purposely didn't allow me to speak into the microphone, no more questions.

When I'm reviewing this, one of the issues you said the patients in the exclusion were not on ACE to be in the study, and yet the document I'm provided with from the FDA says they could not be withdrawn from ACE.

Which is the truth now? They could have been on ACE and they were withdrawn from the study and put in the study as long as they could be withdrawn? Because --

DR. YUSUF: That's right.

DR. THADANI: -- there's a major issue there.

DR. YUSUF: Yeah, I think they could be

withdrawn. Is that right? I mean --

DR. THADANI: But that could have important implications. First of all, one of the exclusions you showed was the patients should not have been -- you know, patients in heart failure and ACE were excluded, and I think the assumption could be patients who were on ACE because of their heart failure, and if that is true, I'm not denying the results, but that could skew some of the results.

If that is true, then some of the patients in heart failure actually could have been withdrawn from ACE for whatever reason, or for hypertension is possibility, and then that could have pushed the results in your favor because we know some of the patients did have low yields.

I'm saying that --

DR. YUSUF: Can I answer the question?

DR. THADANI: Yeah, sure.

DR. YUSUF: I mean, it's a good question.

We explicitly said that ACE inhibitors were indicated for two conditions and those patients should not be included: those with heart failure and

those with proteinuria.

So even if they were not on an ACE inhibitor, if they have heart failure, they can't get into the trial. So that was stated right throughout. In fact, that was an explicit decision by the steering committee.

What I don't know is what proportion of the hypertensives were on ACE and were withdrawn and gotten. I don't know the answer because of I don't think we recorded that.

DR. THADANI: I think it might have implication because even if your EF data is .5-something plus/minus .11 SD, so that if you allow two standard deviations, some of the patients are going to be below 40.

DR. YUSUF: No, no, no.

DR. THADANI: But it was .51.

DR. YUSUF: We actually -- let me -- let me take you through this. We said anybody with an EF 40 percent or under should not be in the trial. That was one. I mean, take that into context.

The other thing is .59, two standard

deviations of .59 reduced by .11 is about .47. Sure, there's still a tail of two and a half percent of people, but it starts to become increasingly unlikely.

Now, let me also tell you we did a sub-study in 700-odd people where echoes were done consecutively, and in that only two percent of people had an EF under 14 percent.

So I can't guarantee it is zero percent, but I can tell you it's going to be in that very low order.

DR. THADANI: The other important issue is the hypertension, the way JNC-6 guidelines are totally different now because hypertension is defined as 160, now is 140 and below. So that incidence could change.

DR. YUSUF: Sure.

DR. THADANI: And if you look at the numbers, I think 50 percent of the population was hypertensive in the last slide you showed in the pressures above 140. So there's a large number of patients who were hypertensive in the study.

I realize the results are going in the right direction, but it has to be kept in mind.

DR. YUSUF: I think, you know, but ten years from now everybody in this trial will be considered to be hypertensive when we get JNC-8.

DR. THADANI: And, you know, one data you really do not show which I'm in the review, everybody talks about the aspirin-ACE interaction. That's one of the issues --

DR. YUSUF: Sure.

DR. THADANI: -- I suppose we could discuss later on, and it seems like you also did not show where the patients came from. A lot of patients came from Canada. There are very few patients from the States, and the benefit is obviously because the sample size is greater there, at least the data I was given.

Now, do you think that could be, although the data you do not show it, could be because of the integration rates are so different in the two countries regarding rewaspiration (phonetic), et cetera, would have impacted your results more so in Canada where it's, you know, waiting six months or one year for bypass, et cetera?

DR. YUSUF: Okay. With the permission of the Chairman, can I show a back-up slide?

ACTING CHAIRMAN CALIFF: I think you should address both the --

DR. YUSUF: Sure.

ACTING CHAIRMAN CALIFF: -- aspirin interaction and the international difference.

DR. YUSUF: Can we have from our back-up slides, Angie -- well, just to be in the order that you are, can we have Slide 28 and then 29, please, first from the back-up?

Okay. This was an issue we examined, and the event rate was reduced. The relative risk was .85 in those people taking aspirin, which is nearly 7,000 people. Two and a half thousand people were not on aspirin. In this group it was reduced by -- the relative risk was .59, and the interaction P value is quite significant.

Now, two things to note. First, this is significant on its own and for no reason would we say don't give aspirin. Don't give aspirin and ACE inhibitors together. We're going to say use them

together so that there's an additive benefit.

Now, the issue: is this real or not? We have done over 100 subgroups, and some of them will be real, and some of them may be, you know, due to the play of chance, and some of them may be even in subgroups where we think there is likely to be an effect.

So we did two things. If there is an aspirin interaction, it's likely to occur in other trials, and it could also occur on the other events in our trial that you expect treatment to have the benefit of.

So we looked at revascularizations, and here, if anything, the effects are slightly greater in those on aspirin compared to those not on aspirin, no interaction P value. On all heart failures the effects are similar, if anything greater here than here, and on nephropathy, which you will hear later, again, the effects are similar, slightly greater here, slightly smaller here, slightly greater there, but, again, there is no interaction on these.

And if you take any of these outcomes,

because in the end you will give treatment to prevent a number of different outcomes, you will see the relative risk is .83 compared to .74, numerically a bigger effect here, but in each case highly statistically significant benefit there, as well as there, and there is no interaction for between these events.

We then did another thing because, as you know, I've been involved in coordinating a worldwide meta analysis of ACE inhibitor trials, and so we got data from not only HOPE, from SOLVD, SAVE, TRACE, and AIRE, and what we got was the individual data points.

So we now have individual data points on 22,000 people on 7,000 events. So this is now getting to be reasonable numbers to look at subgroups.

On non-DETS (phonetic), you will see there's a 14 percent relative risk reduction here compared to 26 percent, nominally significant P value for interaction.

Myocardial infarction, again, a somewhat greater effect there compared to here. Again, significant, but note in no case does the confidence

limits cross one. So you would use it in those circumstances.

But for strokes we don't see that. For revascularizations, we don't see that. For heart failure hospitalizations we don't see that, and when you take all of these together, you get a 20 percent risk reduction for those receiving aspirin for the effects of ramipril or for the effects of an ACE inhibitor, and those not receiving aspirin, there's a 30 percent effect, which is nominally significant.

So there may be a weak quantitative interaction, but there is no qualitative interaction, and clearly based on these data, you would not withhold aspirin or ACE inhibitors should there be an indication to use it.

ACTING CHAIRMAN CALIFF: Can you address the international differences in outcome if there are any?

DR. YUSUF: Sure, I'd be happy to do that.

Can we have Slide 16, please, of the back-ups?

Okay. This is the recruitment from

different parts of the world. You were right, Udho, that we had more people from Canada in the trial, and if you look at it, you'll think Canada is the most populous country in the world, but that would be a mistake.

Five thousand seven hundred patients from Canada, 2,000 from Europe, 800 from the U.S., 730 from South America, and 300 from Mexico. So this is about 1,000; this is 800; that's 2,000. So there are reasonable numbers in each of these categories.

What I'm showing you now is North America, and you will see in North America there's a clear reduction on the primary and the composite secondary. In Europe there's a trend in favor, and remember European intervention rates are lower than North American intervention rates, and when you add the secondary endpoint, it's almost an identical effect.

And Latin America, again, these are the results. There is no evidence of heterogeneity by these categories.

We also did it another way, and each of these ways are data dredging. So just be cautious.

This is Canada, USA, Europe, Latin America, but remember the numbers in each now start to get small, and you will see the rates of interventions between USA and Canada were closer. I won't say they were identical. They were closer. The lowest was here, and you will see these are the relative risk reductions for the primary, for the secondary, and the confidence limits overlap, and the interaction P values are certainly not significant.

Now, remember these are data dredge. We've been doing so many of them. So at the very least we can say directionally the benefits are similar in different countries. Of course, this trial was never set out to prove they were similar in each individual country.

DR. THADANI: I think you can probably come back to some more because one of the criteria for inclusion --

DR. YUSUF: Can we switch that off, please? Thank you.

DR. THADANI: One of the criteria for inclusion is patients who did not have a previous MI

could be entered in the trial provided they had a positive stress test or two SOCAD (phonetic), not one vessel, and it's possible that the intervention rate in the two countries are different because at least in our center they have got estimated depression of two millimeters. With Italian (phonetic) positive, they are going to have some intervention. So it might have some relevance.

I'm not saying the totality of the result. You have to keep that in mind.

My last question before you go is how you define heart failure in this population when your secondary endpoint of hospitalization due to heart failure is not different because when the EFs are relatively preserved, I won't say normal, heart failure is not easy to diagnose. So what was your definition of heart failure?

DR. YUSUF: Well, heart failure is tough to -- equally tough or equally easy to diagnose whether you have EF or not.

DR. THADANI: I realize.

DR. YUSUF: So it's not an EF criterion.

I think the hospitalization, there was a set of criteria. I don't remember them offhand. There was an adjudication. There was a specific --

DR. THADANI: But it makes no difference in hospitalization due to heart failure?

DR. YUSUF: Well, there was a trend.

DR. THADANI: Yeah.

DR. YUSUF: Okay? There was a trend. Okay. I think no difference does not accurately reflect the data.

DR. THADANI: It's a trend.

DR. YUSUF: And if you look at other forms of heart failure, that was a check box. In the opinion of the investigator, based on a blinded -- remember there's a truly double blind trial with very few unblinding. So there were check boxes for heart failure, and then they said whether an ACE inhibitor was used or not. That's all there was.

DR. THADANI: My last question is the use of lipid lowering drugs.

DR. YUSUF: Right.

DR. THADANI: Especially the statens are

fairly low. These are high risk patients given the scenario of LDL cholesterol not required less than 100 probably.

You think your results would be valid if everybody was given the risk reduction of stroke, given the risk reduction of revascularization and MIs with the lipid lowering recent trials? Would it still hold or you need another trial to prove that this will be additive if the lipid reduction was more aggressive?

DR. YUSUF: Can I have my back-up Slide 32, please? Actually 31 first and then we'll go to 32.

This is 31. We looked at these two therapies in addition to aspirin. You're absolutely right. It's a good question. We know beta blockers save lives. Lipid lowering also save lives. So this is the results on the primary endpoint. This is on the secondary endpoint.

If they were taking beta blockers or no beta blockers, similar relative risk reduction, both for the primary and the secondary. If they were

taking lipid lowering medications, similar risk reductions both on the primary and the secondary.

We also did a further analysis, and let's look at the next slide, and this is any of the above. These are the three drugs that save lives, and remember aspirin, there was a nominal interaction.

But if you take any one of these three, there is benefit in those, taking any of the above, 19 percent risk reduction, and here there's a 14 percent risk reduction if they weren't taking any, but I think that the entire thing is be contributed by aspirin.

And you will see here on the secondary endpoint, which is more numerous, the relative risk reductions are identical or if you go to the subgroup taking all of the three. So you've got a patient on a beta blocker or an aspirin and a lipid lowering. You will see the relative risk reductions are similar, and there's no evidence of interaction.

So I think although one could say that the benefits of ramipril are on top of the three other therapies we know that saves lives.

DR. THADANI: Thanks.

DR. YUSUF: Thank you.

Could you switch that off?

ACTING CHAIRMAN CALIFF: Okay. Thanks, Dr. Thadani.

Now, Dr. Fleming, do you have questions?

DR. FLEMING: Salim, I'd like to thank you for your terrific efforts in such a very informative and well conducted study.

Some of the questions that I've had we've certainly got into. I was interested in your subgroup analyses and some of the ones I was particularly interested in I didn't see, although you've begun to address them: the issue of potential interaction by baseline aspirin use and by region. You've begun to try to explain this.

It's interesting to me. You've interpreted the results on aspirin use after you went back and looked at the meta analysis as there may be a weak quantitative interaction. Even with your study alone the significance level is 002, and I realize this is in the context of many subgroup analyses.

And you're right. That has to be taken

into account, but the meta analysis seems to strongly confirm there is absolutely a quantitative interaction. Is it qualitative, i.e., is there still adequate evidence that there is benefit in those that are on aspirin?

One of the ways that I'd be interested in getting additional insight beyond what you've presented there comes back to one of your earlier comments about competing risks. And you had noted earlier that when you leave out, for example, certain events that are censored, that can create some difficulties, and in fact, it absolutely can statistically if we're looking at the primary endpoint, for example, of events that are death, stroke, and cardiovascular related deaths.

By leaving out other deaths --

DR. YUSUF: Sure.

DR. FLEMING: -- those people who die for other causes aren't left out of the analysis. They are, in fact, censored, and their future outcome is, in essence, in a Kaplan-Meier self-consistency approach estimated by other people who didn't die.

So essentially if the two of us are moving along and we're matched in certain ways and I die and you don't, if I die from a non-CV related cause, I'm censored, and my subsequent risk of these events is represented by you, and it always leaves me completely uncomfortable to say what it is we're really estimating.

DR. YUSUF: Sure.

DR. FLEMING: So having said that, it is reassuring to see when you look at all cause mortality in the global analysis that results are so strong that even though you have, as you expected, essentially no difference in the non-CV related deaths, the results are still robust and positive.

Where I begin to wonder a bit more though is when we start looking at these two important interactions, and the first of these interactions is baseline aspirin use, yes versus no.

Could you give us two analyses? Could you show us the mortality data in those people who were on aspirin at baseline, and could you show us the endpoint I would have preferred, which is the

composite endpoint of MI, stroke, and all cause mortality?

Those two analyses --

DR. YUSUF: I don't have it. I don't think we did it. So --

DR. FLEMING: Could you -- these are really critical to interpreting the aspirin subgroup. Could they be generated for us and presented before the votes?

DR. YUSUF: No, it's not possible to do that.

DR. FLEMING: Because it is interesting that in your analysis in those people who started on aspirin, and your point was you still have evidence to say there's benefit there.

DR. YUSUF: Un-huh.

DR. FLEMING: The relative risk estimate, I think, was .89, but the upper limit of the confidence interval was approaching one, and if you put the deaths in that were non-CV related --

DR. YUSUF: But, Tom, you know that's methodologically invalid for subgroup analysis. I'm

not talking of competing risk. I accept your concept.

DR. FLEMING: Well, I'm talking competing risks here. That's --

DR. YUSUF: Yeah, well, let me tell you the problem with subgroup analysis because you want to take your biggest delta, your most sensitive endpoint, and then do a subgroup analysis because, you know, you could say why didn't you add in cancers. The reason we're not adding cancers is we don't expect an effect on cancers. So it's meaningless to do a subgroup analysis on cancers.

So my approach, for which I've written for 15 years on subgroup analysis, is take your most sensitive endpoint and then look for interactions in that, and that's what we've done.

DR. FLEMING: So if, in fact, the most sensitive endpoint is truly a statistically valid endpoint, the problem is censoring the deaths does not protect the --

DR. YUSUF: But, Tom, I think we could spend a lot of time on cost specific mortality.

DR. FLEMING: -- a statistically valid

endpoint. That's the problem.

DR. YUSUF: Well --

DR. FLEMING: And so it is fortunate in your composite analysis where you do show it to us, you do show us the analysis when you look at all cause mortality that it's significant.

The concern that I have is when you see considerable evidence that there is, in fact, at least a qualitative or quantitative interaction, that it would be at least of interest to look at mortality in that group.

DR. YUSUF: Let me say one thing. First, there is absolutely no indication of a qualitative interaction. So we shouldn't use that term.

There is a --

DR. FLEMING: Quantitative interaction.

DR. YUSUF: Quantitative, yes.

DR. FLEMING: There's clearly a quantitative interaction.

DR. YUSUF: Sure.

DR. FLEMING: The question is: is it qualitative? That's the question.

DR. YUSUF: Well --

DR. FLEMING: Let me move on because this is an analysis that unfortunately should have been done because it's certainly of interest to know whether or not when you include all cause -- you do include all cause mortality in your global analysis. So it certainly would have been of interest --

DR. YUSUF: Actually I don't. Nowhere do I include that.

DR. FLEMING: Well, you present us all cause mortality.

DR. YUSUF: As a curve.

DR. FLEMING: A global analysis.

DR. YUSUF: As a single curve.

DR. FLEMING: Right.

DR. YUSUF: Yeah.

DR. FLEMING: The second issue, and you've addressed the Canadian issue, and the tests for interactions that you showed us, actually you didn't show us the test for interaction on Canada versus non-Canada. The non-Canadian sites seem to have consistently far less evidence of benefit. The

relative risk estimate in Canada of .71, in the U.S. .91, and in all non-Canadian sites is .89.

So there is here, again -- there are issues of attempt to dissect noise from signal, but it's very interesting to see a fairly consistent evidence of much less effect outside of Canada.

What is your best sense of what could be causing what would be maybe a threefold higher effect in Canada?

DR. YUSUF: I think I -- first, I do not accept there is a higher effect in Canada compared to the rest of the thing. First, it's an extremely data derived analysis, and let us give you a scenario.

The overall results were nonsignificant, and in Canada there was a striking result. I don't think any of us could come to the conclusion that it works in Canada and doesn't work in the rest of the world. We would base --

DR. FLEMING: So you're arguing that basically there really is no difference --

DR. YUSUF: Yes.

DR. FLEMING: -- in any factors in Canada

versus, for example, delivery of care of supportive measures in the U.S.

DR. YUSUF: No, no. What we're saying is there is no strong evidence that the treatment varies to a considerable extent by region. I mean we can keep on dissecting this out, and I'm sure we'll find 50 centers where actually the treatment would go slightly the wrong way.

DR. FLEMING: Well, we're not looking for 50 centers. We're looking for major groupings, and --

DR. YUSUF: But, Tom, I've already presented about 50 subgroup analyses. Some things are going -- there was no hypothesis around this. There is no pre-specified hypothesis.

If you really wanted to address that question, I would say let's take the meta analysis of all the trials, 22,000 patients, and then look at it by region. That would be interesting.

DR. FLEMING: And what did that show?

DR. YUSUF: We haven't done it.

DR. FLEMING: Okay.

DR. YUSUF: We haven't done it, but I can

tell you what it's likely to show because the SOLVD trial was predominantly U.S. The SAVE trial was substantially U.S. The likelihood is that it will show that Canada and the rest of the world would be very similar results.

ACTING CHAIRMAN CALIFF: Just an editorial note here. We're going to come back to this discussion later because certainly when it comes to the U.S. FDA, there are a host of international trials now with results that look sort of like this, and so we'll come back to the generalizable issue later.

DR. FLEMING: Let's do that. Let me move on to the next -- the last of the separate issues: race. Could you show us the race? You didn't show us the race subgroups, and give us any comments you have on those.

DR. YUSUF: I mean the race subgroups have even bigger problems because of the small numbers. I'll show you the data, but just be very careful in interpreting them.

Can we have Slide No. 20, please, back-up?

Okay. The commonest race in the study is

white, Caucasian. There was no hypothesis related to race when we went into the study, no attempt at sampling by race, and you will see if you look at that the relative risks overlap and the confidence limits overlap, and if you take the secondary endpoint, which in a sense is twice the number of events, this is primary plus secondary, not secondary alone. You will see the relative risks are identical.

Now, if you further subdivide, which is -- the first one itself I would say is methodologically problematic. If you further subdivide, you're starting to get tiny numbers in many of the races, and it's all noise. You know, it's all over the place.

You will see for one endpoint it seems there's no effect. Another endpoint, there is an effect, and vice versa out here.

So I think, you know, really the totality of the data on the whole thing is what you really must emphasize, and all of these are interesting to look at, but they are so problematic with lack of power and the play of chance.

DR. FLEMING: It's absolutely true that

one has to be cautious in interpreting subgroups because of the multiplicity of testing. At the same time, to basically ignore what they say because of the multiplicity of testing is also a dissatisfying conclusion.

DR. YUSUF: Sure.

DR. FLEMING: I guess there are two things that are evident there. One is how strikingly unrepresented the blacks were in this study, and the second is the relative risk estimate, granted in small numbers, is in the wrong direction.

DR. YUSUF: On one endpoint, not the other endpoint.

DR. FLEMING: Is there any -- are you suggesting that there's no other data from other related studies that would also suggest lack of benefit in blacks?

DR. YUSUF: It's very hard to get the data. I'll tell you why. We tried to do this before this because we have a meta analysis of the ACE inhibitor paper in press in the Lancet prior to this, and at the last minute this was an issue that came up.

We tried to get it.

There are only 200 or 300 such patients in the SAVE trial. There it seemed to be consistent out of 2,000, and in the SOLVD trials, on some endpoint the results were the same; other endpoints it wasn't. The AIRE trial and the TRACE trial were done in Europe so that there are no blacks.

So that if you take the world literature in blacks, it'll be about 600 or 700 people in randomized trials, long term treatment.

DR. FLEMING: And the overall conclusion there about relative risks in the meta analysis?

DR. YUSUF: I don't really know because I haven't done a meta analysis of HOPE plus the other ones. I've done one with the other ones separately, and there is absolutely no hint of heterogeneity.

DR. FLEMING: Last question. Why did you do the secure sub-study? Obviously one answer is to look at the lower dose. You did. What was your intention in doing that when you designed the trial?

DR. YUSUF: Okay. There were two things that happened. First, the secure sub-study in our

mind was primarily done to look at the effects on atherosclerosis. We as investigators only wanted to study in the whole study one dose, ten milligrams.

There was a very strong push from the marketing people to study two and a half milligrams. In fact, they wanted the whole study at two and a half milligrams.

We came to an impasse. Secure the three dose thing was a compromise whereby we said, "Okay. Let's test two and a half, as well, in a sub-study. It won't hurt the main study."

The argument was very simple. You know, if you need 10,000 people to show an effect, you'd better go with your best dose, especially when you know the --

DR. FLEMING: So essentially to obtain at least some evidence as to whether there is a dose response.

DR. YUSUF: And would you like to see the secure data? It's actually interesting.

DR. FLEMING: Well, you did show it to us. You can show it again, sure.

DR. YUSUF: No, I haven't actually.

DR. FLEMING: You showed us in the book.

DR. YUSUF: Have we? Okay.

DR. FLEMING: And it looked as though the effect was there in the lower dose.

DR. YUSUF: Yes, there is a trend, but there are some more interesting data actually worth looking at.

Can we go to 39 on the back-up?

Okay. Now, this is the randomization and secure where a third went to ten milligrams, a third went to two and a half milligrams, a third went to placebo, and then there was the further randomization to Y2ME (phonetic). I won't show you any data.

Primary endpoint in this was progression of atherosclerosis using the carotid evaluation, and the next slide will show you the blood pressure changes.

First, you would be interested. The mean blood pressure was 131 systolic by 76 diastolic, even more normal. The degree of blood pressure drop was small for both ramipril arms, but interestingly

identical for both ramipril arms. So although we used two different doses, the blood pressure lowering was the same.

Now, these are the data on atherosclerosis progression. You will see there was a dose dependent reduction of atherosclerosis progression, and this P value is one for trend, and this is showing that that's different from that.

So using a trend analysis that's significant. Using just this, this is significant.

So we have this interesting observation that the low dose had the same effect on blood pressure as the full dose, yet had visually less of an effect on atherosclerosis progression. So this actually helps us in thinking about the dissociation of the blood pressure effect with this atherosclerosis progression further.

And the clinical events were very few. Oh, sorry. They switched that off. Is there one more slide?

DR. FLEMING: That's the most important slide.

DR. YUSUF: Okay. Actually there must be another slide.

Here are the clinical -- well, it isn't the most important slide. It's the least common event, and --

DR. FLEMING: That's the most important event.

DR. YUSUF: Yeah, that's why we did HOPE, Tom, you know,, and you will see the primary outcome, there's a trend towards a lower effect. Again, it seems to be -- I mean, I don't know what you'd make of it. It fits in, but it's in between this and this, and it would be too much if I made anything of this.

I mean these are the data.

DR. FLEMING: Well, then essentially I come back. What was your intention, again? It shouldn't have been to be establishing blood pressure. You have given appropriate arguments that blood pressure is not the mechanism through which the effects are mediated.

DR. YUSUF: Actually the primary endpoint was carotid atherosclerosis. So we were interested in

the clinical outcomes, not -- sorry. We were interested in the atherosclerosis outcome and LV hypertrophy. We haven't yet analyzed the LV hypertrophy data.

So I hope I've answered your question clearly. It was the B mode ultrasound, and we powered the study for that, which is going back as I -- it's not working backwards anyway.

ACTING CHAIRMAN CALIFF: Okay. Tom, anymore questions?

DR. FLEMING: Not at this point.

ACTING CHAIRMAN CALIFF: Okay. Dr. Armstrong.

DR. ARMSTRONG: Salim, could I just return to a couple of points and then raise a couple of others that my colleagues have identified?

There is historic evidence for biologic plausibility about less of a blood pressure lowering effect in blacks and a higher frequency of angioedema. As I understand it, none of the angioedema in the ramipril group occurred in blacks. Please confirm.

DR. YUSUF: That's true.

DR. ARMSTRONG: And, secondly, do you have information on the blood pressure lowering in the black population in HOPE as it relates to the general population?

DR. YUSUF: Actually we haven't looked at it, Paul. I don't know the answer to that.

DR. ARMSTRONG: The second point was that there is, as you know, biologic plausibility concerning the attenuation of the hematodynamic effects of ACE inhibitors with concurrent aspirin, and in relationship to the difference in the treatment effect, while still significant in the aspirin ramipril group, do you have information on the blood pressure in those patients as opposed to those not receiving aspirin in ramipril?

DR. YUSUF: Did we look at that?

I don't think we've looked at that. So I'm sorry. We can't answer.

But one little point that's worth noting. I mean, yes, there was that interaction on the primary, but the event that is most closely linked to blood pressure and also most closely at least in my

mind linked to hemodynamic changes is heart failure, and on heart failure it was the other way around.

You know, we had a bigger effect on those who were on aspirin.

DR. ARMSTRONG: My third question relates to the issue of cigarette smoking, which is in the label for secondary rationale, and just to inquire as to the definition. In other words, was any cigarette consumption perceived to be cigarette smoking since that's relevant to the label?

DR. YUSUF: What was the answer, Jackie?

I don't know the answer.

DR. ARMSTRONG: So one or two cigarettes would qualify for this label.

DR. YUSUF: I think it was current smokers.

DR. ARMSTRONG: Okay. The other question relates to the echo sub-study, and I recognize that you've taken care to try and address the issue of ejection fraction. I continue to be surprised that in excess of half of the overall population in HOPE had a prior myocardial infarction, and yet the ejection

fraction as reported is, you know, well up into the normal range, which raises in my mind the question as to whether the distribution of prior infarction in the sub-study that received echo cardiography was similar to the overall population.

DR. YUSUF: Do you have the baseline secure data, the secure paper with you?

All I can say, I haven't looked at this specifically, but we wrote the paper, and it didn't seem to us there was any major differences in baseline characteristics in the secure because the secure was done in five centers, every consecutive patient. So I --

DR. ARMSTRONG: I'm sorry. I'm confused.

DR. YUSUF: I don't have the numbers with me. So sorry.

Is it 50 percent? So it's the same.

DR. ARMSTRONG: Are you surprised that despite a population in excess of 50 percent with prior infarction that there would be normal ejection fractions?

DR. YUSUF: No, we deliberately excluded

people, you see. If they had a low EF, they would be excluded. So obviously whatever value we have in EF is -- is sort of an artificial value.

DR. ARMSTRONG: I'm just a little surprised that with over half of the population with prior infarction their injection fractions are normal and wondered if the other half who hadn't had echo cardiography also had normal ejection fractions.

There are two issues around dichotomy for unstable angina and heart failure that have been previously raised, and it would be helpful to me if you would just address them again, and that is since, again, revascularization is perceived as a secondary component of the label, yet unstable angina and unstable angina with electrocardiographic changes were not affects, could you comment on the reconciliation of those phenomena?

DR. YUSUF: I don't have a good explanation why unstable angina was not changed, and like you I'm puzzled actually. We had a reduction in MI. We had a reduction worsening angina, and we had a reduction revascularization. So I don't understand

that.

DR. ARMSTRONG: And I believe in SOLVD you had a reduction.

DR. YUSUF: That's right, but SAVE did not. You know, it's -- you know, maybe it's not a good endpoint. I don't know.

DR. ARMSTRONG: Okay. Ordinarily hospitalization for heart failure tracks heart failure fairly well, but in this study it did not. Comments?

DR. YUSUF: Well, it did, except that as soon as somebody got mild heart failure, they were given an ACE inhibitor, and the protocol allows it. So directionally it tracks it. Magnitude-wise it doesn't.

So, for instance, we found a 27 percent impact on the earliest manifestation of heart failure. Then if you take hospitalization as being more severe but a later manifestation, we only had a 13 or 14 percent effect.

And if you take death, it was a smaller effect, and I think it is partly due to the fact at least because of the noncompliance. Sixty percent

were given ACE inhibitors when they got heart failure, and the protocol allowed that.

DR. ARMSTRONG: My final question, which may be a function of my imperfect memory, as I recall in SOLVD there was a statistically significant increase in the incidence of carcinoma, which was thought to be a chance finding in I thought it was colorectal, but I can't remember.

And I understand that there's a similar trend in this study which is under observation. Could you comment on --

DR. YUSUF: No.

DR. ARMSTRONG: -- this tricky issue associated with cancer and all cause mortality? I'm having a little trouble understanding it.

DR. YUSUF: I think in this trial it will be fair to say there was a ten percent nonsignificant lower rate of cancers with ramipril compared to placebo, but it's nowhere near significant, and I don't recall us ever doing an analysis by site for ramipril. No, we haven't even looked at it by site for ramipril.

DR. ARMSTRONG: Did you say lower or higher?

DR. YUSUF: I don't know where they got those numbers.

DR. ARMSTRONG: Nine colorectal cancers in ramipril and one in placebo?

DR. YUSUF: Can I see that?

DR. THADANI: It was the other way around.

DR. YUSUF: No, no, no. I'm talking about overall cancers. Okay?

DR. ARMSTRONG: And I was talking about the incidence of colorectal cancer in SOLVD and the incidence in --

DR. YUSUF: Actually in SOLVD there was a numerical excess, but it wasn't significant, and when you looked at the data in SOLVD, and it's there in the paper, we said it was unlikely to be real because it was from mouth down to rectum, and obviously mouth etiology is very different from rectum.

The second thing is all those excesses in SOLVD occurred in the first two years, and cancer takes time to develop. So we felt it was implausible.

I can speak to SOLVD because I wrote the paper. This one we actually -- "we," CCC -- didn't do any analysis beyond overall cancer. So what you're seeing is what the FDA statistician has done. We haven't done those analyses.

DR. ARMSTRONG: Thank you.

ACTING CHAIRMAN CALIFF: Dr. Lindenfeld.

DR. YUSUF: Okay. That's worth pointing out, Paul. It's based on AE reporting. Now cancers weren't required to be reported. So actually most of the cancers that occurred in the study weren't part of the AE file. We know this because we -- for another part of the study this is an issue, and so we looked at cancers and pulled our cancers from every source.

So I think that's an incomplete part of the data.

DR. LINDENFELD: Okay. It's been a pleasure to listen to this data. I want to go to a different issue for a minute. One of the entry criteria was to be diabetics with a single risk factor, and yet the data is presented as all diabetics.

DR. YUSUF: Sure.

DR. LINDENFELD: I wonder if in the interest of people who may be using ramipril for this indication, could you show us the results in diabetics with no vascular disease?

DR. YUSUF: I don't have the slide, but Hertzel will address that issue.

DR. LINDENFELD: Okay.

DR. YUSUF: Dr. Gerstein in the next presentation.

DR. LINDENFELD: And then I guess at the same time maybe we could see what risk factors were in those diabetics, how many had, in fact, just a single risk factor and how many had multiple.

DR. YUSUF: Actually we don't know that, Joann. I can't recall. Did we ever do that analysis? No, I don't think we've done that.

DR. LINDENFELD: Because I think that will be an important group to see, just in terms of indications.

Again, in terms of entry, patients were entered for one of four reasons: coronary disease,

vascular disease, stroke, and then the diabetes indication.

Do you have those divided by how many -- I recognize that many of these patients had one or more of the vascular complications, but was there a specific reason for entry?

In other words, what I'm getting back at is in a patient who's had a stroke and no other evidence of disease, do you know how many patients like that were entered for that reason or for the reason of peripheral vascular disease?

DR. YUSUF: What we have done is to look at the primary reason for entry. I don't -- I'm afraid we didn't bring any slides on it, but the results are consistent. What we have not done is how many people had stroke only or coronary artery disease only. I don't think we ever did that analysis.

DR. LINDENFELD: I understand that this is a large group of patients, and we think of vascular disease similarly, but there have been studies where there appeared to be differences in benefits by -- such as Capri, for instance, in which there may have

been differences in the --

DR. YUSUF: But here we have, you know, the same kind of Capri analysis I've actually shown you.

DR. LINDENFELD: Right.

DR. YUSUF: And there there's consistent benefit in all the groups.

DR. LINDENFELD: Okay, and then in terms of the blood pressure, I'd like to get back to that for just a minute. Do you have the blood pressure draft? You said that two years was three millimeters systolic and two diastolic approximately.

DR. YUSUF: Yeah, about 3.3 and 1.8.

DR. LINDENFELD: And then at the end of the study?

DR. YUSUF: It's about the same delta. I just focused on the middle for presentation. It was there on the slide. It's actually slightly less towards the end because of noncompliance.

DR. LINDENFELD: And then in the ramipril 2.5 dose, do we know what the blood pressure drop was?

DR. YUSUF: It was on that curve. It

paralleled what ten did. So it's about the same order of magnitude.

DR. LINDENFELD: About the same.

DR. YUSUF: About the same. It may be off by a second decimal point, but it's about the same.

DR. LINDENFELD: Okay, but perhaps -- again, I know this is getting down to analysis that's difficult, but perhaps an intermediate effect with a similar --

DR. YUSUF: No, no. Actually it was numerically slightly greater than the ten.

DR. LINDENFELD: I see.

DR. YUSUF: Although not significantly greater, but numerically in one case it was 3.5 at the lower dose and 3.3 at the higher dose. So it was opposite to what you might have expected.

DR. LINDENFELD: And then just as a clarification, in our FDA booklet, the primary outcome events were adjudicated; is that correct?

DR. YUSUF: Yes, all the primary, secondary, heart failure, hospitalization, revascularizations, nephropathy, and unstable angina

were also adjudicated.

DR. LINDENFELD: And then just as a comment, I think as we talk about race here, there is some data, albeit in small numbers, to suggest there might be differential effects.

DR. YUSUF: Yes.

DR. LINDENFELD: For instance, in VHEFT (phonetic) there may have been a differential effect in blacks and heart failure, and I think the best study will show potentially a similar one.

DR. YUSUF: We actually -- Jay Kohn (phonetic) rang me when he had that analysis, and we redid the SOLVD analysis, and we couldn't find it the way he did. Then he asked for all kinds of combinations to try to get something close, and one out of seven or eight analyses hinted at it, but overall in SOLVD it's an analysis we've done.

One of the problems with analyses like RACE, which is not a prespecified hypothesis in trials, is if you did many trials, in one or two of them there'll be an interesting trend, and if only the people who have the interesting trend reported, you

have a biased impression of the literature because the others didn't report it because it was uninteresting.

And I can tell you for SOLVD we've looked at it, and the reason we've never presented it is there was nothing interesting in it.

DR. LINDENFELD: Okay.

ACTING CHAIRMAN CALIFF: Dr. Borer.

DR. BORER: One of the very good things about sitting in the middle of the table with such a sharp group here is that by the time you get to me there's not much to ask, but I have a couple of questions anyway.

First of all, you indicated a reduction in heart failure by whatever definition, heart failure development at any point during the study on ramipril. I didn't see in any of the materials we received the definition used to identify heart failure. I understood heart failure hospitalizations, and you showed a category of new use of angiotensin converting enzyme inhibitors as supportive evidence that heart failure was present, but how did you define new onset heart failure that didn't require hospitalization?

DR. YUSUF: I mean, it was basically at the discretion of the clinical investigator. So he or she thought there was heart failure. There was a check box. So to be fair we didn't even ask was JVP elevated. We said it was, and then we asked did you use ACE inhibitor or not, and you know, 60-odd percent used an ACE, initiated ACE inhibitors.

So that's all the data we have, Jeff, and that's it. That's what we have.

DR. BORER: Okay. Similarly, with regard to peripheral arterial disease, the plan was to enter about ten percent of the patients, I guess, with peripheral arterial disease?

DR. YUSUF: No, we didn't have a quota for it.

DR. BORER: Well, there was some discussion for that, but it doesn't matter. That's not important here.

DR. YUSUF: Yeah.

DR. BORER: The point is that there was the expectation that a certain percentage of patients might have or some proportion of patients might be

entered with PAD.

As I looked at the data, in fact, about half the patients had PAD, which was comforting to me to see, but I didn't understand the criterion because -- the criterion by which the diagnosis was made.

The entry criteria included in addition to critical limb ischemia evidence, an ABI of less than .8, and I would assume that you didn't have an ABI of less than .8 or claudication or both in 50 percent of the patients, or did you?

DR. YUSUF: Okay. There are two different things, and then I can show you some data as well. The first is if they had clinical evidence of PAD, either symptoms or surgery or something else, then they're in. Okay? And if it's only symptoms they need the low ABI as well, so that it was both.

Then we have data on ABI and everybody. Okay? So I can show you the data both ways, clinical symptoms and just by ABI if you'd like.

And can we see, yes, 33, Angie, please. Thank you.

Okay. These are the data. This is

clinical PAD. Okay. So we had 1,700 people with some evidence of PAD clinically, and that's the risk reduction on the primary and the secondary.

Then we took everybody, including these people, okay, and divided them into quartiles. What's not included here are the people that we couldn't record ABI because they couldn't palpate the dosalisbeaters (phonetic) or the posterior tibial, but leaving that out, which is about 800 people, this is the rest of the people by quartiles.

And you will see, you know, the relative risk is there right through our -- there's no evidence of interaction.

DR. BORER: Okay. So the point is that about a quarter of the population had either an ABI that was relatively low plus --

DR. YUSUF: Can we switch the light off, please?

DR. BORER: -- plus or minus claudication, or they had had surgery, or they had angiography showing significant obstruction?

DR. YUSUF: Right, right.

DR. BORER: Okay. Finally, I don't want to beat a horse that's already been riding for a great deal of time here, but I would like to get back to the race issue as well because I was concerned by it, too, for the same reasons that Tom indicated initially.

It's true you didn't power the study to look at the impact of race, and it's true that the sample size of blacks particularly was very small. Nonetheless, I too think that there is a potential biological basis for hypothesizing that there might be a difference in blacks and in others, and the labeling consideration here would be potentially important.

Despite the very compelling pathophysiologic construct of Dr. Zow, we don't really know how ACE inhibitors cause their apparent clinical benefit in this setting, but we do know that renin levels vary within the population, and that by and large black people have lower renins than non-black people.

And I wonder. Do you have any information at all about renin levels in any part of the population, in any subpopulation, and can you look at

the impact of this drug on the endpoints that are of interest here with regard -- as a function of that parameter?

DR. YUSUF: Jeff, that's a good question. It's one of the many analyses we intended to do with stored bloods. In three and a half thousand people we have stored bloods. Now, the unfortunate part -- not the unfortunate part -- the reality is that those bloods are all collected in Canada. So we wouldn't have many blacks in it.

But we could look at it by measured renin levels, high, low, intermediate, and try to explore those questions, but it's one of those things that we intend to write a grant and raise money to do.

One little point just worth noting. You know, yes, on the primary endpoint in blacks. Numerically the odds ratio was 1.59 with white confidence limits from .66 to 3.79.

But if you look at the secondary endpoint, you get a relative risk of .70 with confidence limits that go from .38 to 1.3. It's exactly the opposite. It just emphasizes the unreliability of small numbers.

It will be incorrect for me to use the secondary endpoint to claim we have proof that it works in blacks.

I mean, I'm glad Tom's nodding his head in agreement. I think the point is we don't have many people there, and we shouldn't try to make too much of that subgroup.

ACTING CHAIRMAN CALIFF: Okay. I'm going to reserve my questions until the end.

John Di Marco.

Bad luck with the microphones here.

DR. Di MARCO: Salim, a very nice presentation. Can I ask you just a couple of questions? Most of your events are myocardial infarction, and can you review for me how the diagnosis of myocardial infarction was made in this study which is carried out across the world and what your criteria were and what your events committee, you know, required for the diagnosis?

DR. YUSUF: Would you mind? We have the -- we'll do two things. One is I can give you what the events committee's criteria is, but the chairman

of the events committee is Dr. Dagenais, and maybe, Giles, you'd like to come up to the microphone.

I mean, we had very detailed criteria.

DR. Di MARCO: Part of the reason that comes up, because if you look at your deaths, the vast majority of your deaths are related to myocardial infarction, and you have very few sudden deaths. You have a bunch of resuscitated cardiac arrests, but did you classify a sudden death as a myocardial infarction?

DR. DAGENAIS: No. What we did was to use unexpected death, which was 24 hour. It was at the 60 minute. So it was unexpected cardiovascular death as a definition. So we cannot say that this was really the death within one hour. We didn't make that difference.

DR. Di MARCO: But what I'm just saying, were they classified --

DR. YUSUF: I've got the criteria here. I can help you. Unexpected deaths within 24 hours were classified as cardiovascular presumed MI. Then we have fatal MI. Then we have heart failure deaths.